3. NON-TECHNICAL ABSTRACT

Approximately 60,000 new cases of cervical cancer are diagnosed each year. The overall five-year survival rate for cervical cancer is 71%. Early detection by routine screening of pre-neoplastic lesions has made a serious impact on cervical cancer mortality in the Western hemisphere. However, cervical cancer is still the second leading cause of cancer death in women worldwide and a significant source of cancer death for poor and/or uninsured women in the US. Immunotherapy represents one of the potential new treatments for cervical cancer.

Approximately 50% of cervical cancer is caused by Human Papilloma Virus (HPV). Squamous cell carcinoma of the cervix as a result of transformation by HPV is associated with the HPV transforming proteins E6 and E7. Thus, the E6 and E7 antigens have been an intense focus of cancer immunotherapies using a variety of vaccine vectors. Because of the intracellular localization of these antigens, these therapies are mostly directed at cellular immune responses. *Listeria monocytogenes* (Lm) has been shown to be an unusually potent stimulator of such responses to secreted antigens including recombinant antigens that the bacterium has been engineered to express and secrete. The purpose of this study is to see if we can safely immunize against HPV induced cervical cancer using a biologic product called Lm-LLO-E7. Lm-LLO-E7 is a live, laboratory-modified form of *Listeria monocytogenes* bacteria that has been engineered to express the gene for the E7 protein. In particular, we are trying to immunize against the E7 protein present in tumors caused by HPV type 16. The bacterial vaccine expresses the LLO-E7 fusion protein, inducing an immune response in the host targeting E7-expressing cervical tumor cells and leading to tumor regression.

Patients will receive Lm-LLO-E7 administered intravenously every 21 days for a total of three treatments. Groups of patients will receive increasing doses of Lm-LLO-E7. Because of this, the first patients to be treated in this study will receive lower doses of Lm-LLO-E7 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 this vaccine could result in the production of immune substances (cytotoxic T-cells) that recognize cervical cancer cells.

Because this agent has not been used in human trials to date, this preliminary Phase 1 study will be conducted in patients with advanced disease for whom no standard effective curative or palliative therapy is available. A major consideration is the safety of using a live bacterium in potentially immunocompromised advanced cancer patients who may have received heavy pretreatment with radiation and chemotherapy. *L. monocytogenes* is responsible for clinical infections, and clinical listeriosis has been shown to be treatable in both immune competent and immune compromised individuals with a wide range of antibiotics. In addition, the pathogenicity of the Lm-LLO-E7 is significantly reduced, in animal (mouse) studies the engineered bacteria are roughly three thousand times less deadly than wild type *Listeria* bacteria. Further, as an added safety measure for the proposed clinical study, we intend to incorporate antibiotic intervention in order to ensure clearance of the vaccine.