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LETTERS TO THE EDITOR

What Should Be Chronic: The Animal, the Model, or Both?

The systematic review of mesenchymal stromal cell (MSC) therapy in pulmonary fibrosis by Srour and Thébaud [1] was of great interest to our group. It presents a comprehensive review of the current preclinical literature involving murine models of bleomycin-induced pulmonary fibrosis, as well as current human clinical trials using MSCs in idiopathic pulmonary fibrosis (IPF).

The authors raise several important points regarding the current limitations of animal studies and their clinical applicability to IPF. The first issue focuses on modeling a chronic pulmonary fibrotic state in mouse models that more closely resembles chronic IPF. The authors correctly point out that most animal studies administered MSCs within the first 1 to 3 days. The reported efficacy may be limited to preventing the acute inflammatory response to bleomycin rather than reversing the fibrotic phase. They suggest this may be a more appropriate model for acute exacerbations of IPF rather than the chronic progressive IPF state. This observation is supported by the study by Peng et al. that reported an initial inflammatory phase during the first week after bleomycin instillation in mice, followed by active fibrosis between 7 and 14 days after injury [2]. That study further showed that bleomycin-induced fibrosis resulted in molecular changes involving upregulation of profibrotic factors during the fibrotic phase, but not during the acute inflammatory phase, that correlated with those seen in patients with IPF. Therefore, we agree with Srour and Thebaud that to increase clinical relevance, preclinical studies need to further examine the therapeutic potential of MSCs to "rescue" the pulmonary fibrotic process once fibrosis has occurred [1].

However, another important limitation of the studies examined in the Srour and Thebaud review is the use of young mice to model chronic IPF, which is a disease of advanced age [3, 4]. Thus, we strongly believe that aged mice are a more clinically applicable model for chronic pulmonary fibrosis. Studies have demonstrated that old mice develop more severe pulmonary fibrosis than young mice as a result of bleomycin administration [3, 5]. More importantly, young mice have been shown to undergo spontaneous resolution of bleomycin-induced pulmonary fibrosis, which has not been observed in old mice [6, 7]. Therefore, while young mice may serve as an adequate model for acute exacerbations, as suggested by the authors, their applicability in a chronic model of pulmonary fibrosis may be limited because of age-related effects, even if MSCs are administered at later time points. Furthermore, we recently published results showing that adipose-derived MSCs from young mice, but not old mice, prevent bleomycin-induced pulmonary fibrosis in an aged mouse model [8]. This further illustrates that age-related effects play an important role in the ability of MSCs to decrease lung fibrosis, an important consideration with use of autologous or other adult sources of MSCs in human clinical trials.

GUSTAVO A. RUBIO
Department of Surgery, University of Miami Leonard M. Miller School of Medicine, Miami, Florida, USA

SHARON J. ELLIOT
Department of Surgery, University of Miami Leonard M. Miller School of Medicine, Miami, Florida, USA

MARILYN K. GLASSBERG
Department of Surgery; Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, Department of Medicine; and Division of Pediatric Pulmonology, Department of Pediatrics, University of Miami Leonard M. Miller School of Medicine, Miami, Florida, USA

Disclosure of Potential Conflicts of Interest

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