Background: Improvements in the identification of tumor-associated antigens and in our understanding of the mechanisms regulating antitumor immune responses have revived interest in the use of therapeutic cancer vaccination. Due to their unique characteristics, hematologic malignancies represent an ideal target for vaccine-based therapeutic interventions.

Methods: A review of published vaccine studies in experimental models as well as the results of clinical trials using vaccines for patients with hematologic tumors is presented.

Results: Tumor vaccine strategies can be divided into two categories: antigen-specific strategies, in which the tumor antigens have been identified and can be isolated to develop a molecularly defined vaccine, and cellular or non–antigen-specific, in which the tumor-specific antigens are unknown but presumed to exist within the material used to generate the vaccine. Early clinical trials have shown not only the feasibility and safety of either approach but also the obstacles in therapeutic cancer vaccination as an effective treatment modality for hematologic malignancies.

Conclusions: Active immunization using current cancer vaccine approaches is feasible and safe. Although no major successes have been reported, the positive clinical results observed in some patients support the potential for therapeutic cancer vaccination in the management of hematologic malignancies. Results of studies that are testing vaccine formulations, targets, and settings (eg, bone marrow transplantation) may support the use of cancer vaccination as an efficient therapeutic strategy against tumors of hematologic origin.

Initial clinical results support the potential for therapeutic cancer vaccination to become part of the management of several hematologic malignancies.

Cancer Vaccines for Hematologic Malignancies
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Introduction

The past several years have witnessed a significant progress in the treatment of hematologic malignancies. This improvement has been largely the result of newer and more effective combination chemotherapy, improved radiation delivery, and the major impact conferred by bone marrow transplantation (BMT). In spite of these successes, a significant portion of patients with hematologic tumors will ultimately die of their disease. In recent years, therefore, much attention has been given to identify novel non–cross-resistant therapeutic strategies that may positively affect the management of these diseases.1,2

A growing body of evidence suggests that immune-mediated mechanisms may aid in the killing of malignant cells in patients with hematologic malignancies. Indeed, the potential of the immune system to favorably affect the management of patients harboring hematologic tumors has been highlighted by the reduced relapse rates observed in the allogeneic transplant setting compared with those of autologous BMT,3 the dramatic clinical benefit achieved with donor lymphocyte infusions (DLIs),4 and the recent clinical successes of antibody-based therapies for the treatment of non-Hodgkin’s lymphomas.5 These clinical observations, together with the recent demonstration that cells of the immune system are capable to destroy chemotherapy-resistant chronic myelogenous leukemia (CML) and multiple myeloma cell lines,6,7 have led to the development of novel immunotherapeutic strategies against cancers of hematologic origin. Among these strategies, active immunization with cancer vaccines is emerging as a valuable tool to harness the immune system against antigens expressed by these tumors.

In light of the evolving role of cancer vaccines in the treatment of hematologic malignancies, this article reviews the preclinical studies as well as the results of recently completed clinical trials using these approaches. Furthermore, we will discuss the obstacles that must be overcome to increase the efficacy of cancer vaccines for hematologic malignancies in the foreseeable future.

Cancer Vaccines: Objectives and Barriers

A major objective of cancer vaccination is to elicit an active systemic immune response against antigen(s) expressed by tumor cells that results in a therapeutically useful antitumor effect. Studies using this approach were initially reported by William Coley in the late 19th century. In these early studies, patients with advanced cancer were treated with bacterial extracts, also called Coley’s toxins, in an attempt to activate a nonspecific systemic immune response that was hoped would impart an immune-mediated antitumor effect.8 This concept was expanded many years later by using killed tumor cells or tumor cell lysates mixed with adjuvants such as bacille Calmette-Guérin (BCG) and Corynebacterium parvum to further enhance tumor-specific immune responses.9 However, the lack of clinically significant antitumor effect in response to these adjuvant cocktails generated skepticism towards active immunization as a viable therapeutic approach in cancer patients. This view of cancer vaccination has changed dramatically during the past several years due to not only the significant advances made in the identification of tumor-associated antigens,10,11 but also the growing understanding of the cellular and molecular mechanisms regulating host-tumor interactions12-14 and the discovery and cloning of several genes encoding immunologically relevant molecules. These important advances have provided the appropriate framework to create better antitumor vaccines with enhanced tumor potency and specificity and with diminished toxicity for normal tissues.

An ideal tumor vaccine should be able to generate an active systemic immune response in the cancer-bearing host, leading not only to specifically reject disseminated malignant cells, but also, and more importantly, to provide long-lived immunologic memory capable of protecting the vaccinated host against relapse. Two major obstacles in developing such a vaccine thus far include (1) identifying appropriate antigens to target and (2) generating immune responses against tumor antigens to which the immune system has been already exposed and thus rendered “tolerant” or unresponsive.

Identification of Appropriate Antigens to Target

A rational development of cancer vaccines depends on the molecular definition of tumor-associated antigens that are capable of being targeted by the immune system.15 In recent years, several broad categories of tumor antigens recognized by T cells have been identified mainly through the establishment of T cell lines or clones from cancer-bearing patients.16,17 Antigens identified in this fashion fall into general categories that include (1) unique tumor antigens expressed exclusively in the tumor from which they were identified, (2) shared tumor-specific antigens, expressed in many tumors but not in normal adult tissue, (3) tissue-specific differentiation antigens, expressed by the normal tissue from which the tumor arose, (4) oncogene and tumor
suppressor gene products as tumor antigens, and (5) viral-associated antigens. It should be noted that most of the advances in the identification of human tumor antigens has occurred in the field of solid malignancies, especially in patients with melanoma (among human tumors, melanoma-reactive T cells are easier to culture in vitro). In sharp contrast, the identification of tumor-associated antigens in tumors of hematologic origin has lagged (Table 1). However, methods such as the serologic expression cloning, or “SEREX,” will likely rapidly alter this horizon.18

As with most malignancies, the relative immunogenicity of the antigens expressed by hematologic tumors has yet to be defined. In addition, as described below, each category of these tumor antigens presents interesting features and challenges in the design of effective vaccine strategies.

**Unique Tumor Antigens**

Unique tumor antigens are considered unsuitable targets in the formulation of generic vaccines because of their patient-restricted expression. However, if capable of mediating major immune responses, vaccine strategies using unique antigens would be highly effective.15 A common finding in hematologic malignancies, especially leukemias, is the presence of chromosomal translocations that result in the generation of fusion genes encoding chimeric proteins. The joining region segments of these chimeric proteins represent true tumor-specific antigens and are, therefore, appealing targets for immunotherapy.19 Furthermore, for certain gene products, tumor escape through antigen loss in response to selective immunological pressure may not occur if the fusion protein is essential for transformation. The chimeric protein Bcr/Abl resulting from a t(9;22) chromosomal translocation in patients with CML represents the best example in this category of unique tumor antigens. Indeed, Bcr/Abl is tumor-specific, is required for malignant transformation, and displays a limited variability with only two breakpoints.20

The cytoplasmic location of this chimeric protein as well as the lack of evidence that protease cleavage can generate candidate antigenic peptides for effective presentation to T-cells had initially diminished enthusiasm towards Bcr/Abl as a suitable target for vaccination. Recently, however, Clark et al21 provided direct proof that human CML cells can process and present HLA-associated immunogenic peptides derived from the Bcr/Abl fusion protein. Furthermore, these peptides were recognized by antigen-specific cytotoxic T cells resulting in destruction of autologous leukemic cells.

B-cell lymphomas and multiple myeloma represent clonal expansions of lymphoid cells with rearranged immunoglobulin genes. The V-D-J recombination sequence results in a unique hypervariable region characteristic of each individual tumor. This sequence is known as the idiotype (Id). Although not the product of a gene mutation, this Id represents a truly tumor-specific antigen that has been the target for both passive immunotherapy using anti-Id antibodies and active immunization with Id vaccines.26 In the mid 1970s, Stevenson and colleagues27 successfully treated a murine B-cell leukemia by

<table>
<thead>
<tr>
<th>Category of Antigen</th>
<th>Hematologic Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Unique Tumor Antigens</td>
<td></td>
</tr>
<tr>
<td>Fusion genes products:</td>
<td></td>
</tr>
<tr>
<td>- Bcr/Abl CML</td>
<td></td>
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<tr>
<td>- DEK-CAN AML</td>
<td></td>
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<tr>
<td>- AML/ETO AML</td>
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<tr>
<td>- PML-RARα AML-M3</td>
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<tr>
<td>Idiotypic epitopes:</td>
<td></td>
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<tr>
<td>- Idiotypic immunoglobulin B-cell lymphomas</td>
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<tr>
<td>- T-cell-receptor idiotypes T-cell lymphomas</td>
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<tr>
<td>II. Shared Tumor Antigens</td>
<td></td>
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<tr>
<td>Cancer testis antigens:</td>
<td></td>
</tr>
<tr>
<td>- MAGE, BAGE, LAGE, GAGE Multiple myeloma</td>
<td></td>
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<tr>
<td>- PRAME AML</td>
<td></td>
</tr>
<tr>
<td>III. Overexpressed Antigens</td>
<td></td>
</tr>
<tr>
<td>- Proteinase-3 AML, CML</td>
<td></td>
</tr>
<tr>
<td>- WT-1 AML, CML, ALL</td>
<td></td>
</tr>
<tr>
<td>- MUC-1 Multiple myeloma</td>
<td></td>
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<tr>
<td>IV. Mutated Oncogenic Proteins</td>
<td></td>
</tr>
<tr>
<td>- p53, Ras Many tumors</td>
<td></td>
</tr>
<tr>
<td>V. Viral-Associated Antigens</td>
<td></td>
</tr>
<tr>
<td>- Epstein-Barr virus (EBV antigens) Burkitt’s lymphoma, Hodgkin’s lymphoma</td>
<td></td>
</tr>
<tr>
<td>- HTLV-1 Adult T-cell leukemia</td>
<td></td>
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</tbody>
</table>
passive immunotherapy with a polyclonal Id antisera. Years later, Levy’s group at Stanford University28,29 not only generated monoclonal anti-Id antibodies against human B-cell lymphoma, but also showed tumor regression in a significant number of patients treated with these custom-made, Id-specific monoclonal antibodies. However, a major drawback of this strategy was the difficulty and labor intensity of tailor-made antibodies as well as the emergence of Id variants with no reactivity to the monoclonal antibodies.30 Because of these obstacles, the emphasis shifted towards active vaccination with Id protein, a strategy that offers the advantages of being easier to perform and capable of providing a broader antitumor immune response. Indeed, numerous studies in experimental models and in patients with low-grade B-cell lymphomas have shown that both a polyclonal antibody response that might cover Id variants and Id-specific T cells are generated following active immunization with tumor-specific Id protein.31,32

Shared Tumor Antigens

Shared tumor antigens are commonly present on various samples of the same histologic subtype of malignancy and on different tumor types, but not in normal tissues except for testis and placenta. Because they are not patient-restricted, shared tumor antigens represent prime candidates for the development of broadly applicable vaccine formulations.33 Although the cancer testis antigens (ie, MAGE, BAGE) were initially identified in the early 1990s in patients with solid malignancies (especially patients with melanoma),34,35 the presence of these shared tumor antigens in hematologic tumors has just been recently documented. Indeed, van Baren et al36 have found that genes encoding the tumor antigens MAGE, BAGE, LAGE and GAGE are expressed in a high proportion of patients with advanced-stage multiple myeloma but are less common in MGUS (monoclonal gammopathy of unknown significance) or smoldering, early-stage myeloma. In addition, PRAME (preferentially expressed antigen of melanoma), another cancer testis antigen, is selectively expressed in 47% of AML patients but not in healthy volunteers.37

Overexpressed Tumor Antigens

Although not truly tumor-specific, the antigens proteinase-3 (PR-3), Wilms’ tumor gene-encoded transcription factor-1 (WT-1), and mucin-1 (MUC-1) are markedly overexpressed in different types of hematologic tumors.

PR3, a primary neutrophilic granule protein, is overexpressed in leukemic progenitors from patients with AML and CML but is minimally expressed by normal marrow progenitors. This protein has the interesting immunologic attribute of being the target autotarget in Wegener’s granulomatosis. Using algorithms based on HLA class I peptide-binding motifs, Moll trem et al38 have identified proteinase-3 peptides that bind common HLA alleles. These peptides have been used to stimulate T-cell populations leading to the generation of PR-3-specific cytotoxic T cells able to recognize and kill unmodified AML cells while sparing normal bone marrow cells. Furthermore, by using PR-1/HLA-A*0201 tetrameric complexes, CD8+ T cells specific for a peptide derived from PR-3 have been identified in CML patients in remission following allogeneic BMT or interferon treatment.39 Given these results, such candidate peptides are currently being explored for their ability to amplify leukemia-specific T-cell populations for adoptive therapy as well as for their use directly in a phase I vaccine trial.

A second candidate antigen is WT-1, which is also overexpressed by most human leukemias including AML, CML, and acute lymphocytic leukemia (ALL). WT-1 is a zinc finger transcription factor involved in leukemogenesis. This critical role in malignant transformation makes the generation of tumor escape by antigen loss unlikely with this target.40 Recently, an HLA-A201-restricted epitope of WT-1 has been identified. T cells specific for this epitope were generated and shown to lyse leukemia cell lines and inhibit colony formation by transformed CD34+ progenitor cells from CML patients while not affecting normal CD34+ progenitors.41,42 The recent demonstration that antibodies against WT-1 are present in the serum of patients with AML43 make this antigen a enticing target for vaccine strategies aimed to generate both cellular and humoral antileukemic immune responses.

MUC-1, an immunogenic epithelial mucin present in an underglycosylated form on solid tumors such as breast, pancreatic, and ovarian carcinomas, also has been found to be overexpressed in multiple myeloma.44 In its aberrantly glycosylated form, MUC-1 exposes and immunodominant epitope on the polypeptide core of the protein, which is recognized by both the B- and T-cell arm of the immune system.45

Viral-Associated Antigens

An increasing number of hematologic tumors are now recognized to be associated with specific viral infections. Posttransplant lymphoproliferative disease (LPD) and adult T-cell leukemia are the best examples in which the viral etiology of the neoplastic transformation has been clearly documented (Epstein-Barr virus [EBV] and HTLV-1, respectively). Hodgkin’s lym-
phomas and certain subtypes of non-Hodgkin’s B-cell lymphomas also appear to be associated with viral infections. Viral-encoded proteins expressed by these tumors therefore represent additional targets for cellular immunotherapy. As an example, malignant B cells from patients with EBV-associated LPD express 9 EBV-encoded proteins: 6 nuclear proteins (EBNA1, 2, 3-A, 3-B, 3-C, and LP), 2 latent membrane proteins (LMP-1 and LMP-2), and the product of the BamHI-A open reading frame. Peptides derived from these proteins can be presented in the context of HLA class I and II molecules to the T-cell arm of the immune system. Indeed, T-cell adoptive immunotherapy with EBV-specific T cells generated in vitro has been used in the management of EBV-associated LPD. Despite the large number of EBV-encoded antigens expressed by malignant cells, their relative immunogenicity is markedly different, with EBNA3-A, -B, and -C proteins being the most immunogenic and most frequent antigens targeted by cytotoxic T lymphocytes. Although these antigens represent appealing targets for EBV-specific T-cell therapy, the recent demonstration of tumor cell outgrowth with variants that have lost expression of EBNA3B epitopes underlies the risks associated with selective antigen targeting, especially when the antigens seem not to be essential for maintaining the transformed phenotype. Future vaccine strategies will more likely be aimed at eliciting a broader polyvalent response against multiple EBV-encoded antigens or at targeting antigens that are essential for the malignant phenotype.

The identification of increasing numbers of tumor antigens expressed by hematologic tumors has led to the development of several vaccine strategies that are currently being evaluated in preclinical models and/or clinical trials. Such strategies include immunization with protein plus adjuvant (Id + keyhole limpet hemocyanin [KLH]), antigenic peptide vaccines (Bcr/Abl peptide vaccine), naked DNA vaccines (Id-GM-CSF–encoding plasmid DNA), recombinant viruses encoding antigen (Id-encoding adenovirus), recombinant bacteria (Listeria monocytogenes) and, more recently, immunization with antigen-loaded dendritic cells (Id-pulsed dendritic-cell [DC] vaccine).

**Generation of Immune Responses Against Tumor Antigens to Which the Immune System Has Been Exposed**

In contrast to vaccination to infectious agents in which immunization seeks to prime an immune response to antigens not yet encountered by the immune system (prophylactic vaccination), cancer vaccination is aimed at eliciting immune responses against tumor antigens to which the immune system has already been exposed (therapeutic vaccination). In the clinical arena, it should be noted that by the time a patient is diagnosed with cancer, the immune system has already been exposed to tumor antigens and still allows tumor growth. Although the basis for this failure of the immune system to control tumors arising de novo is not completely understood, it is plausible that the patient’s immune system may have been rendered “tolerant or unresponsive to the tumor.” This explanation was first evoked after a set of surprising experimental findings in human tumors demonstrating that most of the human tumor antigens identified are not neoantigens uniquely expressed by cancer cells, but rather are tissue-specific differentiation antigens also expressed in normal tissues. Therefore, it is possible that the immune system may “see” tumors more as a “self” than as a “foreign,” resulting in tolerance to tumor antigens in a fashion similar to the induction of peripheral tolerance to self-antigens. Recent studies in experimental models, in which T cells specific for tumor-associated antigens could be marked and monitored in vivo, are providing increasing evidence that the natural response of the immune system to tumor antigens seems to be tolerance induction rather than immune activation.

Using T-cell receptor (TCR) transgenic mice specific for a model tumor antigen, we indeed obtained direct evidence supporting the existence of tumor antigen-specific tolerance that develops during B-cell lymphoma progression. In these studies, early in the course of growth of the murine lymphoma A20, tumor-specific CD4+ T cells lost their naive phenotype (indicative of having encountered tumor antigen in vivo) and even became partially activated. In spite of these features, these T cells rapidly become unresponsive to subsequent antigenic stimulation. Furthermore, by using parent-into-F1 bone marrow chimeras, we have unambiguously demonstrated that tumor antigen processing and presentation by bone marrow–derived antigen-presenting cells (APCs), and not direct presentation by lymphoma cells, is the dominant mechanism underlying the development of tumor antigen-specific T-cell tolerance. Importantly, the induction of this unresponsive state was associated with an impaired response to therapeutic vaccination, pointing therefore to tumor-induced immune tolerance as a critical barrier to be faced in the design of effective cancer vaccines.
thus are unable to control melanoma growth. Taken together, the sobering findings of tumor-induced antigen-specific immune tolerance raise the bar for effective therapeutic vaccination, since tolerance must first be broken for cancer vaccines to trigger meaningful immune responses against established tumors.

The requirement for bone marrow-derived APCs in the induction of tolerance to tumor antigens\textsuperscript{56} and in priming effective antitumor T-cell responses\textsuperscript{12,58} not only places APCs at the crossroads of these highly divergent outcomes, but also points to modulation of these cells as a critical strategy to overcome tumor-induced tolerance. Current strategies using genetically modified tumor cells as vaccines are largely based on engaging APCs in several ways: attracting APCs to the vaccine site (GM-CSF tumor-cell-based vaccines),\textsuperscript{59} enhancing APCs function (GM-CSF/CD40 ligand tumor-cell-based vaccine)\textsuperscript{60} or even converting the tumor itself into APCs.\textsuperscript{61} Furthermore, approaches aimed at enhancing APC function are also being utilized to improve the effectiveness of therapeutic cancer vaccines. Such strategies include treatment with anti-CD40 activating antibodies\textsuperscript{62,63} and aminobisphosphonates.\textsuperscript{64}

Targeting Vaccine Strategies in Hematologic Malignancies

Hematologic malignancies offer unique characteristics that make them an ideal target of vaccine-based therapeutic interventions. The generation of effective immunotherapeutic strategies is facilitated by the ease of tumor accessibility, the ability to achieve a minimal residual state with current treatments, the APC properties of many of these tumors of lymphoid origin, and the ability of myeloid cells to differentiate in vitro to functional DCs. These features, coupled with the non-cross-reactive nature of immunotherapy plus chemotherapy, have brought to reality the integration of tumor vaccination with current treatment paradigms in the clinical arena. However, the optimal vaccine formulation or clinical scenario required to achieve the greatest clinical benefit is currently being investigated.

In general, tumor vaccine strategies can be divided into two general categories: (1) antigen-specific strategies, in which the tumor antigens have been identified and can be isolated to develop a molecularly defined vaccine, and (2) cellular or non-antigen-specific, in which the tumor-specific antigens are unknown but presumed to exist within the material used to generate the vaccine (usually the tumor cell or its respective extracts). Both approaches have entered clinical trials where their respective therapeutic efficacy remain to be determined (Table 2).

Antigen-Specific Vaccine Strategies

**Id Vaccinations for Lymphoma and Multiple Myeloma** The first clinical trial using an Id vaccine for low-grade lymphomas was initiated in 1988.\textsuperscript{32} Id protein was produced by a hybridoma obtained through fusion of tumor cells from a lymph node biopsy with a myeloma cell line. The protein was then conjugated to KLH and emulsified in an immunologic adjuvant. Of the first 32 patients vaccinated in complete remission, approximately 50% generated Id-specific responses although these were mostly humoral responses. Analysis of these patients revealed a statistically significant prolonged long-term survival in those vaccinated patients who mounted a vaccine-specific immune response as compared to those who did not (7.9 years vs 1.3 years). While the relative contribution of the humoral vs cellular response to vaccination is unknown, cytotoxic T-cell responses against autologous tumor were found to be increased in association with vaccination and appeared to correlate with an improved clinical outcome.\textsuperscript{65}

While encouraging in terms of demonstrating the ability to maintain or prolong clinical remissions with vaccination, the above-mentioned study did not examine the role of Id vaccine on pre-established disease. A recent study sought to determine the ability of Id-vaccines coupled to KLH and co-administered with GM-CSF to eradicate residual disease in patients with a t(14;18) lymphoma following chemotherapy.\textsuperscript{66} Of the 11 patients with detectable translocations on completion of chemotherapy, 8 had complete elimination of their tumor as determined by the absence of the translocation by polymerase chain reaction (PCR) sequencing. All these patients had detectable tumor-specific CD4+ and CD8+ T cells, whereas antibody responses were less frequent and not apparently necessary for clinical remission. Long-term follow-up demonstrated 90% disease-free survival after a median follow-up of 3 years when compared to a historical control population with 44% disease-free survival treated with analogous chemotherapy but no vaccine. Results of this trial have prompted the design and implementation of a randomized phase III study through the National Cancer Institute where the relative therapeutic benefit of this vaccine strategy will be prospectively determined.

Multiple myeloma, as a B-cell-derived lymphoid malignancy, also produces a tumor-specific Id protein that is secreted and can easily be followed in the blood of patients as a correlate of disease status. The demonstration of pre-existing tumor-specific T-cell immunity\textsuperscript{67,68} together with evidence of immune susceptibility of chemoresistant myeloma cells with either vaccina-
Table 2.—Currently Open Clinical Vaccine Trials for Hematologic Malignancies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Stage</th>
<th>Eligibility Criteria</th>
<th>Vaccine</th>
<th>Phase</th>
<th>Patients</th>
<th>Site</th>
<th>Protocol No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML, CML, MDS</td>
<td>Chronic accelerated phase</td>
<td>HLA-A2 - Not eligible for BMT/chemotherapy</td>
<td>PR-1 peptide + montanide</td>
<td>I/II</td>
<td>60</td>
<td>M D Anderson Cancer Center</td>
<td>MDA-DM-97325</td>
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<tr>
<td>CML</td>
<td>Chronic phase</td>
<td>b3a2 breakpoint</td>
<td>Bcr/Abl breakpoint peptide + QS21 adjuvant</td>
<td>II</td>
<td>24</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
<td>MSKCC-99012</td>
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<tr>
<td>AML</td>
<td>De novo disease</td>
<td>Autologous transplant candidate</td>
<td>Autologous tumor + GM-CSF bystander cell pre- and post-autologous transplant</td>
<td>I/II</td>
<td>20</td>
<td>Johns Hopkins Oncology Center</td>
<td>K0009</td>
</tr>
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<td></td>
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<td></td>
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<td>Dana-Farber Cancer Center,</td>
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<td></td>
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<td>Cell Genesys, Inc</td>
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<tr>
<td>Follicular lymphoma</td>
<td>Stage III, IV</td>
<td>De novo or recurrent disease - Accessible 2-cm lymph node</td>
<td>Autologous tumor + IL-2 sc</td>
<td>II</td>
<td>20</td>
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<td>Mantle cell lymphoma</td>
<td>All stages de novo disease</td>
<td>- EPOCH-R</td>
<td>1d-KLH + GM-CSF sc</td>
<td>II</td>
<td>26</td>
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<td>NCI-00-C-0133</td>
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<tr>
<td>Follicular lymphoma</td>
<td>Failed induction therapy</td>
<td>Accessible tumor - Autologous BMT candidate</td>
<td>1d-KLH + GM-CSF post-autologous transplant</td>
<td>II</td>
<td>20</td>
<td>University of Nebraska</td>
<td>UNMC-260-00</td>
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<tr>
<td>Low-grade non-Hodgkin’s</td>
<td>All stages</td>
<td>No more than 4 prior therapies</td>
<td>1d-KLH + GM-CSF sc</td>
<td>II</td>
<td>9-25</td>
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<tr>
<td>lymphoma</td>
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<tr>
<td>Follicular lymphoma</td>
<td>III/IV</td>
<td>CVP response</td>
<td>1d-KLH + GM-CSF sc vs KLH + GM-CSF sc</td>
<td>III</td>
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<td>PACE response</td>
<td>1d-KLH + GM-CSF sc vs KLH + GM-CSF</td>
<td>III</td>
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<td>NCI-00-C-0050</td>
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<tr>
<td>Multiple myeloma</td>
<td>II/III</td>
<td>De novo responsive disease</td>
<td>Autologous tumor + GM-CSF bystander cell pre- and post-autologous transplant</td>
<td>I/II</td>
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<td>Johns Hopkins Oncology Center, Cell Genesys, Inc</td>
<td>JHCC-J0115, K0007</td>
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<td>Multiple myeloma</td>
<td>II/III</td>
<td>Partial remission with autologous transplant - HLA-identical sibling</td>
<td>Donors: Id-KLH + GM-CSF sc pre-stem cell collection Patients: Id-KLH + GM-CSF sc post-allogeneic stem cell transplant</td>
<td>I/II</td>
<td>10-22</td>
<td>National Cancer Institute</td>
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</tbody>
</table>

Data obtained from CancerNet (http://www.cancer.gov/clinical_trials).

AML = acute myeloid leukemia
BMT = bone marrow transplant
PACE = cyclophosphamide, doxorubicin, etoposide, prednisone
CML = chronic myelogenous leukemia
CVP = cyclophosphamide, prednisone, vincristine
EPOCQ-R = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab
GM-CSF = granulocyte-macrophage colony-stimulating factor
Id = idiotype
IL-2 = interleukin-2
KLH = keyhole limpet hemocyanin
MDS = myelodysplastic syndrome
sc = subcutaneous
While tumor rejection in CML has been described, evidence of tumor-specific recognition and little secretion, whereas the reverse is true for myeloma. There is, therefore, a concern that although immune responses can be generated against the Id protein in myeloma, the primary target of such responses would be the circulating Id protein and not the tumor cell itself. However, these concerns are more relevant to antibody responses where they can bind circulating Id and thus not reach the target tumor cell in sufficient concentration to be effective. In contrast, T cells do not recognize intact protein but require peptide to be processed and presented by APCs in the context of either class I or II molecules. Thus, the cellular immune response would be unaffected by circulating protein and could be generated to recognize Id-specific peptides present on the surface of plasma cells or their precursors. Evidence of tumor-specific recognition of myeloma cells by Id-induced CD8+ has been described.

In a vaccine trial using Id-KLH conjugates with subcutaneous interleukin-2 (IL-2) or GM-CSF, 12 patients who had previously undergone an autologous stem cell transplant and were in a complete remission were subsequently vaccinated at varying time-points posttransplant. Nine of 11 patients tested showed evidence of cellular response to KLH, whereas 2 of these 11 patients demonstrated a positive T-cell response to Id. Interestingly, no humoral anti-Id response was detected. The absence of demonstrable responses to the Id vaccine underscores the need for better immunogens or vaccination platforms.

Early-stage myeloma is a clinical scenario in which chemotherapeutic interventions have demonstrated the ability to induce clinical responses but have no effect on disease-free survival. Yet, Yi et al demonstrated Id-reactive Th-1 cells. Interestingly, with disease progression there was an accompanying shift towards the Th2 phenotype. Early-stage disease thus offers an appealing platform for effective antitumor immunotherapy. In a trial utilizing Id-alum combined with GM-CSF, Id-specific T-cell responses were observed in all 5 patients. In 1 patient, a greater than 50% tumor reduction was also achieved. Whether such a strategy is capable of inducing a T-cell memory response with long-term clinical impact remains to be determined.

To date, most antigen-specific vaccine studies in multiple myeloma have utilized the easily accessible and patient-specific Id protein. However, other tumor-specific antigens have recently been identified and can serve as potential targets of immunotherapy. These include MUC-1 as well as cancer testis antigens that include MAGE, BAGE, LAGE, and GAGE. These antigens have been detected in a high proportion of patients with advanced-stage myeloma and therefore are enticing targets for vaccine trials.

**Acute Myeloid Leukemia** While tumor rejection antigens have yet to be formally identified in AML, several candidates are being explored. Proteinase-3, a primary neutrophilic granule protein, is markedly overexpressed in myeloid leukemias. Proteinase-3-specific cytotoxic T cells have been generated that are capable of recognizing and killing myeloid leukemic cells in an antigen-specific fashion. Furthermore, the presence of polymorphisms in the proteinase-3 gene was analyzed in 23 HLA-A2 patients and their HLA-identical donors. In 4 donor-recipient pairs, in which at least 1 allele was absent, no relapse was detected. In contrast, in 15 of the remaining patients in which no allelic differences were detected, 7 patients relapsed. This suggests a role of proteinase-3-specific T-cell responses in the graft-vs-leukemia effect of allogeneic transplants and underscores the role of this protein as an immunogen in AML vaccine trials.

Another potential tumor antigen is WT-1, which is markedly overexpressed in AML, CML, and several solid tumors. As with proteinase-3, T cells have also been generated to recognize HLA-restricted WT-1 peptides capable of selectively killing WT-1 leukemia cells. PRAME (preferentially expressed antigen of melanoma), a cancer testis antigen, was recently found to be selectively expressed in 47% of AML patients but not healthy volunteers. PML-RARA HLA-DR-restricted peptides can generate CD4+ lymphocytes with specific cytotoxicity against autologous peptide pulsed acute promyelocytic leukemic cells. These data demonstrate the ability of neoplastic cells to process and present intracellular proteins on its surface. However, the absence of peptide-specific immune responses upon vaccination with a 25-mer PML-RARApeptide likely reflects the inability of an HLA class II negative cell to present the peptides on the leukemia blast cell surface. The role these proteins will have in developing vaccine strategies remains to be determined.

**Chronic Myeloid Leukemia** CML has demonstrated significant immune susceptibility through its ability to respond to DLIs with sustained remissions in patients who relapsed following an allogeneic T-cell-depleted BMT. While this response is largely mediated by minor histocompatibility antigen differences between the donor and recipient, the presence of a measurable clinical benefit in CML compared with other myeloid leukemias suggests a tumor-specific
response. A vaccination strategy with greater tumor specificity and significantly lower toxicity than that associated with allogeneic transplantation and DLIs has therefore a considerable appeal.

One possible tumor antigen candidate is the Bcr-Abl fusion protein (p210). This chimeric protein is uniquely expressed in CML, and the junctional amino acid sequence is not expressed on any normal protein. Pinilla-Ibarz et al recently completed a dose escalation study of a multivalent peptide vaccine (5 peptides) spanning the b3a2 breakpoint of p210. This study demonstrated peptide-specific delayed-type hypersensitivity reactions in vivo and proliferation. No peptide-specific cytotoxic T-lymphocyte responses were observed.

### Tumor-Cell-Based Vaccine Strategies

A limitation of an antigen-specific vaccine approach is that the immune responses will be restricted to the single antigen targeted by the vaccine. There is the risk that while this strategy may initially eliminate tumors expressing this antigen, the patient will ultimately relapse with a tumor no longer expressing the antigens against which they were vaccinated. The recurrence of disease lacking the expression of the initially targeted antigens is known as relapse with "antigen escape variants." Furthermore, with few exceptions, it is still not clear whether tumor-specific antigens identified to date also represent immunodominant proteins to which effective immune responses can be generated. With this in mind, a vaccine formulation using the tumor cell itself as an antigen source offers the advantage of a broad spectrum of tumor antigens present on the surface of the tumor cell (polypeptide vaccination) that can potentially serve as targets for the immune system. The efficacy of this approach relies on the ability to induce stronger immunity against tumor-selective antigens than against normal tissue antigens present on the surface of the tumor cell.

Critical to vaccine development is the ability to modify the tumor cell with genes encoding immunologically relevant molecules, and the production of a sustained, local release of its product that leads to a local inflammation at the vaccine site without systemic toxicity. The initial studies using genetically altered tumors to enhance their immunogenicity were performed by Lindenmann and Klein in the late 1960s. In these studies, vaccination with lysates of influenza-infected tumor cells resulted in the generation of systemic immune responses. In contrast, nonviral infection of tumor lysates alone or admixed with the same virus elicited no measurable immune response. More recently, due to the significant advances in gene transfer techniques, a variety of tumor cells have been genetically modified to either secrete cytokines locally or express new or increased levels of cell-membrane molecules such as adhesion or co-stimulatory molecules. With this approach, the immunogenicity of malignant cells is increased by either enhancing the presentation of tumor antigens and/or by providing enhanced co-stimulatory signals to the T-cell arm of the immune system. In preclinical models, these tumor-cell-based vaccine strategies prime systemic immune responses capable of rejecting a subsequent tumor challenge or eradicating established micrometastatic tumors. A systemic comparison of 10 different cytokines or cell surface molecule-based tumor vaccines showed that immunization with tumors transduced with a retroviral vector expressing GM-CSF produced the greatest degree of systemic immunity, which was enhanced relative to irradiated nontransduced tumors. Priming with GM-CSF–transduced tumor cells led to a potent, long-lived antitumor immunity that required the participation of both CD4+ and CD8+ T cells. Further dissection of the mechanisms mediating this strong anti-tumor effect showed that GM-CSF produced at the vaccine site promotes the recruitment and activation of host APCs. At the vaccine site, the APCs are then primed to efficiently capture and process the antigen. They subsequently traffic to the draining lymph nodes where the tumor antigens are presented to antigen-specific T cells. Upon activation, the primed T cells are then capable of leaving the draining lymph nodes and imparting a systemic, tumor-specific immune response. Multiple reports have since confirmed the bioactivity of GM-CSF–transduced tumor cells in a number of different tumor model systems, including hematologic malignancies.

### GM-CSF Tumor-Cell-Based Vaccine Strategies

To date, GM-CSF–secreting vaccines that have been tested clinically have fallen into two categories: (1) autologous tumors virally transduced to secrete GM-CSF (renal cell carcinoma, melanoma, prostate carcinoma, and lung cancer) and (2) GM-CSF–producing allogeneic tumor cell lines (pancreatic carcinoma and prostate carcinoma). In the first category, vaccine development was hampered by several factors: the ability to harvest adequate amounts of tumor, the expense, the labor intensity, and the GM-CSF variability of each patient’s vaccine formulation. In the second category, the strategy relies on the ability to prime immune responses to shared tumor antigens of similar histologies and is ideal in situations in which tumor tissue is limited. This strategy relies on the requirement of antigen processing and presentation by host APCs, and thus MHC compatibility between host and vaccinating tumor is not required. However, a limitation of this approach is the possible generation of allogeneic responses to the tumor vac-
Hematologic malignancies represent a unique situation in that tumor is readily available for many diseases. Furthermore, we have recently shown that although GM-CSF secretion is a critical parameter in the generation of systemic antitumor responses, autocrine secretion is not critical to the vaccine formulation, and that paracrine production is equally effective. Therefore, we have developed an allogeneic bystander cell line that secretes large and stable amounts of GM-CSF (K562/GM-CSF). This cell line was chosen because it can be easily grown in suspension and has no detectable levels of HLA class I or class II expression, thus minimizing the likelihood of anti-bystander allogeneic responses with multiple vaccinations. This universal bystander vaccine approach obviates the requirement of gene modification for each individual tumor source and guarantees uniform cytokine production, thereby eliminating intra- and inter-patient variability with each vaccination. The bystander cell line has been licensed to Cell Genesys, Inc, and is presently being employed in two trials described below.

The Johns Hopkins Oncology Center, in collaboration with Cell Genesys, Inc, is currently conducting two phase I/II clinical trials examining the safety, feasibility, and efficacy of this approach. The multiple myeloma trial requires that newly diagnosed patients with greater than 30% plasma cell involvement of the marrow undergo a full bone marrow harvest to obtain the necessary amount of tumor for vaccine development. The AML trial will utilize the circulating tumor obtained either via peripheral phlebotomy or pheresis. The autologous tumor and the GM-CSF producing bystander cell line will be admixed to compose the autologous tumor and the GM-CSF producing bystander vaccine approach obviates the requirement of gene modification for each individual tumor source and guarantees uniform cytokine production, thereby eliminating intra- and inter-patient variability with each vaccination. The bystander cell line has been licensed to Cell Genesys, Inc, and is presently being employed in two trials described below.

Dendritic Cell-Based Vaccine Strategies

A critical requirement for the generation of effective antitumor immune responses is the ability to effectively process and present the tumor-specific antigens in the appropriate MHC context to the T cells. DCs represent the most potent APCs capable of initiating effective T-cell responses. Many features appear to be responsible for the unique antigen-presenting capabilities of DCs. They express 50-fold higher levels of MHC molecules than macrophages, thus providing more peptide/MHC ligand for T-cell receptor engagement. DCs also express extremely high levels of co-stimulatory and adhesion molecules critical for T-cell activation.

The enhanced ability to prime T-cell responses, coupled with the recent development of techniques for obtaining large numbers of human DCs, has therefore opened the possibility of using these cells for therapeutic vaccination. Two general strategies have been used to obtain human DCs for clinical studies: (1) purification of immature DC precursors from peripheral blood and (2) the in vitro differentiation of DCs from peripheral blood CD14+ monocytes or CD34+ hematopoietic stem cells. The former approach requires the isolation of DC precursors that represent 0.5% of peripheral blood mononuclear cells. These cells are isolated in vitro from a T cell-monocyte-depleted cytokine-free culture. These culture conditions usually yield 5 × 10^6 DCs from a single leukapheresis. In vitro culture of DCs from CD14+ monocytes or hematopoietic stem cell cultures occurs in a two-step fashion. Immature DCs are initially generated in the presence of GM-CSF and IL-4 with a 5- to 7-day culture. These cells express high levels of MHC, adhesion, and co-stimulatory molecules and are capable of processing and presenting antigens to T cells. Additional culture with TNF-α, RANK-L, CD40L, or a “monocyte conditioned medium” results in a stable maturation of these DCs. With this method, 5 × 10^6 DCs can be generated from 50 mL of blood.

Recent reports have demonstrated the ability to generate DCs from even more committed myeloid precursors. Leukemic cell progenitors provide a unique setting to derive DCs expressing the entire antigenic repertoire in the presence of the necessary co-stimulatory elements. Various groups have reported the generation of leukemic-derived DCs obtained by culturing leukemic blasts in the presence of varying combinations of GM-CSF, IL-4, TNF-α, and CD40L. Furthermore, Harrison et al. were able to demonstrate the stimulation of autologous proliferative and cytotoxic responses of T cells cultured in the presence of the “leukemic DCs” in approximately 25% of patients from whom the DCs were obtained. These data demonstrate the unique possibility of using this strategy in the development of future vaccine strategies but also highlight the obstacles that still need to be overcome before clinical studies can be performed.

Few clinical trials have been reported to date utilizing DC-based vaccine strategies in hematologic malignancies. Hsu et al. conducted a study with PBMC-derived DCs pulsed with either the Id protein or KLH and then infused intravenously in 4 patients with non-Hodgkin's lymphoma. Three monthly infusions of Id-pulsed DCs were followed by Id-KLH vaccines administered subcutaneously followed by an additional infusion of pulsed DCs. No toxicity was demonstrated, and evidence of cellular proliferative responses was
shown in all patients. Clinical responses were also detected that included resolution of two pulmonary lesions in 1 patient, conversion from Id-specific PCR positivity to negativity in another, and stabilization of disease in the remaining 2 patients.

Id-pulsed DC vaccines were also evaluated in patients with multiple myeloma. In a study by Reichardt et al,93 12 patients who had undergone an autologous peripheral stem cell transplant went on to receive a series of monthly immunizations that consisted of two intravenous infusions of Id-pulsed autologous DCs followed by boosters with Id-KLH subcutaneous vaccinations. This strategy was well tolerated with patients experiencing only minor side effects. Furthermore, 2 of the 12 patients developed an Id-specific cellular proliferative immune response, and 1 of 3 patients developed an Id-specific cytotoxic T-cell response despite recent high-dose therapy. Therefore, DC-based Id vaccination is feasible after peripheral blood stem cell transplantation and can elicit Id-specific T-cell responses in patients with multiple myeloma.93 More recently, Titzer et al94 demonstrated the feasibility of CD34-derived Id-pulsed DC vaccines. These infusions were followed by Id GM-CSF or Id DCs. Cellular or antibody immune responses were detectable in 4 of 10 patients upon completion of vaccination, and 1 patient demonstrated a reduction in the plasma cell infiltration of the bone marrow. Similar evidence of both cellular and humoral immune responses to Id-pulsed DCs was also observed in another study.95

These early results using DC-based vaccine strategies are promising. However, the growing appreciation of different functional subtypes of DCs, as well as the importance of the route of DC administration, necessitates careful comparative studies to determine the best DC-based strategy that would translate into maximal systemic antitumor immunity in vivo.

Cancer Vaccines as an Adjunct to BMT

BMT has demonstrated a significant clinical benefit in the treatment of many hematologic malignancies. Nevertheless, the long-term benefit of this modality remains limited as many patients will ultimately die of their disease or undergo the morbidity and mortality of graft-vs-host disease (GVHD) associated with allogeneic transplantation. Integration of cancer vaccines in the autologous transplant setting offers several theoretical as well as real advantages. The posttransplant setting is a period of minimal residual disease in which the likelihood of vaccine strategies to impart a clinically effective response is greatest. Furthermore, the adaptive transfer of tumor-specific immunity from the pretransplant period through the infusion of “primed” lymphocytes, the skewing of the developing immune repertoire with vaccinations during the period of immune reconstitution, and the abolition of tolerogenic mechanisms as a result of the myeloablative regimen are all theoretical advantages that must be counterbalanced by the global immunosuppression accompanying the early posttransplant period.

In an attempt to model the integration of GM-CSF-based tumor cell vaccines in the autologous BMT setting, we recently established a syngeneic murine model.96 This model demonstrates the effectiveness of antitumor vaccines as measured by the ability to cure a pre-established tumor burden when such vaccines were administered early posttransplant, long before full immune reconstitution. Surprisingly, the ability to elicit effective antitumor responses was significantly greater in the transplanted mice than in their nontransplanted counterparts with an equivalent tumor burden. Furthermore, in the model of minimal residual disease, T cells were found to undergo a significant clonal expansion and activation early posttransplant that declined with the development of macroscopic disease. Interestingly, vaccination with irradiated GM-CSF-producing autologous tumor during the period of immune reconstitution maintained T-cell responsiveness and enhanced survival. These data demonstrate the presence of an “autologous graft-vs-host” effect in the posttransplant period, which is normally transient but can be prolonged following vaccination.

These results serve as the rationale for the design of two clinical trials currently open at the Johns Hopkins Oncology Center (J0115 and J0136) utilizing autologous tumor cells admixed with the allogeneic GM-CSF-producing bystander cell line (K562/GM).82 In these studies, tumor will be harvested from patients with de novo multiple myeloma or AML. Patients who show evidence of disease responsiveness to chemotherapy and meet the eligibility requirements for autologous peripheral stem cell transplantation will then proceed with a pretransplant vaccination followed 2 weeks later by a leukapheresis. This pretransplant vaccine will serve the purpose of priming tumor-specific lymphocytes that will be collected and reinfused together with the stem cells following the myeloablative preparative regimen. The patients will then proceed with a series of 8 posttransplant vaccinations that will start 6 weeks following BMT. It is hoped that the primed lymphocytes will be capable of exerting the autologous “graft vs tumor” effect observed in the murine model, which will then be sustained with the postransplant vaccinations. The primary end points of these studies are feasibility, safety, and determination of measurable antitumor responses to this vaccine formulation.
Strategies to augment the intrinsic graft-vs-tumor effect of allogeneic transplants are also being explored. The ability to enhance the immune-mediated antitumor benefit of allogeneic transplants with an autologous tumor cell-based vaccine formulation must be counter-balanced with the potential risk of exacerbating GVHD through priming of immune responses to MHC-matched, minor antigen differences between donor and host. Interestingly, while donor immunization exacerbated GVHD in murine models presumably through the priming of immune responses to minor histocompatibility antigens, immunization of recipients following BMT did not worsen GVHD and still generated tumor-specific immunity.97 Tumor-specific immune responses could be augmented when tumor vaccination was given after DLIs in a nonmyeloablative allogeneic transplant setting.98 These findings suggest it may be possible to achieve donor-host tolerance with these transplants and subsequently utilize DLI plus vaccination to maximize the antitumor effect.

Conclusions

The role of the immune system in the treatment of hematologic malignancies has been well documented in a variety of settings. The significant clinical effects observed by the withdrawal of immunosuppression in patients with posttransplant lymphoproliferative disorders, the increased antitumor effect of allogeneic transplants over autologous, and the ability to reinduce remissions with DLIs in a substantial number of patients are all settings that point to the critical role of the immune system in these diseases. However, what these interventions have gained in clinical efficacy, they lack in tumor specificity. Nevertheless, these data contribute to a growing body of literature supporting the role of immunotherapy in the treatment of hematologic malignancies. These treatment paradigms need to be refined to obtain greater tumor specificity and to reduce toxicity. While early clinical studies utilizing cancer vaccines demonstrated the ability to achieve such a goal, thus far they have shown limited success in imparting clinically significant benefits. Reasons for this are multifactorial and include the inability to overcome the inherent tumor-specific tolerogenic mechanisms of cancer-bearing hosts, ineffective vaccine formulations, and excessive tumor burdens. New studies are being conducted or planned to test different vaccine formulations and/or targets as well as settings in which immunomodulation may result in enhanced efficacy. The recent successes of antibody therapies in the treatment of lymphomas and leukemias have highlighted the important antitumor role of the immune system. It is now time to demonstrate similar successes with cancer vaccines.

References


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