The past three decades have seen substantial research on vaccines for the treatment of metastatic melanoma and the prevention of recurrence following resection. Despite their enormous promise, the actual results have been disappointing, with several high-profile vaccine clinical trials failing to show a benefit. Nonetheless, enthusiasm for melanoma vaccines remains and has increased with our expanding understanding of the immune response to tumor. Cellular vaccines can be divided into autologous, derived from the patient’s own tumor and allogeneic vaccines. Autologous vaccines have the advantage of containing all potentially relevant tumor-associated antigens for that particular patient. However, autologous vaccines are difficult to obtain from most patients with advanced disease and impossible to obtain from patients who present after resection of all clinically evident disease. No consensus exists for how tumors should be processed, preserved, modified, and delivered to serve as an effective vaccine. The amount of autologous tumor available is rarely enough to produce more than two or three vaccination doses, and the time between initial tumor harvest and ultimate availability of the vaccine may result in interval tumor progression that diminishes the likelihood of vaccine efficacy. All these drawbacks of autologous tumor vaccination limit its applicability and also limit the ability to test autologous vaccines in prospective trials. Allogeneic vaccines avoid many of these problems, but may not contain all of the tumor-associated antigens present on the patient’s own tumor. In particular, neoantigens created by mutations in the patient’s tumor would be unlikely to be represented in an allogeneic vaccine. Although allogeneic vaccines can be manufactured in sufficient quantities to allow large-scale trials, there remain significant limiting issues in the manufacture and standardization of the vaccine product.

Immunotherapy in general, and vaccine therapy in particular, has been widely studied in the management of melanoma. The reasons for this include the lack of effective conventional therapies for metastatic and high-risk melanoma, the now century-old observation that patients with melanoma occasionally have dramatic responses to immunologic manipulations, and most importantly, our continually expanding understanding of the human immune system and the mechanisms of antitumor immune responses. Despite the extensive effort to develop melanoma vaccines, none are currently available as approved therapeutics. Only a handful of vaccines have even been evaluated in phase 3 clinical trials that could potentially lead to regulatory approval. To date, none of these phase 3 trials has had an overall positive result. Moreover, virtually all of the vaccines that have reached a stage of development sufficient to allow phase 3 trials to begin have faced significant hurdles in terms of manufacturing, distribution, and quality assurance that have affected both the likelihood of obtaining regulatory approval and the ability to commercialize the vaccine (1, 2).

Where Have We Been?

The demonstration of a vaccine’s efficacy in melanoma seems relatively straightforward. Similar to other systemic therapies, a significant level of objective responses in patients with advanced disease would be required to achieve initial regulatory approval and then to consider expanding the indications via controlled clinical trials in the adjuvant setting. Unfortunately, the vaccines available have uniformly failed to result in significant levels of objective response in patients with advanced measurable melanoma (3). In a review of the National Cancer Institute experience with 440 patients who received a total of 541 different vaccines (most of whom were melanoma patients), only 4 complete and 9 partial responses were seen, for an overall response rate of 3% (4). A randomized comparison of a peptide-pulsed dendritic cell vaccine to single-agent dacarbazine in patients with advanced melanoma showed similarly low levels of objective response for the vaccine and a disappointing median time to progression and a median survival of 3.2 and 9.0 months, respectively, which were no different than those achieved with dacarbazine alone. Indeed, if anything, the dendritic cell vaccine–treated arm fared
slightly worse than the dacarbazine arm (5). These disappoint-
ing clinical results in patients with advanced melanoma are perhaps not surprising when one considers that most vaccines generate only weak immune responses (as detectable by current methods), and even these weak responses are difficult to detect in most patients. It is likely that those immune responses we do detect are not directly relevant to immune-mediated tumor destruction because the detection of an immune response has thus far not correlated directly with tumor regression.

In the face of these results, many have argued that vaccines are more appropriately tested in the adjuvant therapy setting than in the face of advanced measurable disease. It is an oft-stated, but never proven, tenet of tumor immunotherapy that the lower the tumor burden, the more likely a vaccine is to be successful. Certainly, this expectation makes intuitive sense and is empirically grounded in observations from vaccination for microbial diseases. However, remarkably few scientific data can be cited to corroborate this widely held supposition. Nonetheless, a number of randomized clinical trials have been conducted involving vaccines for the adjuvant therapy of melanoma.

One of the largest compared a GM(2) ganglioside vaccine (GMK vaccine, Progenics, Tarrytown, NY) to high-dose IFN in the adjuvant therapy of patients with resected melanoma at high risk of recurrence (primary tumors >4 mm or positive regional nodes). In this trial, antibody responses to the ganglioside immunogen were achieved in a high percentage of patients, but the overall study results were strongly in favor of IFN in terms of both relapse-free and overall survival (6, 7). In fact, the results were sufficiently in favor of IFN that the clinical trial was halted and the results disclosed early. Recently, two randomized trials of a polyvalent whole cell melanoma vaccine (Canvacxin, CancerVax, Carlsbad, CA) plus Bacillus Calmette-Guerin compared with Bacillus Calmette-Guerin alone in patients with resected stage III melanoma and resected stage IV melanoma (an even higher-risk population than in the aforementioned ganglioside study) were also halted early because of a lack of vaccine efficacy (8). One large randomized phase 3 trial of a different polyvalent melanoma vaccine (Melacine, Corixa, Seattle, WA) was conducted in patients with resected stage II melanoma. This trial had a negative overall result for both relapse-free and overall survival (9). A subset analysis, however, indicated an effect of the vaccine on relapse-free survival (10) and overall survival (11) for vaccine-treated patients expressing HLA antigens HLA-A2 or HLA-C3. This substantial subset of patients, accounting for 59% of the study patients, was deemed appropriate for a follow-up phase 3 clinical trial to verify the result. It was estimated that the completion and analysis of this second trial would likely take close to a decade. Faced with the uncertain prospect of a commercially viable product even after the commitment of an additional decade of support, the manufacturer of this vaccine simply decided not to support the follow-up randomized trial and terminated the development of Melacine. To date, efforts to secure development of the vaccine through alternative sources have been unsuccessful, although the technology to mass-produce this vaccine is relatively straightforward.

Where Are We Going?

Fortunately, the news on the vaccine front is not all bad. The disappointing results of the recent past have to be placed in the context of exciting developments in our understanding of the human immune system, the identification of new antigenic targets on melanoma tumor cells, and increasingly clever strategies to improve the effectiveness of antitumor vaccines. A few representative examples will be discussed. These are intended to illustrate different approaches that are being explored in clinical trials and are not intended to represent a catalog of all the efforts currently under way. Peptide and dendritic cell vaccines will be discussed separately and are not further covered herein.

**Autologous tumor vaccines.** Autologous vaccines have numerous theoretical advantages. Most importantly, they are likely to contain unique or rare tumor antigens that develop through mutational events. Autologous tumor vaccines are, of course, appropriately HLA-matched for optimum antigen presentation to T cells. Even in melanoma, however, a disease in which tumor tissue for autologous vaccination is relatively accessible compared with other malignancies, few patients have sufficient tumor available for most autologous vaccine strategies. Moreover, autologous tumor vaccines are virtually impossible to obtain from patients who present after resection of all clinically evident disease. When autologous tumor is available and harvested, no consensus as yet exists regarding how the tumor should be processed, preserved, modified, and delivered to serve as an effective vaccine. The amount of autologous tumor available is rarely enough to produce more than two or three vaccination doses, and the time between initial tumor harvest and ultimate availability of the clinical vaccine may result in interval tumor progression that diminishes the likelihood of vaccine efficacy.

Until recently, no autologous melanoma vaccine had ever been successfully tested in a phase 3 clinical trial. A phase 3 clinical trial using autologous tumor processed to extract heat shock proteins (Oncophage, Antigenics, New York, NY) has completed accrual. These proteins act as “chaperones” for peptide antigens within the cells and hence have the potential to present tumor antigens to the immune system in a readily recognizable manner (12, 13). This represents an innovative approach to the generation and testing of autologous tumor vaccines. Moreover, the extracted product is relatively quantifiable, which has important advantages for quality assurance in securing regulatory approval. The study accrued 322 patients (of 451 patients screened) who were randomized 2:1 to vaccine therapy versus physician’s choice of therapy, which could be interleukin 2, single-agent chemotherapy, or complete resection. Only the preliminary results of this trial are as yet available (in the form of a press release available on the internet), indicating no statistically significant benefit (or detriment) for the heat shock vaccine compared with physician’s choice of therapy (14). Of note, however, an intriguing preliminary observation is that the group of patients with M1a disease (skin, soft tissue, or nodal metastasis with a normal serum lactate dehydrogenase level) treated with the vaccine lived longer than those receiving physician’s choice of therapy, albeit not statistically significantly so (14). As we await the detailed and mature results of this phase 3 trial, the limitations of this approach remain apparent: only a percentage of melanoma patients have accessible tumor from which the heat shock protein autologous vaccine can be generated, the randomized clinical trial is being conducted in patients with advanced metastatic disease,
and the vaccine is being compared with a variety of therapies of varying efficacy. Whether the advantages of this particular autologous vaccine formulation will be sufficient to allow it to show clinical efficacy in a setting in which so many other vaccines have failed remains to be seen.

**Allogeneic vaccines.** Allogeneic vaccines are composed of intact or modified melanoma cells from other patients selected for the presence of shared antigens found on a large percentage of melanomas. They have significant advantages over autologous tumor vaccines in terms of availability for patients in all stages of the disease and provide the capability to administer multiple vaccinations over a protracted period. They may also be more inherently recognizable to the patient’s immune system than an autologous cell preparation. On the other hand, they may lack unique or rare antigens that could be important antigenic targets in any given patient’s melanoma. Although allogeneic vaccines are amenable to a degree of standardization and can be manufactured in sufficiently large quantities to allow large-scale randomized trials in multiple institutions, there remain significant issues in the manufacture and standardization of the final vaccine product that have had a notable adverse effect on the commercialization of vaccines.

One allogeneic vaccine that has overcome most if not all of the challenges regarding standardization and manufacture is Canvaxin, a polyvalent irradiated melanoma vaccine originally developed by Dr. Donald Morton and was commercially developed by CancerVax in partnership with Serono (Geneva, Switzerland) (15, 16). This vaccine has been studied in two multi-institutional randomized phase 3 trials in patients with resected stage III and resected stage IV melanoma. Recently, the Data Safety Monitoring Board overseeing these two studies determined that the trials were sufficiently unlikely to result in a determination of vaccine efficacy that each trial was ended and all protocol treatments were discontinued. This was certainly a disheartening result for everyone involved in melanoma therapy. Examining why these trials may have been negative is instructive and at the same time illustrative of the challenges facing melanoma vaccine researchers.

The two randomized trials using this promising allogeneic melanoma vaccine could have yielded negative results for any or all of the following reasons: the play of chance, the burden of disease, and/or the heterogeneity of the disease being treated. On the other hand, the negative results of the trials call into question the wealth of phase 2, historically controlled clinical data that was initially invoked to support the conduct of the phase 3 studies.

**The play of chance.** Any single randomized trial, if conducted exactly according to the study protocol under conditions that closely mirror the original statistical assumptions of the study designers, has a 5% (1 in 20) chance of being falsely positive, that is, showing a statistically significant difference when in fact none exists. Conversely, however, most studies are designed to have between a 10% and 20% chance of yielding a false-negative result when in fact a difference does exist. That is because most studies are designed with a statistical power of between 80% and 90%, and the value of 1 minus the statistical power is the likelihood of a false-negative trial result. If in fact, the study assumptions or the conditions of accrual do not match the prespecified expectations, the likelihood of a false-negative study could dramatically increase. In the current high-stakes environment of pharmaceutical development, many pharma-

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**The burden of disease and the clinical heterogeneity of the disease stage.** There are multiple reasons to anticipate that a vaccine would be more useful in patients with earlier stage compared with later stage disease (17). First, increasing evidence suggests that tumor progression leads to increases in tumor-induced immunosuppression, mediated by factors directly secreted by tumor cells and/or their microenvironment but also by the presence of increasing numbers of negative regulatory T cells (18). Moreover, increasing numbers of tumor cells are increasingly likely to express antigenic heterogeneity that would limit the ability of an induced immune response to completely eradicate the tumor (19). Finally, in a patient with a relatively high residual tumor burden (as is routinely the case in patients with resected stage IV melanoma), tumor progression could readily occur during the period required for initial induction of an immune response. In that case, a vaccination failure may be concluded before the vaccination had ever truly had a chance to be successful. Certainly, the cohort of patients with resected stage IV disease had a high tumor burden, and may in retrospect have been unlikely to derive much benefit from a relatively weak immunogenic stimulus. The group of patients with resected stage III disease constitute a more heterogeneous group, including some with very minimal tumor burden (e.g., a single microscopically positive sentinel lymph node) and others with significant tumor burden (e.g., multiple grossly positive palpable regional nodes). These patients could conceivably respond differently to allogeneic tumor vaccination, and further analysis of the mature results of this trial should shed light on the degree to which outcomes differed by initial clinical presentation.

**Robustness of the phase 2 clinical data.** Perhaps the most disappointing aspect of the failure of the two Canvaxin trials is the wealth of phase 2 clinical data which suggested that this vaccine was beneficial in this cohort of patients (15, 20, 21). In nonrandomized trials, Morton and colleagues treated 935 resected stage III melanoma patients with Canvaxin and compared their outcome to a contemporaneous historical control group of 1,667 patients who received similar surgical therapy but no vaccine. Median and 5-year survival rates were significantly higher for the vaccine-treated patients than the controls (56.4 versus 31.9 months median and 49% versus 37% alive at 5 years, respectively; \( P = 0.0001; \) ref. 20) This apparent benefit persisted even after matching vaccine patients to
controls for known prognostic variables. Similar benefits were seen in nonrandomized studies with this vaccine in patients with resected stage IV melanoma (21). In the absence of a fuller understanding of the specific study results, it must be concluded that the phase 2 nonrandomized data that seem so highly favorable to a vaccine intervention actually reflected nothing more than a strong selection bias for the most favorable patients to be treated with the vaccine.

**Conclusion**

Only time will tell what, if any, role vaccines will ultimately play in the treatment of patients with melanoma. The challenges facing allogeneic and autologous vaccine strategies in melanoma are multiple and substantial, but not insurmountable. There is no question that improvement in our understanding of the immune system and the development of clinical reagents to augment immune response to self-antigens and minimize the negative regulatory influences on the antitumor immune response will contribute to a renaissance for vaccine research. Well-conducted clinical trials will be the vehicle by which this renaissance may result in substantiated improvement in outcome for our melanoma patients.

**Open Discussion**

**Dr. Weinstock:** I was a little puzzled by your comment regarding the way we’re testing vaccines. Just giving patients one strike and they’re out is illogical and nonsensical. There is always a tradeoff between sensitivity and specificity in any test of efficacy of a new agent.

**Dr. Sondak:** What I’m saying is this is not restricted to vaccines. For new agents, a lot of pharmaceutical companies are simply saying, “We’ll give it one shot; we’ll do one trial in one group of patients, and if that’s negative, we’re just going to move onto something else.” Now, if we have such a plethora of agents that we know that we only want the ones that can hit the ball out of the park on the first try, that’s great. But instead, what happens is we only do one trial, but we’ll try seven times to take it to the Food and Drug Administration. This is not the right way to go.

**Dr. Hwu:** As for your comments about selection of antigen, I think the question is, “Is there a magic antigen?” We know from the T cell transfer trials that differentiation antigens such as MART can be important. If you give patients T cells which are 97% specific against MART-1, you can observe MART-1-reactive T cells infiltrating large tumors and causing regression. There are even some effects of MART T cell receptor–transduced T cells causing regression in an ongoing study at the NIH. The differentiation antigens can induce clinical regressions, but with monitoring, we need to figure out how to immunize, because clearly we’re not immunizing in the correct way right now.

**Dr. Haluska:** I was going to challenge you on one of the assertions you made about the difference between stage IV and stage III resected patients. I tend to think of them as the same. We’re biased by the large proportion of stage III patients who are actually cured by the resection, and in fact, the only thing that separates them is lead-time bias. The stage III patients who are relevant to these trials are really the ones who have occult stage IV disease, and maybe 90% of patients with resected stage IV disease still have occult stage IV disease. Many of our conceptions about how good the stage III patient is doing biologically come from the fact that the patients with poor prognoses are diluted out by the patients who are cured.

**Dr. Sondak:** In a lot of diseases other than melanoma, the benefit of adjuvant therapy has been quantitatively about the same across different risk groups. The absolute effect is different because it’s multiplied by the proportionate risk. From the standpoint that a lot more people with stage IV disease are at risk of progression than those with stage III disease—as you say, fewer are cured—that may be the only difference between the groups. But, if you look only at time to failure, there seems to be a real quantitative difference in the stage III and stage IV curves. Maybe when you get into stage III disease that is greater than 10 cm in size, those patients are going to be the same as a patient with say an adrenal metastasis. There is a lot of overlap, but both stage III and stage IV are comprised of very heterogeneous groups of patients.

**Dr. Atkins:** Are there any data looking at autoantibodies in the vaccine world? How do you put into the context of this discussion the results from the Melacine population of patients where benefit from a vaccine appears to be linked to HLA type?

**Dr. Sondak:** As far as autoantibodies and vaccines, I’m not aware of anything other than if treatment gives the patient vitiligo, it’s a good thing—the outcomes in immunotherapy patients developing vitiligo are usually better. Do I think HLA matters? We learned that in the Melacine trial there was an HLA effect that was statistically apparent and one of the key molecules was HLA-2. That is an important HLA molecule to all of us in the room, because it’s important in melanoma, but biologically, whether that vaccine exerted a better effect on HLA-2—positive patients because of a specific immunologic response to an A2-restricted antigen or antigens is another question. Still, it wouldn’t be surprising to us that vaccines would have different effects in patients with different HLA types. Who knows what other factors would influence antigen presentation, when the result of our vaccinations are as hit and miss as they are right now?

**References**


