Author has nothing to disclose with regard to commercial support.

STEP BY STEP TOWARD THE SUMMIT

Reply to the Editor:

I read with great interest the original article by Oishi and colleagues¹ and the corresponding letter to the Editor composed by Katz and colleagues. Oishi and colleagues' work is one of the most recent publications from the Toronto lung transplant laboratories and has to be interpreted as such. Having established a protocol, which can be used to safely perfuse human donor lungs ex vivo, the research group has consequently taken the next step and applies this platform to treat and improve organs. Several approaches have been described, including stem cell therapy,² therapeutic gases,³ administration of surfactant,⁴ addition of α 1-antitrypsin to the perfusate,⁵ and antibiotic treatment of pneumonic donor lungs.⁶

One promising approach of improving allograft function is to manipulate interleukin (IL)-10 expression in the organ. It has previously been shown that IL-10 ameliorates primary graft function and reduces the risk for rejection. Based on these findings, adenoviral transfection of IL-10 during ex vivo lung perfusion has been successfully established by Machuca and colleagues⁷ in a pig survival lung transplant model. Post-transplant lung function was significantly better in IL-10 transfected donor lungs compared with controls. The current publication by Oishi and colleagues builds on these results and tests the impact of IL-10 modulation in a mouse model of chronic allograft dysfunction. Based on Machuca and colleagues' work,⁷ it is not surprising that less fibrotic changes equivalent to chronic allograft dysfunction are seen in the long term.

Katz and colleagues rightfully argue that IL-10 is only one of a myriad of cytokines involved in allograft rejection. Thus, exclusively targeting IL-10 would be an

oversimplification. We would like to challenge this view. In fact, IL-10 is a master regulator of the immune system and is considered the main anti-inflammatory molecule. It exhibits pleiotropic effects by modulating the function of antigen-presenting cells, macrophages, B cells, natural killer cells, and T-helper 1 and 2 cells. The lentiviral vector described in Oishi and colleagues' publication offers the unique possibility of a spatial control of IL-10. A strong and stable expression of IL-10 restricted to the donor lungs minimizes potential systemic side effects. To date, viral vector-based IL-10 transfection of allografts has been tested only in proof-of-concept animal studies. Whether a lentivirus construct or other vectors, such as adeno-associated viruses or baculoviruses, are most suitable in humans remains to be determined. New, more specific gene delivery systems such as CRISPR/Cas9 could address the safety concerns raised by Katz and colleagues.

The publication by Oishi and colleagues is an important contribution and adds another part to a complex puzzle. We are getting closer to modify human donor lungs toward "better" allografts. The key prerequisite of these advances was the development of a clinically applicable ex vivo lung perfusion platform in Toronto more than 10 years ago. We are not quite on the summit, but we are getting closer.

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