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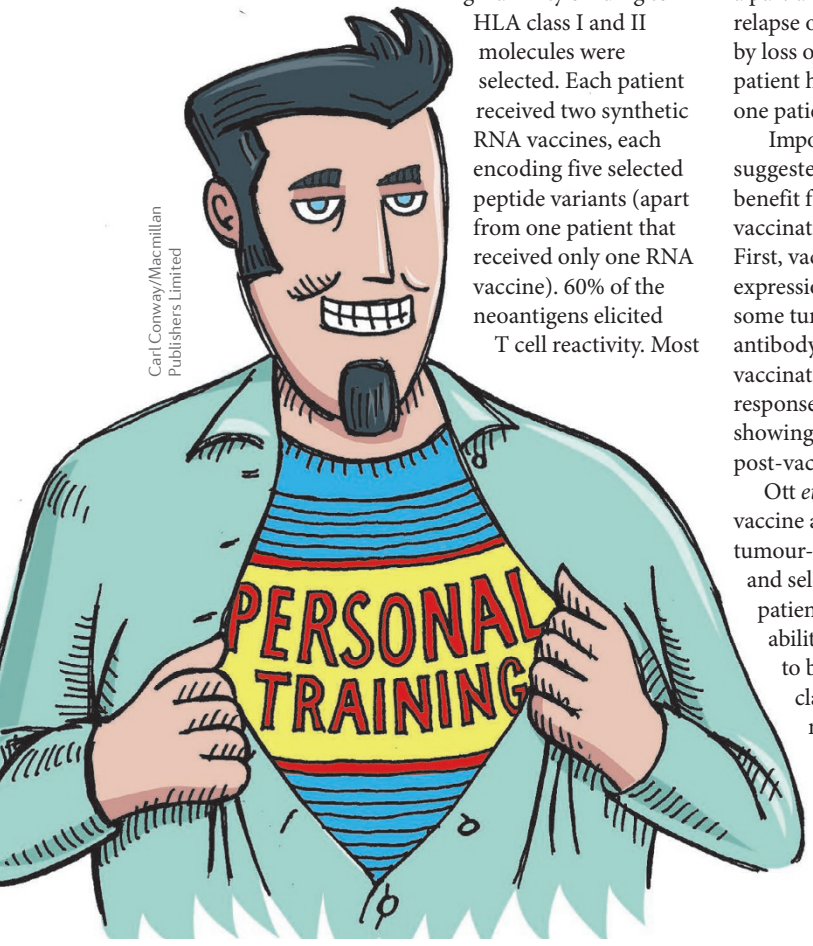
TUMOUR VACCINES

Personal training by vaccination

> feasibility and potential clinical success of vaccines targeting multiple neoantigens in patients with melanoma

The heterogeneity of cancer makes individualized treatment options necessary, even in immunotherapy. Although neoantigens can induce spontaneous tumour-specific immune responses, these responses are mostly insufficient to stop tumour growth. Two groups have now independently demonstrated that, through the use of personalized neoantigen-based vaccines, T cell responses can be efficiently triggered and outcomes improved in patients with melanoma.

Sahin *et al.* used an RNA-based vaccine approach. They identified tumour-specific, non-synonymous mutations in 13 patients with stage III and IV melanoma through exome-sequencing and RNA-sequencing. Mutations encoding peptide variants with predicted high-affinity binding to HLA class I and II molecules were selected. Each patient received two synthetic RNA vaccines, each encoding five selected peptide variants (apart from one patient that received only one RNA vaccine). 60% of the neoantigens elicited T cell reactivity. Most responses were generated *de novo* (68%), and were mediated mainly by $CD4^+$ T cells. Indeed, non-existant or weak pre-existing T cell reactivity towards neoantigen-loaded dendritic cells was boosted by vaccination and was highly specific.



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Following vaccination, all 13 patients showed significantly reduced cumulative recurrent metastatic events and sustained progression-free survival. Eight patients that presented with no detectable lesions pre-vaccination remained completely free of melanoma relapses. Of the five patients that presented with lesions pre-vaccination, two patients showed complete responses (one of whom required combination treatment with antibody against programmed cell death 1 (PD1)); one patient had a partial response (suffering a late relapse owing to resistance conferred by loss of β_2-microglobulin); one patient had a mixed response; and one patient showed stable disease.

Importantly, several observations suggested that patients could benefit from combining neoantigen vaccination with PD1 blockade. First, vaccination led to increased expression of PD1 ligand 1 in some tumours. Second, anti-PD1 antibody treatment following vaccination induced a complete response in a patient that was still showing fast disease progression post-vaccination.

Ott *et al.* used a peptide-based vaccine approach. They identified tumour-specific somatic mutations and selected 13–20 mutations per patient, based on the predicted ability of the encoding peptide to bind to autologous HLA class I molecules. For each neoantigen, a clinical grade immunizing long peptide was synthesized, pooled in four groups and given to the patient. Interestingly, even though peptides had been selected for HLA class I binding, most immune responses, only detected post-vaccination, were mediated by $CD4^+$ T cells (60%) and less by a mix of $CD4^+$ and $CD8^+$ T cells (10%) or $CD8^+$ T cells (16%). More than 30% of the $CD4^+$ and $CD8^+$ T cells was polyfunctional, and their neoantigen reactivity was highly specific. Moreover, gene expression profiling revealed that post-vaccination, neoantigen-specific $CD4^+$ T cells clustered separately from pre-vaccination $CD4^+$ T cells and showed elements of effector and memory functions.

Six of the ten initially enrolled patients, presenting with previously untreated, high-risk melanoma (stage III or stage IV), received the vaccination. Four patients, who had presented with stage IIIB/C melanoma, showed complete responses and no disease recurrence post-vaccination, whereas the two patients who had presented with stage IV melanoma showed disease recurrence. However, following treatment with anti-PD1 antibodies, these two patients showed complete responses. In these patients, the number of neoantigens that elicited $CD4^+$ or $CD8^+$ T cell responses was increased after anti-PD1 treatment.

Together, these two studies demonstrate the feasibility and potential clinical success of vaccines targeting multiple neoantigens in patients with melanoma. This approach, in combination with PD1 checkpoint blockade, will hopefully benefit patients with late-stage cancer with a high mutational load, for whom treatment options are very limited.

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ORIGINAL ARTICLES Sahin, U. *et al.* Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature* **547**, 222–226 (2017) | Ott, P. A. *et al.* An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature* **547**, 217–221 (2017)