PUBLICATION REVIEW

A lung tropic AAV vector improves survival in a mouse model of surfactant B deficiency

Summary

Many acute respiratory distress syndromes arise from poor expression of surfactant protein B (SP-B), which stabilizes the air-liquid interface throughout the lung and allows efficient air to liquid diffusion in alveoli. Lung transplant is the current standard of care, but this is often not an option for infants born with SP-B deficiency. Gene therapy is a promising therapeutic pathway, but delivery of genes is challenging due to site specific insertion requirements and delivery efficiency.

In this work, researchers developed a novel delivery capsid for direct insertion of a gene (AAV6.2) directly into alveoli cells which promote the expression of SP-B. The capsid vector also contained genetic code for the expression of Firefly Luciferase which was used to monitor the expression of the gene insertion via bioluminescence imaging as a correlative measure of SP-B production. Using Revvity IVIS® SpectrumCT system for longitudinal high throughput 2D *in vivo* imaging, the researchers were able to non-invasively monitor AAV6.2 gene expression (Figure 1). Mice weights were measured to track overall health and the treated mice were shown to gain more weight than the untreated cohort indicating an overall improvement in health. Lung volume capacity was also measured at each timepoint for each mouse to assess the overall improvement of lung function. Quantitative 3D bioluminescence imaging (diffuse light imaging tomography, DLIT) was also used to confirm successful AAV6.2 gene insertion using their novel capsid delivery vector into the lungs (yellow arrow, Figure 2) and monitor clearance of the delivery vehicle from the intratracheal administration site (white arrow, Figure 2). The work highlights the importance of accurate imaging in longitudinal therapeutic evaluation and has yielded a high chance of success for the clinical translation of this vital treatment to infants born with SP-B deficiency.

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Publication highlights:

This study took advantage of the diverse capabilities of Revvity IVIS SpectrumCT system, including highly sensitive 2D bioluminescence imaging and 3D bioluminescence for accurate localization of gene expression. The large imaging field of view enabled high throughput longitudinal study for the expression of the inserted gene (AAV6.2), a surrogate of SP-B production. Additionally, the high precision and quantification made possible by the finely tuned tomographic 3D bioluminescence reconstruction allowed the researchers to accurately pinpoint expression of luciferase expression near the intratracheal injection site.

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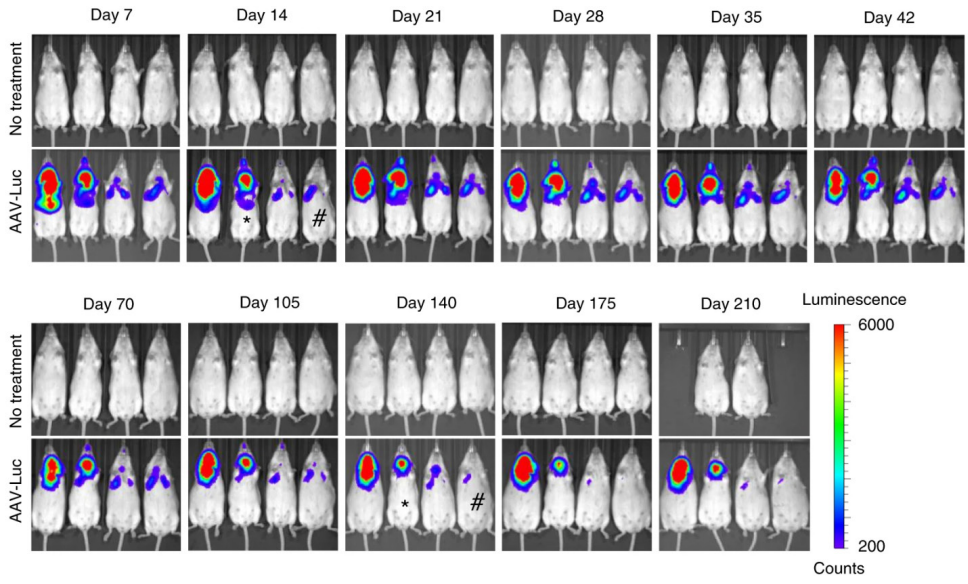

Figure 1: High throughput longitudinal assessment of gene therapy efficacy through monitoring Luciferase expression of the inserted gene as a surrogate marker for the promotion of SP-B. A marked increase in expression of the gene was noticed over time showing long term normalized lung function (measured by volume pressure measurements for each mouse) and homeostasis of SP-B production (via *in vivo* imaging and post-mortem validation) required for normal lung health.

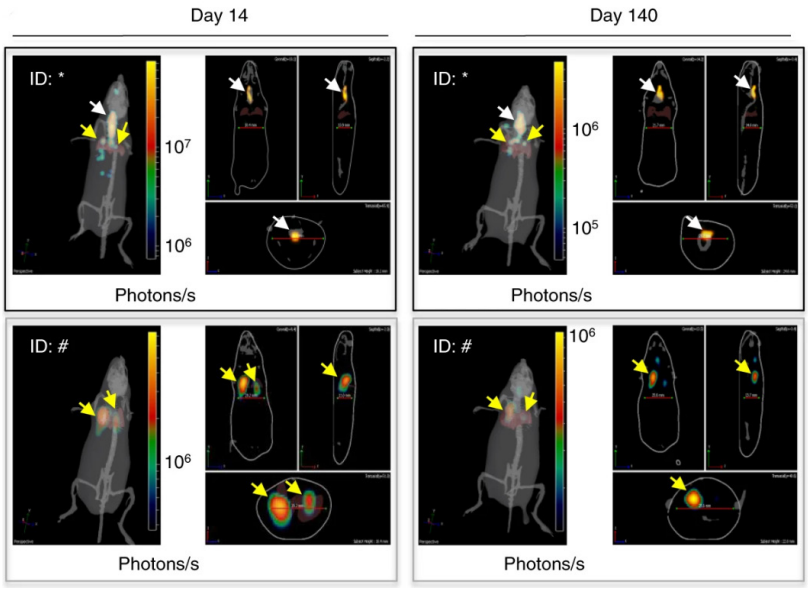

Figure 2: 3D tomographic imaging (DLIT) validating location of luciferase expression from lungs (yellow arrow) and site of injection (intratracheal, white arrow) over the course of the experiment.

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