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LENTIVIRAL INTERLEUKIN-10 GENE THERAPY: SAFETY AND QUESTIONS

Reply to the Editor:

Gene therapy and gene editing (functional modification of genes) represent a future direction for treatment of human diseases. Viral vector-based gene delivery or gene transfer is crucial for this purpose. Thoracic and cardiovascular surgery provides great opportunities for translating experimental discoveries toward clinical applications. Awareness of the challenges and limitations of gene delivery is essential for clinician investigators in this field.

We are very glad that our recent article¹ has drawn interest and stimulated discussion on this subject. Katz and colleagues raise several questions related to our work for further dialogue. Clarification of these concerns may improve understanding of the scientific work related to gene therapy and help us to further develop our research focused on prevention and treatment of chronic lung allograft dysfunction, a major complication after lung transplantation.

In our report, we chose to use recombinant lentivirus (LV) as a delivery vehicle specifically for its ability to infect a variety of cells and generate persistent transgene expression in vivo. Katz and colleagues raise concerns about the safety of using LV. The first approved clinical trial using recombinant LV was in 2002. According to Gene Therapy Clinical Trials Worldwide (<http://www.abedia.com/wiley/>), there are at least 196 independent LV-based clinical trials that have opened worldwide. Fortunately, the “deleterious serious side effects of an induced host response” that concern Katz and colleagues have not been seen in clinical trials. Furthermore, although recombinant LV vectors were derived from human immunodeficiency virus (HIV), patients with HIV display negligible increases in blood cancers that are not due to immune dysfunction. In contrast to wild-type HIV, recombinant

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LVs integrate once and do not replicate in treated cells because these recombinant virions do not establish a productive infection themselves nor do they produce HIV proteins from their integrated proviral state. Lastly, whereas LV integration is relatively random, the effective multiplicity of infection we are achieving in productively infected cells is likely not high enough to cause a large number of integrative effects that could disrupt many pathways simultaneously. The safety of viral-based gene delivery is important. More evidence from experimental research and clinical trials should be collected and closely monitored.

Katz and colleagues further challenge the use of interleukin (IL) 10 as the choice of therapeutic gene. We agree that IL-10 has well known and important immunomodulatory effects on monocytes, macrophages, and dendritic cells, and it can inhibit T cell activation.²⁻⁴ Conversely, IL-10 can drive B cell immunoglobulin class switching and thus promote humoral immune responses.⁵ It is these immunomodulatory functions and anti-inflammatory properties that make us interested in IL-10 as a candidate to prevent the development of chronic lung allograft dysfunction, a process with complicated immunologic and inflammatory mechanisms. Whether long-lasting IL-10 gene expression in the lung allograft is beneficial was the subject of our study. Nevertheless, further mechanistic and safety studies are warranted before clinical use.

Our observation that LV-driven human IL-10 increased mouse IL-10 expression in the grafts certainly supports the concept that regulation of the alloimmune response may result from such a therapy. Whether the attenuated chronic rejection we observed is attributable primarily to the exogenously administered human IL-10 or to the endogenously upregulated mouse IL-10 is unclear from our study and merits further investigation. At the same time, we concede that tonic IL-10 expression may impair protective immunity, and we were unable to test this possibility in our specific pathogen-free mice. Effects of IL-10 gene therapy on secondary infection susceptibility in a lung transplant setting are indeed important and interesting and merit further study. Treatment of the allograft with IL-10 ex vivo before transplantation without a subsequent in vivo component is also an attractive approach that we are currently examining.

Overall, the safety of viral vectors should be considered both in experimental studies and through clinical trials.

Many unanswered questions can be addressed using the mouse lung transplant model, with the results serving to inform the design of future clinical studies to establish whether LV-based IL-10 gene transfer might prevent the development of chronic lung allograft dysfunction in our patients.

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