T Cells Migrate to Thymus to Mature

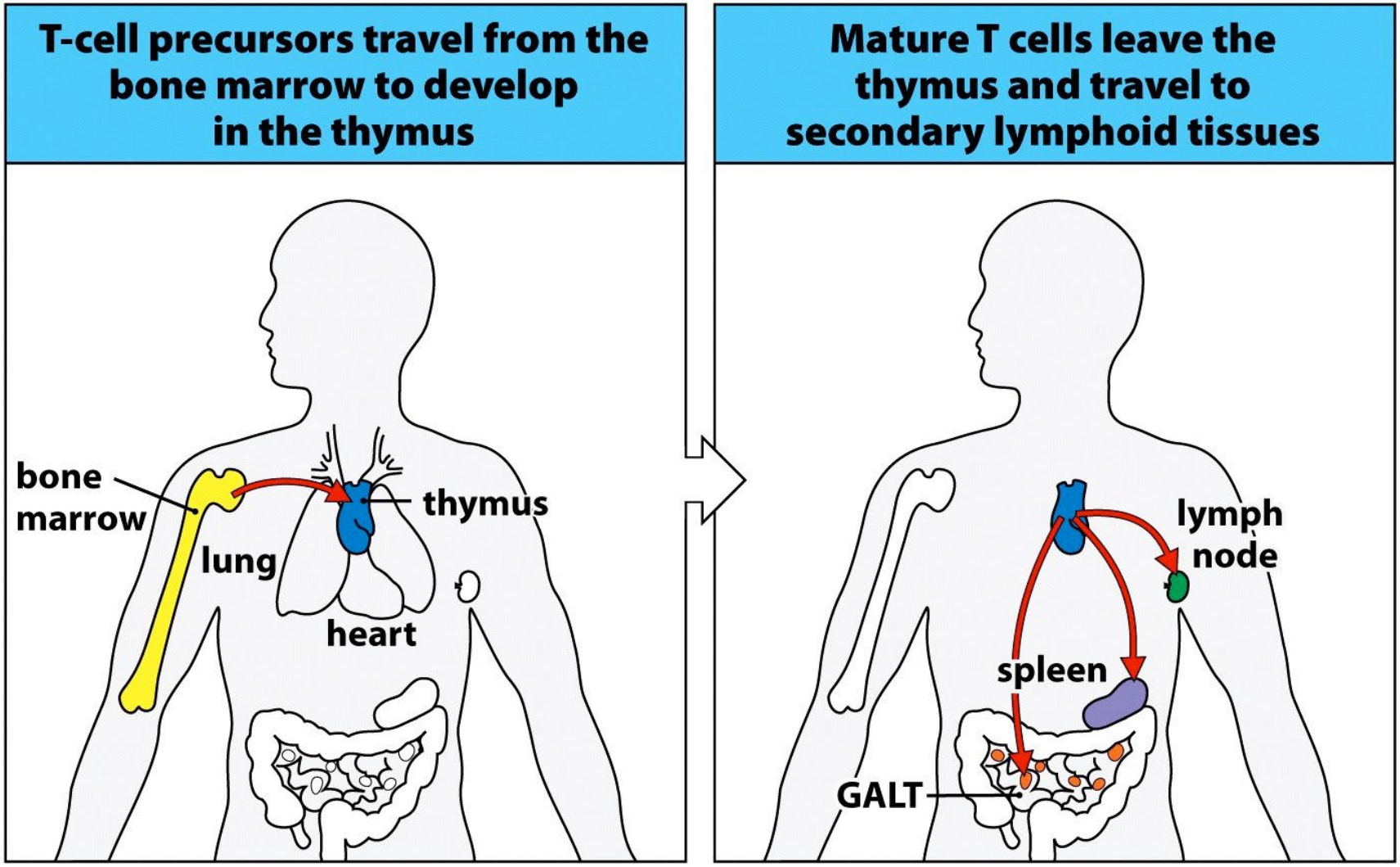
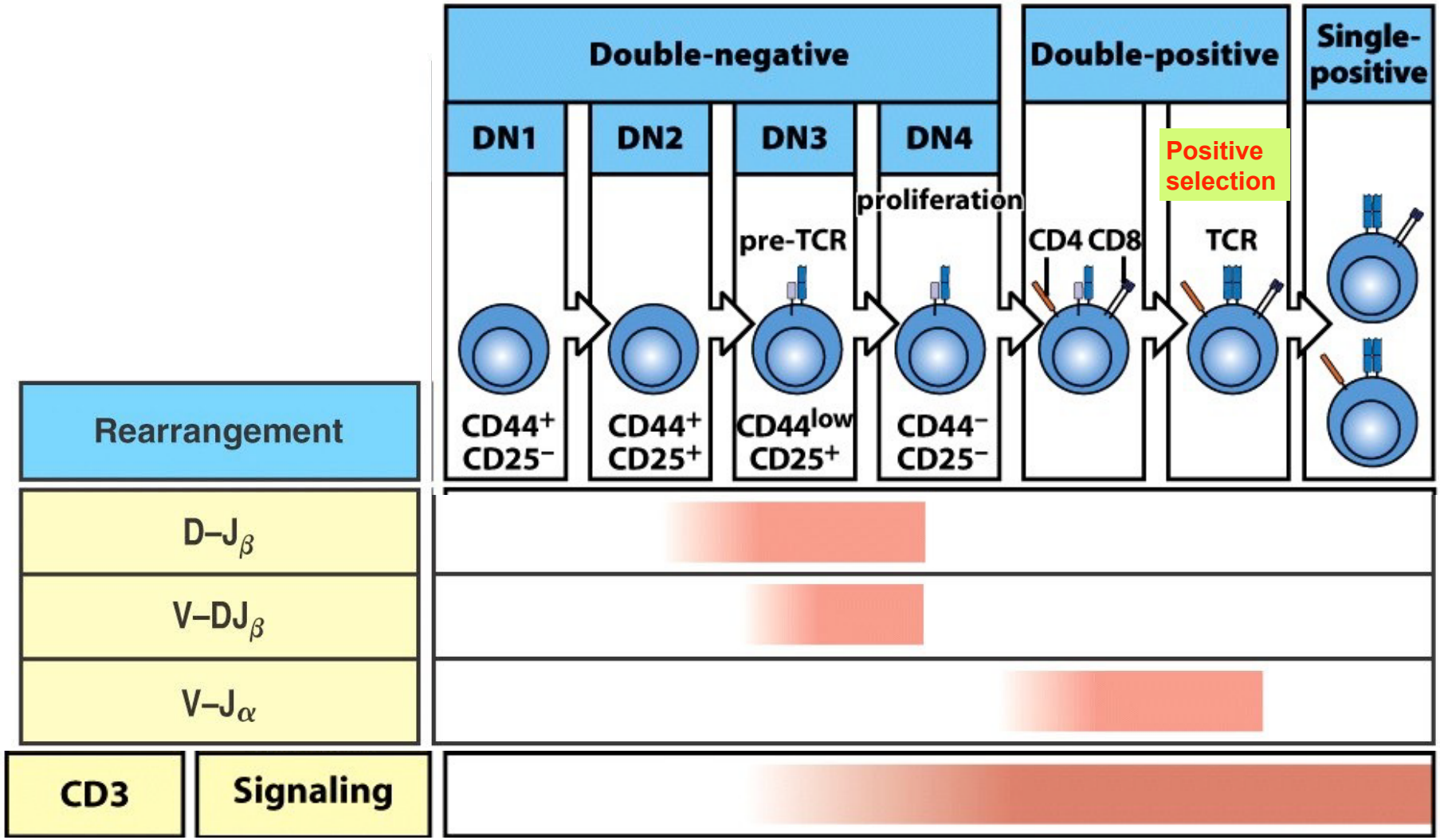


Figure 7.1 The Immune System, 3ed. (© Garland Science 2009)

Stages of T-Cell Development



Checkpoints During T-Cell Development

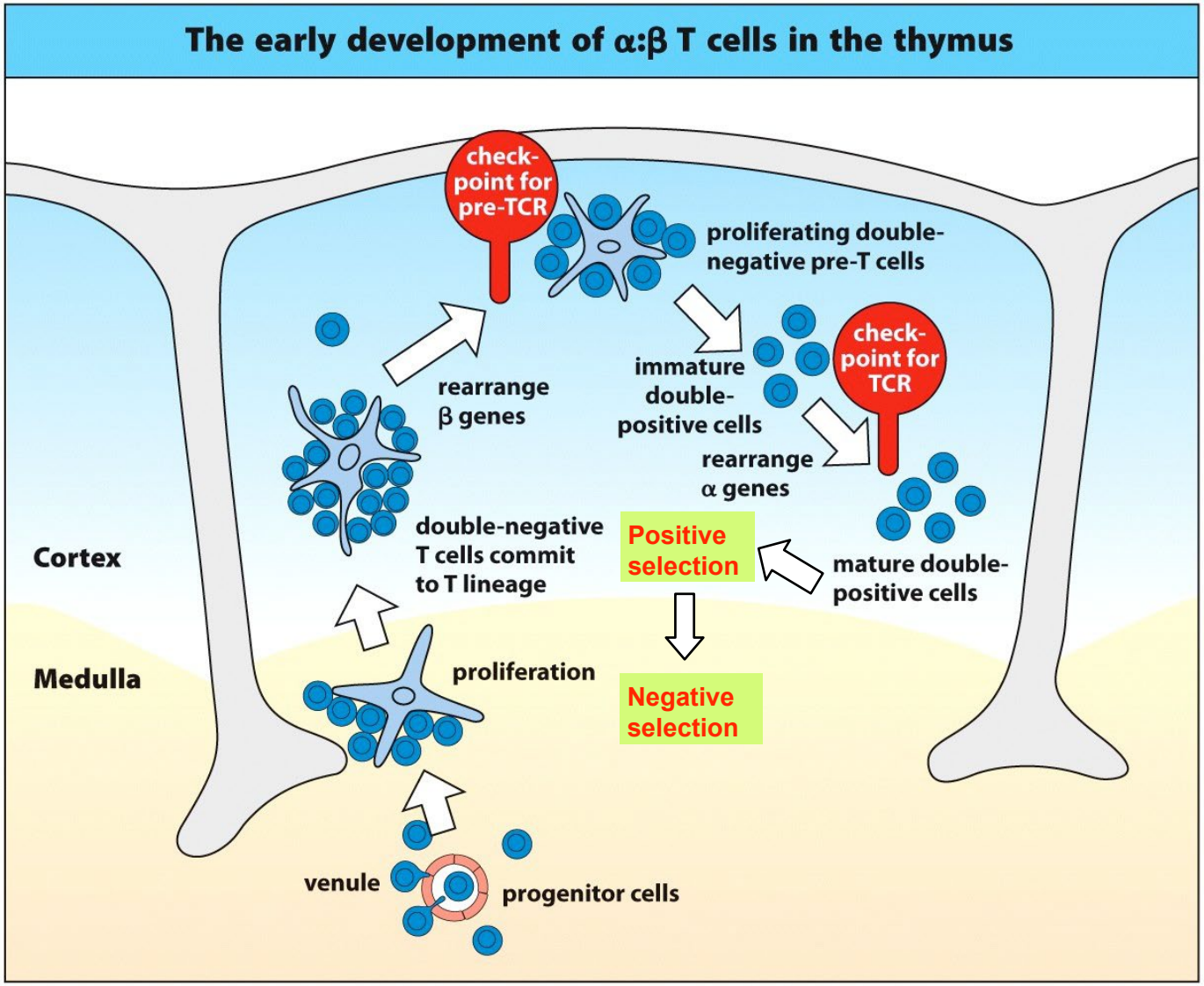


Figure 7.15 The Immune System, 3ed. (© Garland Science 2009)

T-Cell Selection

Positive selection:

–Survival signal for further maturation of T-cells capable of weak binding to MHC:self-peptide (MHC restricted cells)

– Cortex of the thymus

– Cortical epithelial cells

Negative selection:

–Apoptosis of self-reacting T-cells due to strong binding of TCR to MHC:self-peptide complex

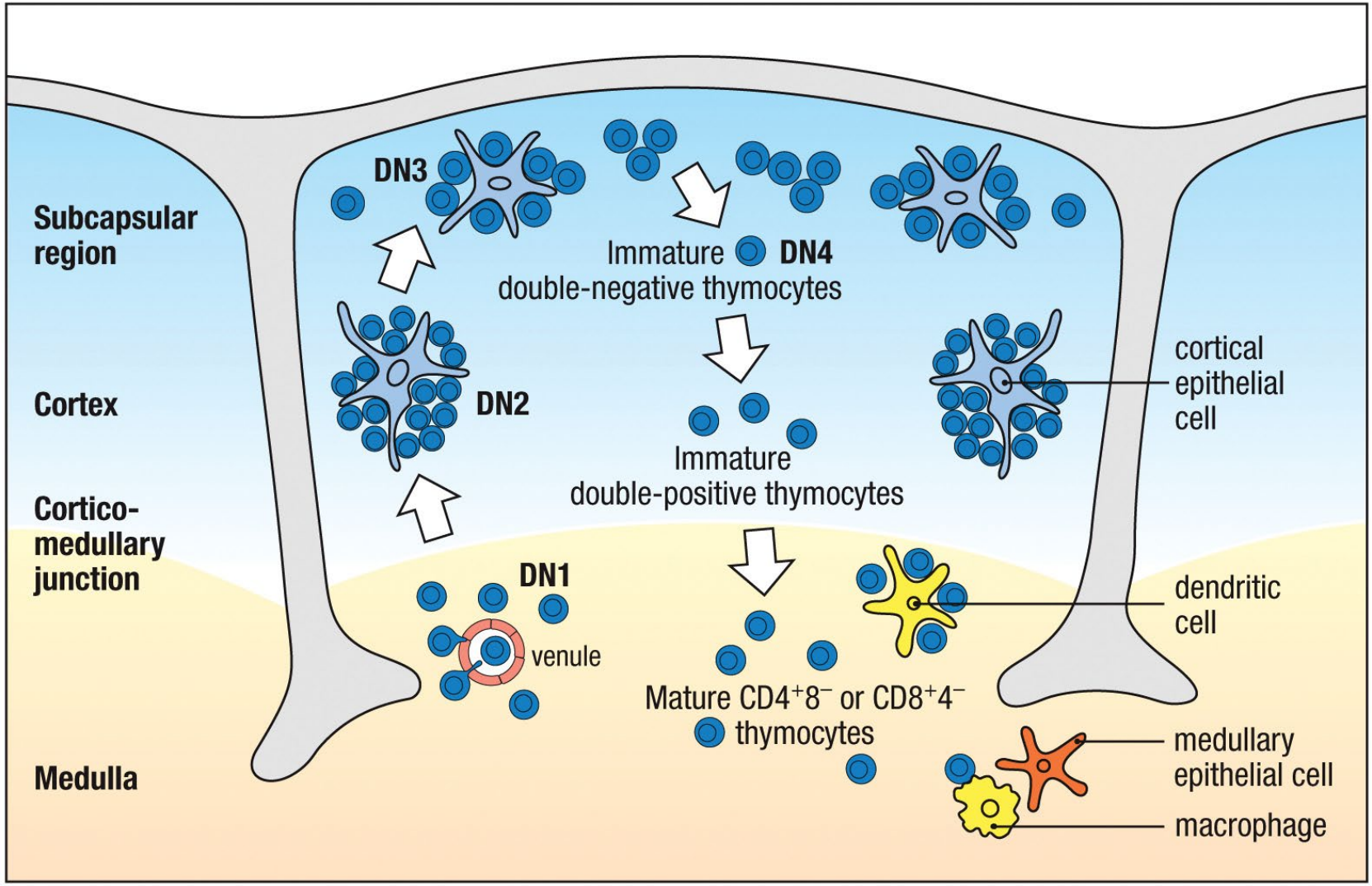
– Cortex and medulla of the thymus

– Bone marrow derived DCs and macrophages

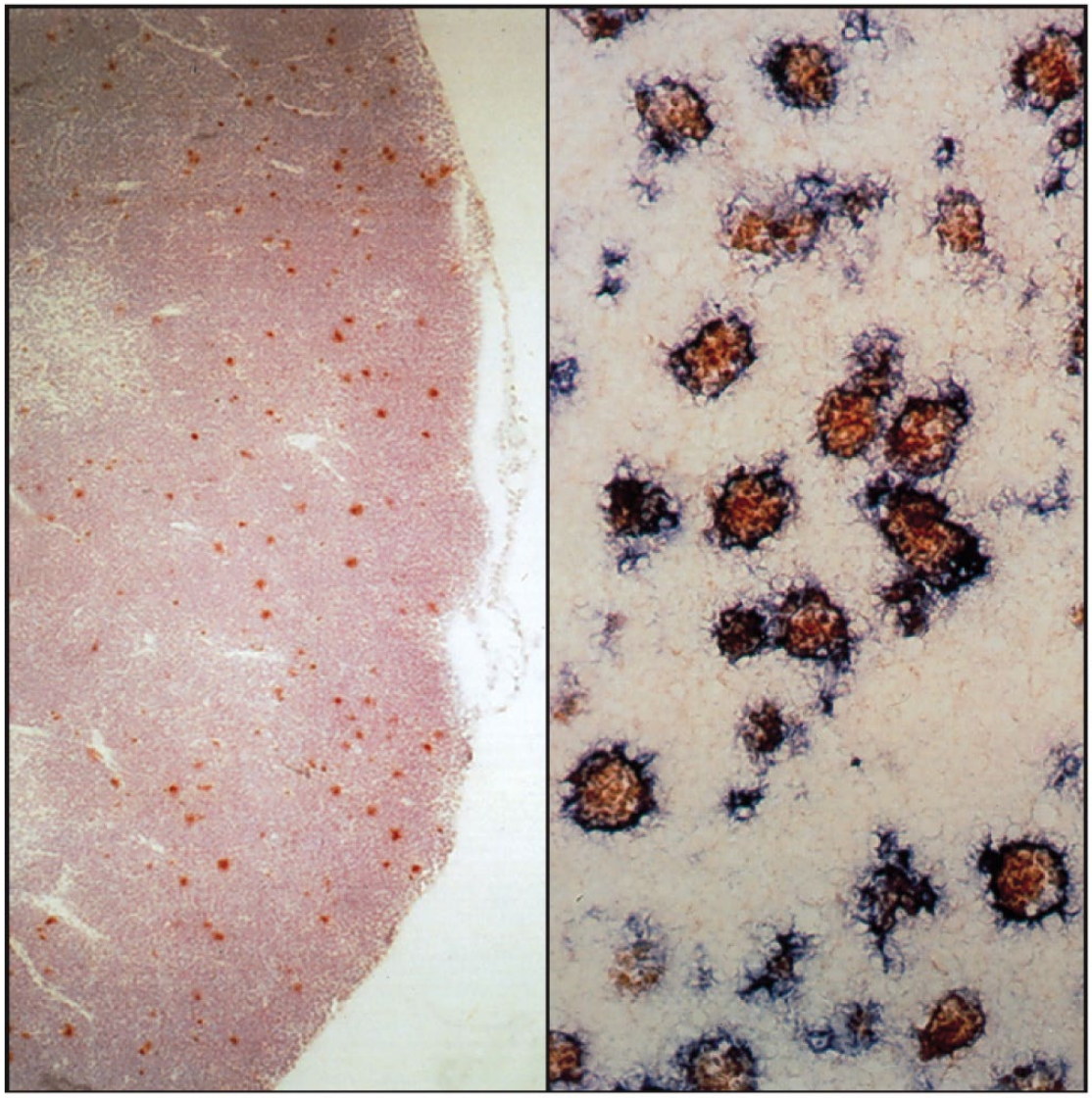
– Medullary stromal cells

TOLERANCE

Different Cells Mediate Positive and Negative Selection



Cortical Macrophages Clear Dead T-Cells



Photographs courtesy of Jonathan Sprent

Red: apoptotic cells
Blue: macrophages

Positive Selection Shown in Bone Marrow Chimeras

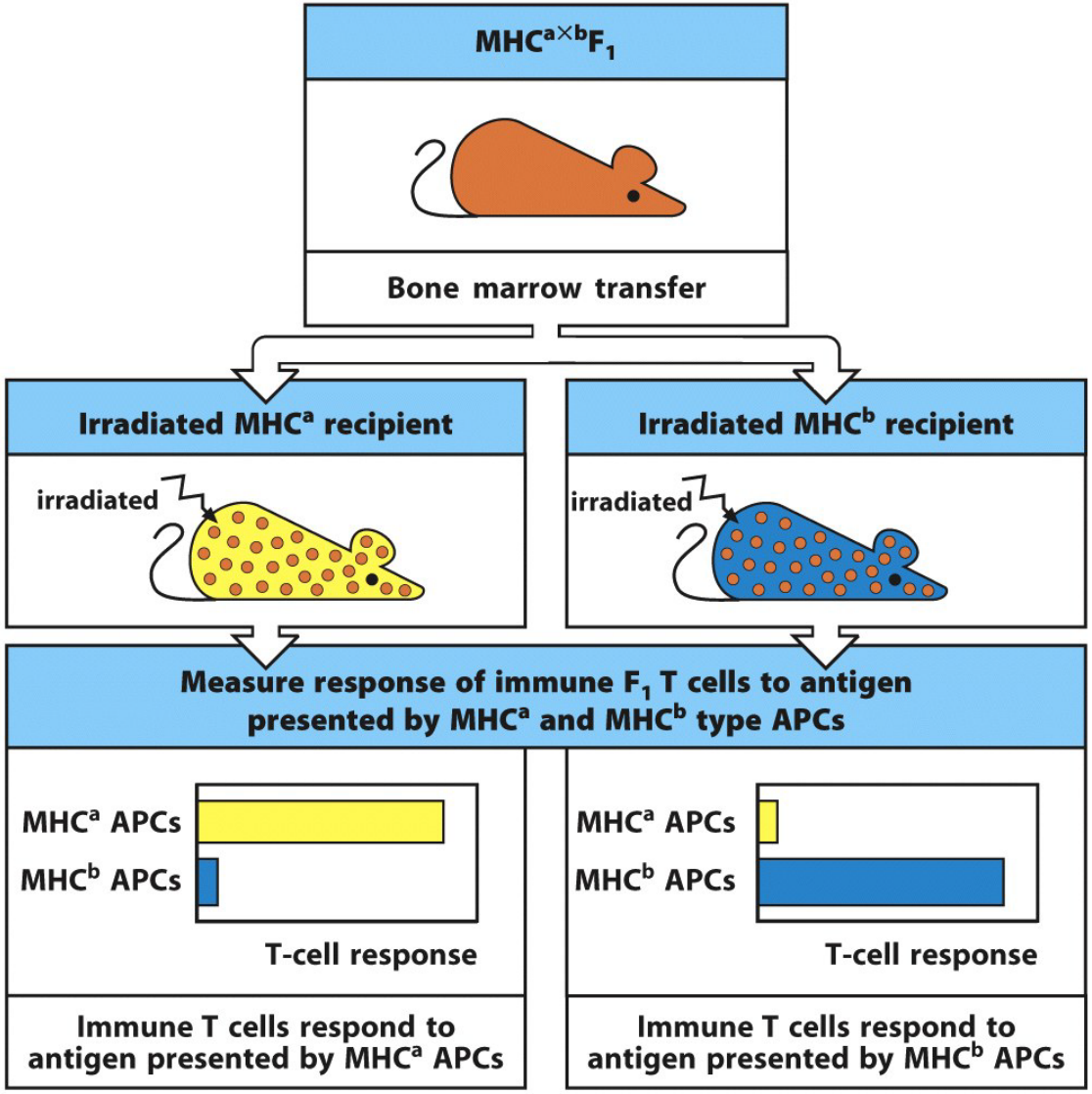
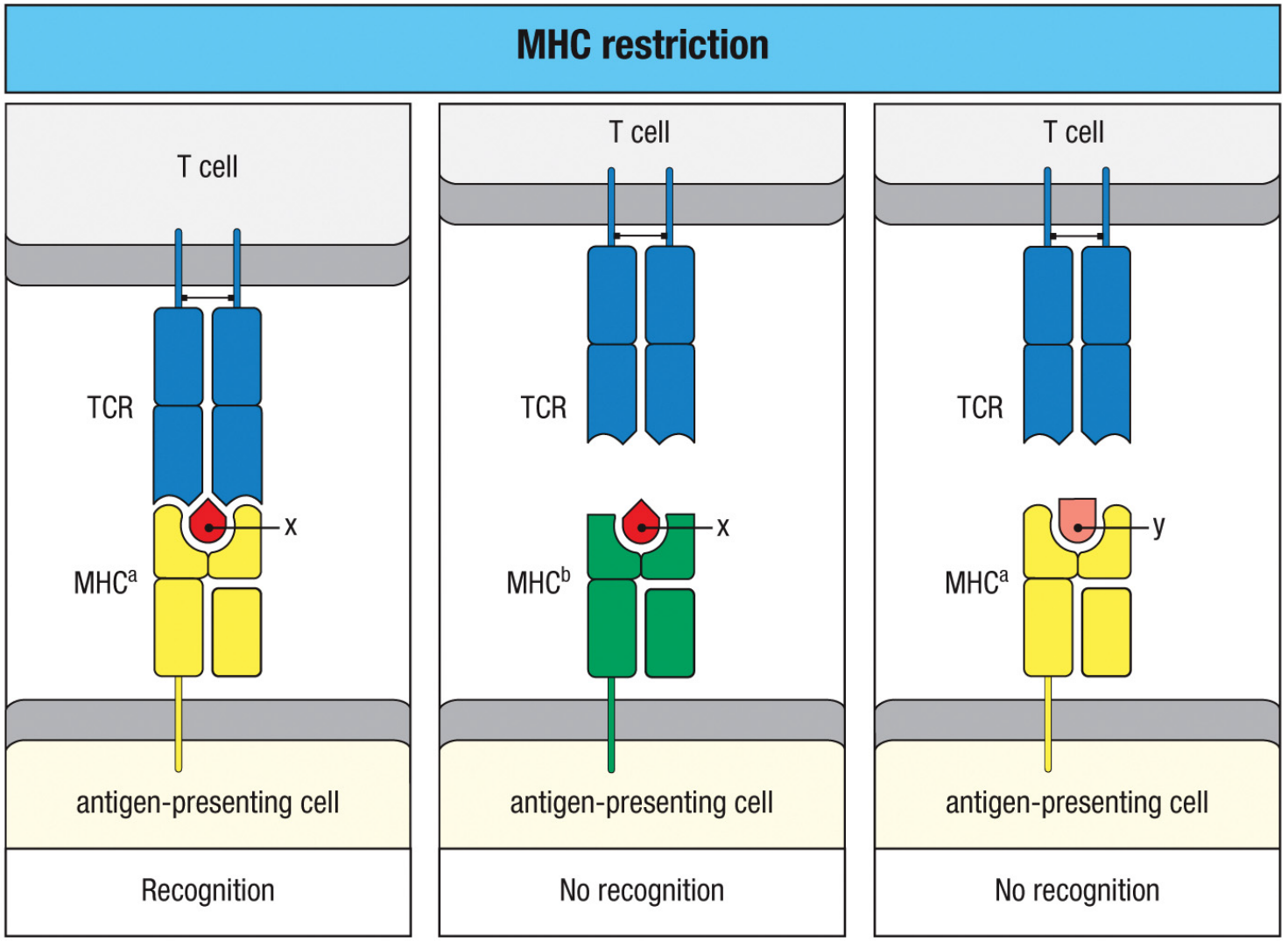


Figure 8.28 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

T-Cell Recognition of Antigens Is MHC Restricted



Positive Selection Requires TCR Recognition of MHC:Peptide Complex

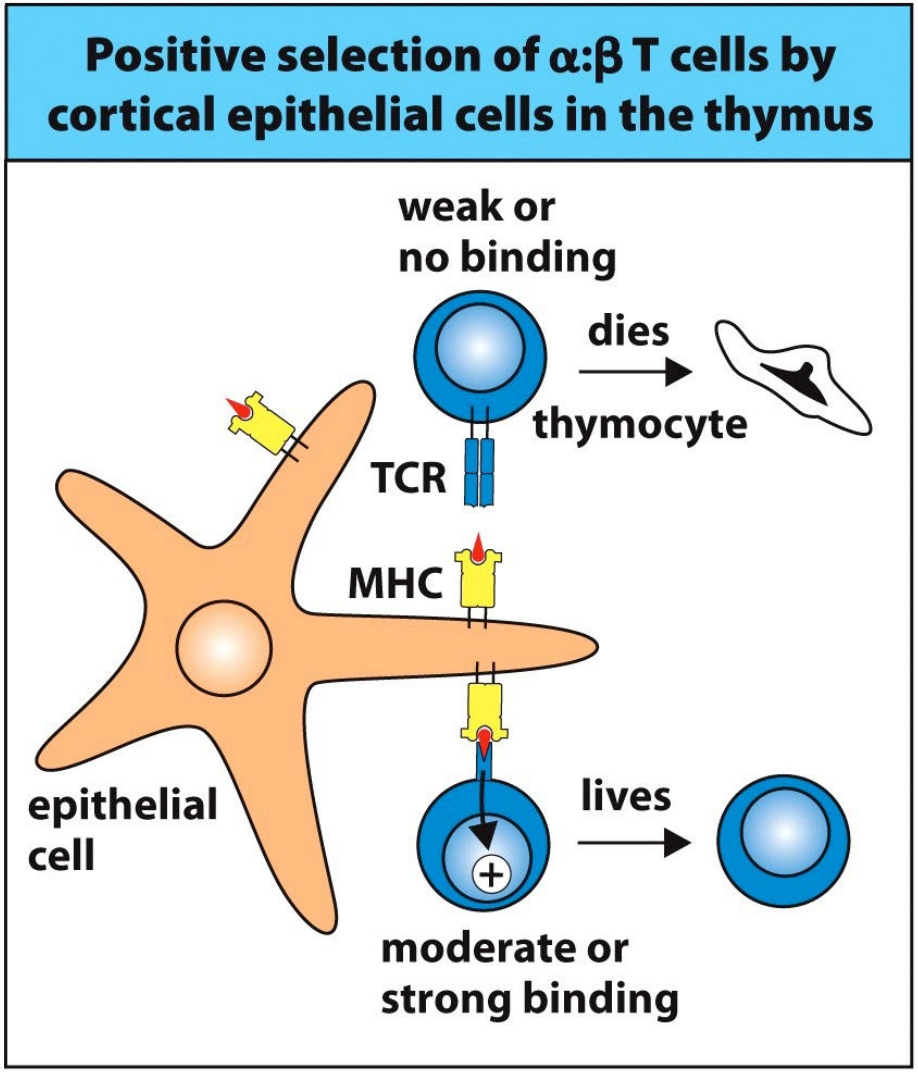
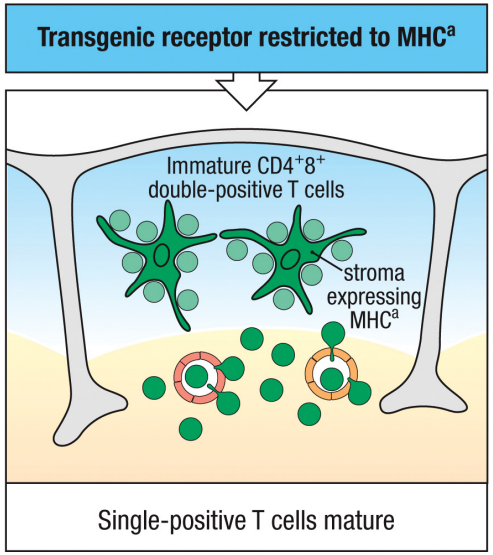
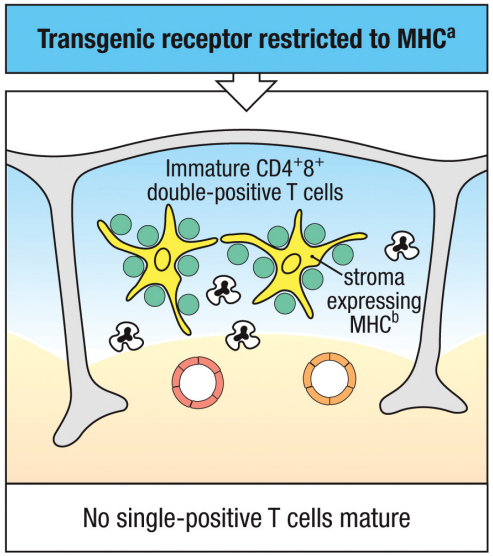


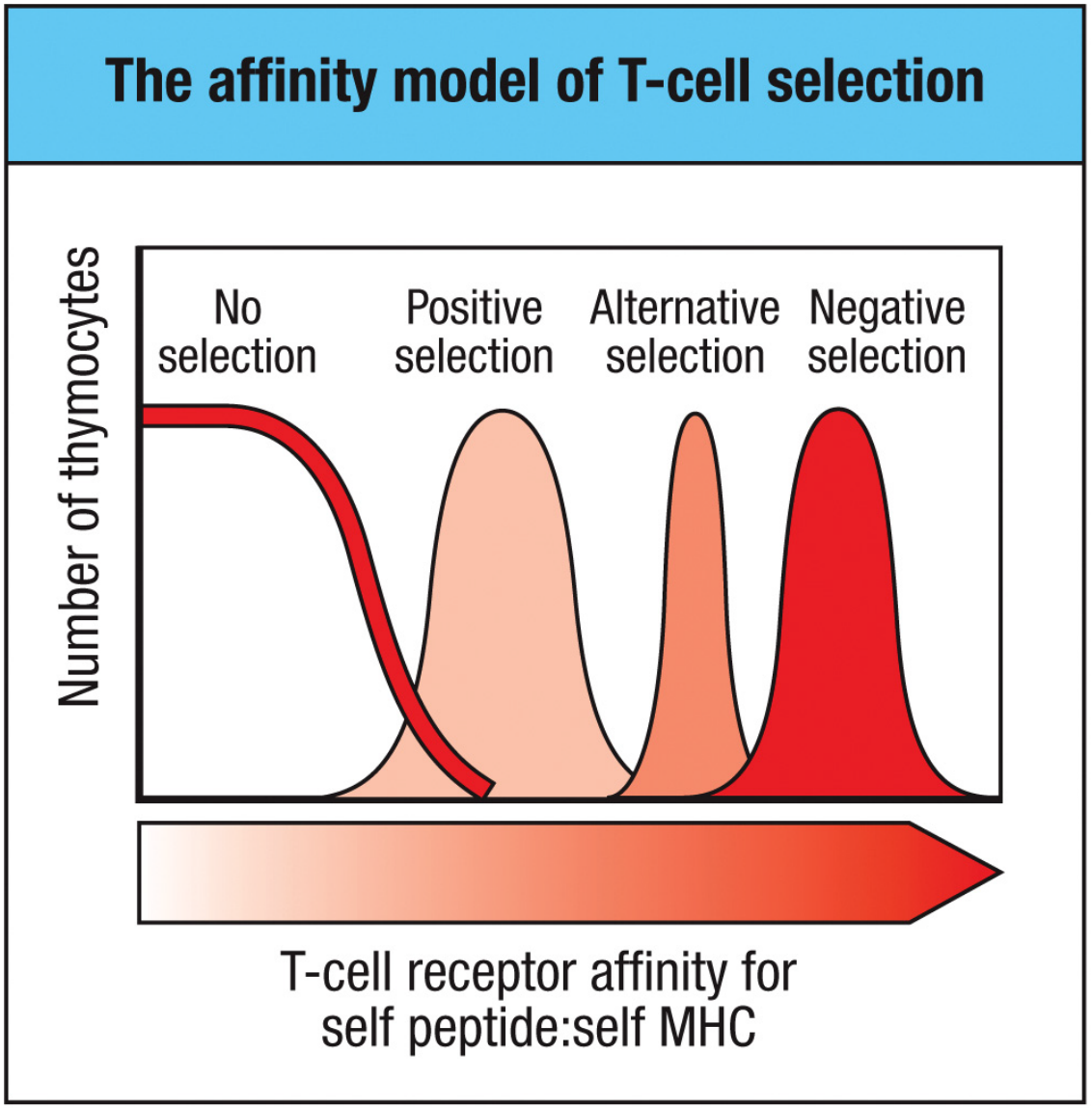
Figure 7.16 The Immune System, 3ed. (© Garland Science 2009)

Thymic Cortical Epithelial Cells Mediate Positive Selection

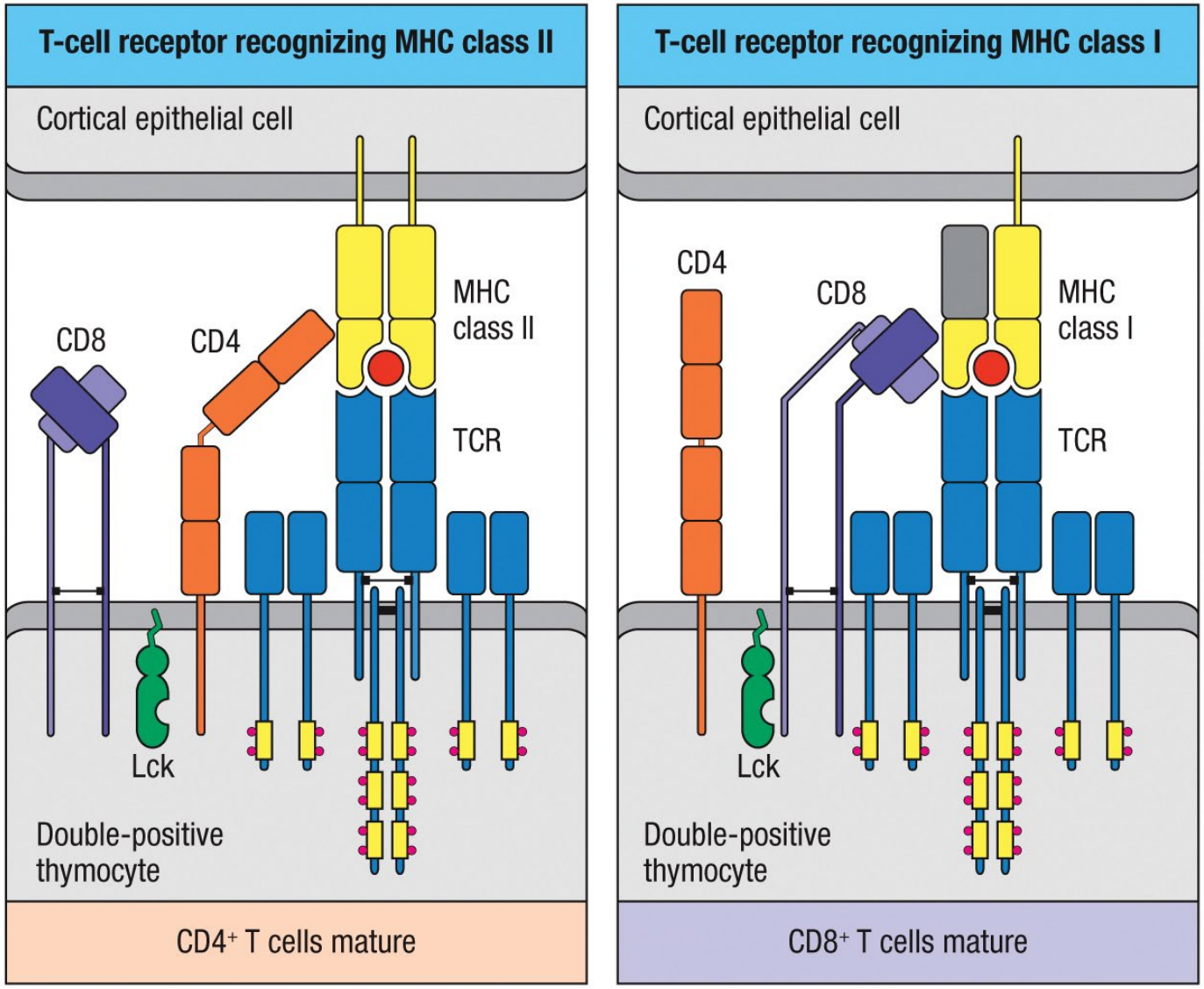




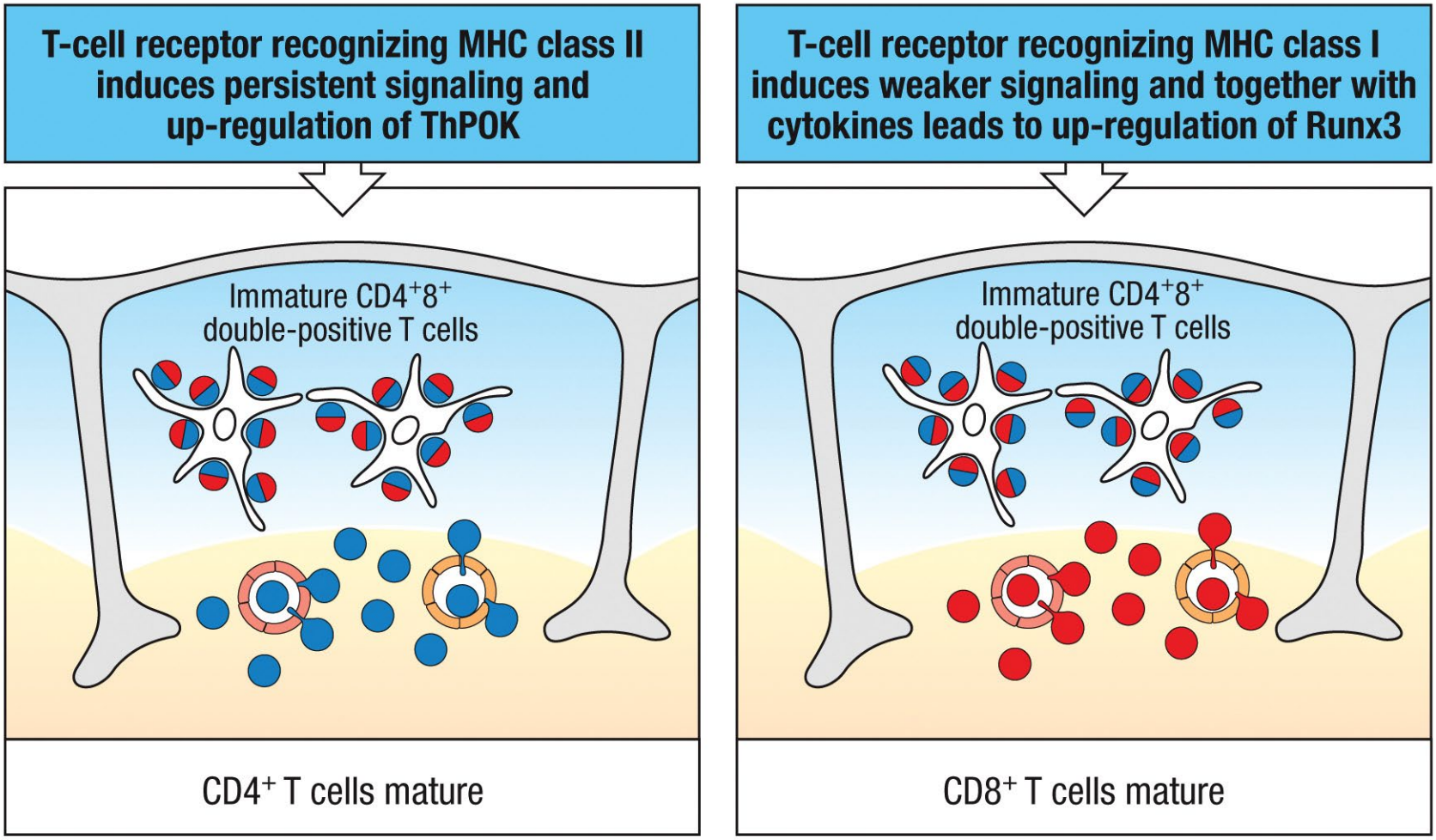
Affinity Model of Thymocyte Selection



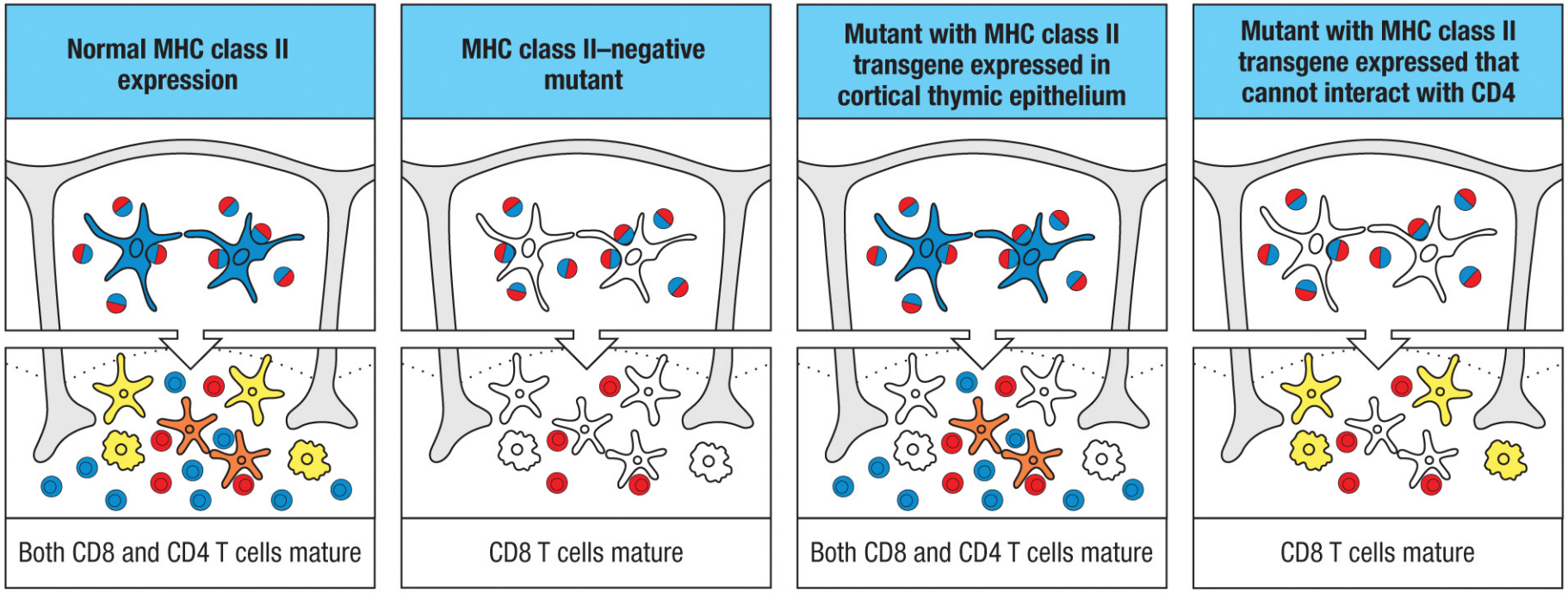
MHC Class I and Class II



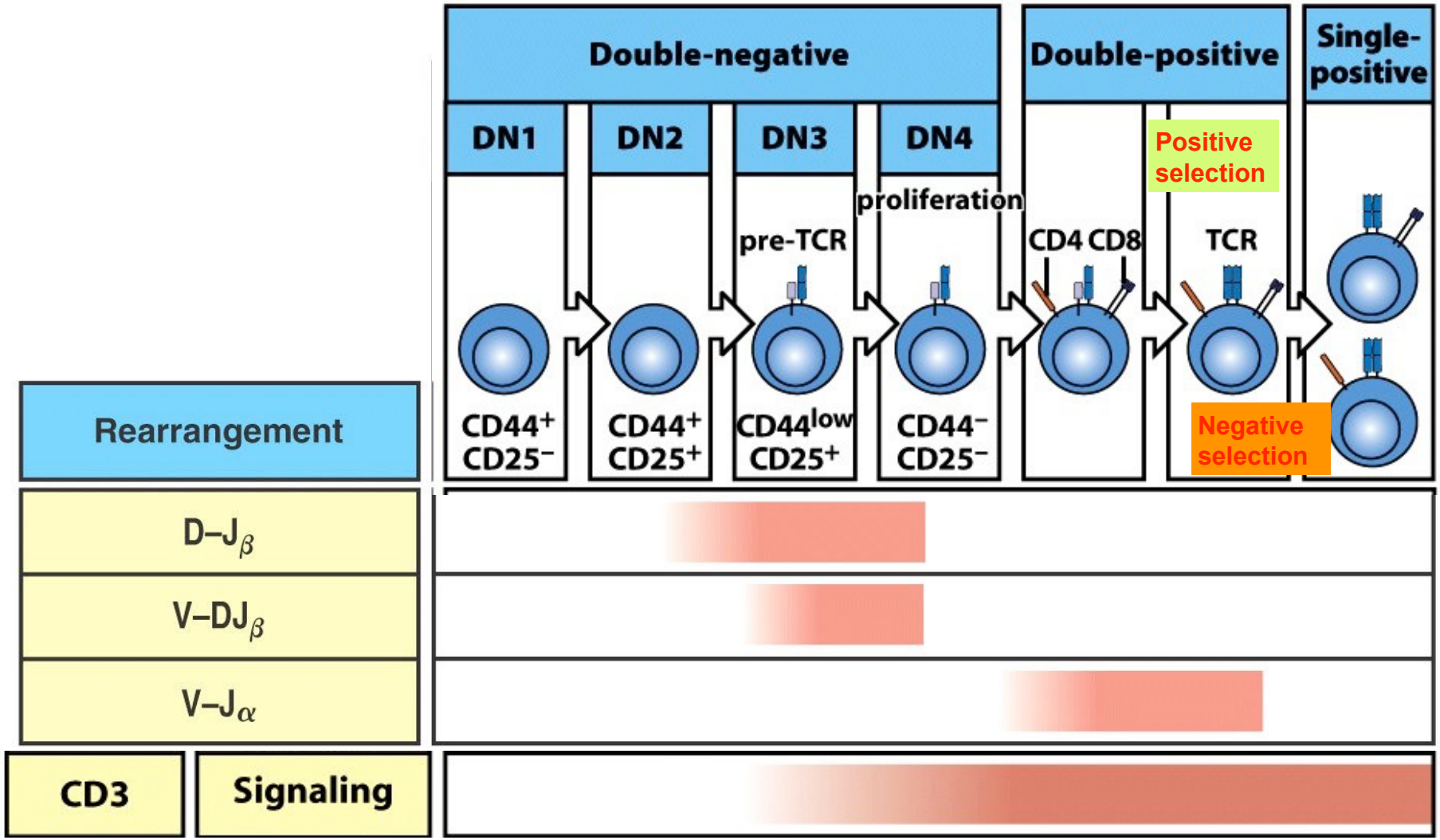
MHC Restriction



Thymic Cortical Epithelial Cells Mediate Positive Selection



Alpha Chain Rearrangement Stops When the Cell Is Positively Selected



Question

- T cell positive selection
- What is the purpose of positive selection?
- What cells and molecules mediate positive selection?

T-Cell Selection

Positive selection:

–Survival signal for further maturation of T-cells capable of weak binding to MHC:self-peptide

– Cortex of the thymus

– Cortical epithelial cells

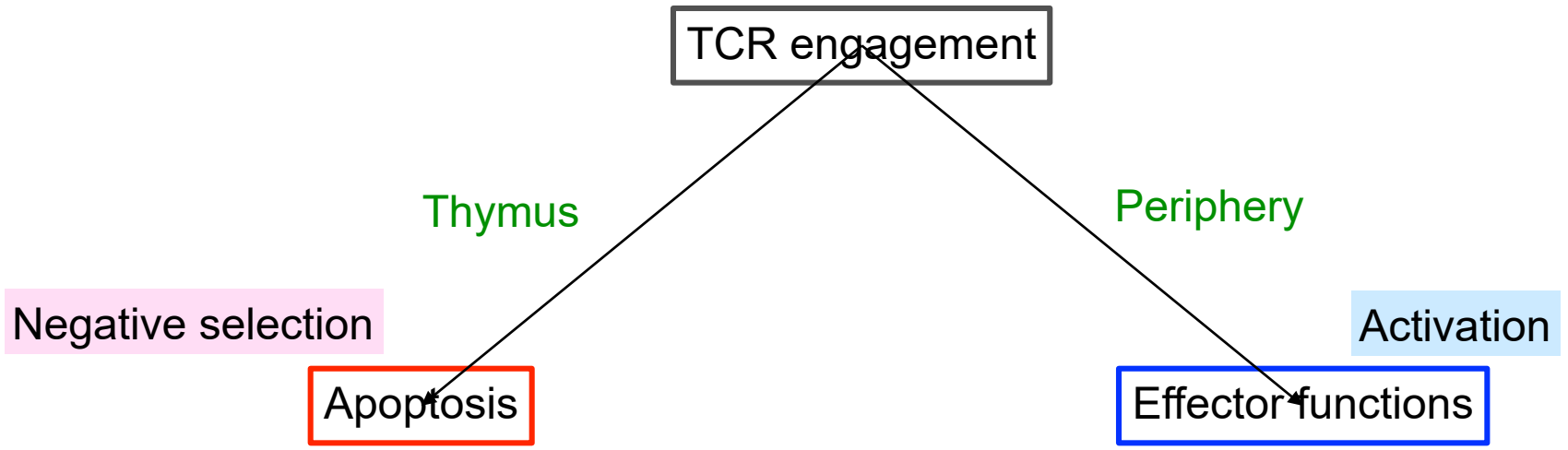
Negative selection:

–Apoptosis of self-reacting T-cells due to strong binding of TCR to MHC:self-peptide complex

– Cortex and medulla of the thymus

– Bone marrow derived DCs and macrophages

T Lymphocyte Differentiation



T-Cells Specific for Self-Antigens Are Deleted in the Thymus

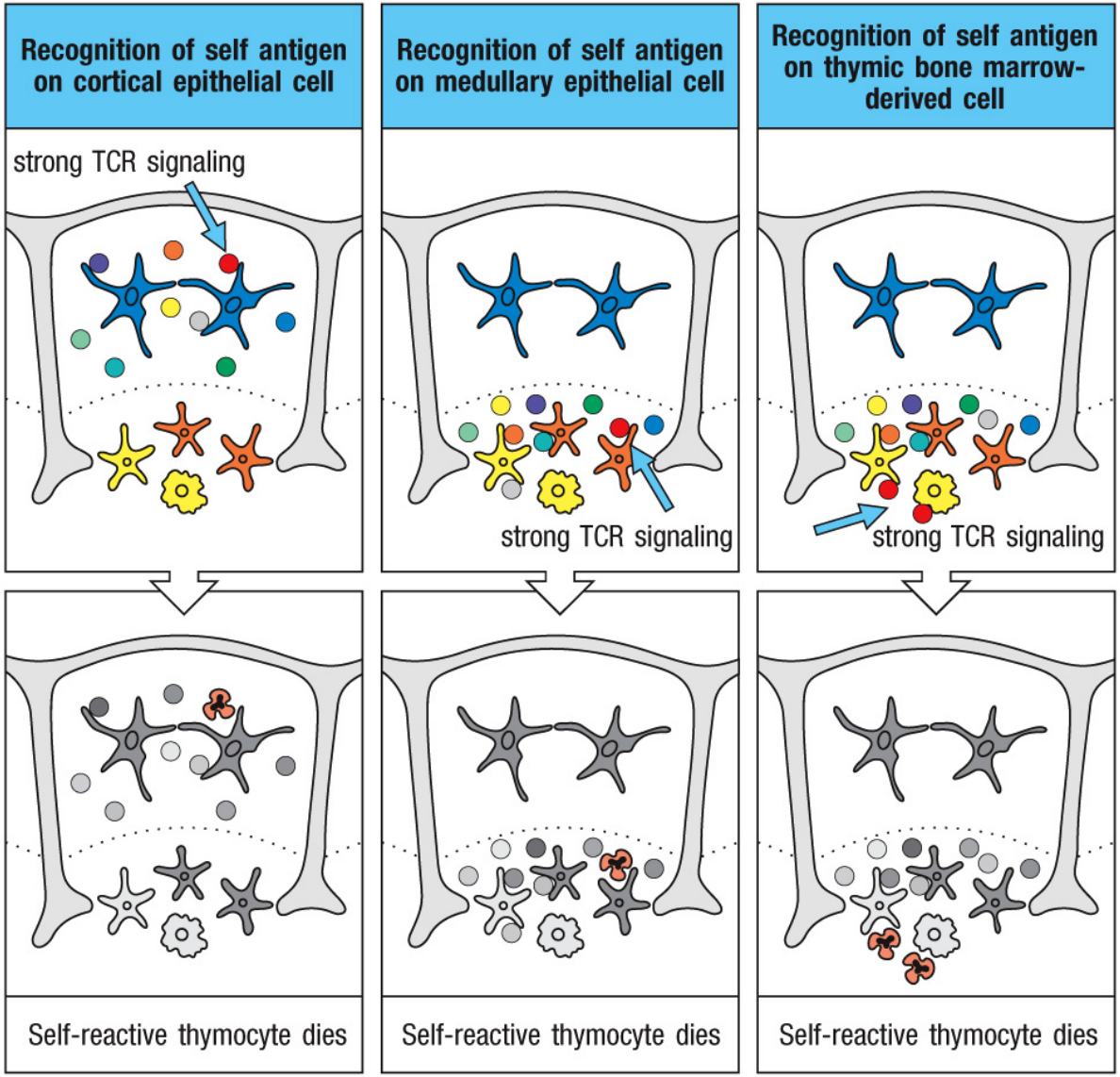
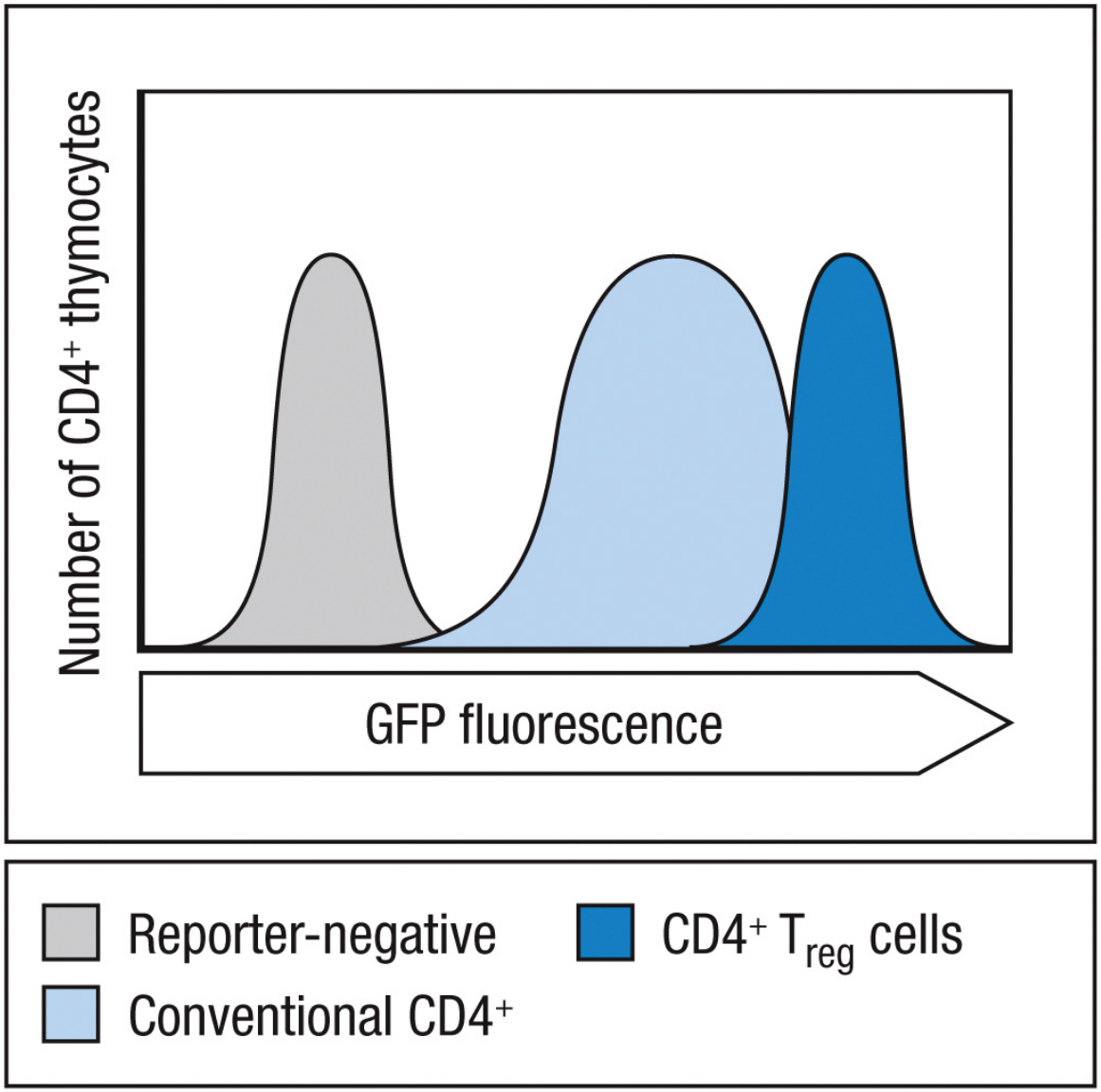


Figure 8.29 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

T_{reg} cells requires moderately high affinity for self peptide:self MHC



Bone Marrow Derived Cells Mediate Negative Selection in the Thymus

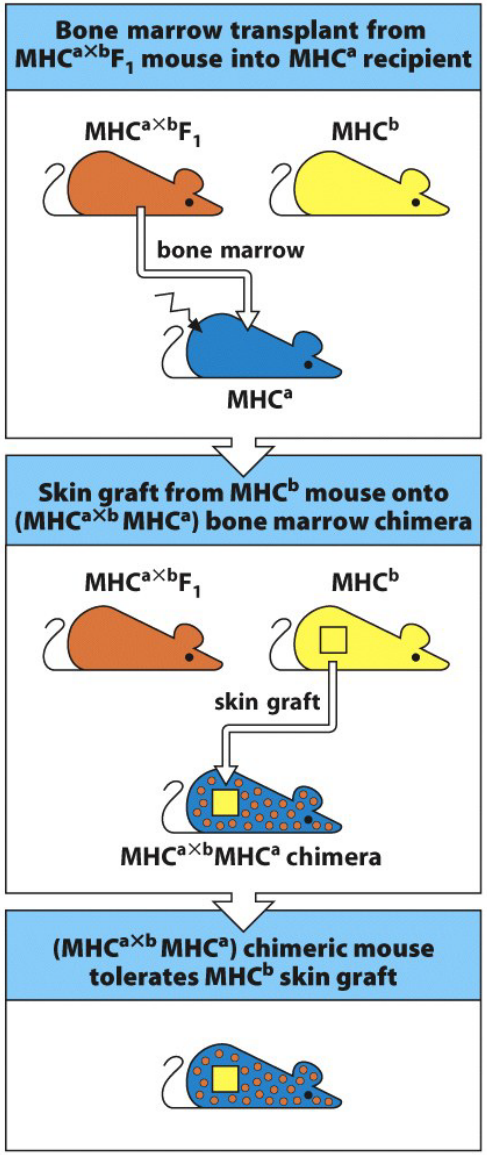


Figure 8.35 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Positive selection: a
Negative selection: axb

Bone Marrow Transplant

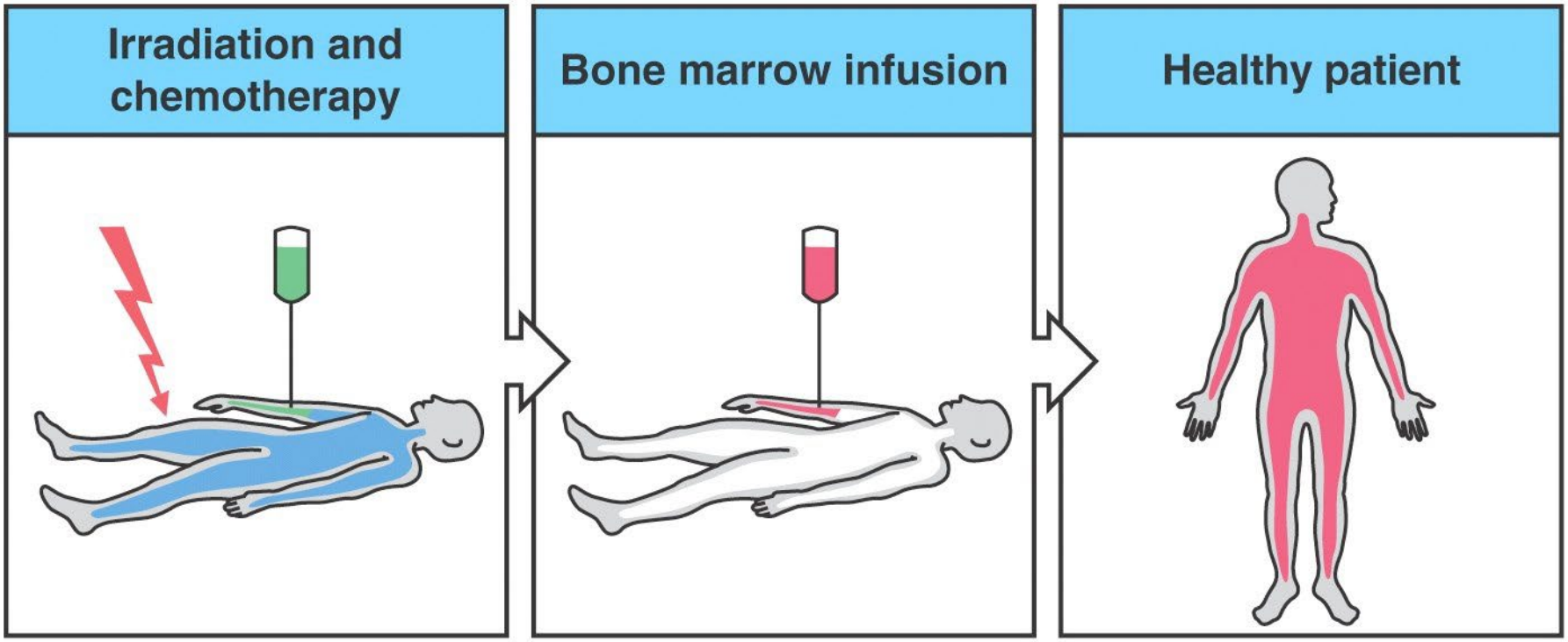
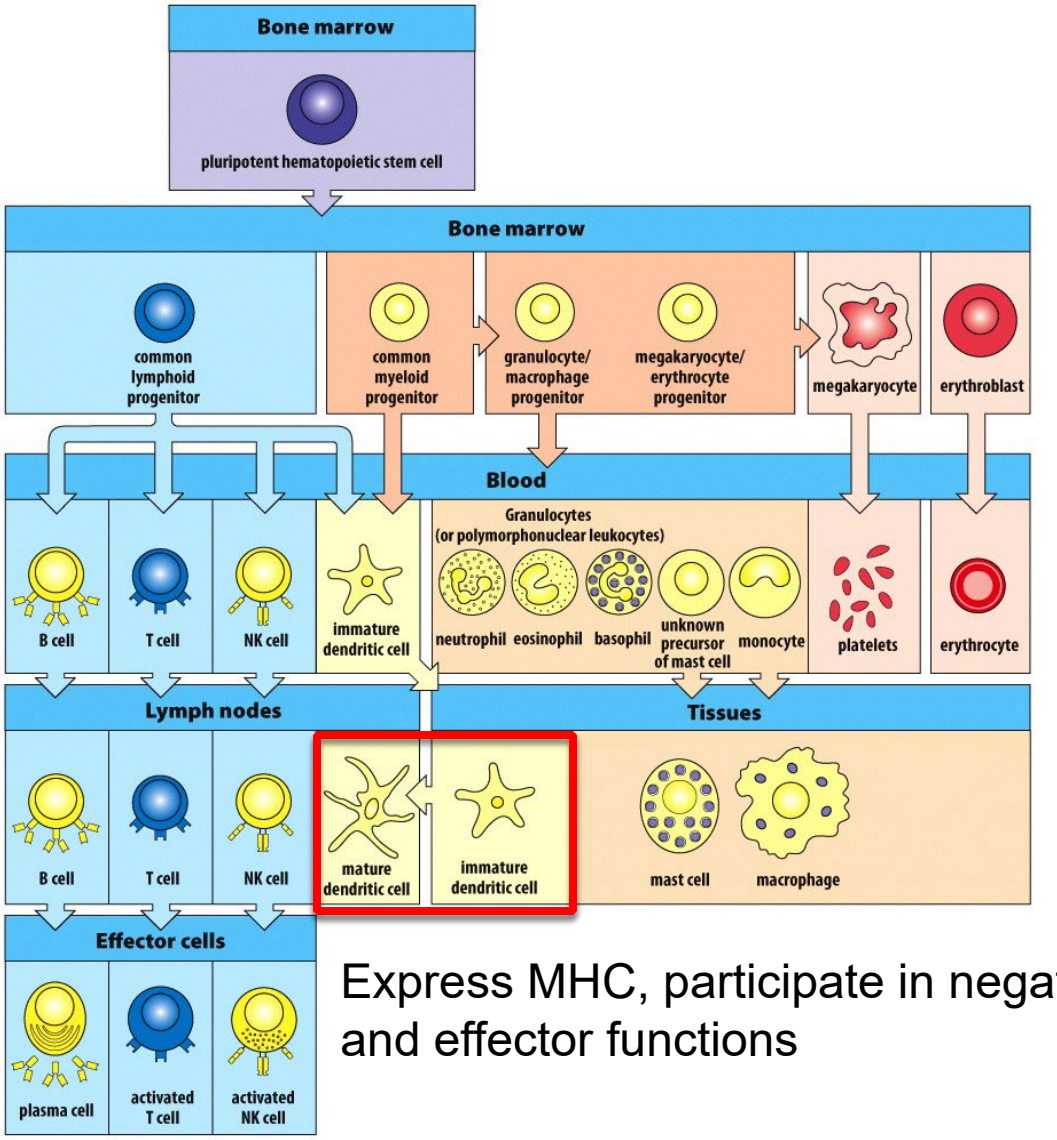


Figure 5-10 The Immune System, 2/e (© Garland Science 2005)

Newly generated cells don't attach
How does selection result in tolerance?

Bone Marrow Transplant Corrects Blood Cell Defects



Express MHC, participate in negative selection and effector functions

Figure 1.3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Cellular Organization of the Thymus

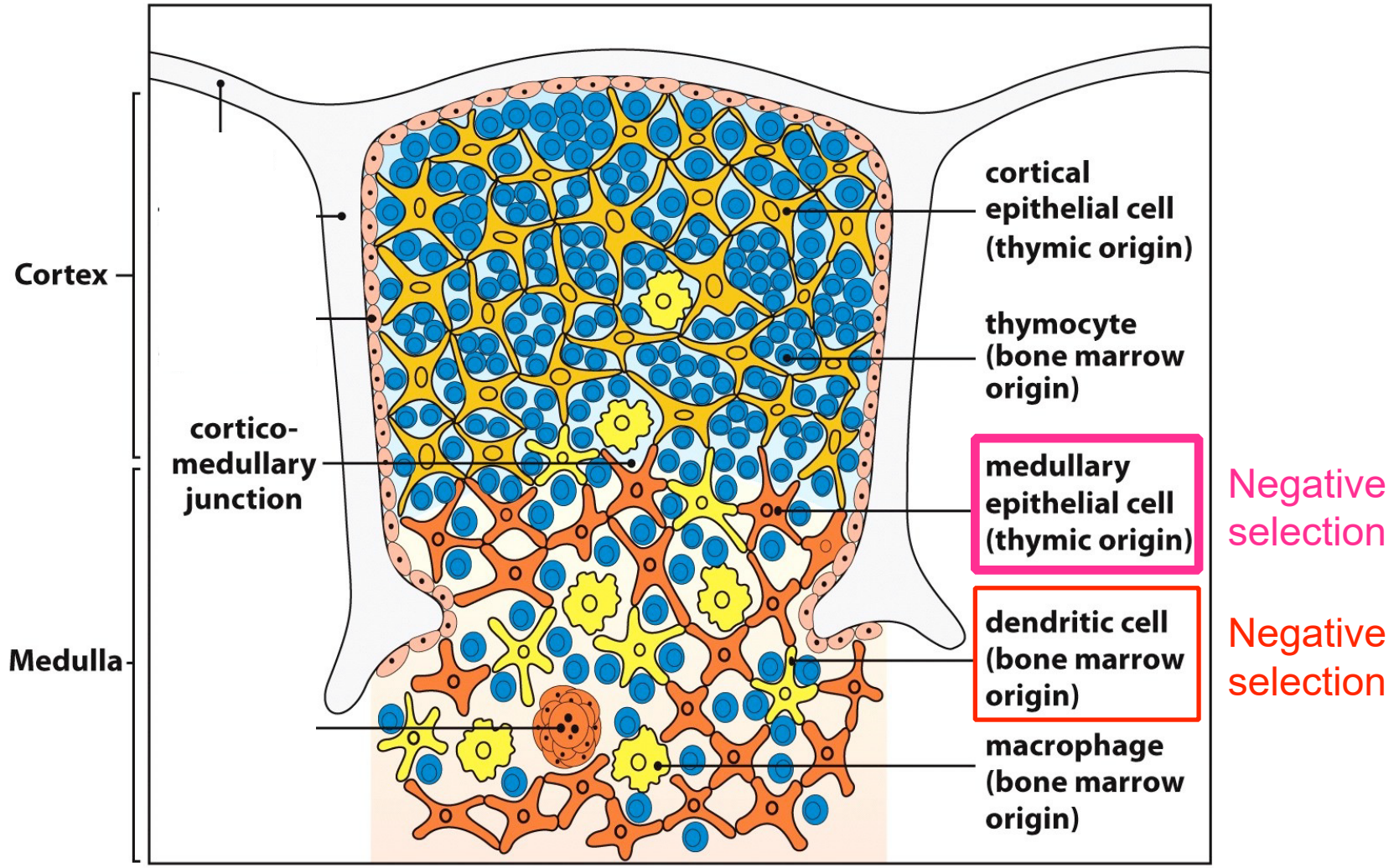


Figure 7.3 part 2 of 2 The Immune System, 3ed. (© Garland Science 2009)

AIRE (autoimmune regulator) Is Expressed by the Medullary Epithelial Cells of the Thymus

controls presentation of tissue restricted self-antigens (i.e. from tissues outside of thymus, such as insulin)

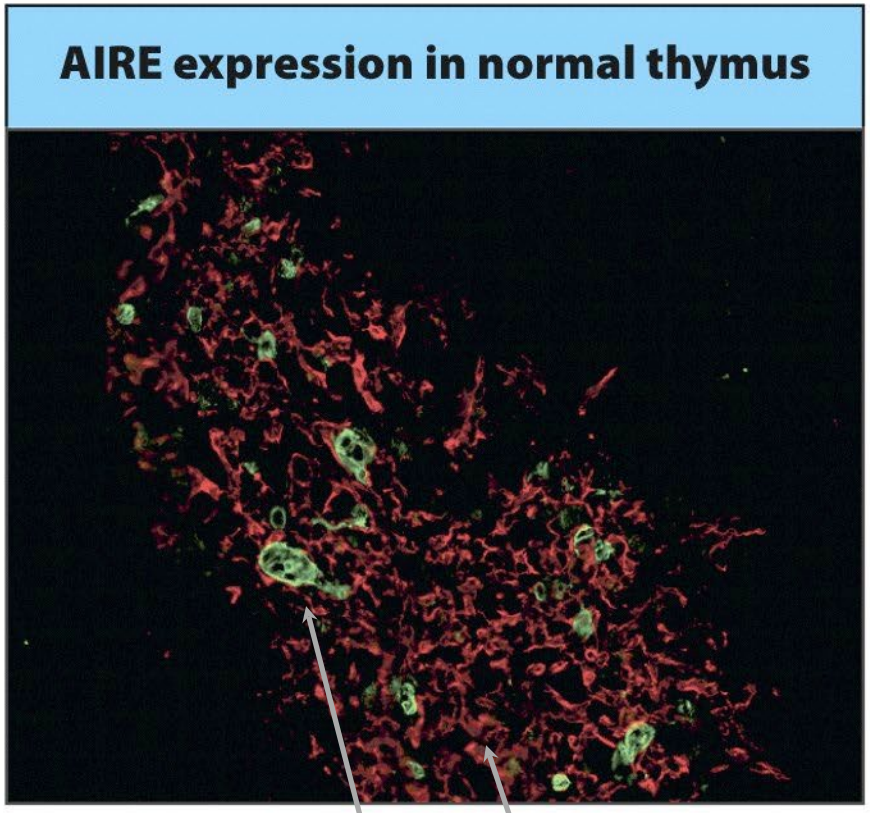
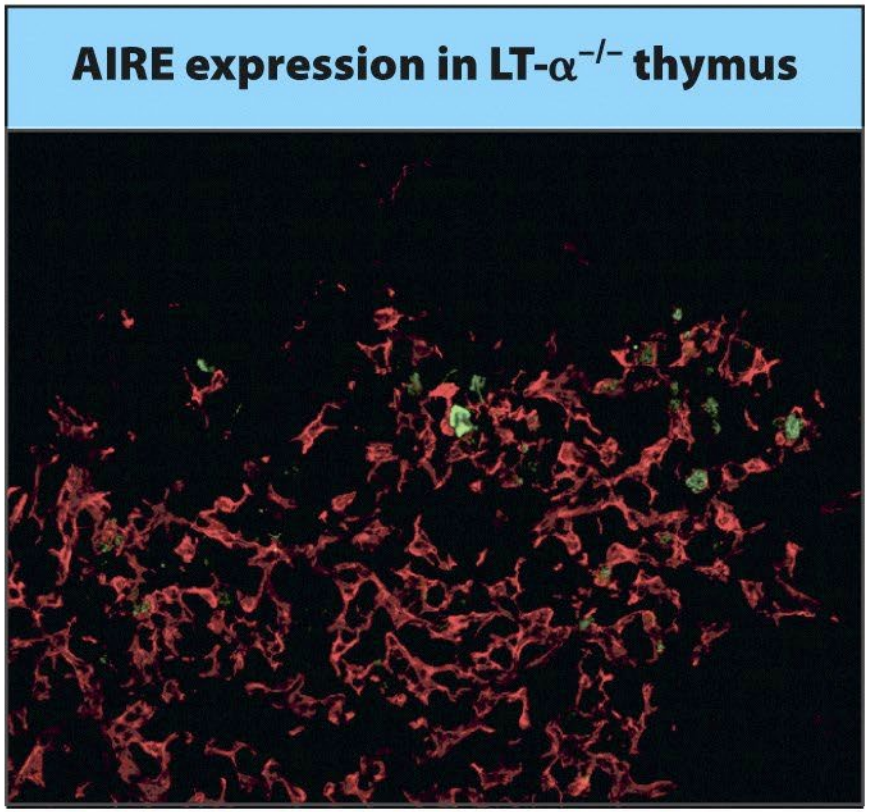


Figure 7-34 Immunobiology, 7ed. (© Garland Science 2008)

AIRE

Medullary cells

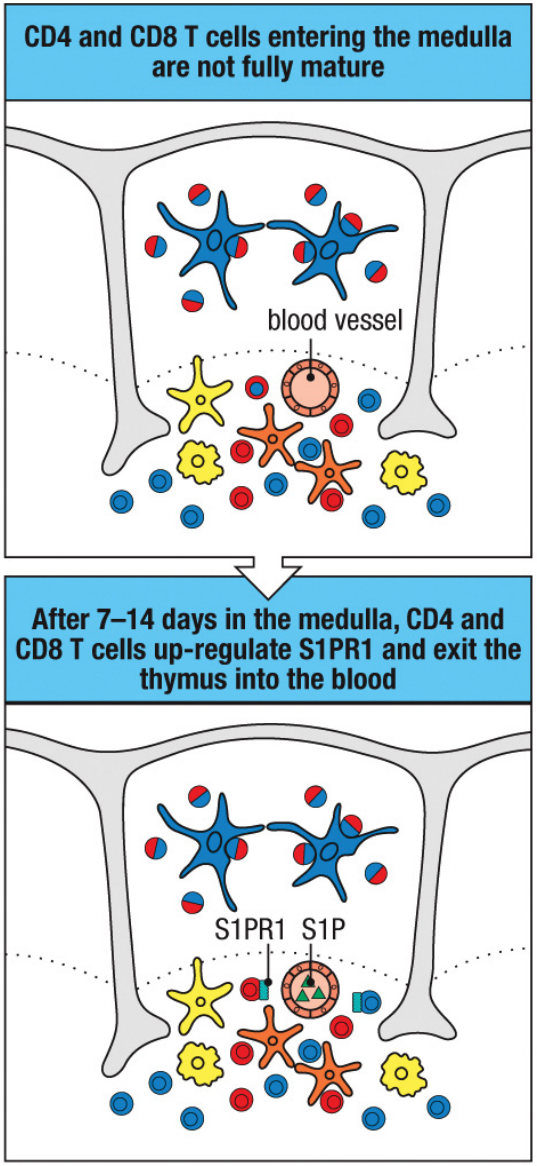


Impaired tolerance to **insulin**

Question

- T cell negative selection
- What is the purpose of the negative selection?
- Which cells and molecules mediate the negative selection?

Mature T Cells Leave Thymus



Donor and Recipient Must Share HLA Class I and II Molecules to Reconstitute T-Cell Function

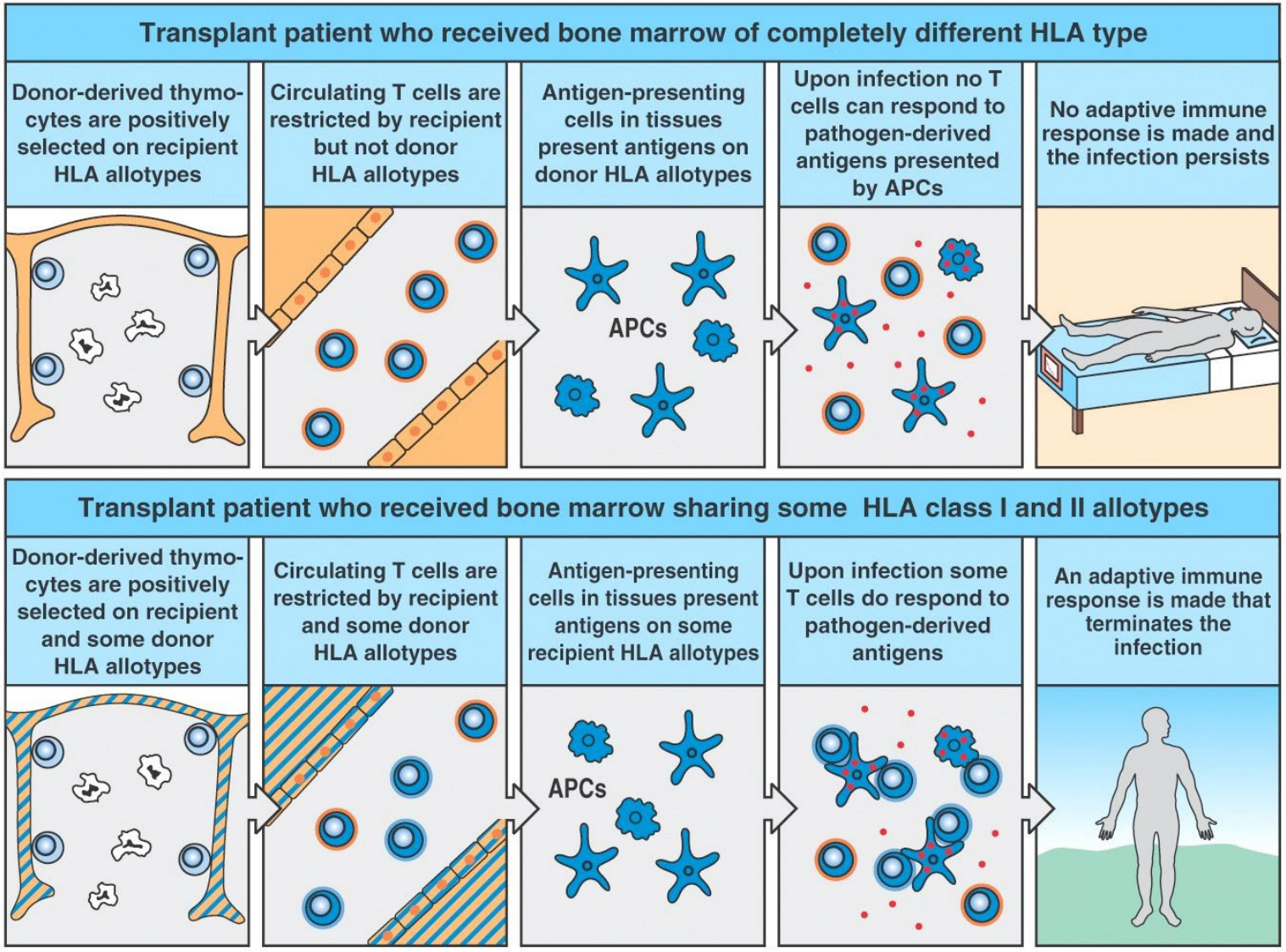


Figure 5-11 The Immune System, 2/e (© Garland Science 2005)

Problem 1

T cells restricted by which MHC will pass positive selection?

MHC^{F} bone marrow transplanted into MHC^{FxZ} recipient

A) F
B) Z
C) Both
D) Neither

Problem 2

T cells restricted by which MHC will pass <u>positive</u> selection?

MHC^{FxZ} bone marrow transplanted into MHC^{W} recipient

A) F
B) Z
C) W
D) All
E) None

Problem 3

Will the skin graft from MHC^{Z} animal be tolerated?

MHC^{FxZ} bone marrow transplanted into MHC^{F} recipient

A) Yes

B) No

Skin: All cells express **MHC^{Z}**

Problem 4

Will the skin graft from MHC^{W} animal be tolerated?

MHC^{FxZ} bone marrow transplanted into MHC^{F} recipient

A) Yes

B) No

Problem 5

Will the majority of developed T cells be activated in response to infection?

MHC^F bone marrow transplanted into MHC^Z recipient

A) Yes

B) No

Case Study-APECED

Patient:

- 18 month-retarded growth due to insufficient thyroid hormones
- 6 year-same thing plus hair loss
- 8 year-Candida infection in the mouth
- 18 years-bruise easily due to idiopathic thrombocytopenic purpura

Family history:

2 year older sister similar condition

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy

Autoantibody to IL-17 and IL-22, which is critical in fighting fungal infection

Figure 17.3 Case Studies in Immunology, 6ed. (© Garland Science 2012)

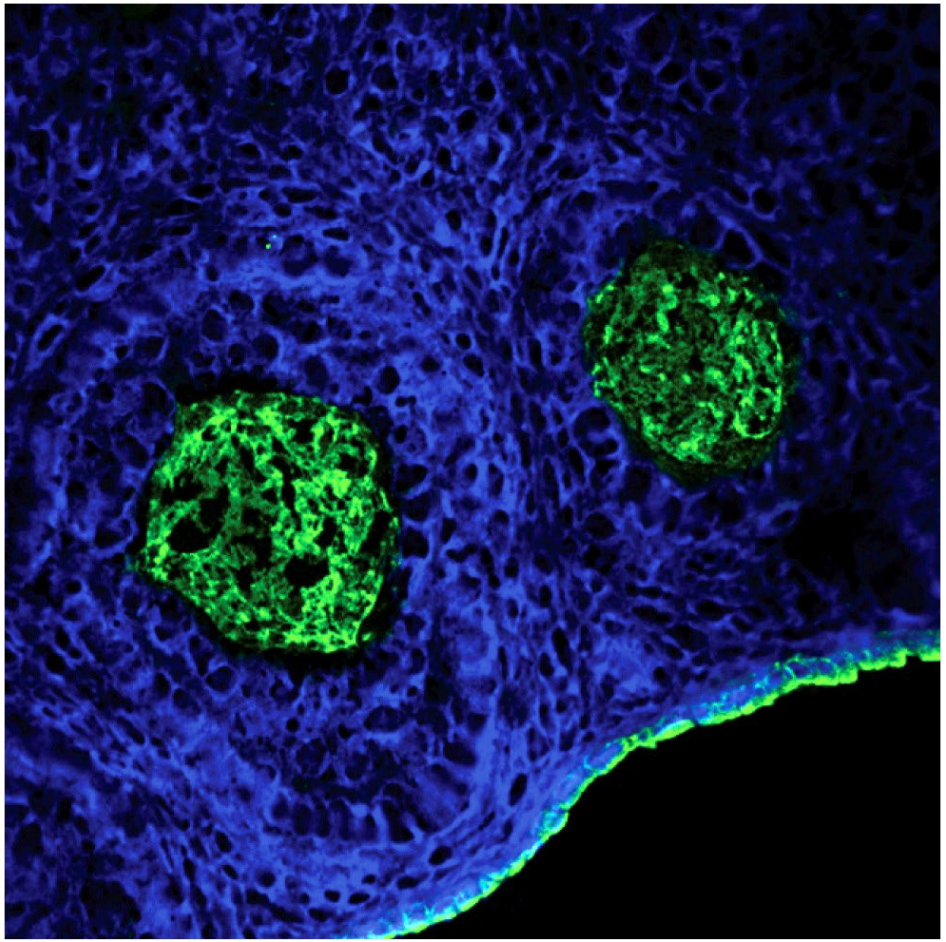


Figure 17.4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

self reactive antibody against ovarian oocyte

What's Wrong with the Patient?

- Defect in the AIRE gene, autoimmune regulator

- A transcriptional regulator expressed mainly in medullar epithelial cells
- -negative selection

AIRE

- How are tissue specific antigens present in the thymus for negative selection?

Question

- What cells mediate negative selection in thymus?
- A) bone marrow derived
- B) thymic cells
- C) both
- D) neither