Oligomers

Oligomers

homo-oligomers by self-association

hetero-oligomers by binding to a different protein.

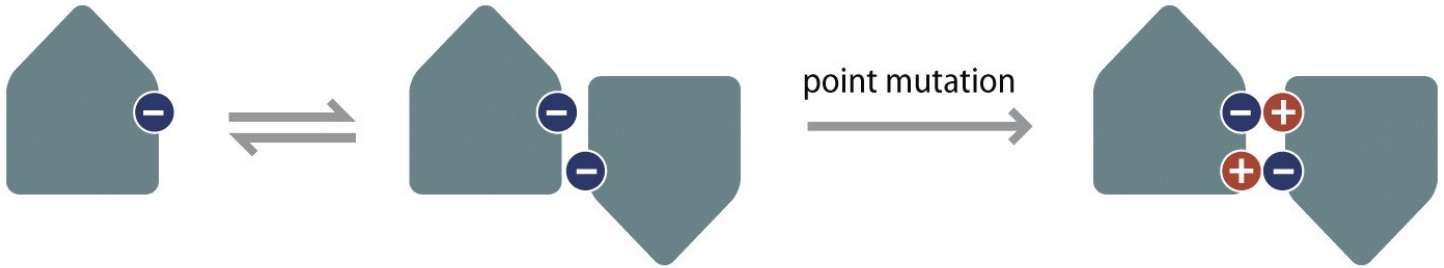


Figure 3.1 How Proteins Work (©2012 Garland Science)

triose phosphate isomerase

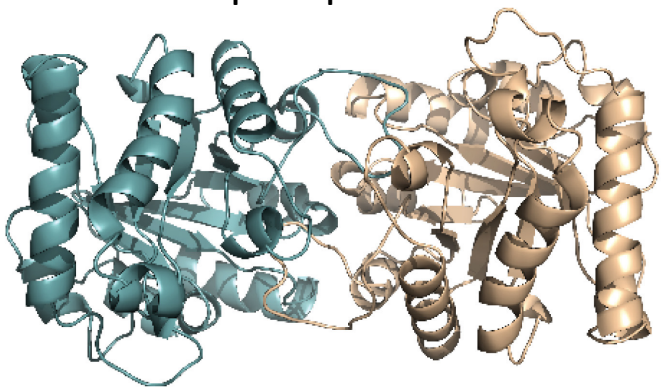


Figure 1.14b Molecular Biology of Assemblies and Machines (© Garland Science 2016)

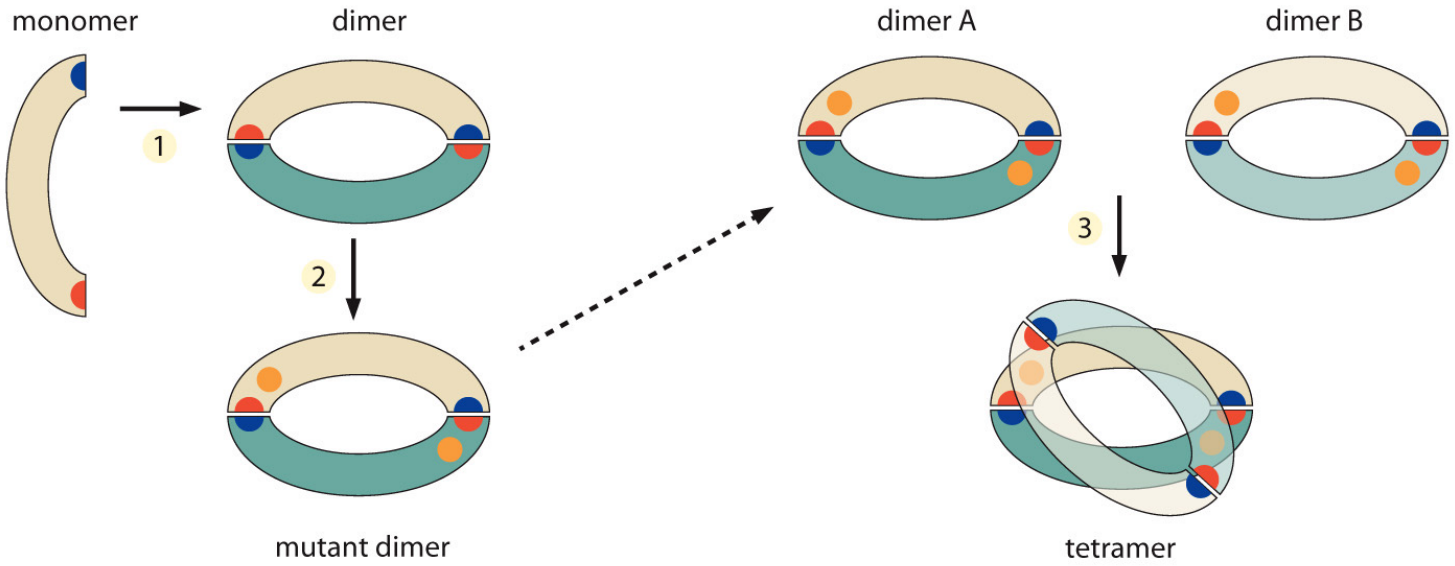


Figure 1.14a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

rabbit muscle fructose-1,6- bisphosphate aldolase.

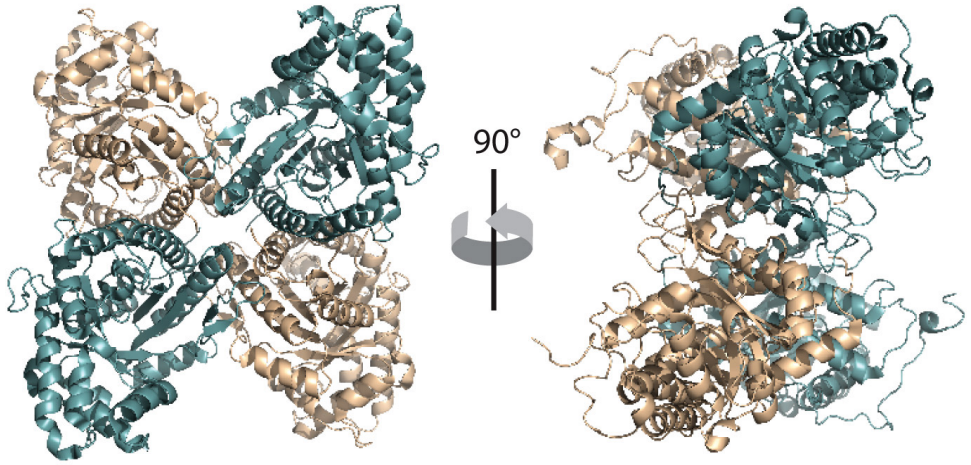


Figure 1.14c Molecular Biology of Assemblies and Machines (© Garland Science 2016)

symmetry

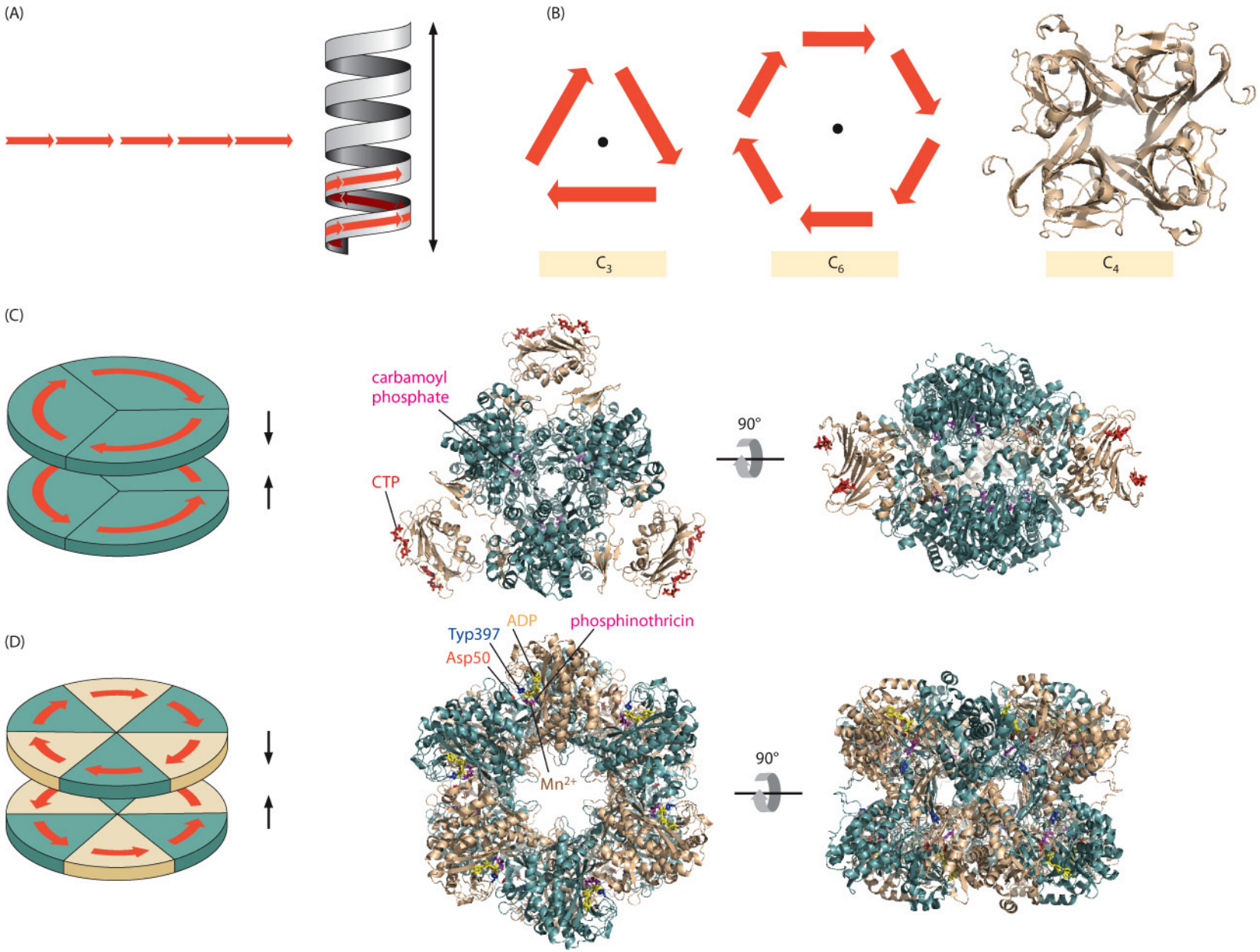


Figure 1.15 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Protein surface

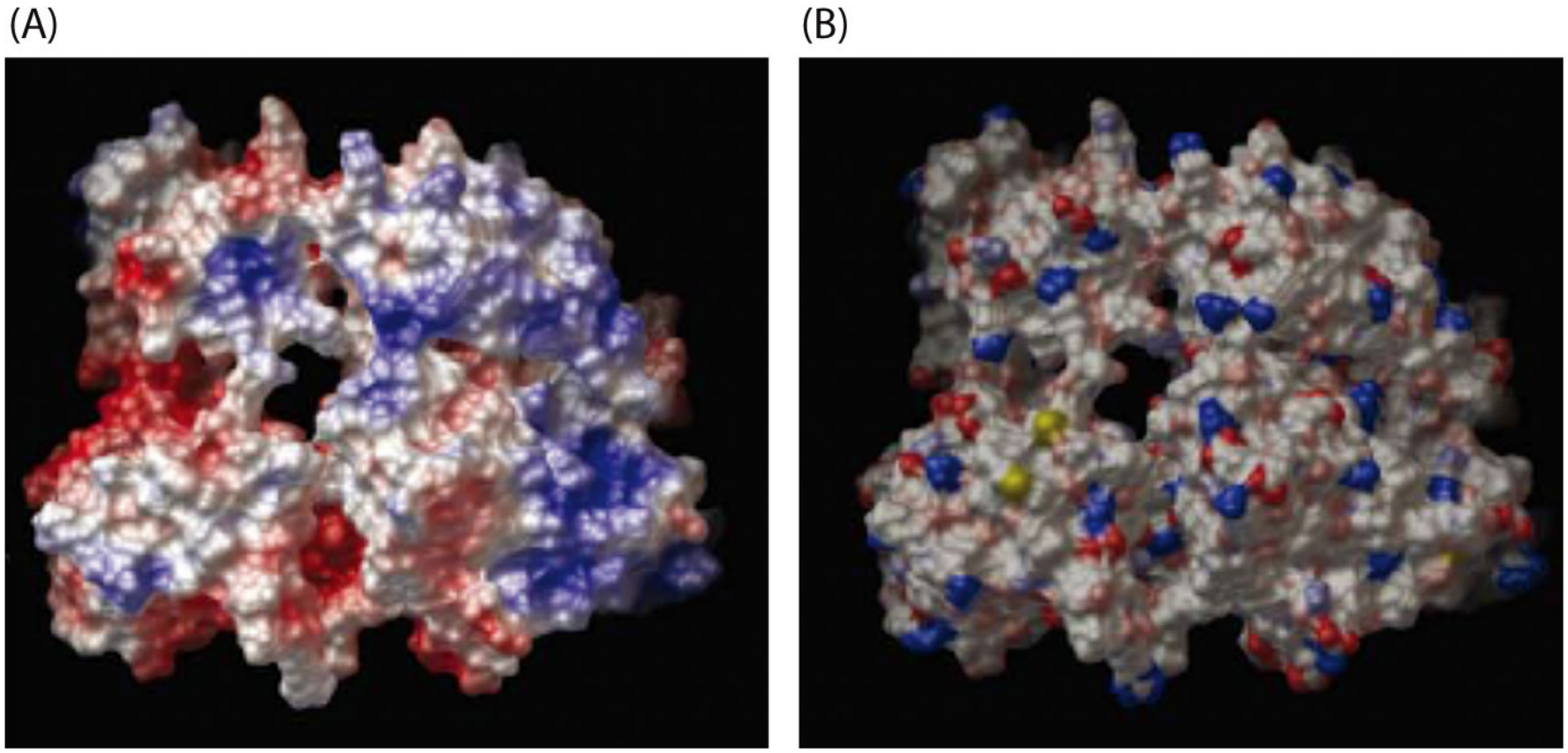
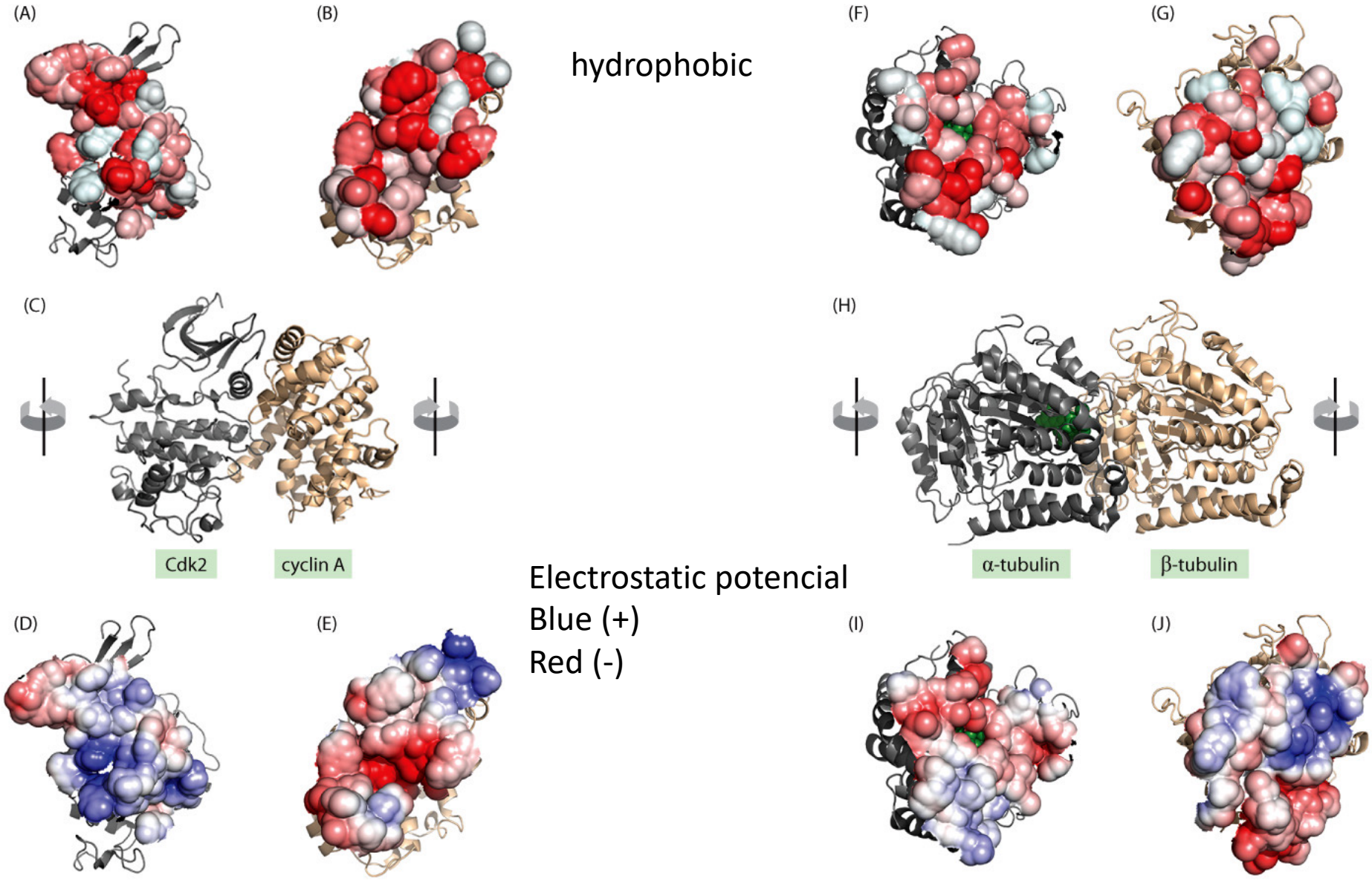


Figure 1.7 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Interactions



hydrophobic

Electrostatic potencial
Blue (+)
Red (-)

Figure 1.10 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Amino acid in oligomeric interfaces

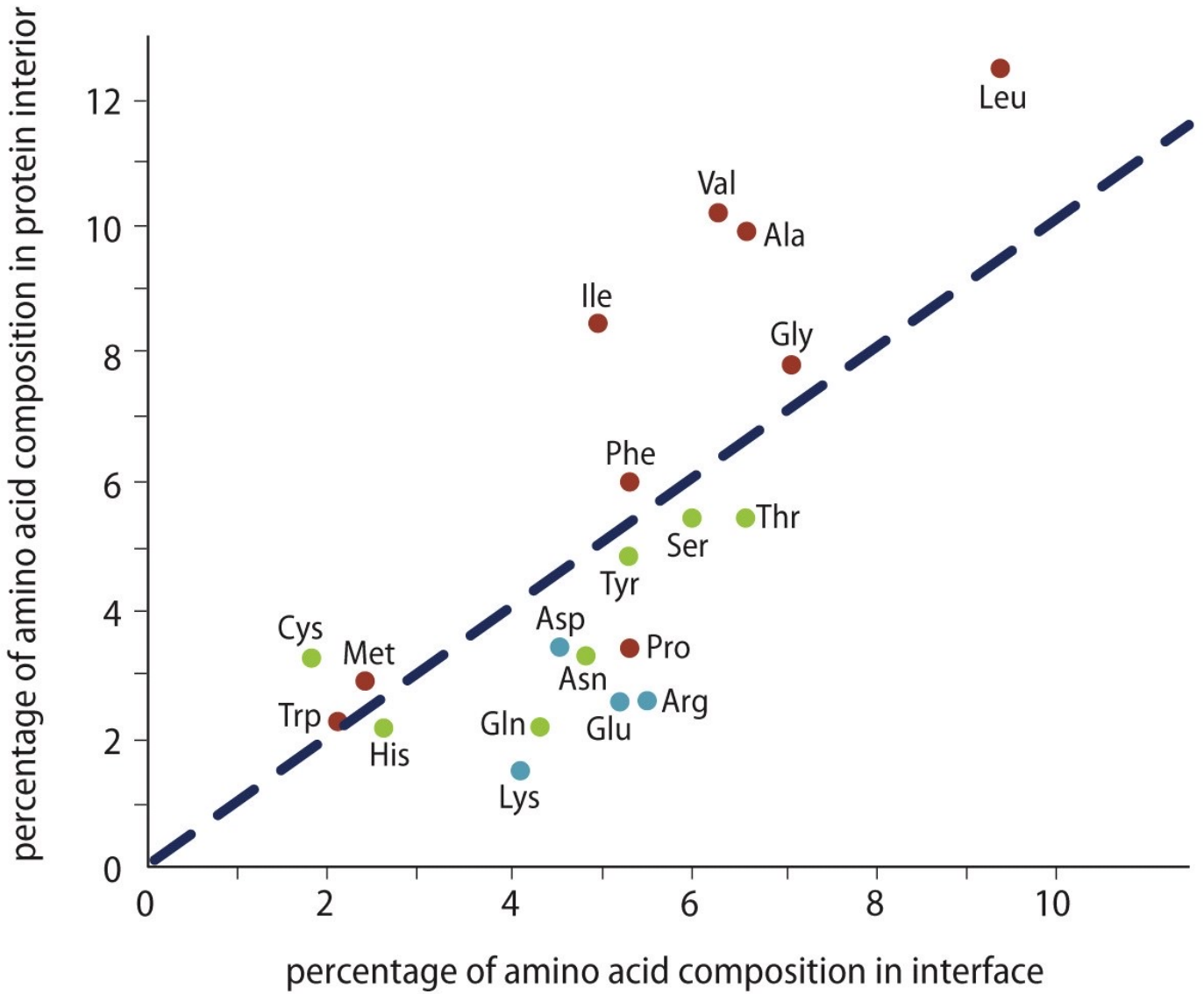


Figure 3.2 How Proteins Work (©2012 Garland Science)

regulation the accessibility of the active site

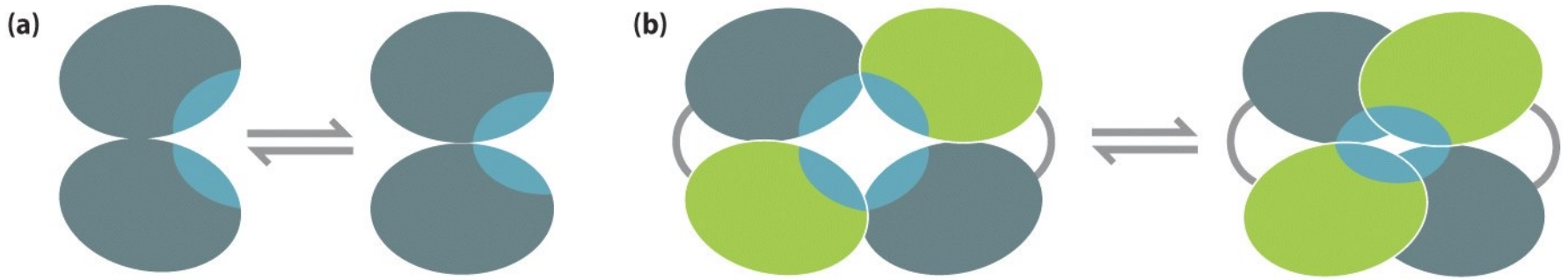


Figure 3.3 How Proteins Work (©2012 Garland Science)

Active site

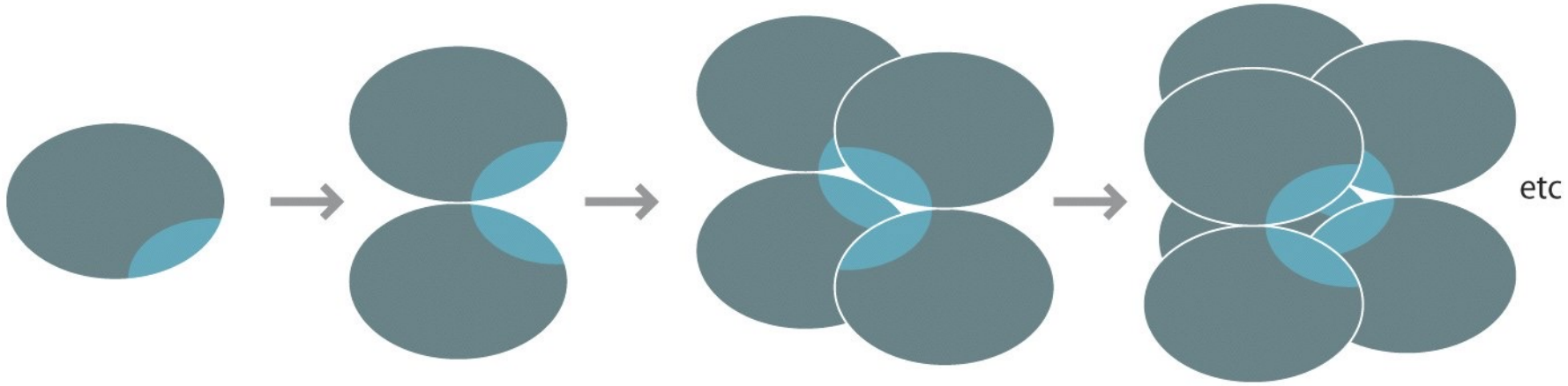
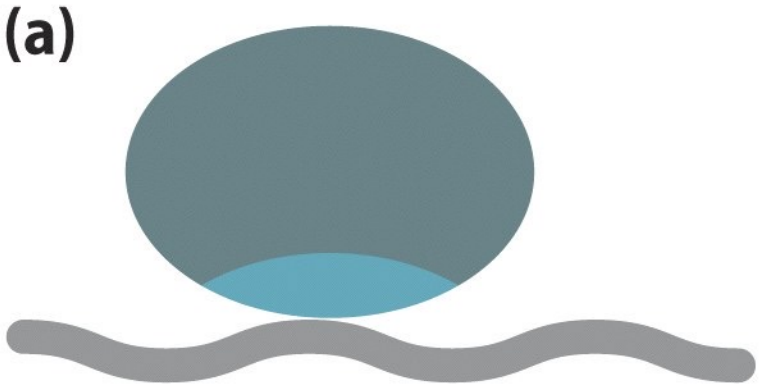


Figure 3.6 How Proteins Work (©2012 Garland Science)

selectivity

Exolytic and endolytic



Exolytic

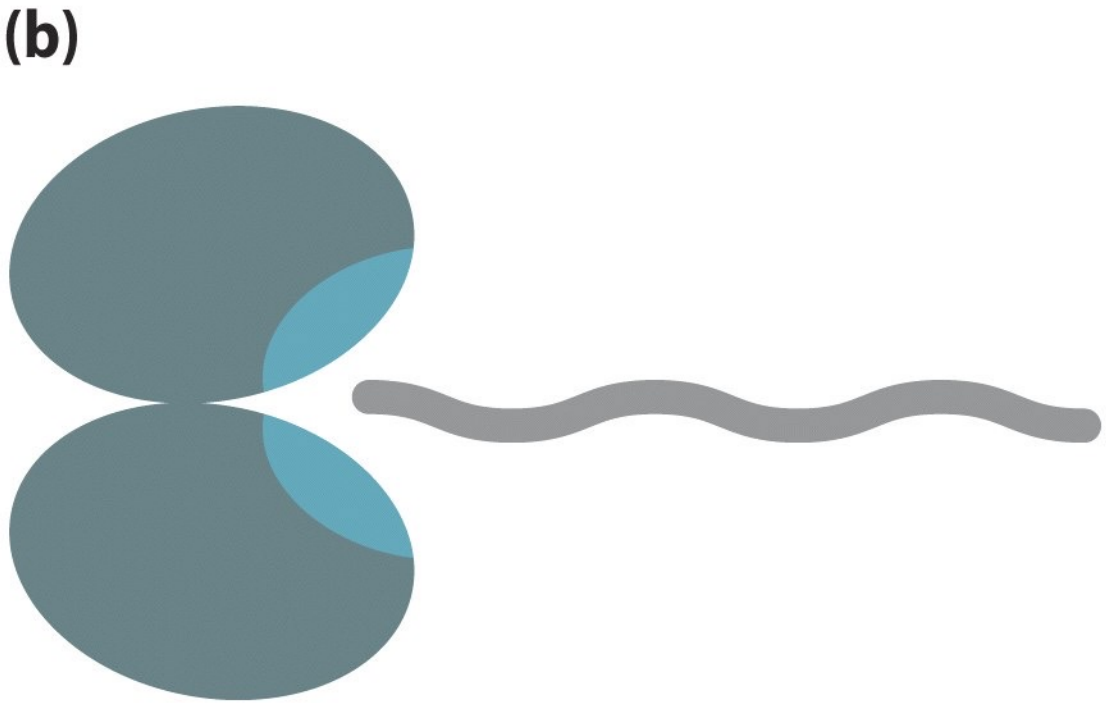


Figure 3.4 How Proteins Work (©2012 Garland Science)

evolution of allosteric effectors

The interface of two domains also creates the possibility of **allostery**

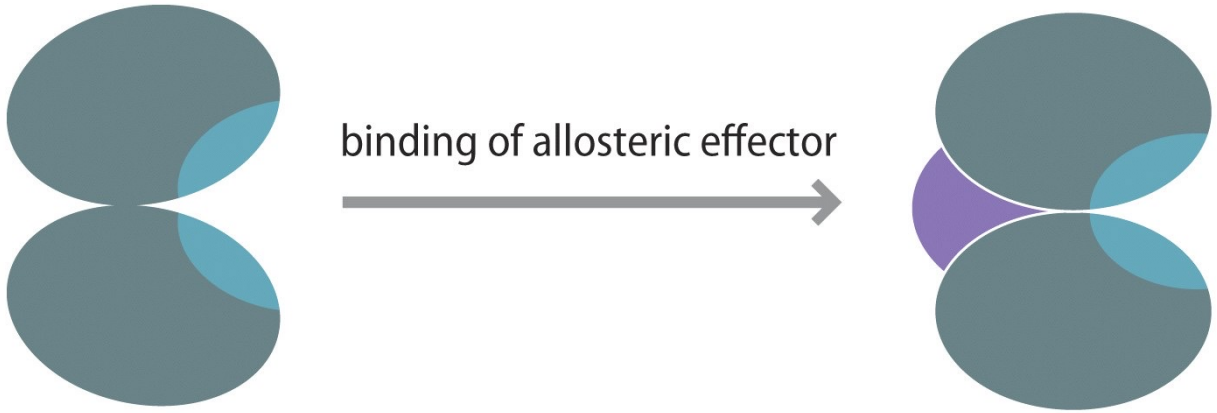


Figure 3.5 How Proteins Work (©2012 Garland Science)

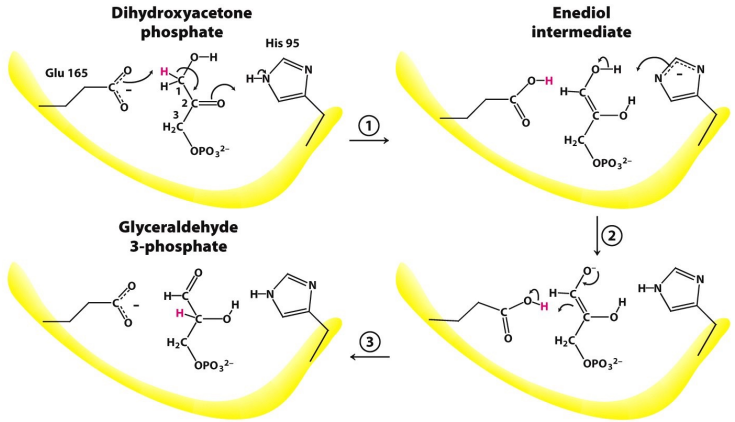


Figure 16.5
Biochemistry, Seventh Edition
© 2012 W. H. Freeman and Company

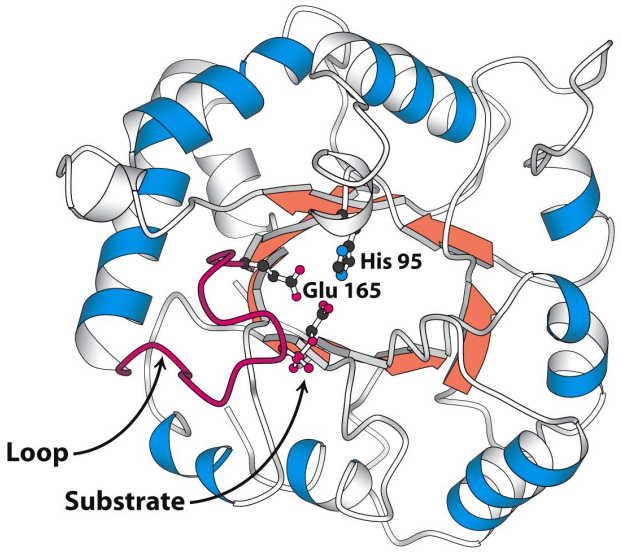


Figure 16.4
Biochemistry, Seventh Edition
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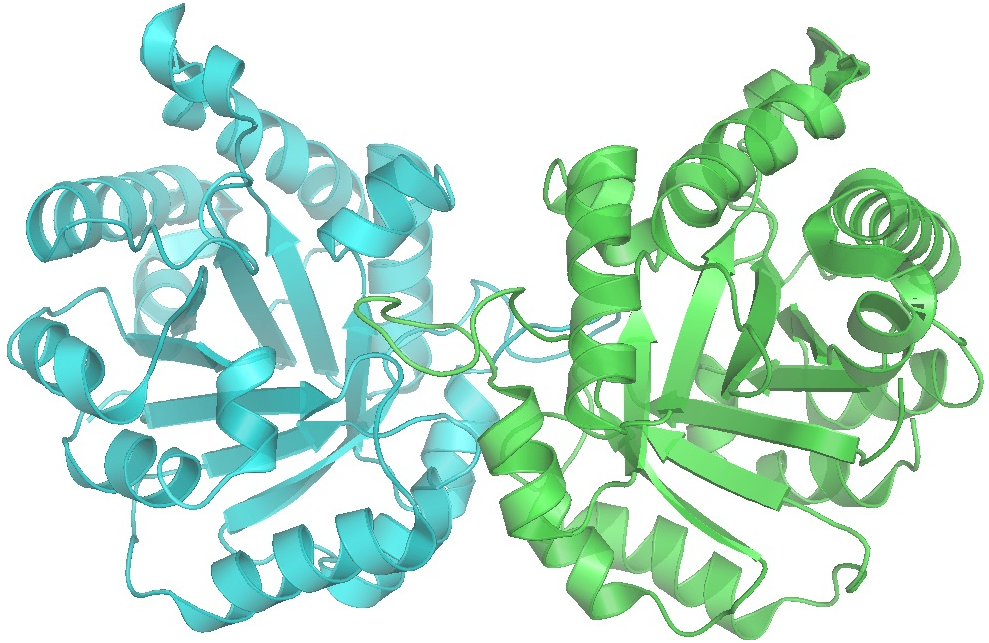
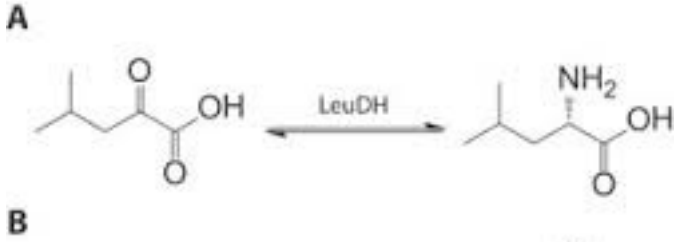
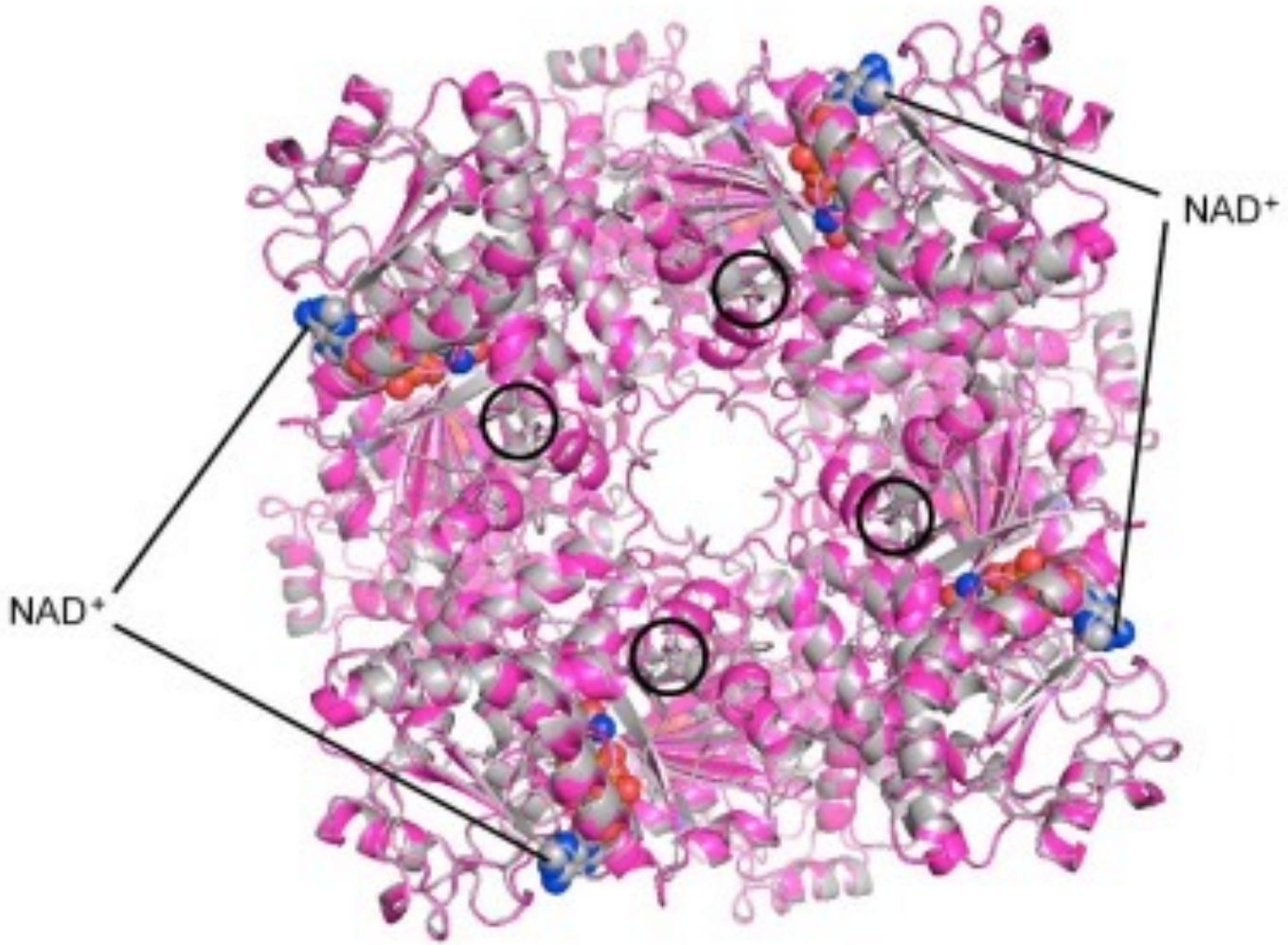
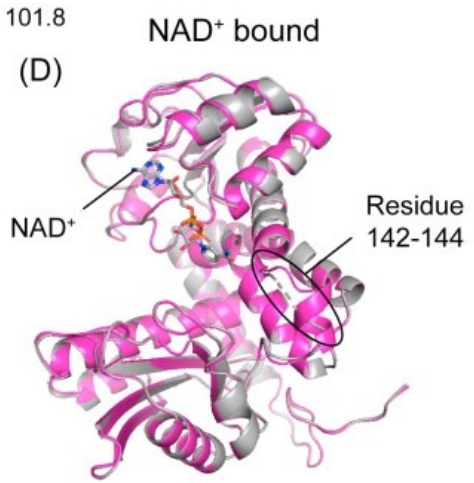


improve of enzyme functionality

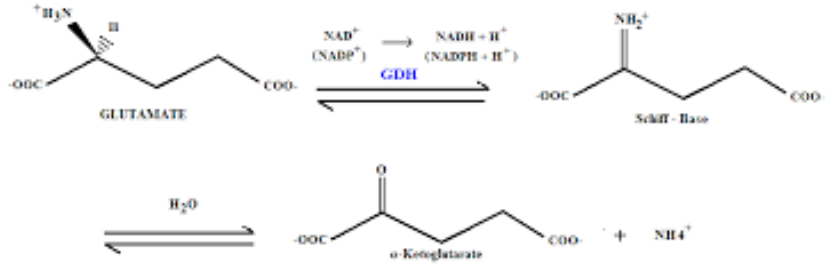
Enzymes
low K_m high k_{cat}

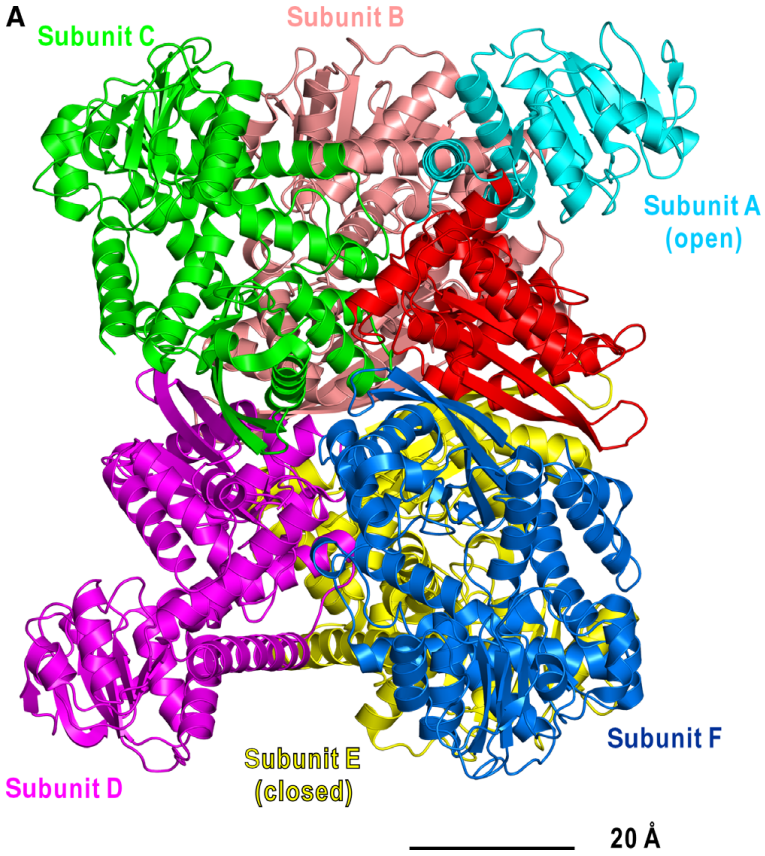


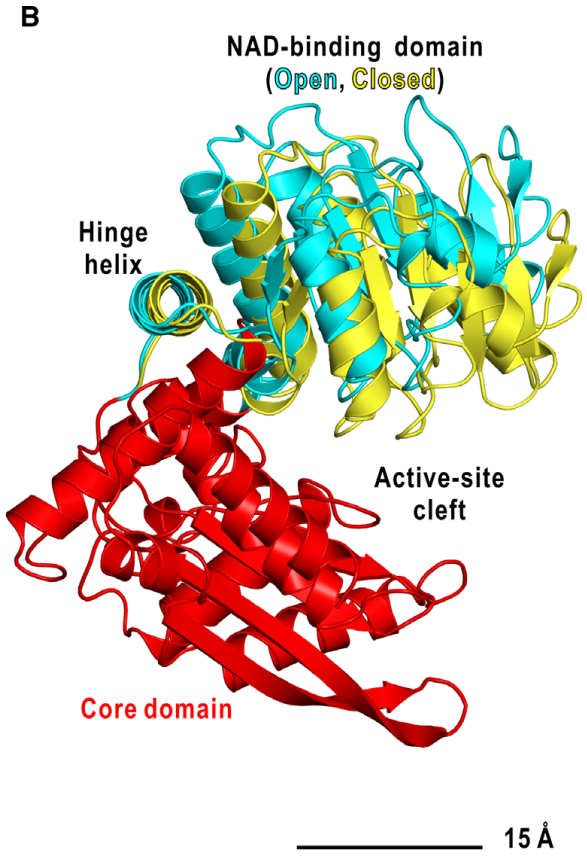




improve of enzyme functionality



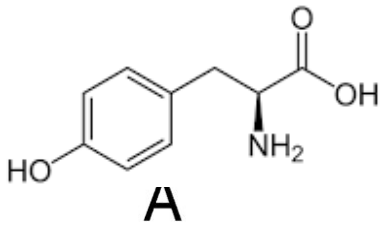


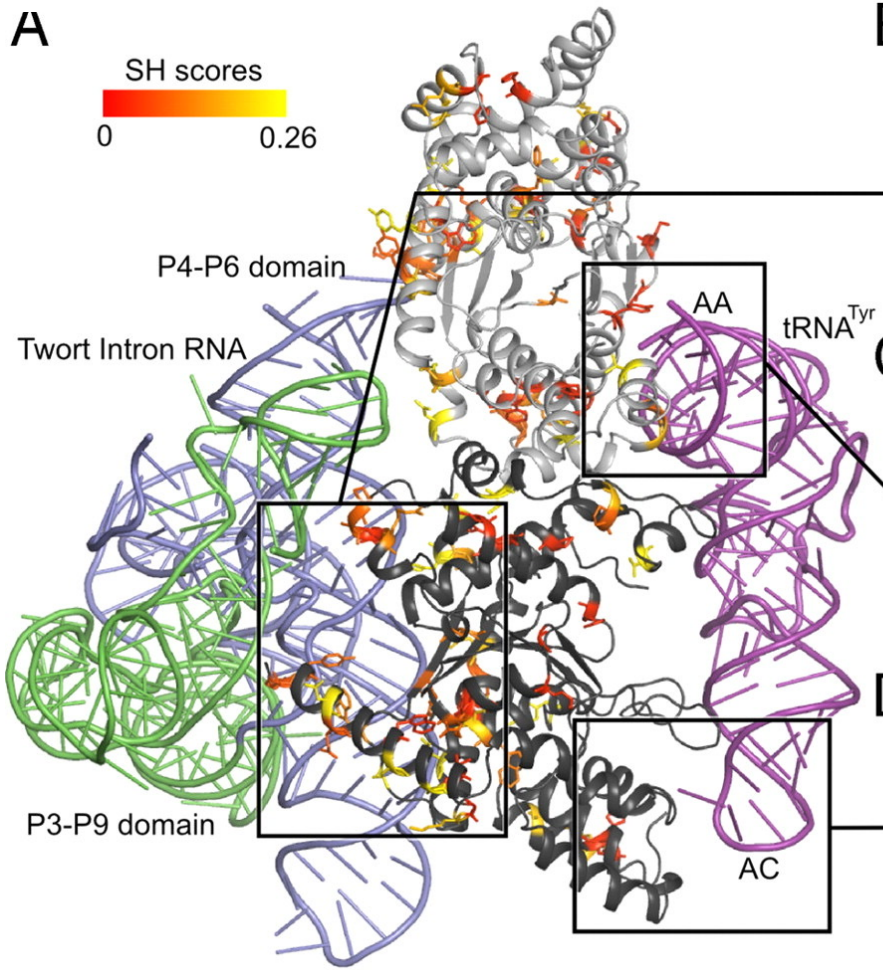


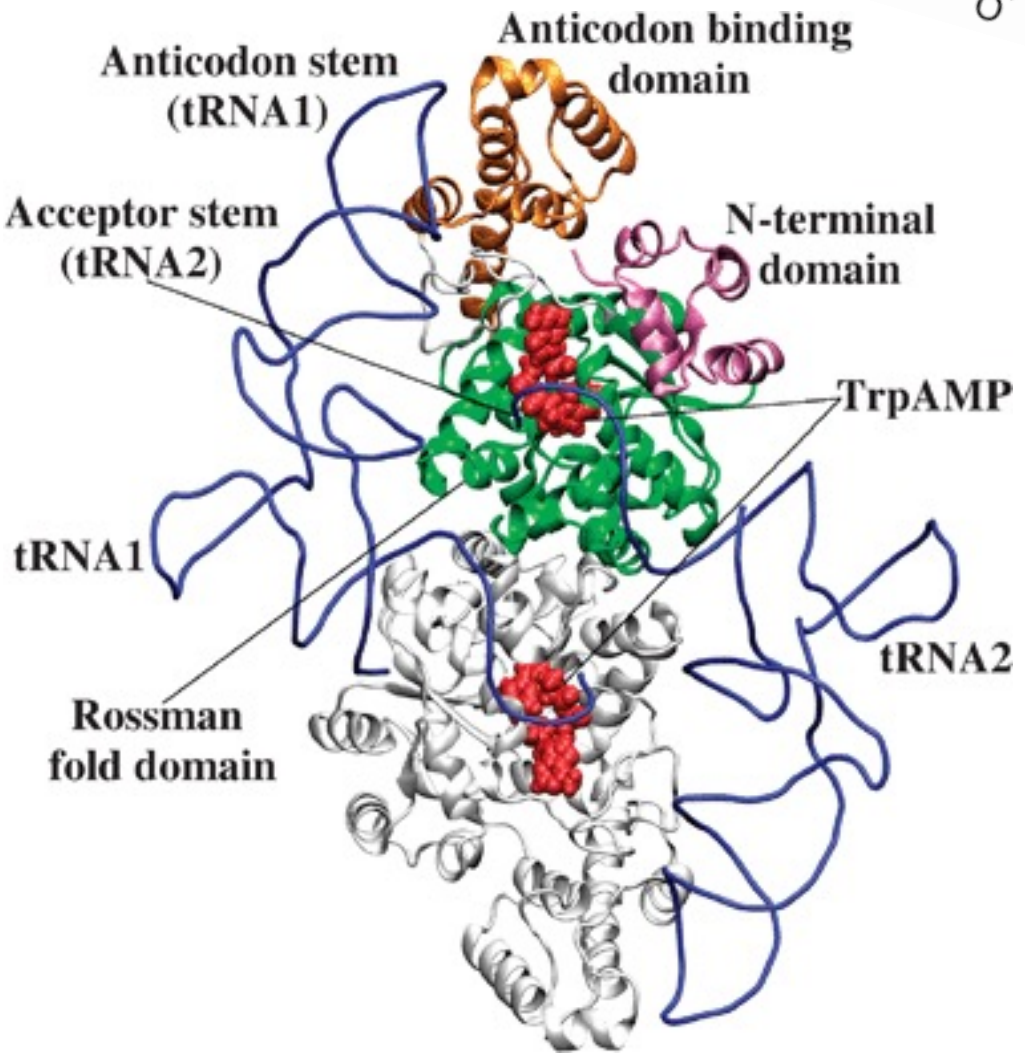
Glutamate dehydrogenase

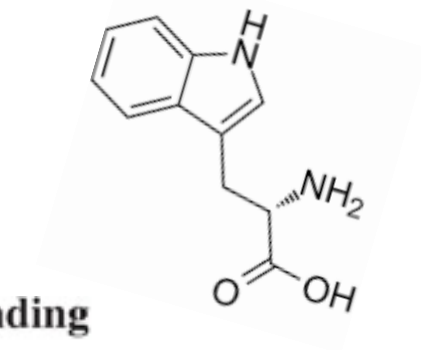
improve of enzyme functionality

tyrosyl-tRNA and tryptophanyl-tRNA synthetases









monomer/oligomer

activation of caspase-7 by proteolytic cleavage

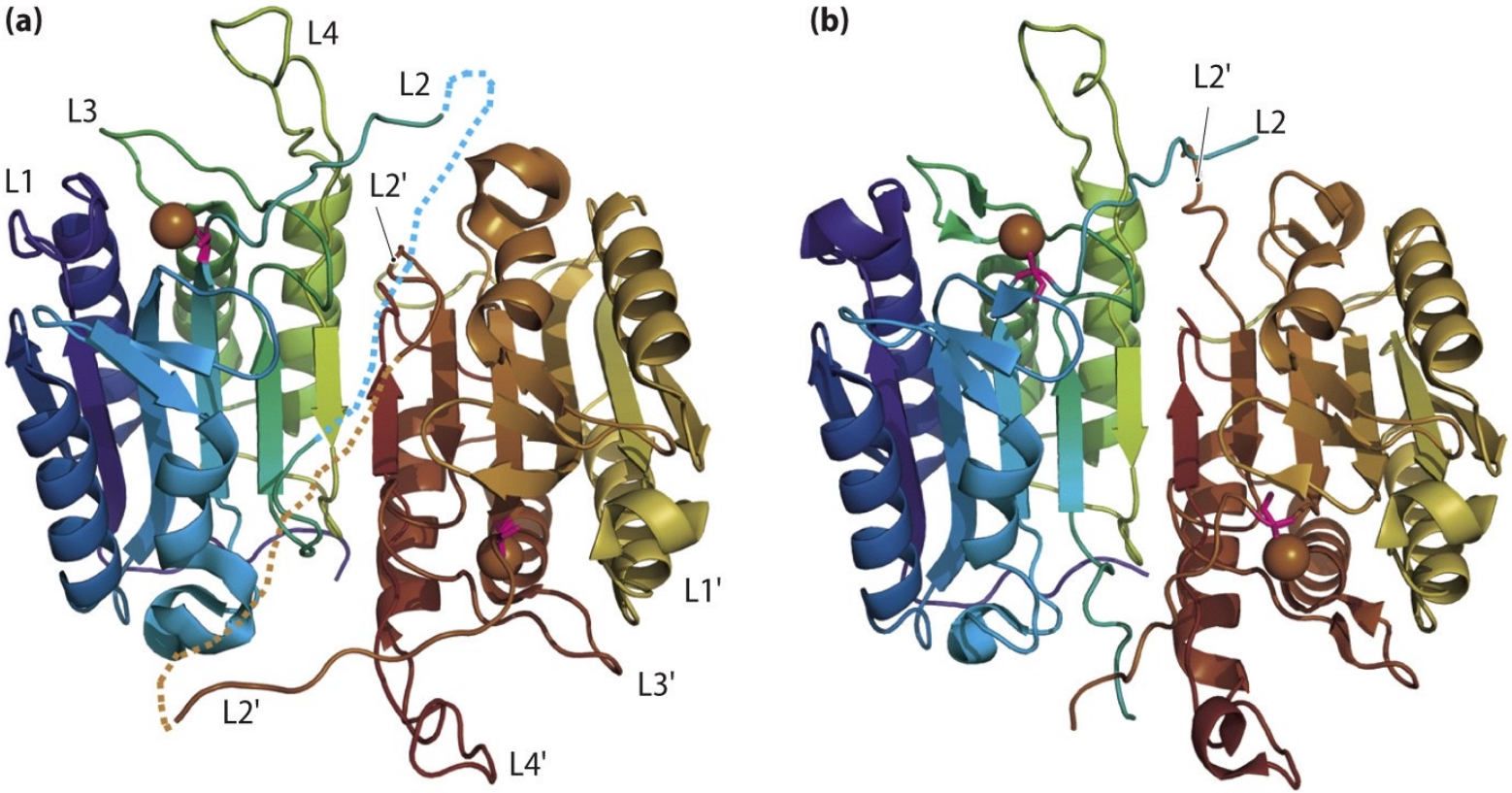
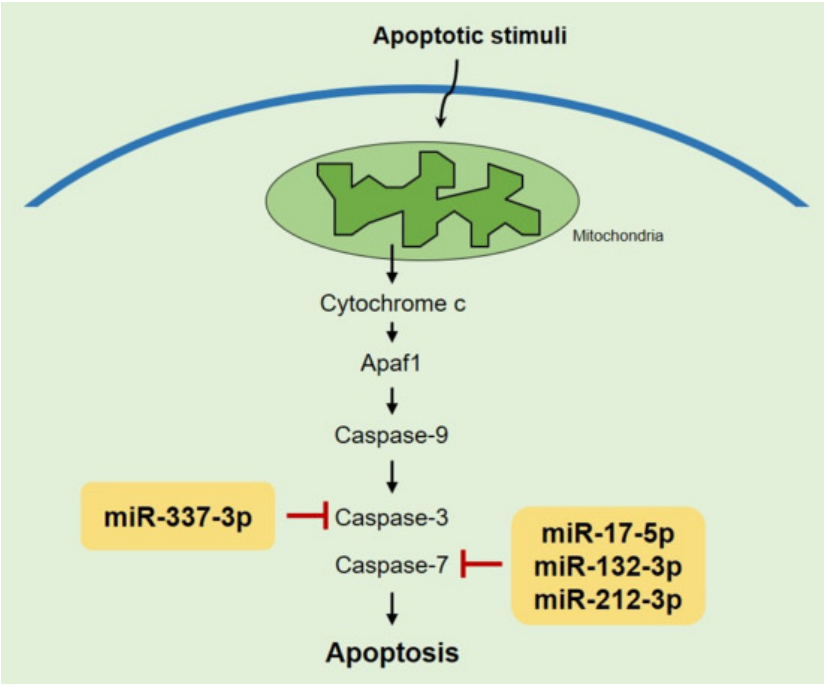
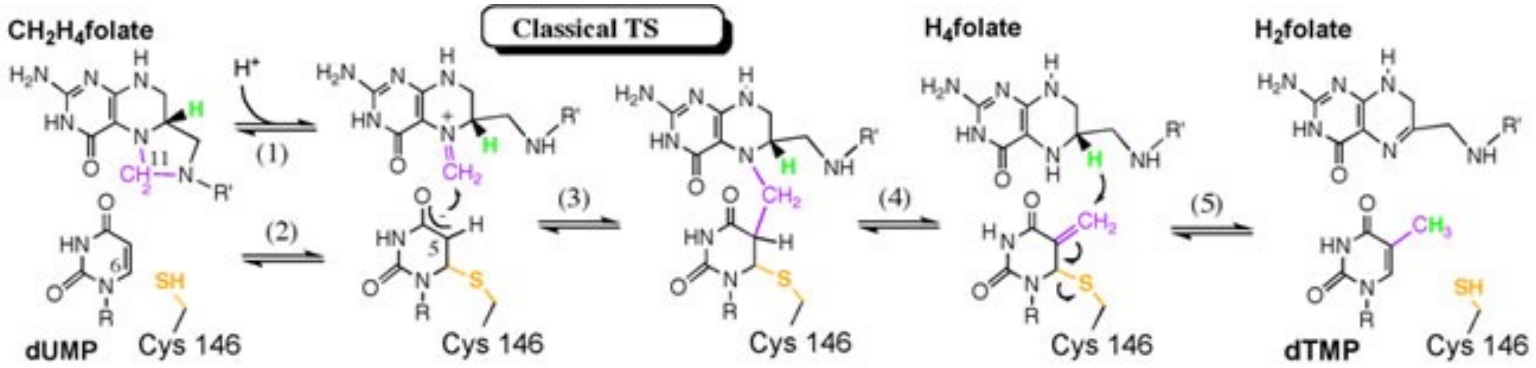
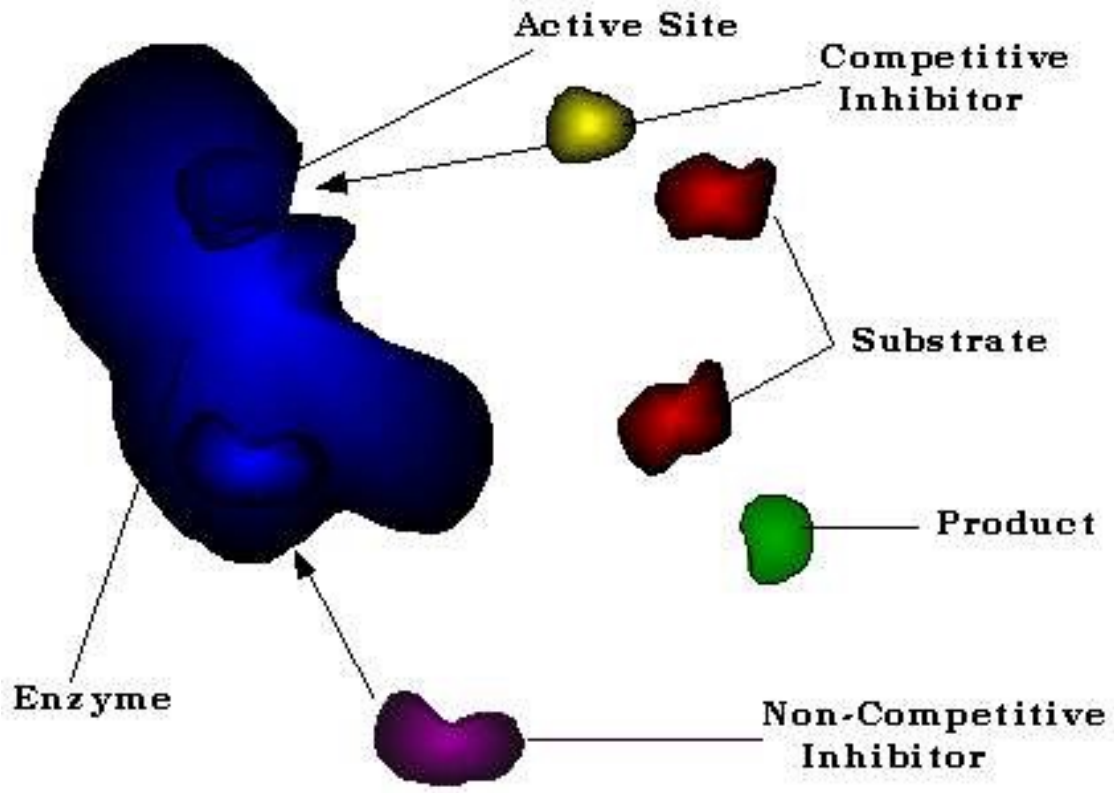


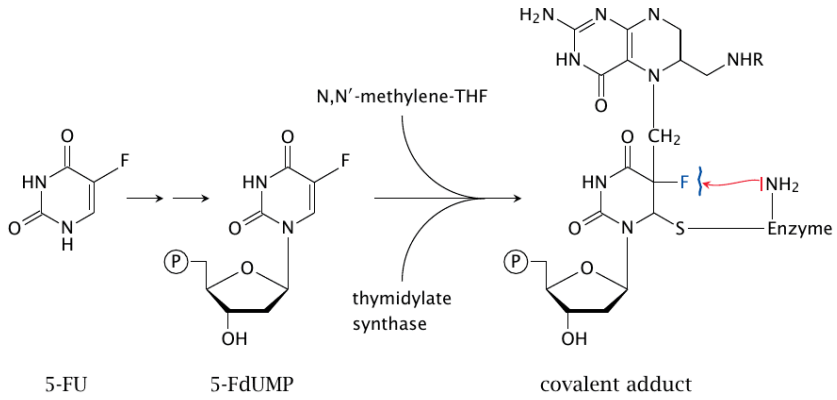
Figure 3.7 How Proteins Work (©2012 Garland Science)



Enzyme regulation







Irreversible
Active site-directed inhibitors

ligand-induced conformational change

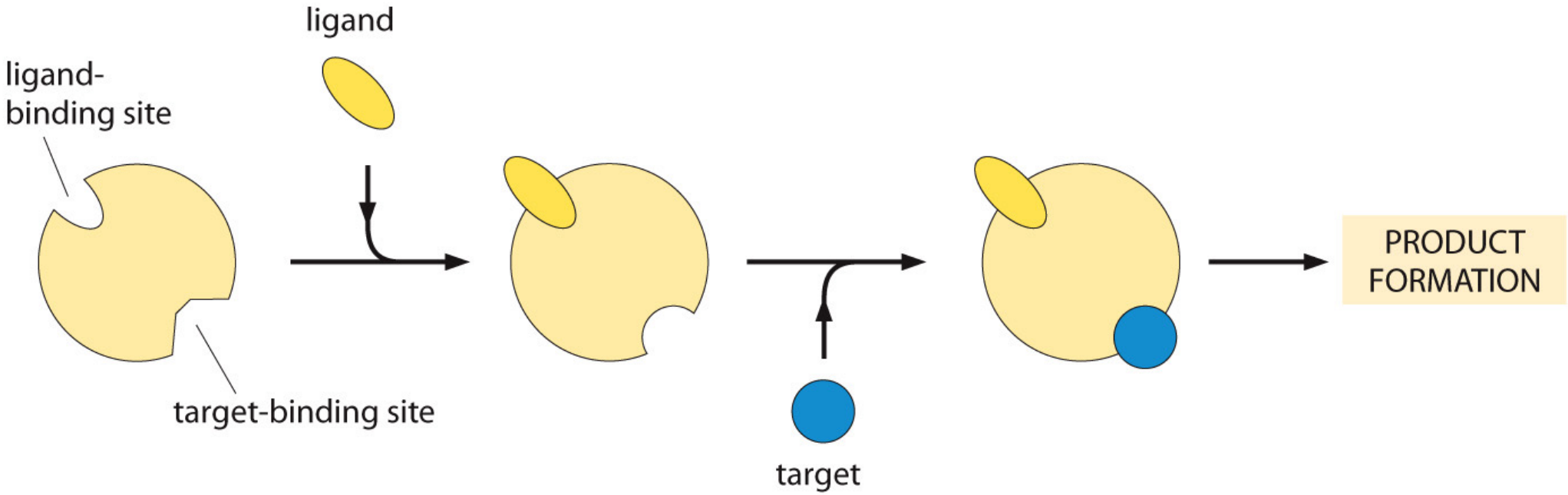


Figure 1.30 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

allosteric regulation of a multi-subunit enzyme

A → B → C→ D → E

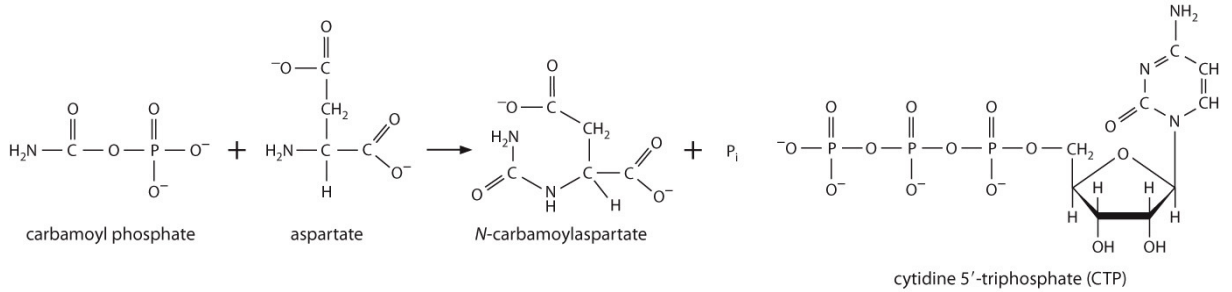


Figure 1.31 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

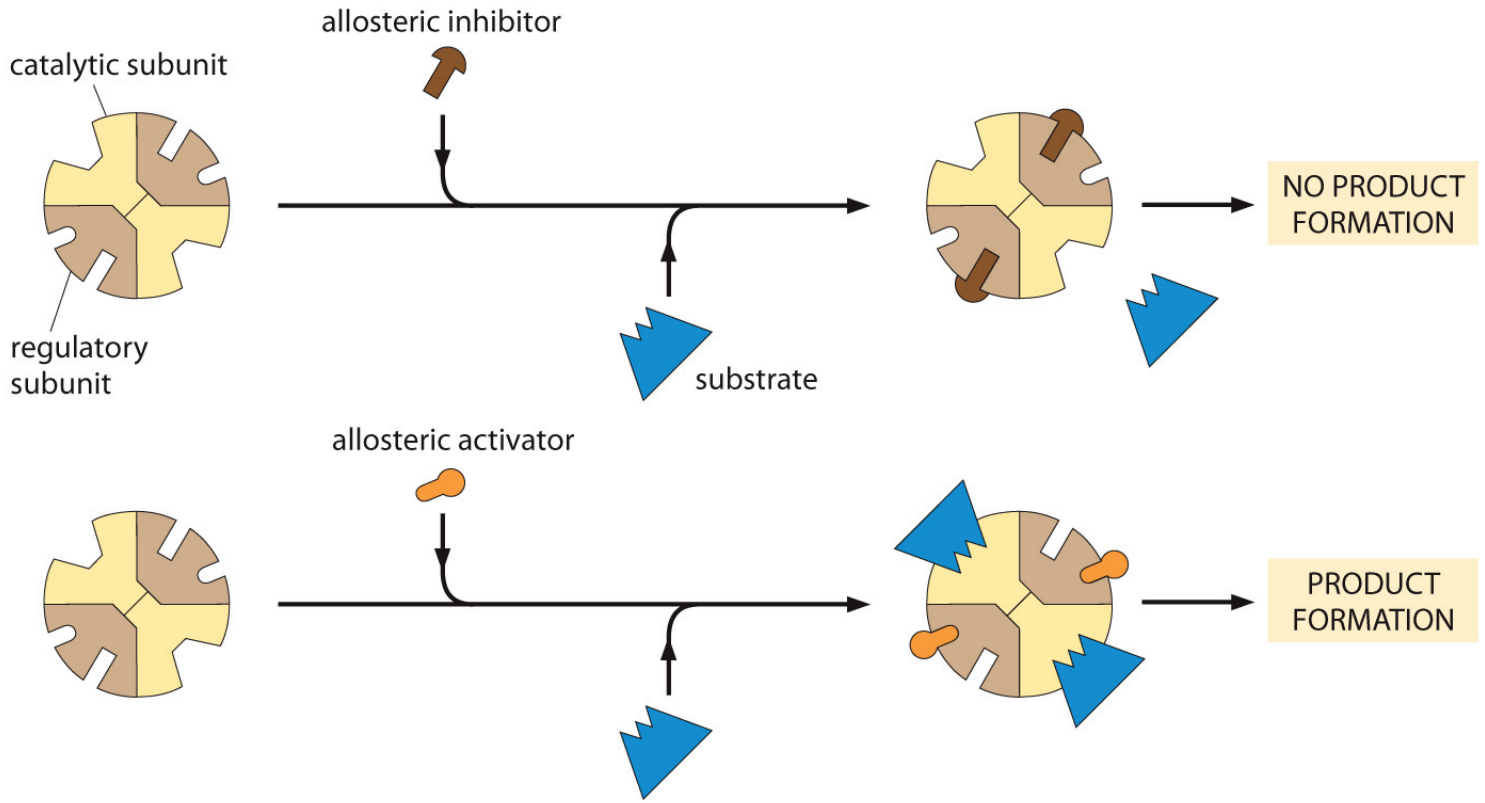


Figure 1.32 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

kinetics of allosteric enzymes

L_0=[T]/[R]

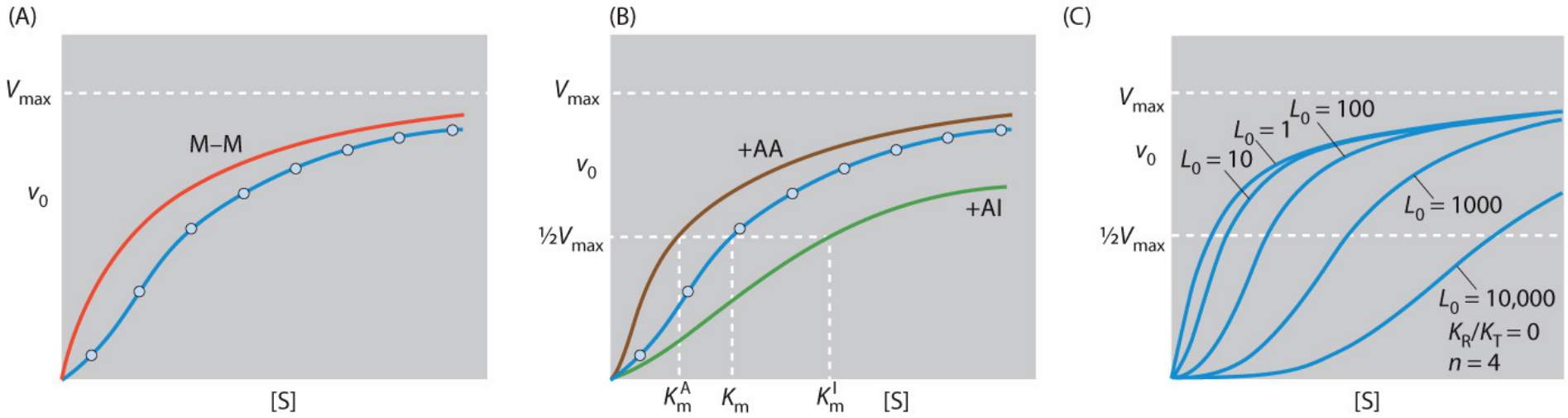


Figure 1.33 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

allostery

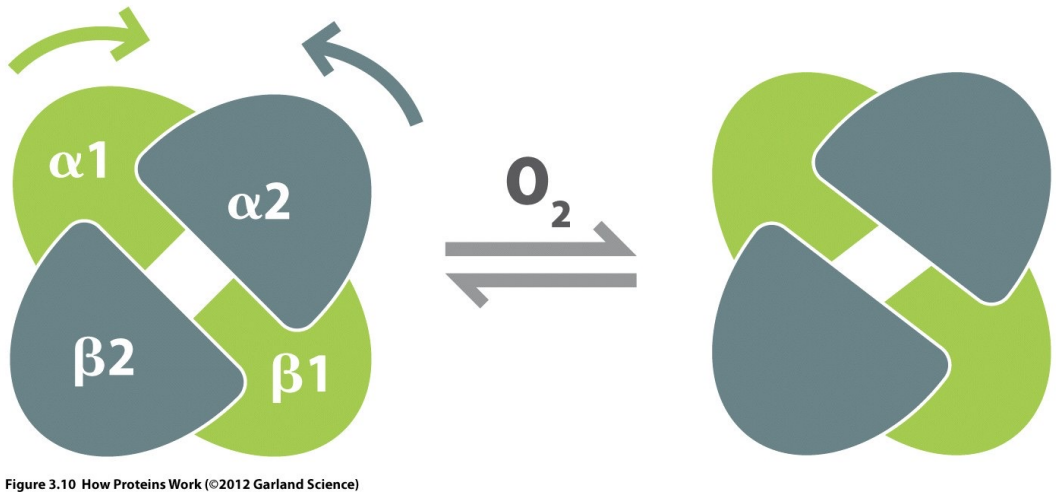
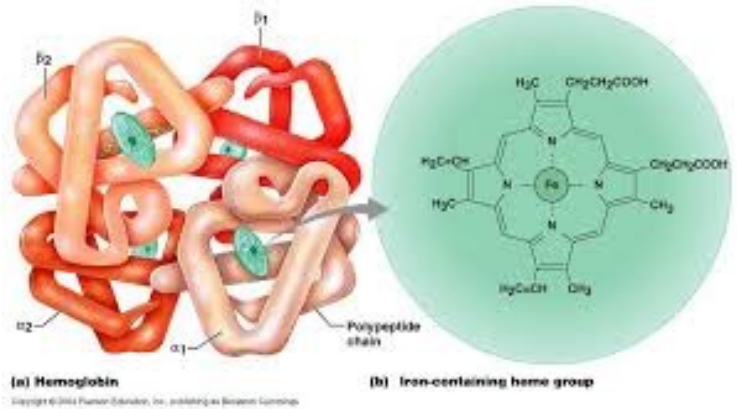
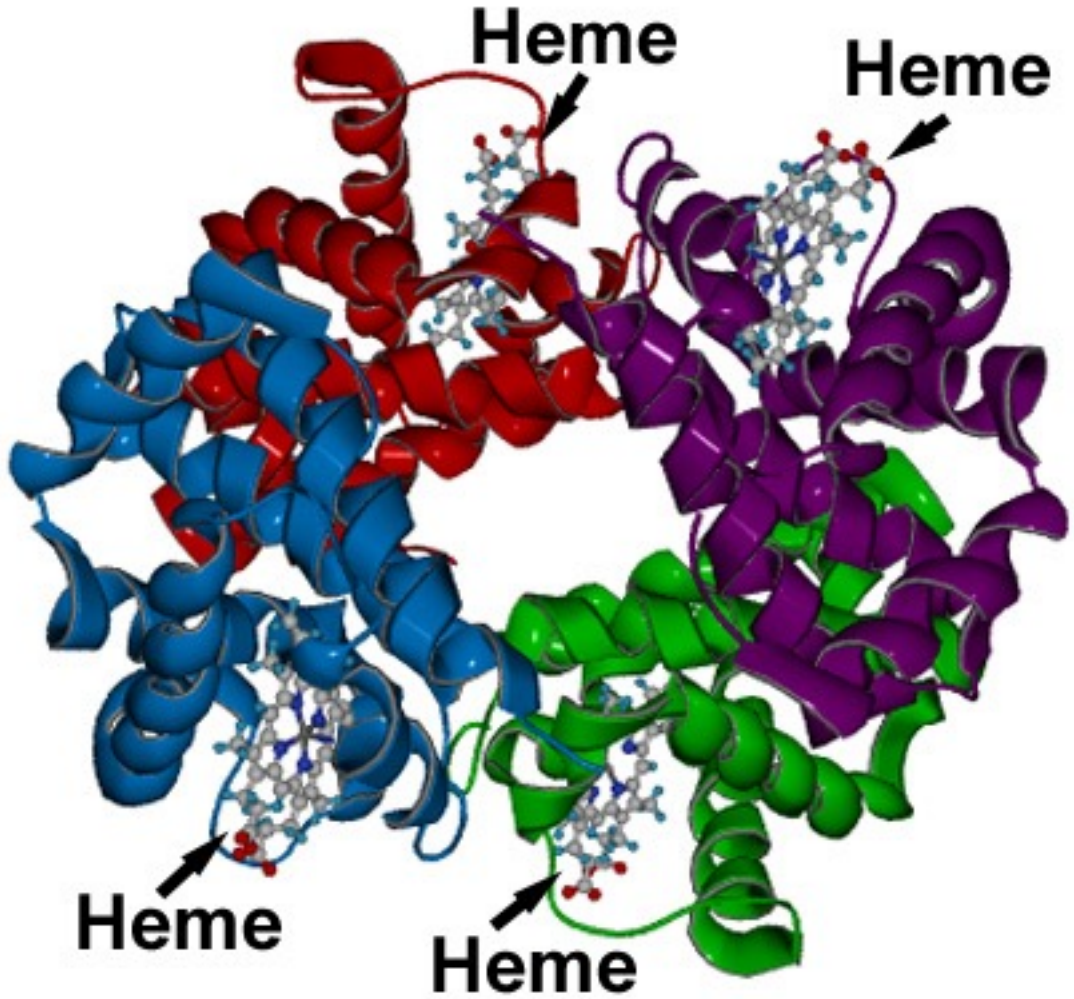


Figure 3.10 How Proteins Work (©2012 Garland Science)





Hemoglobin

effects of oxygen binding

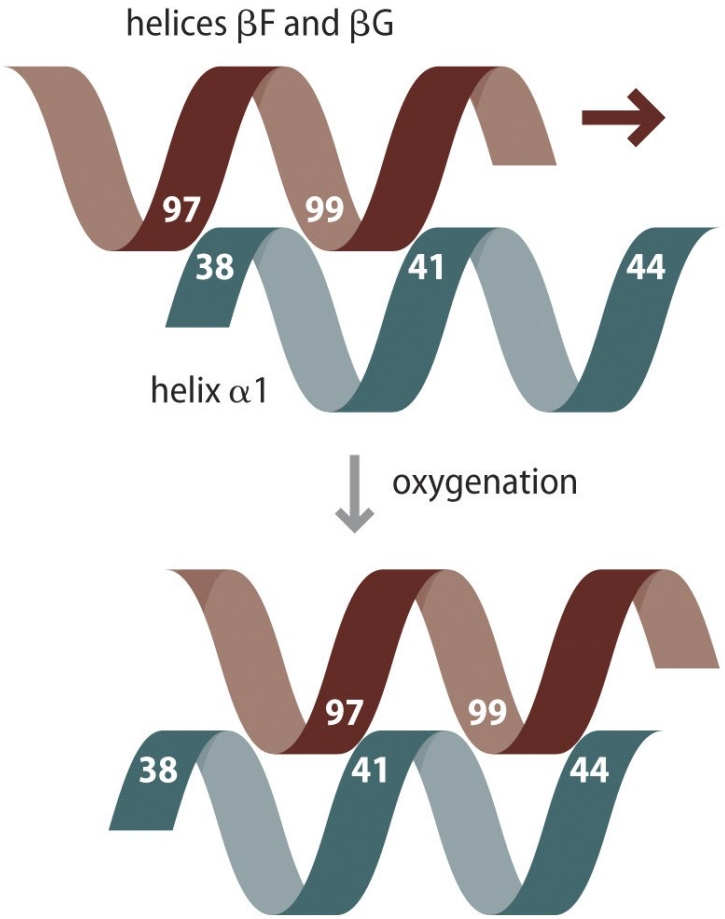


Figure 3.12 How Proteins Work (©2012 Garland Science)

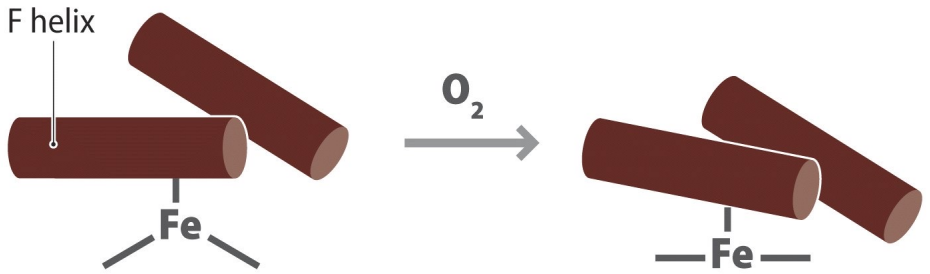
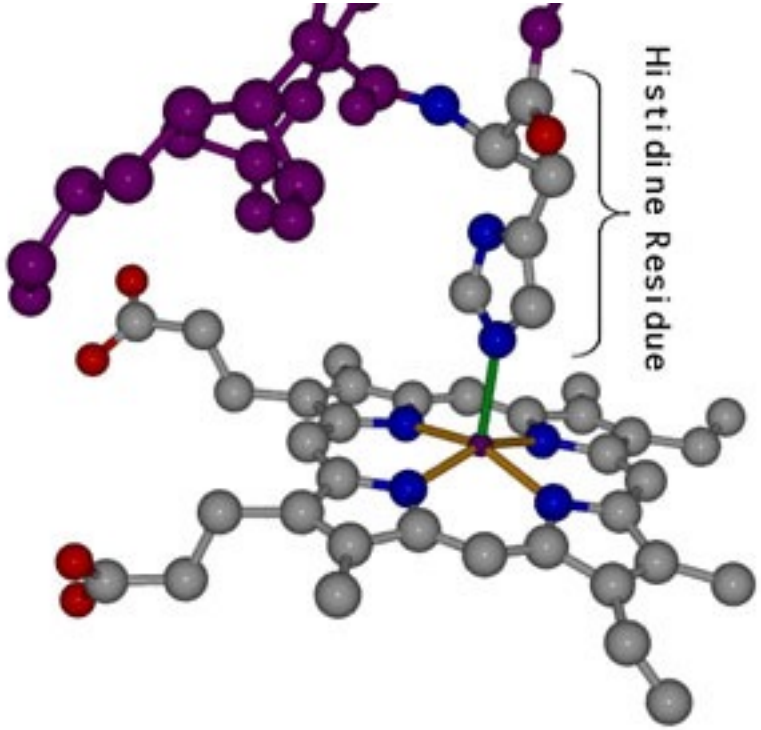
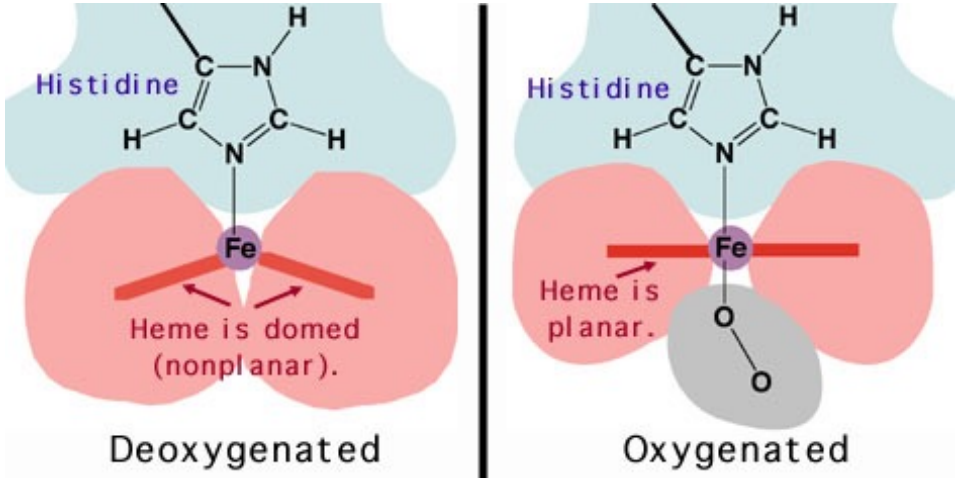


Figure 3.11 How Proteins Work (©2012 Garland Science)





oxygen saturation-cooperative binding

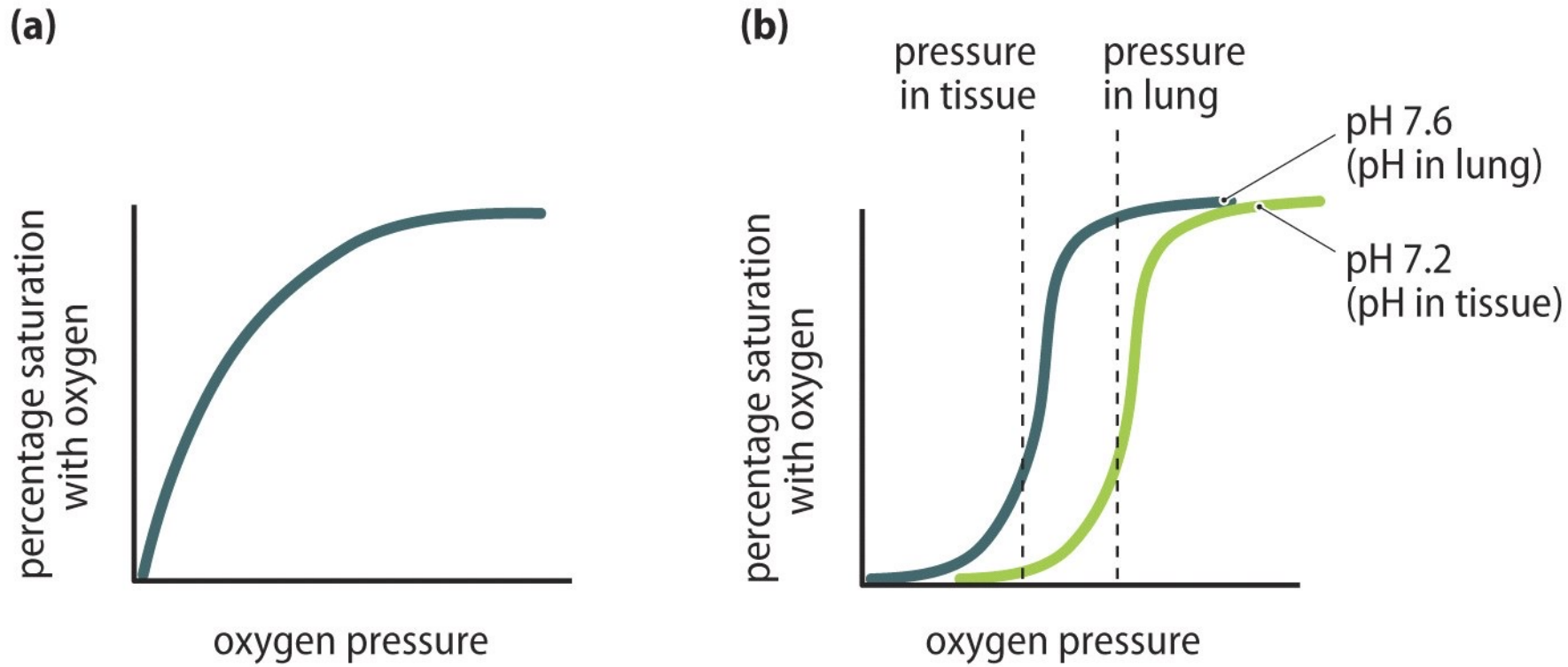
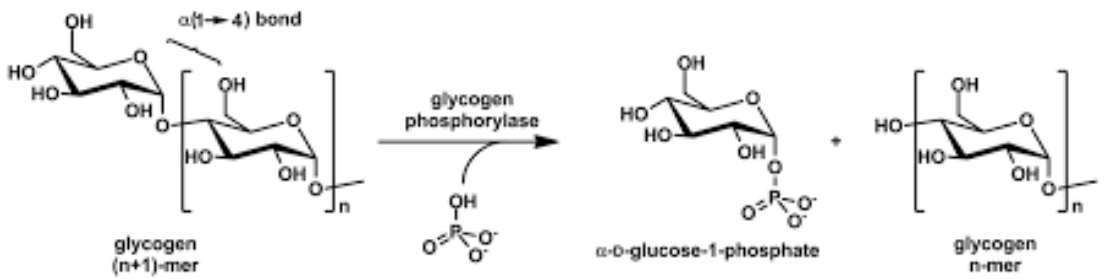


Figure 3.14 How Proteins Work (©2012 Garland Science)

$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$

glycogen phosphorylase



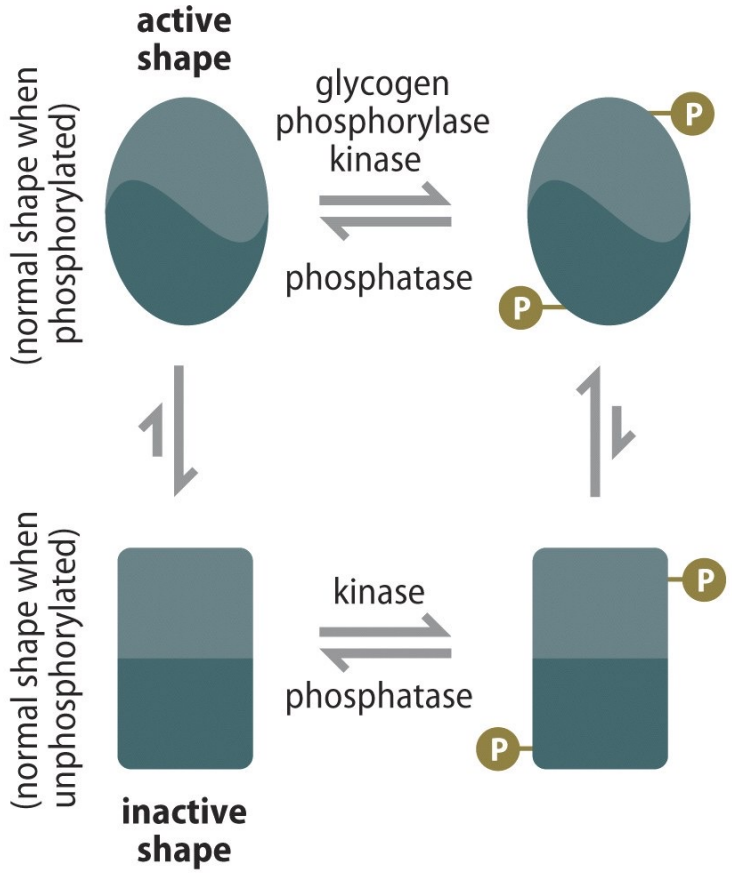
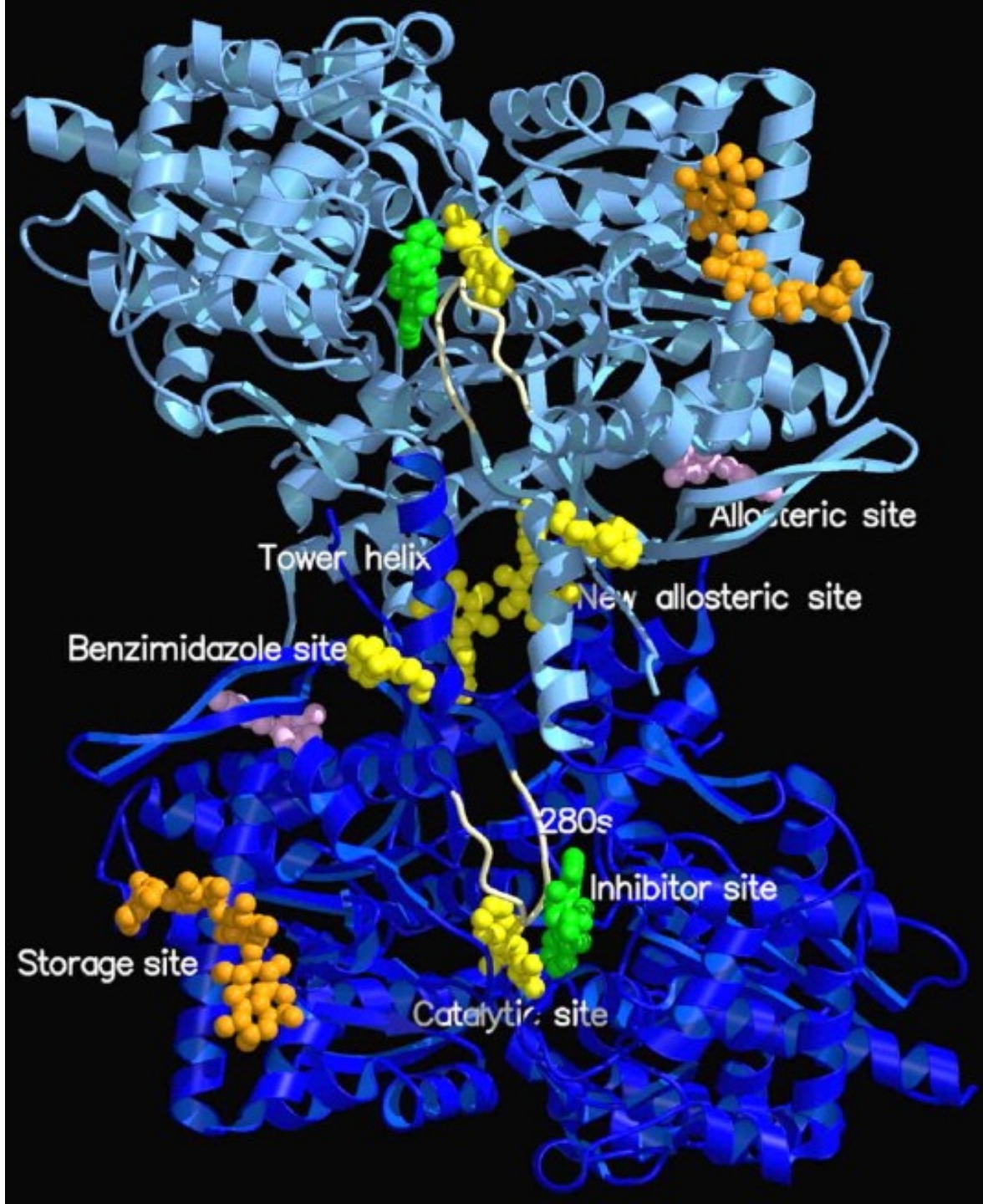


Figure 3.19 How Proteins Work (©2012 Garland Science)



glycogen phosphorylase

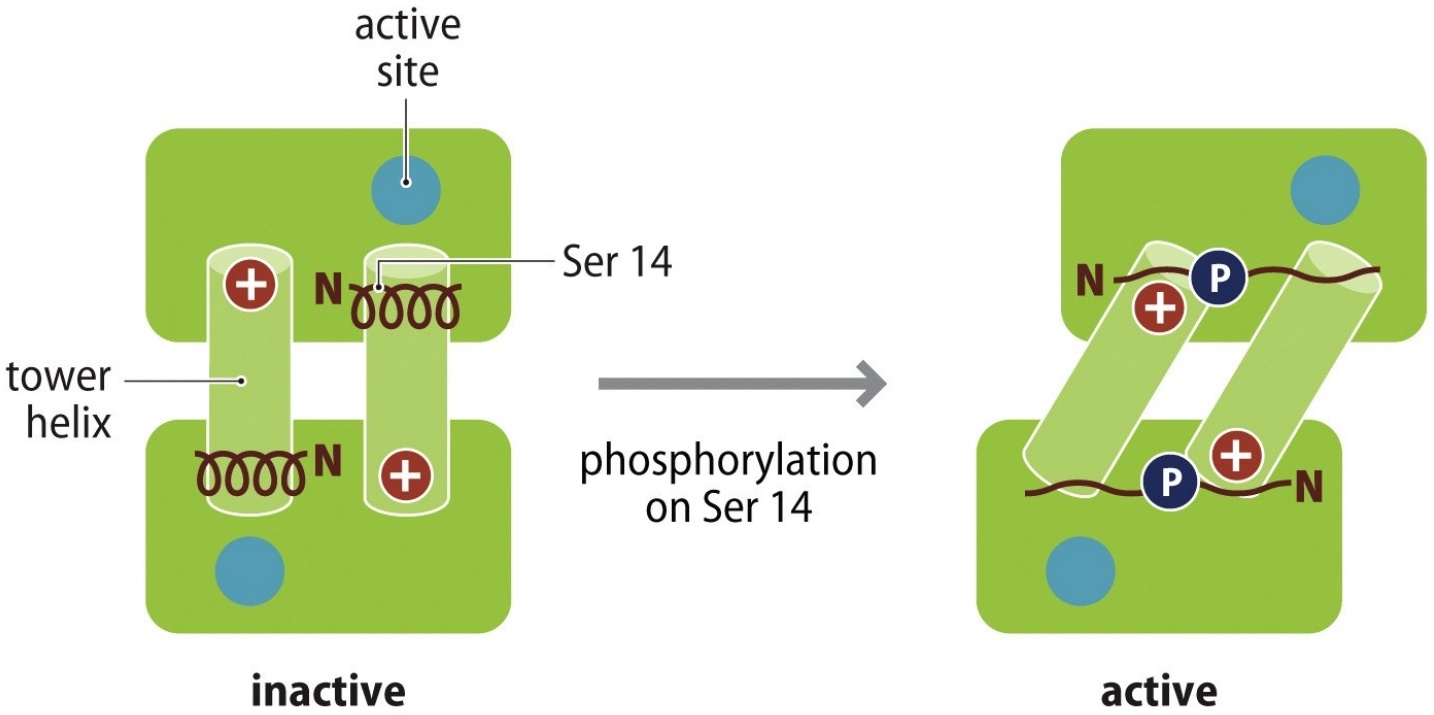
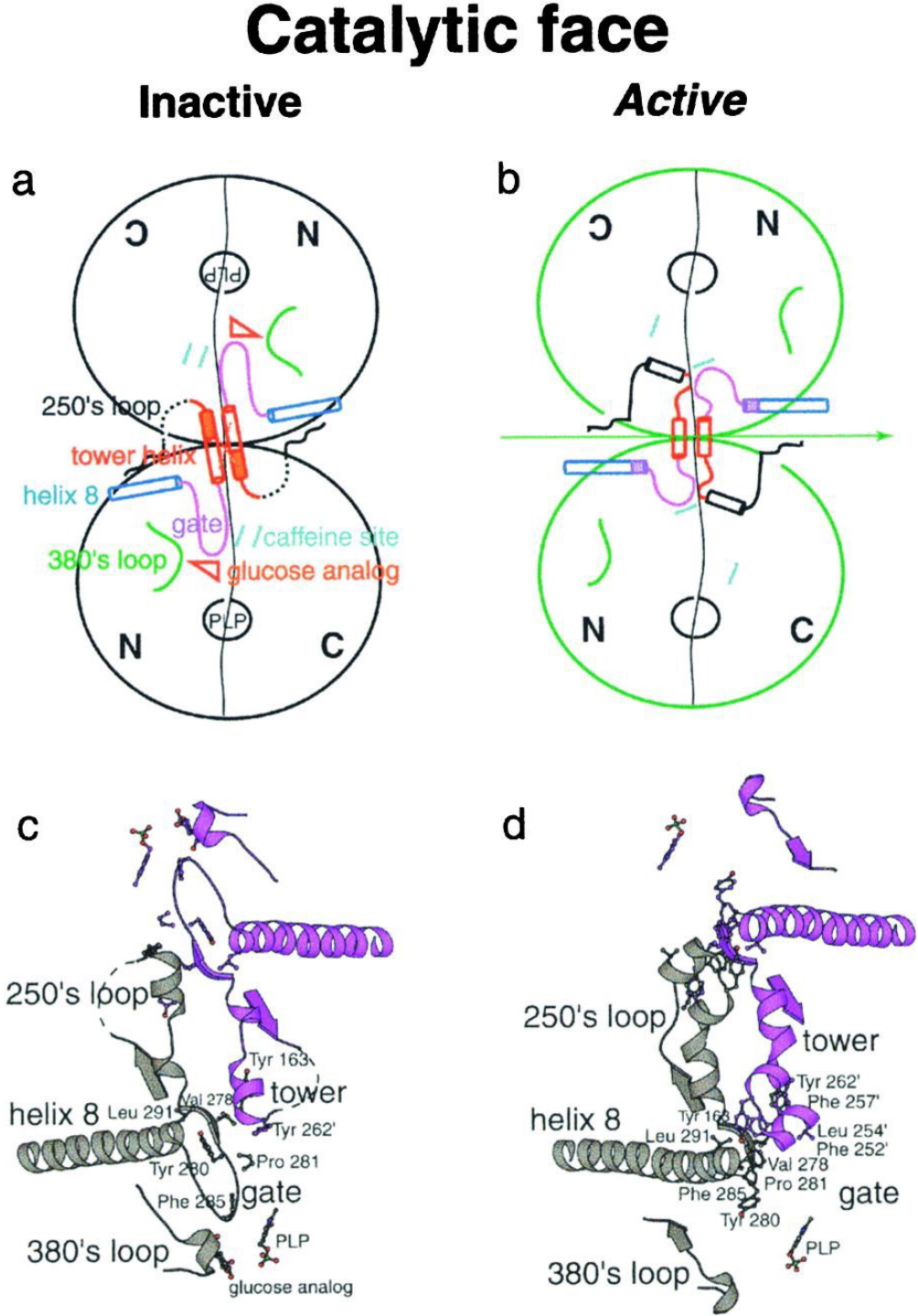
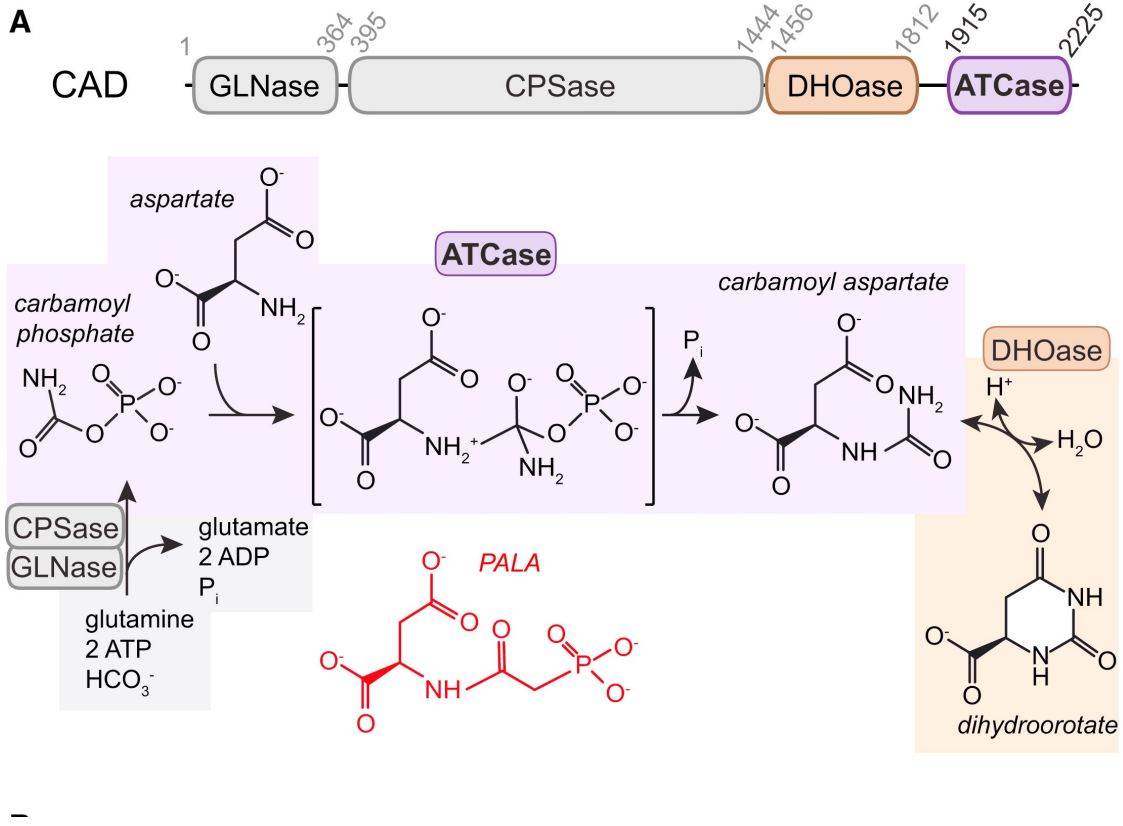
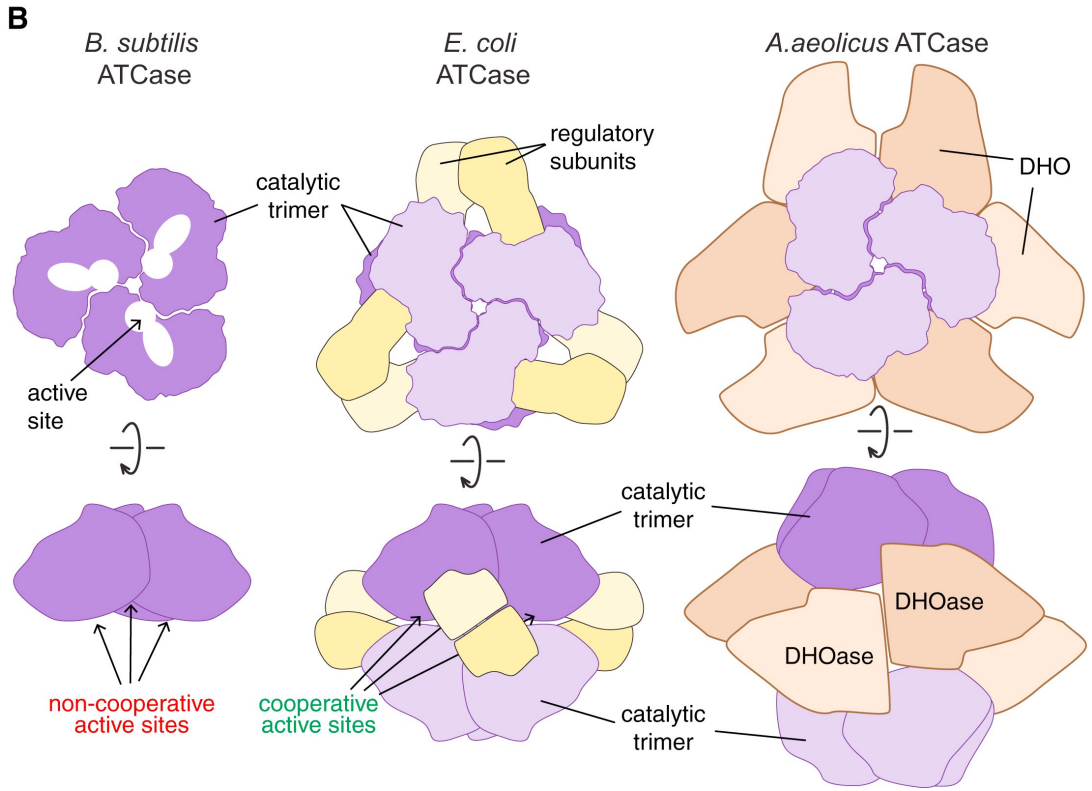


Figure 3.20 How Proteins Work (©2012 Garland Science)



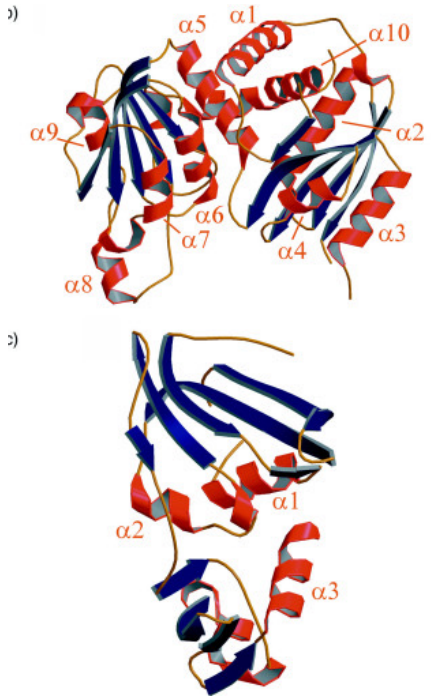
aspartate transcarbamoylase

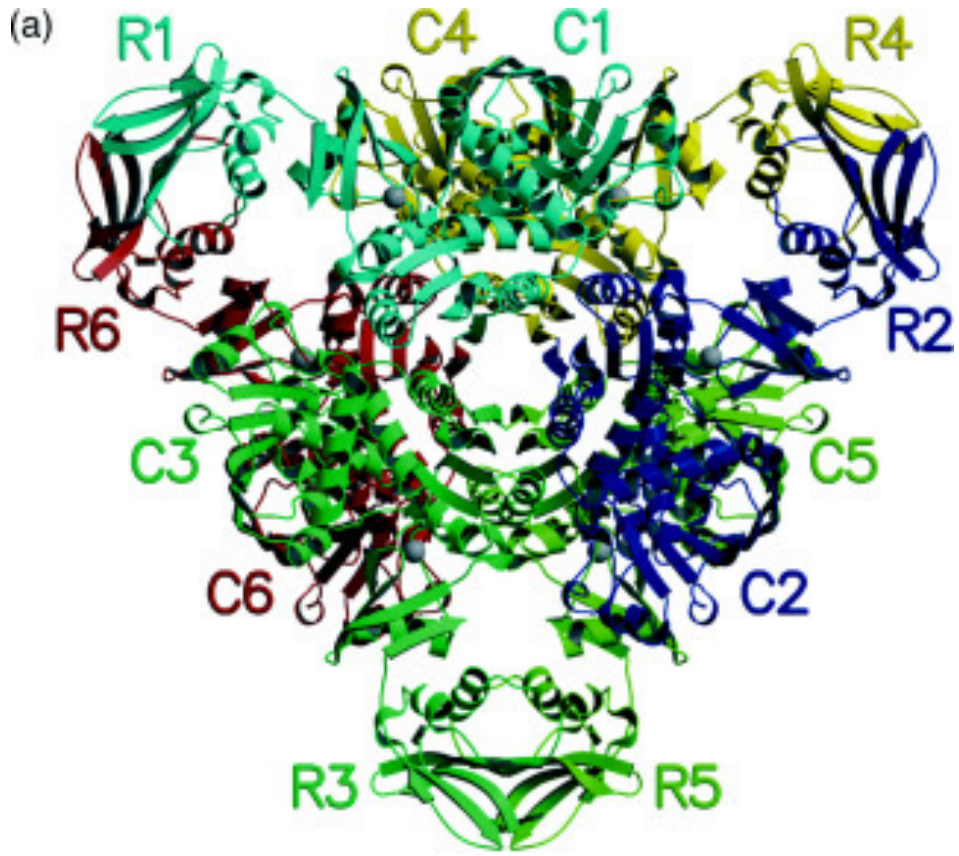


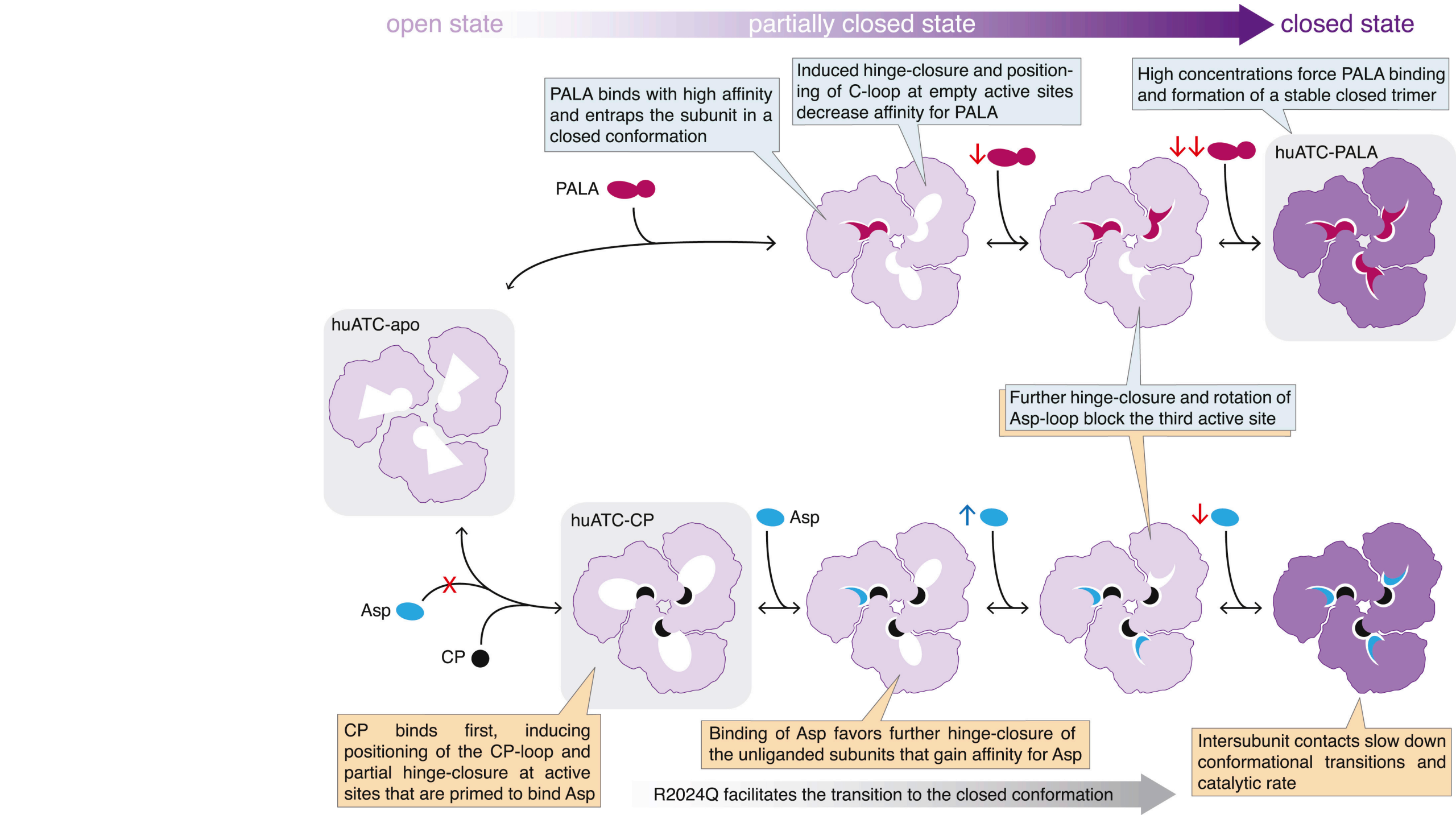


Anti-tumoral Drug PALA

aspartate transcarbamoylase






open state
partially closed state
closed state
PALA binds with high affinity and entraps the subunit in a closed conformation
Induced hinge-closure and positioning of C-loop at empty active sites decrease affinity for PALA
High concentrations force PALA binding and formation of a stable closed trimer
PALA
huATC-PALA
huATC-apo
Further hinge-closure and rotation of Asp-loop block the third active site
huATC-CP
Asp
Asp
CP
CP binds first, inducing positioning of the CP-loop and partial hinge-closure at active sites that are primed to bind Asp
Binding of Asp favors further hinge-closure of the unliganded subunits that gain affinity for Asp
Intersubunit contacts slow down conformational transitions and catalytic rate
R2024Q facilitates the transition to the closed conformation

activation

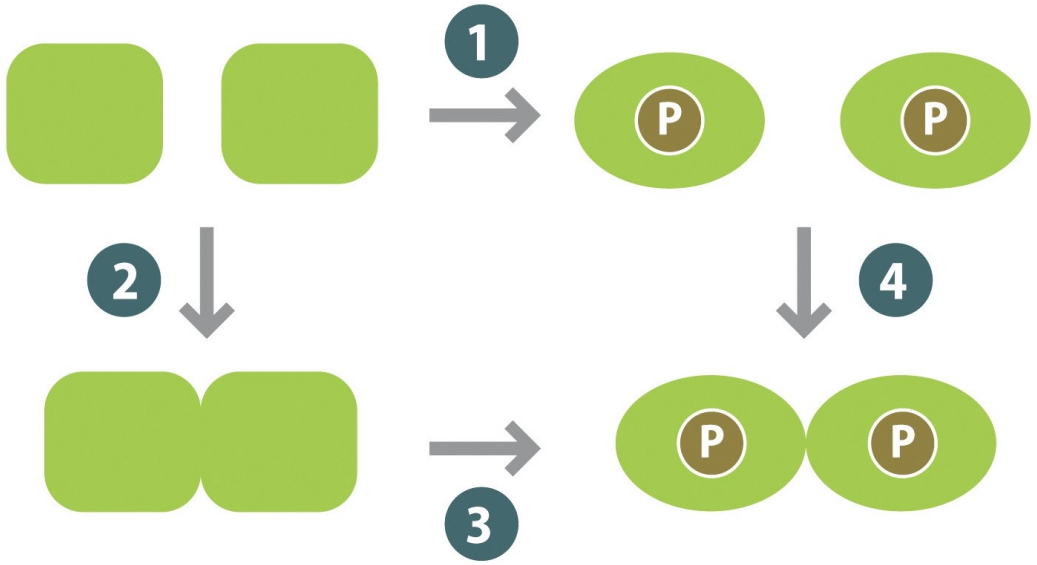


Figure 3.23 How Proteins Work (©2012 Garland Science)

$$\Delta G_1 + \Delta G_4 = \Delta G_2 + \Delta G_3$$

Translation and rotation entropy

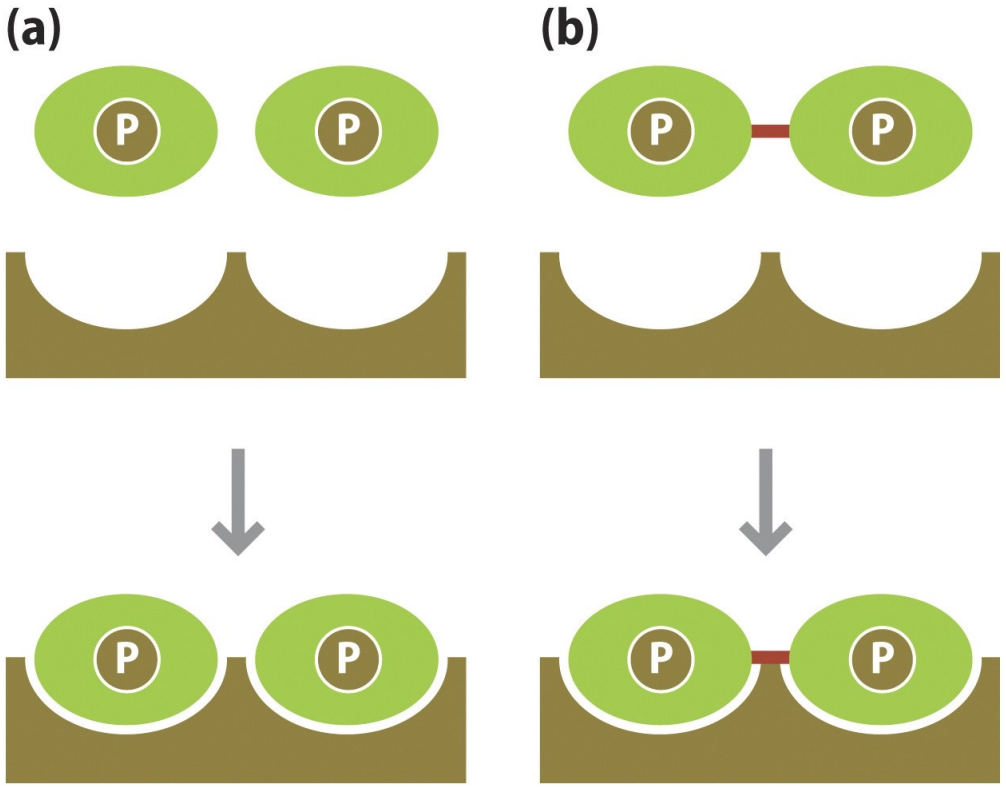


Figure 3.24 How Proteins Work (©2012 Garland Science)

Sequence-specific binding to DNA

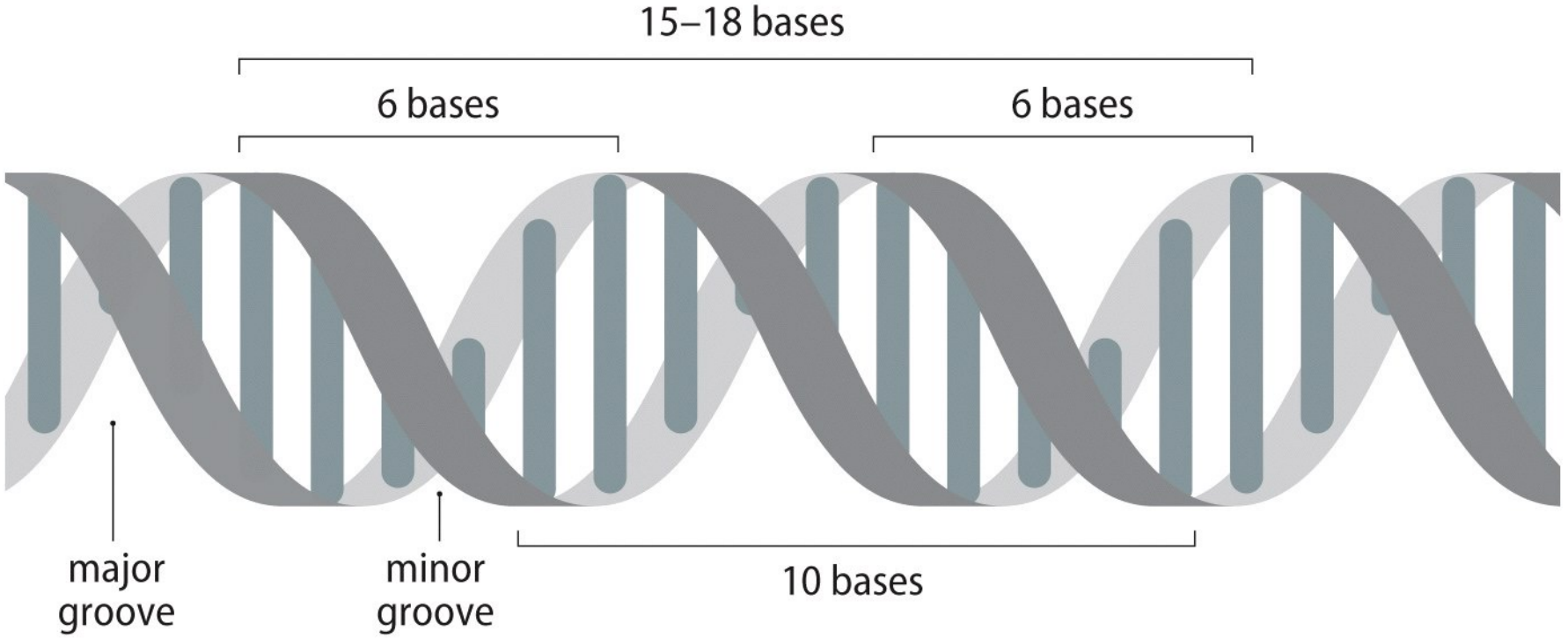


Figure 3.25 How Proteins Work (©2012 Garland Science)

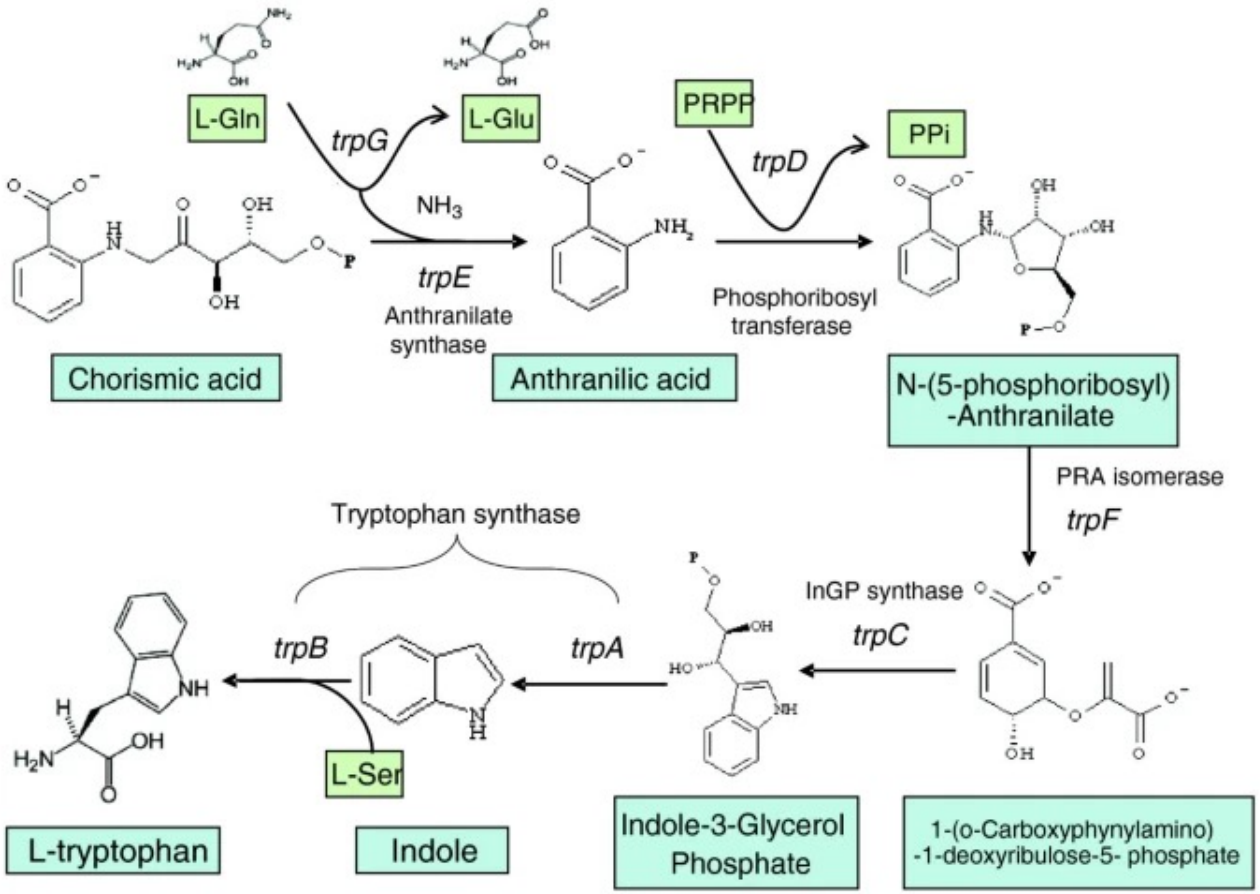
10^7 base pairs long
4^{-n}

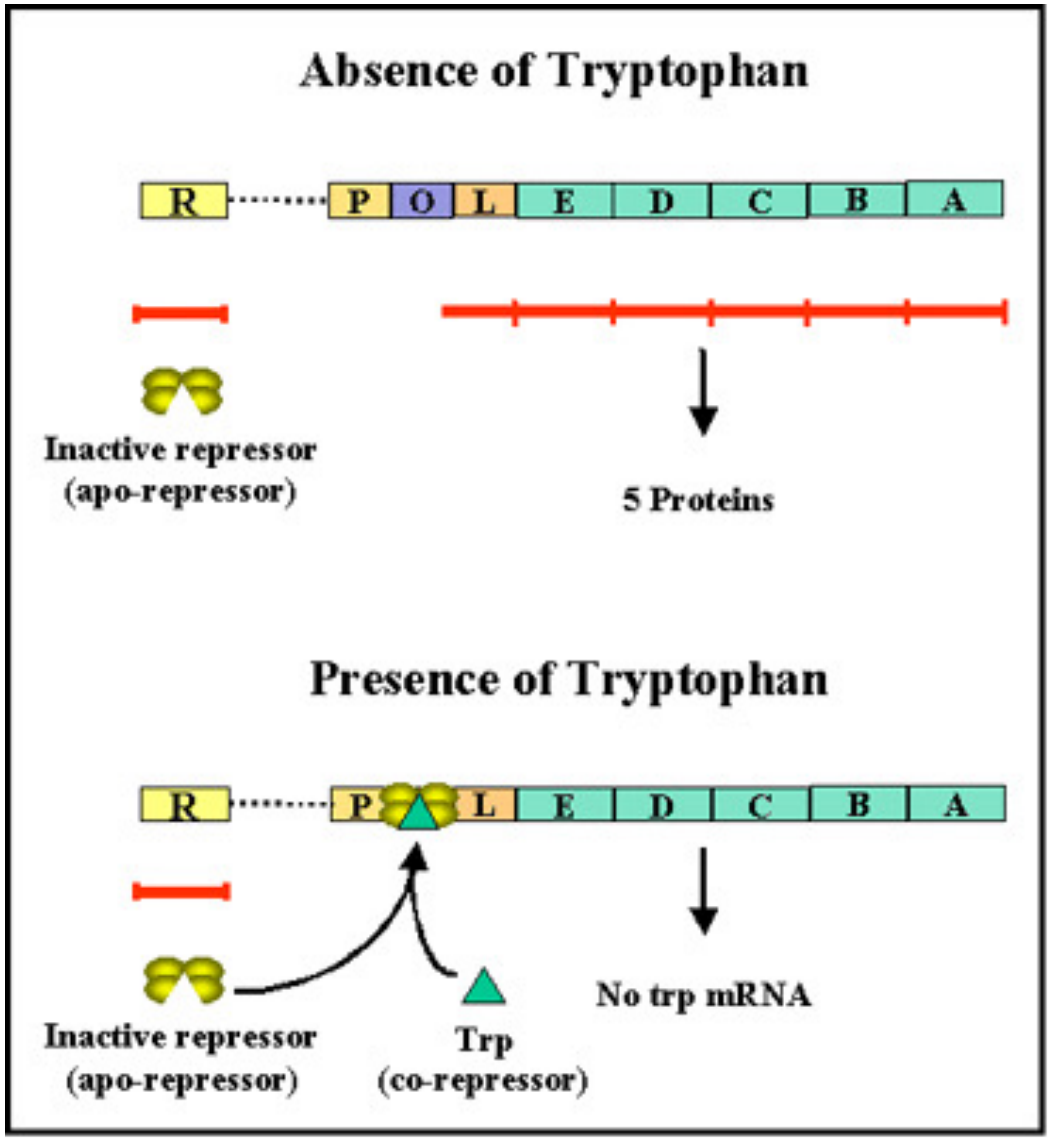
3-mer $p = 0.0156$ or $1.6*10^5$
4-mer with $p = 0.0039$ or $4*10^4$
6-mer 2500
8-mer 150 times
10-mer 10 times
12-mer less than once.

a protein that binds to DNA as a dimer

Figure 3.26 How Proteins Work (©2012 Garland Science)

trp repressor





a helix–turn–helix repressor

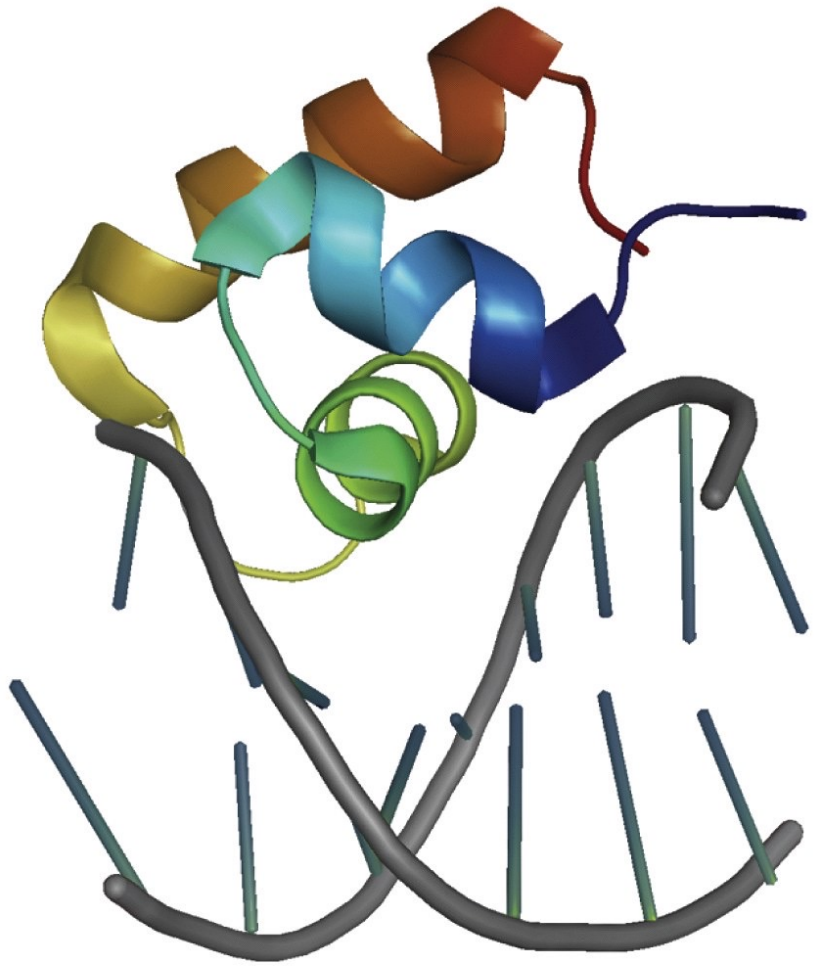
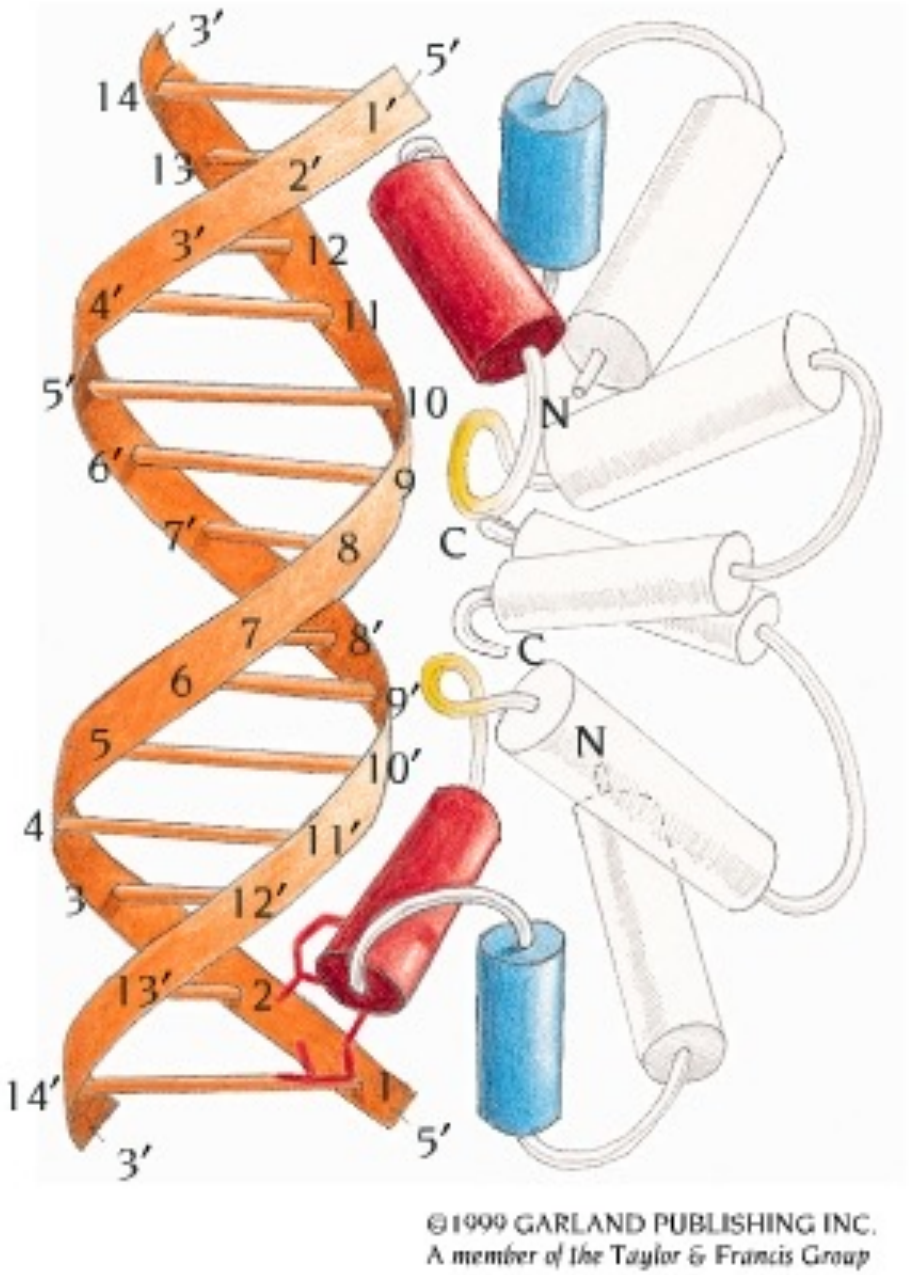
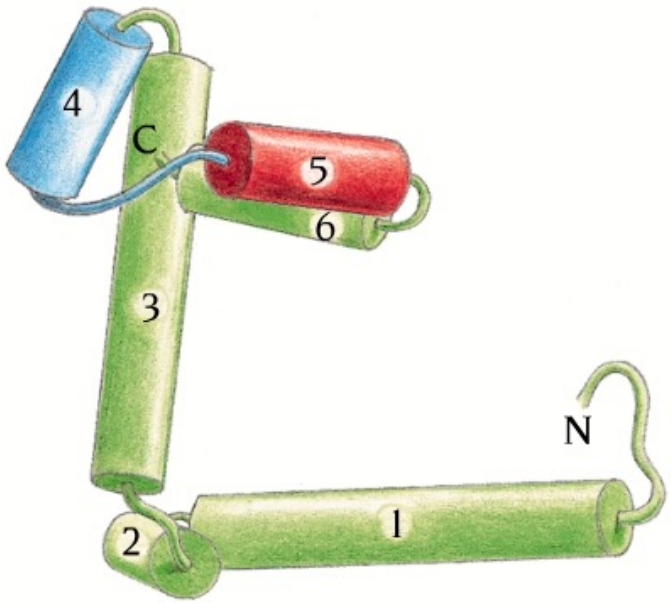
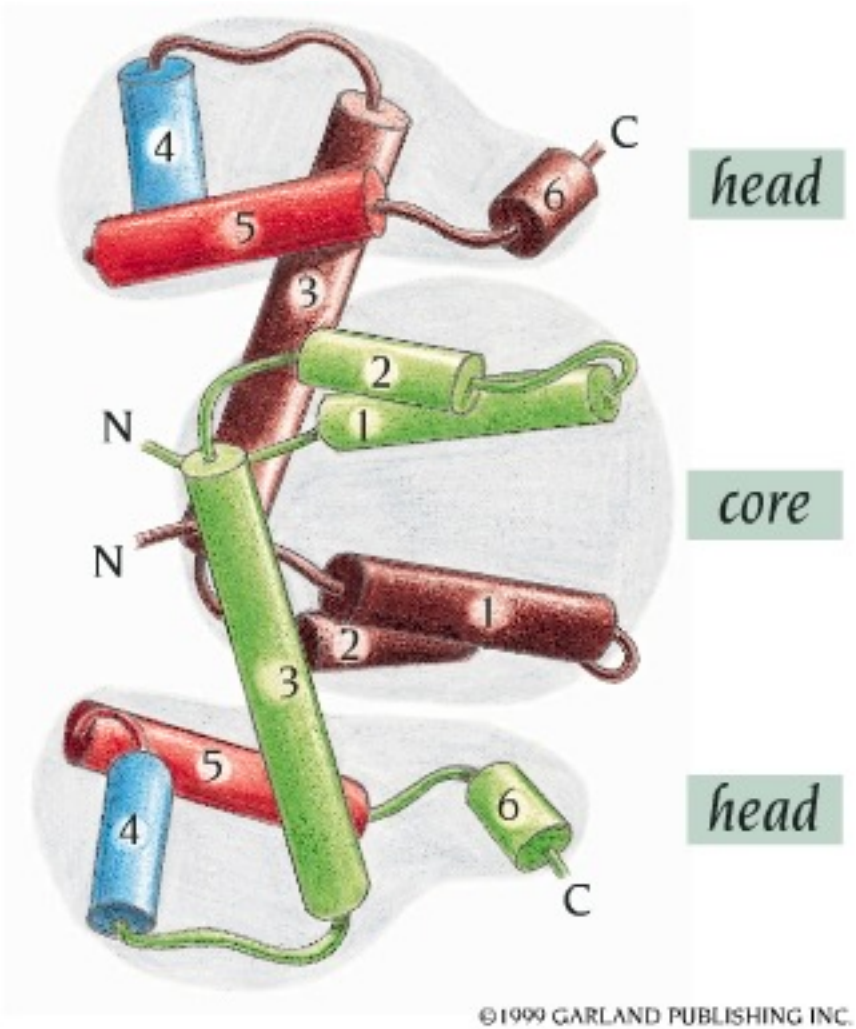


Figure 3.29 How Proteins Work (©2012 Garland Science)



trp repressor





the DNA-binding domain of *trp* repressor

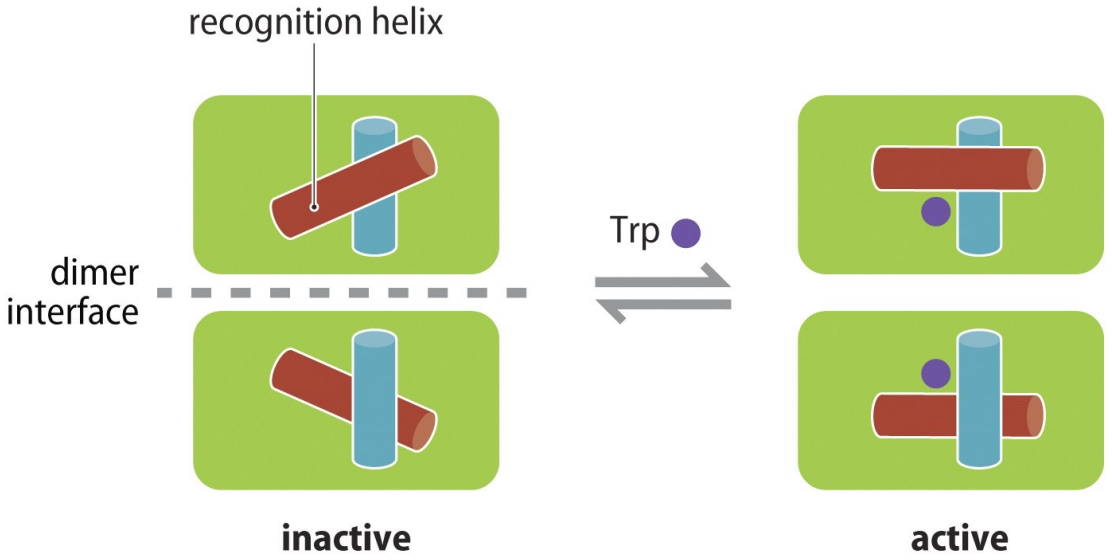
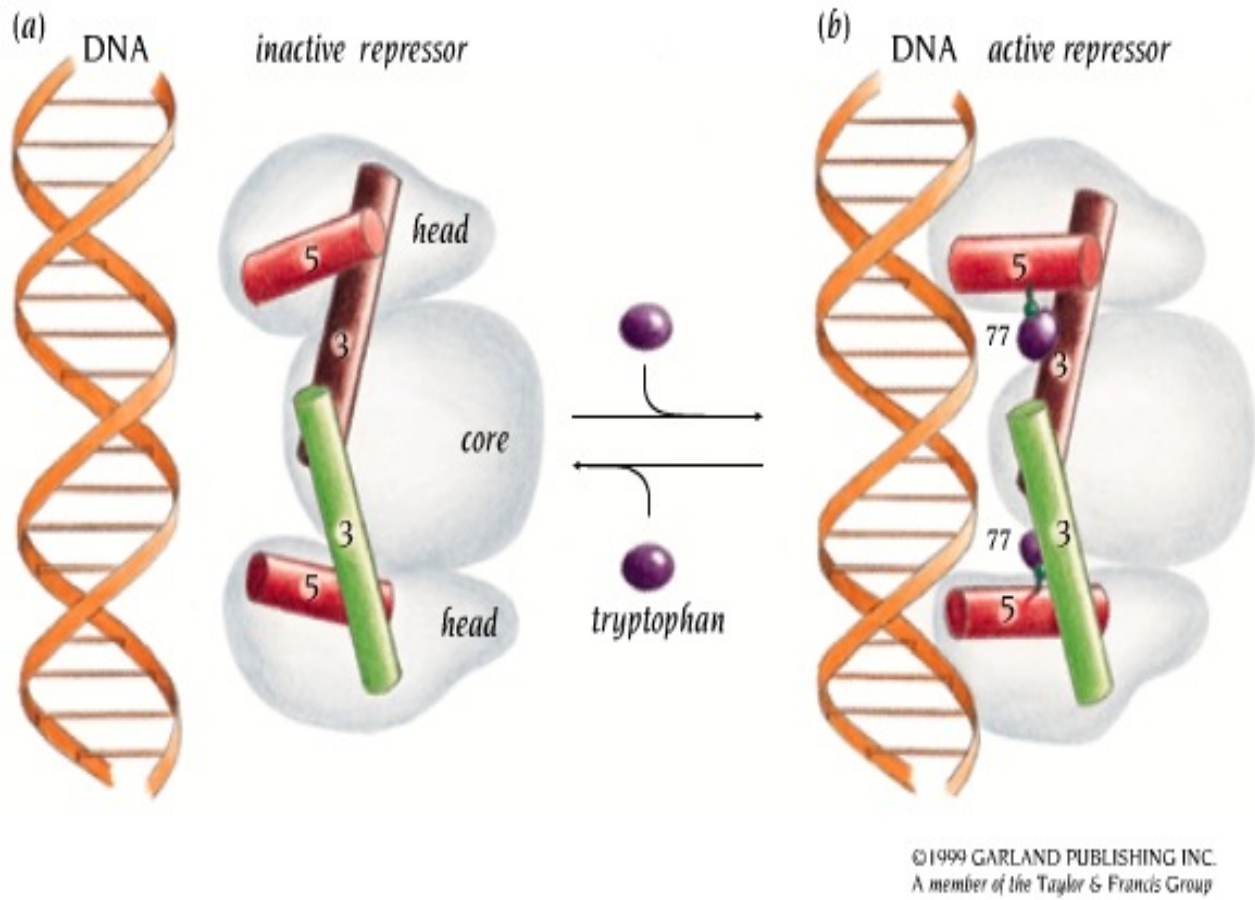
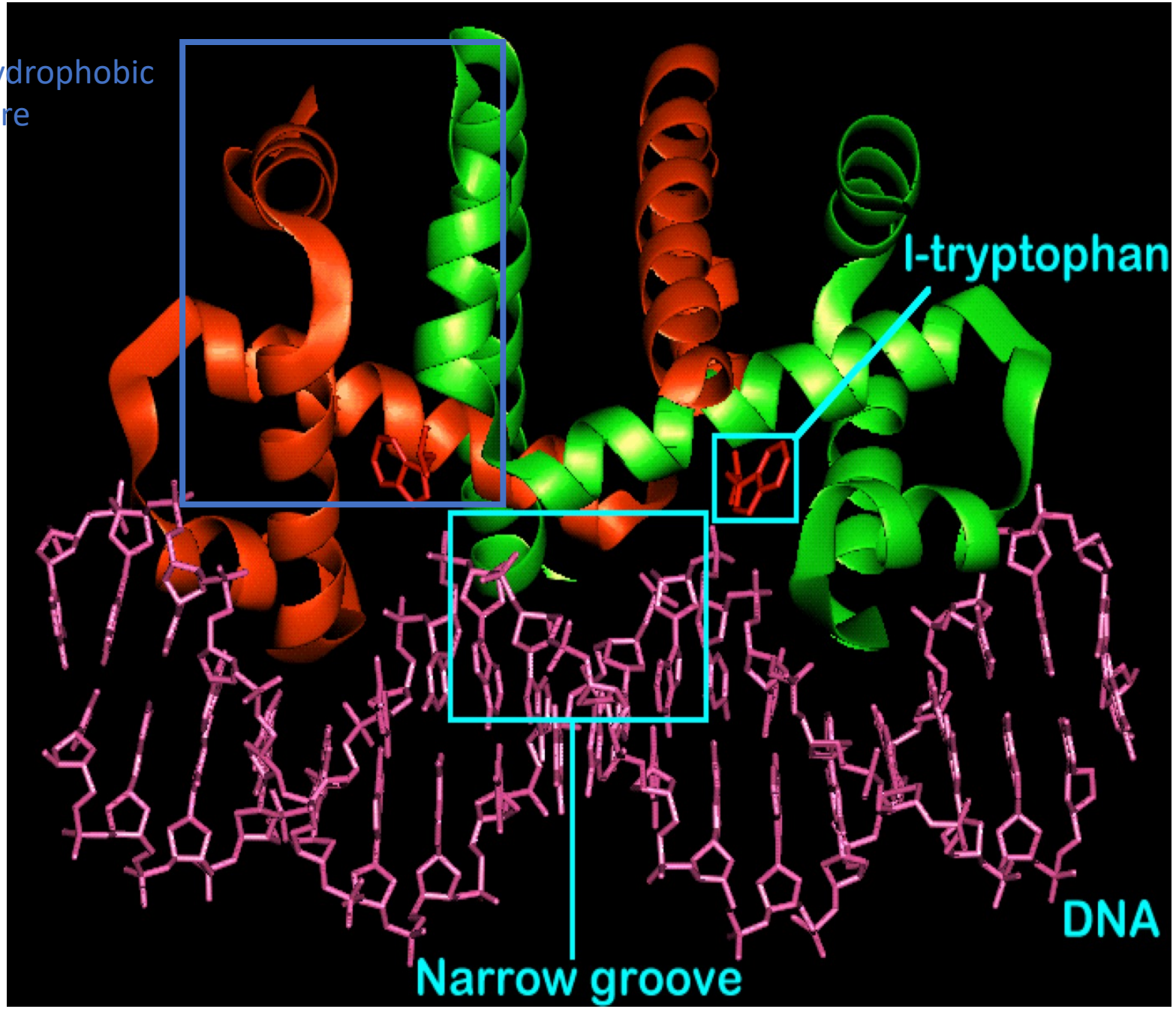


Figure 3.30 How Proteins Work (©2012 Garland Science)

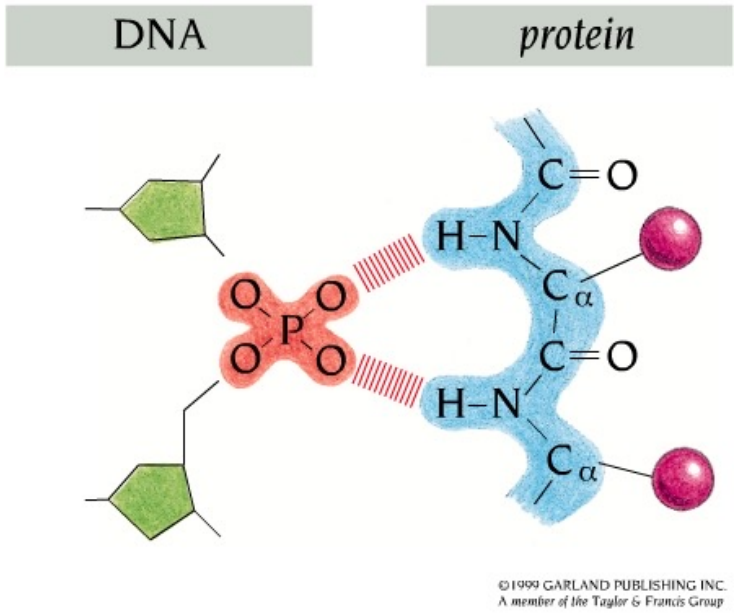


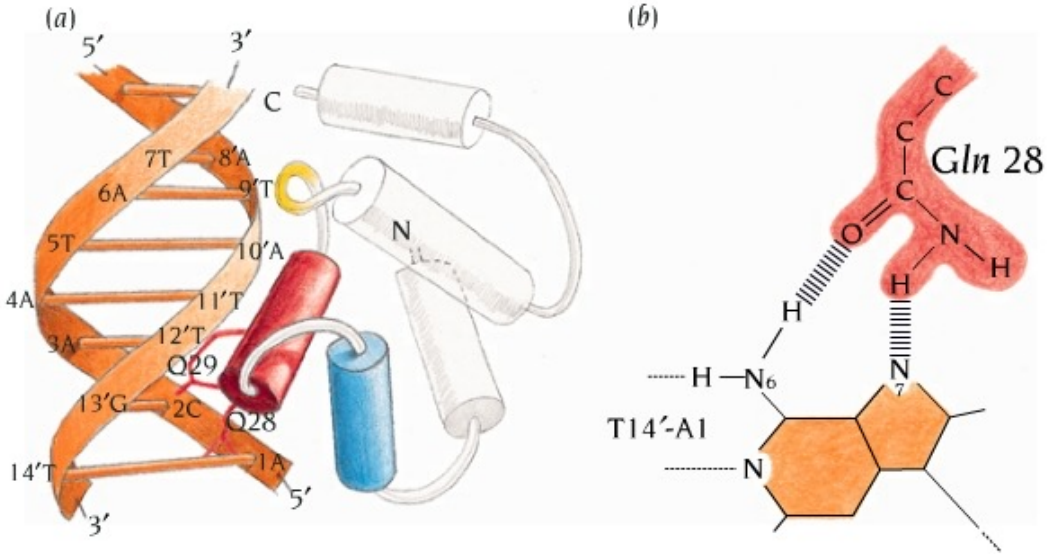
Ala 77---> Val

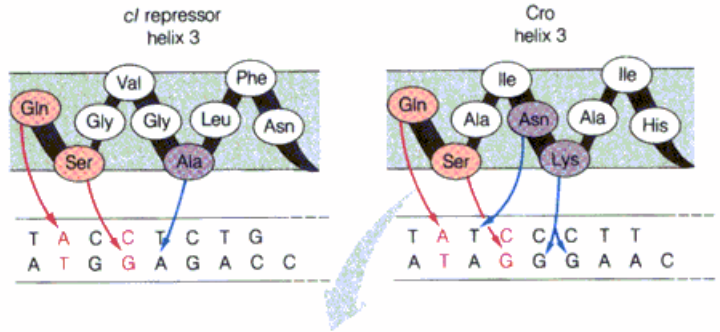
DNA-binding

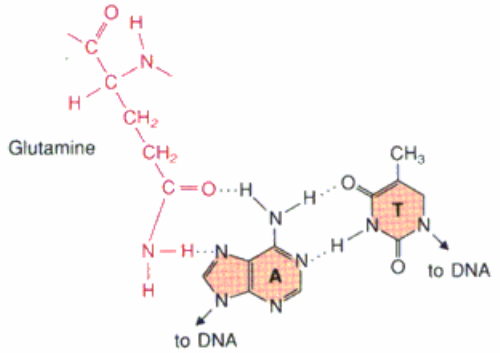


interactions
specific/non specific









CAP protein

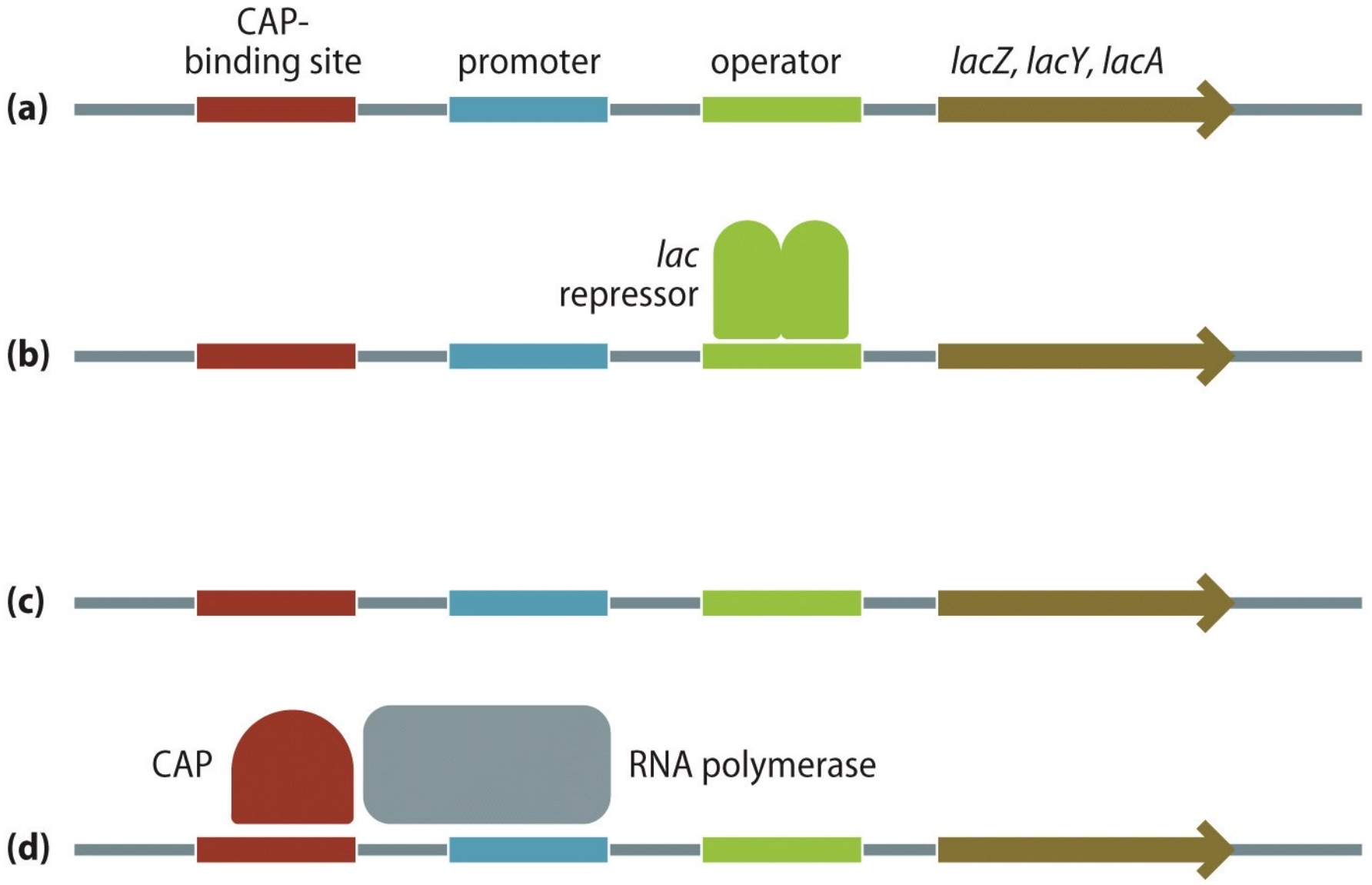


Figure 3.31 How Proteins Work (©2012 Garland Science)

inactive and active form of CAP

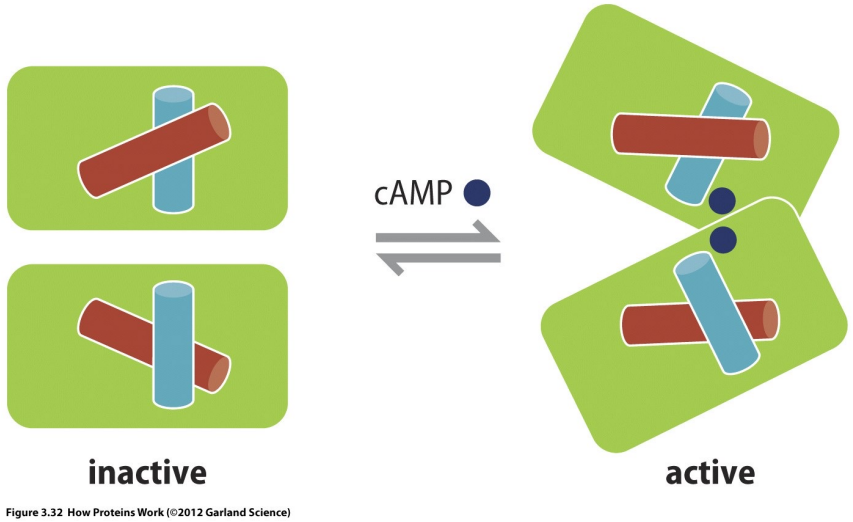
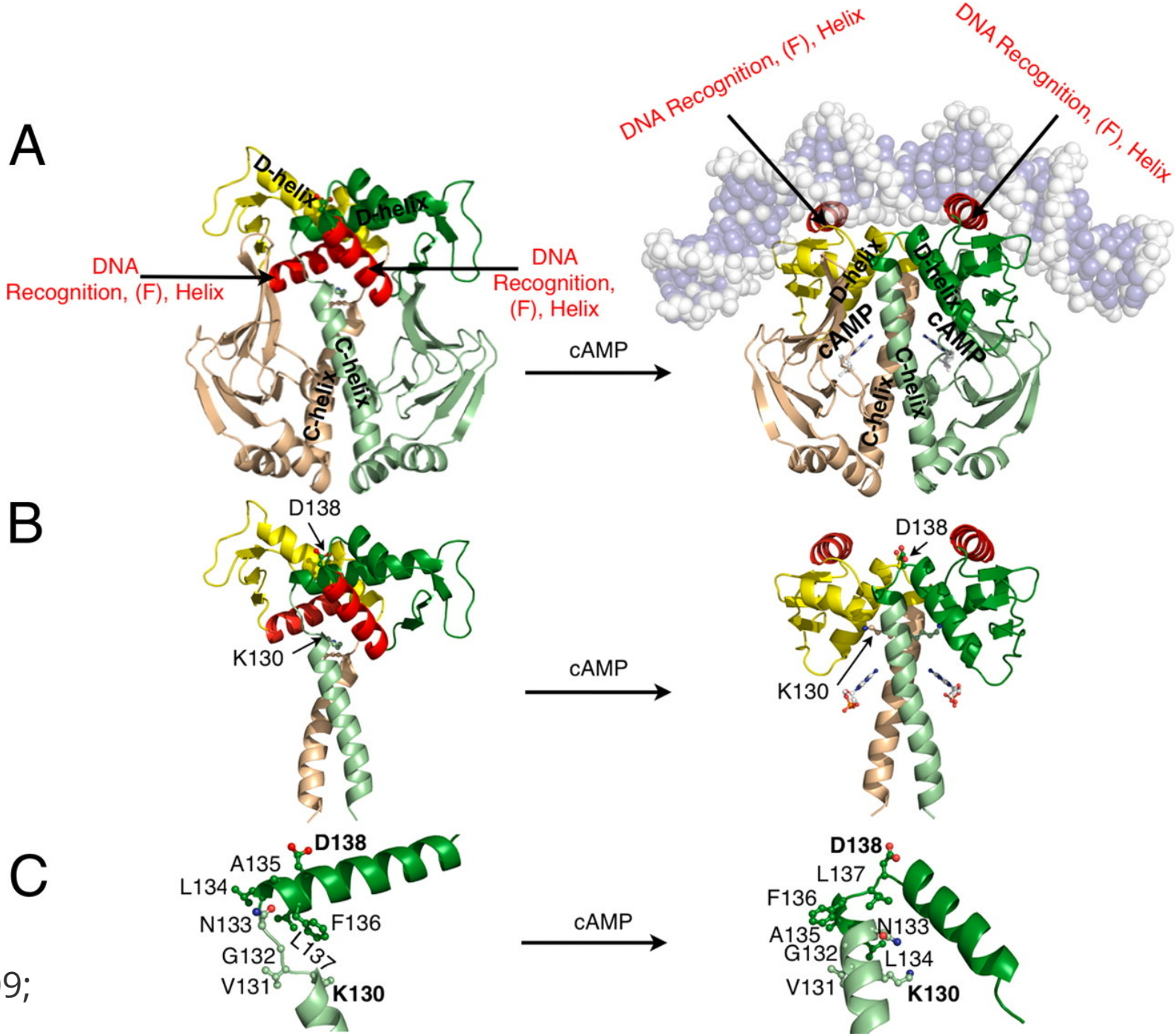


Figure 3.32 How Proteins Work (©2012 Garland Science)



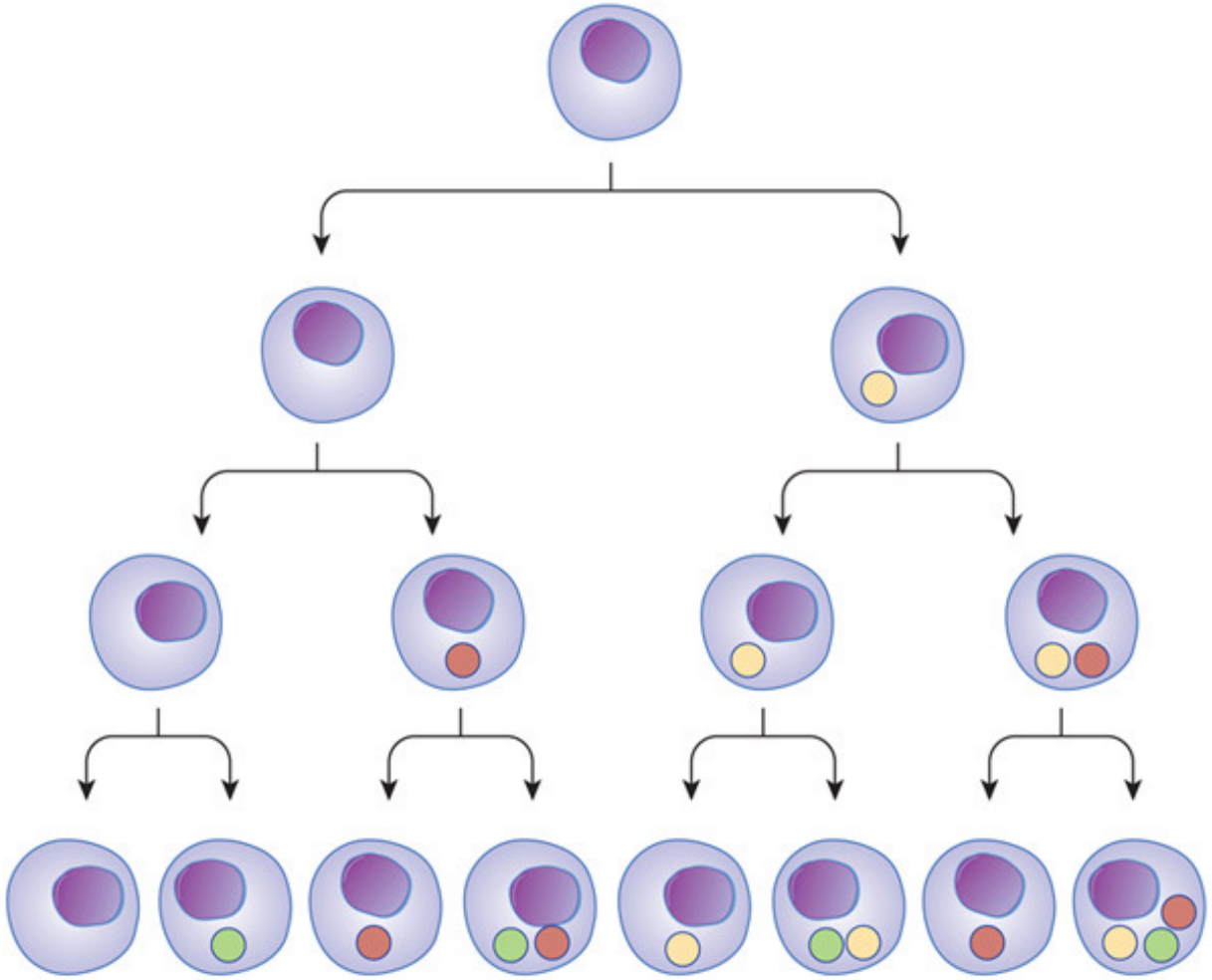
PNAS , 2009 106 (39) 16604-16609;

homeodomain proteins

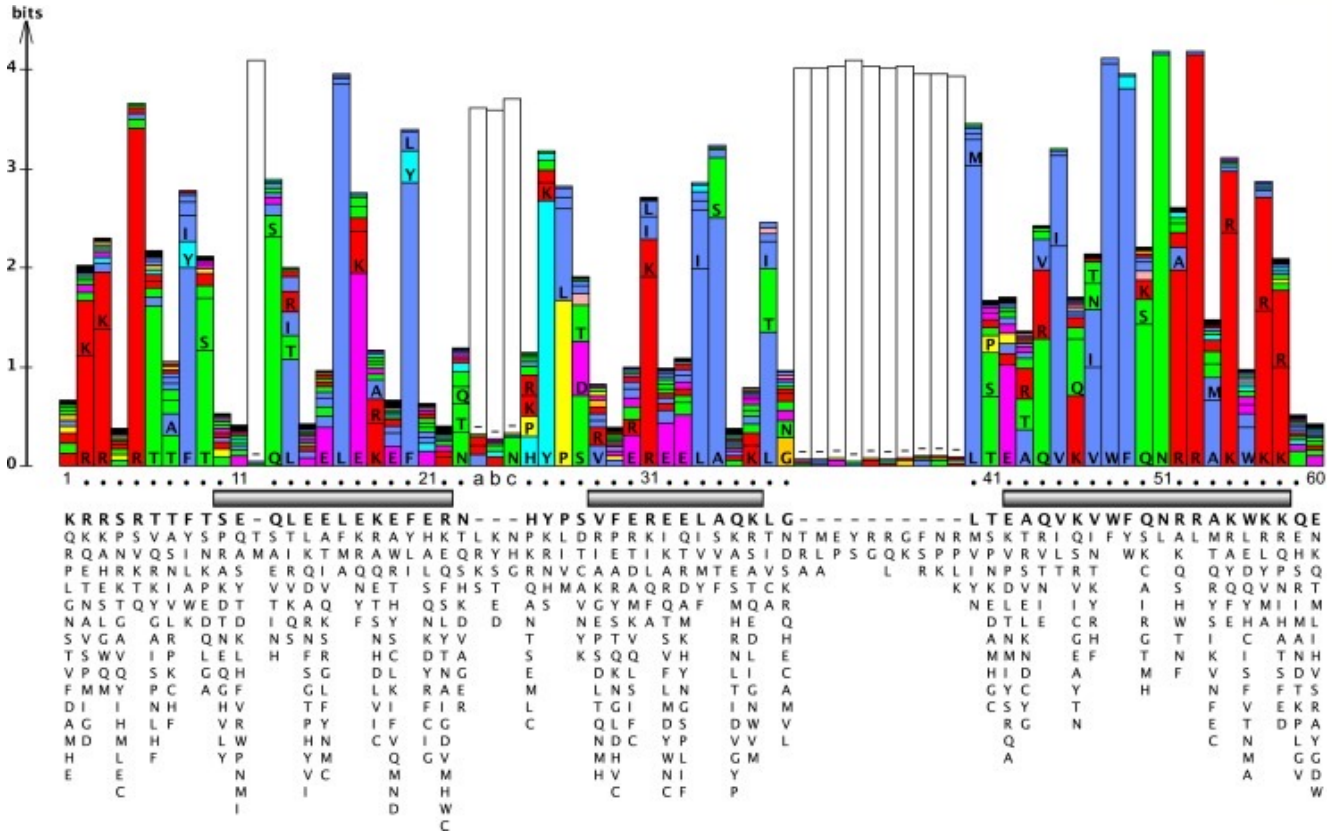
Homeodomain proteins direct the formation of the body axes and body structures during early embryonic development. Many homeodomain proteins induce cellular differentiation by initiating the cascades of coregulated genes required to produce individual tissues and organs.

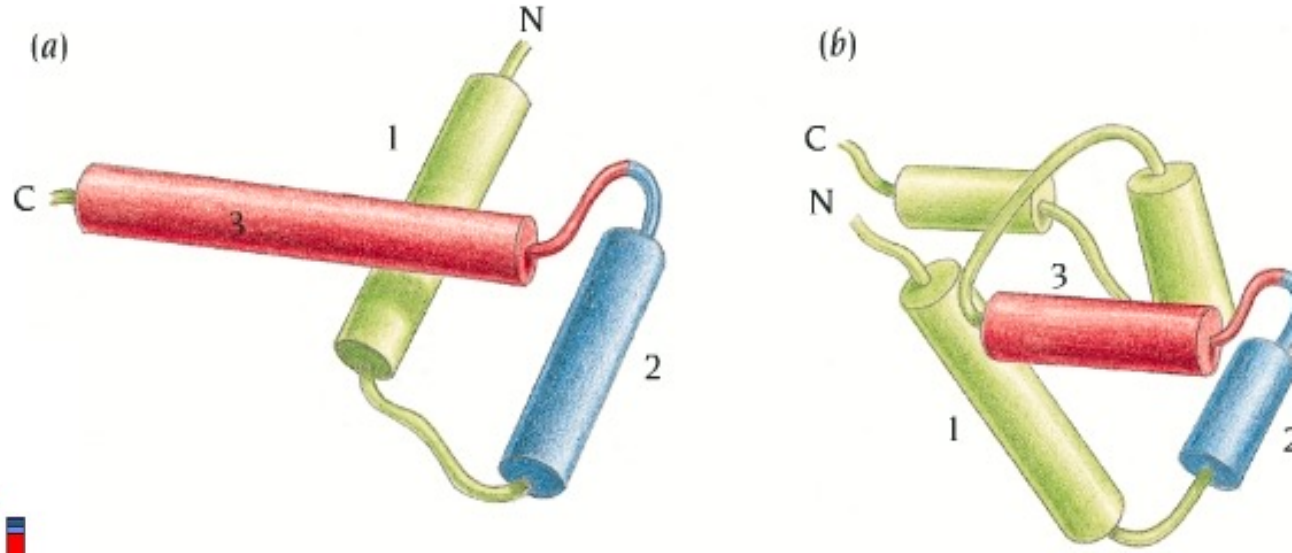
The homeobox sequence encodes the HD, a globular domain of about 60 amino acids that normally functions as a DNA-binding domain. We now know that in animals, there are usually around 100 homeobox genes

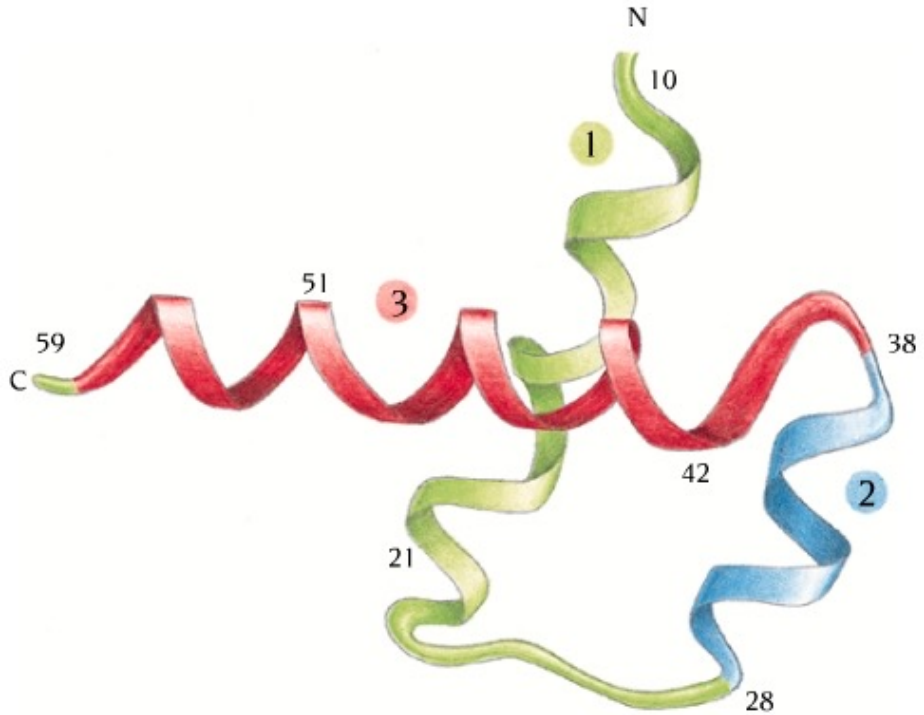
Overall, about 15–30 % of all transcription factors in animals are HD proteins which represents about 0.5–1.25 % of all proteins in a given species.



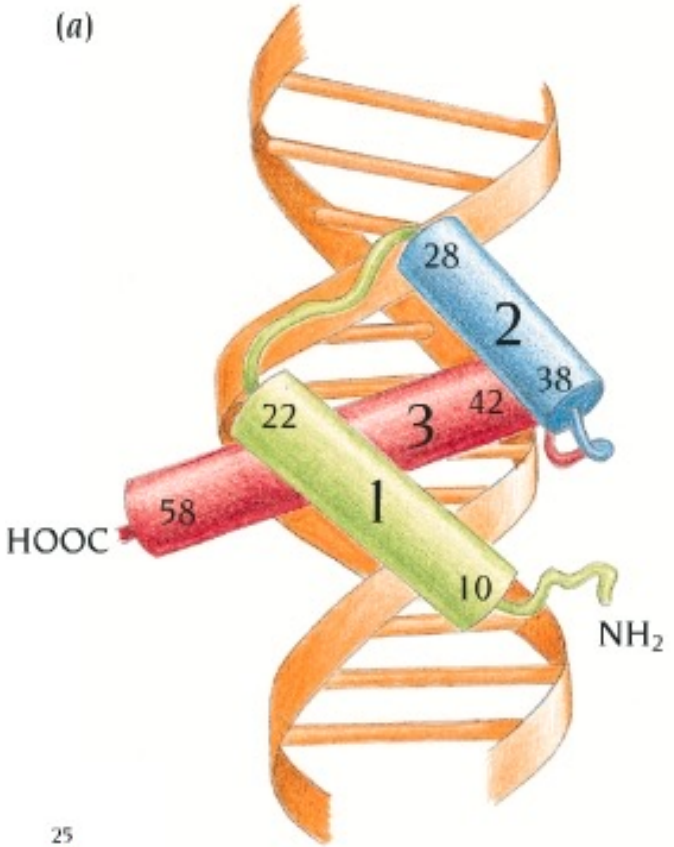
homeodomain proteins

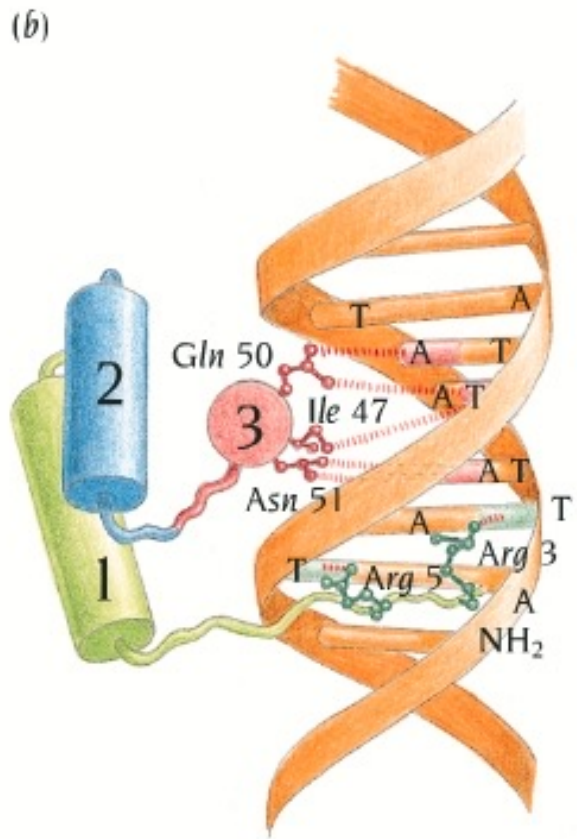


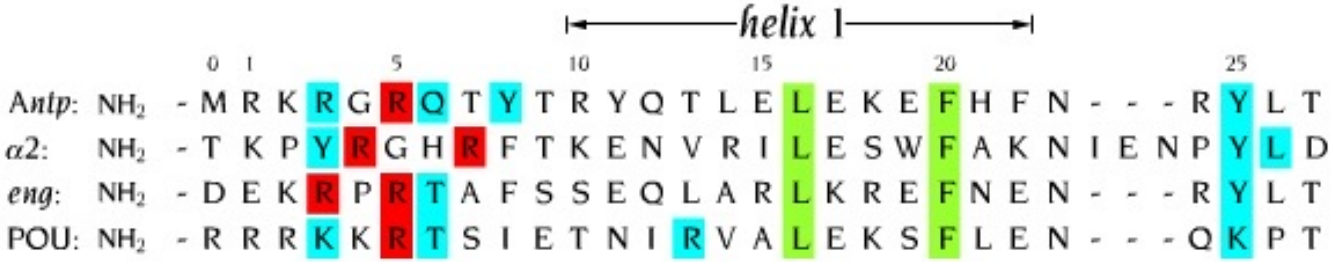




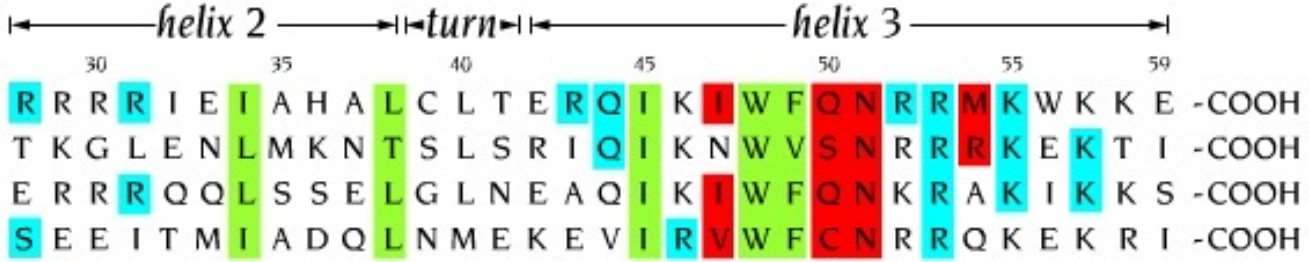
Interactions



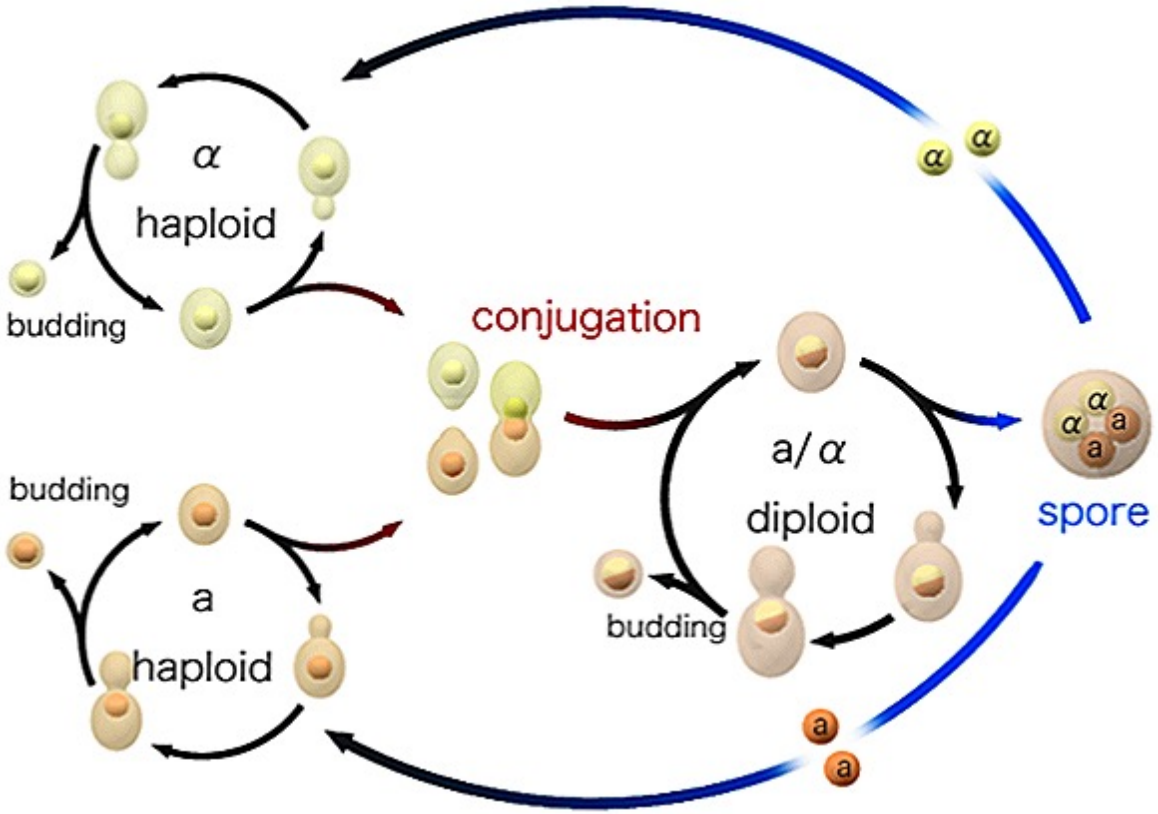


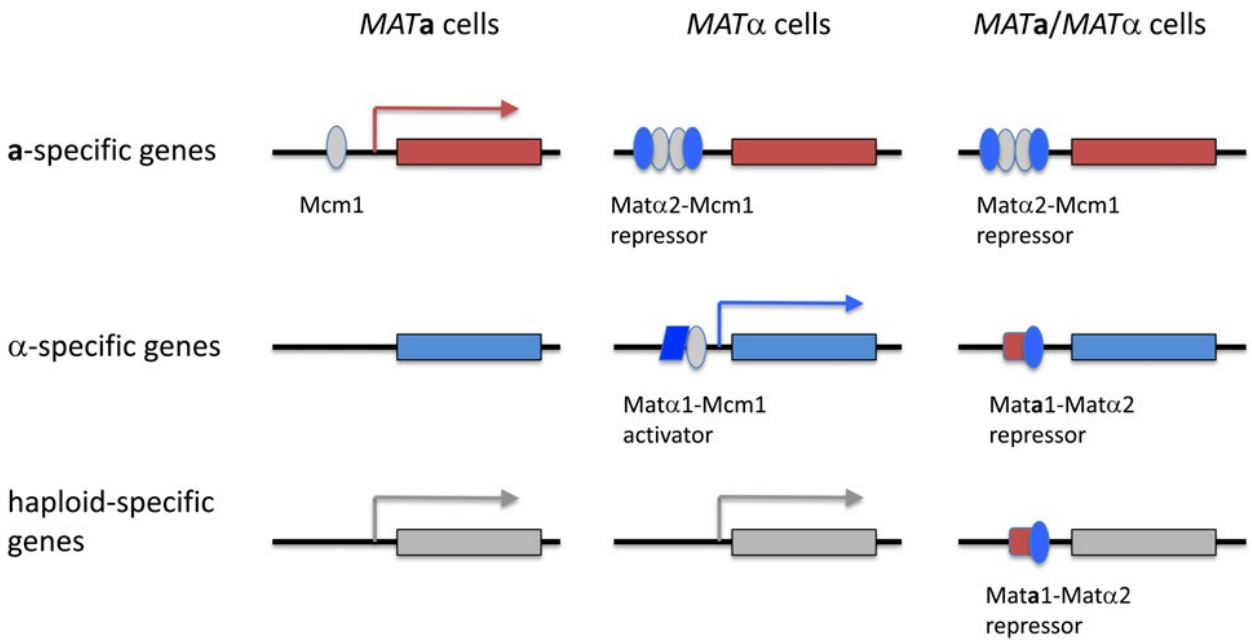


Drosophila
Yeast
Drosophila
mammalian

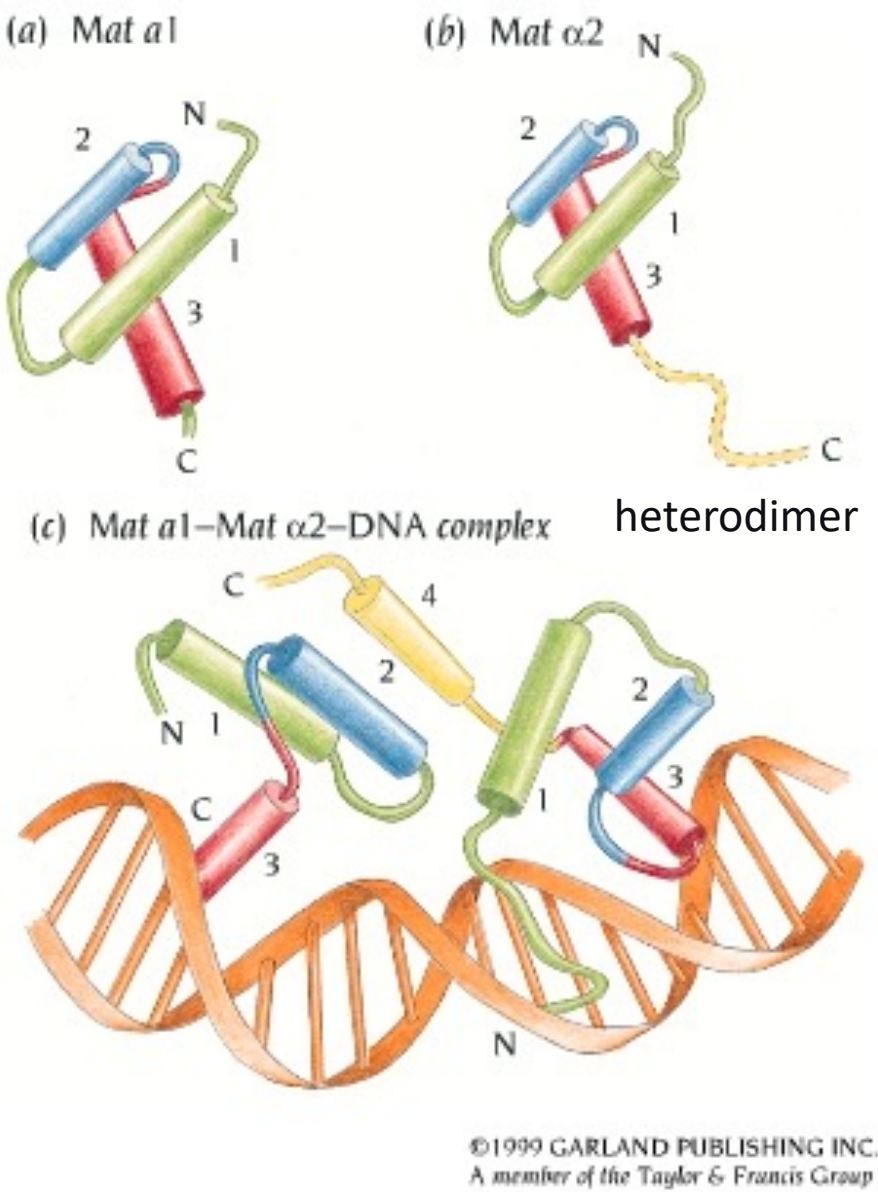


Saccharomyce cerevisiae





interactions with other proteins



heterodimer

MAT a2 heterotetramer with MCM1

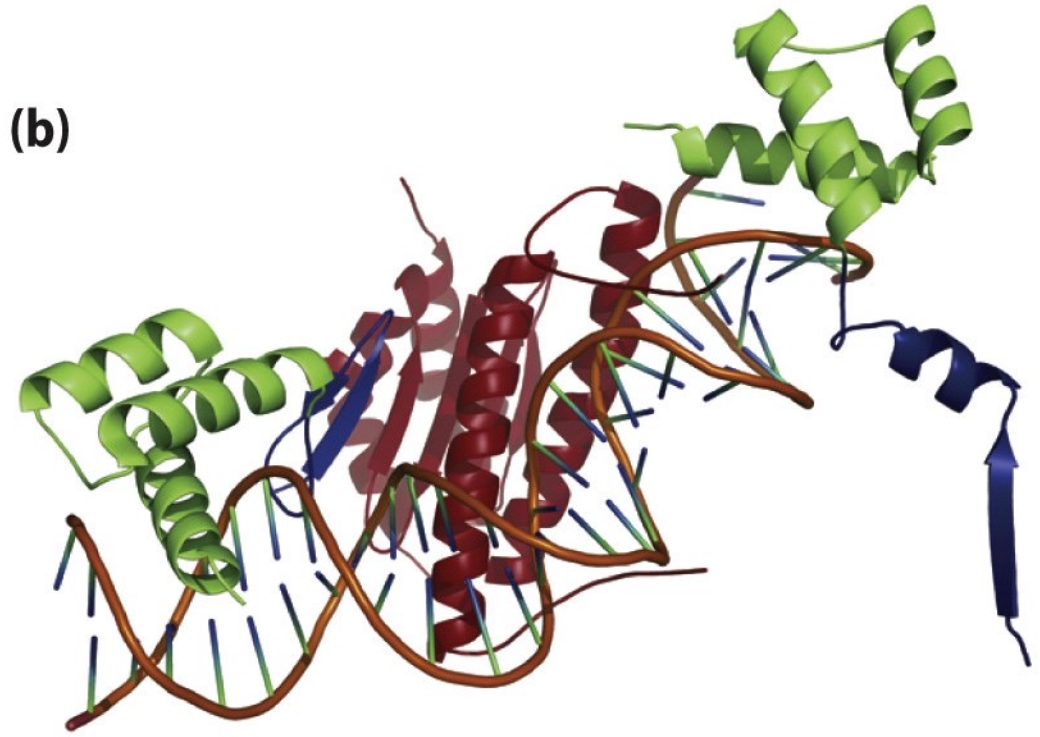
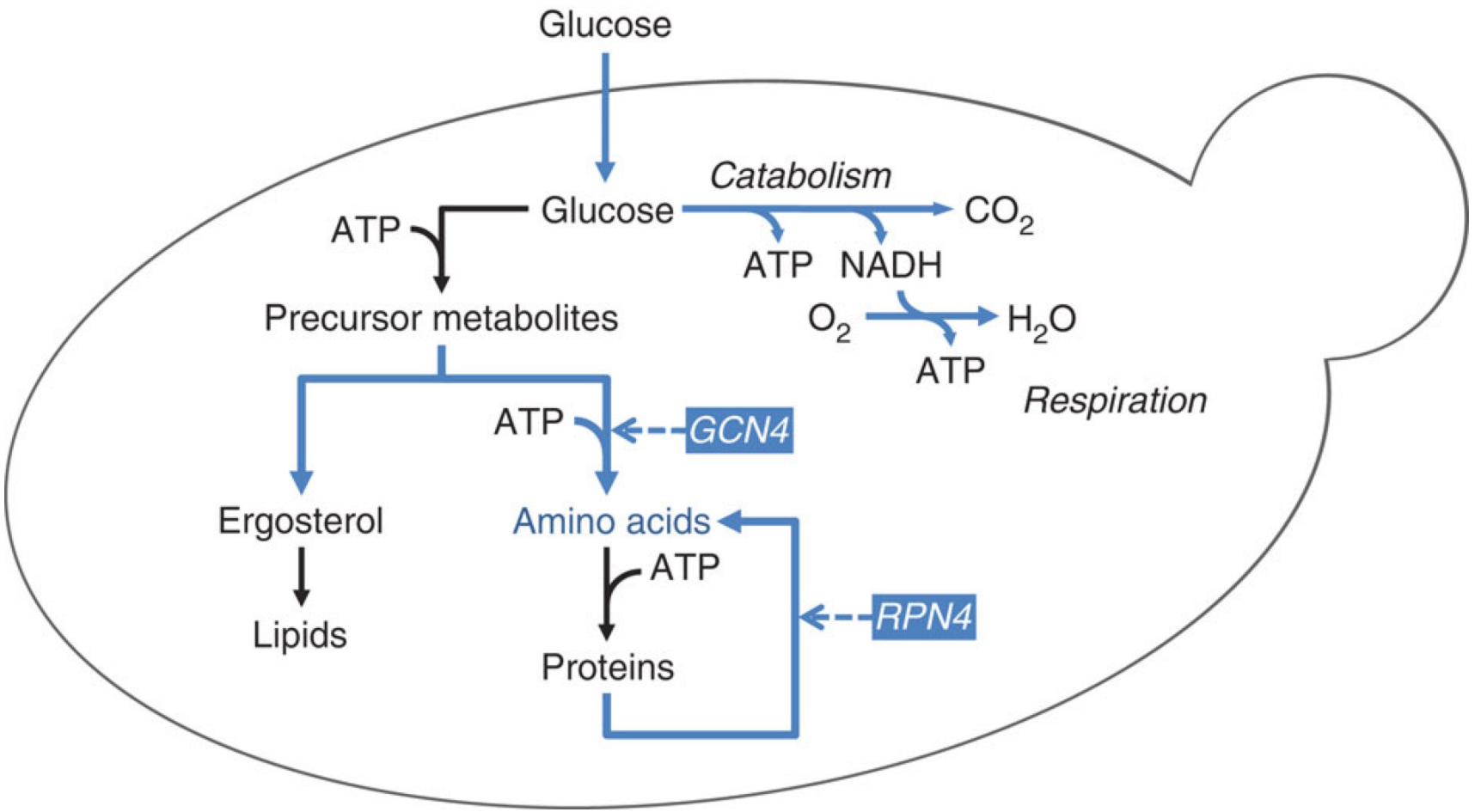


Figure 3.27 How Proteins Work (©2012 Garland Science)

Transcription factor

GCN4 protein

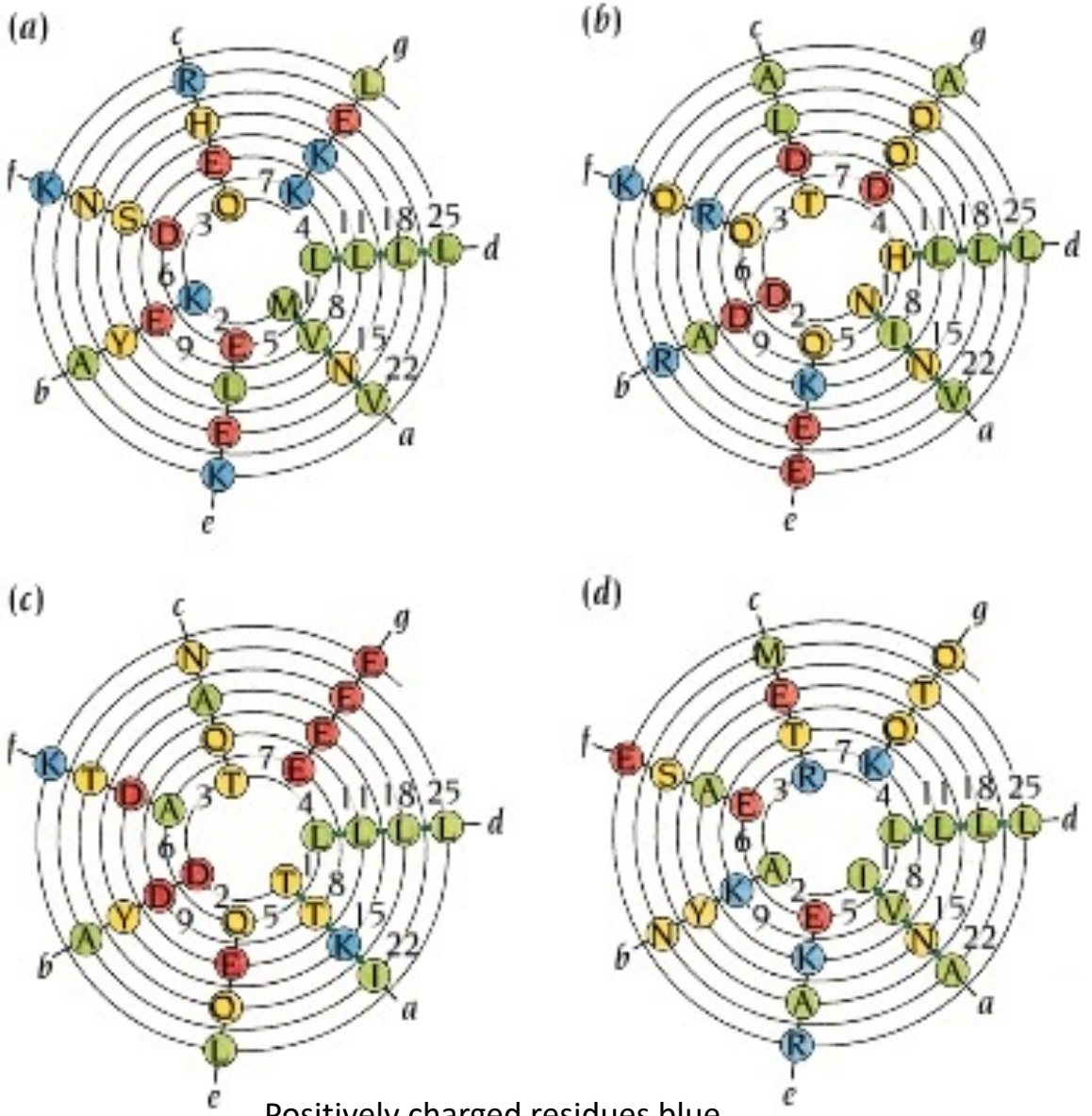
General control transcription factor



symmetric leucine zipper

Transcriptions factors

a) GCN4
b) Max
c) Fos
d) Jun



Positively charged residues blue
negatively charged red
polar residues yellow
Hydrophobic green

Regions

(a) Amino acid and DNA sequences used in the structure determination

basic region

H_2N - M - K - D - P - A - A - L - K - R - A - R - N - T - E - A - A - R - R - S - R - A -

224 230 240

zipper region

R - K - L - Q - R - M - K - Q - L - E - D - K - V - E - E - L - L - S - K - N - Y - H -

250 260

L - E - N - E - V - A - R - L - K - K - L - V - G - E - R - COOH

270 280

5′ - T - T - C - C - T - A - T - G - A - C - T - C - A - T - C - C - A - G - T - T - 3′

3′ - A - G - G - A - T - A - C - T - G - A - G - T - A - G - G - T - C - A - A - A - 5′

(b) AP1-binding site

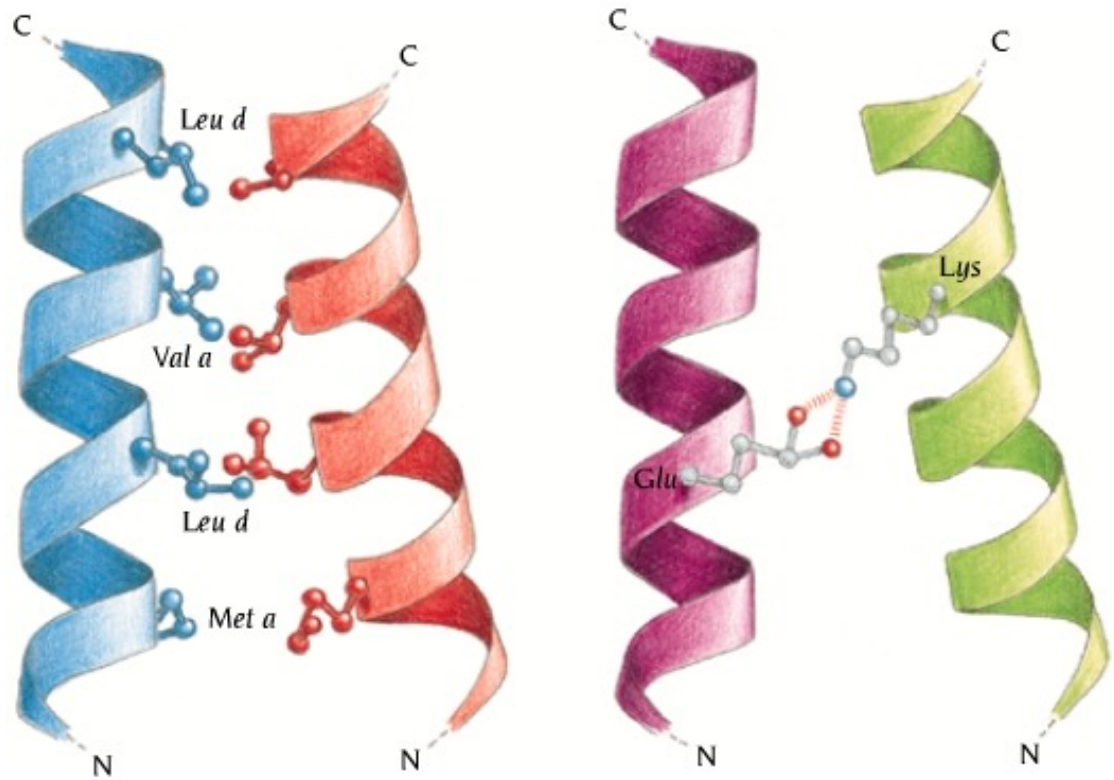
5′ - A - T - G - A - C - T - C - A - T - 3′

3′ - T - A - C - T - G - A - G - T - A - 5′

(c) Symmetric GCN4-binding site

5′ - A - T - G - A - C - G - T - C - A - T - 3′

3′ - T - A - C - T - G - C - A - G - T - A - 5′



interactions

(a) Amino acid and DNA sequences used in the structure determination

basic region

H_2N - M - K - D - P - A - A - L - K - R - A - R - N - T - E - A - A - R - R - S - R - A -
224 230 240

zipper region

R - K - L - Q - R - M - K - Q - L - E - D - K - V - E - E - L - L - S - K - N - Y - H -
250 260

L - E - N - E - V - A - R - L - K - K - L - V - G - E - R - COOH
270 280

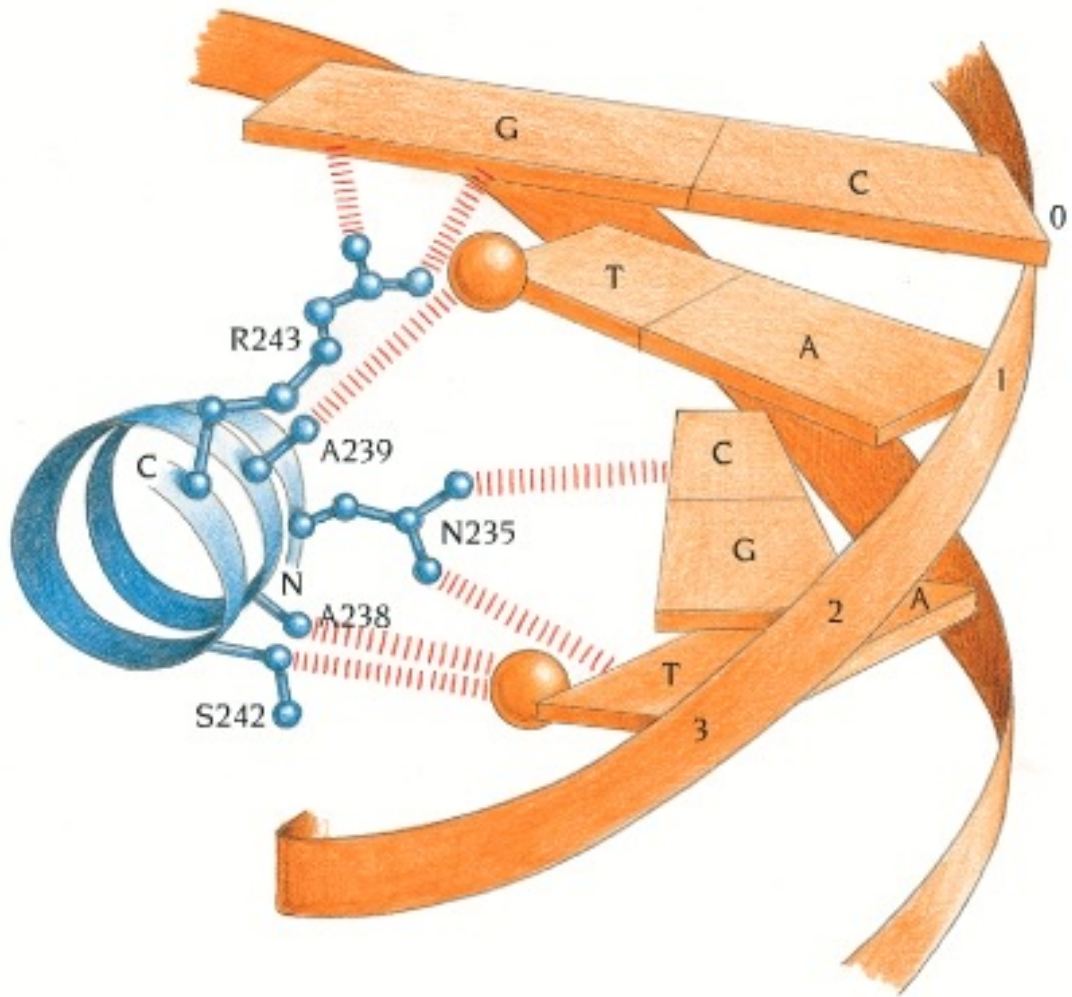
5′ - T - T - C - C - T - A - T - G - A - C - T - C - A - T - C - C - A - G - T - T - 3′
3′ - A - G - G - A - T - A - C - T - G - A - G - T - A - G - G - T - C - A - A - A - 5′

(b) AP1-binding site

5′ - A - T - G - A - C - T - C - A - T - 3′
3′ - T - A - C - T - G - A - G - T - A - 5′

(c) Symmetric GCN4-binding site

5′ - A - T - G - A - C - G - T - C - A - T - 3′
3′ - T - A - C - T - G - C - A - G - T - A - 5′



Fos-Jun

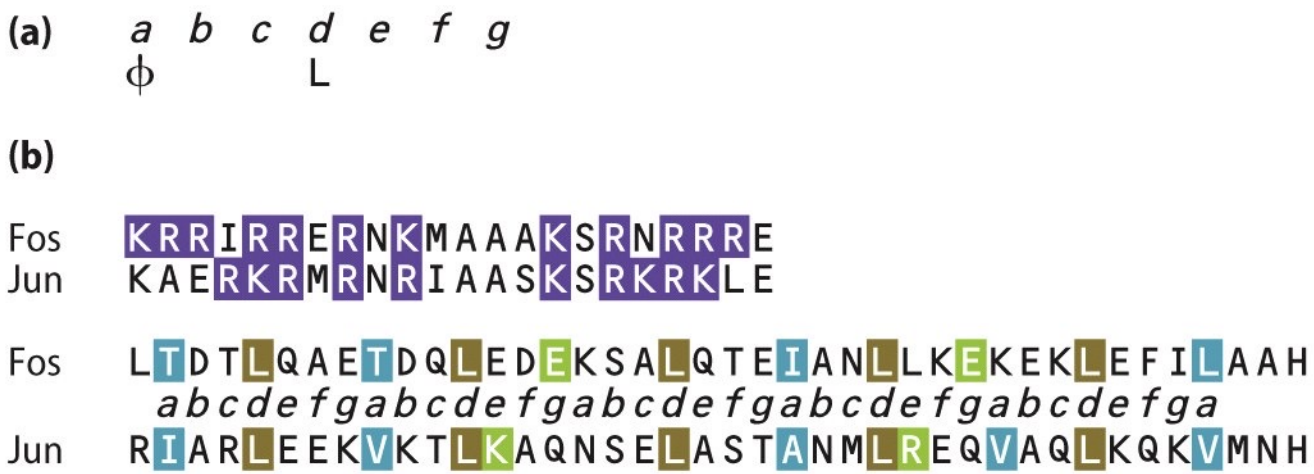


Figure 3.35 How Proteins Work (©2012 Garland Science)

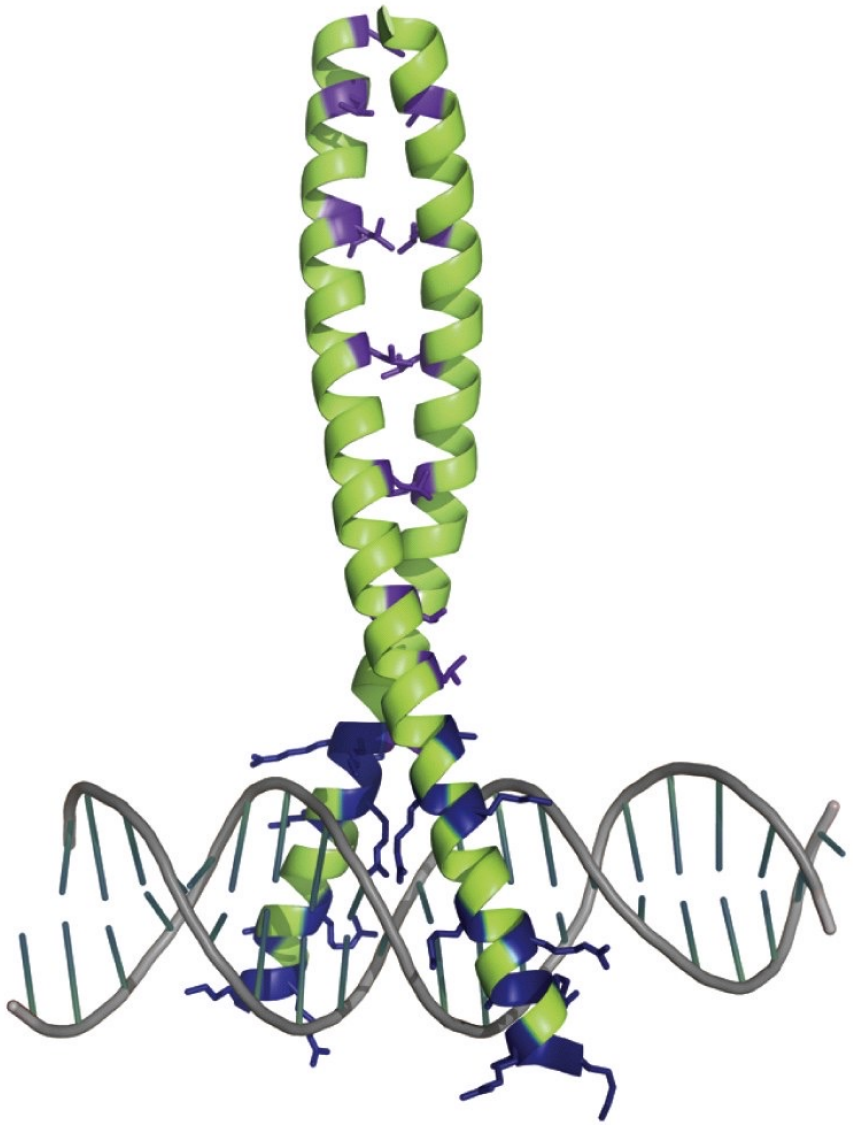


Figure 3.34 How Proteins Work (©2012 Garland Science)

Heterodimerization of leucine zipper proteins

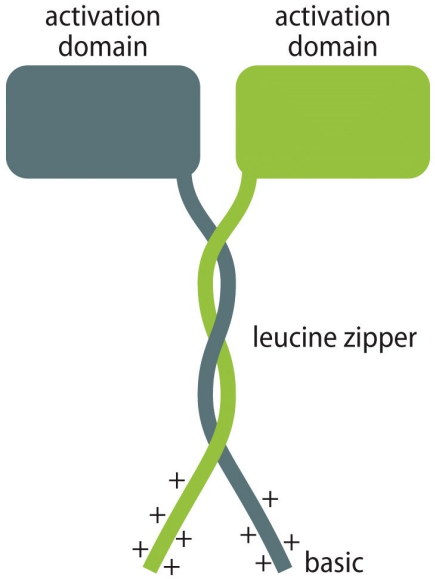
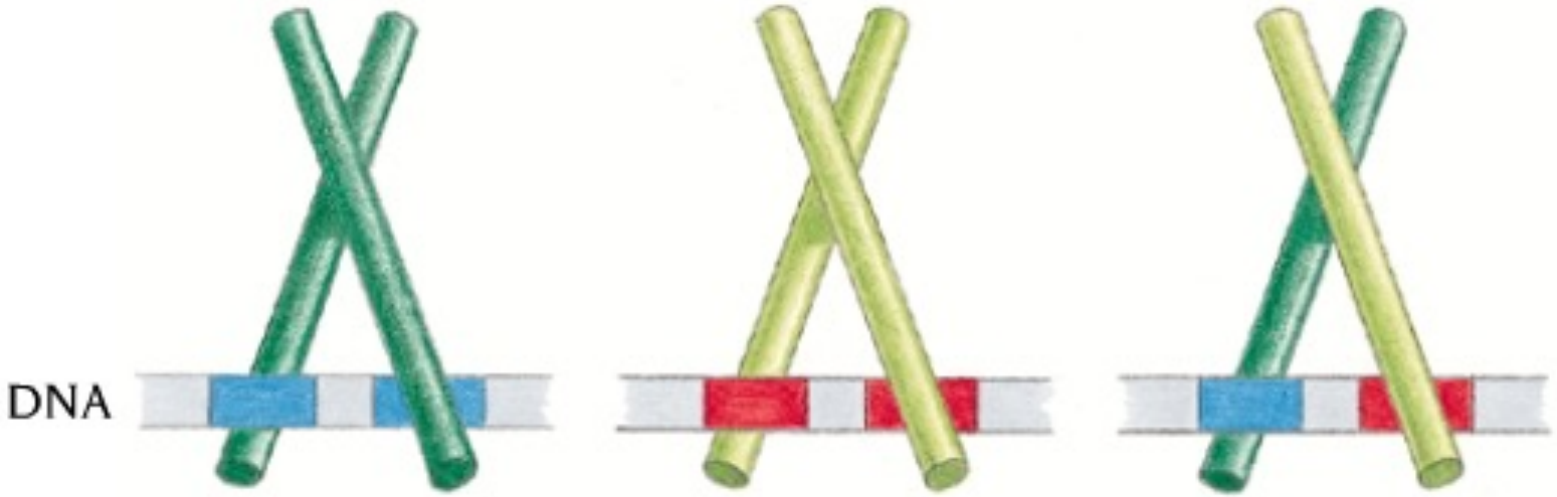


Figure 3.36 How Proteins Work (©2012 Garland Science)



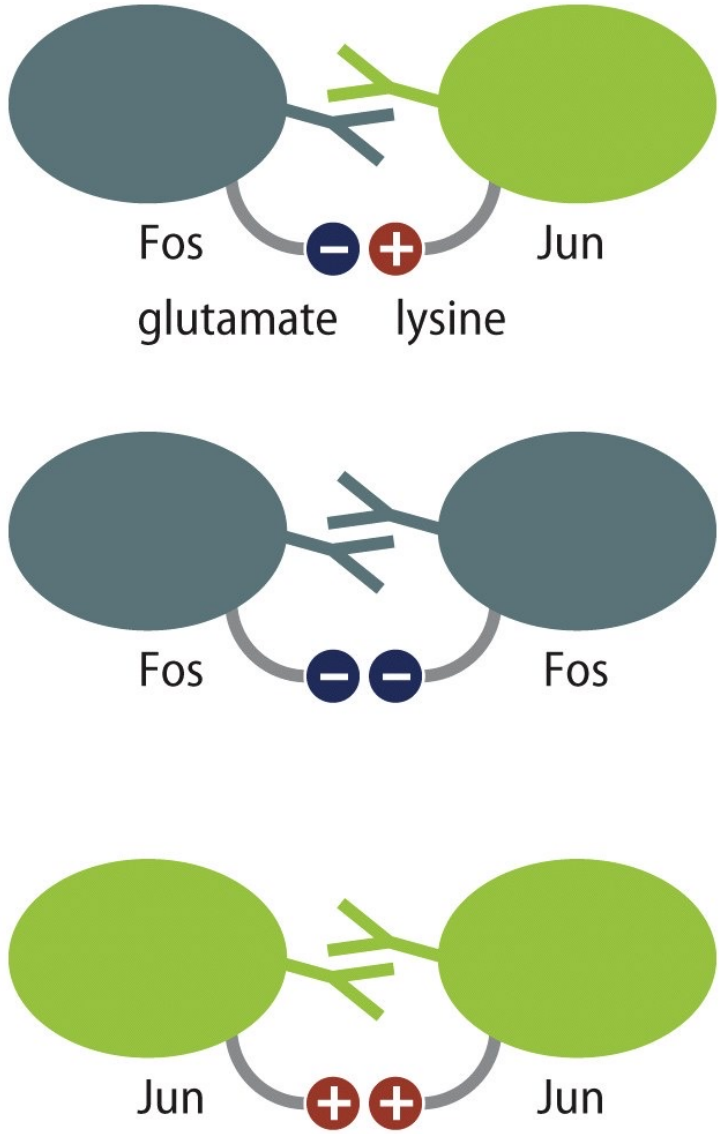
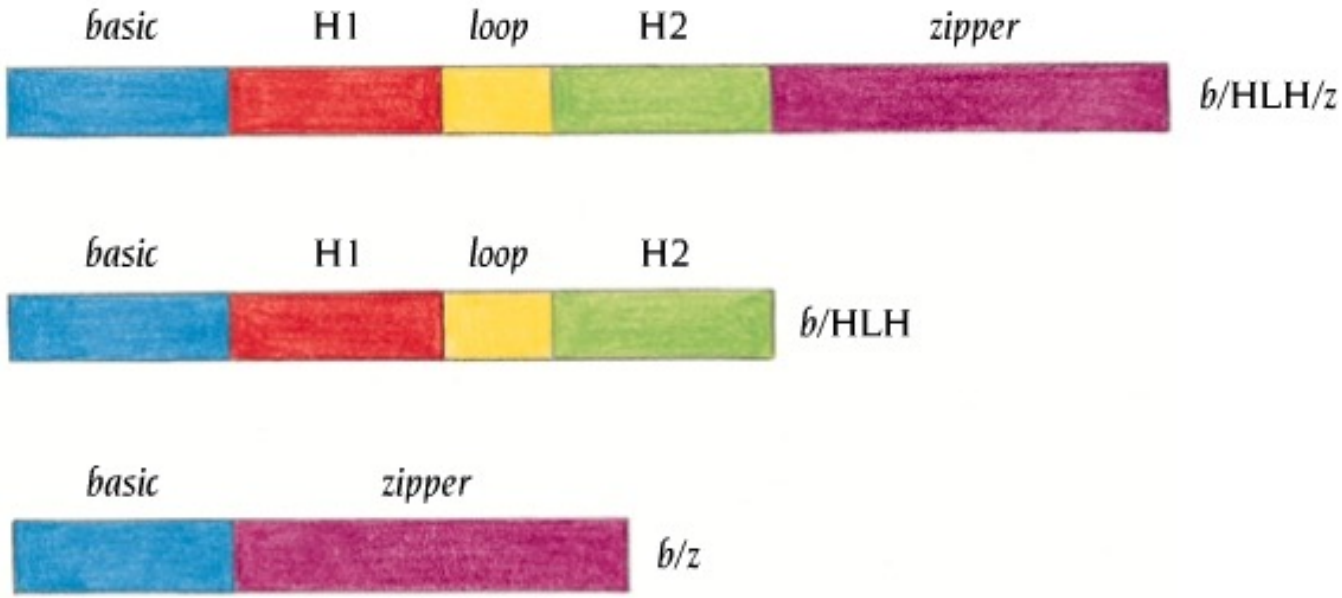
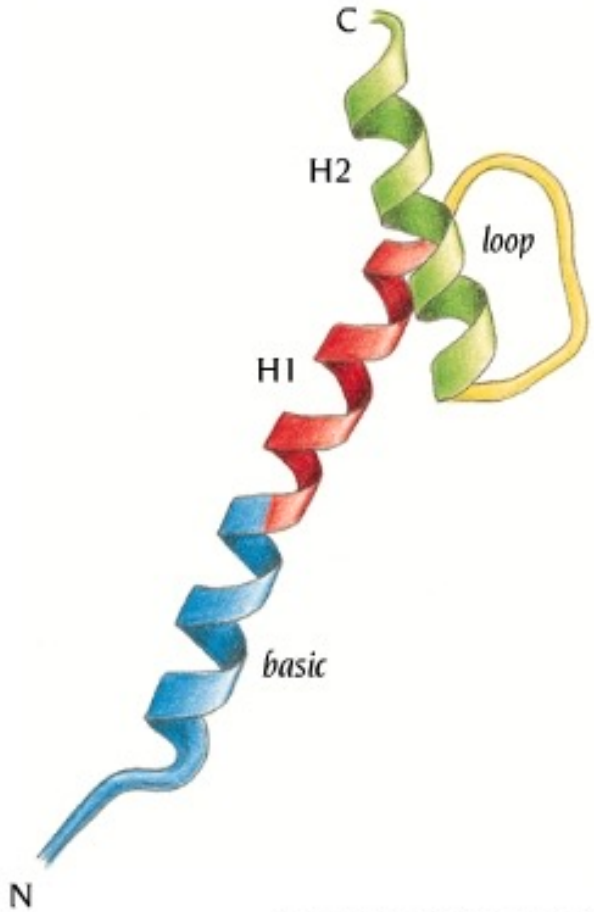


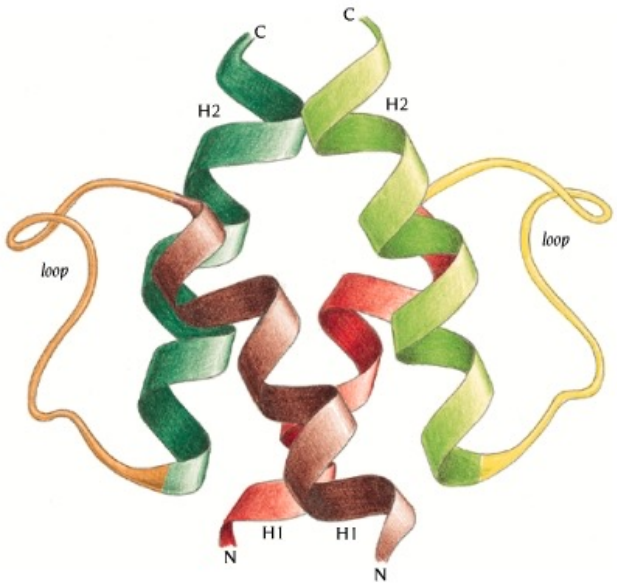
Figure 3.37 How Proteins Work (©2012 Garland Science)

HLH motif

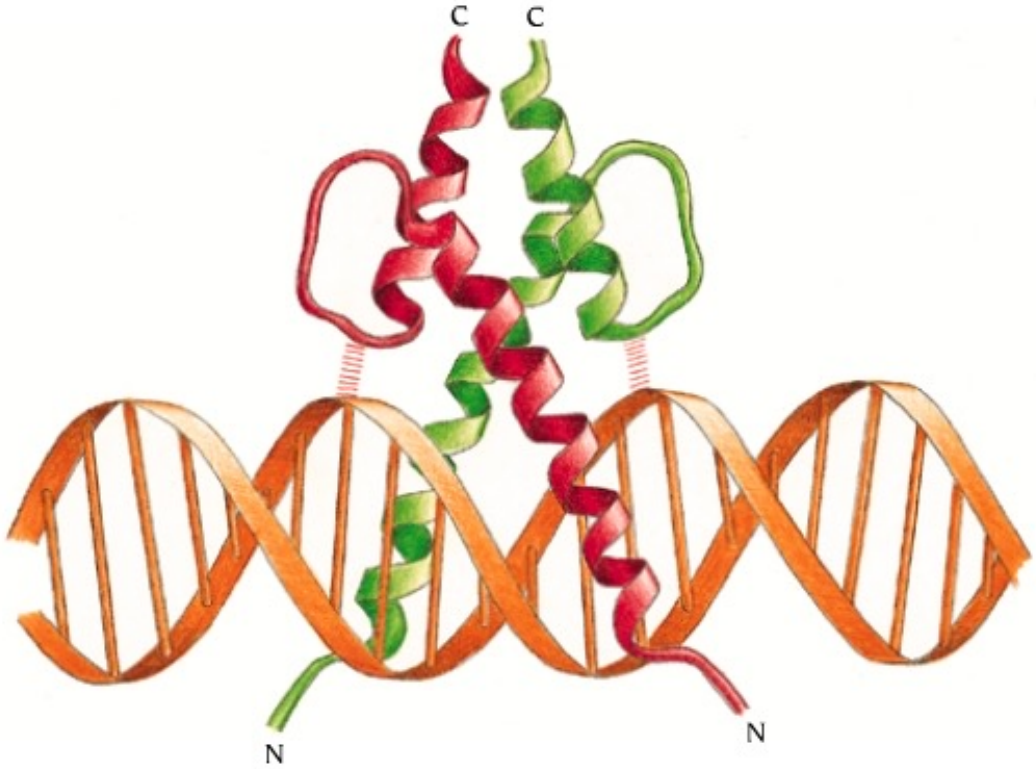


HLH motif

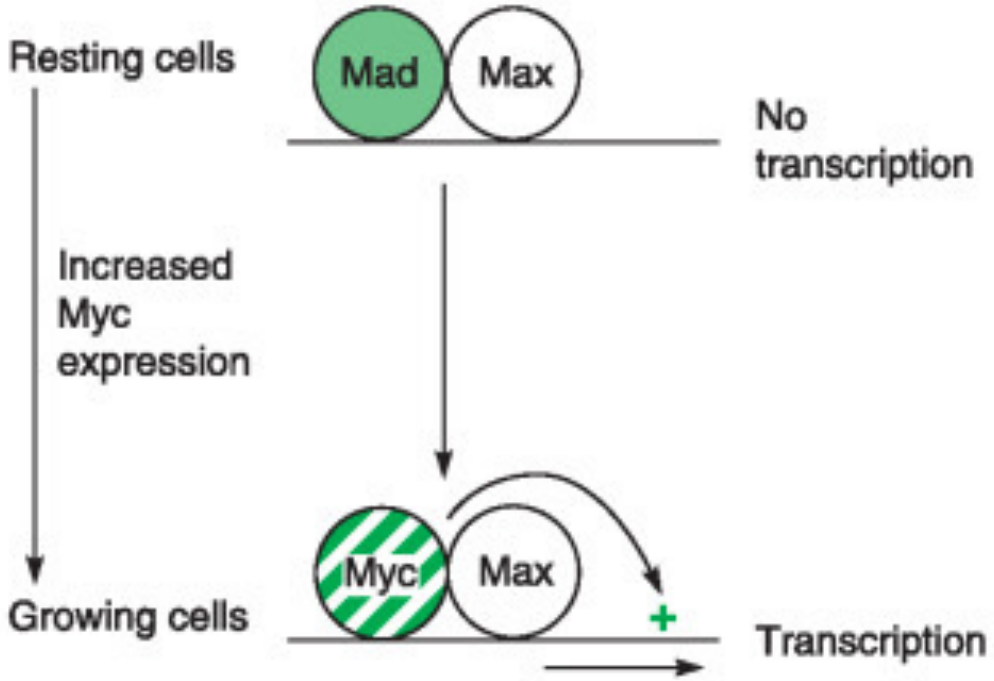




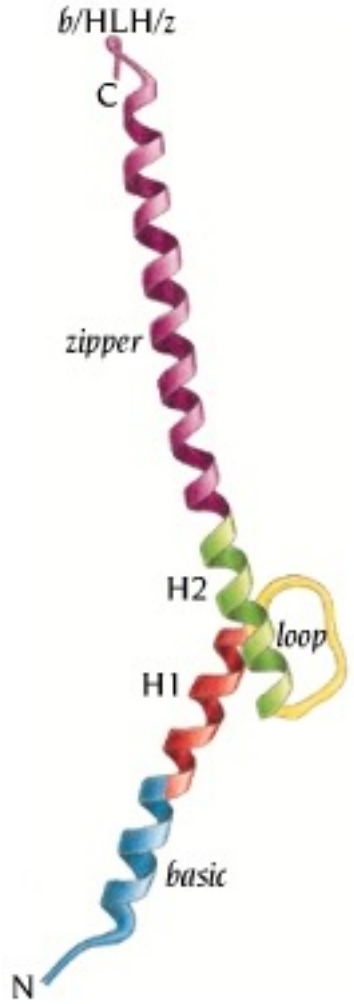
MyoD



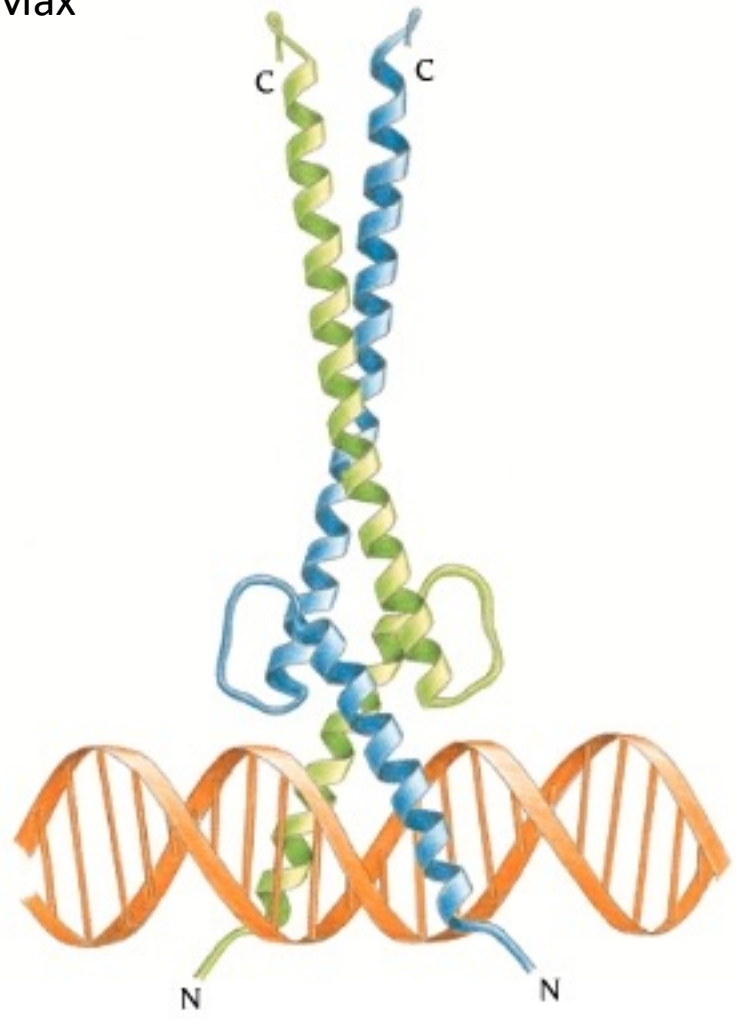
HLH motif

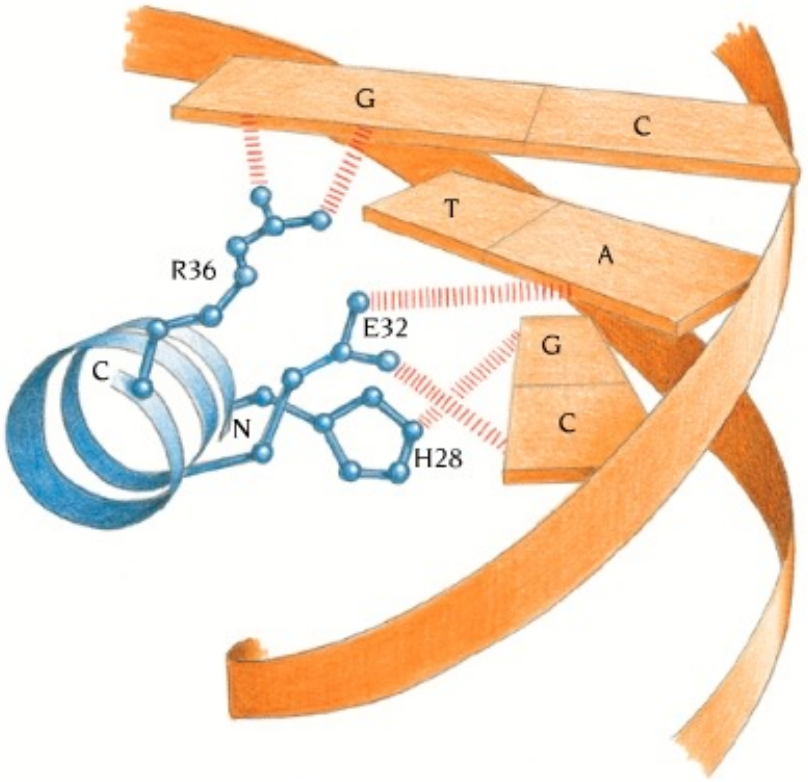

Resting cells
Mad
Max
No transcription
Increased Myc expression
Myc
Max
+
Growing cells
Transcription

HLH motif

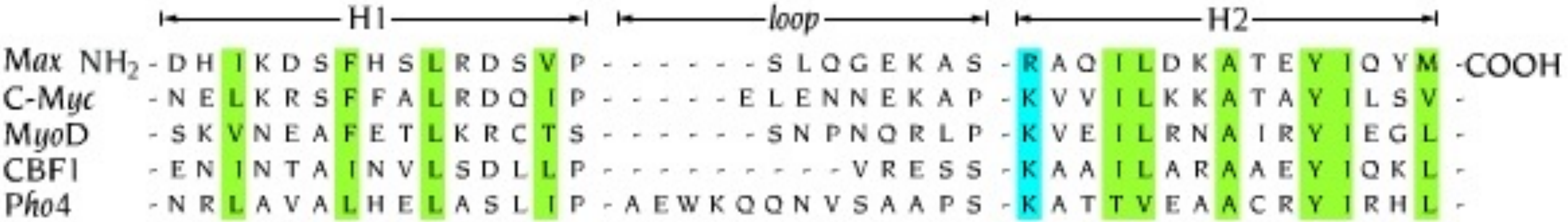


Max

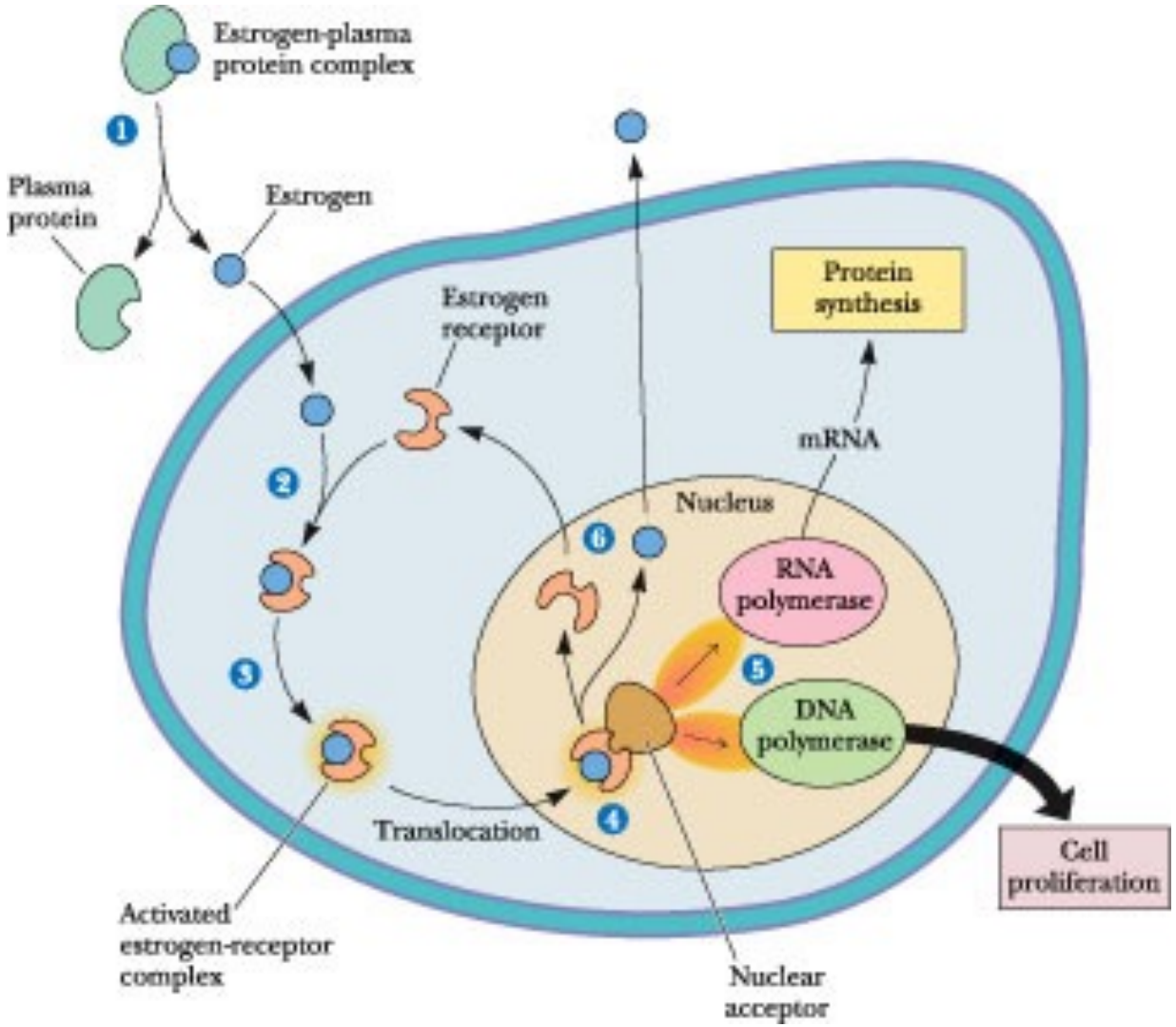




HLH motif



Steroid hormone action



Tandem dimer

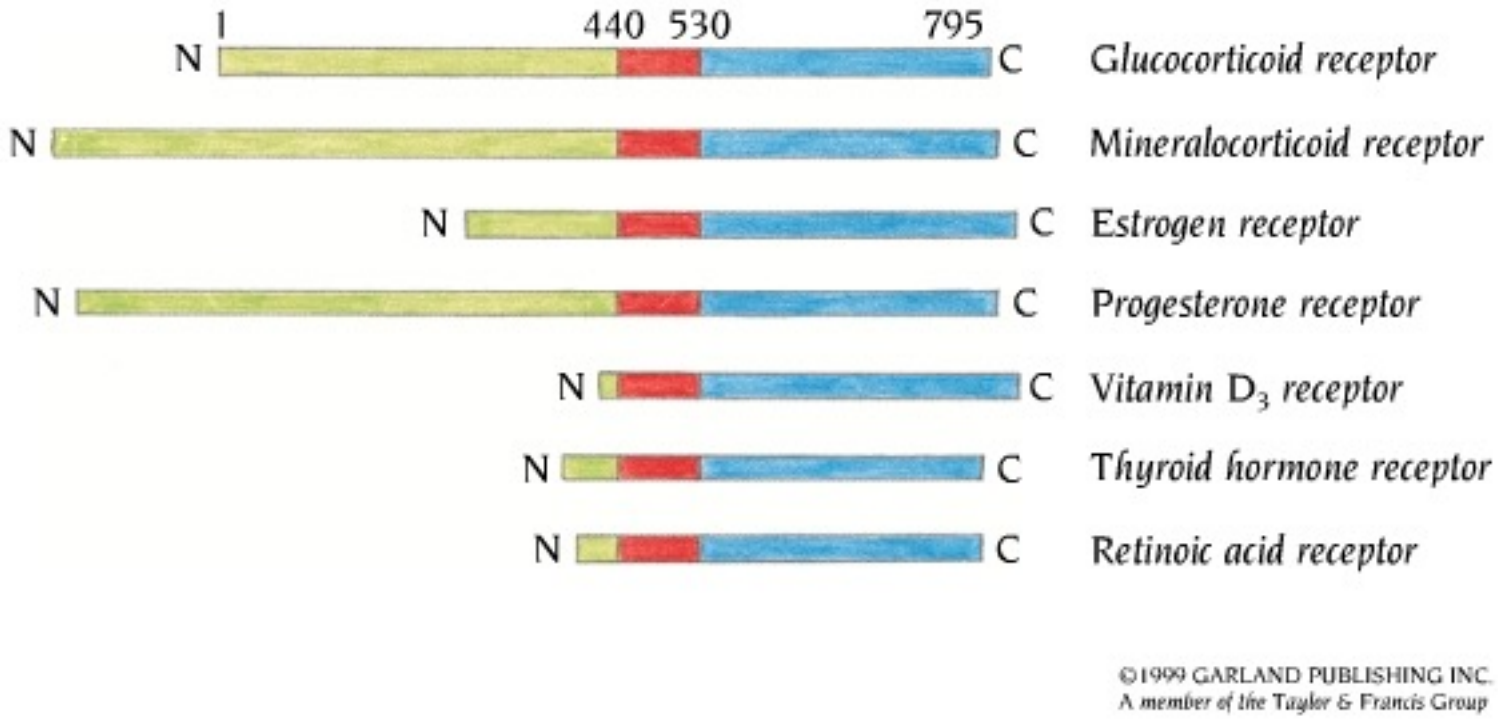


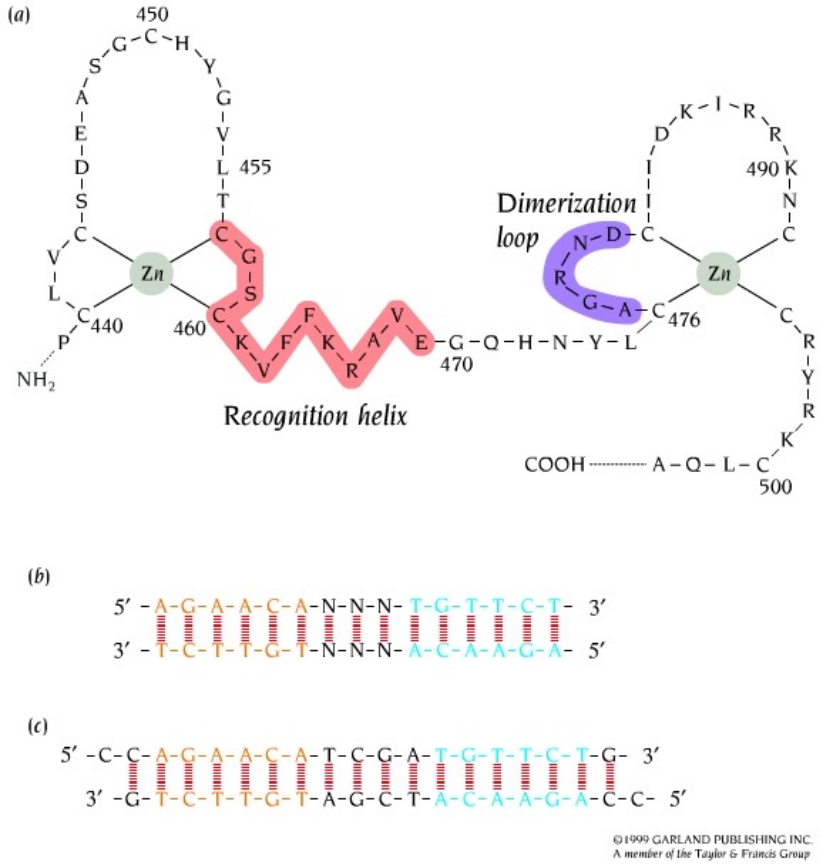
TABLE 3.1 Lipophilic hormone receptor targets

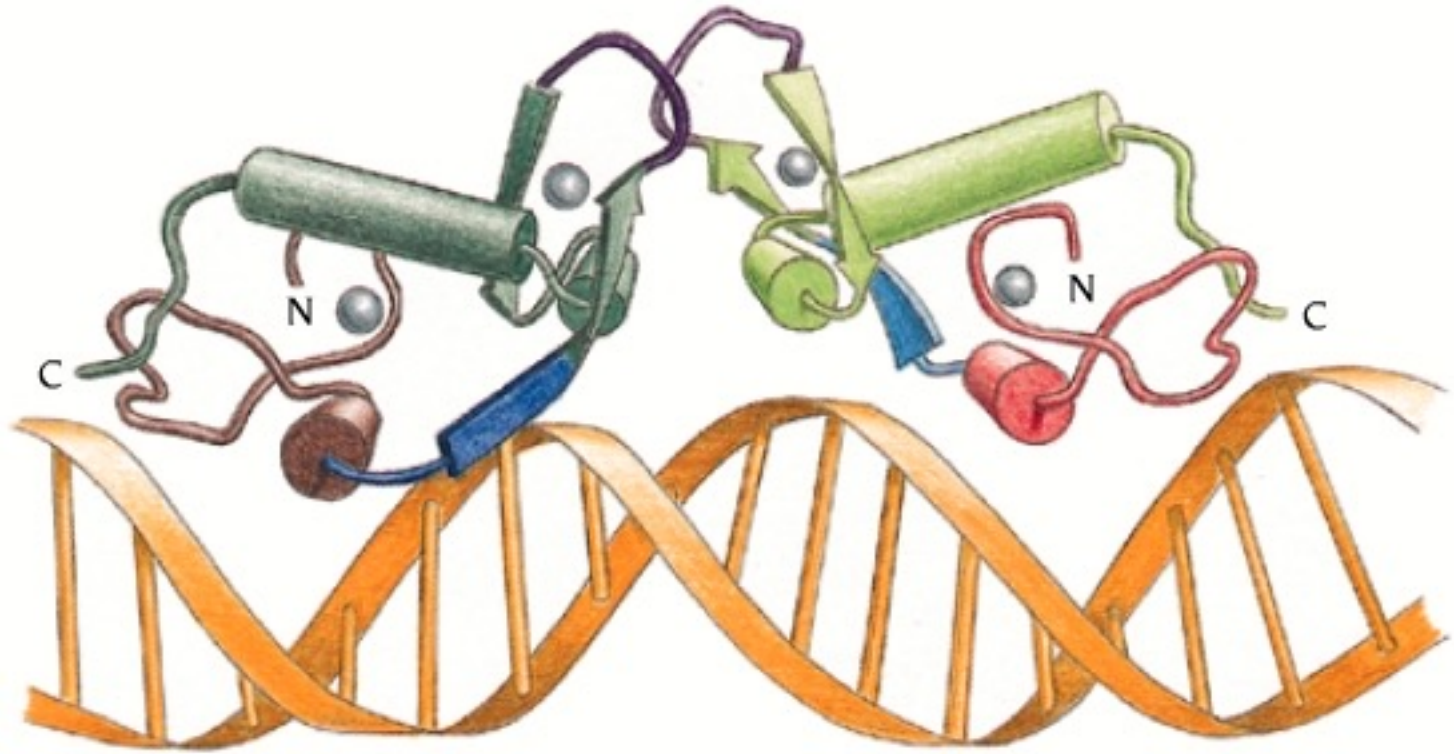
RXR.RXR	AGGTCA*n*AGGTCA
RXR.RAR	AGGTCA*nn*AGGTCA
RXR.VDR	AGGTCA*nnn*AGGTCA
RXR.TR	AGGTCA*nnnn*AGGTCA
RXR.RAR	AGGTCA*nnnnn*AGGTCA

RXR = 9-*cis* retinoic acid receptor; RAR = all-*trans* retinoic acid receptor; VDR = vitamin D1 receptor; TR = thyroid hormone receptor. (Based on a Table in F. Rastinejad, *Curr. Opin. Struct. Biol.* 11:33–38, 2001. With permission from Elsevier.)

Table 3.1 How Proteins Work (©2012 Garland Science)

Zinc containing motifs





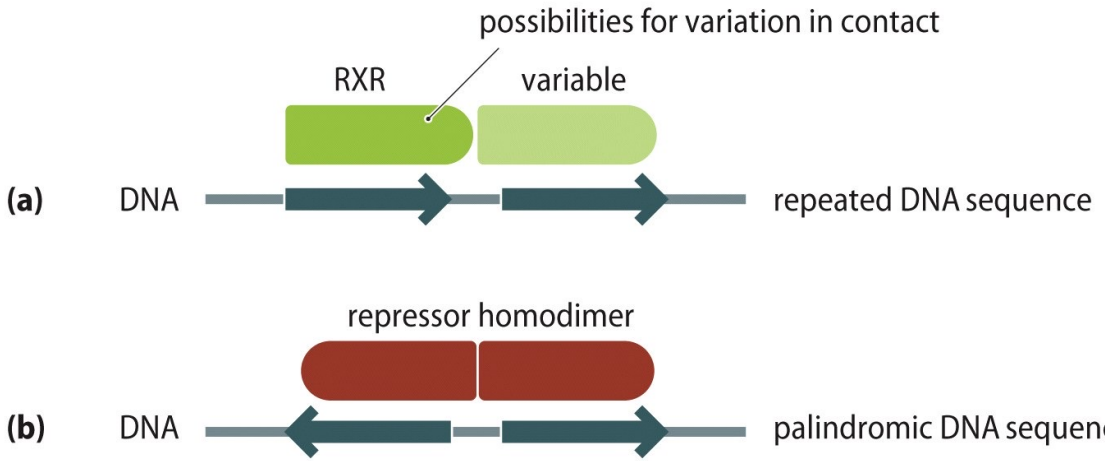


Figure 3.39 How Proteins Work (©2012 Garland Science)

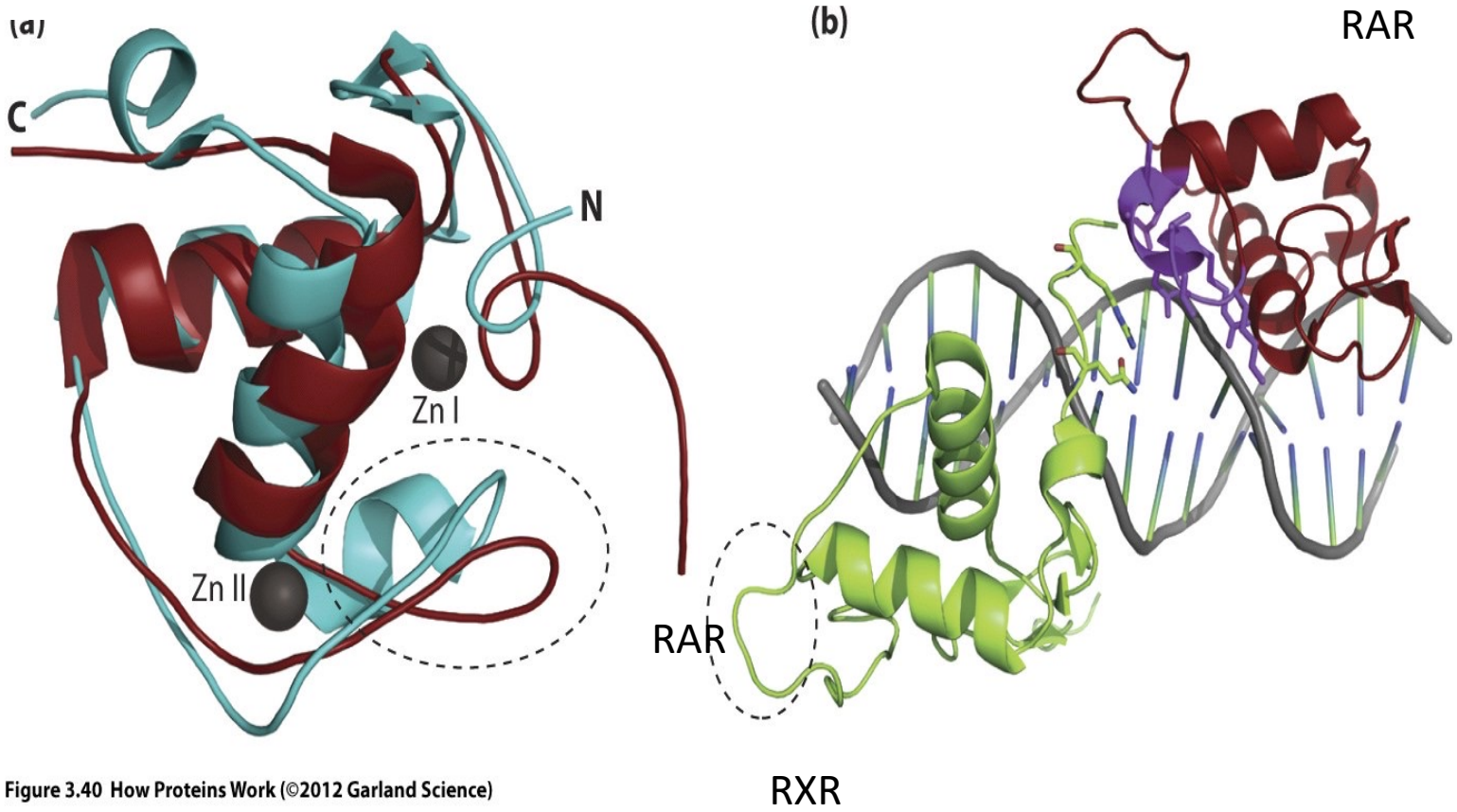
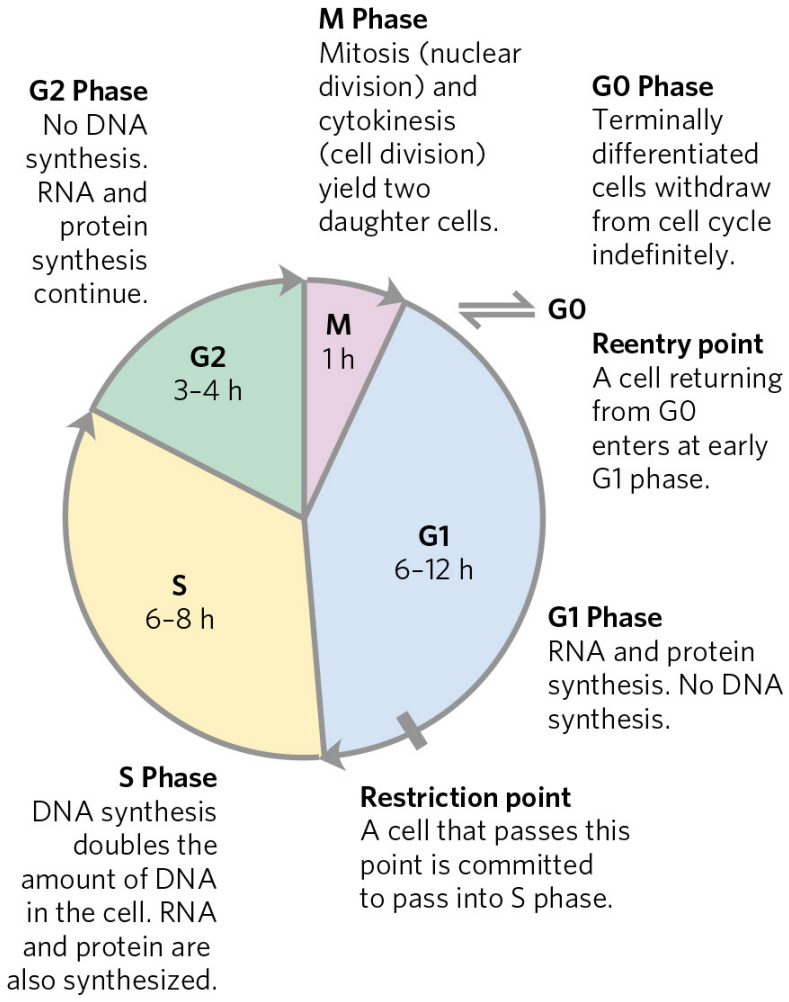
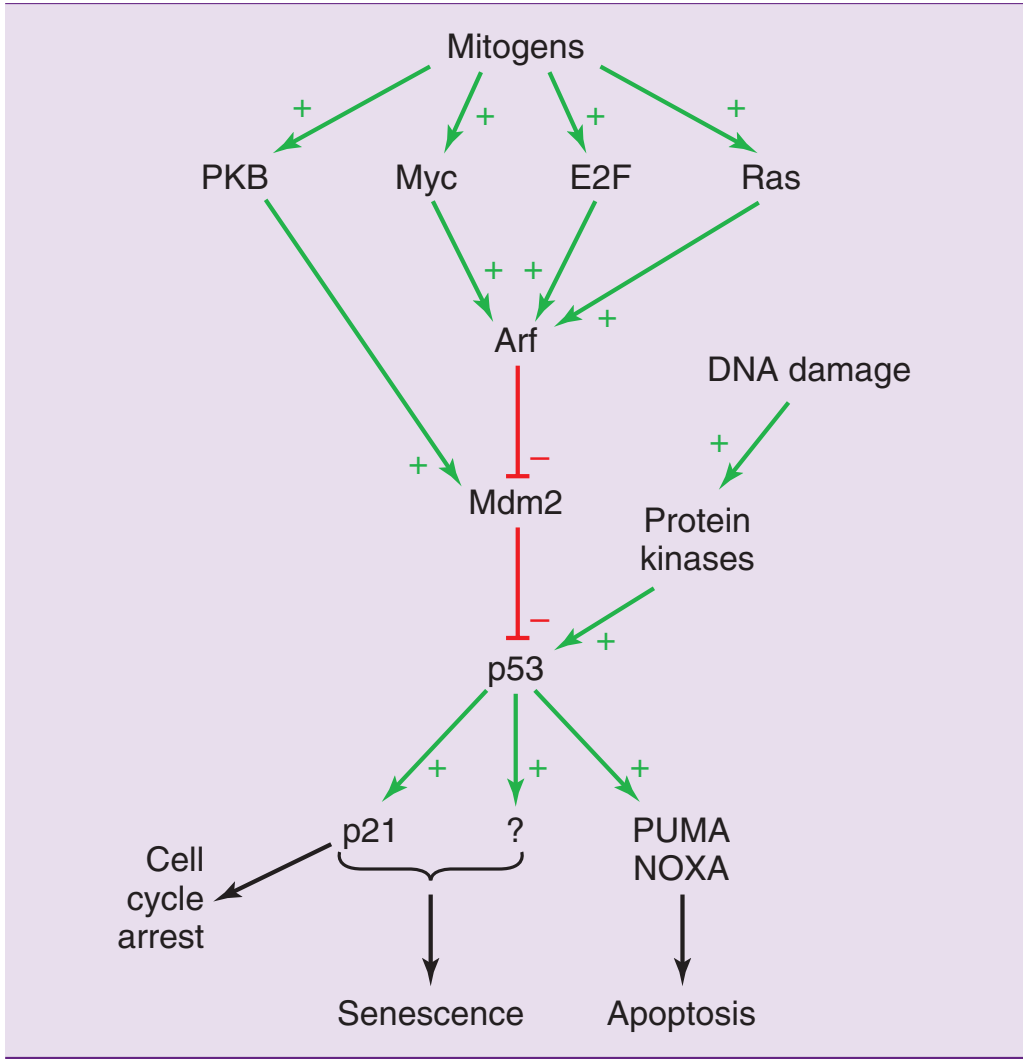


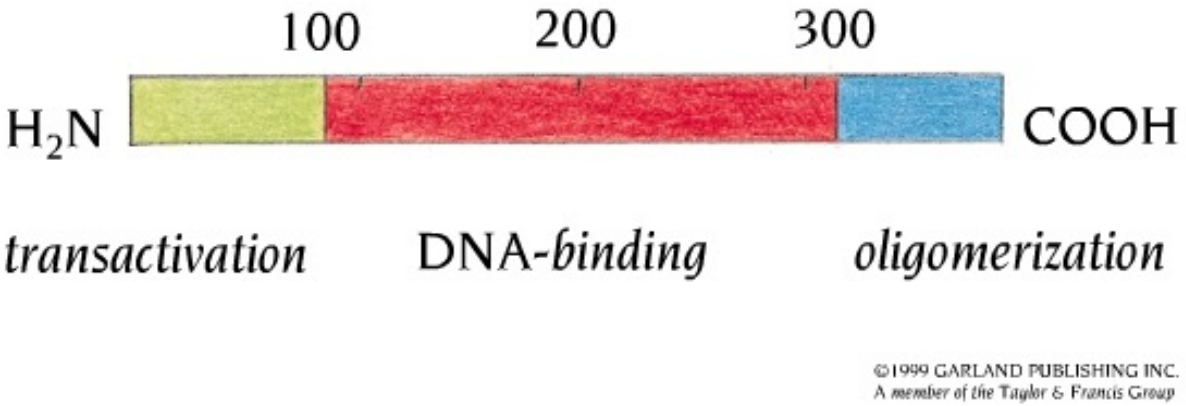
Figure 3.40 How Proteins Work (©2012 Garland Science)

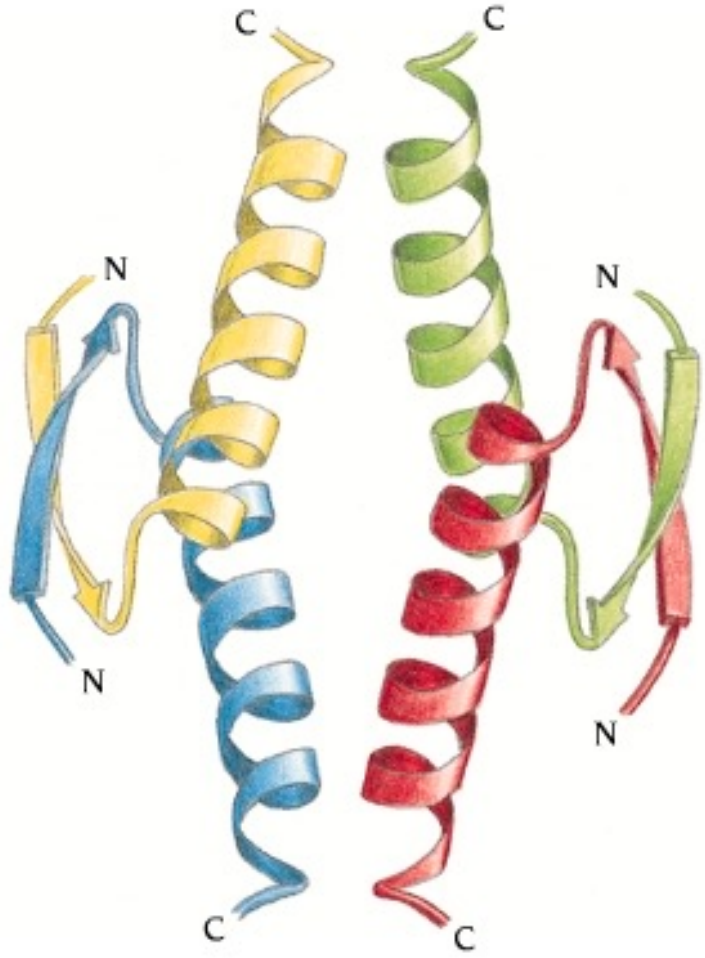
Understanding tumorigenic mutations



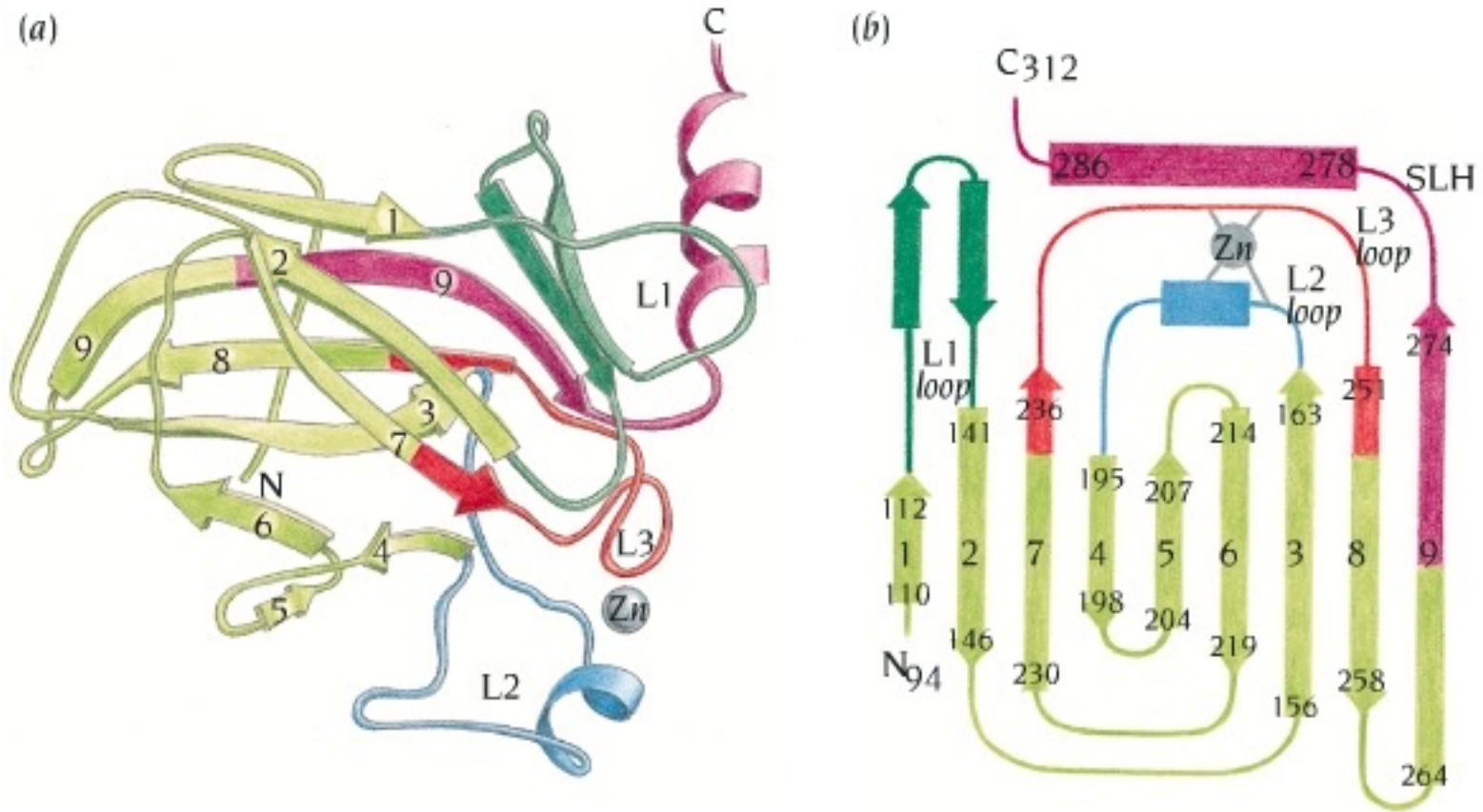


Understanding tumorigenic mutations

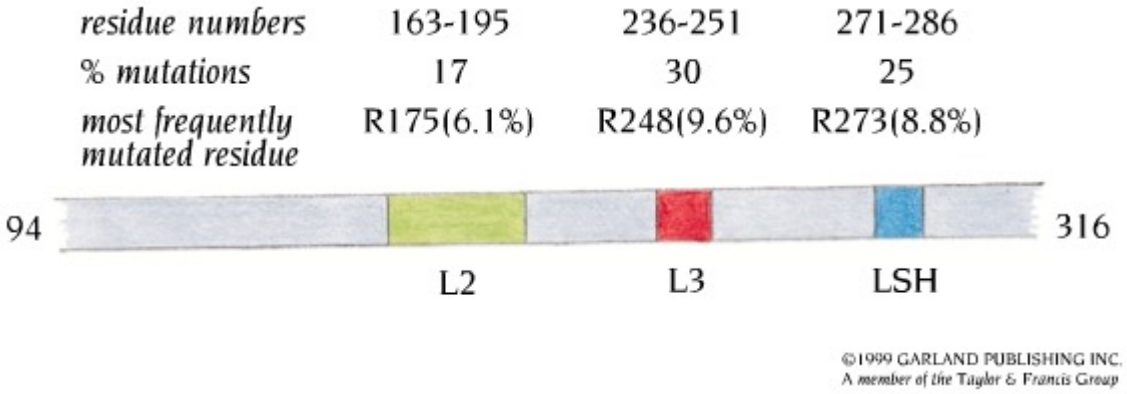


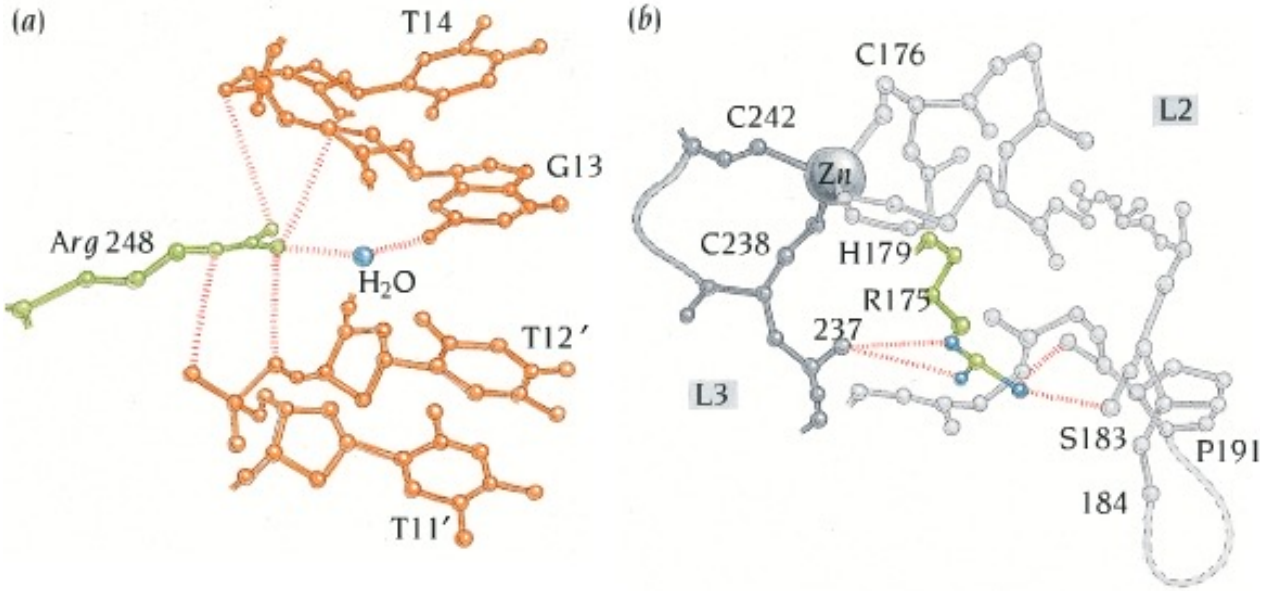


Understanding tumorigenic mutations

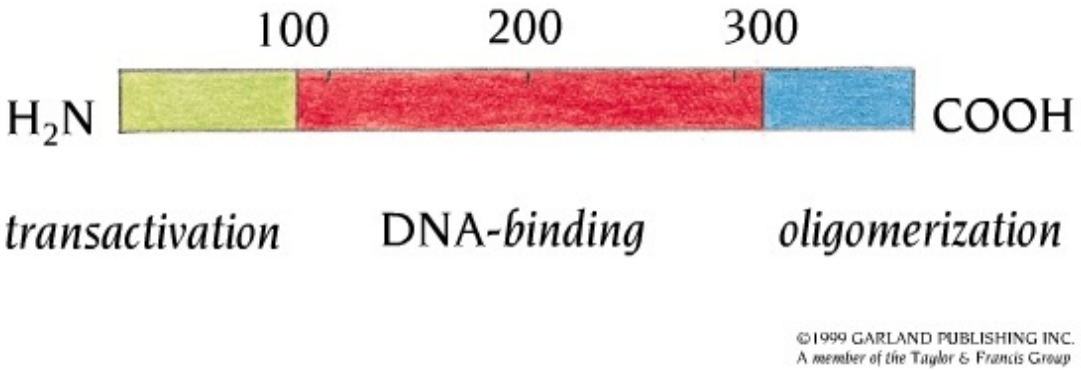


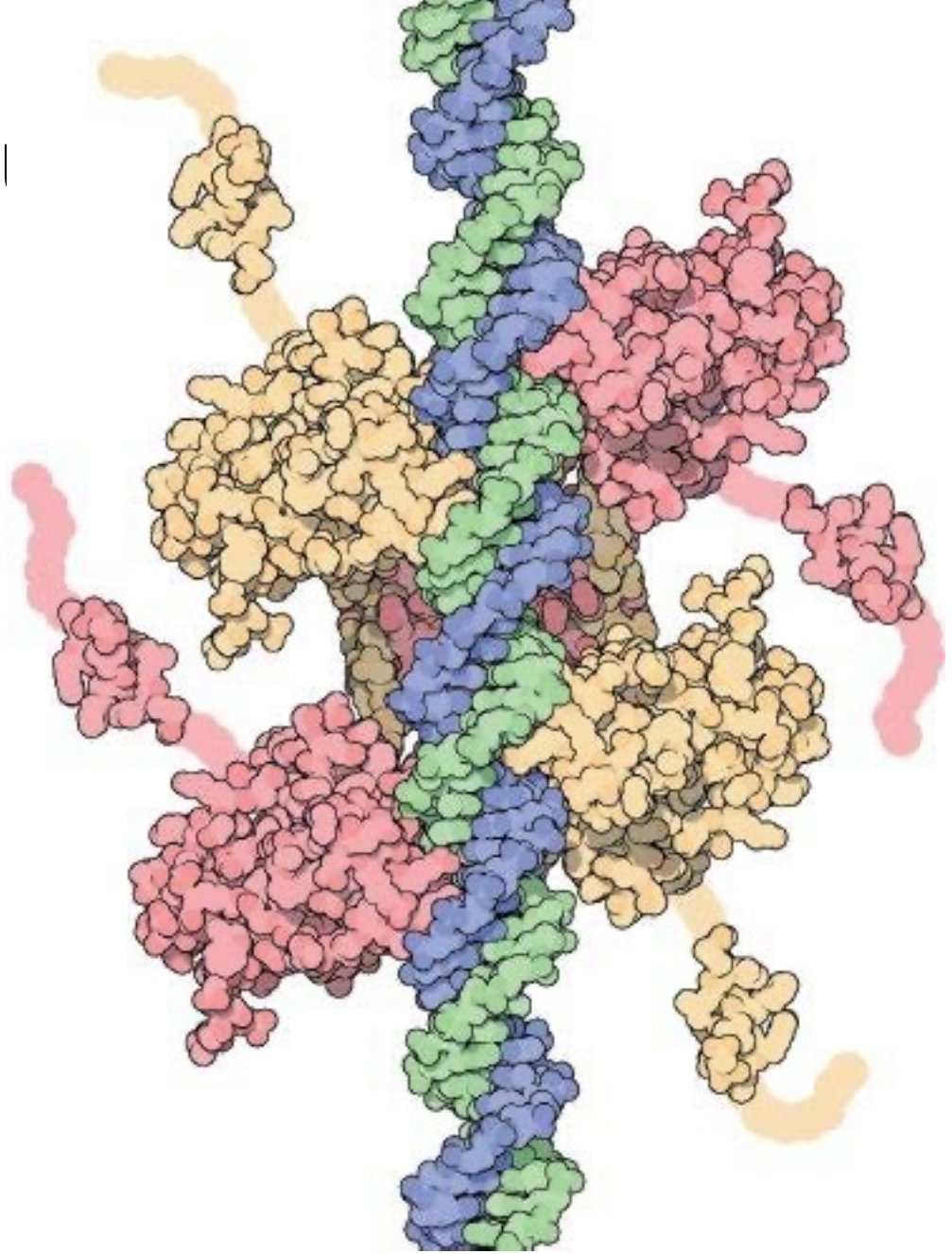
Understanding tumorigenic mutations





Understanding tumorigenic m





Isozymes

Isozymes or Isoenzymes are proteins with different structure which catalyze the same reaction.

Frequently they are oligomers made with different polypeptide chains, so they usually differ in regulatory mechanisms and in kinetic characteristics.

From the physiological point of view, isozymes allow the existence of similar enzymes with different characteristics, “customized” to specific tissue requirements or metabolic conditions.

The existence of isozymes permits the fine-tuning of metabolism to meet the needs of a given tissue or developmental stage.

Lactate Dehydrogenase

Muscle heart

$$\text{pyruvate} + \text{NADH} \rightleftharpoons \text{lactate} + \text{NAD}^+$$

M_4

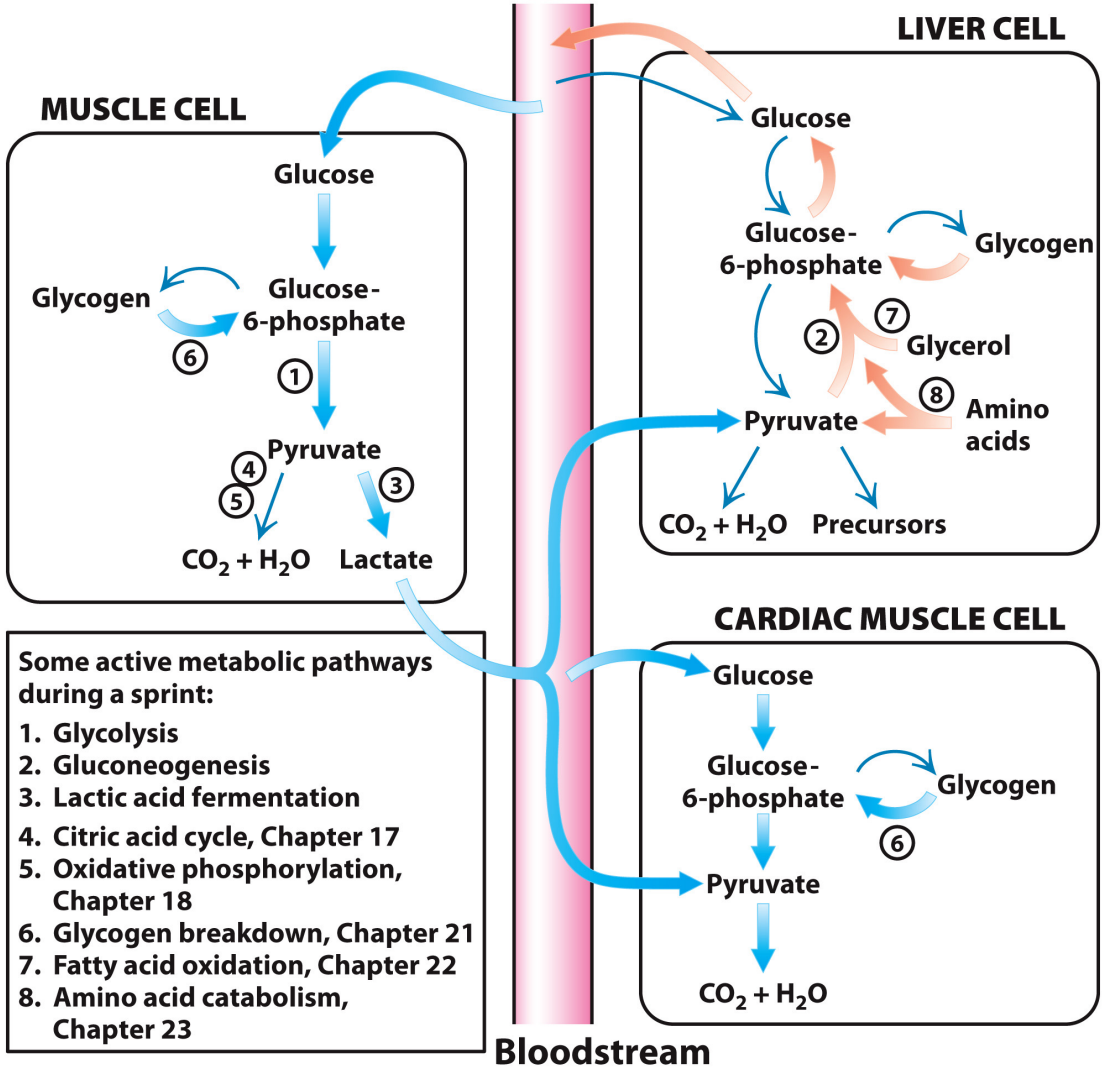


Figure 16.34
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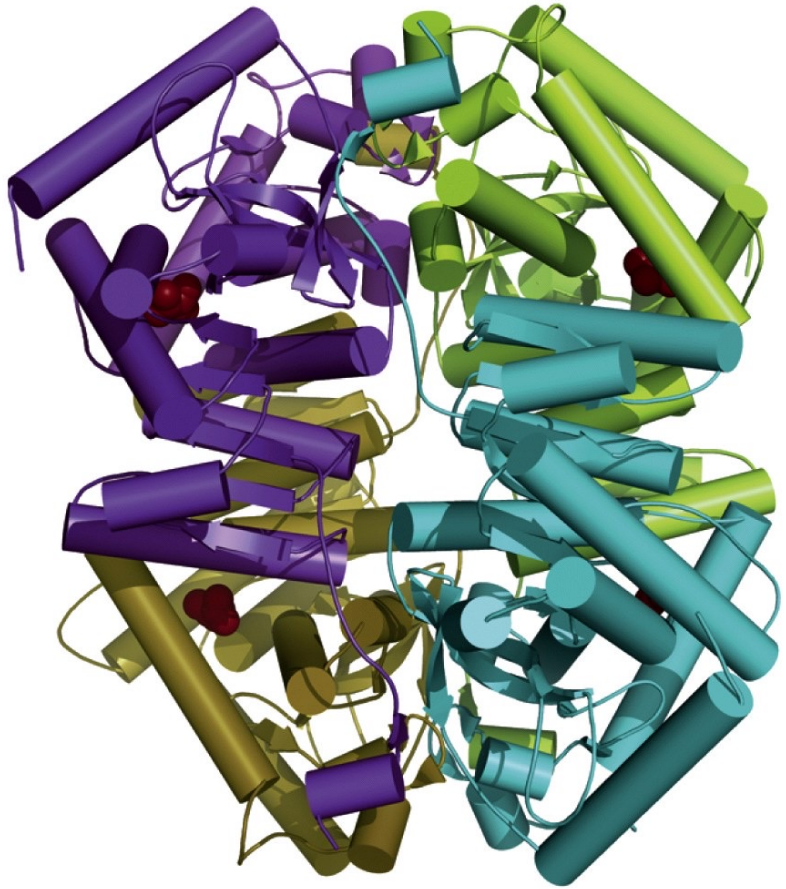
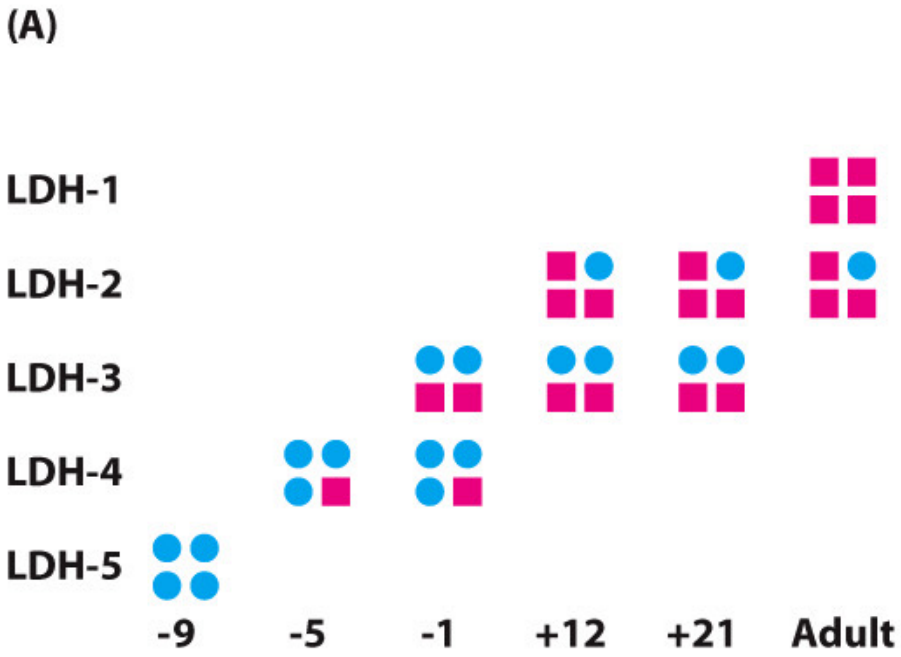


Figure 3.41 How Proteins Work (©2012 Garland Science)

Lactate Dehydrogenase

H isozyme by squares
M isozyme by circles

$$\text{pyruvate} + \text{NADH} \rightleftharpoons \text{lactate} + \text{NAD}^+$$



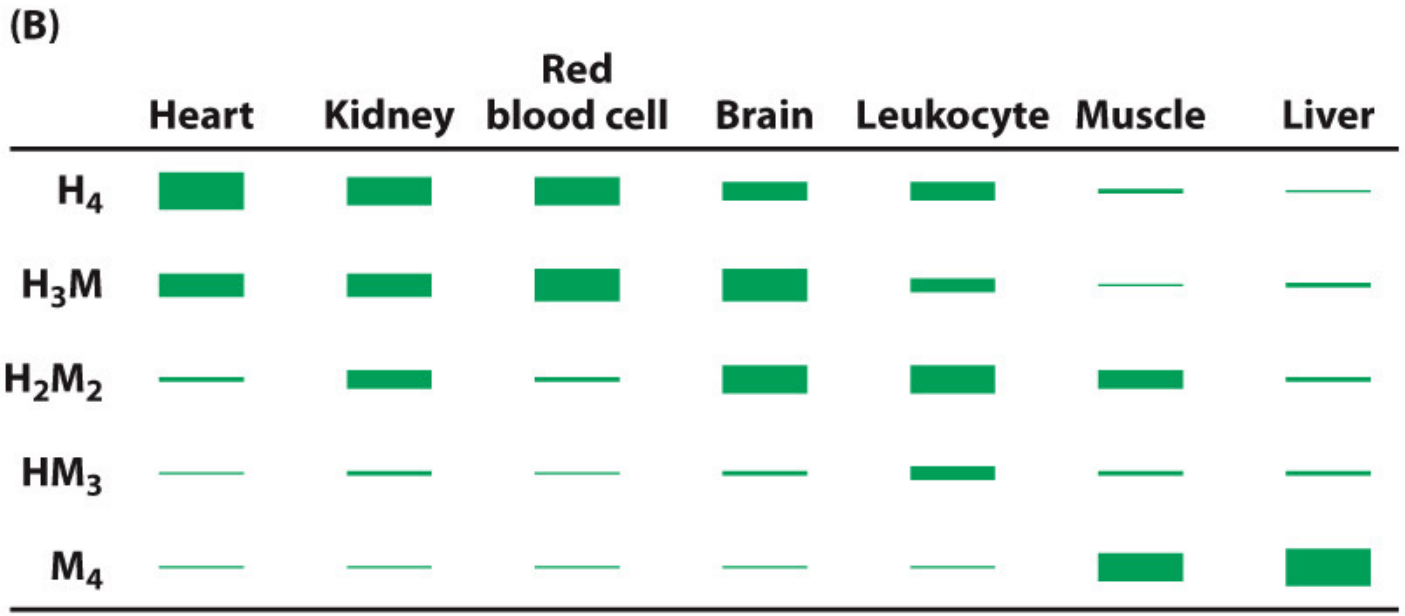


Figure 10.15
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