

Nontechnical Abstract

Every year in the United States, prostate cancer claims thousands of lives. In 1998 alone it killed 39,500 Americans making it the second most deadly form of cancer for men, second only to lung cancer. Caught in its earliest stages, prostate cancer has a high cure rate. But at many levels of the disease, an absence of satisfactory treatment continues. For these men, treatment options are generally not curative.

Historical Diagnosis Methods and Treatment Modes for Prostate Cancer

Prostate cancer is typically diagnosed through a blood test in which prostate-specific antigen (PSA) can be detected and measured. While elevated PSA levels are sometimes a natural phenomena of aging or of other physiological states, they are also the most useful marker for malignant disease.

Following discovery of elevated PSA levels, physicians use a variety of tools to assess the spread of the tumor using the results as a guide to how the cancer should be treated. The stages of the disease are commonly described as follows:

- T1: microscopic tumor confined to prostate gland; in a physical examination, the gland feels normal
- T2: tumor can be detected through a physical examination but has not spread beyond the prostate gland
- T3: tumor that has begun to expand beyond the prostate
- T4: tumor that is fixed and has pushed well beyond the prostate into adjacent organs
- Metastatic cancer: tumor has spread to and/or beyond the pelvic lymph nodes and/or has become resistant to hormonal therapy (i.e. hormone refractory).

At this time, depending on the cancer stage, typical treatments are as follows: radical surgery to remove the prostate gland; radiation of the tumor by external beam; radiation of the tumor through brachytherapy in which radioactive, rice-size pellets are inserted directly into the prostate where they emit radiation from within the gland; and hormonal therapy in which the production of testosterone - which fuels the growth of malignant prostate cells - is inhibited, thus causing the tumor to shrink. In some cases, a combination of therapies is used. Almost all of the treatment modes, particularly those for later stage prostate cancer, carry with them the risk of serious side effects. For surgery and radiation, complications can include incontinence and impotence. Hormonal therapy can result in impotence, feminization and loss of libido, energy, and bone density.

Exploring a New Approach to Prostate Cancer Treatment

The trial described in the CV706-003 Protocol is a randomized, multi-center research study designed to compare two treatment regimens: (1) the combination of a single dose of CV706 plus radiation, or (2) radiation alone.

This trial, as was the original study (CN706-001), is based on the use of a genetically engineered virus which is injected into the prostate tumor and from within the tumor destroys cancer cells as identified by the presence of PSA

The technology begins with the common cold virus known as *adenovirus*. Calydon has altered this virus by injecting it with *promoter* and *enhancer* elements cloned from the human PSA gene. As a result of this engineering, Calydon's new therapeutic, called ARCA™ (Attenuated Replication Competent Adenovirus), reproduces in the prostate cancer cells (or those cells containing PSA) causing cancer cell death. Conversely, ARCA™ affects a minute number of cells that do not contain PSA (10,000:1) thus limiting the death of non-cancerous cells.

On a preclinical level, this technology shows considerable promise. In experiments in laboratory mice, a single injection of Calydon's viral therapeutic, CV706, caused implanted tumors to shrink on average by more than 80 percent. At the same time, PSA dropped to undetectable levels. A dose-finding experiment in the same animal studies showed increasing tumor shrinkage as the dose of CV706 was increased. As measured through physical examinations and through biodistribution and toxicology studies, no significant side effects appeared in the treated animals. In addition, the cancer did not reappear.

In laboratory animal models of prostate cancer we were able to eliminate the tumor after a single injection of CV706 directly into the tumor at doses of 5×10^8 particles/mm³. Recently, a series of preclinical studies (*in vitro* and *in vivo*) have demonstrated substantial and significant synergy between CV706 and radiation therapy. When CV706 treatment of human prostate cancer tumors in nude mice were followed by radiation, tumor eradication was seen with doses as low as 1×10^7 particles/mm³; e.g., complete tumor responses were seen with the combination of CV706 and radiation at doses where little effect was seen when each agent was used individually.

Human studies using CV706 began in 1997 at the Brady Urological Institute at Johns Hopkins Oncology Center. To date, twenty (20) patients have been treated one time with gradually increasing amounts of CV706 injected directly into the prostate. In general, treatments have been well tolerated and showed only mild to moderate side effects or adverse events. Evidence of clinical activity has been observed in several patients. The maximum dose to be tolerated by patients has still not been established.

The proposed study will assess the safety and efficacy of CV706 (via direct injection into the prostate) combined with radiation versus radiation alone. Patients will receive a single dose of CV706 at a total dose level of 1×10^{13} (10 trillion) viral particles, and radiation therapy at a prescribed dose determined by the Radiation Oncologist, 4 or 5 times per week for either 7 or 8 weeks in a row.