Cancer Immunology for the Clinician

Louis M. Weiner, MD

Abstract: Cancer immunotherapy is coming of age. It has become abundantly clear that immunotherapy—which has been described as treating the body’s immune system so the immune system can treat the cancer—can be routinely effective, and may indeed cure advanced cancers. Accordingly, it is important to understand the basic, clinically relevant principles of cancer immunology to better prepare for an increasingly exciting future. The host immune system is the only active enemy faced by a malignant cell population as it develops. So it is helpful to think of the battle between the cancer cell population and the developing cancer as a Darwinian crucible in which only the malignant cells most fit to thrive in the face of active immune system attack are able to survive in the reluctant host. All successful cancers thus have overcome the defenses mounted by host immune systems by actively thwarting the evolution of anticancer immunity. A malignant cell population that has “solved” the riddle of the host immune system need not employ all of these mechanisms in order to survive in a particular host. Hence, it may be that the dominant mechanism or mechanisms of immune evasion in fact represent potential Achilles’ heels that can be therapeutically attacked to restore immune control of a cancer. To better understand where opportunities exist for immunotherapy, it is important to first consider how developing cancers overcome host immunity: by overwhelming, hiding from, subverting, shielding from, defending against, and outlasting the host immune response. Clearly, more than one of these mechanisms may be present in any particular patient, but it is likely that many cancer types employ dominant immune defense mechanisms. There can be no doubt that mobilizing the immune system to attack a cancer, remember the enemy, and continually target emerging clones represents an extremely promising path to cancer prevention and cure.

Introduction

Clinical Advances in Hematology & Oncology Volume 13, Issue 5 May 2015 299

Keywords
Antibodies, B cells, dendritic cells, immunotherapy, T cells, vaccines
therapy for advanced melanoma and renal cell carcinoma, and local type I interferon or bacillus Calmette-Guérin instillations to treat early-stage bladder cancer. Monoclonal antibodies such as rituximab (Rituxan, Genentech/Biogen Idec) and trastuzumab (Herceptin, Genentech) have significant utility in lymphomas and breast cancer, respectively, and are important components of curative regimens for these malignancies. Other monoclonal antibodies, such as cetuximab (Erbitux, Bristol-Myers Squibb/Lilly), have important activity against colorectal cancer and cancers of the head and neck. One vaccine, sipuleucel-T (Provenge, Dendreon), prolongs life in men with prostate cancer. Infusions of genetically modified autologous or allogeneic T cells have impressive antitumor activity in selected hematologic malignancies. Antibodies targeting immune checkpoints, such as anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), anti–programmed death 1 (PD-1), and anti–programmed death ligand 1 (PD-L1), have transformed the treatments of melanoma, renal cell carcinoma, and other malignancies (see the table).

### Historical Perspective

Some historical perspective should be considered. Recent decades have been marked by fundamental advances in our understanding of immunology and the relationship of developing cancers with the immune system. However, aside from a few isolated examples of clinical successes, harnessing the power of the immune system to treat human malignancies has remained more of a dream than a reality. Genuine hope and progress have been inadvertently undermined by a heightened state of excitement in response to occasional spectacular responses, such as complete responses to high-dose interleukin 2 therapy for advanced melanoma and renal cell carcinoma. However, the occasionally unwarranted hype about some advances has obscured genuine progress that has led to this era, where it has become abundantly clear that immunotherapy—which has been described as treating the body's immune system so that the immune system can treat the cancer—can be routinely effective, and may indeed cure advanced cancers.

This is remarkable news. Despite the legitimate excitement about targeted therapies for cancer, it has become evident that resistance to any single agent is likely to emerge, as cancer-based signaling networks are remarkably flexible and adaptive. High response rates and short durations of response are to be expected with BRAF inhibitors in melanoma, and epidermal growth factor receptor inhibitors in non–small cell lung cancer. With a few notable exceptions, such as BCR-ABL inhibitors in chronic myelogenous leukemia, targeted therapy is neither curative, nor functionally able to induce very prolonged remissions. In contrast, immunotherapy with checkpoint inhibitors such as anti–CTLA-4, anti–PD-1, or anti–PD-L1 antibodies has somewhat lower response rates but remarkably prolonged

---

### Table. Examples of Successful Cancer Immunotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Impact</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic hematopoietic stem cells</td>
<td>Hematologic malignancies</td>
<td>Curative</td>
<td>1</td>
</tr>
<tr>
<td>High-dose interleukin 2</td>
<td>Metastatic melanoma, metastatic renal cell adenocarcinoma</td>
<td>Occasionally curative as monotherapy</td>
<td>2,3</td>
</tr>
<tr>
<td>Type I interferon</td>
<td>Superficial bladder cancer</td>
<td>Curative as monotherapy</td>
<td>4</td>
</tr>
<tr>
<td>BCG</td>
<td>Superficial bladder cancer</td>
<td>Curative as monotherapy</td>
<td>5</td>
</tr>
<tr>
<td>Antitumor monoclonal antibodies</td>
<td>Lymphomas (rituximab)</td>
<td>Durable responses; improved cure rates in combination with chemotherapy</td>
<td>6-8</td>
</tr>
<tr>
<td></td>
<td>HER2+ breast cancer (trastuzumab)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer (cetuximab)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sipuleucel-T vaccine</td>
<td>Prostate cancer</td>
<td>Improved time to progression</td>
<td>9</td>
</tr>
<tr>
<td>Genetically modified T-cell infusions</td>
<td>Leukemias, lymphomas</td>
<td>Responses in refractory disease</td>
<td>10,11</td>
</tr>
<tr>
<td></td>
<td>Renal cell adenocarcinoma (anti–PD-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung (anti–PD-1), bladder (anti–PD-1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCG, bacillus Calmette-Guérin; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; HER2, human epidermal growth factor receptor 2; PD-1, programmed death 1; PD-L1, programmed death ligand 1.
Innate Immunity

Innate immunity is a primitive system that has been conserved throughout vertebrate evolution. It is characterized by rapid responsiveness, meaning that it occurs within minutes to hours. This is accomplished using the protein products of germline genes that need not undergo receptor rearrangements that underlie the specificity and activity of B cells and T cells. Hence, the innate immune response is not specifically directed against a particular organism or target. The “ready to wear” recognition properties of the innate immune response have low specificity, and typically are based on recognition of molecular patterns, exemplified by toll-like receptors. The innate immune response thus has no immunologic memory. Components of the innate immune response include neutrophils, mononuclear phagocytes, macrophages, dendritic cells, and natural killer cells and their cellular products, which can include a large number of cytokines and chemokines.

Adaptive Immunity

Adaptive immunity is based upon rearrangements of antigen receptors that can endow B cells and T cells with the ability to recognize specific structures—epitopes—on antigens that elicit immune responses. B-cell receptor rearrangements endow B cells and the antibodies secreted by these cells with the ability to recognize both linear (ie, peptide sequences) and conformational epitopes with exquisite specificity and high affinity. In contrast, the T-cell antigen receptor can only recognize defined linear peptide sequences expressed on antigen-presenting cells, such as dendritic cells, when those fragments are presented in the grooves of self–major histocompatibility complex (MHC) loci. MHC class I loci typically present short peptide fragments to CD8+ T cells with cytotoxic properties, whereas MHC class II loci present somewhat longer peptide fragments to CD4+ T cells that can be cytotoxic, but also regulate B-cell function and secrete immunoregulatory cytokines.

Importantly, effective adaptive immunity requires the cooperation of the innate and adaptive arms of immunity. The early warning system of innate immunity

A Clinically Focused Primer on Cancer Immunity

What are the host immune system’s defenses and how do they function? First, it is important to remember that the immune system detects both external threats (eg, bacteria, viruses, fungi, parasites) and internal ones (eg, malignantly transformed cells). The capacity of the immune system to identify, reject, and remember external threats is well established, dating back to the seminal work of Edward Jenner, who developed the first vaccine against smallpox. Vaccines directed against smallpox, polio, measles, mumps, rubella, diphtheria, and tetanus have undoubtedly saved uncounted millions of lives and untold levels of human misery. These results indicate that the immune system is capable of host-protective memory. This memory is the product of both innate and adaptive immunity.
leads to activation and engagement of antigen-presenting cells (APCs), which then attract T cells and B cells that can sample the peptides displayed by the APC and, as discussed later, determine whether any of the sampled peptides pose a danger that requires further action.18

**Antibodies**

Antibodies are proteins produced by activated B lymphocytes that bind specifically to native (unaltered and unprocessed) antigens, which typically are located on the cell surface and thus are readily accessible. The epitopes recognized by antibodies typically are hydrophilic sequences of 6 to 7 amino acids. Immunoglobulin M (IgM) antibodies are pentavalent structures that typically emerge early in the developing adaptive immune response. IgG antibodies emerge subsequently, and can act to remove pathogens or manipulate cell biology in a number of ways that include clearance of circulating antigens, complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions. The most cancer-relevant antibodies are of the IgG subclass, which consists of a 150-kDa dimeric structure containing 2 heavy chains and 2 light chains (see the figure). The heavy-chain dimers contain the constant region (Fc domain) that regulates antibody effector functions such as complement fixation, antibody-dependent cellular cytotoxicity, and manipulation of target cell signaling. IgA antibodies primarily provide mucosal immunity, and IgE antibodies mediate allergic reactions.
Cancer and Immunity

Until recently, the role of immunity in the control of cancer was unresolved. For example, the identification and cloning of human tumor antigens was first reported less than 30 years ago, and there was little evidence to support the idea that cancer represents a failure of immune surveillance. Notably, patients with various immunodeficiencies (including chronic HIV infection) do not experience globally increased cancer incidence. It has long been assumed, and increasingly demonstrated over the past decade, that developing malignancies actively thwart the evolution of antitumor immunity.

One of the first clues that cancers indeed work hard to overcome host immunity comes from simple examination of tumor architecture by light microscopy or immunohistochemistry. As elegantly demonstrated by Jain and colleagues, the angiogenic landscape is profoundly altered in solid malignancies. In addition, the tumor stroma are characterized by zones of hypoxia; by dense, activated collagenous stroma; and by elevated intratumoral oncotic pressures.23 Cancers would not resort to such extremes unless it were necessary, and the only true enemy faced by a developing malignancy is the immune response it needs to overcome.

Compounding these challenges is the fact that cancers look like “self” to the host immune system. Many recent studies have demonstrated that even the most heavily mutated malignancies express no more than a few hundred mutations.24 Although this is certainly sufficient to provide targets for immune recognition, it is also true that these malignant cells contain many thousands of perfectly normal genes and gene products. Therefore, a powerful immune response that “spreads” to target both mutated and wild-type protein products might induce powerful immunity directed against normal cells that are required for normal function.

A further challenge is that the immune landscape in any cancer patient is the product of the unique mutational landscape and the properties of the host immune system. Hence, although there may be common mutations (eg, TP53, KRAS), the actual sequences and their influences on host immunity may differ. Moreover, the critical mutations that drive immune responses may frequently be less heavily shared and more idiosyncratic. As a consequence, it may be difficult to effectively and safely break tolerance to “self” antigens. However, as will be discussed, this challenge frequently can be surmounted, with gratifying clinical outcomes.

Cancer’s Defeat of the Host Immune Response

The centrality of the war between cancer and the immune system in the development of malignancies can be inferred by the large array of mechanisms by which cancers induce specific immune suppression. For example, important advances in understanding cellular immune responses in cancer have identified regulatory T cells (Tregs), typically identified as CD4+, CD25+, and expressing the forkhead box P3 (FOXP3) transcription factor, as important in suppressing active T-cell antitumor immunity.25 These same cells are well known to regulate T-cell immunity in both health and disease. Immunosuppressive granulocytes expressing CD11c have similar properties,26 as do various subsets of mononuclear phagocytes.27 Immunosuppressive cytokines28 and chemokines29 can be expressed by malignant cells, or by cells in the malignant stroma. More recent evidence suggests that these molecules can have important roles in preventing the tumor infiltration of cytotoxic antitumor T cells.30 Many studies have demonstrated that malignant cell signaling can contribute to the loss of class I MHC expression of tumor cells,31 to the degradation of tumor-related T-cell signaling molecules such as the T-cell receptor ζ-chain32 and transcription factors such as STAT-3,33 and to the generation of immunosuppressive small molecules such as indoleamine 2,3-dioxygenase.34

Evolutionary biology principles suggest that a malignant cell population that has "solved" the riddle of the host immune system need not employ all of these mechanisms in order to survive in a particular host, and would do only what was necessary. Hence, it may be that the dominant mechanism(s) of immune evasion in fact represent potential Achilles’ heels that can be therapeutically attacked to restore immune control of the malignant population. This has been the focus of much work over that past decade, and in fact has been remarkably productive and promising.

The Prognostic Significance of Cancer-Associated Immune Infiltrates

A rapidly increasing body of evidence suggests that the content and location of certain types of immune cell infiltrates have prognostic significance in colorectal, breast, ovarian, and lung cancers. Galon and colleagues have developed a score called an “Immunoscore” based on immunohistochemical analysis of activated T cells and other immune cells that is more accurate than conventional TNM staging.25 Although these findings have important potential clinical applicability, it is perhaps even more important to consider the biological lessons. First, if immune infiltrates are frequently found, it stands to reason that these malignancies are stimulating an immune response. Second, that immune response is not effective at preventing the development of the malignancy, so it is reasonable to conclude that the malignant cells have developed mechanisms to evade, subvert, or disable the cancer-directed immune response. Next, because the immune infiltrates have prognostic significance, cancers
that can effectively exclude immune infiltrates are more successful than those that cannot. In aggregate, these observations support the approach of therapeutically inducing cancer-directed immune infiltrates containing CD8+ cytotoxic T cells that recognize cancer-specific antigen targets.

**Immune Editing**

Contemporary thinking about the role of immunity in cancer development has been profoundly influenced by the work of Robert Schreiber and Mark Smyth, who have provided a mechanistic framework for the concept of immune shaping. First described in 2001, Schreiber and colleagues conducted a series of seminal experiments demonstrating this phenomenon.36

In these experiments, wild-type and immune-deficient recombination-activating gene 2 (Rag2)−/− mice developed malignant sarcomas after treatment with the powerful carcinogen methylcholanthrene. Not surprisingly, the tumors growing in the wild-type mice grew more slowly than those in the Rag2−/− mice, suggesting that T-cell immunity was relevant in the development of these malignancies. When the wild-type tumors were then explanted into naive wild-type and Rag2−/− mice, the tumors grew at similar rates, with no evidence of preferential immune rejection in the wild-type mice. Hence, the tumors that originally grew in wild-type mice had already undergone immune editing, and were not the targets of T-cell–related immune attacks.

Remarkably, when tumors that originally grew in the Rag2−/− mice were explanted into groups of naive mice, the tumors grew rapidly in the Rag2−/− recipients, but were rejected by the wild-type mice. Hence, tumors that originally developed in the immunodeficient mice did not face T-cell–based immune selection pressures, and so still expressed antigenic determinants and lacked the defenses that had to be acquired in tumors that originally developed in the wild-type mice. This process of immune editing creates malignant cell populations that have acquired the properties needed to succeed in an immuno-competent host.36

Subsequent work has further characterized this process as consisting of 3 phases.37 In the first phase, known as elimination, the immune system and the developing cancer are engaged in active combat. Cells bearing strong antigens are identified and eliminated, and malignant cells that have either lost strongly immunogenic antigens or developed immune defense mechanisms are able to survive that conflict. In the equilibrium phase, the malignant cells and host immune system experience a truce, until there is an event—the emergence of either a resistant malignant cell variant with a different antigen profile, or the capacity to evade host immunity—that leads to escape.

**How Cancers Solve the Challenge of Host Immunity**

To better understand where opportunities exist for immunotherapy, it is important to first consider the general mechanisms employed by developing cancers to overcome host immunity. The broad categories of cancer-based immune defense mechanisms can be classified as (1) overwhelming, (2) hiding from, (3) subverting, (4) shielding from, (5) defending against, and (6) outlasting. Clearly, more than one of these mechanisms may be present in any particular patient, but it is likely that many cancer types employ dominant immune defense mechanisms, such as PD-L1 expression in some patients with malignant melanoma.

**Cancers Can Overwhelm the Host Immune System.**

Some malignancies can simply outrun the host immune system. Examples include Burkitt lymphoma and acute leukemias. Although ancillary mechanisms of immune suppression may be important in the development of these malignancies, when they are diagnosed there may not be sufficient time for manipulation of the host immune response to achieve meaningful therapeutic benefit. This might be construed as an argument for cytotoxic therapies; however, it should be noted that infusions of antigen-specific T cells have had remarkable antitumor effects in some patients with acute leukemias.30,11 Accordingly, although there may not be sufficient time to evolve a therapeutically useful in vivo immune response, infusions of fully competent, antigen-specific, autologous or allogeneic T cells can produce remarkable clinical outcomes.

**Cancers Can Hide From the Immune System.**

Some cancers adapt to immune selection pressures by losing target antigen expression, or through diminished expression of MHC class I or class II on malignant cells or APCs, thus reducing antigen presentation. Potential solutions to these obstacles include the use of vaccines to induce host immunity against existing or new antigens, with the use of adjuvant strategies that can induce MHC class I and class II expression, alone or in concert with additional costimulatory strategies.39

Cancers can also hide physically from the immune system through disordered angiogenesis, profound hypoxia, and dense collagenous stroma.41 These properties offer opportunities for incorporating immunotherapy strategies in concert with antiangiogenic agents, metabolism-targeted therapies and cytotoxic approaches to
achieve cytocidal activity and reverse factors that promote malignant stromal proliferation.

**Cancers Can Subvert the Immune System.** Malignant cells can secrete chemokines and cytokines to create an immune-suppressive microenvironment, sometimes referred to as a Th2 milieu. Immune cellular components associated with a Th2 milieu include Treg cells, myeloid-derived suppressor cells, tumor-associated fibroblasts, “type 2” macrophages, and dendritic cells. Antagonistic antibodies (eg, anticytokine antibodies) or small molecules can therapeutically target these immunosuppressive networks.

**Cancers Can Erect Shields to Deflect the Immune System.** T cells that cannot infiltrate into tumors cannot exert significant antitumor effects. Cancers erect these perimeter shields in a variety of ways. Cancers may shed antigens into the tumor microenvironment, and it is intriguing to speculate that T cells may be accordingly diverted. Immunosuppressive cytokines and chemokines can actively interfere with the gradients that are required to direct T cells to malignant cells. This represents an underexplored opportunity to identify targets for therapeutic intervention using antibody or small-molecule cytokine and chemokine antagonists.

**Cancer Cells Can Defend Against T-Cell Frontal Assaults.** Immune checkpoints are used by cancers to deactivate T cells that penetrate tumor defenses and engage malignant cells. The best example of this is PD-L1 expression by malignant cells and APCs. PD-L1 is also induced by γ-interferon secreted by tumor-infiltrating cytotoxic T lymphocytes. When PD-L1 engages PD-1 expressed on the surfaces of activated T cells, those T cells adopt an “exhausted” phenotype and are not effective. Antibodies that block the binding of PD-L1 to PD-1 can reverse this exhaustion phenotype, and the T cells are then liberated to attack relevant antigen-expressing tumor cells. This biology has been targeted by a number of therapeutic antibodies with significant antitumor activity in diseases such as malignant melanoma, renal cell carcinoma, non–small cell lung cancer, bladder cancer, and Hodgkin lymphoma.

PD-L1 is but one of many immune checkpoints. Other regulators of T-cell function include CD47, which sends a “don’t eat me” signal that blocks macrophage-based phagocytosis and has been shown to regulate the induction of T-cell immunity as well. It is plausible that blocking antibodies or small molecules would disable at least some of these checkpoints, removing the last line of defense possessed by many malignancies against destruction by the immune system.

**A Role for Combinations?**

It is possible, and indeed likely, that many immunotherapy combinations will be tested over the next few years. Such clinical trials will require virtuosity in design, execution, and analysis. Anti–PD-1 antibodies have been successfully combined with anti–CTLA-4 antibodies, yielding promising results in malignant melanoma. As new agents therapeutically target additional checkpoints, they too will be combined. It is certain that these therapies will be combined with cytotoxic chemotherapy, radiation, and various targeted therapies to exploit cytodestructive strategies and to manipulate malignant cell signaling to favor successful immunotherapy. Combinations of cellular therapies with checkpoint inhibitors are on the horizon as well. Regardless of how these exciting new treatments are administered, there can be no doubt that mobilizing the immune system to attack a cancer, remember the enemy, and continuously target emerging clones represents a promising path to cancer prevention and cure.

In some cases, it will be necessary to employ combinations to address relevant survival mechanisms in specific cancers. However, it is evident that in some patients, a single immunotherapy manipulation is both necessary and sufficient for prolonged clinical benefit and even cure. It should be remembered that interleukin 2 therapy is curative in some patients with melanoma or renal cell carcinoma. This is in accord with the principles of natural selection; when cancers have solved the obstacles posed by the host immune system, multiple mechanisms of immune escape may not be needed, and monotherapy may be sufficient to reawaken the anticancer immune response. However, it will behoove researchers to understand the mechanisms of resistance that are relevant to clinically effective immunotherapy so that nascent resistance mechanisms can be anticipated and intercepted before they are clinically manifested.

**Conclusion**

Cancer immunotherapy has come of age. Harnessing the power of the immune system to recognize, attack, and remember malignancies offers new possibilities for effective therapy and prevention. Oncologists now have a widened range of weapons at their disposals to turn the tide in the war against cancer.

**Acknowledgment**

This work was supported by NIH grants NCI CA51008 and NCI CA50633.

**Disclosures**

Dr Weiner has served as a consultant or advisor to Merrimack Pharmaceuticals, Celldex Therapeutics, Targeted Diagnostics...
References


