Immunotherapy of Cancer

OLLI, Fall 2020, Lecture 2

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Quick Review

- Coley's experiments over 100 years ago showed that arousing the immune system could sometimes cure cancers
- Immunotherapy for cancer has the advantage that antibodies and T cells can specifically recognize the small differences between normal cells and cancer cells
- Where is the immune system? Everywhere, in bone marrow, thymus, spleen, lymph nodes, circulating in blood and lymph, in tissues; cells are highly mobile
- Cells of the immune system communicate by cytokines and chemokines, proteins
- An antigen is a molecule that can stimulate an immune response

Update on Bacillus Question

- Genus of bacteria, rod-shaped, contains more than 250 species
- Mentioned *Bacillus prodigiosus* that Coley used toxin from
- Question about *Bacillus Calmette-Guerin* (BCG) for bladder cancer
  - BCG is a mycobacterium, like *Mycobacterium tuberculosis* (TB)
  - BCG was developed as a vaccine for TB in 1921
  - Noticed that TB patients were less likely to have cancer

BCG continued

- BCG has been used as treatment for bladder cancer for 4 decades
- BCG has to be taken up by bladder cells, prompts cytokine release
- Many different kinds of immune cells respond
- T cells have been shown to be necessary in animal studies
- Milkmaids again: no TB
- BCG is in clinical trials for COVID-19 in Australia

Learning Objectives for Week 2

- Learn basic features of innate and adaptive immunity
- Appreciate the diversity of antibodies and T cell receptors and understand the role of clonal selection from that diversity in adaptive immunity
- Learn about Helper T cells (CD4) and Cytotoxic T cells (CD8)
- Learn how Dendritic cells bridge innate and adaptive immunity, sensing danger and activating T cells
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Two Components of Immune System, Innate and Adaptive

- Highly interdependent
- Innate: born with it
  - Pathogen recognition and removal components that have evolved against conserved aspects of pathogens
  - **First Responders:** Ready immediately; some cells in tissues
  - Does not change much on second exposure to pathogen
- Adaptive: changes across one's lifetime
  - Very **specific** for novel aspects of pathogens
  - Takes **time** to develop (5-7 days)
  - Once activated, it retains **memory** and provides "immunity"

Cells of Innate and adaptive immunity

- Innate immunity: "ready to go"; first responders

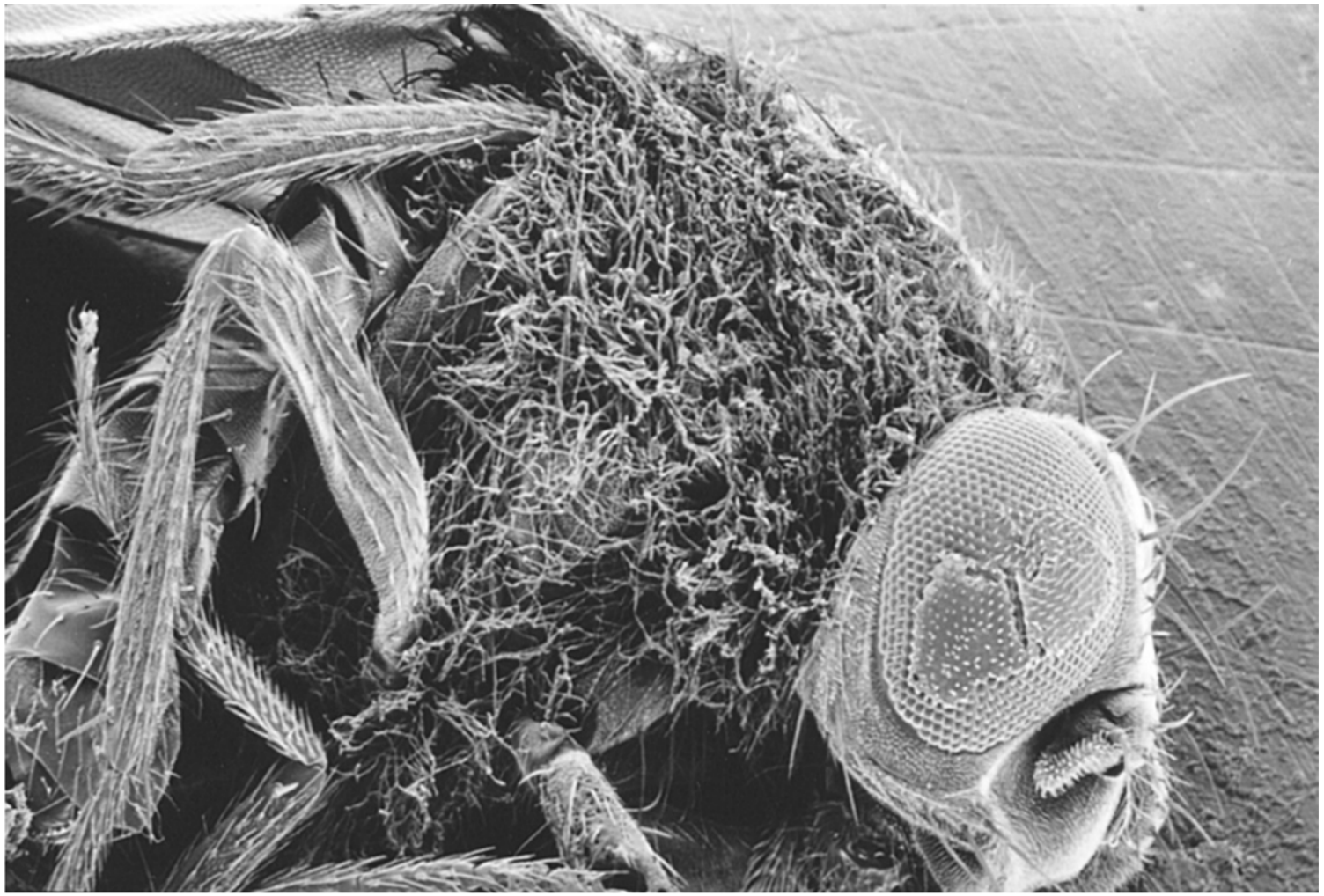
  Phagocytes:
  - Macrophages
  - Neutrophils
  - Dendritic Cells

- Adaptive (acquired) immunity: takes time to develop

  Lymphocytes:
  - B cells
  - T cells
  - (Natural Killer Cells)

Innate Immune Cells: 2011 Nobel Prize to Beutler/Hoffman for TLRs and Steinman for Dendritic Cells

- Charles Janeway proposed in 1989 that innate cells have receptors that recognize conserved components of pathogens, “pathogen associated molecular patterns” and called the receptors “pattern recognition receptors”. Janeway died in 2003.
- Jules Hoffmann discovered in 1996 receptors in fruit flies responsible for fighting off fungi, called “Toll receptors.” Bruce Beutler discovered a similar receptor in mice in 1998, and called them “Toll-like receptors”.
- Ralph Steinman discovered dendritic cells in 1973 and showed how they coordinate the activity of T cells



Adaptive

- B cells and T cells
- Requires time to become effective
- Constantly generating random diversity by gene rearrangements
- Effective cells proliferate in response to pathogens
- Retains memory of pathogen: Second exposure response is higher faster stronger
  - This memory is what we call “immunity”

Pause for Questions

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Lymphocytes: T cells and B cells

- Pieces of pathogen (antigens) are recognized by T cell Receptors (TCRs) and B cell receptors (BCRs)
  - BCRs are antibodies when soluble (initially on the surface of B cells, later secreted into the blood and other fluids)

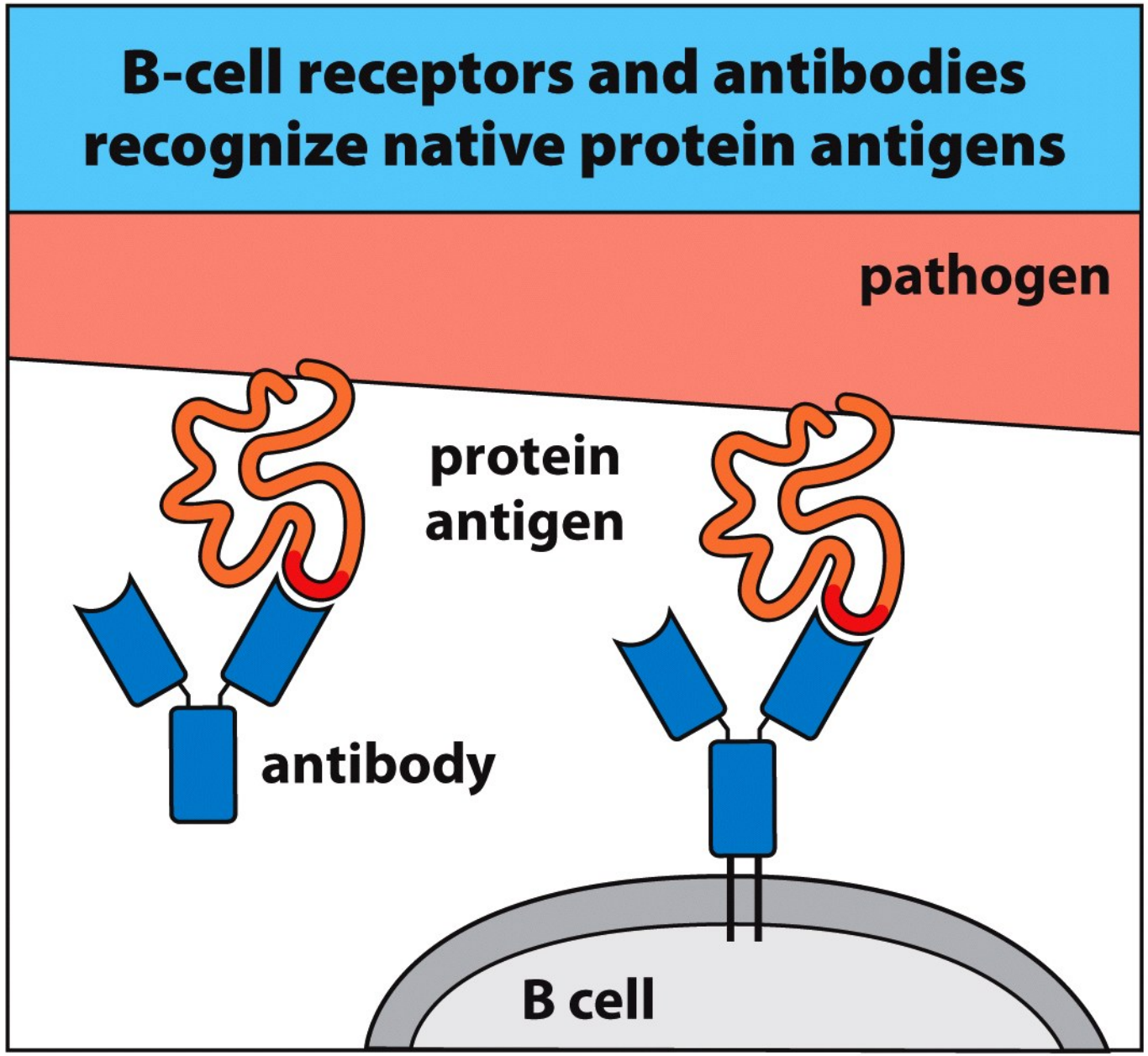
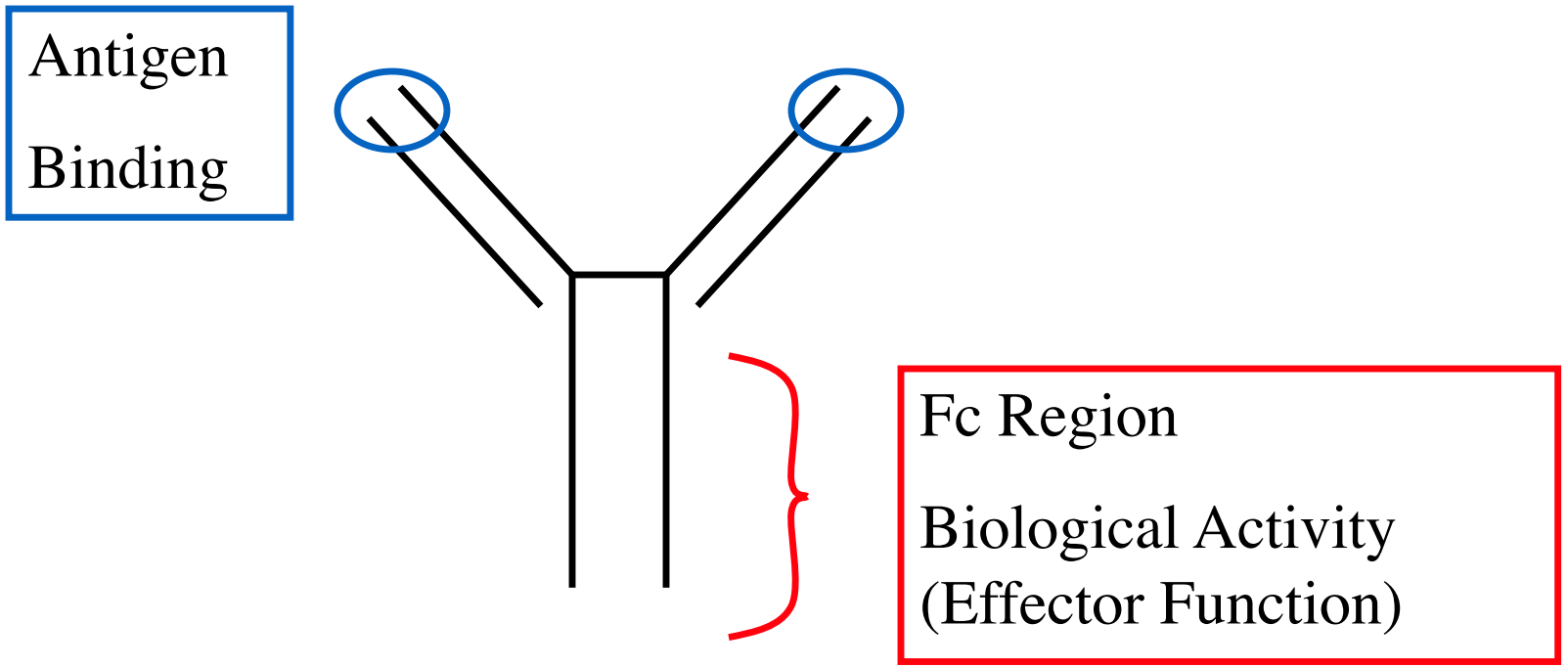


Figure 3.12 The Immune System, 3ed. (© Garland Science 2009)

Antibody Structure



Antibodies and TCRs are structurally similar

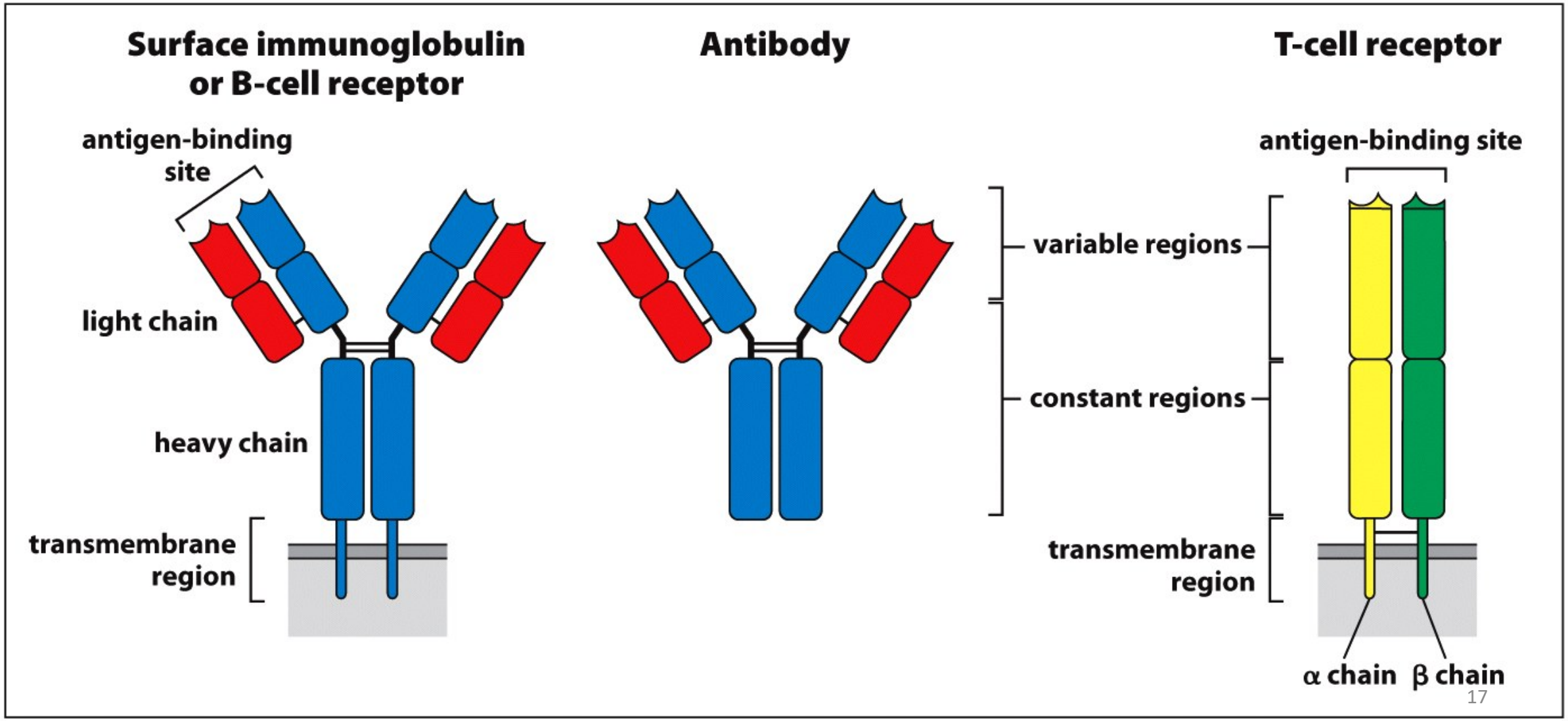
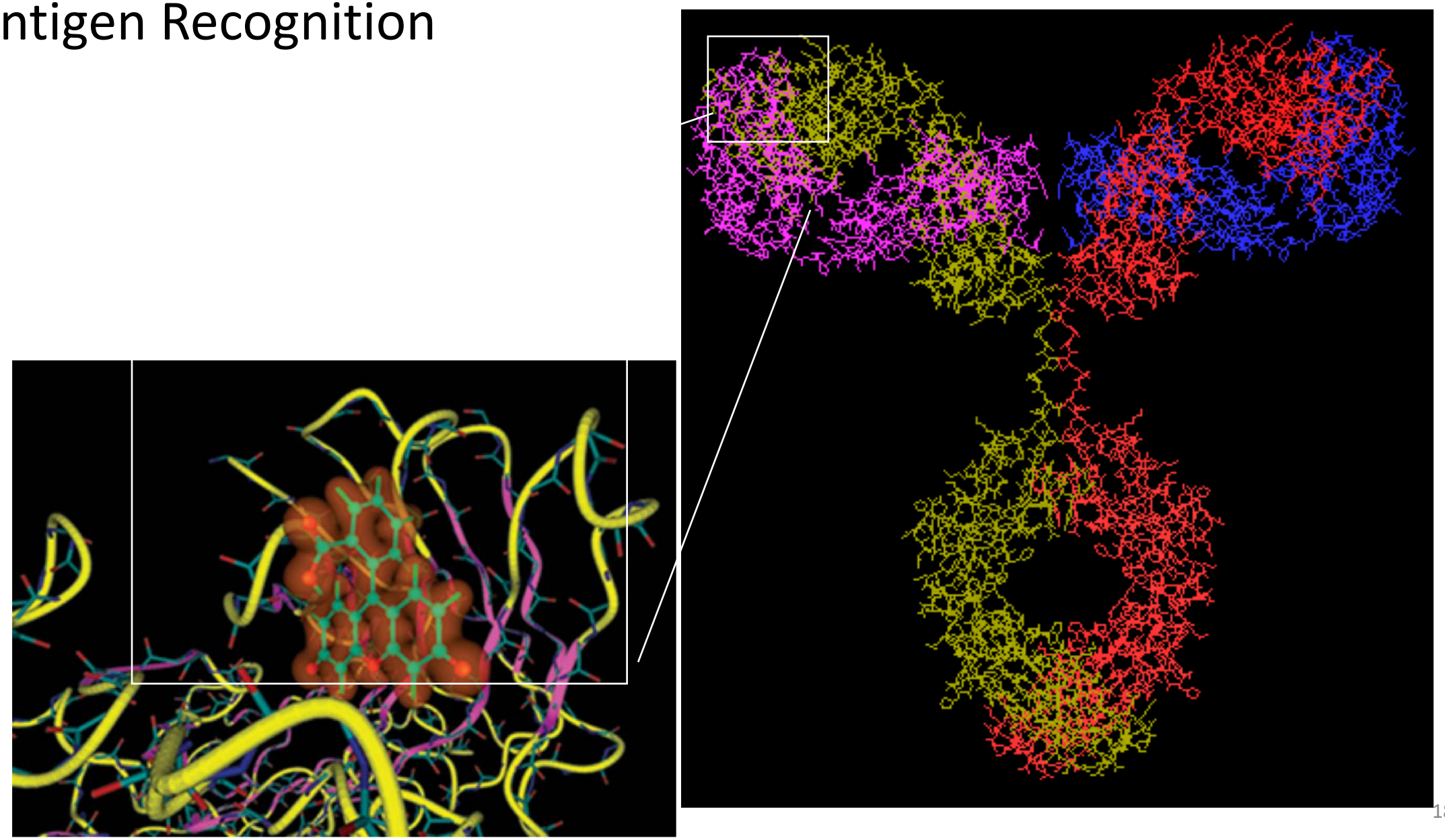


Figure 3.1 The Immune System, 3ed. (© Garland Science 2009)

Antibody Heavy and Light Chains together form site of Antigen Recognition



- Each T cell or B cell has receptors on its surface that all recognize the same antigen (about 100,000 per cell)
- Each TCR or antibody is slightly different than the TCR and antibodies of all other cells
- Diversity is between cells, not within one cell

Antibody (Ab) Diversity

- Extremely Specific
  - A single Ab binds a single or very few similar molecules
- Antibodies can be targeted against anything
  - Protein, carbohydrate, nucleic acids, small molecules, drugs, etc
- Antibody diversity is theoretically more than 10^{15} different specificities: 1,000,000,000,000,000, one quadrillion

Antibodies as tools for research and medicine

- Research Tools: For example, make antibodies against the surface molecules that define different kinds of immune cells
  - CD3 on T cells, CD4 on helper T cells, CD8 on cytotoxic T cells, CD20 on B cells
- Medicine: B cell lymphomas have CD20, an anti-CD20 antibody can be used to treat lymphoma (Rituxan, rituximab)

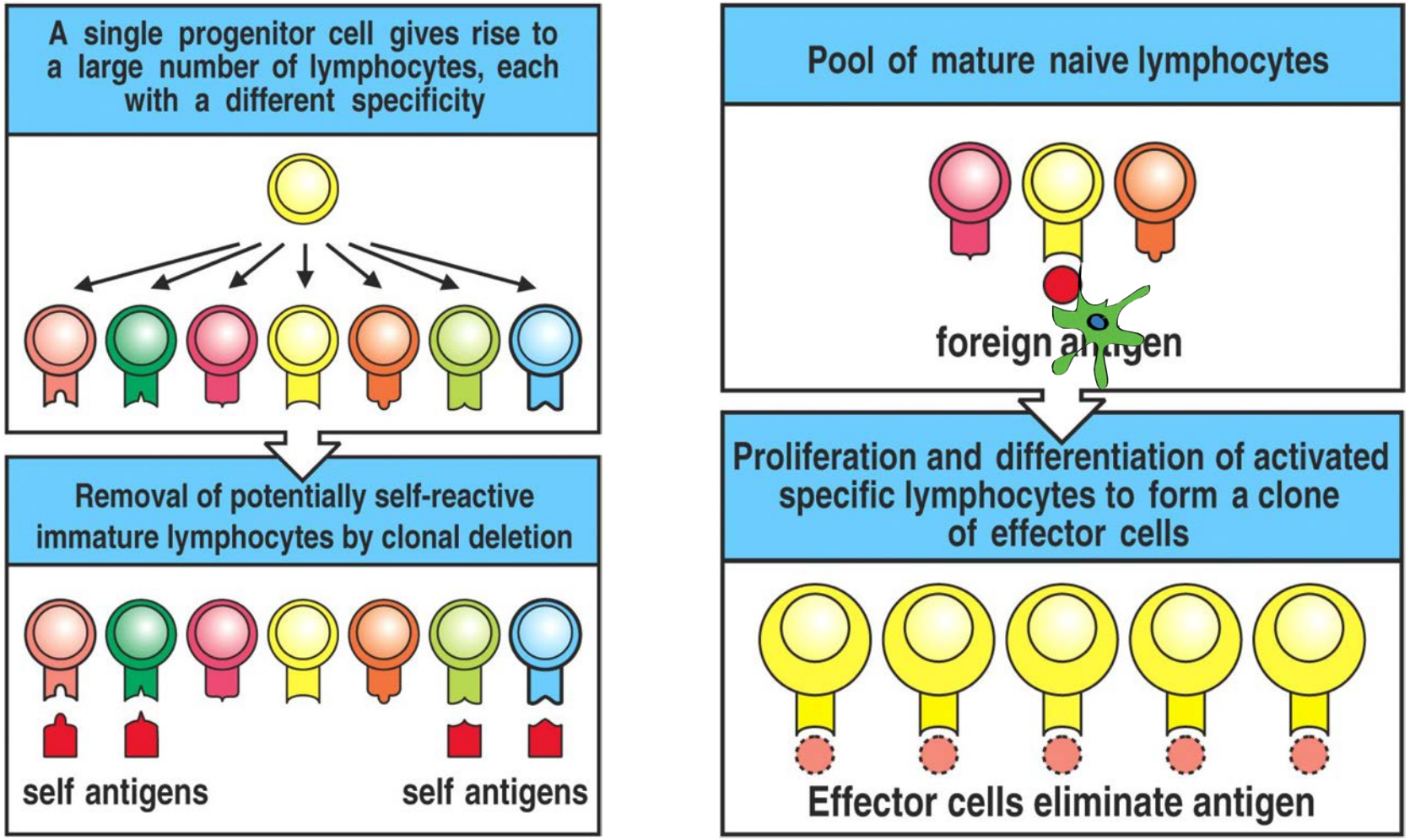
Antibody and TCR Diversity

- Diversity is generated by gene rearrangement (somatic recombination)
- No other somatic cells of the body recombine genes
  - Lots of other cells change transcription by epigenetic means, but B cells and T cells actually change their gene sequence

T cell TCR Diversity

- Most TCRs bind only peptides, 8 – 25 amino acids in length
- Recognize linear sequence, not conformation in native state of protein
- Similar theoretical number of possible TCR specifities, 10^{15}, but there are only 4 x 10^{11} T cells (10^{15} cells would weigh about 500 kg)

Clonal selection of lymphocytes is the central principle of adaptive immunity



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Two Main Categories of T cells

- Helper T cells (CD4+)
  - Help macrophages
  - Help B cells become activated
  - Help cytotoxic T cells
- Cytotoxic T cells (CD8+)
  - Kill infected cells and cancer cells

Cytotoxic T cells are Serial Killers

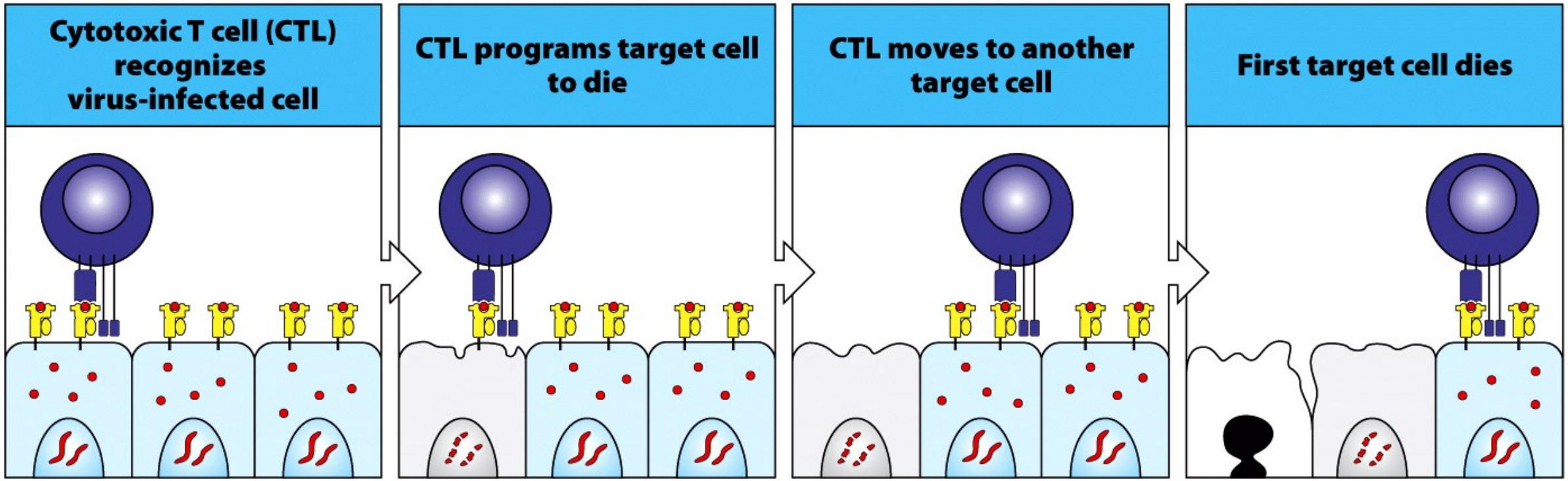
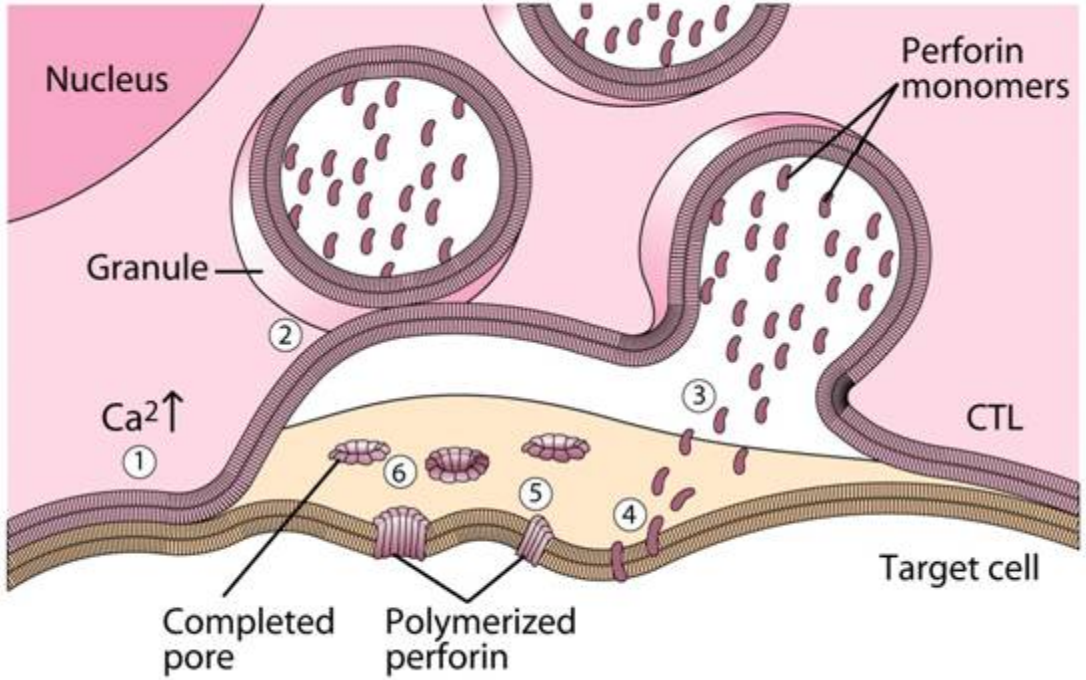
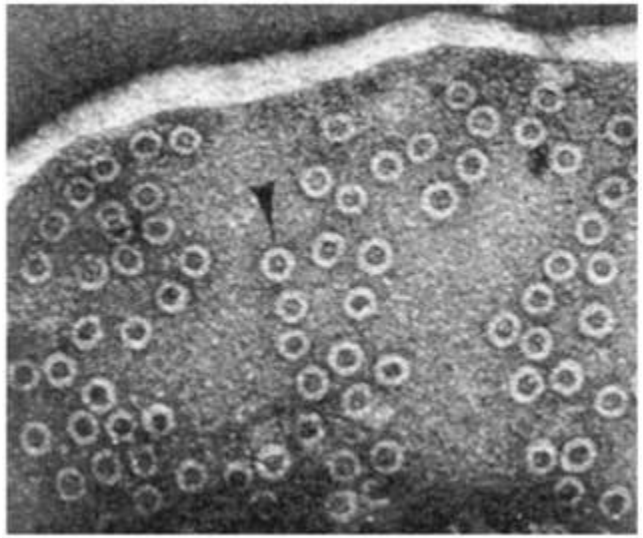


Figure 8.30 The Immune System, 3ed. (© Garland Science 2009)

CTL-mediated pore formation in the target cell membrane.



Delivery of Granzyme B which induces apoptosis



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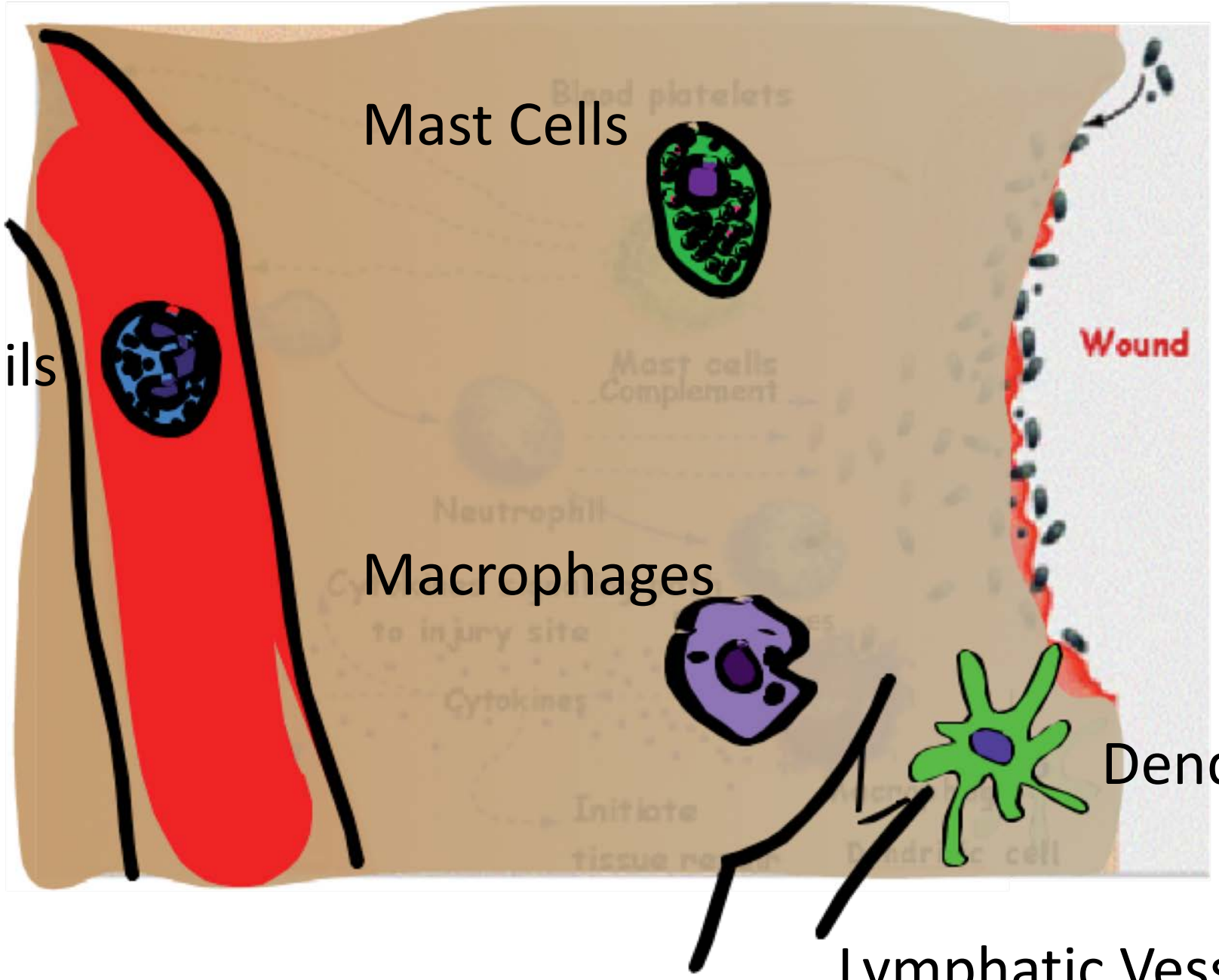
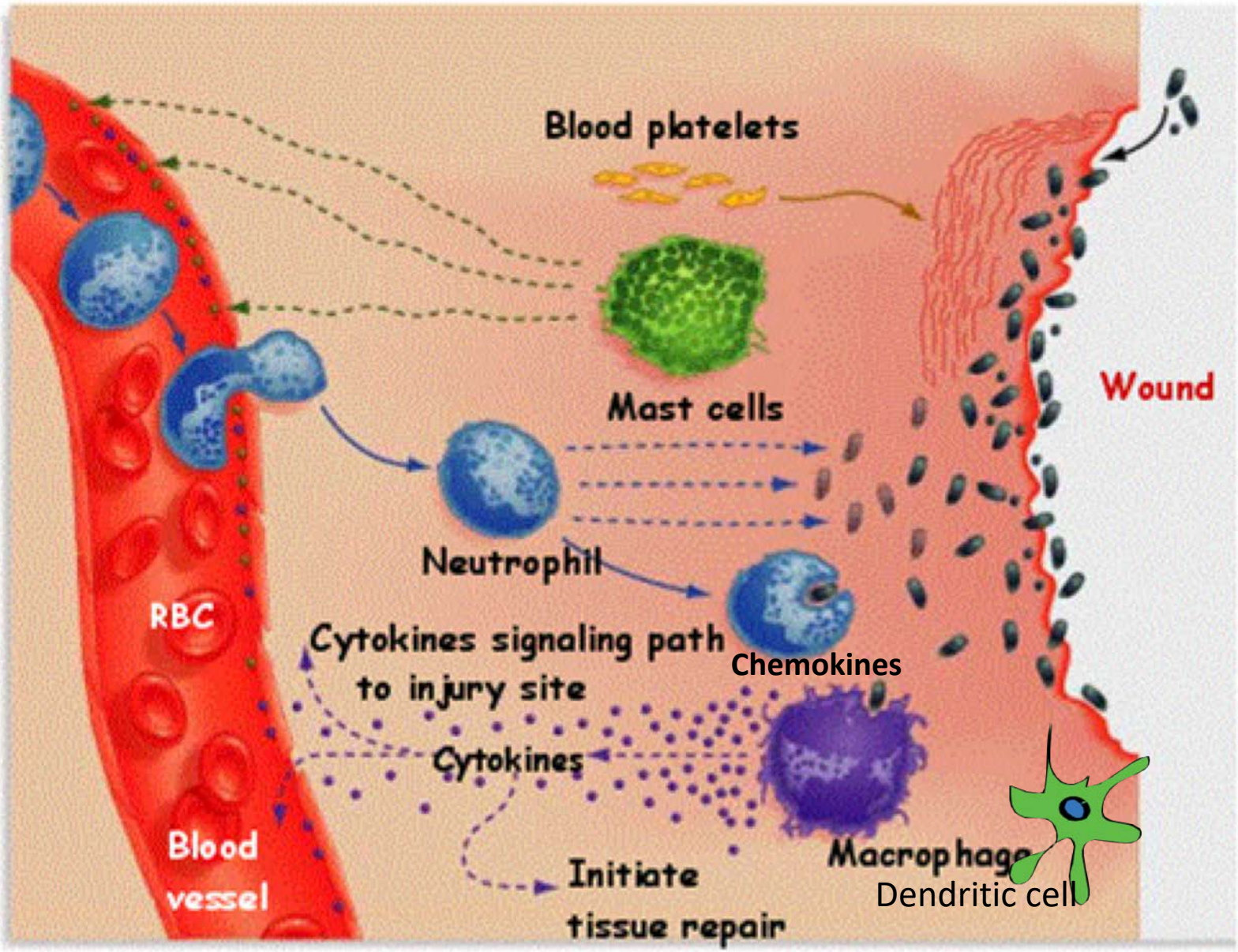
Innate cells activate Adaptive T Cells

- They “present” antigen to T cells
- Antigens that T cells recognize are peptides, and the peptides are presented on a larger molecule called MHC (major histocompatibility complex) on the surface of dendritic cells
- Peptides are also presented on MHC on surface of target cells


Mast Cells
Neutrophils
Wound
Macrophages
Dendritic Cells
Lymphatic Vessel

Tissue resident Macrophages and Dendritic Cells become activated by tissue damage and by microbes to release proinflammatory molecules that cause increased vasodilation and vascular leakage which enables circulating immune components to access the site of infection.



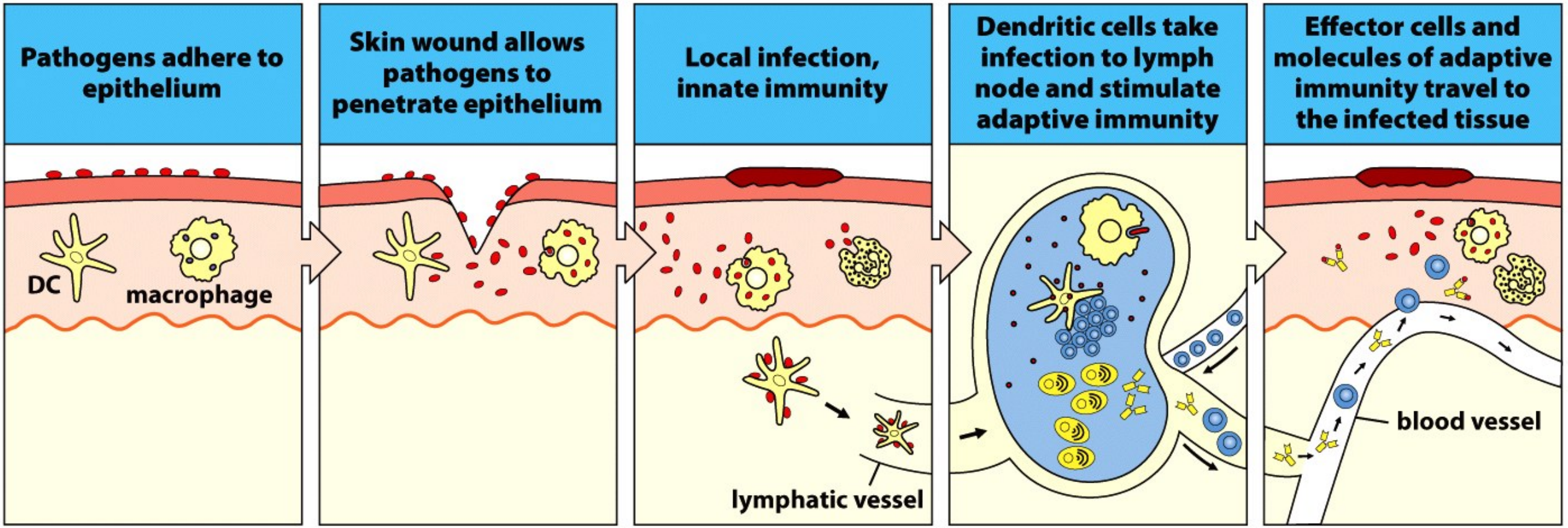


Figure 3.6 The Immune System, 3ed. (© Garland Science 2009)

Antigen presenting cells activate T cells

Danger signal alerts the police (the dendritic cells)

The dog is the cytotoxic T cell, tracks down the tumor

The scent is a fragment of the tumor or pathogen called an antigen

However, these dogs have only a very few scents that activate them

- And instead of just finding the criminals, they execute them

After the pathogen is cleared

- T cells die off except for memory T cells, which are long-lived
- The process of defervescence is an active process
- Memory cells allow a more rapid and strong response upon subsequent exposure to pathogen
- After first exposure and successful response, “immunity” is conferred
- Immunity is highly specific

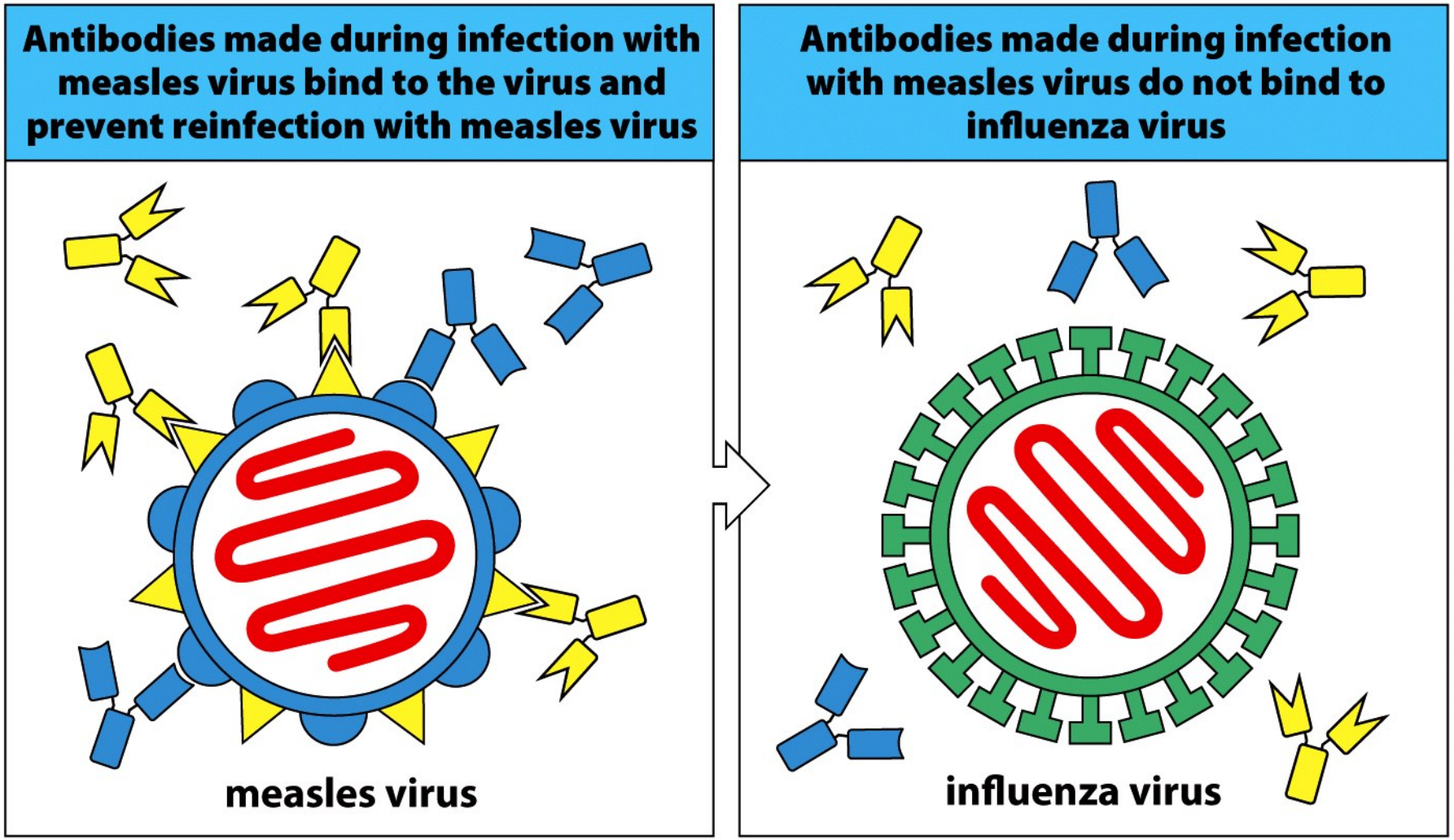


Figure 3.2 The Immune System, 3ed. (© Garland Science 2009)

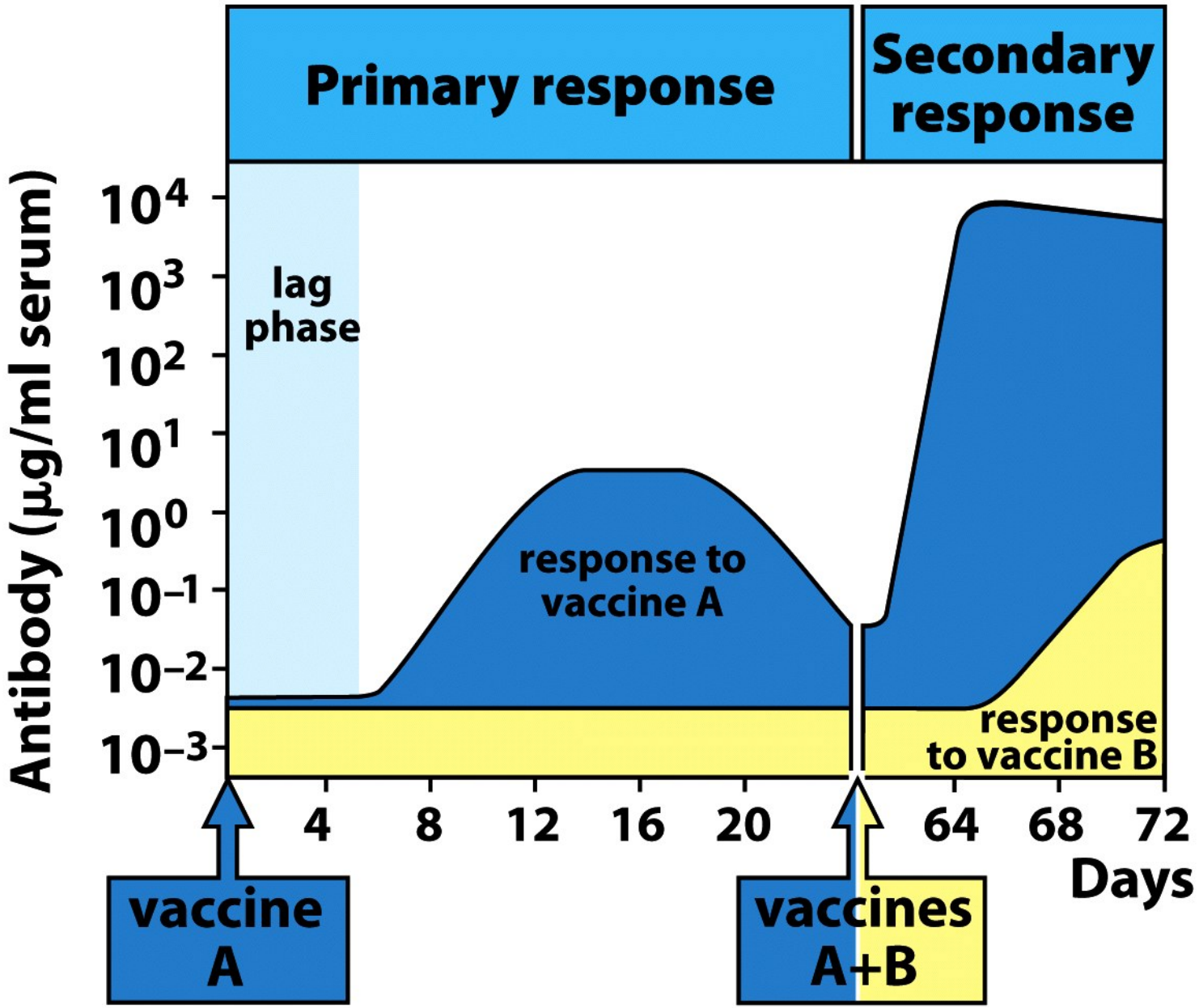


Figure 1.26 The Immune System, 3ed. (© Garland Science 2009)

Tolerance

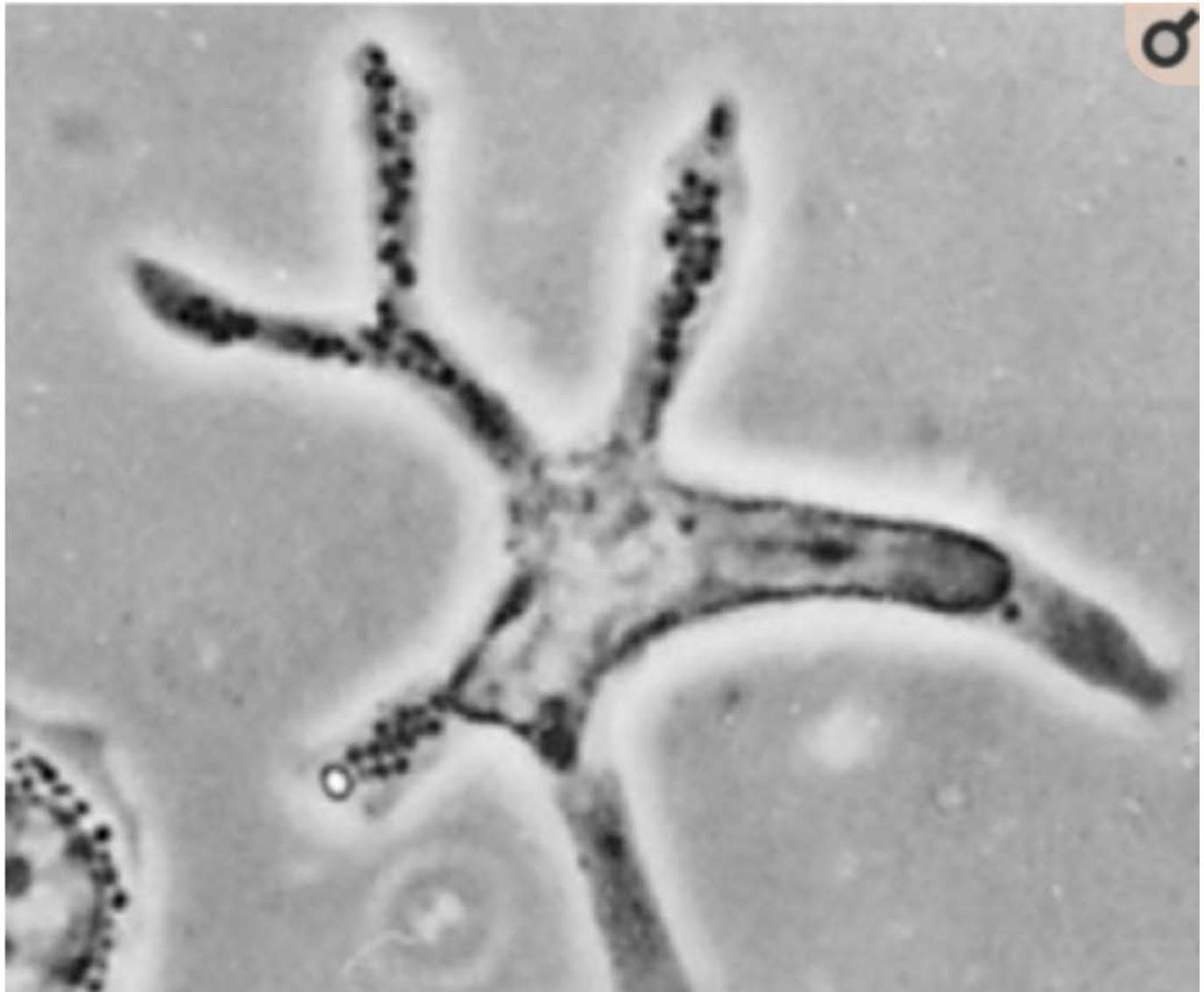
- Central and Peripheral Tolerance
  - Central: during generation of diversity, highly reactive self-reactive T cells and B cells are eliminated, losers killed (“Thymic Education”)
  - Peripheral: moderately self-reactive T cells and B cells are kept from attacking self by a variety of active mechanisms
  - Cancer cells take advantage of tolerance mechanisms

Pause for Questions

How are T cells “triggered” or “activated”?

- Dendritic cells “present” antigen to T cells
- If the dendritic cell has previously sensed “danger”, the presentation of antigen will activate the T cell
- If the dendritic cell has not sensed danger, the T cell is instructed to chill or die

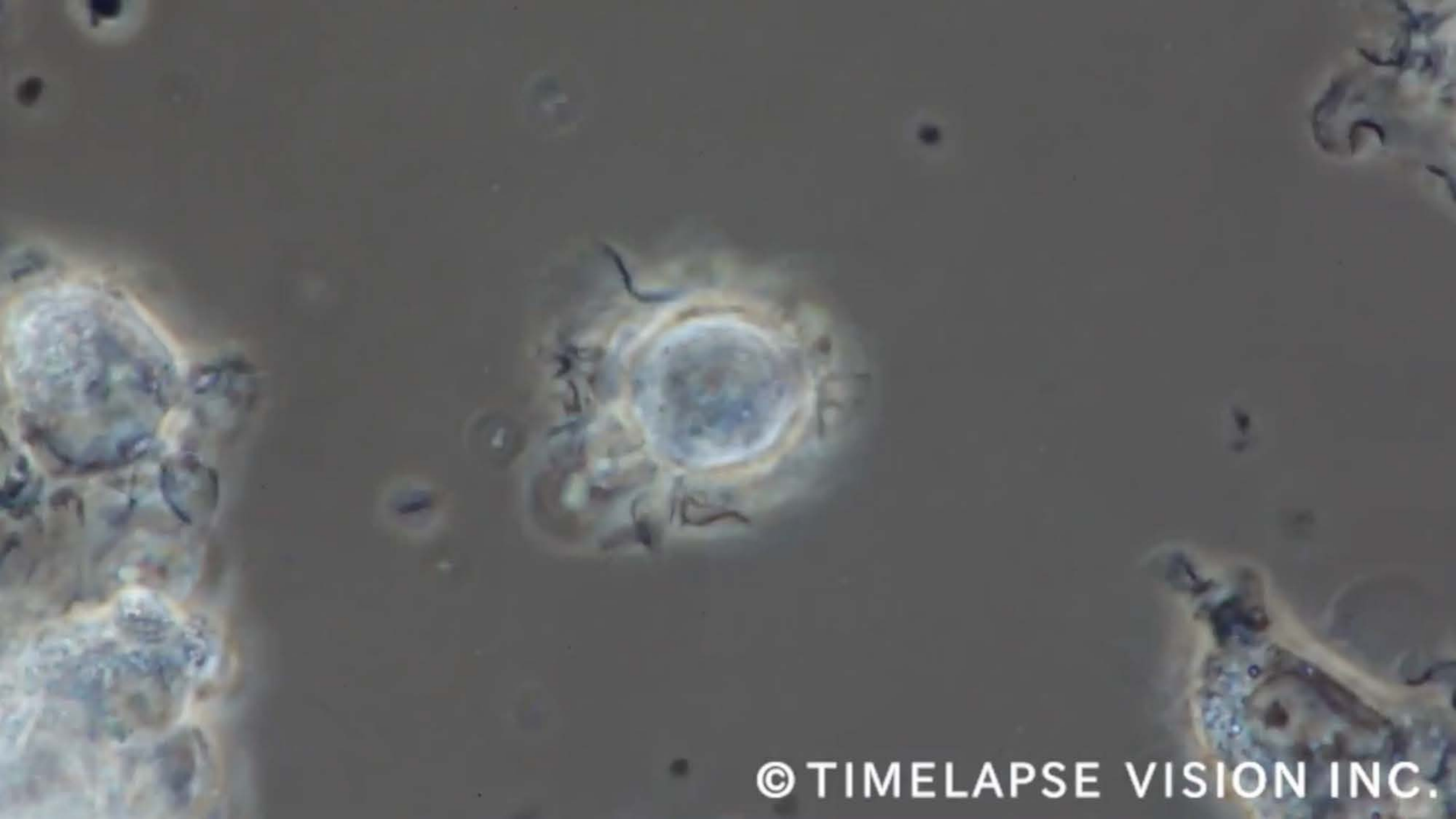
Dendritic Cells



Steinman and Cohn, 1973

Dendritic cells are the bridge between innate immunity and adaptive immunity

- Depending on how the dendritic cells are activated, they can direct the development of T cells along several different lines, appropriate for different pathogen types, or even produce an inhibitory type of T cell, called “regulatory T cells”, or Tregs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The discovery of dendritic cells

- Ralph Steinman discovered dendritic cells in 1973; not readily accepted by other scientists
- Recognized potential to improve vaccines for disease and cancer
- Diagnosed with stage IV pancreatic cancer in 2007, at 64 years old
- Used dendritic cell vaccines to prolong his life for 4 ½ years
- Received Nobel prize in 2011, 3 days after he died at the age of 68; never heard the news

Difference between vaccine for infectious disease and vaccine for cancer

- Prophylactic vs Ongoing disease
- No viral disease is treated with vaccine, because viral load is already too high, and immune system is already attempting to respond

- Passive vaccination vs Active vaccination

- Advanced cancer is also probably too late for vaccine strategy by itself

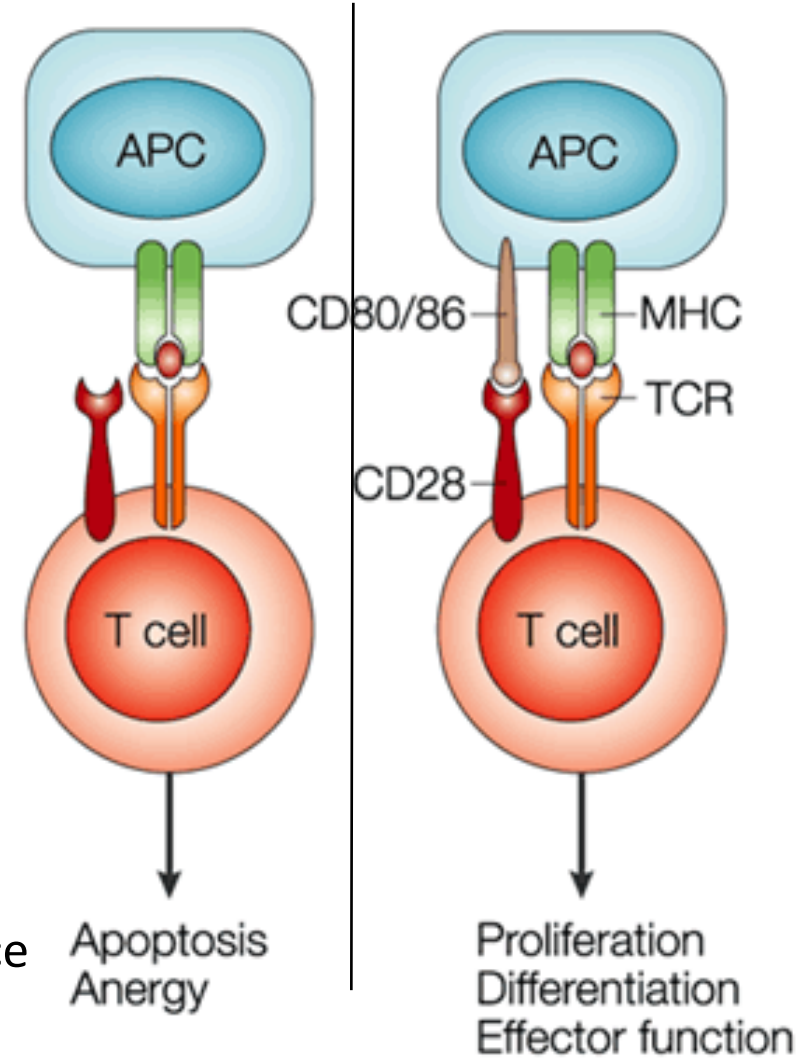
FDA-approved Cancer Vaccine

- Provenge (Sipuleucel-T) for advanced prostate cancer approved in 2010
  - Prolonged median survival time by 4.5 months (compared to 2 months for additional chemo)
  - Requires isolation of patient's dendritic cells, loading with peptide ex vivo, and re-introduction to patient
  - $93,000 price tag for Provenge, $44,000 for chemo

Dendritic cells provide at least three types of signals to T cells

- Signal 1: a short peptide from a pathogen or normal self proteins
- Signal 2: a “co-stimulatory signal” that is generated if the dendritic cell has recognized a danger signal on a pathogen
- Signal 3: any of many cytokines that the dendritic cell secretes in response to pathogens or other cytokines it has sensed

T-cell fate is dependent upon the state of the dendritic cell when the TCR interacts with the peptide antigen



Peripheral Tolerance

Other Signal 2 CoStimulatory Pairs

Table 1

Effect of costimulatory molecules on virus-specific memory CD8+T cells

The major costimulatory interactions that affect anti-viral memory CD8+ T cells are shown. The specific actions re
from these interactions are diverse and can affect many aspects of memory CD8+ T cell responses.

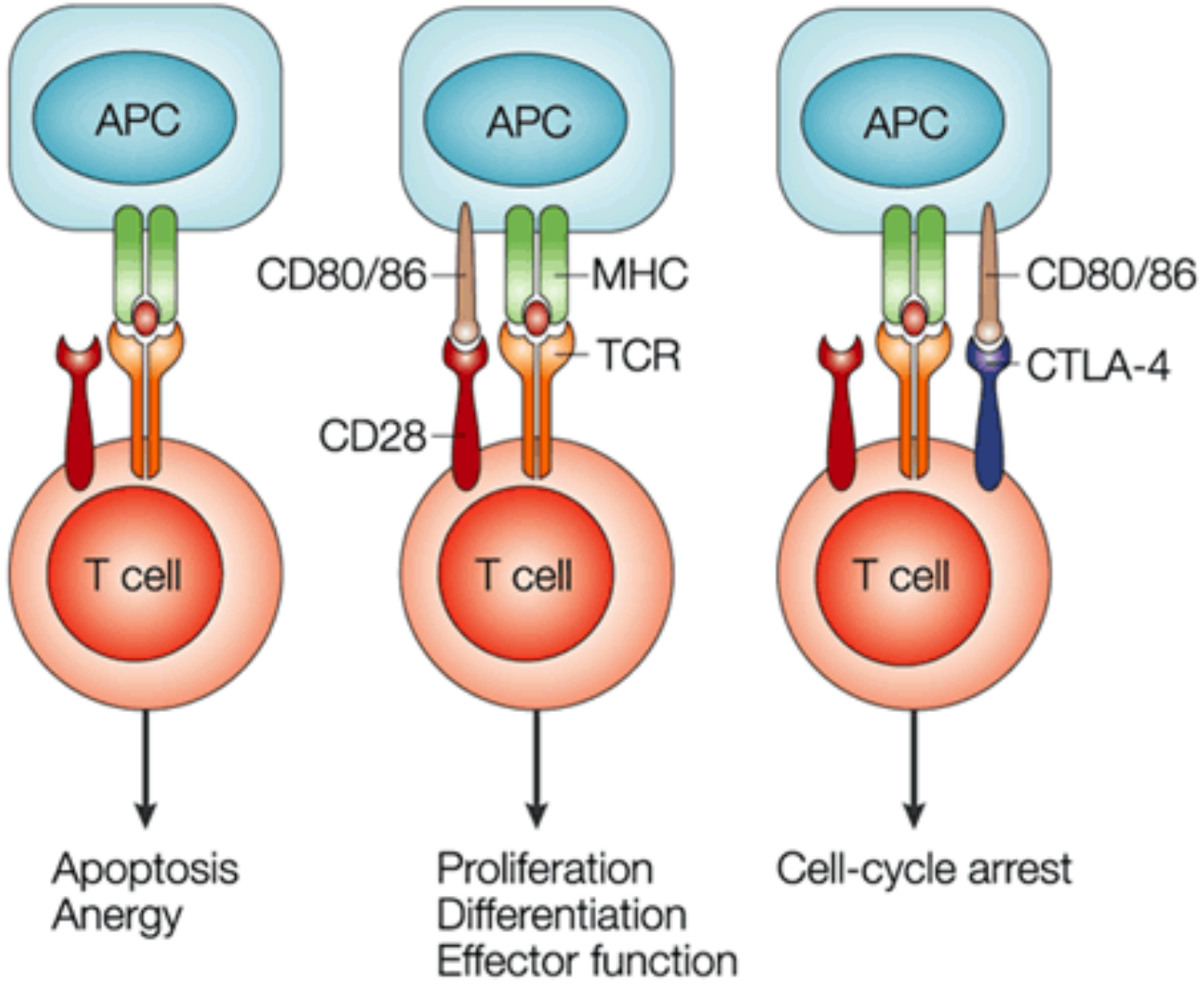
Receptor	Ligand	Effect on memory CD8+ T cell
CD28	B7-1, B7-2	↑ expansion and IL-2 production[82,84]
PD-1	PD-L1/B7-H1, PD-L2/B7-DC	↓ proliferation of helpless CD8+ T cells[91]
CD27	CD70	↑ expansion with $CD4^+$ T cell help and maintenance[92,115–117]
4-1BB	4-1BBL	↑ generation, maintenance and enhances proliferation[95,97,99,105–108]
OX40	OX40L	↑ survival and expansion in presence of $CD4^+$ T cells [109–114]
CD40	CD40L	↑ quality[91,122]
TRAIL receptors	TRAIL	↓ survival of helpless memory $CD8^+$ T cells[119,120]

From: Crit Rev Immunol. Author manuscript; available in PMC 2010 September 10.
Published in final edited form as:
Crit Rev Immunol. 2009; 29(6): 469–486.

Signal Three

Cytokines provide a Signal Three that prolongs survival (IL-12 and Type 1 interferons for CD8+ T cells, and IL-1 for CD4+ T cells) and determines differentiation

Activation sets in motion multiple mechanisms to end the response, e.g. CTLA-4 and PD-1 on T cells



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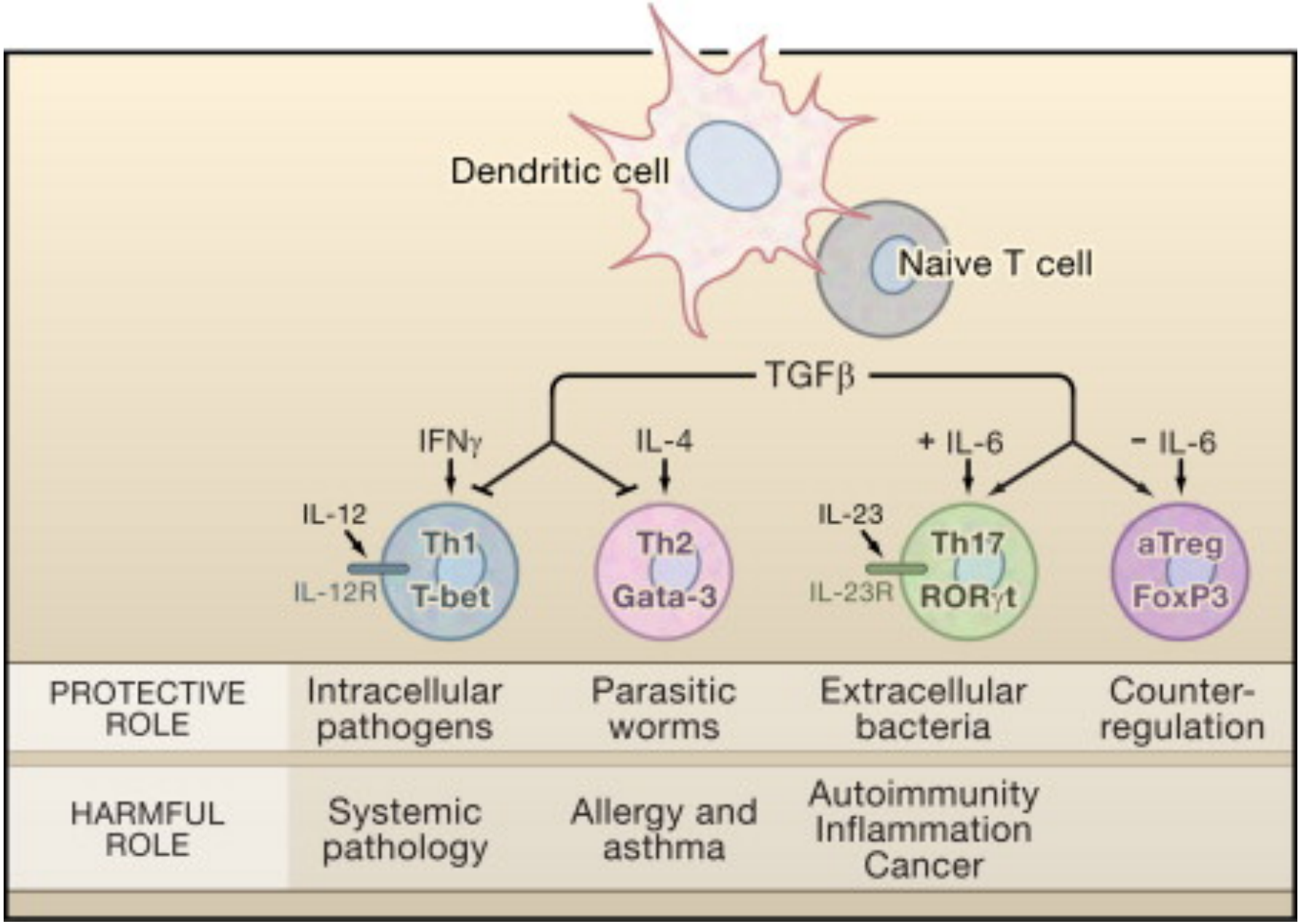
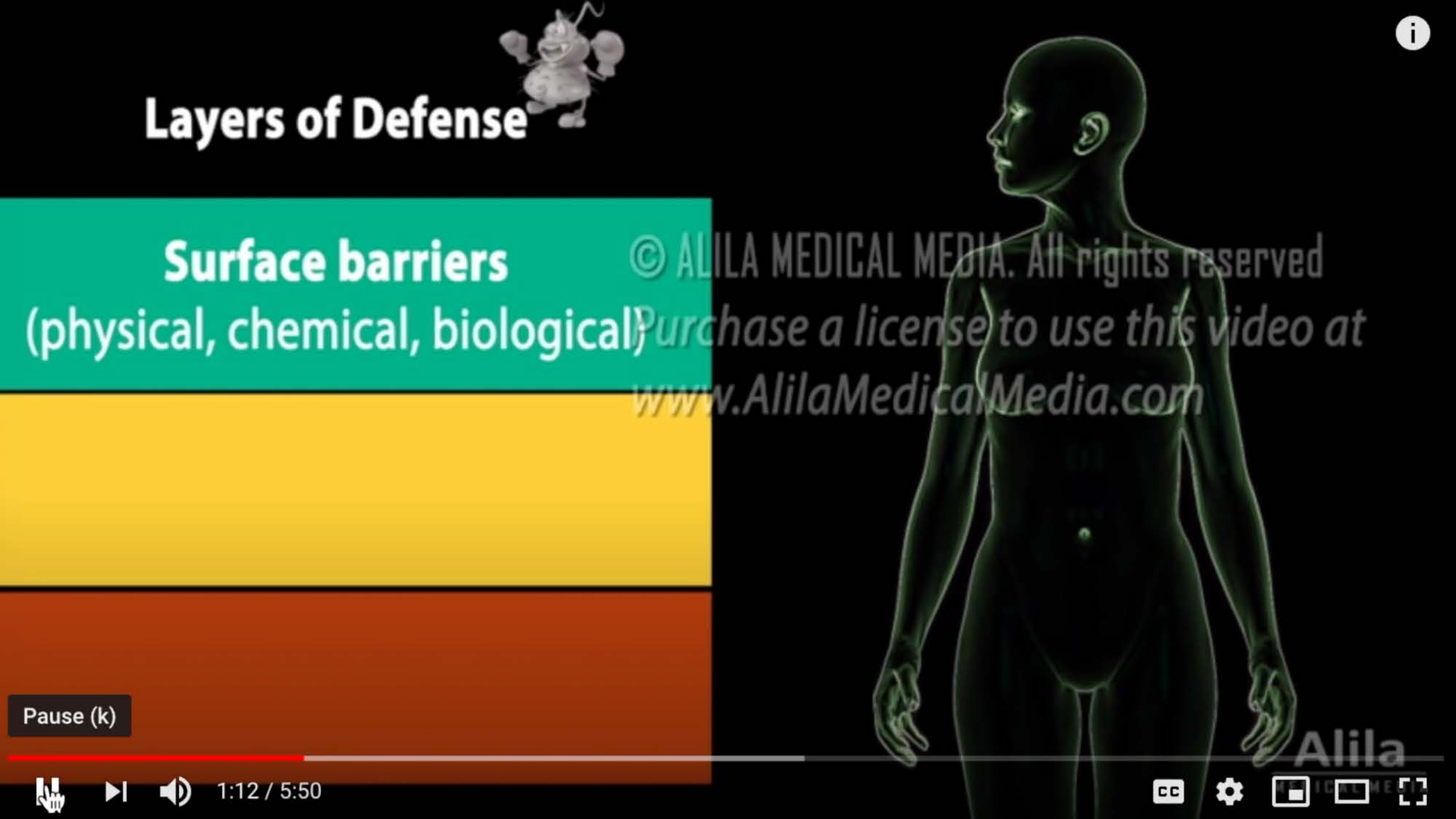
Depending on the cytokine milieu and the activation state of the dendritic cell, CD4+ cells take on different phenotypes when activated

Effector helper T cells come in different flavors



- Nice overview of innate and adaptive immune systems with animations

- https://www.youtube.com/watch?v=lxC-3MpIMUo&vl=en


Layers of Defense
Surface barriers
(physical, chemical, biological)
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Categories of Immunotherapy for Cancer

- Biologics: Antibodies and Cytokines
- Vaccines including Dendritic Cell Vaccines
- Checkpoint Inhibitors
- BiSpecific T cell Engagers (BiTEs)
- Adoptive Transfer of T cells
  - Tumor Infiltrating Lymphocytes (TILs)
  - Engineered TCR T cells
  - Chimeric Antigen Receptor (CAR)-T cells
- Modification of Tumor Micro-Environment (TME) to reverse immunosuppression