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Section 3: Non-technical Abstract

A Phase I Clinical Trial Assessing the Safety and Feasibility of Administration of pNGVL4a-CRT/E7(detox) DNA Vaccine using the Intramuscular TriGrid™ Delivery System in Combination with Cyclophosphamide in HPV-16 Associated Head and Neck Cancer Patients

Head and neck squamous cell carcinoma (HNSCC) is a worldwide public-health problem, with more than 500,000 cases reported annually. In the United States alone, there are an estimated 45,000 people who are diagnosed with HNSCC each year. Despite treatment advances over the past several decades, the overall 5-year survival in the United States has not changed significantly and remains approximately 55%. Established etiological factors include tobacco, alcohol use, betel nut chewing, and infection with the human papillomavirus (HPV). HPV-associated head and neck squamous cell carcinomas (HPV-HNSCC) represent a growing patient population. The International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence in humans to establish the carcinogenicity of HPV in causing cervical cancer and a subset of head and neck cancers. HPV DNA has been detected in the tumor nuclei of up to 25% of all head and neck cancers, and up to 80% of those tumors localized to the oropharynx, also known as the tonsil and base of tongue. HPV type 16 (HPV-16) is the most prevalent HPV type detected in head and neck cancers and is present in greater than 90% of HPV-HNSCC.

This study, to be conducted at the Johns Hopkins Hospital, in Baltimore, Maryland, will give patients an HPV vaccine following chemoradiation therapy as adjuvant therapy in HPV-related head and neck cancer. A vaccine is a way of delivering a cancer antigen (something that stimulates the immune system to recognize the cancer) to the immune system so that it recognizes the antigen as foreign and destroys any cells with that antigen. The vaccine that we have generated consists of a DNA plasmid which contains the HPV-16 E7 gene linked to calreticulin which is able to direct the E7 antigen to the immune system. The DNA plasmid was generated by the National Institutes of Health in a manner which allows the DNA to be administered safely to humans. The vaccine will be given through an electroporation device which enhances the delivery of the DNA to human cells by several fold. The electroporation device has been used in several human clinical trials involving other DNA vaccines and the device has been found to be safe and well tolerated. The vaccine will be given at three different time points in the arm muscles. This same vaccine has already been given to several patients with HPV-related cervical disease at Johns Hopkins Hospital using either intramuscular needle injection or intradermal gene gun delivery and is found to be safe and well-tolerated thus far. Local symptoms have been experienced at the vaccine site, such as swelling and redness, around 2 to 7 days after vaccination. These reactions resolve without requiring any interventions.

Our bodies have a natural checkpoint to avoid the attack of our own cells by the immune system. This checkpoint is also one of the major reasons why cancer cells can evade immune attack. By using the vaccine, we hope the body's natural immune system will be awakened and reject the cancer cells. However, plenty of evidence from the laboratory research has suggested the immune check point suppresses the capacity of the immune system in attacking cancer cells. It has also convinced us that the efficacy of vaccines is limited largely by this immune check point system.

Cyclophosphamide is chemotherapy that is used to treat many different types of cancer but has not been proven of benefit specifically for head and neck cancer. Cyclophosphamide

given at an intravenous dose lower than that of standard chemotherapy has been suggested to overcome one of these immune checkpoints found to be important in head and neck cancer patients. In one scientific report, the type of immune cells (so called "T regulatory cells") that are believed to participate in immune cell inhibition is largely depleted from patients who were treated repetitively with an oral dose of cyclophosphamide.

This research is being done to see if our experimental HPV cancer vaccine can safely be given using the electroporation device and in combination with a single intravenous injection of cyclophosphamide one day prior to each vaccination. In addition, this study wants to see if the vaccine is able to generate HPV-specific immune responses and if cyclophosphamide can overcome this immune checkpoint by depleting T regulatory cells and allow the vaccine to work better.

Blood samples to measure the numbers of different types of immune cells including HPV-specific immune cells and T regulatory cells will be taken prior to vaccination and at several time points after vaccination. Other tests and evaluations include vital signs, history and physical examination.