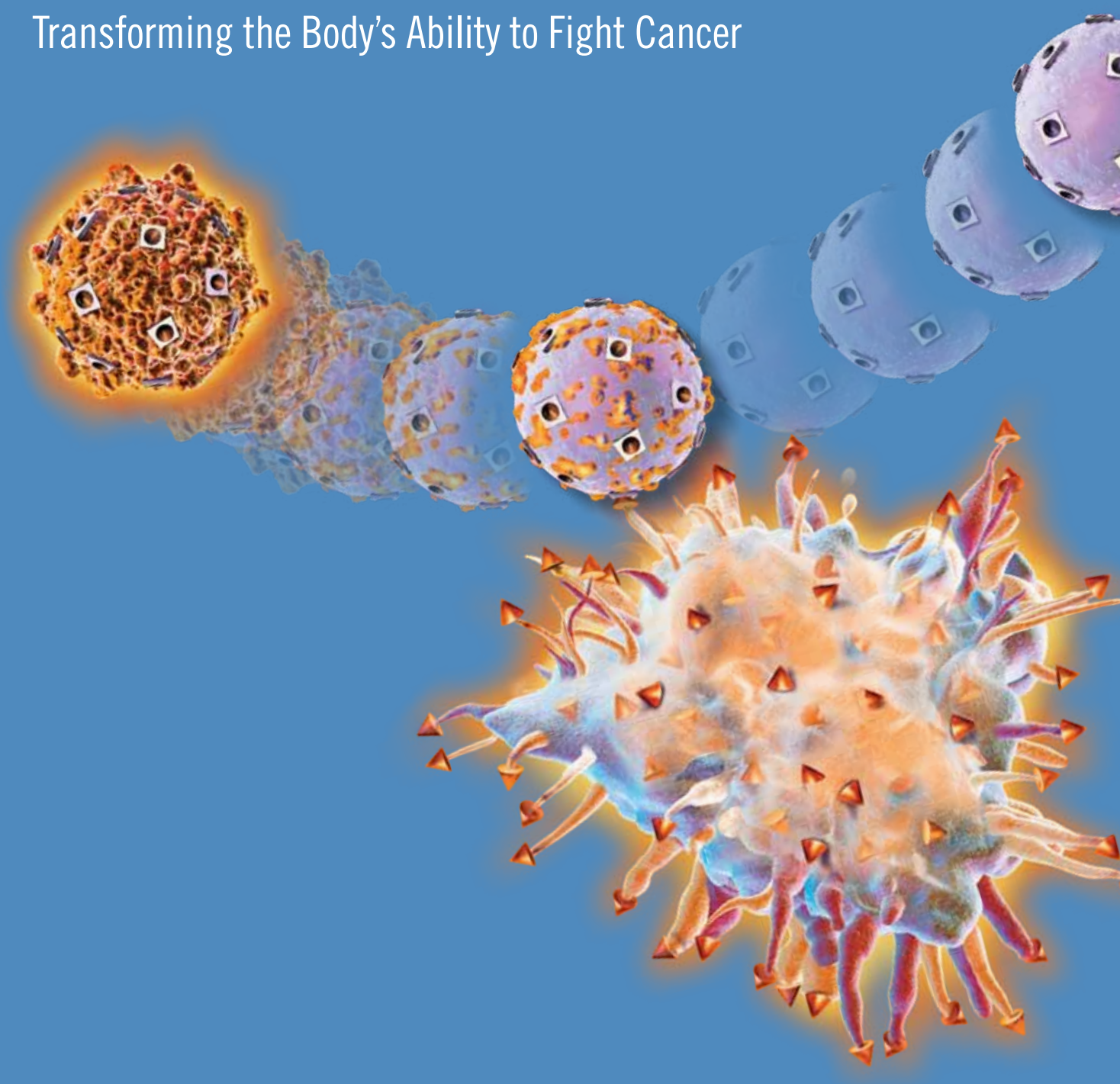
ACTIVE CELLULAR IMMUNOTHERAPY

Transforming the Body's Ability to Fight Cancer



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Targeting Cancer, Transforming Lives®

A New Approach to Cancer Treatment

Cancer is the second most common cause of death in the United States with an estimated 562,340 deaths in 2009, or more than 1500 people each day.[1] Survival rates remain poor for many cancers despite improvements in our ability to detect and treat this constellation of diseases. Furthermore, improvements in survival have historically been gained in conjunction with significant morbidity.[2]

This situation has led to the development of alternative treatment strategies that seek to confer therapeutic benefit while minimizing side effects.[3] The study of how cancer interacts with the immune system continues to lead to new advances in the treatment of cancer, including the development of many different immunomodulatory strategies such as cytokine-based therapies, antibody-based therapies, adoptive cell transfer, and therapeutic vaccines.[4-8] One of the most promising advances is a new therapeutic class called active cellular immunotherapy (ACI).

ACI has the potential to revolutionize the treatment of cancer

This monograph will clarify the unique features of ACI by illustrating:

- How cancer cells evade detection by the immune system
- Which components of the immune system can be leveraged to treat cancer
- What distinguishes ACI from other classes of immunotherapy

The Fundamental Role of the Immune System

Although the importance of the interaction between the immune system and cancer cells was first recognized in the 1890s when William Coley used streptococcal cultures to treat advanced sarcoma, much remains to be learned about how the immune system interacts with cancer cells.[9,10]

The possibility of leveraging the immune system to treat cancer remains a rich field of study due to its complex pathways and multiple cellular components

The immune system is capable of mounting a response to cancer cells; however, the ability of tumors to vary their antigenic profile helps them avoid normal surveillance.[11] Overcoming the ability of tumor cells to suppress or evade immune responses is a key issue in the design of immunologic therapies for cancer.[12]

A primary goal of immunotherapy is to generate a robust T-cell–mediated response capable of recognizing and destroying tumor cells.[13] In patients with advanced-stage cancer, the goal of immunotherapy may not be the complete eradication of tumor cells, but rather the restoration of a dynamic balance between tumor cells and the immune response.[14]

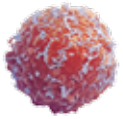
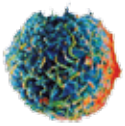
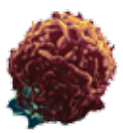
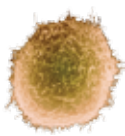
A fundamental goal of immunotherapy is to generate an immune response against specific cancers that would otherwise grow unchecked

Maximizing the Potential of the Immune System

The immune system is composed of 2 major arms that may be leveraged in the fight against cancer: 1) the innate or nonspecific immune system and 2) the adaptive or specific immune system.[15] The innate system functions as the first line of defense against infectious organisms. The adaptive system manifests immunologic memory by reacting more rapidly upon reexposure to the same pathogens. Although responsible for distinct functions, these 2 systems interact with, and influence, each other.

Peripheral blood mononuclear cells, which include lymphocytes (T cells, B cells, and natural killer cells) and monocytes (precursors to dendritic cells and macrophages) are of particular importance in the immune response. These cells are components of both the innate and adaptive arms of the immune system and have roles in fighting infection and general immunosurveillance (Table 1).[15-18]

Table 1. Peripheral Blood Mononuclear Cells and Their Functions[15-18]

T cells		• An essential component of the antigen-specific immune response • There are 2 types of T cells—killer and helper - Killer T cells are the effector cells responsible for cell-mediated immunity - Helper T cells help B cells differentiate into plasma cells, which secrete antibodies • A subset of T cells kills tumor cells or cells infected by pathogens • Can perpetuate an initiated immune response once activated
B cells		• The effector cells for antigen-specific humoral immunity • Play a supporting role in antitumor activity by secreting antibodies, which bind to a specific antigen, thereby marking cells expressing that antigen for destruction by a macrophage
Natural killer cells		• Nonspecific lymphocytes that recognize foreign cells of many different types • Possess lytic enzymes that are an important first-line defense against newly malignant cells • One of the cell types that destroys cells that have been "tagged" by an antibody via the mechanism called *antibody-dependent cell-mediated cytotoxicity* (ADCC)
Monocytes		• Antigen-presenting cells (APCs), including dendritic cells and macrophages • Function as effector cells and confer innate immunity (surround and kill microorganisms, ingest foreign material, and remove dead cells) as well as adaptive immunity (boost immune responses) • APCs can destroy cells that have been tagged by an antibody

APCs—Integral Components of Immune System Activation

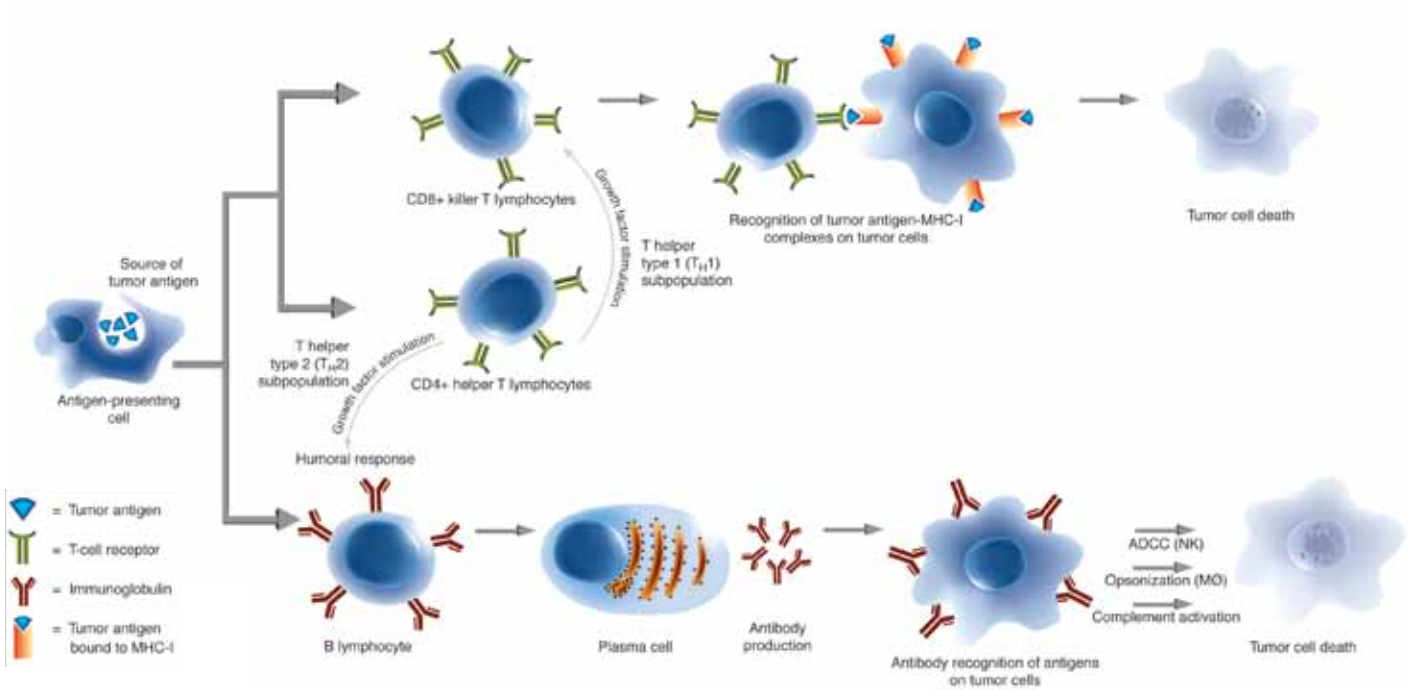
Monocytes differentiate into dendritic cells and macrophages, which are classified as APCs because they possess the following properties[18,19]:

- Ingest foreign antigenic material, which is then presented as fragments on their surface
- Initiate an adaptive immune response by then signaling to antigen-specific T cells

APCs are able to elicit both cellular (via cytotoxic T cells) and humoral (via helper T cells) immune responses against tumor cells (Figure 1).

> APCs have the ability to activate the immune system against tumor cells

Figure 1. The Antitumor Immune Response[19]



Lymphocyte interactions in the development of cell-mediated and antibody-mediated antitumor immune responses are depicted. ADCC=antibody-dependent cell-mediated cytotoxicity; MØ=macrophage; MHC=major histocompatibility complex; NK=natural killer lymphocyte.

With permission from Meniscus Educational Institute.

A Closer Look at Cancer Immunotherapy

Cancer immunotherapies can be either passive or active.[18,20] Passive therapy is based on the adoptive transfer of immunomodulators (including cytokines), tumor-specific antibodies, or immune cells.[8,20] These substances, or cells, are then administered to the patient to initiate an antitumor action. In general, these therapies do not generate immunologic memory and, therefore, require chronic infusion-based treatment.[8,18,20] Several passive immunotherapies have been approved for use in breast cancer, melanoma, renal cell carcinoma, leukemia, and various other hematologic and solid tumors.[7,8]

Active immunotherapy, on the other hand, stimulates the patient's immune system, with the intent of promoting an antigen-specific antitumor effect using the body's own immune cells.[8,20] In addition, active immunotherapy seeks to create a durable antitumor response that can protect against minimal residual disease and tumor recurrence.[21-23]

Immunotherapy can be further divided into nonspecific and specific types:

1. Nonspecific immunotherapy involves the administration of cells or substances that are not targeted to a specific antigen. Lymphokine activated killer (LAK) cell therapy is an example of a nonspecific cellular immunotherapy currently being investigated for the treatment of cancers such as melanoma, renal cell carcinoma, and non-Hodgkin's lymphoma.[24,25] This approach is based on the concept that leukocytes activated ex vivo by interleukin-2 can lyse tumor cells that are resistant to natural killer cells. Other types of nonspecific approaches have been approved for renal, bladder, and other cancers, and may exert a wide range of effects on the immune system.[26,27]

2. Conversely, active specific immunotherapy involves the priming of the immune system in order to generate a T-cell response against tumor-associated antigens.[22,23] One example of the active specific approach is adoptive T-cell therapy, which involves the ex vivo cultivation of T cells with demonstrated activity against a specific target cancer antigen.[5,28] The goal is to increase the frequency of these T cells to achieve therapeutic levels and then infuse them back into the patient. This approach is highly specific and has been investigated for the treatment of melanoma.

Active specific immunotherapies primarily seek to stimulate an immune response against a tumor-associated target

ACI is a distinct class that falls under the active specific category of cancer immunotherapies. It uses a patient's own cells to stimulate the immune system.[29-32] Adoptive T-cell therapy is one example of an ACI approach that focuses on T-cell stimulation only.[6] There are other ACI approaches that seek to involve a broader cross-section of the immune system. One such approach involves exposing APCs to a cancer-specific antigen.[29] This antigen is then processed and presented on the surface of the APCs to invoke an immune response. Several different compounds are being investigated using this approach, including GRNVAC1 for acute myeloid leukemia,[33] IDM-2 for superficial bladder cancer,[34] IDD-3 for melanoma,[35] INGN 225 for small-cell lung cancer,[36] sipuleucel-T and Prostvac-VF for prostate cancer,[30,32] and lapuleucel-T for breast, ovarian, and colon cancers.[31]

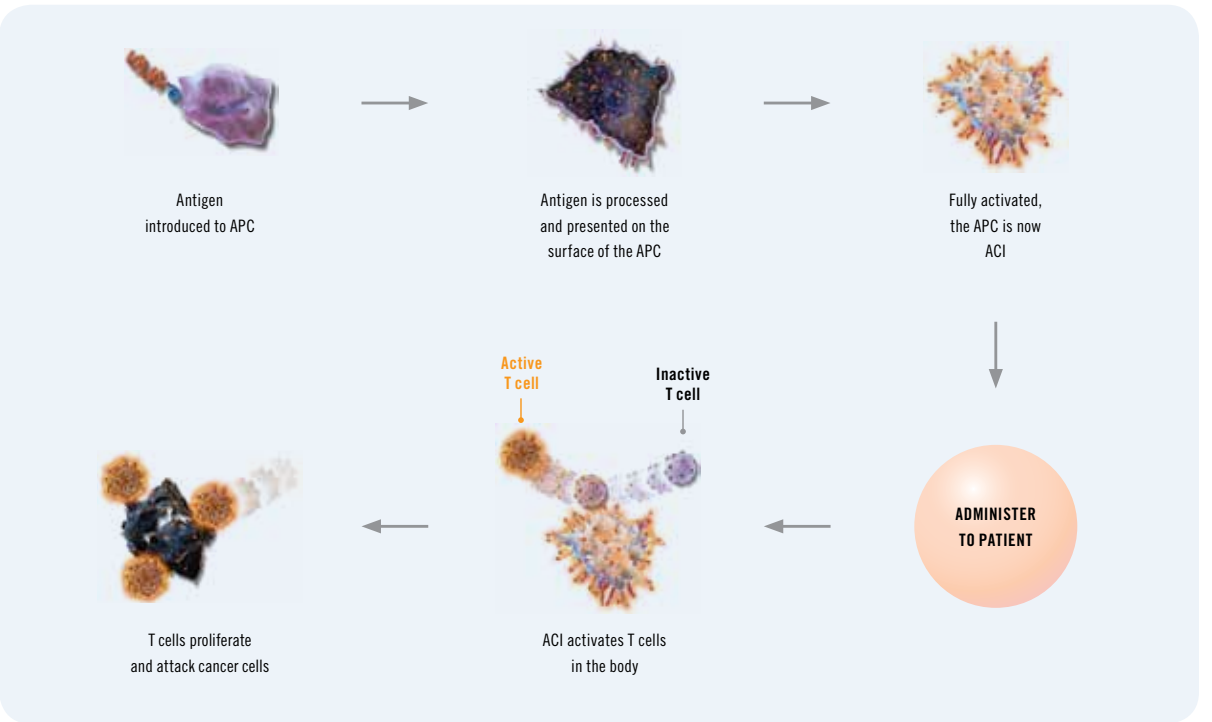
Therapeutic Cancer Vaccines

ACIs are a type of therapeutic cancer vaccine.[29,37,38] Unlike prophylactic vaccines, therapeutic cancer vaccines are designed to combat already existing disease.[39] Generating an immune response against cancer is different from generating an immune response against foreign organisms (eg, bacteria or viruses) because tumor cells have self-antigens.[40] Thus, mounting an immune response against tumor cells involves overriding the tolerance that the immune system manifests toward cancer cells.[41]

ACI: Harnessing the Power of the Immune System

ACI engages the immune system to stimulate a tumor-directed immune response.[29-32] Figure 2 illustrates a proposed mechanism of action for ACI, which is focused on the immune system's strongest defense in detecting and destroying cancer cells—activated T cells. Through the use of distinct tumor-associated antigens, such as melanoma-associated antigen, NY-ESO-1, HER2/neu, and prostatic acid phosphatase, the ACI platform could be adapted to a variety of cancers.[19]

Figure 2. A Proposed Mechanism of Action for ACI



Immune system activity with ACIs has been demonstrated by enzyme-linked immunosorbent spot assays, humoral assays, and phenotypic markers, which show activation of specific T-cell immune responses.[31,32,34,42]

In clinical trials, ACIs have demonstrated measurable clinical response.[30-32,43] These findings suggest that ACI may be an important new approach to treating cancer.

ACI: A Potential New Treatment for Cancer

After a century of research, the immune system has been harnessed for the development of a revolutionary new treatment approach for cancer. ACI is the first class of active specific immunotherapy that uses living cells to mount an attack against cancer. ACI is unique in that it takes advantage of key effector components of the immune system—offering innate, adaptive, cellular, and humoral responses against cancer. By leveraging the power of the immune system, ACI may provide patients with a new treatment alternative in the fight against cancer.

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