3. The non-technical abstract

Telomerase is a ribonucleoprotein reverse transcriptase complex containing an RNA subunit (hTERT) and a protein catalytic subunit (hTERT) that is involved in maintaining telomeric DNA and thereby inhibiting replicative senescence. hTERT expression and telomerase enzymatic activity are absent in most human adult somatic cells. In contrast, telomerase enzymatic activity and/or hTERT expression are increased in various cancers and may serve as prognostic factors in some cancers. Moreover, hTERT can elicit cytotoxic lymphocytes (CTLs) that lyse tumors of various histologic types but not normal cells in which telomerase activity is detected. hTERT is thus a common tumor associated antigen and efforts at enhancing immune reactivity against hTERT may hold promise as a novel anti-cancer strategy.

V934 is a plasmid DNA construct to be used for vaccination against hTERT. The product consists of a covalently closed circle plasmid DNA (pV1J/TPA-hTERT-LTB; 8691 bp) carrying the TPA (human tissue plasminogen activator; aa 1-23), fused via a 2-aa cleavage sequence to the codon-optimized cDNA of hTERT (aa 2-1132), fused itself via a 2-aa cloning site to the β-subunit of Escherichia coli heat labile enterotoxin (LTB; aa 22-124). Transcription is controlled by the human cytomegalovirus (CMV) major immediate early (IE) enhancer/promoter and is terminated by the bovine growth hormone (bGH) polyadenalytion signal. The hTERT sequence in this construct contains mutations to functionally eliminate telomerase catalytic activity.

V935 is an adenoviral vector to be used as a boost vaccination agent. The MRKAd6 vector is a modification of a prototype Group C Adenovirus serotype 6, whose genetic sequence was determined at Merck and used for the HIV trigene vaccine. The El region of the wild type Ad6 was deleted and replaced by the hTERT transgene cassette. Deletion of the El sequence means there is no potential for recombination with the host cell line (PER.C6) that could produce replication competent adenovirus (RCA), whether by homologous or non-homologous recombination. The E3 region was also deleted in the Ad6 vector in order to accommodate the expression cassette, which consists of: the immediate early gene promoter from the human cytomegalovirus, the coding sequence of hTERT, and the bovine growth hormone polyadenylation signal sequence. The codon usage in the hTERT reading frame is the native wild type; for safety purposes, the nucleotide sequence was mutated in the region corresponding to the protein catalytic site. In preclinical studies, cell-mediated immune responses have been generated in animals treated with TERT-based vaccination regimens using DNA and/or adenovirus, and combined vaccination with DNA and adenovirus induces immune responses that are more substantial than that induced by vaccination with either DNA or adenovirus alone. These studies demonstrate that tolerance to self-antigens such as TERT can be broken using this vaccination regimen. Further, vaccination with DNA plus adenovirus (i.e. V934/V935) can induce immune responses that translate to therapeutic efficacy in preclinical tumor models. In light of these data, the approach being taken is to develop a heterologous cancer vaccine regimen consisting of DNA plasmid-EP vaccination, V934, followed by vaccination with adenoviral vector, V935. It is hypothesized that sequential treatment with these vaccines in a heterologous prime-boost regimen will give rise to a superior immune response that may result in increased therapeutic efficacy and ultimately clinical benefit.