To the Editor:

We read the article by Gao and colleagues\(^1\) with great interest and extend our congratulations for conducting this elegant study. It nicely highlights that the adeno-associated virus serotype 9-mediated gene delivery to the lung graft can be achieved during a short course of ex vivo lung perfusion. Furthermore, we commend the clinical translational lung transplantation program, under the leadership of Dr Hartwig. We align with their overall enthusiasm on this matter.\(^3\) We would like to contribute to the discourse by introducing several points for discussion.

Recent clinical successes in gene therapy, employing AAV viral vectors, have been evident across various diseases such as Leber amaurosis, adrenoleukodystrophy; B-cell lymphoma; epidermolysis bullosa; spinal muscular atrophy; and, in cardiology, addressing lipoprotein lipase deficiency and heart failure. These successes underscore the growing popularity of AAV vectors, attributed to their nonpathogenic nature, low immunogenicity, absence of integration into the human host genome, and the capability to infect postmitotic cells. Nevertheless, studies have also shed light on critical challenges in clinical translation of AAV. Specifically, we are aware that the variability observed among different species in comparison to humans raises concerns about the translation of findings to clinical applications; that the potential for off-target transduction to organs poses a challenge, necessitating careful consideration in therapeutic applications; and that the neutralization of AAV due to preexisting humoral immunity presents a hurdle that warrants attention for further advancements.\(^3\)

We are of the opinion that the study provides valuable insights into adeno-associated virus serotype 9-mediated delivery at a single dose of \(4 \times 10^{11}\) vector genomes. It would be advantageous to incorporate a dose-response curve, exploring both lower and higher doses, to ascertain if there exists a threshold or saturation effect, especially for the circuit group. It is also possible that much of the AAVs attached to the circuit, lowering the transduction in this group.

We are confident that pretreatment with immunosuppressive drugs can effectively prevent lung tissue damage, and an inflammatory response, even in a syngeneic lung transplant model. An evaluation of cytokines levels, T and B cell responses will be also helpful of this approach.

A crucial element absent in the experiments is a negative control, including empty vector or a vehicle solution. These controls are imperative for assessing cell toxicity.

Although only 1 animal each for airway and pulmonary artery delivery groups were studied, transgene distribution resulting in vascular dominant expression. Particle size is known to influence transgene expression and distribution in intra-airway delivery. Instillation is an effective approach, but it may not be clinically relevant to transduce the whole lung.\(^4\)\(^5\) Thus, for translational purpose, airway delivery alone needs to be separated into different groups, including instillation with different volume/concentration of the vectors and aerosol delivery.

Gao and colleagues\(^3\) have documented the feasibility of gene delivery using an adeno-associated virus serotype 9 vector in rat lung transplant model. Future large animal studies are needed to confirm the efficacy of this protocol.

Conflict of Interest Statement

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