

**Technical Abstract:**

Colorectal cancer is the third most common cancer in men and women, with an estimated 146,940 new cases and 56,730 deaths in 2004. Up to 25% of patients have liver metastases at diagnosis, and an additional 25% develop liver metastases through the course of their disease. For patients who develop liver metastases, surgical resection of the metastatic foci within the liver has become acceptable treatment, with surgical mortality rates of 0% to 6% and 5-year survival rates of 25% to 51%. However, less than 25% of patients with liver metastases are candidates for resection. The 5-year survival rate for patients who are not eligible for surgery is less than 2%. In summary, surgical resection of colorectal carcinoma liver metastases is not indicated in the majority of patients, and many of the patients who receive such surgery subsequently relapse.

We propose in this protocol, a Phase I/II study, to assess the safety and feasibility of treating patients with refractory colorectal carcinoma with liver metastases by intravenous injection of an adenoviral vector, BG00001, which encodes the human interferon-beta (hIFN- $\beta$ ) gene. The rationale for this study was based on preclinical studies in animal models that demonstrate the local production and secretion of hIFN- $\beta$  protein following gene transfer has demonstrated potent tumoricidal effects that extend beyond the transfected cells. It is hoped that local delivery of the hIFN- $\beta$  gene will have similar anti-tumor activity in humans with refractory colorectal carcinoma with liver metastases.

BG00001 is a human serotype 5 adenovirus vector from which most of the E1 and E3 genes have been deleted, and into which the hIFN- $\beta$  gene has been inserted and renders the vector replication-deficient.

The proposed Phase I/II study is a multi-center, open label, two part, dose escalation by cohort protocol. The primary objective is to determine the safety of a single intravenous injection of BG00001 in subjects with refractory colorectal carcinoma with liver metastases. The secondary objectives are as follows: a) evaluate the maximum-tolerated dose (MTD) or maximum-feasible dose (MFD) of BG00001, b) evaluate IFN- $\beta$  and BG00001 serum concentrations, c) evaluate immunogenicity of BG00001 by measuring human anti-adenovirus and human anti-IFN- $\beta$  antibody formation, and d) explore preliminary clinical activity.

This study will provide the scientific and clinical foundation for future Phase II clinical trials for the treatment of patients with refractory colorectal carcinoma with liver metastases.