

## **Gene Therapy of Pleural Malignancies Technical Abstract**

Malignant mesothelioma is a primary neoplasm of the mesothelial lining of the pleural or peritoneal cavity and accounts for approximately 6000 deaths per year. Many more patients die each year from metastatic lesions of the pleura. Although virtually all patients die within two years of diagnosis, primary and metastatic pleural malignancies have a number of characteristics that make them attractive models to study the feasibility of using gene therapy for localized malignancy. First, no effective therapy currently exists. Second, their location in the potential space of the thoracic cavity, makes these tumors uniquely accessible, facilitating directed administration of therapeutic agents and subsequent analysis of treatment effects. Third, local extension of disease is responsible for the majority of the morbidity and mortality associated with these neoplasms.

We propose in this protocol, a Phase I trial to assess the safety and feasibility of treating patients with pleural malignancies by direct delivery of an adenovirus containing the human interferon-beta gene (IFN- $\beta$ ) into the pleural space. The rationale for this human protocol was based on our own preclinical studies in animal models that demonstrated the efficacy of the IFN- $\beta$  gene delivered by an adenoviral vector in eradicating established human mesothelioma and other tumors growing within the peritoneal and pleural cavities of immunocompetent mice via generation of a powerful anti-tumor immune response.

In the Phase I protocol, patients will be treated with an IFN- $\beta$  -expressing replication deficient adenovirus and followed for a) evidence of IFN- $\beta$  gene transfer and expression, b) immunological responses to IFN- $\beta$  or adenoviral proteins, and c) toxicity. Adult patients with malignant mesothelioma and metastatic pleural malignancies who are considered acceptable candidates will be considered. After pathologic confirmation of diagnosis, a suspension of virus will be delivered into the pleural space via a tunneled pleural catheter. Pleural fluid will be serially withdrawn from the catheter for gene transfer and immunologic assays after instillation of virus. Patients will subsequently be carefully evaluated using clinical, laboratory, and radiographic analyses.

These studies will provide the scientific and clinical foundation for future Phase II clinical trials for the treatment of mesothelioma and metastatic pleural neoplasms. In addition, information will be obtained that will be useful for the planning of additional clinical trials focused on the treatment of other localized malignancies such as brain tumors, ovarian and bladder carcinomas, and metastatic disease to the meninges.