



*A colored scanning electron micrograph shows T cells (purple) attached to cancer cells. (Image by Steve Gschmeissner/Science Photo Library)*

## HELPING THE IMMUNE SYSTEM FIGHT CANCER

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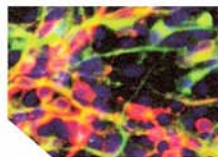
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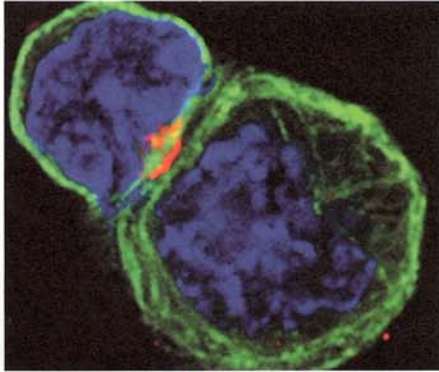
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Memorial Sloan-Kettering  
Cancer Center

# Cancer Immunotherapy

*Harnessing the Immune System to Help the Body Fight Cancer*



A T cell (left) is shown interacting with an antigen-presenting cell (right). The red indicates the presence of CTLA-4 in the region of interaction between the two cells. (Image by Jackson Egen and James Allison)

Since the earliest days of cancer immunotherapy, Memorial Sloan-Kettering clinicians and researchers have been at the forefront of developing new ways to guide the body's immune system toward producing a response that targets and destroys cancer cells. [This article is the first in a series that will highlight various ways the immune system can be used to fight cancer.]

**M**ore than 110 years ago, William B. Coley, a surgeon working at New York Cancer Hospital (the predecessor to MSKCC), made the discovery that patients who suffered from infections following surgery to remove their cancer often fared better than patients who did not, leading him to conclude that the immune system was capable of attacking cancer cells in addition to infections. His finding led to the development of Coley's toxins, a cocktail of inactive bacteria that could be injected into tumors and that occasionally resulted in complete disease remission. Coley's toxins began to fall out of favor after the development of radiation therapy in the early 1900s, but the stage was set for the theory that the body's immune system could be harnessed to recognize and attack cancerous cells.

Cancer immunotherapy is based on the idea that the immune system can be trained to attack tumors in the same way that it targets infectious agents. The immune system consists of many different types of white blood cells, including B lymphocytes (or B cells), T lymphocytes (or T cells), and others such as natural killer cells, monocytes, eosinophils, and basophils. Immune cells circulate throughout the body and are responsible for recognizing

foreign substances, molecules known as antigens, and eliminating them. Vaccines help the immune system to recognize the antigens that unwanted invaders are carrying and to mount a defense against them. Unlike more traditional vaccines, which prevent diseases from arising — usually by targeting the infectious virus or bacterium that causes disease — the goal of therapeutic cancer vaccines is to prevent recurrence after cancer has been detected and treated through more-conventional means such as chemotherapy, radiation therapy, and surgery.

(Today, there are a few vaccines targeted against viruses that also prevent cancer. The hepatitis B vaccine prevents hepatitis B disease, a major cause of liver cancer, especially in Asian countries. The vaccine for human papillomavirus [HPV], approved by the Food and Drug Administration [FDA] last summer, prevents infection with strains of HPV that cause most cases of cervical cancer.)

Over the past several decades, the field of cancer immunology — and particularly the development of therapeutic cancer vaccines — has experienced a variety of exciting developments — and some setbacks. “When they moved into the clinic in the 1980s, many of the early vaccines developed as potential therapies for patients were not as successful as we had hoped they would be,” said James P. Allison, Chair of

the Immunology Program in the Sloan-Kettering Institute (SKI). “One problem was that the field of clinical cancer immunology got ahead of the basic science and our understanding of the various components of the immune response.” But the general feeling among MSKCC investigators now is that immunologists, chemists, clinicians, and others have reached a critical mass of understanding, and that the vaccines and other immunology-based treatments for patients that are being studied in clinical trials today hold great promise for the control of cancer recurrence.

One investigator who has been a champion of cancer immunology research at the Center for decades is Lloyd J. Old, currently a Member of SKI's Immunology Program and Director of the New York Branch of the international Ludwig Institute for Cancer Research. He is also Director of the Cancer Vaccine Collaborative, a partnership between the Ludwig Institute and the Cancer Research Institute. According to Dr. Old, there are three key questions that are critical to developing more-effective immune-based treatments: “How does the immune system recognize cancer? What are the antigens that the immune system targets? And, how can you strengthen the immune response?”

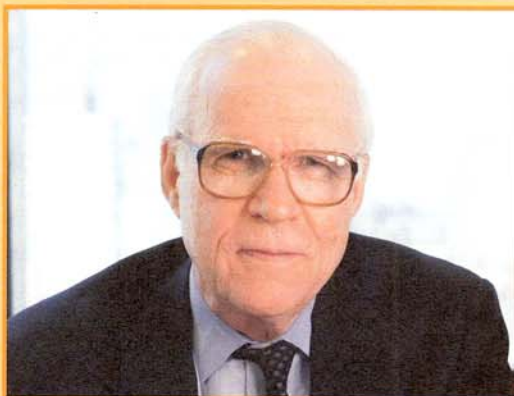
Much of Dr. Old's work has been focused on the identification of antigens.

Using a variety of cell cultures grown from tumor cells, he developed a system that allowed him to search for tumor-specific antigens on the surface of cells. He then exploited a technique for cloning the antigens so that they could be used to study T cell recognition. One important class of antigens studied by Dr. Old is called the cancer-testis (CT) antigens. CT antigens are tumor-associated antigens expressed in the development of a number of solid tumors but not in normal tissues, except the testes. One of these CT antigens, known as NY-ESO-1, is the basis for a variety of vaccines that are now being evaluated in a number of early stage clinical trials for many different types of solid tumors.

Dr. Old was also instrumental in developing the first widely used immunologic treatment for cancer, infusion with Bacillus Calmette-Guérin (BCG) — an inactivated form of the bacterium *Mycobacterium bovis* — as a treatment for early stage bladder cancer. The treatment is a modern version of Dr. Coley's approach because it does not specifically target antigens on the cancer cell. In fact, its exact mechanism of action is unknown. But the treatment, in which BCG is infused directly into the bladder, has been used since the 1980s and is still considered the most effective first-line treatment for early, noninvasive bladder cancer.

### Developing vaccines for melanoma

Much of the early research on cancer vaccines was done with melanoma, and many of the most promising vaccine trials underway today are focused on this deadly form of skin cancer. According to Alan N. Houghton, a pioneer in cancer immunology who has been at the Center for 30 years, there are several reasons why melanoma was chosen for early vaccine research. One is that melanoma is a disease for which ther-



*James Allison (top) will direct the new Ludwig Center at MSKCC. Lloyd Old (bottom) has been studying cancer immunology for more than 50 years.*

apies such as chemotherapy and radiation rarely work, so there was a need to find other methods to treat it. Another is that there was clinical evidence that the disease can spontaneously regress on its own. This regression is rare, but it indicated to researchers that there was a natural immune response to the disease. In addition, melanoma cells are easy to grow in culture, so investigators had an abundance of material to work with when they began their research.

Although an effective vaccine for melanoma has not yet been realized for human patients, Dr. Houghton and physician-scientist Jedd D.

Wolchok, along with collaborators at Manhattan's Animal Medical Center, have developed a vaccine for melanoma in dogs that last month received conditional approval from the US Department of Agriculture. (The USDA is responsible for approving medications for animals whereas the FDA approves treatments for humans.) Melanoma, particularly in the mouth, is an aggressive form of cancer in dogs, and the vaccine has been shown to significantly improve survival, with many dogs living more than a year. Without the vaccine, survival is usually about three months. It is the first therapeutic cancer vaccine to receive US government approval for either animals or people.

Dr. Wolchok is currently leading several clinical trials for Memorial Sloan-Kettering patients, including trials of a melanoma vaccine that is very similar to the one that has been successful in dogs. There are a number of other early stage clinical trials currently underway at the Center for vaccines to treat different cancers including prostate, breast, kidney, and ovarian cancers and lymphoma.

Basic research is ongoing, as well, to determine the best way to construct cancer vaccines, including what delivery system (or "vector") is best to carry the vaccine and what material the vaccines should be made of, for example peptides, proteins, or DNA.

### Using the immune system as a cancer-fighting tool

According to Dr. Allison, there are many reasons why the immune system can be an effective tool against cancer. It has specificity, and is able to pick up a single amino acid mutation in a protein and recognize that protein as a different antigen. It has memory, meaning that T cells can stay in the body and prevent disease recurrence even years later. And immune cells can target individual cancer cells and the very beginning of metastases — the means by which cancer cells spread from the original tumor to

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other parts of the body.

For the past 20 years, Dr. Allison's work has focused on trying to determine how T cells are activated and the mechanisms that regulate their immunological response. He has discovered several key molecules in T cell activation, including one called cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). The function of CTLA-4 is to inhibit the activation of T cells, which is an important mechanism that the body uses to prevent autoimmunity, when the immune system attacks the body's own tissues. (Diseases such as rheumatoid arthritis and Crohn's disease are the result of autoimmunity.)

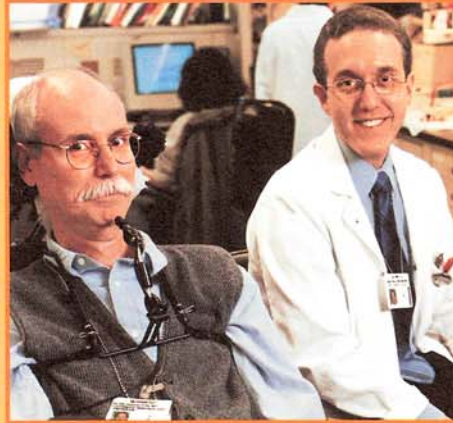
"The body's mechanisms to prevent autoimmunity have been a huge hurdle in the development of cancer vaccines," Dr. Houghton explained. "The immune system naturally keeps itself in check, and many of the molecules expressed by cancer cells are also expressed by normal cells, which means that it has been difficult to get the immune system to target them."

Applying his discovery to developing treatments for cancer, Dr. Allison hypothesized that finding a way to block CTLA-4 might greatly enhance antitumor T cell responses, so he began to make antibodies to block CTLA-4's signal so that the T cells could do their work unrestrained.

In laboratory mice, anti-CTLA-4 did, indeed, prove to boost the immune system's ability to fight cancer, and it became the first in a new class of biologic agents that researchers call immune modulators. Anti-CTLA-4 is now being tested in several multi-institutional clinical trials as a stand-alone treatment and also in combination with vaccines and more-traditional chemotherapy drugs.

Medarex and Bristol-Myers Squibb, the two companies developing anti-CTLA-4 (which is also called ipilimumab or MDX-010), are focusing their trials particularly on melanoma and prostate cancer, but it's also being evaluated for the treatment of kidney and ovarian cancers.

There are several newer immune modulators being developed at MSKCC by Drs. Houghton



*Alan Houghton (left) and Jedd Wolchok have collaborated on the development of vaccines to treat melanoma.*

and Wolchok. Two of the most promising ones, currently being tested in preclinical laboratory studies, are called anti-GITR and anti-OX40. "Like anti-CTLA-4, these agents appear to induce an antitumor response in combination with other treatments," Dr. Wolchok said. "They have a similar function, and both appear to turn on T cell responses, opening the eyes of the immune system to cancer and allowing it to 'see' where tumor cells are located.

"We think these kinds of treatments are going to be most effective in combination therapies," Dr. Wolchok continued. "In the past, people didn't think vaccines could be used in combination with chemotherapy, because chemotherapy suppresses the immune system. But now we know that chemotherapy can be used in combination with various types of immunotherapy to get a much better, synergistic response. Timing is important, and a particularly good time to use both vaccines and immune modulators is when chemotherapy treatment is over and the immune system is beginning to bounce back."

"I believe that we are on the verge of bringing the manipulation of immune responses into the mainstream of cancer therapy," Dr. Allison said. "Recent work in cancer biology has shown that the genetic instability that is inherent in cancer results in a large number of mutations in proteins that create new antigens that the body has never seen before and ought to be readily recognized as foreign by the immune

system. If we can kill some tumor cells, either as a result of a vaccine or treatment with more-conventional therapies, using agents such as anti-CTLA-4 ought to result in induction of potent immunity to these new targets. Thus, I believe that it is not unreasonable to think of many of the new targeted therapies as immunosuppressive, and to use them in conjunction with the new approaches to enhancing immune responses."

## **Creation of the new Ludwig Center**

One important component in the future of cancer immunology research at MSKCC

will be the new Ludwig Center, which was established in November 2006 with \$20 million from the Virginia and D.K. Ludwig Fund for Cancer Research. Memorial Sloan-Kettering was one of six centers in the US that was granted a collaborative Ludwig Center. The particular focus of the center housed at MSKCC will be to enhance immunological research and translational research, developing new strategies for manipulating the immune response as a way to eradicate tumors. According to Dr. Allison, who will direct the Ludwig Center, "The work of the center will go well beyond that of SKI's Immunology Program. Basic scientists will collaborate with leaders of various disease management teams within Memorial Hospital to work with animal models and eventually develop new treatments that can be tested in patients."

"We are entering a new era in the development of cancer vaccines," Dr. Old said. "We have identified key antigens for constructing vaccines, and we are beginning to learn how to put them together. We have immune modulators like anti-CTLA-4 that can take the brakes off the immune response once it has started. And we have the ability to monitor that immune response, so that we can predict who will best respond to these vaccines and also continue to modify and improve them. In all of this, human benefit is the most important thing we're looking for." ☼