self-antigens may provide important targets for cancer vaccines.

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A clinical trial of a DNA vaccine (SCIB1) that targets dendritic cells *in vivo* in fully resected melanoma patients; a vaccine to prevent disease recurrence?

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Background:

SCIB1 is a DNA vaccine encoding a human IgG1 antibody with CDRs that contain four epitopes from two melanoma antigens (three from gp100 and one from TRP2). The vaccine elicits potent anti-tumour responses by stimulating high frequency, high avidity T-cells via both direct and cross-presentation of antibody. A clinical study in stage III/IV melanoma patients, all with tumour present at study entry, showed that 2-8mg doses could induce T-cell responses in 7/9 patients with no associated toxicity. Encouragingly overall survival was 31 months. This study addresses the question as to whether SCIB1 can be used as an adjuvant therapy in fully resected melanoma patients to prevent further disease.

Methods:

Sixteen patients with fully resected stage III (n=9) or stage IV (n=7) melanoma were immunised with 4mg of SCIB1 by intramuscular electroporation at 3 weekly intervals and subsequently at 3 and 6 months. Patients could continue treatment for 5 years.

Results:

All 16 patients showed vaccine-epitope-specific T-cell responses (i.e. proliferation *ex vivo* and/or γIFN Elispot responses *in-vitro*). Twelve patients responded to all four epitopes, two patients to three epitopes, one to two epitopes and one to a single epitope. Five patients remain in the continuation phase - all show strong T-cell memory responses following boosting. At present, median survival time is 37 months from trial entry and 41.5 months from diagnosis of metastases. Overall survival is 100% for both groups. Five patients relapsed at 1, 4, 14, 17 and 18 months but have shown no further recurrences at follow-up.

Conclusion:

These results show that a DNA vaccine encoding epitopes from melanoma antigens can induce measurable T-cell responses and, furthermore, it may confer protection from recurrence of melanoma with little associated toxicity. SCIB1 deserves further evaluation as an adjuvant therapy.

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TCR modifications that enhance proper chain pairing may also augment reactivity against naturally occurring mutant peptides

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Using TCR gene modified T cells for adoptive cell transfer has been shown to have clinical success in treating melanoma and other malignancies. One of the challenges in using TCR gene modified T cells include proper expression of the introduced TCR and function. Mispairing between endogenous and introduced TCR chains allows for the potential of unanticipated off-target reactivity, autoimmunity, and impaired therapeutic efficacy against targeted antigens. One approach to improve TCR expression, pairing, and T cell function involves the modification of the introduced TCR genes to promote proper pairing. Some of these modifications include introducing a disulfide bridge in the alpha/beta constant regions, murine constant regions, codon optimization, TCR chain leucine zipper fusions, and a single chain TCR. We have previously cloned a novel TCR from a HLA-A2 restricted, HCV NS3:1406-1415-reactive T cell clone. We have developed a surface transduction marker, CD34t, that allows for measurement of TCR expression due to the 1:1 stoichiometric ratio between CD34t and TCR proteins. Our results revealed that the murinized Cβ2 TCR and the leucine zipper TCR have the highest levels of expression per transduced T cells when compared to the wild type TCR. It is evident that while some modifications have higher levels of TCR expression, this does not always result in increased function. Although, on a transduced