Cancer Vaccines

National Cancer Institute (http://www.cancer.gov/about-cancer/causes-prevention/vaccines-fact-sheet)

What is the immune system?

The immune system is complex network of cells, tissues, organs, and the substances they make that helps the body fight infections and other diseases. The immune system's role in defending against disease-causing microbes has long been recognized. Scientists have also discovered that the immune system can protect the body against threats posed by certain damaged, diseased, or abnormal cells, including cancer cells (1).

White blood cells, or leukocytes, play the main role in immune responses. These cells carry out the many tasks required to protect the body against disease-causing microbes and abnormal cells.

Some types of leukocytes patrol the circulatory system, seeking foreign invaders and diseased, damaged, or dead cells. These white blood cells provide a general—or nonspecific—level of immune protection.

Other types of leukocytes, known as lymphocytes, provide targeted protection against specific threats, whether from a specific microbe or a diseased or abnormal cell. The most important groups of lymphocytes responsible for carrying out immune responses against such threats are B cells and T cells.

B cells make antibodies, which are large secreted proteins that bind to, inactivate, and help destroy foreign invaders or abnormal cells. Cytotoxic T cells, which are also known as killer T cells, kill infected or abnormal cells by releasing toxic chemicals or by prompting the cells to self-destruct (in a process known as apoptosis).

Other types of lymphocytes and leukocytes play supporting roles to ensure that B cells and killer T cells do their jobs effectively. These supporting cells include helper T cells and dendritic cells, which help activate both B cells and killer T cells and enable them to respond to specific threats.

Antigens are substances that have the potential to cause the body to mount an immune response against them. They help the immune system determine whether something is foreign, or "non-self." Normal cells in the body have antigens that identify them as "self." Self antigens tell the immune system that normal cells are not a threat and should be ignored (2). In contrast, microbes are recognized by the immune system as a potential threat that should be destroyed because they carry foreign, or non-self, antigens.

Are cancer cells recognized by the immune system?

Cancer cells can carry both self antigens as well as what are referred to as cancer-associated antigens. Cancer-associated antigens mark cancer cells as abnormal or foreign and can cause killer T cells to mount an attack against them (1–7). Cancer-associated antigens may be:

- Self antigens that are made in much larger amounts by cancer cells than normal cells and, thus, are viewed as foreign by the immune system
- Self antigens that are not normally made by the tissue in which the cancer developed (for example, antigens that are normally made only by embryonic tissue but are expressed in an adult cancer) and, thus, are viewed as foreign by the immune system
- Newly formed antigens, or neoantigens, that result from gene mutations in cancer cells and have not been seen previously by the immune system

However, several factors may make it difficult for the immune system to target growing cancers for destruction:

- Many cancer-associated antigens are only slightly altered versions of self antigens and therefore may be hard for the immune system to recognize.
- Cancer cells may undergo genetic changes that may lead to the loss of cancer-associated antigens.
- Cancer cells can evade anticancer immune responses by killer T cells. As a result, even when the immune system recognizes a growing cancer as a threat, the cancer may still escape a strong attack by the immune system (8).

What are vaccines?

Vaccines are medicines that boost the immune system's natural ability to protect the body against “foreign invaders,” mainly infectious agents, that may cause disease.

When an infectious microbe invades the body, the immune system recognizes it as foreign, destroys it, and “remembers” it to prevent another infection should the microbe invade the body again in the future. Vaccines take advantage of this defensive memory response.

Most vaccines are made with harmless versions of microbes—killed or weakened microbes, or parts of microbes—that do not cause disease but are able to stimulate an immune response against the microbes. When the immune system encounters these substances through vaccination, it responds to them, eliminates them from the body, and develops a memory of them. This vaccine-induced memory enables the immune system to act quickly to protect the body if it becomes infected by the same microbes in the future.

What are cancer vaccines?

Cancer vaccines belong to a class of substances known as biological response modifiers. Biological response modifiers work by stimulating or restoring the immune system's ability to fight infections and disease. There are two broad types of cancer vaccines:

- **Preventive (or prophylactic) vaccines**, which are intended to prevent cancer from developing in healthy people
- **Treatment (or therapeutic) vaccines**, which are intended to treat an existing cancer by strengthening the body's natural immune response against the cancer (9). Treatment vaccines are a form of immunotherapy.

Two types of cancer preventive vaccines (human papillomavirus vaccines and hepatitis B virus vaccines) are available in the United States, and one treatment vaccine (for metastatic prostate cancer) is available.

How do cancer preventive vaccines work?

Cancer preventive vaccines target infectious agents that cause or contribute to the development of cancer (10). They are similar to traditional vaccines, which help prevent infectious diseases, such as measles or polio, by protecting the body against infection. Both cancer preventive vaccines and traditional vaccines are based on antigens that are carried by infectious agents and that are relatively easy for the immune system to recognize as foreign.

Most preventive vaccines, including those aimed at cancer-causing viruses (hepatitis B virus and human papillomavirus), stimulate the production of antibodies that bind to specific targeted microbes and block their ability to cause infection.

What cancer preventive vaccines are approved in the United States?

- **Human papillomavirus (HPV) vaccines.** Persistent infections with high-risk HPV types can cause cervical cancer, anal cancer, oropharyngeal cancer, and vaginal, vulvar, and penile cancers. Three vaccines are approved by the US Food and Drug Administration (FDA) to prevent HPV infection: Gardasil®, Gardasil 9®, and Cervarix®. Gardasil and Gardasil 9 are approved for use in females ages 9 through 26 for the prevention of HPV-caused cervical, vulvar, vaginal, and anal cancers; precancerous cervical, vulvar, vaginal, and anal lesions; and genital warts. Gardasil and Gardasil 9 are also approved for use in males for the prevention of HPV-caused anal cancer, precancerous anal lesions, and genital warts. Gardasil is approved for use in males ages 9 through 26, and Gardasil 9 is approved for use in males ages 9 through 15. Cervarix is approved for use in females ages 9 through 25 for the prevention of cervical cancer caused by HPV.
- **Hepatitis B virus (HBV) vaccines.** Chronic HBV infection can lead to liver cancer. The FDA has approved multiple vaccines that protect against HBV infection. Two vaccines, Engerix-B and Recombivax HB, protect against HBV

infection only. Both vaccines are approved for use in individuals of all ages. Several other vaccines protect against infection with HBV as well as other viruses. Twinrix protects against HBV and hepatitis A virus, and Pediarix against HBV, poliovirus, and the bacteria that cause diphtheria, tetanus, and pertussis. Twinrix is approved for use in persons 18 years of age or older. Pediarix is approved for use in infants whose mothers are negative for the HBV surface antigen (HBsAg) and is given as early as 6 weeks of age through 6 years of age. The original HBV vaccine was approved by the FDA in 1981, making it the first cancer preventive vaccine to be successfully developed and marketed. Today, most children in the United States are vaccinated against HBV shortly after birth (11).

How are cancer treatment vaccines designed to work?

Cancer treatment vaccines are used to treat cancers that have already developed. They are intended to delay or stop cancer cell growth; to cause tumor shrinkage; to prevent cancer from coming back; or to eliminate cancer cells that have not been killed by other forms of treatment.

Cancer treatment vaccines are designed to work by activating cytotoxic T cells and directing them to recognize and act against specific types of cancer or by inducing the production of antibodies that bind to molecules on the surface of cancer cells. To do so, treatment vaccines introduce one or more antigens into the body, usually by injection, where they cause an immune response that results in T cell activation or antibody production. Antibodies recognize and bind to antigens on the surface of cancer cells, whereas T cells can also detect cancer antigens inside cancer cells.

Producing effective treatment vaccines has proven more difficult and challenging than developing cancer preventive vaccines (12). To be effective, cancer treatment vaccines must achieve two goals. First, like preventive vaccines, cancer treatment vaccines must stimulate specific immune responses against the correct target. Second, the immune responses must be powerful enough to overcome the barriers that cancer cells use to protect themselves from attack by killer T cells.

Has the FDA approved any cancer treatment vaccines?

In April 2010, the FDA approved the first cancer treatment vaccine. This vaccine, sipuleucel-T (Provenge®), is approved for use in some men with metastatic prostate cancer. It is designed to stimulate an immune response to prostatic acid phosphatase (PAP), an antigen that is found on most prostate cancer cells. In clinical trials, sipuleucel-T increased the survival of men with a certain type of metastatic prostate cancer by about 4 months (13).

Unlike some other cancer treatment vaccines, sipuleucel-T is customized to each patient. The vaccine is created by isolating immune system cells called dendritic cells, which are a type of antigen-presenting cell (APC), from a patient’s blood through a procedure

called leukapheresis. These cells are sent to the vaccine manufacturer, where they are cultured together with a protein called PAP-GM-CSF. This protein consists of PAP linked to a protein called granulocyte-macrophage colony-stimulating factor (GM-CSF). The GM-CSF stimulates the immune system and enhances antigen presentation.

APC cells cultured with PAP-GM-CSF constitute the active component of sipuleucel-T. The cells are returned to the patient's treating physician and infused into the patient. Patients receive three treatments, usually 2 weeks apart, with each round of treatment requiring the same manufacturing process. Although the precise mechanism of action of sipuleucel-T is not known, it appears that the APCs that have taken up PAP-GM-CSF stimulate T cells of the immune system to kill tumor cells that express PAP.

In October 2015, the FDA approved the first oncolytic virus therapy, talimogene laherparepvec (T-VEC, or Imlygic®) for the treatment of some patients with metastatic melanoma that cannot be surgically removed. In addition to infecting and lysing cancer cells when injected directly into melanoma tumors, T-VEC induces responses in non-injected lesions, suggesting that it triggers an antitumor immune response similar to those of other anticancer vaccines.

How are cancer vaccines made?

All cancer preventive vaccines approved by the FDA to date have been made using antigens from microbes that cause or contribute to the development of cancer. These include antigens from HBV and specific types of HPV. These antigens are proteins that help make up the outer surface of the viruses. Because only part of these microbes is used, the resulting vaccines are not infectious and, therefore, cannot cause disease.

Researchers are also creating synthetic versions of antigens in the laboratory for use in cancer preventive vaccines. In doing this, they often modify the chemical structure of the antigens to stimulate immune responses that are stronger than those caused by the original antigens (14).

Similarly, cancer treatment vaccines are made using cancer-associated antigens or modified versions of them. Antigens that have been used thus far include proteins, carbohydrates (sugars), glycoproteins or glycopeptides (carbohydrate–protein combinations), and gangliosides (carbohydrate–lipid combinations).

Cancer treatment vaccines are also being developed using weakened or killed cancer cells that carry a specific cancer-associated antigen(s) or immune cells that are modified to present such an antigen(s) on their surface. These cells can come from a patient himself or herself (called an autologous vaccine, such as with sipuleucel-T) or from another patient (called an allogeneic vaccine).

Some cancer vaccines in late-stage development use viruses, yeast, or bacteria as vehicles (or vectors) to deliver one or more antigens into the body (15). The vectors themselves

are naturally immunogenic (that is, they can stimulate an immune response) but are modified so that they cannot cause disease.

Other types of cancer treatment vaccines that are under development include those made using molecules of DNA or RNA that contain the genetic instructions for cancer-associated antigens. The DNA or RNA can be injected alone into a patient as a "naked nucleic acid" vaccine, or packaged into a harmless virus. After the naked nucleic acid or virus is injected into the body, the DNA or RNA is taken up by cells, which begin to manufacture the tumor-associated antigens. Researchers hope that the cells will make enough of the tumor-associated antigens to stimulate a strong immune response.

A number of different cancer-associated antigens are now being used to make experimental cancer treatment vaccines. Some of these antigens are found on or in many or most types of cancer cells. Others are unique to specific cancer types (1, 5, 6, 13, 16–19).

Are adjuvants used with cancer vaccines?

Substances known as adjuvants are often added to vaccines to boost their ability to induce potent anticancer immune responses (20).

Adjuvants used for cancer vaccines come from many different sources. Some microbes, such as the bacterium Bacillus Calmette-Guérin (BCG), can serve as adjuvants (21). Substances produced by bacteria, such as Detox B (an oil droplet emulsion of monophosphoryl lipid A and mycobacterial cell wall skeleton), are also frequently used as adjuvants. Biological products derived from nonmicrobial organisms can also be used as adjuvants. One example is keyhole limpet hemocyanin (KLH), which is a large protein produced by a marine mollusk. Attaching antigens to KLH has been shown to increase their ability to stimulate immune responses. Even some nonbiological substances, such as an emulsified oil known as montanide ISA–51, can be used as adjuvants.

Natural or synthetic cytokines can also be used as adjuvants. Cytokines are substances that are naturally produced by white blood cells to regulate and fine-tune immune responses. Some cytokines increase the activity of B cells and killer T cells, whereas other cytokines suppress the activities of these cells. Cytokines frequently used in cancer treatment vaccines or given together with them include interleukin 2 (IL2, also known as aldesleukin), interferon alpha, and granulocyte-macrophage colony-stimulating factor (GM–CSF, also known as sargramostim) (22).

Do cancer vaccines have side effects?

Before any vaccine is licensed, the FDA must conclude that it is both safe and effective. Vaccines intended to prevent or treat cancer appear to have safety profiles comparable to those of other vaccines (6). However, the side effects of cancer vaccines can vary among vaccine formulations and from one person to another.

The most commonly reported side effect of cancer vaccines is inflammation at the site of injection, including redness, pain, swelling, warming of the skin, itchiness, and occasionally a rash.

People sometimes experience flu-like symptoms after receiving a cancer vaccine, including fever, chills, weakness, dizziness, nausea or vomiting, muscle ache, fatigue, headache, and occasional breathing difficulties. Blood pressure may also be affected. These side effects, which usually last for only a short time, indicate that the body is responding to the vaccine and making an immune response, as it does when exposed to a virus.

Other, more serious health problems have been reported in smaller numbers of people after receiving a cancer vaccine. These problems may or may not have been caused by the vaccine. The reported problems have included asthma, appendicitis, pelvic inflammatory disease, and certain autoimmune diseases, including arthritis and systemic lupus erythematosus.

Vaccines that use cells or microbes might have additional side effects. For example, serious side effects of sipuleucel-T include infection near the site of injection and blood in the urine.

Vaccines, like any other medication affecting the immune system, can cause adverse effects that may prove life threatening. For example, severe hypersensitivity (allergic) reactions to specific vaccine ingredients have occurred following vaccination. However, such severe reactions are rare.

Can cancer treatment vaccines be combined with other types of cancer therapy?

Yes. In many of the clinical trials of cancer treatment vaccines that are now under way, vaccines are being given with other forms of cancer therapy. Therapies that have been combined with cancer treatment vaccines include surgery, chemotherapy, radiation therapy, and some forms of targeted therapy, including therapies that are intended to boost immune system responses against cancer.

Several studies have suggested that cancer treatment vaccines may be most effective when given in combination with other forms of cancer therapy (18, 23). For example, preclinical studies and early-phase clinical trials have demonstrated that radiation therapy can enhance the efficacy of cancer treatment vaccines (24). In addition, in some clinical trials, cancer treatment vaccines have appeared to increase the effectiveness of other cancer therapies (18, 23).

Additional evidence suggests that surgical removal of large tumors may enhance the effectiveness of cancer treatment vaccines (23). In patients with extensive disease, the

immune system may be overwhelmed by the cancer. Surgical removal of the tumor may make it easier for the body to develop an effective immune response.

Researchers are also designing clinical trials to answer questions such as whether cancer treatment vaccines work best when they are administered before, after, or at the same time as other therapies (7). Answers to such questions may not only provide information about how best to use a specific cancer treatment vaccine but also reveal additional basic principles to guide the future development of combination therapies involving vaccines.

What additional research is under way to improve cancer treatment vaccines?

Recent advances in understanding how cancer cells escape recognition and attack by the immune system are now giving researchers the knowledge required to design cancer treatment vaccines that can accomplish both goals (16, 25).

Although researchers have identified many cancer-associated antigens, these molecules vary widely in their ability to stimulate a strong anticancer immune response. Two major areas of research are aimed at addressing this issue. One involves the identification of novel cancer-associated antigens, or neoantigens, that may prove more effective in stimulating immune responses than the already known antigens. For example, a neoantigen-based personalized vaccine approach that is in early-phase clinical testing involves the identification and targeting of patient-specific mutated antigens to create treatment vaccines for patients with glioblastoma and melanoma (26, 27). The other major research area involves the development of methods to enhance the ability of cancer-associated antigens to stimulate the immune system. Research is also under way to determine how to combine multiple antigens within a single cancer treatment vaccine to produce optimal anticancer immune responses (28).

Improving our understanding of the basic biology underlying how immune system cells and cancer cells interact will be very important for developing cancer vaccines. New technologies are being created as part of this effort. For example, a new type of imaging technology allows researchers to observe killer T cells and cancer cells interacting inside the body (29).

Researchers are also trying to identify the mechanisms by which cancer cells evade or suppress anticancer immune responses. A better understanding of how cancer cells manipulate the immune system could lead to the development of drugs that block those processes, thereby improving the effectiveness of cancer treatment vaccines (30).

For example, some cancer cells produce chemical signals that attract white blood cells known as regulatory T cells, or T regs, to a tumor site. T regs often release cytokines that suppress the activity of nearby killer T cells (18, 31). The combination of a cancer treatment vaccine with a drug that prevents the inactivation of killer T cells might improve the vaccine’s effectiveness in generating potent killer T cell antitumor responses.

Immune checkpoint modulators may also improve the effectiveness of cancer vaccines (32). These modulators target another immune regulatory mechanism used by cancer cells to evade destruction, one that involves immune checkpoint proteins such as PD-1, which is expressed on the surface of T cells. The binding of PD1 to specific partner proteins (or ligands), called PD-L1 and PD-L2, on the surface of some normal cells or cancer cells creates an "off" signal that tells the T cell not to mount an immune response against those cells. (This binding keeps the immune system from overreacting against normal cells and prevents autoimmunity.) Some tumor cells express high levels of PD-L1, which causes T cells to shut down and helps the cancer cells evade immune destruction. Antibodies that block the binding of an immune checkpoint protein to its ligand on a cancer cell remove this "off' signal and allows an immune response to proceed against the cancer cells.

Several such antibodies have been approved by the FDA for treatment of some cancers and are showing promising effects in other cancers (33). Because these agents allow T cells against cancer to be more effective, it is expected that they will also improve the effectiveness of cancer vaccines. Indeed, they have been found to do so in animal models, and clinical trials that combine a vaccine with PD1 or PD-L1 inhibition are ongoing (34).

A number of vaccines designed to treat specific cancers are currently under development (35–38). These include dendritic cell vaccines for metastatic renal cell carcinoma, glioblastoma, and metastatic hormone-refractory prostate cancer; autologous tumor cell vaccines for colorectal cancer and follicular lymphoma; anti-idiotype vaccines for lymphomas and some solid tumors; vaccines designed to stimulate an immune response against hormones required for the growth and survival of gastrointestinal malignancies; allogeneic vaccines for lung cancer; and a DNA-based vaccine for metastatic breast cancer.

What types of vaccines are being studied in clinical trials?

The list below shows the types of cancer that are being targeted in active NCI-supported cancer prevention or treatment clinical trials using vaccines. The cancer names are links to search results from NCI's clinical trials list. This list can also be searched in NCI's clinical trials database.

Active Clinical Trials of Cancer Treatment Vaccines by Type of Cancer:

- Bladder Cancer
- Brain Tumors
- Breast Cancer
- Cervical Cancer
- Colon Cancer
- Hodgkin Lymphoma
- Kidney Cancer

- Leukemia
- Lung Cancer
- Melanoma
- Multiple Myeloma
- Non-Hodgkin Lymphoma
- Ovarian Cancer
- Pancreatic Cancer
- Prostate Cancer
- Solid Tumors