Schertler part of the course

I recommend that you read chapters 1-3 for general background !!!

This will strengthen your understanding of the science of Biology!!

Material in Alberts text book edition 5 (English version): Chapters 9, 10, 12, 13, 16 and in chapter 25 pages 1431-1440.

Topic: Membrane proteins

Chapter 10

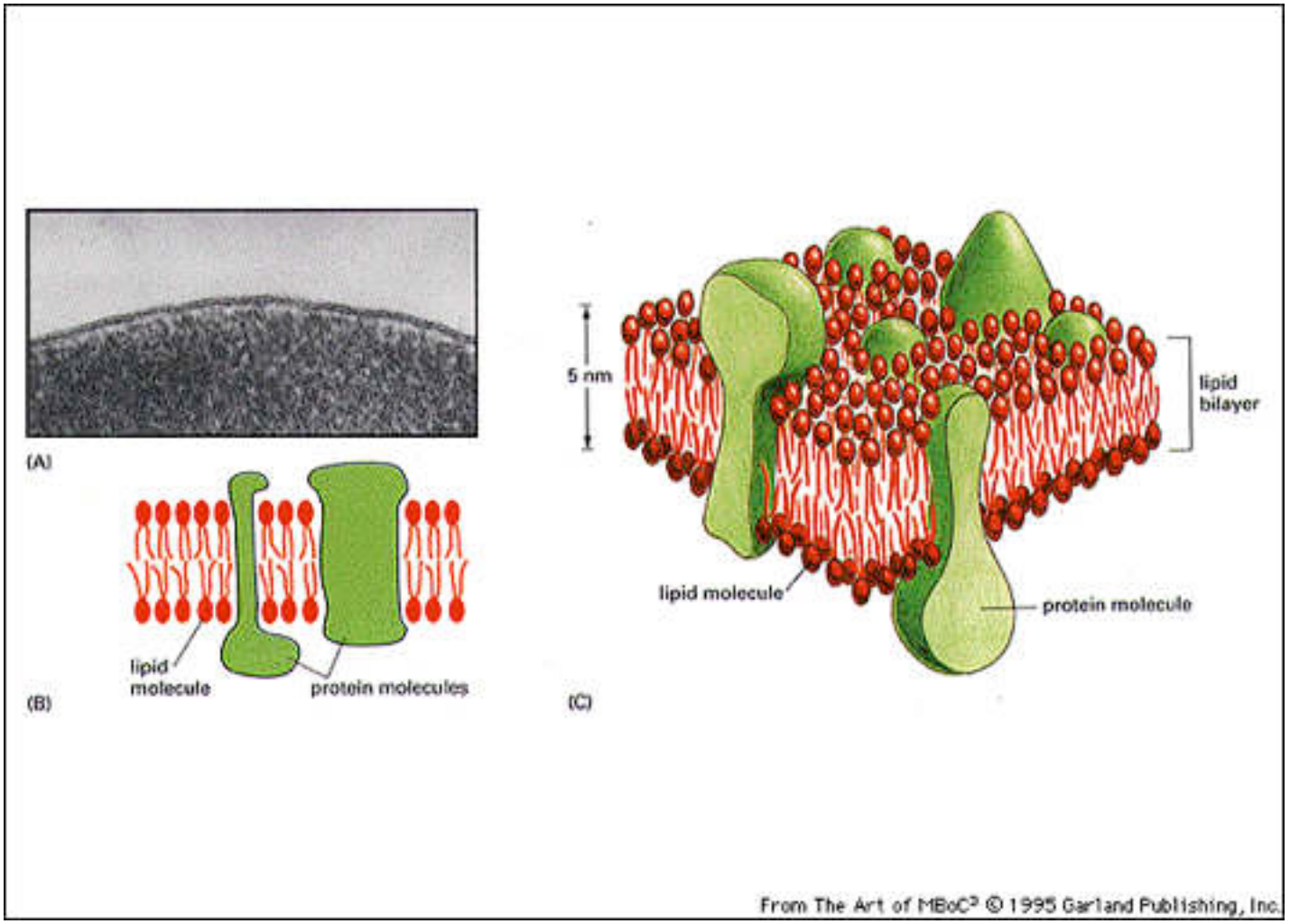
- What do membrane proteins do?
- Different categories of membrane proteins
- Lateral mobility of membrane proteins

Topic: How to work with membranes

Recommended reading Chapter 8

- Patch clamping
- Fractionation of cells and organelles
- Tissue culture
- Affinitiy purification
- Use of detergents
- Structurebestimmung: NMR, EM, and Crystallography
- Immunoblotting
- Membrane reconstitution

Three views of a cell membrane



The fraction of genes encoding membrane proteins is 20-25%, and rather invariable between organisms

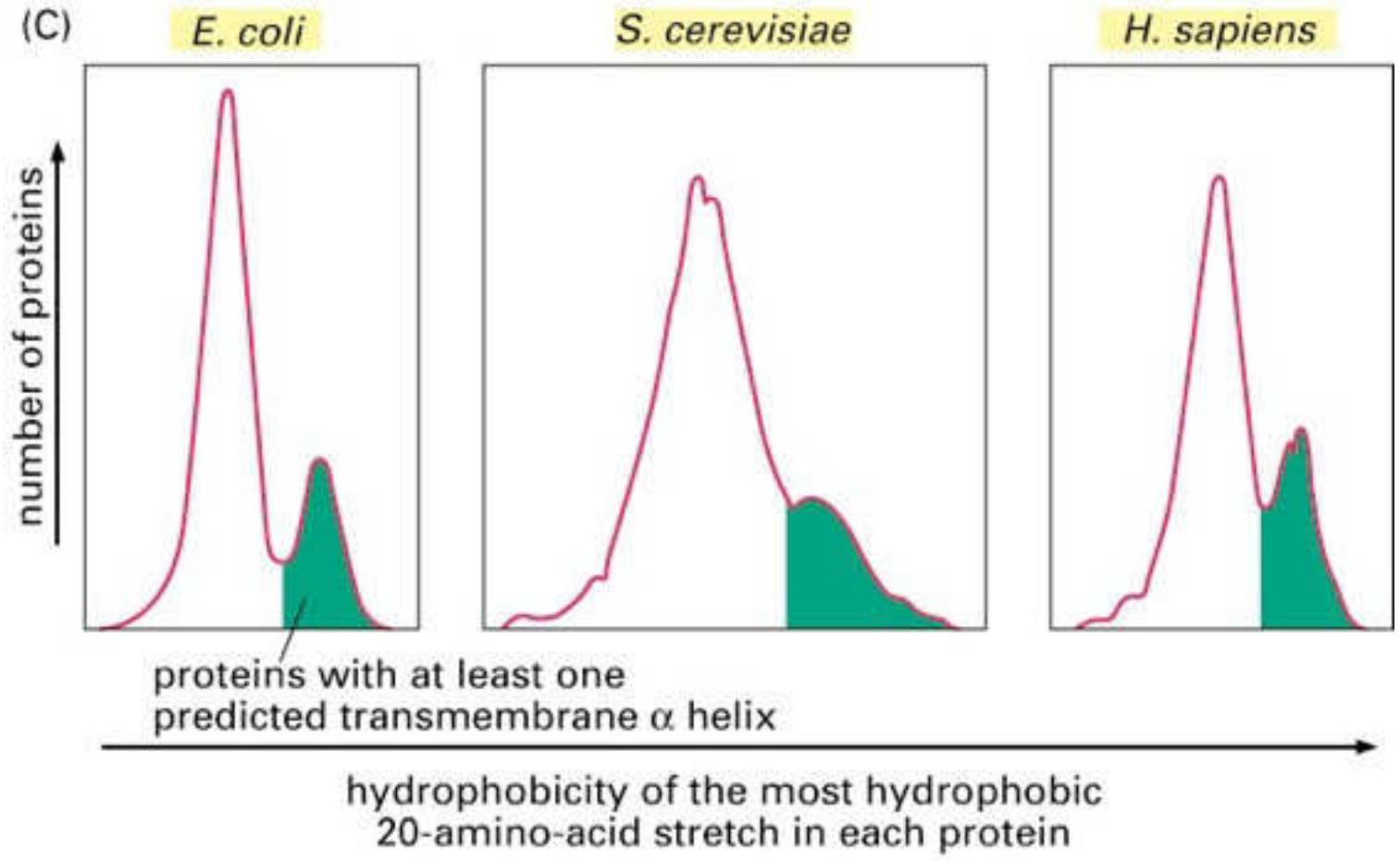


Figure 10–20 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Protein:lipid:carbohydrate ratios in different membranes

Tab. 11-4 Zusammensetzung einiger biologischer Membranen

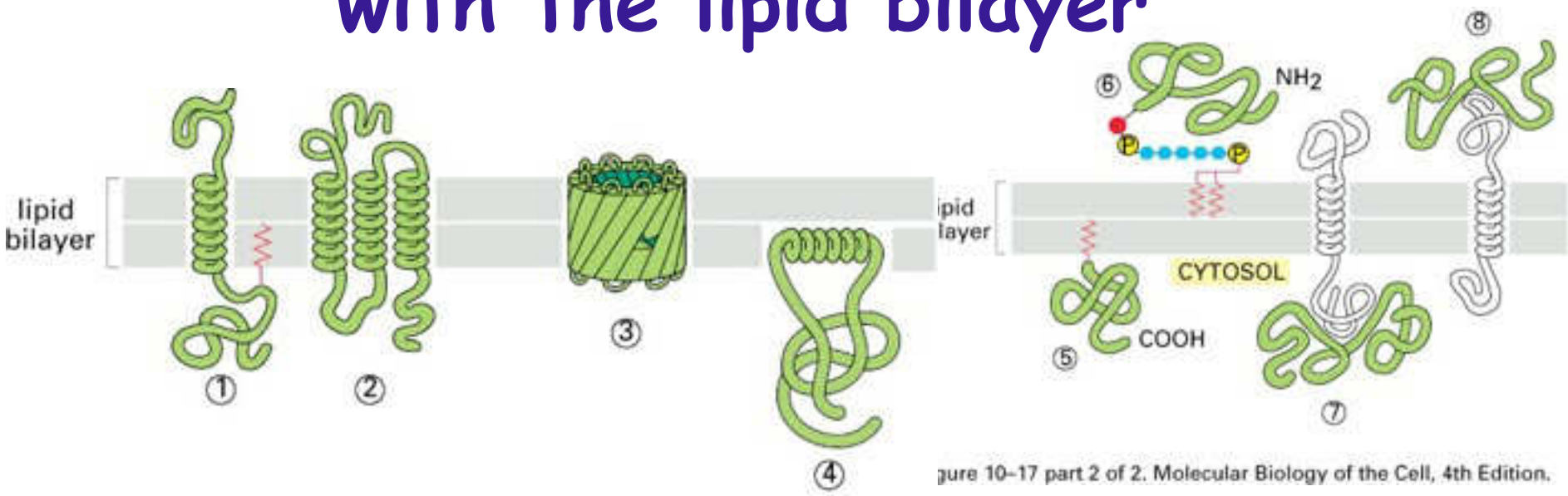
Membran	Protein (%)	Lipid (%)	Kohlenhydrat (%)	Protein-Lipid-Verhältnis
Plasmamembranen:				
Maus-Leberzellen	46	54	2–4	0.85
Menschlicher Erythrocyt	49	43	8	1.1
Amöben	52	42	4	1.3
Kernmembran aus Rattenleber	59	35	2.0	1.6
Äußere Mitochondrienmembran	52	48	(2–4)[a]	1.1
Innere Mitochondrienmembran	76	24	(1–2)[a]	3.2
Myelin	18	79	3	0.23
Gram-positive Bakterien	75	25	(10)[a]	3.0
Purpurmembran von *Halobacterium*	75	25		3.0

[a] Analytisch abgeleitete Werte.
Quelle: Guidotti, G., *Annu. Rev. Biochem.* **41**, 732 (1972).

Membrane proteins are needed to modify and diversify properties of the lipid bilayer

- Modify permeability properties in order to:
  - allow transport of substances across (ions, nutrients, vitamins, waste products, water)
  - receive and transmit signals (transfer of information)
  - generate gradients and a membrane potential
  - control osmotic properties
- Increase mechanical resistance
- Carry out biosynthetic and other enzymatic activities
- Induce or stabilize curvature
- Mediate fusion and fission (cell fusion and division, secretion, endocytosis)
- Allow recognition of the membrane and cell
- Support binding to other structures (cytoskeleton, extracellular matrix, other membranes, chromatin)
- Provide regulation of size, shape, composition, motility, etc.
- Provide membrane specializations and domains (i.e. synapses, junctions)

How membrane proteins associate with the lipid bilayer



gure 10–17 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

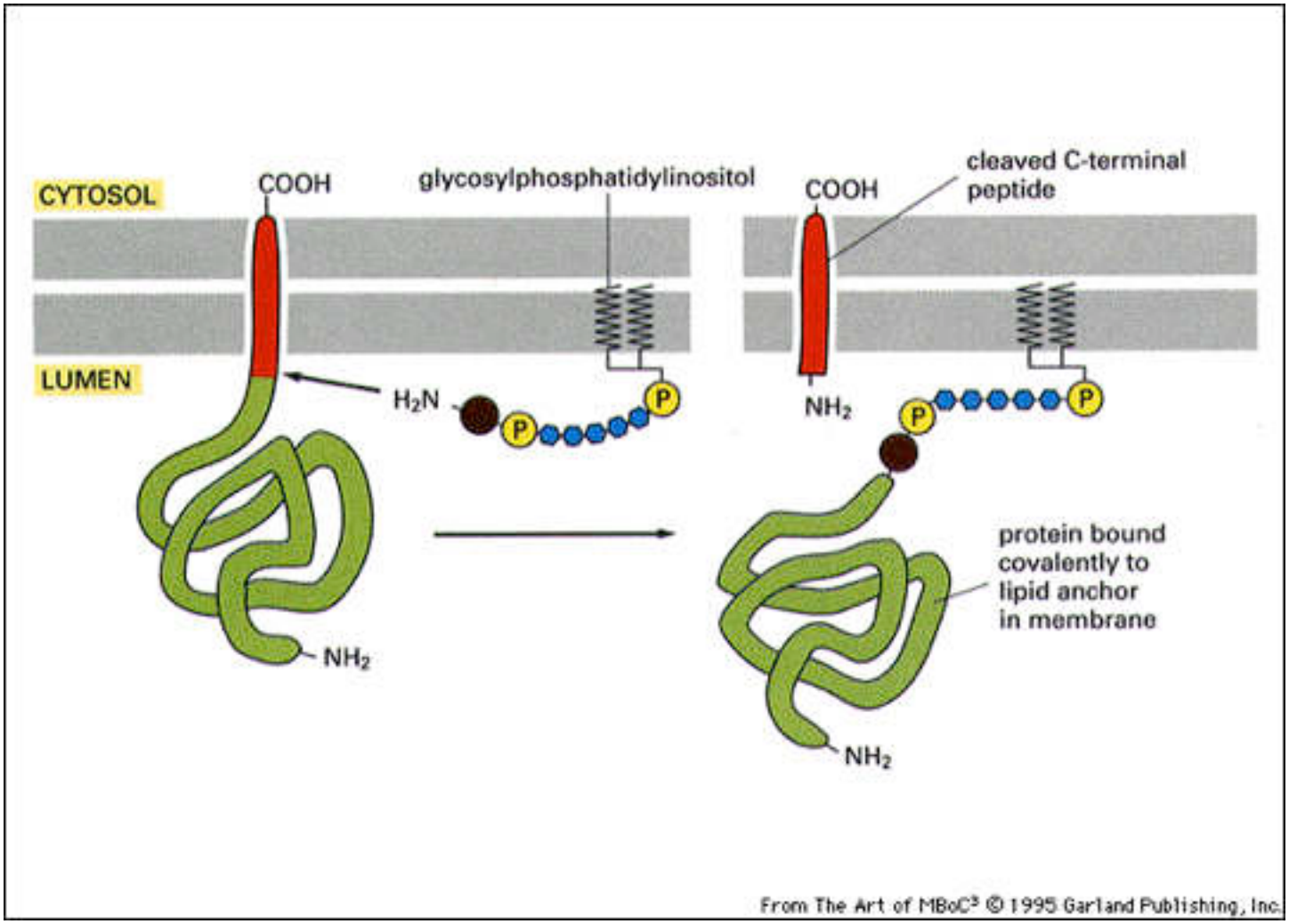
Figure 10–17 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Membrane proteins are either 'dissolved' in the bilayer phase (in one leaflet only, or both), or attached to the surface of it. Alone without lipids they cannot form a membrane.

Classical categories of membrane proteins

A. Peripheral Detached by manipulating conditions in the water phase (high salt, extremes of pH)	Bound peripherally to other membrane proteins, to the polar head groups of lipids. These proteins are polar. Behave like soluble proteins when not attached to membrane	
B. Integral Detached only by solubilizing the membrane by detergents	Type 1	Single membrane span C-terminus in the cytosol
	Type 2	Single span N-terminus in the cytosol
	Polytopic	Have various lipid groups attached covalently to polypeptide chain
	Lipid-anchored	Multiple spans Location of terminae is variable

Glycosylphosphatidyl inositol (GPI) anchor



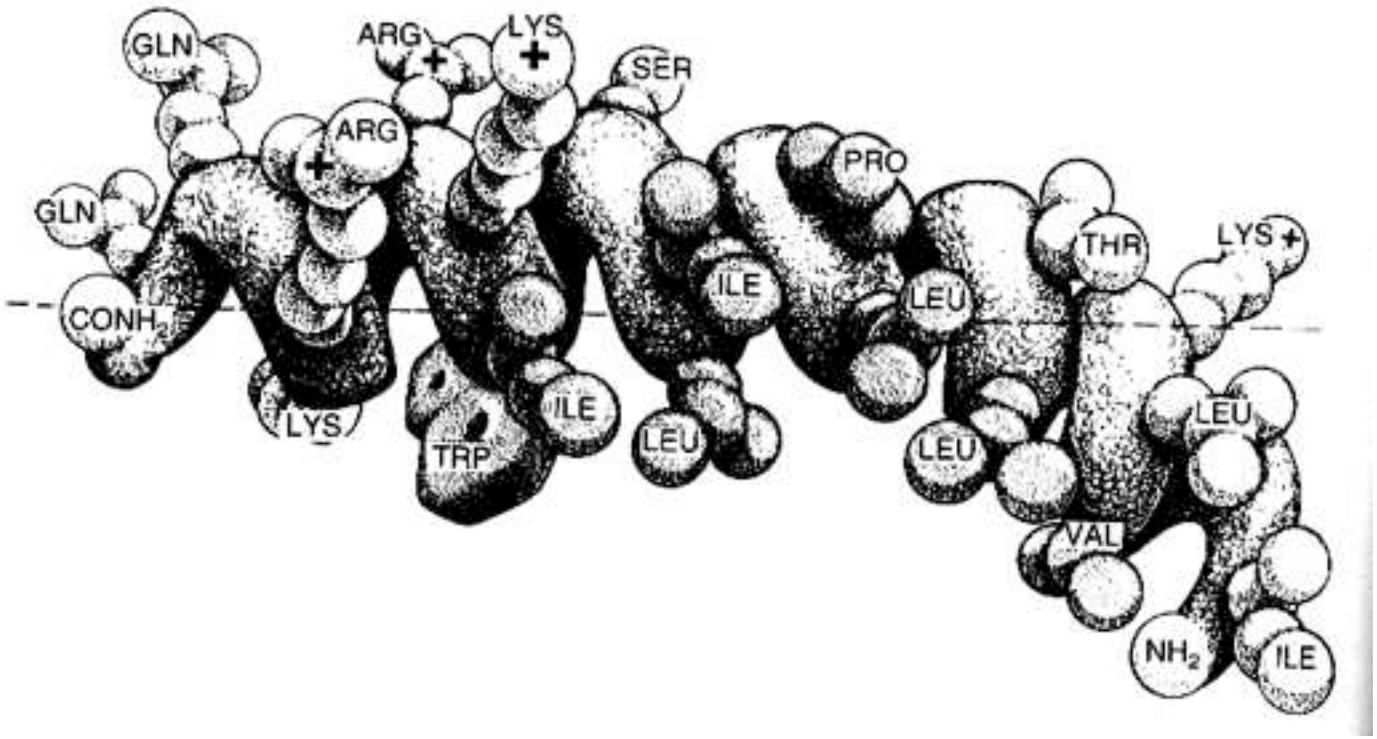
Covalent lipid modifications in eukariotic membrane proteins

- Myristylation (C14).
  - amide-linkage, permanent, via amide linkage to N-terminal glycine. Co-translationally added in the cytosol. Not sufficient alone for membrane anchoring. Nearby positive charges that bind electrostatically to negatively charged lipids often help to increase affinity.
- Palmitylation (C16), acylation.
  - Thioester bond with cystein residue, reversible, cytosolic, usually palmitic acid, double palmitylated proteins often occur in lipid rafts
- Prenylation (farnesyl [C15] or geranylgeranyl [C20] group)
  - Thioether bond, permanent, C-terminal, cytosolic
- Glycosylphospatidyl inositol (GPI) anchor
  - C-terminal, permanent, extra-cytosolic, permanent, plasma membrane, synthesized and added to proteins in the ER

There are other types of membrane attachments:

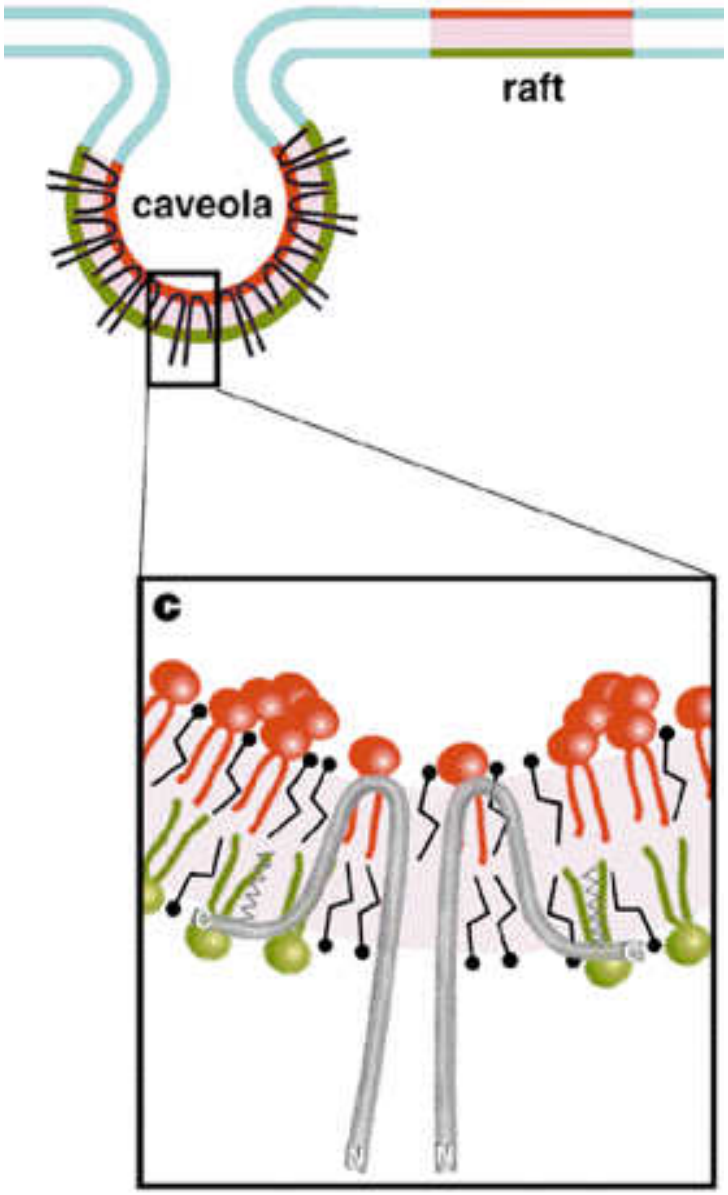
Some proteins are bound to one bilayer leaflet via amphipathic helices (in the helix the hydrophobic amino acid residues are located on side

and the polar residues on the other)



Unsual integral proteins: Caveolin-1,an integral protein in caveolae, has a hydrophobic domain (a 'loop') that does not span the membrane.

In addition, it is palmitylated, and binds cholesterol.

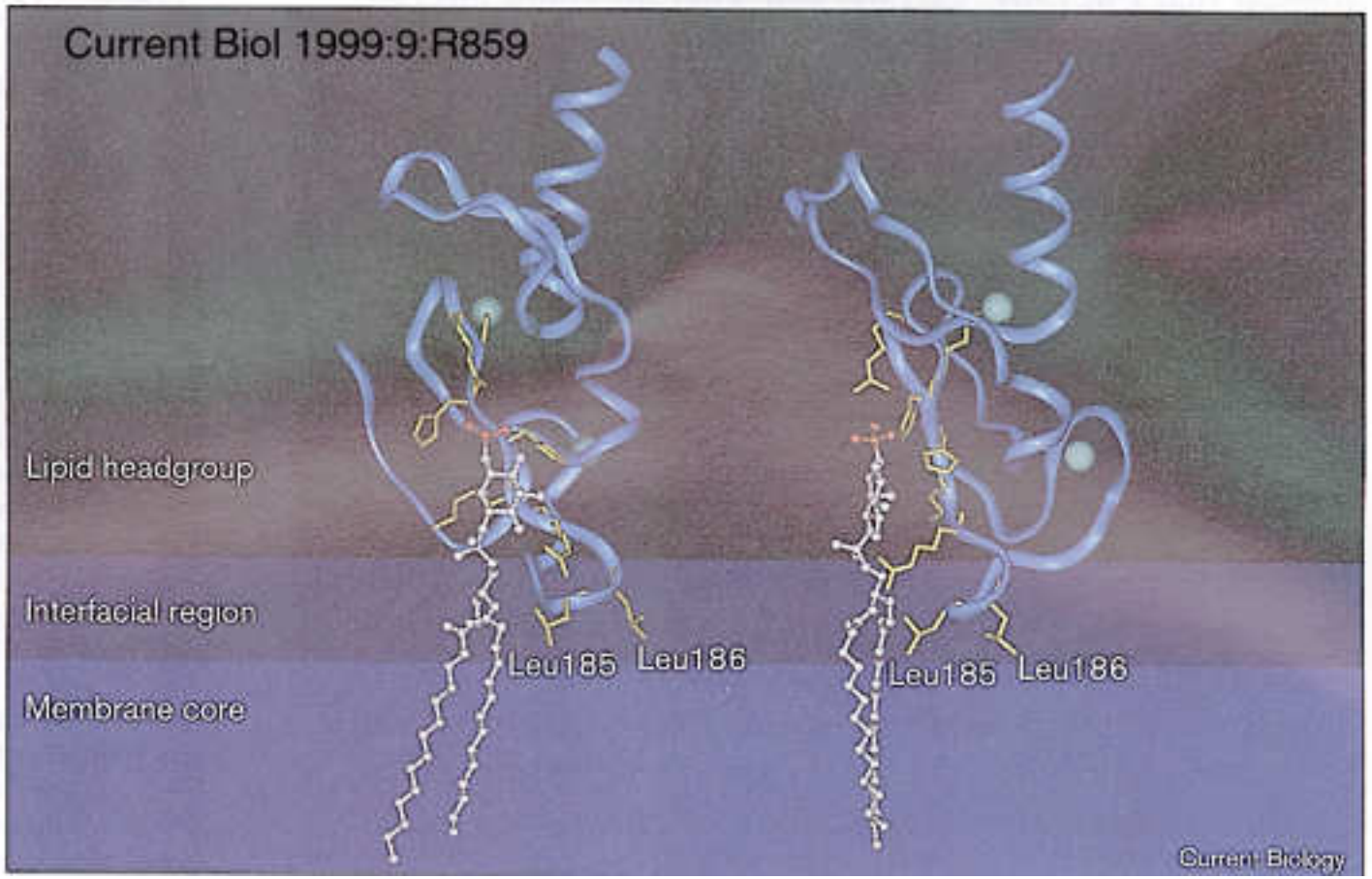


Periferal proteins are numerous and important

- Some are permanently bound
- Others switch between soluble cytosolic and membrane-bound forms
- Switching is regulated by conformational changes, covalent modifications, addition Ca++, etc.
- They bind to lipid head groups, or to external protein domains in membranes
- Some associate with the bilayer interior, and have the characteristics of integral proteins when bound
- Some are partially inserted via exposed covalent lipid or hydrophobic groups including amphiphatic alpha

Example: Some periferal proteins bind to lipid head groups. This can play important role in signal transduction: Here a so called FYVE domain in a protein that binds to the inositol group of phosphatidyl inositol 3 phosphate,PI(3)P. It also

interacts hydrophobically via Leu 185 and Leu 186



Example: Positive charges are sometimes found to promote interaction of a protein with negatively charged phospholipid head groups

Human beta-2-glycoprotein I
Bouma EMBO J 18:5166

Positive surface is shown with blue

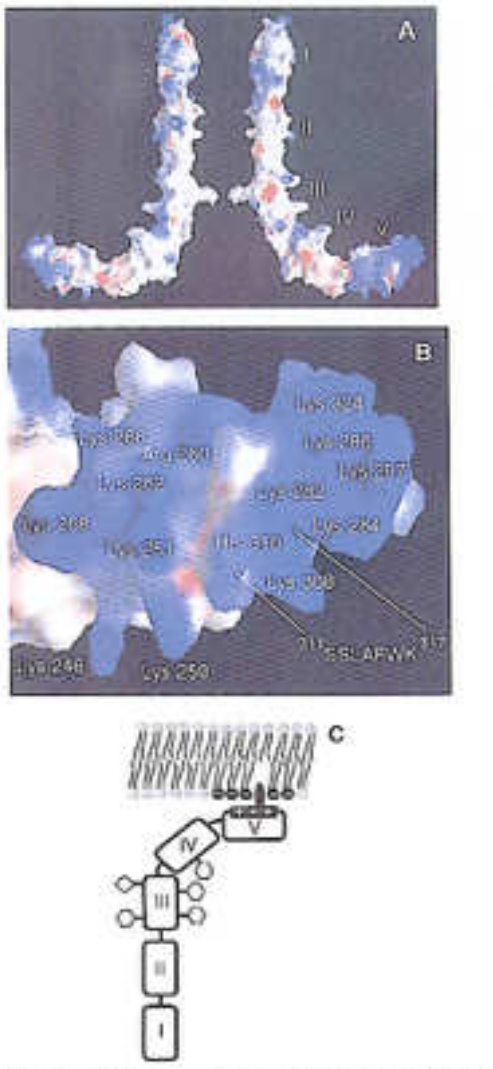
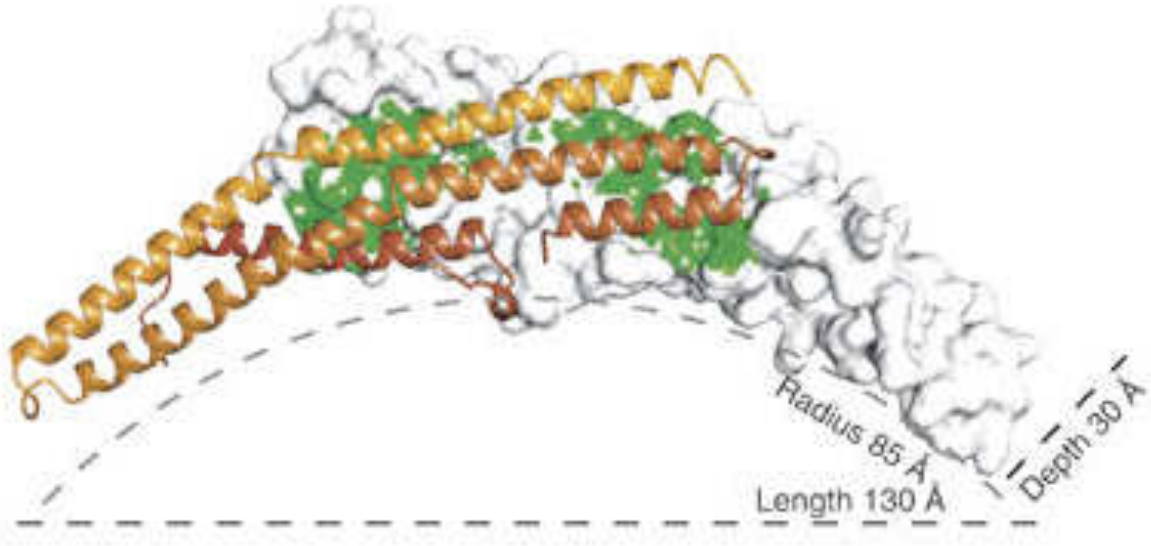


Fig. 5. Binding of β2GPI to an anionic phospholipid surface. (A) Two views, related by 180° rotation, of the electrostatic potential surface of β2GPI. Domains are labelled I–V. The electrostatic potential is scaled from red for negative to blue for positive. (B) Positively charged patch on the aberrant half of domain V. The 14 residues contributing to this patch and the position of the disordered loop Ser311–Lys317 are indicated. (C) Diagram of the proposed model for binding of β2GPI to acidic phospholipids. The positively charged patch on the surface of domain V is indicated by '+', acidic phospholipids are depicted by '–' and the putative membrane-insertion loop Ser311–Ser–Leu–Ala–Phe–Trp–Lys317 is shown to insert into the phospholipid layer. The positions of *N*-glycans are indicated by hexagons and the putative site for O-linked glycosylation is indicated by a diamond.

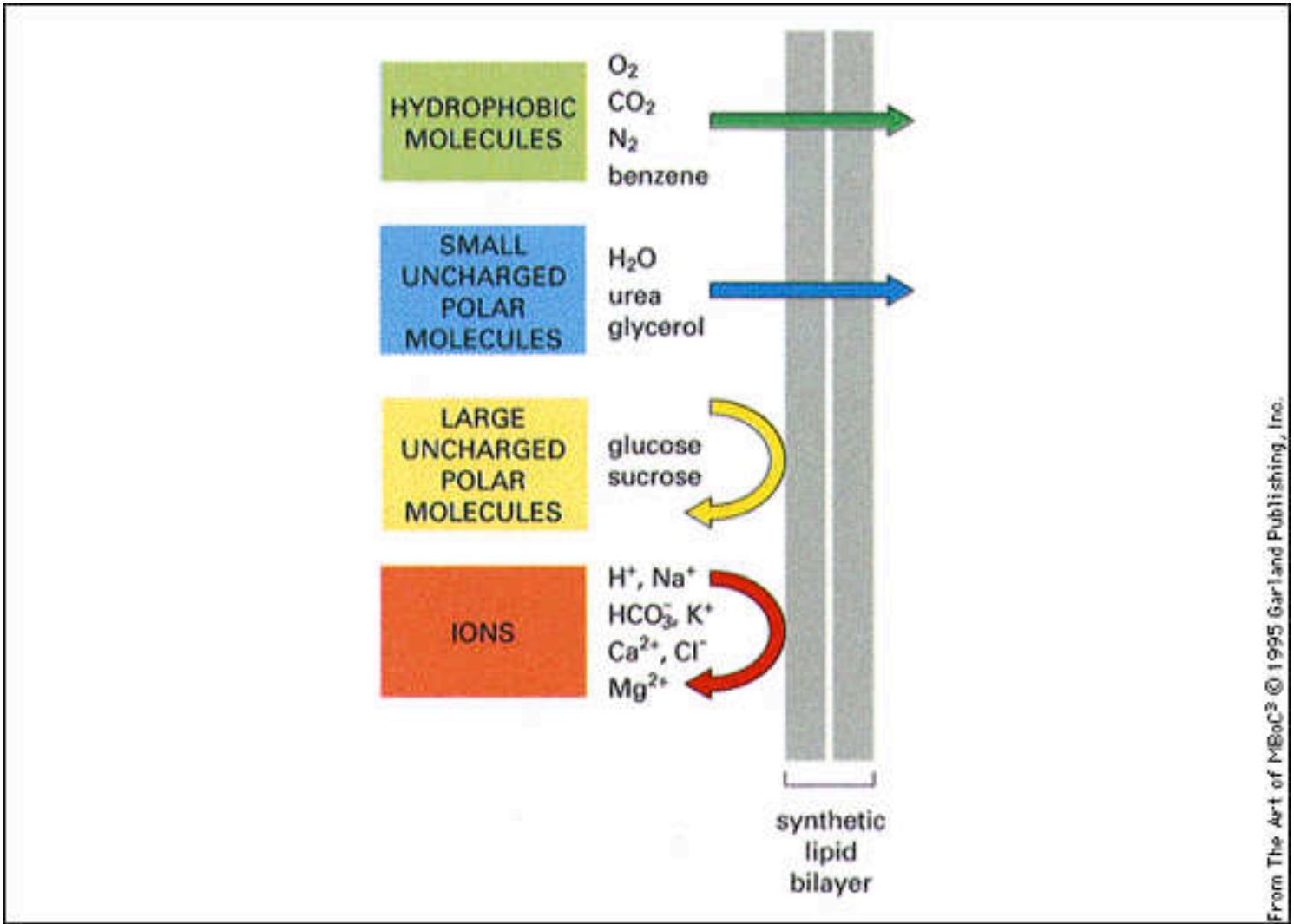
Bouma Embo J 18:5166

Some proteins have domains that induce or sense membrane curvature

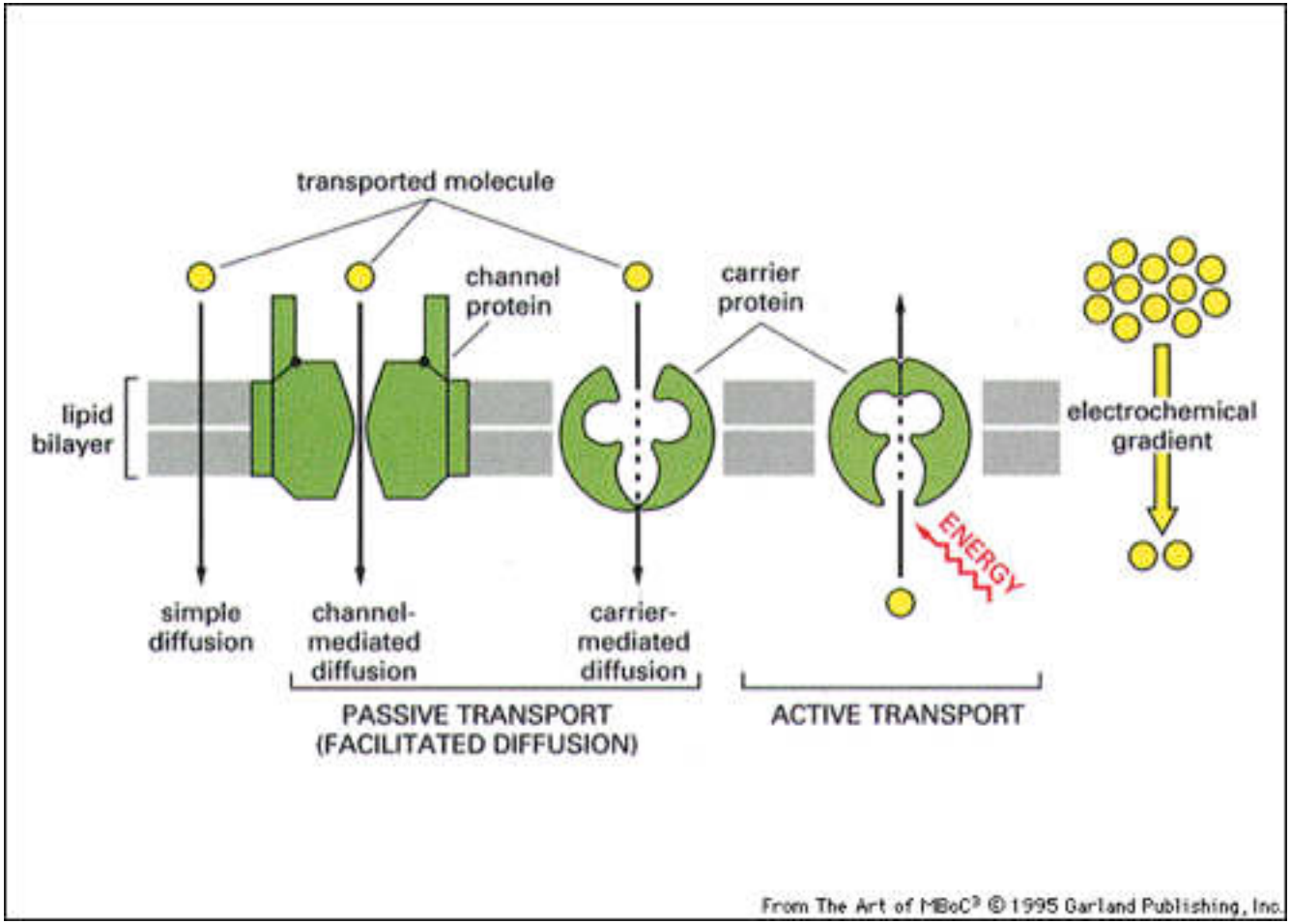
- A wedge: Amphipathic helix inserted in one membrane bilayer
- So called C2 domains: Calcium ion binds to such domains and induces exposure of a small hydrophobic membrane insertion patch
- BAR domains: Banana shaped protein dimers that bind the membrane on their convex surface



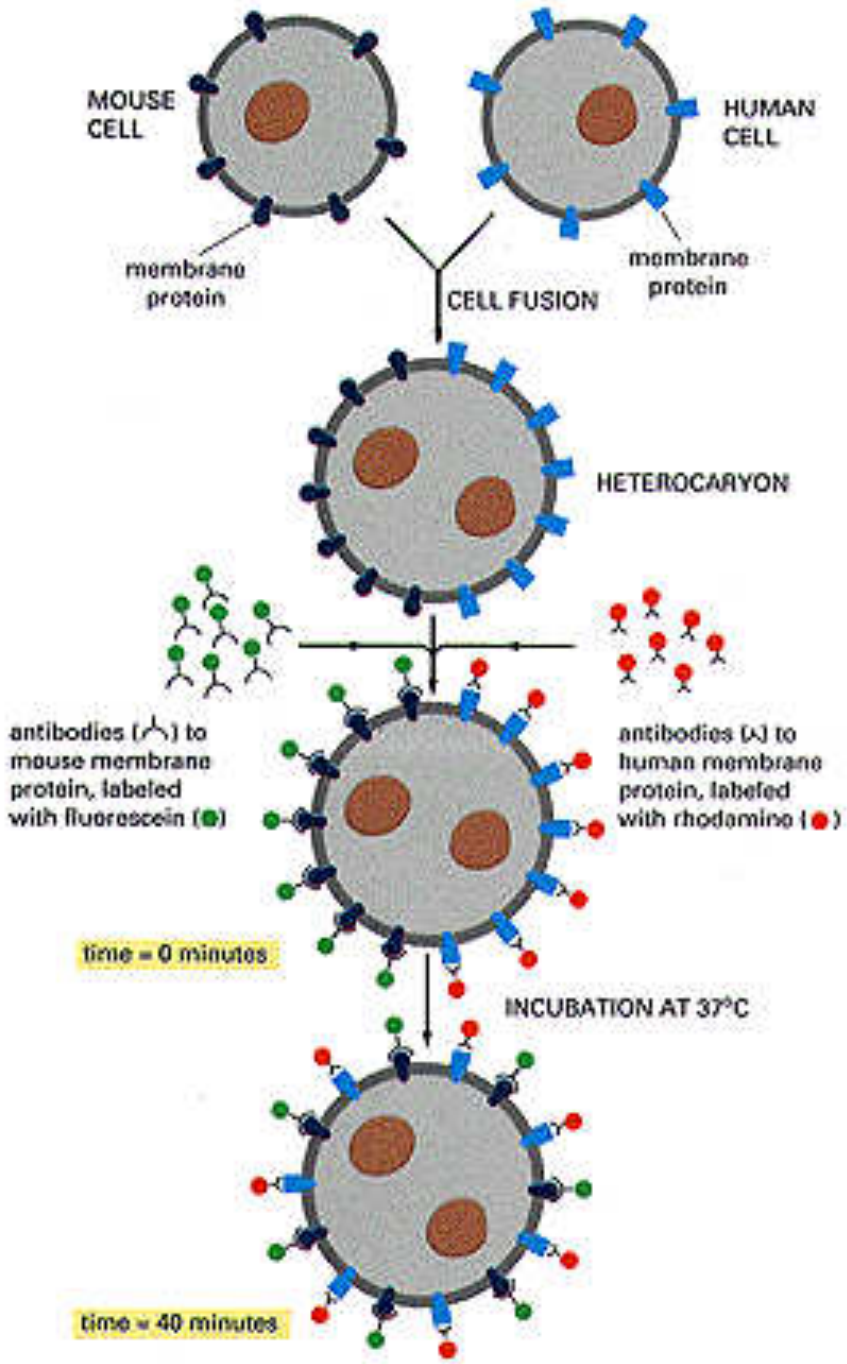
A large group of integral membrane proteins serve to modify the membrane's permability properties. Permeability of a protein-free lipid bilayers is limited to hydrophobic molecules and some small uncharged polar molecules.



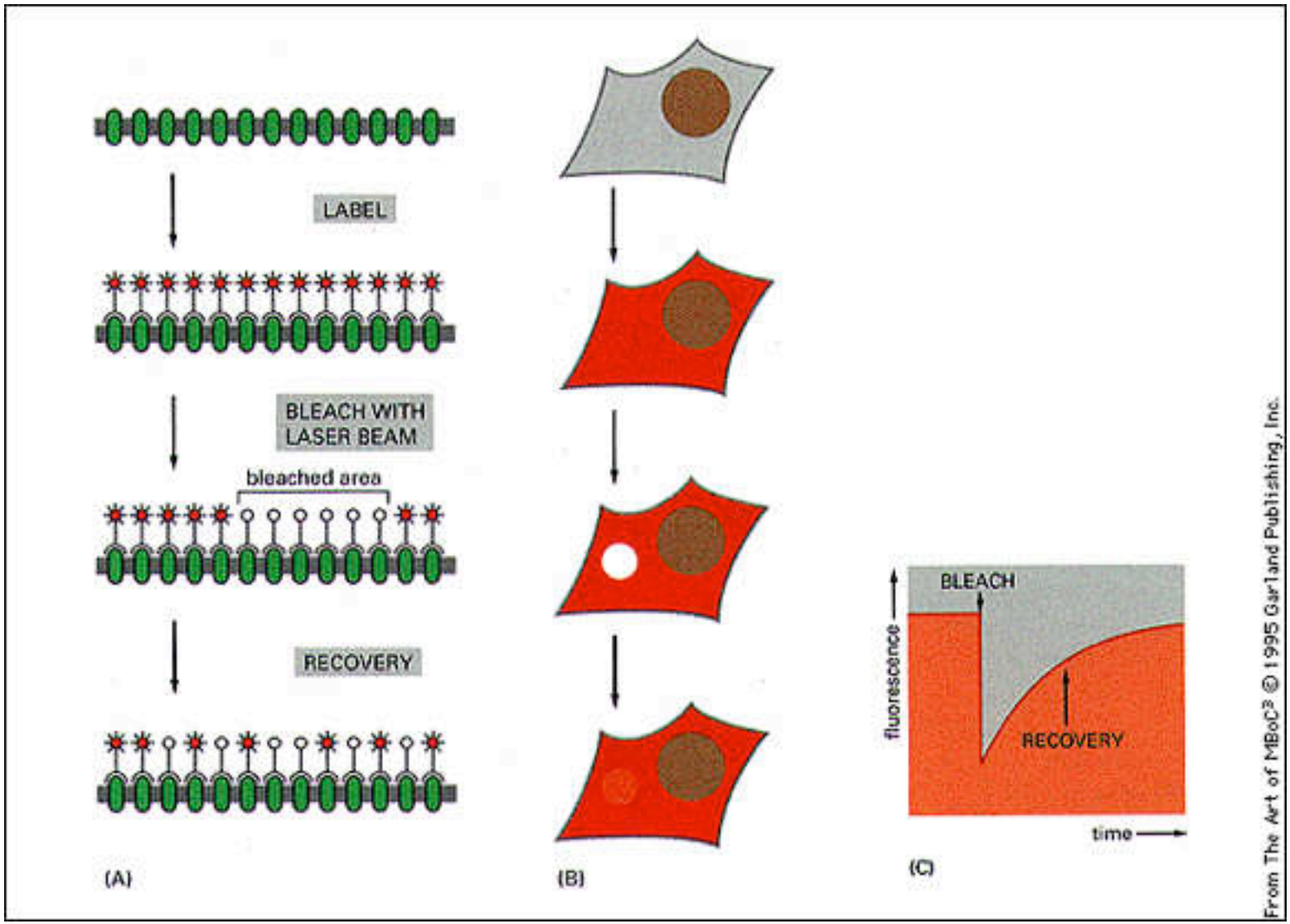
Proteins can promote passive transport specific substances down an electro-chemical gradient, or active transport against such a gradient.



Proteins are mobile in the plasma-membrane: Here a classic experiment with fused mouse/ human hybrid cells



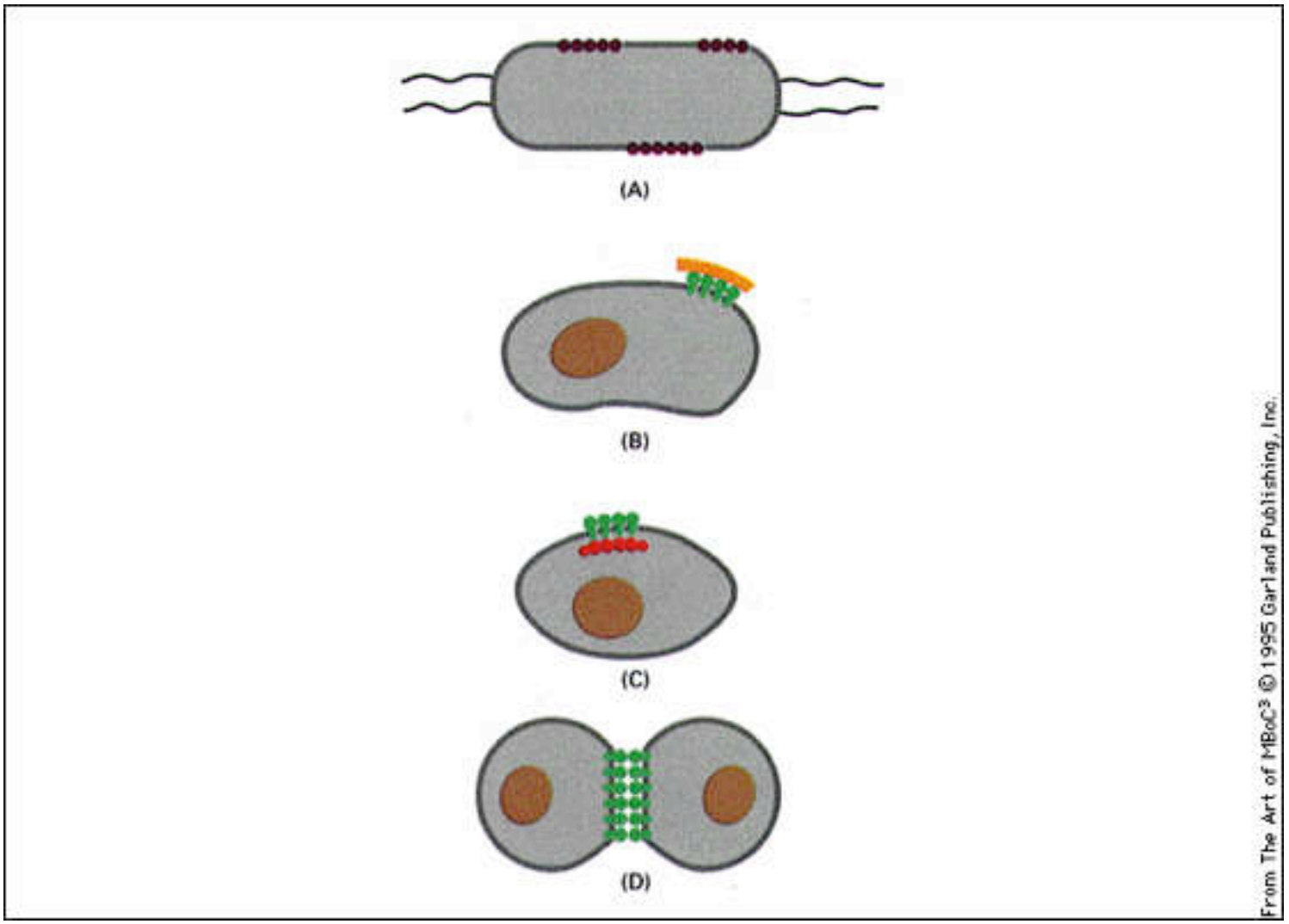
Fluorescence recovery after bleaching (FRAP) allows lateral mobility to be measured



Lateral and rotational diffusion of membrane proteins

- The lateral diffusion rate of membrane proteins in biological membranes is generally 10-30 times slower than in liposomes.
- Translational diffusion rate is relatively insensitive to size (linearly dependent on radius r)
- Rotational diffusion is quite sensitive to size (function of r^3)

Different ways to restrict lateral movement of plasma membrane proteins



Lipid rafts contain a distinct set of integral proteins

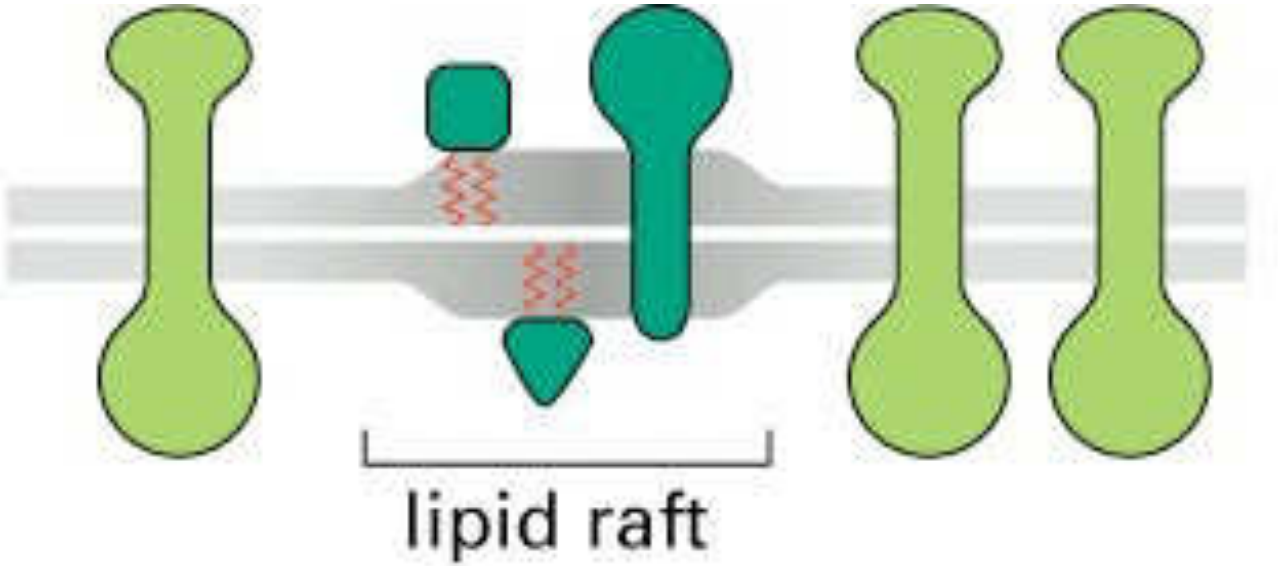


Figure 10–13. Molecular Biology of the Cell, 4th Edition.

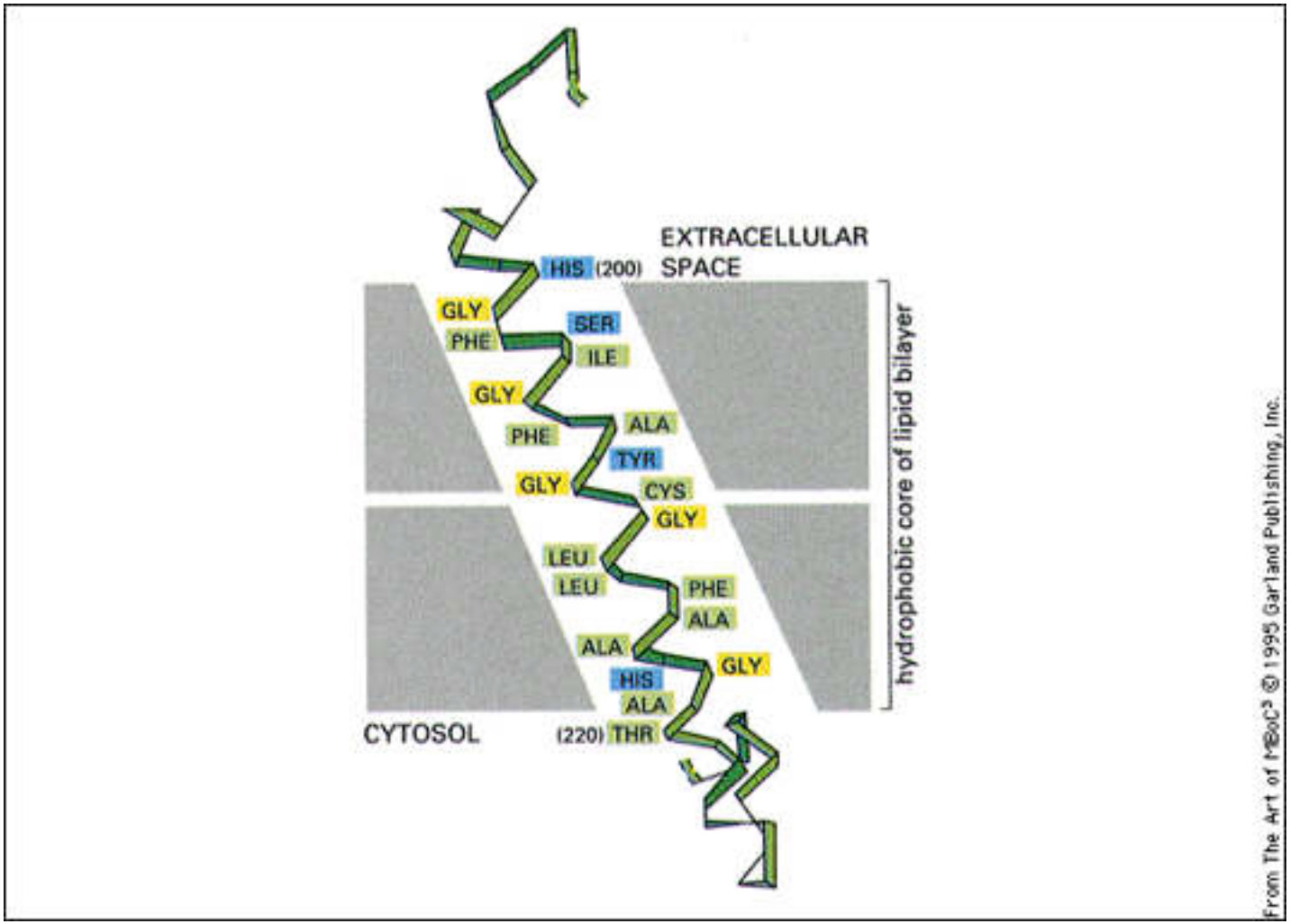
The above classification is oversimplified

- Many membrane proteins are oligomeric
- Some are composed of subunits that belong to different classes of membrane proteins
- Some proteins occur both in soluble and membrane-bound forms
  - Some cytosolic proteins use conformational changes and/or lipid modifications to switch from membrane-bound to soluble forms. In the membrane bound form, they can be either integral or periferal.
  - Many toxins convert from soluble to membrane-bound forms

    Addition or removal of lipid groups

    Conformational change

α-helical, trans-membrane (TM) segment of integral membrane protein

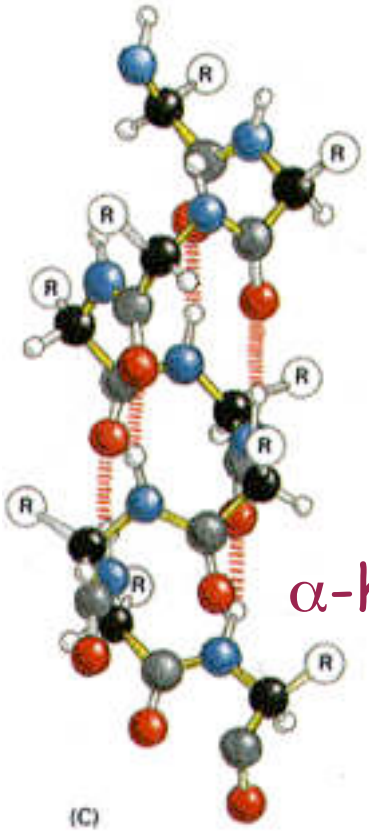


Some characteristics of TM segments

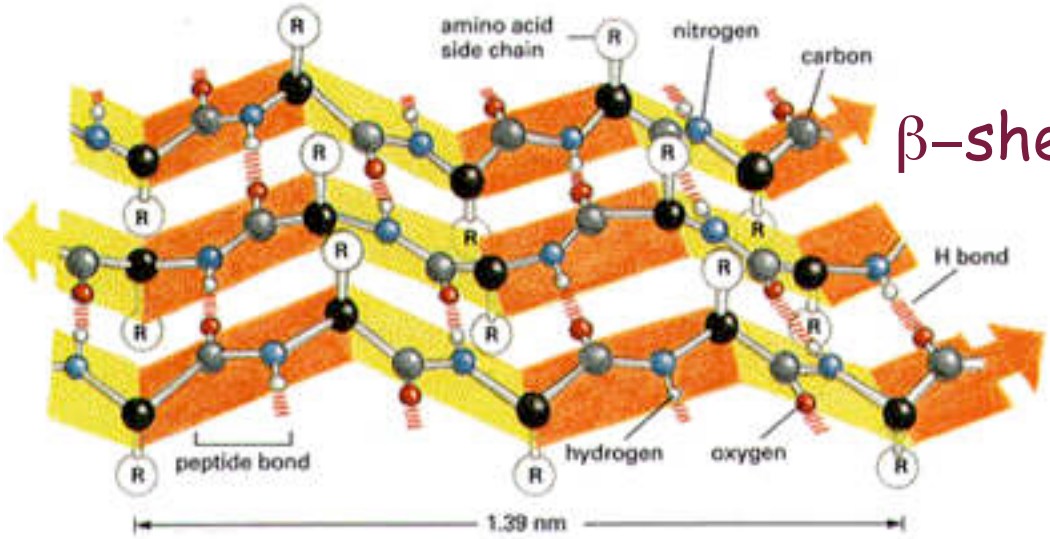
- Typical length of alpha-helical trans membrane segment is 18-28 residues depending on angle of tilt
- Sequence is hydrophobic, but not necessarily uniformly so.
- The 'positive inside rule'.

  The location of positive charges on the cytosolic side of TM.
  This not only correlates with orientation of TM,
  but controls it during synthesis.
- Aromatic amino acids (Tyr, Phe, Trp) usually positioned in the phospholipid head group region
- In polytopic membrane proteins the 'loops' outside the membrane are often quite short (average 10-15 amino acids)
- In polytopic proteins the amino acid side chains of the helices pack against each other in 'lock and key' fashion

Why restricted secondary structures in the membrane?



α-helix

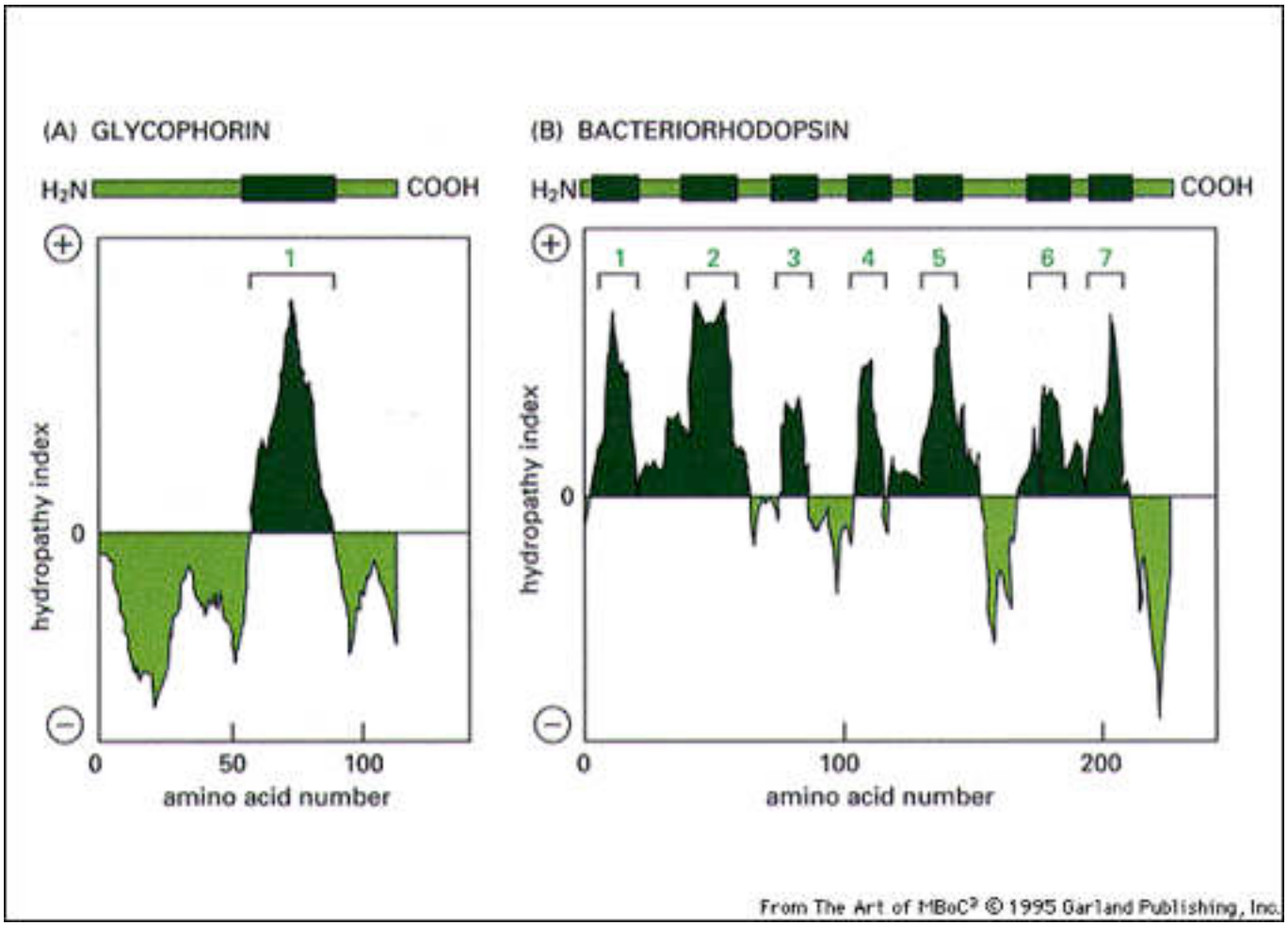


β–sheets

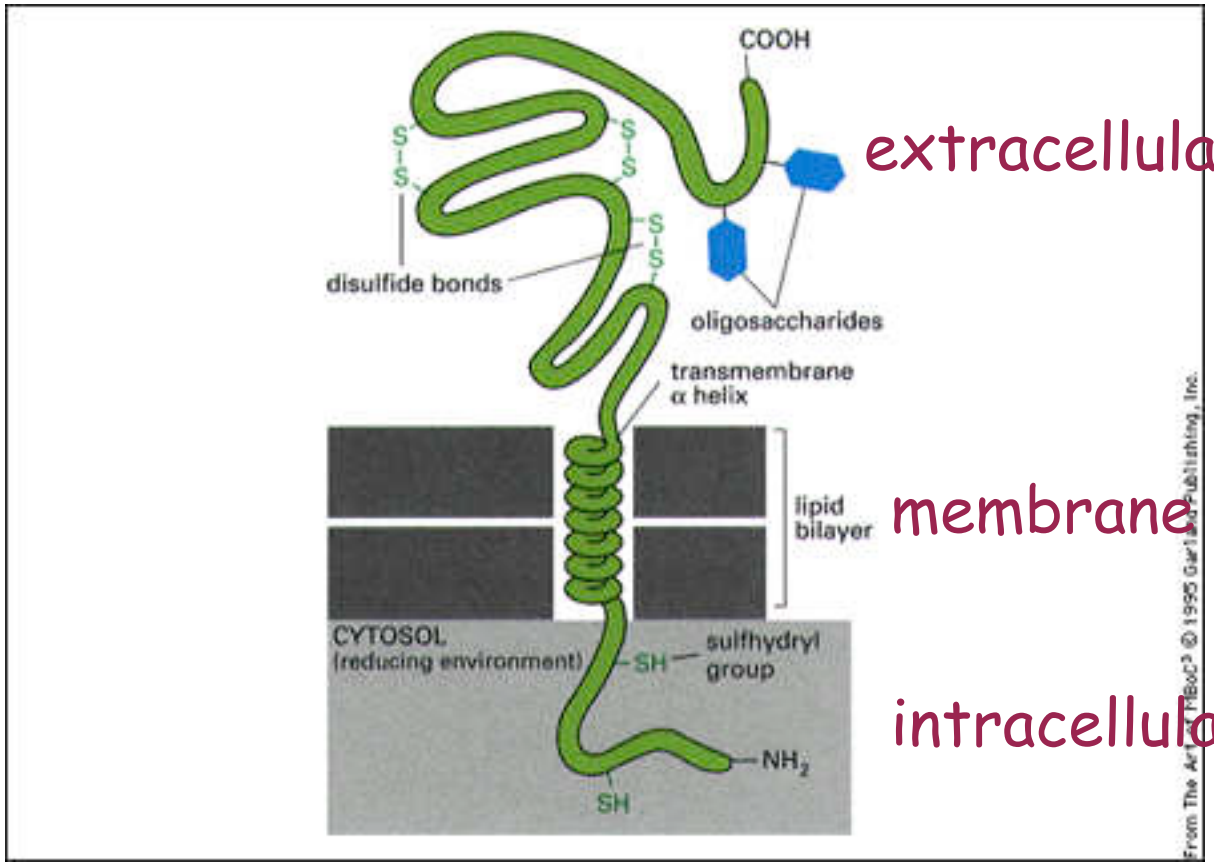
α-helices and β–sheets allow all main chain -NH- and =CO groups to form hydrogen bonds in the absence of water. These secondary structures are therefore energetically favored.

Note the positions of the amino acid side chains; they alternate from one side to the other of the beta-sheet

Localizing potential TM sequences in a 'hydropathy plot'. Computer programs calculate hydrophobicity in a 10-20 residue window 'sliding' along the sequence.

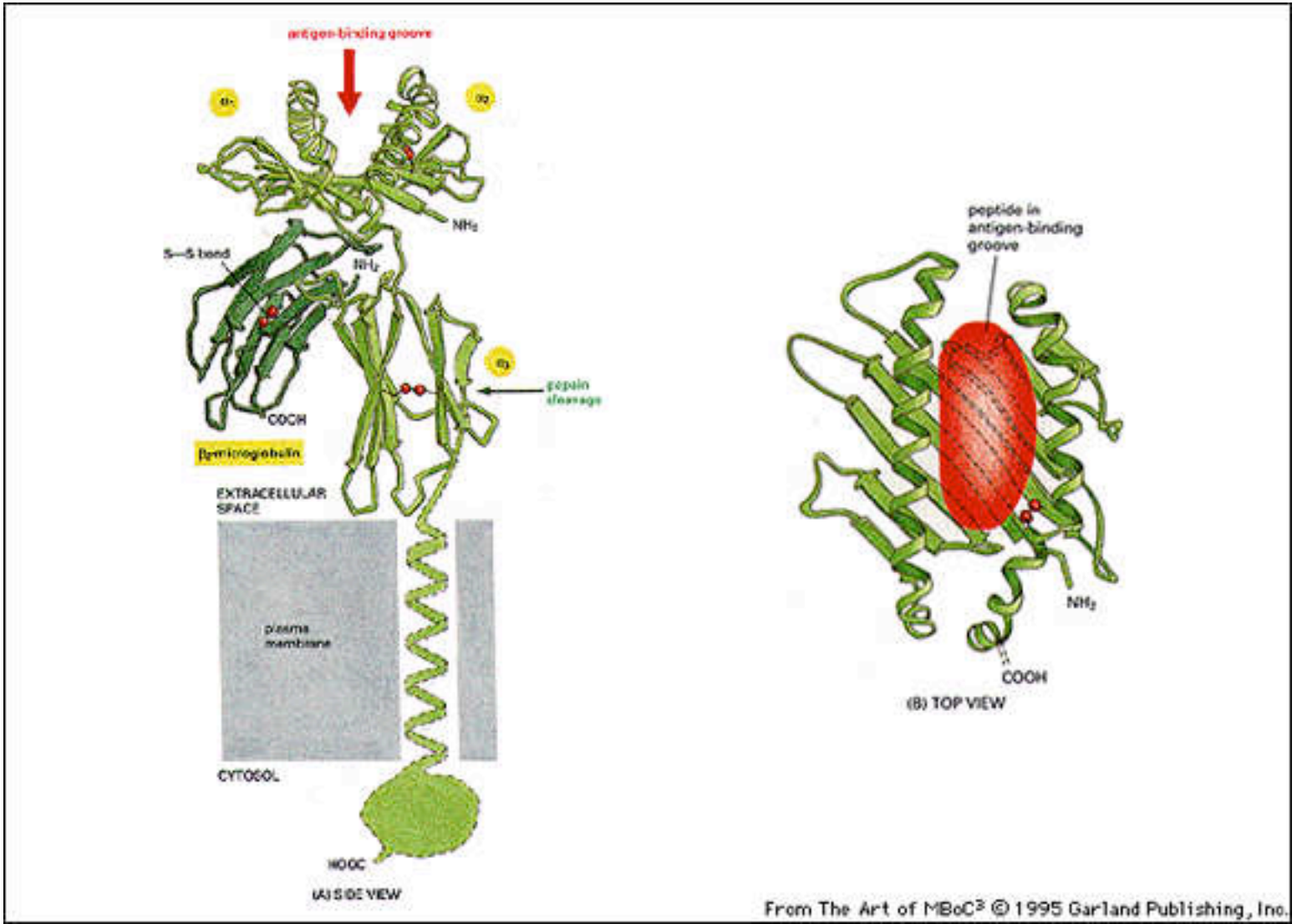


Trans-membrane proteins have at least three distinct domains



In type 1 and 2 proteins the three domains often fold independently of each other. For example, a recombinant anchor-free ectodomain can often fold correctly as a soluble protein.

Example: Type 1
Major Histocompatibility Antigen Class I
A hetero-dimeric glycoprotein



Transferrin receptor

A type 2 homodimeric membrane glycoprotein

Function: trapping and internalization of iron-carrying transferrin from the blood stream into the cell.

Single span

N-terminus in the cytosol

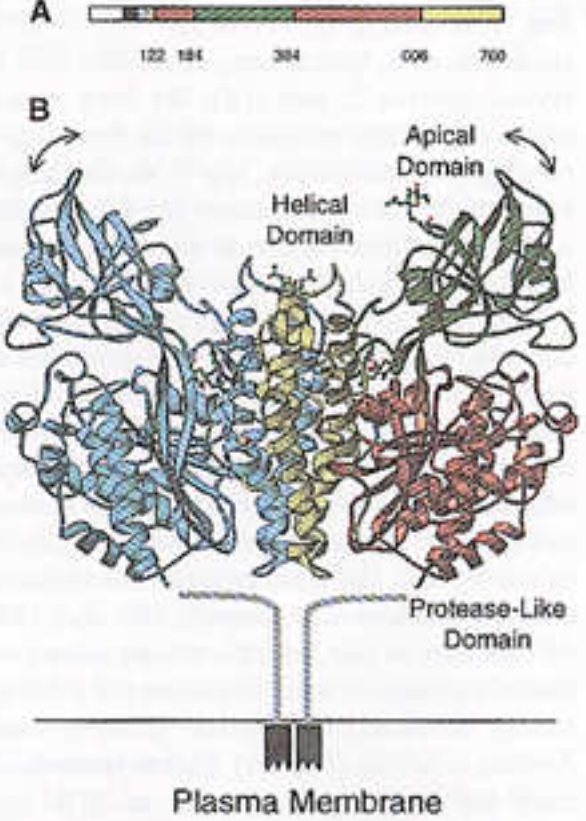
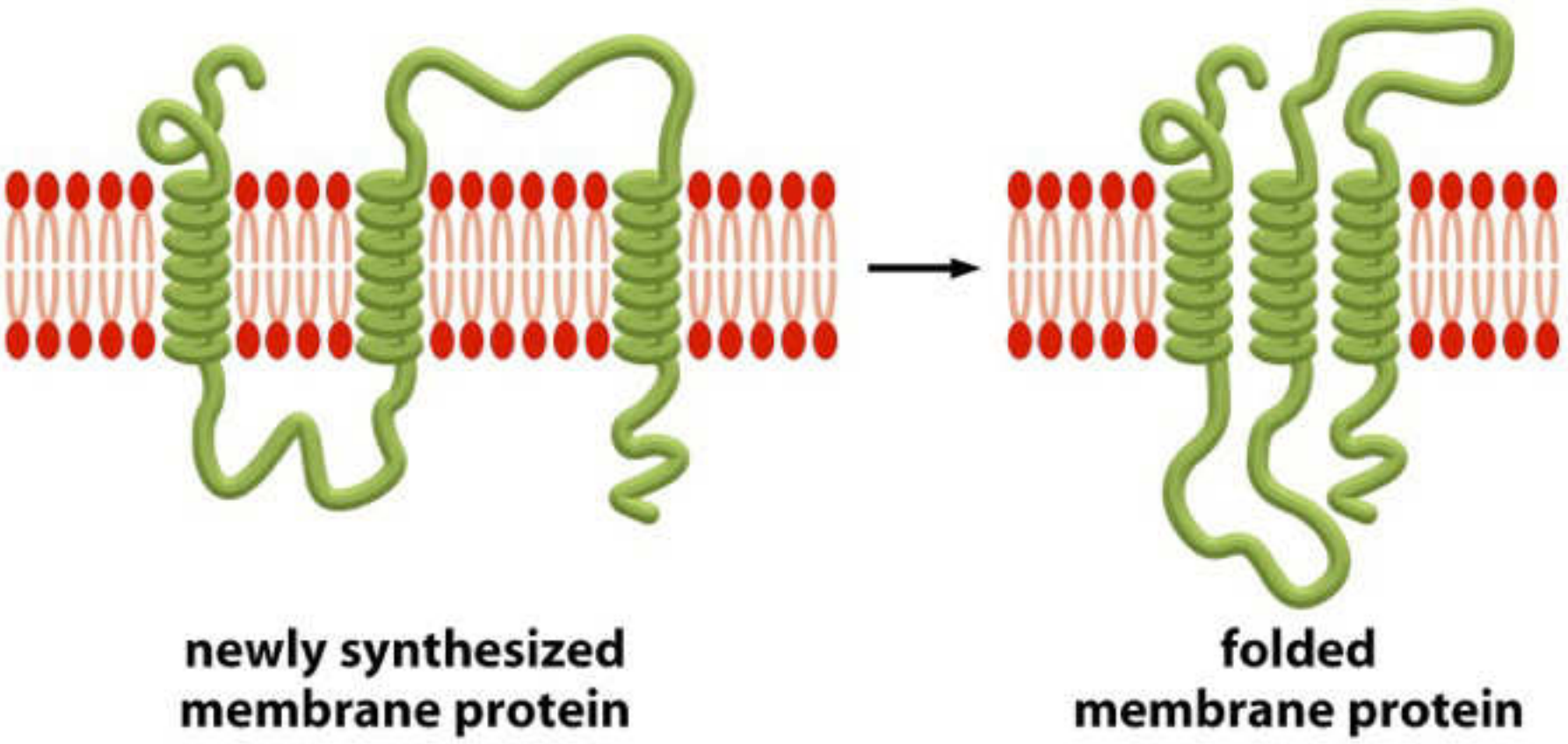


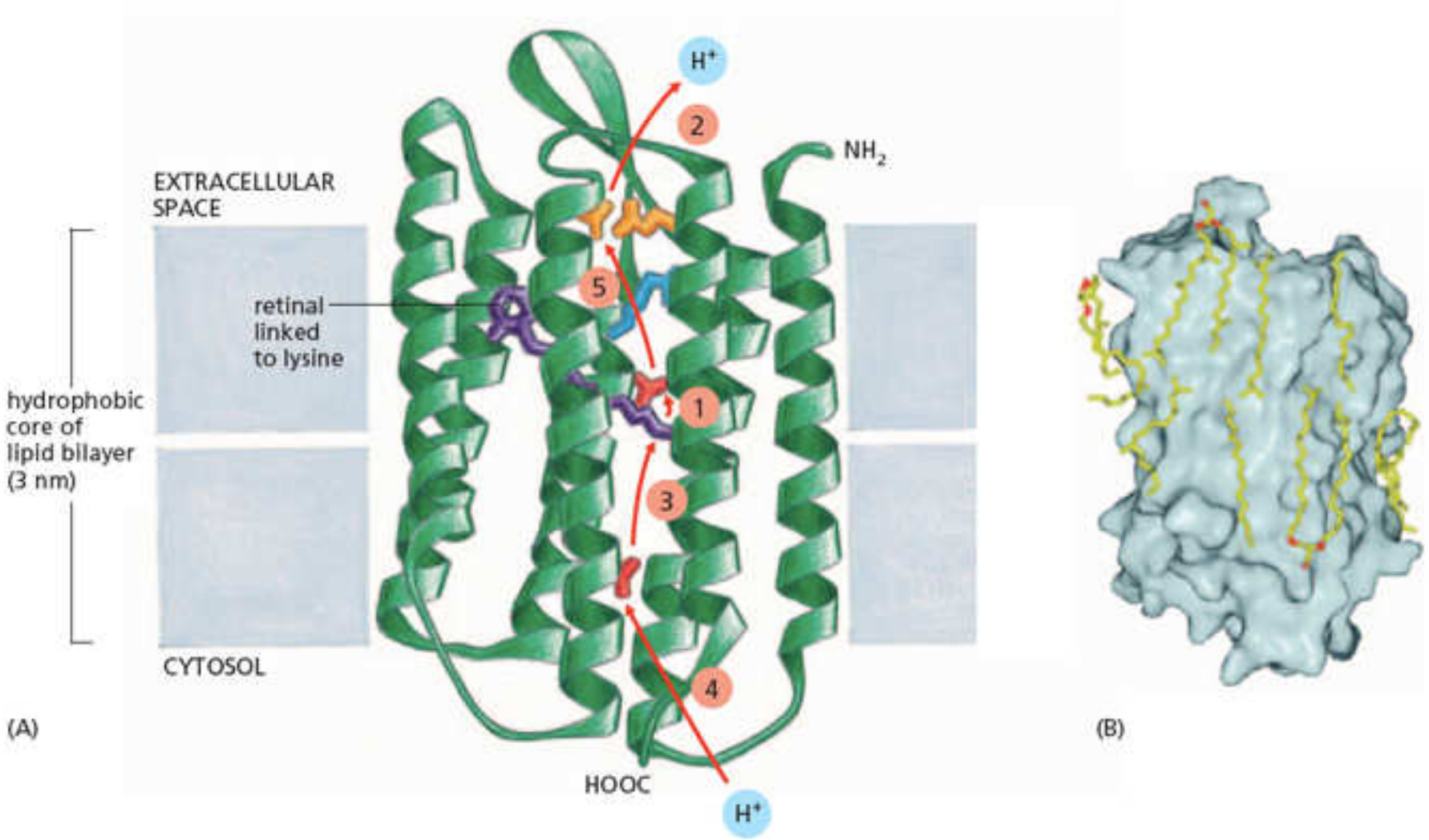
Fig. 1. Structure of the ectodomain of the TfR. (A) Domain organization of the TfR polypeptide chain. The cytoplasmic domain is white; the transmembrane segment is black; the stalk is gray; and the protease-like, apical, and helical domains are red, green, and yellow, respectively. Numbers indicate residues at domain boundaries. (B) Ribbon diagram of the TfR dimer depicted in its likely orientation with respect to the plasma membrane. One monomer is colored according to domain (standard coloring as described above), and the other is blue. The stalk region is shown in gray connected to the putative membrane-spanning helices. Pink spheres indicate the location of Sm^{3+} ions in the crystal structure. Arrows show direction of (small) displacements of the apical domain in noncrystallographically related molecules. Science 1999:288:780

Biosynthesis of multipass proteins occurs
in two steps: Insertion of TM sequences into the bilayer is followed by helix-helix contacts



Example: Bacteriorhodopsin, a light-driven proton pump

Polytopic (seven-spanning membrane protein family member)



First view of a GPCR
cryo-EM Projection of Rhodopsin

NATURE · VOL 362 · 22 APRIL 1993

LETTERS TO NATURE

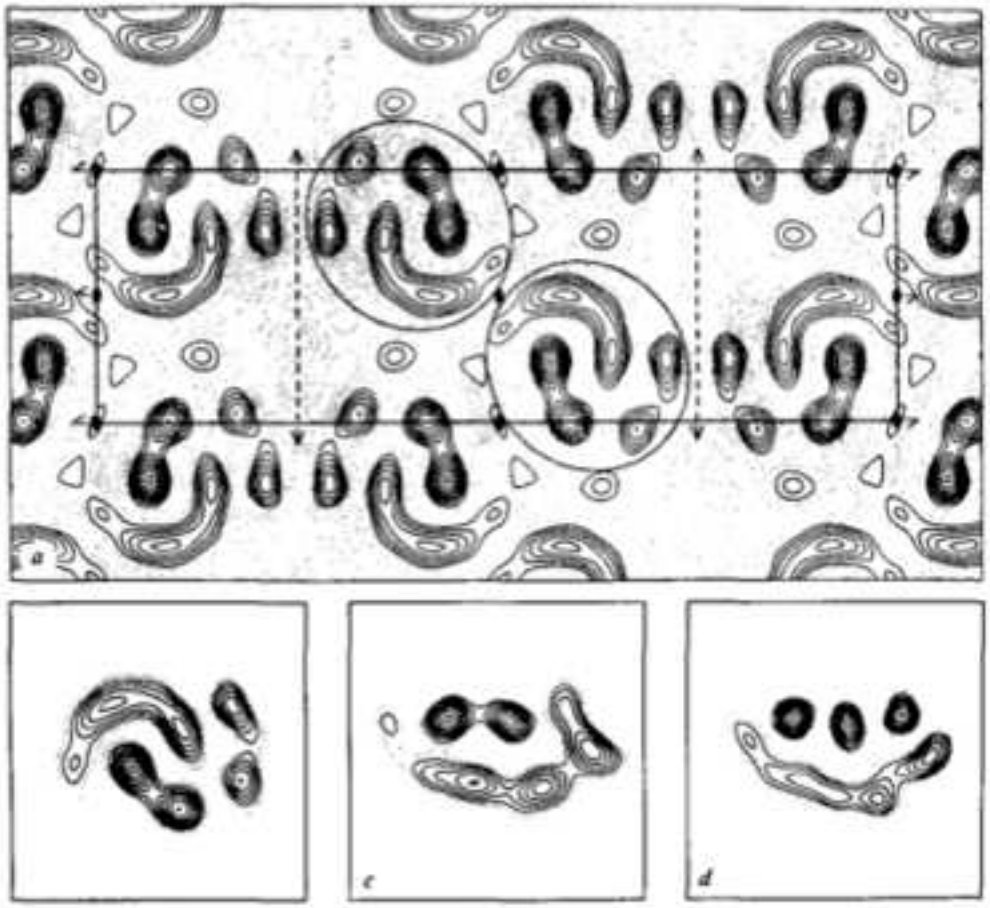
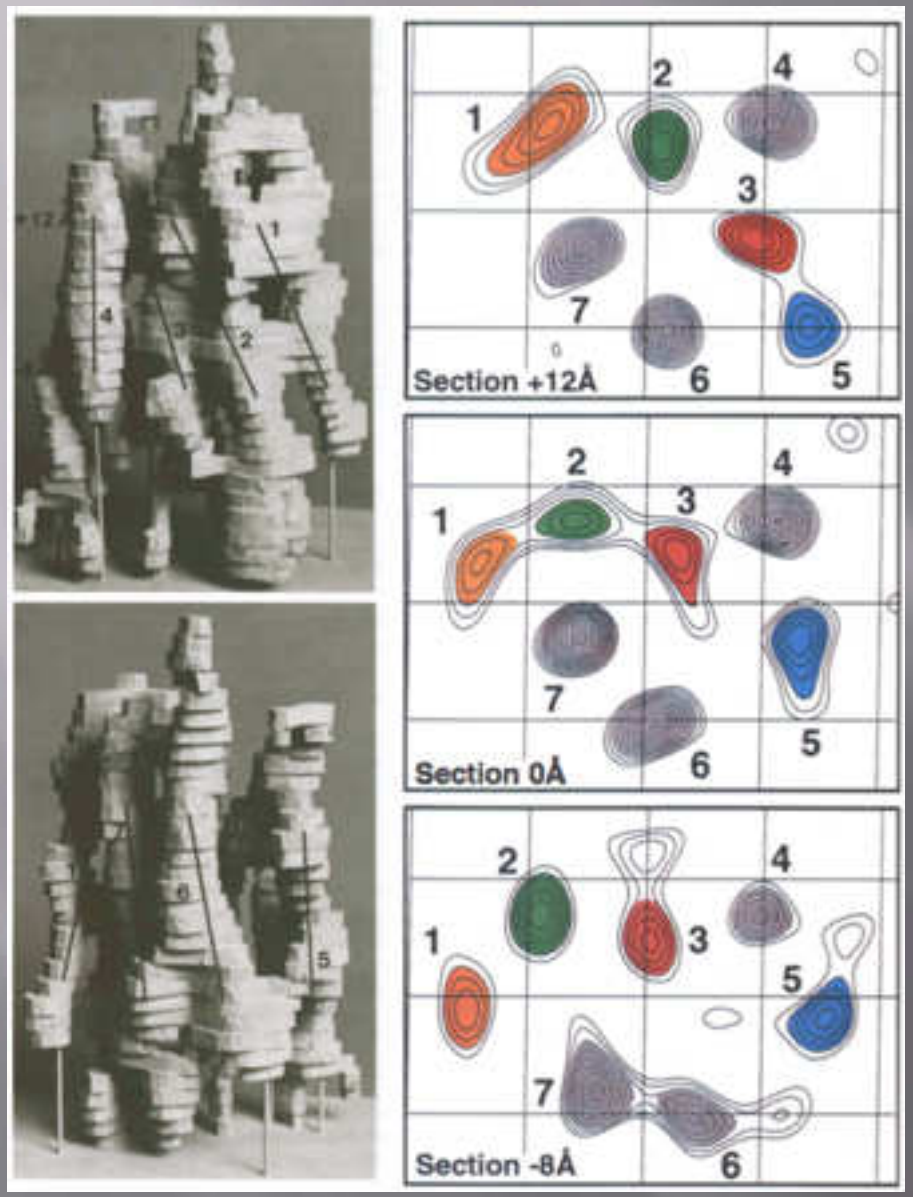


FIG. 2 *a* Projection density map of rhodopsin at 9 Å resolution, calculated from merged and corrected image amplitudes and phases obtained from 13 independent crystalline areas. A unit cell with the *a*-axis vertical and the *b*-axis horizontal is shown. The space group is $p222_1$ ($a = 43$ Å, $b = 140$ Å). The 2-fold axes perpendicular and parallel to the membrane plane and the 2-fold screw axes along *b* are indicated. One unit cell contains four rhodopsin molecules, two of which have been circled. Zero and negative contours are shown as dotted lines. *b*, The density for a single rhodopsin molecule at 9 Å resolution is shown, negative contours were omitted and the zero contour is represented by a dotted line. *c*, The density for a single bacteriorhodopsin molecule at 9 Å resolution is shown using the same contour levels and the same scale. *d*, The density for a single bacteriorhodopsin[28] molecule at 7 Å resolution is shown in the same way.

Arrangement of 7 GPCR membrane helices 1997



Unger, Villa and Schertler Nature 1997

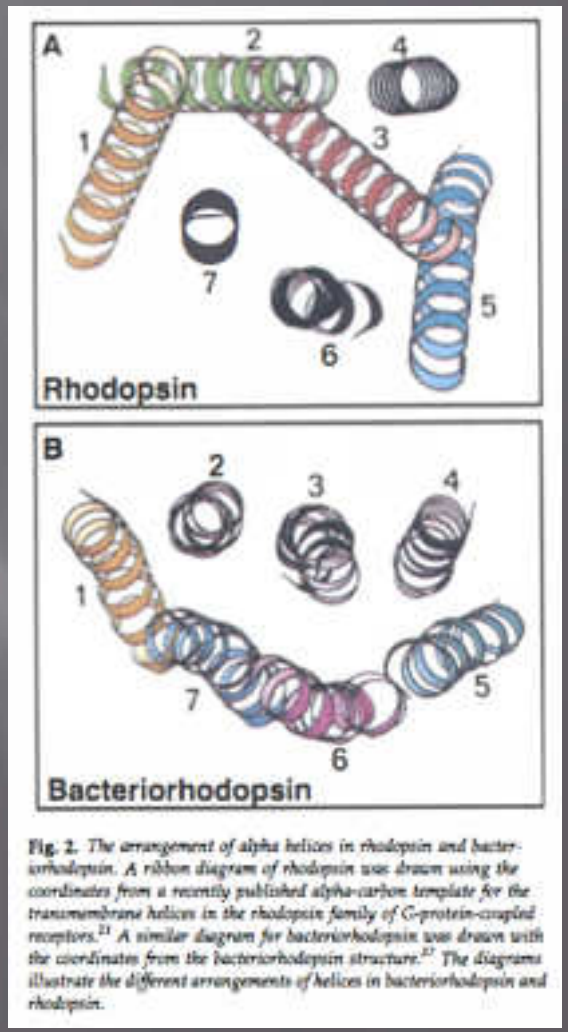
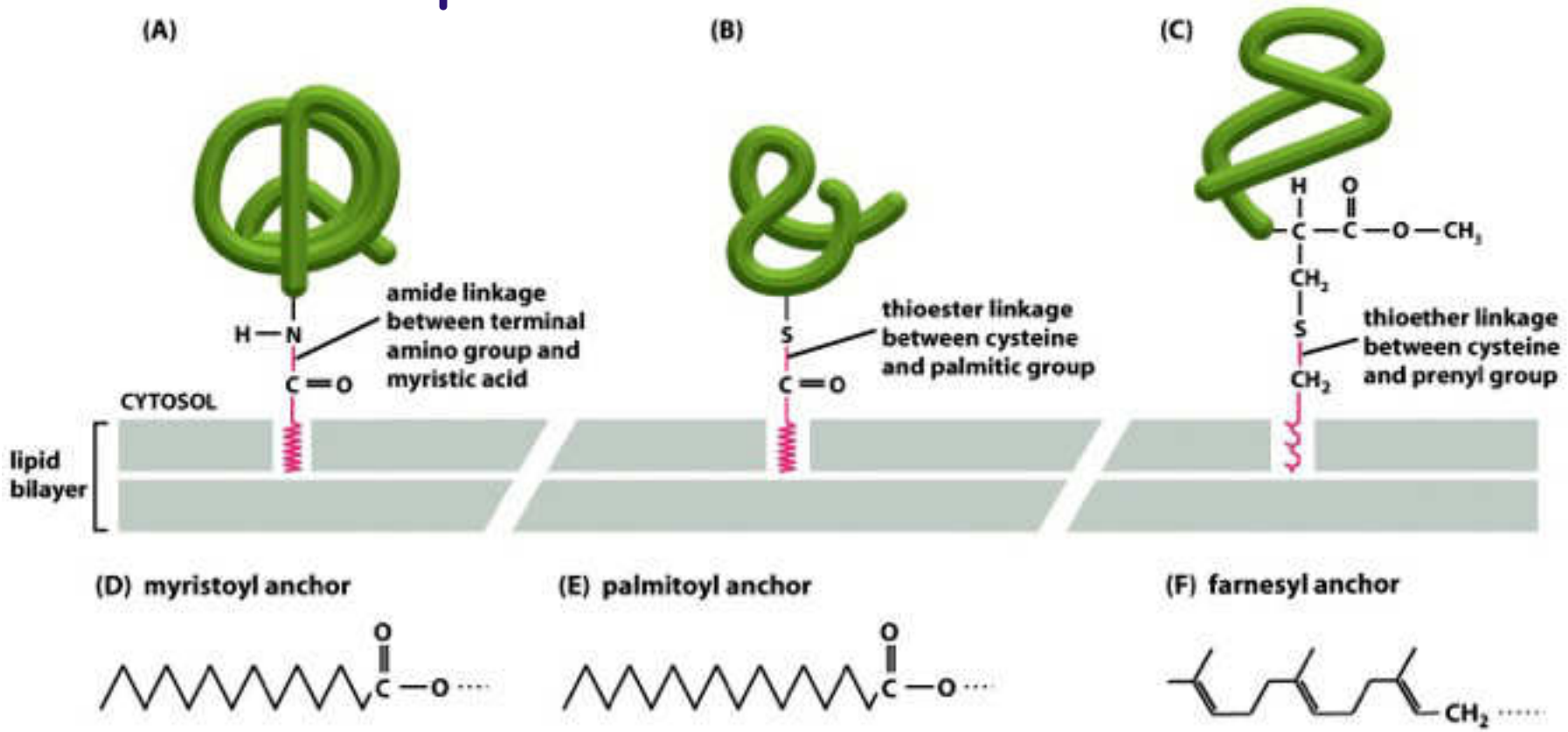


Fig. 2. *The arrangement of alpha helices in rhodopsin and bacteriorhodopsin. A ribbon diagram of rhodopsin was drawn using the coordinates from a recently published alpha-carbon template for the transmembrane helices in the rhodopsin family of G-protein-coupled receptors.[21] A similar diagram for bacteriorhodopsin was drawn with the coordinates from the bacteriorhodopsin structure.[27] The diagrams illustrate the different arrangements of helices in bacteriorhodopsin and rhodopsin.*

Schertler, EyeEye (1998) 12,504-510

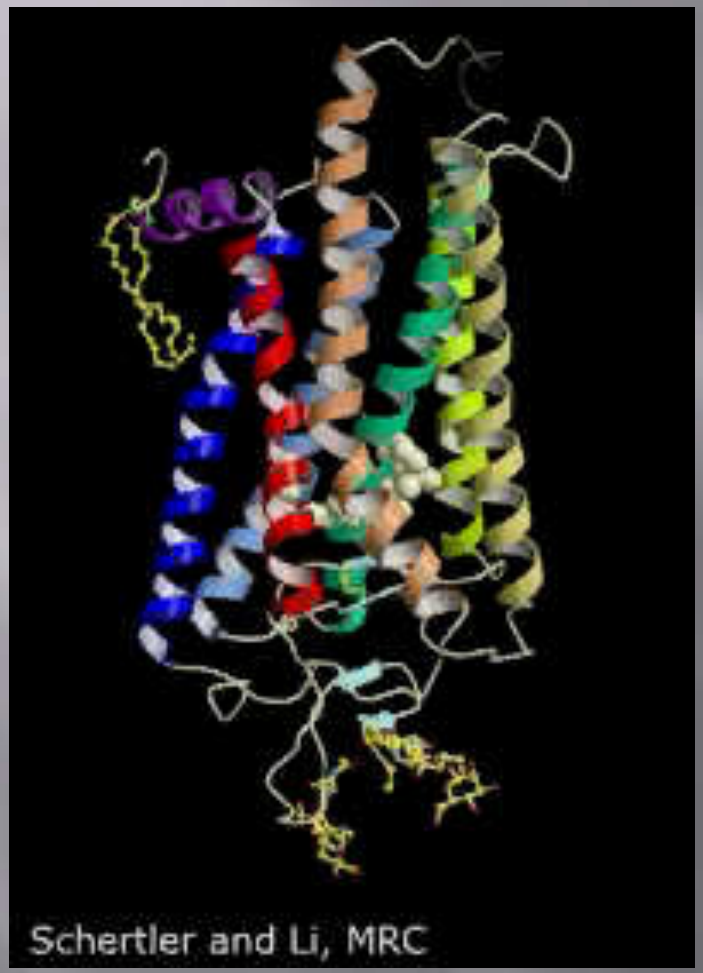
Covalently bound lipids anchor some proteins to membranes

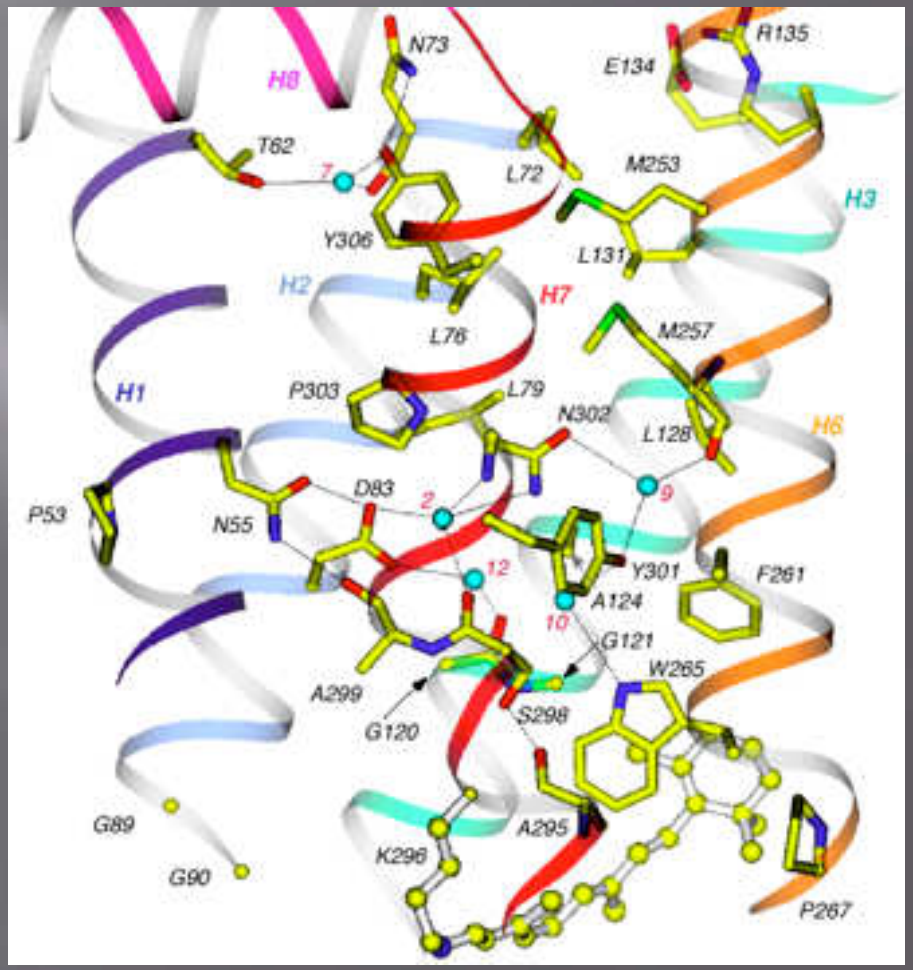


(Attached to N-terminal glycin residue in the cytosol)

Either farnesyl (C15) or the longer geranylgeranyl (C20) Group at the C-terminus

The Structure of rhodopsin has revealed an important internal hydrogen bond network partially mediated by water

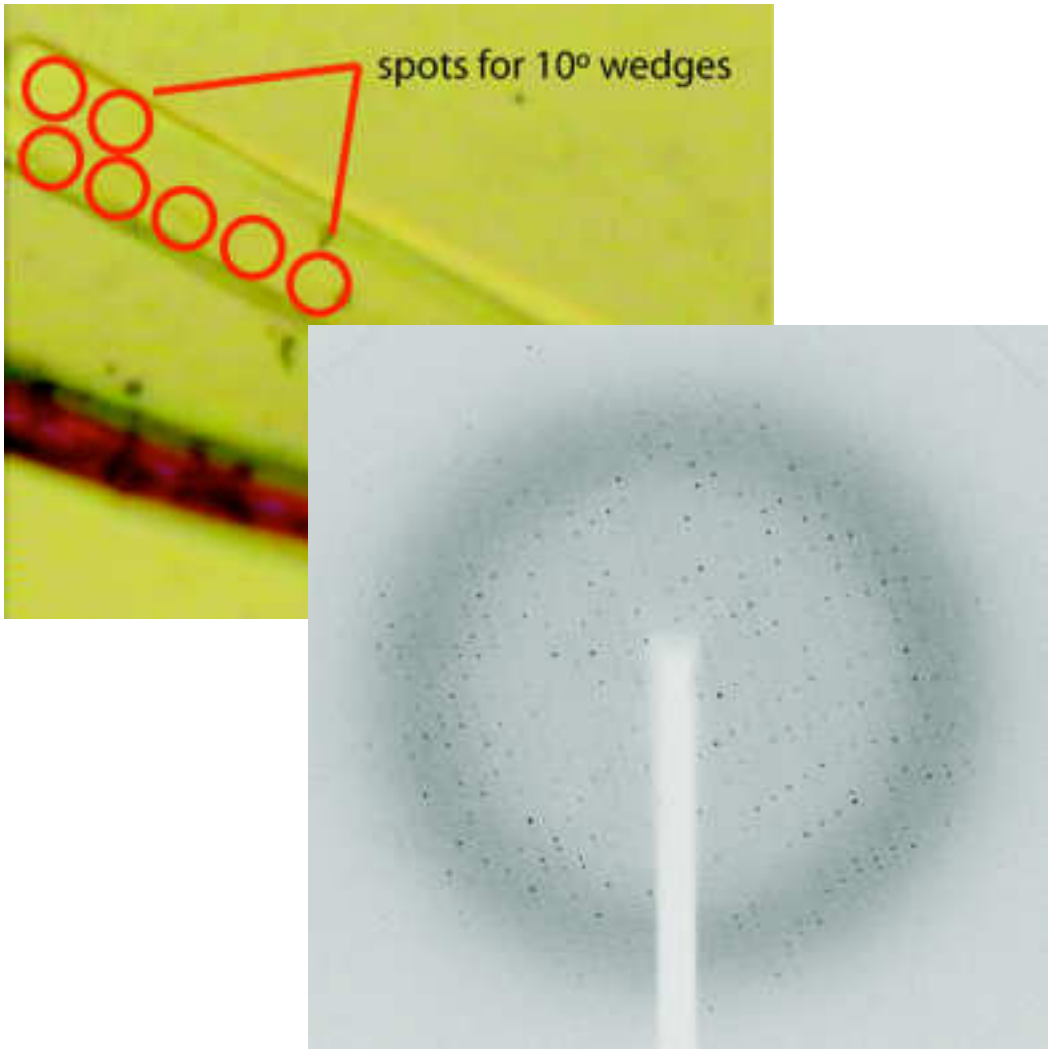




Li, Edwards and Schertler JMB 2004

PDB: 1GZM

Data collection
beta 1 adrenergic receptor



Relatively long exposures

Narrow wedges (10º)

1º oscillations

Recording from good positions only

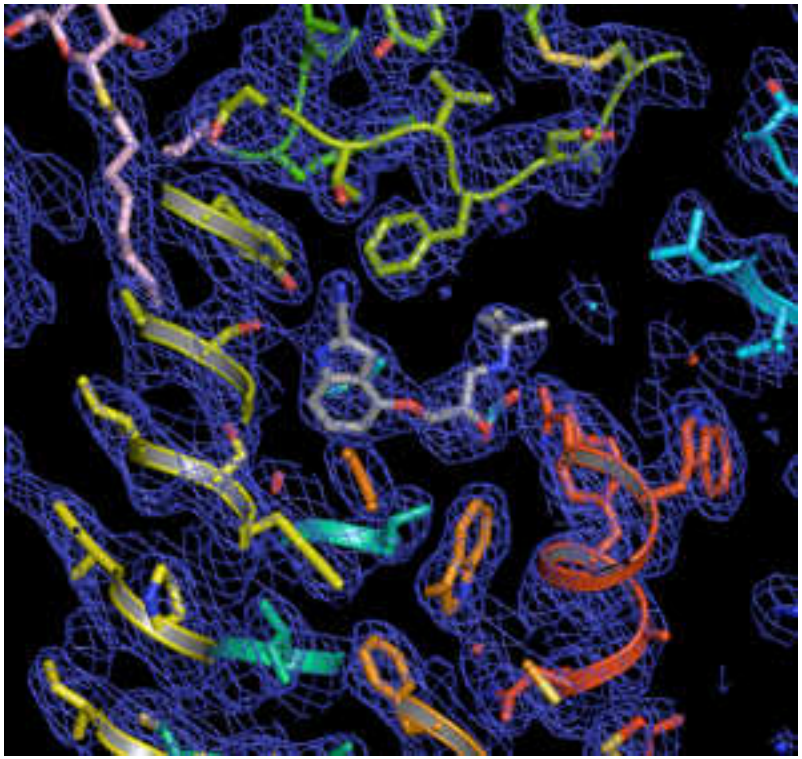
At least 18 wedges (180º of data for 100% data completeness due to monoclinic space group)

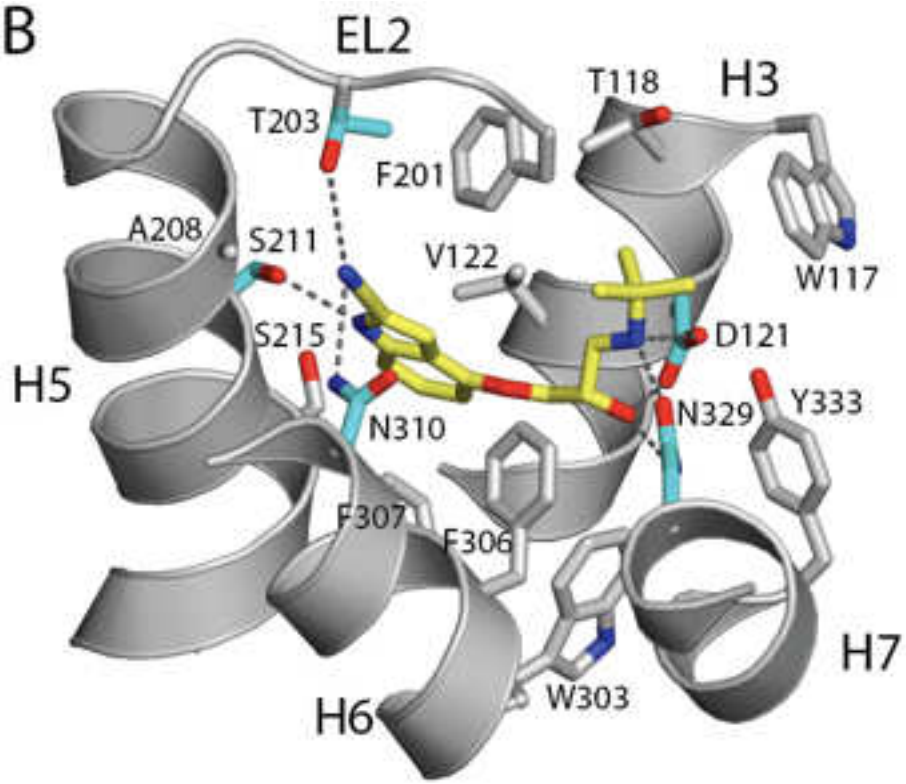
Beta1 Adrenergic Receptor

How does a ligand bind to a GPCR?

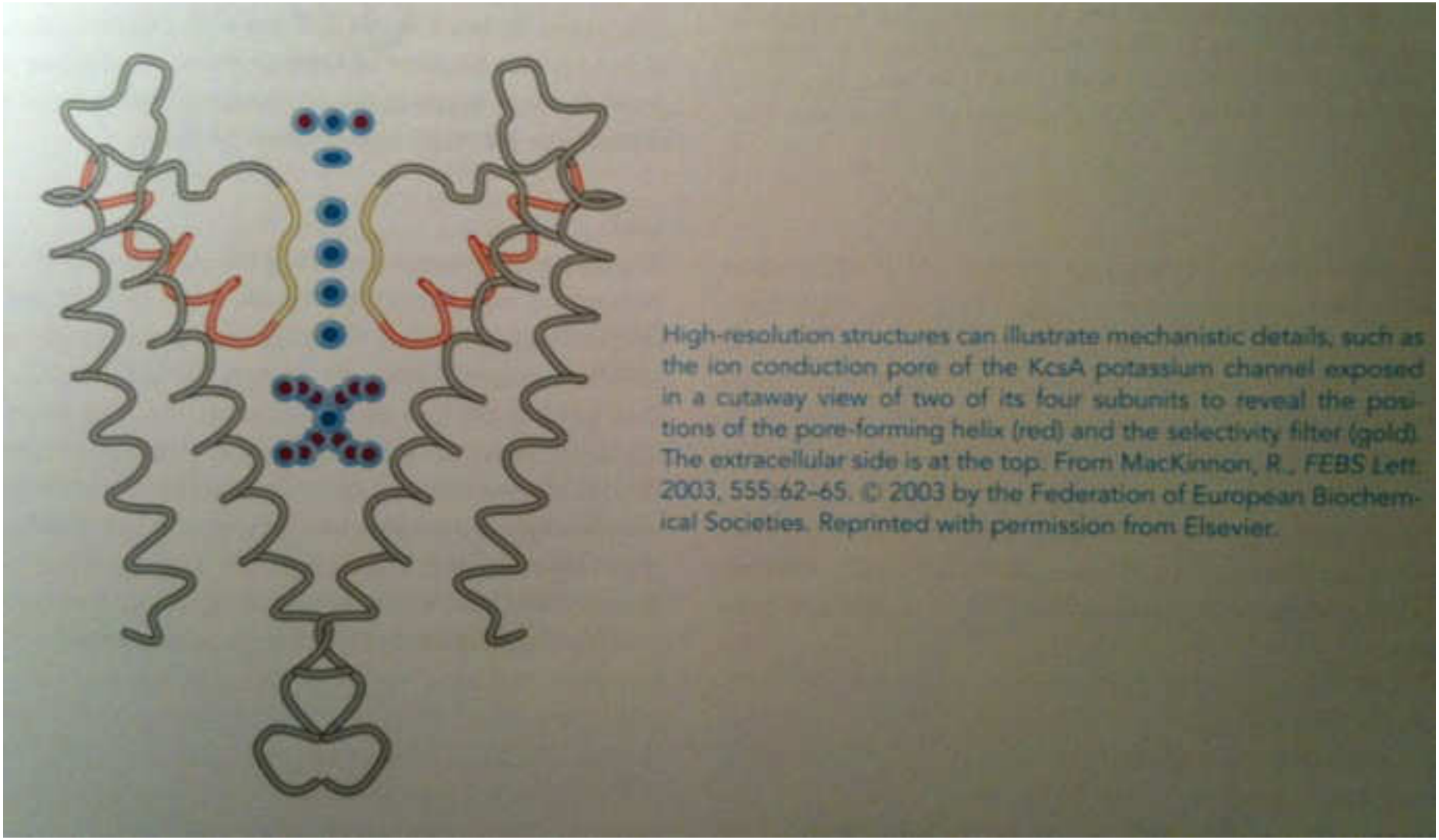
Structure of stabilised beta 1 adrenergic receptor

For the antagonists Carazolol and Cyanopindolol 13 residues from 4 helices and 2 residues from the second extra cellular loop between helix 4 and 5 contact the beta blocker.



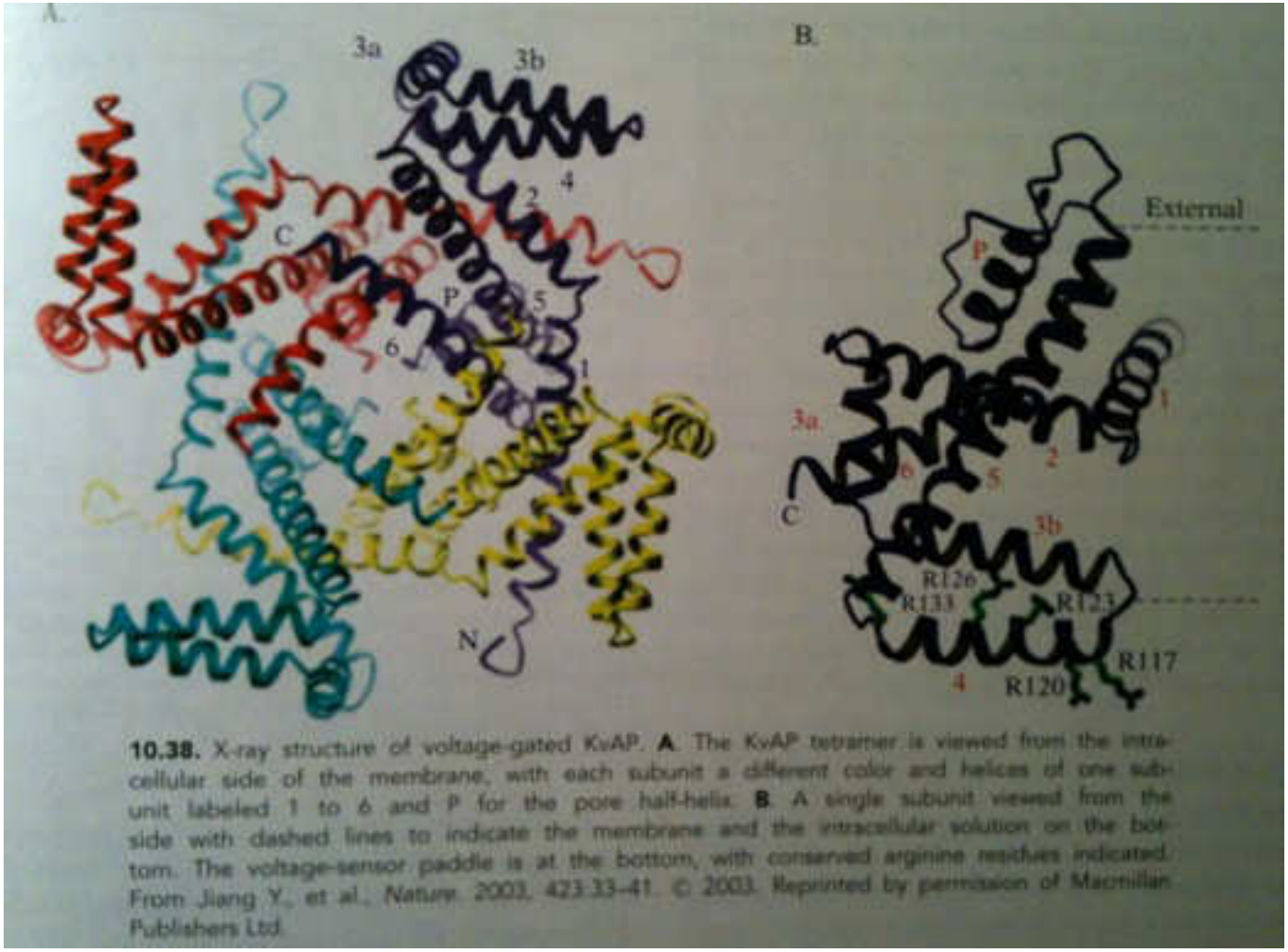


Channel Selectivity Filter



High-resolution structures can illustrate mechanistic details, such as the ion conduction pore of the KcsA potassium channel exposed in a cutaway view of two of its four subunits to reveal the positions of the pore-forming helix (red) and the selectivity filter (gold). The extracellular side is at the top. From MacKinnon, R., *FEBS Lett.* 2003, 555:62–65.

Channel: Voltage-sensor Paddel

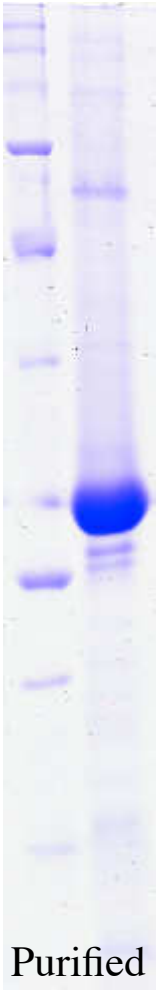


10.38. X-ray structure of voltage-gated KvAP. **A**. The KvAP tetramer is viewed from the intracellular side of the membrane, with each subunit a different color and helices of one subunit labeled 1 to 6 and P for the pore half-helix. **B**. A single subunit viewed from the side with dashed lines to indicate the membrane and the intracellular solution on the bottom. The voltage-sensor paddle is at the bottom, with conserved arginine residues indicated. From Jiang Y., et al., *Nature*, 2003, 423:33-41. © 2003. Reprinted by permission of Macmillan Publishers Ltd.

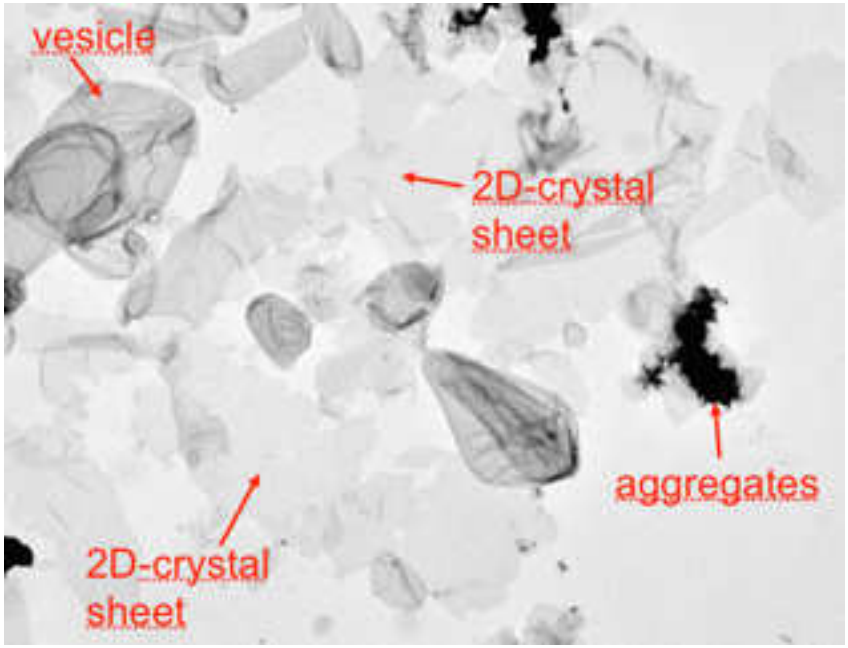
2D crystals of Voltage Gaited Channel

3D structure of Channel in 2 Dimensional crystals obtained by cryo-EM

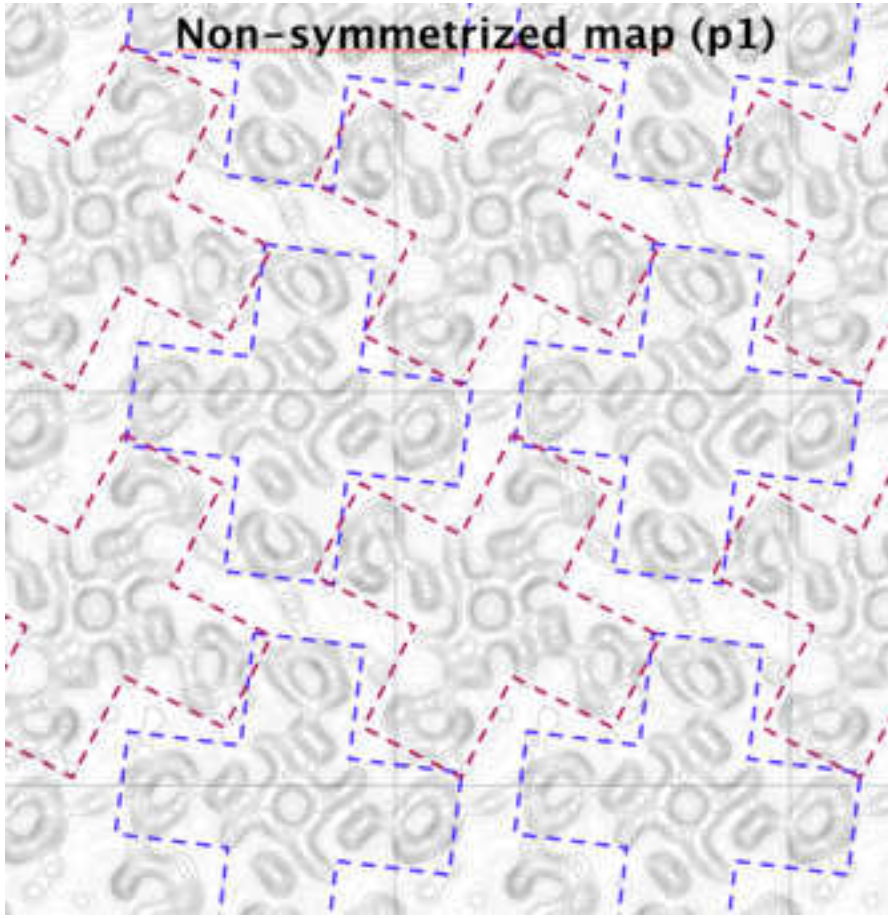
Prepared in the Biomolecular Research Laboratory at PSI
by Ching Ju Tsai with Xiao Dan Li propject start 2010



Purified channel

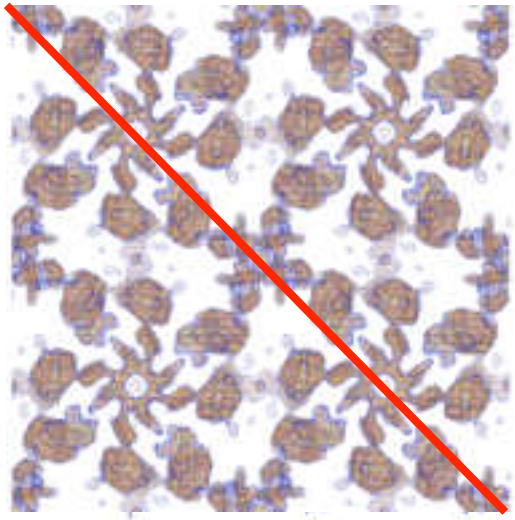


Suspension of 2D crystal on carbon film

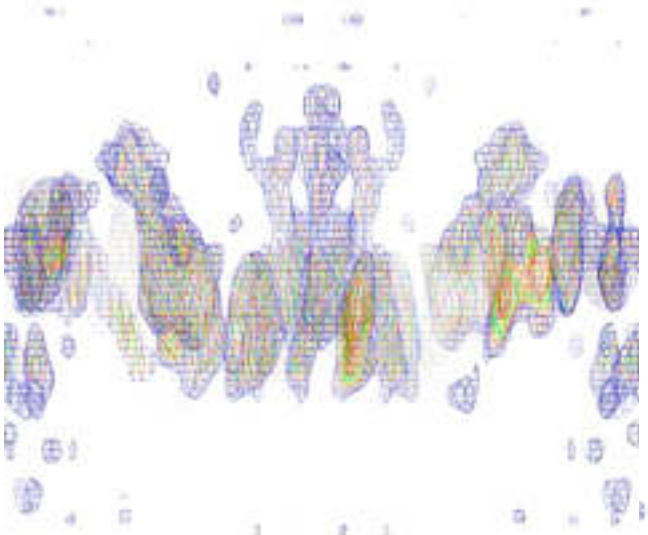


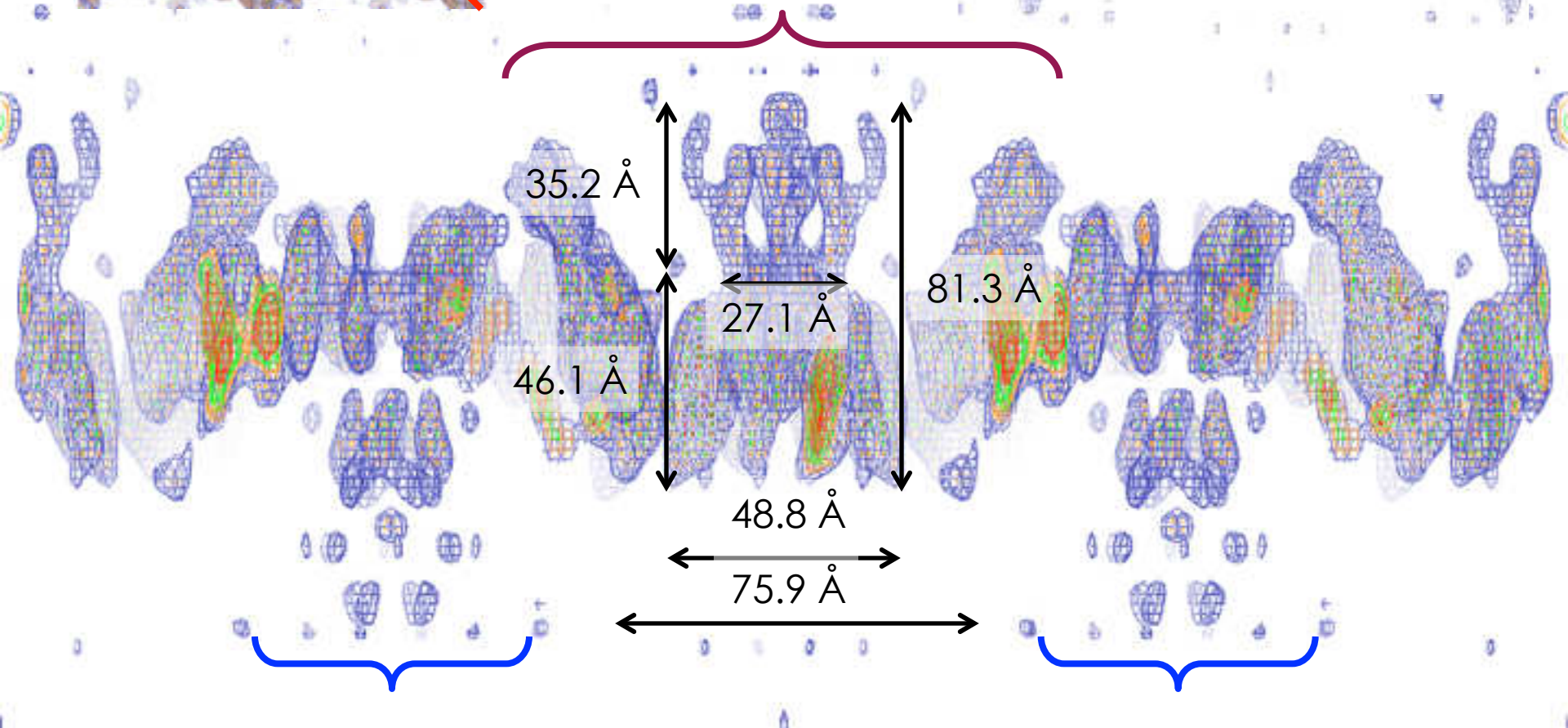
Cryo-EM projection structure of 2D crystal

3D structure of Channel



115 A

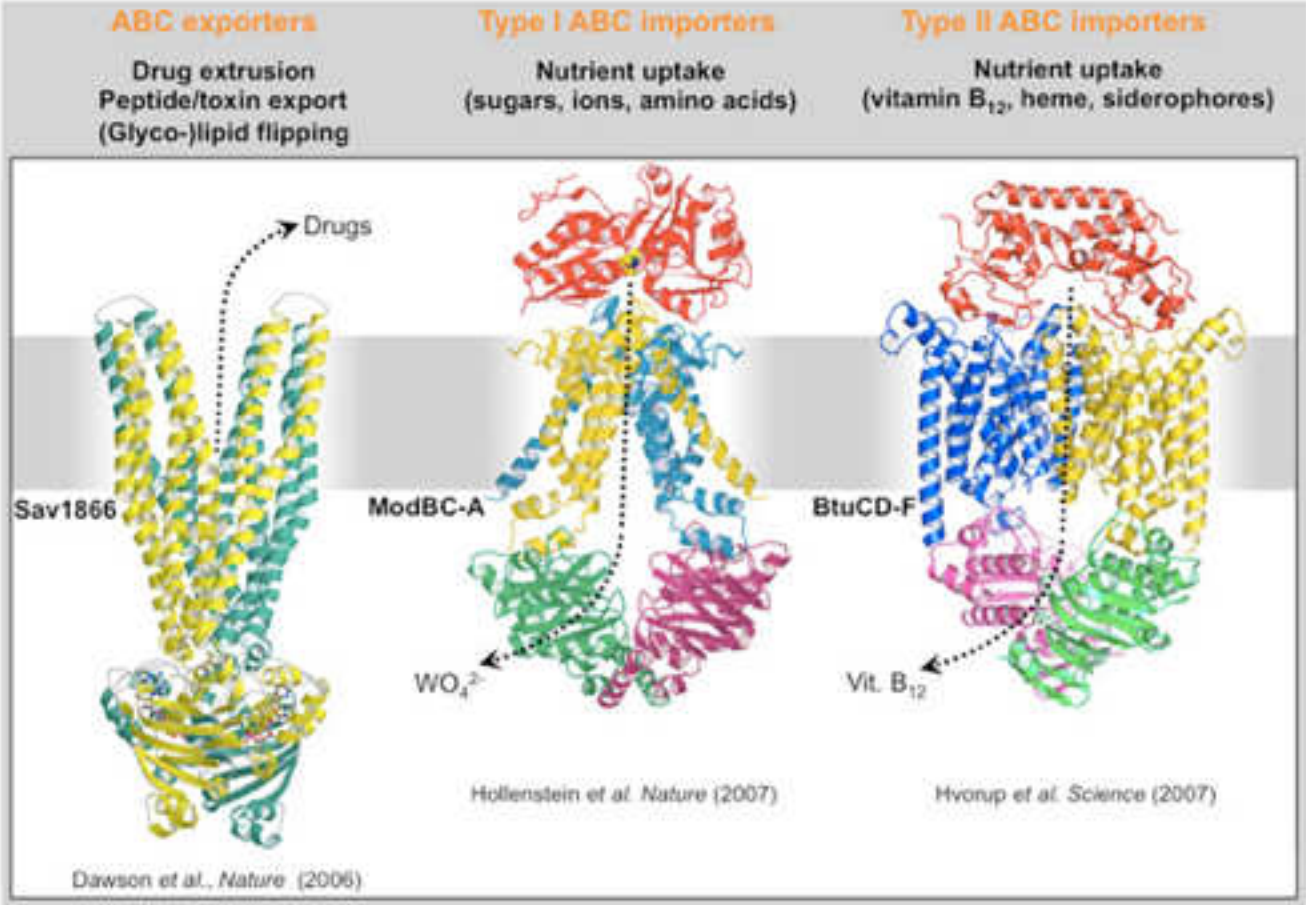




Transporter

ABC transporters

ATP-binding cassette (ABC) transporters hydrolyze ATP to drive the translocation of substrates across membranes. **ABC importers** are expressed in bacteria (including pathogens), where they facilitate the uptake of essential nutrients. **ABC exporters** are ubiquitous and catalyze the extrusion of diverse substrates, including drugs, lipids, cofactors, hormones, peptides, and toxins. Some ABC exporters contribute to multidrug resistance of cancer cells or bacterial pathogens, whereas the dysfunction of others has been linked to hereditary diseases. We have determined the first high resolution crystal structures of ABC transporters, revealing distinct protein folds and suggesting basic mechanisms of coupling ATP hydrolysis to substrate translocation. We collaborate with *Enrica Bordignon* in the group of *Gunnar Jeschke* (ETH Zurich) to study intermediate states of the transporters using **electron paramegnetic resonance (EPR) spectroscopy**.

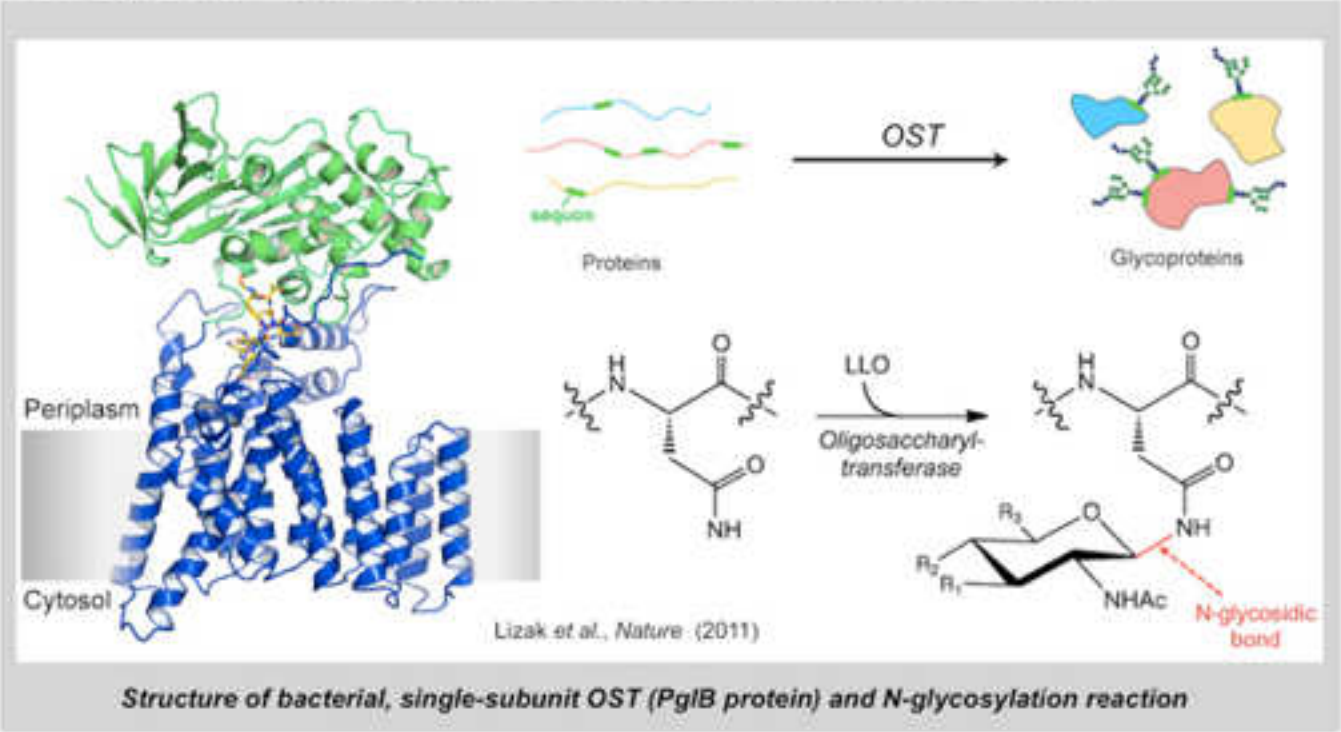


Prototypic ABC transporter structures determined in the Locher lab

Membrane embedded Enzyme

Oligosaccharyltransferase

One of the most abundant post-translational modifications of proteins is ***N-linked glycosylation***, where complex glycans are attached to asparagine residues of proteins secreted into the endoplasmic reticulum (ER) or the periplasmic space of certain bacteria that contain a N-glycosylation machinery. The central enzyme catalyzing the reaction is **oligosaccharyltransferase (OST),** an integral membrane protein that recognizes glycosylation sequons **(N-X-S/T)** and transfers the glycan moiety from a lipid-linked donor (LLO) onto the acceptor asparagine. Several diseases are associated with the dysfunction of this process.
In collaboration with the group of *Markus Aebi* (ETH Zurich), we study the reaction mechanism of N-linked glycosylation at the molecular and chemical level. In 2011, we have determined the first structure of a complete OST, the PglB protein from the bacterium *Campylobacter lari*. This allows us to study the structure and function of OST-catalyzed protein N-glycosylation using a variety of biochemical, chemical, biophysical, and structural techniques. In collaboration with the group of *Jean-Louis Reymond* (University of Bern), we are also engaged in the development of inhibitors of bacterial OST that could be the basis of novel antibiotics.

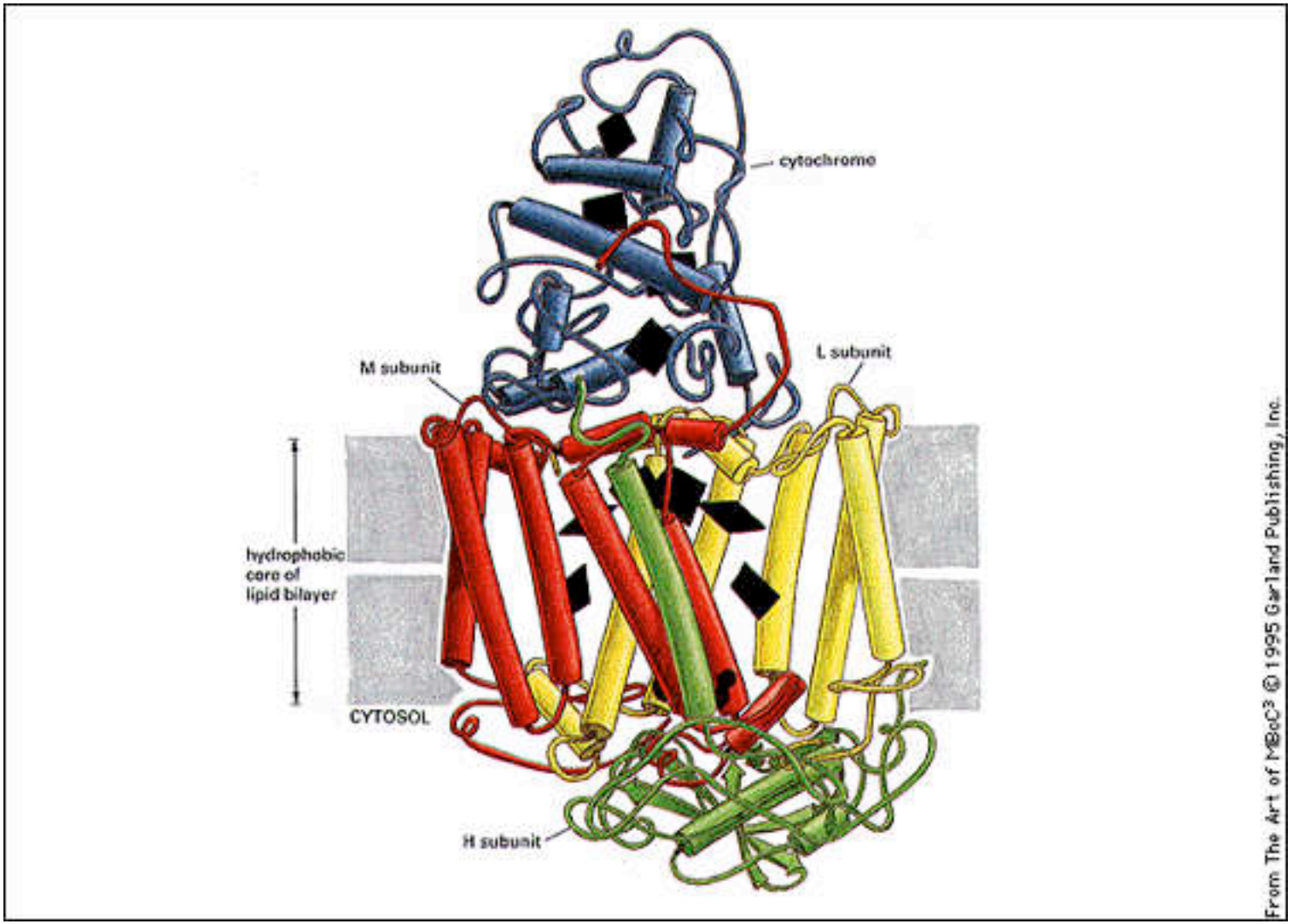


Structure of bacterial, single-subunit OST (PglB protein) and N-glycosylation reaction

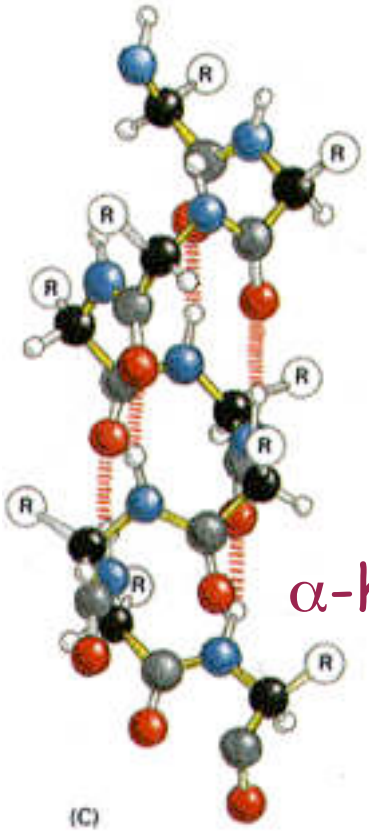
• Lizak C, Gerber S, Numao S, Aebi M, Locher KP. X-ray structure of a bacterial oligosaccharyltransferase. ***Nature*** 474: 350-355 (2011).

Photosynthetic reaction center

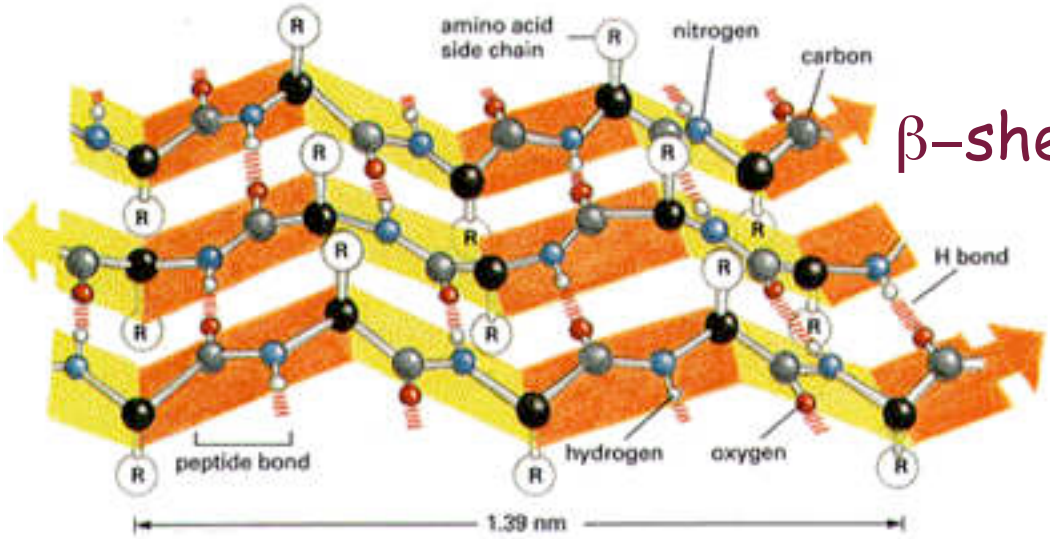
Rhodopseudomonas viridis Four subunits; and numerous hemes



Why restricted secondary structures in the membrane?



α-helix



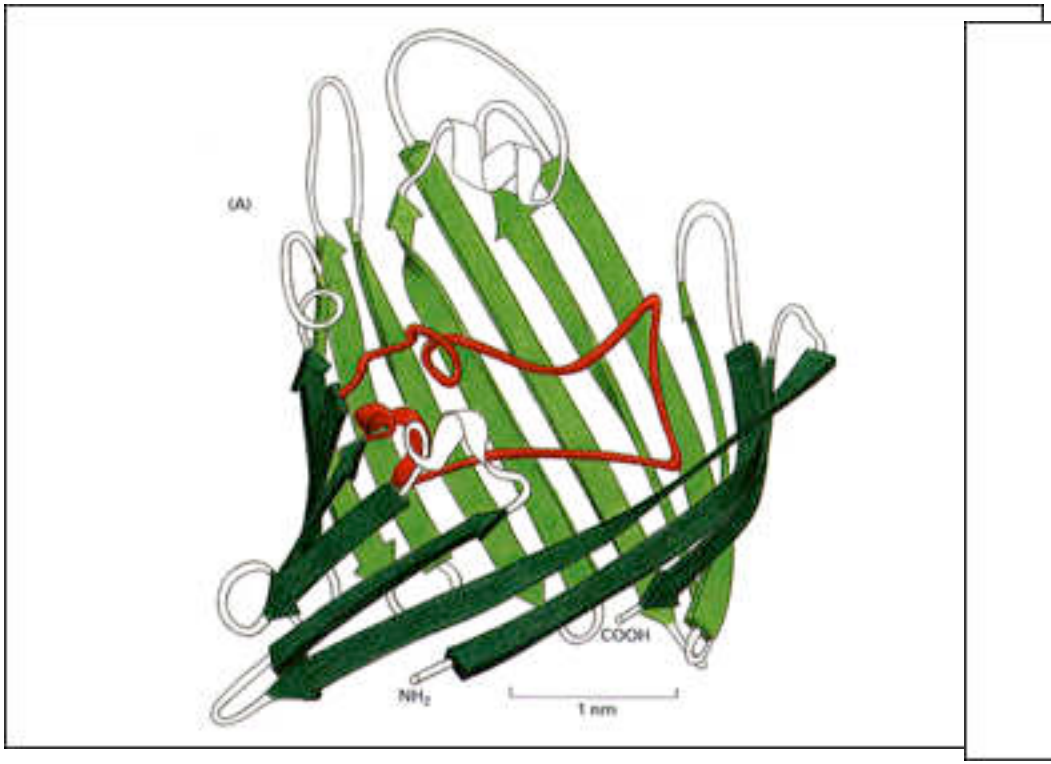
β–sheets

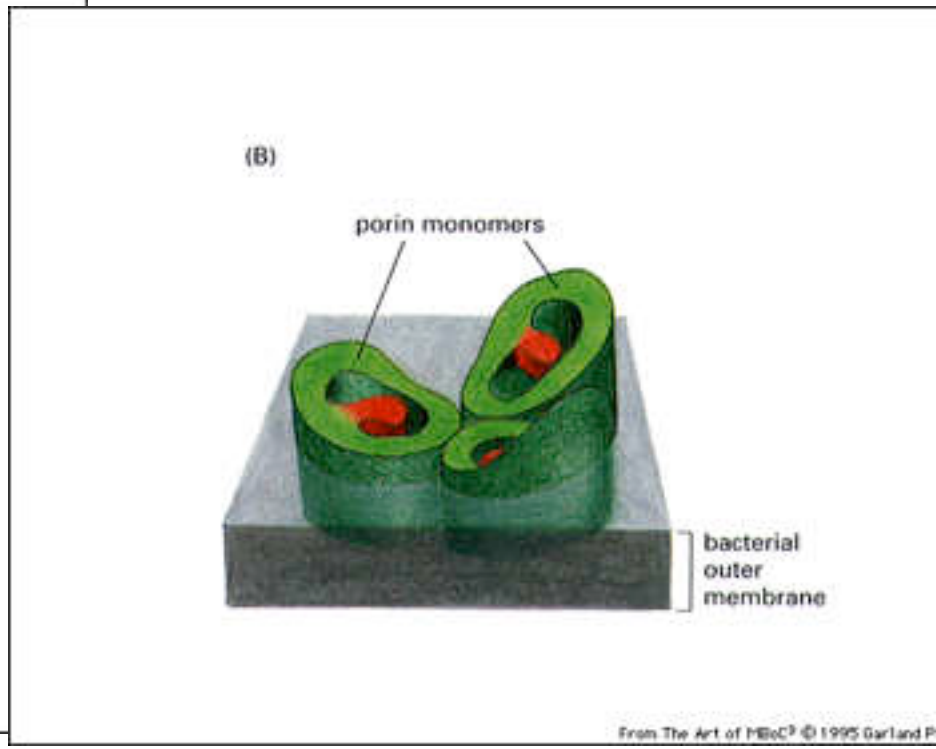
α-helices and β–sheets allow all main chain -NH- and =CO groups to form hydrogen bonds in the absence of water. These secondary structures are therefore energetically favoured.

Note the positions of the amino acid side chains; they alternate from one side to the other of the beta-sheet

Example 3: Porin in gram negative bacterial outer membrane

Anti parallel beta-barrel, homotrimer





Extended Beta Sheet

Alpha-toxin of Staphylococcus Aureus

Soluble protein that can heptamerize and insert into bilayers as a beta barrel, and thus create a channel

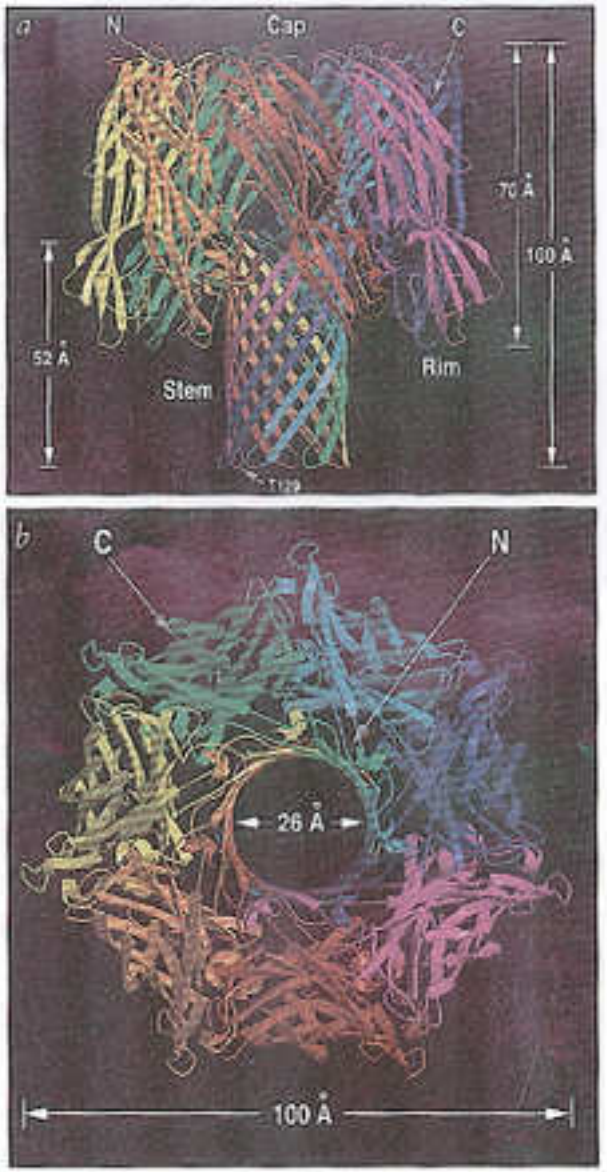
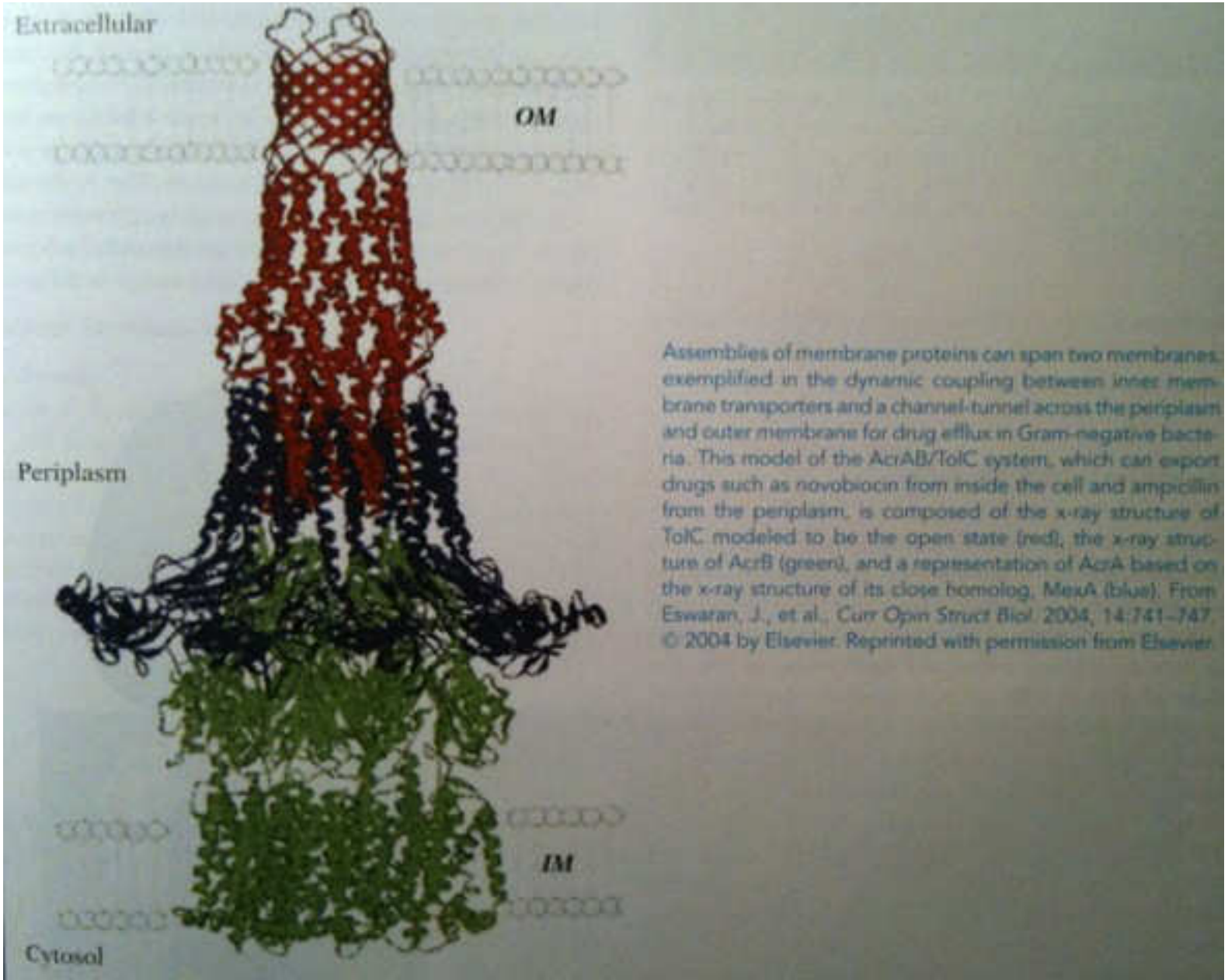


Fig. 2 Ribbon representations of the α-haemolysin heptamer, in which each protomer has been coloured differently. a, View perpendicular to the molecular seven-fold axis and presumably parallel to the membrane plane. b, View from the top of the molecule along the seven-fold axis. The diameter of the transmembrane 'stem' is 26 Å from Cα to Cα. (Figure reproduced from ref. 2 with

Drug Efflux System



Assemblies of membrane proteins can span two membranes, exemplified in the dynamic coupling between inner membrane transporters and a channel-tunnel across the periplasm and outer membrane for drug efflux in Gram-negative bacteria. This model of the AcrAB/TolC system, which can export drugs such as novobiocin from inside the cell and ampicillin from the periplasm, is composed of the x-ray structure of TolC modeled to be the open state (red), the x-ray structure of AcrB (green), and a representation of AcrA based on the x-ray structure of its close homolog, MexA (blue). From Eswaran, J., et al., *Curr Opin Struct Biol* 2004, 14:741–747.

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Host-Pathogen Interactions
Elaine Fuchs
Stem Cells
Cynthia Kenyon
Mechanisms of Aging
Chaitan Khosla
Polyketide Biosynthesis
Satyajit Mayor
Lipid Rafts
John McKinney
Tuberculosis
Toto Olivera
Cone Snail Toxins and Medicine
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Molecular Motors and Mitosis
Xiaodong Wang
Apoptosis

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Toxoplasma, Parasite Evolution, and Bioinformatics

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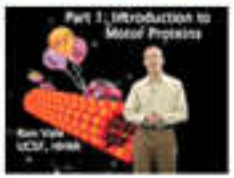
	Satyajit 'Jitu' Mayor	Cellular Organisation and Signalling, National Centre for Biological Sciences, Bangalore, India	Membrane Rafts	05/2007	3 parts / 01:40:13	Biological Mechanisms
	Dick McIntosh	Department: Molecular, Cellular, and Developmental Biology, University of Colorado Boulder	Separating Duplicated Chromosomes in Preparation for Cell Division	12/2008	3 parts / 109:60	Biological Mechanisms
	Martin Raff	MRC Laboratory for Molecular Cell Biology	Growth Control in Animal Development	11/2006	2 parts / 01:18:09	Biological Mechanisms
	Randy Schekman	Department of Molecular and Cell Biology, HHMI, University of California, Berkeley	Protein Secretion and Vesicle Traffic	03/2007	3 parts / 01:34:17	Biological Mechanisms
	Julie Theriot	Stanford University, Dept of Biochemistry, Dept of Microbiology & Immunology, Program in Biophysics	Cell Organization & Cell Motility	05/2006	3 parts / 01:59:26	Biological Mechanisms
	Ron Vale	HHMI /Dept of Cellular and Molecular Pharmacology, University of California, San Francisco	Cytoskeletal Motor Proteins	07/2007	3 parts / 01:42:14	Biological Mechanisms
	Bonnie Bassler	Howard Hughes Medical Institute and Princeton University	Cell-Cell Communication in Bacteria	06/2008	2 parts / 01:13:37	Biological Mechanisms