Idiopathic pulmonary fibrosis: do scientists focus on publishing rather than on clinical relevance?

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Advocating the use of therapeutic treatment strategies in preclinical IPF research remains challenging
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Idiopathic pulmonary fibrosis (IPF) is a progressive chronic interstitial lung disorder characterised by excessive accumulation of extracellular matrix in the interstitial and alveolar spaces, resulting in scar formation and destruction of the normal pulmonary epithelium with consequent respiratory failure and eventual death [1]. Around 3 million people are affected by IPF, and the prognosis of these patients is devastating, with a median survival after diagnosis of approximately 3 years [2–4]. Despite the US Food and Drug Administartion approval of pirfenidone [5] and nintedanib [6] for the treatment of IPF in 2014, pharmacological treatment options for IPF remain limited. Although both drugs reduce the decline of lung function in IPF patients, they have serious side-effects, show no benefit on quality of life and do not stop nor reverse the disease [7–11]. Additional therapies to improve the prognosis and quality of life of IPF patients are thus urgently awaited [12].

Animal models are pivotal for the understanding disease pathogenesis and for identifying novel therapeutic targets [13]. Importantly however, numerous compounds show efficacy in animal models but only a minority of these compounds have replicated such beneficial effects in clinical trials. Among multiple explanations, the inappropriateness of the chosen animal model is a key factor in the poor translation of basic animal work into clinical efficacy. In the setting of pulmonary fibrosis, the intratracheal instillation of bleomycin is considered the best-characterised animal model available for preclinical testing [14]. Intratracheal delivery of bleomycin into the lung results in direct cell injury through the induction of DNA strand breaks, the generation of free radicals, and the induction of oxidative stress. This results in pulmonary inflammation in the first few days after bleomycin instillation with subsequent interstitial fibrosis starting at around day 7 and peaking between day 14 and 21 after bleomycin instillation [15, 16]. Consequently, it has been strongly advocated that the timing of intervention with potential antifibrotic compounds is essential to maximise translatability to the clinic. Indeed, pharmacological treatment should start after day 7 in the so-called therapeutic phase [17].

A systematic review on drug efficacy studies in the bleomycin model in 2008 showed that more than 95% of studies executed between 1980 and 2006 used a preventive treatment strategy (*i.e.* treatment started within the first 7 days), whereas in less than 5% treatment was started during the therapeutic phase [17].

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In this issue of the *European Respiratory Journal*, Kolb *et al.* [18] present a new systematic review to examine whether the use of the bleomycin model to study antifibrotic effects of compounds has changed since their 2008 publication. They screened 976 studies using the bleomycin model published between 2008 and 2019, of which 75% investigated the potential of an intervention on pulmonary fibrosis. Again, the large majority of studies started the intervention in the preventive phase but already 37% of the studies evaluated the intervention during the therapeutic phase. As indicated by the authors, although the shift in preventative studies from 5 to 37% over the past decade is encouraging, it is not yet sufficient.

We can only speculate about the reasons that scientists stick to preventive treatment strategies instead of clinically more relevant therapeutic strategies. Despite the 2017 guidelines drawn up by the American Thoracic Society [14], ignorance may still play a role, which makes the review of Kolb *et al.* [18] timely and relevant. In addition, the pressure to publish may be an important reason to start treatment before or immediately after bleomycin administration. Early long-term interventions increase the likelihood to obtain significant differences which expedites subsequent publication. We envision, however, that the nature of the intervention correlates with the impact factor of publication and that therapeutic strategies outscore preventative strategies. Unfortunately, Kolb *et al.* [18] did not address this issue and it remains to be seen whether delaying interventions pays off in this perspective. Obviously, increased impact factors do not solely rely on the type of intervention [19] and additional factors like novelty, the inclusion of patient data and confirmation in alternative models are also key decision points for editors and reviewers. A firm statement by high impact factor journals that studies using the bleomycin model and claiming clinical relevance will only be considered for publication when treatment is started during the therapeutic phase may, however, be very helpful in shifting focus from preventative to therapeutic treatment strategies. In addition, high-quality hypothesis-driven studies analysing novel compounds in a therapeutic strategy should not be rejected solely based on the lack of efficacy and could even be prioritised above studies with significant differences in preventative studies.

Candidate novel compounds are routinely evaluated in preclinical animal models before clinical trials are initiated. It is therefore rather surprising that Kolb *et al.* [18] show that the large majority of clinical trials for IPF (73.1%) lack supporting evidence from the bleomycin model. At a first glance this suggests that clinical trial designers have limited faith in the predictive value of the bleomycin model and select their targets based upon other considerations. Importantly, however, most of the interventions in clinical trials for IPF target proteins or pathways that have been assessed in the bleomycin model though not by using the same drug as used in the clinical trial. For instance, endothelin receptors have been extensively explored in the bleomycin model and specific antagonists, like sitaxentan [20] and bosentan [21], limit bleomycin-induced pulmonary fibrosis. Based on these results, the endothelin receptor antagonists bosentan, ambrisentan and macitentan have been pursued in clinical trials [22, 23]. Although the latter have indeed not been analysed in the bleomycin model, their target is evidently identified based on preclinical results in the bleomycin model. It thus seems that most novel compounds have not been analysed in the bleomycin model but the majority of targets has been studied in this preclinical model before moving forward to clinical trials. Overall, preclinical data from the bleomycin model seem pivotal in target selection and the optimisation and proper use of the bleomycin model is thus imperative in drug development for the treatment IPF.

To facilitate drug development for IPF and to improve translation from preclinical animal experiments to clinical practice, shifting from preventative to therapeutic treatment strategies is important but may not be sufficient. Reducing bias by randomisation, allocation concealment, and blinding outcome assessment reduces effect size [24] and avoiding these biases will help to translate experimental work for human benefit [25]. Including and reporting multiple end-points, appropriate statistical analysis and supporting *in vitro* and/or patient data are obviously also imperative [26], but most may be gained by the development of alternative, more robust models that better reflect human IPF [17]; in particular, models that recapitulate slow disease onset and progressive disease without spontaneous resolution, as observed in the bleomycin model, would be much appreciated. As long as such models are, however, not available, optimising the bleomycin model is the best we can do at this particular moment. As fibrosis starts at day 7 after bleomycin instillation, it should be considered to even further delay treatment till the time of established fibrosis. It would be worth investigating whether starting therapeutic treatments at around day 10 after bleomycin instillation could further benefit translation of novel drugs to clinical practice.

Emphasising that the potential clinical efficacy of novel drugs for IPF should be explored using a therapeutic treatment strategy does not imply that knockout animals or early preventative interventions should not be further pursued. Although such studies lack direct clinical relevance, they may provide important insight into the biology underlying acute lung injury, wound healing and defective regeneration. In particular, knockout animals are relevant in defining the function of genes for which no pharmacological option is available [27, 28]. To fully appreciate the importance of the gene/intervention, it

is, however, imperative to thoroughly characterise the animals during disease progression, and only analysing fibrosis at (for instance) the 2 week time point does not suffice. Only in the case that initial bleomycin-induced injury and subsequent inflammation are also assessed, one could appreciate the function of the targeted gene. Identified genes/interventions that diminish fibrosis without affecting initial injury and inflammation should be further pursued using a therapeutic treatment strategy (for interventions) or in alternative models (for knockout animals) before eventual translation to clinical trials.

In conclusion, timing of intervention in the bleomycin-induced pulmonary fibrosis model is a key determinant when aiming for translation of preclinical studies into clinical practice. Kolb *et al.* [18] are to be commended for their comprehensive review of the literature and their continuous strive to improve the quality of preclinical research in IPF. Advocating the use of therapeutic treatment strategies in preclinical IPF research will likely facilitate drug development, providing clinicians with better tools to treat patients with this devastating disease. We look forward to the next systematic review in about 10 years and hope the scientific community has embraced the message and that all studies focusing on the identification of novel treatment modalities for IPF use a therapeutic treatment strategy. Let us all remember that although publishing is key for scientists, clinical relevance should always prevail in preclinical scientific research.

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