

**A Primer on Immunology**  
**The Galaxy Within, and Its Constellations**  
**in Health and Disease**

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# Immune Reaction



*Body's response to injury or infection*—“army” of different cells, circulating in the blood, as well as resident in the injured or infected tissue, move in to:

- fight germs,
- clear debris and repair damage.

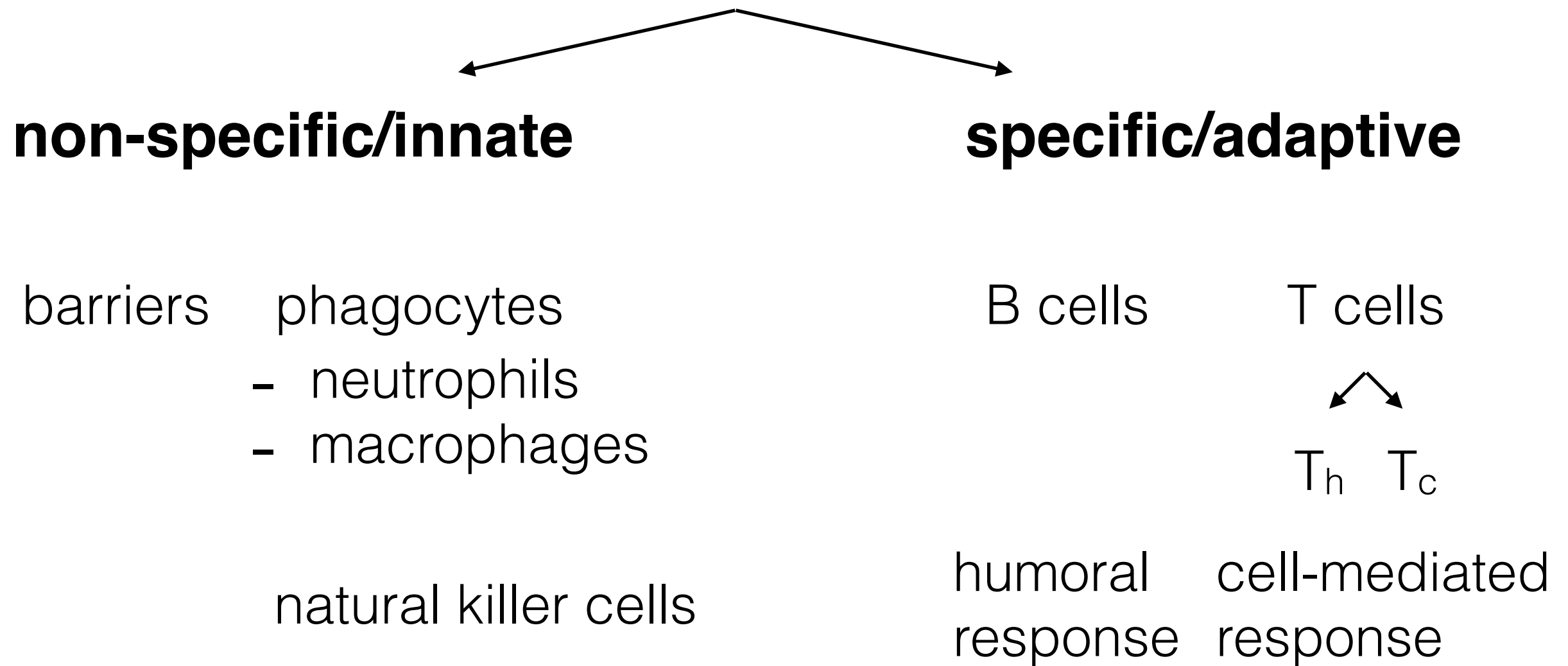
# Immune Reaction



*Body's response to injury or infection.*

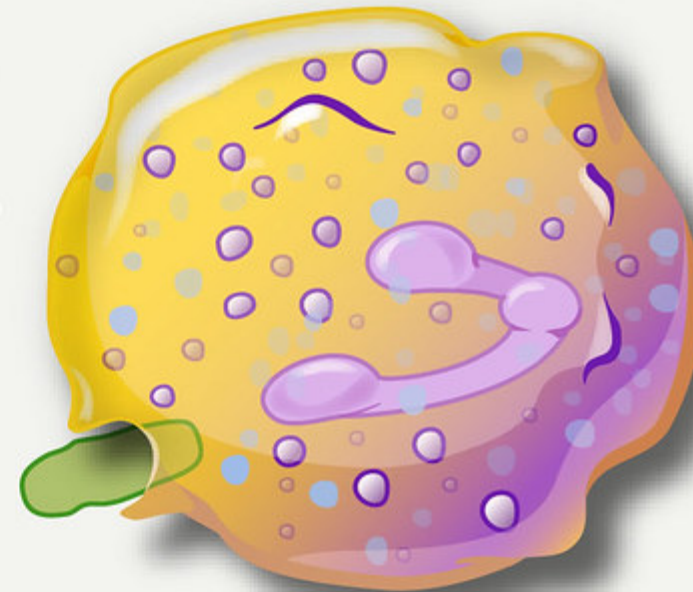
Majority of illnesses are cured by the body's natural defenses.

# Immune System



# Neutrophil

White Blood Cell



**Function:** Neutrophils engulf and destroy bacteria and other pathogens.

They are the most abundant type of white blood cell in most people's bloodstreams and play a large role in fighting many types of infection.

**Disease:** Because of genetic anomalies, some people are born with too few neutrophils, a condition known as neutropenia, or with neutrophils that do not function properly. This causes people to be more prone to infections.

**Location:** Neutrophils circulate in the blood and quickly move to sites of infection or injury to fight off pathogens.



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# Macrophage

White Blood Cell



**Function:** Also known as “big eater” cells, macrophages ingest pathogens, cancer cells and microscopic debris, which are then destroyed, degraded and recycled with harsh chemicals and enzymes.

**Disease:** Unfortunately, macrophages sometimes fail to destroy ingested pathogens, which then may replicate inside the macrophage and hide from other immune responses. Macrophages also play a large roll in controlling inflammation and their malfunction can impact inflammatory diseases.

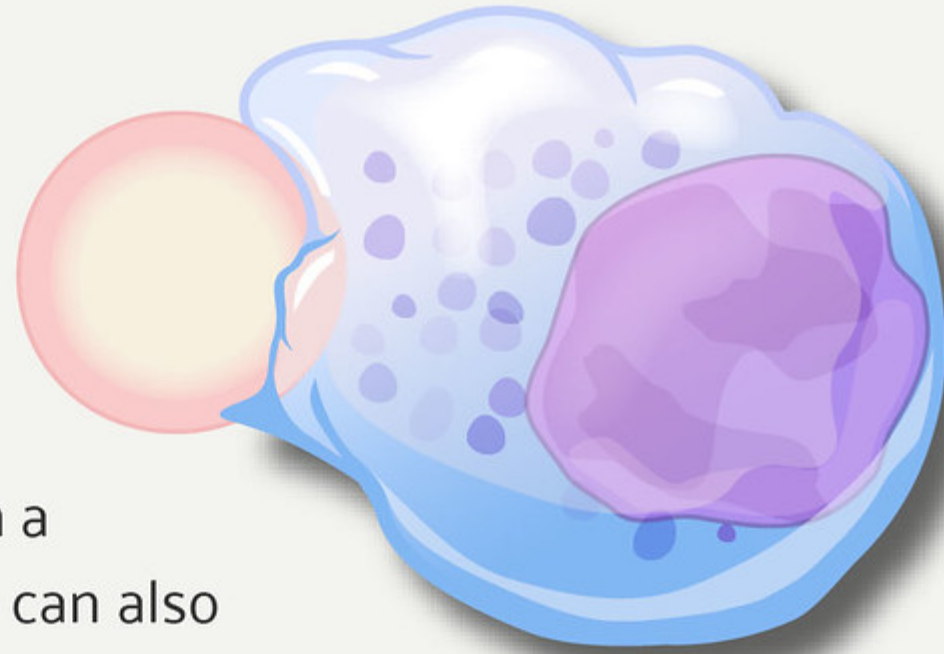
**Location:** Macrophages develop in the bone marrow as “monocytes,” which circulate in the blood stream and then settle down in other body tissues. Macrophages are given different names depending on the type of tissue they are found in. For example, they are called microglia in the central nervous system and osteoclasts in bone.



# Natural Killer Cell

White Blood Cell

**Function:** These immune cells can recognize and kill the cells of someone's body that have been infected with a pathogen. Natural killer cells can also recognize and destroy tumor cells.



**Disease:** People who have deficient natural killer cells, usually because of an inherited immune disorder, may be more prone to certain viruses.

**Location:** Natural killer cells, or NK cells, are present in the blood and can move into other tissues to find targets.



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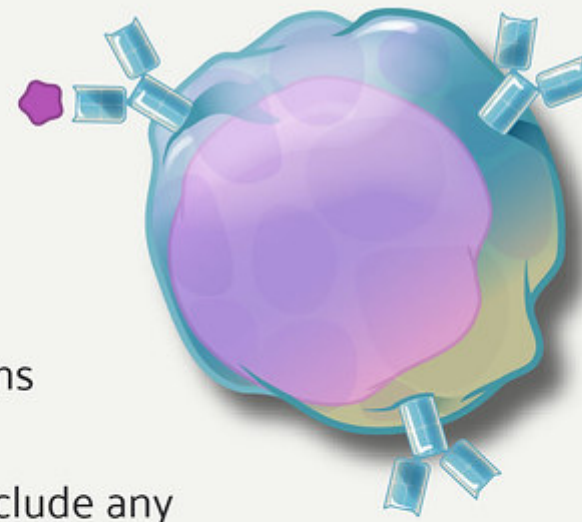
# B Cell

White Blood Cell

**Function:** B cells produce proteins called antibodies that bind very selectively to antigens, which include any substance that prompts an immune response, including part of a pathogen. Antibodies fight infections by blocking the ability of pathogens to enter host cells and by flagging the pathogen for destruction. Each B cell makes a unique antibody, and all the body's B cells together make a collection of antibodies that can bind to many different targets.

**Disease:** Because of the vital role B cells and antibodies play in the immune system, the absence of B cells in inherited diseases like severe combined immunodeficiency, or SCID, can leave individuals extremely vulnerable to infection. B cells also play a role in allergies when they produce antibodies to substances that the body should not reject, such as peanut proteins or tree pollen.

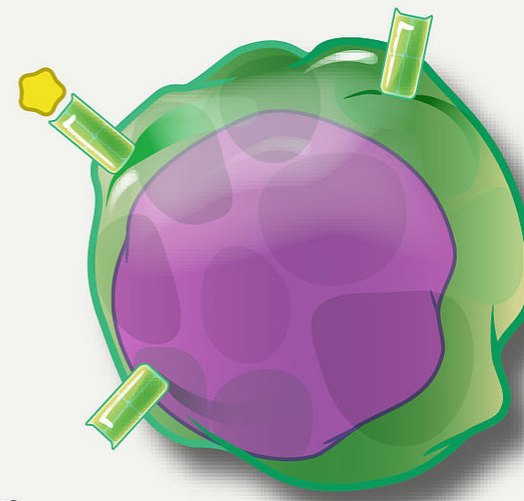
**Location:** B cells originate in bone marrow and circulate in the blood, but spend most of their life cycle in the lymphatic system. As a result, they are also called B lymphocytes.





# T Cell

White Blood Cell



**Function:** T cells recognize antigens—substances that prompt an immune response—that the body has encountered before. However, unlike another immune cell called a B cell, T cells do not make antibodies, or proteins that correspond to specific antigens and help fight infection. Instead, some T cells help B cells make antibodies and others directly kill an infected cell or a cancerous cell. T cells also help prevent the immune response from attacking normal host cells inappropriately.

**Disease:** A person with an insufficient number of T cells, such as a person who has developed AIDS from an uncontrolled HIV infection, may be more prone to infections and certain cancers.

**Location:** T cells originate in the bone marrow and become specialized in the thymus, a small organ just under the breastplate. They then recirculate between the bloodstream and the lymphatic system and also patrol the tissues. T cells are also called T lymphocytes.

# Immune System



Until 1989, most immunology research focused on how the immune system is able to respond to germs *faster and more efficiently* the second time around.

At the heart of this process are B cells and T cells.

## **specific/adaptive**

B cells

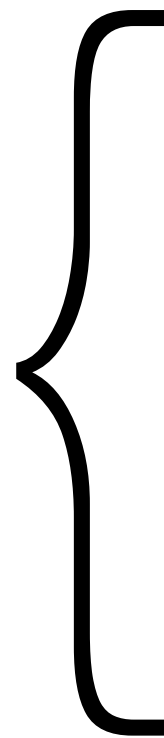
T cells



T<sub>h</sub> T<sub>c</sub>

humoral  
response

cell-mediated  
response



# Immune Memory



B and T cells have receptor molecules (proteins), each with slightly different shape (through shuffling of genes).

The B or T cell receptor reaches out from the cell surface, and if it connects with *something foreign to the body*, it ‘switches on’ the immune cell.

Switched on B and T cells kill the germ or diseased cell directly, or summon other immune cells to help.

# Immune Memory



Activated B and T cells multiply, populating the body with more cells that have the same usefully shaped receptors.

Some of these cells stay in the body for a long time, which is what gives the immune cells a *memory for germs that have been encountered before*.

This is at the heart of how vaccinations work.



# Distinguishing Self From Non-Self



B and T cell receptors are not made to bind to germs per se; they have *randomly* shaped ends which allows them to lock onto all kinds of molecules.

B and T cell receptors are acquired while cells develop in the bone marrow.

A wonder of immune system: each B and T cell is tested before entering the bloodstream in case its receptor can bind to healthy body cells. If yes, the cell is killed off.

# Receptors That Specifically Interlock With Germs



Simple view: our immune system is programmed to fight whatever is not part of us. *This cannot be the whole story ...*

For example, food isn't part of our bodies, yet the immune system should not react to everything we eat. And our immune system must be able to tell the difference between beneficial gut bacteria and dangerous bacteria that cause disease.

# Receptors That Specifically Interlock With Germs

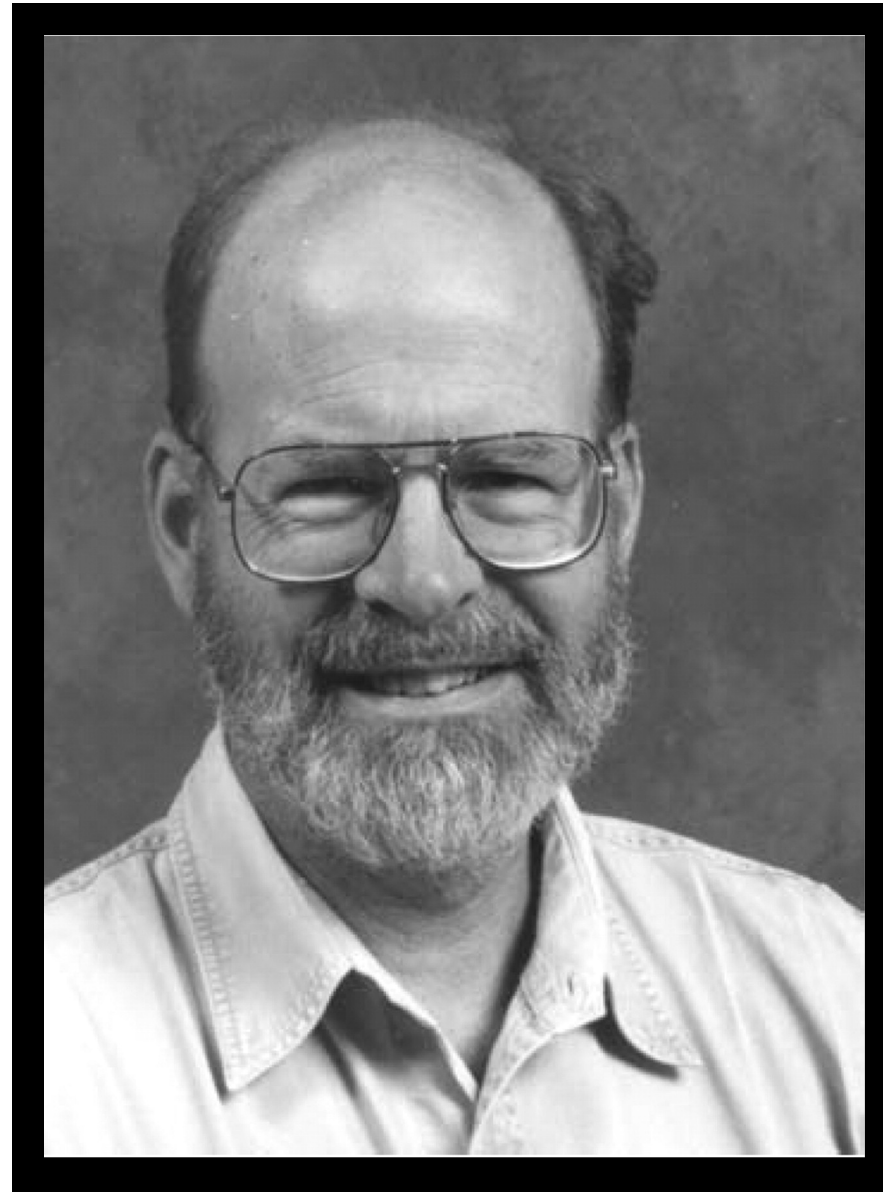


**Distinguishing between self and non-self is not enough:** the immune system has to be able to tell if something is likely to be a threat to the body before an immune reaction takes place.

***How does an immune reaction start?***

**Charles Janeway (1989):** There had to be a whole mechanism in our immune system, yet to be identified, that enables it to detect specific signs of germs or infected cells.

# Receptors That Specifically Interlock With Germs



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**Approaching the asymptote? Evolution and revolution in immunology.**

*Janeway CA Jr.*

*Cold Spring Harb Symp Quant Biol.* 1989;54 Pt 1:1-13.



# Receptors That Specifically Interlock With Germs



Janeway predicted that there must be receptors, which he called *pattern-recognition receptors (PRRs)*, that *are not randomly generated* and then selected, but rather *have fixed shapes that lock specifically onto molecular patterns found on germs or infected cells.*

Problem with this idea: when germs reproduce, they acquire random changes in their genes. Some germs will randomly acquire genetic changes which alter the part of the germs the PRRs was designed to lock onto.

# Receptors That Specifically Interlock With Germs



To overcome this problem, Janeway predicted that *“the pattern recognized should be the product of a complex and critical process in the microorganism.”*

That is, the specific pattern of a germ would have to be something so critical to its lifecycle that the germ would not survive without it.

Janeway had the foresight to hypothesize a fundamental mechanism of how the immune system works, even though, as he himself put it, *“experimental verification is not available.”*



# The Search for Genes Encoding PRRs

In mid-1960s biologist Pierre Joly noted that insects are also under threat from germs, like bacteria and fungi, yet never seem to suffer from infection. They also do not reject transplanted organs!

*Insects must have some type of potent immune defense.*

Jules Hoffman (1978): Which genes control the fruit fly's immune response?

# The Search for Genes Encoding PRRs



The fruit fly's genetic makeup was being investigated at the time by other researchers.

One clue: a fruit fly gene called *TOLL* (important for embryonic development of the fruit fly) turned out to be similar to a human gene (*IL-1R*) known to play a role in immunity.

Bruno Lemaitre (1993-5): discovered that fruit flies were dependent on the *TOLL* gene to be able to clear fungal infection.





# The Search for Genes Encoding PRRs

## Fungal Infection in *TOLL*-Mutant *Drosophila*



**The dorsoventral regulatory gene cassette *spätzle/Toll/cactus* controls the potent antifungal response in *Drosophila*.**

*Lemaitre B, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA.  
Cell. 1996 Sep 20;86(6):973-83.*



# The Search for Genes Encoding PRRs

## Toll-like Receptor (*TLR*) Genes

Other research teams discovered covered more toll-like receptor (*TLR*) genes. They each encode for a receptor protein similar to the fruit fly/*drosophila* *TOLL* gene.

There are ten in humans, the first of which was discovered in Janeway's lab after Lemaitre's discovery. It was later given the name *TLR4*.

Yet, while it was clear that *TLR* genes were important for immunity, it was not clear how they worked.



# The Search for Genes Encoding PRRs

## **Toll-like Receptor (*TLR*) Genes**

Lipopolysaccharide (LPS), a large molecule found in the outer coating of bacteria, induces systemic inflammation in mice.

Bruce Beutler (1993): *which gene is crucial for an immune reaction to occur in mice that have been exposed to LPS?*

The gene involved would give a big clue as to how LPS is sensed by the immune system.



# The Search for Genes Encoding PRRs

## Toll-like Receptor (*TLR*) Genes

In 1998, Beutler discovered that the crucial gene for detecting LPS in mice was very similar to the human gene *TLR4*, discovered by Janeway's team.

*TLR4* encodes for a pattern-recognition receptor, the very type of receptor that Janeway predicted in 1989.

PRRs receptors are now known to be expressed on the surface of cells of the innate immune system.



# 2011 Nobel Prize in Physiology or Medicine



Janeway died in 2003 from lymphoma, aged sixty.

Bruce Beutler, Jules Hoffman were award the 2011 Nobel Prize for *“their discoveries concerning the activation of innate immunity.”*

They shared the prize with Ralph Steinman for *“his discovery of the dendritic cell and its role in adaptive immunity.”*



## **Renaissance of Research in Innate Immunity**

Innate immunity is more than a non-specific defense.

Multitude of PRRs are positioned differently in the body, each able to detect a specific type of germ and switch on an immune response appropriate to the particular threat.

Infections that resolve within 2-3 days are usually dealt with through the innate immune response. It is estimated that about 95% of our defenses against germs are attributable to innate immunity.

# Janeway's Legacy

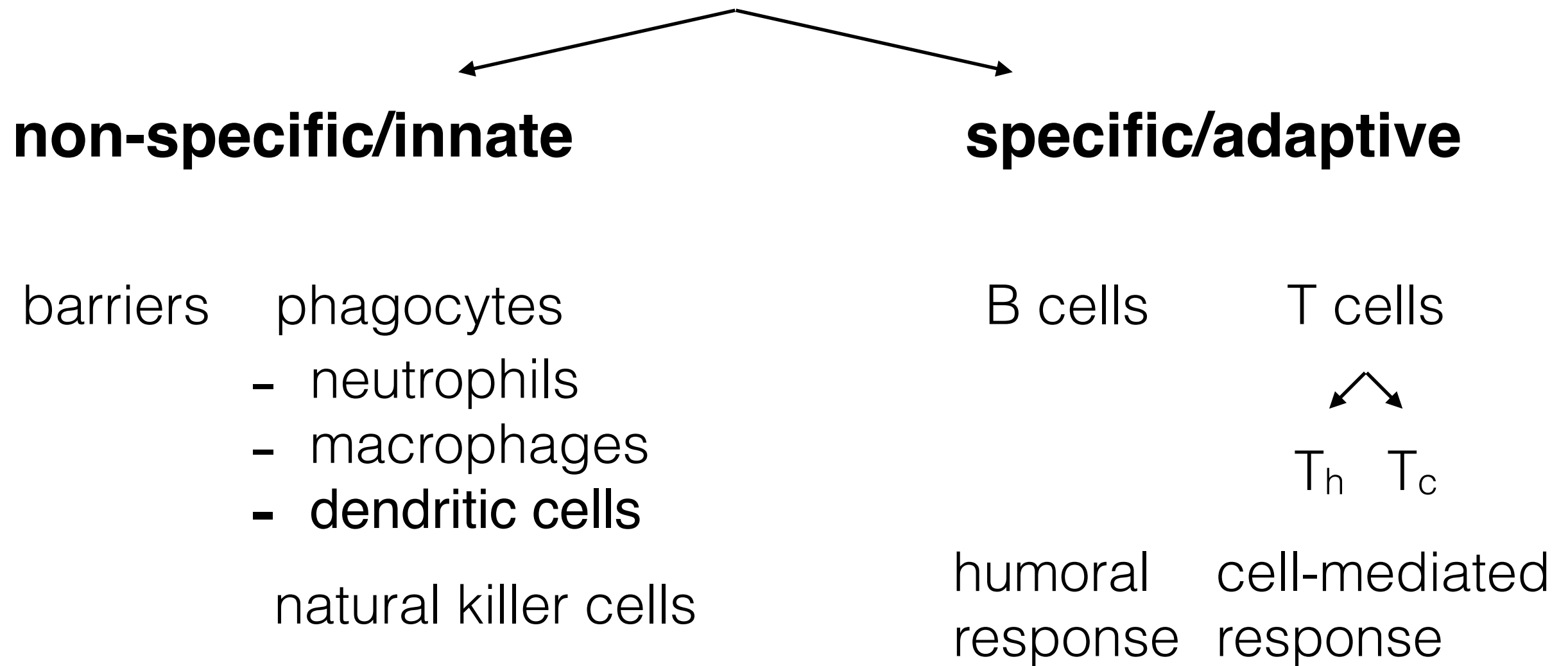


Janeway's service was themed by the recited words of Robert Frost, beloved by Janeway:

My long two-pointed ladder's sticking through a tree  
Toward heaven still,  
And there's a barrel that I didn't fill  
Beside it, and there may be two or three  
Apples I didn't pick upon some bough.  
But I am done with apple-picking now.

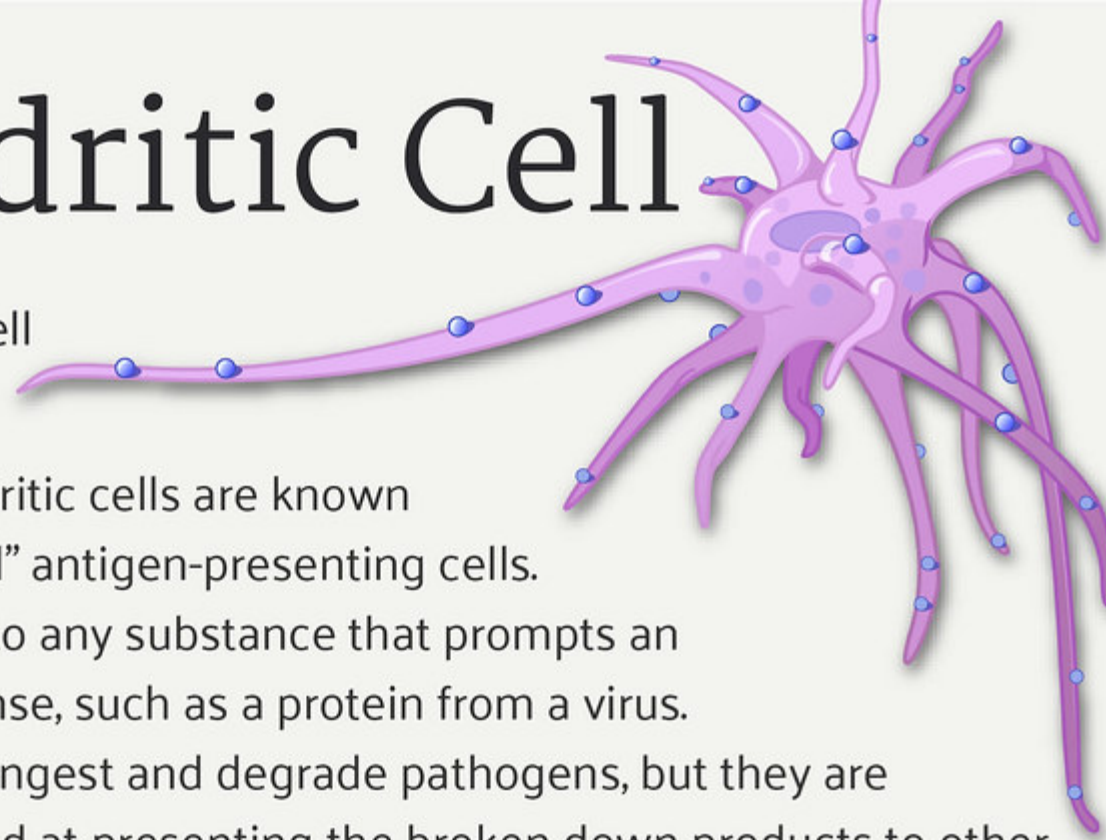
— Robert Frost, *After Apple Picking*

# Immune System



# Dendritic Cell

White Blood Cell



**Function:** Dendritic cells are known as “professional” antigen-presenting cells.

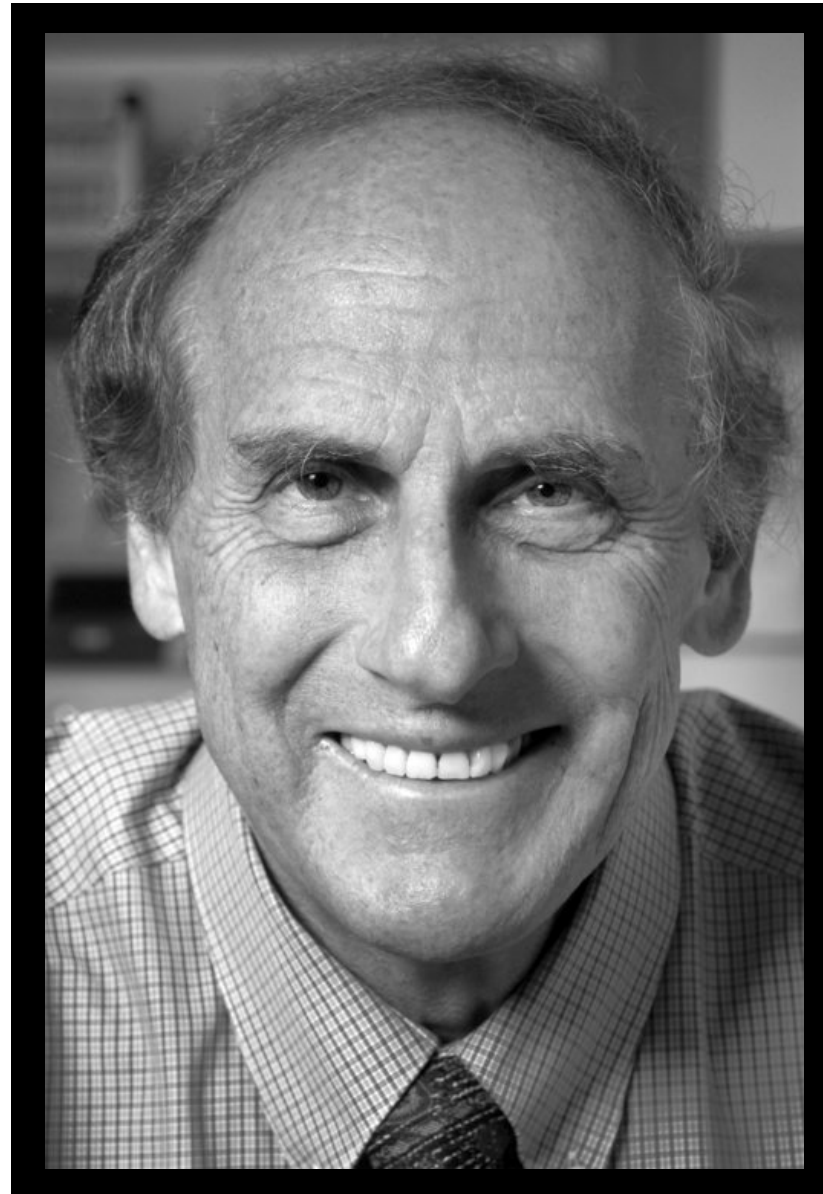
Antigens refer to any substance that prompts an immune response, such as a protein from a virus.

Dendritic cells ingest and degrade pathogens, but they are particularly good at presenting the broken down products to other cells of the immune system as antigens. Other immune cells can present antigens, but none do so as efficiently as dendritic cells.

**Disease:** Some microbes have evolved to attack dendritic cells and replicate inside of them. Because dendritic cells move between body tissues when they present antigens, any infectious agent tagging along may spread more easily throughout the body.

**Location:** Dendritic cells are most common in body tissues that interact with the external environment, like the skin, lungs and gut lining. They travel to lymph nodes and the spleen when they have a concerning antigen to present to other immune cells.

# Sounding the Alarm to Adaptive Immunity



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**Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution.**

*Steinman RM, Cohn ZA.*

*J Exp Med.* 1973 May 1;137(5):1142-62.



# Sounding the Alarm to Adaptive Immunity



The question that motivated Steinman's career was: ***how does the body decide to make an immune response with the right level of caution?***

A crucial question, for knowing the answer, one would learn how to potentially regulate immunity to tackle problems that occur when the immune response goes awry, as in autoimmunity.

# Sounding the Alarm to Adaptive Immunity



Steinman's lab discovered that dendritic cells exist in *mature ("on")* and *immature ("off")* states.

Mature dendritic cells are those that are switched "on" to trigger an immune reaction.

Immature dendritic cells are phagocytes that have at their surface many PRRs, as well as other receptors that allow them to sense and capture germs and fragments of dead cells from their surroundings.

# Sounding the Alarm to Adaptive Immunity



Dendritic cells in skin, lung and gut (tissues exposed to the outside environment) were found to be immature — while those in spleen and lymph nodes were mature.

In the 1990s a narrative finally emerged of what dendritic cells do in the body ...

# Sounding the Alarm to Adaptive Immunity



Immature dendritic cells engulf and destroy germs that their PRRs have locked onto. They then mature (switch on).

Upon maturation they travel via the lymphatic vessels to the spleen or nearest lymph nodes.

Special (MHC Class II) proteins on the surface of dendritic cells clasp small samples of protein molecules inside the cell, including molecules from the germs that have been engulfed.

# Sounding the Alarm to Adaptive Immunity



A second class of *co-stimulatory* proteins inside the dendritic cell are shuttled to the surface of the cell when a PRR has locked onto a germ.

The spleen and lymph nodes are densely packed with B and T cells.

The stellate shape of dendritic cells, with multiple protrusions, allows them to connect simultaneously to many T cells.

# Sounding the Alarm to Adaptive Immunity



If a T cell locks onto something presented by a dendritic cell but does not detect co-stimulatory proteins on the dendritic cell surface, it recognizes that it is reacting against something not from a germ.

This T cell becomes a *tolerant* T cell unable to cause an immune reaction.

In this way, dendritic cells have the power to *switch off* T cells which could otherwise attack healthy cells or tissues.



# Sounding the Alarm to Adaptive Immunity



On the other hand, if the T cell meets a dendritic cell that has engulfed a germ that it is able to recognize, that T cell starts multiplying in the spleen or lymph node. (That is why lymph nodes swell when there is an infection).

‘Cytotoxic/killer’ T cells ( $T_c$ ) move out and into the bloodstream to kill diseased cells.

‘Helper’ T cells ( $T_h$ ) stimulate immune other immune cells, including B cells, into action.

# Sounding the Alarm to Adaptive Immunity



## In Summary

Dendritic cells detect a problem and switch on the right kind of immune response to deal with the threat.

They connect the innate immune response to the adaptive immune response, which is longer-lasting and more precise, involving T and B cells.

Macrophages can also do this, but only when the body needs to reignite an immune response against something that has been encountered before.

# Sounding the Alarm to Adaptive Immunity



## In Summary

Dendritic cells have an ability to switch the immune system on *and* off, both to control our immunity against germs and to stop our immune system from attacking healthy cells and tissues.

# Steinman's Legacy



## **Advent of T Cell Based Immunotherapy**

Steinman died in 2011 from pancreatic cancer, three days before he was awarded the Nobel Prize.

He opened up a new world of immunotherapy in which dendritic cells can be taught to elicit a T cell mediated immune response to infections and cancers.

He tried to cure his own cancer with dendritic cell based experimental vaccines. These and other conventional therapies may have ultimately extended his life by a few years.

# Steinman's Legacy



After the Nobel announcement, Steinman's daughter, Alexis, described both the sadness and pride she felt, captured in a quote read at her parent's wedding:

Your joy is your sorrow unmasked. And the selfsame well from which your laughter rises was oftentimes filled with your tears. [...] When you are sorrowful look again in your heart, and you shall see that in truth you are weeping for that which has been your delight.

—Khalil Gibran, *The Prophet*



## Further Reading

Medzhitov R. Pattern recognition theory and the launch of modern innate immunity. *J Immunol.* 2013 Nov 1;191(9):4473-4.

Nussenzweig, M. C. Ralph Steinman and the discovery of dendritic cells. *Nobel Lecture.* 2011.

Steenhuysen, J., Nichols, M. Insight: Nobel winner's last big experiment: Himself. *Reuters.* 2011 Oct 6.

Davis, D. M. The Beautiful Cure: The Revolution in Immunology and What It Means for Your Health. *University of Chicago Press.* 2018.