

Non-technical

Cystic fibrosis (CF) is a genetic disease that affects ~1 in 2,500 live births in the United States. The gene that is abnormal in CF produces problems particularly in the tissues that line various body cavities. Generally, these tissues, termed epithelia, secrete a combination of water and mucus to protect the surfaces of these tissues from toxic/environmental insults from the outside world. These fluids are abnormally secreted and cleared from the lungs of CF patients, which leads to a chronic cycle of bacterial infection and damage of airway walls. Ultimately, most deaths from CF (>95%) result from lung tissue destruction and pulmonary failure.

The current therapies for treating CF lung disease focus on promoting clearance of secretions from the lungs and antibiotics designed to control the lung infection. Whereas these therapies have been effective in prolonging the life-span of CF patients to a median age of ~25 years, they have reached their maximum benefit. A recent series of studies in the laboratory has shown that if the normal version of the CF gene is inserted into CF cells, a correction of the epithelial defect in these cells is readily detected. This type of experiment, in which a gene (the normal CF gene) is transferred to a defective (CF) cell, is a type of gene transfer and has raised the question of whether similar types of gene transfer may be utilized clinically for therapy of CF lung disease.

The adenovirus is a "cold" virus that has a natural tendency to infect many tissues of the nasal cavity and lung. This feature, plus the ready access of the lung tissues to delivery of this kind of virus via aerosol or direct liquid instillation, indicates that this virus is potentially useful for delivering the normal CF gene therapeutically to the CF lung. Consequently, this virus has been genetically engineered by recombinant DNA technology so that some of the potentially toxic components of this virus have been removed and the normal copy of the CF gene inserted. A series of studies in animals and in human tissues in laboratory culture have shown that this virus appears to be very effective in introducing the normal CF gene into affected tissues without any major detectable toxic effects. In the current study, we plan to test this virus vector in the nasal cavity of CF subjects. The major focus of the study is designed to test whether the administration of this virus to a very localized region of the nasal cavity is safe, and whether it has the capacity to restore the functions of the nasal lining tissue to normalcy. The nasal cavity was chosen for these initial studies because of the small volume of virus needed to perform the tests, the fact that the nasal lining tissue exhibits the same types of abnormalities as are expressed in the lung, and that testing the effects of the virus can be performed repetitively with relatively little discomfort to the patient. The long-range goal of these studies is to test the feasibility of this type of virus for gene therapy of CF lung disease and to develop information that will lead to the design of better viruses and better modes of delivery.