

## **Scientific Abstract**

The purpose of this Phase I study is to evaluate the safety of escalating doses of plasmid DNA, expressing regulatable human growth hormone releasing hormone (hGHRH), administered intramuscularly to patients with cachexia due to metastatic cancer. The Secondary Objectives of our study are to study the effects of a fixed low dose mifepristone (MFP), on plasmid expression of human GHRH measured in serum; to estimate the clearance rate and maximum concentration of hGHRH after this therapy, to study the effects of plasmid DNA expressing human GHRH on weight, lean and fat body mass, hemoglobin, protein, lipid, carbohydrate metabolism, CD4 and CD8 cell count and quality of life. GHRH stimulates the synthesis and secretion of GH from the anterior pituitary that in turn stimulates IGF-I production. These molecules have been previously used to treat conditions associated with metastatic cancer, but their side effects in long-term therapy (associated with protein peaks and troughs) may be detrimental. A gene therapy approach will overcome the primary limitation to GHRH use (short half-life in serum), and a single injection into the patient's skeletal muscle of a plasmid GHRH would ensure physiologic expression for more than 1 year. In a study on adult mice, we showed that GHRH can be efficiently regulated long-term in a mifepristone specific system, and induce increased weight, lean body mass, bone mineral density, hemoglobin, and hematocrit levels. In large animal studies on more than two hundred pigs and on dogs, we showed that long-term expression of GHRH consistently produces significant physiological changes in weight, body composition and has a positive effect on protein and bone metabolism, with no discernable adverse effects.