1. The scientific abstract.

There has been increasing interest in recent years in developing immunologic approaches to malignancies, and there is good evidence that the growth of renal cell carcinoma (RCC), melanoma, non-small cell lung cancer (NSCLC), and other malignancies can be modulated by the host's immune system. A recently described strategy involves the use of a vaccine in which a universal MHC-negative GM-CSF-producing “bystander cell” is mixed with irradiated but otherwise unmodified fresh autologous tumor cells (antigen source). This vaccine, calledK562 Bystander GVAX®, is being developed by the Johns Hopkins Oncology Center in collaboration with Cell Genesys, Inc., and is currently being tested in Phase I/II clinical trials in patients with multiple myeloma and NSCLC (http://www.cellgenesys.com/products-cancer-vaccines.shtml).

A similar bystander cell line (GM.CD40L) has been created within our institution. The GM.CD40L line secretes GM-CSF and expresses CD40L on its cell surface. The rationale is that, in the context of autologous or allogeneic tumor cell-based vaccine formulations, these bystander cells will help recruit professional antigen presenting cells (APCs) in the form of dendritic cells (DCs) by secreting GM-CSF in the vaccine site microenvironment. The DCs will then be activated by expression of CD40L on the universal bystander cells. DCs will take up apoptotic bodies from the irradiated tumor cells and in turn will present tumor antigens in the context of MHC class I and class II. Tumor-specific DCs will then migrate to the regional lymph nodes, where T cell activation can occur, ultimately leading to systemic tumor cell killing. Mouse experiments with a murine equivalent GM-CSF-secreting bystander have supported this hypothesis, with cure of mice after vaccination with a mixture of autologous tumor and bystander cell.

This protocol describes a phase I study for patients with myelodysplastic syndrome MDS with high risk features for transformation to acute leukemia. As the underlying neoplasia from which the parent cell line (K562) for the GM.CD40L cell line was, in fact, a leukemia, we hypothesize that these cells may serve as their own antigen source. Patients will receive three intradermal GM.CD40L vaccine injections at 14-dayintervals, and adjacent to dosing with the immune modulating drug lenalidomide. On the day of vaccination, a vial (or multiple vials at higher cell doses) of radiated GM.CD40L cells will be rapidly thawed, diluted in 10 mL sterile saline for 15-30 min, centrifuged, and

resuspended in 1.0 mL sterile PlasmaLyteA™. This vaccine formulation will then be administered to the patient. Patients will be monitored for evidence of toxicity, the development of a specific immune response, and objective tumor responses. The maximum tolerated dose (MTD) will be determined by escalating the dose of the bystander in 4 cohorts of patients ($10x10^6$, $30x10^6$, $60x10^6$ and $120x10^6$ cells per dose).