

## I. Abstract

Cystic Fibrosis (CF) is an autosomal recessive disorder caused by defective ion transport across various epithelia. Multiple organ systems are affected in this disease; however, the pulmonary complications are the most morbid and life limiting. The primary defect in the lung appears to be abnormal mucociliary clearance. Isolation of the gene responsible for CF in 1989 provided impetus for the development of new therapies based on gene therapy. We propose in this protocol a phase I trial to assess the safety and feasibility of treating CF pulmonary disease by directly delivering CFTR-expressing, replication-defective adenoviruses to the airway. The rationale for this human protocol was based on extensive preclinical studies in a variety of animal models including human CF airway xenografts and nonhuman primates.

In this protocol, 10 CF patients will be treated with CFTR-expressing virus and followed for a) evidence of CFTR gene transfer and expression, b) immunological responses to CFTR or adenoviral proteins, and c) toxicity. Adult CF patients with advanced disease who are considered acceptable candidates for bronchoscopy will be considered. A suspension of virus will be delivered to an isolated segment of the lung via a bronchoscope. Pulmonary samples will be harvested for analyses by follow-up bronchoscopies 4 days, 6 weeks, and 3 months following administration of the virus.

## II. Background

### II.A. Cystic Fibrosis

Cystic fibrosis (CF) is the most lethal autosomal recessive disease in the Caucasian population [Boat et al., 1989]. The underlying pathology involves defects in anion transport across various epithelia. Approximately 1 in 2,500 live births are affected by this disease indicating that the carrier frequency is 1 in 25. Cystic fibrosis manifests itself in multiple organ systems including liver (focal biliary cirrhosis), intestines (bowel destruction), pancreas (malabsorption, pancreatitis, and diabetes), vas deferens (sterility in males) and lung (obstructive pulmonary disease and chronic infections).

Although all mucus secreting organs of the body are affected in cystic fibrosis, it is the pulmonary disease that is responsible for the vast majority of the morbidity and mortality [Wood et al., 1976]. The age at onset of symptoms and the rate of progression of pulmonary disease can vary considerably from patient to patient. However, it is generally accepted that virtually every patient with cystic fibrosis who lives long enough will develop pulmonary complications from their disease. Recent progress in the areas of genetics and cell biology has done much to further our understanding of the pathogenesis of cystic fibrosis. Although a number of significant gaps still exist, the pathogenesis of the pulmonary disease is likely related to the recently described abnormalities in electrolyte transport within the airways. These abnormalities lead to production of an abnormal mucus with altered rheologic properties. This leads to impaired clearance of the bronchial lining fluid with resulting pooling of secretions within the airways. The stagnant secretions are suitable substrates for bacterial growth. For uncertain reasons, staphylococci and pseudomonas species are the most frequently cultured organisms found in the sputum of patients with cystic fibrosis. The repeated episodes of infection cause permanent airway damage of a type that leads to chronic obstruction in airflow and bronchiectasis. Symptomatically, the patient develops cough with sputum production and shortness of breath with exercise. As the disease advances, the level of dyspnea increases until it occurs at rest. With advanced disease, hypoxemia leading to cor pulmonale and right heart failure appear. Eventually ventilatory failure occurs followed by death. Data from 1990 show that the median survival for cystic fibrosis in the United States is 27.6 years.