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A one-page scientific abstract of the proposal.

Cystic fibrosis (CF), a common hereditary disorder of Caucasians, is caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The major clinical manifestations are on the airway epithelial surface, with purulent mucus, opportunistic infections, chronic inflammation and progressive loss of lung function. Consequent to mutations in both parental genes, the airway epithelial cells have insufficient CFTR function. Since this can be corrected in vitro by transfer of the normal CFTR gene into airway epithelial cells derived from individuals with CF, it is reasonable to hypothesize that the respiratory manifestations of CF could be prevented by transfer of the normal human CFTR gene to the airway epithelium in vivo. In vitro and in vivo studies have demonstrated this is feasible with a replication deficient E1⁻E3⁻ recombinant adenovirus (Ad) vector based on the Ad5 genome and containing a normal human CFTR cDNA. Safety studies in vitro in human epithelial cells and in vivo with cotton rats and non-human primates (rhesus) have demonstrated minimal adverse effects from vectors of this design. Based on these studies, a clinical protocol has been developed to treat the respiratory manifestations of cystic fibrosis by airway instillation of the replication deficient CFTR cDNA containing vector. Following a period of extensive evaluation, the modified adenovirus will be instilled into the nose and airways of individuals with CF. A variety of biologic and clinical parameters will be used to assess safety, biologic efficacy and clinical efficacy. Ten patients will be studied, two each at increasing doses of the modified adenovirus. The therapy will be given one time only to each patient in order to assess safety, efficacy and the response of the immune system to this modified adenovirus. At the conclusion of this study, it should be possible to assess whether the strategy of using a modified Ad as a vector for the normal CFTR cDNA will be a rationale approach to compensate for the genetic abnormalities of cystic fibrosis in the lung, and thus treat the respiratory manifestations of this disease.