Phenotypic Characterization of Repetitive Bleomycin-Induced Chronic Pulmonary Fibrosis Model in Mice

Rashmi Munshi, Matthew Marrazzo, Donovan Unks, Sarieh Azshirvani, Danhui Zhang, Malavika Ghosh
Aragen Bioscience, Inc., Morgan Hill, CA, USA

Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive and ultimately fatal disease that causes scarring and thickening of the lung tissue leading to respiratory failure.

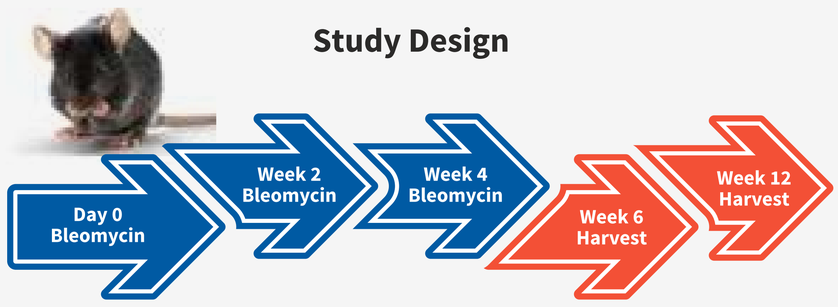
Bleomycin-induced IPF in mice is a well-established model that recapitulates clinical endpoints; however, a single instillation of bleomycin (Bleo) resolves the fibrotic parameters spontaneously. We established a repetitive bleomycin model in mice that shows important characteristics of human IPF. Three bi-weekly instillations of bleomycin led to persistent and progressive pulmonary fibrosis. Bleomycin induced impaired lung function, and increased Ashcroft score, collagen deposition and alpha-SMA expression. Lung gene expression and cytokine profiling are also consistent with lung injury. These endpoints increased at 6 weeks and persisted for 12 weeks in most of the parameters.

The biological analyses demonstrate that this model is a relevant model for studying progressive fibrosis as seen in human IPF.

Methods

Bleomycin mouse model of lung fibrosis was conducted at Aragen under IACUC approved protocol. Histological analysis was performed at Aragen and evaluated by board certified pathologist & by digital pathology with Visiopharm's AI based imaging software.

Lung hydroxyproline assay was used to measure tissue collagen content. Inflammatory cytokines from lung bronchoalveolar lavage fluid (BALF) were evaluated by MSD 19-Plex. Gene expression was analyzed by qPCR.



Statistics: *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 by one-way ANOVA, with Tukey's post hoc test, or two-way ANOVA with Sidak's test for whole body plethysmography; mean +/- SEM.

Conclusions

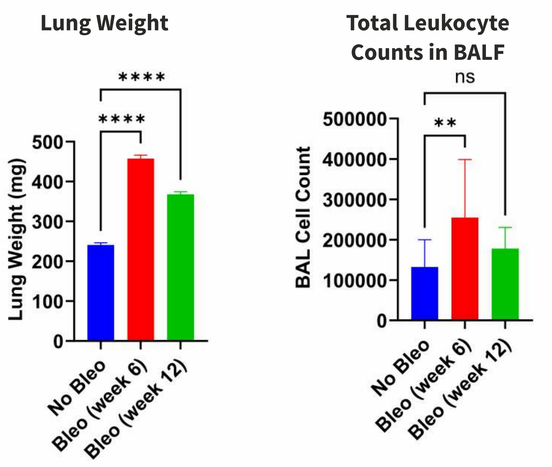
Repetitive bleomycin administration increased the fibrotic parameters in mice lung and extended for 12 weeks. The lung shows a chronic injury that is consistent with many features of IPF in humans.

This chronic model represents the clinically relevant model of persistent progressive fibrosis and may be a good tool for studying recurring fibrosis lung disease and evaluating new potential drug candidates.

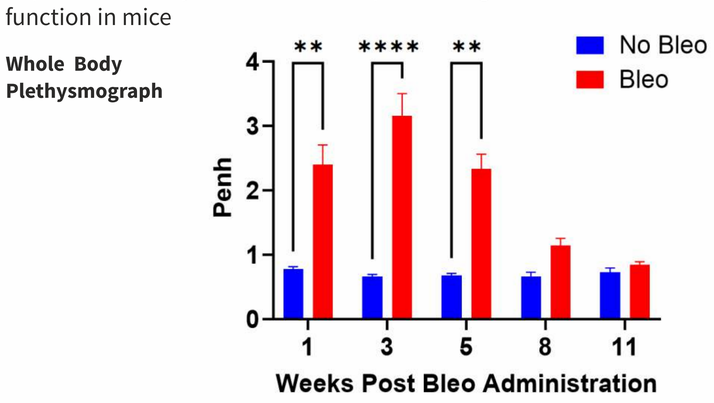
Our expert and experienced staff provide scientific input and support for all project stages. Visit our website at www.aragenbio.com and have Aragen become your partner for characterization and development of new drugs for this important medical need.

Results

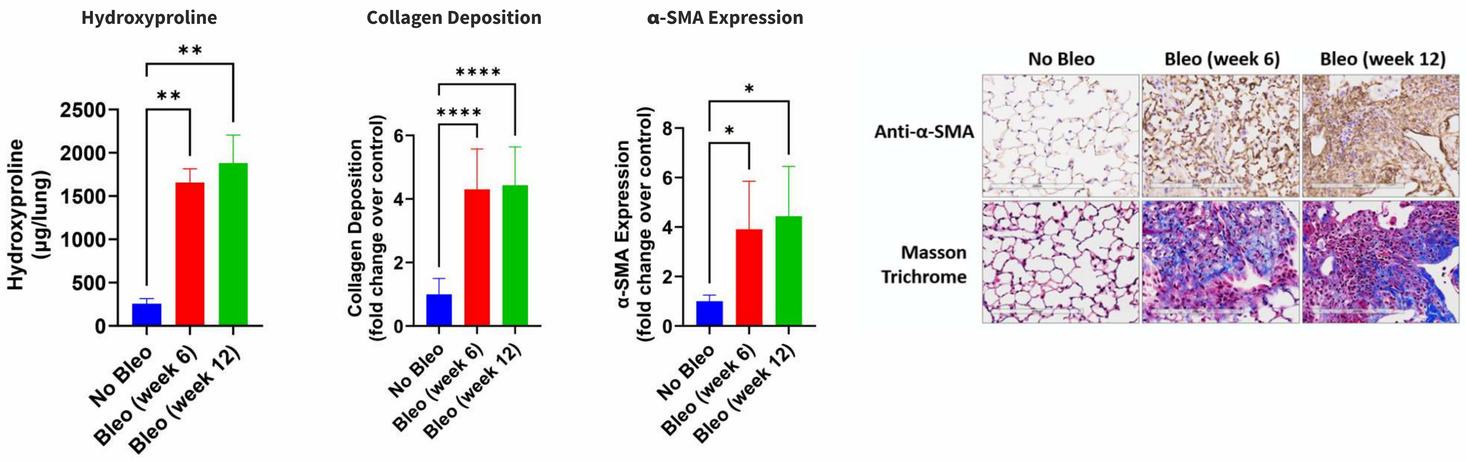
Repetitive bleomycin instillation increased mouse lung weight and leukocytes in BALF



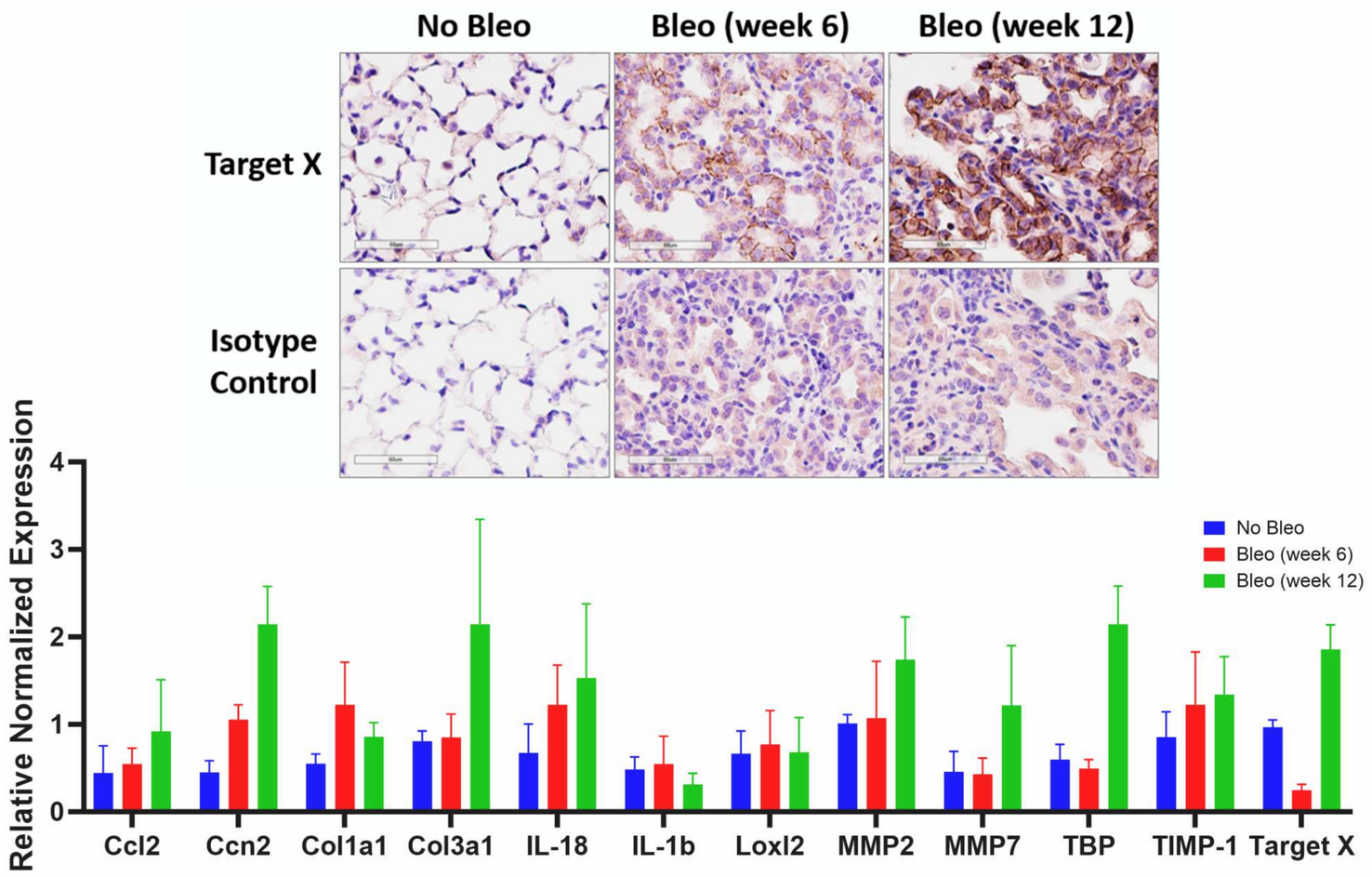
Repetitive bleomycin instillation impaired lung function in mice



Repetitive bleomycin instillation led to lung fibrosis in mice



Repetitive bleomycin instillation increased therapeutic target and lung fibrosis-related gene expression in mice



Repetitive bleomycin instillation increased cytokine production in lung BALF in mice