Clinical Roundtable Monograph

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Emerging Strategies in Regulatory T-cell Immunotherapies

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Abstract

The ability of tumors to evade immune system surveillance is an important characteristic that allows for their growth and survival. Accumulating evidence suggests that the mechanisms which allow for tumor cell evasion are similar to those that exist to prevent autoimmune diseases. Thus, targeting the immune system may be a major strategy to develop novel anti-tumor therapies. Among these strategies are therapies directed against regulatory T cells, as well as therapies designed to enhance the immune response triggered by CD8+ T cells. In this clinical roundtable, several experts discuss emerging strategies in regulatory T-cell immunotherapies. First, the major concepts behind immune suppression of solid tumors are described, including the current challenges and therapeutic targets under investigation. Then, the strategies under development are examined for their ability to overcome the regulatory T-cell effects in tumors. Finally, the roundtable concludes with a discussion of how these basic immunomodulatory concepts are being translated into clinical application. By understanding this roundtable, the clinician or oncologist will have a strong understanding of the current state-of-the-art strategies under investigation for anti-tumor immunotherapy.

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Activity Overview

The immune system plays a critical role in preventing malignant transformation and inhibiting tumor growth. However, through a variety of mechanisms, tumors are often able to evade immune surveillance. Immunotherapeutic options available to clinicians for use in combating tumors include promoting immune-mediated surveillance, suppressing tumor growth, or inhibiting tumor-induced immune suppression. This article reviews the mechanisms used by solid tumors to evade immune surveillance, clinical strategies for overcoming immune suppression mediated by regulatory T cells in patients with cancer, and future directions in immunomodulatory concepts for clinical applications.

Target Audience

This activity has been designed to meet the educational needs of medical oncologists and other health care providers who manage patients with malignancies.

Learning Objectives

After completing this activity, participants should be able to:

- Describe the role of regulatory T cells and their interaction with cytotoxic T cells in tumor suppression and surveillance
- Compare and contrast the mechanisms and efficacy of different strategies used to deplete or downregulate regulatory T cells
- Evaluate the clinical data on the effect of regulatory T-cell depletion or downregulation on outcomes for patients with specific malignancies

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Fludarabine phosphate	Fludara®	Treatment of adult patients with B-cell chronic lymphocytic leukemia	Regulatory T-cell depletion in patients with solid tumors

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Immune Suppression in Solid Tumors

Thomas F. Gajewski, MD, PhD

Current Challenges

For several years, it has been established that tumors express antigens that are recognizable by T cells in the immune system. Although this intuitively suggests that tumors are good candidates for recognition and clearance through immune mechanisms, for example following vaccination against tumor antigens, this only rarely occurs clinically. This low level of response has prompted investigation into the mechanisms of resistance by which tumors may evade immune clearance. Two main escape mechanisms have been identified: the insufficient recruitment of T cells into tumor sites, and the inhibition of the function of T cells that are successfully recruited.

T Cell Migration into Tumor Sites

To examine the impact of the tumor microenvironment on resistance mechanisms, several approaches have been taken. One of these approaches involves the gene expression profiling of melanoma patient samples obtained prior to vaccination.[1] The rationale behind this strategy is to associate patient-specific clinical outcome data with particular gene expression patterns, revealing those genes that are predictive of favorable or unfavorable outcomes, respectively. This was done in an initial clinical trial of 20 patients with metastatic melanoma, and was subsequently supplemented with samples from 50 additional metastatic melanoma patients to increase the robustness of the data set. Analysis of the gene expression profiles of these patients has revealed 2 major barriers to successful immune-mediated rejection. The first of these is a patient set with a particular profile of chemokines, or chemo-attracting cytokines that participate in the immune cell trafficking. This profile is suggestive of the presence of chemokines that can recruit activated T cells into the tumor microenvironment. Only tumors from a subset of patients have this chemokine signature. This suggests the remaining tumors that lack key factors necessary to recruit activated T cells into the tumor, thus preventing the T cells from executing their goal of inducing tumor cell death. Two additional studies, one in melanoma and another in nonsmall cell lung cancer, have similarly analyzed tumor samples taken prior to immunization with a MAGE3 vaccine. These studies have also observed the presence of a chemokine signature in the favorable clinical outcome patients.[2]

Negative Regulatory Factors in the Tumor Microenvironment

The second barrier exists in those tumors which do express the chemokines necessary for T-cell recruitment, but are still not effectively rejected by the immune system. An illustration of this barrier is provided by a patient who has undergone vaccination, resulting in a large induction of T cells that are specific against the tumor antigens present within that individual. While the tumor microenvironment within that patient expresses the correct chemokines necessary to recruit T cells to the tumor site, the patient does not have obvious tumor regression. It is within this subset of tumors in which active investigation is underway to identify the presence of immunosuppressant mechanisms that inhibit the function of the T cells.

Using tumors from melanoma patients who do not display a robust tumor regression following vaccination, 4 negative regulatory mechanisms have been identified within the tumor microenvironment.[3] (Figure 1) These escape mechanisms are thought to inhibit the function of the T cells that are successfully recruited to the tumor. The first of these is a molecule termed programmed death ligand 1 (PD-L1). PD-L1 engages an inhibitory receptor expressed on the surface of T cells, programmed death 1 (PD-1), and mediates inhibition of T-cell activation.[4] PD-L1 has been found to be highly expressed in many tumor types.[5] The second of these factors, indoleamine 2,3-dioxygenase (IDO), is an enzyme involved in metabolic dysregulation. IDO has been identified in a subset of tumors, either as a result of direct expression by the tumor cells or through expression by infiltrating dendritic or endothelial cells.[6,7] IDO is responsible for metabolizing tryptophan and has previously been shown to be important in the induction of immune tolerance at the maternal/fetus interface.[8] The third mechanism which negatively mediates the tumor microenvironment is a hyporesponsive state termed T-cell anergy. Anergy arises in the setting of T-cell stimulation that occurs in the absence of costimulatory ligands, including B7-1 and B7-2.[9,10] Recently, a mouse model showed that T-cell anergy occurred in mice expressing B7-negative tumors, and studies in other animal models have found that subsequent transfection of B7 leads to successful tumor rejection.[11-13] Most tumors appear to lack expression of these costimulatory ligands. The fourth mechanism involves regulatory T cells (Treg). Treg cells may be identified by positive surface expression

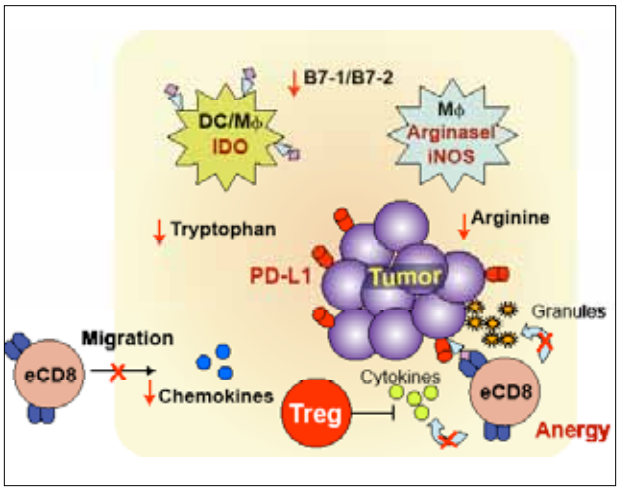

Figure 1. Summary of tumor microenvironment barriers: Need to promote T cell trafficking and overcome local immunosuppression.

DC=dendritic cells; eCD8=effector CD8; IDO=indoleamine 2,3-dioxygenase; INOS=inducible nitric oxide synthase; M =macrophages; PD-L1=programmed death 1

Adapted from Gajewski TF. *Clin Cancer Res*. 2007;13:5259.

of CD25 and CD4, as well as intracellular expression of the transcription factor Foxp3.[10] Treg cells function to inhibit the activation of conventional T cells. Treg cell levels have been reported to be elevated in patients with multiple forms of advanced-stage tumors, and occur at relatively high levels within the tumor microenvironment.[14-18] Research has shown that the tumors which have successfully recruited an active immune response, and theoretically should be leading to tumor rejection, also have the highest quantity of Treg cells. Interestingly, assessment of the expression of these main factors, namely PD-L1, IDO, and Foxp3, using quantitative reverse-transcription polymerase chain reaction (RT-PCR) has revealed that their magnitude of expression increases coordinately.[1]

Opportunities for Therapeutic Intervention

Recent work has shown that interference of each of these mechanisms alone can be sufficient to improve T-cell mediated tumor control in specific animal models. For example, inhibiting the PD-L1/PD-1 interaction results in improved T-cell function in vitro, as well as increased tumor control in several mouse models.[19,20] A fully human anti-PD-1 monoclonal antibody is completing phase I testing in patients.[2] However, an even more profound impact is observed when 2 or more of these escape mechanisms are depleted or inhibited in concert. The most striking example of this was shown in animal studies, with the depletion of Treg cells in conjunction with the reversal of T-cell anergy using a process termed homeostatic proliferation, which results in the spontaneous proliferation of T cells and maintenance of T-cell function. The combination of these 2 strategies resulted in a profound and spontaneous rejection of melanoma tumors in these mice.[21] These data suggest not only that Treg depletion is an important strategy for combating tumor escape, but that depletion of Treg cells in combination with other immunomodulatory interventions may be even more beneficial than Treg depletion alone.

Based on impressive results in animal models, interference with these escape mechanisms is under investigation in the clinical setting as well. One important strategy being evaluated in the clinic involves the fusion protein denileukin diftitox. This is a recombinant fusion protein comprised of the interleukin (IL)-2 ligand linked to diphtheria toxin. IL-2-mediated binding to the CD25 receptor on the surface of Treg cells allows Treg-specific targeting of the diphtheria toxin. Once bound with CD25, the diphtheria toxin portion of the ligand is internalized, thus inducing Treg cell death. Denileukin diftitox is being tested as a strategy which, when combined with the T-cell activation induced by vaccination, may result in tumor regression and tumor cell death.[22,23] In the second strategy, translation from animal studies is underway to investigate the combination of Treg cell depletion and homeostatic proliferation. In this way, the preclinical data suggesting synergistic antitumor activity when multiple immune suppressive mechanisms are countered simultaneously can be investigated in patients.

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Strategies to Overcome Regulatory T-Cell Effects in Cancer

Jason Chesney, MD, PhD

Rationale for Treg-Cell Depletion in Cancer Patients

Multiple lines of evidence provide rationale for targeting Treg cells in cancer patients. First, studies using immunofluorescence to identify Foxp3-positive cells report that Treg cells may be found at elevated levels within tumors. An initial demonstration of this occurred in patients with early-stage non-small cell lung cancer or late-stage ovarian cancer.[1] Subsequently, several tumor types have been found to have increased Treg cells, including but not limited to breast cancer, pancreatic cancer, and melanoma.[2-4] This finding was confirmed by another study, which demonstrated a striking Treg accumulation in carcinogen-induced tumors.[5] Treg cells also have been demonstrated to be increased amongst the tumor-infiltrating lymphocytes of patients with gastric and esophageal cancers.[6] This same study showed that the number of Treg cells, reported as a percentage of total CD3+ cells, in gastric cancer patients with advanced disease was higher than those with early-stage disease (19.8% vs 4.8%, respectively), indicating a role in tumor progression. The second major line of evidence providing rationale for targeting Treg cells in cancer patients comes from preclinical studies in mice. These studies used an antibody directed against CD25, a cell surface protein highly expressed on Treg cells. Antibody-mediated depletion of CD25-positive Treg cells caused tumor regression, reduction in tumor growth, and improved tumor immunity in multiple cancer types.[7] For example, in a mouse model of melanoma, Treg depletion led to induction of tumor immunity through a T-cell response that was found to be specific for the melanoma antigen tyrosinase.[8]

Homeostatic T-cell proliferation is a concept that has also been well-studied in animal models. This response is defined as the proliferation of T cells induced as a consequence of severe T-cell depletion.[9] The cytokines IL-7 and IL-15, but not IL-2, have been shown to be important for this process; in the absence of these cytokines, homeostatic proliferation fails to occur.[10] This rebound results in a near constant pool of T cells. In humans, unlike in animals, this phenomenon has generally not been well studied. One setting in which it has been studied in humans, however, is in HIV-positive patients, who may develop an autoimmune syndrome following a homeostatic proliferation response.[11] The T-cell expansion resulting from homeostatic proliferation is controlled, in part, by the peptide MHC complex. Therefore, if a particular antigen is present, T cells specific for that antigen will proliferate.[12] This concept has been applied to melanoma, where it was hypothesized that if homeostatic proliferation could be induced, the expanding T cells would be specific to the melanoma-specific antigens highly expressed by the tumor.

The IL2/diphtheria toxin fusion protein denileukin diftitox should prove useful in both depleting Treg cells and inducing homeostatic proliferation. Denileukin diftitox was originally developed as a treatment for cutaneous T-cell lymphoma, and targets the CD25 protein which is highly expressed on the surface of these cells, activated T cells, and Treg cells.[13] By IL-2-mediated binding to CD25, and internalization of the diphtheria toxin, denileukin diftitox can lead to inhibition of protein synthesis and cell death. Interestingly, a recent clinical study reported that the CTCL cells may function similarly to Treg cells, in that they can inhibit CD4+ T-cell proliferation through a contact-dependent manner.[14]

A phase II clinical trial was designed to evaluate denileukin diftitox in the setting of unresectable stage IV melanoma.[15] In this ongoing study, denileukin diftitox was administered at an intermediate dose of 12 µg/kg. In order to deplete both T cells and Treg cells in a transient manner, a multiple dosing schedule was used. Data from the first interim analysis of 16 patients have been published.[16] Using automated complete blood counts, the total lymphocyte population was found to be decreased by approximately half with denileukin diftitox treatment, showing that denileukin diftitox was not just leading to elimination of Treg cells. Interestingly, with the depletion of total lymphocytes from the peripheral blood, an inverse effect was shown on monocytes and granulocytes, of which the total number had increased. Both of these effects were observed by 48 hours post-denileukin diftitox treatment. By day 7, the peripheral blood lymphocyte count returned to approximately 70% of control, and reached normal baseline concentration by day 21. This was also true for CD4+ and CD8+ T cells. No functional analysis of the Treg cells was performed. Instead, triple positive (CD4+, CD25+, and Foxp3+) T cells were analyzed using 3-color flow cytometry, in order to quantitate the peripheral blood Treg cells. Because denileukin diftitox specifically targets CD25, it was not thought that this agent would have an effect on CD4+CD25- cells. However, the number of these cells was reduced to approximately 70% of control, a less dramatic decrease as the reduction to 30% of control observed in CD25+ cells. By day 21, the number of both of these cell populations returned to baseline, a phenomenon speculated to be due to homeostatic proliferation. The levels of triple-positive Treg cells also dropped within 1–2 days of denileukin diftitox initiation, and rebounded to baseline levels by day 21.

Individual patient data, which included the first 10 patients in this population, showed that over 4 treatment cycles, the Treg cell depletion observed with the first cycle of denileukin diftitox was markedly attenuated with each subsequent cycle. This was not well-correlated with the onset of anti- denileukin diftitox antibodies, a common phenomenon after administration of this recombinant protein. The investigators also determined the presence of CD8+ cells specific for melanoma antigens, using a fluorescent dye-linked tetramer to target CD8+ cells. Of the 16 patients in the interim study, only 7 expressed the HLA-A2*0201 class I MHC needed for tetramer-based measurement of the CD8+ T cells specific for melanoma antigens. Within these 7 identified patients, 4 exhibited *de novo* appearance of CD8+ cells specific for the melanoma antigens tested in this study (MART1, gp100, and tyrosinase).

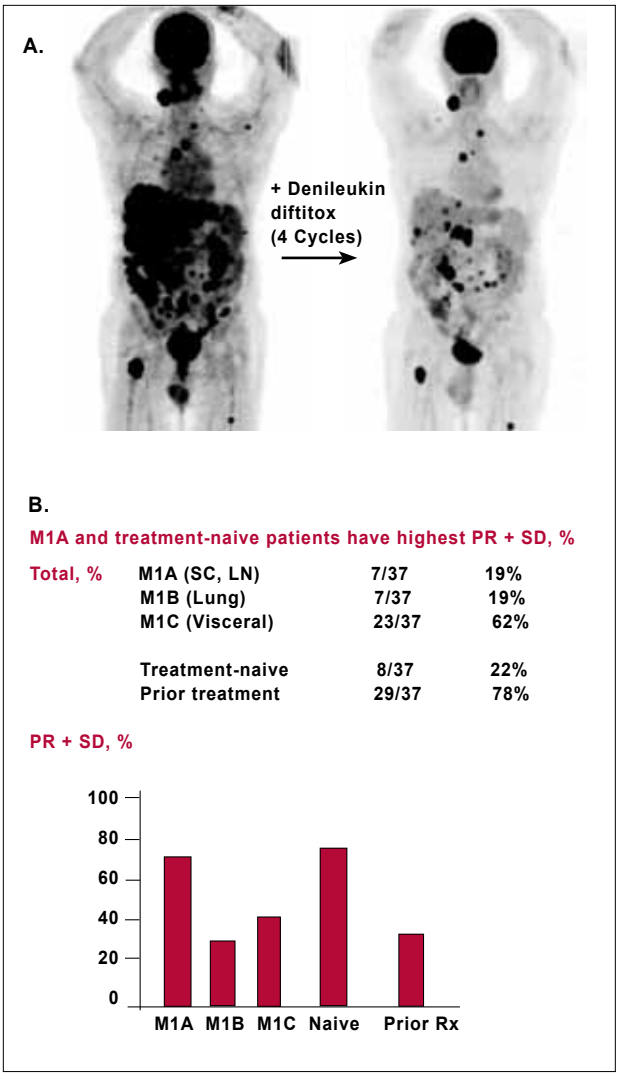

Figure 2. Interim Analysis of Phase II Trial of denileukin diftitox in Stage IV Melanoma. (A)Typical partial response confirmed by FDG-PET scan after 4 cycles of denileukin diftitox. (B)Trend towards increased response rate in M1A and treatment naïve melanoma patients.

LN=lymph node; M1A=M1a subtype; PR=partial response; SC=subcutaneous; SD=stable disease

Adapted from author's unpublished data; trial identifier NCT00299689.

Of these first 16 melanoma patients treated with denileukin diftitox, a total of 5 had measurable objective responses. Recently, an interim analysis of the first 37 patients in this trial was completed for evaluation by the Data Safety Monitoring Committee. In these 37 patients, 32.4% achieved a partial response (PR), 10.8% had stable disease (SD), and the remaining 56.8% exhibited progressive disease (PD). Importantly, some of the responses classified as PR involved elimination of the majority of melanoma metastases (Figure 2A). At the 3-month imaging point, no complete responses (CR) have been observed. The 6-month progression-free survival rate was 23%, considered to be above the benchmark used for the consideration of a novel therapy for a phase III clinical study. A patient subanalysis showed that while all subtypes of stage IV melanoma responded, the M1a subtype, described as lymph node-positive and subcutaneous, may respond slightly better, whereas the M1c subtype, described as visceral disease with organ involvement, did not respond as well (71% vs approximately 39%, respectively; Figure 2B). Interestingly, of the 8 treatment-naïve patients who were older than the study population as a whole, 6 patients exhibited either a PR or SD. This was compared with 10 patients with PR or SD of the 29 remaining patients who had received prior therapy. Although it was anticipated that there would be an association between response and prior exposure to IL-2, no such correlation was observed. The most common adverse events observed in this study were nausea, fatigue, and rash; all adverse events were grade 1 or 2 in severity. A single patient developed vitiligo, a CD8+ T cell-driven autoimmunity against melanocytes. This patient had exhibited a fairly dramatic response to denileukin diftitox, with the complete regression of approximately 60 tumors, leaving only a single tumor located next to the patient's aorta. This tumor was resected, and upon biopsy was shown to have no CD4+ or CD25+ T cells, whereas CD8+ T cells were observed to be infiltrating the melanoma (author's unpublished data; trial identifier NCT00299689).

This study showed that denileukin diftitox treatment clearly depletes Treg cells, but also leads to the depletion of CD4+ and CD8+ cells at the dosage used. The investigators concluded that denileukin diftitox was able to induce melanoma-specific immunity. Importantly, this was possible using the patient's own tumors without the need to manipulate the tumors themselves. All responses were qualified as PRs, and treatment-naïve individuals tended to respond slightly better. Although the side effect profile of denileukin diftitox was determined to be acceptable, future investigation is required in order to identify the optimal dosage of denileukin diftitox therapy. A recent report has confirmed that the combination of Treg depletion and induction of homeostatic proliferation is critical for the antitumor effect observed in an aggressive mouse melanoma model.[17] These studies thus may form the basis for future denileukin diftitox-driven clinical trials using vaccine strategies. Additionally, Treg cell depletion with denileukin diftitox may provide added benefit to the humanized monoclonal antibodies currently under investigation as monotherapy for melanoma. Regarding alternative strategies, the author does not know of any other drugs to this date that are effective in depleting Tregs and inducing melanoma regressions.

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Translating Basic Immunomodulatory Concepts into Clinical Application

Tyler J. Curiel, MD, MPH

Early-Stage Novel Regulatory T Cell-Targeted Agents in Solid Tumors: Clinical and Immunologic Efficacy and Safety Data

Tumors express antigens that are not normally found in the host. Although abnormal antigen expression should elicit a protective immune response, clinically-apparent tumors are not usually immunologically eliminated. The reasons for this lack of immune elimination are not well understood. Further, many investigators use fundamental immunologic principles identified in infectious disease models to attempt to understand tumor immunology, but these infectious disease principles may not bear useful insights into tumor immunopathology.[1]

In the infectious disease model, antigen is taken up by an antigen presenting cell, usually a dendritic cell, which will then elicit a specific and protective immune response against that particular antigen. This immune response includes antigen-specific CD8+ cytotoxic T cells that mediate antigen elimination. Based on this understanding, most anticancer immune-based therapies to date have attempted to improve antigen presenting cell activation or antigen-specific CD8+ T-cell generation or function. Several lines of investigation have also focused on the identification of novel tumor-specific antigens, and the generation of CD8+ cytotoxic T cells specific for these antigens. These strategies usually require the ex vivo production of large numbers of dendritic cells, followed by activation, and incubation with tumor-specific antigens or large numbers of CD8+ T cells followed by adoptive transfer into patients. Active vaccinations have also been used to induce tumor-specific immunity. However, with a few minor exceptions, all of these strategies have largely failed. Additionally, they are very expensive, logistically difficult to undertake, subject to significant regulatory hurdles, and not easily applicable to large patient populations.

Two possibilities exist regarding lack of complete immunologic tumor eradication: 1) an ineffective immune response against the tumor, or 2) otherwise effective antitumor immunity is inhibited. In many cases, there is no lack of immunogenic tumor-specific antigens, antigen-presenting cells, or cytotoxic T cells. Instead, the problem likely lies in the inhibition of these responses, preventing immunologically-mediated tumor clearance. Tregs are implicated as important mediators inhibiting otherwise effective antitumor immunity. Studies in animal models and human patients have identified specific agents to deplete Tregs. For example, as discussed by Dr. Chesney and as we have shown, low doses of the IL-2/diphtheria toxin fusion protein denileukin diftitox will deplete Tregs in patients with various epithelial cancers. Treg depletion is not simple lymphopenia, as other T-cell populations increase following Treg depletion, including $CD8^{+}$interferon-γ^{+} T cells.

We conducted a phase 0/I trial and determined that denileukin diftitox could deplete Tregs in patients with advanced-stage epithelial carcinomas. We also observed that a patient with stage IV metastatic ovarian cancer experienced significant immunologic improvement following a single infusion of 12 µg/kg of denileukin diftitox. We received IRB approval to give her 6 additional weekly infusions and achieved a partial clinical response (our unpublished data). This evidence, together with preclinical data, led to our current phase II trial evaluating denileukin diftitox 12 mg/kg once every 4 weeks to treat advanced-stage epithelial ovarian carcinoma failing taxane plus platinum therapy. Although this trial is ongoing, early observations suggest that this dose and schedule is well-tolerated, with generally only grade 1 toxicities. Importantly, in addition to depletion of circulating Tregs, data from this trial also show depletion of phenotypic and functional Tregs specifically at the tumor site. Demonstrating Treg depletion at the tumor site is especially important, as tumor immunity is compartmentalized.[2-4] Thus, we now have evidence that observing Treg depletion in peripheral blood might reflect events occurring specifically within the tumor microenvironment, although additional work in this regard is needed.

Differences and Similarities in Conventional Versus Biologic Therapy

Cyclophosphamide is another therapy under investigation for Treg depletion. Several animal studies have provided evidence that this conventional chemotherapeutic agent depletes Tregs.[5,6] Early evidence in humans also suggests that cyclophosphamide may boost the efficacy of vaccination.[7] However, its efficacy as an immunomodulatory therapy is still under debate.[8] Another agent, fludarabine, initially developed to treat chronic lymphocytic leukemia, can also deplete Tregs.[9,10] However, fludarabine is highly toxic and may also greatly deplete beneficial antitumor T cells, sug-

gesting its unlikely use as a potential immunomodulatory agent. Two separate antibodies directed against CD25 have been investigated in clinical trials.

Recently, a dose-finding study of one of these, basiliximab, was reported, which found low-dose administration to be clinically safe.[11] A phase II study of basiliximab is currently planned.

A novel fusion toxin, IL-2-conjugated with a pseudomonas exotoxin, has been developed and also demonstrated to deplete Tregs in humans.[12,13] However, unlike denileukin diftitox, cyclophosphamide, and fludarabine, this pseudomonas-IL-2 fusion toxin is not yet approved by the US Food and Drug Administration.

Future Directions and Applicability in Cancers and Other Diseases

Many tumor types respond clinically to Treg depletion in animal models. Ovarian cancer, melanoma, and renal cell carcinoma have been studied in humans with encouraging preliminary clinical results. The fact that Treg depletion could be effective in different tumor types is not surprising in that this strategy is not targeted to the tumor itself, but instead targets host antitumor immunity. Nonetheless, immune-targeting strategies will be limited by tumor immune evasion including mutation of tumor-associated antigens, or lack of sufficient antigen processing or presentation by tumor (such as reduced expression of MHC class I). Immunoediting, the sculpting of immunity by the tumor, could present another significant hurdle.[14]

Another important point to consider regarding antitumor immunotherapy is that tumor burden will generally be lower in early-stage versus late-stage disease. Although this therapeutic strategy may best be applied to patients with earlier stage disease, it is usually difficult to include these patients into current clinical trials.

Recent data suggest that while depleting Tregs is a potentially useful point of attack for immune-based therapy, it is unlikely to be sufficient for inducing a fully therapeutic antitumor immune response.[2] One cause for failure is that Tregs that are initially depleted will subsequently get regenerated. Thus, much effort is focused on the mechanism which controls this regeneration to identify potential means to prevent it. In addition to Treg depletion, we have identified other strategies to manage Tregs in cancer including inhibiting Treg function, raising the threshold of Treg-mediated suppression (which could in part explain how anti-CTLA-4 antibodies work), preventing Treg trafficking to relevant sites, and preventing Treg differentiation or proliferation.

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Emerging Strategies in Regulatory T-cell Immunotherapies

CME Post-Test: *Circle the correct answer for each question below.*

1 _____ describes the concept that depletion of the T-cell population triggers the total circulating concentration of T cells to rebound.

a. T-cell anergy
b. Homeostatic T-cell proliferation
c. Chemokine T-cell recruitment
d. T-cell extrinsic suppression

2. Which of the following DOES NOT describe the drug denileukin diftitox?

a. It is an engineered protein comprised of IL-2 and diphtheria toxin
b. It is being tested as a strategy that may result in tumor regression and tumor cell death.
c. It is directed against the CD25 receptor
d. It is directed against the CD20 receptor

3. Which malignancy was denileukin diftitox originally developed for?

a. Non-small cell lung cancer
b. Peripheral T-cell lymphoma
c. Mantle cell lymphoma
d. Cutaneous T-cell lymphoma

4. In a phase II trial of denileukin diftitox, described by Dr. Chesney, denileukin diftitox treatment reduced the CD25+ T-cell population to approximately _____ of control.

a. 30% b. 50% c. 70% d. 90%

5. In the phase II trial described by Dr. Chesney, what proportion of patients achieved a partial response among the first 37 patients evaluated?

a. 10.8% b. 17.6% c. 32% d. 56.8%

6. True or False? In early results of a phase II trial discussed by Dr. Curiel, denileukin diftitox treatment did not lead to the depletion of phenotypic and functional Treg cells at the tumor site.

a. True b. False

7. Which of the following immunotherapies are not currently FDA approved?

a. Denileukin diftitox
b. Cyclophosphamide
c. Pseudomonas-IL2 fusion toxin
d. Fludarabine

8. Which of these is NOT a negative regulatory mechanism against the immune response that has been identified within the tumor microenvironment?

a. IL-2 b. IDO
c. T-cell anergy d. PD-L1

9. Which of the following is NOT a characteristic of Treg cells?

a. CD25+ b. CD25-
c. CD4+ d. Intracellular Foxp3 expression

10. _____ describes the setting in which T-cell stimulation occurs in the absence of costimulatory ligands, including B7-1 and B7-2.

a. T-cell anergy
b. Homeostatic T-cell proliferation
c. Chemokine T-cell recruitment
d. T-cell extrinsic suppression

Activity Evaluation Form:

Release date: January 2009 **Expiration date:** January 31, 2010

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Posttest answers: Please fill in your answers to the right: 1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10____

Signature _____

✹ I would like to receive information about future educational activities on the topic of neuropathic pain.

(Evaluation continues on the following page.)

EVALUATION

1. Please rate on a 5-point scale (1=Poor; 5=excellent).

	Poor				Excellent
• Immune Suppression in Solid Tumors (Thomas F. Gajewski, MD, PhD)					
– Content of section	1	2	3	4	5
– Relevance to practice	1	2	3	4	5
– Content was fair, balanced, and free of commercial bias	1	2	3	4	5
• Strategies to Overcome Regulatory T Cell Effects in Cancer (Jason Chesney, MD, PhD)					
– Content of section	1	2	3	4	5
– Relevance to practice	1	2	3	4	5
– Content was fair, balanced, and free of commercial bias	1	2	3	4	5
• Translating Basic Immunomodulatory Concepts into Clinical Application (Tyler J. Curiel, MD, MPH)					
– Content of section	1	2	3	4	5
– Relevance to practice	1	2	3	4	5
– Content was fair, balanced, and free of commercial bias	1	2	3	4	5

(If you felt the activity was biased, please explain.) _____

_____

2. Rate the extent to which you agree or disagree:

	Strongly Disagree				Strongly Agree
• I am satisfied with the overall quality of this activity.	1	2	3	4	5
• Participation in this activity changed my knowledge/attitudes.	1	2	3	4	5
• I will make a change in my practice as a result of participation in this activity.	1	2	3	4	5
• The activity presented scientifically rigorous, unbiased, and balanced information.	1	2	3	4	5

3. This activity helped me to achieve the following objectives:

	Strongly Disagree				Strongly Agree
• Describe the role of regulatory T cells and their interaction with cytotoxic T cells in tumor suppression and surveillance	1	2	3	4	5
• Compare and contrast the mechanisms and efficacy of different strategies to deplete or downregulate regulatory T cells	1	2	3	4	5
• Evaluate the clinical data on the effect of regulatory T cell depletion or downregulation on outcomes for patients with specific malignancies	1	2	3	4	5

(If you felt the learning objectives were not met, please explain.) _____

_____

4. What information remains unclear:_____

_____

5. Questions or comments regarding this activity _____

_____

6. How did you hear about this activity? (Please check all that apply.)

✹ Direct mailing ✹ Curatio Web site ✹ Colleague

✹ Other (Please specify.) _____

7. Time spent completing this activity: ✹ <.5 hours ✹ .5–1 hr ✹ 1-1.5 hrs ✹ >1.5 hrs

8. What is/are your preferred format(s) for earning continuing medical education credits? (Please check all that apply.)

✹ Satellite symposium ✹ Grand rounds ✹ CD-ROM ✹ Dinner meetings ✹ Internet activities ✹ Podcast

✹ Teleconference ✹ Journal supplement ✹ Newsletter/monograph

✹ Other (Please specify.) _____