National Cancer Institute

FactSheet

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Cancer Vaccines

Key Points

- Cancer vaccines are designed to boost the body's natural ability to protect itself, through the immune system, from dangers posed by damaged or abnormal cells such as cancer cells.
- The U.S. Food and Drug Administration (FDA) has approved two types of vaccines to prevent cancer: vaccines against the hepatitis B virus, which can cause liver cancer, and vaccines against human papillomavirus types 16 and 18, which are responsible for about 70 percent of cervical cancer cases.
- The FDA has approved one cancer treatment vaccine for certain men with metastatic prostate cancer.
- Researchers are developing treatment vaccines against many types of cancer and testing them in clinical trials.

1. 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.

The immune system is a complex network of organs, tissues, and specialized cells that act collectively to defend the body. 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 response.

Traditional vaccines usually contain 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.

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).

2. How do vaccines stimulate the immune system?

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 circulation, 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 cytotoxic (cell-killing) T cells.

B cells make antibodies, which are large secreted proteins that bind to, inactivate, and help destroy foreign invaders or abnormal cells. Most preventive vaccines, including those aimed at hepatitis B virus (HBV) and human papillomavirus (HPV), stimulate the production of antibodies that bind to specific, targeted microbes and block their ability to cause infection. 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 (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 killer T cells and enable them to recognize specific threats.

Cancer treatment vaccines are designed to work by activating B cells and killer T cells and directing them to recognize and act against specific types of cancer. They do this by introducing one or more molecules known as antigens into the body, usually by injection. An antigen is a substance that stimulates a specific immune response. An antigen can be a protein or another type of molecule found on the surface of or inside a cell.

Microbes are recognized by the immune system as a potential threat that should be destroyed because they carry foreign or “non-self” antigens. In contrast, 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).

Cancer cells can carry both self antigens and cancer-associated antigens. The cancer-associated antigens mark the cancer cells as abnormal, or foreign, and can cause B cells and killer T cells to mount an attack against them.

Cancer cells may also make much larger amounts of certain self antigens than normal cells. Because of their high abundance, these self antigens may be viewed by the immune system as being foreign and, therefore, may trigger an immune response against the cancer cells (1–6).

3. What are cancer vaccines?

Cancer vaccines are medicines that 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; and

- ***Treatment (or therapeutic) vaccines***, which are intended to treat an existing cancer by strengthening the body’s natural defenses against the cancer (7).

Two types of cancer preventive vaccines are available in the United States (see Question 5), and one cancer treatment vaccine has recently become available (see Question 8).

4. How do cancer preventive vaccines work?

Cancer preventive vaccines target infectious agents that cause or contribute to the development of cancer (8). 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.

5. What cancer preventive vaccines are approved in the United States?

The U.S. Food and Drug Administration (FDA) has approved two vaccines, Gardasil® and Cervarix®, that protect against infection by the two types of HPV—types 16 and 18—that cause approximately 70 percent of all cases of cervical cancer worldwide. At least 17 other types of HPV are responsible for the remaining 30 percent of cervical cancer cases (9). HPV types 16 and/or 18 also cause some vaginal, vulvar, anal, penile, and oropharyngeal cancers (10).

In addition, Gardasil protects against infection by two additional HPV types, 6 and 11, which are responsible for about 90 percent of all cases of genital warts in males and females but do not cause cervical cancer.

Gardasil, manufactured by Merck & Company, is based on HPV antigens that are proteins. These proteins are used in the laboratory to make four different types of "virus-like particles," or VLPs, that correspond to HPV types 6, 11, 16, and 18. The four types of VLPs are then combined to make the vaccine. Because Gardasil targets four HPV types, it is called a quadrivalent vaccine (11). In contrast with traditional vaccines, which are often composed of weakened whole microbes, VLPs are not infectious. However, the VLPs in Gardasil are still able to stimulate the production of antibodies against HPV types 6, 11, 16, and 18.

Cervarix, manufactured by GlaxoSmithKline, is a bivalent vaccine. It is composed of VLPs made with proteins from HPV types 16 and 18. In addition, there is some initial evidence that Cervarix provides partial protection against a few additional HPV types that can cause cancer. However, more studies will be needed to understand the magnitude and impact of this effect.

Gardasil is approved for use in females to prevent cervical cancer and some vulvar and vaginal cancers caused by HPV types 16 and 18, and for use in males and females to prevent anal cancer and precancerous anal lesions caused by these HPV types. Gardasil is also approved for use in males and females to prevent genital warts caused by HPV types 6 and 11. The vaccine is approved for these uses in females and males ages 9 to 26. Cervarix is approved for use in females ages 9 to 25 to prevent cervical cancer caused by HPV types 16 and 18.

The FDA has also approved a cancer preventive vaccine that protects against HBV infection. Chronic HBV infection can lead to liver cancer. The original HBV vaccine was approved 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 (12).

6. Have other microbes been associated with cancer?

Many scientists believe that microbes cause or contribute to between 15 percent and 25 percent of all cancers diagnosed worldwide each year, with the percentage being lower in developed than developing countries (4, 8, 13).

The International Agency for Research on Cancer (IARC) has classified several microbes as carcinogenic (causing or contributing to the development of cancer in people), including HPV and HBV (14). These infectious agents—bacteria, viruses, and parasites—and the cancer types with which they are most strongly associated are listed in the table below.

Infectious Agents	Type of Organism	Associated Cancers
hepatitis B virus (HBV)	virus	hepatocellular carcinoma (a type of liver cancer)
hepatitis C virus (HCV)	virus	hepatocellular carcinoma (a type of liver cancer)
human papillomavirus (HPV) types 16 and 18, as well as other HPV types	virus	cervical cancer; vaginal cancer; vulvar cancer; oropharyngeal cancer (cancers of the base of the tongue, tonsils, or upper throat); anal cancer; penile cancer; squamous cell carcinoma of the skin
Epstein-Barr virus	virus	Burkitt lymphoma; non-Hodgkin lymphoma; Hodgkin lymphoma; nasopharyngeal carcinoma (cancer of the upper part of the throat behind the nose)

Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV8)	virus	Kaposi sarcoma
human T-cell lymphotropic virus type 1 (HTLV1)	virus	adult T-cell leukemia/lymphoma
Helicobacter pylori	bacterium	stomach cancer; mucosa-associated lymphoid tissue (MALT) lymphoma
schistosomes (*Schistosoma hematobium*)	parasite	bladder cancer
liver flukes (*Opisthorchis viverrini*)	parasite	cholangiocarcinoma (a type of liver cancer)

7. How are cancer treatment vaccines designed to work?

Cancer treatment vaccines are designed 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.

Developing effective cancer treatment vaccines requires a detailed understanding of how immune system cells and cancer cells interact. The immune system often does not “see” cancer cells as dangerous or foreign, as it generally does with microbes. Therefore, the immune system does not mount a strong attack against the cancer cells.

Several factors may make it difficult for the immune system to target growing cancers for destruction. Most important, cancer cells carry normal self antigens in addition to specific cancer-associated antigens. Furthermore, cancer cells sometimes undergo genetic changes that may lead to the loss of cancer-associated antigens. Finally, cancer cells can produce chemical messages that suppress 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 (15).

Producing effective treatment vaccines has proven much more difficult and challenging than developing cancer preventive vaccines (16). To be effective, cancer treatment vaccines must achieve two goals. First, like traditional vaccines and cancer 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 B cells and killer T cells. 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 (17, 18).

8. Has the FDA approved any cancer treatment vaccines?

In April 2010, the FDA approved the first cancer treatment vaccine. This vaccine, sipuleucel-T (Provenge®, manufactured by Dendreon), 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 a clinical trial, sipuleucel-T increased the survival of men with a certain type of metastatic prostate cancer by about 4 months (19).

Unlike some other cancer treatment vaccines under development, sipuleucel-T is customized to each patient. The vaccine is created by isolating immune system cells called antigen-presenting cells (APCs) from a patient’s blood through a procedure called leukapheresis. The APCs are sent to Dendreon, where they are cultured with a protein called PAP-GM-CSF. This protein consists of PAP linked to another protein called granulocyte-macrophage colony-stimulating factor (GM-CSF). The latter protein stimulates the immune system and enhances antigen presentation.

APC cells cultured with PAP-GM-CSF constitute the active component of sipuleucel-T. Each patient's 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.

9. What types of vaccines are being studied in clinical trials?

Vaccines to prevent HPV infection and to treat several types of cancer are being studied in clinical trials.

The list below shows the types of cancer that are being targeted in active cancer prevention or treatment clinical trials using vaccines. If you are accessing this fact sheet online (http://www.cancer.gov/cancertopics/factsheet/Therapy/cancer-vaccines), the cancer names are links to search results from NCI's clinical trials database. This database can also be searched at http://www.cancer.gov/clinicaltrials/search.

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

- Bladder Cancer
- Brain Tumors
- Breast Cancer
- Cervical Cancer
- Hodgkin Lymphoma
- Kidney Cancer
- Leukemia
- Lung Cancer
- Melanoma
- Multiple Myeloma
- Non-Hodgkin Lymphoma
- Pancreatic Cancer
- Prostate Cancer
- Solid Tumors

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

- Cervical Cancer
- Solid Tumors

10. 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 (see Question 5). 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.

Similarly, cancer treatment vaccines are made using antigens from cancer cells 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 or immune cells that are modified to express such an antigen. These cells can come from a patient himself or herself (called an autologous vaccine, such as sipuleucel-T) or from another patient (called an allogeneic vaccine).

Other types of cancer treatment vaccines are made using molecules of deoxyribonucleic acid (DNA) or ribonucleic acid (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 researchers can insert the DNA or RNA 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.

Scientists have identified a large number of cancer-associated antigens, several of which 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, 18–22).

11. Can researchers add ingredients to cancer vaccines to make them work better?

Antigens and the substances discussed in Question 10 are often not strong enough inducers of the immune response to make effective cancer treatment vaccines. Researchers often add extra ingredients, known as adjuvants, to treatment vaccines. These substances serve to boost immune responses that have been set in motion by exposure to antigens or other means. Patients undergoing experimental treatment with a cancer vaccine sometimes receive adjuvants separately from the vaccine itself (23).

Adjuvants used for cancer vaccines come from many different sources. Some microbes, such as the bacterium Bacillus Calmette-Guérin (BCG) originally used as a vaccine against tuberculosis, can serve as adjuvants (24). Substances produced by bacteria, such as Detox B, are also frequently used. Biological products derived from nonmicrobial organisms can be used as adjuvants, too. One example is keyhole limpet hemocyanin (KLH), which is a large protein produced by a sea animal. 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 (INF–a), and GM–CSF, also known as sargramostim (see Question 8).

12. Do cancer vaccines have side effects?

Vaccines intended to prevent or treat cancer appear to have safety profiles comparable to those of traditional 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.

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, 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 quite rare.

13. 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 (21, 25). In addition, in some clinical trials, cancer treatment vaccines have appeared to increase the effectiveness of other cancer therapies (21, 25).

Additional evidence suggests that surgical removal of large tumors may enhance the effectiveness of cancer treatment vaccines (25). 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 a specific cancer treatment vaccine works best when it is administered before chemotherapy, after chemotherapy, or at the same time as chemotherapy. 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.

14. What additional research is under way?

Although researchers have identified many cancer-associated antigens, these molecules vary widely in their capacity to stimulate a strong anticancer immune response. Two major areas of research aimed at developing better cancer treatment vaccines involve the identification of novel cancer-associated antigens that may prove more effective in stimulating immune responses than the already known antigens and 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 (26).

Perhaps the most promising avenue of cancer vaccine research is aimed at better understanding the basic biology underlying how immune system cells and cancer cells interact. 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 (27).

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 new drugs that block those processes and thereby improve the effectiveness of cancer treatment vaccines (28). For example, some cancer cells produce chemical signals that attract white blood cells known as regulatory T cells, or Tregs, to a tumor site. Tregs often release cytokines that suppress the activity of nearby killer T cells (21, 29). The combination of a cancer treatment vaccine with a drug that would block the negative effects of one or more of these suppressive cytokines on killer T cells might improve the vaccine's effectiveness in generating potent killer T cell antitumor responses.

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Related Resources

- *Biological Therapies for Cancer* (http://www.cancer.gov/cancertopics/factsheet/Therapy/biological)
- *Human Papillomavirus (HPV) Vaccines* (http://www.cancer.gov/cancertopics/factsheet/Prevention/HPV-vaccine)
- *Taking Part in Cancer Treatment Research Studies* (http://www.cancer.gov/clinicaltrials/learningabout/Taking-Part-in-Cancer-Treatment-Research-Studies)
- *Understanding Cancer Series: HPV Vaccine* (http://www.cancer.gov/cancertopics/understandingcancer/HPV-vaccine)
- *Understanding Cancer Series: The Immune System* (http://www.cancer.gov/cancertopics/understandingcancer/immunesystem)

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