# OLLI SG 492
# Human Immune System

## Session 2 - March 16, 2022

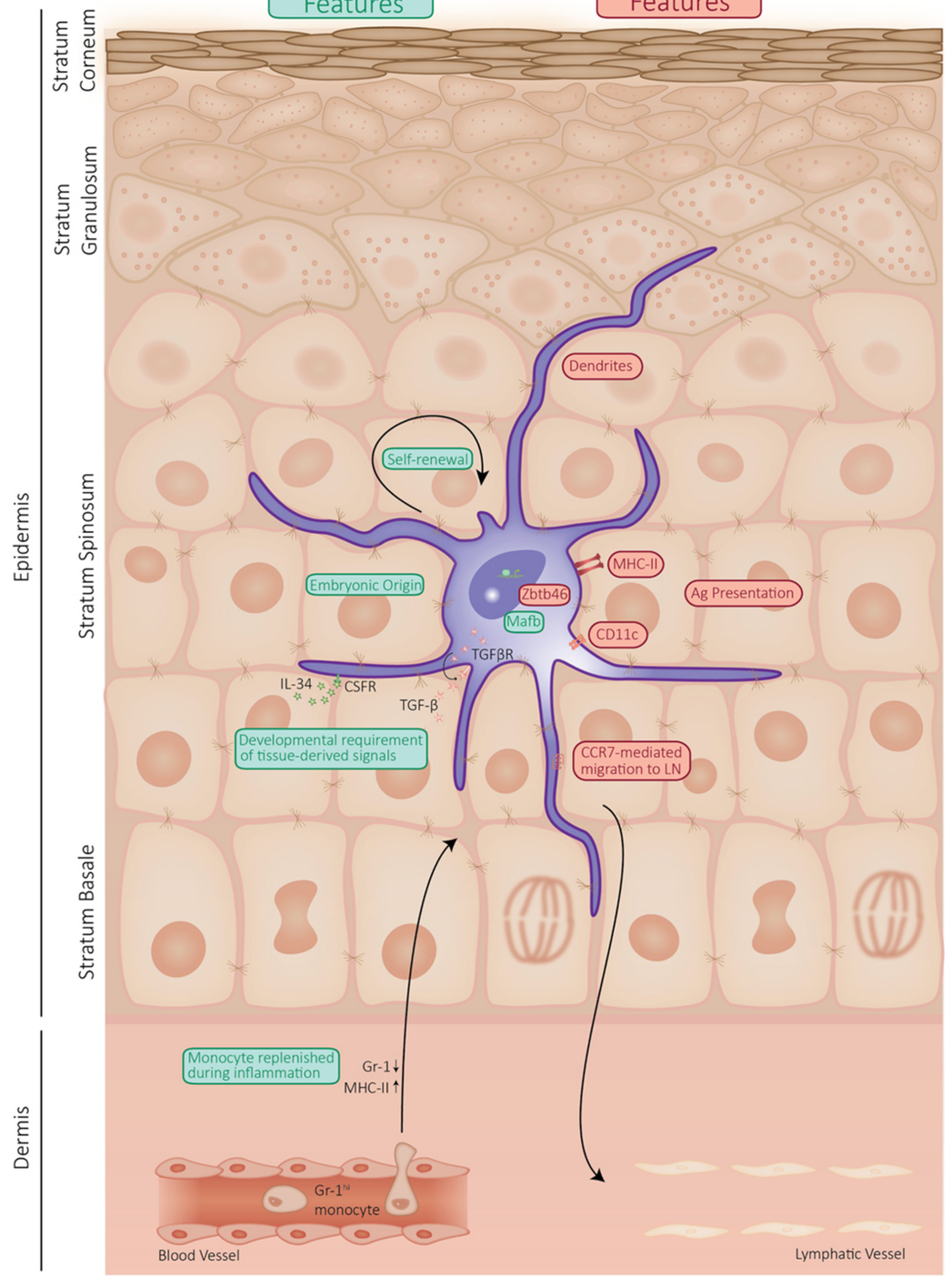
# Today’s Meeting

- Corrections, Modifications, Amplifications, Etc.
- Recap of last week’s meeting
- Some definitions of terms that will become more prominent
- Overview of the Lymphatic System
- A side-bar on stem cells and cell differentiation
- Overview of the types of cells that constitute the immune system
- Janeway, et al., and the discovery of the innate immune system

# Corrections, Amplifications, Modifications, Etc.

- “Germ” - Davis uses this term for dangerous organisms; I will be using pathogen.
- Immune response to non-organismic substances:
  - Langerhans Cells
  - Marshall other immune system cells (e.g., T cells) to fight infection, inflammation, and other dangers to the epidermis, e.g., poison ivy.
  - Has features of macrophage and dendritic cells.
  - Link to technical article on Langerhans Cells is here.

# Langerhans Cell

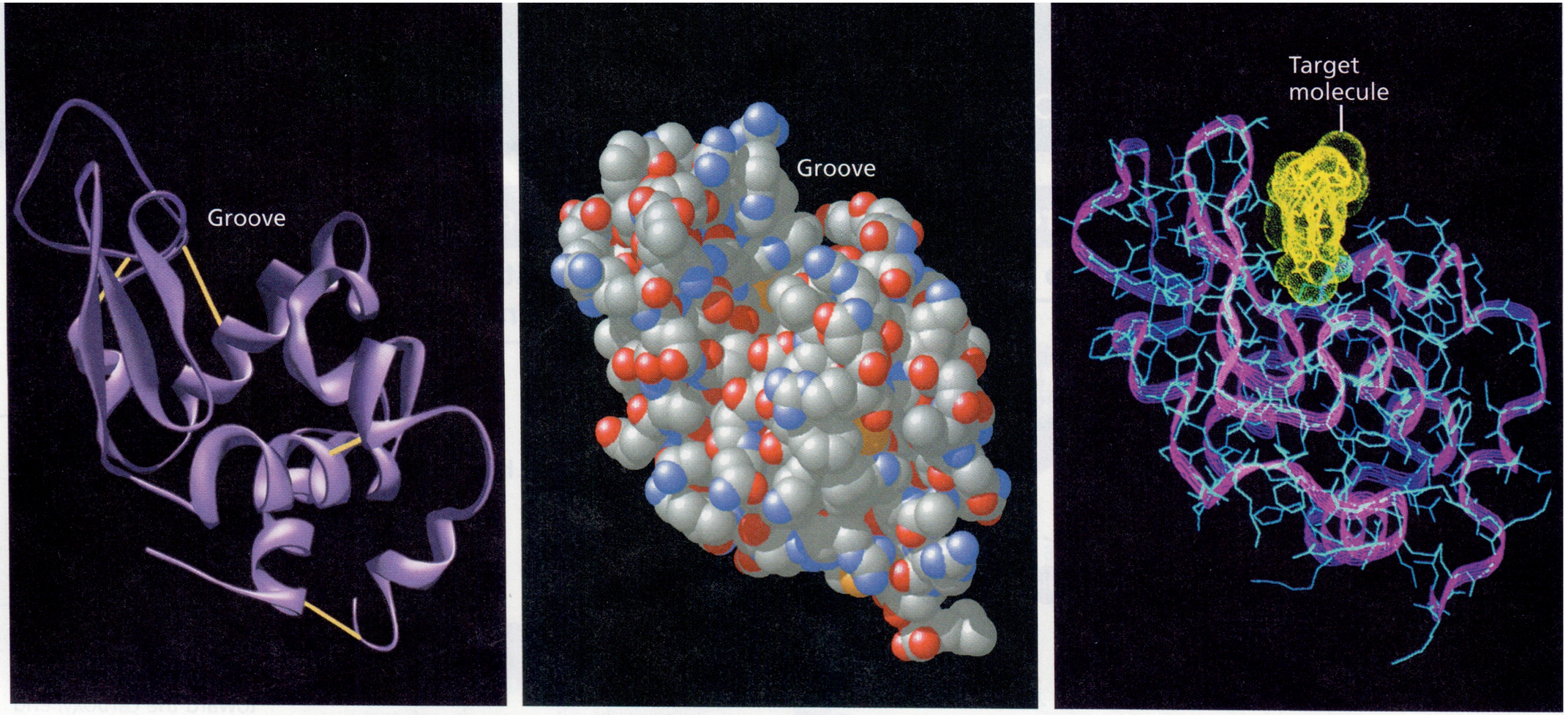


# Recap

- About the book - good on the recent advances, but assumes too much background knowledge.
- About the subject - It’s complicated!
- Incredibly small size of the organisms being studied is an impediment to researchers; processes are occurring at the molecular level.
- Proteins and protein folding are central issues in the immune system.
- Innate immune cells kill pathogens in many instances by “eating” them - phagocytosis.

# Basics of the Immune System - 2

## Proteins and Protein Folding




**(a)** A **ribbon model** shows how the single polypeptide chain folds and coils to form the functional protein. (The yellow lines represent disulfide bridges that stabilize the protein's shape.)

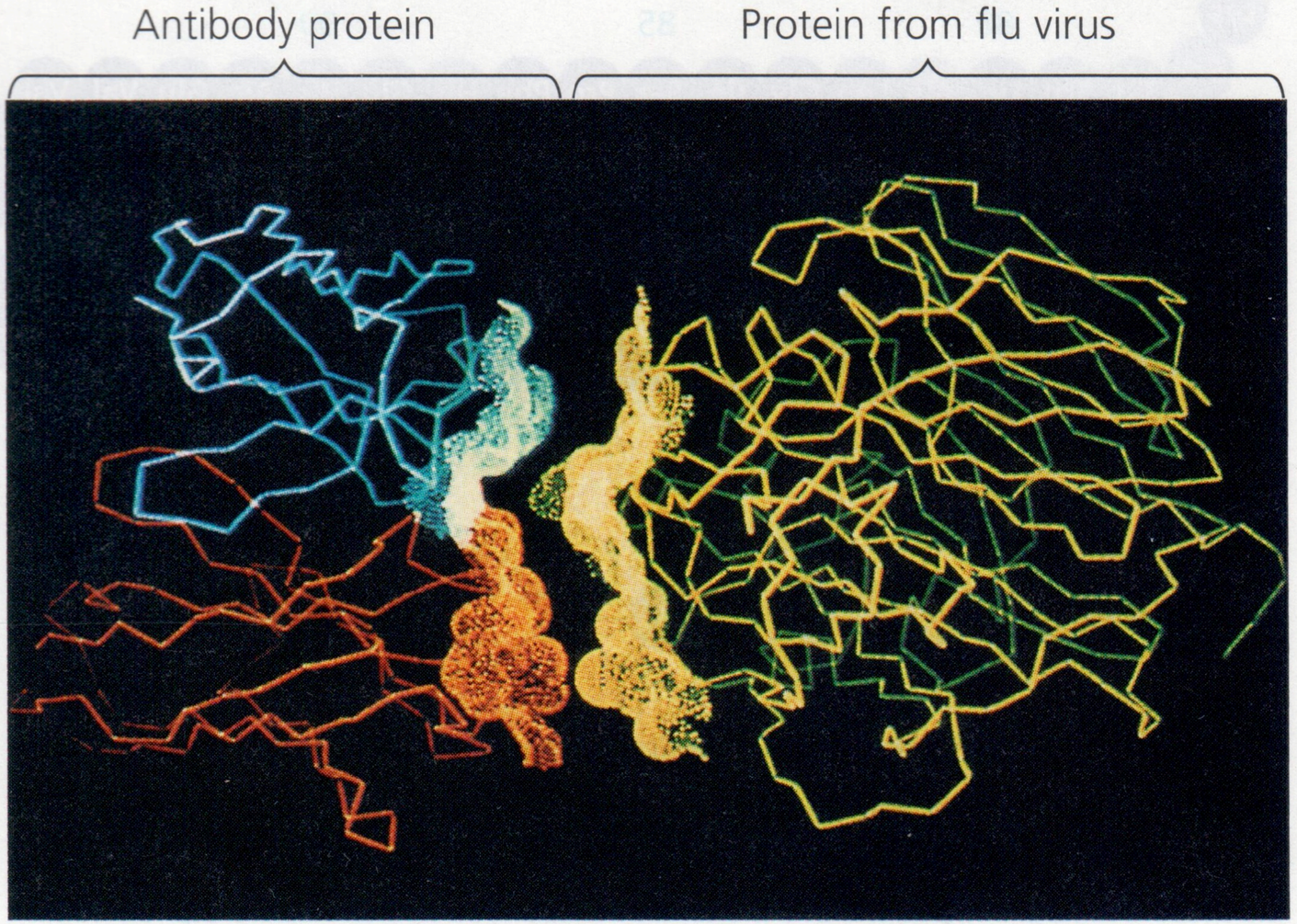
**(b)** A **space-filling model** shows more clearly the globular shape seen in many proteins, as well as the specific three-dimensional structure unique to lysozyme.

**(c)** In this view, a ribbon model is superimposed on a **wireframe model**, which shows the backbone with the side chains extending from it. The yellow structure is the target molecule.

▲ **Figure 5.16 Structure of a protein, the enzyme lysozyme.** Present in our sweat, tears, and saliva, lysozyme is an enzyme that helps prevent infection by binding to and catalyzing the destruction of specific molecules on the surface of many kinds of bacteria. The groove is the part of the protein that recognizes and binds to the target molecules on bacterial walls.

# Basics of the Immune System - 2

## Protein Binding

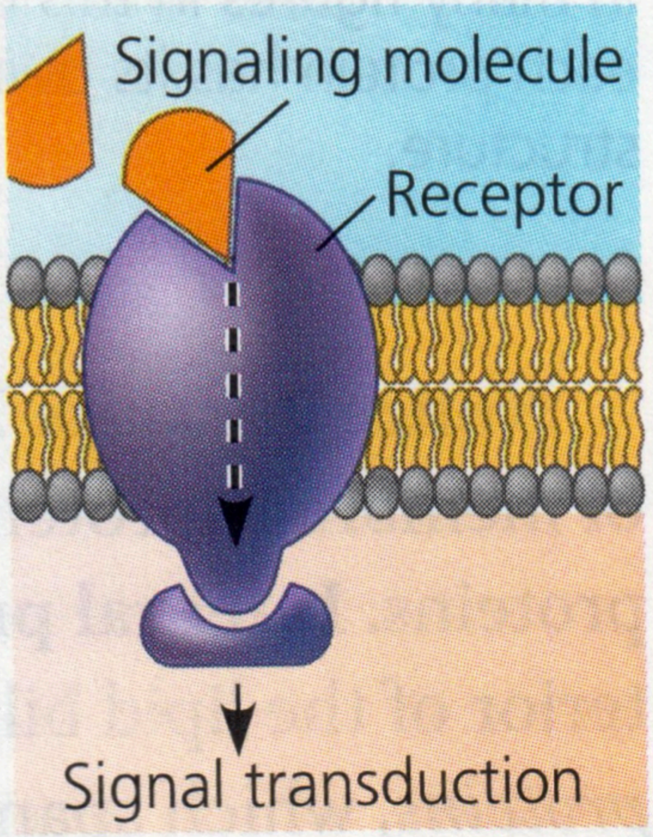



▲ **Figure 5.17 An antibody binding to a protein from a flu virus.** A technique called X-ray crystallography was used to generate a computer model of an antibody protein (blue and orange, left) bound to a flu virus protein (green and yellow, right). Computer software was then used to back the images away from each other, revealing the exact complementarity of shape between the two protein surfaces.

# Basics of the Immune System - 2

## Proteins and Protein Folding

**(c) Signal transduction.** A membrane protein (receptor) may have a binding site with a specific shape that fits the shape of a chemical messenger, such as a hormone. The external messenger (signaling molecule) may cause the protein to change shape, allowing it to relay the message to the inside of the cell, usually by binding to a cytoplasmic protein (see Figure 11.6).



# Basics of the Immune System

## Definitions

**Antigen**: Any molecule that can bind specifically to an antibody or generate peptide fragments that are recognized by a T-cell receptor.

**Antibody**: A protein that binds specifically to a particular substance—called its antigen. Each antibody molecule has a unique structure that enables it to bind specifically to its corresponding antigen, but all antibodies have the same overall structure and are known collectively as immunoglobulins. Antibodies are produced by differentiated B cells (plasma cells) in response to infection or immunization, and bind to and neutralize pathogens or prepare them for uptake and destruction by phagocytes.

**Lymphocyte**: A class of white blood cells that bear variable cell-surface receptors for antigen and are responsible for adaptive immune responses. There are two main types—B lymphocytes (B cells) and T lymphocytes (T cells)—which mediate humoral and cell-mediated immunity, respectively. On antigen recognition, a lymphocyte enlarges to form a lymphoblast and then proliferates and differentiates into an antigen-specific effector cell.

# Basics of the Immune System

## The Lymphatic System

- Site of activation and proliferation of lymphocytes - primarily T cells and B cells.
- Lymphocytes are presented with antigens and antigen fragments in lymph nodes by dendritic and macrophage cells.
- Lymphocytes circulate between the lymphatic system and the blood stream through the organs of the lymphatic system, primarily lymph nodes.
- Drains and processes lymph from peripheral tissue before returning it to the blood stream.

# Basics of the Immune System

## The Lymphatic System

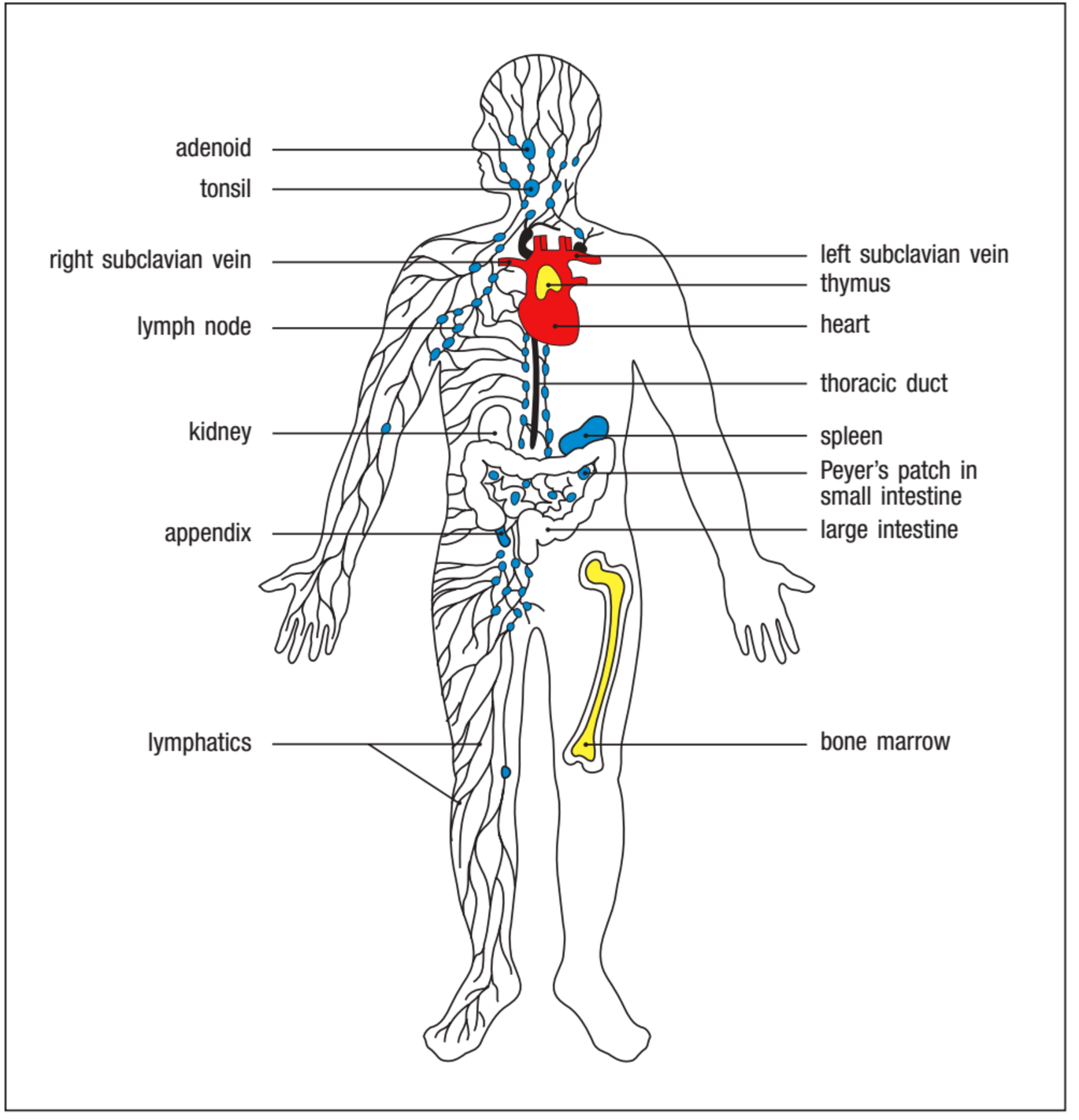
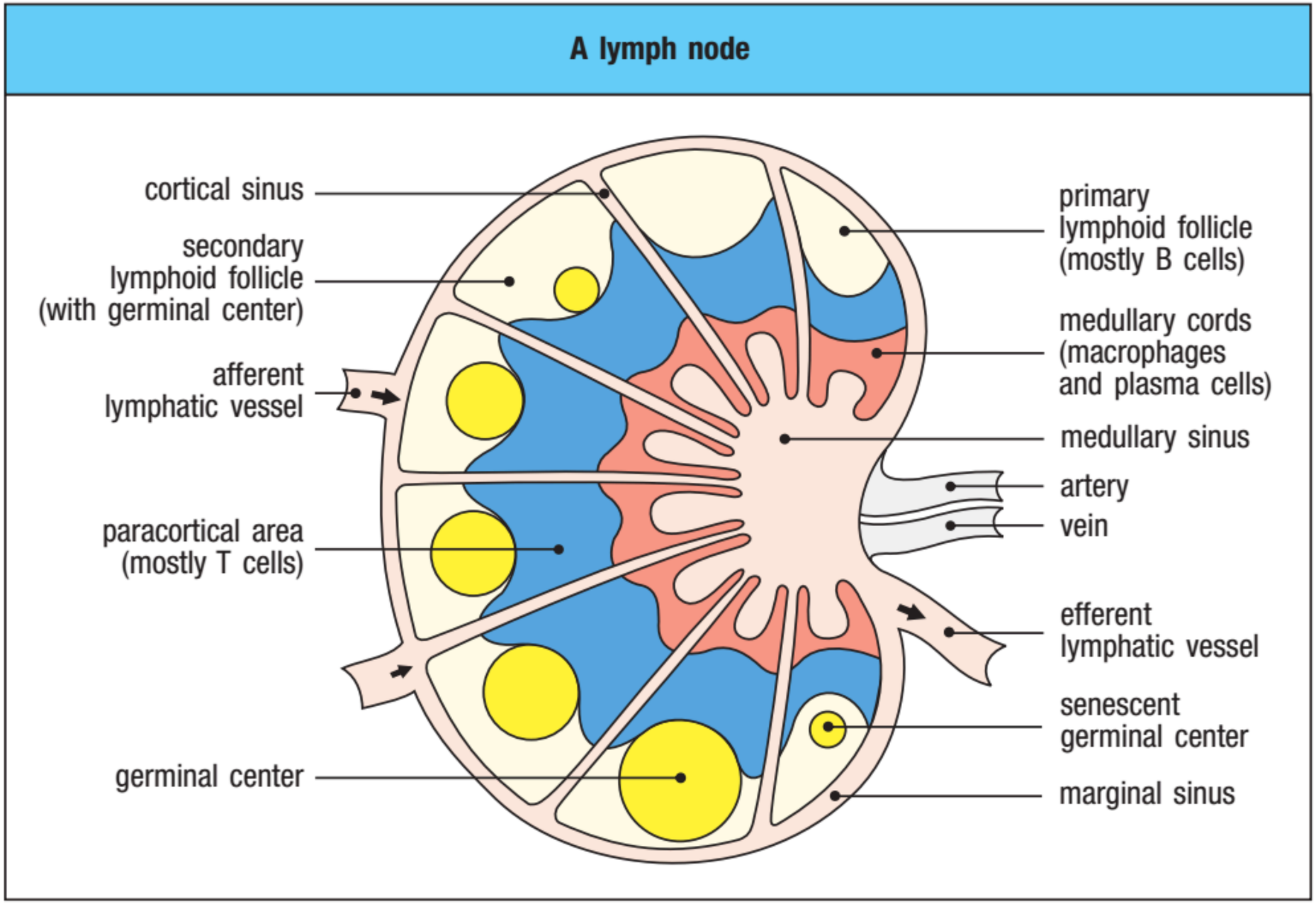



**Fig. 1.18 The distribution of lymphoid tissues in the body.** Lymphocytes arise from stem cells in bone marrow and differentiate in the central lymphoid organs (yellow)—B cells in the bone marrow and T cells in the thymus. They migrate from these tissues and are carried in the bloodstream to the peripheral lymphoid organs (blue). These include lymph nodes, spleen, and lymphoid tissues associated with mucosa, such as the gut-associated tonsils, Peyer's patches, and appendix. The peripheral lymphoid organs are the sites of lymphocyte activation by antigen, and lymphocytes recirculate between the blood and these organs until they encounter their specific antigen. Lymphatics drain extracellular fluid from the peripheral tissues, through the lymph nodes, and into the thoracic duct, which empties into the left subclavian vein. This fluid, known as lymph, carries antigen taken up by dendritic cells and macrophages to the lymph nodes, as well as recirculating lymphocytes from the lymph nodes back into the blood. Lymphoid tissue is also associated with other mucosa such as the bronchial linings (not shown).

# Basics of the Immune System

## The Lymphatic System



## Basics of the Immune System

# The Lymphatic System

**Fig. 1.22 Organization of a lymph node.** As shown at left in the diagram of a lymph node in longitudinal section, a lymph node consists of an outermost cortex and an inner medulla. The cortex is composed of an outer cortex of B cells organized into lymphoid follicles and of adjacent, or paracortical, areas made up mainly of T cells and dendritic cells. When an immune response is under way, some of the follicles—known as secondary lymphoid follicles—contain central areas of intense B-cell proliferation called germinal centers. These reactions are very dramatic, but eventually die out as germinal centers become senescent. Lymph draining from the extracellular spaces of the body carries antigens in phagocytic dendritic cells and phagocytic macrophages from the tissues to the lymph node via the afferent lymphatics. These migrate directly from the sinuses into the cellular parts of the node. Lymph leaves via the efferent lymphatics in the medulla. The medulla consists of strings of macrophages and antibody-secreting plasma cells known as the medullary cords. Naive lymphocytes enter the node from the bloodstream through specialized postcapillary venules (not shown) and leave with the lymph through the efferent lymphatic. The light micrograph (right) shows a transverse section through a lymph node, with prominent follicles containing germinal centers. Magnification ×7. Photograph courtesy of N. Rooney.

# Cell Differentiation

## Types of Stem Cells

- Totipotent - Can form all cell types, including the placental cells.
- Pluripotent - Can form all cell types that are lineage specific.
- Multipotent - Can form more than one cell type.
- Unipotent - Can form only one specific type of cell, e.g., adult stem cells.

# Cell Differentiation

## Steps in Differentiation

- The fertilized egg, the zygote, is a totipotent stem cell, capable of becoming any cell.
- After several rounds of cell division, pluripotent stem cells are differentiated that become lineage-specific progenitor cells.
- These lineage-specific progenitor cells become germ layer-specific progenitor cells.  Germ layers are the endoderm, mesoderm, and ectoderm.
- Finally, the germ layer-specific progenitor cells become the cells (somatic cells) that constitute the organs and tissue of each layer.

# Cell Differentiation

## The Germ Layers

- Endoderm - Embryonic Endoderm cells develop into the interior linings of the gastrointestinal and respiratory tacts.
- Mesoderm - Embryonic Mesoderm cells develop into muscle, cartilage, and bone; subcutaneous tissue of the skin; urogenital structures (kidneys, gonads, adrenal glands); and heart, blood vessels and blood cells.
- Ectoderm - Embryonic Ectoderm cells develop into the nervous system (spine, peripheral nerves, brain); tooth enamel; and the epidermis.

**Table 1.1. Embryonic Germ Layers From Which Differentiated Tissues Develop [1]**

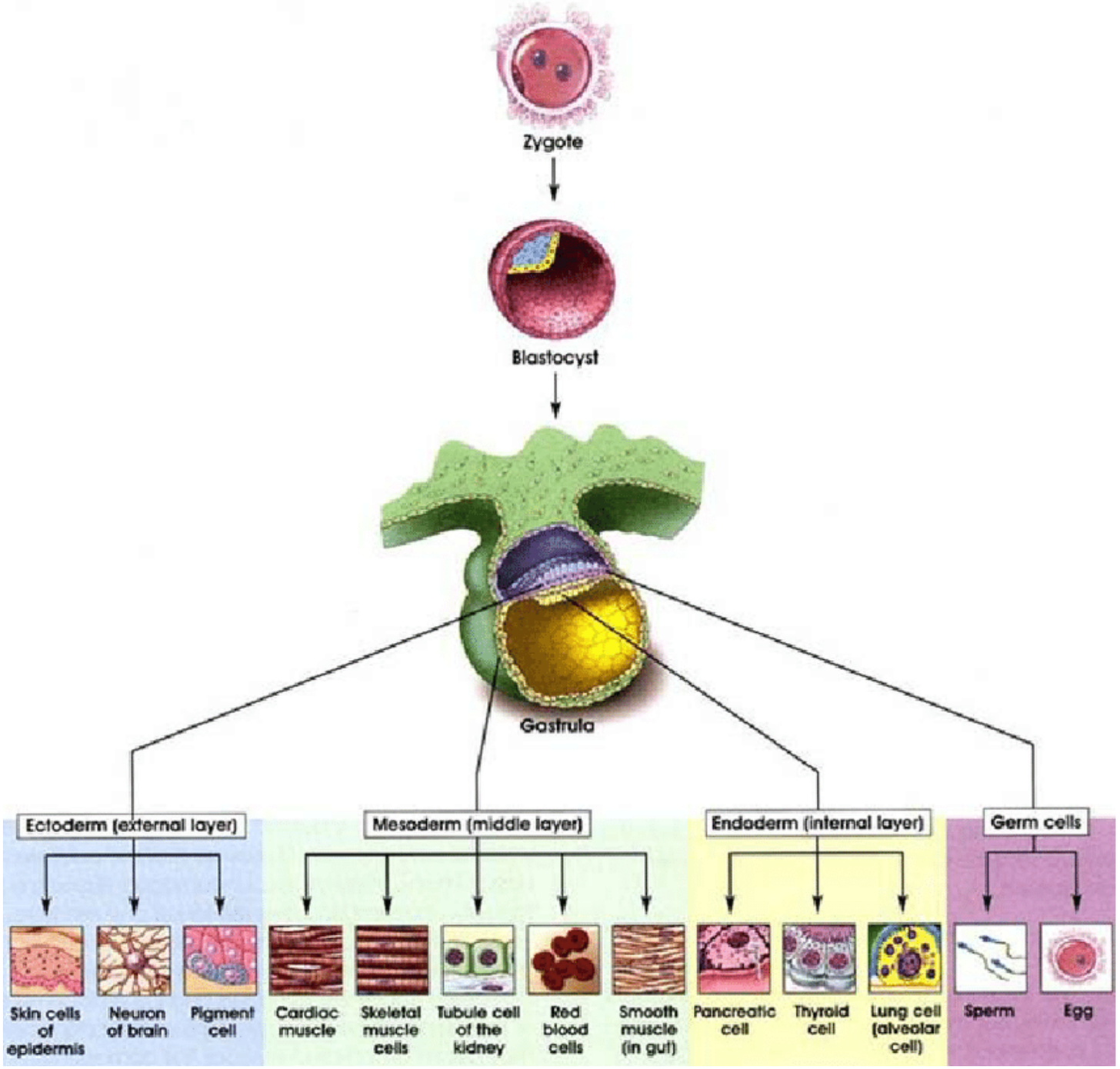
| Embryonic Germ Layer | Differentiated Tissue |
|---|---|
| Endoderm | Thymus<br>Thyroid, parathyroid glands<br>Larynx, trachea, lung<br>Urinary bladder, vagina, urethra<br>Gastrointestinal (GI) organs (liver, pancreas)<br>Lining of the GI tract<br>Lining of the respiratory tract |
| Mesoderm | Bone marrow (blood)<br>Adrenal cortex<br>Lymphatic tissue<br>Skeletal, smooth, and cardiac muscle<br>Connective tissues (including bone, cartilage)<br>Urogenital system<br>Heart and blood vessels (vascular system) |
| Ectoderm | Skin<br>Neural tissue (neuroectoderm)<br>Adrenal medulla<br>Pituitary gland<br>Connective tissue of the head and face<br>Eyes, ears |

# Cell Differentiation

# The Germ Layers

# Cell Differentiation

## The Germ Layers



# Basics of the Immune System

## Cells of the Immune System

- All the cellular elements of the blood, including the cells of the immune system, arise from **pluripotent hematopoietic stem cells** in the bone marrow.
- T cells migrate to the Thymus (hence the T) where they mature; B cells mature in the bone marrow (hence the B).
- During embryonic development, macrophages are created.
- Additional innate immune cells and enzymes are passed by the mother through the placenta to the embryo.
- Innate immune cells - macrophages, neutrophils, mast cells and dendritic cells - are created in the bone marrow.

# Basics of the Immune System

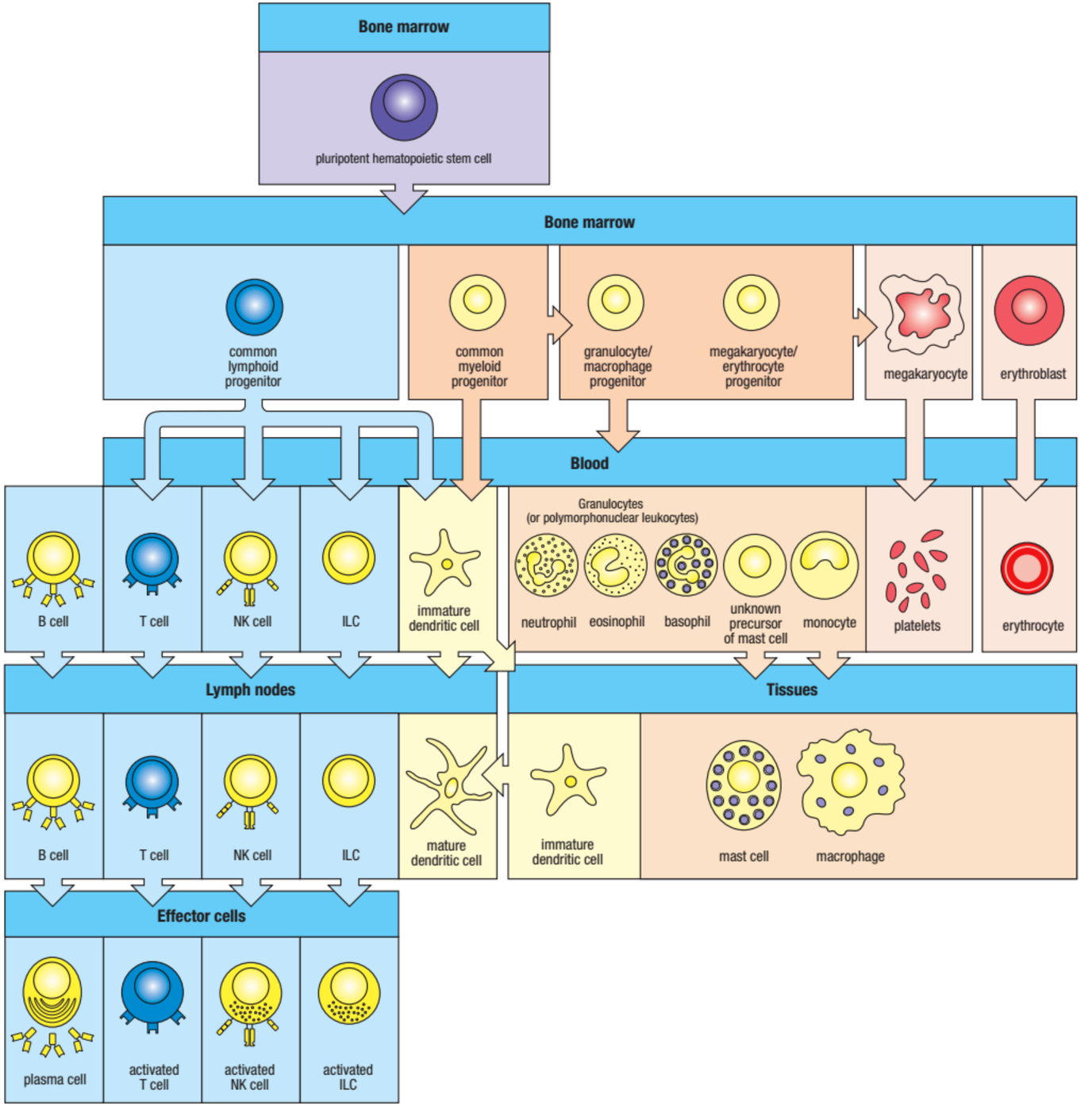
## Cells of the Immune System

- Innate immune cells eliminate pathogens (mostly) by phagocytosis.
- Innate immune cells identify pathogens through pattern-recognition receptors.
- These receptors are fixed, not randomly generated.
- Innate immune cells circulate in the blood system, but crossover into the lymphatic system.
- Dendritic and macrophage cells break down pathogens into small segments, and present these segments to lymphocytes in lymph nodes.

# Cells of the Immune System

**Fig. 1.3 All the cellular elements of the blood, including the cells of the immune system, arise from pluripotent hematopoietic stem cells in the bone marrow.** These pluripotent cells divide to produce two types of stem cells. A common lymphoid progenitor gives rise to the lymphoid lineage (blue background) of white blood cells or leukocytes—the innate lymphoid cells (ILCs) and natural killer (NK) cells and the T and B lymphocytes. A common myeloid progenitor gives rise to the myeloid lineage (pink and yellow backgrounds), which comprises the rest of the leukocytes, the erythrocytes (red blood cells), and the megakaryocytes that produce platelets important in blood clotting. T and B lymphocytes are distinguished from the other leukocytes by having antigen receptors and from each other by their sites of differentiation—the thymus and bone marrow, respectively. After encounter with antigen, B cells differentiate into antibody-secreting plasma cells, while

T cells differentiate into effector T cells with a variety of functions. Unlike T and B cells, ILCs and NK cells lack antigen specificity. The remaining leukocytes are the monocytes, the dendritic cells, and the neutrophils, eosinophils, and basophils. The last three of these circulate in the blood and are termed granulocytes, because of the cytoplasmic granules whose staining gives these cells a distinctive appearance in blood smears, or polymorphonuclear leukocytes, because of their irregularly shaped nuclei. Immature dendritic cells (yellow background) are phagocytic cells that enter the tissues; they mature after they have encountered a potential pathogen. The majority of dendritic cells are derived from the common myeloid progenitor cells, but some may also arise from the common lymphoid progenitor. Monocytes enter tissues, where they differentiate into phagocytic macrophages or dendritic cells. Mast cells also enter tissues and complete their maturation there.



# The Innate Immune System

## Charles Janeway

- February 1943 - April 2003
- B.S. Chemistry, Harvard, 1963
- M.D. Harvard Medical School, 1969
- Long family history of medical doctors and professionals
- Founding member School of Immunology, Yale Medical School
- Had three daughters, all with M.D.s

# The Innate Immune System

## Ruslan Medzhitov

- Sterling Professor of Immunobiology, Yale School of Medicine
- Investigator, Howard Hughes Medical Institute
- Born March 1966, Tashkent
- Elected to U.S. National Academy of Science in 2010
- Won the Shaw Prize in 2013

# The Innate Immune System

## Janeway's Puzzle

- Vaccines require an adjuvant to be effective - "Dirty Little Secret".
- Janeway was puzzled by two questions:
  - How does an immune reaction start?
  - How do adjuvants work?
- Beyond differentiating between self and non-self, the immune system must determine that something is actually a threat to the body - a germ.

# The Innate Immune System

## Janeway's Puzzle

- Janeway hypothesized that some immune cells must have pattern-recognition receptors that identify critical features of pathogens.
- Bacteria utilize lipopolysaccharide (LPS) in their cell walls.
- This molecule is highly critical during cell division and is highly conserved.
- LPS would thus be indicative of the presence of a foreign bacteria.

# The Innate Immune System

## Hoffmann's Contribution

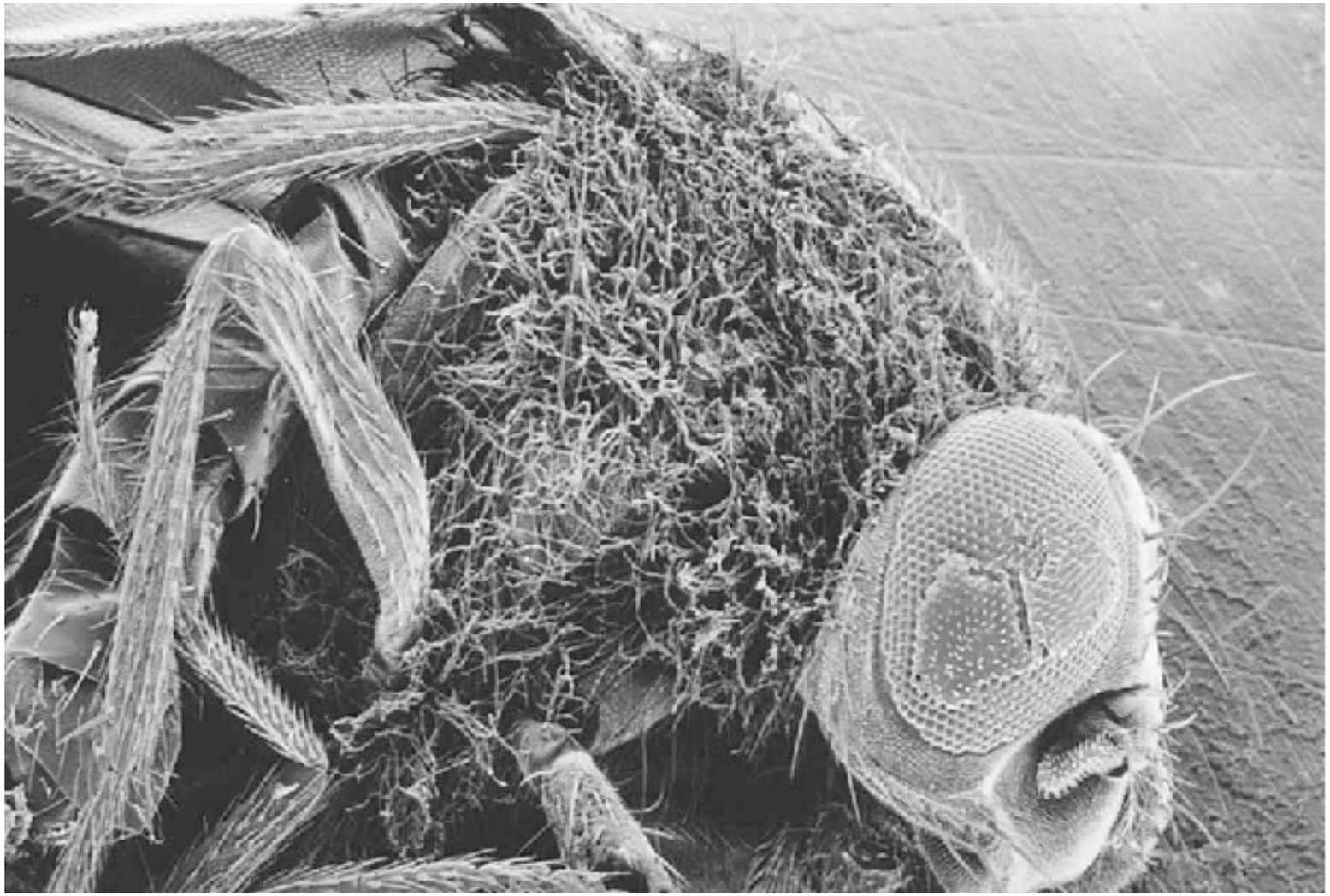
- Drosophila (fruit fly) can fight off infections; Jules Hoffmann's lab worked on finding the genes responsible.
- It was known that drosophila has several genes, known as **toll** genes, that code for proteins involved in motoneuron and muscular development.
- The proteins produced by these genes are transmembrane proteins.
- They also act as receptors that detect pathogens and that can initiate protective, immune-like processes.
- These insect toll genes are similar to genes in humans, the IL-1receptor gene.

# The Innate Immune System

## Hoffmann's Contribution

- The human genes produce toll-like receptors.
- Working in Hoffmann's lab, Bruno Lemaitre was able to show that Drosophila was dependent on toll receptors to ward off infections.
- Subsequent work showed that the human genome contains 10 genes that code for proteins that are insect toll-like receptors.

# Drosophila Fungal Infection



# The Innate Immune System

## Medzhitov's Contribution

- Ruslan Medzhitov, working in Janeway's lab, discovered that a human toll-like gene could switch-on the activity of other genes known to have an immune response role.
- Other researchers were able to identify additional human genes which code for insect toll-like receptors.
- Thus far, there are ten toll-like receptor genes in humans.
- Medzhitov's gene is TLR4.

# The Innate Immune System

## Beutler's Contribution

- Bruce Beutler's lab discovered that the gene involved in the immune reaction of mice exposed to LPS was very similar to Hoffman's insect toll gene and Medzhitov's human gene, TLR4.

- This result solidified the case for the pattern-recognition receptor theory of Janeway, and the existence of the innate immune system.

# The Innate Immune System

## Puzzle Solved

“Finally the pieces came together to reveal the big picture: the TLR4 gene encodes for a protein molecule that is able to interlock with a component from the outer wall of bacteria (LPS). In other words, the TLR4 gene encodes for a **pattern-recognition receptor**, the very type of molecule that Janeway had predicted existed – one of the eyes of the immune system, as Beutler puts it – giving immune cells with this receptor protein protruding from their surface an innate ability to lock onto bacteria. When TLR4 locks onto the bacterial molecule LPS, this signifies that there is something in the body that may very well require an immune response.”

# Up Next

- More on innate immune cells - macrophage, neutrophils, mast cells and immature dendritic cells
- Overview of lymphocytes - T cells, B cells, and natural killer (NK) cells
- Ralph Steinman, dendritic cells and the adaptive immune system
- Read Chapter 2 - The Alarm Cell