Melanoma Vaccines: What We Know So Far

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Vaccines are a promising but still experimental treatment for melanoma. They are intended to stimulate immune responses against melanoma and by so doing, increase resistance against and slow the progression of this cancer. Key requirements for vaccines to be effective are that they contain antigens that can stimulate tumor-protective immune responses and that some of these antigens are present on the tumor to be treated. Unfortunately, these antigens are still not known. To circumvent this problem, polyvalent vaccines can be constructed containing a broad array of melanoma-associated antigens. Several strategies are available to construct such polyvalent vaccines; each has advantages and disadvantages. Clinical trials have shown that vaccines are safe to use and have much less toxicity than current therapy for melanoma. Vaccines can stimulate both antibody and T-cell responses against melanoma, with the type of response induced, its frequency, and its magnitude depending on the vaccine and the adjuvant agent used. A growing body of evidence suggests that vaccines can be clinically effective. This evidence includes correlations between vaccine-induced antibody or T-cell responses and improved clinical outcome, clearance of melanoma markers from the circulation, improved survival compared to historical controls, and most convincingly, two randomized trials in which the recurrence-free survival of vaccine-treated patients was significantly longer than that of control groups.

There is an urgent need for better treatments for melanoma. No therapy prolongs survival in patients with widely disseminated disease. Only one treatment is approved by the US Food and Drug Administration (FDA) for patients with resected disease at high risk of progression-interferon alfa-2b (Intron A)-and it has limited effectiveness as well as frequent and potentially severe side effects.

Vaccines are receiving increasing attention as a still-experimental treatment for this cancer. Theoretically, vaccines should permit the selective and safe destruction of melanoma cells. The rationale for believing that melanoma vaccines can be effective, the relative advantages and disadvantages of the different strategies used to construct melanoma vaccines, and the results obtained to date are summarized below.

Rationale for a Melanoma Vaccine

The progression of melanoma is influenced by immune factors, and stimulation of these factors with vaccines can increase resistance to this cancer.[1] The two most compelling observations that support this belief are:

![Partial Regression of Primary Melanoma](image)

Partial Regression of Primary Melanoma

(1) In vivo mechanisms can kill melanoma cells selectively, without harming normal melanocytes. This is evidenced by the partial regression of melanoma in 15% to 20% of primary lesions,[2,3] and by the rare but dramatic, spontaneous, and complete regression of advanced tumors.[4] Partial regression in primary melanomas is actually visible as areas of white depigmentation within the tumor (Figure 1). The white areas are due to the destruction of melanoma cells. As regression occurs spontaneously without any treatment, it clearly indicates that humans possess protective mechanisms that have the ability to destroy melanoma cells. These defense mechanisms are very
selective, as they destroy melanoma cells without harming adjuvant normal melanocytes. This is evident from the skin adjacent to areas of regression retaining its normal pigmentation. The selectivity of this process, which destroys malignant melanocytes without harming normal melanocytes, indicates it is mediated by immune mechanisms, as only the immune system has the exquisite ability to recognize the difference between malignant and normal cells. Stimulating these immune defenses is the purpose of vaccines.

FIGURE 2

Prevention of Melanoma in Mice by Vaccine Immunization

(2) Vaccines can markedly increase resistance to melanoma—at least in animals. Murine B16 melanoma is invariably fatal when injected into mice, killing all within 6 to 8 weeks. By contrast, almost all mice preimmunized to vaccines against melanoma can survive,[5] as illustrated in Figure 2. The protection is specific for melanoma. Melanoma vaccine-immunized mice are not protected against an unrelated tumor. This specificity indicates that the protective mechanisms stimulated by vaccine treatment are immunologic in nature.

Tumor Regression vs Absence of Progression

An incidental observation in mice has an important implication for the clinical impact of vaccine treatment in humans and the end point of such trials. That is, vaccine-treated mice can live in an apparent state of good health for months while bearing large tumors that would invariably and rapidly kill nonimmunized mice. This is apparent from examining vaccinetreated mice that survive challenge with lethal doses of melanoma cells. Such mice appear clinically healthy, gain weight, and have no evidence of tumor. Yet autopsy performed months after tumor challenge reveals that many of the animals have very large melanomas in their internal organs, of a size that would kill nonimmunized mice within days.

Thus, the degree of resistance induced by vaccine treatment in these animals was insufficient to cause tumor regression, but was sufficient to prevent tumors from continuing to progress and kill the animals. The implication of this observation extended to humans is that vaccine treatment may improve survival by slowing tumor progression rather than by causing tumor regression. It implies that the key end point in evaluating vaccine clinical trials should be absence of tumor progression rather than the conventional end point of tumor regression.

Additional observations supporting the idea that immune mechanisms play an important role in slowing the progression of melanoma include the presence on melanoma cells of antigens that are either unique or present in larger amounts than on normal melanocytes, the ability of these antigens to stimulate antibody and/or T-cell responses in patients with melanoma, and the infiltration of lymphocytes into melanoma nodules of vaccinetreated patients.[6] Investigators have noted correlations between the presence of these immune responses and an improved clinical outcome, indicating that these responses can play an active role in controlling the progression of melanoma.[7-11]

Thus, there are theoretical reasons for believing that vaccines can increase resistance to melanoma and practical observations that they actually do so in animals. The challenge is to develop vaccines that will be as effective in humans.

What Is Required for Melanoma Vaccines to Be Effective

Melanoma vaccines are intended to stimulate patients' immune systems to react more effectively against their own melanoma and, by so doing, destroy the tumor or slow its progression. To do so, the vaccines must satisfy several requirements. The two most important are:

(1) The vaccine must contain antigen(s) that can stimulate tumorprotective immune responses.
(2) Some of these antigens must be present on a patient's own tumor; otherwise, the vaccine-induced immune responses will be unable to recognize and attack the tumor.
A number of other requirements must be satisfied for a vaccine to be effective and practical to use, as discussed subsequently. Vaccines must also be safe to use, their composition well characterized, and their manufacture reproducible. To retain their potential to provide cost-effective therapy, the vaccines should be relatively simple to prepare and administer.

**Challenges in the Design of Melanoma Vaccines**

Unfortunately, there are major problems satisfying the two major requirements described above.

- **Selection of Antigens Used to Prepare the Vaccine**—This is the most critical issue in preparing a cancer vaccine, as the vaccine must contain antigen that can stimulate tumor-protective immunity or it will not work. Although many antigens associated with melanoma have been identified, we do not know which ones are appropriate for this purpose. Establishing this ability is arduous, requiring a large-scale phase III randomized clinical trial of each antigen, to demonstrate objectively whether it slows the progression of melanoma. Taking into account the number of candidate antigens, the size and expense of phase III trials, and the limited number of melanoma patients available, it is not possible to conduct such trials for every currently known melanoma-associated antigen and for new ones that will be discovered. Thus, it will be difficult to find out which melanoma antigens actually stimulate protective immunity against this cancer and should be used to construct vaccines.

- **Antigenic Heterogeneity**—Another complication in selecting antigens to construct melanoma vaccines is that some of the unknown antigen(s) that stimulate protective immunity must also be expressed by the tumor to be treated. Unfortunately, the expression of tumor antigens by melanoma cells is heterogeneous. It varies between melanomas in different individuals, between different tumor nodules in the same individual, and between different melanoma cells within the same tumor nodule. [12-14] Furthermore, the actual antigens expressed by residual melanoma cells in a patient at the time treatment is instituted cannot be known. A solution suggested to circumvent this problem is to prepare autologous vaccines from a patient’s own tumor. However, this would not resolve the problem, because there is no assurance that the antigens present in the tumor tissue used to prepare the vaccine will be the same as those in the residual tumor(s) that need treatment.

- **Antigen Modulation**—The pattern of antigens expressed by tumor cells can change during tumor progression. [15] This reflects the changes that occur in tumors as they metastasize, in part due to immunologic pressures on the tumor. Vaccine-induced immune responses destroy tumor cells bearing the targeted antigen(s), resulting in the selection and expansion of surviving cells that lack these targets and that now resist the action of the vaccine.

Thus, it is unknown which antigens should be used to construct melanoma vaccines, whether these are expressed by the tumor to be treated, or whether they will still be there once treatment begins.

- **HLA Restriction**—Some immune responses that are critical in tumorprotective immunity, such as antigenspecific CD8+ and CD4+ T-cell responses, are human leukocyte antigen (HLA) restricted. As a consequence, each vaccine peptide antigen will induce these responses only in patients who have the particular type of HLA molecule that can bind that peptide. As there are a large number of HLA molecules, and as the expression of each varies from individual to individual, only a minority of patients express the HLA molecule required to bind a particular peptide. Even the most common HLA molecule (HLA-A0201) is expressed by only 40% of white individuals, the population most at risk for melanoma. Many HLA molecules are expressed by only a small percentage of patients to be treated. Thus, even if one could identify a peptide capable of stimulating a tumor-protective cellular response, a vaccine made from that peptide would at best be effective in less than half of the population at risk for melanoma. Because of the variable expression of antigens on melanoma cells, the proportion of patients who can theoretically benefit from vaccines prepared from any one antigen is even smaller.

- **HLA-Unrelated Heterogeneity in Immune Responses**—Independent of HLA restriction, investigators have also found heterogeneity in the ability of different patients to develop cellular immune responses to antigens. [16] That is, patients who express the same HLA phenotype and who are immunized identically to the same antigen can vary in their ability to develop a CD8+ T-cell response to that antigen. This is not due to lack of immune competence by the patients, as patients who do not respond to one peptide will respond well to another peptide presented by the same HLA molecule. Similar heterogeneity is seen in the ability of individuals to develop antibody responses. [17] This heterogeneity further limits the proportion of patients who can develop effective antitumor immune responses to any single antigen.

- **Number of Antigens Required to Induce Effective Protective Immunity**—It is unknown whether clinically effective tumor-protective immunity in humans can be induced by immunization to
a single antigen or whether responses against multiple antigens are required for cancer cells to be killed. Even if immune responses to a single antigen can kill melanoma cells, stimulating responses to multiple antigens should do so more effectively. Thus, the larger the number of antigens in a vaccine, the better it should work. However, there is a price to be paid for increasing the number of antigens in a vaccine, as described below.

Polyvalent Vaccines

One strategy that can minimize the problems listed above is to construct "polyvalent" vaccines that contain a large number of different tumor-associated antigens. The greater the number of antigens in a vaccine, the greater the chance that it will contain the still-unknown antigens that stimulate tumor-protective immunity. The greater as well will be the chance that some of the effective antigens in the vaccine will be expressed by the patient's own tumor, and that some of these antigens will be recognized in the context of the patient's own HLA haplotype. Furthermore, stimulation of immune responses against multiple targets on melanoma cells should increase the chances of killing these cells and minimize the chances that tumor cells will be able to downmodulate the expression of all the targeted antigens to avoid immune attack. Reflecting this strategy, the field of melanoma vaccines has moved sharply in the recent past from constructing vaccines from single, highly purified, antigens to polyvalent vaccines that contain a broad range of antigens.

Constructing Polyvalent Cancer Vaccines

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Relative Advantages of Cancer Vaccine Design Strategies

Three strategies are currently available to construct polyvalent cancer vaccines that contain many tumor antigens. They differ in the purity and number of tumor antigen(s) used to prepare the vaccine. In one strategy, the vaccines are prepared from nonpurified antigens; in another, from antigens that are partially purified; and in the last, from pure antigens. None of the strategies is completely satisfactory; each has certain advantages and disadvantages, as listed in Table 1 and discussed below.

The dilemma is that while nonpurified vaccines contain multiple tumor antigens and thus are more likely to contain relevant antigens, these account for only a very small fraction of the material in the vaccine. The bulk of the material in such vaccines is irrelevant and possibly detrimental. Conversely, vaccines prepared from pure antigens do not contain any irrelevant material, but it is uncertain whether the few selected are "correct" antigens that stimulate protective immunity. Partially purified vaccines strike a middle course between these two polar approaches.

- **Nonpurified or Cellular Vaccines**—The traditional method of constructing cancer vaccines is to prepare them from whole tumor cells or their nonpurified extract. The tumor cells are often pooled from different donors to increase the number of tumor antigens in the vaccine. Examples of such vaccines, which are currently in advanced clinical trials, include Canvaxin, a polyvalent vaccine prepared from three lines of intact, irradiated, melanoma cells combined with bacille Calmette-Gurin (BCG) as an adjuvant[18]; Melacine, a mechanical lysate of two melanoma cell lines admixed with Detox as an adjuvant (Salmonella endotoxin and components of mycobacterial cell wall) [19]; autologous melanoma cells conjugated to a hapten[20]; and lysates of cells infected with vaccinia or other nonpathogenic viruses.[21,22]

The tumor cells can be genetically engineered to express certain cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) or other molecules or antigens that may increase the ability of the cells to stimulate desired immune responses.[23-27] Genetic vaccines made from DNA or RNA extracted from tumor cells fall into the category of nonpurified vaccines, as such vaccines will code for many molecules other than the ones of interest.

Cellular vaccines are made either from a patient's own tumor cells (autologous vaccines) or from those of other patients (allogenic vaccines). It is claimed that autologous vaccines have an antigenic
profile that more closely resembles what is present on a patient's remaining tumors. However, this claim is uncertain for the reasons discussed earlier. Autologous vaccines can only be used in patients with advanced disease who have bulky tumors that can provide the amount of tissue required for vaccine preparation. They are costly, as a custom vaccine must be made for each individual patient. The major advantage of nonpurified vaccines is that they contain the widest variety of tumor antigens. The major drawback to this approach is that tumor antigens constitute only a small fraction of the material in the vaccine. The overwhelming bulk of material in the vaccine is irrelevant and dilutes the concentration of the relevant antigens. In addition, the nonantigenic material may decrease effectiveness due to the presence of suppressive or immunoinhibitory factors[28] or to stimulation of competitive immune responses to unrelated antigens. Furthermore, the irrelevant material may contain components that increase toxicity.

- **Vaccines Prepared From Pure, Defined Antigens**—The polar opposite approach is to prepare polyvalent vaccines from a cocktail of purified or defined antigens.[29-35] This is now feasible as a result of the identification and purification of some melanoma-associated antigens recognized by antibodies or T cells.[36] Use of peptides that are recognized by T cells and that are derived from melanoma-associated antigens is particularly favored because these can be readily manufactured. The amino acids can be substituted to increase their binding affinity to HLA and boost their immunogenicity.[37,38]

The major advantages of this approach are that pure antigen vaccines are more easily characterized and prepared in a reproducible manner than nonpurified vaccines, that the concentration of antigen in the vaccine is high, and that there is little irrelevant contaminating material. The approach is elegant and takes advantage of major advances in our understanding of melanoma immunology, and for these reasons, is attractive to scientists. However, this approach has several drawbacks, chief of which is the fact that the appropriate antigens remain unknown. These vaccines are made from available antigens, not from those known to induce clinically effective immune responses. Most of the vaccines prepared using this strategy are based on antigens that are HLA-A0201 restricted, because this is the most common HLA phenotype expressed by patients with melanoma. However, this phenotype is expressed by less than half of patients who develop melanoma. That, together with the restricted expression of these antigens in different melanomas, means that such vaccines cannot be used in most patients. The number of melanoma antigens that can be used to prepare such vaccines is also strictly limited to the small number (approximately a dozen) that have been identified. This number is further restricted by intellectual property rights issues, which make it difficult to obtain permission to use the antigens.

Thus, vaccines made from purified antigens, while attractive scientifically and from a manufacturing perspective, can only be prepared from a sharply limited number of antigens whose clinical effectiveness is not known. Consequently, their ultimate chances of being clinically effective is probably less than that of more broadly polyvalent vaccines. The purified vaccine in the most advanced stage of clinical testing is a ganglioside vaccine constructed from GM2 conjugated to KLH and administered with the adjuvant QS21.[33] Other purified antigen vaccines are still in early phases of clinical trials. Most of these are prepared from peptides derived from the melanoma-associated antigens MAGE-1, MAGE-3, Melan A/Mart-1, tyrosinase, NYES01, or gp100, which are recognized by CD8+ T cells.[29-32] Some vaccines are prepared from monoclonal antibodies to gangliosides GD2 or GD3. The use of these anti-idiotypic monoclonal antibodies is an alternative approach to stimulating responses to tumors using a purified protein.[34,35,39]

- **Vaccines Prepared From Partially Purified Tumor Antigens**—The third design strategy attempts to balance the advantages and disadvantages of the two approaches described above. It does so by preparing vaccines from the extract of melanoma cells that are enriched in the cellular elements most likely to contain tumor antigens relevant for vaccine therapy, and depleted of material likely to be irrelevant.

The advantages of this approach are that it retains the most critical element required for vaccine effectiveness, ie, that the vaccine contains a very broad range of tumor antigens, while being much purer than vaccines prepared from whole tumors. Such vaccines are intended to retain the advantages of cellular vaccines while minimizing their disadvantages. Two examples of this approach are currently in clinical trials. One is a polyvalent vaccine made from antigens shed by melanoma cells.[40] This preparation exploits a natural phenomenon—the rapid release or shedding of cell-surface material by tumor cells that are in culture. Because cell-surface material is released much more rapidly than the bulk of unrelated cellular material in the cytoplasm
and the nucleus, it is partially purified and enriched in surface antigens. To increase the spectrum of melanoma antigens in the vaccine, the cell lines used for vaccine production were selected based on each expressing different and complementary patterns of melanoma-associated antigens. The vaccine contains multiple melanoma antigens including MAGE-1, MAGE-3, MelanA/Mart-1, tyrosinase, gp100, S100, TRP-1, and other immunogenic antigens ranging in molecular weight from 30 to 150 kd, which are expressed by melanoma cells in vivo.[16,41] It is made from allogeneic melanoma cell lines maintained in cell banks, so that the vaccine is generic (an individual vaccine does not have to be made for each patient) and can be administered to all patients regardless of their HLA phenotype.

The other approach being used to prepare a partially purified vaccine is to construct it from autologous heat shock proteins (HSPs).[42,43] HSPs are a family of proteins produced in response to stress. They function as chaperones that transport peptides within cells. Purified HSP provides a source of multiple processed peptides that include both normal self-peptides and tumor antigen-derived peptides.[42,43] These compounds may be enriched with peptides able to bind to HLA class I, and thus it is hoped may be particularly effective in stimulating T-cell responses. The HSP vaccine furthest in development is Oncophage, which is based on purified gp96 HSP.[43] This vaccine is made from the patient's own tumor cells, which, like all autologous vaccines, restricts its use to patients with melanomas sufficiently bulky to provide the material required for vaccine preparation.

**Adjuvant Strategies**

The immune responses induced by tumor antigens are weak. Hence, a critical component of all cancer vaccines is an adjuvant used to enhance the ability to stimulate strong immune responses. Adjuvants can enhance immune responses by a wide variety of mechanisms. The approaches in use include modifications of the physical or biochemical properties of the antigens[44]; various types of emulsions or bacterial extracts such as alum, incomplete Freund's adjuvant, BCG, QS21, or Detox; slow-release vehicles such as liposomes[50]; immunomodulators such as interleukin-2 (IL-2, Proleukin), IL-4, IL-12, interferon gamma (Actimmune), GM-CSF (Leukine), T-helper cell epitopes[30]; and the use of antigen-presenting cells such as dendritic cells.[31,32,45] Other approaches include coupling the antigen to strongly immunogenic molecules such as KLH[46] or to a hapten[20]; binding the antigen to the surface of inert beads or other structures such as immunostimulating complexes (ISCOMs); using recombinant techniques to express the antigen of interest on viruses such as vaccinia or adenoviruses[47]; or transfecting tumor cells to express molecules that hopefully will increase their immunogenicity.[23-27]

These approaches can be used alone or in combinations. They all can enhance vaccine immunogenicity, but little is known about their relative effectiveness. Different adjuvants potentiate humoral and cellular immune responses differently, and their effect can vary depending on the antigen with which the adjuvant is coupled. Thus, results obtained with one vaccine-adjuvant combination will not necessarily translate to another vaccine coupled with the same adjuvant. One of the more effective adjuvant strategies is to present the antigen on dendritic cells. These are professional antigen-presenting cells that are potent inducers of T-cell immunity.[31,32,45,48] There are a variety of approaches to loading the antigen(s) onto the dendritic cells, but it is not clear which results in the most effective vaccine. Early clinical trials with dendritic cells pulsed with melanoma peptides have shown immune responses and some clinical responses,[49] but this approach is limited by the need to obtain the dendritic cells from the patient to be treated; ie, a custom vaccine must be prepared for each individual patient.

Another promising approach is to encapsulate the vaccine into liposomes together with a small amount of a cytokine such as IL-2 or GM-CSF that can upregulate immune responses. This has the advantage of greatly prolonging the half-life of the cytokine and delivering it together with the vaccine antigen(s) to draining lymph nodes where stimulation of immune cells occurs. This approach markedly increases melanoma vaccine-induced cellular immune responses in humans.[50]

In summary, adjuvants are required to improve the effectiveness of vaccines for melanoma. A large number of these agents are available, but it is unclear which is best. These choices, however, further complicate the selection of the vaccine.

**Clinical Trials of Melanoma Vaccines**

TABLE 2
Melanoma Vaccines: What We Know So Far

Several melanoma vaccines are currently in clinical trials. A partial list of these preparations is provided in Table 2.[3,18-27,29-35,40,43,45] Three criteria are used to evaluate their clinical activity: safety, immunologic activity (ability to stimulate immune responses against melanoma), and clinical effectiveness (ability to slow the progression of melanoma). Vaccines have proven very safe to use. Their ability to induce antimelanoma immune responses varies with the vaccine and adjuvant used. Little information is available on the clinical effectiveness of most of these vaccines, as the bulk of them are still in early phase I or II trials.

Safety

Little toxicity has been seen in the several thousand patients treated with melanoma vaccines to date. That which has occurred was usually due to the adjuvant rather than the vaccine.

The most common side effects are local reactions at the site of injection such as induration, swelling, or pain, which normally clear in a few days. Ulcerations can occur if an irritating adjuvant such as BCG or Detox is used. Other potential toxicities include swelling of nodes, chills, fever, and infections. The more serious side effects are usually due to the adjuvant, and depend on the adjuvant used. They can range from self-limited transfusion-type reactions to dendritic cell vaccines to very severe systemic toxicity in patients receiving high doses of cytokines such as IL-2.

There are two potentially severe but theoretical side effects. One is enhancement of tumor growth, which could occur if the vaccine induces the wrong type of immune response. This has occurred in animals and has been reported in a few vaccine-treated patients with advanced disease, where it is not possible to determine whether the rapid tumor growth resulted from the vaccine or from the natural behavior of advanced melanoma. In the vast majority of melanoma vaccine trials, no adverse effect on tumor progression has been reported.

The other concern is that of inducing autoimmunity, particularly against normal melanocytes, which in some cases has resulted in vitiligo or uveitis. These changes have not been associated with functional disturbances or induction of autoimmunity to other organs. However, autoimmunity may become a larger problem as stronger adjuvants are used to enhance the immunogenicity of the vaccines that may break down tolerance to normal tissue antigens.

As all cancer therapy is toxic, the real issue is not whether vaccines have toxicity, but whether that toxicity is more common or severe than alternate treatments. Vaccines are clearly less toxic than the current FDA-approved therapy for resected melanoma at high risk of recurrence, ie, interferon alfa-2b, which causes major toxicity (grade 3/4) in two-thirds of patients.[51] By contrast, less than 1% grade 3 toxicity and no grade 4 toxicity was observed in a group of over 200 patients who were treated with a shed antigen vaccine. Thus, whatever its merit, vaccine treatment provides a quality-of-life advantage.

Immunologic Activity

Immunologic activity is the most common end point currently used to judge the activity of cancer vaccines. It is an important parameter, as vaccines will not be effective unless they can stimulate
potent and clinically effective antitumor immune responses. Unfortunately, it is difficult to use this end point to compare the activity of different vaccines. The results depend on the type of immune responses that are measured, how they are measured, and when they are measured, and the manner in which these parameters are measured varies between trials. Complicating comparisons is that the assay procedures used to measure these responses are not standardized.[52] In addition, the clinical relevance of the different types of vaccine-induced immune responses remains unclear. The frequency with which vaccines induce antitumor immune responses and the type of response they stimulate is related to the nature of the vaccine and the manner in which it is administered. For example, peptide-based vaccines do not usually induce antibody responses; ganglioside vaccines stimulate antibody but not cellular responses; and cellular and protein-based vaccines can stimulate both types of responses. Potent adjuvants can markedly increase the frequency with which the same vaccine stimulates antibody and/or cellular responses. The frequency and magnitude of response normally increases with time and with the number of immunizations to an optimum level. However, overly intensive immunizations can sometimes lead to tolerance.

Both antibody and cellular immune responses against melanoma can be induced by the administration of vaccine treatment.[7-11,53-56] It is unclear which is the more important mediator of protective immunity and which should be used as the end point. The dogma, based mostly on animal studies, is that cellular responses are more important. In humans, however, there is good correlation between vaccine-induced antibody[7-9,53] or T-cell responses[10,11,54-56] and improved outcome. Probably, both types of responses are important, and their relative importance may depend on the actual nature of the response, the antigens against which they are directed, and the stage of the disease. Critical evaluation of this issue is difficult, as few trials evaluate both types of responses concurrently.

Clinical Effectiveness

There is increasing evidence that melanoma vaccines can be clinically effective, based on four different sets of observations: (1) correlations between vaccine-induced immune responses and improved clinical outcome, (2) the effect of vaccine treatment on intermediate markers of clinical outcome, (3) comparisons of survival with that of historical controls, and most convincingly, (4) the results of randomized trials.

Correlations between vaccine-induced immune responses and improved clinical outcome have been observed in multiple studies. Improved outcome is seen in patients with antibody[7-9,53,57] or T-cell responses,[10,11,54-56] so that both types of responses appear to be important in mediating tumor-protective immunity. Whether or not a correlation is present appears to depend on the antigen against which the response is directed. Thus, in one recent study, a correlation was found between vaccine-induced CD8+ T-cell responses to MAGE-3 and improved outcome, but none with CD8+ T-cell responses to tyrosinase.[10] Caution must be used when interpreting correlations in studies involving small numbers of patients, as the power and hence the confidence of such analysis is limited.

• Molecular Markers—It has recently been found that molecular markers of melanoma can be present in the blood, even in patients with resected disease. The markers include melanoma cells,[58] and individual proteins and antigens such as lactate dehydrogenase, S100, melanomainhibitory activity,[59] cytoplasmic melanoma-associated antigen (CYTMAA), human high molecular weight melanoma-associated antigen (HMWMAA), and total serum ganglioside levels. There can be correlations between the presence and/or level of these markers and the stage of melanoma, indicating the markers may reflect tumor load.FIGURE 3
What is interesting is that the presence of some of these markers can decrease in patients treated with melanoma vaccines, and that there can be a correlation between the decrease in marker and improved clinical outcome. For example, the proportion of patients with circulating melanoma cells decreased by over 55% following treatment with a polyvalent vaccine and the recurrence-free survival of those patients in whom melanoma cells disappeared was significantly longer than that of patients in whom circulating melanoma cells remained or appeared, as illustrated in Figure 3. The melanoma treatment-associated clearance of the marker from blood suggests the vaccine was clinically effective and may be clearing tumor deposits elsewhere in the body.

**Clinical Trial Results**—Vaccine treatment appears effective in prolonging survival in historically controlled studies. Most convincing are trials involving a large number of patients. Two are particularly compelling because of the size of the patient populations. Morton's group reported that in a matched-pair analysis, the 5-year overall survival rate of 107 patients with resected stage IV melanoma treated with a whole-cell vaccine was 39%, compared to 19% for the control group.

Bystryn's group reported that the overall survival of 94 vaccine-treated patients with stage IV disease was two to four times longer than that of similar historical controls matched for site of metastatic disease and presence of measurable disease—the two most powerful risk factors in stage IV melanoma. Particularly striking was the fact that 35% of patients with resected, nonvisceral disease survived 5 years, compared to 13% of historical controls.

A number of vaccines have been reported to induce occasional partial or complete regression of established tumors. Similar remission rates occur with almost all other modalities used to treat melanoma, so the significance of this observation is unclear.

### Results of Randomized Trials of Melanoma Vaccines

Several randomized, concurrently controlled, trials of melanoma vaccines have now been conducted (see Table 3). In two of these trials, the melanoma vaccine-treated patients did better than the control group. One trial was a double-blind placebo-controlled trial of a polyvalent, shed-antigen melanoma vaccine developed by Bystryn. The vaccine stimulates antibody responses to multiple melanoma-associated antigens expressed in vivo by melanoma, cellular responses to a patient's own melanoma in vivo, and CD8+ T-cell responses to multiple peptides derived from MAGE-1, MAGE-3, MART-1, tyrosinase, and TRP-1, which are presented by the class I HLA molecules most common among melanoma patients.

![Placebo-Controlled Trial of Melanoma Vaccine](image)

The recurrence-free and overall survival of patients with stage III disease treated with this vaccine is approximately 50% longer and that of patients with early-stage IV disease is two to four times longer than that of similar historical controls. In a double-blind placebo-controlled trial, the recurrence-free survival of the melanoma vaccine-treated patients was over twice as long as that of patients treated with placebo vaccine (Figure 4). This difference was statistically significant after
Cox multivariate analysis ($P = .03$). That said, the results must be interpreted cautiously as they are based on a small number of patients ($n = 38$).

The other promising randomized trial is that of Melacine, a vaccine prepared by Mitchell from the lysate of two melanoma cell lines enhanced with the adjuvant Detox. The response rate and median survival of patients with stage IV melanoma treated with the vaccine or with standard chemotherapy using the Dartmouth regimen were similar, but the vaccine produced less toxicity, resulting in improved quality of life.[62] A randomized trial of this vaccine in 689 resected stage II melanoma patients has been conducted by the Southwest Oncology Group.[19] Overall, the investigators found no difference in recurrence-free survival between the vaccine-treated patients and observation-only control group. However, in a preplanned subset analysis, the relapse-free survival was significantly prolonged in patients who were HLA-A2- or C3-positive.[19] These results suggest that a patient's HLA type can influence the results of vaccine therapy.

Another vaccine in advanced clinical trials is Canvaxin, an irradiated, whole-melanoma-cell, polyvalent vaccine developed by Morton and associates at the John Wayne Cancer Center (Santa Monica, Calif). In a case-controlled study, the recurrence-free and overall survival of stage III and IV patients treated with this vaccine was longer than that of similar historical patients treated by the same investigator.[18] This vaccine is currently in two large-scale phase III trials, with results still pending.

A vaccine prepared by Livingston from the purified ganglioside GM-2 has also been studied in a large-scale randomized trial, which demonstrated that it was less effective than interferon-alfa.[33] However, the trial may have been interrupted early, before the full benefits of vaccine treatment became evident. Two other large randomized trials of melanoma vaccines— one developed by Hersey, the other by Wallack—have been conducted in resected melanoma at high risk of recurrence.[21,22] Both vaccines consisted of viral lysates of melanoma cells. Neither trial showed a difference in outcome between the vaccine-treated and control groups.

A listing of melanoma vaccines in active clinical trials and a description of the entry requirements can be obtained from the National Cancer Institute at 301-496-4000, or online at www.nci.nih.gov/clinicaltrials.

### Indications for Melanoma Therapy With Vaccines

Melanoma vaccines are still experimental, and none has been approved by the FDA. However, taking into account the limited effectiveness and the toxicity of standard therapy for melanoma, experimental therapy is considered standard of care for patients with melanoma at high risk for recurrence or progression.[63,64] Because vaccines are experimental, they can only be administered in the context of a clinical trial.
There are no standard criteria for determining whether a patient is a candidate for vaccine treatment. Eligibility and exclusion criteria are set by the investigator(s) conducting a particular trial. Generally, the types of patients most often treated with vaccines are those with resected melanoma that has a high chance of recurrence, i.e., American Joint Committee on Cancer (AJCC) stage IIB (primary lesions 4 mm or thicker) or stage III (metastatic to regional nodes) melanoma. A few trials are being conducted in patients with thinner primary melanomas (lesions 1.5 to 4 mm in thickness or ulcerated) or with disseminated stage IV disease, either resected or with limited tumor load. While it is often believed that vaccines will not be effective in patients with advanced disease, two historically controlled but large studies suggest they can be effective in that setting.[18,60]

There are a few contraindications to vaccine treatment. They include widely disseminated disease, known allergies to any of the components used to construct the vaccine, concurrent administration of immunosuppressive agents, or underlying medical conditions that would contraindicate the use of the particular adjuvant used with a vaccine.

**Melanoma Prevention With Vaccines**

No discussion of melanoma vaccines should end without mention of their unique and potentially most significant application—the prevention of melanoma in individuals at high risk of developing this cancer. Such individuals can now be identified with a fair degree of precision based on genetic background, skin type, sun exposure, and presence of multiple intradermal and/or dysplastic nevi.
Some observations suggest that prophylactic melanoma vaccines may ultimately be feasible. It is well established that melanoma vaccines can prevent this cancer in animals.[5,65] It is also clear, in animals, that vaccines are more effective in preventing melanoma than treating it once the tumor is established. As noted above, cancer vaccines appear to be clinically effective in some patients. Consequently, the logic of the animal studies suggests that it should be possible for vaccines to prevent melanoma in humans and that, in fact, this might prove easier than treating patients who already have the disease.

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