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Cancer vaccines: translation from mice to human clinical trials

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Therapeutic cancer vaccines have been a long-sought approach to harness the exquisite specificity of the immune system to treat cancer, but until recently have not had much success as single agents in clinical trials. However, new understanding of the immunoregulatory mechanisms exploited by cancers has allowed the development of approaches to potentiate the effect of vaccines by removing the brakes while the vaccines step on the accelerator. Thus, vaccines that had induced a strong T cell response but no clinical therapeutic effect may now reach their full potential. Here, we review a number of promising approaches to cancer vaccines developed initially in mouse models and their translation into clinical trials, along with combinations of vaccines with other therapies that might allow cancer vaccines to finally achieve clinical efficacy against many types of cancer.

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Introduction

Cancer vaccines have been long sought as a therapy that could marshal the exquisite specificity of the immune system to fight cancer without the side effects of other less precisely targeted therapies. Despite successes in preventing cancers in mouse models, the difficulty in treating large established tumors in mice, together with failures in translation to humans, led to the expectation that cancer vaccines may not be feasible [1,2]. The successful pivotal trial and licensing of Sipuleucel-T (Provenge) in 2010 reinvigorated the field, despite the limited increase in survival time [3]. More academic labs and companies have invested in cancer vaccines since that milestone event. However, concurrently, other forms of immunotherapy have emerged that have taken hold of the field and attracted most of the new effort. These include checkpoint inhibitors such as anti-CTLA-4, anti-PD-1, and anti-PD-L1 that block immunoregulatory mechanisms inhibiting the immune response to cancer and allow the immune system to reject the cancer in some cases [4,5,6••,7], and adoptive T cell therapies, involving T cells from patients selected for their anti-tumor activity or genetically engineered to express a T or B cell receptor targeting a cancer antigen, that are expanded ex vivo and infused [8••,9,10,11••]. Both of these approaches have now been licensed by the Food and Drug Administration (FDA) and are showing impressive results in certain malignancies. At the same time, newer cancer vaccines are emerging that also show great promise, and it is becoming clear from animal models that cancer vaccines can synergize with both checkpoint inhibitors [12,13••] and adoptive cell therapy [2,8••,14–16]. Moreover, the barrier to success of many cancer vaccines now appears to be the presence of so many immunosuppressive mechanisms in cancer that inhibit the immune response in the tumor microenvironment even when the vaccine can induce a response that is measurable systemically. Besides checkpoint molecules, there are immunosuppressive cytokines like TGF-beta [17–19] and IL-10 [20], and immunosuppressive cells like T-regulatory cells [21–23], myeloid-derived suppressor cells [24–27], regulatory NKT cells [28], tumor-associated M2 macrophages [27,29,30], B-regulatory cells [31], tolerogenic dendritic cells, and others. Therefore, we believe that the future of cancer immunotherapy is to combine cancer vaccines with these other therapies, especially treatments to overcome immunosuppression.

Here, we will review a sampling of cancer vaccines, including two from our own lab and several from others, that were originally developed in mouse models and then successfully translated into human clinical trials showing promising results. While this short review cannot cover a comprehensive survey of the field, these examples will illustrate how preclinical mouse tumor models are effective to develop cancer vaccines that can work in humans, and how different strategies for cancer vaccines can benefit cancer patients and potentially synergize with methods to overcome immunosuppression. Thus, cancer vaccines should soon become the third pillar of cancer immunotherapy and a key component of combination immunotherapy.

Novel promising cancer vaccine strategies from the Vaccine Branch, National Cancer Institute, NIH

Both the cellular and the humoral arms of the immune system can be used to attack cancer. However, antibodies are limited to detecting tumor antigens on the surface of intact tumor cells, whereas T cells can detect any protein made in the cell, because fragments of all proteins made are transported to the surface by Major Histocompatibility Complex (MHC) molecules such as human leukocyte antigens (HLA antigens), which serve an internal surveillance mechanism [32]. Thus, most cancer vaccines have aimed to induce T cells, because these can recognize any protein-based tumor antigen. Here, we will illustrate examples of both.

In order for peptide fragments of protein tumor antigens to bind to MHC molecules, they must fit in the peptide binding groove, and higher affinity binding usually corresponds to greater immunogenicity [33]. Tumor antigens did not evolve to be good MHC binders, so we developed a strategy called '*epitope enhancement*' in which we modified the sequence to improve affinity without affecting the surface seen by the T cell receptor (TCR), so that we could still elicit T cells recognizing the unmodified antigen [34–36]. Others have seen similar improvements by such epitope enhancement of cancer antigens [37,38] or modifications improving T cell recognition [39]. We applied epitope enhancement to peptides we mapped to bind to HLA-A*0201, the most common human class I MHC molecule, present in nearly half the population, from TARP, a prostate and breast cancer antigen described by Ira Pastan's lab [40]. We showed improved immunogenicity in HLA-A2-transgenic mice and ability to recognize the natural sequence, and confirmed this with human T cells, which could kill human cancer cells [41]. We translated this to a phase I clinical trial in HLA-*0201 stage D0 prostate cancer patients, in which a rising prostate-specific antigen (PSA) indicated microscopic recurrence after prostate removal, despite no radiographic evidence of tumor. In this setting, the rate of rise of PSA is a validated predictor of clinical course and response to therapy [42–47]. Patients got immunized 5 times with peptides either in Montanide-ISA51 adjuvant or coated onto autologous dendritic cells (DCs), and since the two arms gave comparable results, they were pooled for statistics. We found that 74% of vaccinated patients had a decreased PSA slope at 1 year compared to their own baseline slope ($p = 0.0004$), and the median tumor growth rate constant fell in half ($p = 0.003$), with no significant adverse events [48••] 78% also made a new T cell response to the peptides. Based on these results, a randomized placebo-controlled phase II trial, with more peptides to expand beyond HLA-A*0201, has been opened.

Human epidermal growth factor receptor 2 (HER2) is a driver oncogene product expressed on the surface of about 25% of breast cancers and to a lesser extent on many other solid tumors, where it is accessible to antibodies. Monoclonal antibodies to HER2, and other HER2-directed agents, have already shown clinical benefit [49–51]. However, no vaccine is available to induce such antibodies. We made an adenovirus expressing the extracellular and transmembrane (ECTM) domains of rodent HER2 and used it to immunize either HER2 transgenic mice that develop autochthonous breast cancers or wild type mice with large established syngeneic TUBO breast tumors [52–54]. The vaccine prevented growth of the autochthonous tumors and cured nearly 100% of mice with large established TUBO mammary tumors (up to 2 cm), and established lung metastases [54], but surprisingly was independent of effector T cells, requiring only antibody production. The HER2 antibodies were Fc-receptor (FcR) independent, unlike trastuzumab [55], but rather blocked HER2 phosphorylation [54]. We translated this to a human phase I trial with an adenovirus expressing human HER2 ECTM, used to transduce autologous DCs. First tested in non-breast cancer patients naïve to HER2 therapies (with gastroesophageal, colorectal, ovarian, lung and bladder cancers), it was safe and showed clinical benefit in 5/11 (45%) of evaluable patients at the second and third dose levels [56]. This trial has now been opened to breast cancer patients who have failed other HER2-directed therapies. In addition, there are peptide-based and other vaccines under study to induce T cell responses to HER2 [57,58].

Representative other examples of promising novel cancer vaccines

Prostvac

Cancer/testis antigens and other antigens whose expression is limited to cancer and non-vital organs, can be a good target for vaccines. A hurdle of targeting such antigens is that we need to break self-tolerance. Prostate-specific antigen (PSA) is such a self-antigen expressed in prostate cancer. Schlom and his coworkers developed PROSTVAC to deal with this problem by incorporating two simultaneous approaches. One is the use of viral vectors expressing PSA, which induces strong inflammation to induce massive T cell responses. The viral vaccines in therapeutic use have been shown to be able to break tolerance in multiple mouse tumor models [59–61]. Furthermore, they have demonstrated that the T cell-mediated immune responses induced by a viral vector can be maximized by taking a prime-boost strategy in which immune responses were primed by a recombinant vaccinia virus followed by boosts with a recombinant fowlpox virus [62,63]. Second is to strengthen co-stimulation for T cells by transducing genes of three co-stimulator molecules, LFA-3, ICAM-1 and B7, whose ligands are CD2, LFA-1, and CD28, respectively (together called TRICOM vectors). The effect of the combination is more dramatic when there is a weak TCR signal or low frequency of T cells against target cells [64]. These