"Dendritic Cell Targeting: A Novel Approach to Tumor Vaccination"

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Abstract: Tumor vaccines represent a formidable challenge in immunology requiring the development of novel strategies to overcome tolerance to self-antigens and the immunosuppressive properties of tumors. Large numbers of high quality T cells are required to effectively attack the cancer and resist the development of metastasis in a tumor specific manner. Inducing such a response will require new technologies and a better understanding of the principles that underlie the human immunity and tolerance to cancer. The object of this proposal is to bring together a group of Rockefeller and Memorial Sloan Kettering Cancer Center investigators to focus on new approaches to cancer vaccination. The underlying strategy for this consortium evolved from seminal studies demonstrating that specific antibodies to dendritic cell subsets can be modified to deliver antigens to these cells and greatly enhance antigen delivery and presentation. When combined with a DC maturation stimulus this targeting approach resulted in sustained immunity to the targeted antigen. The maturation signals required to convert DCs into cells capable of stimulating effective T cell responses could be delivered by the antibody Fc region, if manipulated to overcome inhibitory signaling on immature DCs. These studies demonstrated the feasibility of delivering an antigen and a maturation signal in a single, modified anti-DC antibody to result in effective T cell stimulation and tumor protection in a mouse model system. We propose to apply this approach to metastatic melanoma, using the gp75 melanosome antigen as our tumor antigen and both spontaneous and spontaneous and transplantable mouse models of melanoma to demonstrate the validity of DC targeting of the gp75 antigen to achieve immunity to melanoma. These studies will provide the proof-of-concept required to proceed to clinical trials using a DC targeting strategy for melanoma.