

## Cell Therapy for Pulmonary Hypertension: What Is the True Potential of Endothelial Progenitor Cells?

To the Editor:

We read with great interest the recent report by Nagaya et al<sup>1</sup> describing a “novel” therapeutic approach for experimental pulmonary hypertension using hybrid cell and gene therapy. We are happy to see that these data provide independent confirmation of the efficacy of cell-based gene therapy for pulmonary vascular disease that we have previously described in a series of earlier reports.<sup>2–4</sup>

The novel feature of the Nagaya et al<sup>1</sup> report is the use of a “regenerative” cell that potentially could contribute to vascular repair, ie, endothelial progenitor cells (EPCs); however, their data suggest that the majority of the benefit was still derived from the “gene” rather than the “cell therapy.” In our published reports, somatic cells (ie, pulmonary smooth muscle cells) were used to target gene therapy to the distal lung vasculature, and thus the improvement in pulmonary hemodynamics and remodeling could be attributed entirely to gene therapy. In these experiments, mock-transfected cells conferred no benefit, and the efficacy of cell-based gene transfer was attributed to subselective targeting of the therapeutic transgene to the distal arteriolar bed by virtue of the ability of the lung microcirculation to filter and trap these genetically engineered cells.<sup>3</sup> Nagaya et al<sup>1</sup> used the potent vasodilator gene, adrenomedullin, whereas we have described a similar benefit with another vasodilator gene,<sup>2</sup> as well as with angiogenic genes (vascular endothelial growth factor and angiopoietin-1).<sup>3–4</sup>

Indeed, our studies have raised the possibility that the improvement in pulmonary hemodynamics may have been due to the ability of “angiogenic” genes to induce regeneration of damaged distal pulmonary vasculature.<sup>3,4</sup> With this in mind, the relatively small benefit described in the recent *Circulation* report in response to EPC therapy alone (16% decrease in pulmonary vascular resistance) is of interest and is perhaps consistent with the ability of these cells to repair and regenerate vascular endothelium in ischemic models. However, the modest nature of the effect of EPCs alone (compared with adrenomedullin-transfected cells) in the Nagaya et al<sup>1</sup> study might not reflect the true therapeutic potential of this approach, as these cells were isolated from human cord blood and used in a rat model. It is possible that as a result of important interspecies differences, these xenogenic cells may not be as well suited for pulmonary vascular repair as “autologous” progenitor cells. Indeed, very recent results from our group show near-complete prevention of pulmonary hypertension in the rat monocrotaline model using syngeneic bone marrow-derived EPCs,<sup>5</sup> suggesting substantial benefit of progenitor cell therapy alone.

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### Response

We thank Drs Stewart, Zhao, and Courtman for their letter to the editor. In our study,<sup>1</sup> human umbilical cord blood-derived endothelial progenitor cells (EPCs) were transplanted to immunodeficient nude rats. Transplantation of EPCs alone modestly attenuated monocrotaline-induced pulmonary hypertension (16% decrease in pulmonary vascular resistance). On the other hand, recent results from Stewart's group have shown near-complete prevention of monocrotaline-induced pulmonary hypertension using syngeneic EPCs.<sup>2</sup> Thus, autologous EPCs may be more suitable for pulmonary vascular repair than xenogenic cells, as they stated. In addition, we agree with them regarding the inhibitory effects of angiogenic factors on monocrotaline-induced pulmonary hypertension in rats. In humans, however, little information is available regarding the effects of angiogenic factors on pulmonary hemodynamics. Some investigators have reported that angiogenic factors including vascular endothelial growth factor and angiopoietin-1 contribute to the development of pulmonary vascular remodeling.<sup>3</sup> Thus, it remains unknown whether angiogenic factors have beneficial effects on pulmonary arterial hypertension in humans.

Nevertheless, intravenously administered EPCs home to sites of injured endothelium without wedging into the distal pulmonary vasculature.<sup>1</sup> These findings raise the possibility that transplanted EPCs may serve not only as a tissue-engineering tool to reconstruct the pulmonary vasculature, but also as a vehicle for gene delivery to injured pulmonary endothelium. Adrenomedullin, a potent pulmonary vasodilator peptide, plays an important role in the regulation of pulmonary vascular tone.<sup>4</sup> Therefore, in the clinical setting, vasodilator gene-transduced EPCs would be a promising therapeutic strategy if transplantation of EPCs alone failed to ameliorate pulmonary hypertension in humans.

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