



**Mediar**  
Therapeutics

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

Keystone Symposia on Fibrosis: Inflammation, Drivers, and  
Therapeutic Resolution

Paul Yaworsky

# Conflict of Interest Disclosure



- PY is an employee and shareholder of Mediar Therapeutics

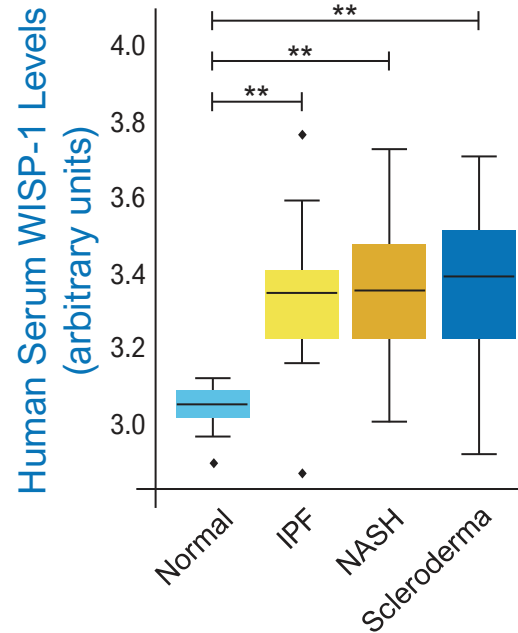
# CCN4/WISP-1: a Member of the CCN Family of Secreted Matricellular Proteins



Parameters	Description
<b>Protein Structure</b>	<ul style="list-style-type: none"> <li>• CCN4 was originally described as WISP-1 (Wnt-inducible signaling-pathway protein 1)</li> <li>• Four conserved and distinct cysteine-rich domains with homology to: insulin-like growth factor binding proteins (IGFBP), von Willebrand factor (VWF), Thrombospondin (TSP1) and Cysteine-knot-like (CT)</li> <li>• ~40kDa matricellular glycoprotein (4-N-glycosylation sites)</li> <li>• No known high affinity receptor(s); integrin binding</li> </ul>
<b>Biological Functions</b>	<ul style="list-style-type: none"> <li>• KO mice are protected from fibrosis in several models of disease</li> <li>• KO phenotype presents mild decreased bone mass</li> <li>• Bone cartilage biology: bone homeostasis and chondrocyte differentiation</li> <li>• Cell survival: attenuates p53-mediated apoptosis in response to DNA damage through AKT-activation</li> <li>• Fibroblast activation and myfibroblast differentiation</li> </ul>

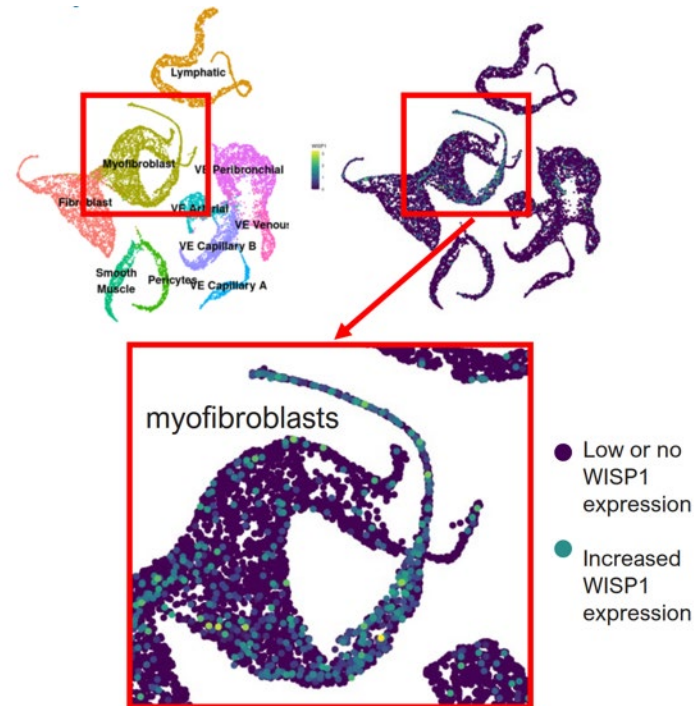
# WISP1: Detected and Induced in Human Fibrotic Diseases

WISP1 is elevated in serum of fibrotic disease patients



Somalogic probe WISP-1 aptamer 1 (SeqID: 13692-154).  
Statistical test: Kruskal-Wallis with Bonferroni correction.  
\*\* = p-value < 0.01.

WISP1 is up-regulated in myofibroblasts of IPF patients



SOURCE: IPFCellAtlas.com; Modified from Adams et al (2020)

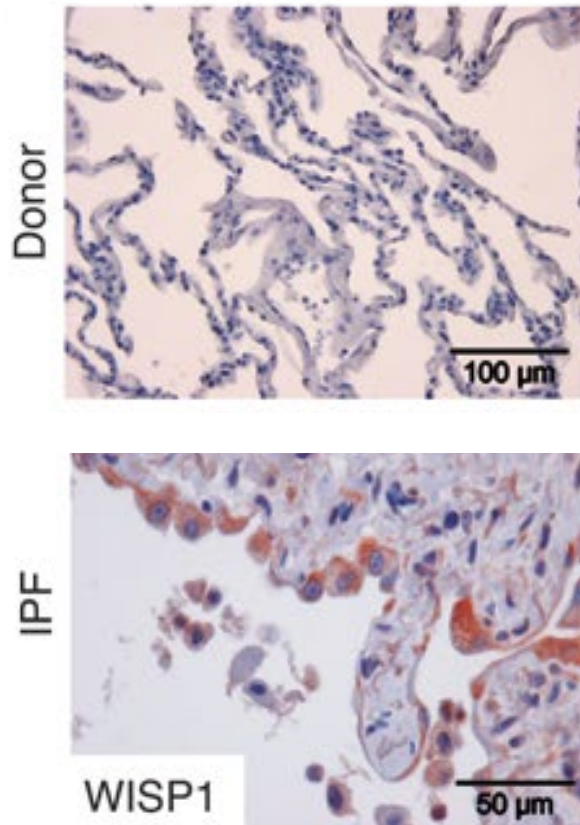
WISP1 is a secreted matricellular protein with a role in collagen architecture

WISP1 was identified in a genetic screen for reprogramming activated myofibroblasts back to a quiescent state<sup>1</sup>

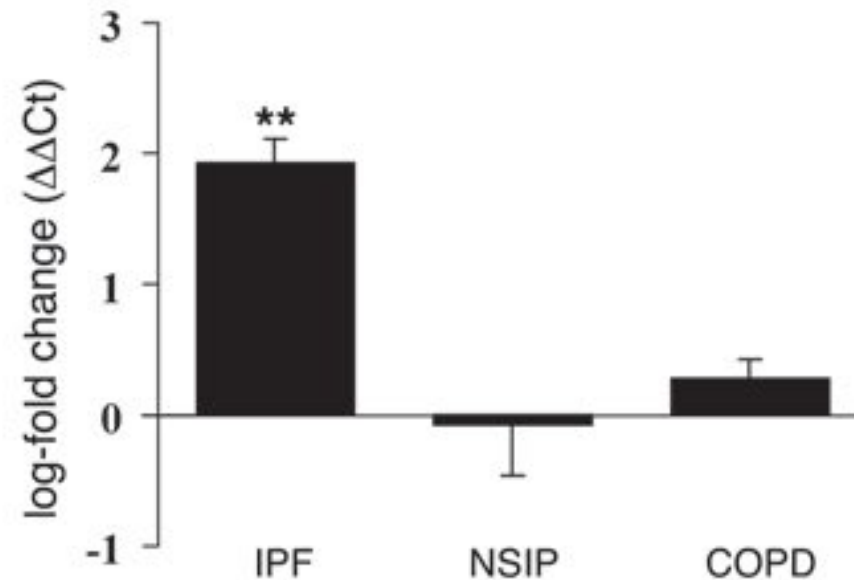
**WISP1 drives the myofibroblast phenotype:** promotes collagen secretion, induces cytoskeletal changes including  $\alpha$ SMA expression

Mediar has identified neutralizing antibodies that demonstrate *in vivo* efficacy in mouse lung and liver fibrosis models as well as in *ex vivo* human liver slices and organoids

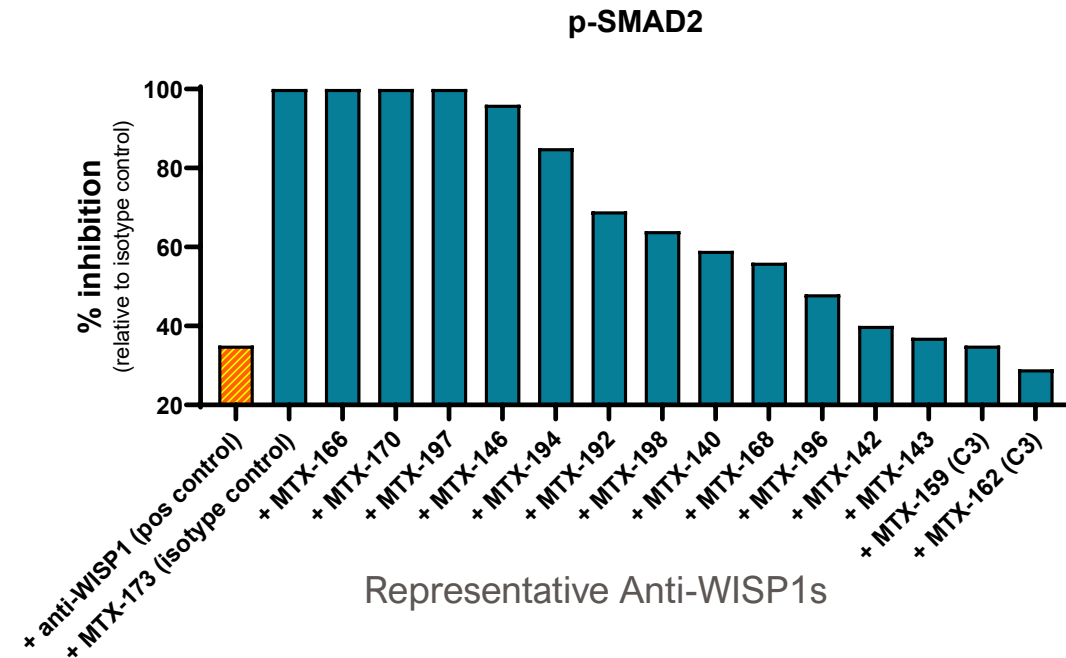
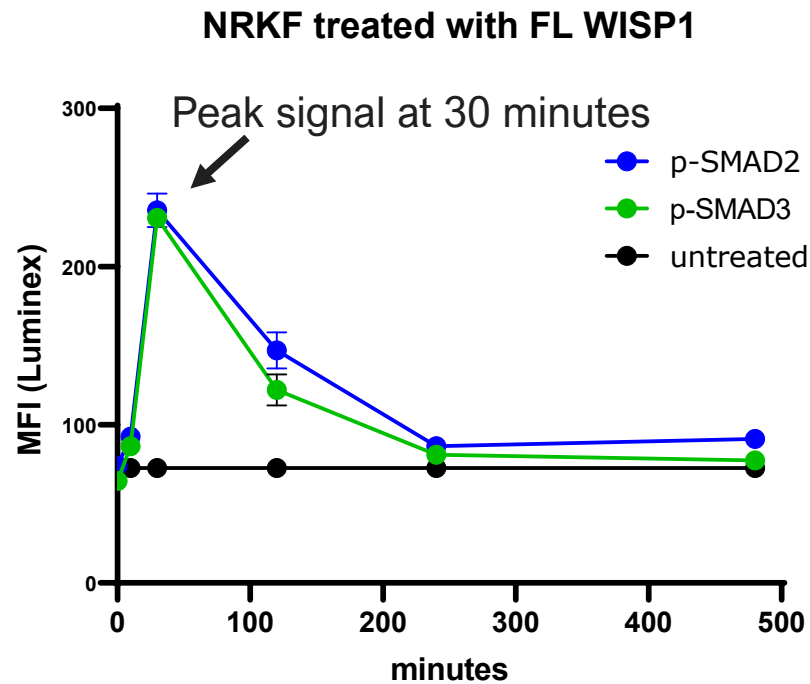
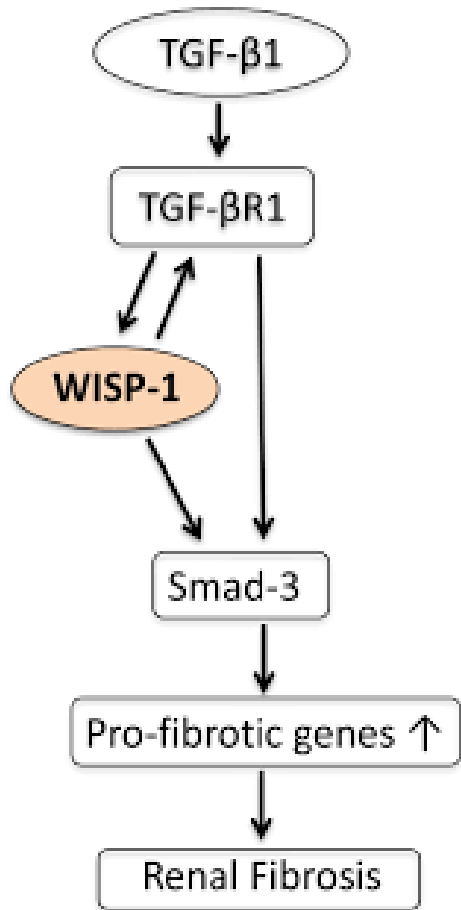
# WISP1 Had Previously Been Identified in Pulmonary Fibrosis: Levels are Elevated in the Lungs of IPF Patients



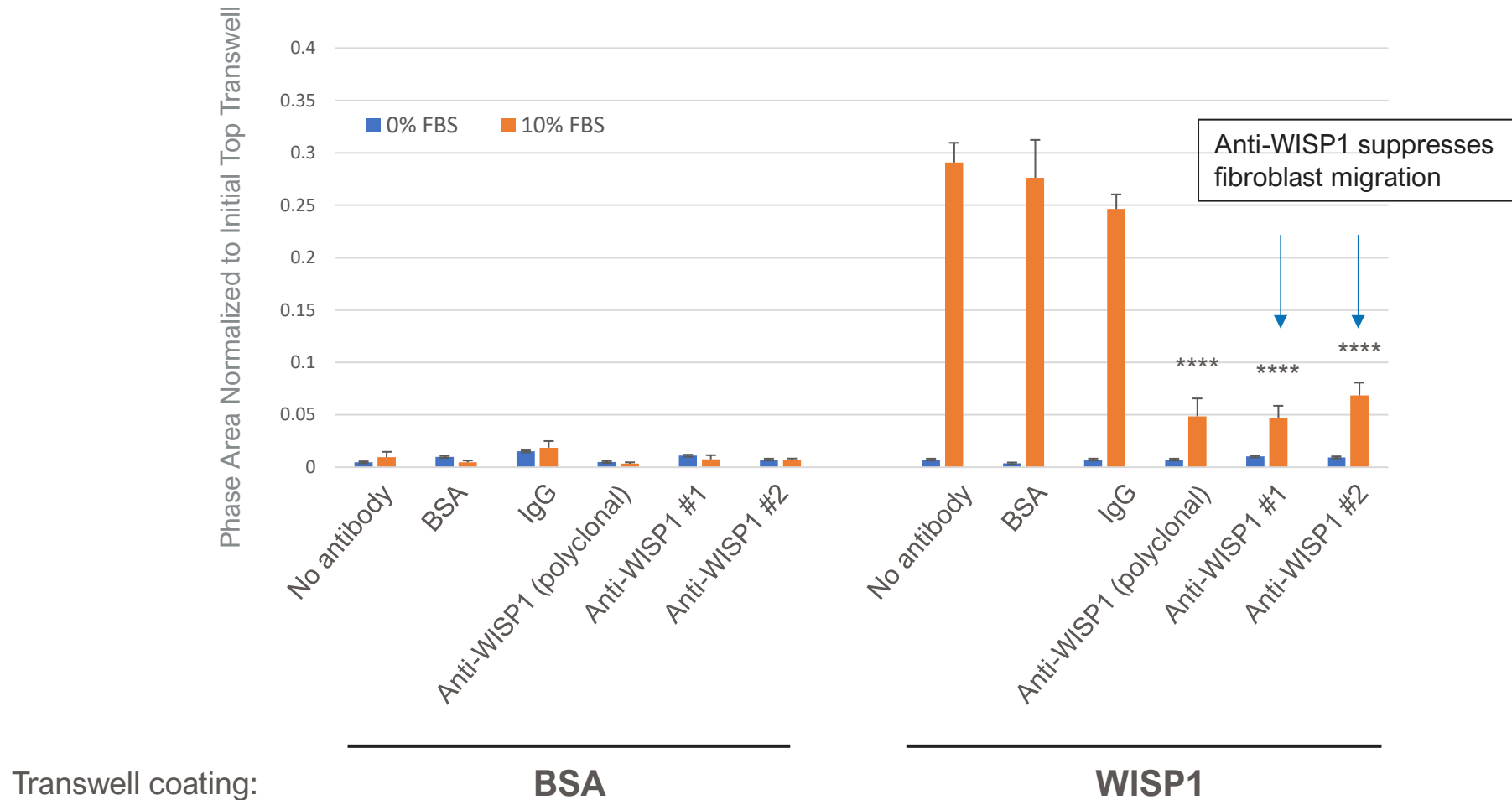
- Greater WISP1 mRNA and protein in lungs from IPF patients as compared to controls
- WISP1 elevation was specific to IPF and not other lung disorders



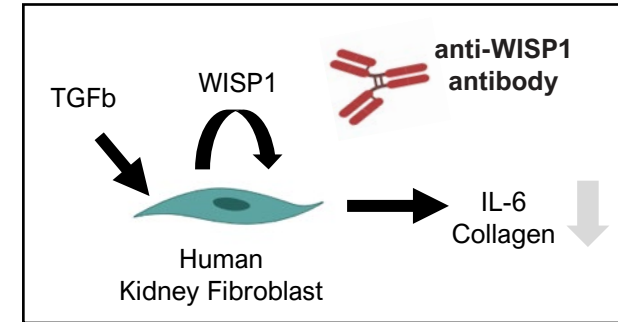
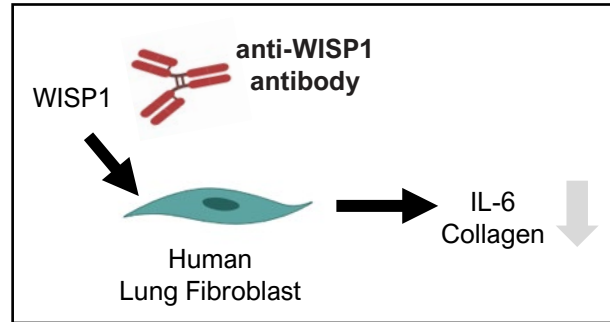
# WISP1 Induces Smad2/3 Phosphorylation (TGF $\beta$ Signaling) in Fibroblasts Which Anti-WISP1 Can Suppress



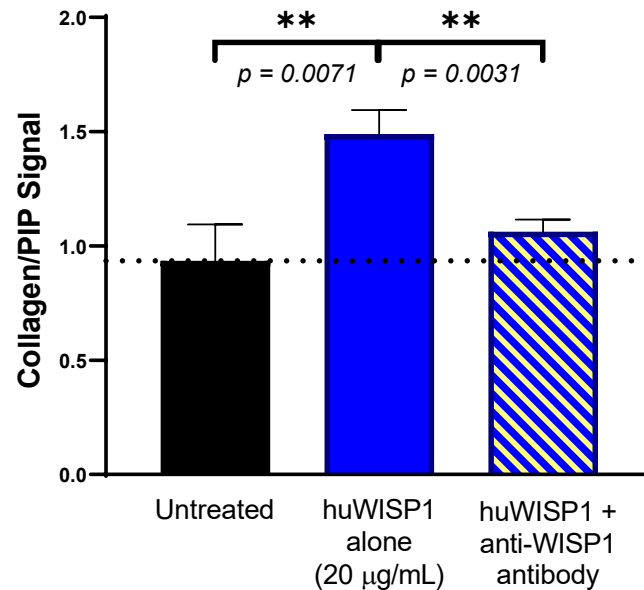
# WISP1 Neutralization: Anti-WISP1 Reduces Primary Human Fibroblast Migration



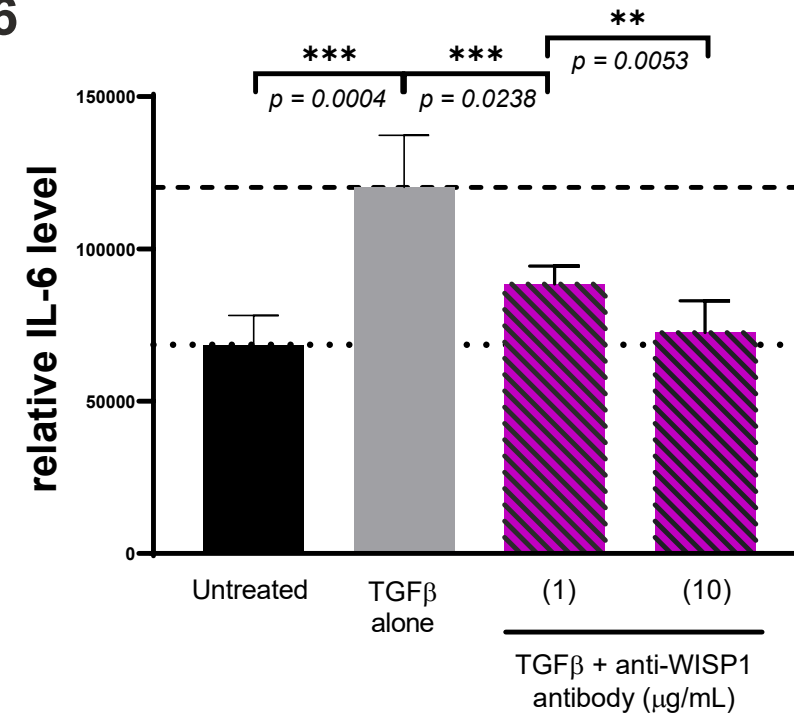
# Anti-WISP1 Reduces Collagen and IL-6 in Primary Human Lung Fibroblasts



## Collagen



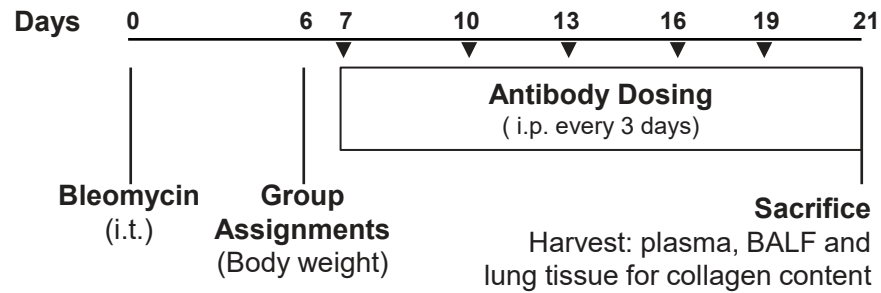
## IL-6



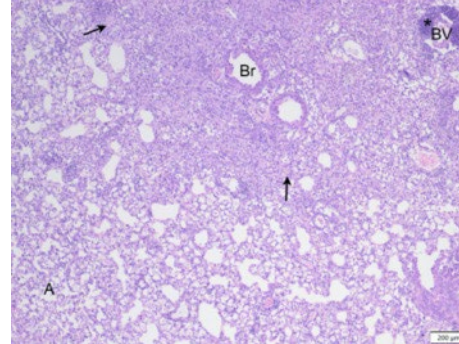


# Anti-WISP1 Dramatically Reduced Lung Fibrosis in Bleomycin-Treated Mice

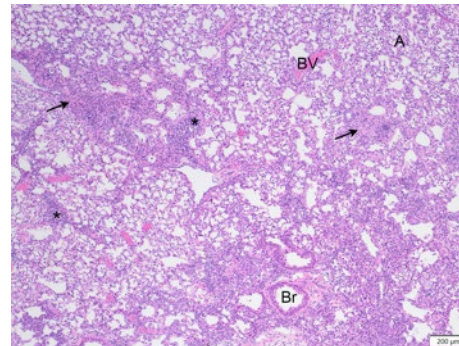
## Study Design



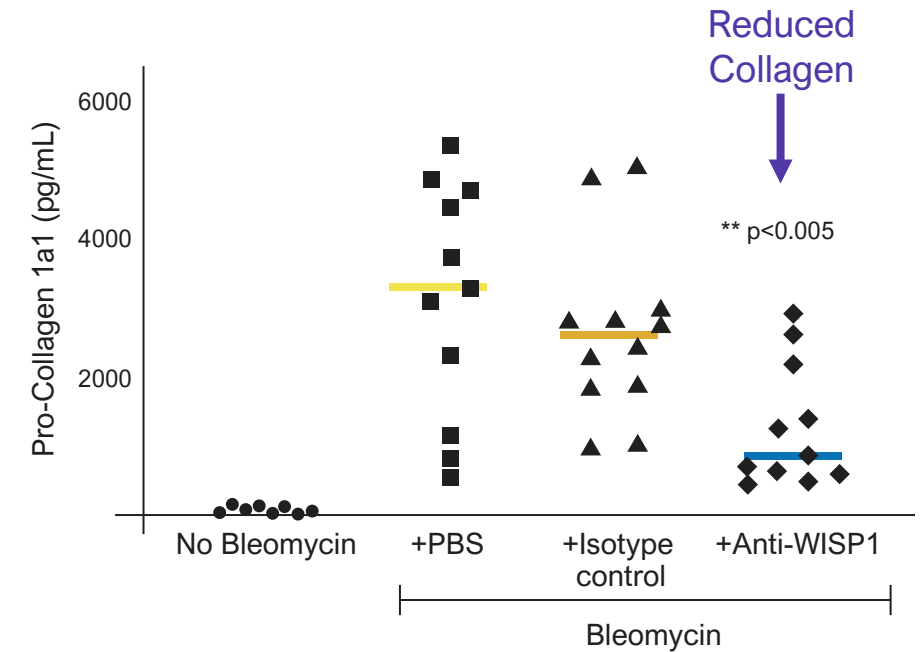
Isotype control



Anti-WISP1

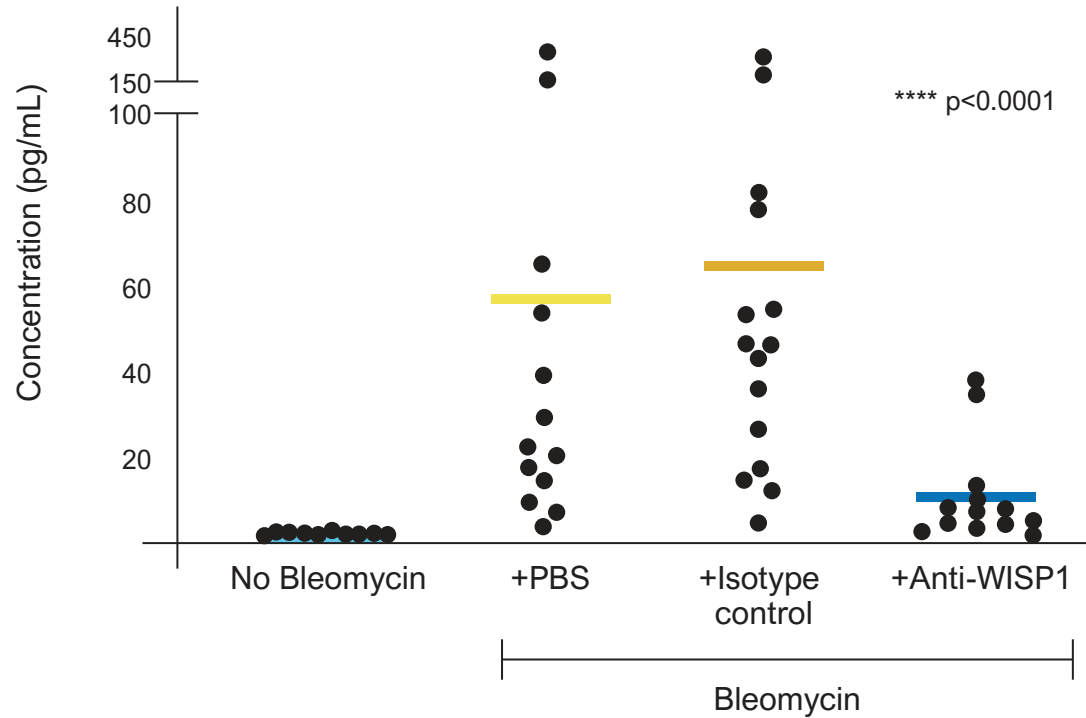


## Collagen (BALF)

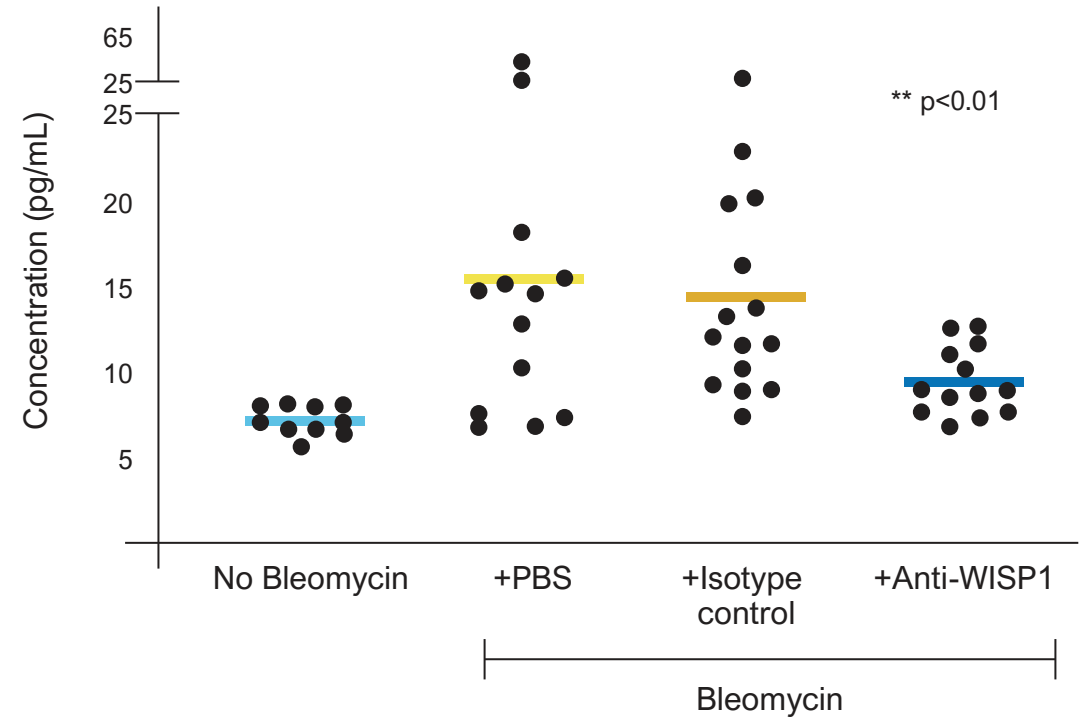


# Anti-WISP1 Represses Clinically Relevant Inflammatory Markers in a Bleomycin Model of Lung Fibrosis

## IL-6

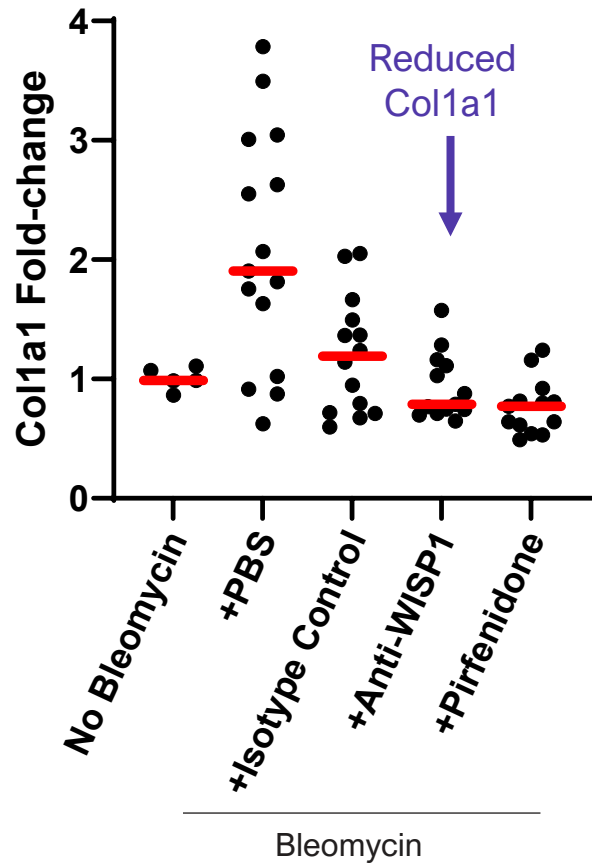


## MCP1/CCL2

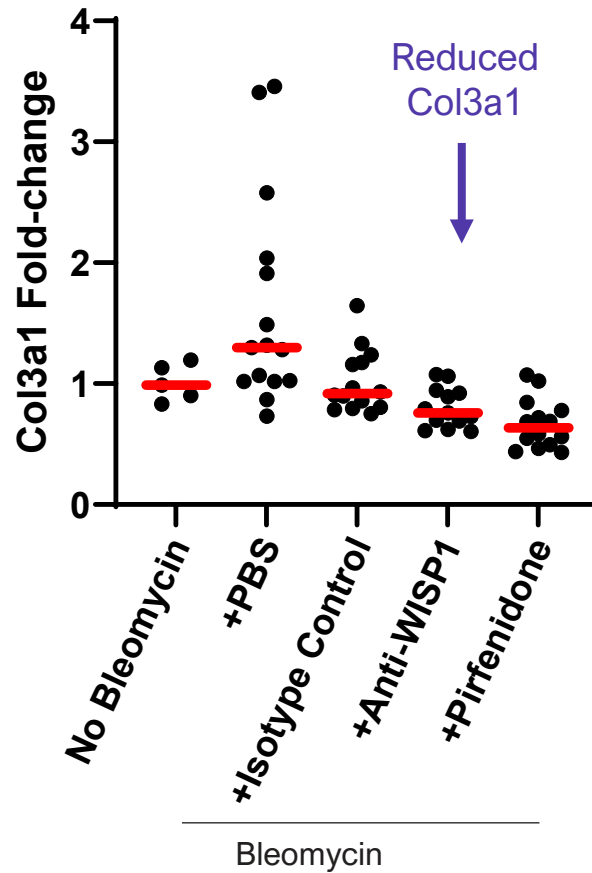


# Anti-WISP1 Suppresses Pro-Fibrotic Gene Expression in the Bleomycin Mouse Model

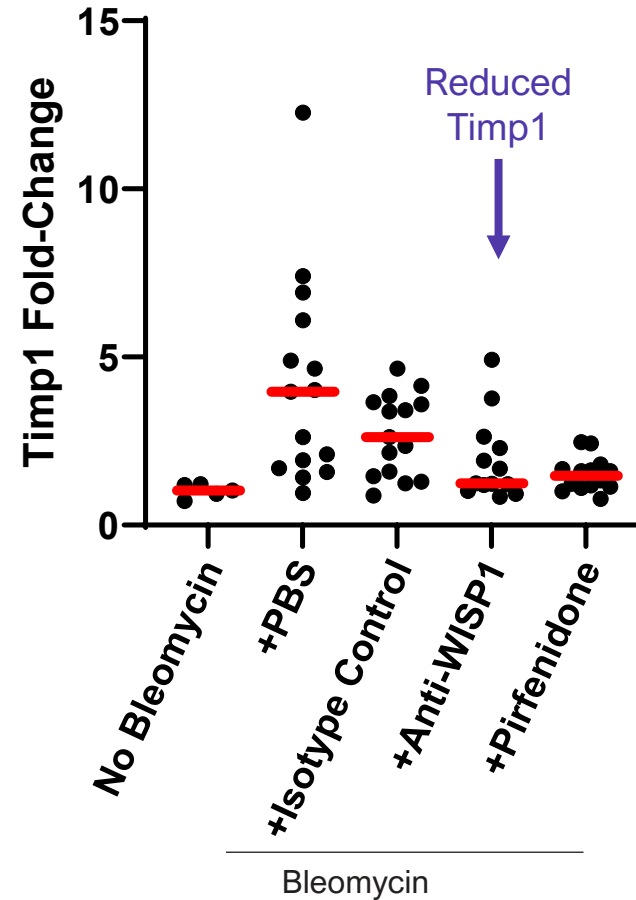
## Collagen1a1



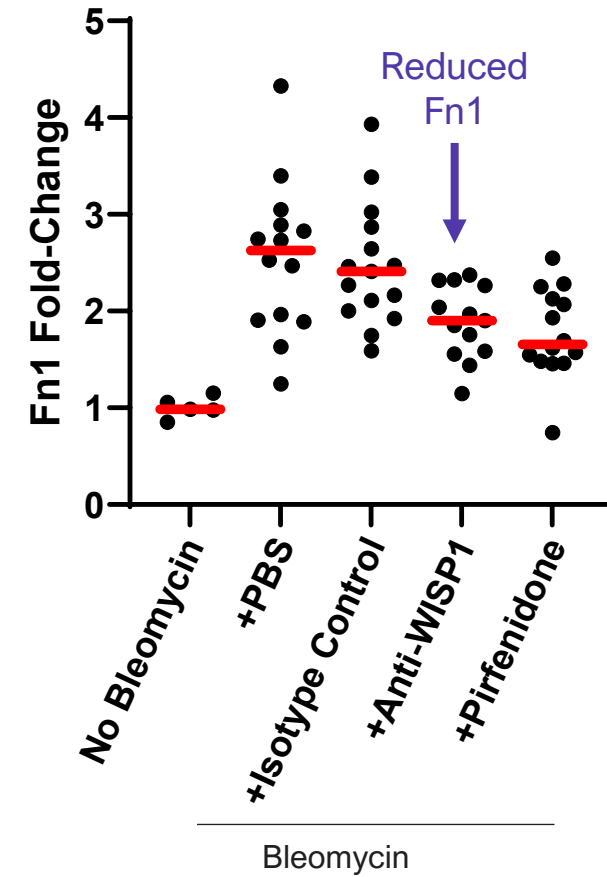
## Collagen3a1



## Timp1

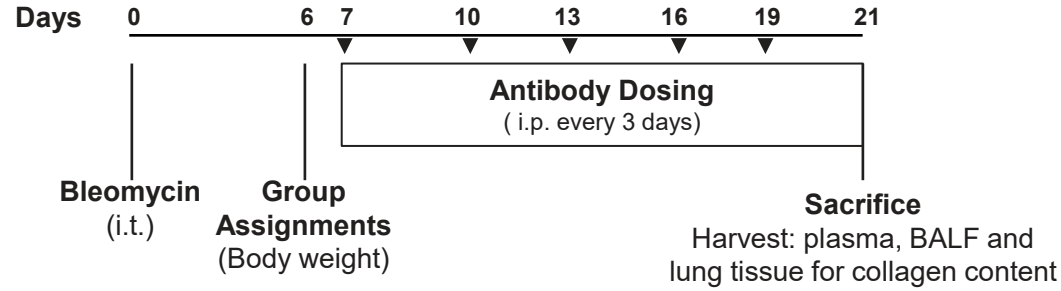


## Fn1

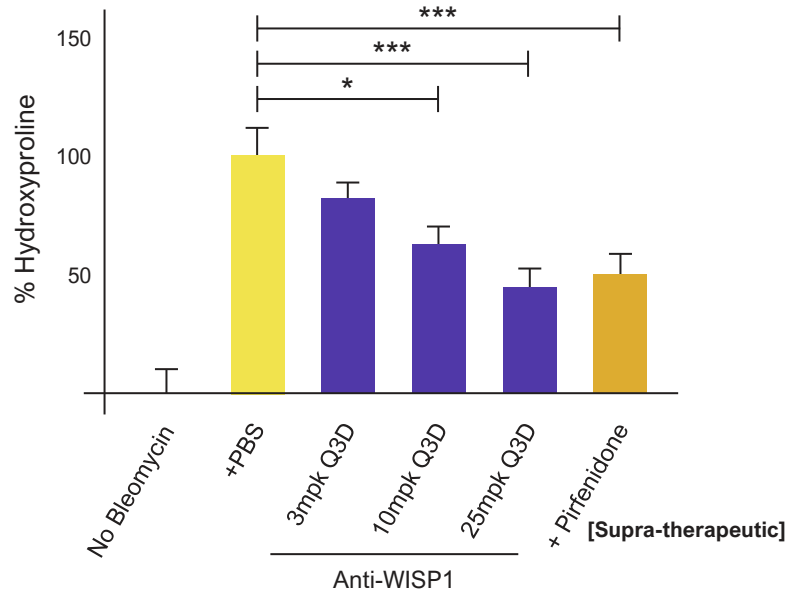


# Anti-WISP1: Determining Exposure/Response Relationship

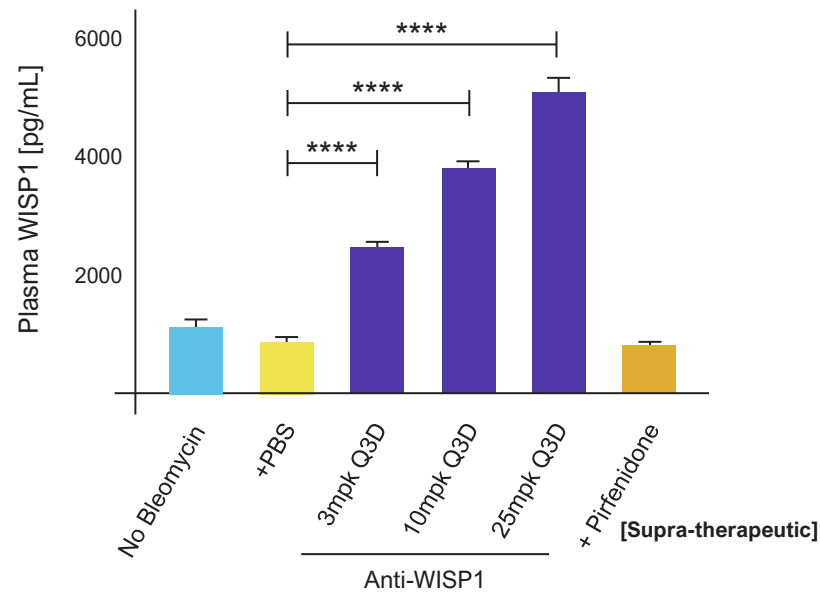
## Study Design



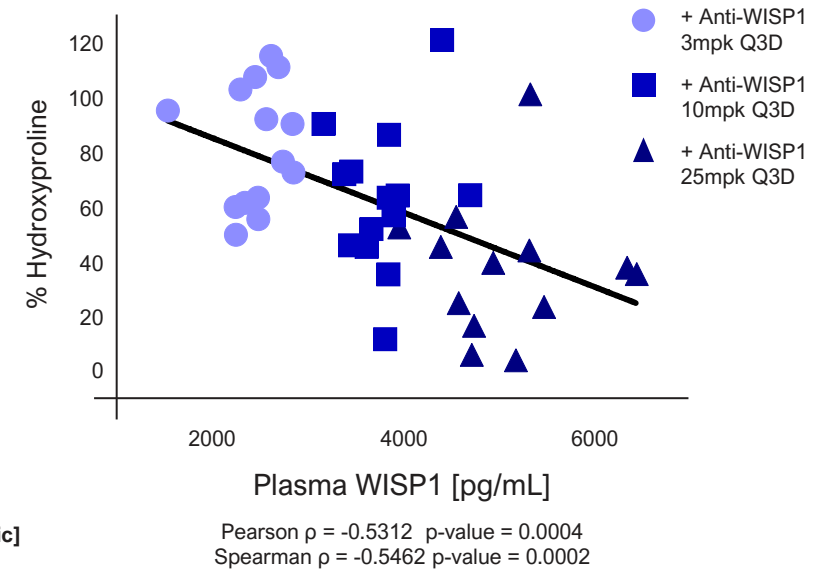
## Lung collagen content



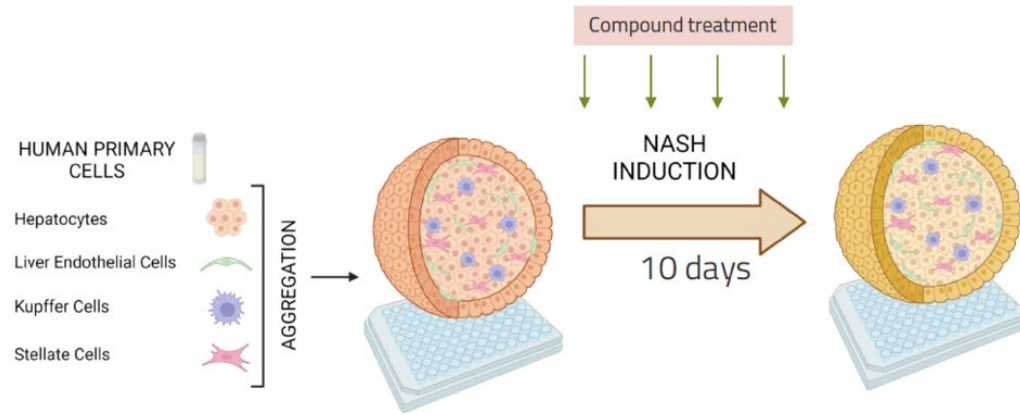
## WISP1 stabilization



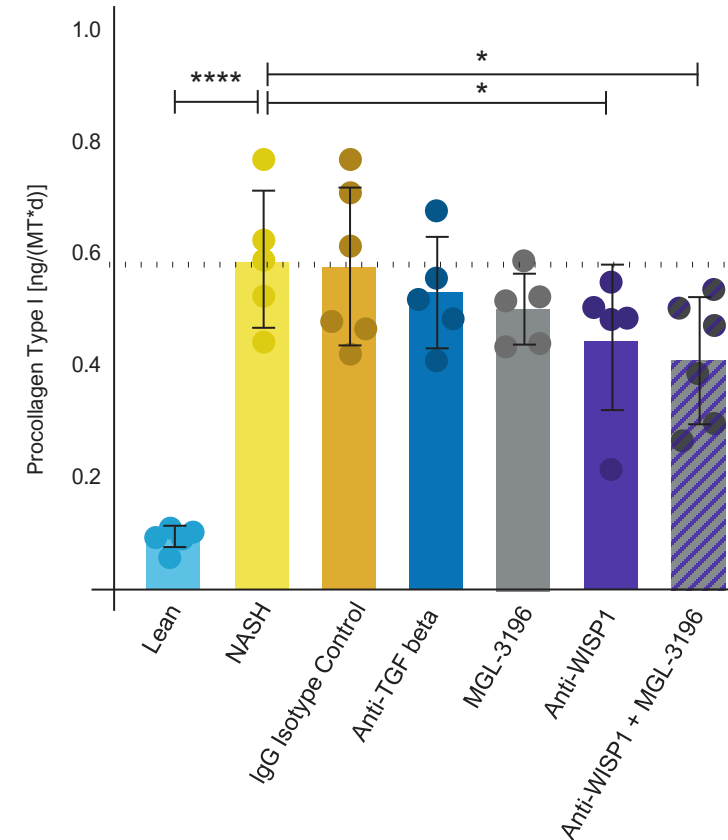
## Anti-fibrotic dose relationship



# Liver: Anti-WISP1 Inhibits Collagen Secretion in a Human Organoid Model



- 3D *in vitro* co-culture model consisting of primary human hepatocytes, Kupffer cells, liver endothelial cells, and hepatic stellate cells.
- NASH and fibrosis modeled by supplementation with NASH medium for 10 days, inducing pro-collagen secretion.



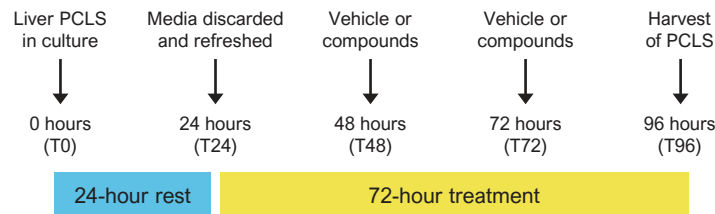
Anti-WISP1 shows additional anti-fibrotic activity when combined with a THR $\beta$  agonist

# Liver: Anti-WISP1 Dose-Dependently Decreases Fibrotic Markers in a Human *ex vivo* Model

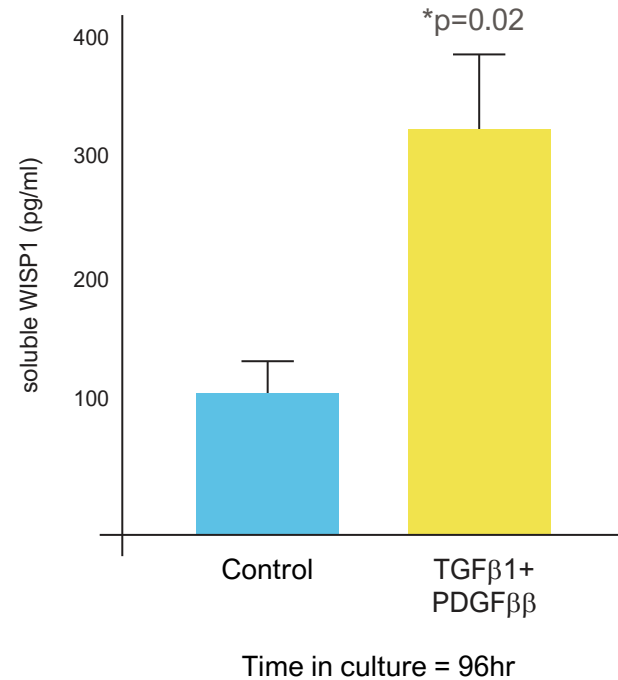


## Precision Cut Liver Slices (PCLS) generated from human organs

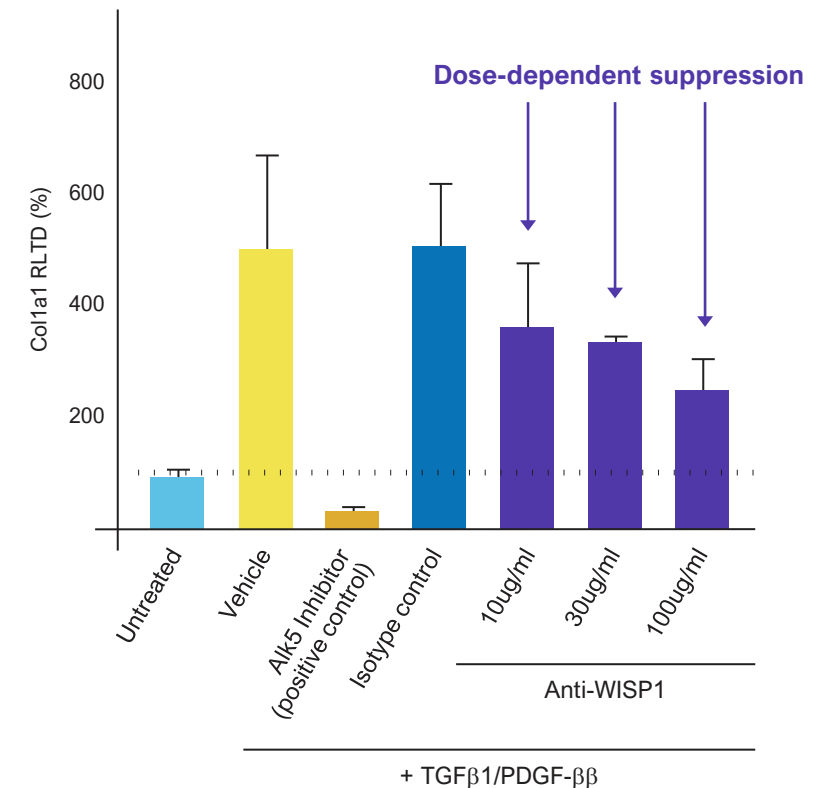
- Human liver obtained from surgical resection
- Fibrosis induced with TGFβ1+ PDGFββ
- PCLS maintained in a bespoke bioreactor that allows culturing of fully functional tissue



## Soluble WISP-1 is induced in PCLS following TGFβ1+ PDGFββ treatment

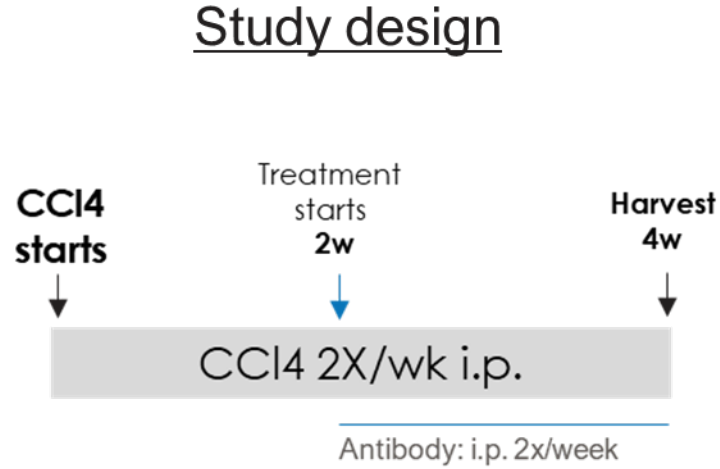


## Anti-WISP1 reduces Collagen1 transcript in a dose-dependent manner

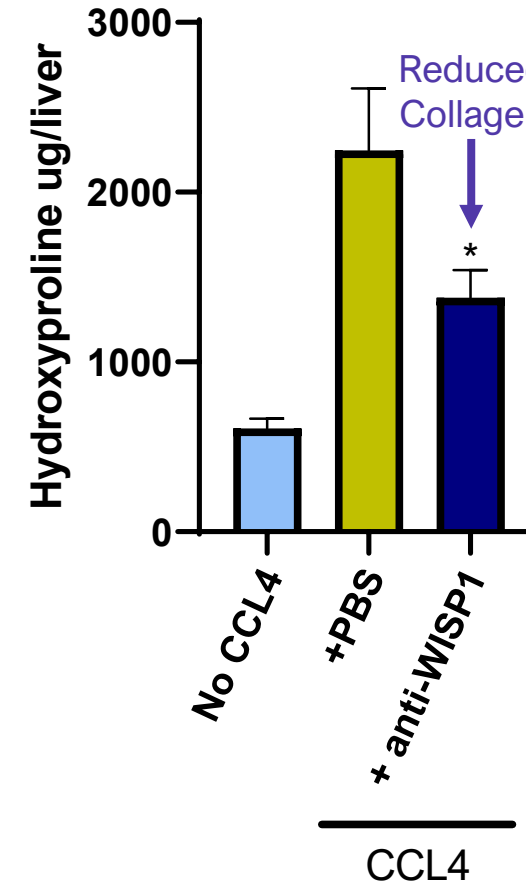


RLTD% (Relative level of transcriptional difference); Col1a1 normalized to β-actin

# Liver: Anti-WISP1 Reduced Liver Fibrosis (Collagen Content) in CCl<sub>4</sub>-Treated Mice

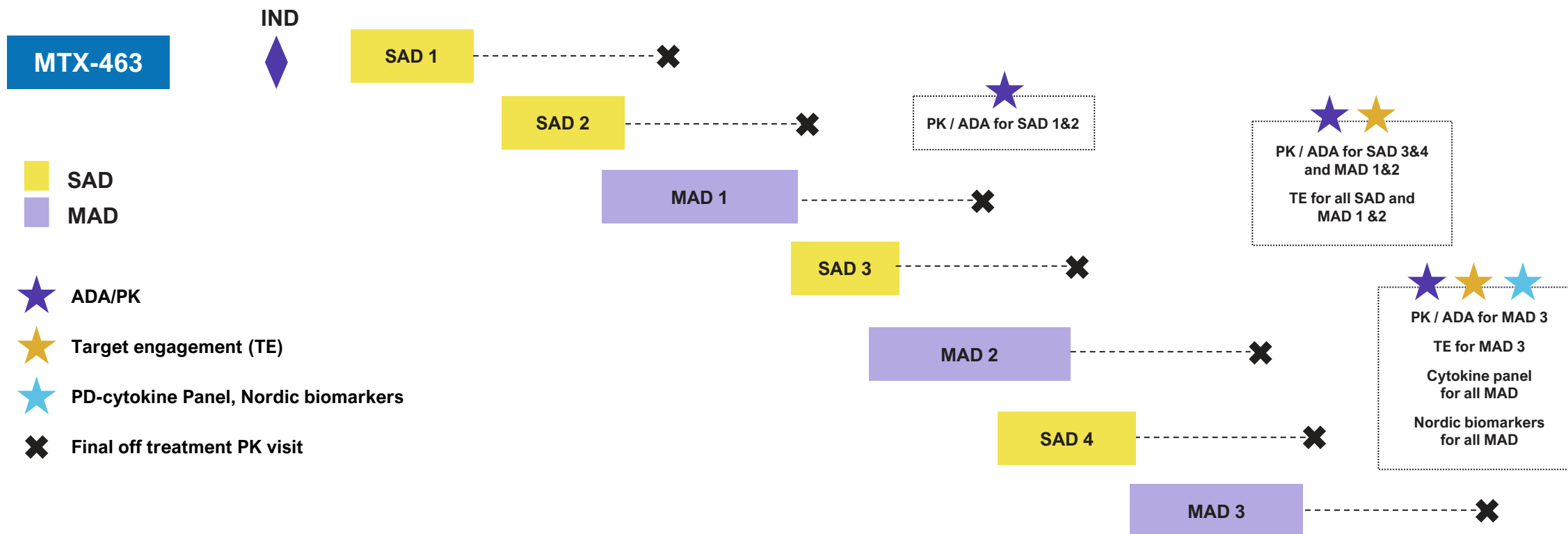


Hydroxyproline quantifies collagen deposition



Data expressed as Mean +/- SEM  
\*p<0.05 vs PBS, t-test

# MTX-463: Ph-1 Study Details





# Summary Rationale for Anti-WISP1

- WISP1 identified in a genetic screen: reprogramming myofibroblasts to quiescence
- WISP1 is induced in IPF patient lung tissue and serum
- In mouse models of lung fibrosis, Anti-WISP1:
  - Suppresses lung fibrotic area (histology scoring)
  - Suppresses fibrotic markers in BALF and plasma (including Collagen and TIMP1)
  - Suppresses inflammation markers in BALF (including IL6 and MCP1)
  - Suppresses fibrotic gene expression in lung tissue
- Anti-WISP1 has expected PK properties and modelling supports clinically feasible dose/dose frequency
- IL6 is emerging as a potential PD biomarker (additional work ongoing)
- Phase 1 clinical trial has completed

# The Mediar Team



Thank you

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