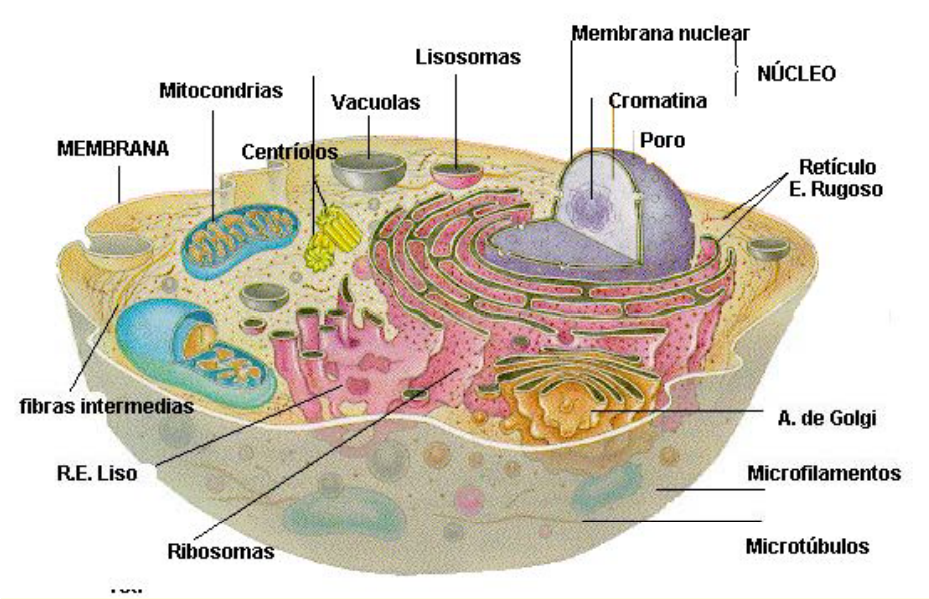
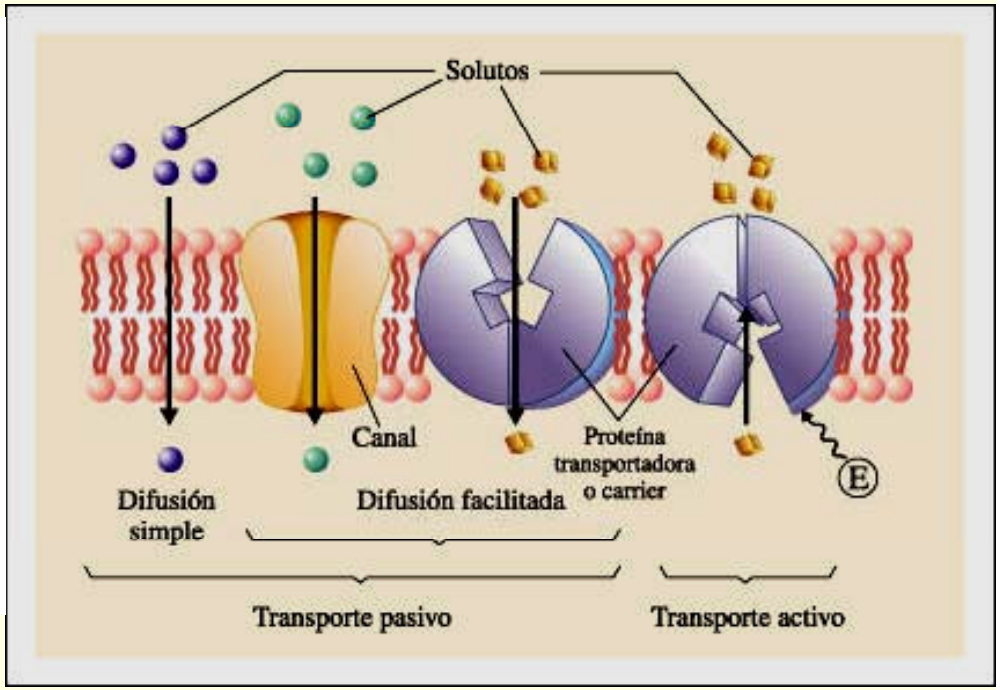
Proteínas como blancos farmacológicos

Jenny Fiedler

Lab. Neuroplasticidad y Neurogenética.
Depto. Bioquímica y Biología Molecular

Componentes de la célula





POLÍMEROS

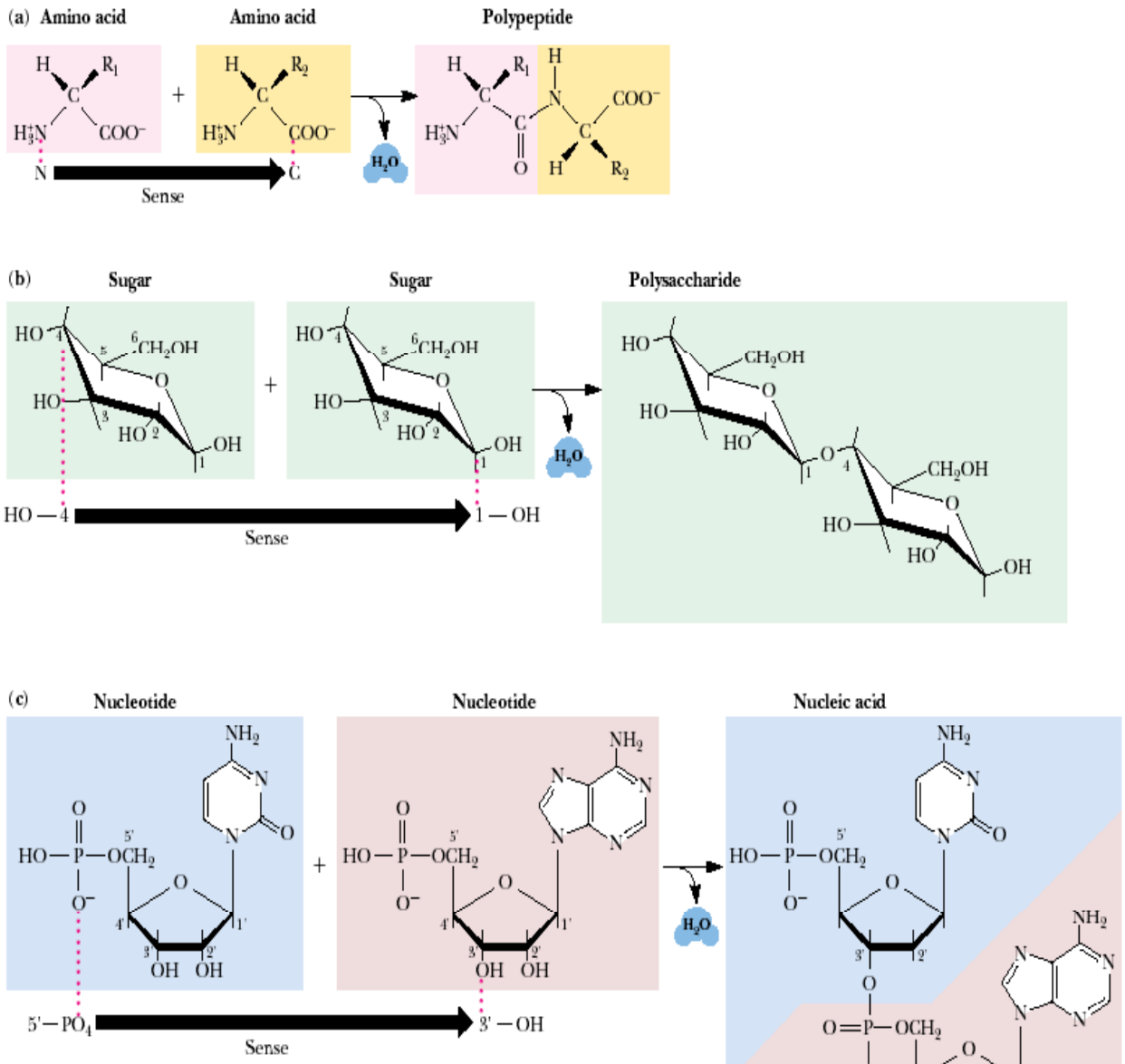


FIGURE 1.9 • (a) Amino acids build proteins by connecting the α-carboxyl C atom of one amino acid to the α-amino N atom of the next amino acid in line. (b) Polysaccharides are built by combining the C-1 of one sugar to the C-4 O of the next sugar in the polymer. (c) Nucleic acids are polymers of nucleotides linked by bonds between the 3′-OH of the ribose ring of one nucleotide to the 5′-PO_4 of its neighboring nucleotide. All three of these polymerization processes involve bond formations accompanied by the elimination of water (dehydration synthesis reactions).

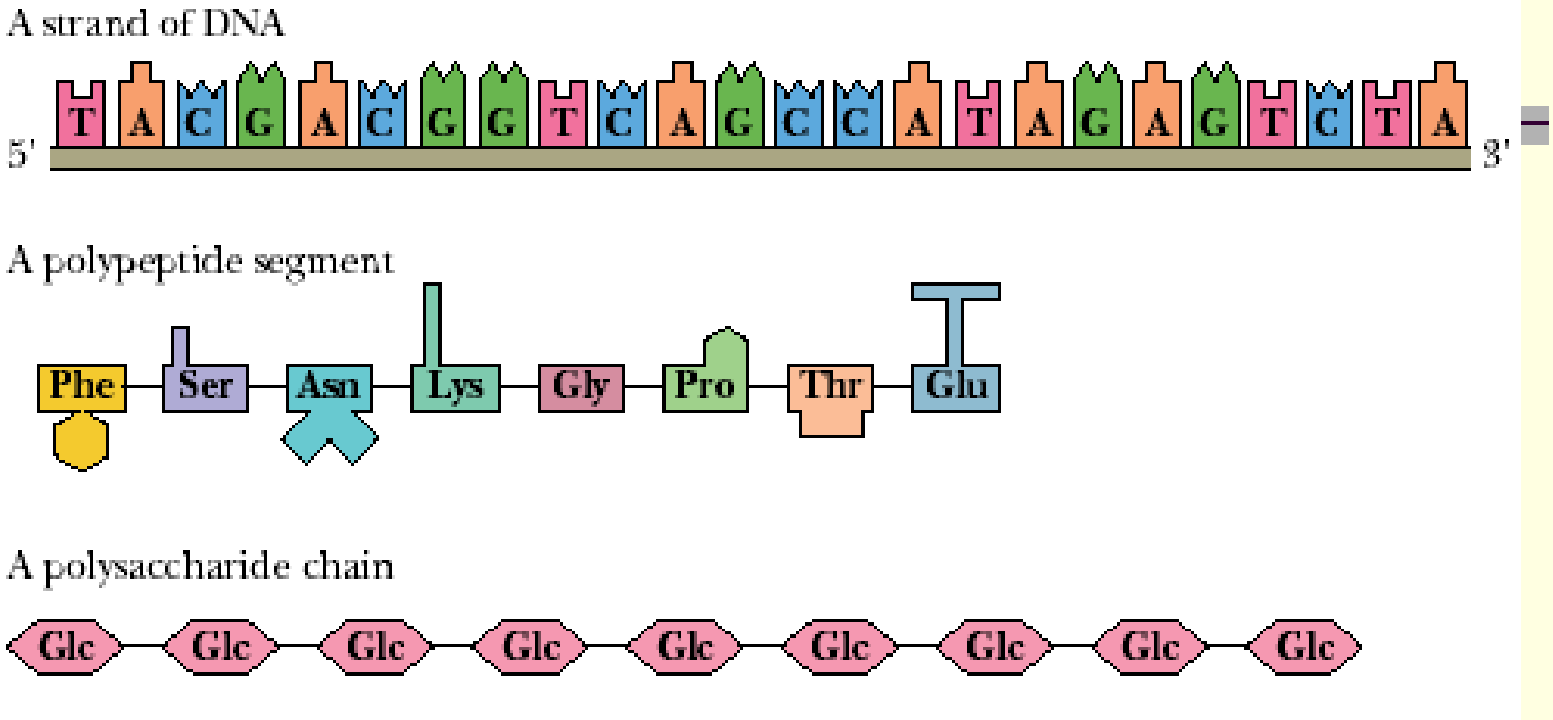
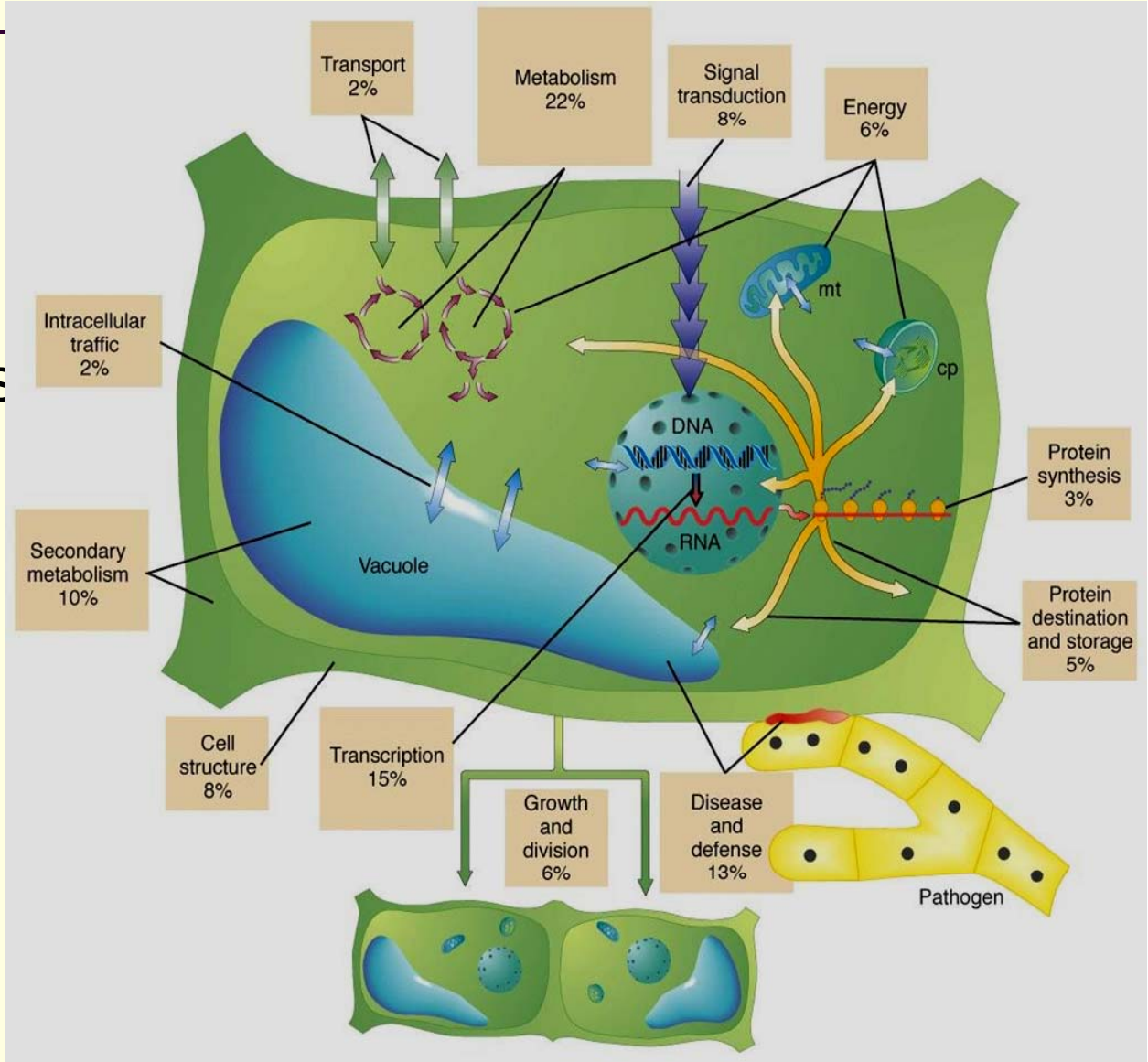


FIGURE 1.10 • The sequence of monomeric units in a biological polymer has the potential to contain information if the diversity and order of the units are not overly simple or repetitive. Nucleic acids and proteins are information-rich molecules; polysaccharides are not.

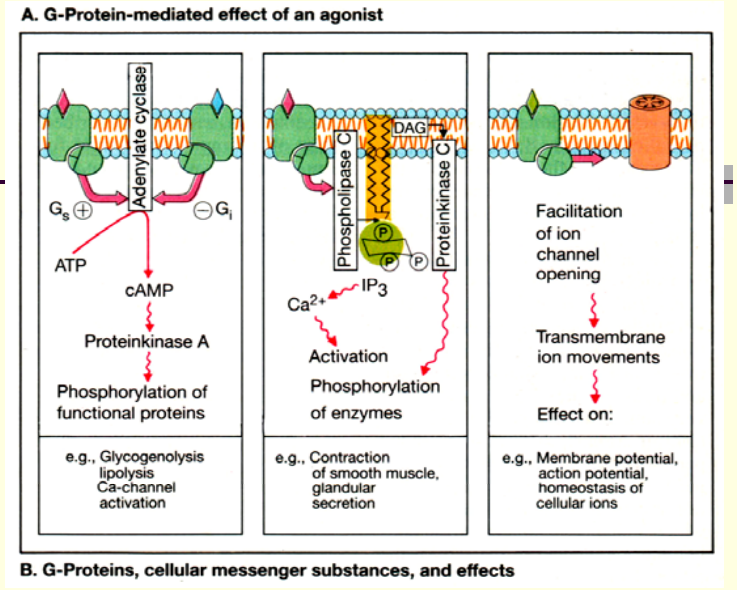
Blancos farmacológicos

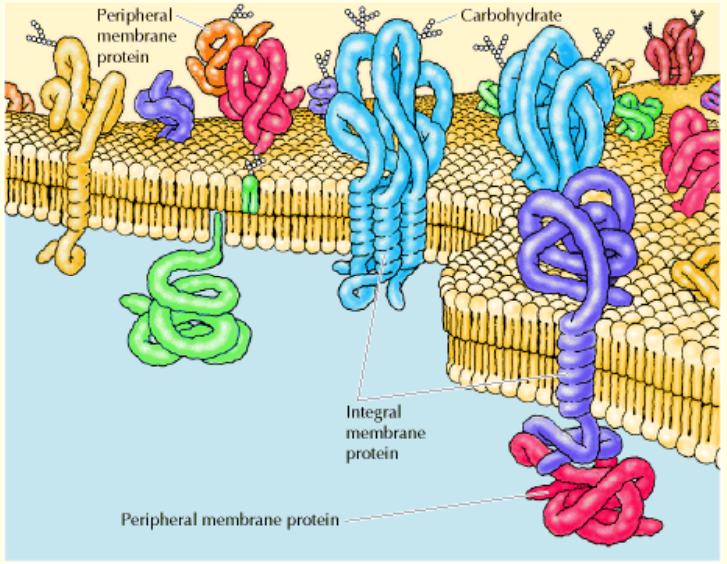
- DNA
- Proteínas
  - Enzimas
  - Transportadores
  - Canales iónicos
  - Receptores



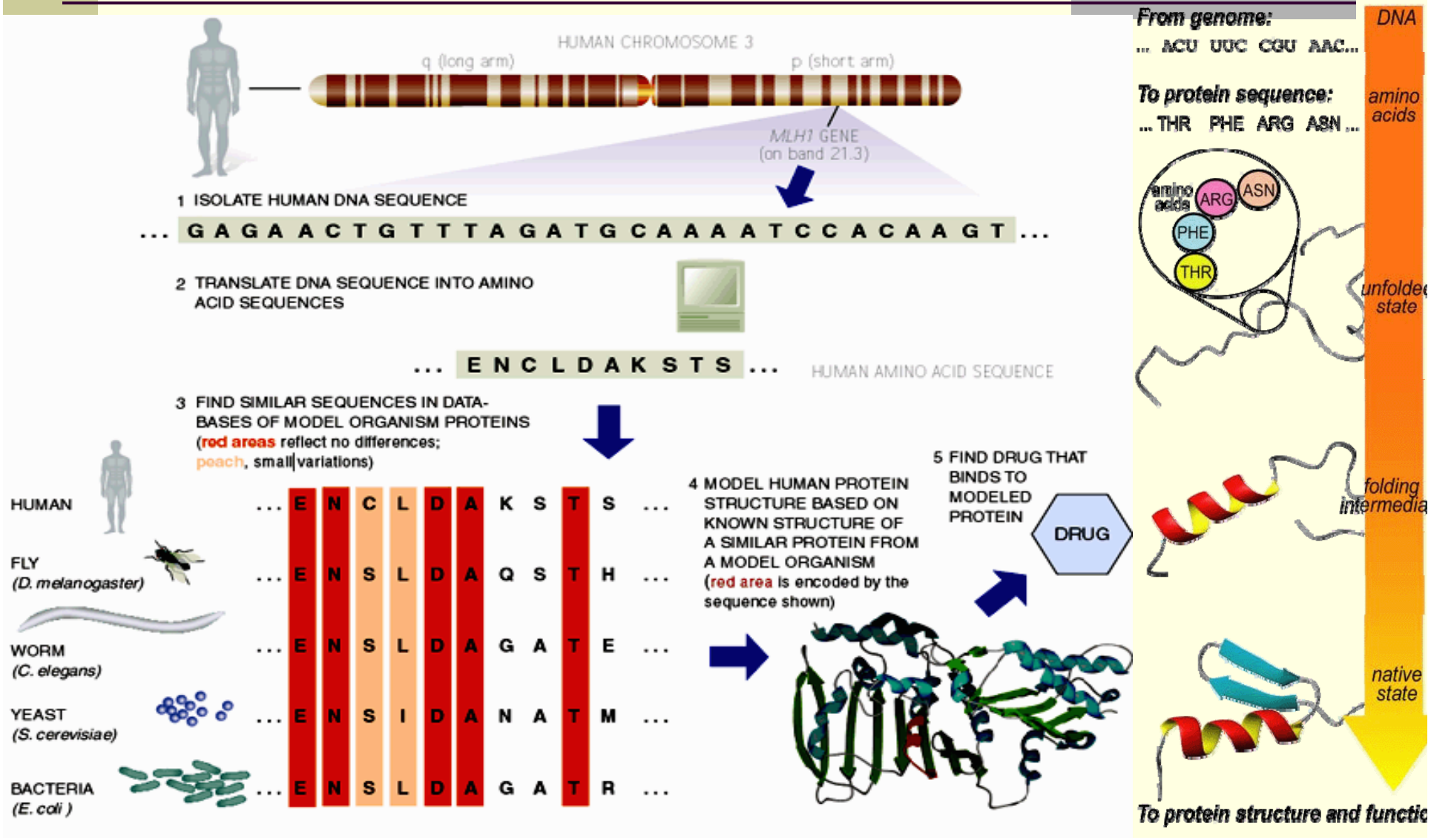
Blancos farmacológicos

- **muchos fármacos actúan sobre receptores**
- en la superficie celular, citosólicos, nucleares
- establecen enlaces con los ligando
- *deben existir requerimientos* espaciales (tamaño, forma y estereoselectividad)
  - pueden ser agonistas o antagonistas
- **la interacción ligando-receptor produce respuestas celulares**

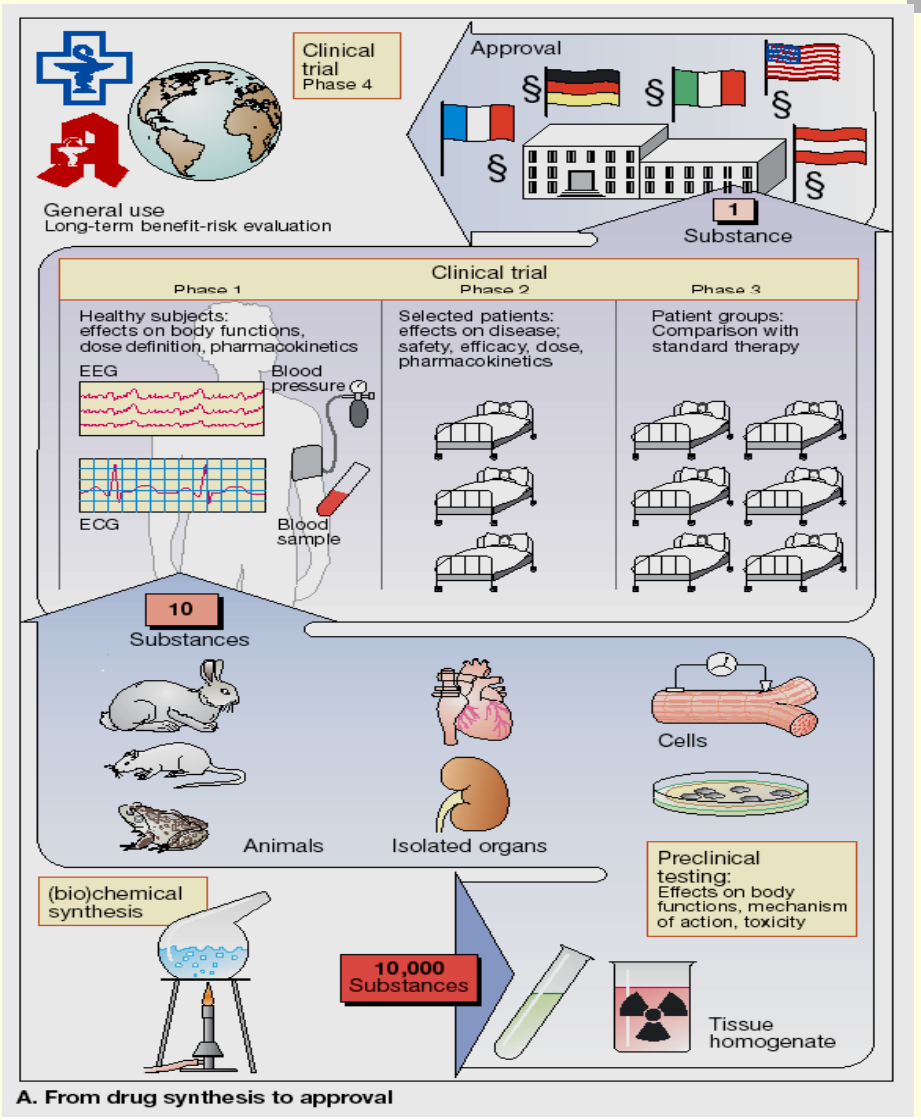




¿Por qué es importante conocer la estructura de las proteínas?



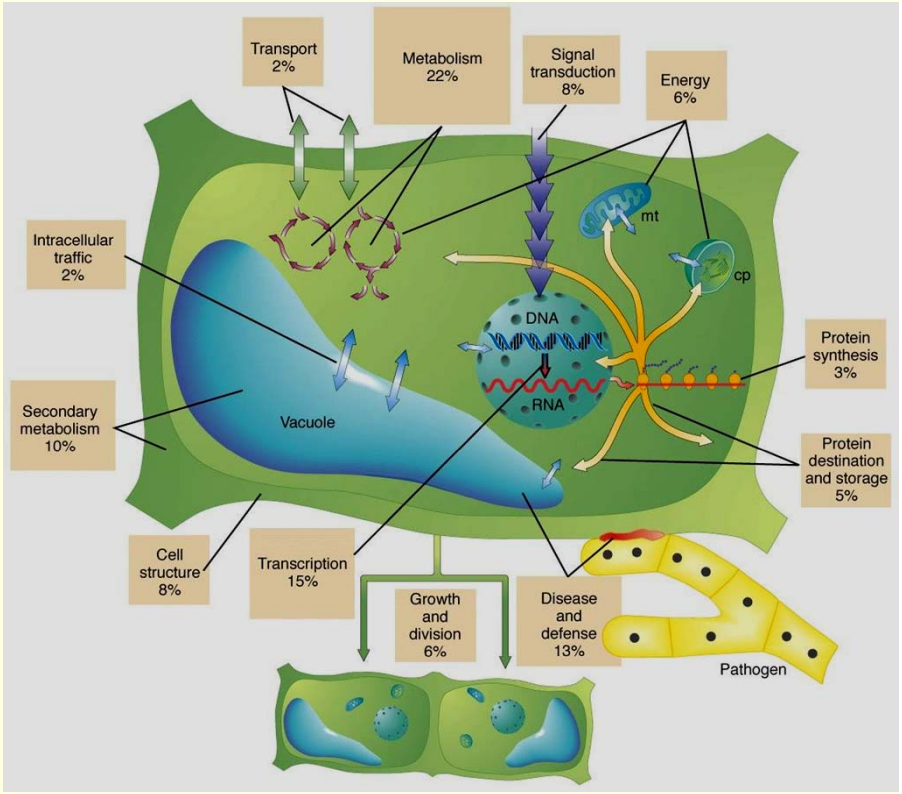
¿Por qué es importante conocer la estructura de las proteínas?



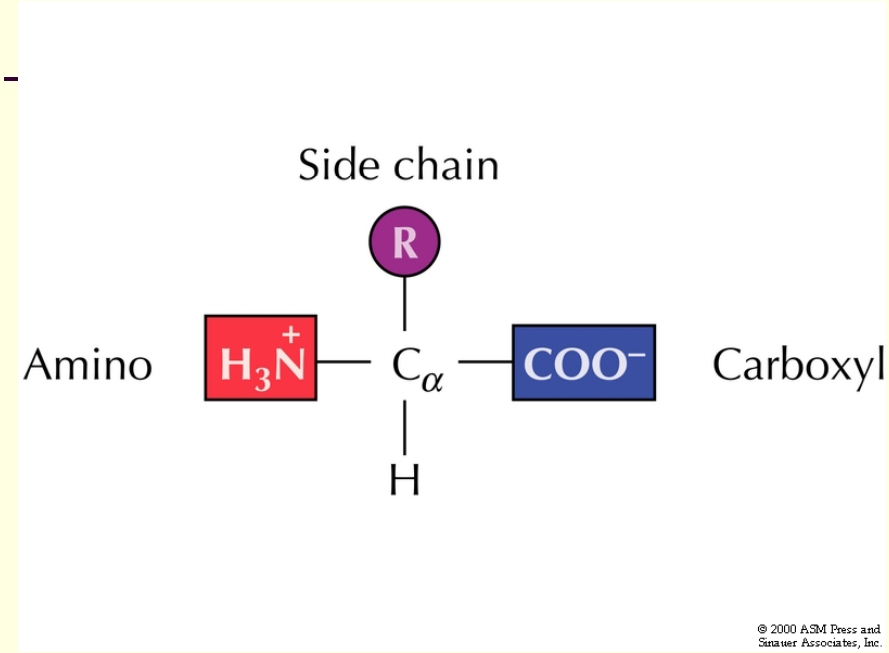
A. From drug synthesis to approval

Función de las proteínas

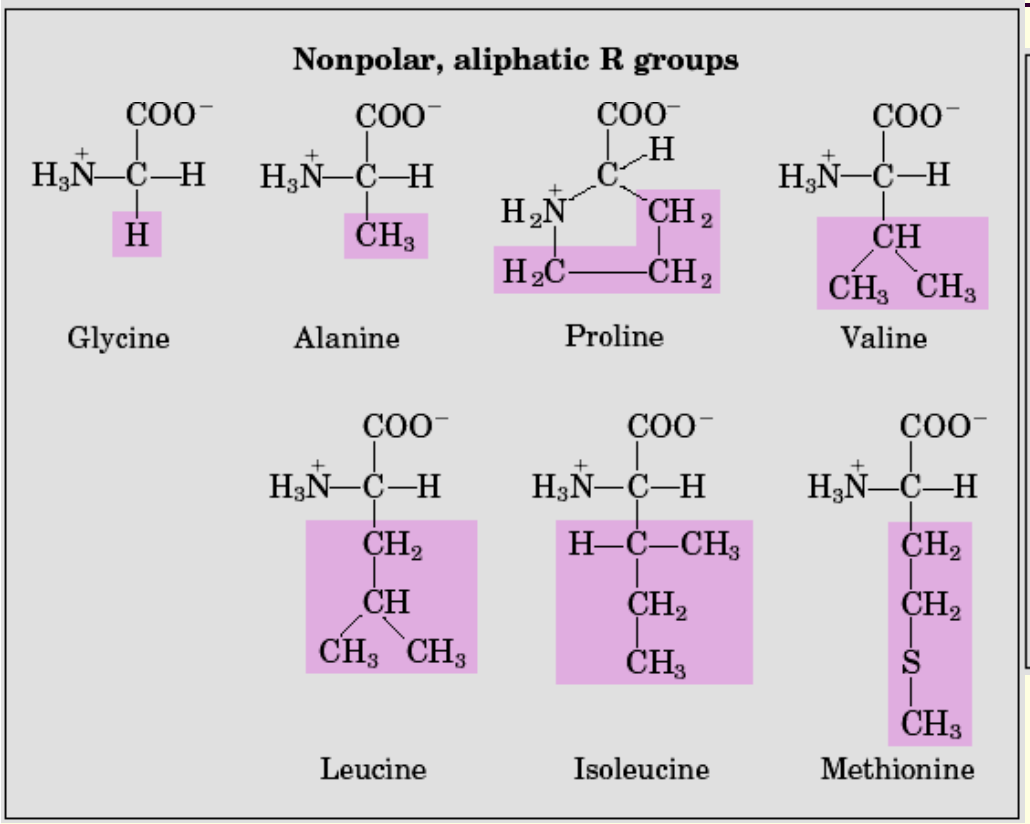
- Enzimas (biocatalizadores)
- Estructurales (membranas)
- Activador y represor de genes
- Receptores / transportadores
- Elementos contráctiles

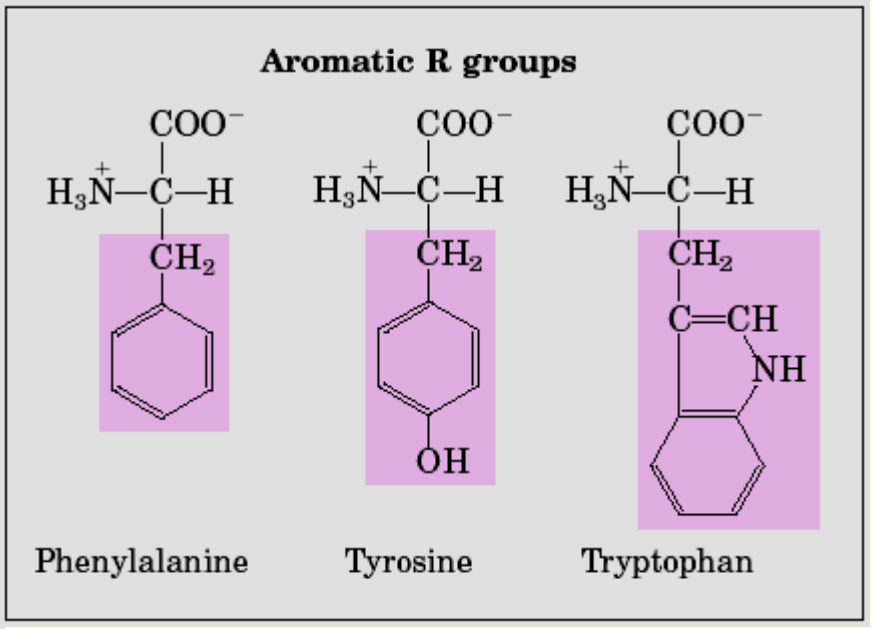


- Proteínas
  - Aminoácidos –
    - Carboxilo y un grupo amino separado por un átomo –carbono α.
    - A pH fisiológico el α carboxilo pierde un protón y el grupo amino acepta un protón.
    - R proveen una diversidad de estructura y actividades en las proteínas

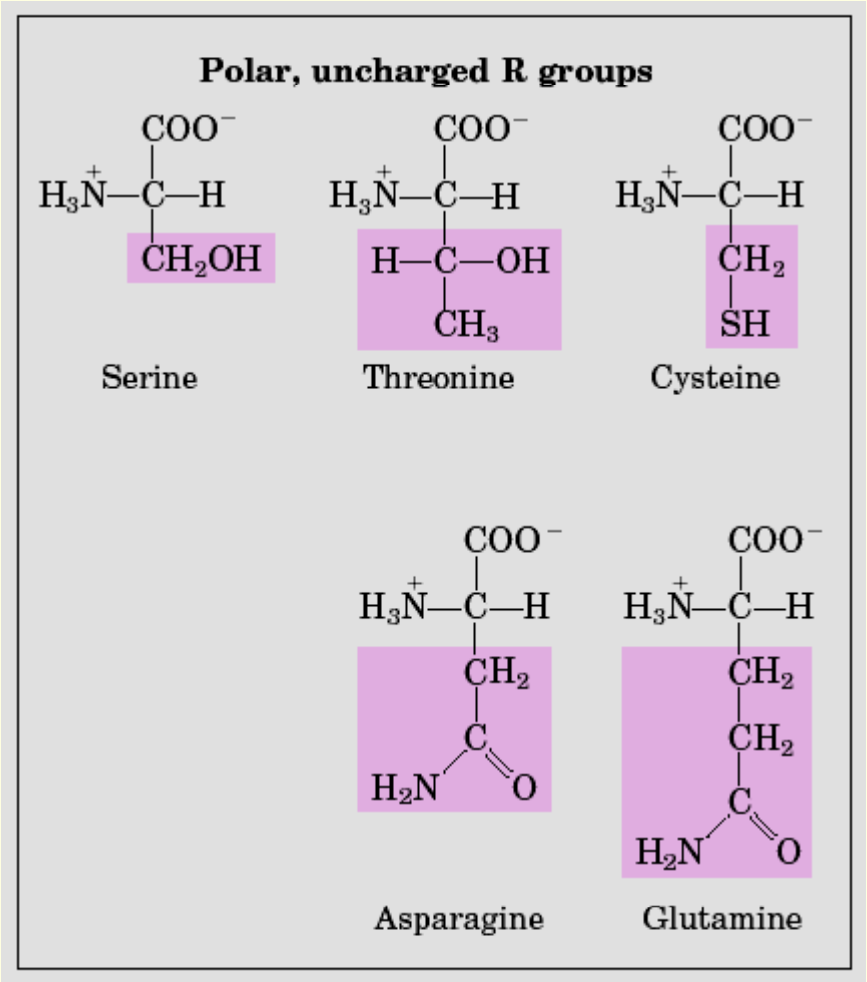


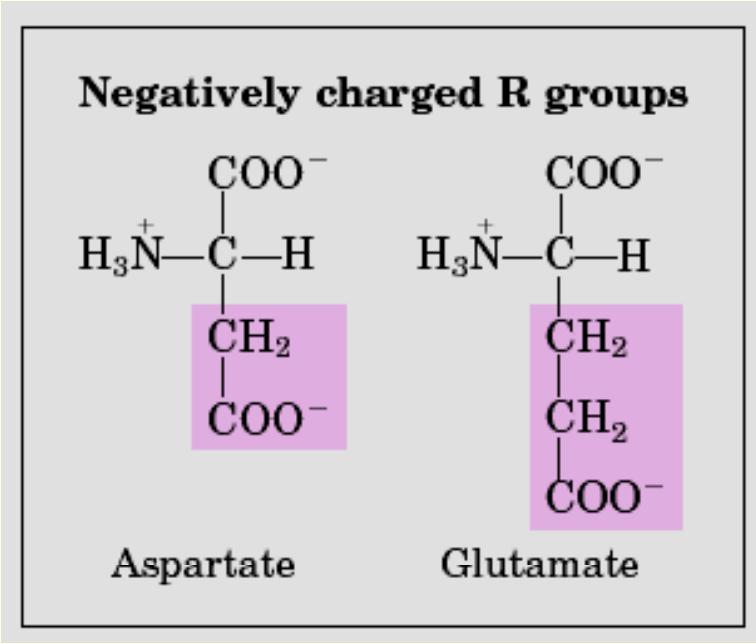
Clasificación de los aminoácidos





Clasificación de los aminoácidos





Reactividad de los aminoácidos

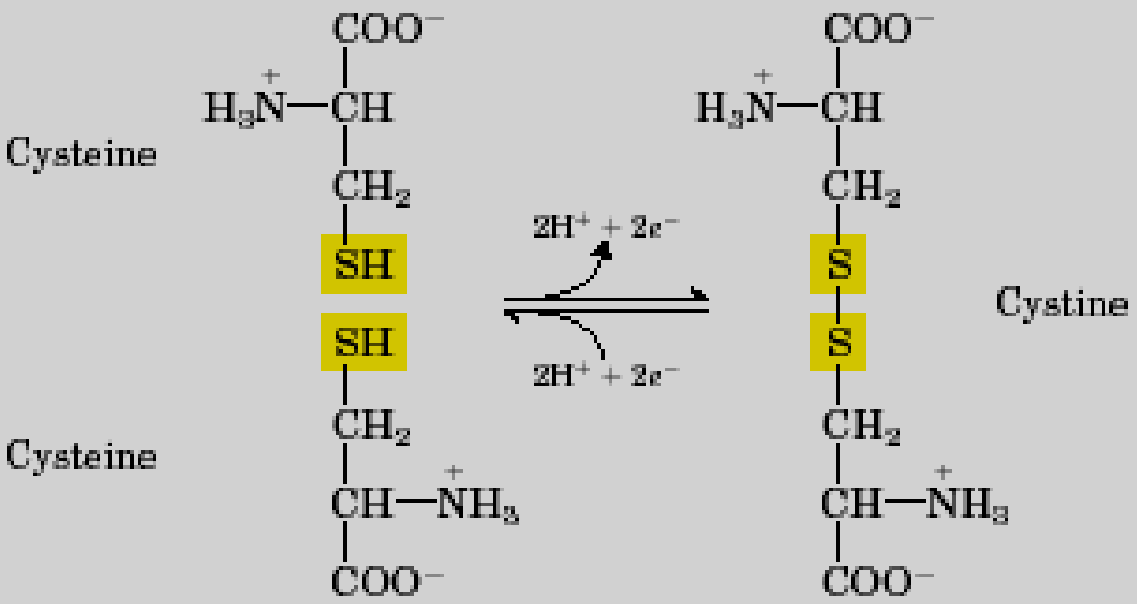
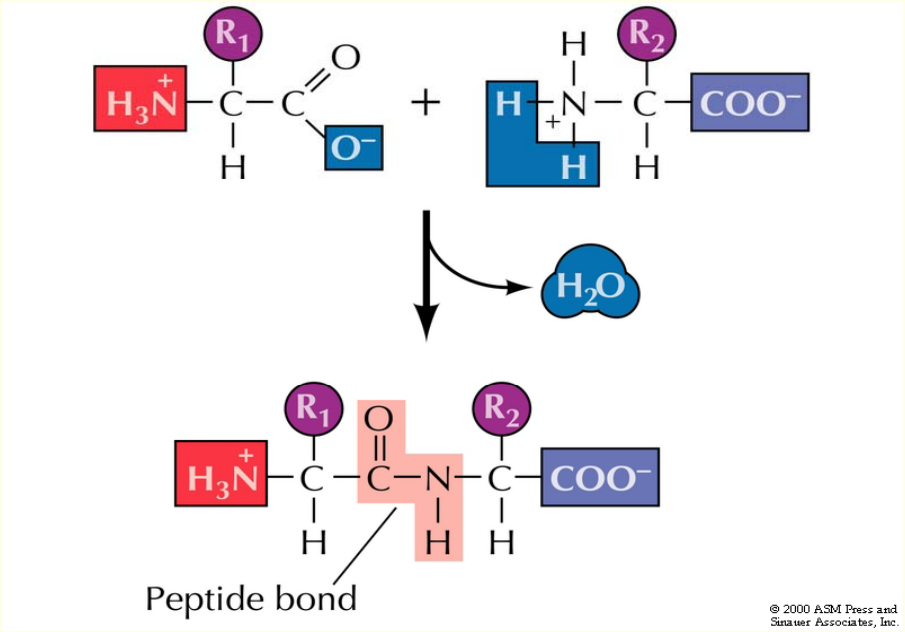


FIGURE 3–7 Reversible formation of a disulfide bond by the oxidation of two molecules of cysteine. Disulfide bonds between Cys residues stabilize the structures of many proteins.

Síntesis de proteínas

- Proteínas
  - Durante la síntesis de proteínas cada aminoácido se enlaza al siguiente mediante enlace peptídico



Secuencia de aminoácidos en una proteína

1 2 3 4 5 126 127 128 129
Lys-Val-Phe-Gly-Arg...Gly-Cys-Arg-Leu

NH2-terminal **COO- terminal**

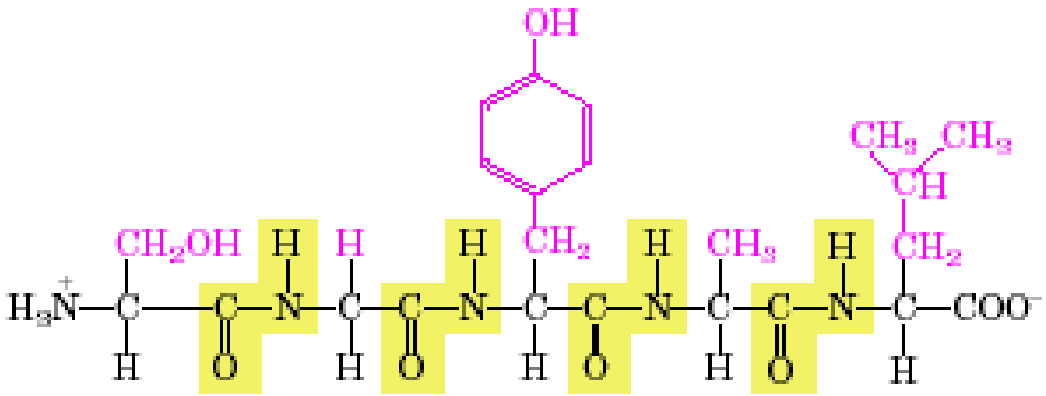


FIGURE 3–14 The pentapeptide serylglycyltyrosylalanylleucine, or Ser–Gly–Tyr–Ala–Leu. Peptides are named beginning with the amino-terminal residue, which by convention is placed at the left. The peptide bonds are shaded in yellow; the R groups are in red.

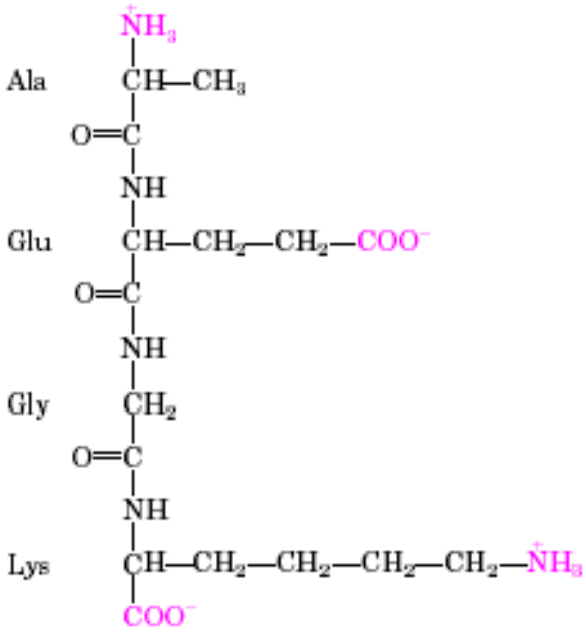
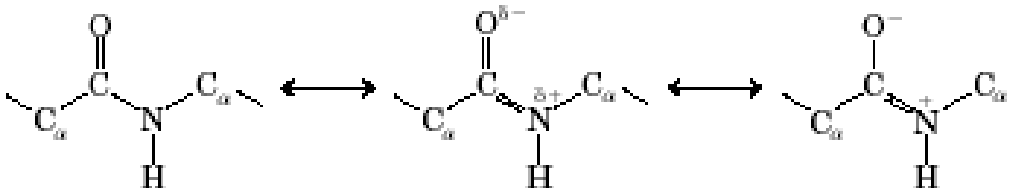


FIGURE 3–15 **Alanylglutamylglycyllysine.** This tetrapeptide has one free α-amino group, one free α-carboxyl group, and two ionizable R groups. The groups ionized at pH 7.0 are in red.

•Estructura de proteínas

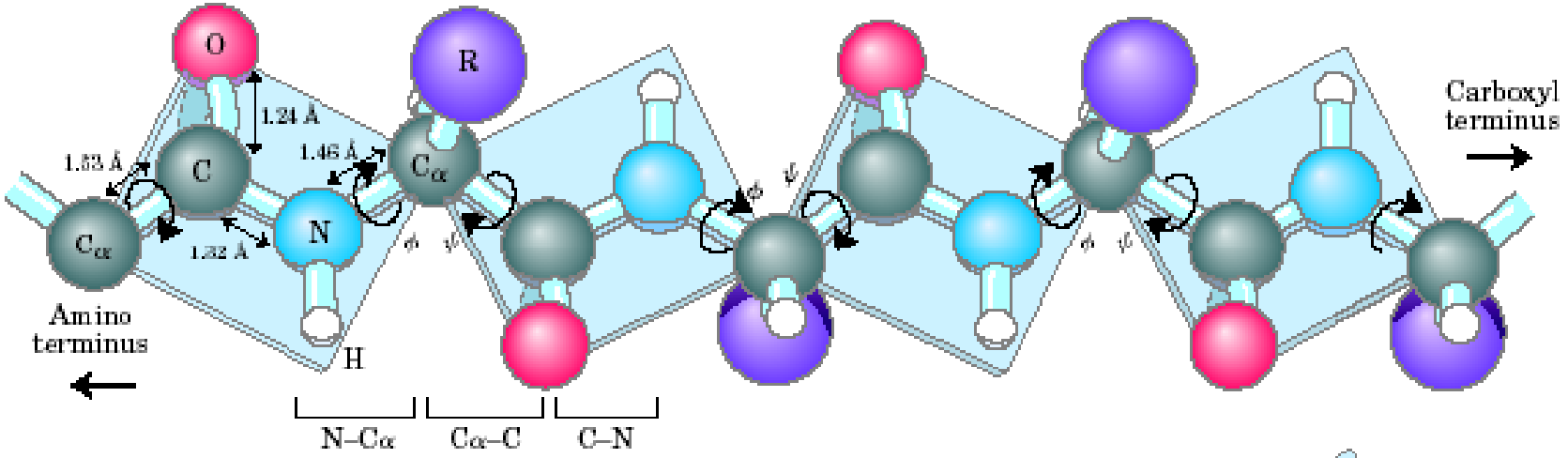
Niveles de organización

Primaria



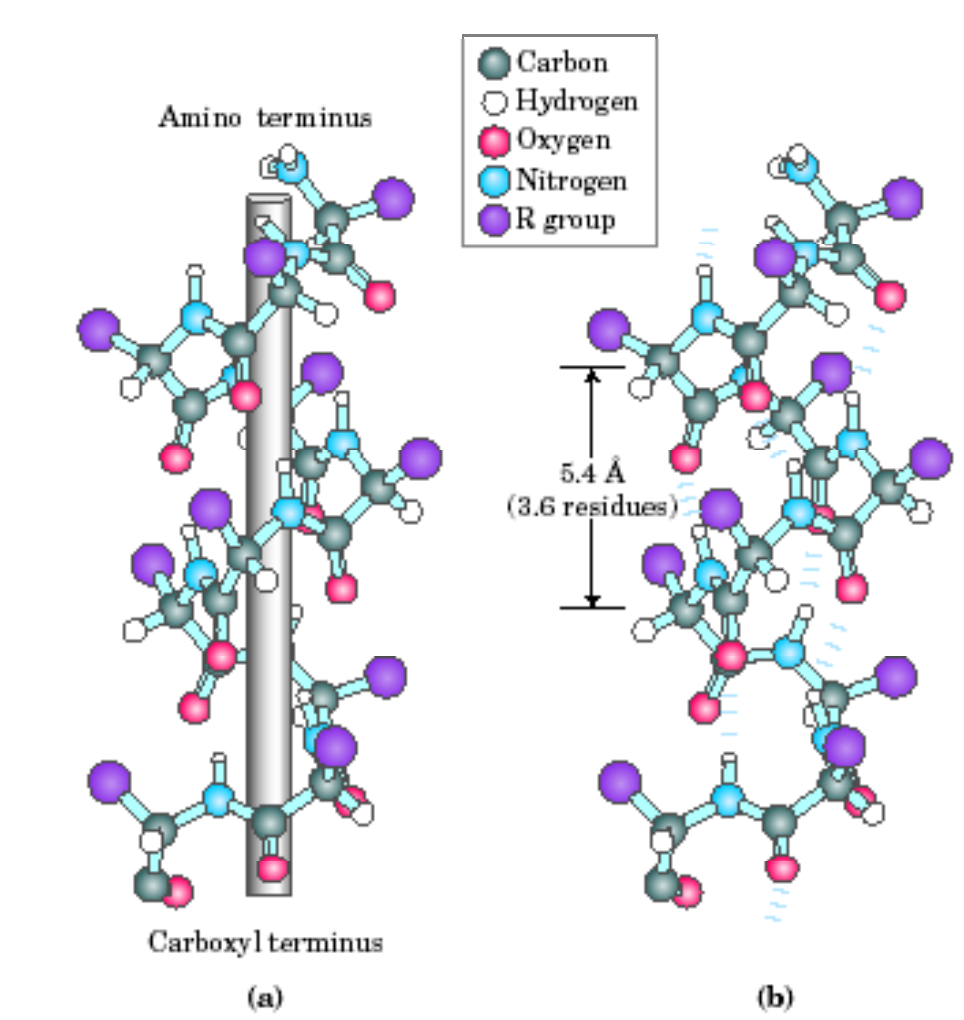
The carbonyl oxygen has a partial negative charge and the amide nitrogen a partial positive charge, setting up a small electric dipole. Virtually all peptide bonds in proteins occur in this trans configuration; an exception is noted in Figure 4–8b.

(a)

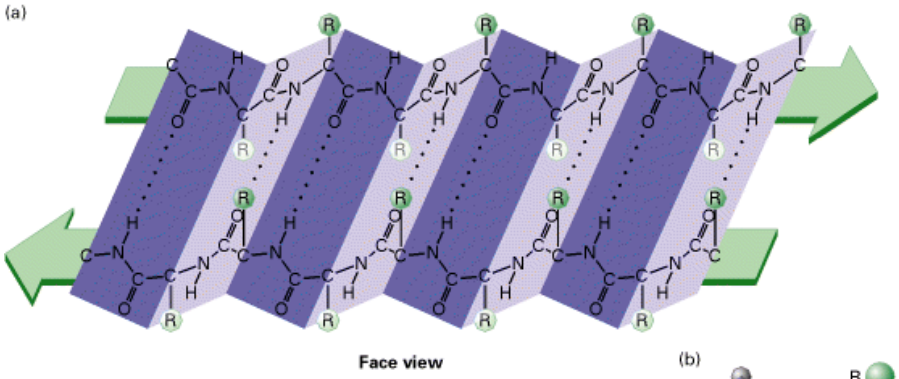


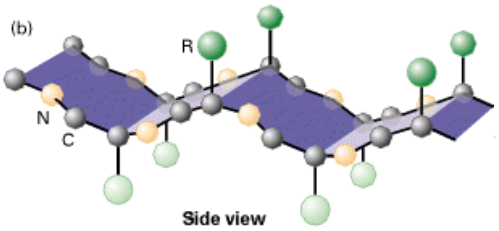
(b)

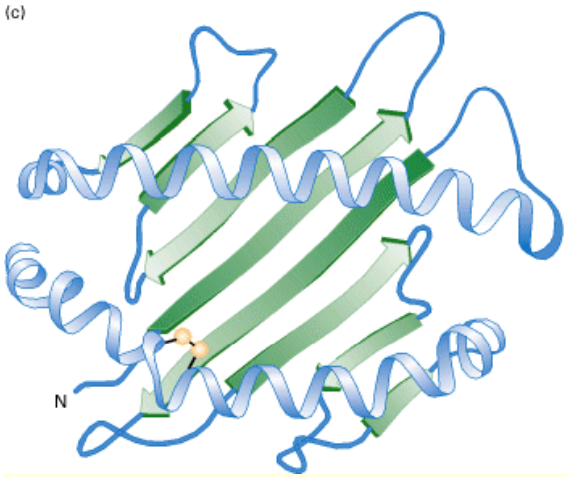
- Proteina
  - estructura
    - Secundaria
      - α-hélice

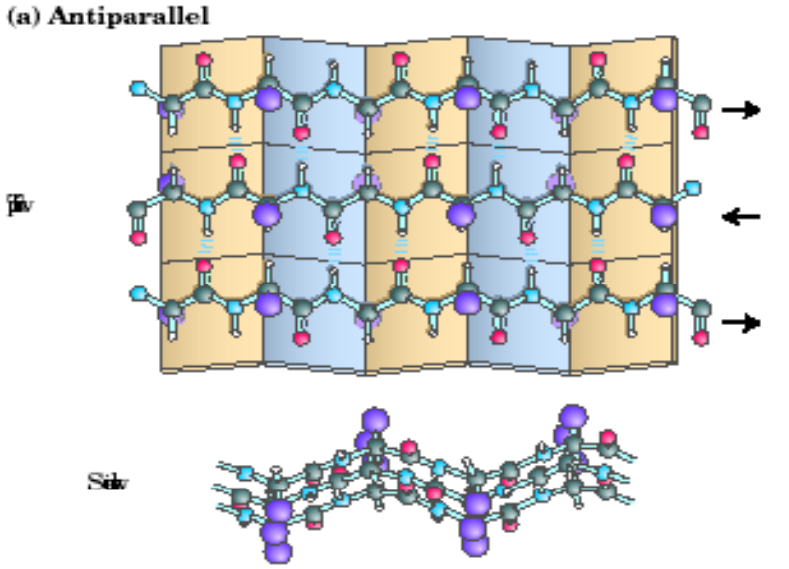


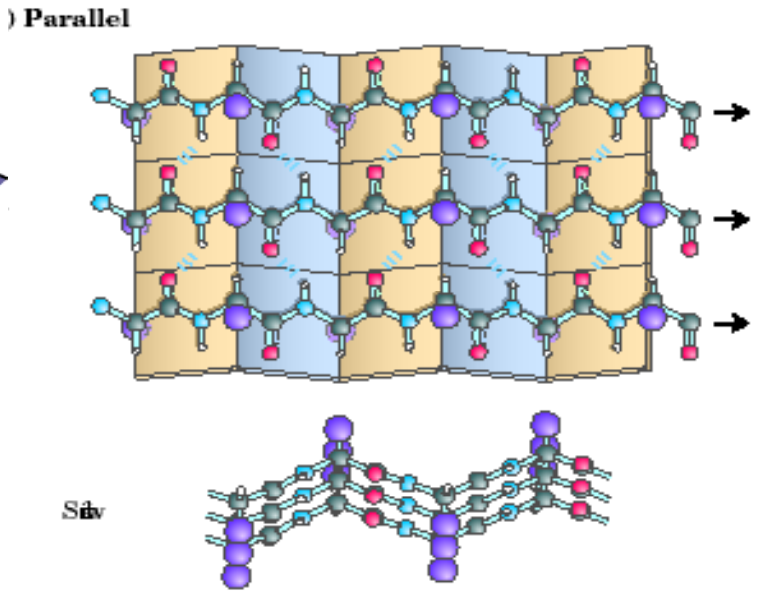
- Proteina
  - estructura
    - Secundaria
      - Estructura β plegada





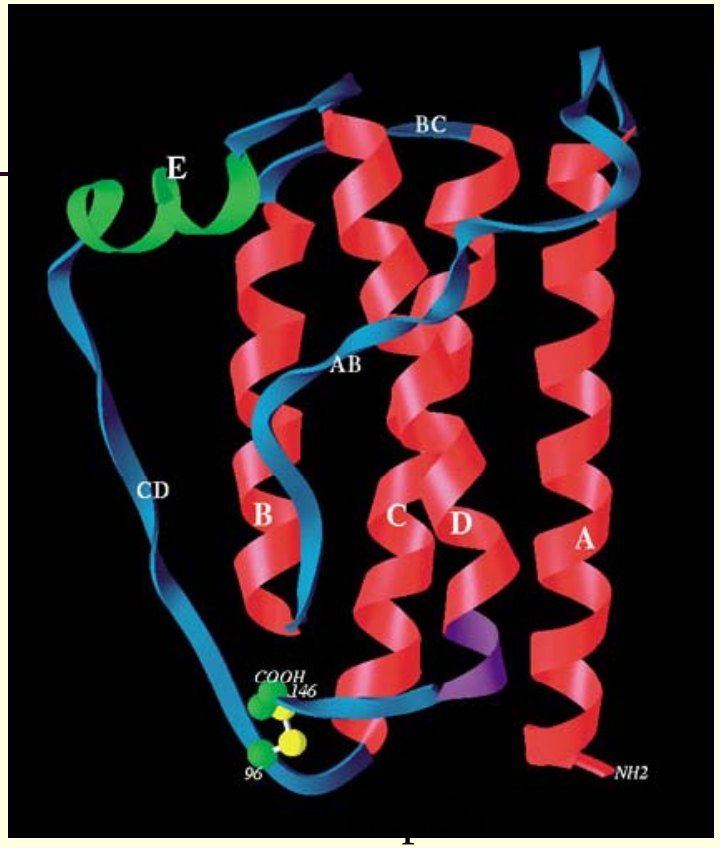




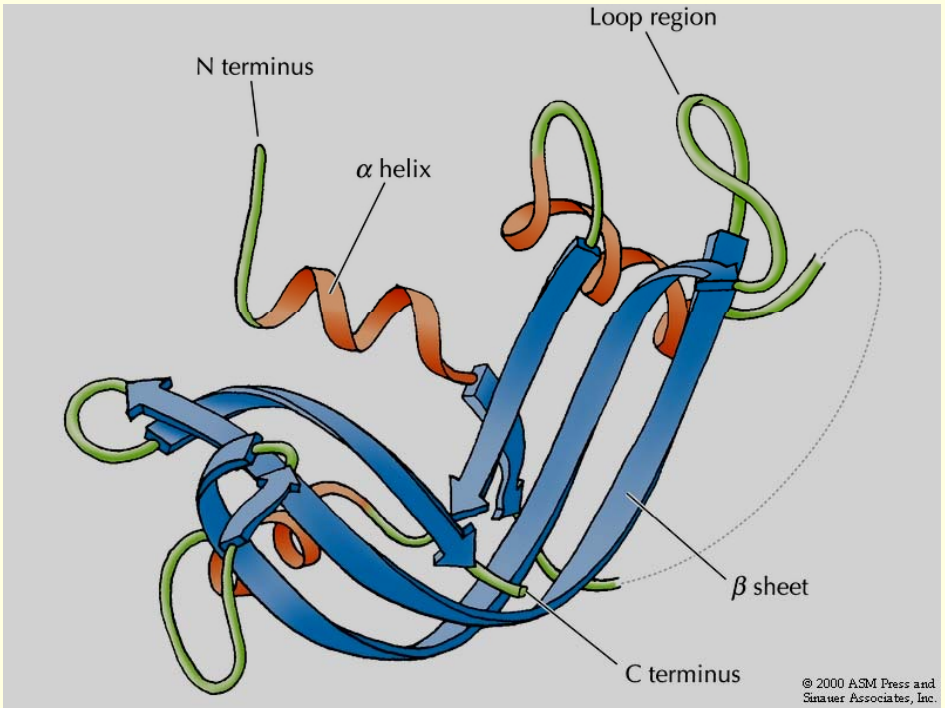


- Proteinas
  - Estructura
    - Porciones no organizadas en estructura α helice o estructura β consiste en vueltas, loops u otras extensiones

- Proteína
  - Estructura
    - Terciaria
      - Conformación de toda la proteína

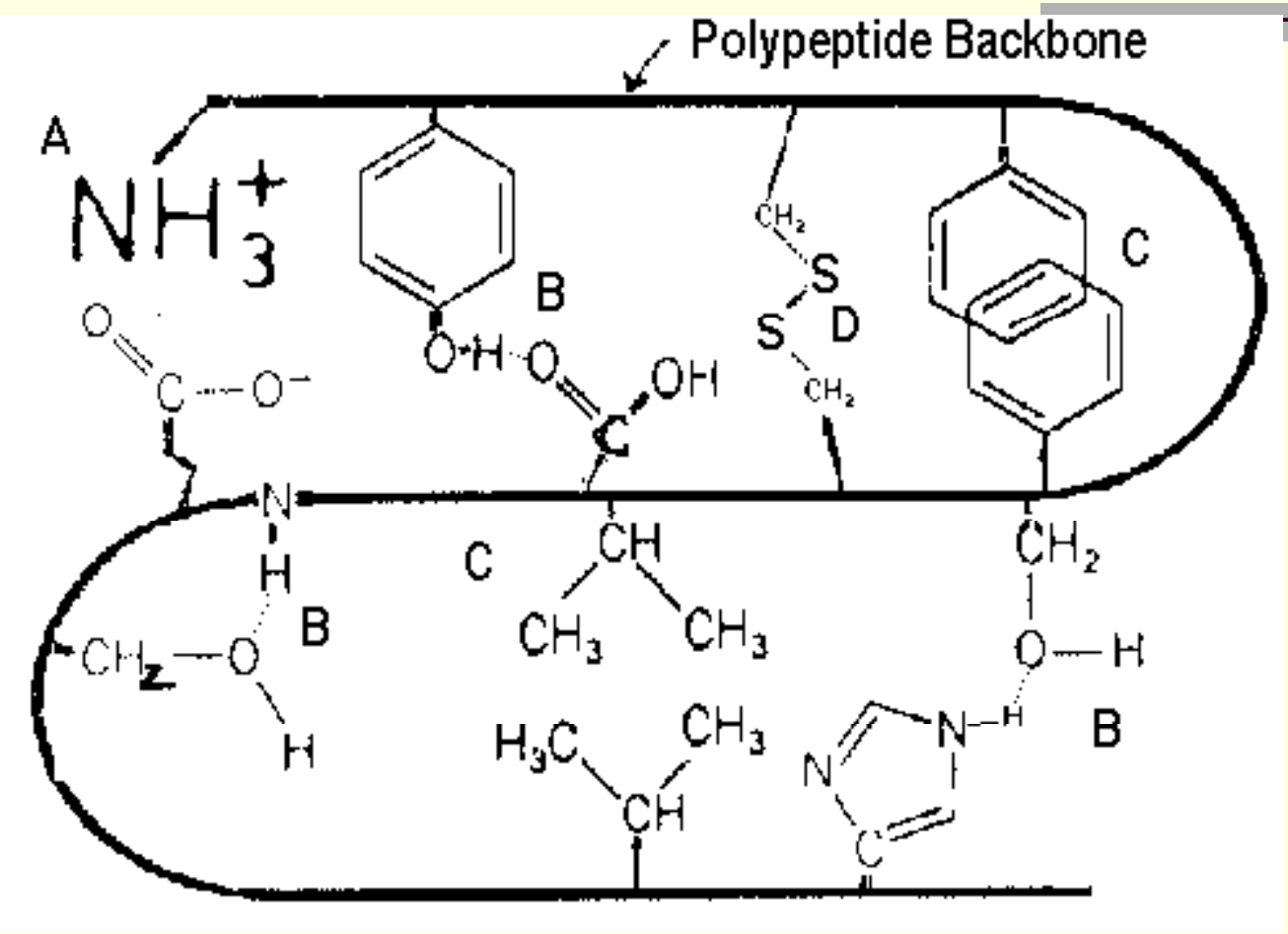


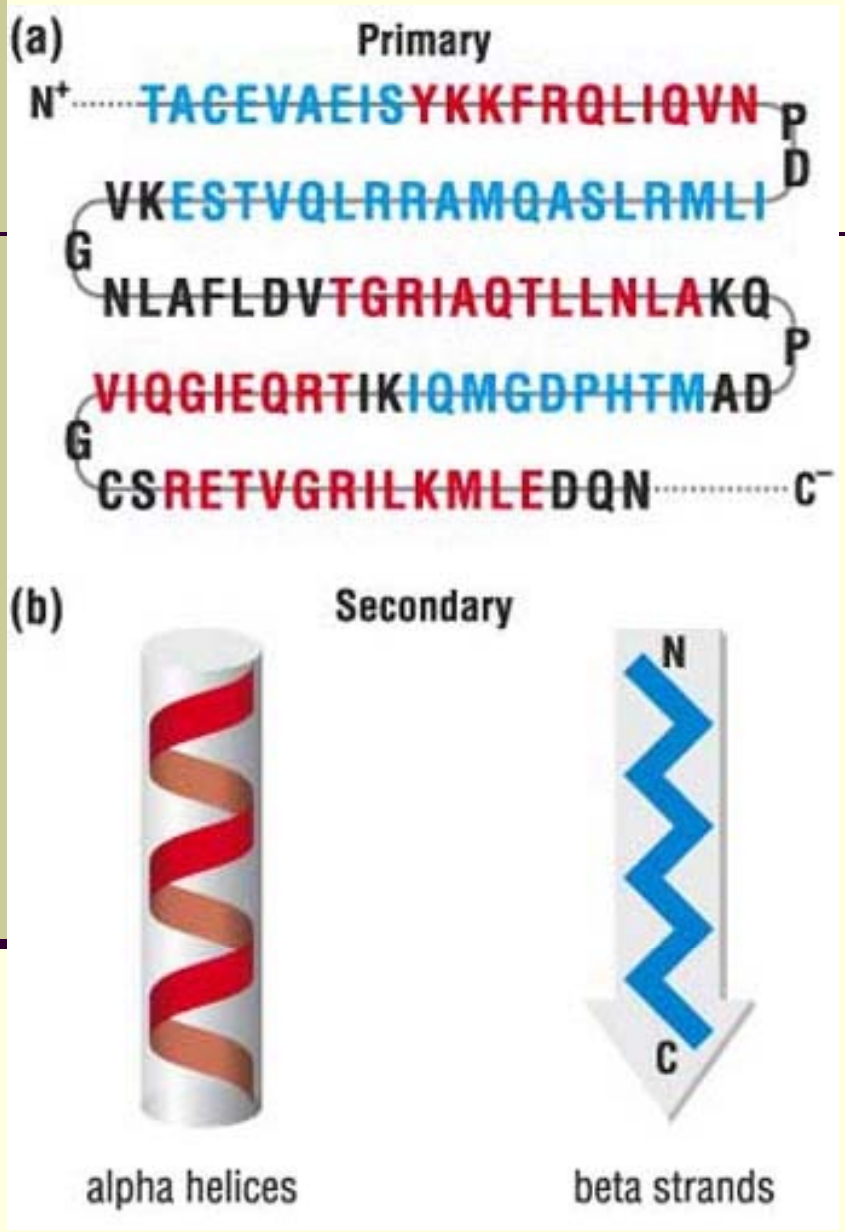
Ribonucleasa

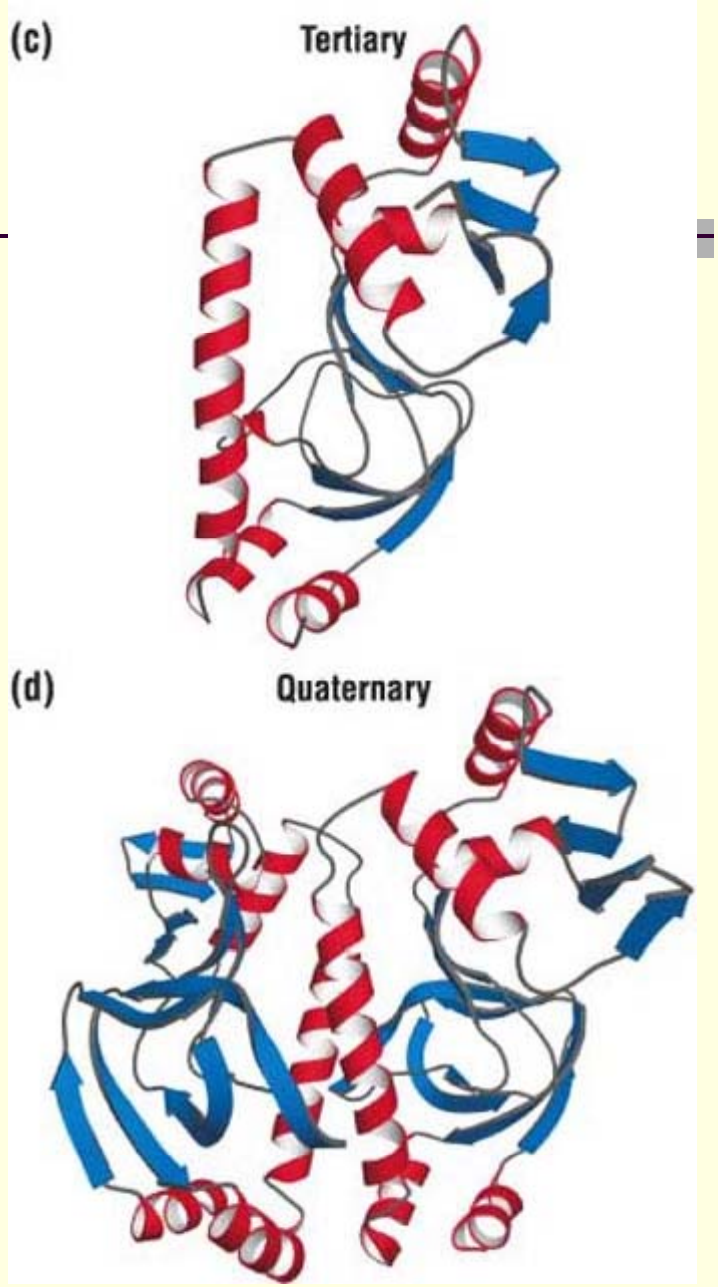


- Proteína
  - Estructura
    - Cuaternaria
      - Varias cadenas polipeptídicas unidas (subunidades)
      - Pueden estar unidos por
        - enlaces disulfuro
        - No covalentes

Tipo de interacciones

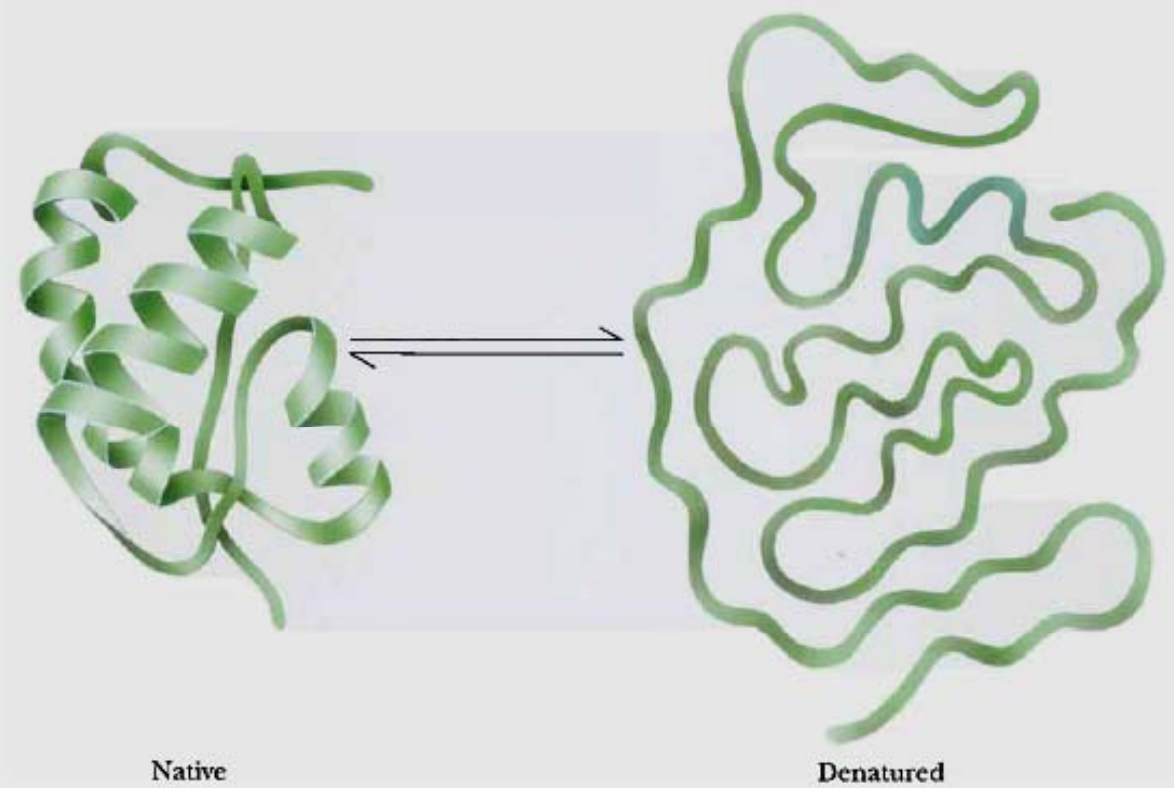



(a)
Primary
N+
TACEVAEISYKKFRQLIQVN
P
D
VKESTVQLRRAMQASLRMLI
G
NLAFLDVTGRIAQTLLNLAKQ
P
VIQGIEQRTIKIQMGDPHTM
AD
G
CSRETVGRILKMLEDQN
C−
(b)
Secondary
N
C
alpha helices
beta strands


(c)
Tertiary
(d)
Quaternary

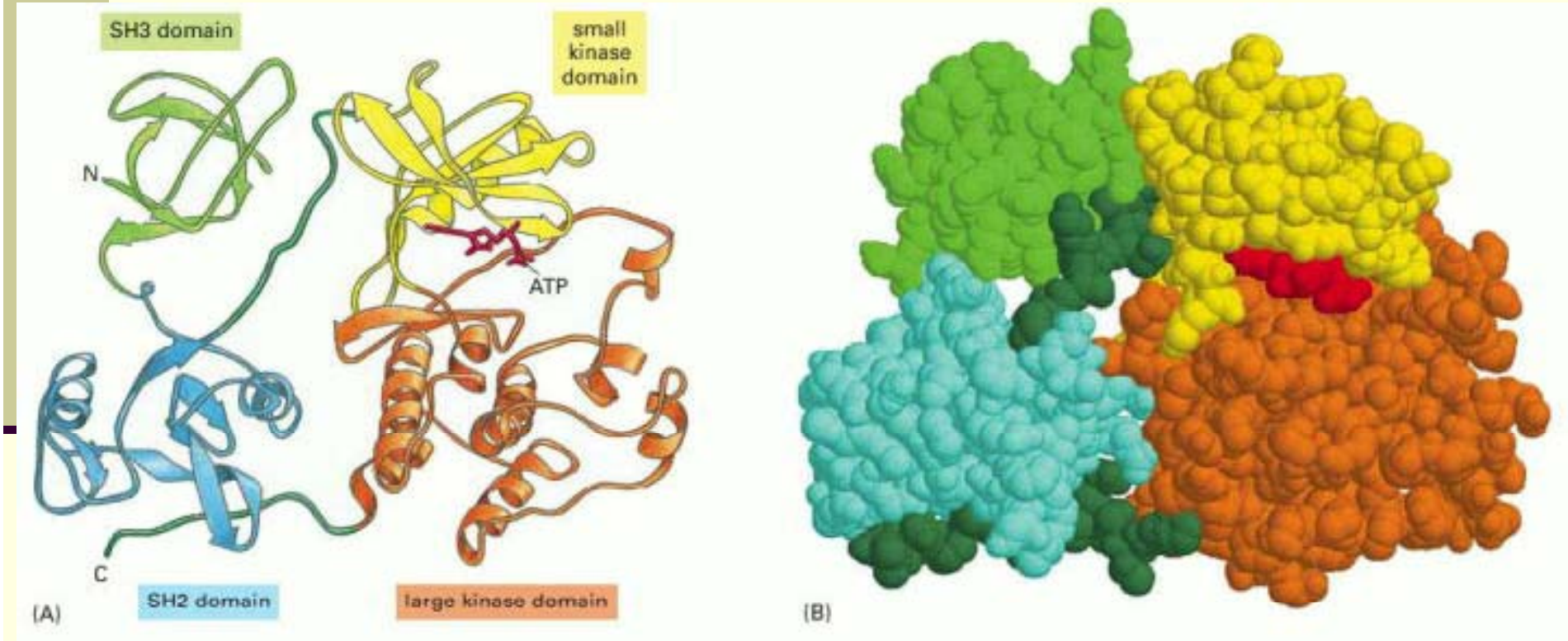
¿Qué sucede si aplicamos calor a una proteína?

FIGURE 1.17 • Denaturation and renaturation of the intricate structure of a protein.



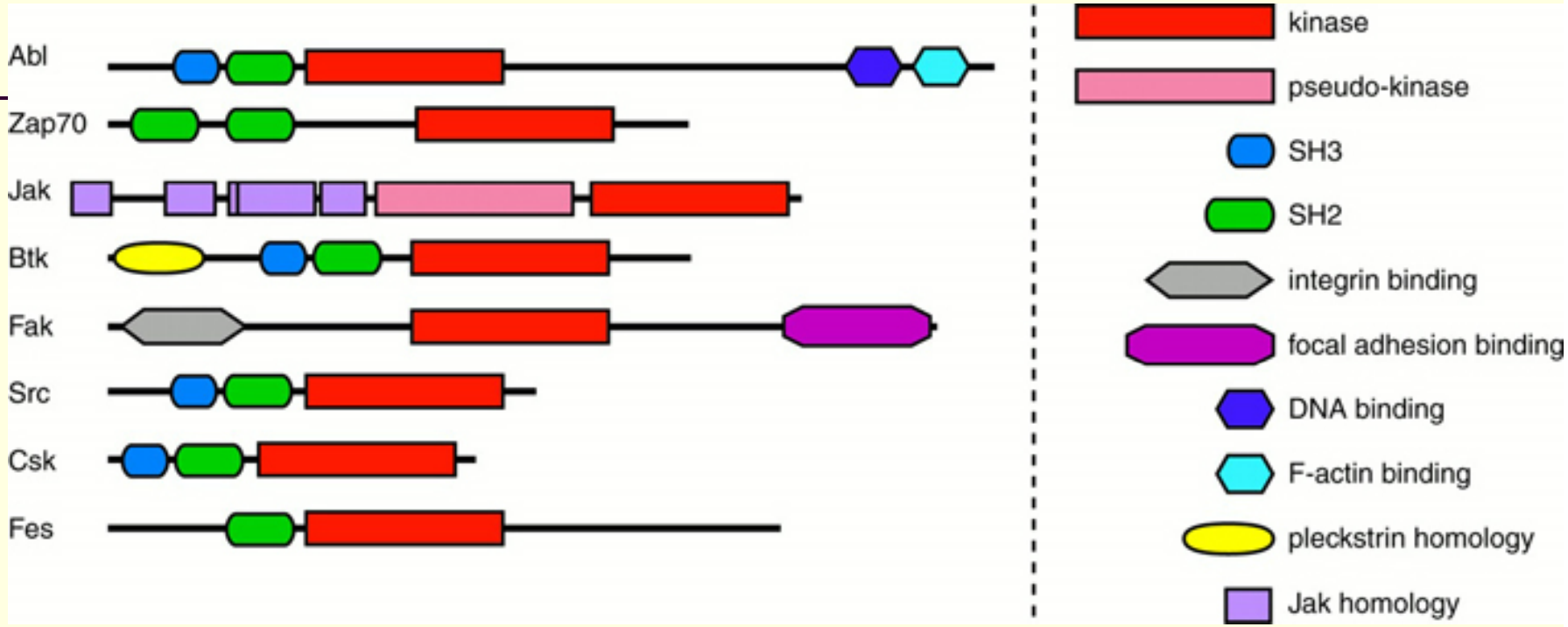
Dominio asociado a una función

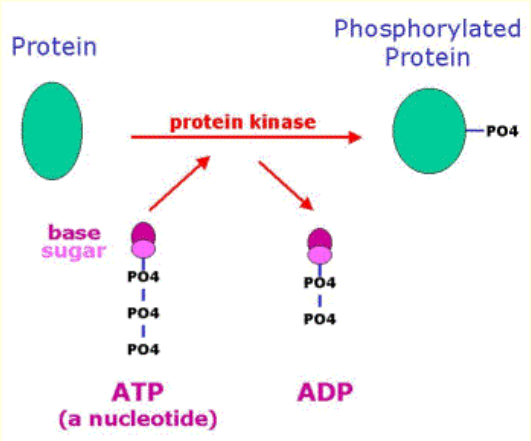
Dominio SH3 tiene una estructura de beta e interactúa con residuos hidrofóbicos (X-P-p-X-P- con X siendo aminoácidos alifáticos)



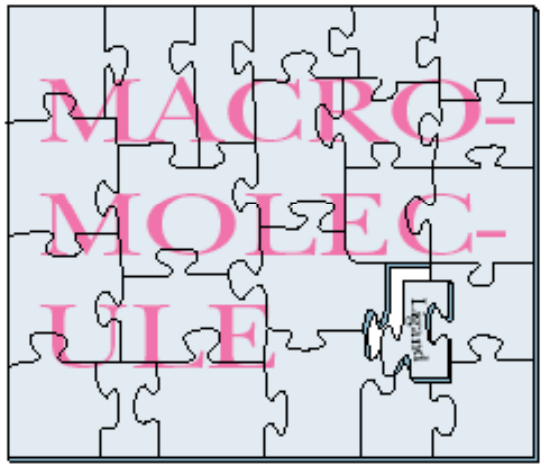
Dominios SH2 interactúan con residuos fosfotirosina

Dominio asociado a una función

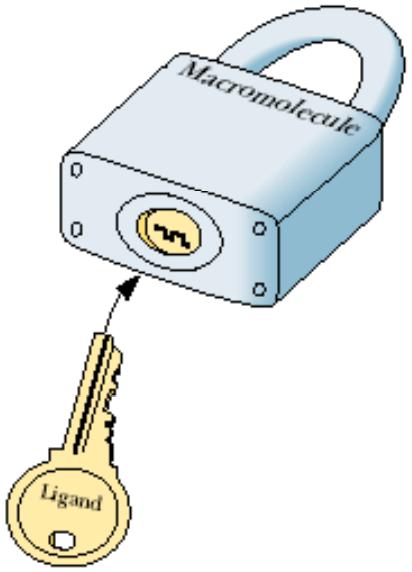




Puzzle



Lock and key



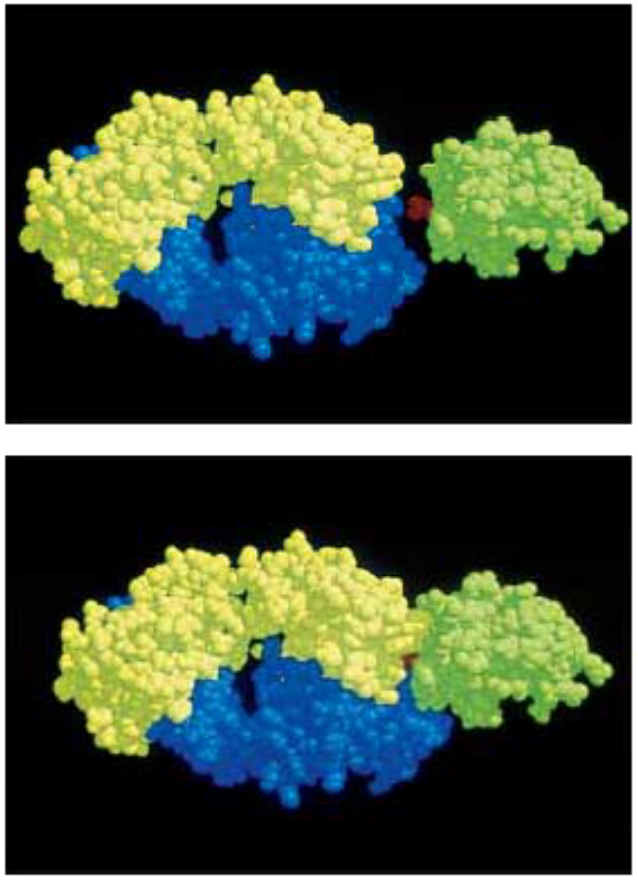
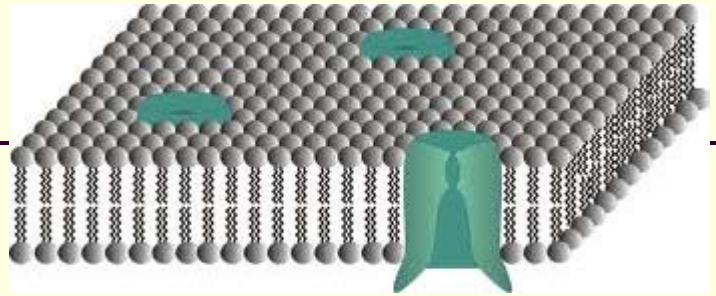
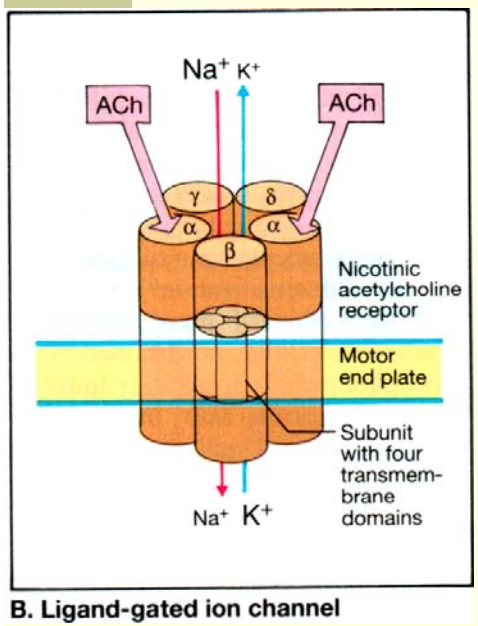


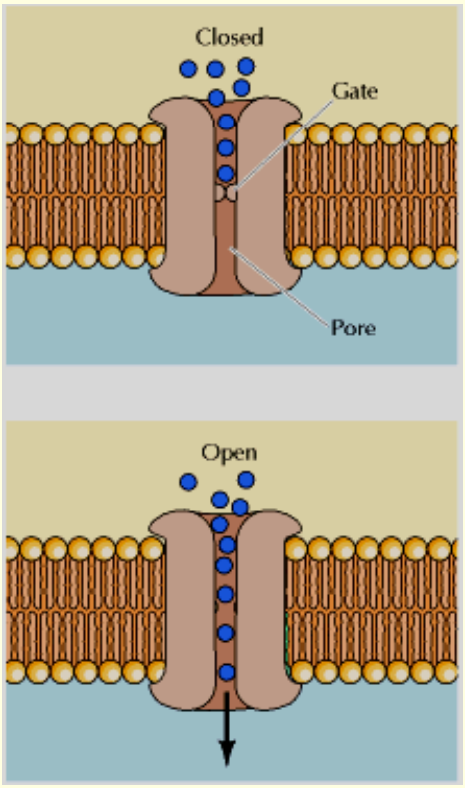
FIGURE 1.16 • Structural complementarity: the pieces of a puzzle, the lock and its key, a biological macromolecule and its ligand—an antigen–antibody complex. (a) The antigen on the right (green) is a small protein, lysozyme, from hen egg white. The part of the antibody molecule (IgG) shown on the left in blue and yellow includes the antigen-binding domain. (b) This domain has a pocket that is structurally complementary to a surface protuberance (Gln^{121}, shown in red between antigen and antigen-binding domain) on the antigen. (See also Figure 1.12.) (*photos, courtesy of Professor Simon E. V. Philips*)

Estructura de canales





B. Ligand-gated ion channel



Estructura de canales

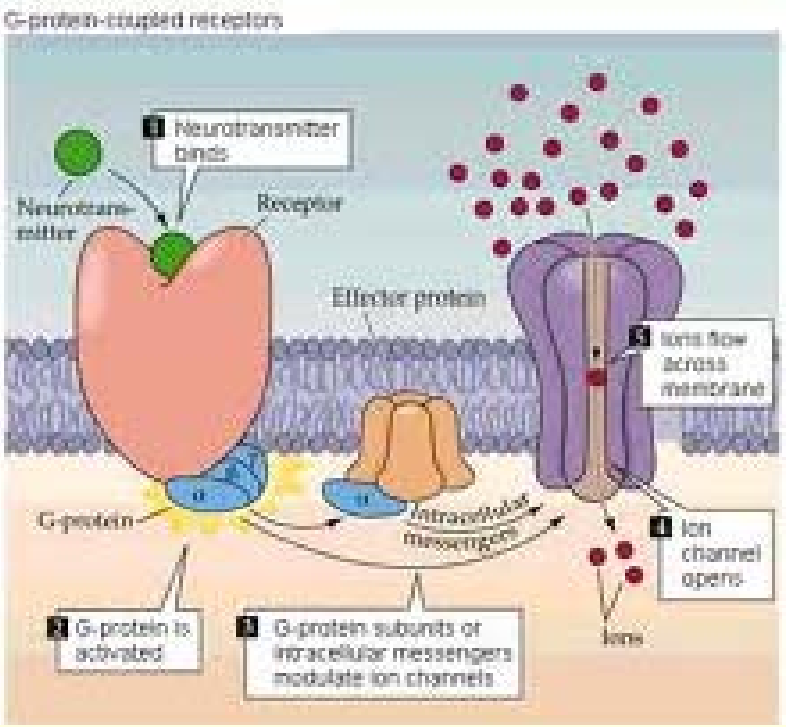
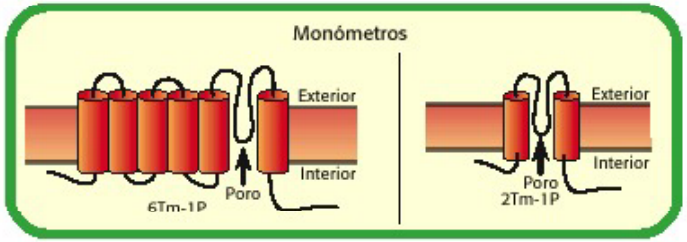
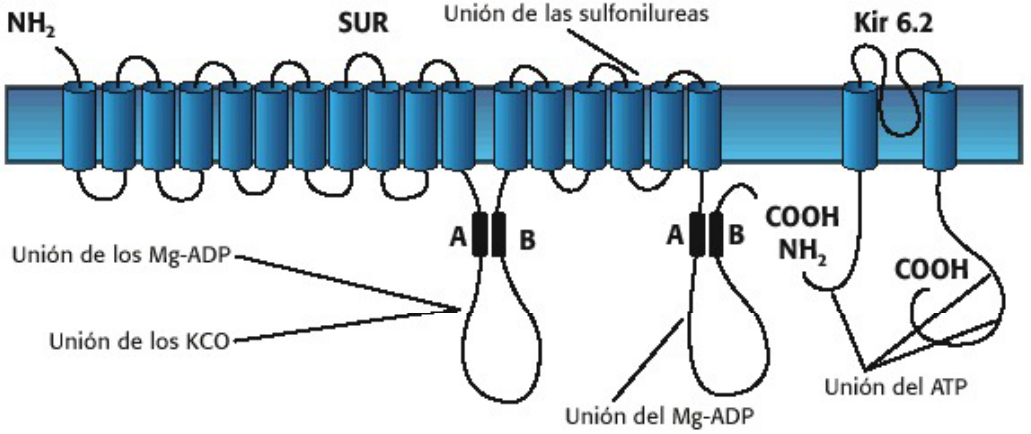


Figura 1.

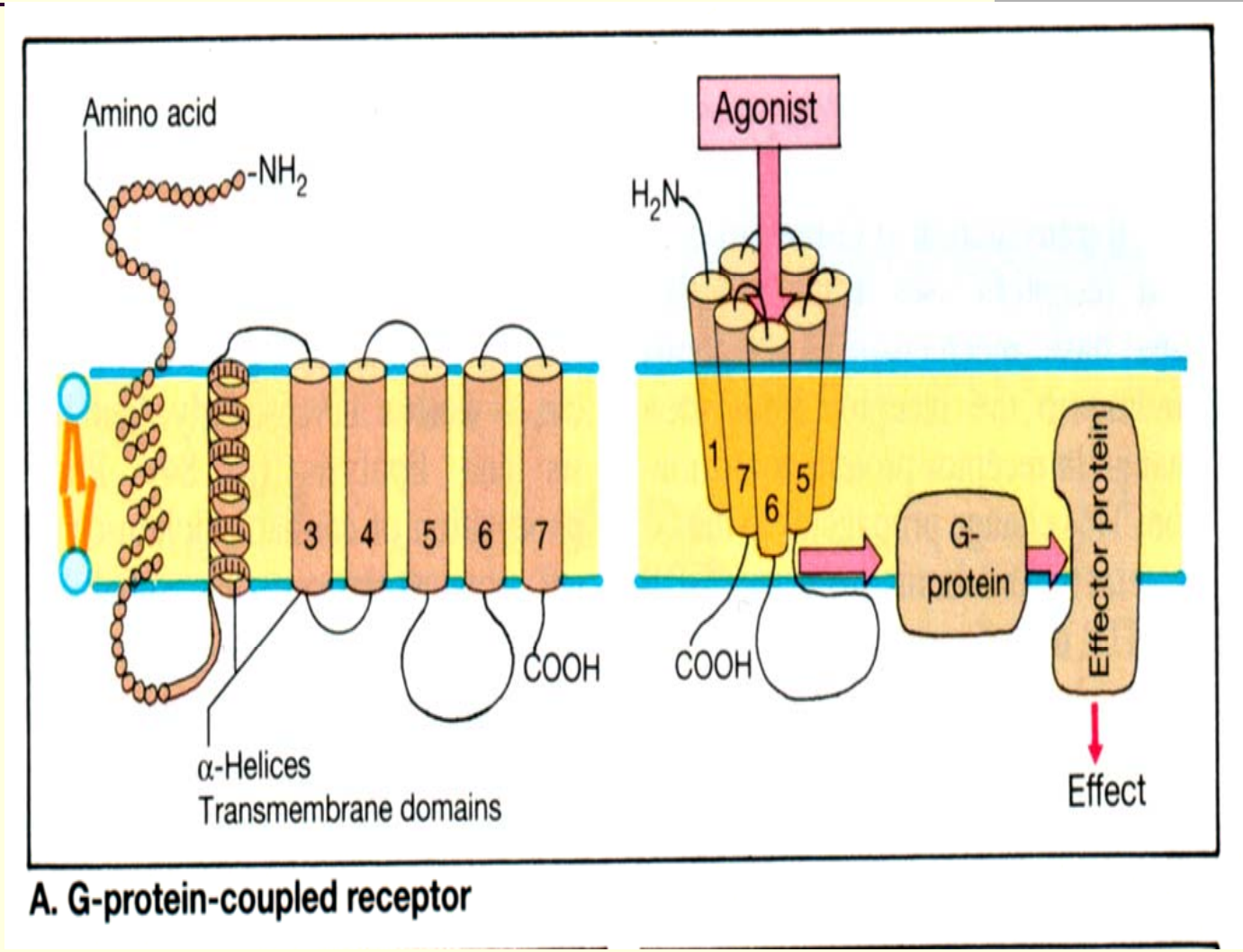
A Esquema de la estructura de los canales de potasio Kv y Kir.



B Estructura molecular de un canal de potasio sensible a ATP



Estructura de receptores



A. G-protein-coupled receptor

Table 1.3

Weak Chemical Forces and Their Relative Strengths and Distances

Force	Strength (kJ/mol)	Distance (nm)	Description
Van der Waals interactions	0.4–4.0	0.2	Strength depends on the relative size of the atoms or molecules and the distance between them. The size factor determines the area of contact between two molecules: The greater the area, the stronger the interaction.
Hydrogen bonds	12–30	0.3	Relative strength is proportional to the polarity of the H bond donor and H bond acceptor. More polar atoms form stronger H bonds.
Ionic interactions	20	0.25	Strength also depends on the relative polarity of the interacting charged species. Some ionic interactions are also H bonds: $—NH_3^+ \ldots {}^-OOC—$
Hydrophobic interactions	<40	—	Force is a complex phenomenon determined by the degree to which the structure of water is disordered as discrete hydrophobic molecules or molecular regions coalesce.