Genes to vaccines for immunotherapy: how the molecular biology revolution has influenced cancer immunology

Dan A. Laheru, Drew M. Pardoll, and Elizabeth M. Jaffee

Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland

Abstract

Recent advances in our understanding of the complex signaling pathways involved in immune system regulation, along with analyses of genetic differences between tumors and their normal cellular counterparts, have accelerated development of immune-based strategies for cancer treatment and prevention. More clinically relevant animal models have shown that successful immune-based strategies will require the integration of interventions that target specific tumor antigens with regulators of the antitumor immune response. Immunotherapy for cancer is at a critical crossroad, as therapeutics designed to target cancer-associated antigens and regulatory signaling molecules enter clinical trials. We outline here a paradigm for early-stage clinical development of immunotherapy combinations that use vaccines to drive tumor antigen-specific responses while simultaneously targeting immune regulatory pathways. [Mol Cancer Ther 2005;4(11):1645–52]

Introduction

A major goal of immune-based therapies is to recruit and activate T cells that recognize tumor-specific antigens. In addition, recombinant monoclonal antibodies are being designed to target tumor-specific antigens. Several monoclonal antibodies have already been Food and Drug Administration approved for the treatment of lymphomas and breast cancer. Monoclonal antibodies have been shown to kill tumor cells either by direct lysis or via delivery of a conjugated cytotoxic agent. Both approaches are attractive for the treatment of most cancers for several reasons. First, these immune-based therapies act via a mechanism that is distinct from chemotherapy or radiation therapy and represent a non-cross-resistant treatment with an entirely different spectrum of toxicities. Second, through the genetic recombination of their respective receptors, the B-cell and T-cell arms of the immune system are capable of recognizing a diverse array of potential tumor antigens. In addition, both T and B cells can distinguish small antigenic differences between normal and transformed cells, providing specificity while minimizing toxicity. New insights into the mechanisms by which T cells are successfully activated and by which tumors evade immune recognition are driving the development of new combinatorial immunotherapy approaches. In addition, recent advances in gene expression analysis have allowed for the identification of new antigen targets, including candidate tumor antigens that might serve as T-cell and antibody targets. These advances now make it possible to exploit the immune system in the fight against most cancers. It is now clear that for vaccines to show clinical efficacy against existing cancer they will likely require integration with other targeted therapies that modify one or more mechanisms of immune tolerance (Fig. 1).

Tumor Immune Surveillance versus Tumor Evasion and Progression

The premise of successful immunotherapy is predicated on the existence within patients of a T-cell and/or antibody repertoire specific for antigens specifically or selectively expressed by tumors. Numerous studies have confirmed the existence of tumor-reactive T cells and antibodies in patients with many different cancer types, particularly at early and middle stages of disease (1, 2). Murine models of tumorigenesis in immunodeficient mice have confirmed the capacity of the immune system to inhibit tumor growth (3). However, successful tumors have clearly developed multiple mechanisms to evade immunity, beginning with tolerance induction (4). As they develop, tumors seem to
Tregs can traffic to the tumor’s microenvironment and inhibit effective immune responses, including B7-H1 and B7-H4. In addition, there is evidence to suggest that the expression of cyclooxygenase-2, and through negative signaling molecules on the tumor, is mediated via the EGFR and VEGF signaling pathways, through cyclooxygenase-2, and through negative signaling molecules on the tumor, including B7-H1 and B7-H4. In contrast, checkpoints in the tumor’s microenvironment are down-modulated by proinflammatory cytokines, such as transforming growth factor-β, and dendritic cell maturation, such as vascular endothelial growth factor (VEGF; refs. 9, 10).

Down-modulation of proinflammatory cytokine production as well as immune sensing of inflammatory signals by dendritic cells. This leads to tolerance induction among tumor-specific T cells. Later-stage tumors develop additional mechanisms of immune evasion largely through down-modulation of antigen-processing machinery and induction of immune-inhibitory molecules, such as B7-H1 or B7-H4 (see below), which are normally expressed within tumors to limit the amplitude of natural immune responses to pathogens, thereby avoiding tissue pathology. Importantly, these mechanisms of immune evasion are blockable and even potentially reversible, now that their molecular basis is becoming defined.

Despite the extraordinary features of the immune system that make it possible to discern self from nonself, most human cancers typically elicit weak immune responses based on the mechanisms described above. Furthermore, promising immunotherapeutic approaches used for relatively immunogenic cancers, such as melanoma, have met with variable success (5). These observations support the hypothesis that, in order for tumors to form and progress, they must develop local and/or systemic mechanisms that subsequently allow them to escape the normal surveillance mechanisms of the intact immune system. Immune-based therapies must therefore incorporate at least one agent that targets the cancer cell as well as one or more agents that will modify both local and systemic mechanisms of cancer-induced immune tolerance. Specific mechanisms of immune tolerance can become operative systemically, involving both immunizing lymph node groups and the tumor site itself. It is now clear that both local characteristics of the tumor microenvironment as well as systemic factors are important for immune evasion and progression (3, 6–8). For example, T-cell recognition of tumors might be inhibited or suppressed due to the down-regulation of HLA class I-tumor antigen complexes on tumor cells by several intracellular mechanisms. Such alterations within a tumor cell would not be unexpected because they have unstable genomes. The local inflammatory reaction is also an important triggering event in the recruitment of professional antigen-presenting cells (APC) and effector cells, such as T cells and natural killer cells, to the tumor site. However, tumor cells express a variety of proteins that inhibit proinflammatory cytokines, such as transforming growth factor-β, and dendritic cell maturation, such as vascular endothelial growth factor (VEGF; refs. 9, 10).

The inhibitory pathways, termed “immunologic checkpoints,” together comprise important elements in regulating T-cell recognition of tumors (Fig. 2). Regulation via these pathways may occur systemically or at the progressing tumor sites. Immunologic checkpoints serve two host-survival functions. One is to help generate and maintain self-tolerance, by eliminating T cells that are specific for self-antigens. The other is to restrain the amplitude of normal T-cell responses so that they do not “overshoot” in their natural response to foreign pathogens. The prototypical immunologic checkpoint is mediated by CTLA-4 counter-receptor that is expressed by T cells when they become activated (11). CTLA-4 binds two B7 family members on the surface APCs, B7.1 (CD80) and B7.2 (CD86), with ~20-fold higher affinity than the T-cell surface protein CD28 that binds these molecules. CD28 is a costimulatory signal that is constitutively expressed on naive T cells. Because of its higher affinity, CTLA-4 outcompetes CD28 for B7.1/B7.2 binding, resulting in the down-modulation of T-cell responses (11–13).

Two recently discovered B7 family members, B7-H1 (PD-L1) and B7-DC (PD-L2) also seem to interact with T-cell costimulatory and counter-regulatory inhibitory receptors (14, 15). PD-1, which is up-regulated on T cells when they become activated, seems to represent an important counter-regulatory immunologic checkpoint when it binds B7-H1 (16). Activating receptor(s) for B7-DC and B7-H1 has not yet been definitively identified. B7-DC...
and B7-H1 are expressed on dendritic cells and are likely to have costimulatory roles in increasing activation of naive or resting T cells. In contrast to B7.1, B7.2, and B7-DC, B7-H1 is also expressed on multiple peripheral tissues and on many tumors (15, 17).

Another new B7 family member, B7-H4, seems to mediate a predominantly inhibitory function in the immune system (18, 19). B7-H4 has been shown recently to be expressed on certain murine and human tumors. Both B7-H1 and B7-H4 likely protect tumors from immune system attack. Preclinical studies have already shown that it is possible to down-regulate B7-H1 signaling in mice, improving the antitumor response on vaccination (20, 21). Monoclonal antibodies that down-regulate B7-H1 and B7-H4 are currently under clinical development. These antibodies will likely begin clinical testing in patients within 2 to 3 years.

CD4+CD25+ T regulatory cells (Treg) are another mechanism by which antitumor immunity is suppressed. Treg are a subset of T cells that are important in the suppression of self-reactive T cells (peripheral tolerance) and have been shown to accumulate in murine and human tumors (22, 23). Other Treg markers have been described, including constitutive expression of CTLA-4, GITR (a member of the tumor necrosis factor receptor family), and the FoxP3 transcription factor (24–27). They secrete interleukin-10, transforming growth factor-β, and/or interleukin-4 (24, 25, 28) and can suppress both helper CD4+ and cytotoxic CD8+ T cells (29). Scurfin is the protein product of FoxP3 and a member of the forkhead/winged-helix family of transcription factors (26, 27, 30). Scurfin can act as a repressor of transcription and may function as a negative regulator of T-cell activation and function. Although Treg are likely activated during the immunization process, they also localize to tumor sites. Increased levels of Treg have been isolated from several human tumors, including breast, ovarian, and pancreatic tumors, tumors not typically thought of as being immunogenic (22, 23, 31). Tumor production of the chemokine CCL22 is one potential mechanism that attracts Treg to the tumor’s microenvironment by interacting with the CCR4 receptor expressed by these cells (31). Depletion or inhibition of these cells before immunization has been shown to significantly enhance the potency of most vaccine strategies in preclinical models and in early-phase clinical trials.

Nonimmune Signaling Pathways That Affect Immune Interactions in the Tumor Microenvironment

Several signaling pathways have been identified that are implicated in the growth and metastasis of cancers. For example, epidermal growth factor receptor (EGFR), HER-2/neu, cyclooxygenase-2, and the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin pathway kinases are known to mediate tumor growth and progression (9, 32, 33). In addition, new blood vessel formation (angiogenesis) is required for the growth of both primary tumors and metastases. Neovascular formation seems to be regulated by fibroblast growth factor, platelet-derived endothelial cell growth factor, and VEGF family members (9, 10, 34, 35). Several oncogenes have been linked to angiogenesis. As an example, in pancreatic cancer, deleted in pancreas cancer-4 up-regulates VEGF expression, and mutated K-RAS expression is associated with increased microvessel density (36).

Monoclonal antibodies that target several of these pathways have shown efficacy in preclinical models (9, 33, 37). In addition, monoclonal antibodies that target EGFR and VEGF receptor have been tested in patients with several cancers (38). Non–small cell lung cancers with mutations in EGFR show significant clinical responses to the anti-EGFR antibody, gefitinib, and renal cancers have shown significant clinical responses to VEGF receptor inhibition. Although these antibodies have shown only modest results as single agents in most cancers, the pathways they target are also candidate targets for immune intervention.

One example of an oncogenic pathway that affects immunity to tumors is signal transducers and activators of transcription 3, which is constitutively activated in >50% of tumors. Signal transducers and activators of transcription 3 activation in cancer occurs not by mutation but rather because it is downstream of several tumor-associated receptor-linked tyrosine kinases, such as c-met and EGFR, as well as nonreceptor tyrosine kinases, such as src and certain Janus kinases (8). In addition to regulating cell cycling genes (i.e., cyclin D1) and antiapoptotic genes (i.e., Bcl-xL), signal transducers and activators of transcription 3 activation in tumors inhibits release of proinflammatory cytokines and chemokines and induces release of factors, such as interleukin-10 and VEGF, which block dendritic cell activation (8). Blockade of signal transducers and activators of transcription 3 might therefore significantly enhance antitumor immune responses, particularly in combination with vaccination.

The interaction of a few of these pathways with immune regulatory pathways have already been shown. For example, VEGF is a key inhibitor of proinflammatory cytokines, dendritic cell maturation, and T-cell development (35). Preclinical data have shown that antibodies that block signaling by this growth factor can promote antitumor immune responses. Furthermore, down-regulation of the HER-2/neu receptor with drugs, such as Herceptin, promotes tumor antigen processing and presentation by HLA class I molecules, improving the potential for T-cell recognition and lysis (39). Monoclonal antibodies that target these signaling pathways are about to undergo clinical testing in combination with other immune-based approaches, specifically with antigen-targeted vaccines.

Knowledge of Genes Encoding for Tumor Antigens and Immune Regulatory Pathways Should Lead to More Effective and Targeted Immune-Based Therapies

Several proteins, such as carcinoembryonic antigen, EBV, human papillomavirus, Bcr-Abl, mutated K-RAS,
HER-2/neu, prostate-specific antigen, prostate-specific membrane antigen, p53, tyrosinase, and Mart-1, have been shown to be specifically overexpressed by a range of cancers relative to the normal cells of origin (4, 40). As such, these antigens have been the targets of several antibody and vaccine approaches that have been tested in early-phase clinical trials (41, 42). These antigens were identified >10 years ago through several technologies employed to analyze gene expression in cancer cells. To date, a few studies have shown postvaccination immune responses to the HLA-restricted peptides derived from these antigens or to whole-protein forms of the antigen. However, significant clinical responses have not yet been observed. This may be due to the paucity of available immune relevant antigen targets, to the existence of host mechanisms of immune tolerance, or to both.

**How Are New Antigen Targets Being Identified?**

The majority of antigens currently employed in antigen-based vaccine approaches were chosen because they were shown to be overexpressed or genetically altered by a given type of tumor and not because they had been shown to be immunogenic. Malignant melanoma is the only human cancer for which a larger number (>10) antigens have thus far been identified. Most of these antigens were identified using strategies that employed T cells isolated from patients with progressing melanomas. However, most of the T cells used were not from patients who were successfully immunized against that particular antigen. As such, there remain additional as yet unidentified antigens expressed by different types of cancers that may be more immunogenic for inducing effective immunity than the currently employed antigens.

Until recently, two methods were routinely used in an attempt to identify new targets. The first method, serologic analysis of recombinant tumor cDNA expression libraries, employs serum to screen phage display libraries prepared from tumor cells to identify candidate antigen targets that have elicited humoral and immune responses in cancer patients. Identified antigens can then be screened for recognition by T cells (Fig. 3A). This method has identified several antigens, the most commonly studied being NY-ESO-1, a meiosis-specific protein that is a member of the class of cancer/testis antigens (43–45). This antigen is expressed by several different cancers. This method also identified coactosin-like protein, an actin filament-binding protein that interacts directly with 5-lipoxygenase and plays an important role in cellular leukotriene synthesis as a potential pancreas cancer target antigen. This protein seems to be recognized by antibody and T-cell responses in patients with pancreatic cancer (45). This method is tedious and it is not clear whether the antigens identified as B-cell targets are also the best targets of T cells.

The second method employs tumor-specific T cells isolated from patients with cancer to screen cDNA libraries prepared from autologous tumor cells. This method requires isolation and culture of tumor-specific T cells, along with tumor cells, from the same patient with cancer. This approach has been most successful in identifying melanoma-associated antigens (2, 46, 47). However, it has been technically challenging to employ this method for the identification of other cancer antigens because it is difficult to isolate T-cell lines and clones from patients with most other cancers (Fig. 3B). Another limitation of this approach is that it requires long-term stable T-cell clones or lines for screening. The antigenic specificities of these long-term cultures may not be representative of the full repertoire of T cells present in the patient.

A relatively newer, more promising method of tumor antigen identification employs functional genomics, whereby patient lymphocytes are used to evaluate candidate antigens found to be differentially expressed by cancers (Fig. 3C; ref. 48). This approach has several advantages. First, it allows for a rapid screen of a large number of candidate antigens. Second, it requires the isolation of only a few lymphocytes from patients, which are often limited in availability. Third, this approach is not dependent on the availability of autologous tumor cells that are difficult to isolate in large enough numbers for generating cDNA libraries. Fourth, this approach can be used to identify tumor antigens that are expressed by any HLA type, allowing for the generalization of this approach to most patients. Finally, the strategies use freshly isolated lymphocytes and thus avoid specificity bias introduced with long-term culture procedures. This approach has the potential to rapidly identify ‘‘immune relevant’’ antigens, especially if it employs immunized lymphocytes from patients vaccinated with a tumor whole-cell vaccine approach who ideally have shown clinical evidence of immune activation following vaccination. Thus, this method provides the best insurance that the antigens identified are ones that the patient’s immune system are reacting to following immunization.

Mesothelin is one example of an antigen that was recently identified using immunized lymphocytes to screen differentially expressed gene products as candidate tumor antigens. Mesothelin is a transmembrane glycoprotein and derives from a larger protein, mesothelin/megakaryocyte potentiating factor (49, 50). Mesothelin is overexpressed by most pancreatic tumors (51). This antigen was recently identified as a T-cell target using lymphocytes isolated from three pancreatic cancer patients immunized with an allogeneic, granulocyte macrophage colony-stimulating factor–secreting pancreatic tumor vaccine who showed other evidence of immune and clinical responses. Interestingly, mesothelin has also been identified as an antibody target. Monoclonal antibodies against mesothelin are currently being tested as therapeutic agents for patients with advanced mesothelin-expressing tumors, including pancreatic and ovarian cancers, and mesotheliomas (49).

**What Antigen-Based Vaccine Strategies Are Being Employed to Deliver New Candidate Targets?**

As additional immune relevant tumor antigens are identified, the next significant challenge lies in developing strategies to improve the in vivo delivery of these antigens. Based on a large body of published data, the best vaccine strategies require the delivery of antigens to professional
APCs for effective processing and presentation and subsequent activation of both T-cell and antibody responses (52). Dendritic cells, in particular, are now accepted as the most efficient APCs in B-cell and T-cell activation. Several clinical trials have tested ex vivo expanded and primed dendritic cells as the vaccine. However, these studies have revealed the difficulty in reliably producing phenotypically mature dendritic cells for clinical testing as only mature dendritic cells are capable of efficiently presenting antigens to T cells. The variability in dendritic cell generation even between patient preparations or between patients on the same study is difficult to control. In addition, if antigen is not presented in the proper context by mature dendritic cells, immune down-regulation or tolerance can occur. In fact, immature dendritic cells have been shown to induce T-cell tolerance in several animal models.

As an alternative to dendritic cell–based delivery, recombinant viral and bacterial vector delivery systems are currently under development or are already undergoing clinical testing. The use of modified viral particles or targeted bacteria to deliver tumor antigens to the immune system is based on the agent’s innate ability to efficiently infect APCs in vivo (41, 42, 53, 54). A major recent advance has been the identification of a family of signaling molecules, Toll-like receptors (TLR), which are key mediators of signaling of innate immune responses (55, 56). TLR represent a critical link between innate and adaptive immunity because they are expressed by immature dendritic cells and their engagement provides critical signals for dendritic cell activation. Intracellular sensors, including NOD proteins, also contribute to dendritic cell activation under circumstances where the dendritic cell is infected by a virus or an intracellular bacterium. It is now clear that viruses and bacteria initially activate one or more of these TLRs as an initial first step in inducing the cascade of inflammatory events required for successful initiation of anti-infection immunity. Early cancer vaccine approaches have included viruses, such as vaccinia and bacterial DNA sequences (57, 58). However, the use of immunogenic vectors in cancer patients who have been exposed previously to a similar vector often induce vigorous humoral antivector immune responses before effective priming against the tumor antigen can occur. As such, other viruses, viral particles, and bacterial delivery systems are currently nearing or are already undergoing clinical development for the treatment of several cancers. These include fowlpox viruses given in a prime boost sequence with vaccinia and Listeria monocytogenes (54, 59–65).

As additional ligands for TLRs are identified, recombinant vaccines that link antigen to the TLR ligand are being developed. Two TLR ligands [imiquimod (TLR7) and CpG oligonucleotides (TLR9)] are already in active clinical testing.

**What Have We Learned from Doing Combinatorial Gene-Targeted Immune-Based Studies in Patients?**

As discussed above, new molecular technologies and sequencing of the human genome have facilitated the identification of pathways involved in the regulation of immune responses. In turn, these new findings have provided new insights into the mechanisms that regulate T-cell and B-cell activation and down-regulation. Furthermore, these discoveries provide new opportunities for designing
combinatorial immune-based interventions that enhance vaccine-induced antitumor immune responses. An informative example is the case of CTLA-4 blockade. CTLA-4 is a fundamental T-cell checkpoint that limits the magnitude of immune responses. The central role of CTLA-4 as an immune checkpoint is shown by CTLA-4 knockout mice, which display a dramatic multiorgan hyperimmunity/autoimmunity syndrome that is lethal by 4 weeks of age. However, partial blockade of CTLA-4 in tumor-bearing adult mice with an antibody strongly augments tumor vaccine responses while limiting autoimmunity to the tissue type from which the tumor arose (i.e., vitiligo in melanoma and autoimmune prostatitis in prostate cancer; refs. 11, 66–71). Clinical studies with an anti-CTLA-4 antibody are compatible with the preclinical data. Thus, high-dose anti-CTLA-4 antibody administration induces tumor regressions in melanoma patients but also induces multisystem autoimmunity/hyperimmunity, including dermatitis, colitis, pneumonitis, hepatitis, and hypophysitis (68). Additional clinical trials that analyze the effects of combining antigen-targeted vaccines with antibodies that block CTLA-4 signaling in patients with these and other cancers are either ongoing or will be initiated soon. It will be interesting to determine whether lower doses of anti-CTLA-4 blocking antibodies will synergize with effective vaccines without causing the frequent systemic autoimmunity/hyperimmunity toxicities seen with high doses of anti-CTLA-4 alone.

We now know that Treg provide another immune checkpoint for the systemic regulation of antigen-specific T-cell responses. These cells can be isolated from peripheral blood but are also found within developing tumors. Administration of Treg-inhibiting agents, such as interleukin-2 receptor-targeted antibodies or immune-modulating doses of cyclophosphamide, to naive hosts increases the antitumor effects of immune-based therapies in several preclinical models (72–76). Several clinical studies have suggested that cyclophosphamide given before vaccination can enhance the antitumor immune response against several cancers, including malignant melanoma and breast cancer (77). Clinical studies employing immune-modulating doses of cyclophosphamide in sequence with newer vaccine approaches are ongoing. As an example, a recently completed vaccine phase II study compared a whole-cell pancreatic cancer vaccine given either alone or in combination with immune-modulating doses of cyclophosphamide in patients with metastatic pancreatic cancer who were treated previously with two or more chemotherapies. The study reported an increased number of patients experiencing progression-free survival in the cohort that received cyclophosphamide plus the vaccine (40% of patients at 16 weeks) compared with the cohort that received the vaccine alone (16% of patients at 16 weeks). The side effects associated with this vaccine approach were limited to local, transient vaccine skin site reactions. Immune-modulating doses of cyclophosphamide did not worsen these side effects, nor did it cause additional side effects. The fact that the side effects associated with immune-modulating doses of cyclophosphamide given in sequence with vaccine are minimal and tolerable allows this approach to be easily integrated with other treatment modalities. These studies are paving the way for other combination approaches, such as combining immune-based therapies with targeted therapies that are believed to have multiple mechanisms (immune and nonimmune mediated) of antitumor activity, such as inhibitors to the VEGF receptor and EGFR.

Building on the Past, Looking toward the Future

Several lessons have been learned from vaccine studies completed in the past 10 years in which vaccines were tested as single agents in patients with cancer. First, few clinical responses have been observed in patients with large burdens of cancer regardless of the vaccine approach tested. Second, multiple mechanisms of immune tolerance are likely inhibiting effective immunization of cancer patients, even those patients with minimal residual disease. However, despite these largely negative studies, some studies have shown evidence of biological activity and immune activation, even in cancers not typically thought to be immunogenic. As an example, a phase I study of an allogeneic, granulocyte macrophage colony-stimulating factor–secreting whole-cell tumor vaccine approach was tested in sequence with adjuvant chemoradiation in patients with resected pancreatic adenocarcinoma. This approach is based on the concept that certain cytokines are required at the site of the tumor to effectively prime cancerspecific immunity. In the only study to directly compare a large number of immune-stimulating cytokines, granulocyte macrophage colony-stimulating factor stood out as the most potent cytokine capable of inducing systemic antitumor immunity when expressed by the tumor cells for the initial 24 to 72 hours of immune priming. Granulocyte macrophage colony-stimulating factor is now recognized to be the critical growth and differentiation factor for dendritic cells, which are the most potent professional APC responsible for priming immune responses against infectious agents and tumor antigens. In the study, postvaccination delayed-type hypersensitivity responses were observed in three of eight patients that were vaccinated with either 10⁸ or 5 × 10⁸ cells following surgical resection (78). Postvaccination delayed-type hypersensitivity responses to autologous tumor cells have been used in previously reported vaccine studies as a surrogate to identify and characterize specific immune responses that are associated with vaccination. Toxicities were limited to minor local reactions at the vaccine site and to self-limited systemic rashes. Importantly, this study served as a “proof of principle” that showed allogeneic vaccine cells can induce CD8⁺ T-cell responses against

¹ D.A. Laheru and E.M. Jaffee, personal communication.
Antigens expressed by the autologous tumor via a cross-priming mechanism of antigen processing and presentation, a mechanism thought previously to be inefficient and unlikely to induce significant clinical responses (48). This analysis supports the rationale for the continued development of allogeneic vaccines. A confirmatory phase II study has recently completed accrual.

Clinical trials employing vaccines in sequence with agents that modulate one or more mechanisms of immune tolerance are already showing clinical promise. It is clear that the most effective therapy will require a combined approach, incorporating the best targeted interventions for modulating systemic and local mechanism of immune tolerance. Preclinical models have already revealed the synergy between immunotherapy and other targeted therapeutics, such as inhibitors of CTLA-4, VEGF receptor, and EGFR family signaling. These combinations are already under clinical development. The rapid accumulation of new information identifying other targets of immune regulation will likely translate into additional therapeutic interventions for augmenting antitumor immune responses in patients with cancer. This is the molecular technology age of discovery. The sequencing of the human genome and the development of powerful gene analysis technologies and informatics systems are affecting all fields of biomedical research, including immunotherapy. The future looks cautiously optimistic for immunotherapy of cancer.

References

Genes to Vaccines for Immunotherapy


Molecular Cancer Therapeutics

Genes to vaccines for immunotherapy: how the molecular biology revolution has influenced cancer immunology

Dan A. Laheru, Drew M. Pardoll and Elizabeth M. Jaffee


Updated version  Access the most recent version of this article at:
http://mct.aacrjournals.org/content/4/11/1645

Cited articles  This article cites 75 articles, 31 of which you can access for free at:
http://mct.aacrjournals.org/content/4/11/1645.full.html#ref-list-1

Citing articles  This article has been cited by 3 HighWire-hosted articles. Access the articles at:
/content/4/11/1645.full.html#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.