

VIEWPOINT

Immune Checkpoint Blockade in Cancer Therapy

The 2015 Lasker-DeBakey Clinical Medical Research Award

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Viewpoint

The 2015 Lasker-DeBakey Clinical Medical Research Award has been presented to James P. Allison, PhD, for pioneering work in enabling T cells of the immune system to attack cancer cells by removing "checkpoints" that normally inhibit T-cell activity. This Viewpoint provides a summary of these discoveries involving regulation of the T-cell response, development of immune checkpoint blockade in cancer therapy, and implications of engaging the immune response as a new modality for cancer treatment.

The idea of using the immune system to treat cancer is an old concept. The approach of relying on an immune response against a bacterial component to stimulate an anti-tumor immune response, as pioneered by Old in the 1960s, led to the development of intravesical BCG, which is now an FDA-approved treatment for superficial bladder cancer. These successes are now attributed to activation of the innate immune system and an inflammatory response capable of killing tumor cells.

By the mid-1950s Old, Klein, and others began an exciting period of discovery by showing in mice the existence of tumor-specific transplantation antigens and that mice could be immunized to tumor challenge. This led to Burnet and Thomas, by the late 1950s, to propose the concept of immunosurveillance. This hypothesis suggested that tumors are constantly arising, but they are detected by lymphocytes that specifically eliminate them, and that cancer only occurs when this surveillance fails. While a compelling and hopeful hypothesis, immunosurveillance sustained a major setback in the early 1970s when Stutman showed that nude (*nu/nu*) mice, which have defects in the immune system, did not, as would be expected according to the hypothesis, have higher tumor incidence rates after exposure to carcinogens.

Over the next several decades the possibility of immunotherapy to treat cancer had successes and failures, followed by optimism and pessimism. In the mid-1980s there was some support for the hypothesis when Rosenberg showed that IL-2 was effective in some patients with melanoma and renal cancer, but it only worked in a small fraction, was extremely toxic, and did not work in other tumor types.

There was another period of optimism when Boone, Rosenberg, Old, and others showed that some T lymphocytes in human tumors could recognize antigens expressed by those tumors, and many of these antigens were shared by different tumors. These findings renewed hope that the adaptive immune system, consisting of T and B cells, each composed of a vast repertoire of clonally elaborated receptors, could be trained to engage cancer, eliminate tumor cells, and produce long-lived immunologic memory to provide protection against recurrence.

The field of cancer immunotherapy quickly and broadly focused on developing therapeutic vaccines to enhance the number and function of T cells. These used many strategies, including many various types of vaccines (eg, peptide, protein, whole tumor cell) given alone or in combination with various adjuvants or cytokines. Although these trials were conducted with the best available science at the time, there were only anecdotal responses. The field of cancer immunotherapy began again to lose credibility as the number of failed clinical trials mounted. However, the emergence of an appreciation for the complexity of T-cell activation and regulation in the 1980s and 1990s paved the way for a revival of cancer immunotherapy.

Positive and Negative Signals Regulate T-cell Responses

T cells are the soldiers of the immune system. It has been known since the late 1970s that T cells recognize antigens as peptides displayed on the surface of cells in the context of protein products of the major histocompatibility complex (MHC). These peptides can be derived from virtually any protein in the cell, including those involved in normal cell functions as well as those from viruses or bacteria that infect cells and those associated with cancer. Thus, the peptide/MHC complexes on cells represent foreign, non-self antigens that might be associated with disease.

In the early 1980s the structure of the T-cell antigen receptor α and β chains were defined, and the genes encoding them cloned by Allison and other investigators. It appears that each human has perhaps 100 million T cells with different receptors circulating in the body, examining cells for evidence of a foreign peptide indicative of a change that might reflect infection or cancer. An encounter of a T cell with a foreign antigen results in T-cell activation, rapid proliferation, and development of the functional capacity to directly kill or make cytokines to help kill the offending cell.

However, by the late 1980s it became clear that the process was more complicated. Schwartz and colleagues showed that engagement of a foreign peptide/MHC complex was not sufficient for full T-cell activation: a second, costimulatory signal was required. Also, only very specialized antigen presenting cells (APCs) could provide the costimulatory signal. Most cells, including solid tumor cells, could not provide this signal. In the early 1990s, Allison showed that the molecule CD28, found on all T cells, was a sufficient and necessary receptor for the costimulatory signals.¹ Subsequently, Linsley and colleagues showed that B7, the prototype of a family of costimulatory molecules, was the CD28 ligand on APCs. In mouse models, Allison showed that tumor cells that were transduced to express B7 molecules were rapidly rejected by the immune system.

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Thus it seems that one of the reasons that tumor cells are virtually invisible is because they cannot provide the second, costimulatory signal. Initiation of T-cell responses to tumor cells seems to require death of the tumor cell, with resultant inflammation and attraction of innate immune cells to the site, phagocytosis of dying tumor cells by APCs, and activation of T cells by both antigen receptor and costimulatory signals by the loaded APC in a process called cross-priming.

Yet the process is even more complicated. In 1998, Golstein identified a novel gene, *CTLA-4*, that is not found in resting T cells but only in activated cells. The function of CTLA-4 (cytotoxic T lymphocyte-associated protein 4) was unknown, but the fact that its DNA sequence was highly homologous to that of CD28 generated considerable interest. Linsley showed that CTLA-4, like CD28, bound B7 molecules, based on the results of in vitro studies, and proposed that it was another costimulatory receptor that synergized with CD28 in sustaining costimulation. Bluestone and colleagues and Allison's laboratory conducted similar experiments and came to the opposite conclusion—that CTLA-4 in fact opposed CD28 costimulation.^{2,3} From 1994 until 1996 the controversy continued: was CTLA-4 another costimulator or instead the first cell-intrinsic negative regulator of T-cell responses. In 1996 the controversy was largely resolved by a series of reports by Mak, Sharpe, and Chambers describing the effect of genetic ablation of CTLA-4 in mice. In each case the absence of CTLA-4 resulted in the early death of mice from a rampant lymphoproliferative disorder, confirming that the function of CTLA-4 is to restrain and terminate T-cell responses.

Immune Checkpoint Blockade in Cancer Therapy

In the meantime, Allison considered the possibility that CTLA-4 limits the potency of anti-tumor responses, and that blocking it might enhance T-cell responses to a level to achieve rejection of tumors. The hypothesis was that administration of antibodies that block the inhibitory effect of CTLA-4 might allow the T-cell response to be sustained long enough to achieve complete tumor eradication. Beginning in 1996,⁴ Allison's laboratory published a series of studies showing that antibody-mediated CTLA-4 blockade, alone or in combination with other agents, resulted in tumor rejection and long-lived immunity in animal models using a wide variety of tumor types.

These results suggest a delicate balance between CD28, which is constitutively expressed on T cells, and CTLA-4, which is only expressed after T cells are activated, enabling control of T-cell responses and thereby minimizing damage to normal tissues. T cells that initiate an anti-tumor response but cannot eradicate the cancer cells within a short period will eventually be turned off as a result of CTLA-4 expression. Blockade of this off signal, or checkpoint with a monoclonal antibody, permits

enhanced anti-tumor T-cell responses and tumor rejection.⁵ The concept of checkpoint blockade as a strategy for cancer therapy was a major scientific shift in 2 ways. First, the therapy does not target the tumor cell but rather engages a target on the patient's immune system. Thus, there is no inherent reason that it would not be successful against a wide variety of tumors, regardless of histotype or causative lesion. Second, it is not directed toward activating the immune system to attack any particular target; rather it involves unleashing the immune system by removing inhibitory pathways.

Clinical trials with anti-CTLA-4 demonstrated tumor regression in patients with a variety of tumor types, with phase I/II trials showing clinical responses in patients with melanoma, renal cell carcinoma, prostate cancer, urothelial carcinoma, and ovarian cancer. Two phase III clinical trials with anti-CTLA-4 (ipilimumab) were conducted in patients with advanced melanoma and demonstrated improved overall survival. Importantly, these trials indicated long-term durable responses with more than 20% of treated patients living for more than 4 years, including a recent analysis indicating survival of 10 years or more for a subset of patients.⁶ The FDA approved ipilimumab as treatment for patients with melanoma in 2011.

The clinical success of anti-CTLA-4 created a new field termed immune checkpoint therapy. Additional pathways that regulate T-cell responses are being targeted as cancer treatments. One such pathway is PD-1 (programmed death 1) and its ligand PD-L1. Antibodies to PD-1 have been approved to treat late-stage melanoma and lung cancer.

Because CTLA-4 and PD-1/PD-L1 regulate different inhibitory pathways on T cells, Allison's laboratory tested a combination therapy with antibodies targeting these molecules and showed improved anti-tumor responses in a preclinical murine model,⁷ which led to multiple ongoing clinical trials. A phase III clinical trial with anti-CTLA-4 (ipilimumab) plus anti-PD-1 (nivolumab) recently reported an objective response rate of greater than 50% for patients with metastatic melanoma, showing the power of blocking multiple checkpoints in cancer therapy.⁸

Hope for a Cure

The field of oncology has long relied on surgery, chemotherapy, radiation therapy, and targeted therapy that directly attack cancer cells to treat patients. Now, immune checkpoint therapy can be added as a new modality: for the first time, the treatment engages the patient's immune response to target the cancer. This novel treatment, and the myriad potential combination strategies that exist, as well as an understanding that the immune system can generate durable responses lasting decades, continues to move the field forward with the hope of finding a cure for many types of cancer.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Allison reports being an inventor of intellectual property owned by the University of California, Berkeley, and licensed to Bristol-Myers Squibb.

Correction: This article was corrected on September 8, 2015, to add clarification to the first sentence under the heading "Immune Checkpoint Blockade in Cancer Therapy."

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