Society for Immunotherapy of Cancer (SITC)

Immunology 101 for the Non-Immunologist

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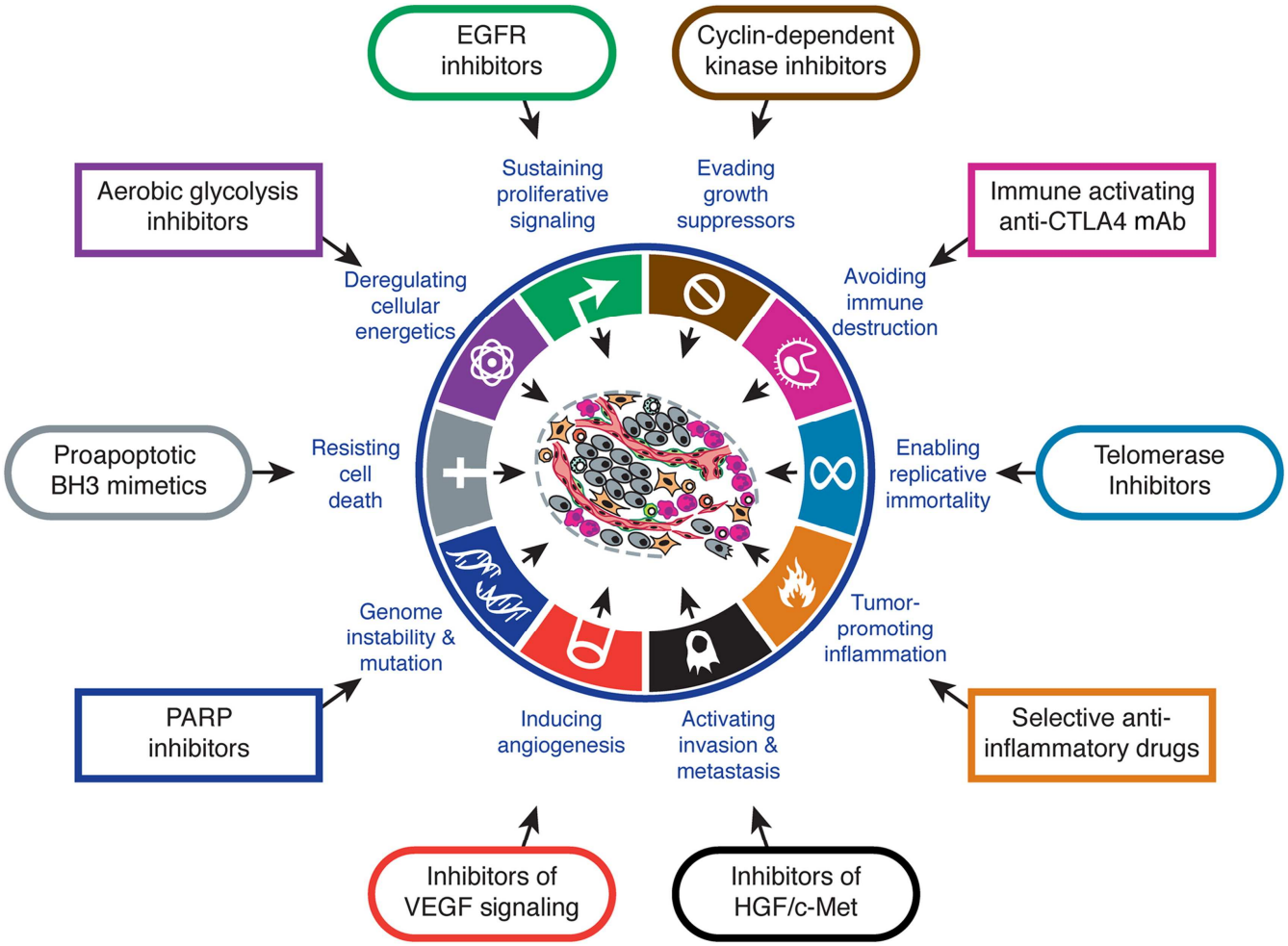
Vanderbilt-Ingram Cancer Center

Advances in Cancer Immunotherapy™ - Nashville
October 2, 2015

Society for Immunotherapy of Cancer

Avoiding Immmunity is a Hallmark of Cancer



Hanahan and Weinberg *Cell* 2011

What is the immune system

- A network of organs, tissues, cells and proteins all coordinated to defend the host from outside organisms/invaders
- In an infinitely adaptable system to combat the complex and endless variety of pathogens that it comes into contact with

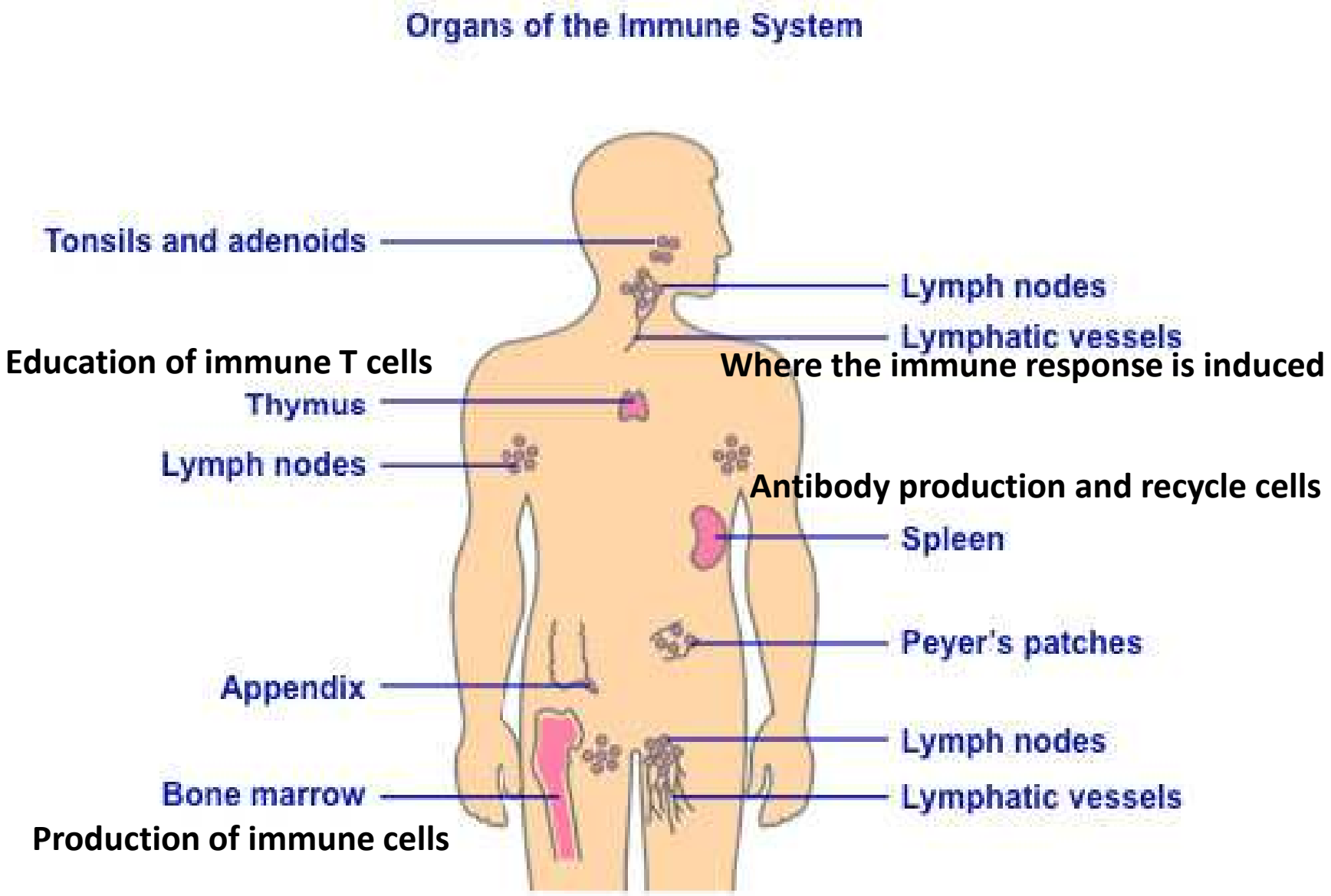
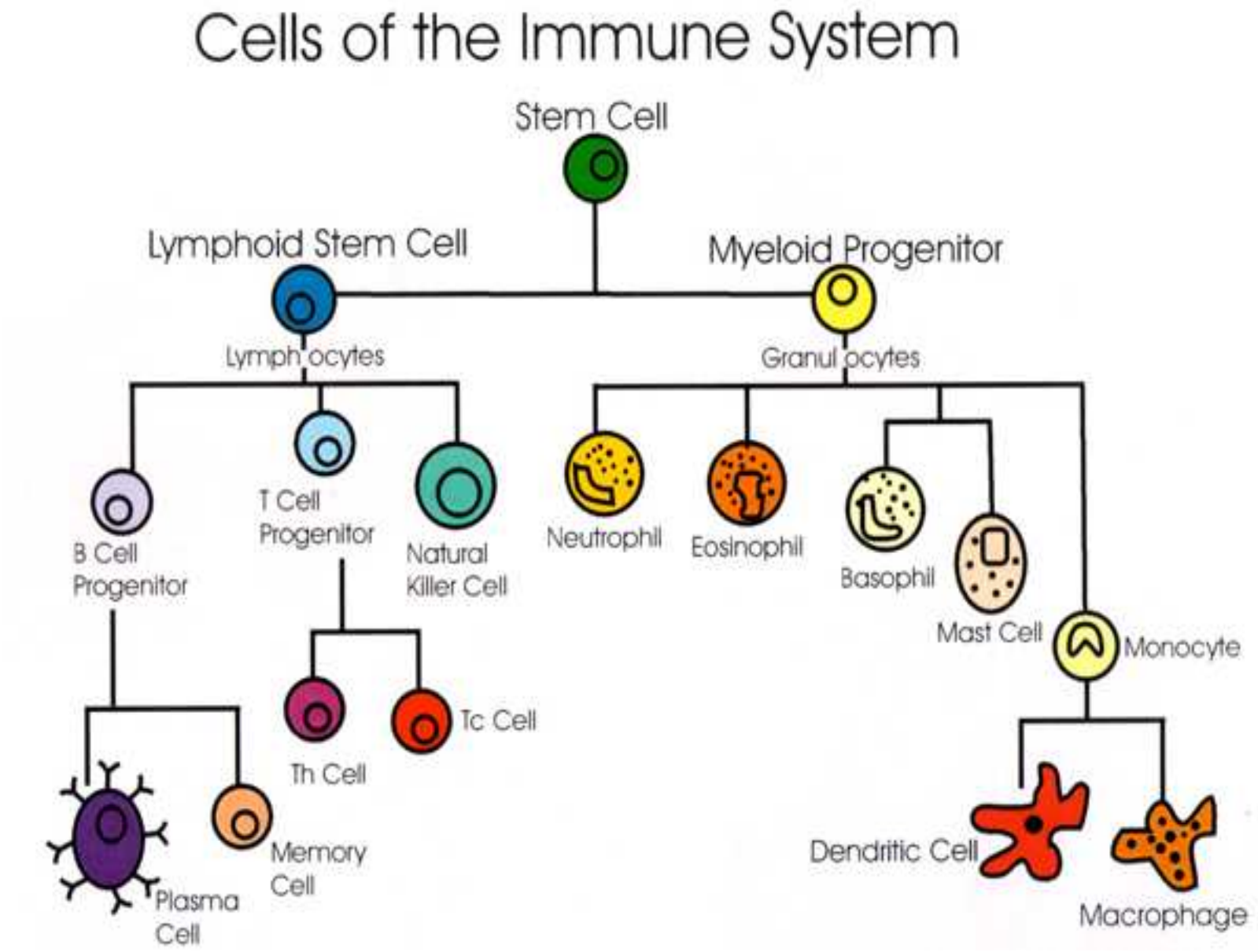


Image courtesy of the National Cancer Institute

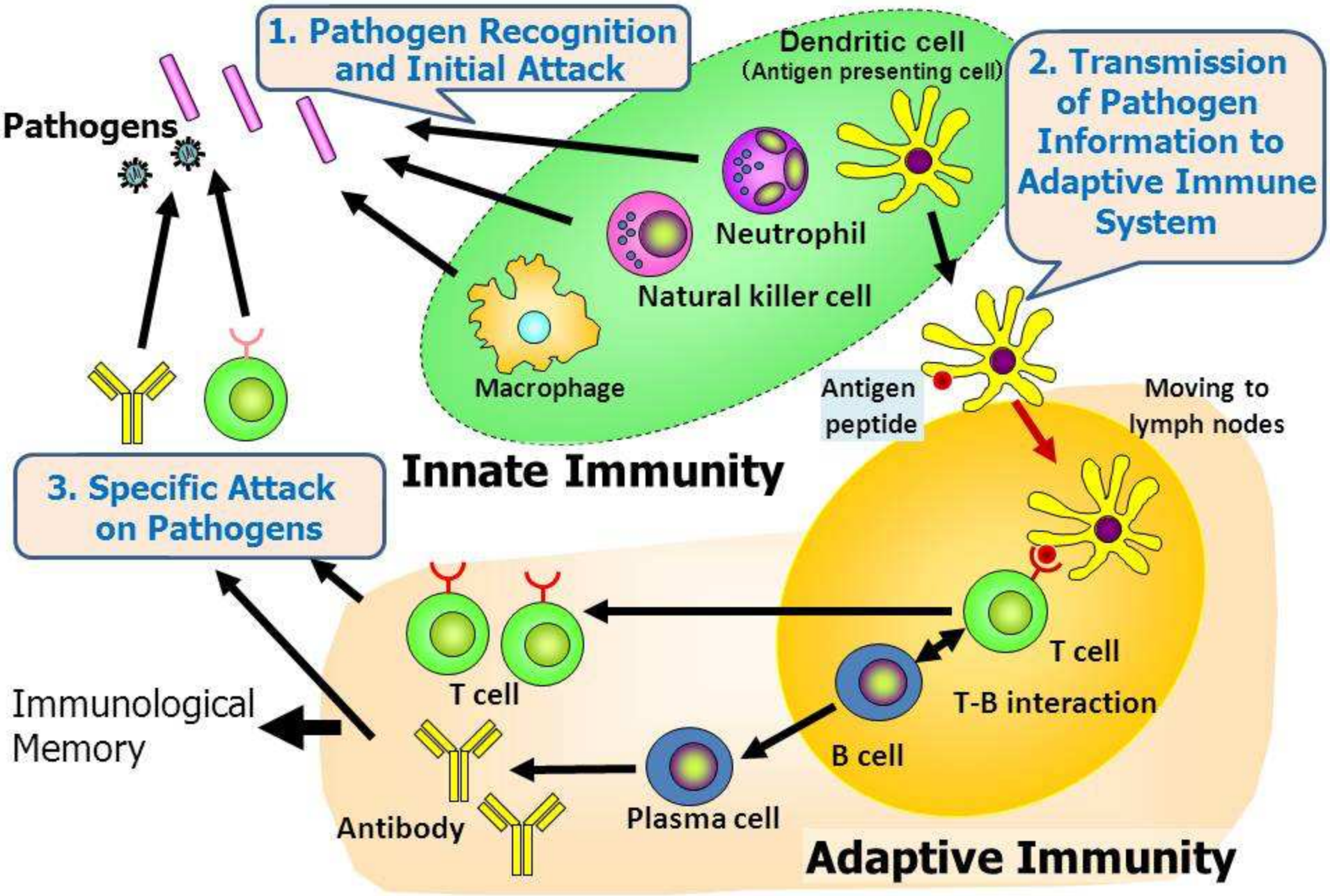


Kenneth Todar, Ph.D www.textbookofbacteriology.net

Innate and Adaptive Immunity

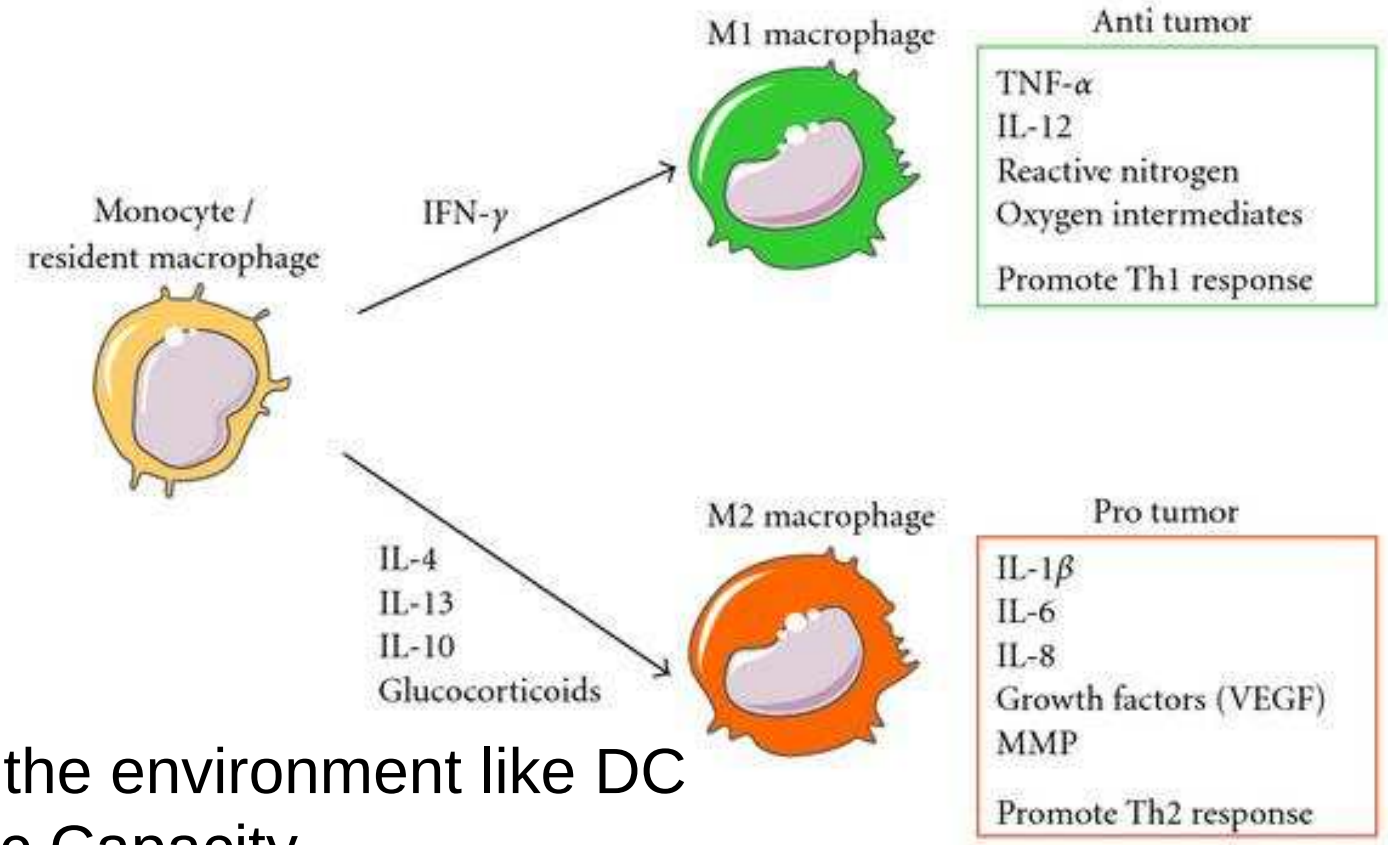
- **Innate Immunity- first line of defense**
  - Neutrophils, macrophages, natural killer cells, dendritic cells
  - Recognizes conserved molecular patterns- low specificity
  - Rapid Response – minutes to hours
    - Uses products of germline genes (no receptor rearrangements)
  - Kills pathogens and processes antigen to initiate adaptive immunity
  - A primitive system conserved through evolution
  - Not specifically directed against the invading microorganism
  - **NO IMMUNOLOGICAL MEMORY**
- **Adaptive Immunity**
  - specialized/memory
  - T cells (cellular) and B cells (humoral/antibody)
  - T-cell receptor and B-cell receptor for specificity
  - **MEMORY CAN LAST A LIFETIME**
- Cytokines and chemokines regulate both types of immunity

Innate Immunity



Shizuo Akira *Philos Trans R Soc Lond B Biol Sci* 2011

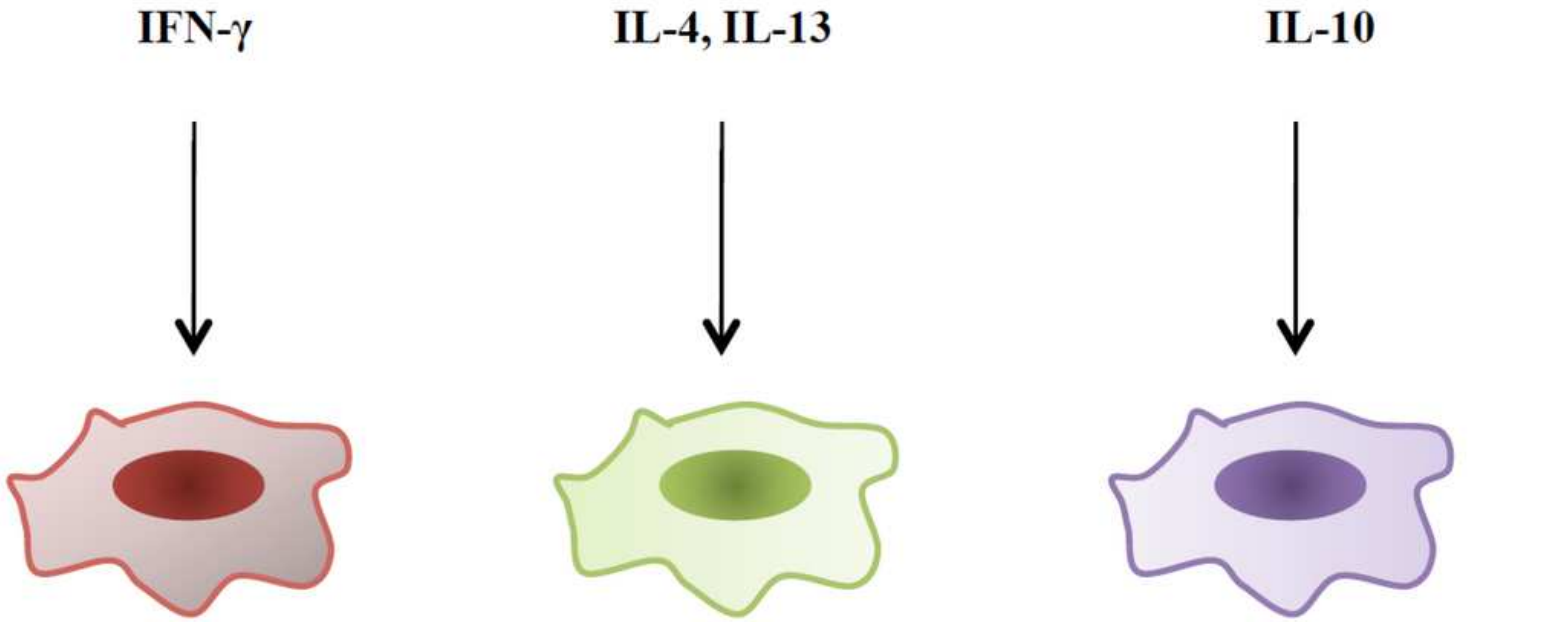
Macrophages- M1 and M2



- Sample the environment like DC
- Cytotoxic Capacity
- Key regulators of wound repair and resolves an immune response

Schmid, Journal of Oncology, 2010

Regulation of Macrophage Differentation by Cytokines



Pro-inflammatory cytokines IL-1, IL-6, TNFα

Antigen endocytosis & tissue repair

Immune suppression IL-10, TGFβ

Abbas, Viruses, 2015

FcR on surface of monocytes/macrophages

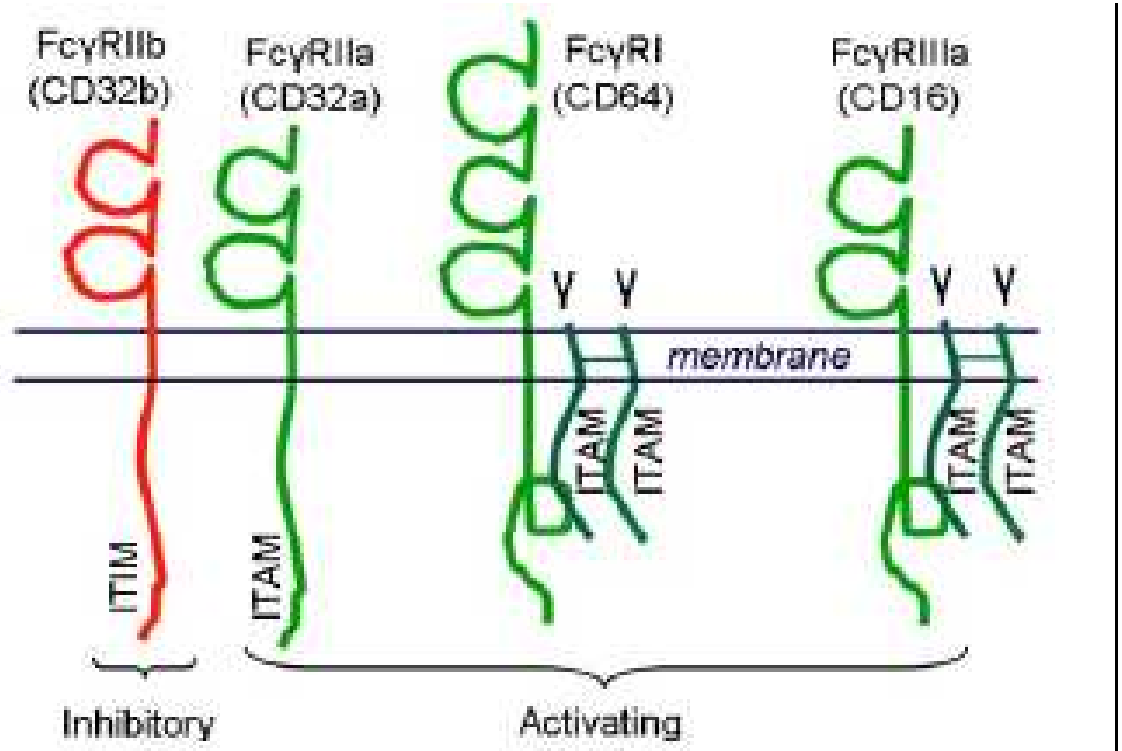
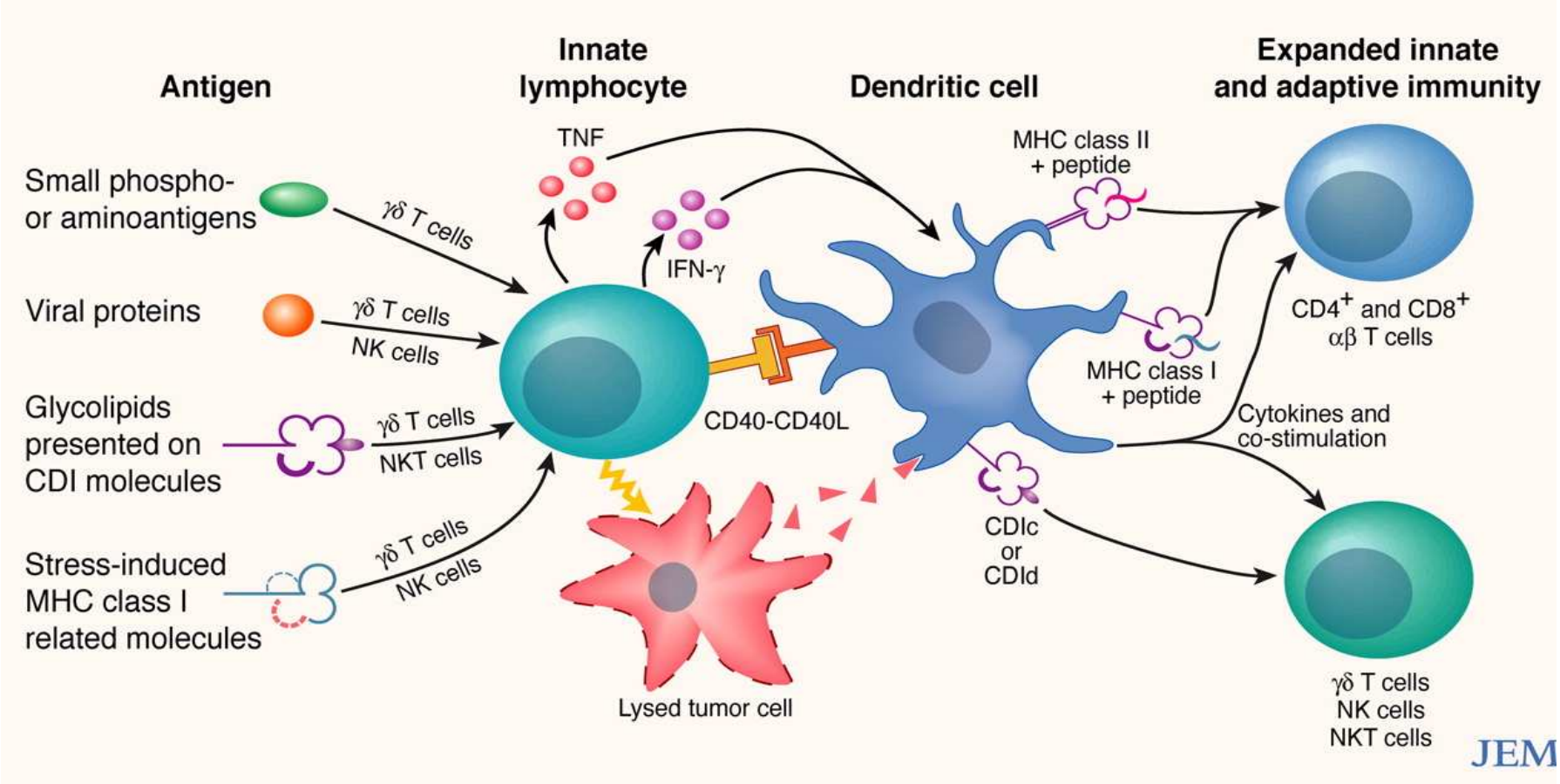


Figure 1. Schematic of FcγR, showing activating and inhibitory receptors.

FcR can act to activate or inhibit macrophage/NK cell function- such as ADCC and ADCP

Dendritic Cell: Bridge between Innate Immunity and Adaptive Immunity



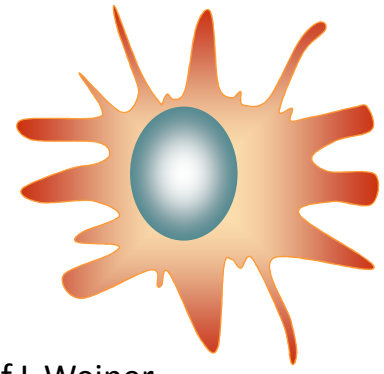
Munoz, JEM, 2005

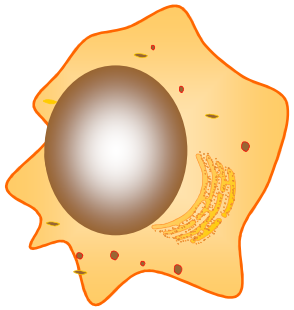
Antigen Presenting Cells (APCs)

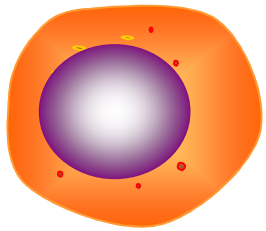
- The ability to process and present Ags on MHC class I molecules is a property of virtually all mammalian cells

- Professional APCs are highly specialized cells that can
  - Process and present an Ag associated with MHC class II
  - Provide a 2nd, co-stimulatory signal to T cells

Dendritic Cells Macrophages B Cells

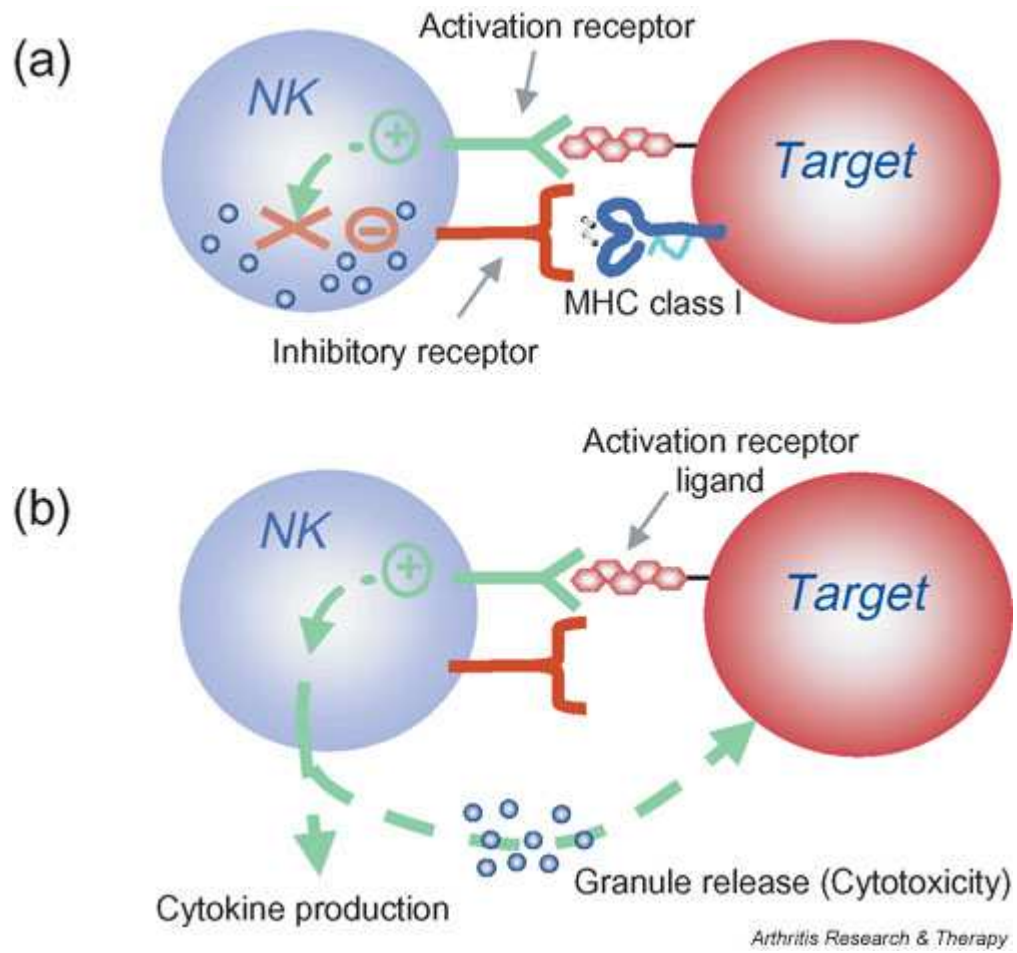






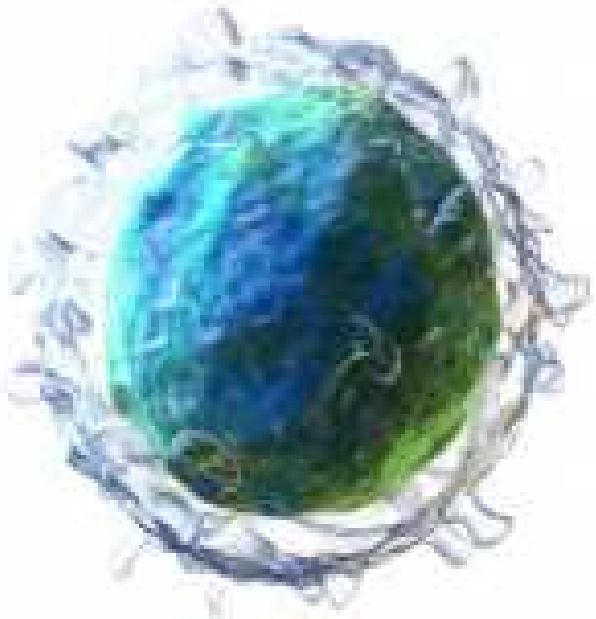
Courtesy of L Weiner

Natural Killer Cells- sensor of altered self
- loss of MHC class I or upregulation of stress molecules



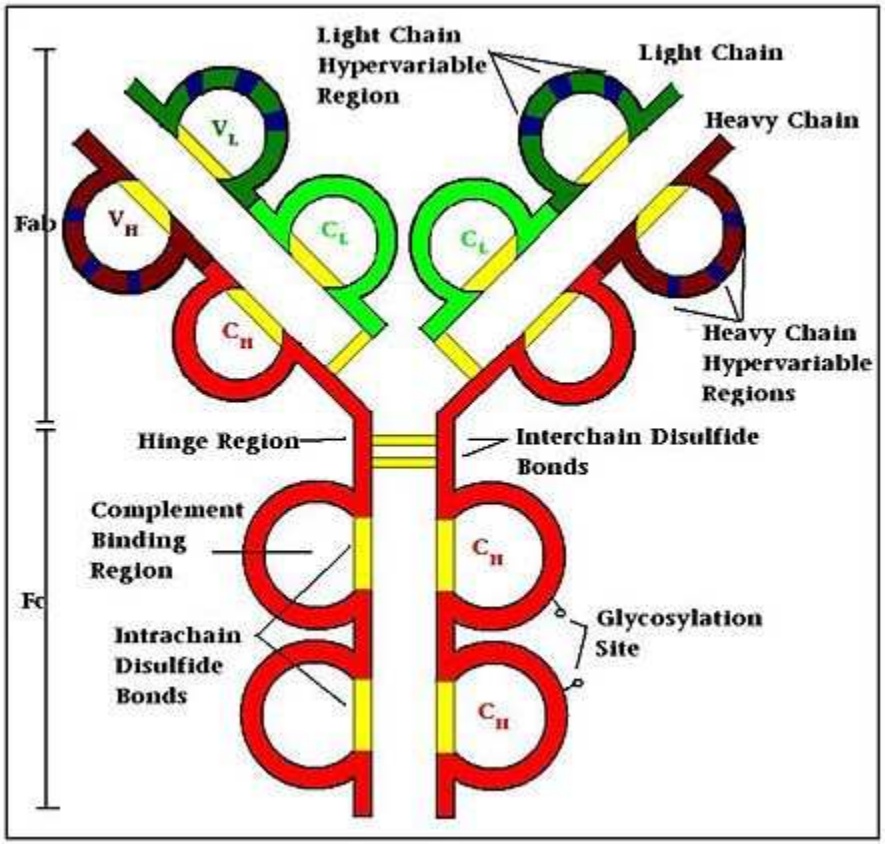
French and Yokoyama *Arthritis Res Ther* 2004 **6**:8-14

B lymphocyte- Antigen Binding Receptor- Ig receptor



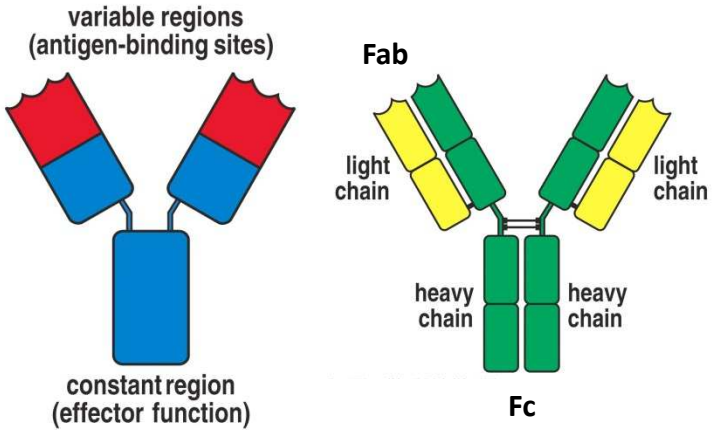
Lymphocyte

B cell



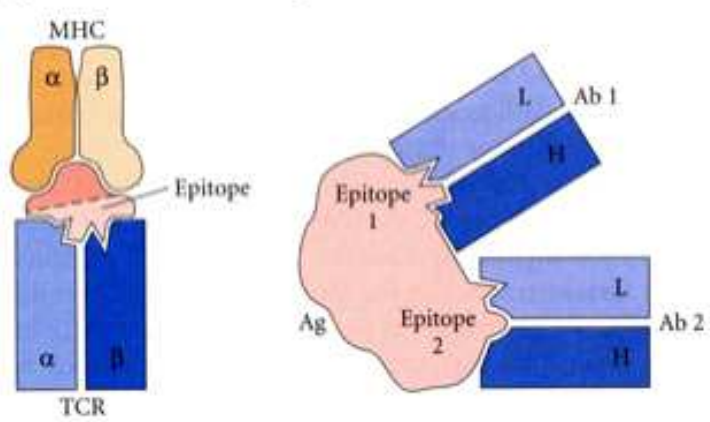
Antigen Receptors Underlie Specificity

Antibody



A protein produced by activated B lymphocytes that binds specifically to a particular substance – its antigen

T Cell Receptor



T cells bind to processed antigens via T cell receptor (TCR) recognition of peptides derived from proteins that were processed and presented by APC in the context of self-MHC

Antibodies bind to native antigens by recognizing protein conformations

Portions of antigens = epitopes

Courtesy of L Weiner

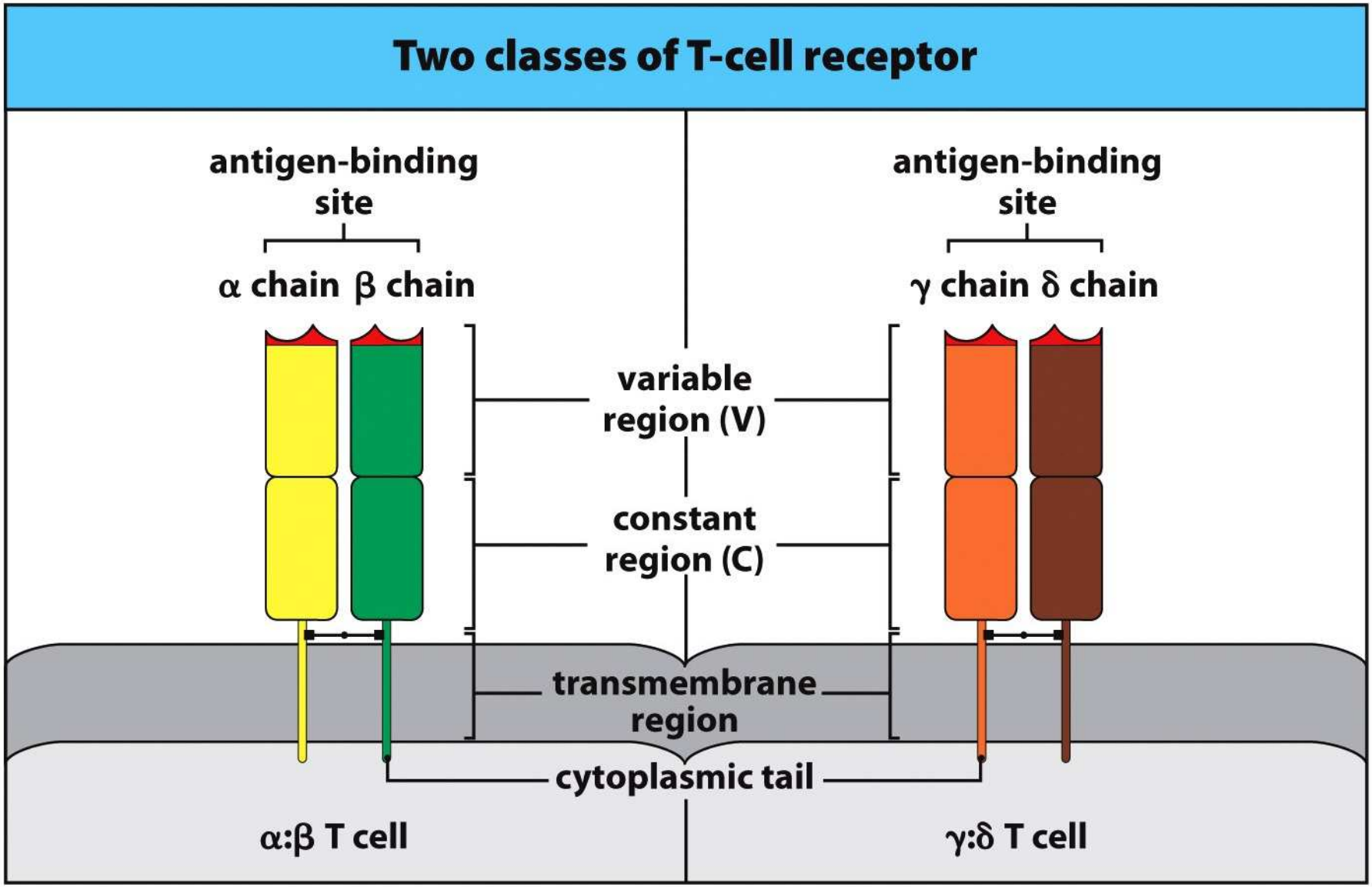
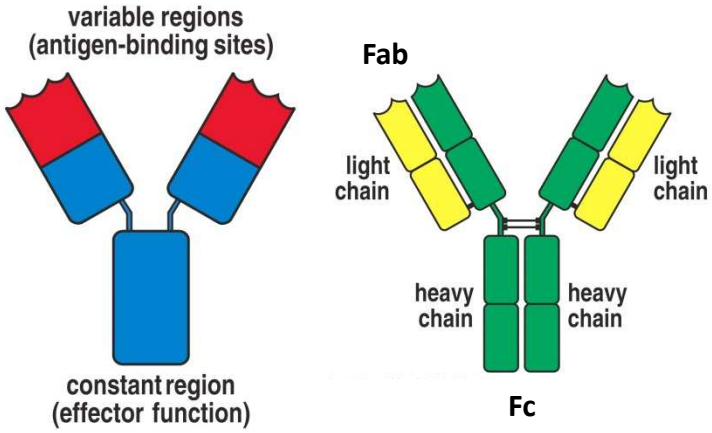


Figure 5.7 The Immune System, 3ed. (© Garland Science 2009)

Antigen Receptors Underlie Specificity

Antibody



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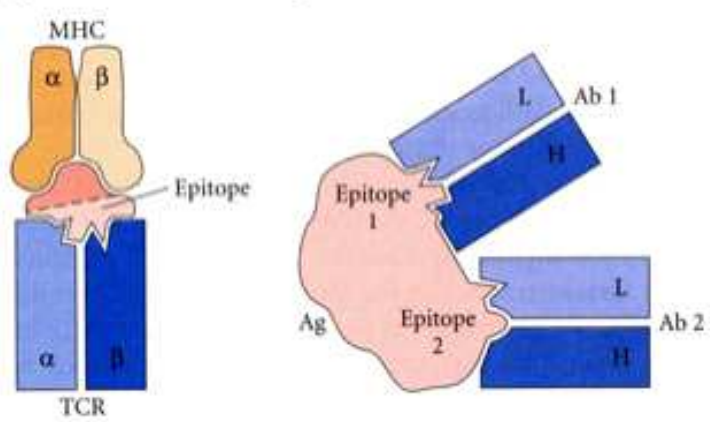

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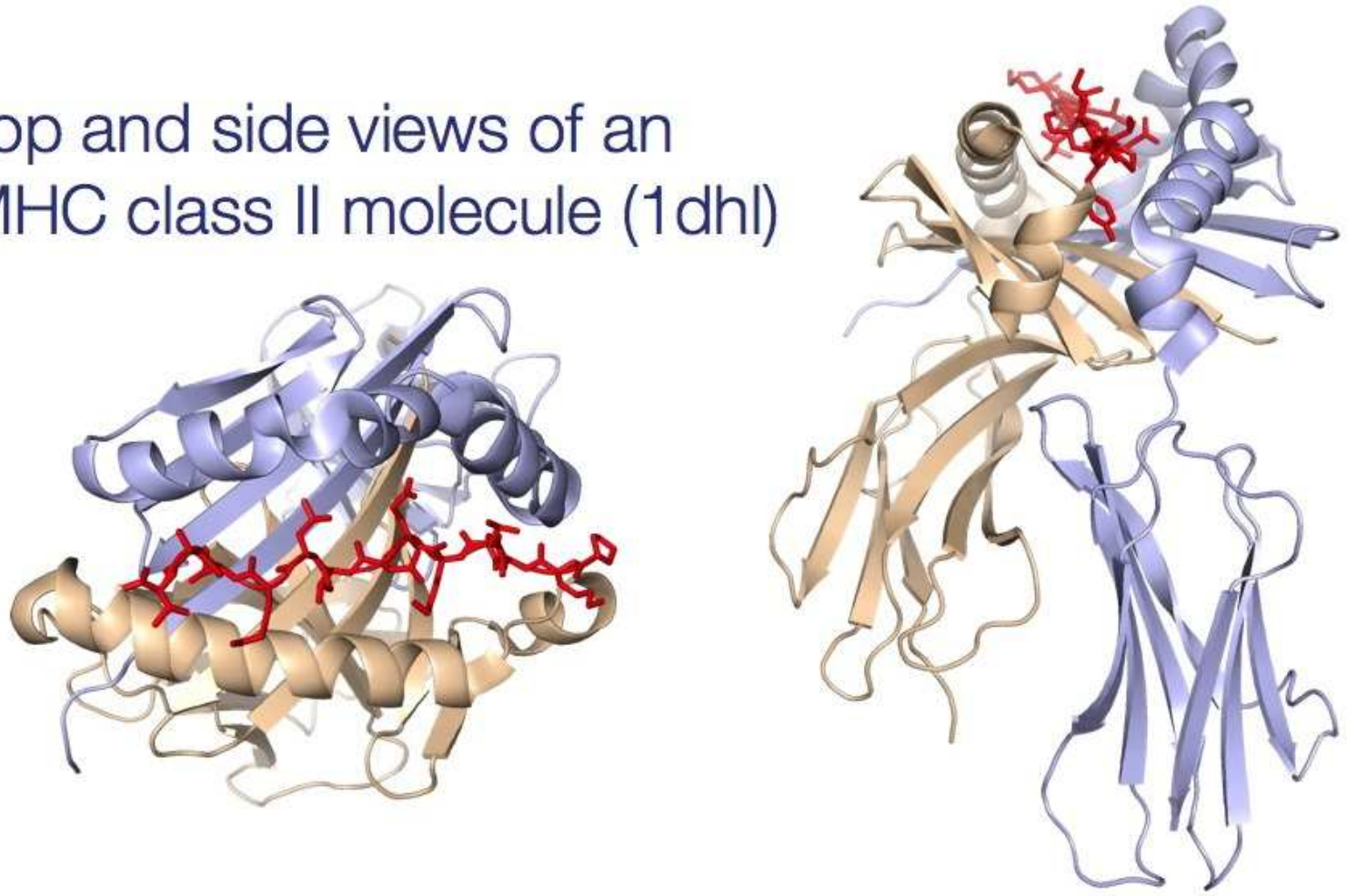
Courtesy of L Weiner

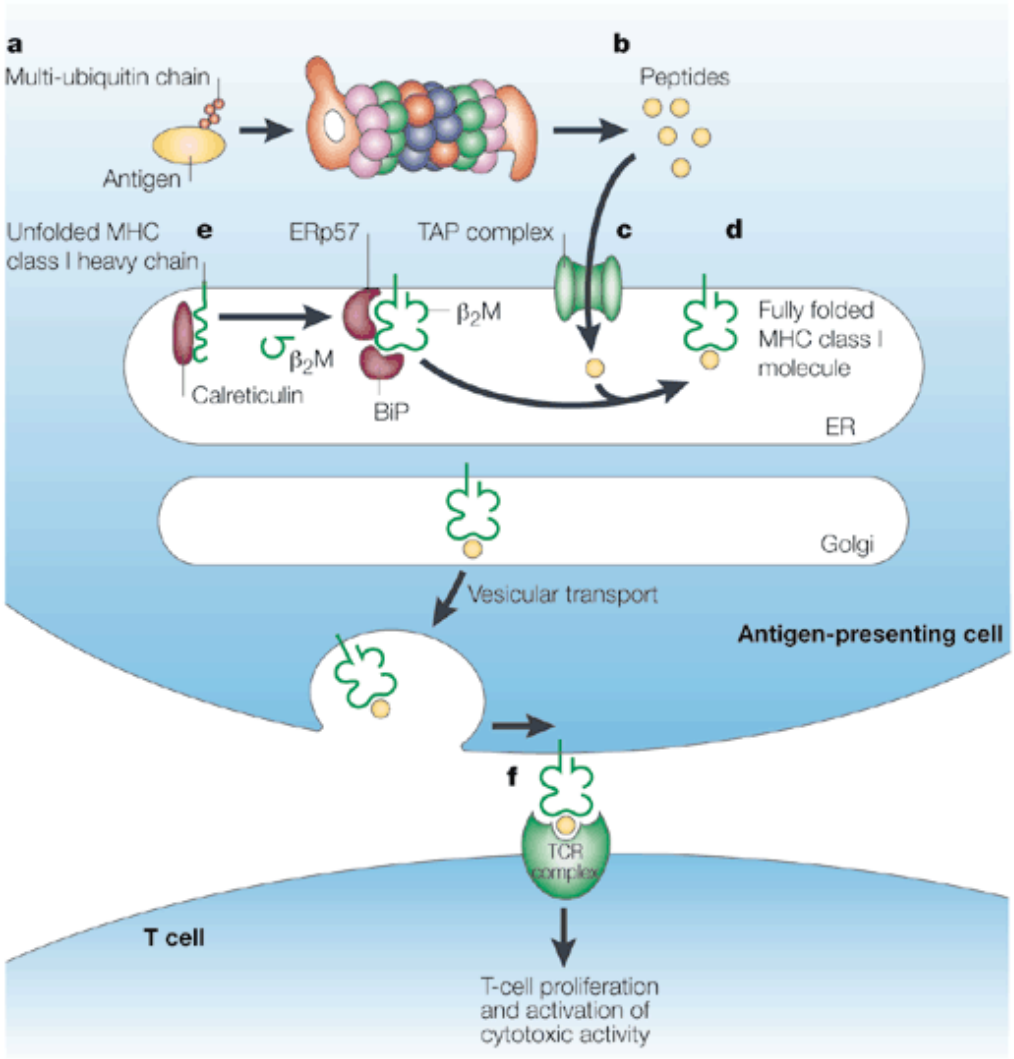
What does the T cell receptor see?

Top and side views of an MHC class II molecule (1dhl)



Adapted from Rudolph, MG et al. Annu Rev Immunol 2006

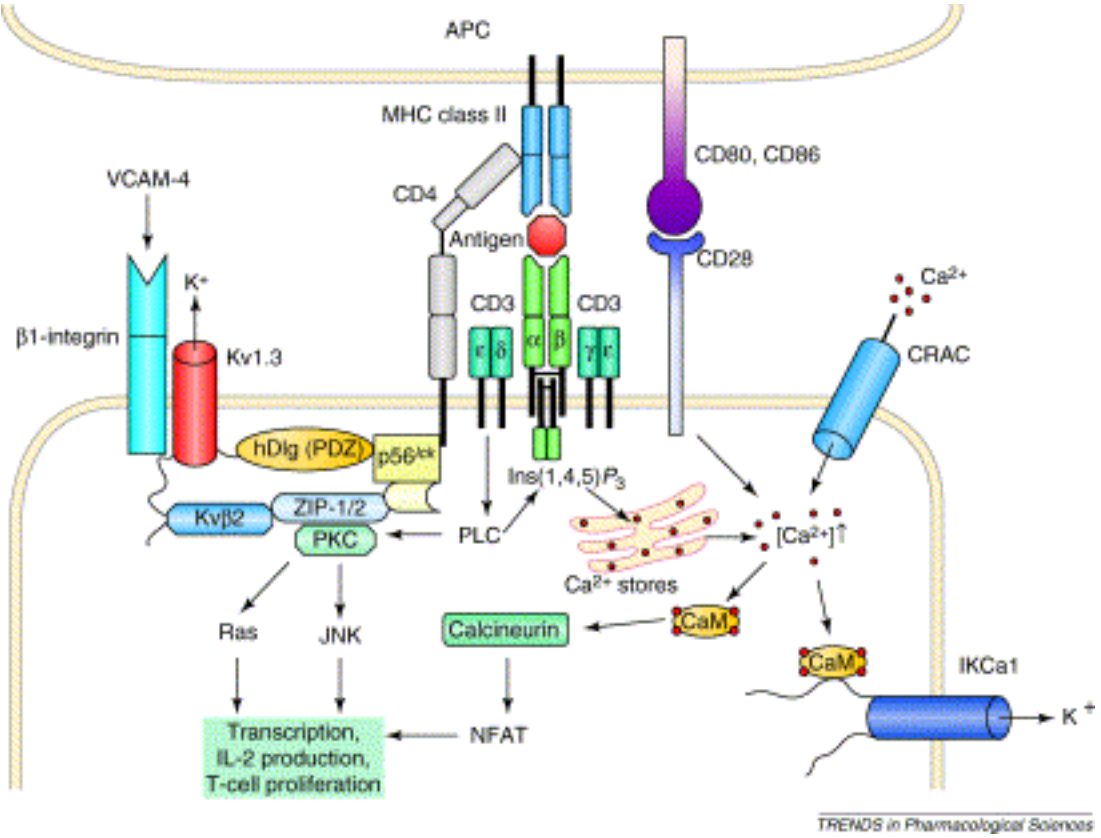
Antigen Processing and Presentation



Kloetzel, Nature Reviews Molecular Cell Biology 2001

Nature Reviews | Molecular Cell Biology

TCR Signaling Complex



Chandy, Trends in Pharmacological Sciences, 2004

Activation of naïve T cells requires two independent signals delivered by same APC

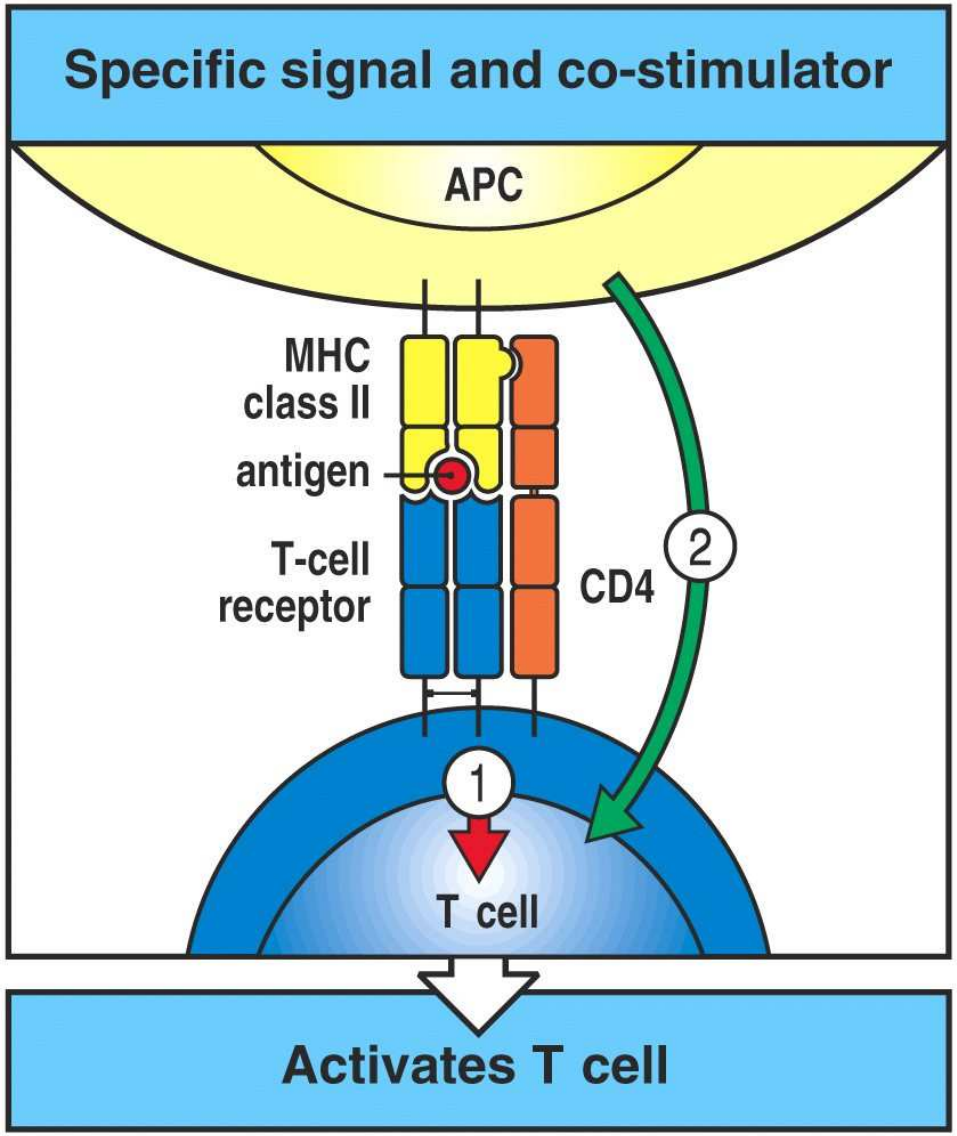


Figure 8-10 Immunobiology, 6/e. (© Garland Science 2005)

Only one signal - no activation or anergy

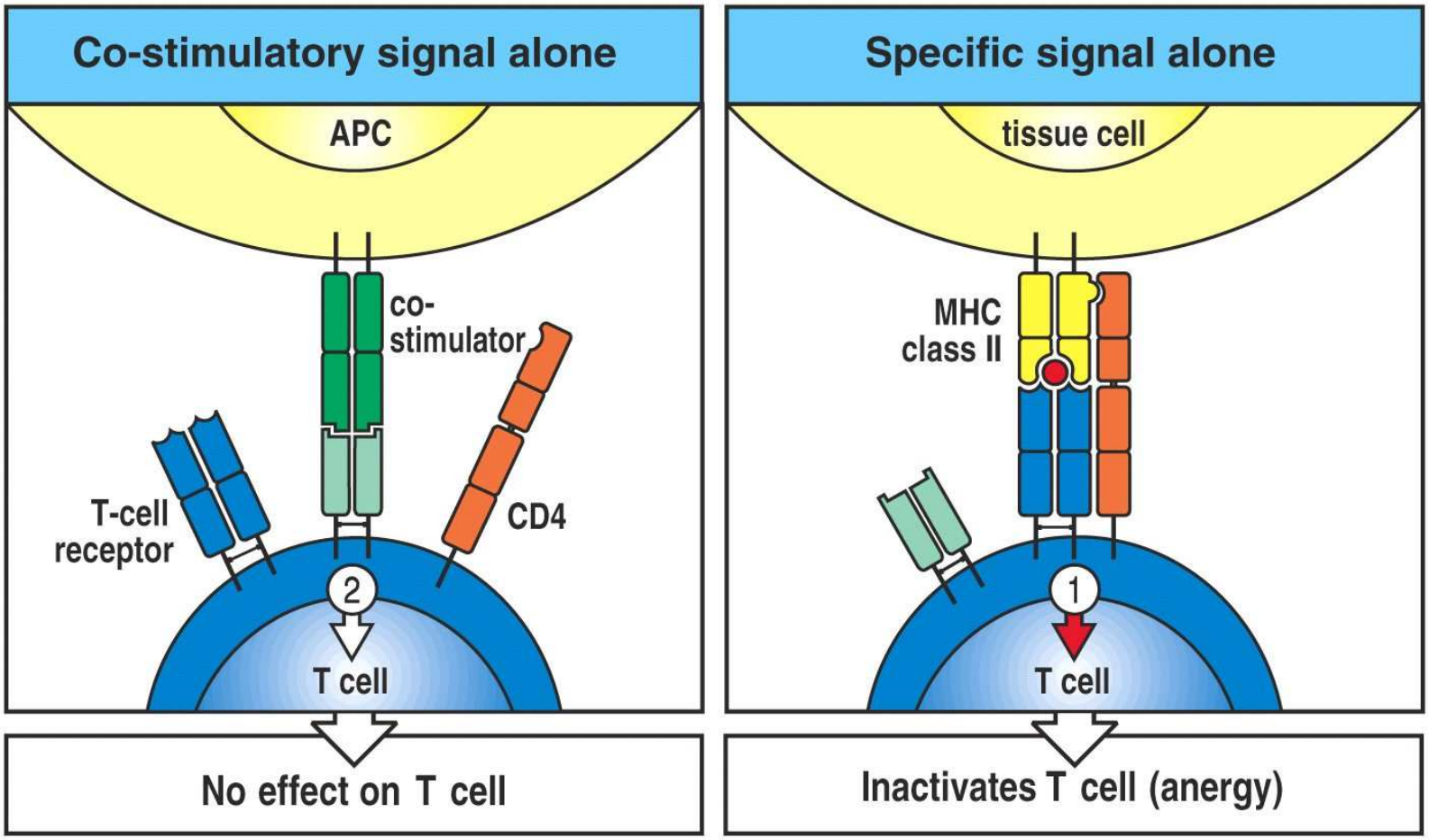
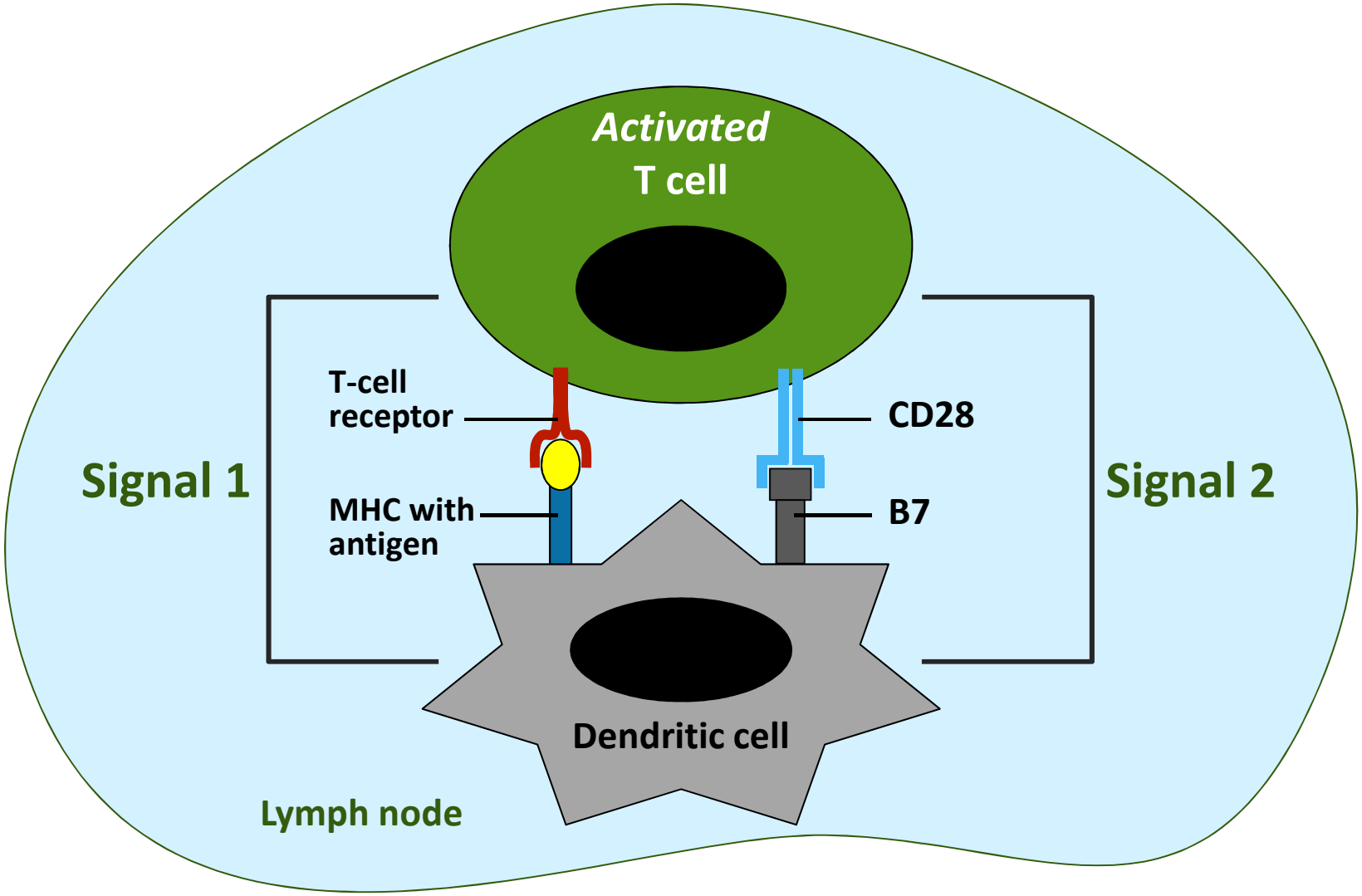


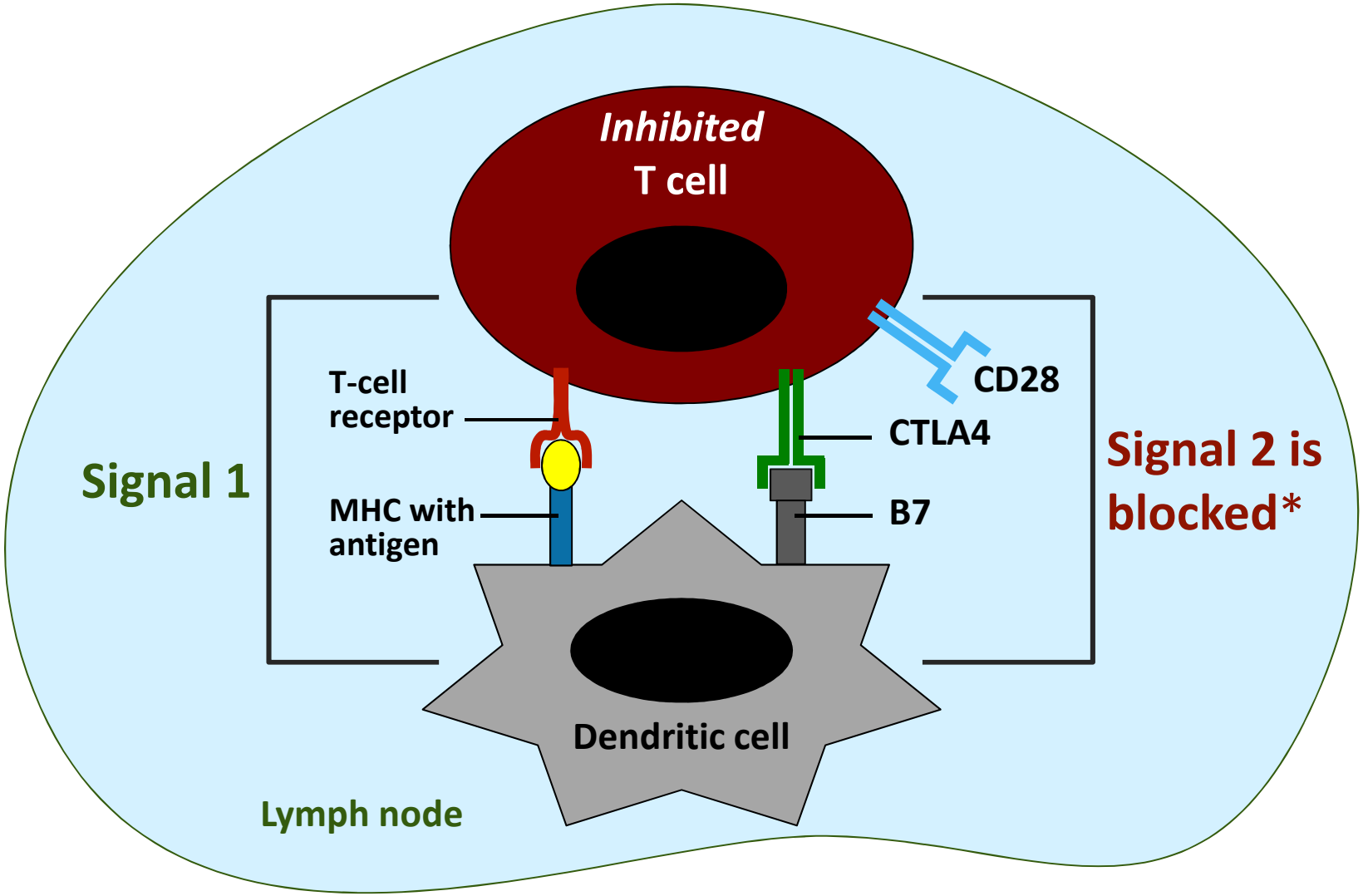
Figure 8-21 Immunobiology, 6/e. (© Garland Science 2005)

Two Signals required for T-Cell Activation



Postow MA, et al. *J Clin Oncol.* 2015 Jan 20. [Epub ahead of print][4]

CTLA4 in its role the inactivation of the Immune Cell



*Antibody to CTLA4 blocks its interaction with B7, restoring the ability of B7 to interact with CD28.

Postow MA, et al. *J Clin Oncol.* 2015 Jan 20. [Epub ahead of print][4]

T cell activation through the TCR and CD28 leads to the increased expression of CTLA4

CTLA4 is an inhibitory receptor for B7 Molecules that shuts down Signal 2

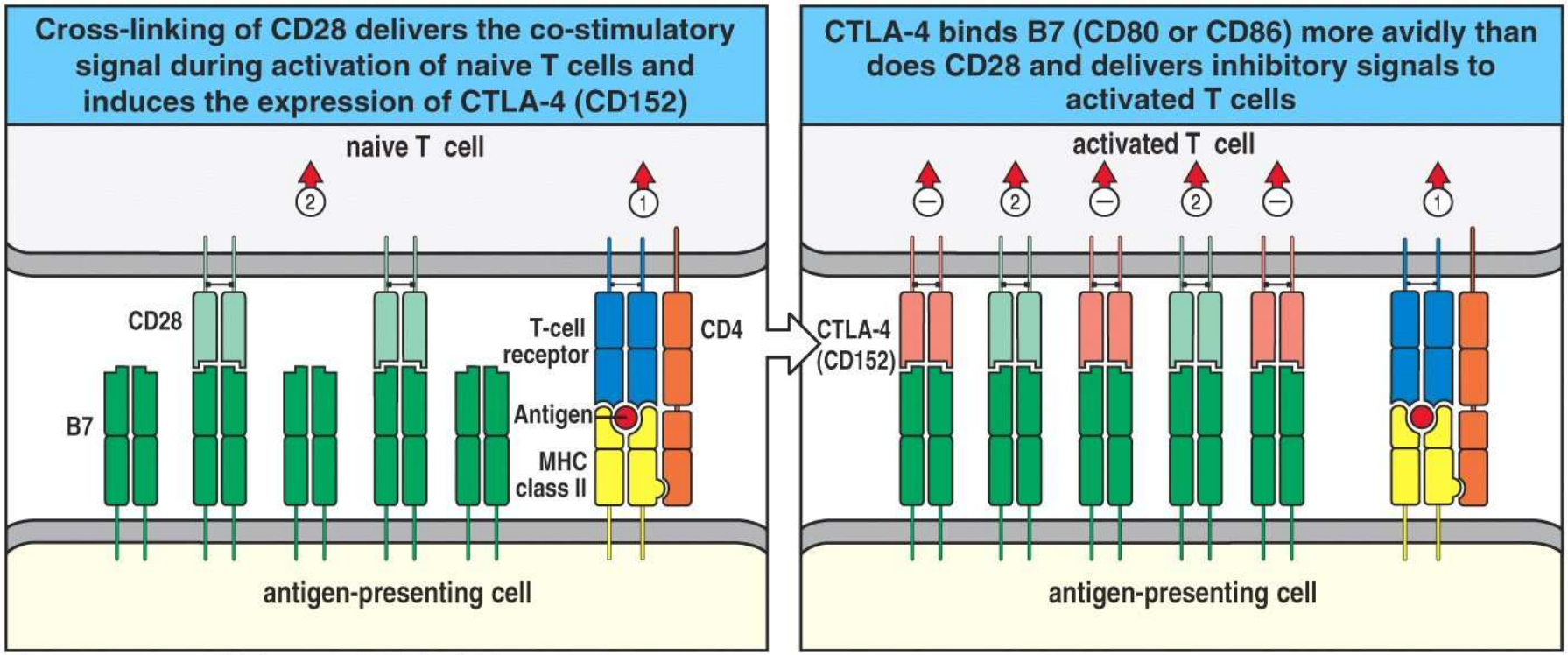
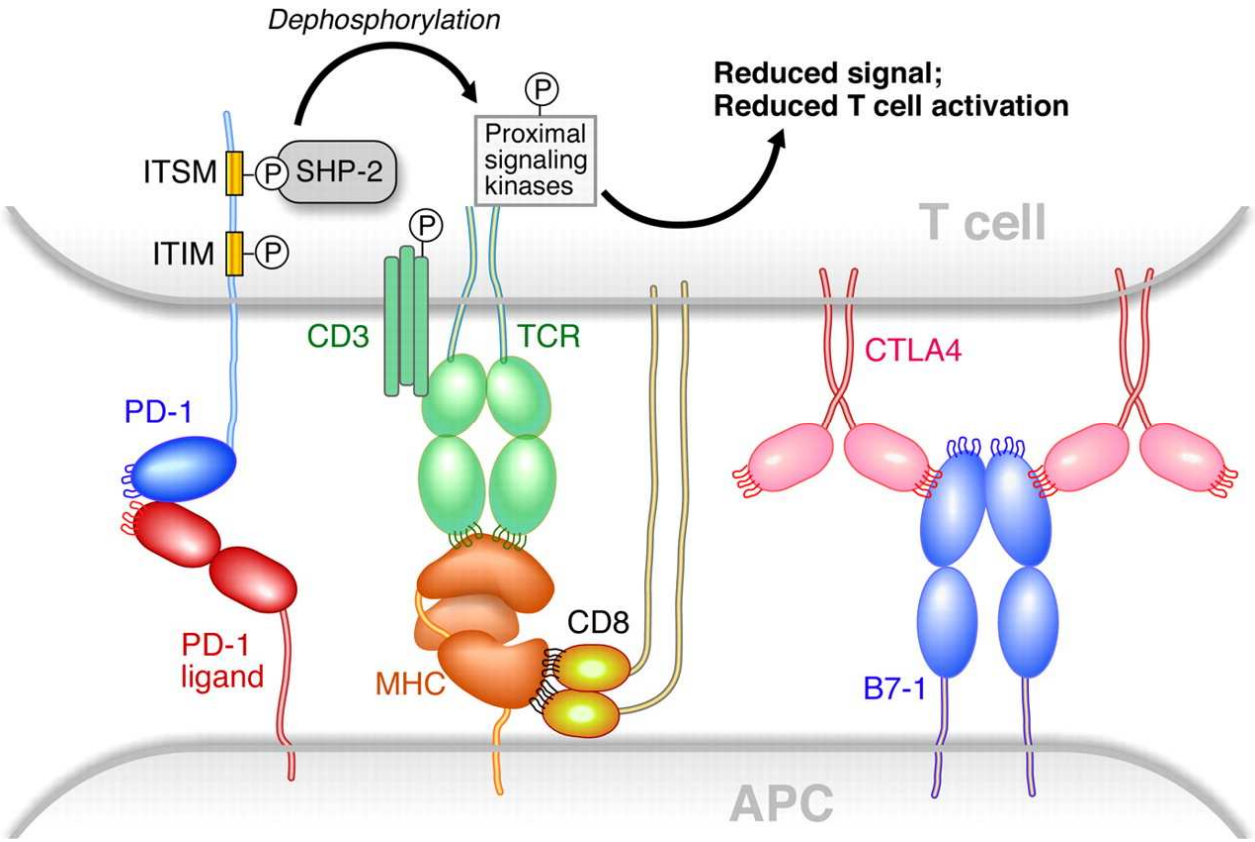


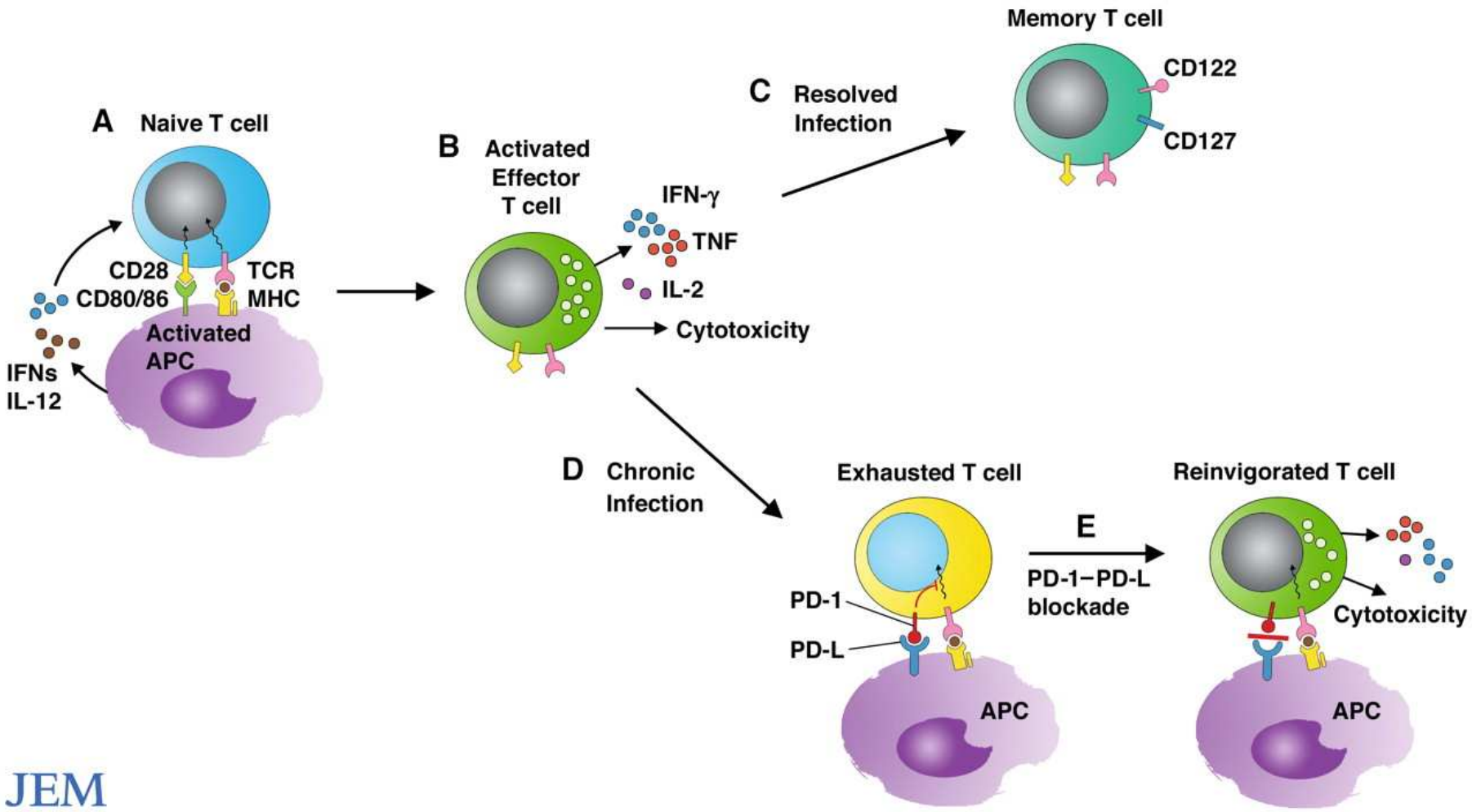
Figure 8-12 Immunobiology, 6/e. (© Garland Science 2005)

Structures of PD-1 with its ligands



Freeman,G etal, PNAS, 2008

Reinvigorating exhausted T cells.



JEM

Gordon J. Freeman et al. J Exp Med 2006;203:2223-2227

Control of the T Cell

T-cell activating receptors

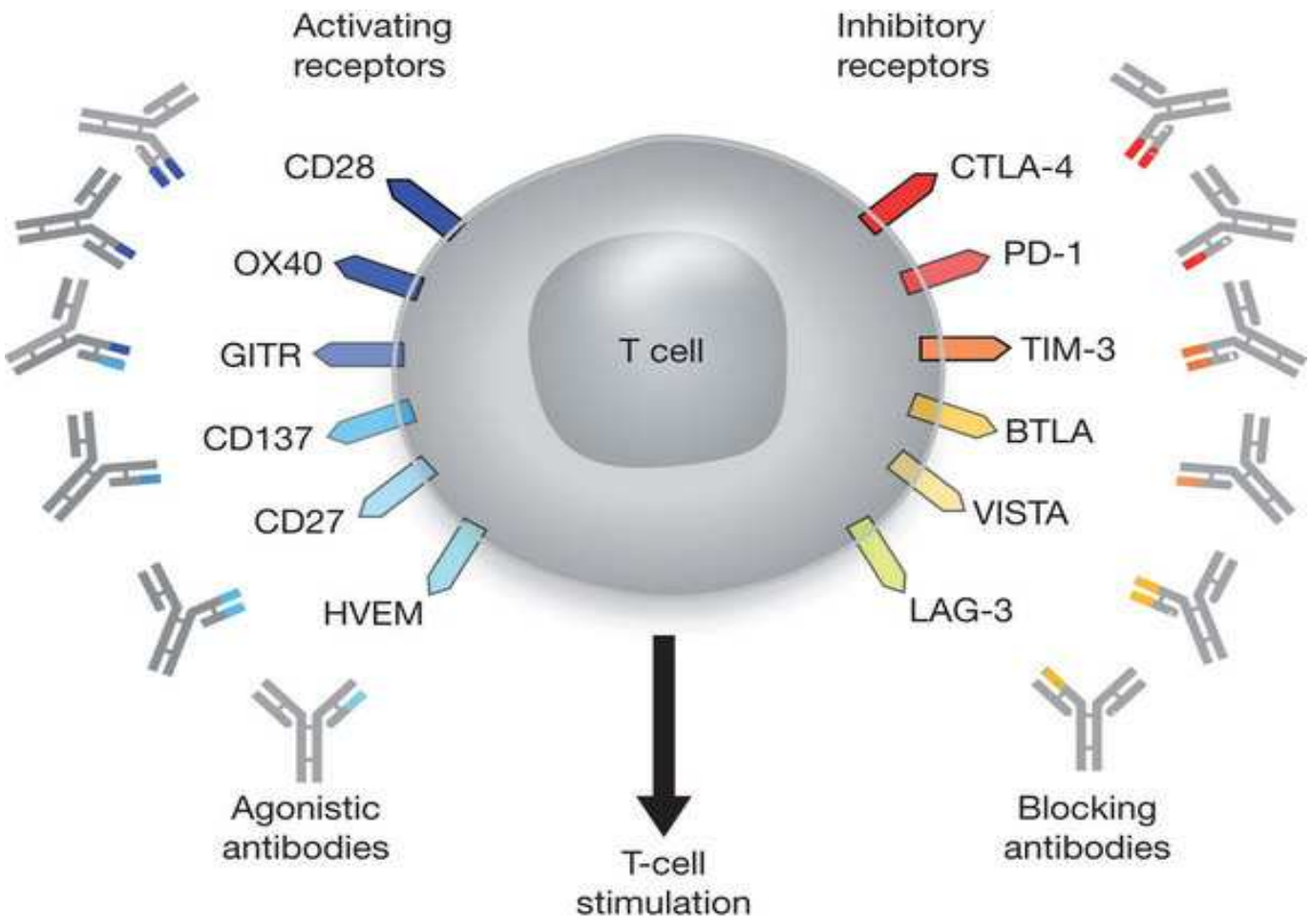
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM
- Agonistic antibodies to T-cell activating receptors stimulate the immune system by turning up the activation

T-cell inhibitory receptors

- CTLA4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG3
- Antibodies that block T-cell inhibitory receptors stimulate the immune system by blocking this inhibition

Mellman I, et al. *Nature.* 2011;21:480-489.[9]

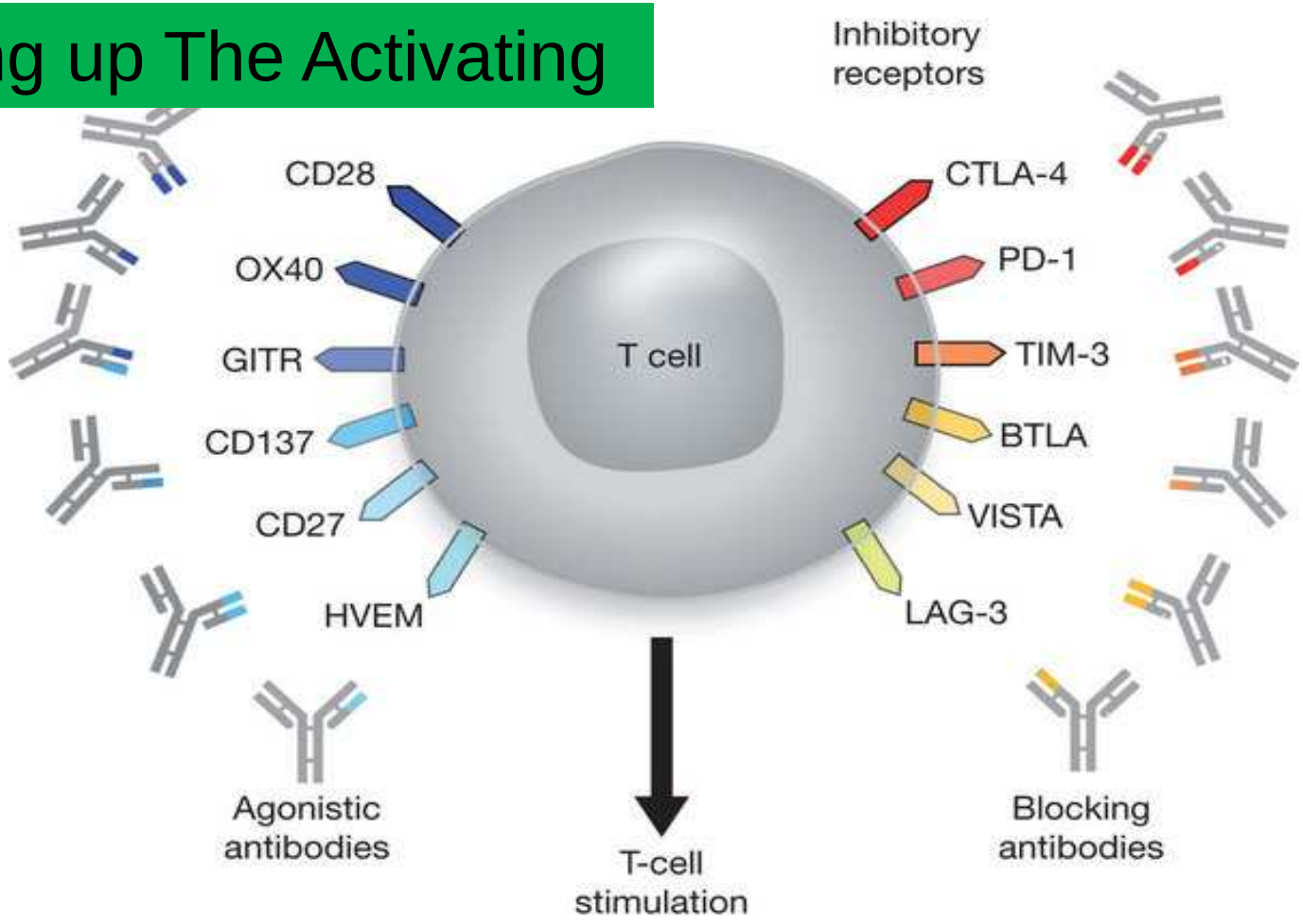
T Cell Regulation



Mellman et al. *Nature* 2011

T Cell Regulation

Turning up The Activating

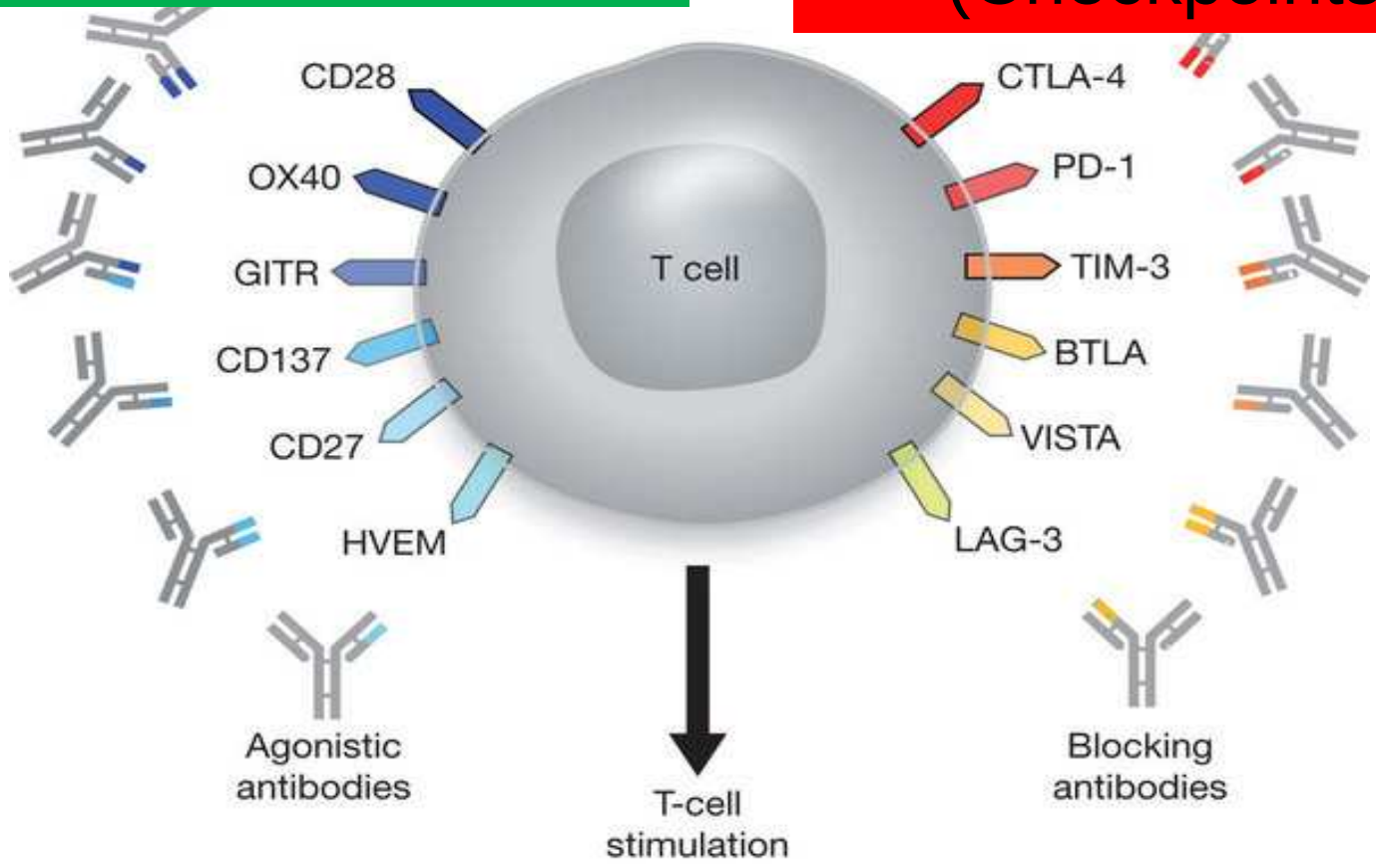


Mellman et al. *Nature* 2011

T Cell Regulation

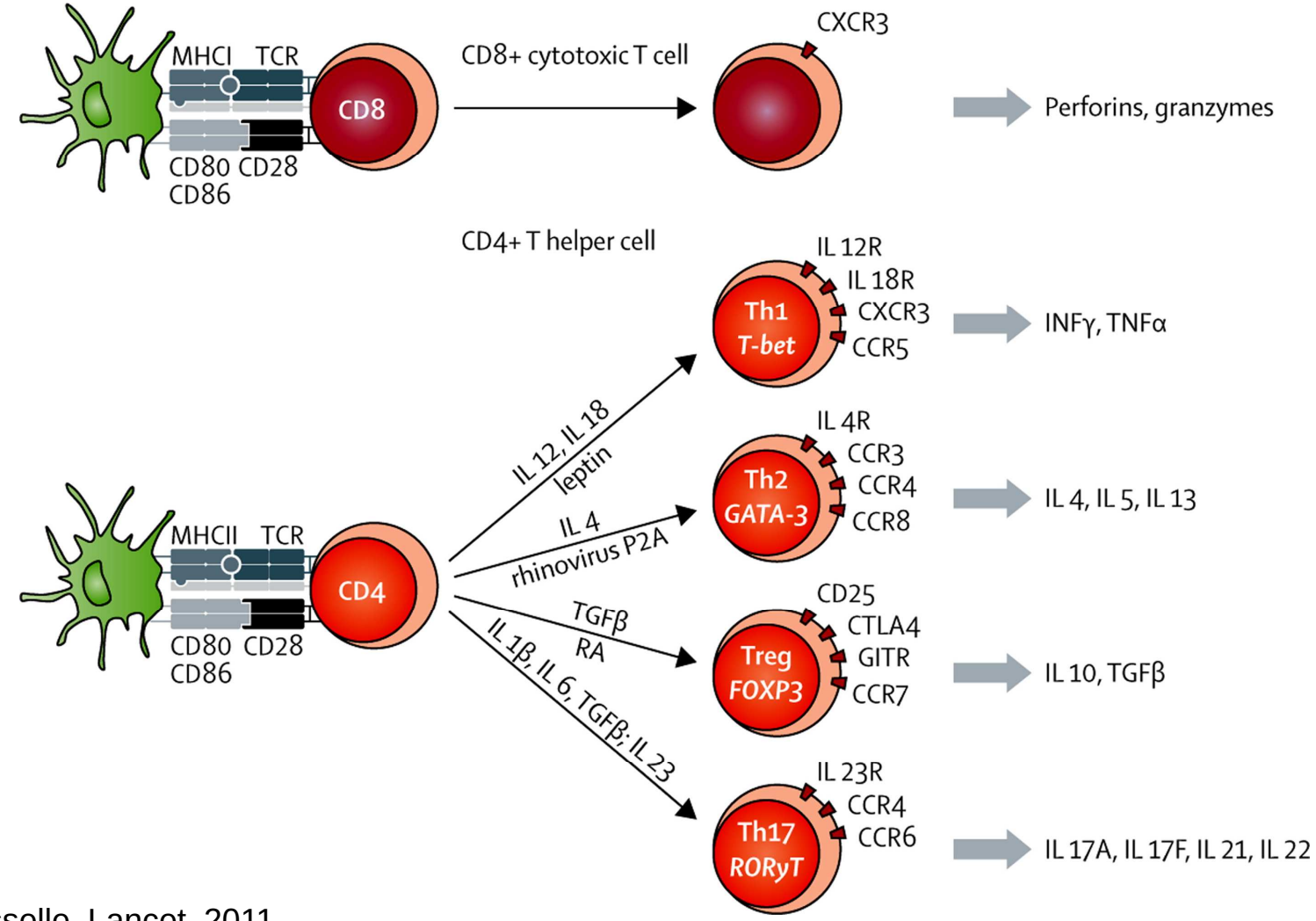
Turning up The Activating

Blocking the Inhibiting (Checkpoints)



Mellman et al. *Nature* 2011

Dendritic Cells regulate T cell differentiation to functional subsets



Brusselle, Lancet, 2011

Armed effector T cells

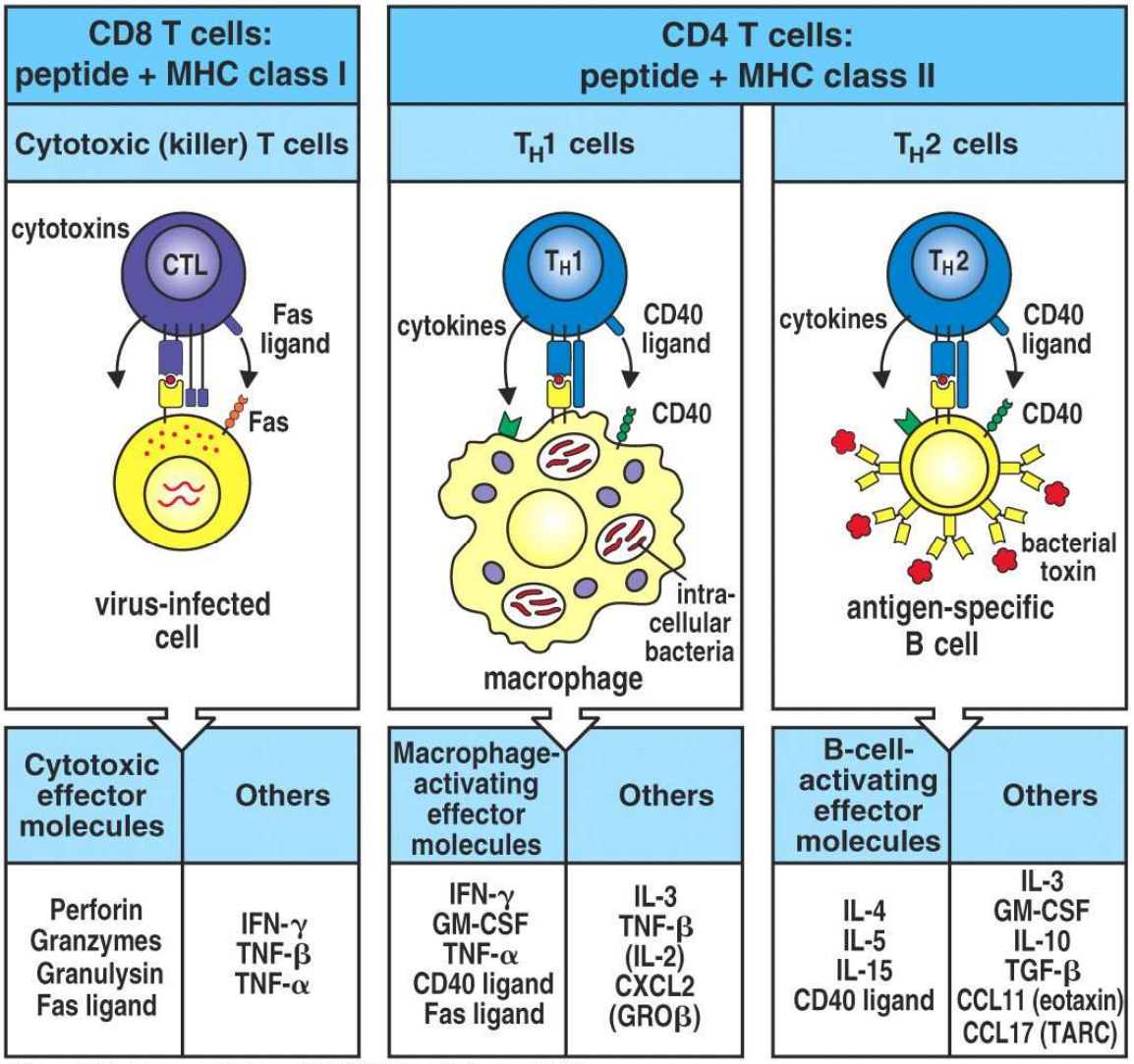
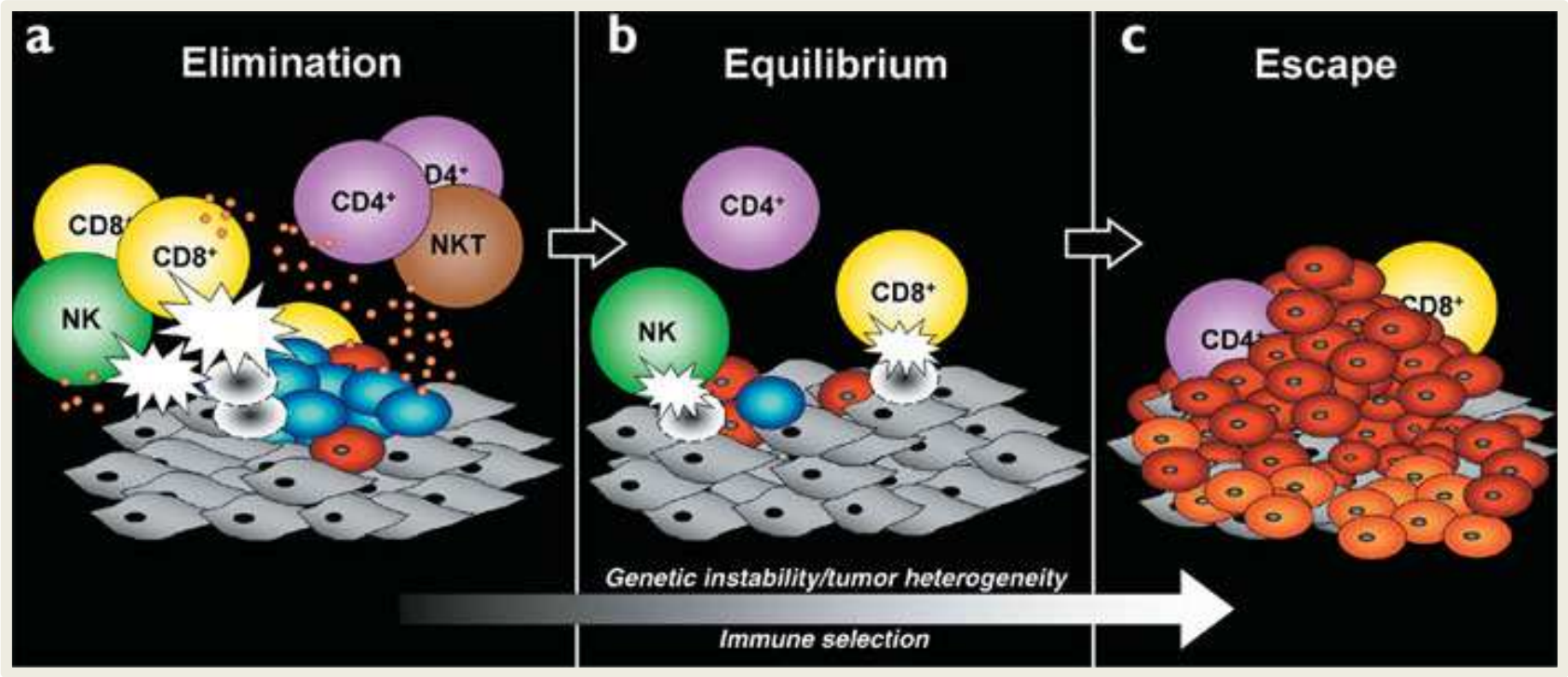


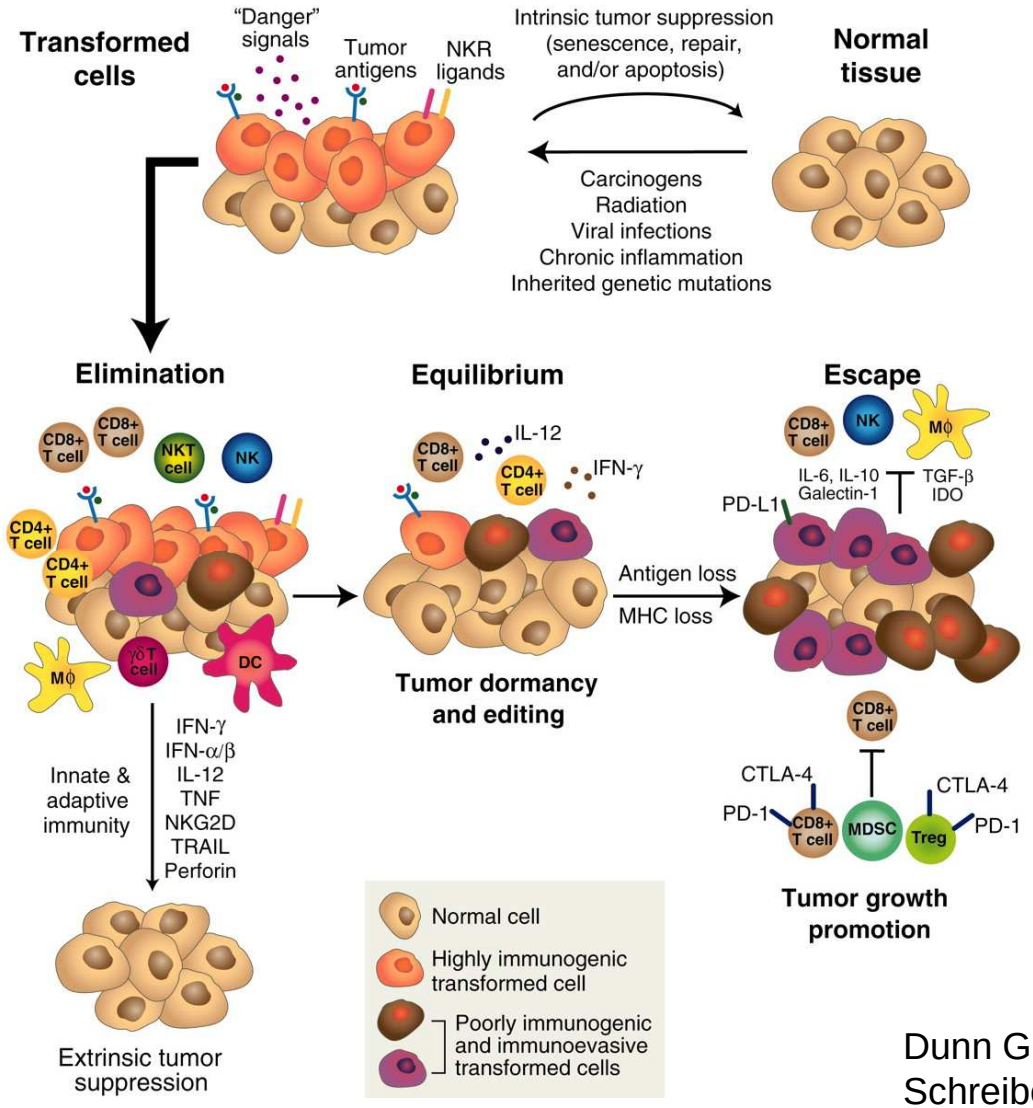
Figure 8-31 Immunobiology, 6/e. (© Garland Science 2005)

The immune system's interactions with cancer



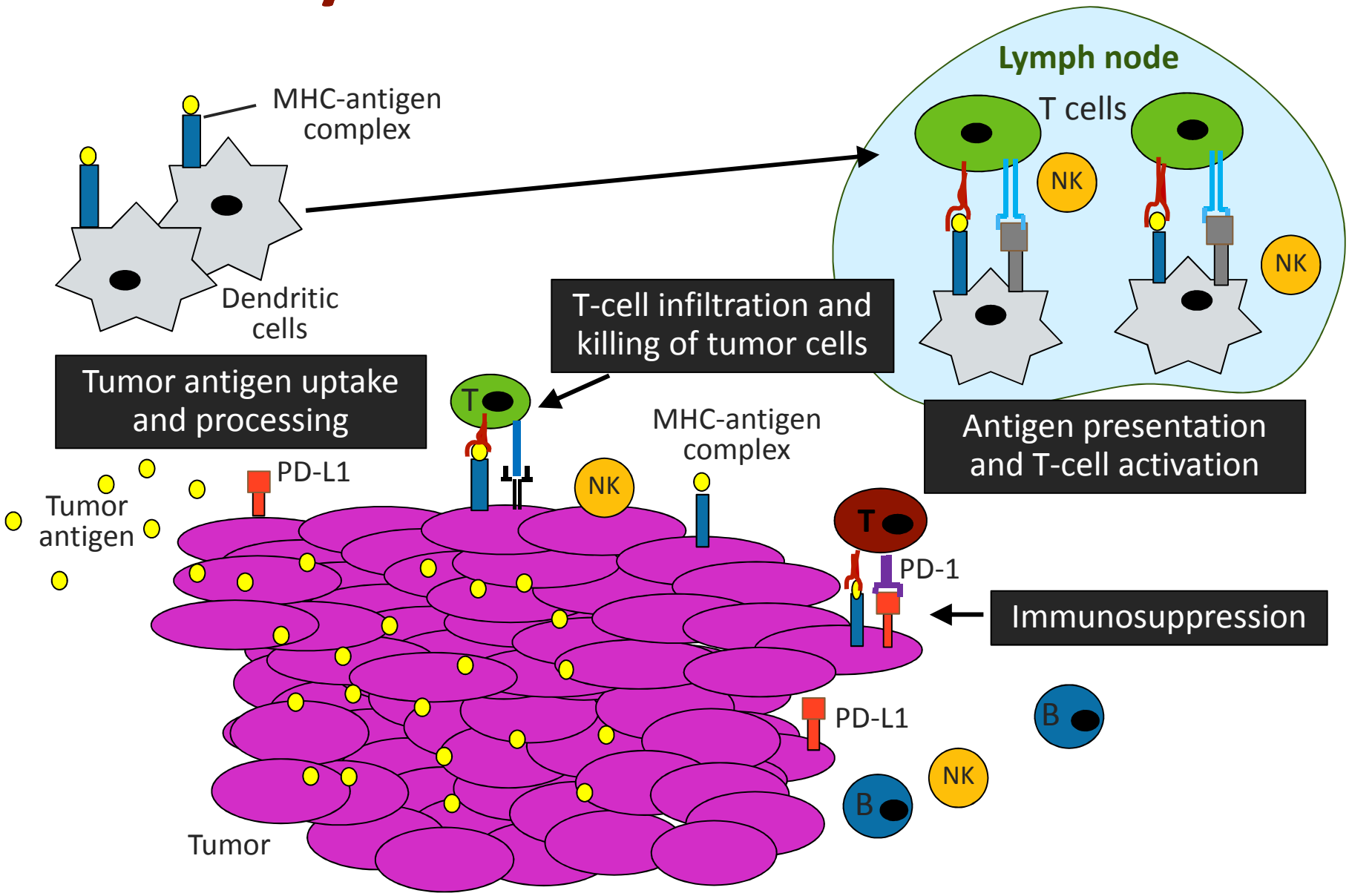
Dunn GP, et al. *Nat Immuno* 2002
Schreiber R, et al. *Science* 2011

Immunoediting of Tumors by Immune System



Dunn GP, et al. *Nat Immuno* 2002
Schreiber R, et al. *Science* 2011

Immunity in Tumor Control



Adapted from Mellman I, et al. *Nature.* 2011;21:480-489.[9]