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EDITORIAL COMMENTARY

Gene-enhanced cell therapy for pulmonary arterial hypertension: Knocking at the clinical door?

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See related article on pages 621-32.

Pulmonary arterial hypertension (PAH) is a progressive disease, characterized by increased resistance in the pulmonary circulation as a result of obstructive remodeling of the pulmonary arterioles. Hyperkinetic PAH represents an old

yet fundamental problem in congenital heart disease, contributing significantly to morbidity and mortality even before the complete development of Eisenmenger syndrome.

The classic surgical concept for palliation of hyperkinetic PAH, namely pulmonary artery banding, was already described by Muller and Danimann¹ in 1951. More recent pharmacologic concepts in both adult and pediatric patients include such treatments as nitric oxide inhalation and the application of prostacyclin analogs or endothelin antagonists. Although there has been success in improving symptoms and the quality of life for patients with PAH, the long-term outcome of these concepts remains to be proved, especially with respect to survival and

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relevant hemodynamic improvement. A genuine problem of these therapies seems to be the fact that they rely on the so-called vasodilator hypothesis but do not address the occlusive pulmonary artery remodeling.² Furthermore, in the case of inhaled nitric oxide a possible clinical rebound after withdrawal has been recognized as a relevant problem.³

On the basis of this background, new therapeutic concepts following the principles of regenerative medicine and gene therapy have been developed and explore the ability of gene-enhanced endothelial precursor cells to repair the pulmonary vasculature in the setting of PAH.

In their article published in this issue of the *Journal*, Cao and colleagues⁴ present solid in vivo data underlining the possible therapeutic efficacy of hypoxia-inducible factor 1 α -transfected endothelial progenitor cells in hyperkinetic PAH. In an elaborate animal model of hyperkinetic PAH, they describe the capability of hypoxia-inducible factor 1 α -transfected endothelial progenitor cells to attenuate shunt flow-induced PAH by an angiogenic effect and reverse pulmonary vascular remodeling.

After this proof-of-principle level, which is certainly indispensable, further challenging steps need to be undertaken before cell-based gene therapy strategies for PAH can enter the clinical practice. First, the underlying mechanisms of attenuated PAH need to be further analyzed in depth, with precise description of the downstream genes ultimately promoting vascular remodeling and neovascularization. Second, subsequent animal models should focus on extended hemodynamic assessment, including calculation of pulmonary arterial resistance in addition to isolated right-sided pressure measurement, as well as on functional testing (for example the treadmill test) to determine whether the right ventricular improvement is “clinically significant.” Third, the experiences gained from stem cell therapy in ischemic heart disease, in which solid preclinical animal models have led to phase I studies followed by multicenter phase III trials that have been completed or are currently

recruiting patients,⁵ should be transferred to cell-based therapy protocols for PAH. The evidence from promising preclinical work should lead to the design of clinical trials of equivalent quality. In this context, it is very encouraging that a phase I clinical trial investigating autologous endothelial progenitor cell-based endothelial nitric oxide synthase gene therapy is currently recruiting patients (Pulmonary Hypertension and eNOS Cell Therapy Trial; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00469027) identifier NCT00469027). The results from this kind of phase I clinical testing are mandatory to determine whether the promising results from animal models are truly capable of mimicking human disease. If so, they will subsequently advance further translation to phase II and III levels for the whole field of cell-based gene therapy. Finally, because the function of the right ventricle is a critical determinant of survival in patients with PAH and a molecular signature of right heart failure has already been described,⁶ specific therapies targeting the right ventricle should be evaluated in parallel with those primarily addressing the pulmonary vasculature.

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