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The generation and analysis of a novel combination of recombinant adenovirus vaccines targeting three tumor antigens as an immunotherapeutic

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We have reported on a novel adenovirus serotype 5 (Ad5) vector gene delivery platform (Ad5 [E1-, E2b-]), in which regions of the early 1 (E1), early 2 (E2b), and early 3 (E3) genes have been deleted. The unique deletions in this platform result in a dramatic decrease in late gene expression, leading to a marked reduction in host immune response to the vector. CEA, MUC1, and brachyury are tumor-associated antigens (TAA) expressed on a wide range of human tumors. Ad5 [E1-, E2b-]–CEA vaccine (ETBX-011) has been employed in clinical studies as an active vaccine to induce immune responses to CEA in metastatic colorectal cancer patients. The Ad5 [E1-, E2b-]–CEA vector encodes the entire CEA sequence modified to express an enhancer T-cell epitope. We report here the development of novel Ad5 [E1-, E2b-]–brachyury and Ad5 [E1-, E2b-]–MUC-1 vaccine constructs. The Ad5 [E1-, E2b-]–brachyury vector was constructed to encode the entire brachyury gene devoid of 25 amino acids involved in DNA binding, and modified to express an enhancer T cell epitope. The Ad5 [E1-, E2b-]–MUC-1 vector was constructed to encode the entire MUC-1 transgene with eight agonist epitopes, including five in the C-terminus. Our results show that these constructs (CEA, MUC1 and brachyury) are capable of activation, as well as generation of antigen specific T cells *in vitro*, and of inducing antigen-specific T cells in vaccinated mice. We have also demonstrated that the use of a combination of the three vaccines (designated Tri-Ad5) displays little, if any, antigenic competition in *in vitro* studies of human dendritic cells for antigen-specific T cell activation and generation, or in murine vaccination studies. The studies reported here support the rationale for the application of Tri-Ad5 as a therapeutic modality to induce immune responses to a diverse range of human TAAs for potential clinical studies.

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