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Peptide Vaccine Strategies in the Treatment of Cancer

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Abstract

The goal of vaccine researchers has been induction of a specific and active immune response, which offers patients cancer therapy with limited toxicity and long-standing protection. There have been great strides made toward this goal, as evidenced by the recent FDA approval of Sipuleucel-T (Provenge). The simplest, most efficacious and most affordable vaccine strategy, however, remains an area of great debate. Multiple strategies exist, varying by number and type of target, as well as delivery method. The following review will summarize the most promising strategies for application of the cancer vaccine strategy, focusing on the bright future of peptide-based vaccines.

There have been great advances in immunotherapy for the treatment of cancer in the last decade. The clinical success of recently FDA approved ipilimumab in advanced melanoma demonstrates the strength of the immune system in treating cancer. This monoclonal antibody, through CTLA-4 blockade, uses a non-specific activation of the immune system, augmenting the natural immune response to tumors by decreasing T cell inhibition. The lack of specificity, however, leads to substantial, and sometimes life-threatening, autoimmune toxicity [1,2] which shows the destruction that an uncontrolled immune response can cause. The use of Tumor Associated Antigen (TAA)-specific monoclonal antibodies (ie. trastuzumab, cetuximab, rituximab) has become commonplace in standard oncology practices. The specificity of these therapies significantly decreases the side-effect profile. Monoclonal antibodies are a type of passive immune therapy, which does not induce immune memory and, thus, offers no ongoing immune protection after completion of therapy. The goal of cancer vaccine researchers has been to achieve specific stimulation of active immunity, which should offer both safety and long-standing benefit. The recent FDA approval of Sipuleucel-T (Provenge), the first cancer vaccine to achieve such approval, has sparked renewed enthusiasm for the potential of cancer vaccines. The following review will focus on advances in the development of an effective cancer vaccine, primarily discussing peptide-based, HLA-presented cancer vaccines.

Attempts to create an efficacious cancer vaccine have led researchers to a number of targets. Some advocate for a more broad stimulation of immunity to entire (autologous or allogenic) tumor cells or to whole proteins within a tumor cell. These strategies allow patients to generate a personalized immune response—by cleaving and processing peptides that are HLA-specific and most immunogenic to the individual. These strategies, however, rely on the individual's immune system to efficiently lyse, process, and present the limited number and relatively low concentration of immunogenic epitopes within the much larger structures. This also creates difficulty assessing immune responses to the numerous potential targets within the tumor cell or protein. Often, clinical response is the only reliable marker of success and this, to date, has remained elusive for this approach. An alternative is to utilize a known immunogenic peptide, derived from a TAA, as the target. This can be done in a number of ways. One approach is a DNA vaccine which involves injection of a bacterial plasmid that encodes the desired antigen. This antigen is then produced by the host cell. This strategy again uses the body's machinery to process and present the desired immunogenic peptide. This strategy can be easily monitored with immunologic assays that can identify specific immune responses against the target peptide. It again relies, however, on often unreliable and inefficient mechanisms of antigen processing and presentation without a real sense of the amount of effective epitope presentation that is taking place.

In order to more efficiently stimulate immune responses against a specific immunogenic peptide, many researchers have advocated for giving the peptide itself as a vaccine. The most effective method of delivering this peptide, however, continues to be widely debated. One popular method is dendritic cell (DC)-mediated vaccines. This strategy involves drawing a patient's blood, isolating and artificially maturing circulating monocytes into DCs, then priming them against an immunogenic peptide(s). These primed DCs, are then re-injected into a patient as a vaccine. DCs are seen as the most important type of antigen presenting cell (APC) for developing immunity to specific antigens [3] and are, therefore, the most common target cell in these vaccines. The most promising results with this type of therapy were recently published in the results of the IMPACT trial. Kantoff et al. [4] conducted a double-blind, placebo-controlled, randomized phase III trial of Provenge, a cellular immunotherapy consisting of APCs that have been activated against a prostate antigen and GM-CSF fusion protein. Men with metastatic, castration-resistant, prostate cancer were randomized to three infusions of Provenge vs. placebo. The vaccinated group showed a 22% relative reduction in risk of death and a 4.1 month improvement in median survival. These results led to the first FDA approval of a cancer vaccine.

Despite these promising results with Provenge, the production of this vaccine is elaborate and expensive, which raises a number of

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questions about the practicality and financial viability of this strategy. The process of isolating, maturing and priming APCs must be repeated for each patient and in sufficient amounts for multiple infusions. This process creates high costs that make widespread application of this technology less feasible. A full course of three treatments with Provenge, for example, costs roughly $93,000 [5], which translates to a cost of $23,250 for each month of increased survival.

The high costs of cell-mediated vaccines make a cancer vaccine that is more easily produced and with a larger target population more commercially appealing, particularly in a time of increased scrutiny of the cost of healthcare. A simpler approach is a peptide-based vaccine, which combines an immunogenic peptide and an immunoadjuvant in one solution, which is then injected subdermally. Though typically limited to a specific TAA, and often to a specific HLA-type, peptide vaccines are not specific to an individual patient. Thus, a large number of patients could potentially benefit from one commercially prepared vaccine in this simple, affordable approach. A recent study conducted by Rahma and colleagues [6] compared DC-mediated and peptide-based vaccines directly. They randomized patients with advanced ovarian cancer to receive either a wild type-p53 peptide vaccine or a DC-mediated vaccine. They found that there was no significant difference in response or survival between the two groups and concluded that the "less demanding" peptide vaccine strategy may be preferable. Slingluff et al. [7] conducted a similar clinical trial in melanoma patients, where they randomized patients to receive multiple melanoma peptides either as a soluble peptide vaccine or a DC vaccine. Their results showed a significantly improved cytotoxic T lymphocyte (CTL) response rate (measured by ELISPOT, 22% vs 75%, p=0.017) as well as a non-significant increased objective clinical response rate (15% vs 8%) in the peptide vaccine group compared to the DC group. While DC vaccine trials have shown promise, peptide vaccines offer the potential of similar efficacy with lower cost and a larger potential market.

Peptide vaccines have been shown repeatedly to induce a specific and sometimes long-lasting response by the immune system, both in vitro and in vivo [8-11]. Despite this encouraging immunologic data, clinical response rates have been inconsistent, fueling the debate over how best to administer peptide vaccines. One area of debate has been which class of MHC molecules and, therefore, which population of T cells, must be targeted in order to elicit an effective response. It is clear that involvement of the CD8+, or CTL, population is necessary to have the ability to directly lyse tumor cells. Stimulation of CD4+ T cells alone can sufficiently cross-prime CTLs to lyse tumor cells [12] and also may lead to greater immunologic memory [13]. What remains unclear is whether stimulation of CTLs, CD4+ T cells, or a combination of both is the optimal strategy. To investigate this question, Zeng et al. [14] developed a single NY-ESO-1-specific peptide containing HLA-DP4-restricted helper T-cell epitope as well as an HLA-A2-restricted cytotoxic T-cell epitope. They vaccinated patients with different segments of this long peptide, giving the CD4+ T cell and CD8+ T-cell epitopes separately as well as both in one peptide. Their results showed that vaccination with neither the HLA-DP4-restricted peptide alone nor the full combination peptide generated as effective CTL activity as the HLA-A2-restricted peptide alone. Slingluff et al. [15] conducted a similar study in advanced stage melanoma patients. All patients in this study received vaccination with 12 MHC Class I-restricted peptides and were then randomized to vaccination with either a tetanus helper peptide (control) or a mixture of six melanoma-associated helper peptides (6MHP). The assumption was that the addition of melanoma-associate helper peptides would augment the magnitude and persistence of CD8+ T cell response. They found, however, that CD8+ T cell responses to the 12 peptides that all patients were vaccinated against were significantly decreased in the 6MHP arm (78% vs 19%, p<.001) [15].

Multiple theories have arisen as to why CD4+ T cell stimulation may not augment CTL activation [16-18]. Slingluff et al. stated that one possible explanation is induction of regulatory T cells by the helper peptide vaccine [15]. Zhou et al. supported this theory, showing that broad stimulation of CD4+ T cells increased circulating regulatory CD4+ T cells, which correlated with a decreased CTL response on re-challenge of peripheral blood lymphocytes [19]. Whether peptide presentation through MHC Class II molecules will serve to augment CD8+ T cell responses to vaccines remains to be seen, but this is an interesting area of continuing research.

As discussed with Slingluff's work above, another method for developing a more effective immune response is to give multiple peptides in one vaccine. This strategy has the advantage of developing immunity to multiple TAAs to prevent selection of cancer cells that do not express a targeted TAA under immunologic pressure. Additionally, by administering a vaccine with multiple peptides with differing HLA-binding abilities, it may be possible to make a single vaccine formulation that is effective in all populations without HLA-typing. Rosenberg, et al. studied the effects of vaccination with two peptides emulsified together in one solution. Their results demonstrated a decreased response to either peptide when the two were given in a combination vaccine as compared to each peptide given alone [20]. They, therefore, concluded that mixing peptides in this manner negatively impacted response to vaccination and hypothesized that this may be due to competition for binding to MHC molecules. Prior to studying the combination of peptides within a single vaccine, investigators have conducted trials investigating single peptide vaccines. This strategy has the advantage of ensuring clarity in immunologic and clinical data; removing potential confusion regarding which peptide or strategy is responsible for eliciting an immune response, toxicity and any clinical successes.

Despite the apparent over simplicity of a single peptide vaccine, Rosenberg and colleagues demonstrated that vaccination with a single peptide could augment the clinical benefit of standard-of-care IL-2 therapy in patients with metastatic melanoma. Their phase II trial using a combination of vaccination with an HLA-A0201-restriced peptide derived from gp100 (a well known melanosomal glycopeptide) plus IL-2 showed an objective response rate of 42%, which was higher than the established rate of IL-2 2 alone (17%) [21]. These encouraging results led to a phase III trial, the results of which were recently published. This trial by Schartzentruber et al. involved randomization of 185 patients with advanced cutaneous melanoma to either IL-2 or vaccination with a gp100 peptide and Montanide ISA-51 (immunoadjuvant), followed by IL-2. There was a significant improvement in clinical response (16% vs 6%, p=0.03) and median overall survival (17.8 months vs. 11.1 months, p=0.06) for patients randomized to receive the vaccine [22]. These results have increased the interest in the use of peptide vaccines for the treatment of cancer.

Despite these results, there is evidence that large tumor burden can generate an environment that allows for tolerance and likely immune escape from the effects of vaccine therapy [23,24]. Therefore, active immunotherapy may be more effective when administered in the adjuvant setting to patients with minimal residual disease and, hence,

less cancer-induced tolerance. This has been the focus of our early work with the E75 peptide, a nine amino acid, MHC class I-restricted, peptide derived from the extracellular domain of the HER2 protein. As reviewed by Mittendorf et al., E75 vaccines were shown in multiple trials to be safe and effective in eliciting a peptide-specific immune response [25]. Our group has completed phase I/II trials investigating E75 mixed with the immunoadjuvant GM-CSF administered to node positive and high risk, node negative breast cancer patients in the adjuvant setting. At the time of our initial, planned analysis of this trial at a median follow-up of 20 months, the recurrence rate was 5.6% in the vaccine group vs. 14.2% in the unvaccinated controls (p=0.04) [26,27]. After a median follow-up of 60 months, there has been a persistent decrease in recurrences observed in the vaccinated patients compared to the control patients (10.6% vs 20.3%, p=0.098). Although the difference has lost statistical significance, we have used the data from these trials to identify a population of patients most likely to benefit from vaccination: patients with node-positive breast cancer with low to intermediate HER2 expression (1+ or 2+ by immunohistochemistry) [28]. A phase III trial randomizing HLA-A2/3+ patients meeting these criteria to E75+GM-CSF versus GM-CSF alone has received Special Protocol Assessment approval from the FDA and will begin enrolling patients in early 2012.

Our promising results in the adjuvant setting were supported by Apostolopoulos et al. They conducted a randomized, double-blind trial in which 31 patients with Stage II breast cancer who were clinically disease-free were vaccinated with either placebo or a MUC1-based glycopeptide vaccine. After a median follow-up of 5.5 years, they reported a recurrence rate of 27% in control patients vs 0% in vaccinated patients (p = 0.029) [29]. These encouraging results showed that vaccination can be quite effective when used to prevent recurrence in disease-free cancer patients.

Our work with the E75 peptide vaccine has shown the efficacy of a single peptide vaccine that is MHC-Class I-restricted. We have also completed a phase I trial investigating AE37, a modified peptide derived from the HER2 protein's intracellular domain that is an MHC class II-restricted and targets a CD4+ T cell response. This phase I trial demonstrated this vaccine to be safe and capable of eliciting a specific immune response. We are currently conducting a phase II trial investigating vaccination with AE37. We are also interested in using AE37 as a component of a multi-eptiope vaccine. As discussed above, previous attempts by Rosenberg et al. as well as Zeng et al. [14], at combination vaccines have led to some troubling results. We are currently conducting a Phase I trial to study our combination strategy, which involves concurrent, but separate, vaccination with both CD8-eliciting and CD4-eliciting peptides. Having systematically tested the individual peptide vaccines prior to combining them will hopefully lead to clarity in interpreting toxicity, immunologic, and clinical results.

In conclusion, there is great interest in the use of the immunotherapy to treat malignancy. There are numerous approaches to this interesting clinical problem, and it is likely that there will be roles for many, but the simplicity and potential broad applicability of peptide vaccines make this strategy particularly enticing. The recent publication of promising results with the gp100 vaccine gives credibility to the clinical effectiveness of these vaccines, but future studies may reveal this strategy to be even more effective in the adjuvant setting to prevent recurrence. Our future work will pursue advancement of the peptide vaccine strategy into broader applications, targeting multiple TAAs in hopes of advancing cancer therapy.

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