Immunology 101
(for the Non-Immunologist)

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Presentation based in part on that of Stephen Shiao MD, PhD

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Disclosures

- NeoStem EAB
- Astellas, Oxford Immunotec – Consulting Fees
- Kite Pharma – Ownership Interest

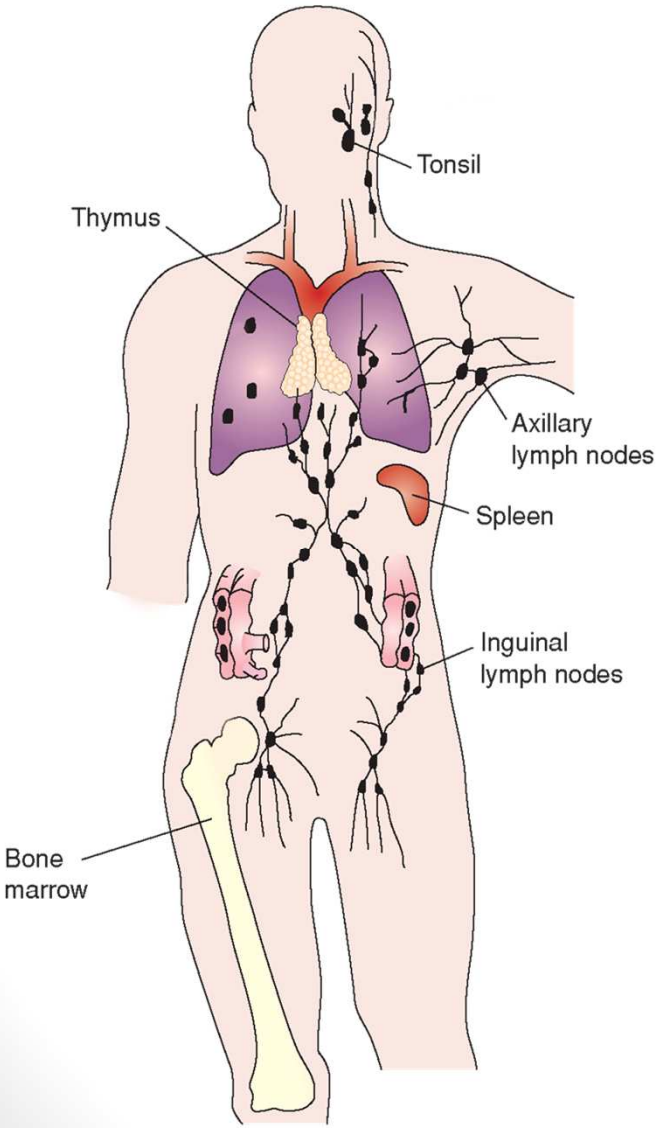
What is the immune system?

- A network of proteins, cells, tissues and organs all coordinated for one purpose: **to defend one organism from another**

- It is an infinitely adaptable system to combat the complex and endless variety of pathogens it must address

Outline

- Structure of the immune system
- Anatomy of an immune response
- Role of the immune system in disease



- Major organs of the immune system
  1. **Bone marrow** – production of immune cells
  2. **Thymus** – initial education of immune cells
  3. **Lymph Nodes** – where most immune responses are produced
  4. **Spleen** – dual role for immune responses (especially antibody production) and cell recycling

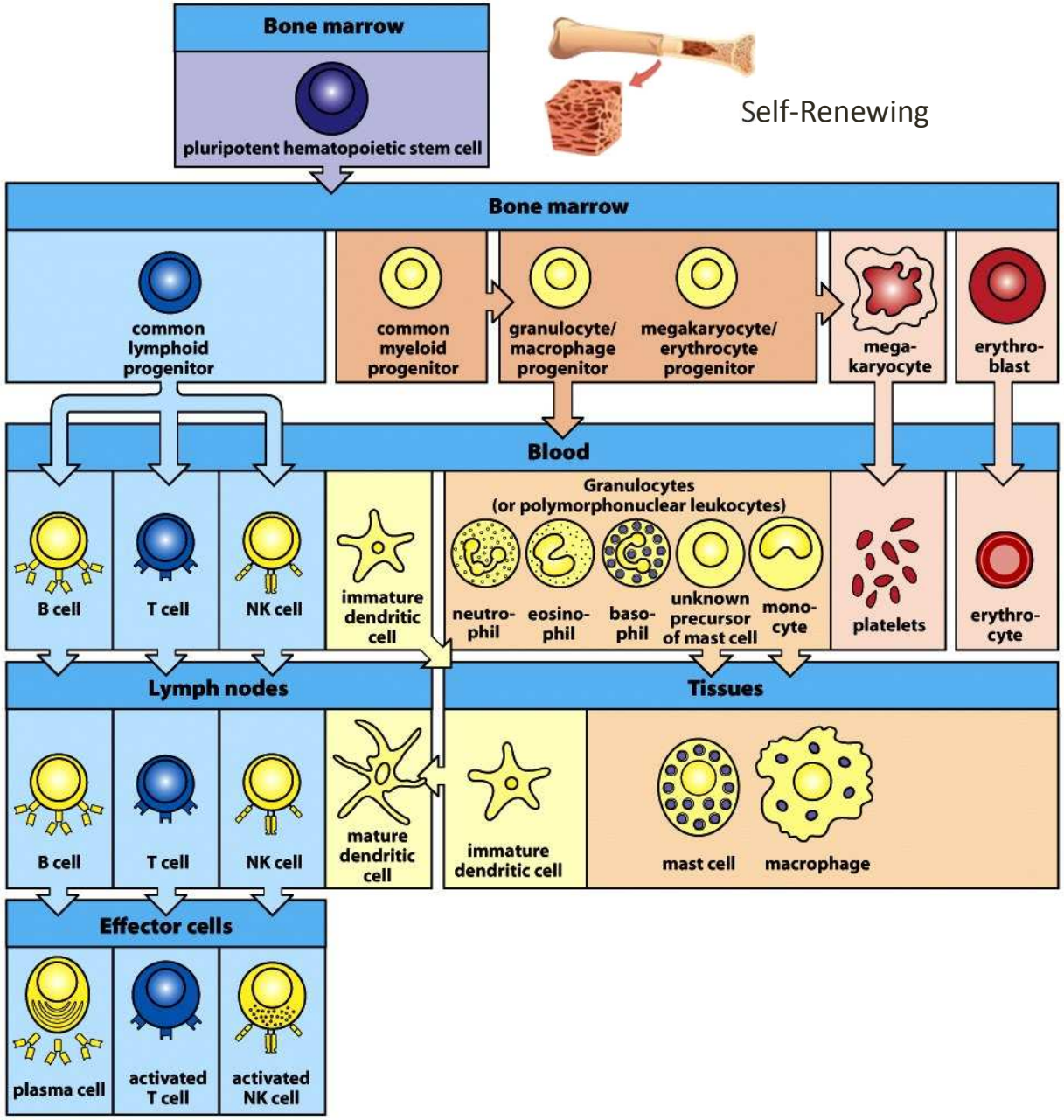
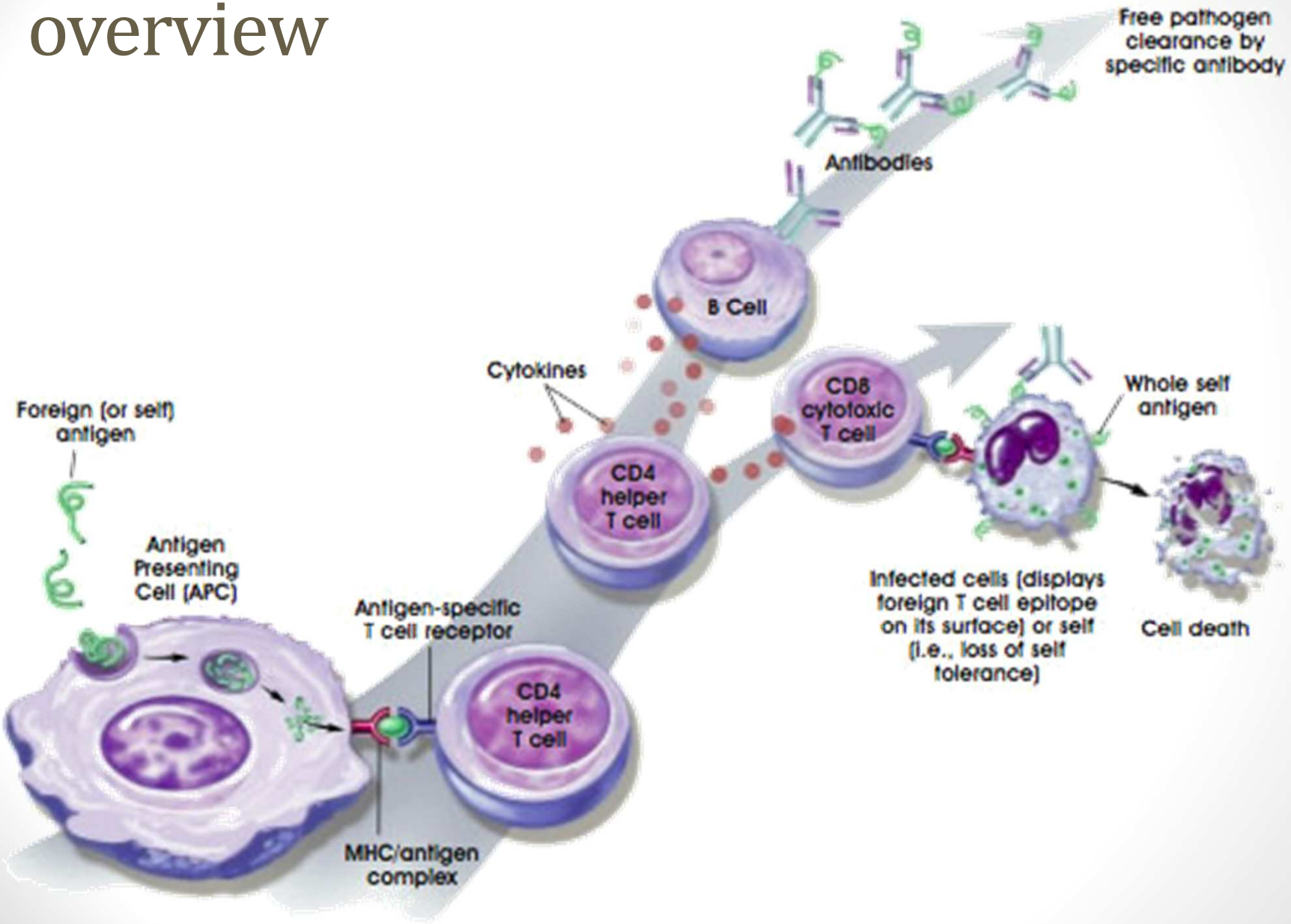


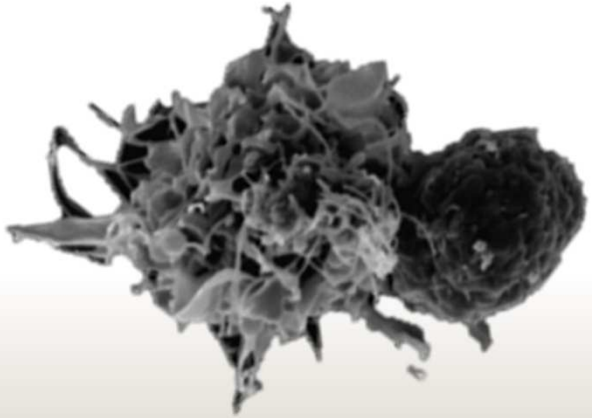
Figure 1-3 Immunobiology, 7ed. (© Garland Science 2008)

All cellular elements of the blood arise from HSC in bone marrow.

The Immune Response: overview

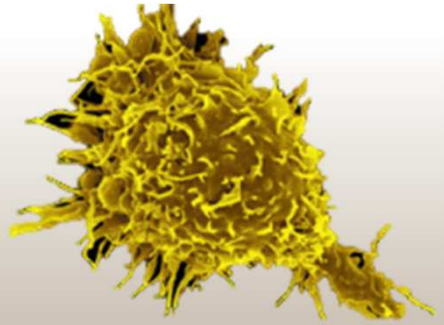


Immunity:
Two Systems and Key Players

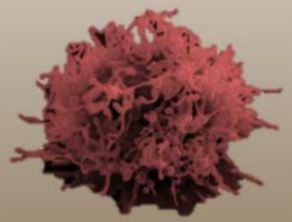


Dendritic cells (DC)

Innate Immunity

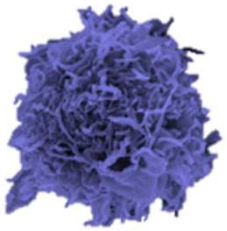


Phagocytes and Granulocytes
(Macrophages, Neutrophils)

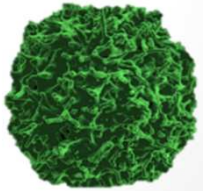


Natural Killer (NK) Cells

Adaptive Immunity

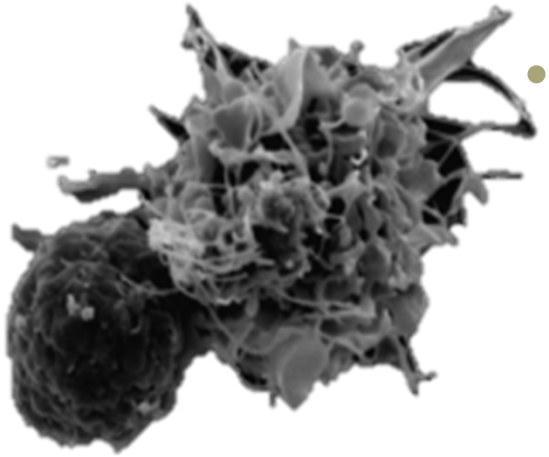


B cells



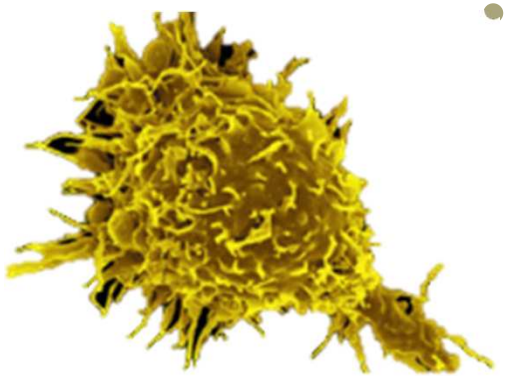
T cells

Dendritic Cells:
Orchestrate and shape immunity



- Function: Serve as the **connection** between the innate and adaptive immune systems.
  - Sample the surrounding environment and determine whether or not to initiate an immune response
  - Multiple different functional subsets regulate and shape the ensuing immune response
- Location: interfaces with the environment (lung, intestine and skin) and sites of immune interactions (spleen, lymph nodes, Peyer's patches)
- Key Markers: CD11c+

Phagocytes (Macrophages):

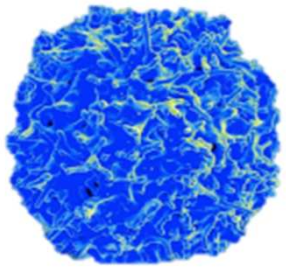


- Function: “Big Eaters” with multiple overlapping roles in both the beginning and end of the immune response
  - Like DC they also sample the environment, but also have cytotoxic capabilities
  - They are key regulators of wound repair and resolving an immune response
- Location: Everywhere. Interfaces with the environment (lung, intestine, liver, skin, placenta, brain), sites of immune interactions (spleen, lymph nodes, Peyer’s patches), sites of inflammation
- Key Markers: CD11b+, CD68+

NK Cells: Natural Killers

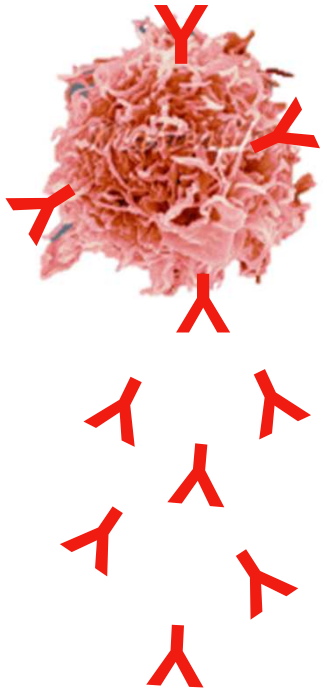
- Function: Early responders that have cytolytic potential as well as the ability to activate the immune system
  - "Natural Killing" is the ability to kill tumor cells without prior activation
  - Sensors of altered self – e.g. loss of MHC Class I or upregulation of stress molecules (e.g. heat shock protein)
- Location: bone marrow, immune sites (lymph nodes, spleen, tonsils and thymus) and the circulation
- Key Markers: CD56+, CD16+/-

T Cells:
Helpers and Killers



- Function: **Antigen-specific** killing and orchestrate an immune response through direct killing (CD8+ T cells) and helping the response with cytokine release (CD4+ T cells)
  - Two main types: **CD4+ and CD8+ T cells (cytotoxic T lymphocytes, CTL)** that recognize antigens presented in MHC Class II and Class I respectively
- Location: immune sites (lymph nodes, spleen, tonsils and thymus) and sites of inflammation
- Key Markers: CD3+, CD4+, CD8+,
  CD152+ (CTLA-4), PD-1

B Cells: Antibodies



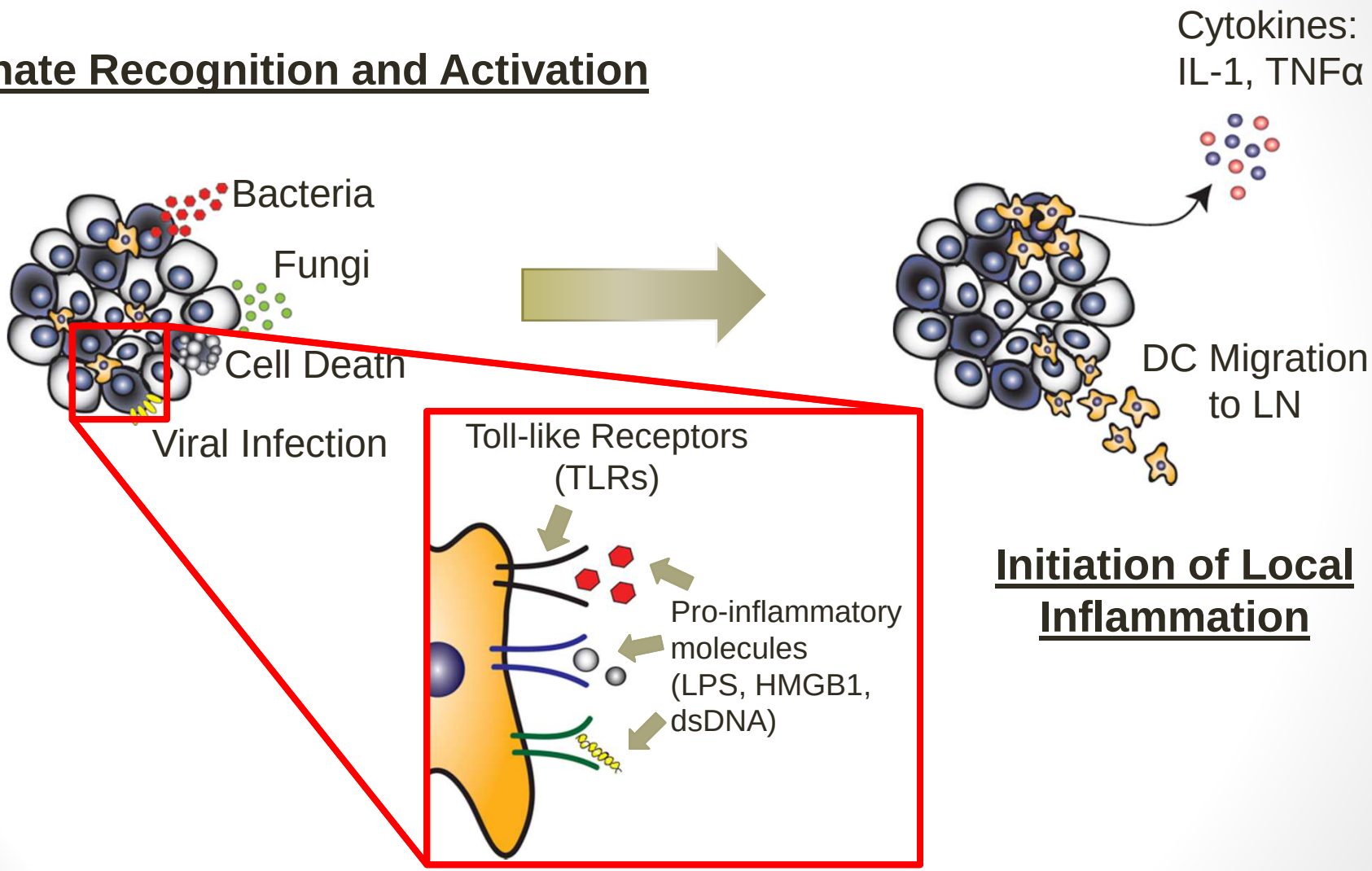
- Function: **Antigen-specific** production of **antibodies**
  - They also help propagate an immune response through their function as antigen presentation and cytokine production
- Location: immune sites (lymph nodes, spleen, tonsils and thymus) and sites of inflammation
- Key Markers: CD19+, CD20+

Structure of the Immune System: Summary

- There are four key “organs” of the immune system: **Bone Marrow, Lymph Node, Spleen and Thymus**
- There are two broad categories of the immune system: **Innate Immunity (Antigen Non-specific)** and **Adaptive Immune (Antigen Specific)**
- There are five major immune cells: **Dendritic cells (DC), Macrophages, NK Cells, T cells (helpers and killers) and B cells**

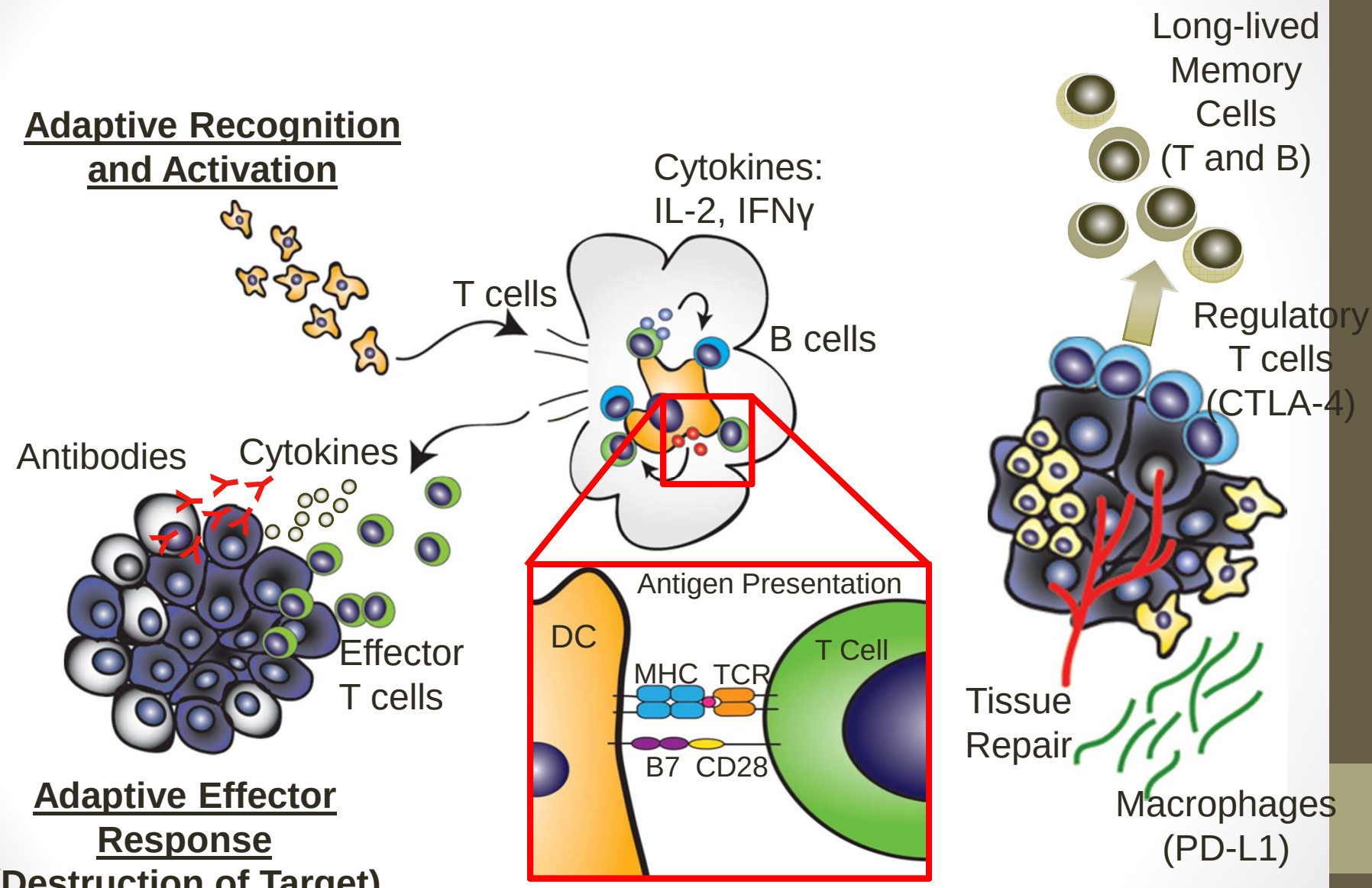
Anatomy of the Immune Response

Innate Recognition and Activation



Initiation of Local Inflammation

Anatomy of the Immune Response



Infection and Vaccination

- How does the immune system protect us from the infinite variety of pathogens?
  - **Enormous numbers of "sensors"**
    (recombinant T cell receptors, antibody shapes)
  - **Immunological Memory**

Immunologic Memory and Vaccination

- Bacteria and viruses divide much more quickly than mammalian cells, how can we fight their numbers?
  - Effector T cells and antibodies persist for weeks to years after exposure to antigen – “protective immunity” and is the reason vaccines prevent infections
  - Second exposure to the same antigen produces a much faster response and is referred to as **Immunologic Memory**

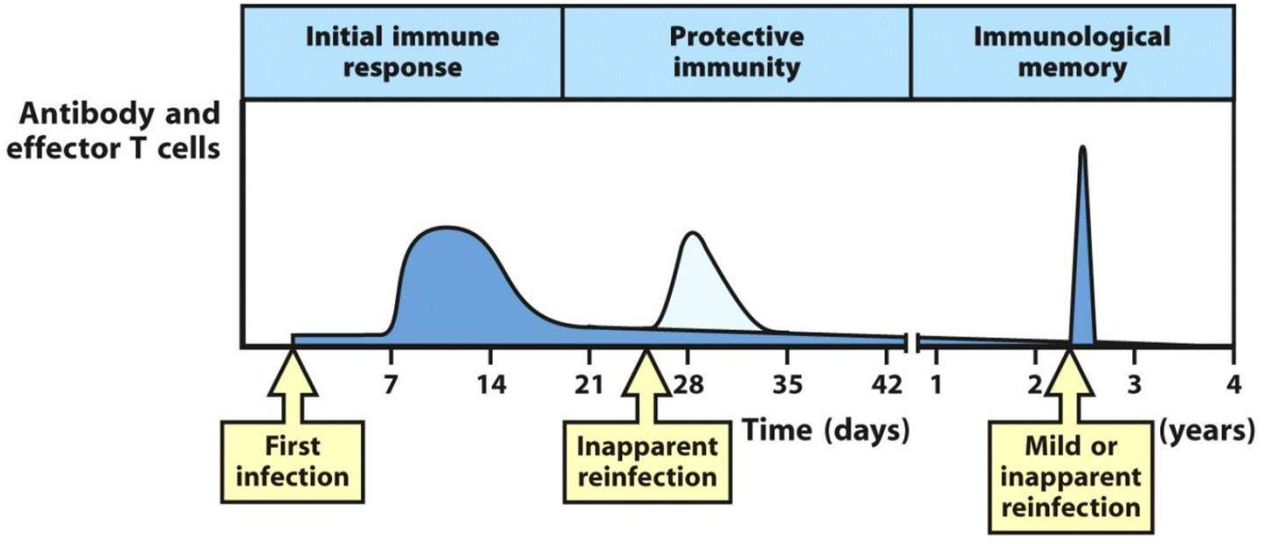
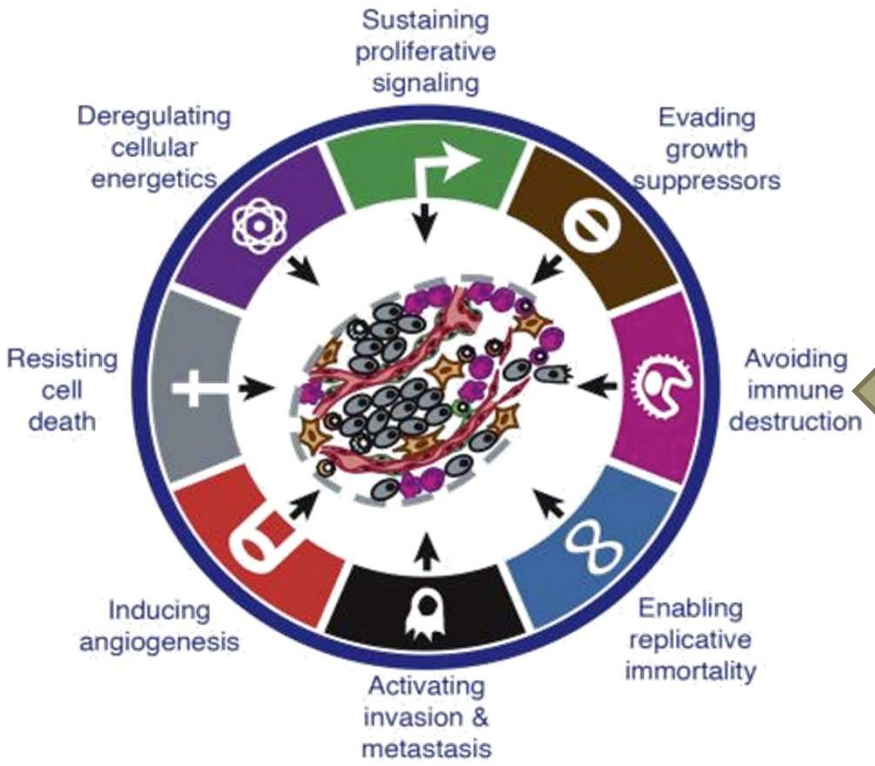


Figure 11.16 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)

Hallmarks of Cancer



- Cancer arises in part due to the failure of the immune system to detect and act on mutant/aberrant cells

- **THE CHALLENGE** –
  - Recognition of "self" cancer cells
  - Eliminating normal immune response suppression co-opted by cancer cells

Hanahan and Weinberg, *Cell* 2011.

Autoimmunity

The most important question that the immune system must answer over and over:
<u>Is this cell/tissue/protein self?</u>

- **Self** – uninfected, healthy, normal (i.e. no genetic mutations)
- **Non-self** – viruses, bacteria, fungus, parasites, etc., cells that are infected by these pathogens and diseased cells that are dangerous (including cancer)

Immune Surveillance

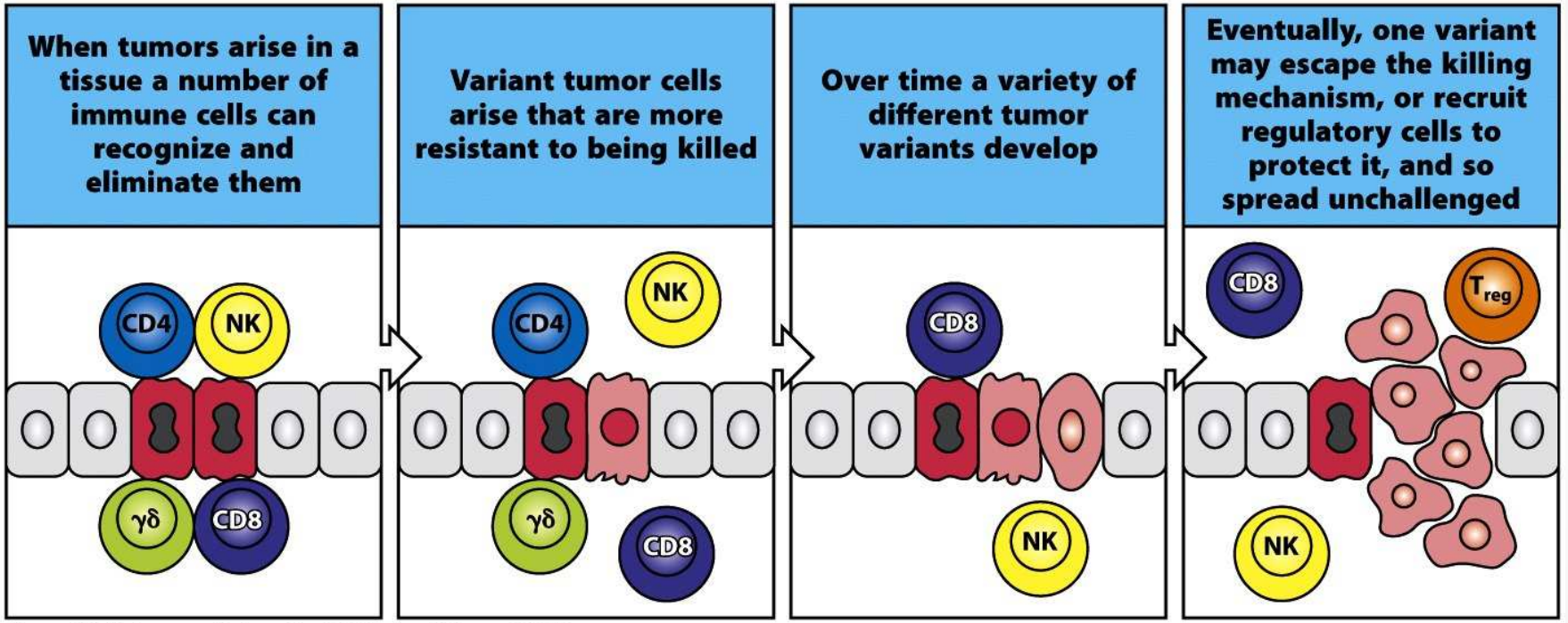


Figure 15-13 Immunobiology, 7ed. (© Garland Science 2008)

Autoimmunity

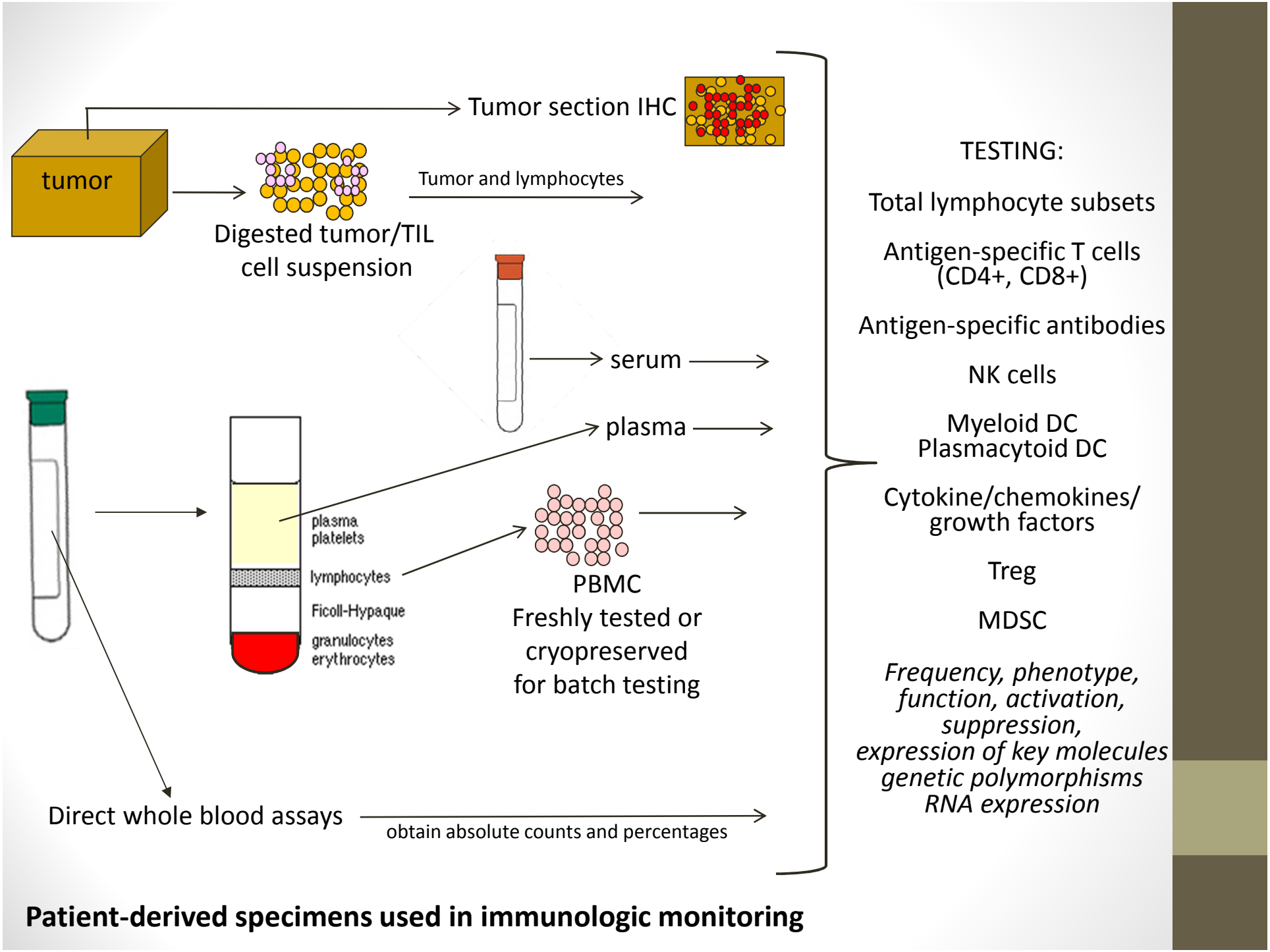
The most important question that the immune system must answer over and over:
<u>Is this cell/tissue/protein self?</u>

- If the immune system answers this question incorrectly: the disease will not be cleared or, even worse, autoimmunity
- **AUTOIMMUNITY** – *failure of tolerance to self* leading to the destruction of healthy tissues (lupus, type I diabetes, vitiligo)

Measuring Immunity:

Did the intervention “hit the target”?
Did the desired immune modulation occur?
Was anti-tumor immunity induced?
Was immune suppression reversed?
Were the target cells/molecules activated?

Did the target cells/molecules get to the tumor site and show activity?



Patient-derived specimens used in immunologic monitoring

Take Home Messages

- The immune system consists of a series of structures and cells that give it system wide access to protect against a tremendous variety of targets
- The immune response involves a series of specific steps starting from detection of a target to its elimination and finally returning the body to its normal state
- Many disease states, particularly cancer, arise from failed immune surveillance responses and activating and re-directing the immune system is the goal of of all immunotherapy from vaccination to checkpoint inhibitors