

M-I (1) Scientific Abstract. Cystic Fibrosis (CF) is a common, lethal, hereditary disorder caused by mutations of the CF transmembrane conductance regulator (CFTR) gene. The clinical manifestations of CF are primarily in the lung, intestinal tract, pancreas and liver. The respiratory manifestations dominate, with thick mucus, chronic airway infections and inflammation beginning in early childhood and leading to progressive loss of lung function. The classic biologic phenotype of CF is the abnormal function of the sweat gland in which the abnormal CFTR prevents sodium chloride reabsorption in the duct, resulting in a higher than normal sweat chloride concentration. This protocol is a “proof-of-principle” study to assess the ability of intradermal administration of the Ad_{Gv}CFTR.10 vector (an E1-E3- adenovirus vector expressing the normal human CFTR cDNA under control of the CMV promoter) to correct the abnormalities in the sweat glands in individuals with CF. A total of 15 individuals with a confirmed diagnosis of cystic fibrosis will be studied. They will be split into two groups: Part A (n=7) and B (n=8). Only patients with proven CF (either genotypically or by a previous sweat chloride test > 60 mmol/L and clinical features of CF) who are currently healthy, not receiving systematic antibiotics or immunosuppressives, and who have < 1:40 titer of neutralizing antibodies to adenovirus serotype 5 will be eligible to participate. The two groups will receive different treatments. Group A will have Ad_{Gv}CFTR.10 and vehicle (the solution in which the Ad_{Gv}CFTR.10 vector is contained) administration and group B will have Ad_{Gv}CFTR.10, Ad_{Gv}CD.10 (adenovirus vector expressing the cytosine deaminase gene as a control for CFTR gene), and vehicle administrations. The timelines will be equal for both groups. Group B will only be started after group A is finished. In addition to safety and toxicity, the efficacy of the Ad_{Gv}CFTR.10 vector will also be determined in this study by assessing the sweat chloride concentration and sweat rate. The skin biopsies at the site of vector administration will allow for persistence of the vector genome and expression of the CFTR mRNA and DNA to be measured. At the conclusion of the study, the following objectives will be met: (1) to determine whether intradermal administration of an adenovirus vector containing the cystic fibrosis transmembrane conductance regulator gene to cystic fibrosis patients can alter the sweat chloride concentration and/or sweat rate, and (2) to establish the persistence of the vector genome and expression of CFTR mRNA and DNA as indications of association between their presence and alteration in sweat chloride response and sweat rate.