Term Paper

- Any topic related to SARS-COV-2

- 8-10 pages
- Timer New Roman, 12, 1” margin

- Due 12/12 at midnight

- Homework and other make ups are due the same time.

Outline

Primary Immunodeficiency
- T cells
- B cells
- Innate Immunity

Acquired Immunodeficiency
- HIV/AIDS

Immunodeficiency

- A defect in one or more components of the immune response
- History of recurrent infections with similar pathogens suggests a diagnosis of immunosuppression

Involves Both Innate and Adaptive Immunity

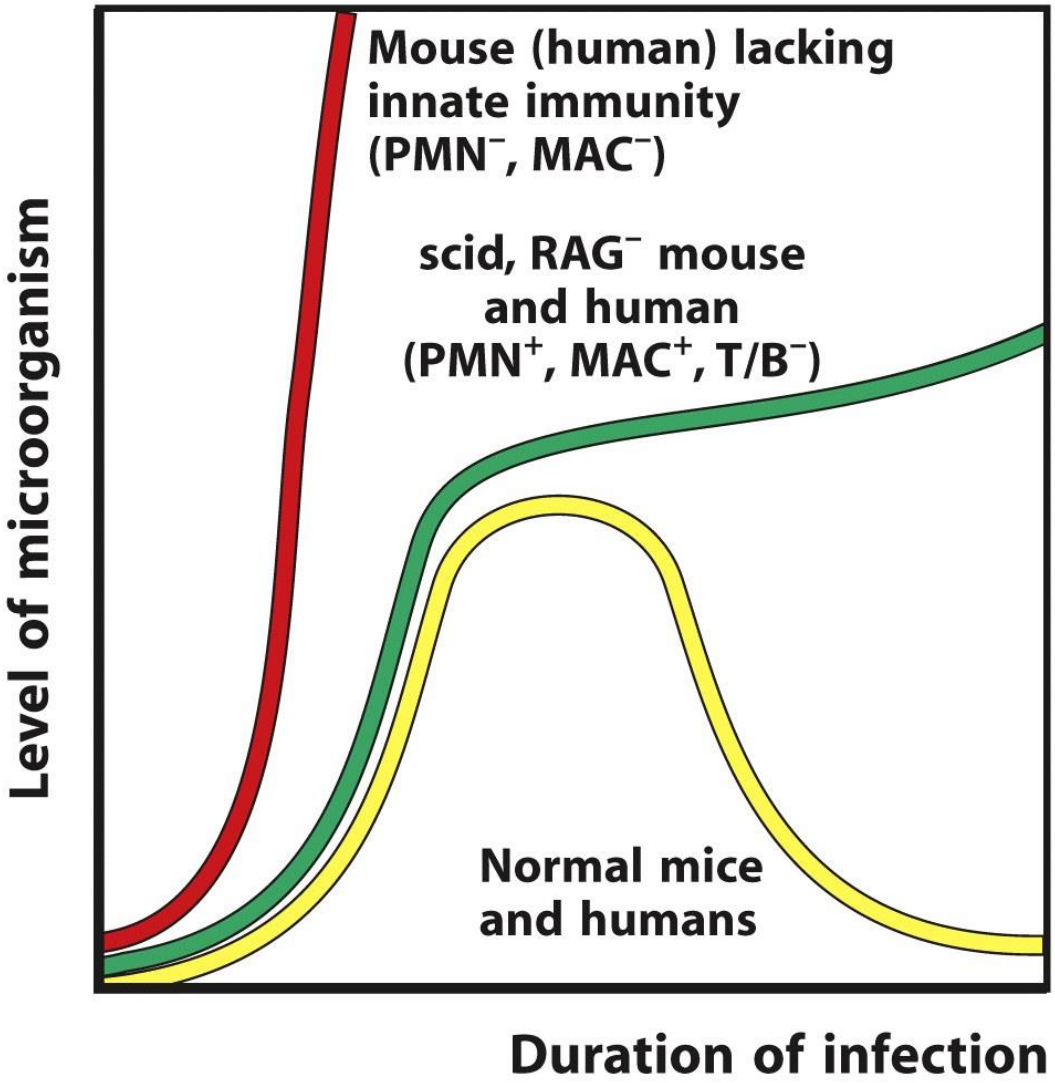


Figure 11.3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Human Immunodeficiency Syndromes

Major category	Example	Gene defect	Inheritance	Cells affected	Immune defect	Antibody levels	Common infections/ other features
Combined immunodeficiencies (CIDs) limited to the immune system	γ_c deficiency	*IL2RG*	XL	T cells, NK cells	Deficient T-cell and NK-cell development	Low	General susceptibility to opportunistic and standard pathogens
	RAG-1 or RAG-2 deficiency	*RAG1; RAG2*	AR	T cells, B cells	Deficient T- and B-cell development	Low	General susceptibility to opportunistic and standard pathogens
CIDs with defects in tissues outside the immune system	FOXN1 deficiency; Nude phenotype	*FOXN1*	AR	Thymic epithelium, T cells	Deficient T-cell development	Decreased	General susceptibility to opportunistic and standard pathogens
	Job syndrome	*STAT3*	AD	T_H17 and T_{FH} cells	Defective T_H17 and T_{FH} cell development	High IgE	Extracellular bacteria, mucocutaneous candidiasis, bone development abnormalities
Antibody deficiencies	Bruton's X-linked agammaglobulinemia (XLA)	*BTK*	XL	B cells	Absent mature B cells	Low	Pyogenic bacteria and enteroviruses
	AID deficiency	*AICDA*	AR	B cells	Defective Ig class-switching and somatic hypermutation	IgG and IgA low; IgM increased	Bacterial infections, enlarged germinal centers
	Selective IgA deficiency	*Unknown*	?	B cells	Deficient clas-switched IgA B cells	Low–absent IgA; other isotypes	Typically asymptomatic

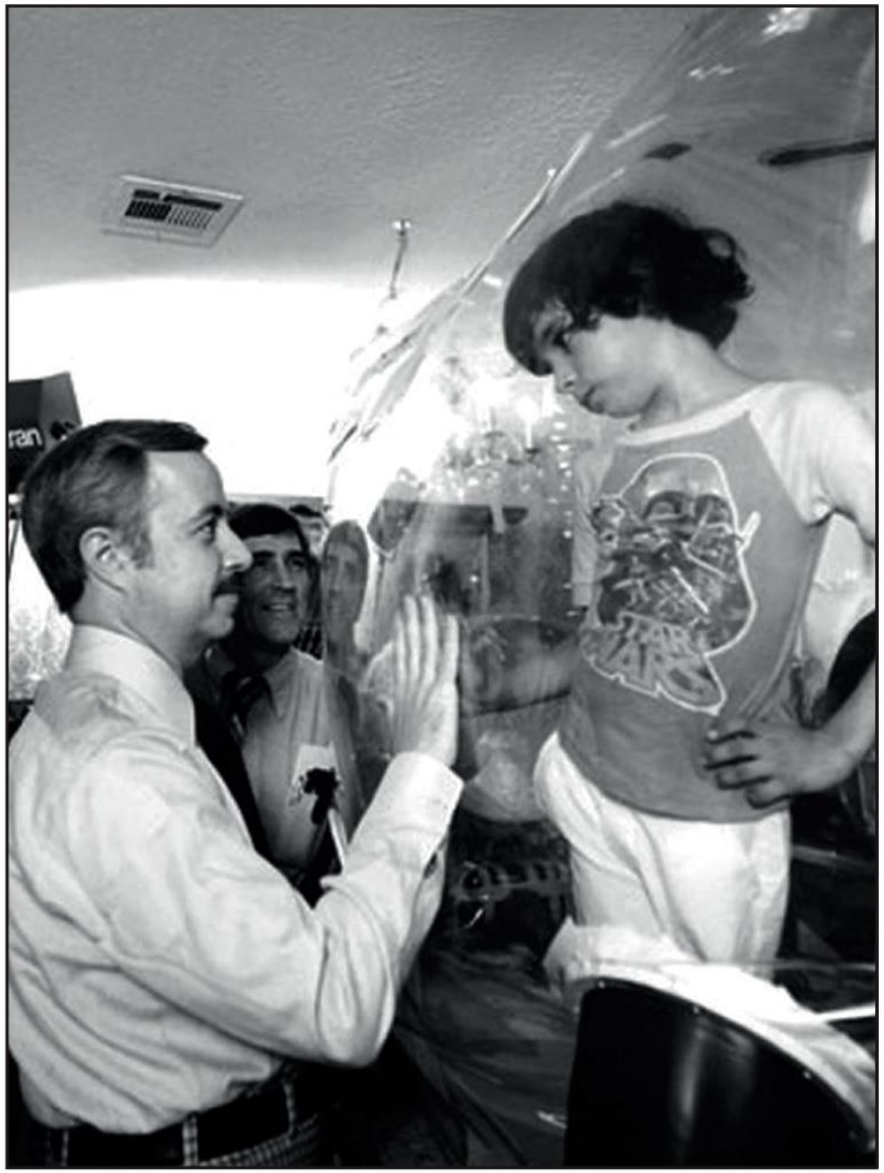
Human Immunodeficiency Syndromes

Major category	Example	Gene defect	Inheritance	Cells affected	Immune defect	Antibody levels	Common infections/ other features
Immune dysregulation	Perforin deficiency	*PRF1*	AR	CTLs and NK cells	Impaired CTL and NK-cell cytotoxicity	Normal	Fever, hepatosplenomegaly
	IL-10 deficiency	*IL10*	AR	Multiple	No IL-10	Normal	Inflammatory bowel disease (IBD)
Phagocyte defects	Elastase deficiency	*SCN1*	AD	Neutrophils	Neutrophil deficiency	Normal	Severe bacterial infections; myelodysplasia/leukemia
	GATA2 deficiency	*GATA2*	AD	Monocytes and DCs	Monocyte and DC deficiency	Normal	Susceptibility to mycobacteria, HPV, histoplasmosis; myelodysplasia/leukemia
Innate immunity defects	IL-12p40 deficiency	*IL12B*	AR	DCs, monocytes, and macrophages	IFN-γ secretion	Normal	Mycobacterial and *Salmonella* infections
	IFN-γ receptor 1 deficiency	*IFNGR1*	AR/AD	Multiple	IFN-γ signaling	Normal	Mycobacterial and *Salmonella* infections

Human Immunodeficiency Syndromes

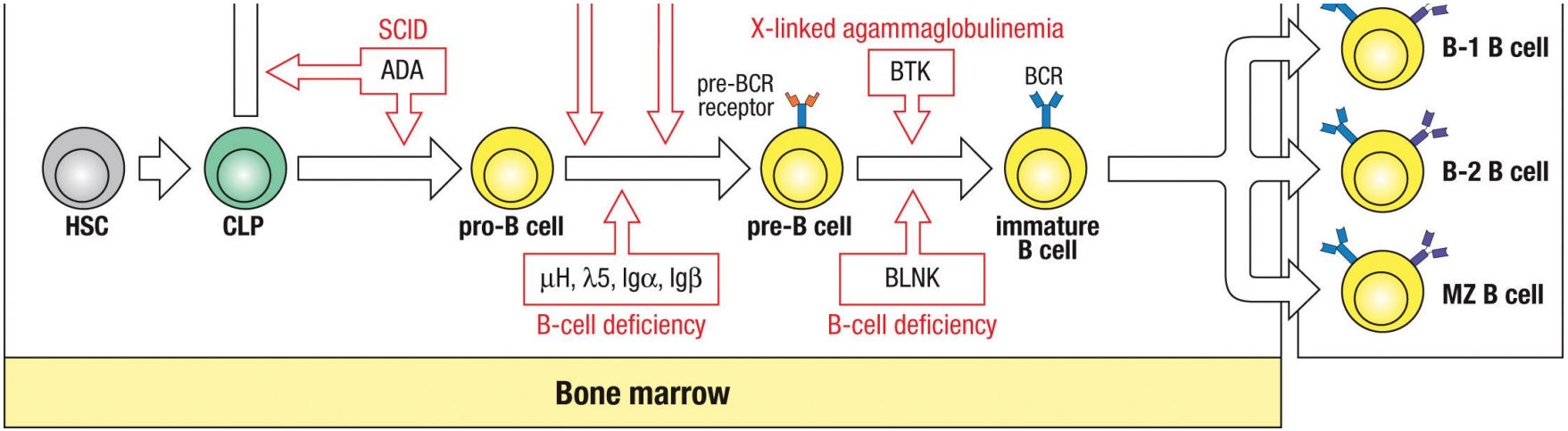
Major category	Example	Gene defect	Inheritance	Cells affected	Immune defect	Antibody levels	Common infections/ other features
Autoinflammatory disorders	Muckle–Wells syndrome	*NLRP3*	AD (GOF)	Neutrophils and monocytes	Inflammasome hyperactivity	Normal	Recurrent fever, urticaria
Complement deficiencies	C1q deficiency	*C1QA*	AR	Apoptotic cells	Deficient activation of classical complement pathway	Normal	Infections by encapsulated bacteria (e.g., *Streptococcus pneumoniae*, *Klebsiella pneumoniae*), immune- complex disease (e.g., SLE)
	MASP deficiency	*MASP2*	AR	None	Deficient activation of lectin complement pathway	Normal	Pyogenic bacteria, autoimmunity
Phenocopies of inborn errors of immunity	APECED syndrome	*AIRE*	AR	T cells	Impaired negative selection of T cells	Normal, with autoantibodies	Chronic mucocutaneous candidiasis, multiple endocrinopathies

The Boy in the Bubble

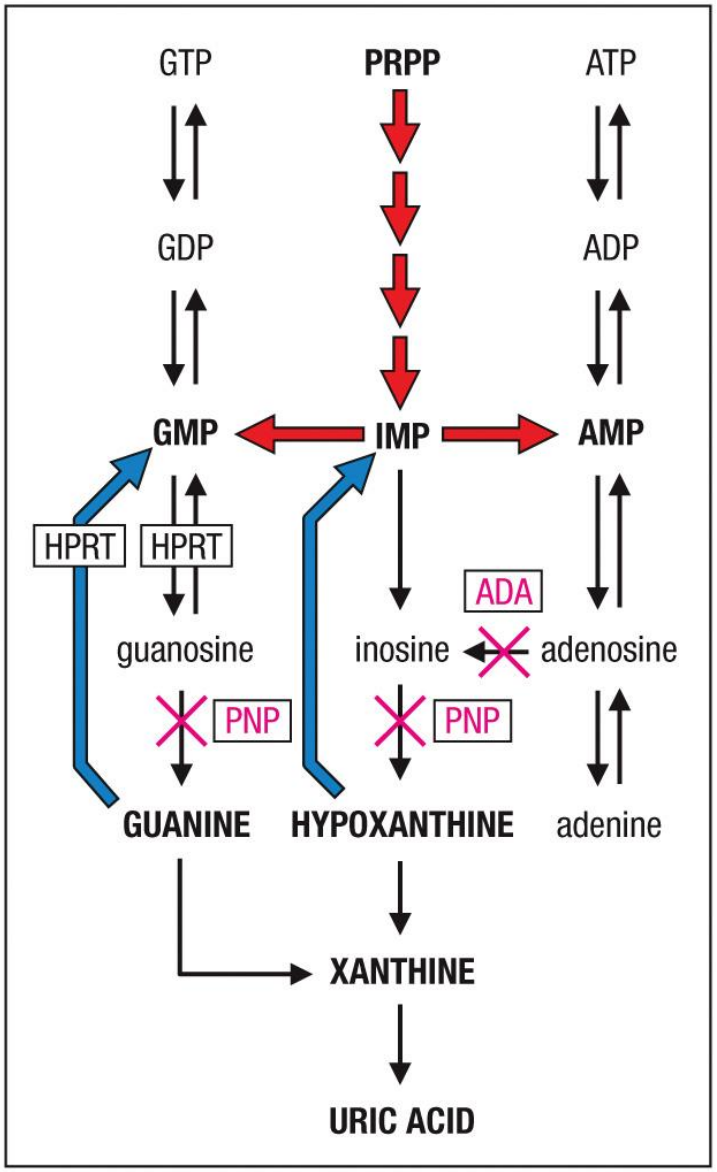


Courtesy of Carol Ann Demaret

Lymphocytes Development Defects Lead to Immune Deficiency



Purine Salvage Pathway

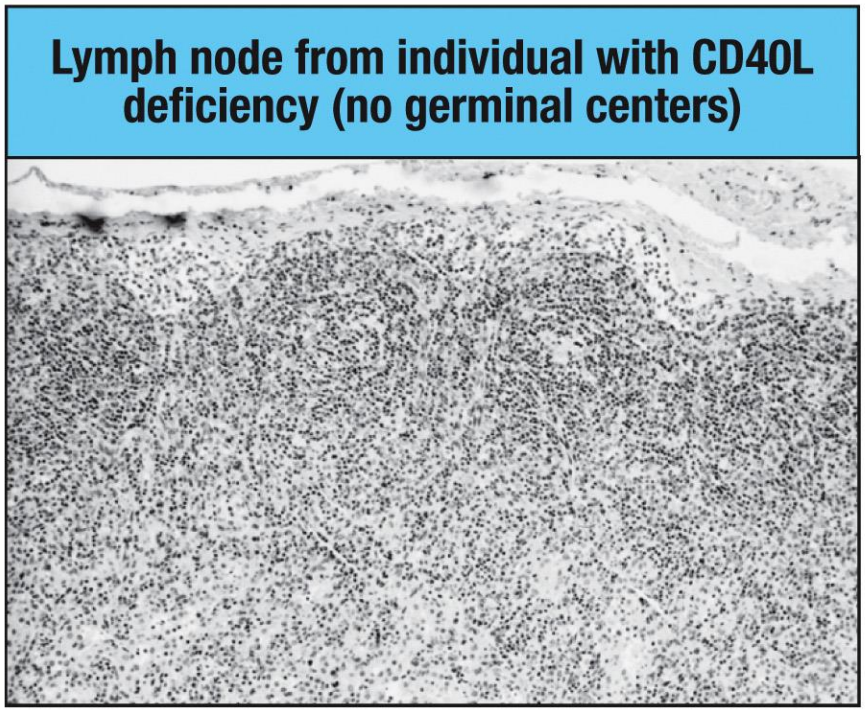


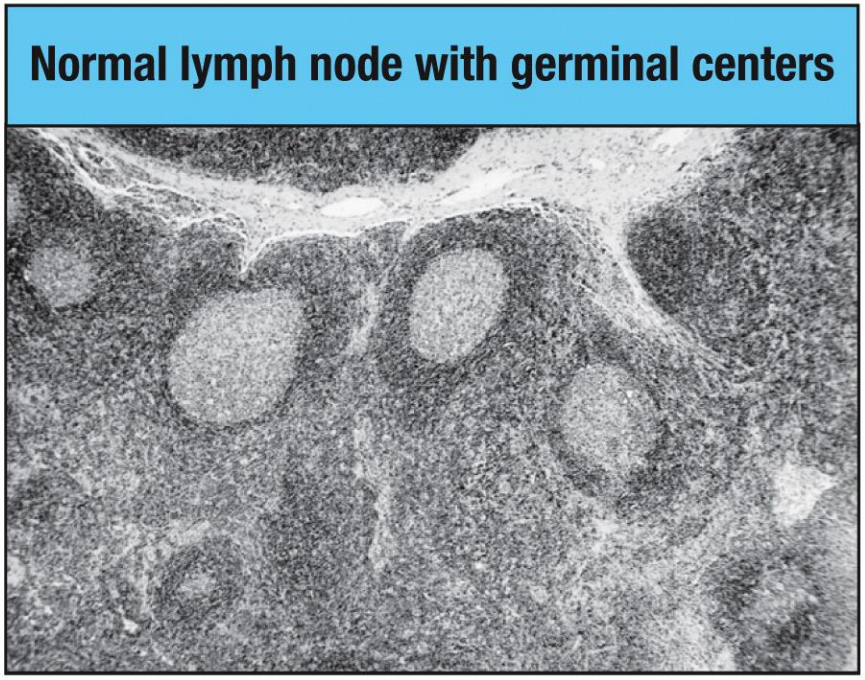
B Cell Defects

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Wiskott–Aldrich syndrome	X-linked; defective WASp gene	Defective anti-polysaccharide antibody, impaired T-cell activation responses, and T_{reg} dysfunction	Encapsulated extracellular bacteria Herpesvirus infections (e.g., HSV, EBV)
X-linked agamma-globulinemia	Loss of BTK tyrosine kinase	No B cells	Extracellular bacteria, enteroviruses
Hyper-IgM syndrome	CD40 ligand deficiency CD40 deficiency NEMO (IKK) deficiency	No isotype switching and/or no somatic hypermutation plus T-cell defects	Extracellular bacteria *Pneumocystis jirovecii* *Cryptosporidium parvum*
Hyper-IgM syndrome— B-cell intrinsic	AID deficiency UNG deficiency	No isotype switching +/– normal somatic hypermutation	Extracellular bacteria
Hyper-IgE syndrome (Job's syndrome)	Defective STAT3	Block in T_H17 cell differentiation Elevated IgE	Extracellular bacteria and fungi
Common variable immunodeficiency	Mutations in TACI, ICOS, CD19, etc.	Defective IgA and IgG production	Extracellular bacteria
Selective IgA	Unknown; MHC-linked	No IgA synthesis	Respiratory infections

Figure 13.1 (part 2 of 3) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Results of B Cell Defects

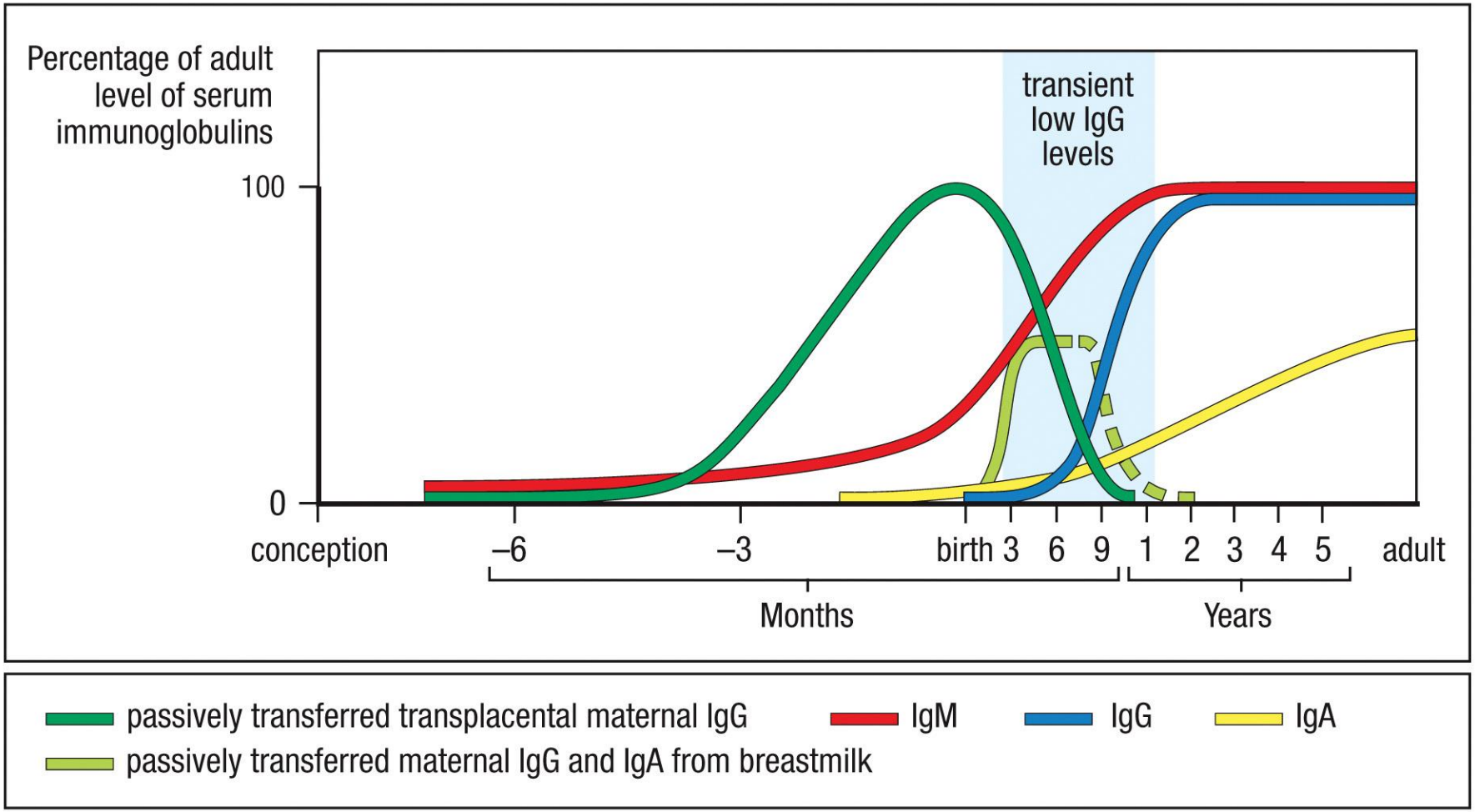




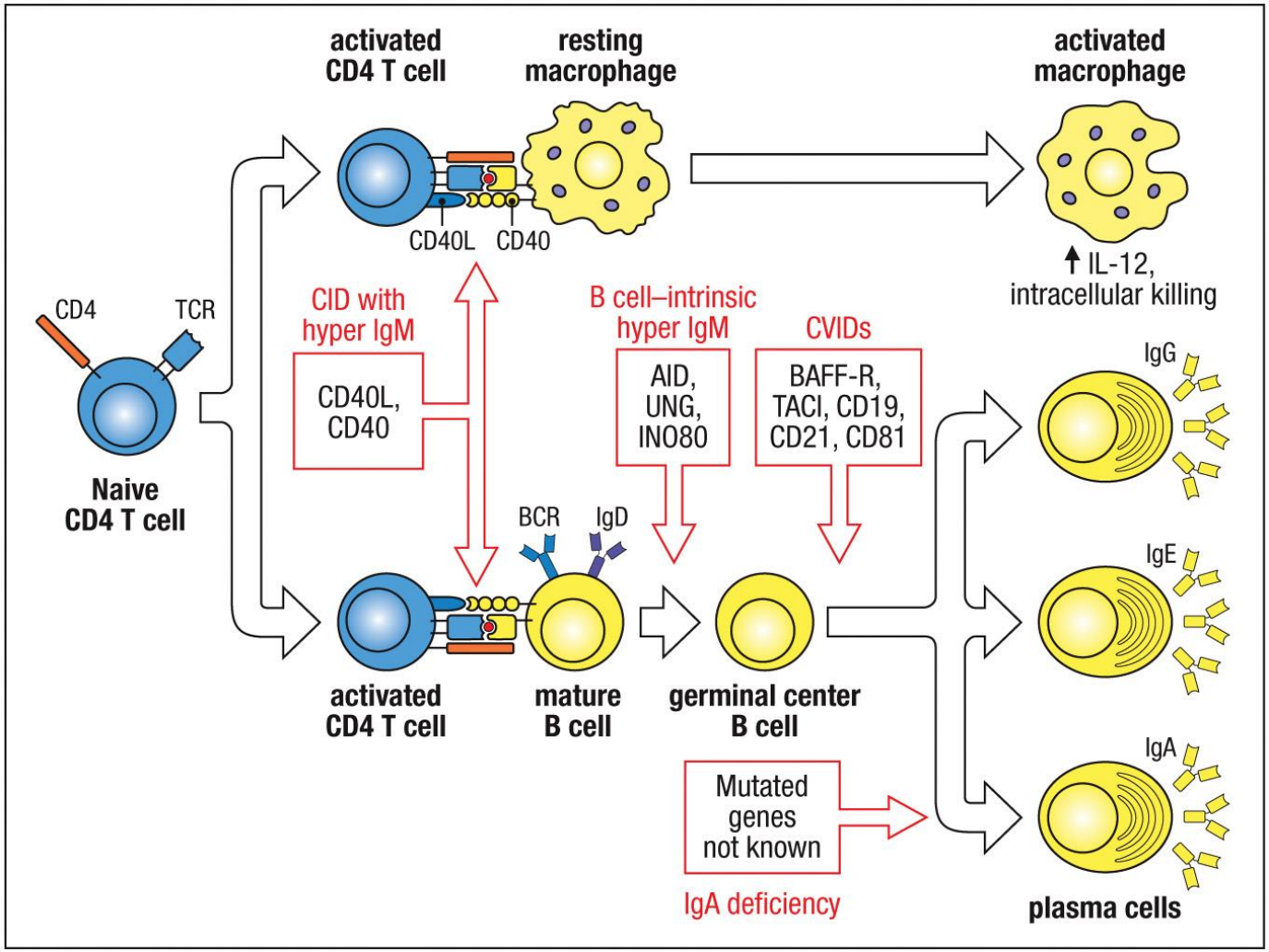
(both): Dr. Raif Geha

Loss of T cell help: Susceptible to extracellular bacteria an d some viral infection

Transient IgG Deficiency in Newborns



Lymphocytes Activation Defects Lead to Immune Deficiency



CVID, common variable immune deficiency

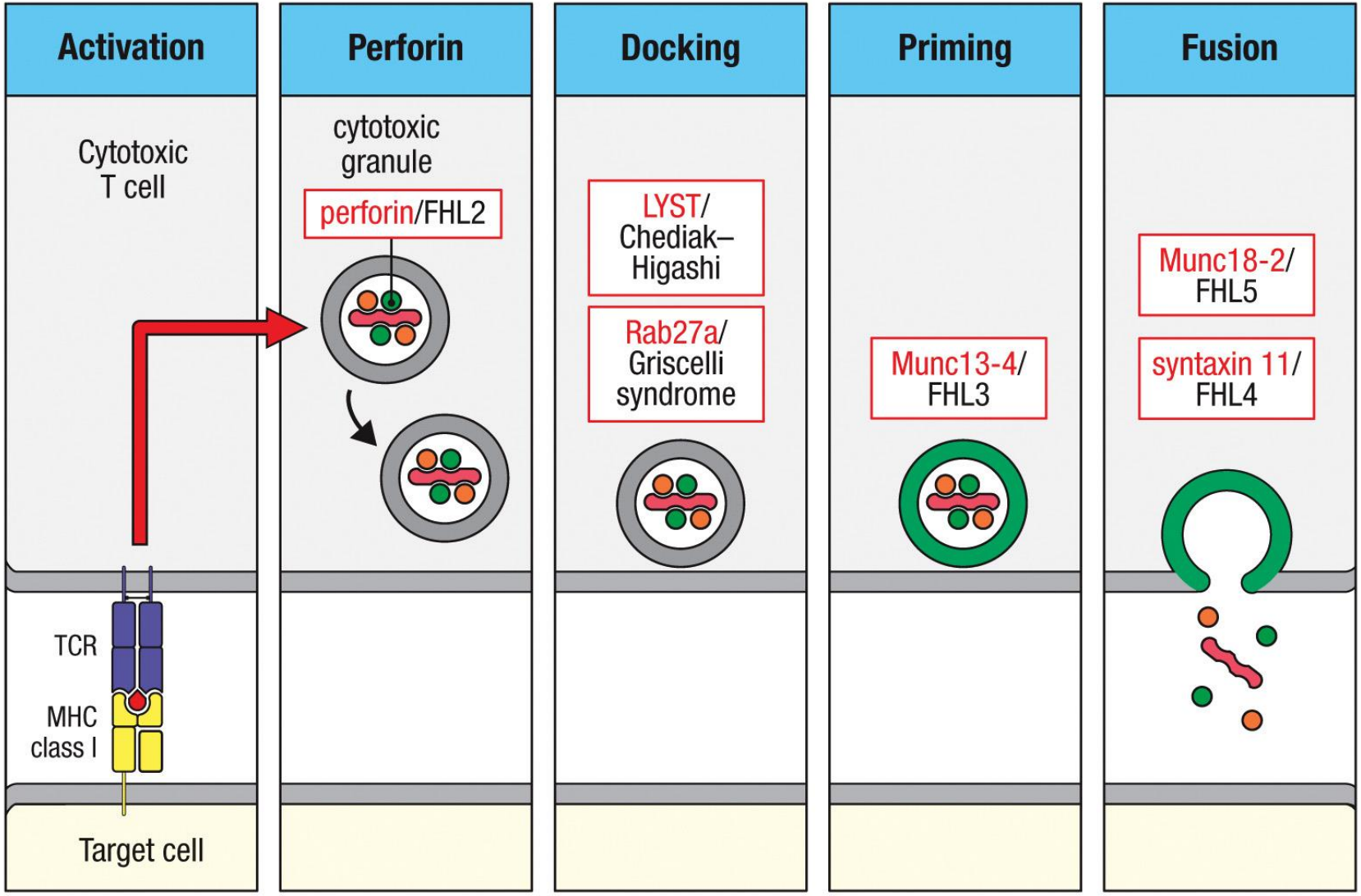
Results of T Cell Defects

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Severe combined immune deficiency	See text and Fig. 13.2		General
DiGeorge's syndrome	Thymic aplasia	Variable numbers of T cells	General
MHC class I deficiency	Mutations in TAP1, TAP2, and tapasin	No CD8 T cells	Chronic lung and skin inflammation
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General

Figure 13.1 (part 1 of 3) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

- CD 4 T cells activates macrophages, dendritic cells and B cells

Defects in Cytotoxic T Cell Function



Defects in Innate Immunity

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Phagocyte deficiencies	Many different	Loss of phagocyte function	Extracellular bacteria and fungi
Complement deficiencies	Many different	Loss of specific complement components	Extracellular bacteria especially *Neisseria* spp.

Defects in Phagocytic Cells Are Associated with Persistence of Bacterial Infection

Disease	Examples	Gene defect	Inheritance	Immune defect	Common infections
Severe congenital neutropenia	Elastase-2 deficiency (SCN1)	*ELANE*	AD	Neutrophil deficiency	Severe pyogenic bacterial infections
	GFI-1 deficiency (SCN2)	*GFI1*	AD		Severe pyogenic bacterial infections
	HAX1 deficiency (SCN3, or Kostmann's disease)	*HAX1*	AR		Severe pyogenic bacterial infections
	G6PC3 deficiency (SCN4)	*G6PC3*	AR		Severe pyogenic bacterial infections
Leukocyte adhesion deficiency	β2 integrin deficiency (LAD-1)	*ITGB2*	AR	Defective leukocyte extravasation	Ulcerating skin infections without pus
	GDP-fucose transporter deficiency (LAD-2)	*SLC35C1*	AR		Recurrent bacterial infections
	Kindlin-3 deficiency (LAD-3)	*FERMT3*	AR		Severe bacterial infections
TLR/IL-1R signaling defects	MyD88 deficiency	*MYD88*	AR	Impaired TLR and IL-1 receptor signaling	Noninvasive bacterial infections, skin and respiratory tract
	IRAK4 deficiency	*IRAK4*	AR		Noninvasive bacterial infections, skin and respiratory tract
	TLR-3 deficiency	*TLR3*	AD or AR	Impaired types I and III interferon responses	Herpes simplex and varicella-zoster encephalitis
	TRAF3 deficiency	*TRAF3*	AD		Herpes simplex and varicella-zoster encephalitis
Non-TLR PRR signaling defect	CARD9 deficiency	*CARD9*	AR	Defective phagocyte recognition of fungi; impaired T_H17 response	Invasive fungal infections
Chronic granulomatous disease	X-linked CGD	*CYBB*	XL	Impaired intracellular killing in neutrophils and monocyte/macrophages	Severe, recurrent bacterial infections of barrier tissues

Leukocyte Adhesion Deficiency

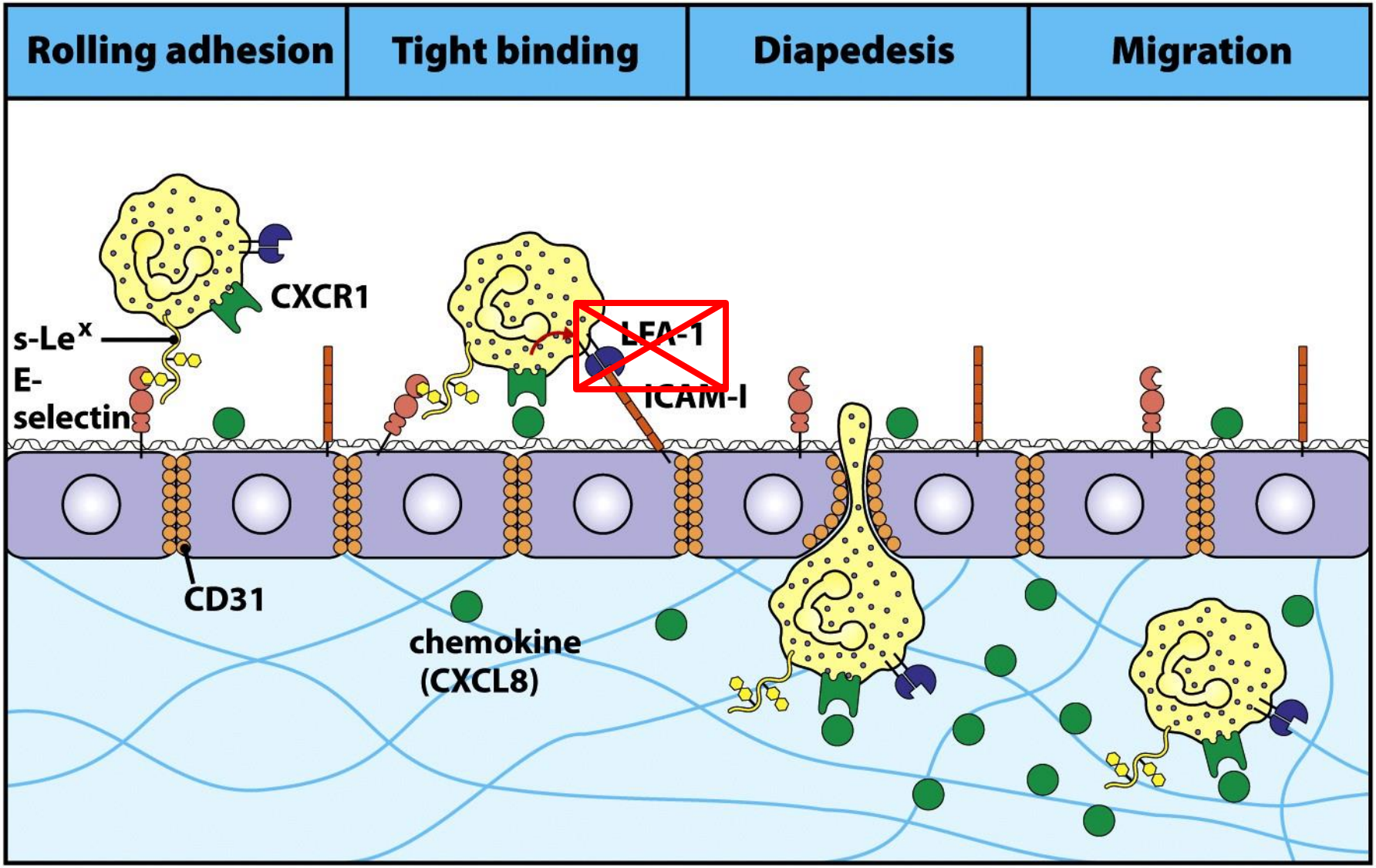
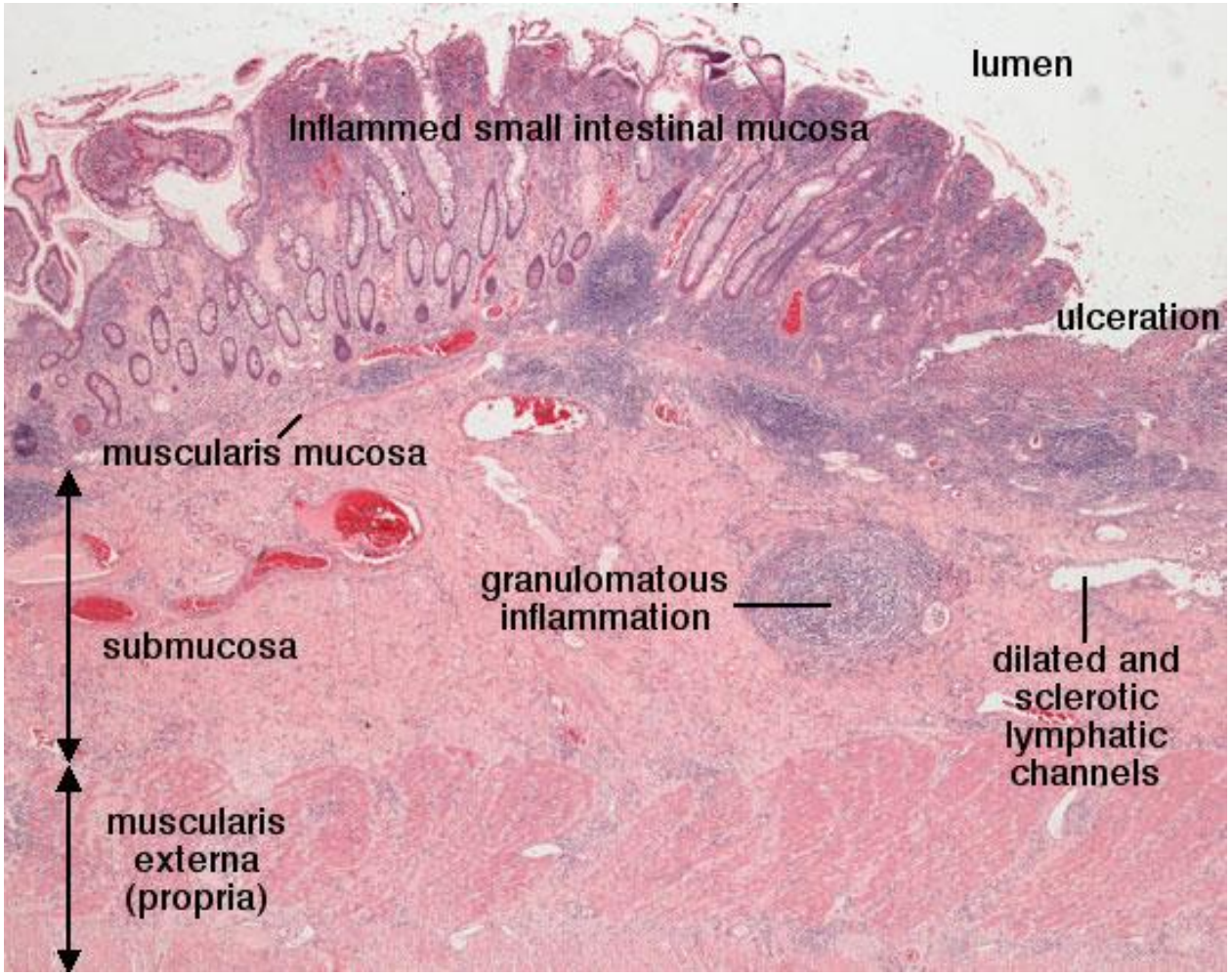


Figure 3-1 part 2 of 2 Case Studies in Immunology, 5ed. (© Garland Science 2008)

Granuloma-Defect Killing



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Complement Deficiency

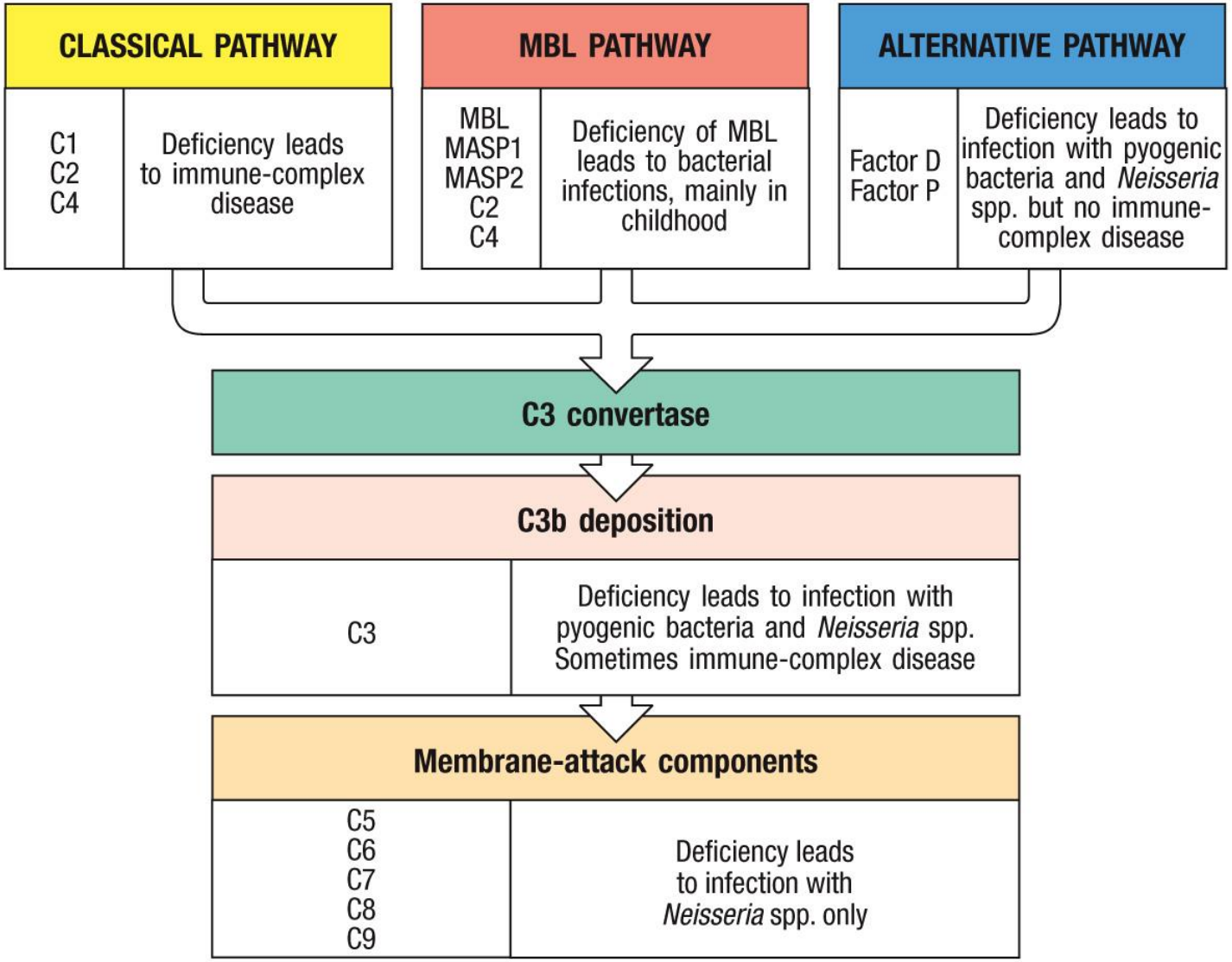


Figure 13.11 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Complement Deficiency

Complement protein	Effects of deficiency
C1, C2, C4	Immune-complex disease
C3	Susceptibility to encapsulated bacteria
C5–C9	Susceptibility to *Neisseria*
Factor D, Factor P (properdin)	Susceptibility to encapsulated bacteria and *Neisseria* but no immune-complex disease
Factor I	Similar effects to deficiency of C3
MCP, factor I, or factor H	Atypical hemolytic uremic syndrome
Polymorphisms in factor H	Age-related macular degeneration
DAF, CD59	Autoimmune-like conditions, including paroxysmal nocturnal hemoglobinuria
C1INH	Hereditary angioedema (HAE)

Immune Complex is Removed in the Spleen

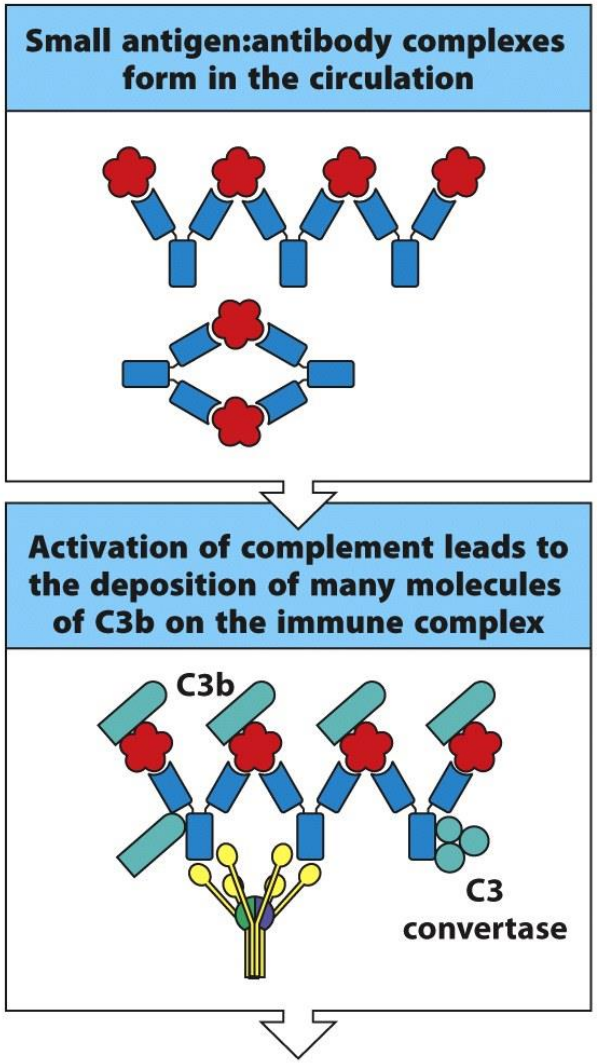


Figure 10.31 part 2 of 4 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

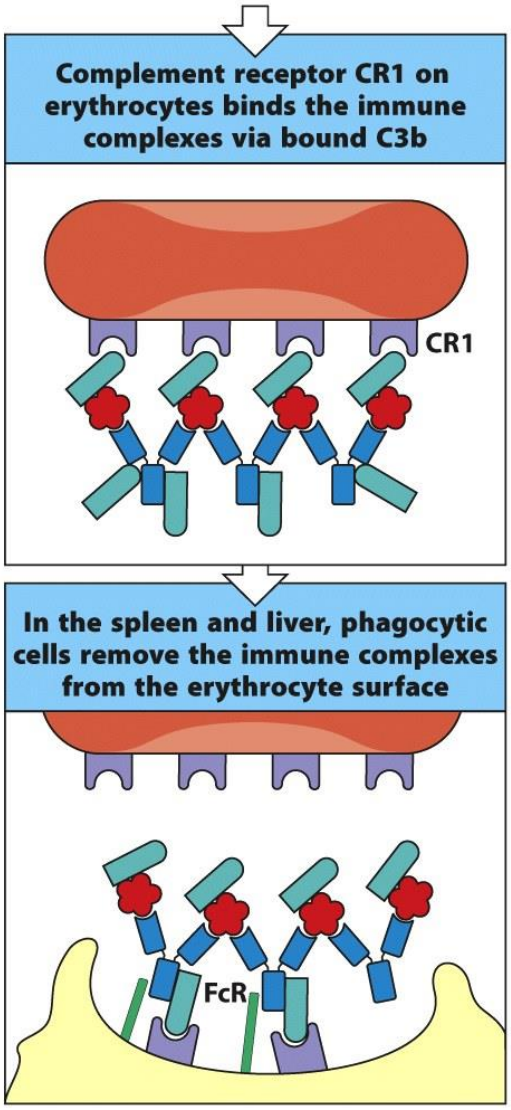


Figure 10.31 part 4 of 4 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

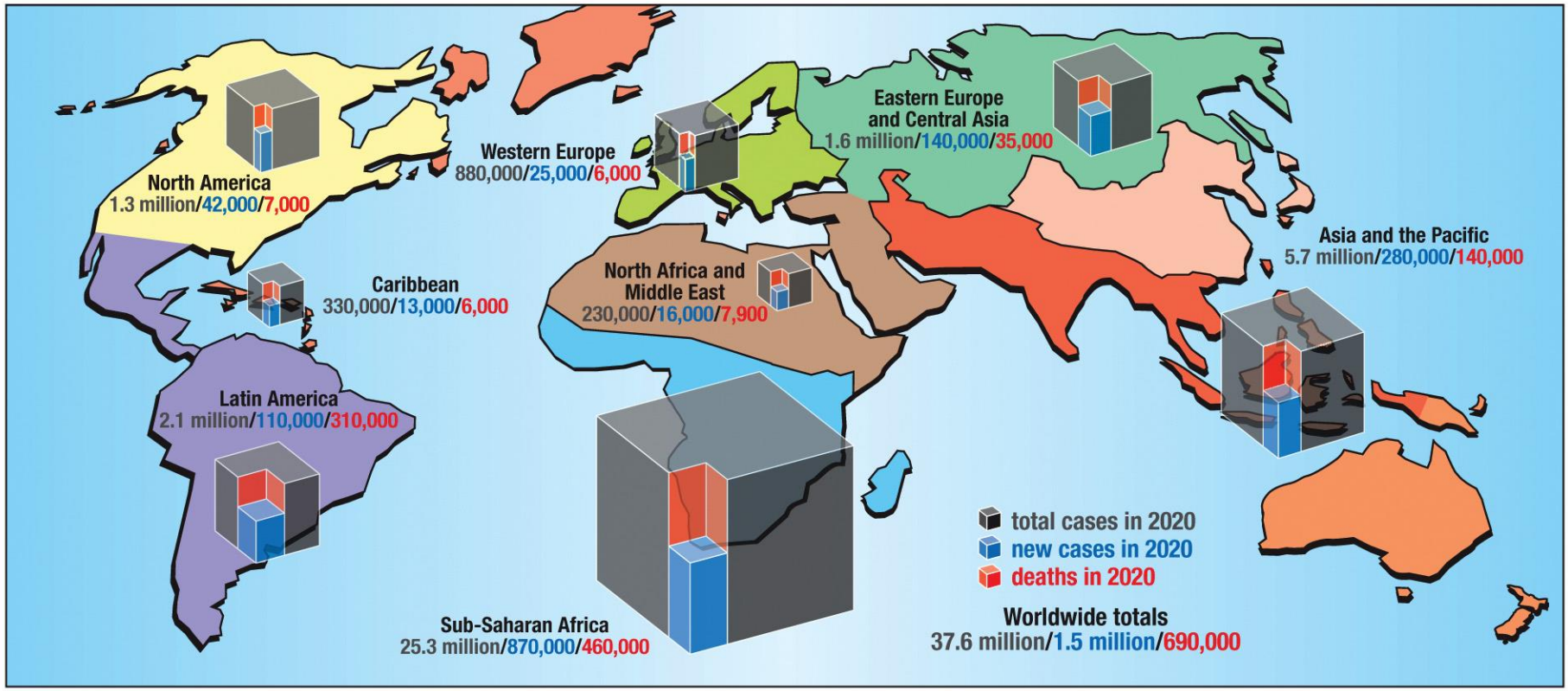
Question

- Defects in which gene results in the most severe immune deficiency?
- A) MHC I
- B) MHC II
- C) AID
- D) C3

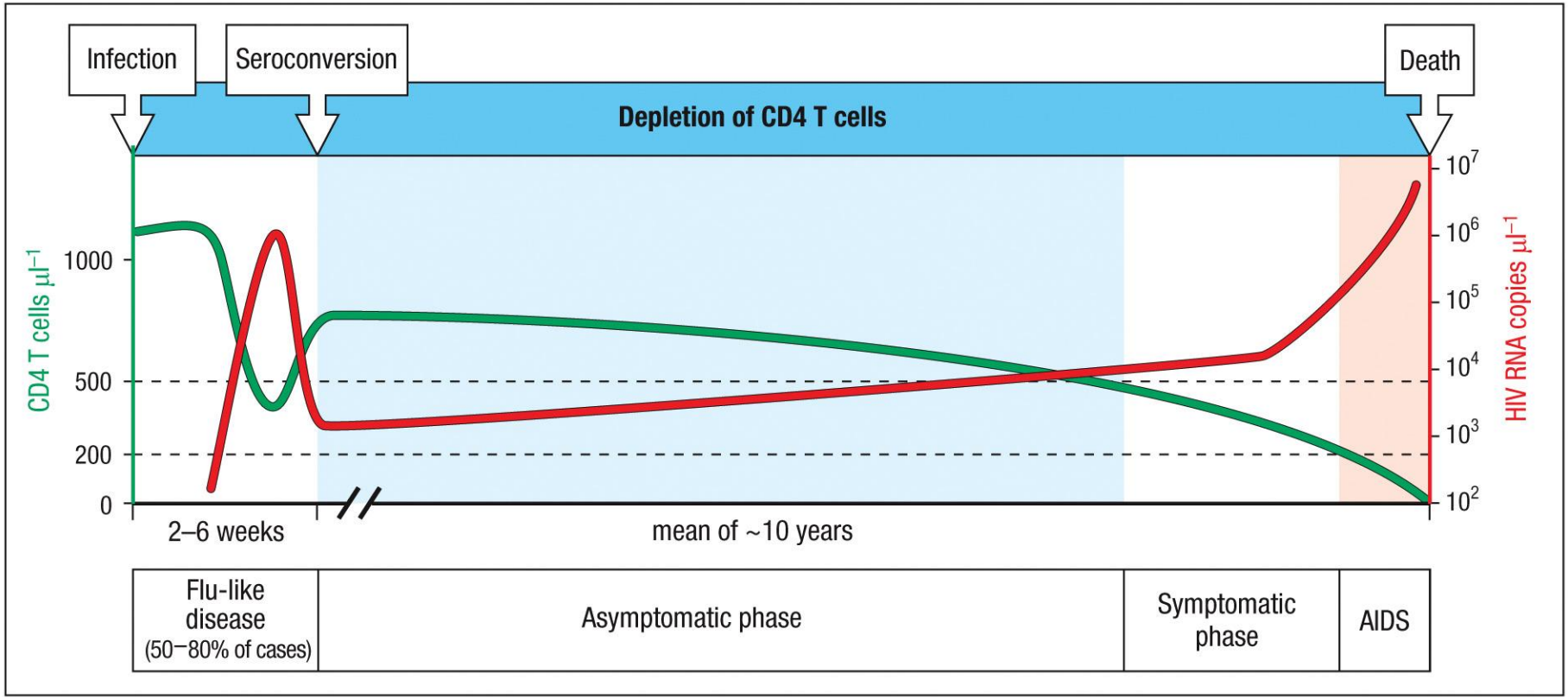
Outline

- Primary Immunodeficiency
  - T cells
  - B cells
  - Innate Immunity
- Acquired Immunodeficiency
  - HIV/AIDS

Acquired Immune Deficiency Syndrome (AIDS)



Course of Untreated HIV Infection

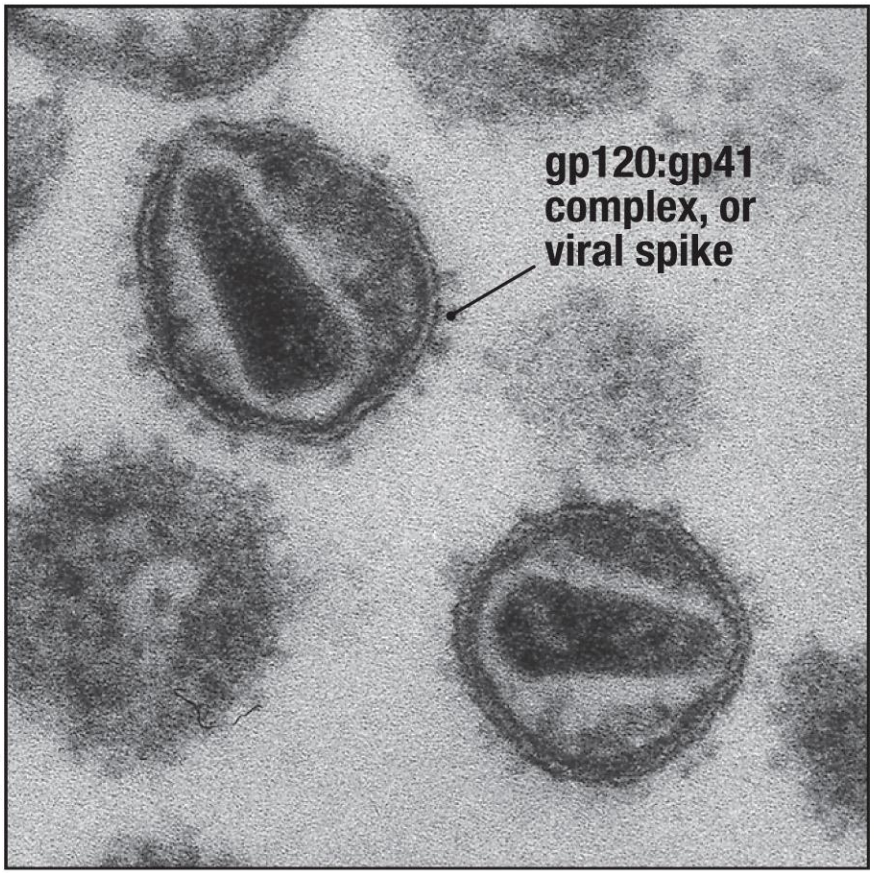


Opportunistic Infections and Malignancies Are the Cause of Death of Patients with AIDS

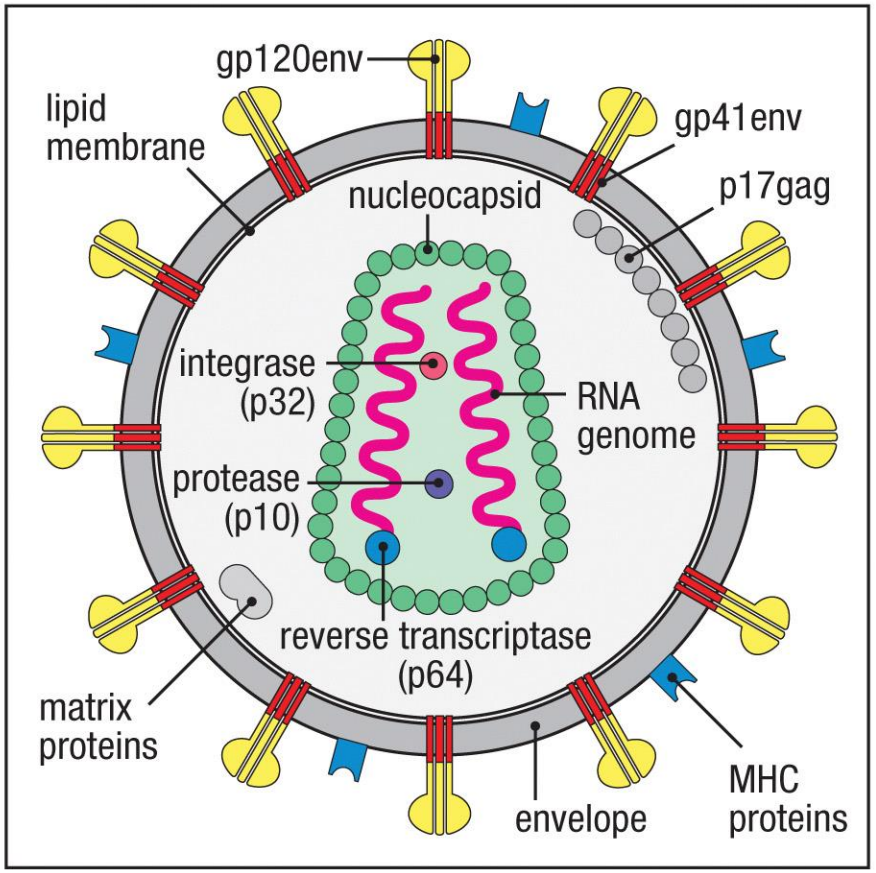
Infections	
Parasites	*Toxoplasma* spp. *Cryptosporidium* spp. *Leishmania* spp. *Microsporidium* spp.
Intracellular bacteria	*Mycobacterium tuberculosis* *Mycobacterium avium intracellulare* *Salmonella* spp.
Fungi	*Pneumocystis jirovecii* *Cryptococcus neoformans* *Candida* spp. *Histoplasma capsulatum* *Coccidioides immitis*
Viruses	Herpes simplex Cytomegalovirus varicella-zoster

Malignancies
Kaposi's sarcoma – (HHV8) Non-Hodgkin's lymphoma, including EBV-positive Burkitt's lymphoma Primary lymphoma of the brain

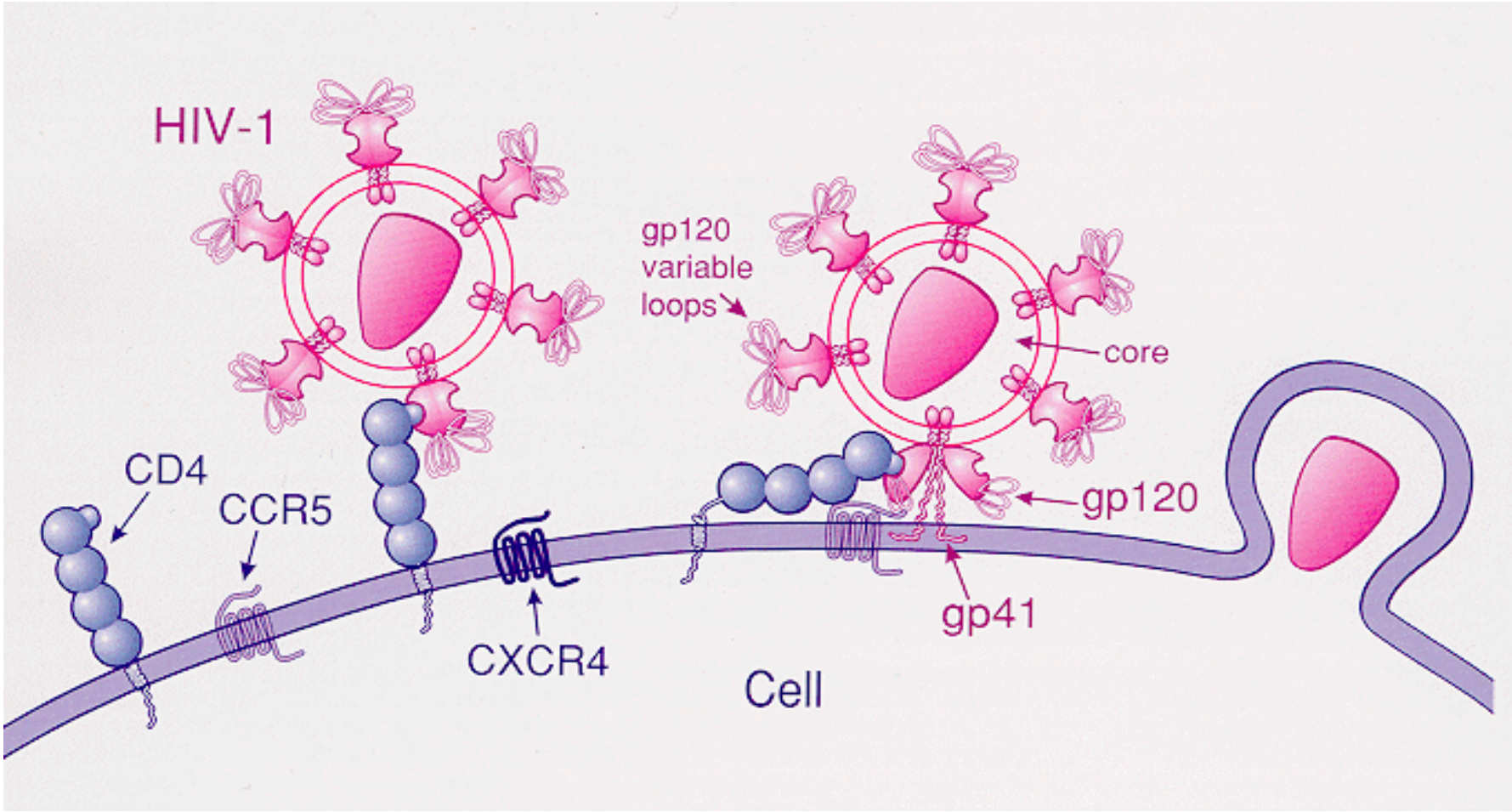
HIV Structure



Photograph courtesy of Dr. Hans Gelderblom

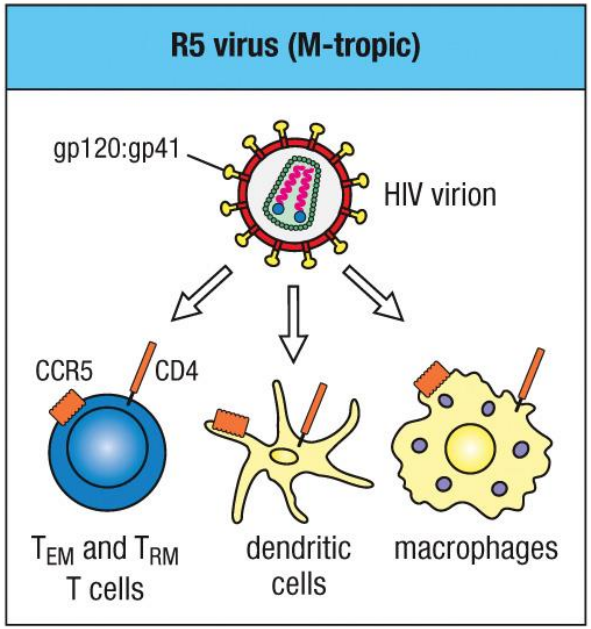


Cellular Tropism of HIV Is Determined by Expression of CCR5 and CXCR4 Receptors

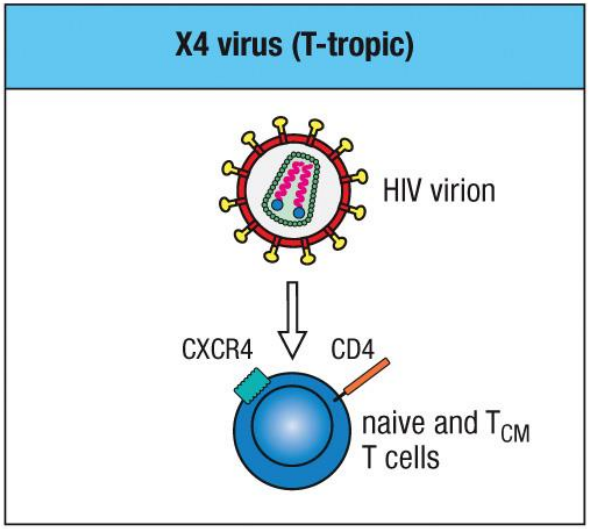


http://scienceblogs.com/denialism/HIV_attachment.gif

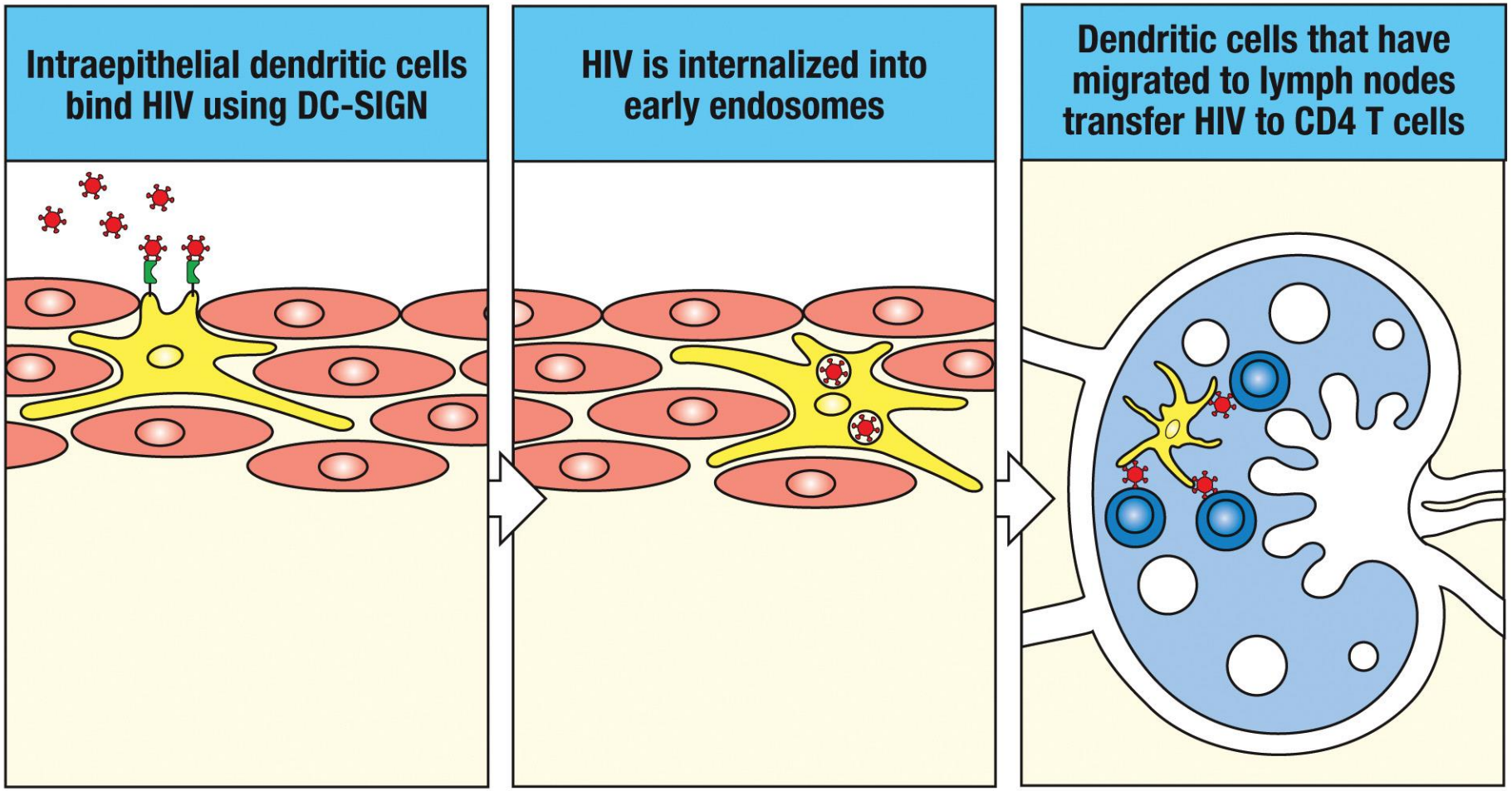
HIV Tropism


R5 virus (M-tropic)
gp120:gp41
HIV virion
CCR5
CD4
T_{EM} and T_{RM} T cells
dendritic cells
macrophages

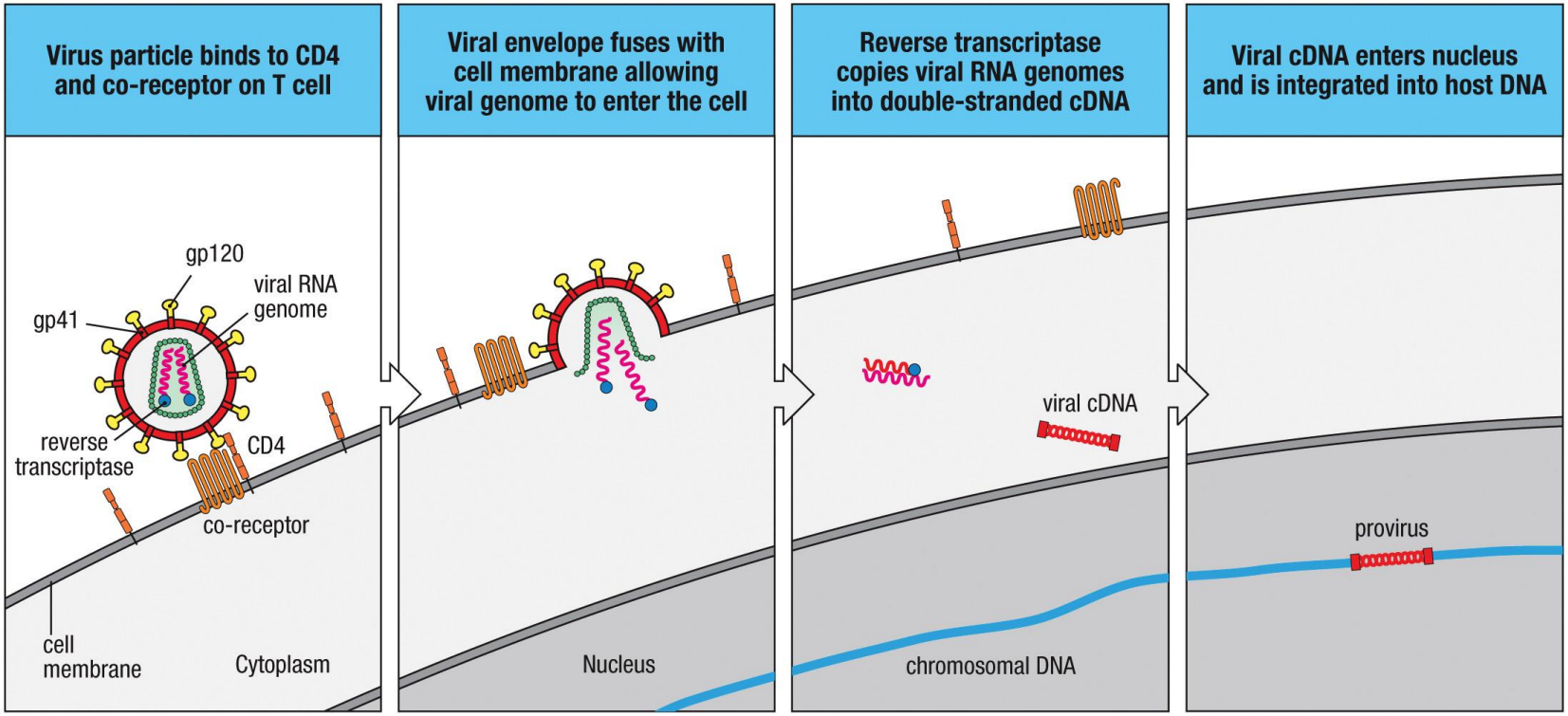

HIV virions infecting T cell
NIAID


X4 virus (T-tropic)
HIV virion
CXCR4
CD4
naive and T_{CM} T cells

HIV Enters Through Mucosal Surfaces

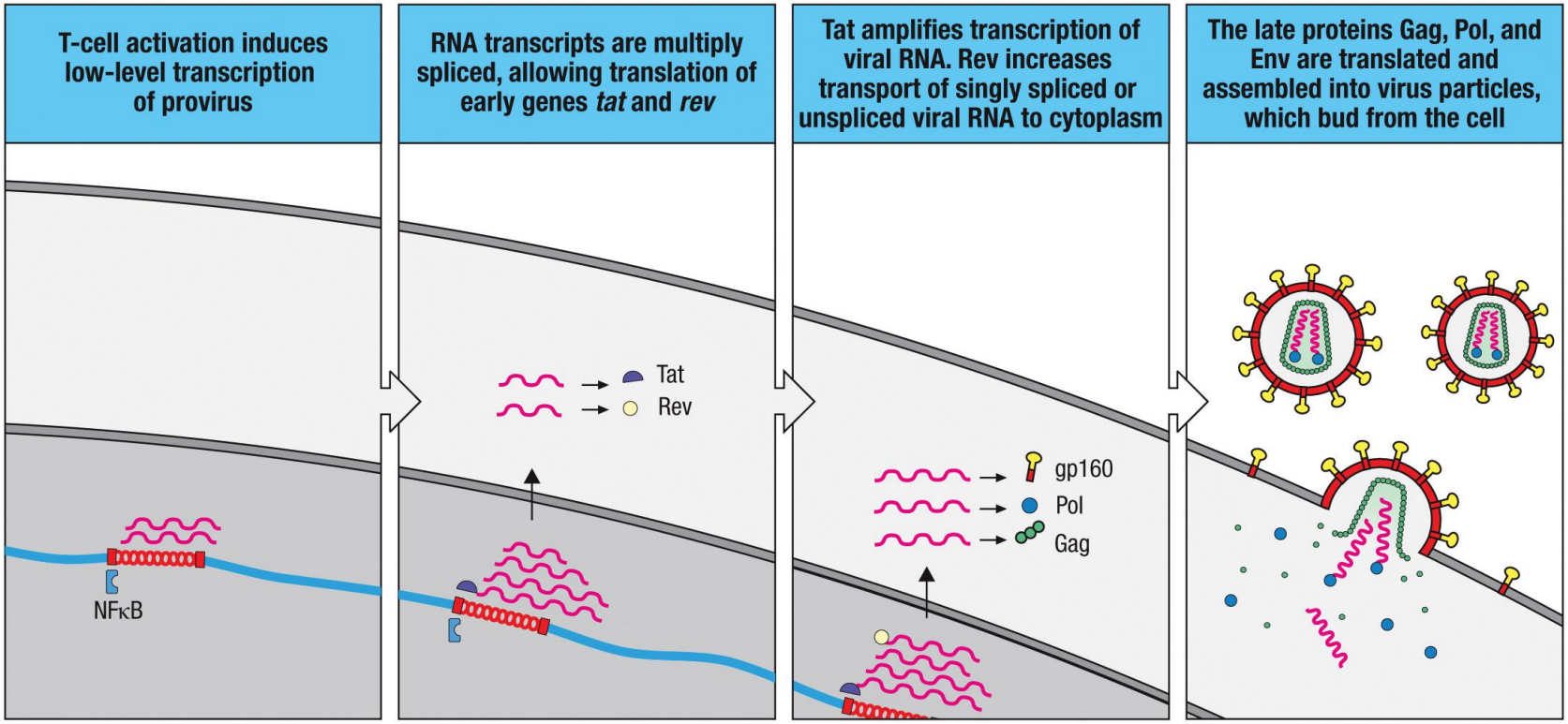


The Life Cycle of HIV



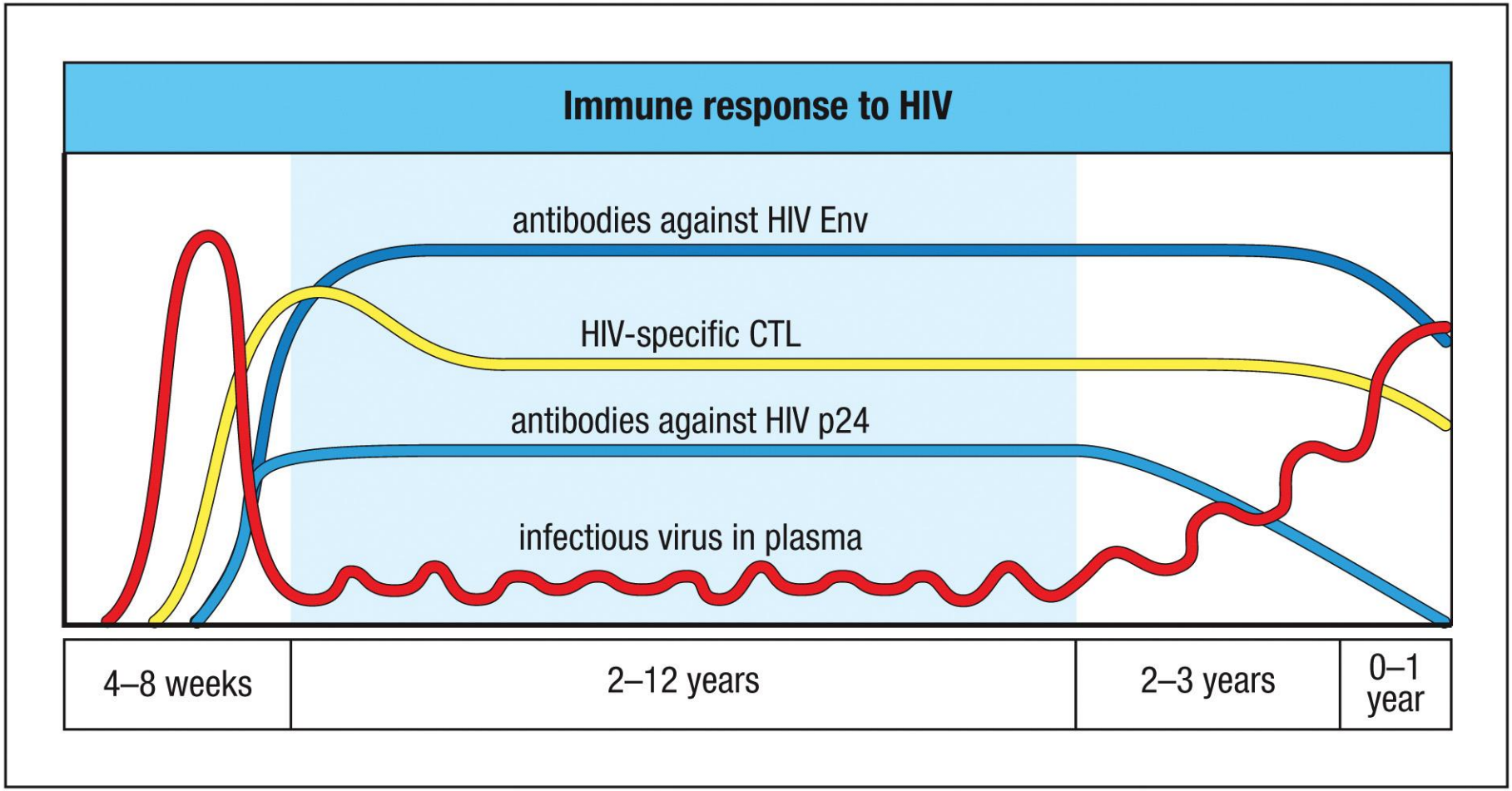
HIV can latently infect cells

The Life Cycle of HIV

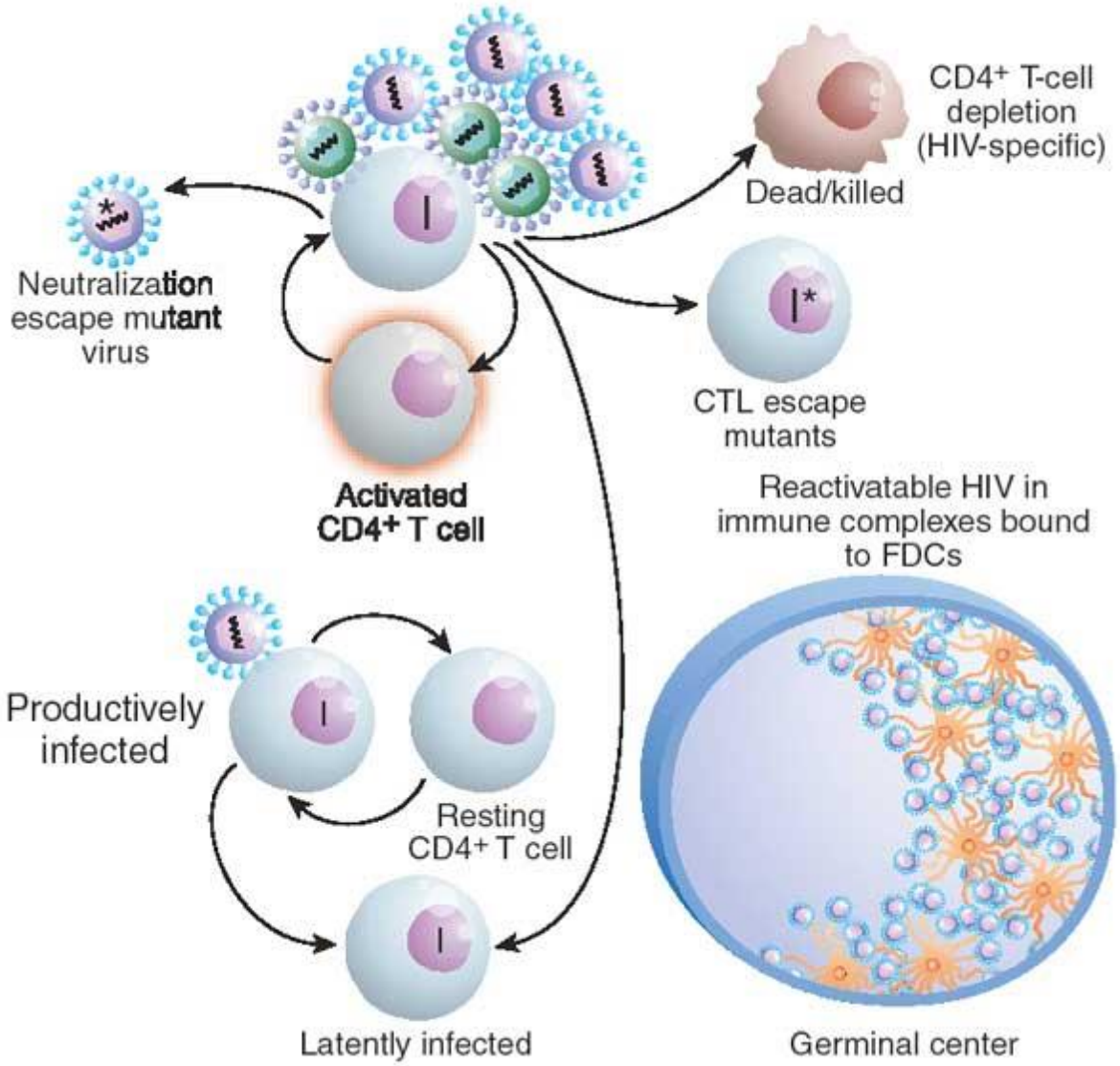


HIV replication requires activation of infected cells

HIV Evades Host Immune Responses

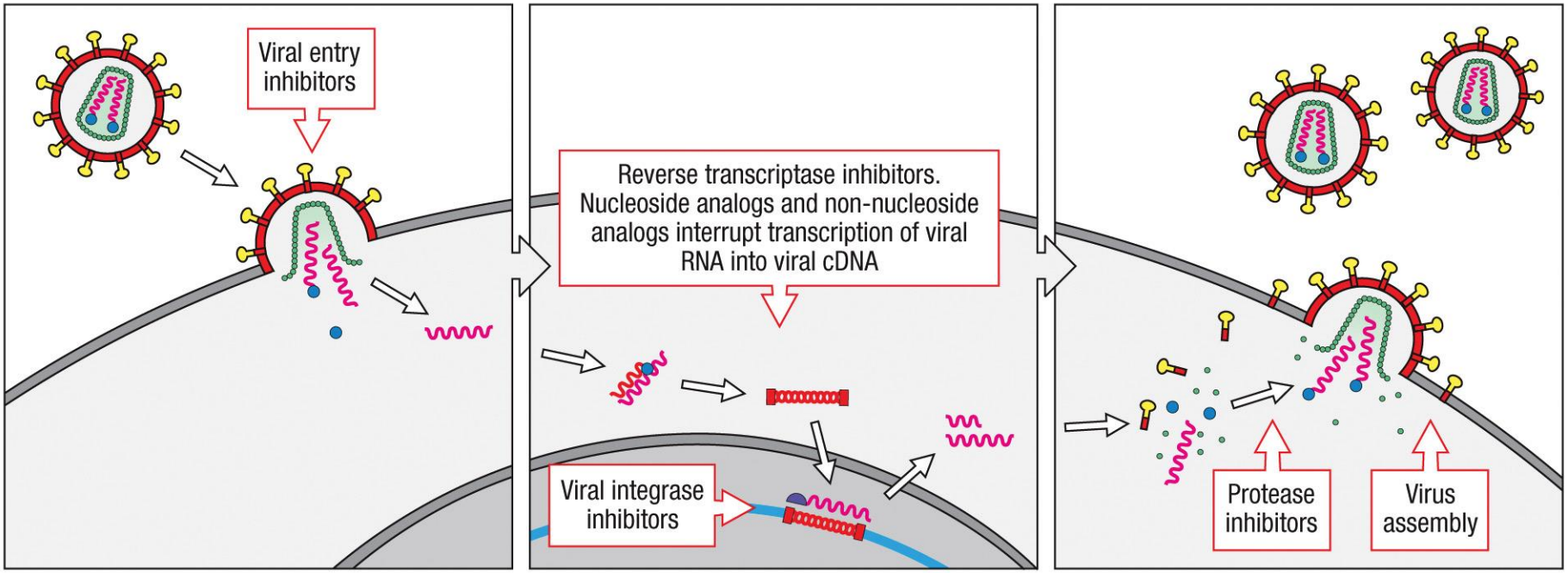


Lymphoid Tissue is the Major Reservoir of HIV Infection

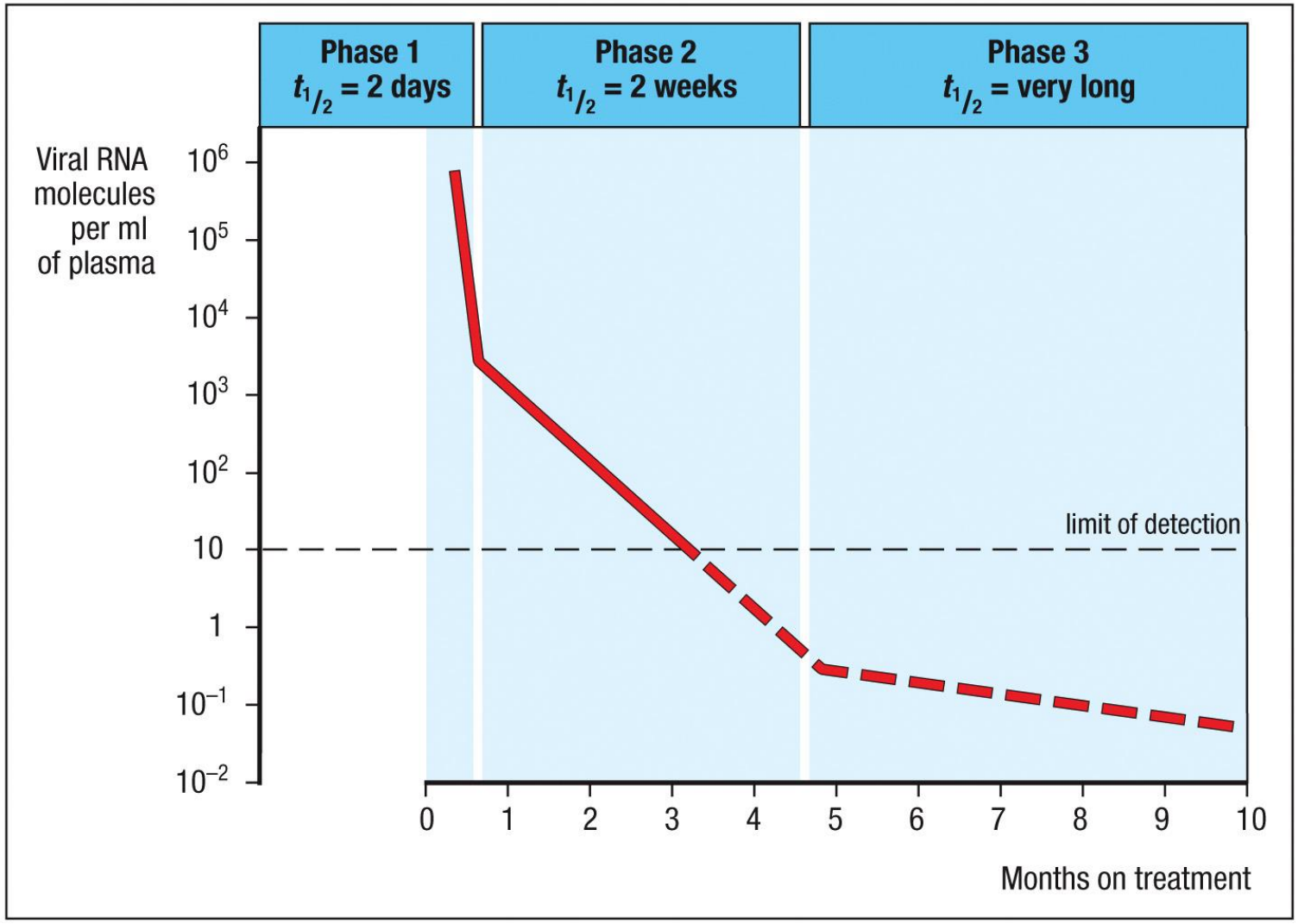


Nature Medicine 9, 847 - 852 (2003)

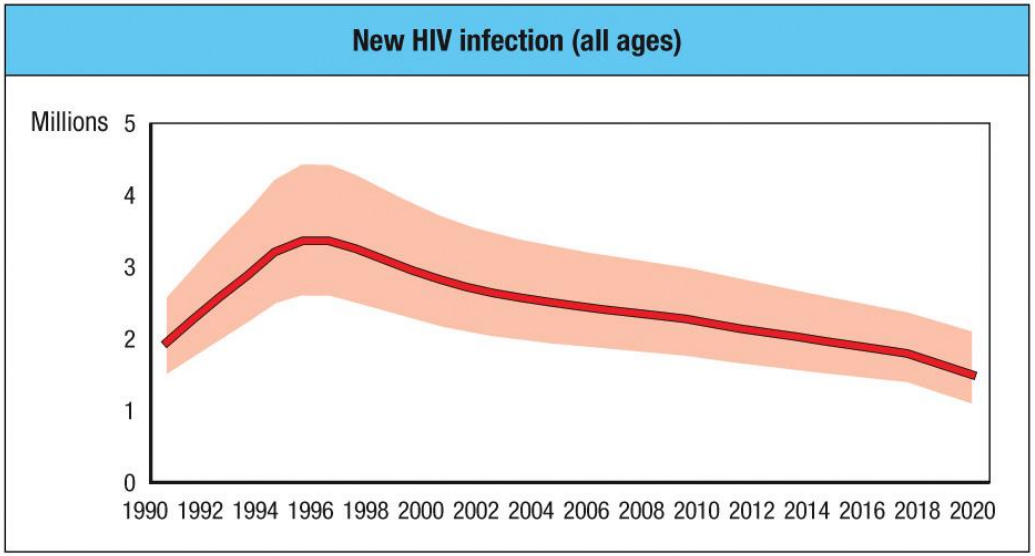
Strategies to Combat HIV Infection

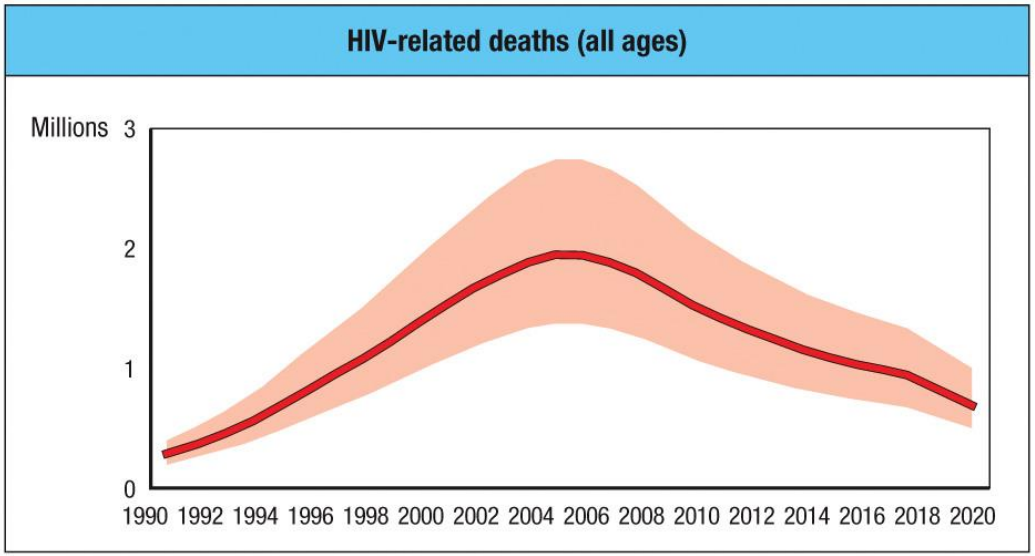


Success of Anti-Retroviral Therapy



Success of Anti-Retroviral Therapy





Why is HIV So Hard to Control?

- Kill CD4 T cells
  - The cells required to control infection
- High mutation rates
  - Combination drugs
- Latent infection
  - Most effectively controlled by blocking colonization
    - Entry blocker
    - Vaccine (various strains? neutralizing antibodies)
    - Prevent the spread of HIV

Bone Marrow Transplant As a Treatment for AIDS

Genes that influence progression to AIDS				
Gene	**Allele**	**Mode**	**Effect**	**Mechanism of action**
HIV entry				
CCR5	Δ32	Recessive	Prevents infection	Knockout of CCR5 expression
		Dominant	Prevents lymphoma (L)	Decreases available CCR5
			Delays AIDS	
	P1	Recessive	Accelerates AIDS (E)	Increases CCR5 expression
CCR2	I64	Dominant	Delays AIDS	Interacts with and reduces CXCR4
CCL5	In1.1c	Dominant	Accelerates AIDS	Decreases CCL5 expression
CXCL12	3′A	Recessive	Delays AIDS (L)	Impedes CCR5–CXCR4 transition (?)
CXCR6	E3K	Dominant	Accelerates *P. jirovecii* pneumonia (L)	Alters T-cell activations (?)
CCL2-CCL7-CCL11	H7	Dominant	Enhances infection	Stimulates immune response (?)

Figure 13.35 (part 1 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)