

Information transfer

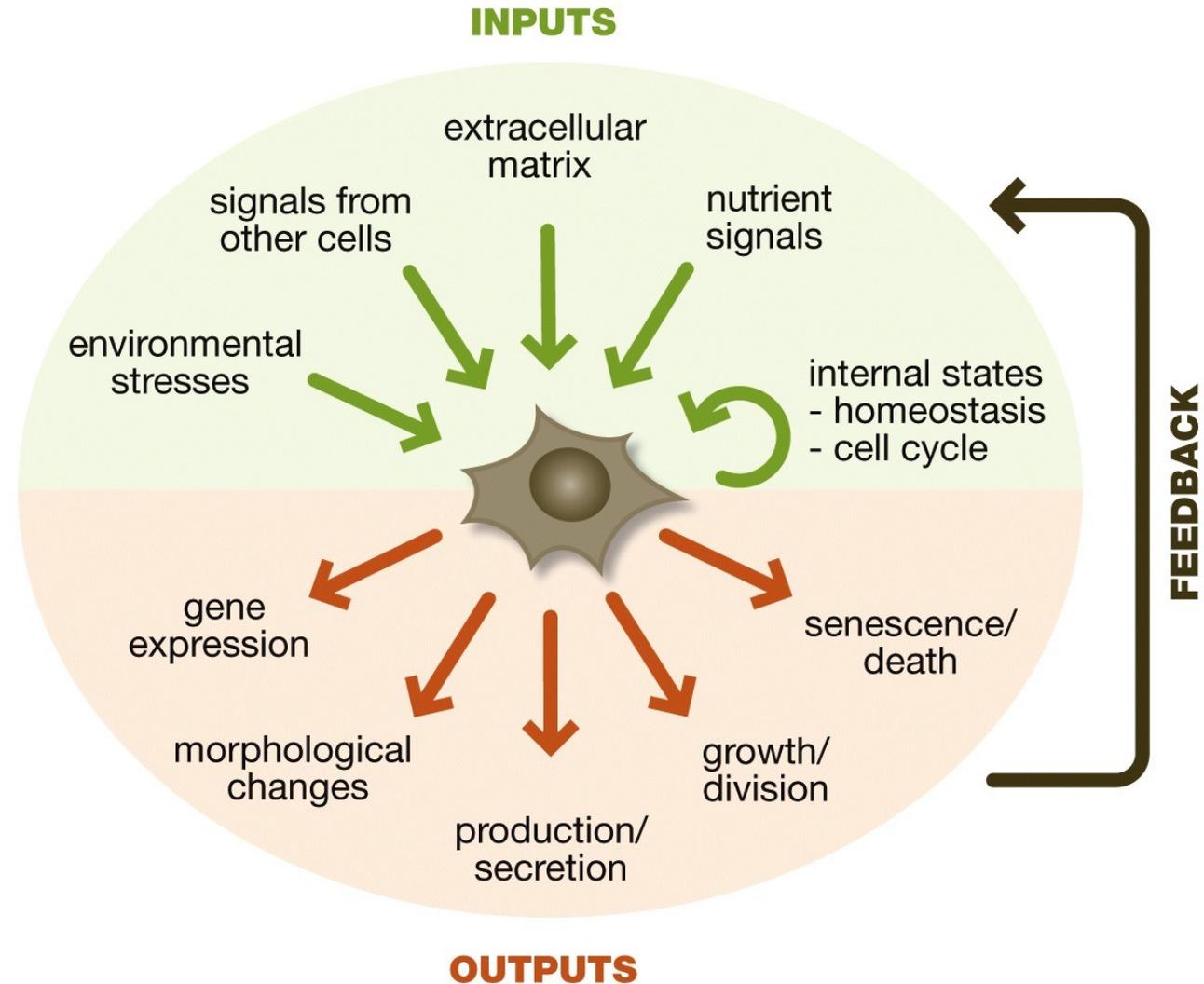
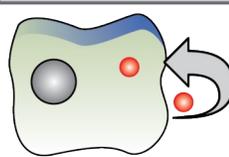
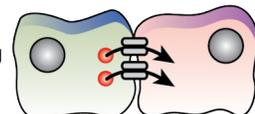
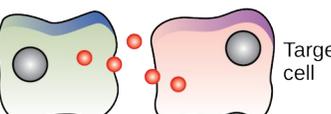
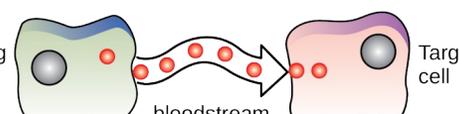
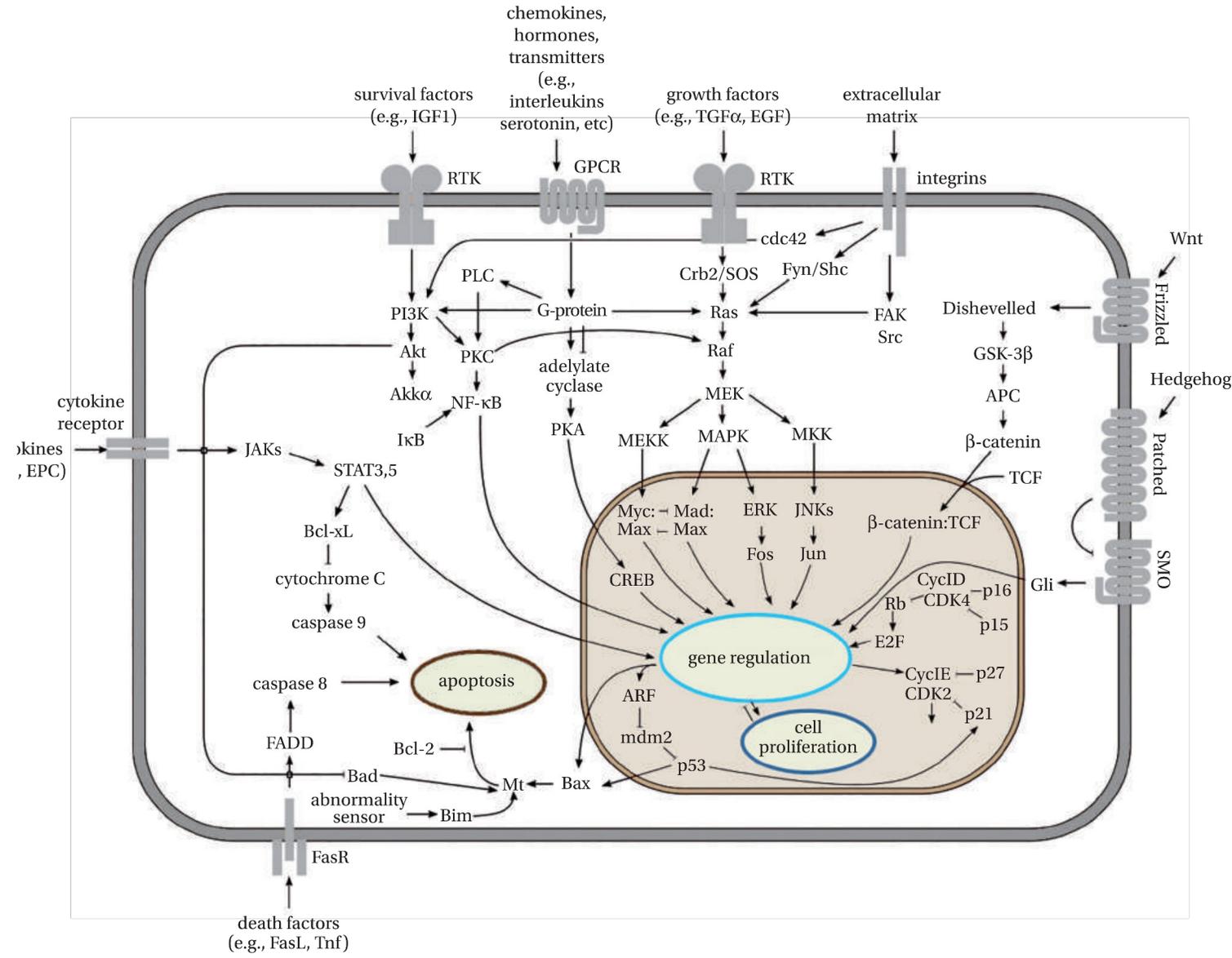


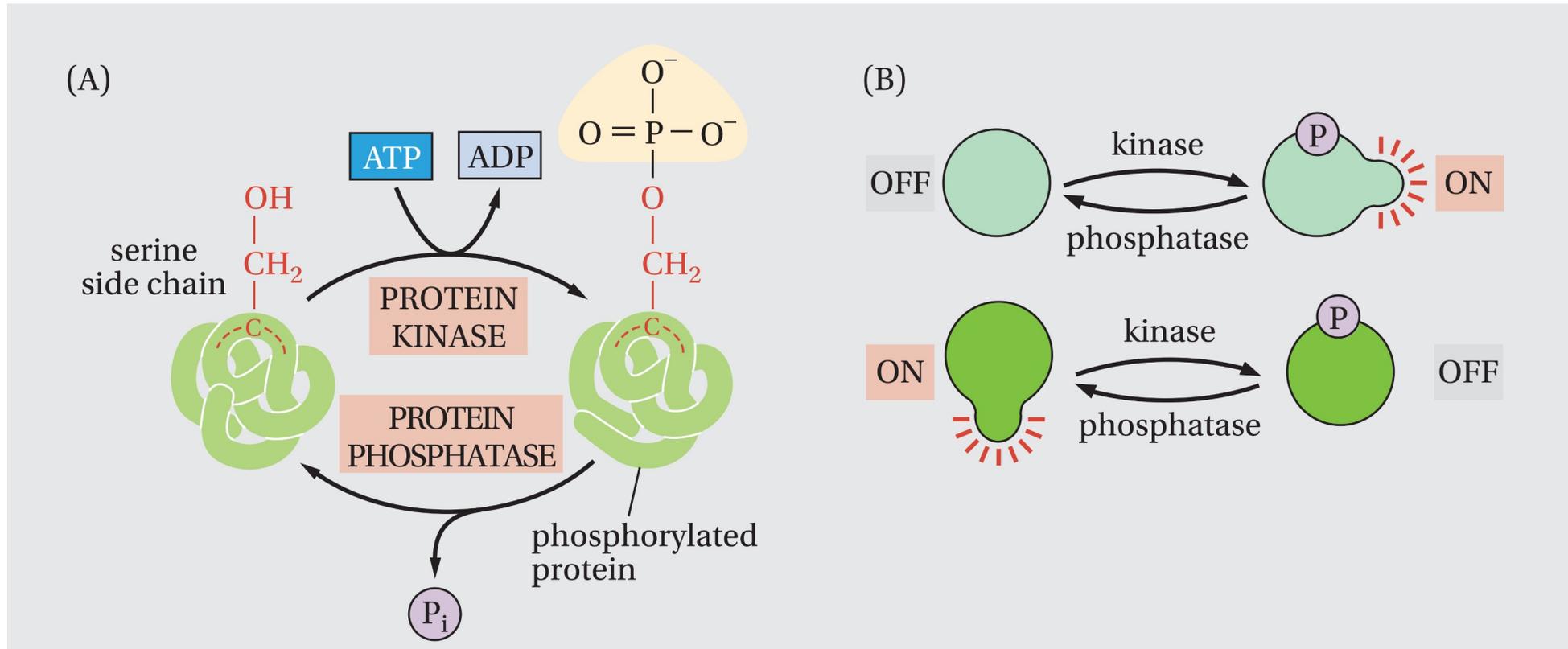
Figure 1.2 Cell Signaling (© Garland Science 2015)

The signal transduction pathways in eukaryotes

Forms of Chemical Signaling	
Autocrine	A cell targets itself.
	
Signaling across gap junctions	A cell targets a cell connected by gap junctions.
	
Paracrine	A cell targets a nearby cell.
	
Endocrine	A cell targets a distant cell through the bloodstream.
	



signals



transfer of information across the membrane

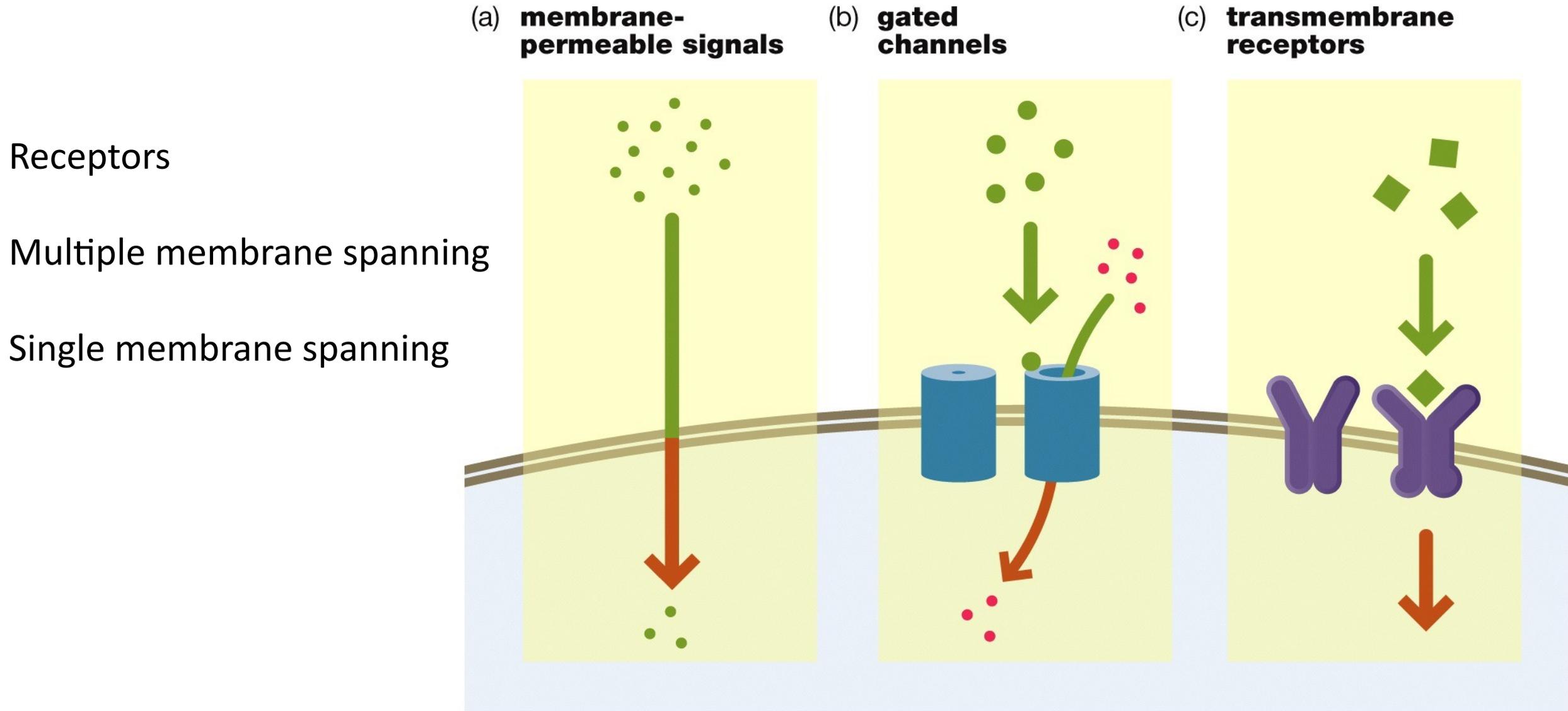
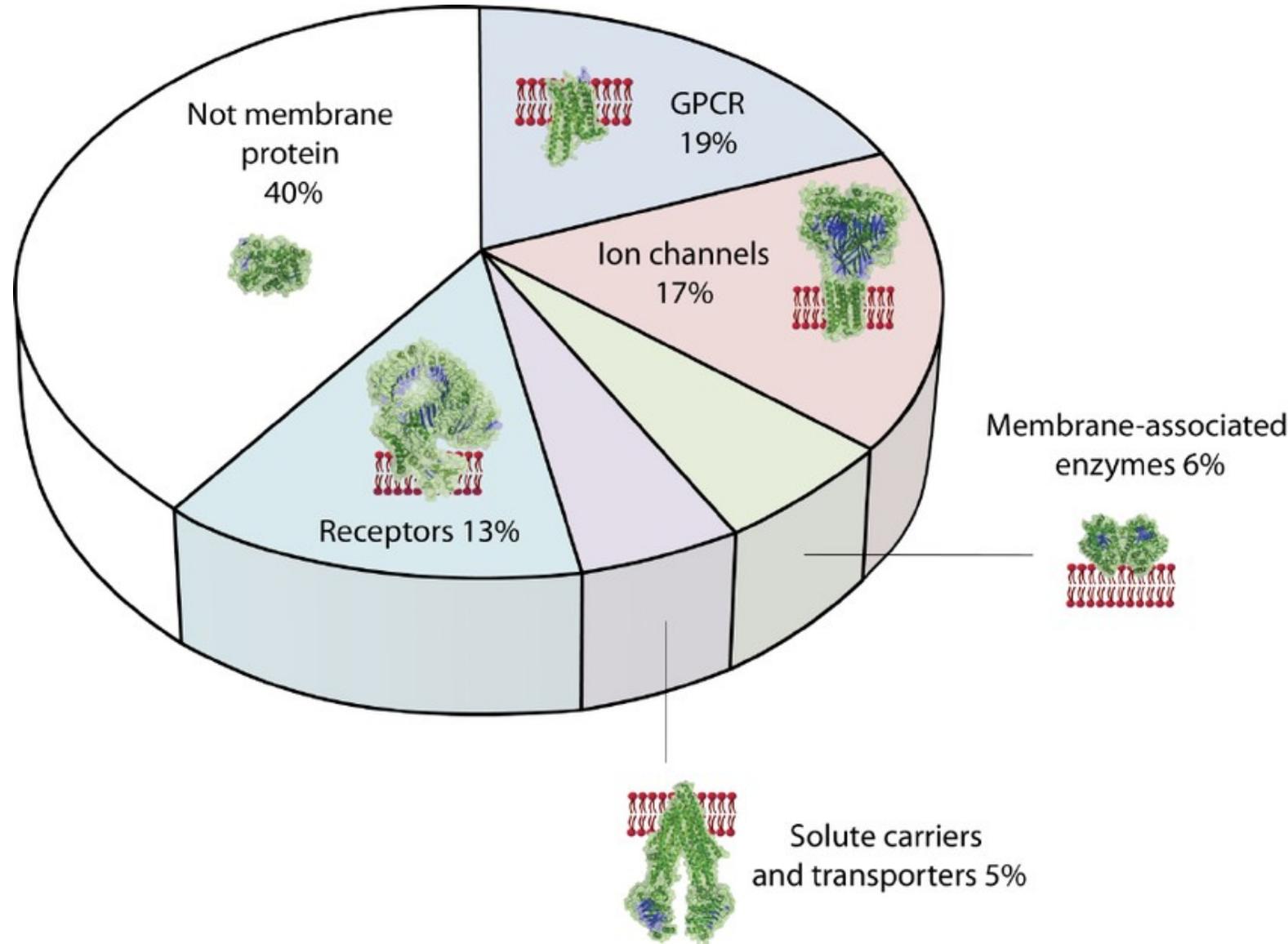


Figure 8.2 Cell Signaling (© Garland Science 2015)

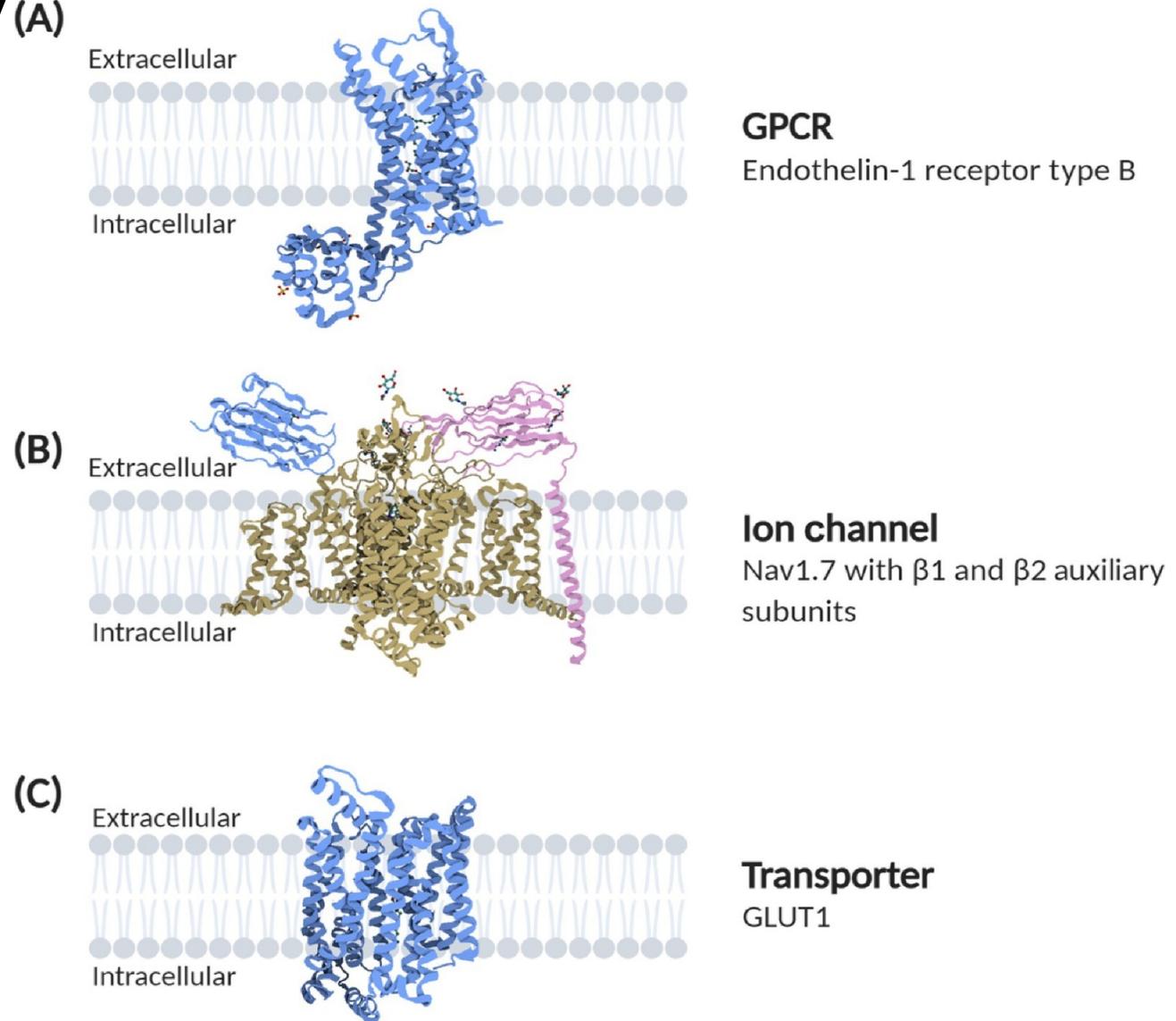
Human membrane proteins as drug targets

G protein-coupled receptors (GPCRs) are cell-surface receptors mediating the responses of 2/3rds of human hormones¹ 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.

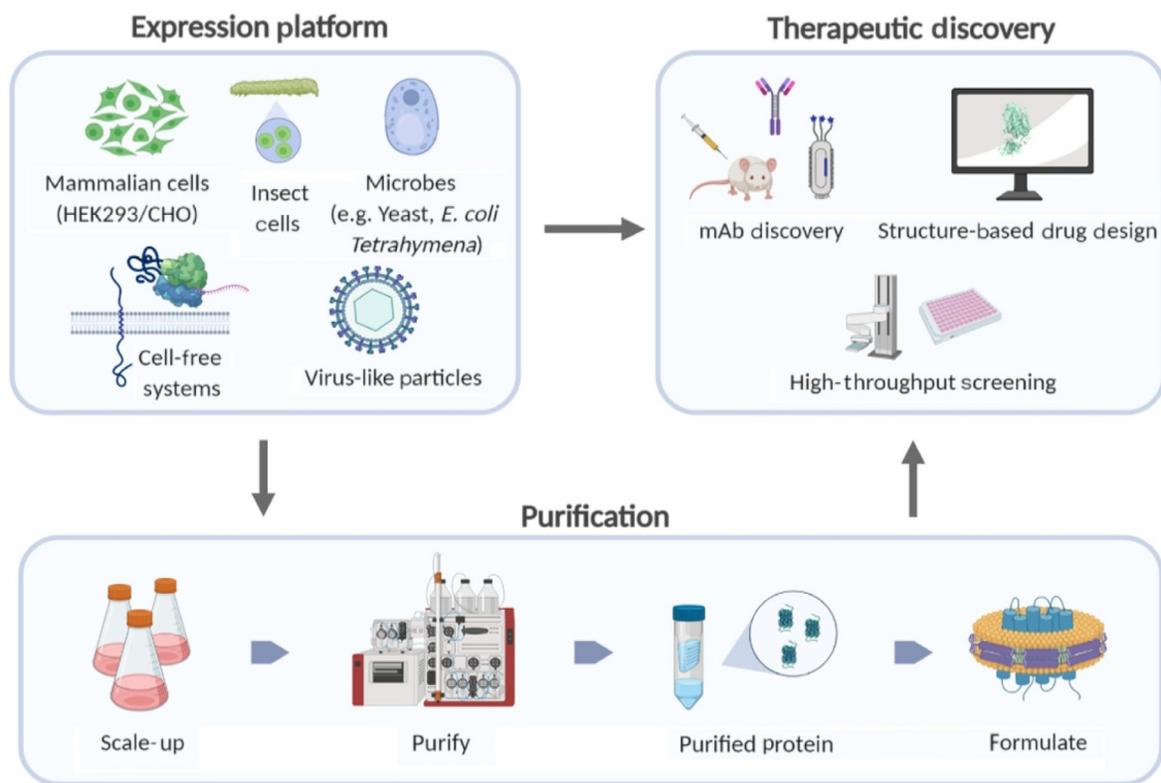


Membrane protein production and formulation for drug discovery

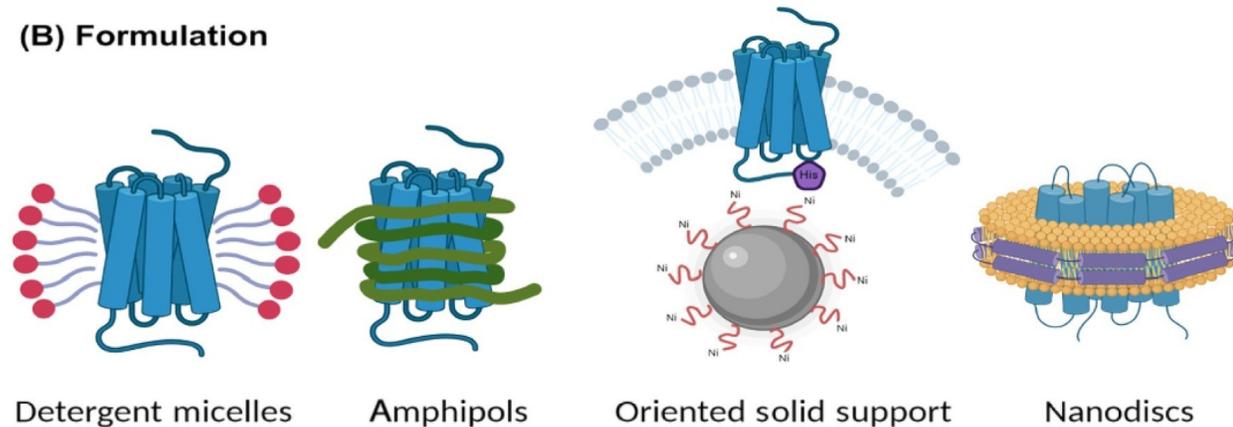


Production

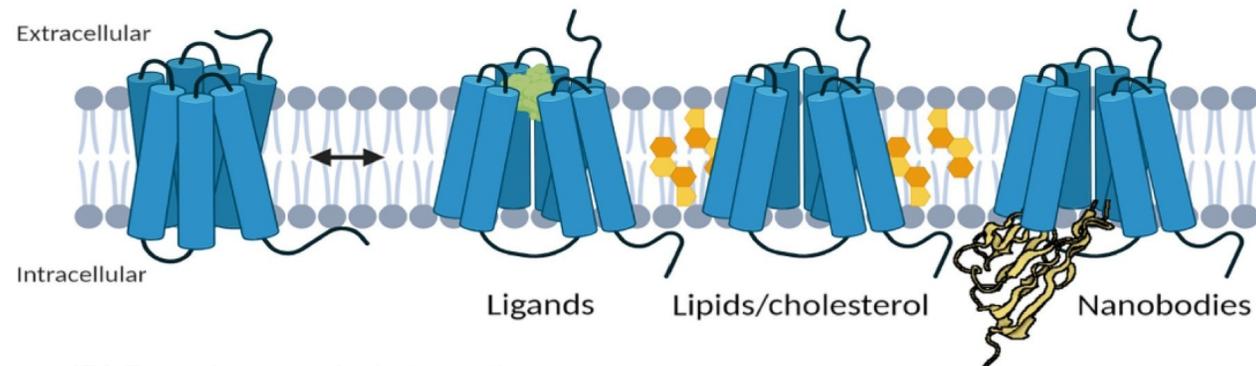
(A) Membrane protein production and formulation for drug discovery



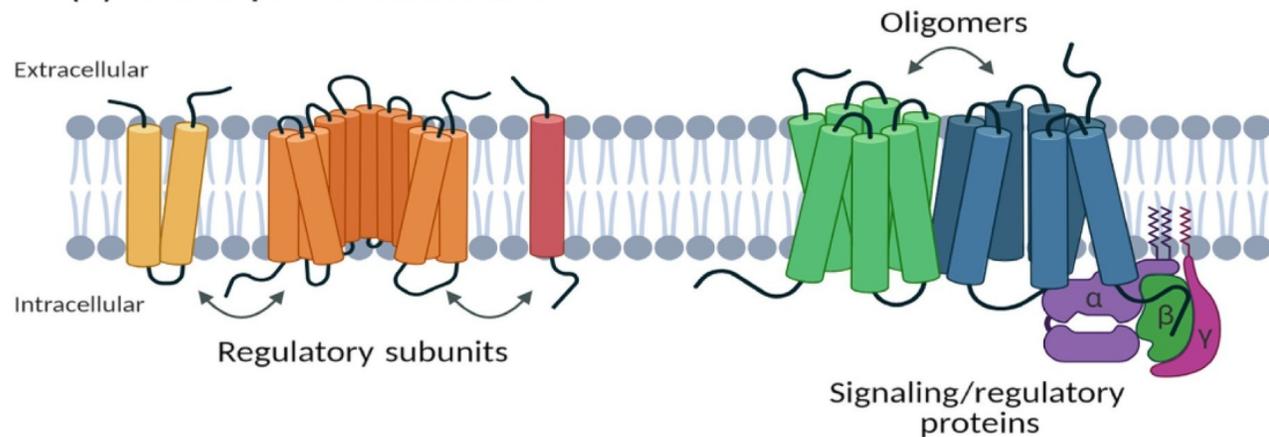
(B) Formulation



(C) Stabilizing active/inactive conformations



(D) Protein-protein interaction



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

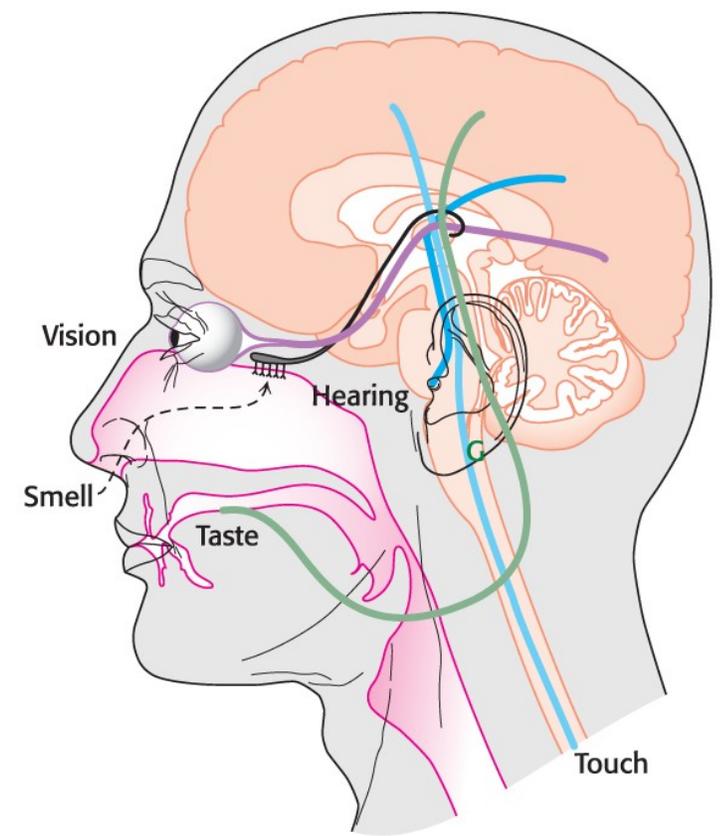
3. Vision

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"

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



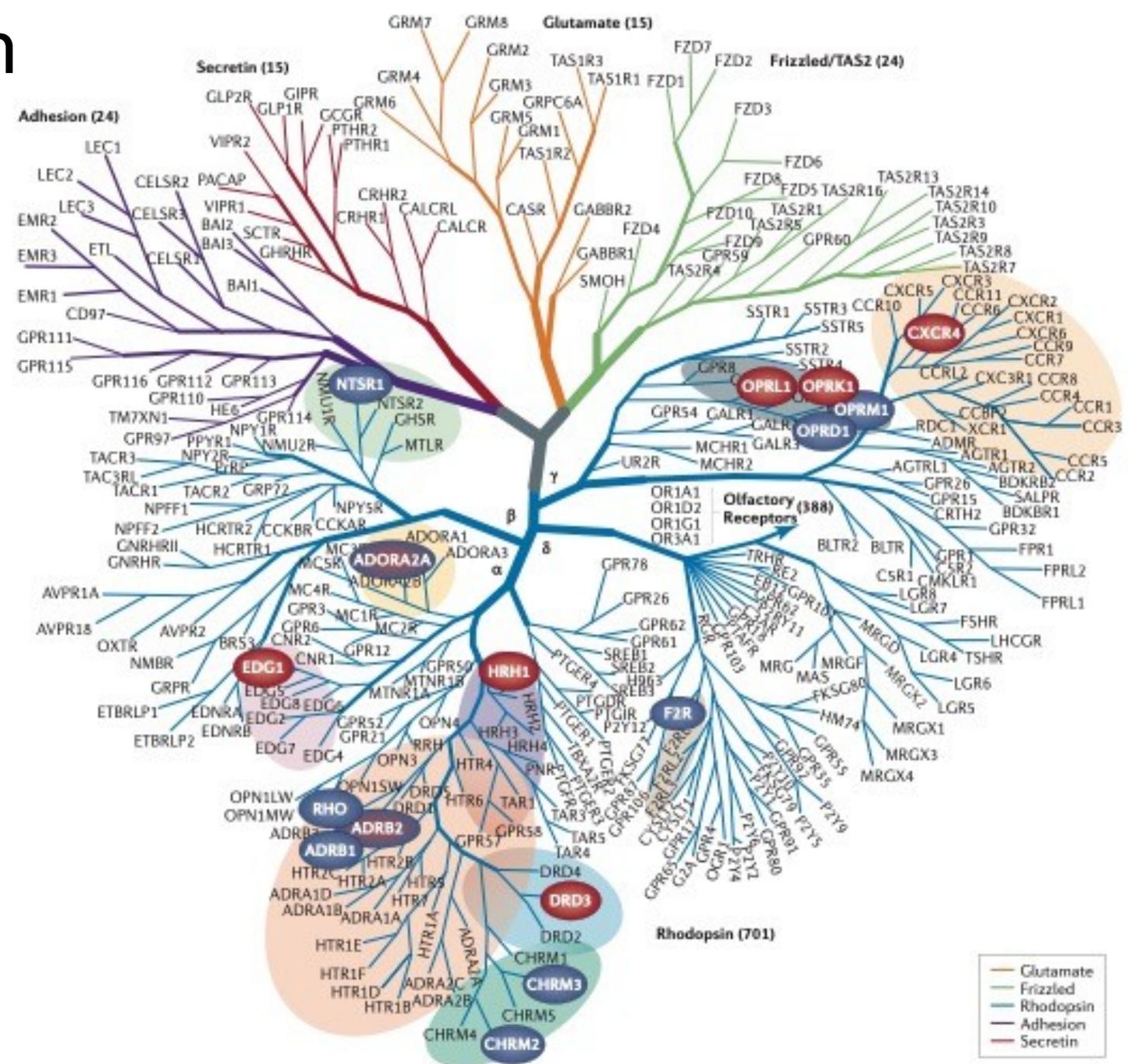
Berg et al., *Biochemistry*, 9e, © 2019
W. H. Freeman and Company

The family tree of human GPCRs

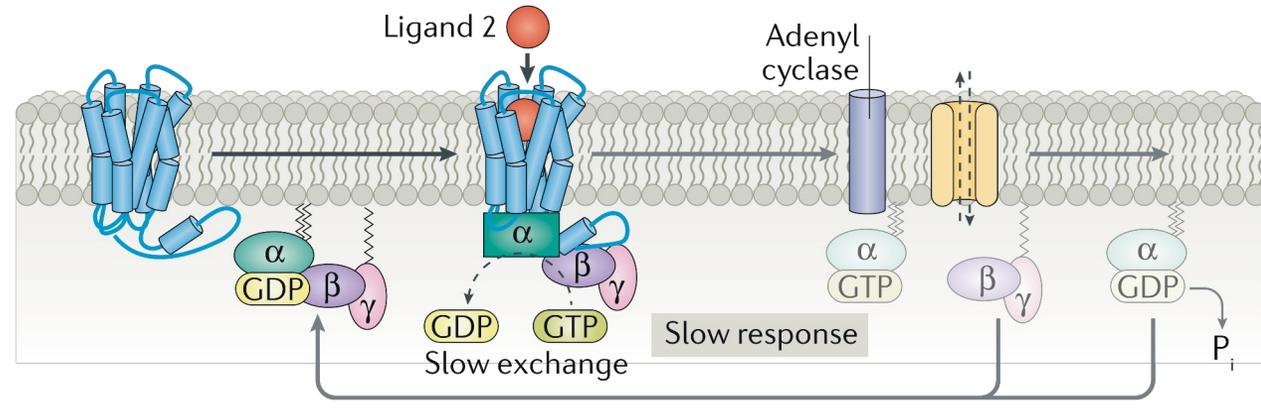
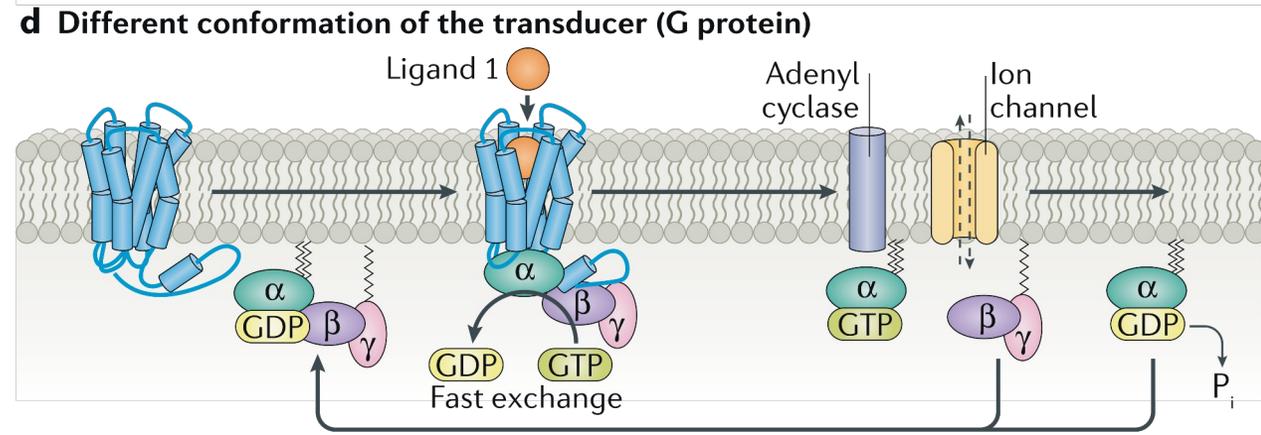
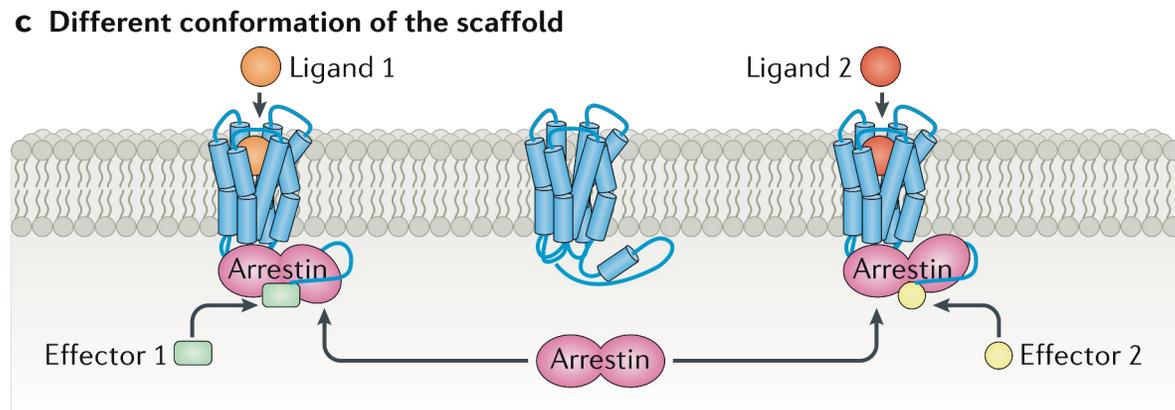
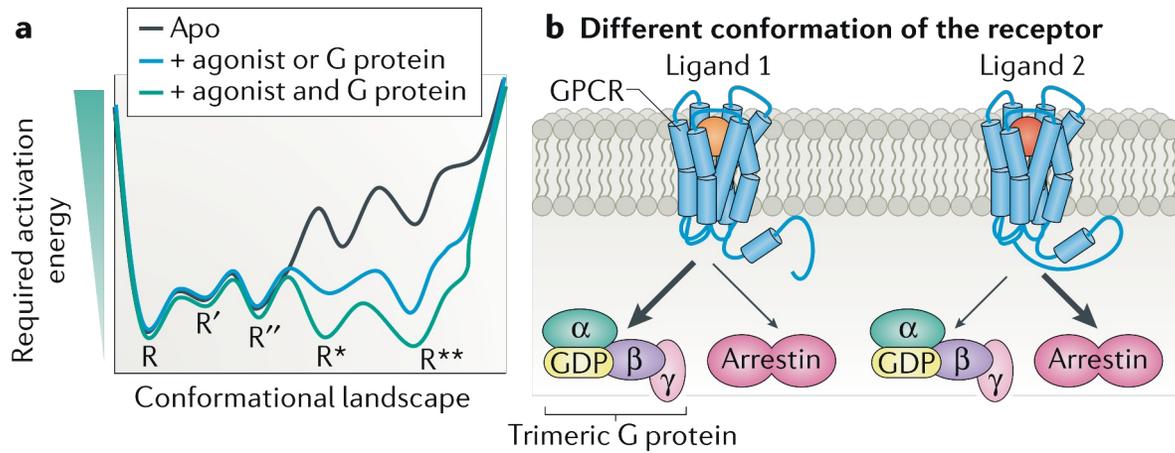
2013
 AA2AR: adenosine receptor A2a,
 OPRD: δ -type opioid receptor,
 PAR1: proteinase-activated receptor 1,
 PAR2: proteinase-activated receptor 2,
 ADRB1: β -1 adrenergic receptor,
 DRD4: dopamine D4 receptor,
 CLTR1: Cysteinyl leukotriene receptor 1

2022
<https://gpcrdb.org>

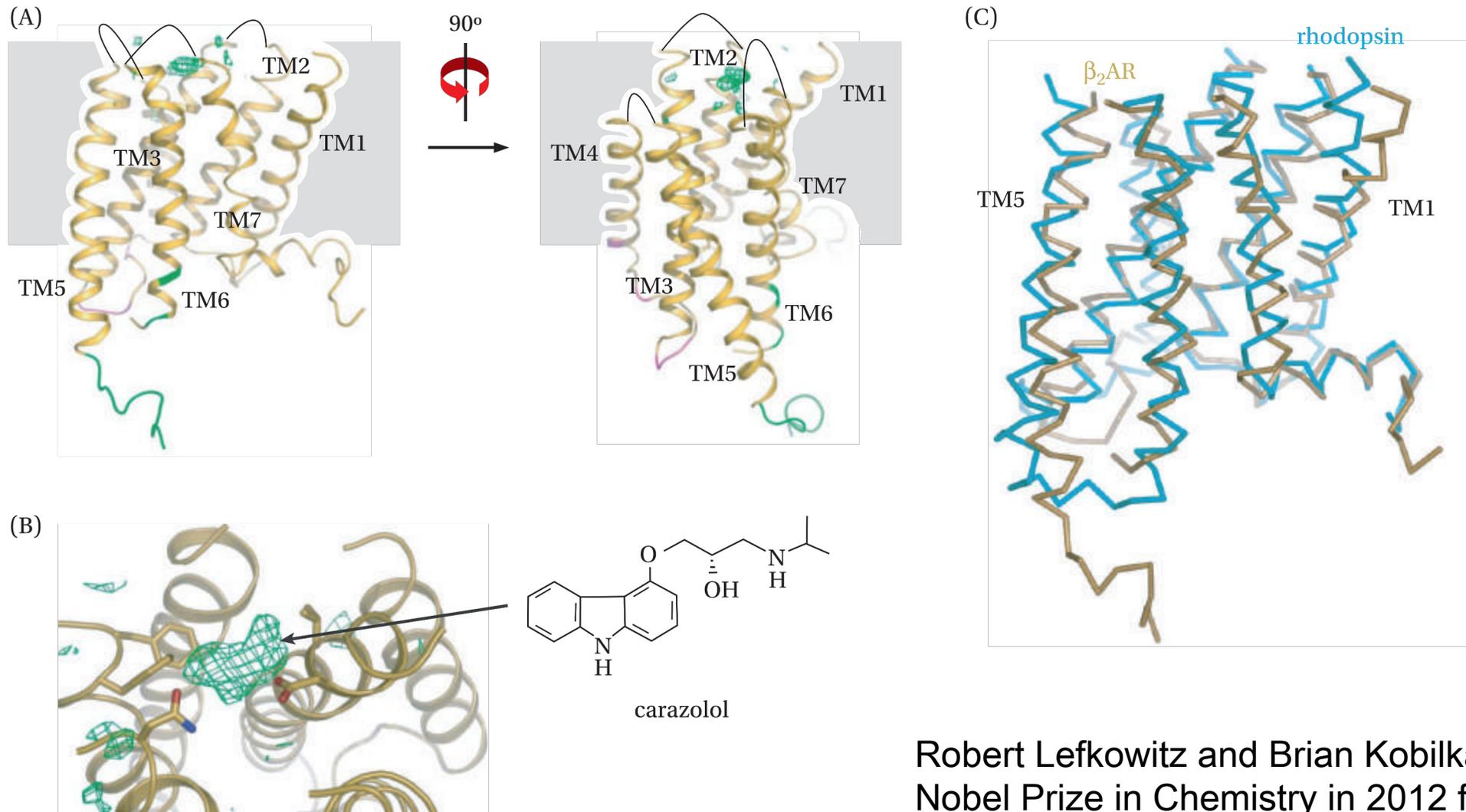
- Data
- 423 Human proteins
 - 974 Drugs
 - 174 Drug targets
 - 411 Disease indications
 - 793 GPCRs structures
 - 844 GPCRs structure models
 - 2,910 Generic residues
 - 663 Refined structures



GPCR signalling



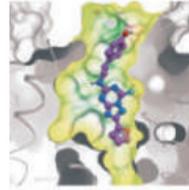
structures of rhodopsin and β_2 adrenergic receptor



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

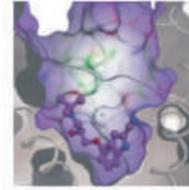
Binding pocket

adenosine A_{2A} receptor



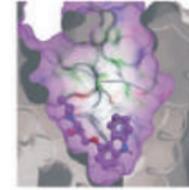
caffeine

β₁-adrenergic receptor



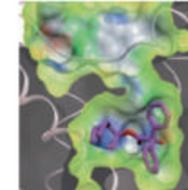
carazolol

β₂-adrenergic receptor



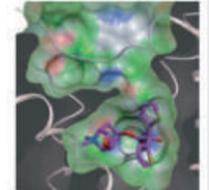
carazolol

muscarinic ACh receptor M₂



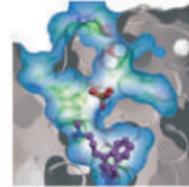
3-quinuclidinylbenzilate (antagonist)

muscarinic ACh receptor M₃



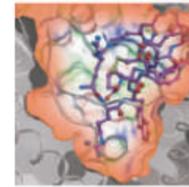
tiotropium (drug)

histamine H₁ receptor



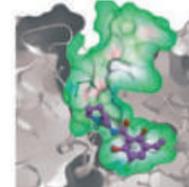
doxepin (drug)

CXC chemokine receptor 4



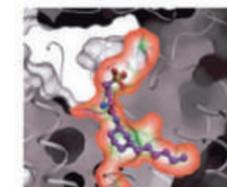
CVX15 cyclic peptide inhibitor

dopamine D₃ receptor



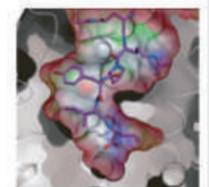
eticlopride (antagonist)

sphingosine-1 phosphate receptor 1



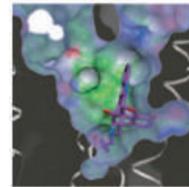
sphingolipid mimic (antagonist)

neurotensin receptor 1



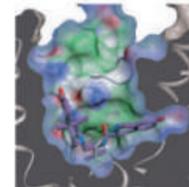
neurotensin

δ-type opioid receptor



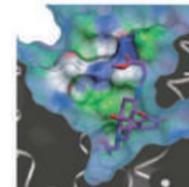
naltrindole (antagonist)

κ-type opioid receptor



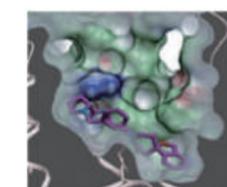
"JDtic" (antagonist)

μ-type opioid receptor



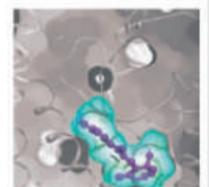
irreversible morphinan antagonist

opiate-receptor-like 1



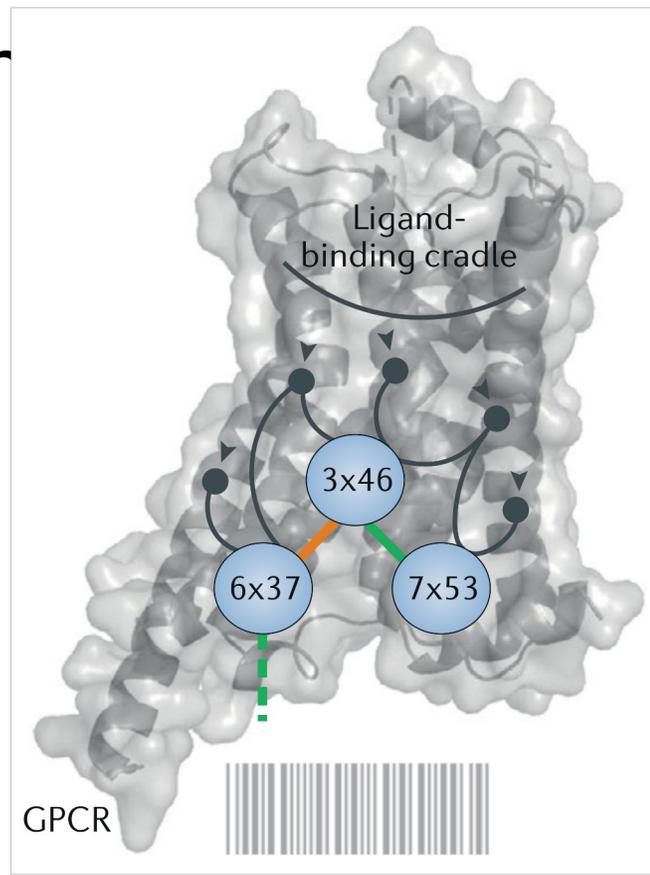
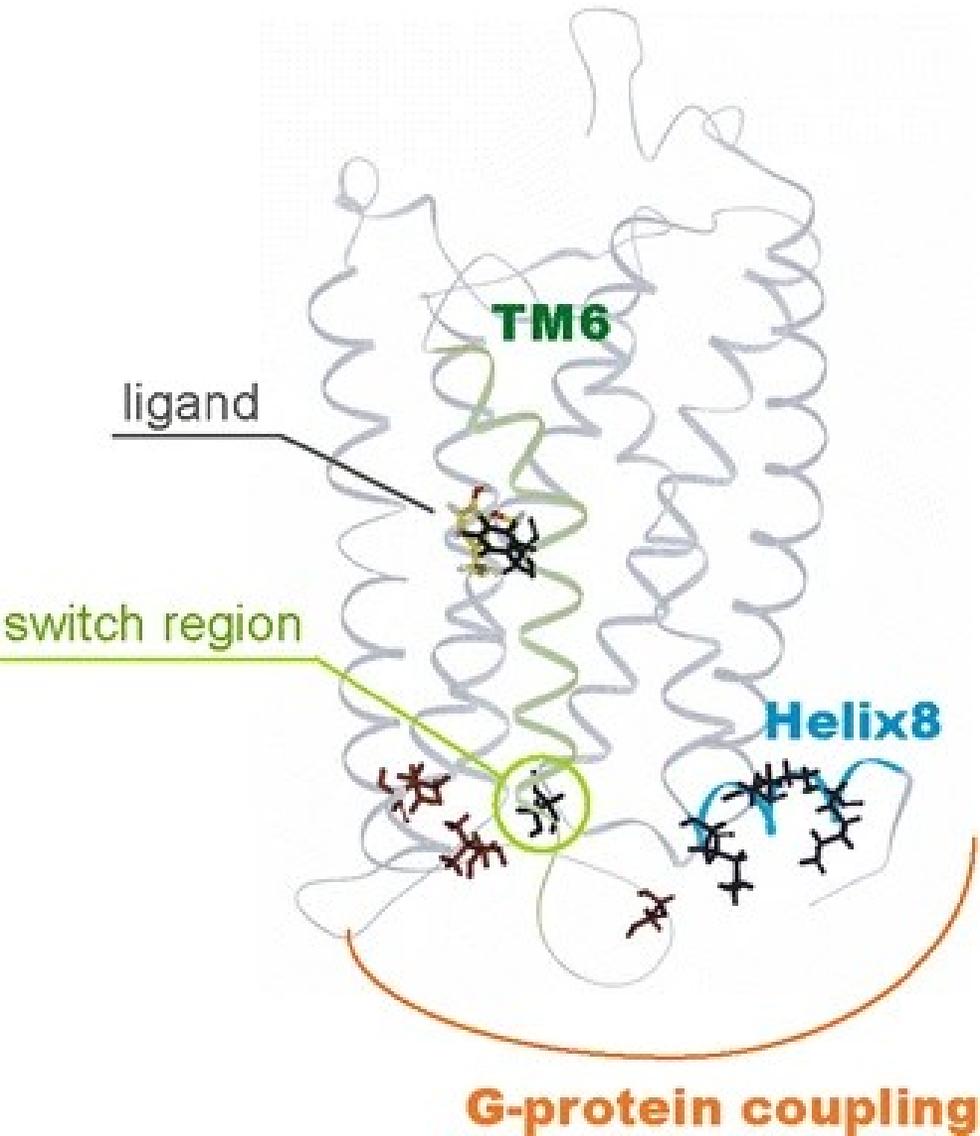
peptide mimetic (antagonist)

rhodopsin



retinal

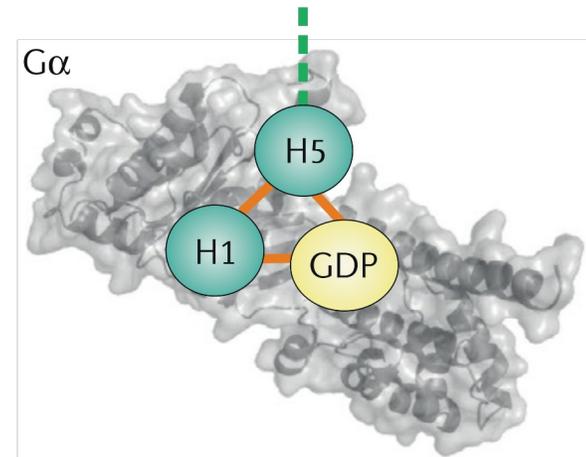
contact networks between GPCRs and G proteins



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

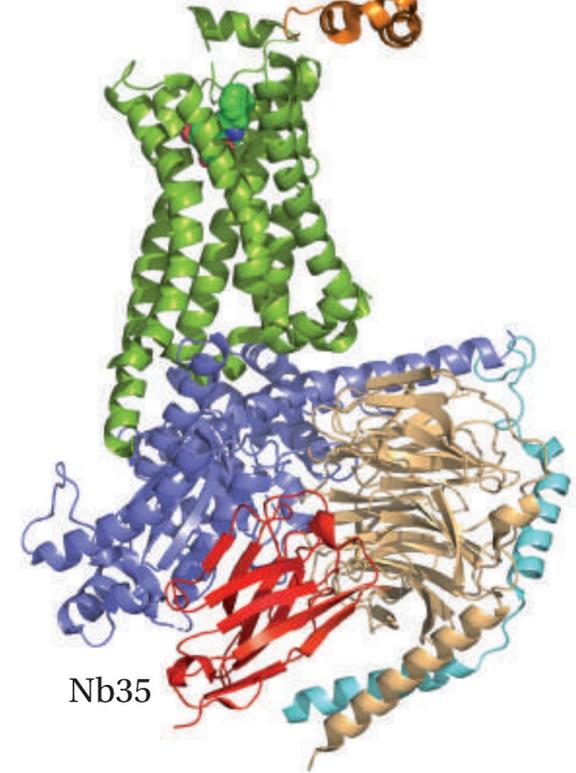
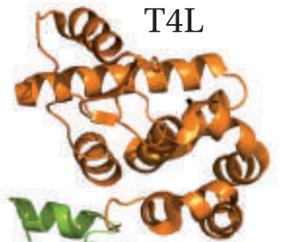
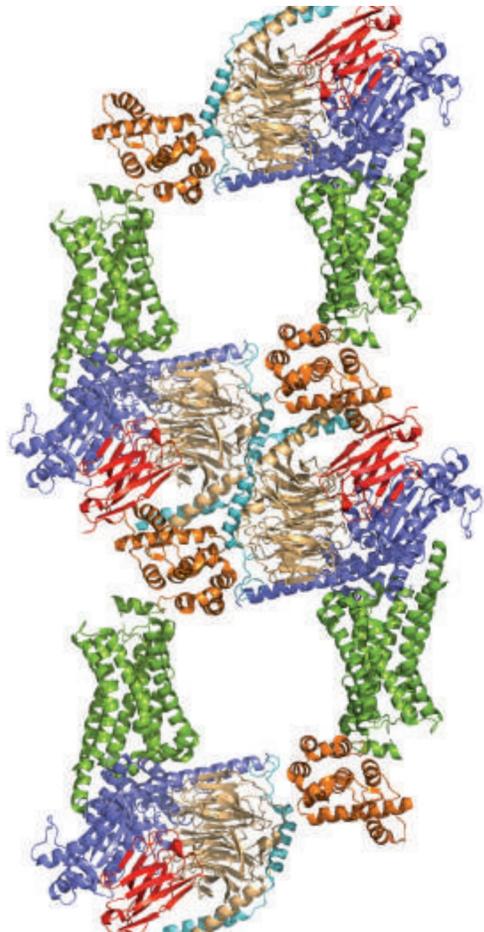
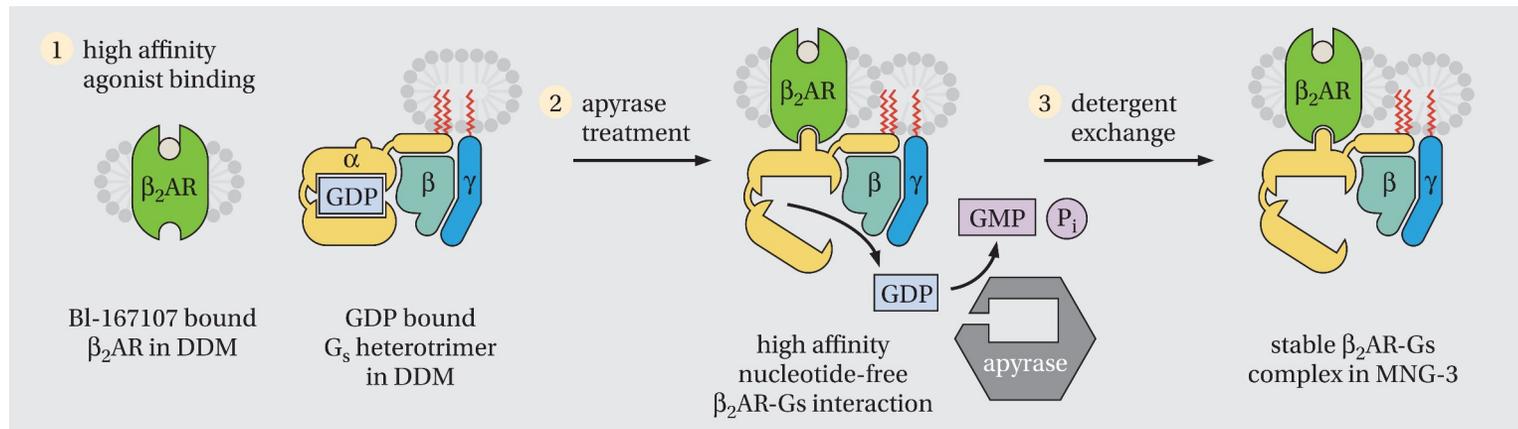
- Activation signals converge near the transducer-binding region of the receptor
- Conserved rewiring of non-covalent receptor contacts exposes G protein-binding residues

- 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



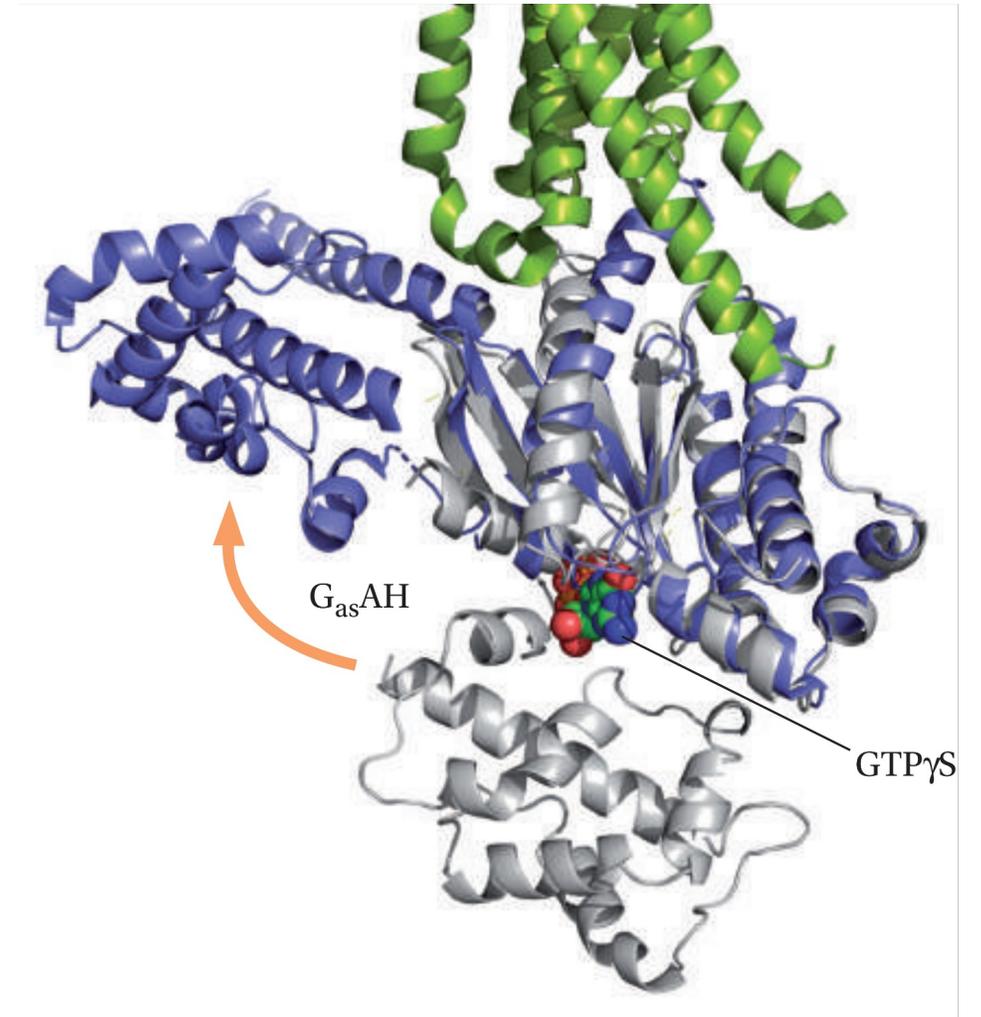
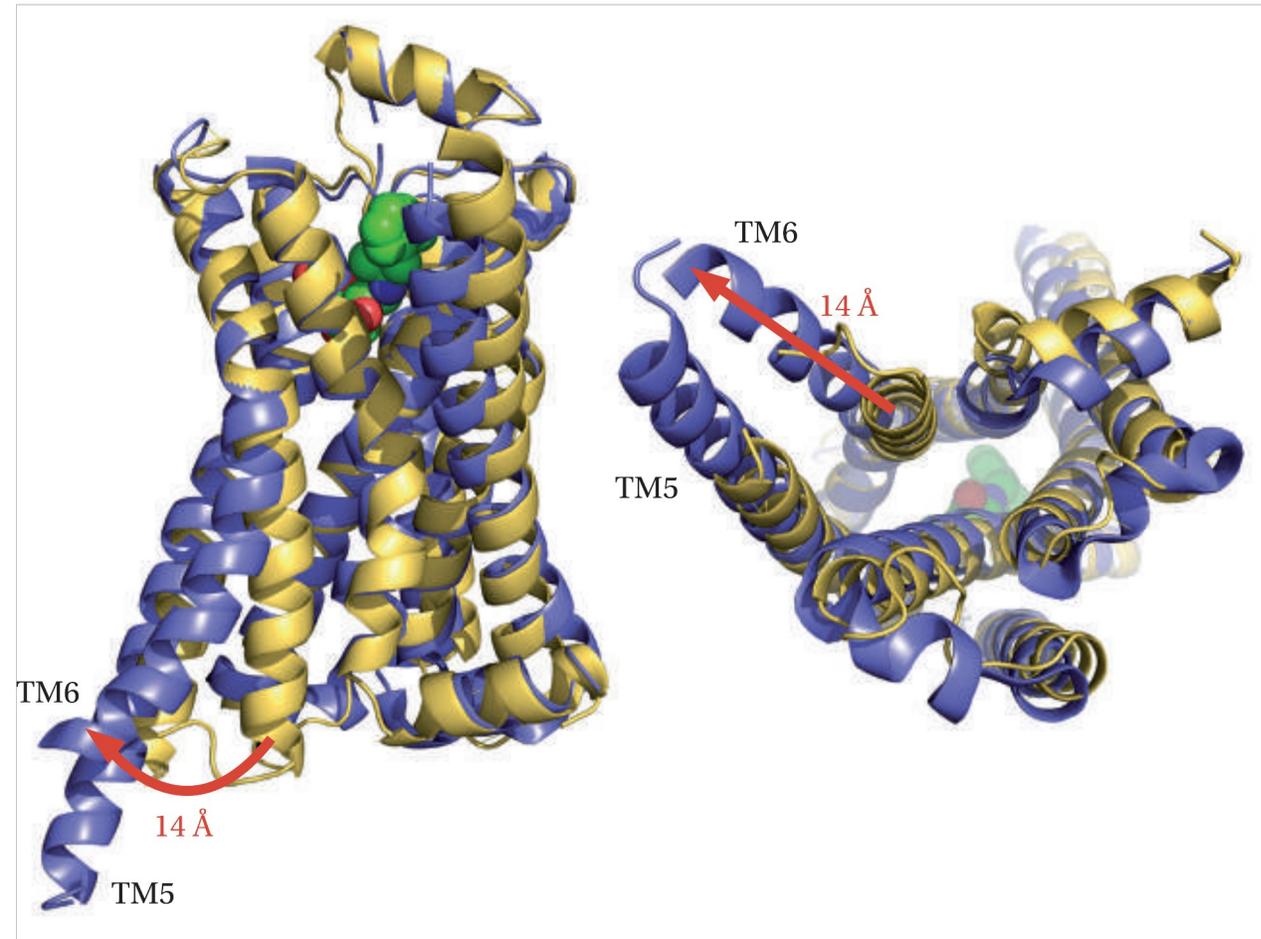
- GPCR binding induces GDP release and G protein activation
- Disruption of the H1–H5 interaction and H1 unfolding are conserved mechanisms linking GPCR binding to GDP release

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

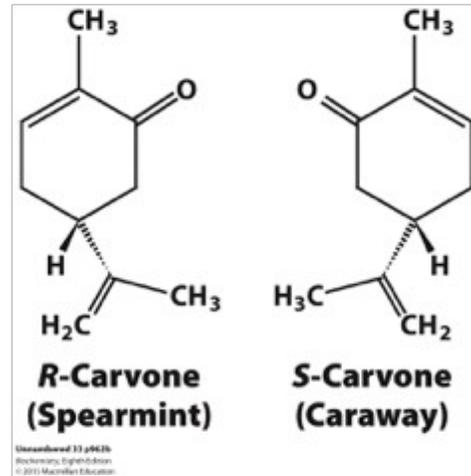
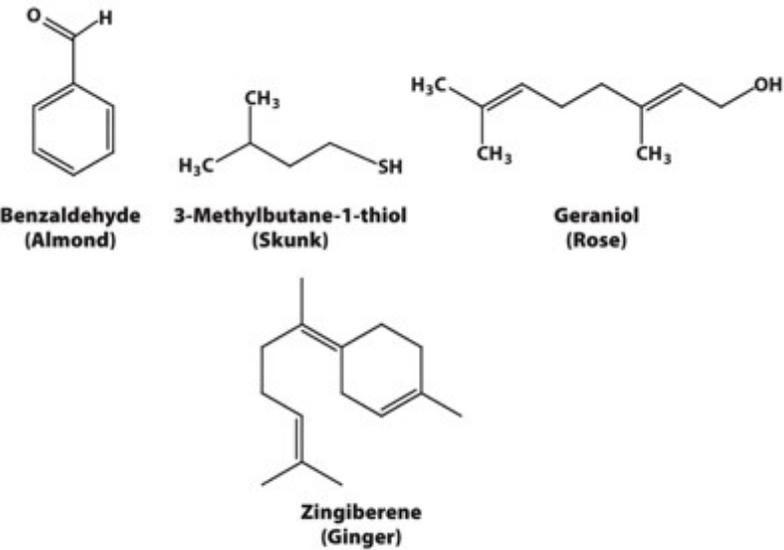


by Brian Kobilka and his collaborators in 2011.

$\beta 2$ adrenergic receptor

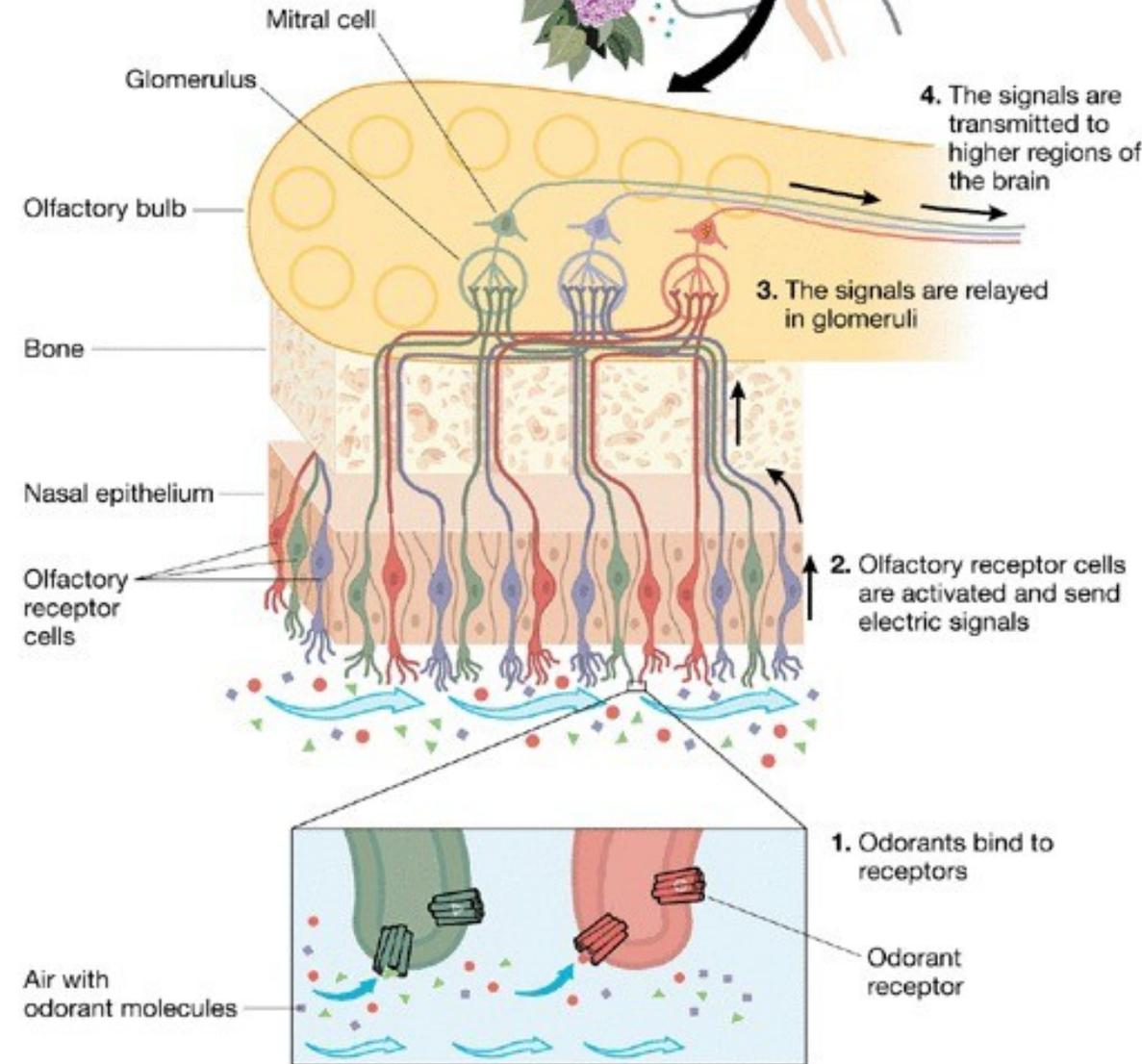
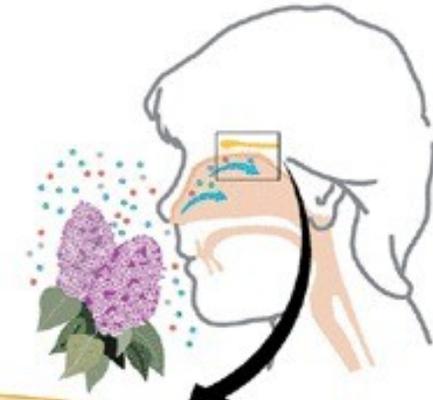


odorants



Unnumbered 33 p962a
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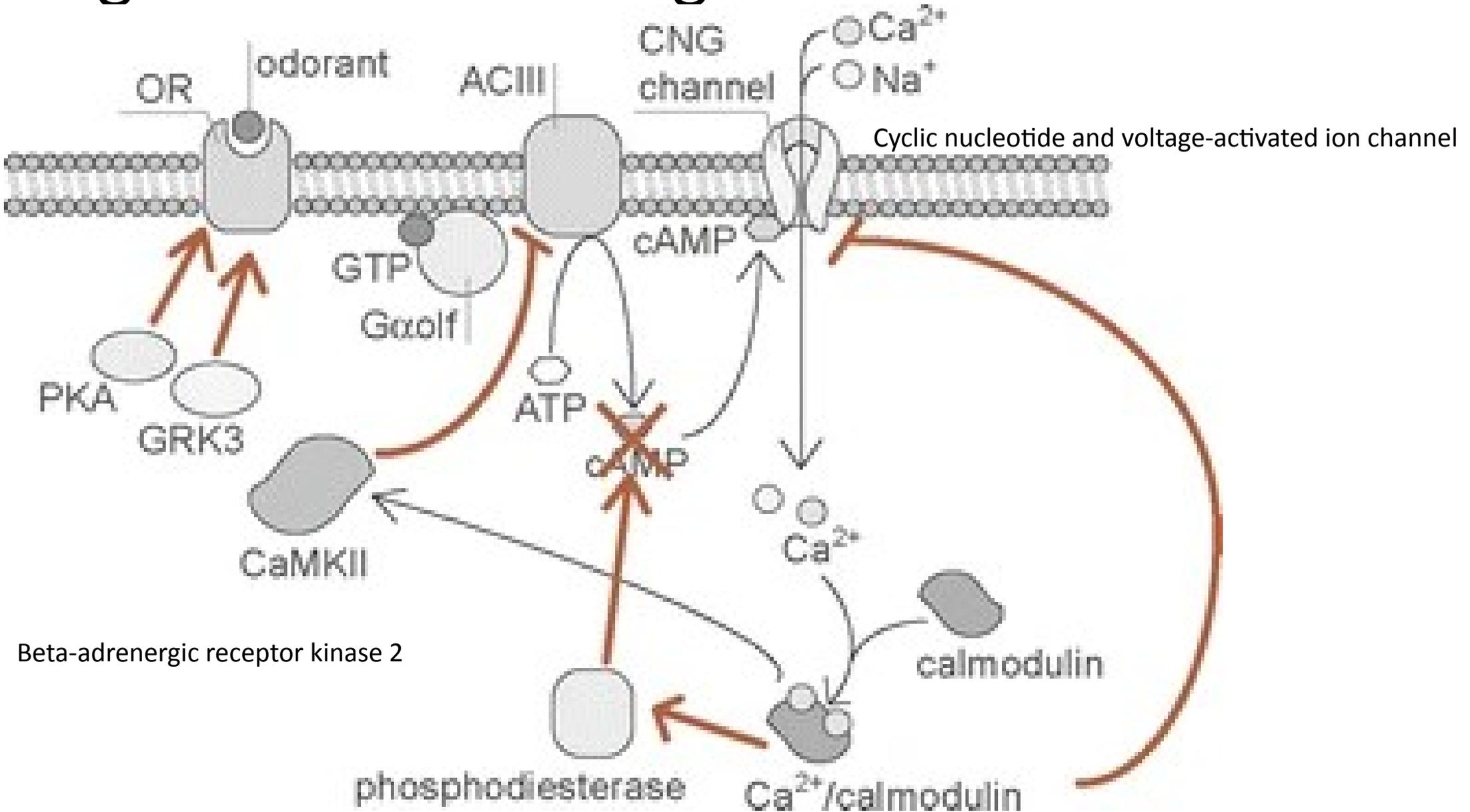
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Most odorants are small organic compounds that interact with receptors in specific neurons.

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

negative feedback regulation



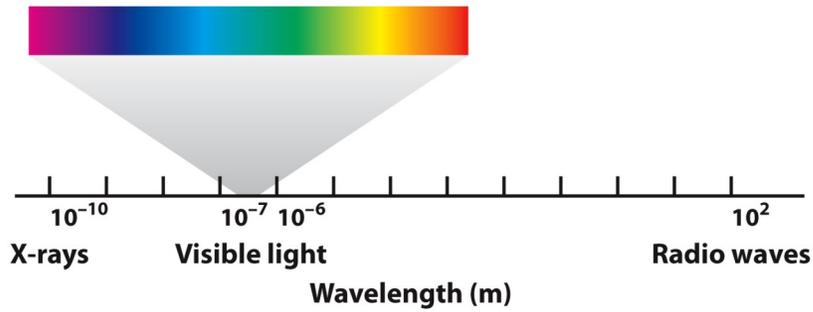


Figure 33.18
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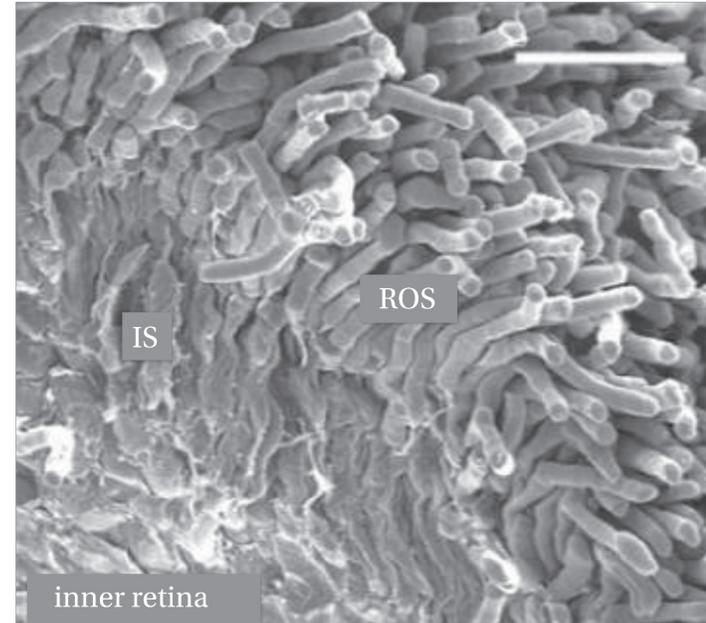
Photoreceptor cells detect electromagnetic radiation in the region between 390 and 750 nm visible light.

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

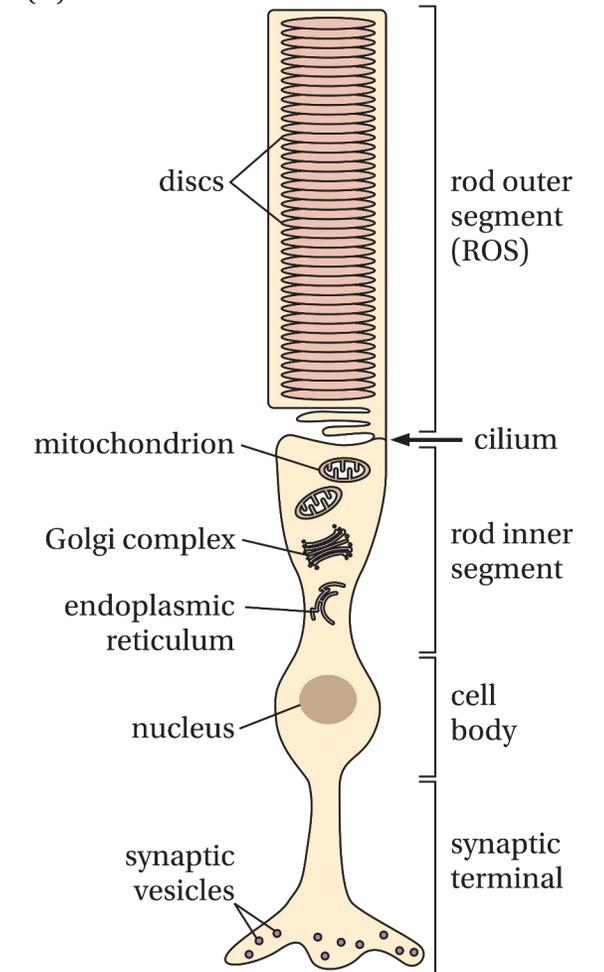
Cones function in bright light and perceive color. Rods function in dim light, but cannot detect color.

Detection of visible light

(A)



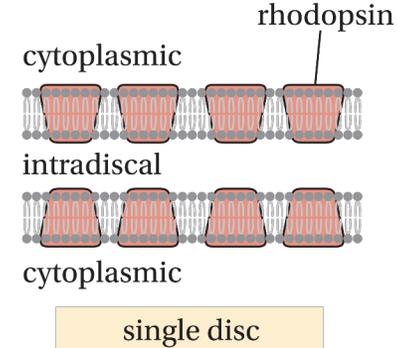
(B)



(C)



(D)



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

Color vision

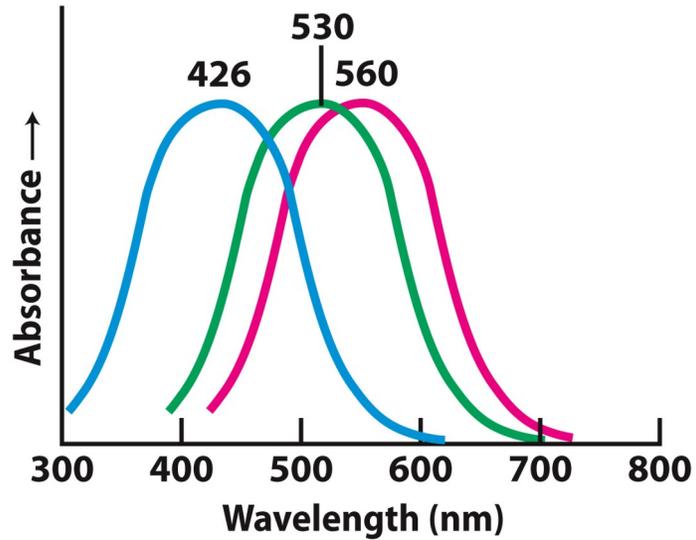
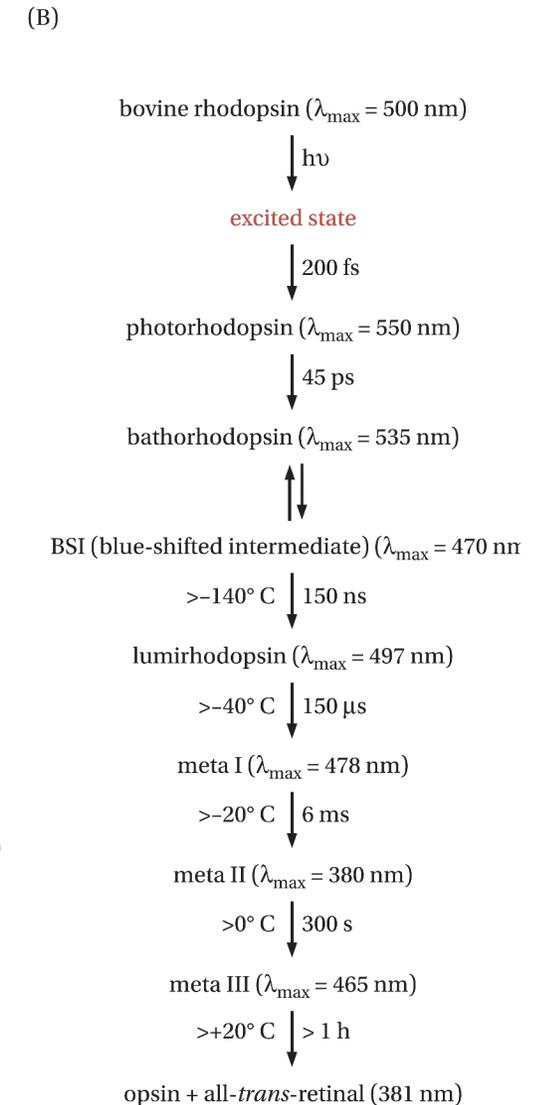
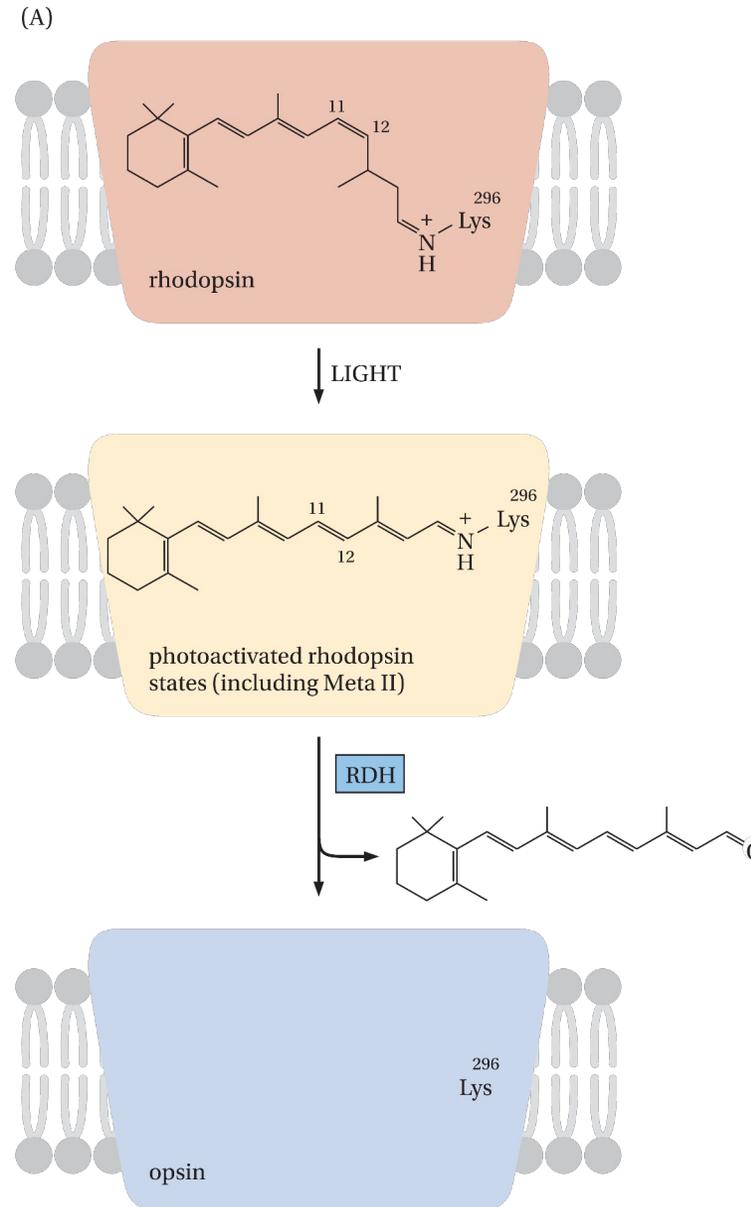


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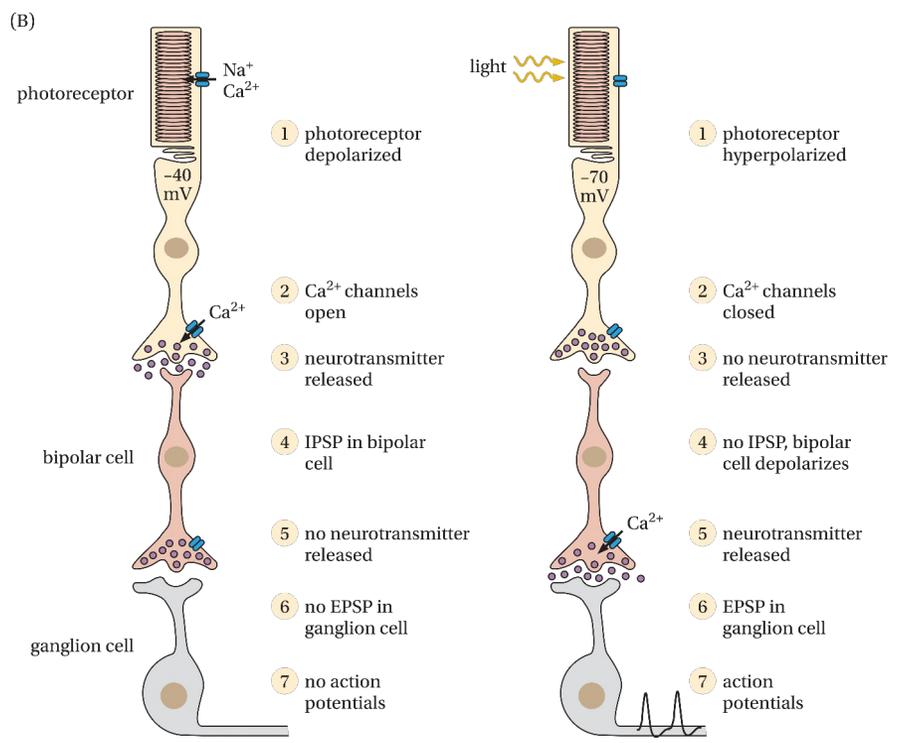
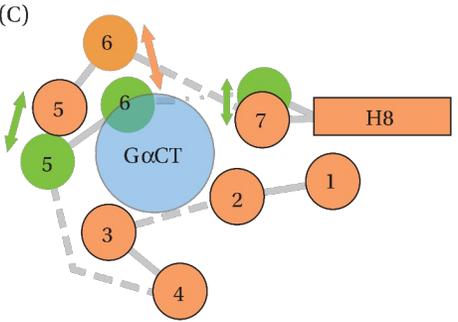
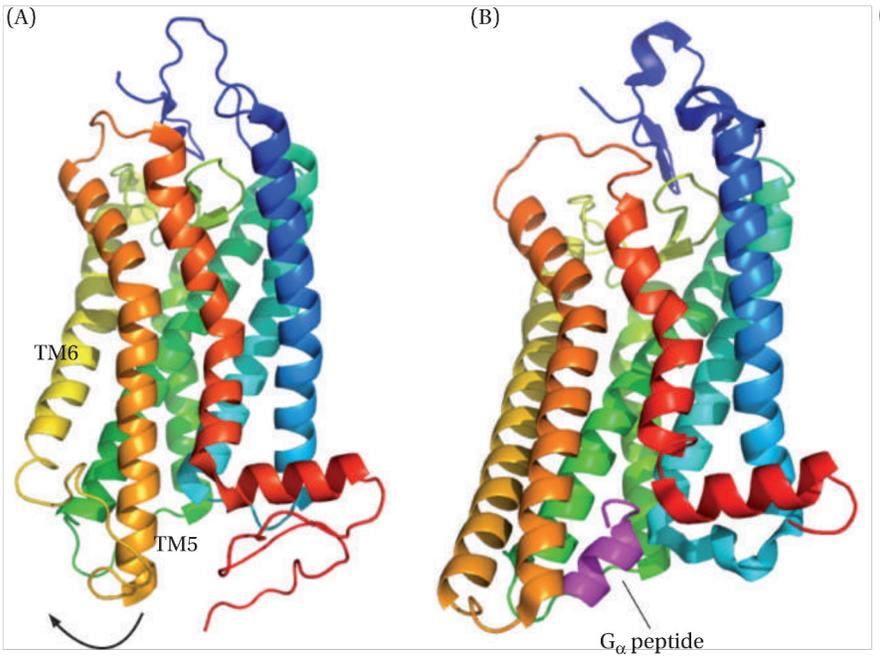
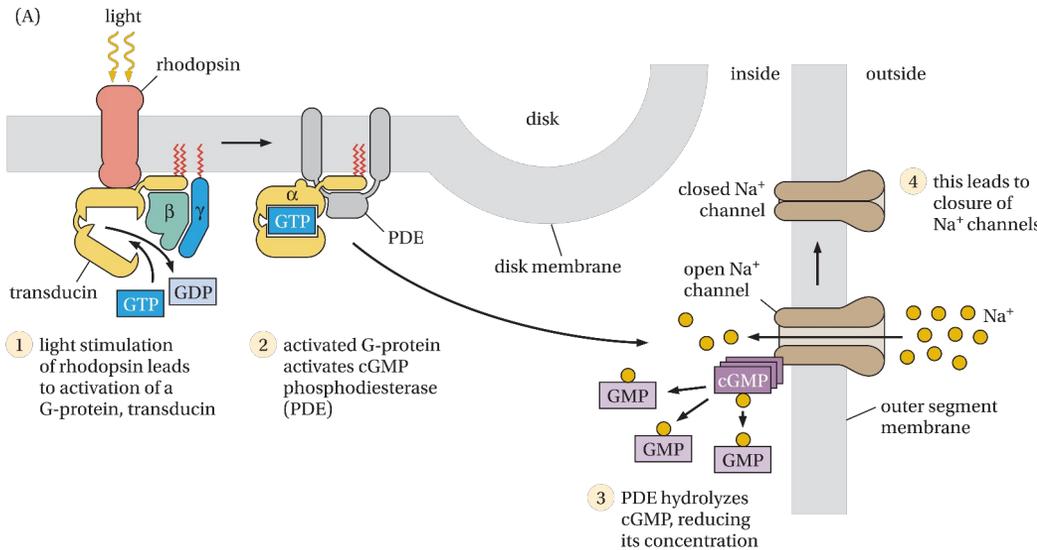
Three distinct photoreceptors in cone cells, homologs of rhodopsin, are responsible for perception of color.

The receptors absorb blue, green, and red light.

The visual receptors have evolved by gene duplication.



Signaling by photoactivation of rhodopsin in ROS membranes.



EPSP: excitatory postsynaptic potential
IPSP: inhibitory postsynaptic potential

rhodopsin

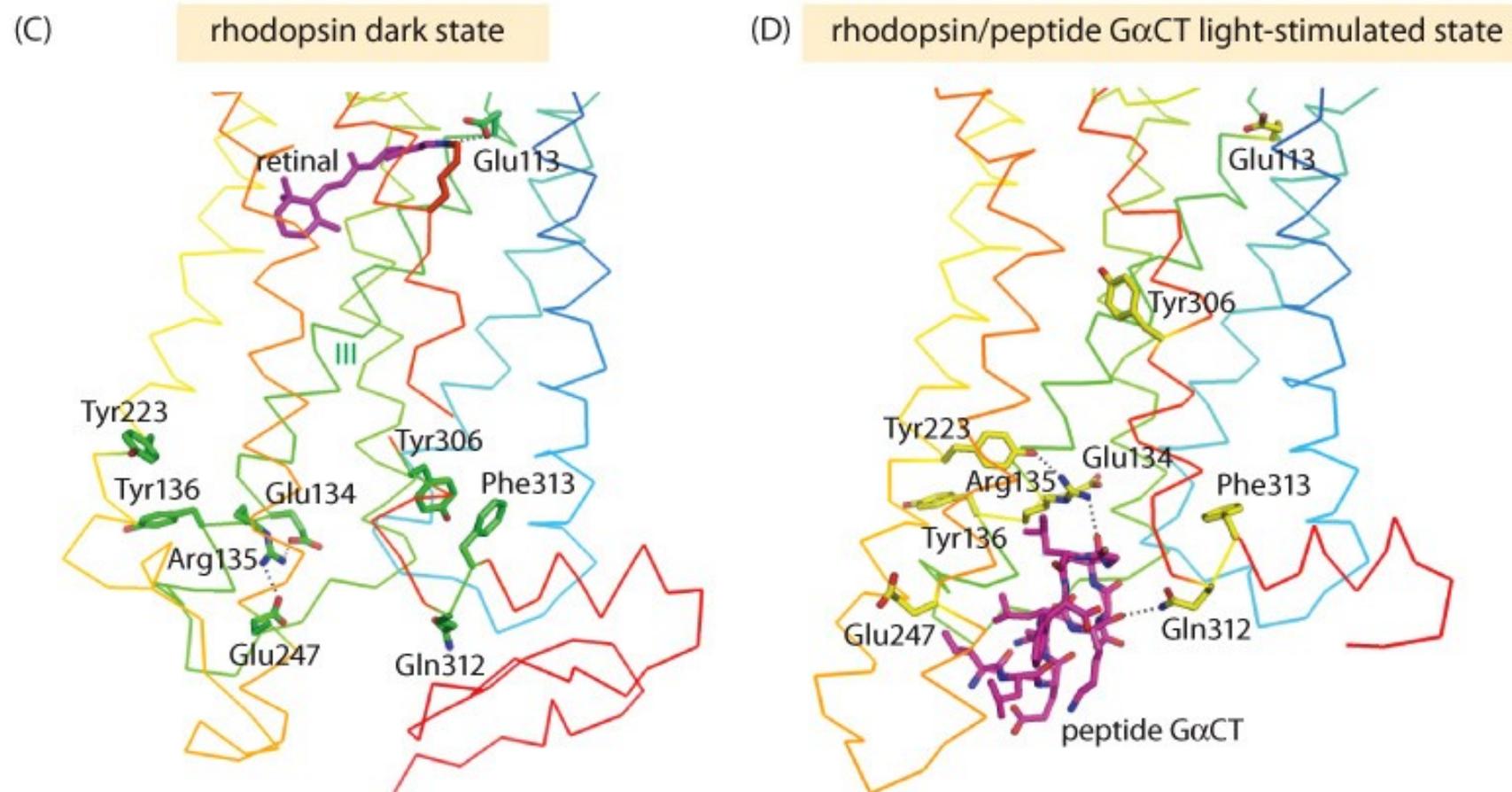
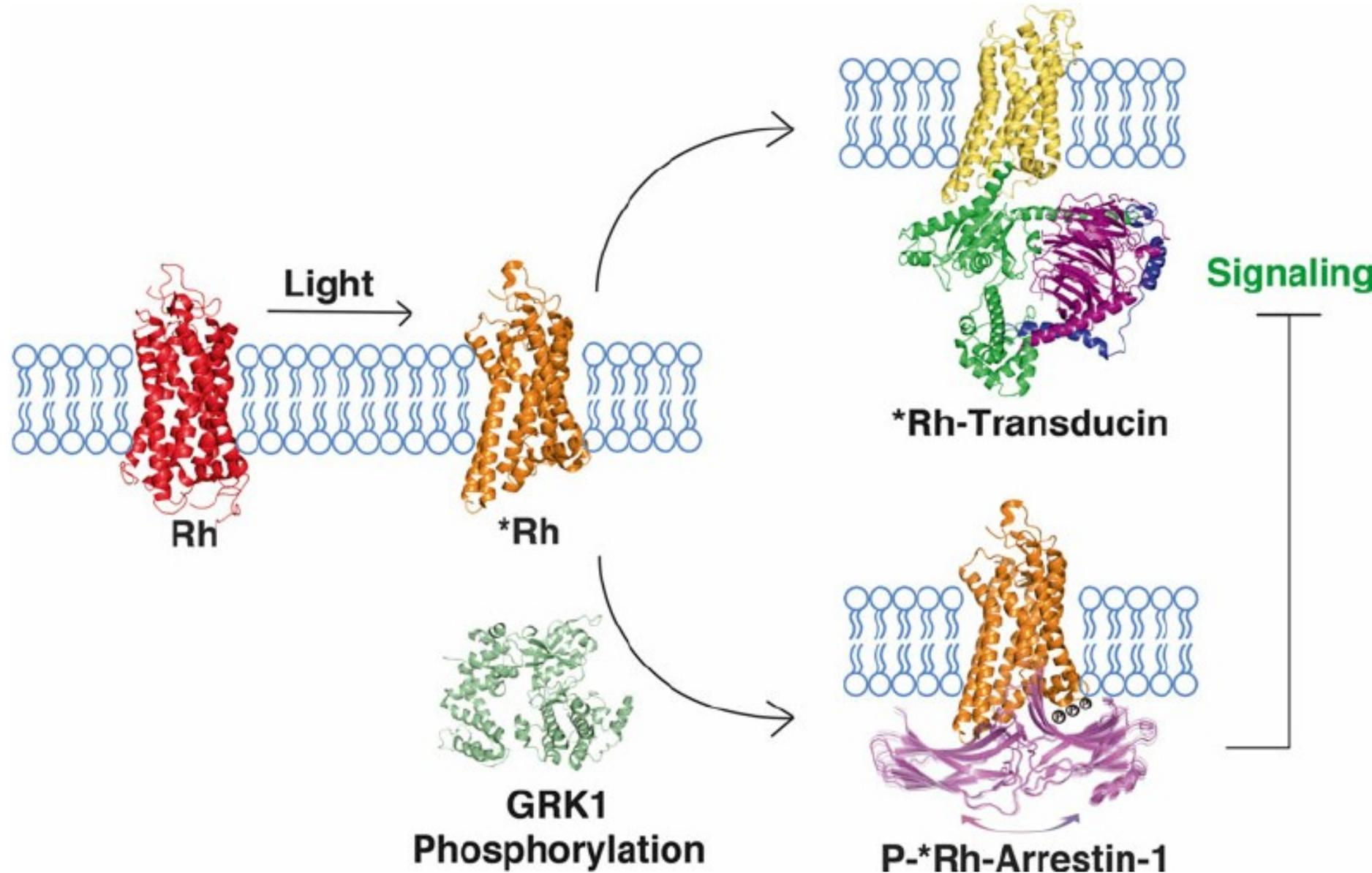


Figure 12.3 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Visual signal transduction



Heterotrimeric G proteins

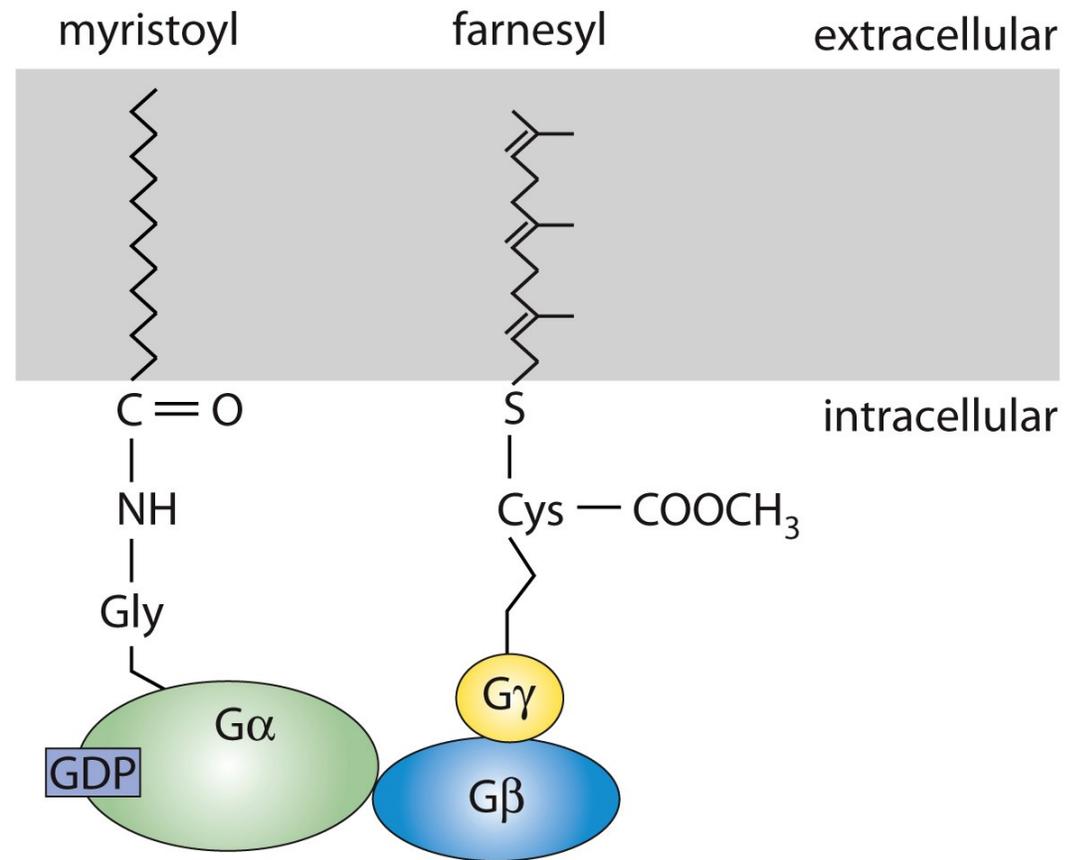


Figure 12.5b Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Lipidation of proteins as membrane anchors

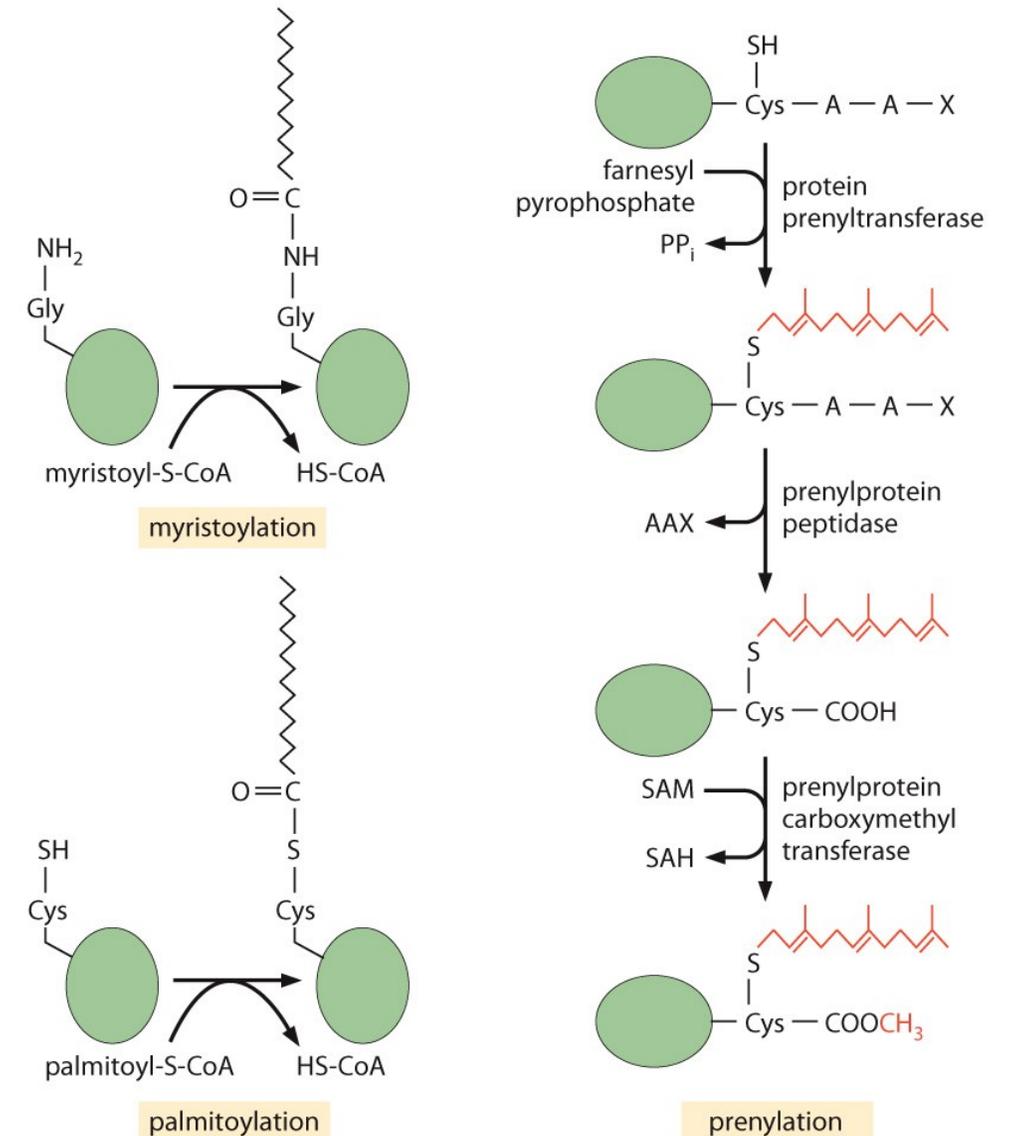


Figure 12.5a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

GDP/GTP exchange

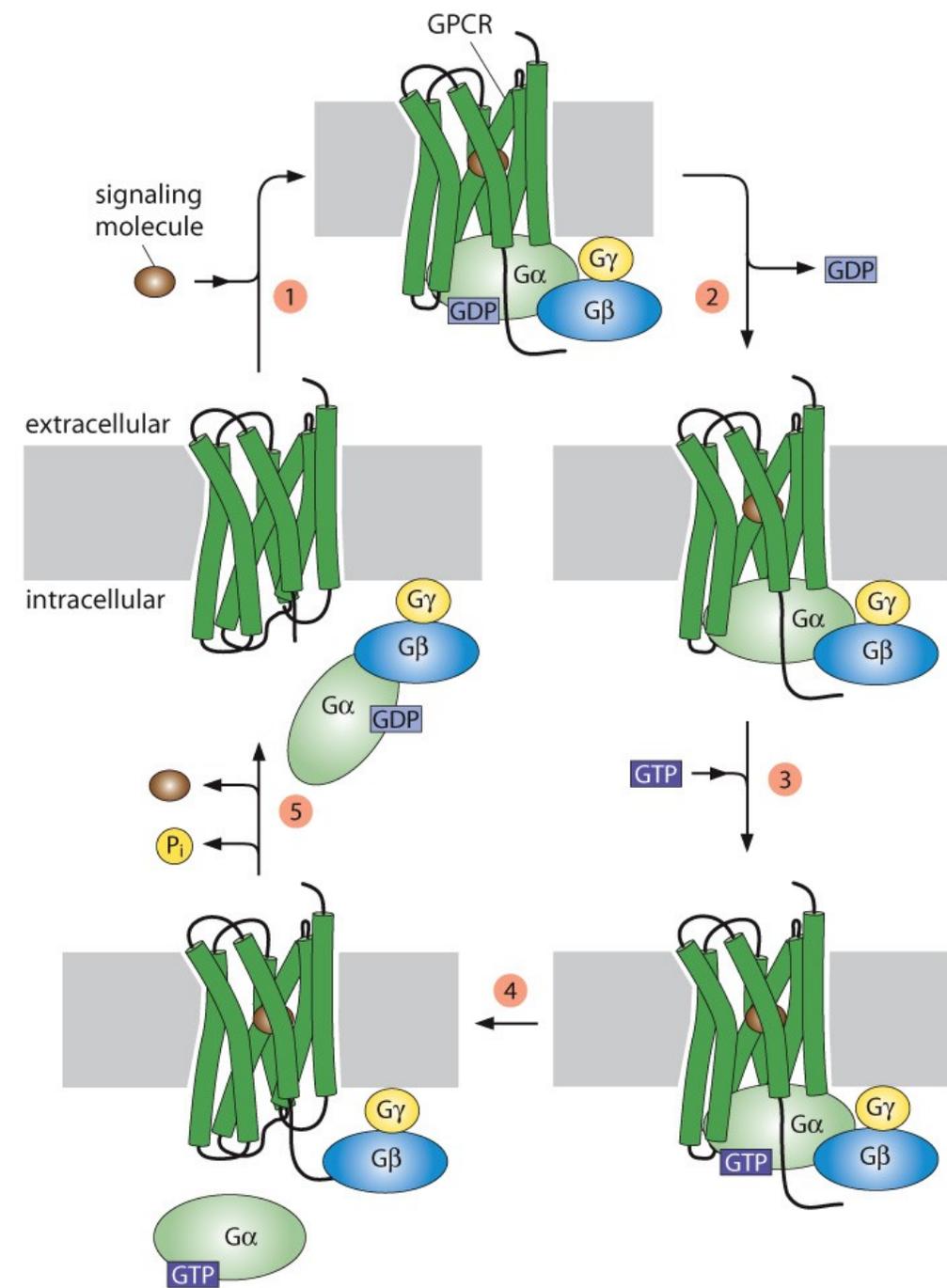
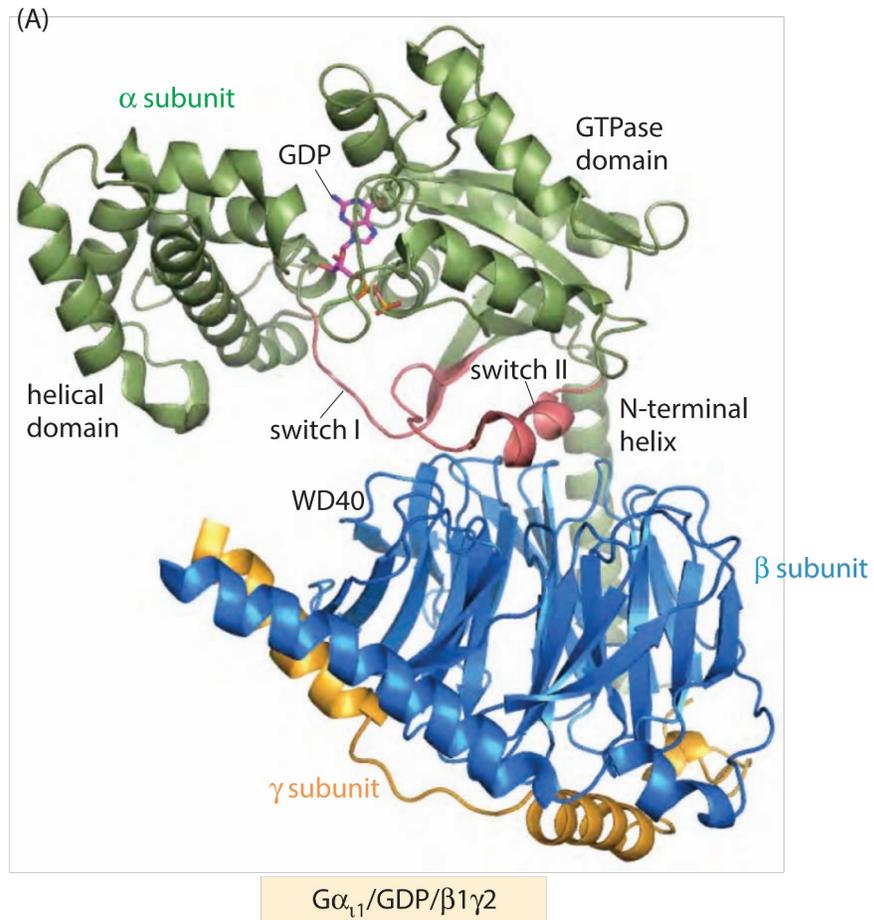
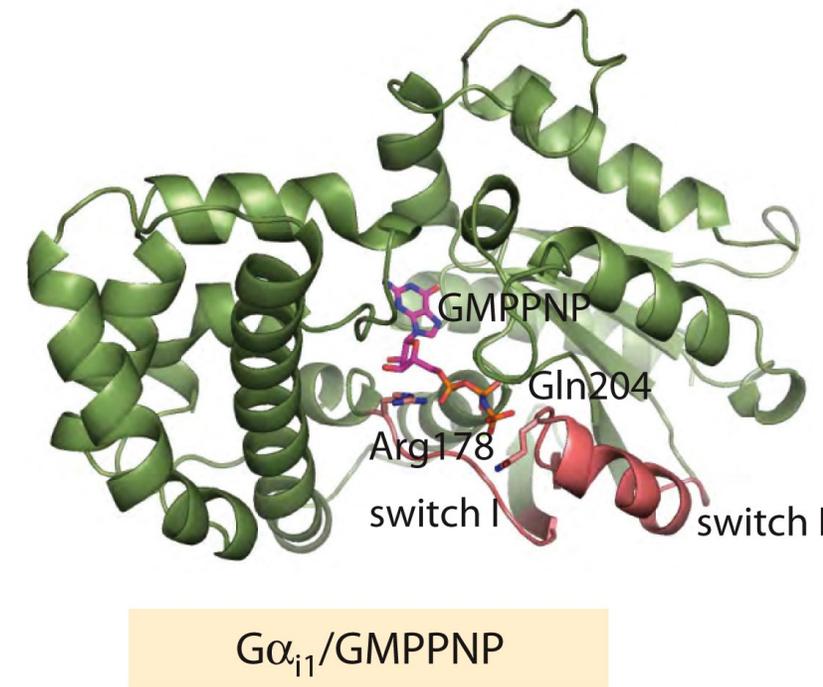
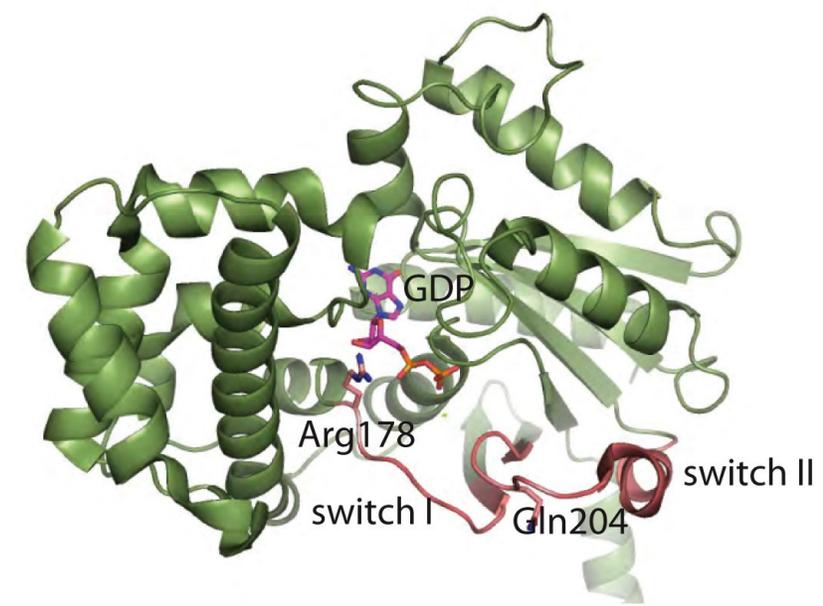
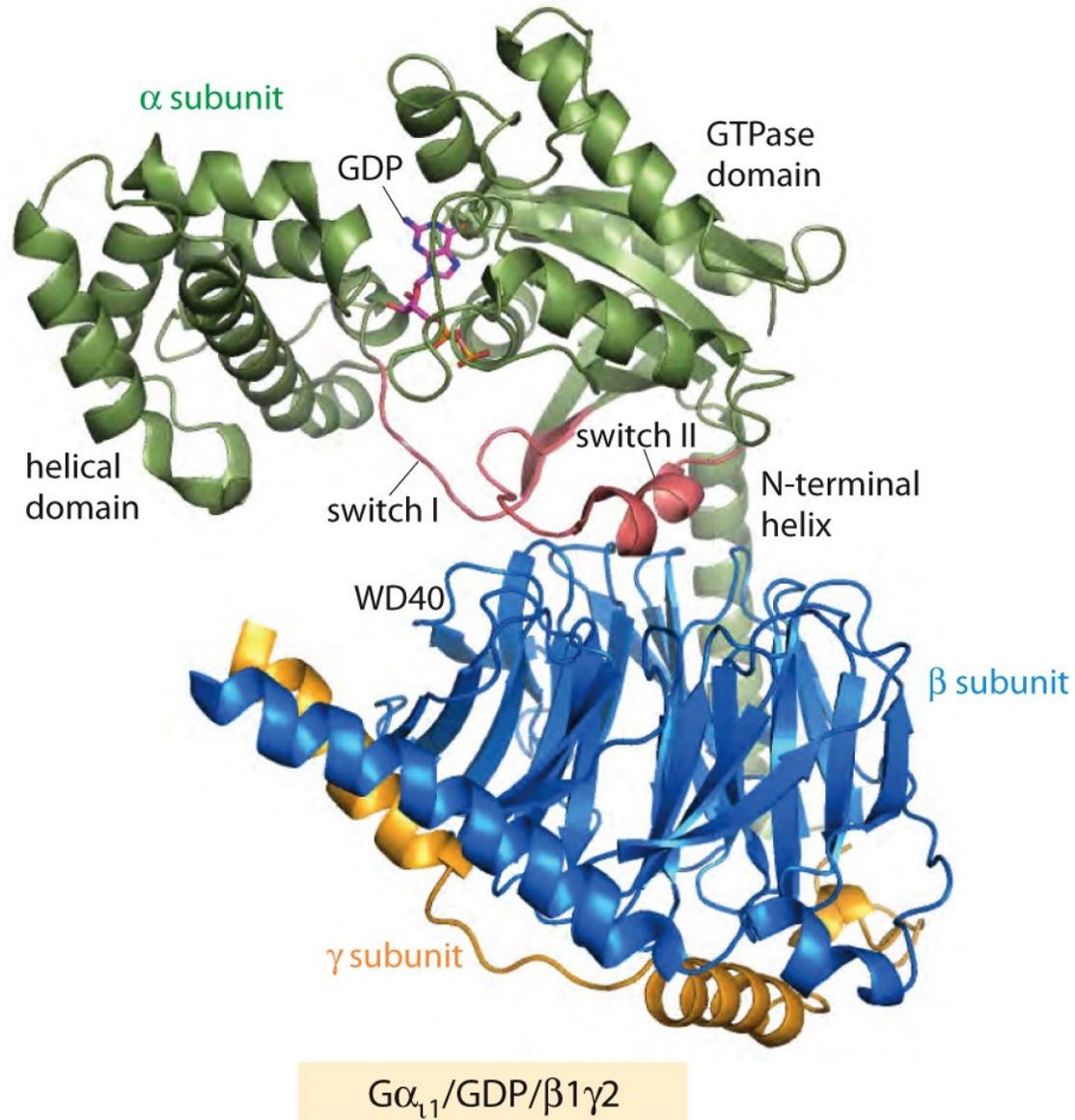
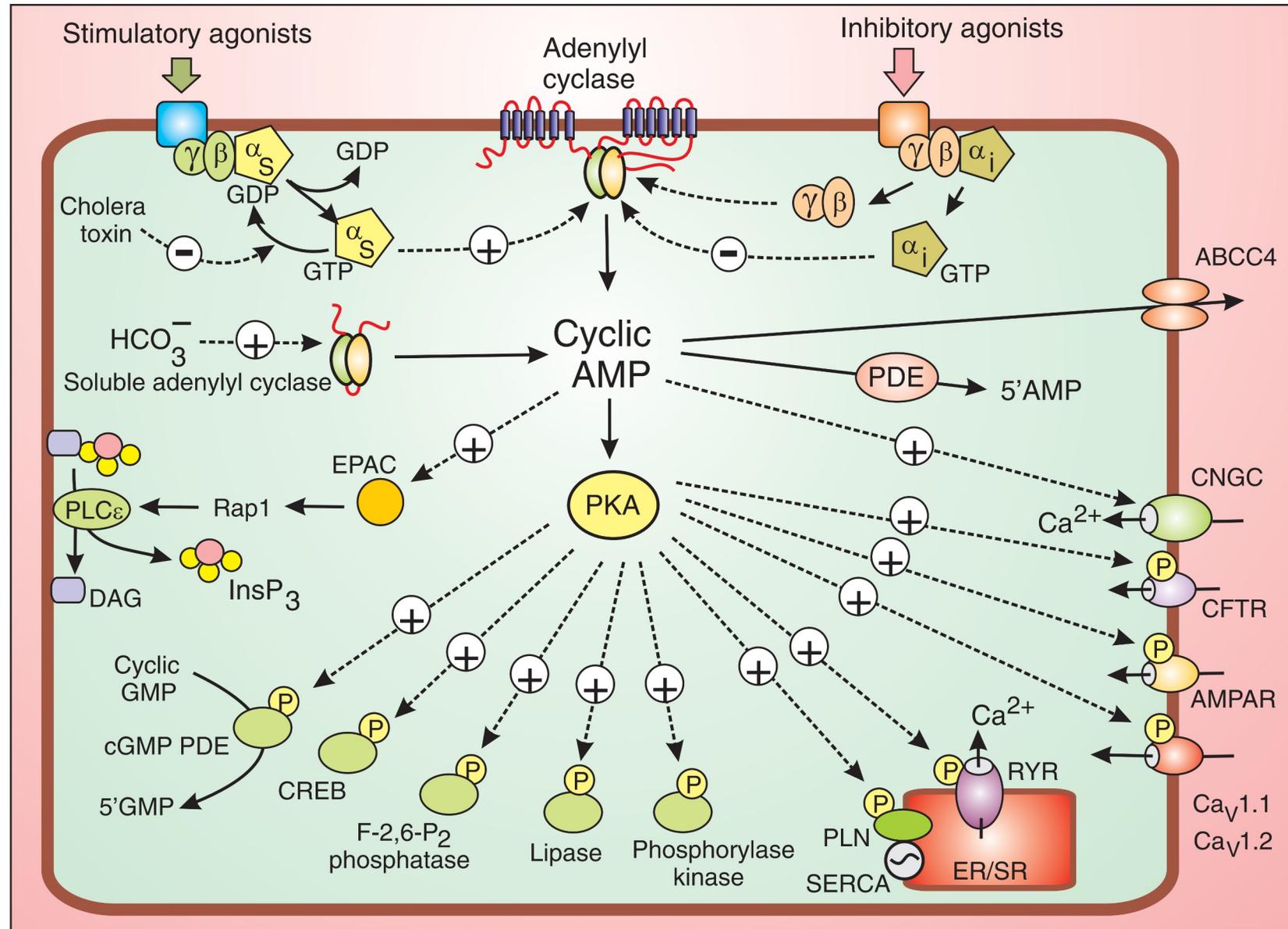


Figure 12.6 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Conformational changes



Organization and function of the cyclic AMP signaling pathway



Second messenger

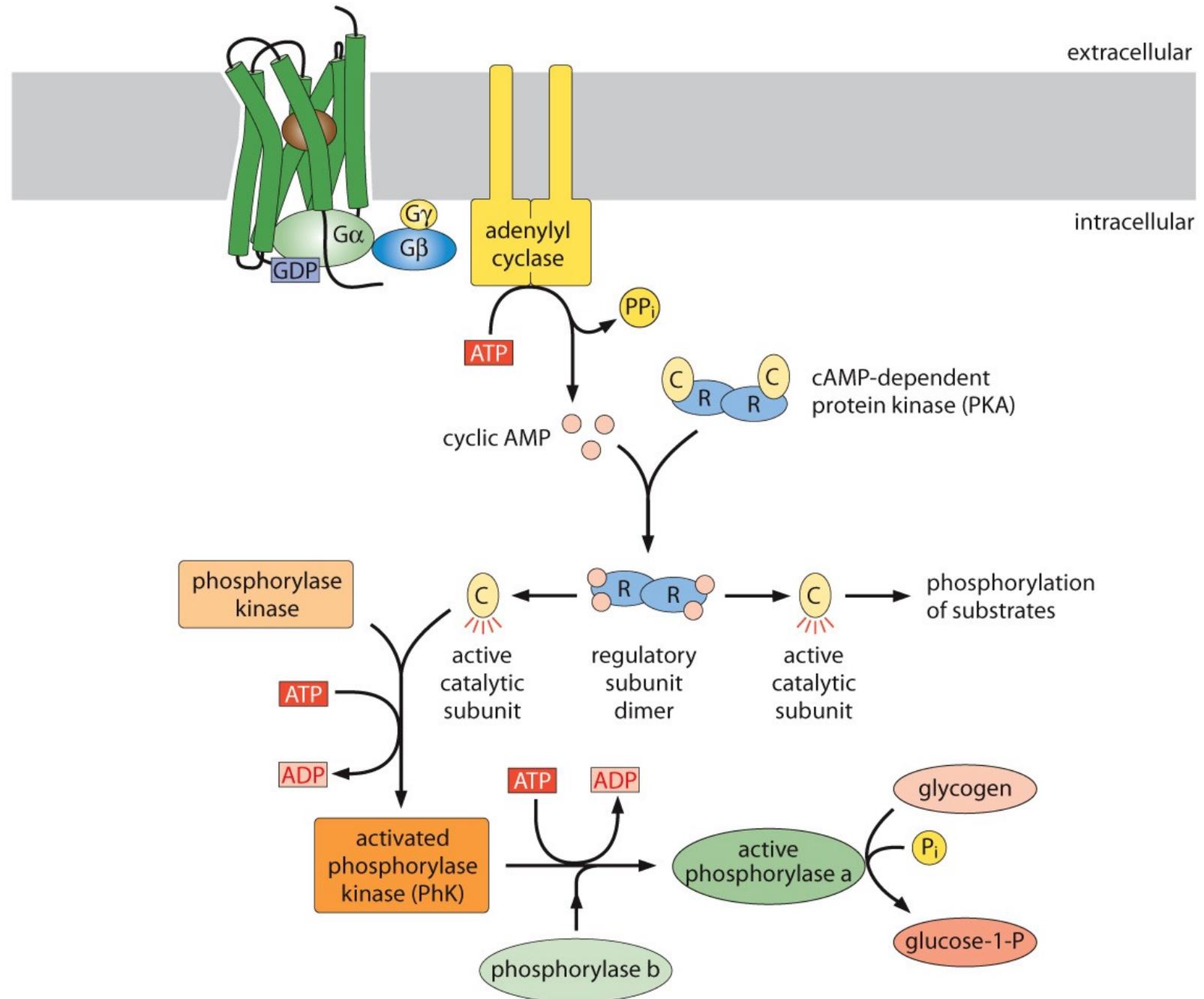
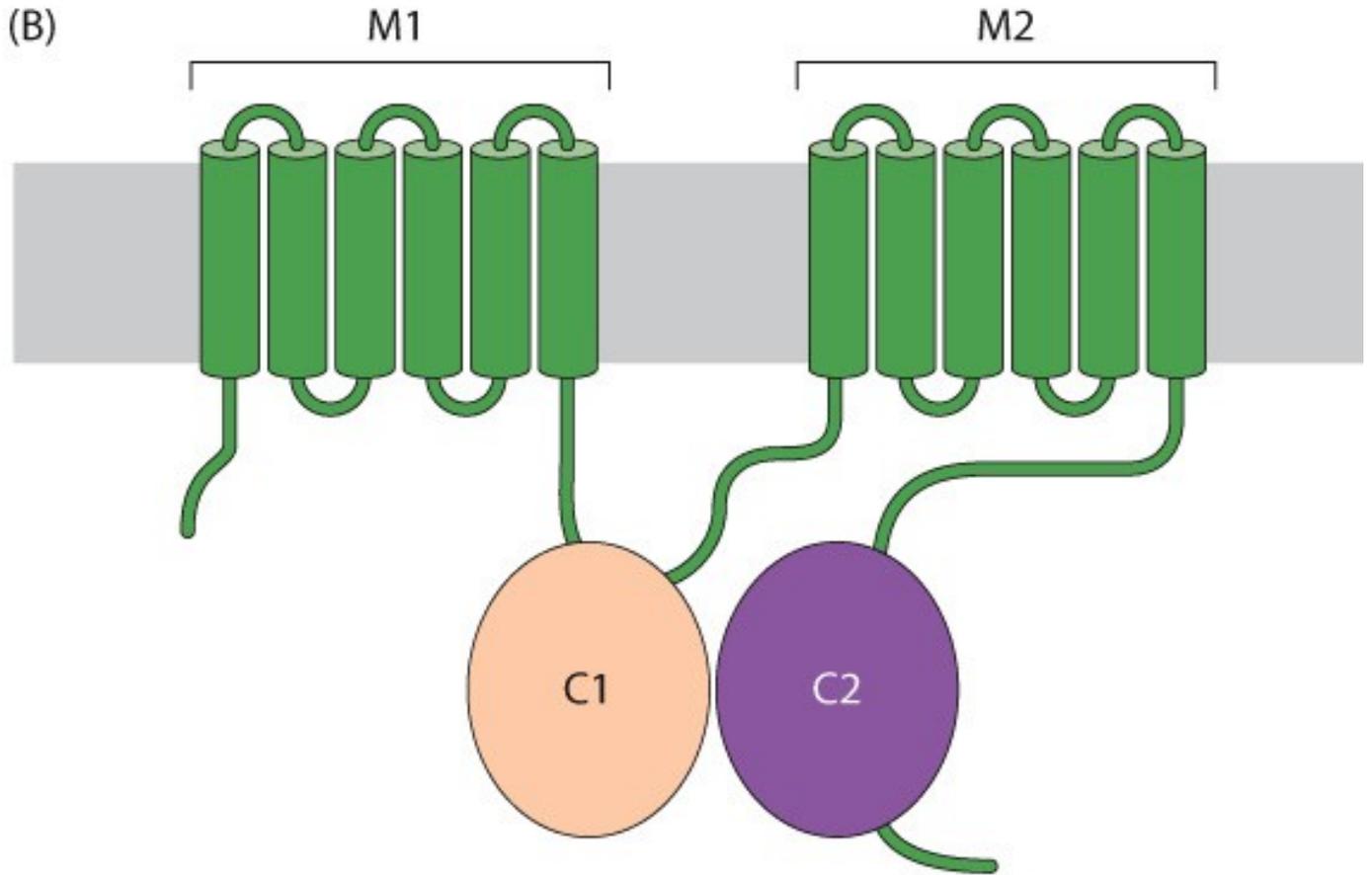
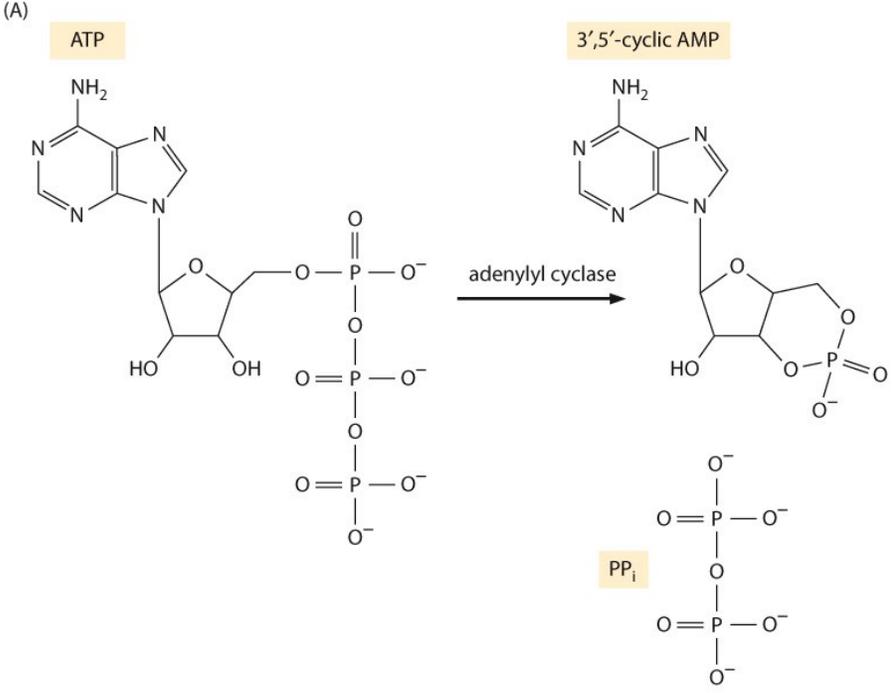
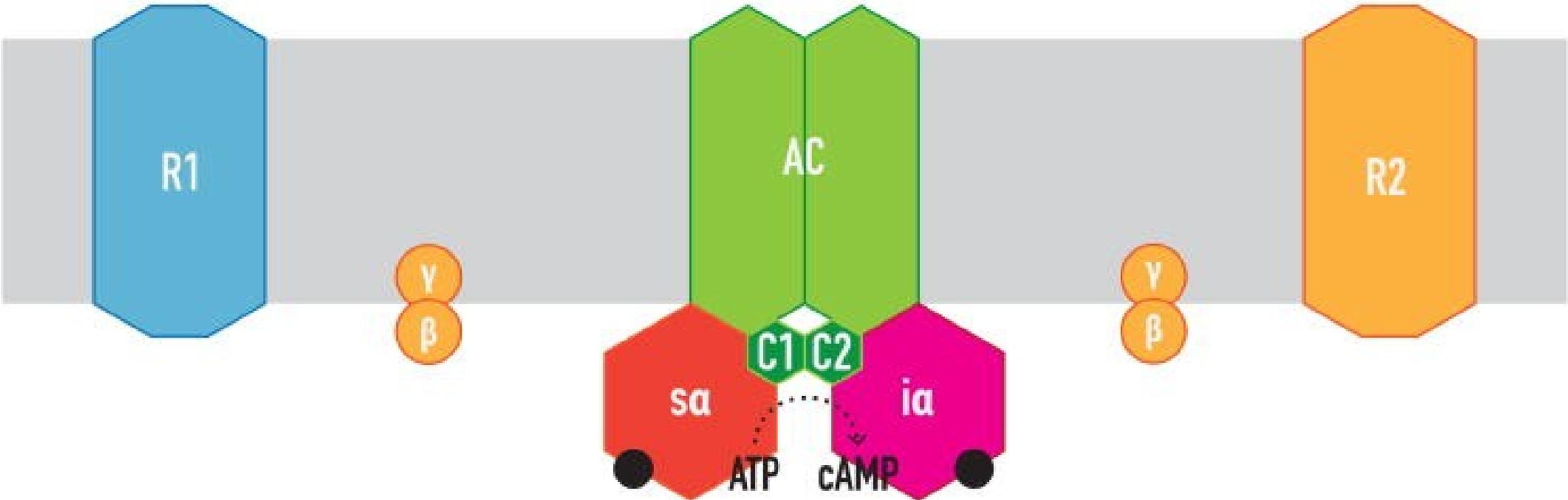


Figure 12.8 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

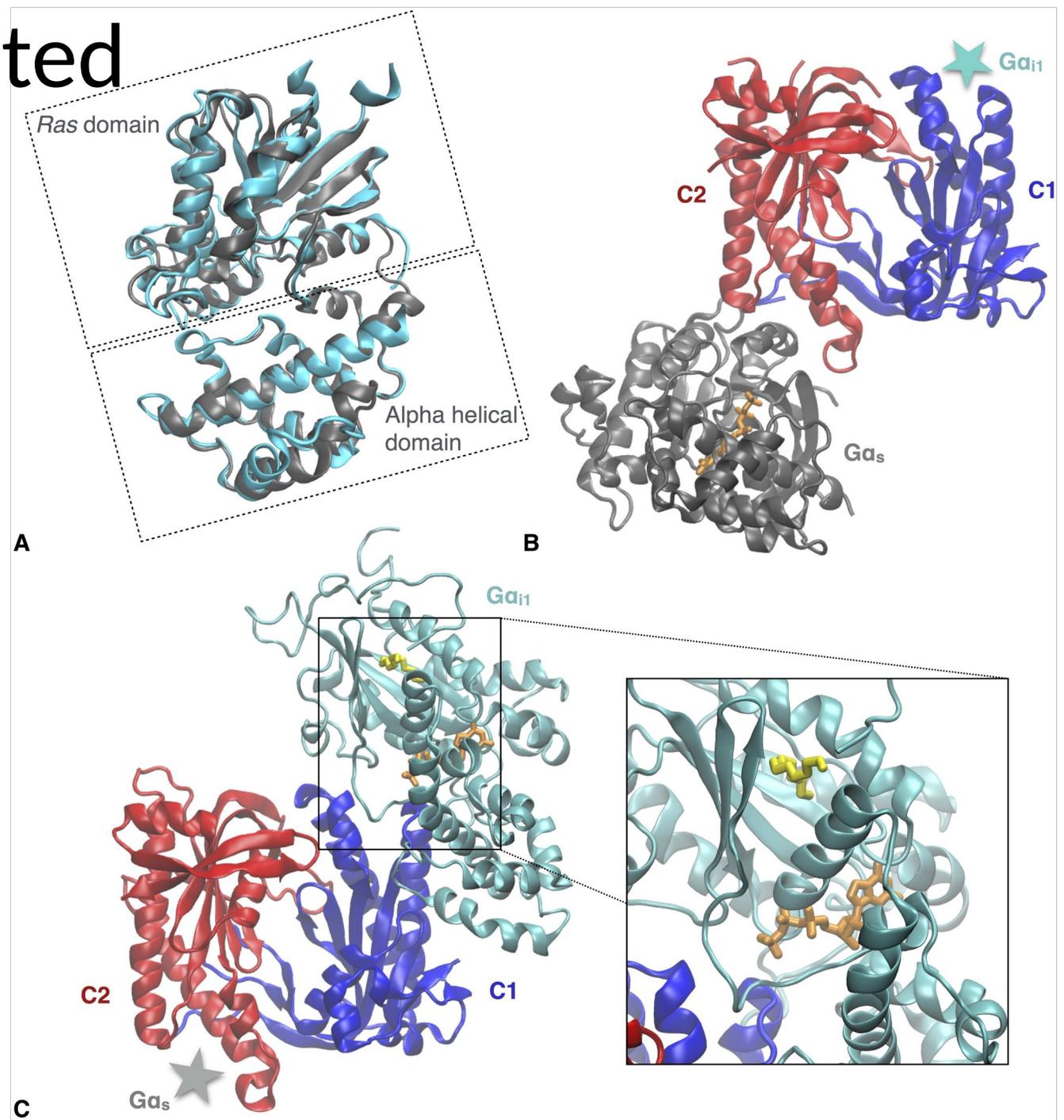
Adenylyl cyclase



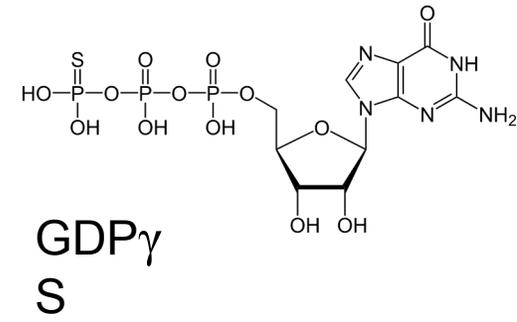
Second messenger



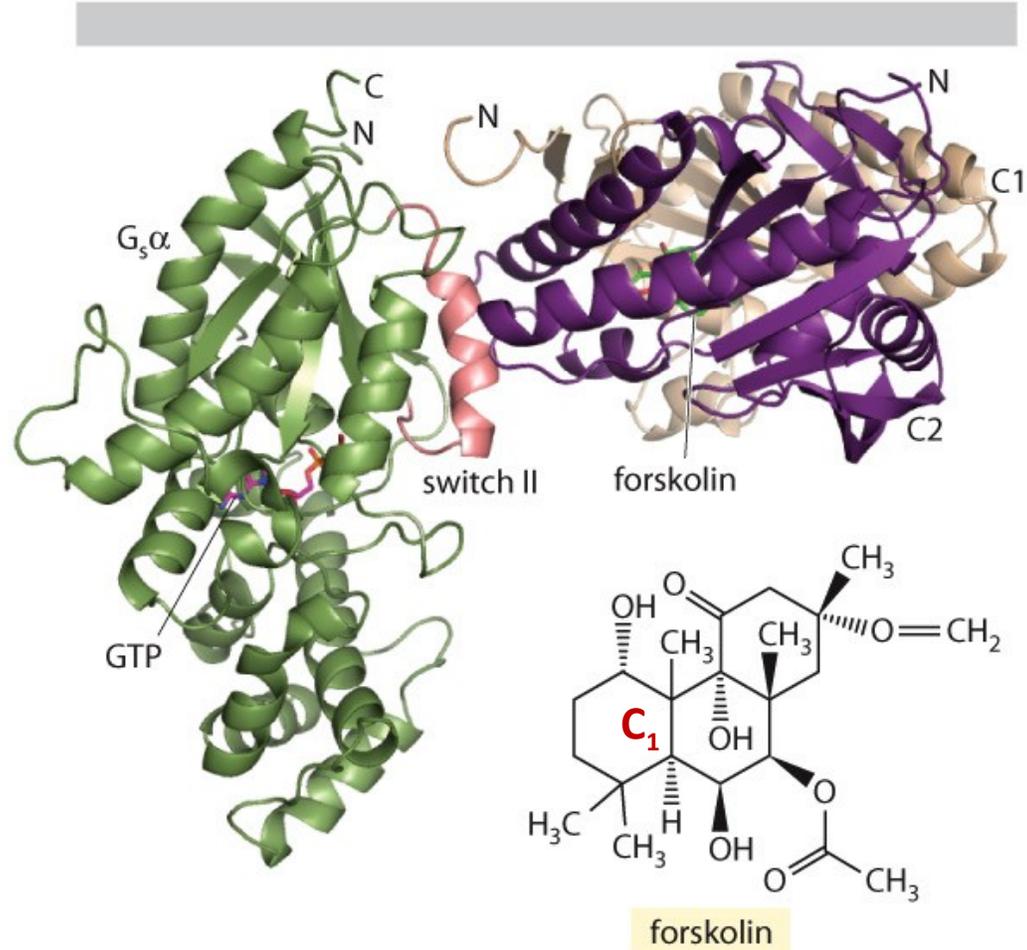
AC complexes and activated G α subunit structures



Catalytic domain



(A) plasma membrane



(B)

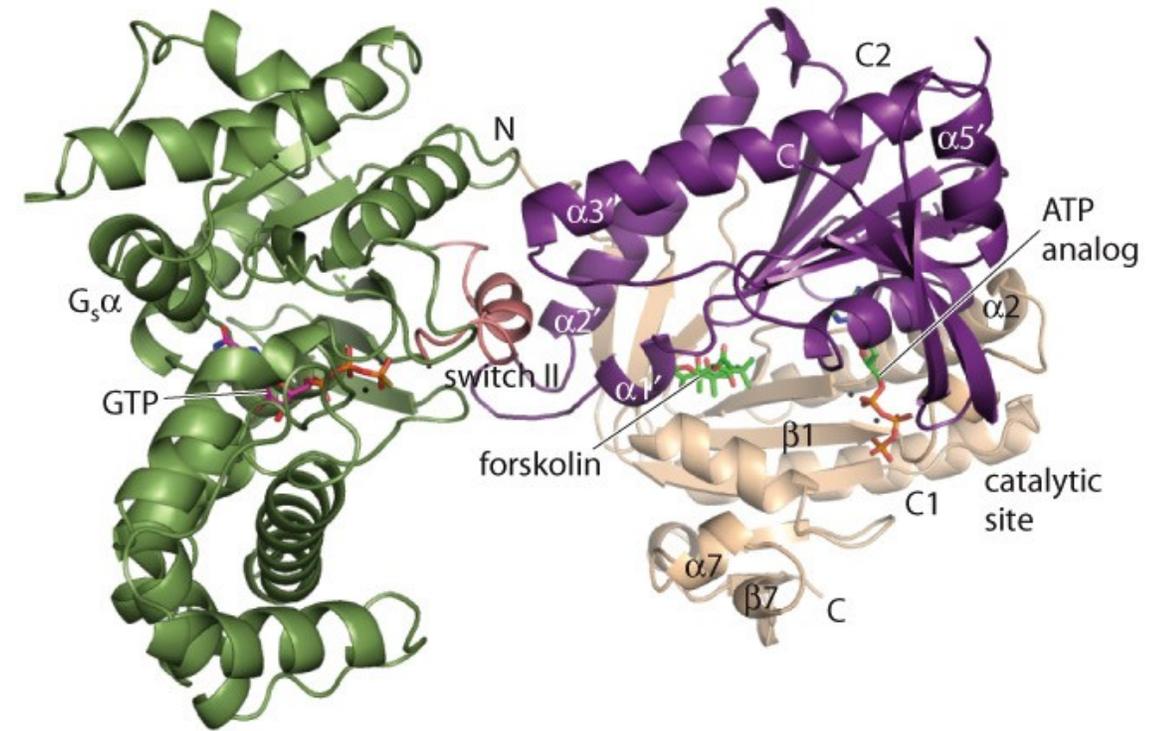


Figure 12.10 Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Catalytic mechanism

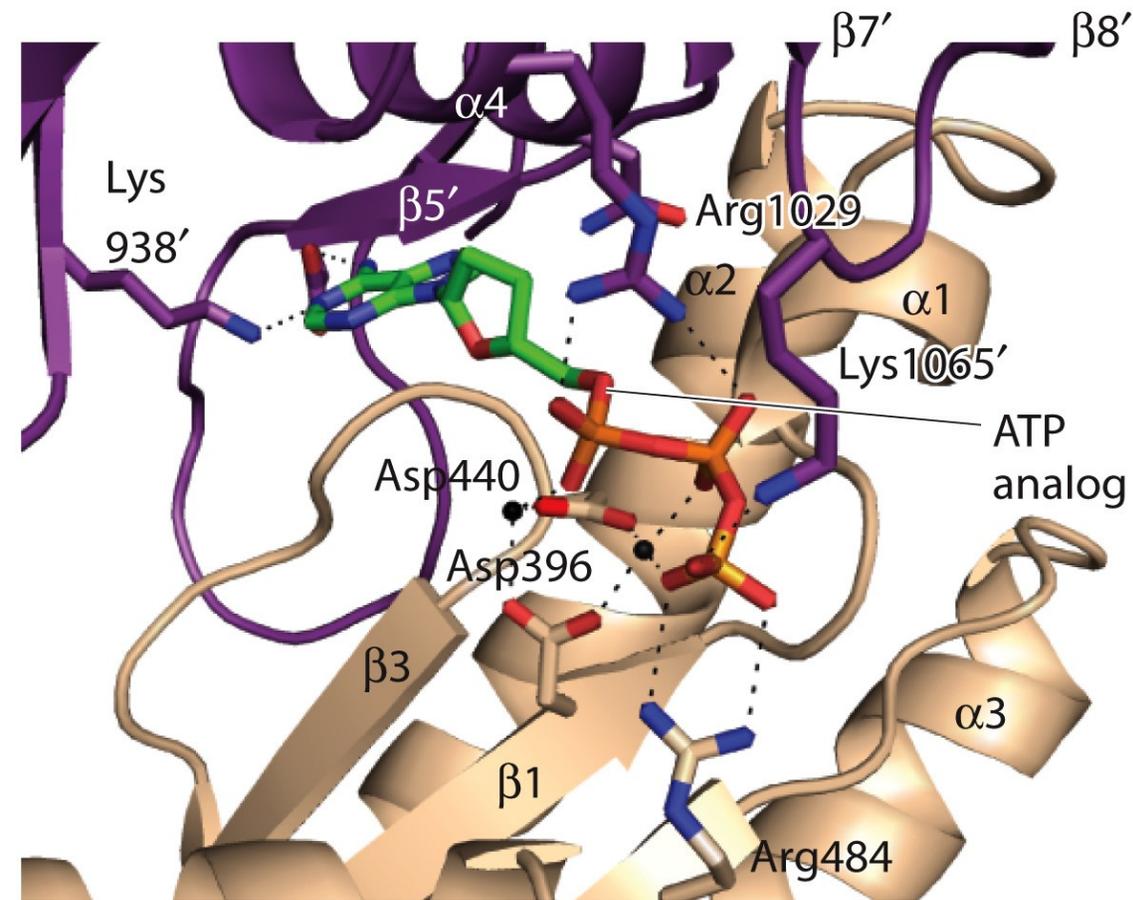


Figure 12.11a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

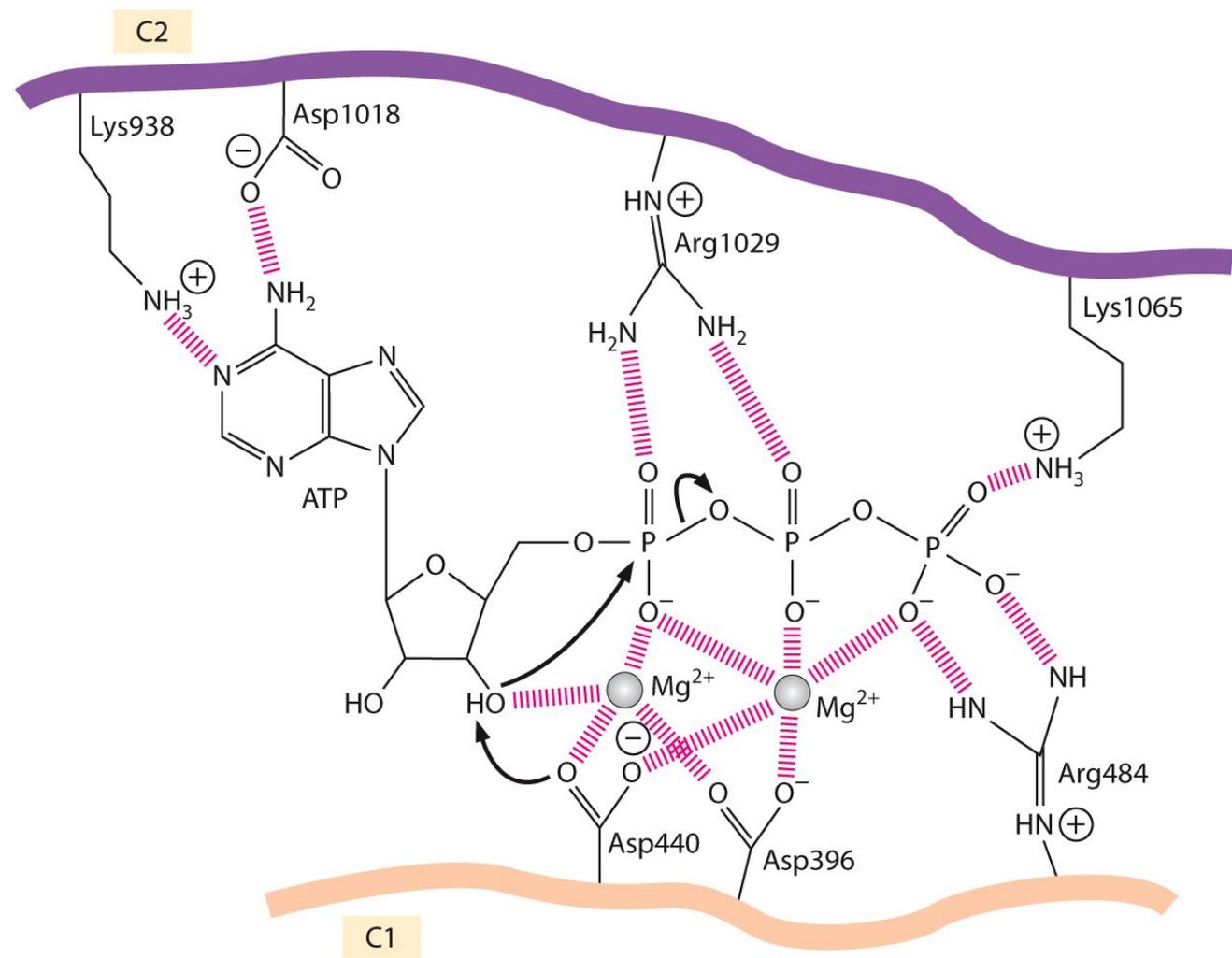
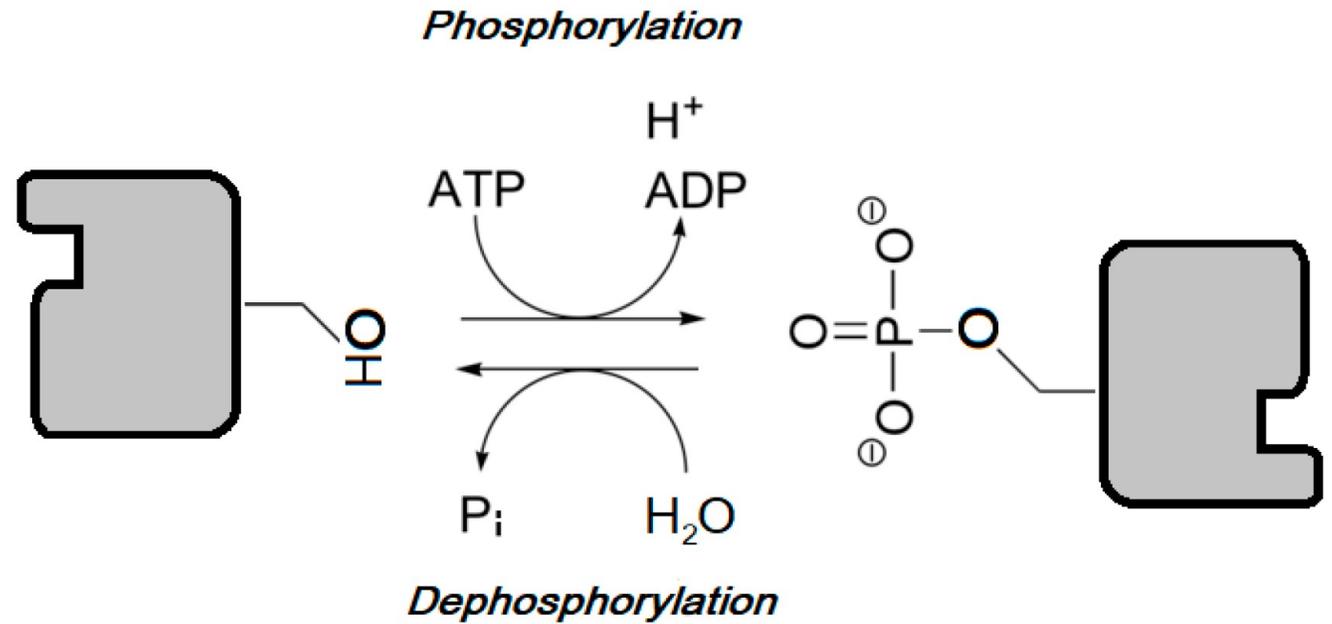


Figure 12.11b Molecular Biology of Assemblies and Machines (© Garland Science 2016)

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

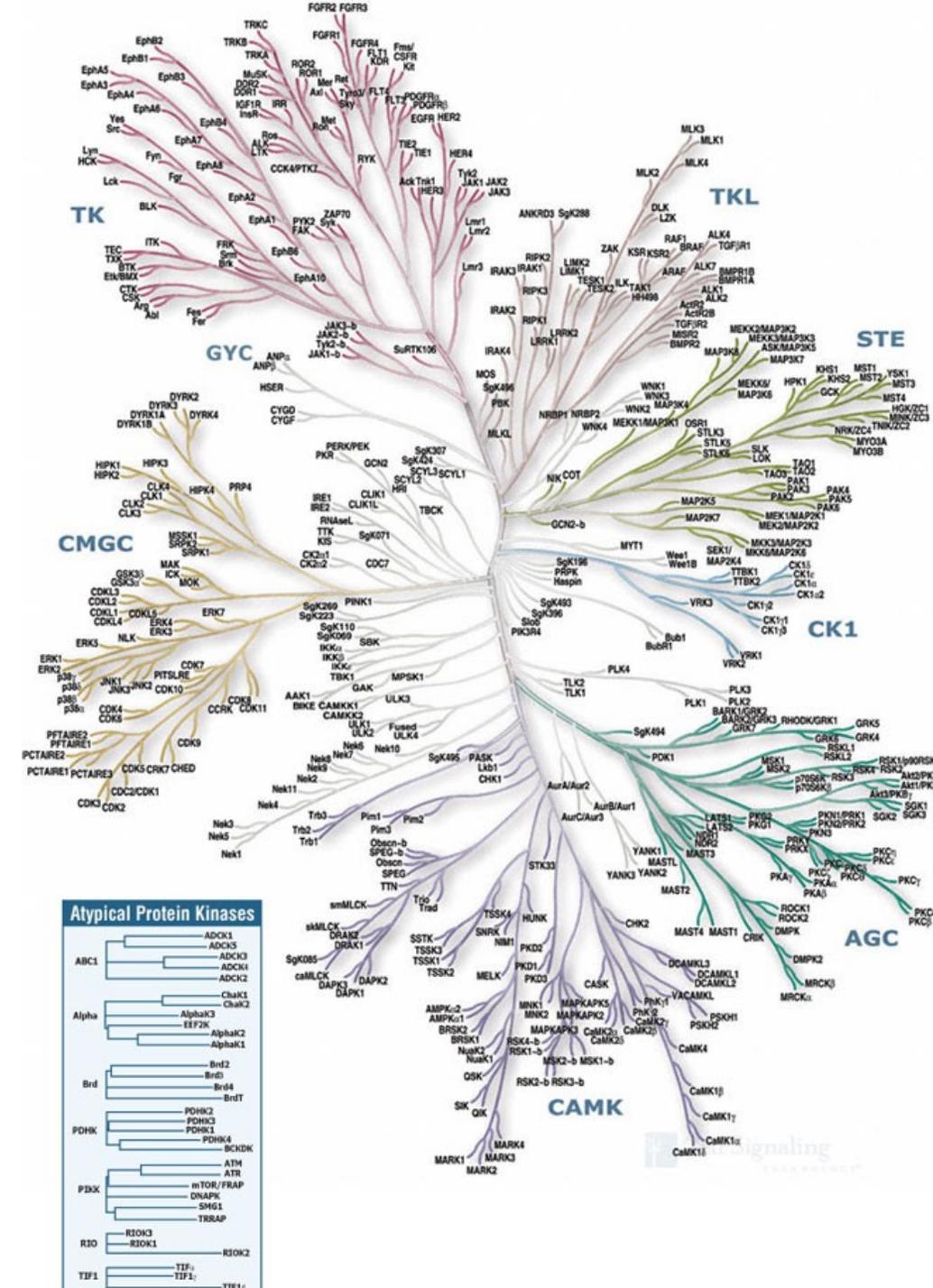
Transition between structural disorder and order

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



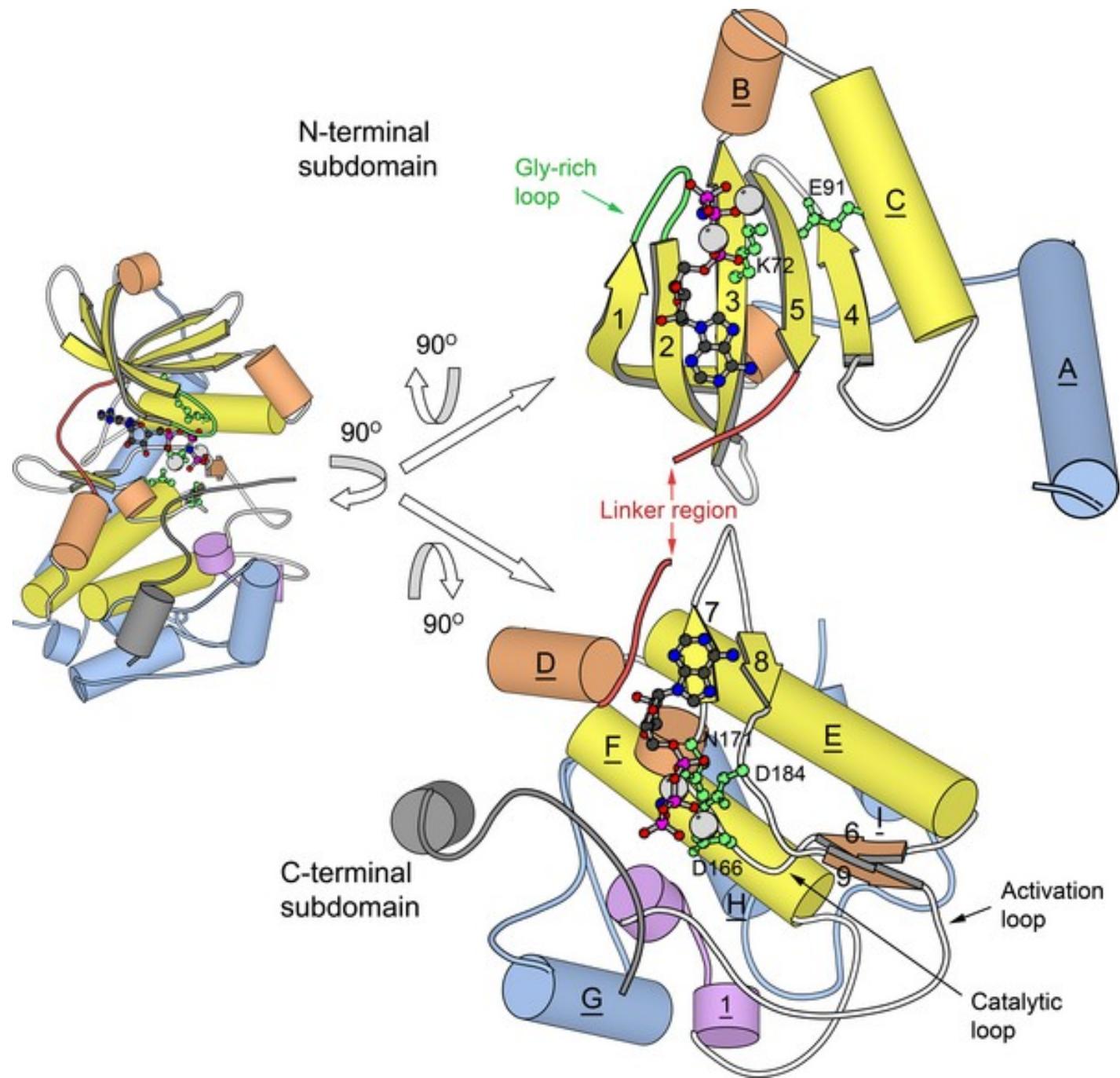
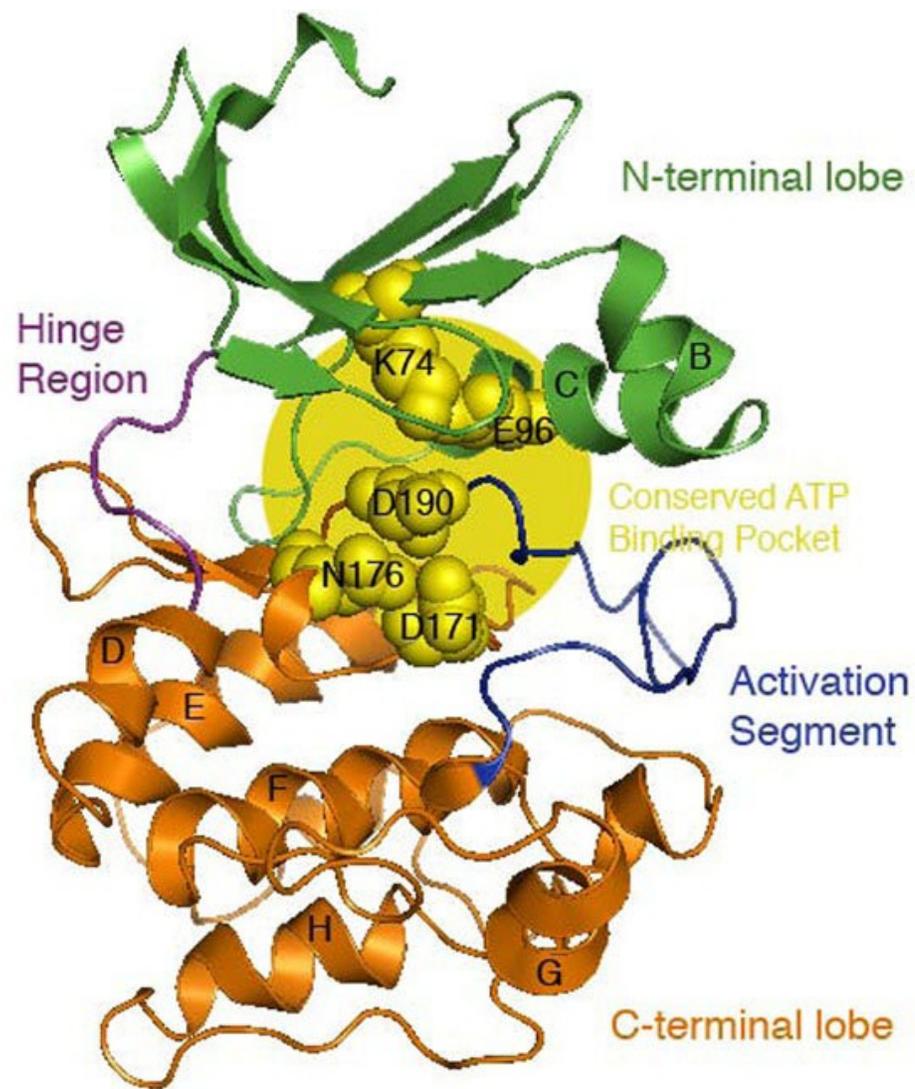
Protein kinase

Table 12.2.1 Selected protein kinases and their preferred substrate specificities.

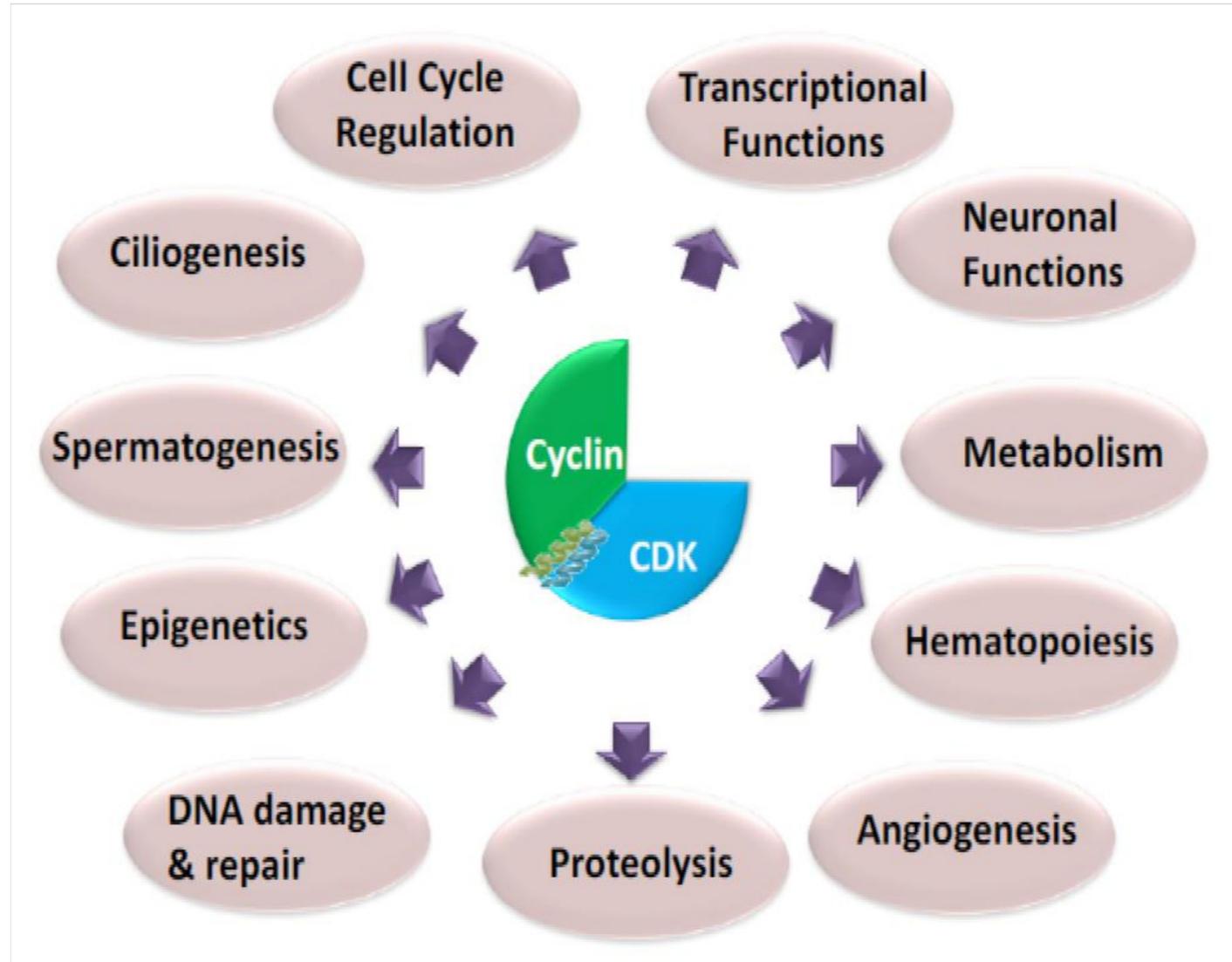
Name	Full name	Consensus sequence
Ser/Thr kinases		
PKA	Protein kinase A	-R-R-X- S/T -Φ
PhK	Phosphorylase kinase	-R-X-X- S/T -Φ-R
Cdk2	Cyclin-dependent protein kinase 2	- S/T -P-X-K/R
ERK2	Extracellular signal-regulated kinase 2	-P-X- S/T -P
Plk1	Polo-like kinase 1	-D/E/N-X- S/T -Φ/not P
Aurora B	Aurora 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- YX -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.

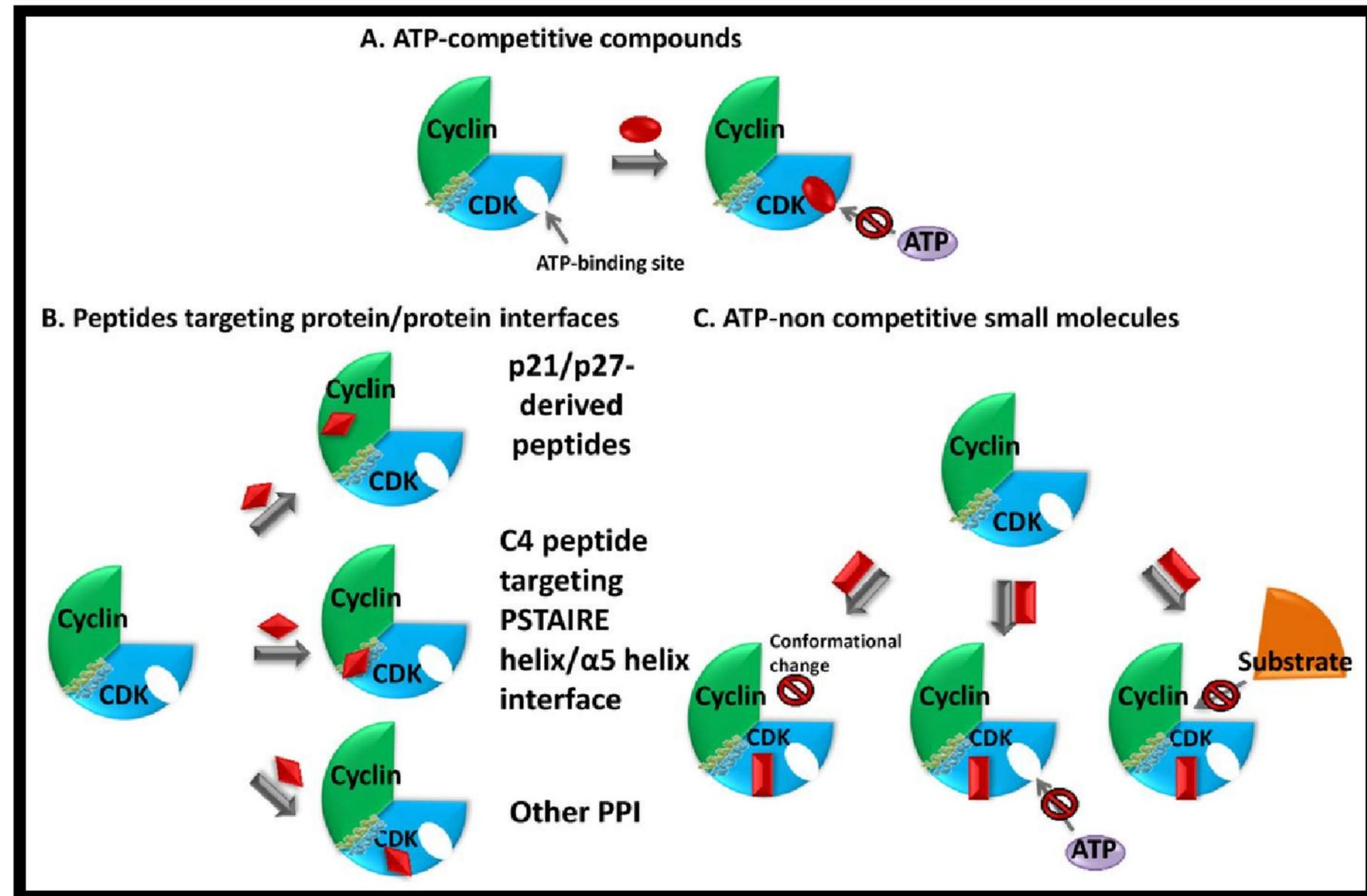
protein kinase fold



Functional diversity of Cyclin-dependent Kinases



Strategies for targeting Cyclin-dependent kinases



Tyrosine kinases

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

Polypeptide
Growth factors
Cytokines
Hormones

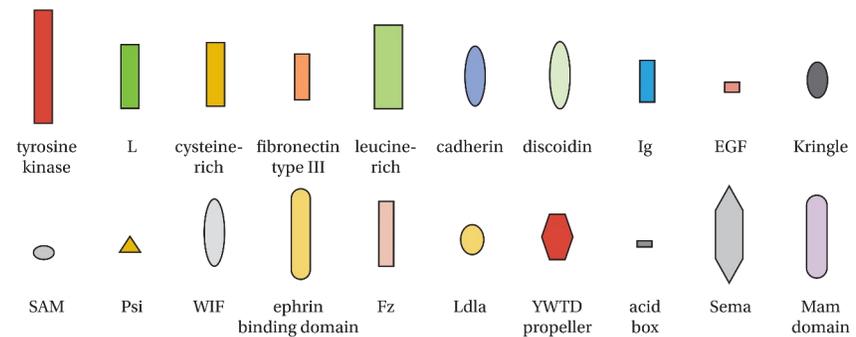
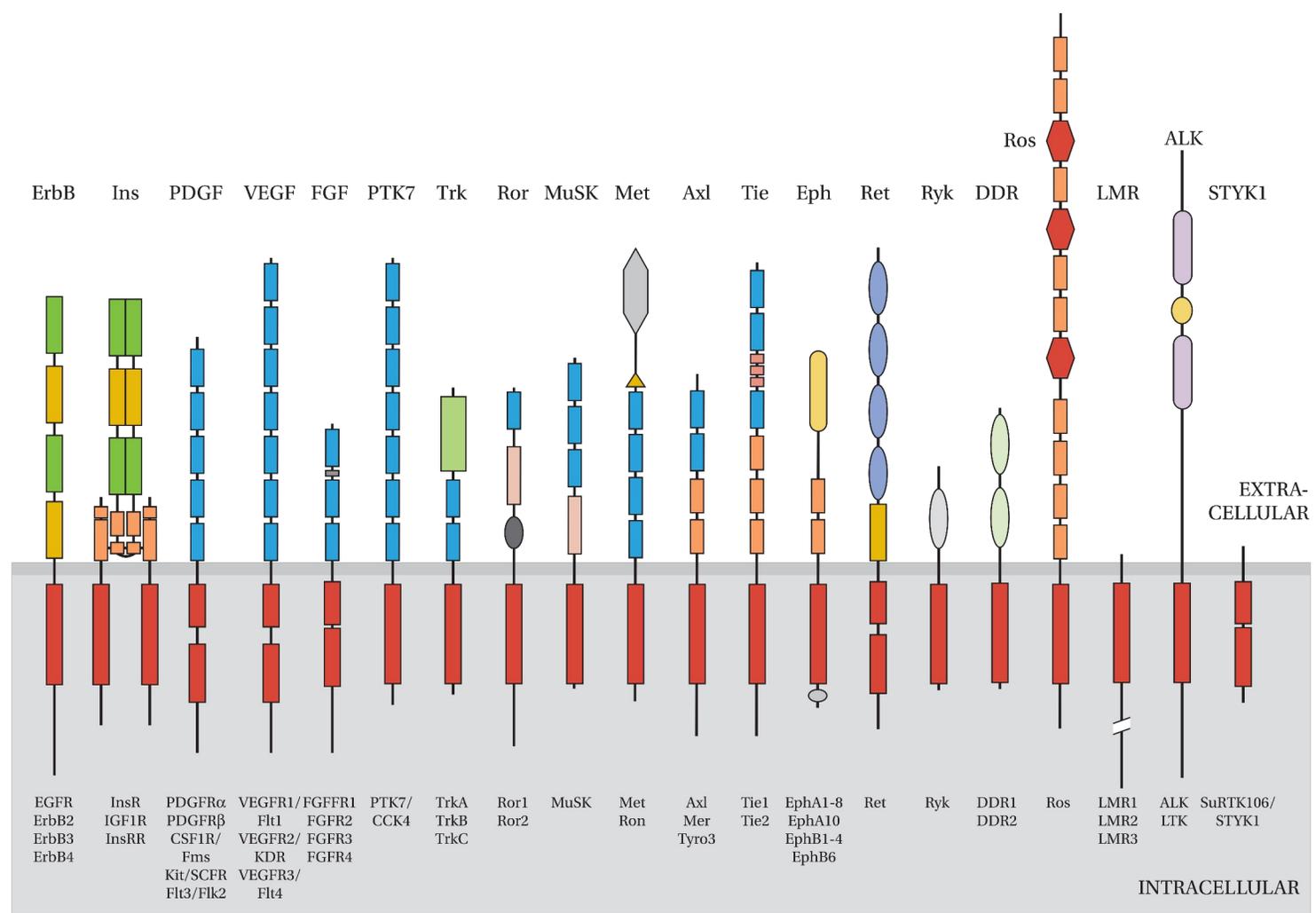
RTKs are characterized by specific domains

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

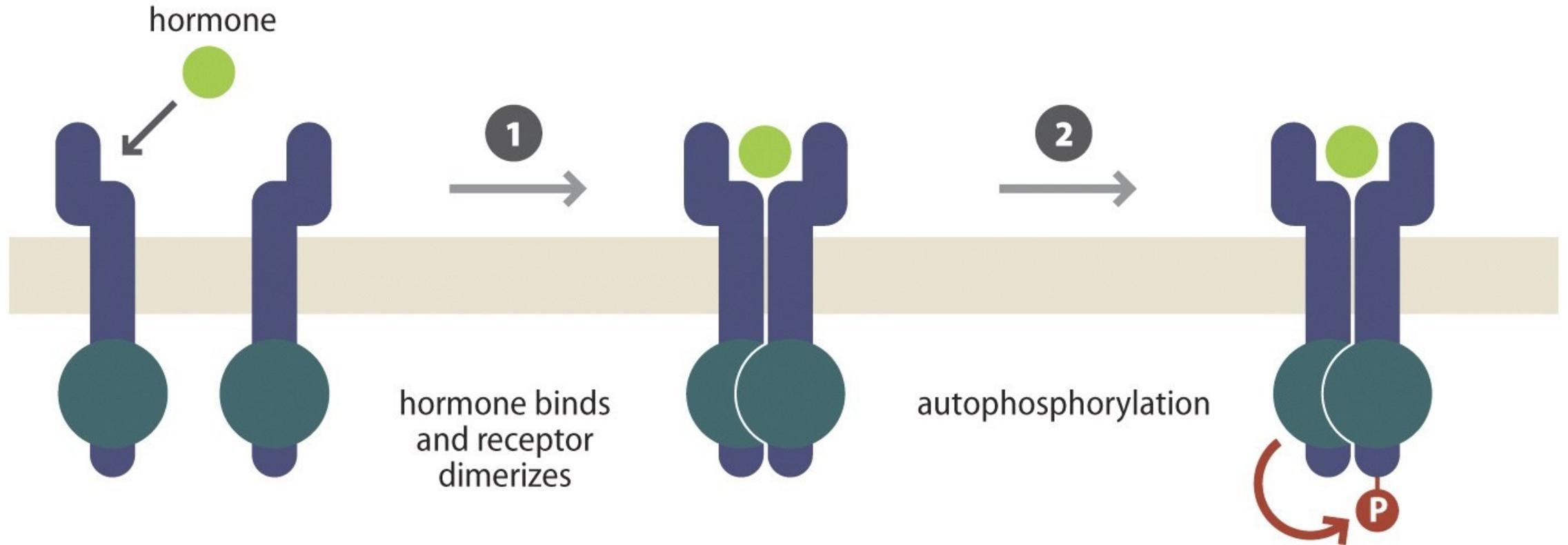
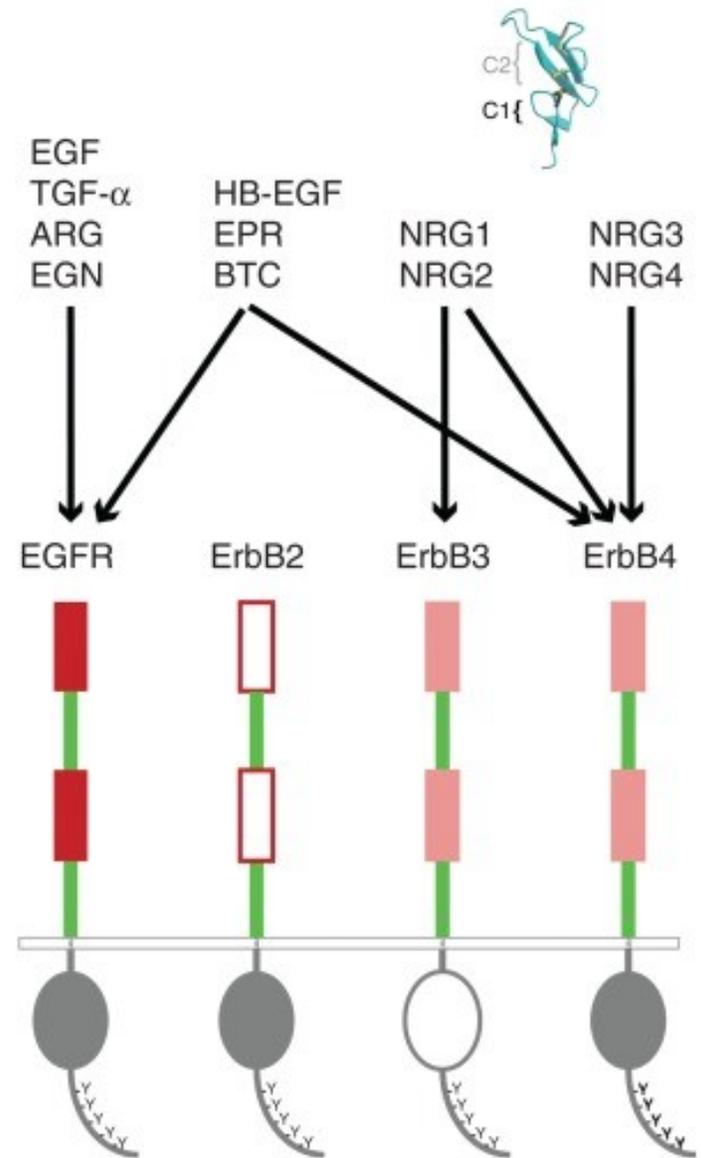
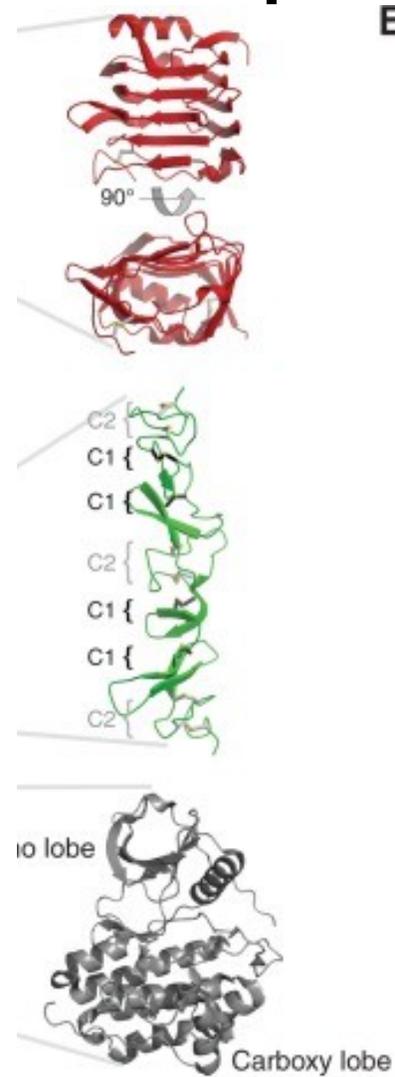
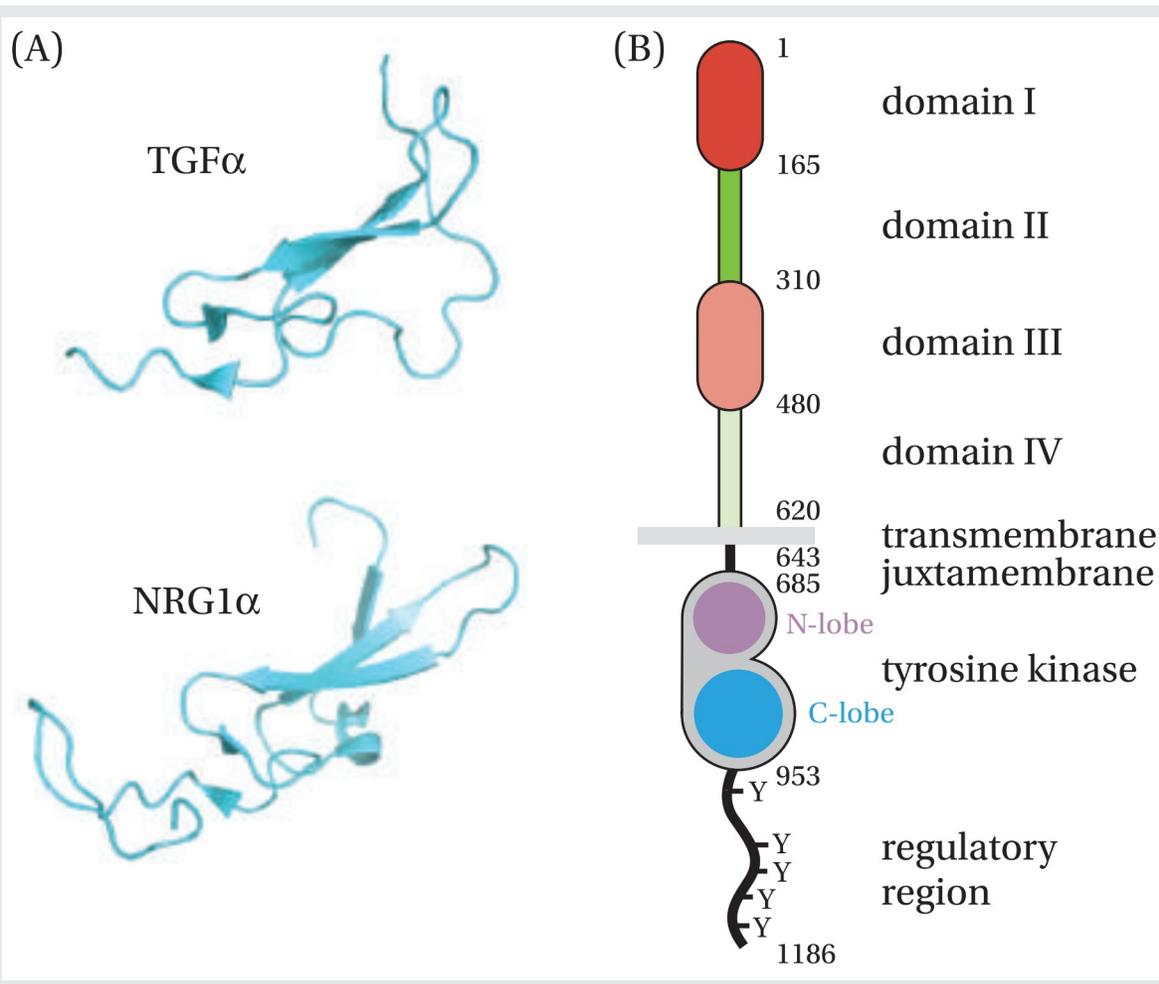


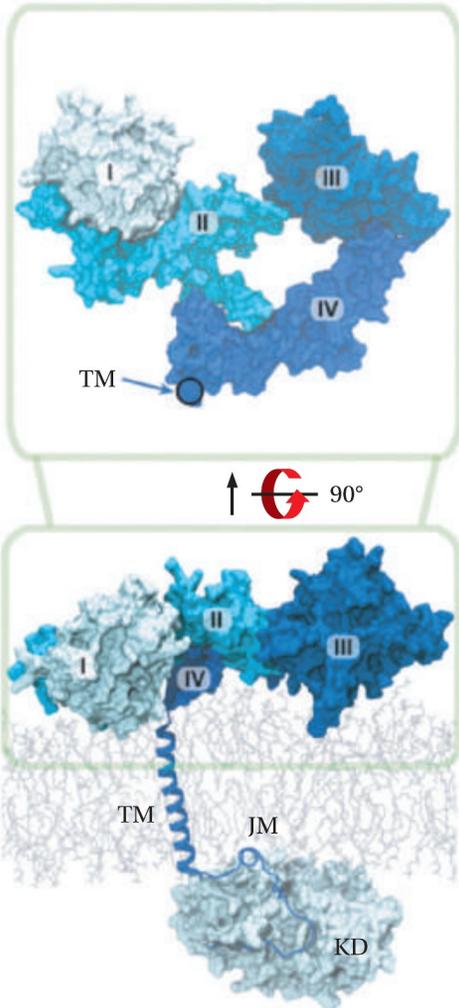
Figure 8.3 How Proteins Work (©2012 Garland Science)

epidermal growth factor receptor

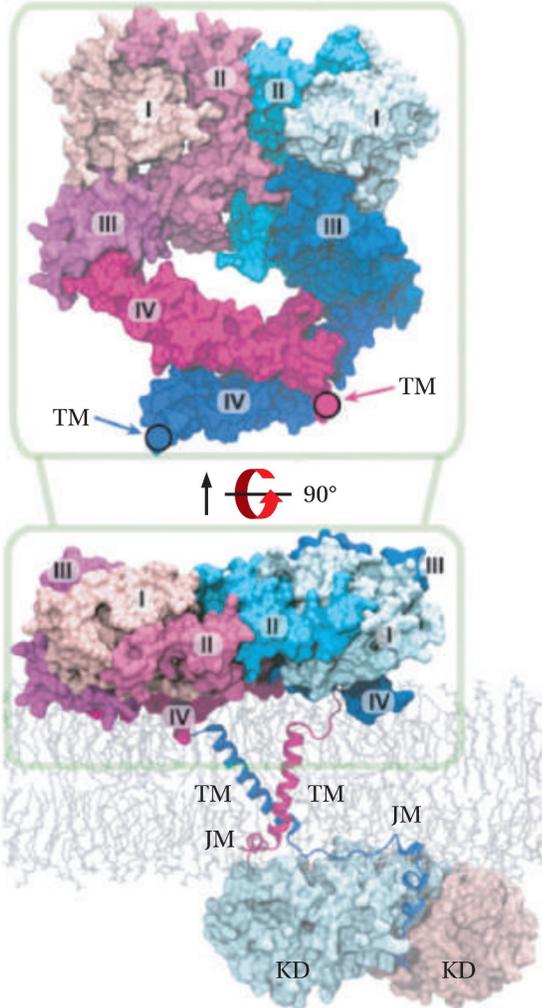


the epidermal growth factor

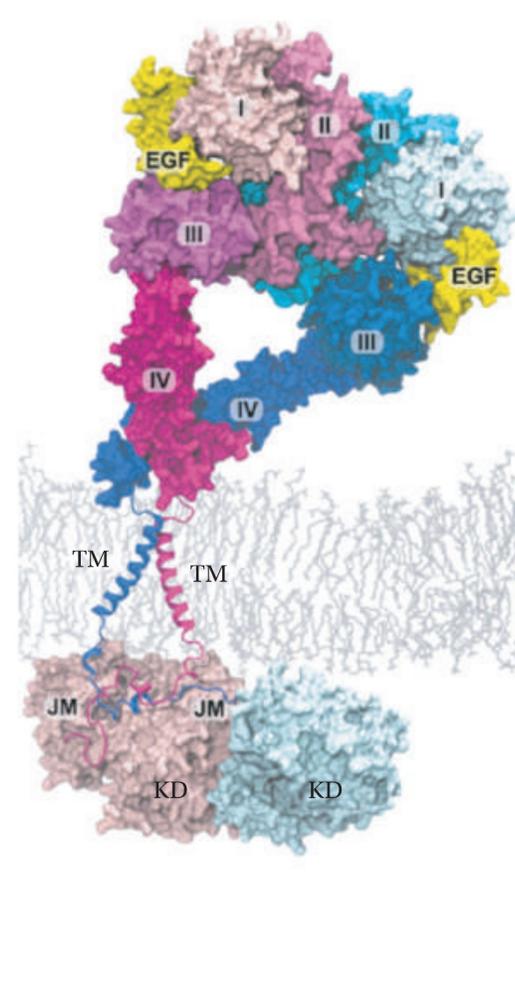
(A) monomer $t = 4.7 \mu\text{s}$



(B) inactive dimer $t = 4.1 \mu\text{s}$



(C) active dimer $t = 4.7 \mu\text{s}$

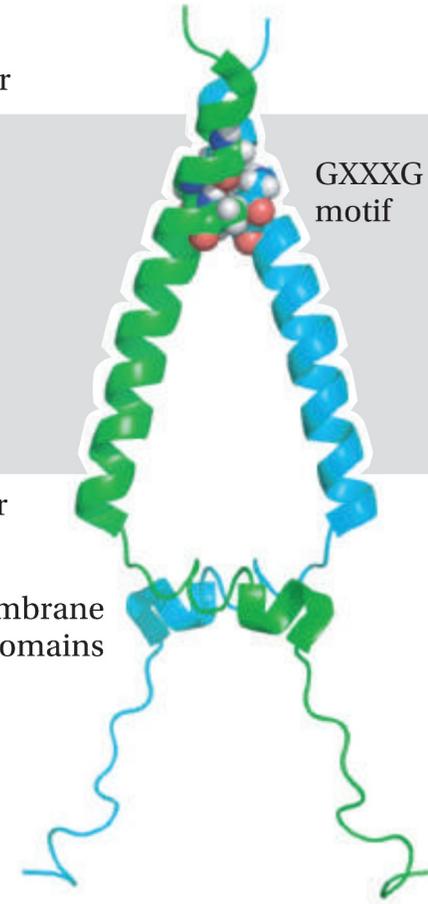


extracellular

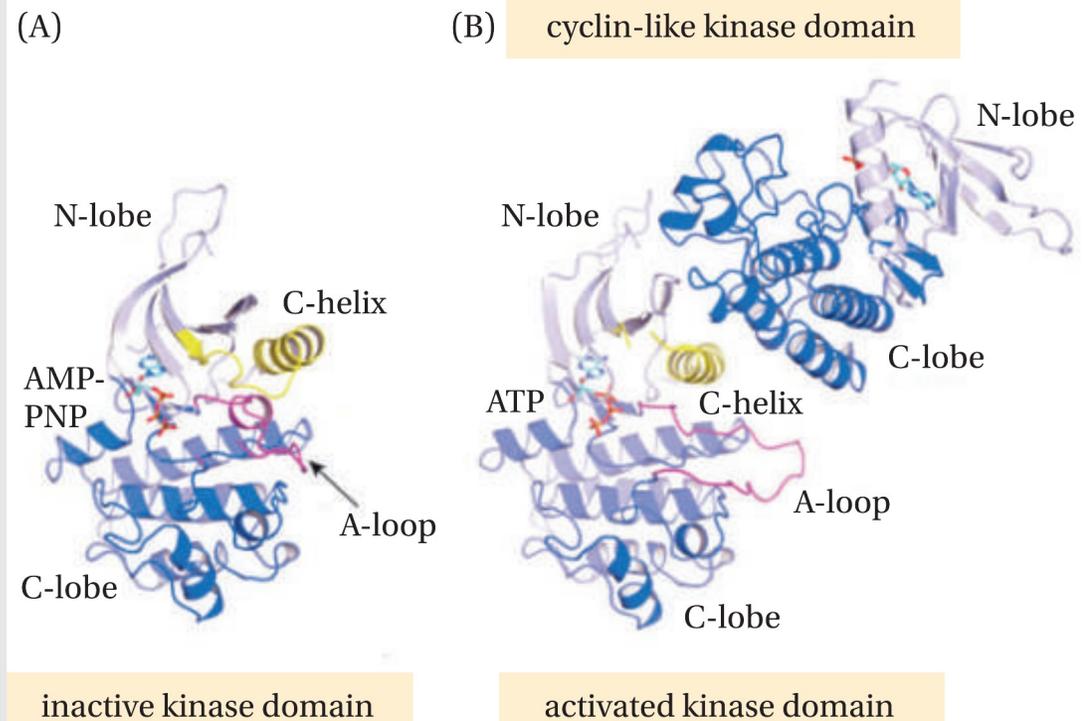
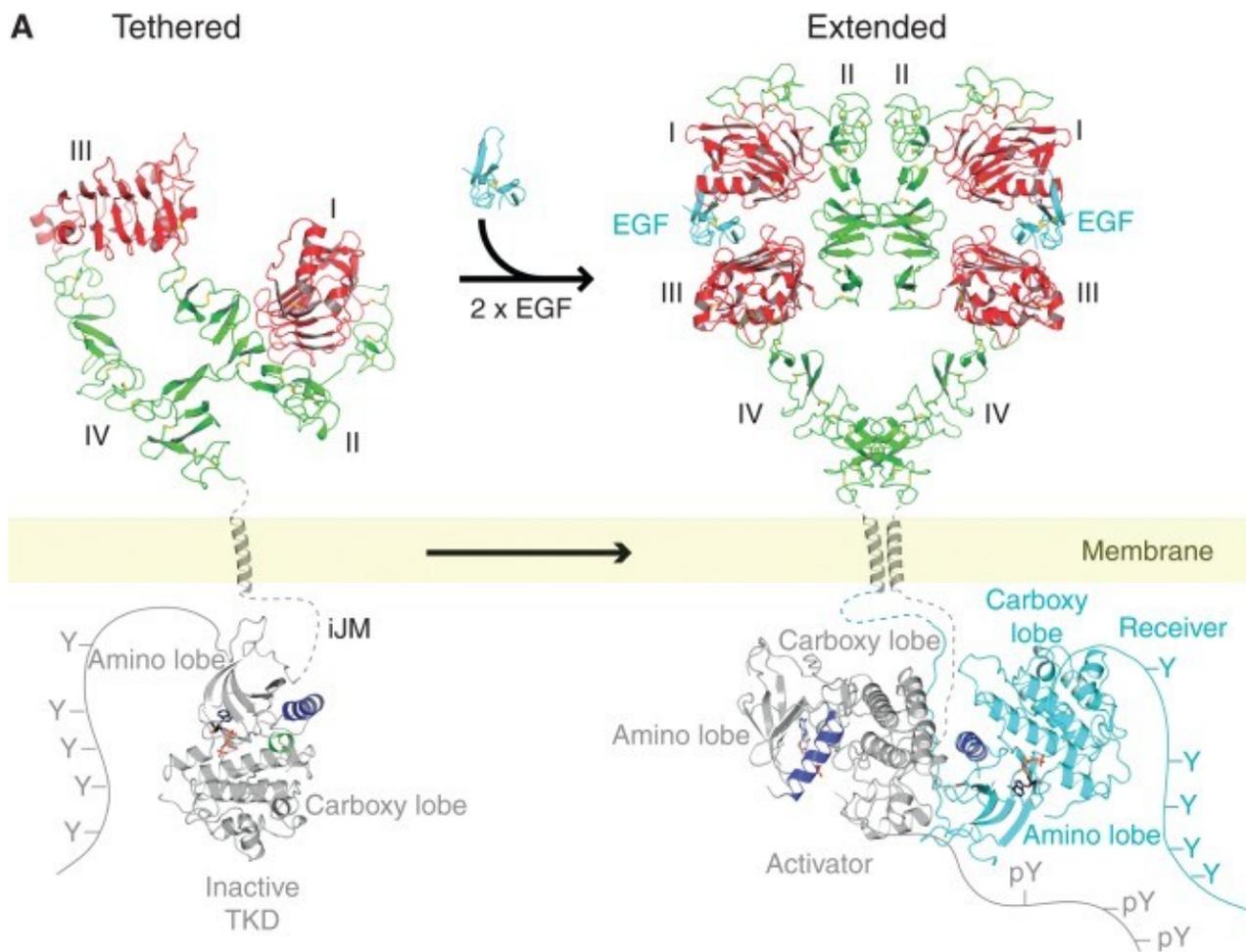
intracellular

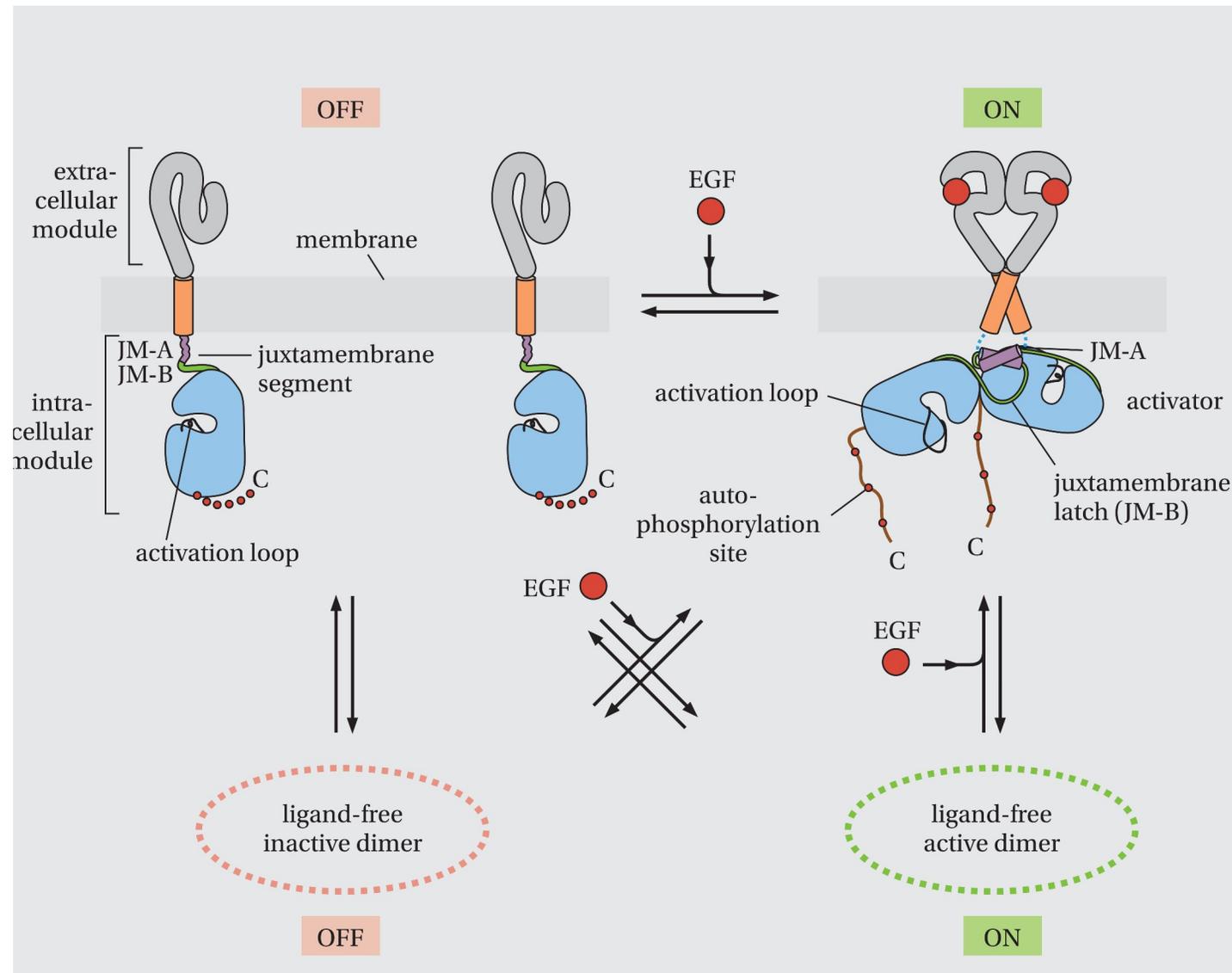
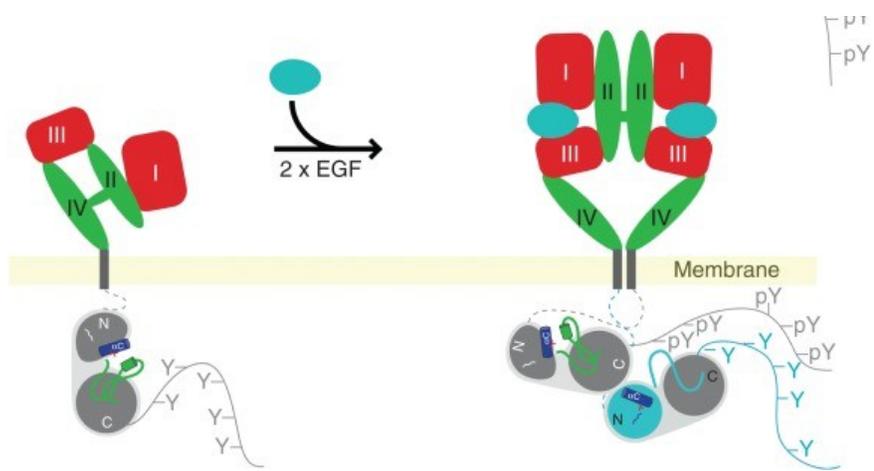
juxtamembrane domains

GXXXG motif

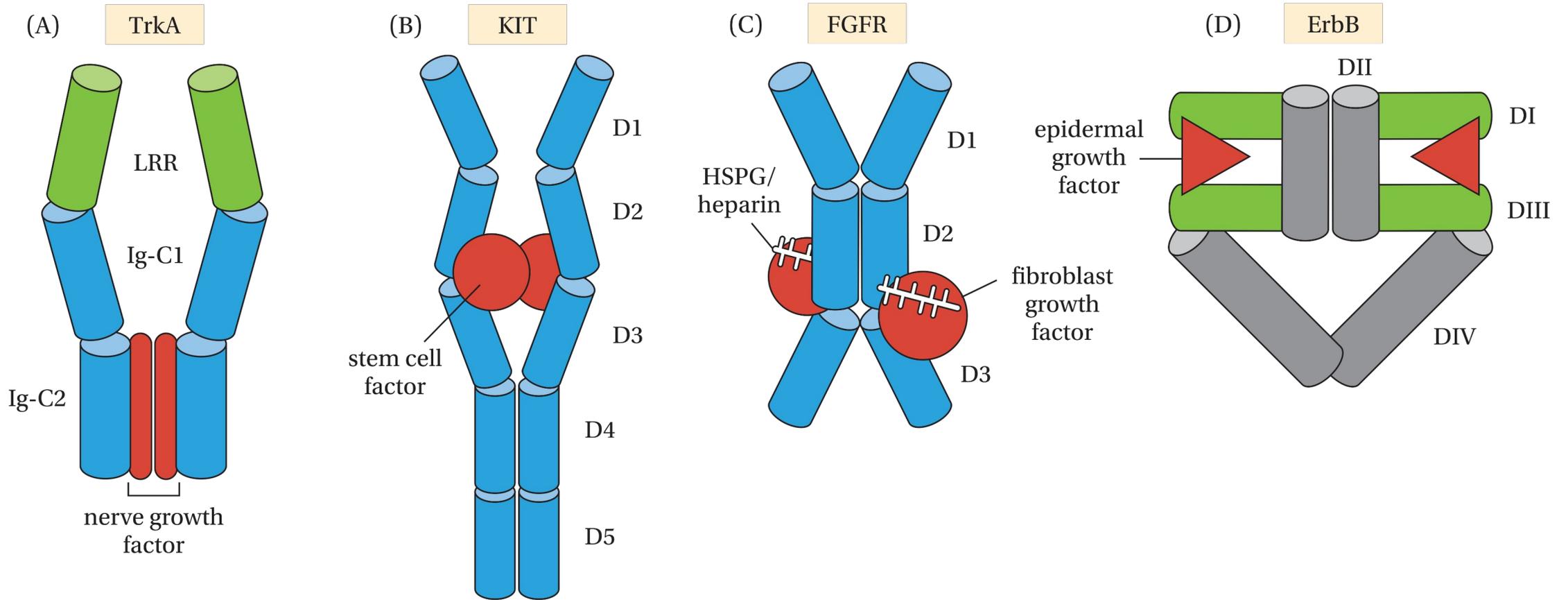


Activation



B

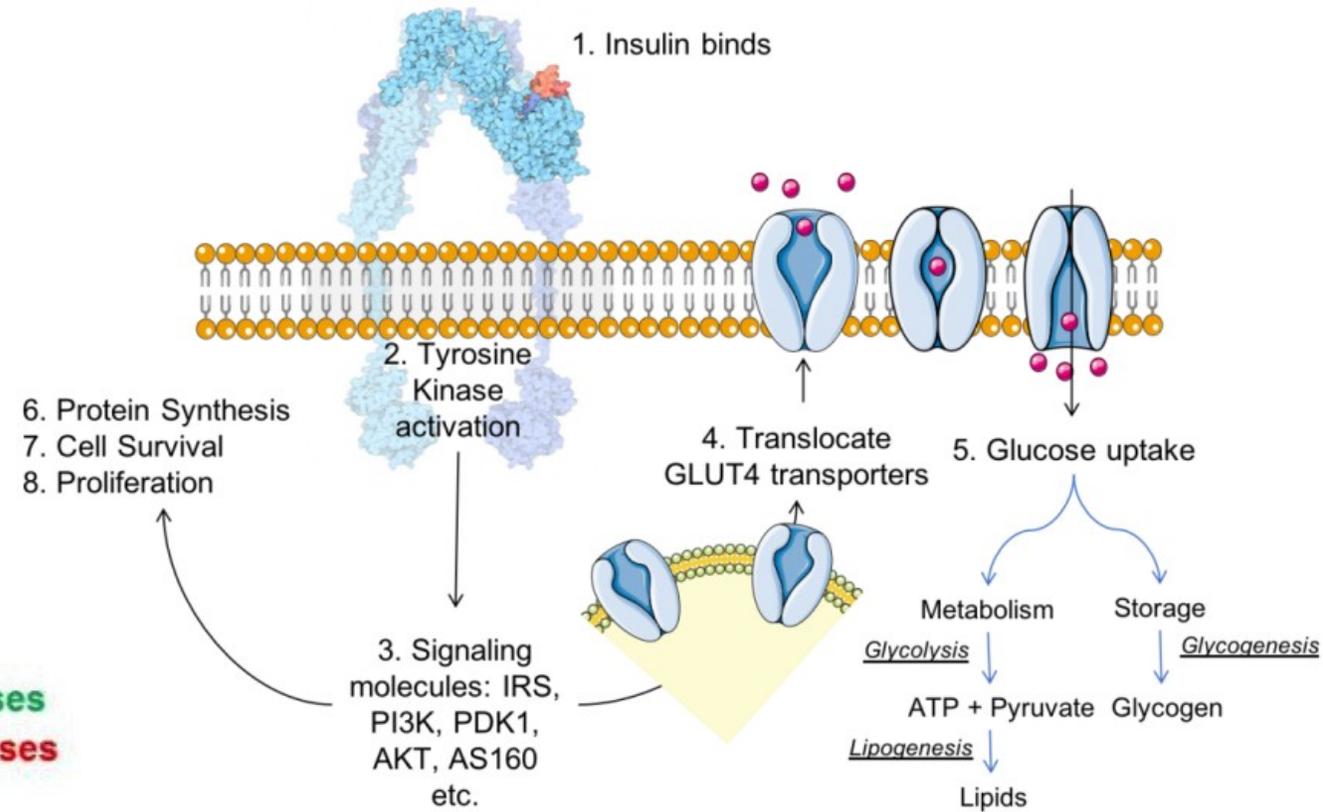
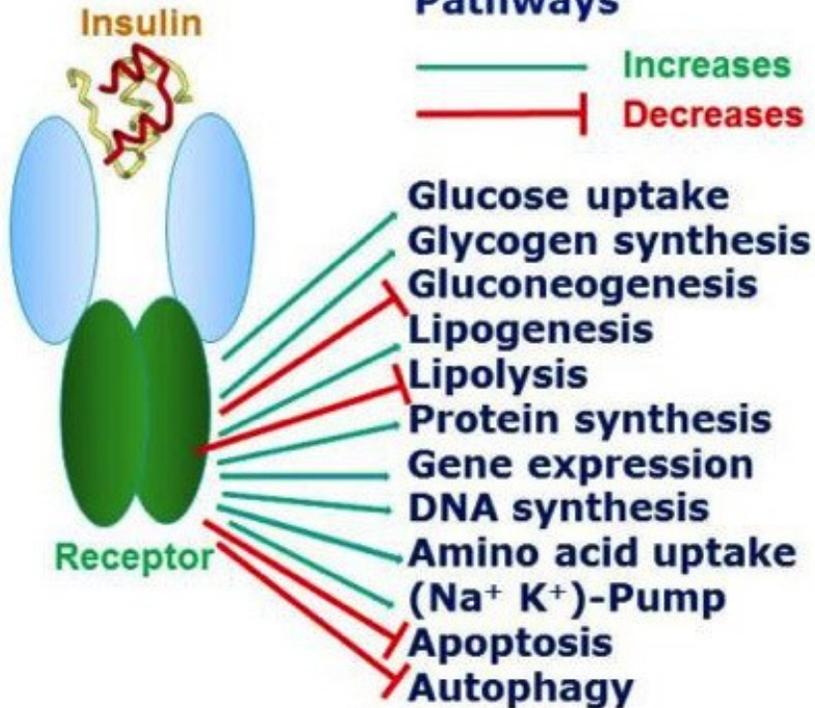
four different ways to induce signaling.



Insulin receptor

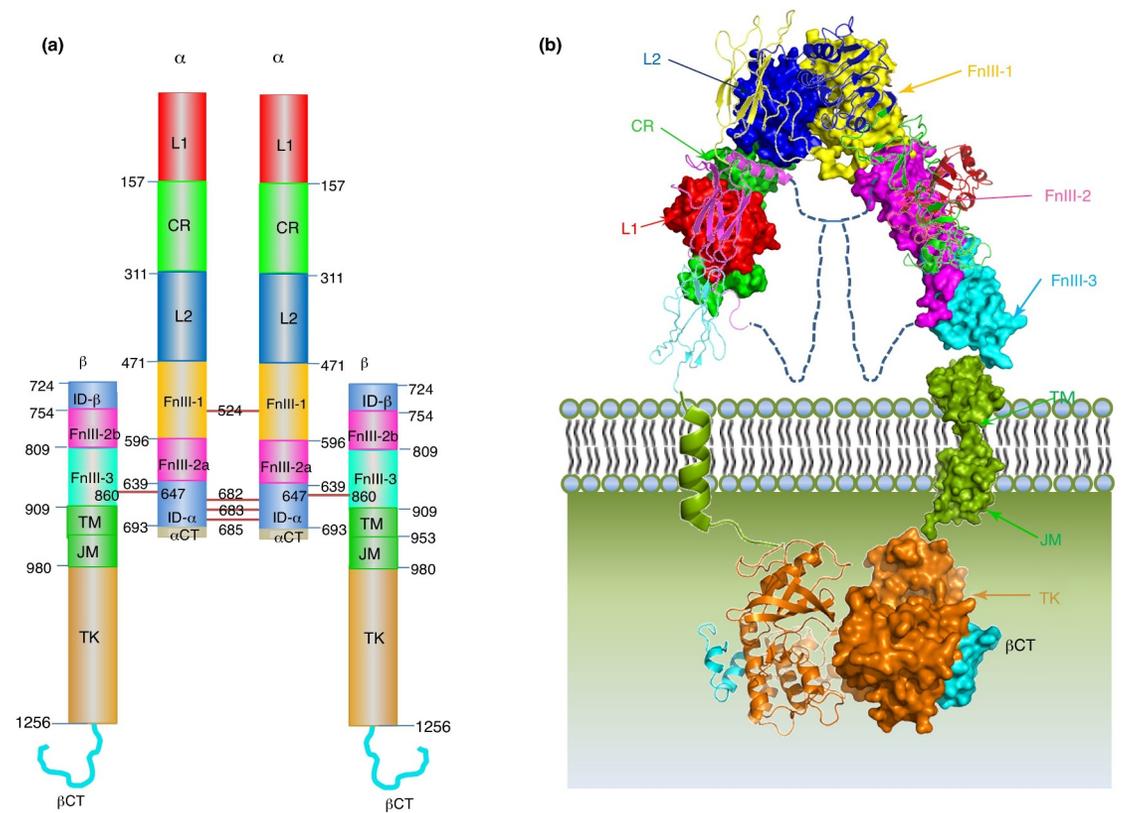
Processes

Anabolism
 Glucose homeostasis
 Lipid metabolism
 Protein metabolism
 Growth/mitogenesis
 Reproduction
 Lifespan
 Cognition



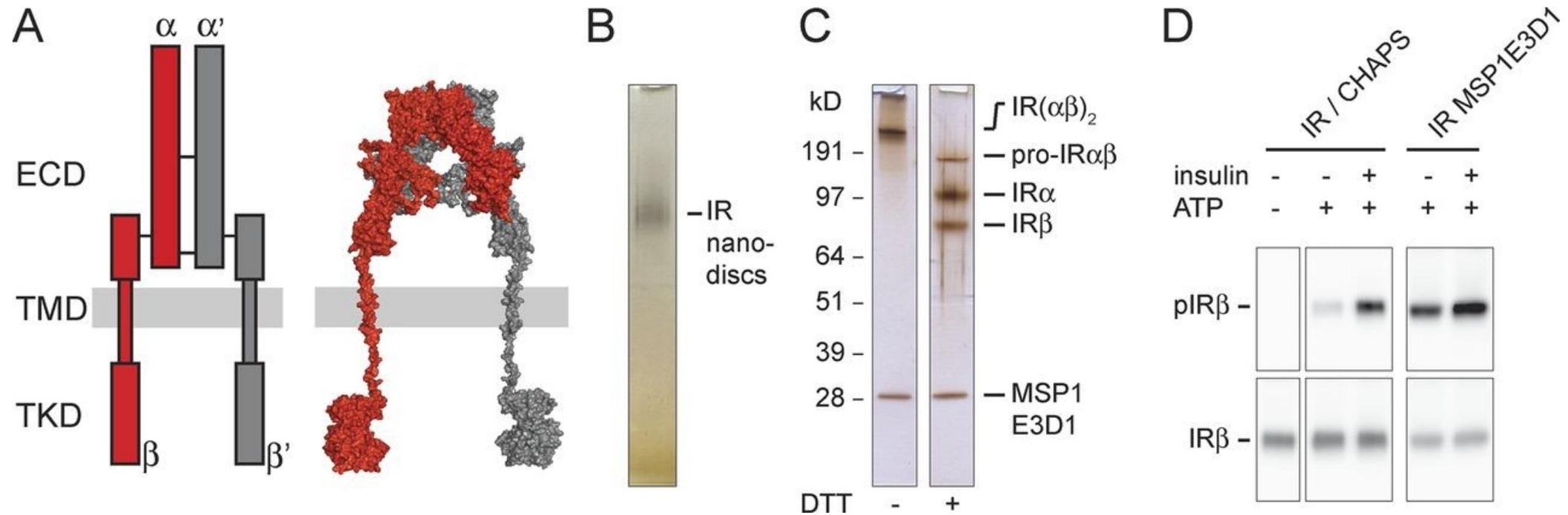
insulin receptor

$\alpha_2\beta_2$ heterotetramer

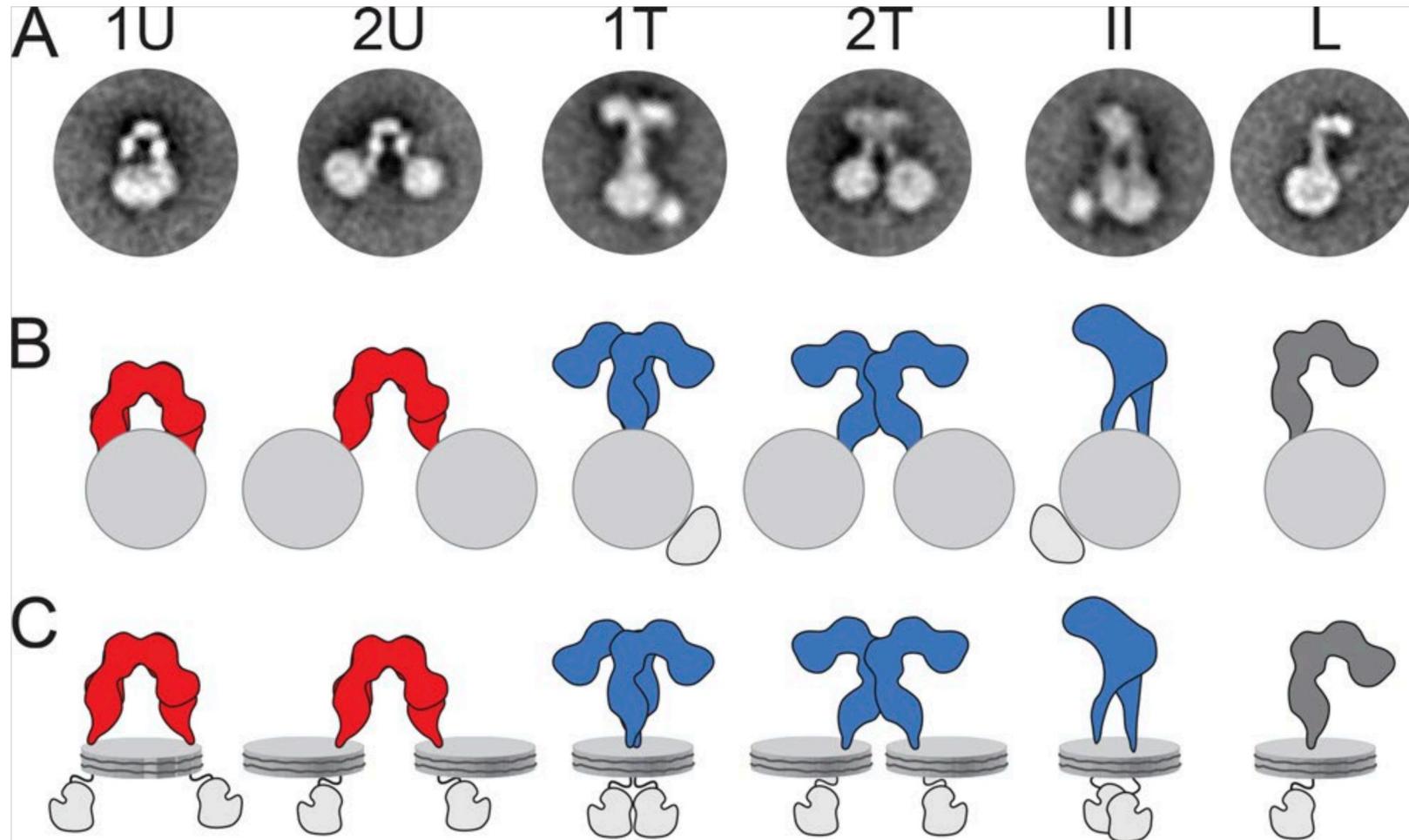


(e) Domain architectures of resolved IR structures	PDB IDs
	Composition of full-length IR (no structure)
	4ZXB [11], 3LOH [14]
	2DTG [13,78]
	3W14 [10]
	3W11, 3W12, 3W13 [10], 4OGA [29]
	2HR7 [23]
	2MFR [16]
	1IRK [9], 1IR3 [32], 1GAG [79], 1I44 [80], 1P14 [81], 2AUH [82], 2B4S [83], 3BU3, 3BU5, 3BU6 [84], 2Z8C [85], 4XLV [18]

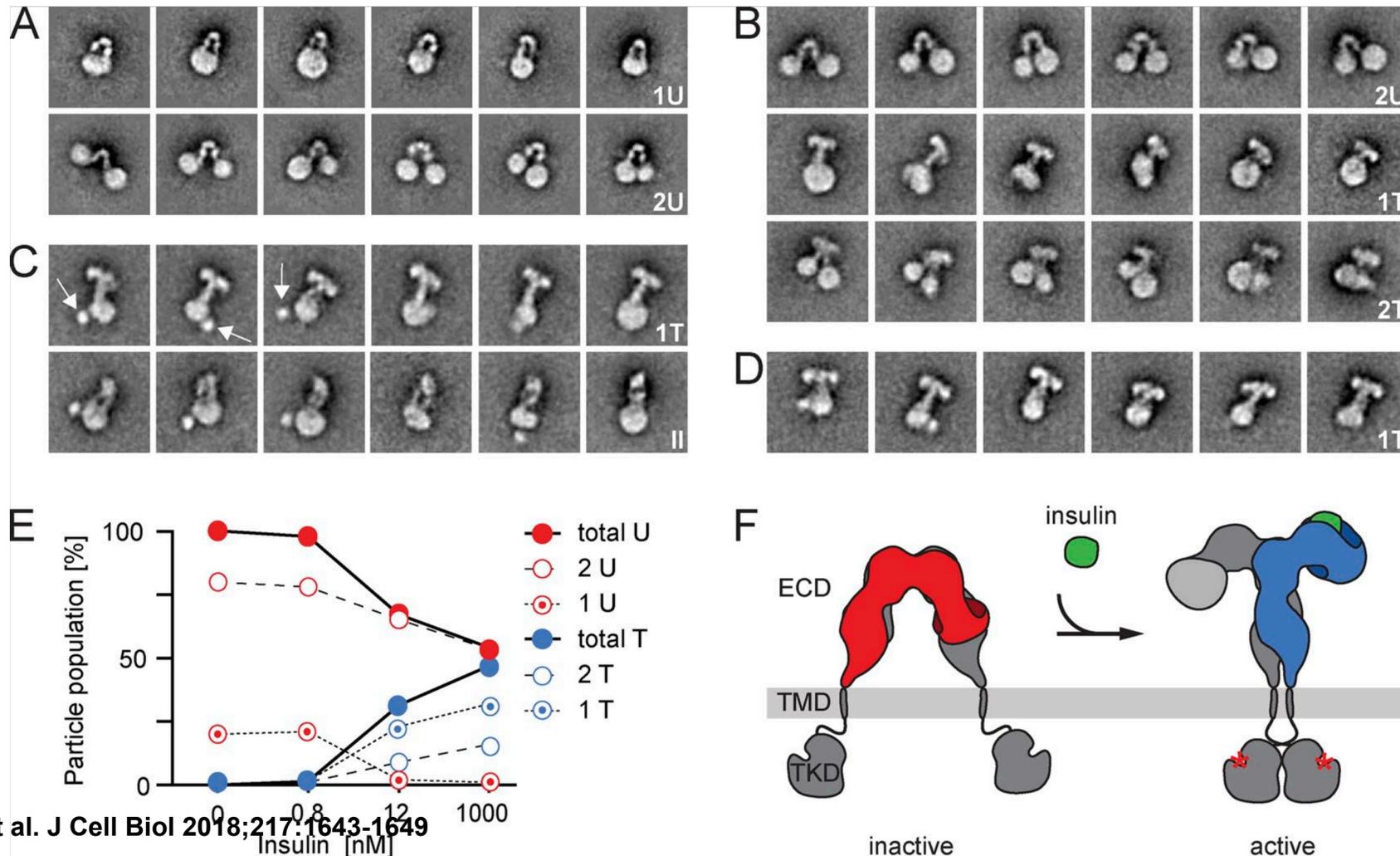
IR reconstitution into nanodiscs and activity assay



Conformations assigned to IRs in nanodiscs.



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



Insulin receptor TKD

IRK inactive

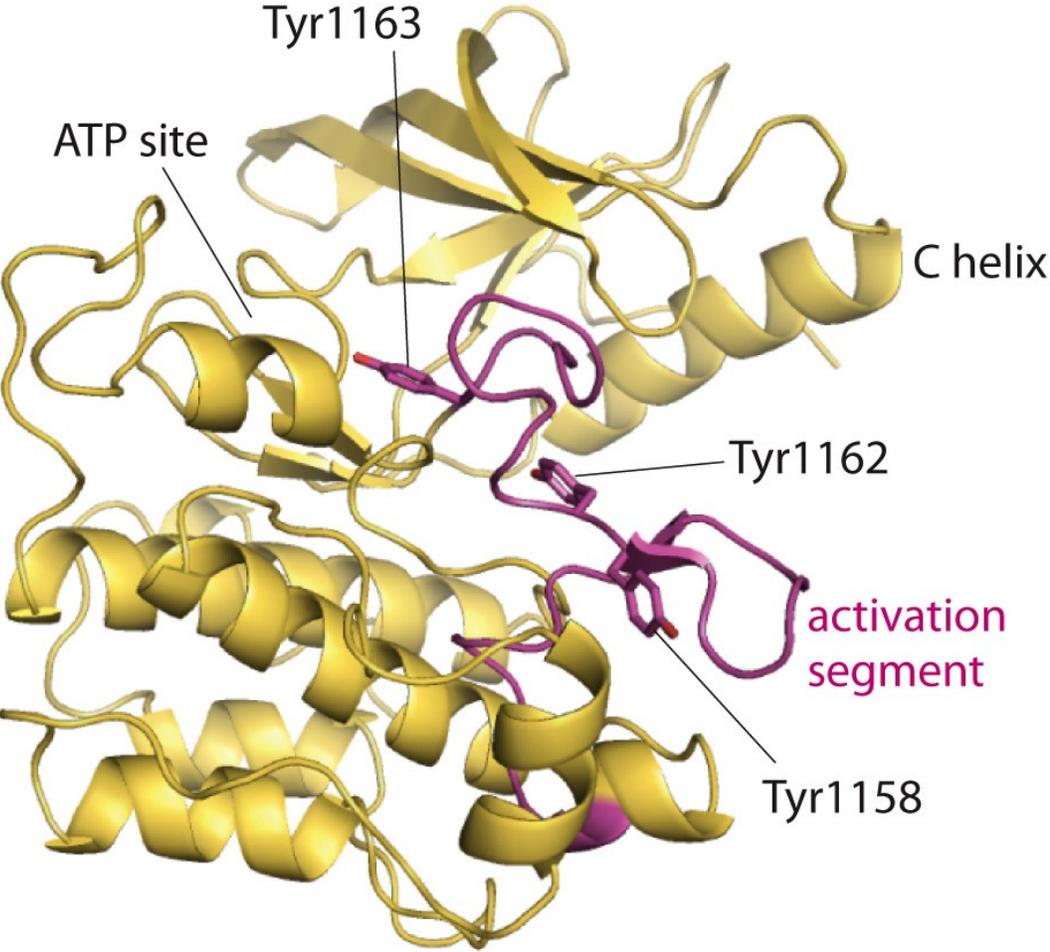


Figure 12.19a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

IRK active

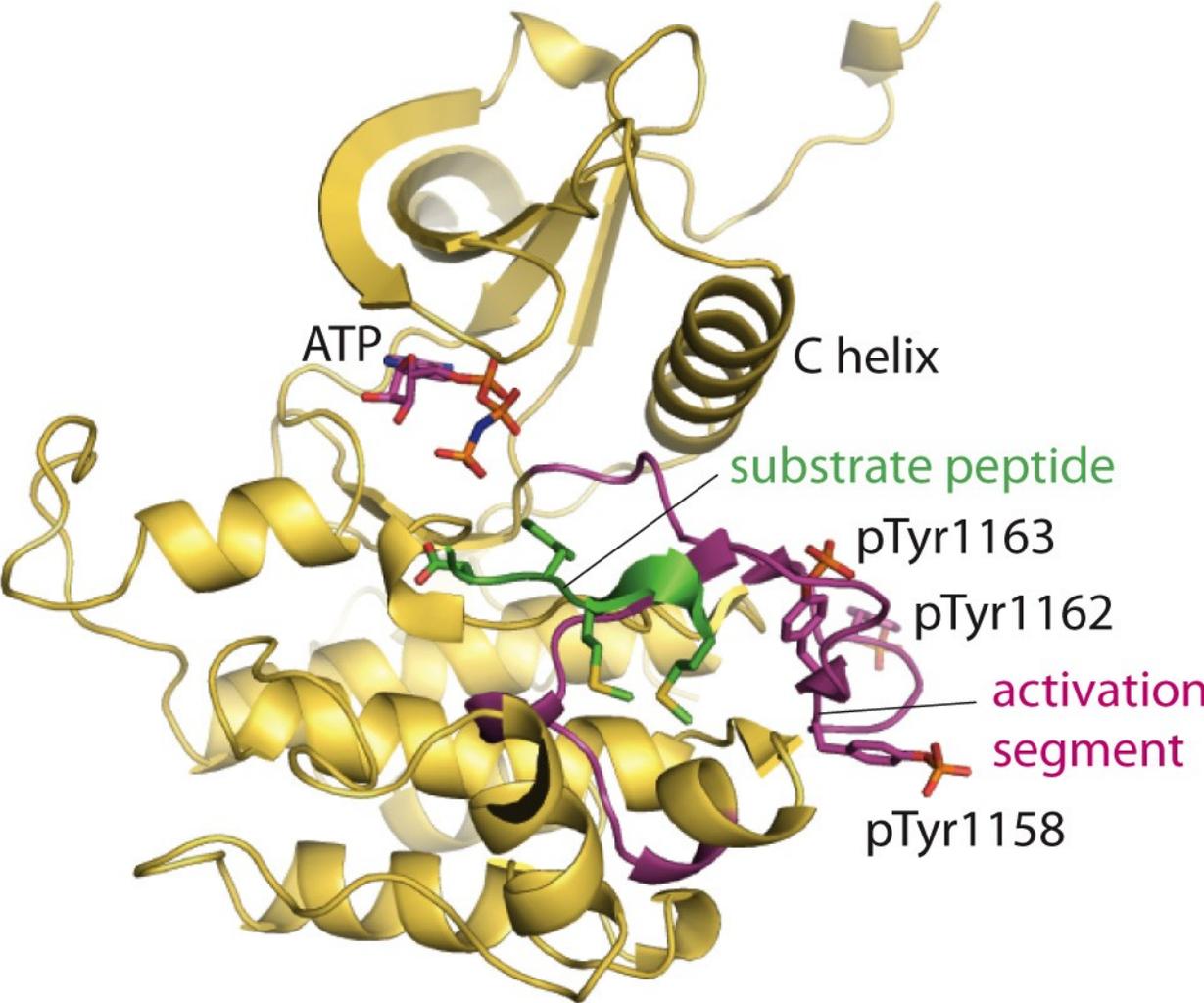


Figure 12.19b Molecular Biology of Assemblies and Machines (© Garland Science 2016)

specificity

Gly-Asp-Tyr-Met-Asn-Met

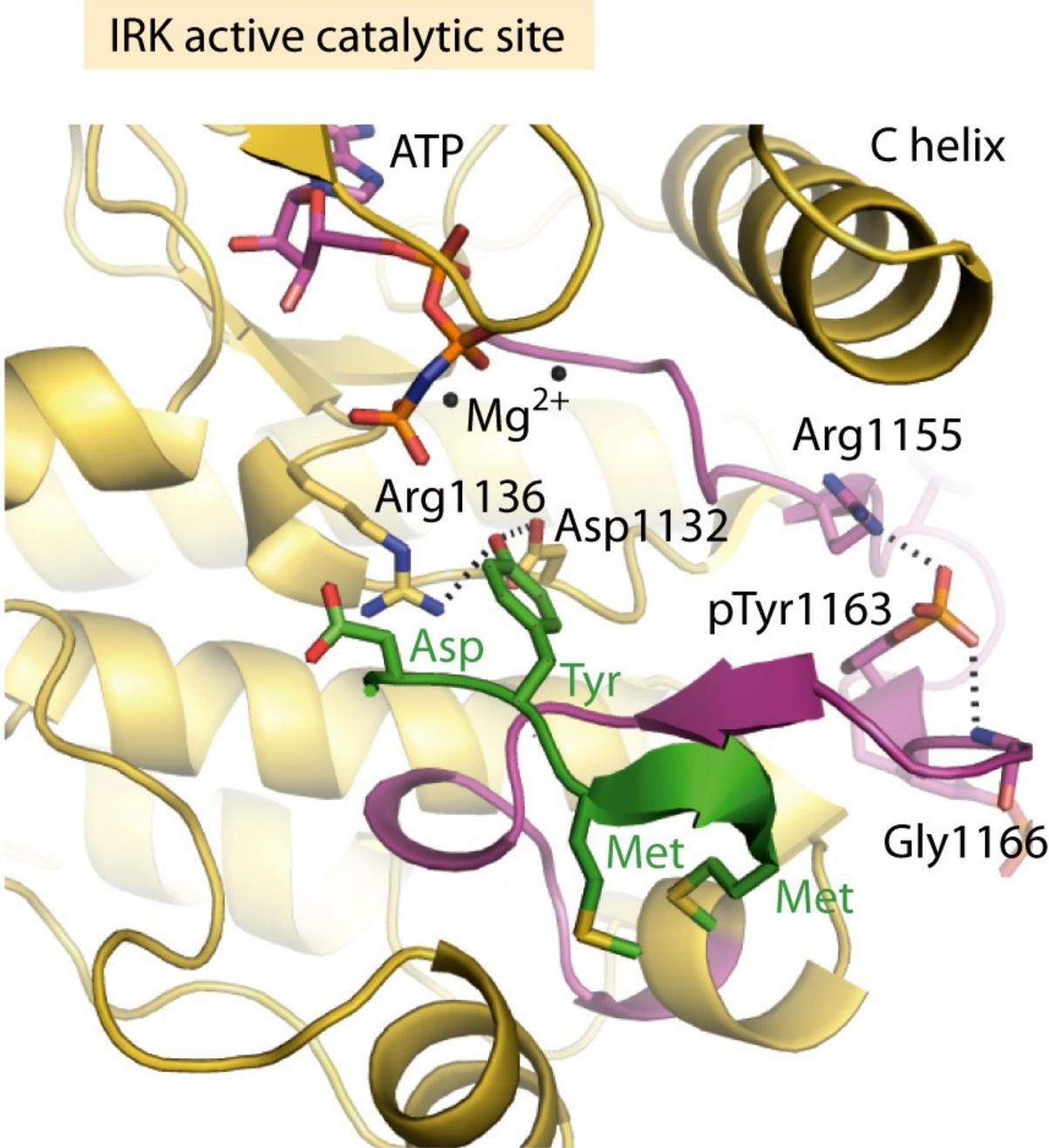


Figure 12.19c Molecular Biology of Assemblies and Machines (© Garland Science 2016)

Two forms

inactive EGFR kinase domain

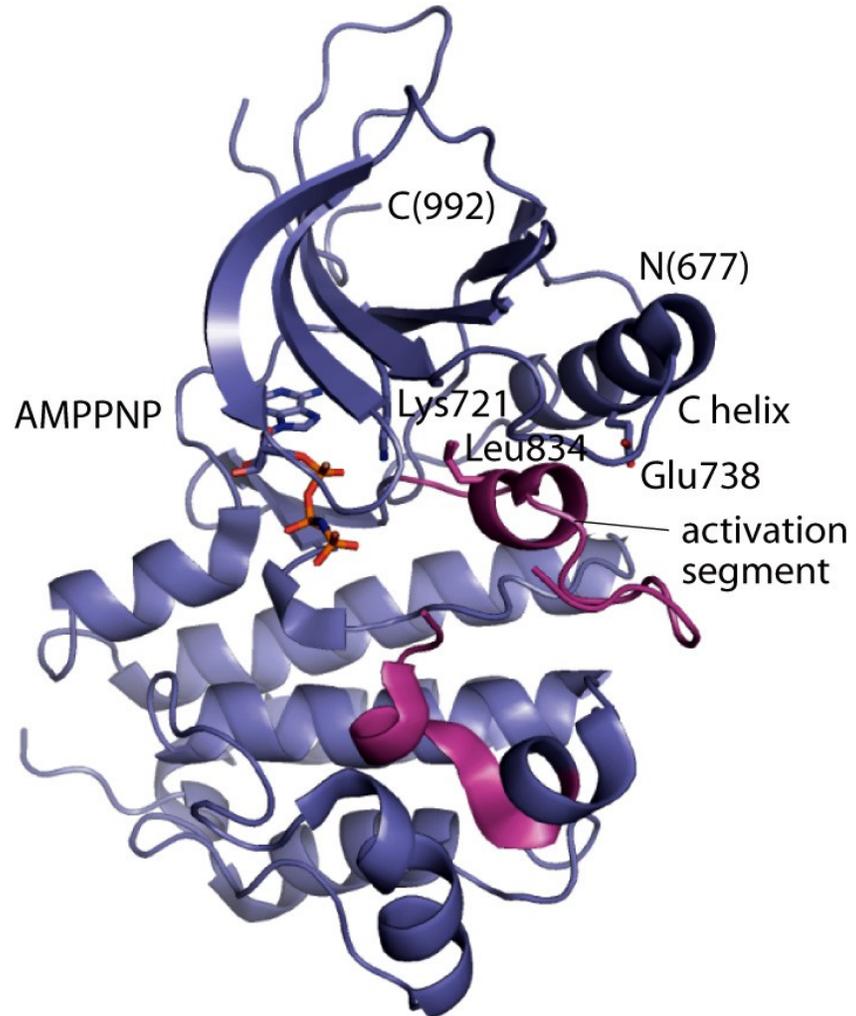


Figure 12.20a Molecular Biology of Assemblies and Machines (© Garland Science 2016)

active EGFR kinase domain

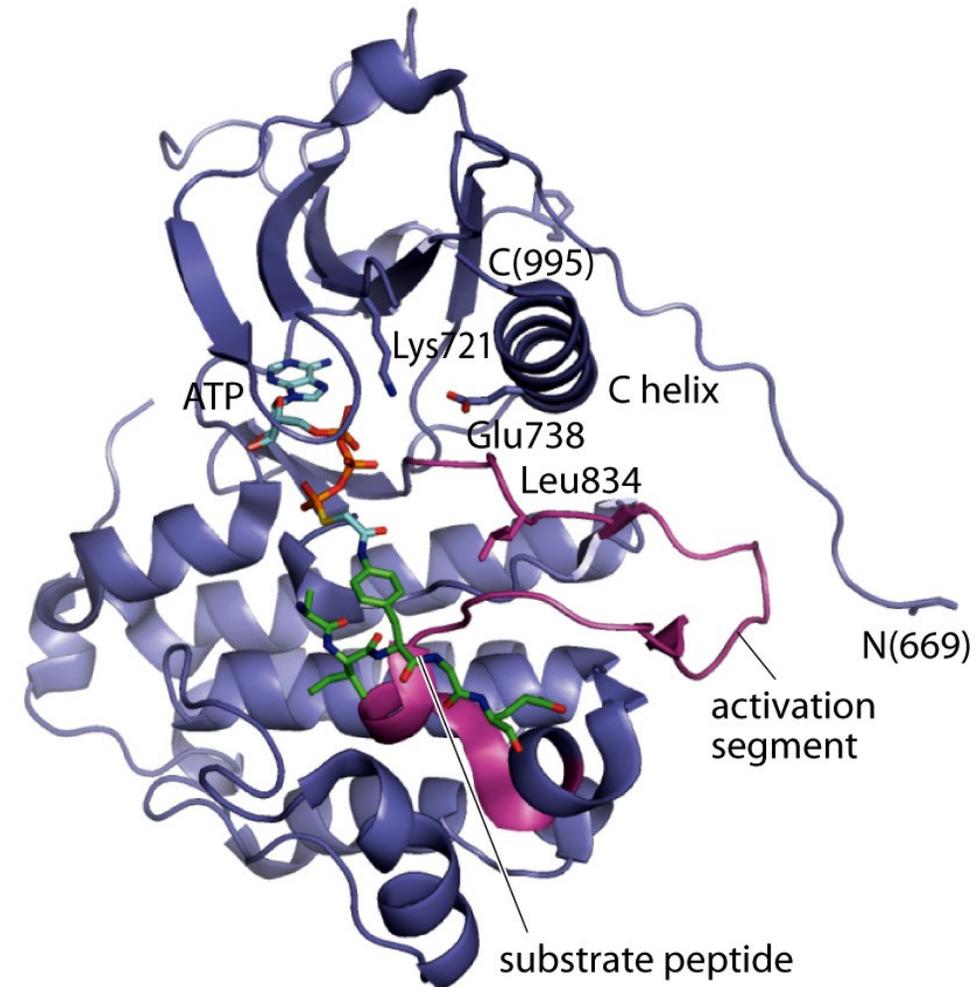
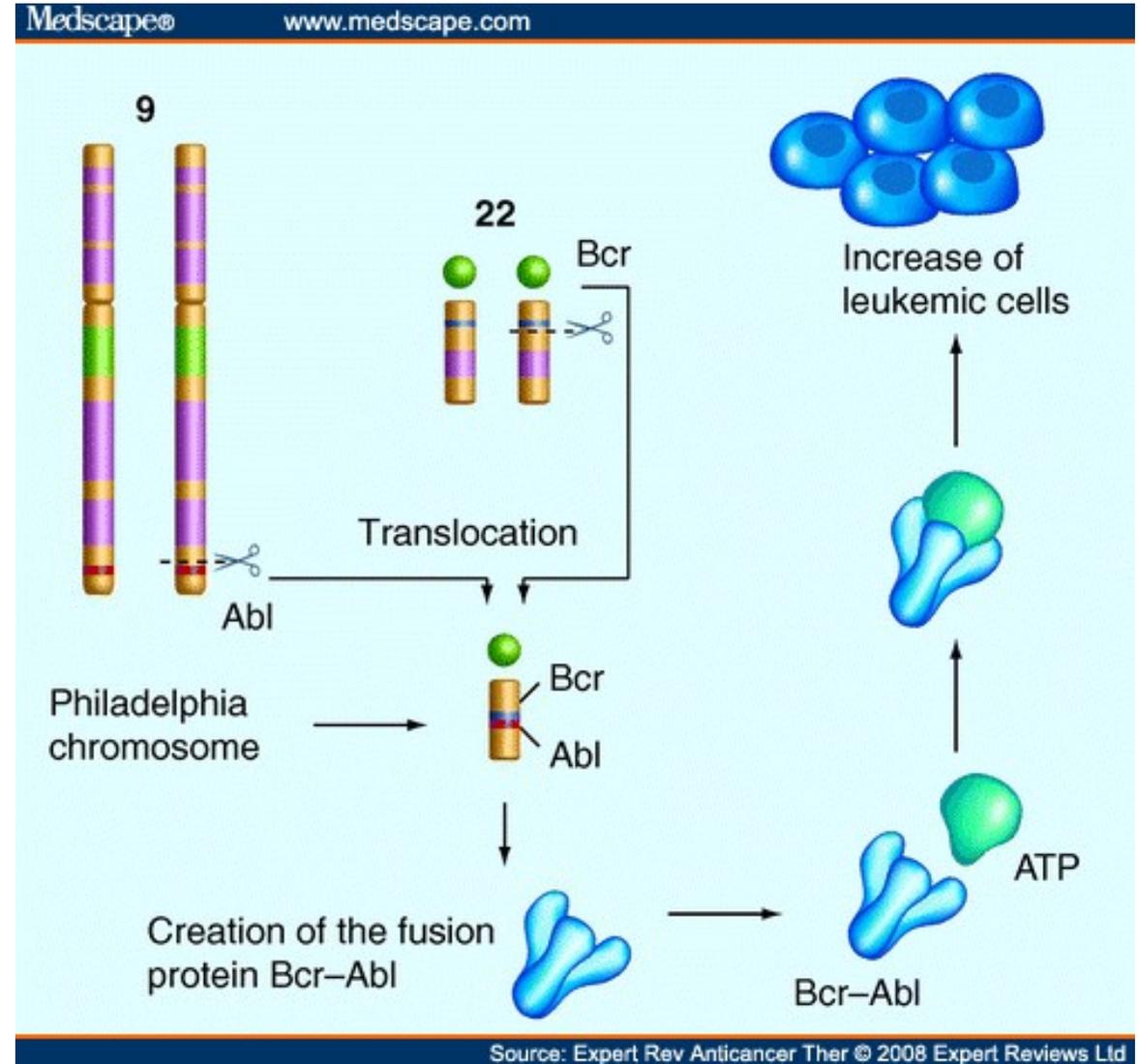
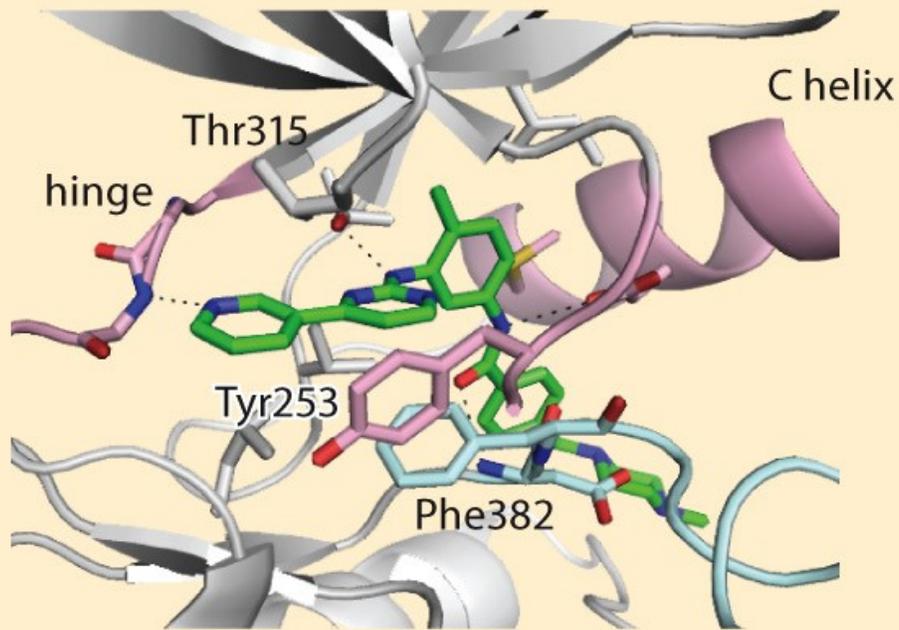


Figure 12.20b Molecular Biology of Assemblies and Machines (© Garland Science 2016)

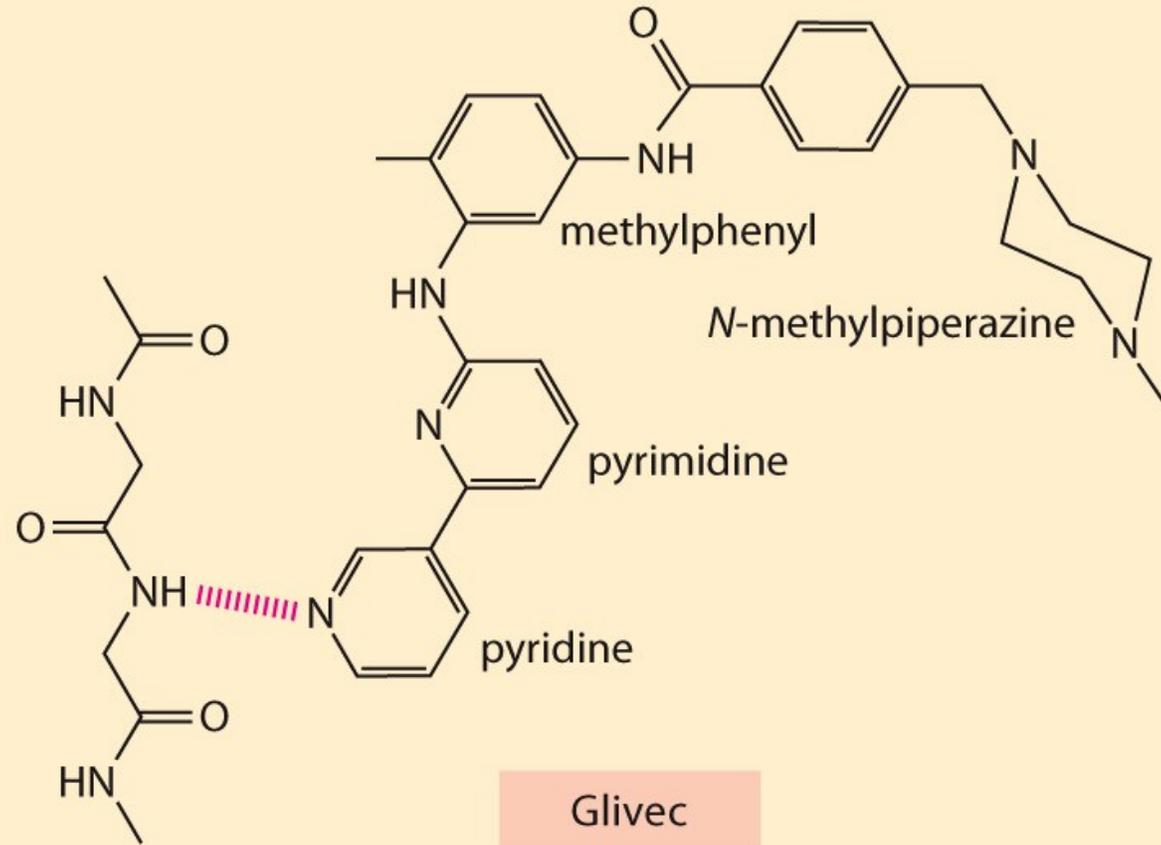
kinase as target



kinase as target



Abl tyrosine kinase/Glivec



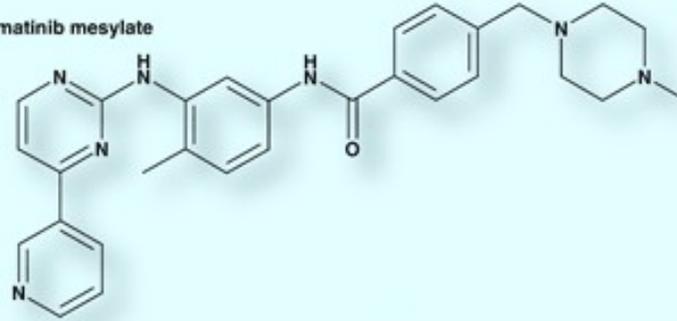
Glivec

Abl kinase inhibitors

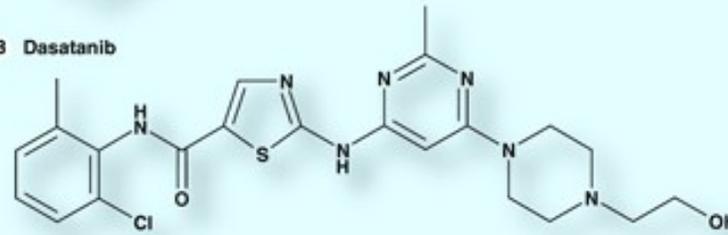
Medscape®

www.medscape.com

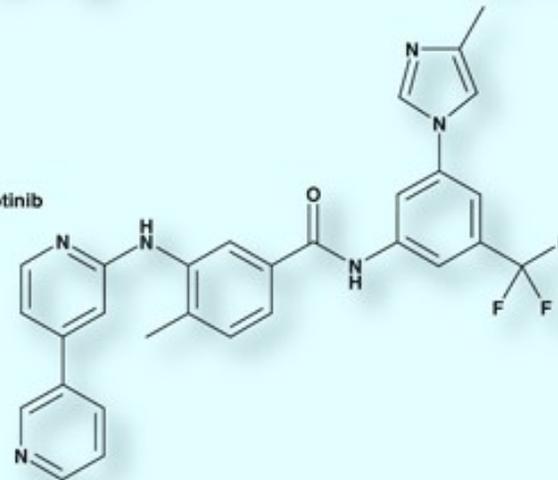
A Imatinib mesylate



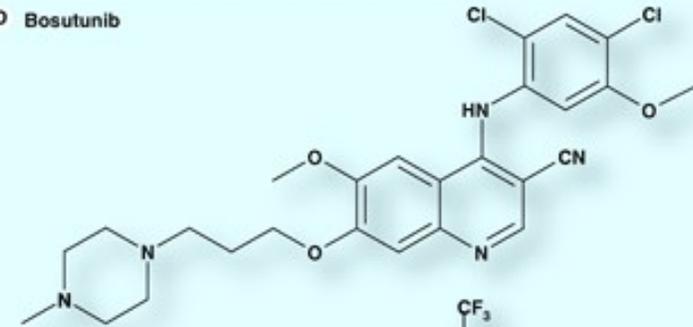
B Dasatinib



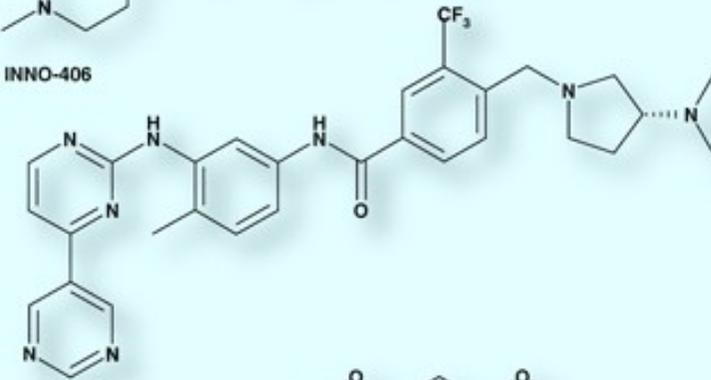
C Nilotinib



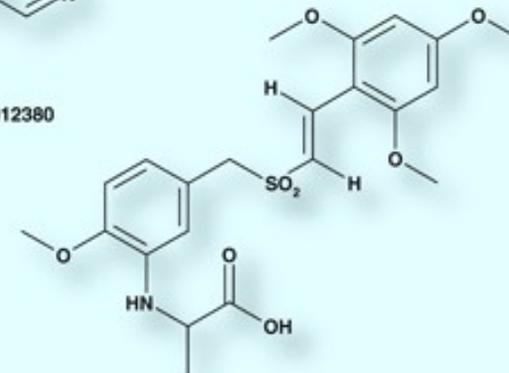
D Bosutinib



E INNO-406



F ON012380



Structure of novel agents for T315I

