

Non-technical Abstract

Injection of a DNA vaccine into various animal models results in the ultimate expression of that DNA in the muscle cells of the injected animal. Concomitantly, tumor antigens exposed to the DNA vaccine in these animals elicit immune response developing protection against a tumor challenge. Phase I human clinical trials utilizing similar DNA vaccines have demonstrated no significant adverse effects.

Melanoma antigen recognized by T cells-1, abbreviated MART-1, is identifiable in many melanoma patient lymphocytes. Additionally, HLA-A2 patient tissue types can generate melanoma-reactive cytotoxic T cell lines from the MART-1 antigen. Consequently, MART-1 is currently being targeted in numerous immunization trials. We propose to conduct a dose escalation study of a DNA vaccine encoding MART-1 to be administered to high-risk melanoma patients who have been shown to have a $\geq 50\%$ risk of relapse and death within the next ten years. This proposal is based upon not only the high recurrence of disease in resected melanoma patients but also upon the lack of effective therapy in recurrent melanoma and the role of MART-1 that has apparently served to facilitate tumor regression. To the best of our knowledge, this trial will be the first to use the full-length MART-1 cDNA delivered by a non-viral vector. This approach provides several advantages including effective booster administration which is not limited by development of immunity to a viral vector. A separate vaccine encoding the hepatitis B surface antigen (HBsAg) will also be administered in conjunction with the MART-1 vaccine to serve as a positive control. This strategy of having two separate plasmid preparations for MART-1 and HBsAg should prove beneficial since it will bypass competition between the two promoters causing decreased tumor antigen expression and also eliminating shortened survival of desirably affected cells that could feasibly be destroyed by the HBsAg expression. The MART-1 and HBsAg vaccines will be injected into opposite arms to eliminate any negative affects that may be caused by interference of the MART-1 immune response.

We propose to evaluate the MART-1 vaccine in patients with minimal residual disease rather than terminally ill patients with widely disseminated disease so as to avoid the misrepresentation of a treatment that could potentially play an important role in the adjuvant setting.