AAV delivery of PD-L1 with concomitant CTLA-4 immunoglobulin attenuates acute cellular rejection in a rat lung transplant model

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Introduction

- Acute cellular rejection (ACR) is a frequent and significant complication in lung transplant (LTx) recipients and the leading predictor of chronic lung allograft dysfunction (CLAD)[1]. Utilizing viral vectors to deliver genes that generate proteins with anti-inflammatory or immunosuppressive properties to donor lung allografts is an attractive strategy to prevent ACR.
- **Primary Goal:** To evaluate whether Programmed Death Ligand 1 (PD-L1) gene transduction via AAV9 vector can be used to abrogate acute rejection in a clinically relevant, allogeneic LTx model.

Methods

- Orthotopic left LTx was performed by implanting grafts procured from Brown Norway donors into Fischer F344 recipients using a “cuff” technique[3] (n=11).
- Upon graft procurement, AAV9 vectors were administered during static cold storage. Experimental animals received 4e11 VG AAV9 PD-L1 through the left bronchus (n=6). Negative controls received no viral vector. Both cohorts received a 500 ug dose of CTLA-4 immunoglobulin (Abatacept) on the first post operative day (POD1) and were sacrificed on POD14. Tissue was collected and stained with PD-L1 IHC or H&E to assess gene expression or ACR, respectively. ACR was graded by a blinded lung pathologist following ISHLT guidelines.

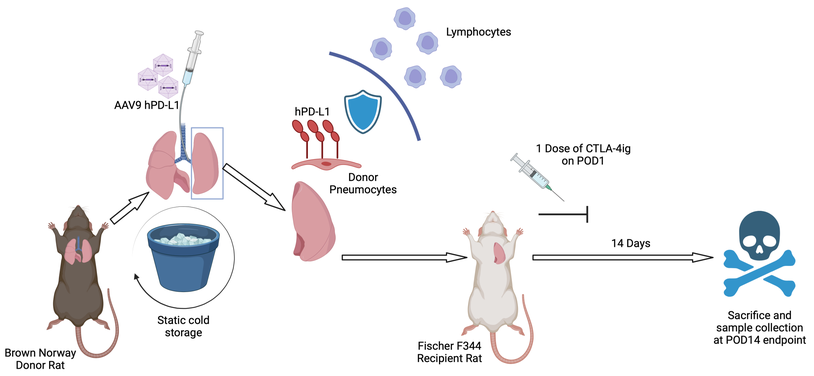
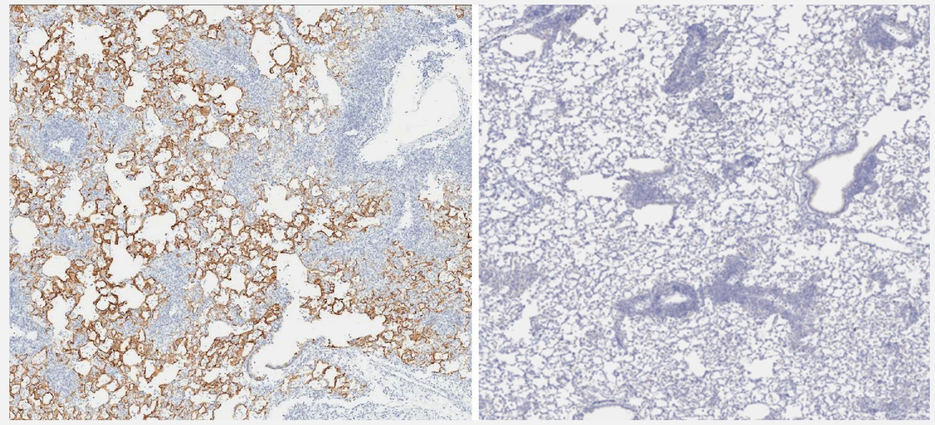


Figure 1 (Above): Transduction and transplantation workflow.

Figure 2 (Right) IHC stain for PD-L1 in transplanted left lung tissue collected on POD14. Left image is of tissue from an animal that received 500 ug abatacept and 4e11 VG AAV9 PD-L1. Right image is of tissue from an animal that received only 500ug abatacept.



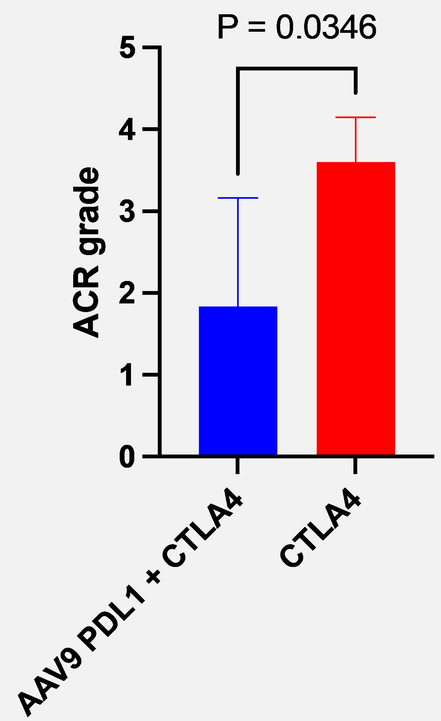


Figure 3 (Left): ACR grade of H&E stained tissue based on ISHLT rejection scoring guidelines. Vascular rejection graded from 0 (normal) – 4 (severe rejection)[2]. Pathologist grading was blinded to animal ID and condition.

Negative controls exhibited more severe ACR than experimental animals (p = 0.0346).

Conclusions

- We demonstrate successful transgene expression using a novel AAV9 PD-L1 vector during static cold storage in an allogeneic rat lung transplant model.
- Difference between groups indicates potential for using transgenic PD-L1 to protect against ACR after lung transplantation

Next Steps

- Further studies will elucidate the inflammatory effect of the viral vector itself by incorporating a control group that receives the same dose of viral vector carrying a reporter gene (luciferase).
- Intervention dose, AAV serotype and cell target, and concomitant immunosuppression regimen can likely be further optimized to better abrogate ACR after lung transplantation.

References

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