Immunology 101

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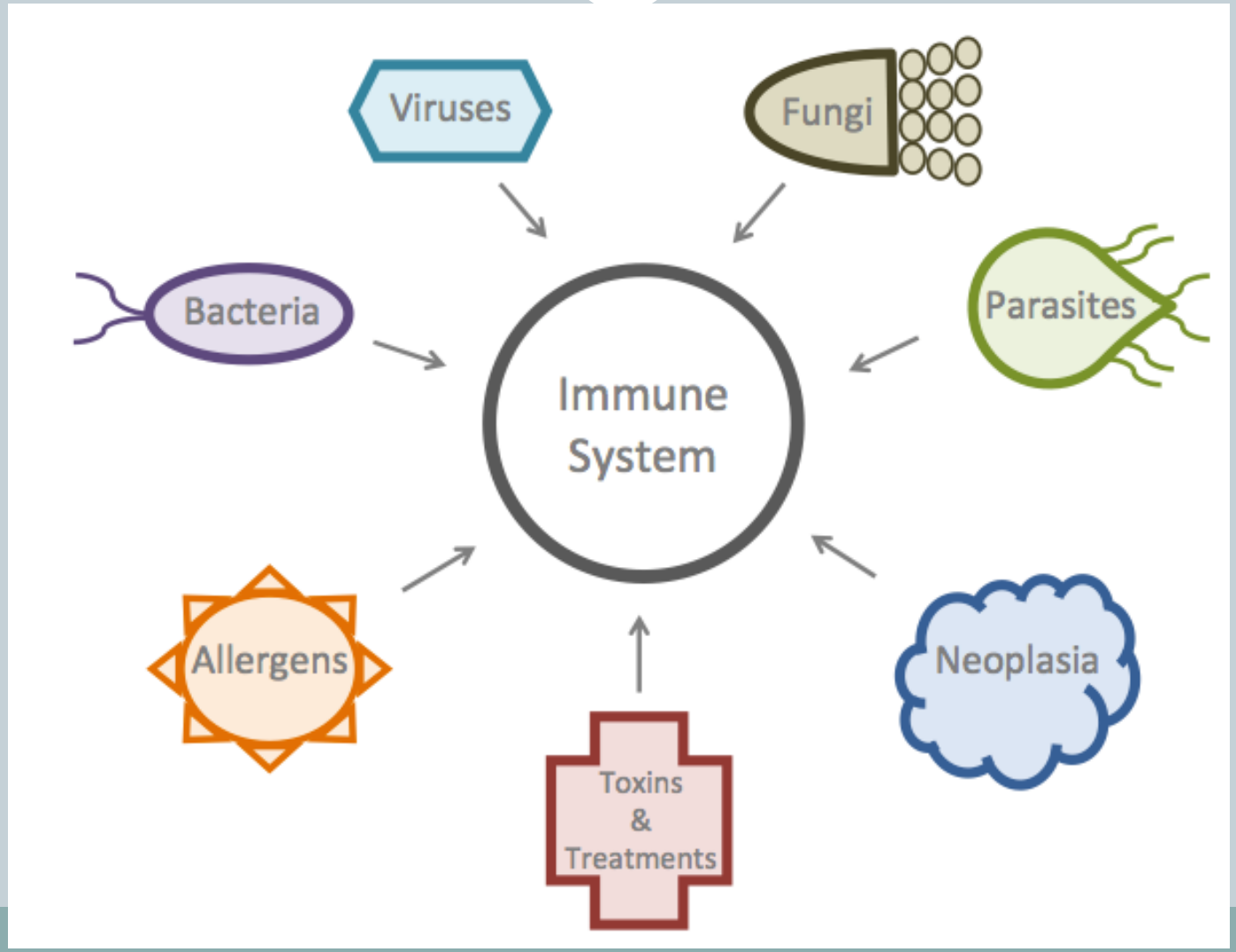
Key Concepts

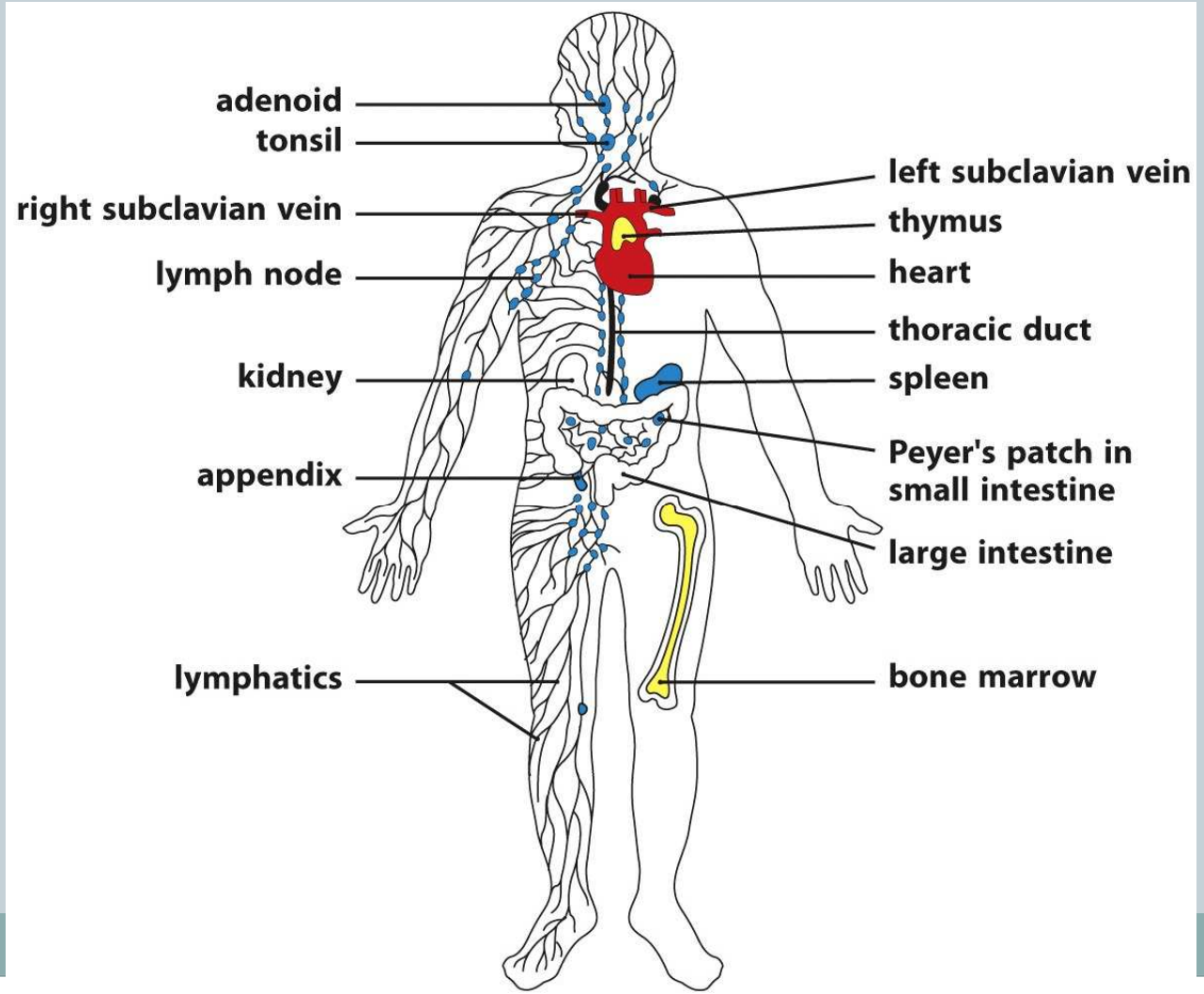
- Anatomy of the immune system
- Hematopoiesis
- Innate Immunity
  - Cellular players
- Adaptive Immunity
  - Antigen recognition (cellular and humoral immunity)
  - Costimulation
- Immune Regulation
- Tumor immunology
  - Immune checkpoints
  - Modulation of cellular responses
- Tumor Immunotherapy

Activation of the Immune System

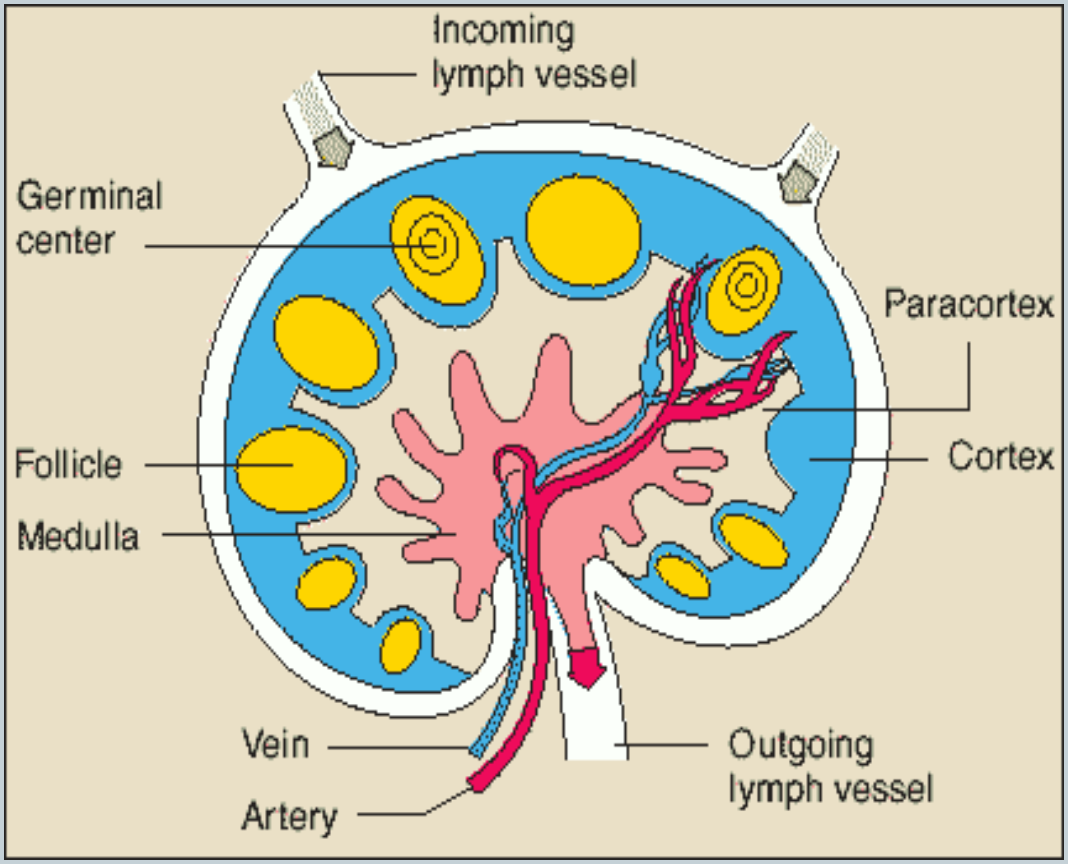


Anatomy of the Immune System

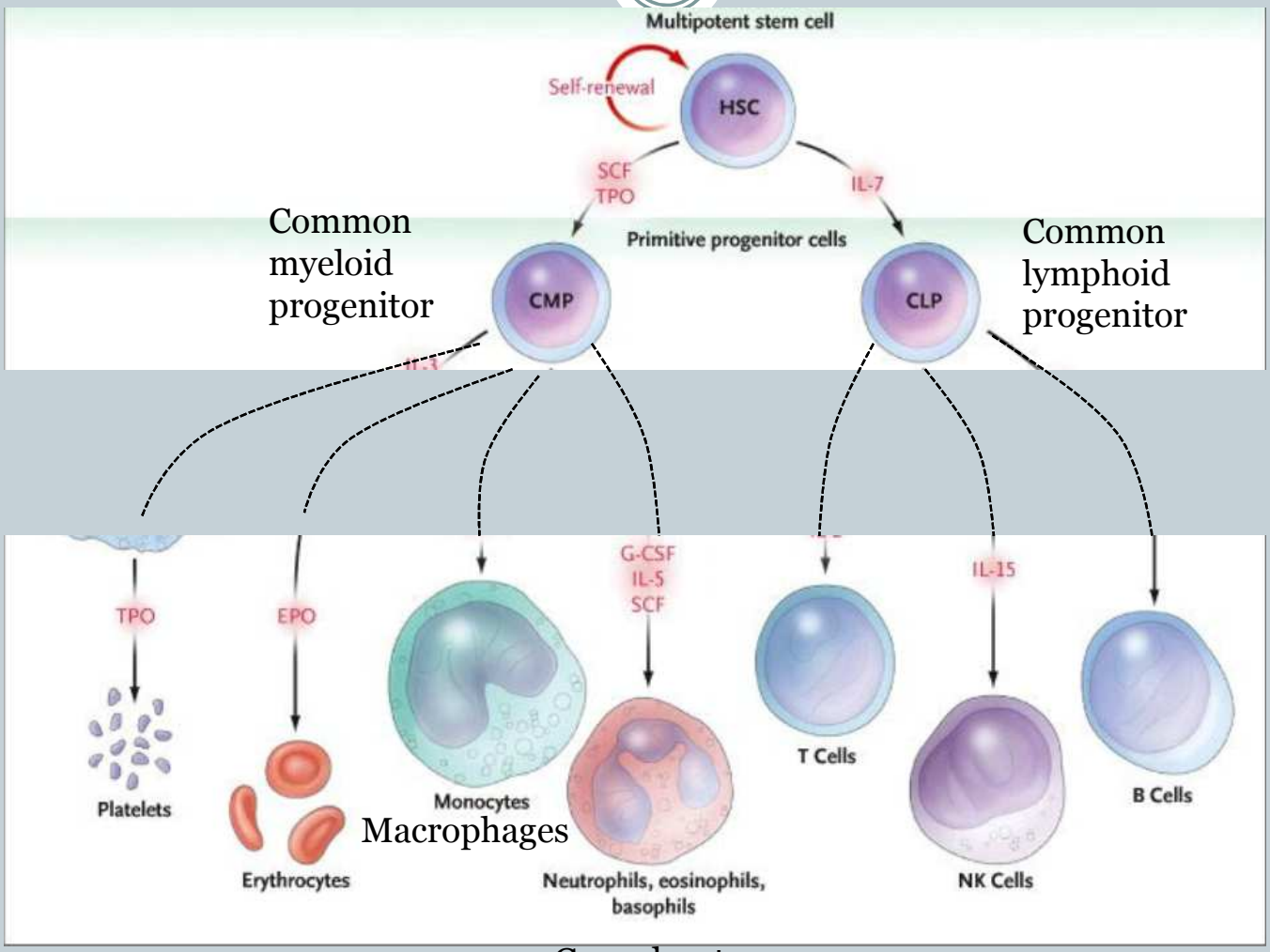
Organs of the Immune System



Anatomy of a Lymph Node



Hematopoiesis

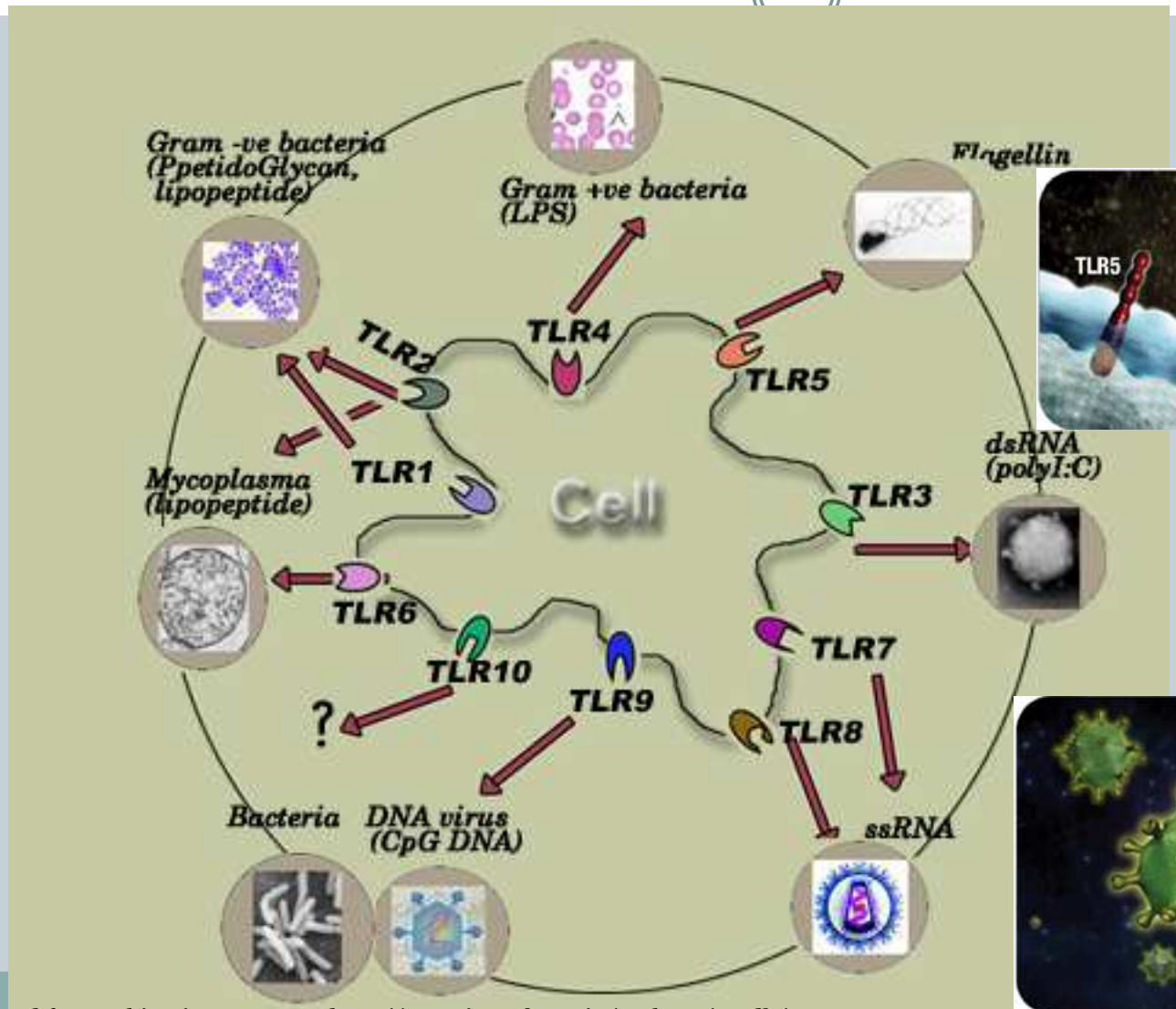


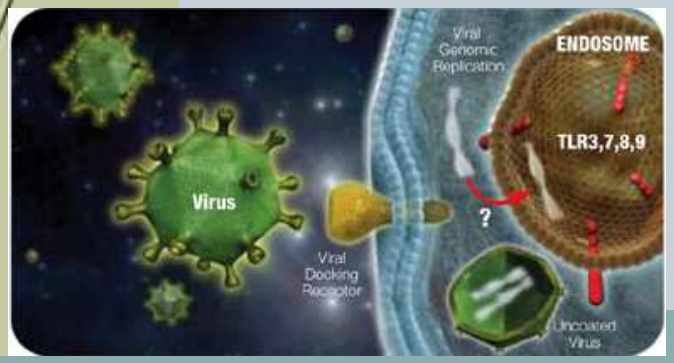
Adapted from Kaushansky K *NEJM*. 2006

Innate vs Adaptive Immunity

	Innate Immunity	Adaptive Immunity
Speed	Fast	Slow
Long-lasting memory	No	Yes
Encoding of receptors	Germline	Somatic
Distribution of receptors	Nonclonal	Clonal
Repertoire of receptors	Limited	Very large
Recognition	Perfect	Imperfect

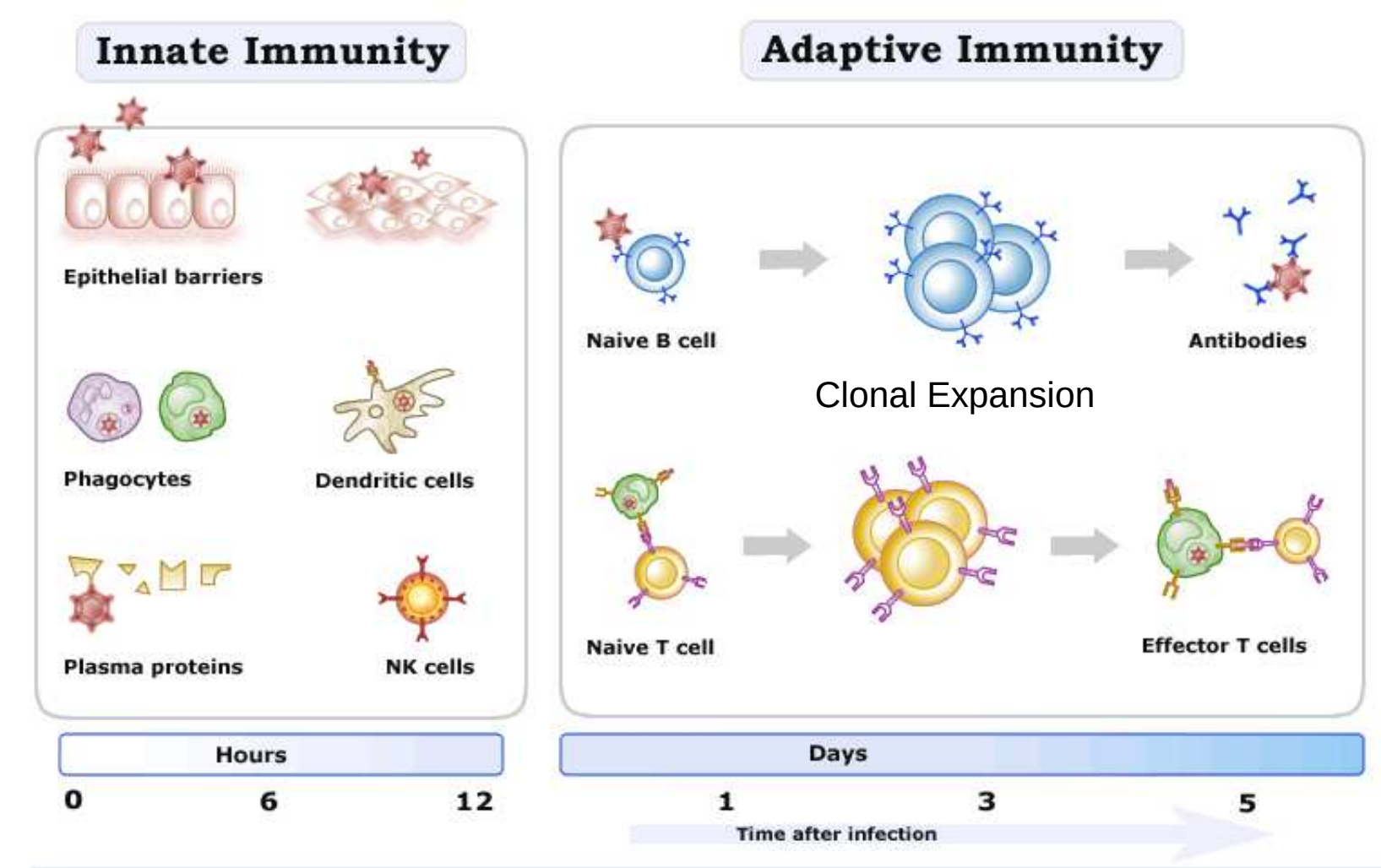
Innate Immune System Activation:
Repertoire of receptors and pathogen recognition





Adapted from sabiosciences.com & http://www.imtech.res.in/raghava/prrdb/

Innate vs Adaptive Immunity: Speed



http://missinglink.ucsf.edu/lm/immunology_module/prologue/objectives/obj02.html

Linking Innate & Adaptive Immunity: Dendritic Cells

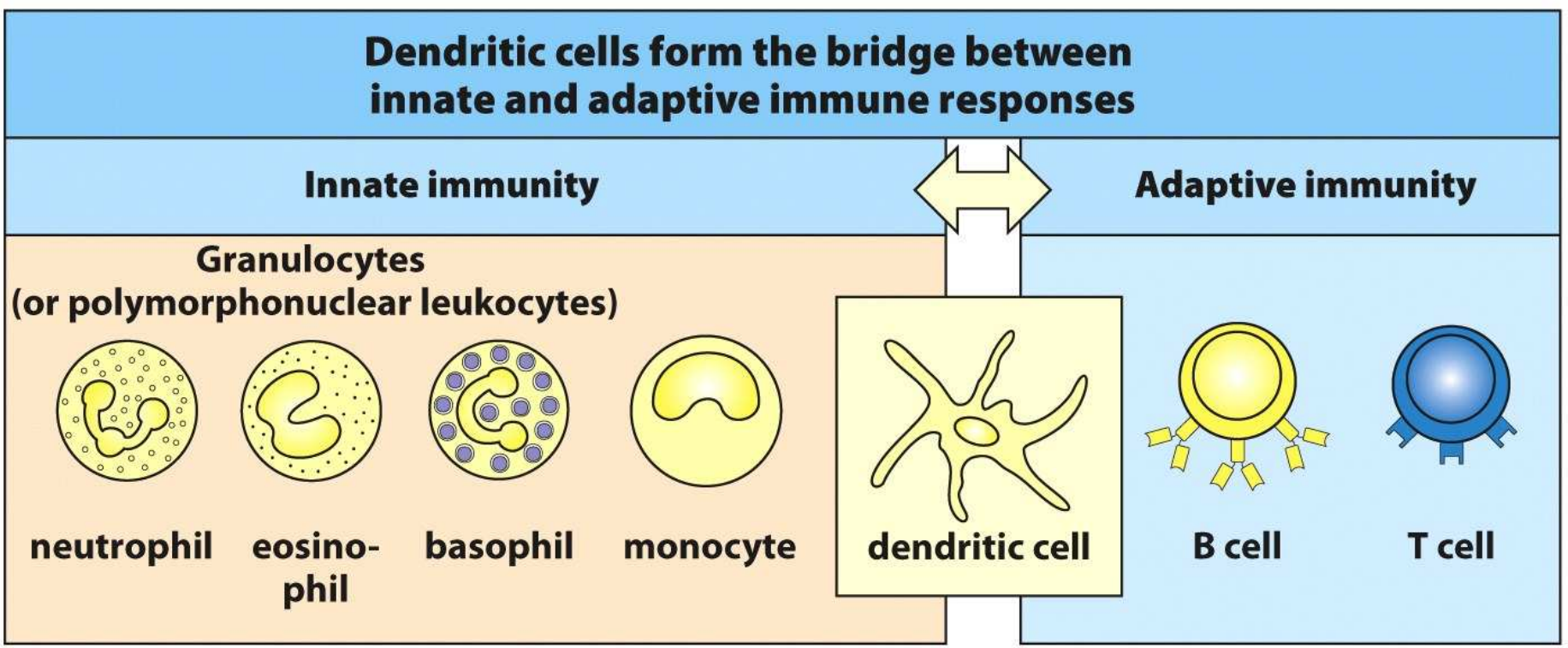
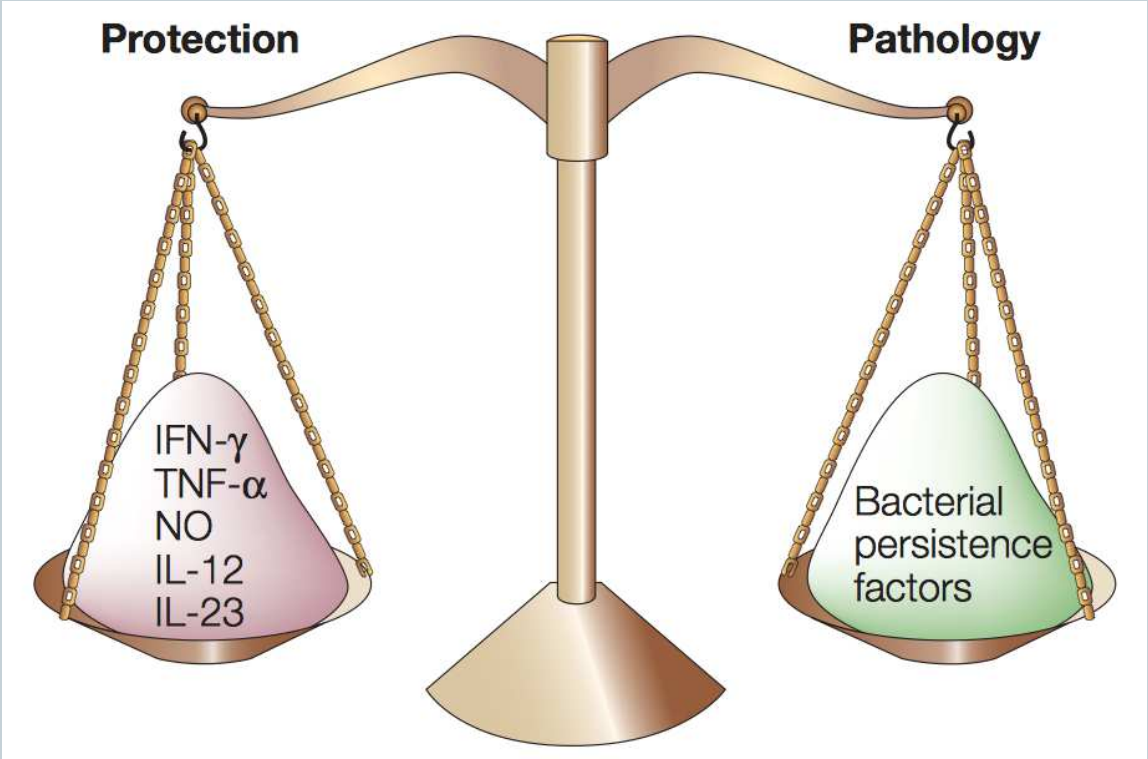


Figure 1.5 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Effective Immunity Requires Balance



Falkow S. *Nature Reviews. Microbiology* 2004

Adaptive Immunity is Epitope Specific

The human genome is composed of ~21,000 genes but has the capability of providing immunological protection against a nearly limitless number of antigens. How does the immune system achieve this level of protection?

	Innate Immunity	Adaptive Immunity
Encoding of receptors	Germline	**Somatic**
Repertoire of receptors	Limited	**Very large**

Antigen Receptor Diversity

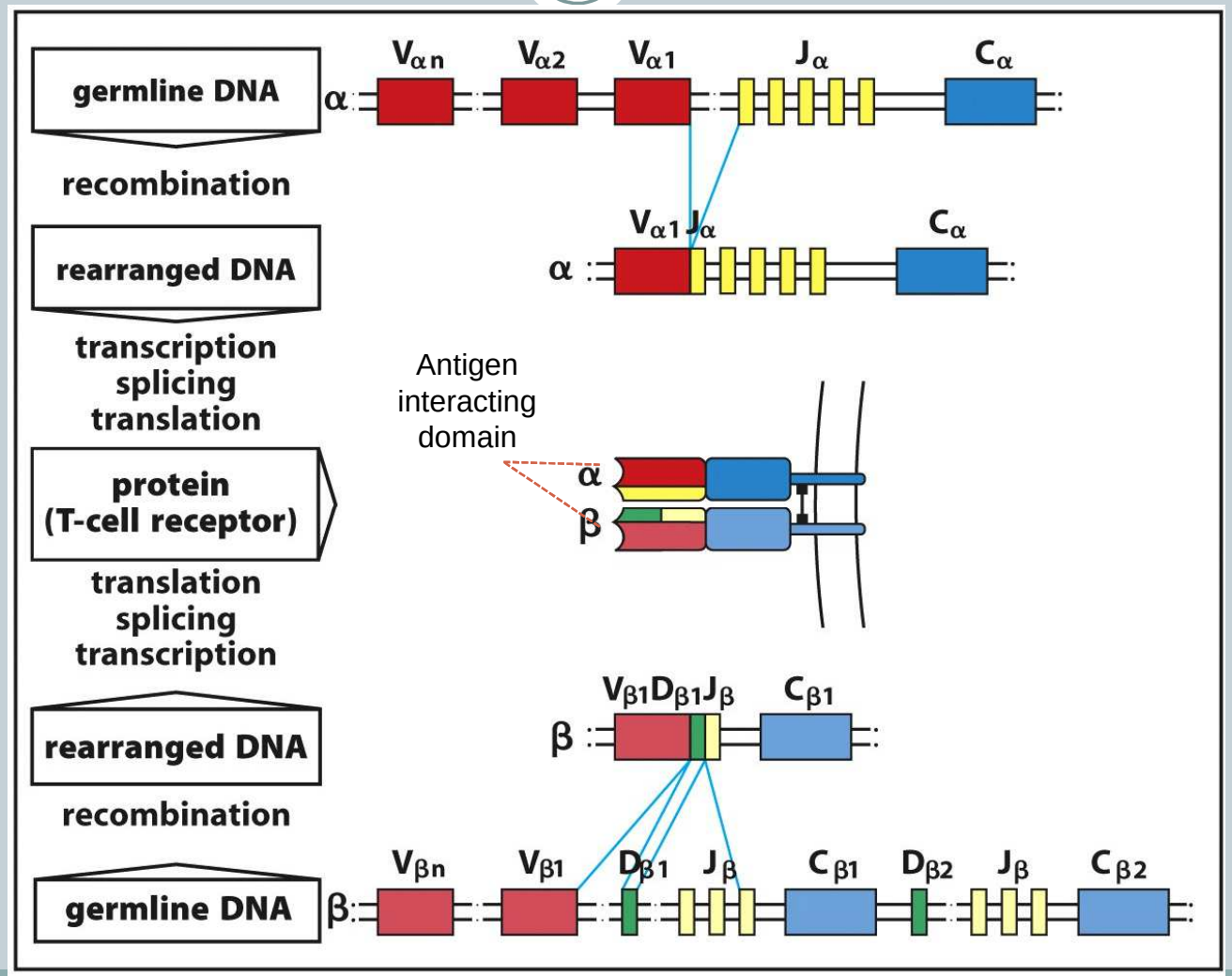
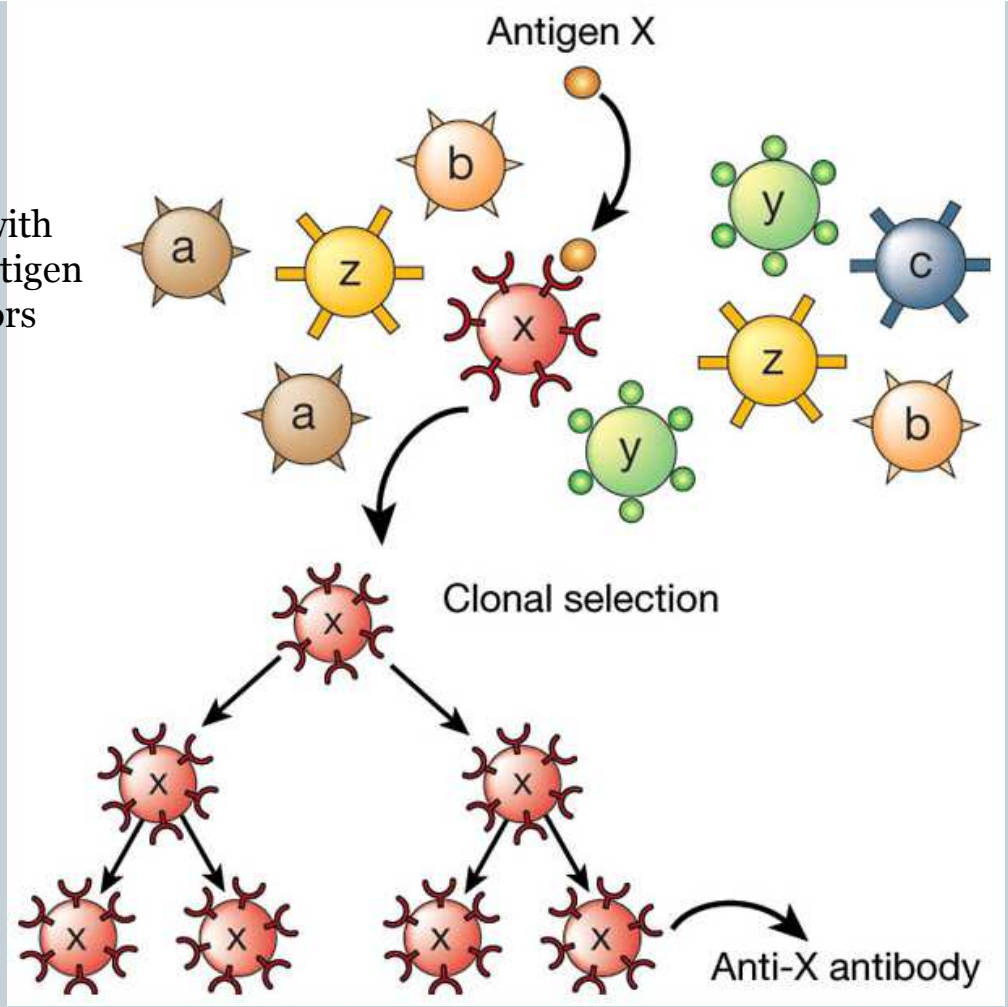


Figure 5.9 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

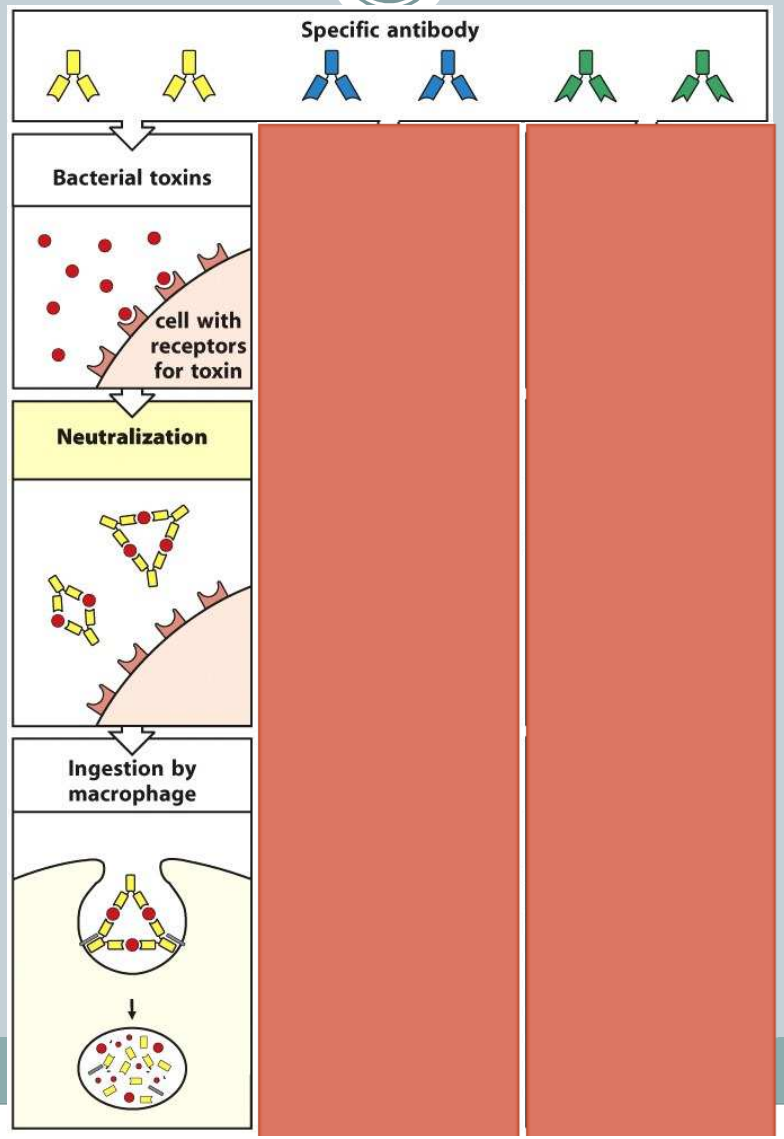
Adaptive Immune System Activation:
B cells and Antibody Formation

B cells with unique antigen receptors



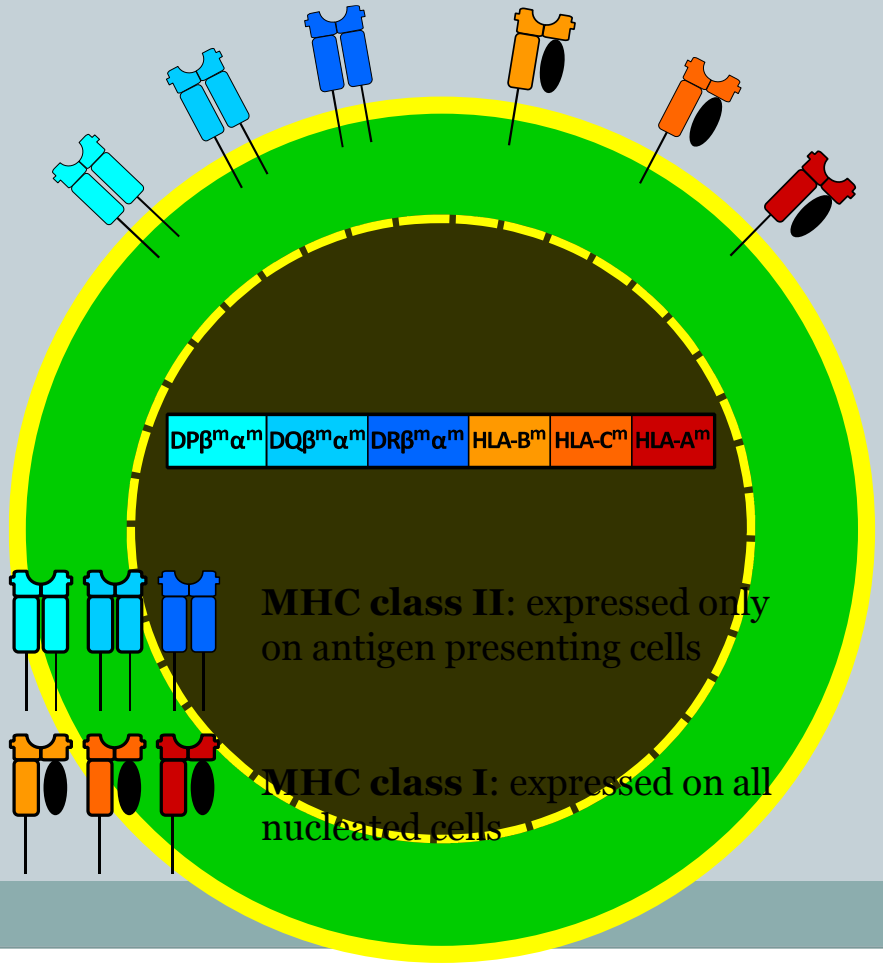
Gustave JV Nossal. *Nature*. 2003

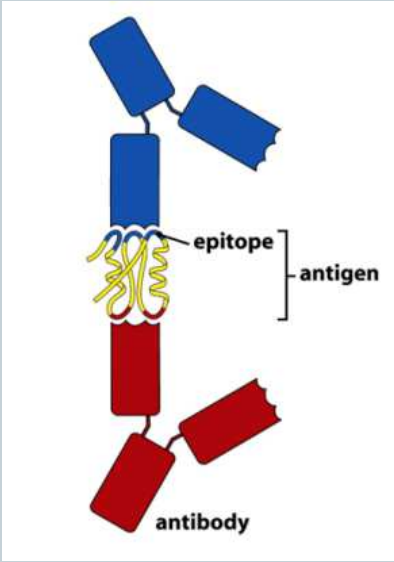
Traditional Antibody Mechanisms of Action



Adaptive Immune System Activation:
T cells and Antigen Recognition

Major histocompatibility antigens (HLA)





http://en.wikipedia.org/wiki/Human_leukocyte_antigen

Antigen Presentation: T cell recognition of antigen fragment and self molecule

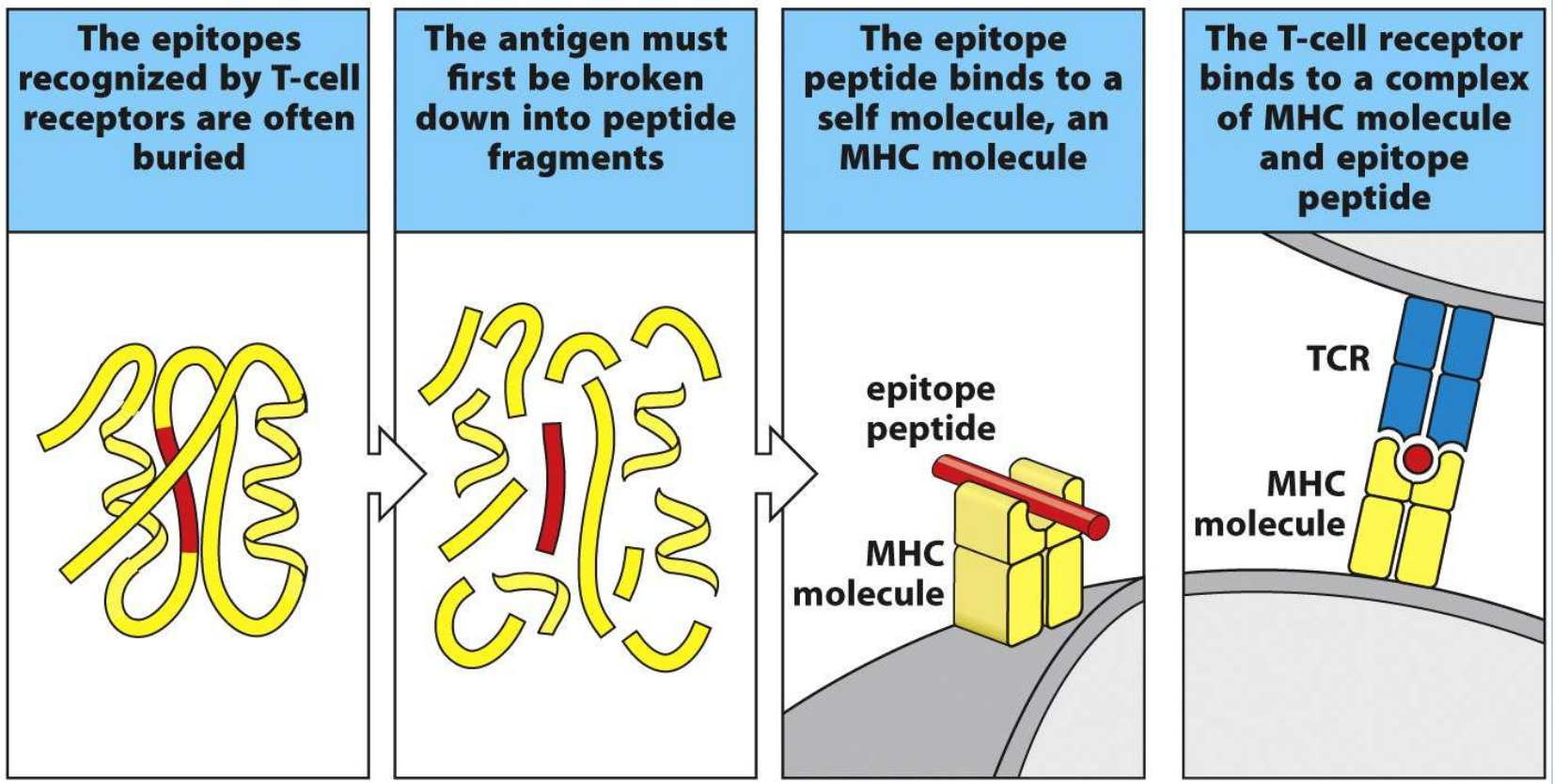
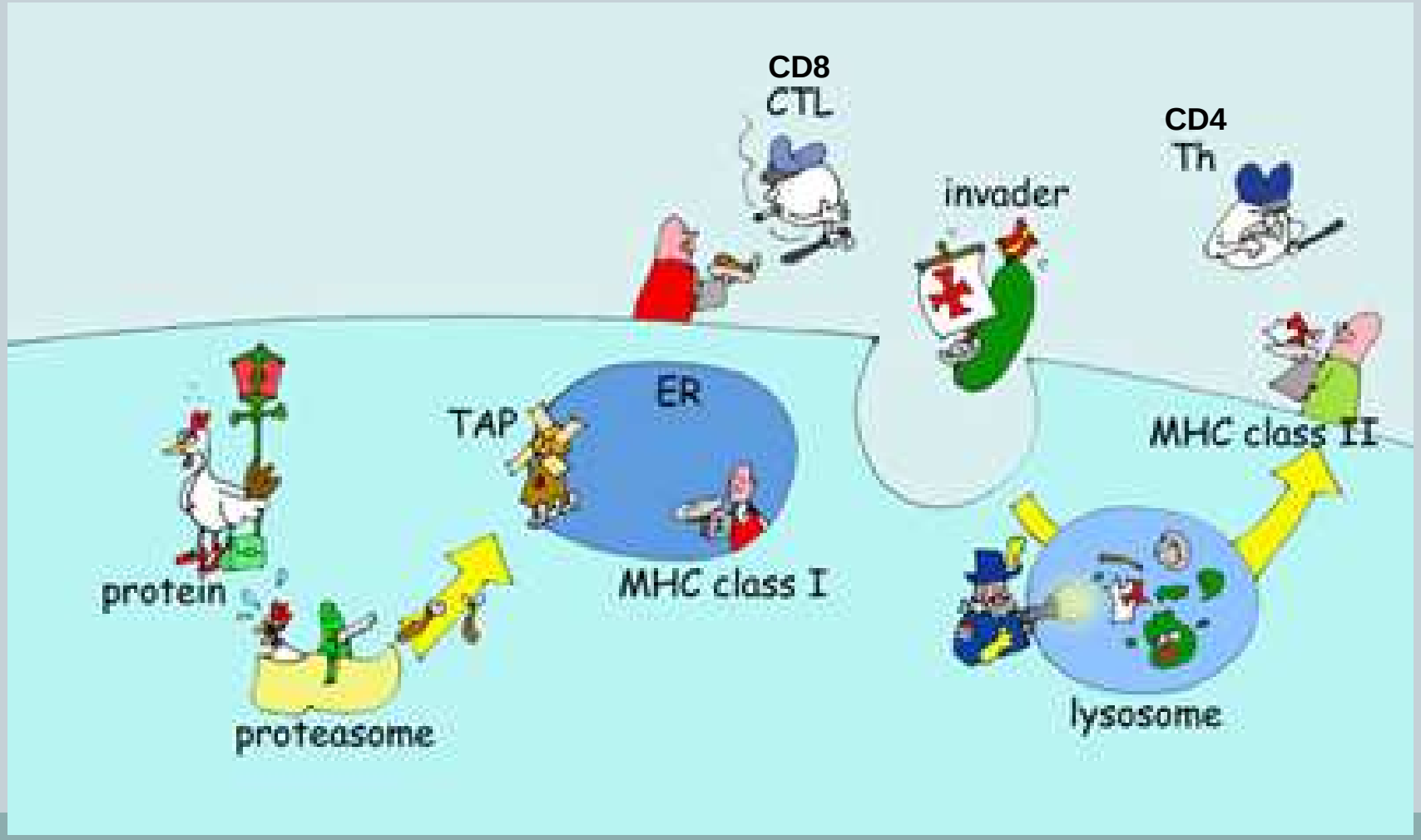


Figure 1.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Antigen Presentation: The Generation of Antigens



Adapted from J. Yewdell; Nature Immunology 2003.

Review

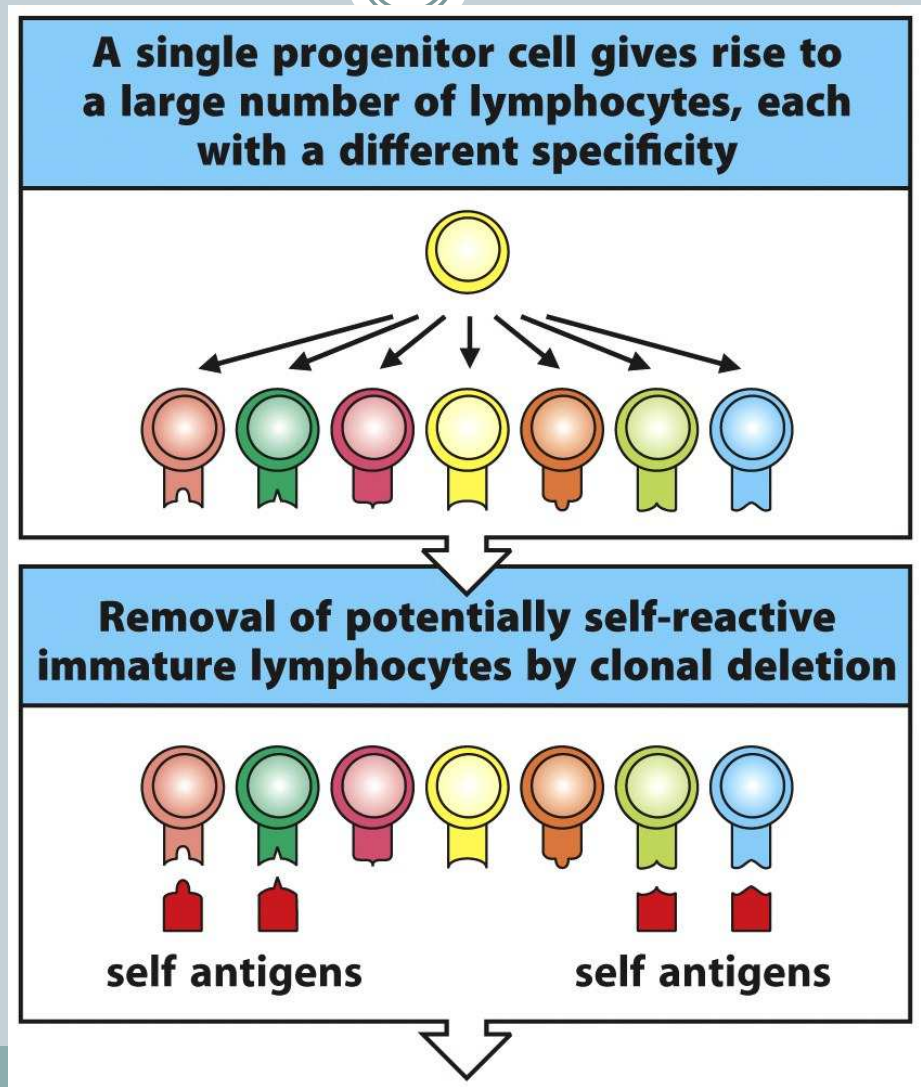
- Activation of the innate immune system by microbes alerts the adaptive immune system and the bridge between these two systems are dendritic cells.
- While the innate immune system has a limited number of pathogen recognition receptors, the adaptive immune system has a nearly limitless number; the result of gene rearrangements in developing lymphocytes.
- Antigen receptors on B cells recognize native proteins while T cell antigen receptors require the peptide to be degraded and an antigenic epitope paired with a self MHC molecule (known as peptide·MHC)

How does the adaptive immune system differentiate between self and foreign proteins to prevent immune mediated pathology (autoimmunity)?

T Cell Selection:
A Balance Between Protection and Pathology

Bone Marrow

Thymus



Thymus

Figure 1.12 part 1 of 3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

T Cell Selection:
A Balance Between Protection and Pathology

Thymus

Lymph nodes/
Circulating
lymphatics

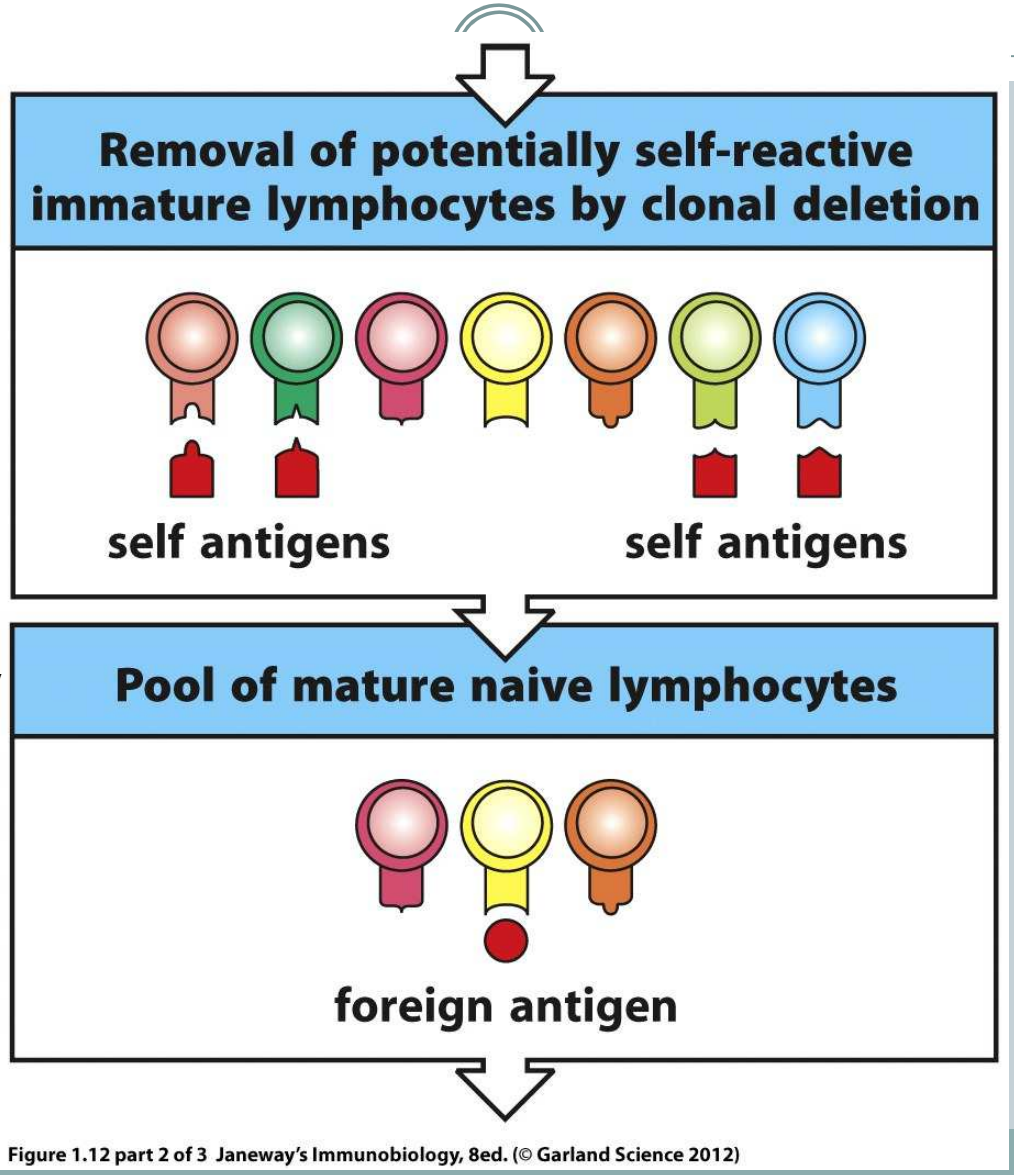


Figure 1.12 part 2 of 3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

T Cell Selection:
A Balance Between Protection and Pathology

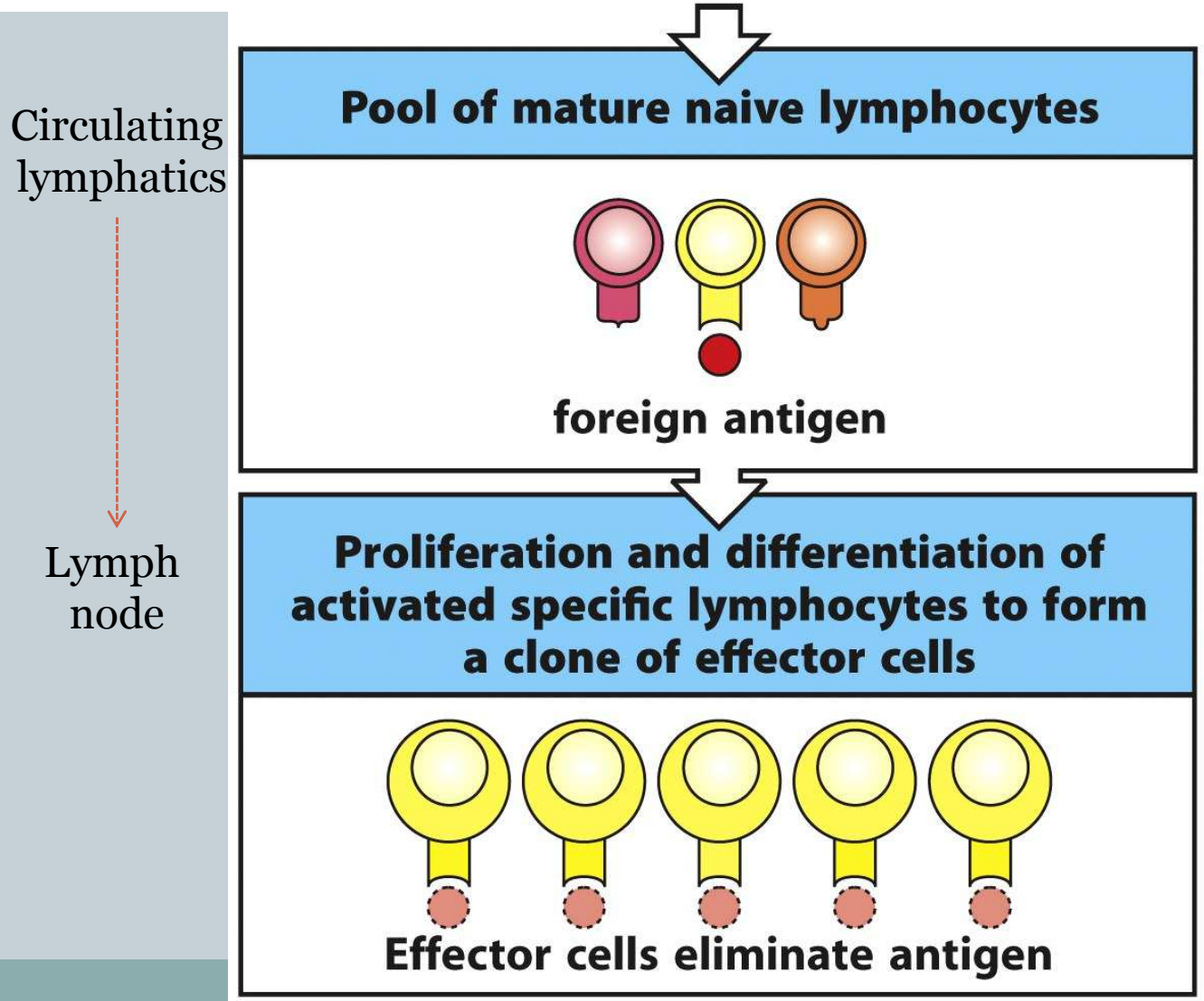
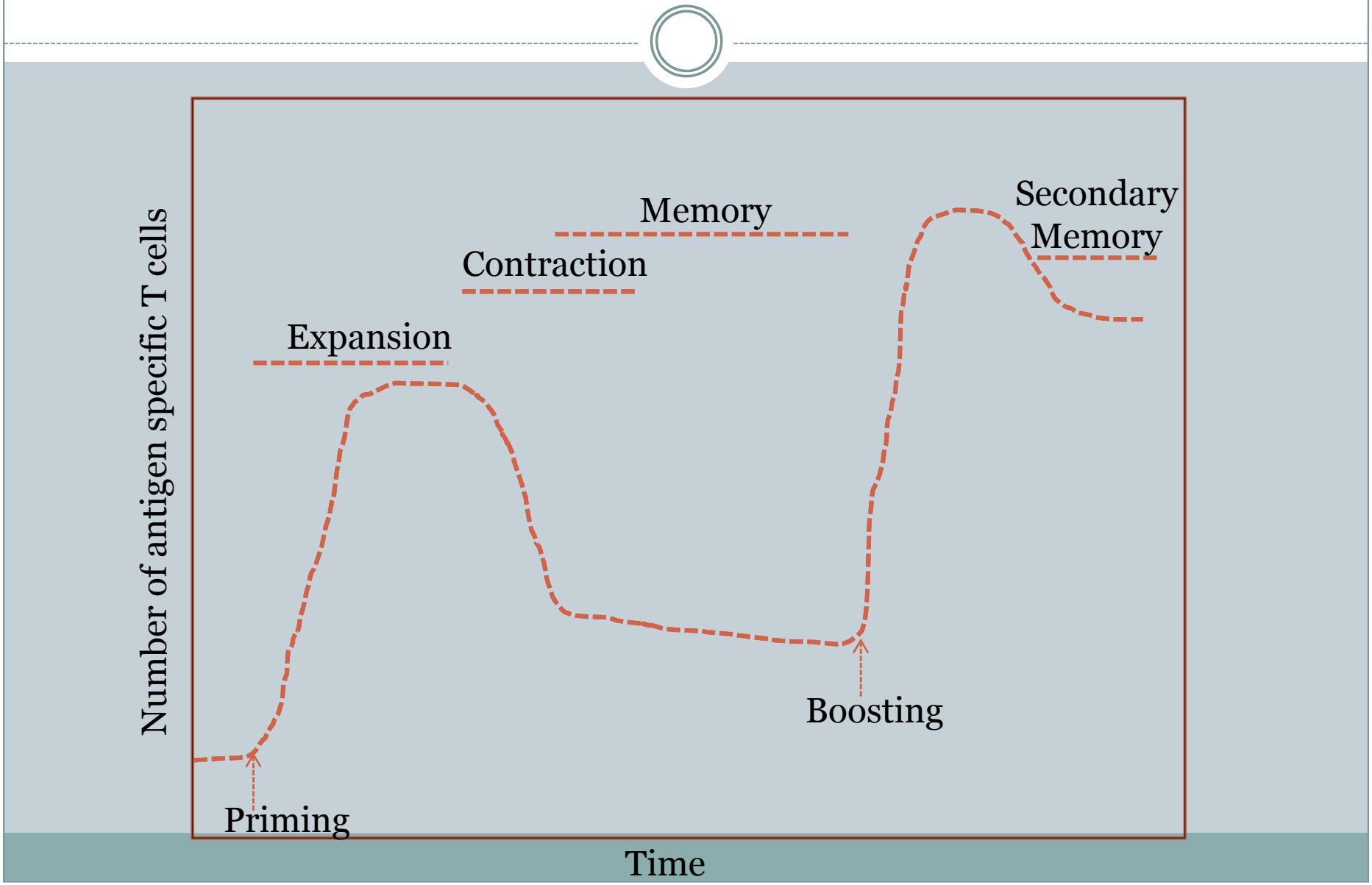


Figure 1.12 part 3 of 3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Kinetics of an Adaptive Immune Response



T Cell Subsets: Cytotoxic and Helper T Cells

CD8 (Cytotoxic)

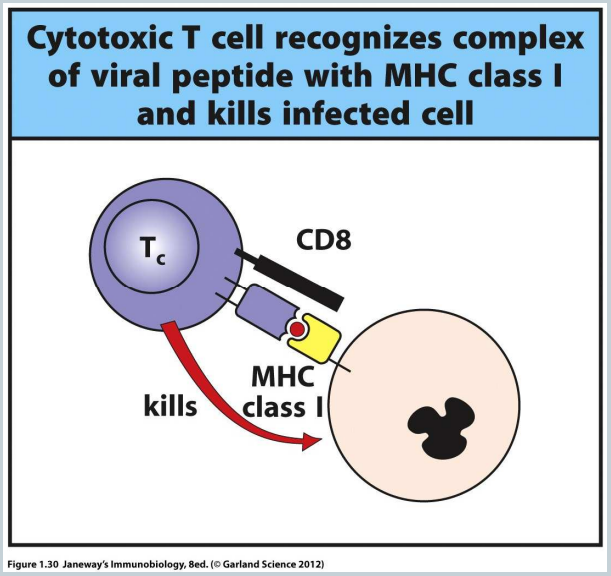


Figure 1.30 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

CD4 (Helper)

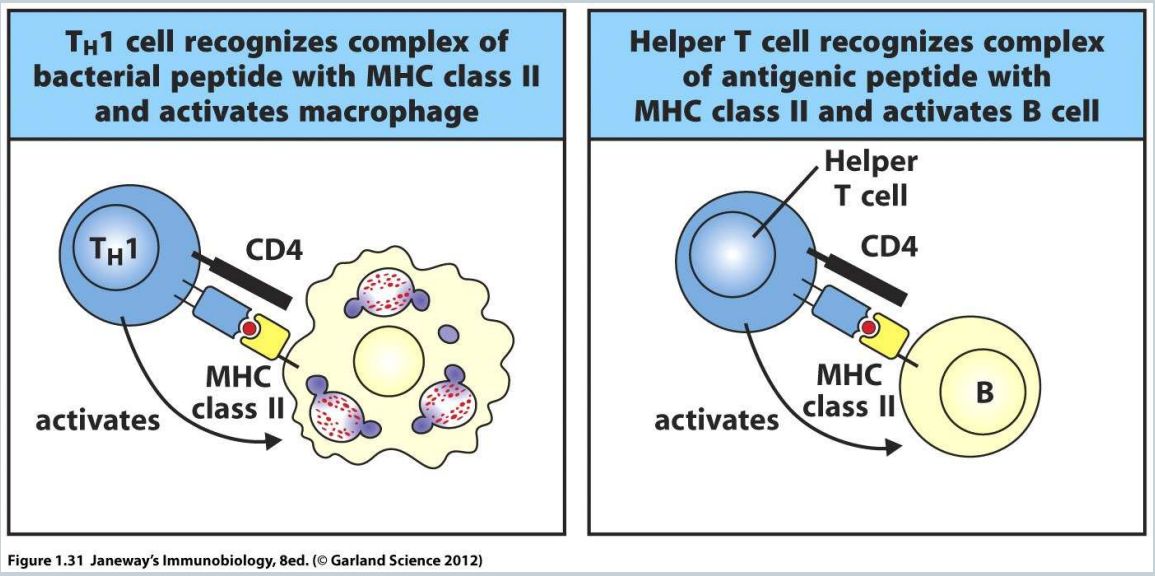


Figure 1.31 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Antigen Presenting Cells Provide 3 Signals

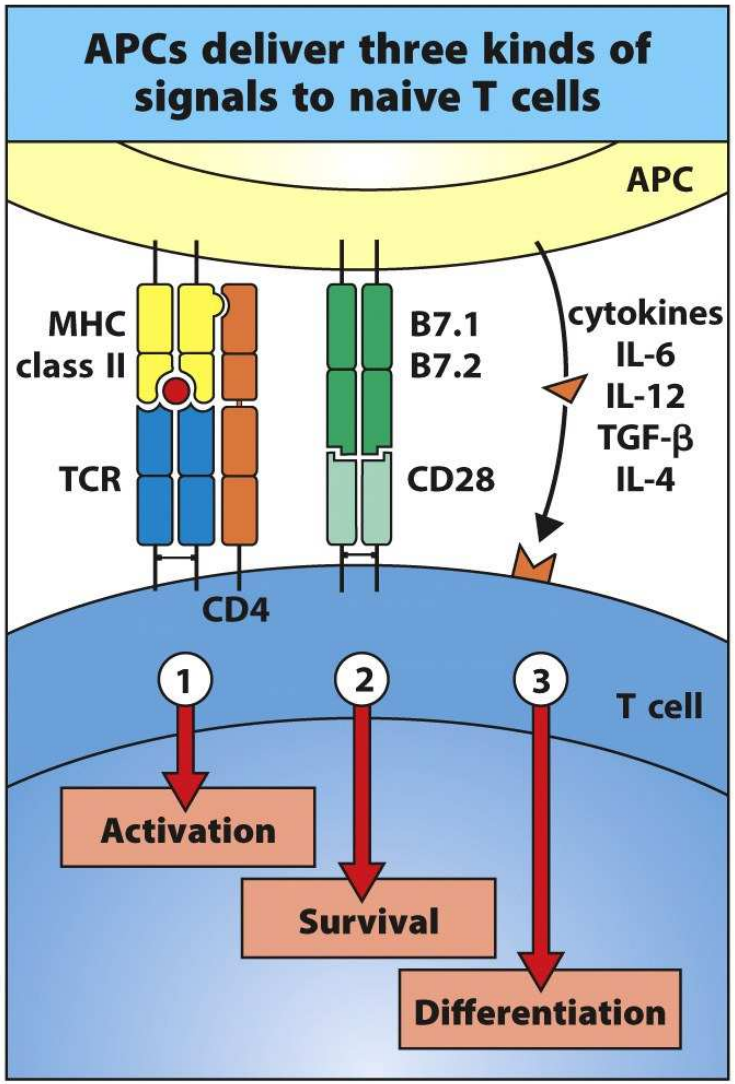
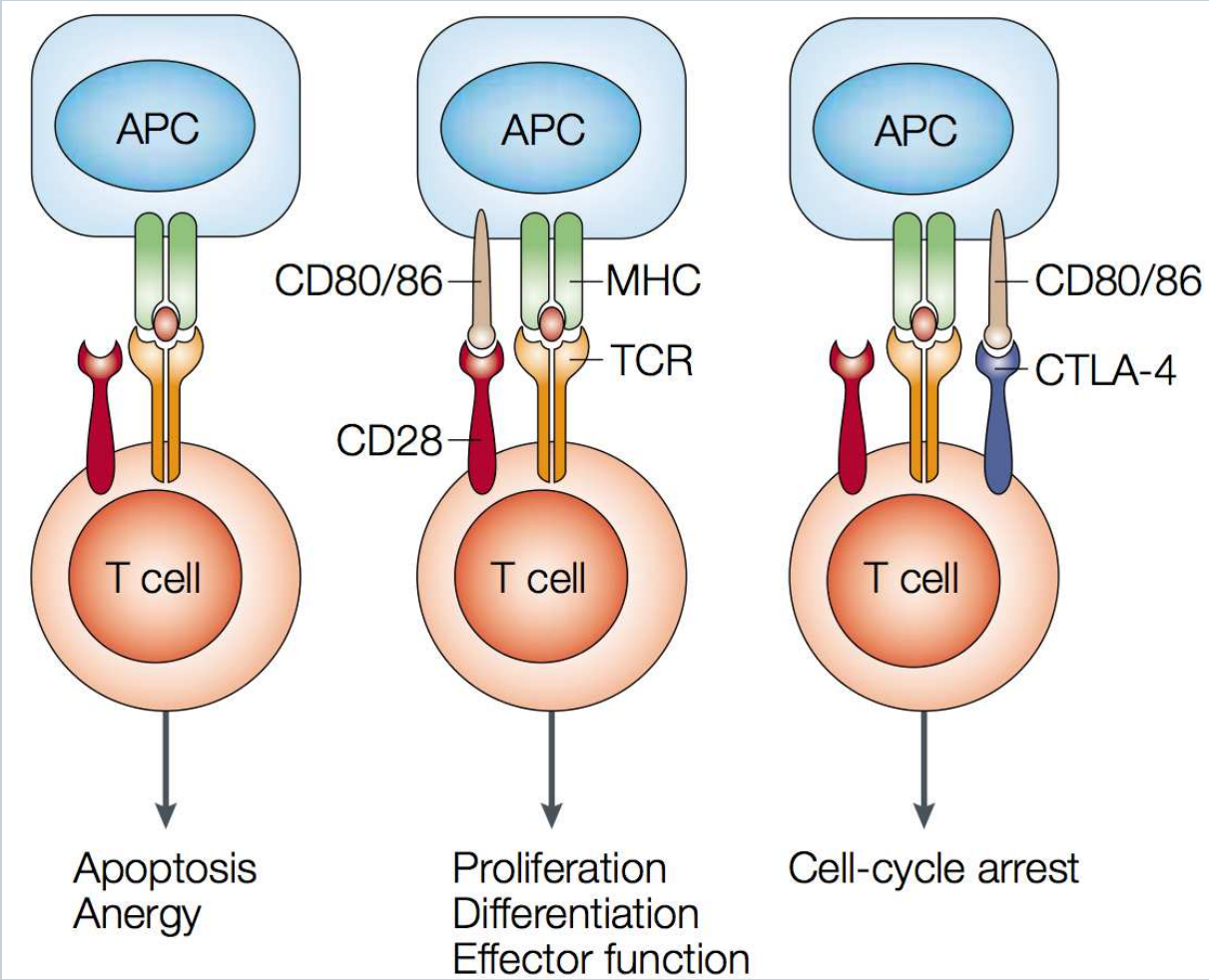
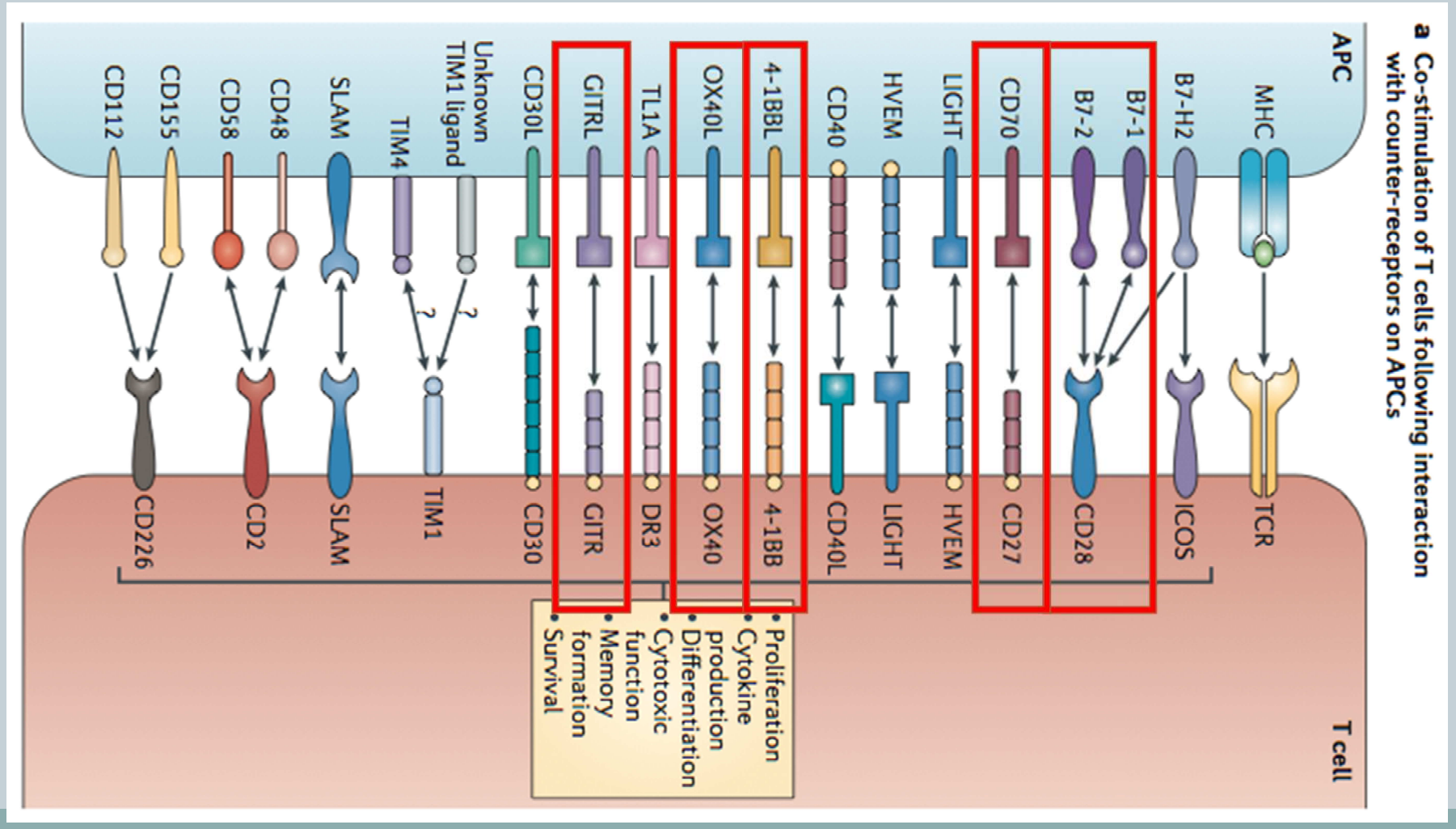


Figure 9.19 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

T Cell Activation:
The Importance of 3 Signals

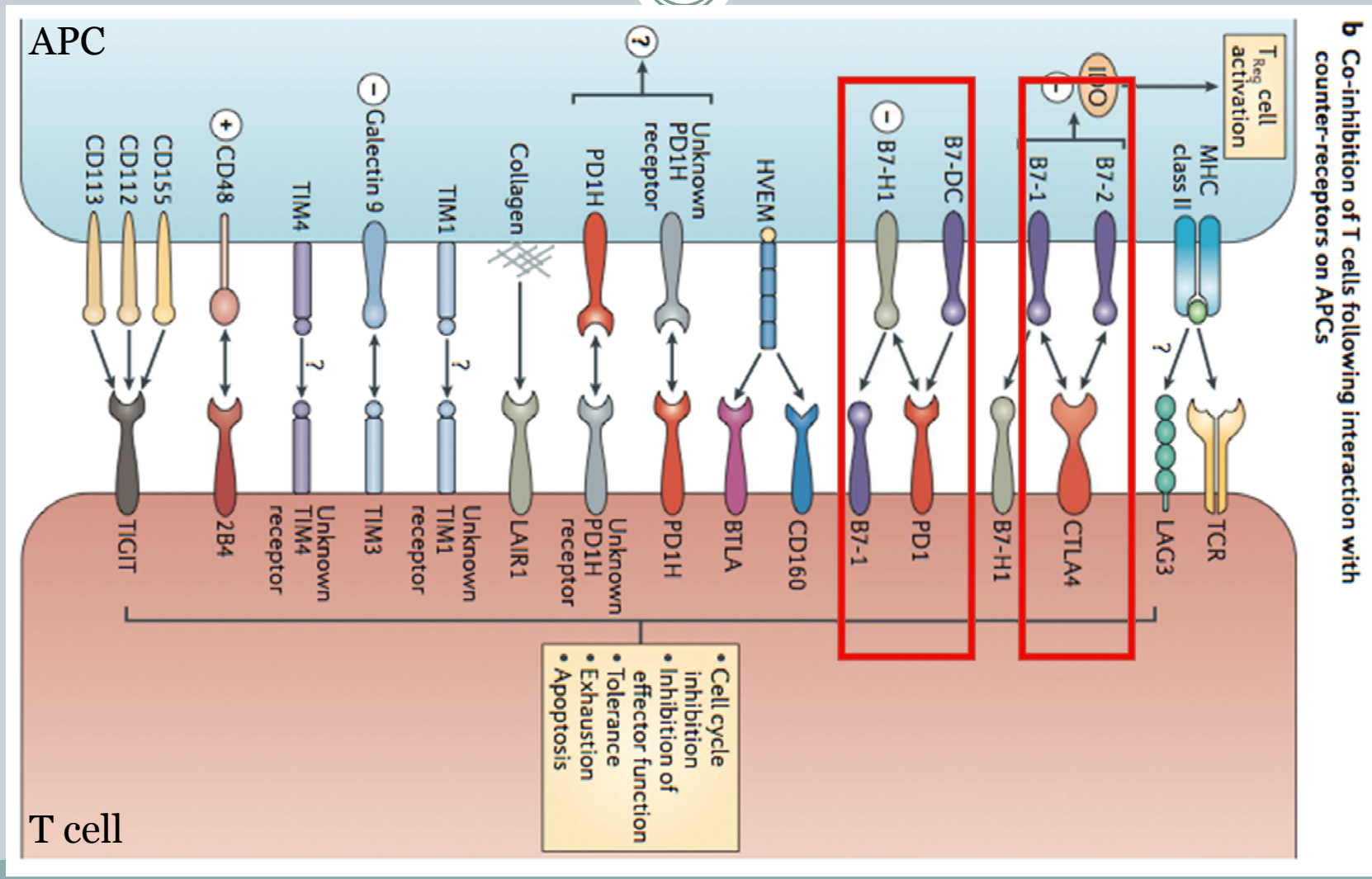


Signal 2: Multiple Means of Costimulation



Chen & Flies. *Nature Reviews Immunology* 2013

Signal 2: Dampened by Co-Inhibitory Molecules



Chen & Flies. *Nature Reviews Immunology* 2013

Antigen Presenting Cells & Signal 3:

Directors of Helper T Cell Responses

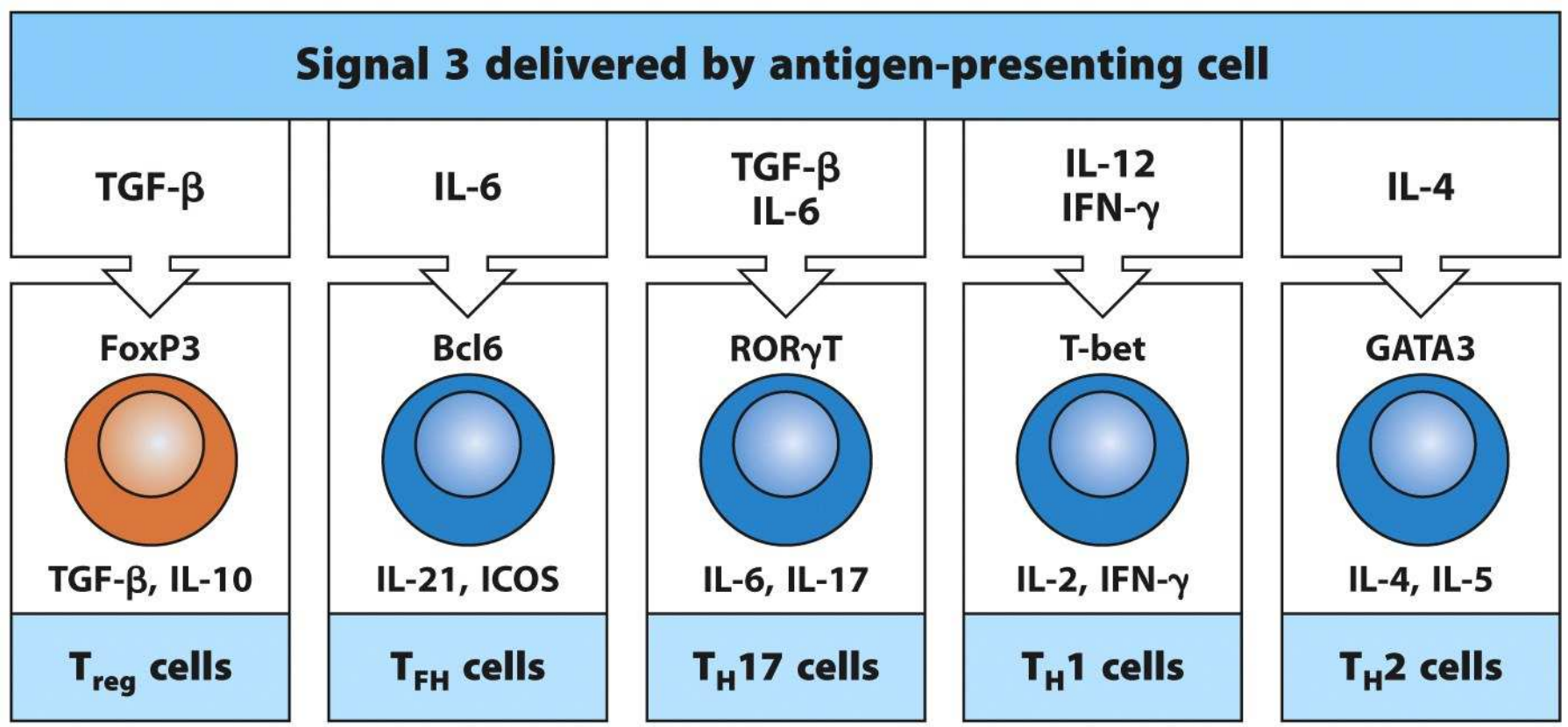
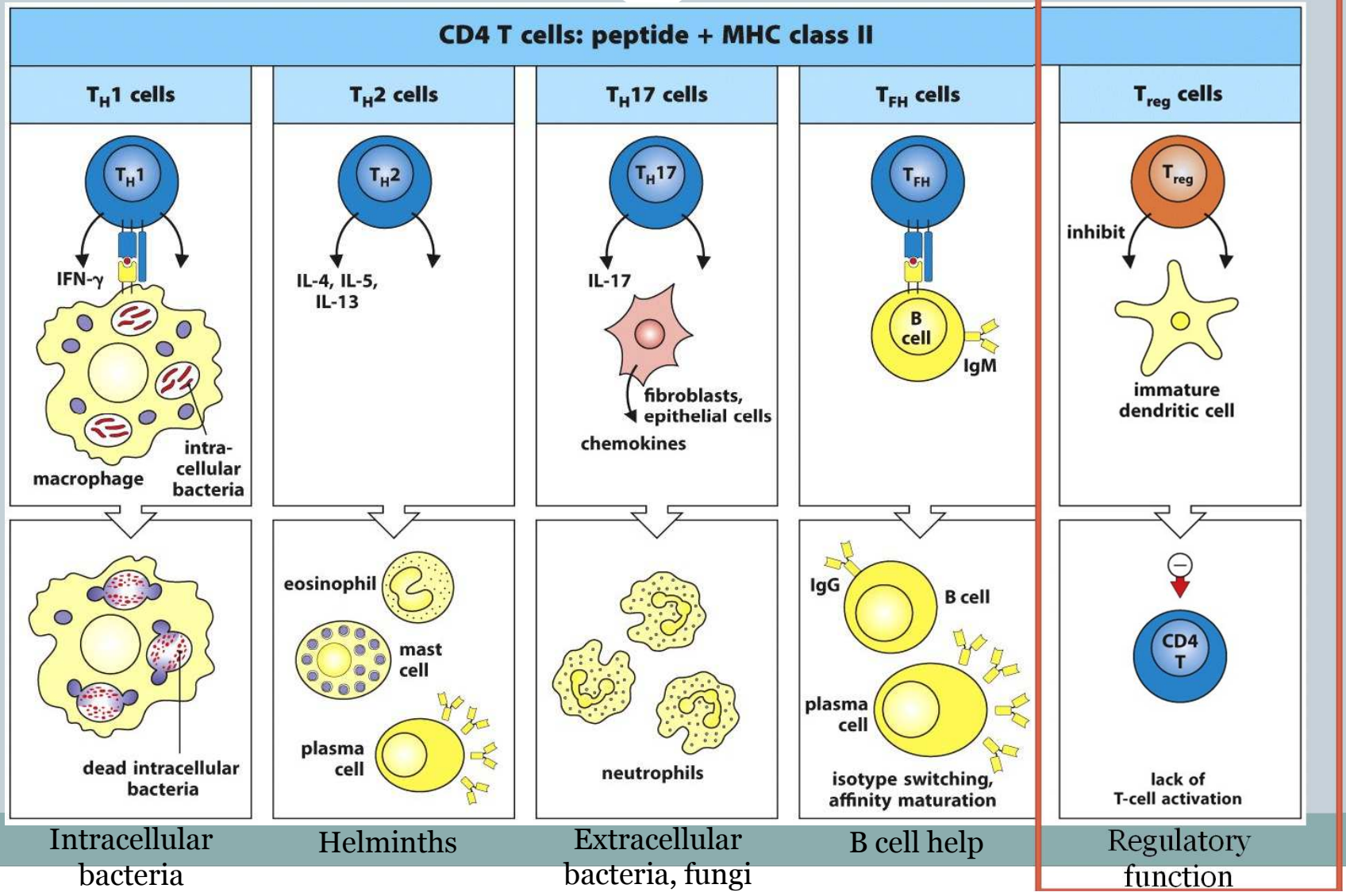


Figure 9.29 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

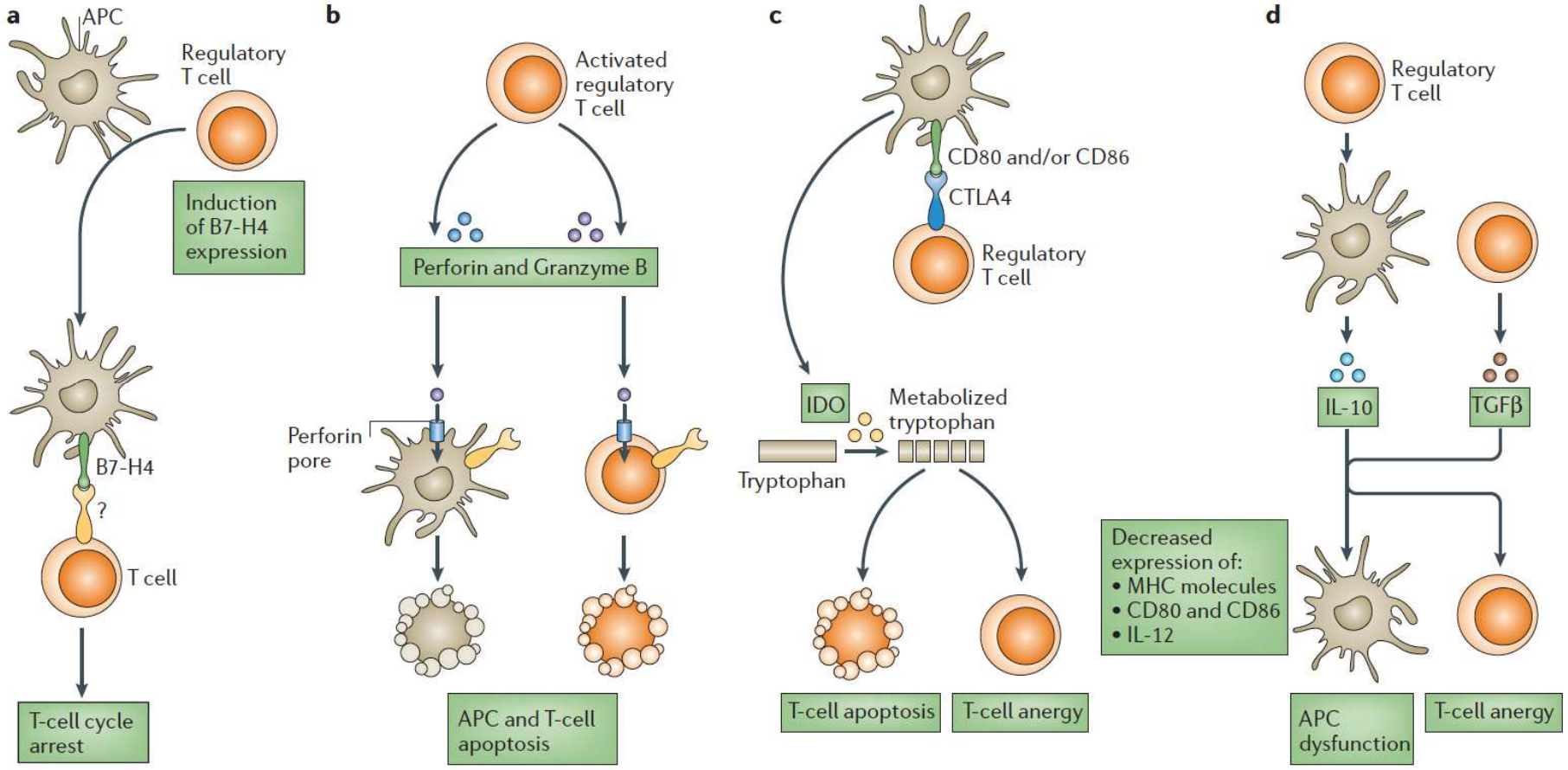
Antigen Presenting Cells:

Directors of Helper T Cell Responses



Intracellular bacteria | Helminths | Extracellular bacteria, fungi | B cell help | Regulatory function

Regulatory T Cells (Tregs):
Mechanisms of Suppression



Weiping Zou. *Nature Rev. Imm* 2006

Review

- The immune systems role is to protect the host from foreign pathogens and neoplasia.
- This is accomplished via the presentation of fragments of antigens (peptides) by self molecules known as MHC.
- Antigen presenting cells (APC) present these pMHC molecules to T cells (priming). These APCs also provide co-stimulation to the T cells for optimal activation.

How do these principles play out in the context of a tumor?

Tumor Immunology:
Immune Surveillance of Malignant Cell Growth

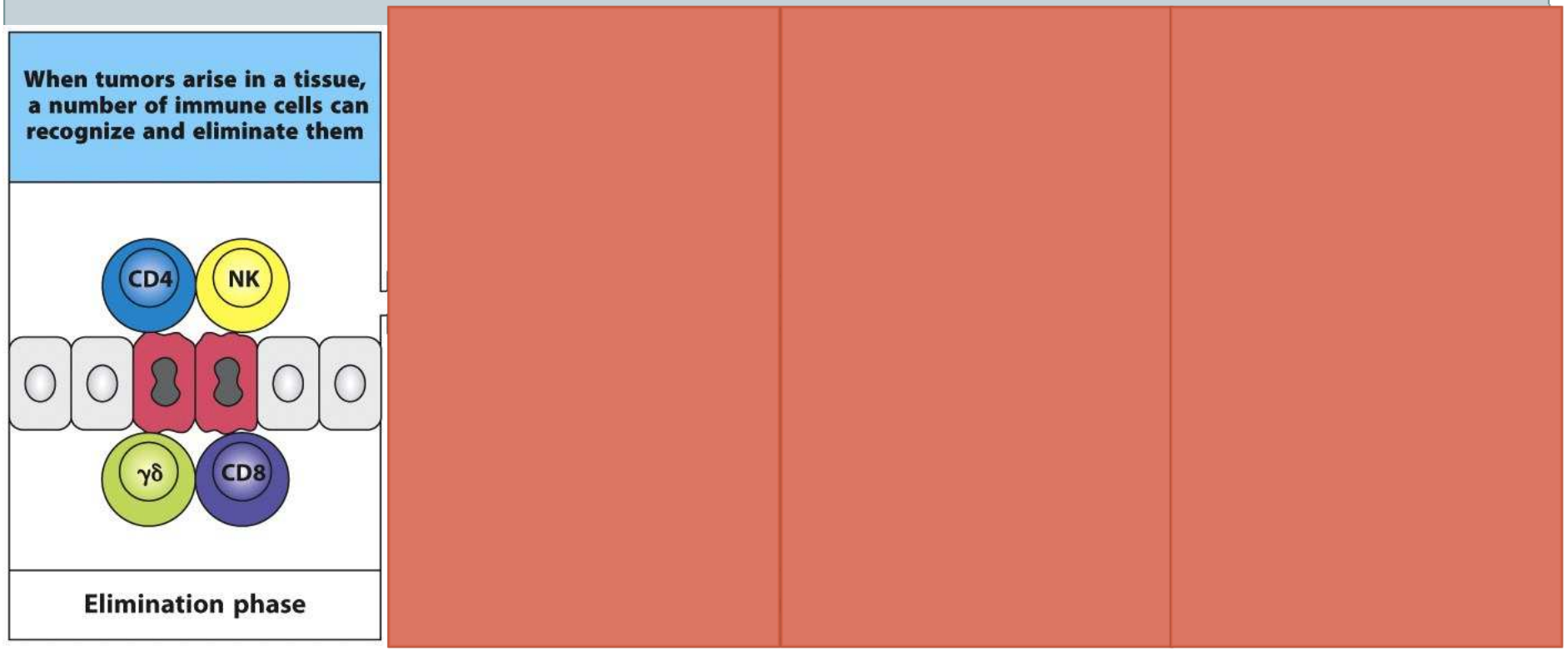
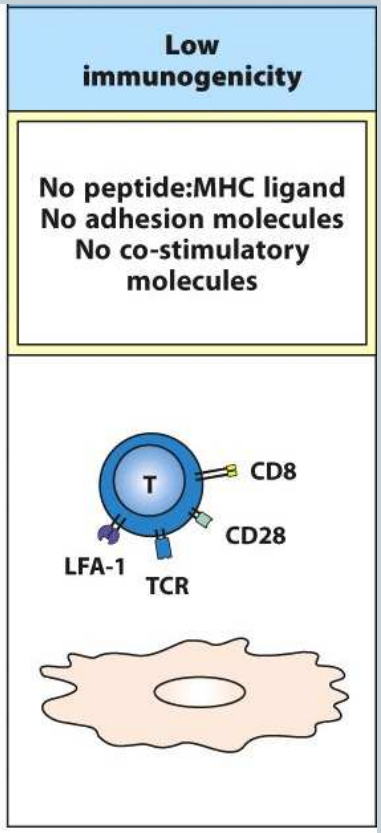
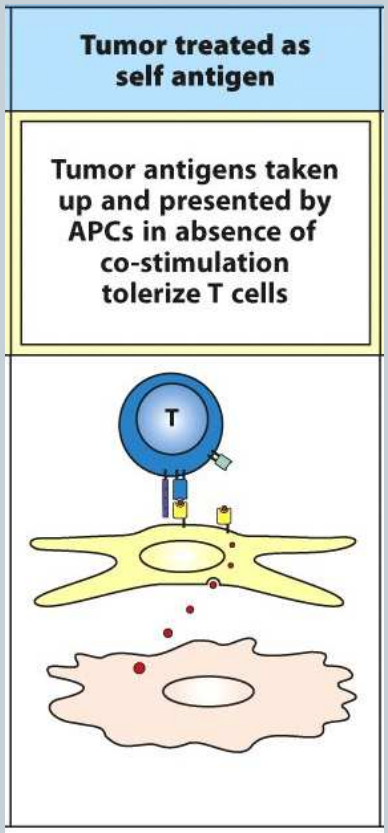


Figure 16.12 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Mechanisms of Escape:
Tumor Cell Evasion of Immune Recognition





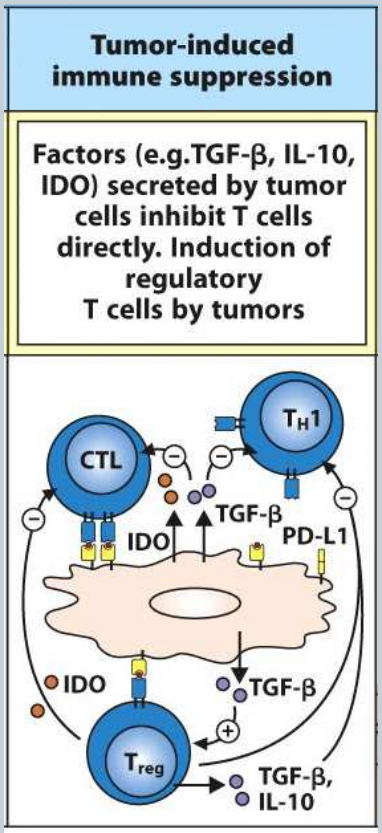
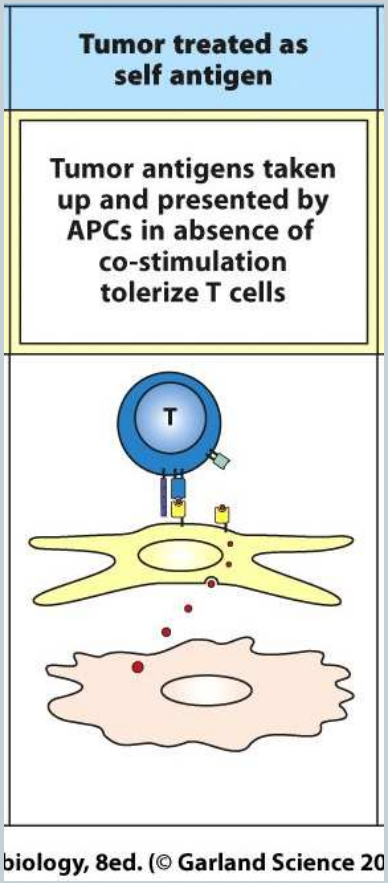
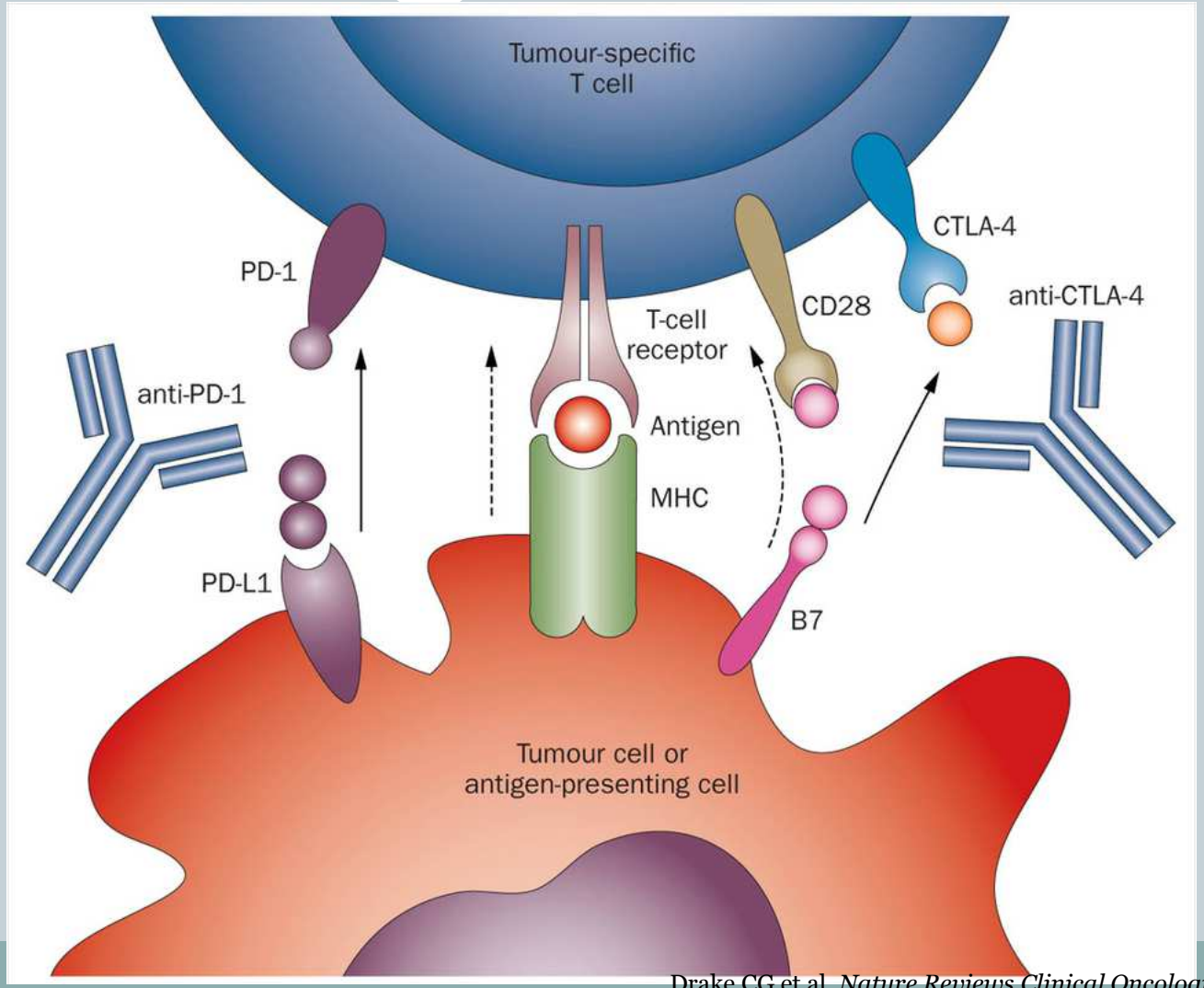


Figure 16.13 Janeway's Immunob biology, 8ed. (© Garland Science 2(

Tumor Immunology: Immune Checkpoints





Drake CG et al. *Nature Reviews Clinical Oncology*. 2014

Cancer Vaccines

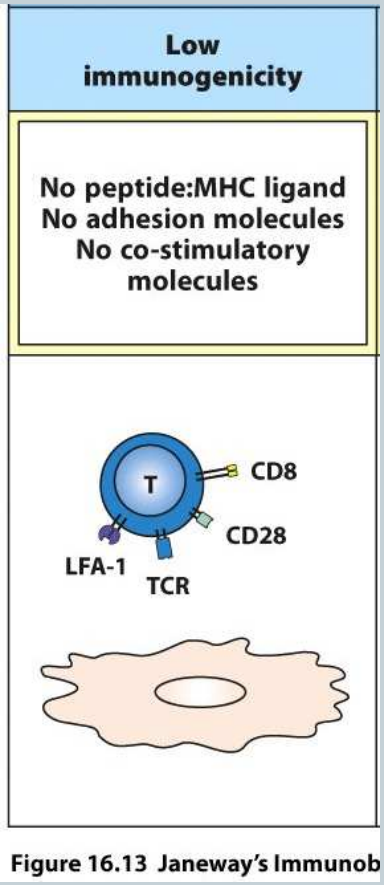
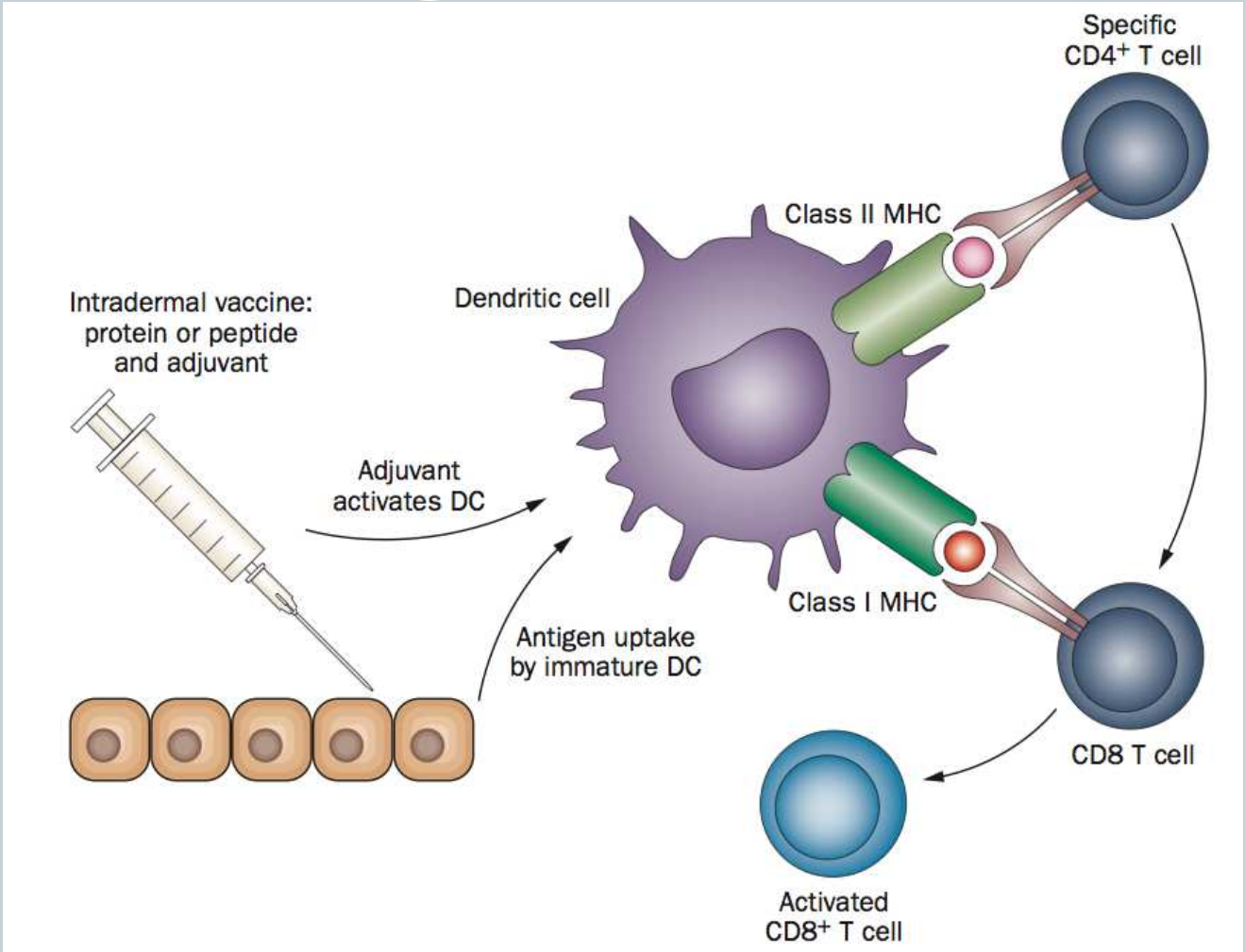
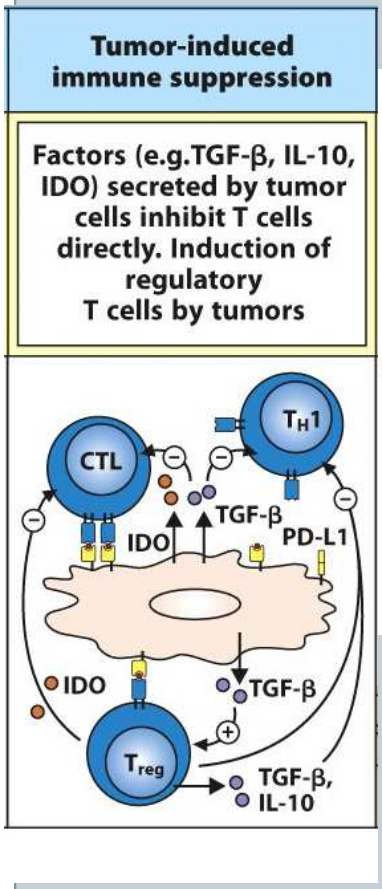


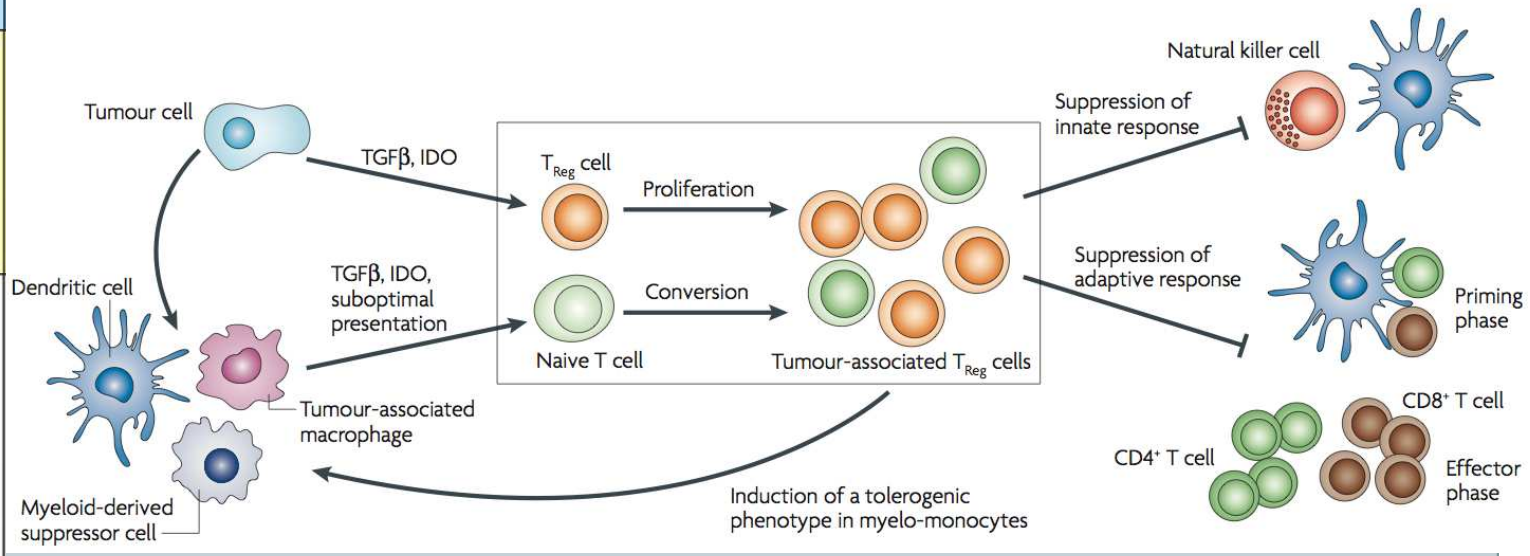
Figure 16.13 Janeway's Immunob



Drake CG et al. *Nature Reviews Clinical Oncology*. 2014

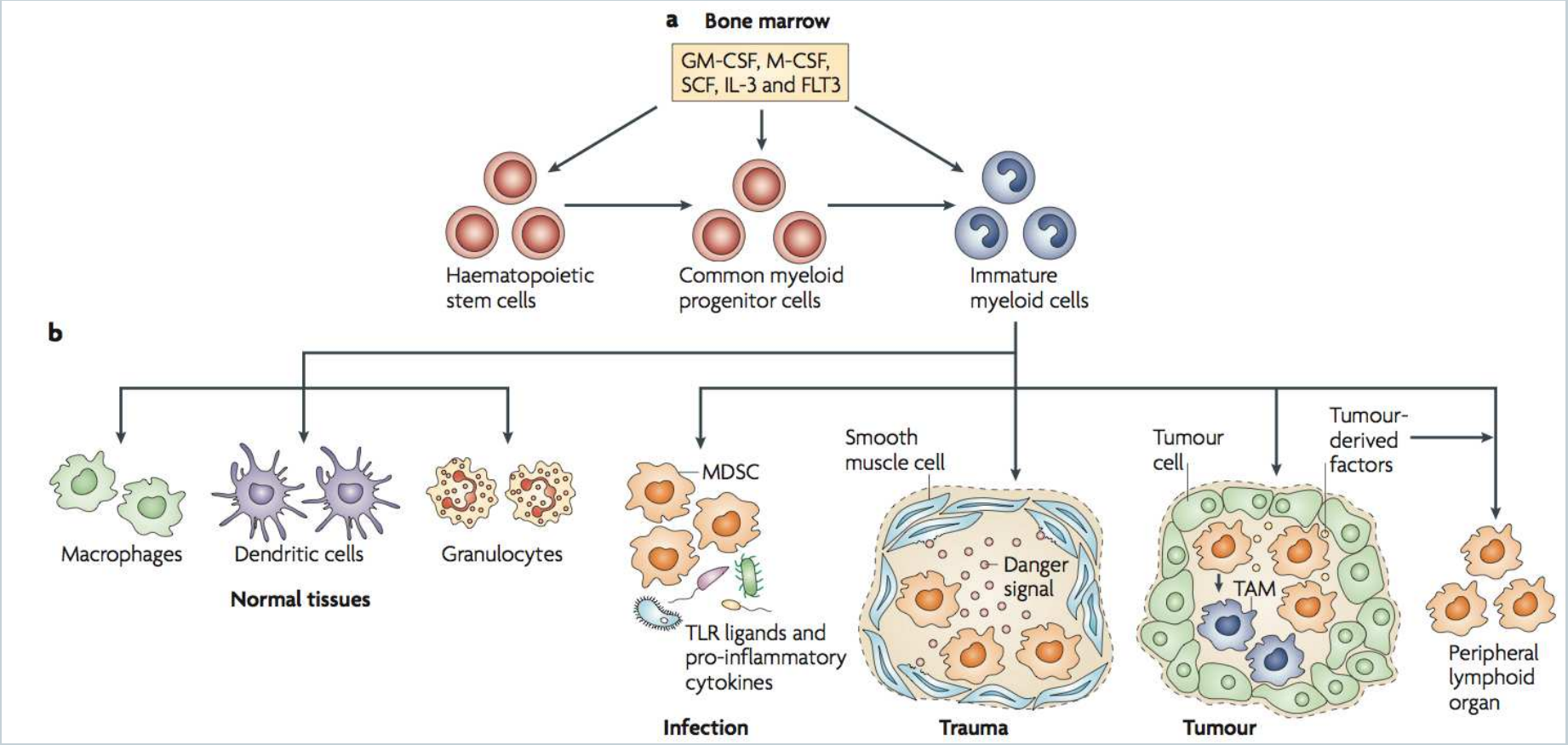
Regulatory T Cells Promote Tumorigenesis





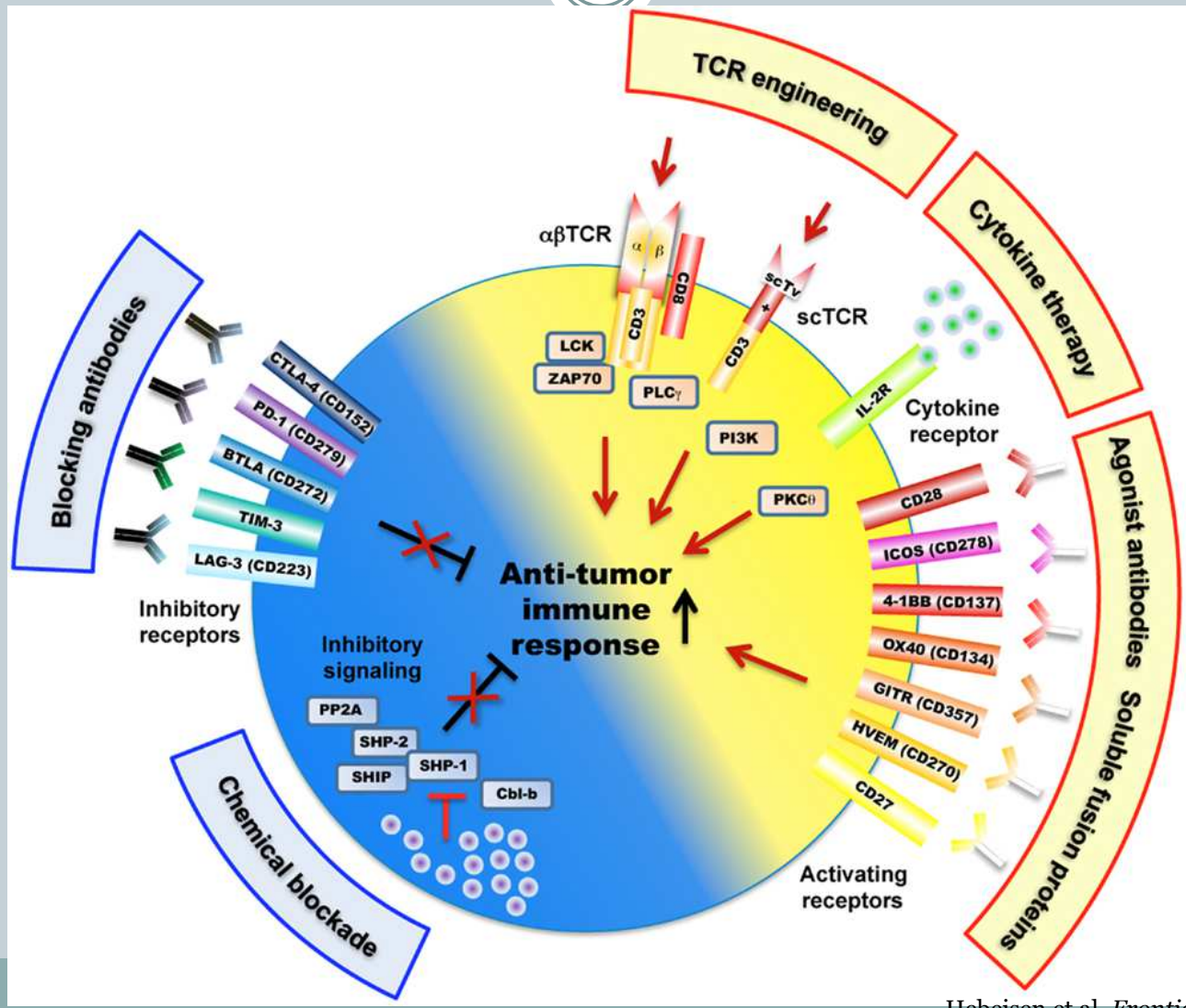
Colombo & Piconese. *Nature Reviews Cancer*. 2007

Myeloid Suppressor Cells Promote Tumorigenesis



Gabrilovich & Nagaraj. *Nat Reviews Immunology*. 2009

Targeting T Cells for Immunotherapy



Hebeisen et al. *Frontiers in Immunology*. 2013

Review: Objectives of Tumor Immunotherapy

- Shift the immune balance; break tolerance, elicit antigen specific responses to 'self' (or tumor) antigens.
- Overcome mechanisms of anergy; block negative regulators of T cell immune responses.
- Stimulate antigen specific T cells with cytokines or agonist antibodies.
- Overcome the suppressive immune microenvironment within the tumor.
- Generate durable anti-tumor 'memory' responses.
- Improve patient outcomes.

Questions?

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