SCIENTIFIC ABSTRACT: Clinical Trial of an *in Situ* Cancer Vaccine Strategy

Memory T cells are present in the microenvironment of human tumors but fail to control the growth and metastasis of these tumors. T cells isolated from human lung and ovarian carcinomas are functionally quiescent due to an arrest in the T cell receptor signaling cascade that occurs upstream of NF-κB and NFAT activation. The hyporesponsiveness of the tumor-associated T cells is reversible by IL-12 and mediated by a combination of as yet incompletely defined mechanisms that are likely to be dependent upon soluble (TGF-β and IL-10) and membrane bound molecules produced by and present on stromal cells in the tumor microenvironment that include fibroblasts, antigen presenting cells, regulatory T cells (T_{reg}), and the tumor cells themselves. We have tested IL-12 as an anti-cancer therapy in a SCID mouse/human xenograft model. Intact pieces of human tumor, that contain tumor infiltrating lymphocytes, are implanted subcutaneously into SCID mice. The tumor and its infiltrating cells remain viable after implantation and will continue to grow after implantation unless treated. After implanting SCID mice with non-disrupted pieces of human tumors we injected the engrafted tumor with irradiated human cells transfected with the human IL-12 gene. Our pre-clinical model, human lung tumor xenografts in the SCID mouse, has shown that intra-tumor IL-12 will activate tumor infiltrating T-cells and stimulate the release of IFNγ resulting in lung cancer tumor regression. Therefore, we have selected to test our IL-12 delivery device in patients with cutaneous, subcutaneous or superficial metastatic lung cancer tumors. The proposed Phase 1 clinical trial will determine the toxicity and the effective dose of the intra-tumor injection of a slow release IL-12 delivery device; an irradiated human allogeneic cell line that has been transfected with both chains of the human IL-12 gene. This is a dose escalation study with the intra-tumor injection of $1x10^6$ cells producing 3.4ng/24 hours the first dose to be tested.

.