## Membrane Transport

**OUTLINE**

Review of 421
Goals of 422
Review of chemical principles
- Thermodynamics
- C/O cycles
- Overview of Metabolism
- ATP cycles

Energy Coupling
Chemical Reactivity
Bioenergetics
Membranes and Transport
- Review of membrane structure, dynamics, & proteins
- Membrane transport
  - Energetics
  - Facilitative Diffusion
  - Active Transport

Examples:
- Facilitative Diffusion
  - Ionophore
  - Maltoporins
  - GLUT1 transprter
  - Aquaporin
  - Selective ion channel for potassium (K-channels)
- Active Transport
  - Primary (1°)
    - Na/K pump
    - ABC
  - Secondary (2°)
    - Na/Glc

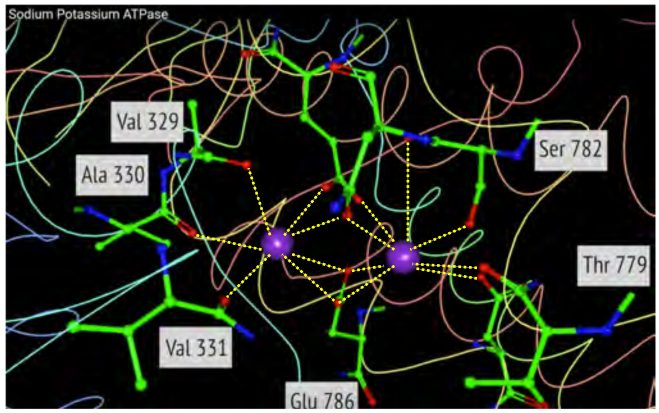
**Catabolism of Glucose**
- Glycogenolysis
  - phosphorylase
  - debranching enzyme
  - phospho-gluco-mutase (PGM)

## Membrane Transport

# Active Transport

# Membrane Transport

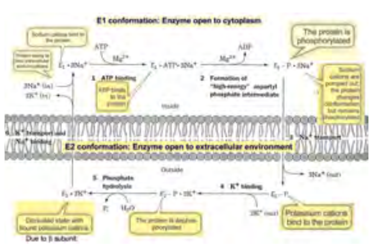
## Sodium–potassium ($Na^+$–$K^+$) pump

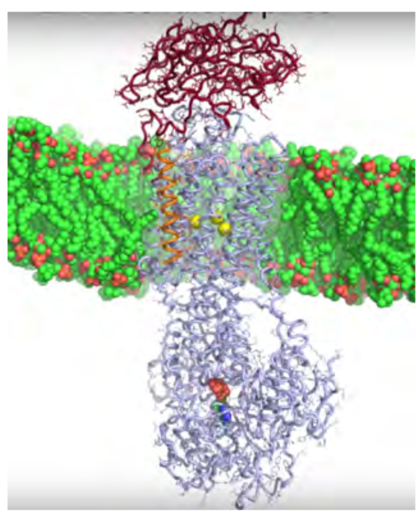



The E2 enzyme has the same geometry for specifically binding $K^+$ as we saw for the Potassium channel

# Membrane Transport

## Sodium–potassium ($Na^+$–$K^+$) pump

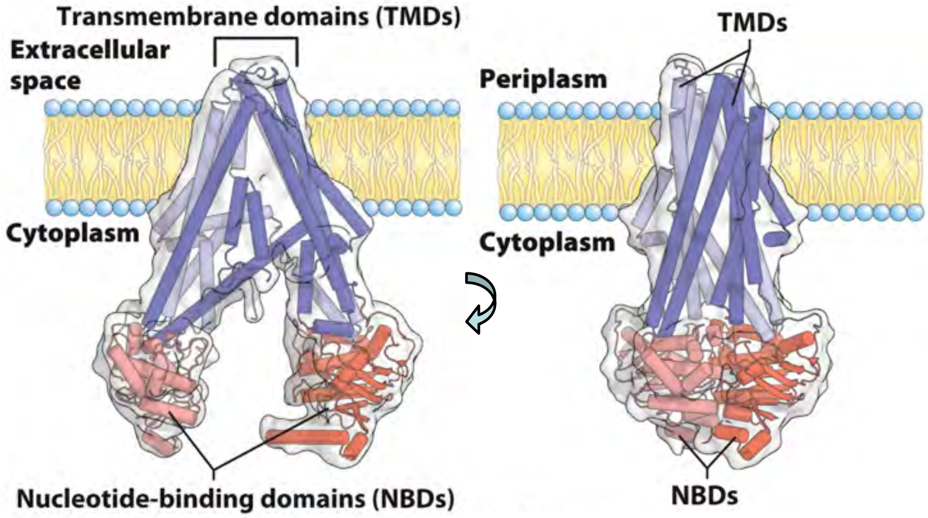


[Molecular Dynamics video]

https://youtu.be/1zvnsrKQ2Jg

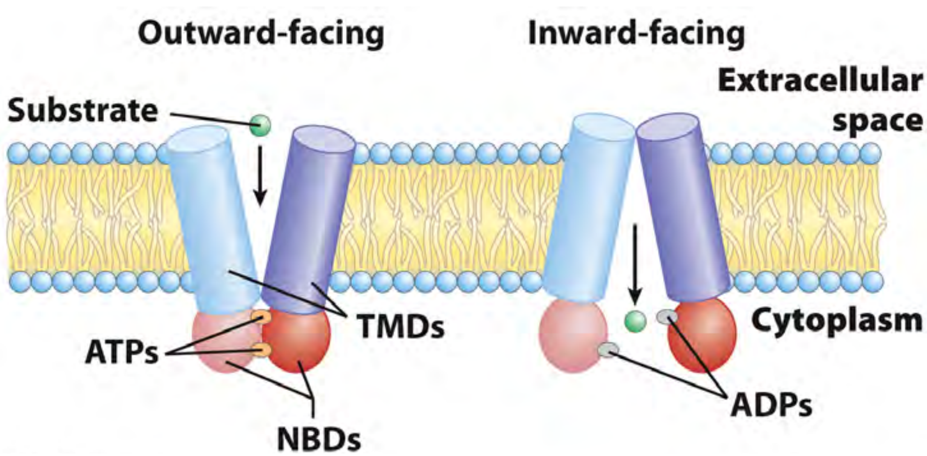
## Membrane Transport




ABC Transporters Use ATP Hydrolysis
to Drive Transport of Substrates IN or OUT

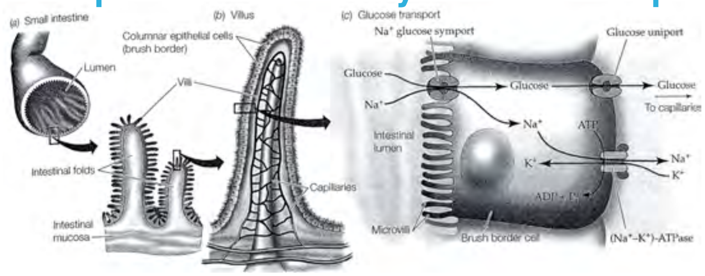
## Membrane Transport

ABC Transporters Use ATP Hydrolysis
to Drive Transport of Substrates IN

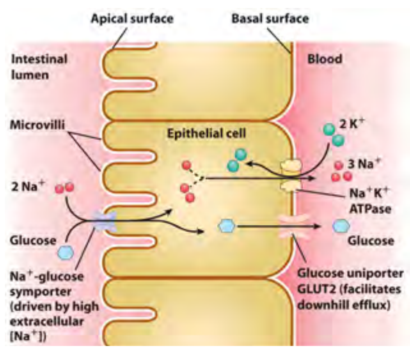


# Membrane Transport

## Examples of Secondary Active Transport




Efficient Import of Glucose uses Multiple Glucose Transporters




- A $Na^+$-glucose symporter and a glucose uniporter operate on opposite sides of epithelial cells to facilitate movement of glucose from the intestine to the blood.
- Uses the Na/K gradient set up by "the pump."

# Membrane Transport

**TABLE 11-7a Transport Systems Described Elsewhere in This Text**

| Transport system and location | Figure | Role |
|---|---|---|
| $IP_3$-gated $Ca^{2+}$ channel of ER | 12-11 | Allows signaling via changes in cytosolic $[Ca^{2+}]$ |
| Glucose transporter of animal cell plasma membrane; regulated by insulin | 12-20 | Increases capacity of muscle and adipose tissue to take up excess glucose from blood |
| Voltage-gated $Na^+$ channel of neuron | 12-29 | Creates action potentials in neuronal signal transmission |
| Fatty acid transporter of myocyte plasma membrane | 17-3 | Imports fatty acids for fuel |
| Acyl-carnitine/carnitine transporter of mitochondrial inner membrane | 17-6 | Imports fatty acids into matrix for β oxidation |
| Complex I, III, and IV proton transporters of mitochondrial inner membrane | 19-16 | Act as energy-conserving mechanism in oxidative phosphorylation, converting electron flow into proton gradient |
| $F_oF_1$ ATPase/ATP synthase of mitochondrial inner membrane, chloroplast thylakoid, and bacterial plasma membrane | 19-25, 20-20a, 20-24 | Interconverts energy of proton gradient and ATP during oxidative phosphorylation and photophosphorylation |
| Adenine nucleotide antiporter of mitochondrial inner membrane | 19-30 | Imports substrate ADP for oxidative phosphorylation and exports product ATP |
| $P_i$-$H^+$ symporter of mitochondrial inner membrane | 19-30 | Supplies $P_i$ for oxidative phosphorylation |
| Malate-α-ketoglutarate transporter of mitochondrial inner membrane | 19-31 | Shuttles reducing equivalents (as malate) from matrix to cytosol |
| Glutamate-aspartate transporter of mitochondrial inner membrane | 19-31 | Completes shuttling begun by malate-α- ketoglutarate shuttle |

# Membrane Transport

| TABLE 11-7b | Transport Systems Described Elsewhere in This Text | |
|---|---|---|
| **Transport system and location** | **Figure** | **Role** |
| ✓ Uncoupling protein UCP1, a proton pore of mitochondrial inner membrane | 19-36, 23-35 | Allows dissipation of proton gradient in mitochondria as means of thermogenesis and/or disposal of excess fuel |
| ✓ Cytochrome *bf* complex, a proton transporter of chloroplast thylakoid | 20-19 | Acts as proton pump, driven by electron flow through the Z scheme; source of proton gradient for photosynthetic ATP synthesis |
| ✓ Bacterorhodopsin, a light-driven proton pump | 20-27 | Is light-driven source of proton gradient for ATP synthesis in halophilic bacterium |
| $P_i$-triose phosphate antiporter of chloroplast inner membrane | 20-42, 20-43 | Exports photosynthetic product from stroma; imports $P_i$ for ATP synthesis |
| ✓ Citrate transporter of mitochondrial inner membrane | 21-10 | Provides cytosolic citrate as source of acetyl-CoA for lipid synthesis |
| ✓ Pyruvate transporter of mitochondrial inner membrane | 21-10 | Is part of mechanism for shuttling citrate from matrix to cytosol |
| ✓ LDL receptor in animal cell plasma membrane | 21-41 | Imports, by receptor-mediated endocytosis, lipid-carrying particles |
| Protein translocase of ER | 27-40 | Transports into ER proteins destined for plasma membrane, secretion, or organelles |
| Nuclear pore protein translocase | 27-44a | Shuttles proteins between nucleus and cytoplasm |
| Bacterial protein transporter | 27-46 | Exports secreted proteins through plasma membrane |

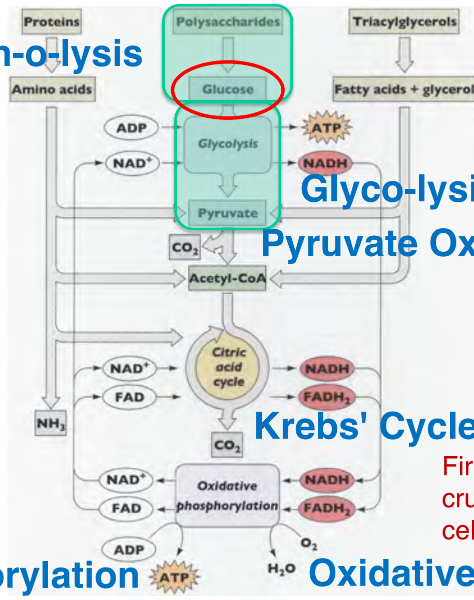
# Membrane Transport

## Summary

We learned that:

- Membrane proteins play an important functional role in the transport of solutes across the membrane
- Transport is mediated or non-mediated.
- In mediated transport, there is a facilitative diffusion mechanism or an active transport mechanism
- Active transport is either primary or secondary
- Primary active transport of solutes across membranes requires ATP
- The most important, and one of the best examples of primary active transport, is the Na/K ATPase.
- Secondary active transport but can be accomplished in many ways, but uses the potential energy established by primary active transport or pre-established concentration gradients

# CATABOLISM




Glycogen-o-lysis

Glyco-lysis

Pyruvate Oxidation

Krebs' Cycle

First, let's discuss how crucial **glucose** is for cellular metabolism

Phosphorylation

Oxidative

# CATABOLISM

## Glucose Importance:

- Glucose is an excellent fuel.
  - yields good amount of energy upon oxidation
    - –2840 kJ/mol glucose (–678 kcal/mol)
  - can be efficiently stored in the polymeric form
  - Many organisms and tissues can meet their energy needs on glucose only.
- Glucose is a versatile biochemical precursor.
  - Many organisms can use glucose to generate:
    - all the amino acids
    - membrane lipids
    - nucleotides in DNA and RNA
    - cofactors needed for the metabolism of EVERYTHING
    - IOW, EVERYTHING!!

# CATABOLISM

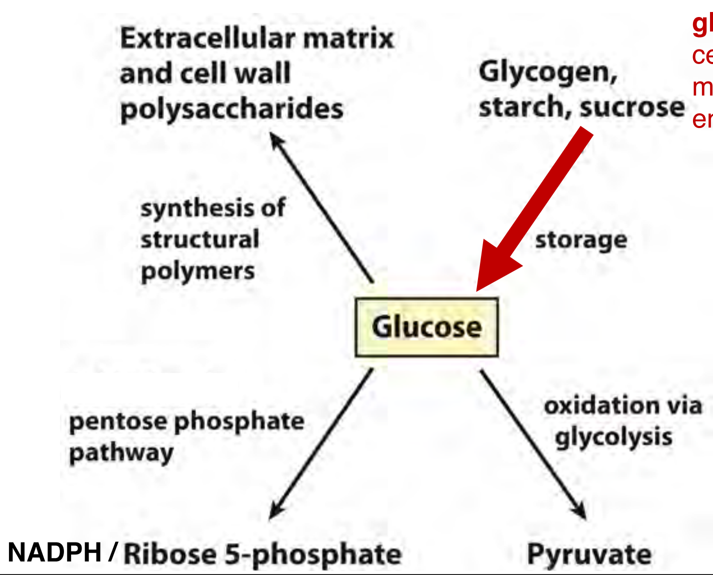
## Glucose Utilization:

- Storage
  - can be stored in the polymeric form (starch, glycogen)
  - used for short-term energy needs
- Energy production
  - generates energy via oxidation of glucose
- Production of NADPH and pentoses
  - generates NADPH for use in relieving oxidative stress and synthesizing fatty acids, amino acids, etc. (anabolism)
  - generates pentose phosphates for use in DNA/RNA biosynthesis
- Structural carbohydrate production
  - used for generation of cellulose and chitin
  - used for generation of alternate carbohydrates used in cell walls of bacteria, fungi, and plants

# CATABOLISM

## Glucose Utilization: Four Major Fates of Glucose

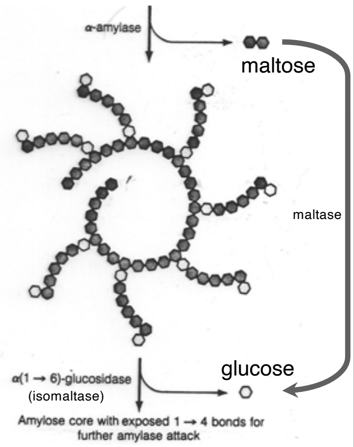
What if you need **glucose** for cellular metabolism and energy?



# Glucose is Stored for Later Use as Glycogen (animals) or Starch (plants)

- Glycogen/starch are branched polymers of $\alpha(1 \rightarrow 4)$-linked glucose with $\alpha(1 \rightarrow 6)$ linkages (glycogen every 8-12 glucose units; starch every 24-30 glucose units).
- Glycogen storage occurs mainly in the liver and muscle.
- Starch storage occurs mainly in the leaves

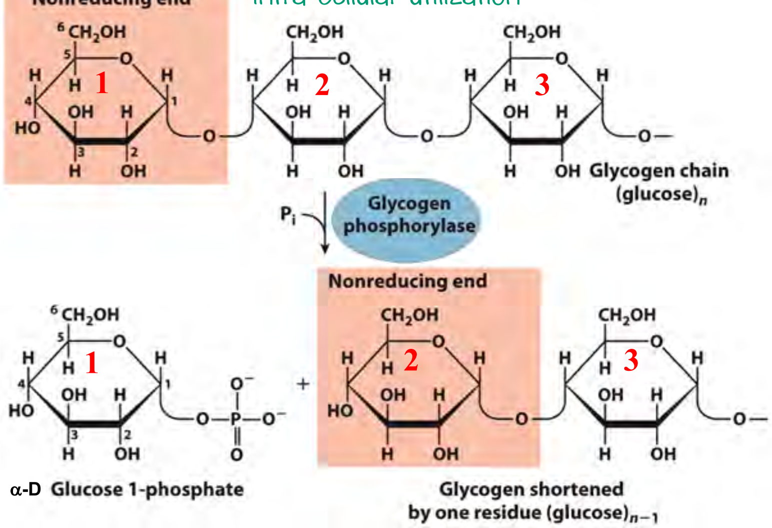
Digestion



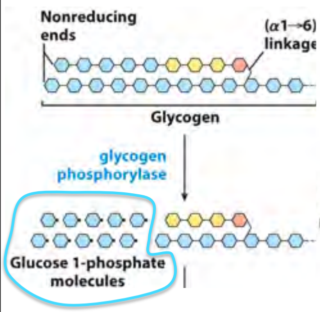

Digestion *versus* intra-cellular utilization

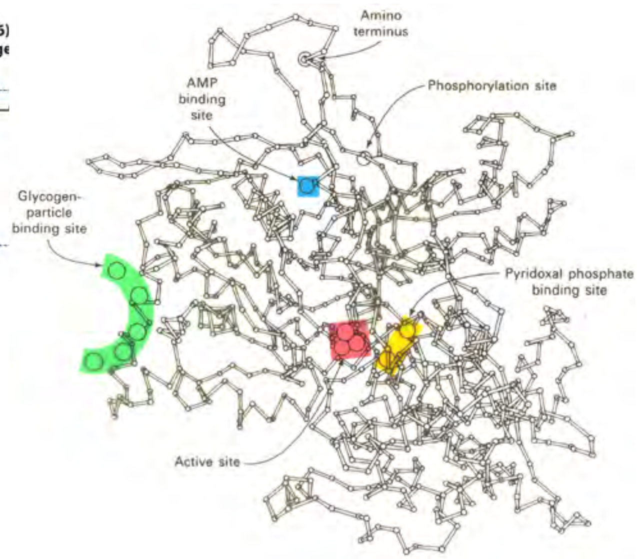
# Glycogenolysis is performed mainly by Glycogen Phosphorylase

intra-cellular utilization

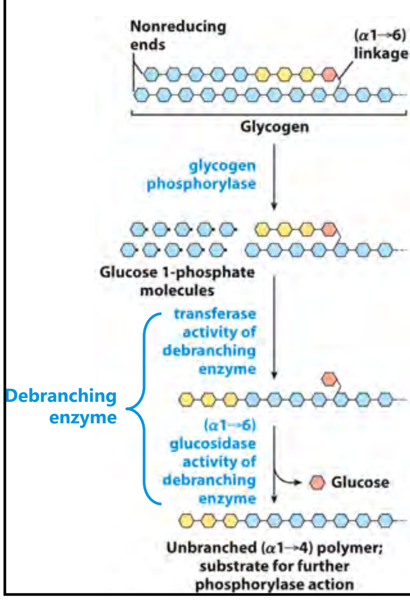


# Glycogenolysis is performed mainly by Glycogen Phosphorylase



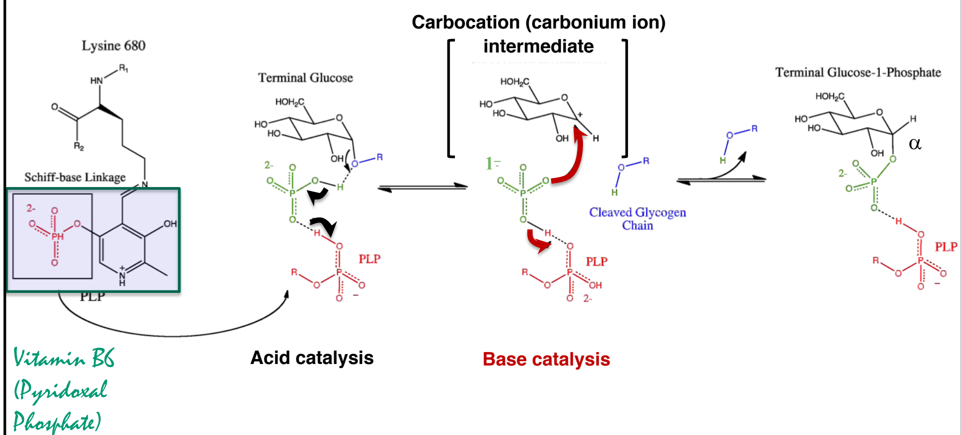

# Glycogenolysis must deal with Branch Points in Glycogen



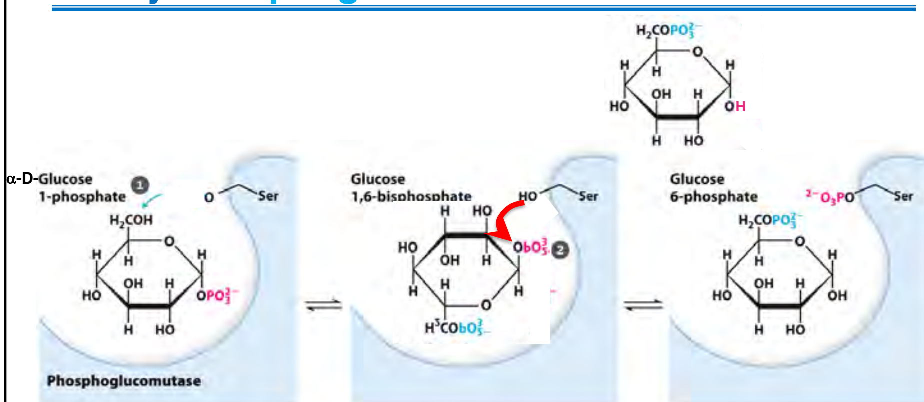

- Glycogen phosphorylase works on nonreducing ends until it reaches four residues from an ($\alpha$1$\rightarrow$ 6) branch point.
- Debranching enzyme has two activities; a glycosyltransferase and a glycosidase
  - Debranching enzyme transfers a block of three residues to the nonreducing end of the chain.
  - Debranching enzyme hydrolyzes the single remaining ($\alpha$1$\rightarrow$6)-linked glucose, which becomes a free glucose unit (i.e., NOT glucose 1-phosphate).
- The Glc enters glycolysis, but the Glc 1-P must be converted to the glycolytic intermediate Glc 6-P first.
- How?

# Glycogenolysis is performed mainly by Glycogen Phosphorylase

*Mechanism*




# Glycogenolysis produces Glucose 1-Phosphate, which must be converted to Glucose 6-Phosphate by Phosphoglucomutase for Metabolism




- Phosphoglucomutase must be phosphorylated at an active-site Ser.
- This is performed by a Glc 1,6-$P_2$ to initiate the active form.
- During turnover, the bisphosphate flips within a “vestibule”

# Clinical Correlations

Facilitative Diffusion

**Aquaporins** are important in the kidney nephron.  Here water reabsorption is critical for maintaining water balance.

- Loss of these aquaporins leads to NDI (nephrogenic diabetes insipidus), hypokalemia, and hypercalcemia.

Fructose malabsorption arises from a number of known and unknown causes.

- One known cause is loss of **GLUT-5**, the facilitative diffusion transporter specific for fructose

# Clinical Correlations

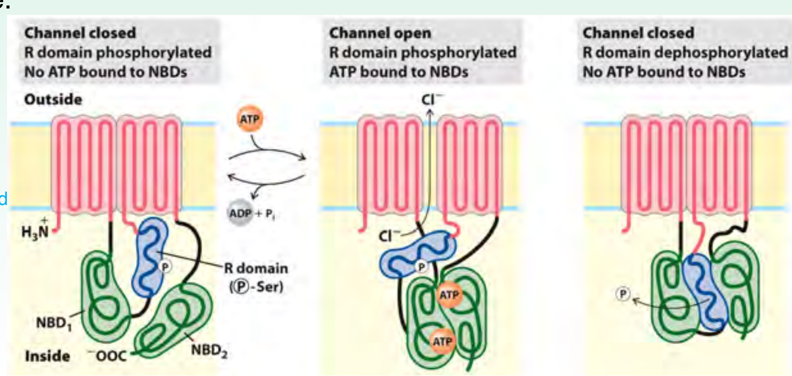
**Active Transport**

Failure of ABC-Transporters Can Lead to Human Disease

- Mutations in the human CFTR transporter (an ABC-type transporter-like **channel** for chloride ions)(cystic fibrosis transmembrane-conductance regulator) result in the human disease cystic fibrosis.
- Single-amino-acid mutations can render the protein misfolded and/or unable to transport chloride ions, resulting in an imbalance of water across the membrane.

Regulated Facilitative Diffusion

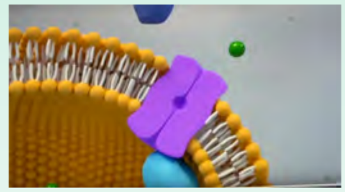
- Phosphorylated by PKA
- Puts it in ATP cycle



# Clinical Correlations

## Failure of ABC-Transporters Can Lead to Human Disease

Diseases such as Tangier's (ABC-A1), Juvenile macular degeneration and retinitis pigmentosa (ABC-R), Progressive familial intrahepatic cholestasis (BSEP), and Celiac disease (TAP1) have all been associated with ABC transporters (named in parenthesis).



Nearly all these transports named above are transporting membrane lipids.

While there are about 50 genes for ABC transporters in humans, there are thousands in bacteria and plants were they are involved in transport of many other things such as amino acids, sugars, peptides and even entire proteins.

One of the most clinically relevant ones is the MRP1 transporter, which leads to multi-drug resistance

Dr. Kornberg's "Giraffe" story