Introduction to Nanotechnology

- Textbook：
  Nanophysics and Nanotechnology
  by:
  Edward L. Wolf

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

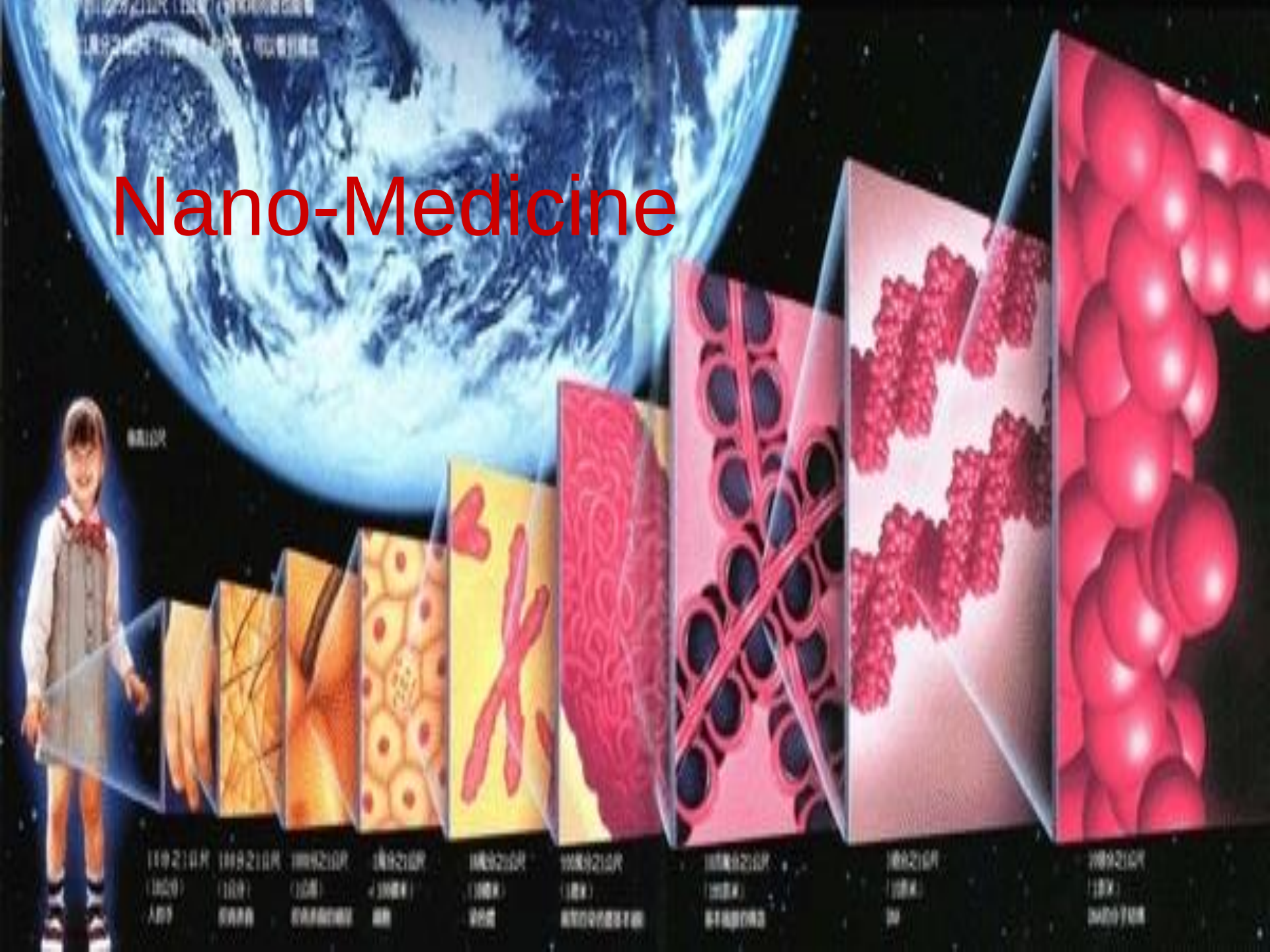
Objective of the course

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

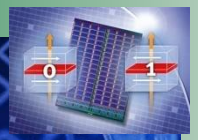
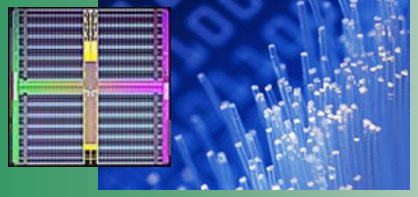


Subjects:

Biodegradable and Biocompatible Nano materials

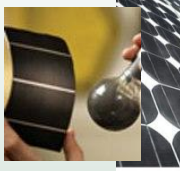
1. Drug Delivery
2. Tissue Engineering
3. Diagnostic Tools

Nanotechnology Applications

Information Technology

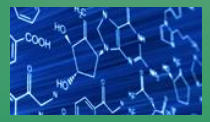
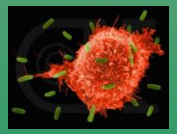
- Smaller, faster, more energy efficient and powerful computing and other IT-based systems



Energy

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

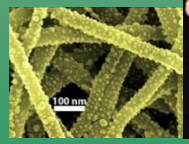


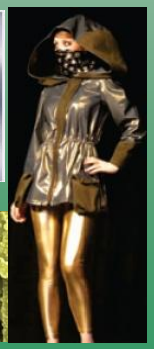



Medicine

- 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.

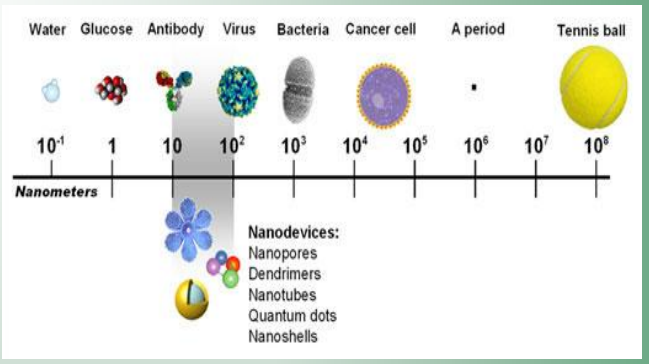
What is nanomedicine?

- Nanobiotechnology: Convergence of nanotechnology with modern biology

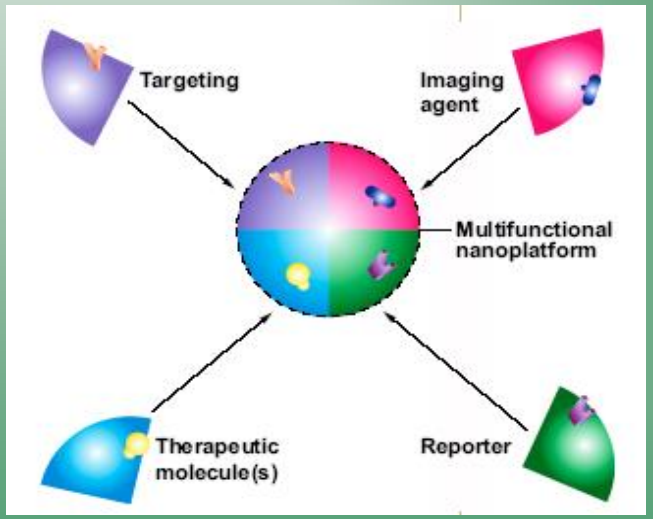
- Nanomedicine:

  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.

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

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

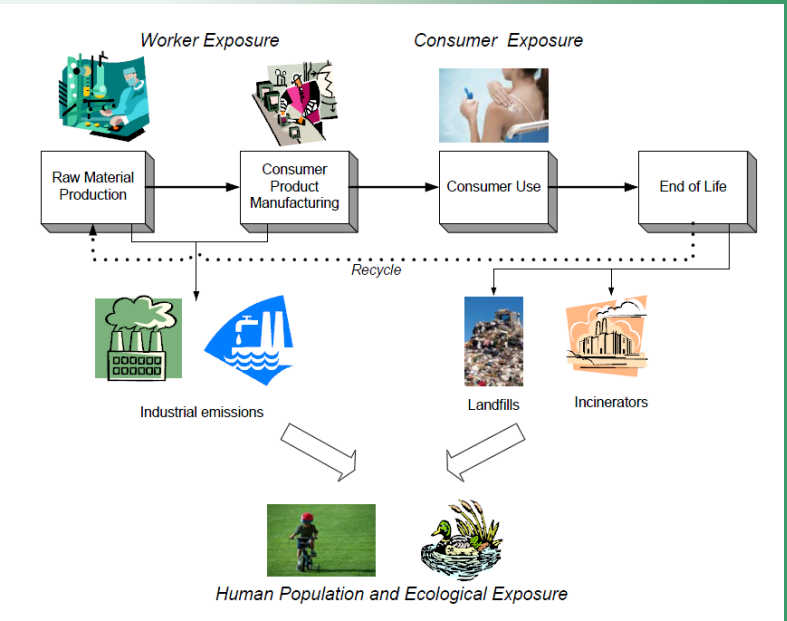
- Extremely bad conditions (as cancer) will be treated easily by modifying the body's genetic material.
- Disease elimination will become normal, so we no longer will need to be worry about living with heath conditions.
- Diagnose diseases before there are any symptoms.
- Administer drugs that are precisely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



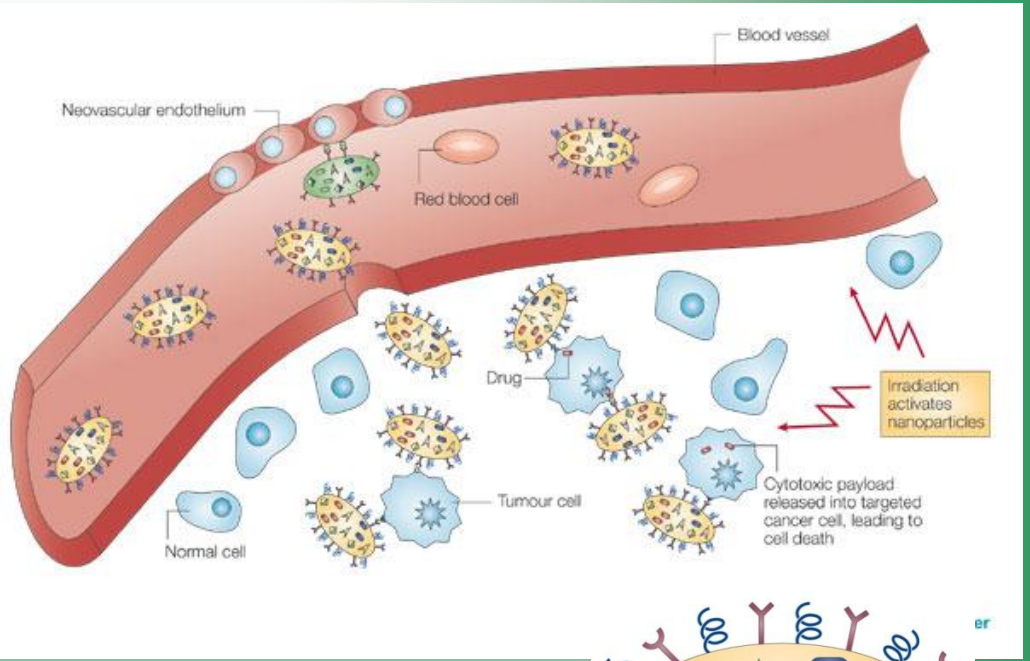
Exposure of human and the environment to nanomaterials at different stages of product life cycle – *US environmental protection agency, 2007 (epc.gov)*

The *Nanotechnology* continues to change our lives

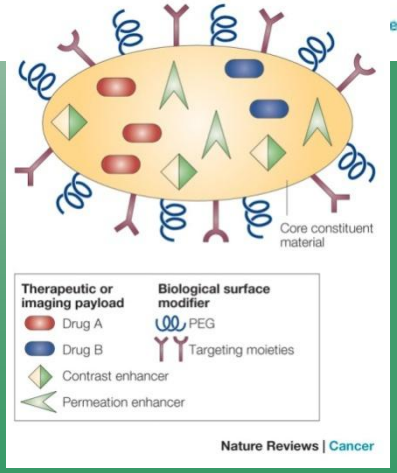
Nanotechnology in Health Care

Treatment

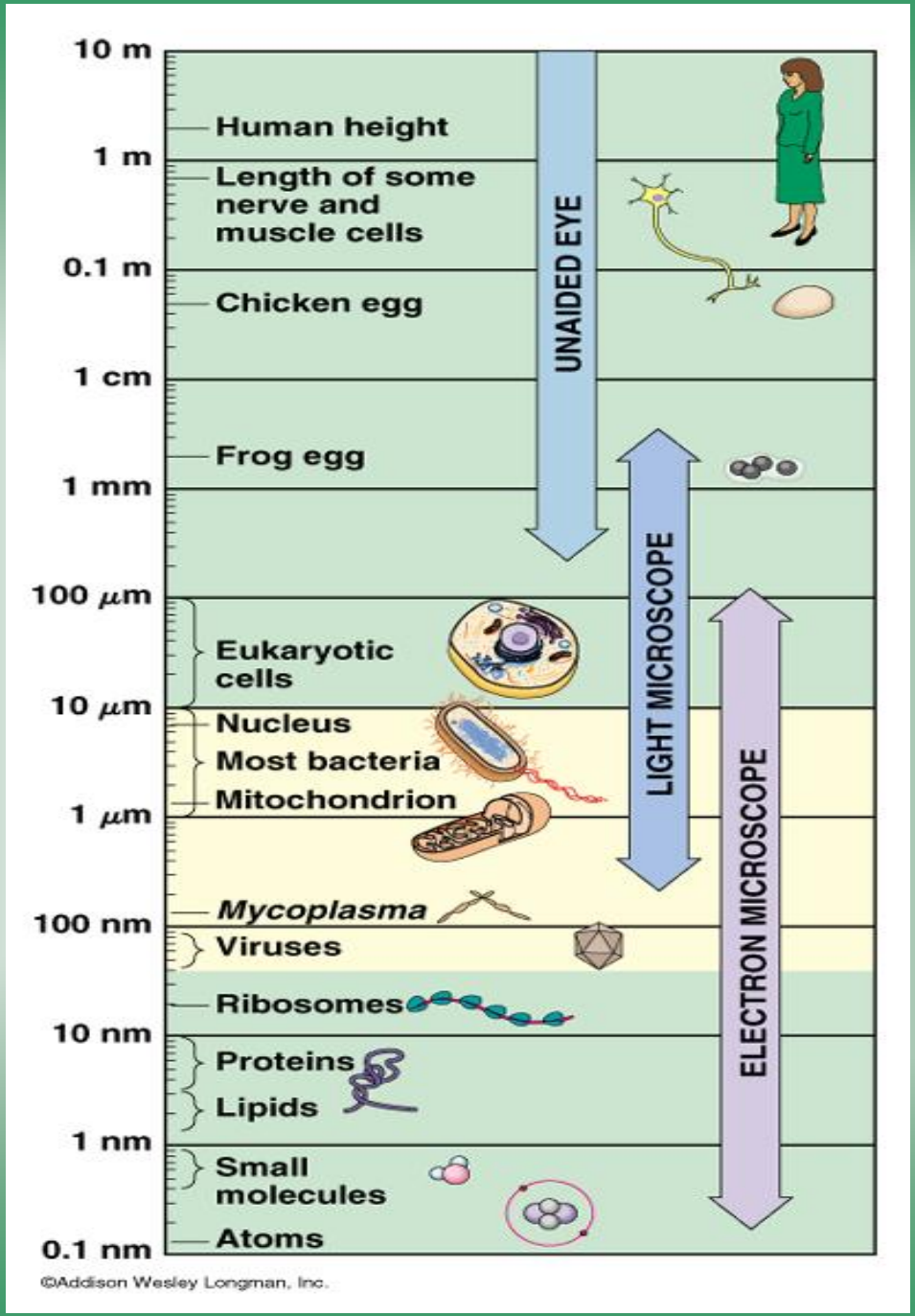
- Targeted drug delivery
  - Nanoparticles containing drugs are coated with targeting agents (e.g. conjugated antibodies)
  - The nanoparticles circulate through the blood vessels and reach the target cells
  - Drugs are released directly into the targeted cells



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



Scale


10 m
1 m
0.1 m
1 cm
1 mm
100 μm
10 μm
1 μm
100 nm
10 nm
1 nm
0.1 nm
Human height
Length of some nerve and muscle cells
Chicken egg
Frog egg
Eukaryotic cells
Nucleus
Most bacteria
Mitochondrion
Mycoplasma
Viruses
Ribosomes
Proteins
Lipids
Small molecules
Atoms
UNAIDED EYE
LIGHT MICROSCOPE
ELECTRON MICROSCOPE
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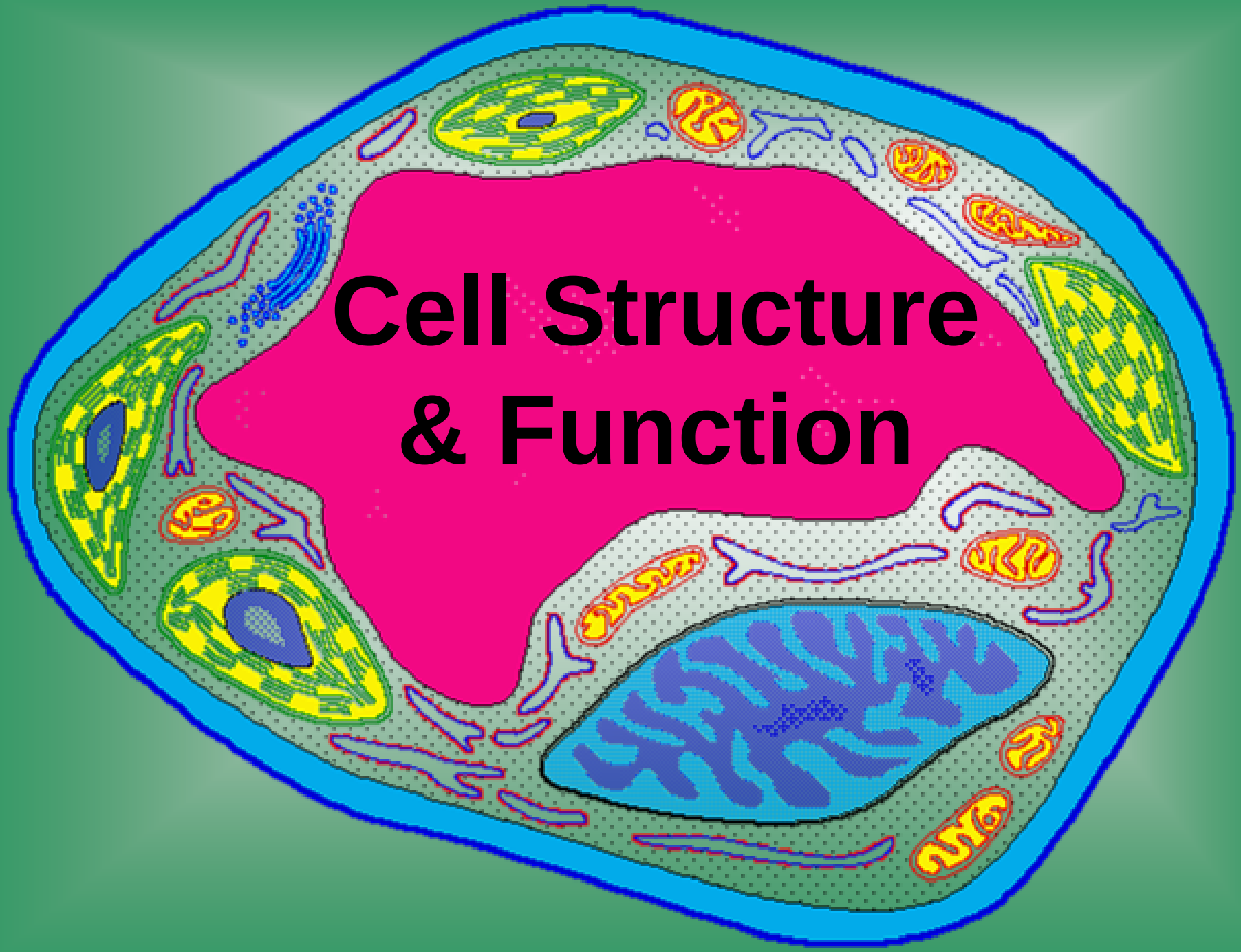
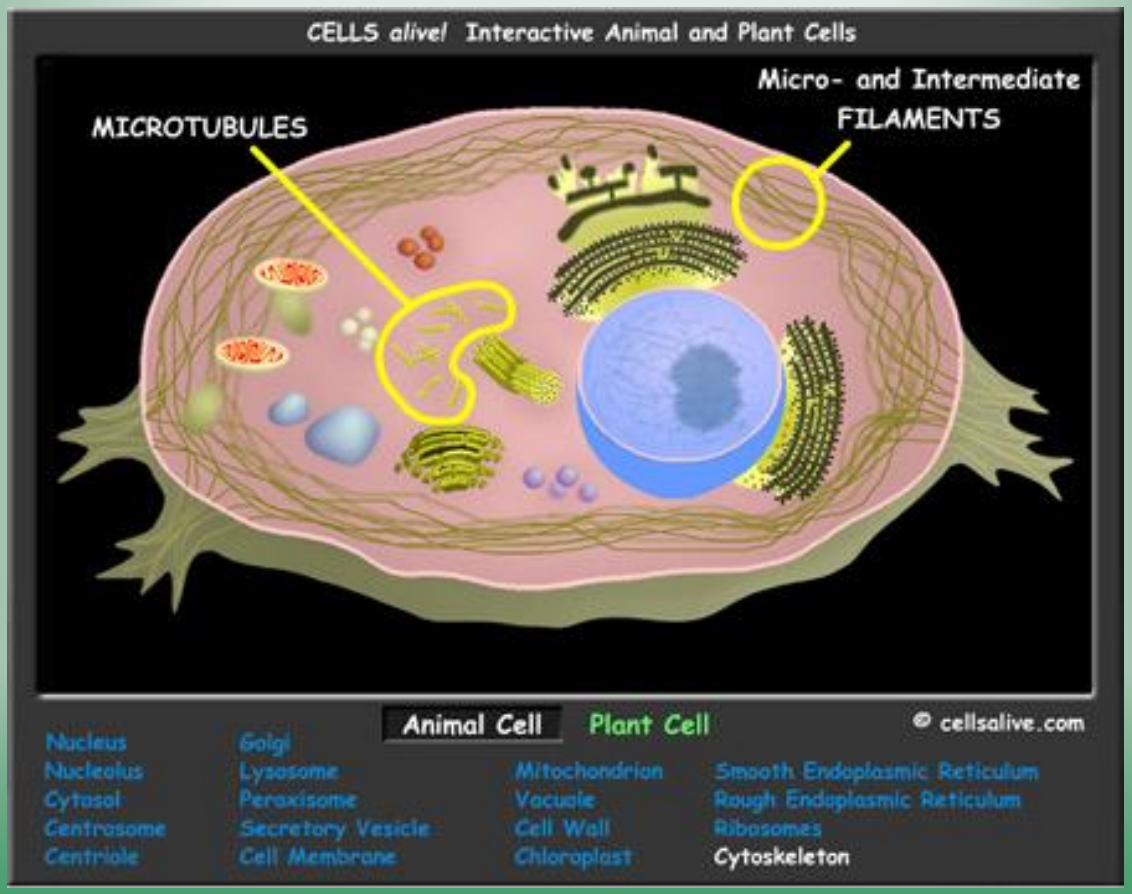
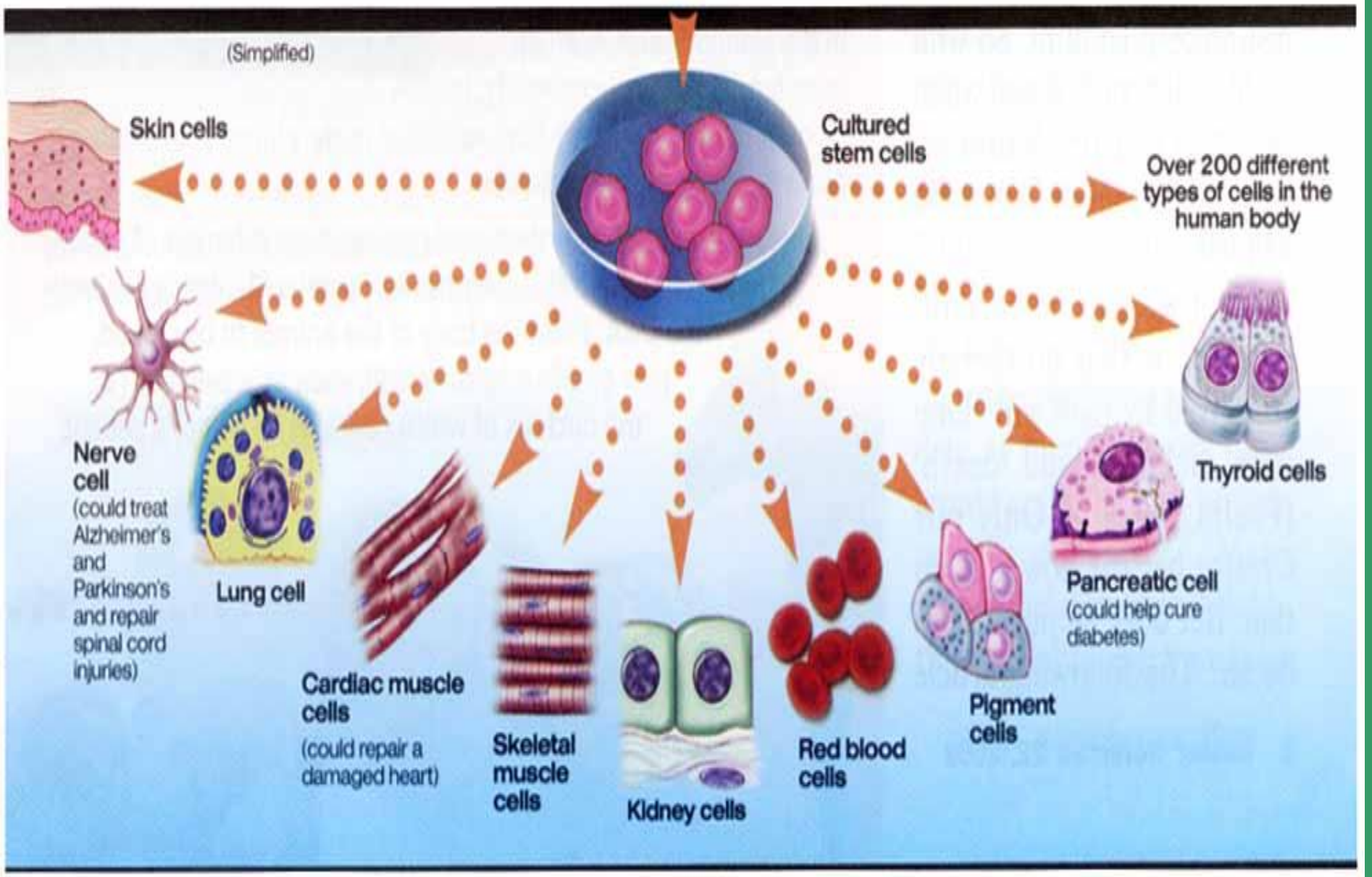

Cell Structure
& Function

A walking Avogadro being

Each adult human is made of ~ 100 trillion cells (10^{14} cells) !

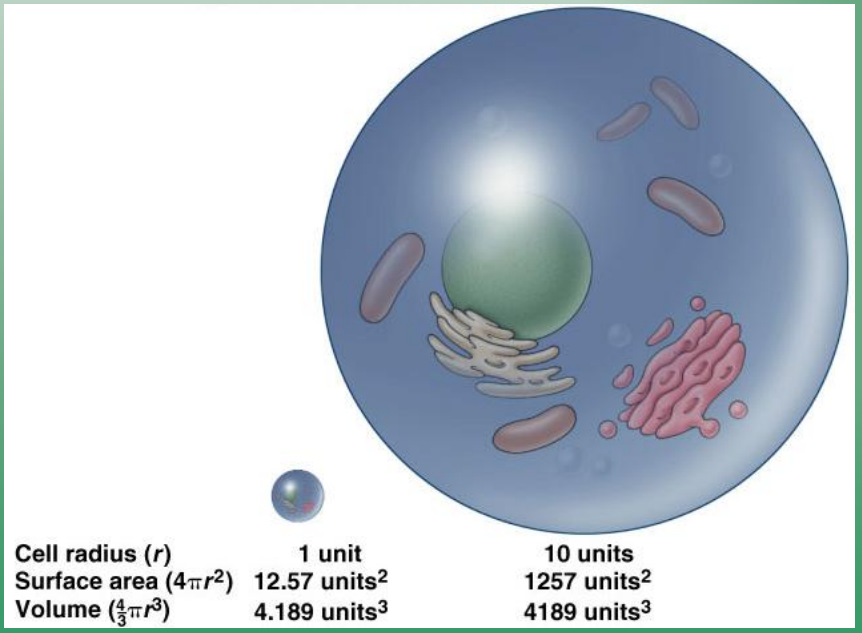
(Guyton, A.C. & Hall, J.E. (2000) Text Book of Medical Physiology 10th ed. W.B. Saunders.



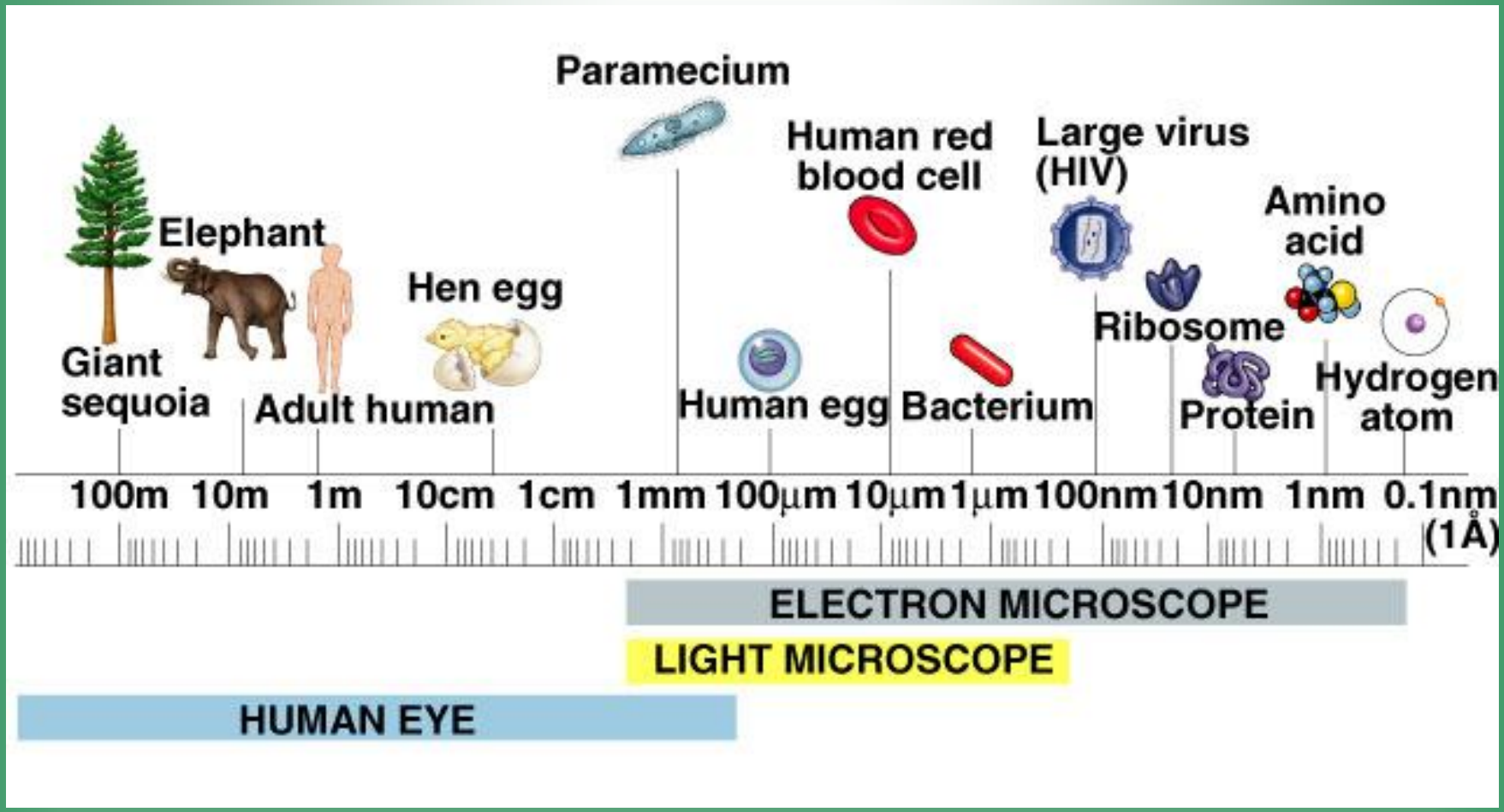

(Simplified)
Skin cells
Cultured stem cells
Over 200 different types of cells in the human body
Nerve cell
(could treat Alzheimer's and Parkinson's and repair spinal cord injuries)
Lung cell
Cardiac muscle cells
(could repair a damaged heart)
Skeletal muscle cells
Kidney cells
Red blood cells
Pigment cells
Pancreatic cell
(could help cure diabetes)
Thyroid cells

Cell Size

- Most cells are relatively small because as size increases (10~100 μm), 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

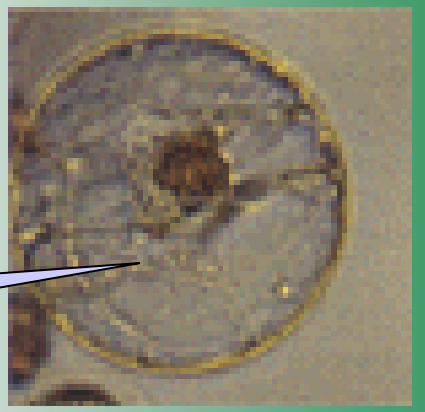
- All living things are made up of cells.
- Cells are the smallest working units of all living things.
- All cells come from preexisting cells through cell division.

Definition of Cell

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

Examples of Cells

Amoeba Proteus

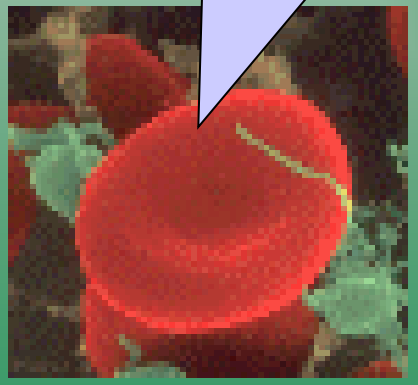


Plant Stem

Bacteria

Nerve Cell

Red Blood Cell

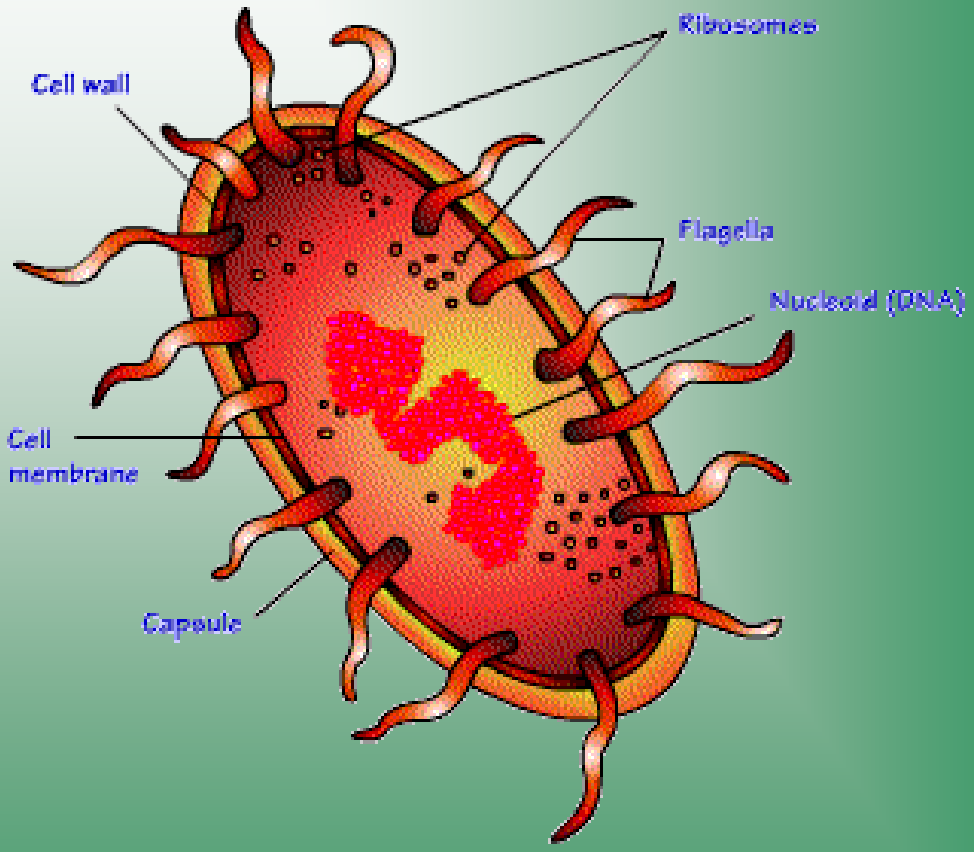


Two Types of Cells

- Prokaryotic
- Eukaryotic

Prokaryotic

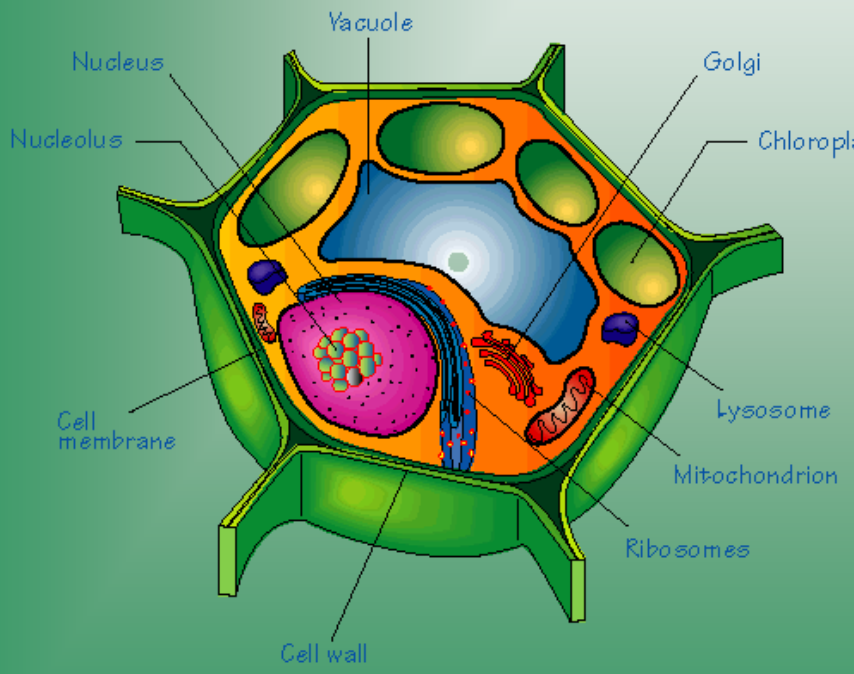
- Do not have structures surrounded by membranes
- Few internal structures
- One-celled organisms, Bacteria



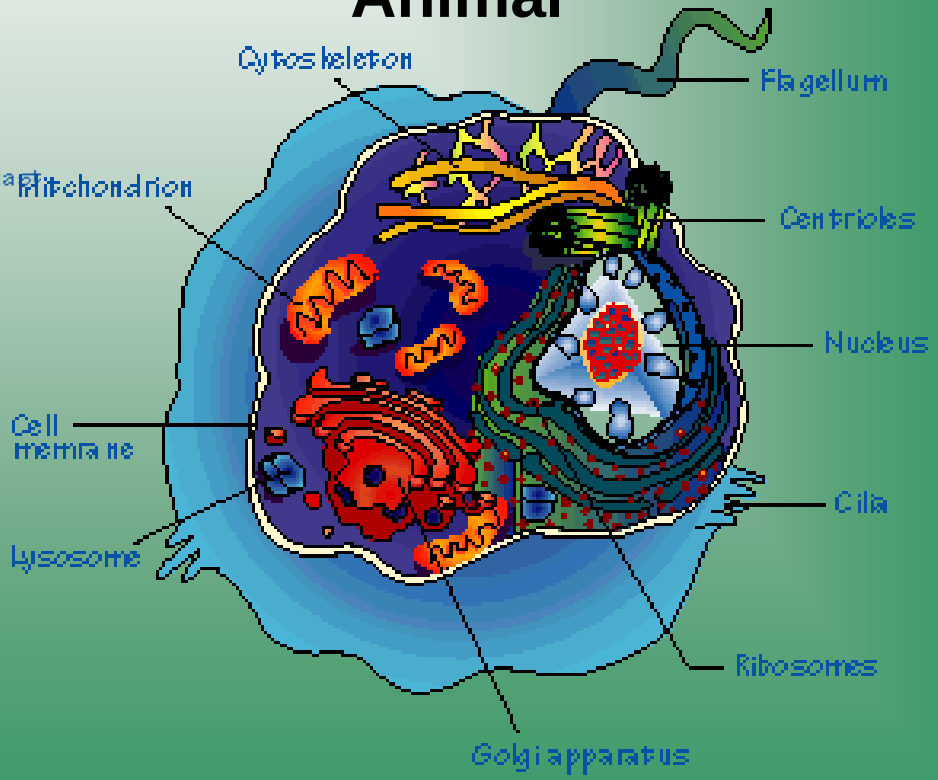
Eukaryotic

- Contain *organelles* surrounded by membranes
- Most living organisms

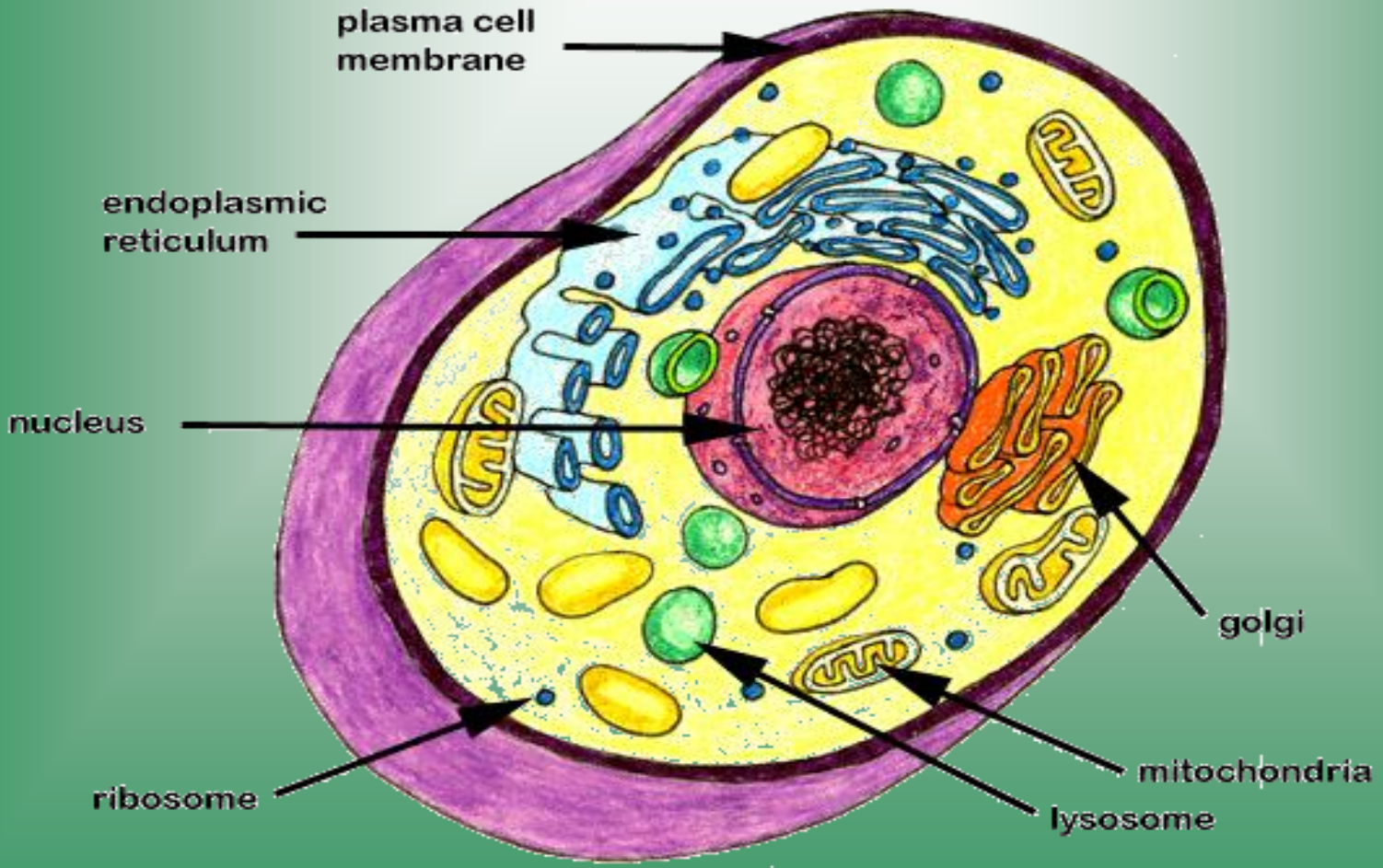
Plant



Animal



“Typical” Animal Cell



“Typical” Plant Cell

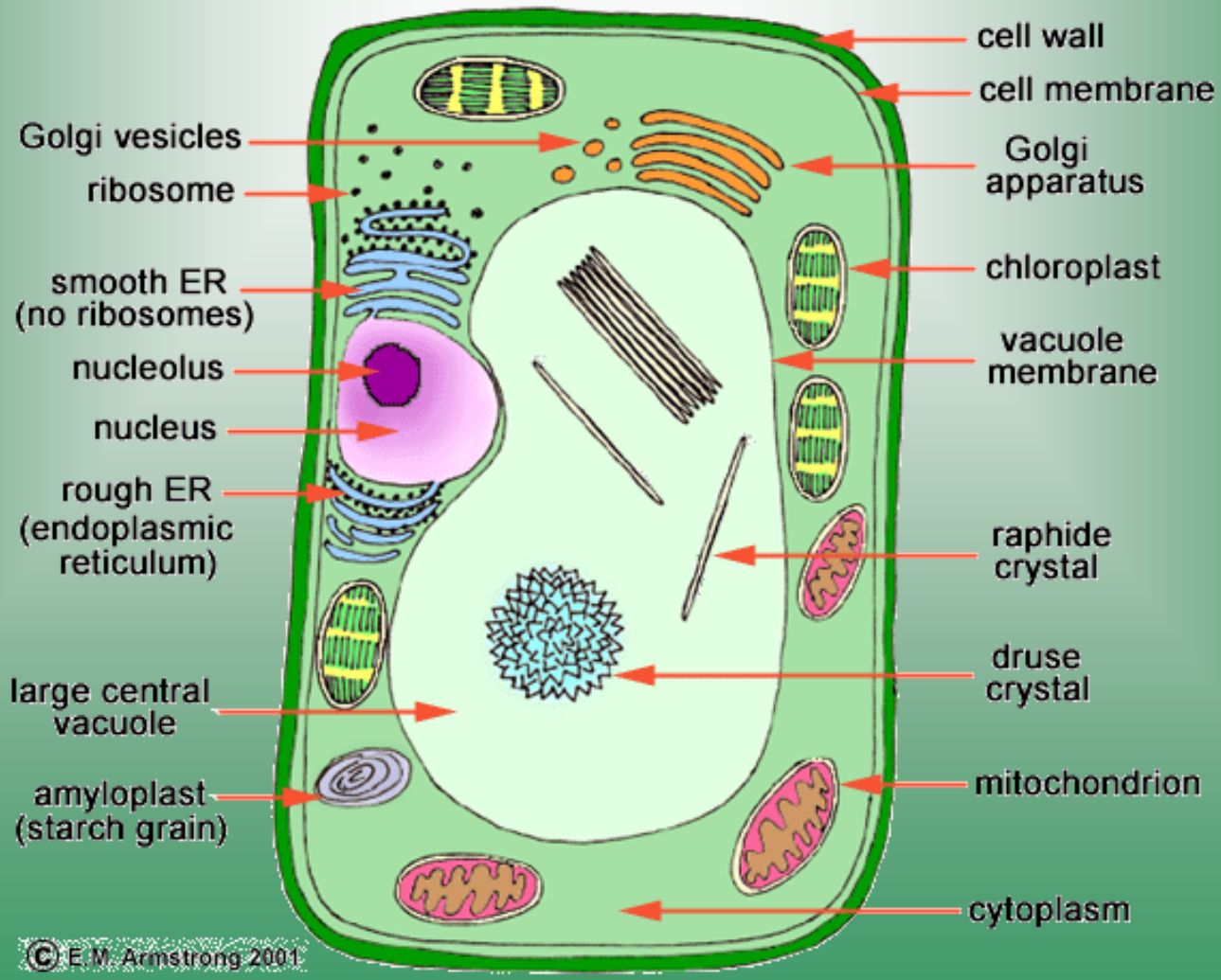


Table 5.3 A Comparison of Prokaryotic, Animal, and Plant Cells

	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

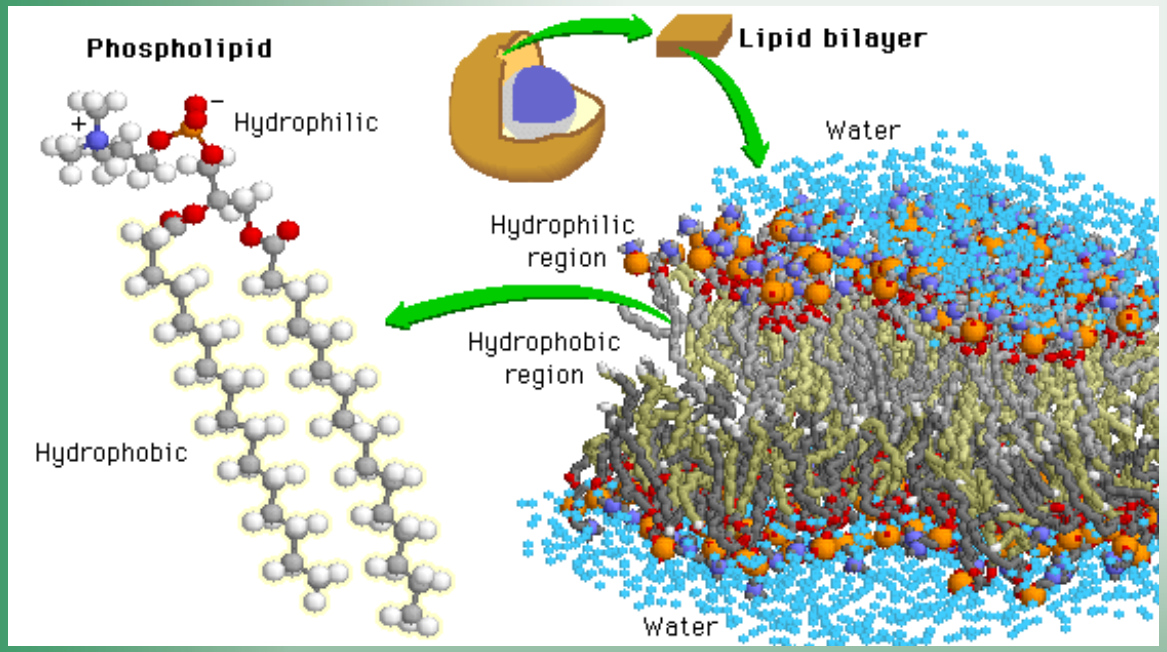
Organelles

Surrounding the Cell

Cell Membrane

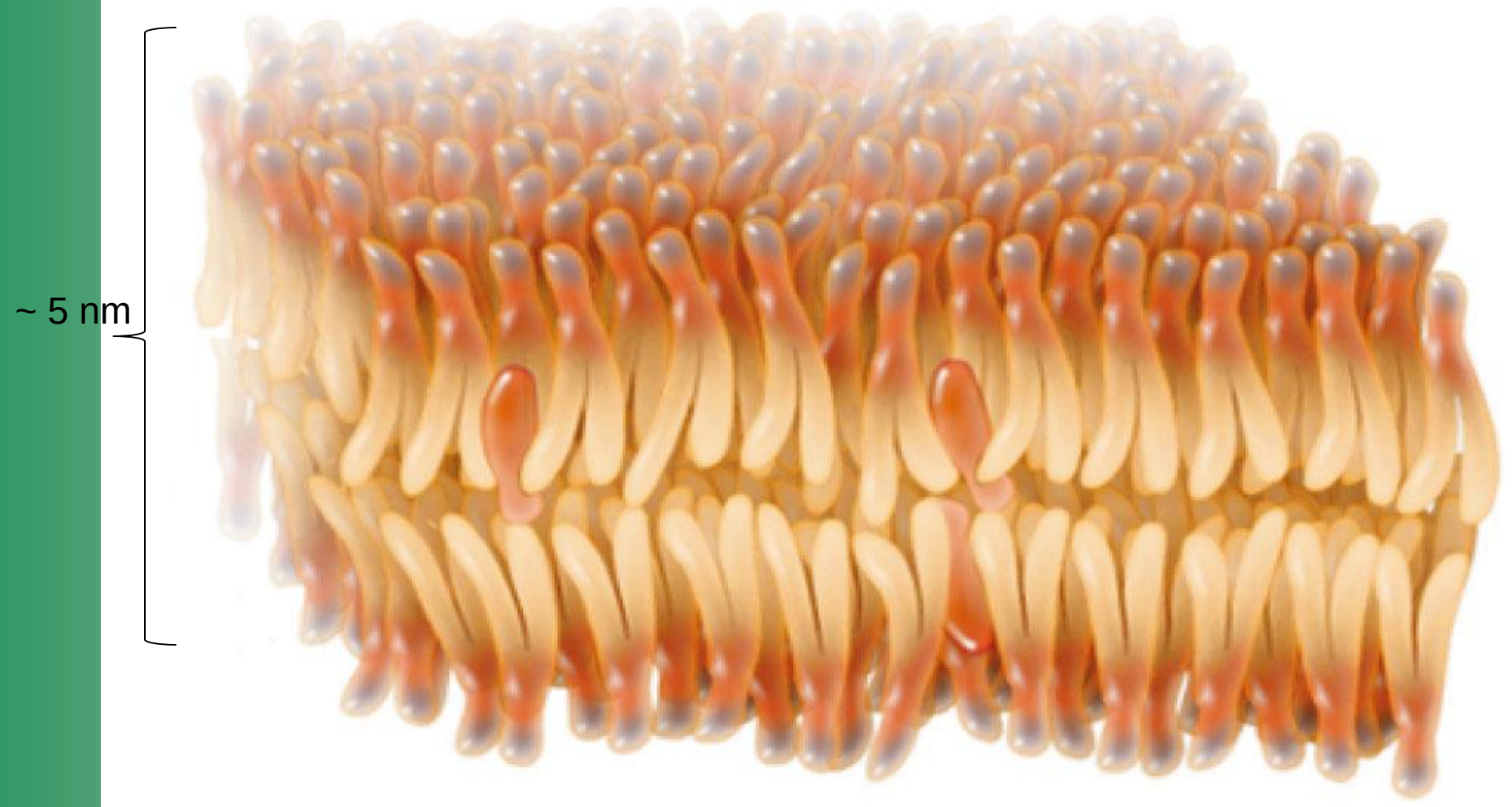
- Outer membrane of cell that controls movement in and out of the cell
- Double layer

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.



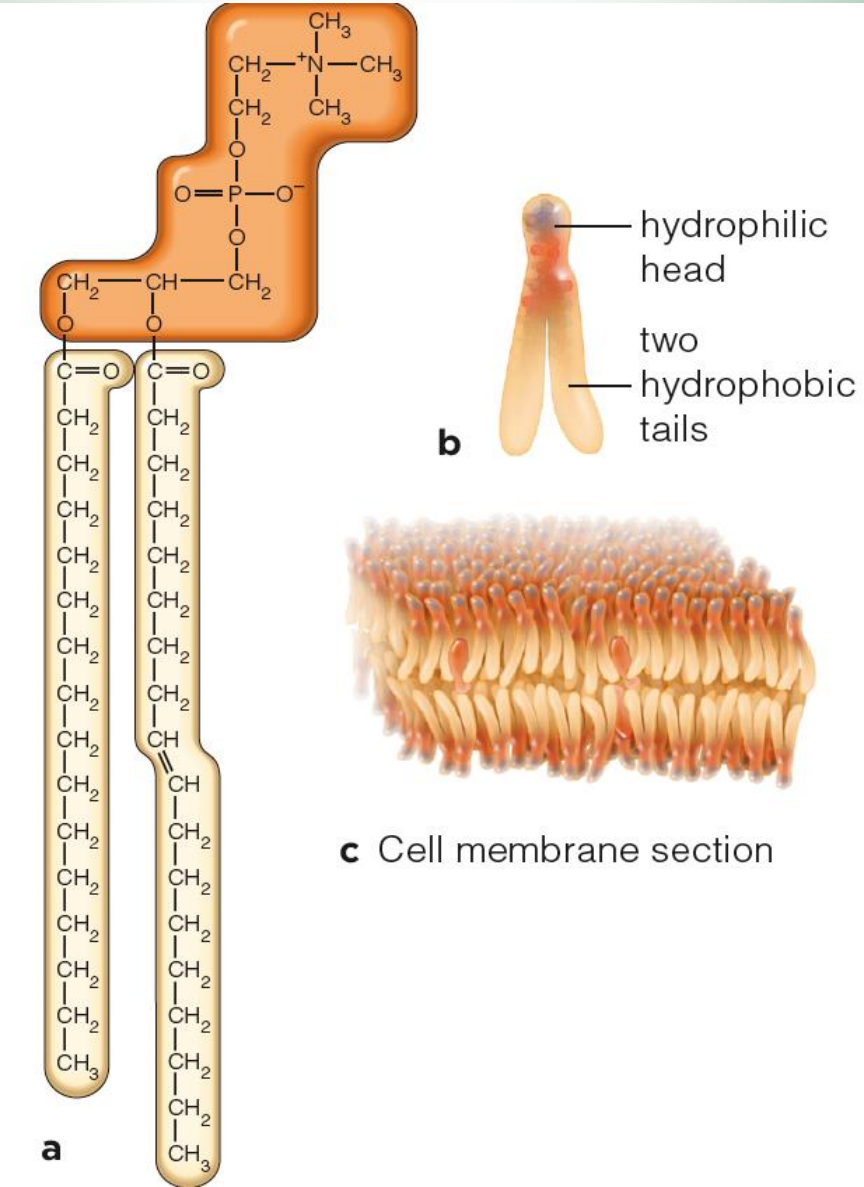
The resulting structure is called a lipid bilayer. All biological membranes (except for those found in certain unusual bacteria, members of the Archaea) contain lipid bilayers, as well as proteins, which provide membranes with stability and specialized functions.

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.



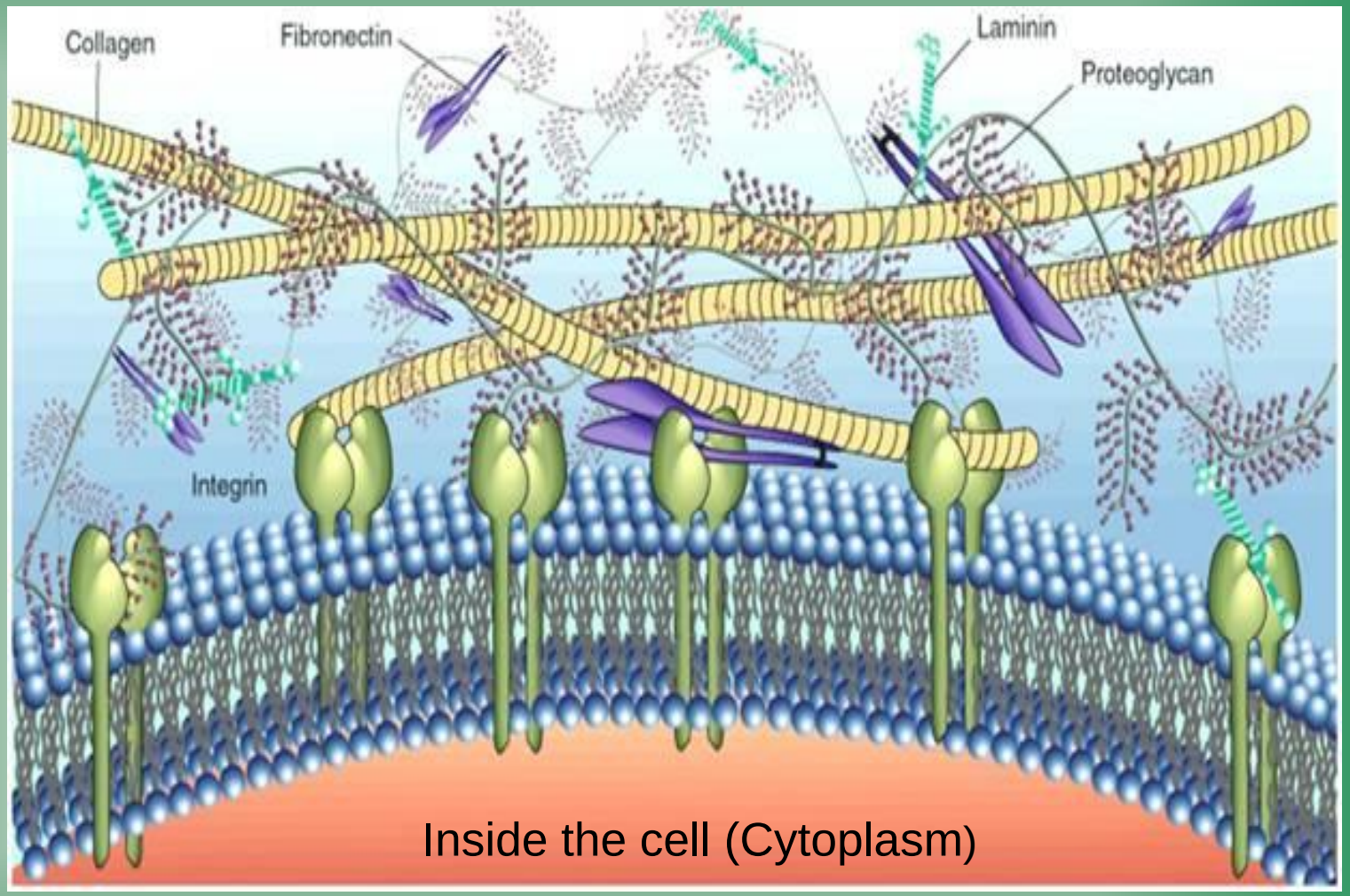
Cell membrane section

Phospholipid Structure



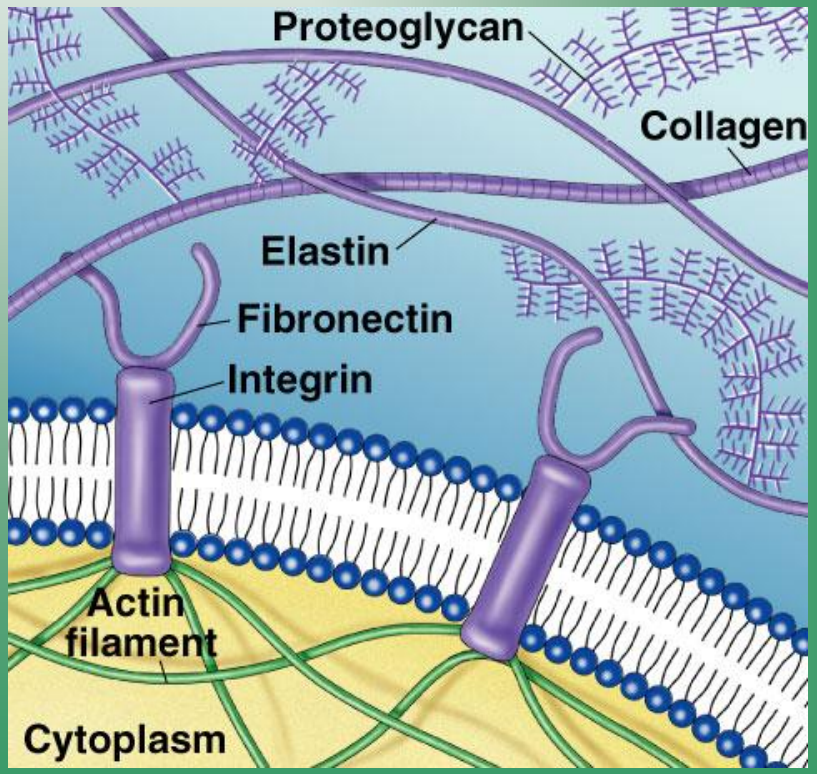
Extracellular Matrix (ECM)

Cell Membrane ~ 5 nm

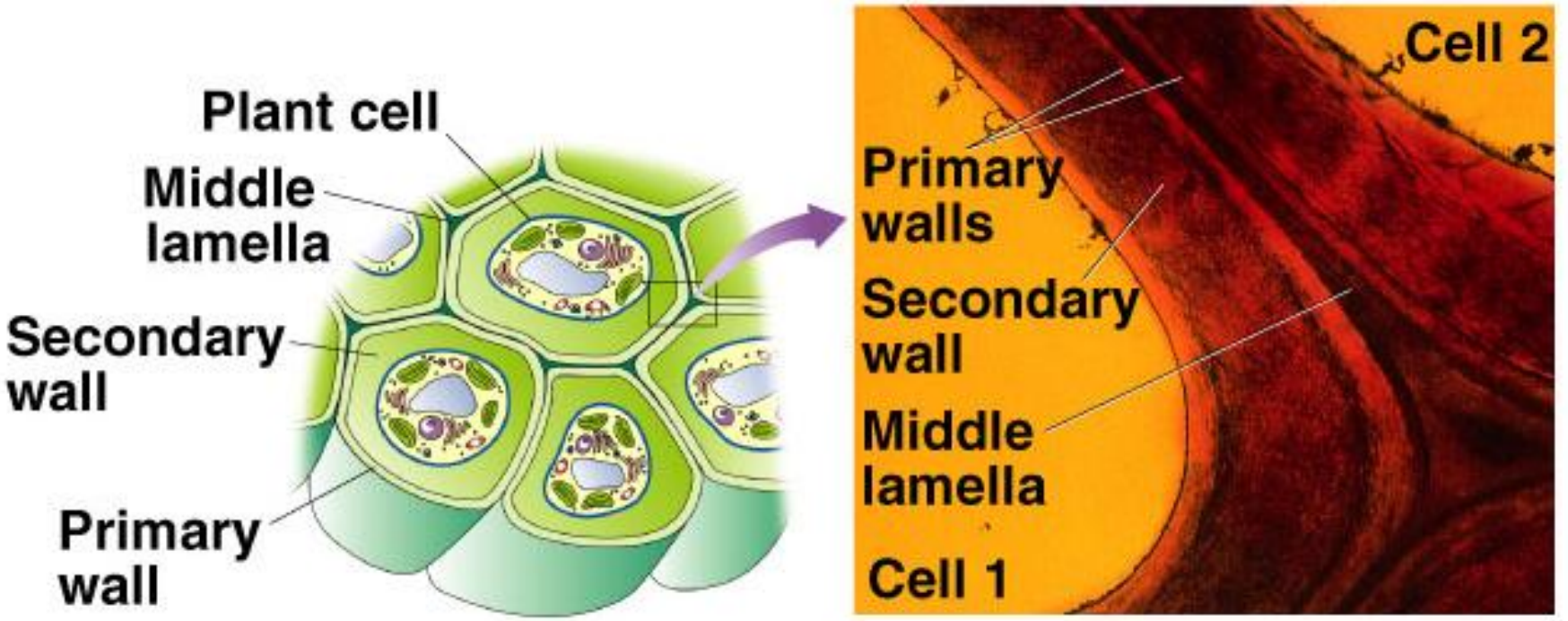


Animal Cells

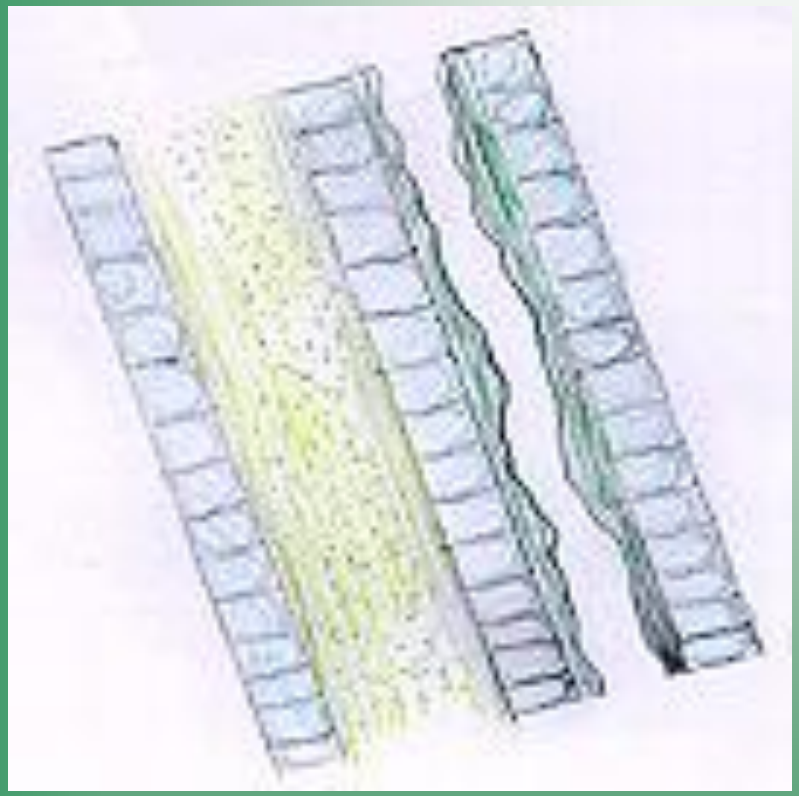
- Animal cells lack cell walls.
  - form extracellular matrix
    - provides support, strength, and resilience



Plant Cell


Plant cell
Middle lamella
Secondary wall
Primary wall
Cell 2
Primary walls
Secondary wall
Middle lamella
Cell 1

Cell Wall

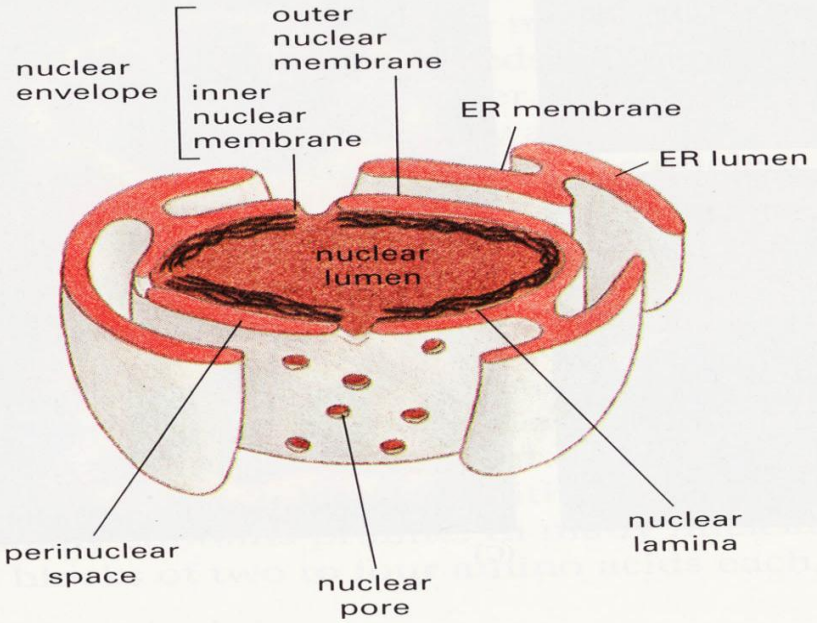


- Most commonly found in plant cells & bacteria
- Supports & protects cells

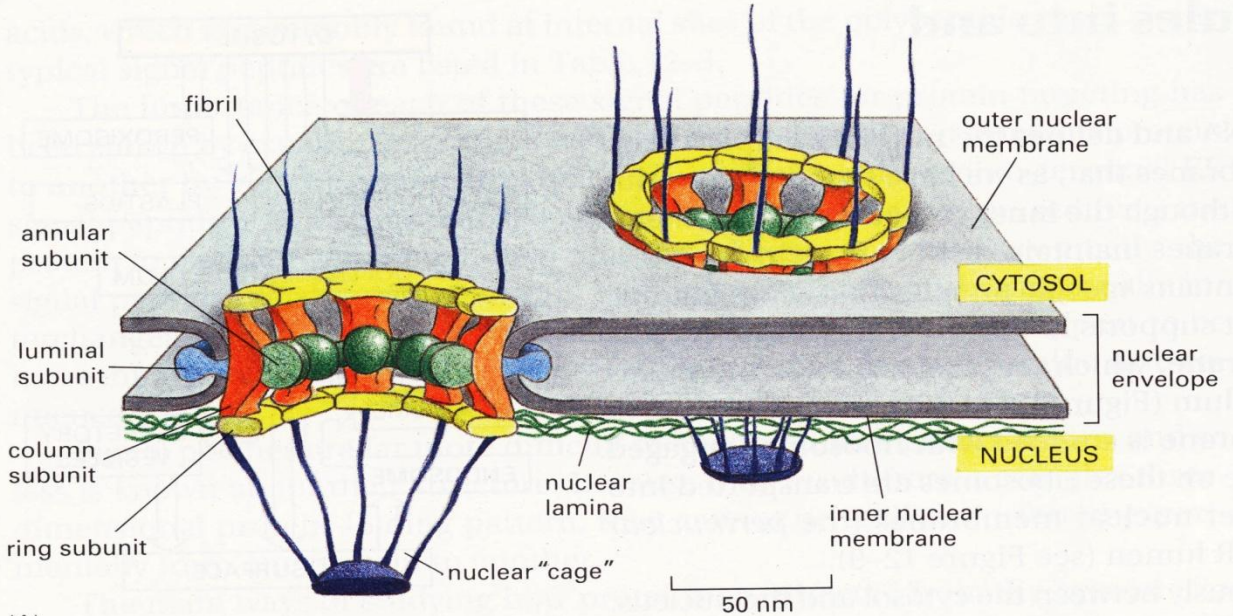
Inside the Cell

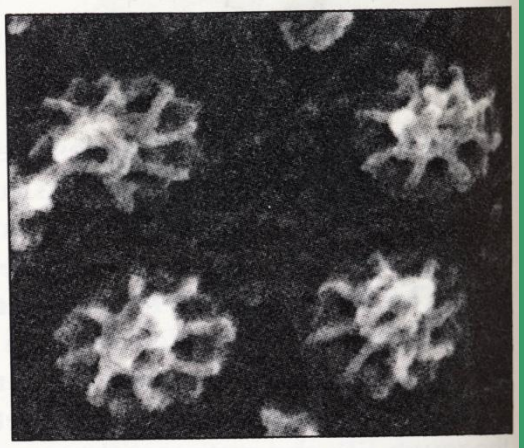
Nucleus

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



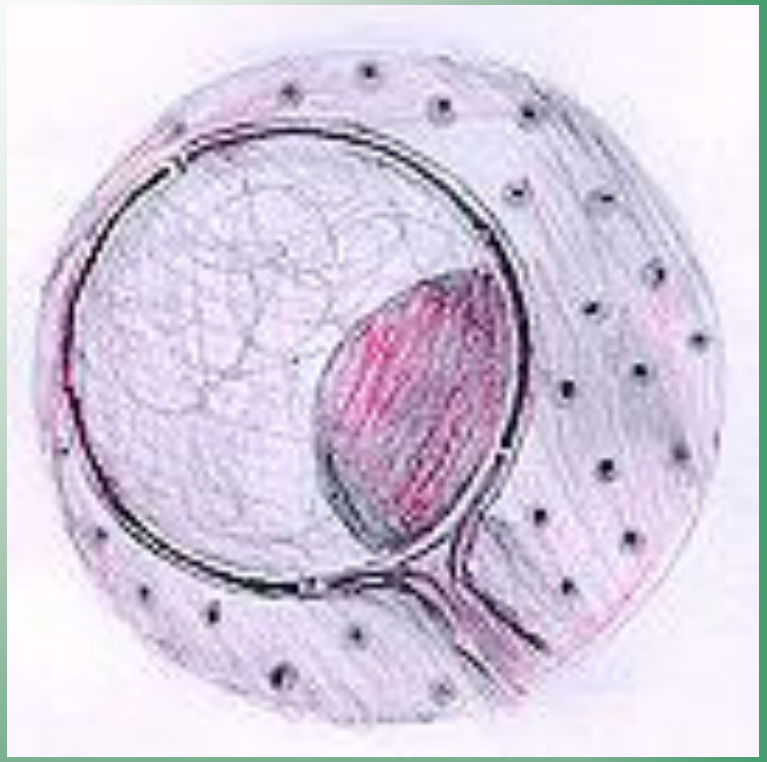
Nuclear Pore Structure

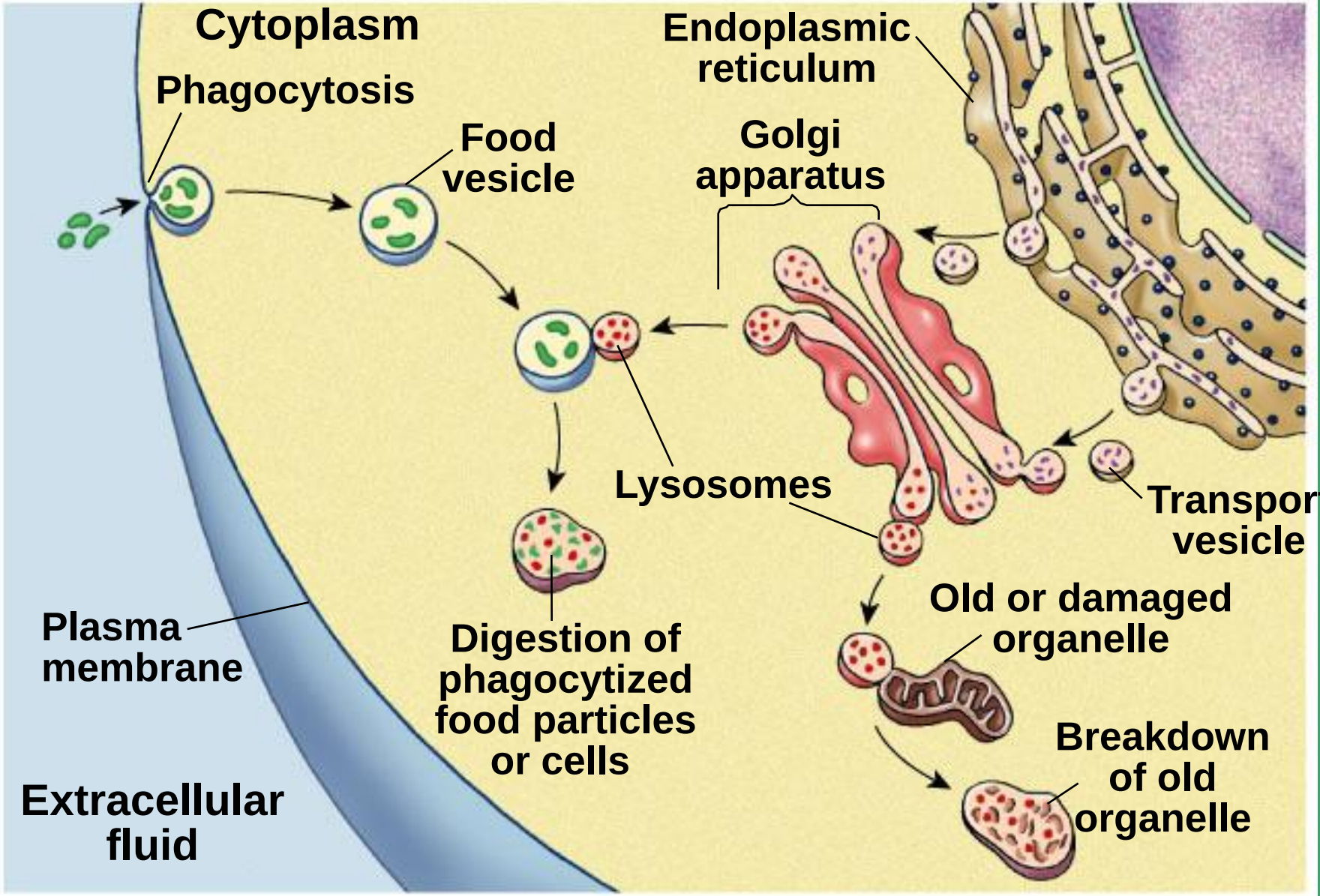



(B)

Nuclear Membrane

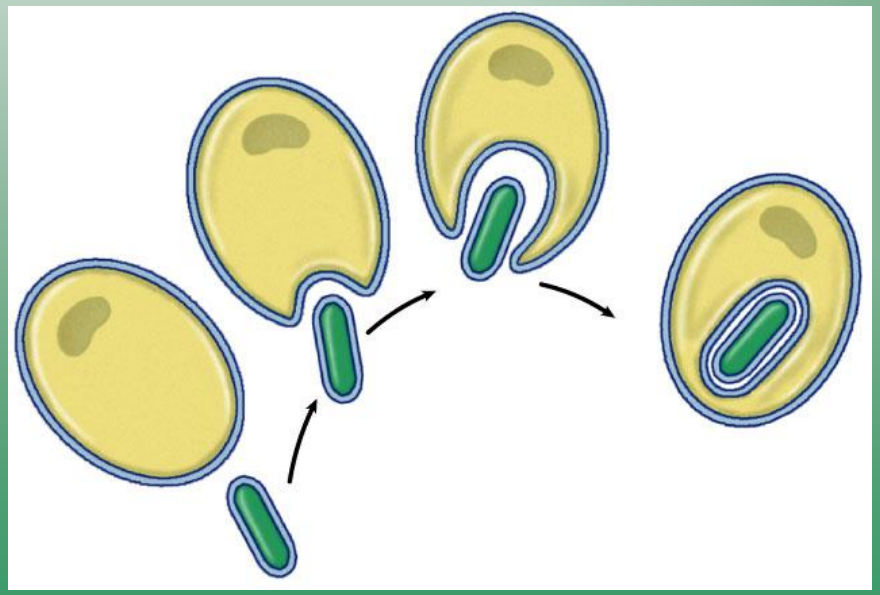
- Surrounds nucleus
- Made of two layers
- Openings allow material to enter and leave nucleus





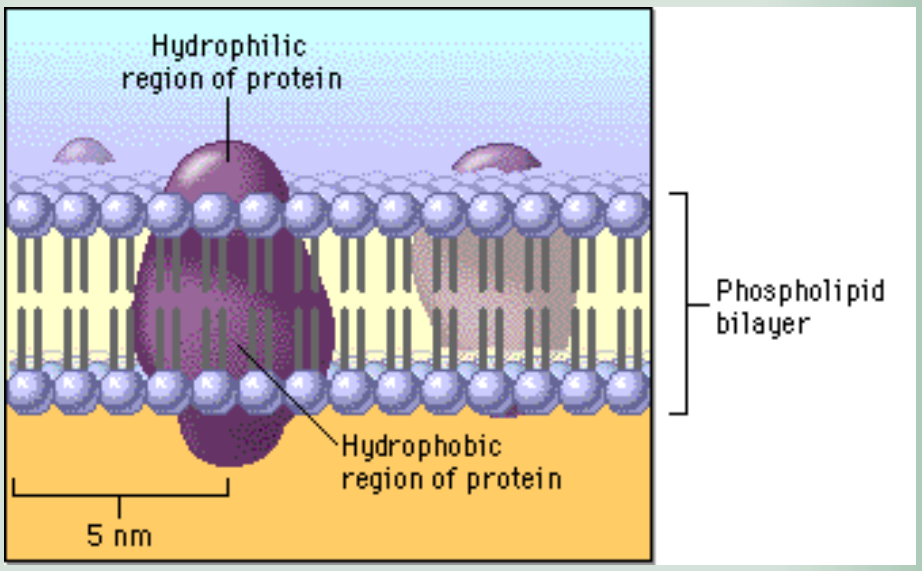
Endosymbiosis
Protection (act as Intelligent Secret Service)

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



Concept 1: Membrane Structure

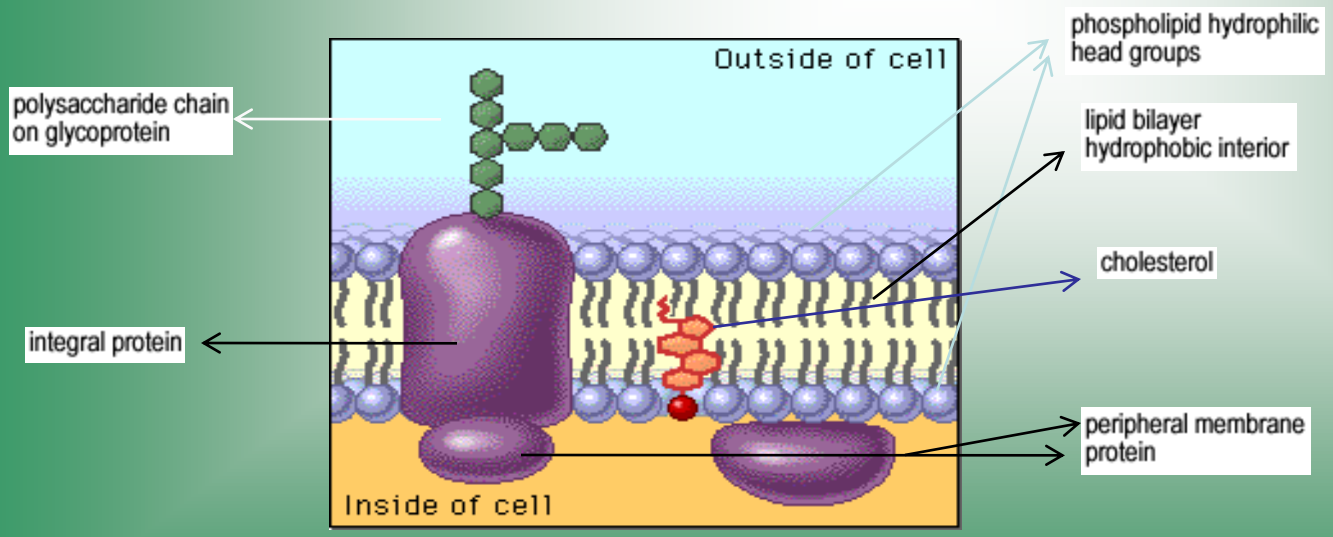
Membranes consist of a phospholipid bilayer combined with a variety of proteins in a fluid mosaic arrangement.



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**

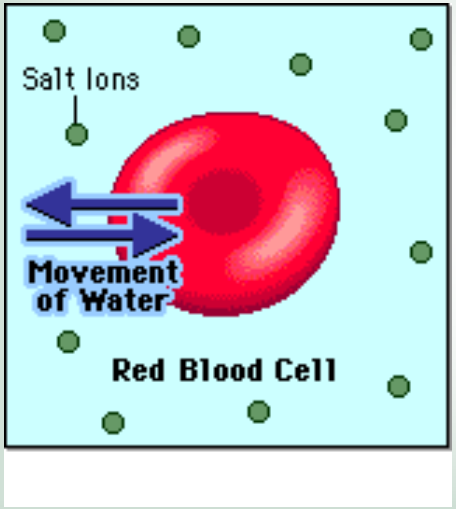
A membrane protein found on either the inner or outer face of the bilayer. Peripheral proteins bind either to integral proteins or to the polar head groups of membrane phospholipids.

• **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.



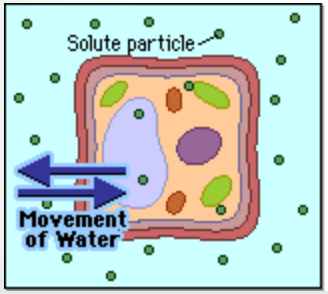
The presence or absence of cell walls influences how cells respond to osmotic fluctuations in their environment.

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

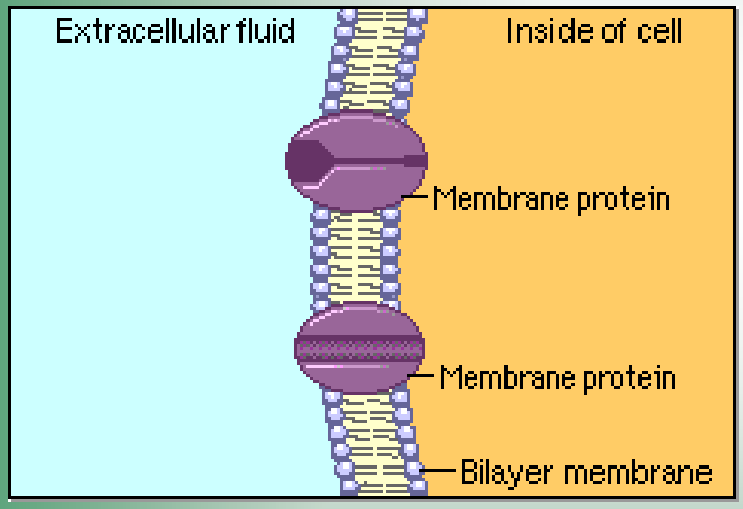
Plant cells are surrounded by rigid cell walls. When plant cells are exposed to hypotonic environments, water rushes into the cell, and the cell swells, but is kept from breaking by the rigid wall layer. The pressure of the cell pushing against the wall is called turgor pressure, and is the desired state 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

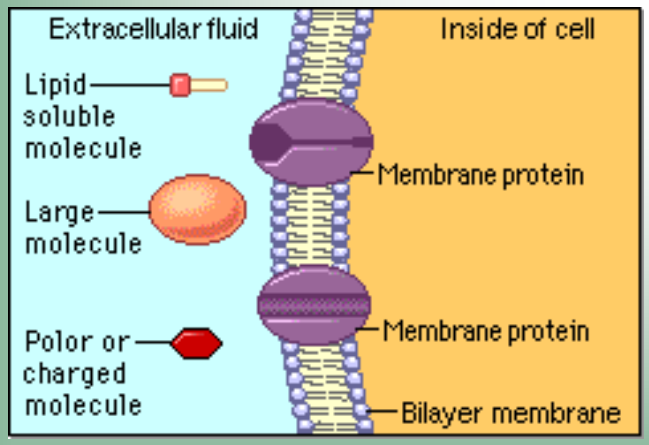
Cell membranes are selectively permeable. Some solutes cross the membrane freely, some cross with assistance, and others do not cross at all.



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

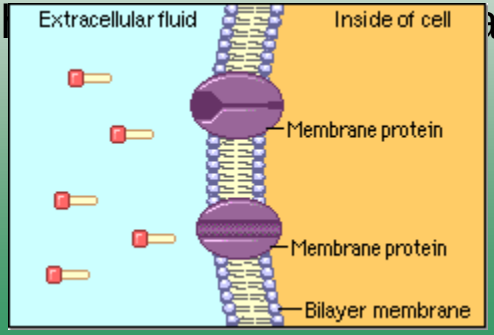
- Molecules that cross the membrane due to protein-mediated transport

- Molecules, usually of very large size, that do not cross the membrane at all

Concept 3 Review: Passive Diffusion of Small Lipophilic Molecules

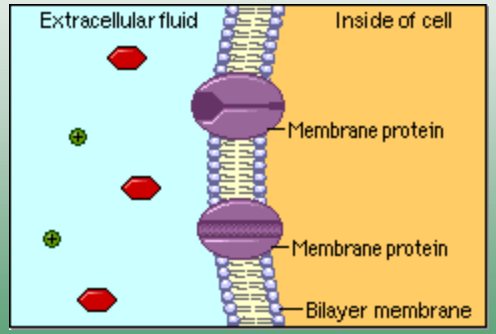
Studies with pure phospholipid membranes show that certain substances easily cross the membrane by a process known as passive diffusion. Diffusion refers to the dispersal of molecules by random motion. For example, if someone opens a perfume vial (or a smelly cheese) in one corner of a room, the odor 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 phospl ll.



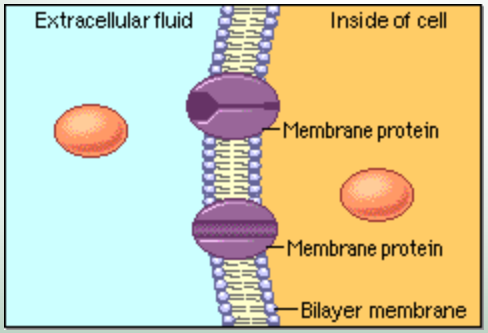
Concept 3 Review: Transport of Polar and Charged Molecules

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.



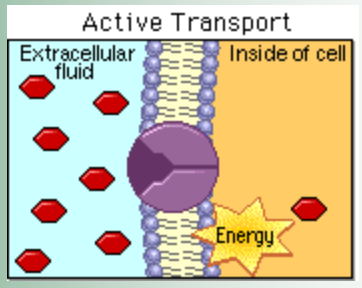
Concept 3 Review: Membrane Barriers to Large Molecules

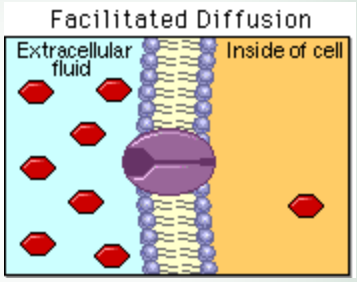
Large molecules, such as proteins, polypeptides, polysaccharides, or nucleic acids, do not diffuse across cell membranes at all. These molecules must be broken down into their component monomers, e.g., amino acids, sugars, or nucleotides, if their components are to cross the cell membrane.



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.





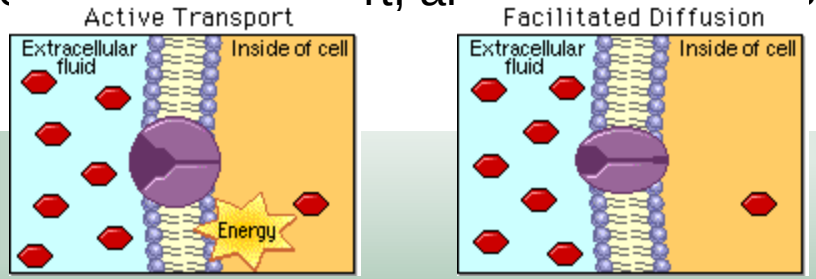
Active transport uses energy to move a solute "uphill" against its gradient, whereas in facilitated diffusion, a solute moves down its concentration gradient and no energy input is required.

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.

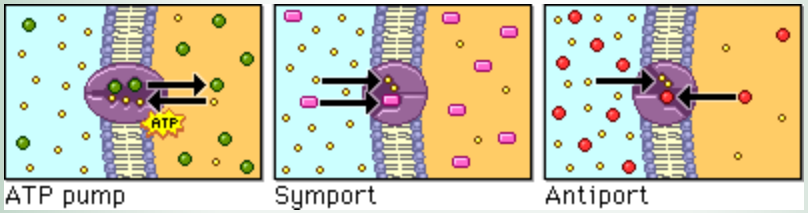
• The solute can move "uphill," from regions of lower to higher concentration. This process is called active transport, and requires some form of chemical energy.



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

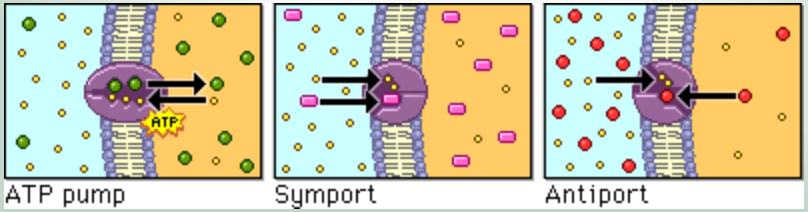
Active transport can occur as a direct result of ATP hydrolysis (ATP pump) or by coupling the movement of one substance with that of another (symport or antiport).



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.

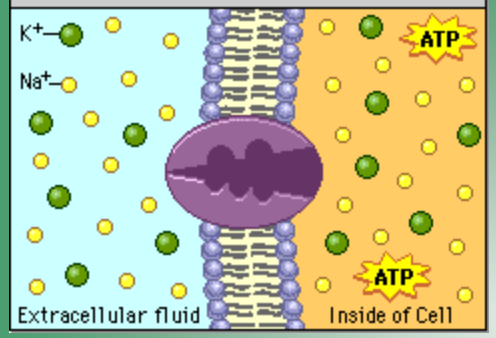
Concept 5 Review: ATP-powered Pumps

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:

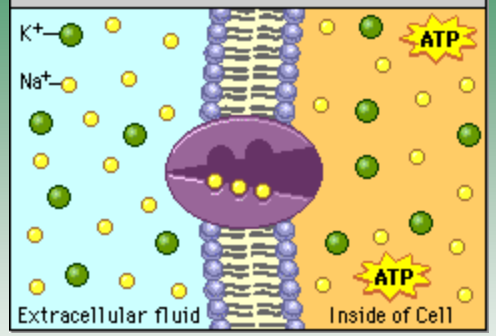
• The Na^+-K^+ ATPase pumps Na^+ out of the cell while it pumps K^+ in. Because the pump moves three Na^+ to the outside for every two K^+ that are moved to the inside, it creates an overall charge separation known as polarization. This electrical potential is required for nervous system activity, and 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.

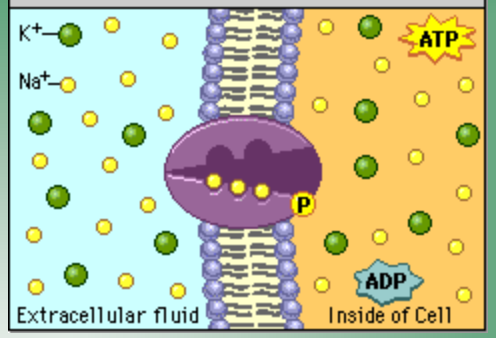
Step 1. Three Na+ ions bind to cytoplasmic high-affinity binding sites.



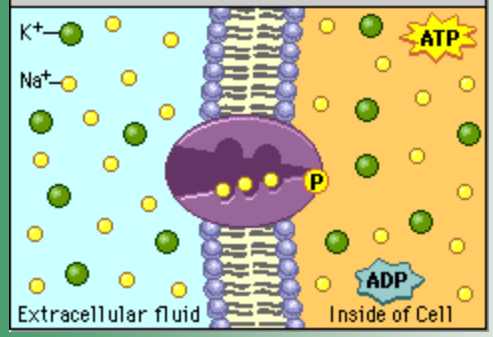
Step 2. ATP is hydrolyzed, transferring a phosphate group to the pump.



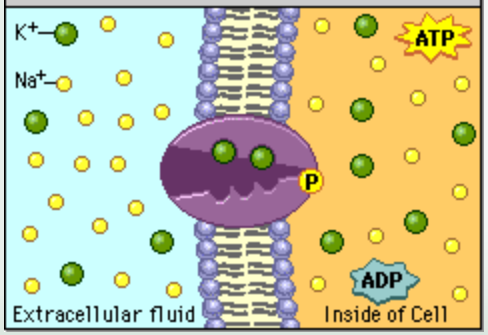
Step 3. The pump conformation changes, moving Na+ ions to the extracellular side of the membrane.



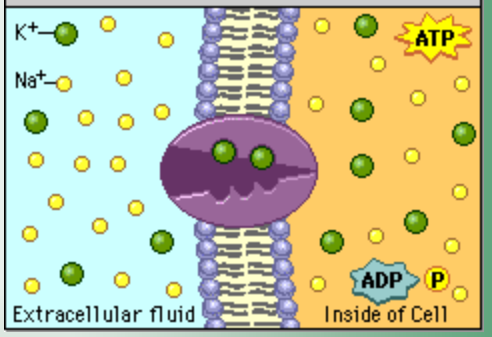
Step 4. Na+ ions dissociate, and two K+ ions bind to high-affinity extracellular sites.



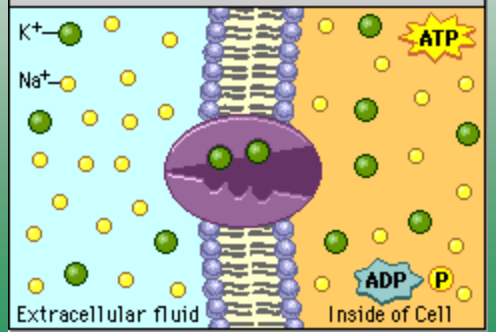
Step 5. The bond linking phosphate to the pump protein is hydrolyzed, releasing inorganic phosphate.



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

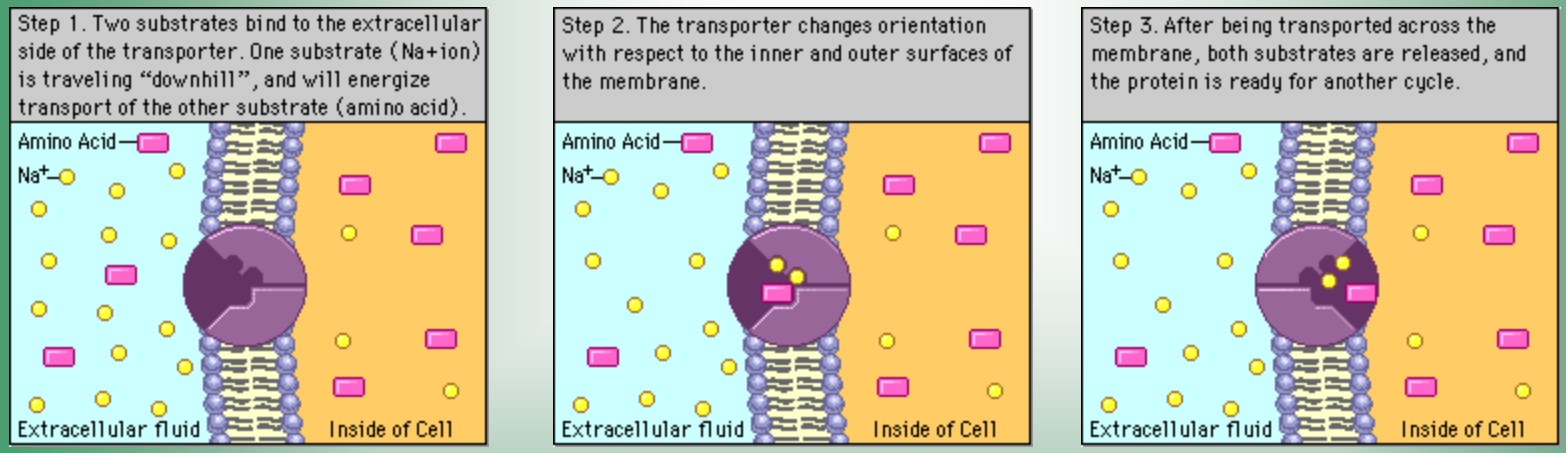


Step 7. K+ ions dissociate, and the pump is ready for another cycle.



Concept 5 Review: Symport

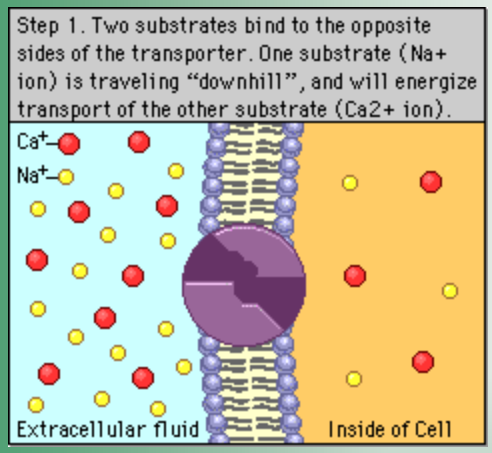
To transport some substances against a concentration gradient, cells use energy already stored in ion gradients, such as proton (H^+) or sodium (Na^+) gradients, to power membrane proteins called transporters. When the transported molecule and the co-transported ion move in the same direction, the process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



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

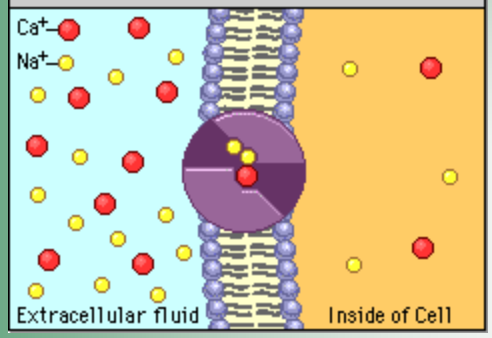
Concept 5 Review: Antiport

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.

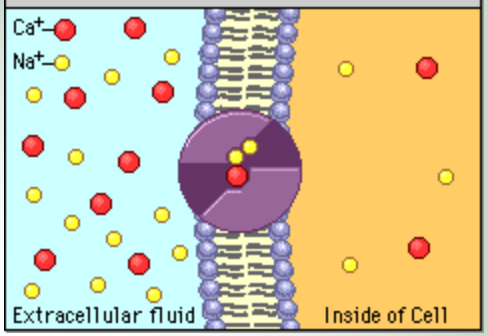


An example of an antiport process is the transport of Ca^{2+} ions out of cardiac muscle cells. Muscle cells are triggered to contract by a rise in intracellular Ca^{2+} concentration, so it is imperative that Ca^{2+} be removed from the cytoplasm so that the muscle can relax before contracting again. 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.

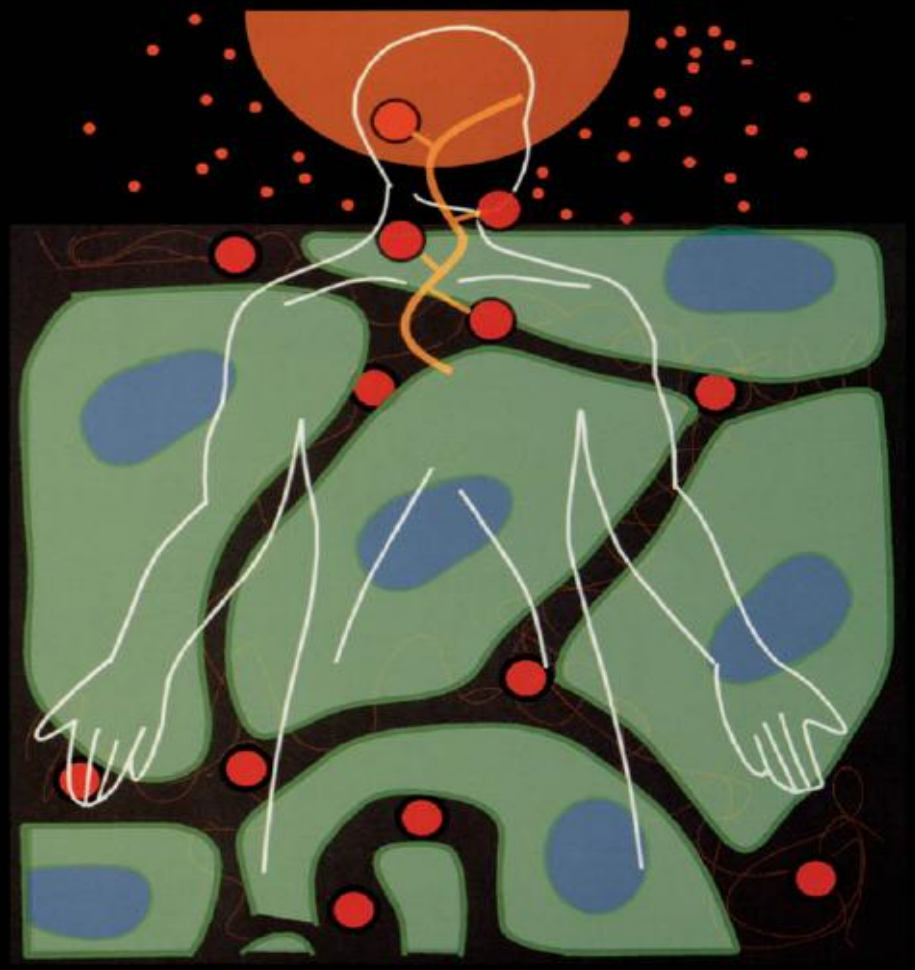


Step 3. After being transported across the membrane, both substrates are released, and the protein is ready for another cycle.



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

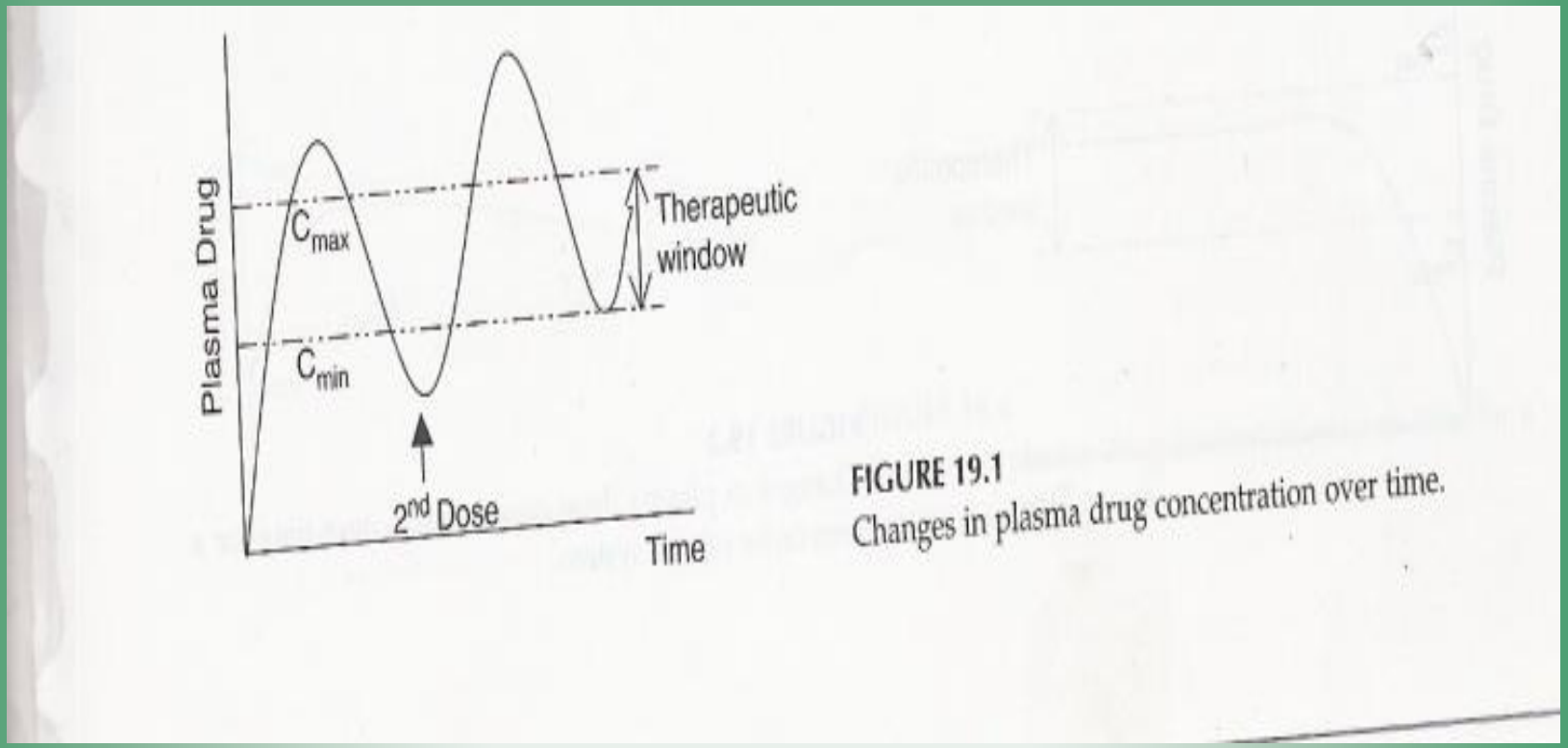


FIGURE 19.1
Changes in plasma drug concentration over time.

- 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 excreation by the kidneys

Controlled release

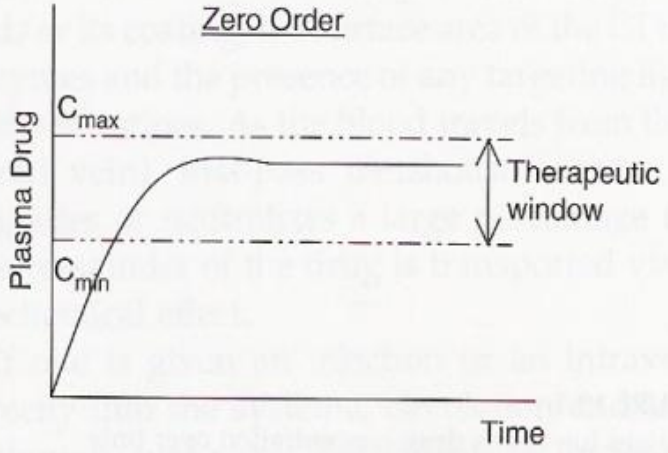
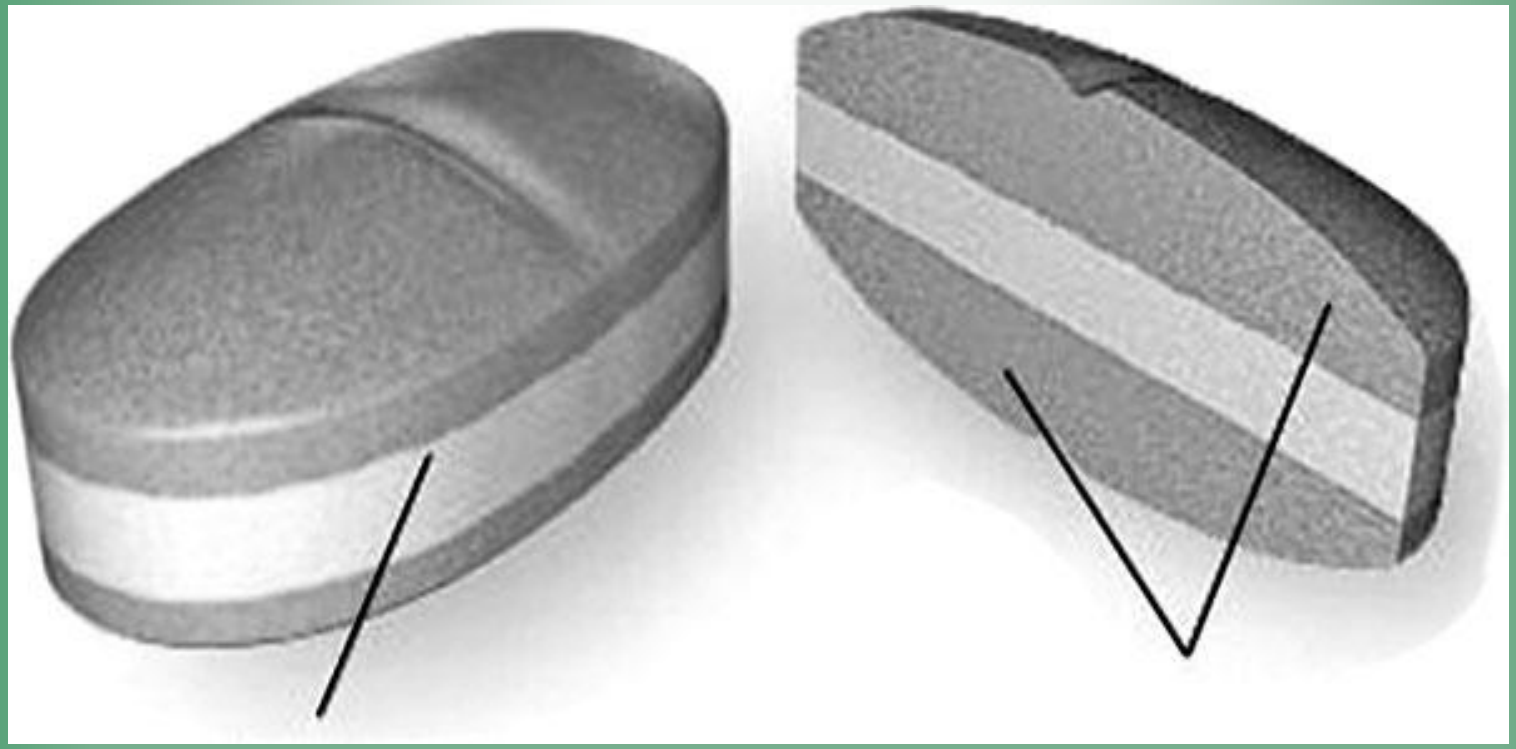


FIGURE 19.2
Changes in plasma drug concentration over time for a zero-order release system.

- In long run, the rate at which the drug is absorbed by the body is equivalent to the physiological drug clearence, 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

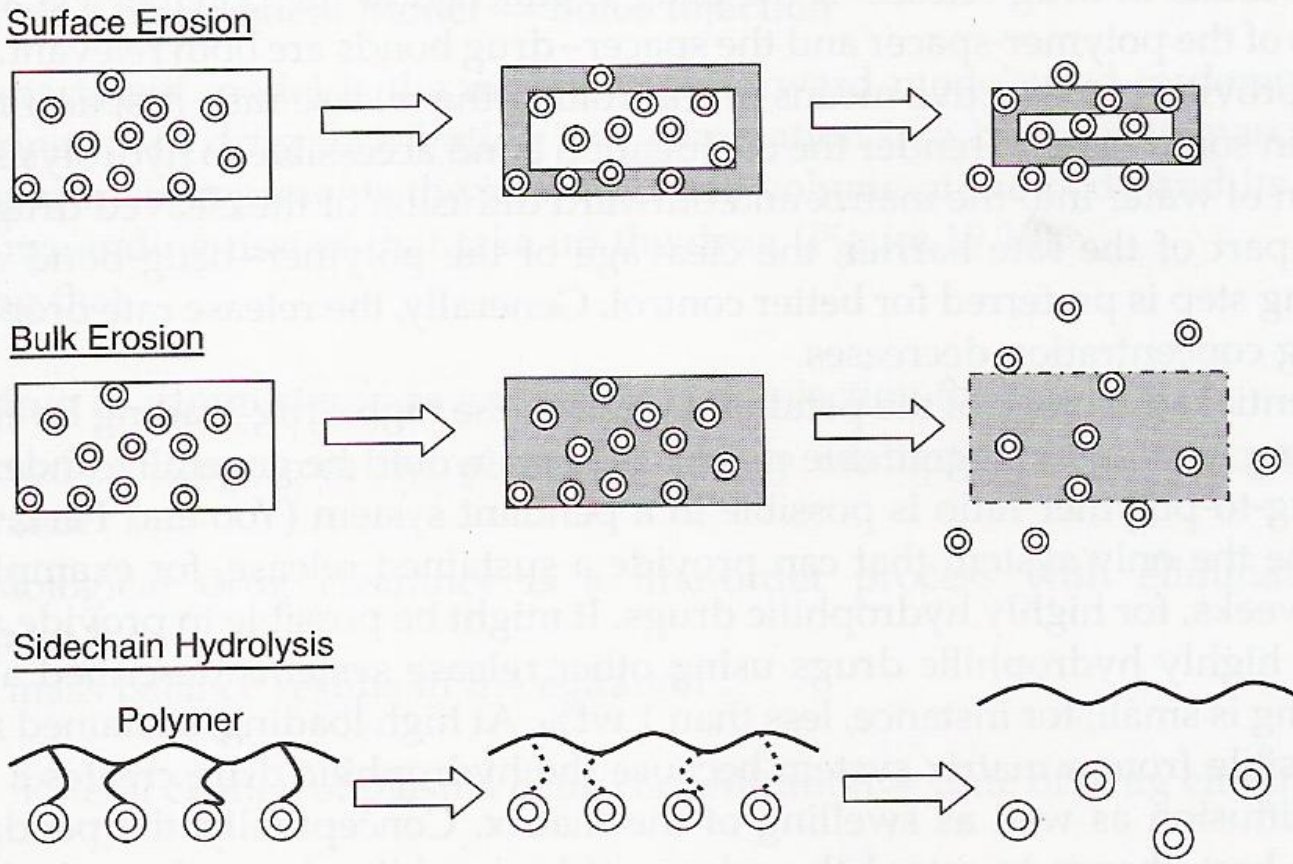


FIGURE 19.8
Schematic illustrating surface erosion, bulk erosion, and side chain hydrolysis.

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 enviroment, water is osmotically driven across the membrane
- Pressure on the movable partition, delivery from orifice

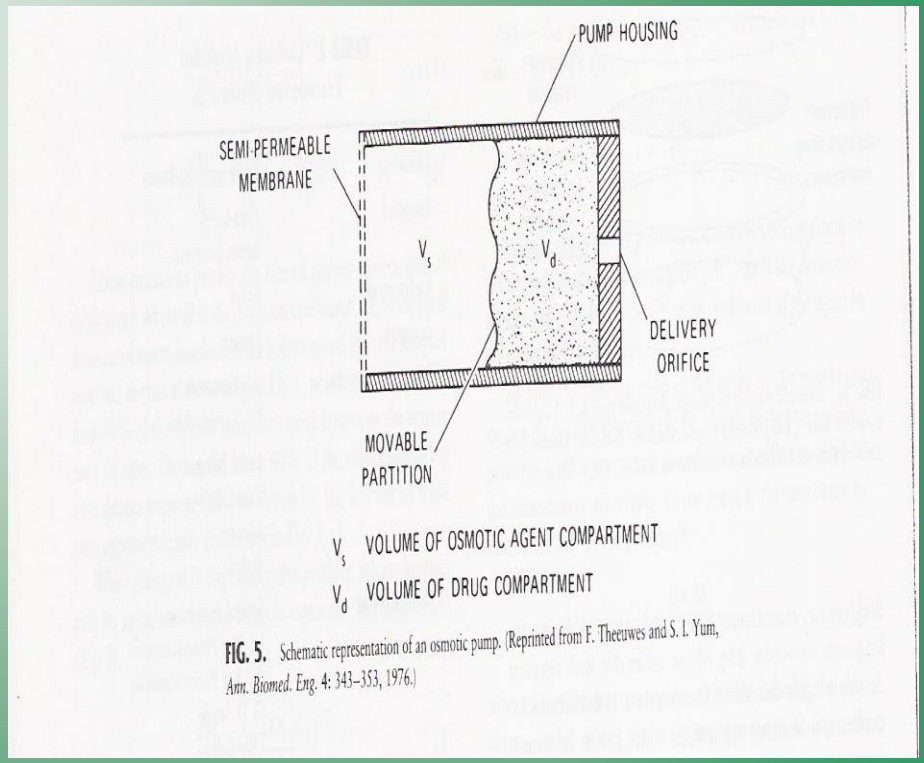
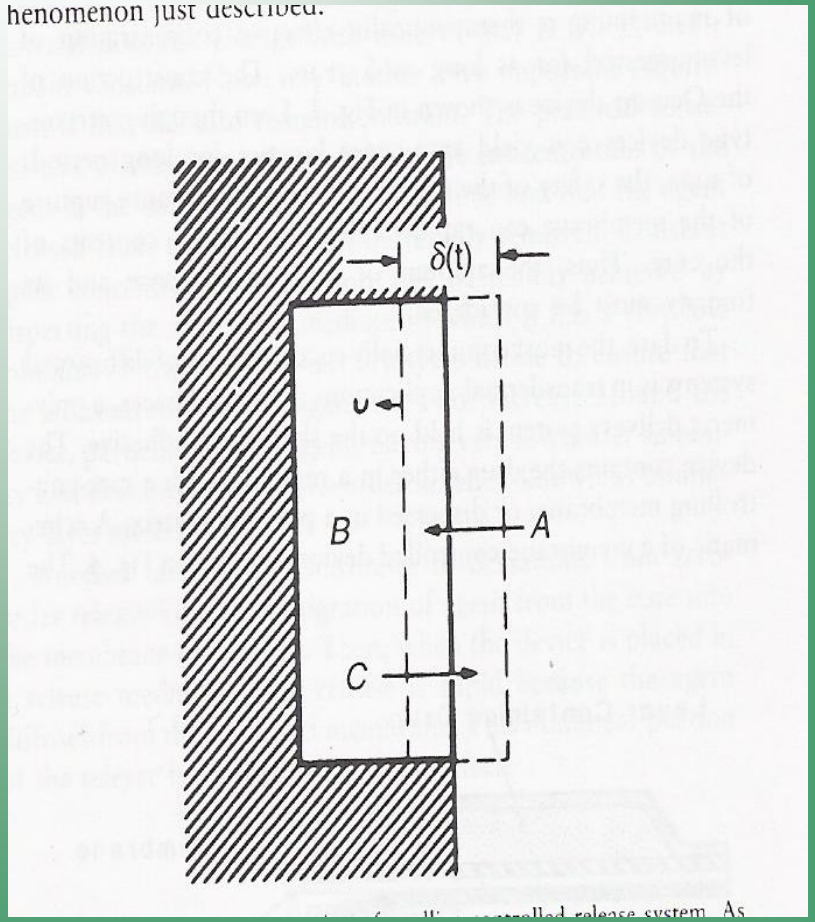


FIG. 5. Schematic representation of an osmotic pump. (Reprinted from F. Theeuwes and S. I. Yum, *Ann. Biomed. Eng.* 4: 343–353, 1976.)

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



Nanoparticles

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

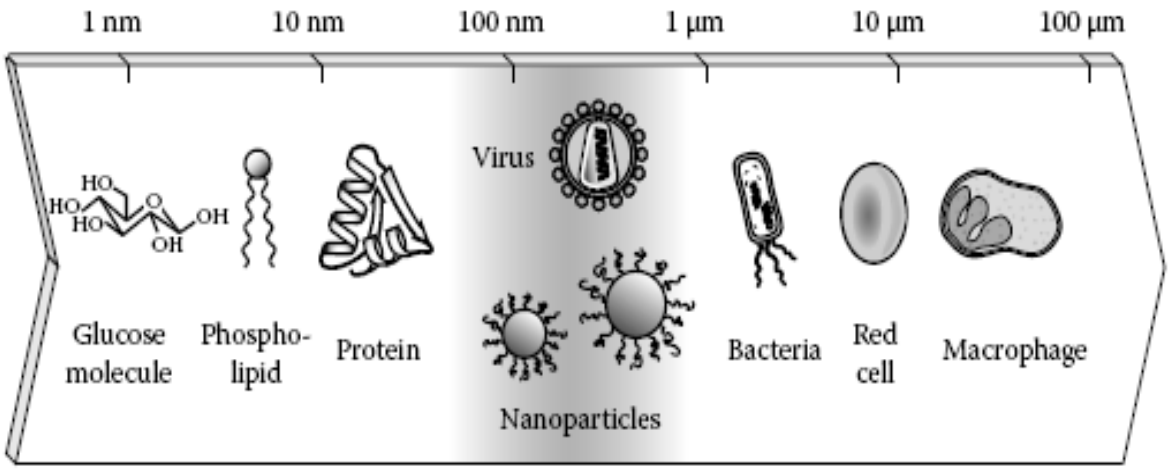


FIGURE 8.2 Sizes of nanoparticles compared with other biological entities.

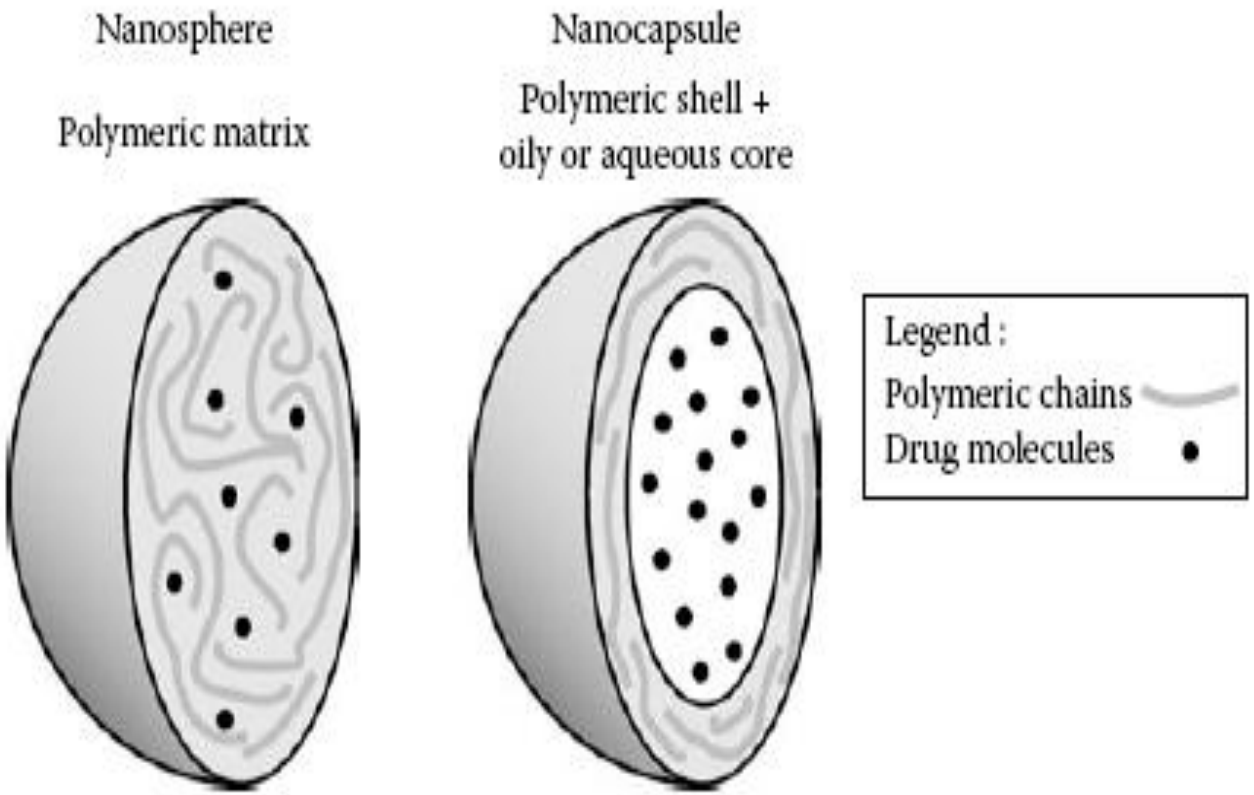
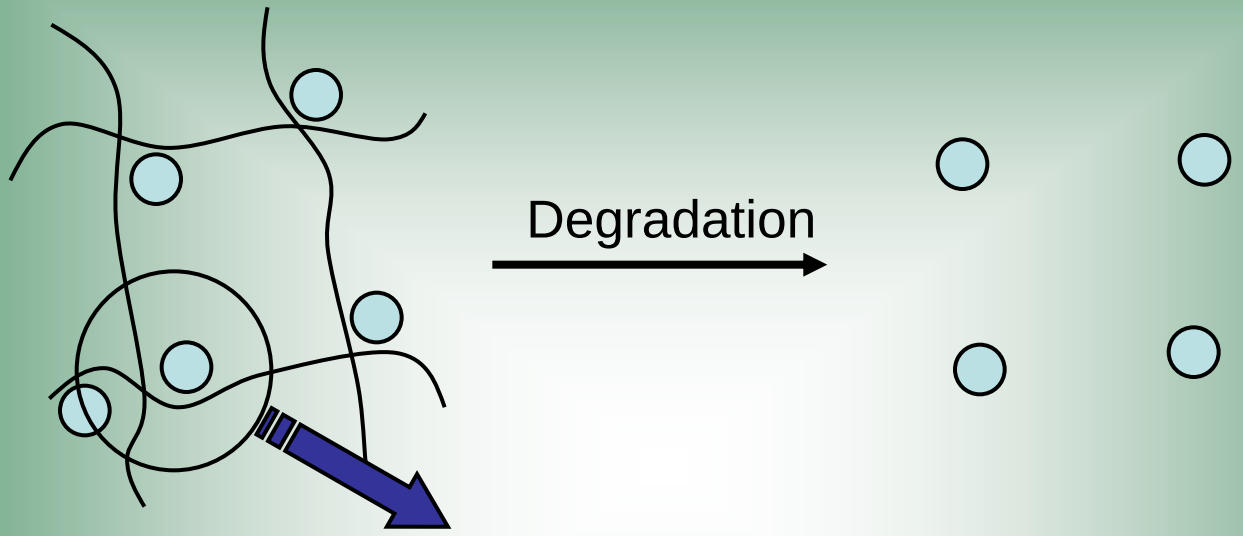
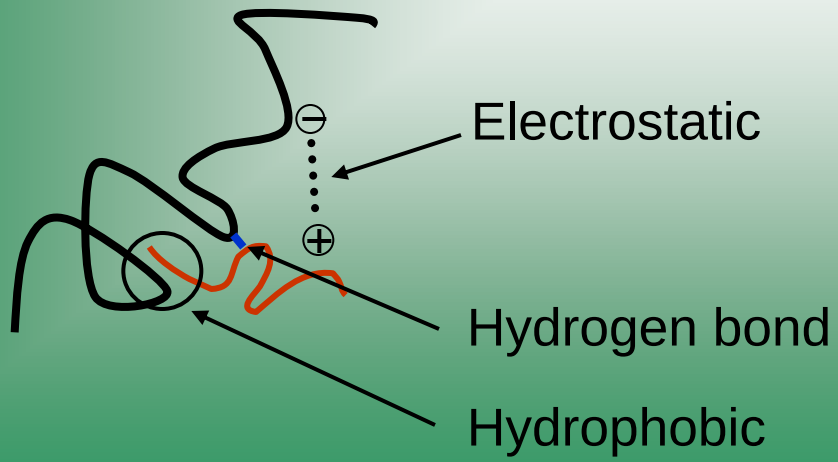


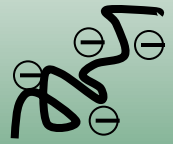
FIGURE 8.3 Morphology of nanospheres and nanocapsules.

Mechanism on the controlled release of Drug



Possible intermolecular interaction between carrier matrix and drug





: Carrier matrix

: Growth factor

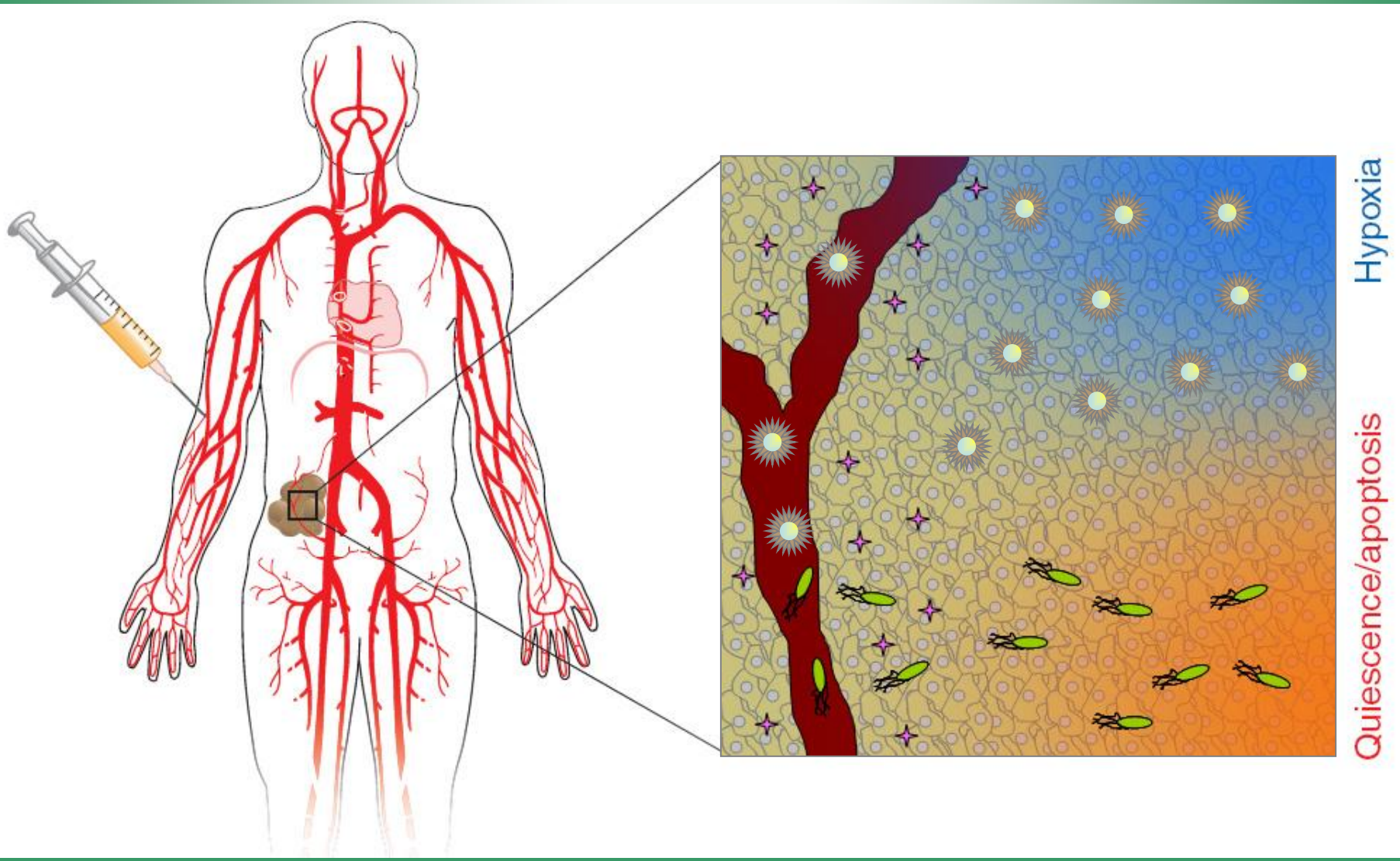
Characteristic Atomic Bonds

		Bonding Energy		
Bonding Type	**Substance**	**kJ/mol**	**eV/Atom, Ion, Molecule**	**Melting Temperature (ºC)**
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_2O	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

Administration of Nanomaterials to Tissue:

Failure to reach to Target cells/Tissue



Cellular response to Nanomaterials/biomaterials

The response of cells to biomaterials is critical in medical devices. Traditionally inert biomaterials were used to minimise the reaction in cells in contact with the material. However, it has been realised that specific cell responses may be beneficial in such areas as encouraging adhesion, healing or cell multiplication. *Cellular response to biomaterials discusses* the response of cells to a wide range of biomaterials targeted at specific medical applications.

The success of any implant introduced into the body is determined by the initial reaction of the cells at the tissue-implant interface. Several factors have been identified that modulate the response of cells to an implant, and one area of increasing interest, is the topography of the material. In vitro and in vivo research have shown the potential benefits of altering the surface topography of the implant material to ensure optimal integration of the implant into the surrounding tissue. The focus of this entry is on the effects of surface topography on the reactions of a variety of cell types in vitro and in vivo.

Can cells and biomaterials in therapeutic medicine be shielded from innate immune recognition?

Biomaterials (e.g. polymers, metals, or ceramics), cell and cell cluster (e.g. pancreatic islets) transplantation are beginning to offer novel treatment modalities for some otherwise intractable diseases. The innate immune system is involved in incompatibility reactions that occur when biomaterials or cells are introduced into the blood circulation. In particular, the complement, coagulation and contact systems are involved in the recognition of biomaterials and cells, eliciting activation of platelets and leukocytes. Such treatments are associated with anaphylactoid and thrombotic reactions, inflammation, and rejection of biomaterials and cells, leading to treatment failures and adverse reactions.

Foreign body reaction to biomaterials

The foreign body reaction composed of macrophages and foreign body giant cells is the end-stage response of the inflammatory and wound healing responses following implantation of a medical device, prosthesis, or biomaterial.

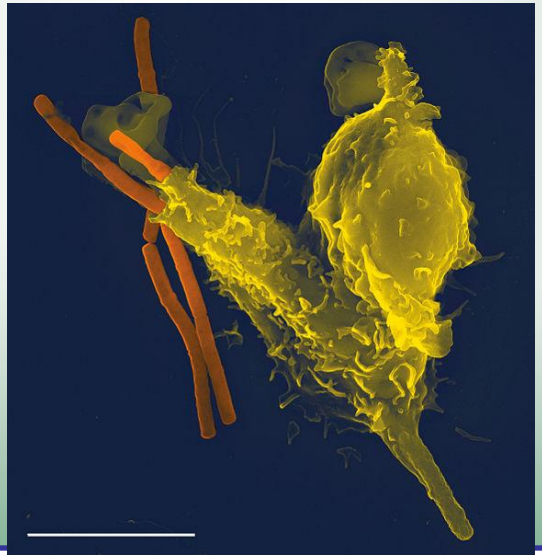
factors that modulate the interaction of macrophages and foreign body giant cells on synthetic surfaces where the chemical, physical, and morphological characteristics of the synthetic surface are considered to play a role in modulating cellular events. These events in the foreign body reaction include protein adsorption, monocyte/macrophage adhesion, macrophage fusion to form foreign body giant cells, consequences of the foreign body response on biomaterials, and cross-talk between macrophages/foreign body giant cells and inflammatory/wound healing cells.

Immune System and Medical Devices

Even before the concept of immunity (from immunis, Latin for “exempt”) was developed, numerous early physicians characterized organs that would later prove to be part of the immune system. The key primary lymphoid organs of the immune system are thymus (T lymphocyte maturation) and bone marrow (Hematopoietic Stem Cells (HSCs)), while the secondary lymphatic tissues are the spleen (Reserve of monocytes; Active immune response), tonsils (produce antibodies), lymph vessels (transports antigen presenting cells and immune cells), lymph nodes (location lymphocytes meet the antigens), and skin (part of adaptive immune system). Nevertheless, the majority of the immune response to Biomaterials is derived from HSCs that give rise to all the blood cell types including myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells, NK-cells). For the most part, a Biomaterials interaction with the immune system arises from exposure of the Biomaterial/Medical Device to the host defense mechanisms, which function to protect organisms from deleterious external threats. The nature of the reaction is largely dependent on the chemical and physical properties of the Biomaterial. How does mans immune system play a role in the function of medical devices?

Macrophages are the dominant infiltrating cells that respond rapidly to biomaterial implantation in soft and hard tissues. These cells and their fused morphologic variants, multinucleated giant cells or foreign body giant cells, usually remain at biomaterial–tissue interfaces for the lifetime of the device *in vivo*. As a component of the immune system, macrophage activities are closely related to immune responses, inflammation and foreign body responses. However, macrophages also mediate biodegradation of bioresorbable materials via phagocytosis and extracellular degradation. In addition, macrophages are essential for effective tissue regeneration as they regulate the recruitment, proliferation and differentiation of target cells, such as fibroblasts, osteoblasts, endothelial cells and keratinocytes during healing processes.

An **immune system** is a system of biological structures and processes within an organism that protects against disease by identifying and killing pathogens and tumour cells. It detects a wide variety of agents, from viruses to parasitic worms, and needs to distinguish them from the organism's own healthy cells and tissues in order to function properly. Detection is complicated as pathogens can evolve rapidly, producing adaptations that avoid the immune system and allow the pathogens to successfully infect their hosts.



A scanning electron microscope image of a single neutrophil (yellow), engulfing anthrax bacteria (orange).

To survive this challenge, multiple mechanisms evolved that recognize and neutralize pathogens. Even simple unicellular organisms such as bacteria possess enzyme systems that protect against viral infections. Other basic immune mechanisms evolved in ancient eukaryotes and remain in their modern descendants, such as plants, fish, reptiles, and insects. These mechanisms include antimicrobial peptides called defensins, phagocytosis, and the complement system. Vertebrates such as humans have even more sophisticated defense mechanisms.[1] The immune systems of vertebrates consist of many types of proteins, cells, organs, and tissues, which interact in an elaborate and dynamic network. As part of this more complex immune response, the human immune system adapts over time to recognize specific pathogens more efficiently. This adaptation process is referred to as "adaptive immunity" or "acquired immunity" and creates immunological memory. Immunological memory created from a primary response to a specific pathogen, provides an enhanced response to secondary encounters with that same, specific pathogen. This process of acquired immunity is the basis of vaccination.

Hemocompatibility

Artificial surfaces can induce thrombosis, embolization, consumption of platelets and plasma coagulation factors, as well as systemic effects from platelet activation and activated coagulation and complement factors. Upon contacting blood, Biomaterials rapidly adsorb a film of plasma proteins, which ultimately determine its Hemocompatibility. The first step is to utilize ELISA and/or protein radiolabeling to determine the adherent proteins and immune factors activated by the biomaterial. Evaluation of this data provides an initial view of the blood compatibility and whether surface modification is necessary. For example, certain hydroxyl environments activate the Alternate Pathway of Complement and fluorinated (hexafluoropropene, C3F6) surfaces will activate platelets. Also to be considered is how the new surface characteristics would affect the overall function of the device. Once this initial phase is completed, other in vitro testing, such as exposure of the functioning device to whole blood or serum, will bring in other factors like mechanical shear and fluid dynamics that also effect blood compatibility.

Tissue Compatibility

Most Biomaterials in contact with tissue elicit a foreign body reaction (FBR), or nonspecific inflammation. The most prominent cells are macrophages, which attempt to phagocytose the material and are variably successful. The macrophages now activated by this process may elaborate cytokines that stimulate inflammation or fibrosis. Multinucleated giant cells in the vicinity of a Biomaterial are generally considered evidence of a more severe FBR. The more tissue-compatible the implant the more quiescent the response (less inflammation). Tissue interaction with an inert Biomaterial usually results in encapsulation by a relatively thin fibrous capsule. Final testing involves preclinical testing in animals and clinical testing in humans for Class III devices. Selection of the in vivo model is particularly important. For example, most animal models endothelialize synthetic vascular grafts, while humans display a reduced endothelialization and healing response. As mentioned earlier, interactions with blood or tissue can be modified by changing the surface chemistry of the Biomaterial to cause a favorable protein to bind, stimulate adhesion or bone formation in orthopedics, modifying the roughness or porosity for tissue ingrowth, incorporating agents to attract certain cell types and even utilizing a resorbable polymer to allow slow replacement by native tissue. Consequently, if a polymer is performing adequately, but is activating the immune system, a surface modification could be used with out changing its mechanical performance.

New Medical Devices Can Cause New Immune Problems

Medical devices are traditionally thought of as fairly simple implants such as stents and hip replacements - pieces of plastic or metal that are placed in the body to handle a very specific function. But biomedical devices now on the drawing board are considerably more sophisticated and represent an unprecedented melding of man and machine.

Combination products, devices that include a combination of drug, biological and device components, are expected to be the next big thing in biomedical devices. An example of a combination product is a tissue-engineered device that combines living cells with a polymer scaffold. When implanted into a patient, the device can replace or restore damaged tissue or organ function. While the response of the body to each component is well known, considerably less is known about how their new union may affect the body's reaction to a combination device.

The body can have a different and potentially detrimental reaction when there's more than one component involved.

When a biomedical implant is introduced into a patient's body, the body's response is a threat to the acceptance of the implant and could result in device failure. The body responds to biomaterials with an inflammatory reaction and to foreign biological components with an immune reaction. But the two reactions may affect one another when triggered simultaneously, as they would be in a combination device if the combination product contains any foreign biological material.

If you're combining a polymer with a biological component, the body may respond differently to that combination than it would to either component by itself. The immune response towards a foreign biological component of the device may be affected by the inflammatory response to the biomaterial component.

…There is a need to better understand more complex combination products so that as they move into wider use, they can be designed to integrate as smoothly as possible into the patient.

strategies for designing biomaterials and devices that can best integrate into the body by controlling host responses. In some combination products, biomaterials (in the form of polymer sponges) are used in the medical device to provide sites for transplanted cells to grow on to help it be better incorporated, strengthening its connection to the body.

Initial in-vivo research findings indicate that the inflammatory response to a biomaterial can affect the immune response to a foreign protein that is delivered at the same time. The presence of the biomaterial (a polymer) enhanced the body's immune response to a foreign protein. The polymer boosts the immune response by spurring the dendritic cells (cells that direct immune responses) to mature so that they can effectively initiate an immune response.

The finding means that for combination devices, if there was a potential immune response to a biological component, the biomaterial component could further exacerbate the immune response, making it more difficult for the device to integrate smoothly.

Different materials seem to have varying effects on the dendritic cells. This may indicate which biomaterials will be good for which application. For example, biomaterials that support dendritic cell maturation may be best suited as polymeric carriers for vaccine delivery and those that do not support dendritic cell maturation may be used as sponges in tissue engineering.

To better understand the body's reaction to biomedical devices that incorporate both biomaterials and biological components, works with human blood cells, treating them with a variety of biomaterials to see what response is induced from the dendritic cells.

"These cells control which way the immune response will go, so if we can control their phenotype, the idea is that we can control immune responses,“.

Currently so-called biomaterials are chosen because they are reasonably successful at hiding from the body's immune system, and are consequently not rejected. All the same, within a month of implanting them, the body isolates implants by wrapping them in a collagenous, avascular sac. Materials are considered to be 'biocompatible' if this sac is not too thick.

That's not very clever !

it is time to take a more intelligent approach.

Rather than building implants out of materials that try to hide from the body's systems, he believes that we should be creating them from materials that are specifically designed to engage with biological processes. This could take the form of materials made with specifically sized pores that encourage small blood vessels to actively grow through the implant, or implants coated with DNA that specifically prevents formation of the collagenous capsule.

Both of these let the implant and the body actively work together, rather than simply try to prevent them fighting against each other.

These sorts of ideas will lead to a new biomaterials science that will permit us to make materials for medical devices that function better, last longer, encourage healing and provide enhanced patient satisfaction.

Active Nanobiomaterials for Regenerative Medicine

Description:
Research on active biomaterials for implantation in the human body could lead to in-situ repair and regeneration of damaged tissue as an alternative to surgery and a cure for some diseases.

The first generation of manufactured biomaterials emerged in the 1960s; they were prosthetic parts made of inert substances that were intended to be placed inside the body with minimal likelihood of immune system rejection. A second generation employed bioactive materials that could elicit a desired action and reaction from the body. Employing research at the molecular level, a new generation of biomaterials is in development; these novel materials are being designed to stimulate specific cellular responses, thereby activating genes to stimulate the regeneration of live tissue. While research on active biomaterials is new, the development of biomaterials has been under way for 40+ years.

If regenerative medicine based on active biomaterials can be developed, it is conceivable that the body will be able to heal itself internally, as it does with a cut or scrape today. Tissue regeneration shows the greatest promise with the use of stem cells, so new developments in stem cell research are an important part of the effort. Nanomaterials may provide solutions to the significant challenge of developing mechanisms that will support blood flow in engineered materials.

Implications:

* Vast enhancement of the human body's ability to repair itself
* Potential for reversal of organ damage resulting from disease
* Decreased use of surgery

Early Indicators:

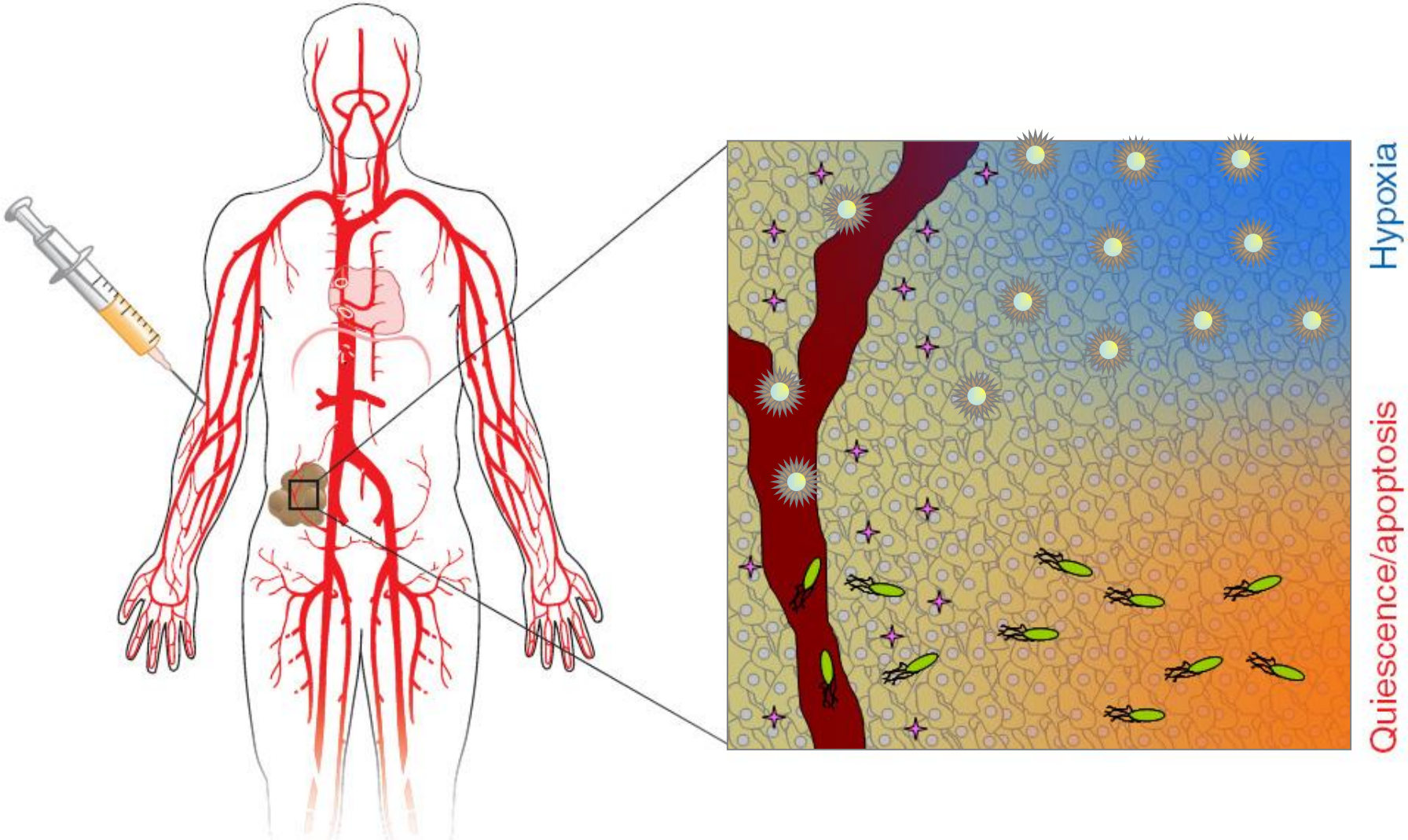
* Employment of biomaterials for skin regeneration in acute wounds such as burns and as scaffolds for guided nerve regeneration at the Institute for Regenerative Medicine at Wake Forest University
* Successful application of research by Stephan Heller (Harvard/Stanford) on using adult and embryonic stem cells to regenerate hearing tissues, leading to improvement of hearing loss due to aging

What to Watch:

* Breakthroughs in stem cell research, nanomaterials and microtextiles lead to procedures that can be tested in clinical trials.

Enablers/drivers:
* Better understanding of the basic mechanisms involved in cell growth and differentiation into different types of tissue
* Resolution of the ethical dilemma associated with the use of embryonic stem cells
* Rapid aging of the population in Western societies, outpacing medicine's ability to perform invasive surgeries and the human and financial resources to do so
* Ongoing nanomaterial research

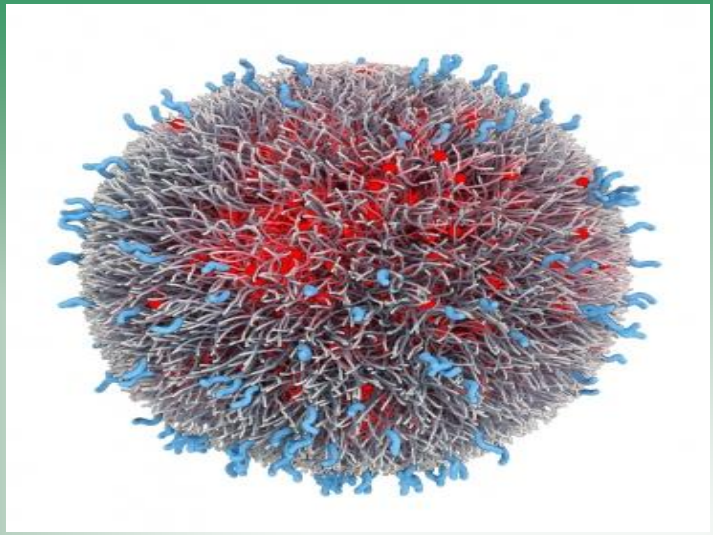
Nanomaterials:
Targeted Therapy



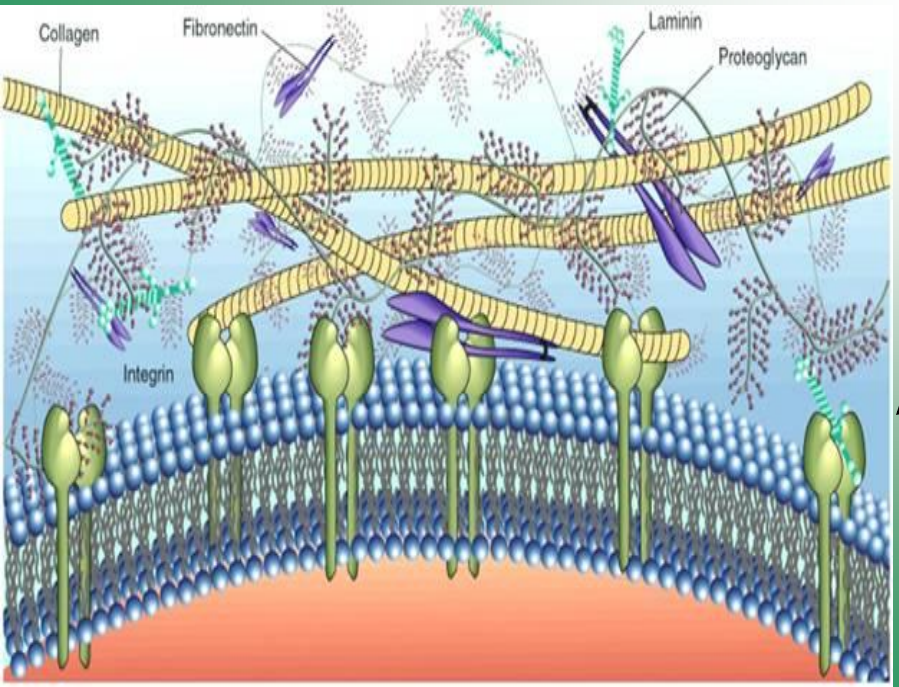
Intelligent Stealth Technology

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.

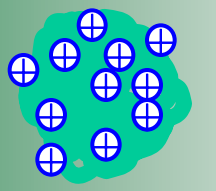


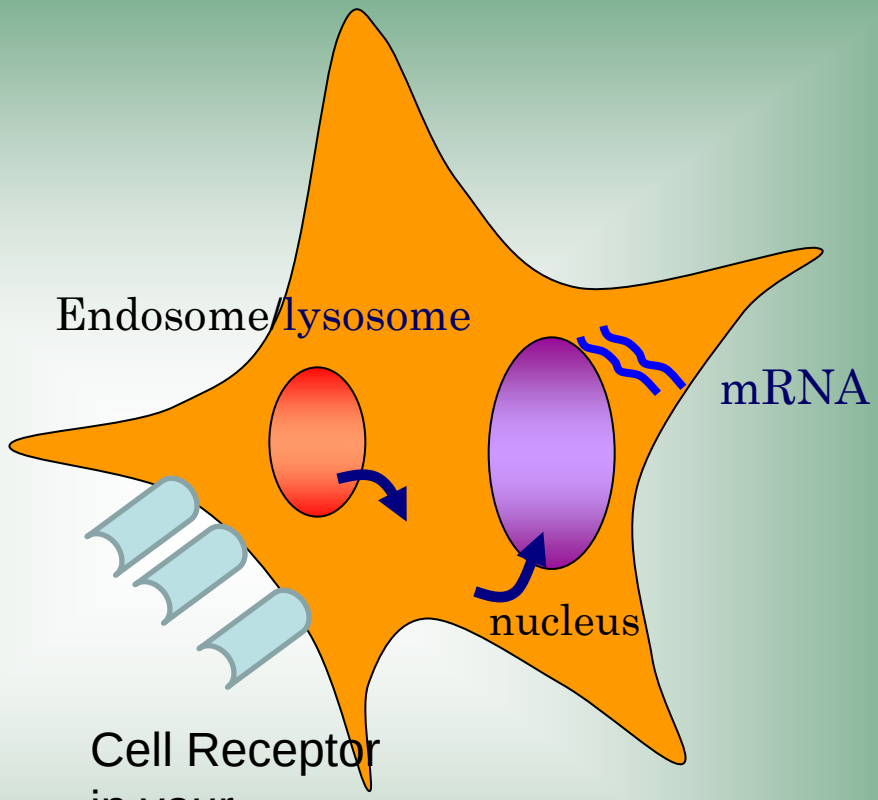
1. Targetable Nanoparticles



Find Cell Receptor in your Target Tissue

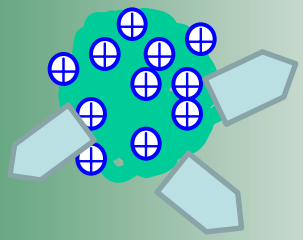
Nanoparticle



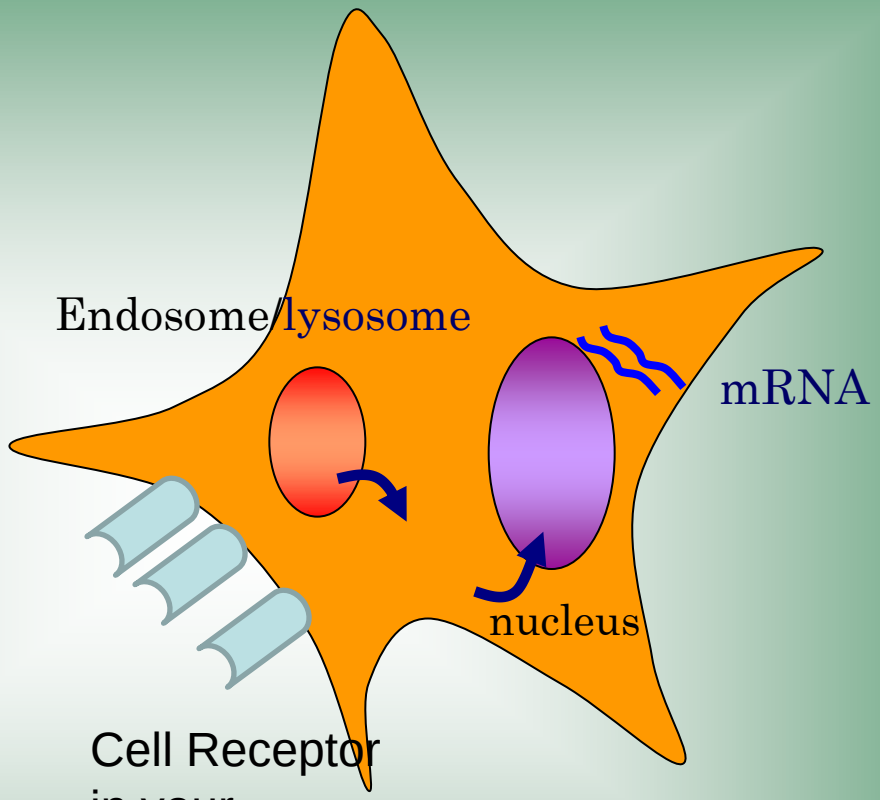


Cell Receptor
in your
Target Tissue

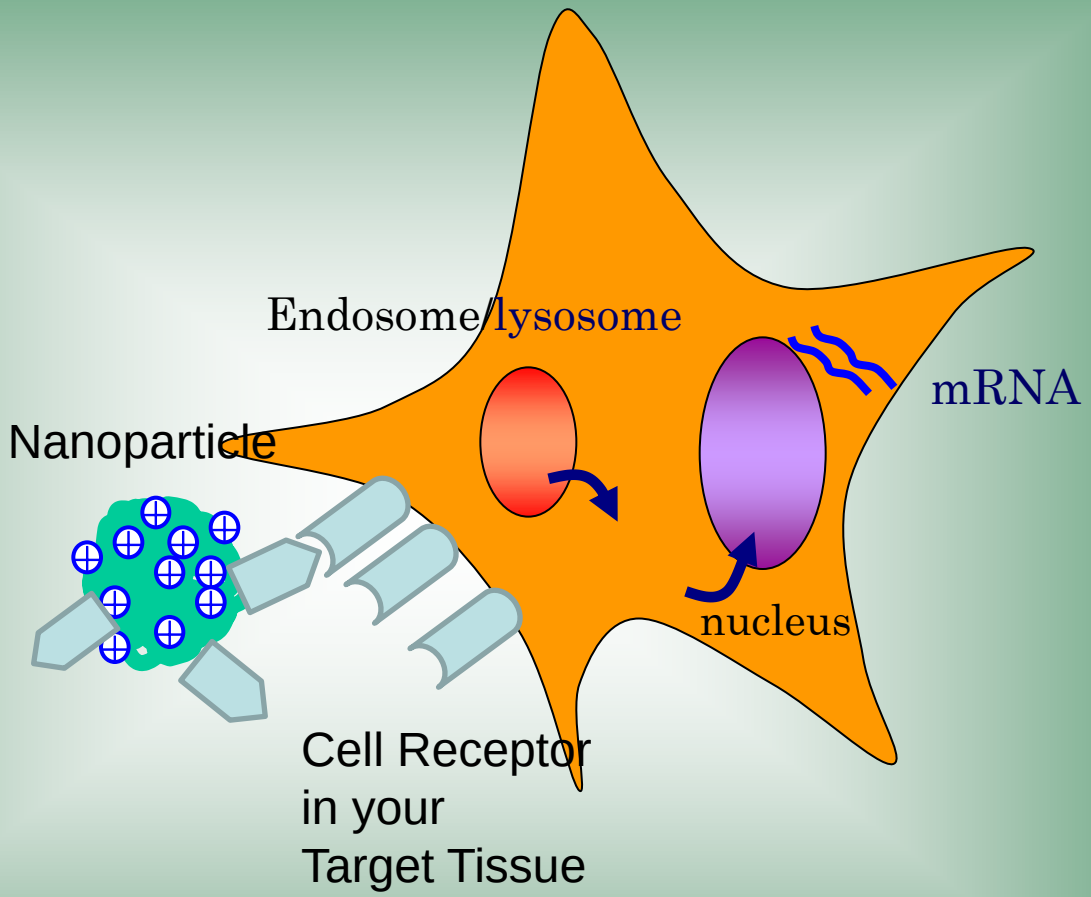
Nanoparticle

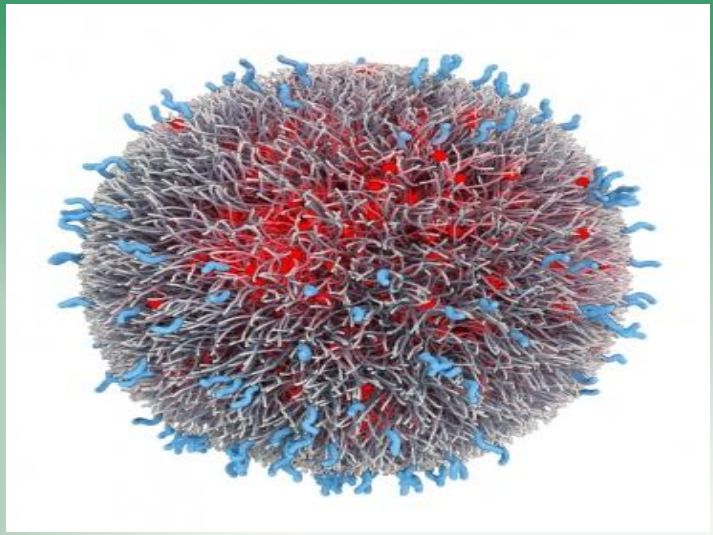


Attach a Ligand Molecule

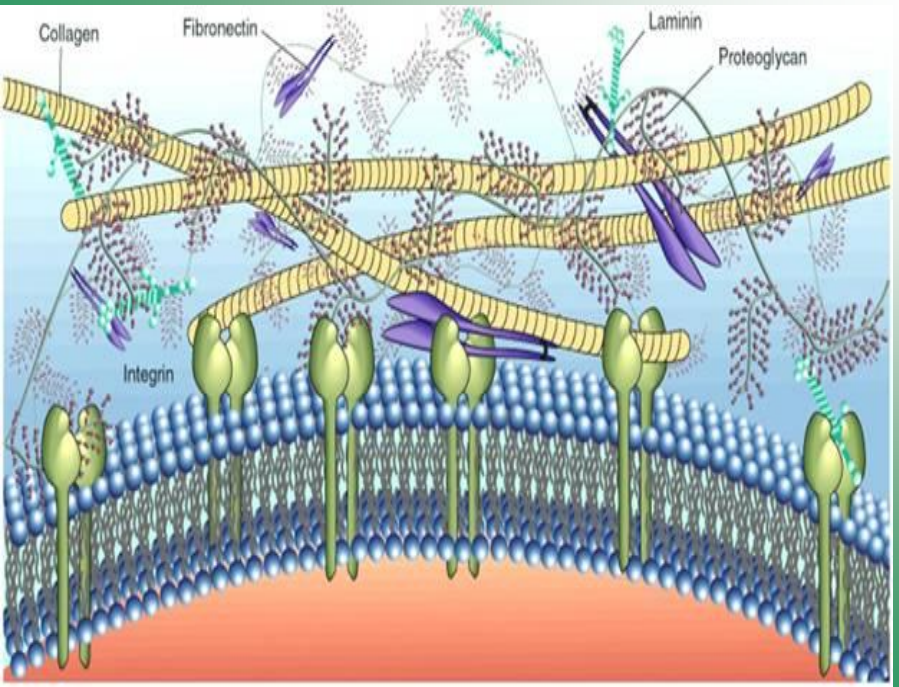


Cell Receptor in your Target Tissue


Endosome/lysosome
mRNA
Nanoparticle
nucleus
Cell Receptor
in your
Target Tissue



2. Invisible Nanoparticles

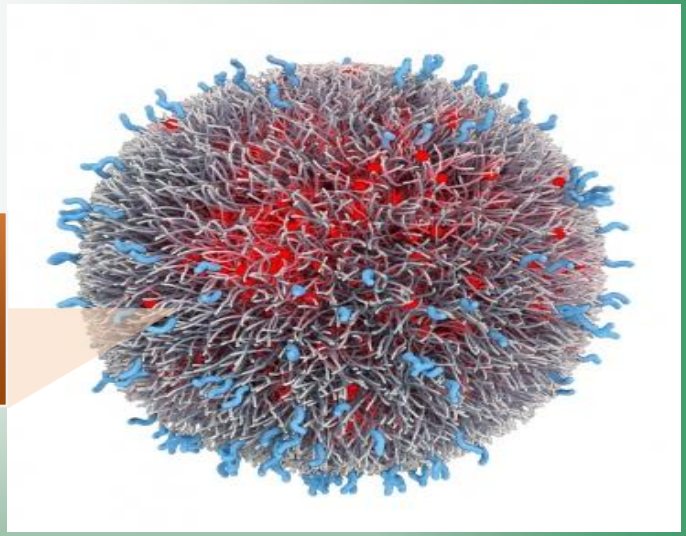


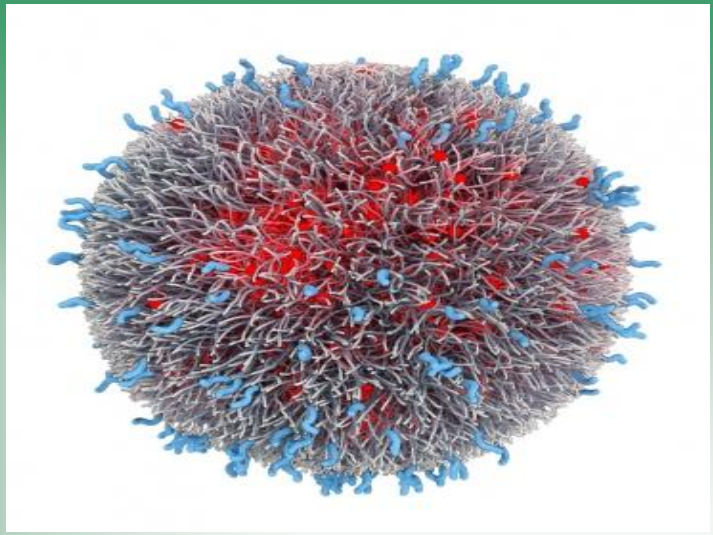
Anti-Radar Stealth Jet-F-119

Anti-Radar Stealth Jet-F-119

Interface
Biology
Engineering

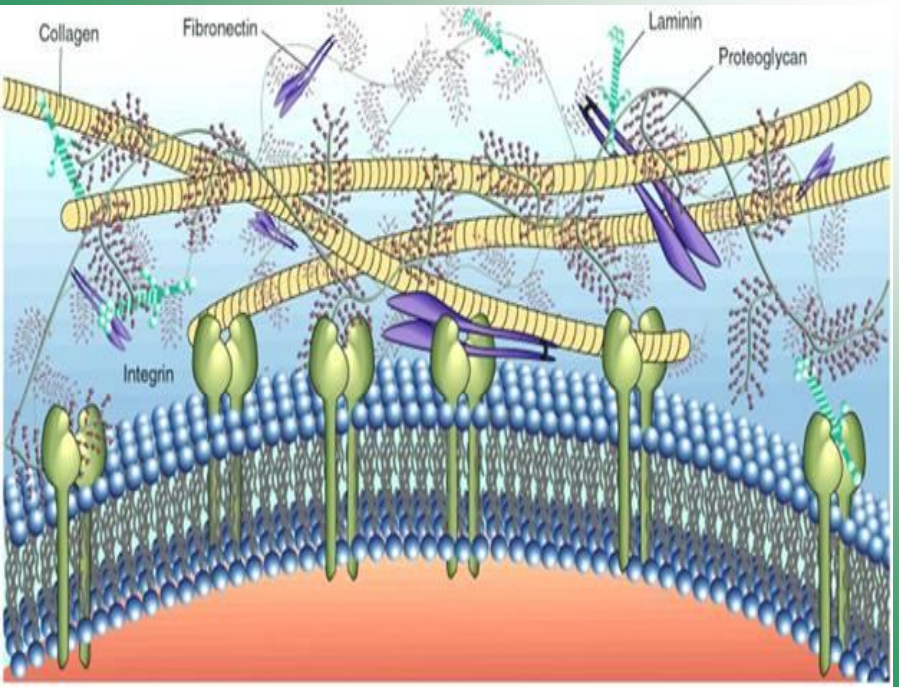
Anti-Immune Response:
Invisible Nanoparticles



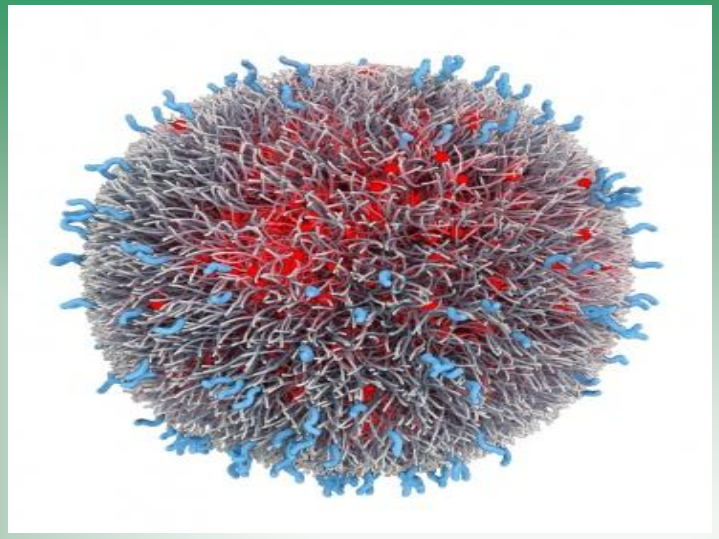


2. Invisible Nanoparticles

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



PEGylation Technology



3. Detectable Nanoparticles

Loaded with:

Iron Oxide Nanoparticles

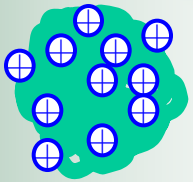
(Detectable by MRI)

Super Paramagnetic
Iron Oxide, Fe_3O_4

Polyanion
(Dextran)

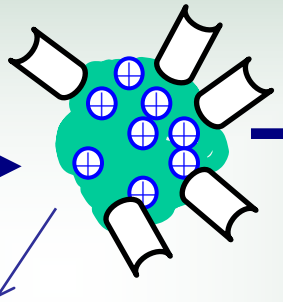
40 C
14 hr
pH 7

Magnetic
Nanoparticles



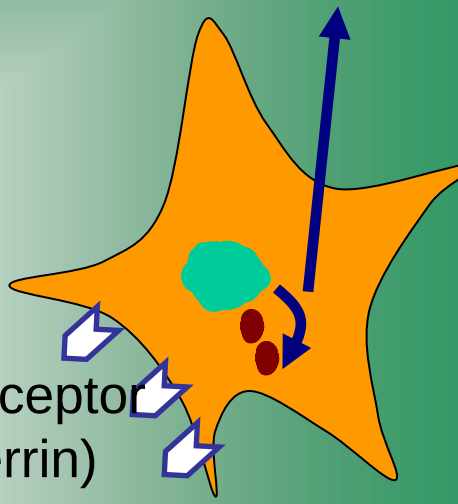
nanoparticle
formation

RGD ligand



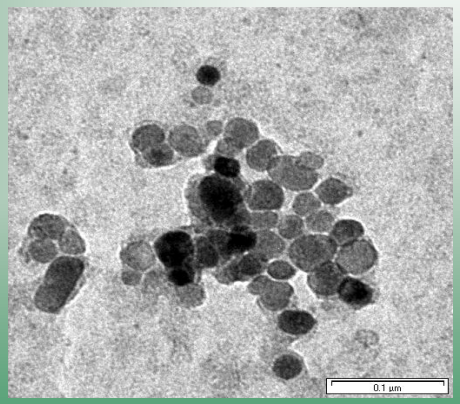
Loaded with Target Molecule

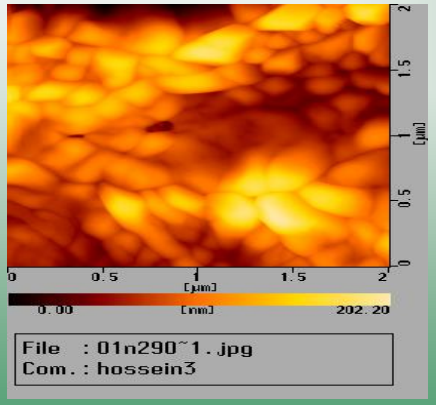
Sustained Release of Iron Oxide



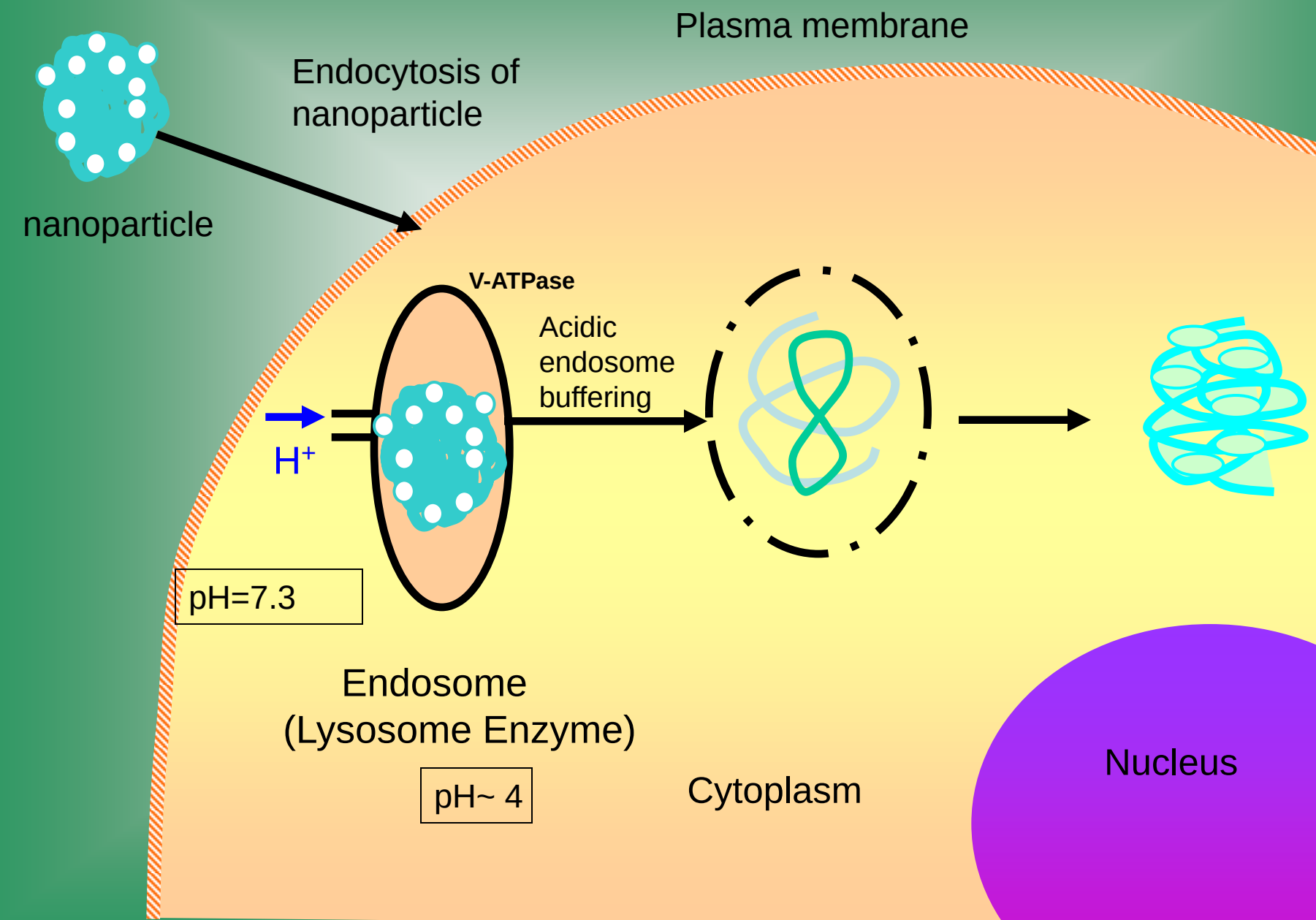
Target receptor
(transferrin)

Double Glue
1.Targeted Cells
2.MRI monitoring

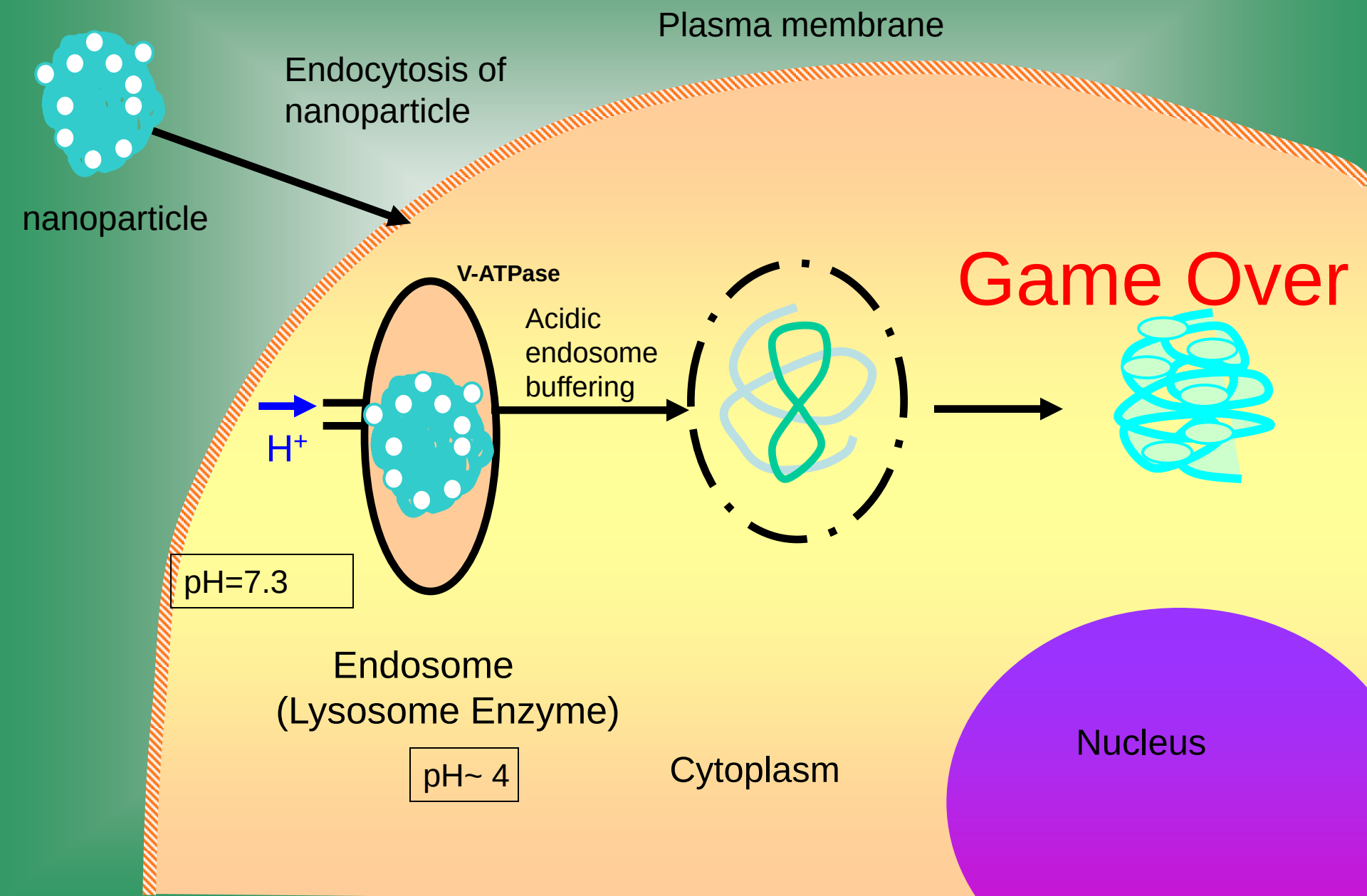




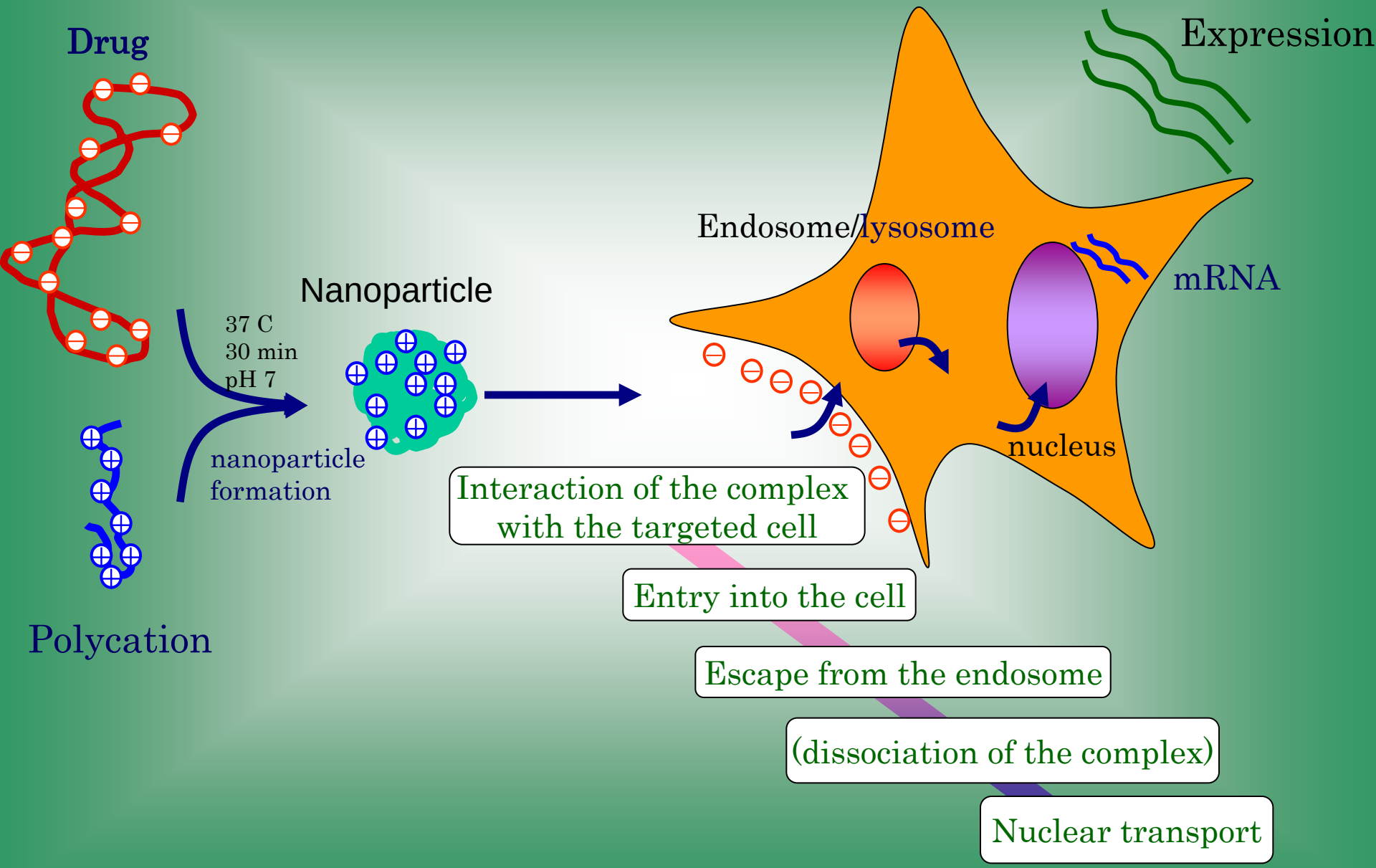
Last Barrier: Intelligent Endosome



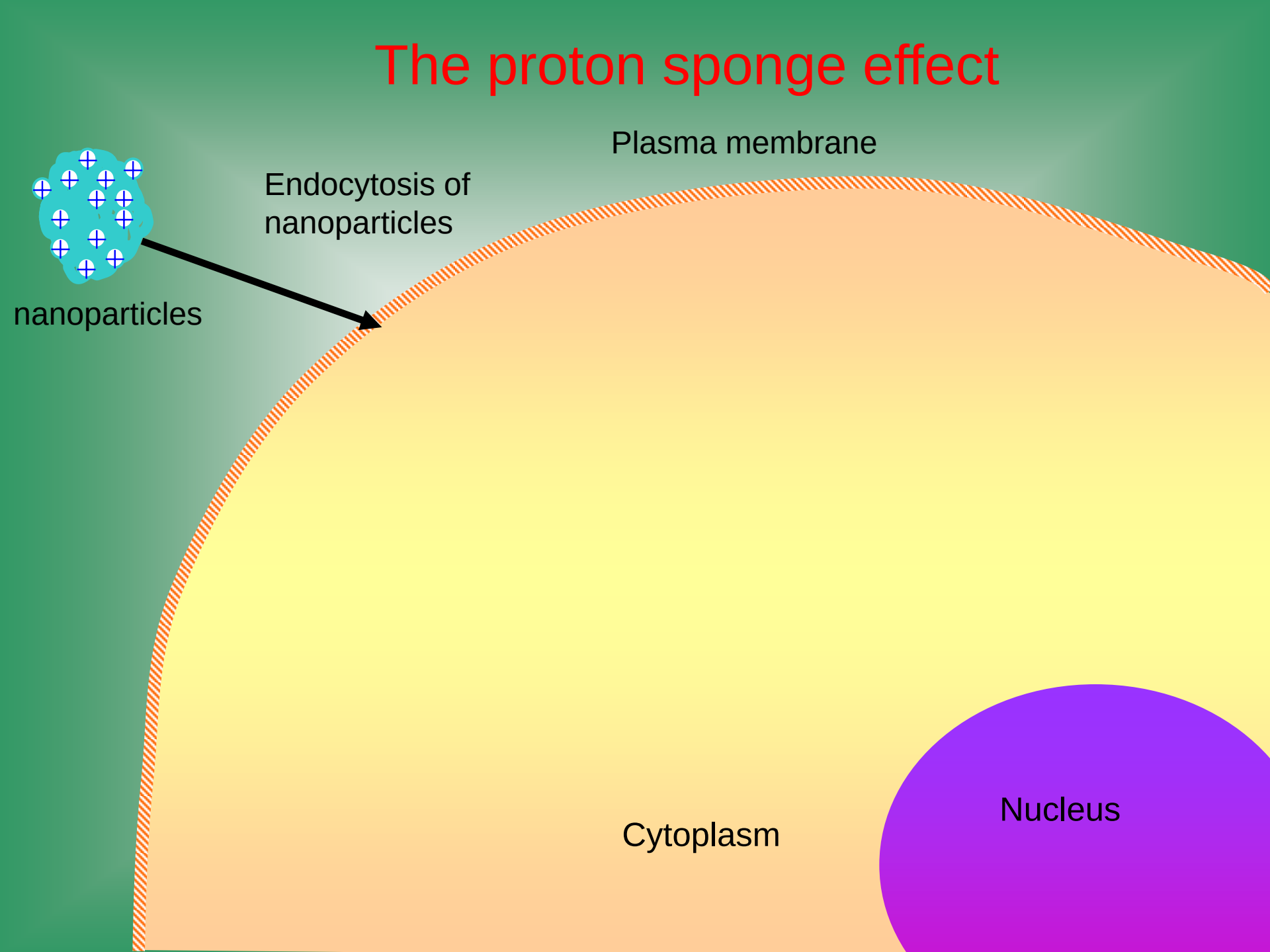
Last Barrier: Intelligent Endosome



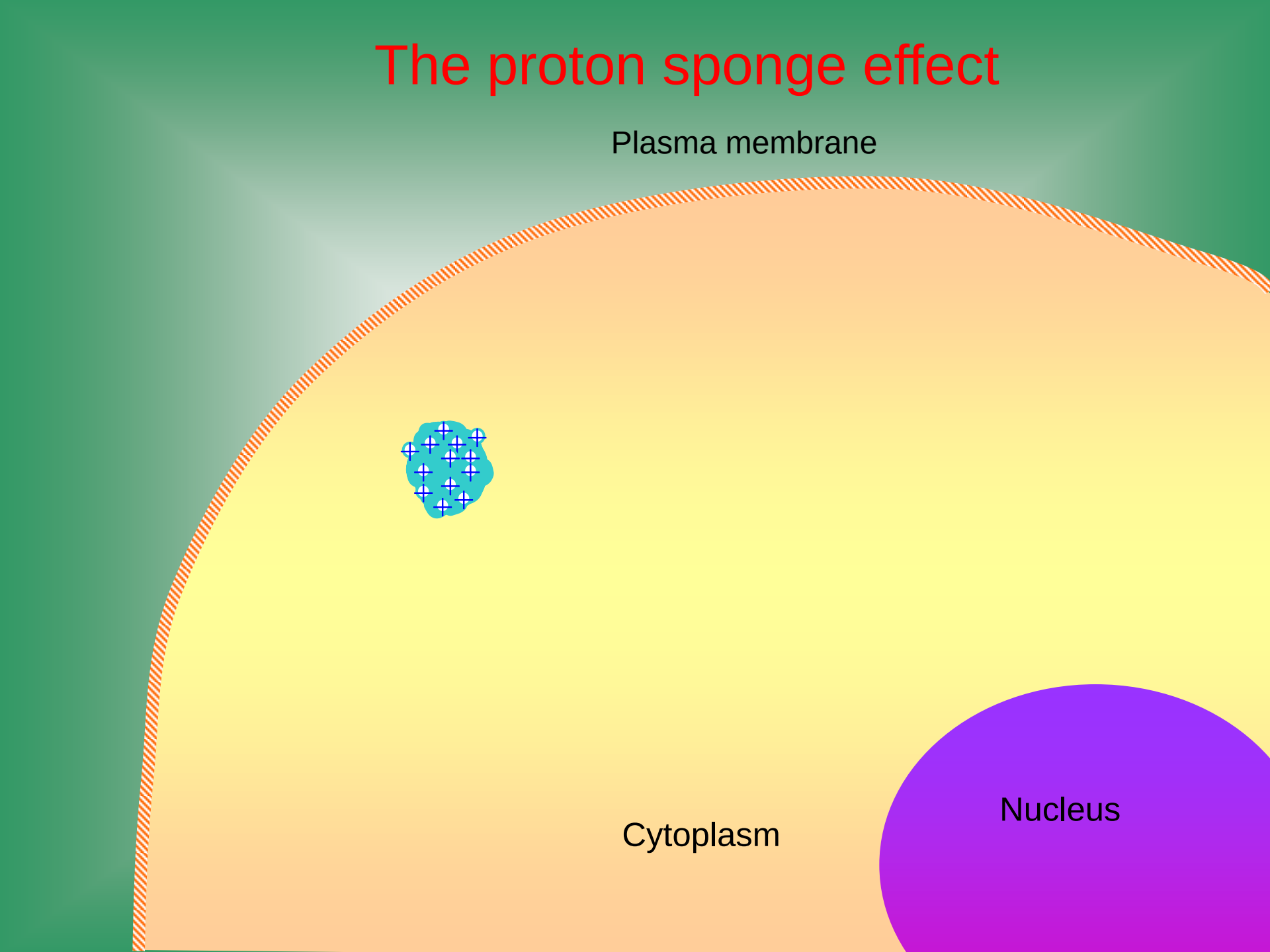
Cellular barriers for *Targeted* delivery (Based on Cationic Polymer)



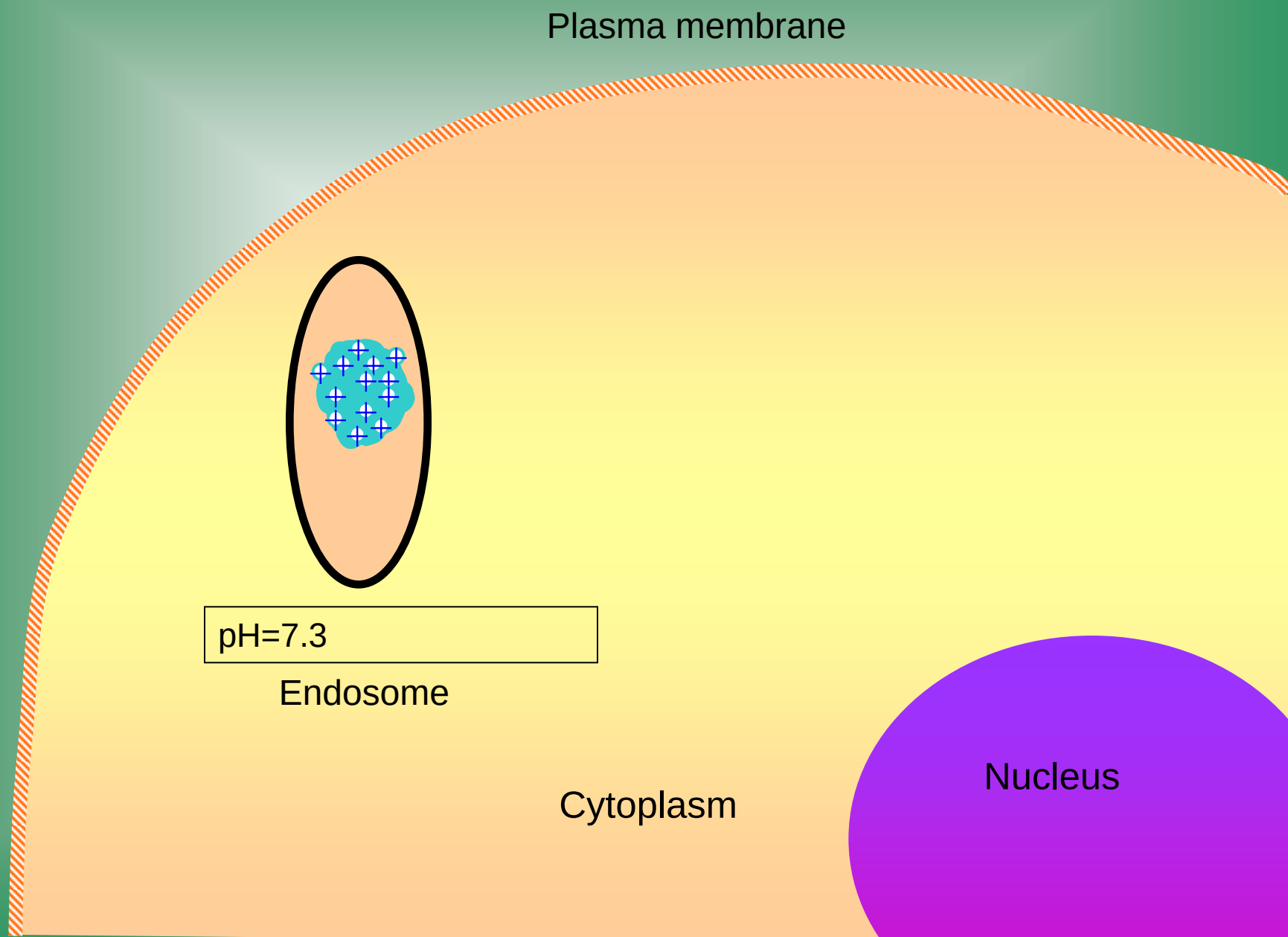
The proton sponge effect



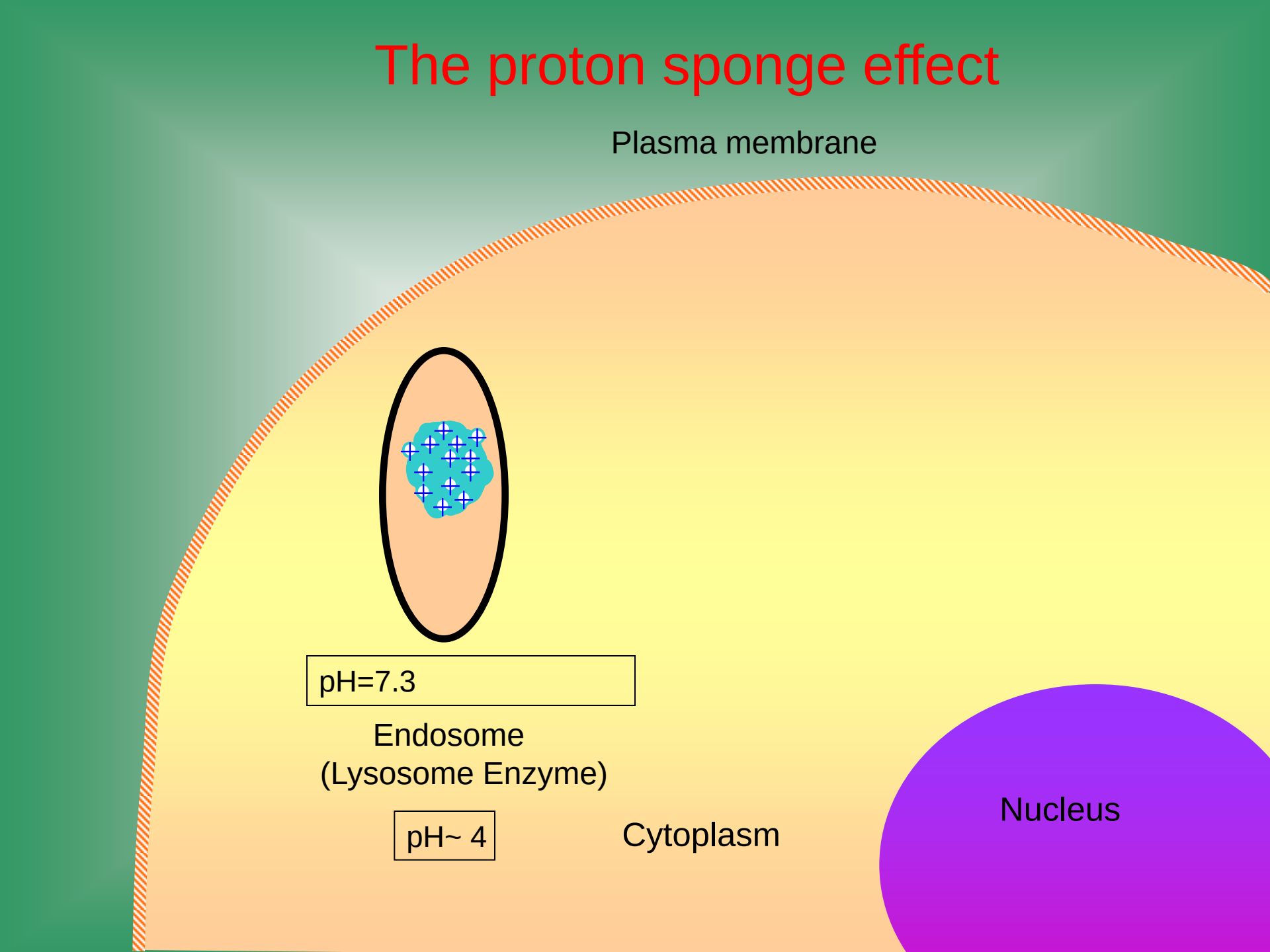
The proton sponge effect



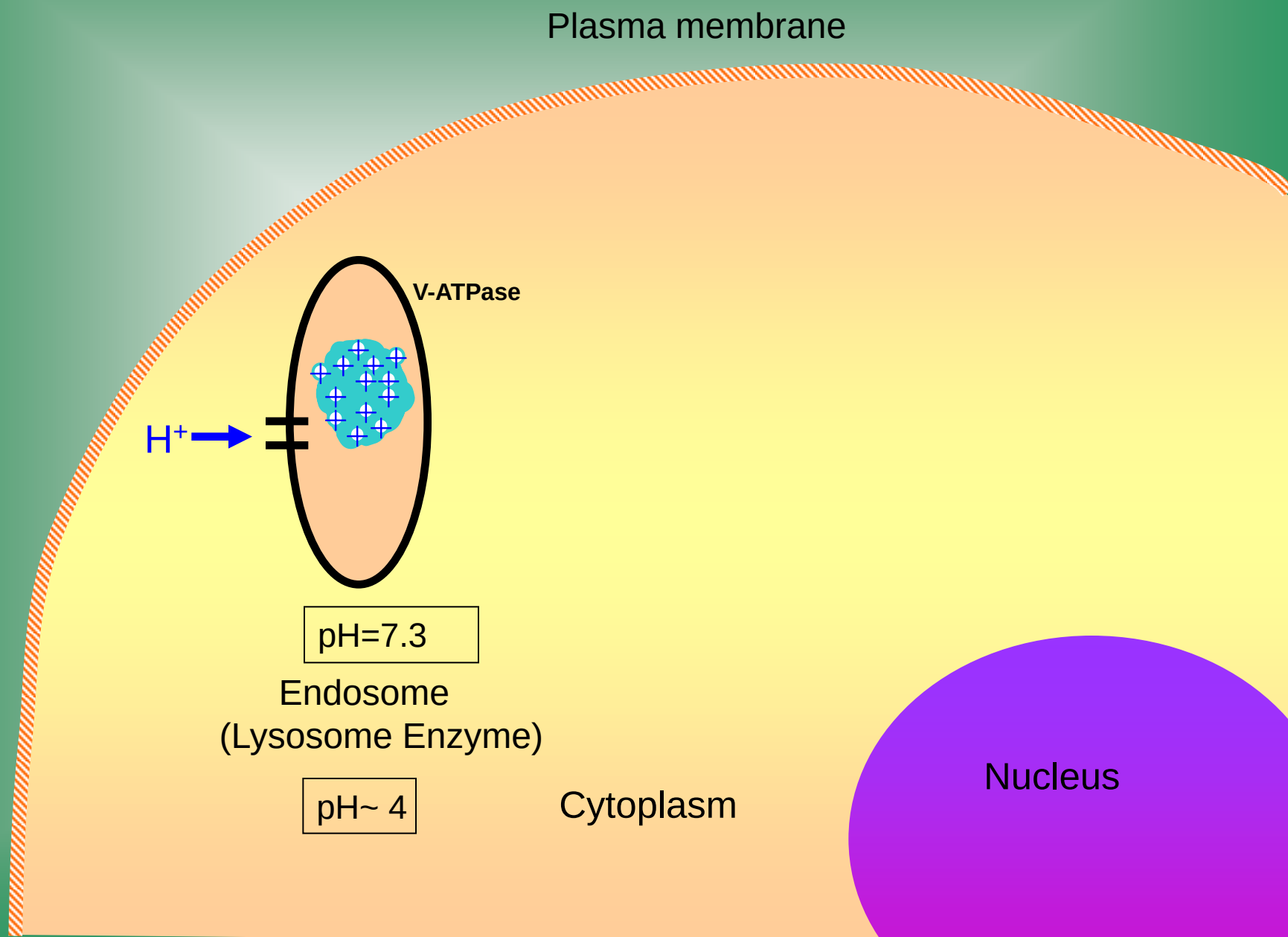
The proton sponge effect



The proton sponge effect

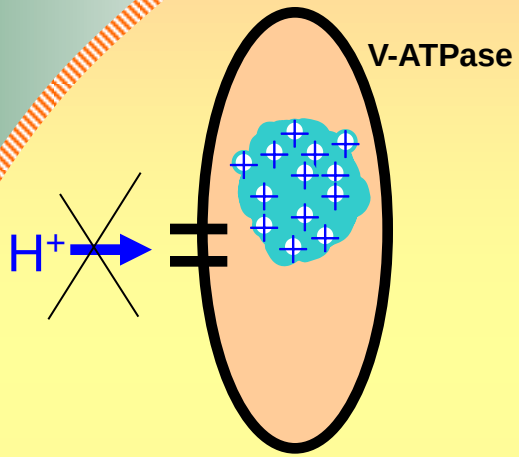


The proton sponge effect



The proton sponge effect

Plasma membrane



pH=7.3

Endosome
(Lysosome Enzyme)

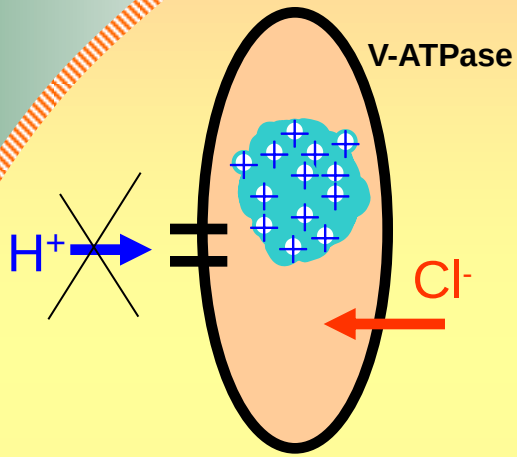
pH~ 4

Cytoplasm

Nucleus

The proton sponge effect

Plasma membrane



pH=7.3

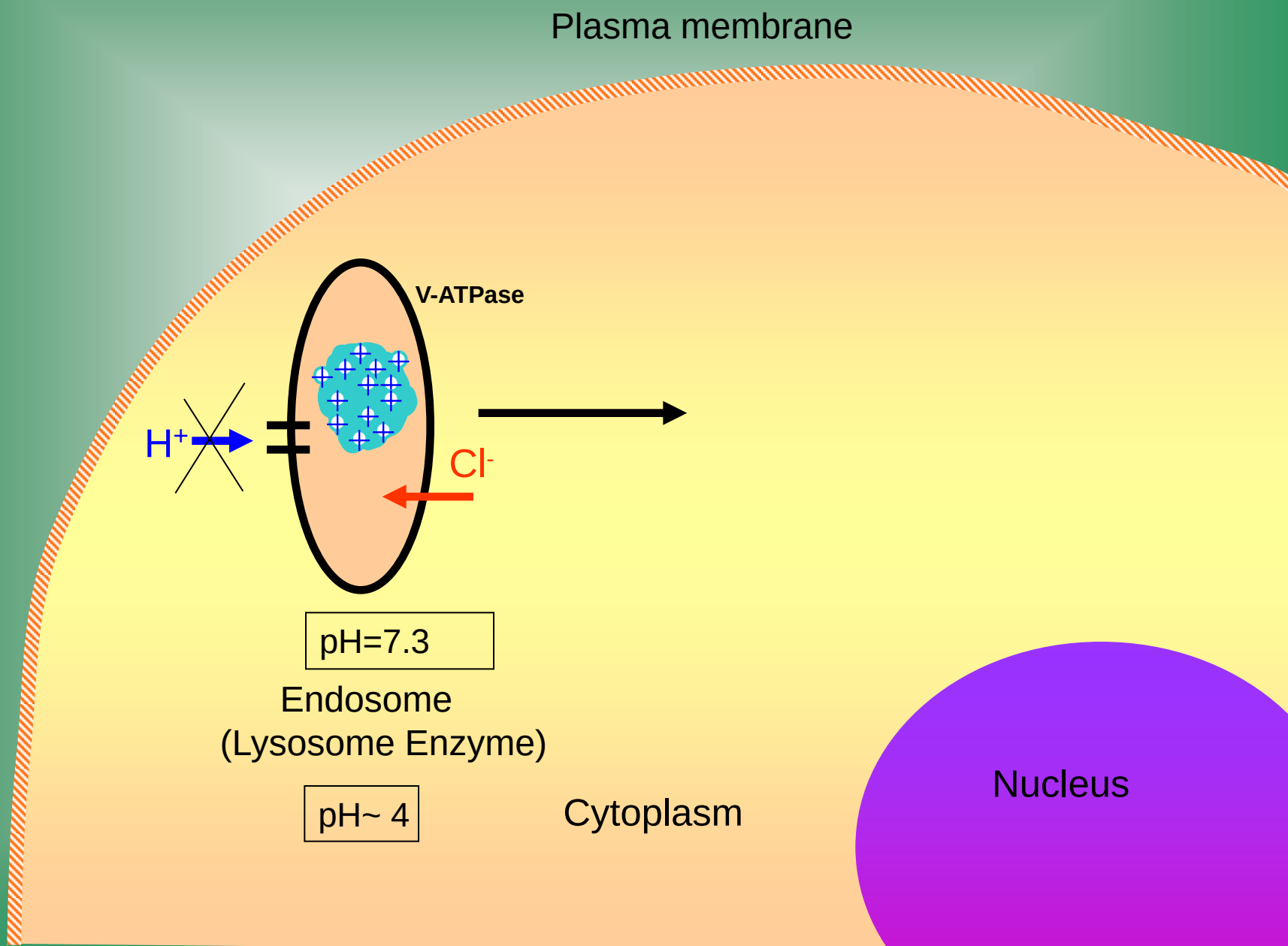
Endosome
(Lysosome Enzyme)

pH~ 4

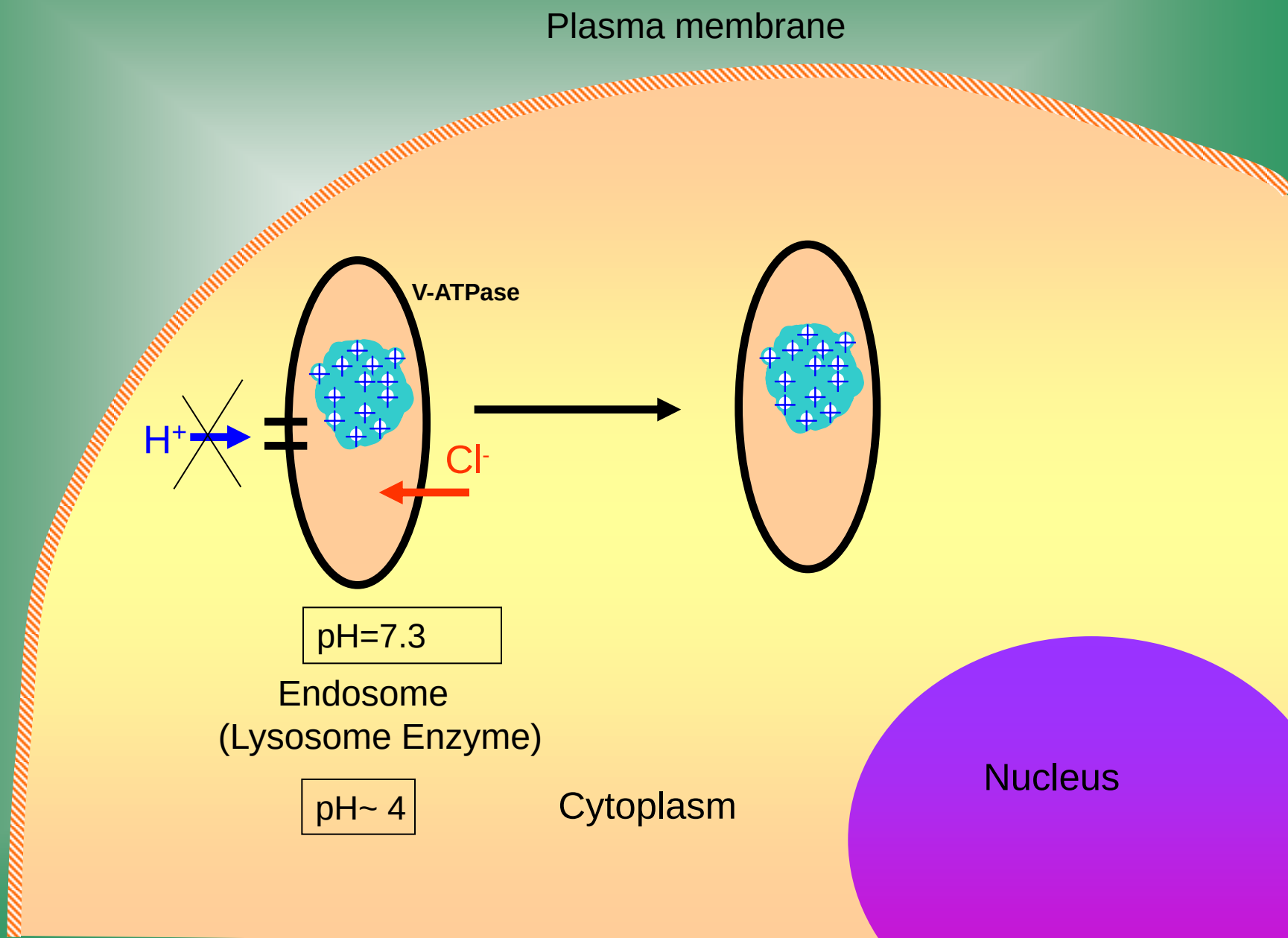
Cytoplasm

Nucleus

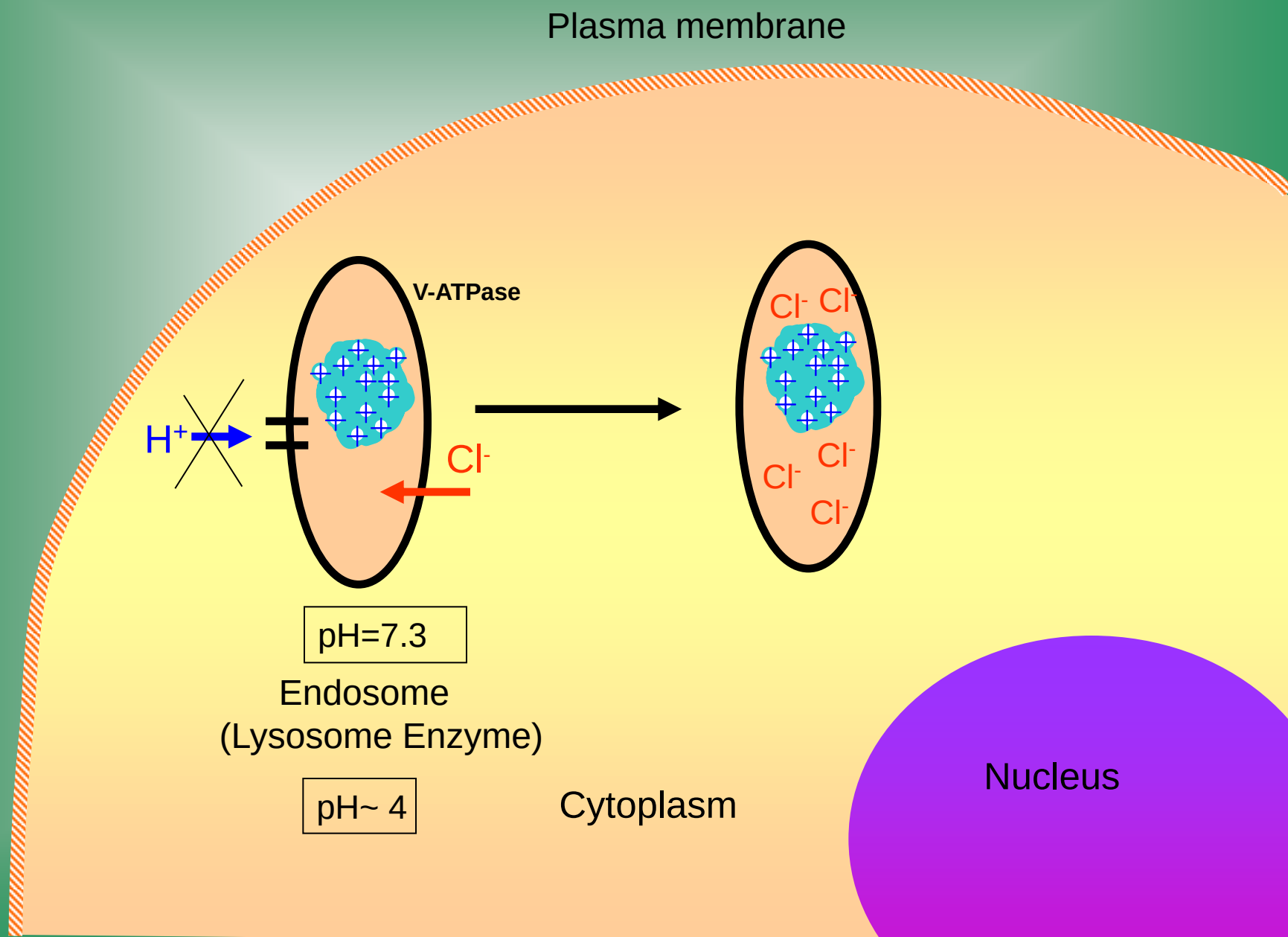
The proton sponge effect



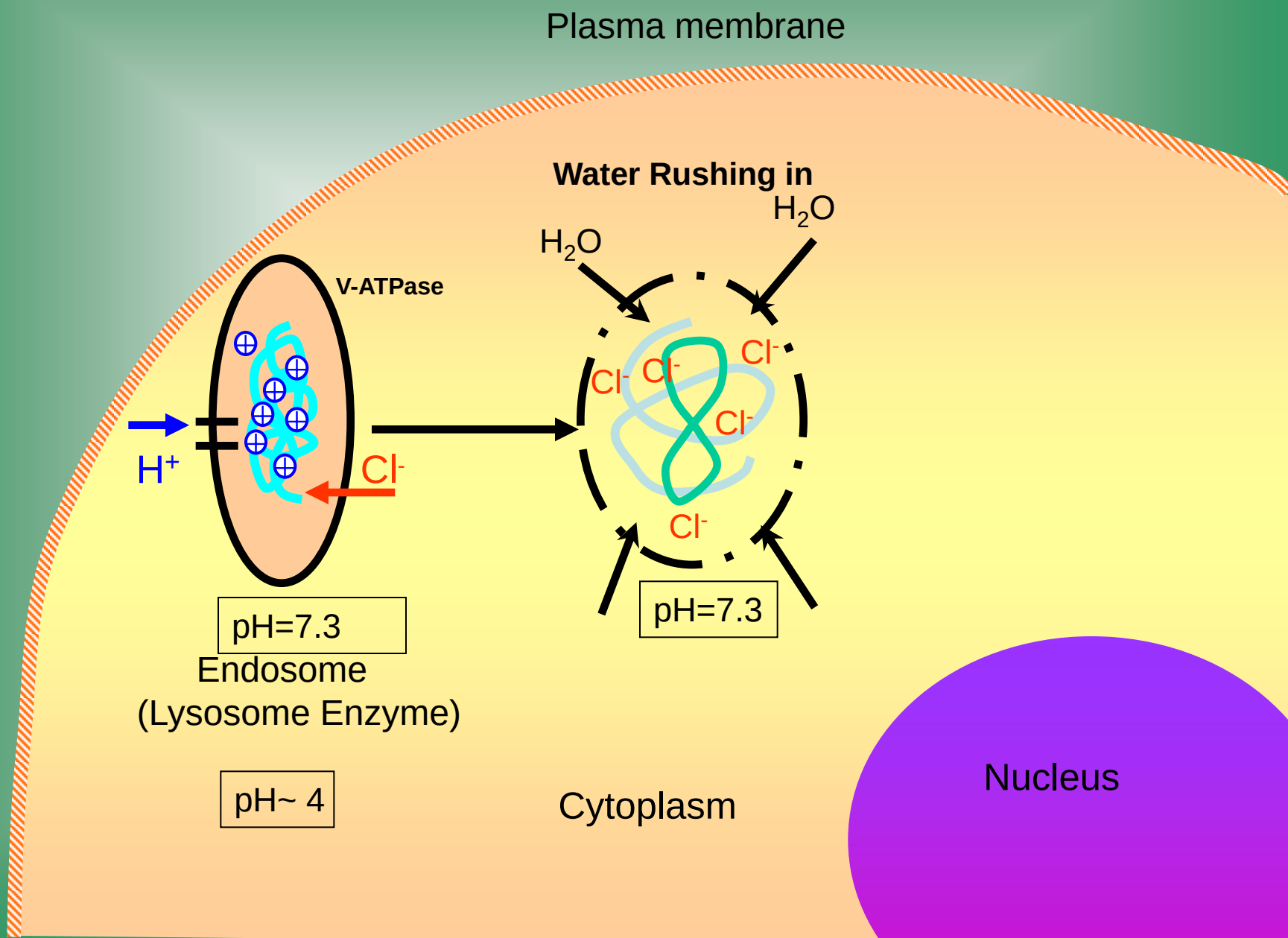
The proton sponge effect



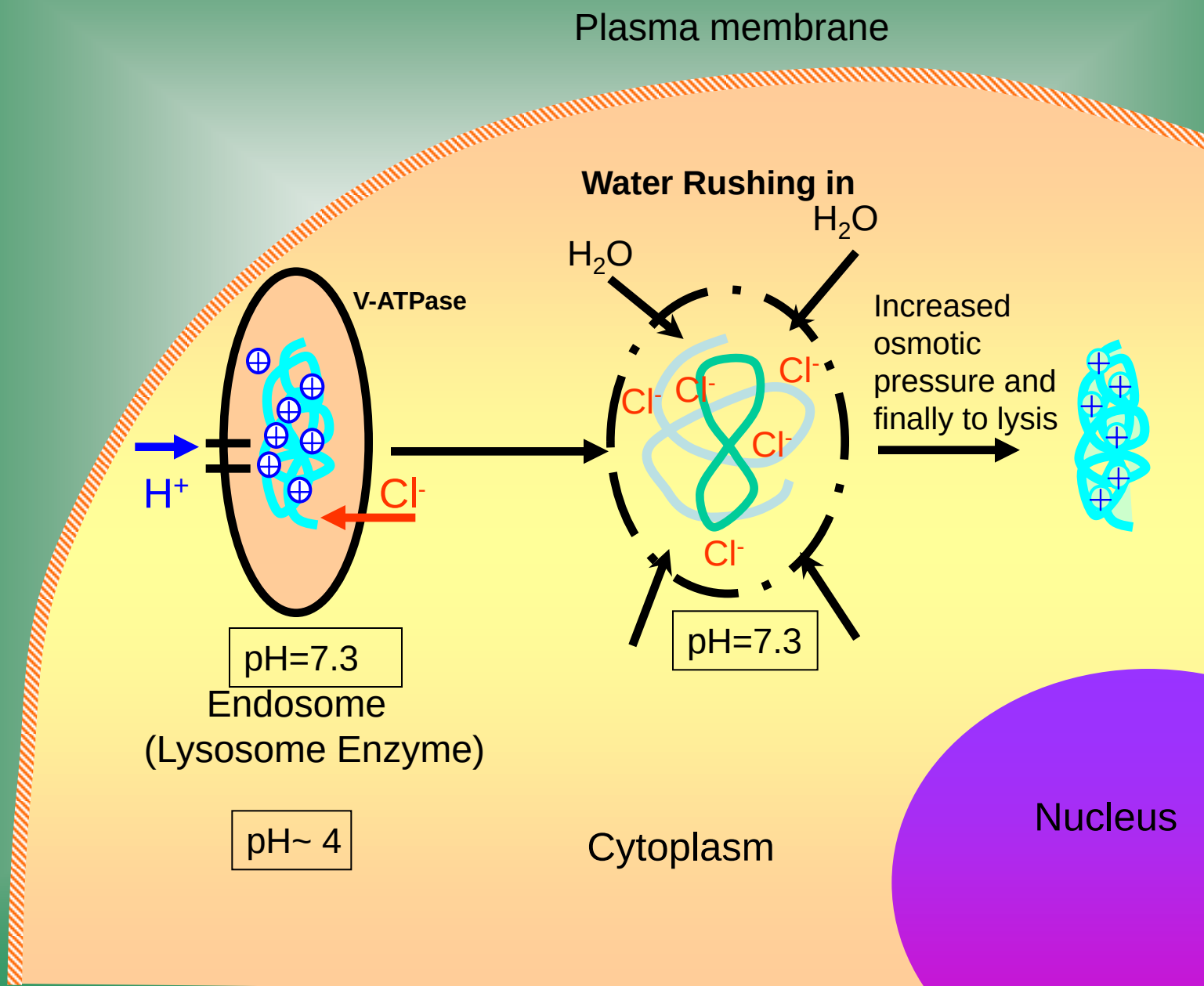
The proton sponge effect



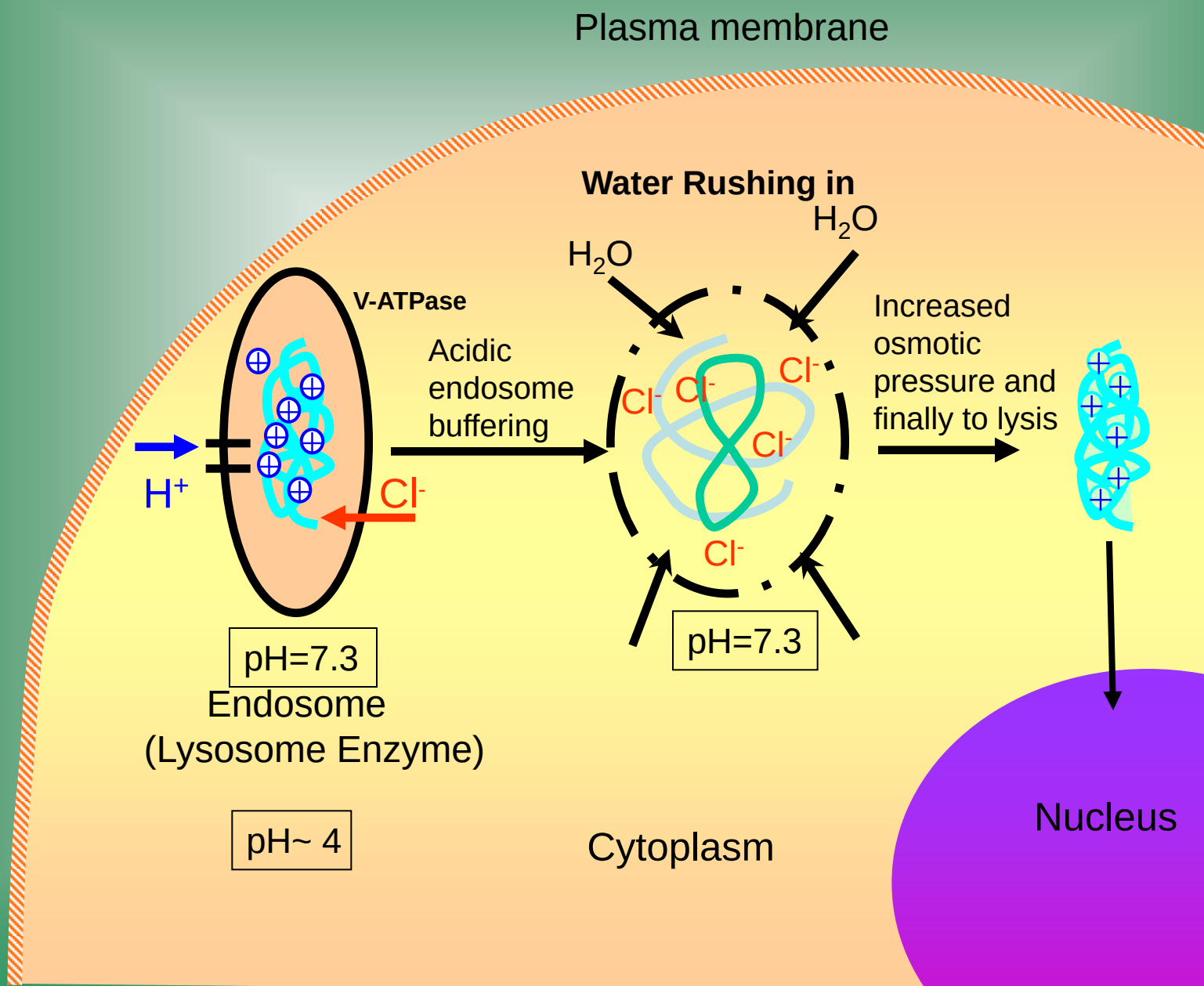
The proton sponge effect



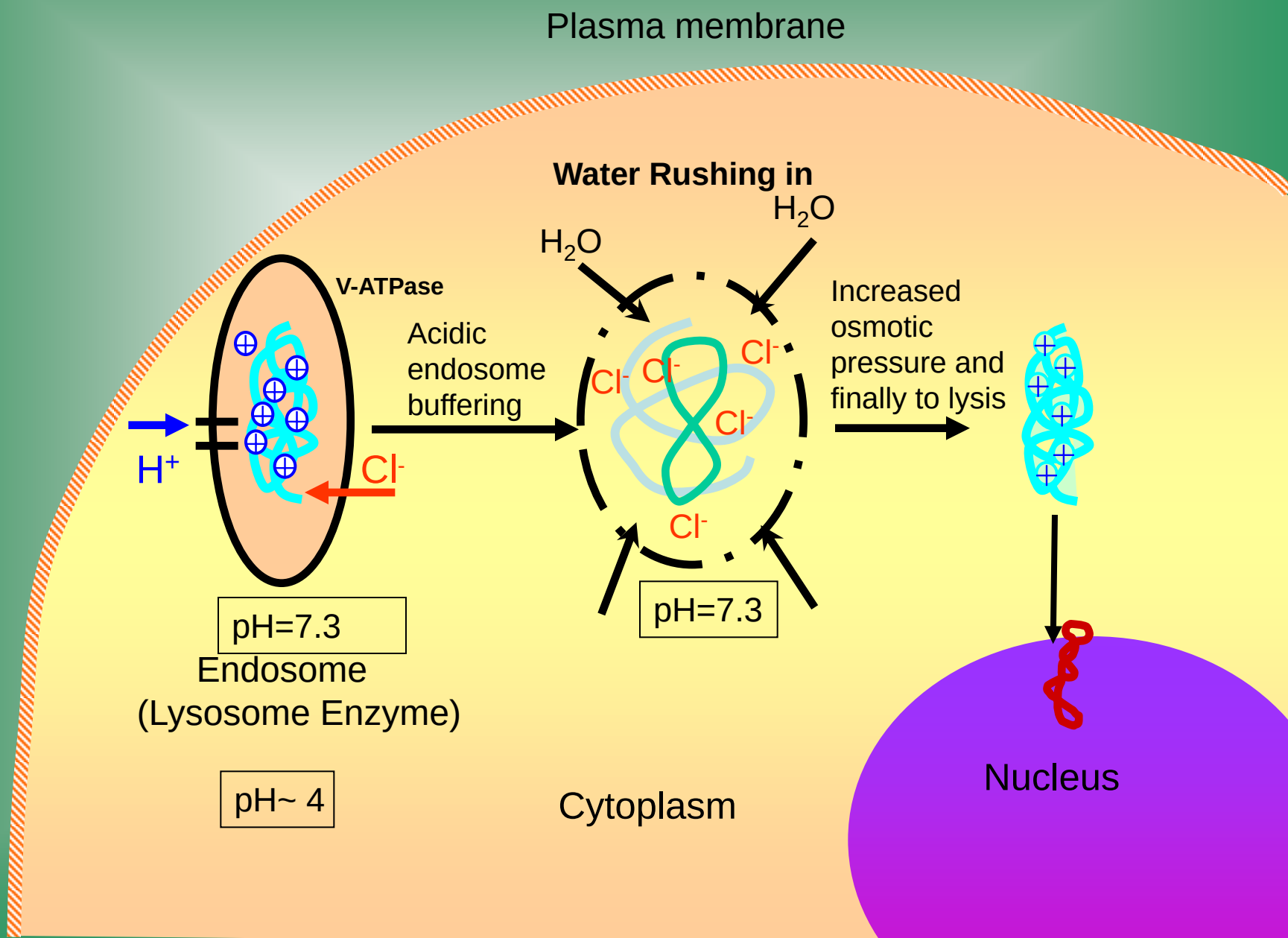
The proton sponge effect



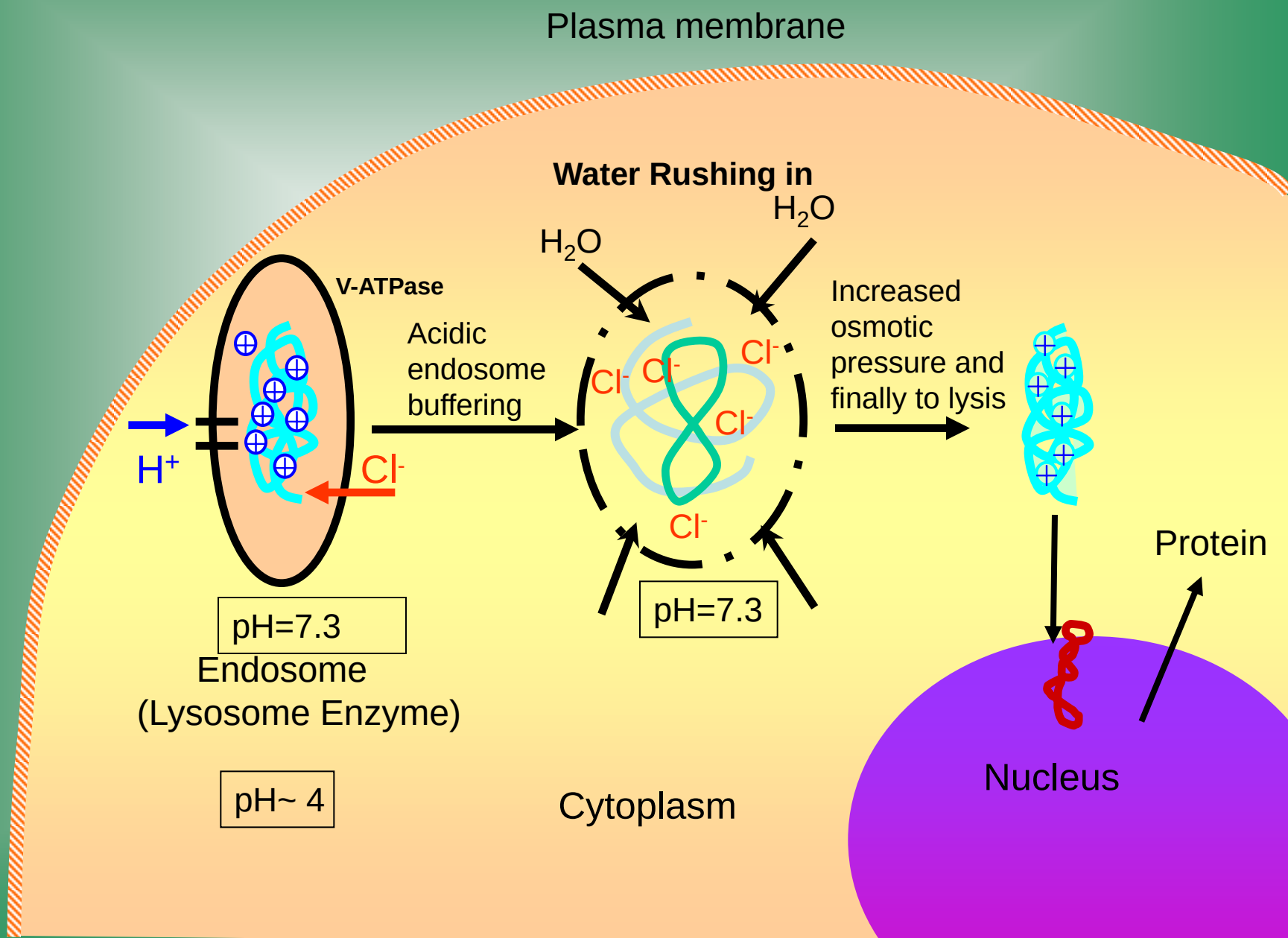
The proton sponge effect



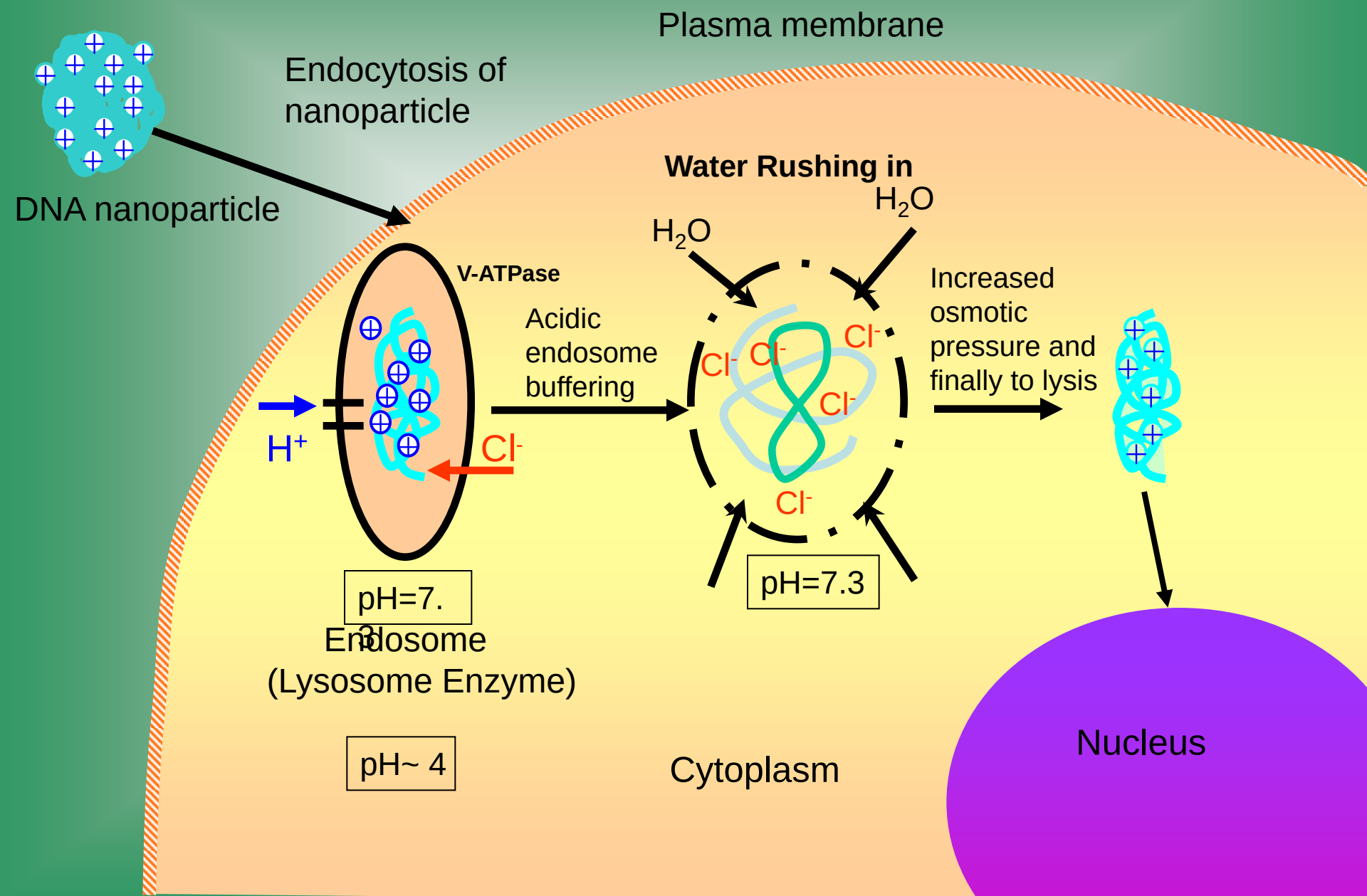
The proton sponge effect



The proton sponge effect



The proton sponge effect



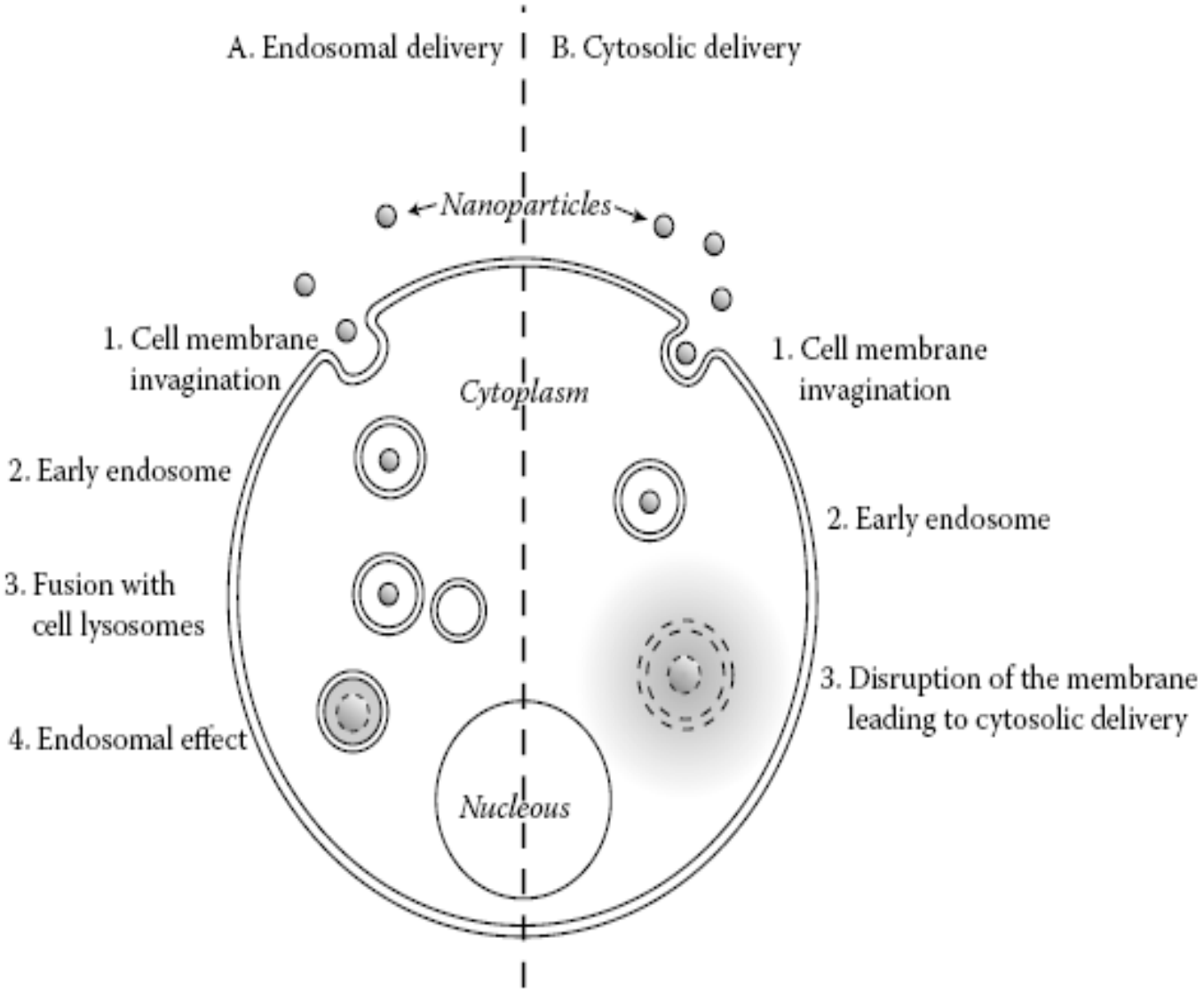


FIGURE 8.6 Cell internalization of nanoparticles can lead to (a) endosomal or (b) cytosolic drug delivery.

Micelles

- Low solubility in water appears to be an intrinsic property of many 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-*b*-PEG	FK506, L-685,818
Polycaprolactone-*b*-methoxy-PEG	Indomethacin
Poly(*N*-isopropylacrylamide)-*b*-PEG	Miscellaneous
Poly(aspartic acid)-*b*-PEG	Doxorubicin, cisplatin, lysozyme
Poly(γ-benzyl-L-glutamate)-*b*-PEG	Clonazepam
Poly(D,L-lactide)-*b*-methoxy-PEG	Paclitaxel, testosterone
Poly(β-benzyl-L-aspartate)-*b*- poly(α-hydroxy-ethylene oxide)	Doxorubicin
Poly(β-benzyl-L-aspartate)-*b*-PEG	Doxorubicin, Indomethacin, KRN, amphotericin B
Poly(L-lysine)-*b*-PEG	DNA
Oligo(methyl methacrylate)-*b*-poly(acrylic acid)	Doxorubicin
PEG-PE	Dequalinium, soya bean trypsin inhibitor, paclitaxel, camptothecin, tamoxifen, porphyrine, vitamin K_3

A. *Structures of micelle-forming copolymers*

A - hydrophilic unit
B - hydrophobic unit

Block copolymers

di - block AAAAAAABBBBBB

tri - block AAAABBBBBAAAA

Graft copolymer

```
AAAAAAAAAAAAA
   B     B
   B     B
   B     B
         B
```

B. *Examples of block copolymers*

Di-block copolymers

1. $HO-(CH_2CH_2O)-(CH_2CH)_m-H$ (with phenyl group)

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

2. $H_3O-(CH_2CH_2O)_n-(CH_2CH)_m-H$ (CH_3 substituent)

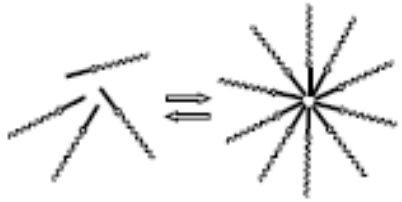
Poly(ethylene oxide)-*b*-poly(D, L-lactide) block copolymer

Tri-block copolymers

3. $HO-(CH_2CH_2O)_n-(CH_2CH)_m-H$ (CH_3 substituent)

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*



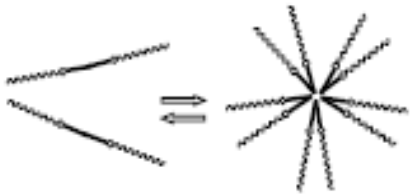


FIGURE 9.1 Micelle-forming copolymers (A and B) and micelle assembly (C).

Polymeric Vesicles

- Closed bilayer systems arise when 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

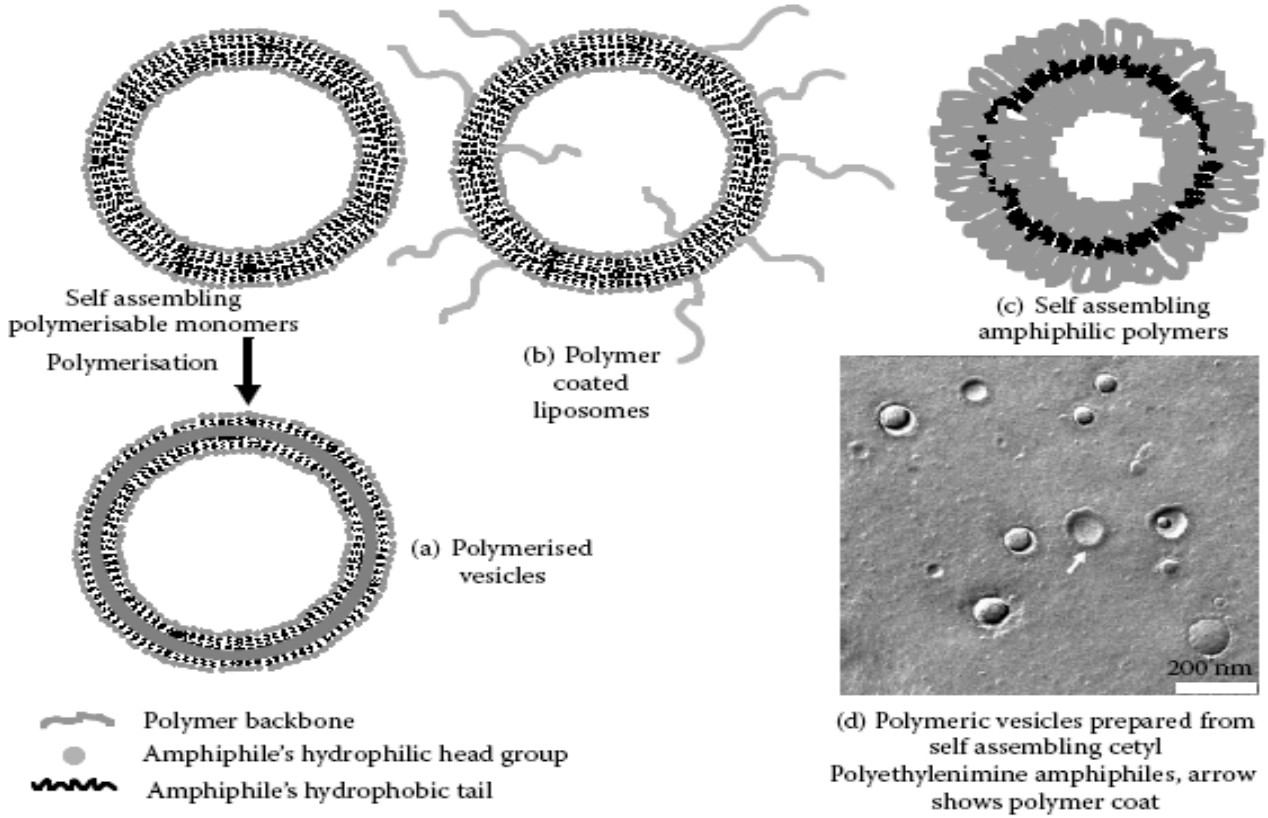


FIGURE 10.1 Polymeric vesicles may arise from (a) the self-assembly of polymerizable monomers that are subsequently polymerized, (b) the cooperative self-assembly of lipids and polymers, or the self-assembly of amphiphilic polymers, both block (c) and random copolymers (d).

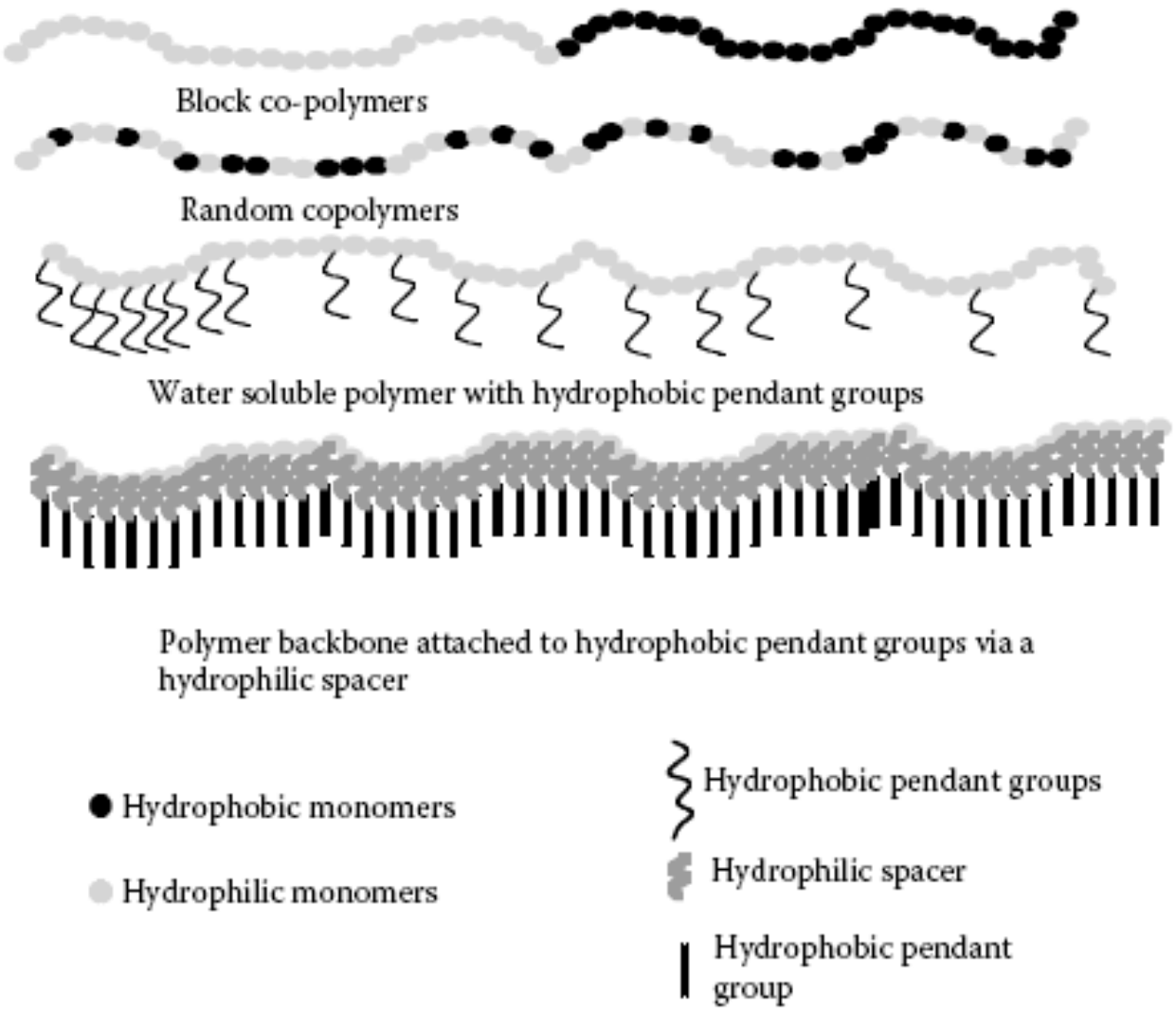


FIGURE 10.2 Schematic representation of self-assembling vesicle-forming polymers.

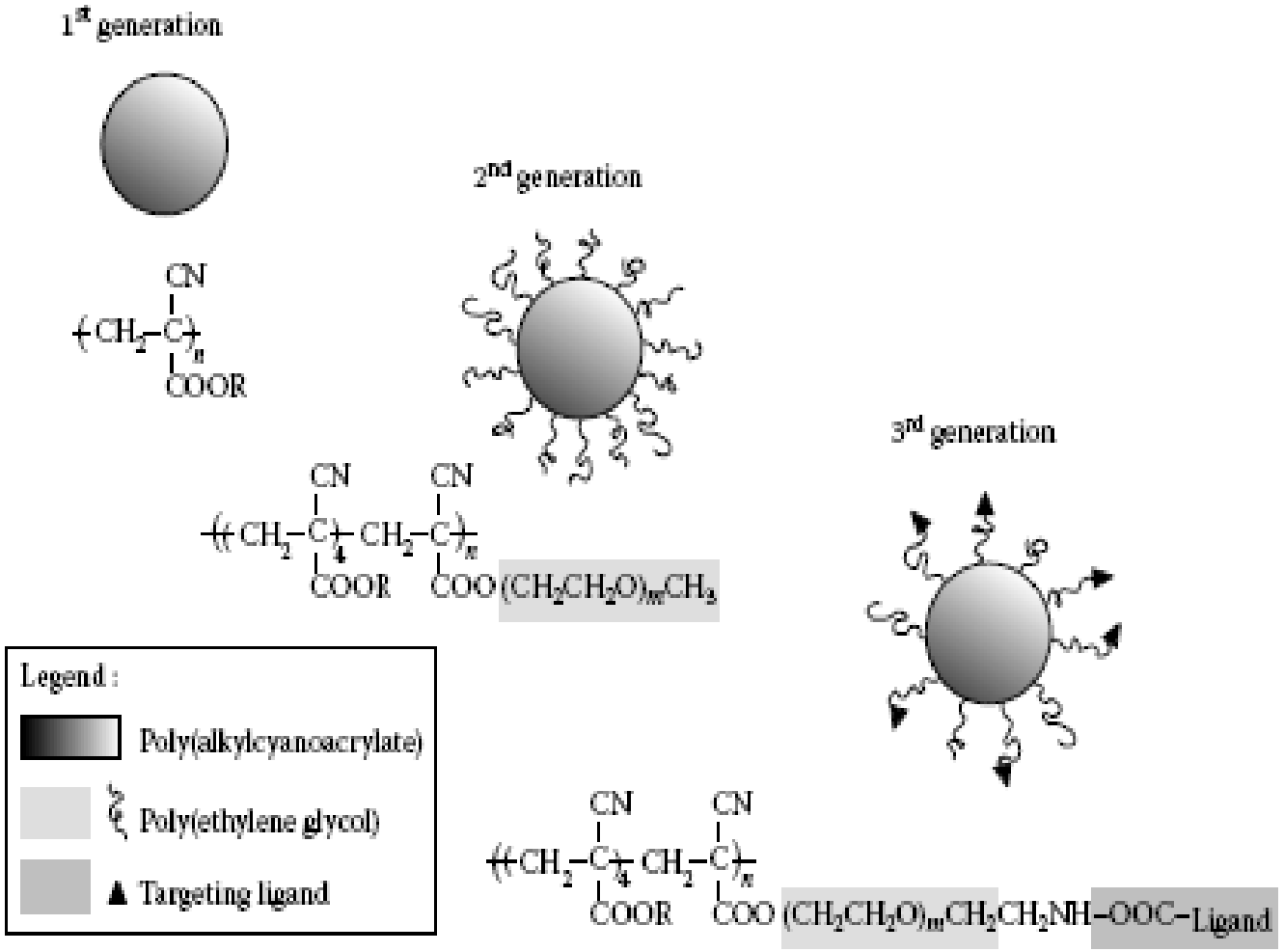


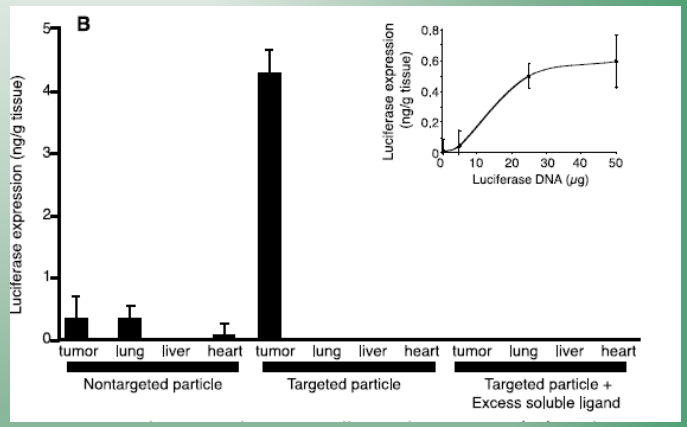
FIGURE 8.4 Three generations of nanoparticles for drug delivery.

Nanoparticle Therapy

- Diagnostics
  - Biosensors
  - Early-warning health monitoring
- Therapeutics
  - Non-viral Gene Therapy
  - Protein, peptide delivery
  - Targetted Chemotherapy
  - Agents for Tissue Engineering

Targeting Tumours: « Smart Bombs »

- Conventional Therapy: Chemotherapy that poisons surrounding tissue
- Strategy: Block angiogenesis selectively at tumour site
- Nanoparticle: DNA + Cationic Polymer directed at tumourous cells
- Starves blood cells



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Gene Therapy

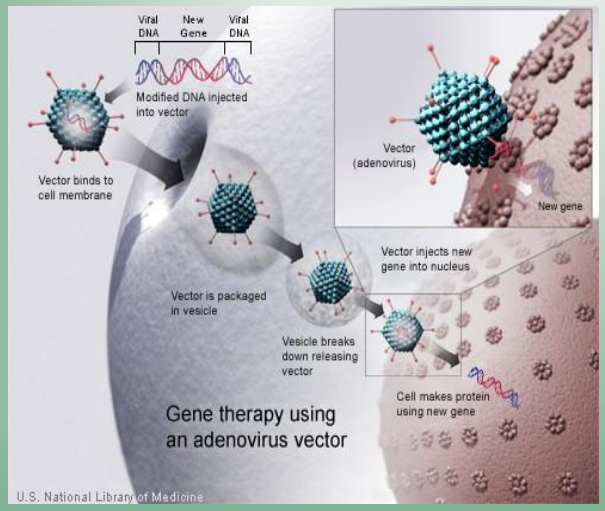


Figure 1: Mary Albury-Noyes

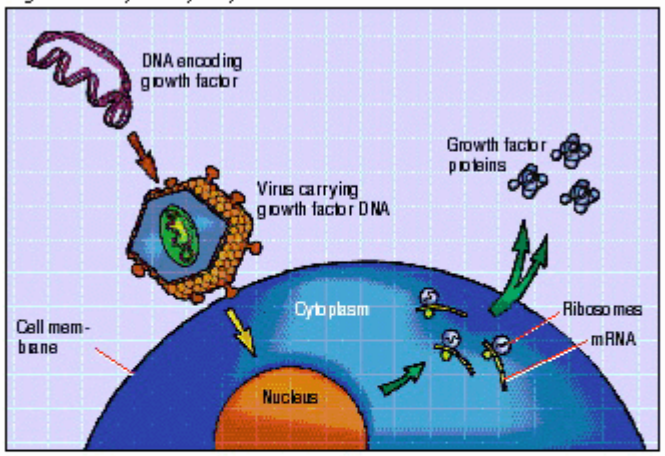
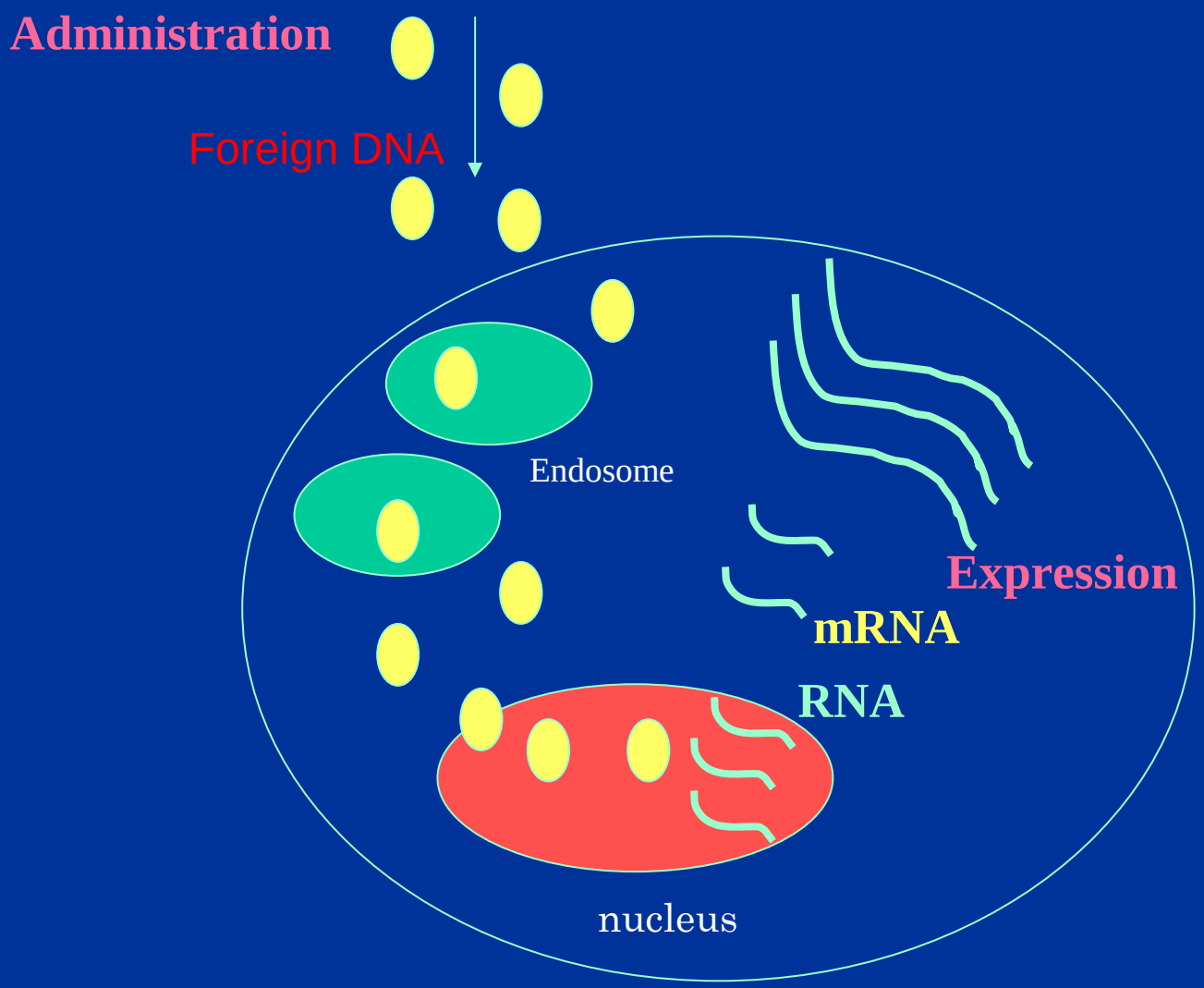


FIGURE 1. Gene therapy can be used to stimulate healing of injured musculoskeletal tissue. Gene transfer can be accomplished by using a viral vector. Genes to be inserted (here a growth factor gene) are incorporated into a truncated viral genome and packaged into a virus particle. Virus particles infect the target cells. where the growth factor gene is transported to the nucleus and is either integrated into hosto chromosomes or maintained as an episome. With the help of viral and cellular proteins. the gene is transcribed into messenger RNA (mRNA). The mRNA is then translated into growth factor protein by the cellular machinery and the ribosomes. Growth factor protein is then secreted and exerts its effect on surrounding tissues.

Steps in Gene Therapy



Methods for Gene Therapy

Viral-mediated methods

Retroviruses, Adenoviruses
Adeno-associated virus

Advantage
- High transfection efficiency

Disadvantages
- Risk of viral infection
- Immunogenicity, toxicity
- limited size of gene, one cop
- Expensive, long procedure
- Stability and regulatory issue
- Limited to certain tissues and cells

Physical-stimulated methods

Hydrodynamic Pressure,
Gene gun, Electroporation,
Sonoporation

Non-viral-mediated methods

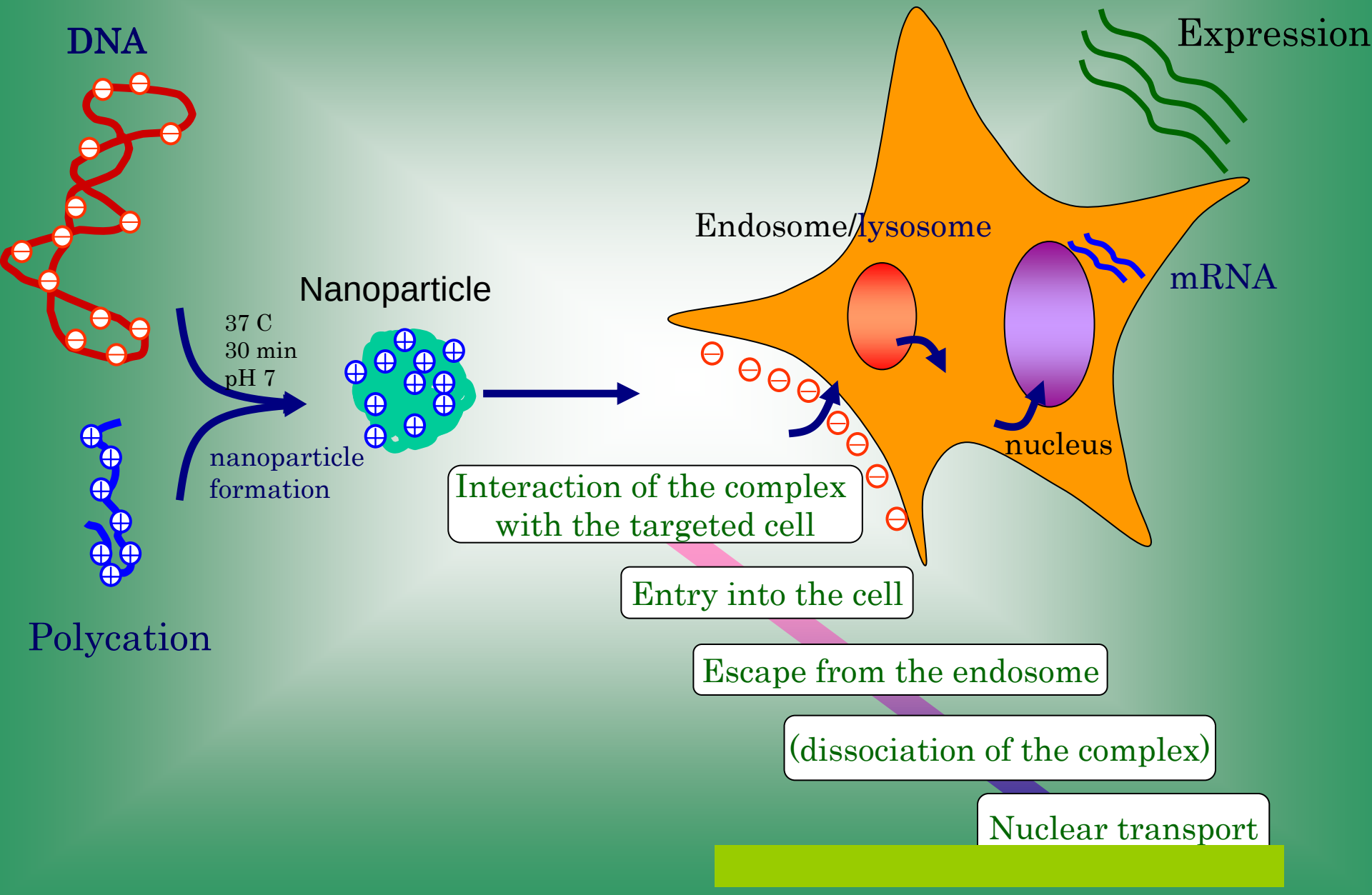
Lipofectin, Cationic polymers
(DEAE-dextran, poly(L-lysine),
poly(ethyleneimine (PEI)

Advantages
- No infection
- Low toxicity
- No limited on the size of gene
- Cheap, easy to prepare
- Stable
- Applicable to all tissues and cells

Disadvantages
- Low transfection efficiency

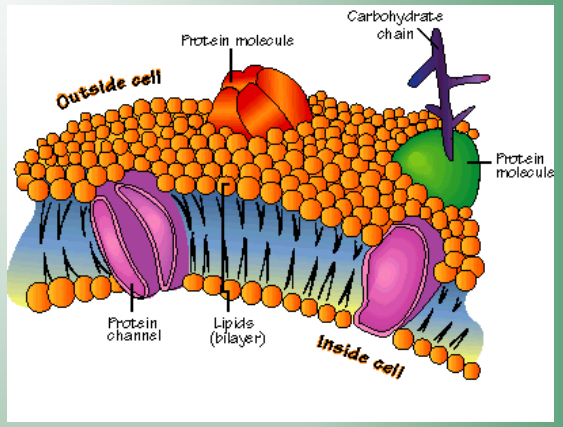
Intermediate methods
to be used to enhance gene transfection

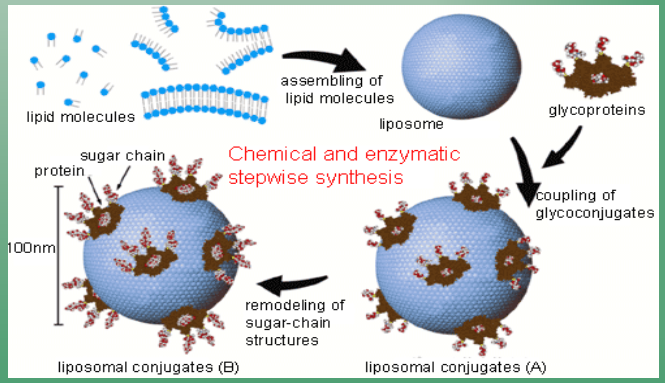
Cellular barriers for *in vitro* gene delivery (Based on Cationic Polymer)

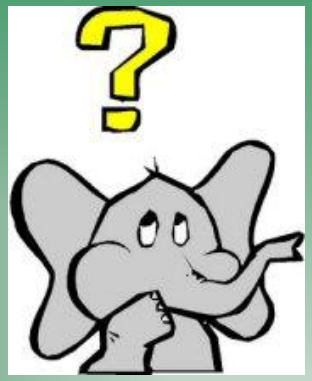


Non-viral Gene therapy: Nanoparticles

- Cell Mmbrane: 6-10 nm thick
- Micelle: Complexatin and condensation of oppositely-charged polyelectrolytes. Can slip past cell membrane
- DNA-Chitosan
- Can be further functionalised for targetting specific cells.







What are the Design Requirements and Constraints for Nanoparticle Vectors ?

Other biomedical applications of nanoparticle vectors?

Disadvantages of nanoparticles vs viral vectors

Conclusion

- Nanotechnology allows for better recognition, integration of bionic implants with host tissue
- Allows for precise, targeted delivery of therepeutic agents
- Stealth technology for health monitoring
- Can lead to design of multifunctional biomaterials. ?