

Introduction to Nanotechnology

- Textbook :
Nanophysics and Nanotechnology
by:
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Classroom: A209
Time: Thursday; 13:40-16:30 PM
Office hour: Thur., 10:00-11:30 AM or by appointment

Objective of the course

The course, Introduction to Nanotechnology (IN), will focus on understanding of the basic molecular structure principals of Nano-materials. It will address the molecular structures of various materials. The long term goal of this course is to teach molecular design of materials for a broad range of applications. A brief history of biological materials and its future perspective as well as its impact to the society will be also discussed.

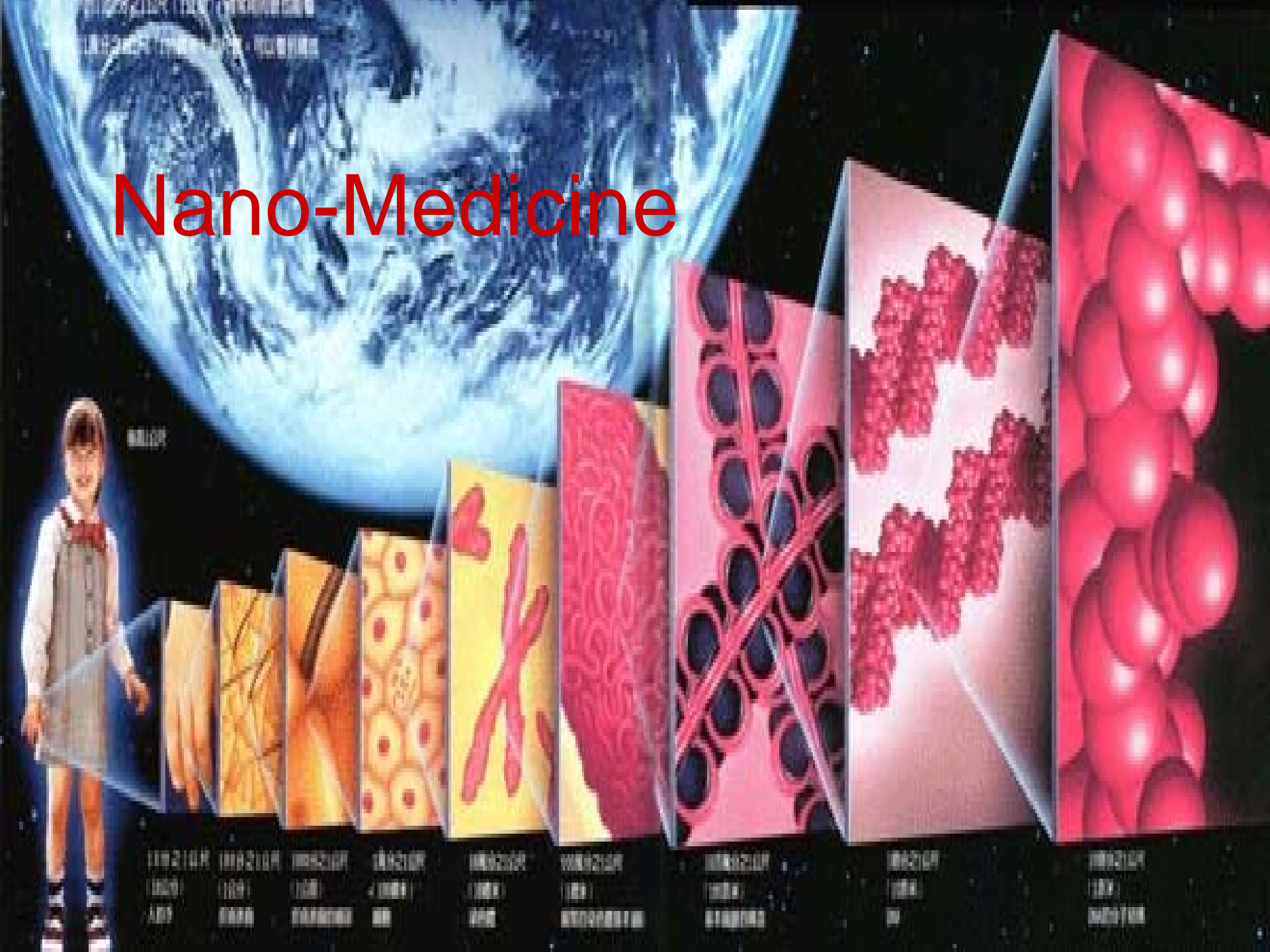
Evaluation; Score: 100%:

Mid-term Exam: 30%

Final Exam: 30%

Scientific Activity: 40 % (Home work, Innovation Design)

Nano-Medicine

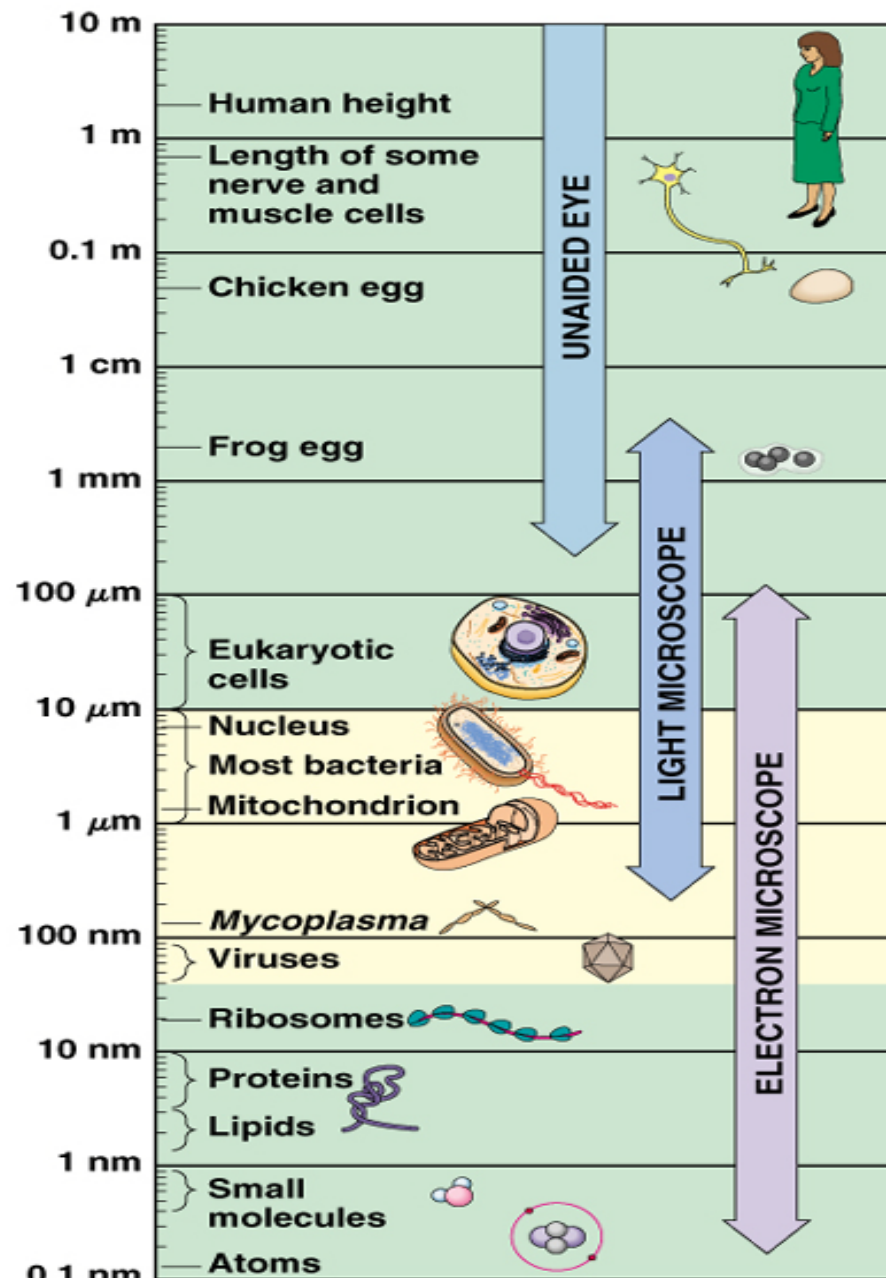


Subjects:

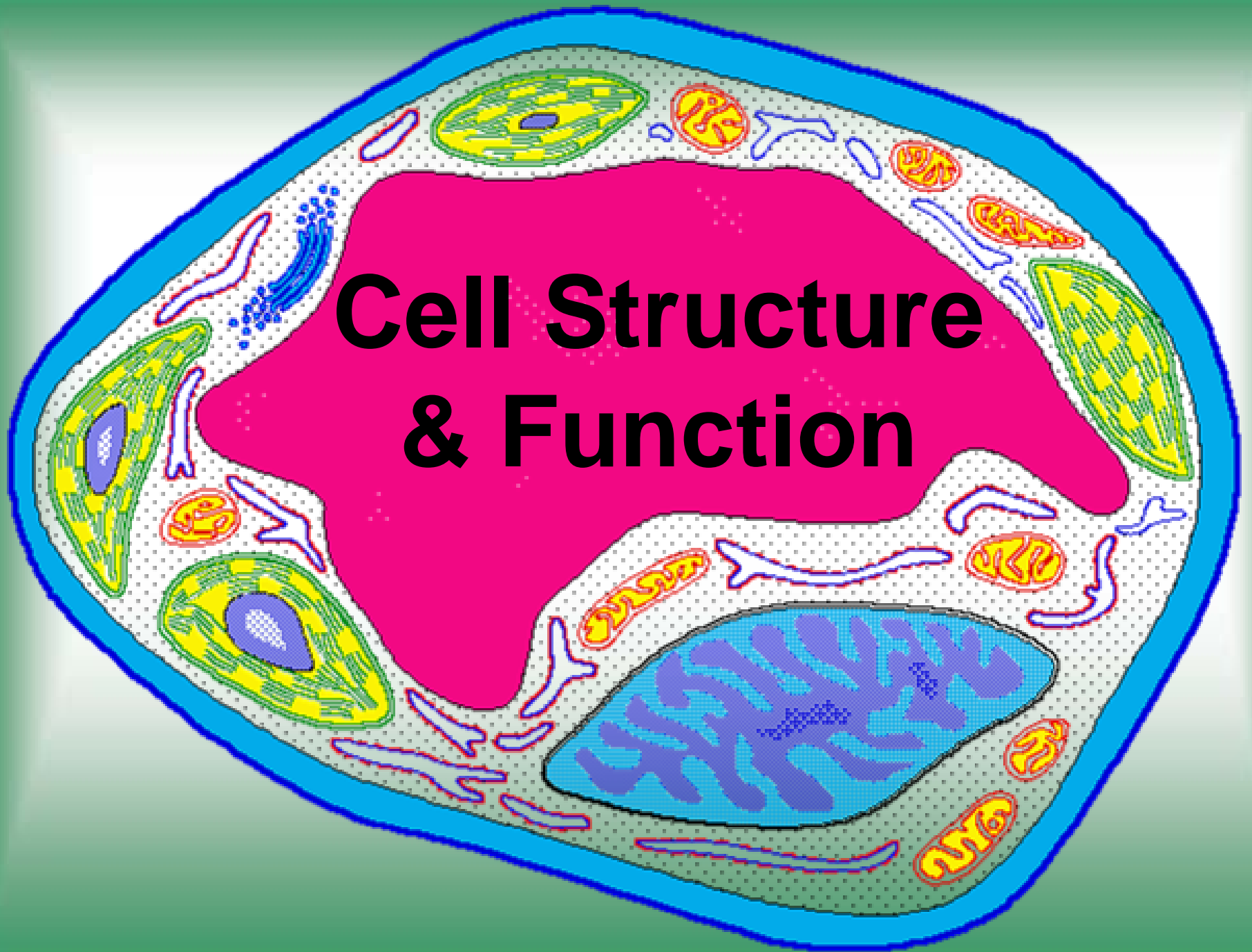
Biodegradable and Biocompatible Nanoparticles, Nanofibers

1. Drug Delivery
2. Tissue Engineering
3. Diagnostic Tools

Scale

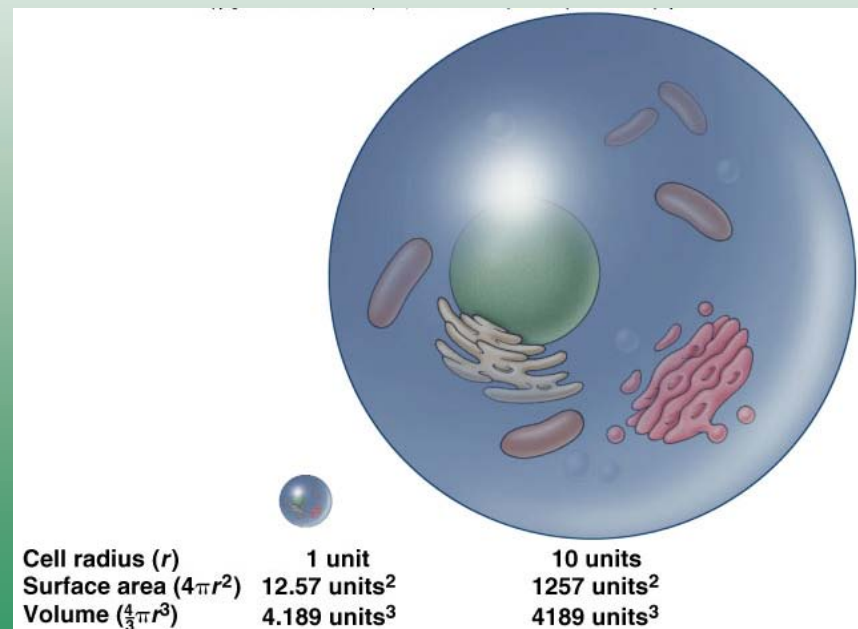


Cell Structure & Function

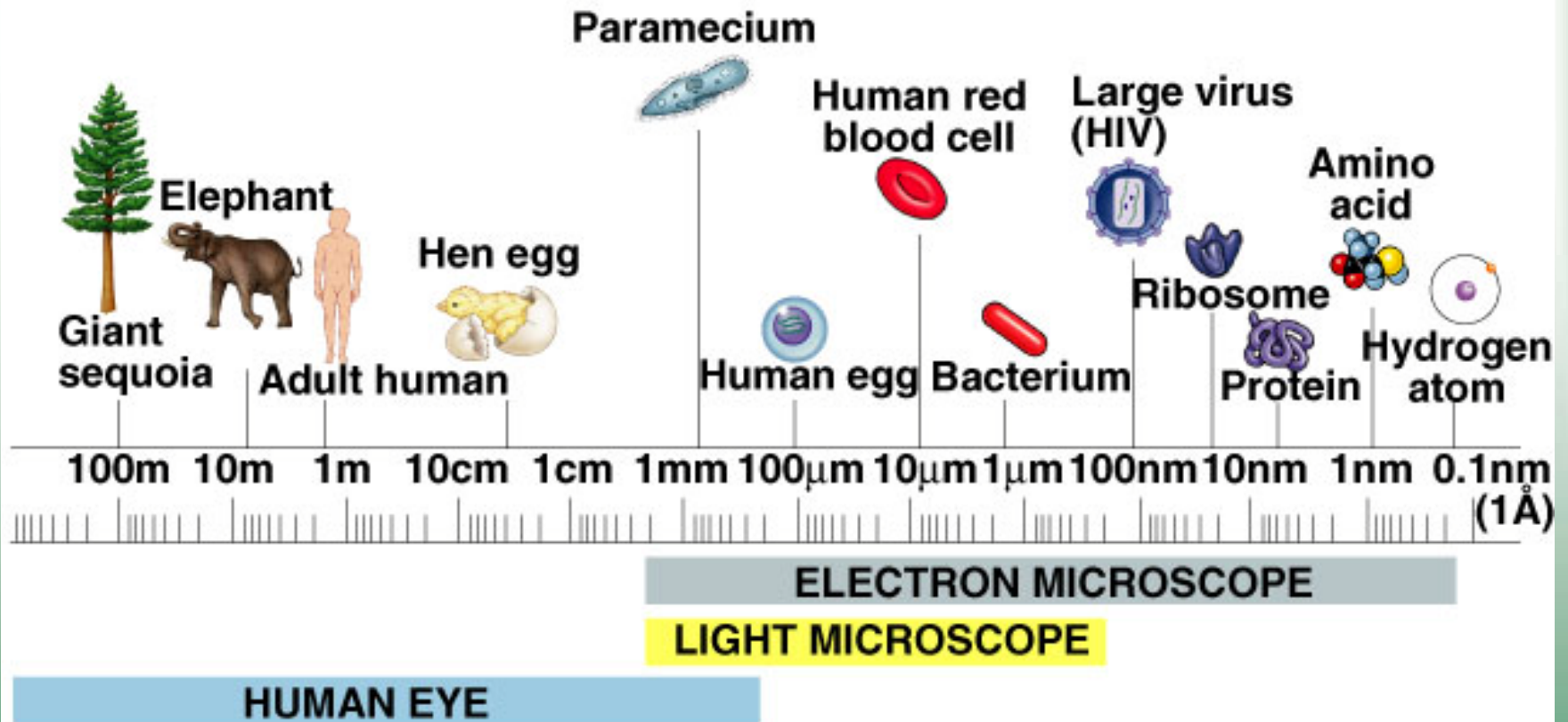


Cell Size

- Most cells are relatively small because as size increases, volume increases much more rapidly.
 - longer diffusion time



Visualizing Cells



Cell Theory

- All organisms are composed of one or more cells.
- Cells are the smallest living units of all living organisms.
- Cells arise only by division of a previously existing cell.

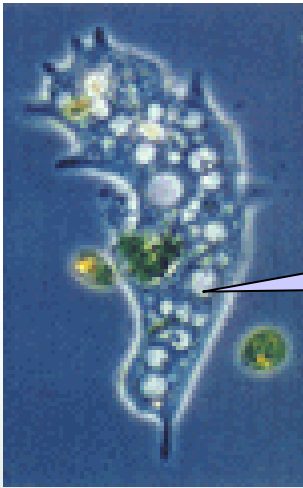
Cell Theory

- All living things are made up of cells.
- Cells are the smallest working units of all living things.
- All cells come from preexisting cells through cell division.

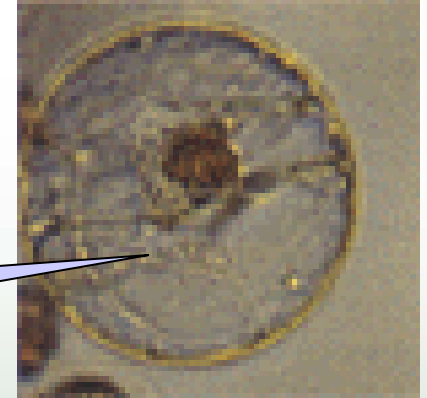
Definition of Cell

A cell is the smallest unit that is capable of performing life functions.

Examples of Cells

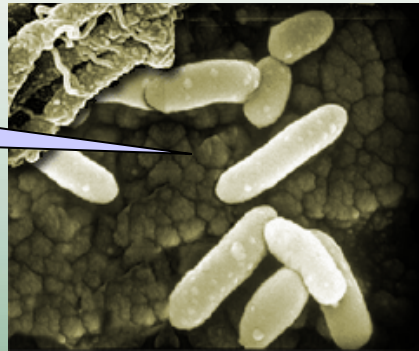


Amoeba Proteus



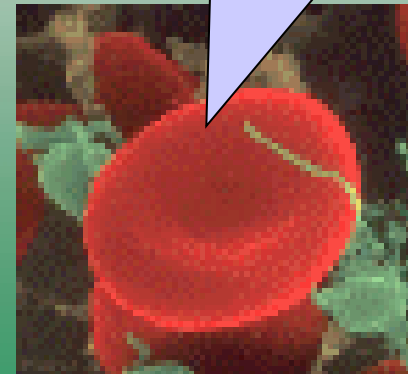
Plant Stem

Bacteria



Nerve Cell

Red Blood Cell

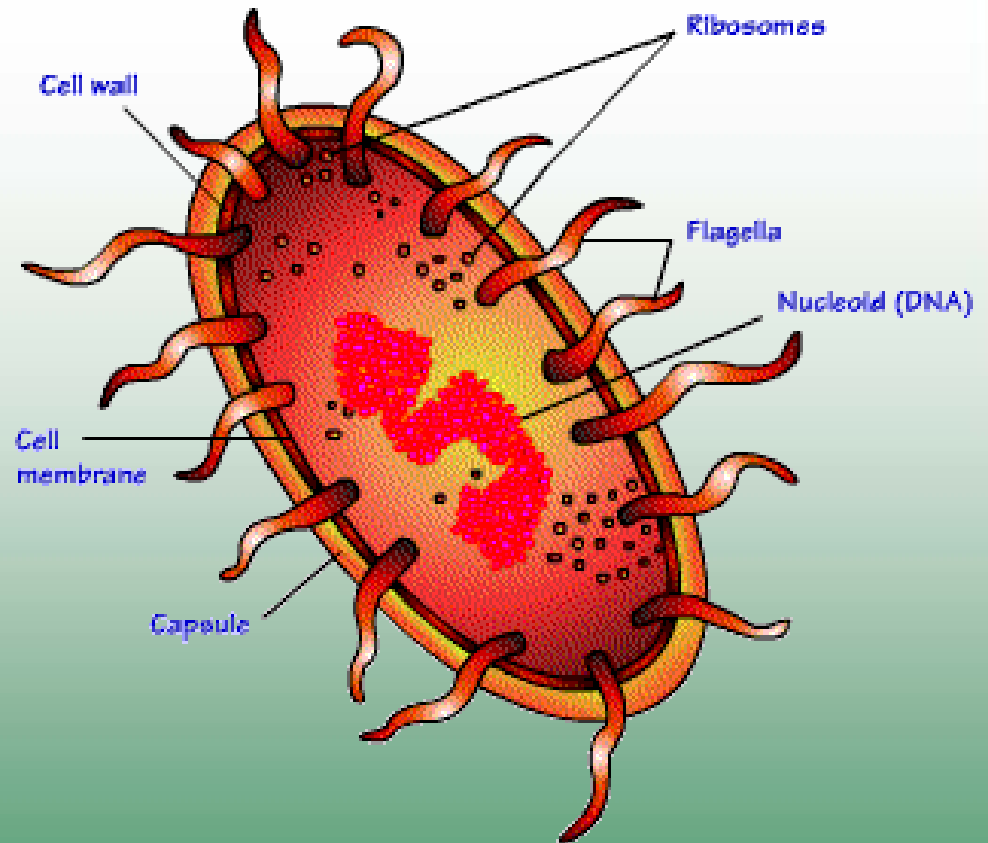


Two Types of Cells

- Prokaryotic
- Eukaryotic

Prokaryotic

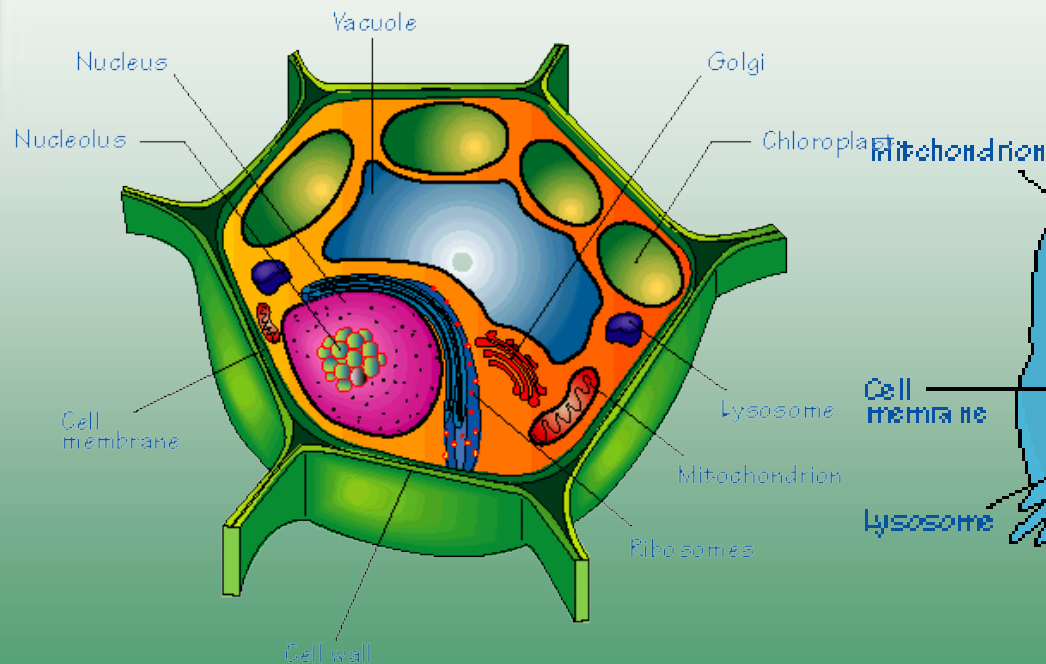
- Do not have structures surrounded by membranes
- Few internal structures
- One-celled organisms, Bacteria



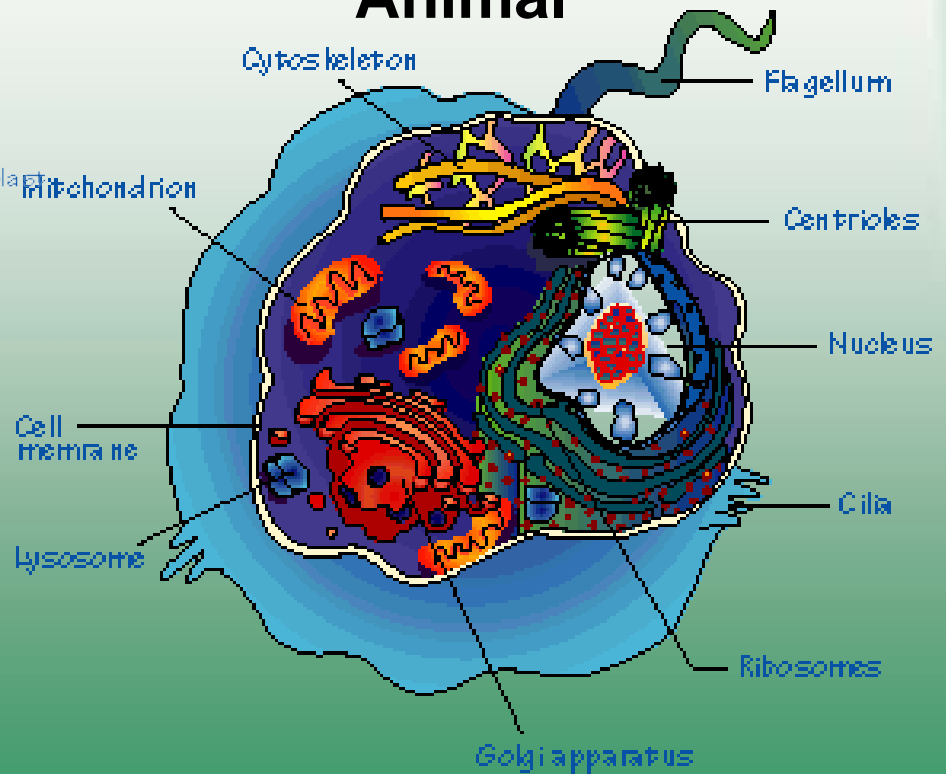
Eukaryotic

- Contain organelles surrounded by membranes
- Most living organisms

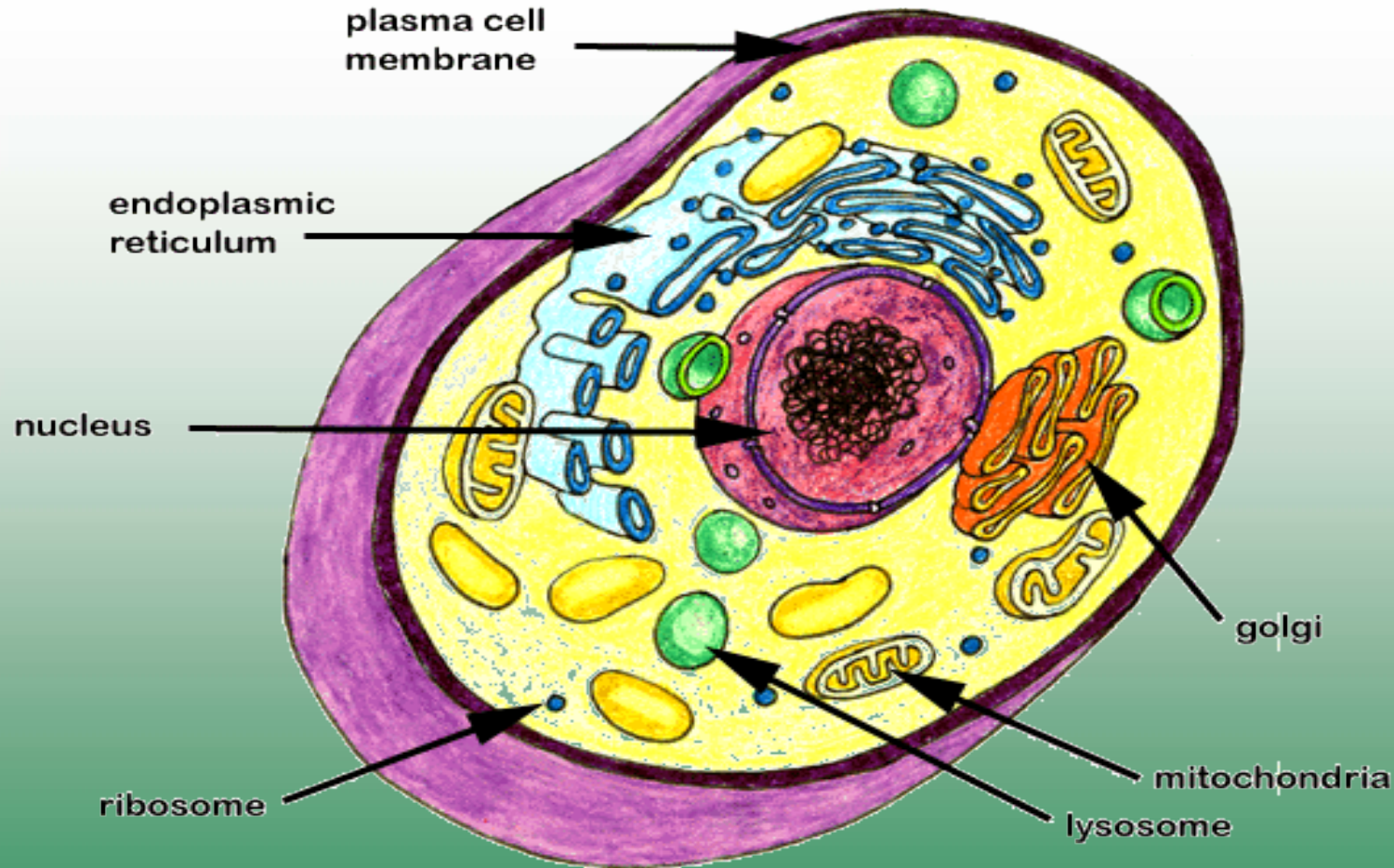
Plant



Animal



“Typical” Animal Cell



“Typical” Plant Cell

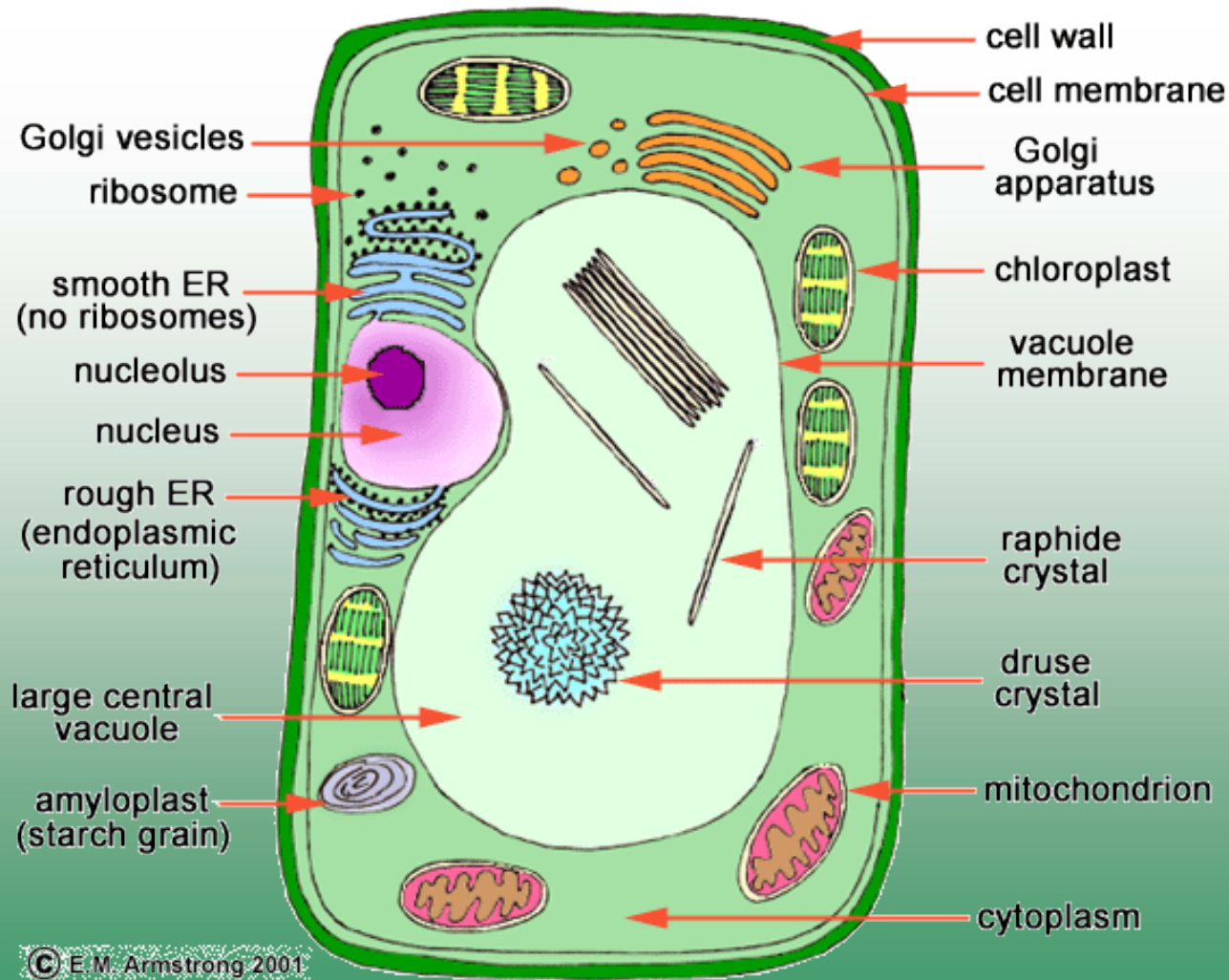
















Table 5.3 A Comparison of Prokaryotic, Animal, and Plant Cells**Prokaryote****Animal****Plant****EXTERIOR STRUCTURES**

| | | | |
|----------------|----------------------------------|----------------|---|
| Cell wall | Present (protein-polysaccharide) | Absent | Present (cellulose) |
| Cell membrane | Present | Present | Present |
| Flagella/cilia | May be present (single strand) | May be present | Absent except in sperm of a few species |

INTERIOR STRUCTURES

| | | | |
|-----------------|------------------------|-------------------------------|--------------------------------|
| ER | Absent | Usually present | Usually present |
| Ribosomes | Present | Present | Present |
| Microtubules | Absent | Present | Present |
| Centrioles | Absent | Present | Absent |
| Golgi apparatus | Absent | Present | Present |
| Nucleus | Absent | Present | Present |
| Mitochondria | Absent | Present | Present |
| Chloroplasts | Absent | Absent | Present |
| Chromosomes | A single circle of DNA | Multiple; DNA-protein complex | Multiple; DNA-protein complex |
| Lysosomes | Absent | Usually present | Present |
| Vacuoles | Absent | Absent or small | Usually a large single vacuole |

Table 5.2 Eukaryotic Cell Structures and Their Functions

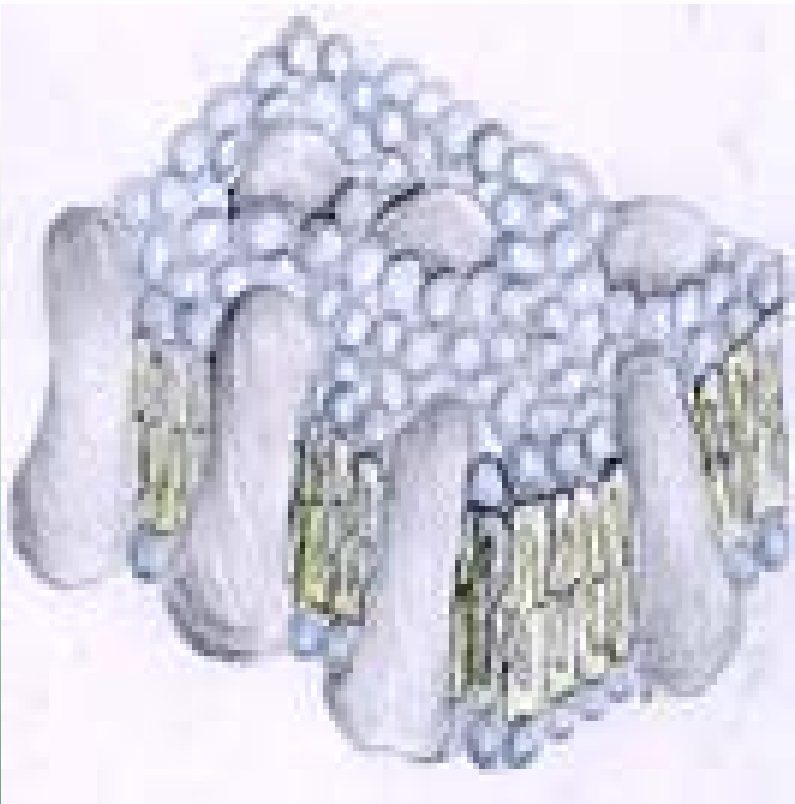
| Structure | | Description | Function |
|----------------------------|---|---|--|
| Cell wall |  | Outer layer of cellulose or chitin; or absent | Protection; support |
| Cytoskeleton |  | Network of protein filaments | Structural support; cell movement |
| Flagella (cilia) |  | Cellular extensions with 9 + 2 arrangement of pairs of microtubules | Motility or moving fluids over surfaces |
| Plasma membrane |  | Lipid bilayer with embedded proteins | Regulates what passes into and out of cell; cell-to-cell recognition |
| Endoplasmic reticulum (ER) |  | Network of internal membranes | Forms compartments and vesicles; participates in protein and lipid synthesis |
| Nucleus |  | Structure (usually spherical) that contains chromosomes and is surrounded by double membrane | Control center of cell; directs protein synthesis and cell reproduction |
| Golgi apparatus |  | Stacks of flattened vesicles | Packages proteins for export from cell; forms secretory vesicles |
| Lysosomes |  | Vesicles derived from Golgi apparatus that contain hydrolytic digestive enzymes | Digest worn-out organelles and cell debris; play role in cell death |
| Microbodies |  | Vesicles that are formed from incorporation of lipids and proteins and that contain oxidative and other enzymes | Isolate particular chemical activities from rest of cell |
| Mitochondria |  | Bacteria-like elements with double membrane | "Power plants" of the cell; sites of oxidative metabolism |
| Chloroplasts |  | Bacteria-like elements with membranes containing chlorophyll, a photosynthetic pigment | Sites of photosynthesis |
| Chromosomes |  | Long threads of DNA that form a complex with protein | Contain hereditary information |
| Nucleolus |  | Site of genes for rRNA synthesis | Assembles ribosomes |
| Ribosomes |  | Small, complex assemblies of protein and RNA, often bound to endoplasmic reticulum | Sites of protein synthesis |

Cell Parts

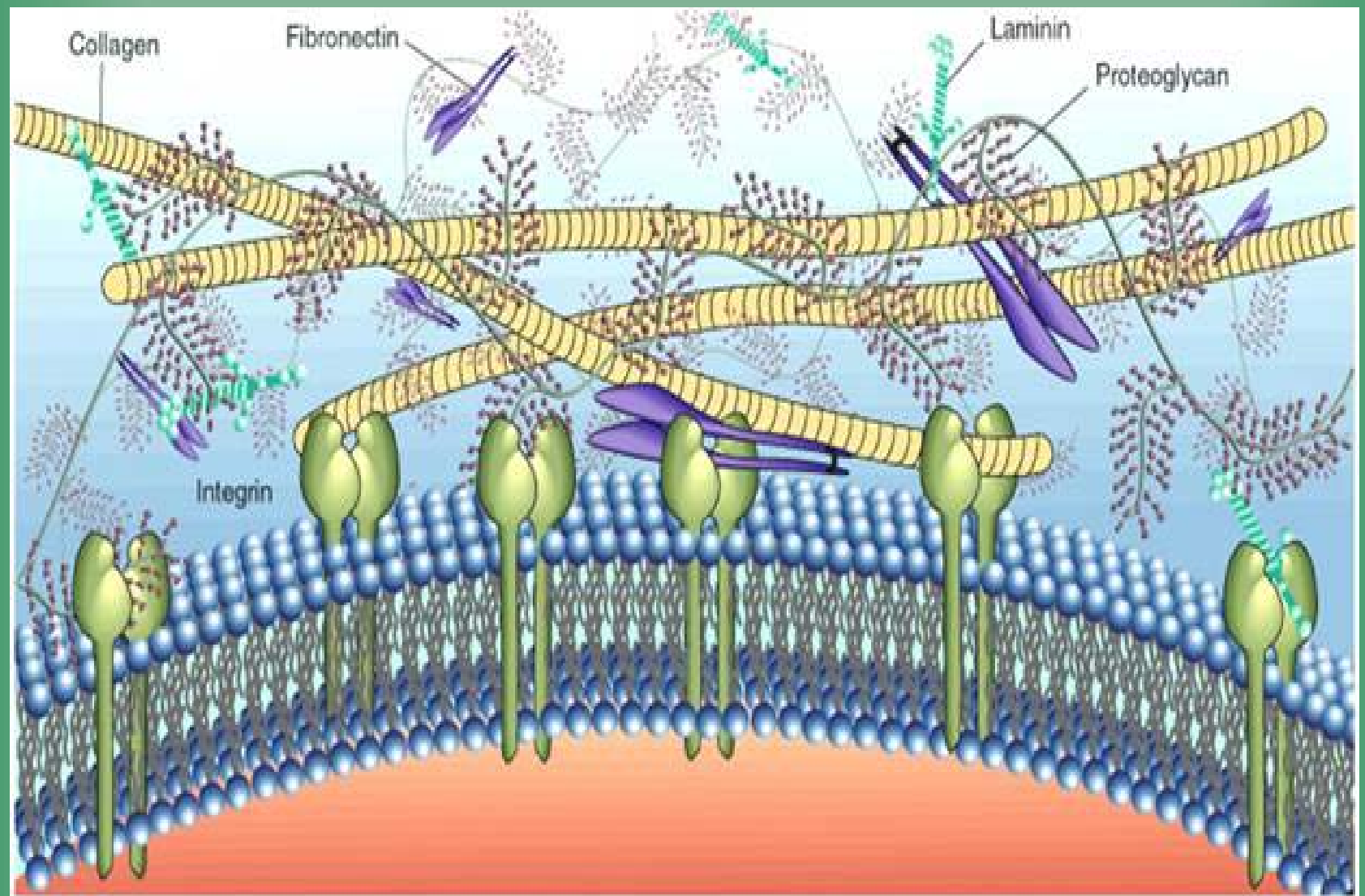
Organelles

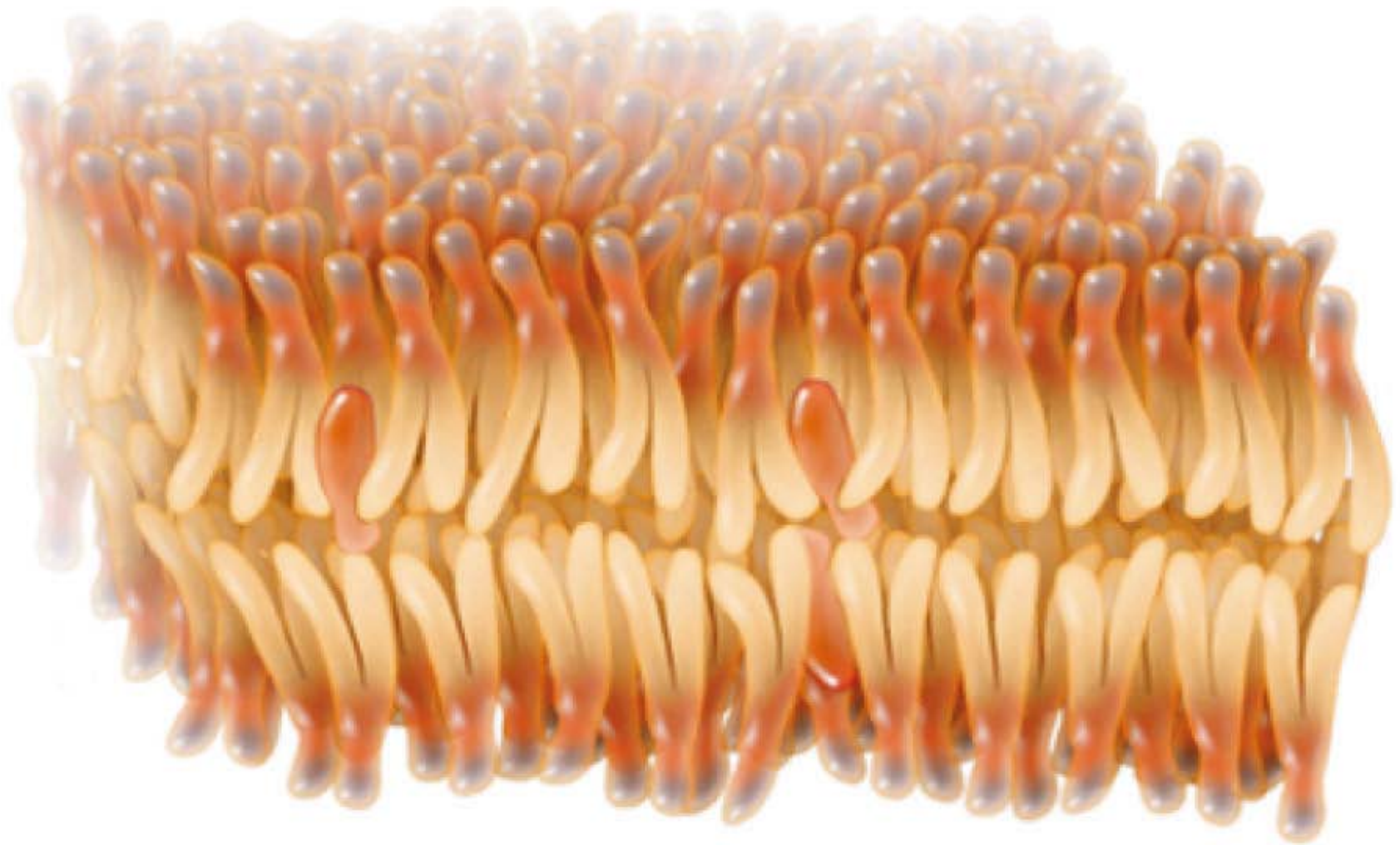
Surrounding the Cell

Cell Membrane



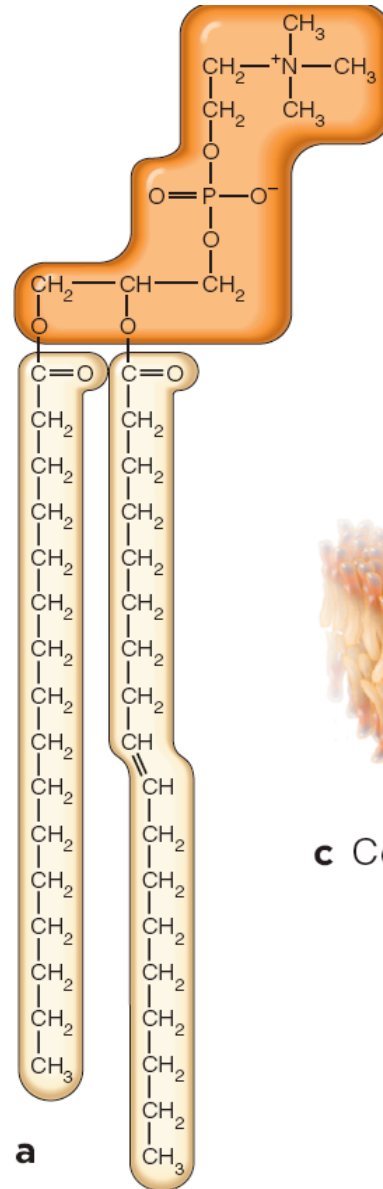
- Outer membrane of cell that controls movement in and out of the cell
- Double layer



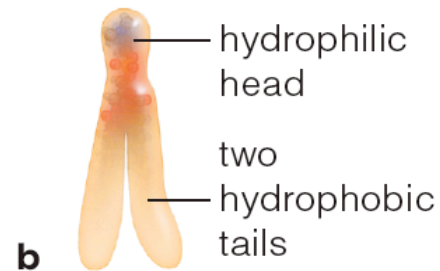


Cell membrane section

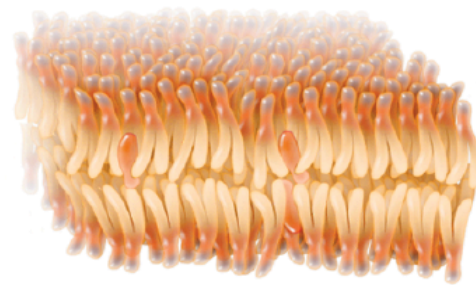
Phospholipid Structure



a

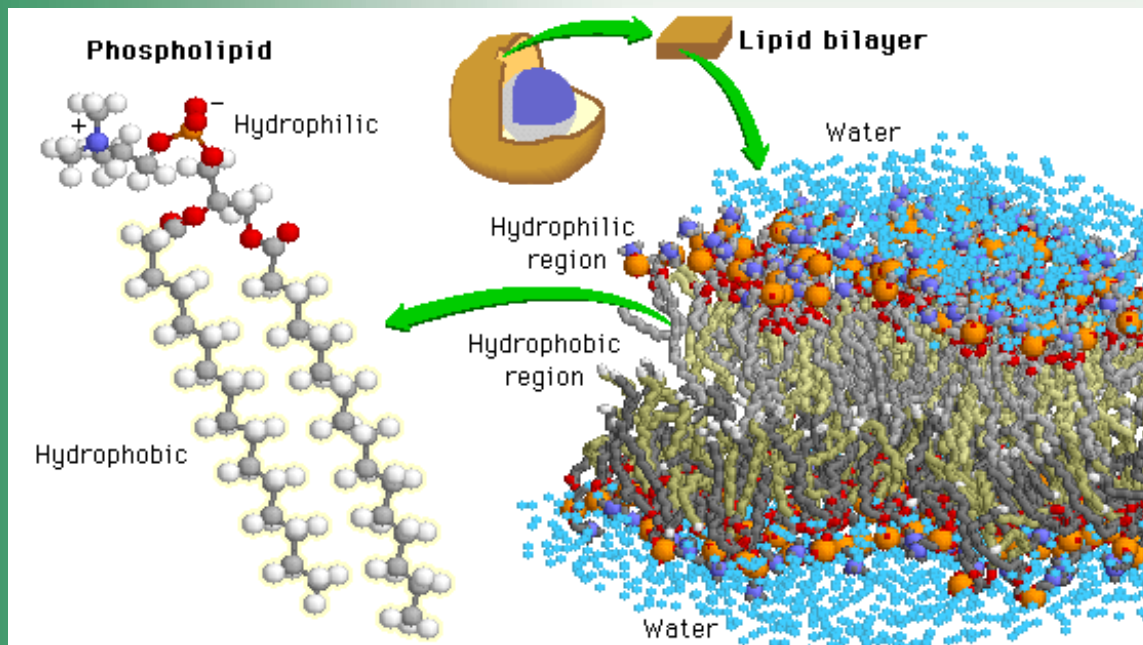


b



c Cell membrane section

In phospholipids, the two fatty acids are hydrophobic, or insoluble in water. But the phosphate group is hydrophilic, or soluble in water. When phospholipids are mixed with water, they spontaneously rearrange themselves to form the lowest free-energy configuration. This means that the hydrophobic regions find ways to remove themselves from water, while the hydrophilic regions interact with water.

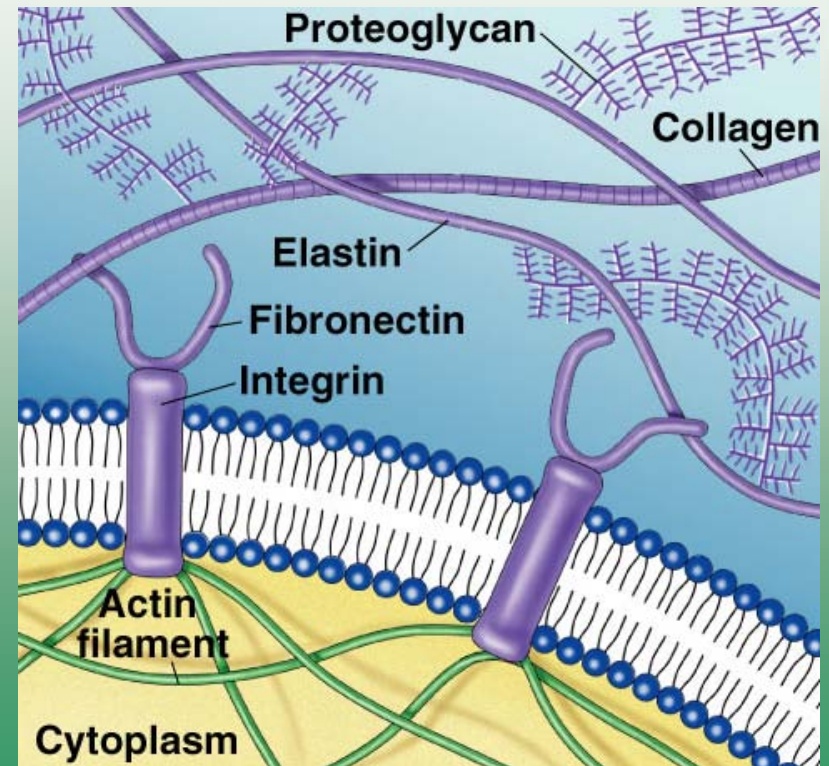


The resulting structure is called a lipid bilayer. All biological membranes (except for those found in certain unusual bacteria, members of the Archaea) contain lipid bilayers, as well as proteins, which provide membranes with stability and specialized functions.

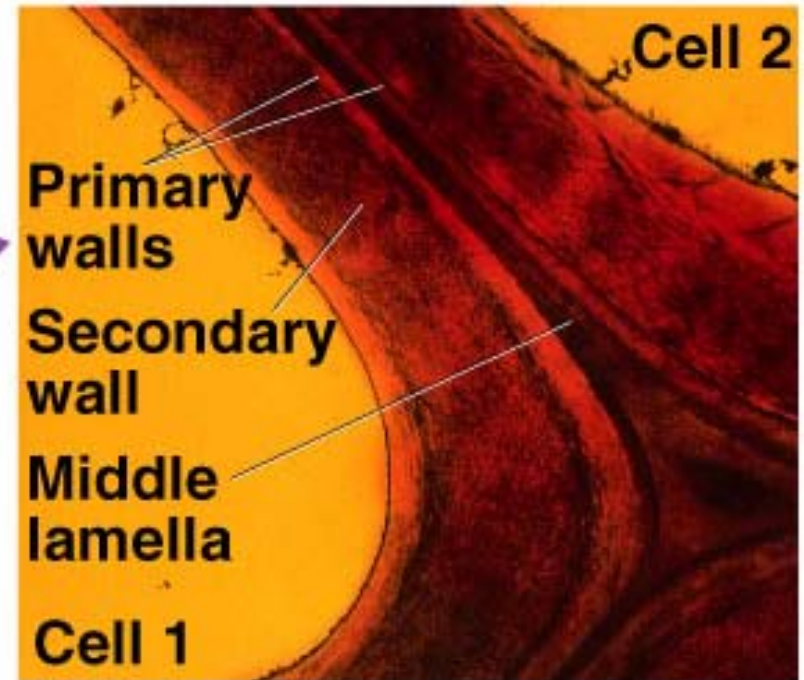
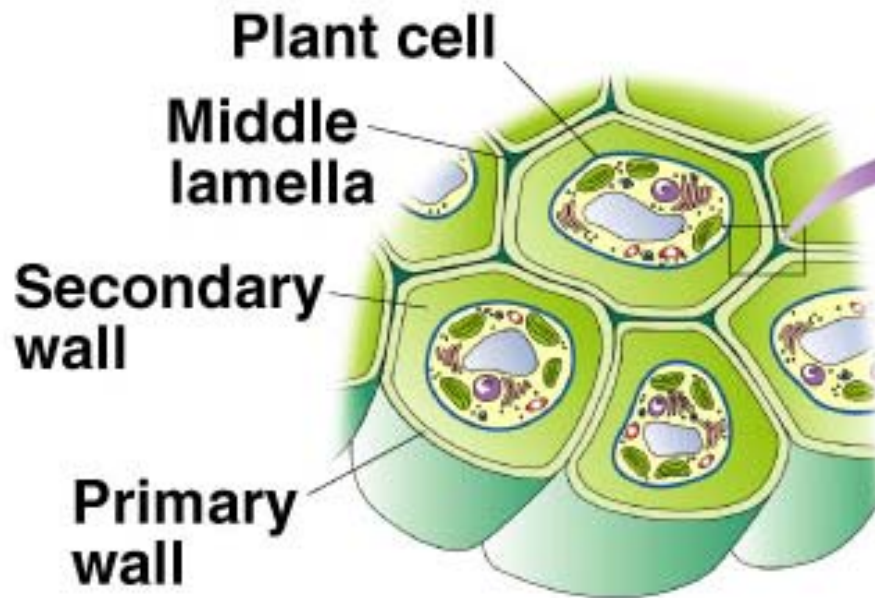
The image above is based on original work by H. Heller, M. Schaefer, & K. Schulten, "Molecular dynamics simulation of a bilayer of 200 lipids in the gel and in the liquid-crystal phases", J. Phys. Chem. 97:8343-60, 1993.

Animal Cells

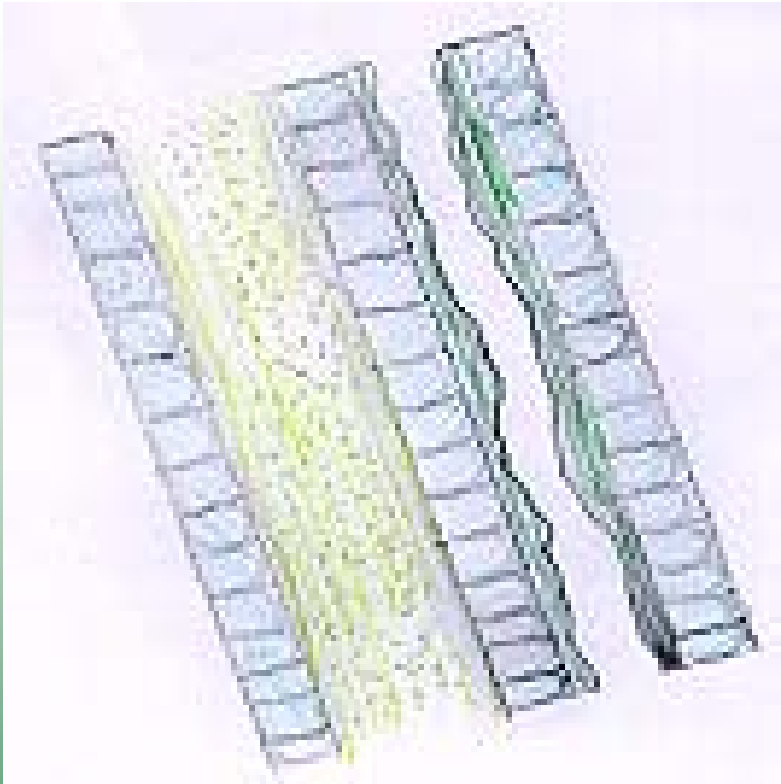
- Animal cells lack cell walls.
 - form extracellular matrix
 - provides support, strength, and resilience



Plant Cell



Cell Wall

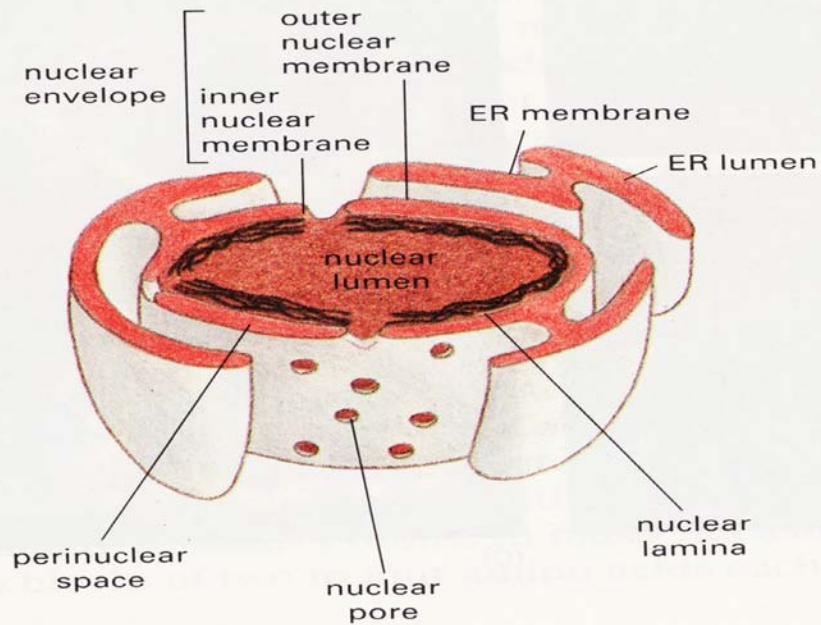


- Most commonly found in plant cells & bacteria
- Supports & protects cells

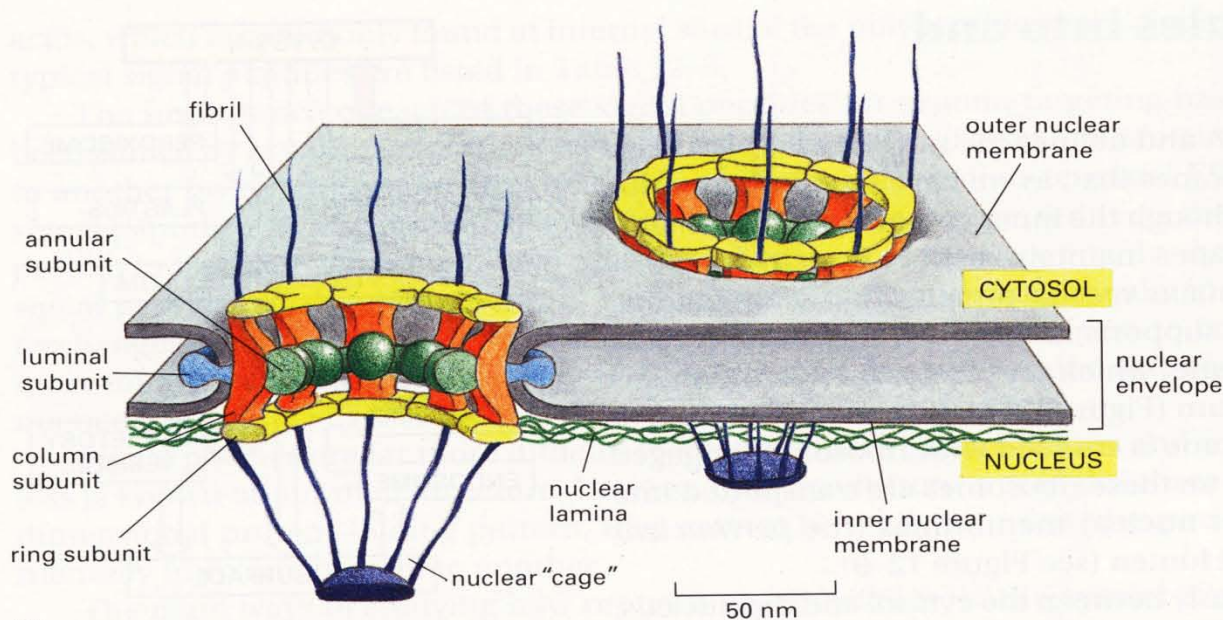
Inside the Cell

Nucleus

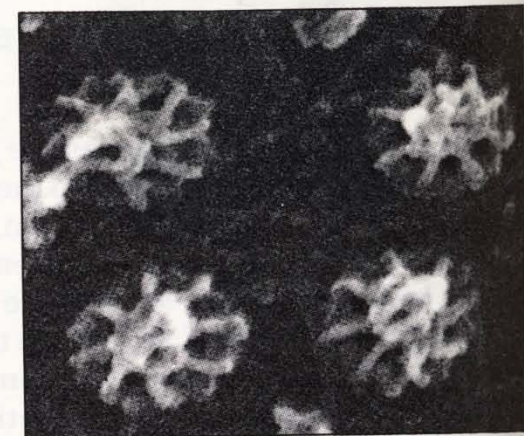
- Directs cell activities
- Separated from cytoplasm by nuclear membrane
- Contains genetic material - DNA



Nuclear
Pore
Structure



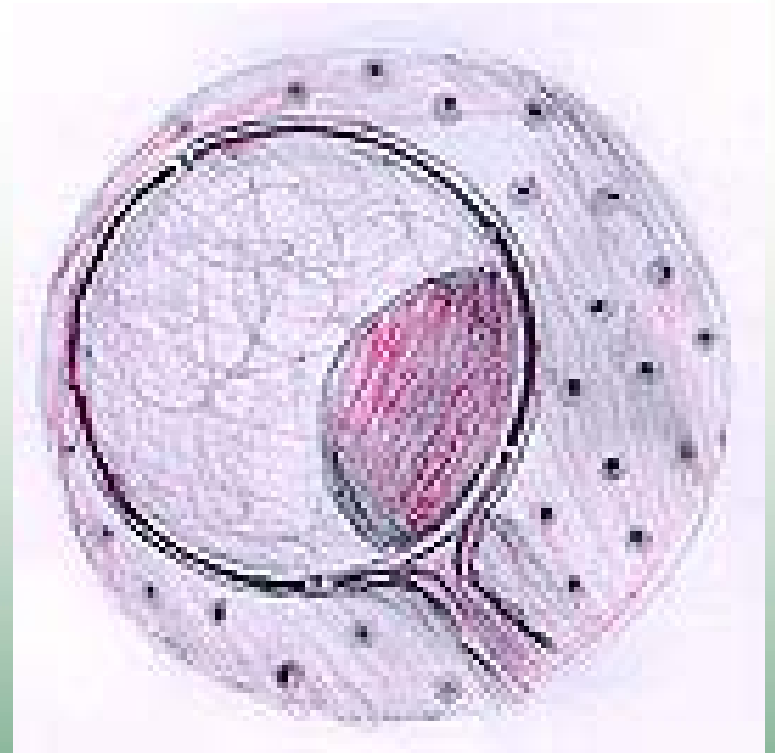
(A)

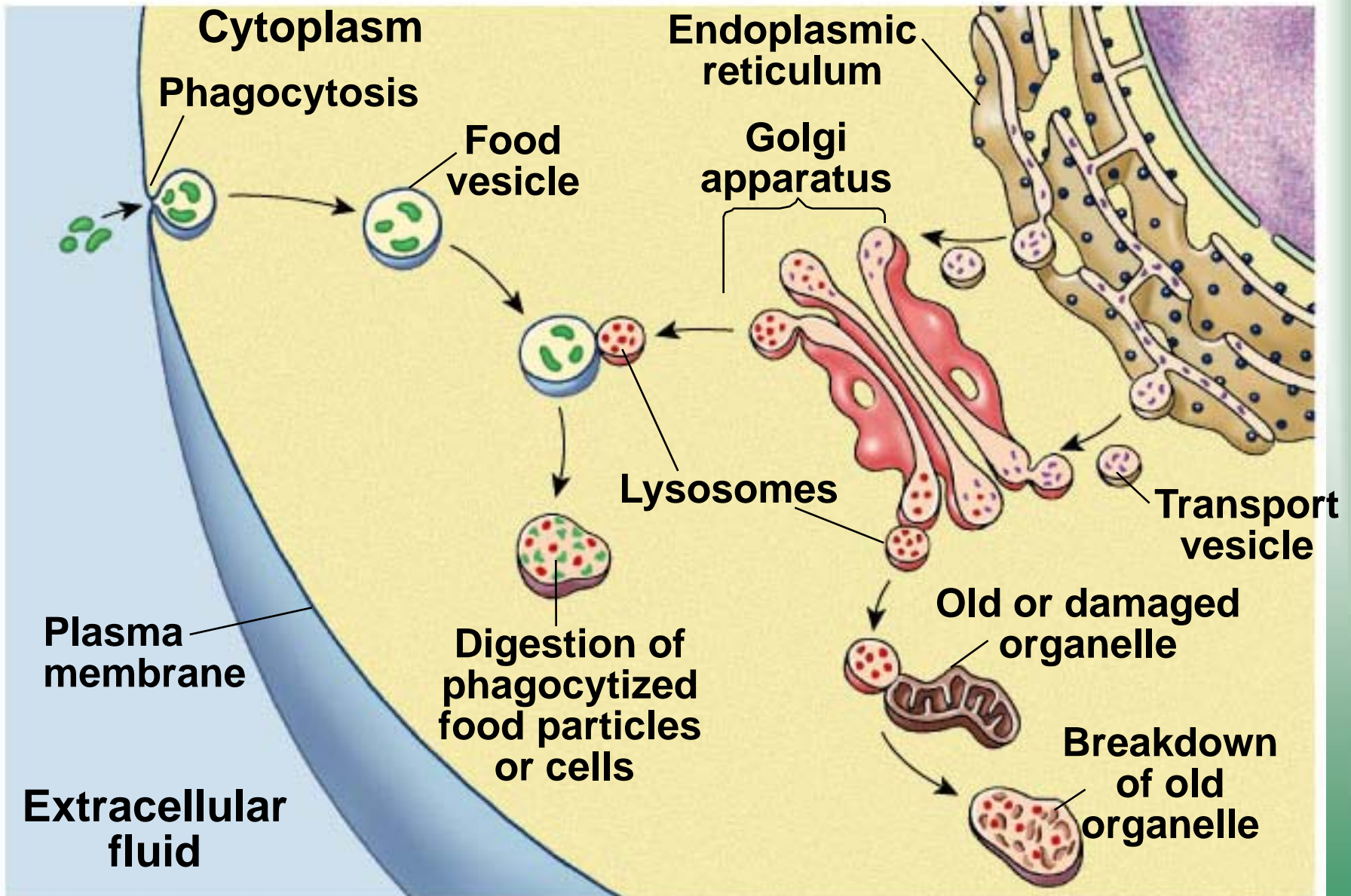


(B)

Nuclear Membrane

- Surrounds nucleus
- Made of two layers
- Openings allow material to enter and leave nucleus

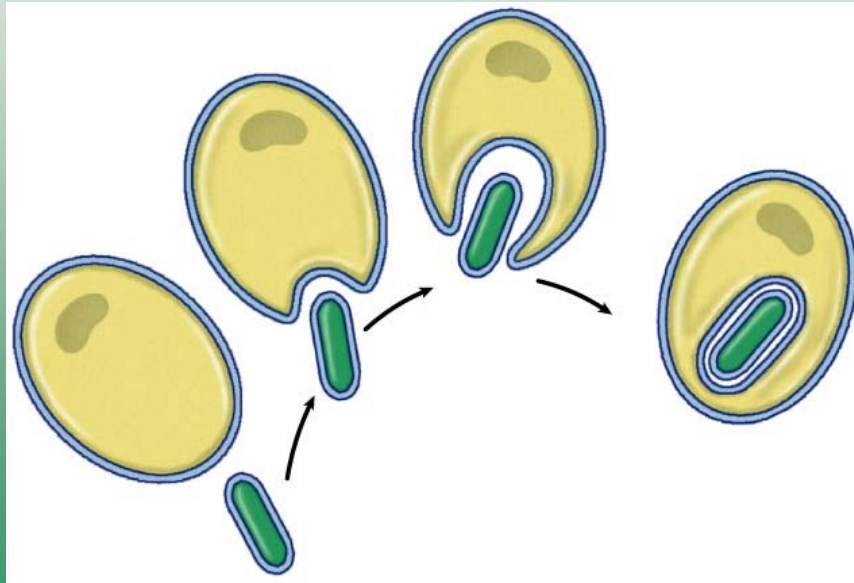




Endosymbiosis

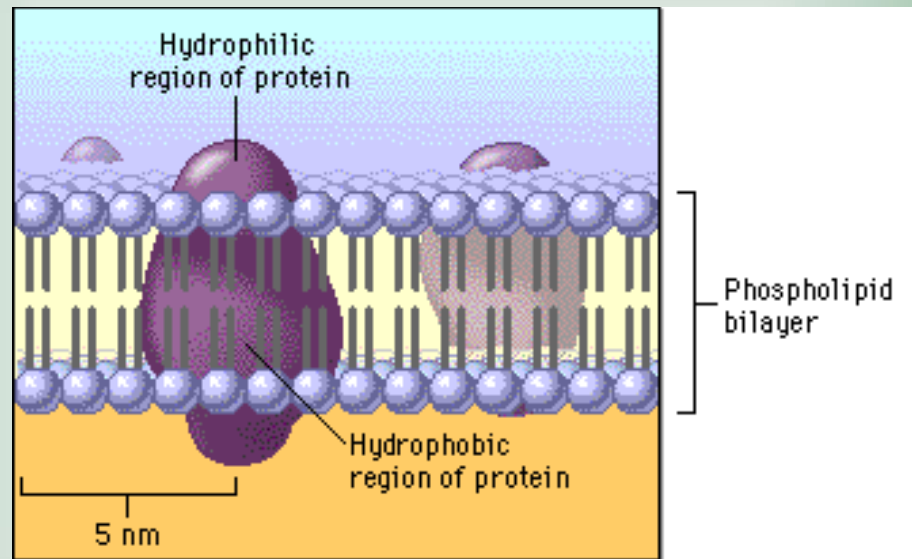
Protection (act as Intelligent Secret Service)

- Endosymbiotic theory suggests engulfed prokaryotes provided hosts with advantages associated with specialized metabolic activities.



Concept 1: Membrane Structure

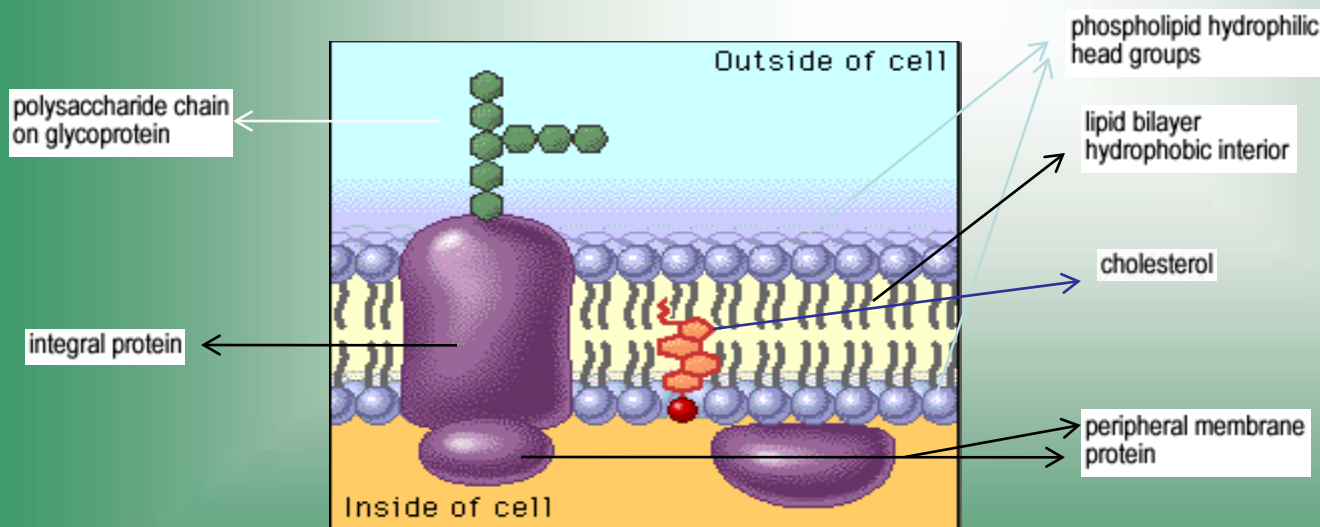
Membranes consist of a phospholipid bilayer combined with a variety of proteins in a fluid mosaic arrangement.



Hydrophilic molecules tend to interact with water and with each other. Hydrophobic molecules avoid interaction with water and tend to interact with other hydrophobic molecules.

Concept 1 Review: Components and Properties of Biological Membranes

Biological membranes are thin, flexible surfaces separating cells and cell compartments from their environments. Different membranes have different properties, but all share a common architecture. Membranes are rich in phospholipids, which spontaneously form bilayer structures in water. Membrane proteins and lipids can diffuse laterally within the membrane, giving it the properties of a fluid mosaic. Membranes are asymmetric; interior and exterior faces carry different proteins and have different properties.



Concept 1 Review: Glossary of Terms

- **Cholesterol**

A steroid widely distributed in all living things. Cholesterol and other a steroids are found in most membranes; they do not form bilayers, but dissolve in the lipid layer. Steroids can account for up to 50% of the lipids in some cell membranes, and are thought to strengthen the membrane and make it less sensitive to lysis.

- **Glycoprotein**

A protein containing short carbohydrate chains. In membranes, these proteins usually face the exterior of the cell. The sugars mannose, galactose, and several others are common in membrane glycoproteins. Many different spatial combinations of these sugars are possible, resulting in many different surface markers or antigens, which are used as signals to distinguish different cells.

- **Integral protein**

A membrane protein that has at least one segment anchored within the lipid bilayer. Many integral proteins contain sequences of about 20 hydrophobic amino acids that fold into a hydrophobic alpha-helix that is embedded in the lipid bilayer. In this shape, the hydrophobic amino acid side chains form hydrophobic bonds with the fatty acid portion of the phospholipids in the bilayer.

- **Lipid bilayer nonpolar region**

Phospholipids spontaneously assemble into lipid bilayers, with a characteristic thickness of 4-5 nm. In cell membranes, the two hydrophobic fatty acid side chains that form the "tails" of the hairpin-shaped phospholipid molecules are oriented to the interior of the membrane.

- **Peripheral protein**

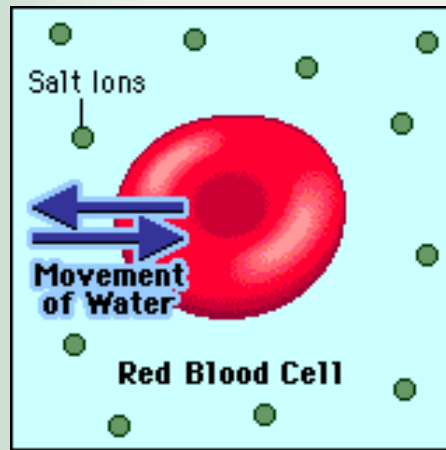
A membrane protein found on either the inner or outer face of the bilayer. Peripheral proteins bind either to integral proteins or to the polar head groups of membrane phospholipids.

- **Polar phospholipid head groups**

The hydrophilic (water-attracting) phosphate groups of phospholipids. These groups interact with water by forming many hydrogen bonds. Each phospholipid also has hydrophobic (water-repelling) fatty acid chains that form the "tails" of the hairpin-shaped molecule. Phospholipids spontaneously assemble into lipid bilayers, with a characteristic thickness of 4-5 nm.

Concept 2: Osmosis: Movement of Water Across Membranes

Osmosis (movement of water across membranes) depends on the relative concentration of solute molecules on either side of the membrane.



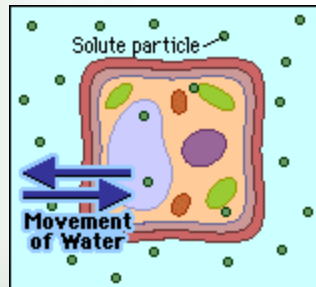
The presence or absence of cell walls influences how cells respond to osmotic fluctuations in their environment.

Lysis in Animals Cells

Animal cells lack rigid cell walls. When they are exposed to hypotonic environments, water rushes into the cell, and the cell swells. Eventually, if water is not removed from the cell, the pressure will exceed the tensile strength of the cell, and it will burst open, or lyse. Many single-celled protists living in freshwater environments have contractile vacuoles that pump water back out of the cell in order to maintain osmotic equilibrium and avoid lysis.

Turgor in Plants

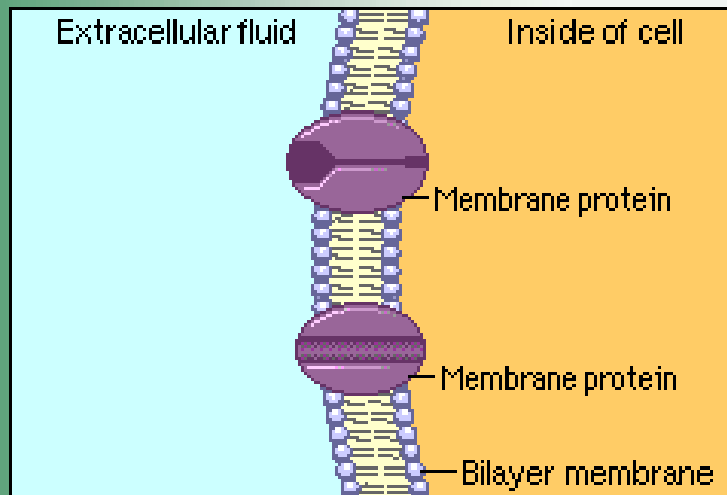
Plant cells are surrounded by rigid cell walls. When plant cells are exposed to hypotonic environments, water rushes into the cell, and the cell swells, but is kept from breaking by the rigid wall layer. The pressure of the cell pushing against the wall is called turgor pressure, and is the desired state for most plant tissues. For instance, placing a wilted celery stalk or lettuce leaf in a hypotonic environment of pure water, will often revive the leaf by inducing turgor in the plant cells.



Hypotonic comes from the Greek "hypo," meaning under, and "tonos," meaning stretching. In a hypotonic solution the total molar concentration of all dissolved solute particles is less than that of another solution or less than that of a cell.

Concept 3: Selective Permeability of Membranes

Cell membranes are selectively permeable. Some solutes cross the membrane freely, some cross with assistance, and others do not cross at all.

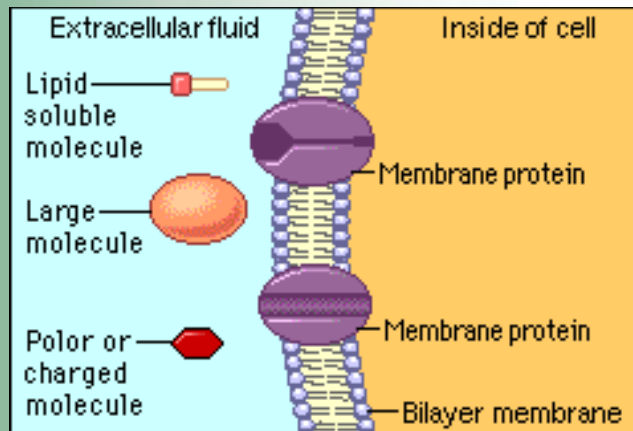


A few lipophilic substances move freely across the cell membrane by passive diffusion. Most small molecules or ions require the assistance of specific protein carriers to transport them across the membrane. Large molecules do not cross intact cell membranes, except in certain special cases.

Concept 3 Review: Mechanisms of Movement Across Cell Membranes

When a membrane separates two aqueous compartments, some molecules can move freely across the membrane, others cannot. This behavior can be seen with pure synthetic phospholipid membranes, which are analogous to biological membranes, but contain no proteins. In living organisms, the membrane proteins play a crucial role in directing the movement of solutes across cell membranes.

Solutes fall into one of three groups:

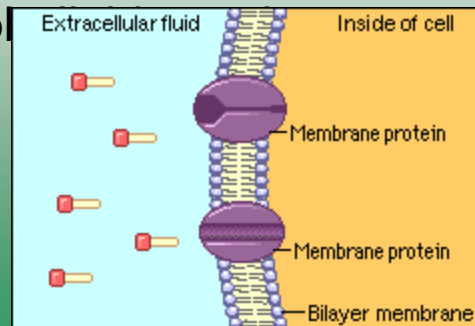


- Small lipophilic (lipid soluble) molecules that cross the membrane by diffusion alone
- Molecules that cross the membrane due to protein-mediated transport
- Molecules, usually of very large size, that do not cross the membrane at all

Concept 3 Review: Passive Diffusion of Small Lipophilic Molecules

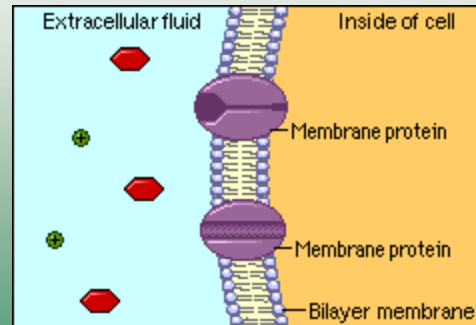
Studies with pure phospholipid membranes show that certain substances easily cross the membrane by a process known as passive diffusion. Diffusion refers to the dispersal of molecules by random motion. For example, if someone opens a perfume vial (or a smelly cheese) in one corner of a room, the odor gradually spreads because molecules of the odoriferous substance are diffusing throughout the air. In the absence of other processes (such as metabolic activity), diffusion would eventually lead to an even distribution of molecules throughout a closed volume.

Substances that diffuse across cell membranes include gases, such as O_2 and CO_2 , and small relatively hydrophobic molecules, such as fatty acids or alcohols. By contrast, it is difficult for water to cross pure phospholipid membranes that lack the proteins found in cell membranes, and most polar or charged molecules such as sugars, amino acids, and ions fail to cross pure phospholipid membranes.



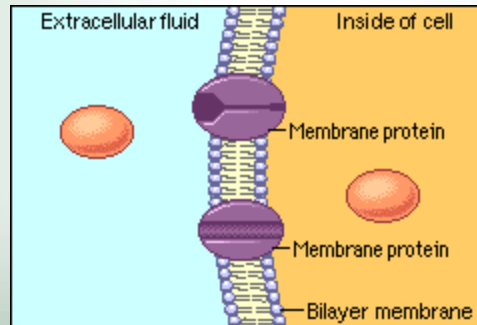
Concept 3 Review: Transport of Polar and Charged Molecules

Biological membranes are permeable not only to gases and small hydrophobic molecules (by passive diffusion processes), but also to many polar and charged molecules, including water. Biological membranes contain many different proteins, the majority of which function as specific transporters to allow certain solutes to cross the membrane effectively. Transport proteins are of two basic types: channel proteins and carrier proteins. Channel proteins form hydrophilic pores that allow water and certain ions to cross the membrane, while carrier proteins bind to specific solutes and "carry" them across the membrane. All channel proteins and some carrier proteins facilitate the movement of solutes "downhill" in terms of the concentration gradient, a process known as facilitated diffusion. Facilitated diffusion requires no energy input, in contrast to active transport processes, which do require energy, as you'll learn in the next section.



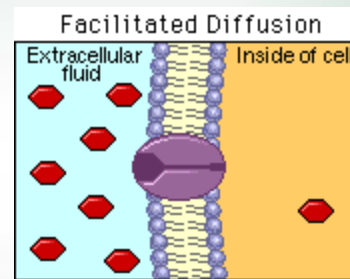
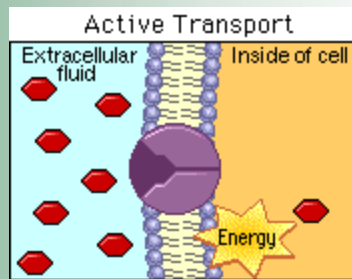
Concept 3 Review: Membrane Barriers to Large Molecules

Large molecules, such as proteins, polypeptides, polysaccharides, or nucleic acids, do not diffuse across cell membranes at all. These molecules must be broken down into their component monomers, e.g., amino acids, sugars, or nucleotides, if their components are to cross the cell membrane.



Concept 4: Passive and Active Transport

Most biologically important solutes require protein carriers to cross cell membranes, by a process of either passive or active transport.



Active transport uses energy to move a solute "uphill" against its gradient, whereas in facilitated diffusion, a solute moves down its concentration gradient and no energy input is required.

Concept 4 Review: Comparing Facilitated Diffusion and Active Transport

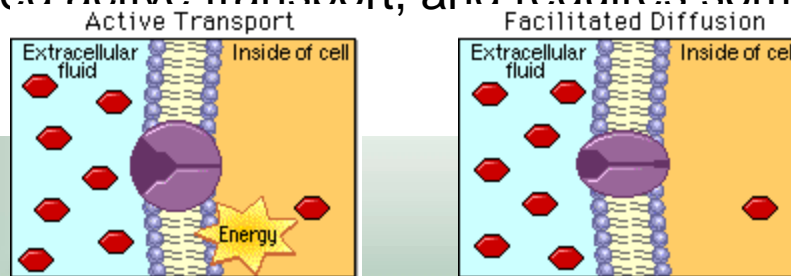
Transport of solutes across cell membranes by protein carriers can occur in one of two ways:

- The solute can move "downhill," from regions of higher to lower concentration, relying on the specificity of the protein carrier to pass through the membrane.

This process is called passive transport or facilitated diffusion, and does not require energy.

- The solute can move "uphill," from regions of lower to higher concentration.

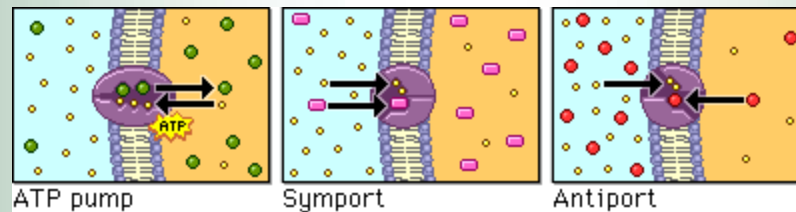
This process is called **active transport**, and **requires some form of chemical energy**.



The transport process a cell uses depends on its specific needs. For example, red blood cells rely on facilitated diffusion to move glucose across membranes, whereas intestinal epithelial cells use active transport to take in glucose from the gut. Facilitated diffusion is effective for red blood cells because the concentration of glucose in the blood is stable and higher than the cellular concentration. On the other hand, active transport is needed in the gut because there are large fluctuations of glucose concentration as a result of eating.

Concept 5: Mechanisms of Active Transport

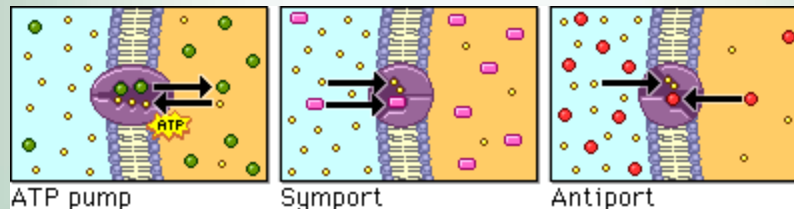
Active transport can occur as a direct result of ATP hydrolysis (ATP pump) or by coupling the movement of one substance with that of another (symport or antiport).



Active transport may move solutes into the cell or out of the cell, but energy is always used to move the solute against its concentration gradient.

Concept 5 Review: Active Transport

Most living cells maintain internal environments that are different from their extracellular environment, as well as concentration differences between the cytosol and internal compartments. In human tissues, for example, all cells have a higher concentration of Na^+ outside the cell than inside, and a higher concentration of K^+ inside the cell than outside. These concentration gradients of Na^+ and K^+ represent a form of energy storage, similar to a battery. An example of a concentration difference between the cytosol and an internal compartment is found in the lysosome, where the concentration of hydrogen ions (H^+) can be 100 to 1000 times greater than the concentration outside, in the cytosol.



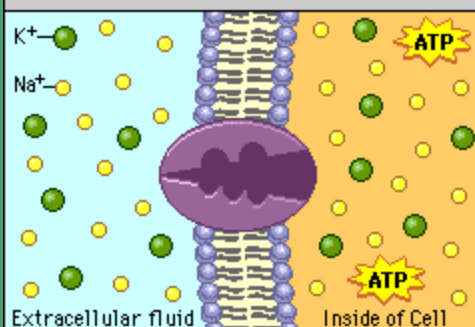
Like pushing an object uphill, moving a molecule against a concentration gradient requires energy. Cells have evolved active transport proteins that can use energy to establish and maintain concentration gradients.

Concept 5 Review: ATP-powered Pumps

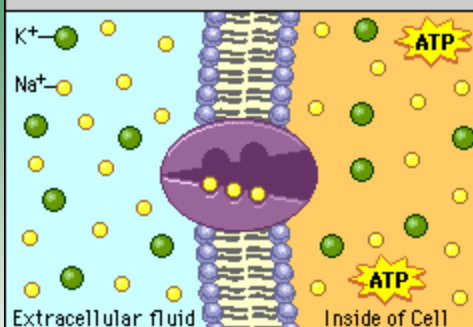
ATP-powered pumps (ATPases) couple the splitting, or hydrolysis, of ATP with the movement of ions across a membrane against a concentration gradient. ATP is hydrolyzed directly to ADP and inorganic phosphate, and the energy released is used to move one or more ions across the cell membrane. As much as 25% of a cell's ATP reserves may be spent in such ion transport. Examples include:

- The $\text{Na}^+\text{-K}^+$ ATPase pumps Na^+ out of the cell while it pumps K^+ in. Because the pump moves three Na^+ to the outside for every two K^+ that are moved to the inside, it creates an overall charge separation known as polarization. This electrical potential is required for nervous system activity, and supplies energy needed for other types of transport such as symport and antiport.
- Ca^{++} ATPases are responsible for keeping intracellular Ca^{++} at low levels, a necessary precondition for muscle contraction.

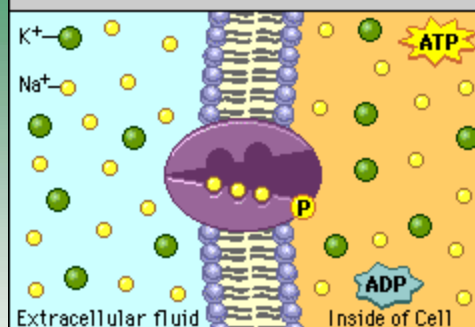
Step 1. Three Na^+ ions bind to cytoplasmic high-affinity binding sites.



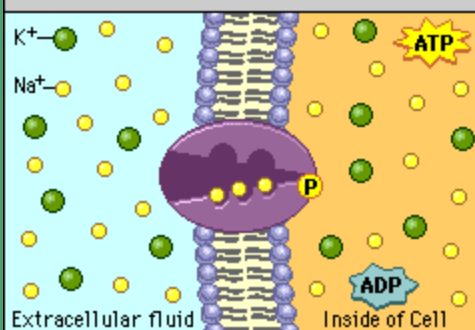
Step 2. ATP is hydrolyzed, transferring a phosphate group to the pump.



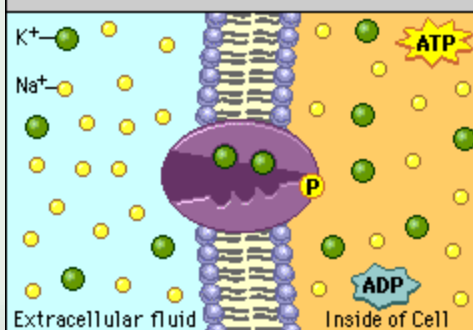
Step 3. The pump conformation changes, moving Na^+ ions to the extracellular side of the membrane.



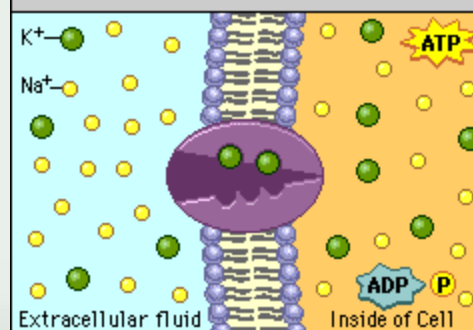
Step 4. Na^+ ions dissociate, and two K^+ ions bind to high-affinity extracellular sites.



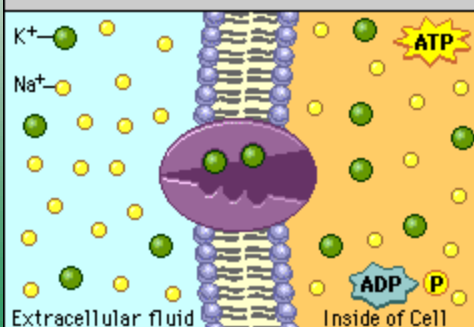
Step 5. The bond linking phosphate to the pump protein is hydrolyzed, releasing inorganic phosphate.



Step 6. The pump conformation changes, moving K^+ ions to low-affinity cytoplasmic sites.

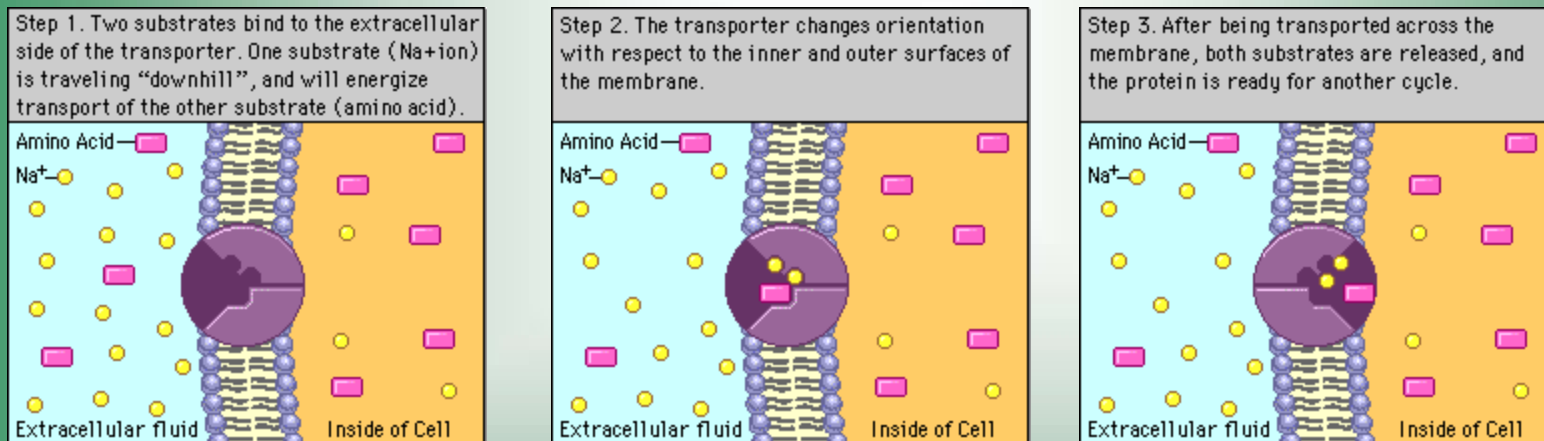


Step 7. K^+ ions dissociate, and the pump is ready for another cycle.



Concept 5 Review: Symport

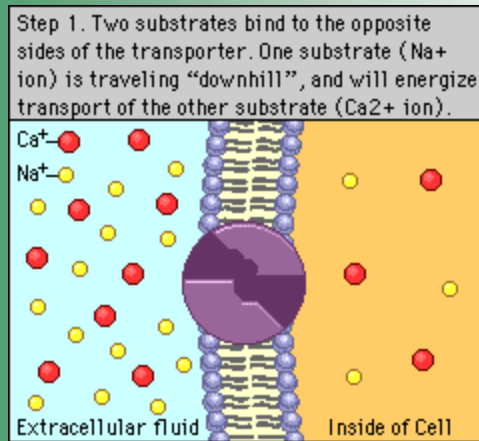
To transport some substances against a concentration gradient, cells use energy already stored in ion gradients, such as proton (H^+) or sodium (Na^+) gradients, to power membrane proteins called transporters. When the transported molecule and the co-transported ion move in the same direction, the process is known as symport.



An example of a symport process is the transport of amino acids across the intestinal lining in the human gut.

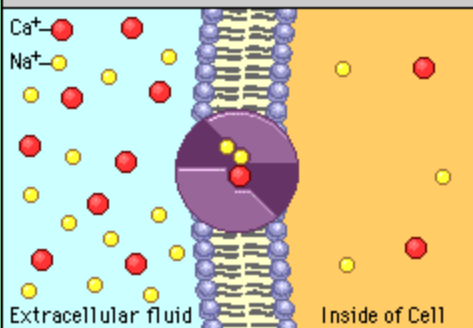
Concept 5 Review: Antiport

In antiport, a cell uses movement of an ion across a membrane and down its concentration gradient to power the transport of a second substance "uphill" against its gradient. In this process, the two substances move across the membrane in opposite directions.

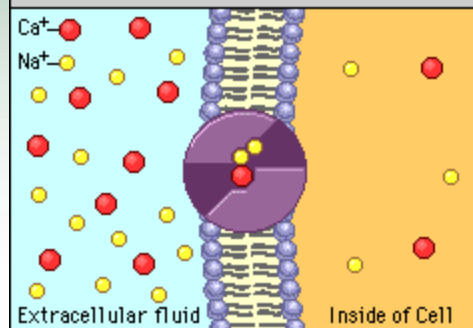


An example of an antiport process is the transport of Ca^{2+} ions out of cardiac muscle cells. Muscle cells are triggered to contract by a rise in intracellular Ca^{2+} concentration, so it is imperative that Ca^{2+} be removed from the cytoplasm so that the muscle can relax before contracting again. This antiport system is so effective that it can maintain the cellular concentration of Ca^{2+} at levels 10,000 times lower than the external concentration. To view animations summarizing operation of an antiporter, click on the buttons, starting with "Step 1."

Step 2. The transporter changes orientation with respect to the inner and outer surfaces of the membrane.



Step 3. After being transported across the membrane, both substrates are released, and the protein is ready for another cycle.



Nanotechnology Applications

Information Technology

- Smaller, faster, more energy efficient and powerful computing and other IT-based systems



Energy

- More efficient and cost effective technologies for energy production
 - Solar cells
 - Fuel cells
 - Batteries
 - Bio fuels



Medicine

- Cancer treatment
- Bone treatment
- Drug delivery
- Appetite control
- Drug development
- Medical tools
- Diagnostic tests
- Imaging



Consumer Goods

- Foods and beverages
 - Advanced packaging materials, sensors, and lab-on-chips for food quality testing
- Appliances and textiles
 - Stain proof, water proof and wrinkle free textiles
- Household and cosmetics
 - Self-cleaning and scratch free products, paints, and better cosmetics

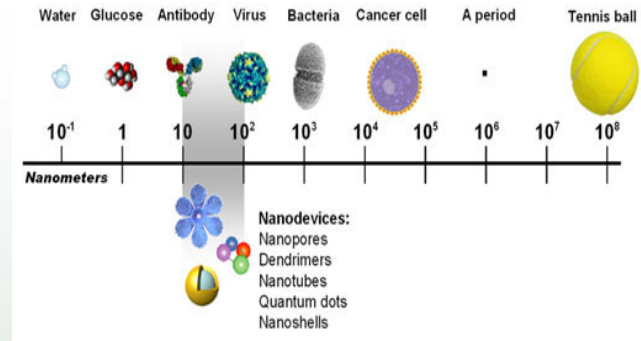


The most promising is Nanomedicine

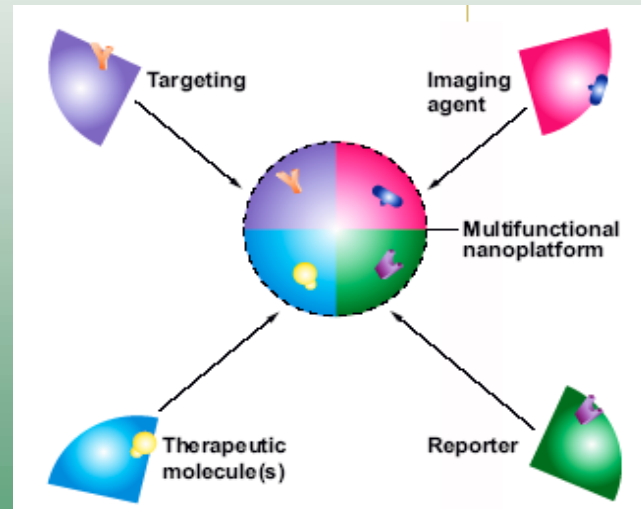
- **Nanomedicine** is the medical application of nanotechnology and related research. It covers areas such as nanoparticle drug delivery and possible future applications of molecular nanotechnology (MNT) and nanovaccinology.

What is nanomedicine?

- **Nanobiotechnology:**
Convergence of nanotechnology with modern biology
- **Nanomedicine:**
The use of nanobiotechnology in medicine
 - Imaging agents and diagnostics
 - Real-time assessment to accelerate clinical translation
 - Multifunctional, targeted devices
 - Monitoring predictive molecular changes
 - Research enablers: chip-based nanolabs
 - Etc.



<http://nano.cancer.gov/>



Technology Platform NANOMEDICINE

Nanomedicine exploits the improved and often novel physical, chemical and biological properties of materials at the nanometer scale. Nanomedicine has the potential to enable **early detection and prevention**, and to essentially **improve diagnosis, treatment** and follow-up of diseases.

Technology Platform NANOMEDICINE

Seamlessly connecting Diagnostics,
Targeted Delivery, and Regenerative Medicine

Diagnostics, targeted delivery and regenerative medicine constitute the core disciplines of nanomedicine. The European Technology Platform on NanoMedicine acknowledges and wishes to actively support research at the interface between its three science areas. It is committed to supporting such activities as theranostics, where nanotechnology will enable diagnostic devices and therapeutics to be combined for a real benefit to patients.

Source:<http://www.etp-nanomedicine.eu/public>

Advantages of Nanomedicine

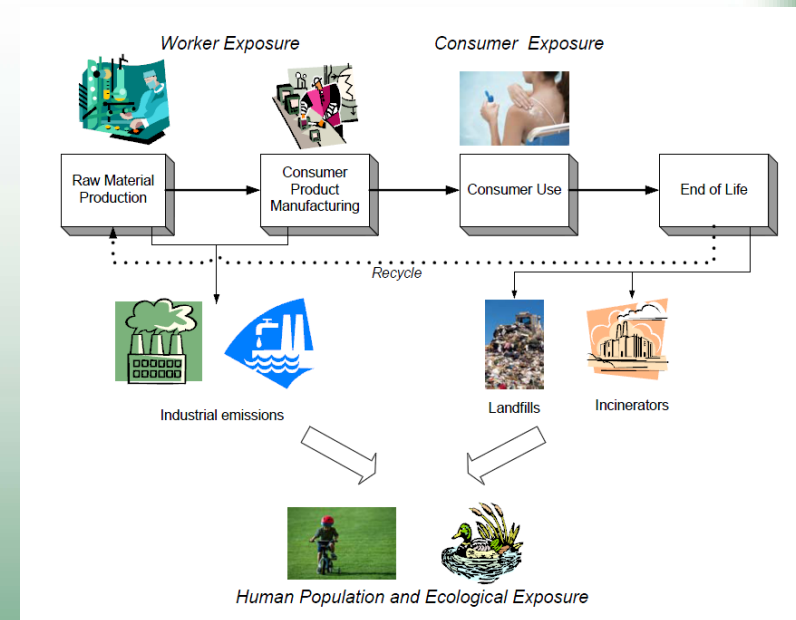
- Extremely bad conditions (as cancer) will be treated easily by modifying the body's genetic material.
- Disease elimination will become normal, so we no longer will need to be worry about living with heath conditions.
- Diagnose diseases before there are any symptoms.
- Administer drugs that are precisely targeted.
- Use non-invasive imaging tools to demonstrate that the treatment was effective.

Disadvantages for Nanomedicine

- What if the modification has unintended consequences for the person or society?
- What if we lose control of the nanoparticles?
- What if society determines everyone needs a certain modification?
- How do we deal with overpopulation?
- How does society ensure the Government doesn't use our money to research methods that are not in the best interests of the citizens?

Nanotechnology Health and Environmental Concerns

- Human and the environment come under exposure to nanomaterials at different stages of the product cycle
- Nanomaterials have large surface to volume ratio and novel physical as well as chemical properties which may cause them to pose hazards to humans and the environment
- Health and the environmental impacts associated with the exposure to many of the engineered nanomaterials are still uncertain
- The environmental fate and associated risk of waste nanomaterials should be assessed
 - e.g. toxic transformation, and interactions with organic and inorganic materials



Exposure of human and the environment to nanomaterials at different stages of product life cycle – US environmental protection agency, 2007 (epc.gov)

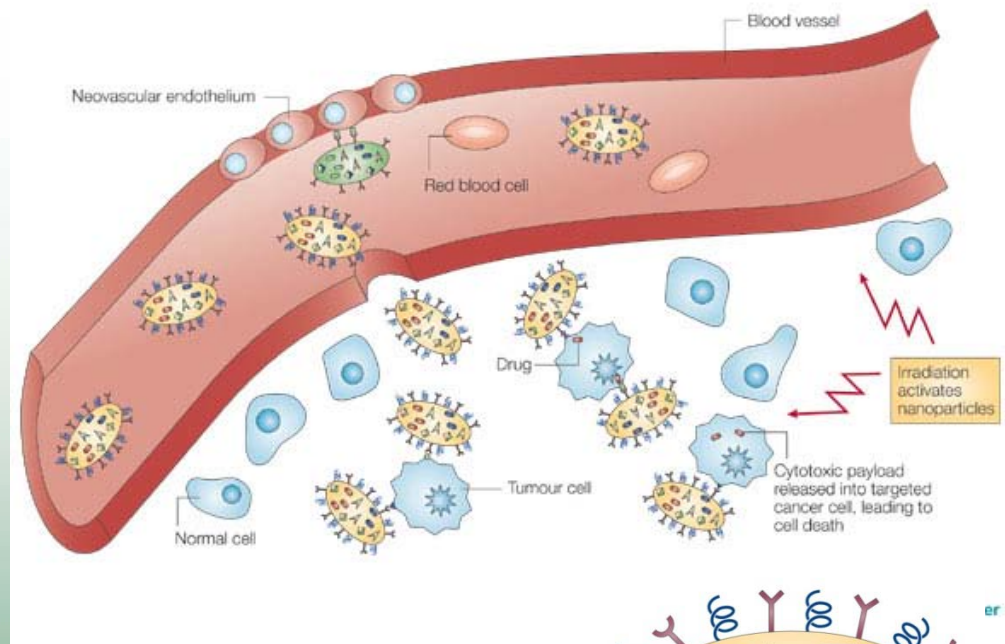
The *Nanotechnology* continues to
change our lives



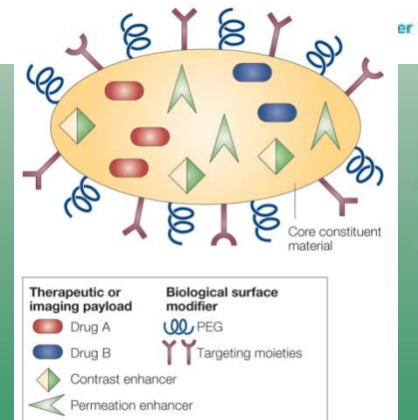
Nanotechnology in Health Care

Treatment

- Targeted drug delivery
 - Nanoparticles containing drugs are coated with targeting agents (e.g. conjugated antibodies)
 - The nanoparticles circulate through the blood vessels and reach the target cells
 - Drugs are released directly into the targeted cells

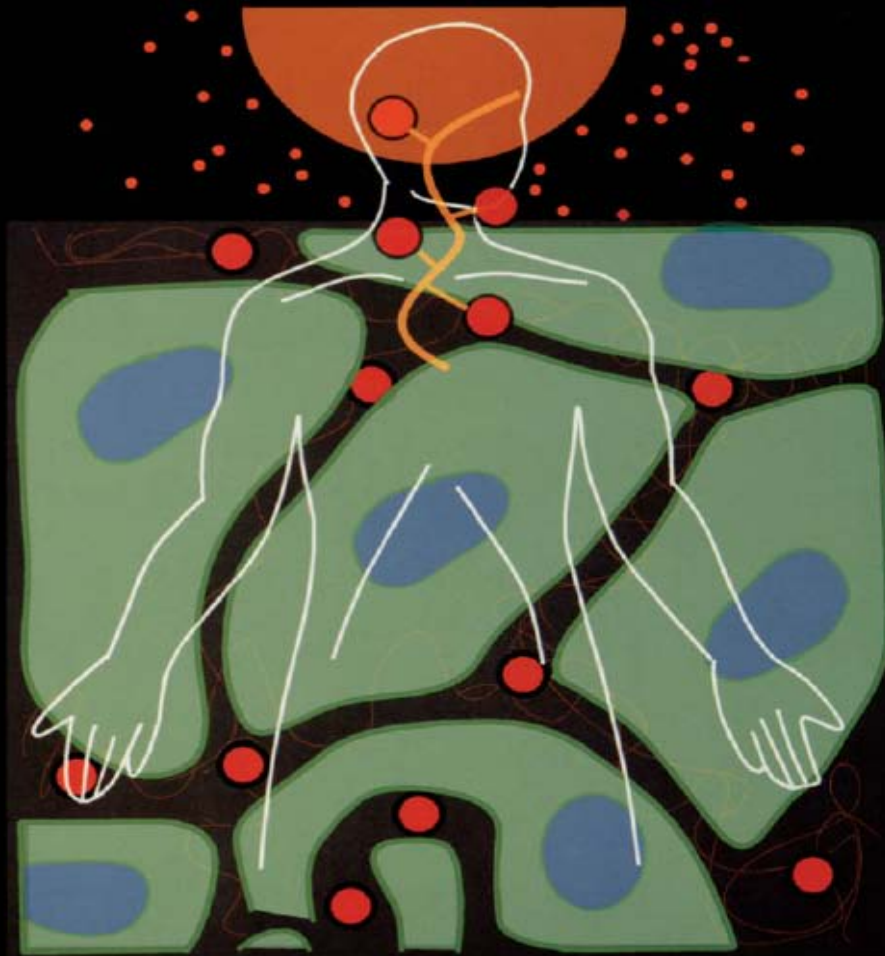


Targeted drug delivery – Targeted drug delivery using a multicomponent nanoparticle containing therapeutic as well as biological surface modifying agents – Mauro Ferrari, Univ. of Cal. Berkley



Drug Delivery

ENGINEERING PRINCIPLES FOR DRUG THERAPY



W. Mark Saltzman

Drug delivery

- The science of drug delivery may be described as the application of chemical and biological principles to control the *in vivo* of drug molecules for clinical benefit
- Scientists researching drug delivery seek to address these issues in order to (1) maximize drug activity and (2) minimize side effects
- The benefits of controlled drug delivery are: (1) more effective therapies
- with reduced side effects, (2) the maintenance of effective drug concentration levels in the blood, (3)
- patient's convenience as medicines are taken less frequently, and (4) increased patient compliance

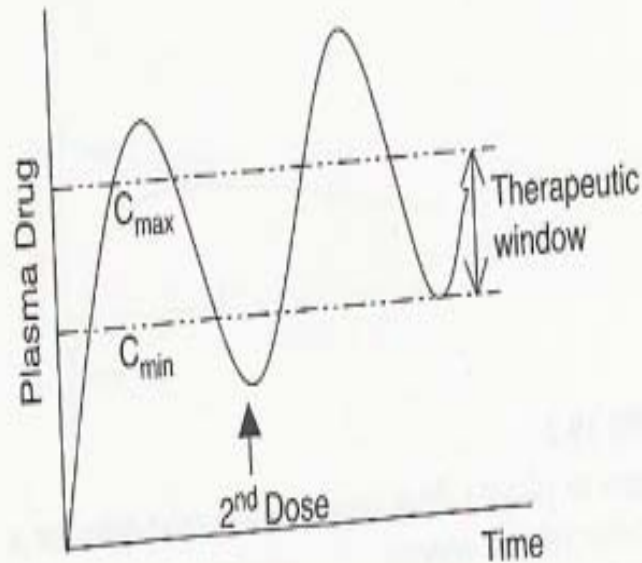


FIGURE 19.1
Changes in plasma drug concentration over time.

- The administration of drug leads to a certain concentration of plasma drug level. This concentration is decimated by uptake at different tissue, drug degradation at the liver, elimination by RES and excretion by the kidneys

Controlled release

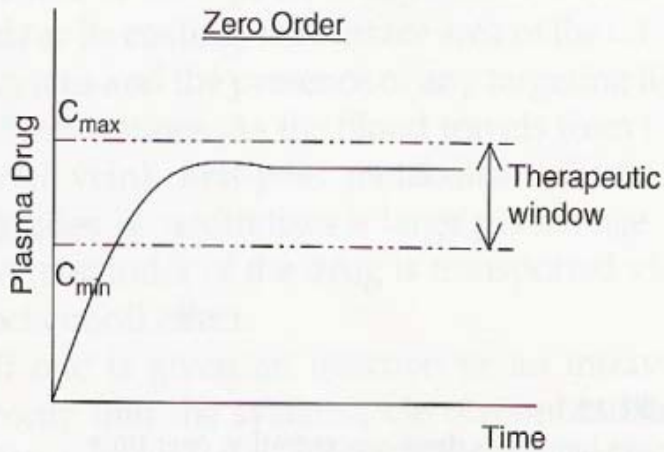
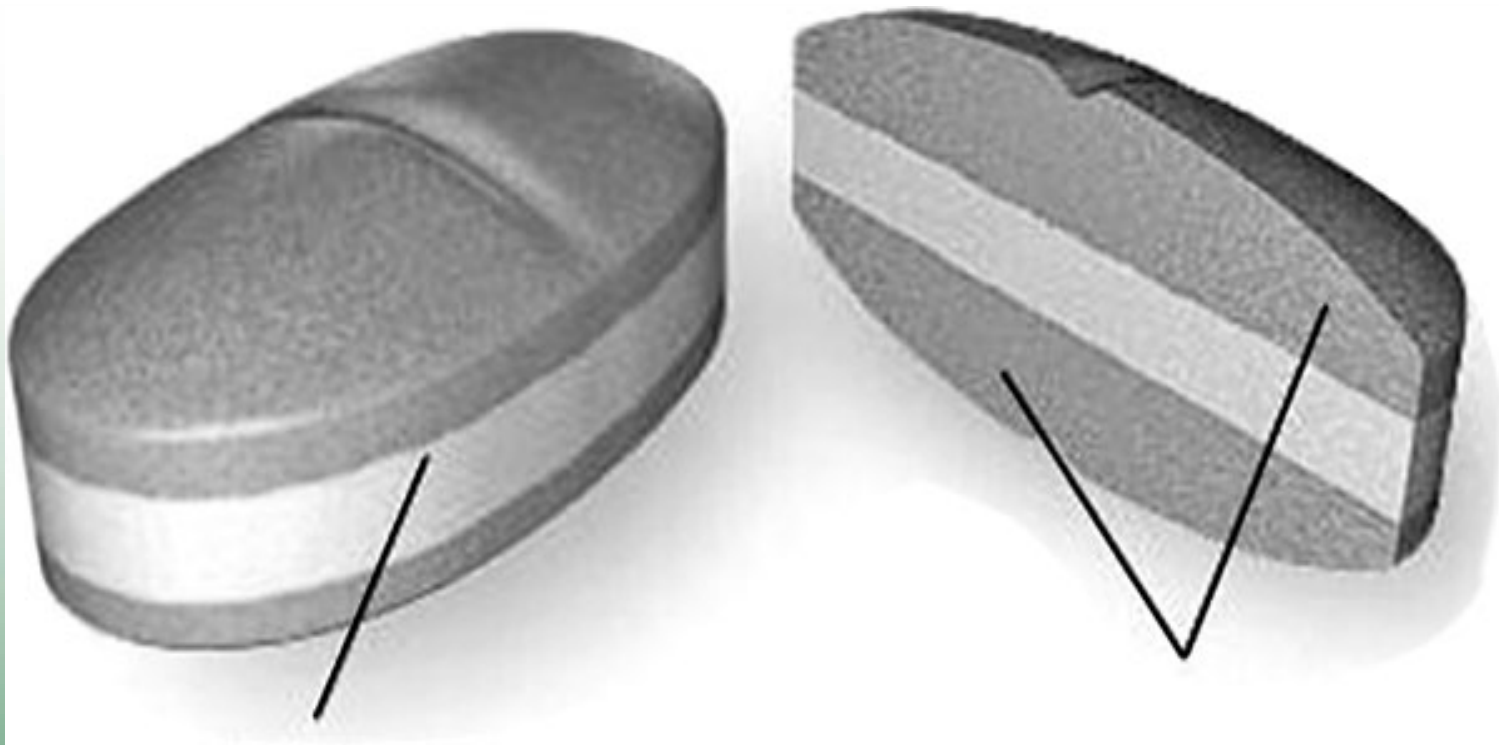


FIGURE 19.2

Changes in plasma drug concentration over time for a zero-order release system.

- In long run, the rate at which the drug is absorbed by the body is equivalent to the physiological drug clearance, the plasma drug concentration remains steady and within the therapeutic window over the duration of use



A core of hydroxypropyl methylcellulose(HPMC) matrix that contains the active drugs

One or two additional barrier layers that control the surface area diffusion of drug or drugs out of the core

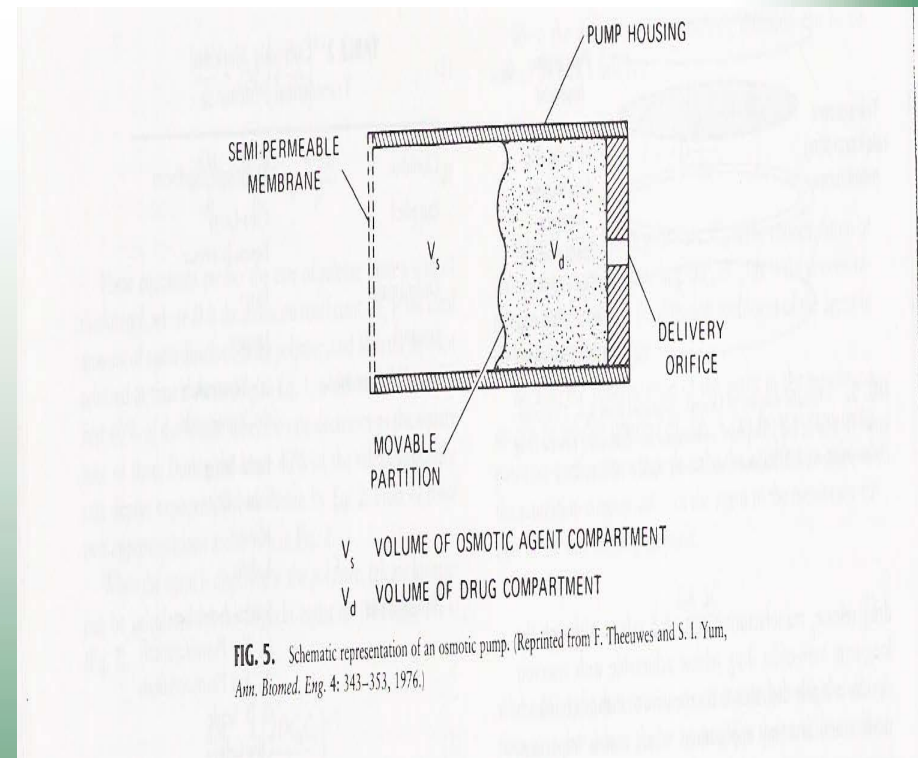
TABLE 19.4

Classification of Rate-Controlled Mechanisms

| Diffusion Controlled System | Water Penetration Controlled System | Polymer Degradation Controlled System |
|-----------------------------|-------------------------------------|---|
| Diffusion through polymer | Osmotic pump | Surface erosion |
| Diffusion through membrane | Swelling controlled | Bulk degradation, Polymer sidechain cleavage |

Water penetration controlled systems

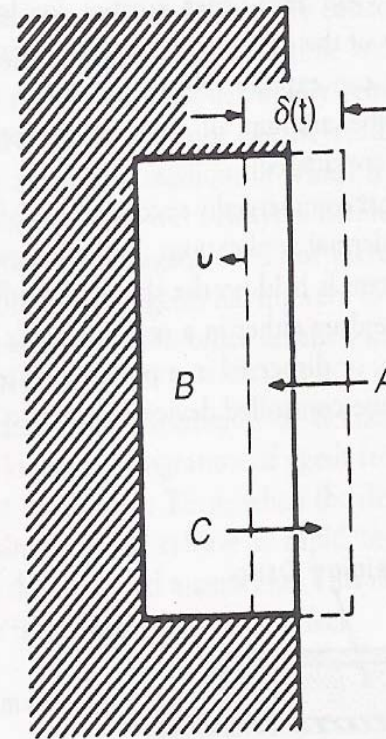
- The rate of delivery is controlled by the penetration of water into the device
- Osmotically controlled devices
- An osmotic agent is contained within a rigid housing and is separated from the agent by a movable partition
- Semipermeable membrane, in an aqueous environment, water is osmotically driven across the membrane
- Pressure on the movable partition, delivery from orifice



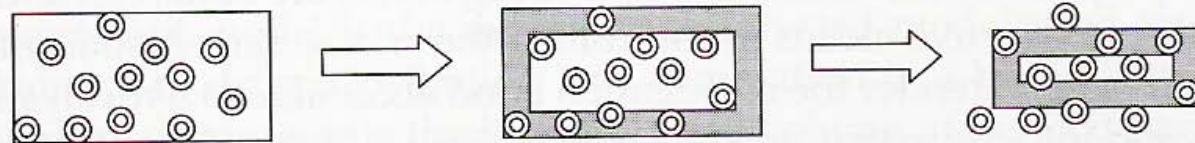
Swelling- controlled devices

- Drug is dispersed in a hydrophilic polymer that is glassy in the dehydrated state but swells when placed in an aqueous environment
- Diffusion of molecules in a glassy matrix is slow, no release occurs while the polymer is in glassy state
- Water will penetrate the matrix and as a consequence of swelling, the glass transition temperature of the polymer is lowered below the temperature of the medium, drug diffuses from the polymer

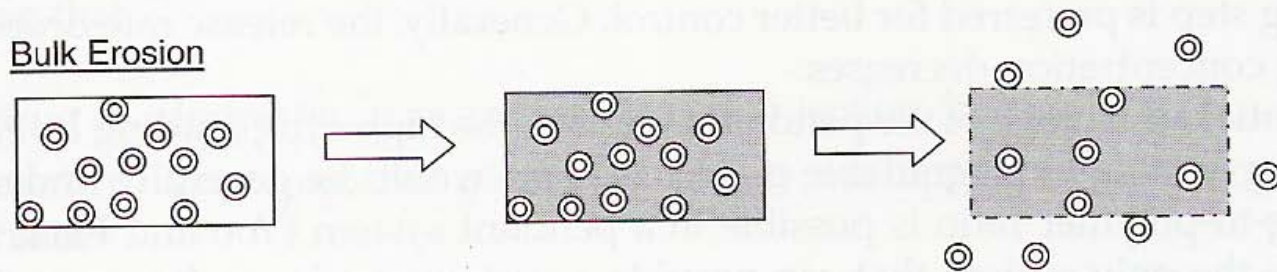
phenomenon just described.



Surface Erosion



Bulk Erosion



Sidechain Hydrolysis

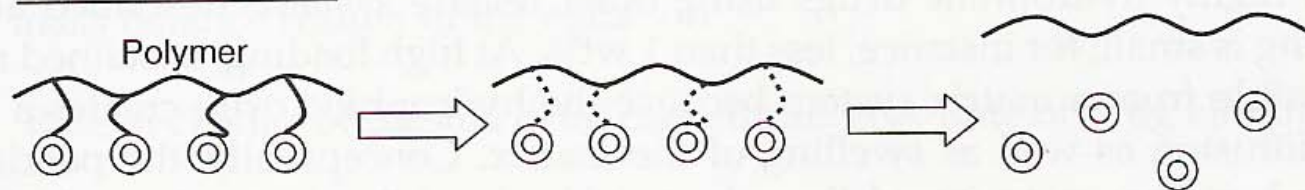


FIGURE 19.8

Schematic illustrating surface erosion, bulk erosion, and side chain hydrolysis.

Nanoparticles

- Vesicular systems, which are formed by a drug-containing liquid core (aqueous or lipophilic) surrounded by a single polymeric membrane

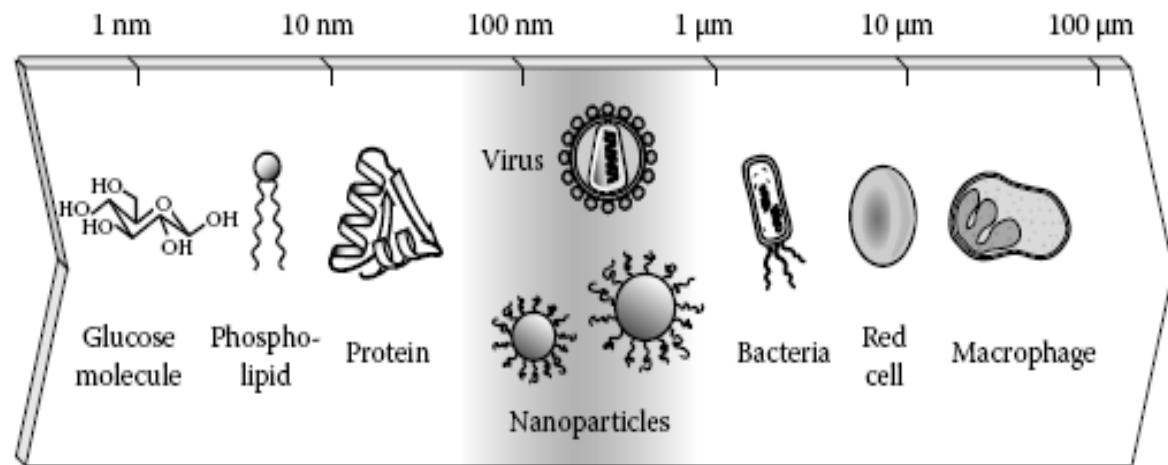


FIGURE 8.2 Sizes of nanoparticles compared with other biological entities.

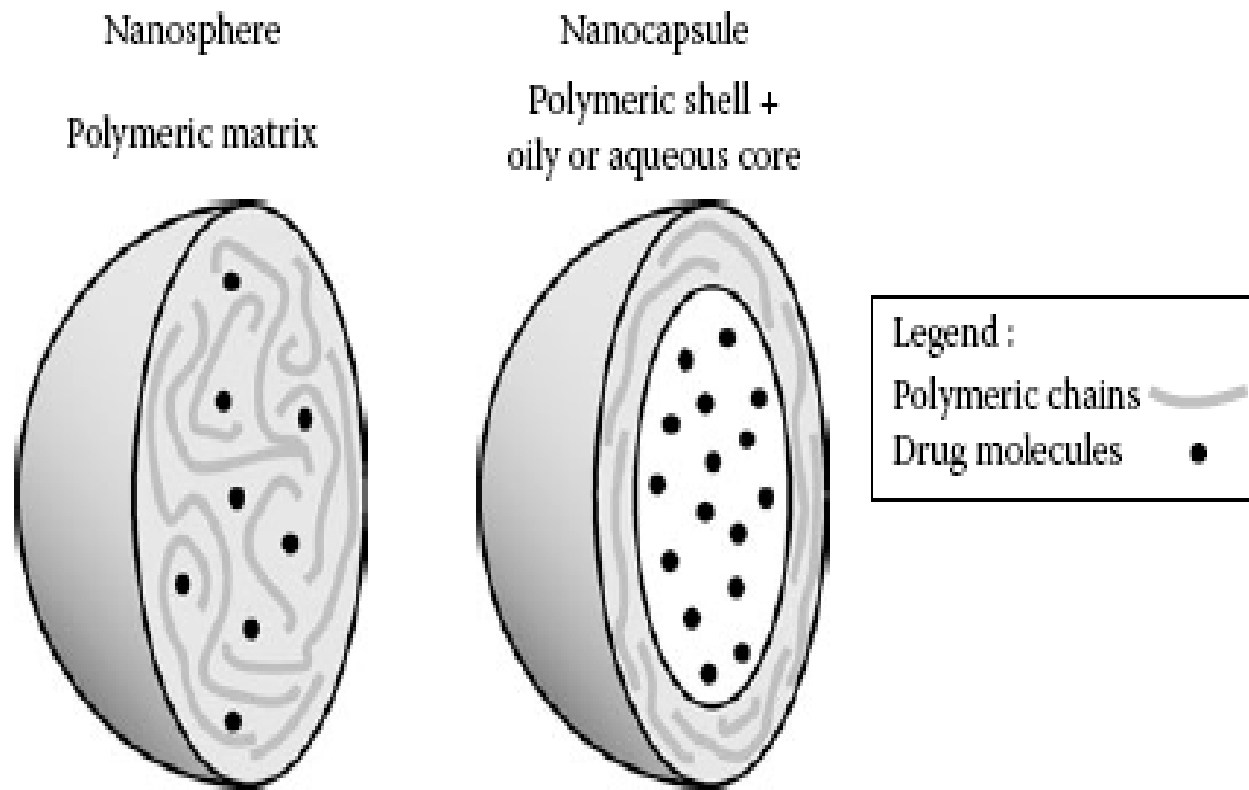
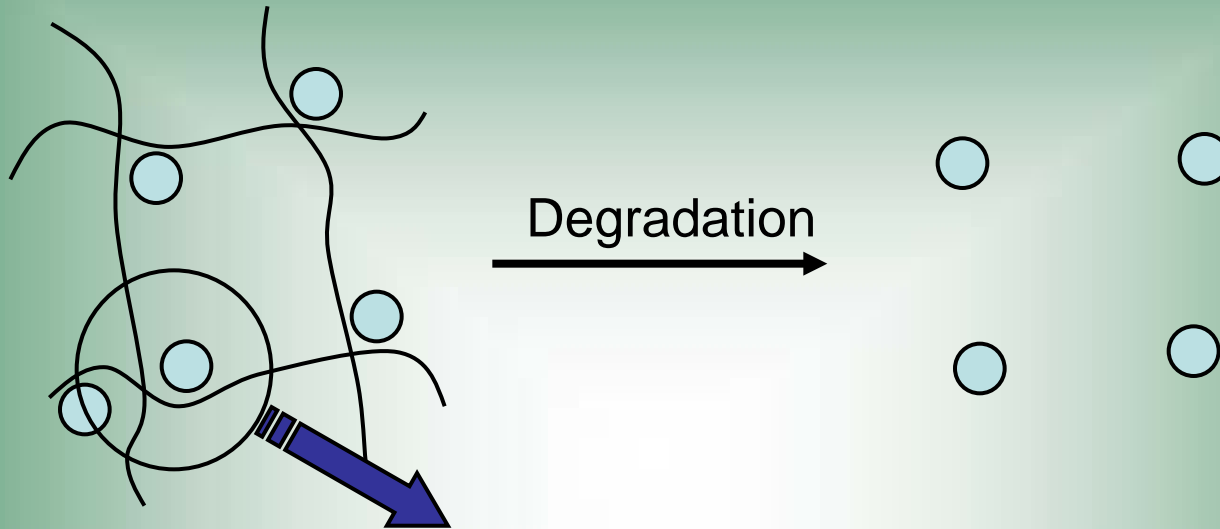
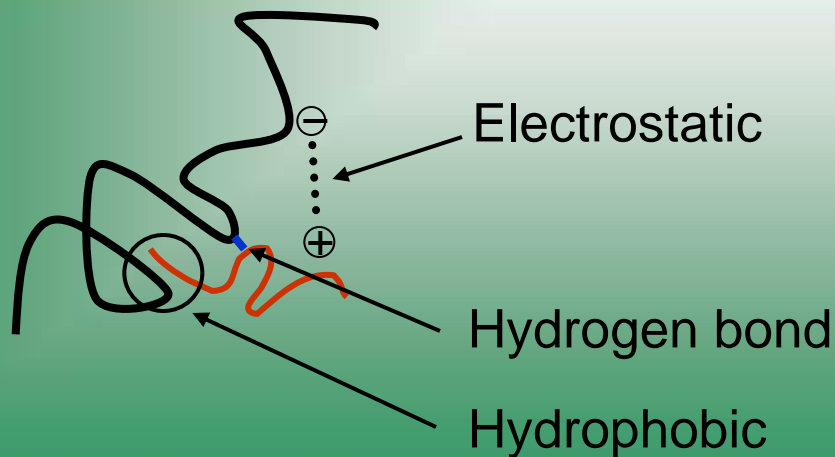


FIGURE 8.3 Morphology of nanospheres and nanocapsules.

Mechanism on the controlled release of Drug



Possible intermolecular interaction between carrier matrix and drug



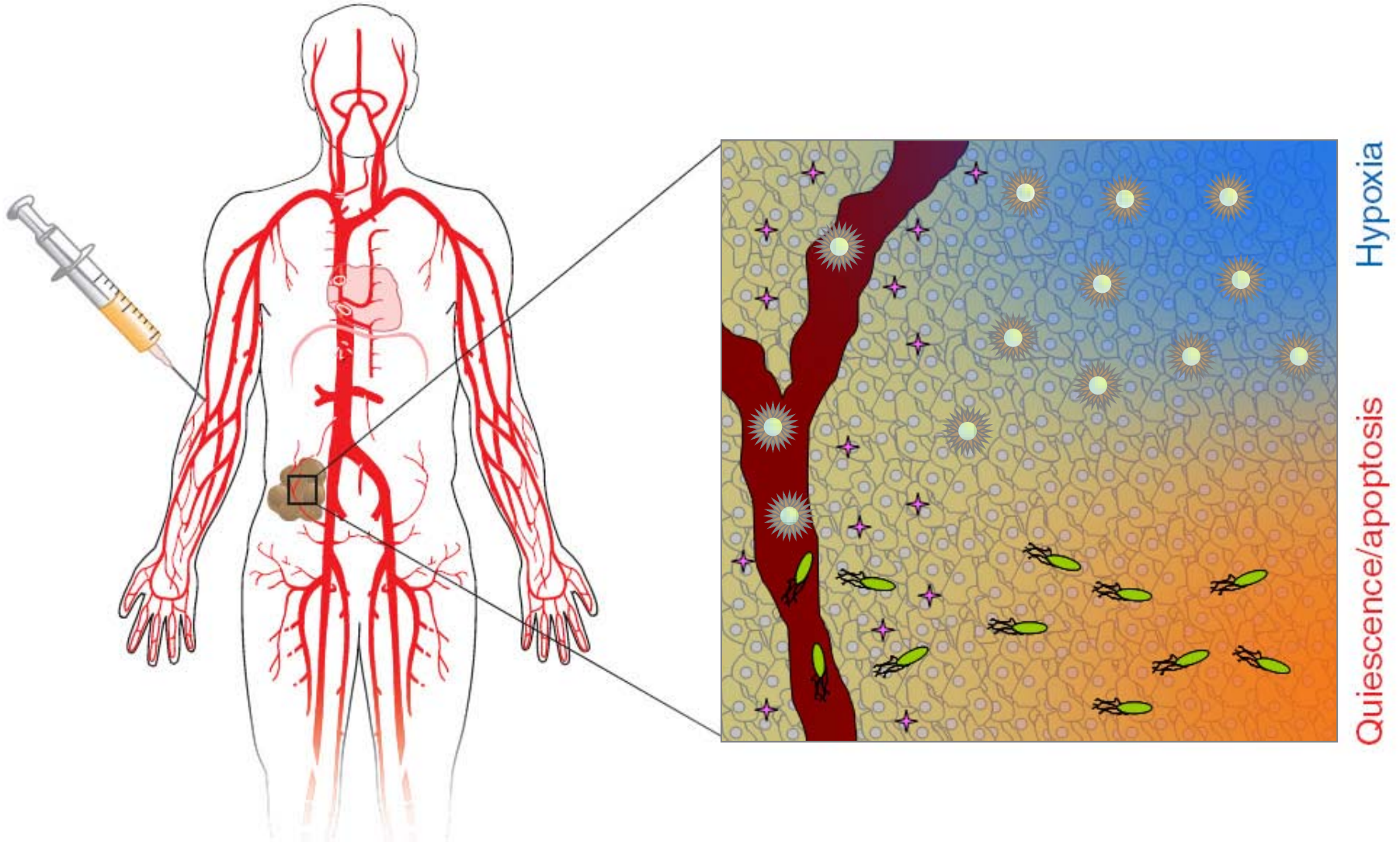
Characteristic Atomic Bonds

| Bonding Energy | | | | |
|----------------|------------------|--------|---------------------------|--------------------------------|
| Bonding Type | Substance | kJ/mol | eV/Atom, Ion, Molecule | Melting Temperature (°C) |
| Ionic | NaCl | 640 | 3.3 | 801 |
| | MgO | 1000 | 5.2 | 2800 |
| | Si | 450 | 4.7 | 1410 |
| Covalent | C (dia) | 713 | 7.4 | >3550 |
| | Hg | 68 | 0.7 | -39 |
| | Al | 324 | 3.4 | 660 |
| Metallic | Fe | 406 | 4.2 | 1538 |
| | W | 849 | 8.8 | 3410 |
| van der Waals | Ar | 7.7 | 0.08 | -189 |
| | Cl ₂ | 31 | 0.32 | 101 |
| Hydrogen | NH ₃ | 35 | 0.36 | -78 |
| | H ₂ O | 51 | 0.52 | 0 |

Adapted from: Fundamentals of Materials Science and Engineering / An Introduction," William D. Callister, Jr., John Wiley & Sons, NY, NY, 2001 or <http://www.scribd.com/doc/8680373/Fundamentals-of-Materials-Science-and-Engineering-Callister>

New Topic in Drug Delivery

Targeted Delivery



Intelligent Stealth Technology

Anti-Immune Response: Invisible Nanoparticles

One of the challenges in developing effective nanoparticles in Health Technology is designing them so they can perform two critical functions: evading the body's normal immune response and reaching their intended targets.

We need exactly the right combination of these properties, because if they don't have the right concentration of targeting molecules, they won't get to the cells we want, and if they don't have the right stealth properties, they'll get taken up by macrophages.

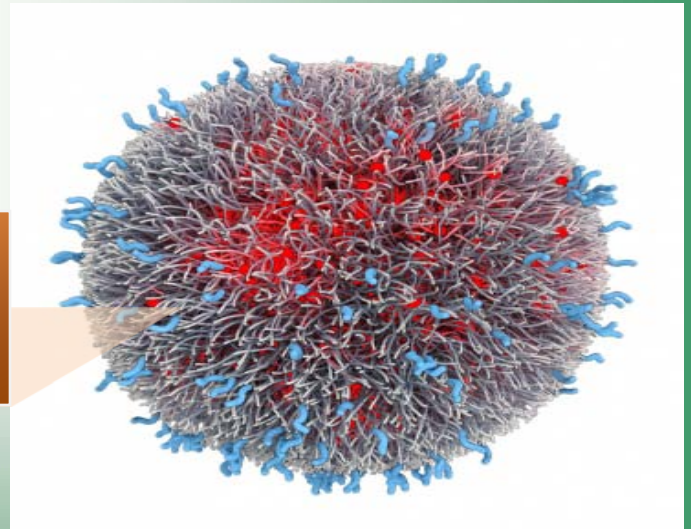
Anti-Radar Stealth Jet-F-119



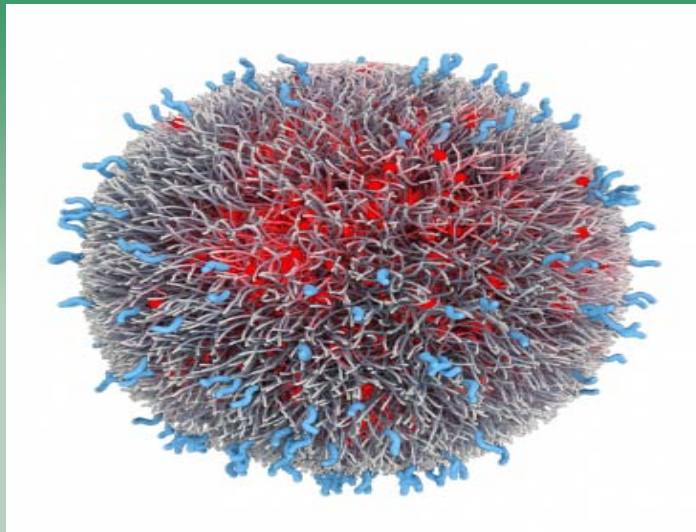
Anti-Radar Stealth Jet-F-119



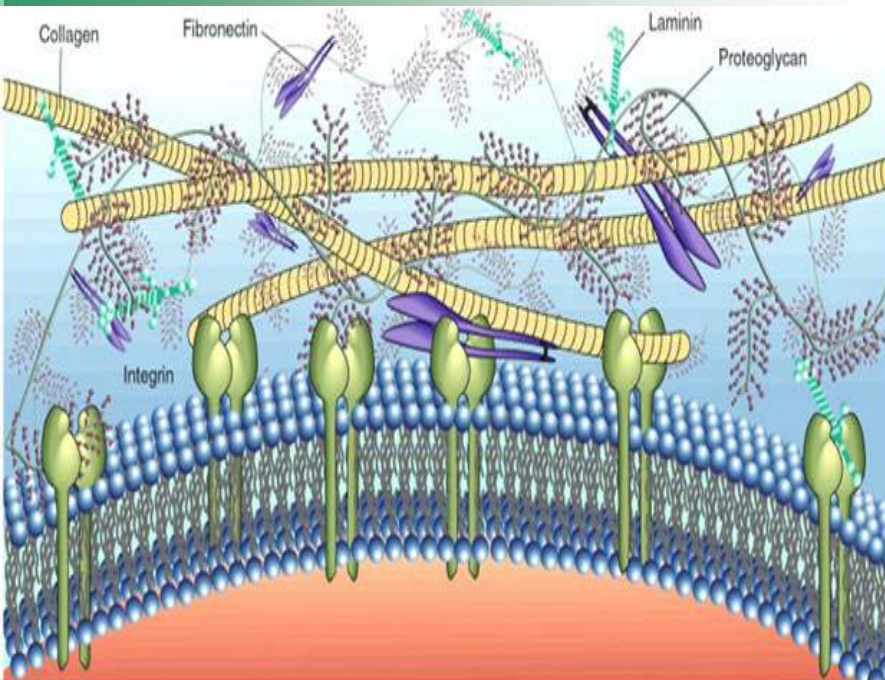
Anti-Immune Response: Invisible Nanoparticles



Interface
Biology
Engineering

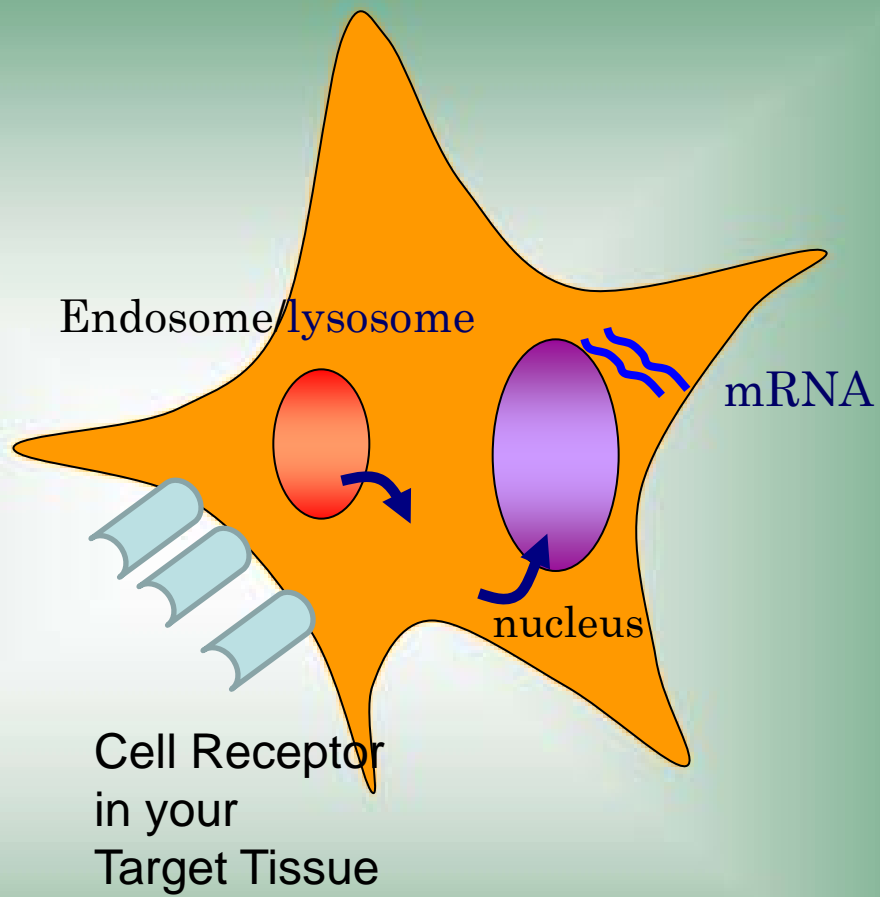
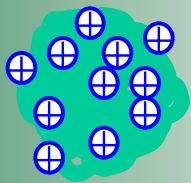


1. Targetable Nanoparticles

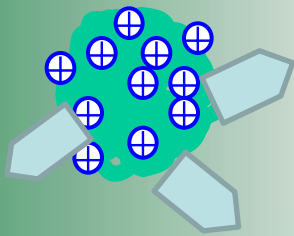


Find Cell Receptor in your
Target Tissue

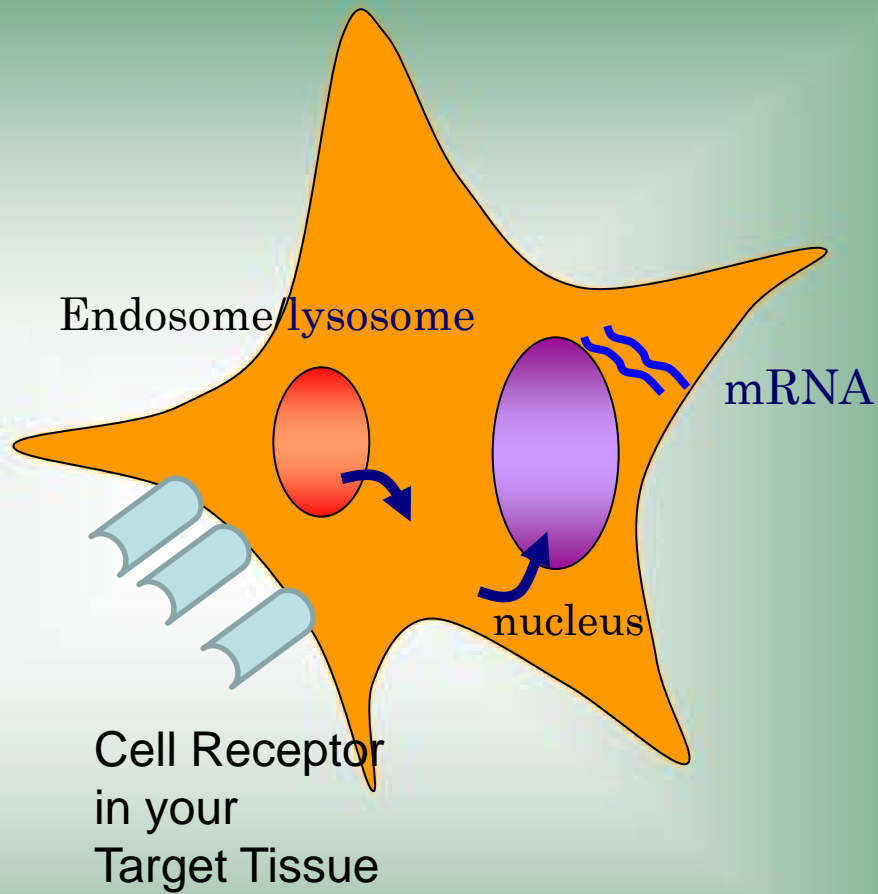
Nanoparticle

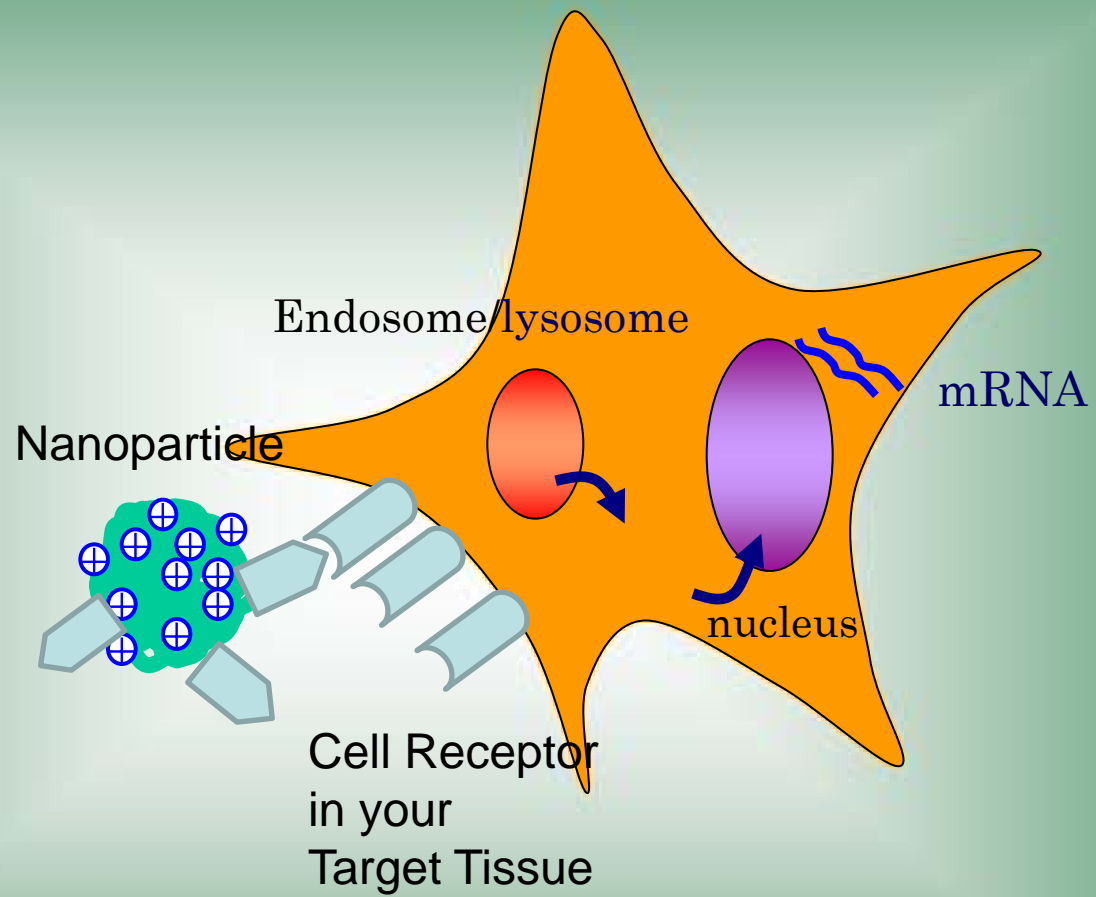


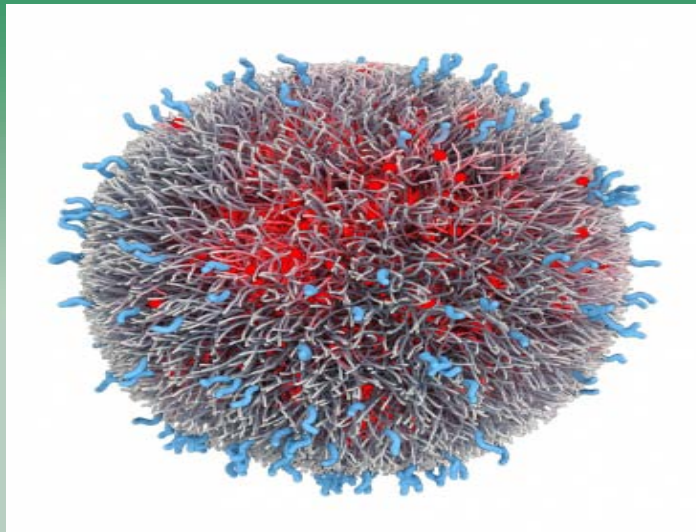
Nanoparticle



Attach a Ligand
Molecule

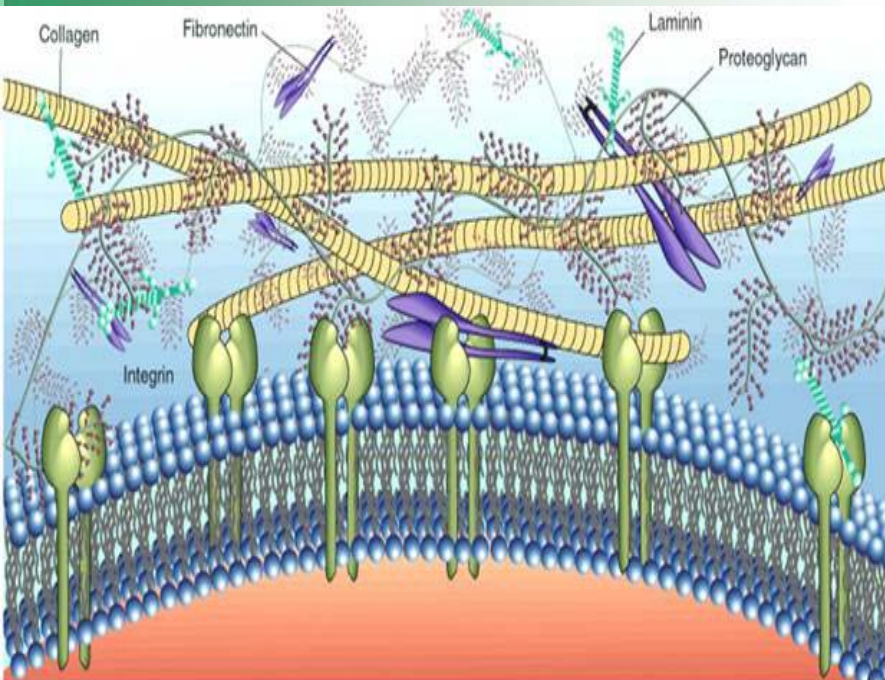




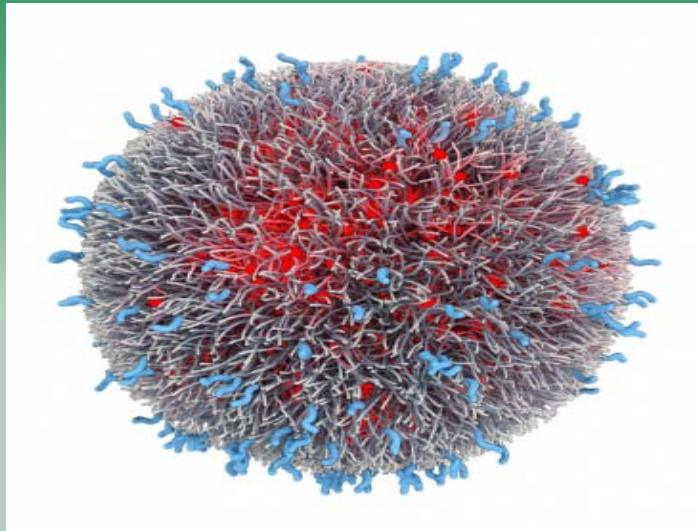


2. Invisible Nanoparticles

Nanoparticles covered with:
Biomolecules
PEG
(Invisible by Immune system)



PEGylation Technology



3. Detectable Nanoparticles

Loaded with:
Iron Oxide
Nanoparticles
(Detectable by MRI)

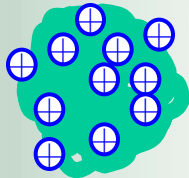
Super Paramagnetic
Iron Oxide, Fe_3O_4



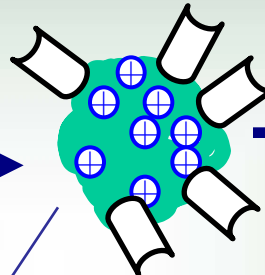
40 C
14 hr
pH 7

nanoparticle
formation

Magnetic
Nanoparticles



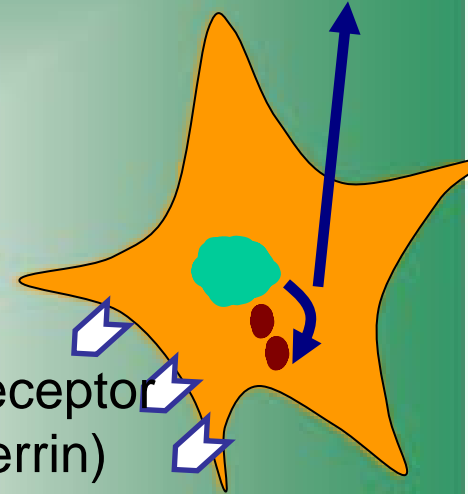
RGD ligand



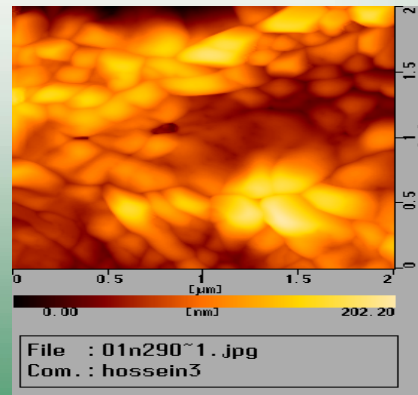
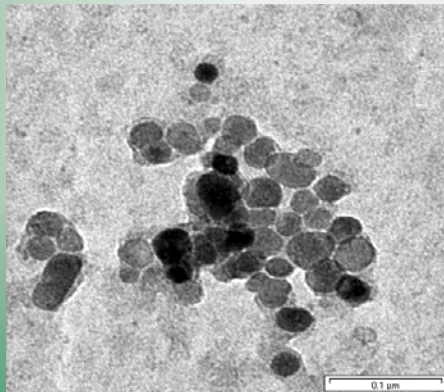
Loaded with Target Molecule

Target receptor
(transferrin)

Sustained Release of Iron Oxide

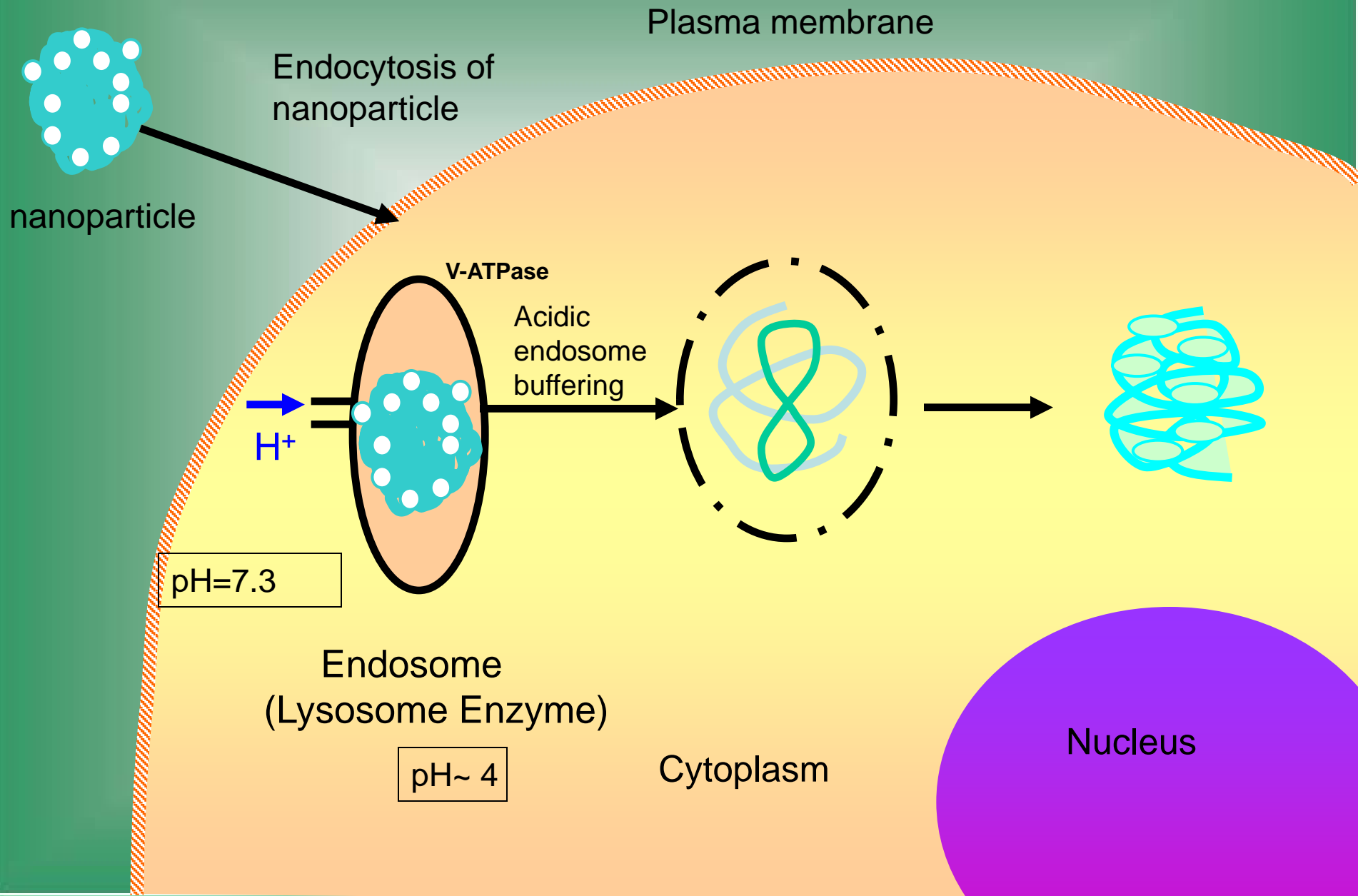


Polyanion
(Dextran)

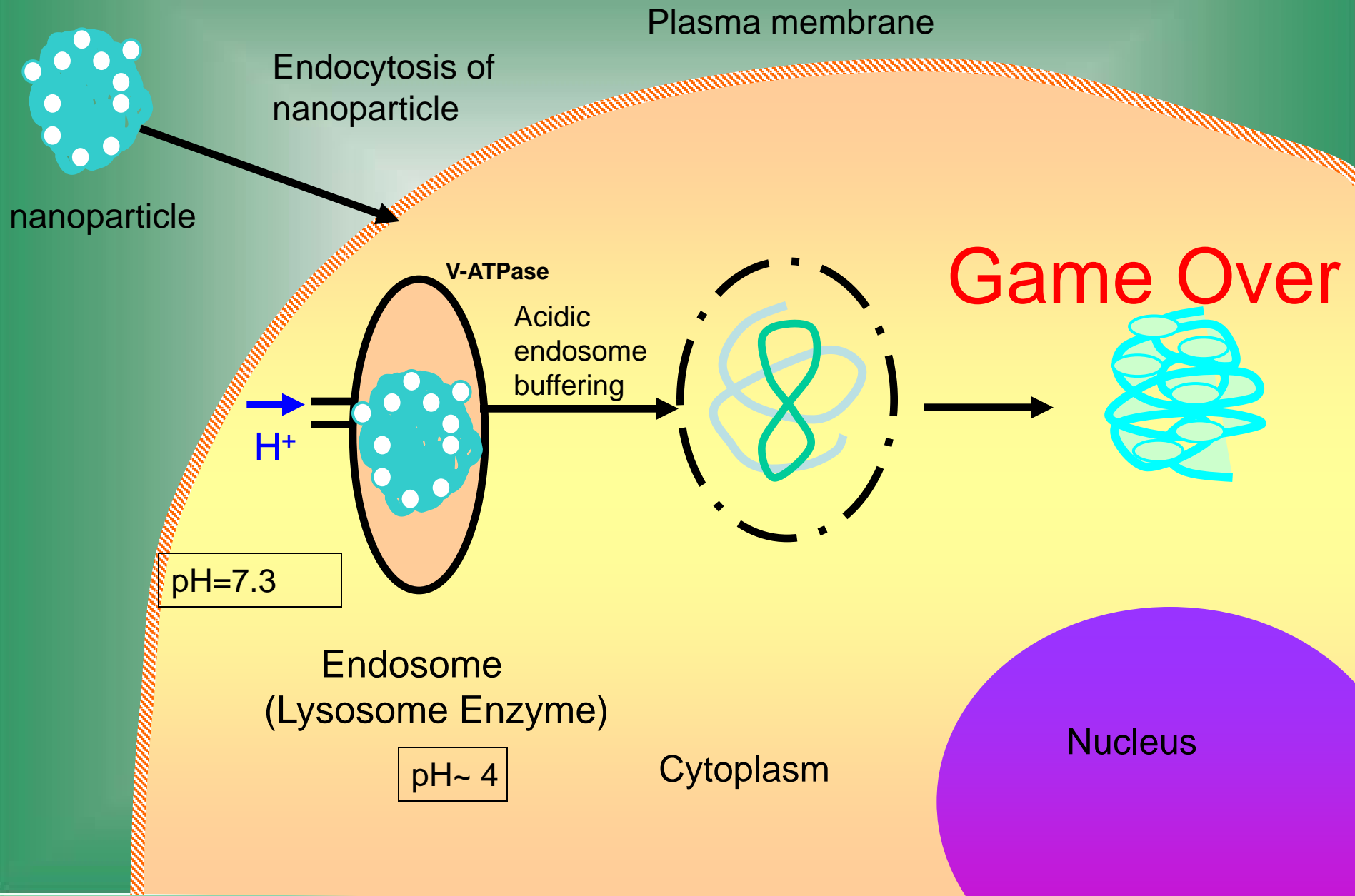


Double Glue
1.Targeted Cells
2.MRI monitoring

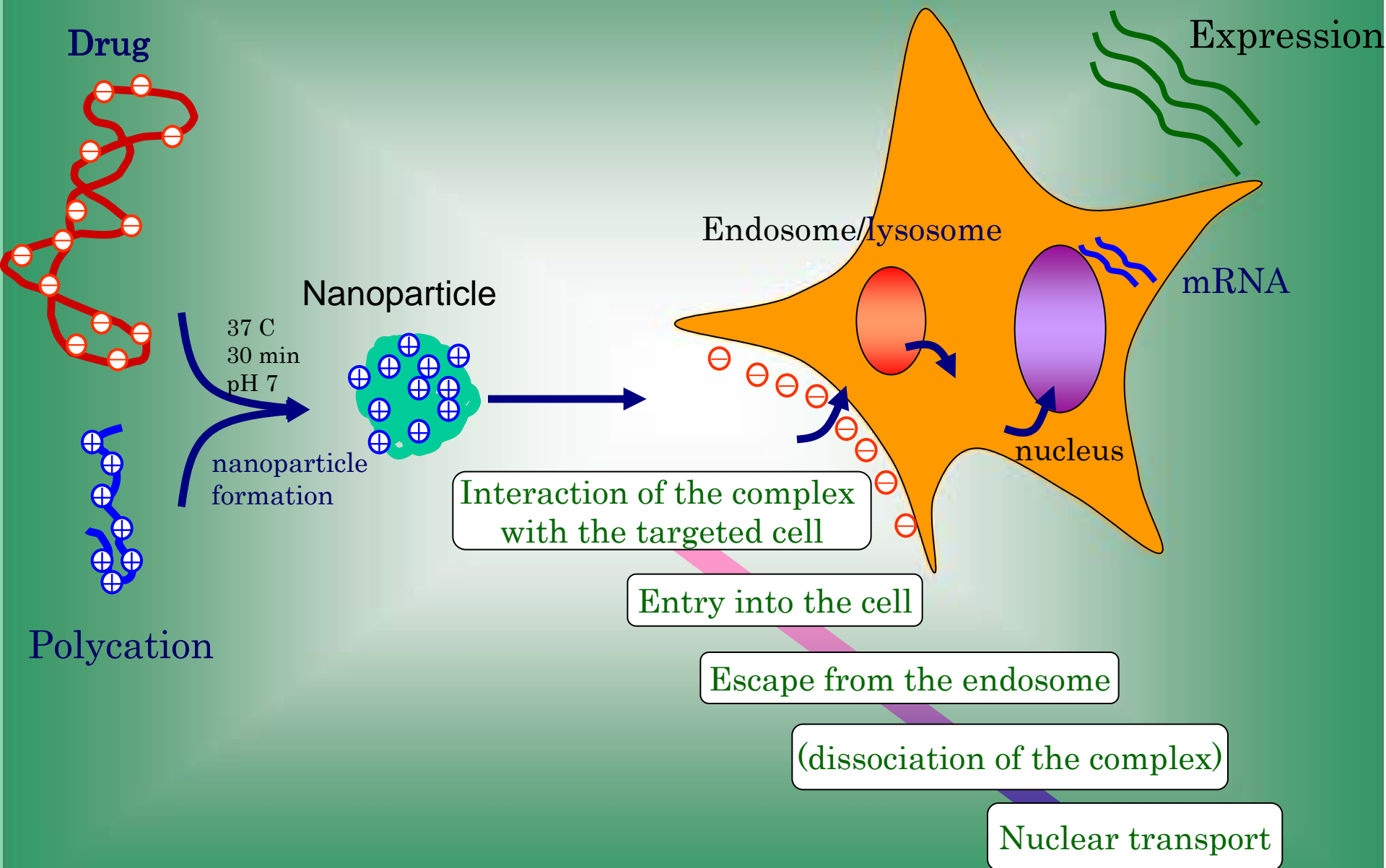
Last Barriers: Intelligent Secret Survive



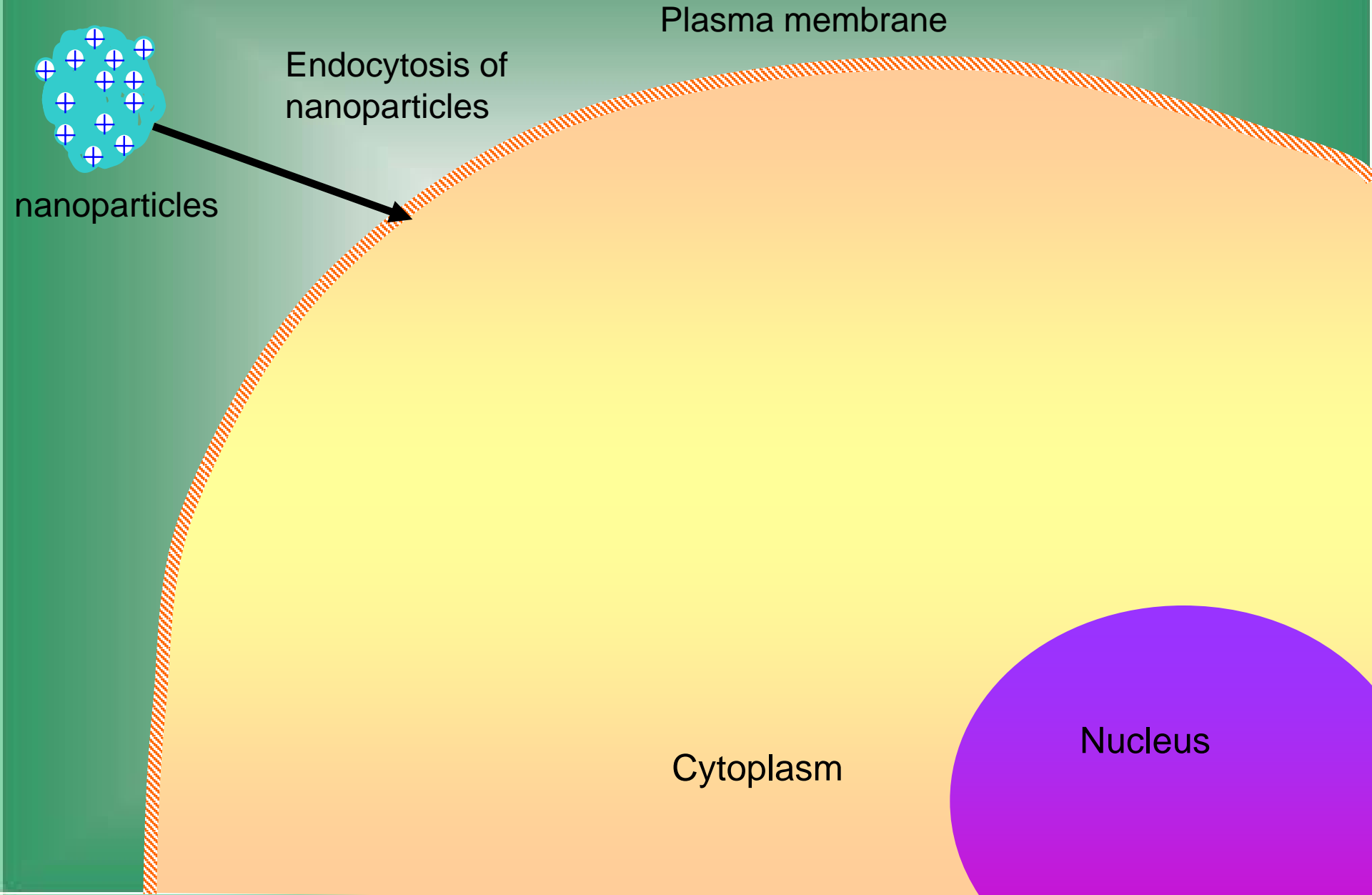
Last Barriers: Intelligent Secret Survive



Cellular barriers for *Targeted* delivery (Based on Cationic Polymer)

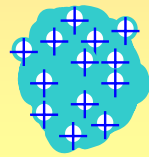


The proton sponge effect



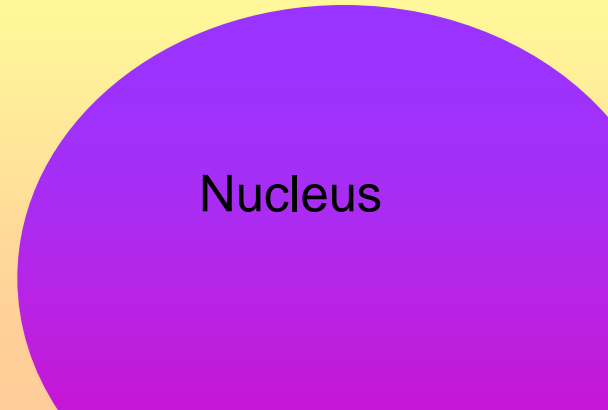
The proton sponge effect

Plasma membrane



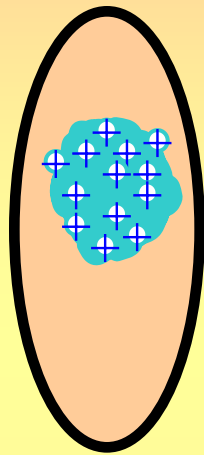
Cytoplasm

Nucleus



The proton sponge effect

Plasma membrane



pH=7.3

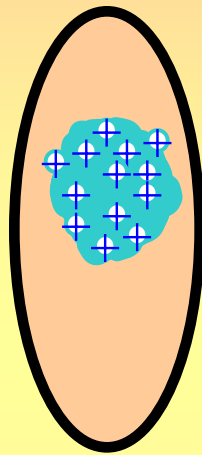
Endosome

Cytoplasm

Nucleus

The proton sponge effect

Plasma membrane



pH=7.3

Endosome
(Lysosome Enzyme)

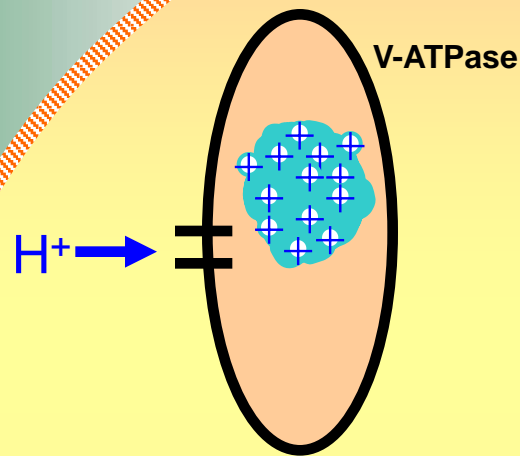
pH~ 4

Cytoplasm

Nucleus

The proton sponge effect

Plasma membrane



pH=7.3

Endosome
(Lysosome Enzyme)

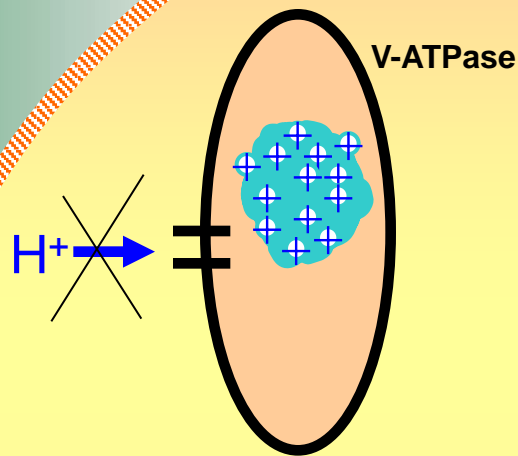
pH~ 4

Cytoplasm

Nucleus

The proton sponge effect

Plasma membrane



pH=7.3

Endosome
(Lysosome Enzyme)

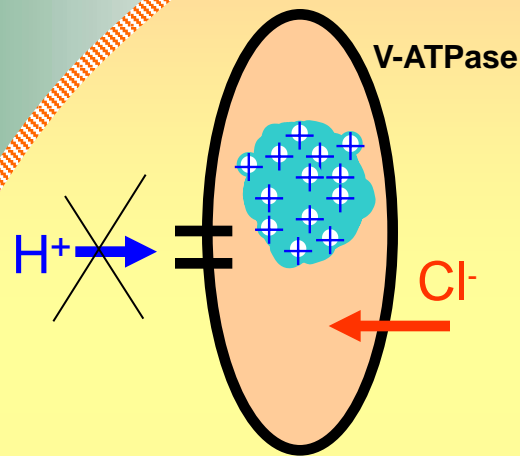
pH~ 4

Cytoplasm

Nucleus

The proton sponge effect

Plasma membrane



pH=7.3

Endosome
(Lysosome Enzyme)

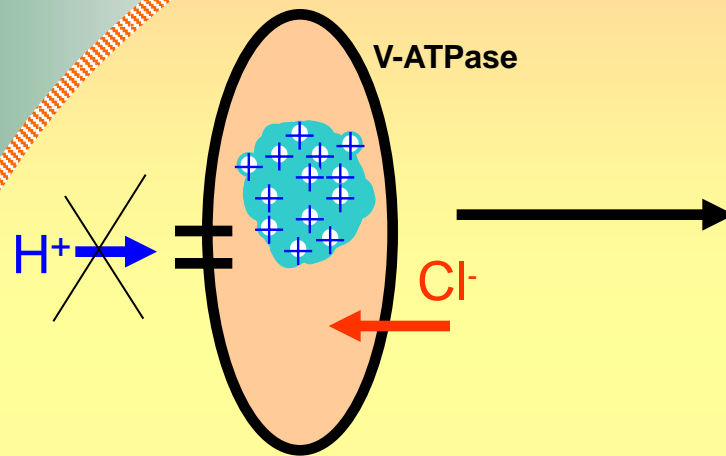
pH~ 4

Cytoplasm

Nucleus

The proton sponge effect

Plasma membrane



pH=7.3

Endosome
(Lysosome Enzyme)

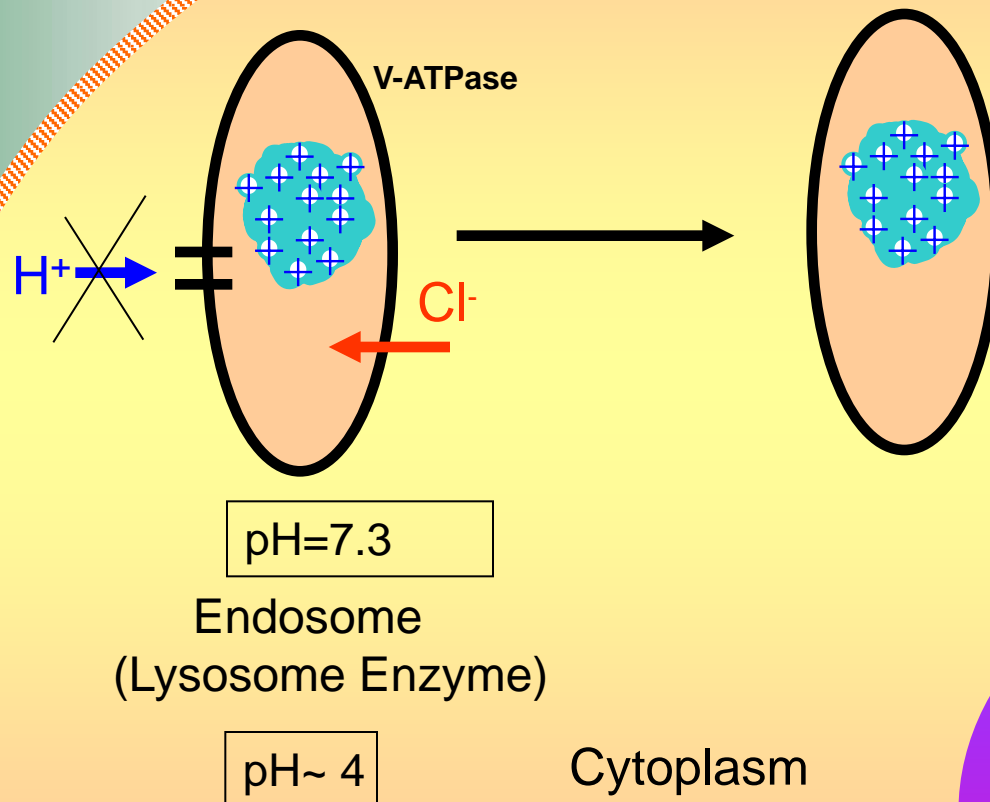
pH~ 4

Cytoplasm

Nucleus

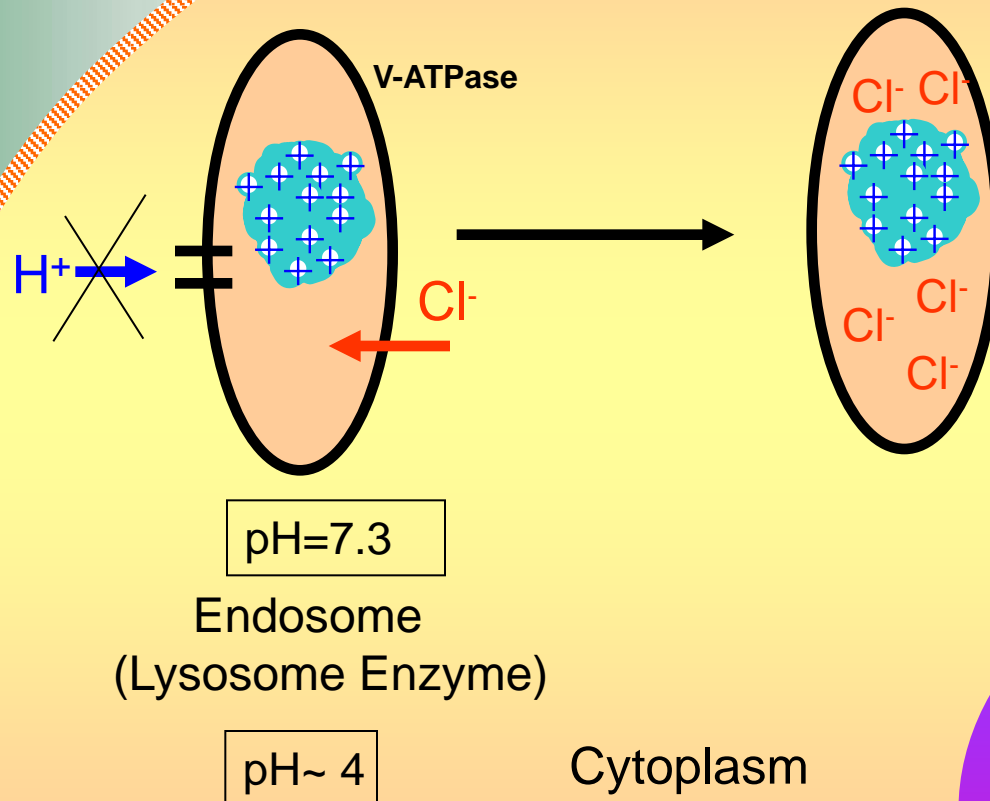
The proton sponge effect

Plasma membrane

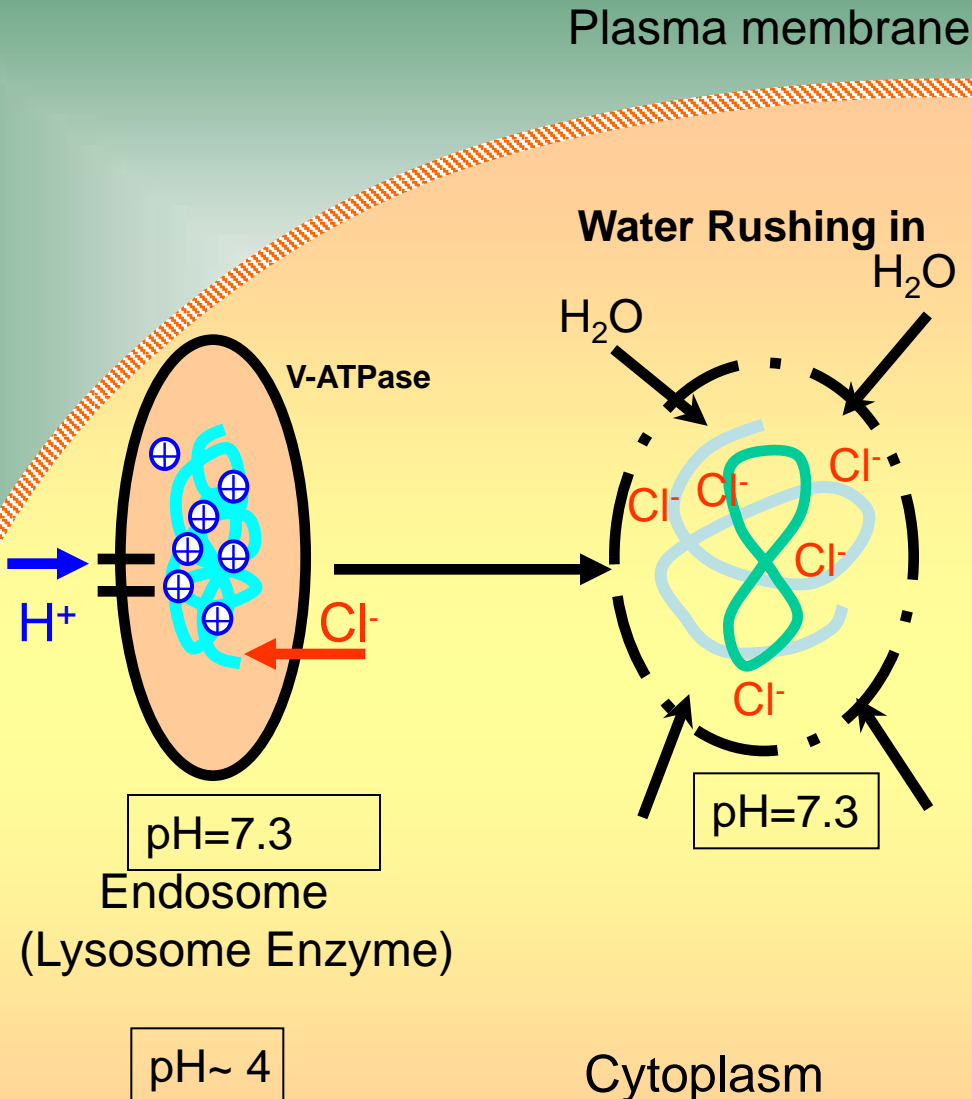


The proton sponge effect

Plasma membrane

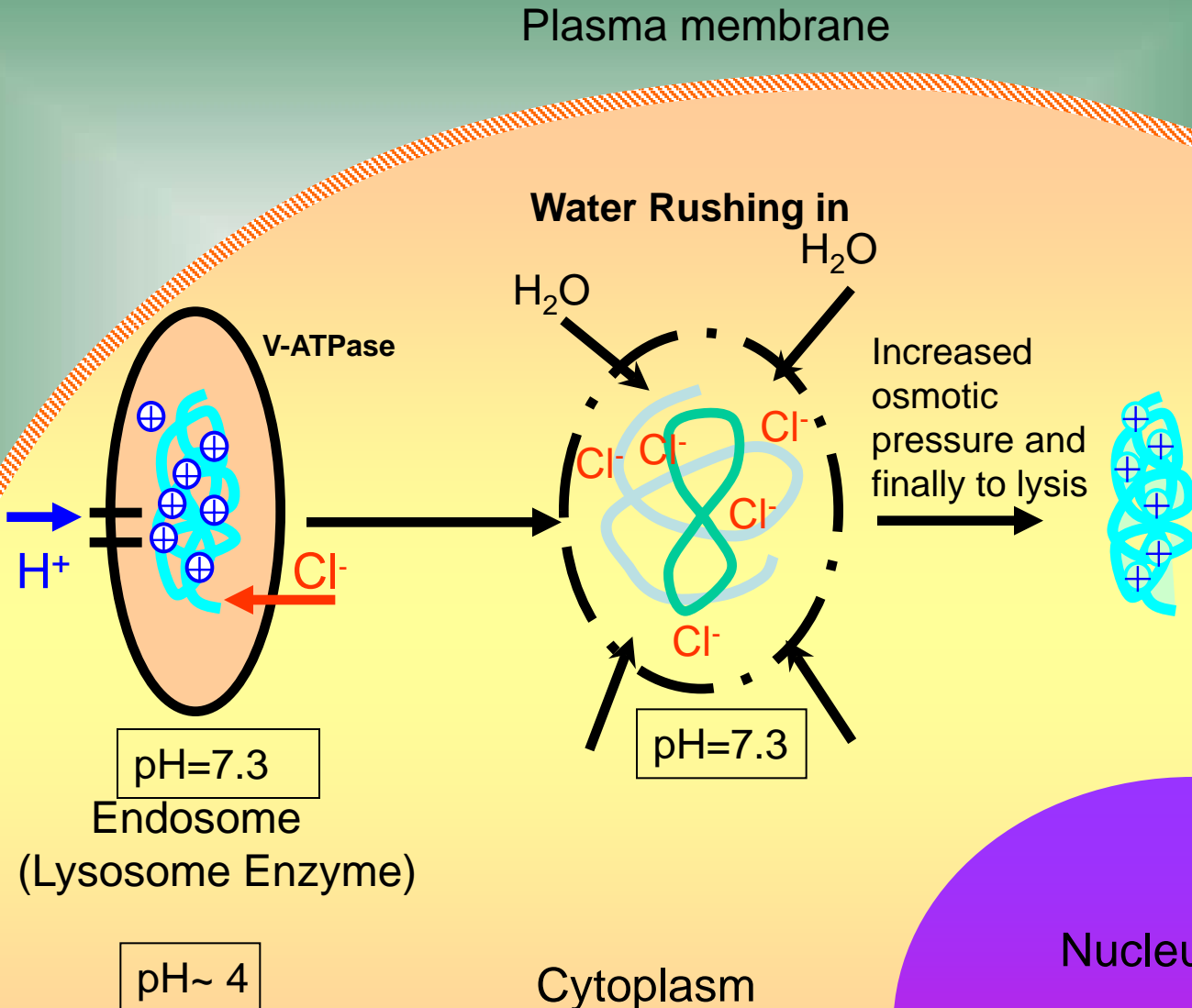


The proton sponge effect

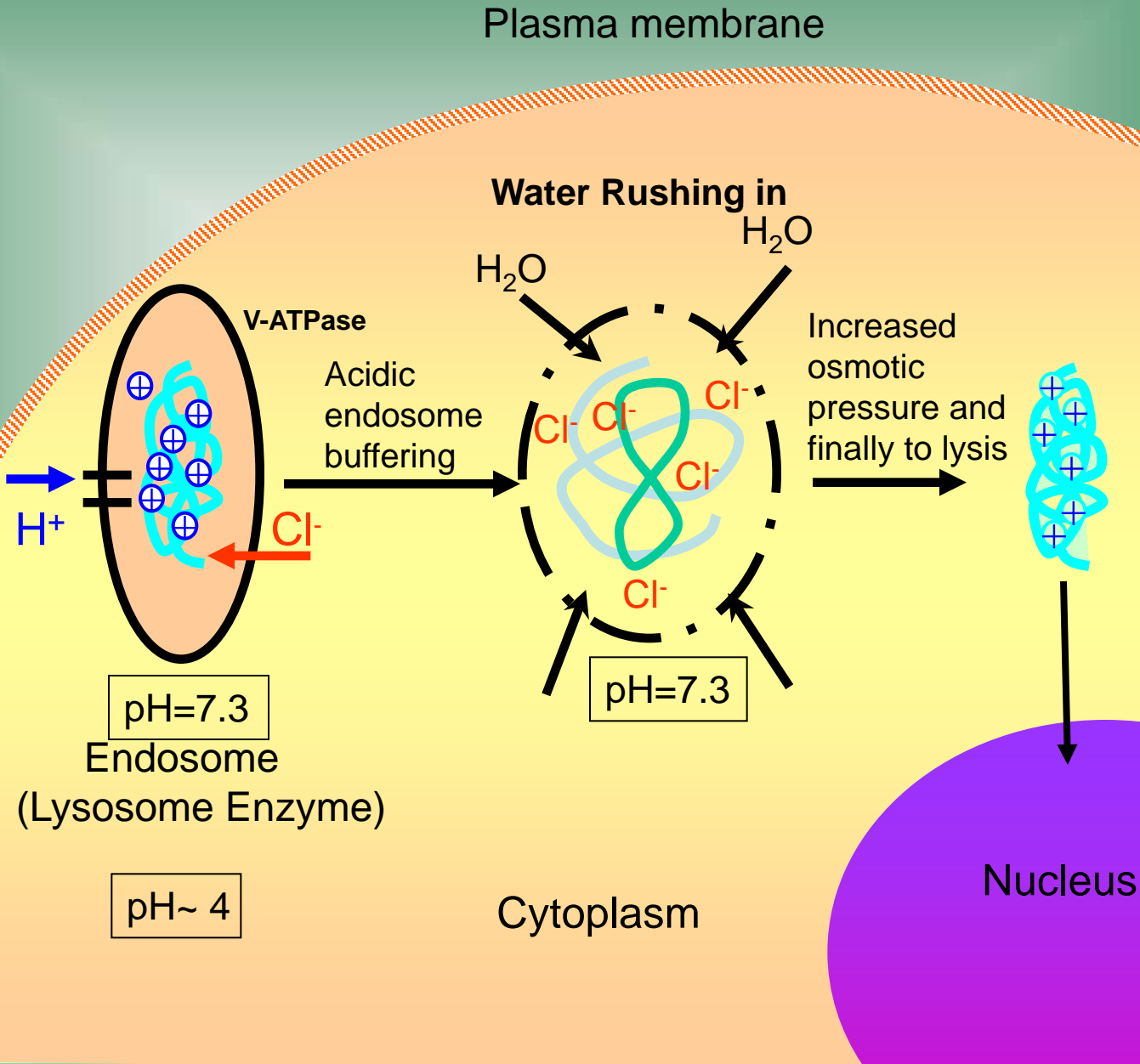


Nucleus

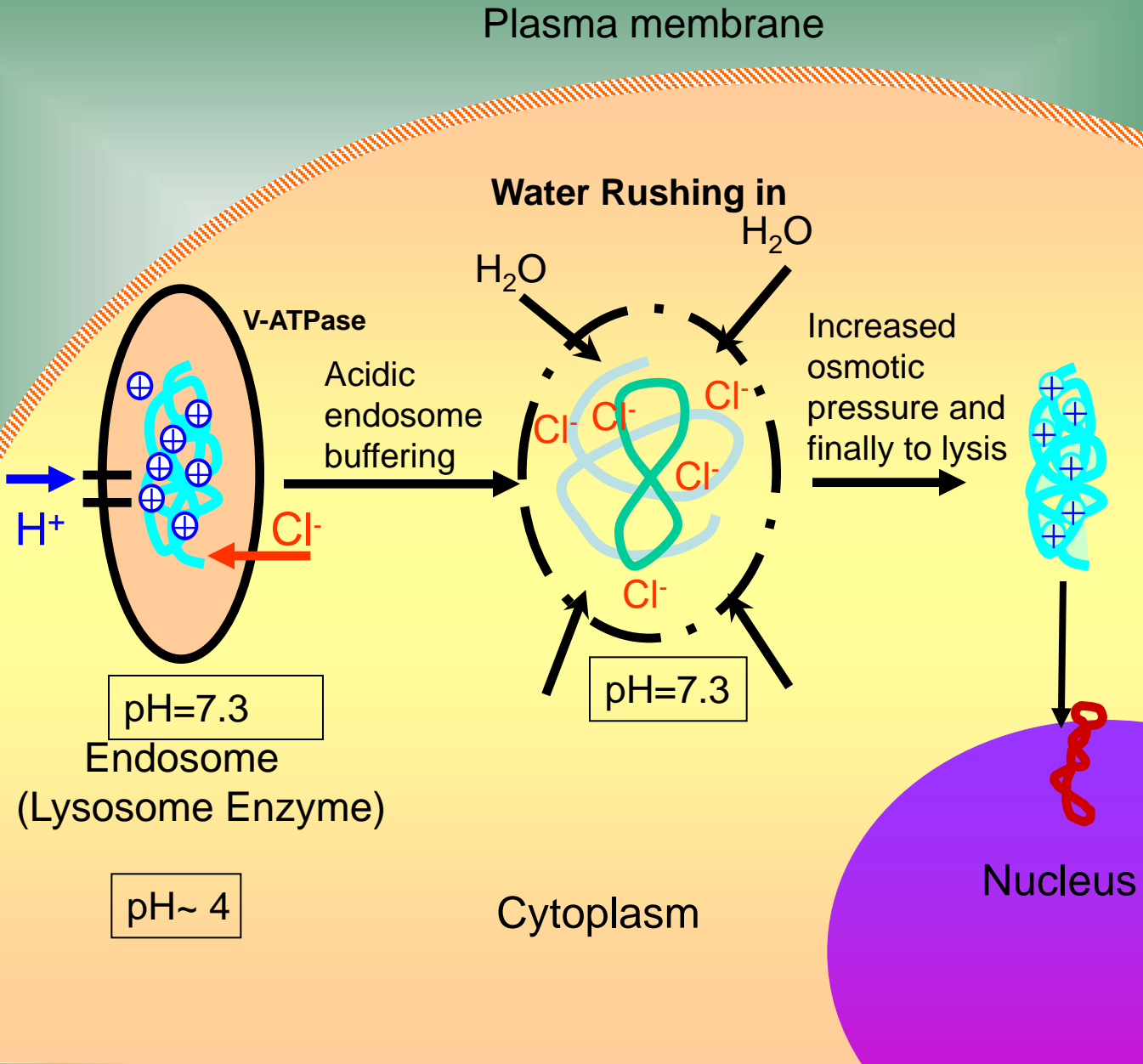
The proton sponge effect



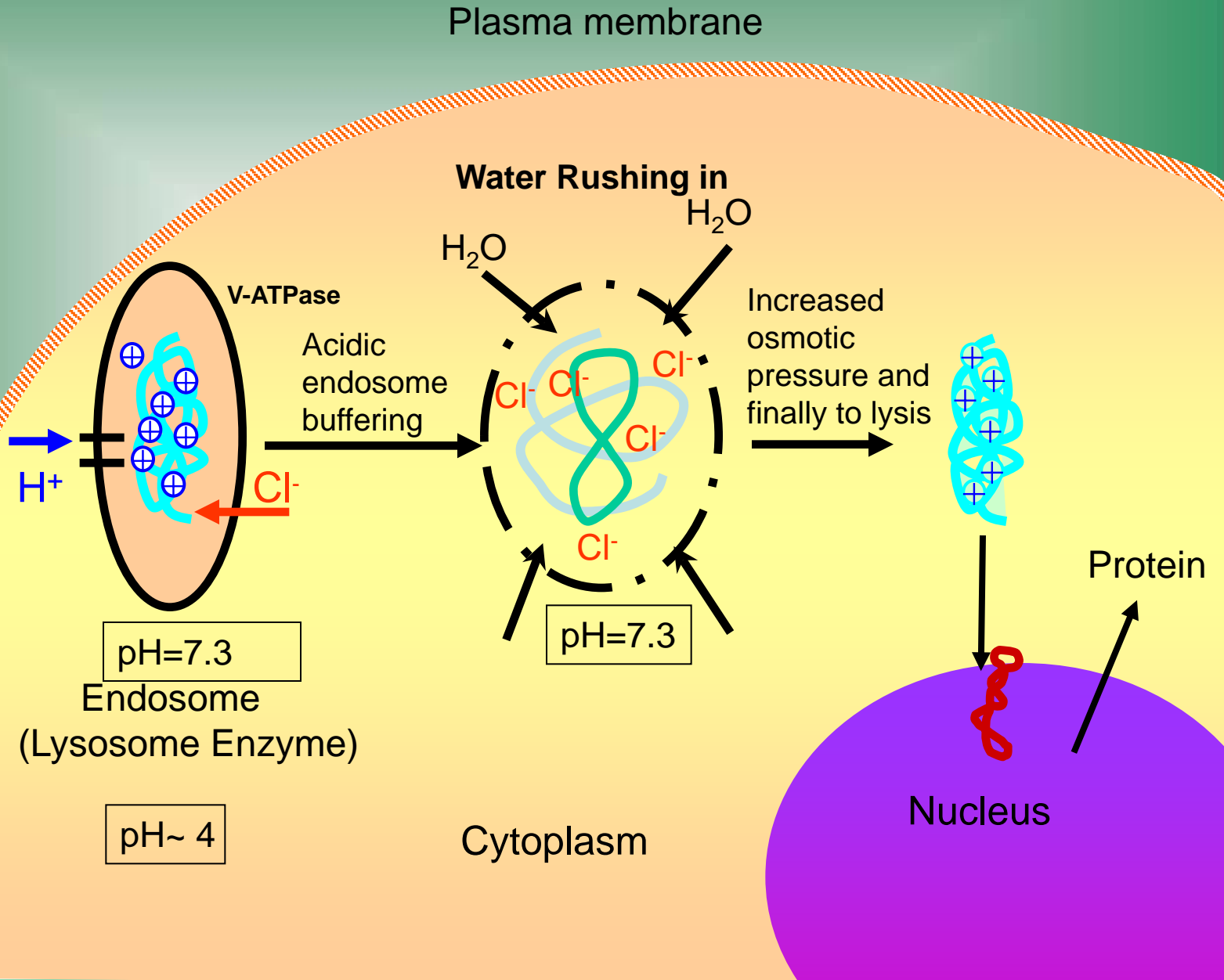
The proton sponge effect



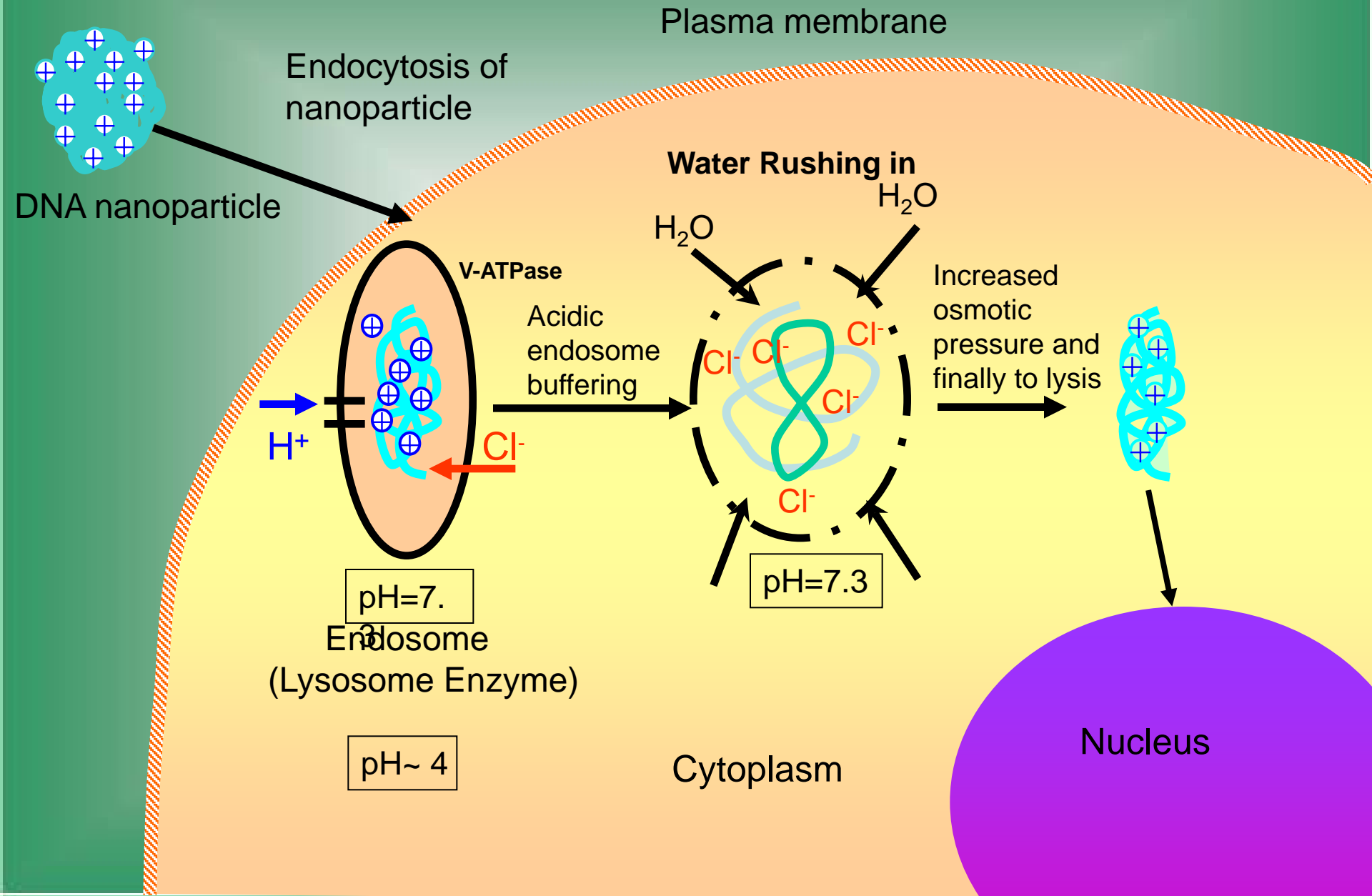
The proton sponge effect



The proton sponge effect



The proton sponge effect



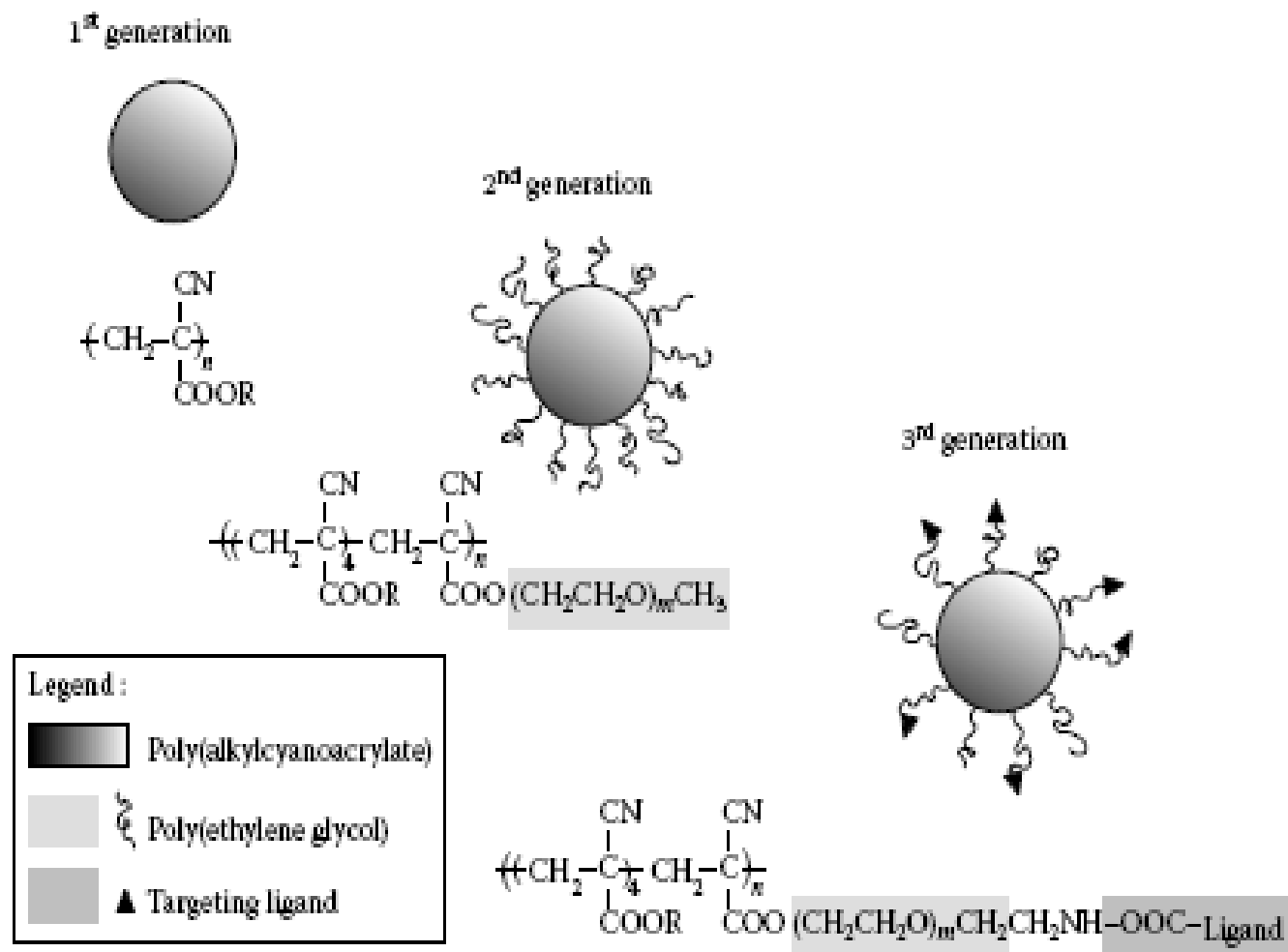


FIGURE 8.4 Three generations of nanoparticles for drug delivery.

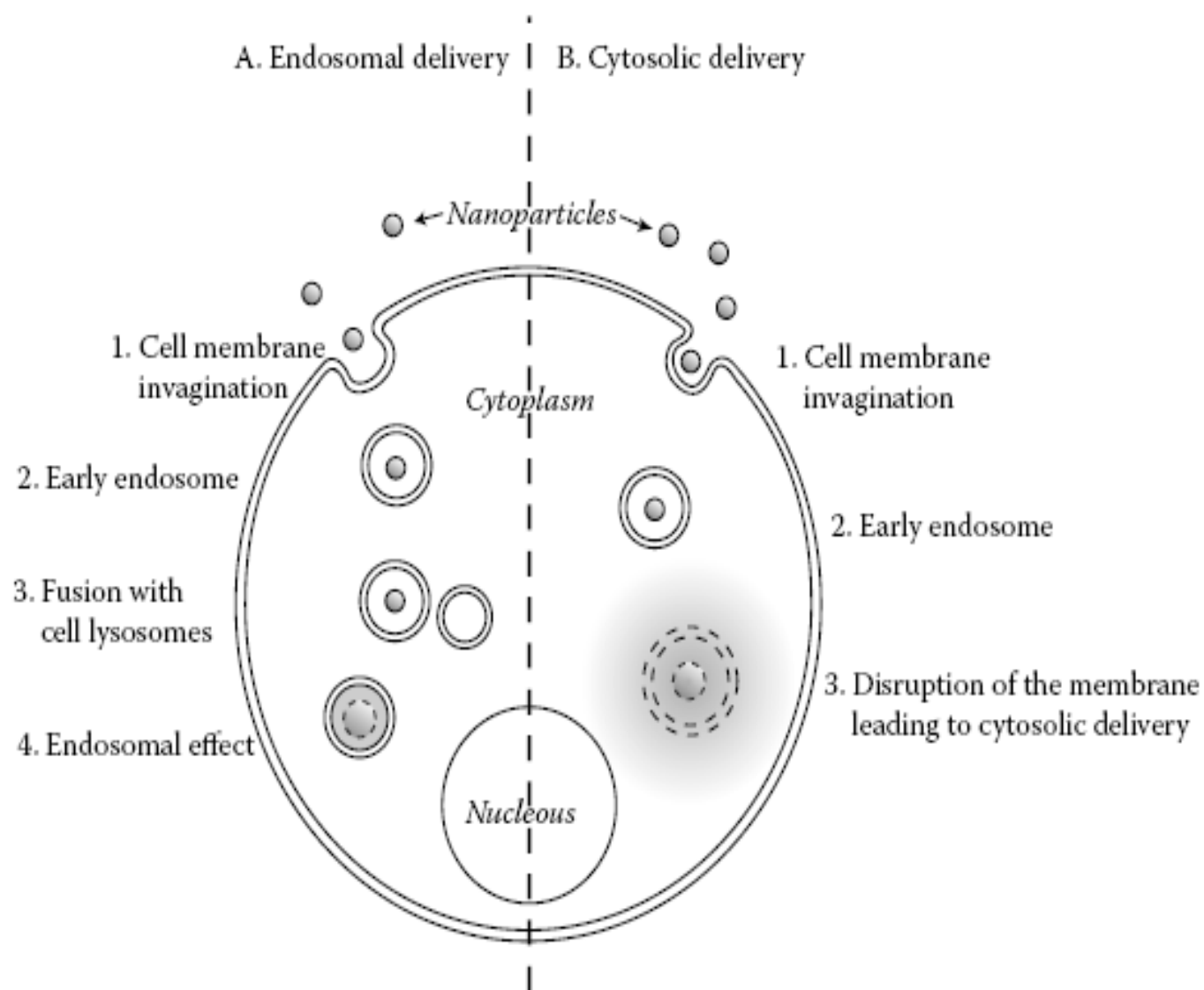


FIGURE 8.6 Cell internalization of nanoparticles can lead to (a) endosomal or (b) cytosolic drug delivery.

Micelles

Low solubility in water drugs can be solubilized by micelles of surfactants
drugs and anticancer agents

- Micelles represent colloidal dispersions with particle sizes between 5 and 50 to 100 nm
- Among colloidal dispersions, micelles belong to a group of association or amphiphilic colloids, which under certain conditions (concentration and temperature), are spontaneously formed by amphiphilic or surface-active agents (surfactants), which are molecules that consist of two clearly distinct regions with opposite affinities towards water

TABLE 9.1

Some Examples of the Block Copolymers Used to Prepare Drug-Loaded Micelles

| Block Copolymers | Drugs Incorporated |
|--|--|
| Pluronics® | Doxorubicin, cisplatin–doxorubicin, epirubicin–doxorubicin, haloperidol, ATP |
| Polycaprolactone- <i>b</i> -PEG | FK506, L-685,818 |
| Polycaprolactone- <i>b</i> -methoxy-PEG | Indomethacin |
| Poly(<i>N</i> -isopropylacrylamide)- <i>b</i> -PEG | Miscellaneous |
| Poly(aspartic acid)- <i>b</i> -PEG | Doxorubicin, cisplatin, lysozyme |
| Poly(γ -benzyl-L-glutamate)- <i>b</i> -PEG | Clonazepam |
| Poly(D,L-lactide)- <i>b</i> -methoxy-PEG | Paclitaxel, testosterone |
| Poly(β -benzyl-L-aspartate)- <i>b</i> - poly(α -hydroxy- ethylene oxide) | Doxorubicin |
| Poly(β -benzyl-L-aspartate)- <i>b</i> -PEG | Doxorubicin, Indomethacin, KRN, amphotericin B |
| Poly(L-lysine)- <i>b</i> -PEG | DNA |
| Oligo(methyl methacrylate)- <i>b</i> -poly(acrylic acid) | Doxorubicin |
| PEG-PE | Dequalinium, soya bean trypsin inhibitor, paclitaxel, camptothecin, tamoxifen, porphyrine, vitamin K ₃ |

A. Structures of micelle-forming copolymers

Block copolymers

di - block AAAAAAABBBBBB

tri - block AAAABBBBBAAAAA

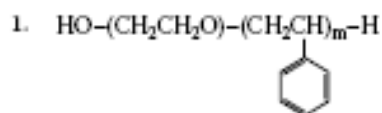
Graft copolymer AAAAAAAAAAAAAA

B B
B B
B B
 B

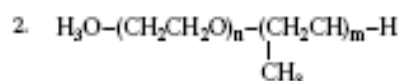
A - hydrophilic unit
B - hydrophobic unit

B. Examples of block copolymers

Di-block copolymers

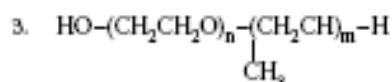


Poly(ethylene oxide)-*b*-poly(styrene) block copolymer



Poly(ethylene oxide)-*b*-poly(D, L-lactide) block copolymer

Tri-block copolymers



Poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) tri-block copolymer

C. Micelle formation from di-block and tri-block co-polymers

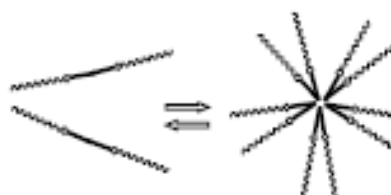
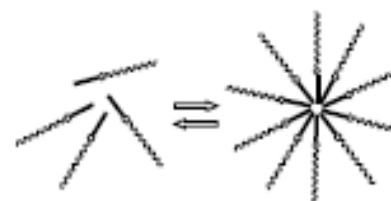


FIGURE 9.1 Micelle-forming copolymers (A and B) and micelle assembly (C).

Polymeric Vesicles

- Closed bilayer system in which amphiphilic molecules self assemble
- in aqueous media in an effort to reduce the high-energy interaction between the hydrophobic portion of the amphiphile and the aqueous disperse phase and to maximize the low-energy interaction between the hydrophilic head group and the disperse phase

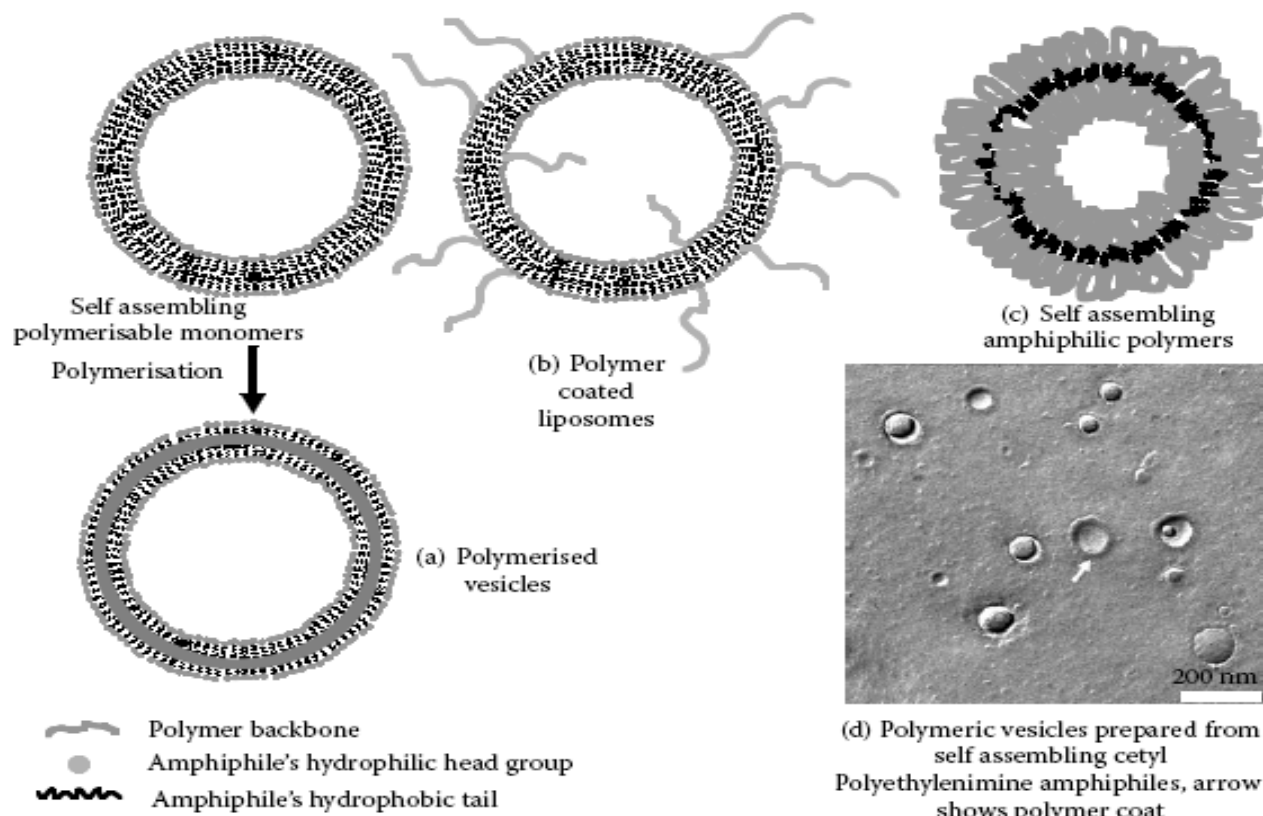


FIGURE 10.1 Polymeric vesicles may arise from (a) the self-assembly of polymerizable monomers that are subsequently polymerized, (b) the cooperative self-assembly of lipids and polymers, or the self-assembly of amphiphilic polymers, both block (c) and random copolymers (d).

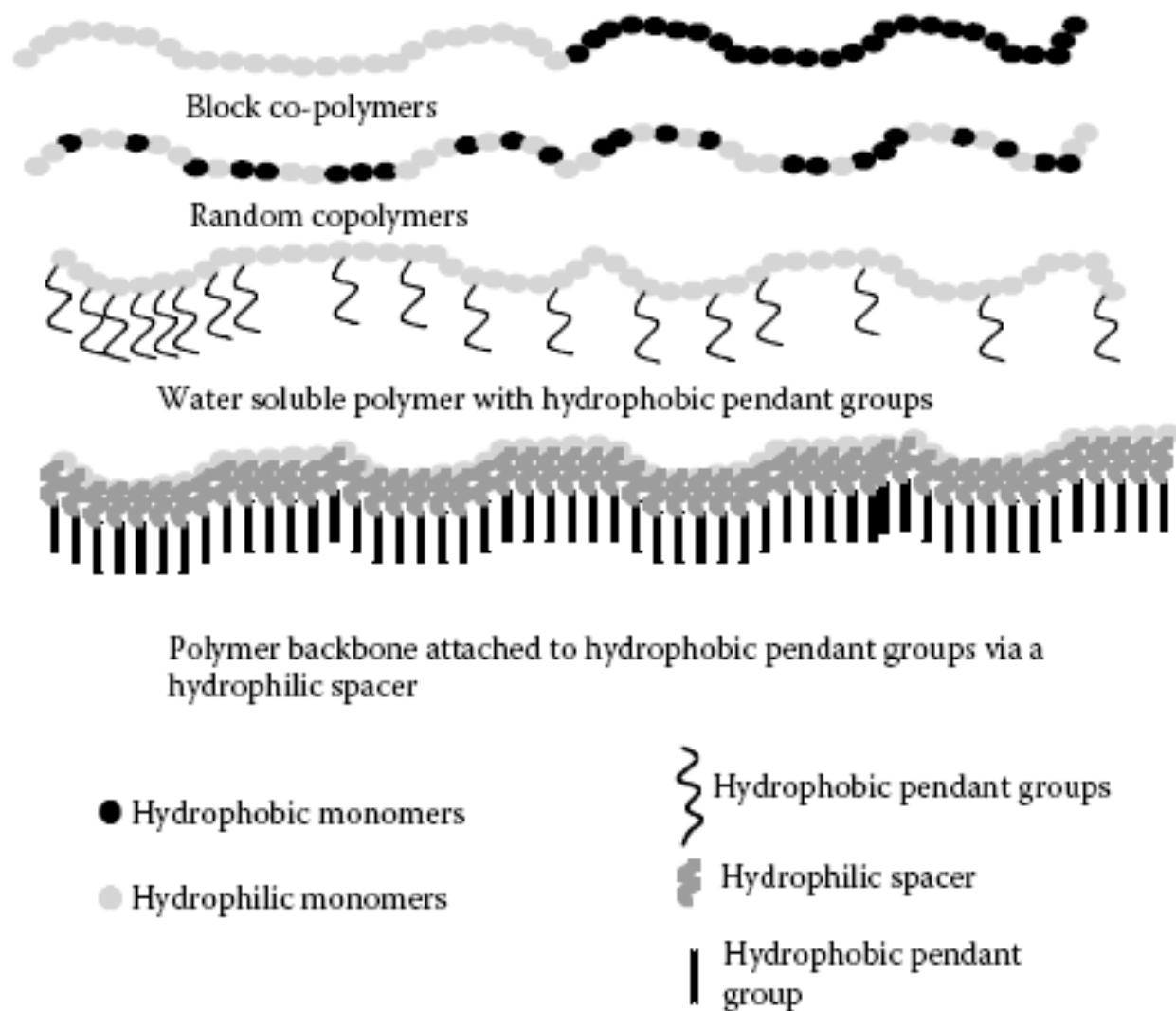


FIGURE 10.2 Schematic representation of self-assembling vesicle-forming polymers.