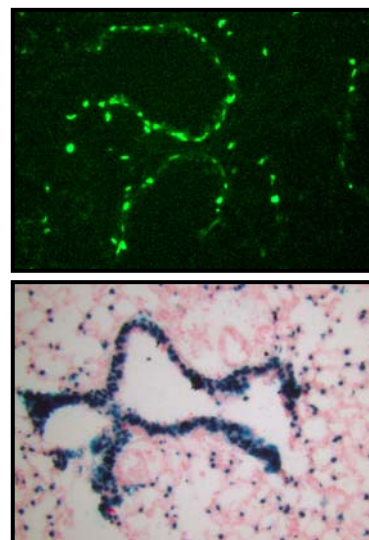


AAV Vectors for Lung-Directed Gene Therapy : Maria P. Limberis, Ph.D.

Delivery of therapeutic genes to the diseased airway epithelium *in vivo* is a promising option for the genetic treatment of diseases such as cystic fibrosis airway disease, α -1-antitrypsin (AAT) deficiency and chronic obstructive pulmonary disease. Of the many viral gene therapy vectors, adeno-associated virus (AAV) vectors hold great promise for efficiently targeting airway epithelium *in vivo*. AAV is a single stranded virus that belongs to the *Parvoviridae* family¹ and is characterized by its safety, low toxicity, and its ability to confer stable expression²⁻⁴. Furthermore, since AAV can transduce non-dividing cells⁵ its use in lung is warranted as less than 1% of airway epithelial cells are actively dividing⁶.

Since 2002, the AAV vector toolkit has been enriched with novel AAV vector serotypes isolated from various species including macaque, porcine, chimp and human. The reasoning for this enormous effort was to uncover novel AAV serotypes that were characterized by enhanced transduction efficiency in different tissues. Most important it became apparent that for AAV-mediated gene therapy to succeed in clinic an AAV vector serotype that does not activate cellular immune responses and is characterized by low immunoprevalence in the target human population was essential. Recently, more than 110 novel AAV vector isolates were identified in various tissues sources derived from human and non-human primates⁸. A subset of these vectors was initially evaluated and AAV9 was identified as a vector with improved transduction efficiency when administered to lung resulting in long-term transgene expression⁸ and subsequently was found to be able to be re-administered in the presence of serum-circulating high level of neutralizing antibody⁷.



(a) AAV-GFP & (b) AAV-LacZ-mediated gene transfer in mouse lung 21 days post gene delivery of 10^{11} genome copies

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Reviews of Note:

Flotte, T. R., Ng, P., Dylla, D. E., McCray, P.B. Jr, Wang, G., Kolls, J.K., Hu, J. (2007). “Viral vector-mediated and cell-based therapies for treatment of cystic fibrosis”. *Molecular Therapy* **15**(2):229-41.