

## **SCIENTIFIC ABSTRACT**

The principal purpose of the trial is to test the safety of administering to Stage IV melanoma patients intratumoral injections of a replication-incompetent adenoviral vector encoding a human fVII immunoconjugate (hfVII icon). The hfVII icon is a bifunctional molecule composed of human fVII as the targeting domain conjugated to the Fc region of a human IgG1 immunoglobulin as the effector domain. Factor VII binds with high specificity and affinity to the transmembrane receptor tissue factor (TF), which is expressed on endothelial cells lining the luminal surface of the vasculature in solid tumors but not in nonproliferating normal tissues, and therefore provides a specific and accessible target for the tumor vasculature. Intratumoral injection of the adenoviral vector results in infection of cells in the injected tumor, which synthesize and secrete the encoded icon into the systemic circulation. The blood-borne icon molecules are transported to the vasculature of all tumors, including uninjected tumors, and bind to TF on the tumor vascular endothelial cells. Binding of the hfVII icon to TF induces a targeted cytolytic immune attack by components of the immune system that contain Fc receptors, resulting in destruction of the tumor vasculature. Because TF also is expressed on the cells of most types of tumors, and because the tumor vasculature is leaky, the fVII icon also binds to TF on the tumor cells, enhancing the cytolytic effect against the tumor.

The primary objective of the proposed trial is to assess the safety of the immunotherapy protocol, by determining whether Grade III or Grade IV toxicity occurs. Early stopping rules are specified in the statistical section. Because the safety of intratumoral injections of a replication-incompetent adenovirus has been documented in extensive clinical tests, as discussed below, the focus of the proposed trial is on the safety of the hfVII icon. The efficacy of the hfVII icon also will be evaluated by monitoring changes in the size and number of the injected and uninjected tumors. Skin tumors will be measured with a caliper, and internal tumors will be measured by CAT scans.