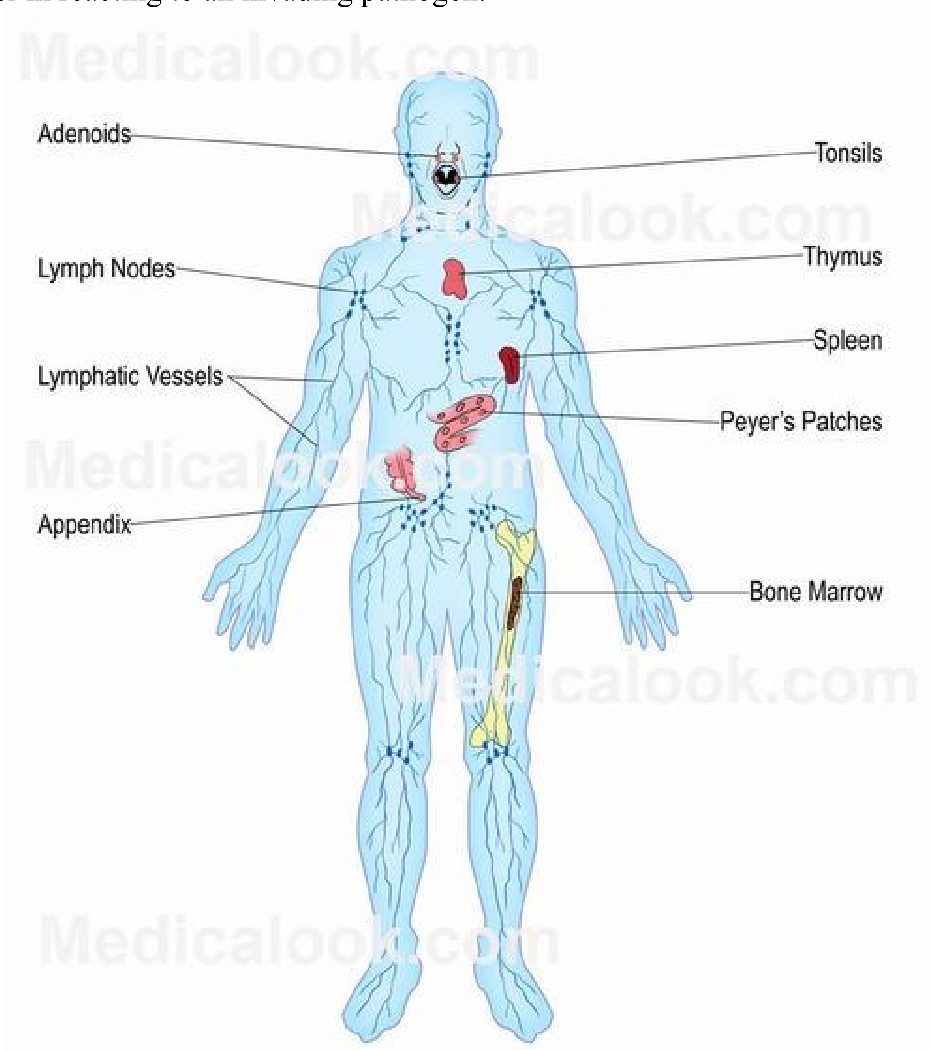
Topic 1. The Anatomy of the Immune System

The immune system consists of a complex network of organs and tissues that work together to prevent infection. Many of these systems are unleashed by activation of other parts of the immune system. The extensive interdependence of the players of the immune system can make it difficult for the beginning student to understand. As we go through the immune system, you will encounter unfamiliar terms, but be patient because they will be explained later in the chapter. To try to make it a bit easier, we will first describe the anatomy of the immune system, then examine the various cell types involved in immunity, and finish this section by describing how these parts work together in reacting to an invading pathogen.



Many different organs and tissues in the body contribute to the function of the immune system. These include the circulatory system, bone marrow, thymus, spleen, lymphatic system and Mucosal Associated Lymphoid Tissue (MALT). Together these tissues are responsible for the creation, transport and successful operation of mammalian immunity. In this section we will look at the role of each tissue and introduce a number of cells and proteins involved in immunity.

The tissues of the immune system fall into two groups based upon their role in host defense. Primary (or central) tissues look after immature immune cells, creating and educating them during their differentiation into mature cells. The bone marrow and thymus gland are parts of the primary immune system. Secondary (peripheral) immune organs look after mature cells that are an active part of defense. The secondary system encompasses the rest of the immune tissues: the spleen, the lymphatic system, lymph nodes and MALT. Of course it is not this simple and the spleen and MALT also help in the maturation of immune cells.

Circulatory system

The **circulatory system** is responsible for the transport of blood throughout the body and consists of the heart (a pump), the lungs (a gas exchanger) and the vascular system of arteries, capillaries and veins (plumbing). Blood, which runs through this vascular system, contains both cellular and non-cellular components. The major cell types found in blood are red blood cells, whose role is to transport oxygen and carbon dioxide into and out of the body respectively. The circulatory system also plays a secondary role as one of the routes immune cells use for transport around the body. Blood contains many types of what are called white blood cells, which are made up of mainly neutrophils, but also monocytes, T-lymphocytes and B-lymphocytes.

The non-cellular portion of the blood is a liquid called **plasma** that contains the protein fibrinogen as a major constituent. Under the right conditions, fibrinogen participates in a complex series of reactions that eventually result in the formation of a fibrin clot in the blood. Platelets also participate in this process. Blood clots are important in stopping bleeding and also in inhibiting the invasion of advancing pathogens by entrapping them. Blood removed from the body will rapidly clot if anticoagulants such as sodium citrate or heparin are not added. If blood is allowed to clot, the liquid left over is **serum**. A major constituent of serum is **immunoglobulins** (antibodies). It also contains various proteins of the **complement** system, which are equally important in the immune system.

Bone marrow

The bone marrow is the source of many immune and blood cells in the healthy adult animal. If the bone is split lengthwise, a marked difference in tissue is noticed. Part of the tissue is red, which is the source of red and white blood cells. The other portion is yellow adipose tissue that is inactive. During an infection, the yellow marrow can be reactivated to become red marrow to help in the production of larger numbers of immune cells.

In the adult animal, all immune cells originate from **stem cells** located in the bone marrow. Stems cells constantly divide and differentiate into various types of immune cells under the influence of **cytokines**. Cytokines are small signaling proteins that help to regulate the behavior of the cells of the body. The bone marrow is ultimately responsible for the synthesis of eight types of cells: red blood cells, platelets, neutrophils, basophils, eosinophils, mast cells, monocytes/macrophages, and T lymphocytes and B lymphocytes. Some of these cell types mature in the bone marrow itself, while others migrate through the circulatory system and undergo final maturation in other tissues. At this point, we will take a short stop and look briefly at some of the features of the cells created in the bone marrow as an introduction to their function. You will learn more details about each immune cell type later when we cover specific immune responses.

Cells made in the bone marrow

The major cell type made by the bone marrow is red blood cells. Platelets also form in the bone marrow and assist in formation of blood clots following any kind of injury. Neither of these cell types plays a role in the immune response, but we mention them here because they also originate from bone marrow stem cells and are essential components of the blood.

Polymorphonuclear cells or **granulocytes** is the general term given to **neutrophils**, **eosinophils** and **basophils**. The first half of the name describes the appearance of the nucleus that seems to be split into a number of different lobes. In reality, the nucleus is contiguous, but contains many infoldings, which give it a polynuclear appearance. The rest of the name comes from the appearance of the cytoplasm, which looks speckled. The cytoplasm is full of granules that contain compounds and enzymes important in fulfilling the function of each cell type. Polymorphonuclear granulocytes make up 50-70% of the white blood cells found in blood. They last only about three days and have to be replaced at a rate of 80 million cells per minute.

Neutrophils are the most common type of polymorphonuclear cells, making up 90% of granulocytes in the blood. These cells function as phagocytes in attacking and destroying infectious agents. We will cover their roles in more detail when we discuss phagocytes.

Eosinophils make up 2-5% of granulocytes in the blood, but this number can rise considerably in people with parasitic diseases as well as asthma, eczema or other diseases associated with allergies. They are primarily found in the blood, but also near epithelia that have high bacterial populations (e.g., intestines, vagina, nasal passages). The granules in these cells bind the red dye eosin, giving the cells their name. Eosinophil granules contain a number of different enzymes including, acid phosphatase, glucuronidase, cathepsins, ribonuclease, and arylsulfatase and peroxidase. They also produce toxic basic proteins. They respond to the chemical signals put out by other immune cells and can then participate in an immune response. The major reactions take three forms.

- They can down-regulate an immune response by destroying histamine secreted by mast cells using the enzyme histinase. Eosinophils also liberate arylsulphatase that breaks down the slow reactive substance of anaphylaxis (a dangerous form of allergic response) that is released by mast cells.
- Eosinophils combat antigenic challenges too big to be attacked by phagocytes. Examples of such challenges are parasitic worms or helminths. In battling these infections, the body will first cover the worm with antibody. This then activates eosinophils, which bind to the parasite and release the contents of their granules, thus causing external digestion of the worm.
- As is the case with neutrophils, eosinophils can phagocytize microorganisms, but this is a secondary role.

Basophils are small cells that make up less than 1% of all white blood cells. The granules of these cells contain heparin, histamine, decarboxylase, histidine, dehydrogenase and diaphorase. Heparin is an important anti-clotting compound, and histamine finds its use modulating the immune response. Histidine is converted to histamine by decarboxylase. The role of basophils in the immune response is not yet clear, but they seem to play a role in the defense against parasitic worms and in severe allergic reactions. They have a very high affinity for IgE antibodies : they are usually found coated with IgE in tissues. Binding of IgE may set in motion a series of events that causes other immune cells to respond to the high concentrations of IgE. Basophils may be cellular alarms that notify the rest of the immune system and help to concentrate the point of attack.

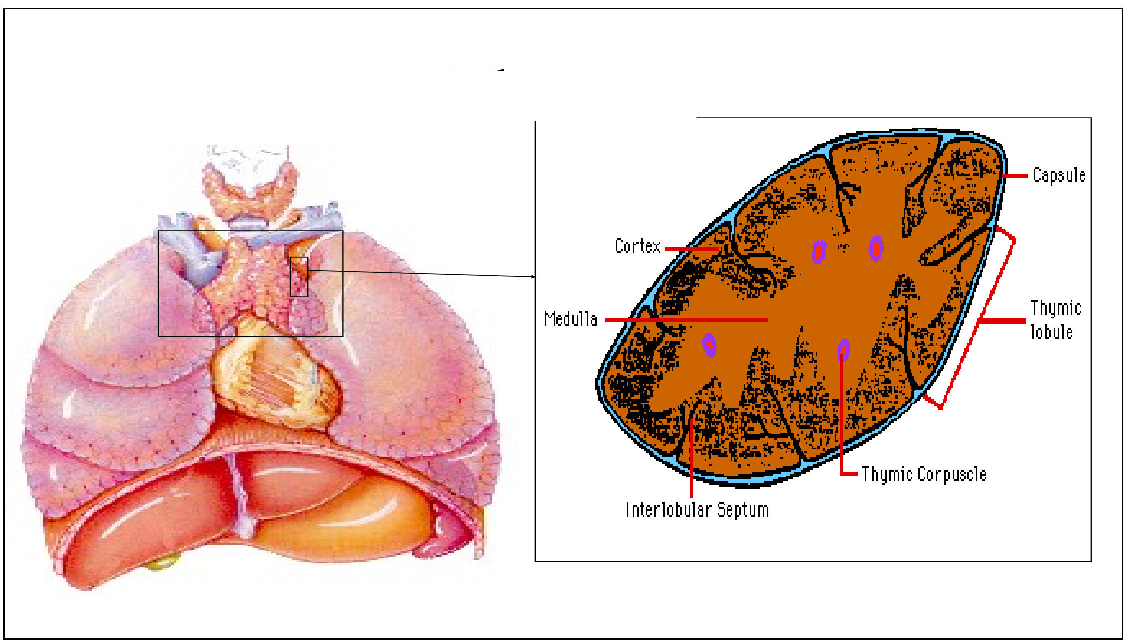
Mast cells are closely related to basophils but are distinct in their reactions to antigens. They are found throughout the body in lymph nodes, spleen, bone marrow, around blood vessels, nerves, glands and in the skin. Mast cells have granules that, like basophils, contain heparin and histamine. They have a high affinity for IgE as well and their activation by antigen triggers histamine release. Until recently, they were mostly thought to trigger unwanted allergic reactions, but it is now becoming clear they participate in immune responses to gram-negative bacteria. Their wide distribution indicates that they are important in many immune responses.

Monocytes and **macrophages** are long-lived specialized phagocytic cells. Monocytes are migrating phagocytic cells found in the bloodstream and when they enter other tissues, they differentiate into macrophages. Macrophages are found in the brain, lungs, liver, spleen, lymph nodes, joints and peritoneum. The key functions of monocytes and macrophages are to remove our own dead cells when they reach the end of their useful life and also to remove pathogens. For example macrophages in the liver, called Kupffer cells, phagocytize old erythrocytes from the blood and remove them. Another one of their functions is the creation of important immune proteins and peptides. They are responsible for synthesizing transferrin (an iron-binding protein), complement proteins and various cytokines necessary for immune function.

B lymphocytes or B cells are antibody-producing cells. They are very important in fighting many different types of infections, especially, bacterial infections. **T lymphocytes** are involved in regulating the immune system and destroying host cells that are out of control, either due to a breakdown in cell division regulation (cancer) or infection by a virus or even an intracellular parasite. We will discuss the functions of these cells in more detail when we cover the adaptive host response.

The thymus

The **thymus** is a fist-sized organ located above the heart that is involved in the maturation of **T**



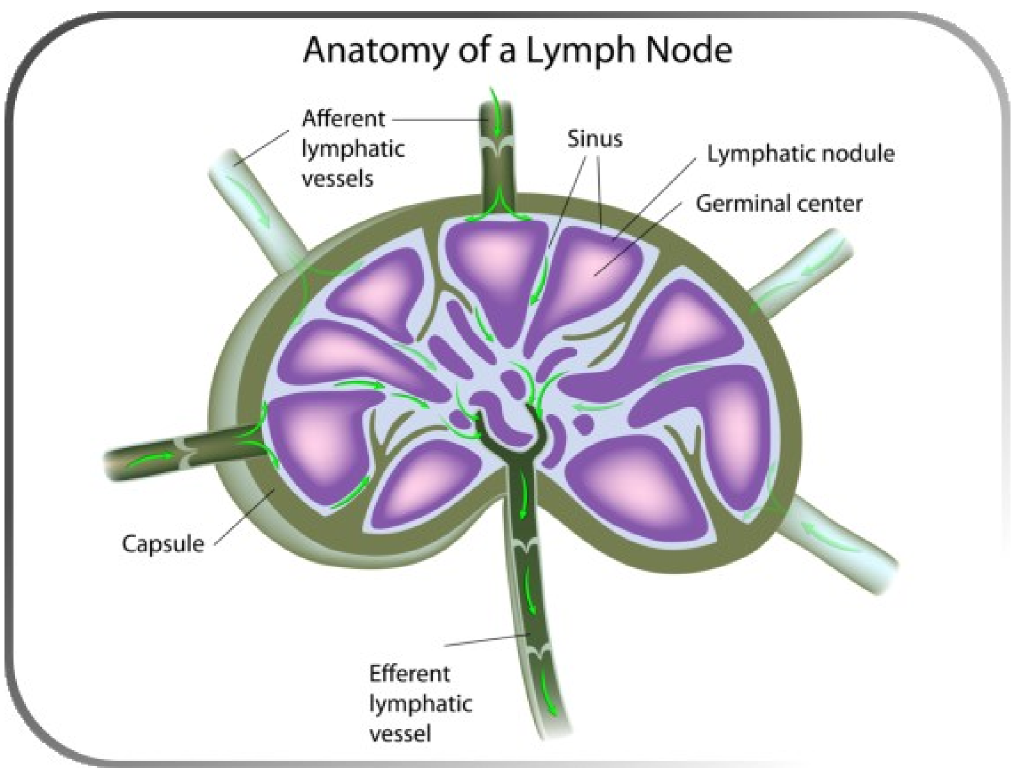
lymphocytes (we will call them T cells from now on). T cells produced by the bone marrow are immature and journey to the thymus through the bloodstream. The blood vessels that supply the thymus with oxygen and other nutrients also contain a blood-thymus barrier that only allows immature T cells in and mature T cells out. The thymus is also connected to the lymphatic system through lymph vessels. We will talk more about thymus function when examining T cell maturation later in the chapter.

Lymphoid tissue

The **lymphatic system** is a separate vascular system, distinct from the bloodstream, through which the lymph moves. It is a branching system whose vessels get ever smaller as it penetrates tissue. Unlike the blood system, the lymphatic system is not circular, but ends in blind capillaries. The system focuses its attention on areas of the body that are most likely to be entry points for pathogens: skin dermis, respiratory tract, gastrointestinal tract and genitourinary tract. It functions are

- To collect excess fluid from surrounding tissue and return it to the bloodstream
- To absorb fat from the villi of the small intestine.
- To Participate in the immune response.

Here we will focus on its major role -- harboring and transporting many of the cells involved in the immune system. Lymph fluid consists of leukocytes and many components of plasma, but does not contain red blood cells. Liquid enters the lymph system from non-vascular tissue draining into lymph capillaries. The capillaries then drain into **lymph nodes** that sit at the junction of a number of lymph vessels.



Lymph nodes are found throughout the body and are major centers for immune function. The smallest lymph nodes are about the diameter of the tip of a pen while the largest are the size of an almond. Large volumes of liquid and cells pass through lymph nodes each day and are filtered to detect antigens and remove microbes. The nodes also interact with phagocytes to begin various immune functions that we will elucidate later. Lymph nodes are dynamic, densely packed structures with the bulk of the cells inside them being mobile. Phagocytes and antigens enter through as many as five vessels, called afferent ducts. The lymph node contains large numbers of B- and T-lymphocytes, but macrophages and plasma cells are also present. Macrophages carry out the job of filtering the incoming fluid and plasma cells (effector cells that differentiate from antigen-stimulated B cells) secrete antibodies that exit along with other immune cells by the single exit, the efferent duct. The lymphatic system then mergers into larger vessels and eventually reconnects to the circulatory system through ducts near the heart. The flow of liquid is therefore from the lymphoid capillaries, into lymph vessels, then lymph arteries and eventually exiting into the bloodstream at the heart. There are actually two lymphatic drainage systems. The right lymphatic duct drains the upper right side of the body, including the right side of the head, the heart and lungs. The rest of the body drains into the thoracic duct. Both of these systems connect back to the bloodstream near the heart. Liquid entering the lymphatic system from the blood and extravascular tissue will filter through typically eight to ten nodes before returning to the bloodstream.

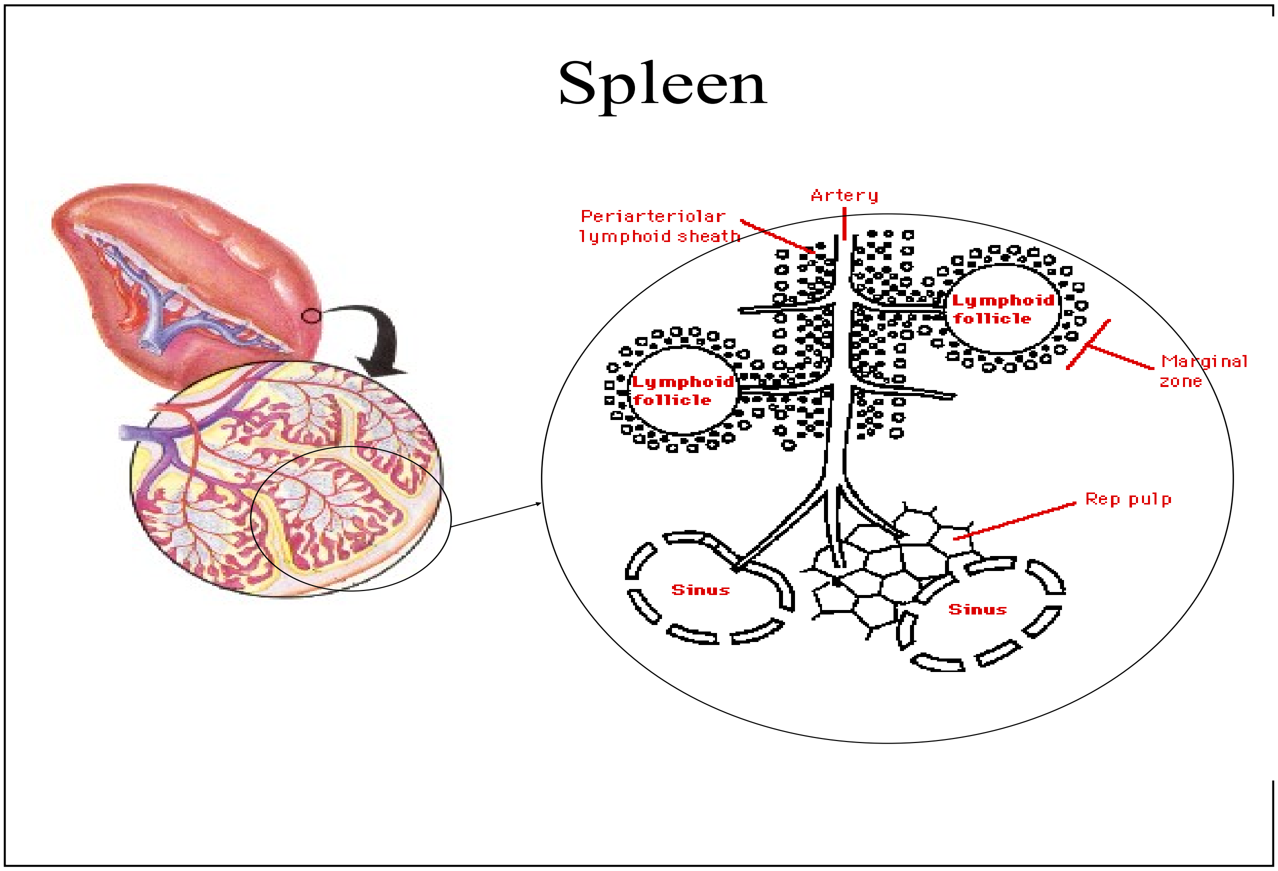
MALT

Mucosal-associated lymphoid tissue (MALT) is scattered throughout the connective tissues of the body, but especially beneath moist epithelial membranes such as those that line the upper respiratory tract, intestine and urinary tract. MALT is strategically distributed to help the body prevent infection by organisms that have penetrated beyond the mucosal surface. MALT consists of small masses of lymphatic tissue (up to a millimeter in diameter) containing mainly lymphocytes. These tissues are far less organized than the lymph nodes. Most MALT consists of small groups of cells, but in certain areas it is found in large clusters. For example, large aggregates of MALT occur in the wall of the lower portion (ileum) of the small intestine and are known as Peyer's patches. Tonsils and adenoids are also aggregates of MALT that protect your body from microorganisms present in the upper respiratory tract. Unlike lymph nodes, MALT is not connected to a vascular system.

The spleen

The **spleen** is a very important secondary lymphoid organ. Individuals that have had their spleens removed due to rupture caused by a car accident or atrophy from sickle cell anemia, can lead nearly normal lives, but they tend to be more susceptible to infection. Some functions of the spleen are similar to those of the lymph nodes, however, it also produces lymphocytes and removes senescent (old) red blood cells from the circulation.

The spleen is highly organized and is a repository for immune cells. It plays an important role in response to pathogens. The spleen contains a circulatory and lymphatic system allowing access to it either through the blood or lymph. Cells in the spleen organize around the blood vessels into two tissues: red pulp and white pulp. Red pulp contains mainly red blood cells, and white pulp is made up predominantly of lymphocytes. The white pulp focuses tightly around the arterioles of the spleen white pulp further differentiates it. T cells are found near the arterioles and further away are areas of B cells. The spleen is a major area for B cells to congregate in the body, where they wait to be activated by antigens. During an illness, activated lymphocytes will be released from the spleen to fight the infection.



while the red pulp fills the rest of the interstitial space. The location of various lymphocytes in the

This completes our tour of the anatc ıe system. In the next section we will more specifically examine how cells and compounds in these tissues recognize and attack invading pathogens.

The two parts of the immune system: innate and adaptive immune systems

Host defenses can be divided into two categories. **Innate immunity** involves general mechanisms in a healthy animal that prevent colonization by microorganisms and antagonize or kill those that do enter the host. They are always present and the strength of their response does not increase with repeated exposure to the inducing microbe. **Adaptive immunity** develops through the mechanisms that are turned on in response to a pathogen. This involves activation of the immune system, where the initial response to a pathogen is weak but becomes quite vigorous over a period of a few days. Adaptive defenses also have a memory of encountered pathogens such that a second infection by a pathogen is met with a more rapid and vigorous immune response.