

## I. SCIENTIFIC 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 sexual functions. Alternative therapies such as radiotherapy have significant complications. Laser therapy has over the past 10 years been used to treat many benign and superficial penile cancers, but with larger tumors, the depth of laser destruction is difficult to define and the documentation of the depth of malignant penetration is not available. Effective treatment combinations are yet to be defined. A therapy for penile cancer that could convert unresectable tumors to resectable ones and/or reduce the size of tumors, thus requiring less surgical resection, would be beneficial to this patient population. Therefore, it is critical to develop new therapeutic modalities, such as gene therapy, which will eradicate carcinoma of the penis.

Direct introduction of therapeutic genes into malignant cells *in vivo* may provide an effective treatment of solid tumors including cancer of the penis. Many approaches to gene therapy are currently being developed and used. Suicide gene therapy is one of these approaches, which involves the transfer and expression of nonmammalian genes encoding enzymes that convert nontoxic prodrugs into toxic antimetabolites. Two suicide genes currently being tested are the *E. Coli* cytosine deaminase (CD) and herpes simplex type-1 thymidine kinase (HSV-f1 TK) genes, which confer sensitivity to 5-fluorocytosine (5-FC) and valaciclovir, respectively. An *E. Coli* CD/HSV-1 Tk fusion gene, involving both suicide genes has been developed to enhance the elimination of neoplastic cells. This fusion gene has then been placed within a replication-competent, mutant adenovirus that preferentially replicates in tumor cells by failing to express the 55-kD E1B protein. The E1B protein binds to and inactivates the cellular tumor suppressor p53. This virus, then, replicates in and preferentially kills, cells lacking functional p53. The injection of this replication-competent adenovirus is cytotoxic to these cells without the use of a prodrug. We plan to further damage this tumor with the administration of the prodrug valaciclovir one week following vector injection.

The current protocol is designed to study the safety of gene therapy as a neoadjuvant treatment in patients with penile cancer. A secondary objective of this study is to assess therapeutic efficacy. Although local control for patients undergoing partial or total penectomy with current standard therapy is satisfactory, the morbidity of surgical resection is substantial. In addition, a significant proportion of patients will subsequently require inguinal lymph node dissections secondary to nodal disease or invasive local disease which also portends significant morbidity such as wound infection and lymphedema. Given the substantial morbidities associated with current management, it is important to explore preoperative adjuvant therapies that may convert unresectable tumors to resectable ones and/or reduce the size of tumors, thus requiring less surgical resection, or possibly even eliminate distant nodal disease. Thus, the potential risks associated with the use of gene therapy in this group would appear reasonable. We will recruit our study participants from patients with biopsy proven carcinoma of the penis. These patients must be in general good health who have chosen partial or total penectomy for the treatment of their cancer. Following a discussion of the protocol, participants will be asked to sign an informed consent form.

After local anesthesia with 1% lidocaine is administered at the site of injection, patients will receive the viral solution percutaneously via a small needle with slow injection at multiple sites within the tumor. This injection will be performed in the Scott Department of Urology clinic at the Methodist Hospital in

Houston, Texas. One week after vector injection, the patient will return to the clinic. On this visit, patients will undergo a core biopsy of the penile tumor, in order to assess histologic changes that may have occurred after a week's effect with replicating-competent virus. Patients will then begin a two-week course of oral valaciclovir at 2 grams three times daily. The most commonly observed complications in patients receiving valaciclovir have been headache, nausea, vomiting, and diarrhea. Patients will, however, be monitored for granulocytopenia and thrombocytopenia after the first and second weeks of administration of valaciclovir.

Three to four weeks following the last dose of valaciclovir, patients will be admitted to the hospital for a partial or total penectomy. The penile specimen will be evaluated in detail by the study pathologist, Dr. G. Ayala. Patients will be followed in a hospital setting with standard post-surgical care, and patients will return for post-surgical evaluation at one month. Subsequently, patients will be followed with physical examinations once a month for one year, then at two month intervals for the second year. Tumor recurrence will be documented both with physical examinations and biopsies. As accepted standard management, patients will undergo inguinal lymph node dissections, when clinically indicated.