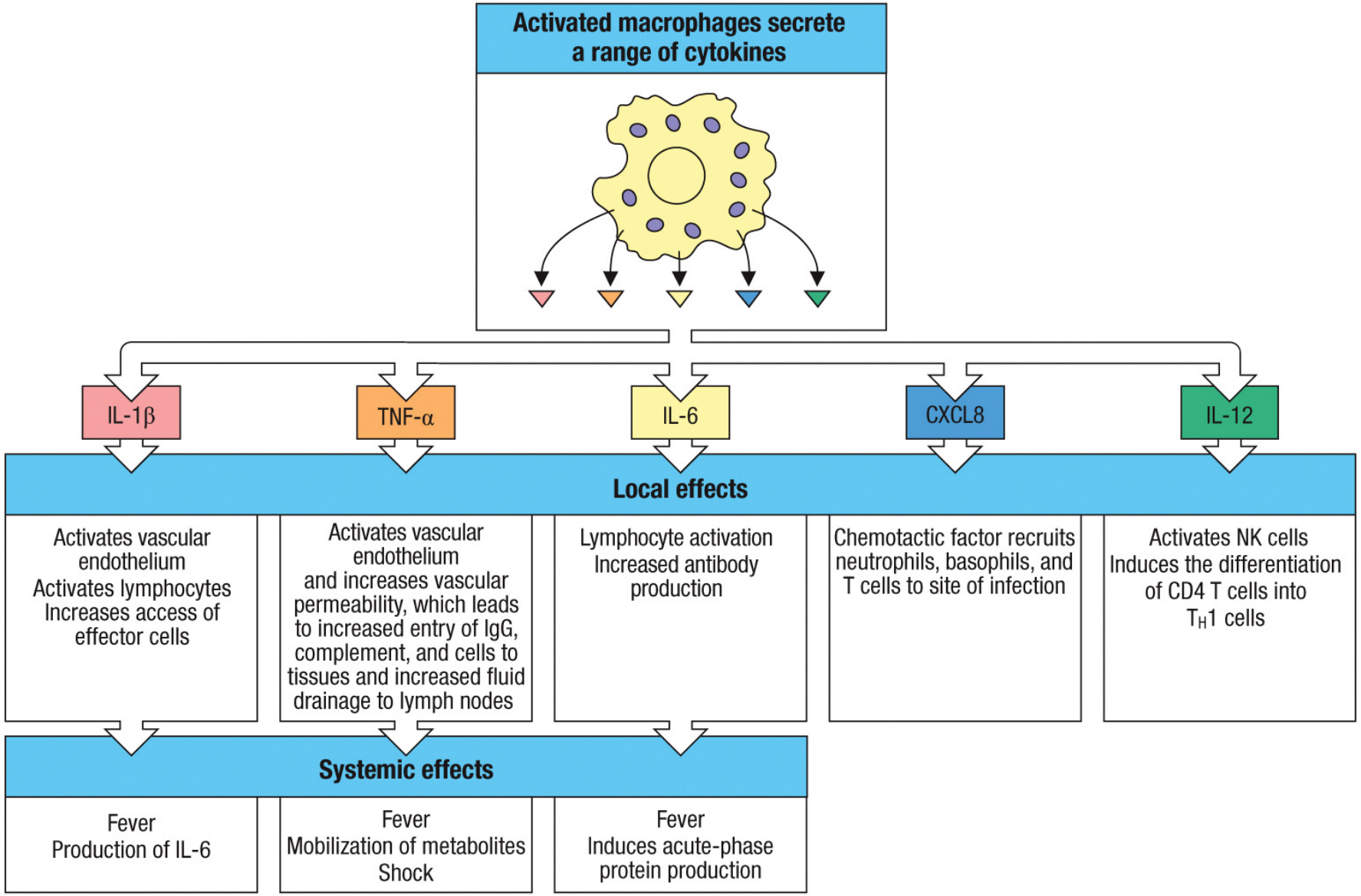
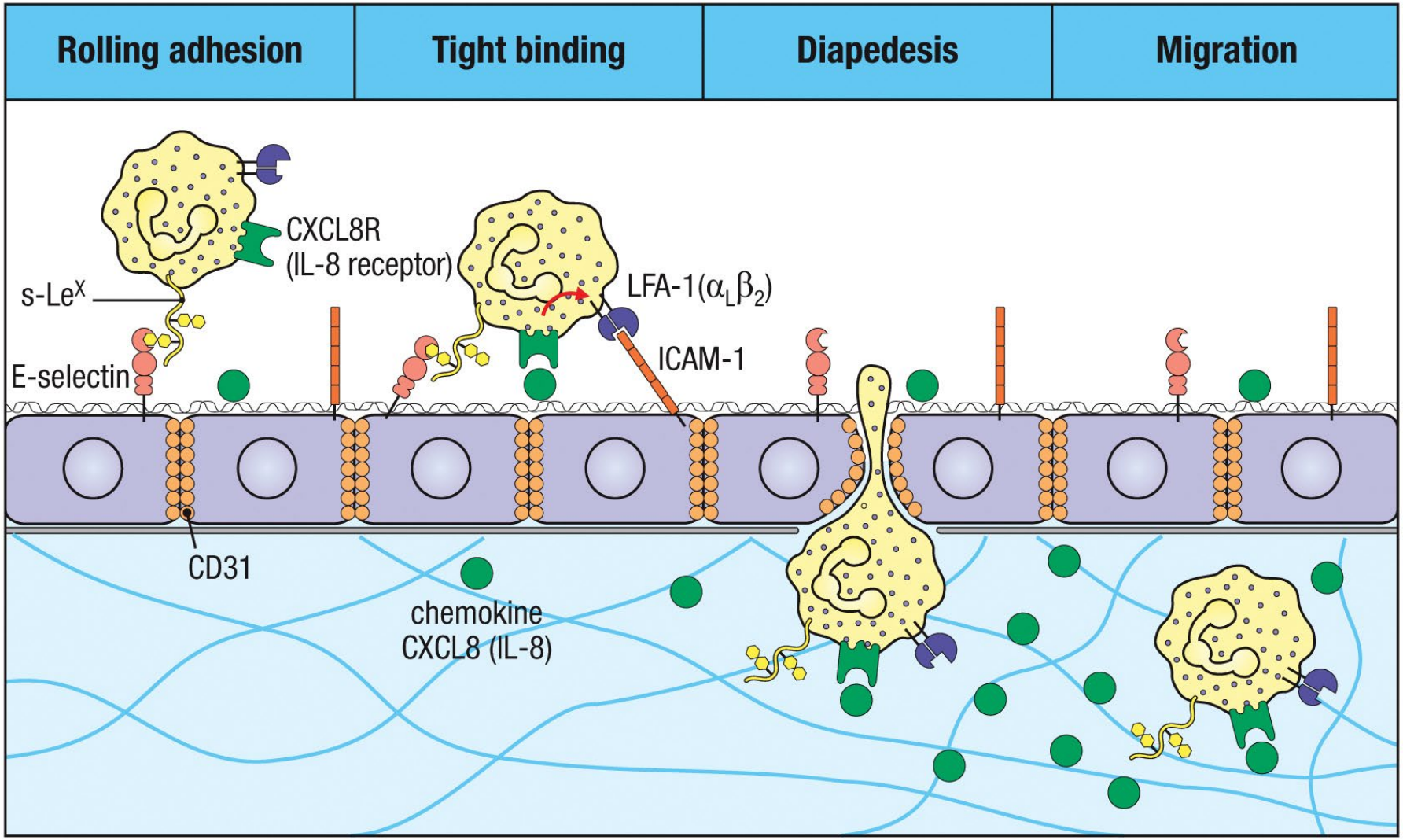
Effects of Cytokine Secretion



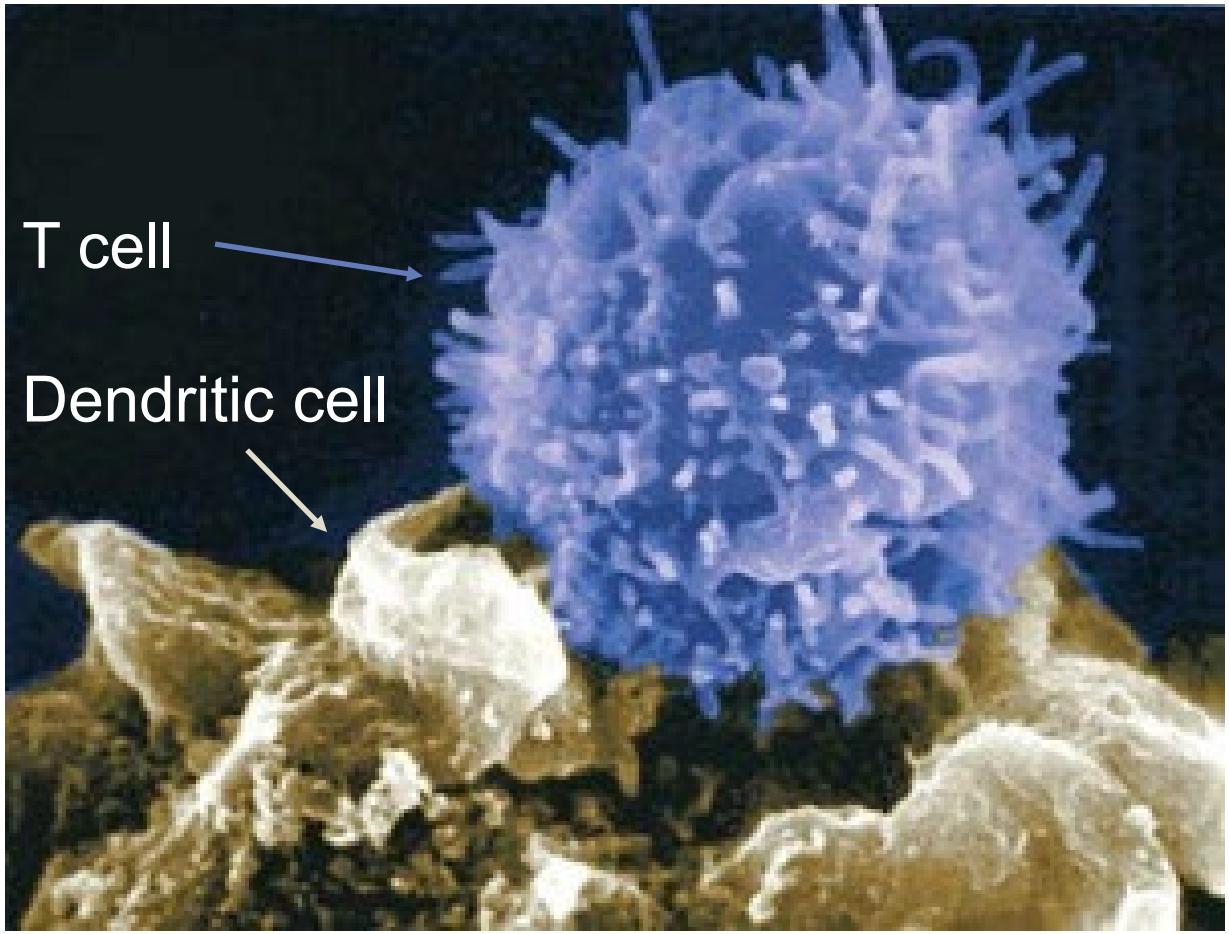
Extravasation: Diapedesis



Outline

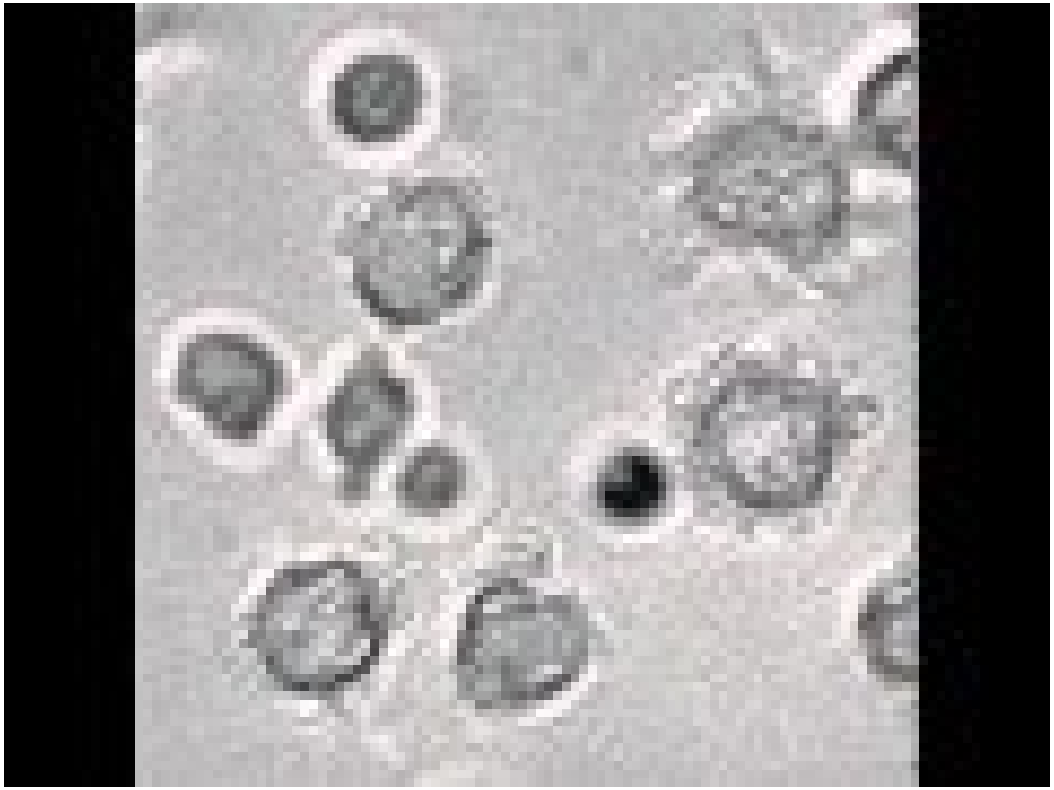
- T cell receptor structure
- Generation of TCR diversity
- Structure of MHC complex

Immunological Synapse



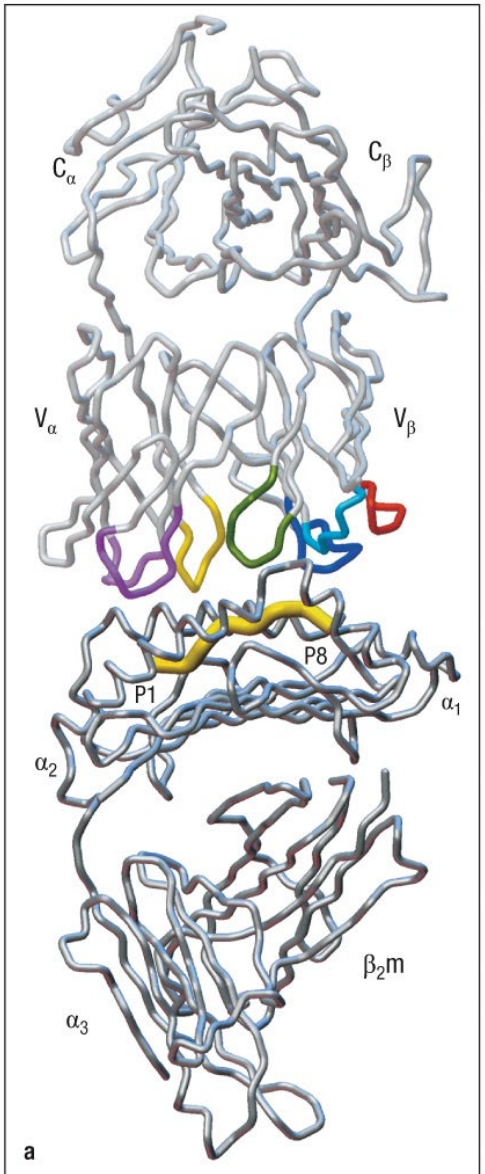
http://www.lbl.gov/Publications/Currents/Archive/Oct-03-2003.html#head0

Lymphocytes Interacting with DCs



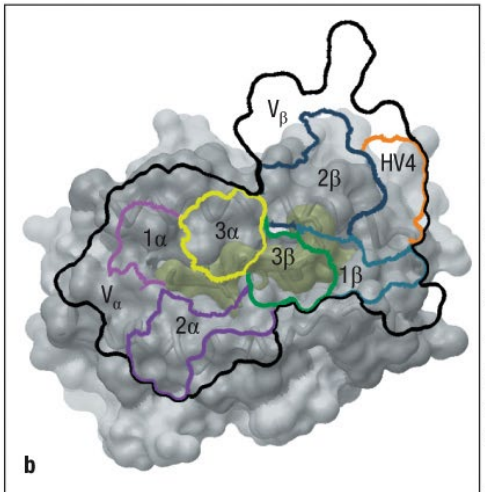
https://www.youtube.com/watch?v=_73xQvaqxk8

TCR Binds to Peptide:MHC Complex



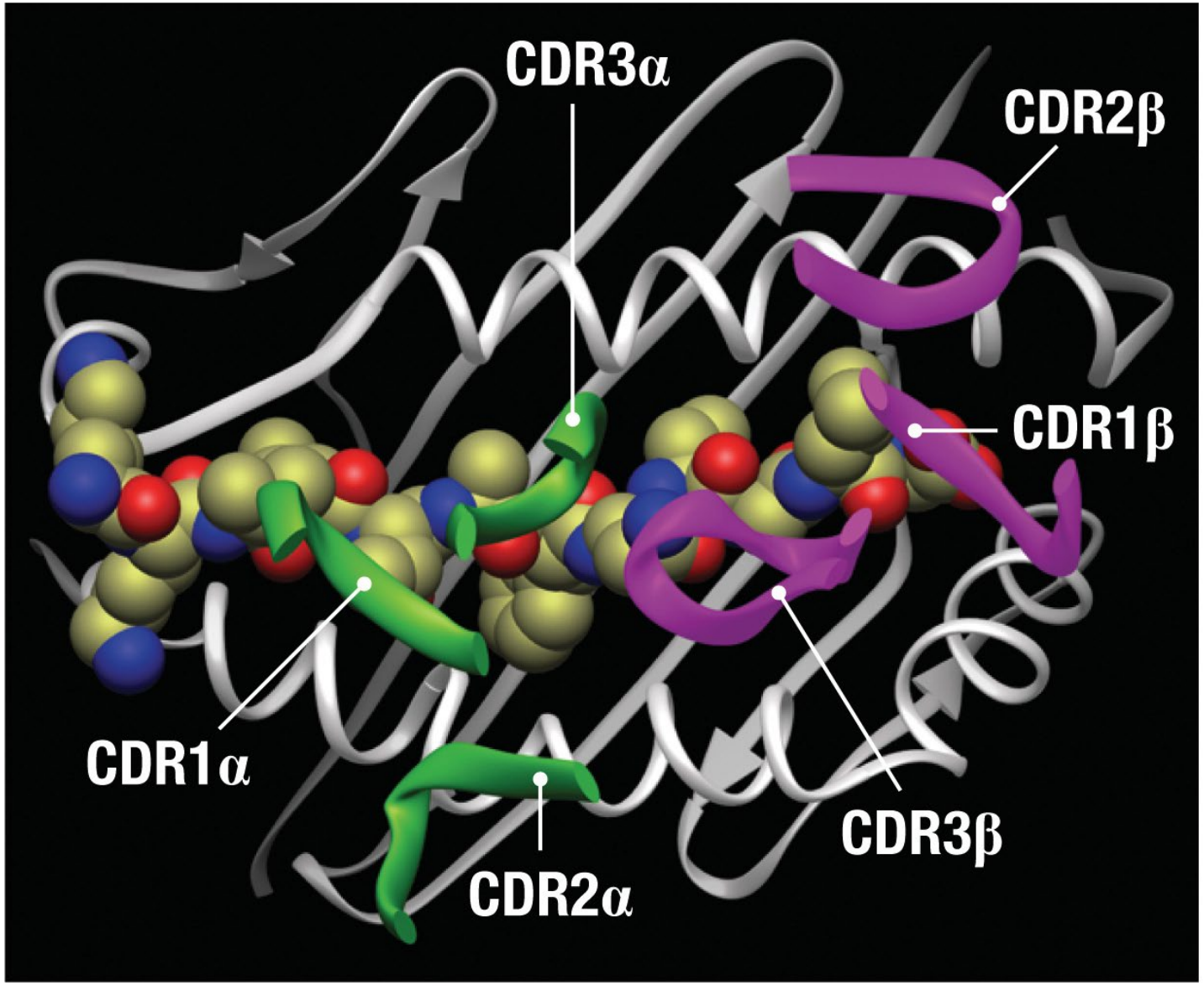
complementarity determining regions

Peptide



From K. Christopher Garcia, Massimo Degano, Robyn L. Stanfield, et al., "An αβ T cell receptor structure at 2.5 Å and its orientation in the TCR-MHC complex," *Science* 274(5285): 209–219, 1996. Reprinted with permission from AAAS.

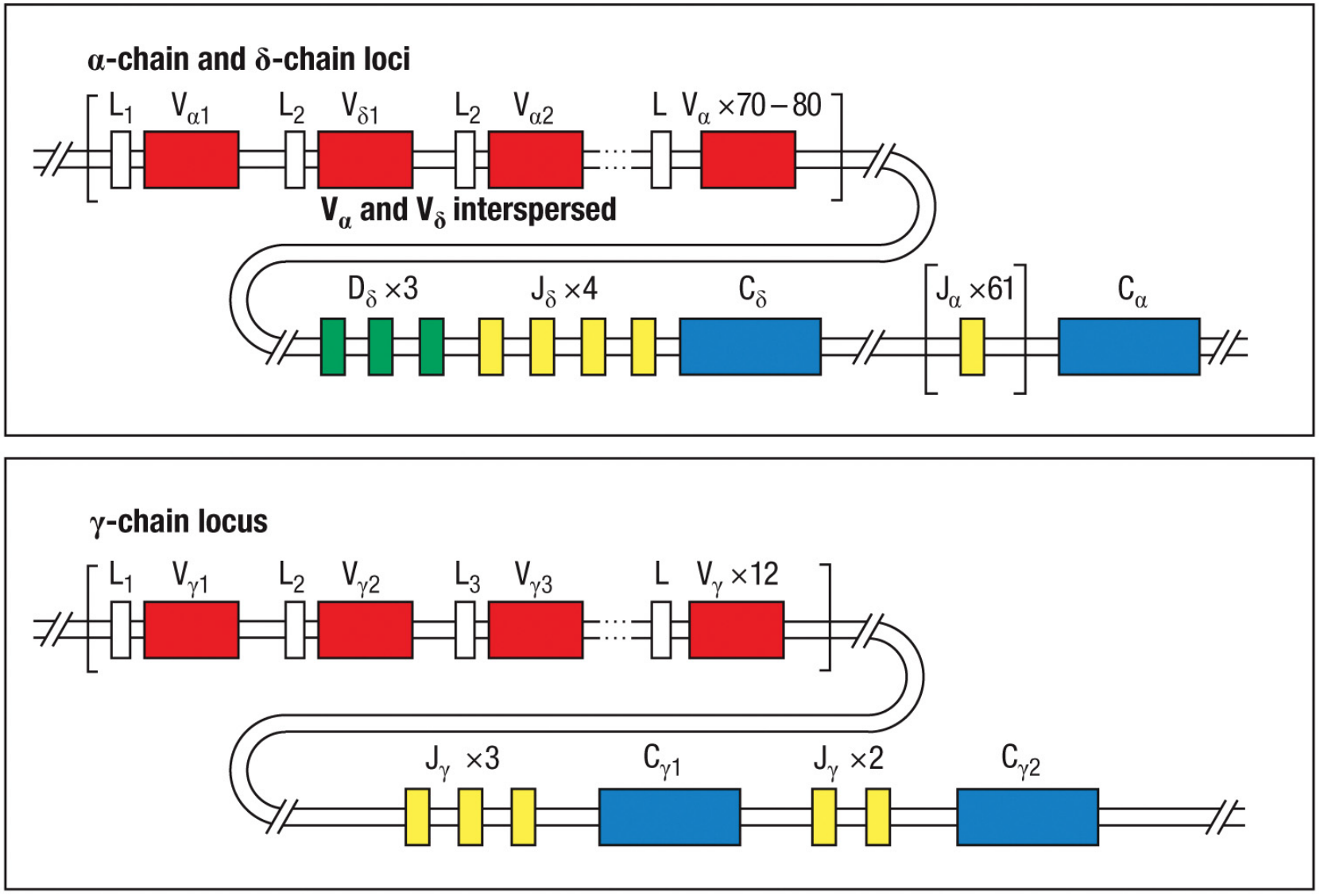
TCR Binds to Peptide:MHC Complex



Outline

- T cell receptor structure
- Generation of TCR diversity
- How do we express so many different TCRs?
- Structure of MHC complex

Germline Organization of the TCR Locus



Two Types of T Cells

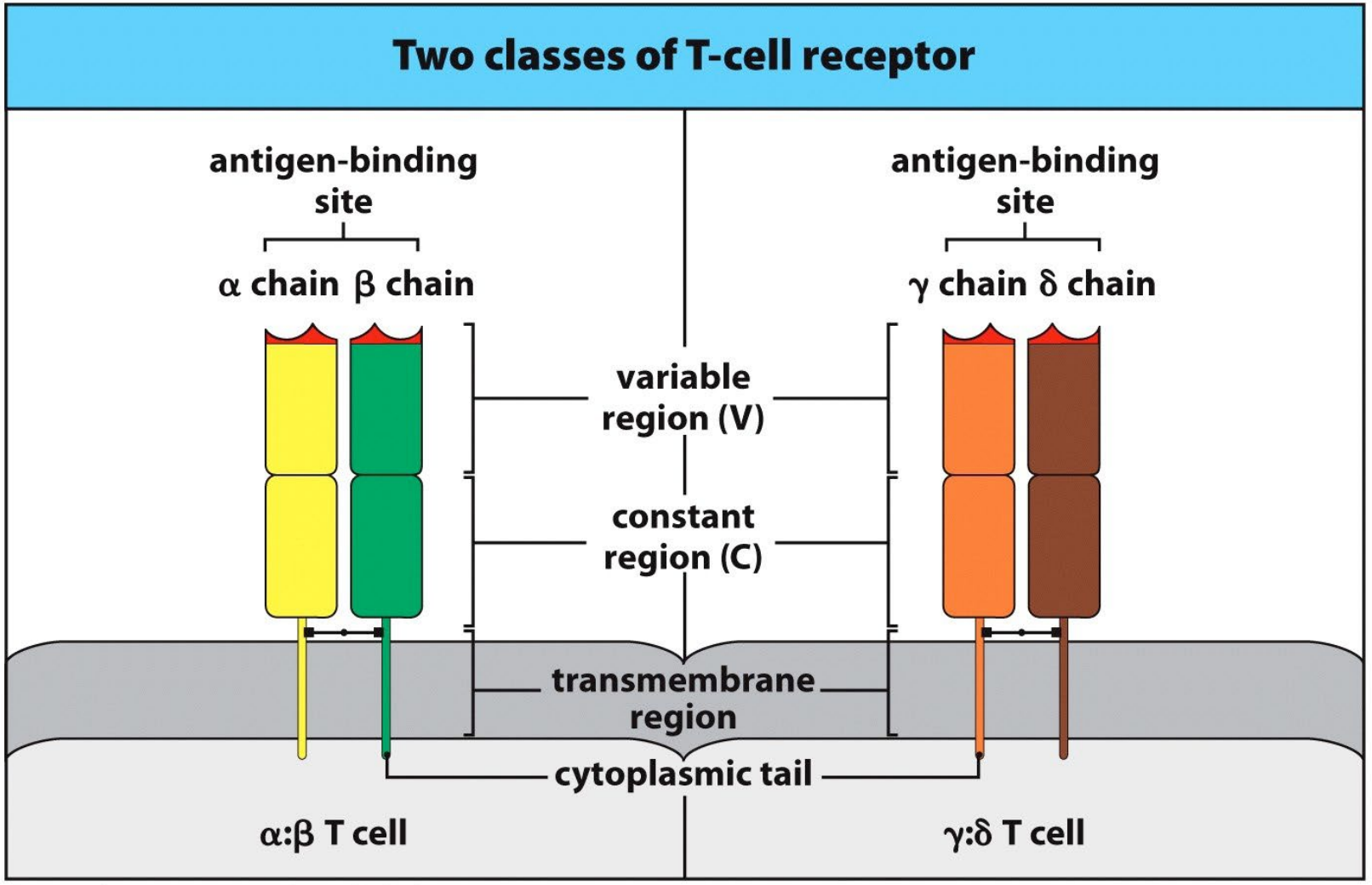
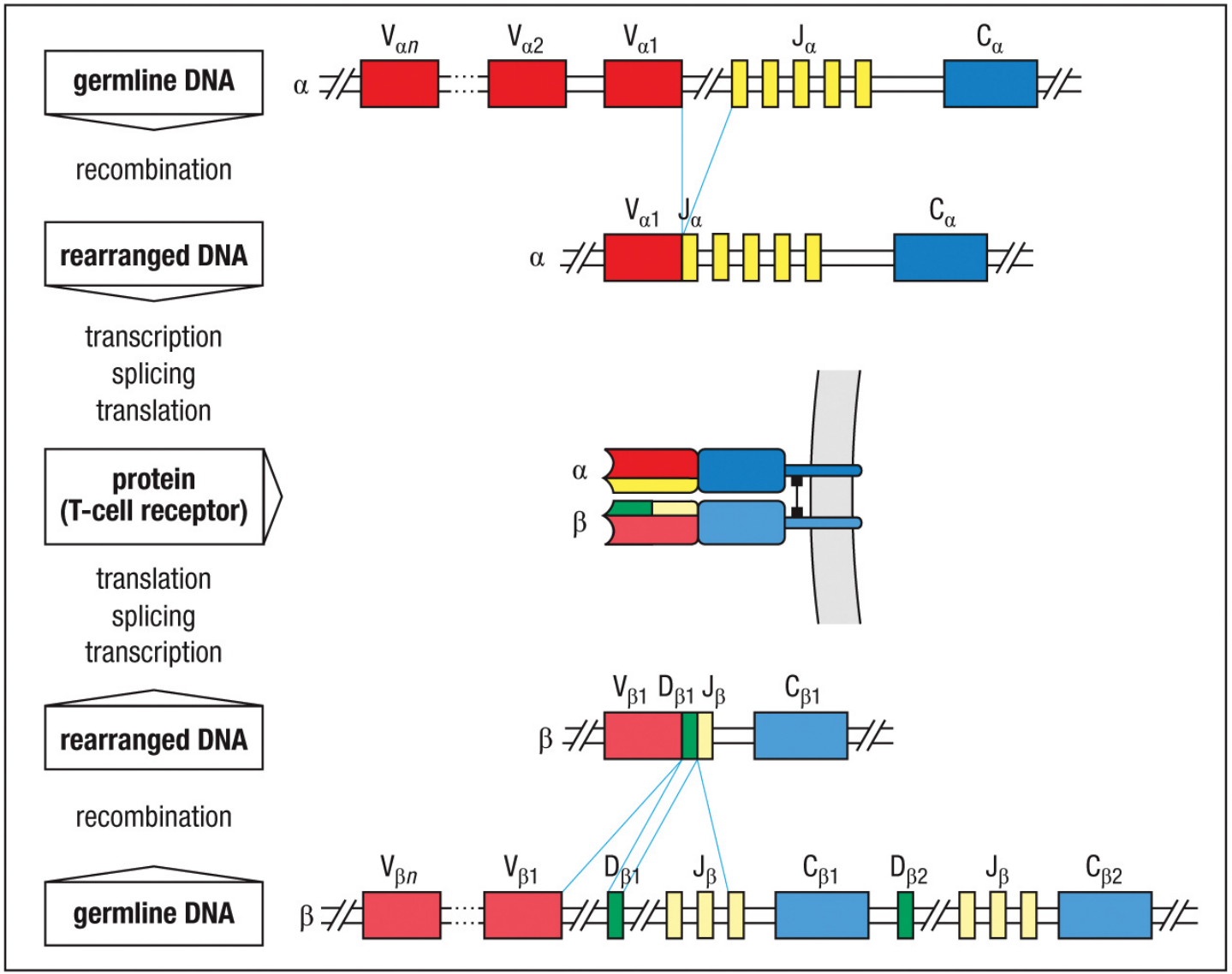
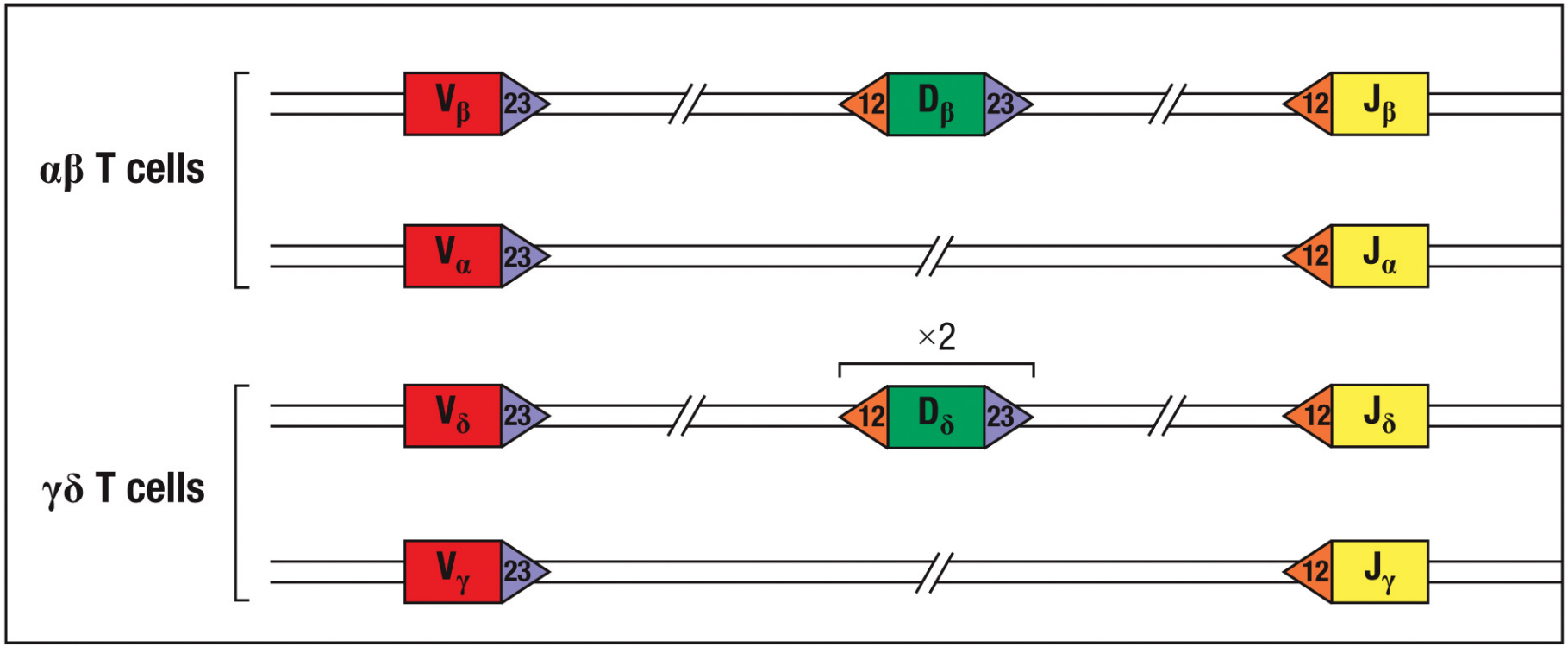


Figure 5.7 The Immune System, 3ed. (© Garland Science 2009)

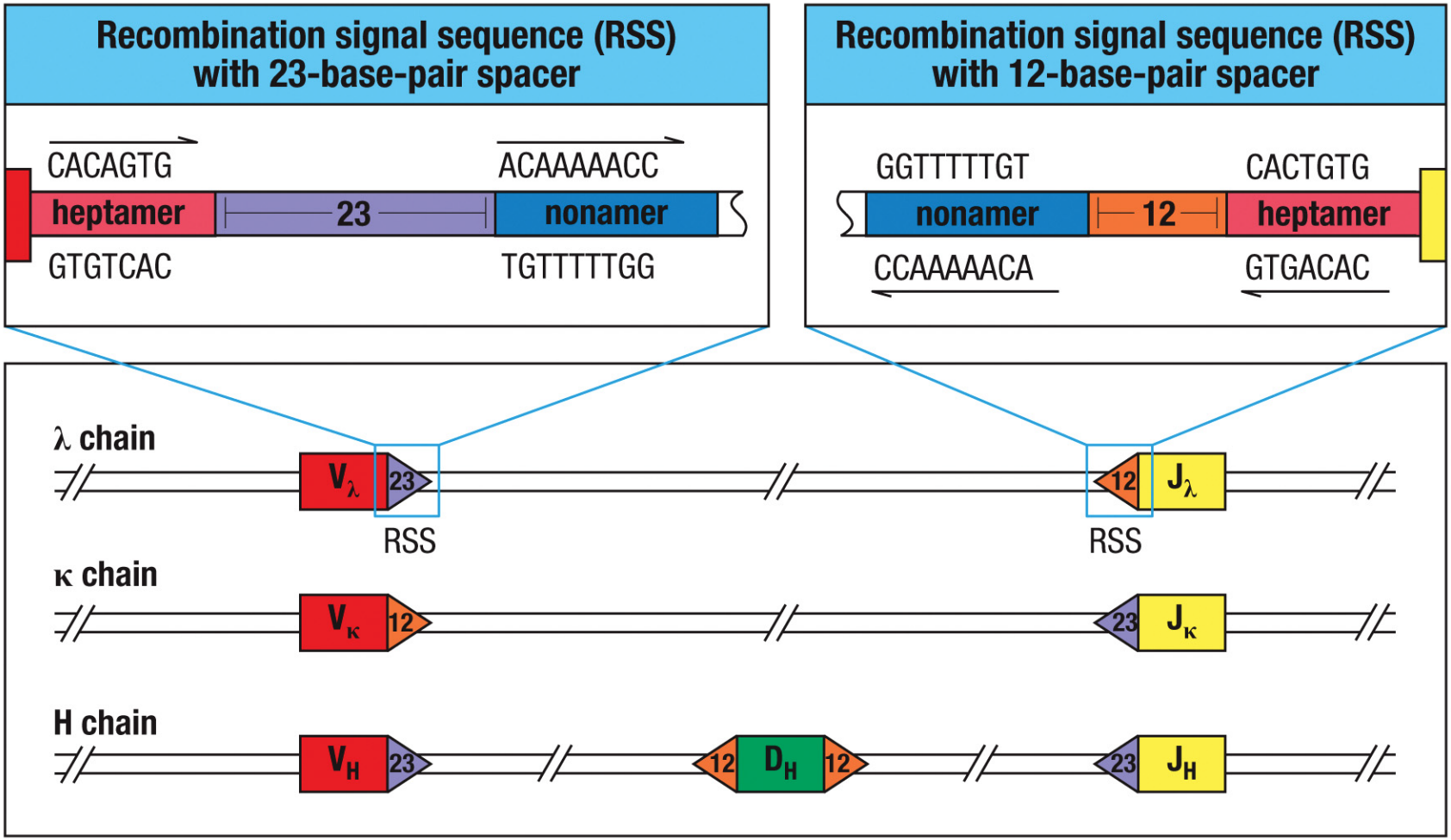
TCRαβ Gene Rearrangement



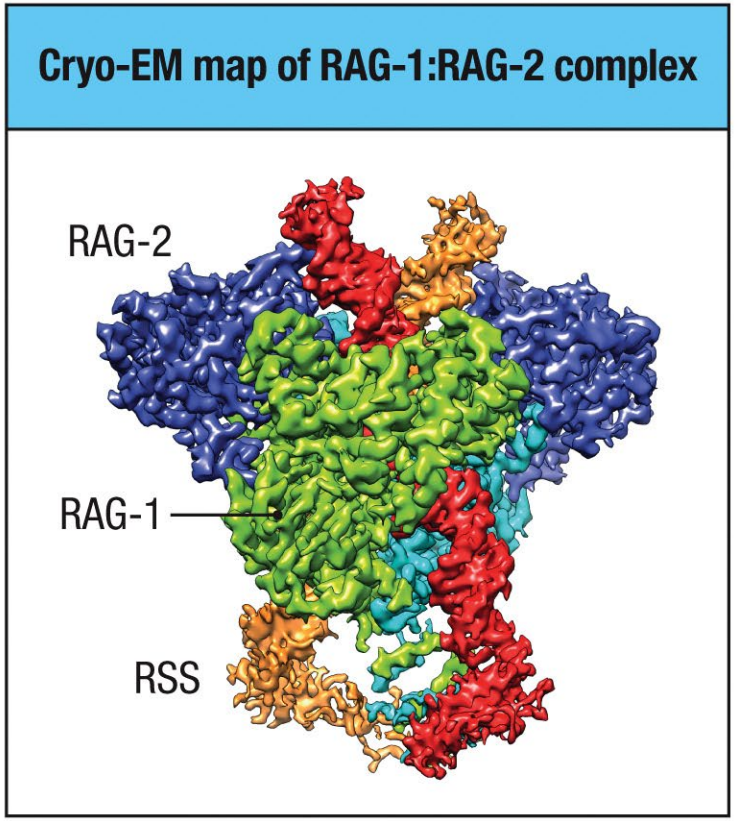
TCR Recombination Follows 12/23 Rule

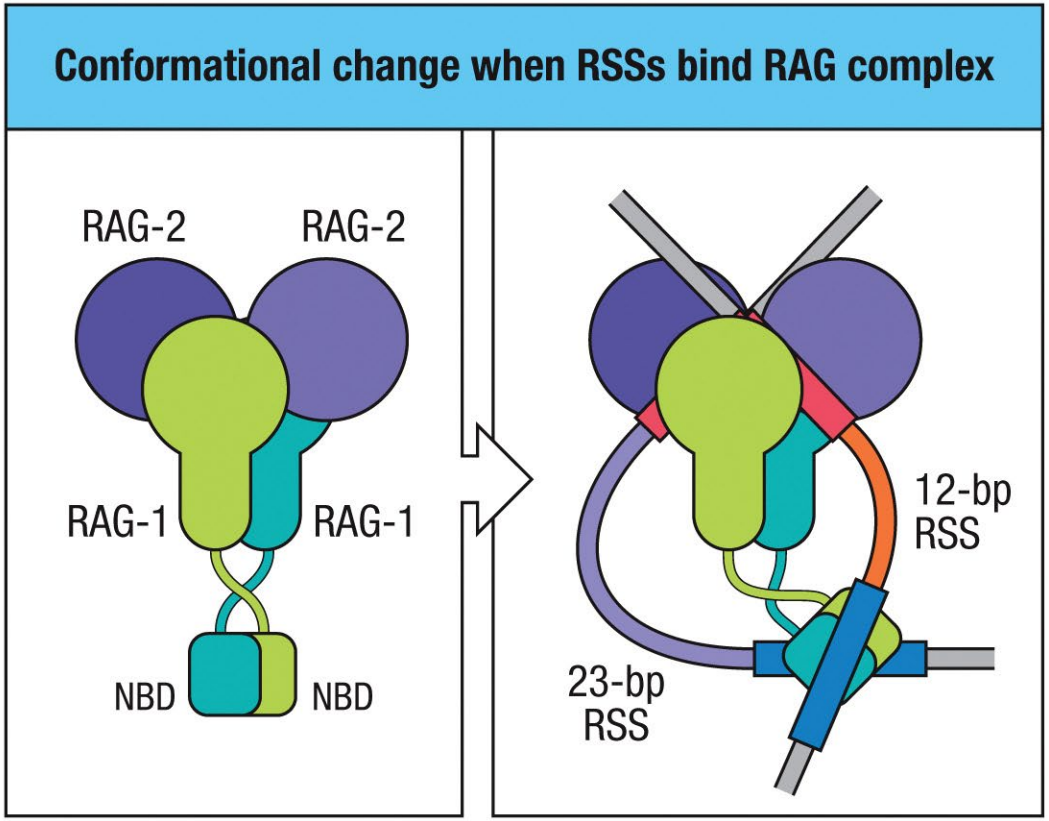


12/23 Rule

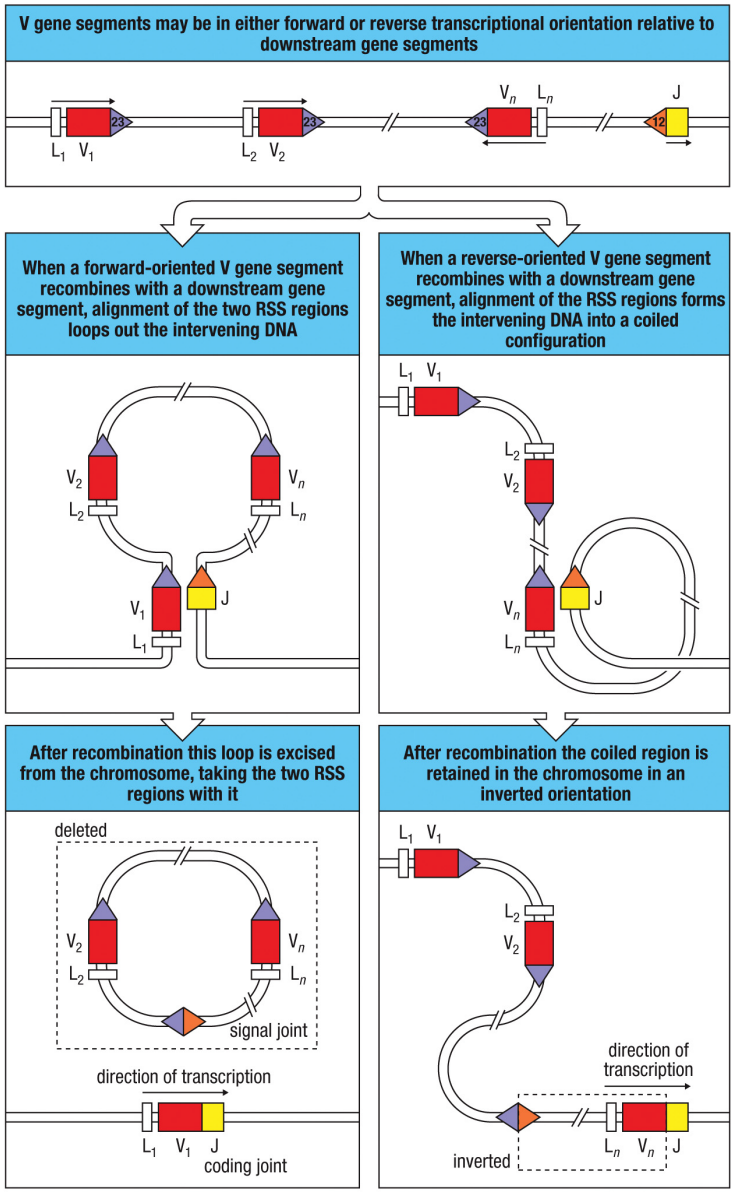

Recombination signal sequence (RSS) with 23-base-pair spacer
CACAGTG
ACAAAAACC
heptamer
23
nonamer
GTGTCAC
TGTTTTTGG
Recombination signal sequence (RSS) with 12-base-pair spacer
GGTTTTTGT
CACTGTG
nonamer
12
heptamer
CCAAAAACA
GTGACAC
λ chain
V_λ
23
RSS
12
J_λ
RSS
κ chain
V_κ
12
23
J_κ
H chain
V_H
23
12
D_H
12
23
J_H

RAG1 And RAG2

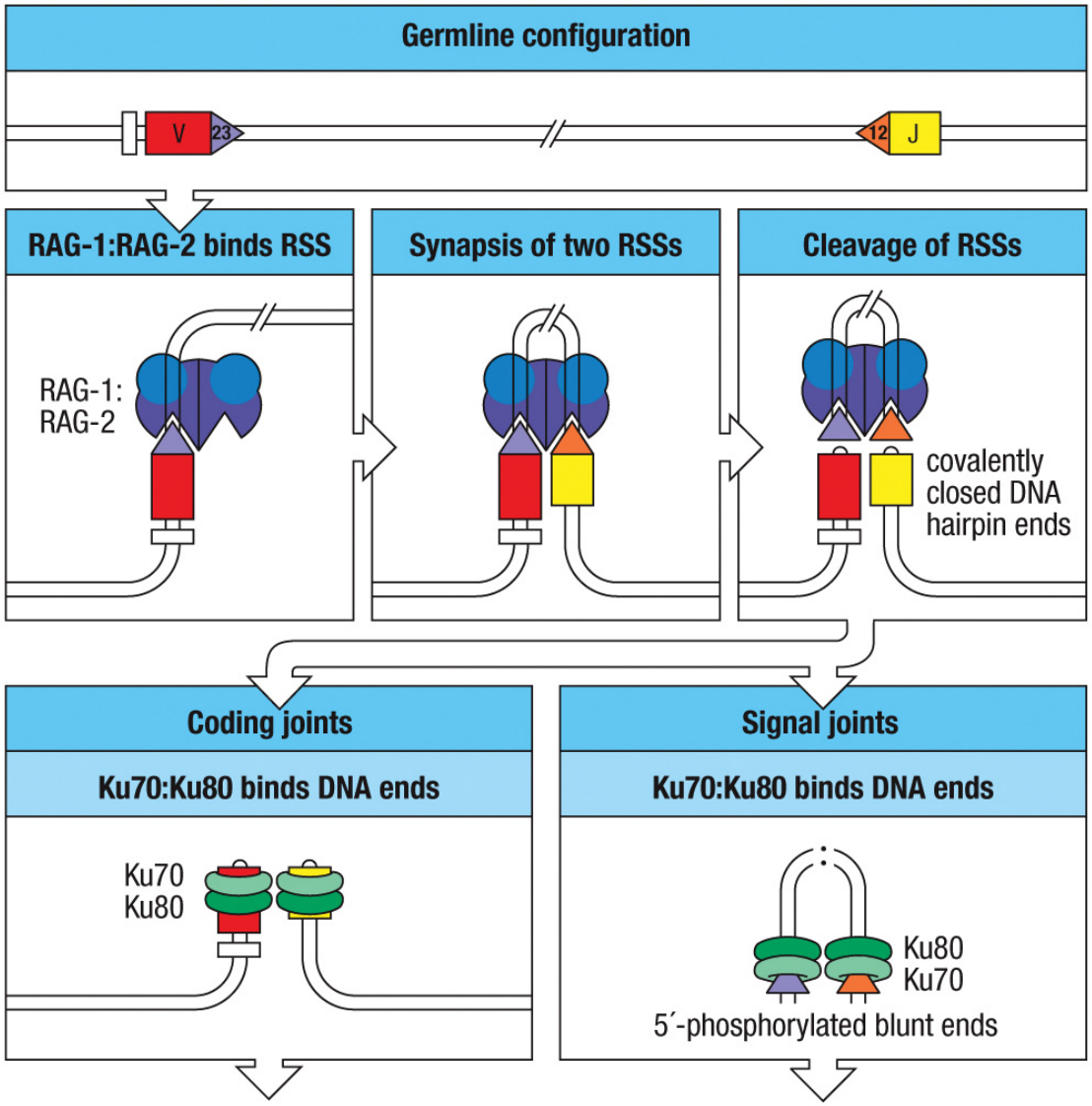


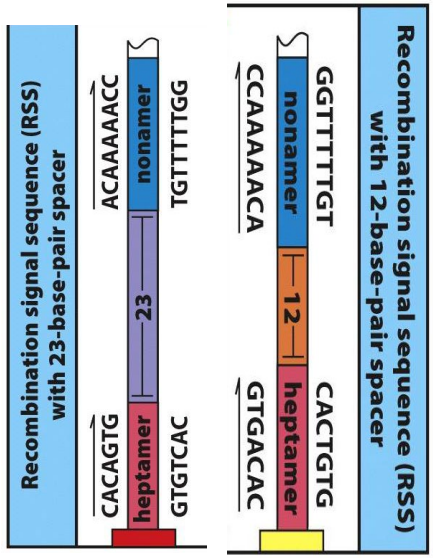


Recombination of V Segments



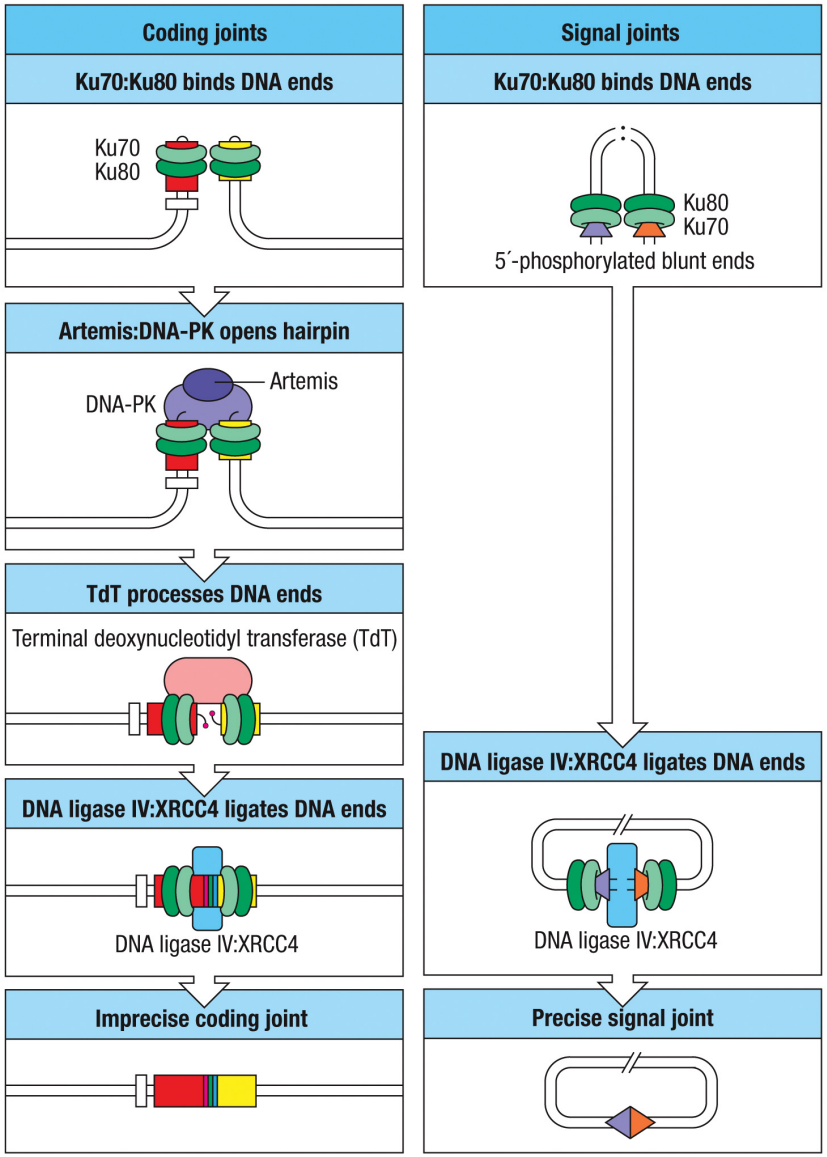
V(D)J Recombination



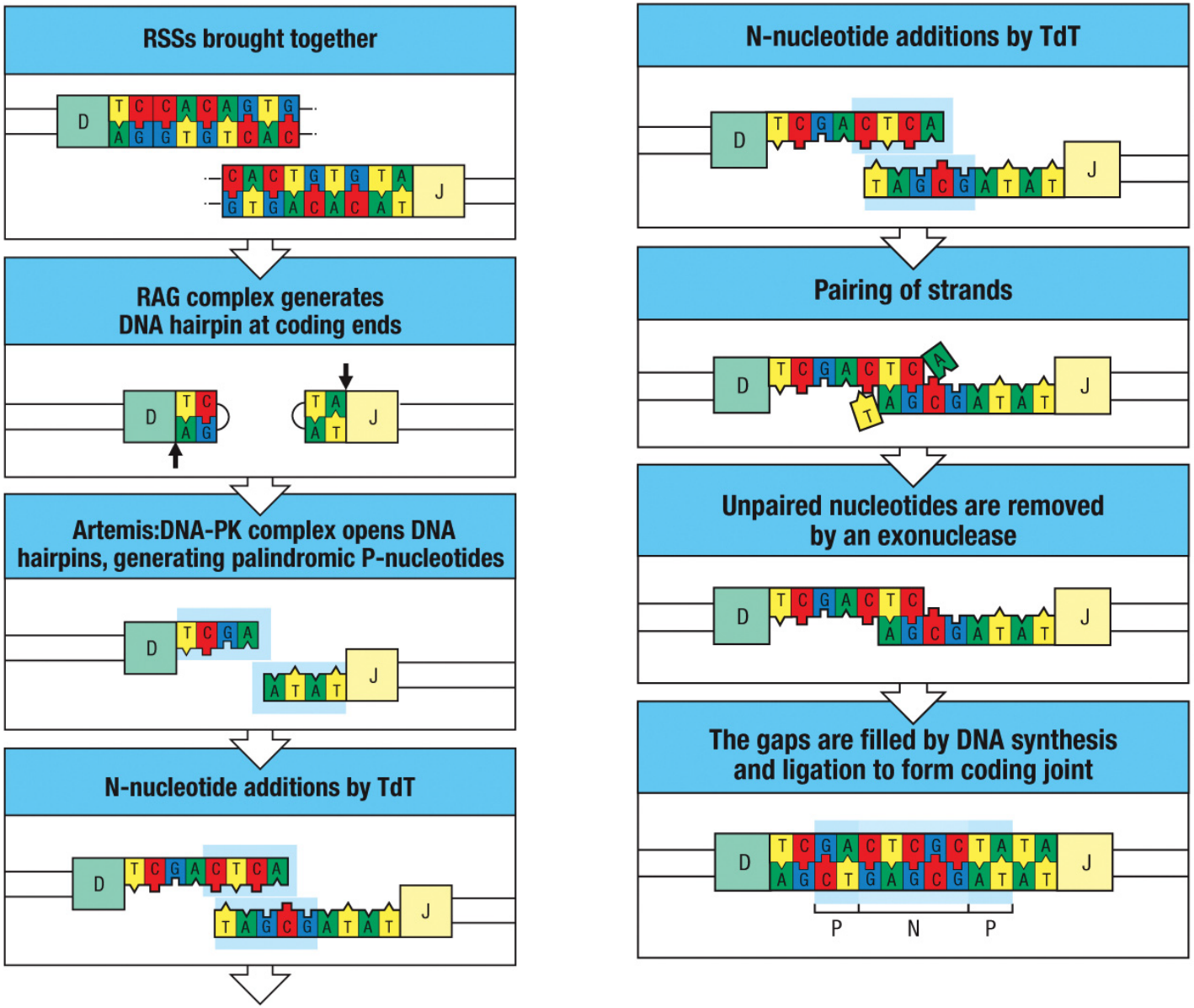


recombination-activating genes

Diversification of VDJ Coding Joints



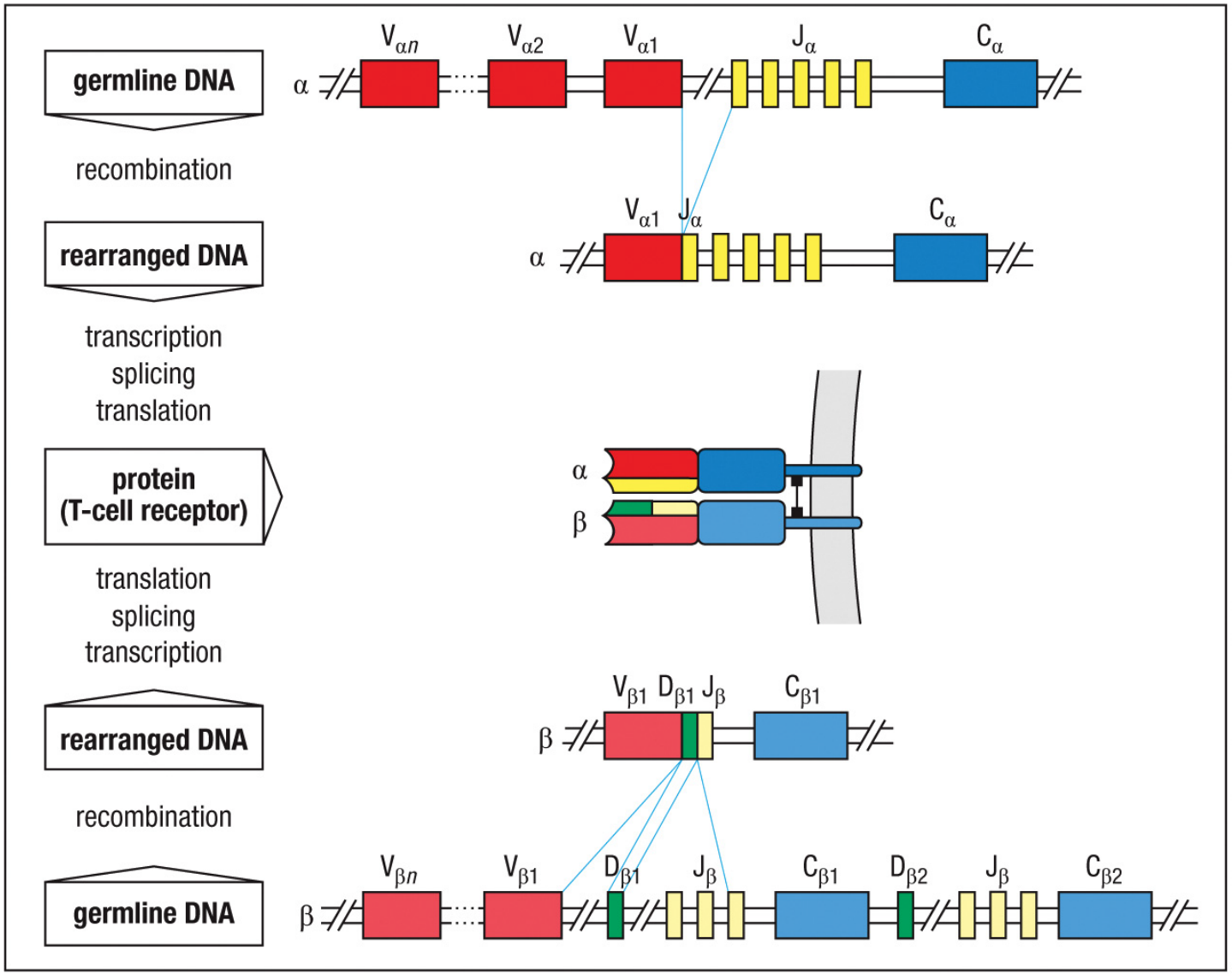
Diversification of VDJ Coding Joints



BCR Vs. TCR Combinatorial Diversity

Element	Immunoglobulin		αβ T-cell receptors	
	H	κ+λ	β	α
Number of variable segments (V)	~40	~60	~30	~100
Number of diversity segments (D)	23	0	2	0
Number of D segments read in three frames	rarely	–	often	–
Number of joining segments (J)	6	5(κ) 4(λ)	12	~50
Number of joints with N- and P-nucleotides	2 (VD and DJ)	50% of joints	2 (VD and DJ)	1 (VJ)
Number of V gene pairs	1.5×10^6		2.7×10^6	
Total diversity with nucleotide addition and deletion	$\sim 5 \times 10^{13}$		$\sim 10^{18}$	

TCRαβ Gene Rearrangement



Sources of TCR Diversity

- Combinatorial diversity
  - Multiple segments of the variable region of α and β-chains
  - Multiple β-chains
  - Multiple α-chains for a single β-chain
- Junctional diversity
  - Addition of N-nucleotides by TdT

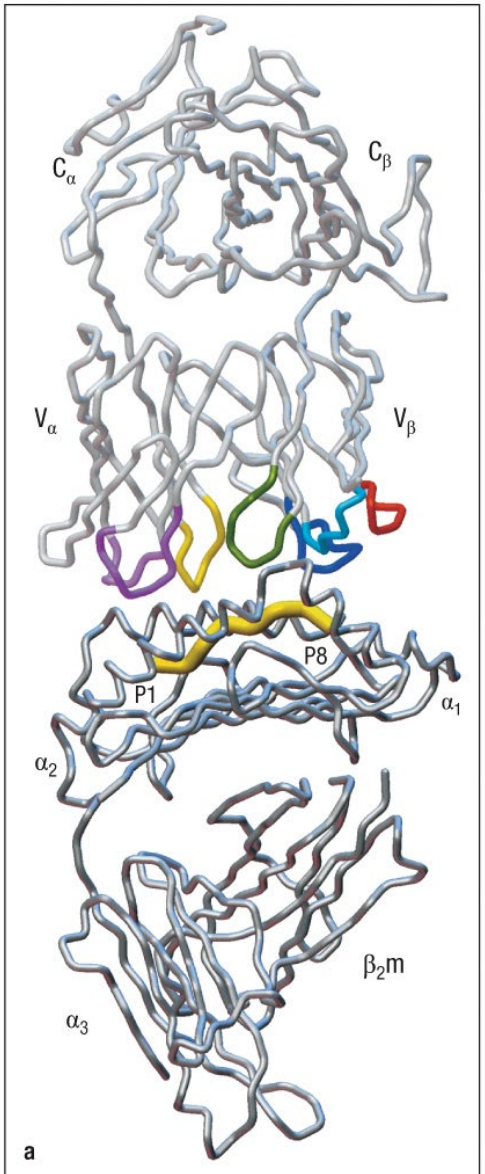
Question

- Every T cell initially starts with the same genomic DNA. How does each of the cells express different TCRs?

Outline

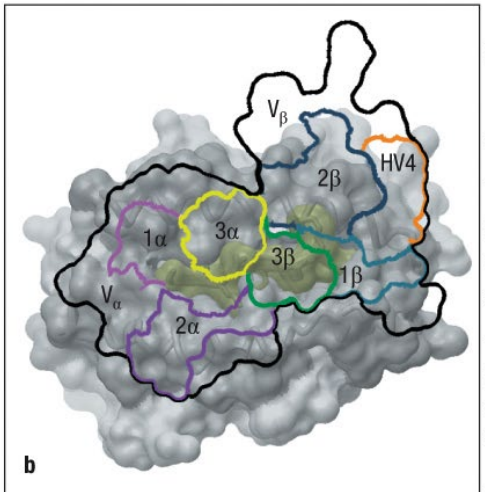
- T cell receptor structure
- Generation of TCR diversity
- Structure of MHC complex

TCR Binds to Peptide:MHC Complex



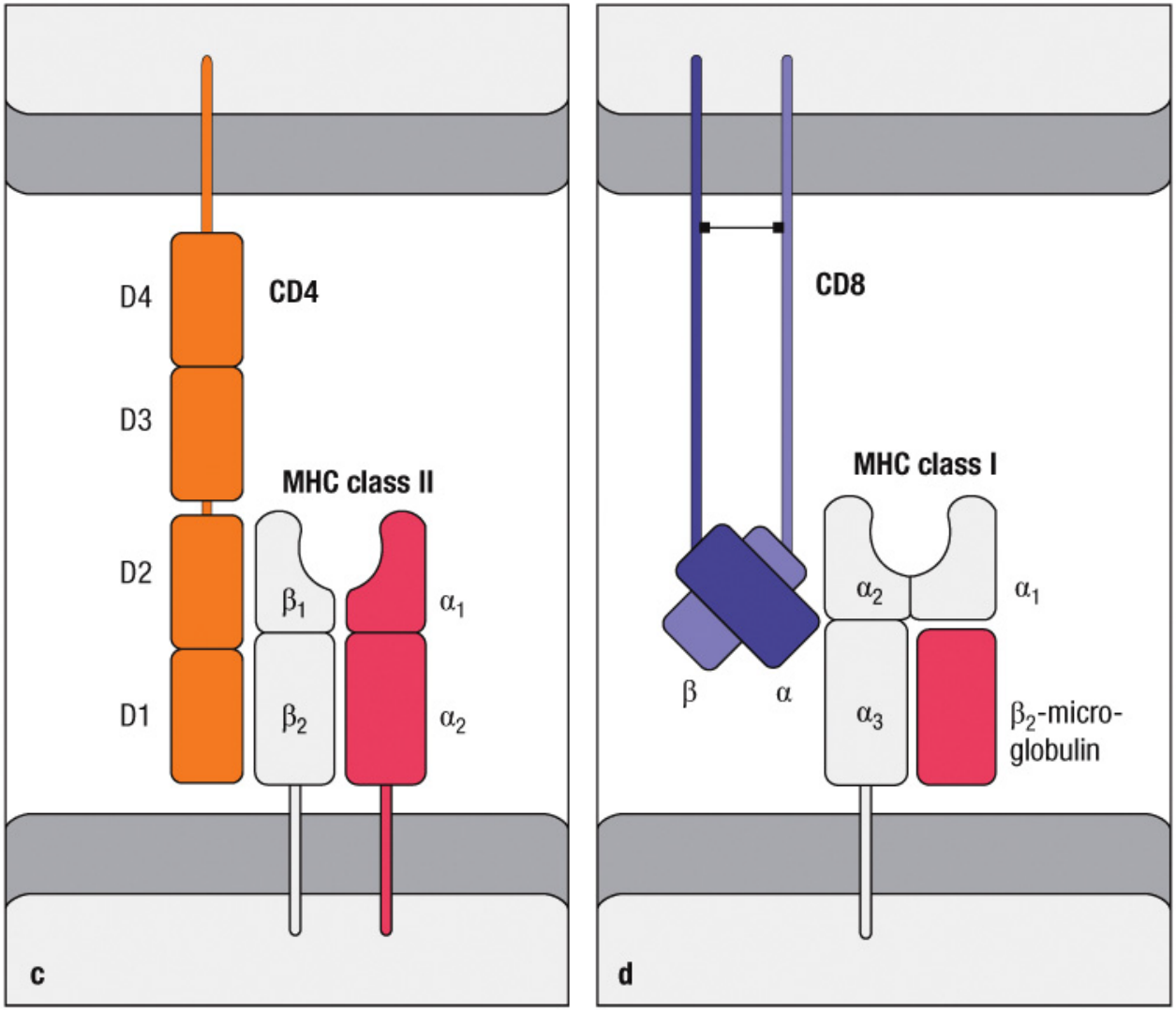
complementarity determining regions

Peptide

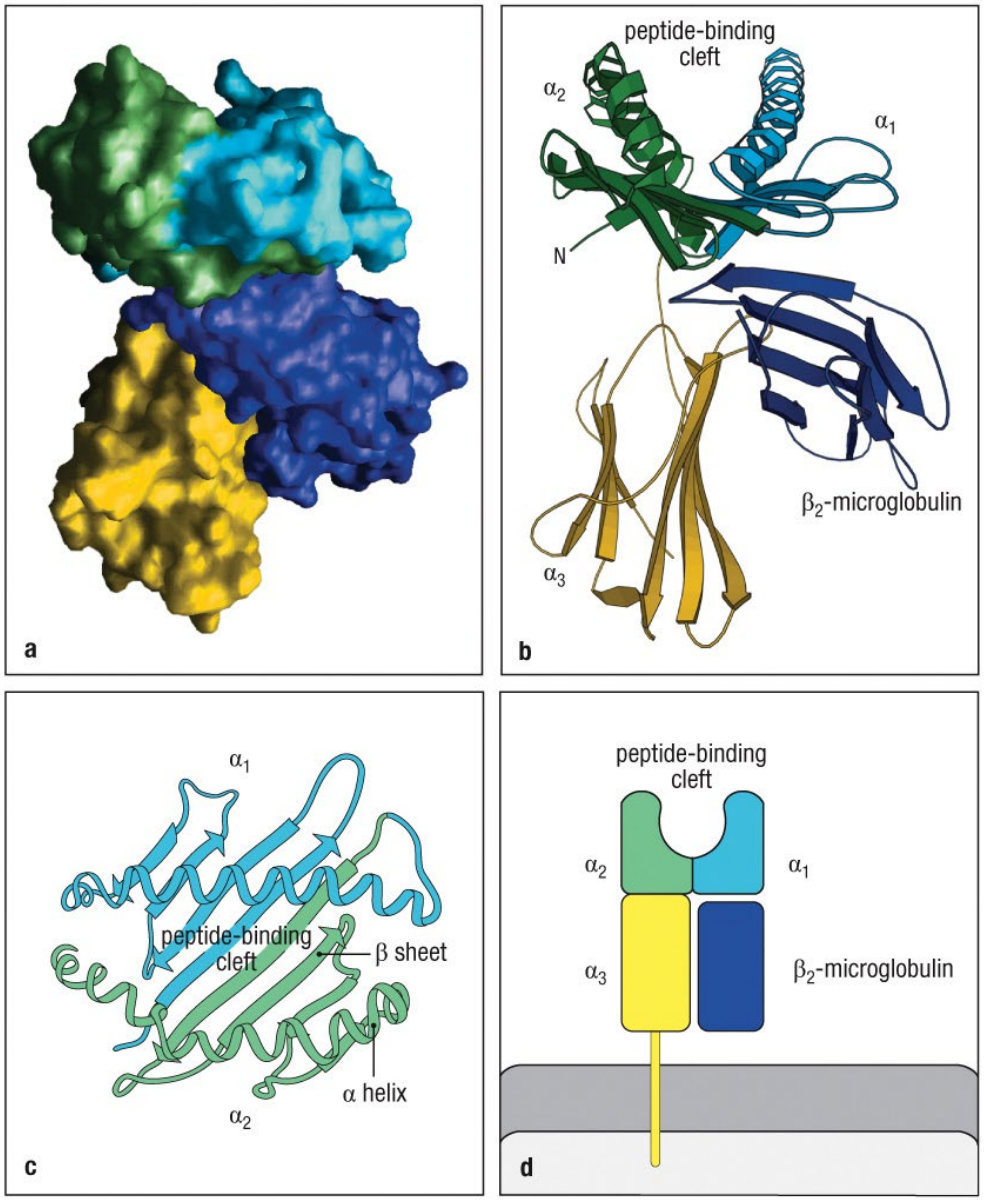


From K. Christopher Garcia, Massimo Degano, Robyn L. Stanfield, et al., "An αβ T cell receptor structure at 2.5 Å and its orientation in the TCR-MHC complex," *Science* 274(5285): 209–219, 1996. Reprinted with permission from AAAS.

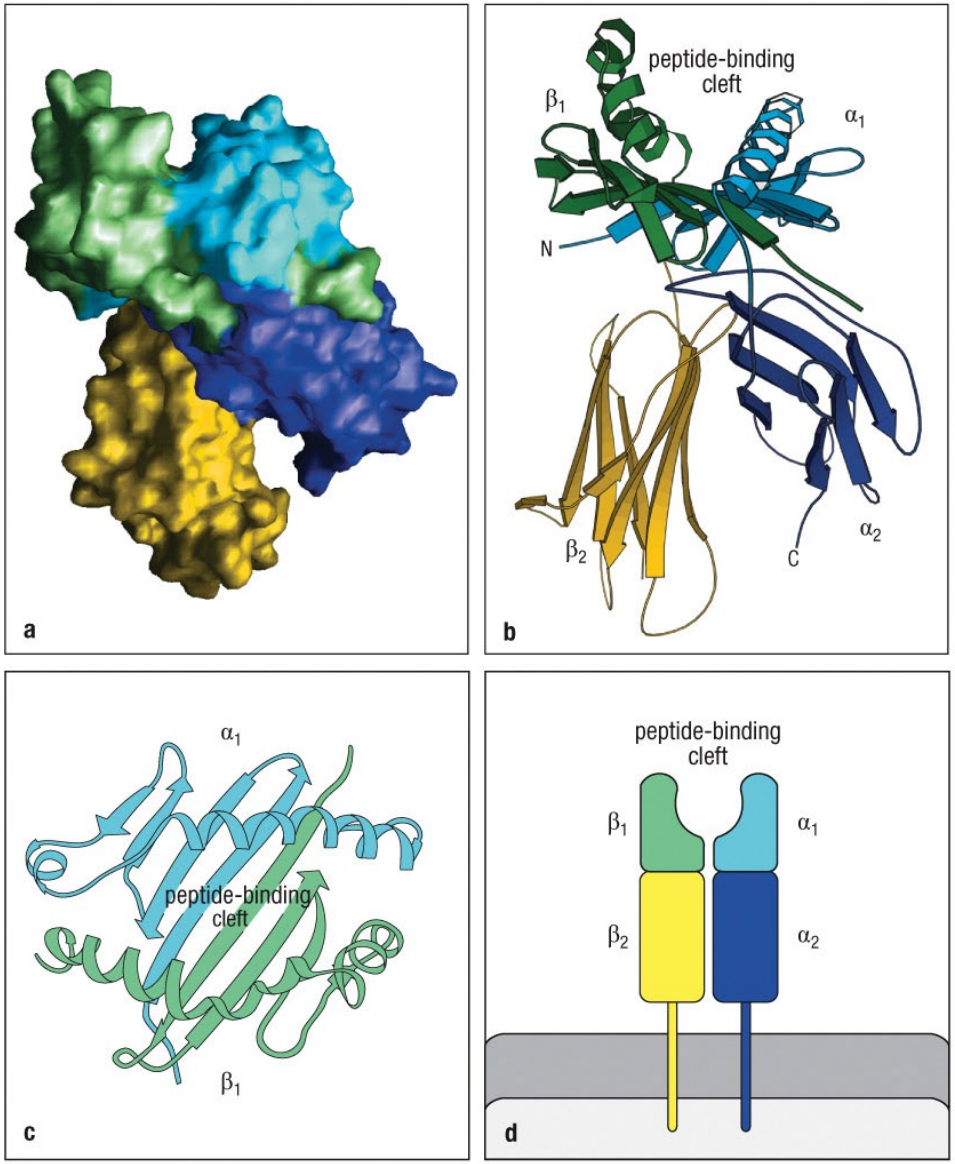
MHC Molecules Display Antigens



Structure of MHC Class I Molecule



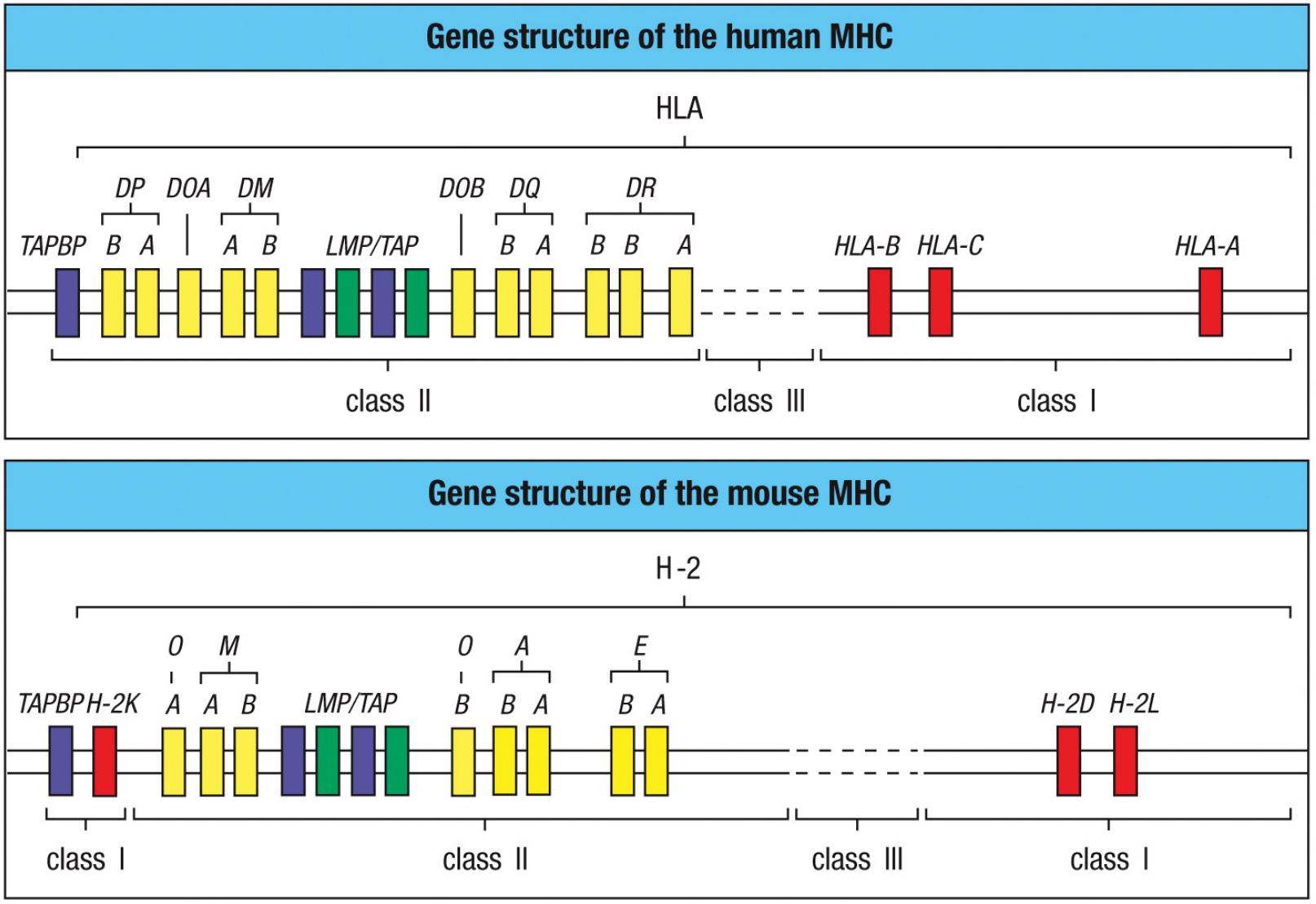
Structure of MHC Class II Molecule



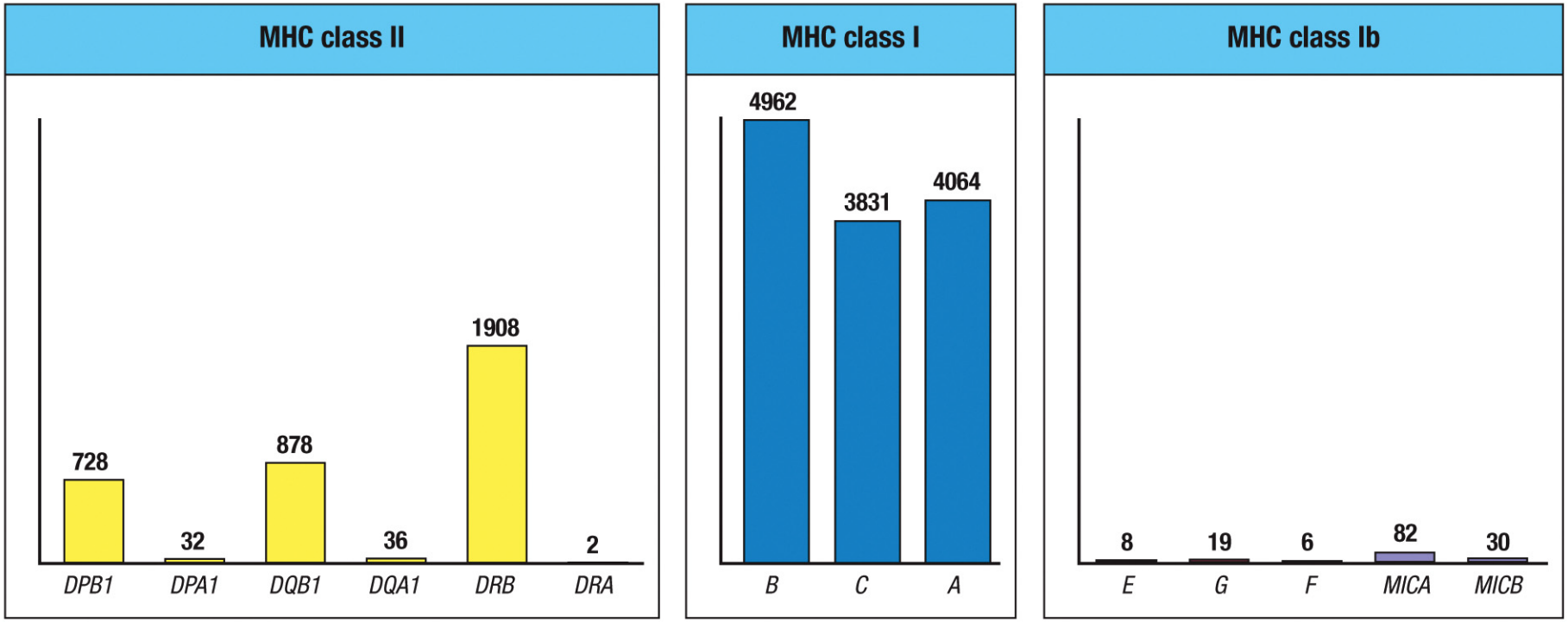
Expression of MHC I/II Molecules

Tissue	MHC class I	MHC class II
Lymphoid tissues		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Dendritic cells	+++	+++
Epithelial cells of thymus	+	+++
Other nucleated cells		
Neutrophils	+++	–
Hepatocytes	+	–
Kidney	+	–
Brain	+	–†
Nonnucleated cells		
Red blood cells	–	–

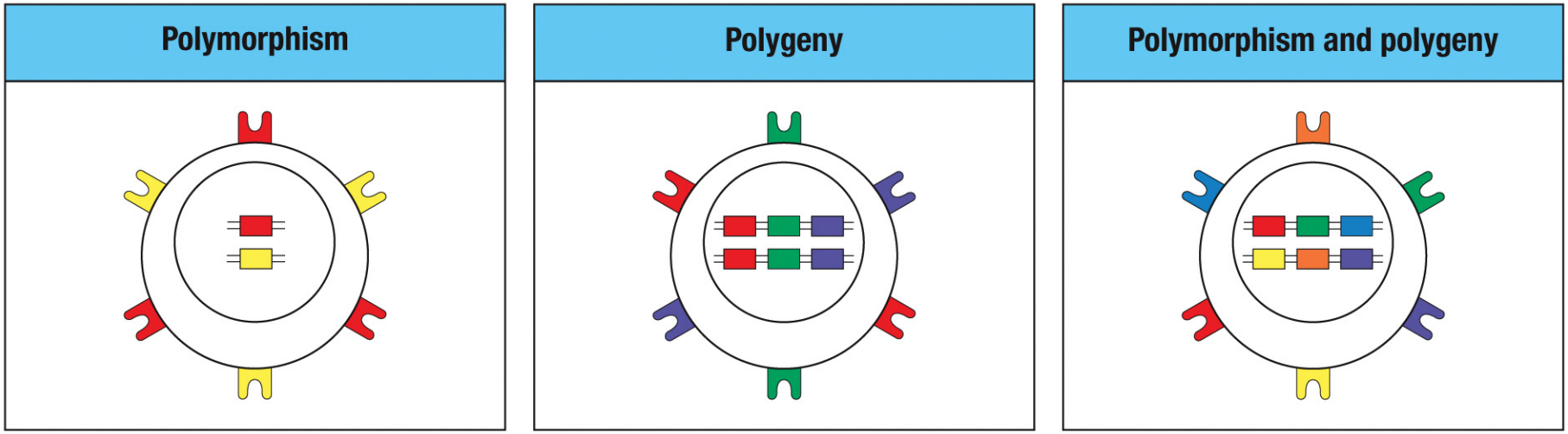
Genetic Organization of MHC Locus



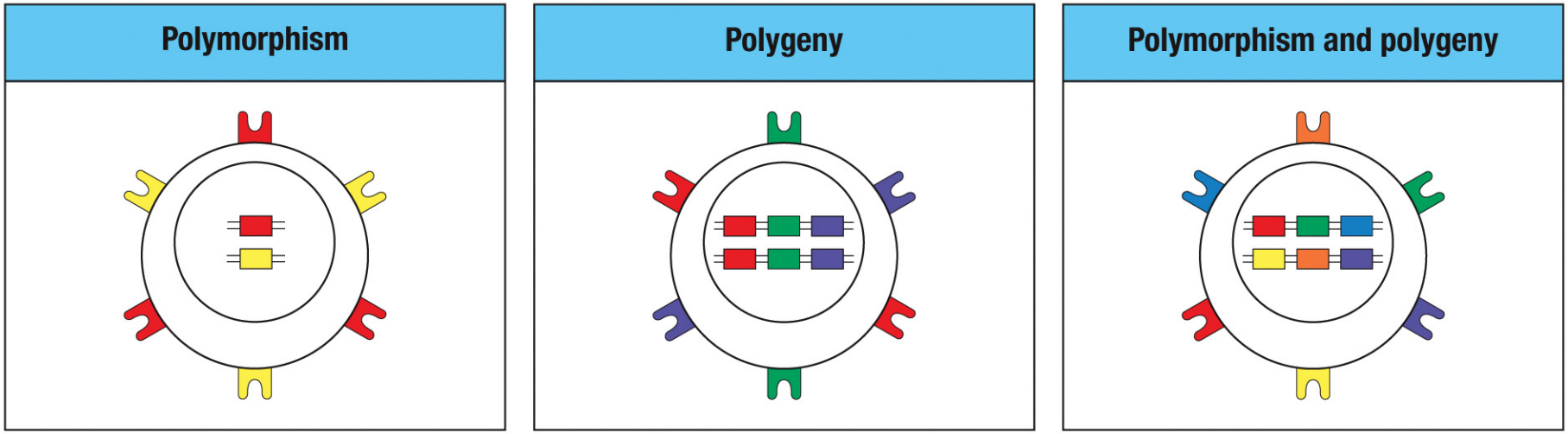
Polymorphism and Polygeny Contribute to MHC Diversity



Expression of MHC Alleles Is Co-Dominant



Gene Conversion Can Create New MHC Alleles



Question

How many MHC I proteins do you express, assuming we are all heterozygous?

How many MHC I proteins do the entire class express?

Why do we need so many different proteins?

Case Studies

- Toxic Shock Syndrome

Toxic Shock Syndrome

Patient:

- 16-year-old female
- Fever 39°C,
- Systemic shock and bright red rash
- WBC count 21,000 cells/microliter (normal range 5,000-10,000)

Diagnosis:

- Vaginal culture positive for abundant *S.aureus*

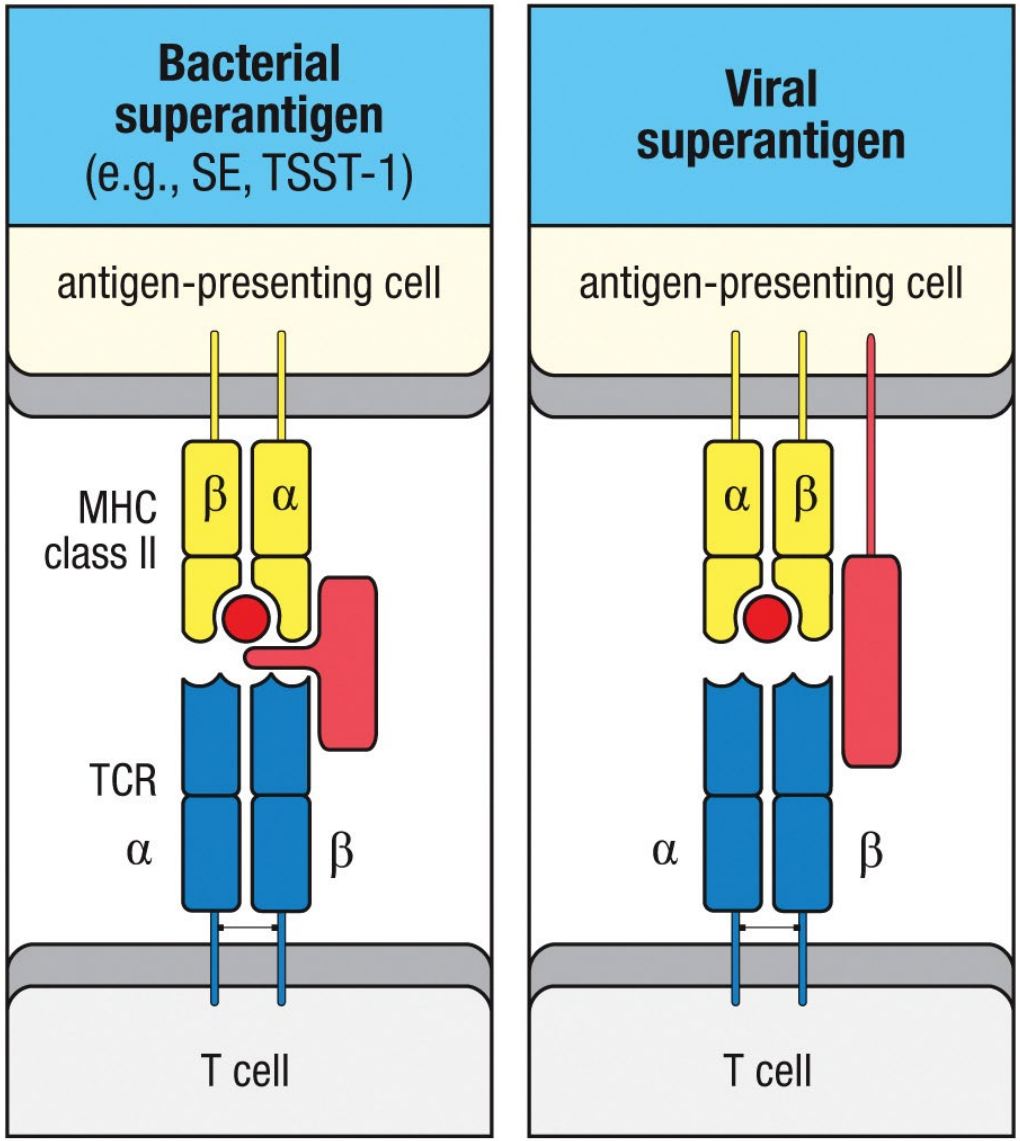
Treatment :

- Anti-staphylococcal antibiotics
- IV fluids
- IV immunoglobulin

Outcome:

- Slowly recovered

Superantigens Bind Directly to TCR Vβ and MHC II



Examples of Superantigens

Disease	Superantigen	TCR V_β
Definite role for superantigen		
Toxic shock syndrome	TSST-1	$V_\beta 2$
Staphylococcal food poisoning	SEA	$V_\beta 3$, $V_\beta 11$
	SEB	$V_\beta 3$, $V_\beta 12$, $V_\beta 14$, $V_\beta 15$, $V_\beta 17$, $V_\beta 20$
	SEC	$V_\beta 5$, $V_\beta 12$, $V_\beta 13.1–2$, $V_\beta 14$, $V_\beta 15$, $V_\beta 17$, $V_\beta 20$
	SED	$V_\beta 5$, $V_\beta 12$
	SEE	$V_\beta 5.1$, $V_\beta 6.1–3$, $V_\beta 8$, $V_\beta 18$
Streptococcal toxic shock syndrome	SPE-A	$V_\beta 8$, $V_\beta 12$, $V_\beta 14$
Scarlet fever	SPE-B	$V_\beta 2$, $V_\beta 8$
Mycoplasma arthritidis (rodent)	MAM	$V_\beta 17$
Clostridium perfringens	Enterotoxin	$V_\beta 6.9$, $V_\beta 22$
Suspected role for superantigen		
HIV	CMV	$V_\beta 12$
Type I diabetes mellitus	MMTV-like	$V_\beta 7$
Rabies virus	Nucleocapsid	$V_\beta 8$
Toxoplasmosis	?	$V_\beta 5$
Mycobacterium tuberculosis	?	$V_\beta 8$
Yersinia enterocolitica	?	$V_\beta 3$, $V_\beta 6$, $V_\beta 11$
Kawasaki disease	?	$V_\beta 2$, $V_\beta 8$

Figure 47.2 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Expansion in Numbers of Superantigen-Specific T Cells

RT-PCR

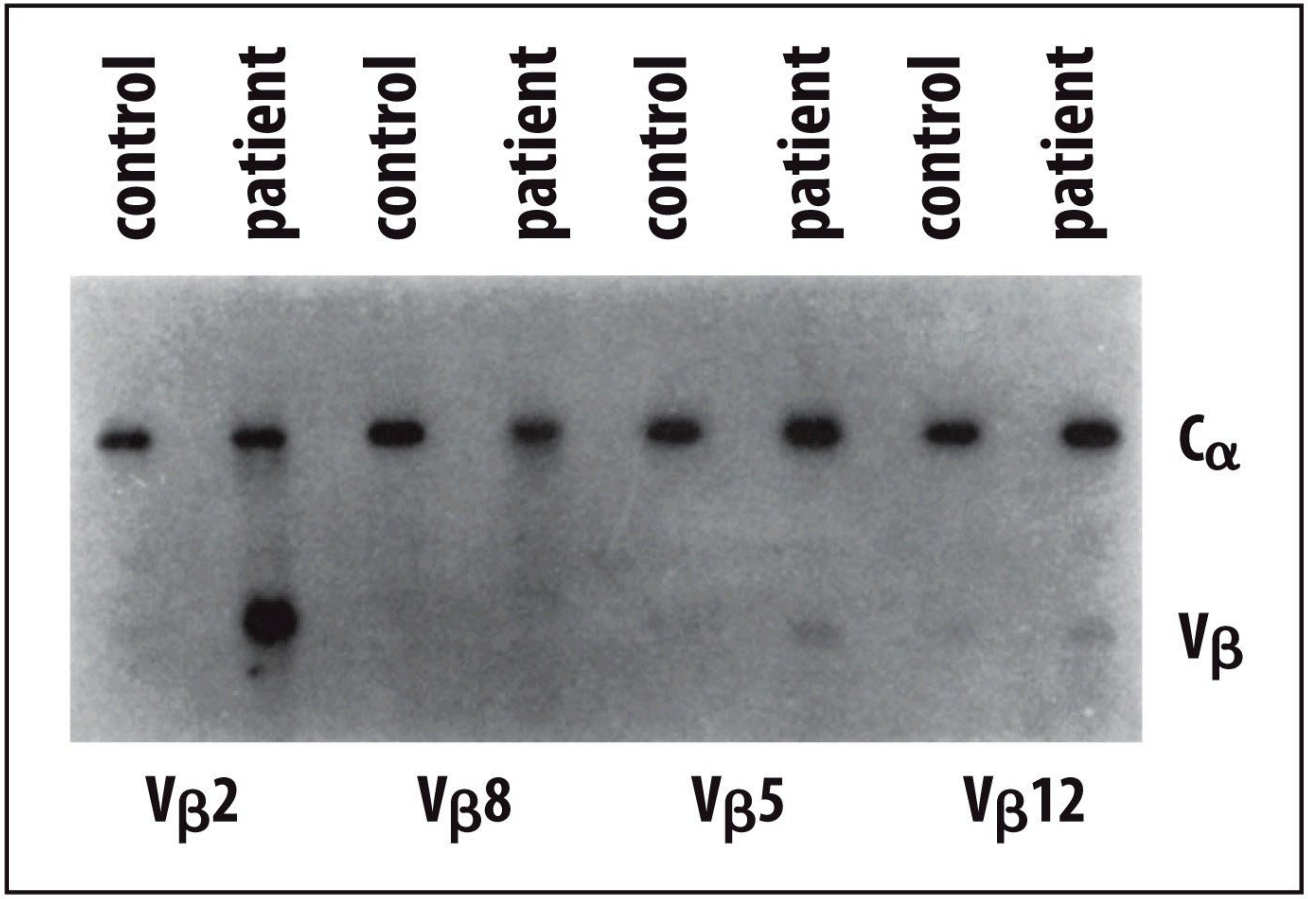
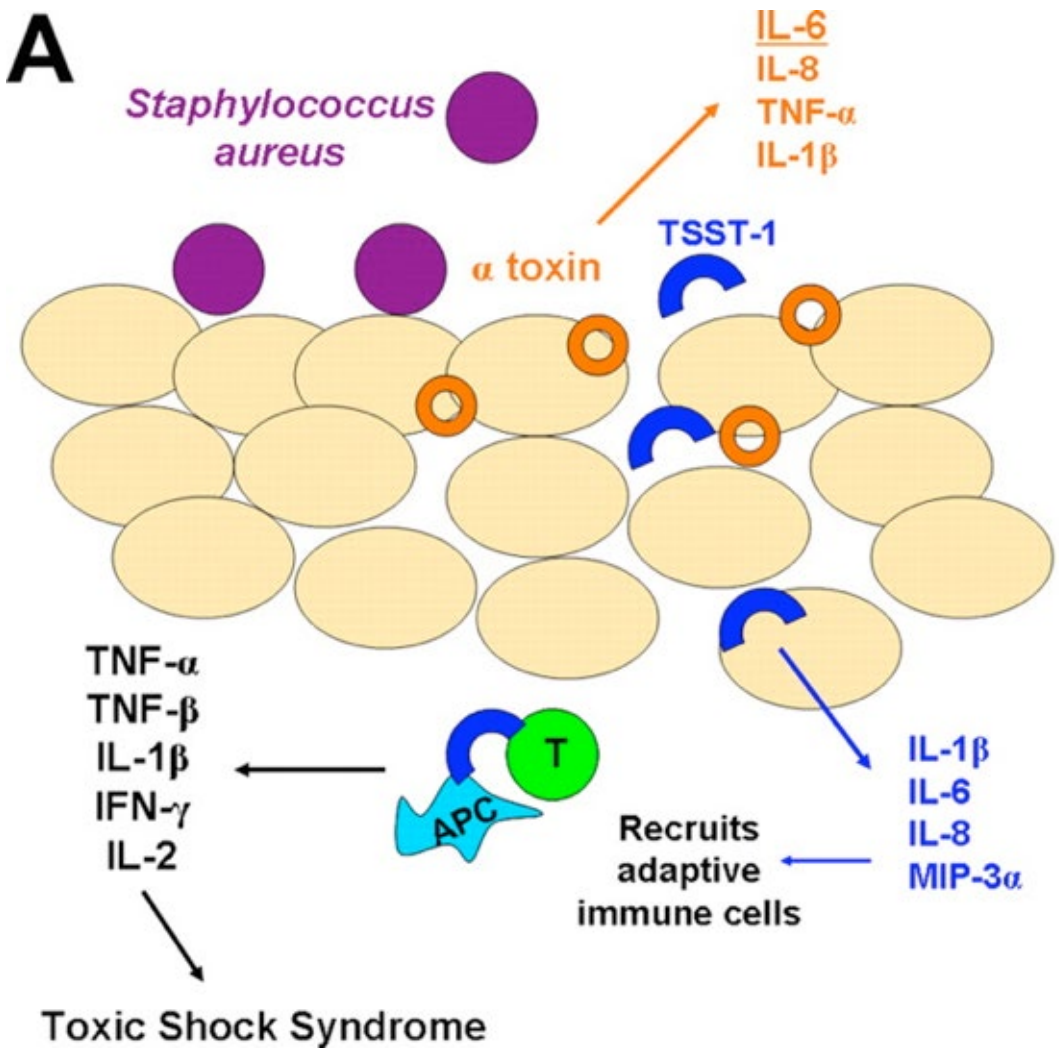


Figure 47.4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

How Do Superantigens Induce Systemic Shock?

- Direct activation of large number of T cells.
  - Tetanus toxoid: 1 in 10,000
  - Superantigen: 2%~20%
  - Massive and unregulated cytokine production

Cytokine Production Induced by Superantigens



The Journal of Immunology February 15, 2009 vol. 182 no. 4 2364-2373

How do you determine whether a protein behaves as a superantigen?

Properties of superantigens:

- Can activate naive T cells
  - will induce proliferation of lymphocytes from newborns and directly from thymus
- No processing is required for T cell activation
  - can induce proliferation of purified T cells in the presence of fixed monocytes (can't process antigen)
- Binding of protein in question to MHC II confirms it as a superantigen

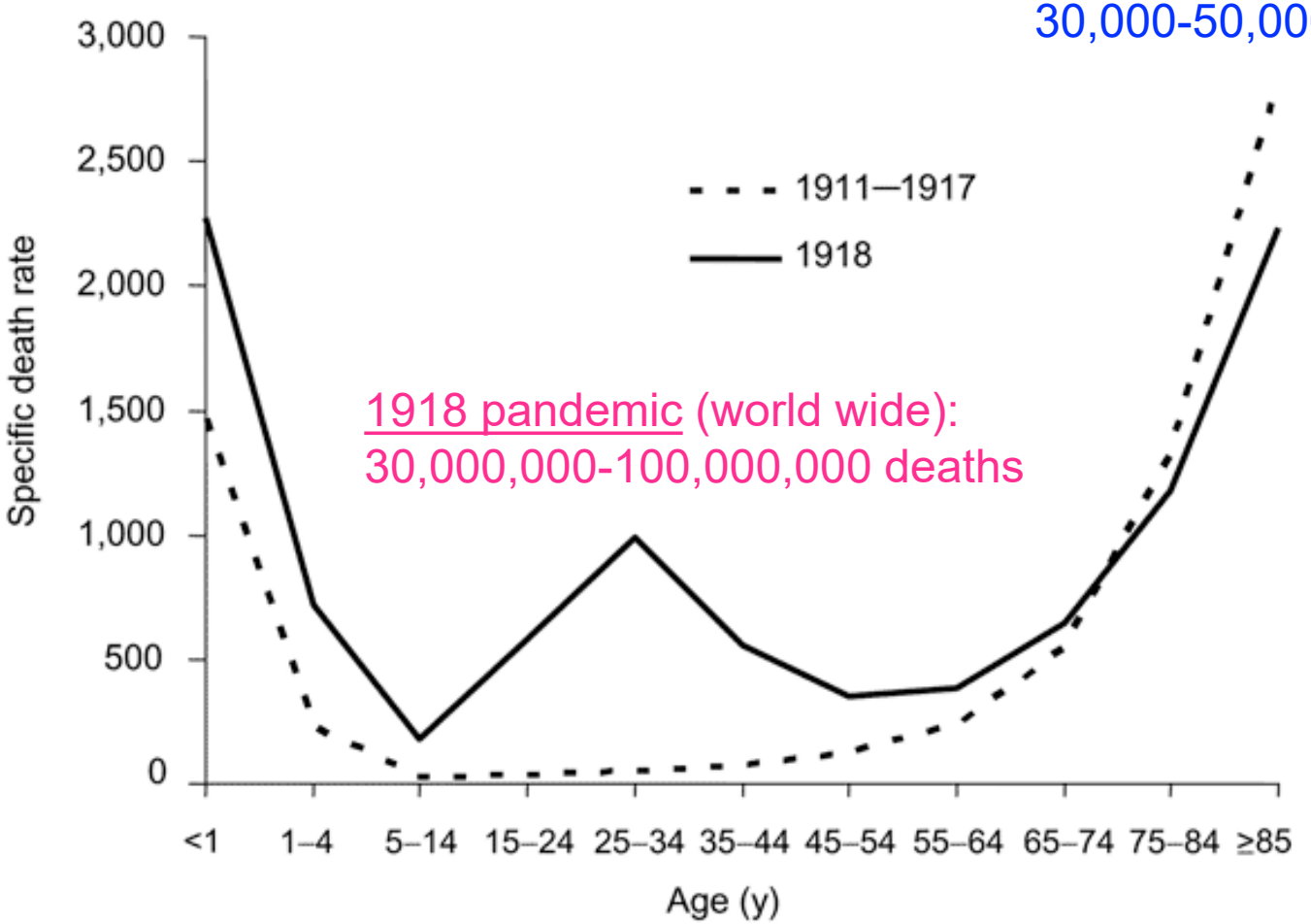
Why is TSST-1 Rare?

- *S. aureus* colonized 25-50% of the population and half of them produce superantigens.

- Protected by toxin specific antibodies

Why Did the 1918 Virus Kill So Many Healthy Young Adults?

Typical year (US):
30,000-50,000 deaths



Taubenberger & Morens. 1918 Influenza: the Mother of All Pandemics. *Emerging Infectious Diseases,* 12(1):15-22. 2006.