Cancer vaccines on the move

Jacques Banchereau and Karolina Palucka

The development of therapeutic cancer vaccines has been pursued for many decades. Many vaccines can elicit immunity to tumour antigens, although their clinical efficacy remains modest. Recent results from two clinical trials highlight the potential of personalized vaccination strategies, made possible by high-throughput approaches to the identification of immunogenic tumour neoantigens. Thus, therapeutic cancer vaccines might soon move into the mainstream.

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

Vaccines against infectious agents — one of the great successes of medicine — act to prevent diseases. These vaccines, which are designed to generate humoral (antibody-based) immunity, have mostly been identified in an empirical manner. By contrast, therapeutic vaccines are designed to treat an established disease, such as cancer, mainly by evoking cellular (T-cell-based) immune responses. The first attempts to vaccinate humans against cancer were made more than a century ago¹. In the 1950s, studies in mice revealed that chemically-induced tumours were immunogenic and could elicit therapeutic immunity. Since then, numerous teams have worked on defining the mechanisms of these responses, with Robert Schreiber propounding the now prominent ‘three Es’ concept of cancer immunity and immunoediting: elimination, equilibrium, and escape². The discovery of co-stimulatory and co-inhibitory pathways controlling the extent of the immune response led to the development of immune-checkpoint inhibitors, such as anti-PD-1 antibodies, which can counter the ‘escape’ of cancers from immunity^{3,4}. Important roles of immune-checkpoint inhibitors in anti-cancer therapy have already been established; their clinical effect, which can be durable across various cancers, is generally associated with a high mutational load, which might, in turn, be associated with the presence of tumour-associated antigen (TAA)-specific

T cells. Only a minority of patients with cancer respond to this treatment modality³, however, which might reflect — among other factors — a low prevalence of such T cells. Thus, expansion of TAA-specific T cells, for example, via vaccination, could potentially increase the rate of clinical responses to immune-checkpoint inhibitors.

Vaccines are composed of antigens and adjuvants — that is, activators of antigen-presenting cells that shape immune responses.

Both components remain the focus of questions surrounding the optimal design of cancer vaccines (FIG. 1). Numerous preclinical studies in mice have provided ample evidence of the value of cancer vaccines, but clinical translation of this approach, as well as the identification of antigens that elicit therapeutic immunity upon vaccination, has proved challenging. The various classes of candidate cancer antigens include non-mutated proteins against which T-cell tolerance is incomplete, possibly owing to a tissue-restricted expression profile that circumvents the mechanisms of central and peripheral immune tolerance. Other classes comprise peptides that are entirely absent from the proteome of nonmalignant human cells — either non-self antigens or neoantigens⁵. Non-self antigens can be derived from viruses, such as human papillomavirus (HPV); such antigens are common between different individuals and, therefore, a personalized approach to vaccination is not required. Nearly a decade ago, vaccination with long, HPV-derived peptides and adjuvants was demonstrated to evoke therapeutic T-cell immunity in patients with intraepithelial cervical neoplasia, which was correlated with clearance of HPV and regression of neoplastic lesions⁶. Neoantigens are created by cancer-specific DNA alterations that result in unique peptide sequences⁵. The identification of these neoantigens has

Figure 1 | Generations of cancer vaccine antigens. Early clinical studies used whole cancer cell preparations (for example, tumour lysates) as the source of tumour antigens, comprising a mixture of self-antigens and undefined neoantigens. These vaccines elicited broad immune responses, possibly not reaching a critical threshold for the frequency of anticancer T cells needed for clinical efficacy. The next stage of cancer vaccine development was focused on purified self-antigens, the use of which requires breaking of T-cell tolerance. Most recently, defined neoantigens have been pursued as drivers of a focused immune response that enables the critical thresholds for the frequency of anticancer T cells and clinical efficacy to be reached.

been made possible by the advent of next-generation sequencing (NGS), which enables efficient sequencing of both RNA and DNA from cancers, and the development of novel algorithms for predicting the binding of peptides to MHC class I and class II proteins. In general, neoantigens are unique to each patient, although patients deficient in mismatch-repair enzymes have exceptionally high numbers of common somatic mutations, which seem to predict a therapeutic response to anti-PD-1 antibodies across different cancers⁷. Some tumours, including most melanomas, have high mutation rates, but whether this is reflected in the generation of neoantigens remains to be established. Indeed, certain criteria need to be met for mutations to create neoantigens: they must be present within the peptides that are processed by the antigen-presentation machinery; the mutated peptide must bind to MHC proteins with sufficient affinity to be presented to T cells; and the MHC-bound mutated peptide must be recognized by the patient's T cells.

Two recent phase I studies illustrate the potential of personalized cancer vaccines targeting neoantigens identified using NGS and predictive MHC-binding algorithms^{8,9}. Ott *et al.*⁸ enrolled 10 patients with stage IIIB/C or IVM1a/b melanoma in order to evaluate a personalized peptide-based vaccination approach. The tumours from eight of the 10 patients had a high mutation rate; for these eight patients, 13–20 neoantigens predicted to be presented on tumour cells were synthesized as immunizing peptides containing 15–30 amino acids. Six of these patients underwent vaccination with these personalized neoantigen peptides, together with the adjuvant poly-ICLC, beginning a median of 18 weeks after tumour resection with curative intent. Vaccine-induced polyfunctional CD4⁺ and CD8⁺ T cells were found to target 58 (60%) and 15 (16%) of the 97 unique neoantigens used across all patients, respectively. At 20–32 months after vaccination, the four patients with stage III disease were recurrence-free. Two patients with lung metastases had disease recurrence shortly after the last vaccination, but both had a complete response to subsequent treatment with the anti-PD-1 antibody pembrolizumab, with evidence of expansion of their neoantigen-specific T-cell repertoires⁸. In the second study, Sahin *et al.*⁹ enrolled 13 patients with stage III or IV melanoma, and used personalized RNA-based ‘poly-epitope’ vaccines: two synthetic RNAs, each encoding five

linker-connected 27-amino-acid (27mer) peptides, corresponding to 10 selected neoantigens per patient (and five in one patient), were delivered via injection into the inguinal lymph nodes. After eight doses, T-cell responses against 60% of the 125 mutations represented in the poly-neoepitope vaccines were detected; each patient developed an immune response against at least three mutations. Eight patients who had no visible tumours at the time of vaccination remained disease-free 12–23 months later. The remaining five patients had relapses and progressive disease at the time of vaccination; notably, in one of these patients, combined treatment with an anti-PD-1 antibody resulted in a complete response⁹. The results of these two studies confirm the immunogenicity of melanoma neoantigens, as observed in a previous proof-of-concept clinical study of a dendritic-cell vaccine¹⁰.

So, what is the next step for the development of cancer vaccines? Randomized phase II studies with larger cohorts of patients will be necessary to assess the actual therapeutic activity of these vaccines. Studies are also needed to optimize the nature of the vaccine components, assess the relative advantage of peptide versus RNA-based approaches, and to develop combination therapies, evaluate their dosing, and ultimately their timing. Future immunological studies will refine the mechanisms of vaccine responses and their clinical efficacy. In the two clinical trials^{8,9}, most of the responses detected involved CD4⁺, rather than CD8⁺, T cells, underscoring the need for further studies to uncover the location of specific T-cell subsets (blood versus tumour versus lymph nodes), as well as their function in the control of cancer. Furthermore, whether the observed responses are attributable to reactivation of memory T cells or priming of naive T cells is not known; even when an anticancer immune response is undetectable in baseline blood samples, memory T cells might be present at frequencies below the detection threshold, and/or might reside in other tissues. A critical question that is at the core of this approach, and remains to be solved, is which antigens should be targeted in tumours with a low mutational burden and, possibly, a low frequency of cancer-specific memory T cells that can be reinvigorated. Immunologically dormant neoantigens might be uncovered, or possibly induced, during chemotherapy, radiotherapy, and/or targeted therapy, with the clonal selection of cancer cells potentially facilitating

enrichment of otherwise poorly represented neoantigens. Under these conditions, the limited choice of mutated peptides will require the development of highly immunogenic vaccines to prime a new T-cell repertoire. Thus, our improved understanding of the functions of dendritic cells might prove essential, by enabling the development of cell-based vaccines that elicit an immune response to rare mutations that is sufficient to induce a novel repertoire of efficient effector T cells.

We are confident that the coming years will witness the emergence of cancer vaccines as a major modality for the management of cancer. Through a logical, evidence-based approach, building on the immense amount of knowledge that has been generated in immunology over the past 50 years, what started more than 100 years ago with empirical findings related to therapeutic cancer vaccines will be transformed into a major instrument of the therapeutic armamentarium.

Jacques Blanchereau and Karolina Palucka are at
The Jackson Laboratory for Genomic Medicine,
10 Discovery Drive, Farmington,
Connecticut 06032, USA.

jacques.blanchereau@jax.org;
Karolina.Palucka@jax.org

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Competing interests statement

The authors declare no competing interests.