

M-I (2) Non-technical abstract. Esophageal cancer is a deadly disease, with only slow advances in therapy over several decades, despite a rapid increase in incidence. Esophageal cancer is estimated to be the seventh most common malignancy worldwide, with incidence rates reaching epidemic proportions in select regions in Asia and Africa. In the United States, it is estimated that 12,300 new cases were diagnosed in 2000, however, the incidence of adenocarcinoma of the esophagus is currently rising faster than that of any other human malignant tumor in this country. Despite advances in surgical technique, chemotherapy, radiotherapy and early detection, only 12% of patients diagnosed with esophageal cancer will survive more than five years, a cure rate more dismal than that seen with cancers of the breast, prostate, colon, and even lung. Survival following treatment for esophageal cancer is stage dependent. This study is directed towards augmenting host anti-tumor immunity by using gene transfer to activate dendritic cells (DC; cells of our immune system that play a central role in initiating immune responses) in tumors of patients with esophageal cancer. Based on extensive pre-clinical data, two proposed clinical trial protocols will evaluate the concept that transient modification of the genetic repertoire of esophageal tumors to express CD40 Ligand (CD40L; a potent activator of DC) will induce the accumulation of activated DC within the tumor, and the *in vivo* interaction of DC with the tumor cells/tumor antigens will induce tumor-specific immunity. To assess this concept, an adenovirus (Ad) vector (Ad_{CU}CD40L) will be used to transfer and transiently express the human CD40L cDNA in esophageal carcinoma by direct injection into the tumor. **Phase I** represents a dose escalation study to determine the maximum tolerated dose of the vector and will include 12 individuals with unresectable, stage III or IV esophageal cancer. **Phase II** is a randomized, double-blinded assessment of biologic efficacy and will include 24 individuals with resectable, stage I-III disease who will be undergoing potentially curative resection. Together, both protocols are designed to assess two hypotheses. First, that it is safe to administer the Ad_{CU}CD40L vector to individuals with esophageal cancer. Second, that intratumoral administration of the Ad_{CU}CD40L vector will induce both the accumulation, in the tumor and in regional lymph nodes, of activated DC, and CD8+ T cells (and other inflammatory cells), including T cells exhibiting tumor-specific responses, as well as systemic antitumor immunity.