

II. NON-TECHNICAL ABSTRACT:

Cancer of the penis is rare among males in the United States, accounting for just 0.4 to 0.6% of all malignancies among American men. Penile carcinoma is common, however, in men in some African and South American countries and is actually one of the leading cancers in men in such countries as Paraguay. Without any therapy, penile cancer is a relentless, progressive disease, causing death for most patients within just two years.

The most common treatment for cancer of the penis is surgical removal of a portion of the penis referred to as a *partial penectomy* or removal of all of the penis referred to as a *total penectomy*. Whether a patient will require a partial versus a total penectomy depends on the size, depth, and extent of the tumor, as well as the body habitus of the patient. Present therapy, therefore, may result in severe cosmetic deformity as well as significant modifications in voiding and in sexual functions. Alternative therapies such as radiotherapy have significant complications. New pre- or perioperative adjuvant therapies are needed to reduce or possibly even eliminate the need for surgical management. Consequently, we believe the risk associated with this new gene therapy approach in these patients is offset by the potential significant therapeutic benefit of reducing or possibly eliminating the cancer.

Direct introduction of therapeutic genes into tumor cells may provide an effective treatment of cancer of the penis. In this trial, we plan to use two strategies of gene therapy to treat penile cancer. First, the vector to be used in this trial is replicating-competent or can continue to make more vectors after it is injected. This adenovirus vector called *Ad5-CD/TKrep* has been constructed so that its infection and replication preferentially affects tumor cells. The vector does this by recognizing that many malignant cells lack a functional signal called p53 relative to normal cells. The second strategy is to confer drug sensitivity to tumor cells by inserting a recombinant gene into them. This gene is from the common Herpes virus and codes for the enzyme thymidine kinase (HSV-tk). Thymidine kinase converts the anti-viral drug valaciclovir into a form that is toxic to rapidly dividing cells such as tumor cells. Non-dividing cells are not harmed. Several techniques have been used to introduce therapeutic genes into tumors. Of these, virus-mediated transfer is currently the most efficient method and the most efficient virus is the genetically engineered adenovirus. We have demonstrated using animal models that *Ad5-CD/TKrep* viral therapy results in ablation of multiple types of malignancies.

This Phase I protocol is designed to study the safety of gene therapy for patients with cancer of the penis. A secondary objective of this study is to assess therapeutic efficacy. There is currently no standard adjuvant therapy used with partial or total penectomy. Thus, the potential risks associated with the use of gene therapy in this group would appear reasonable. Patients with penile cancer will be treated with intra-tumoral injection of a replication-competent adenovirus vector delivering the Herpes Simplex Virus thymidine kinase. Initial tests will use a low dose of vector. Following injection of the vector, the virus will be allowed to replicate for one week. After one week's time, patients will begin a two-week course of oral valaciclovir at 2 grams three times daily. Only one course of therapy will be administered. Each patient will be carefully monitored for adverse effects. A partial or total penectomy will be performed at 3 to 4 weeks after the last dose of oral valaciclovir. The primary objective of this study is to determine the dose dependent toxicity of intra-tumoral administration of the adenoviral vector in patients with penile cancer, as well as the relationship between the viral dose and the biological effects on the tumor. By monitoring patients throughout this study with a core biopsy of the penile tumor taken prior to initiating the trial, another biopsy one week after viral injection, and comparing these biopsies with the pathologic analysis of the surgical specimen, the impact of this therapy can be investigated.