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REPLY FROM THE AUTHORS: FUTURE CONSIDERATIONS FOR ADENO-ASSOCIATED VIRAL GENE THERAPY

IN EX VIVO LUNG PERFUSION

Reply to the Editor:

We thank Katz and colleagues for their comments on our recent work and for recognizing the clinical translational potential of our study. In brief, we demonstrated successful adeno-associated virus (AAV) transgene expression in a rat lung transplant model using an ex vivo lung perfusion (EVLP) circuit with minimal off-target effects.2

In response to the discourse on the dose–response relationship of AAV9-mediated transduction, we agree this information will be important for clinical application. Preliminary investigations in our laboratory, notably by Kesseli and colleagues,3 have indeed explored this aspect outside of the EVLP realm. In that study, using a static cold storage rat lung transplant model, we administered varying doses of AAV9 Luciferase (8e8 or 4e9 viral genome/μL) and observed enhanced luminescence with the greater dose, indicating a dose-dependent effect. However, the maximum effect dose, along with possible toxicities with greater doses, remains to be determined. Although our current study did not explore this relationship, we concur that further examination is needed to detail the dose–response and dose–toxicity relationships, particularly in the circuit group in which there was low transgene expression compared with both airway and vascular delivery.

In response to whether AAVs attach to the circuit, it is possible that viral particles attached to the ELVP tubing or oxygenator. It is important to note that the small animal EVLP has a notably slower flow rate when compared with human clinical EVLP. In this study, our circuit had a flow rate of 5 mL/min with a perfusate total volume of 150 mL; thus, the perfusate only completes 2 passes through the lungs per hour. The greater flow rate seen in clinical EVLP may alter contact times of the virus to the lung endothelium or perfusion circuit and therefore alter the opportunity for viral transfection.2,4 Work in large animal models, where clinical or preclinical EVLP devices can be used, are

FIGURE 1. The multiple approaches to gene therapy in lung transplantation.
ongoing and will allow further exploration of this potential issue.

The comments regarding the method of delivery, specifically airway versus pulmonary artery delivery and the impact of particle size on transgene expression, are thoughtful and accurate. Our study’s findings indicate that airway delivery may be more effective per dose equivalent in our murine model and the translation to clinical application requires further differentiation of delivery methods, including possibly nebulizing or aerosolizing vector delivery (Figure 1). The added benefit of airway administration appears to be a reduction in off-target effects in other organs after transplantation.

As Katz and colleagues highlight, before clinical translation, additional work is necessary to study the potential toxicities of AAV transfection in a lung transplant model such as this. The future work should include the absence and presence of standard immunosuppression, which may impact an inflammatory response to viral transfection and may even enhance transgene expression. Variations of these experiments in an allotransplant model will also allow for assessment of successful attenuation of the recipient alloresponse with targeted gene therapies.

In summary, we greatly appreciate the interest expressed in our work by the group from Mt Sinai. Katz and colleagues highlight important areas of future research to successfully translate the early preclinical work into impactful clinical therapies. This is a proven method treatment, and we believe AAV-based gene therapy represents a potential highly-selective avenue for enhancing all donor organs for transplantation in the future.

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Conflict of Interest Statement
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References

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