

The immune system

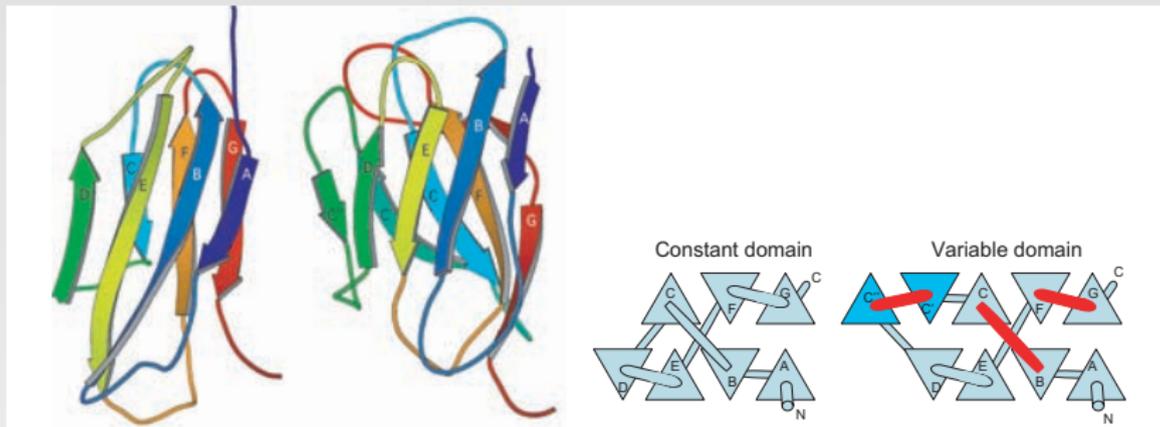
Biophysical Chemistry 1, Fall 2010

B-cells and T-cells

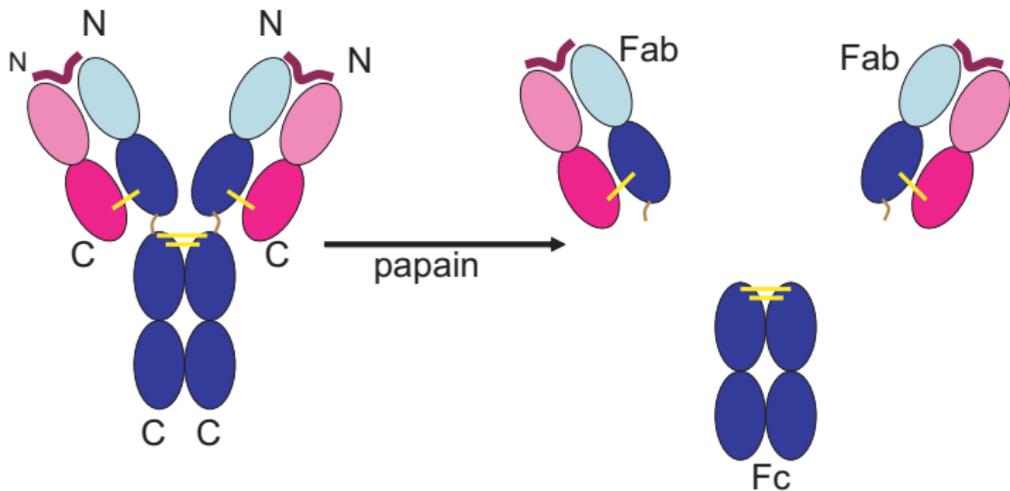
Catalytic antibodies

Reading assignment: Chap. 14

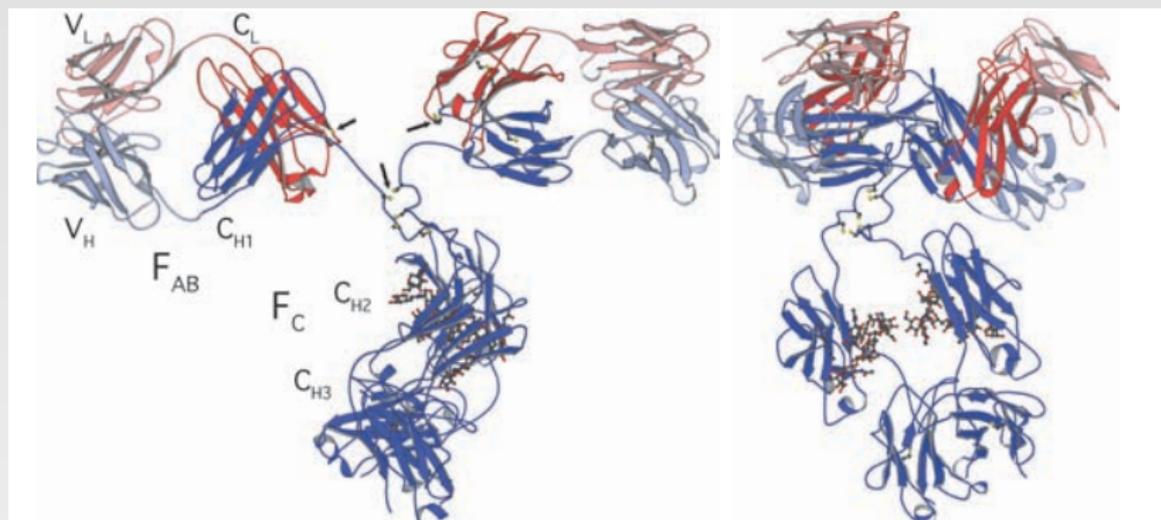
B-cell or humoral immunity uses a protein G fold



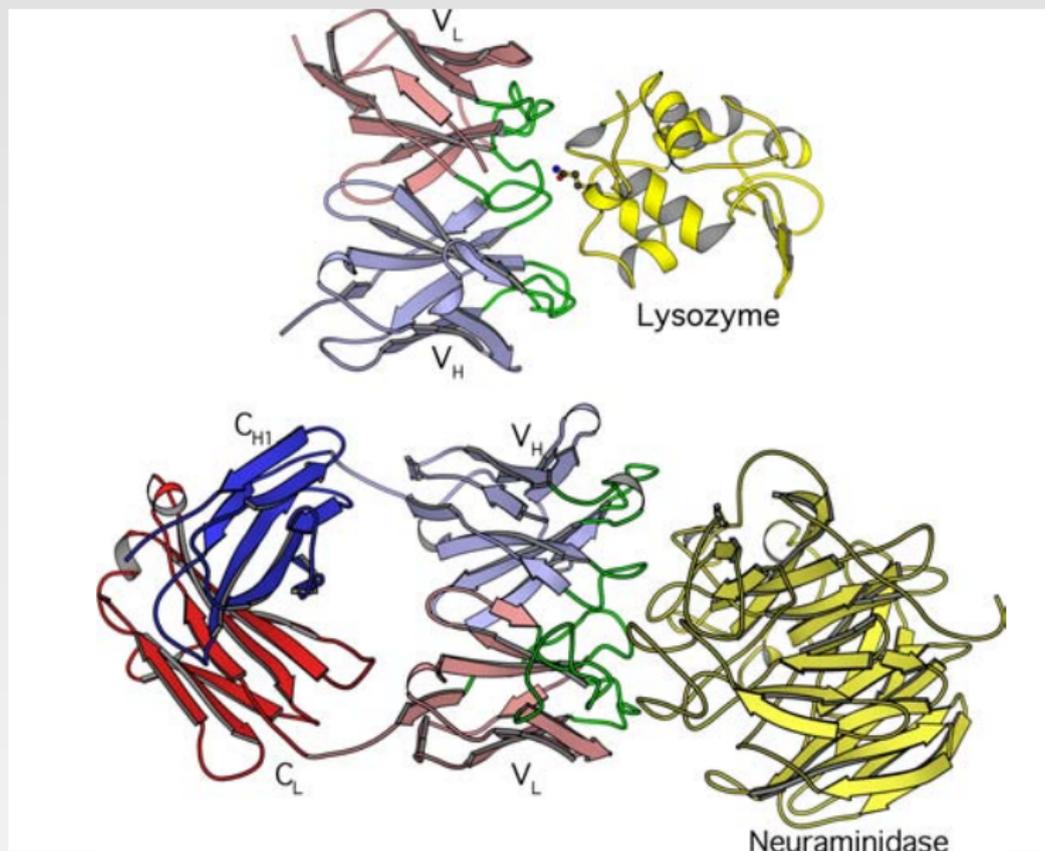
IgG's have a characteristic Y-shape



IgG's can be rather flexible

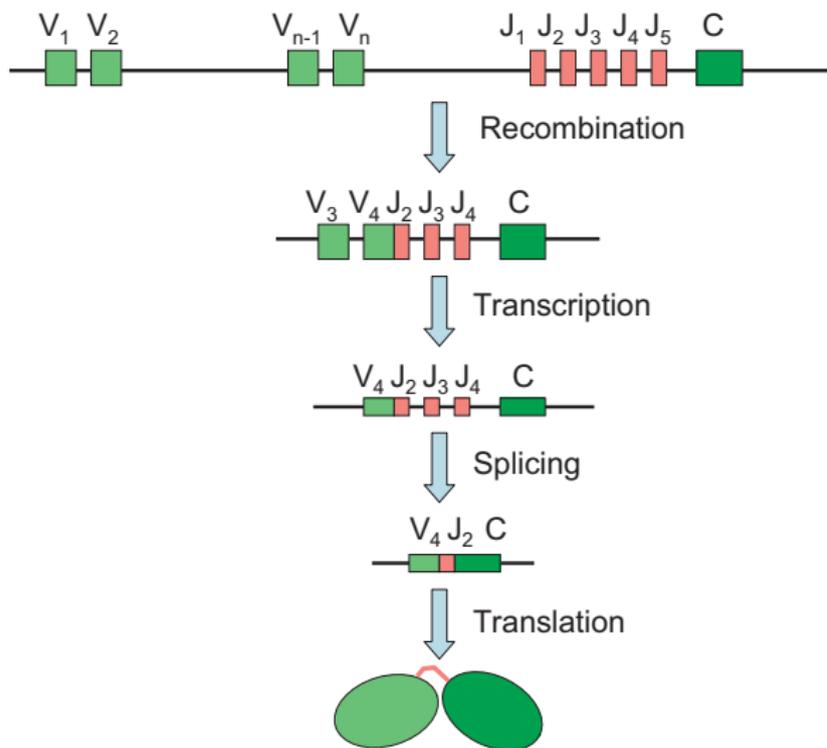


Examples of fab's binding to protein antigens

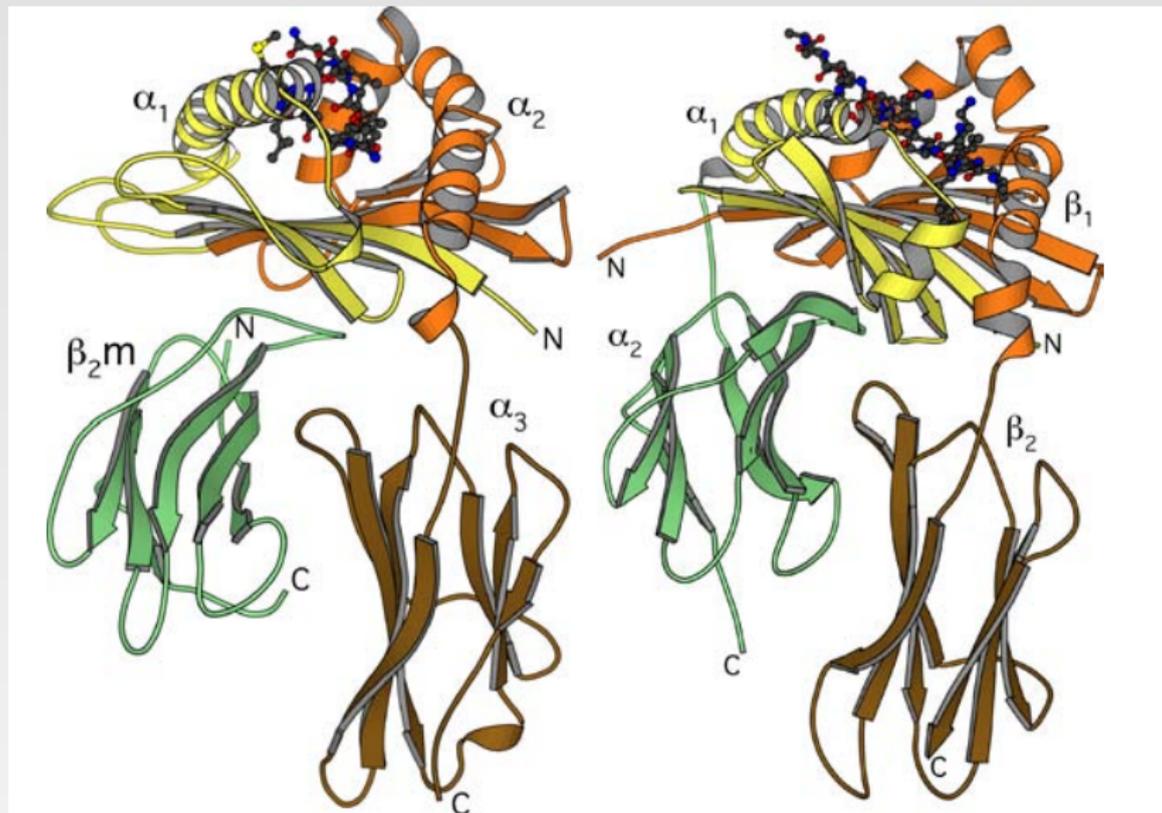


Genetic selection processes are key

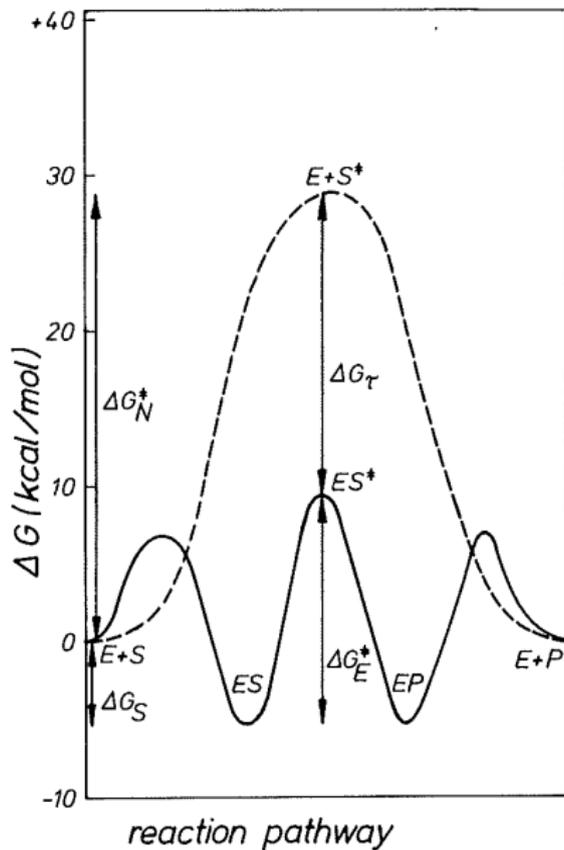
Gene elements for the light chain



B-cell or humoral immunity



Basic ideas of catalysis (again)



Binding Energy and Catalysis: The Implications for Transition-State Analogs and Catalytic Antibodies

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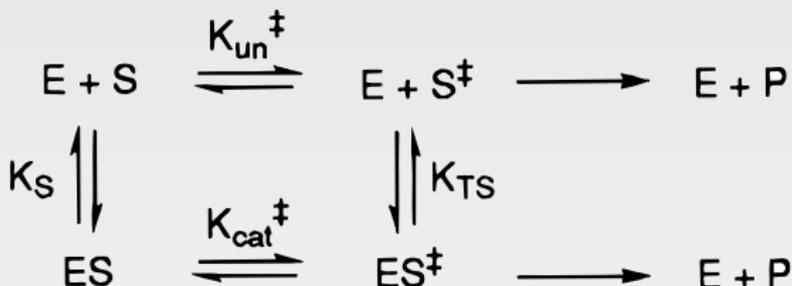
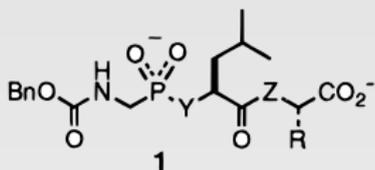


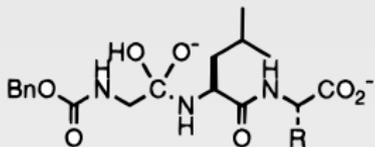
Figure 1. Thermodynamic box illustrating relationship between ground-state and transition-state binding for an enzyme with a single substrate.

Testing the transition state stabilization idea



1

≈



2

R = H, Me, *i*-Bu, Bn

- nn: Y = Z = NH
- ◆ on: Y = O, Z = NH
- cn: Y = CH₂, Z = NH
- ▼ no: Y = CH₂, Z = O

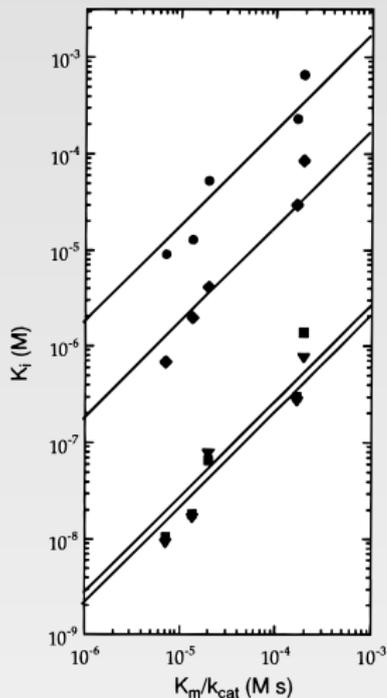
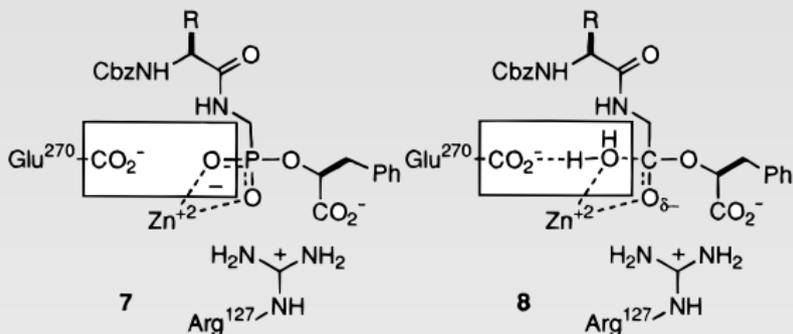
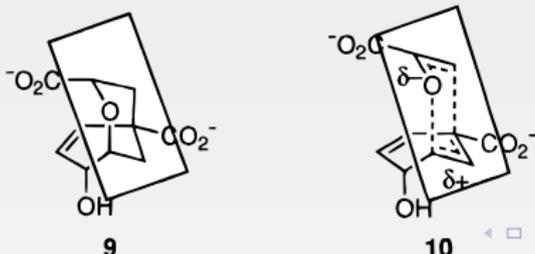


Figure 3. Comparison of K_i values for phosphonate inhibitors of thermolysin with K_m/k_{cat} values for the corresponding substrates.^{23,65} The diagonal lines correspond to slopes of 1.

Proto-typical transition-state analogues



oxabicyclic diacid **9** that inhibits the chorismate mutases⁴⁶ is much more compact than the expanded transition state **10** and does not emulate its charge separation.¹¹⁰ Clearly, we cannot expect even a faithful complement of an imperfect template to compete with an enzyme optimized to bind the true transition state.



T-cell immunity relies on peptide presentations

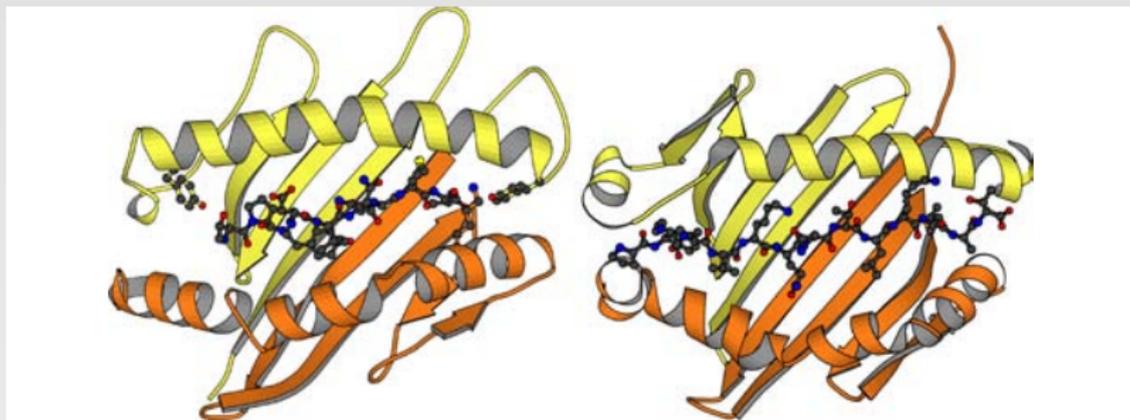


FIGURE 14.7 ■ The binding of peptides to MHC class I (*left*) and class II (*right*) molecules. The peptide-binding site is a groove with a base of eight β strands and two α helices surrounding the peptide. The peptide is shown as a ball-and-stick figure. In MHC class I, some residues block the ends of the groove, while the ends of the groove are open in MHC class II.

Peptides bind to MHC in defined ways

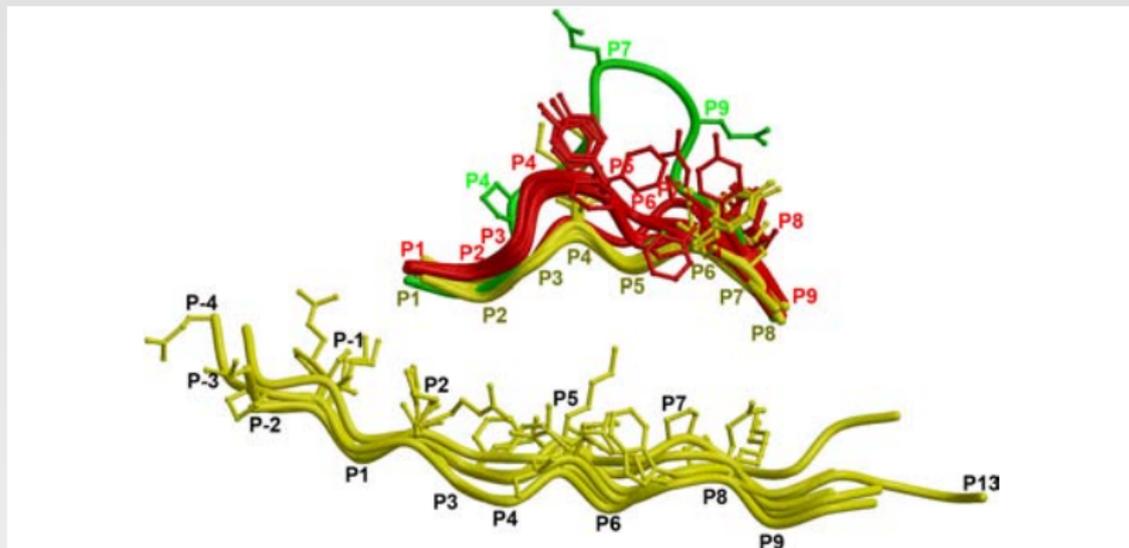
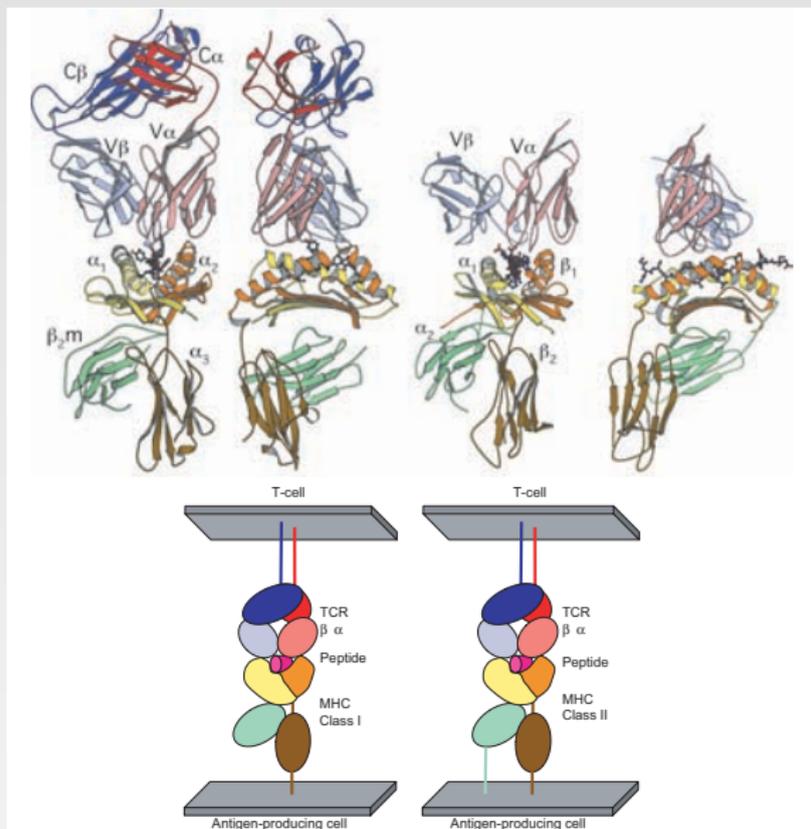
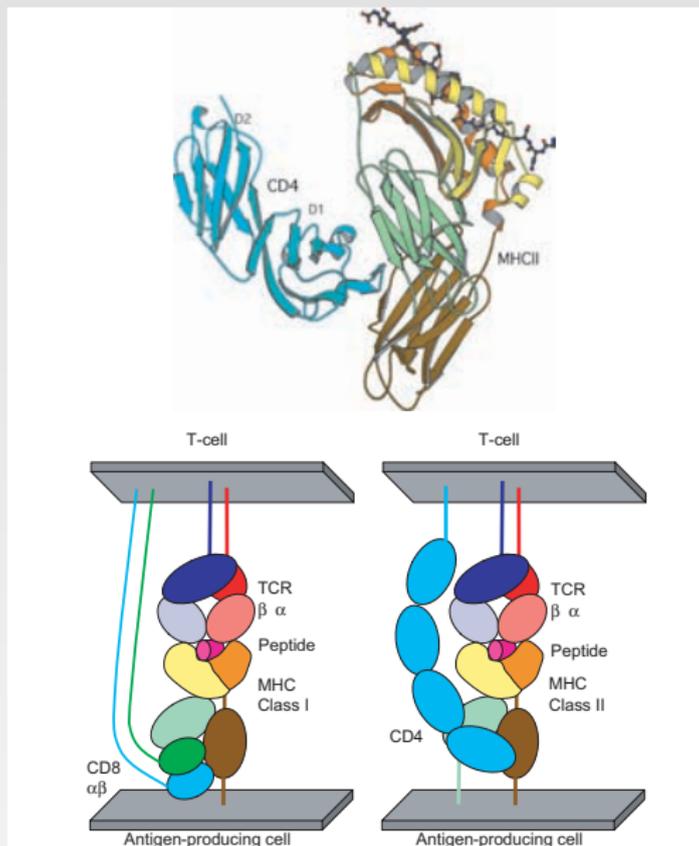


FIGURE 14.8 ■ The structures of the peptides bound to MHC class I (*above*) and class II (*below*). The β sheets of MHC have been aligned but are not shown. They are located below the peptides. The class I peptides are shown in different colors for different lengths: 8 (yellow), 9 (red) and 13 residues (green). The binding groove is closed at the ends in class I; therefore, peptides of lengths longer than eight residues will bulge. (Reprinted with permission from Rudolph MG *et al.* (2006) How TCRs bind MHCs, peptides and coreceptors. *Annu Rev Immunol* **24**: 419–466. Copyright Annual Reviews.)

T-cell immunity involves a complex of many proteins



T-cell immunity, again



T-cell immunity

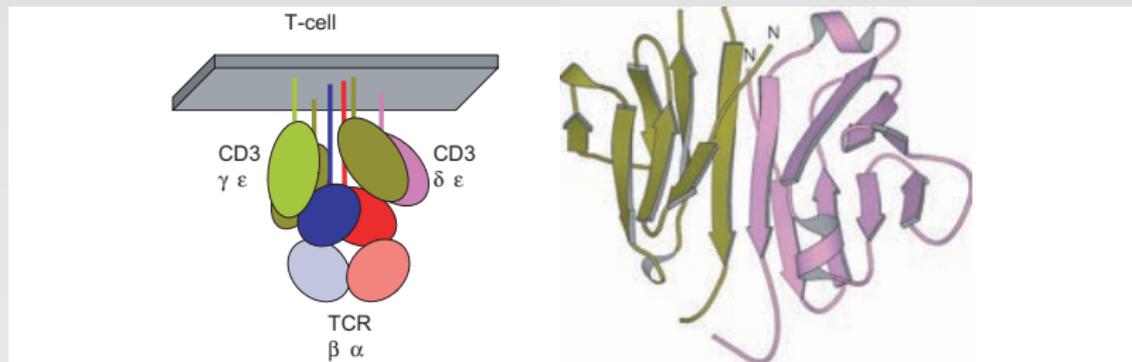


FIGURE 14.11 ■ *Left*: a schematic illustration of the interactions between TCRs and CD3s in the T cells. The CD3 $\gamma\epsilon$ and CD3 $\delta\epsilon$ are heterodimers that interact with TCR. Their location in the membrane defines their interactions and the intracellular signals transmitted. *Right*: the extracellular domains of the CD3- ϵ/δ dimer associate with an approximate twofold axis that is vertical in this view. The ϵ/γ dimer is formed in the same way. The N-termini leads to the transmembrane region (PDB: 1XIW).