

NON-TECHNICAL ABSTRACT

Preliminary studies with a variety of vaccines suggest target accessibility (potential Immunogenicity) in a variety of solid tumors to immune directed approaches. However, four primary factors limit the generation of effective immune mediated anticancer activity in therapeutic application: 1) identifying and/or targeting cancer associated immunogen[s] (target) in an individual patient; 2) insufficient or inhibited level of antigen presenting cell (dendritic cell, macrophage) priming and/or presentation; 3) suboptimal T cell activation (potency) and proliferation; and 4) cancer-induced inhibition of the anticancer immune response in both afferent and efferent limbs. In an effort to overcome these limitations, we have designed a novel autologous vaccine to address inability to fully identify cancer associated antigens, antigen recognition by the immune system (i.e., antigen→immunogen), effector potency, and cancer-induced resistance. We have completed previous clinical investigations using two different gene vaccine approaches to induce enhancement of tumor antigen recognition which have demonstrated therapeutic efficacy. Specifically, both the use of a GMCSF gene transduced vaccine and a TGFβ2 antisense gene vaccine, in separate trials, have demonstrated similar beneficial effects in advanced cancer patients. The GMCSF transgene directly stimulates increased expression of tumor antigen[s] and enhances dendritic cell migration to the vaccination site. TGFβ2 blockade following intracellular TGFβ2 antisense gene expression reduces production of immune inhibiting activity at the vaccine site. These agents have never been used in combination but the rationale of integrating enhancement of an anticancer immune response concurrently with a reduction in cancer-induced immune suppression is conceptually sound. We successfully developed an irradiated autologous cell vaccine transfected with a combination of TGFβ2 antisense / GMCSF expression vector plasmid (TAG vaccine). Patients bearing tumors of different histologic origin have elevated levels of Transforming Growth Factors-βs (TGFβs), which are associated with immunosuppression. TGFβ2 inhibits T cell activation in response to antigen stimulation and is antagonistic to natural killer (NK) cell and lymphokine-activated killer (LAK) cell response.