

III.C. One-page abstracts (scientific and non-technical)

Scientific

Cystic fibrosis (CF) is an autosomal recessive disease that reflects mutations in the CFTR gene. Multiple mutations in this gene have been detected that lead to a protein (CFTR) that is abnormally metabolized, dysfunctional, or both. The full spectrum of the activities of the gene product have not been defined, but it is clear that CFTR can act as a cAMP-regulated Cl⁻ channel. This type of defect is consistent with the physiologic characterization of CF epithelia, which has revealed abnormalities in salt and water transport. In the lung, abnormalities in epithelial salt and water metabolism lead to abnormal mucociliary clearance. This defect in clearance represents a major failure of lung defense and leads ultimately to infection of the lung with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other bacterial organisms. The chronic inflammatory response to this persistent intraluminal bacterial infection leads to protease-induced destruction of airway walls and finally, lung failure. More than 95% of CF patients die of lung disease.

The clinical therapy of CF lung disease is limited to agents designed to promote clearance of secretions from the lung and antibiotics to treat the chronic bacterial infection. Recent laboratory demonstrations that introduction of the normal CFTR cDNA into CF cells corrects the ion transport defects of these cells has led to the hypothesis that gene therapy in the lung can be an effective, novel mode of therapy for this lung disease. The classic gene transfer vectors, e.g., retroviruses, appear to be not well suited for therapy of lung disease because of the low proliferation rate of airway epithelia *in vivo*. Recently, adenoviruses, which have a natural tropism for airway epithelia, have been genetically modified (E1-deleted) in an attempt to reduce potential toxicity of this virus and provide space for the CFTR cDNA. A series of *in vitro* studies have shown that this vector is highly efficient for transferring CFTR into airway epithelial cells in culture and correcting the CF defect. Further, studies in whole animals appear to indicate that this mode of gene transfer is associated with a low degree of toxicity.

The present study is a dose-effect study designed to test for the safety and efficacy of E1-deleted recombinant adenovirus containing the CFTR cDNA under a CMV- β actin promoter in CF nasal epithelia. The nasal epithelium was selected for study because it exhibits the epithelial defects characteristic of CF, allows the administration of a low volume of virus to an accessible area of the epithelium, and is highly suited for multiple studies designed to measure toxicity and efficacy. A single dose will be administered to the nasal turbinate region of CF patients, with doses ranging from 10^8 to 10^{11} pfu/ml. Three patients will be selected for each dose (10^8 , 3×10^9 , 10^{11}). Beginning 24 hr after vector instillation, assessment of the effects of virus on safety will be sought utilizing nasal lavage for measurement of inflammatory cells, mediator release, and viral shedding, and intermittently by biopsies designed to evaluate nasal epithelial morphology and intracellular viral replication. Efficacy will be tested by restoration of electrolyte transport as measurement by the *in vivo* PD technique (a non-invasive measurement). These studies will be completed by immunocytochemical studies designed to test for expression of CFTR in nasal epithelial cells. The goal is to define the safety and efficacy of the various doses as a function of time, with the ultimate goal of using

these studies to understand safety, efficacy, and potential dosing intervals pertinent to this novel mode of therapy.