Membrane Biochemistry

Lectures by

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Copies of materials and presentations

- Cell Biology and Developmental Genetics
- Membrane Biochemistry
- Membrane Proteins
- Inaugural lecture
- The Rudi Lemberg Lectures 2009

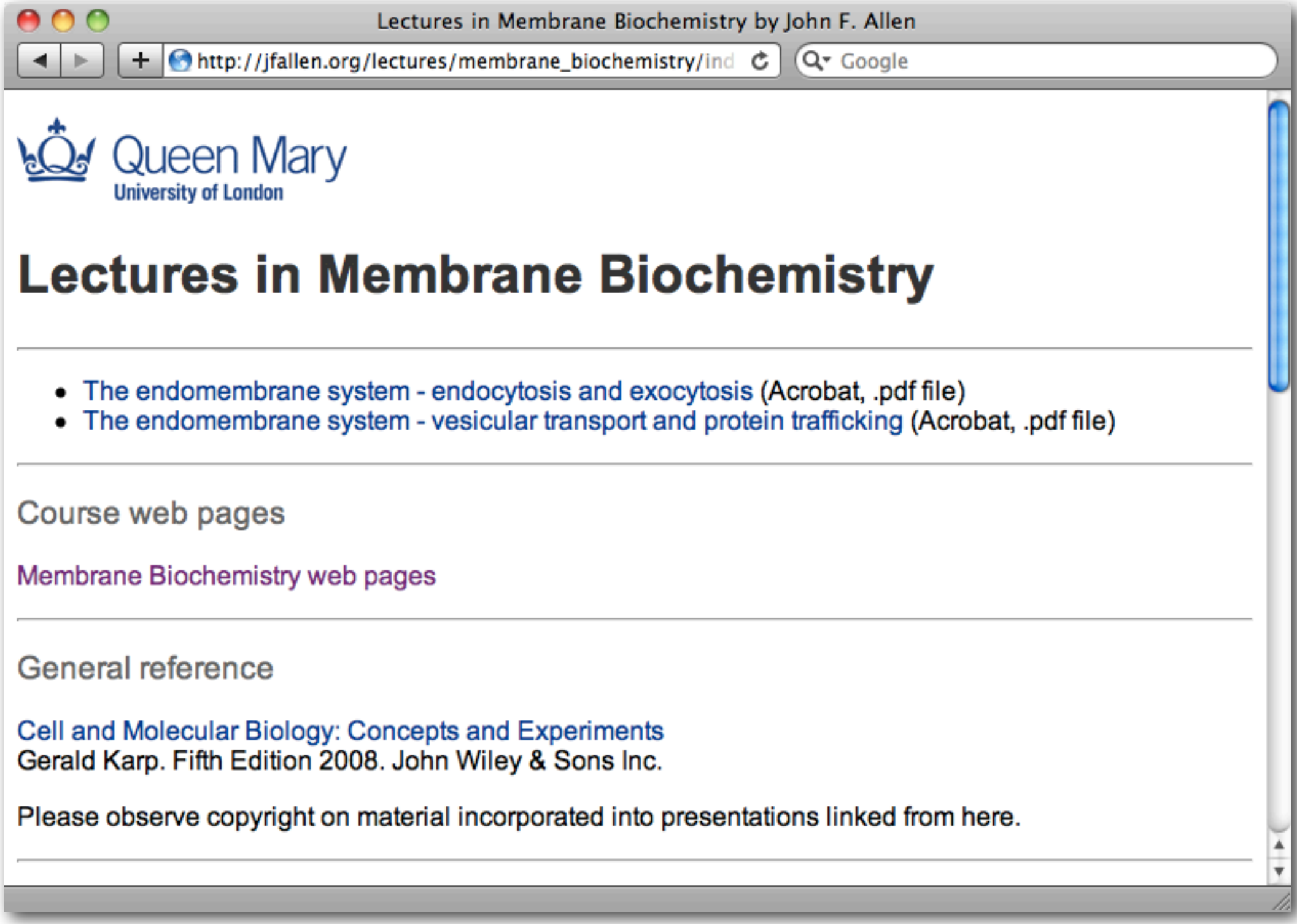
Other lectures

- Biomolecules of Life

Computer application programs, viewers, and readers. From external sites.

- Adobe Reader
- OpenOffice.org
- Quicktime Viewer

John F. Allen web page


Lectures in Membrane Biochemistry by John F. Allen
http://jfallen.org/lectures/membrane_biochemistry/ind
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Lectures in Membrane Biochemistry
The endomembrane system - endocytosis and exocytosis (Acrobat, .pdf file)
The endomembrane system - vesicular transport and protein trafficking (Acrobat, .pdf file)
Course web pages
Membrane Biochemistry web pages
General reference
Cell and Molecular Biology: Concepts and Experiments
Gerald Karp. Fifth Edition 2008. John Wiley & Sons Inc.
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Animations

- The pump cycle of Na,K-ATPase. By Mark Hilge at Protein Biophysics, Nijmegen
- Animation. From Light to ATP. By O. Fritsche and W. Junge, University of Osnabruck. (.avi file, 17.7 mb)
- Molecular animations of ATP synthase. From the research group of John Walker at the MRC Mitochondrial Biology Unit, Cambridge
- Animation. Powering the Cell: Mitochondria. From BioVisions at Harvard University

Relevant Nobel prizes

- 1906 Nobel Prize in Physiology or Medicine to Camillo Golgi and Santiago Ramón y Cajal
- 1974 Nobel Prize in Physiology or Medicine to Albert Claude, Christian de Duve and George E. Palade
- 1978 Nobel Prize in Chemistry to Peter Mitchell
- 1988 Nobel Prize in Chemistry to Johann Deisenhofer, Robert Huber and Hartmut Michel
- 1997 Nobel Prize in Chemistry to Paul D. Boyer, John E. Walker and Jens C. Skou
- 1999 Nobel Prize in Physiology or Medicine to Günter Blobel

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Lectures | Membrane Biochemistry | Membrane Proteins | Cell Biology and Developmental Genetics | Inaugural Lecture | Rudi Lemberg Lectures

Membrane Transport

Transport across biological membranes

- Transport of proteins
- Transport of ions
- Transport of small molecules

Membrane Transport

Transport across biological membranes

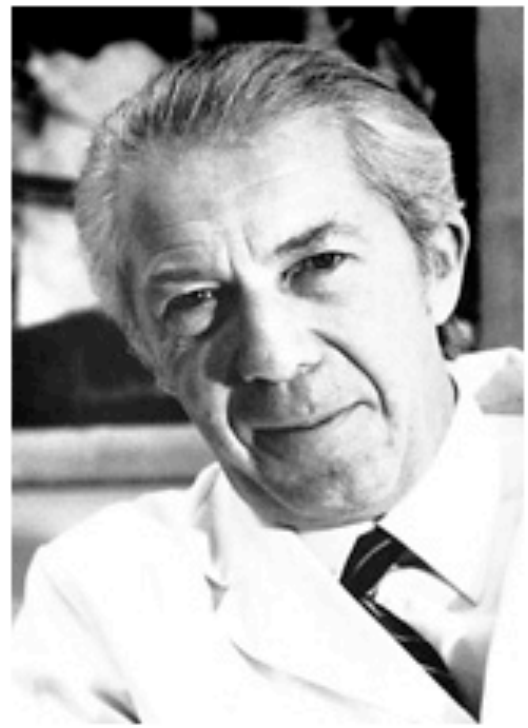
Transport of proteins

- Co-translational
- Post-translational

The Nobel Prize in Physiology or Medicine 1974

Albert Claude, Christian de Duve, George E. Palade

Albert Claude

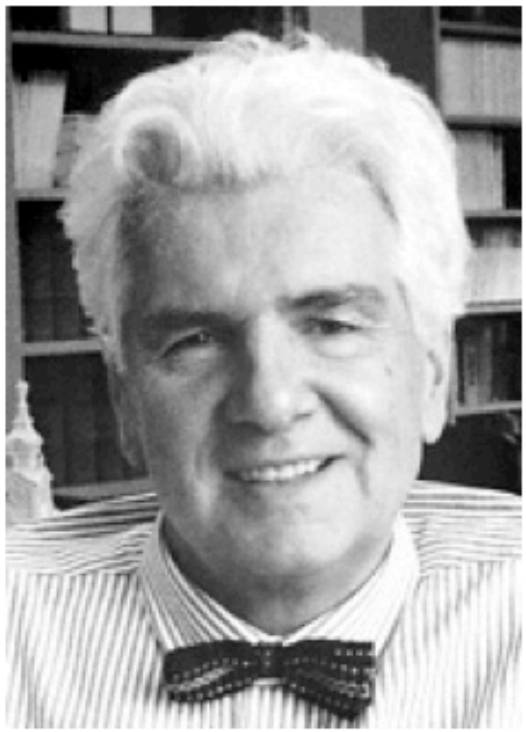


Christian de Duve

George E. Palade

The Nobel Prize in Physiology or Medicine 1974 was awarded jointly to Albert Claude, Christian de Duve and George E. Palade *"for their discoveries concerning the structural and functional organization of the cell"*.

The Nobel Prize in Physiology or Medicine 1999
Günter Blobel



Günter Blobel, born May 21, 1936 in Waltersdorf/Silesia, Germany

Address:
Laboratory of Cell Biology, The Rockefeller University, Howard Hughes Medical Institute, 1230 York Avenue, New York, N.Y. 10021, USA

Günter Blobel

The Nobel Prize in Physiology or Medicine 1999 was awarded to Günter Blobel *"for the discovery that proteins have intrinsic signals that govern their transport and localization in the cell"*.

"The Nobel Prize in Physiology or Medicine 1999". Nobelprize.org. 30 Oct 2010 http://nobelprize.org/nobel_prizes/medicine/laureates/1999/

Press Release

NOBELFÖRSAMLINGEN KAROLINSKA INSTITUTET
THE NOBEL ASSEMBLY AT THE KAROLINSKA INSTITUTE

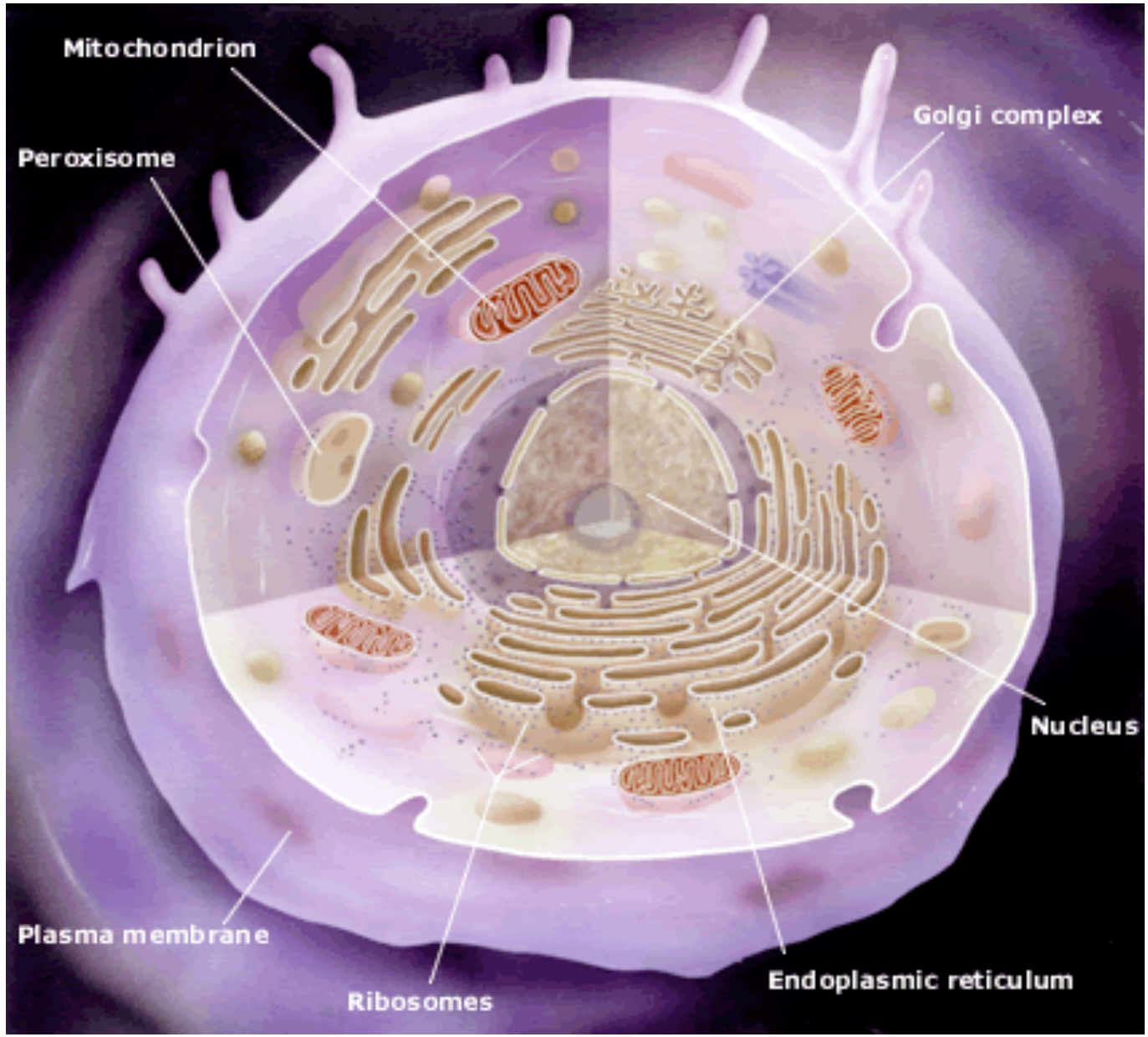
11 October 1999

The Nobel Assembly at Karolinska Institutet has today decided to award the Nobel Prize in Physiology or Medicine for 1999 to

Günter Blobel

for the discovery that **"proteins have intrinsic signals that govern their transport and localization in the cell"**

"Physiology or Medicine for 1999 - Press Release". Nobelprize.org. 30 Oct 2010
http://nobelprize.org/nobel_prizes/medicine/laureates/1999/press.html



All living organisms are made up of cells. The eukaryotic cell contains a number of different types of organelles each of which is surrounded by a tightly sealed membrane.

"Illustrated Information". Nobelprize.org. 30 Oct 2010
http://nobelprize.org/nobel_prizes/medicine/laureates/1999/illpres/illpres.html

"The signal hypothesis"

Günter Blobel's research was built on the traditions of Palade´s laboratory. In particular, Blobel studied how a newly made protein, destined to become transported out of the cell, is targeted to a specialized intracellular membrane system, the endoplasmic reticulum. In 1971 he formulated a first version of the "signal hypothesis". He postulated that proteins secreted out of the cell contain an intrinsic signal that governs them to and across membranes.

Based on elegant biochemical experiments, Blobel described in 1975 the various steps in these processes. The signal consists of a peptide, i.e. a sequence of amino acids in a particular order that form an integral part of the protein. He also suggested that the protein traverses the membrane of the endoplasmic reticulum through a channel (Fig. 1). During the next twenty years, Blobel and coworkers step by step characterized the molecular details of these processes. Eventually it was shown that the signal hypothesis was both correct and universal, since the processes operate in the same way in yeast, plant, and animal cells.

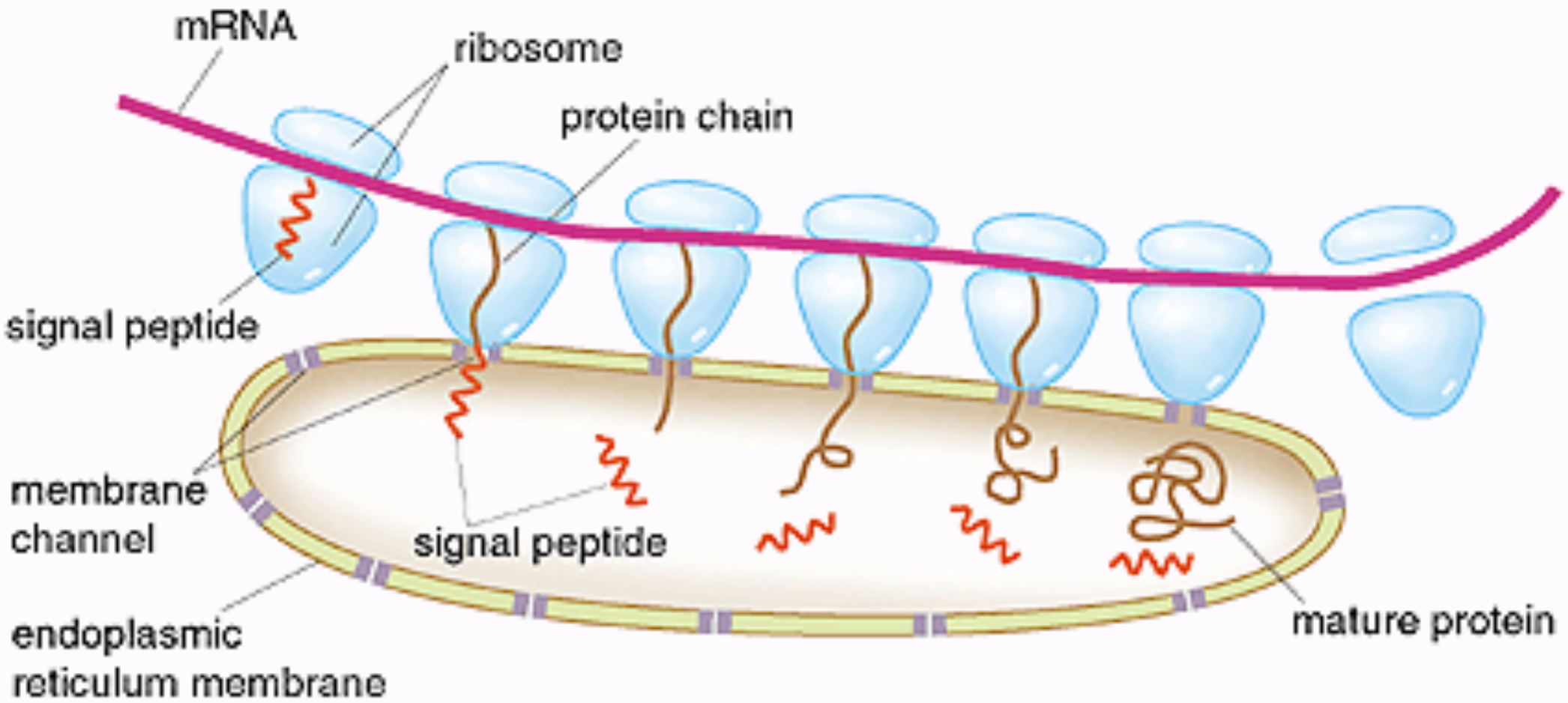


Fig. 1. "The signal hypothesis". Proteins which are to be exported out of the cell are synthesized by ribosomes, associated with the endoplasmic reticulum. The genetic information from DNA is transferred via messenger RNA (mRNA). This information determines how the amino acids build up the proteins. First, a signal peptide is formed as a part of the protein. With the help of binding proteins, the signal peptide directs the ribosome to a channel in the endoplasmic reticulum. The growing protein chain penetrates the channel, the signal peptide is cleaved, and the completed protein is released into the lumen of the endoplasmic reticulum. The protein is subsequently transported out of the cell.

"Address tags" for organelle localization

In collaboration with other research groups, Günter Blobel was soon able to show that similar intrinsic signals target the transport of proteins also to other intracellular organelles. On the basis of his results, Günter Blobel formulated in 1980 general principles for the sorting and targeting of proteins to particular cell compartments. Each protein carries in its structure the information needed to specify its proper location in the cell. Specific amino acid sequences (topogenic signals) determine whether a protein will pass through a membrane into a particular organelle, become integrated into the membrane, or be exported out of the cell.

A range of signals that govern proteins to the different parts of the cell have now been identified (Fig. 2), showing that the principles formulated by Blobel are correct. These signals can be compared to address tags or zip codes which ensure that a traveler's luggage arrives at the correct destination, or a letter reaches its correct addressee. These signal sequences are in fact a chain of different amino acids present either as a short "tail" at one end of the protein, or sometimes located within the protein.

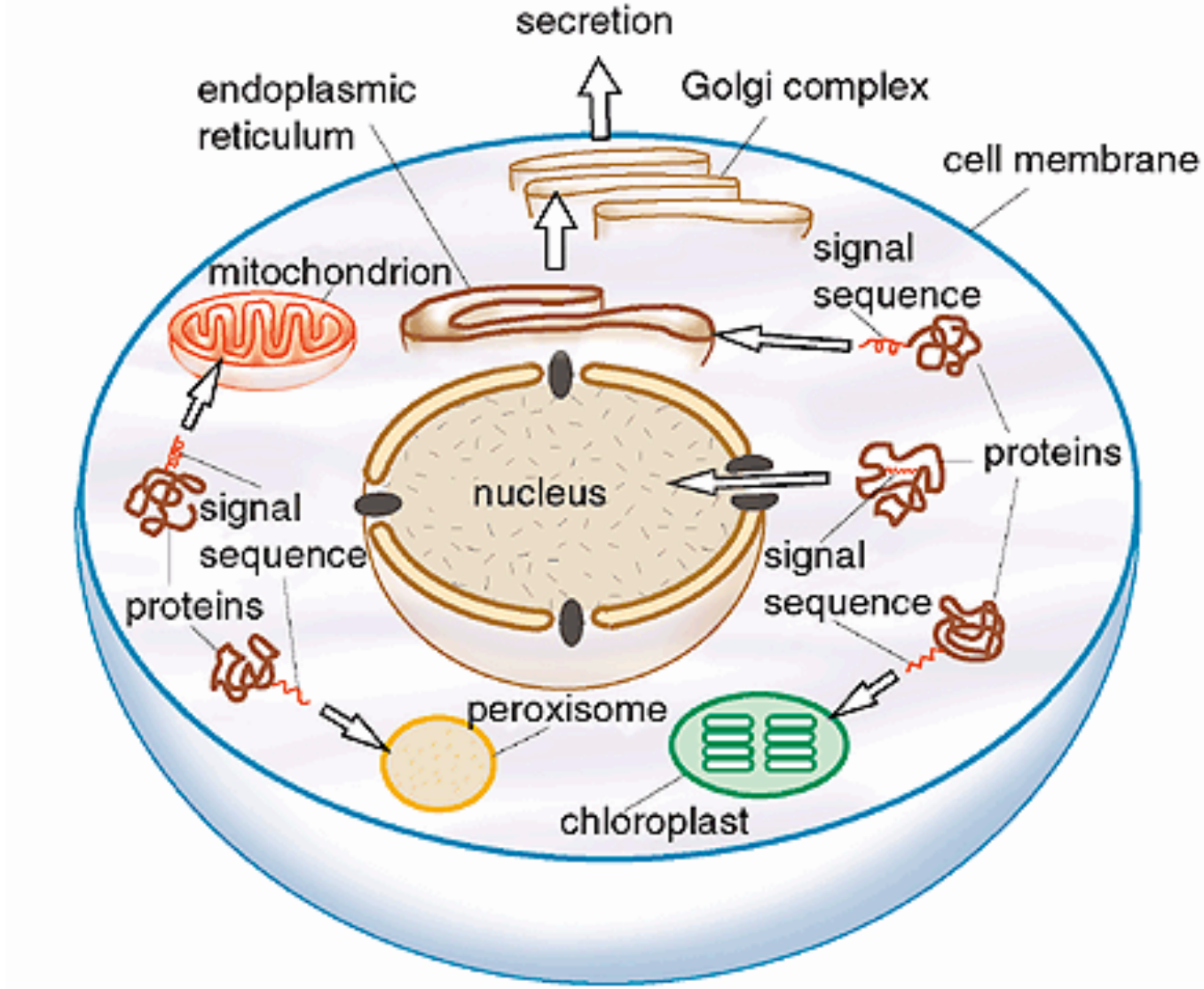
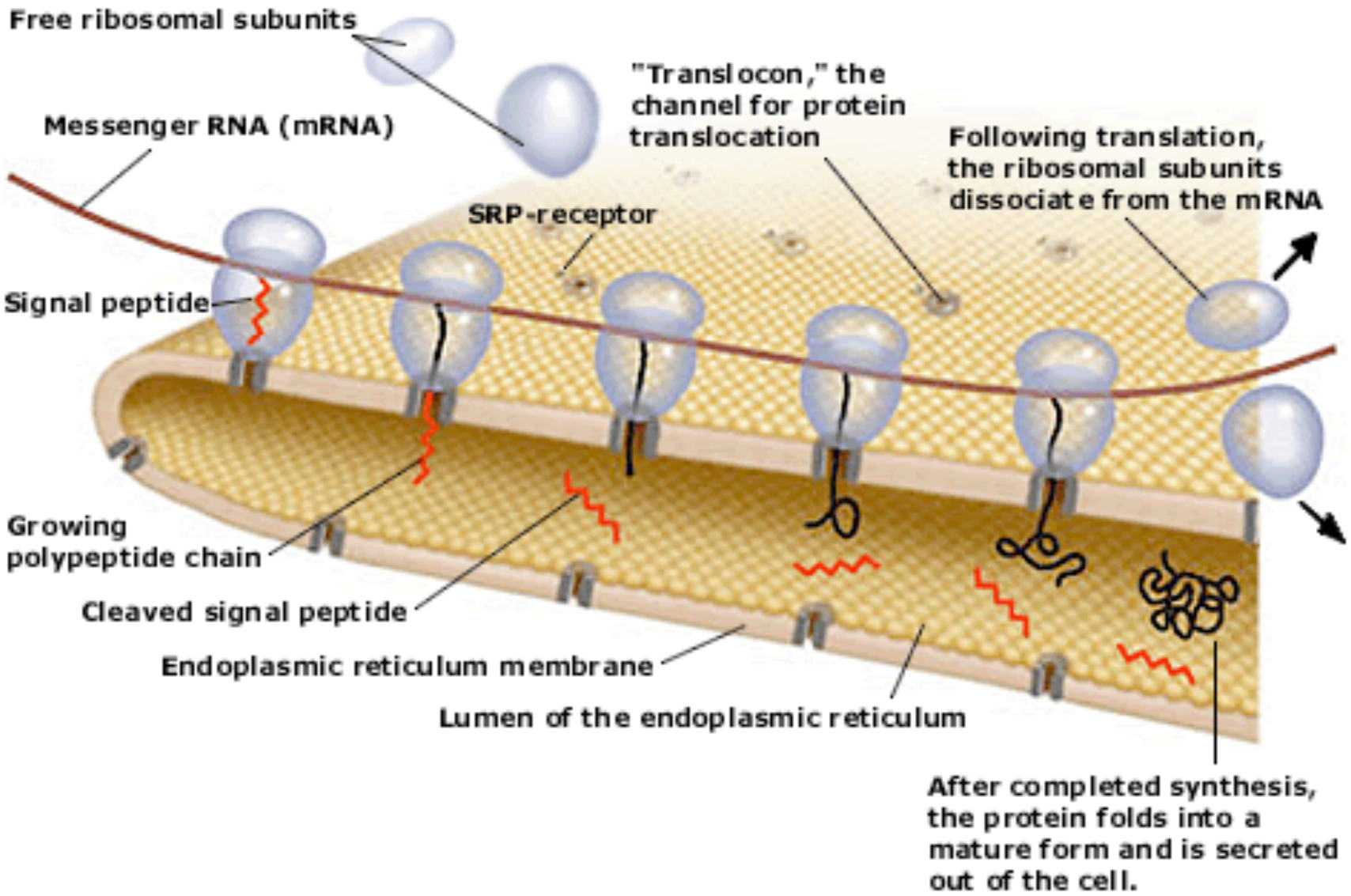


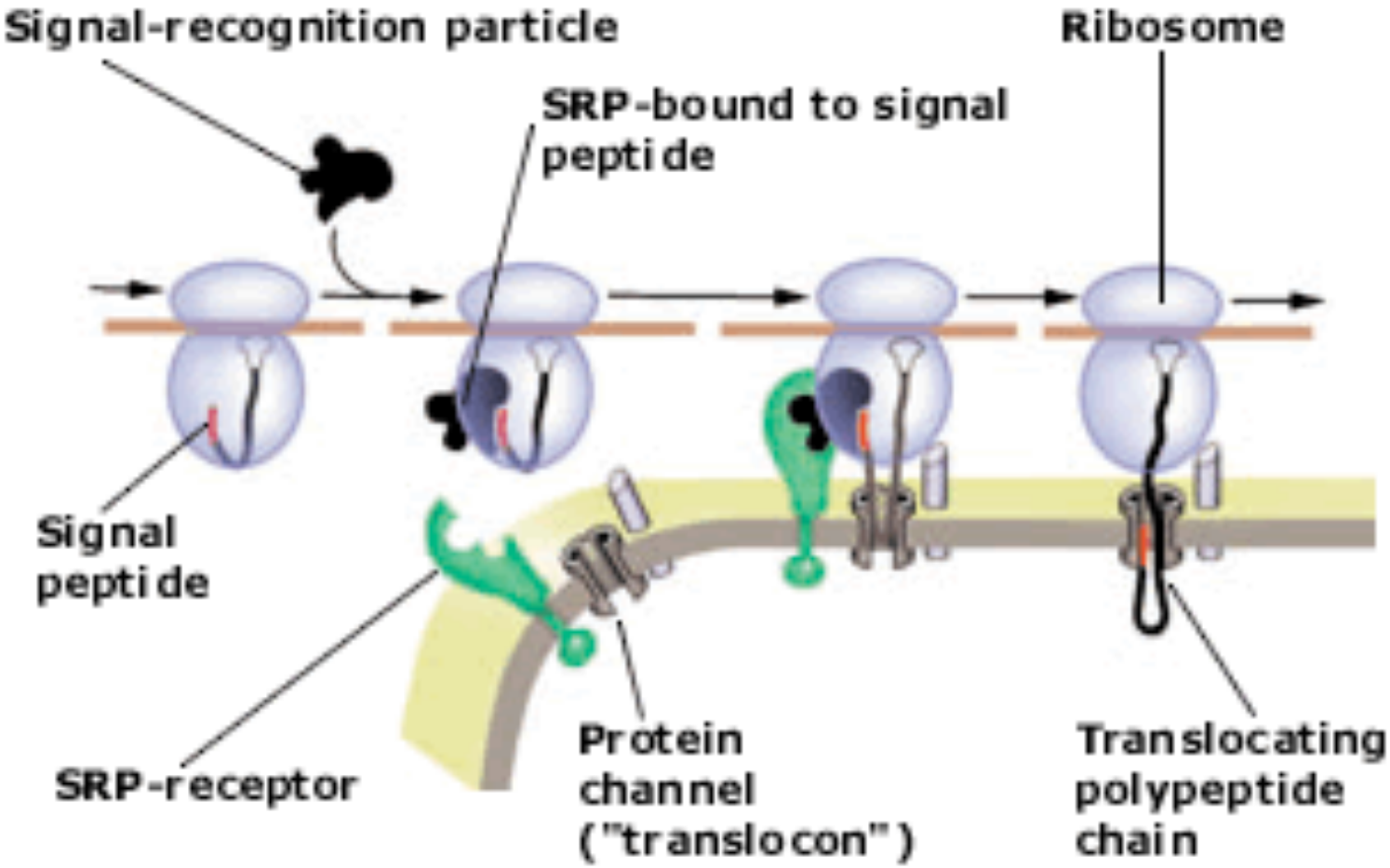
Fig. 2. Examples of directed transport mediated by topogenic signals. The figure shows a schematic cell with some of its compartments, the organelles. (A chloroplast is an organelle that is present in plant cells but not in animal cells). The organelles have special functions and they are surrounded by membranes. Newly synthesized proteins are provided with special "address tags", signal sequences or topogenic signals, which direct the proteins to a correct place within the cell and allow them to cross the membranes of the organelles. The signal itself consists of a chain of amino acids. It is an integral part of the protein, and it is often located at one end of the protein.

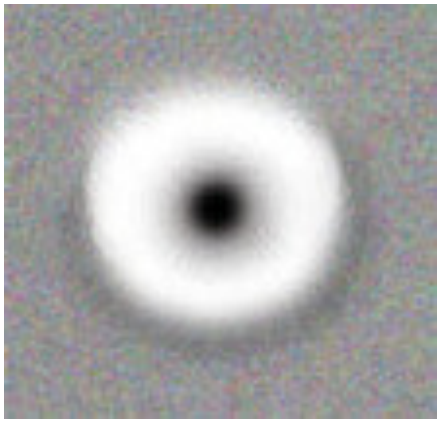
The organization of a cell can be compared to that of a big city such as New York. In order to reach its correct destination, a letter has to be provided with an address label and a zip code, similar to the address tags on proteins.

Protein synthesis

How do newly synthesized proteins find their correct destinations within a cell, and how are they able to pass across the tightly sealed intracellular membranes? These were the central questions that Günter Blobel began to address in the late 1960s. He started by analyzing how newly synthesized secretory proteins are first targeted to and then translocated across the membrane of the endoplasmic reticulum (ER). These two steps are prerequisites for secretion of proteins out of the cell.

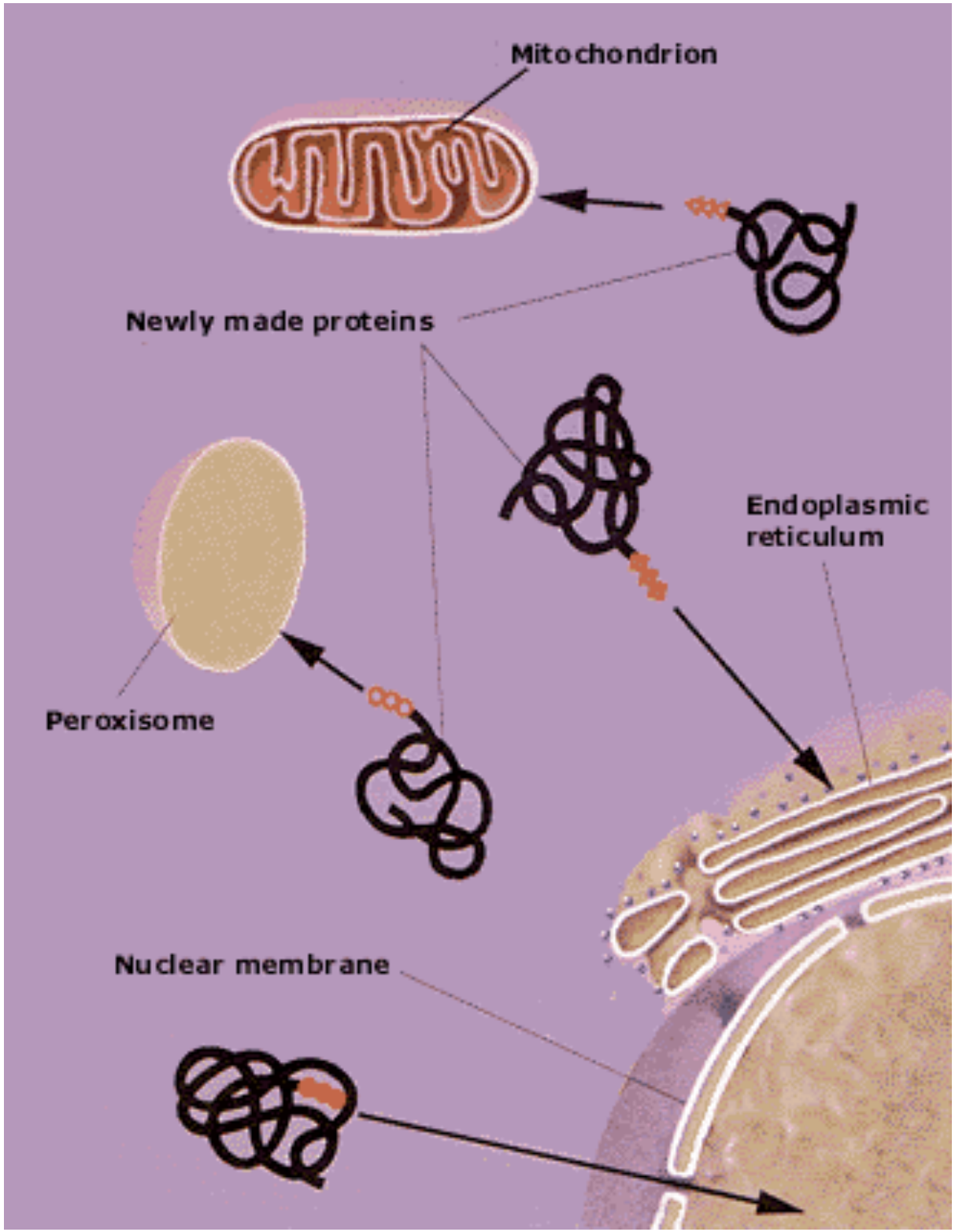






Electron micrograph of the protein translocating channel (the "translocon").

Present view of protein translocation across the ER membrane. The signal peptide, emerging from the ribosome, binds to the signal-recognition particle (SRP). The SRP-ribosome complex then docks to the SRP-receptor and channel ("translocon"). SRP dissociates from the receptor and the nascent polypeptide chain is translocated through the channel into the ER lumen. The signal peptide is finally cleaved and the protein is secreted out of the cell.



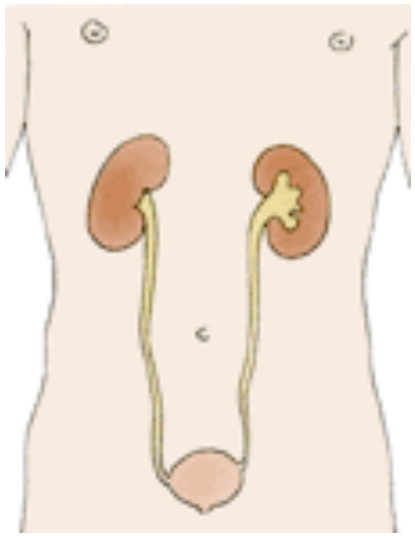
Signal sequences

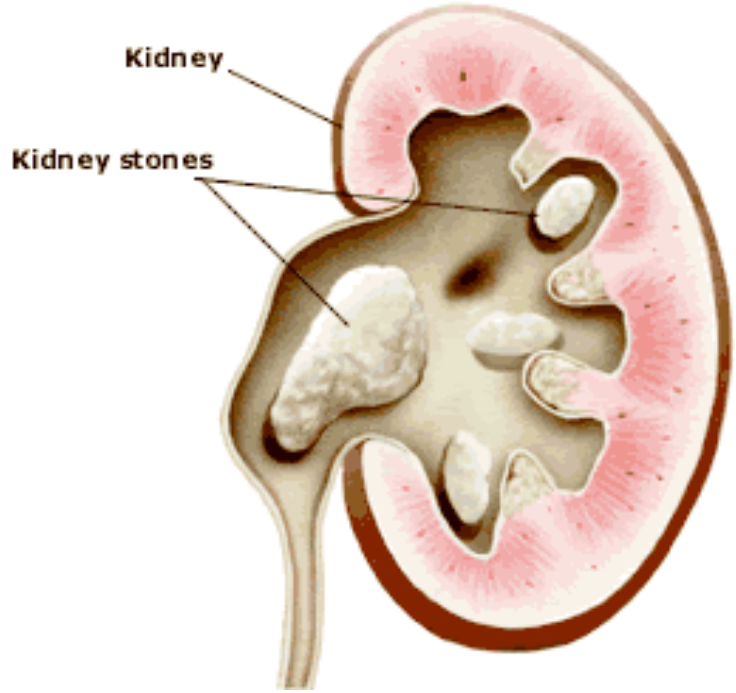
In 1980 Blobel proposed that newly made proteins are targeted to and imported into the various organelles within the cell by built-in signal sequences. The signals are short stretches of amino acids encoded by the gene specifying the protein. They can be located at either end of the protein, or somewhere internally.

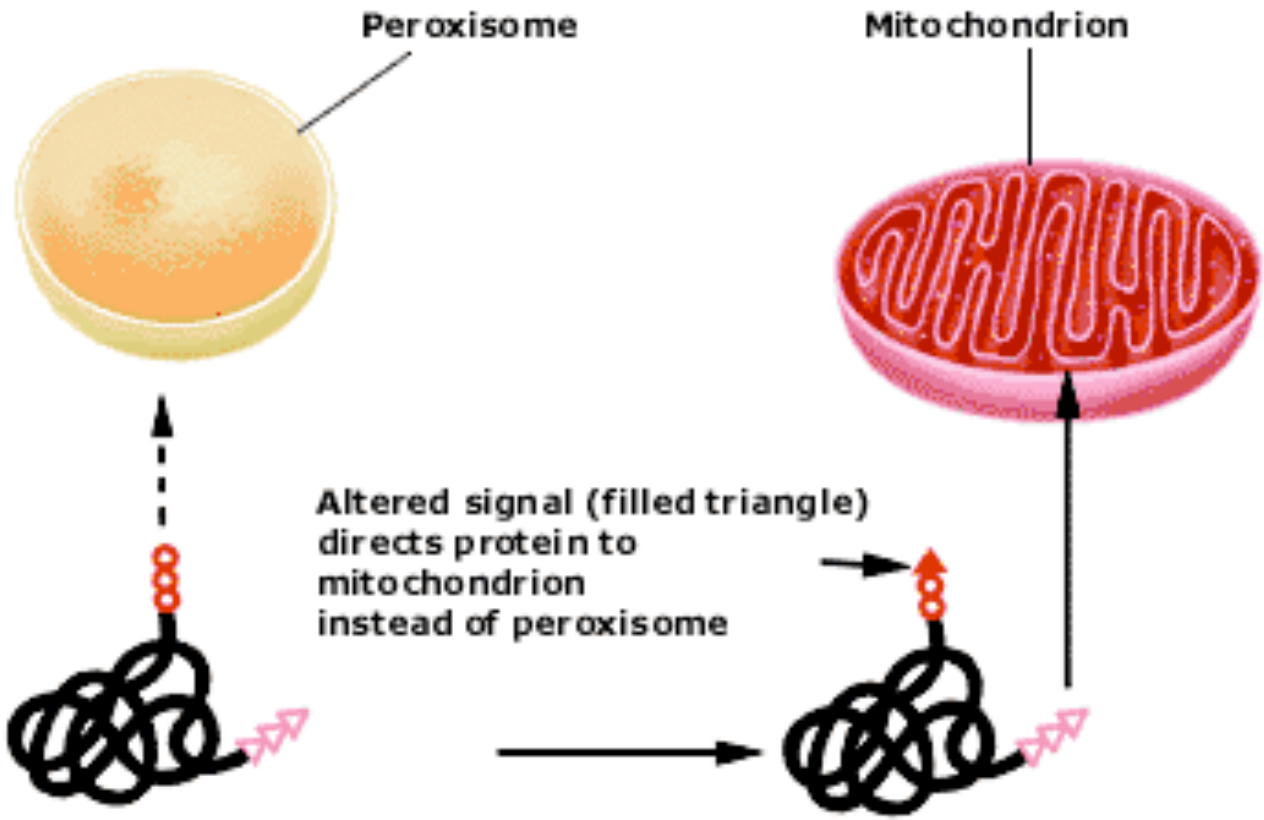
For scale-up production, cells are grown in bioreactors.

Industrial Synthesis

Today many important protein drugs (e.g. growth hormone, erythropoetin, insulin) are produced in living cells. To facilitate easy purification, the proteins are provided with a signal peptide causing them to be secreted out of the cell.







Diseases

In many inherited diseases, proteins are mislocalized in the cell due to errors in targeting signals and transport. One example is "primary hyperoxaluria," a rare disease, which results in kidney stones already at an early age. A signal in the enzyme alanine:glyoxylate aminotransferase normally directs it to the peroxisome. In patients, this signal is altered and the protein is mislocalized to the mitochondrion where it is unable to perform its normal function.

Membrane Transport

Transport across biological membranes

Transport of proteins

Post-translational import of protein precursors into....

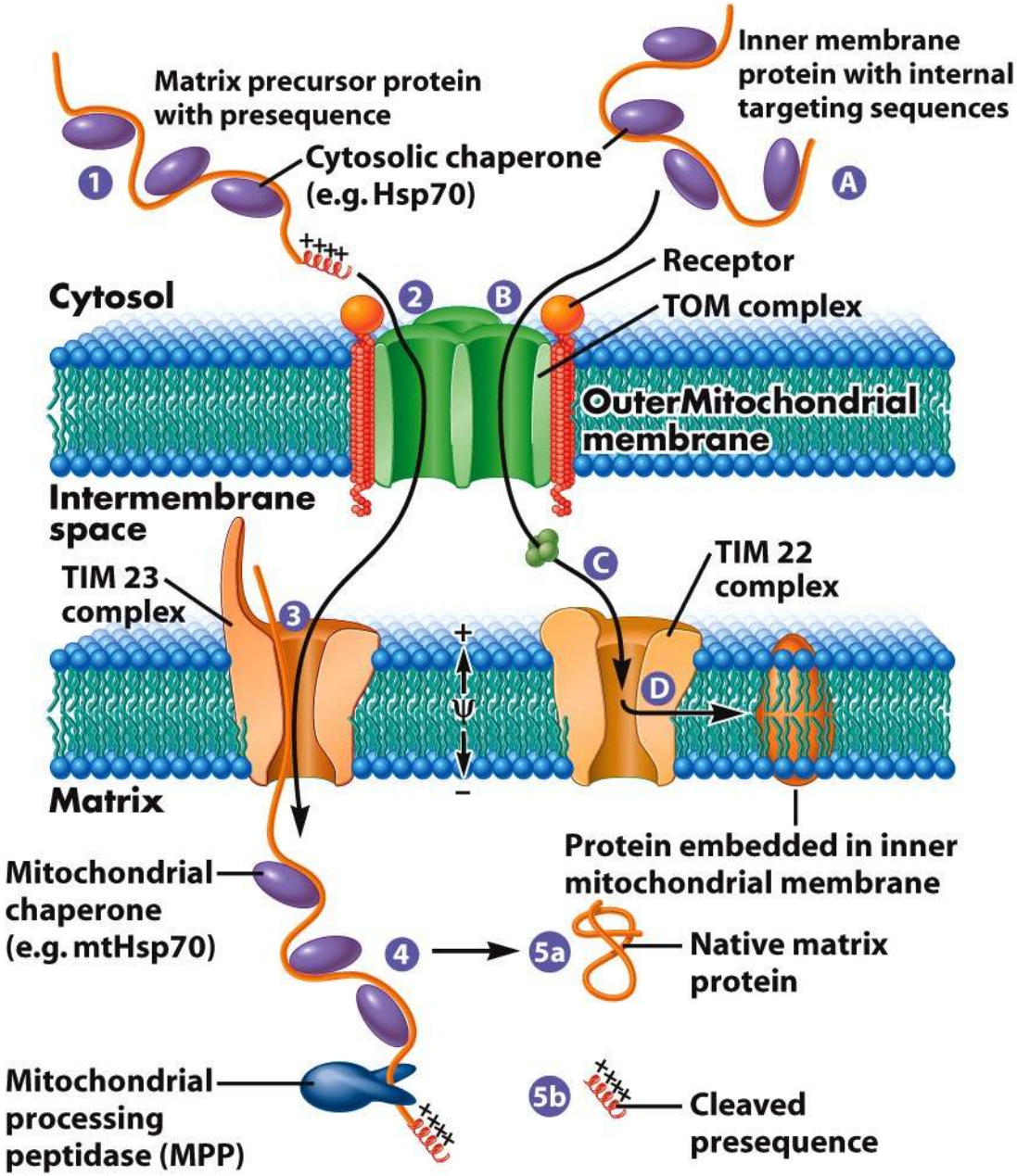
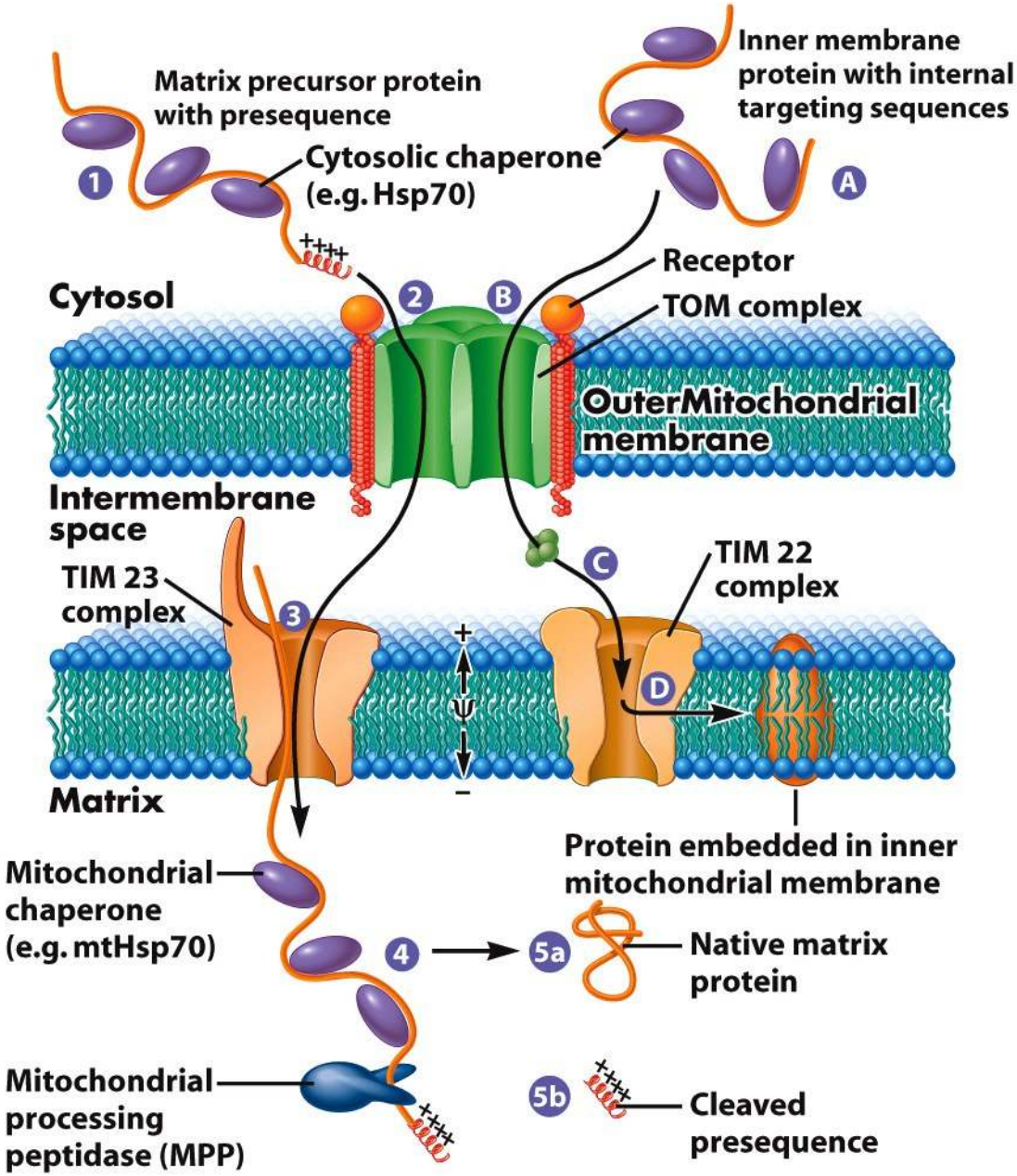


Figure 8-47a Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

Mitochondria

Chloroplasts



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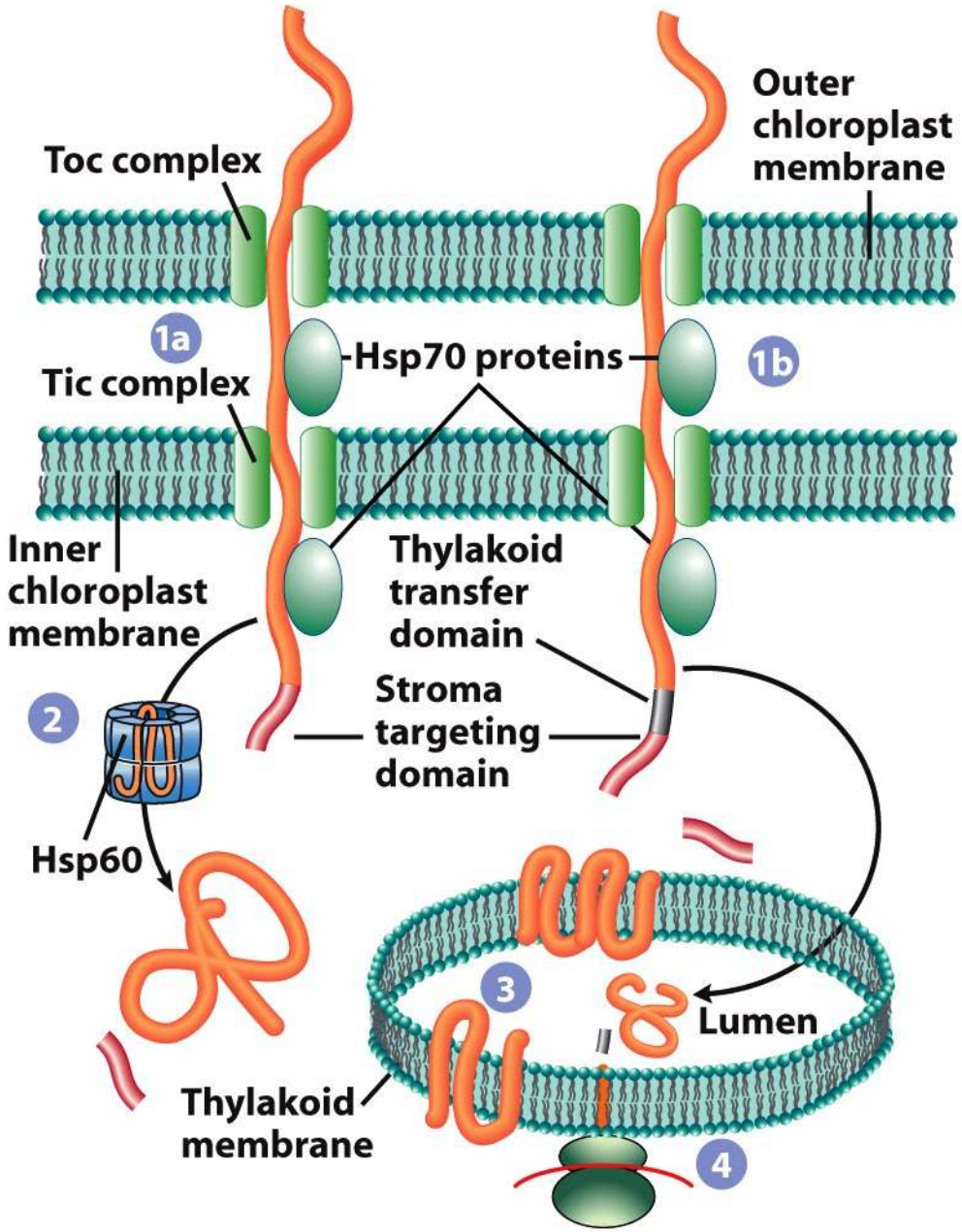
Mitochondria



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Membrane Transport

Transport across biological membranes

Next lecture

- Transport of ions
- Transport of small molecules