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The importance of interventional timing in the bleomycin model of pulmonary fibrosis

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Preclinical models are important to decipher mechanisms of disease, identify novel treatment targets and develop new drugs. The bleomycin model is the standard model for pulmonary fibrosis, but it is often used incorrectly, as shown by this meta-analysis. http://bit.ly/39qboxP

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ABSTRACT Idiopathic pulmonary fibrosis (IPF) is a complex disease of unknown aetiology, which makes drug development challenging. Single administration of bleomycin directly to the lungs of mice is a widely used experimental model for studying pulmonary fibrogenesis and evaluating the effect of therapeutic antifibrotic strategies. The model works by inducing an early inflammatory phase, which transitions into fibrosis after 5–7 days. This initial inflammation makes therapeutic timing crucial. To accurately assess antifibrotic efficacy, the intervention should inhibit fibrosis without impacting early inflammation.

Studies published between 2008 and 2019 using the bleomycin model to investigate pulmonary fibrosis were retrieved from PubMed, and study characteristics were analysed. Intervention-based studies were classified as either preventative (starting <7 days after bleomycin installation) or therapeutic (>7 days). In addition, studies were cross-referenced with current major clinical trials to assess the availability of preclinical rationale.

A total of 976 publications were evaluated. 726 investigated potential therapies, of which 443 (61.0%) were solely preventative, 166 (22.9%) were solely therapeutic and 105 (14.5%) were both. Of the 443 preventative studies, only 70 (15.8%) characterised inflammation during the model's early inflammatory phase. In the reported 145 IPF clinical trials investigating 93 compounds/combinations, only 25 (26.9%) interventions had any preclinical data on bleomycin available on PubMed.

Since 2008, we observed a shift (from <5% to 37.4%) in the number of studies evaluating drugs in the therapeutic setting in the bleomycin model. While this shift is encouraging, further characterisation of early inflammation and appropriate preclinical therapeutic testing are still needed. This will facilitate fruitful drug development in IPF, and more therapeutic strategies for patients with this devastating disease.