# Gene Therapy for ALI/ARDS

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• Gene therapy • Acute lung injury • Viral vectors
• Nonviral vectors

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are life-threatening conditions of acute respiratory failure, which is induced by direct and indirect injury to the lung, such as by pneumonia, sepsis, or trauma. ALI/ARDS has a mortality rate of up to 40% in the United States, leading to 74,500 deaths and 3.6 million hospital days every year.[1] Although many potential therapeutic approaches have been developed to control ALI/ARDS, these treatments have so far proven unable to decrease the mortality of patients with ALI/ARDS. Although laboratories around the world have focused on the disease and uncovered a number of molecular mechanisms involved in its pathogenesis and resolution, translating this into productive treatments has lagged.

Gene therapy is a potentially powerful approach to treat any number of diseases, including ALI/ARDS, but most approaches have serious limitations and thus have hampered the use of this technology in clinical medicine. Gene delivery approaches are based on 2 types of delivery vehicles: those based on viral systems, so-called viral vectors, and those not based on viruses, or nonviral vectors, which are typically plasmid-based. Viral vector systems have been associated with inflammation, immunologic responses, and nonspecificity of cell targeting, despite very high delivery efficiency in the lung. For example, adenovirus appears to be the most widely used vector for pulmonary gene: therapy in the laboratory because of high-efficiency transduction in a variety of target cells and high expression of the delivered genes. However, the use of adenovirus can result in inflammatory responses, which cause cell damage and limit repeated administration. By contrast, much less inflammation and fewer immune responses are generated against nonviral DNA, but the major drawbacks to nonviral gene therapy in the lung are side effects of certain vectors and inefficiency

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of gene transfer, often leading to expression that is 10-fold to 1000-fold less than that seen with their viral counterparts.

Although transfer and expression of therapeutic genes to the lung using both viral and nonviral gene therapy technologies have been performed with some success, there is still a long way to go to move this methodology toward clinical use. In this article, we provide an overview of the current status of viral and nonviral gene therapy for ALI/ARDS, focus on issues of mechanism and applications as they influence in vivo gene delivery, and extend the utility of this strategy for future medical treatments.

## GENE DELIVERY TO THE LUNG

The lung is a complex organ and can be divided into the conducting large and small airways, including the trachea, bronchi, and bronchioles, and the parenchyma, which consists of gas-exchanging alveolar cells. Gene therapy is notably attractive for many acute and chronic pulmonary diseases. However, with the presence of barriers to lung gene transfer, such as pulmonary architecture, the innate immune system, and immune activation, it is somewhat more difficult and less effective to deliver genes into the parenchyma. As a consequence, many investigations have focused on improving gene transfer to the airway and alveolar epithelium to make it more efficient, less inflammatory, and to have extended duration of expression.[2] To date, a number of viral and nonviral vector systems have been used to deliver transgenes into the lung to treat diverse pulmonary diseases.[3]

### *Viral Vectors for Gene Delivery to the Lung*

Adenovirus, perhaps the most widely used of vectors for lung gene therapy, is a double-stranded DNA virus that is made to be replication-deficient for gene therapy by deletion of essential genes. The major advantages of adenovirus are the high-efficiency transduction seen in dividing and nondividing cells and the very high expression of delivered genes. However, inflammation, immunologic responses, and nonspecificity of cell targeting are just a few of the problems associated with adenovirus vectors. Furthermore, immune responses developed against the viral vector limit the success of repeated administration (thus it can be used only once or twice in an individual for effective gene delivery).[4] Adenovirus can directly deliver genes to the airway and alveolar epithelia and have been the vector of choice for animal models of many pulmonary diseases in the laboratory, but in clinical trials, the vector results in acute inflammation and innate immune responses, limiting effectiveness.[5,6] Further, the receptors for adenovirus reside primarily on the basolateral surface of epithelial cells in the lower airways, making high-level gene transfer dependent on transient barrier dysfunction, which is not desirable in many disease states.[7] Much effort has been directed at making vectors that show reduced host immune reactions to the viral gene products, so “gutless” or “helper-dependent” third-generation adenovirus vectors have been developed to extend expression and limit the initial inflammatory responses to administration.[8] However, the safety issues surrounding this vector may outweigh its superior ability to transfer genes for widespread clinical use.

Another popular viral vector is based on adeno-associated virus (AAV), a nonpathogenic single-stranded DNA virus of the *Dependovirus* genus, which requires a helper virus (typically adenovirus) to complete its lytic life cycle.[9] AAV is attractive because it has shown broad specificity of infection and persistent expression in the lung. The vector appears less inflammatory and elicits weaker immune responses than does adenovirus.[10] Furthermore, Moss and colleagues[11] have demonstrated successful