Information transfer

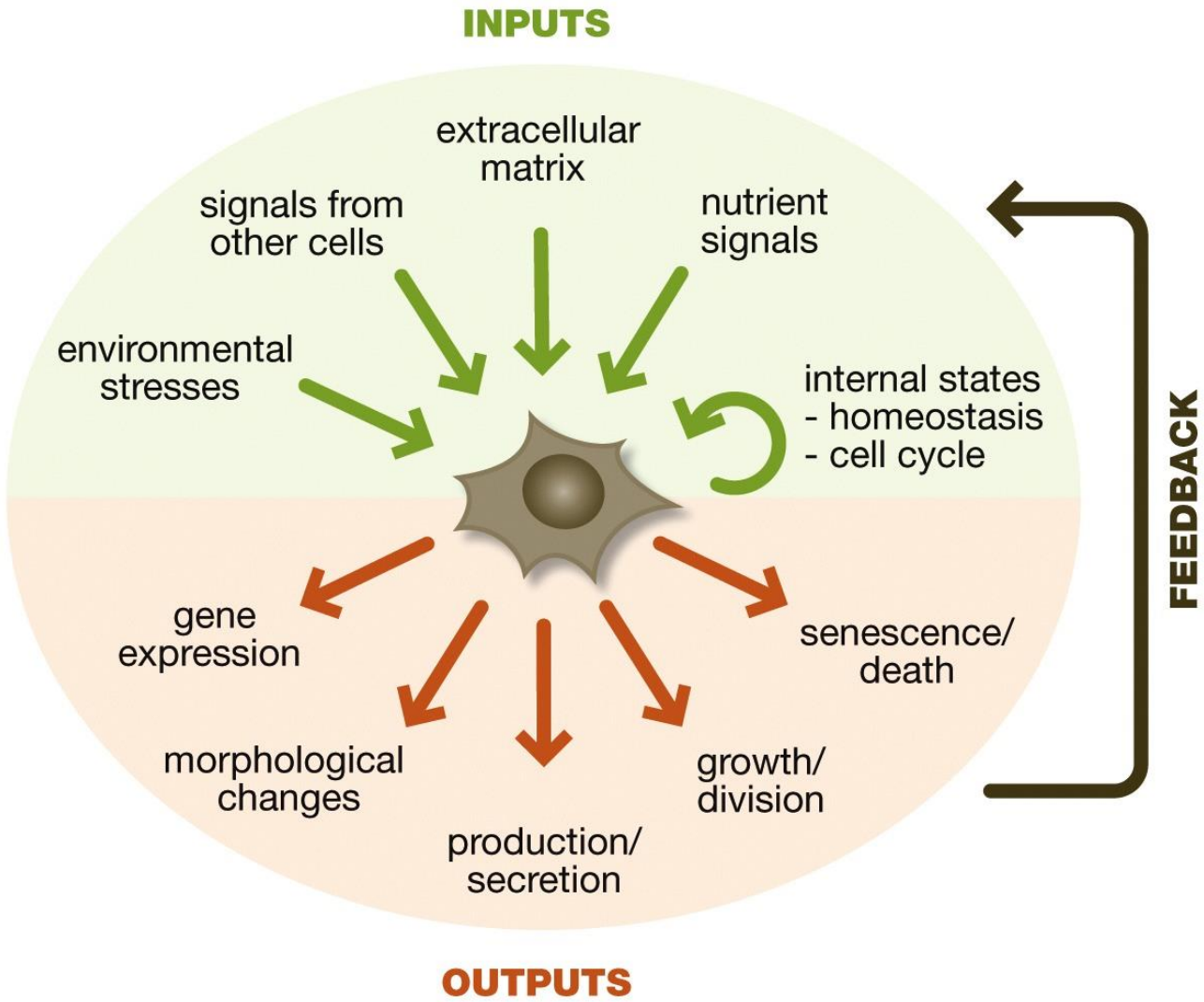
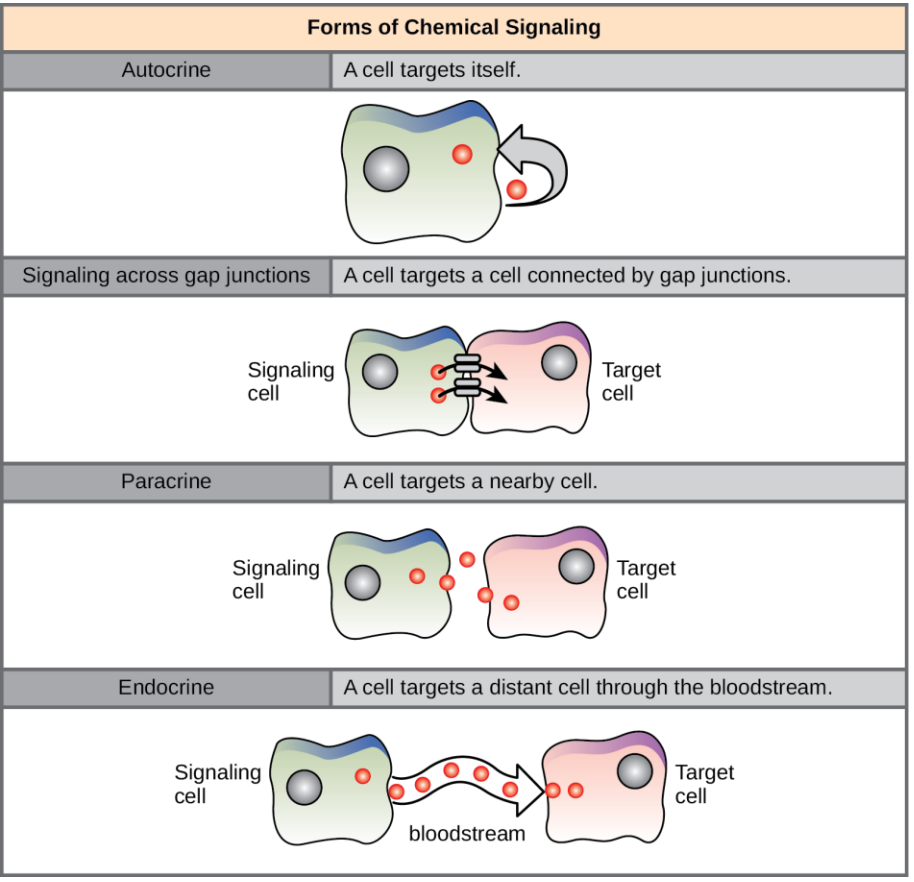
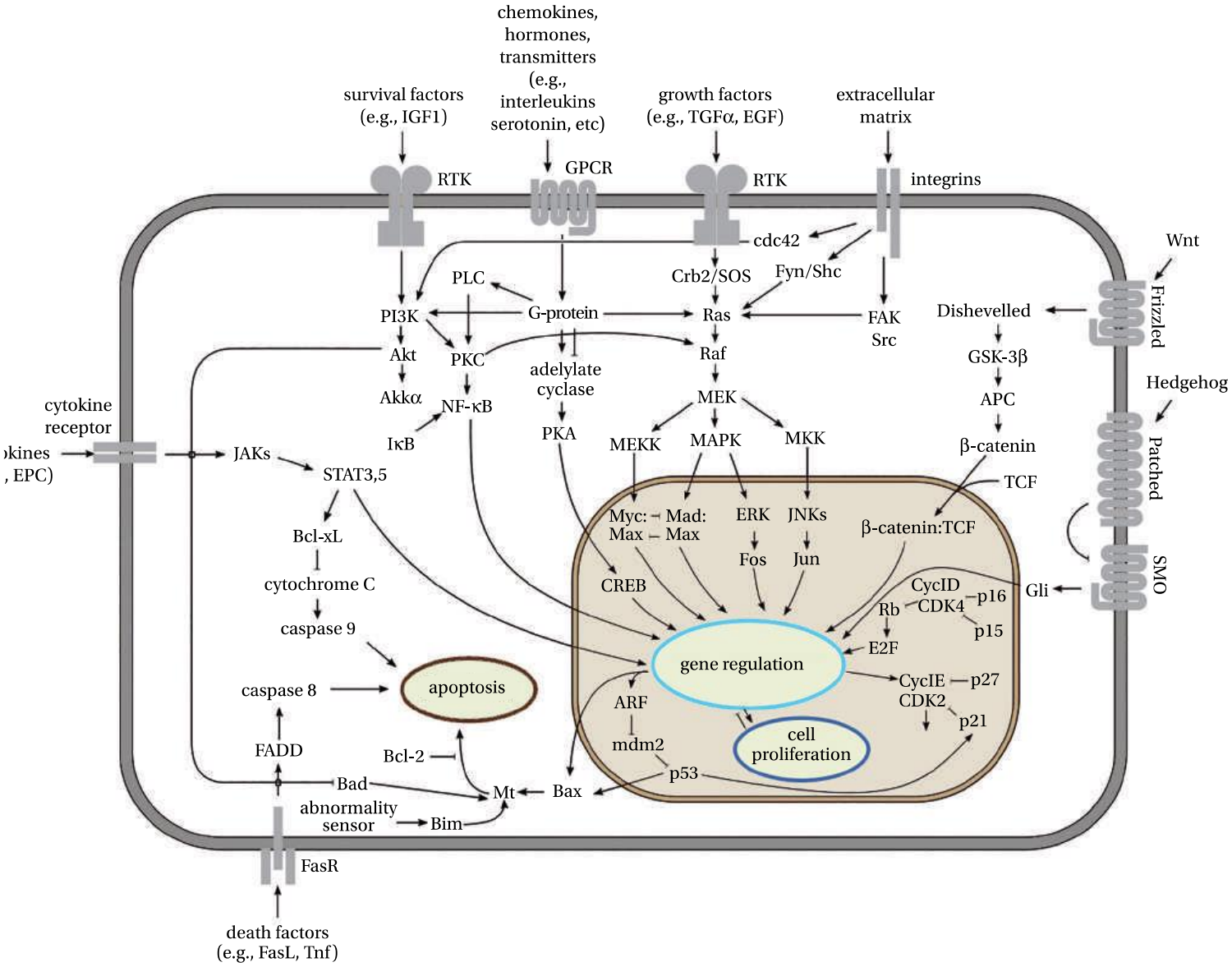


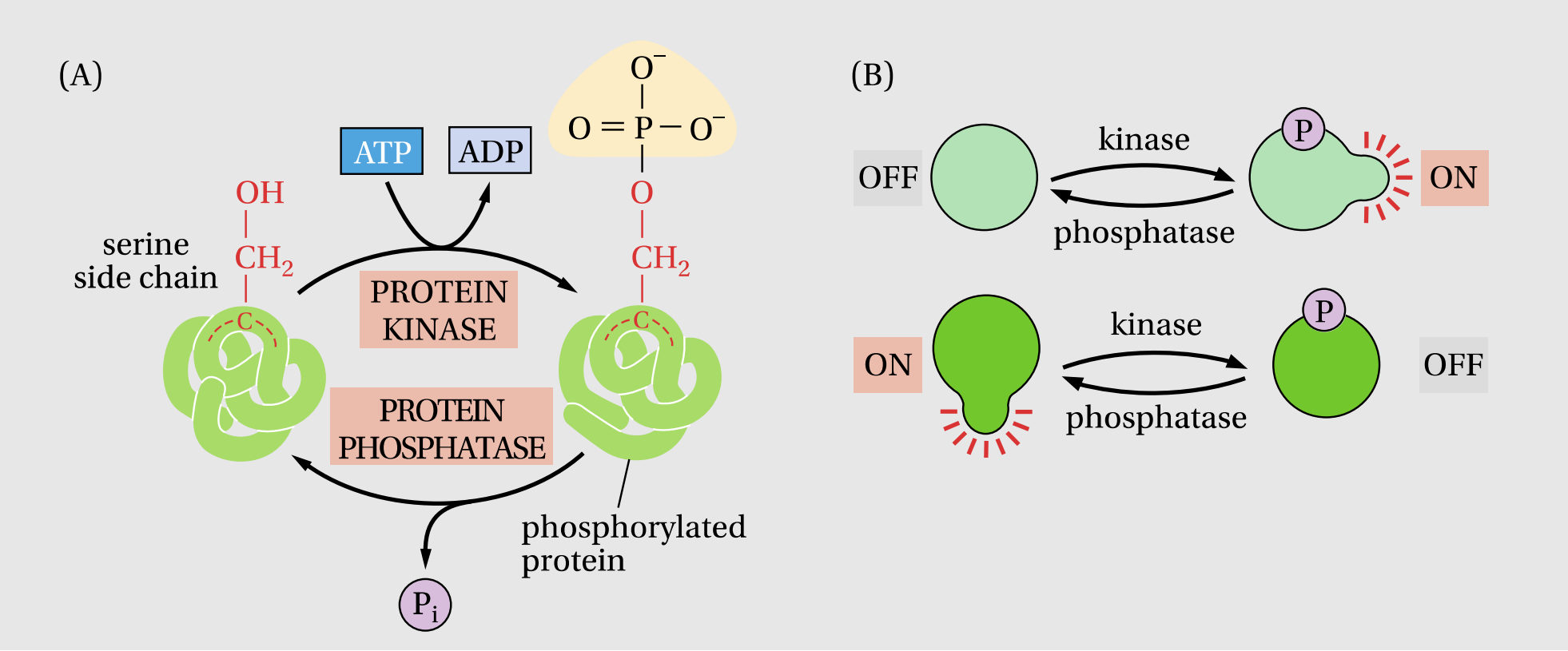
Figure 1.2 Cell Signaling (© Garland Science 2015)

The signal transduction pathways in eukaryotes





signals


(A)
ATP
ADP
O⁻
O = P − O⁻
OH
CH2
serine
side chain
C
PROTEIN
KINASE
O
CH2
C
PROTEIN
PHOSPHATASE
phosphorylated
protein
Pi
(B)
OFF
kinase
P
ON
phosphatase
ON
kinase
P
OFF
phosphatase

transfer of information across the membrane

Receptors

Multiple membrane spanning

Single membrane spanning

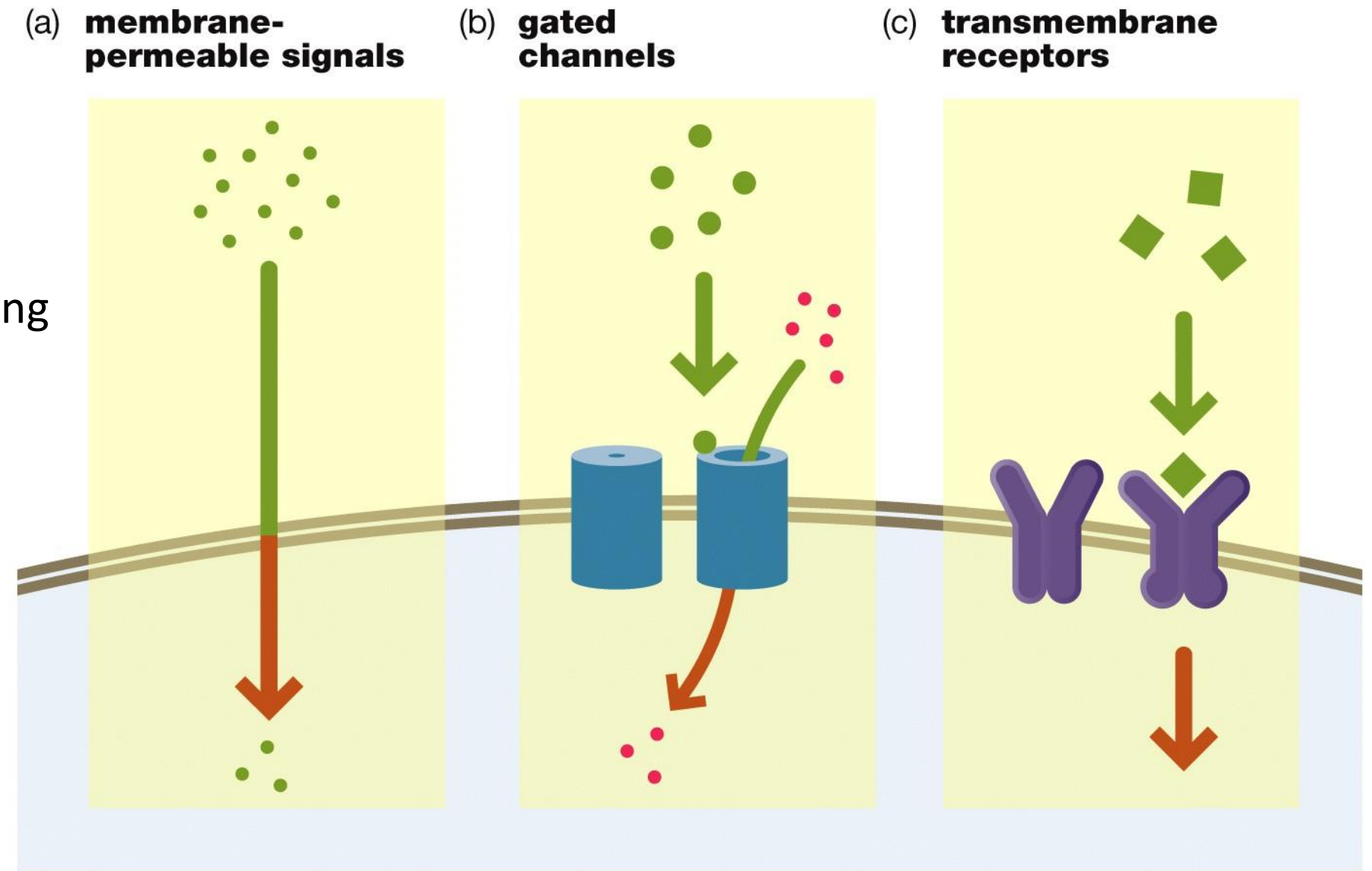
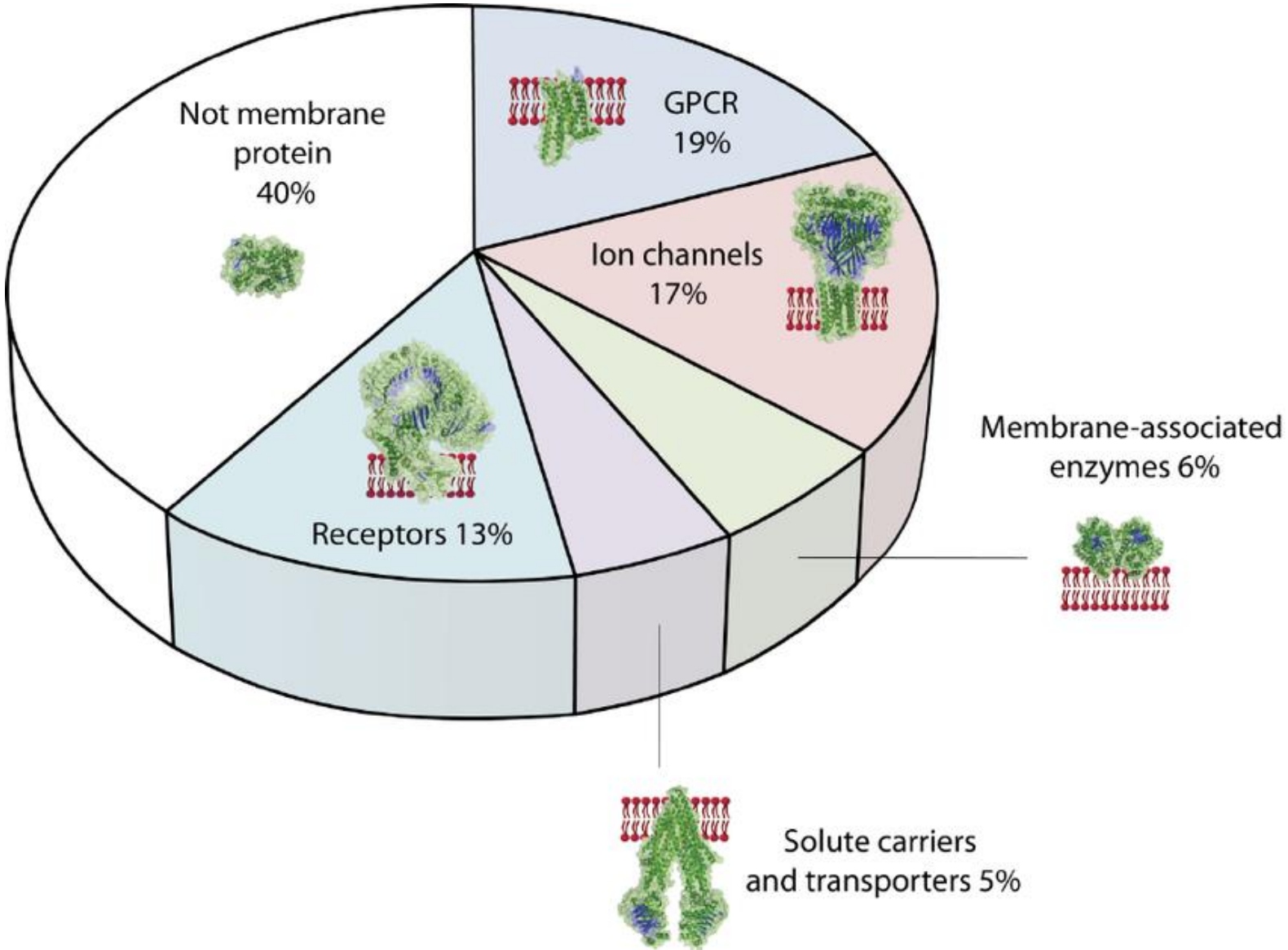


Figure 8.2 Cell Signaling (© Garland Science 2015)

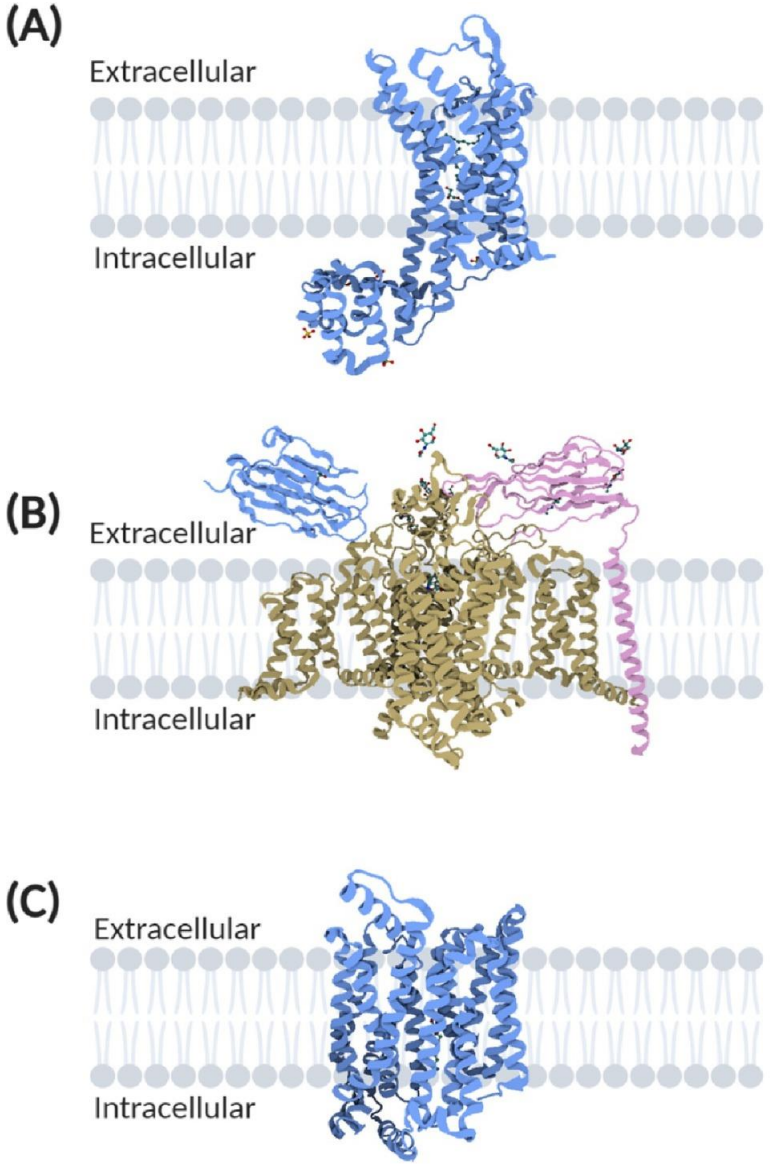
Human membrane proteins as drug targets

G protein-coupled receptors (GPCRs) are cell-surface receptors mediating the responses of 2/3^{rds} of human hormones[1] and 1/3rd of drugs.

Each GPCR can bind several transducers, G proteins, GPCR kinases (GRKs) and arrestins leading to distinct intracellular signaling networks and functional outcomes.

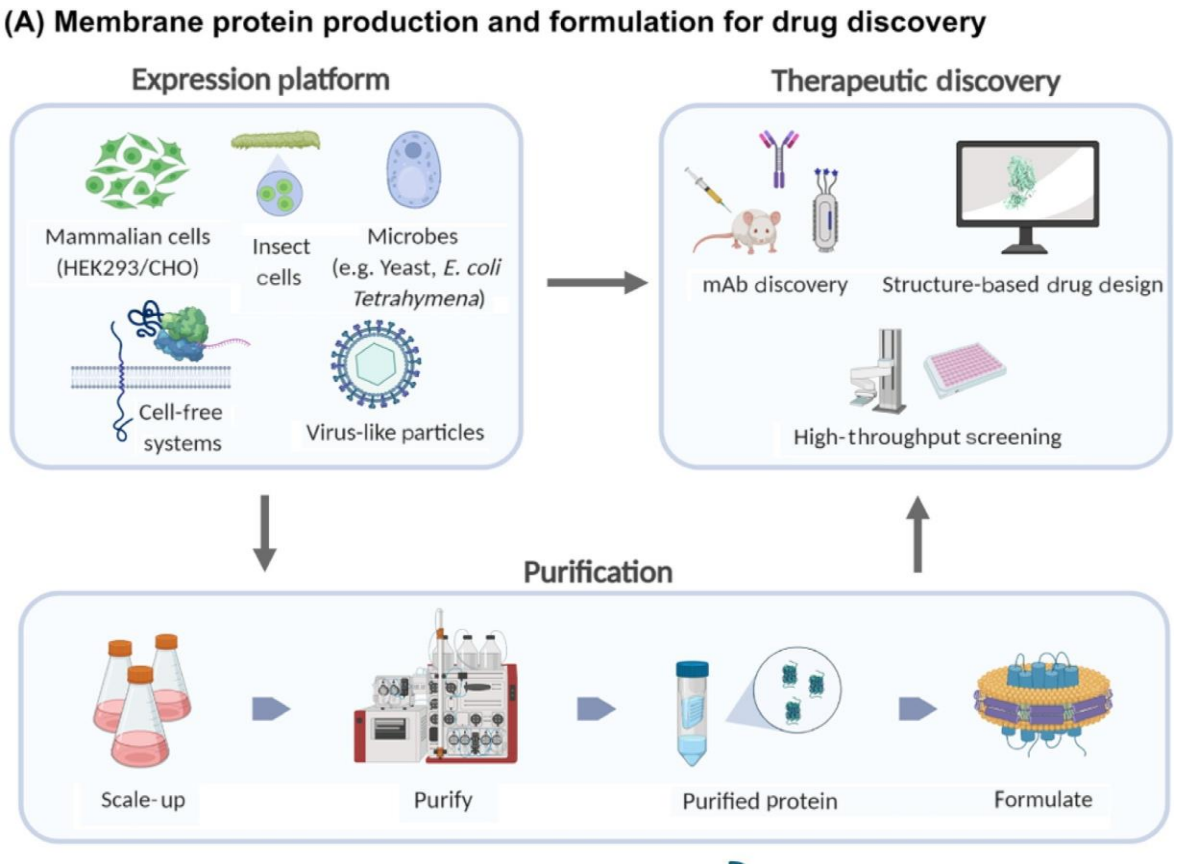


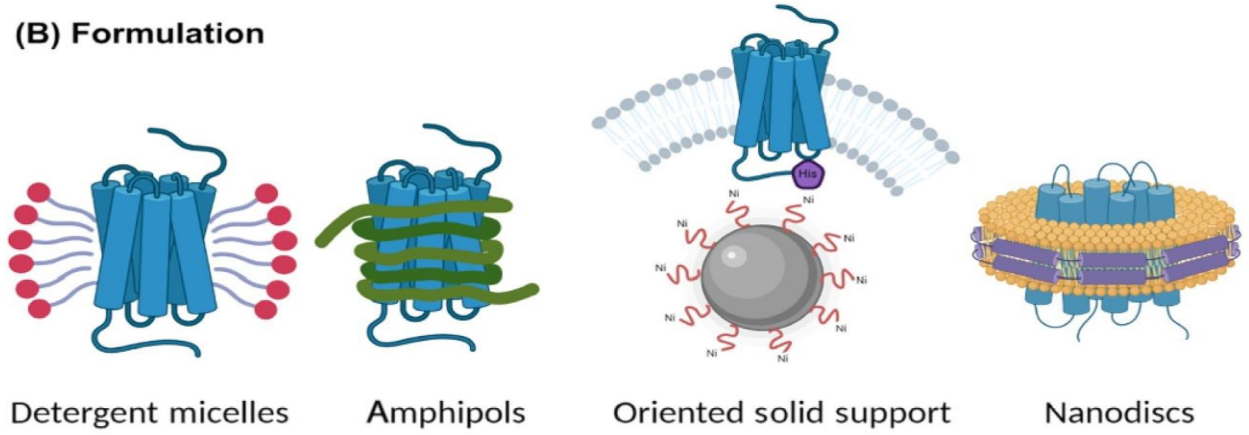
Membrane protein production and formulation for drug discovery

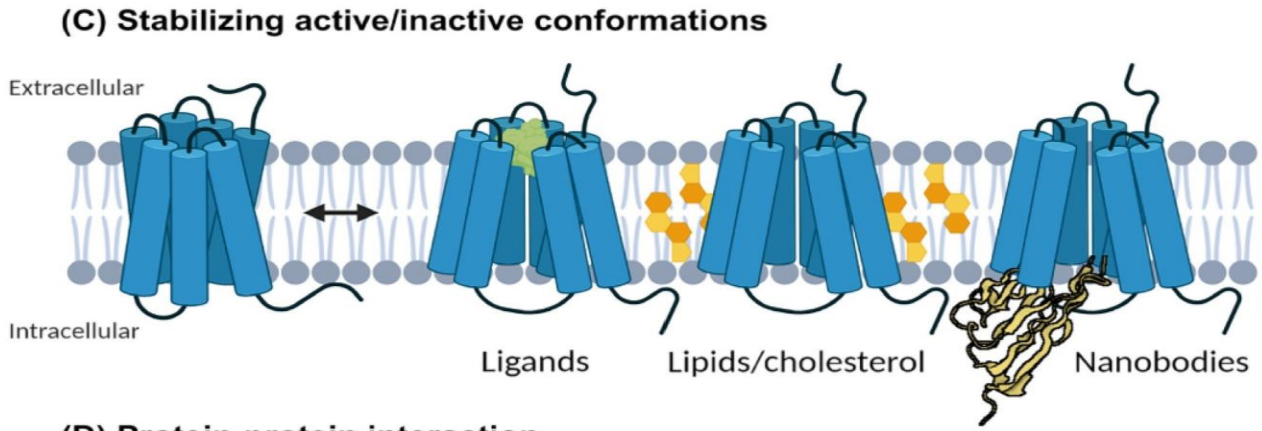


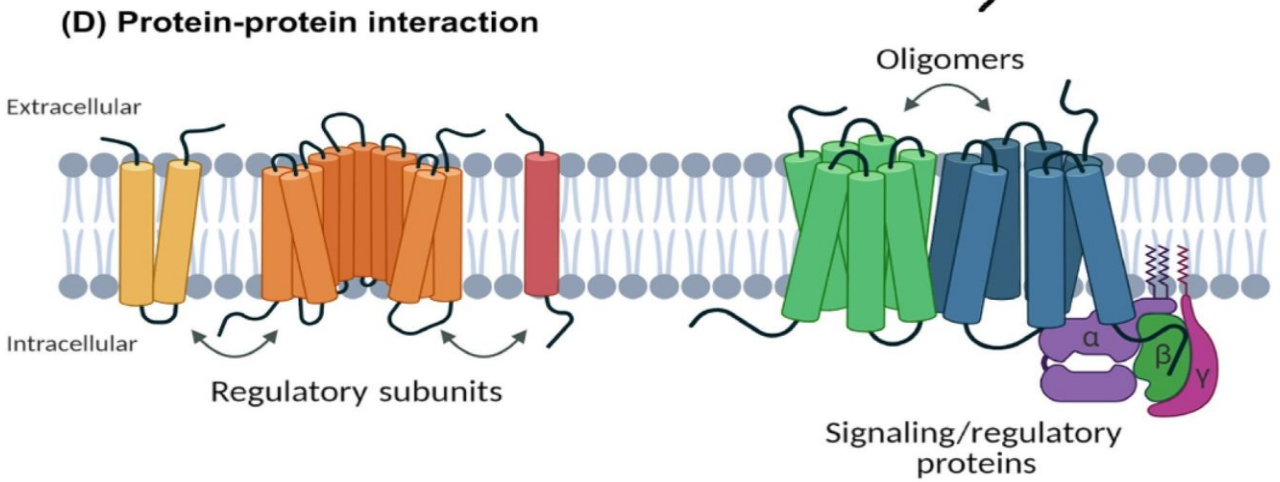
Trends in Pharmacological Sciences 2021 42657-674DOI: (10.1016/j.tips.2021.05.006)

Production









Trends in Pharmacological Sciences

Sense

Humans have five major sensory systems:

1.Olfaction—smell

Nobel Prize in Physiology or Medicine 2004 Richard Axel and Linda B. Buck
"for their discoveries of odorant receptors and the organization of the olfactory system."

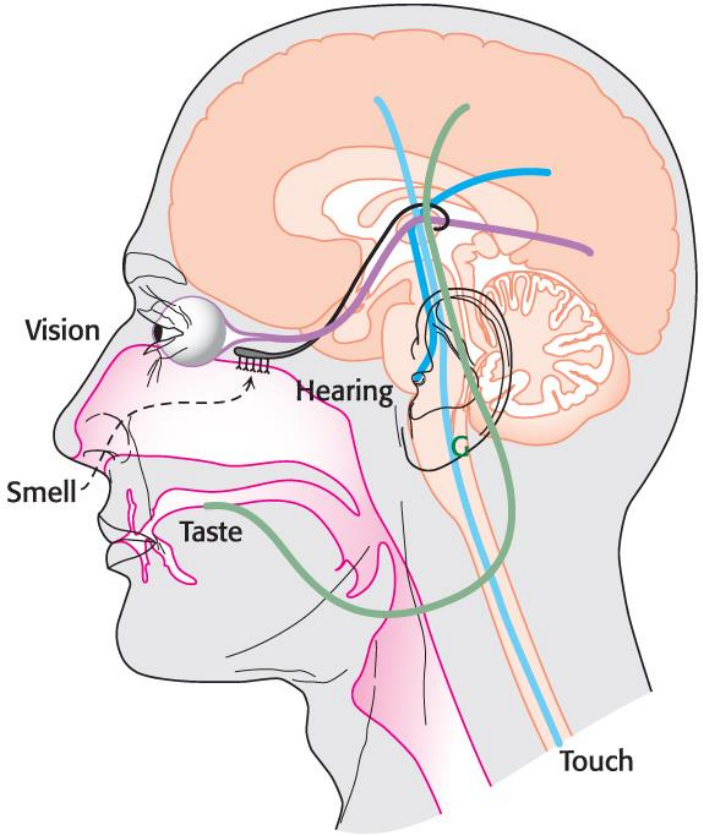
2.Gustation—taste

3.Vision

4.Hearing

5.Touch

Nobel Prize in Physiology or Medicine 2021 David Julius and Ardem Patapoutian
"for their discoveries of receptors for temperature and touch"



Berg et al., *Biochemistry*, 9e, © 2019
W. H. Freeman and Company

Each of the sensory systems has specialized sensory neurons that convey nerve impulses to the central nervous system where they are integrated and analyzed.

The family tree of human GPCRs

2013

AA2AR: adenosine receptor A2a,

OPRD: δ-type opioid receptor,

PAR1: proteinase-activated receptor 1,

PAR2: proteinase-activated receptor 2,

ADRB1: β-1 adrenergic receptor,

DRD4: dopamine D4 receptor,

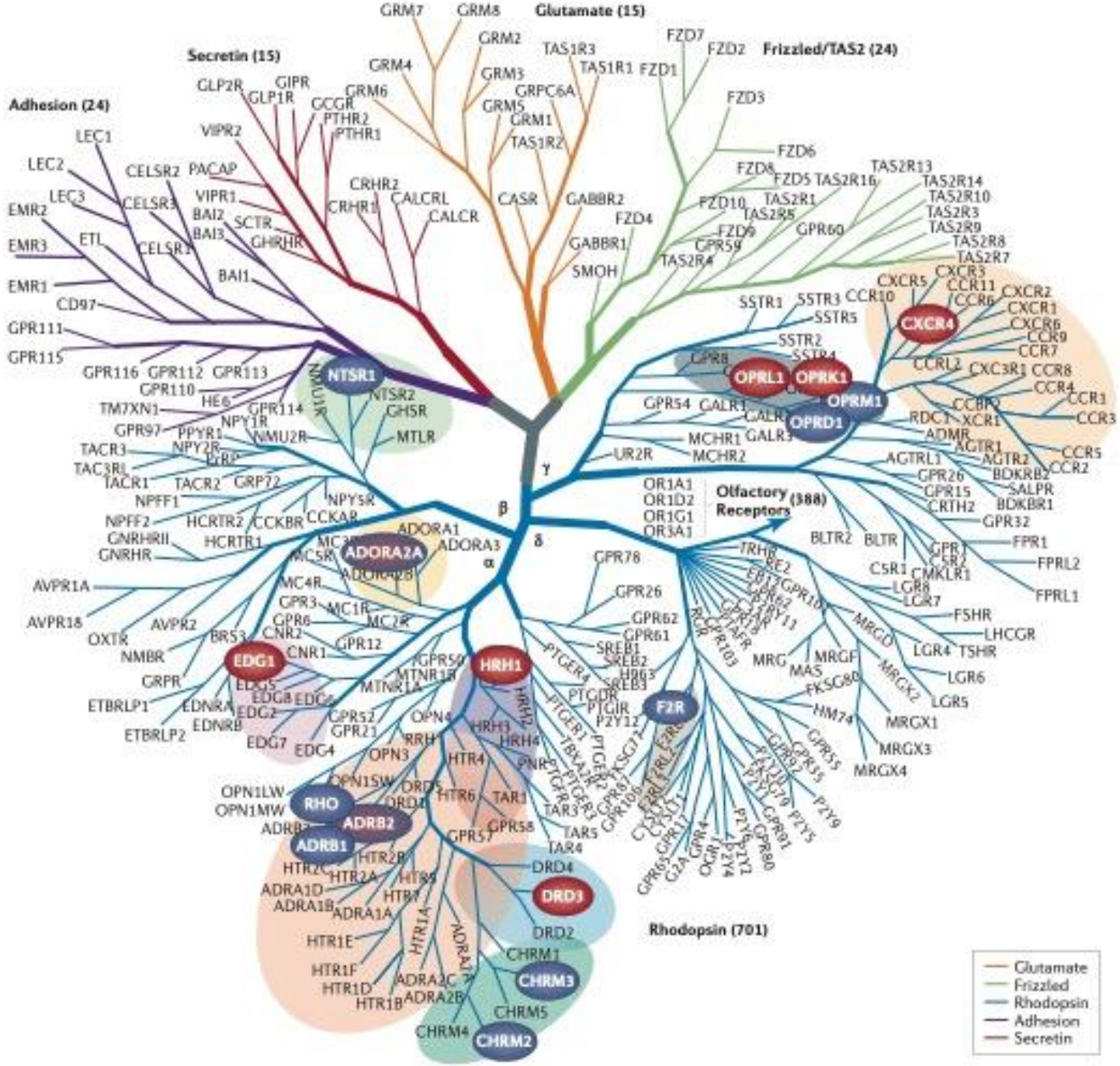
CLTR1: Cysteinyl leukotriene receptor 1

2022

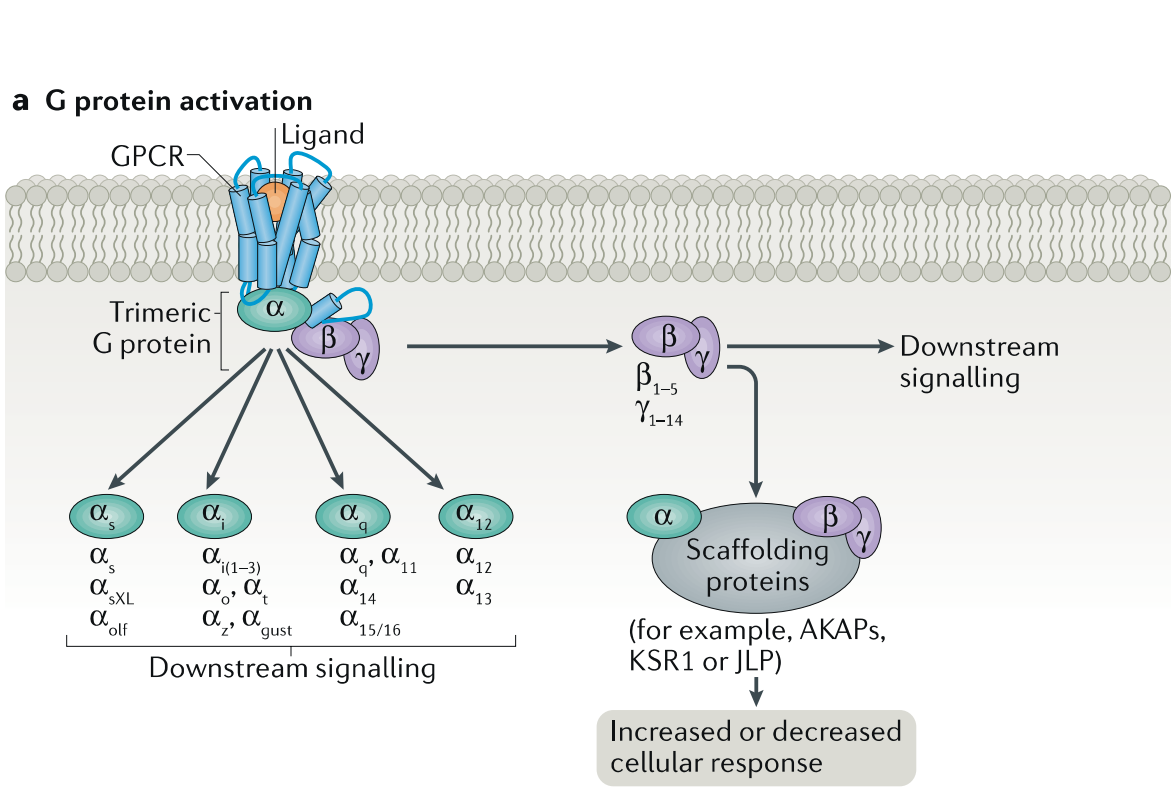
https://gpcrdb.org

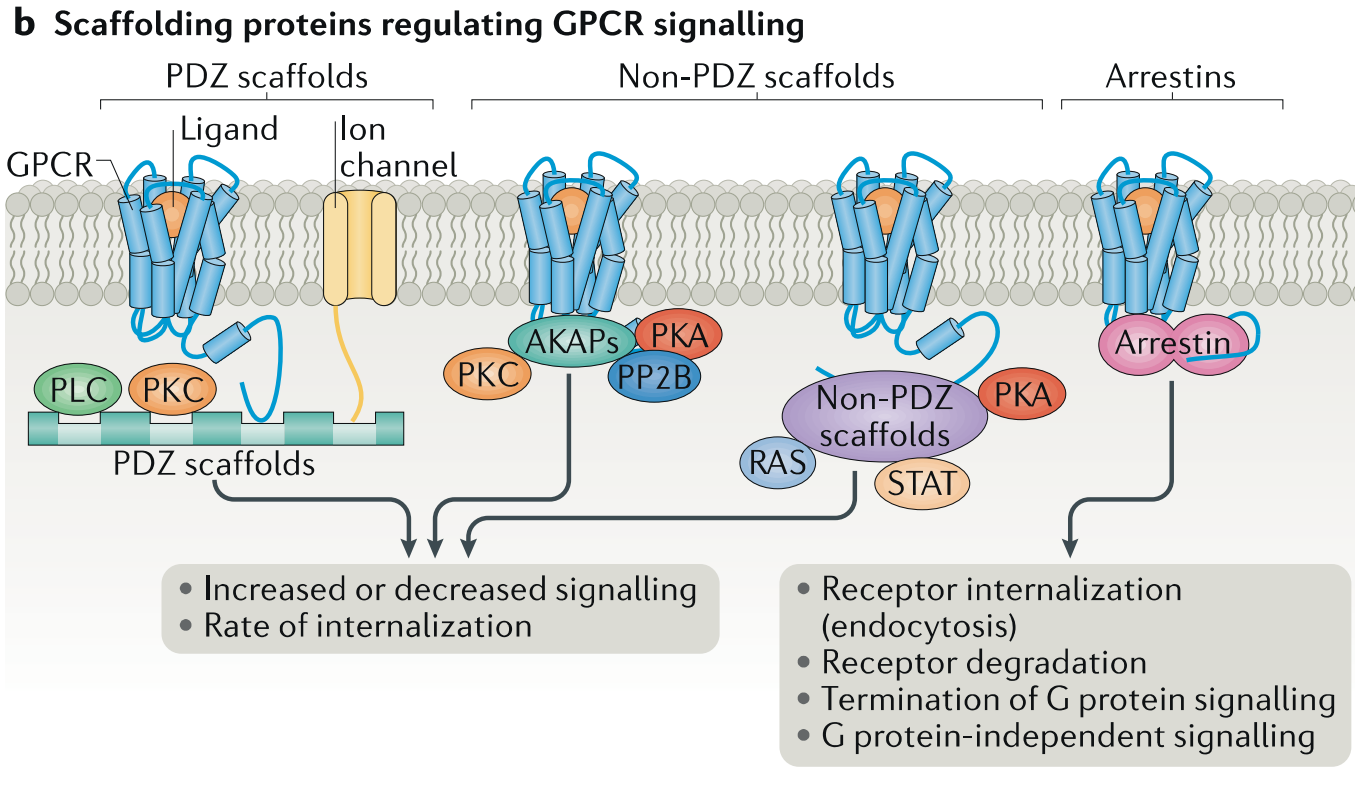
Data

- 423 Human proteins
- 974 Drugs
- 174 Drug targets
- 411Disease indications
- 793GPCRs structures
- 844GPCRs structure models
- 2,910 Generic residues
- 663Refined structures



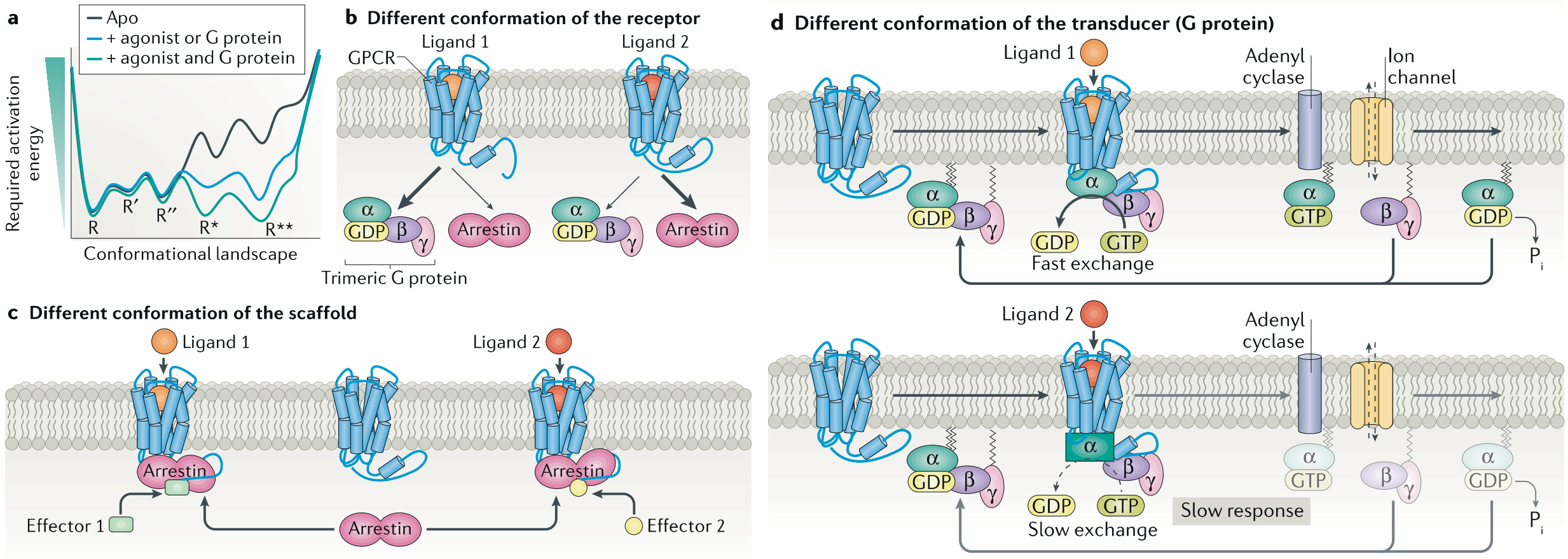
Signaling through G-protein coupled receptors (GPCRs)





NATuRE REvIEWS | MOLeCULAR CeLL BiOLOGy
https://doi.org/10.1038/ s41580-018-0049-3

GPCR signalling



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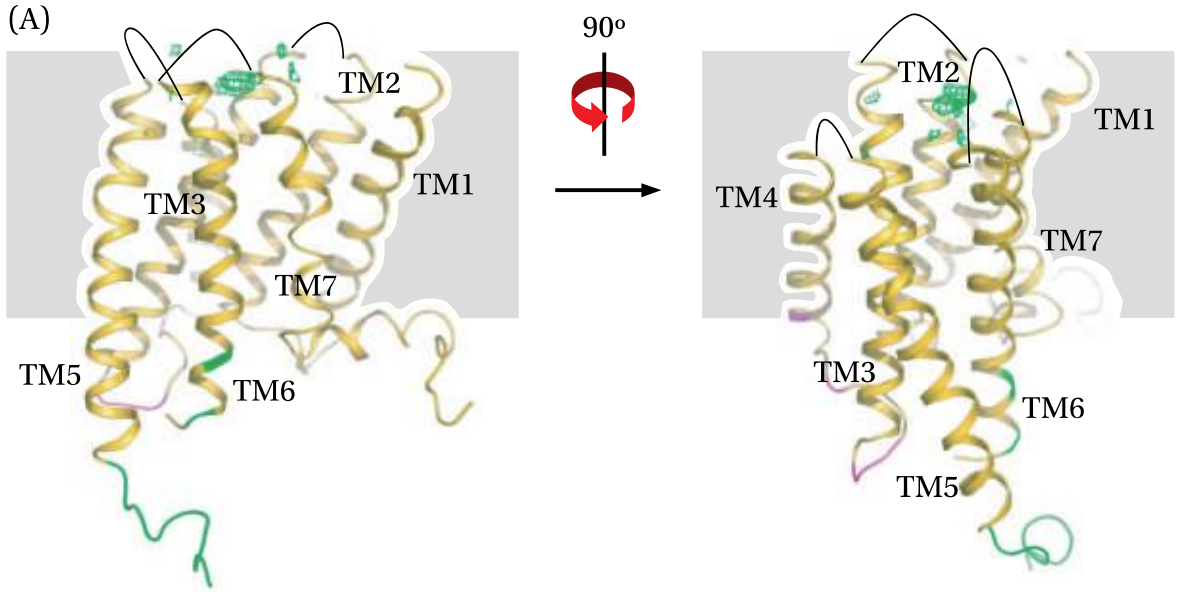
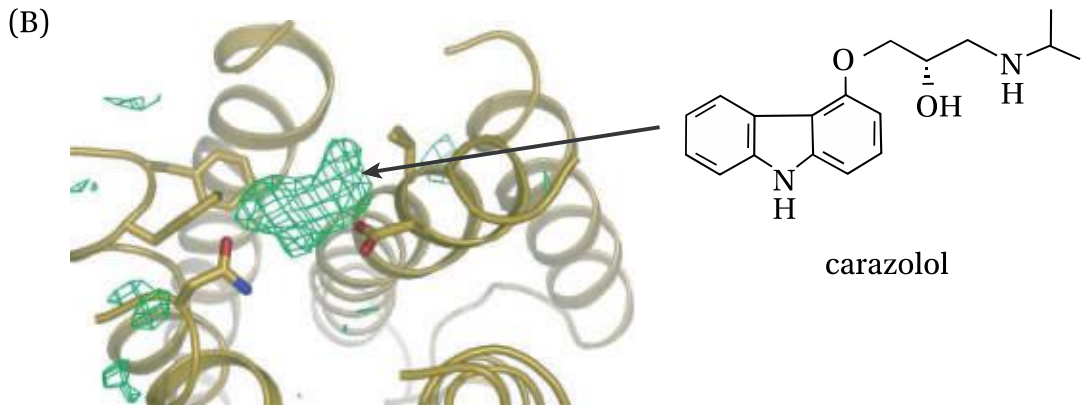
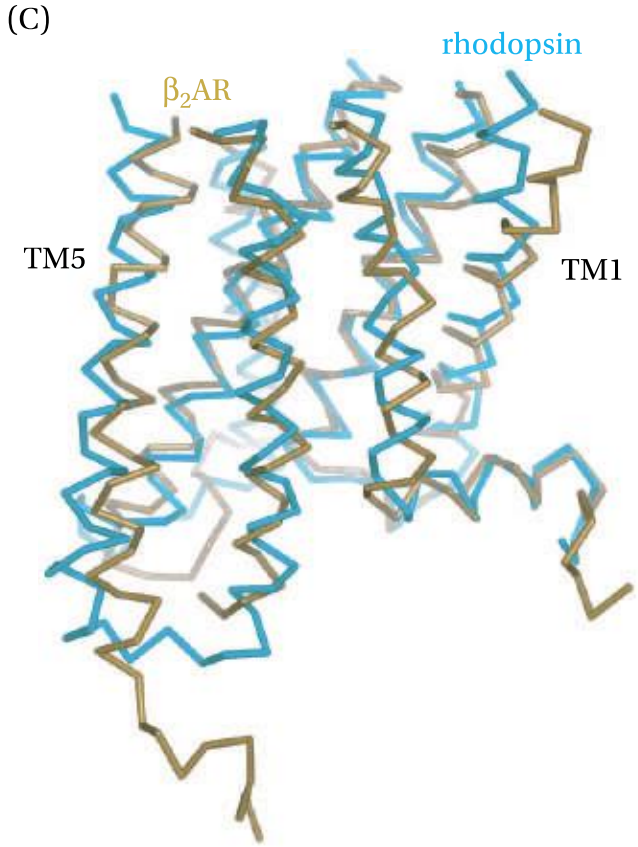
https://doi.org/10.1038/ s41580-018-0049-3

structures of rhodopsin and β2 adrenergic receptor



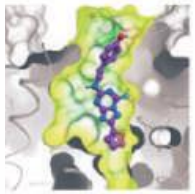
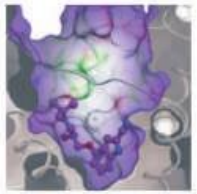
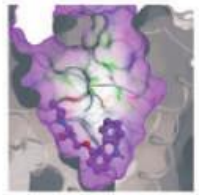
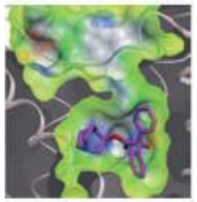
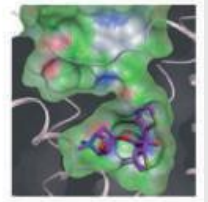
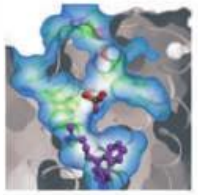
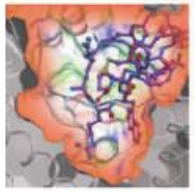
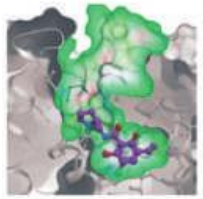
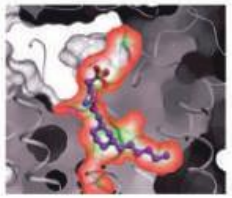
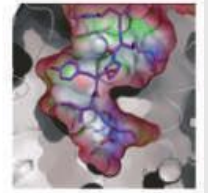
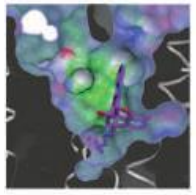
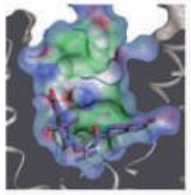
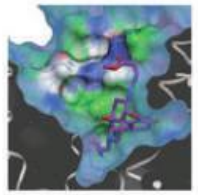
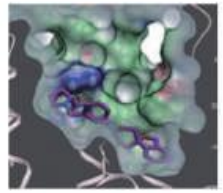
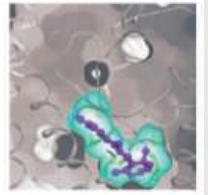




Robert Lefkowitz and Brian Kobilka were awarded the Nobel Prize in Chemistry in 2012 for their work on the β adrenergic receptor.

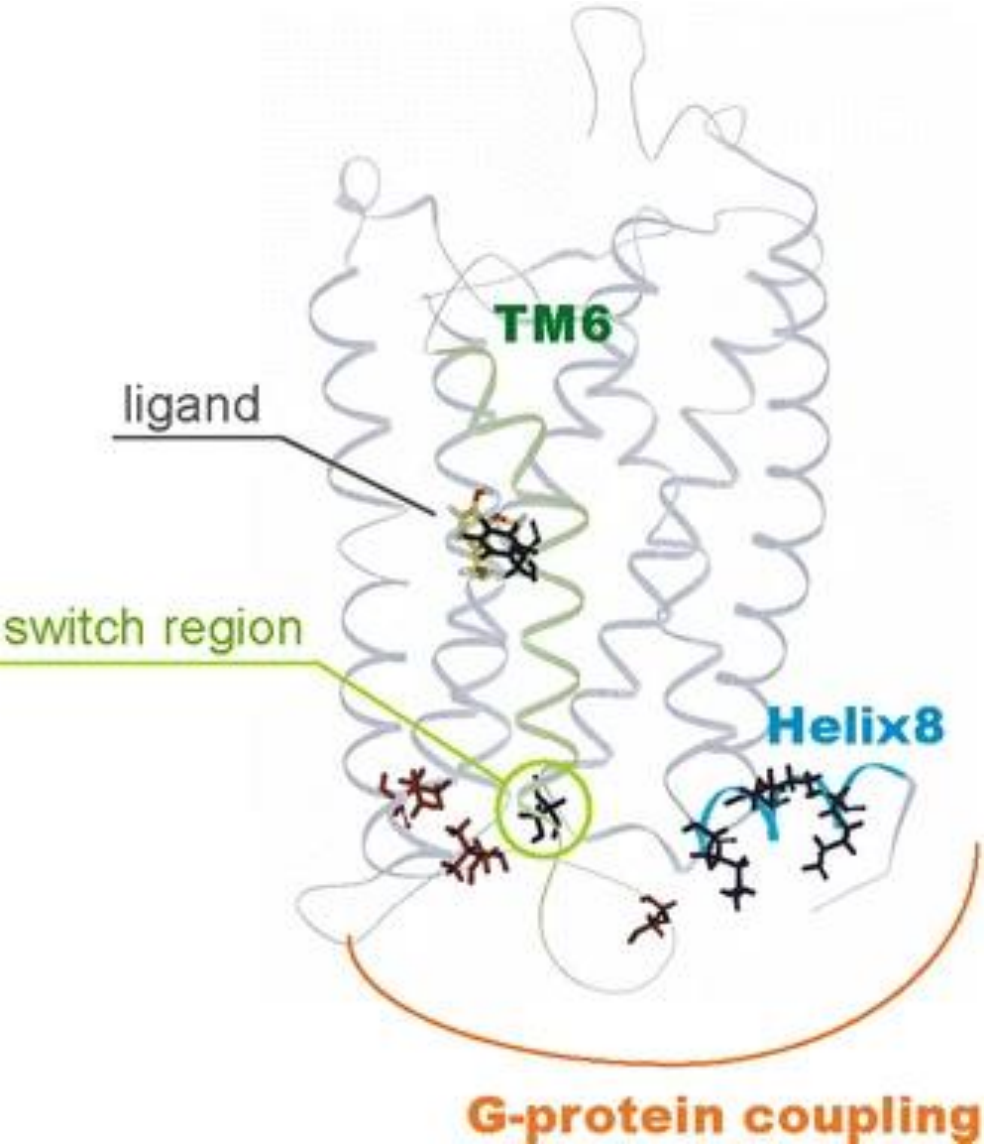
Binding pocket

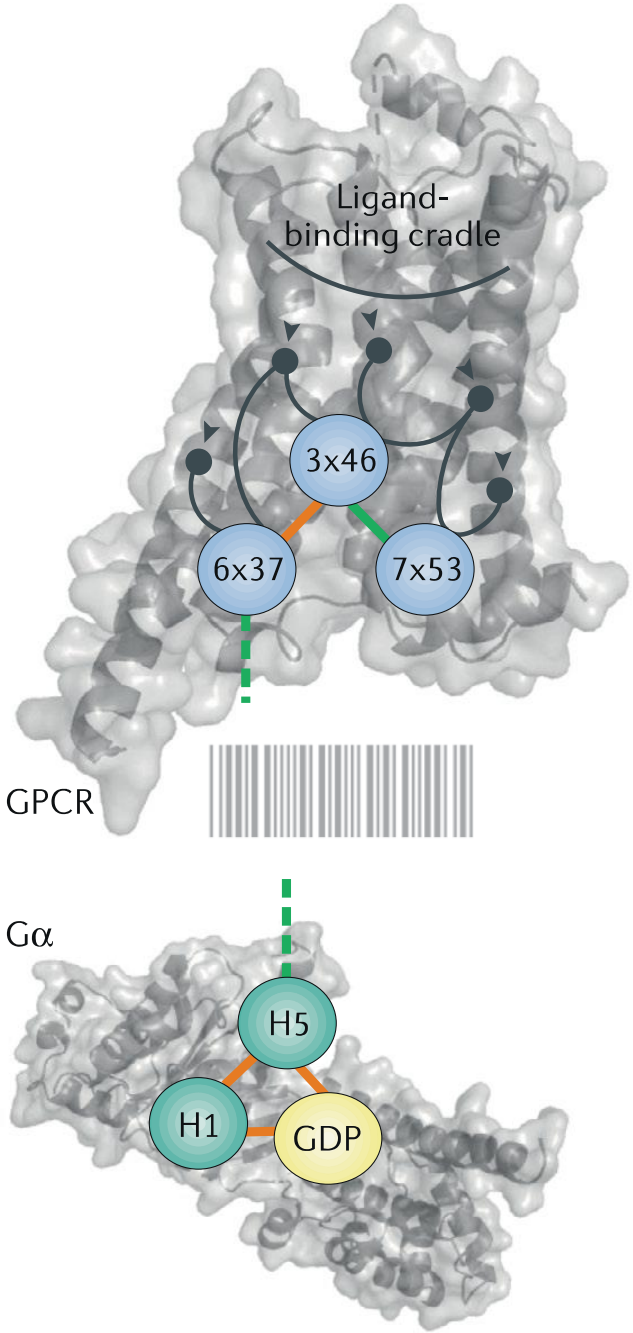
BOX 15.3 GPCRS HAVE CHARACTERISTIC BINDING POCKETS FOR EACH LIGAND

adenosine A_{2A} receptor	β_1–adrenergic receptor	β_2–adrenergic receptor	muscarinic ACh receptor M_2	muscarinic ACh receptor M_3
				
caffeine	*carazolol*	*carazolol*	*3-quinuclidinyl-benzilate (antagonist)*	*tiotropium (drug)*
histamine H_1 receptor	CXC chemokine receptor 4	dopamine D_3 receptor	sphingosine-1 phosphate receptor 1	neurotensin receptor 1
				
doxepin (drug)	*CVX15 cyclic peptide inhibitor*	*eticlopride (antagonist)*	*sphingolipid mimic (antagonist)*	*neurotensin*
δ-type opioid receptor	κ–type opioid receptor	μ–type opioid receptor	opiate-receptor-like 1	rhodopsin
				
naltrindole (antagonist)	*"JDTic" (antagonist)*	*irreversible morphinan antagonist*	*peptide mimetic (antagonist)*	*retinal*

Adapted from Stevens et al. [2013] *Nature Rev Drug Discov* 12:25-34. With permission from Springer Nature.

contact networks between GPCRs and G proteins





- Ligands bind to different regions near the ligand-binding cradle of the receptor
- Diverse ligand interactions trigger distinct conformational changes across the receptor

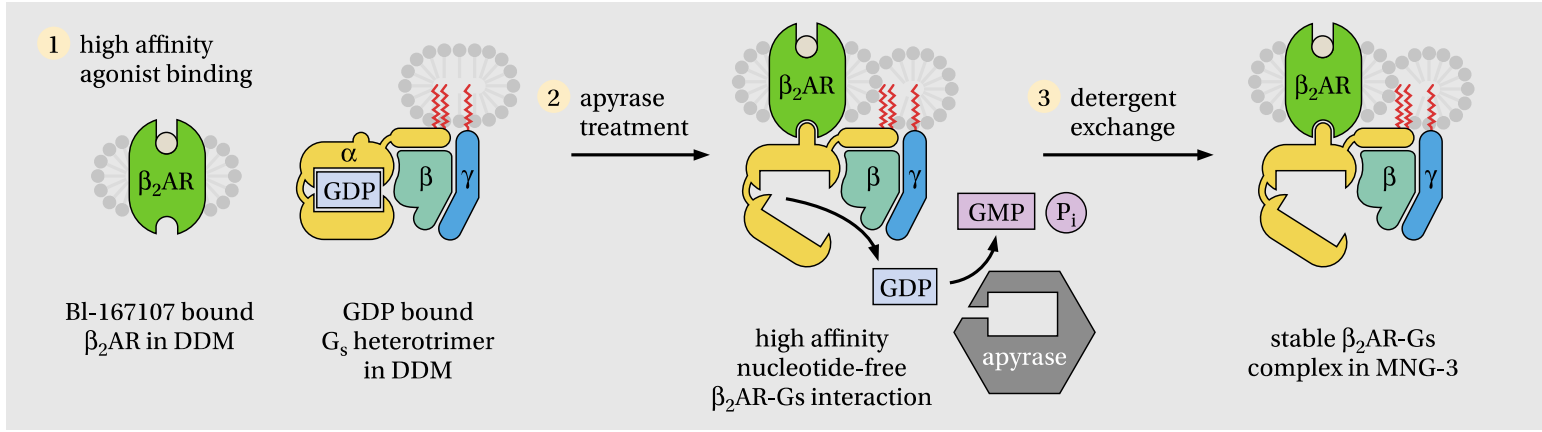
- Activation signals converge near the transducer-binding region of the receptor
- Conserved rewiring of non-covalent receptor contacts exposes G protein-binding residues

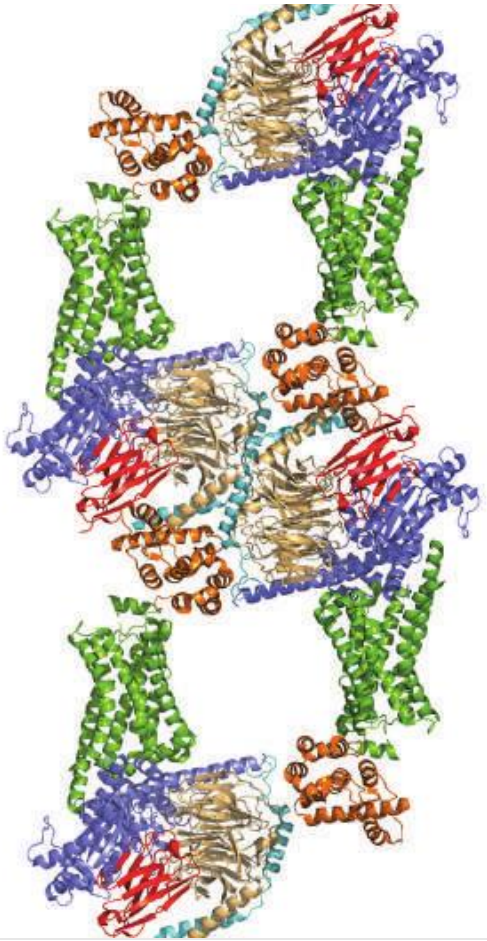
- Receptor coupling is guided by a selectivity barcode specific to each of the 16 Gα proteins
- Different receptors can read the same barcode using distinct regions and conformations

- GPCR binding induces GDP release and G protein activation
- Disruption of the H1–H5 interaction and H1 unfolding are conserved mechanisms linking GPCR binding to GDP release

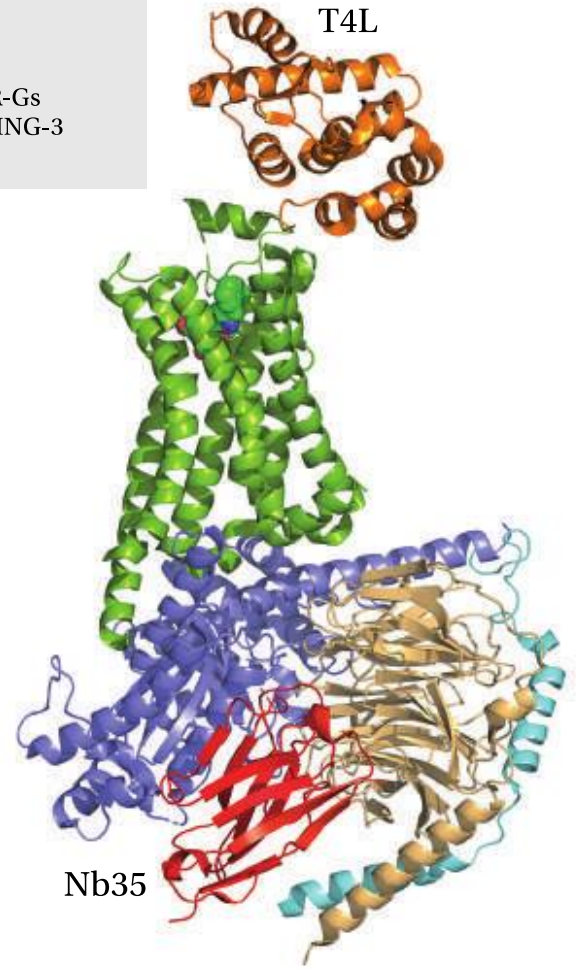
https://doi.org/10.1038/ s41580-018-0049-3

determination of a three-dimensional structure of a GPCR–G

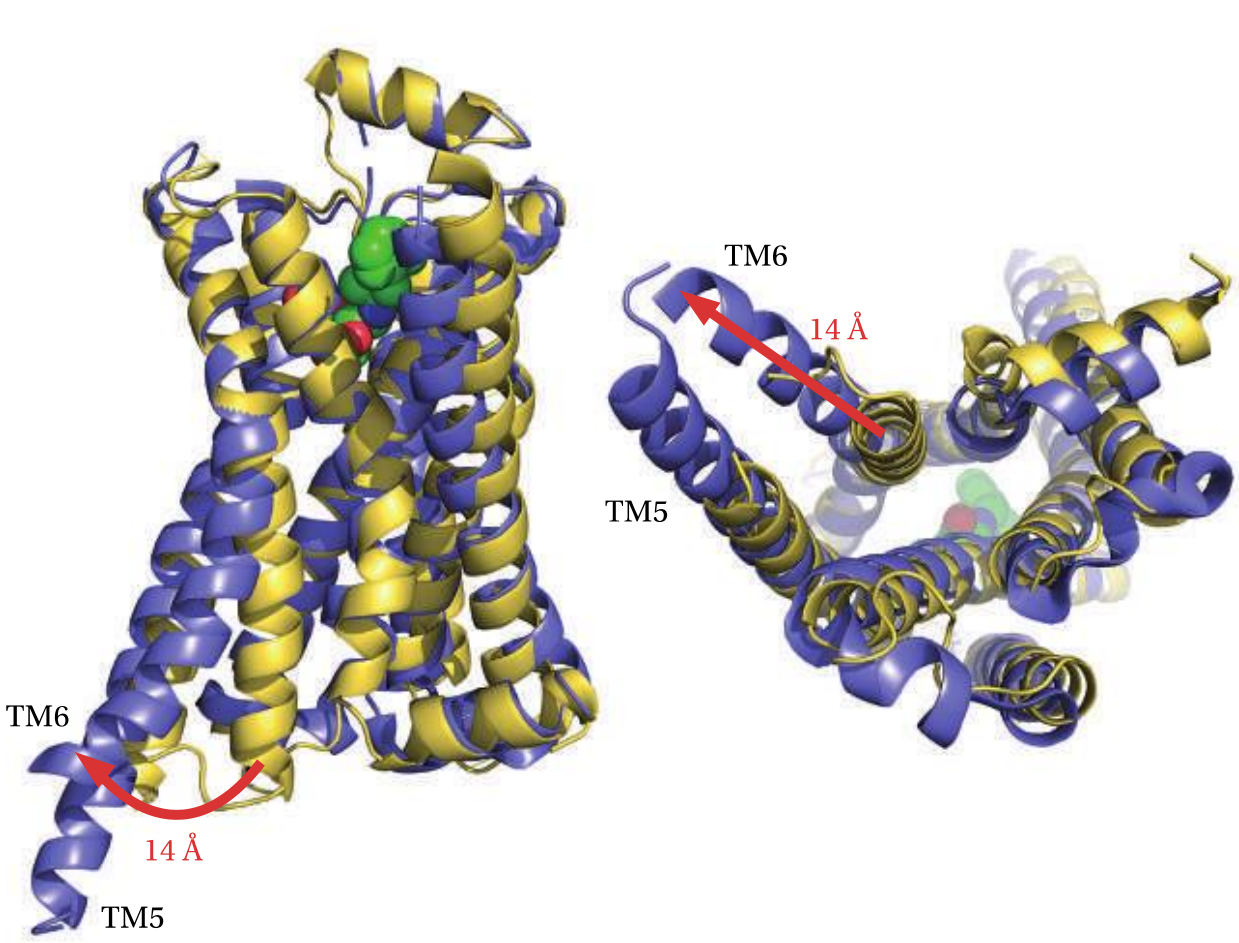


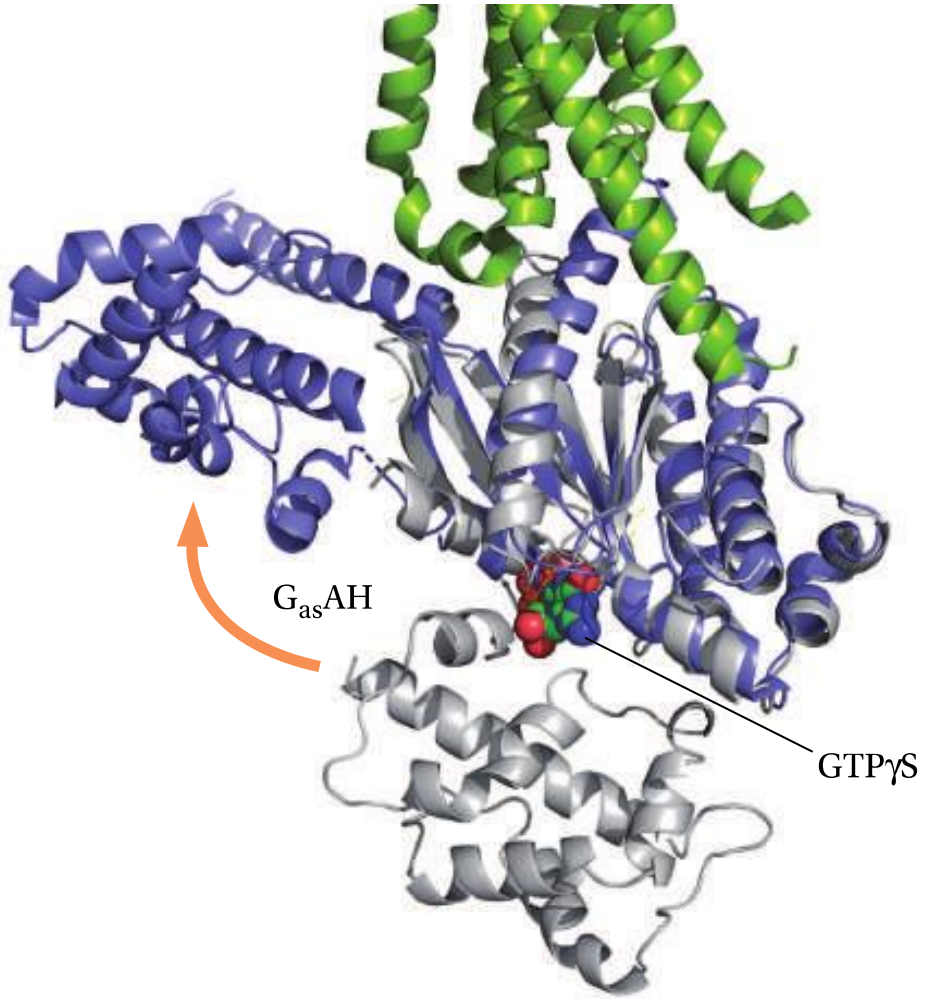


by Brian Kobilka and his collaborators in 2011.

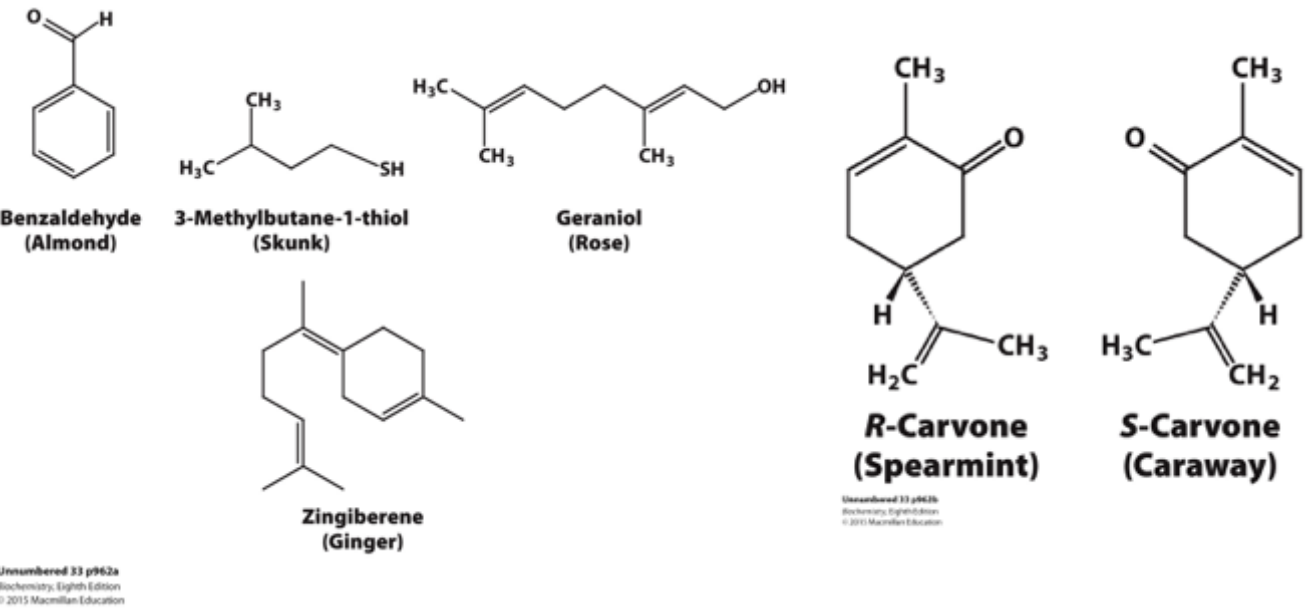


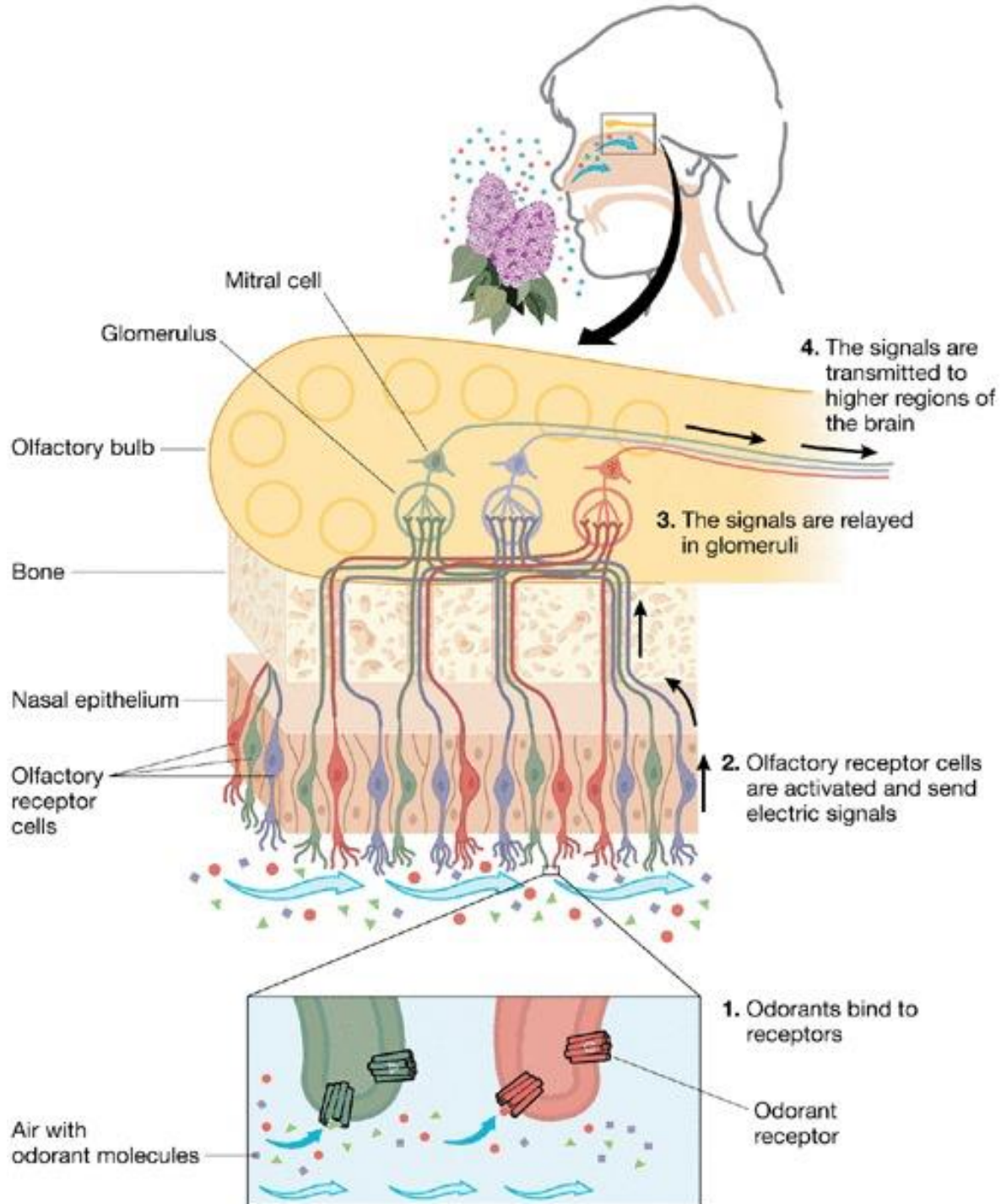
β2 adrenergic receptor





odorants

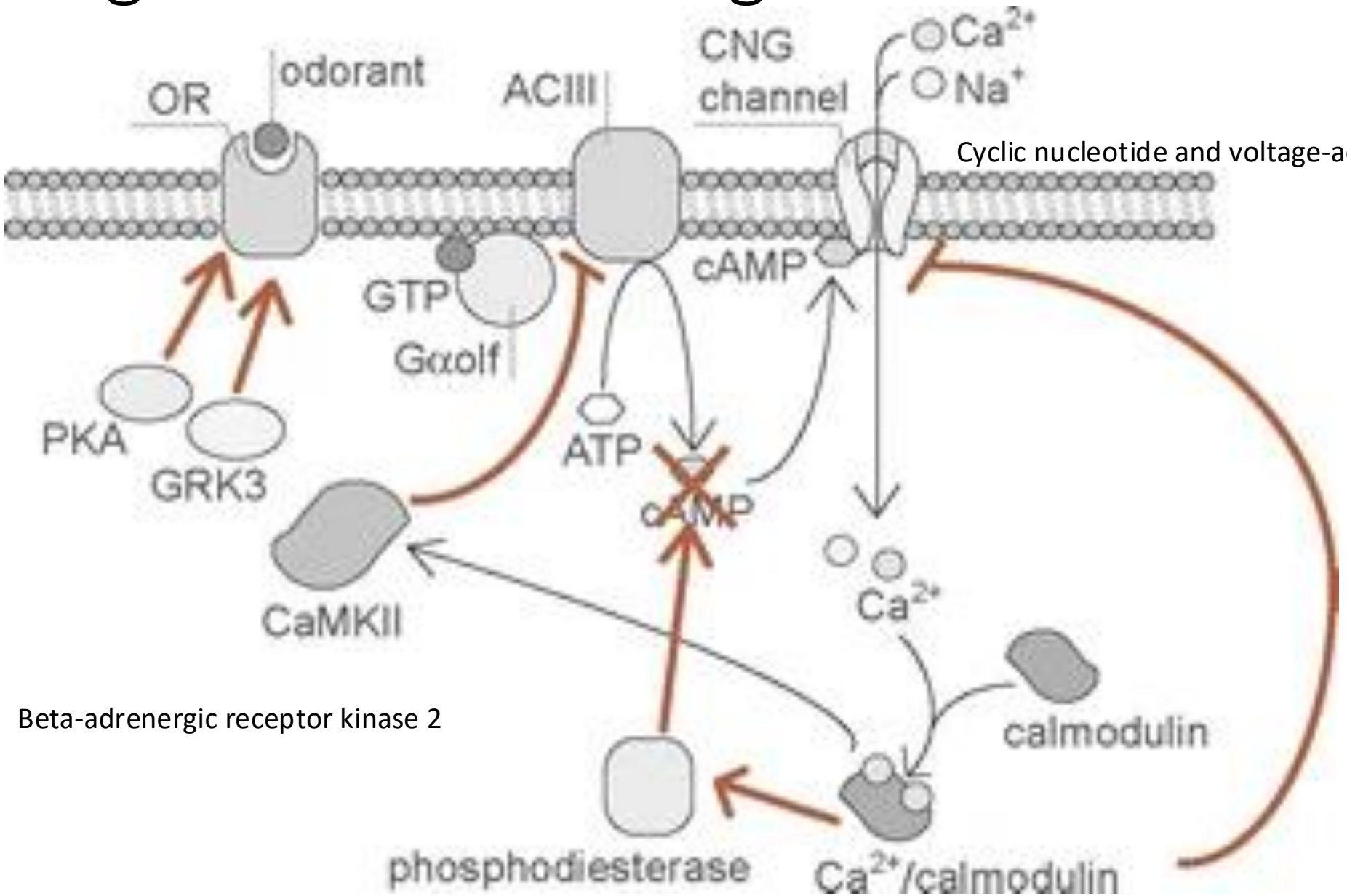




Most odorants are small organic compounds that interact with receptors in specific neurons.

The shape of the molecule rather than any other physical property is crucial for its odorant characteristic.

negative feedback regulation



Cyclic nucleotide and voltage-activated ion channel

Beta-adrenergic receptor kinase 2

Detection of visible light

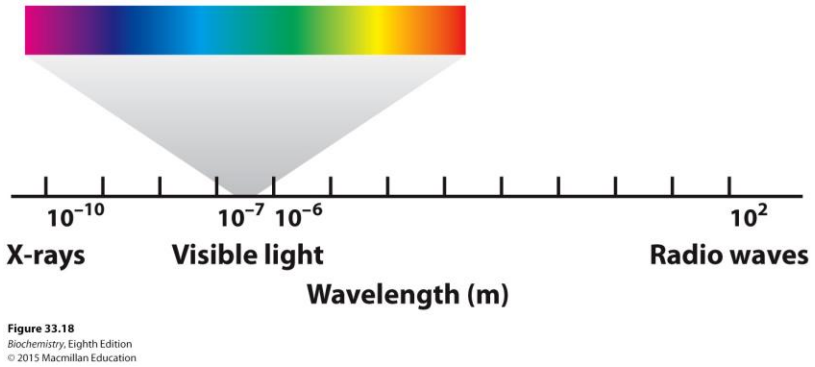


Figure 33.18
Biochemistry, Eighth Edition
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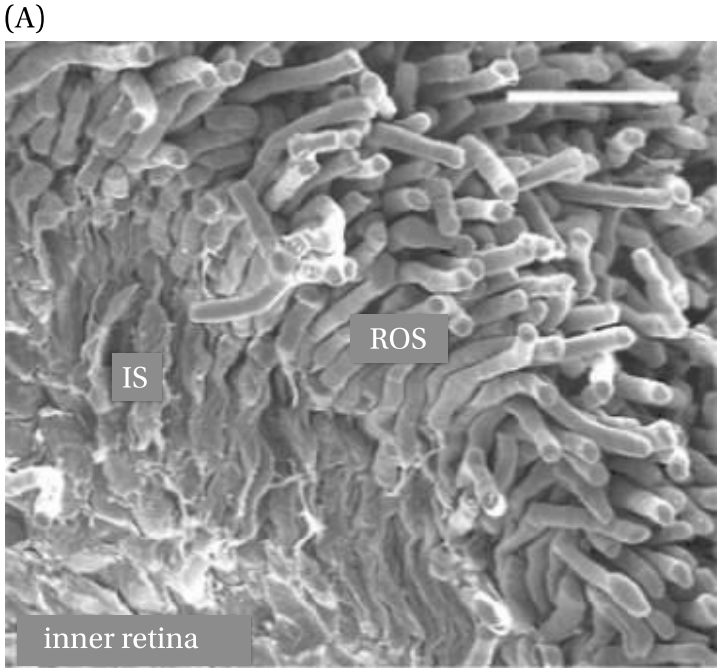
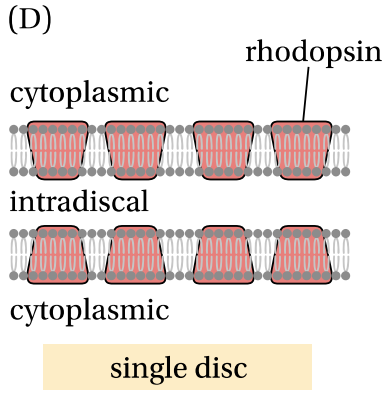
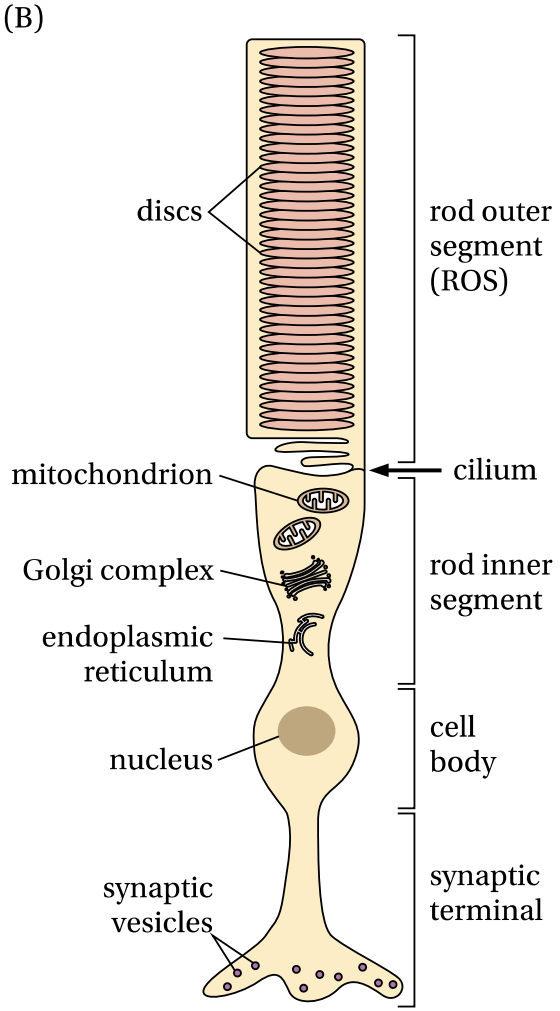
Photoreceptor cells detect electromagnetic radiation in the region between 390 and 750 nmvisible light.

Vertebrates have two types of photoreceptor cells: rods and cones.

Cones function in bright light and perceive color. Rods function in dim light, but cannot detect color.







Color vision

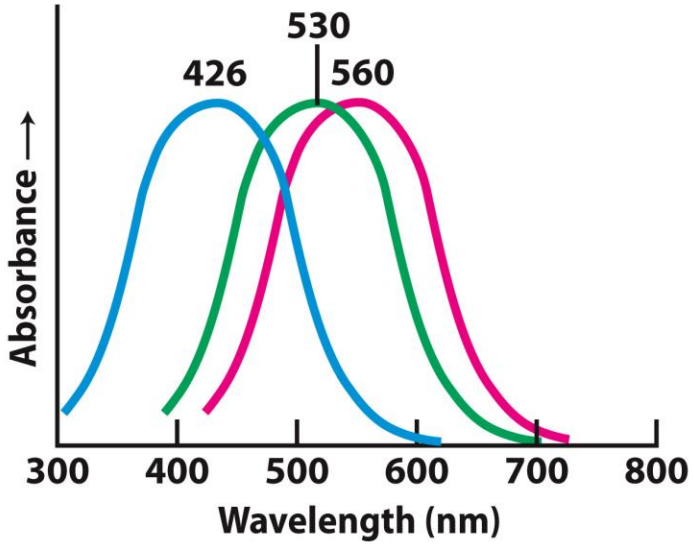


Figure 33.25
Biochemistry, Eighth Edition
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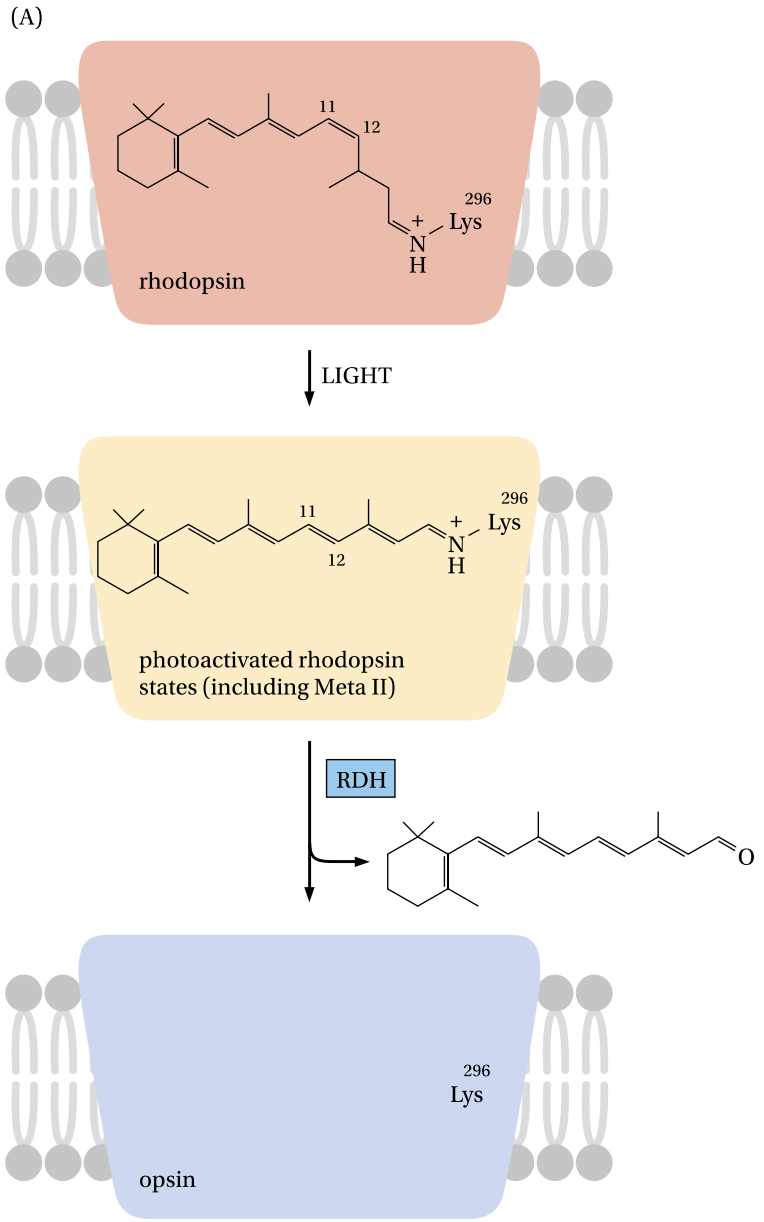
Three distinct photoreceptors in cone cells, homologs of rhodopsin, are responsible for perception of color.

The receptors absorb blue, green, and red light.
The visual receptors have evolved by gene duplication.

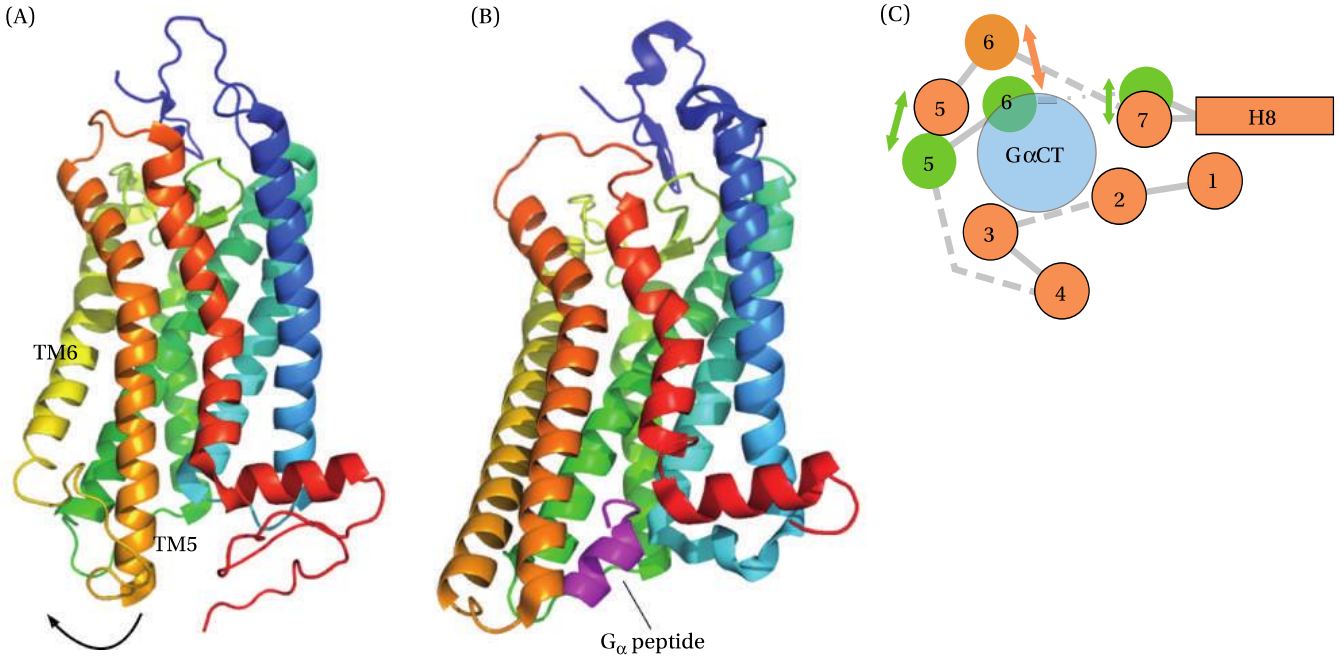
Color vision is mediated by three cone receptors that are homologs of rhodopsin

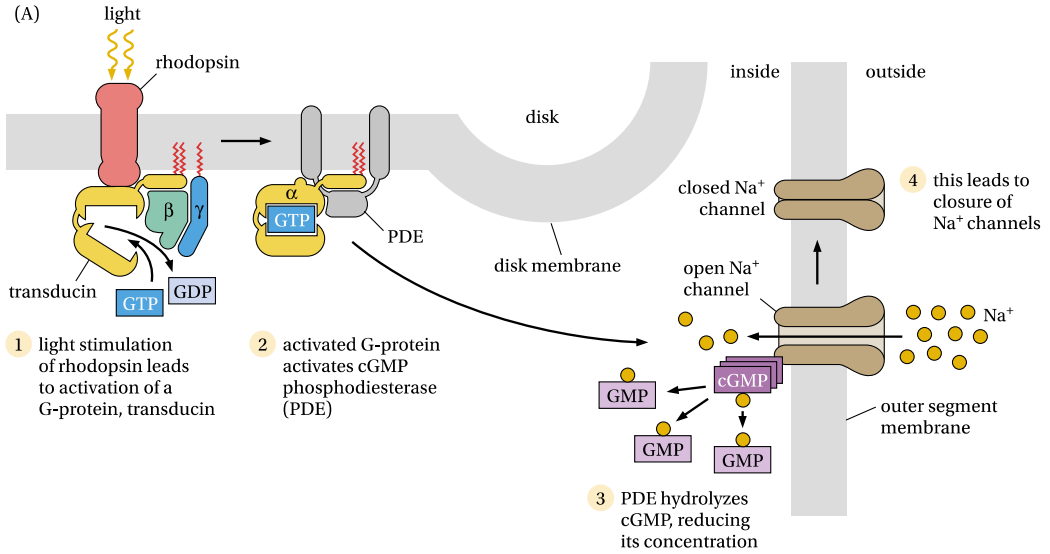


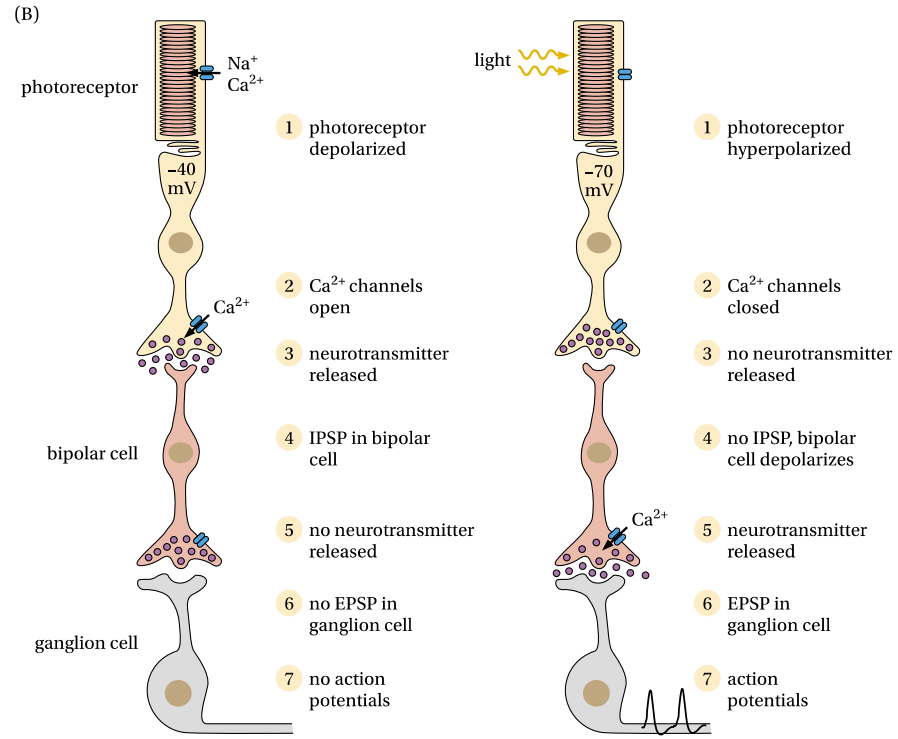
(B)

bovine rhodopsin (λ_{max} = 500 nm)
↓ hυ
excited state
↓ 200 fs
photorhodopsin (λ_{max} = 550 nm)
↓ 45 ps
bathorhodopsin (λ_{max} = 535 nm)
⇅
BSI (blue-shifted intermediate) (λ_{max} = 470 nm
>–140° C ↓ 150 ns
lumirhodopsin (λ_{max} = 497 nm)
>–40° C ↓ 150 µs
meta I (λ_{max} = 478 nm)
>–20° C ↓ 6 ms
meta II (λ_{max} = 380 nm)
>0° C ↓ 300 s
meta III (λ_{max} = 465 nm)
>+20° C ↓ > 1 h
opsin + all-*trans*-retinal (381 nm)

Signaling by photoactivation of rhodopsin in ROS membranes.







EPSP: excitatory postsynaptic potential
IPSP: inhibitory postsynaptic potential

rhodopsin

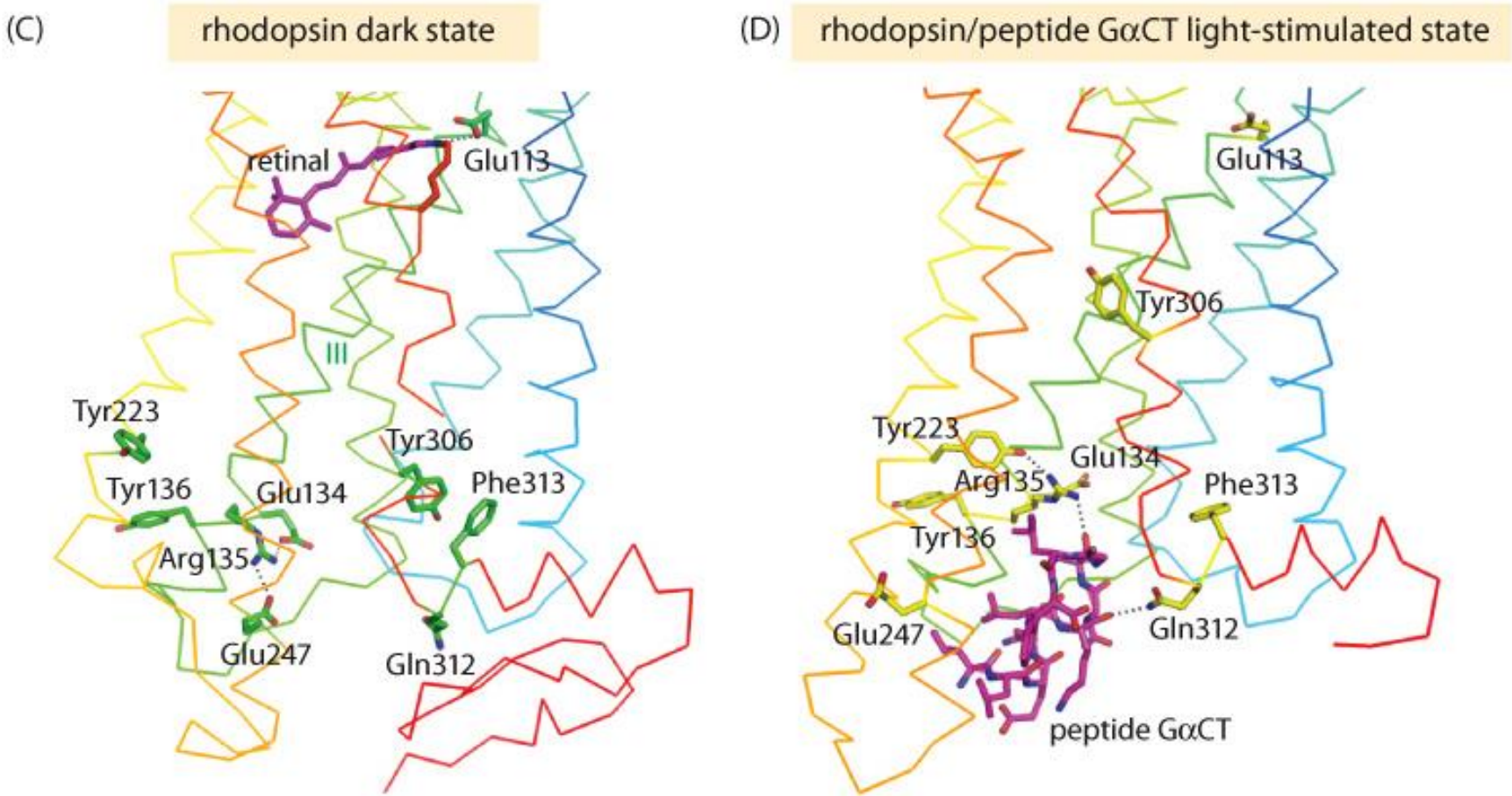
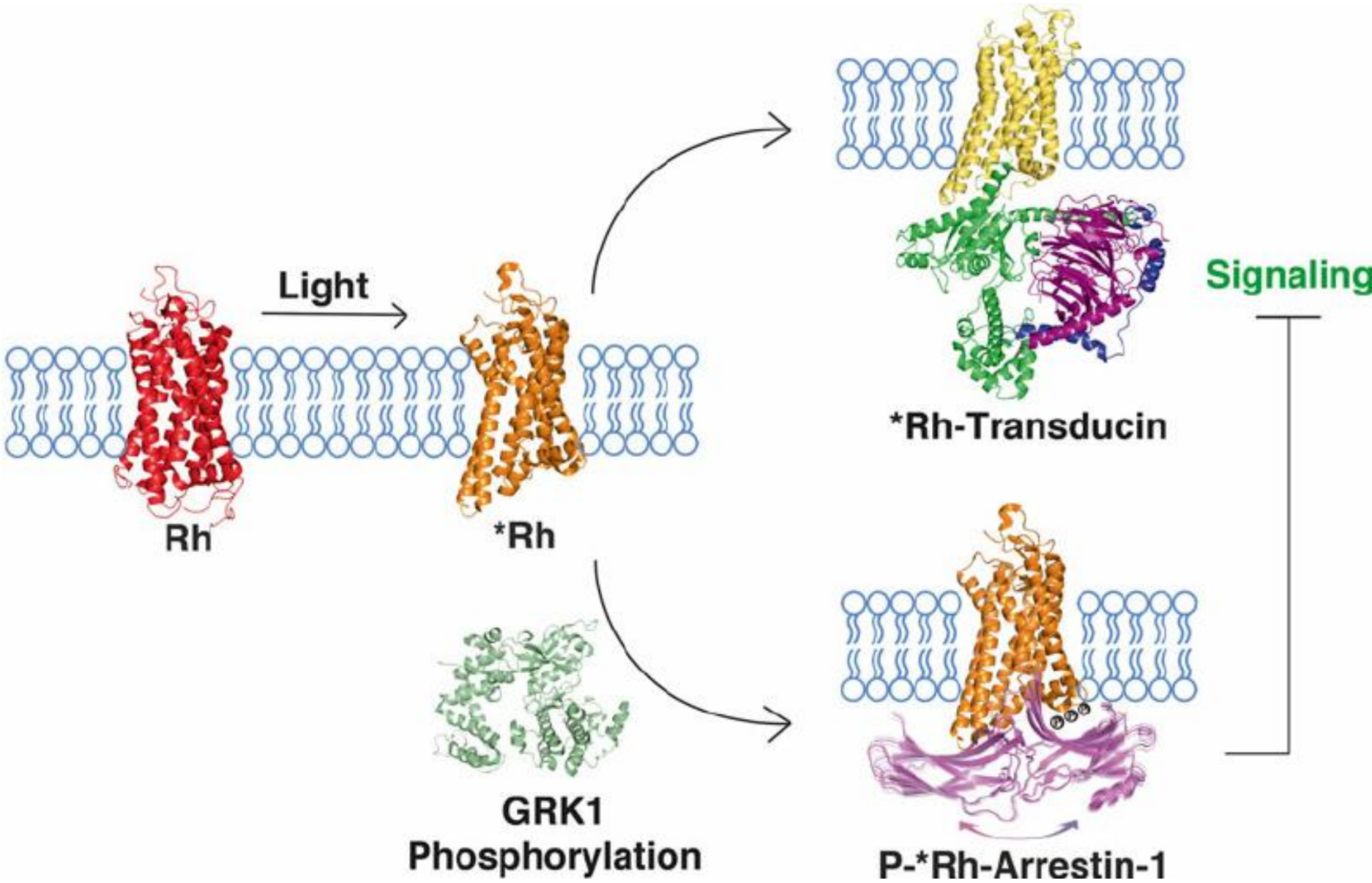


Figure 12.3 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Visual signal transduction



Heterotrimeric G proteins

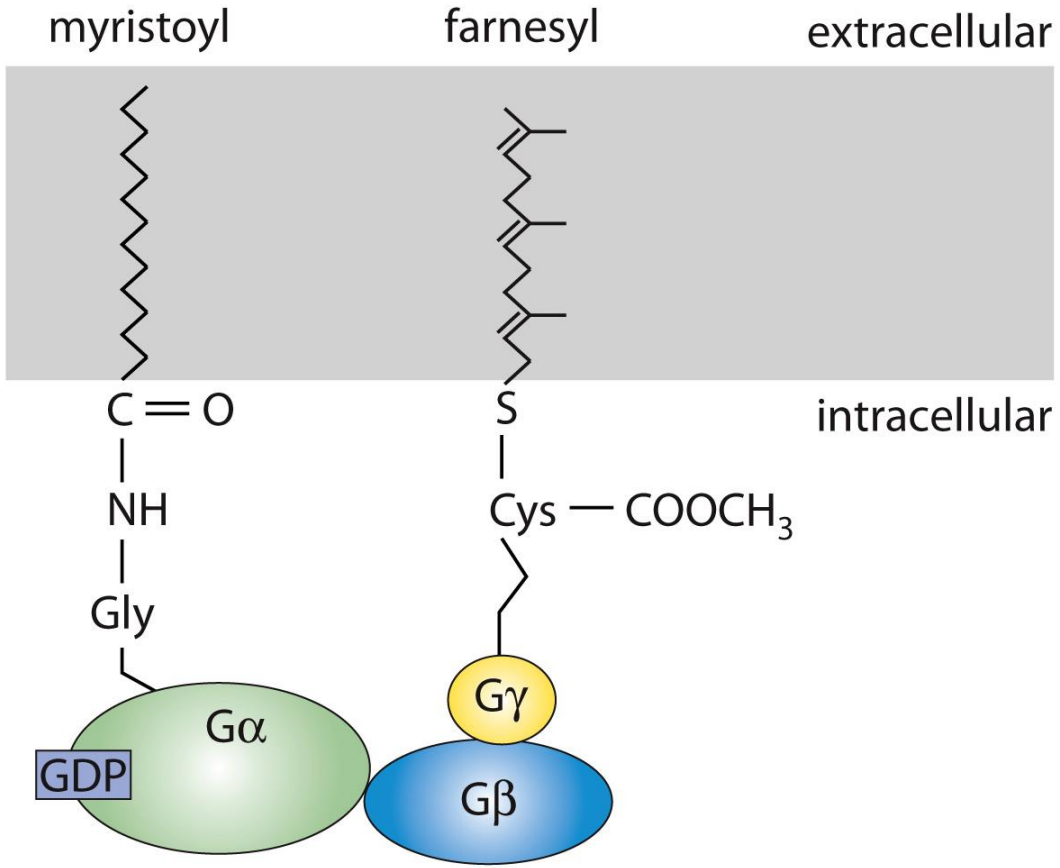


Figure 12.5b Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Lipidation of proteins as membrane anchors

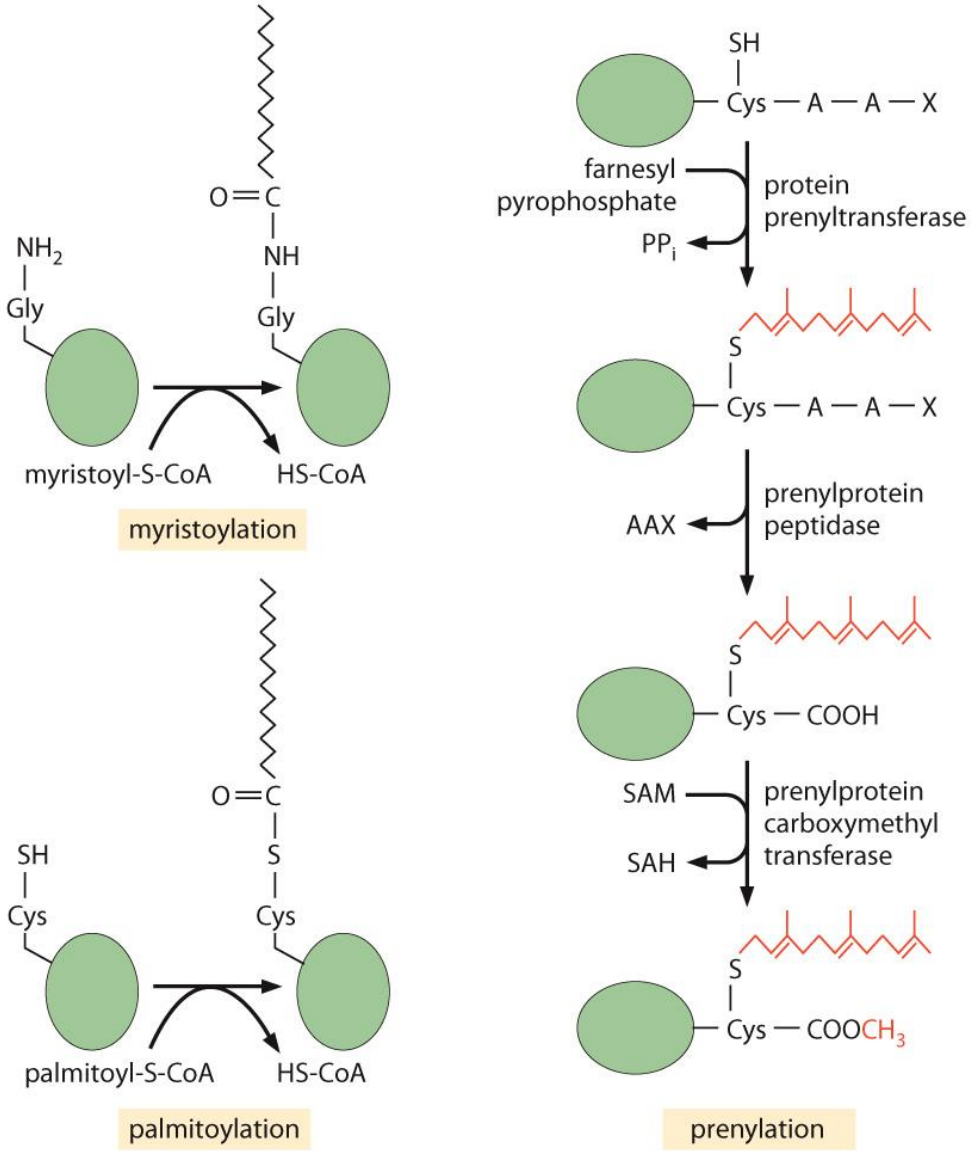
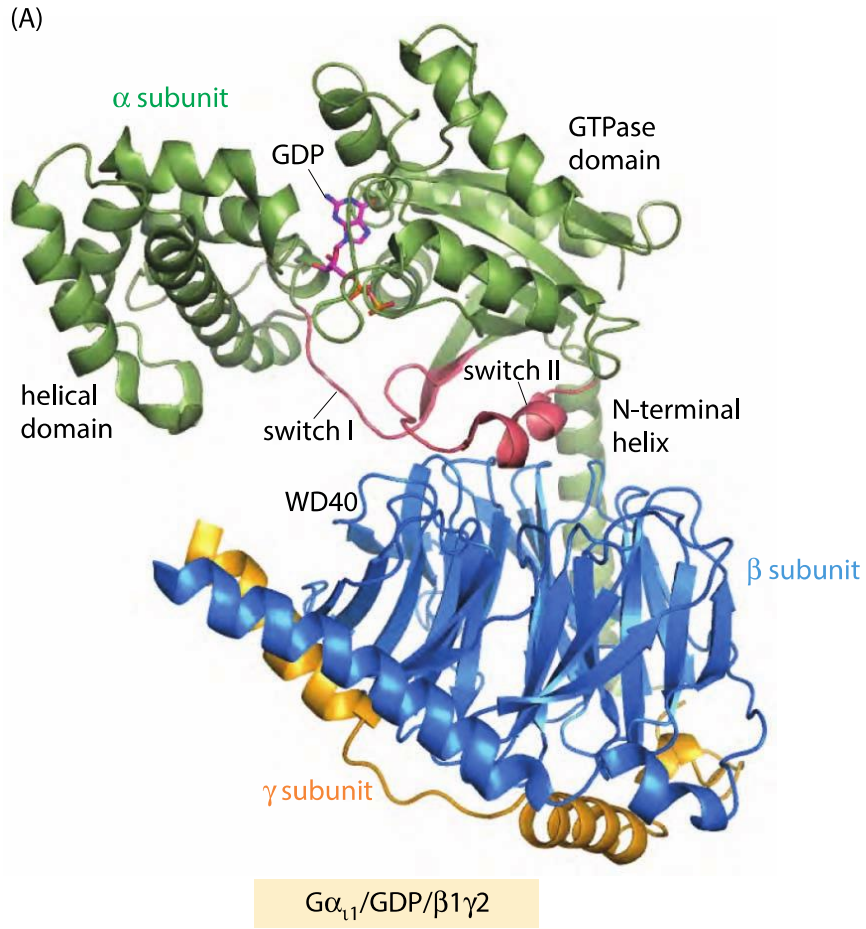


Figure 12.5a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

GDP/GTP exchange



$G\alpha_{t1}$/GDP/β1γ2

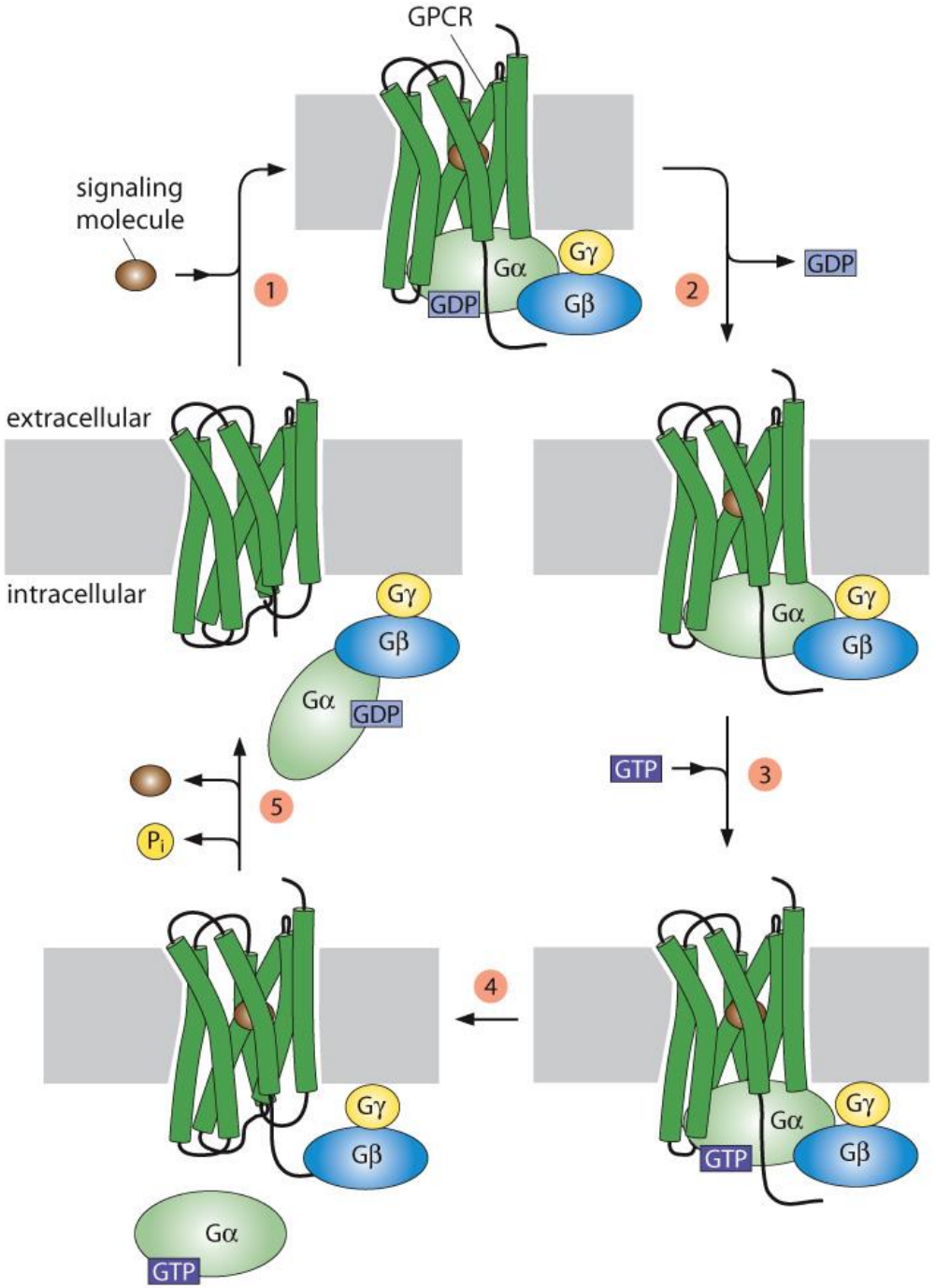
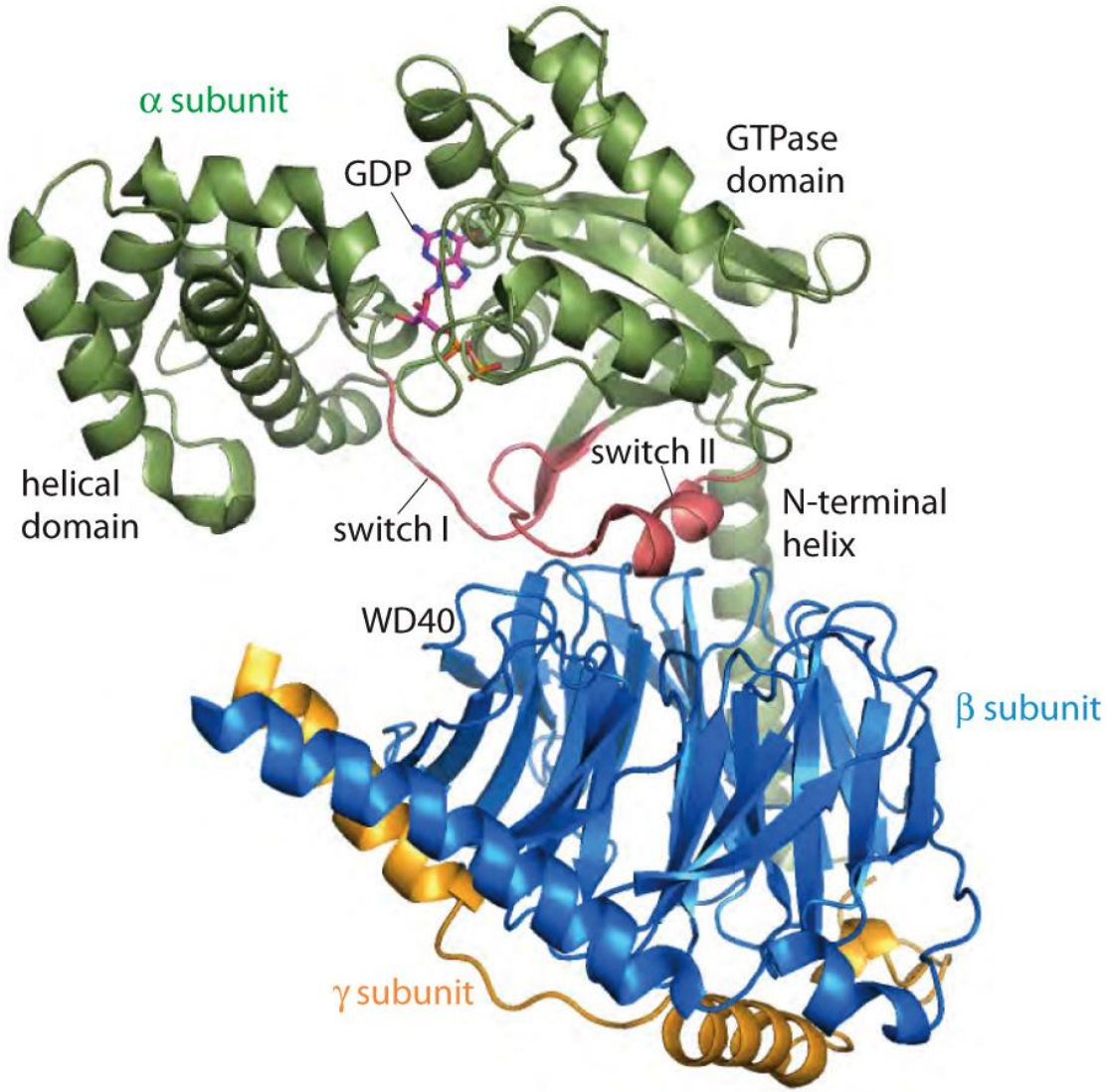
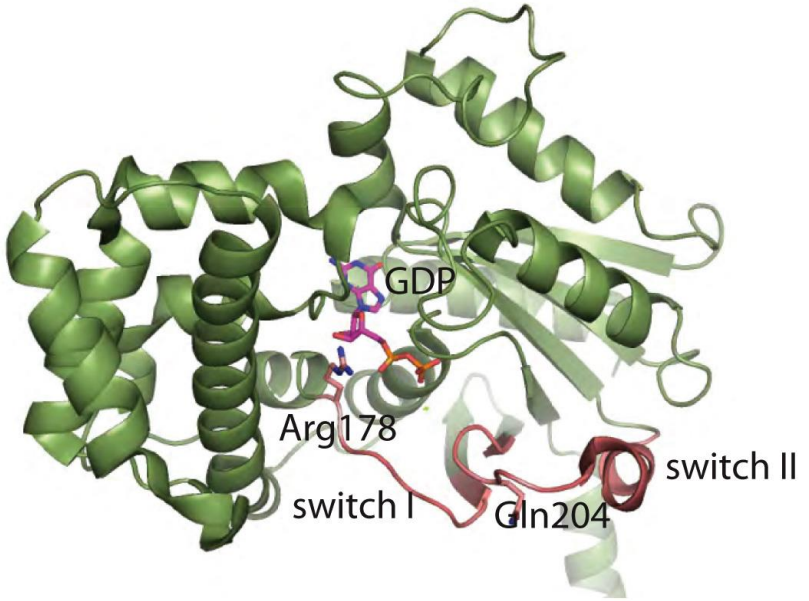


Figure 12.6 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

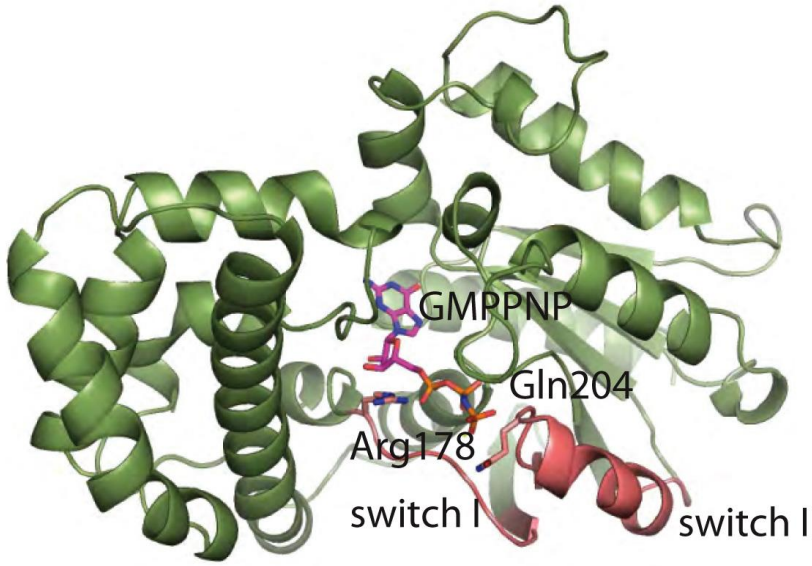
Conformational changes



$G\alpha_{i1}/GDP/\beta1\gamma2$



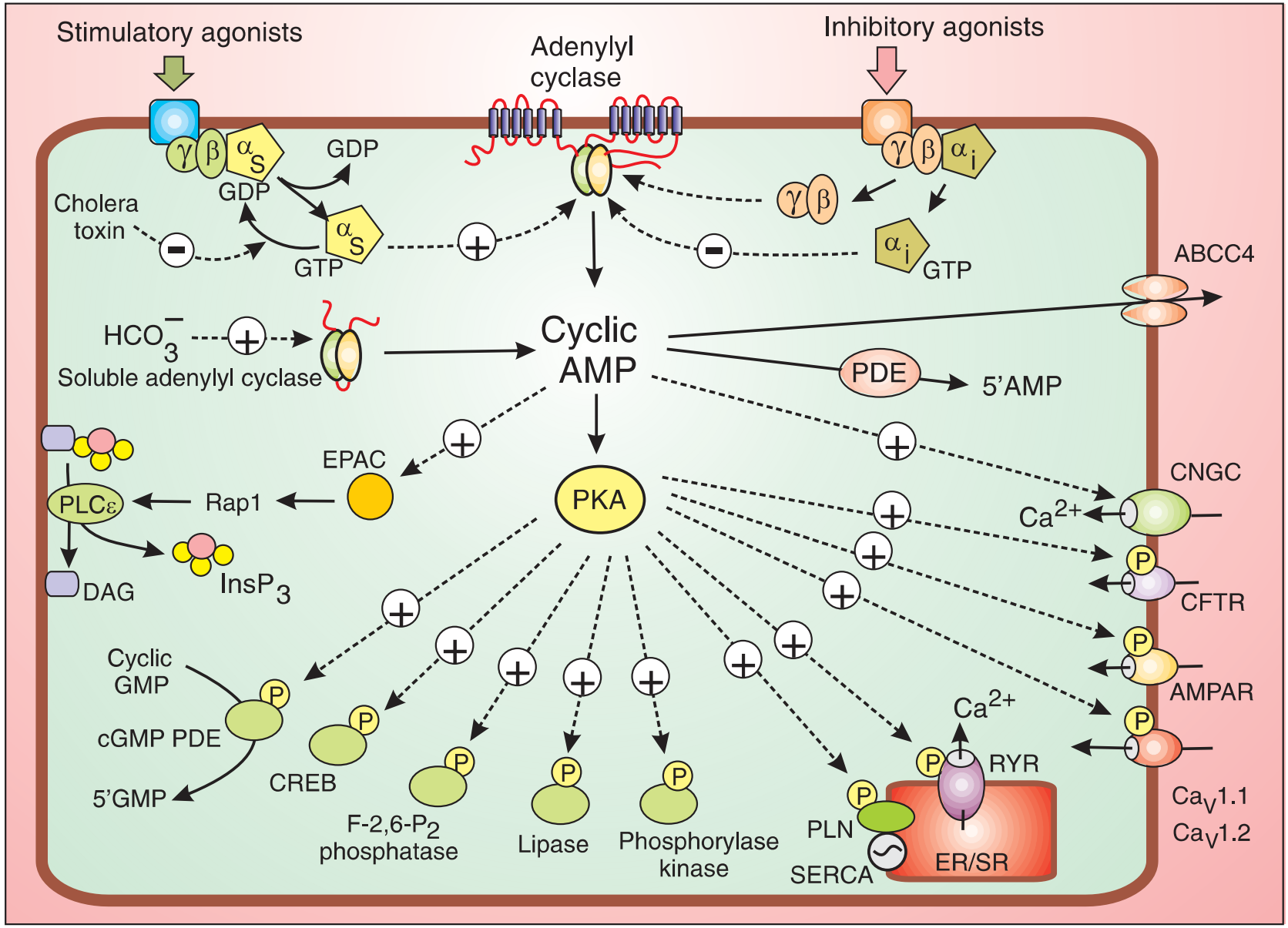
$G\alpha_{i1}/GDP$



$G\alpha_{i1}/GMPPNP$

Figure 12.7a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Organization and function of the cyclic AMP signaling pathway



Second messenger

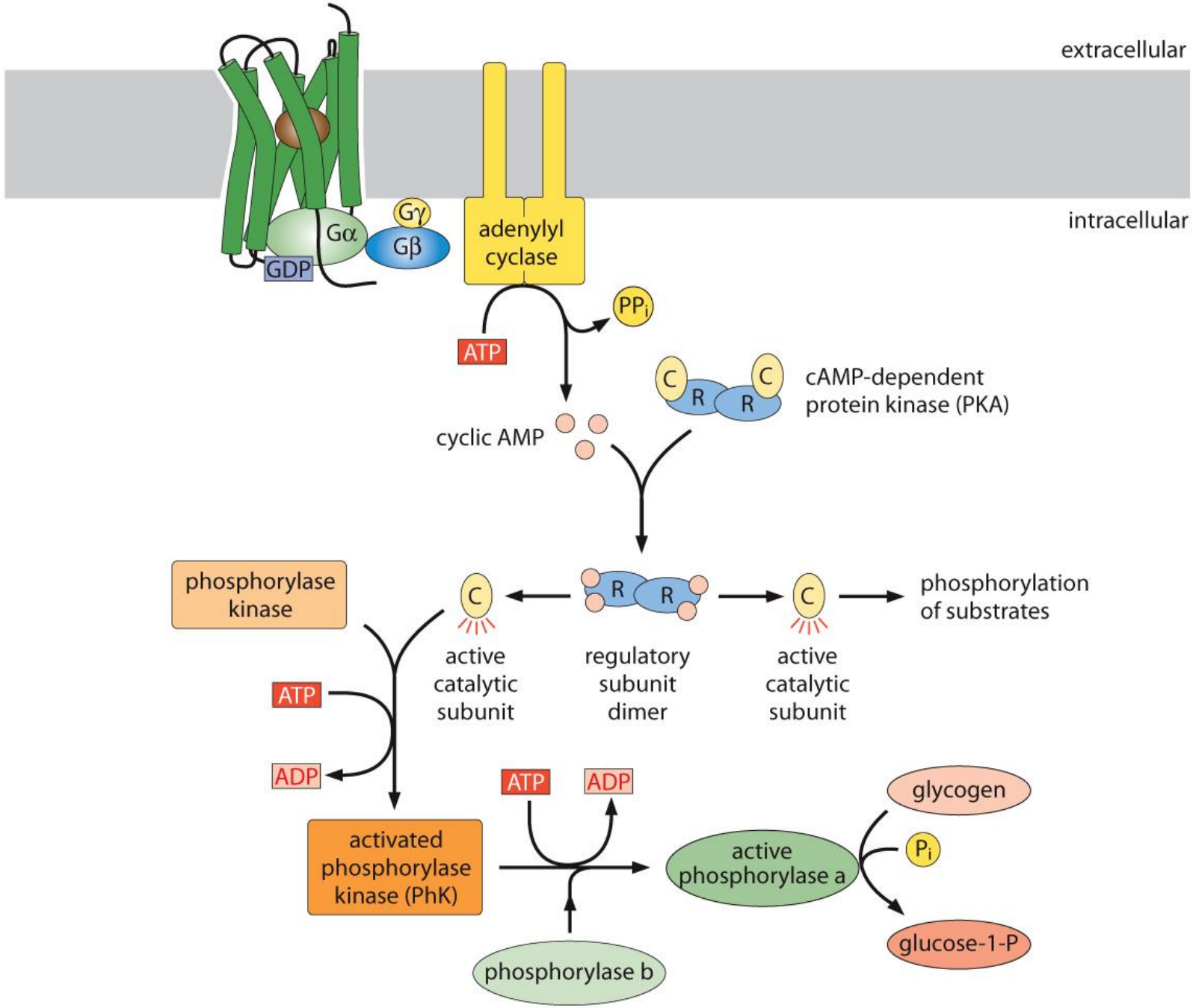
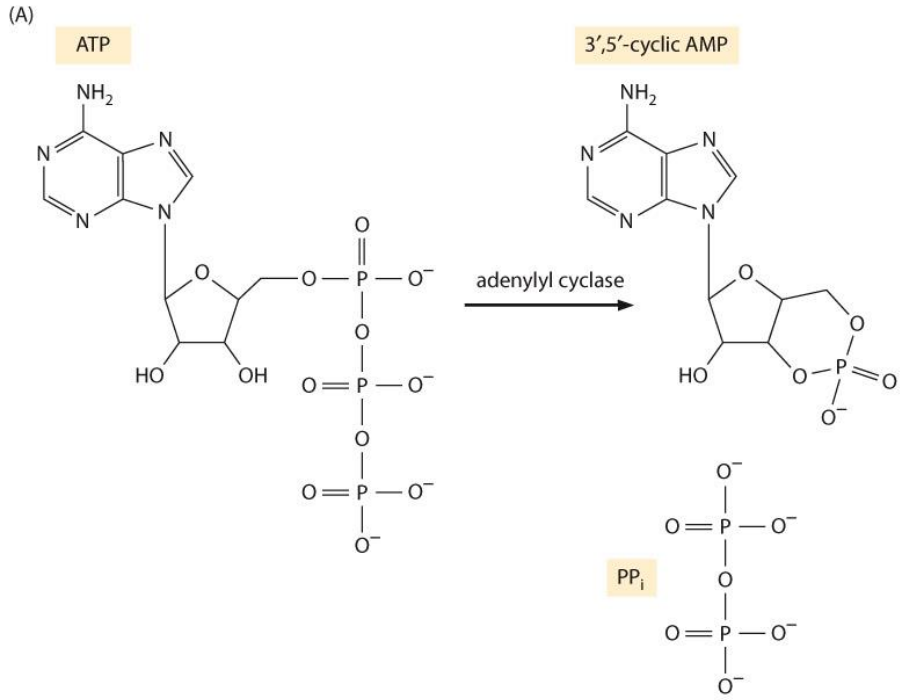
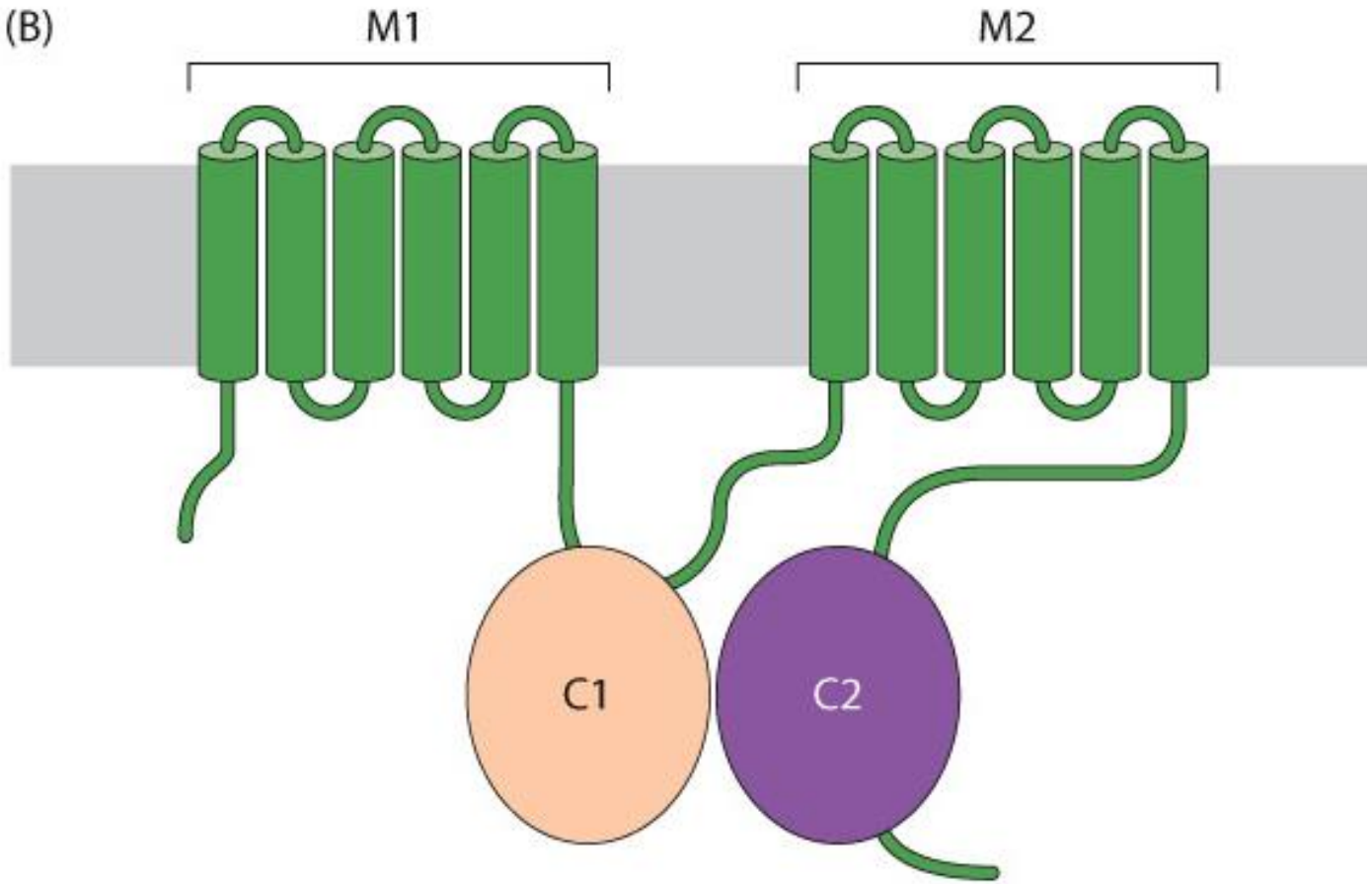


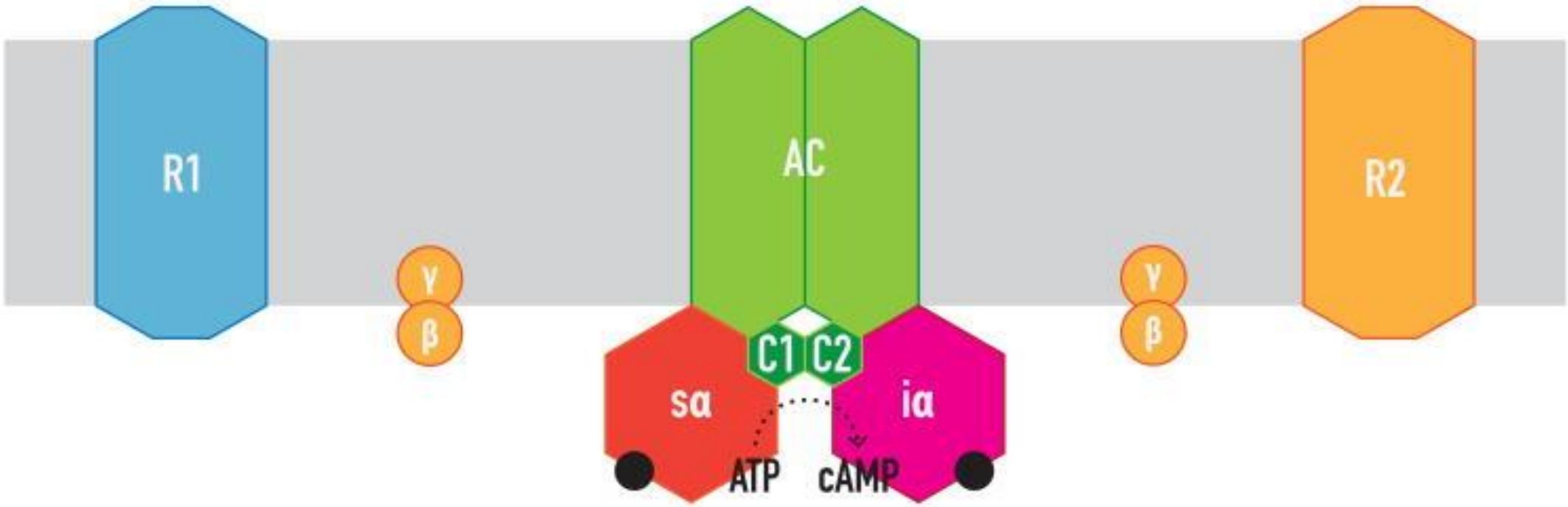
Figure 12.8 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Adenylyl cyclase

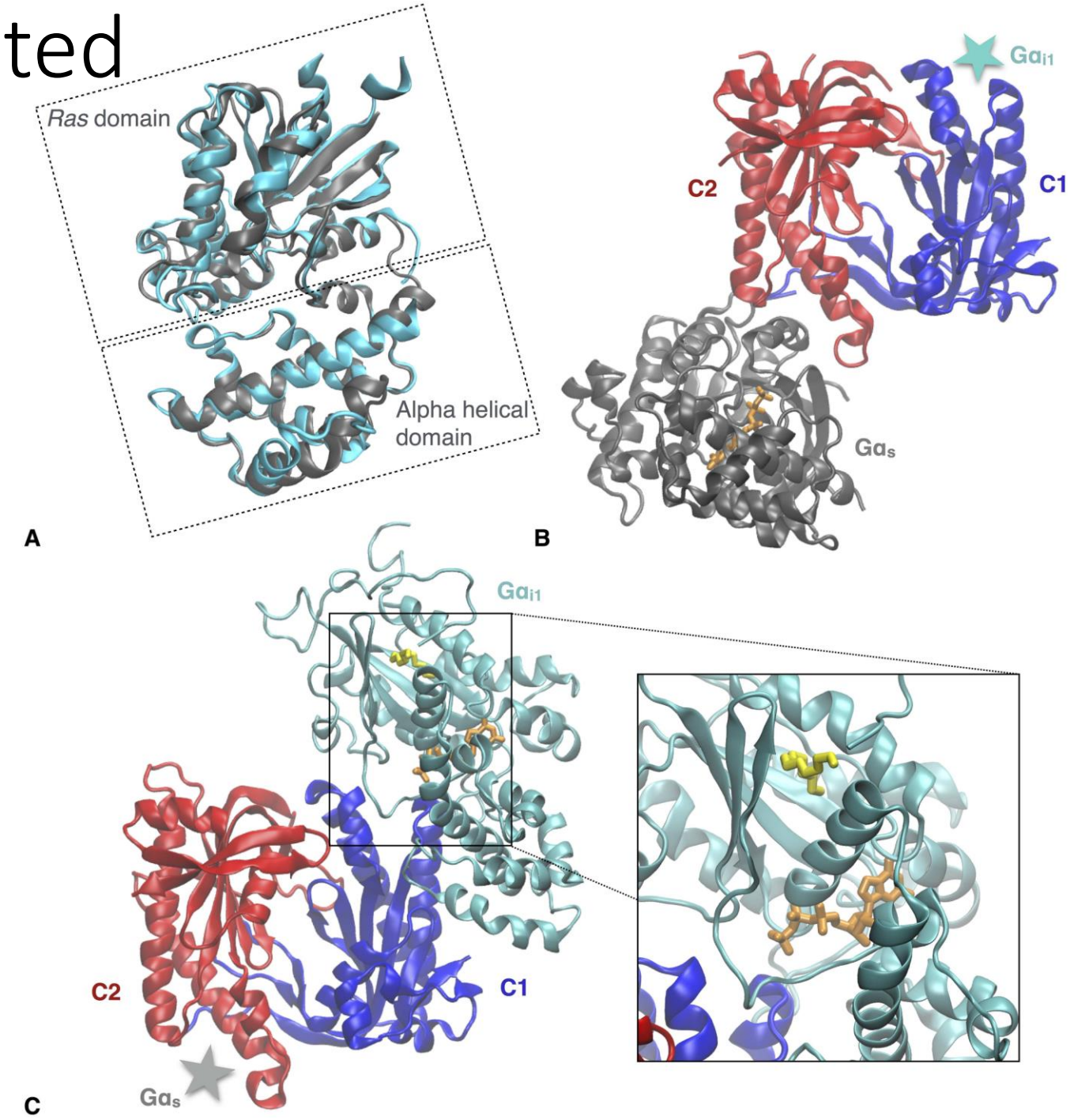




Second messenger

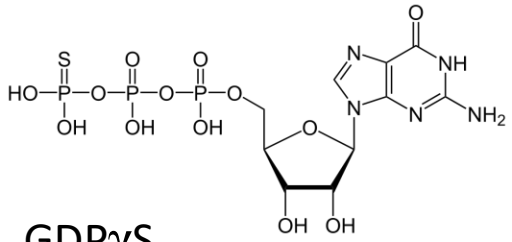


AC complexes and activated Gα subunit structures

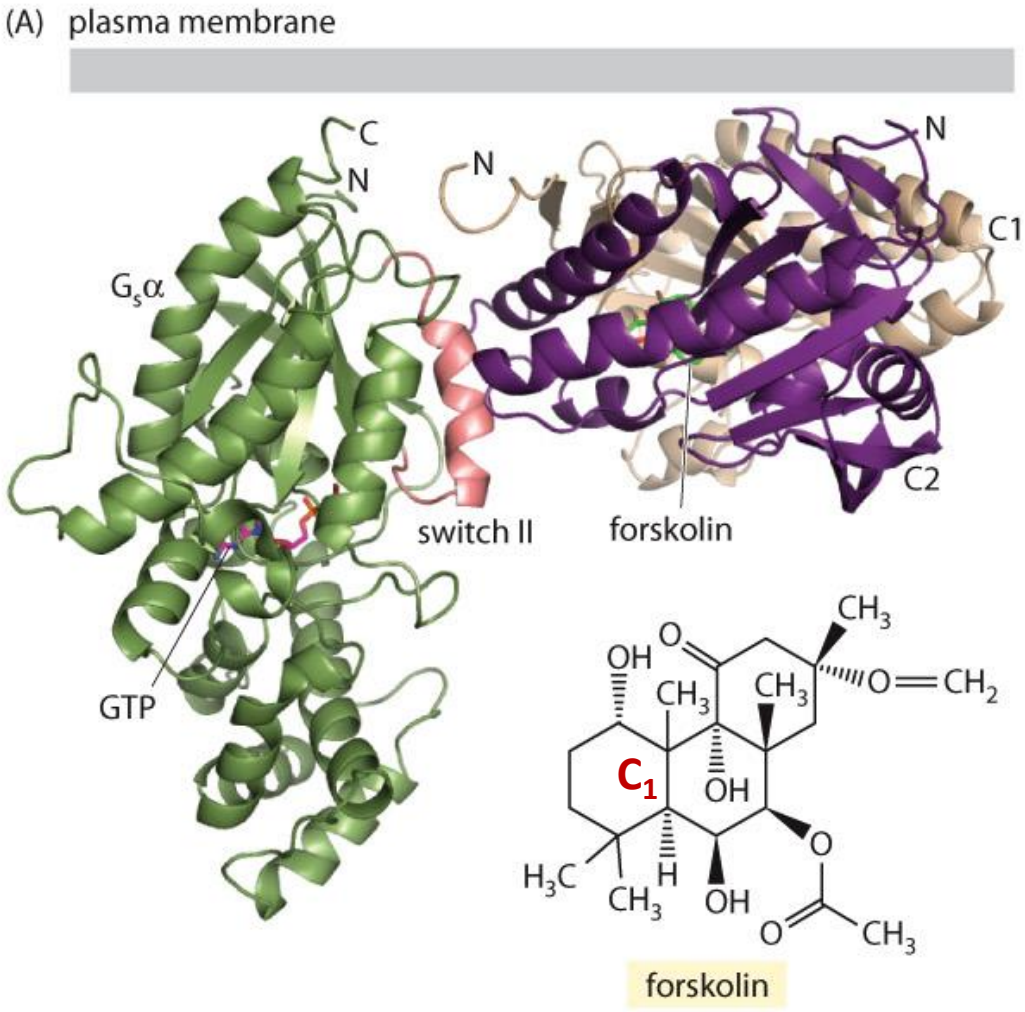


PLOS Computational Biology | https://doi.org/10.1371/journal.pcbi.1005673

Catalytic domain



GDPγS



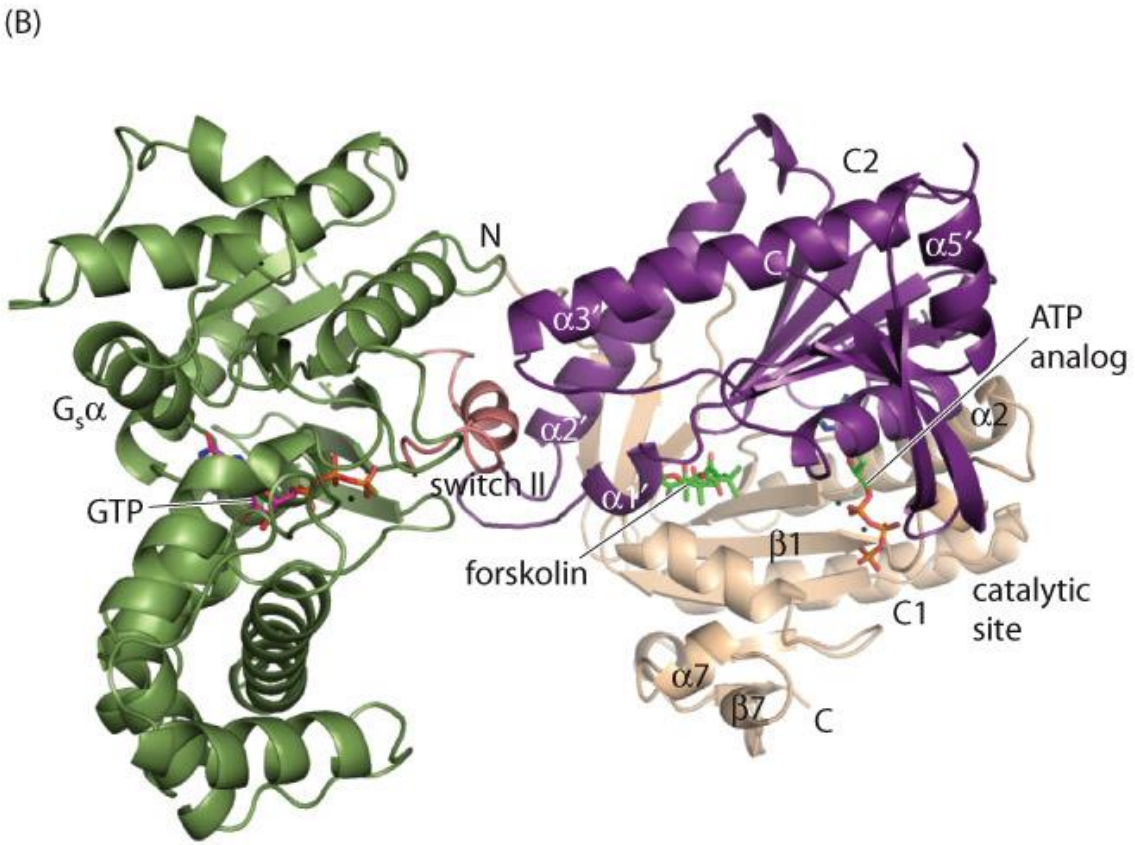


Figure 12.10 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Catalytic mechanism

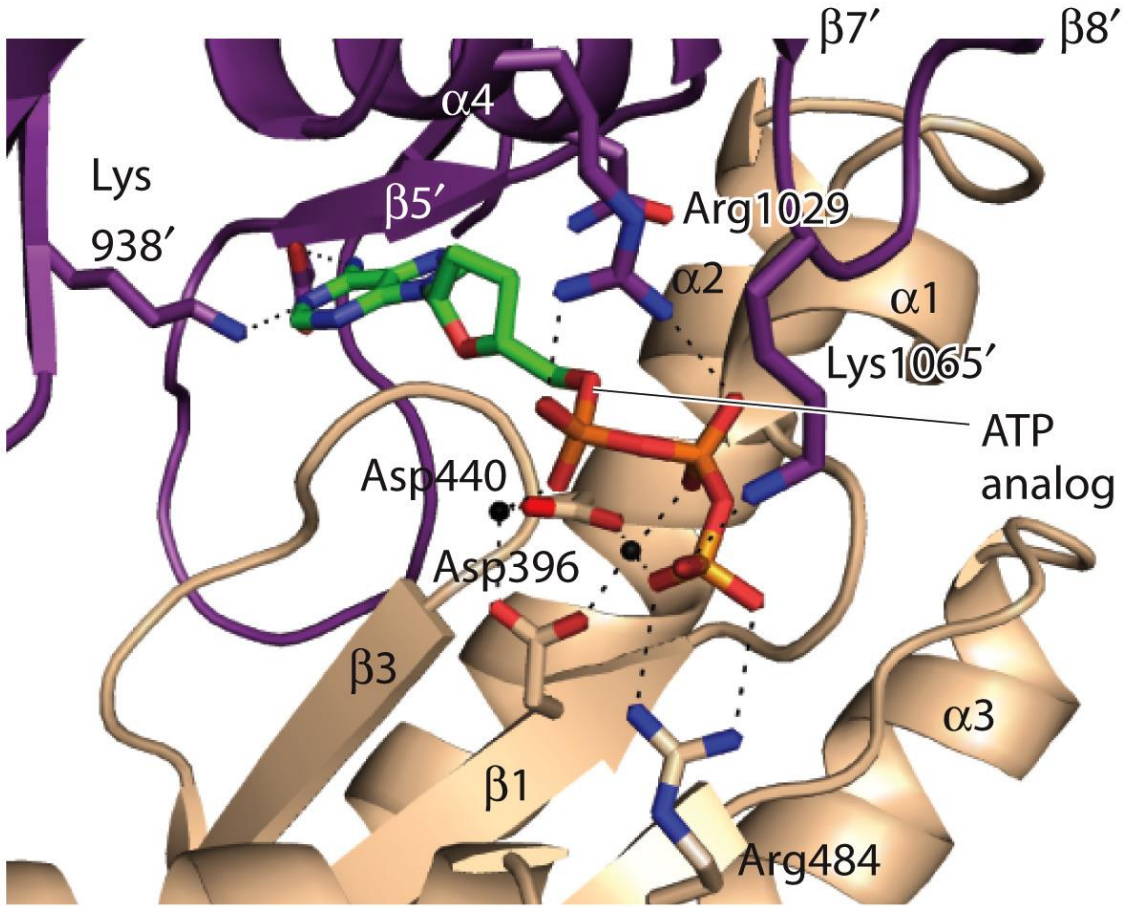


Figure 12.11a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

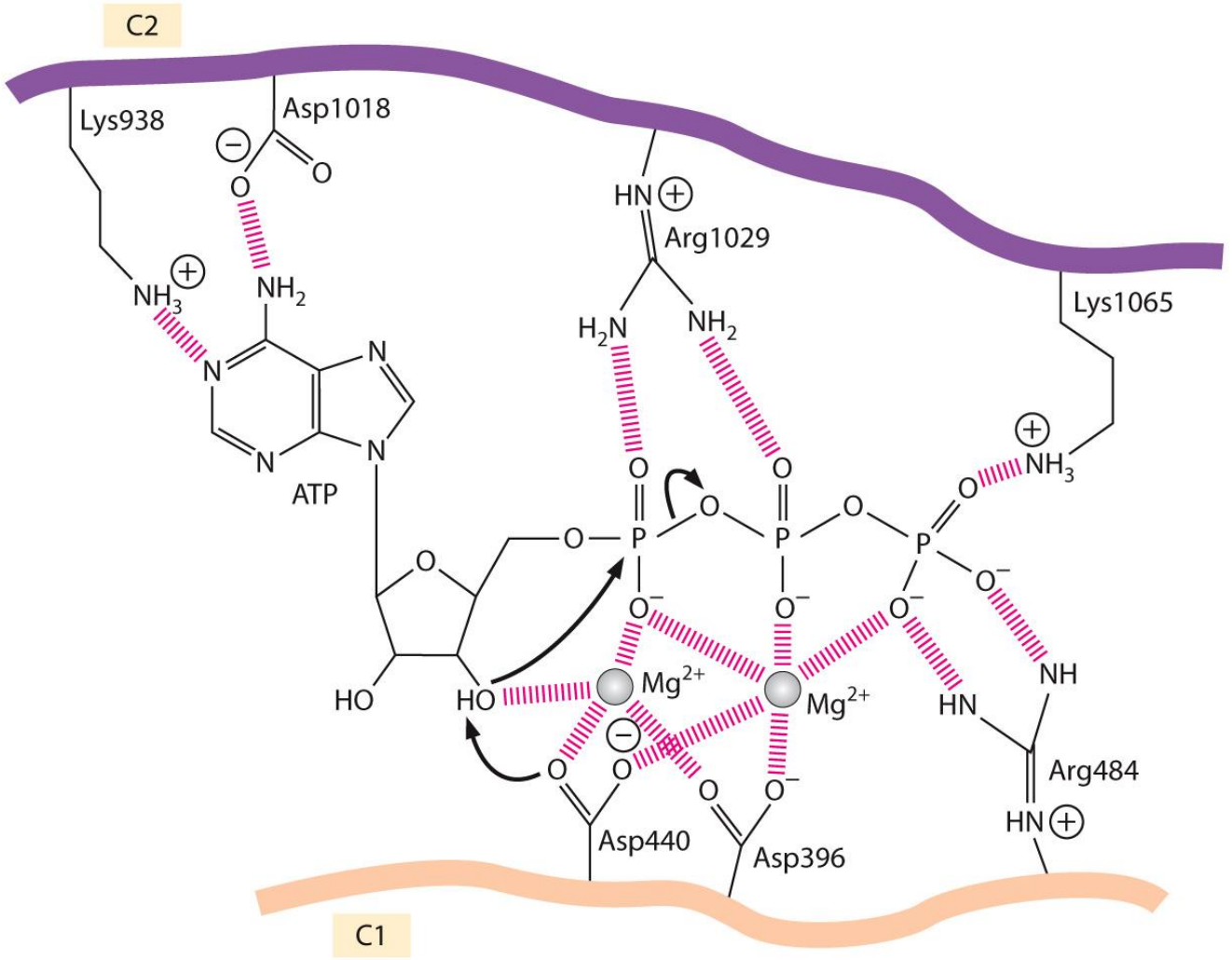
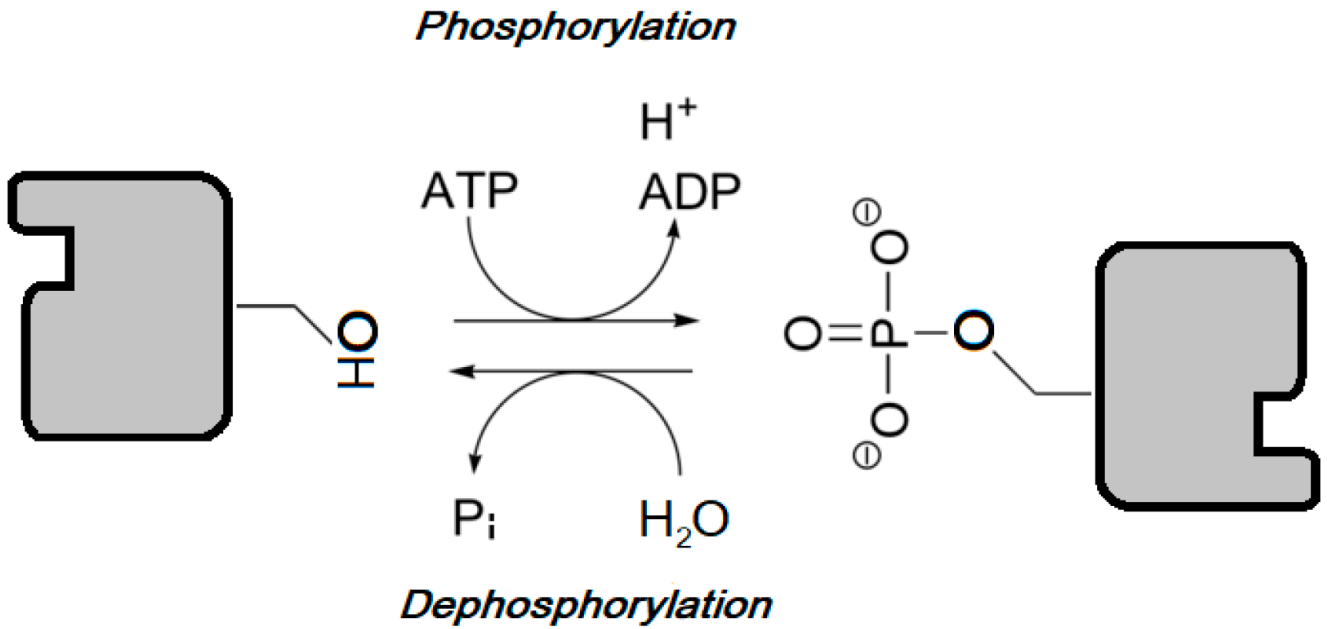


Figure 12.11b Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Protein kinase



Protein Kinases are enzymes that modify the function of other proteins by attaching phosphate groups to them.

They are key controllers of most biochemical pathways and important in health and disease.

Effect

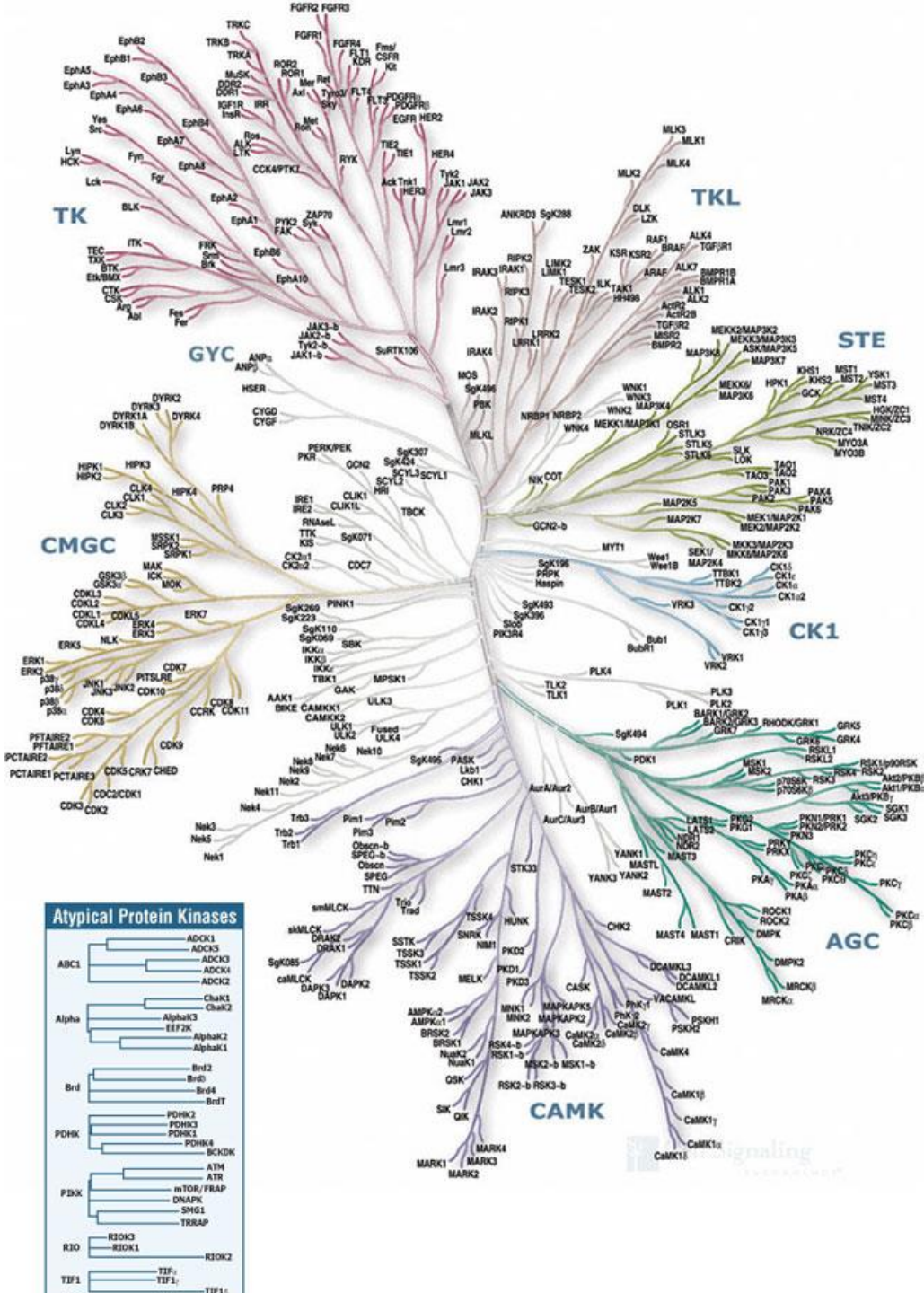
- **Activation**
- **Inactivation**
- **Creation of recognition side for other signaling molecules**
- **Transition between structural disorder and order**

Protein kinase

Over 160 protein kinases are associated with human diseases, and several dozen are the targets of drugs in development or already approved.

the commercial impact of total sales of kinase-related drugs is estimated at $240 billion during 2011-15

Kinase	Description
AGC	Containing PKA, PKG, PKC families
CAMK	Calcium/calmodulin-dependent protein kinase
CK1	Casein kinase 1
CMGC	Containing CDK, MAPK, GSK3, CLK families
STE	Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases
TK	Tyrosine kinase
TKL	Tyrosine kinase-like



Protein kinase

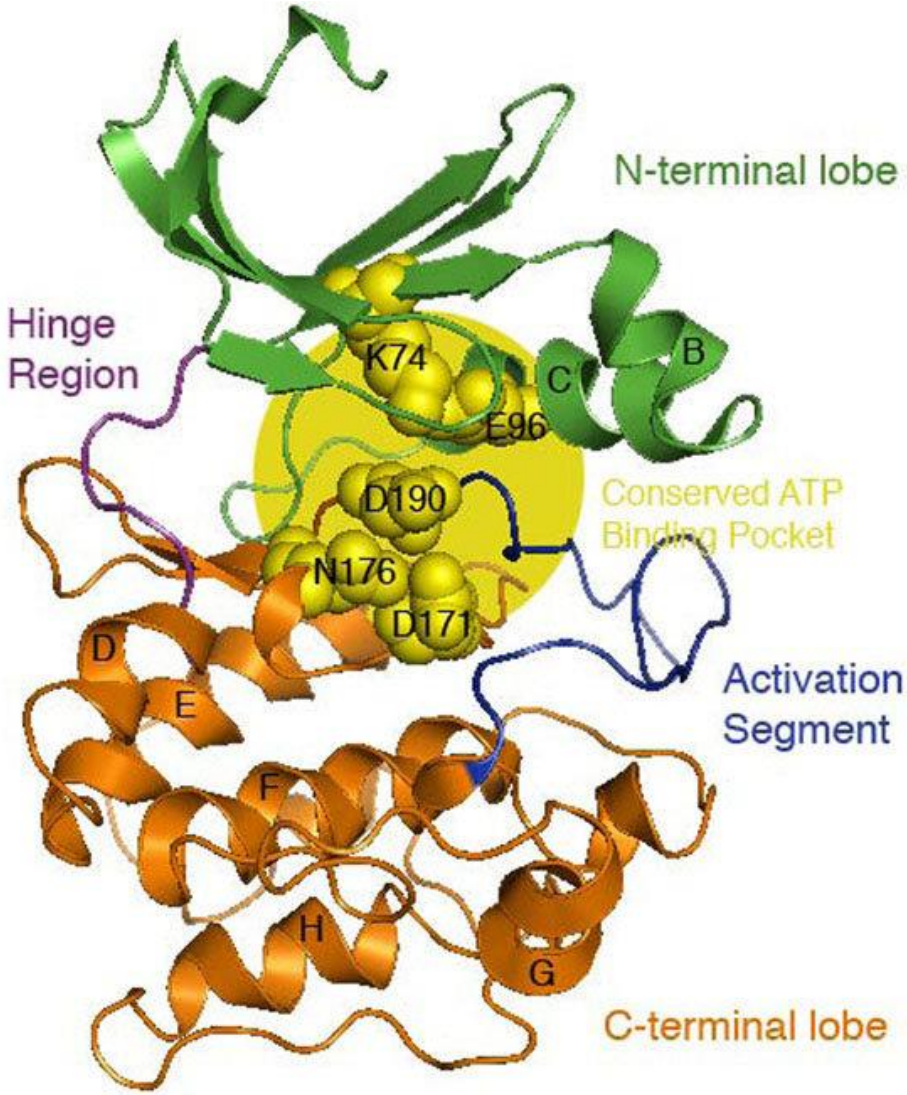
Table 12.2.1 Selected protein kinases and their preferred substrate specificities.

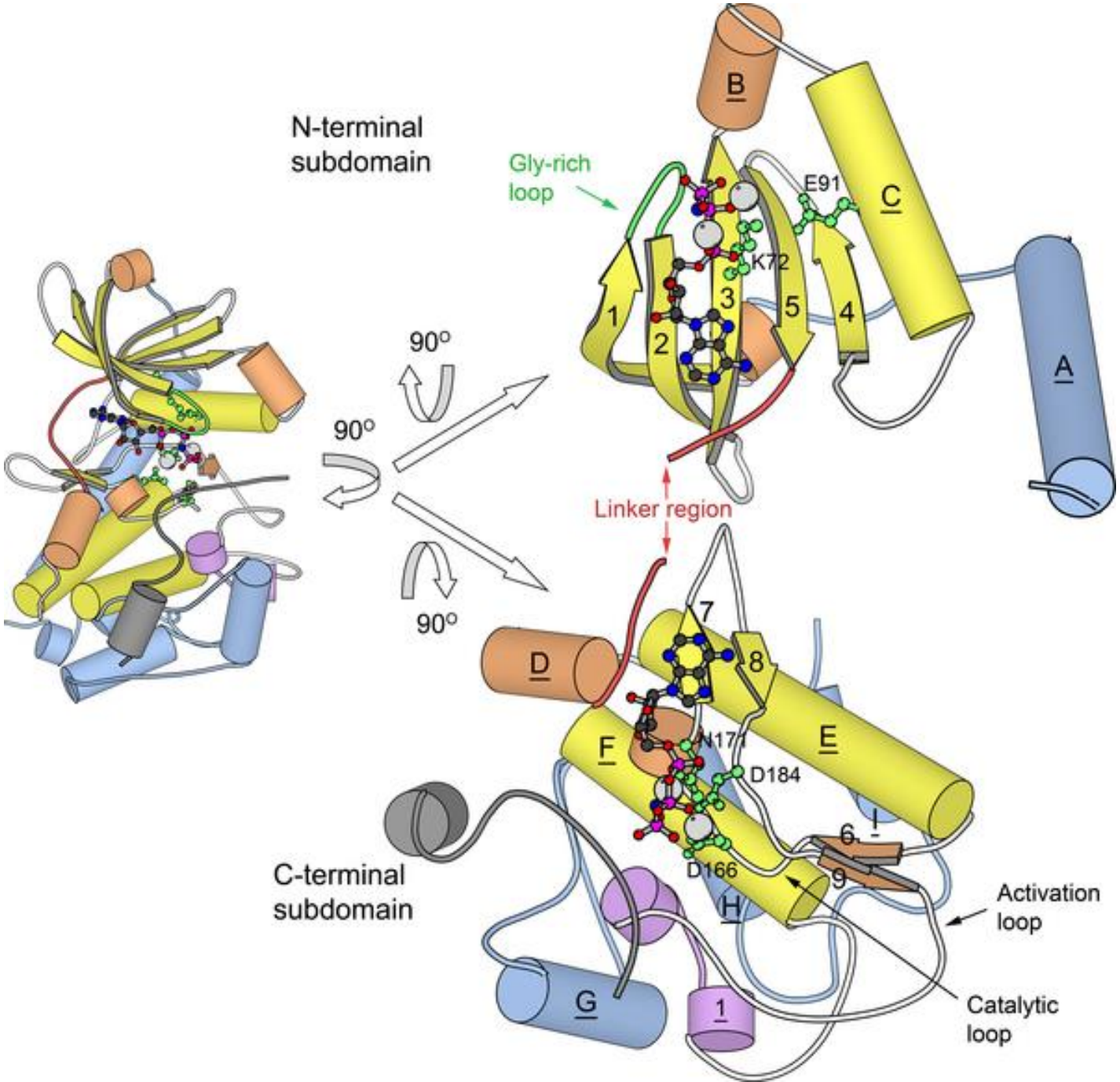
Name	Full name	Consensus sequence
Ser/Thr kinases		
PKA	Protein kinase A	-R-R-X-**S/T**-Φ
PhK	Phosphorylase kinase	-R-X-X-**S/T**-Φ-R
Cdk2	Cyclin-dependent protein kinase 2	-**S/T**-P-X-K/R
ERK2	Extracellular signal-regulated kinase 2	-P-X-**S/T**-P
Plk1	Polo-like kinase 1	-D/E/N-X-**S/T**-Φ/not P
Aurora B	Aurora B	-R-R/K-**S/T**-(not P)
Tyrosine kinases		
Irk	Insulin receptor kinase	-D-**Y**-M-M
c-Src	Cellular form of the Rous sarcoma virus transforming agent	-E-E-I-**Y**X-X-F
Csk	C-terminal Src kinase	-I-**Y**-M-F-F
EGFR	Epidermal growth factor kinase	-E-E-E-**Y**-F

The Ser, Thr, or Tyr residues phosphorylated are indicated in bold. Φ is a hydrophobic residue. Some kinases (such as Plk1 or Aurora B) discriminate against Pro in the P + 1 site.

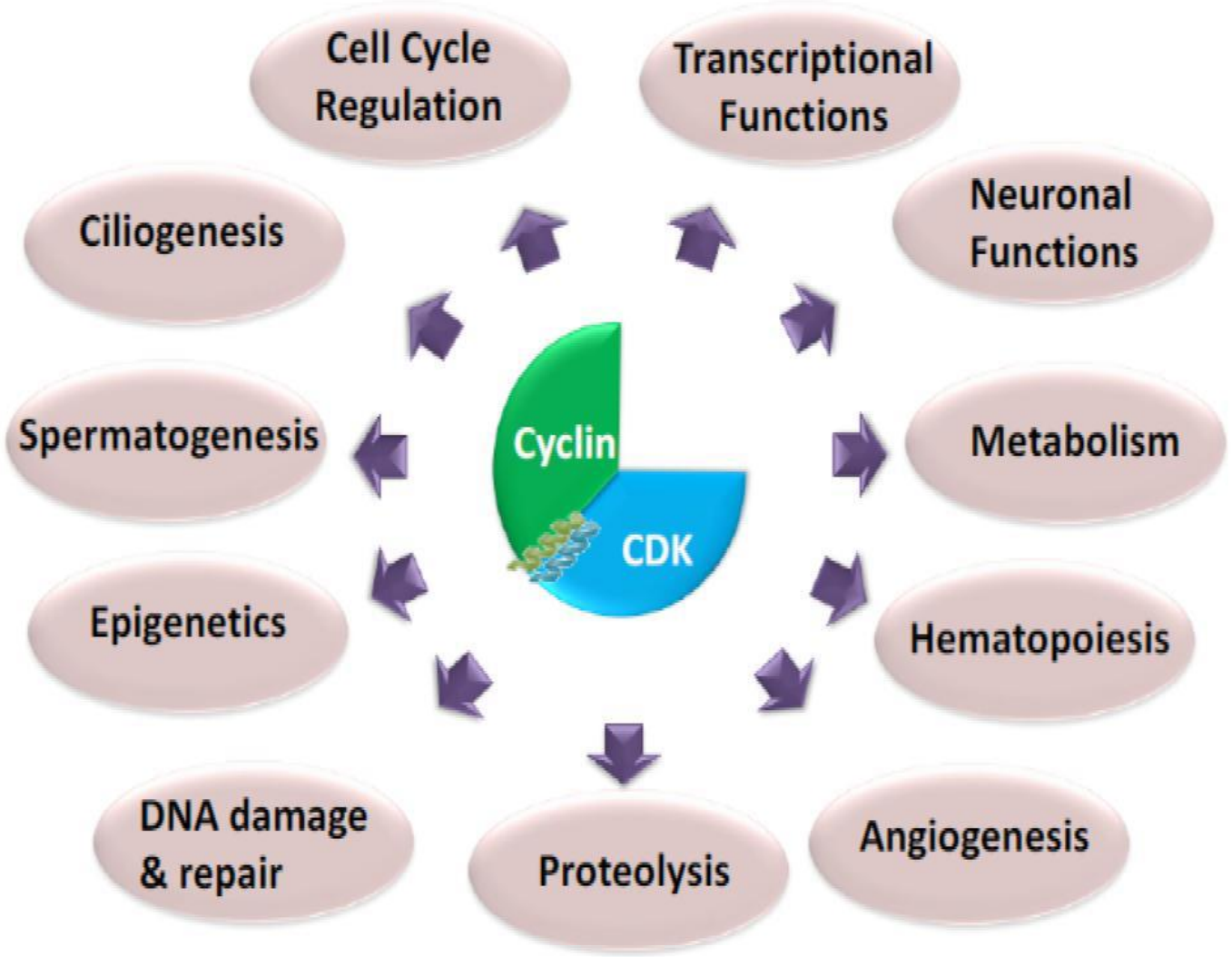
Box 12.2 Table 12.2.1 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

protein kinase fold

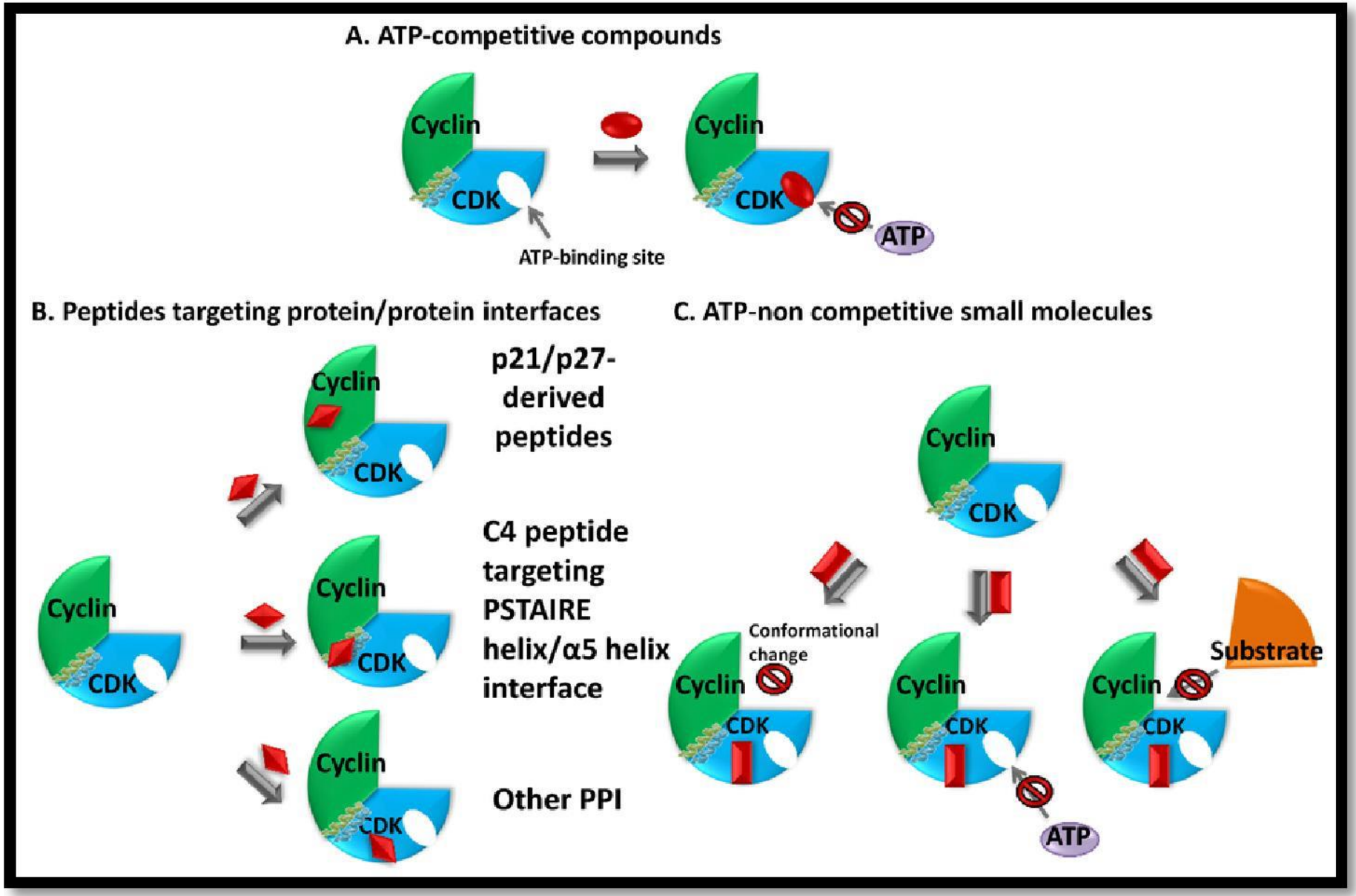




Functional diversity of Cyclin-dependent Kinases



Strategies for targeting Cyclin-dependent kinases



Journal of American Science 2017;13(4)

Tyrosine kinases

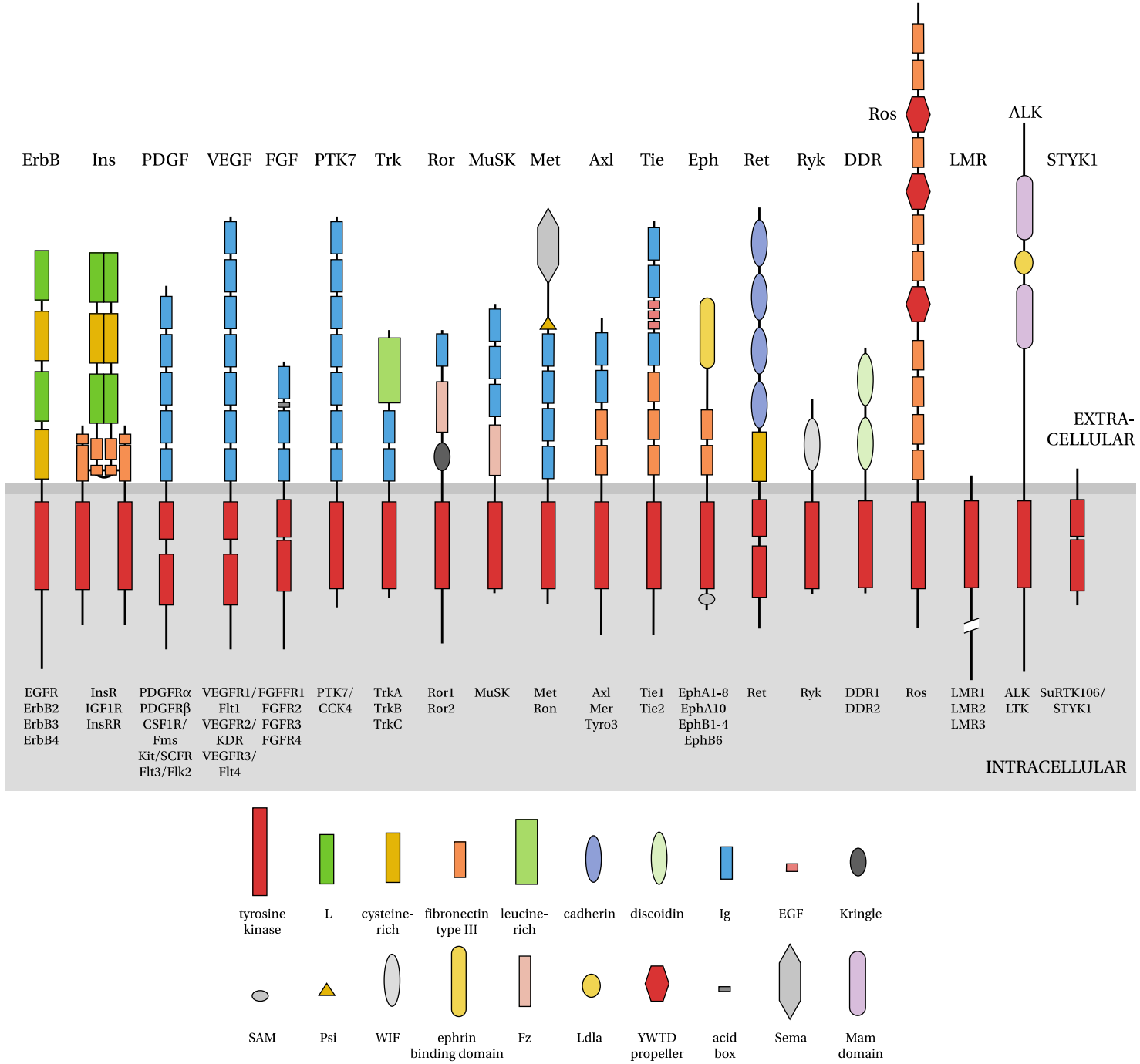
Receptor tyrosine kinases (RTKs) are high affinity cell surface receptors

Polypeptide
Growth factors
Cytokines
Hormones

RTKs are characterized by specific domains

i) Extracellular portion that interact with the ligand
ii) Single transmembrane domain
iii) Tyrosine kinase domain in part exposed to the cell interior.

Human receptor tyrosine kinases (RTKs) contain 20 subfamilies



Receptor kinase mechanism

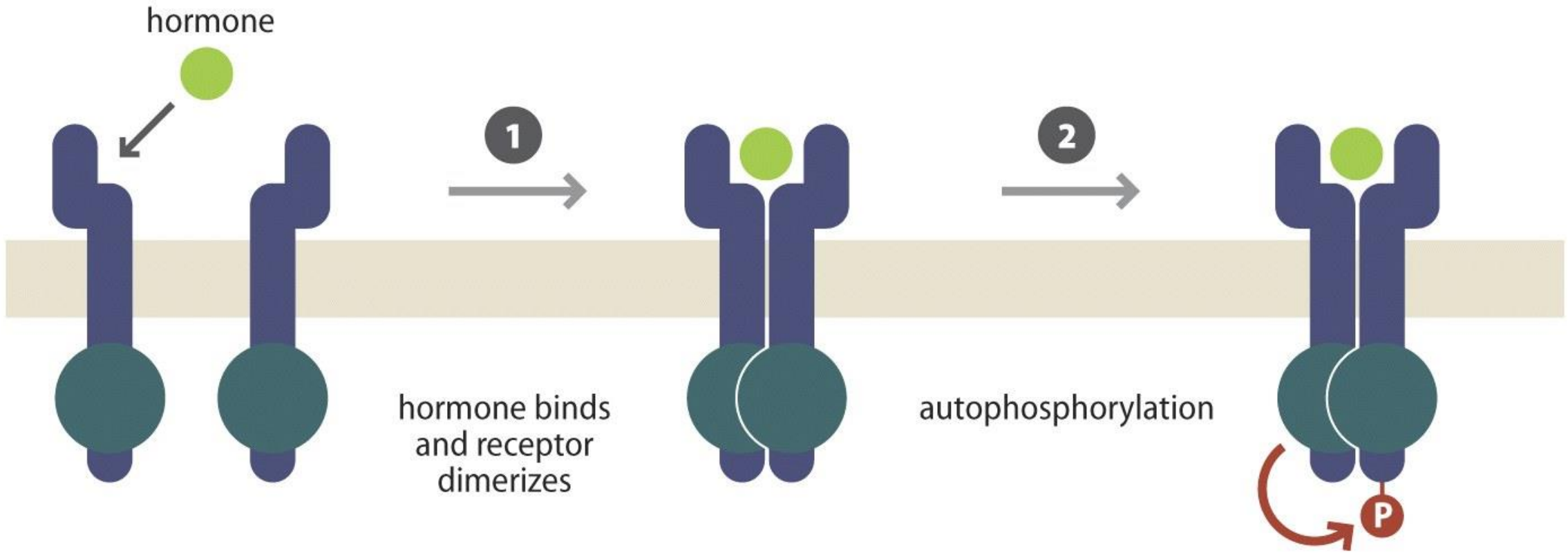
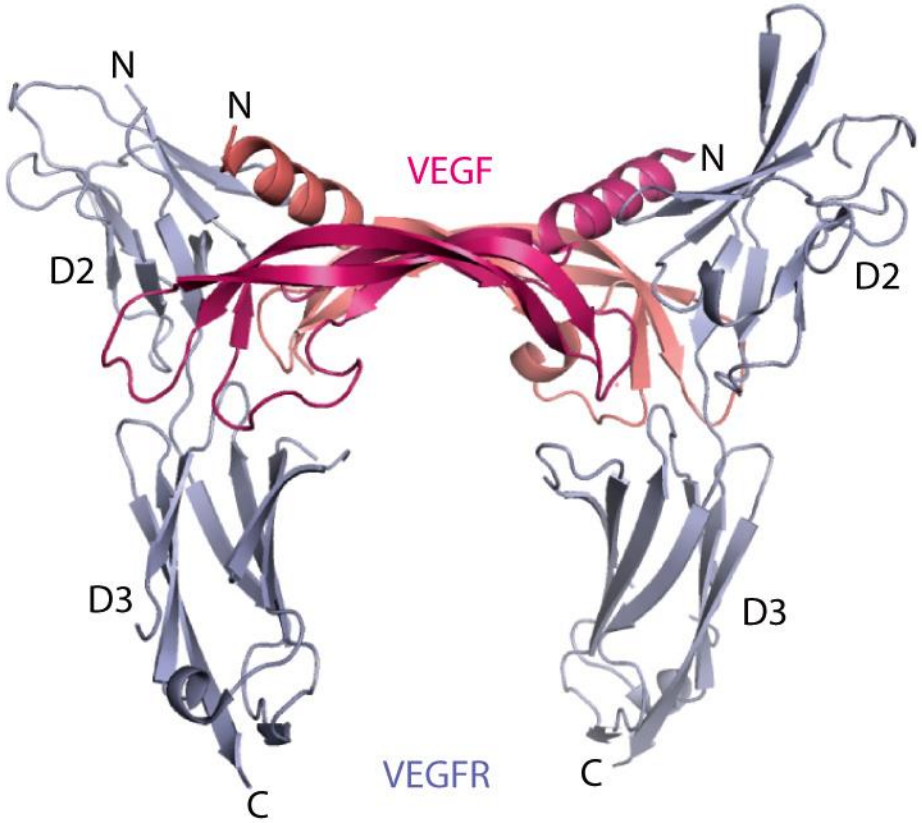


Figure 8.3 How Proteins Work (©2012 Garland Science)

Ligand as dimer

Vascular endothelial growth factor (VEGF)



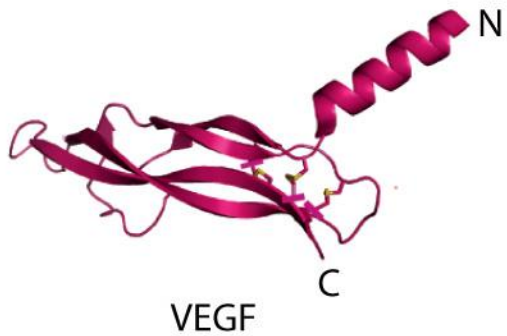
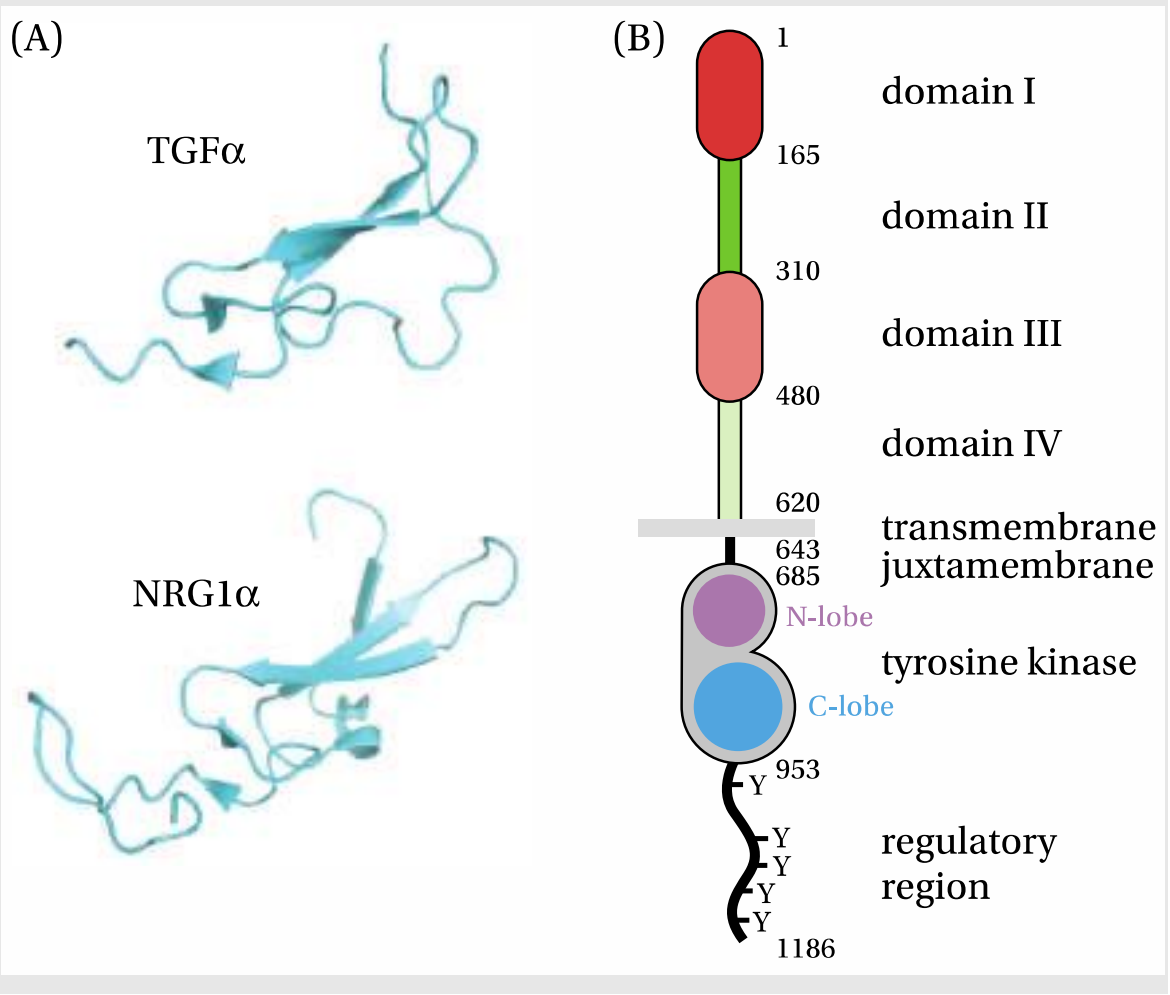
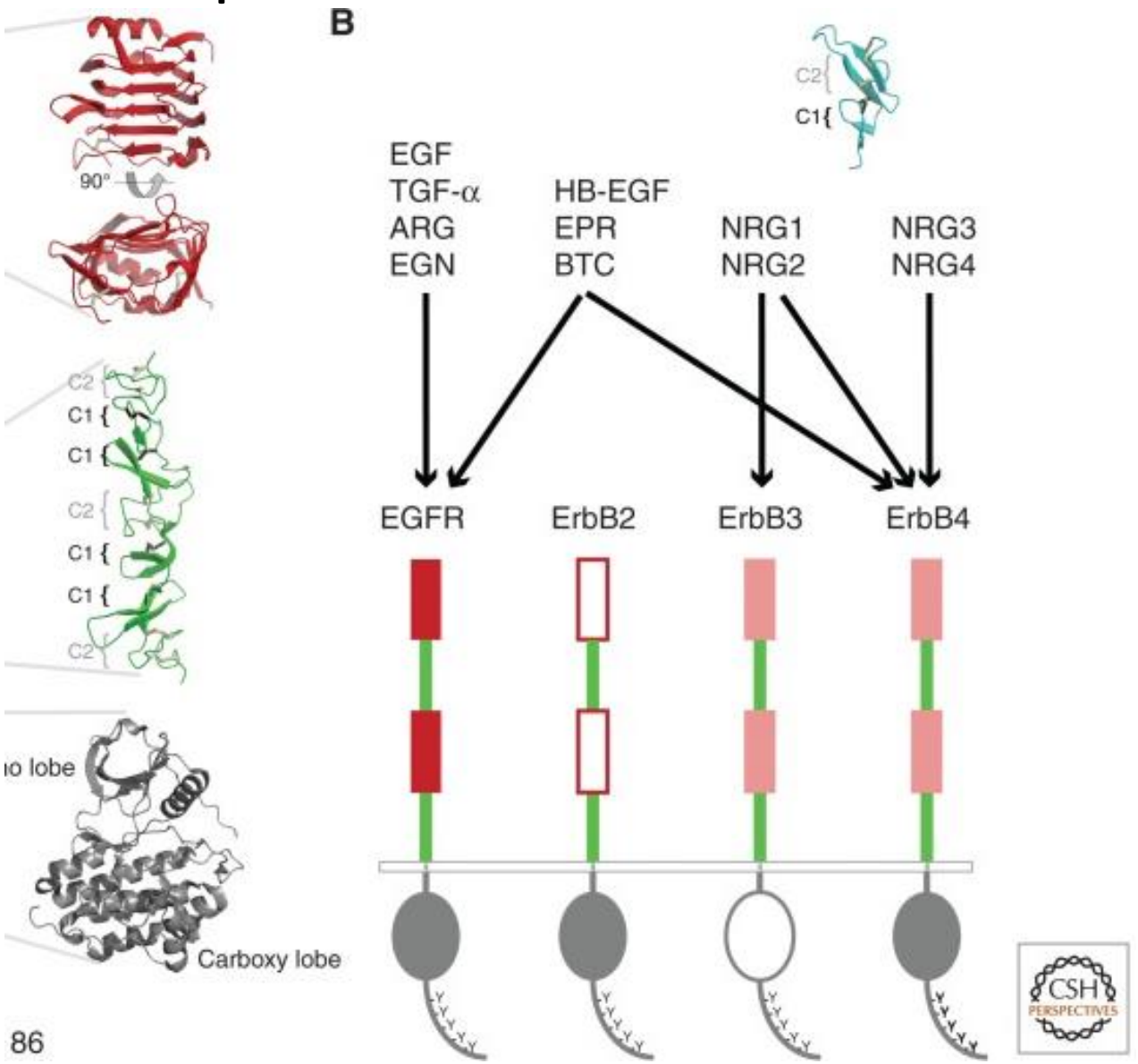


Figure 12.18a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

epidermal growth factor receptor





Dimerization of receptor

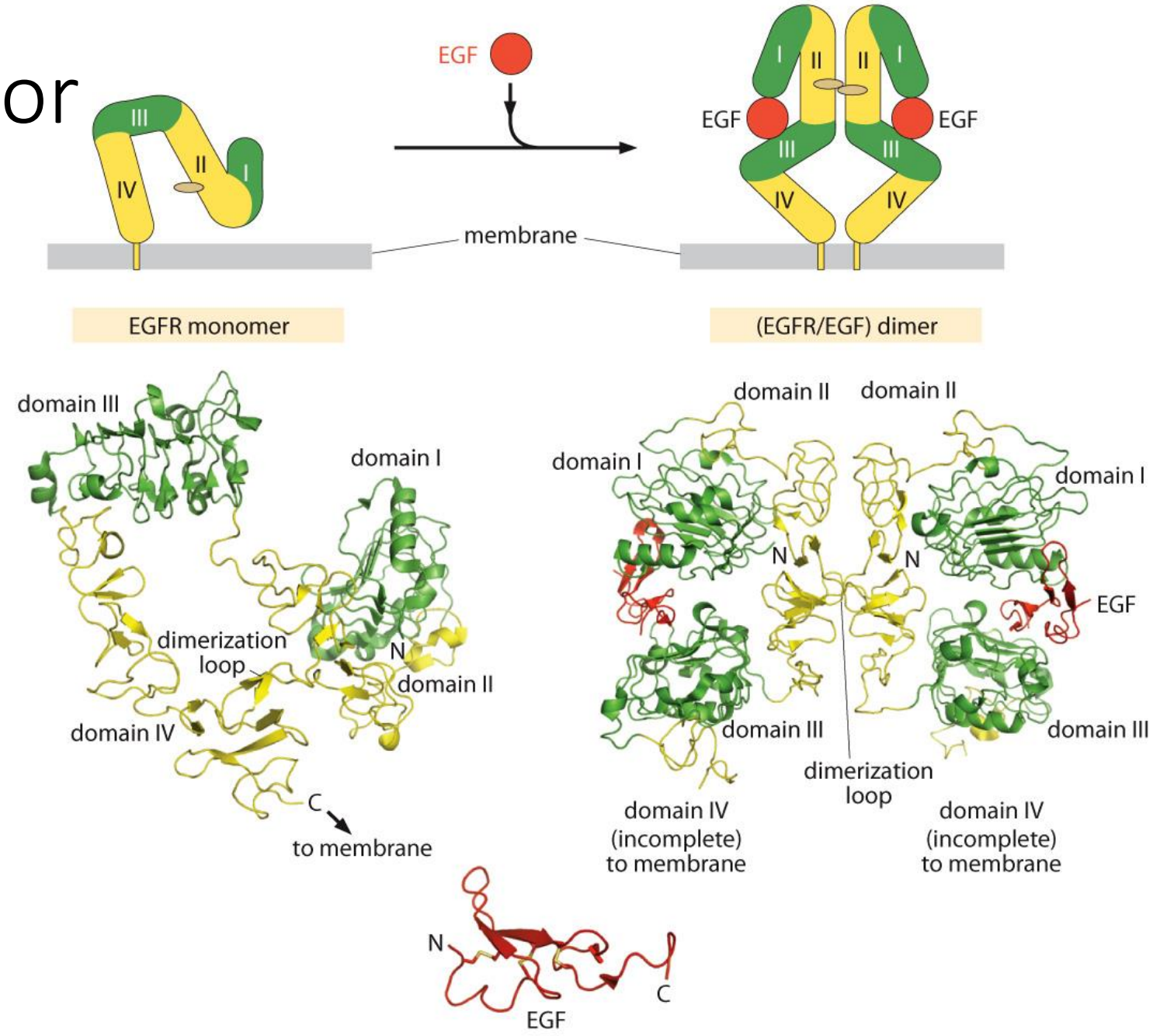
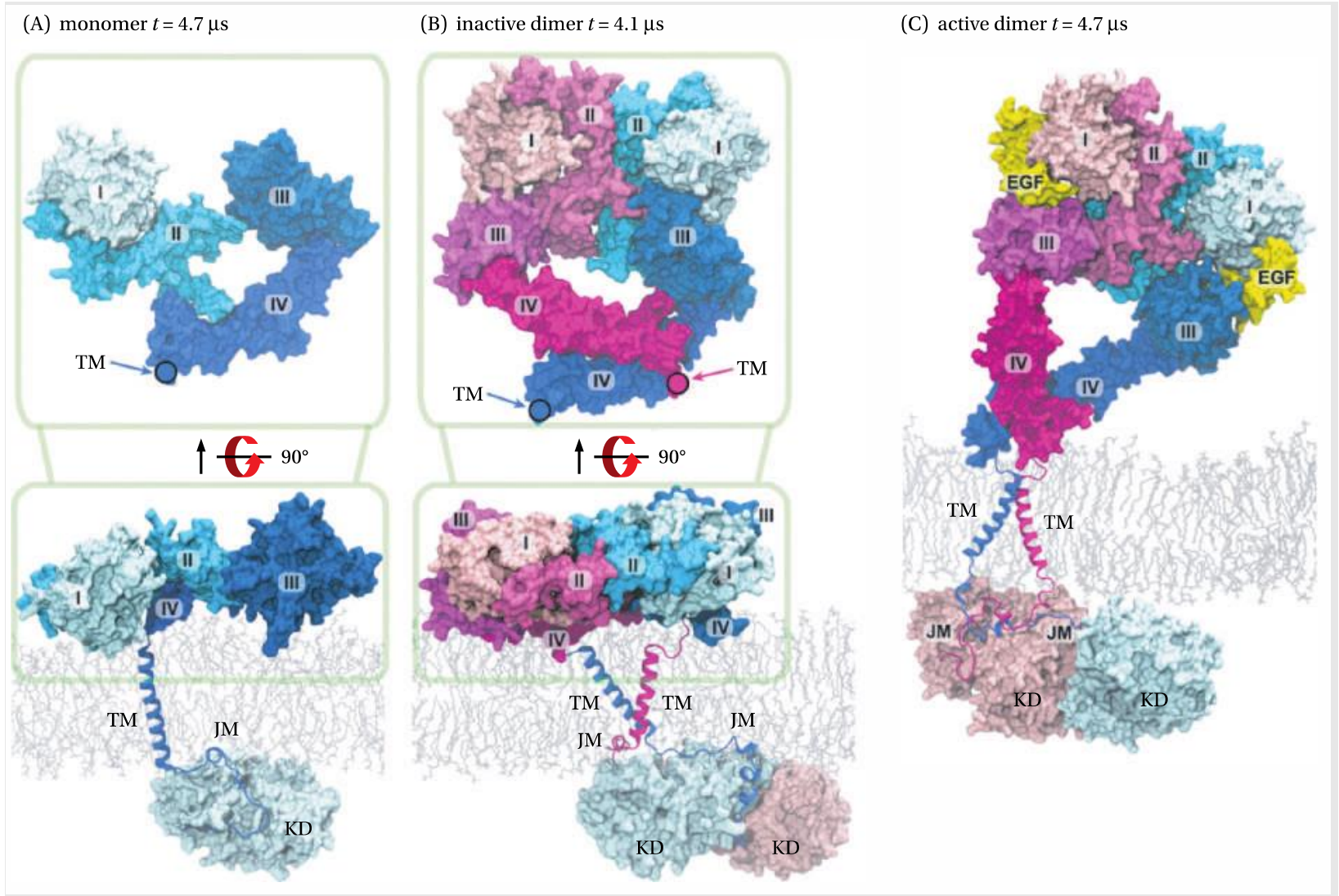
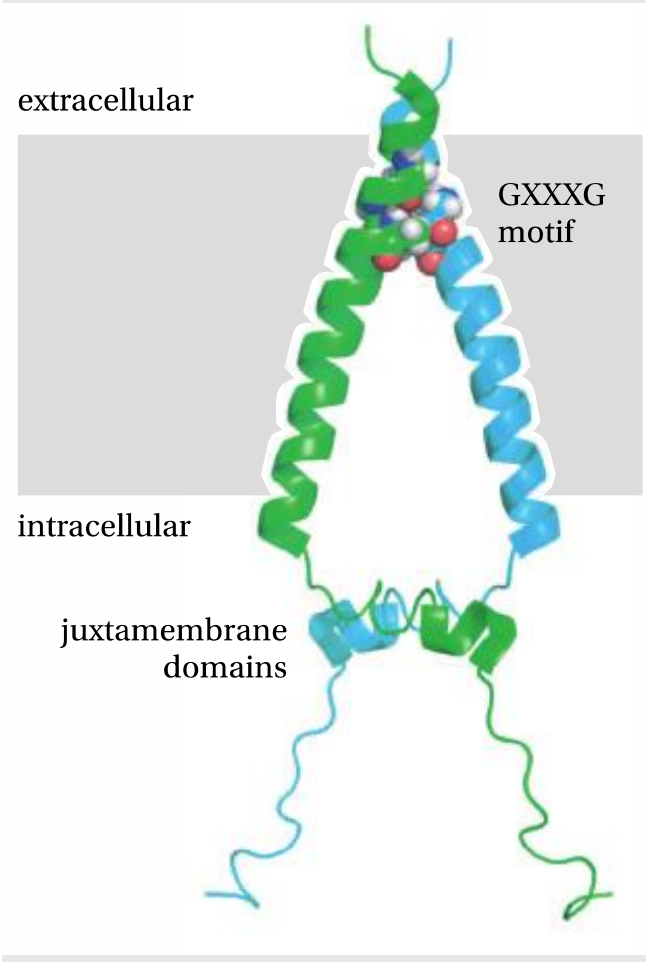


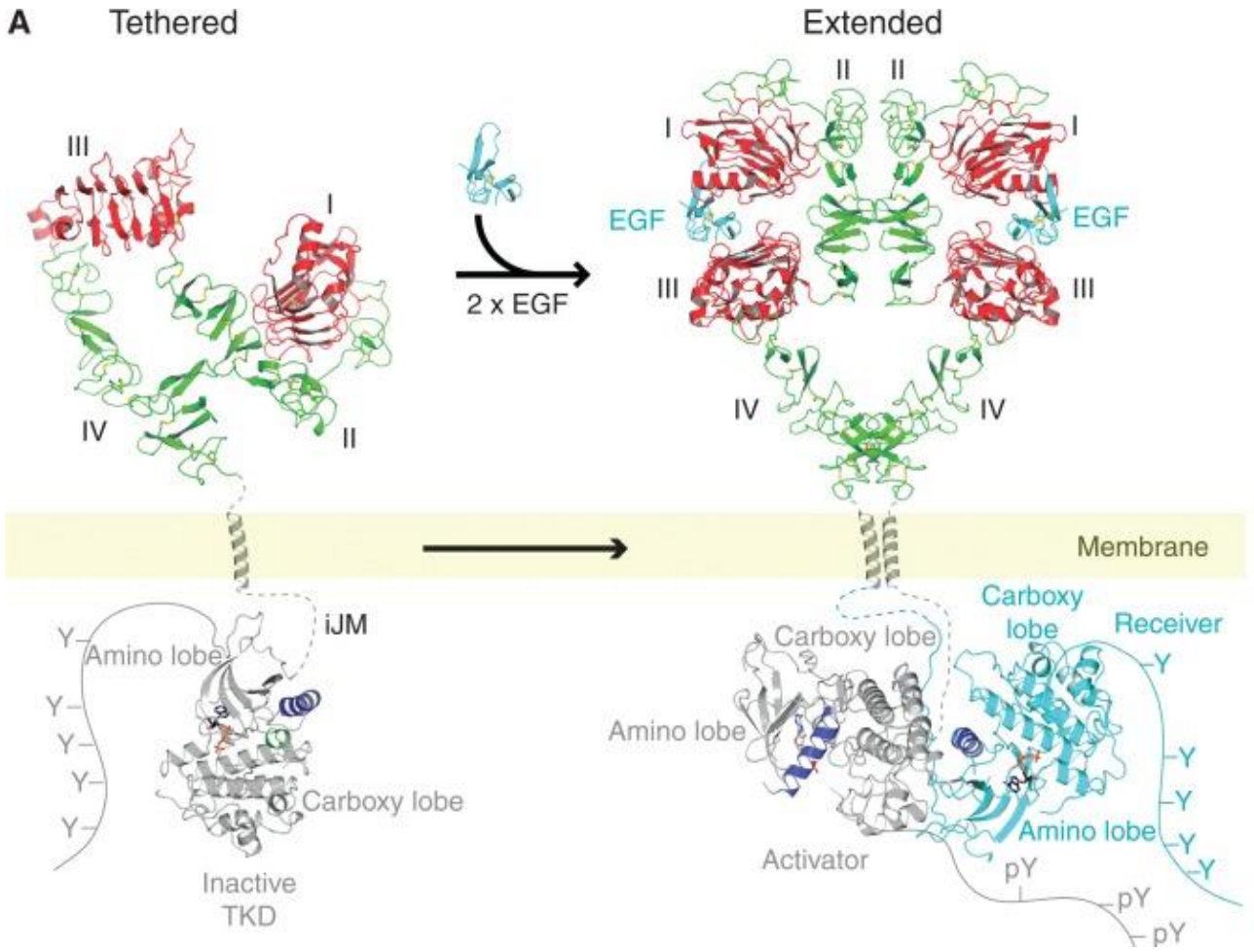
Figure 12.18b Molecular Biology of Assemblies and Machines (© Garland Science 2016)

the epidermal growth factor

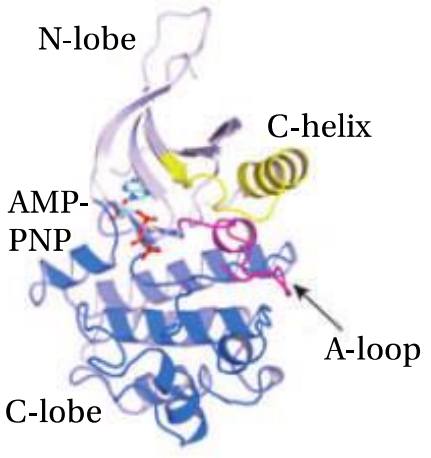




Activation

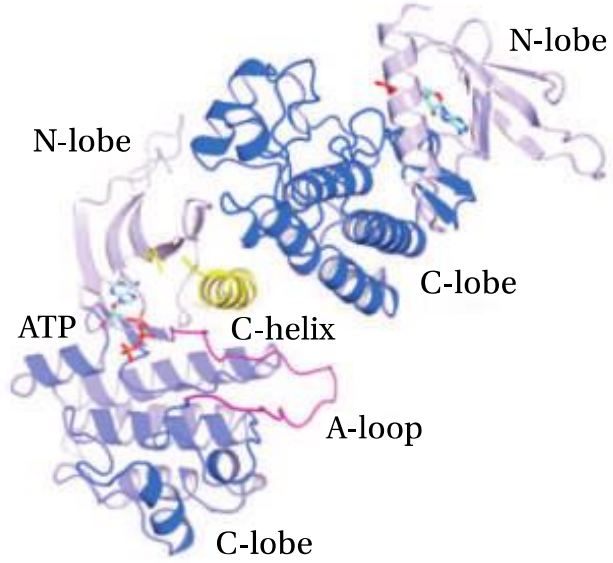


(A)



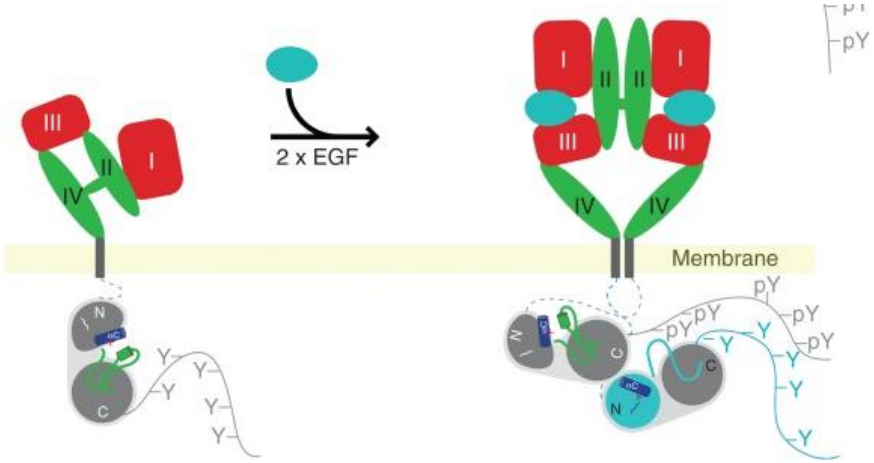
inactive kinase domain

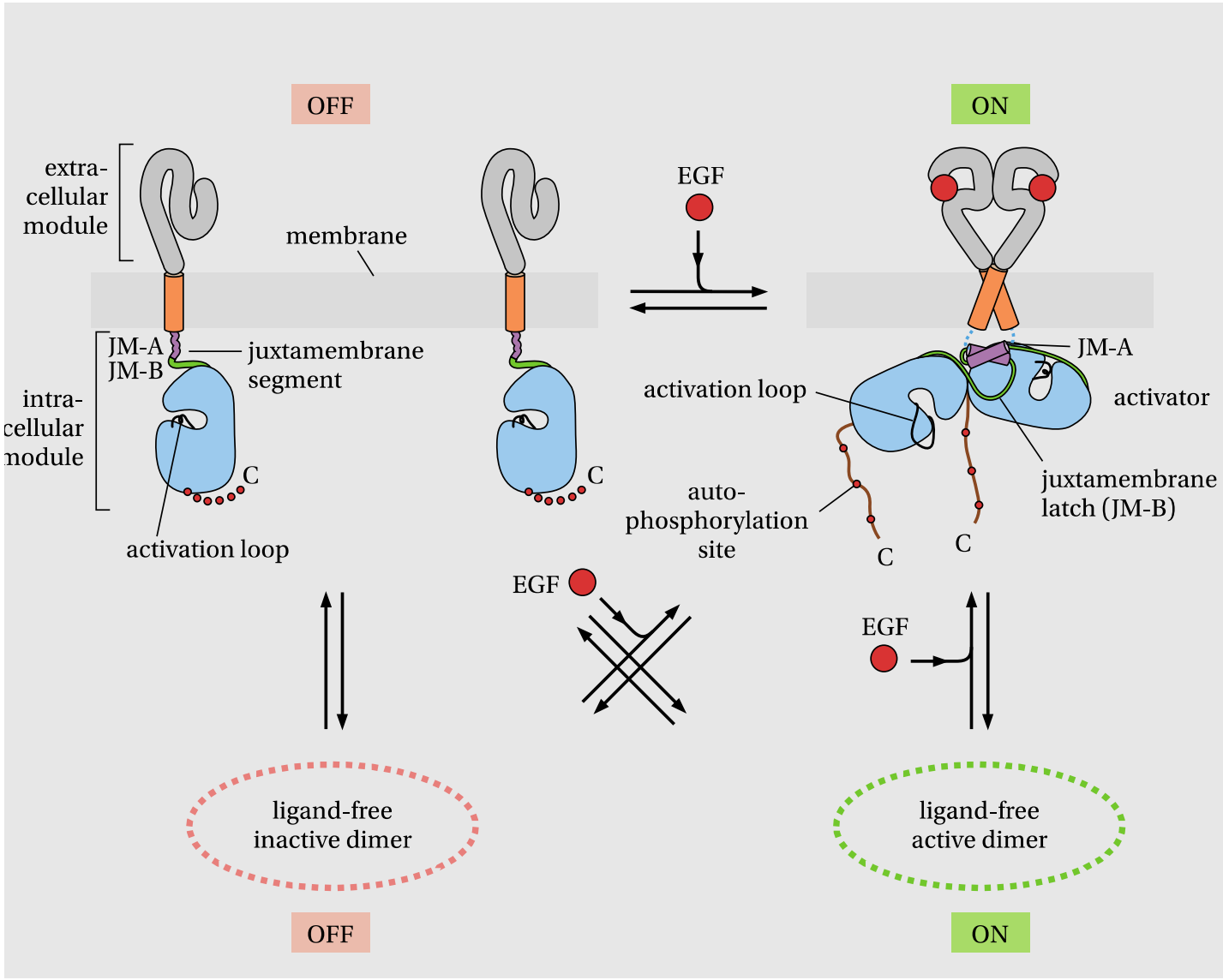
(B) cyclin-like kinase domain



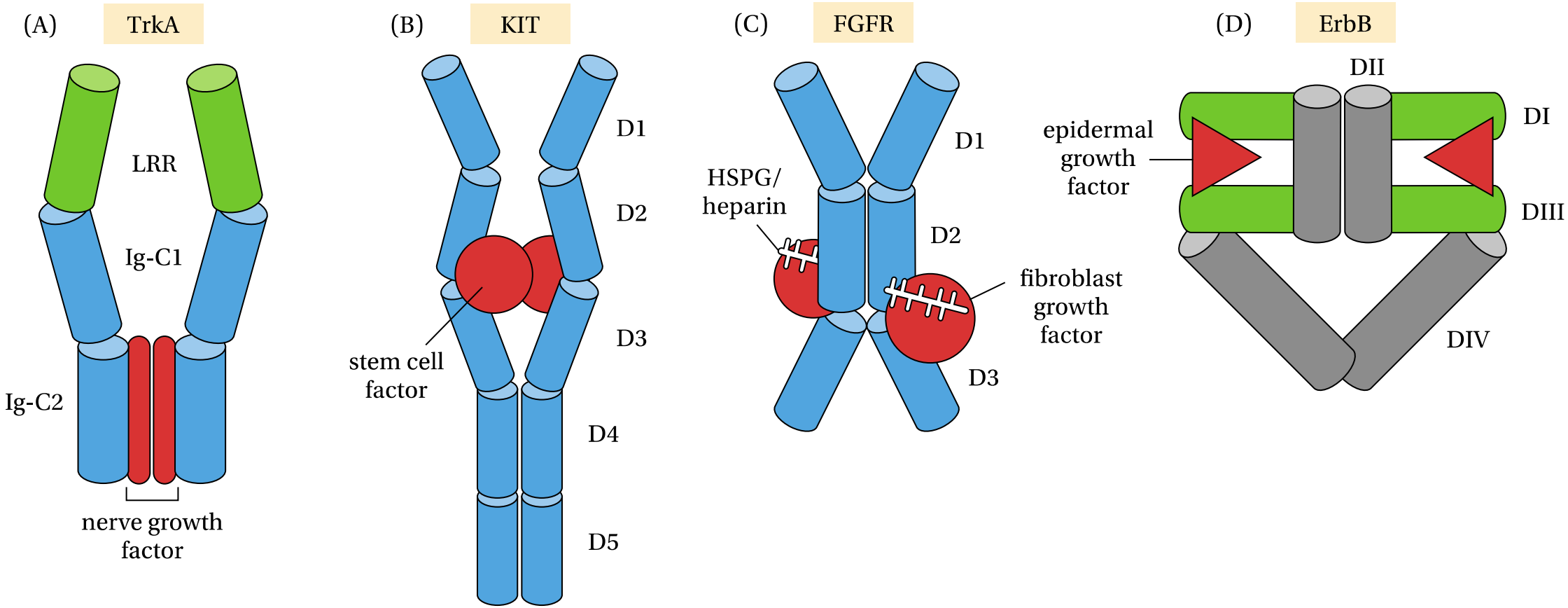
activated kinase domain

B

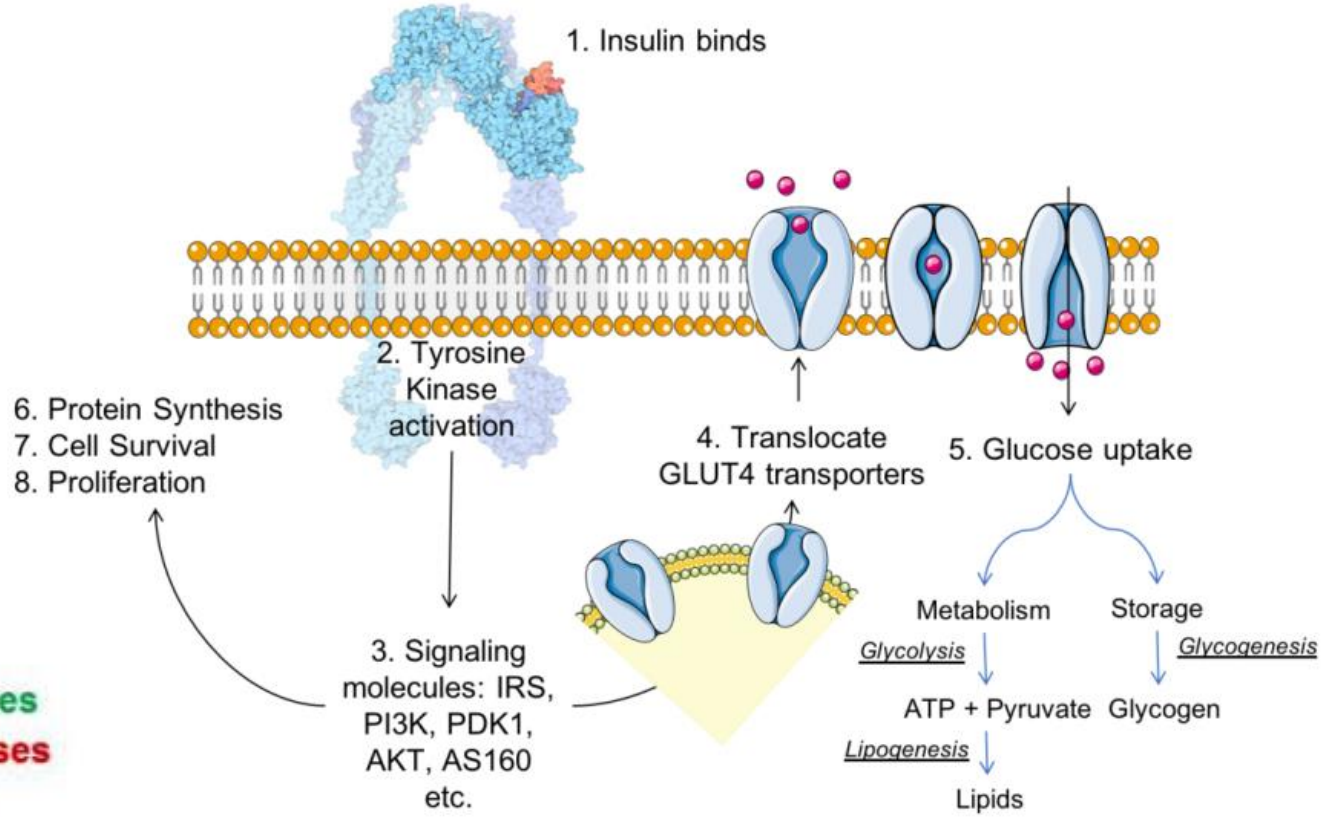

2 x EGF
Membrane
pY
Y

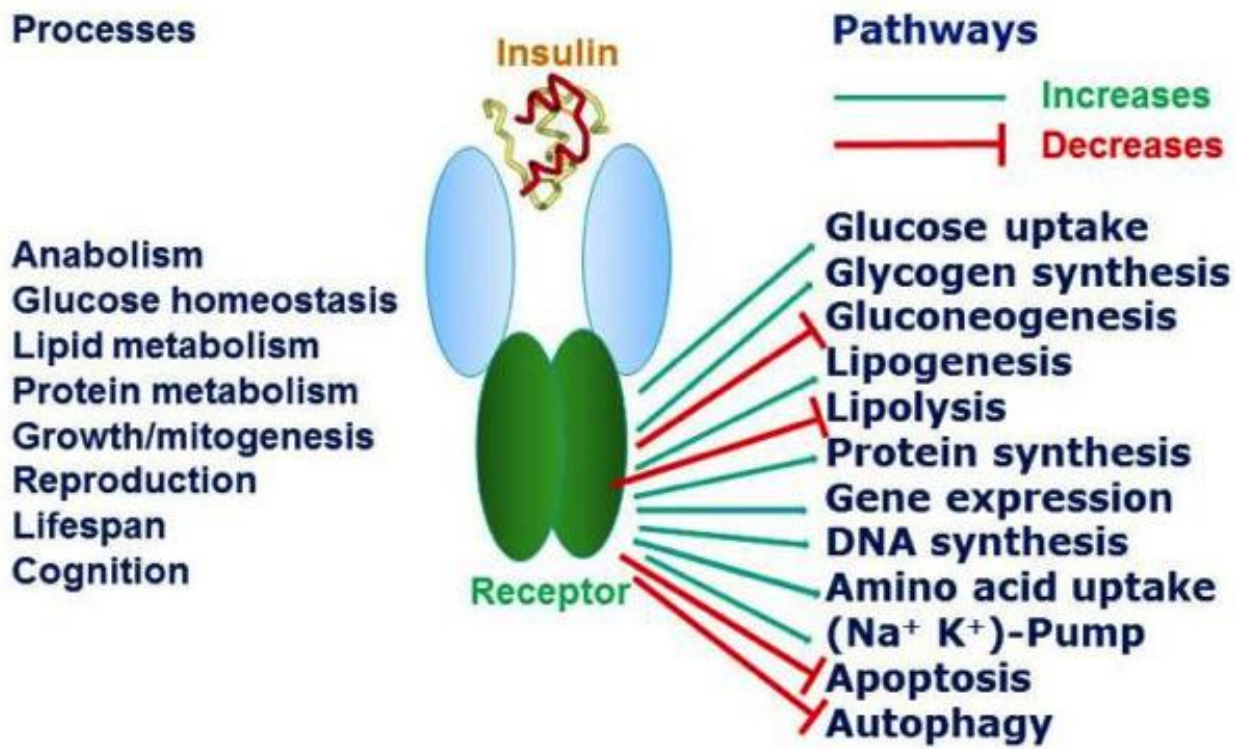

OFF
ON
extra-
cellular
module
membrane
EGF
JM-A
JM-B
juxtamembrane
segment
intra-
cellular
module
activation loop
C
auto-
phosphorylation
site
activator
JM-A
juxtamembrane
latch (JM-B)
ligand-free
inactive dimer
ligand-free
active dimer
OFF
ON

four different ways to induce signaling.



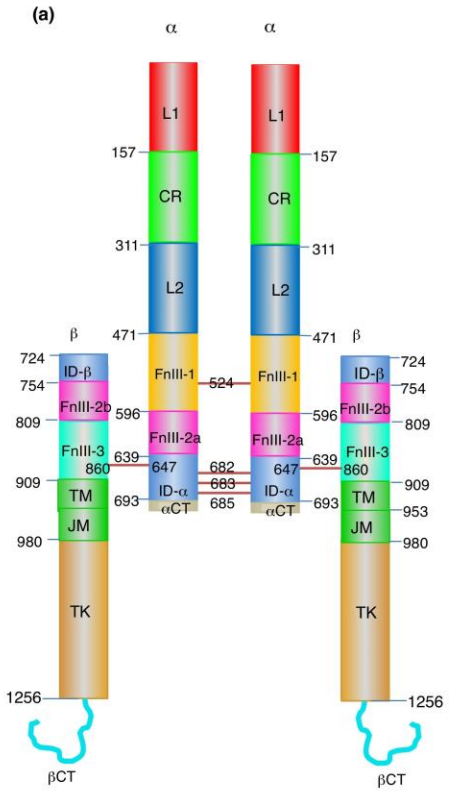
Insulin receptor

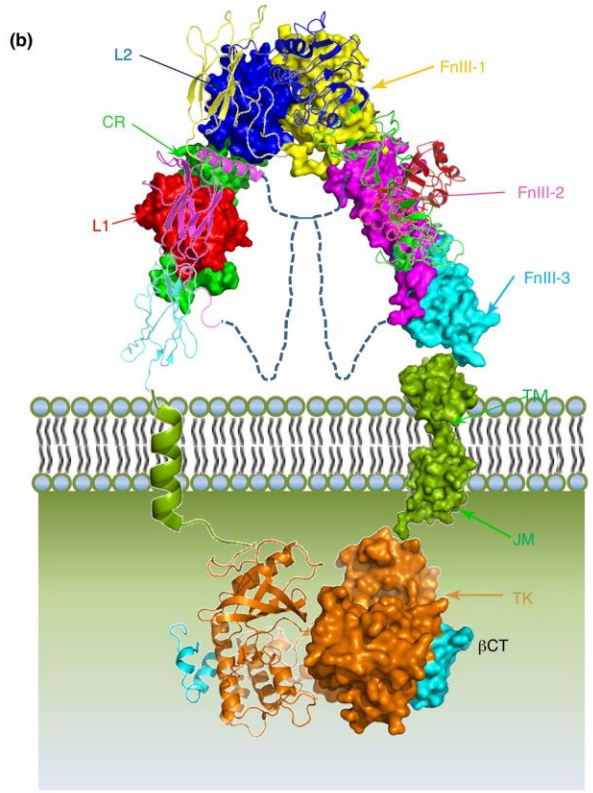




insulin receptor

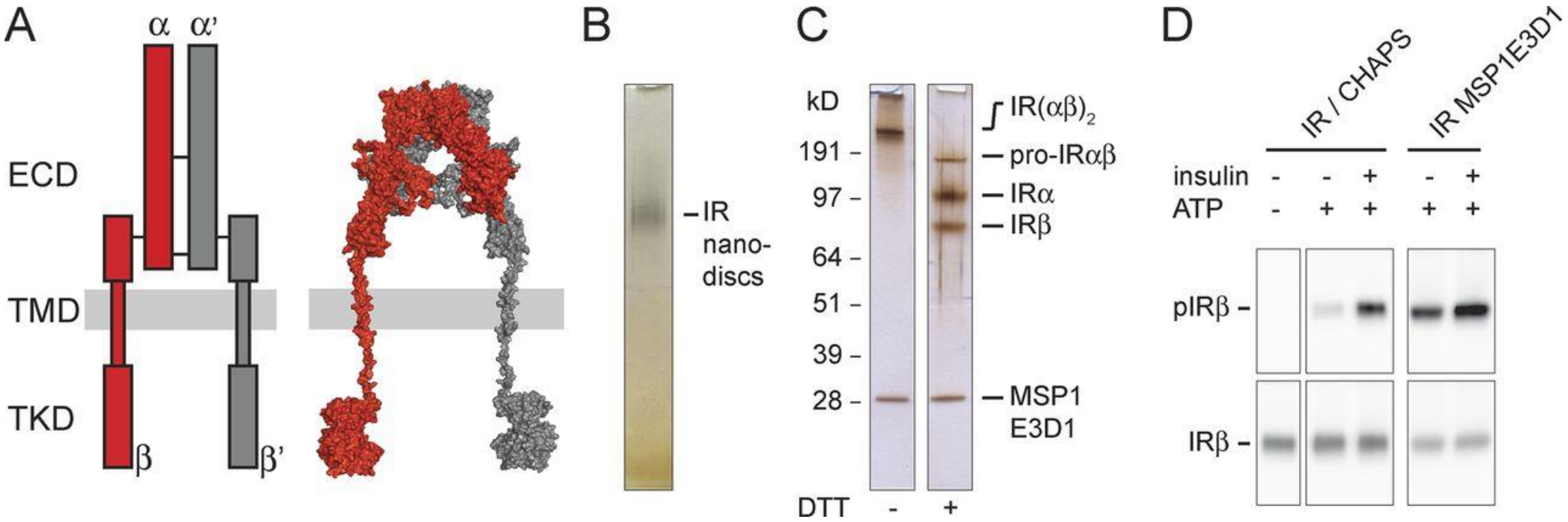
$\alpha_2\beta_2$ heterotetramer





(c) Domain architectures of resolved IR structures	PDB IDs
L1 CR L2 FnIII-1 FnIII-2a ID-α αCT ID-β FnIII-2b FnIII-3 TM JM TK βCT	Composition of full-length IR (no structure)
	4ZXB [11], 3LOH [14]
	2DTG [13,78]
	3W14 [10]
	3W11, 3W12, 3W13 [10], 4OGA [29]
	2HR7 [23]
	2MFR [16]
	1IRK [9], 1IR3 [32], 1GAG [79], 1I44 [80], 1P14 [81], 2AUH [82], 2B4S [83], 3BU3, 3BU5, 3BU6 [84], 2Z8C [85], 4XLV [18]

IR reconstitution into nanodiscs and activity assay



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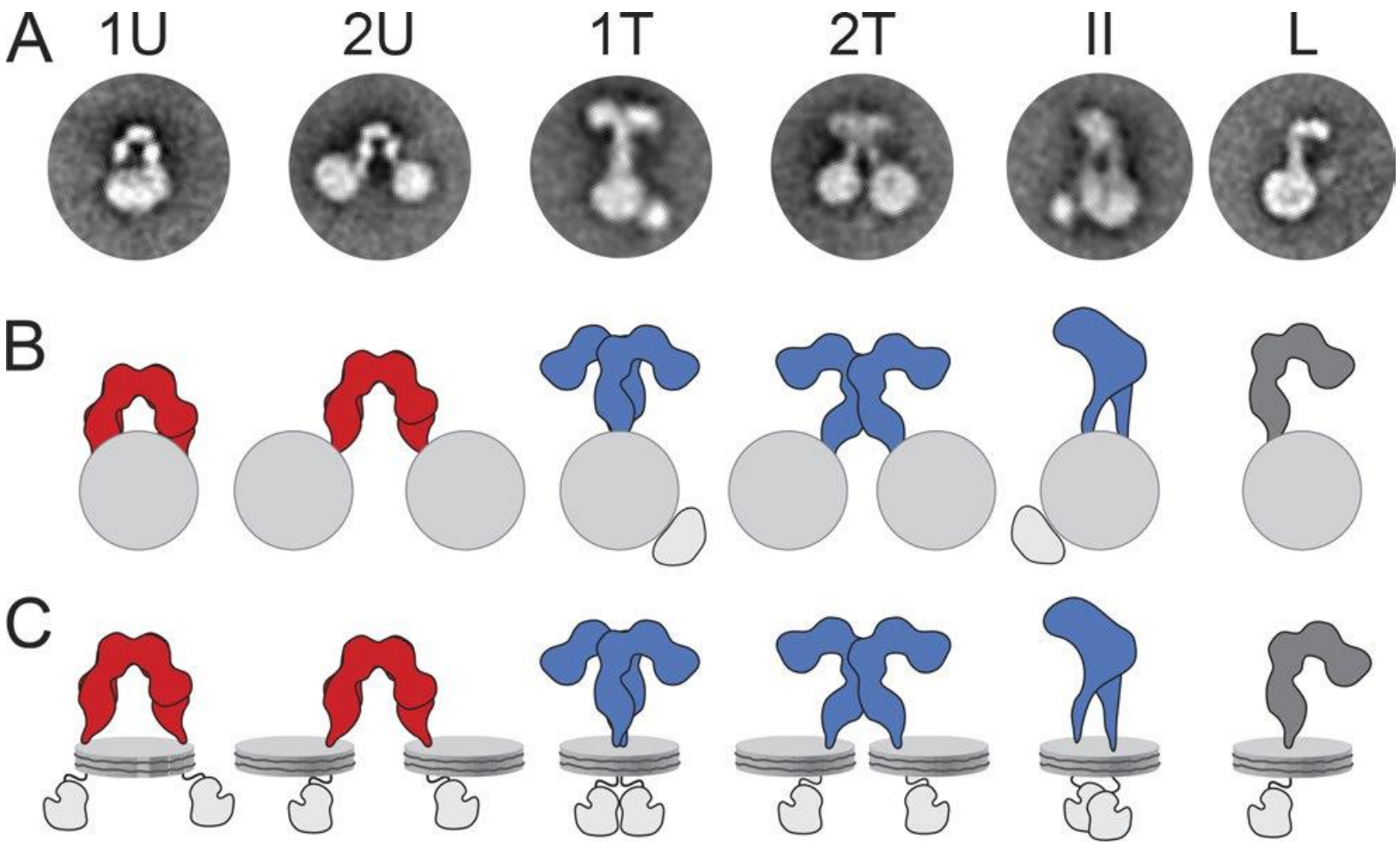
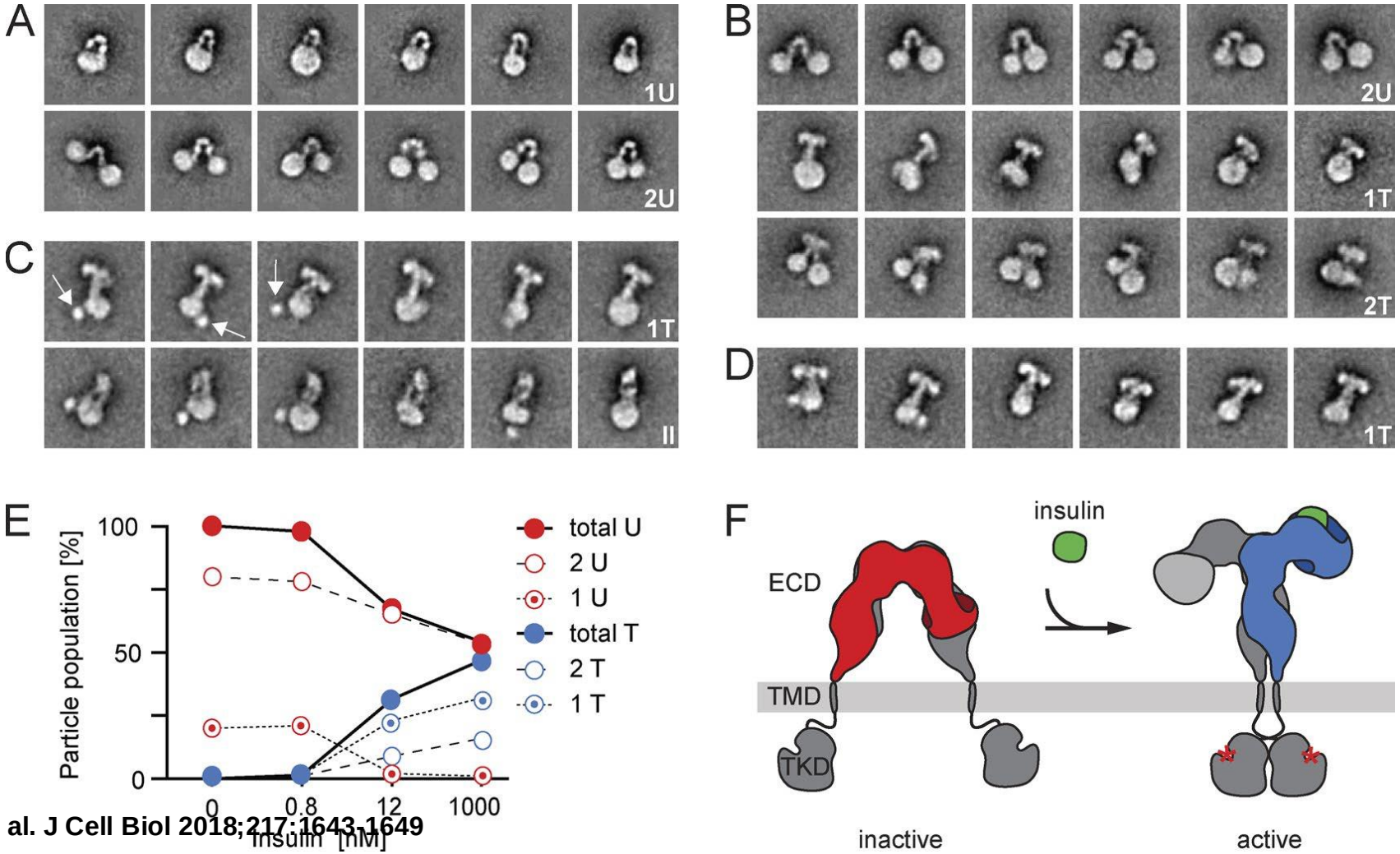
Conformations assigned to IRs in nanodiscs.



Theresia Gutmann et al. J Cell Biol 2018;217:1643-1649

EM averages of IRs reconstituted into MSP1E3D1 nanodiscs and ligand-induced IR activation



Theresia Gutmann et al. J Cell Biol 2018;217:1643-1649

Insulin receptor TKD

IRK inactive

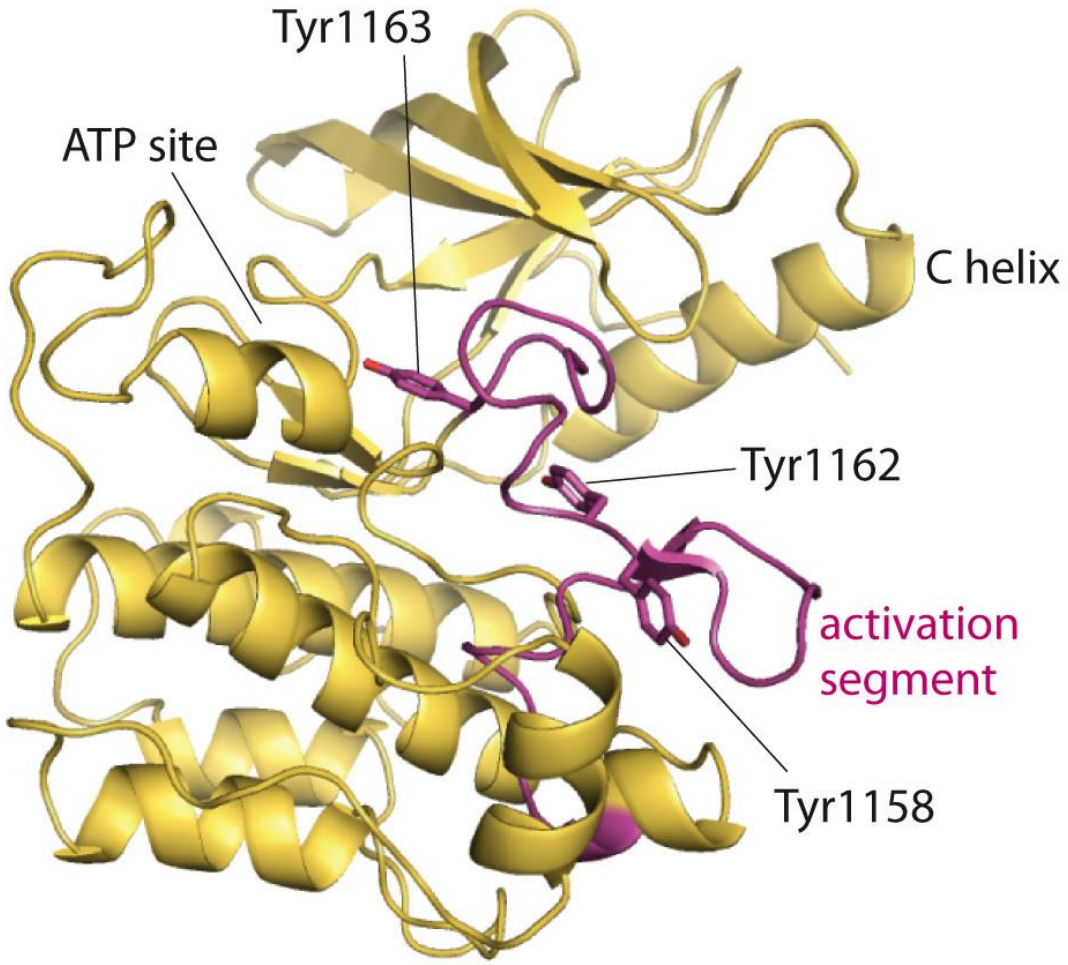


Figure 12.19a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

IRK active

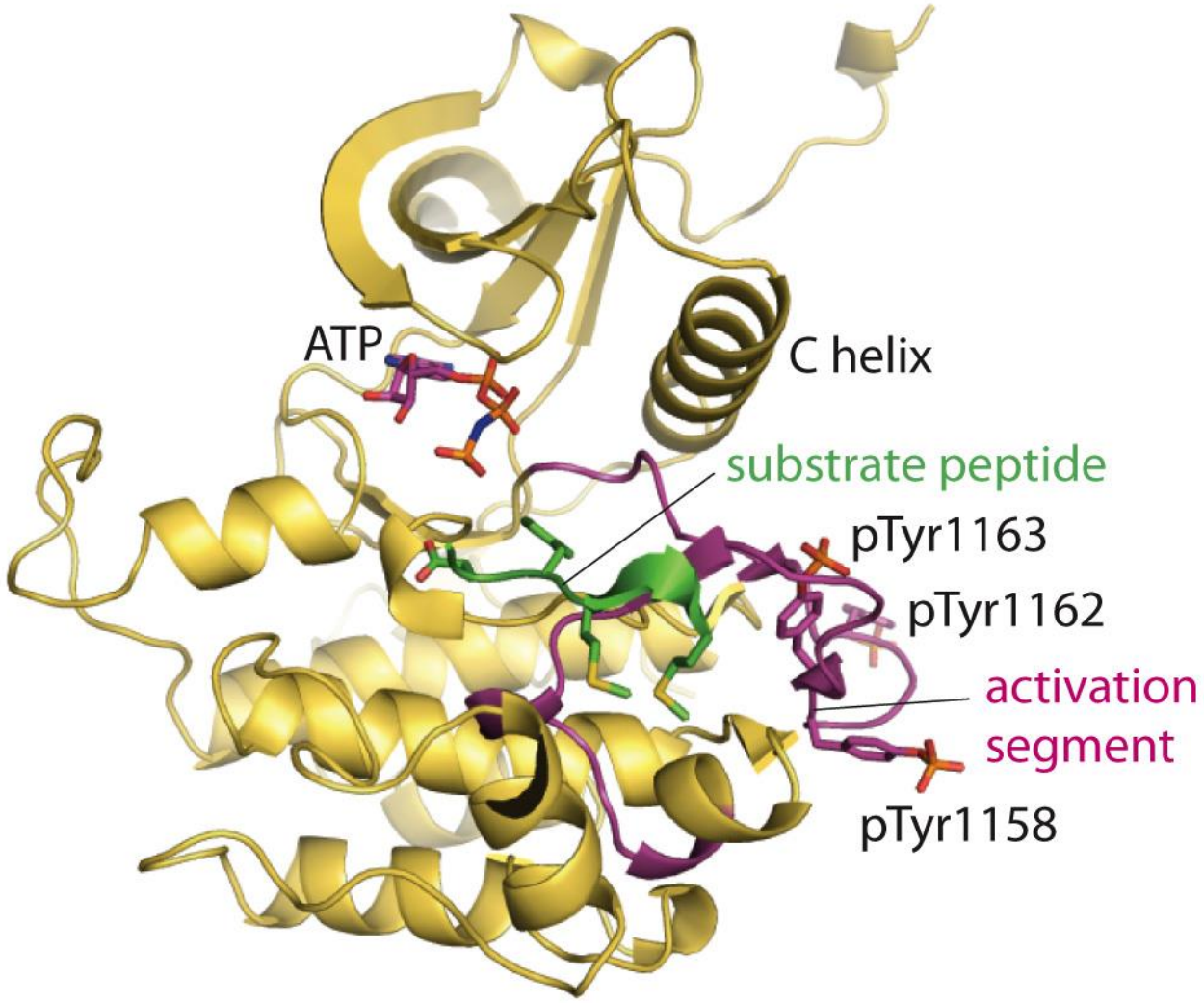


Figure 12.19b Molecular Biology of Assemblies and Machines (© Garland Science 2016)

specificity

Gly-Asp-Tyr-Met-Asn-Met

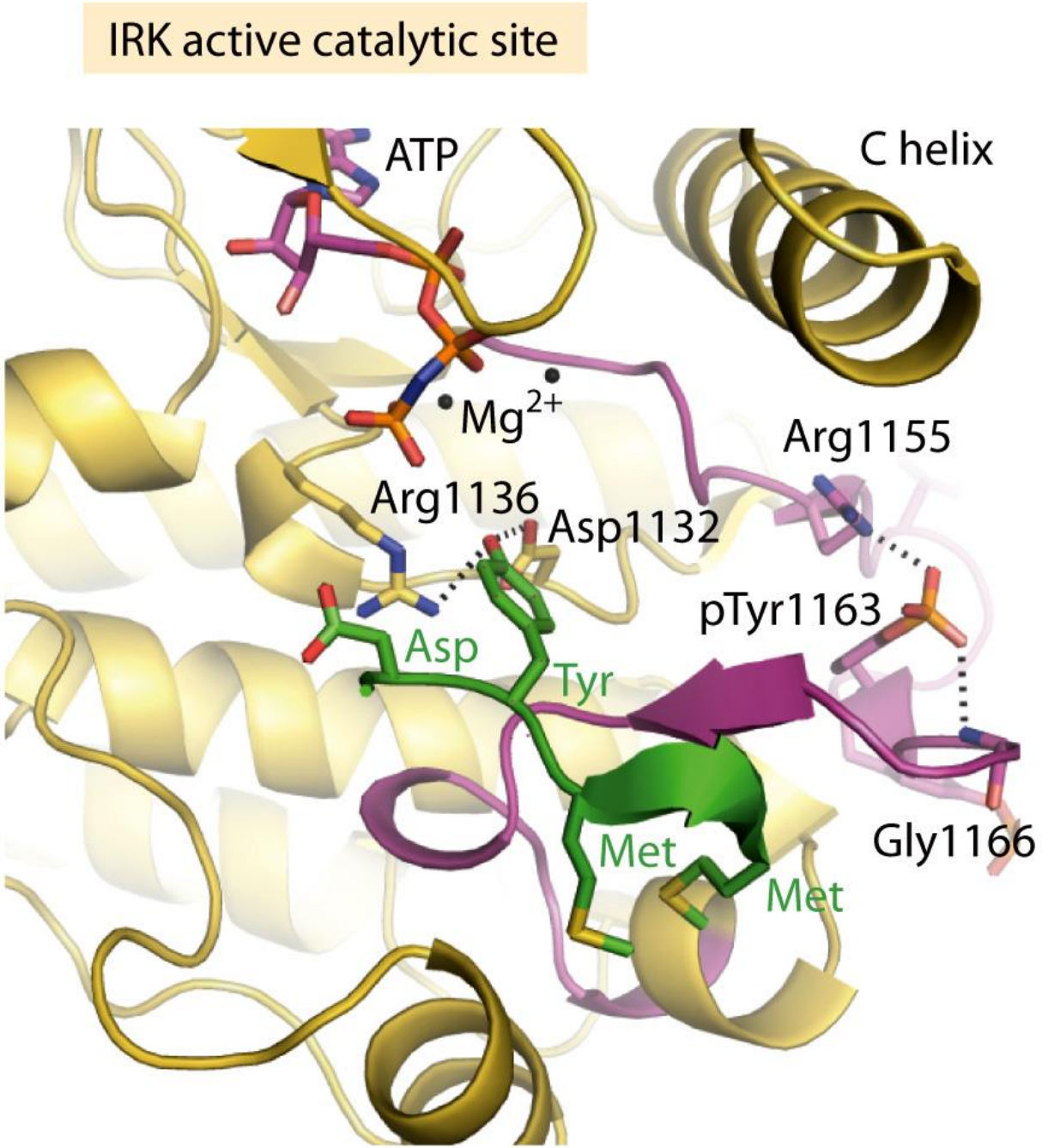


Figure 12.19c Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Two forms

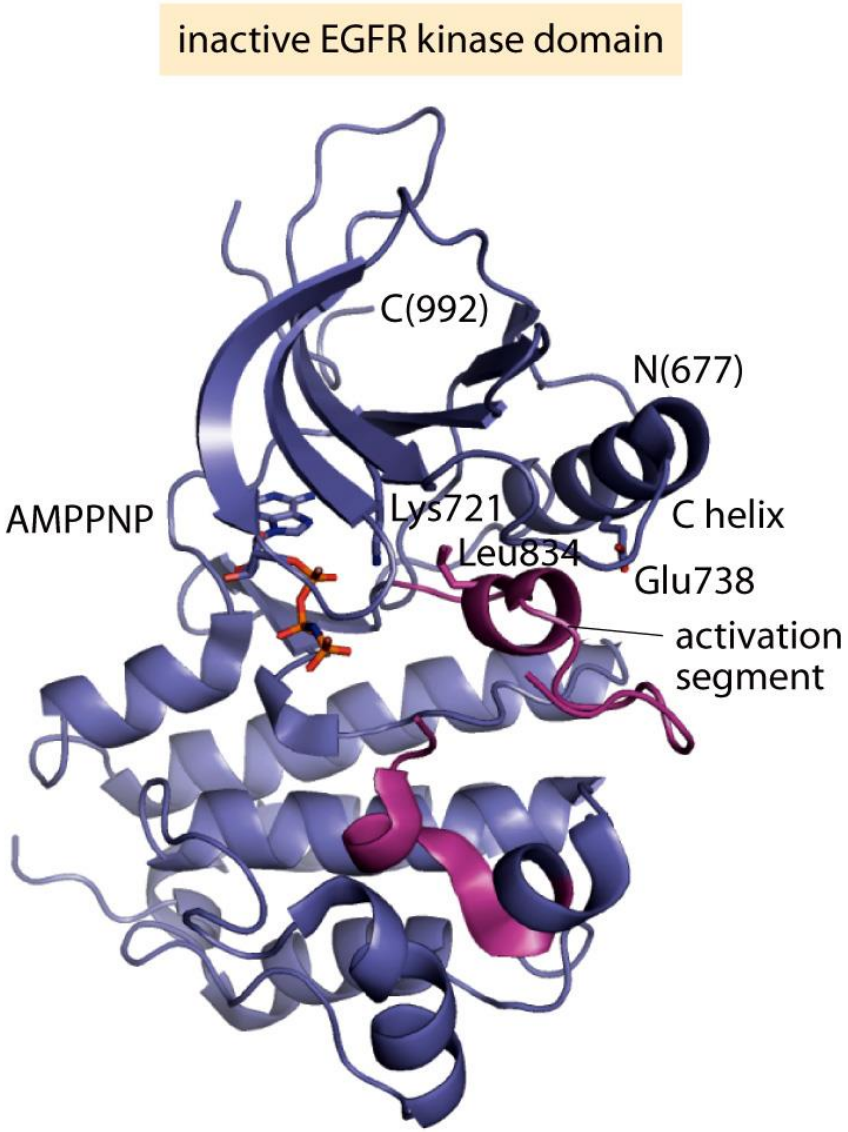


Figure 12.20a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

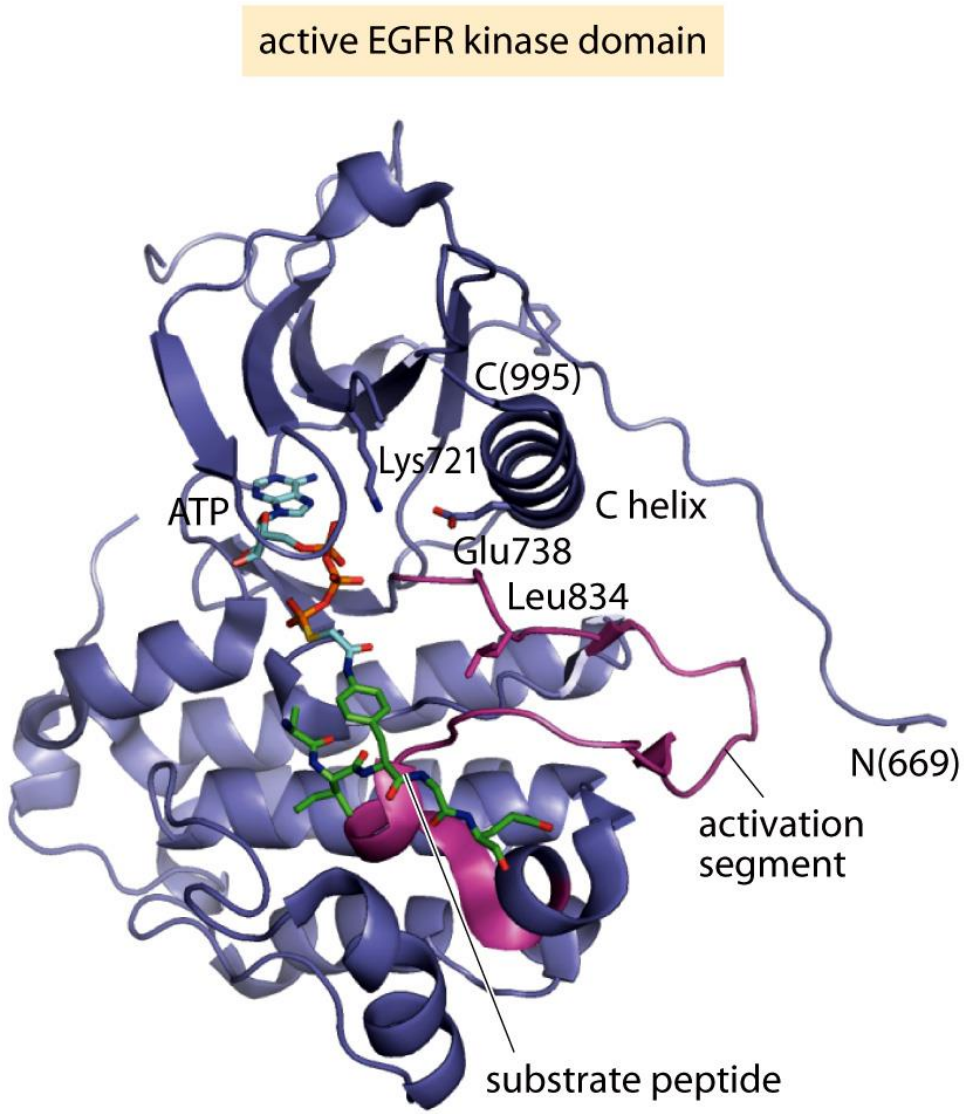
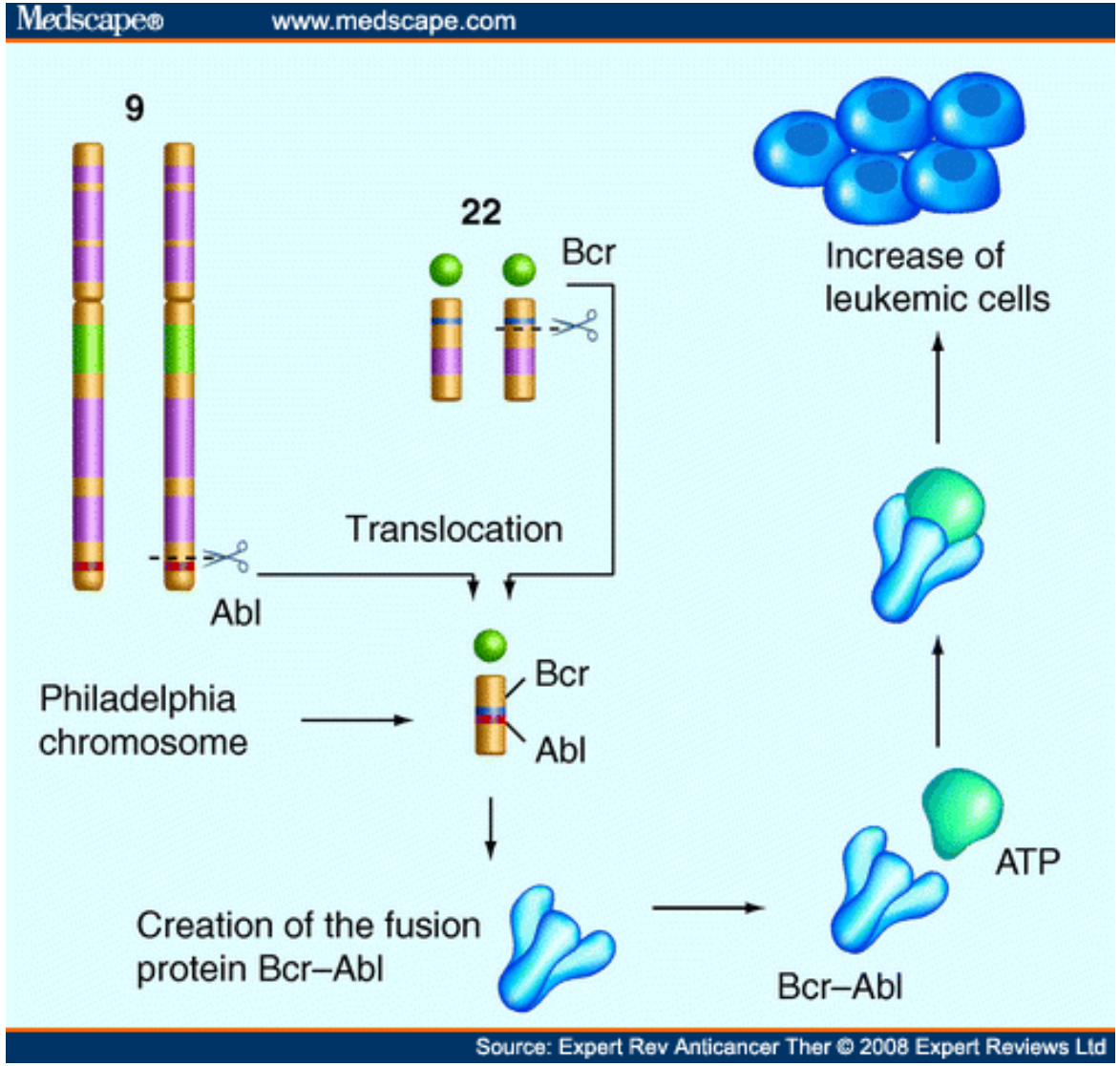
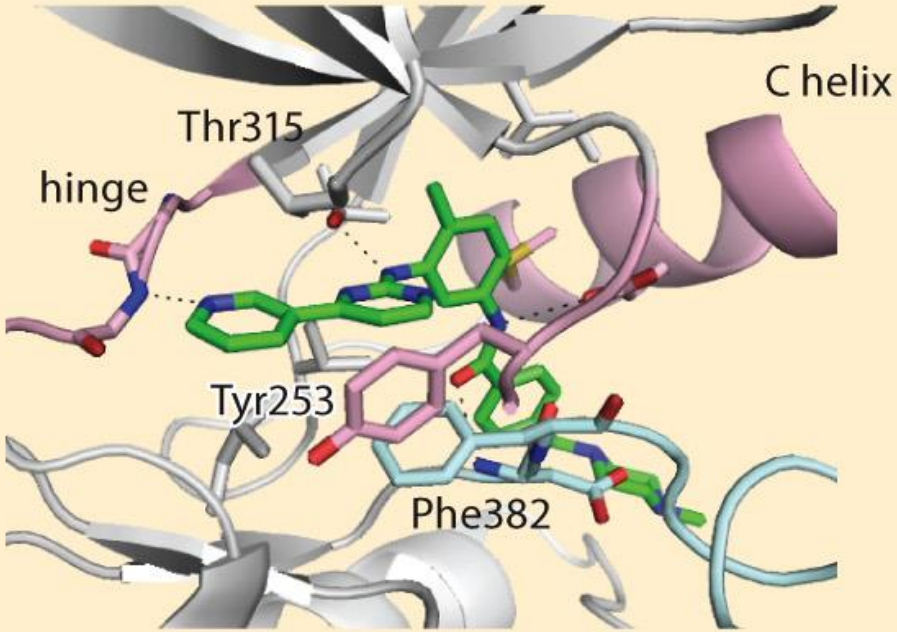


Figure 12.20b Molecular Biology of Assemblies and Machines (© Garland Science 2016)

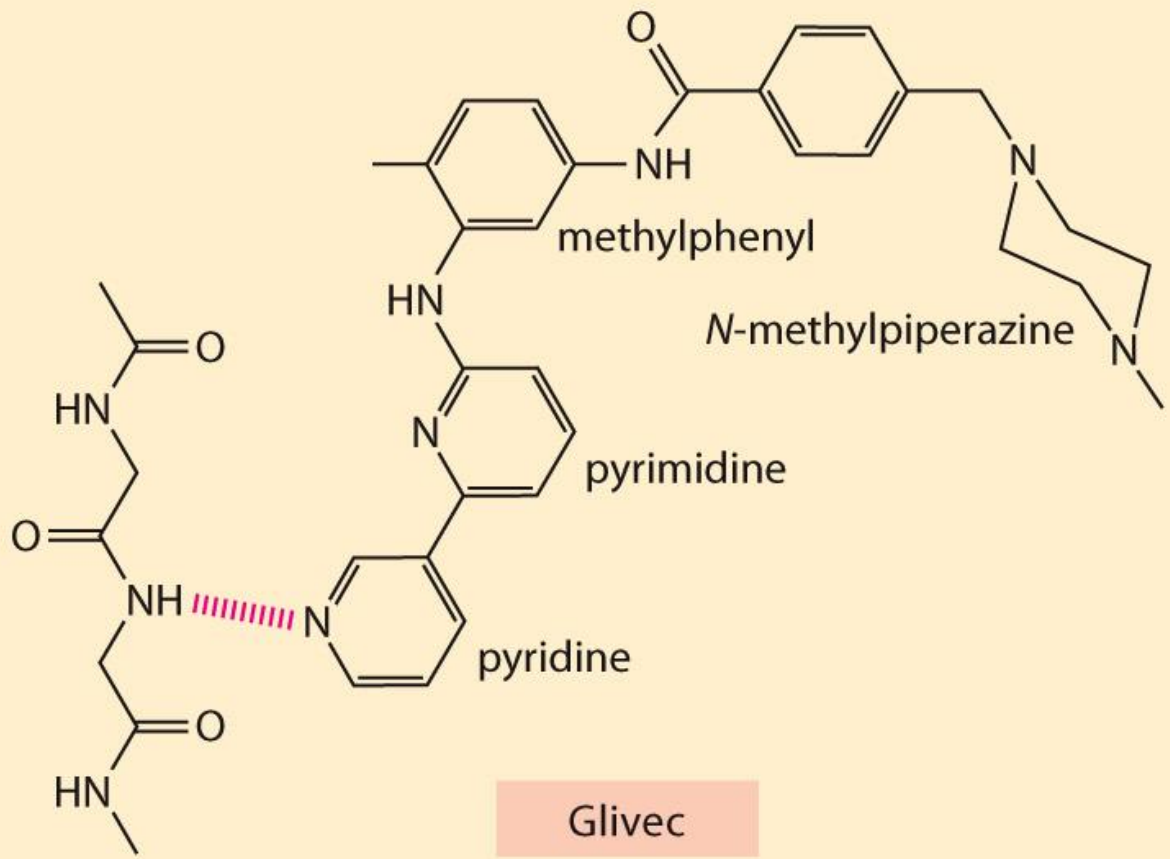
kinase as target



kinase as target



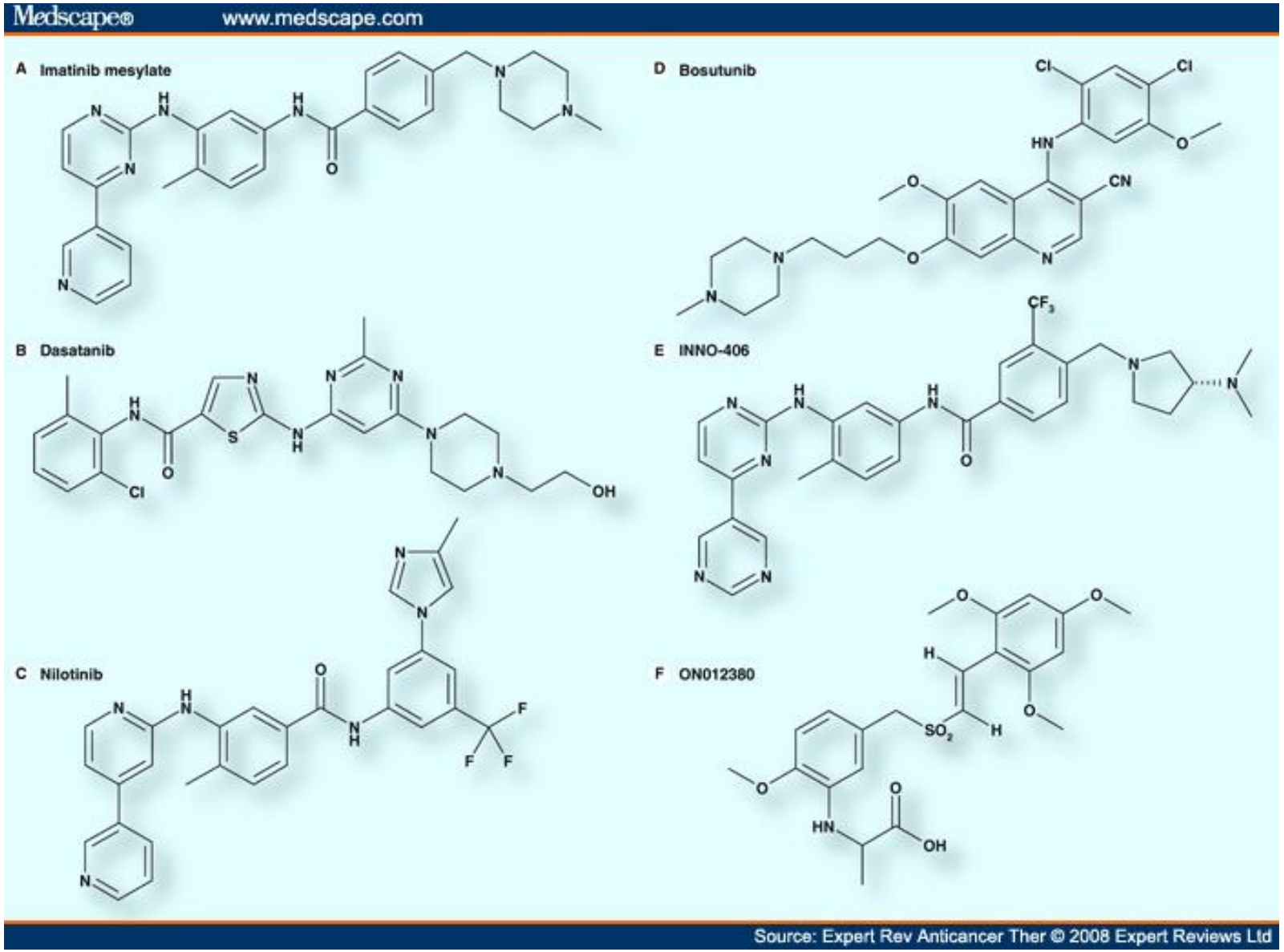
Abl tyrosine kinase/Glivec



Glivec

Box 12.3 Figure 12.3.1a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Abl kinase inhibitors



Structure of novel agents for T315I