T cells and immunity to HIV

Pneumocystis
Fire Island
Gaetan Dugas
HIV
Cleve Jones
Disco
Larry Kramer
Marlboro
Kaposis Sarcoma
Book Title Faggots
Paul Popham
Donna Summer
Poppers
Bill Kraus
Time to AIDS

Prompt:

“Too much is being transmitted here”
(from ATBPO)

Dr. Selma Dritz, 1980 in reference to:
shigellosis, amebiasis, hepatitis A, hepatitis B

How were these agents spread?
Why are they particularly difficult to fight?
What was she referring to and what was her point?

Major Histocompatibility Complex (MHC)

Genetic association in human beings (and all other vertebrates):

All organ transplantation

Autoimmunity

- Rheumatoid Arthritis
- Type I diabetes
- Multiple sclerosis
- Systemic lupus erythematosus
- Crohn's disease-colitis ulcerosa
- Celiac disease
- Ankylosing Spondylitis
- Psoariasis vulgaris
- Narcolepsy
- Hashimoto's thyroiditis
- Graves disease

T cell recognition of antigen

alpha-beta T cells *all* recognize peptide antigen associated with MHC molecules

MHC represents a window to the proteins inside (MHC class I) and outside (MHC class II) of cells

MHC-Nature's Artwork

MHC Class I

MHC Class II

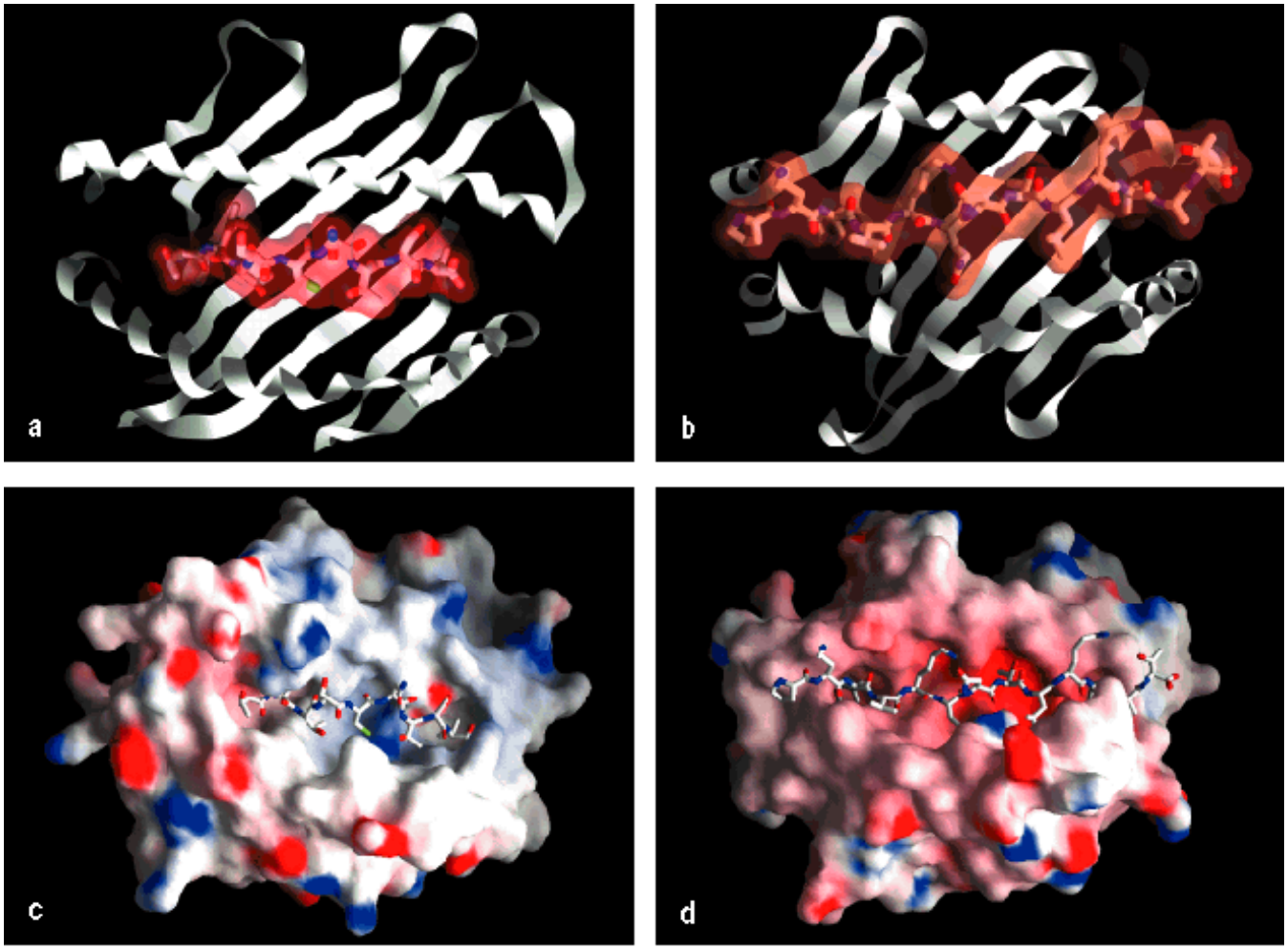
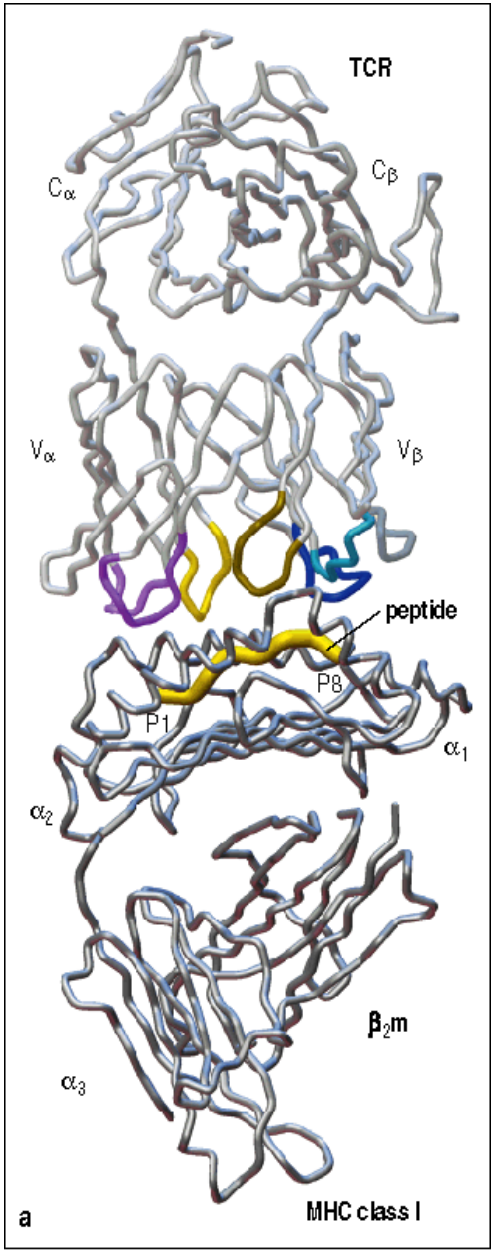
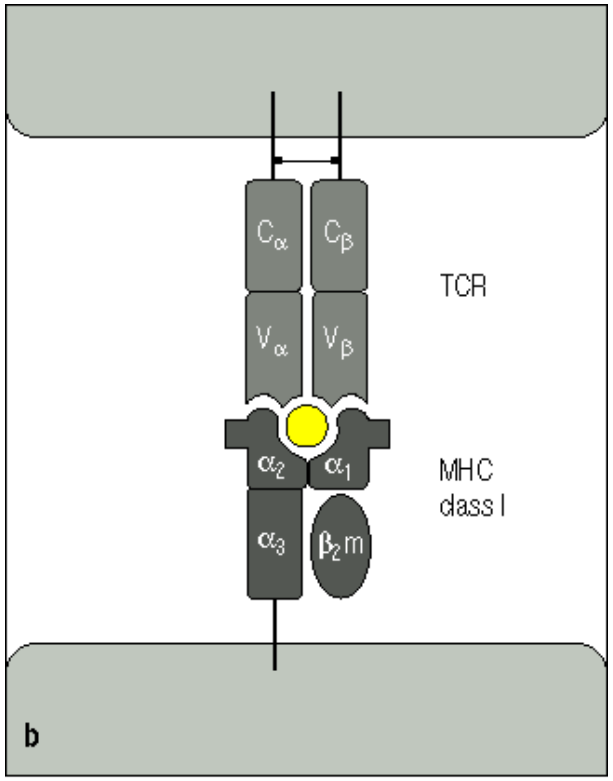
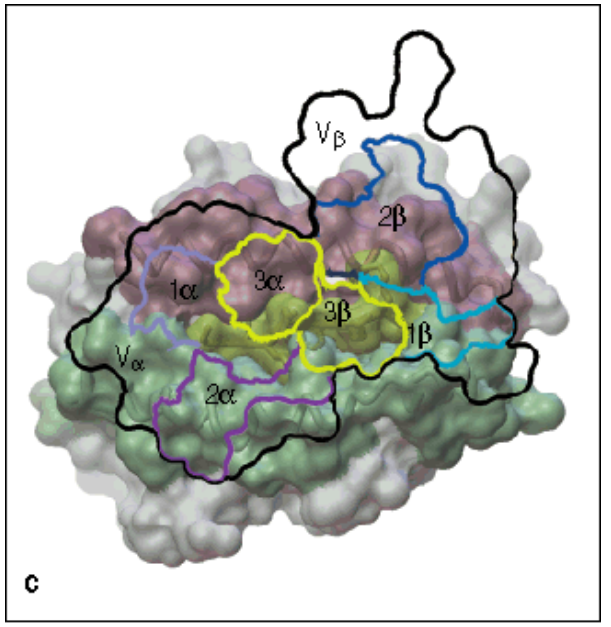


Figure 3.11

TCR binding MHC/peptide







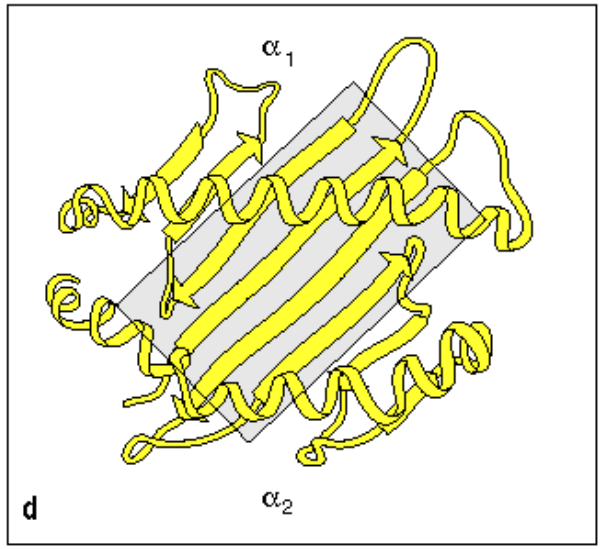
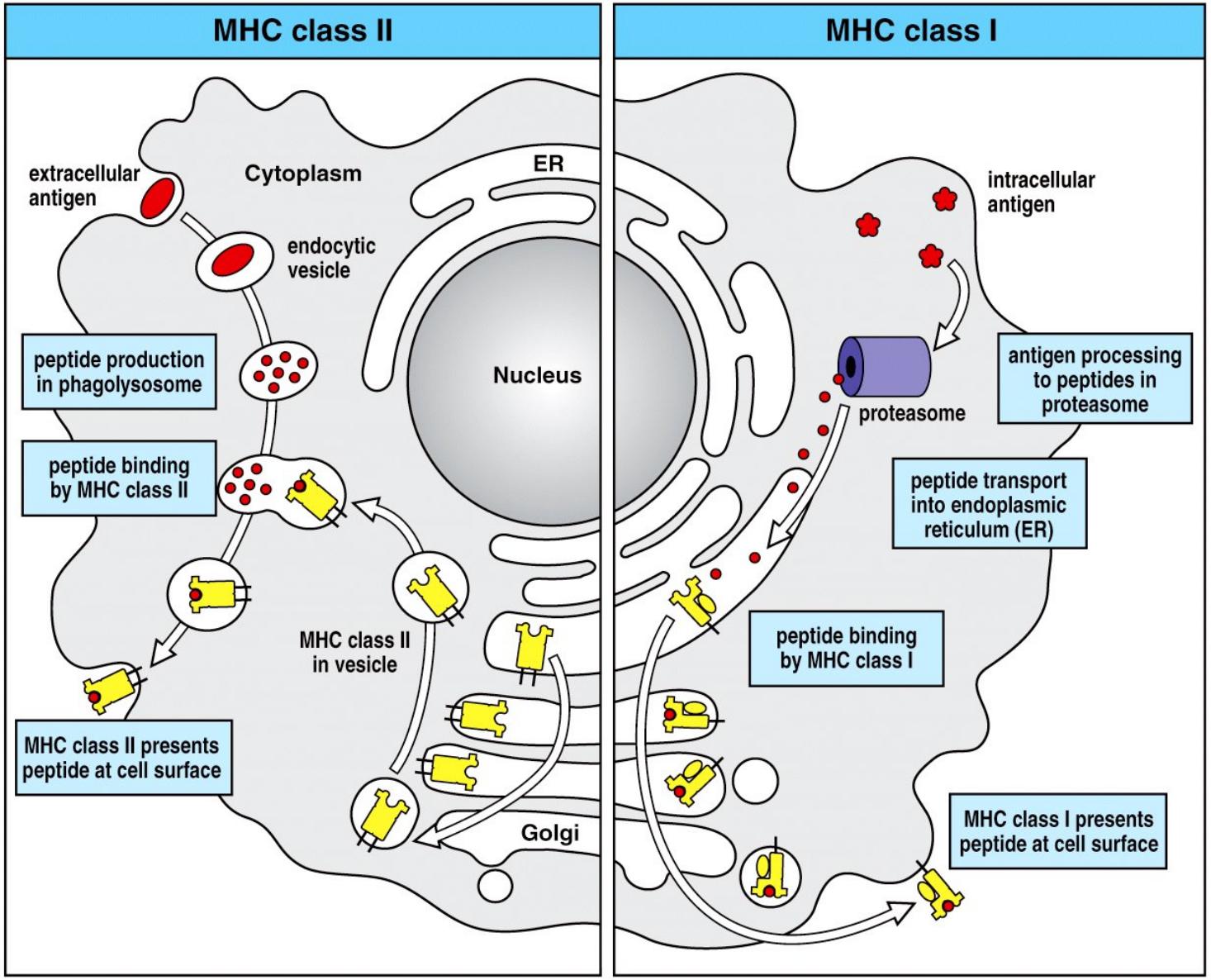
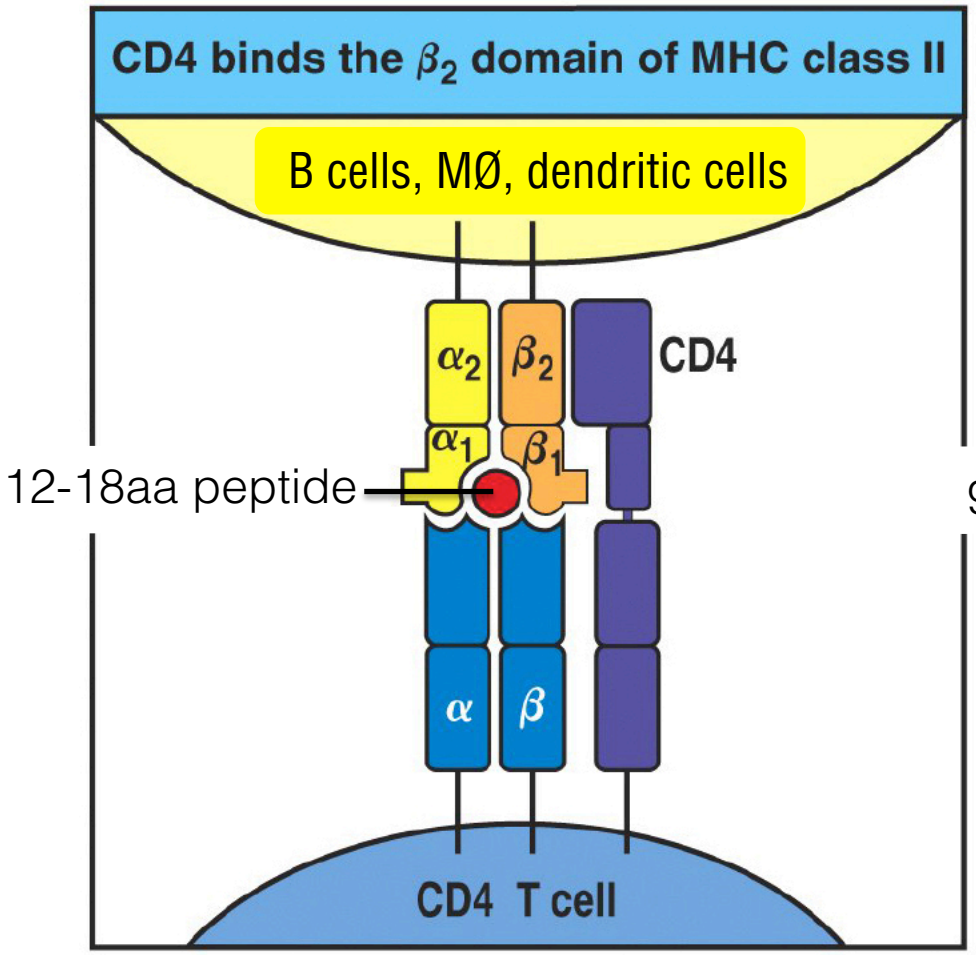


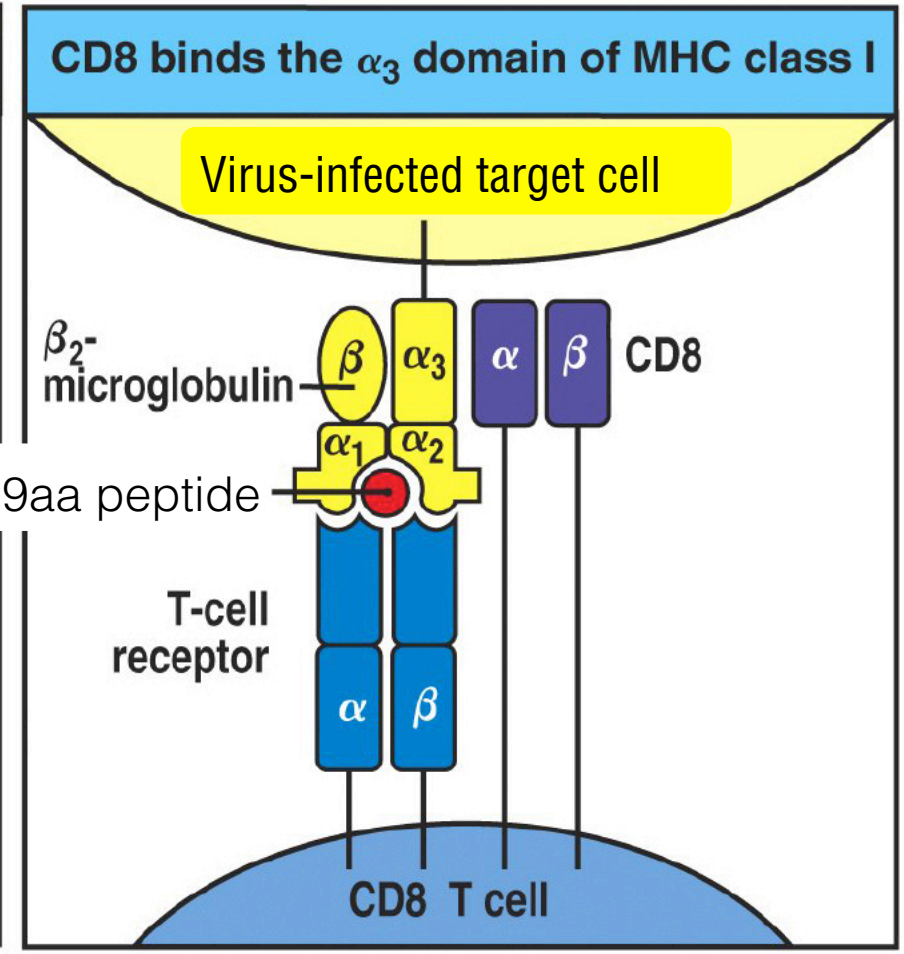
Figure 3.17 a, b, c, d

The *Ins and Outs* of Antigen Presentation



Dendritic Cell





CD4+ Helper T Lymphocyte (Th)

CD8+ Cytotoxic T Lymphocyte (CTL)

T cells are specific for both the antigen peptide and the MHC allele,
this is call MHC restriction

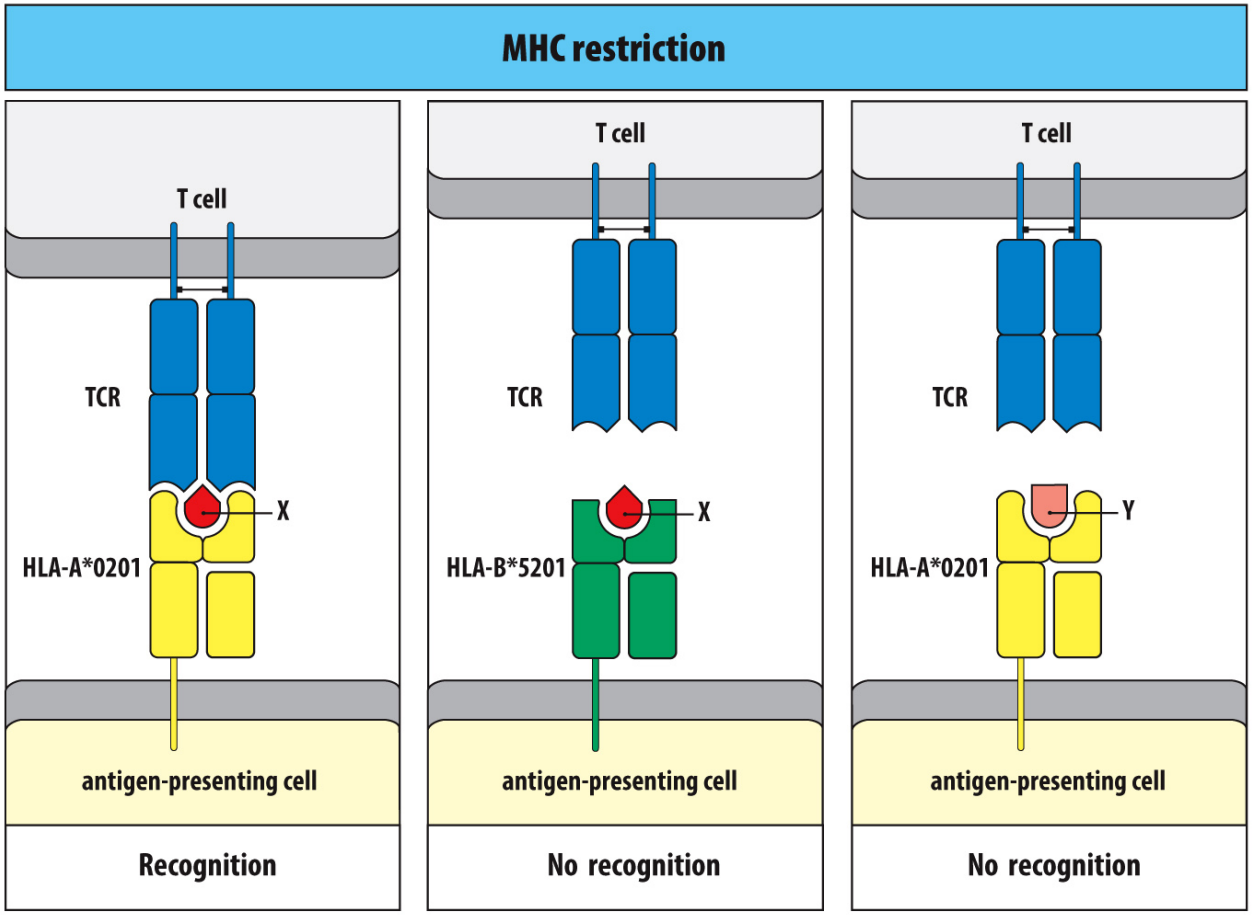
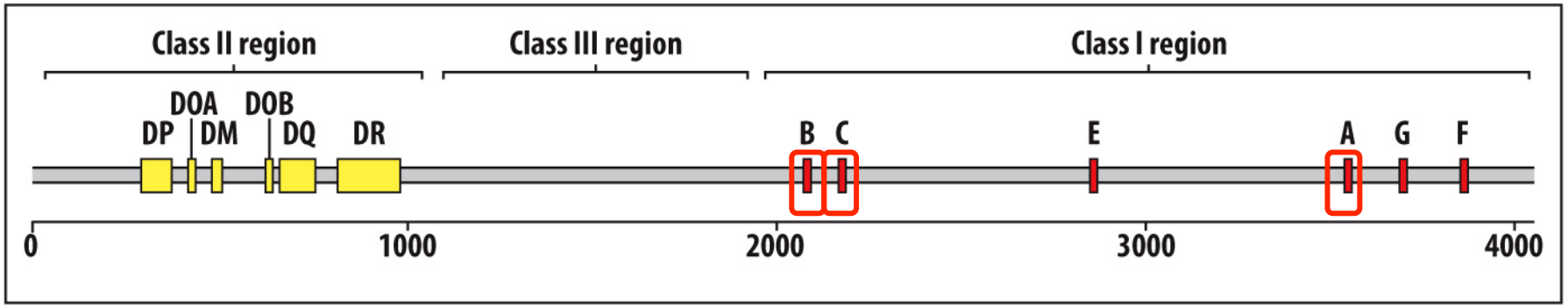


Figure 5.35 The Immune System, 4th ed. (© Garland Science 2015)



HLA polymorphism		
MHC class	**HLA locus**	**Number of allotypes**
MHC class I	A	1939
	B	2577
	C	1595
	E	6
	F	4
	G	16
MHC class II	DMA	4
	DMB	7
	DOA	3
	DOB	5
	DPA1	17
	DPB1	286
	DQA1	32
	DQB1	399
	DRA	2
	DRB1	1158
	DRB3	46
	DRB4	8
	DRB5	17

Science 2015)

alleles within the human population

Figure 5.29 The Immune System, 4th ed. (© Garland Science 2015)

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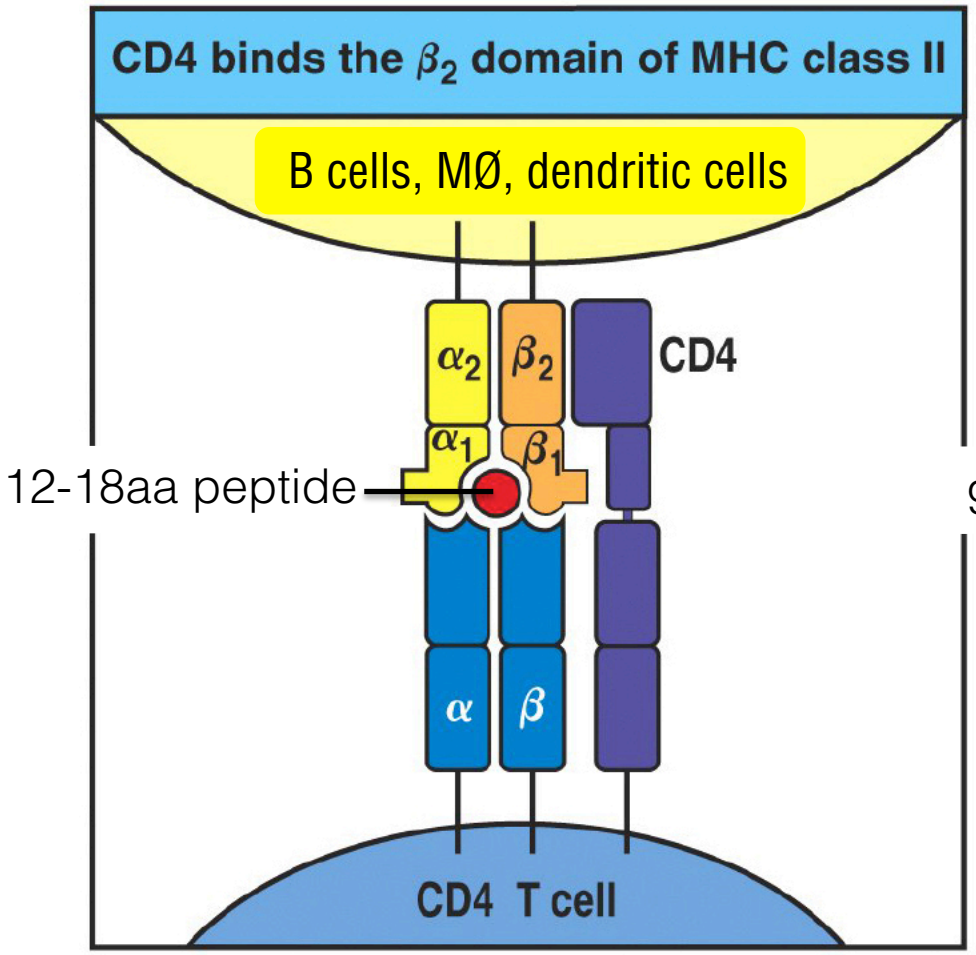

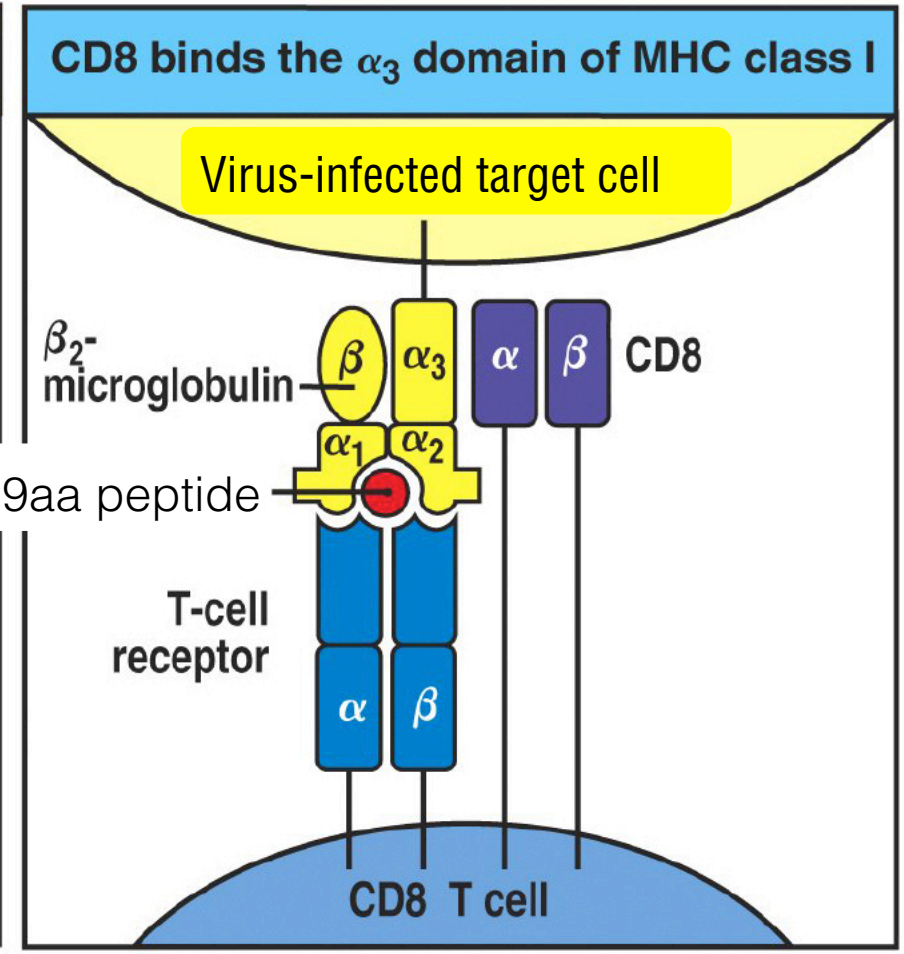

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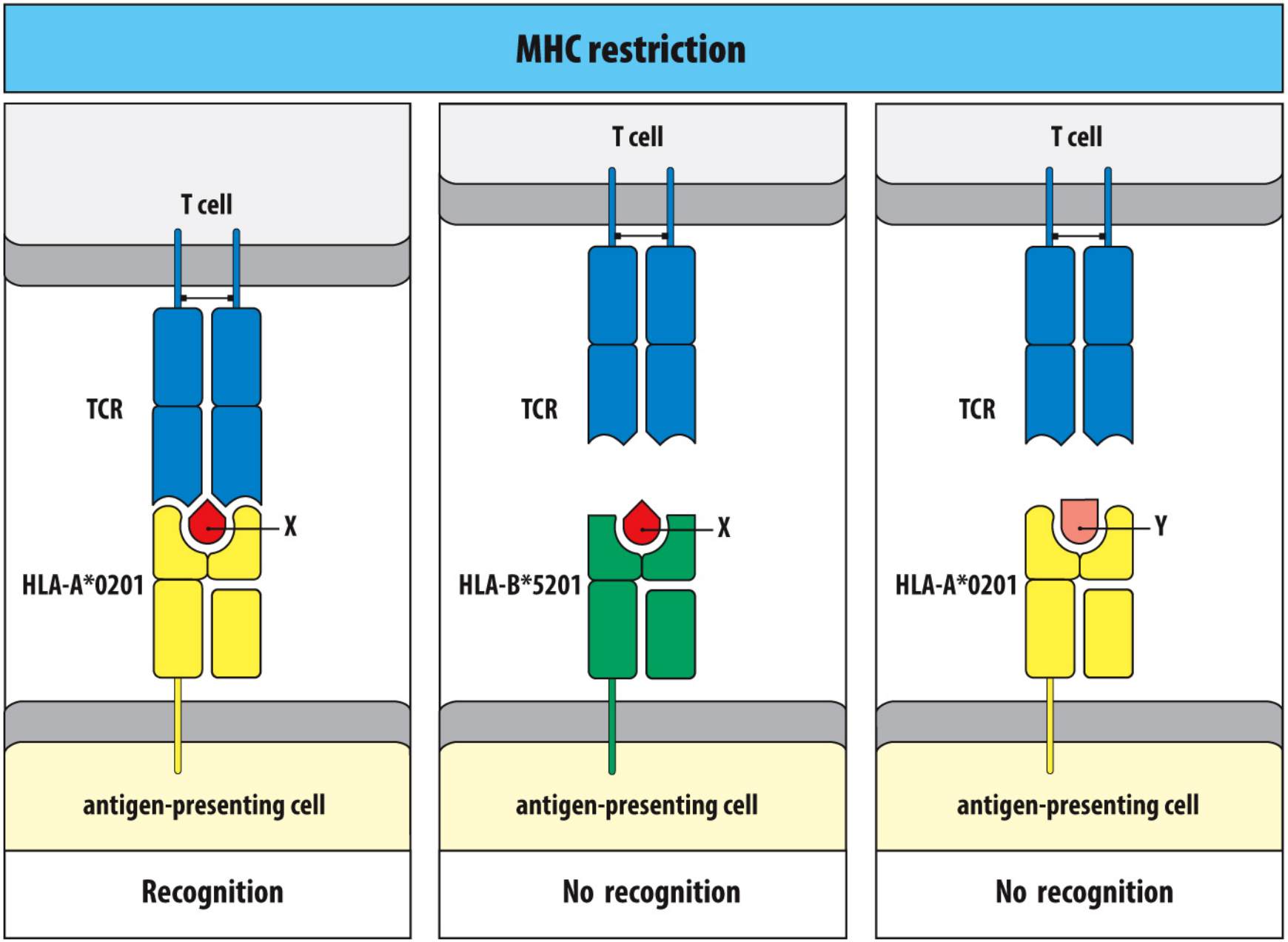


Figure 5.35 The Immune System, 4th ed. (© Garland Science 2015)

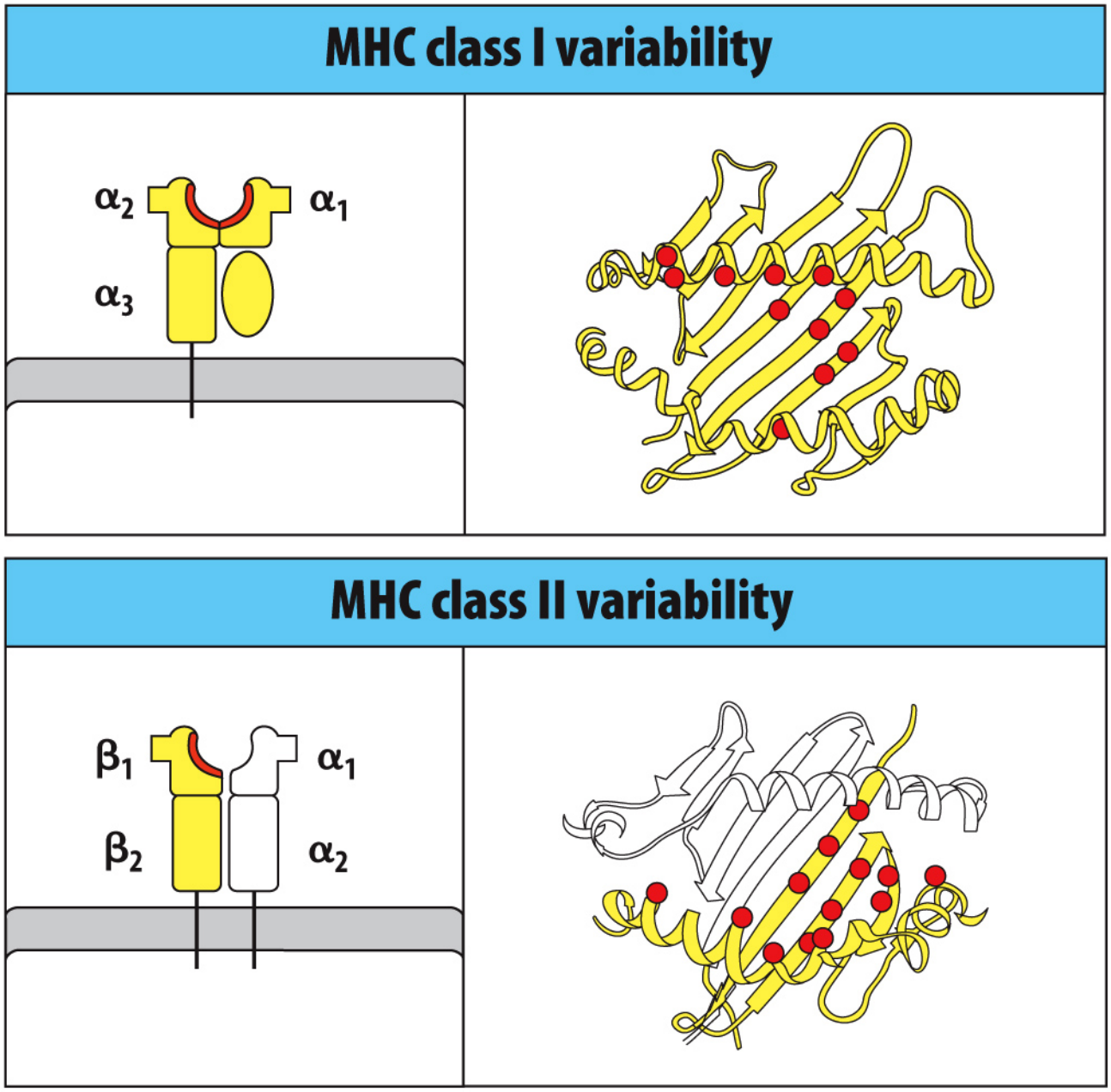
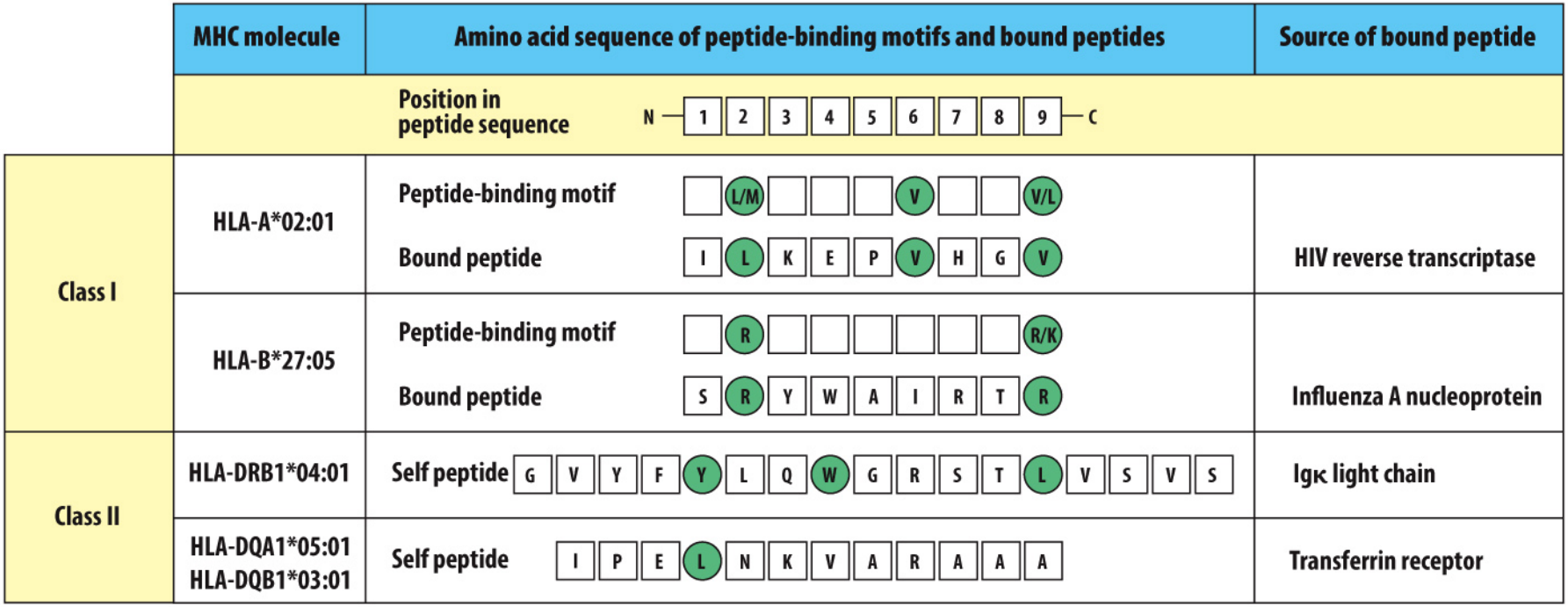


Figure 5.33 The Immune System, 4th ed. (© Garland Science 2015)



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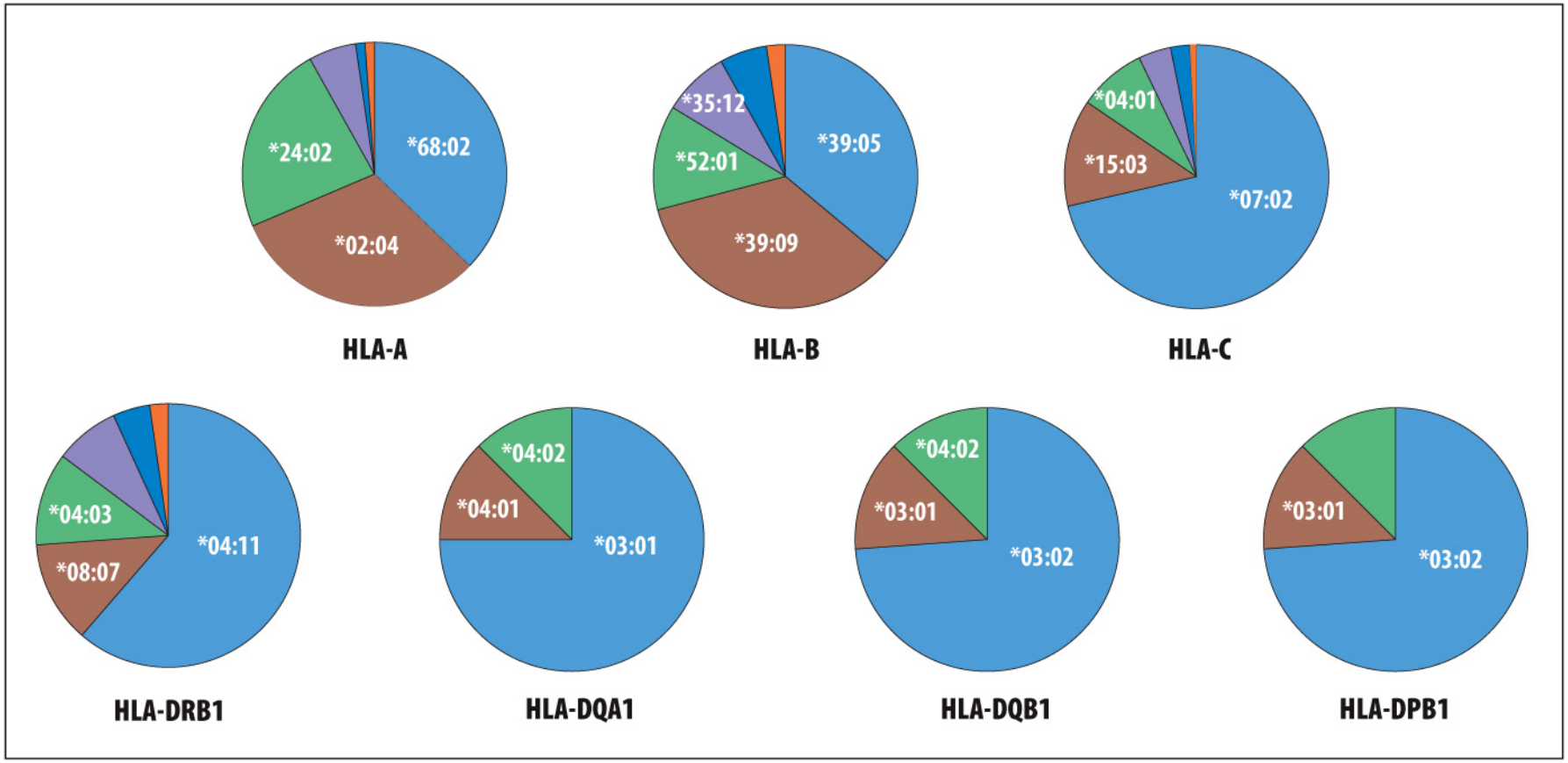


Figure 5.39 The Immune System, 4th ed. (© Garland Science 2015)

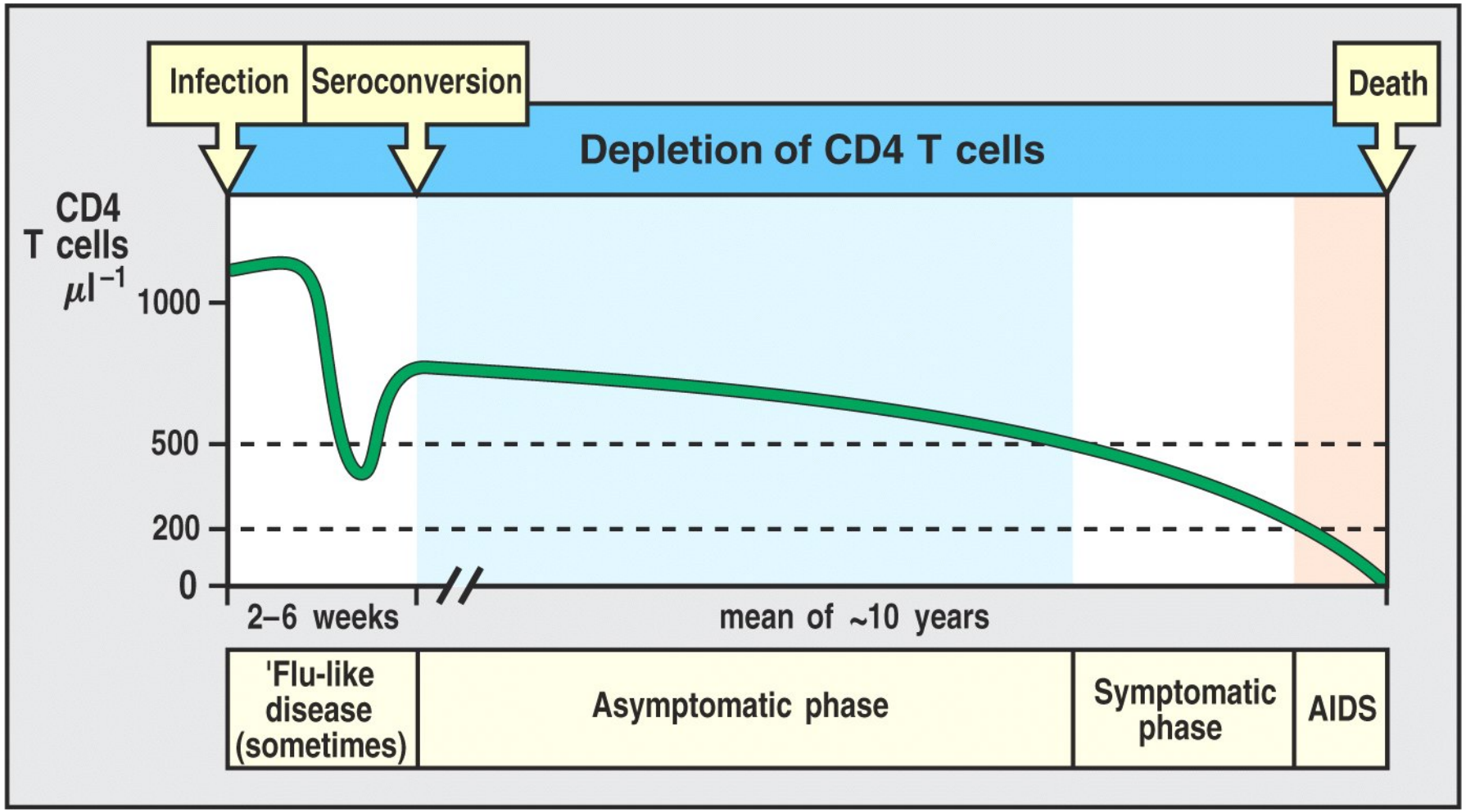


Figure 9-16 The Immune System, 2/e (© Garland Science 2005)

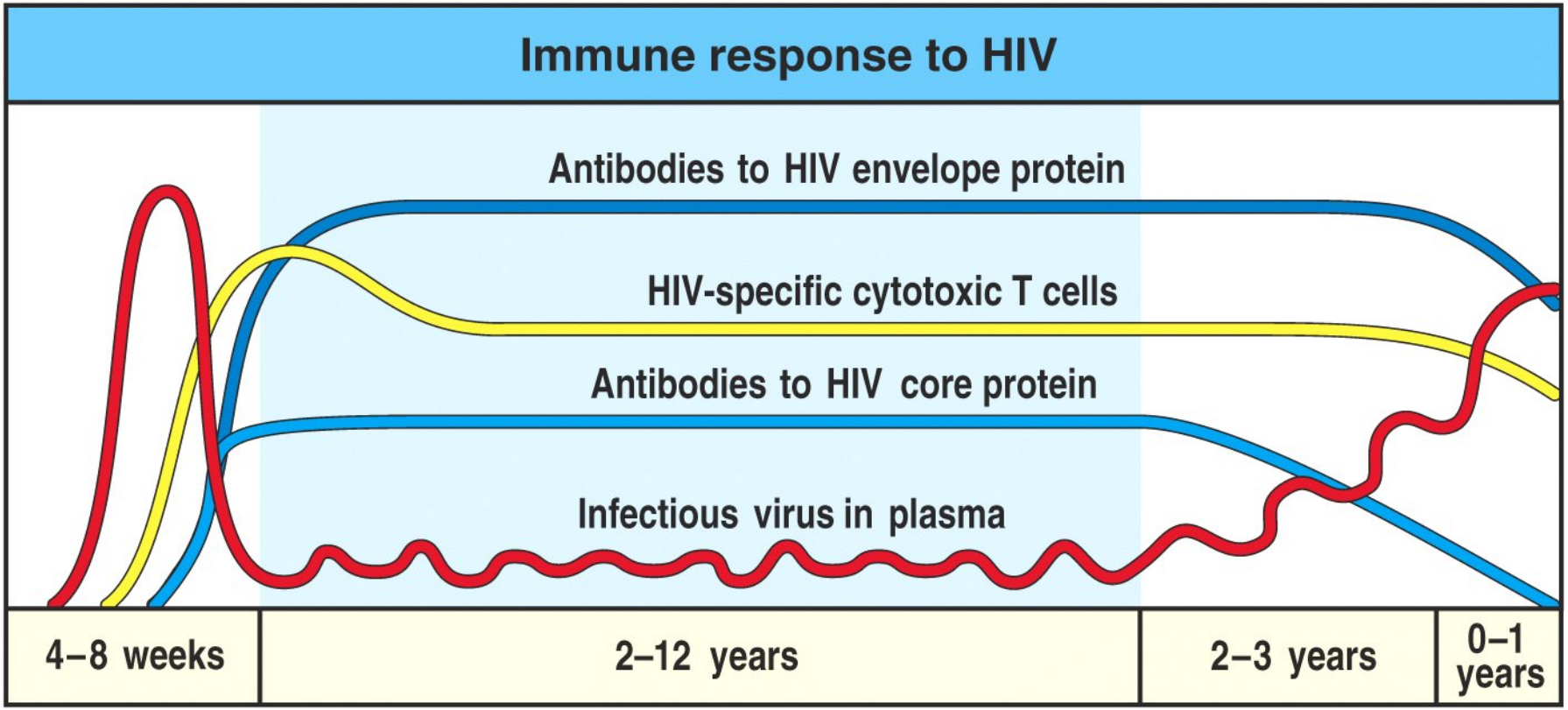
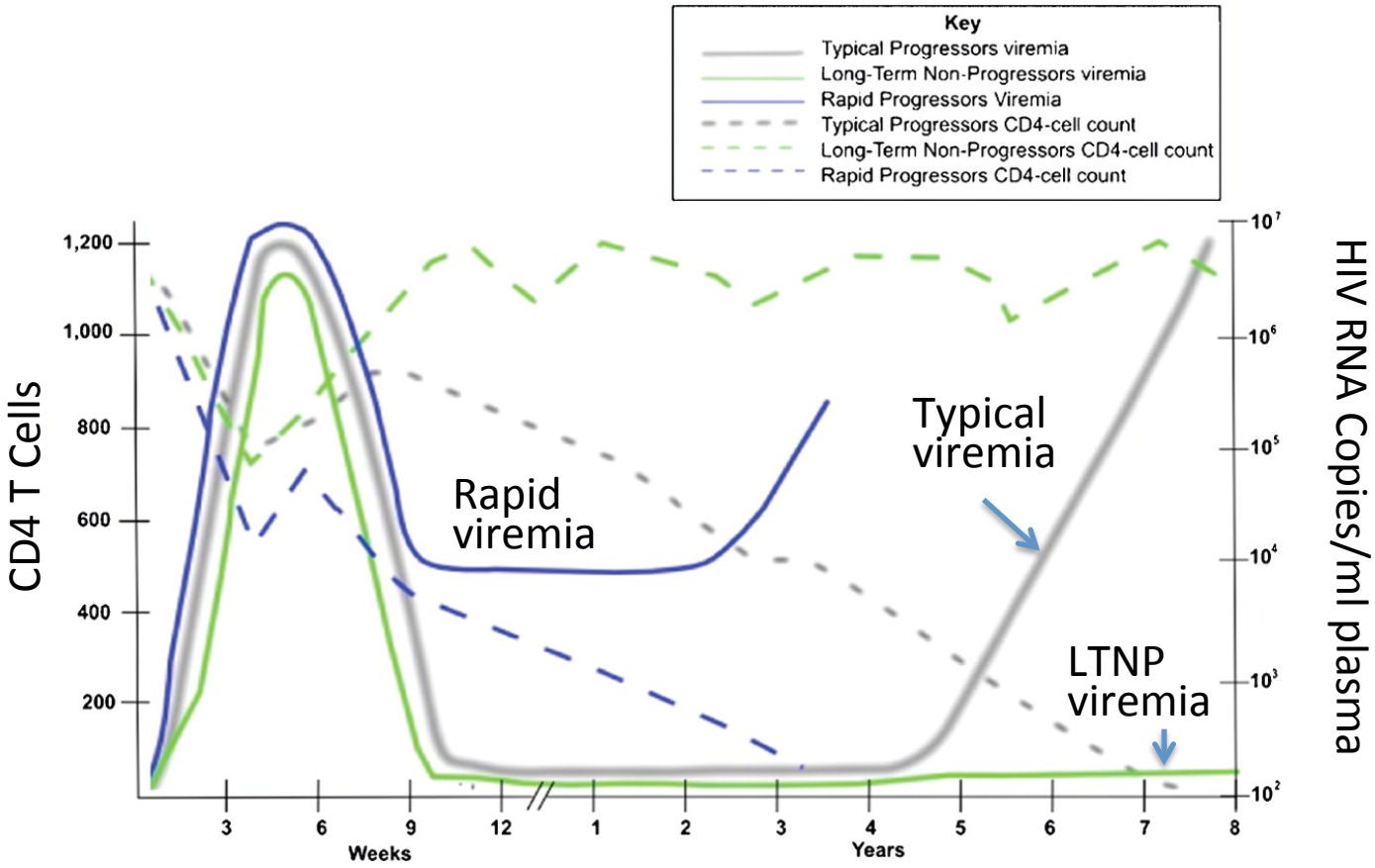
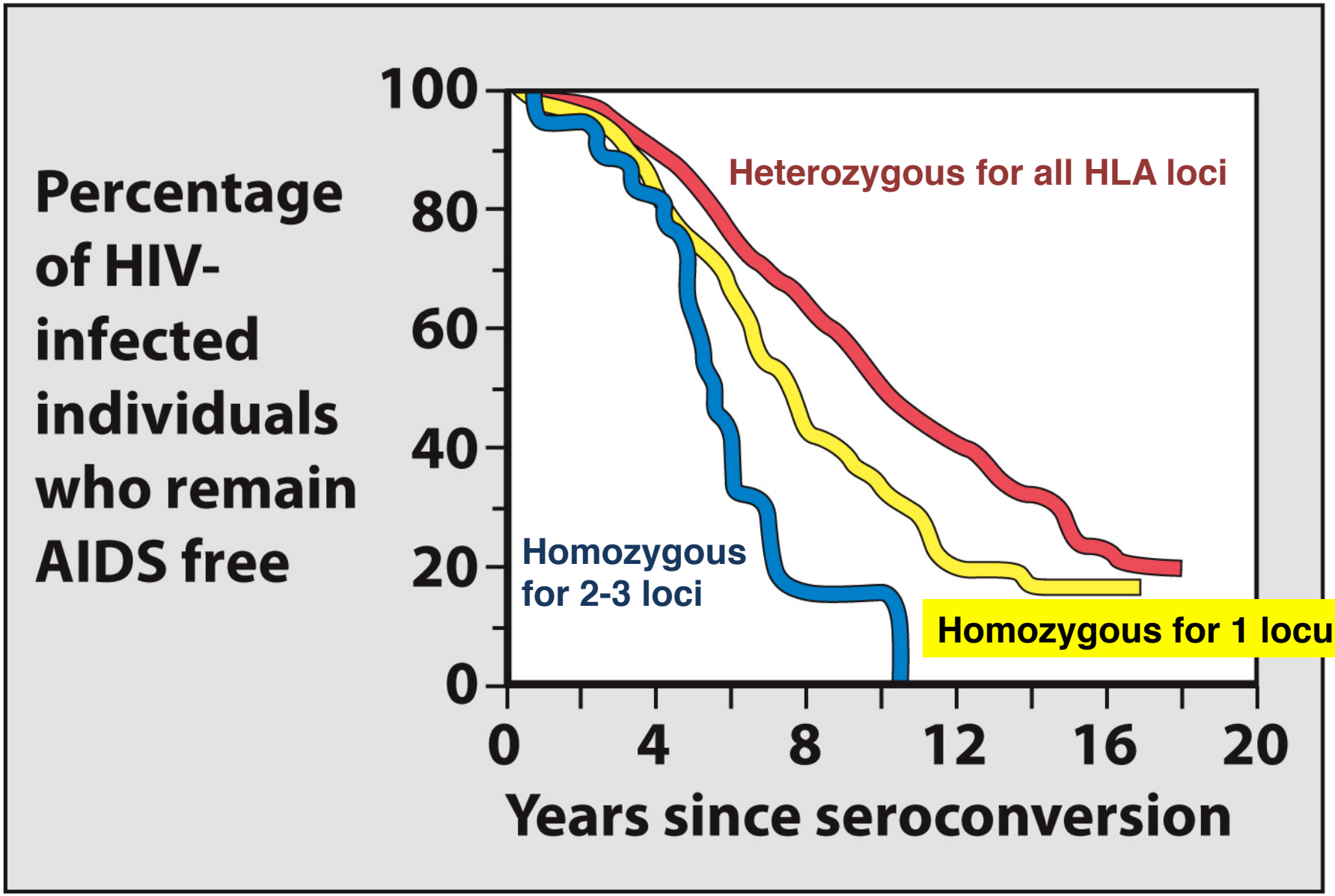


Figure 9-18 The Immune System, 2/e (© Garland Science 2005)

Disease progression in HIV-1-infected typical progressors, LTNPs and rapid progressors according to CD4+ T-cell counts and viraemia.



In studies with cohorts of at least 30 subjects, between 8 and 63% of either Long-term Nonprogressors or Elite Controllers have been found to carry the B57 allele with frequencies being the highest in elite controllers



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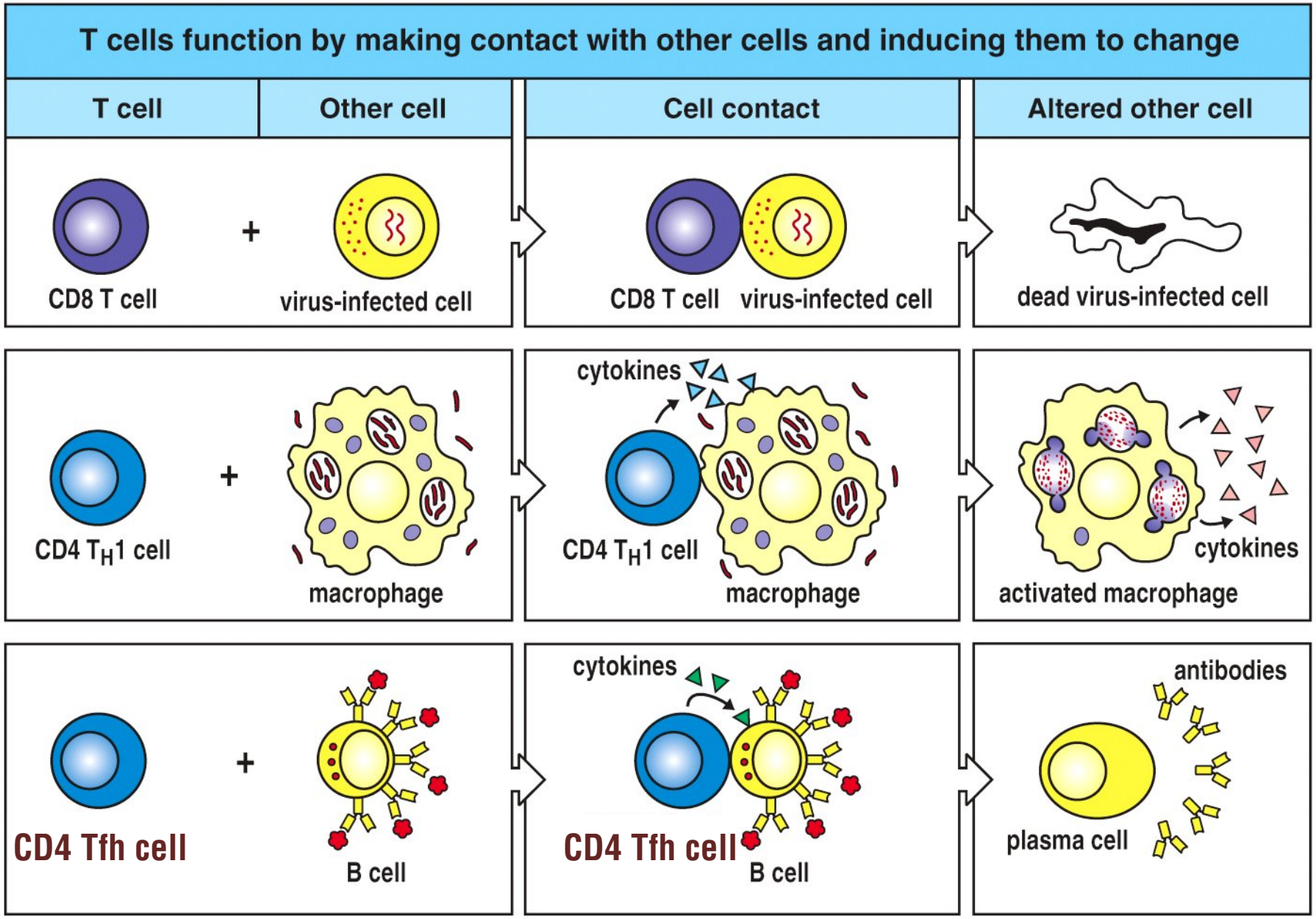

Figure 3-11 The Immune System, 2/e (© Garland Science 2005)

Presentation of an 8-9 aa peptide from a virus bound to MHC class I

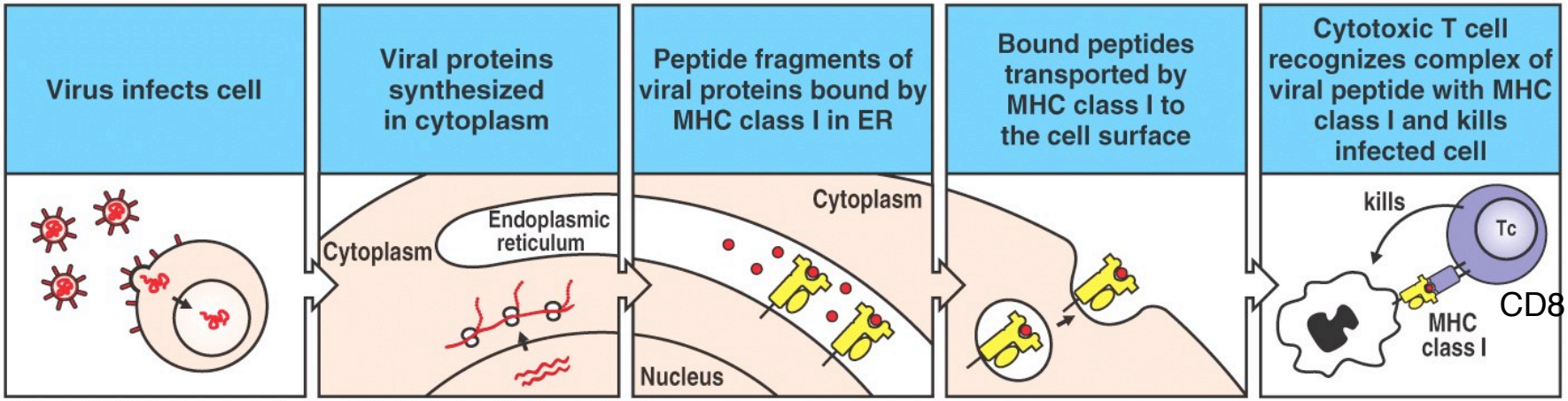

Figure 1-26 The Immune System, 2/e (© Garland Science 2005)

Presentation of an 12-18 aa peptide bound to MHC class II

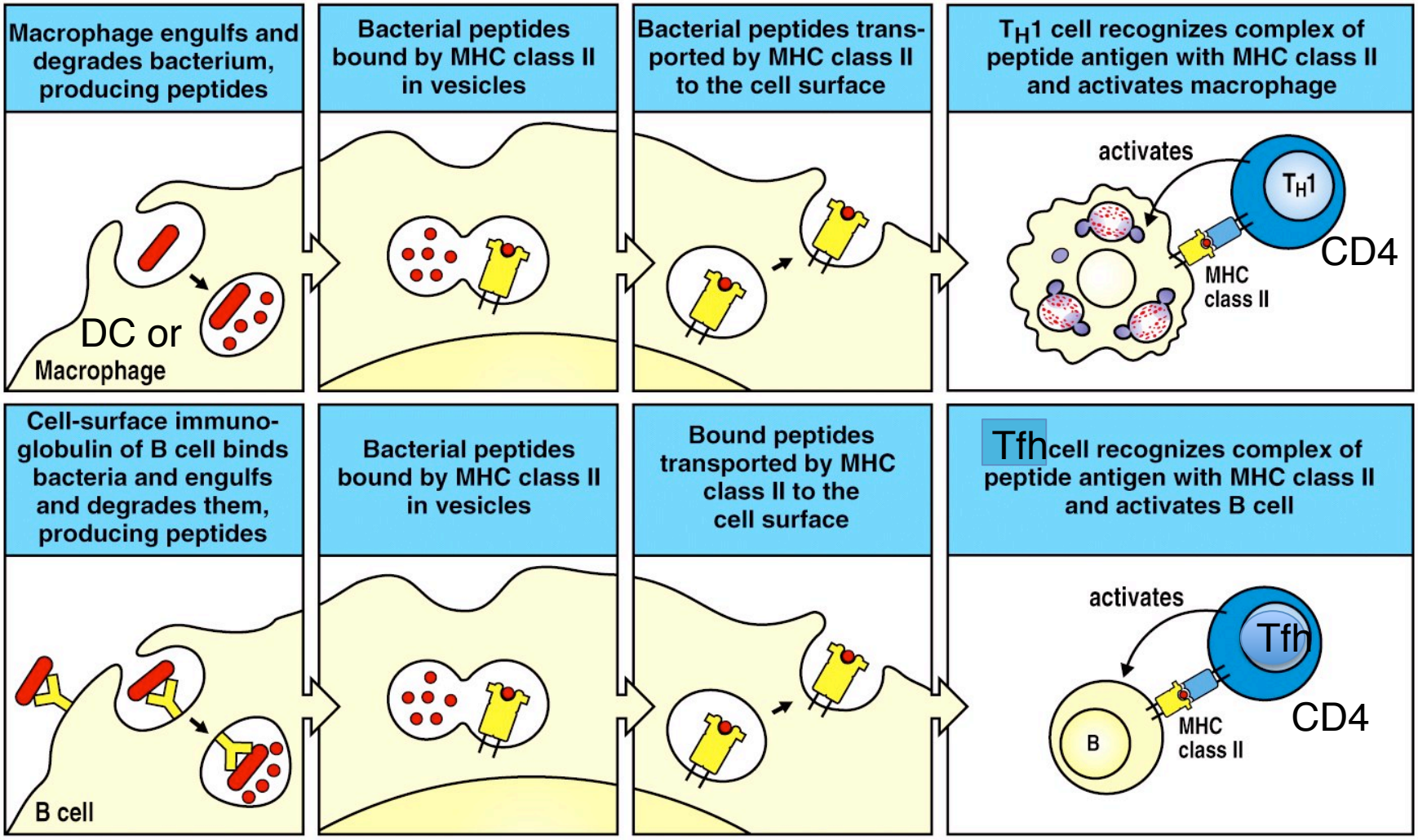

Figure 1-27 The Immune System, 2/e (© Garland Science 2005)

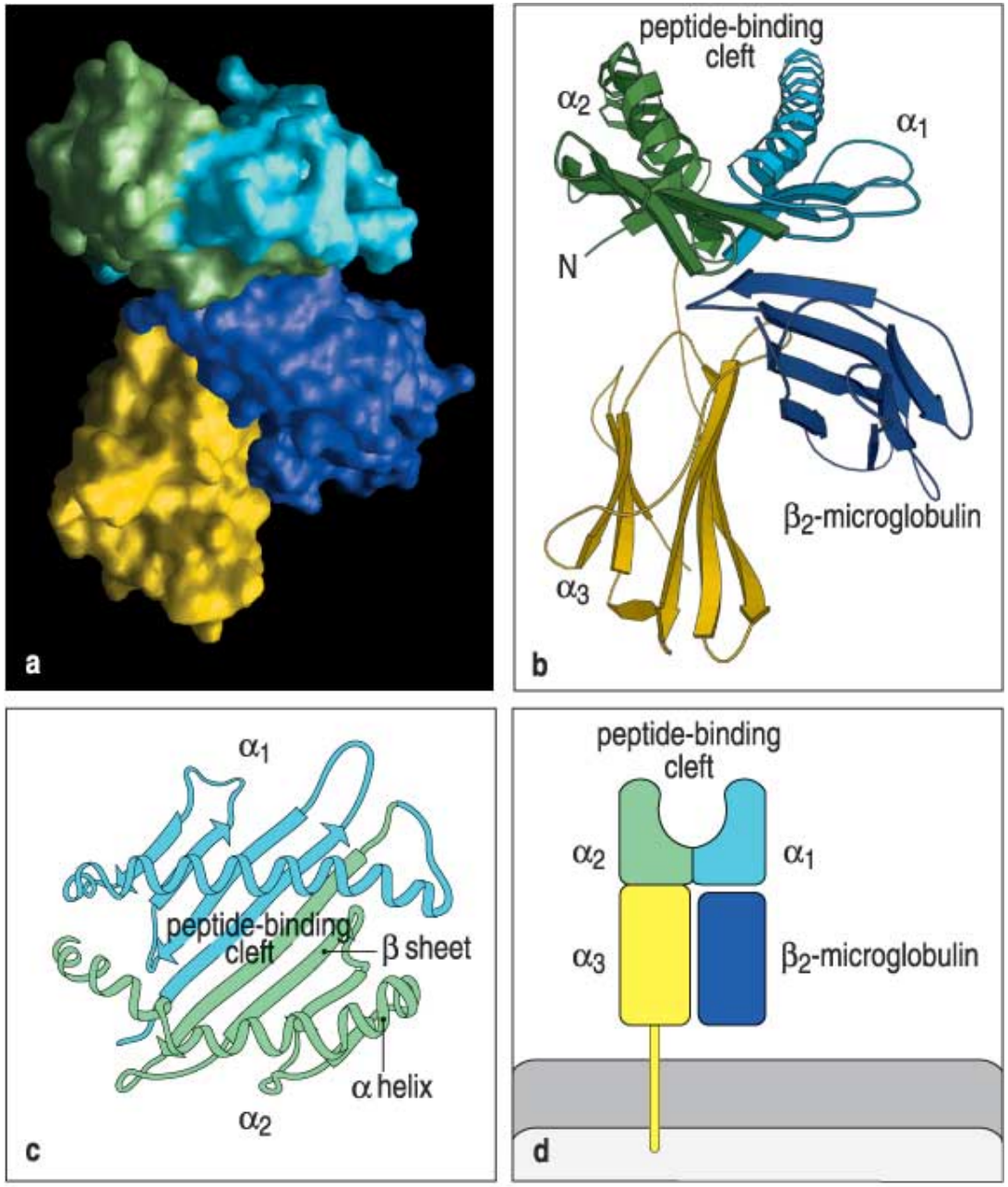

Fig 3.20 © 2001 Garland Science

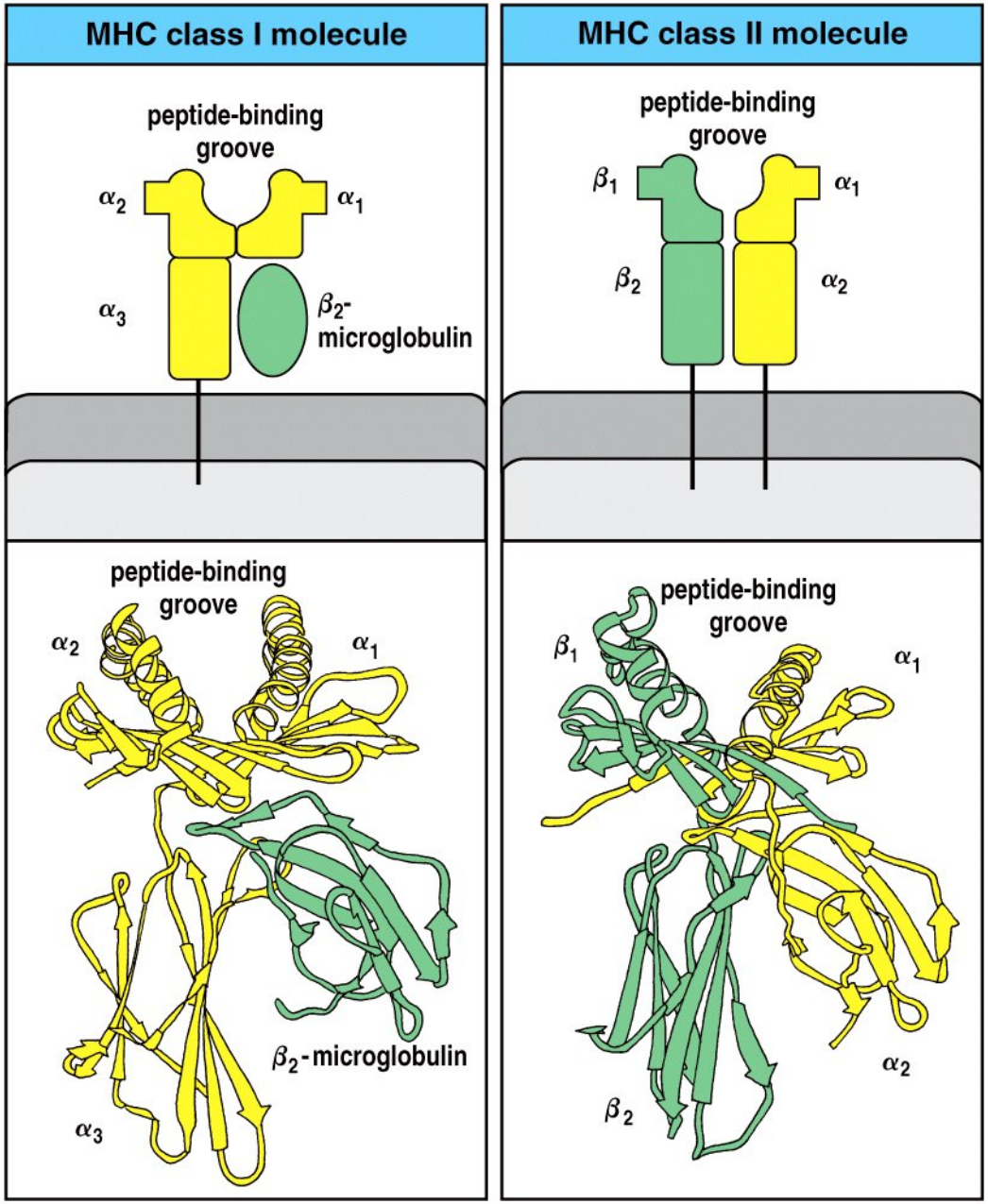

Figure 3-13 The Immune System, 2/e (© Garland Science 2005)

Definitions of major controller populations-Probable involvement of CTLs

	EC	LTNP
$CD4^+$ T-cell level (cells μl^{-1})	variable loss	≥500
Viral load (copies ml–1)	≤50	≤10000
Antiretroviral therapy	No	No
Years without AIDS	Months–years	≥7–20*

*by definition

Long-term non-progressors are characterized by being infected by more than 7 years, have stable CD4 T cell counts always above 500 cell/µl of blood and stable low but detectable viral loads, representing approximately 5% of all chronically HIV infected individuals.
Their CD8+ CTLs are qualitatively superior to chronic progressors: high proliferative capacity and cytotoxic activity. Conversion from LTNP to CP is associated with mutations in the peptides recognized by CTLs.

Elite controllers represents a further restricted population (about 3/1000 of HIV infected individuals), and are defined by stable CD4 cell count (irrespective of a threshold), anti-retroviral therapy naïve, and with viral loads persistently below 50 copies/ml (undetectable) for more than 12 months.

Role of CD4 T cells

CD4+ T cells, or T helper cells (Th), play a central role in immune protection, by inducing

(i) long-term maintenance of antigen-specific CD8+ memory T cells,
(ii) antibody production from B cells
(iii) macrophages to develop enhanced microbicidal activity, to recruit neutrophils, eosinophils, and basophils to sites of infection and inflammation
(iv) expression of cytokines and chemokines to orchestrate the full panoply of immune responses.

Number of CD4 T cells in circulation inversely proportional to the onset of AIDS

MHC alleles and Long-term nonprogressors

LTNP recognition of HLA-B57-restricted and HLA-B27 peptides correlated with long-term control of infection

Viral escape mutations in these epitopes are associated with eventual virologic breakthrough in controllers

In some HLA-B57 patients HIV-1 infection is controlled by inducing a cross-reactive response against immunodominant Gag epitopes

Other protective HLA class I alleles include B13, B15, B44, B51 and B58 – in some cohorts as many as 90–95% of LTNPs carry at least one of these alleles, Controlling HIV-1 infection could be the additive effect of some or all of the HLA B alleles

HLA class I alleles associated with **accelerating** HIV-1 disease progression, which include A24, A29, B35, C4 and Cω4

Specifically, the B35 allele has been linked to accelerated disease progression due to its reduced ability to bind HIV-1 peptides and activate a CTL response

In rhesus monkeys, elite control of viral load infected with SIV is correlated with their carriage of the (MHC) Mamu-B08 allele

Mamu-B08 matches the peptide (epitope) binding profile for HLA-B27

Understanding HIV progression

AIDS, CD4 count <200 cells/mm3 blood
Or
AIDS-defining opportunistic infections

Gaetan Dugas the infamous candidate for patient zero
June, 1980 already diagnosed with Kaposi's Sarcoma
Lymph nodes had been swollen for a year, i.e. infected before June, 1979
Fully blown AIDS, December, 1983
Died March 30, 1984, loss of kidney function

Dale Lawrence , CDC, Atlanta (from ATBPO)

70 yr woman, wife of hemophiliac, late 1983
Her husband infected by blood products
Infections occurred at very different times, yet they came down with AIDS together

Time to disease different:
Gay men
Hemophiliacs (sometimes only months after transfusion)
Partners of Hemophiliacs
Blood transfusion recipients

CDC only seeing the onset of AIDS, no way to track most infections

AIDS incidence curves paralleled gastrointestinal parasites (pandemic) (remember Selma Dritz) in the male gay population—only 5 years displaced! (AND the Band… July 17, 1983)

Meanwhile, HHS Sec. Heckler and Asst. Sec. for Health, Brandt did not move to improve the safety of the blood supply or the blood products supply.

First Blood Banker to act was Dr. Ed Engleman of Stanford. Measured CD4:CD8 ratio
One patient had a CD4:CD8 ratio 0.29, would not return for follow-up. Between 1981 and 1984, donated 13 times. Had Ab to hepatitis B, would have been eliminated had the CDC required hepB-negative blood donors. No AIDS symptoms during this period. Only Stanford Blood Center discarded his blood, and did so because they tested CD4:CD8 ratios.

December 30, 1983 Dr. Dale Lawrence, again
CDC had 21 AIDS patients whose disease was linked to blood transfusions, plus another 10 under investigation.
Infection date, and time to AIDS pinpointed
Mean incubation time: 5.5 years
As long as 11 years
Some came down with AIDS in 6 months

Why is the 50% time to AIDS presently given at 10-11 years?
Time between HIV infection and AIDS (CDC)
Shorter
older age
infection with more than one type of HIV
poor nutrition
severe stress
Longer
closely adhering to your doctor's recommendations
eating healthy foods
taking care of yourself

Other immunological factors

Two studies (Bochud et al., 2007; Soriano-Sarabia et al., 2008) have found that SNPs in the TLR9 gene are associated with a rapid HIV-1 disease progression. The 1635A/G TLR9 and 1174G/A polymorphisms positively correlated with rapid disease progression, higher viral loads and low CD4+ T-cell counts in the studies' large cohorts of therapy-naïve HIV-infected individuals