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Rethinking cancer vaccines to avoid T-cell traps

“While we can avoid the T-cell trap of incomplete Freund’s adjuvant by the use of short-lived adjuvants, the only avoidance of the potential for a tumor T-cell trap is to vaccinate cancer patients earlier in their disease course.”

KEYWORDS: adjuvants ■ cancer vaccines ■ incomplete Freund’s adjuvant ■ Montanide ■ T cells



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Cancer vaccines have gained increasing popularity since the US FDA approved the first cancer vaccine, sipuleucel-T, in 2010 and then approved the active specific immunotherapeutic agent, ipilimumab, in 2011. Several other recently reported positive randomized trials have started reversing the seemingly endless flow of failed cancer vaccine trials [1–4]. This has not been a complete reversal, however, with the recent report at ASCO that the Stimuvax trial failed to meet its primary end point in lung cancer; however, there was a significant improvement in overall survival in a large subset of over 800 patients. Since the majority of cancer vaccine trials have been performed in melanoma, this disease entity has endured more than its share of cancer vaccine failures. However, melanoma has taught us more than any other disease about the endogenous immune response to cancer. Specifically, multiple immunogenic peptides have been described from melanoma-specific antigens such as p-mel and MART-1 that efficiently induce and expand T cells with the capacity to recognize and destroy melanoma cells expressing these antigens. It is understandable then why these peptides have been the focus of many early and ongoing clinical trials. As with most vaccines, the antigenic focus of the vaccine must be joined with an immunoadjuvant to enhance its effectiveness. Incomplete Freund’s adjuvant (IFA) is a water-in-oil emulsion specifically designed not only to enhance the immunogenicity of vaccines but also to serve as a slow-release source of antigen to the immune system. IFA has been one of the most commonly utilized cancer vaccine adjuvants to date and has been frequently used with peptide-based vaccines, especially in melanoma trials. Unfortunately, the vast majority of these peptide/IFA vaccine trials have been negative with rare objective clinical

benefit demonstrated [5]. This has resulted in a variety of more complex vaccination strategies, the search for better tumor-associated antigens and the expansion of the cancer vaccine field beyond melanoma.

In a recently published study from the University of Texas, MD Anderson Cancer Center (USA), Hailemichael *et al.* have specifically addressed the clinical observation from multiple clinical trials that peptide/IFA cancer vaccines effectively and efficiently induce large numbers of peptide-specific cytotoxic T lymphocytes (CTLs), yet fail to produce measurable tumor responses [6]. In an elegant series of experiments, these authors systematically address how these peptide/IFA vaccines initially induce robust peptide-specific CTLs, yet ultimately lead to antigen depots that attract these antigen-specific T cells back to the sites of inoculation instead of to tumor sites. Once at the inoculation sites, these CTLs undergo antigen-driven dysfunction and ultimately deletion.

These authors used a short peptide gp100/IFA vaccine as a means to raise pmel-1 T cells in a mouse model. After showing that this vaccine was effective in raising antigen-specific CTLs, they further show that these T cells did not persist and were unresponsive to boosting, unlike similar T cells that were induced with a virally delivered gp100 vaccine. Furthermore, the latter strategy was negatively impacted if the gp100/IFA vaccine was used to boost the pmel-1 T cells, resulting in a loss of these T cells and loss of substantial memory. These observations were confirmed with another antigen (ovalbumin)-based/IFA vaccine, suggesting that their findings were not restricted to gp100. Furthermore, they suggested that the mechanism of unresponsiveness was not the classical high-zone tolerance since their findings persisted even with small doses

After discussing their findings in the context of multiple clinical trials using IFA with a variety of cancer antigens that have demonstrated reactivation of old inoculation sites, the authors finally conclude “the recognition that persistent antigen at vaccination sites induces strong sequestration and subsequent dysfunction and deletion of vaccination-induced T cells directly points to desired characteristics of new classes of vaccines based on nonpersistent and rapidly biodegradable vaccine adjuvants.” In addition to their suggestion for short-lived vaccine preparations, the authors clearly demonstrate the efficiency of short peptide-based vaccines for eliciting large numbers of tumor-reactive CTLs. Now we have at least some explanation for the ineffectiveness of these peptide-based vaccines using IFA in clinical trials despite the pronounced T-cell responses seen.

Our own research group’s experience has been with peptide-based vaccines but using GM-CSF as an adjuvant as opposed to IFA and targeting HER2. The latter is a widely validated tumor-associated antigen in breast cancer that has been extensively studied, akin to gp100 in melanoma. Immunogenic short peptides have been described from the HER2 sequence and E75 is by far the most well-studied peptide [9]. E75 + adjuvant as a vaccine has been evaluated in a series of Phase I trials [10–13]. All of the trials have shown an effective and efficient expansion of E75-specific CTLs and all but one trial showed that these T cells had antitumor activity. Interestingly, the only trial to show the absence of antitumor killing was the only trial to use IFA [11]. The remainder of the trials utilized GM-CSF.

“Our group’s preferred approach to cancer vaccines is peptides (both short and long) mixed with GM-CSF and injected intradermally.”

GM-CSF as an adjuvant has also met with some criticism, but it is the immunoadjuvant in sipileucel-T, the only vaccine to reach FDA approval, as well as multiple other vaccines in late-phase testing. The issue of GM-CSF-induced myeloid-derived suppressor cells has only been reported in late-stage melanoma patients and appears to be at least partially dose-dependent. The benefits and potential issues of GM-CSF as an adjuvant have been thoroughly reviewed by our research group elsewhere [14].

Our group’s preferred approach to cancer vaccines is peptides (both short and long) mixed

with GM-CSF and injected intradermally. The skin is our largest immunologically active organ and is specially equipped for dealing with foreign or dangerous invaders. GM-CSF effectively induces a cellular infiltrate and helps mature professional APCs, which have ready access to the draining lymph node via the subdermal lymphatic plexus. Very little of the GM-CSF reaches the systemic circulation as it is rapidly consumed locally. As shown in the reviewed article, short peptides are efficiently and ubiquitously presented to the immune system. There has been a suggestion that this overpresentation of CTL epitopes may lead to tolerance (hence the potential benefit of longer peptides that require processing by professional APCs), yet this was not seen in the present study with the short-lived preparation vaccine. We have seen, in our Phase I/II trials of E75 + GM-CSF, very efficient expansion of peptide-specific T cells with the ability to recognize and lyse HER2-expressing cells even at low levels of antigen expression [13,15–17]. Furthermore, these E75-specific CTLs can be repeatedly boosted over years without signs of unresponsiveness [18]. More importantly, these vaccine-specific CTLs appear to confer clinical benefit by reducing the recurrence rate in patients receiving the vaccine in the adjuvant setting. In fact, we have recently reported the final 5-year follow-up results of our E75 + GM-CSF Phase II trial in the adjuvant setting. Among the 187 patients (108 HLA-A2/A3⁺ vaccinated; 79 HLA-A2/A3⁻ controls), the 60-month recurrence rate was reduced by 50% in the vaccinated patients [19].

The latter trial design separates our clinical studies from many other cancer vaccine trials that seek to treat established tumors in later-staged patients. All of our trials have been aimed at clinically disease-free patients at risk of recurrence. Interestingly, we have been able to correlate the clinical benefit in our vaccinated patients with the magnitude of their immune response to the vaccine, a feat that has eluded most therapeutic vaccines [17]. However, the latter situation is complicated by the likely trafficking of T cells to sites of disease burden. Unfortunately, the potential of T-cell trapping and antigen-driven T-cell dysfunction in a hostile environment may also apply to the site of an established tumor. While we can avoid the T-cell trap of IFA by the use of short-lived adjuvants, the only avoidance of the potential for a tumor T-cell trap is to vaccinate cancer patients earlier in their disease course.

Disclaimer

The views expressed in this article are those of the author and do not reflect the official policy of the Department of the Army, Department of Defense or the US Government.

Financial & competing interests disclosure

GE Peoples holds multiple patents on peptide vaccines to include E75. Many of these patents have been licensed to

commercial entities. GE Peoples also consults for these entities in the further development and testing of these vaccines. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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