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LETTER TO THE EDITOR

In Reply

We wish to thank Rubio et al. for their insightful comments [1]. The overarching question is whether the animal models used in the studies included in the systematic review [2] adequately model human disease. We agree with Rubio et al. that the first issue is that the bleomycin rodent model, especially when therapy is administered shortly thereafter, more closely mimics the inflammation seen in acute exacerbations of pulmonary fibrosis rather than the fibrosis seen in chronic disease. In fact, acute exacerbations may be the appropriate indication for mesenchymal stem cell (MSC) therapy in pulmonary fibrosis, given their potent anti-inflammatory mechanism of action.

The second issue raised by Rubio et al. is the discrepancy between the young age of the mice and the usually advanced age of humans with idiopathic pulmonary fibrosis. Indeed, 11 studies in the review used young, 6- to 12-week-old mice, whereas the age of the mice was unclear in 2 studies. The remaining 4 studies used young rats (based on body weights, 200–280 g). However, it is not a foregone conclusion that young rodent models cannot adequately model advanced-age human disease. If young rodent models differ from aged rodent models solely by the severity of disease induced by bleomycin, young rodent models can still be used with an appropriately higher bleomycin dose than would be required in aged rodent models. However, it is a greater challenge if different pathophysiological mechanisms are involved in old compared with young rodents.

One study found that bleomycin injury induced more collagen deposition in aged mice [3]. Another study found that bleomycin induced more severe disease in aged mice, with a greater increase in mortality, lung collagen, broncholaveolar lavage neutrophil count, interleukin-17, and CXCL1 in aged male mice than in younger mice [4]. However, these parameters were also increased to a lesser extent by bleomycin in young male mice compared with mice exposed to saline. In other words, fibrosis in young mice appeared more severe, but could be the result of the same, but attenuated, pathophysiological processes.

In contrast to the studies cited above, another study found that the initial fibrosis (net increase in total lung hydroxyproline 3 weeks after injury) was similar in young and old mice, but failed to resolve in aged mice [5]. In this study, there was persistence of a senescent and apoptosis-resistant fibroblast phenotype in aged mice, whereas this resolved with time in young mice, which suggests that a different mechanism may be involved. Thus, this one study could support the hypothesis that aged rodent models are better suited to model human disease, given the potentially different pathophysiology.

A related issue is whether young rodent models adequately model the response to MSC treatment in older humans. Some laboratory evidence invites speculation. For instance, exposure of young mice to plasma from old mice was shown to negatively regulate neurogenesis [6]. Conversely, somatic telomerase reactivation reversed neurodegeneration with restoration of proliferating Sox^{2+} neural progenitors in another study [7]. In other words, a therapeutic effect was seen, even in old mice, with rejuvenated progenitor cells. Furthermore, connecting the circulatory systems of young and old mice, resulting in exposure of old mice to factors present in young serum, was able to restore the proliferation and regenerative capacity of skeletal muscle stem cell in old mice, as well as hepatocyte proliferation [8]. Thus, although one study suggests that factors from old mice might impair cell proliferation, other studies indicate that old mice may still respond to progenitor cell therapy; evidence from clinical trials will be required to determine whether young rodent models adequately model the response to MSC treatment in older humans

In conclusion, Rubio et al. identified a potential additional limitation to the applicability of our findings to human disease; they may well be right that aged rodents better model some chronic human disease. However, it would be interesting to have further studies confirm and identify the existence of different pathophysiological mechanisms in aged rodents compared with young rodents, rather than merely show differing severity of disease, because the latter possibility does not threaten the external validity of young rodent models. Younger rodent models could also overestimate the response to MSC treatment in aged rodents and potentially in humans, but this will need to be determined in clinical trials.

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Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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