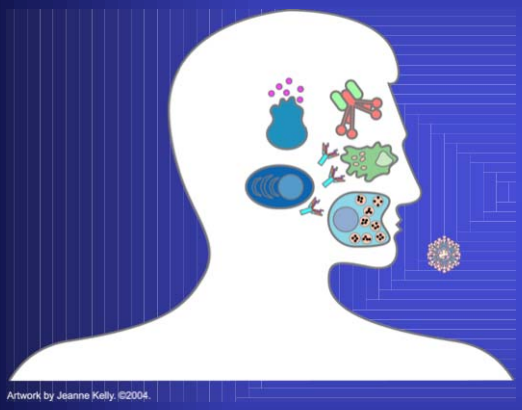
Understanding Cancer and Related Topics

Understanding The Immune System



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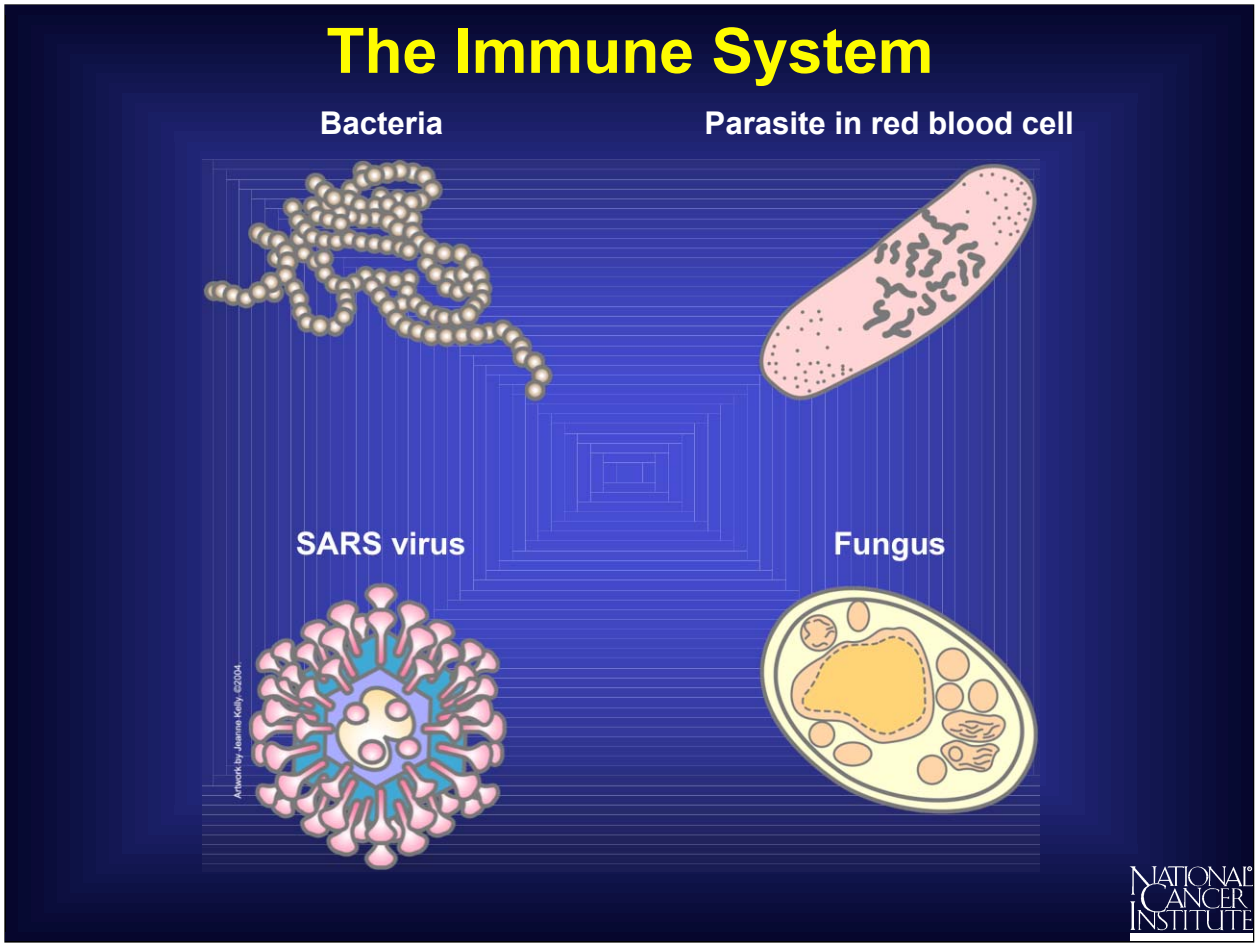
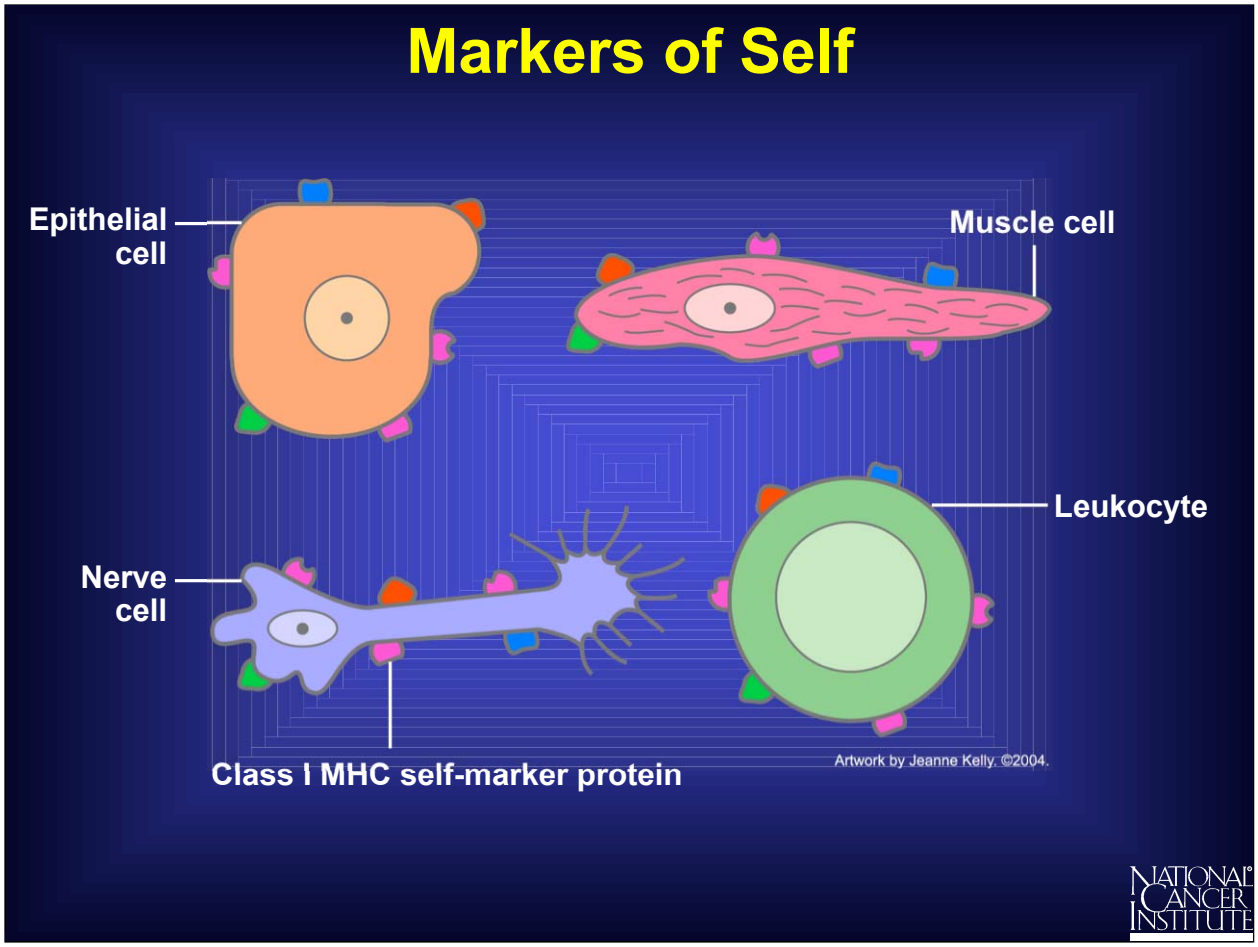
Illustrates the immune system, a complex network of specialized cells and organs that distinguishes between self and foreign molecules inside the body. Explains that a malfunctioning immune system can cause allergies or arthritis and can fail to stop the growth of cancer cells.



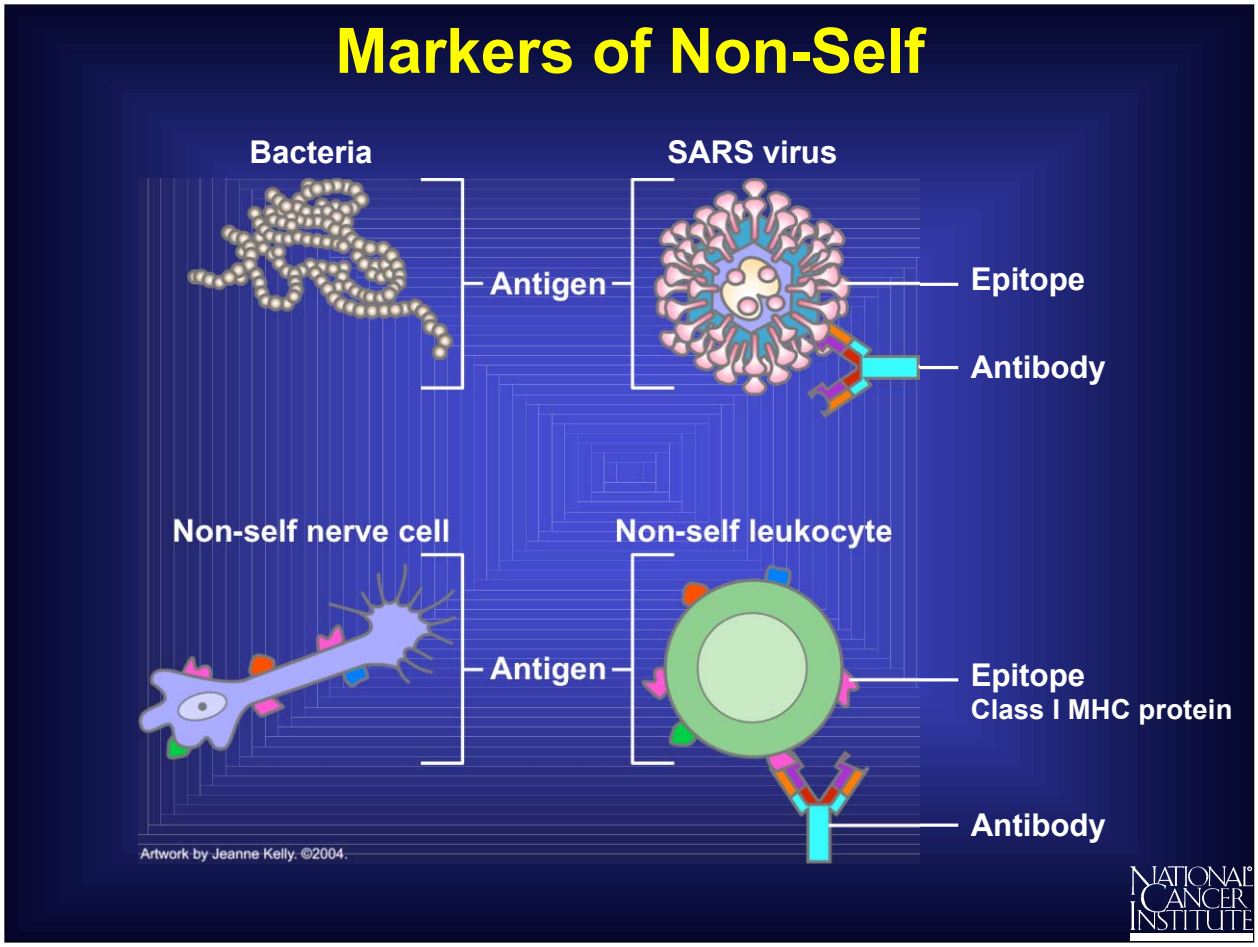
Because the human body provides an ideal environment for many microbes, they try to pass your skin barrier and enter. Your immune system is a bodywide network of cells, tissues, and organs that has evolved to defend you against such "foreign" invasions.

The proper targets of your immune system are infectious organisms--bacteria such as these streptococci; fungi (this one happens to be *Candida*, the cause of yeast infections); parasites, including these worm-like microbes that cause malaria; and viruses such as this SARS virus.



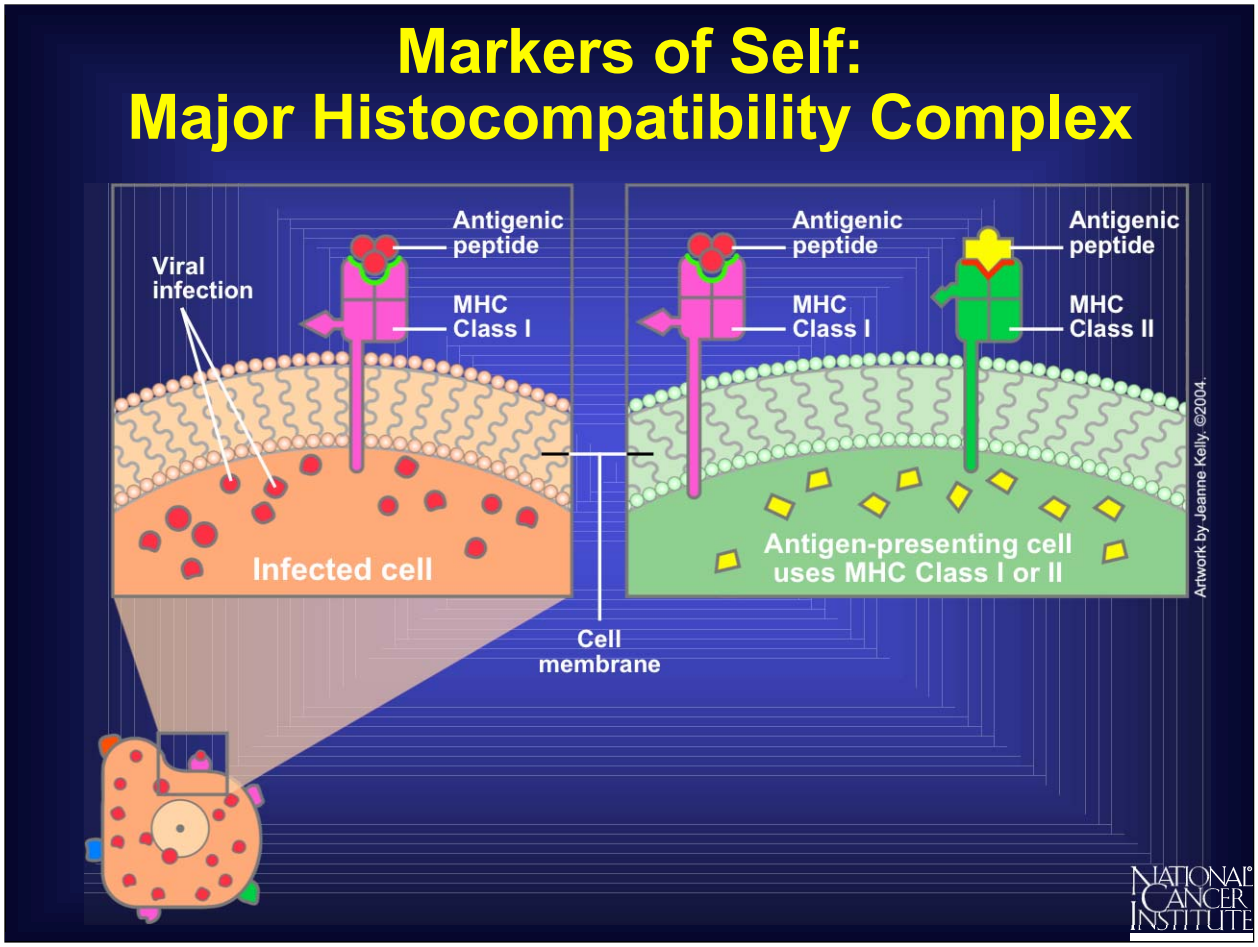
At the heart of the immune response is the ability to distinguish between "self" and "non-self." Every cell in your body carries the same set of distinctive surface proteins that distinguish you as "self." Normally your immune cells do not attack your own body tissues, which all carry the same pattern of self-markers; rather, your immune system coexists peaceably with your other body cells in a state known as self-tolerance.

This set of unique markers on human cells is called the major histocompatibility complex (MHC) proteins. There are two classes: MHC Class I proteins, which are on all cells, and MHC Class II proteins, which are only on certain specialized cells.



Any non-self substance capable of triggering an immune response is known as an antigen. An antigen can be a whole non-self cell, a bacterium, a virus, an MHC marker protein or even a portion of a protein from a foreign organism.

The distinctive markers on antigens that trigger an immune response are called epitopes. When tissues or cells from another individual enter your body carrying such antigenic non-self epitopes, your immune cells react. This explains why transplanted tissues may be rejected as foreign and why antibodies will bind to them.

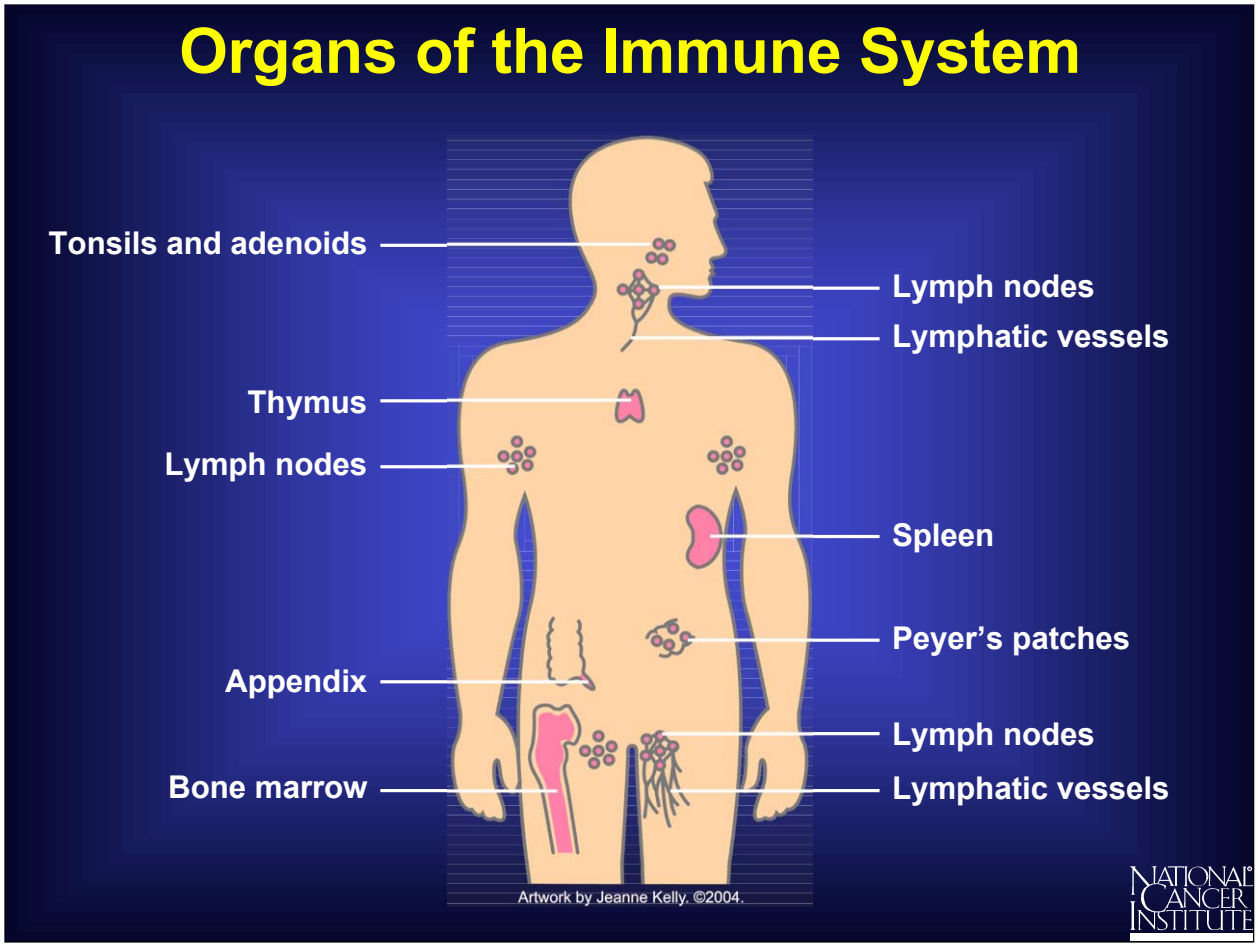


Your immune cells recognize major histocompatibility complex proteins(MHC) when they distinguish between self and non-self. An MHC protein serves as a recognizable scaffold that presents pieces (peptides) of a foreign protein (antigenic) to immune cells.

An empty "foreign" MHC scaffold itself can act as an antigen when donor organs or cells are introduced into a patient's body. These MHC self-marker scaffolds are also known as a patient's "tissue type" or as human leukocyte antigens (HLA) when a patient's white blood cells are being characterized.

For example, when the immune system of a patient receiving a kidney transplant detects a non-self "tissue type," the patient's body may rally its own immune cells to attack.

Every cell in your body is covered with these MHC self-marker proteins, and—except for identical twins—individuals carry different sets. MHC marker proteins are as distinct as blood types and come in two categories—MHC Class I: humans bear 6 markers out of 200 possible variations; and MHC Class II: humans display 8 out of about 230 possibilities.



The organs of your immune system are positioned throughout your body.

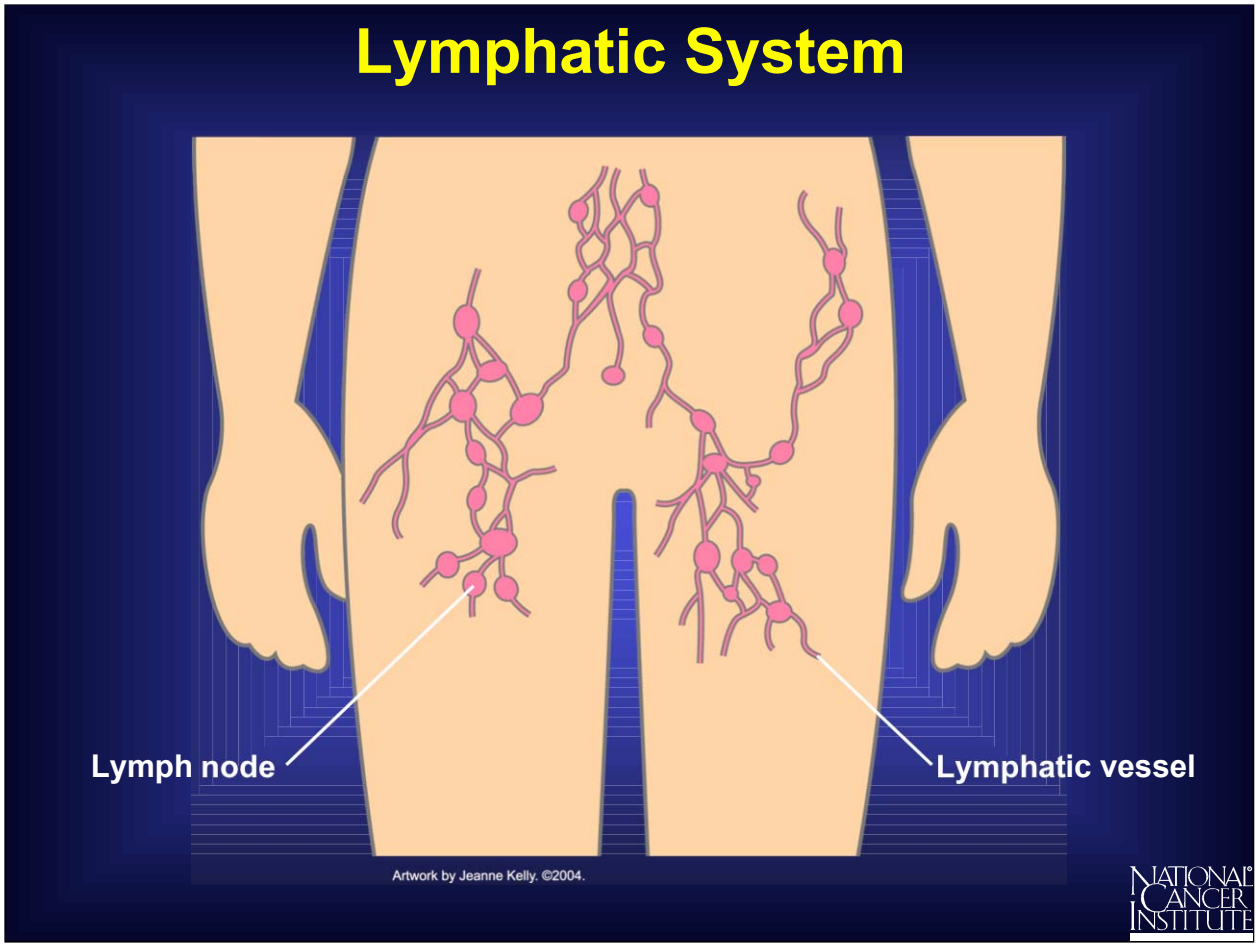
They are called lymphoid organs because they are home to lymphocytes--the white blood cells that are key operatives of the immune system. Within these organs, the lymphocytes grow, develop, and are deployed.

Bone marrow, the soft tissue in the hollow center of bones, is the ultimate source of all blood cells, including the immune cells.

The *thymus* is an organ that lies behind the breastbone; lymphocytes known as *T lymphocytes*, or just *T cells*, mature there.

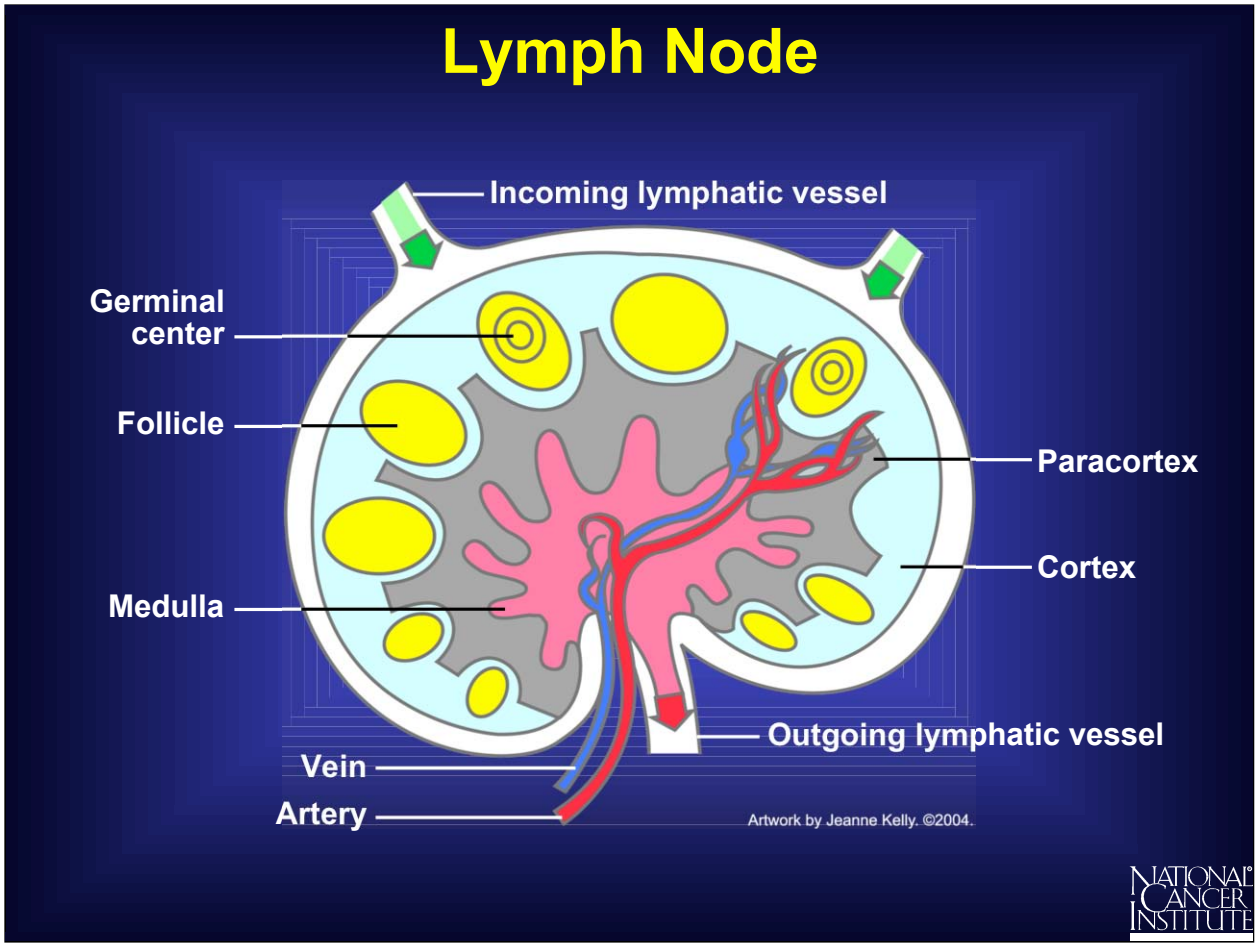
The *spleen* is a flattened organ at the upper left of the abdomen. Like the lymph nodes, the spleen contains specialized compartments where immune cells gather and confront antigens.

In addition to these organs, clumps of lymphoid tissue are found in many parts of the body, especially in the linings of the digestive tract and the airways and lungs--gateways to the body. These tissues include the *tonsils*, *adenoids*, and *appendix*.



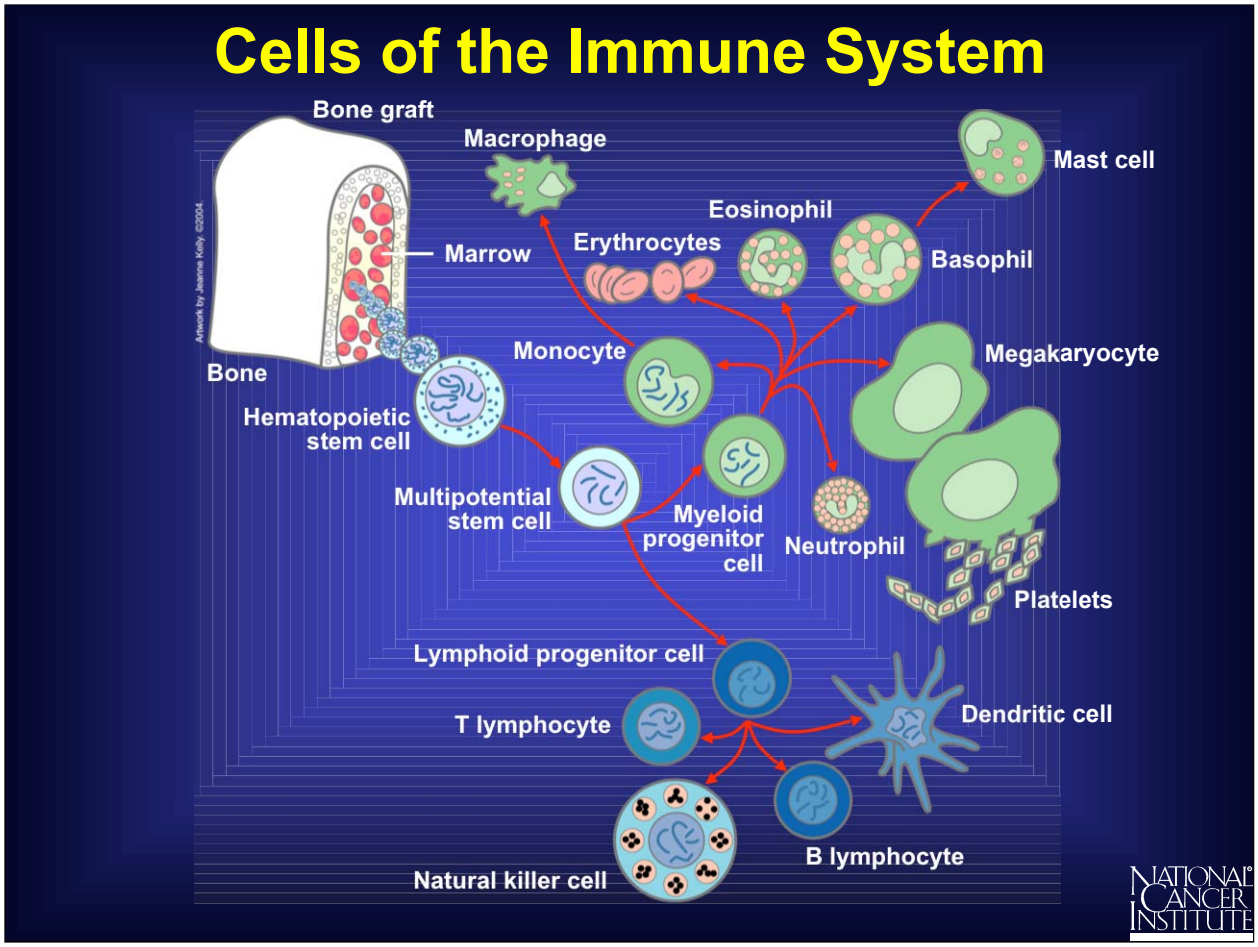
The organs of your immune system are connected with one another and with other organs of the body by a network of lymphatic vessels.

Lymphocytes can travel throughout the body using the *blood vessels*. The cells can also travel through a system of *lymphatic vessels* that closely parallels the body's veins and arteries. Cells and fluids are exchanged between blood and lymphatic vessels, enabling the lymphatic system to monitor the body for invading microbes. The lymphatic vessels carry *lymph*, a clear fluid that bathes the body's tissues.



Small, bean-shaped *lymph nodes* sit along the lymphatic vessels, with clusters in the neck, armpits, abdomen, and groin. Each lymph node contains specialized compartments where immune cells congregate and encounter antigens.

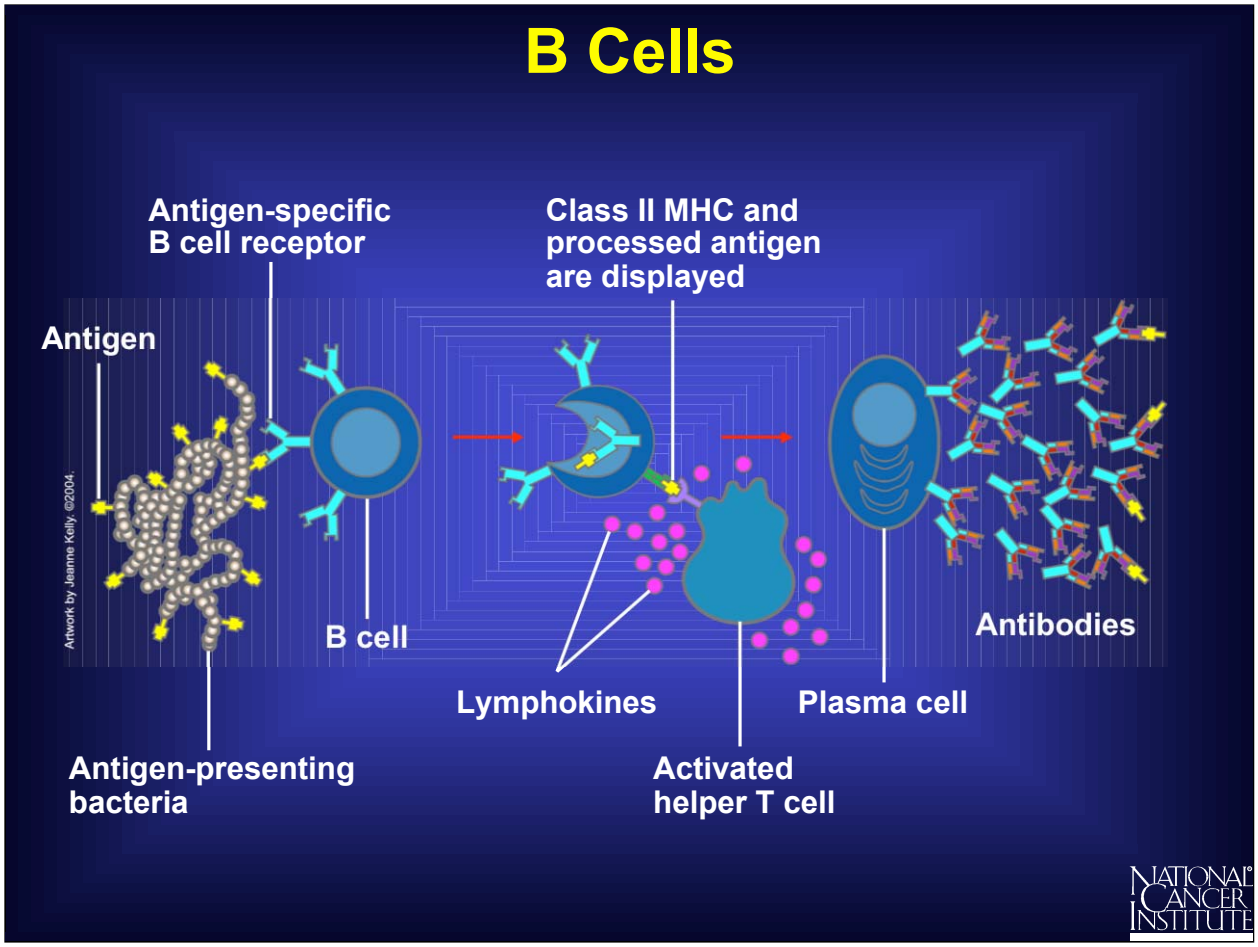
Immune cells and foreign particles enter the lymph nodes via incoming lymphatic vessels or the lymph nodes' tiny blood vessels. All lymphocytes exit lymph nodes through outgoing lymphatic vessels. Once in the bloodstream, they are transported to tissues throughout the body. They patrol everywhere for foreign antigens, then gradually drift back into the lymphatic system to begin the cycle all over again.



Cells destined to become immune cells, like all blood cells, arise in your body's bone marrow from stem cells. Some develop into myeloid progenitor cells while others become lymphoid progenitor cells.

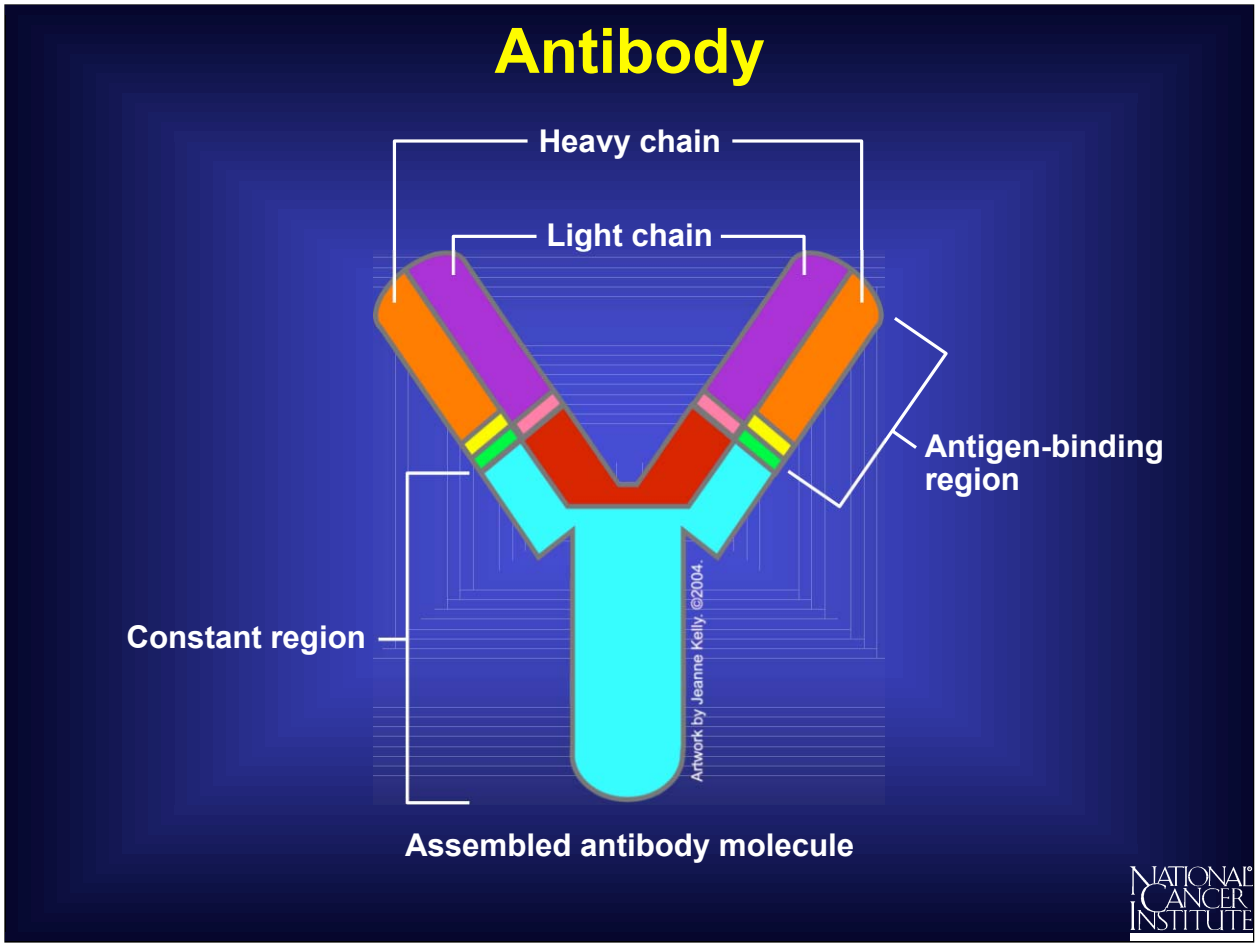
The myeloid progenitors develop into the cells that respond early and nonspecifically to infection. Neutrophils engulf bacteria upon contact and send out warning signals. Monocytes turn into macrophages in body tissues and gobble up foreign invaders. Granule-containing cells such as eosinophils attack parasites, while basophils release granules containing histamine and other allergy-related molecules.

Lymphoid precursors develop into the small white blood cells called lymphocytes. Lymphocytes respond later in infection. They mount a more specifically tailored attack after antigen-presenting cells such as dendritic cells (or macrophages) display their catch in the form of antigen fragments. The B cell turns into a plasma cell that produces and releases into the bloodstream thousands of specific antibodies. The T cells coordinate the entire immune response and eliminate the viruses hiding in infected cells.



B cells work chiefly by secreting soluble substances known as antibodies. They mill around a lymph node, waiting for a macrophage to bring an antigen or for an invader such as a bacteria to arrive. When an antigen-specific antibody on a B cell matches up with an antigen, a remarkable transformation occurs.

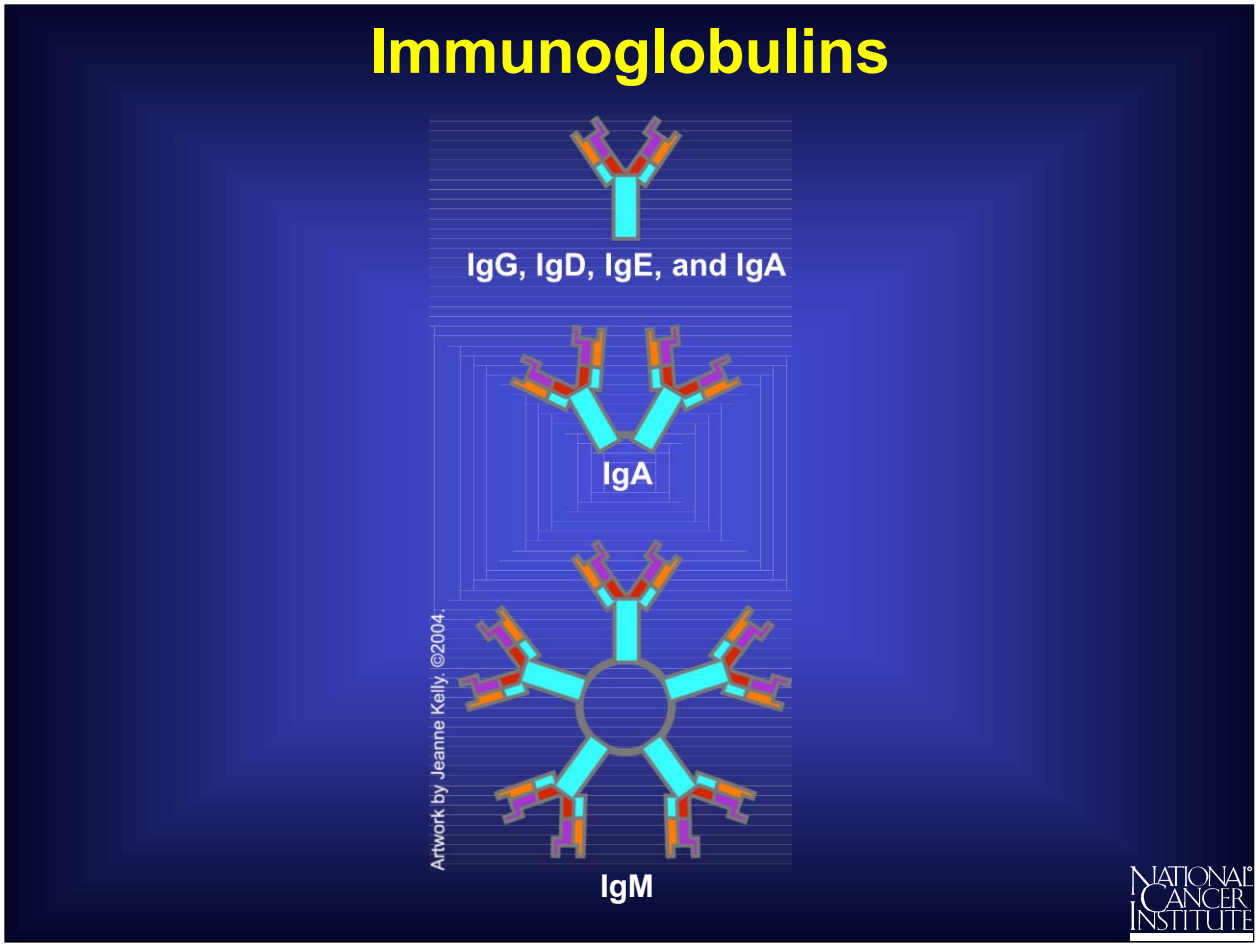
The antigen binds to the antibody receptor, the B cell engulfs it, and, after a special helper T cell joins the action, the B cell becomes a large plasma cell factory that produces identical copies of specific antibody molecules at an astonishing pace--up to 10 million copies an hour.



Each antibody is made up of two identical heavy chains and two identical light chains, shaped to form a Y.

The sections that make up the tips of the Y's arms vary greatly from one antibody to another; this is called the variable region. It is these unique contours in the antigen-binding site that allow the antibody to recognize a matching antigen, much as a lock matches a key.

The stem of the Y links the antibody to other participants in the immune defenses. This area is identical in all antibodies of the same class--for instance, all IgEs--and is called the constant region.



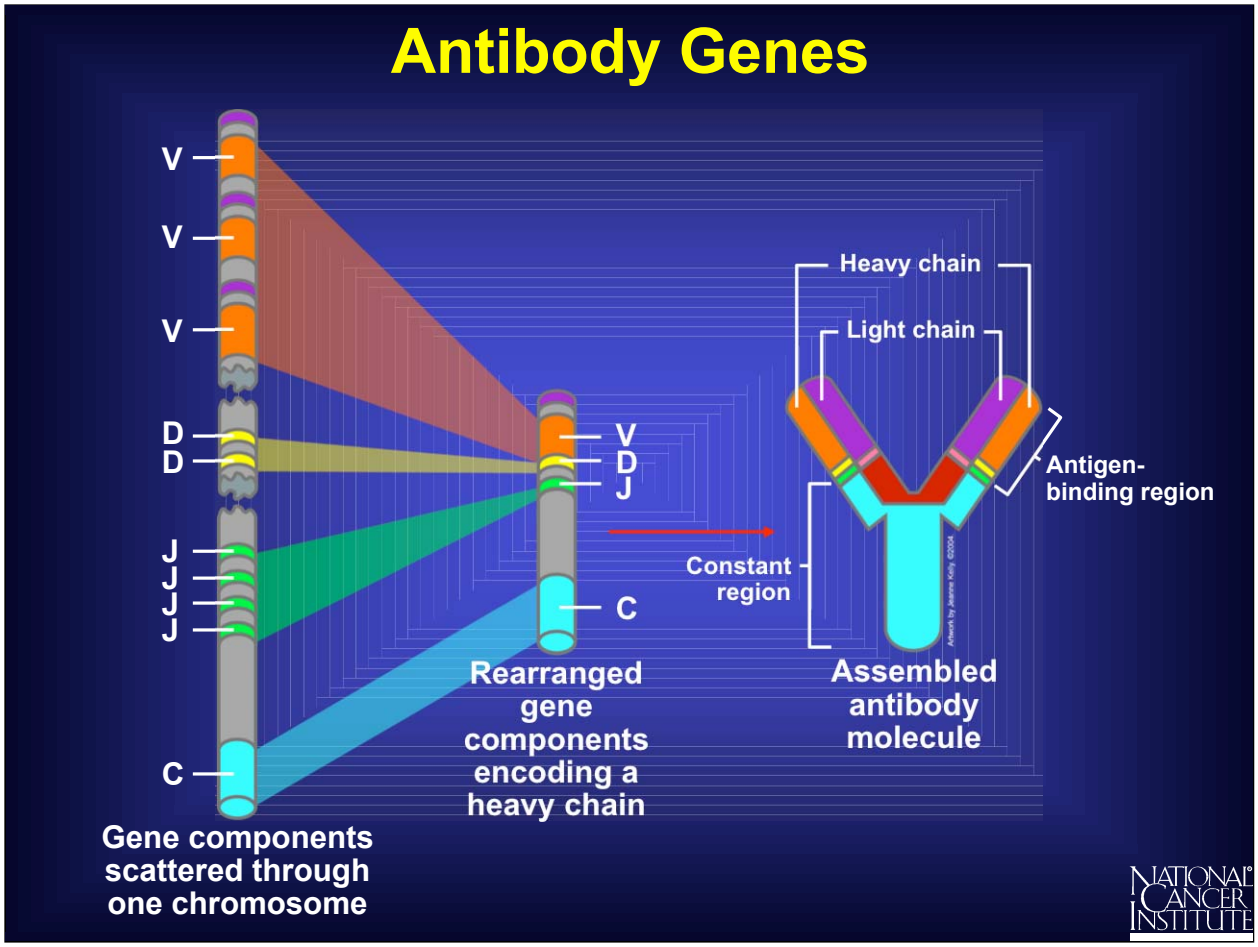
Antibodies belong to a family of large protein molecules known as immunoglobulins.

Scientists have identified nine chemically distinct classes of human immunoglobulins, four kinds of IgG and two kinds of IgA, plus IgM, IgE, and IgD.

Immunoglobulins G, D, and E are similar in appearance. IgG, the major immunoglobulin in the blood, is also able to enter tissue spaces; it works efficiently to coat microorganisms, speeding their destruction by other cells in the immune system. IgD is almost exclusively found inserted into the membrane of B cells, where it somehow regulates the cell's activation. IgE is normally present in only trace amounts, but it is responsible for the symptoms of allergy.

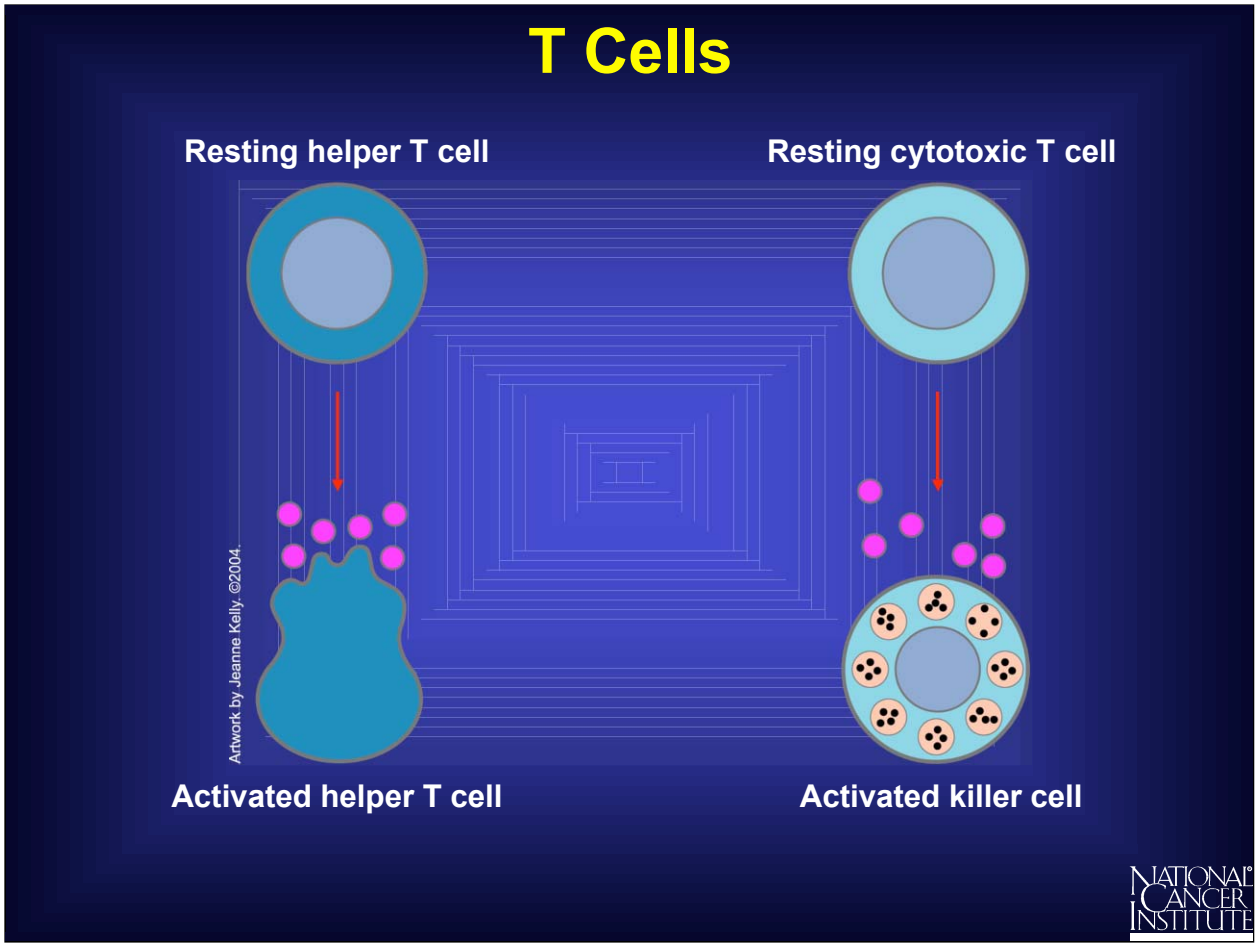
IgA--a doublet--guards the entrance to the body. It concentrates in body fluids such as tears, saliva, and secretions of the respiratory and gastrointestinal tracts.

IgM usually combines in star-shaped clusters. It tends to remain in the bloodstream, where it is very effective in killing bacteria.



Scientists long wondered how all the genetic information needed to make millions of different antibodies could fit in a limited number of genes.

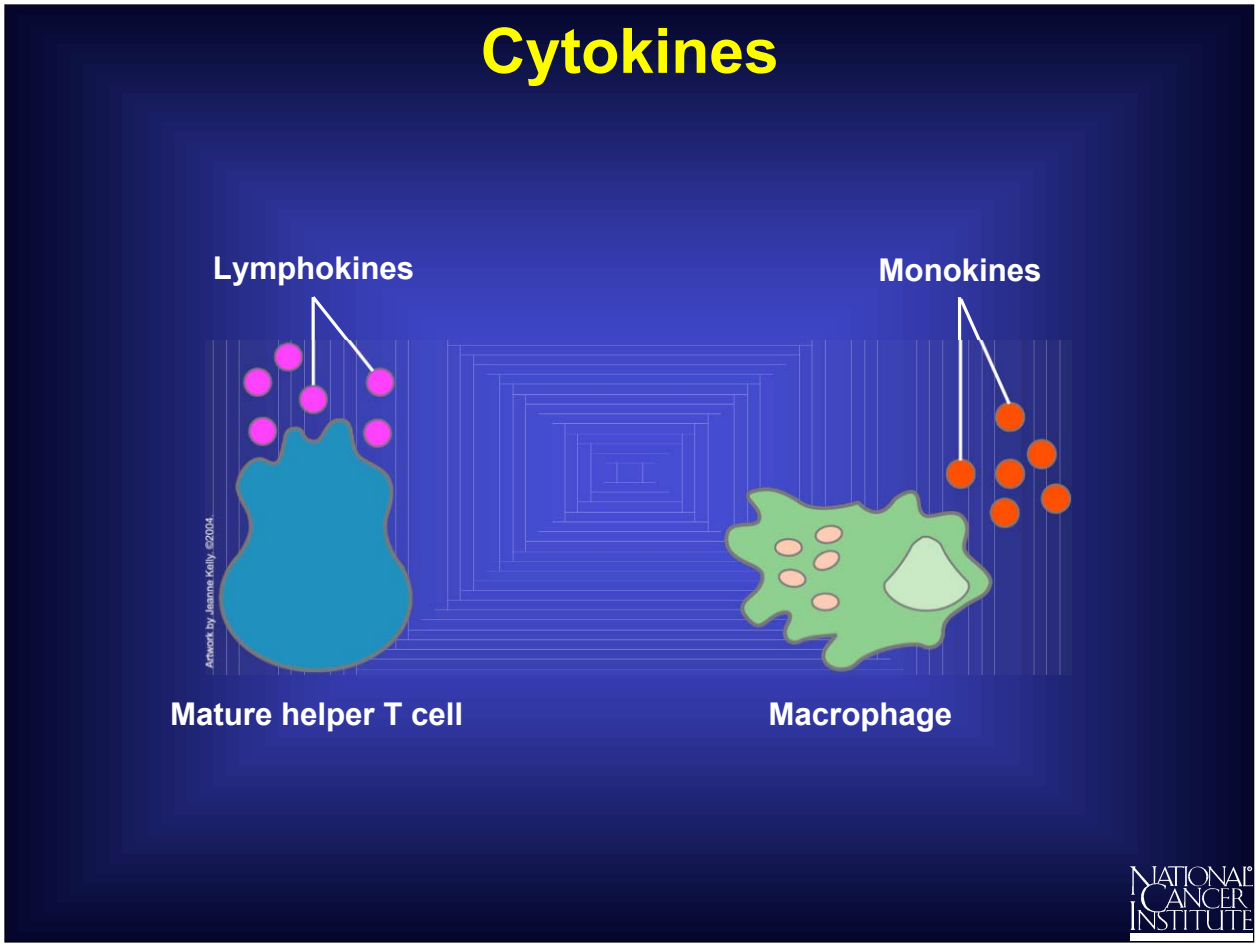
The answer is that antibody genes are spliced together from widely scattered bits of DNA located in two different chromosomes. Each antibody molecule is made up of two separate chains, a heavy chain and a light chain. The heavy chain is where the binding of antigens occurs, so much genetic variation is involved in its assembly. For example, to form a heavy chain, 1 of 400 possible variable gene segments (V) combines with 1 out of 15 diversity segments (D) and 1 out of 4 joining (J) segments. This makes 24,000 possible combinations for the DNA encoding the heavy chain alone. As this part of the gene assembles, it joins the variable coding segments with those for the constant-C segments of the heavy-chain molecule.



T cells contribute to your immune defenses in two major ways. Some help regulate the complex workings of the overall immune response, while others are cytotoxic and directly contact infected cells and destroy them.

Chief among the regulatory T cells are helper T cells. They are needed to activate many immune cells, including B cells and other T cells.

Cytotoxic T cells (sometimes called killer T cells) help rid your body of cells that have been infected by viruses as well as cells that have been transformed by cancer but have not yet adapted to evade the immune detection system. They are also responsible for the rejection of tissue and organ grafts.



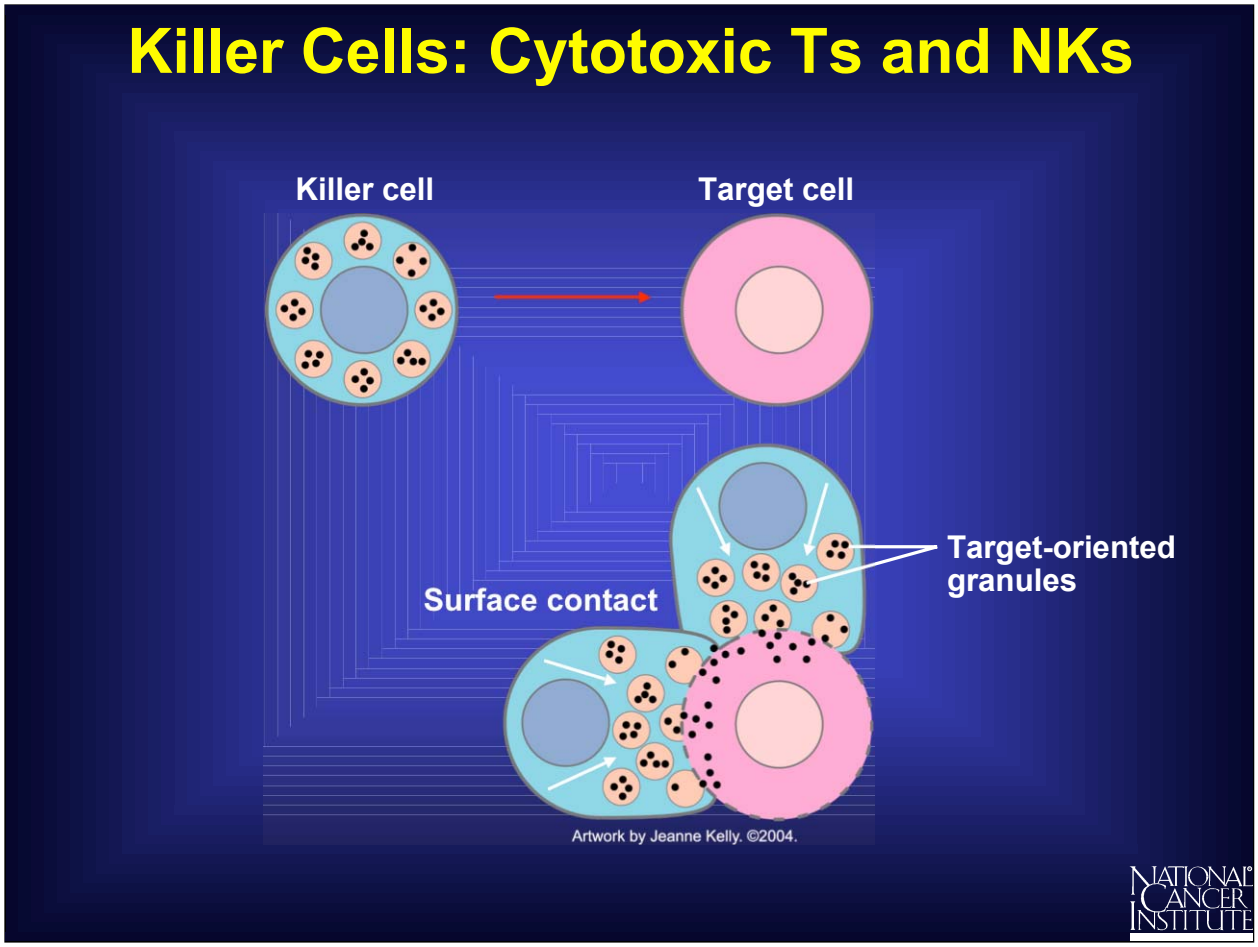
Cytokines are diverse and potent chemical messengers secreted by the cells of your immune system. They are the chief communication signals of your T cells. Cytokines include interleukins, growth factors, and interferons.

Lymphocytes, including both T cells and B cells, secrete cytokines called lymphokines, while the cytokines of monocytes and macrophages are dubbed monokines. Many of these cytokines are also known as interleukins because they serve as a messenger between white cells, or leukocytes.

Interferons are naturally occurring cytokines that may boost the immune system's ability to recognize cancer as a foreign invader.

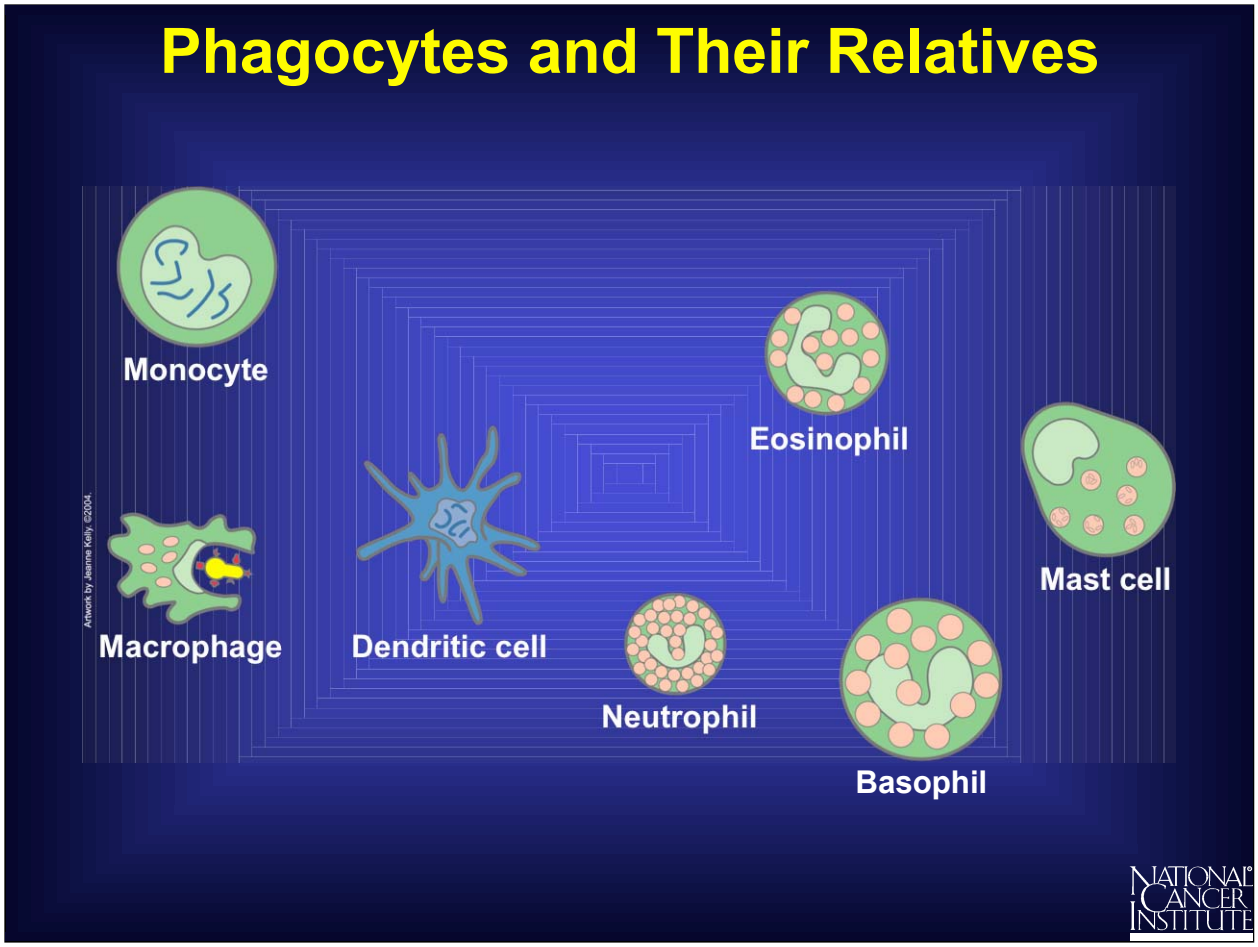
Binding to specific receptors on target cells, cytokines recruit many other cells and substances to the field of action. Cytokines encourage cell growth, promote cell activation, direct cellular traffic, and destroy target cells--including cancer cells.

When cytokines attract specific cell types to an area, they are called chemokines. These are released at the site of injury or infection and call other immune cells to the region to help repair damage and defend against infection.



At least two types of lymphocytes are killer cells--cytotoxic T cells and natural killer cells. Both types contain granules filled with potent chemicals. Both types kill on contact. They bind their targets, aim their weapons, and deliver bursts of lethal chemicals.

To attack, cytotoxic T cells need to recognize a specific antigen bound to self-MHC markers, whereas natural killer (NK) cells will recognize and attack cells lacking these. This gives NK cells the potential to attack many types of foreign cells.



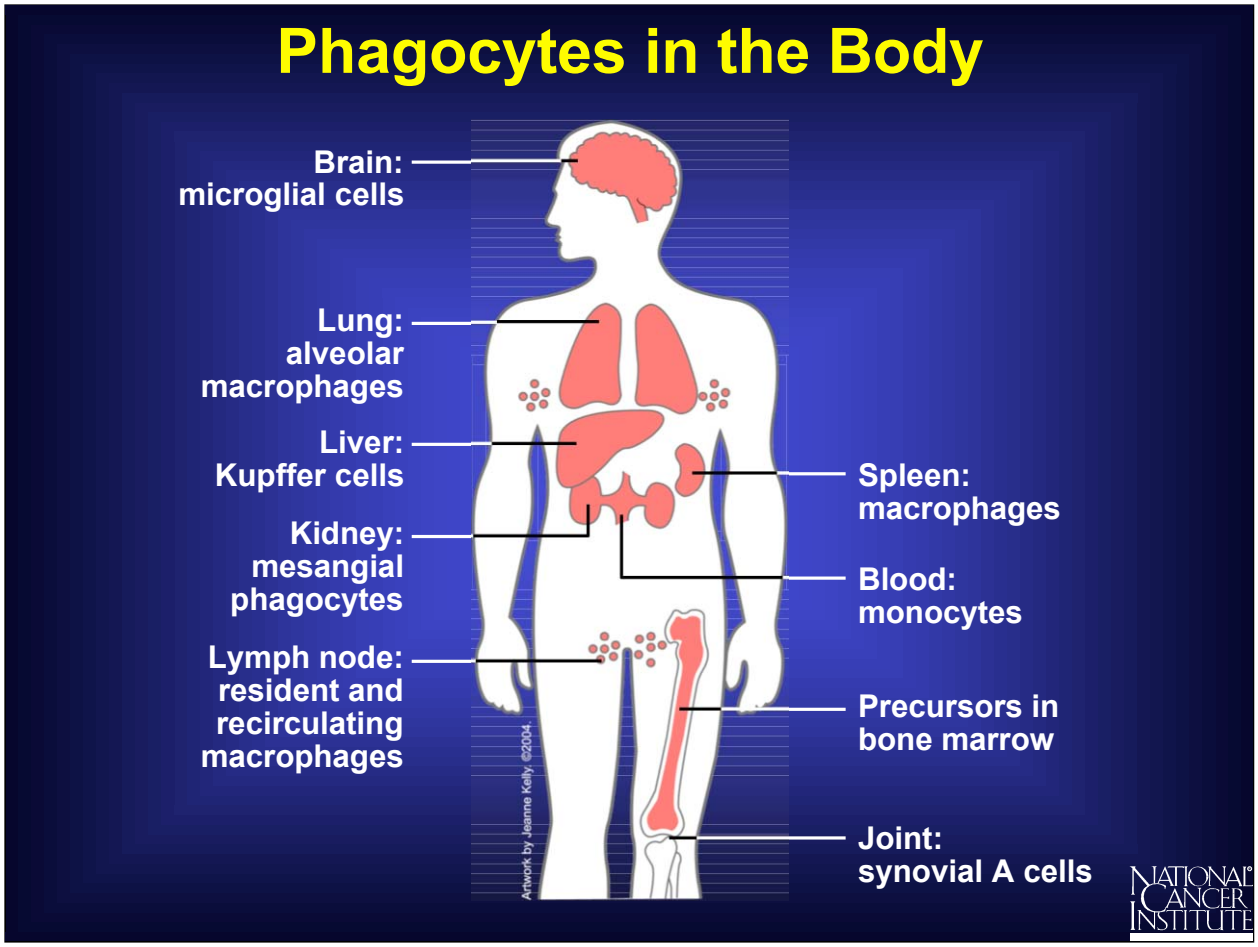
Some immune cells have more than one name. For example, the name "phagocytes" is given to the large immune cells that can engulf and digest foreign invaders, and the name "granulocytes" refers to immune cells that carry granules laden with killer chemicals.

Phagocytes include monocytes, which circulate in the blood; macrophages, which are found in tissues throughout the body; dendritic cells, which are more stationary, monitoring their environment from one spot such as the skin; and neutrophils, cells that circulate in the blood but move into tissues when they are needed.

Macrophages are versatile cells; besides acting as phagocytic scavengers, they secrete a wide variety of signaling cytokines (called monokines) that are vital to the immune response.

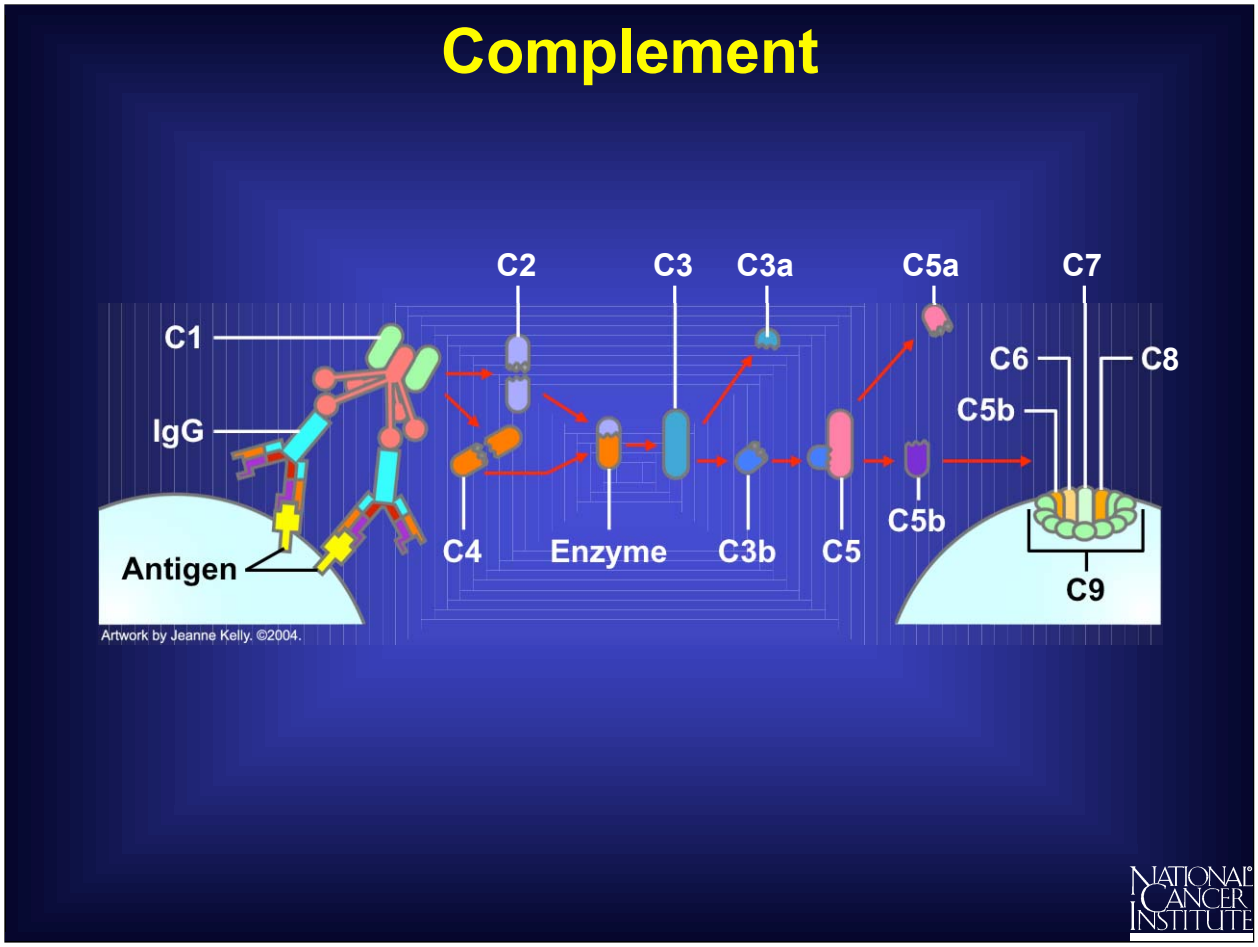
Neutrophils are both phagocytes and granulocytes: they contain granules filled with potent chemicals. These chemicals, in addition to destroying microorganisms, play a key role in acute inflammatory reactions. Other types of granulocytes are eosinophils and basophils, which degranulate by spraying their chemicals onto harmful cells or microbes. The mast cell is a twin of the basophil, except it is not a blood cell. Rather, it is responsible for allergy symptoms in the lungs, skin, and linings of the nose and intestinal tract.

A related structure, the blood platelet, is a cell fragment. Platelets, too, contain granules. They promote blood clotting and wound repair, and activate some immune defenses.



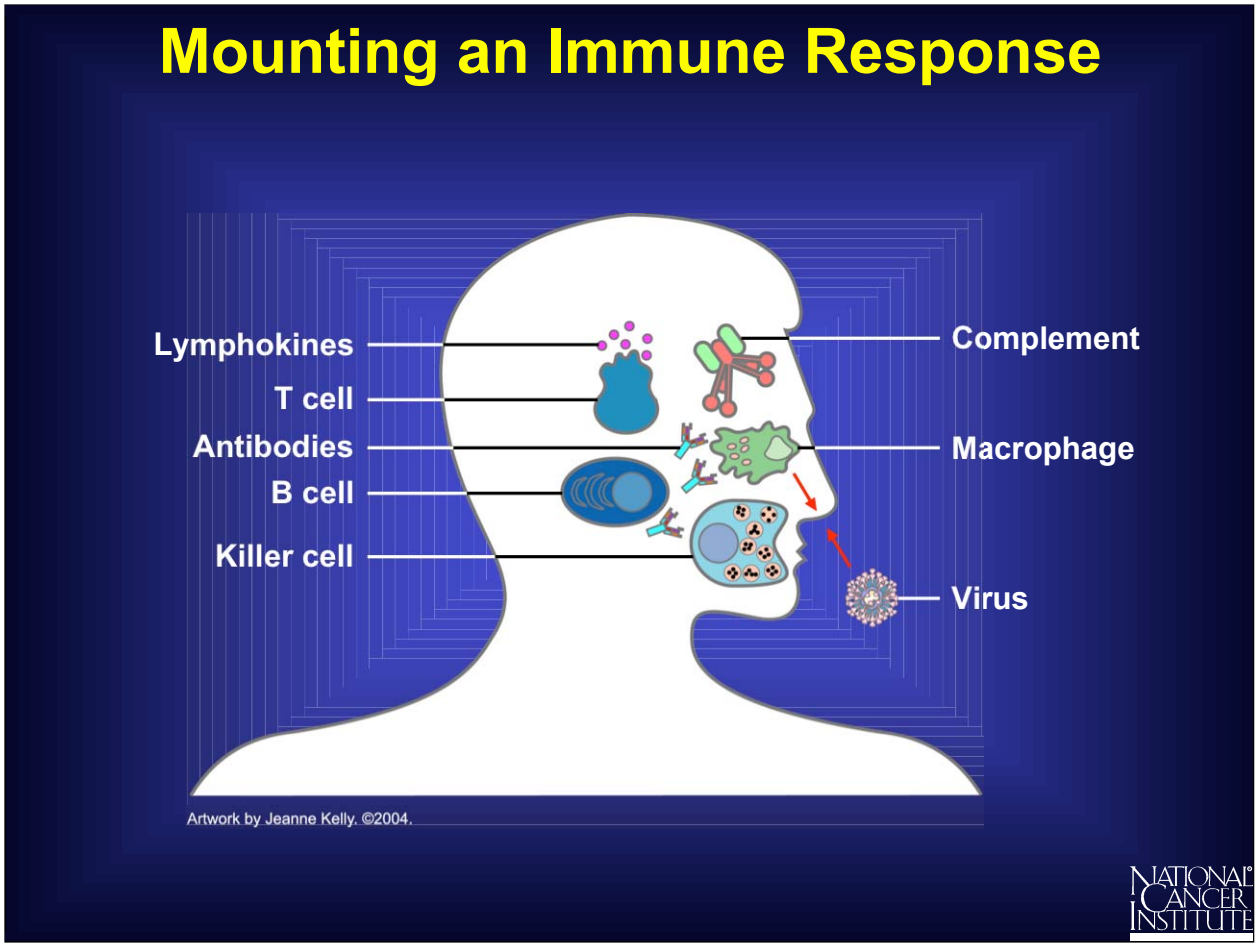
If foreign invaders succeed in getting past your skin barriers and manage to reach body tissues, they are usually recognized, ingested, and killed by phagocytes strategically positioned throughout the body. Macrophages and neutrophils are the main phagocytes involved, with macrophages as the first line of defense. Monocytes stop circulating in the blood and mature into specialized macrophages that migrate into the tissues of the body and prepare for invasion. Large numbers of mature macrophages reside in connective tissue, along the digestive tract, in the lungs, in the spleen, and even along certain blood vessels in the liver, where they are known as Kupffer cells.

Neutrophils are short-lived immune cells that remain circulating in the blood. When tissue-based macrophages encounter an invader, neutrophils soon reinforce their immune response by coming to the site of infection in large numbers.



The complement system consists of a series of about 25 proteins that work to "complement" the work of antibodies in destroying bacteria. Complement also helps rid the body of antigen-antibody complexes. Complement proteins are the culprits that cause blood vessels to become dilated and leaky, causing redness and swelling during an inflammatory response.

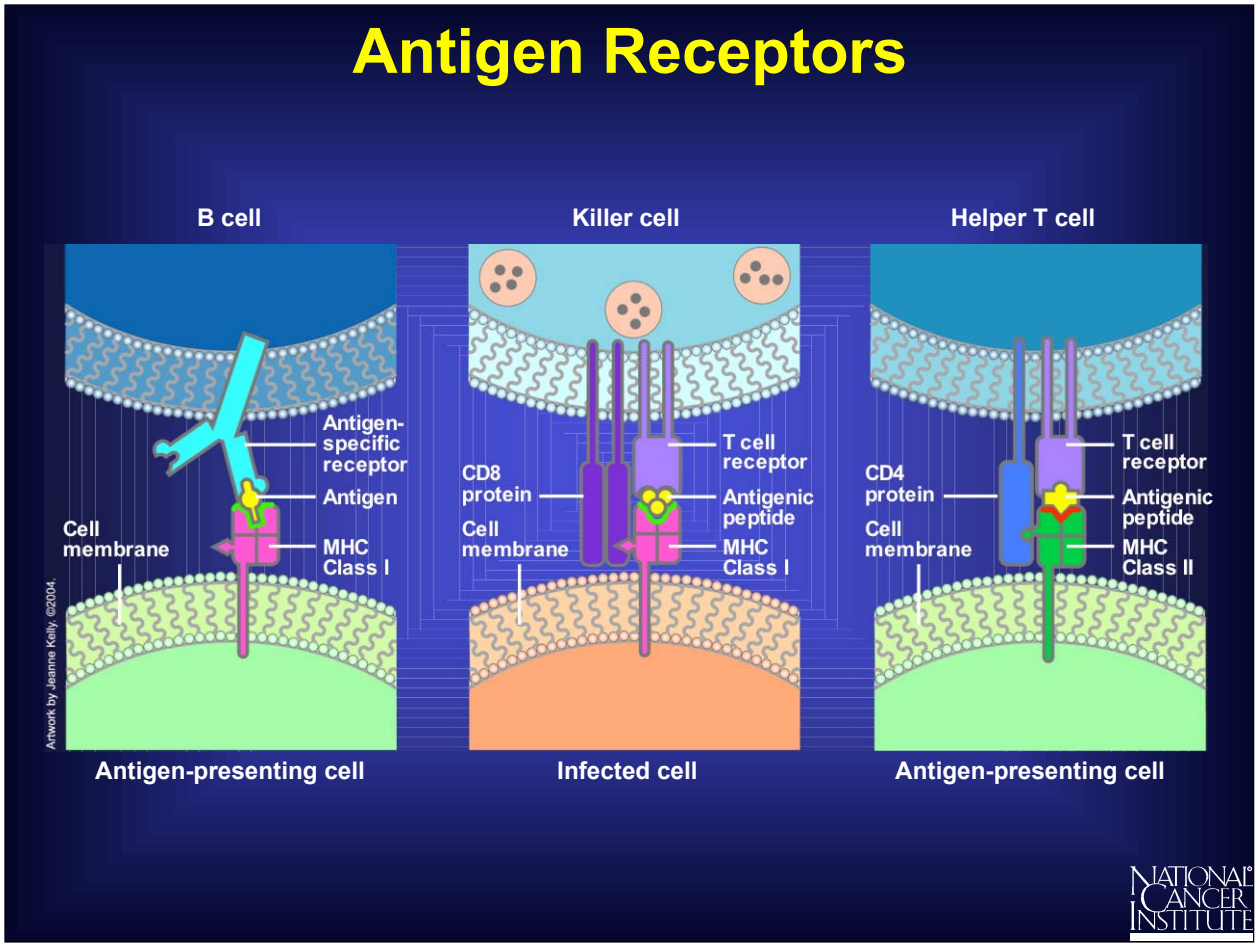
Complement proteins circulate in the blood in an inactive form. The so-called "complement cascade" is set off when the first complement molecule, C1, encounters antibody bound to antigen in an antigen-antibody complex. Each of the complement proteins performs its specialized job, acting, in turn, on the molecule next in line. The end product is a cylinder that punctures the cell membrane and, by allowing fluids and molecules to flow in and out, dooms the target cell.



Microbes attempting to get into your body must first get past your skin and mucous membranes, which not only pose a physical barrier but are rich in scavenger cells and IgA antibodies.

Next, they must elude a series of nonspecific defenses--and substances that attack all invaders regardless of the epitopes they carry. These include patrolling phagocytes, granulocytes, NK cells, and complement.

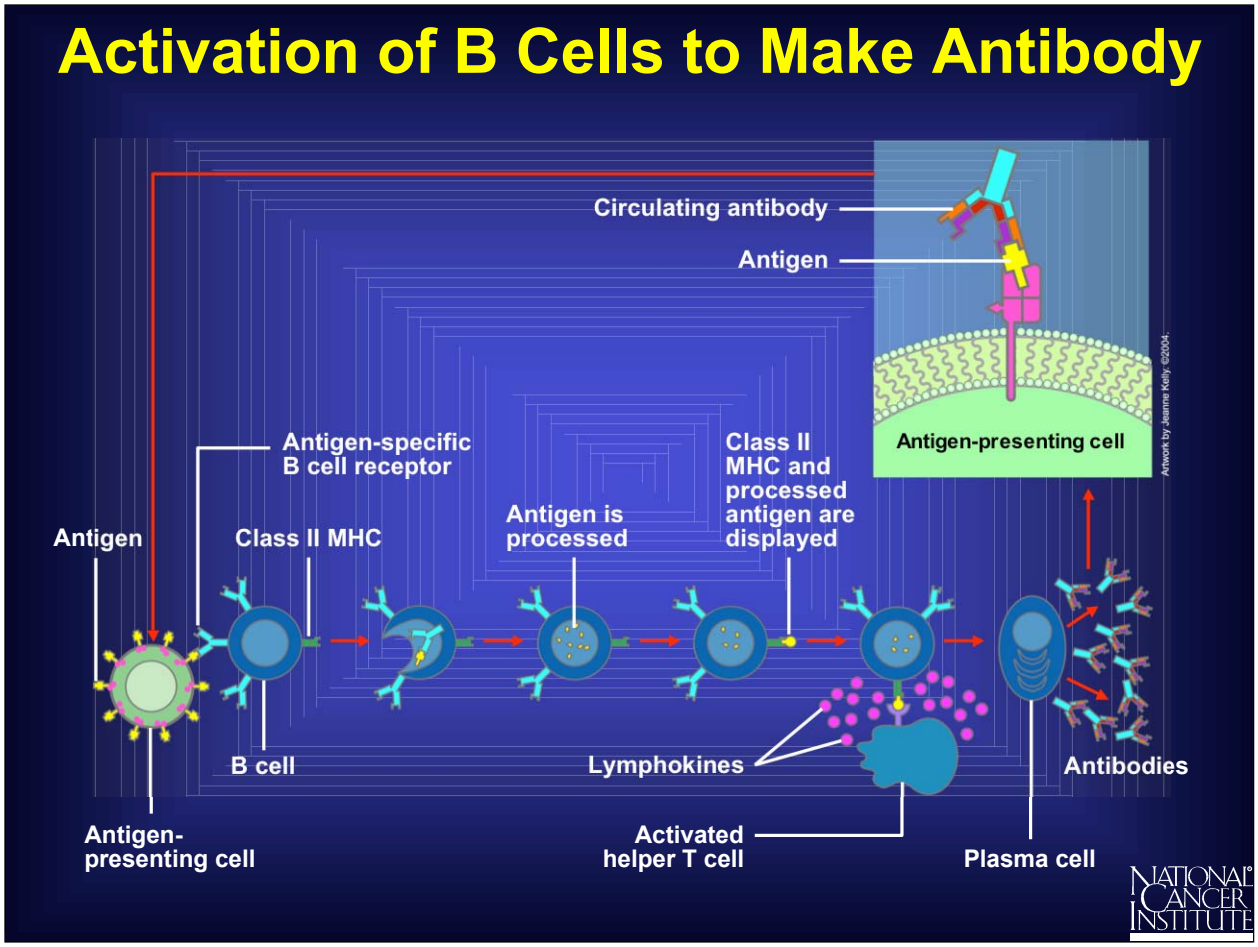
Infectious agents that get past these nonspecific barriers must finally confront specific weapons tailored just for them. These include both antibodies and cytotoxic T cells.



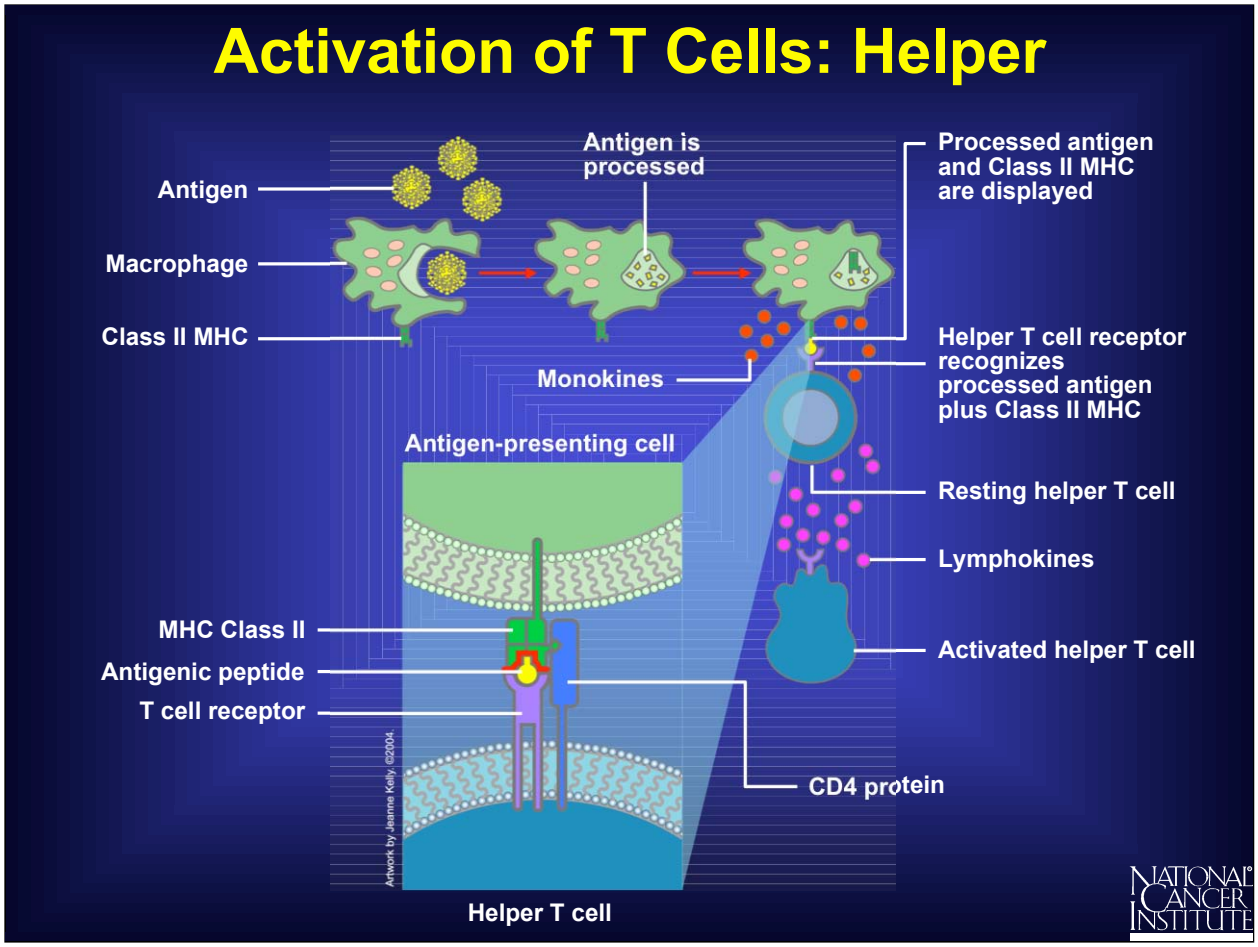
Both B cells and T cells carry customized receptor molecules that allow them to recognize and respond to their specific targets.

The B cell's antigen-specific receptor that sits on its outer surface is also a sample of the antibody it is prepared to manufacture; this antibody-receptor recognizes antigen in its natural state.

The T cell's receptor systems are more complex. T cells can recognize an antigen only after the antigen is processed and presented in combination with a special type of major histocompatibility complex (MHC) marker. Killer T cells only recognize antigens in the grasp of Class I MHC markers, while helper T cells only recognize antigens in the grasp of Class II MHC markers. This complicated arrangement assures that T cells act only on precise targets and at close range.

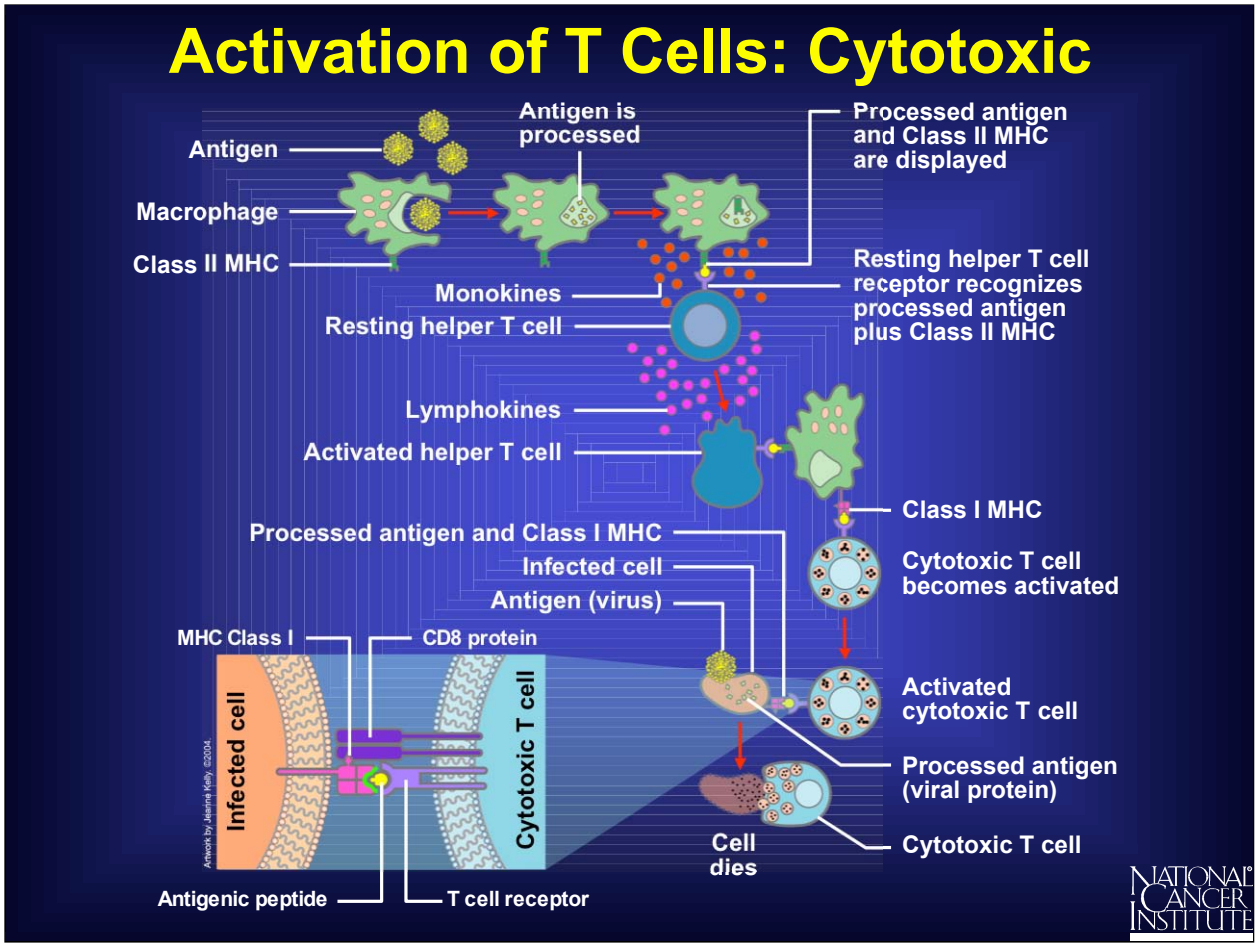


The B cell uses its antibody-receptor to bind a matching antigen, which it then engulfs and processes. This triggers the B cell to become a large plasma cell producing millions of copies of the same specific antibody. These antibodies then circulate in the bloodstream in search of more matching antigens. B cell antibodies cannot themselves kill an invading organism, but they can use their antibodies to mark invaders for destruction by other immune cells and by complement.

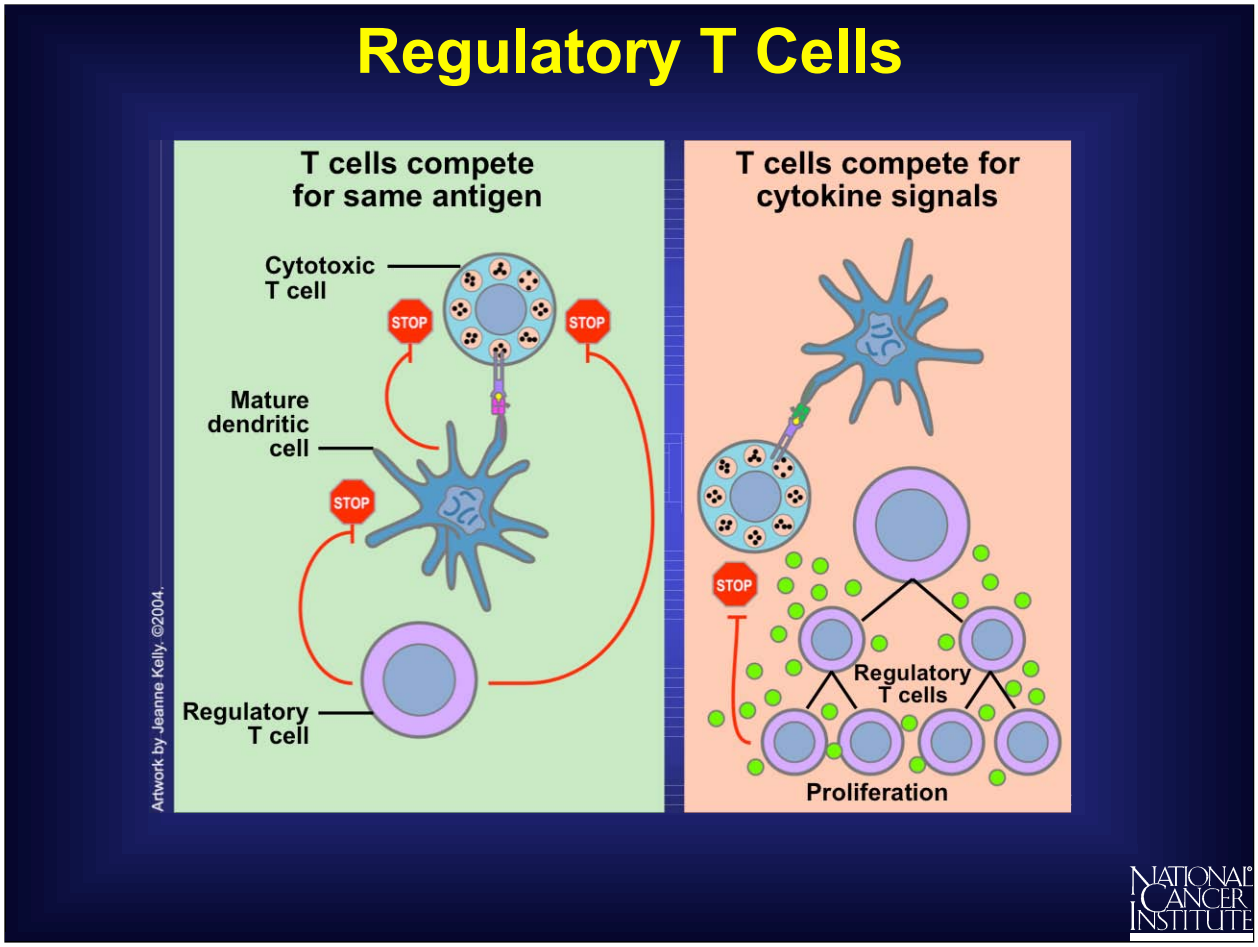


Helper T cells only recognize antigen in the grasp of Class II MHC markers. An antigen-presenting cell--such as a macrophage or a dendritic cell--breaks down the antigen it devours, then it places small pieces (peptides) on its surface along with a Class II MHC marker. By exhibiting its catch in this way, antigen-presenting cells enable specific receptors on helper T cells to bind the antigen and confirm (via CD4 protein) that an invasion has occurred.

After binding, a resting helper T cell quickly becomes an activated helper T. It assumes command of the immune response, giving orders to increase the number of specific antibody-producing plasma cells and the cytotoxic killer cells needed to quell the attack.



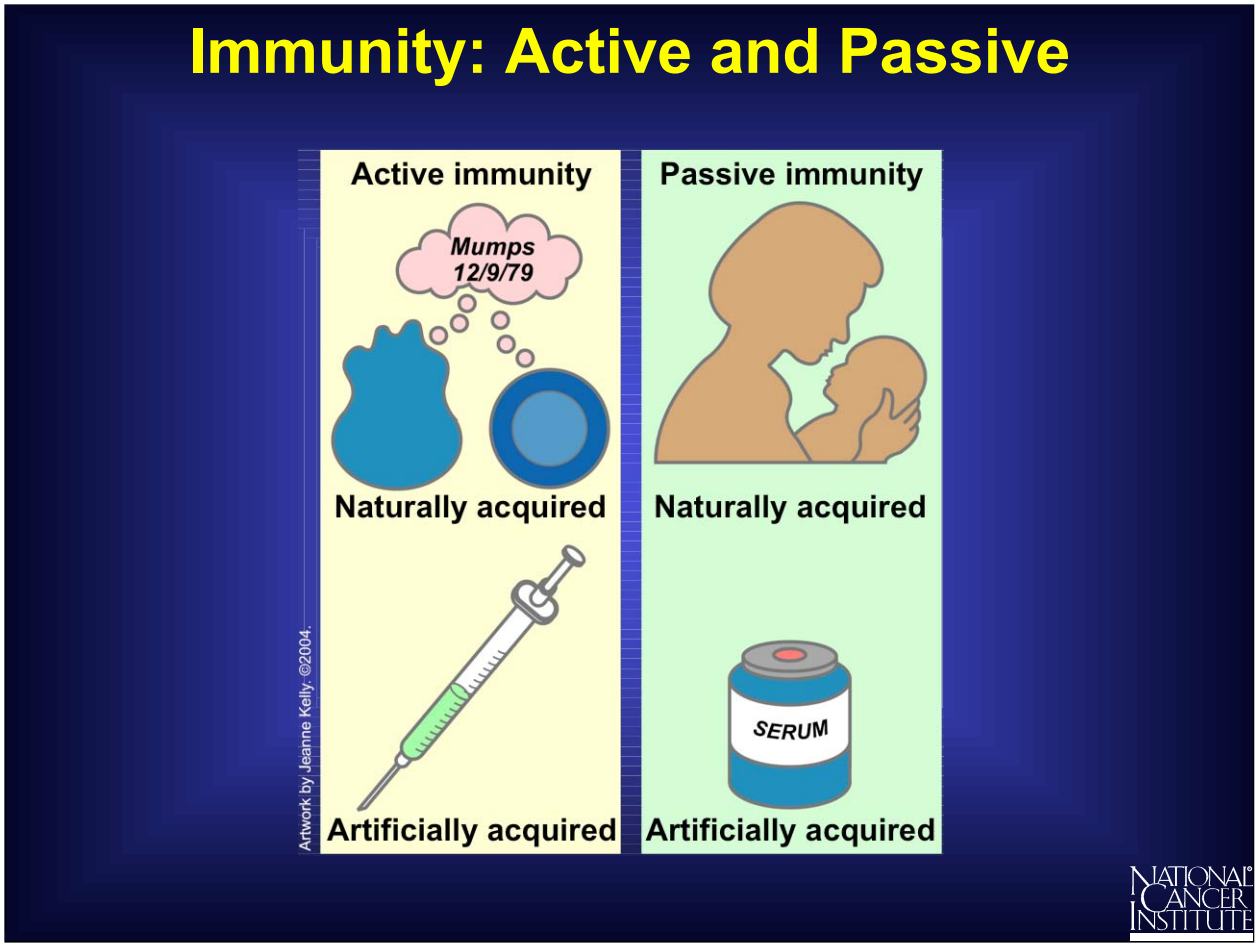
Killer T cells only recognize antigen in the grasp of Class I MHC markers. Here a resting cytotoxic T cell recognizes virus fragments, which are displayed by a macrophage in combination with a Class I MHC marker. A receptor on a circulating, resting cytotoxic T cell (and CD8 protein) recognizes the antigen-protein complex and binds to it. The binding process and an activated helper T cell activate the cytotoxic T cell. Because the surfaces of other infected cells bear the same virus fragments in combination with Class I MHC markers, the activated cytotoxic T cells can quickly recognize, attack, and destroy the diseased cell.



Your immune system also has a braking mechanism, a checkpoint to prevent immune responses to self. Without this checkpoint, autoimmune disease could flourish. An additional type of immune cells--regulatory T cells--are these critical braking agents.

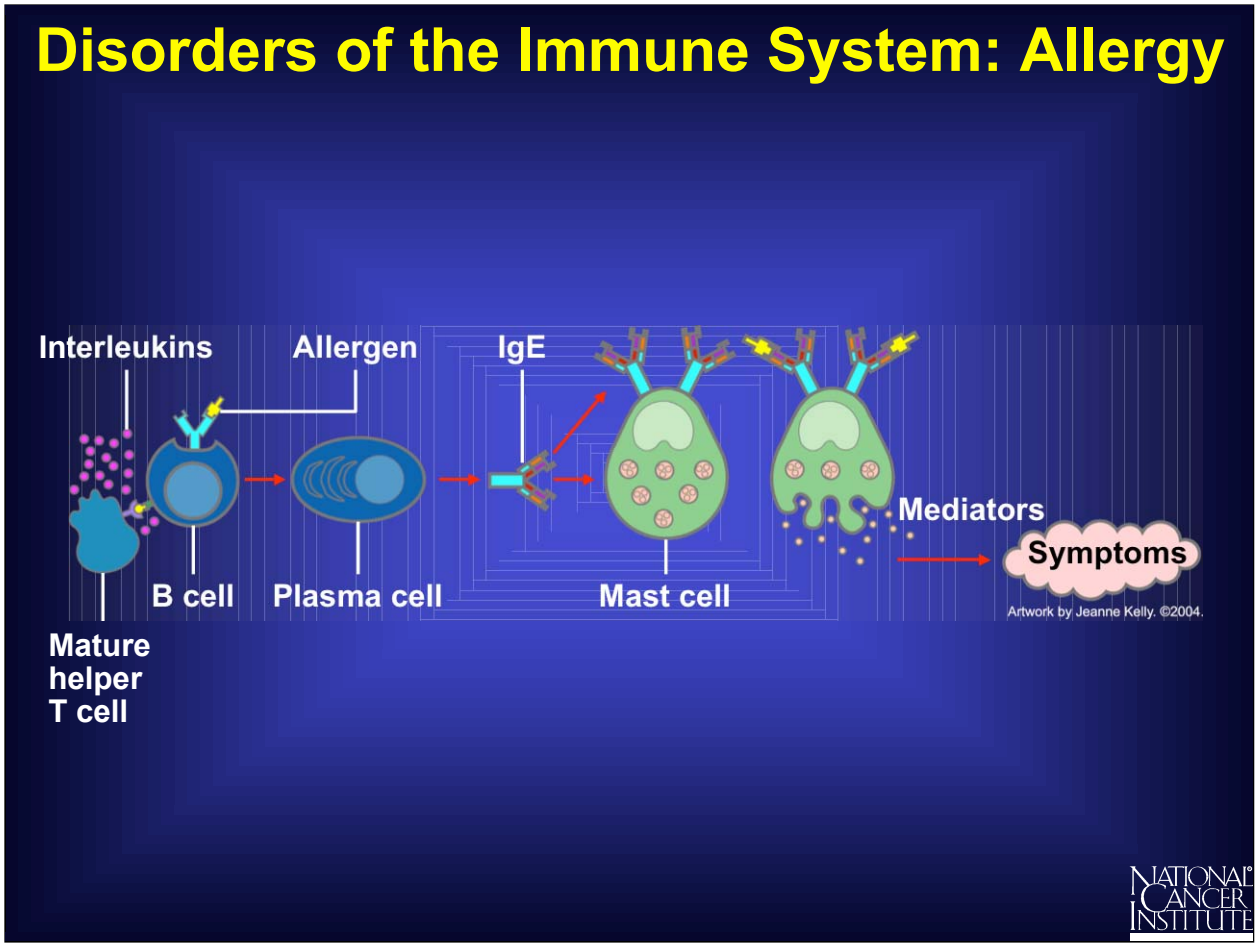
Researchers don't yet know exactly how regulatory T cells operate. Some think these T cells recognize and compete for the same antigens as those that activate helper and cytotoxic T cells, but that regulatory T cells zero in on a different epitope. Another possibility is that cytotoxic or helper T cells only multiply when regulatory T cells are absent.

Regulatory T cells have become important to researchers who are trying to increase the efficacy of vaccines for cancer and AIDS. In addition to increasing the antigenicity of the immunizing element, a better understanding of regulatory T cells will permit scientists to reduce the immune system's brake activity, which often limits the effectiveness of vaccines.



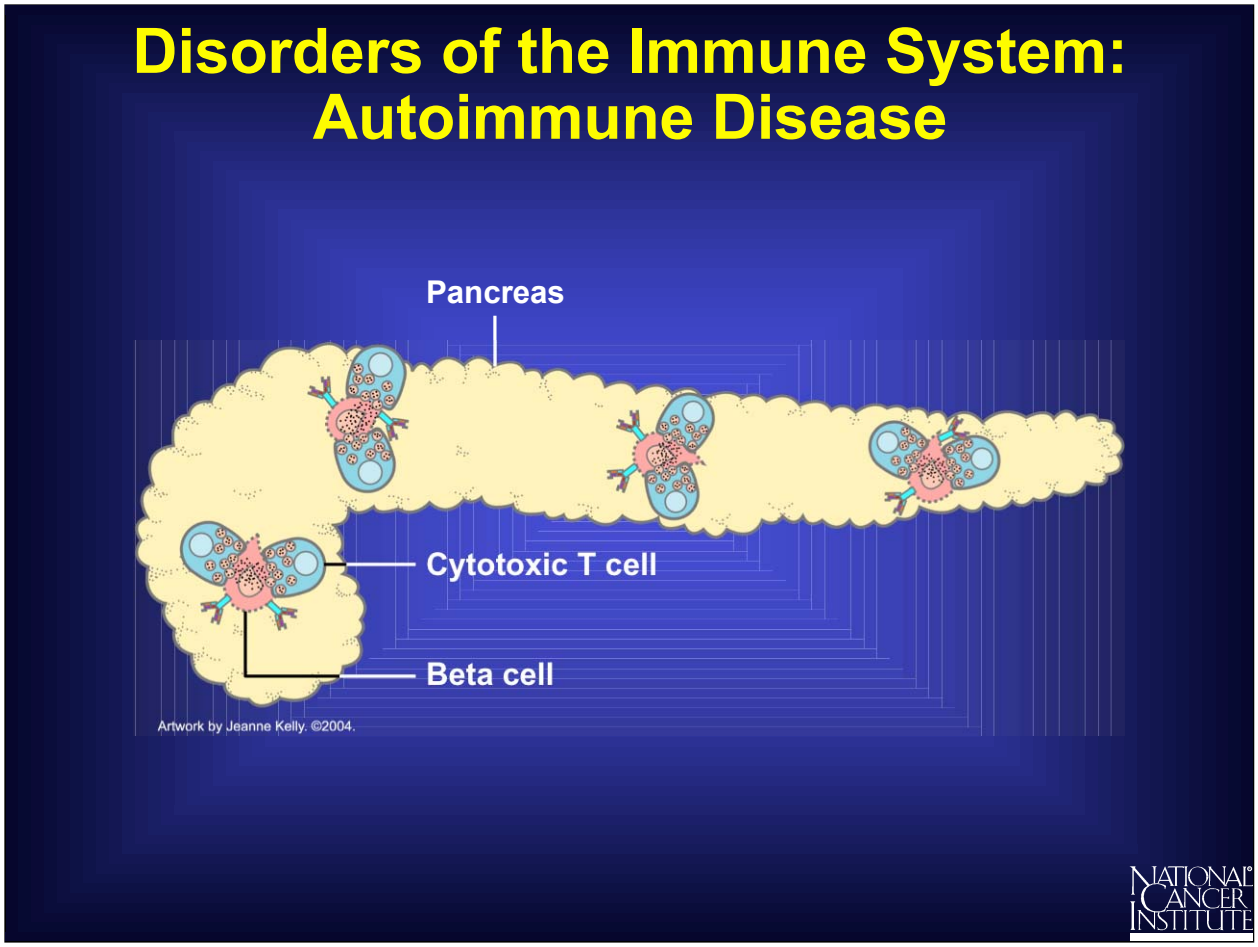
Whenever T cells and B cells are activated, some become " memory" cells. The next time that an individual encounters that same antigen, the immune system is primed to destroy it quickly. This is active immunity because the body's immune system prepares itself for future challenges. Long-term active immunity can be naturally acquired by infection or artificially acquired by vaccines made from infectious agents that have been inactivated or, more commonly, from minute portions of the microbe.

Short-term passive immunity can be transferred artificially from one individual to another via antibody-rich serum; similarly, a mother enables an infant to naturally acquire protection while growing within her by donating her antibodies and certain immune cells. This is passive immunity because the infant who is protected does not produce antibodies, but borrows them.



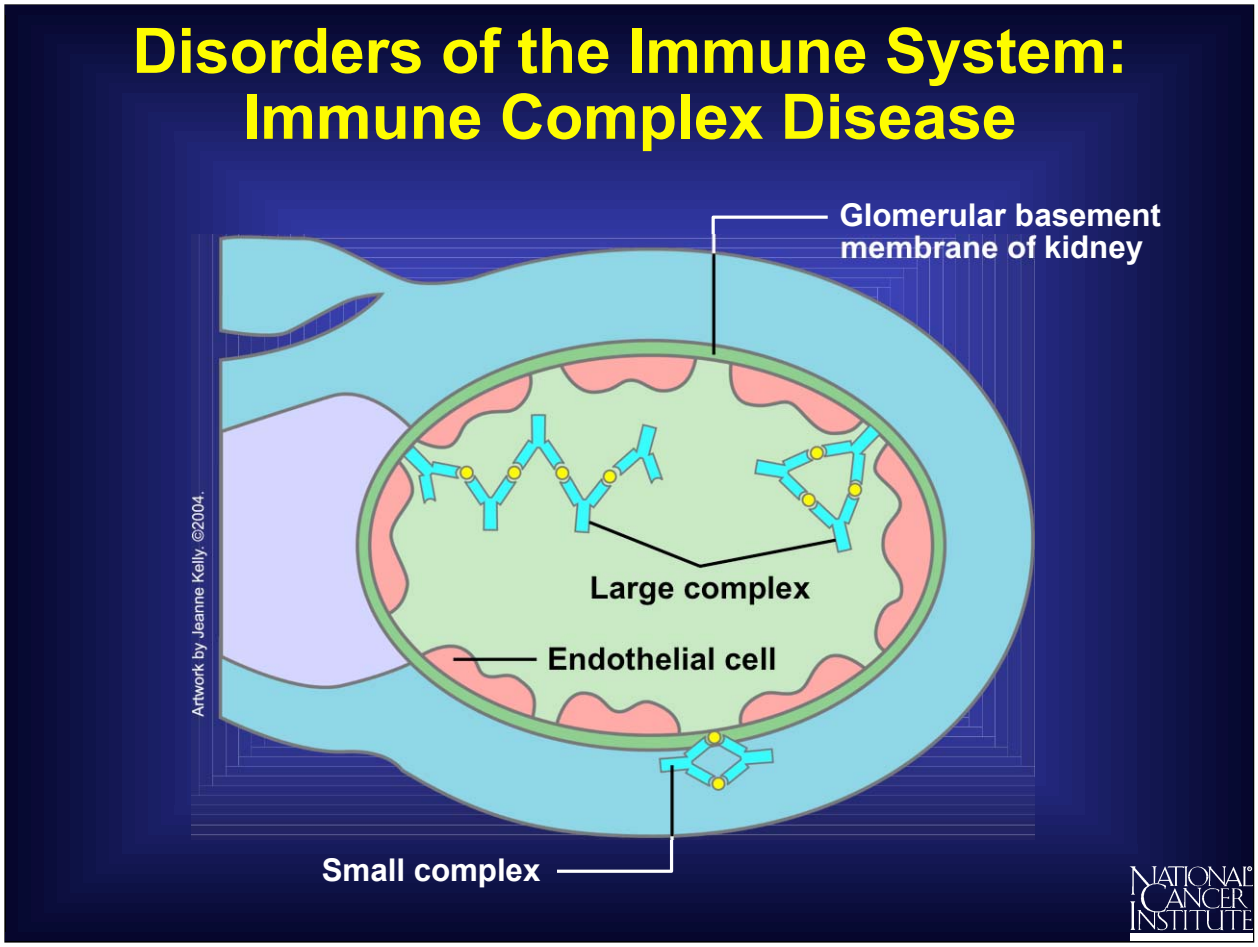
When your immune system malfunctions, it can unleash a torrent of disorders and diseases.

One of the most familiar is allergy. Allergies such as hay fever and hives are related to the antibody known as IgE. The first time an allergy-prone person is exposed to an allergen--for instance, grass pollen--the individual's B cells make large amounts of grass pollen IgE antibody. These IgE molecules attach to granule-containing cells known as mast cells, which are plentiful in the lungs, skin, tongue, and linings of the nose and gastrointestinal tract. The next time that person encounters grass pollen, the IgE-primed mast cell releases powerful chemicals that cause the wheezing, sneezing, and other symptoms of allergy.



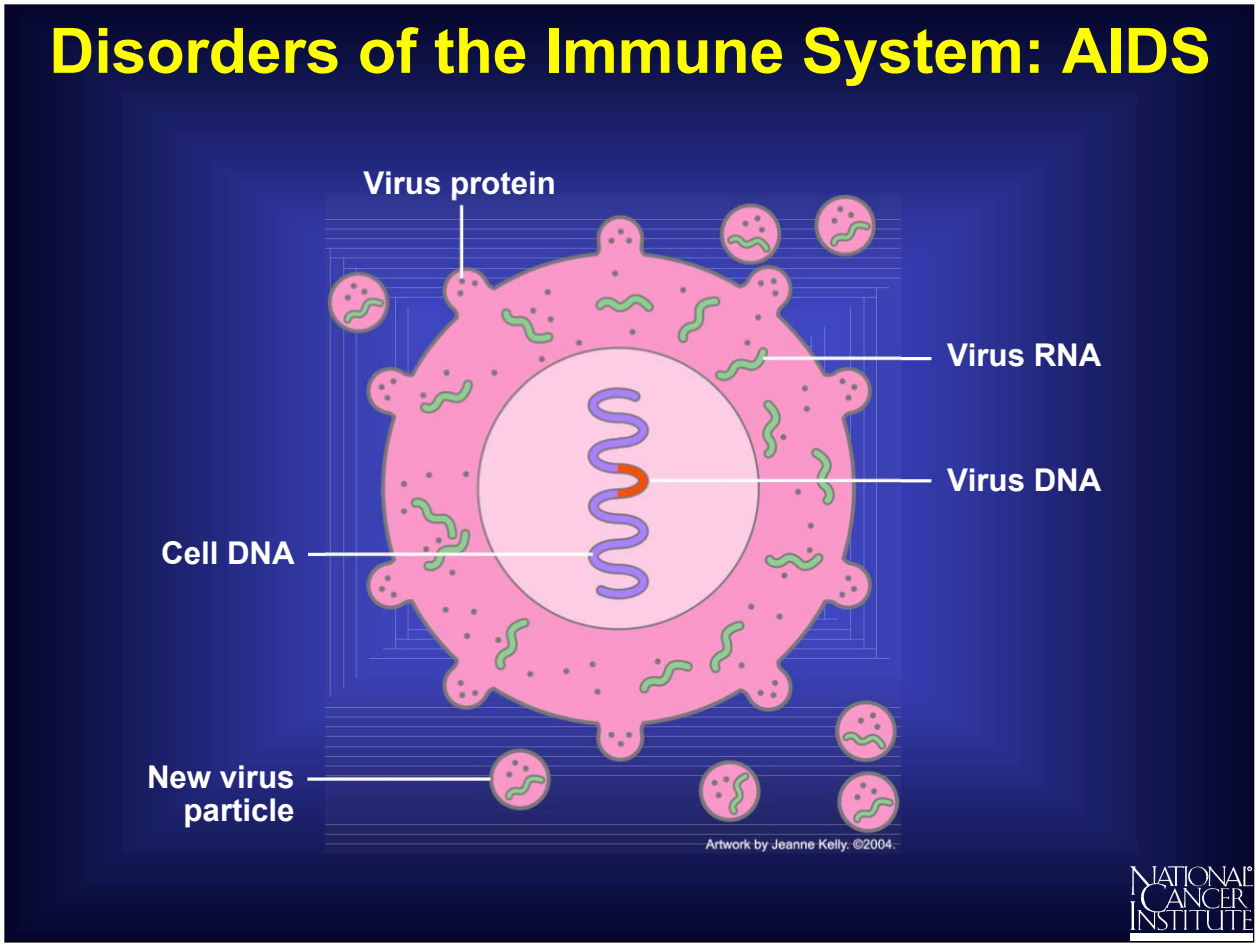
Sometimes the immune system's recognition apparatus breaks down, and the body begins to manufacture antibodies and T cells directed against the body's own cells and organs.

Such cells and autoantibodies, as they are known, contribute to many diseases. For instance, T cells that attack pancreas cells contribute to diabetes, while an autoantibody known as rheumatoid factor is common in persons with rheumatoid arthritis.



Immune complexes are clusters of interlocking antigens and antibodies.

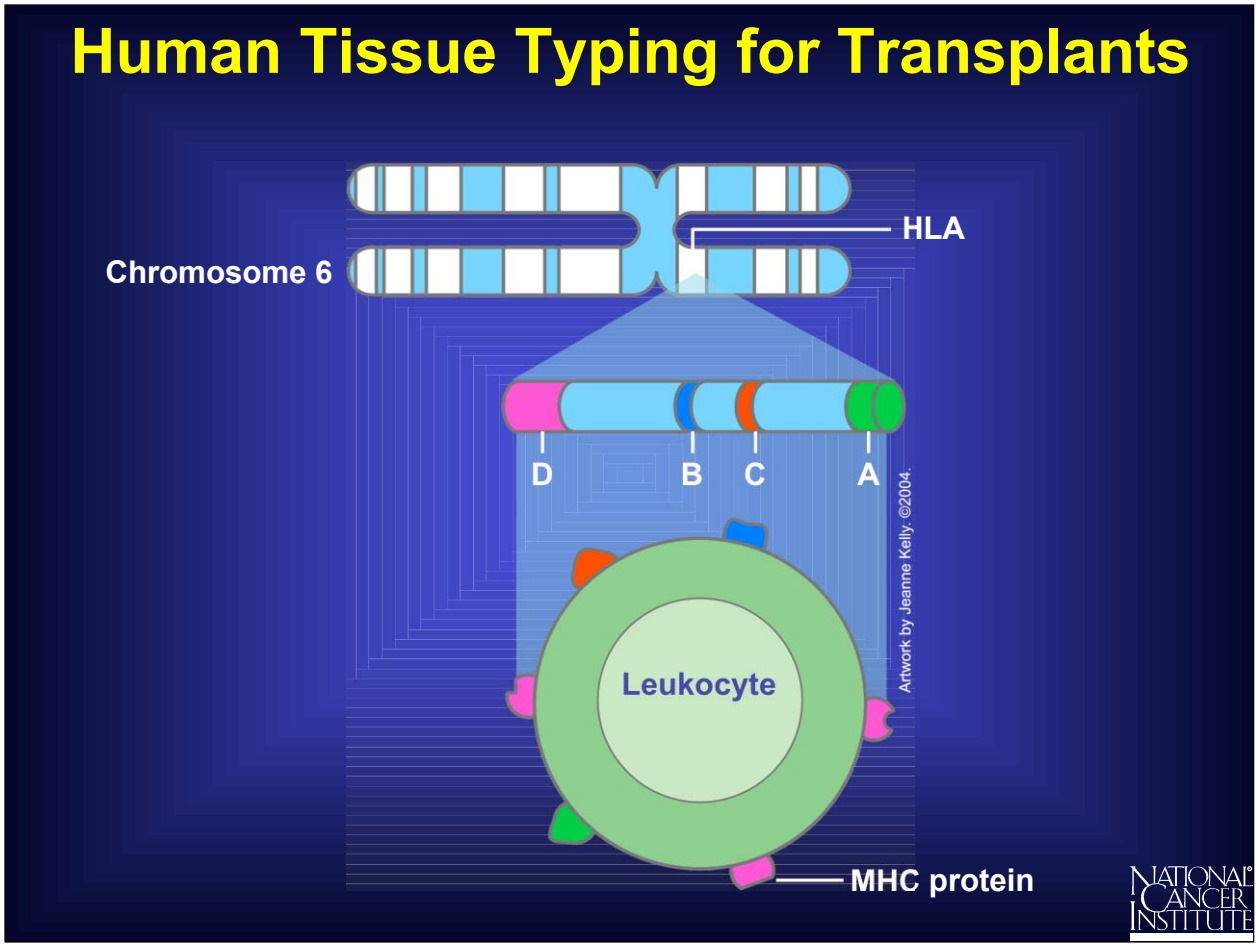
Normally they are rapidly removed from the bloodstream. In some circumstances, however, they continue to circulate, and eventually they become trapped in, and damage, the tissues of the kidneys, as seen here, or the lungs, skin, joints, or blood vessels.



When the immune system is lacking one or more of its components, the result is an immunodeficiency disorder.

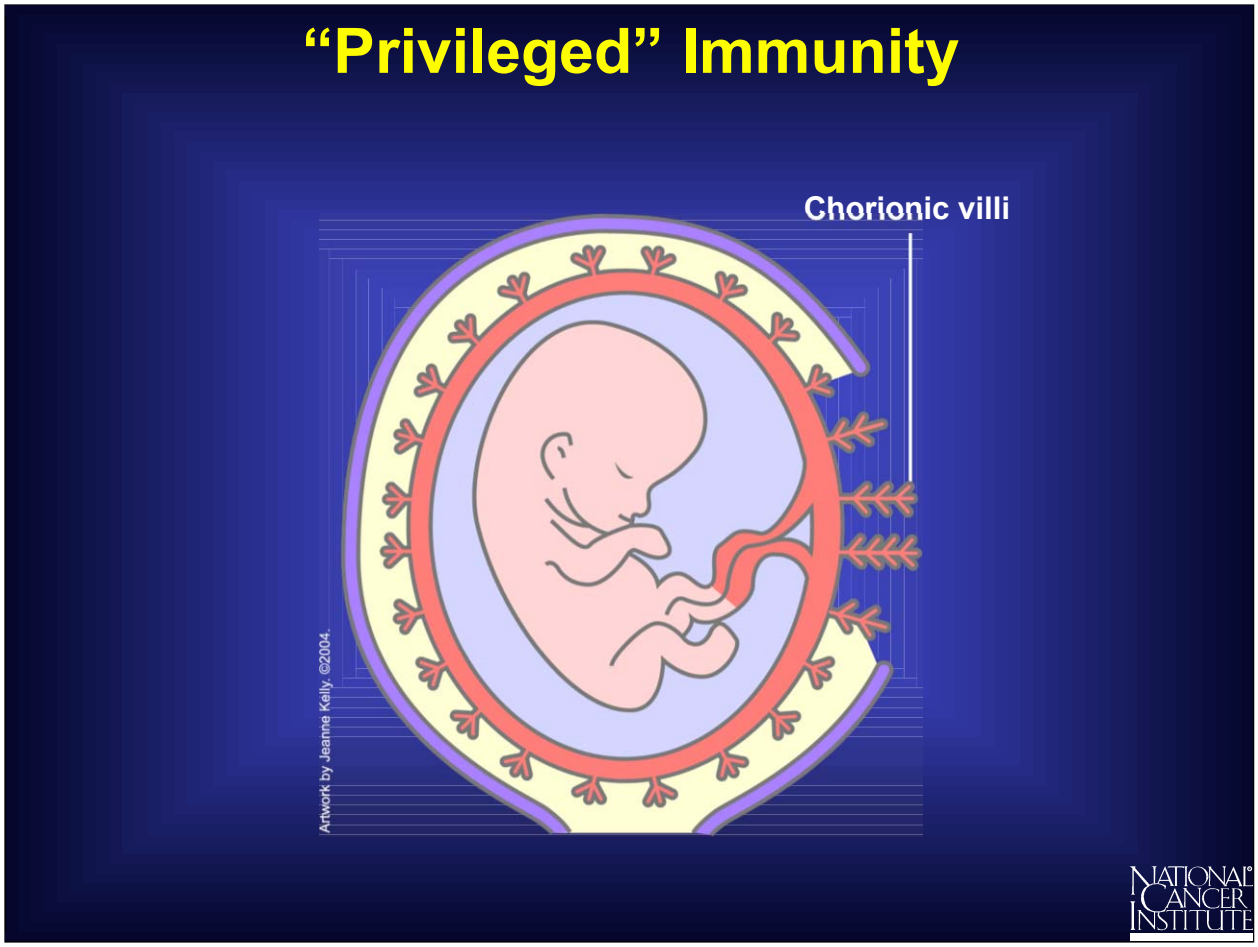
These disorders can be inherited, acquired through infection, or produced as an inadvertent side effect of drugs such as those used to treat cancer or transplant patients.

AIDS is an immunodeficiency disorder caused by a virus that destroys helper T cells. The virus copies itself incessantly and invades helper T cells and macrophages, the very cells needed to organize an immune defense. The AIDS virus splices its DNA into the DNA of the cell it infects; the cell is thereafter directed to churn out new viruses.



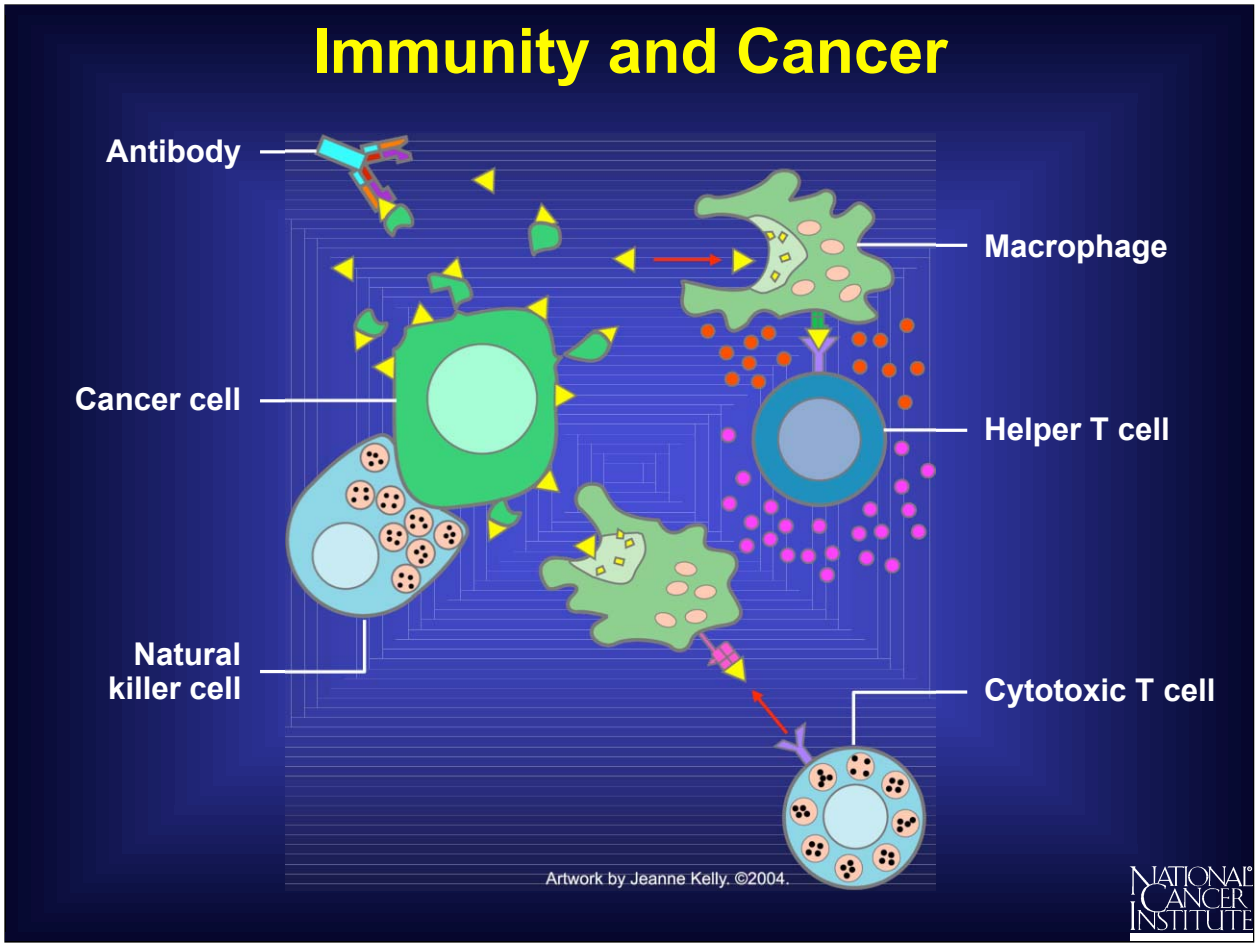
Although MHC proteins are required for T cell responses against foreign invaders, they can pose difficulty during transplantation. Every cell in the body is covered with MHC self-markers, and each person bears a slightly unique set. If a T lymphocyte recognizes a non-self MHC scaffold, it will rally immune cells to destroy the cell that bears it. For successful organ or blood stem cell transplantations, doctors must pair organ recipients with donors whose MHC sets match as closely as possible. Otherwise, the recipient's T cells will likely attack the transplant, leading to *graft rejection*.

To find good matches, tissue typing is usually done on white blood cells, or leukocytes. In this case, the MHC-self-markers are called human leukocyte antigens, or HLA. Each cell has a double set of six major HLA markers, HLA-A, B, and C, and three types of HLA-D. Since each of these antigens exists, in different individuals, in as many as 20 varieties, the number of possible HLA types is about 10,000. The genes that encode the HLA antigens are located on chromosome 6.



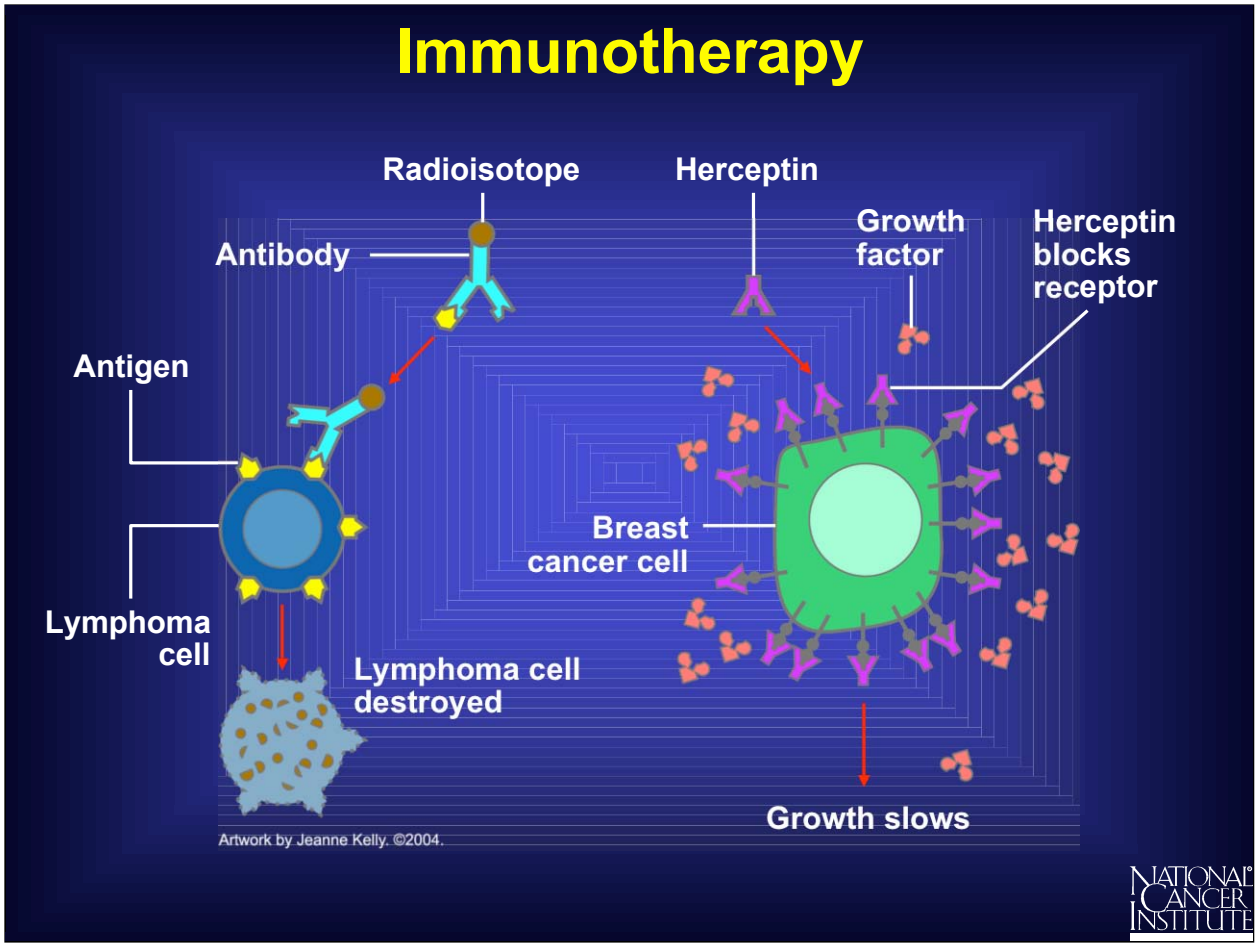
A child in the womb carries foreign antigens from the father as well as immunologically compatible self-antigens from the mother.

One might expect this condition to trigger a graft rejection, but it does not because the uterus is an "immunologically privileged" site where immune responses are somehow subdued.



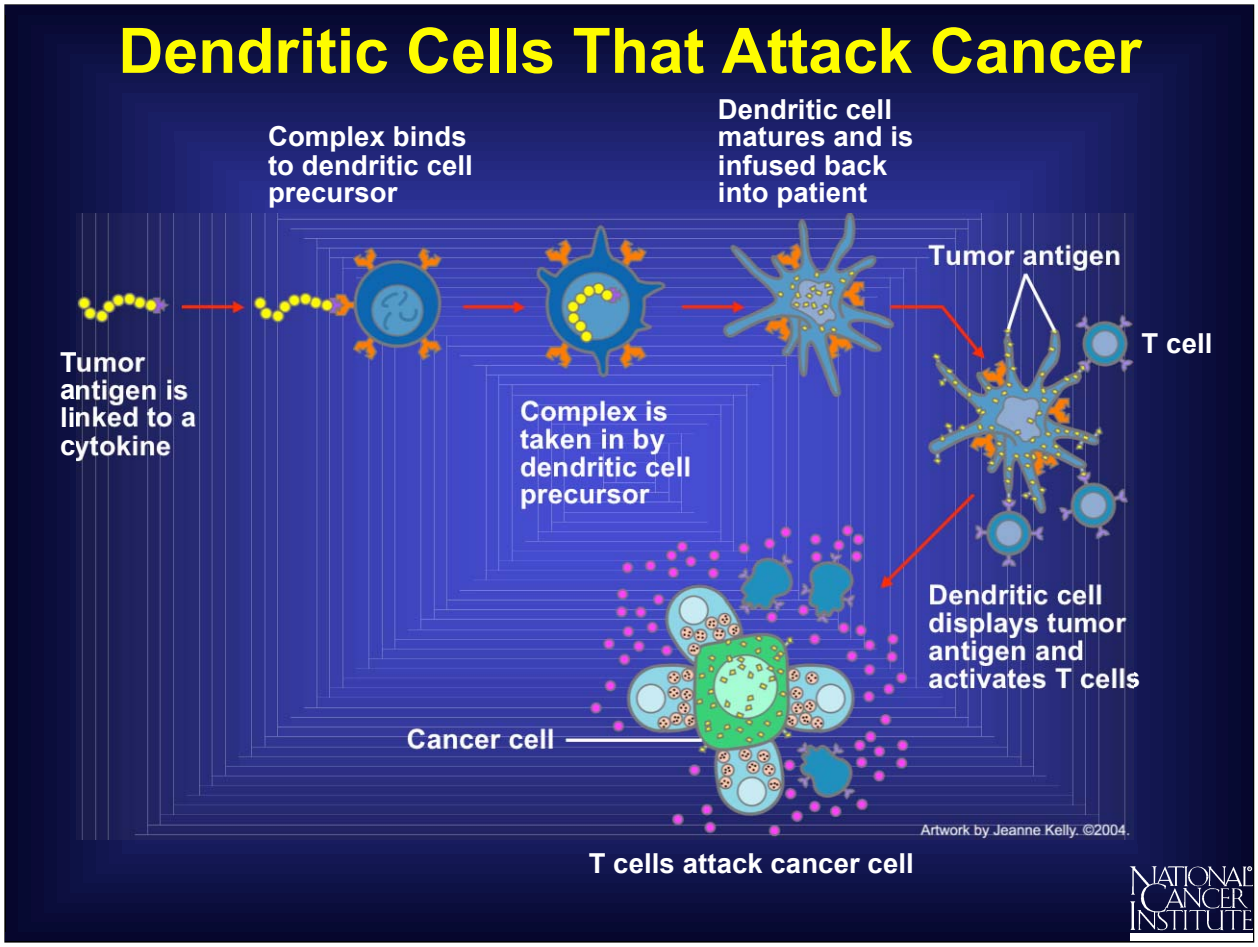
When normal cells turn into cancer cells, some of the antigens on their surface change. These cells, like many body cells, constantly shed bits of protein from their surface into the circulatory system. Often, tumor antigens are among the shed proteins.

These shed antigens prompt action from immune defenders, including cytotoxic T cells, natural killer cells, and macrophages. According to one theory, patrolling cells of the immune system provide continuous bodywide surveillance, catching and eliminating cells that undergo malignant transformation. Tumors develop when this immune surveillance breaks down or is overwhelmed.

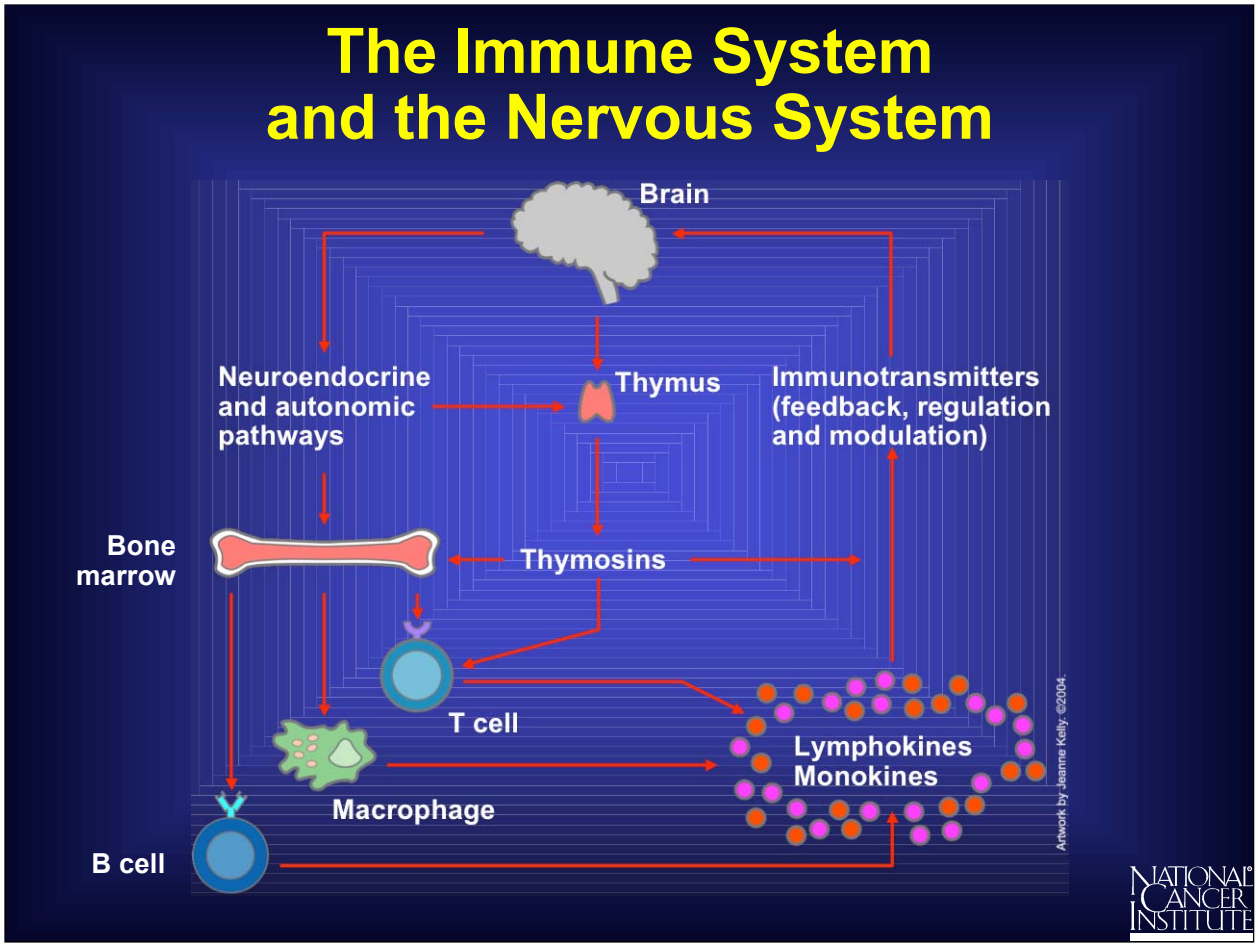


A new approach to cancer therapy uses antibodies that have been specially made to recognize specific cancers.

When coupled with natural toxins, drugs, or radioactive substances, the antibodies seek out their target cancer cells and deliver their lethal load. Alternatively, toxins can be linked to a lymphokine and routed to cells equipped with receptors for the lymphokine.



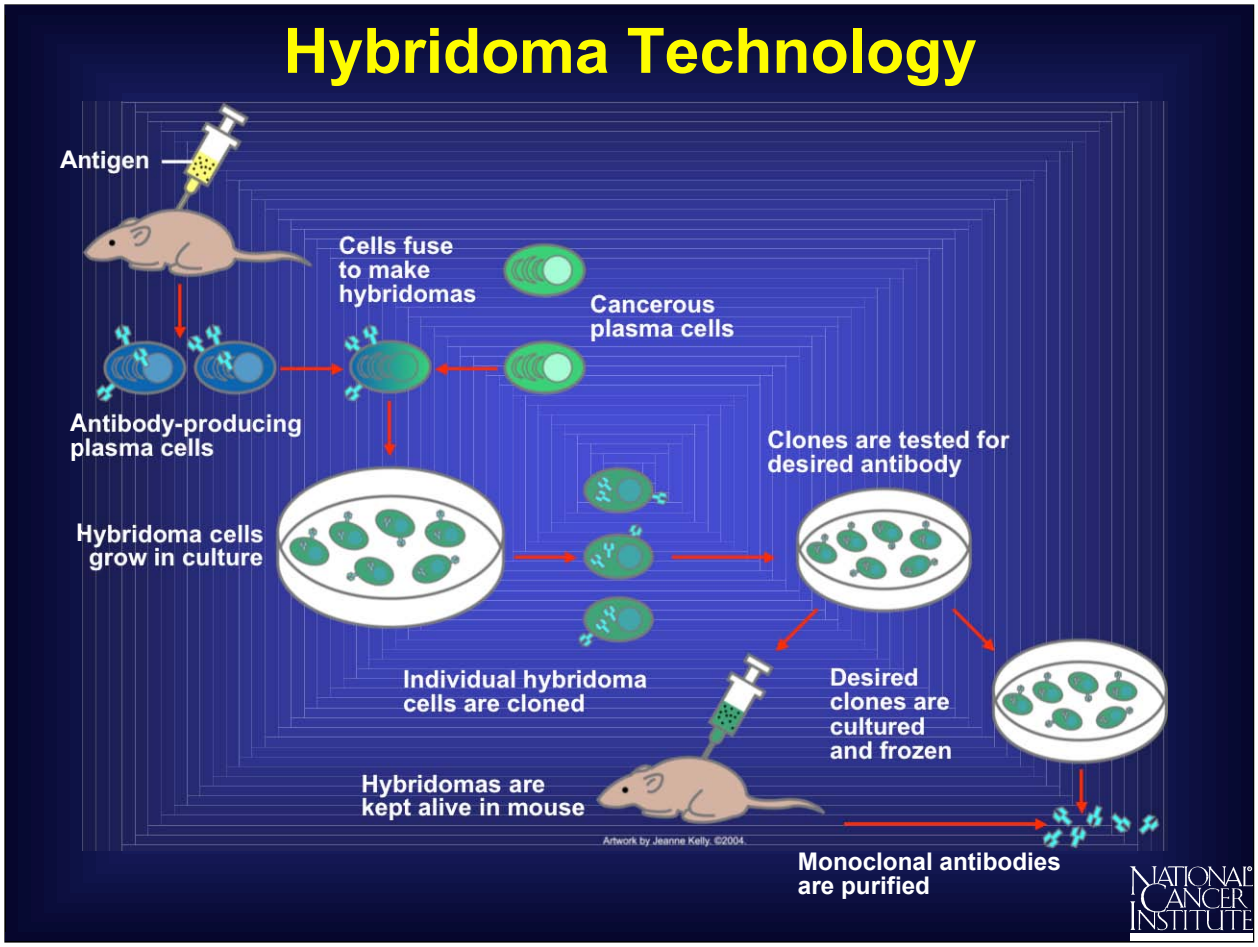
Another approach to cancer therapy takes advantage of the normal role of the dendritic cell as an immune educator. Dendritic cells grab antigens from viruses, bacteria, or other organisms and wave them at T cells to recruit their help in an initial T cell immune response. This works well against foreign cells that enter the body, but cancer cells often evade the self/non-self detection system. By modifying dendritic cells, researchers are able to trigger a special kind of autoimmune response that includes a T cell attack of the cancer cells. Because a cancer antigen alone is not enough to rally the immune troops, scientists first fuse a cytokine to a tumor antigen with the hope that this will send a strong antigenic signal. Next, they grow a patient's dendritic cells in the incubator and let them take up this fused cytokine-tumor antigen. This enables the dendritic cells to mature and eventually display the same tumor antigens as appear on the patient's cancer cells. When these special mature dendritic cells are given back to the patient, they wave their newly acquired tumor antigens at the patient's immune system, and those T cells that can respond mount an attack on the patient's cancer cells.



Biological links between the immune system and the central nervous system exist at several levels.

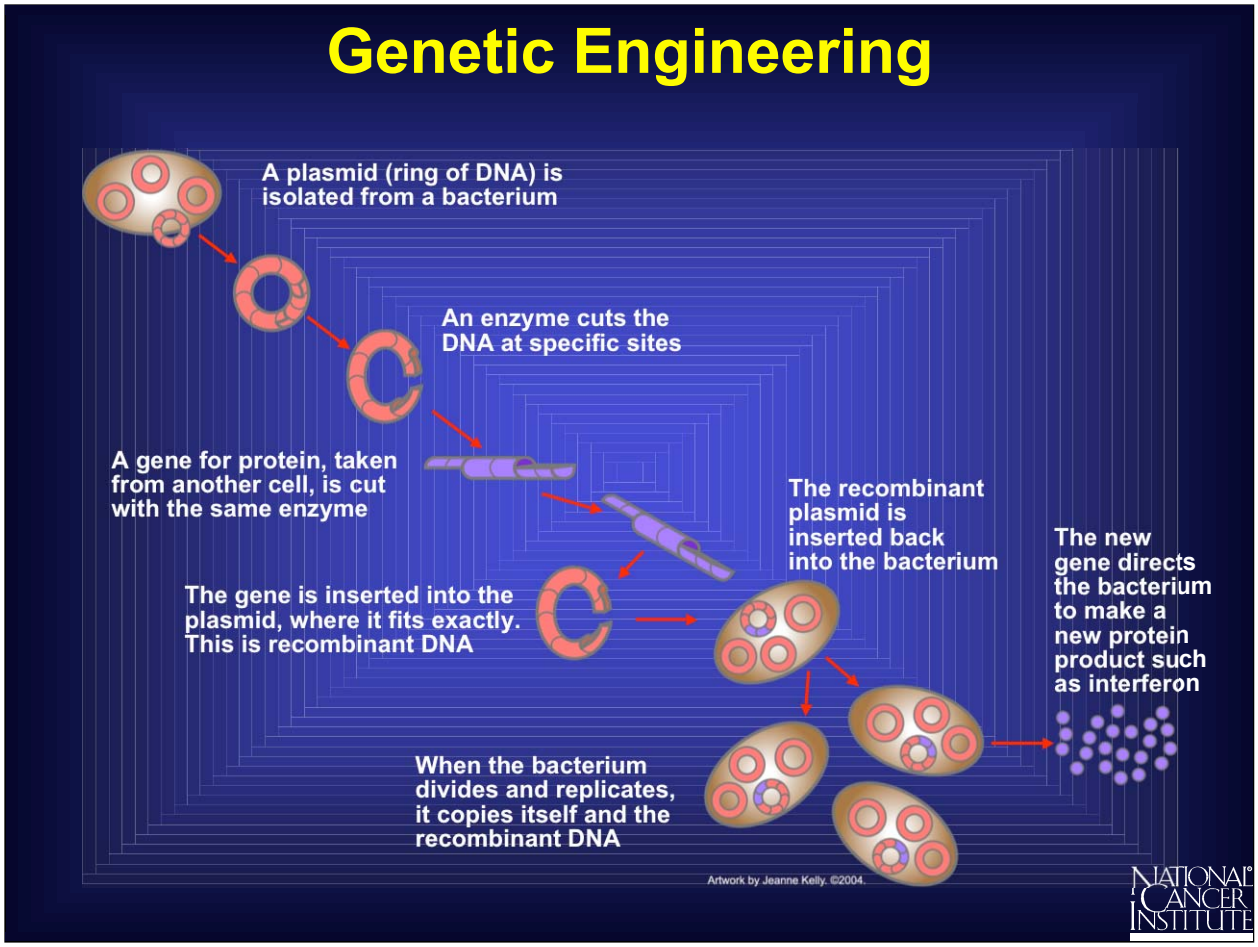
Hormones and other chemicals such as neuropeptides, which convey messages among nerve cells, have been found also to "speak" to cells of the immune system--and some immune cells even manufacture typical neuropeptides. In addition, networks of nerve fibers have been found to connect directly to the lymphoid organs.

The picture that is emerging is of closely interlocked systems facilitating a two-way flow of information. Immune cells, it has been suggested, may function in a sensory capacity, detecting the arrival of foreign invaders and relaying chemical signals to alert the brain. The brain, for its part, may send signals that guide the traffic of cells through the lymphoid organs.



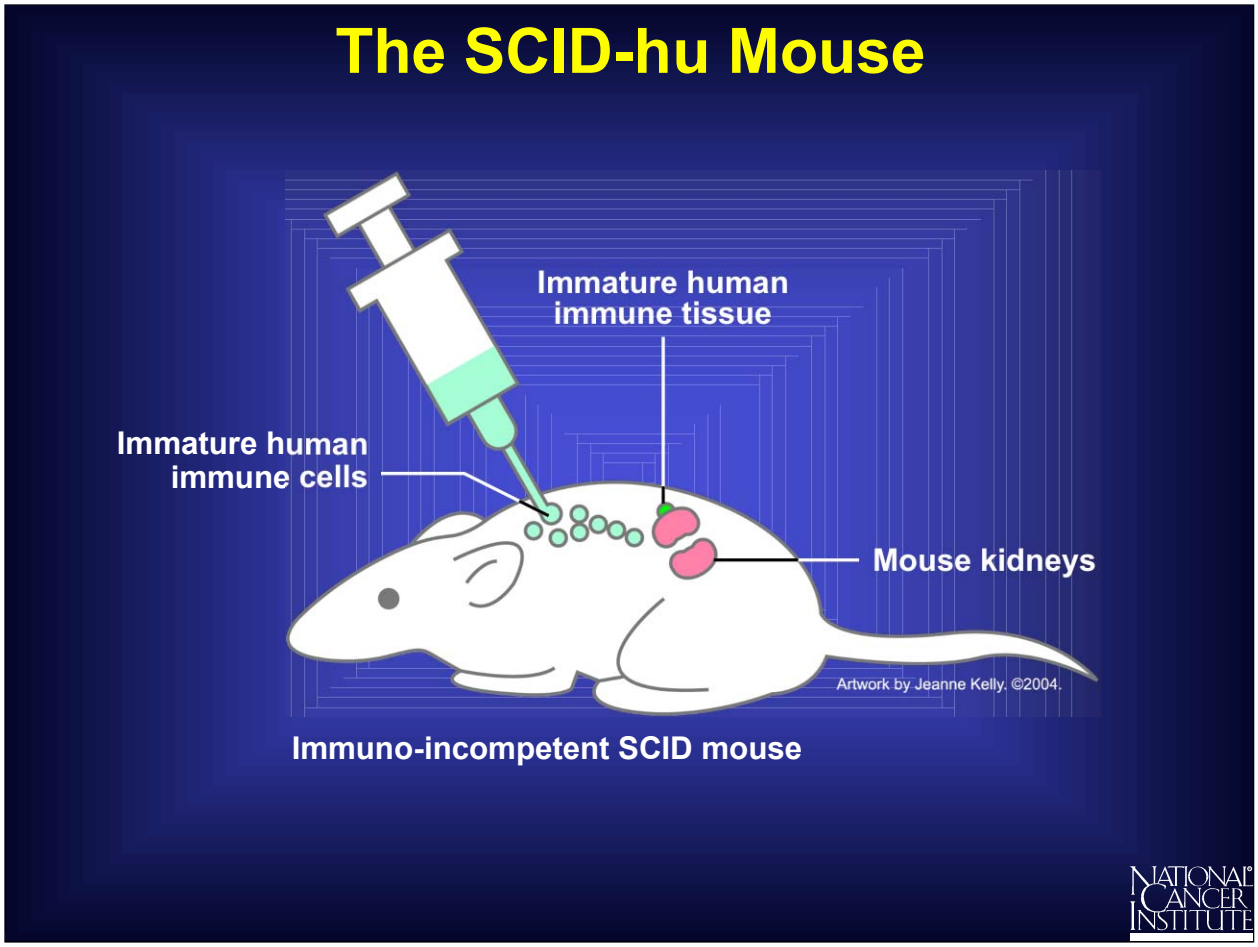
A hybridoma is a hybrid cell produced by injecting a specific antigen into a mouse, collecting an antibody-producing cell from the mouse's spleen, and fusing it with a long-lived cancerous immune cell called a myeloma cell. Individual hybridoma cells are cloned and tested to find those that produce the desired antibody. Their many identical daughter clones will secrete, over a long period of time, millions of identical copies of made-to-order "monoclonal" antibodies.

Thanks to hybridoma technology, scientists are now able to make large quantities of specific antibodies.



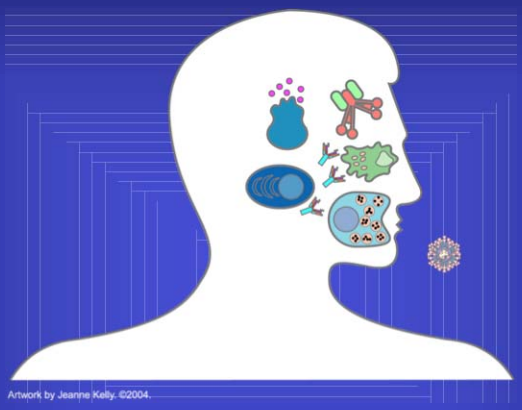
Genetic engineering allows scientists to pluck genes--segments of DNA--from one type of organism and to combine them with genes of a second organism.

In this way, relatively simple organisms such as bacteria or yeast can be induced to make quantities of human proteins, including interferons and interleukins. They can also manufacture proteins from infectious agents, such as the hepatitis virus or the AIDS virus, for use in vaccines.



The severe combined immunodeficiency disease (SCID) mouse, which lacks a functioning immune system of its own, is helpless to fight infection or reject transplanted tissue. Such mice, like patients with SCID, have severe defects in T cell production and function, with defects in B-lymphocytes as a primary or secondary problem and, in some cases, in NK cell production as well.

By transplanting immature human immune tissues and/or immune cells into these mice, scientists have created an in vivo model that promises to be of immense value in advancing our understanding of the immune system.



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