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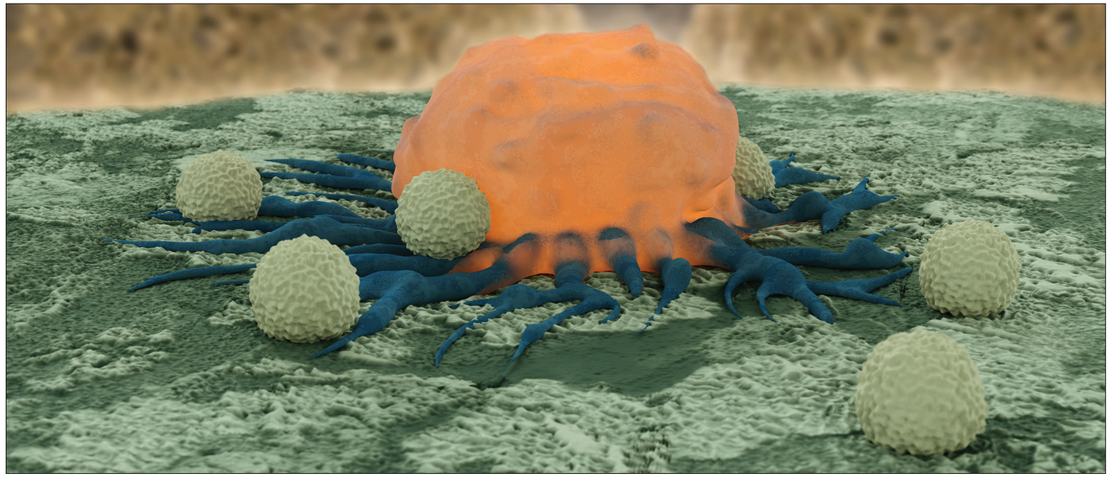
EMERGING ISSUES BRIEF



Immune cells (CD8 T cells) attack a cancer cell

Immunotherapy: Targeting Cancer with the Immune System

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Your immune system normally works to detect and destroy abnormal cells in your body, preventing the development of most cancers. This natural process is called immunosurveillance. However, some cancers are able to avoid detection and destruction by the immune system, resulting in the development of disease. These immune-evading tumors may produce signals that inactivate the immune system (immunosuppression), or they may undergo certain changes that render them more difficult for immune cells to recognize or kill (immune evasion).

Immunotherapies are a class of treatments that trigger or enhance normal anti-cancer immune system activity, restoring the immune system's ability to fight cancer. Beginning in the late 1800s, it was realized that tumors sometimes shrank in patients who had acute infections. It was suggested that the act of stimulating the immune system to eliminate the infectious agents had the unexpected benefit of killing cancer cells. Thus, in the 1890s, crude immunotherapies were tried; dead bacteria were injected into tumors, resulting occasionally in dramatic but inconsistent responses, often with serious side effects (Coley, 1891). Despite the partial successes, the unreliable nature of the results and the discovery of radiotherapy led to declining interest in immunotherapy. The field was largely abandoned for the next half century.

Recently, with better understanding of the cells and molecules that regulate immunity, the medical community has witnessed a revival in cancer immunotherapy. Beginning in the 1980s, with the identification and production of proteins that are immune-stimulating, such as interleukin-2, or IL-2 (Coventry & Ashdown, 2012), immunotherapy was "rediscovered." In just the past decade, the field of cancer immunology has produced a variety of new immune-based methods of treating cancer, culminating with Immunotherapy of Cancer being designated by the journal *Science* as the "2013 Breakthrough of the Year" (Couzin-Frankel, 2013).

Advantages of Immunotherapy Therapy for Cancer

The excitement surrounding immunotherapy arises from its tremendous therapeutic promise and its multiple potential advantages compared to traditional front-line treatments. General advantages of immunotherapy include:

- *Targeting:* Immunotherapies have the potential to generate powerful immune responses that target tumors throughout the body, including tumors that may be inaccessible to surgery or radiation
- *Specificity:* Many immunotherapies train the immune system to recognize and target only cancer cells, sparing surrounding healthy tissues

- *Durability:* Immunotherapies can induce immune memory, meaning protection is lasting and effective against subsequent tumors
- *Universality:* Some immunotherapies boost the patient's own cancer-specific immune responses, meaning they have the potential to work for a wide variety of cancers.

Modern Approaches to Immunotherapy of Cancer

Modern immunotherapies may stimulate specific components of the immune system (to "rev up" anti-cancer immunity), counteract immune-suppressive signals produced by cancer cells (to protect themselves from the immune system), or use modified components of the immune system (such as *antibodies*) to directly target cancers. Advances in these clinical applications have led to a number of recent FDA-approved and experimental therapies:

Immune-Modifying Agents: The most basic immunotherapy consists of immune-modifying agents, which are injected proteins that broadly enhance the body's immune response. Examples include the cell-signaling protein (cytokine) interleukin-2 (Aldesleukin, http://www.cancer.gov/about-cancer/treatment/drugs/aldesleukin), which promotes the survival and activity of tumor-killing immune cells. A second class of modifiers, called interferons (Intron, http://www.cancer.gov/about-cancer/treatment/drugs/recombinant-interferon-alfa-2b), promote the activation and activity of natural killer cells (with direct tumor-killing ability) and dendritic cells (which can promote additional patient-derived immunity to cancer). These agents have been in widespread use over the past decade.

Immune Checkpoint Modulators: The immune system can eliminate pathogens and damaged cells, but, unchecked, it also can damage healthy tissues and even cause death. Thus, the system normally is regulated by a variety of checkpoint proteins that act to prevent the body from attacking itself (i.e., autoimmunity or immune-mediated pathology). Thus, one immunotherapy approach to the treatment of cancer is to block checkpoint protein activity, thereby unleashing the full potential of the immune response. Two immune checkpoint modulators have been approved by the FDA:

- Ipilimumab (Yervoy) blocks the activity of a checkpoint protein called CTLA4, and has been approved to treat advanced melanoma (http://www.cancer.gov/about-cancer/treatment/drugs/ipilimumab).
- Pembrolizumab (Keytruda) blocks the activity of the immune-suppressive protein PD-1, allowing enhanced and sustained immune cell activity against cancer cells (http://www.cancer.gov/about-cancer/treatment/drugs/pembrolizumab).

Another class of checkpoint inhibitor, referred to as VISTA (Lines, Sempere, Broughton, Wang, & Noelle, 2014; Lines, Pantazi, et al., 2014), was discovered by Dartmouth's Norris Cotton Cancer Center researcher Dr. Randolph Noelle. VISTA antagonists will soon enter initial clinical trials in patients.

Immune Cell Therapy: An experimental form of immunotherapy involves collecting a patient's own cancer-killing immune cells (cytotoxic T lymphocytes), growing them to large numbers in the laboratory, and returning them into the patient. This procedure, called Adoptive Cell Transfer (ACT), has shown significant promise in clinical trials (Hinrichs & Rosenberg, 2014; Rosenberg & Restifo, 2015).

Another form of ACT, referred to as CAR (chimeric antigen receptor) T cell therapy, uses a patient's own T cells, which have been modified genetically, in a manner that trains them to recognize cancer cells. CAR therapy has demonstrated impressive efficacy against blood cancers. A novel CAR T cell therapy (Zhang, Barber, & Sentman, 2006), developed by Dr. Charles Sentman of Dartmouth's Norris Cotton Cancer Center, is currently under investigation in clinical trials (see http://cancer.dartmouth.edu/about_us/newsdetail/72793/).

Cancer Treatment Vaccines: Although most people think of vaccines as preventing disease, therapeutic cancer vaccines can induce immune responses that work against established tumors. Made from a patient's own tumor cells, or from substances taken from tumor cells, these vaccines educate the immune response to target and kill cancer cells. Treatment vaccines also may establish long-lasting immunity to prevent cancer recurrence.

In 2010, the FDA approved the first therapeutic cancer vaccine, sipuleucel-T (Provenge) (http://www.cancer.gov/about-cancer/treatment/drugs/sipuleucel-t) for the treatment of metastatic prostate cancer; and a variety of additional vaccines are in development. Dartmouth's Norris Cotton Cancer Center investigator Dr. Richard Barth has performed innovative work in the development of vaccines that use a patient's own immune-activating cells (called dendritic cells) to induce immunity against cancers (Barth et al., 2010). Ongoing preclinical work in the lab of Dr. David Mullins is defining new combinatorial approaches to vaccination that will enhance T cell infiltration of metastatic tumors (Clancy-Thompson et al., 2013, 2015).

Experimental Approaches to Cancer Immunotherapy

Researchers around the world continue to develop potential therapies to activate and target the patient's anti-cancer immune responses. Recognizing that the immune system is uniquely efficient in the elimination of foreign invaders (bacteria) or infected cells (including cells containing viruses or intracellular bacteria), Dartmouth's Norris Cotton Cancer Center researchers have developed unique bacteria-based approaches to treat cancer. Dr. David Bzik's lab has created genetically-modified bacteria that can be used to treat pancreatic cancer in preclinical models (Sanders, Fox, & Bzik, 2015), and Dr. Steve Fiering's lab has used modified bacteria to eradicate established melanomas in mice (Baird et al., 2013). At Dartmouth's Norris Cotton Cancer Center and beyond, researchers are evaluating ways to expand the use of immunotherapy to more types of cancer and to understand how immunotherapies can be used in combination with standard treatments, such as chemotherapy and radiation therapy, to enhance clinical efficacy and survival.

In Conclusion

Mobilizing the immune response provides a means for targeted, durable, and safe therapy for cancer (Topalian et al., 2015). In various therapeutic combinations, the immune system can assist in body-wide treatment of metastatic or locally residual disease following surgery and/or radiation therapy, or boost systemic drug regimens with an additional targeted agent that can readily differentiate between cancer and normal cells. Ongoing research and clinical trials in immunotherapy are driving new discoveries that will likely revolutionize cancer therapy in coming years.

Resources:

The American Cancer Society:
http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/immunotherapy/immunotherapy-toc

The Cancer Research Institute:
http://www.cancerresearch.org/cancer-immunotherapy

Cancer Immunotherapy Trials Network:
http://citninfo.org

Immunology and Cancer Immunotherapy Research Program at NCCC
cancer.dartmouth.edu/res/immunology-cancer.html

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