II. Non-Technical Abstract

The incidence of renal cell carcinoma is estimated to be approximately 26,000 new cases per year in the United States, with a death rate of 10,000 patients per year.[1] At the time of diagnosis approximately 50% of patients have disease localized to the kidney, 30% of patients have distant metastases, and the remaining 20% of patients have locally advanced disease. At present, surgical resection of all discernible disease is the only potentially curative therapy. For patients with localized disease, the five year survival is 66%, however, those patients with more advanced disease beyond the confines of the kidney, the five-year survival is less than 10%. Systemic therapy with hormonal[2], chemo- and immune[3] therapies have all been investigated in the treatment of metastatic renal cell carcinoma and have rarely been successful with response rates less than 5%. Standard immune therapies have been either interferon-alpha and interleukin-2[3] which can achieve major responses in 10-20% of patients, but long-term survival is rare. Several risk factors have been identified which predict how patients will do over time.[4] High risk patients, i.e., those with poor survival included those patients with moderate activity levels, no surgery to remove the kidney, elevated serum calcium and low blood levels. The three year survival percentages for the favorable-risk (no risk factors), intermediate-risk (one or two risk factors), and poor-risk (three or more risk factors) groups were 31%, 7%, and 0%, respectively.

A series of recent studies[5-10] have shown that Prostate Specific Membrane Antigen (PSMA), a “self” antigen first identified as a marker for epithelial cells in the prostate, is also expressed on the vascular endothelium of RCC specimens. PSMA is a transmembrane protein bearing striking similarity to other receptor molecules expressed on the cell surface. The gene for this molecule was cloned at Memorial Sloan-Kettering and has become a focus of interest as a target for therapeutic strategies including radionuclide imaging with a variety of antibodies to PSMA as well as its use in a DNA vaccine. Using immunohistochemistry, anti-PSMA monoclonal antibodies were shown to bind to the neovasculature associated with primary malignant tumors, including RCC. Unlike the neovasculature of primary and metastatic prostate cancer, the neovascular endothelial cells of metastatic clear cell RCC consistently expressed PSMA.[5-7]

Attempts at using alternate immune strategies have been performed by vaccinating patients with RCC with the patient's own (autologous) modified tumor or with dendritic cells are ongoing but have not been successful in reducing tumor burden although generation of immunologic responses have led authors to be quite hopeful that this may translate ultimately to therapeutic benefit. In these small studies, some indication of immunogenicity was indicated; however, no obvious toxicity was described.[11-15] Importantly, these trials indicate that PSMA is an appropriate choice of antigen for this patient population, even in the presence of metastatic disease. These studies employed a technique involving *ex vivo* expansion and manipulation of dendritic cells, which is more complicated than the direct administration of antigen described in this protocol. The current study will be the first trial of full-length PSMA

DNA as a vaccine strategy for renal cell carcinoma. It also represents an attempt to target both tumor tissue and vasculature with a single vaccine.

The purpose of this study is to see if we can immunize against renal cell carcinoma and to compare the two types of vaccine to see if one is better than the other. We will also study whether the vaccines cause any side effects. All of the patients on this study will receive vaccine, but groups of patients will receive increasing doses. Because of this, the first patients to be treated in this study will receive lower doses of the vaccine than the later patients, watching for side effects to be sure that it is safe to give the higher doses. We believe, based on laboratory experiments, that the use of DNA vaccines could result in the production of immune substances (antibodies and T-cells) which recognize renal carcinoma cells.

Patients will be treated in the outpatient Clinical Immunology unit and will receive vaccinations into the skin and into a muscle approximately every three weeks for the first 18 weeks of the study. The injections are given intramuscularly by a needle-less device called a Bioject2000. This device is held in the hand and shoots the vaccine into the muscle. Blood will be drawn at regular intervals for analysis of antibodies and T-cells. We will also be monitoring patients for any evidence of an effect on tumors.