



Immunotherapy

Immunotherapy is treatment that uses your immune system to fight cancer. The 2 main ways that this is done is to boost the patient's own immune system or to give man-made versions of the normal parts of the immune system. Many future advances against cancer will probably come from this field.

What is immunotherapy?

Immunotherapy is a form of *biologic therapy* or *biotherapy*. It is treatment that uses certain parts of the immune system to fight diseases, including cancer. This can be done in a couple of ways:

- Stimulating your own immune system to work harder or smarter
- Giving you immune system components, such as man-made immune system proteins

Immunotherapy is sometimes used by itself to treat cancer, but it is most often used along with or after another type of treatment to boost its effects.

For a long time doctors suspected that the immune system had an effect on certain cancers. Even before the immune system was well understood, William Coley, MD, a New York surgeon, first noted that getting an infection after surgery seemed to help some cancer patients. In the late 1800s, he began treating cancer patients by infecting them with certain kinds of bacteria, which came to be known as *Coley toxins*. Although he had some success, his technique was overshadowed when other forms of cancer treatment, such as radiation therapy, came into use.

Doctors have learned a great deal about the immune system since then. This has led to research into how it can be used to combat cancer and exploring many different approaches. In the last few decades immunotherapy has proven useful in treating several types of cancer.

The idea of using one's own immune system to fight cancer is tempting, but so far, in most cases immunotherapy hasn't been shown to clearly be better than other forms of treatment. For instance, it seems to work best when treating smaller, early stage cancers, and it may be less helpful for more advanced disease. Its main role at this time is making

other forms of treatment better, or giving cancer patients a treatment option that may be less toxic than the usual treatments.

But researchers have made important progress in this field. Newer treatments are now being tested that seem to work better and will have a greater impact on the outlook for people with cancer in the future.

What the immune system does

The immune system is your body's defense force. It helps keep invading germs out, or helps kill them if they do get into your body.

Your immune system is a collection of organs, special cells, and substances that help protect you from some infections and diseases. Immune system cells and the substances they make circulate through your body to protect it from germs that cause infections. They also help protect you from cancer in some ways.

It may help to think of your body as a castle. Think of viruses, bacteria, and parasites as hostile, foreign armies that are not normally found in your body. They try to invade your body to use its resources to serve their own purposes, and they can hurt you in the process. In fact, doctors often use the word *foreign* to describe invading germs or other substances not normally present in the body.

The immune response

Any substance that raises an alarm in the body, causing the immune system to react to and attack it is called an *antigen*. This immune response can lead to destruction of both the antigens and anything they are attached to, such as germs or cancer cells.

Germs such as viruses, bacteria, and parasites have substances on their outer surfaces, such as certain proteins, that are not normally found in the human body. The immune system sees these foreign substances as antigens. Cancer cells are also different from normal cells in the body. They often have unusual substances on their outer surfaces that can act as antigens.

But the immune system is much better at recognizing and attacking germs than cancer cells. Germs are very different from normal human cells and are seen as truly foreign, but cancer cells and normal cells can be very much alike, with fewer clear cut differences. Because of this the immune system may not always recognize cancer cells as foreign. Cancer cells are less like soldiers of an invading army and more like traitors within the ranks of the human cell population. This may be why cancers are often able to grow in spite of a healthy, working immune system.

Key players in your immune system

Your immune system responds to antigens in a highly coordinated process that uses many types of cells.

Most cells of the immune system are *lymphocytes*, a type of white blood cell. Several types of lymphocytes work together to attack cancer cells:

- B cells (B lymphocytes)
- T cells (T lymphocytes): killer T cells, helper T cells, regulatory (suppressor) T cells
- Natural killer (NK) cells

Antigen-presenting cells (APCs) are not lymphocytes but work closely with them to fight cancer. They take part of the foreign cell and carry it to where other immune cells can "see" it. This helps stimulate the immune reaction. The 2 main groups of antigen-presenting cells are:

- Monocytes and macrophages
- Dendritic cells

Other types of white blood cells, known as *neutrophils* or *granulocytes* will not be discussed in this document, but they also make up an important part of the immune system. Their role is to fight and kill bacteria.

Lymphocytes

B cells and plasma cells

B cells (B lymphocytes) are made in the bone marrow, which is the spongy inner part of some bones. After they are made, most B cells move to the lymph nodes, which are bean-sized collections of immune system cells found throughout the body. B cells also collect in the lymph tissue contained in some internal organs such as the spleen, stomach, and intestines.

B cells can't directly destroy germs or cancer cells by themselves. But they play an important role in immune defenses by making *antibodies*, which are large, sticky proteins. Each antibody is made to attach to a certain antigen.

When a B cell comes into contact with an antigen (on a germ or cancer cell), it starts making antibodies and turns into a plasma cell. Plasma cells release antibodies that bind (attach) only to that antigen. The antibodies then help kill any cells that have the antigen. The antibodies may destroy them directly or they may serve as a marker for other immune system cells, such as T cells, to destroy them.

T cells

Some lymphocytes that are formed in the bone marrow enter the bloodstream before they are fully mature. They go to the thymus (a small gland in front of the heart and behind the breastbone), where they mature and gain new disease-fighting properties.

Once they leave the thymus gland, they are known as T lymphocytes or T cells (named for the T in thymus). T cells gather in the lymph nodes and spleen, where they work together with other immune system cells. T cells have special proteins on their surfaces

that allow them to recognize and react to parasites, cancer cells, and cells infected by viruses, much like antibodies do.

There are 3 main kinds of T cells. They each have different jobs.

- *Killer T cells (cytotoxic T lymphocytes)* destroy unwanted cells in the body. When these cells come in contact with the specific foreign cells they recognize, they give off substances that kill the cells.
- *Helper T cells* do not directly kill cancer cells or germs, but they release substances that help B cells and killer T cells work better.
- *Regulatory (suppressor) T cells* act as brakes to help keep the immune system in check. They help ensure that the immune system does not overreact and attack other healthy parts of the body. These are sometimes called *Treg cells*.

Natural killer (NK) cells

Lymphocytes called *natural killer (NK)* cells are not as picky as killer T cells in what they attack. When fighting cancer, they are drawn to areas with cancer cells by substances given off by other cells. They attach to cancer cells and release substances that split the cells open, killing them. They then look for other cancer cells to attack.

Antigen-presenting cells

The main function of *antigen-presenting cells (APCs)* is to help lymphocytes recognize antigens on foreign cells (including cancer cells). Antigen-presenting cells include monocytes, macrophages, and dendritic cells.

Monocytes and macrophages

Monocytes are made by the bone marrow and released into the bloodstream. Some monocytes enter tissues and organs. Here they become macrophages, capable of surrounding and "eating" unwanted cells. They then present antigens from the devoured cells on their outer surface, so that lymphocytes can recognize the foreign antigens if they are found in the body later on. Both monocytes and macrophages can act as APCs to help start an immune response.

Dendritic cells

Like monocytes and macrophages, dendritic cells find unwanted cells in the body, chew them up, and present their antigens on their surfaces. They then travel to an area with many lymphocytes, such as the lymph nodes or spleen. Here, they activate certain lymphocytes to go out and attack any similar cells in the body. Dendritic cells are not common, but they are the most powerful type of antigen-presenting cell. Because of this, they are the focus of many cancer vaccines currently being developed.

Types of immunotherapy

There are good reasons to think the immune system helps in the fight against cancer. For instance, people with weakened immune systems are more likely to get certain cancers. But many people with normal immune systems still develop cancer. This may be because the immune system doesn't see the cancer cells as foreign. Often, this is because the cancer cells (and their antigens) are not different enough from those of normal cells. Sometimes the immune system recognizes the cancer cells, but the response may not be strong enough to destroy the cancer. Cancer cells themselves may also give off substances that keep the immune system in check.

To overcome this, researchers have designed ways to help the immune system recognize cancer cells and strengthen its response so that it will destroy the cancer.

Immunotherapy works in 2 ways:

- *Active* immunotherapies stimulate your body's own immune system to fight the disease.
- *Passive* immunotherapies use immune system components (such as antibodies) made in the lab. They do not rely on your body to start the attack on the disease.

Another way that immunotherapies work is by targeting a certain type of cell. Most of the immunotherapies being used today target one kind of cell or antigen (*specific* immunotherapies), but there are some that stimulate the immune system in general. These are called *non-specific* immunotherapies. Sometimes non-specific immunotherapies are used with other treatments to help increase the attack on the cancer. These kinds of treatments are generally only used along with other treatments, so they are called *adjuvants*.

There are other treatments, called *targeted therapies*, that zero in on one type of cell and don't tend to damage other cells. For more information see our document, *Targeted Therapy*.

Monoclonal antibodies

Monoclonal antibodies are the most widely used form of cancer immunotherapy.

Monoclonal antibody therapy uses antibodies that are made in the lab rather than by a person's own immune system. These treatments do not require the person's immune system to start the fight against the cancer. Once the antibodies are given, they can then recruit other parts of the immune system to destroy the cancer cells.

The first monoclonal antibodies were made in the lab by fusing a myeloma (a type of bone marrow cancer) cell from a mouse with a mouse B cell that makes a certain antibody. The cell that results from this fusion is called a *hybridoma*.

Combining a B cell that can recognize one special antigen and a long-lived myeloma cell makes the resulting hybridoma cell a long-lasting, antibody-making factory. Because the

antibodies made are all identical clones made from a single (mono) hybridoma cell, they are called *monoclonal antibodies* (sometimes abbreviated as MoAbs or MABs).

The first MABs were made entirely from mouse cells. One problem with this is that the human immune system will see these antibodies as foreign (because they're from a different species) and then will mount a response against them. This can sometimes cause allergic-type reactions. It also means that the antibodies may only work the first time they are given; after that, the body's immune system is primed to destroy them before they can be helpful.

Over time, researchers have learned how to replace some parts of these mouse antibody proteins with human parts. Depending on how much of the MAB is human, these are called *chimeric* or *humanized* antibodies. Some MABs are now fully human, which means they are likely to be even safer and may be more effective than older MABs.

An even newer approach uses fragments of antibodies instead of whole ones. Smaller pieces may be better able to reach a tumor, which may make them more effective.

Over the past 10 years or so, the Food and Drug Administration (FDA) has approved several MABs to treat certain cancers, as seen in the table below.

Clinical trials of monoclonal antibody therapy are also being done on almost every type of cancer. As researchers have found more antigens that are linked to cancer, they have been able to make monoclonal antibodies against more and more cancers.

Monoclonal antibodies used to treat cancer

MAB name	Trade name	Used to treat:	Approved in:
rituximab	Rituxan [®]	non-Hodgkin lymphoma chronic lymphocytic leukemia (CLL)	1997 2010
trastuzumab	Herceptin [®]	breast cancer stomach cancer	1998 2010
gemtuzumab ozogamicin*	Mylotarg [®]	acute myelogenous leukemia (AML)	2000**
alemtuzumab	Campath [®]	chronic lymphocytic leukemia (CLL)	2001
ibritumomab tiuxetan*	Zevalin [®]	non-Hodgkin lymphoma	2002
tositumomab*	Bexxar [®]	non-Hodgkin lymphoma	2003
cetuximab	Erbitux [®]	colorectal cancer head & neck cancers	2004 2006

bevacizumab	Avastin [®]	colorectal cancer	2004
		non-small cell lung cancer	2006
		breast cancer	2008
		glioblastoma	2009
		kidney cancer	2009
panitumumab	Vectibix [®]	colorectal cancer	2006
ofatumumab	Arzerra [®]	chronic lymphocytic leukemia (CLL)	2009
denosumab	Xgeva [™]	cancer spread to bone	2010
ipilimumab	Yervoy [™]	melanoma	2011
brentuximab vedotin*	Adcetris [™]	Hodgkin lymphoma anaplastic large cell lymphoma (a type of non-Hodgkin lymphoma)	2011

*conjugated monoclonal antibodies

**approval withdrawn as of October 15, 2010; this drug is only available for use within a clinical trial

Two types of monoclonal antibodies are used in cancer treatments:

- *Naked monoclonal antibodies* are those without any drug or radioactive material attached to them.
- *Conjugated monoclonal antibodies* are those joined to a chemotherapy drug, radioactive particle, or a toxin (a substance that poisons cells).

Naked monoclonal antibodies

Naked MAbs are the most commonly used MAbs at this time. Although they all work by attaching themselves to specific antigens, they can be helpful in different ways.

Markers for destruction

Some naked MAbs attach to cancer cells to act as a marker for the body's immune system to destroy them. Antibodies now in use in this group include:

Rituximab (Rituxan): Rituximab is used to treat B-cell non-Hodgkin lymphoma, chronic lymphocytic leukemia (CLL), and some other diseases. It is a monoclonal antibody against the CD20 antigen, found on B cells. It works, in part, by labeling cells so that the immune system can attack them.

Ofatumumab (Arzerra): Ofatumumab is another antibody against the CD20 antigen. It is used mainly to treat chronic lymphocytic leukemia when other treatments are no longer effective.

Alemtuzumab (Campath): Alemtuzumab is an antibody against the CD52 antigen, which is found on both B cells and T cells. It is used to treat some patients with B-cell chronic lymphocytic leukemia.

Activation blockers

Some naked MAbs don't really interact with a person's own immune system. Their effects come from their ability to attach to the specific antigens that are working parts of cancer cells or other cells that help cancer cells grow, and stop them from working. These MAbs are also referred to as *targeted therapies*. Examples of FDA-approved MAbs of this type include:

Trastuzumab (Herceptin): Trastuzumab is an antibody against the HER2/neu protein. A large amount of this protein is present on tumor cells in some cancers. When HER2/neu is activated, it helps these cells grow. Trastuzumab stops these proteins from becoming active. It is used to treat breast and stomach cancers that have large amounts of this protein.

Cetuximab (Erbix): Cetuximab is an antibody against the EGFR protein, which is present in large amounts on some tumor cells and helps them grow and divide. Cetuximab blocks the activation of EGFR. It is used to treat some advanced colorectal cancers as well as some head and neck cancers.

Panitumumab (Vectibix): This MAb also targets the EGFR antigen. It is used to treat some cases of advanced colorectal cancer.

Bevacizumab (Avastin): Bevacizumab targets the VEGF protein, which is normally made by tumor cells to attract new blood vessels to feed their growth. Bevacizumab attaches to VEGF, which blocks it from signaling for new blood vessels to form. This MAb is used along with chemotherapy to treat some colorectal, lung, breast, and kidney cancers, as well as glioblastomas (a type of brain tumor). It is being studied for use against other cancers.

Antibodies that act in a different way

Denosumab (Xgeva): Denosumab binds to a protein called *Rank ligand*. This protein is made by cancer cells when they attack bone. This drug helps to stop cancer cells that have spread from destroying bone tissue.

Ipilimumab (Yervoy): Ipilimumab does not bind to cancer cells. Instead it binds to CTLA-4, an antigen that is found on both regulatory T cells (Treg cells) and cytotoxic T cells. It works in 2 ways. It lowers the numbers of Treg cells, which in essence takes the brakes off the immune system, allowing it to fight the cancer. It also binds to cytotoxic T cells, revving them up for action to kill cancer cells. For more information about this drug, see the section "Other active specific immunotherapies."

Side effects of treatment with naked monoclonal antibodies

Monoclonal antibodies are given intravenously (injected into a vein). Compared with the side effects of chemotherapy, the side effects of naked MAbs are usually fairly mild and are often more like an allergic reaction. If they do occur, it is most often while the drug is first being given.

Possible side effects can include:

- Fever
- Chills
- Weakness
- Headache
- Nausea
- Vomiting
- Diarrhea
- Low blood pressure
- Rashes

MAbs can also have side effects that are related to the antigens they target. For instance, bevacizumab targets new blood vessel growth, but this can also lead to side effects like bleeding or poor wound healing. MAbs that target EGFR may cause acne-like skin rashes on the face and chest.

Conjugated monoclonal antibodies

Conjugated MAbs are monoclonal antibodies that are attached to drugs, toxins, or radioactive substances. The MAbs are used as homing devices to take these substances directly to the cancer cells. The MAb circulates in the body until it can find and hook onto the target antigen. It then delivers the toxic substance where it is needed most. This lessens the damage to normal cells in other parts of the body.

Conjugated antibodies may pack more of a punch than naked MAbs, and they often cause more side effects. The side effects depend on which type of substance they're attached to.

Conjugated MAbs are also sometimes referred to as *tagged*, *labeled*, or *loaded* antibodies. They can be divided into groups depending on what they are linked to.

- MAbs with radioactive particles attached are referred to as *radiolabeled*, and therapy with this type of antibody is known as *radioimmunotherapy* (RIT).
- MAbs with chemotherapy drugs attached are often referred to as *chemolabeled*.
- MAbs attached to toxins are called *immunotoxins*.

Radiolabeled antibodies

Two radiolabeled antibodies have been approved to treat cancer.

- **Ibritumomab tiuxetan (Zevalin)** delivers radioactivity directly to cancerous B lymphocytes. It is used to treat B-cell non-Hodgkin lymphoma that has not responded to standard treatment.
- **Tositumomab (Bexxar)** is used to treat certain types of non-Hodgkin lymphoma that no longer respond to rituximab (Rituxan) or chemotherapy.

Aside from being used to treat cancer, radiolabeled antibodies can also be used along with special cameras to help find areas of cancer metastasis (spread) in the body. While some radiolabeled antibodies such as ProstaScint (for prostate cancer) have been approved by the FDA, their role in helping to detect cancer has been very limited so far.

Chemolabeled antibodies

The only chemolabeled antibody that has been approved by the FDA to treat cancer is **brentuximab vedotin** (Adcetris, formerly called SGN-35). This drug is made up of an antibody that targets the CD30 antigen attached to a chemo drug called monomethyl auristatin E. It is used to treat Hodgkin lymphoma and anaplastic large cell lymphoma that is no longer responding to other treatments.

Immunotoxins

Immunotoxins are made by attaching MAbs to bacterial toxins such as diphtheria toxin (DT) or pseudomonas exotoxin (PE40), or to plant toxins such as ricin A or saporin.

Immunotoxins have shown some early promise in shrinking a few cancers, particularly lymphomas. But some major problems still need to be solved before this new form of cancer treatment can be used more widely.

There are no immunotoxins approved for treating cancer at this time. **Gemtuzumab ozogamicin** (Mylotarg) was approved for some time to treat some people with acute myelogenous leukemia. It has a toxin called *calicheamicin*, attached to an antibody against the CD33 antigen, which is present on most leukemia cells. Further studies of this drug did not show that it helped patients live longer and the approval was withdrawn. It is no longer available for use outside of a clinical trial.

Another immunotoxin, BL22, showed promising results in early studies against some forms of chronic leukemia, even in patients who no longer responded to chemotherapy. In early clinical trials, about 2 of 3 patients had complete responses to the treatment (no evidence of cancer) that lasted up to 2 years. A newer, improved version of this immunotoxin, known as HA22 (CAT-8015), is now being studied.

Clinical trials of other immunotoxins are also being done in people with certain leukemias, lymphomas, brain tumors, and other cancers.

Other immunotherapies containing toxins

Scientists are also studying toxins linked to hormone-like substances called *growth factors*. Many cancer cells have large numbers of receptors for growth factors on their surfaces. This makes growth factors more likely to attach to these cells than those cells with fewer receptors. When these growth factor receptors are stimulated, the cancer cells reproduce and grow faster.

Researchers have learned how to attach growth factors to toxins. When the growth factor-toxin combination reaches the cancer cell's growth factor receptors, it delivers its payload of toxin to kill the cell. The concept behind these growth factor/toxin drugs is much like that of immunotoxins. But because the toxin-carrying growth factor drugs do not contain antibodies, they are not classified as immunotoxins.

The only growth factor/toxin currently approved by the FDA is **denileukin diftitox** (Ontak). It is the immune system protein known as interleukin-2 (IL-2) attached to a toxin from the germ that causes diphtheria. Denileukin diftitox is used to treat a rare type of skin lymphoma known as *mycosis fungoides* (or cutaneous T-cell lymphoma). It is also being studied to be used against a number of other cancers.

Cancer vaccines

Cancer vaccines have been studied for several decades, but advances in this field have been slower than for other forms of immunotherapy. They are still mostly experimental treatments at this time.

Most of us know about vaccines given to healthy people to help prevent infections, such as measles and mumps. These vaccines use weakened or killed viruses, bacteria, or other germs to start an immune response in the body. Getting the immune system ready to defend against these germs helps it keep the germs from making people sick.

Some so-called "cancer vaccines" are designed to work the same way. For example, new vaccines against the human papilloma virus (HPV) help prevent cervical, vaginal, vulvar, and anal cancer. Vaccines against hepatitis B virus (HBV) may lower some people's risk of getting liver cancer. But these vaccines don't target cancer cells; they target the viruses that can cause these cancers.

True cancer vaccines are different from the vaccines that work against viruses. Instead of preventing disease, they are meant to get the immune system to attack a disease that already exists.

A true cancer vaccine has cancer cells, parts of cells, or pure antigens. The vaccine increases the immune response against cancer cells that are already in the body. It may be combined with other substances or cells called *adjuvants* that help boost the immune response even further.

Cancer vaccines are thought of as *active* immunotherapies because they are meant to trigger your own immune system to respond. They are *specific* because they should only

affect the cancer cells. These vaccines don't just boost the immune system in general; they cause the immune system to attack cells with one or more specific antigens. And because the immune system has special cells for memory, it's hoped that the drugs will help keep cancer from coming back.

At this time, only one true cancer vaccine has been approved by the FDA. Sipuleucel-T (Provenge®) is used to treat advanced prostate cancer. For this vaccine, white blood cells (cells of the immune system) are removed from the patient's blood and exposed to a protein from prostate cancer cells called *prostatic acid phosphatase* (PAP). These cells are then given back to the patient by infusion into a vein (IV). This process is repeated twice more, 2 weeks apart, so that the patient gets 3 doses of cells. In the body, the cells make other immune system cells attack the patient's prostate cancer. Common side effects include fever, chills, fatigue, back and joint pain, nausea, and headache. A few men may have more severe symptoms, including problems breathing and high blood pressure, which improves with treatment. When used in men with metastatic prostate cancer that no longer responds to hormone therapy, the vaccine helps them live more than 4 months longer on average. Studies to see if this vaccine can help men with less advanced prostate cancer are continuing.

Other cancer vaccines have shown some promise in clinical trials, but have yet been approved in the United States to treat cancer. Several types of cancer vaccines are now being studied, with a few reaching late stage clinical trials.

Tumor cell vaccines

Tumor cell vaccines are made from actual cancer cells that have been removed during surgery. The cells are treated in the lab, usually with radiation, so they cannot form more tumors. In most cases, doctors also change the cells in certain ways, often by adding chemicals or new genes, to make them more likely to be seen as foreign by the immune system. The cells are then injected into the patient. The immune system recognizes antigens on these cells, then seeks out and attacks any other cells with these antigens that are still in the body.

In some cases, doctors give the vaccine along with substances called adjuvants that increase the immune response. The general boost that adjuvants give to the immune system is meant to make the vaccine work better.

Some promising newer versions of these vaccines use tumor cells that are fused to dendritic cells, in the hope of further stimulating the immune system.

A possible advantage of tumor cell vaccines over antigen-based vaccines (described in the "Antigen vaccines" section) is that not all cancer antigens have been found yet. Using the whole tumor cell may expose the immune system to a large number of important cancer antigens, including some that researchers have not yet recognized. This may make them more effective.

The 2 basic kinds of tumor cell vaccines are *autologous* and *allogeneic*.

Autologous tumor cell vaccines: *Autologous* (pronounced aw-TAH-luh-gus) means "coming from the self." An autologous tumor cell vaccine is made from killed tumor cells taken from the same person in whom they will later be used. In other words, cells are taken from you (during surgery), the vaccine is made from them in a lab, and the cells are injected back into you. Autologous cancer cells may be reinjected shortly after surgery, or they may be grown in the lab or frozen and given later.

Although autologous tumor cell vaccines are promising, there are some potential drawbacks:

- It can be expensive to create a new, unique vaccine for each patient.
- Cancer cells tend to mutate (change) over time, so an autologous tumor vaccine might become less effective later if the cancer cells in your body change.
- Depending on the surgery and the size of your tumor(s), you may not have enough usable cells in the removed tumor to make a vaccine, or there may not be enough for re-treatment if the cancer starts growing again.

Because of these problems, researchers are also looking at ways to create tumor cell vaccines that could work in any patient with that particular kind of cancer.

Allogeneic tumor cell vaccines: *Allogeneic* (pronounced a-loh-jeh-NAY-ik) means "coming from another." These vaccines use cells of a particular cancer type that originally came from someone other than the patient being treated.

Allogeneic vaccines are easier to make than autologous vaccines. They are more like off-the-shelf drugs than a vaccine made for just one person. The cells for the vaccine are grown in the lab from a stock of cancer cells kept for that purpose. Some allogeneic tumor vaccines use a mixture of cells that were removed from several patients. The cells are treated and are usually injected along with one or more adjuvant substances to stimulate the immune system.

Types of cancers for which tumor cell vaccines are being studied

Although the FDA has not yet approved any tumor cell vaccines for general use, they are being studied in clinical trials against many types of cancer, including:

- Melanoma
- Kidney cancer
- Ovarian cancer
- Breast cancer
- Colorectal cancer
- Lung cancer
- Prostate cancer

- Non-Hodgkin lymphoma
- Leukemia

Antigen vaccines

Antigen vaccines boost the immune system by using only one antigen (or a few), rather than whole tumor cells that contain many thousands of antigens. The antigens are usually proteins or pieces of proteins called *peptides*. Antigen vaccines may be specific for a certain type of cancer, but they are not made for a unique patient like autologous cell vaccines are.

Scientists have learned how to mass-produce many antigens in the lab. They can also change these antigens to make them more easily recognized by the immune system. This new technology means that large amounts of these very specific antigens can now be given to many patients.

Some antigens cause an immune response only in patients with a certain kind of cancer, while others produce immune reactions to more than one kind of cancer. Scientists often combine several antigens in a vaccine to try to get a stronger immune response.

Antigen vaccines are being studied to be used against these cancers, among others:

- Breast cancer
- Prostate cancer
- Colorectal cancer
- Ovarian cancer
- Melanoma
- Kidney cancer
- Pancreatic cancer
- Multiple myeloma

Dendritic cell vaccines

Dendritic cells are special antigen-presenting cells (APCs) that help the immune system recognize cancer cells. They break down cancer cells into smaller pieces (including antigens), then hold out, or "present," these antigens to T cells. This makes it easier for the immune system cells to recognize and attack them. Dendritic cells are the most effective APCs known.

Dendritic cell vaccines are autologous vaccines (made from the person in whom they will be used), and must be made individually for each patient. The process used to create them is complex and expensive:

- Doctors remove some of the cells that grow into dendritic cells (from the blood) and treat them in the lab to make them multiply and turn into dendritic cells. This creates many more dendritic cells than if they just used cells taken from the patient. The dendritic cells are then exposed to cancer cells or cancer antigens.
- Other methods are to change their genes so that they make their own antigens or to fuse the dendritic cells with tumor cells. These procedures lead to dendritic cells with cancer antigens on their surface.
- The dendritic cells are then injected back into the patient.

The dendritic cells that have cancer antigens on their surface are better able to help the patient's immune system recognize and destroy cancer cells that have those antigens on them.

The dendritic cell vaccine approach has shown promise in tests in lab animals and in some human studies. It is being studied for use in people with these and other cancers:

- Prostate cancer
- Melanoma
- Kidney cancer
- Colorectal cancer
- Lung cancer
- Breast cancer
- Leukemia
- Non-Hodgkin lymphoma

Sipuleucel-T (Provenge), which is approved to treat advanced prostate cancer, is an example of a dendritic cell vaccine.

Anti-idiotypic vaccines

Every B cell or plasma cell makes only one kind of antibody. The unique part of each type of antibody is called an *idiotype*.

Antibodies are made when the immune system responds to antigens. But the immune system also makes some antibodies that treat other antibodies like antigens. In other words, sometimes the body makes antibodies against other antibodies. Scientists believe these antibodies against antibodies are important in helping to keep the immune system in check.

Antibodies and antigens fit together like a lock and key. So an antibody to a particular idiotype of another antibody (an *anti-idiotypic*) will usually look like the antigen that triggered cells to make the antibody in the first place (like using the lock itself to make an extra key). Because the anti-idiotypic antibodies look like the antigen and appear foreign,

injecting them into the body causes the immune system to attack the anti-idiotypes, along with the antigens themselves.

Scientists have learned how to make these anti-idiotypic antibodies in the lab. They can be used as part of a cancer vaccine because they look like the antigens on the cancer cells in the patient's body. Therefore, they can trigger an immune response against that specific cancer.

Researchers consider lymphomas to be the most promising targets for anti-idiotypic vaccines. This is because all lymphoma cells have unique antigen receptors not present on normal lymphocytes or other normal cells of the body. These unique antigens can be used to make lymphoma vaccines. Early studies of B-cell lymphoma vaccines have been promising.

DNA vaccines

When tumor cells or antigens are injected into the body as a vaccine, they may cause the desired immune response at first, but they may become less effective over time. This is because the immune system recognizes them as foreign and quickly destroys them. Without any further stimulation, the immune system often returns to its normal (pre-vaccine) state of activity. To get around this, scientists have looked for a way to provide a steady supply of antigens to keep the immune response going.

DNA is the substance in cells that contains the genetic code for the proteins that cells make. Cells can be injected with bits of DNA that code for protein antigens. This DNA might be taken up by cells and instruct them to keep making more antigens. These types of therapies are called *DNA vaccines*.

Scientists may be able to do this by removing some of your cells, treating them with DNA that codes for a certain antigen, and then returning them to you. The altered cells would then make the antigen on an ongoing basis to keep the immune response strong.

DNA vaccines are now being studied in clinical trials for use against the following cancers, among others:

- Melanoma
- Leukemia
- Prostate cancer
- Head and neck cancers

Vector-based vaccines

These vaccines use special delivery systems (called *vectors*) to make them more effective. They aren't really a separate category of vaccine; for example, there are vector-based antigen vaccines and vector-based DNA vaccines.

Vectors are special viruses, bacteria, yeast cells, or other structures that can be used to get antigens or DNA into the body. The vectors are often germs that have been altered to make sure they can no longer cause disease.

Vectors may be helpful in making vaccines for a number of reasons. First, they may be used to deliver more than one cancer antigen at a time, which may make the body's immune system more likely to mount a response. Second, vectors such as viruses and bacteria may trigger their own immune responses from the body, which may help make the overall immune response even stronger. Finally, these vaccines may be easier and less expensive to make than some other vaccines. Many clinical trials of vector-based vaccines are now under way.

Other active specific immunotherapies

Some forms of active immunotherapy are not considered cancer vaccines. Vaccines try to get the body's immune system to react to specific antigens, while these other therapies try to boost specific parts of the immune system.

Lymphokine-activated killer cell therapy

Scientists can make large numbers of active, cancer-fighting T cells in the lab by treating a small number of killer T cells in a test tube with a cytokine (an immune system growth factor) called *interleukin-2 (IL-2)*. After being returned to a patient's bloodstream, these special cells, now called *lymphokine-activated killer cells* (or LAK cells), are more effective against cancer cells. Researchers are now testing several ways to use these very active cancer-fighting cells.

LAK cell therapy has shown promising results in animal studies, where it shrunk tumors in animals with lung, liver, and other cancers. Although clinical trials in humans have not yet been as successful, researchers are constantly improving LAK cell techniques. They are testing these newly improved methods against melanoma, brain tumors, and other cancers.

Tumor-infiltrating lymphocyte vaccine with interleukin-2

Researchers have found immune system cells deep inside some tumors and have named these cells *tumor-infiltrating lymphocytes (TILs)*. These cells can be removed from tumor samples taken from patients and made to reproduce in the lab by treating them with IL-2. When injected back into the patient, these cells can be active cancer fighters. This is a type of autologous vaccine (the same person is the donor and the recipient).

Success with TILs in lab animals has led researchers to try to increase the anti-tumor activity of TILs. Treatments using TILs are being tested in clinical trials in people with melanoma, kidney cancer, and other cancers.

In one study, researchers from the National Cancer Institute used a newer technique with TILs in patients with advanced melanoma. After removing TILs from the body and

increasing their numbers, the researchers treated the patients with chemotherapy to reduce the numbers of other white blood cells in the body. When the TILs were given back into the body, the tumors shrank in about half of the patients, and almost all of the patients lived longer than expected. The results were promising, but the researchers weren't able to get TILs from all of the patients. This limited the treatment's effectiveness, in that it couldn't be used for everyone.

More recently, the researchers took T cells from the blood of patients with advanced melanoma. In the lab, they inserted genes into them that made them more likely to recognize melanoma cells. When the T cells were injected back into the patients, 5 of 11 had their tumors shrink, 2 of which went away completely for at least a year.

Suppressing regulatory T cells

Regulatory T cells normally act as brakes to help keep the immune system in check. They help keep it from overreacting and attacking normal cells in the body. But they may also slow the immune system's ability to attack cancer cells. Researchers have studied whether suppressing these cells might allow the immune system to be more effective against cancer. This is, in part, how ipilimumab (Yervoy) works. Ipilimumab is a monoclonal antibody that targets CTLA-4, a protein on some T-cells that normally helps them suppress the immune response. This drug suppresses regulatory T cells and activates cytotoxic T cells. In studies of advanced melanoma, it caused tumors to shrink and helped patients live longer. Still, taking some of the brakes off the immune system can lead to some serious side effects, such as autoimmune diseases.

Non-specific immunotherapies and adjuvants

Non-specific immunotherapies do not target a certain cell or antigen. They stimulate the immune system in a very general way, but this may still result in more activity against cancer cells.

Some non-specific immunotherapies can be given as treatments. Others are used as adjuvants (along with a main treatment) to boost immune system function to improve how well another therapy (such as a vaccine) works. And some immunotherapies are used by themselves against some cancers and as adjuvants against others.

Cytokines

Cytokines (pronounced SY-toh-kines) are chemicals made by immune system cells. They have a crucial role in regulating the growth and activity of other immune system cells and blood cells.

Some cytokines are used to lessen the side effects of other treatments such as chemotherapy. Man-made versions of cytokines can help the bone marrow make more

white blood cells, red blood cells, or platelets when their levels in the body have gotten too low. While this is important in cancer treatment, it isn't truly immunotherapy.

But man-made versions of cytokines can also be given along with tumor vaccines as *adjuvants* or given alone to boost the immune system.

Cytokines are given as injections, either under the skin, into a muscle, or into a vein. The most common ones are discussed here.

Interleukins

Interleukins are a group of cytokines that act as chemical signals between white blood cells. When interleukin-2 (IL-2) was approved by the FDA in 1992 to treat advanced kidney cancer, it became the first true immunotherapy approved for use alone in treating cancer. Since that time, it has also been approved to treat people with metastatic melanoma.

IL-2 can be used as a single drug treatment for these cancers, or it may be combined with other forms of immunotherapy, such as vaccines. IL-2 helps immune system cells grow and divide more quickly.

Using IL-2 with chemotherapy or with other cytokines (such as interferon-alfa) may make these treatments more effective against some cancers. But the side effects of the combined treatment are also increased.

Side effects of IL-2 may include flu-like symptoms such as chills, fever, fatigue, and confusion. Most people gain weight. Some have nausea, vomiting, or diarrhea. Many people develop low blood pressure, which can be treated with other medicines. An abnormal heartbeat occurs in less than 1 in 10 patients. Chest pain and serious heart problems are rare. Because of these potentially serious side effects, if IL-2 is given in high doses, it must be done in the hospital (as an inpatient).

Other interleukins, such as IL-7, IL-12, and IL-21, are now being studied for use against cancer too, both as adjuvants and as stand-alone agents.

Interferons

This family of cytokines, first discovered in the late 1950s, helps the body resist virus infections and cancers. The types of interferon (IFN) are named after the first 3 letters of the Greek alphabet: IFN-alfa, IFN-beta, and IFN-gamma. Although all 3 types of interferon are FDA approved to treat health conditions, only IFN-alfa is used to treat cancer. Not all of its actions are well understood, but it may work by:

- Directly slowing the growth of cancer cells
- Slowing down *angiogenesis*, the growth of new blood vessels that tumors must have in order to grow

- Causing cancer cells to produce more antigens, making them easier for the immune system to see and destroy
- Boosting the cancer cell-killing ability of natural killer (NK) cells and of other immune system cells that attack cancer with help from antibodies

The FDA has approved IFN-alfa for use against these cancers:

- Hairy cell leukemia
- Chronic myelogenous leukemia
- Follicular non-Hodgkin lymphoma
- Cutaneous (affecting the skin) T-cell lymphoma
- Kidney cancer
- Melanoma
- Kaposi sarcoma

Side effects of interferons may include flu-like symptoms (chills, fever, headache, fatigue, loss of appetite, nausea, vomiting), low white blood cell counts (which increase the risk of infection), skin rashes, and thinning hair. These side effects can be severe, and make treatment with interferon hard to tolerate for many people.

Most side effects do not last long after the treatment stops, but fatigue can last longer. Other rare long-term effects include damage to nerves, including those in the brain and spinal cord.

Granulocyte-macrophage colony-stimulating factor

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine/growth factor that causes the bone marrow to make more of certain types of immune system cells and blood cells. This includes monocytes, macrophages, and dendritic cells. It also boosts the production of other blood cells. A man-made version (also known as sargramostim or Leukine[®]) is often used to boost white blood cell counts after chemotherapy.

GM-CSF is also being tested against cancer as a non-specific immunotherapy and as an adjuvant given with other types of immunotherapies. Clinical trials of GM-CSF, alone or with other immunotherapies, are being done in people with many different types of cancer.

Common side effects of GM-CSF include flu-like symptoms (fever, headaches, muscle aches), rashes, facial flushing, and bone pain.

Adjuvants other than cytokines

Many other compounds are known to boost the activity of the immune system and are now being studied as possible adjuvants, particularly for use with vaccine therapies.

Some of the most commonly studied adjuvants are listed below, but many more are being developed.

Bacille Calmette-Guérin

Bacille Calmette-Guérin (BCG) is a germ related to the one that causes tuberculosis. Unlike its bacterial "cousin," BCG does not cause serious disease in humans, but it does infect human tissues and helps activate the immune system.

This makes BCG useful as a form of cancer immunotherapy. BCG was one of the earliest immunotherapies used against cancer and it is still being used today. It is FDA-approved as a routine treatment for early stage bladder cancer.

Its usefulness in other cancers as an adjuvant is also being tested. Researchers are looking at injecting BCG to give an added boost to the immune system when using chemotherapy, radiation therapy, or other types of immunotherapy.

Keyhole limpet hemocyanin

Keyhole limpet hemocyanin (KLH) is an adjuvant used to boost the effectiveness of cancer vaccine therapies. It is extracted from a type of sea creature related to the snail.

Incomplete Freund's adjuvant

Incomplete Freund's adjuvant (IFA) is given together with some experimental therapies to help stimulate the immune system and to increase the immune response to cancer vaccines. IFA is a water-in-oil emulsion that stimulates the T-cell immune response to antigens.

QS-21

QS-21 is a fairly new immune stimulant made from a plant extract that increases the immune response to some cancer vaccines.

DETOX™

DETOX is an adjuvant made from parts of the cell walls of bacteria and a kind of fat that also comes from bacteria. Since it was first made, other types have been created by using other methods, such as DETOX-B and DETOX-PC, one of which has been named Melacine®. It is used with various immunotherapies to boost the immune system.

Dinitrophenyl

Dinitrophenyl (DNP) is a small molecule that can attach to tumor antigens and boost immune response. It is used to modify tumor cells in certain cancer vaccines.

Immunomodulating agents

Immunomodulating agents are drugs that affect the immune system in a non-specific way, similar to cytokines. The following drugs are different from cytokines in that they

are not naturally found in the body. It is also not clear exactly how they affect the immune system.

Thalidomide

The drug thalidomide (Thalomid[®]) was first used as a sedative in the 1950's. When it was found to cause birth defects, it was taken off the market. Later, it became available again as a treatment for multiple myeloma and other cancers. Side effects of thalidomide include drowsiness, fatigue, severe constipation, and neuropathy (painful nerve damage). The neuropathy can be severe, and may not go away after the drug is stopped. There is also an increased risk of serious blood clots (that start in the leg and can travel to the lungs). Because thalidomide causes severe birth defects if taken during pregnancy, this drug can only be obtained through a special program run by the drug company that makes it.

Lenalidomide

Lenalidomide (Revlimid[®]) is a newer drug that is similar to thalidomide. It is used to treat multiple myeloma and other cancers. The most common side effects of lenalidomide are low platelet and low white blood cell counts. It can also cause painful nerve damage. The risk of blood clots is not as great as that seen with thalidomide, but it is still increased. Like thalidomide, access to lenalidomide is tightly controlled out of concern about possible serious birth defects.

Clinical trials

You may have had to make a lot of decisions since you've been told you have cancer. One of the most important decisions you will make is choosing which treatment is best for you. You may have heard about clinical trials being done for your type of cancer. Or maybe someone on your health care team has mentioned a clinical trial to you.

Clinical trials are carefully controlled research studies that are done with patients who volunteer for them. They are done to get a closer look at promising new treatments or procedures.

If you would like to take part in a clinical trial, you should start by asking your doctor if your clinic or hospital conducts clinical trials. You can also call our clinical trials matching service for a list of clinical trials that meet your medical needs. You can reach this service at 1-800-303-5691 or on our Web site at www.cancer.org/clinicaltrials. You can also get a list of current clinical trials by calling the National Cancer Institute's Cancer Information Service toll-free at 1-800-4-CANCER (1-800-422-6237) or by visiting the NCI clinical trials Web site at www.cancer.gov/clinicaltrials.

There are requirements you must meet to take part in any clinical trial. If you do qualify for a clinical trial, it is up to you whether or not to enter (enroll in) it.

Clinical trials are one way to get state-of-the-art cancer treatment. They are the only way for doctors to learn better methods to treat cancer. Still, they are not right for everyone.

You can get a lot more information on clinical trials in our document called *Clinical Trials: What You Need to Know*. You can read it on our Web site or call our toll-free number (1-800-227-2345) and have it sent to you.

Immunotherapy for specific cancers

The FDA has approved a number of cancer immunotherapies, including Bacille Calmette-Guérin (BCG), interferon-alfa (IFN-alfa), interleukin-2 (IL-2), the sipuleucel-T (Provenge) vaccine, and several monoclonal antibodies.

Many other immunotherapies have shown promising results and are moving through the testing process in clinical trials. The cancers listed here are being studied most intensively, but treatments for other cancers are also being looked at.

Breast cancer

In terms of immunotherapy, only monoclonal antibodies (MAbs) have been approved for use against breast cancer so far. But many other forms of treatment are being studied.

Approved

- The MAb trastuzumab (Herceptin) is used in women with breast cancer whose cancer cells have too many copies of the HER2/neu gene. These genes make extra receptors for growth-stimulating factors on the cells, which results in a more aggressive form of breast cancer. Trastuzumab attaches to the receptors, blocking the access of the growth factors to the cancer cells and slowing their growth. Other HER2/neu antibodies are now being studied in clinical trials.
- Bevacizumab (Avastin), a monoclonal antibody that slows blood vessel growth in tumors, has been used along with chemotherapy in some women with advanced breast cancer.

Being studied

- A conjugated MAb, known as trastuzumab-DM1 (or T-DM1) combines the trastuzumab (Herceptin) antibody with a chemo drug. It has shown promise in early studies of women whose breast cancer is no longer responding to trastuzumab alone.
- Autologous vaccine therapy has lengthened remission and survival times of some women with early breast cancer. This approach is being studied further.
- A HER2/neu peptide (a small part of the protein made by the HER2/neu gene), used as the antigen in a vaccine, has been shown to cause an increased immune response against the HER2/neu receptor on cancer cells; it is Being studied.

- Other specific antigen vaccines are also promising. These vaccines are almost always used after primary therapy (lumpectomy and radiation therapy, or mastectomy) and sometimes together with hormonal therapy or chemotherapy, to try to keep the cancer from coming back.

Cervical cancer

Infection with the human papilloma virus (HPV) plays an important role in causing cervical cancer. HPV vaccines are now approved for use to help prevent cervical cancer. Other vaccines that may help treat this cancer are now being tested in clinical trials.

Approved

- Some HPV vaccines are like more traditional vaccines, which work against infections. They are intended to make women immune to some types of HPV, so that when they are exposed to these viruses they will not develop long-term infections. Most cervical cancers may be prevented, if persistent HPV infection is avoided,. Two vaccines (Gardasil[®] and Cervarix[®]) can protect against most infections from the 2 types of HPV that cause 70% of cervical cancers. These vaccines are used mainly in girls and young women, although Gardasil is approved for use in boys and young men as well (to help prevent genital warts and other cancers).

Under study

- Other vaccines are now being studied to help women who already have advanced cervical cancer. These vaccines try to cause an immune reaction to the parts of the virus that contribute to the growth of cervical cancer cells. This may kill the cancer cells or stop them from growing.

Colorectal cancer

Several monoclonal antibodies are now used to treat colorectal cancer. Clinical trials are also using vaccines and many other immunotherapies as adjuvants to surgery, with and without chemotherapy.

Approved

- Bevacizumab (Avastin) is a monoclonal antibody against vascular endothelial growth factor (VEGF). By attacking VEGF, the antibody stops tumors from being able to form new blood vessels. It is used along with chemotherapy against advanced colorectal cancer.
- Cetuximab (Erbix) is a monoclonal antibody that attacks the epidermal growth factor receptor (EGFR), which normally signals cancer cells to grow and divide. It is used against advanced colorectal cancer, usually along with chemotherapy, in people whose cancer is no longer responding to other treatments.

- Another monoclonal antibody, panitumumab (Vectibix), also targets EGFR. Unlike cetuximab, this MAb has no parts that come from a mouse, so it may be less likely to cause an allergic reaction when it is given. Panitumumab is used to treat advanced colorectal cancer.

Being studied

- A number of autologous and allogeneic tumor cell vaccines have shown early promise, but so far none have improved patient survival time.
- Some carcinoembryonic antigen (CEA) vaccines have improved the immune response (measured by blood tests) in a large percentage of colorectal cancer patients, but the studies have not been going on long enough to see whether this improves remission or survival times.

Kidney cancer

Immunotherapy has been studied a great deal for advanced kidney cancer, least in part because other treatments like chemotherapy often have not been helpful.

Approved

- Two cytokines, IL-2 and IFN-alfa, are treatment options for people with advanced kidney cancer.
- Bevacizumab (Avastin), a monoclonal antibody that slows blood vessel growth in tumors, is approved for use against kidney cancer.

Being studied

- Whole tumor cell vaccines given along with the adjuvant BCG have shrunk tumors in a small number of people with advanced kidney cancer.
- Researchers are studying DNA vaccines that insert genes (segments of DNA) into cancer cells, causing the cells to make cytokines. These cytokines help the immune system recognize the cancer cells and also help activate immune system cells to attack those cells.
- Tumor-infiltrating lymphocytes (TILs) are also being studied to fight kidney cancer. They can be removed from the body and stimulated in the lab by cytokines. When put back into the body, they become more effective than untreated cells from the bloodstream.

Leukemias, lymphomas, and myelomas

Several immunotherapies are now used to treat these blood cell cancers, and many more are being studied.

Approved

- Interferon-alfa can be used to treat people with hairy cell leukemia, chronic myelogenous leukemia, follicular lymphoma, multiple myeloma, and cutaneous (skin) T cell lymphoma. In some cases, interferon is used along with chemotherapy.
- Denileukin diftitox (Ontak), a combination of IL-2 and diphtheria toxin, is sometimes used to treat cutaneous T cell lymphoma.
- Rituximab (Rituxan), a monoclonal antibody (MAb), is used to treat some kinds of B cell non-Hodgkin lymphoma and chronic lymphocytic leukemia. Clinical trials are currently testing rituximab against other lymphomas, leukemias, multiple myeloma, and other diseases.
- Ibritumomab tiuxetan (Zevalin) and tositumomab (Bexxar) are radiolabeled monoclonal antibodies used to treat non-Hodgkin lymphoma, usually in people who aren't helped by other treatments such as chemotherapy or rituximab. They are now being tested to see if they might be helpful earlier in the course of this disease.
- Alemtuzumab (Campath) is an antibody used to treat B-cell chronic lymphocytic leukemia (CLL).
- Ofatumumab (Arzerra) is an antibody used to treat CLL, usually in people whose leukemia is no longer responding to other treatments. It is also being studied for use in other types of cancer.
- Thalidomide (Thalomid) and lenalidomide (Revlimid) are immunomodulating agents that are used to treat multiple myeloma.
- Brentuximab vedotin (Adcetris or SGN-35) is an antibody that targets the CD30 antigen, attached to a chemo drug called monomethyl auristatin E. It is approved to treat refractory Hodgkin lymphoma and anaplastic large-cell lymphoma.

Being studied

- Several other MAbs are being studied in clinical trials for people with leukemia, lymphoma, and multiple myeloma.
- Anti-idiotypic vaccines have shown promising results in clinical trials against B-cell non-Hodgkin lymphomas, but are not yet FDA approved.

Lung cancer

Better treatments are needed for lung cancer, especially for advanced disease. Immunotherapy may help people live longer without the severe side effects sometimes seen with chemotherapy. Thus far, only monoclonal antibodies have been approved for use against lung cancer, although many other forms of immunotherapy are being studied.

Approved

- The monoclonal antibody bevacizumab (Avastin) slows the growth of tumor blood vessels by targeting the VEGF protein. For some patients with non-small cell lung cancer (NSCLC), adding it to standard chemotherapy may help them live longer than chemotherapy alone.

Being studied

- Stimuvax[®] (BLP25) is a peptide (antigen) vaccine that is encased in a fat droplet (liposome) to make it work better. A small study of patients with advanced NSCLC suggested it might improve survival time. Larger studies are needed to confirm this.

Melanoma

Melanoma is probably the most-studied cancer when it comes to immunotherapy. Part of this is because doctors think this cancer may be more vulnerable to immune system responses. In rare cases, these cancers have been seen to shrink or even disappear without treatment. It is thought that this may be because of an effective immune response by the body.

Another reason immunotherapy has been studied more in melanoma is because other treatments, like chemotherapy, don't work as well against this cancer as they do for most cancers.

Approved

- The cytokines IFN-alfa and IL-2 are approved to treat people with metastatic melanoma.
- Ipilimumab (Yervoy) is approved to treat advanced melanoma.

Being studied

- Although no melanoma vaccines are FDA-approved yet, recent studies have found that some autologous and allogeneic tumor cell vaccines, as well as antigen vaccines, have shrunk tumors and helped some patients live longer. Dendritic cell vaccines have also been shown to shrink tumors in some patients. Some newer studies combine vaccines with IL-2 or newer adjuvants to further stimulate the immune reaction. Studies continue.
- A small study showed that treating patients with tumor-infiltrating lymphocytes (TILs), immune system cells found in tumors, could shrink melanoma tumors and possibly prolong life too. More studies using TILs are being done now. Another study found that T cells from the blood that had their genes altered in the lab caused tumors to shrink in a small number of patients.

- Very early study results have suggested that suppressing regulatory T cells with denileukin diftitox (Ontak) can allow the immune system to fight cancers better, making some tumors shrink. A current study is looking to see if combining Ontak with a vaccine will help the vaccine work better.
- Clinical trials are continuing for these and other melanoma immunotherapies.

Ovarian cancer

Immunotherapy is not used routinely to treat ovarian cancer. Several types of immunotherapy, including cancer vaccines and MAbs, are now being studied.

- The monoclonal antibody bevacizumab (Avastin) slows the growth of tumor blood vessels by targeting the VEGF protein. It can slow the growth of advanced ovarian cancer, although it's not yet clear if it helps women live longer.
- Injection of interleukin-2 (IL-2) directly into the peritoneal cavity (the part of the belly that contains the ovaries, uterus, and digestive organs) of women with recurrent ovarian cancer is being studied. Early studies suggest the treatment may increase the length of remissions (periods of time with no signs of cancer) after surgery.
- Placing tumor-infiltrating lymphocytes (TILs) along with interleukin-2 directly into the peritoneal cavity has also shown promise and is being studied.
- A monoclonal antibody that attaches to certain antigens on both ovarian cancer cells and to certain spots on T cells (a bi-specific antibody) has shown promise when used with IL-2. The antibody causes T cells to bind to and attack the cancer cells.
- Early studies have shown that radiolabeled MAbs against ovarian cancer may help more women live longer.
- Several forms of antigen vaccines are being studied to treat ovarian cancer.

Prostate cancer

Immunotherapy has not been a routine part of treating prostate cancer treatment. This may change with the approval of sipuleucel-T (Provenge). Most other prostate cancer immunotherapies now being studied are vaccines. They are designed to cause immune responses to antigens present only on prostate cells, such as prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSMA).

Approved

- For sipuleucel-T (Provenge), white blood cells are removed from a patient's bloodstream and treated in the lab with a prostate cancer antigen and other substances to become dendritic cells. When put back in to the patient, the dendritic cells can show this antigen to other immune system cells, which are then better able to

recognize and attack the cancer cells. When used to treat men with hormone-refractory prostate cancer, this vaccine helped them live longer.

Being studied

- GVAX is an autologous whole cell vaccine. It is made by removing cancer cells from the patient during surgery and modifying them in the lab to express GM-CSF (to help stimulate the immune system). The cells are irradiated so they can't grow any more. They are then injected back into the patient to cause an immune response. Early studies of patients with advanced prostate cancer that no longer responded to hormone therapy have shown some promising results in terms of survival time. This vaccine is now being tested against the current standard chemotherapy regimen for prostate cancer.
- Researchers also are looking into using a part of the prostate-specific antigen (called a peptide) as the basis of a vaccine.
- DNA vaccines, monoclonal antibodies, and cytokines have also shown promise and are being tested in clinical trials.

Additional resources

More information from your American Cancer Society

We have some related information that may also be helpful to you. You can find these on our Web site or order them from our toll-free number, 1-800-227-2345.

Targeted Therapy

Oncogenes and Tumor Suppressor Genes

Clinical Trials: What You Need to Know

Questions People Ask About Cancer (also available in Spanish)

Understanding Chemotherapy: A Guide for Patients and Families (also available in Spanish)

National organizations and Web sites*

Along with the American Cancer Society, other sources of information and support include:

National Cancer Institute

Toll-free number: 1-800-4-CANCER

Web site: www.cancer.gov

**Inclusion on this list does not imply endorsement by the American Cancer Society.*

No matter who you are, we can help. Contact us anytime, day or night, for cancer-related information and support. Call us at **1-800-227-2345** or visit www.cancer.org.

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