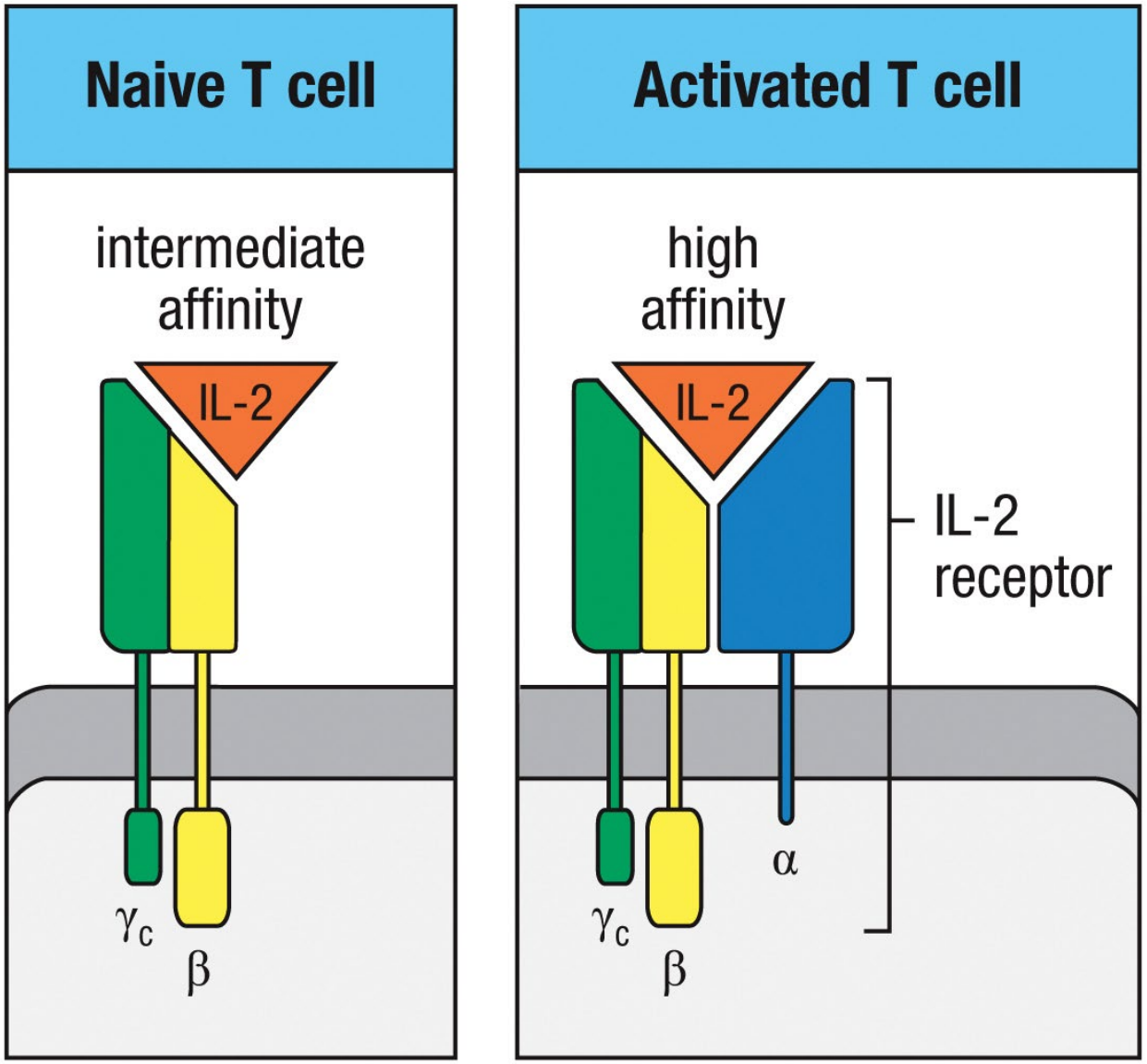
IL-2 Promotes Cell Growth and Differentiation



Outline

T cell mediated immunity

- T cell differentiation
- T cell-mediated cytotoxicity
- Macrophage activation by T_H1 cells
- Peripheral Tolerance

Effector T Cells

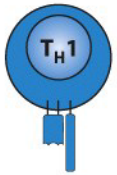
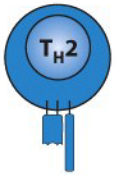
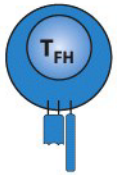
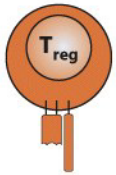
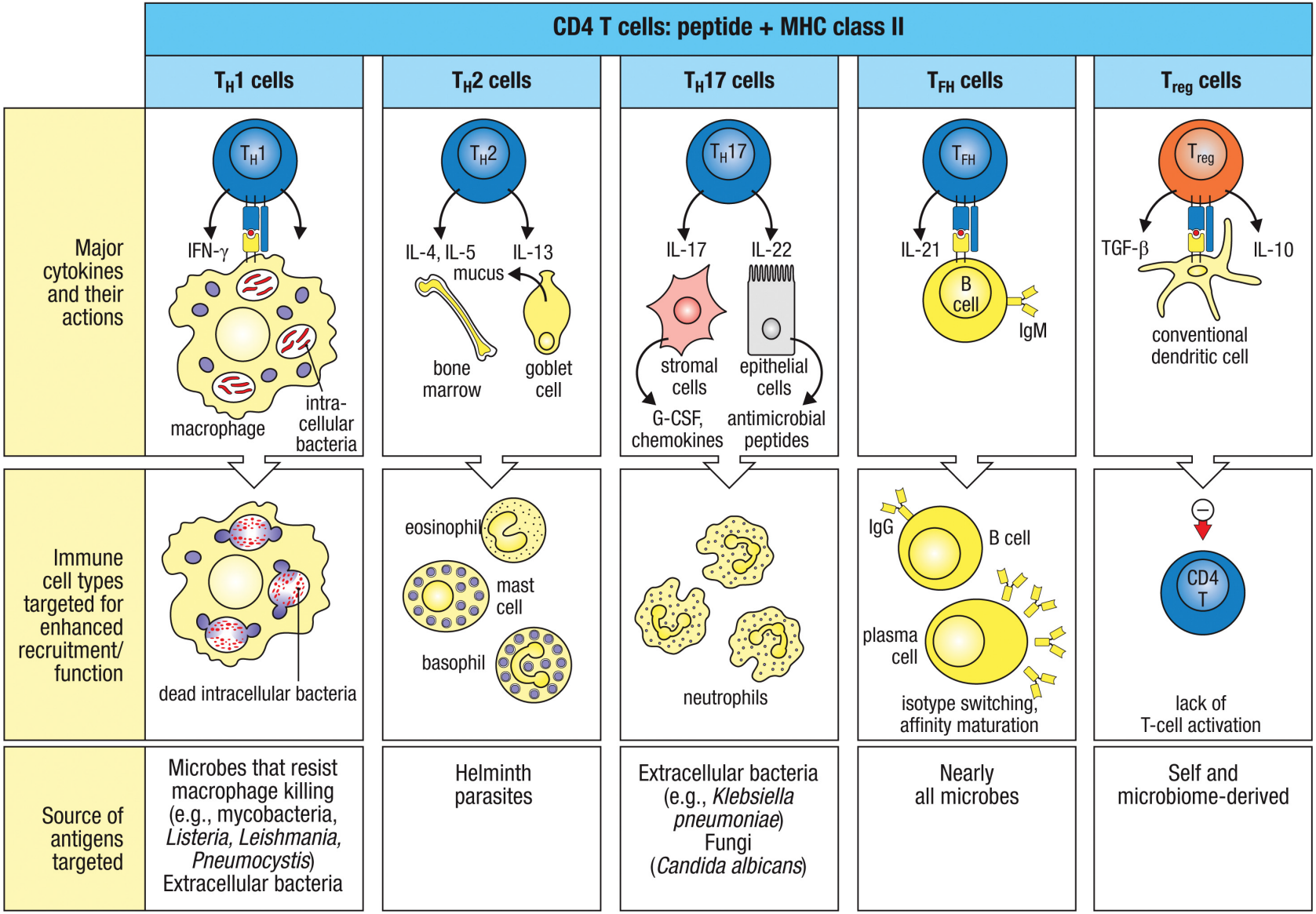
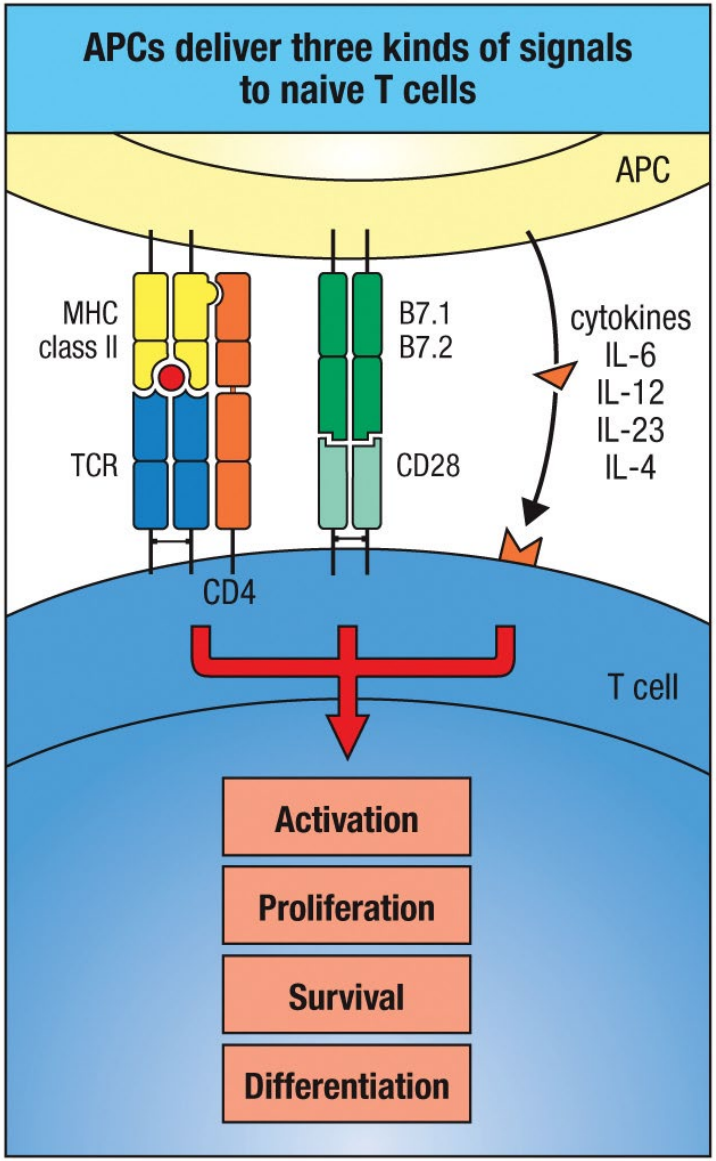
	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells	CD4 T_H17 cells	T_{FH} cells	CD4 regulatory T cells (various types)
Types of effector T cell						
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B cells for antibody production, especially switching to IgE	Enhance neutrophil response Promote barrier integrity (skin, intestine)	B-cell help Isotype switching Antibody production	Suppress T-cell responses
Pathogens targeted	Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria	Microbes that persist in macrophage vesicles (e.g. mycobacteria, *Listeria, Leishmania donovani, Pneumocystis carinii*) Extracellular bacteria	Helminth parasites	*Klebsiella pneumoniae* Fungi (*Candida albicans*)	All types	

Figure 9.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

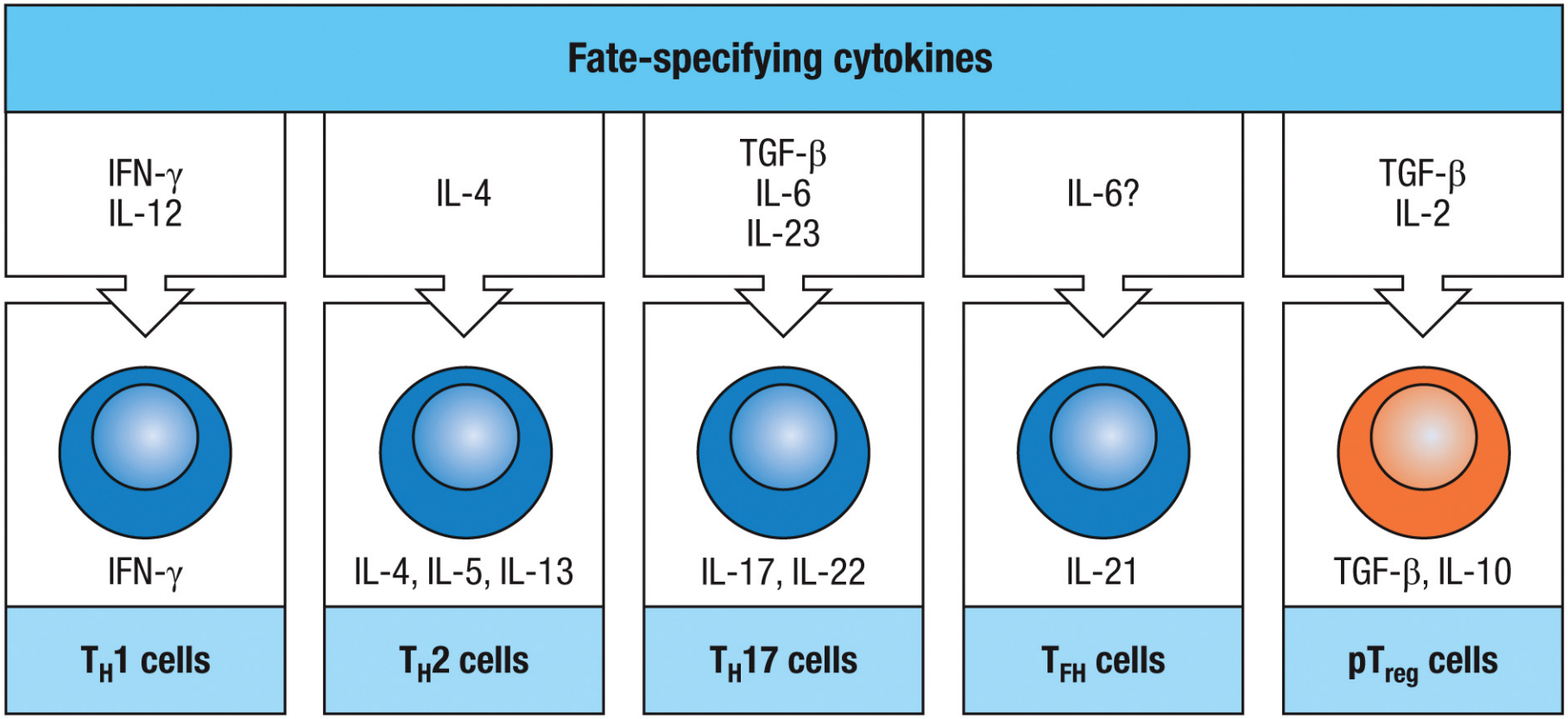
Different Types of T-Cells Are Specialized to Deal with Different Classes of Pathogens



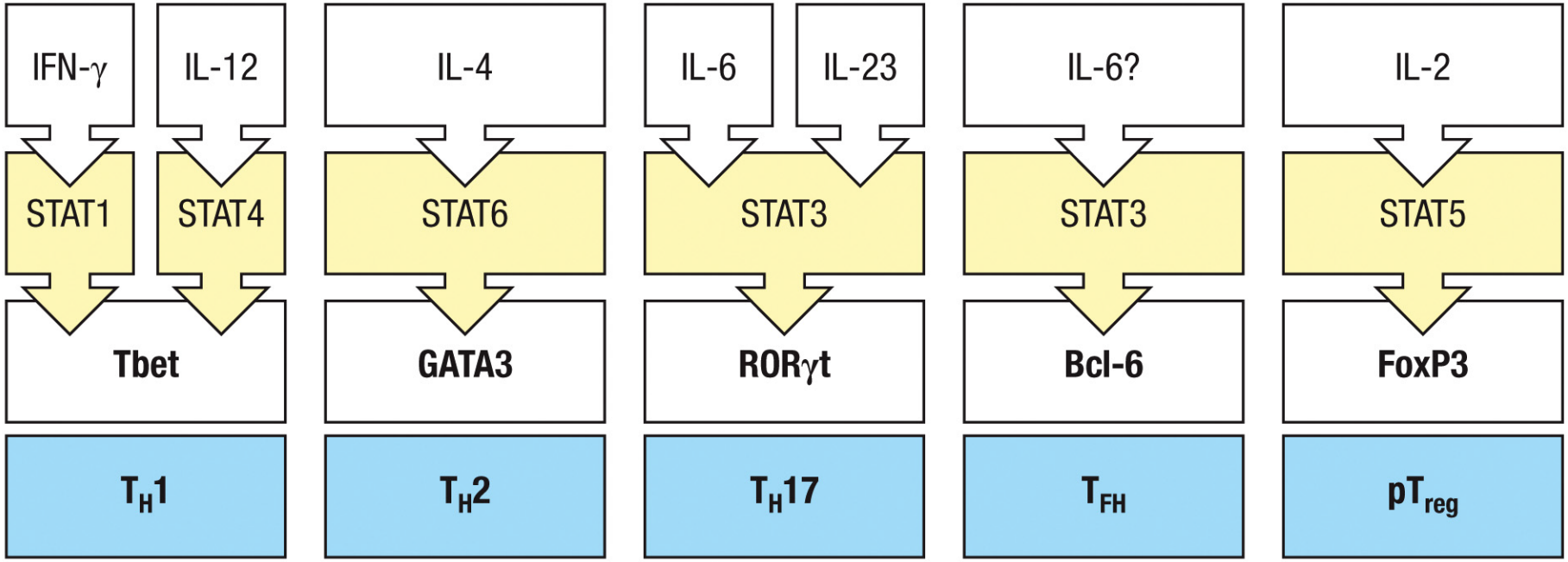
Activation of Naïve T Cells

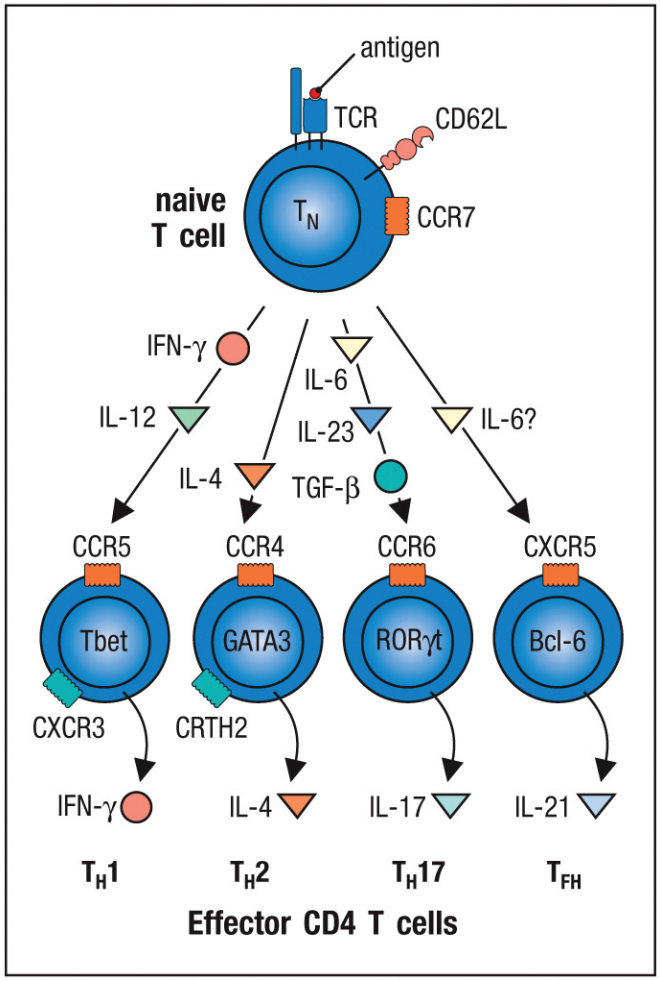


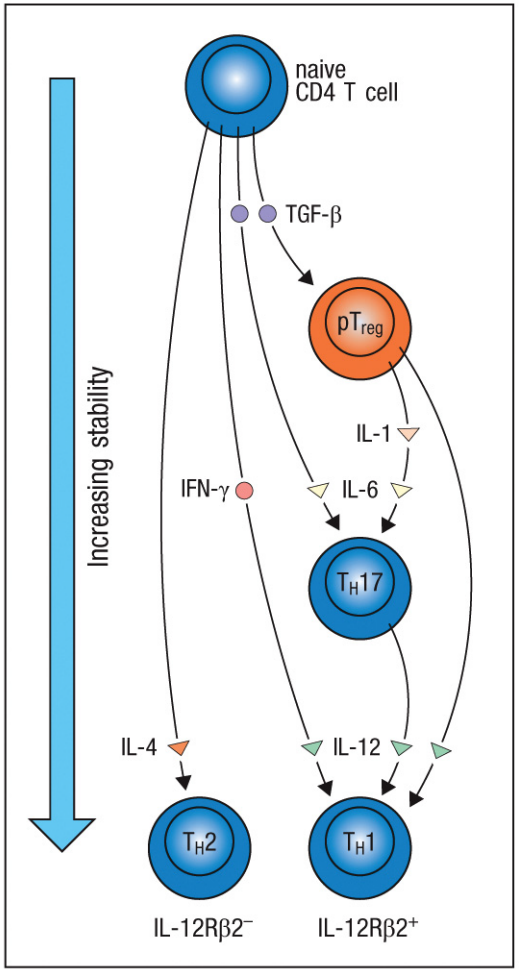
Signal 3


Fate-specifying cytokines
IFN-γ
IL-12
IL-4
TGF-β
IL-6
IL-23
IL-6?
TGF-β
IL-2
IFN-γ
IL-4, IL-5, IL-13
IL-17, IL-22
IL-21
TGF-β, IL-10
TH1 cells
TH2 cells
TH17 cells
TFH cells
pTreg cells

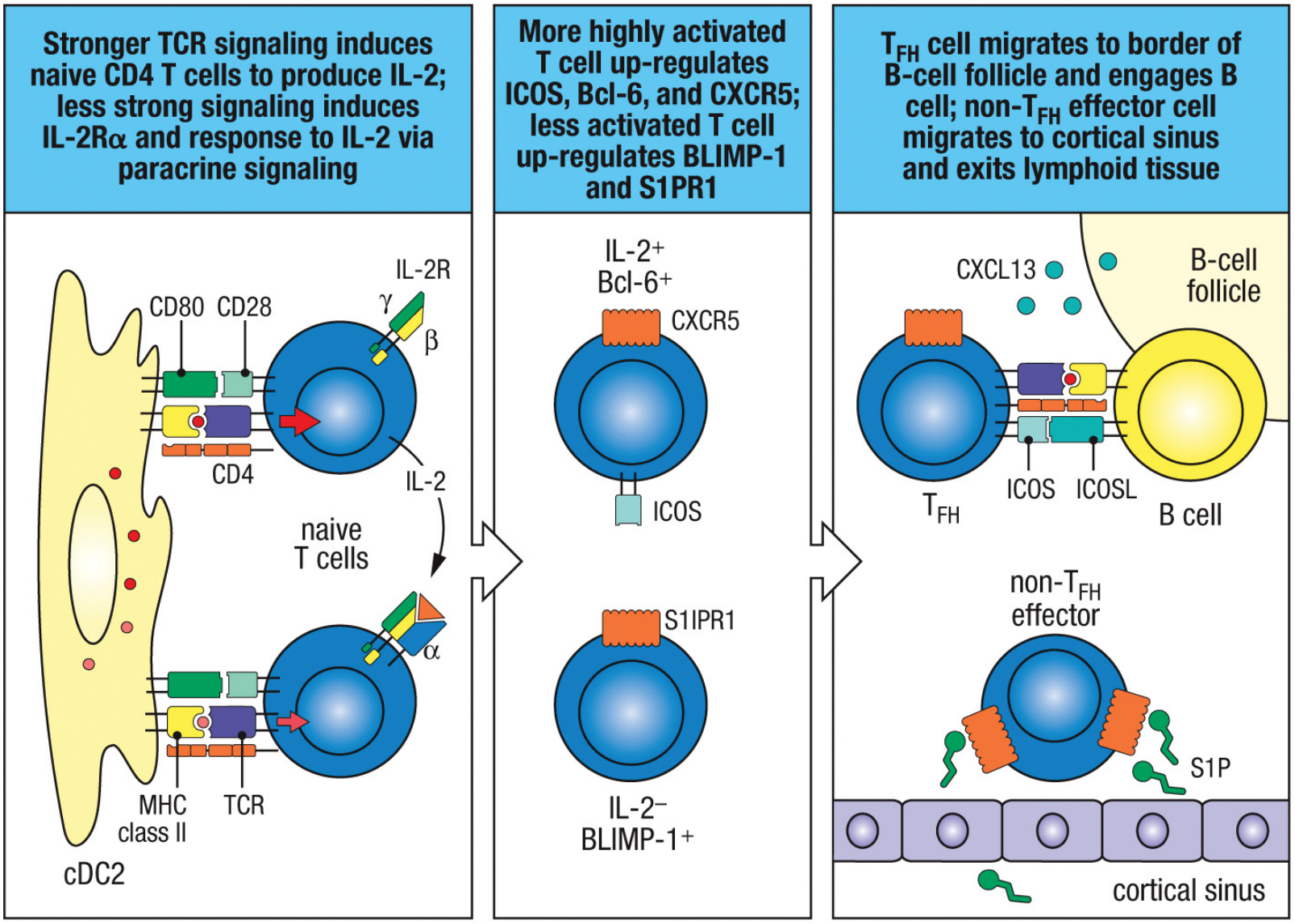
STAT Family of Transcription Factors



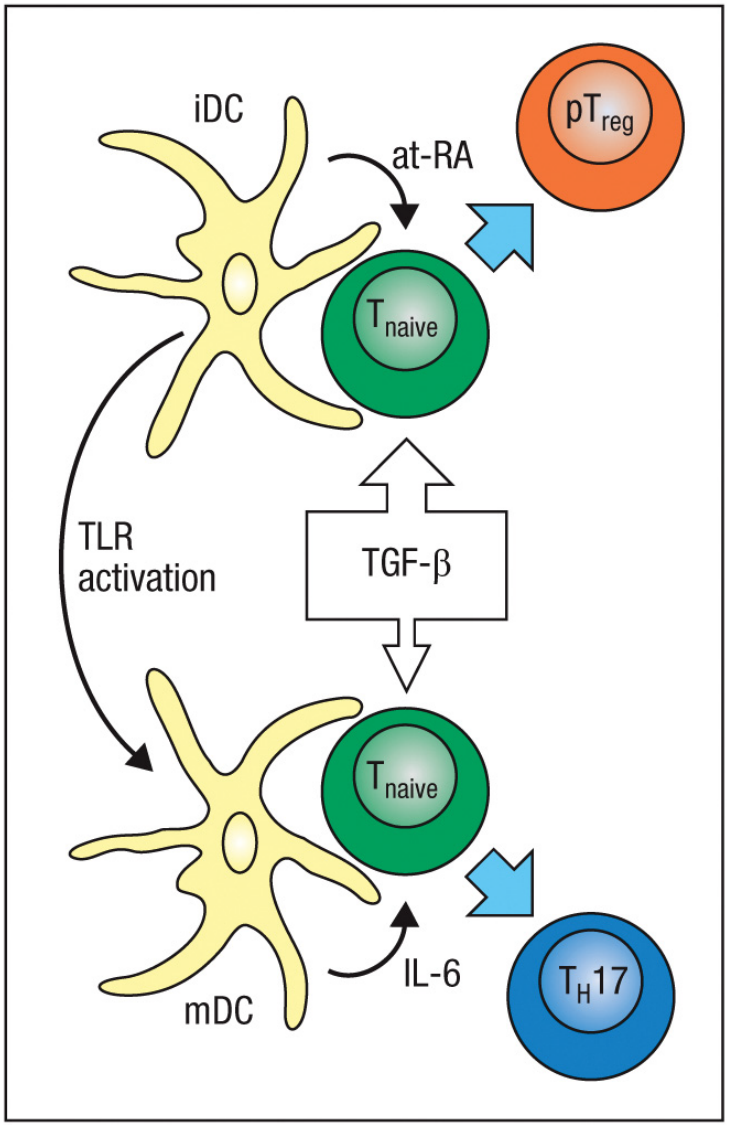

antigen
TCR
CD62L
naive
T cell
T_N
CCR7
IFN-γ
IL-12
IL-4
IL-6
IL-23
TGF-β
IL-6?
CCR5
CCR4
CCR6
CXCR5
Tbet
GATA3
RORγt
Bcl-6
CXCR3
CRTH2
IFN-γ
IL-4
IL-17
IL-21
T_H1
T_H2
T_H17
T_{FH}
Effector CD4 T cells


naive
CD4 T cell
TGF-β
pTreg
IL-1
IFN-γ
IL-6
TH17
Increasing stability
IL-4
IL-12
TH2
TH1
IL-12Rβ2−
IL-12Rβ2+

Strength of TCR Signalling



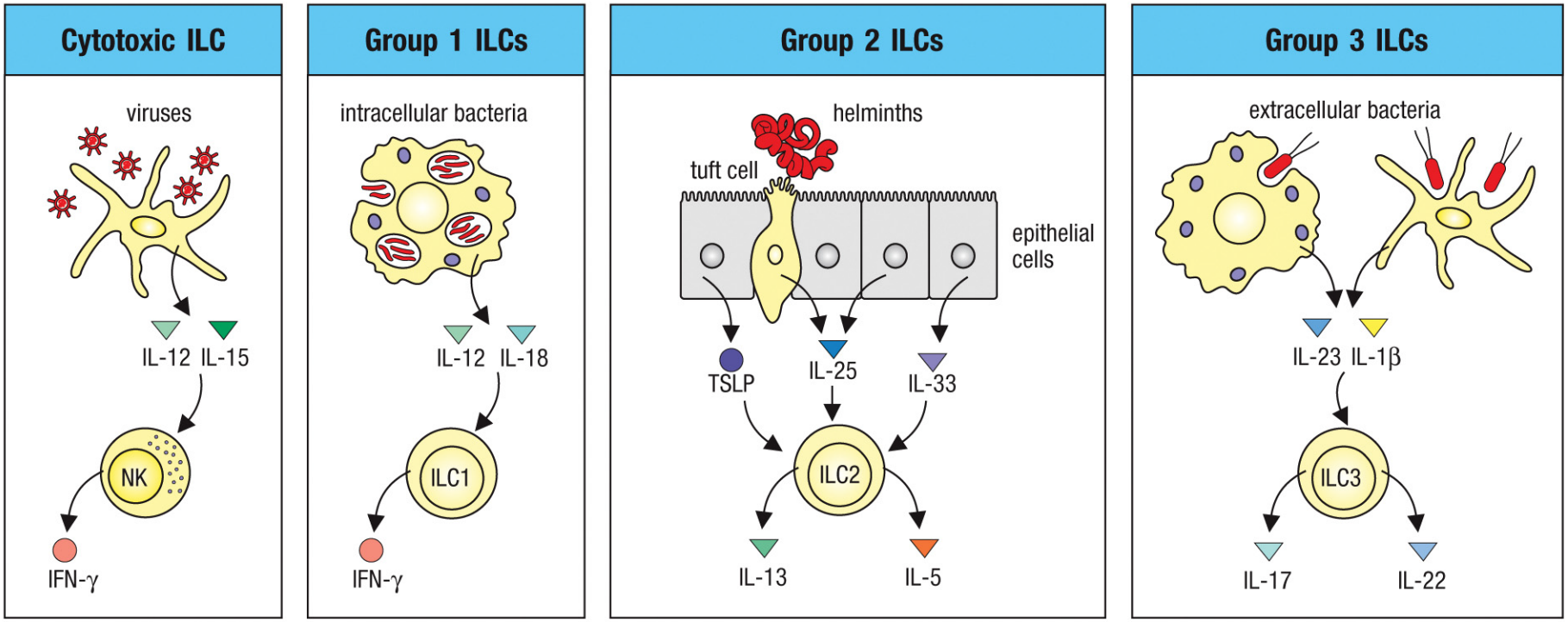
Infection Status Determines the Fate of T Cells



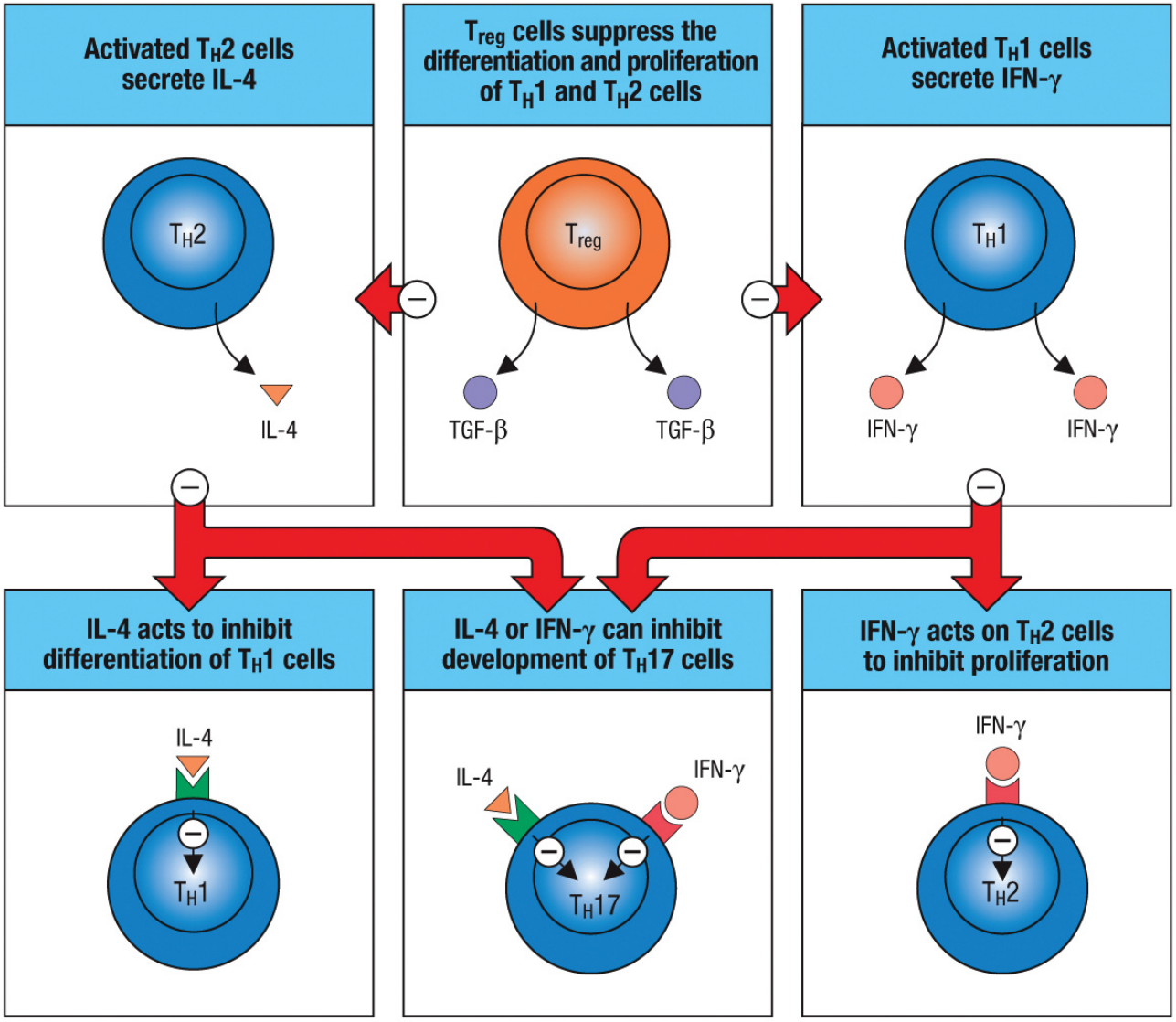
Induced regulatory T cells

All-tran retinoic acid

Innate Lymphoid Cells (ILCs)



Cytokines Sustain Specific T Cell Responses in the Periphery



T Cells Secret Cytokines

Pro-inflammatory

CD8 T cells: peptide + MHC class I		CD4 T cells: peptide + MHC class II							
Cytotoxic (killer) T cells		T_H1 cells		T_H2 cells		T_H17 cells		T_{FH} cells	
Cytotoxic effector molecules	Others	Macrophage-activating effector molecules	Others	Barrier immunity–activating effector molecules	Others	Barrier immunity–activating effector molecules, neutrophil recruitment	Others	B-cell help	Others
Perforin Granzymes Granulysin Fas ligand	IFN-γ LT-α TNF-α	IFN-γ GM-CSF TNF-α CD40 ligand Fas ligand	IL-3 LT-α CXCL2 (GROβ)	IL-4 IL-5 IL-13 CD40 ligand	IL-3 GM-CSF IL-10 TGF-β CCL11 (eotaxin) CCL17 (TARC)	IL-17A IL-17F IL-22 CD40 ligand	IL-3 TNF-α GM-CSF CCL20	IL-21 IL-4 CD40 ligand	TNF-α LT-α CXCL13

Effects of T-Cell Cytokines

Cytokine	T-cell source	Effects on					Effect of gene knockout
		B cells	T cells	Macrophages	Hematopoietic cells	Other tissue cells	
Interleukin-2 (IL-2)	Naive, T_H1, some CD8	Stimulates growth and J-chain synthesis	Growth and differentiation	–	–	–	↓T-cell responses IBD
Interferon-γ (IFN-γ)	T_H1, T_{FH}, CTL	Differentiation IgG2a synthesis (mouse)	Inhibits T_H2 and T_H17 cell differentiation	Activation, ↑MHC class I and class II	Activates NK cells	Antiviral ↑MHC class I and class II	Susceptible to mycobacteria, some viruses
Lymphotoxin-α (LT-α, TNF-β)	T_H1, some CTL	Inhibits	Kills	Activates, induces NO production	Activates neutrophils	Kills fibroblasts and tumor cells	Absence of lymph nodes Disorganized spleen
Interleukin-4 (IL-4)	T_H2, T_{FH}	Activation, growth IgG1, IgE ↑MHC class II induction	Growth, survival	Promotes marginal zone macrophage activation	↑Growth of mast cells	–	No T_H2
Interleukin-5 (IL-5)	T_H2	Mouse: Differentiation IgA synthesis	–	–	↑Eosinophil growth and differentiation	–	Reduced eosinophilia
Interleukin-13 (IL-13)	T_H2	IgG1, IgE class switch	–	Promotes marginal zone macrophage	–	↑Production of mucus (goblet cell)	Impaired helminth expulsion

Effects of T-Cell Cytokines

Cytokine	T-cell source	Effects on					Effect of gene knockout
		B cells	T cells	Macrophages	Hematopoietic cells	Other tissue cells	
Interleukin-17 (IL-17)	T_H17, T_{FH}	Promotes IgG2a, IgG2b, IgG3 (mouse)	–	–	Stimulates neutrophil recruitment	Stimulates fibroblasts and epithelial cells to secrete chemokines	Impaired antibacterial defense
Interleukin-22 (IL-22)	T_H17	–	–	–	–	Stimulates mucosal epithelium and skin to produce antimicrobial peptides	Impaired antibacterial defense
Interleukin-21 (IL-21)	T_{FH}, some T_H1, T_H17, CTL	Stimulates B-cell growth, germinal center formation, IgG class switching	Promotes CTL memory	–	–	–	Deficient antibody responses
Transforming growth factor-β (TGF-β)	T_{reg}, T_{FH}	Inhibits growth IgA switch factor	T_H17 and iT_{reg} differentiation, inhibits T_H1 and T_H2	Inhibits activation	Activates neutrophils	Inhibits/ stimulates cell growth	Death at ~10 weeks
Interleukin-10 (IL-10)	T_{reg}, some T_H1, T_H2, T_H17, CTL	↑MHC class II	Inhibits T_H1	Inhibits cytokine release	Co-stimulates mast cell growth	–	IBD

Effects of T-Cell Cytokines

Cytokine	T-cell source	Effects on					Effect of gene knockout
		B cells	T cells	Macrophages	Hematopoietic cells	Other tissue cells	
Transforming growth factor-β (TGF-β)	T_{reg}, T_{FH}	Inhibits growth IgA switch factor	T_H17 and iT_{reg} differentiation, inhibits T_H1 and T_H2	Inhibits activation	Activates neutrophils	Inhibits/ stimulates cell growth	Death at ~10 weeks
Interleukin-10 (IL-10)	T_{reg}, some T_H1, T_H2, T_H17, CTL	↑MHC class II	Inhibits T_H1	Inhibits cytokine release	Co-stimulates mast cell growth	–	IBD
Interleukin-3 (IL-3)	T_H1, T_H2, T_H17, some CTL	–	–	–	Growth factor for progenitor hematopoietic cells (multi-CSF)	–	–
Tumor necrosis factor-α (TNF-α)	T_H1, T_H17, some T_H2, some CTL	–	–	Activates, induces NO production	–	Activates microvascular endothelium	Susceptibility to Gram + sepsis
Granulocyte–macrophage colony-stimulating factor (GM-CSF)	T_H1, T_H17, some T_H2, some CTL	Differentiation	Inhibits growth?	Activation Differentiation to dendritic cells	↑Production of granulocytes and macrophages (myelopoiesis) and dendritic cells	–	–

Question

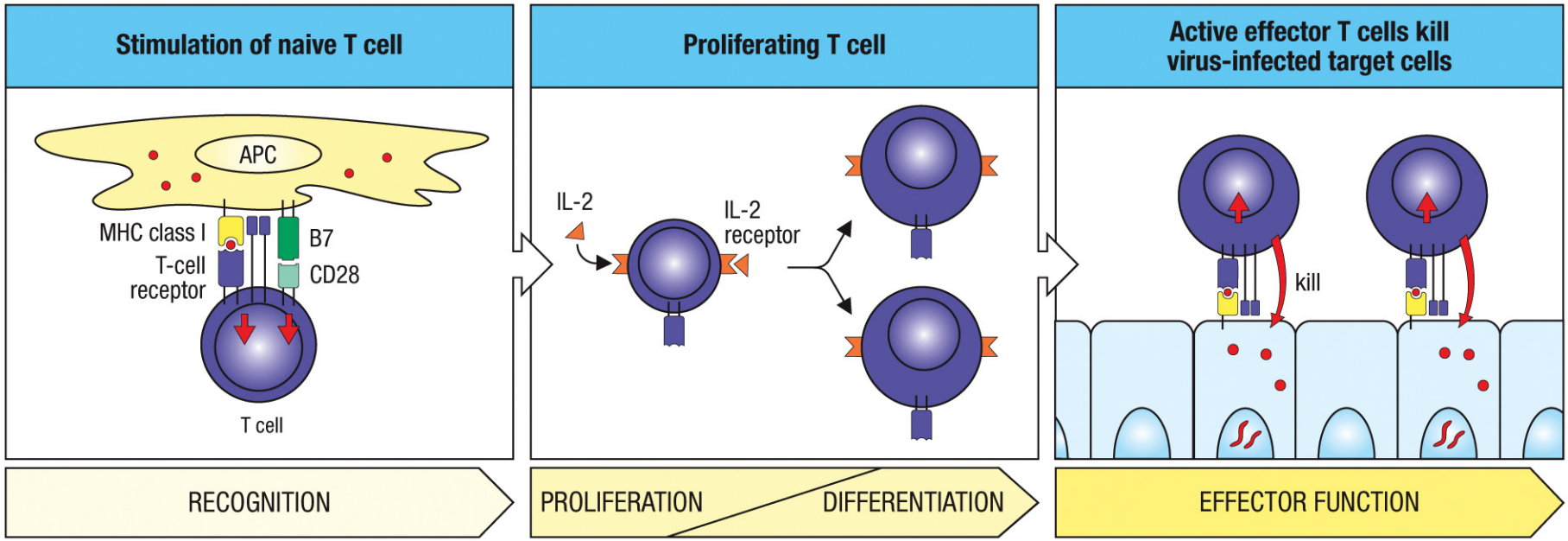
- What are the major subtypes of CD4+ T cells? And their function?
- Which cytokines are required to promote their differentiation, respectively?

Outline

T cell mediated immunity

- T cell differentiation
- T cell-mediated cytotoxicity
- Macrophage activation by T_H1 cells
- Peripheral Tolerance

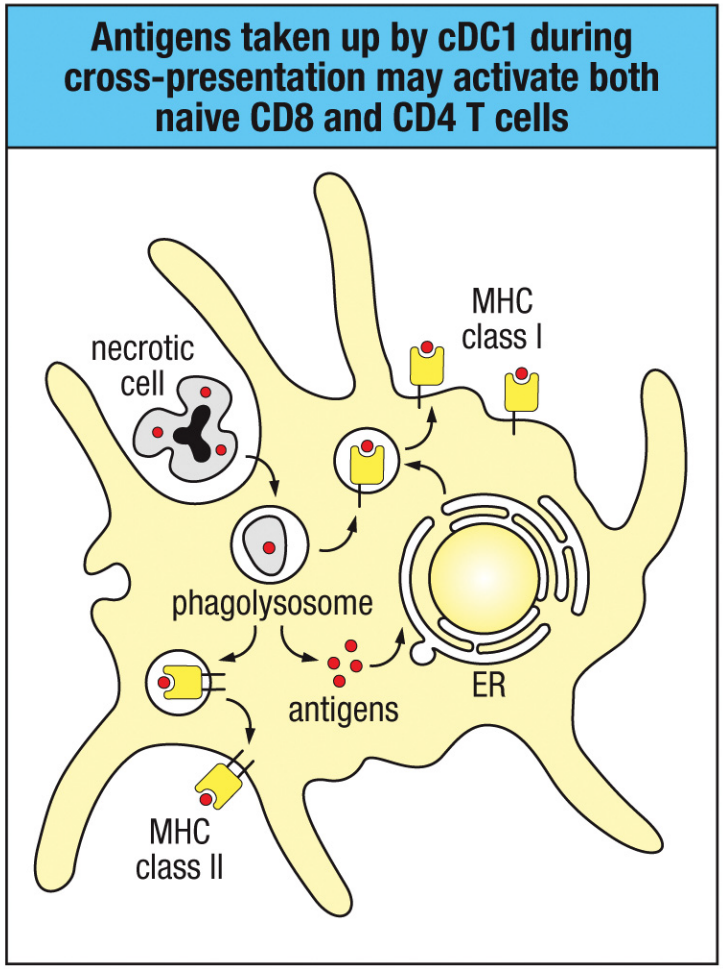
CD8 T Cells

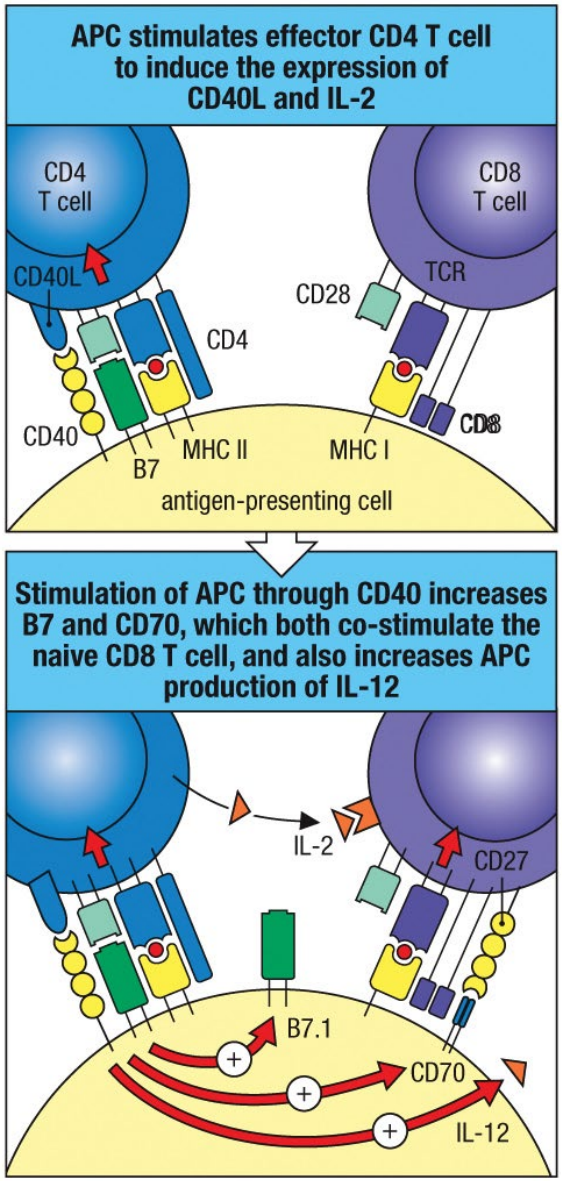


Priming
In lymph nodes

At infection site

Most CD8 T-Cell Responses Require CD4 T-Cells





CD8 T-Cell Memory Requires CD4 T-Cells

With a pathogen that induce an severe acute infection, effector T cells are generated, but not the memory T cells.

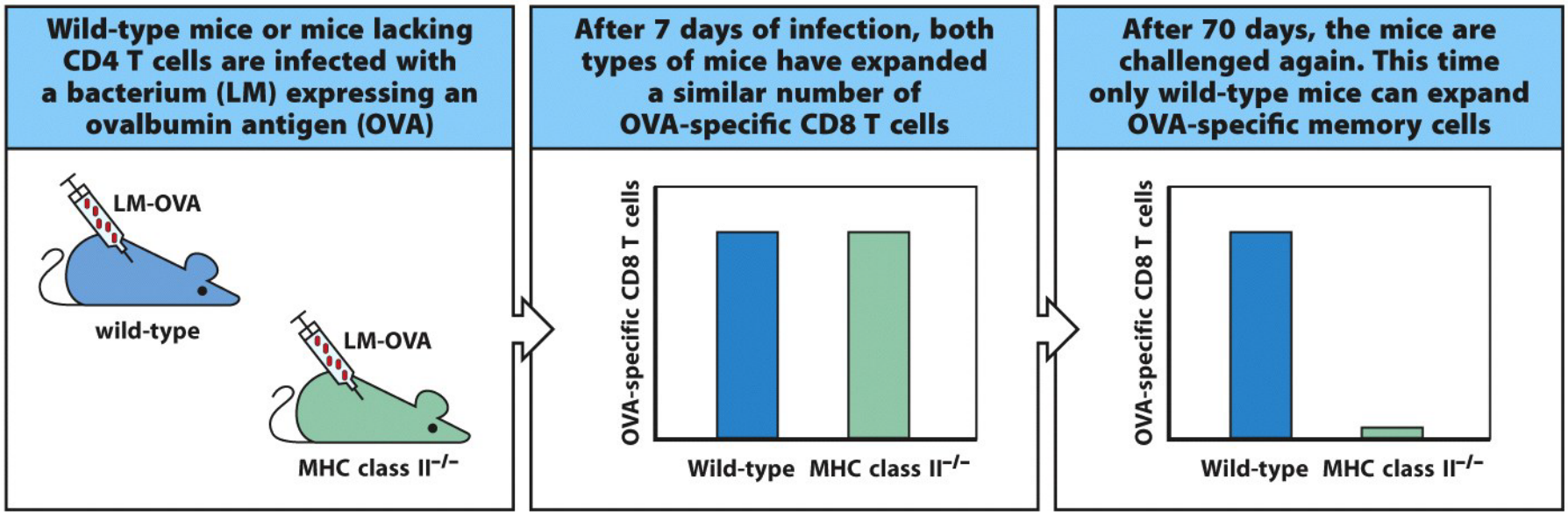
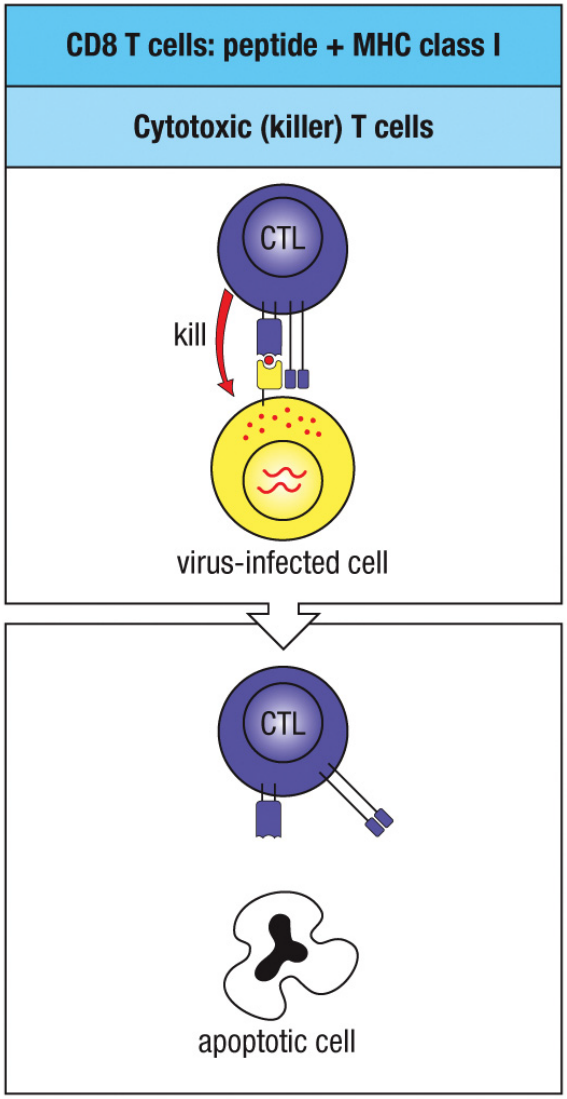


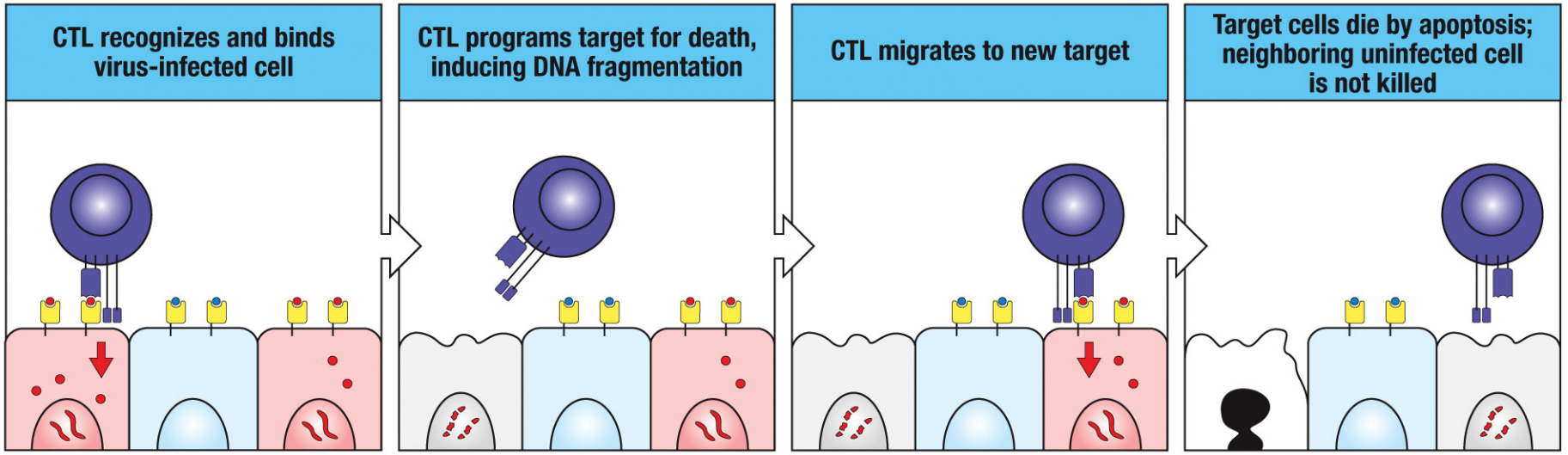
Figure 11.26 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

CD8 T Cells

Target killing does not require co-stimulation

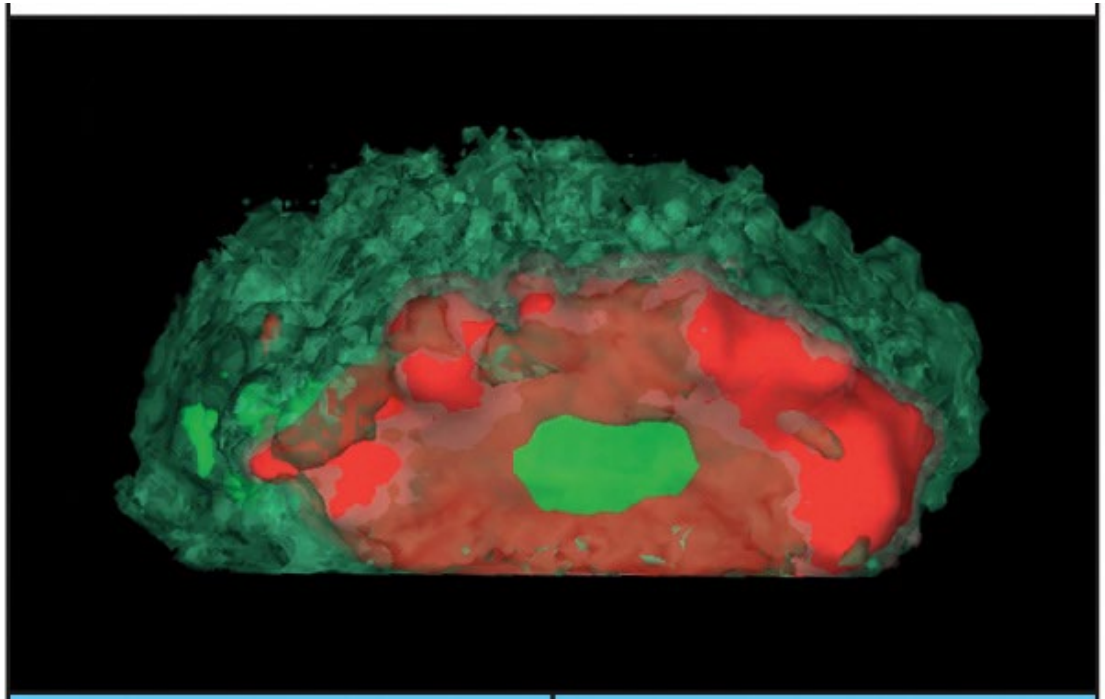


Cytotoxic T Cells are Serial Killers



Immunological Synapse

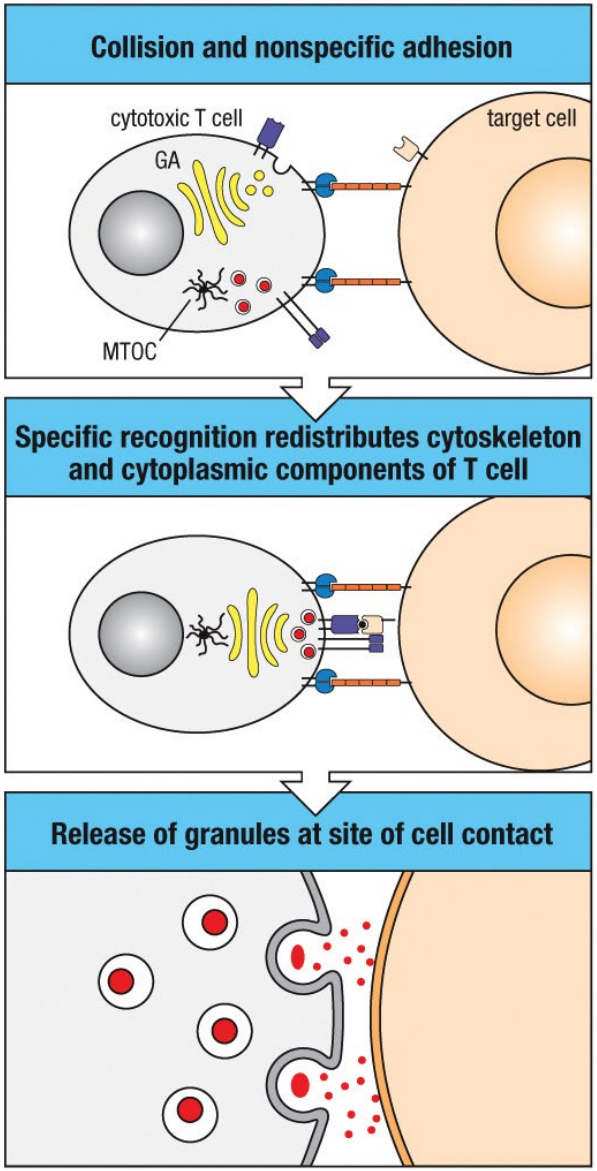
supramolecular adhesion complex

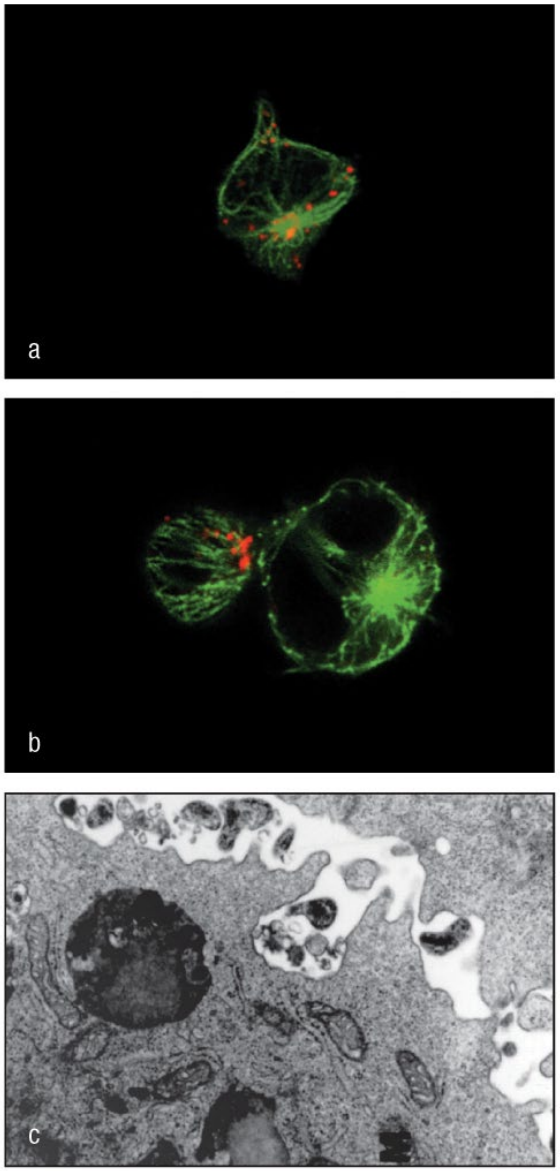


Outer ring (red) pSMAC	**Inner circle (green) cSMAC**
High-affinity LFA-1:ICAM-1	**TCR, CD4 or CD8, peptide:MHC**

Photograph courtesy of Avi Kupfer

Polarization of T-Cells During Antigen Recognition

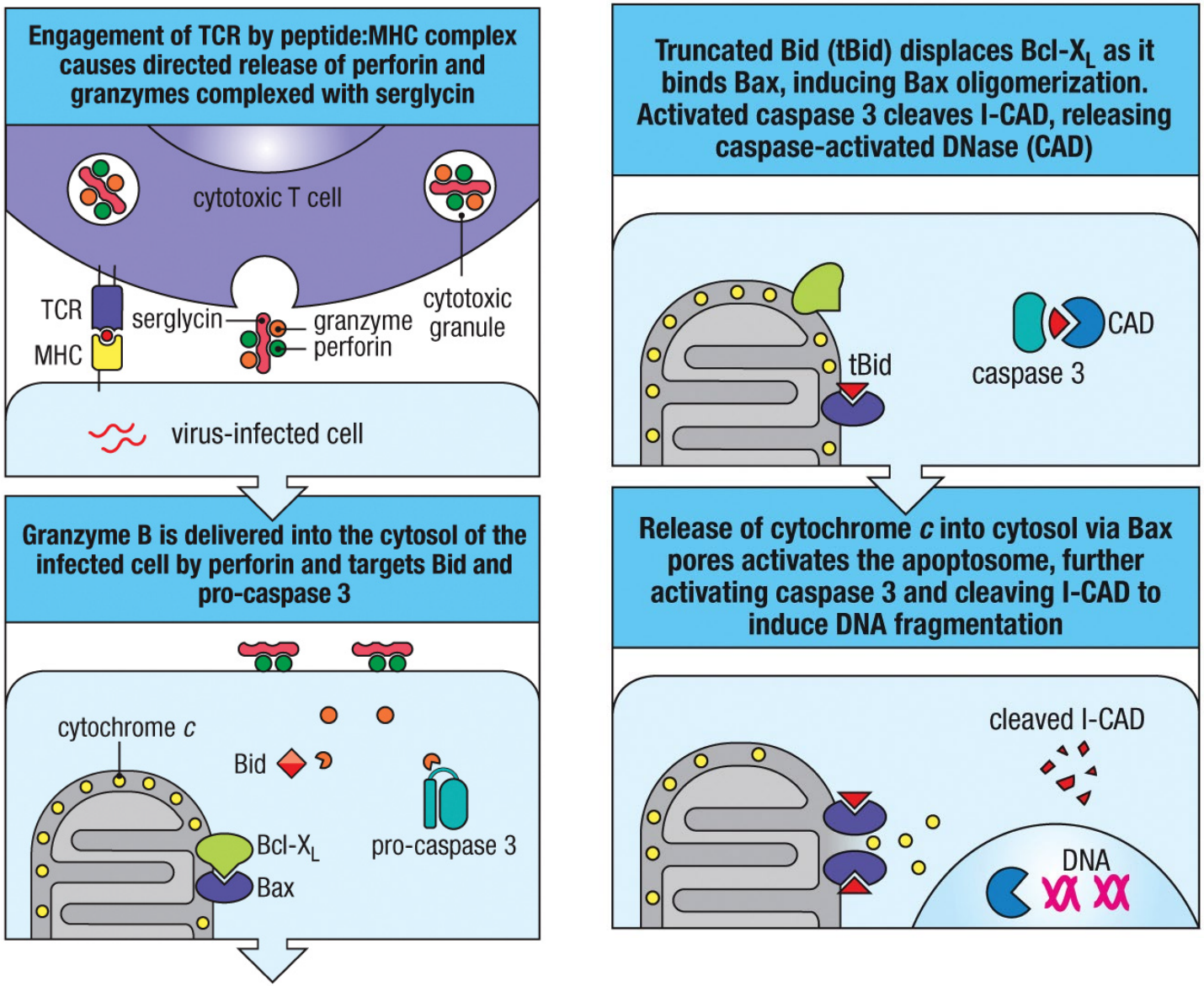




(a, b): Gillian Griffiths; (c): Photo courtesy of Eckhard Podack via Kristin Podack

Cytotoxic granules
Microtubules

Granzyme Induced Apoptosis



Question

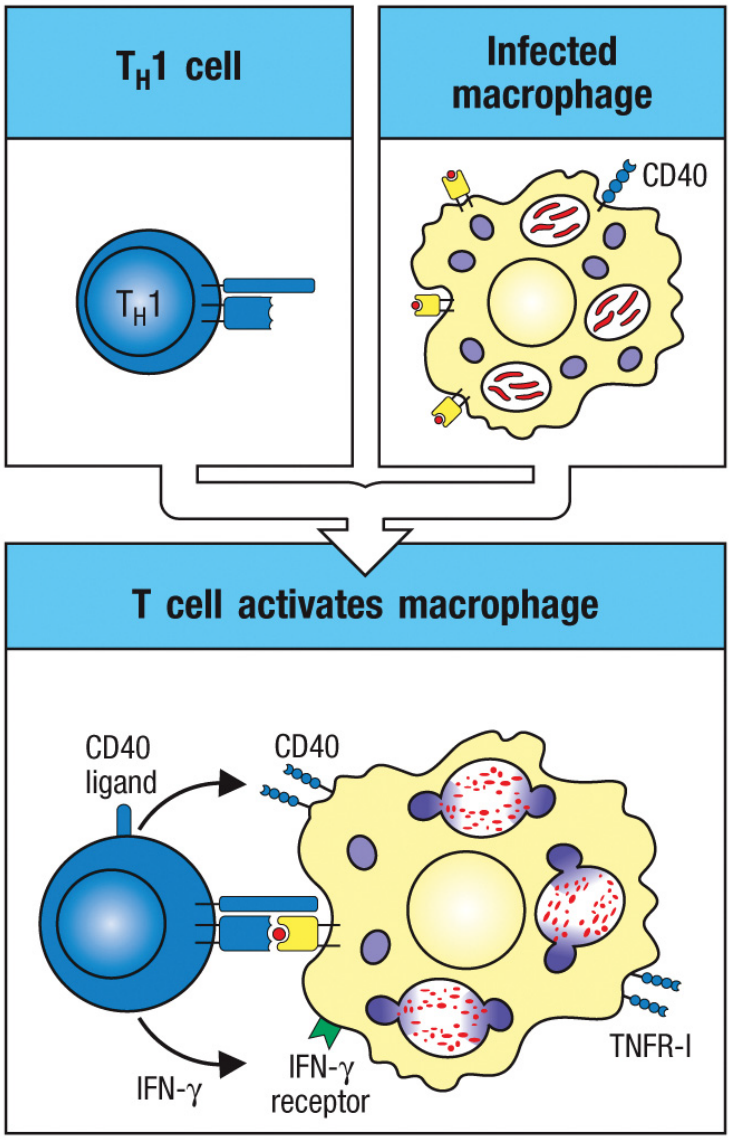
- How does CD4 T cells help CD8 T cells to become activated in the lymph node?

Outline

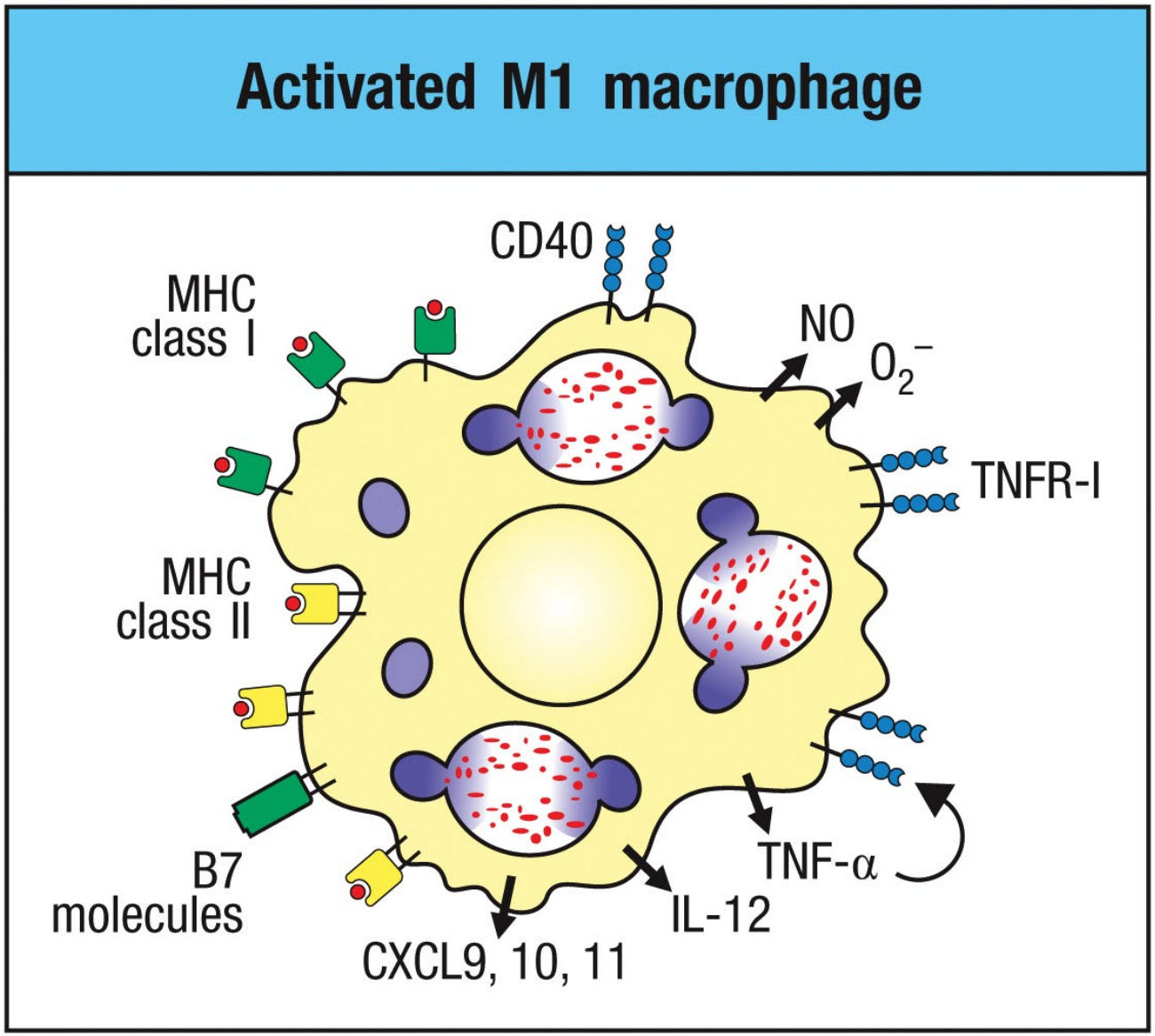
T cell mediated immunity

- T cell differentiation
- T cell-mediated cytotoxicity
- Macrophage activation by T_H1 cells
- Peripheral Tolerance

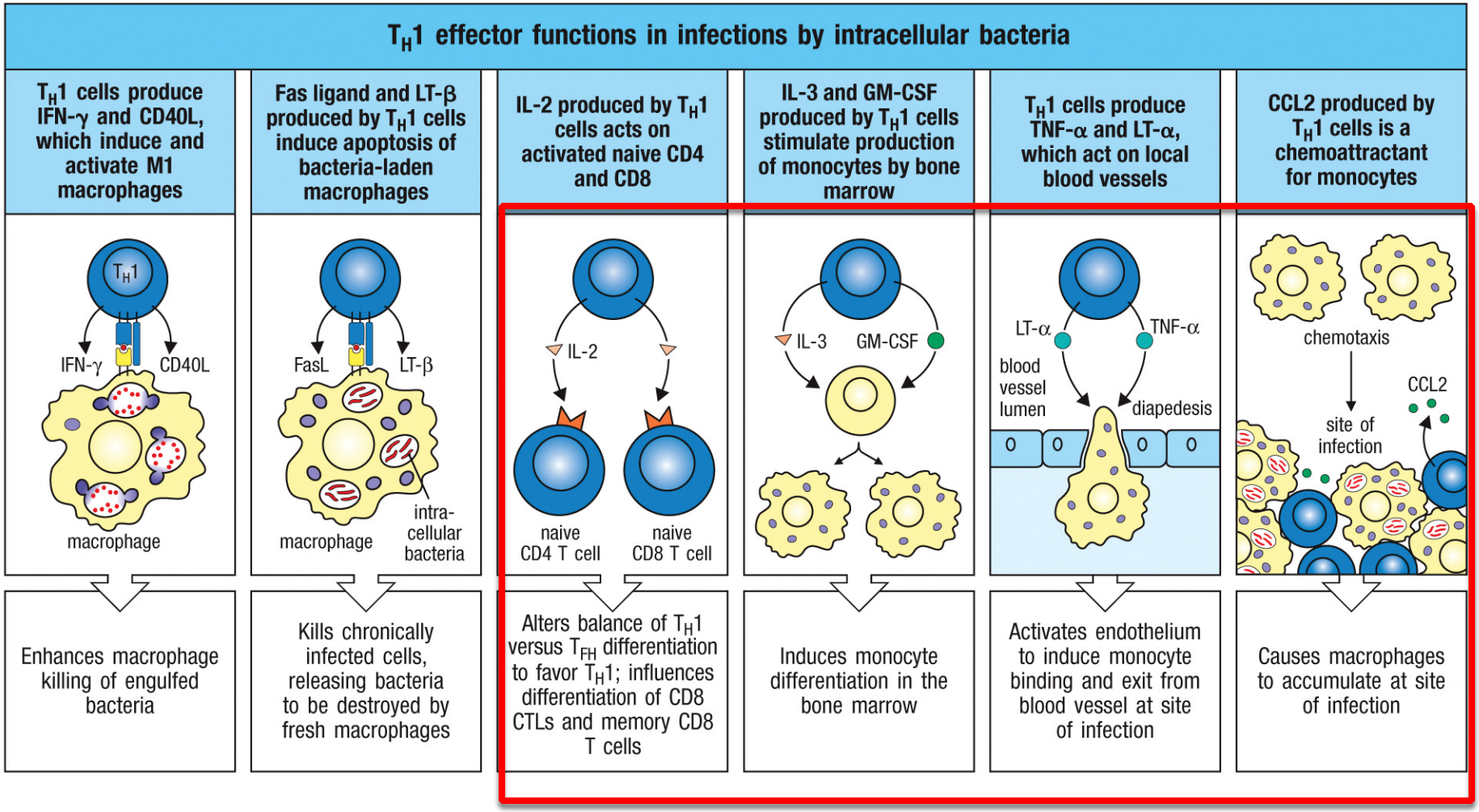
T_H1 Cells Activate Infected Macrophages



Macrophages Activated by T_H1 Cells Are Highly Microbicidal



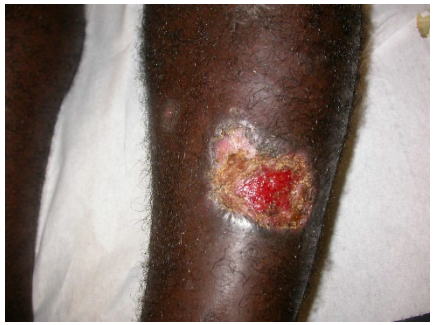
Responses to Intravascular Pathogens Are T_H1 Dependent

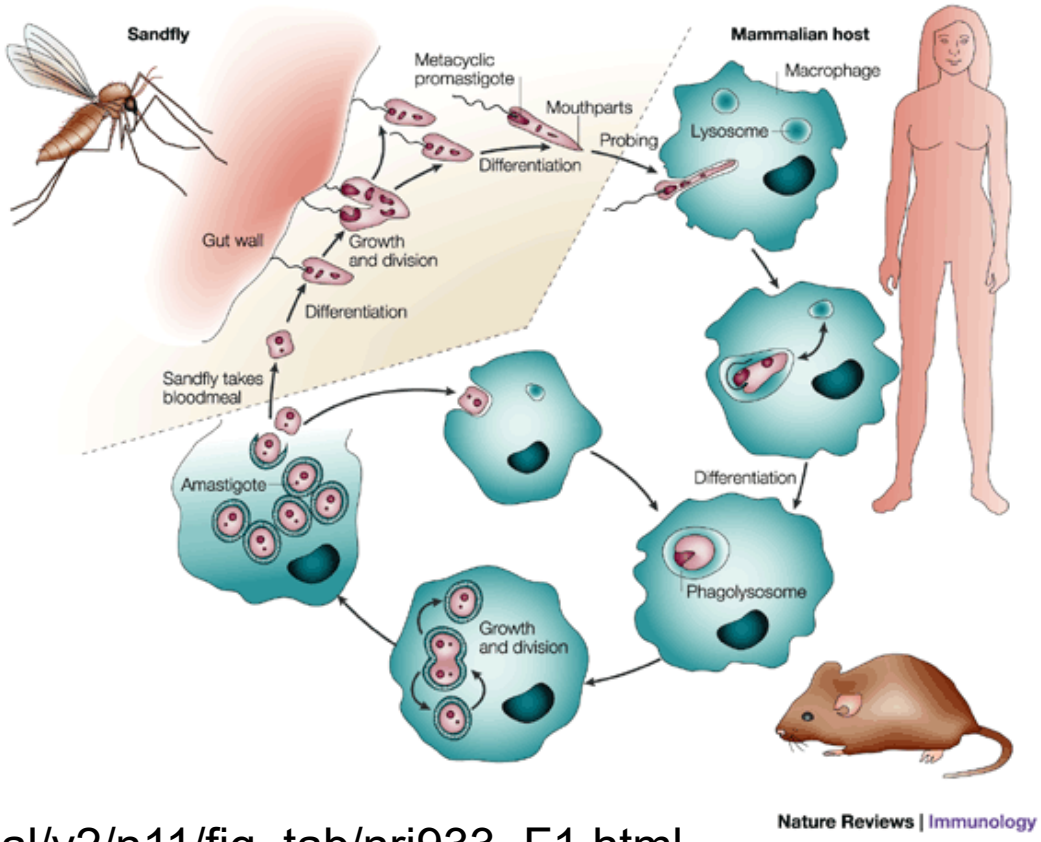


Increase the number of effector cells at infection site
Proinflammatory

Leishmania major

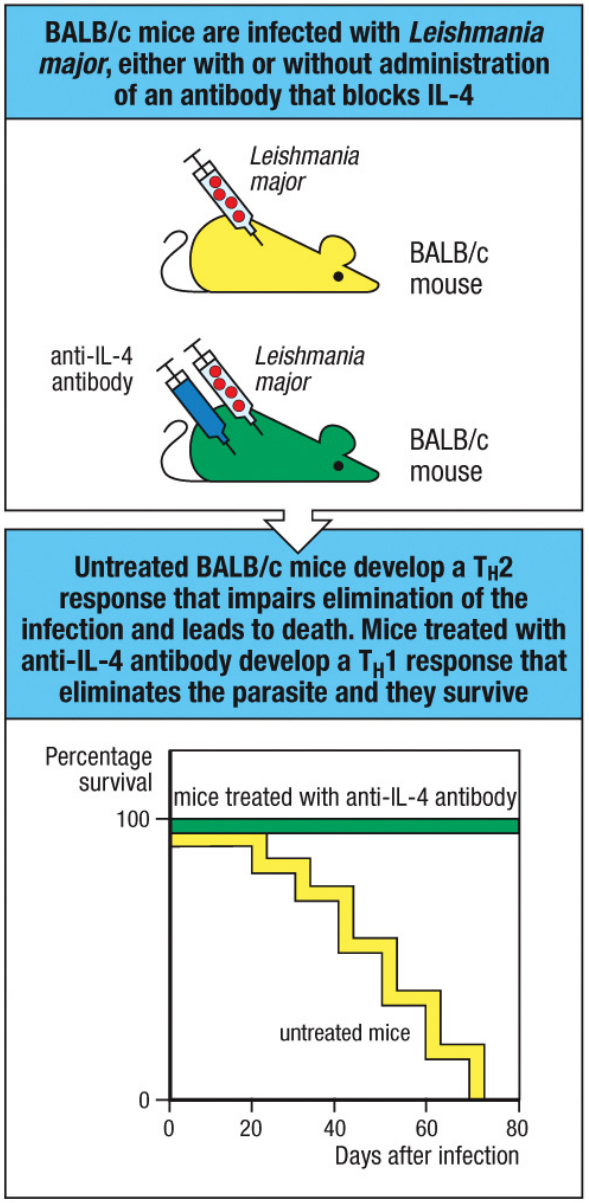
- *L. major* is an intracellular pathogen which infects the macrophages and dendritic cells.



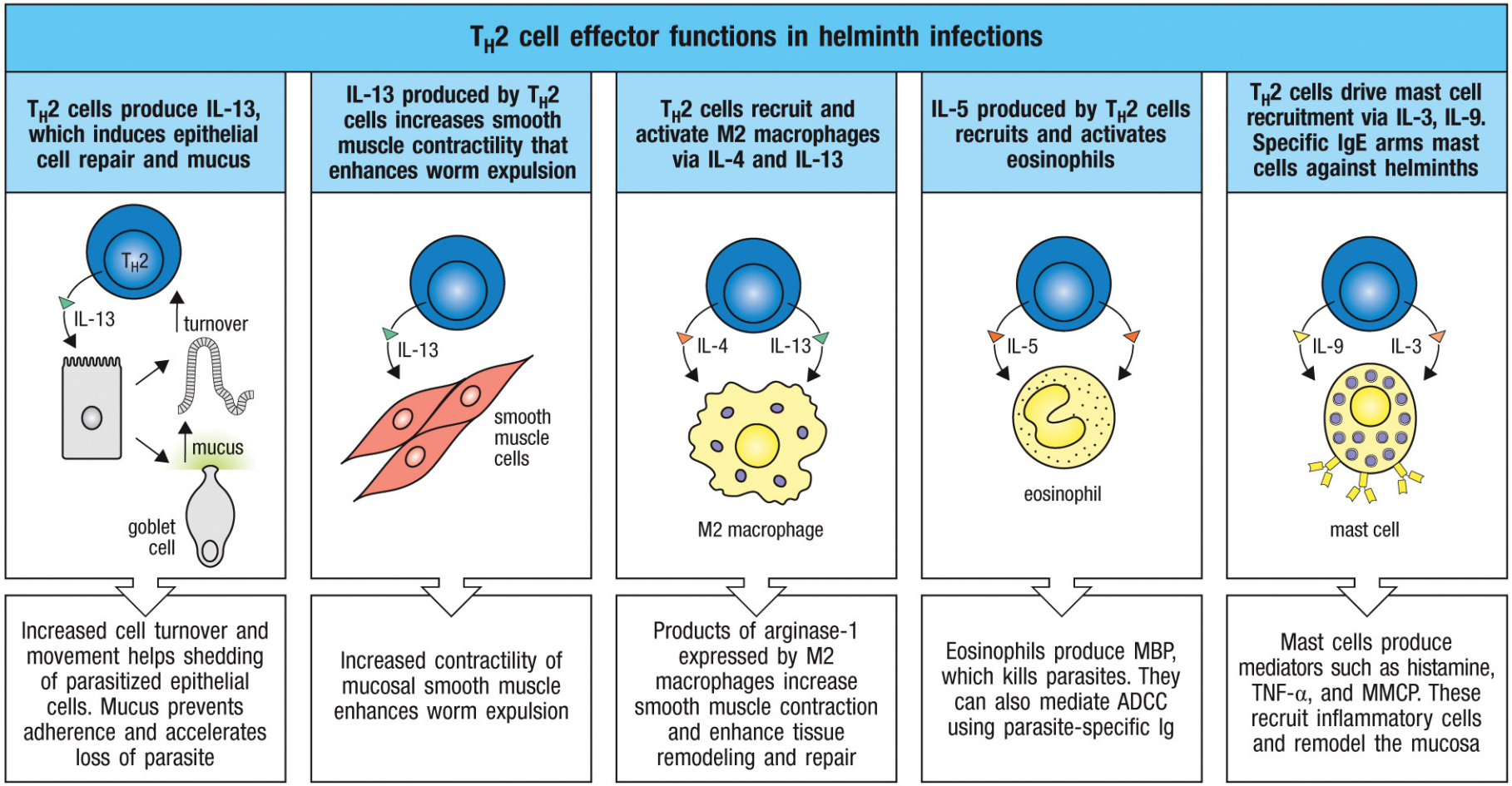


http://www.nature.com/nri/journal/v2/n11/fig_tab/nri933_F1.html

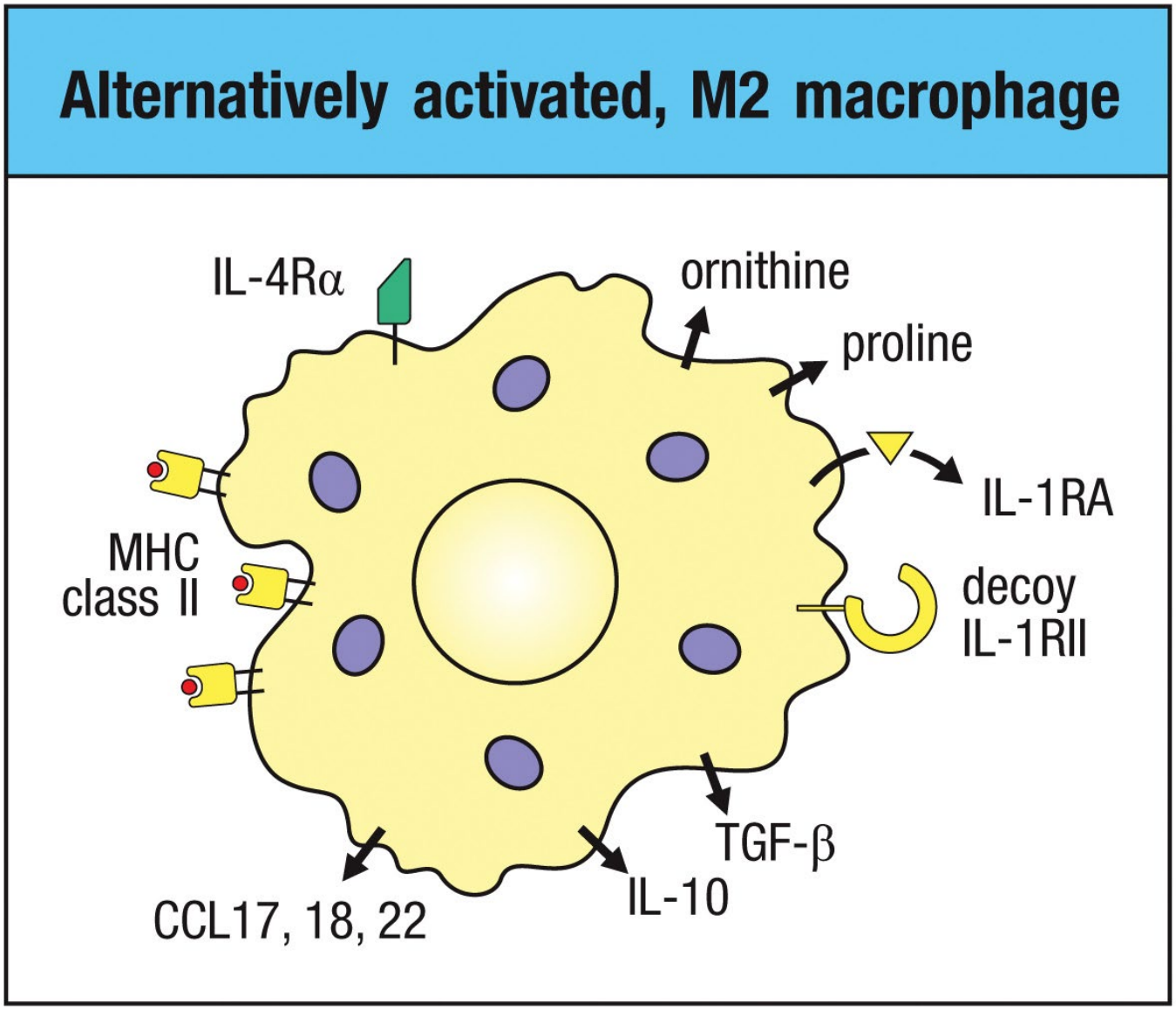
Responses to Intravascular Pathogens Are T_H1 Dependent



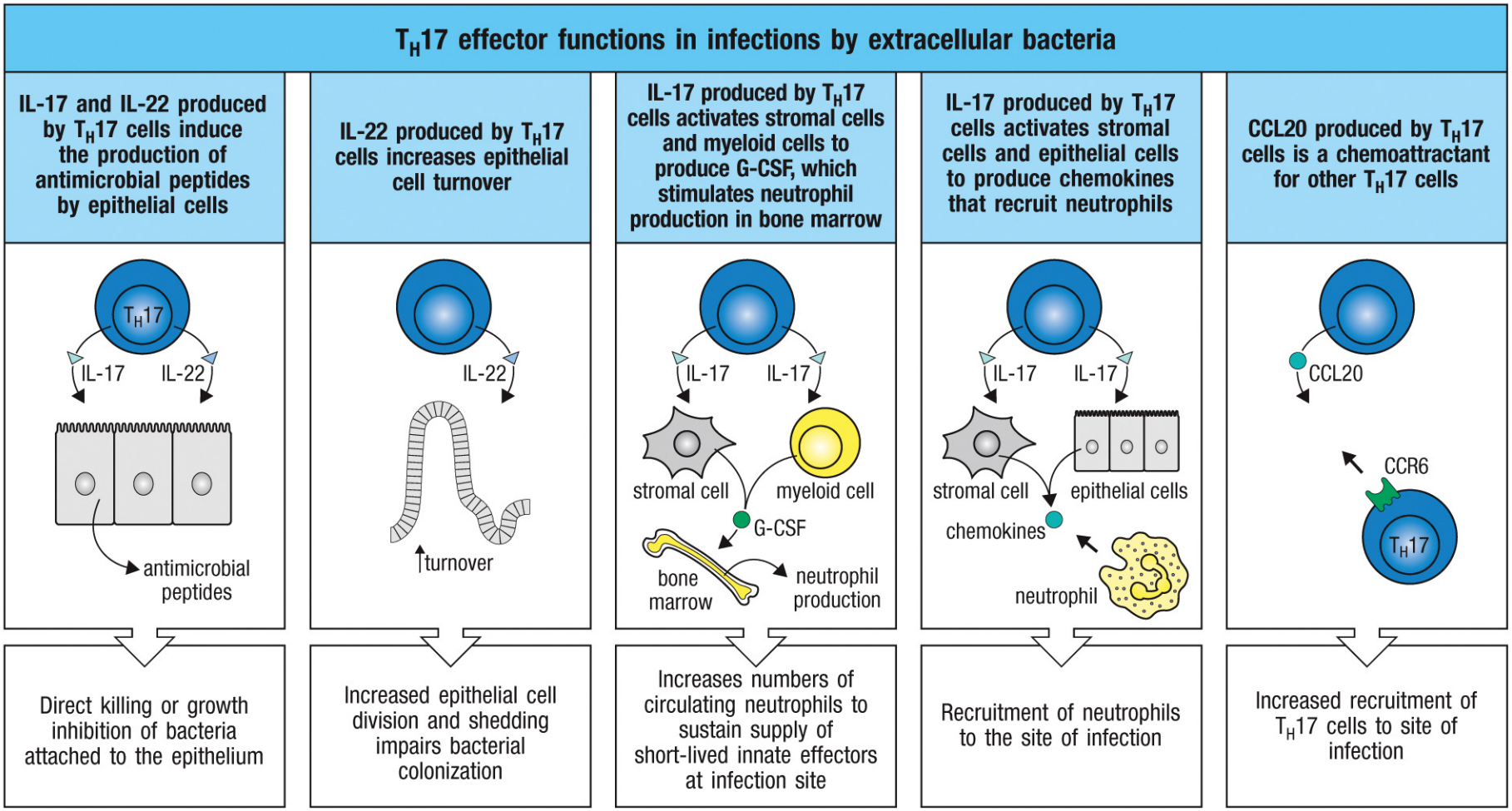
T_H2 Cells in Helminth Infection



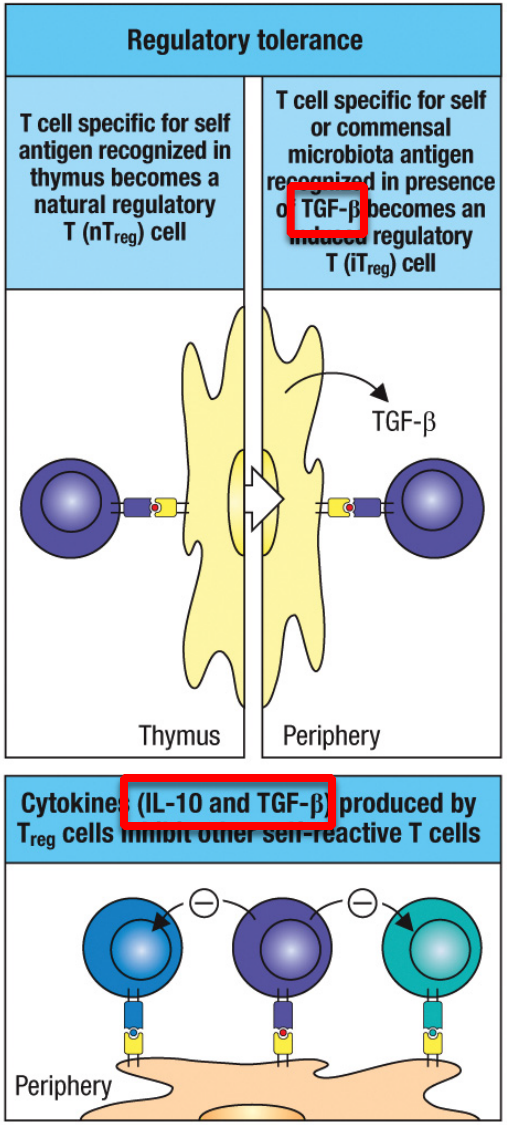
M2 Macrophages



T_H17 Cells in Extracellular Bacterial Infection



Regulatory T Cells



IPEX: Case Study

Patient:

- atopic dermatitis shortly after birth
- diarrhea and type I diabetes
- Enlarged lymph nodes and autoantibodies

Family history:

- A sibling died in infancy

Diagnosis:

- Missense mutation in FOXP3 gene

IPEX

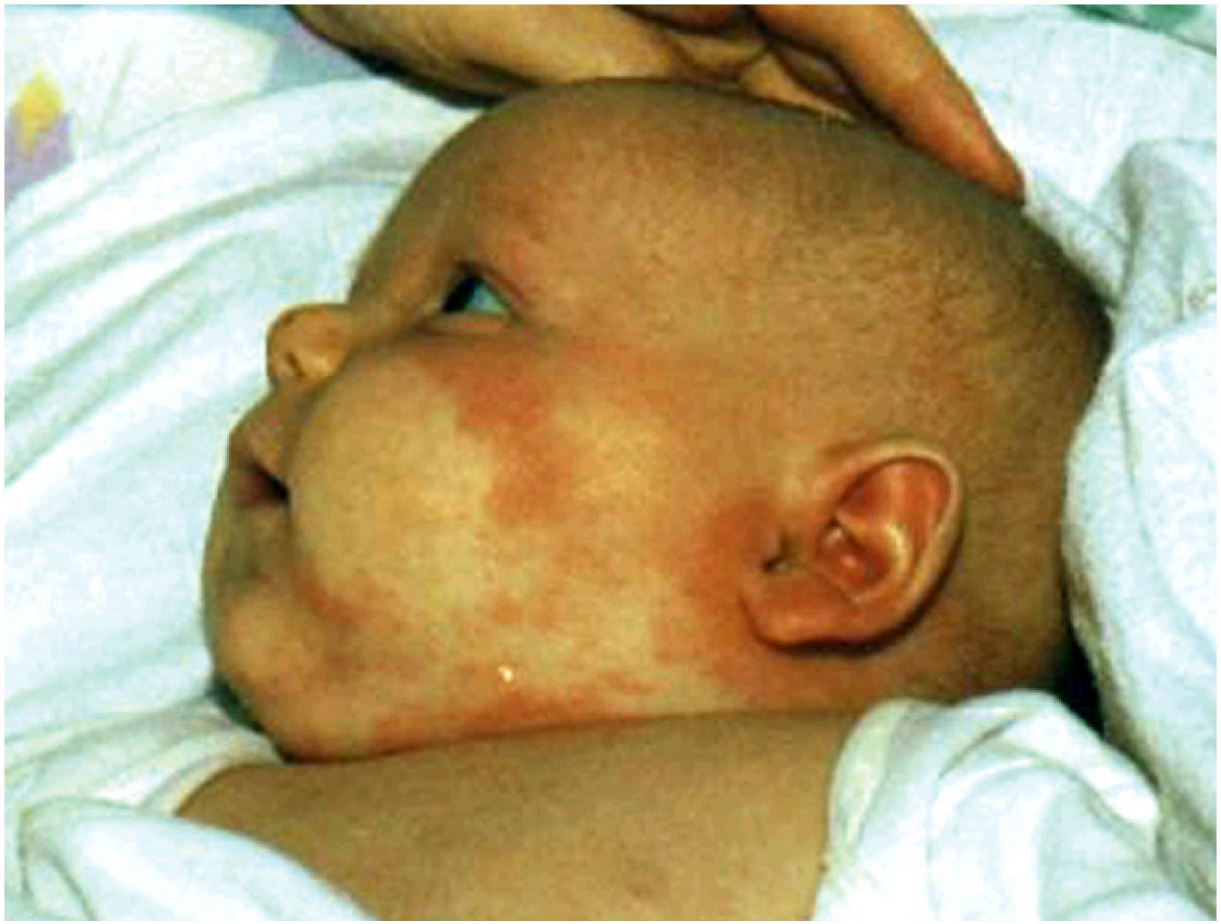


Figure 18.2 Case Studies in Immunology, 6ed. (© Garland Science 2012)

IPEX

- IPEX: Immune dysregulation, polyendocrinopathy, enteropathy X- linked disease
  - Lack of T reg
  - Targeting self organs
    - Endocrine, platelet, skin, etc

Question

- Can IPEX be treated with bone marrow transplantation ?
- A) yes
- B) no

Case Study-Lepromatous Leprosy

- Patient:

  18 year old female

  Hypopigmentation

  Hair loss

  Nose bleed

  Regional lepromatous leprosy
- Diagnosis:

  Acid-fast bacilli from biopsy
- Treatment:

  Drugs that kill *M. leprae*

Cutaneous Nodules

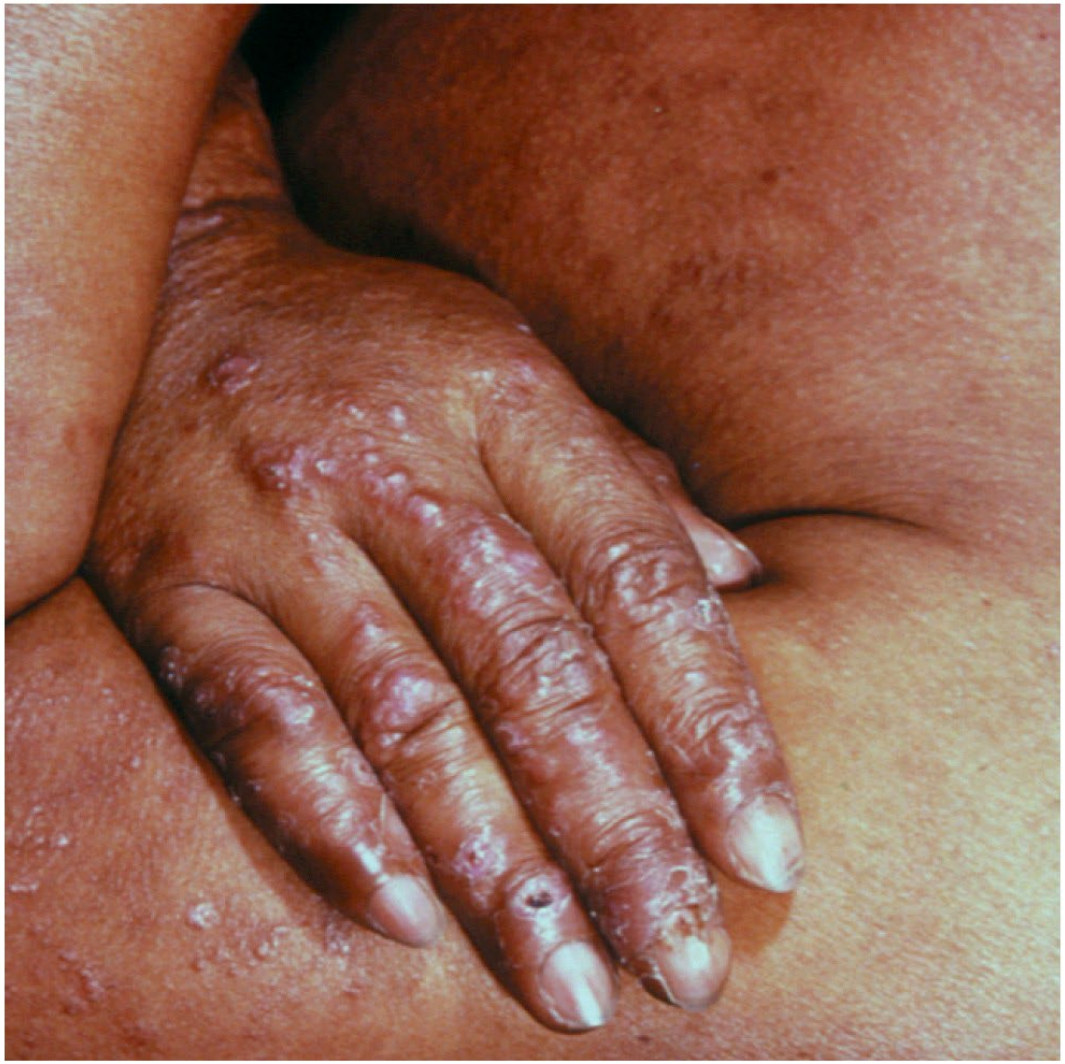


Figure 48.3 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Infection with *Mycobacterium leprae* can result in different clinical forms of leprosy

There are two polar forms, tuberculoid and lepromatous leprosy, but several intermediate forms also exist

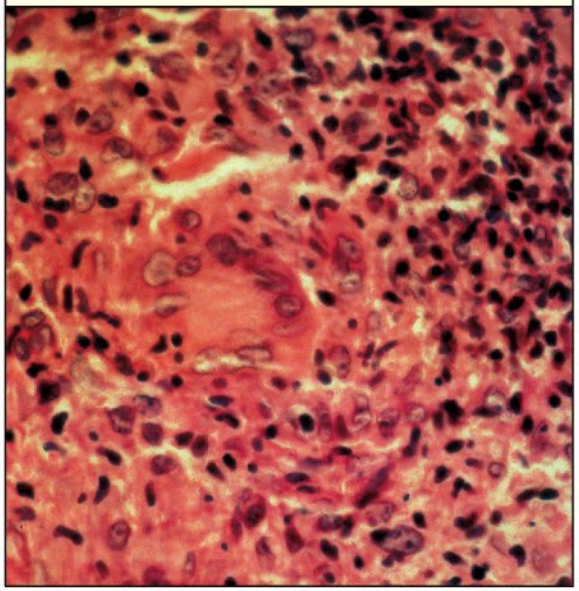
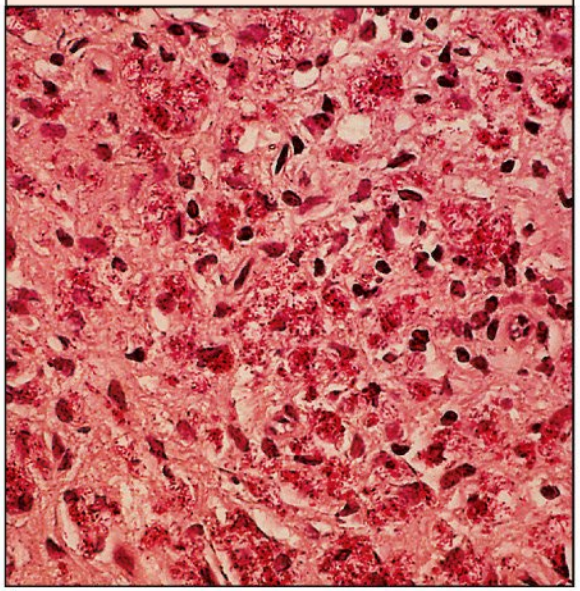
Tuberculoid leprosy	Lepromatous leprosy
	
Organisms present at low to undetectable levels	Organisms show florid growth in macrophages
Low infectivity	High infectivity
Granulomas and local inflammation. Peripheral nerve damage	Disseminated infection. Bone, cartilage, and diffuse nerve damage
Normal serum immunoglobulin levels	Hypergammaglobulinemia
Normal T-cell responsiveness. Specific response to *M. leprae* antigens	Low or absent T-cell responsiveness. No response to *M. leprae* antigens

Figure 48.4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Two Types of Leprosy

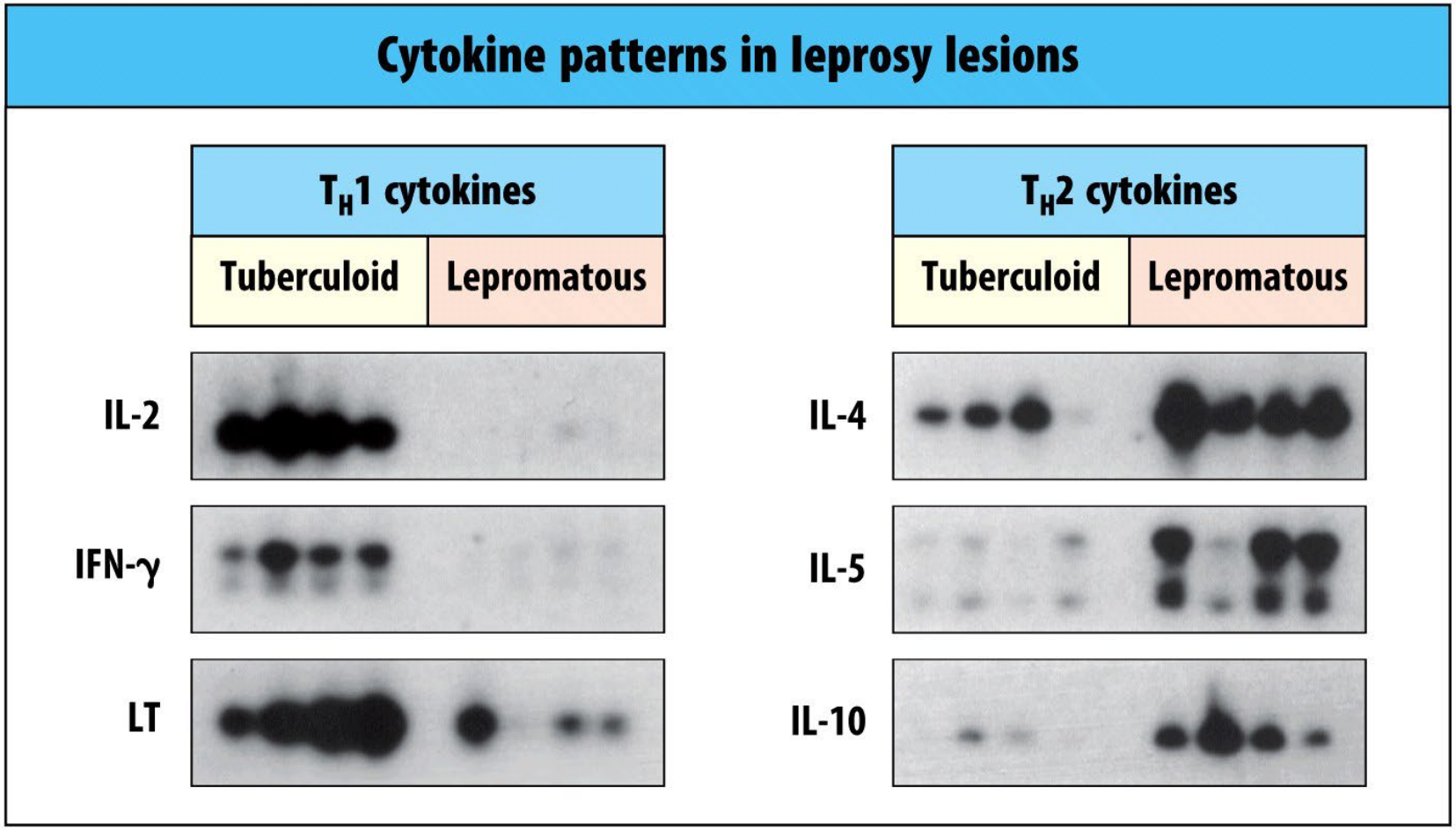


Figure 48.5 Case Studies in Immunology, 6ed. (© Garland Science 2012)

What's Wrong with the Patient?

- Mounting of a Th2 response with does not contain an infection in macrophage phagosomes.

Question

- What can you do to tweak the Th1 vs Th2 response?