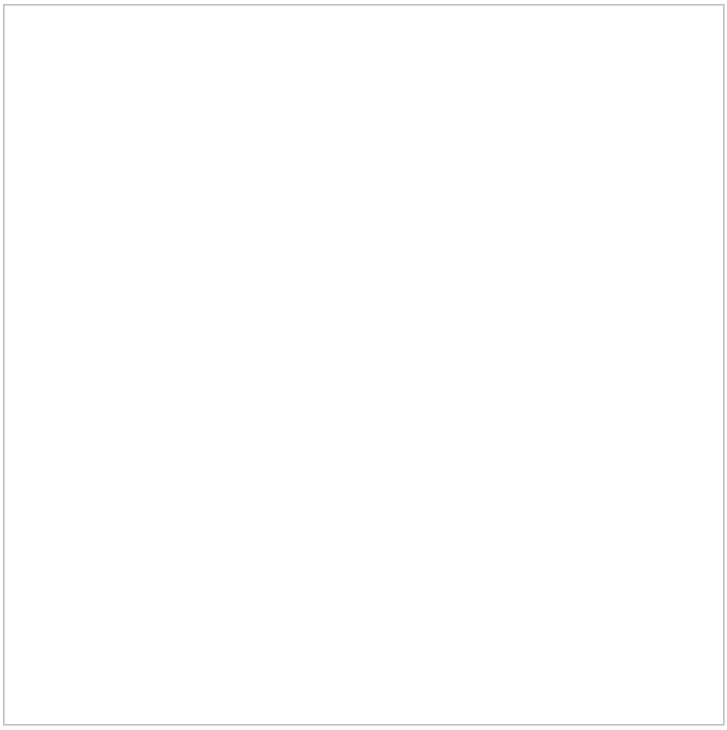
Cancer Treatment Vaccines



The purpose of cancer vaccines is to stimulate the body's defenses against cancer by increasing the response of the immune system. Our immune system provides a dynamic protective system against disease from foreign pathogens and from abnormal body cells. Cancer cells are, in essence, normal body cells that have sustained mutations and no longer function properly.

Tumor vaccines usually contain proteins found on or produced by cancer cells. By administering forms of these proteins and other agents that affect the immune system, the vaccine treatment aims to involve the patient's own defenses in the fight to eliminate cancer cells. Immunotherapy is a new field in cancer treatment and prevention, and many strategies are being examined in clinical trials. In August of 2017, Boise State University researchers created anti-cancer drugs that are killing 58 of the 60 types of tumors. They tested them on the NCI-60 panel of cancer cells, which affect nine human body organ systems. They used proteins, known as nullomers, which are the shortest amino acid sequences that do not exist in the humangenome. It has potential to be toxic to some normal cells, yet they saw promising effects on cancer cells.They are now continuing research and working on making the drugs more specific to tumor cells. 1

The following sections provide information on the immune system and cancer vaccines:

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Vaccines to treat cancer:

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- Prostate Cancer Vaccines
- Glioma Vaccine
- Vaccines to Target Multiple Cancers

Vaccines to **prevent** cancer:

- Cervical Cancer Vaccines Note: choosing this item will take you to the Prevention section of the site.
- Liver Cancer Vaccine (Hepatitis Vaccine) Note: choosing this item will take you to the Prevention section of the site.

Overview of the Tumor Vaccine Strategies

The aim of tumor vaccines is to stimulate the body's immune system in the fight to recognize and eliminate cancer cells. There are many strategies in immunotherapy; some strategies are considered 'passive' while others are 'active'.

- **Passive immunotherapy** involves giving antibodies or mature T cells to the patient to attack the cancer cells[2] This type of therapy does not induce permanent change in the patient's own T cells, but may be effective in a variety of cancers including leukemia and breast cancer. One of the most widely used cellular immunotherapy strategy is the transfer of immune cells from a healthy donor to a recipient who has had a bone marrow transplant or other stem cell transplant.
- **Active immunotherapy** strategies include tumor vaccines, because they directly stimulate the patient's own immune cells to have a long-lasting response against the cancer.[2] All of these strategies aim to stimulate the antigen presenting cells (APCs) and T cells in some way.

There are several broad categories of tumor vaccine strategies[3] :

- **Whole cell vaccines**- Whole cell vaccines target the APCs inside the body (*in vivo*) so that they take up and present the tumor antigens to T cells. These vaccines use modified tumor cells.
- **Antigen therapy vaccines**- Like whole cell vaccines, antigen therapy vaccines target the APCs inside the body (*in vivo*) so that they take up and present the tumor antigens to T cells. These vaccines use purified parts of the tumor cells (tumor antigens).
- **Antigen-presenting cell vaccines**- Antigen-presenting cell vaccines involve the injection modified antigen presenting cells (APC), prepared in the laboratory (*ex vivo*), into a patient, where they will also stimulate the T cells[4]
- **Non-specific therapy and cytokine therapy**- Cytokine therapy involves the administration of immune signaling molecules (usually proteins) that increase the maturation and growth of APCs and T cells. A description of some approved agents of this type can also be found in the Biological Response Modifier (BRM) portion of the section on treatments.

Whole Cell Vaccines

Whole cell vaccines involve the injection of tumor cells that have been weakened or killed so they cannot divide. These whole tumor cells are injected along other compounds, often protein cytokines, that will enhance the immune response.See Cytokine Therapy.

Whole cell vaccines fall under the three general categories:

Autologous vaccines
Whole cell vaccines can be prepared with tumor cells isolated from a patient to be injected into the *same* patient (Auto=self). The idea is that these tumor cells will have the exact same proteins (antigens) on their surface as the patient's tumors. The antigens fragments that are taken up by APCs and presented to T cells will be specific to the patient's tumor. This creates a highly tumor-specific immune response.

Allogeneic vaccines
Whole cell vaccines can also be prepared with tumor cells isolated from a *different* patient with the same type of cancer (Allo=other). As in autologous whole cell vaccines, the idea is that these tumor cells will have a very similar or exact pattern of antigenic proteins as the patient's tumors. The protein fragments taken up by the patient's APCs and presented to T cells will be specific to the patient's tumor. This again creates a highly tumor-specific immune response.

Gene-modified vaccines
The process of preparing whole cell vaccines involves isolating a patient's tumor cells and growing them in the laboratory. An extension of this strategy is to genetically modify the patient's tumor cells while they are in the laboratory. Genes may be inserted into the cells that cause them to have new proteins on their surface. The new proteins include immune signaling and stimulating molecules, such the cytokines interleukin-2, granulocyte-macrophage colony-stimulating factor (GM-CSF) and other stimulatory molecules. Genetically modified tumor cell vaccines create cells that express the tumor-specific antigens as well as the new immunostimulatory molecules on their cell surface. These cells can then be injected into a patient. The combination of molecules on the surface leads to an increased immune response. The added molecules on the surface of the modified tumor cells stimulate the immune system to attack the tumor cells left in the body, even though those cells do not have the new proteins on their surface.[3]

Whole cell tumor vaccines are attractive because they are highly patient and tumor specific. The draw-back to these vaccines, however, is that it is very time consuming and expensive to create individualized vaccines for each patient. Additionally, it may be impossible to isolate and grow a patient's tumor cells in the laboratory, because some tumor cells do not live for a long time outside of the body.

Another concern is that if a vaccine were created with that increased the immune response of the patient to a protein antigen that is found on many normal cells, the vaccine would stimulate the immune cells to kill normal cells, which would obviously be bad for the patient. Nevertheless, there are many ongoing clinical trials using this strategy.

Antigen Based Vaccines

Antigen based tumor vaccines do not involve the insertion of modified tumor cell or immune cell into the body. Instead, purified tumor proteins (antigens) are injected to stimulate the patient's antigen presenting cells (APCs) to take up the antigen and present it to T cells. The challenge to this type of therapy is finding a tumor-specific antigen for any particular type of cancer. It is important that the vaccine therapy does not stimulate an immune response against antigens found extensively on normal body cells, or else the T cells would destroy normal cells as well as cancer cells. Researchers have had some success in identifying tumor-specific antigens for melanomas, but antigens for other cancer types have proven to be more difficult to pinpoint. These tumor vaccine strategies are only effective in cancer types that have well defined tumor antigens.3

Antigen therapy vaccines may be grouped to four general categories:

- **Peptide-based vaccines-** Peptide-based vaccines entail the injection of purified tumor proteins into the patient. These tumor-derived protein fragments have modified segments that make them easily presented by APCs. Since the peptides are tumor-specific, they generate a highly tumor-specific immune response. The challenge is, once again, identifying a tumor-specific protein for a particular cancer type. Due to differences in our genes, the way that the immune systems of different people 'see' antigens is not necessarily the same. That means that a peptide which is very effective in generating an immune response in one individual may not work for someone else. The advantage of this strategy, however, is that these vaccines are relatively easy to manufacture and store.
- **Heat shock protein vaccines-** Heat shock proteins are a group of proteins that are normally found in cells. They function to help proteins fold up into their correct shape and prevent misfolding of proteins in times of stress. The proteins actually get their name from the fact that they are found at increased levels in cells that are kept at a higher than normal temperature (hence-, heat shock). High temperature causes proteins to misfold, much like the very high heat of a frying pan causes the clear portion of an egg to turn white and harden. In addition to this role, heat shock proteins can act as carriers for tumor protein antigens. Highly specialized APCs known as dendritic cels have special receptors on their surface for heat shock proteins (so that they can identify sick cells). If a combination of tumor protein and heat shock protein is injected into a patient, dendritic cells will bind to the heat shock portion of the joined proteins and then take up and present the tumor proteins to T cells.
- **DNA vaccines**- DNA vaccines involve the injection of DNA containing the genes for tumor-specific proteins. The DNA is injected into a patient's muscle. The hope is that normal body cells will take up the DNA and produce a tumor protein from it via transcription and translation. The tumor protein will be taken up by APCs, which will then stimulate tumor-specific T cells. More on transcription and translation
- **Viral and bacterial vector vaccines-** In this strategy, instead of directly injecting naked DNA into a patient, the DNA will be transported into the body in a viral or bacterial 'vector'. Vectors are organisms, like bacteria or viruses, or DNA constructs that are able to take genetic information from one organism and put it into another. (A more common use of the word vector is in the spread of disease; birds are a vector for bird-flu and ticks are a vector for lyme disease). Viral or bacterial vectors can also be used as a second injection after an initial injection of a DNA vaccine. The second dose increased the immune response and may be more effective than either strategy alone.3

No matter which strategy from the above list is used, the general strategy is the same: Expose the patient's immune system to tumor proteins so that they will be able to better respond to those same proteins on the surface of the tumor cells themselves. The differences lie only in HOW the the target proteins are delivered to the immune system for recognition.

Antigen Presenting Cell Vaccines

Much recent attention has been given to the use of ex vivo-modified dendritic cells in tumor vaccine therapy; that is, dendritic cells modified in the laboratory. Dendritic cells are the most potent of the antigen presenting cells (APCs) and are up to 1000 times more effective in stimulating antigen-specific T cells than are other types of APCs. Dendritic cell precursors can be isolated from a patient's blood, and these precursors can be stimulated in the laboratory to mature and to take up and present tumor-specific antigens. To make the dendritic cell present a tumor-specific antigen, the cells can be coincubated with dead tumor cells, tumor cell fragments, tumor proteins, tumor DNA or RNA, or bacteria and viruses that have been engineered to contain tumor antigens. These tumor cells or proteins may come from the patient who will receive the vaccine, or they may come from other patients with the same type of cancer. These mature dendritic cells can then be injected back into the original patient, where they will migrate to the patient's lymph nodes. There, they will encounter the T cell and stimulate tumor-specific T cells to recognize and fight the tumor cells in other parts of the body. Clinical trials are ongoing in various cancer types, including melanoma, myeloma, breast, and prostate. The major limitation to this type of therapy is the need to isolate and grow dendritic cells for each patient; however, if this therapy proves to be effective and becomes widespread, centers could be established for the large-scale processing of dendritic cells much in the way that bone marrow is processed for transplants.

Non-specific and Cytokine Strategies

This group of tumor vaccine strategies stimulates an enduring immune response in the body, but does not directly target tumor-specific T cells. These vaccines and vaccine supplements increase the general immune response, and this includes the

antitumor response.

The two broad categories of this strategy are **BCG** and **cytokines**:

- **BCG**-One of the earliest and, to date, most successful tumor vaccine strategies,dating from the early 1970s, is the use of a bacterium-bacillus Calmette-Guérin (BCG). BCG was originally developed as a vaccine against the bacterial infection that causes tuberculosis, but has been found to work in treating bladder cancer. It is often administered directly to the bladder via a catheter. While the exact mechanism by which BCG works is not clear, it is believed to increase inflammation. While this sounds like it may be counter-productive, Inflammation increases the blood flow to the tumor containing areaand brings in an increased number of antigen presenting cells (APCs) and T cells. So far, BCG has demonstrated the best response in the treatment of bladder cancer.
- **Cytokines**- Cytokines are molecules, usually small proteins, that are naturally produced by immune cells. Immune system cells use cytokines to send messages to each other. The goal of administering cytokines is to attract additional immune cells to the site of the tumor and to stimulate the reproduction of immune cells.

The proteins that have been investigated include:

- **Interleukins**-There are a number of proteins that are produced by white blood cells (leukocytes; leuko=white, cyte=cell). Among them are the interleukins (IL). (inter=between, leuko=referring to white blood cells). Interleukins are used for cell to cell communication and can act to stimulate cell division of the target cells. Those used in cancer treatment include IL-2 and IL-12. Both act as essential growth factors for T cells.
- **Granulocyte-Macrophage Colony-Stimulating Factor(GM-CSF)**: This protein is produced by a variety of cells types and has numerous affects on cells of the immune system. Amont the functions attributed to GM-CSF: attraction of dendritic cells, the key APCs in the body, and stimulation of dendritic cell production and activation.
- **Interferons (IFN-gamma and IFN-alpha)**: stimulate the activation of cytotoxic T cells and promote inflammation. In other roles, the interferons are involved in the defense against viral infection.

The approaches described above stimulate the immune system in general (tumor-specific T cells are not targeted directly). This general stimulation of the immune response has in fact been shown to generate an anti-tumor response in patients. Although administration of these cytokines alone has shown promising results in patients, the high doses used also had toxic side effects. Researchers and physicians are using low doses of cytokines in combination with some of the other tumor vaccines strategies that have been discussed, such as gene-modified tumor cell vaccines and dendritic cell vaccines. When cytokines are injected as supplements to another vaccine strategy, they are called an adjuvant therapy because they act to increase the effectiveness of the primary vaccine being used. 3

Melanoma Vaccines

Spontaneous tumor regression has been observed in some melanoma patients and is thought to be attributable to the immune system. This observation led to current attempts to stimulate the immune system as a treatment option for melanoma patients. Much research on potential melanoma vaccines has utilized antigen presenting cell (APC) vaccine strategies combined with adjuvant therapies and biological response modifiers, including cytokines.

There are currently a number of ongoing clinical trials of perspective melanoma vaccines. Several current Phase III trials are attempting to show definitive evidence of improved survival for melanoma patients receiving vaccines. Current strategies include combining multiple adjuvants and immunomodulators with antigen presenting vaccines in an attempt to strengthen and target vaccine responses to improve their efficacy. 5

View clinical trials of melanoma vaccines (NCI).

More information on this topic may be found in Chapter 16 of The Biology of Cancer by Robert A. Weinberg.

Prostate Cancer Vaccines

Sipuleucel-T, (brand name Provenge®), is the first vaccine approved to fight cancer. Provenge® works by activating a patient's immune system against their prostate cancer. It does this via indirect T cell activation. One way that T cells are activated is via antigen presenting cells (APCs) that 'present' or show the T cells what to find and destroy. In this therapy,the APCs are given PAP, a protein found on 95% of prostate cancers, and they, in turn, activate the patient's T cells to recognize thie PAP protein.

In order to do this, a patient's own APCs are collected via a process called leukapheresis. The APCs are then incubated with a PAP-GM-CSF, a fusion of PAP and GM-CSF, an immune system activator that causes the APCs to mature. The APCs can then take up and process the PAP-GM-CSF and begin to present the PAP. These APCs are then injected back into the patient, where they present the PAP to T cells, which, in turn, attack prostate cancer cells. This has been shown to extend prostate cancer patient survival by four months on average.6 7 The vaccine was developed by Dendreon.

There are numerous prostate cancer vaccines being studied in clinical trials.

View a list of clinical trials for prostate cancer vaccines (NCI).

Glioma Vaccine

Malignant gliomas are the most common form of brain cancer. The outcomes for patients with gliomas is typically very poor, with few patients cured of the disease.[8]

A vaccine is currently in clinical trials and has shown good effects in patients with newly diagnosed glioblastoma.[9]

How the vaccine works:

1. Immune cells called dendritic cells are purified from blood obtained from the patient. Dendritic cells are important regulators of immune responses, including those to cancer cells.
2. The dendritic cells are then exposed to proteins that are made by the cancer cells but not found at high levels on normal cells. Also present are proteins that stimulate the the dendritic cells to maximal activity.
3. The activated dendritic cells are then put back into the patient and are able to lead the attack on the cancer cells.

The vaccine contains parts of the following proteins: 1) the human epidermalgrowth factor 2 (HER2), tyrosinase related protein 2 (TRP-2), glycoprotein 100 (gp100), melanoma antigen (MAGE-1), interleukin 13 receptor alpha 2 (IL13Rα2), and a protein with the strange name 'absent in melanoma 2' (AIM-2). In a phase 1 trial, patients whose tumors expressed more of the proteins had a better response to the vaccine, with some patients showing a complete response. In the same trial, the vaccine was shown to reduce the number of cancer stem cells, a critical event in the elimination of a tumor.[9]

Vaccines to Treat Multiple Cancers

It is possible to design a vaccine to target more than one cancer type. The key is that the cancers all share something that the immune system can recognize and target.

It turns out that many cancer types have too much of the Wilm's tumor (WT1) protein. The protein works to control the activity of several genes - it is a transcription factor. Cancers that can have too much WT1 include some leukemias and lymphomas and several solid cancers, including breast, lung, renal, ovarian, and pancreatic cancers, and glioblastoma.[10] [11] [12]

To make a vaccine to target WT1 researchers fused the WT1 protein to anantibody targeting a protein,CLEC9A , found on the surface of specific immune cells (dendritic cells). When the fused proteins bound to the dendritic cells, the newly 'educated' cells were able to stimulate immune cells to recognize WT1. The work was performed in mice that contain human immune cells.[13] Work on the vaccine is ongoing.

Learn more about cancer vaccines.

Learn more about cancer stem cells.

Learn more about clinical trials.

Find clinical trials for brain cancer vaccines.

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