

# Predicting the efficacy of cancer vaccines by evaluating T-cell responses

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In a preclinical experimental model of human papilloma virus (HPV)-induced cervical carcinoma, we have shown that the efficacy of cancer vaccines can be predicted by the evaluation of vaccine-induced T-cell responses in healthy subjects. We argue that such knowledge can be used to screen candidates for vaccination, which in turn may accelerate the development and increase the overall efficacy of cancer vaccines.

The rationale for the development of cancer vaccines has considerably benefited from key findings regarding the role of the immune system in cancer biology. Accumulating evidence based on experimental mouse models and cancer patients has led to the concept that the immune system controls cancer development.<sup>1</sup> Notably, the clinical outcome of specific types of cancer is associated with the local presence of T cells<sup>2</sup> (Fig. 1A). Moreover, the identification of tumor-associated antigens<sup>3</sup> that are sufficiently immunogenic to induce bona fide CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses (and in some cases also antibody responses) has stimulated the development of various tumor antigen-based vaccines. The antitumor efficacy of such vaccines correlates with the induction of T-cell responses<sup>4</sup> (Fig. 1B).

The identification of immune correlates of protection upon vaccination against pathogen-induced diseases has become an increasingly important pursuit.<sup>5</sup> Besides providing mechanistic insights, such correlates facilitate the prediction of the correct choice of antigens and adjuvants to include (or exclude) in vaccines, allow for the determination of the susceptibility of individuals and populations following vaccination and permit the validation of vaccines without the assessment of field efficacy. Antibody levels are most commonly used as correlates of protection,

and more recently specific T-cell responses have been employed as correlates or co-correlates of vaccine-induced immunity. Given the importance of T cells for the eradication of malignant cells, the development of predictive factors based on tumor-specific T-cell responses is desirable, and such immune correlates would be of great benefit for the development and assessment of anticancer vaccines.

Our recent work (Fig. 1C) has addressed whether the efficacy of therapeutic cancer vaccines can be predicted by evaluating vaccine-induced T-cell responses in healthy subjects.<sup>6</sup> The therapeutic vaccination of mice bearing established subcutaneous human papilloma virus (HPV)-positive tumors with long peptide epitopes adjuvanted with Toll like receptor (TLR) ligands (i.e., CpG oligonucleotides, poly-ICLC and lipopoly-saccharide variants) resulted in diverse outcomes, ranging from negligible to full tumor regression. By testing the same vaccines in tumor-free mice, we found an excellent discriminating immune response profile between efficient and non-efficient vaccines based on the CD8<sup>+</sup> T-cell phenotype and magnitude of response. Evaluation of vaccine-induced T-cell responses in healthy subjects can thus predict the efficacy of cancer vaccines, which enables improved and accelerated identification of candidates for vaccination.

In our experimental model, the generation of effector-memory CD8<sup>+</sup> T cells appeared to be the best prognostic factor for vaccine efficacy. Together with the observation that in cancer patients the presence of such cells has a favorable effect on survival,<sup>2</sup> these findings support the idea that the elicitation of effector-memory cells is critical for positive clinical outcomes and the efficacy cancer vaccines. Effector-memory cells are characterized by the production of the effector cytokines interferon  $\gamma$  (IFN $\gamma$ ) and tumor-necrosis factor  $\alpha$  (TNF $\alpha$ ) and—phenotypically—by reduced levels of CD62L and an elevated expression of killer cell lectin-like receptor G1 (KLRG1). These phenotypic markers have a better predictive value (at late time points post-vaccination) than the magnitude of the global vaccine-specific T-cell response.

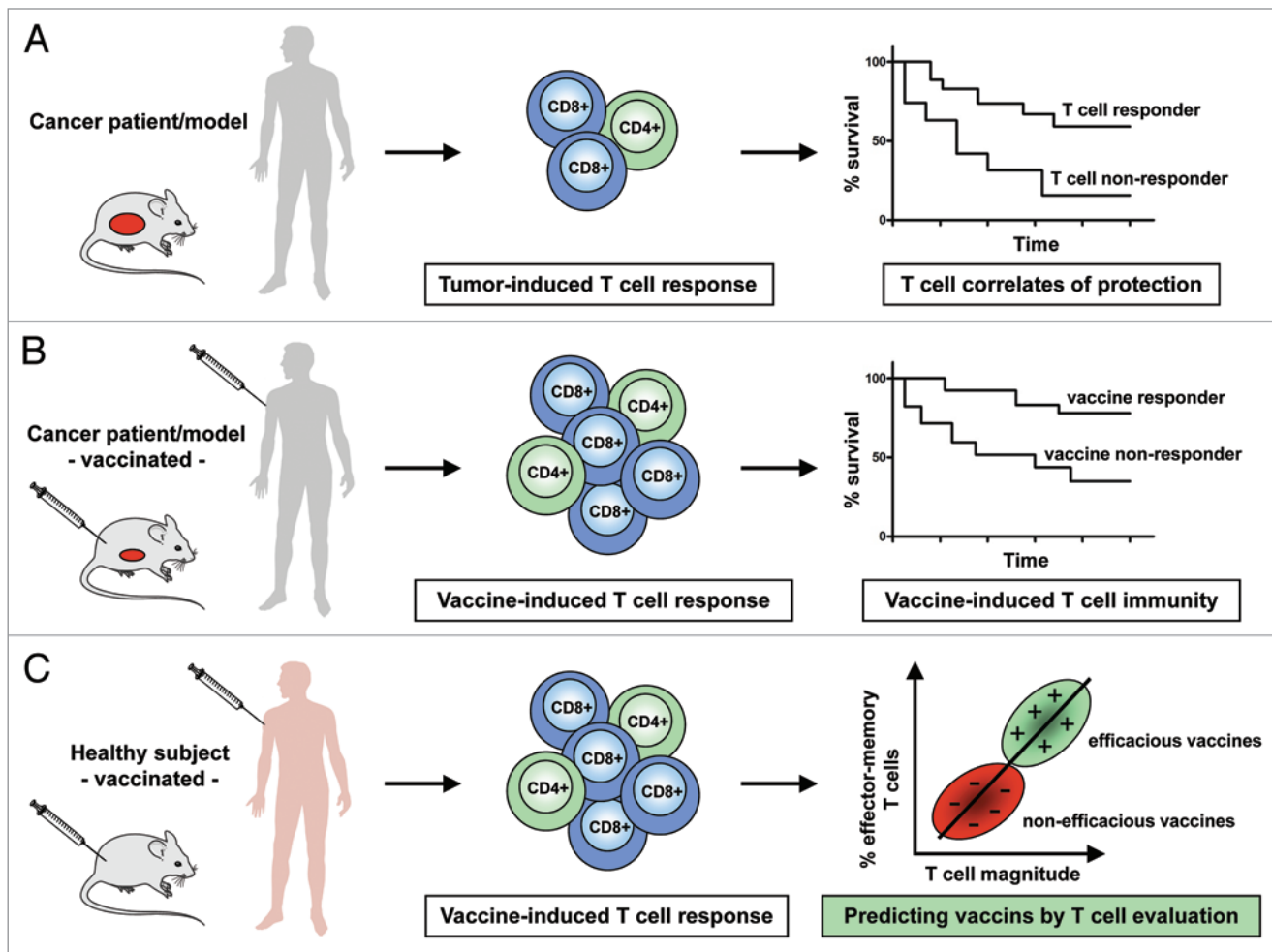
Long peptide vaccination combined with specific TLR agonists apparently leads to the generation of effector-memory cells. However, the mechanisms underlying this phenomenon remain unclear. It would be of interest to study whether vaccine formulations based on other agents have a similar capacity to elicit effector-memory cells in order to decipher whether common pathways for effector-memory T cell development exist. In this respect, it is interesting to note that cytomegalovirus (CMV) is a strong inducer of effector-memory T-cell

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**Figure 1.** T-cell responses and the prediction of anticancer vaccine efficacy. Impact of tumor-specific T-cell responses (A) and vaccine-induced T-cell responses (B) on the survival of cancer patients or tumor-bearing mice. Evaluation of T-cell responses in healthy subjects predicts the efficacy of cancer vaccines (C).

populations, and exploiting this property by developing CMV-based vaccines has led to promising pre-clinical results.<sup>7</sup>

Although it seems that a predominant effector-memory T-cell response is vital for the efficacy of therapeutic cancer vaccines, the induction of at least some central-memory T cells is likely important as well. Central-memory T cells have an unprecedented expansion and survival potential while effector-memory T cells have immediate effector-cell function and can migrate comparatively faster (when they are not present already in extra-lymphoid tissues).<sup>8</sup> Thus, the induction of a heterogeneous mixture of tumor-specific T cells appears to be ideal, but the optimal ratio of effector-memory vs. central-memory T cells presumably differs in each tumor setting.

Immune evasion by neoplastic cells is an important factor contributing to tumor progression.<sup>1,9</sup> Mechanisms of immune evasion by tumors include dampening of immune activation processes (e.g., the downregulation of MHC molecules and T-cell costimulatory pathways) as well as the facilitation of the suppressive arm of the immune system (e.g., the induction of regulatory T cells and myeloid-derived suppressor cells). Although preparing potent vaccine formulations that elicit strong T cell responses could overcome some of these evasion mechanisms, certainly not all escape strategies can simply be defeated by increased numbers of tumor-specific T cells. In highly active antiretroviral therapy (HAART) for human immunodeficiency virus Type 1

(HIV-1)-infected patients, the virus is subjected to selective pressures by cellular immune responses directed against the viral proteome as well as by the antiretroviral treatment, targeting a few HIV-1-specific processes.<sup>10</sup> Likewise, in cancer patients, combinatorial treatments that counter-attack multiple potential immune evasion mechanisms might reduce the number of escape mutants. If targeting several tumor immune evasion mechanisms were possible in the clinical setting without major adverse effects, this could synergize with the induction of effector-memory T-cell responses by vaccines.

**Disclosure of Potential Conflicts of Interest**  
No potential conflicts of interest were disclosed.

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