

1. Scientific Abstract. Cystic Fibrosis (CF) is a common, lethal hereditary disorder dominated by respiratory disease. The purpose of this protocol is to evaluate the ability of repeat administration of a replication deficient recombinant adenovirus (Ad) vector to safely and effectively transfer the normal human cystic fibrosis transmembrane conductance regulator (CFTR) cDNA to the epithelium of large bronchi. The vector to be used, Ad_{cv}CFTR.10, is an E1⁻ E3⁻ Ad 5-based vector with an expression cassette in the E1 region that includes the cytomegalovirus early promoter/enhancer, the CFTR cDNA, and the SV40 stop/poly A signal. The study includes a total of 26 individuals treated over a period of 180 days. It will initially define the safety and pharmacodynamics of expression of the normal CFTR cDNA in the airway epithelium following single dose administration of ascending doses of the vector to the airways in different individuals. Once the dose schedules are defined, it will evaluate repeat administration at these doses, using extensive laboratory and clinical parameters to determine safety and surrogate biologic parameters to evaluate chronicity of expression. Relative to the PI's ongoing study (Rockefeller University IRB and Biosafety Committee RCR-029-0394, NIH DNA Recombinant Advisory Committee (RAC) 9212-034, Food and Drug Administration (FDA) BB IND 4855) of in vivo Ad mediated CFTR cDNA transfer to the airway epithelium in CF, the new key elements of this study are: (1) administration of the vector to more localized areas of the airways; (2) more careful definition of the pharmacodynamics of expression of the normal CFTR cDNA; (3) evaluation of expression of the normal CFTR cDNA following repeat administration; and (4) the use of a more active promoter/enhancer in the expression cassette.