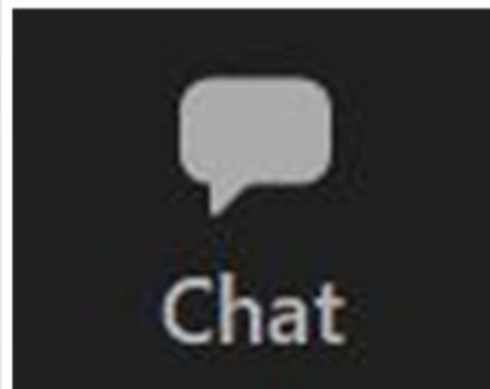


Exploring the Wonderful World of Cell Membranes

Proteins, Lipids, and Ions, Oh My!

Potassium Channels & Scorpion Toxins







Chris Chou

B.S. Bioengineering
Ed.M. Curriculum & Instruction

Longmont High School (Longmont, CO)
Courses: AP Biology, Biotechnology

cn_chou@yahoo.com

Workshop Goals:



Model the structure and functions of the cell membrane

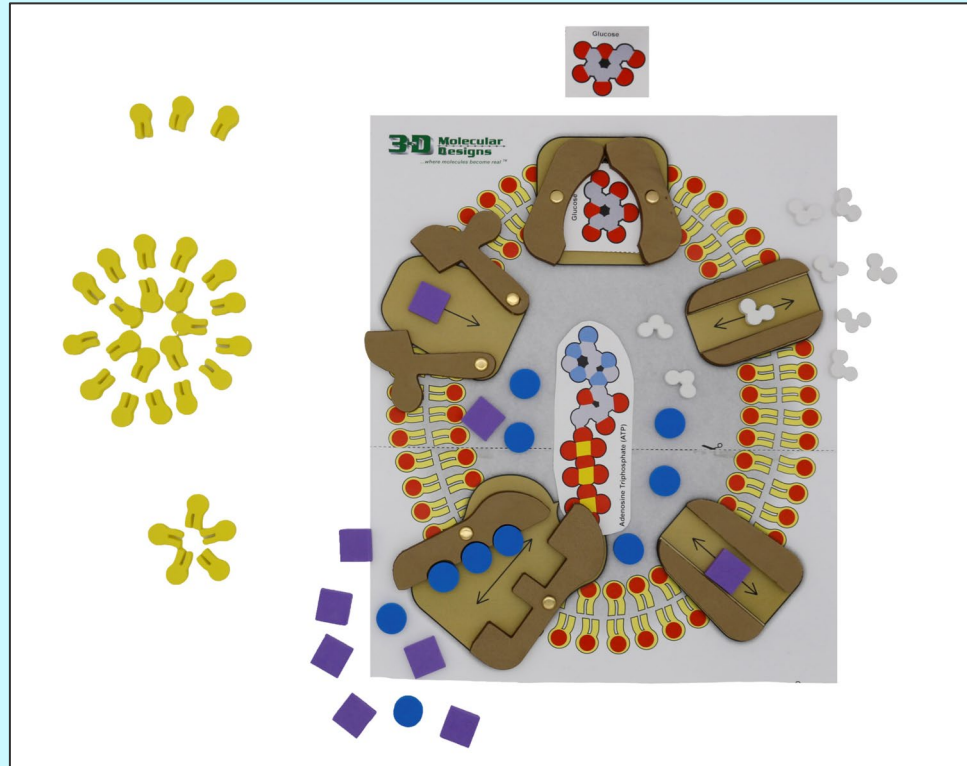


Explore the role of transport proteins in moving ions and small molecules across the cell membrane



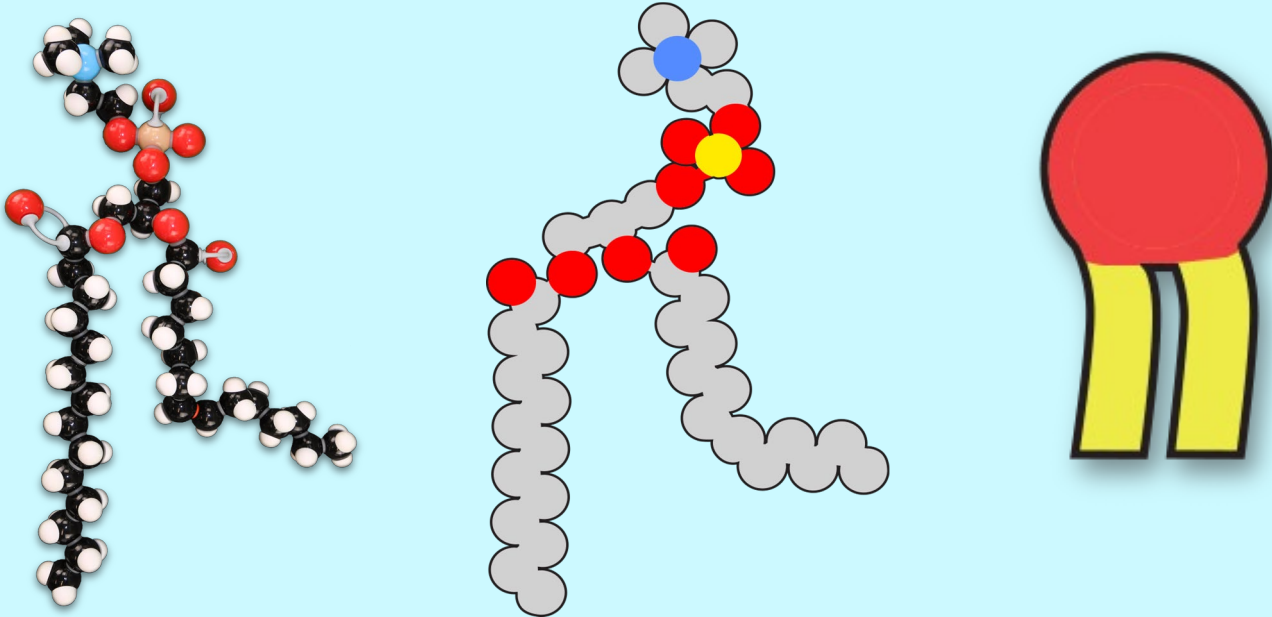
Understand how mutations in the CFTR gene cause cystic fibrosis

Get Ready to Model!

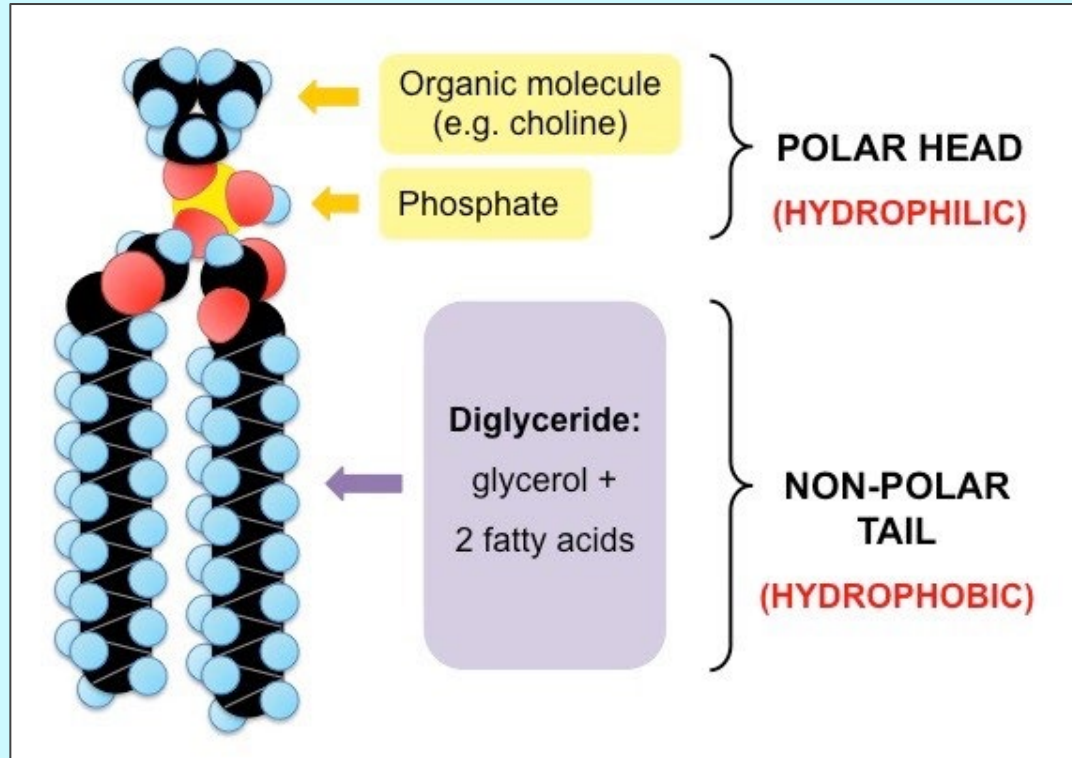


Phospholipids - 3DMD Models

What do you notice? What do you wonder?



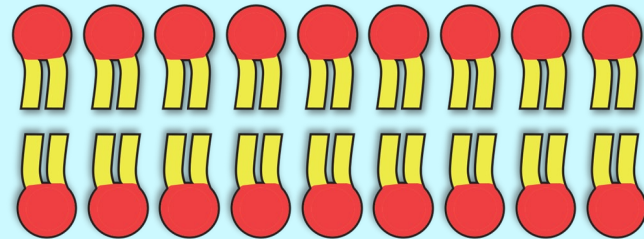
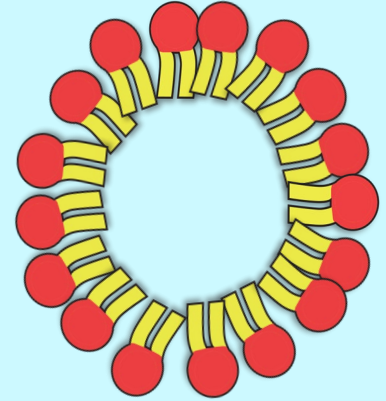
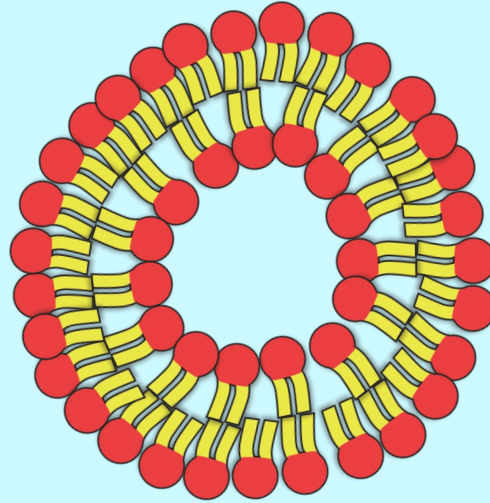
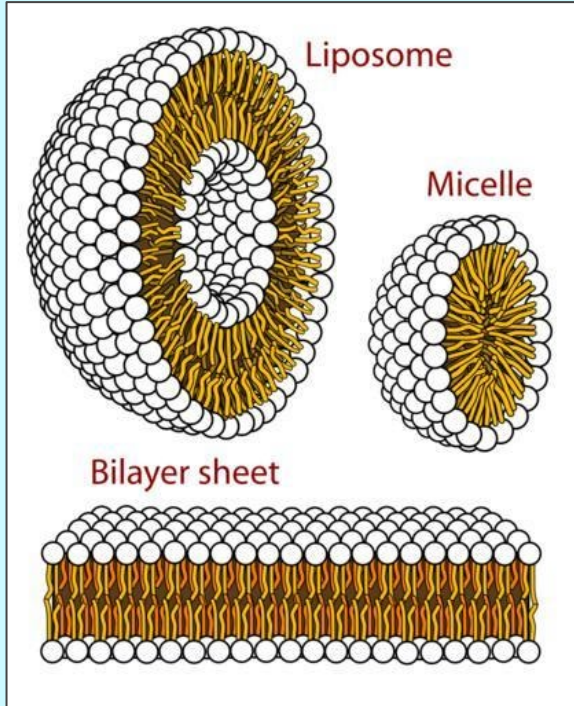
Phospholipid Structure



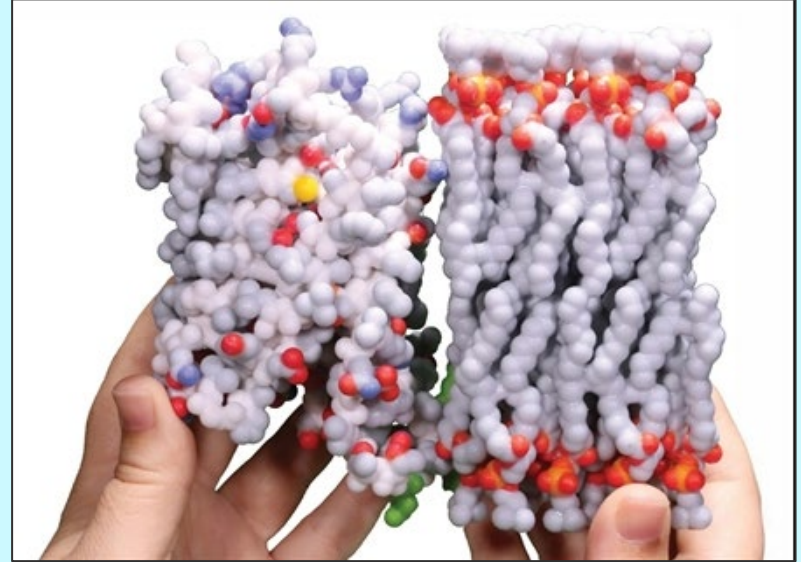
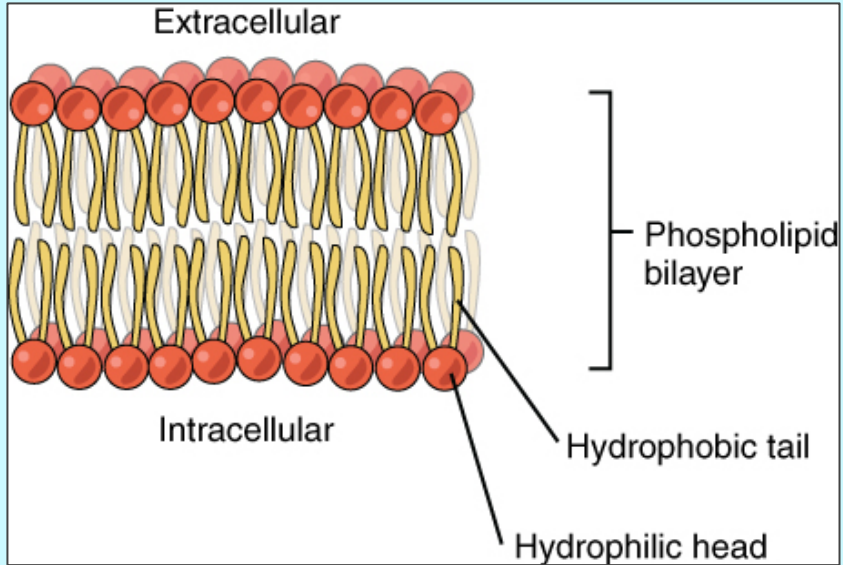
Let's Model!

**What are different ways that
phospholipids can be
arranged within a watery
environment?**

Phospholipid Arrangements

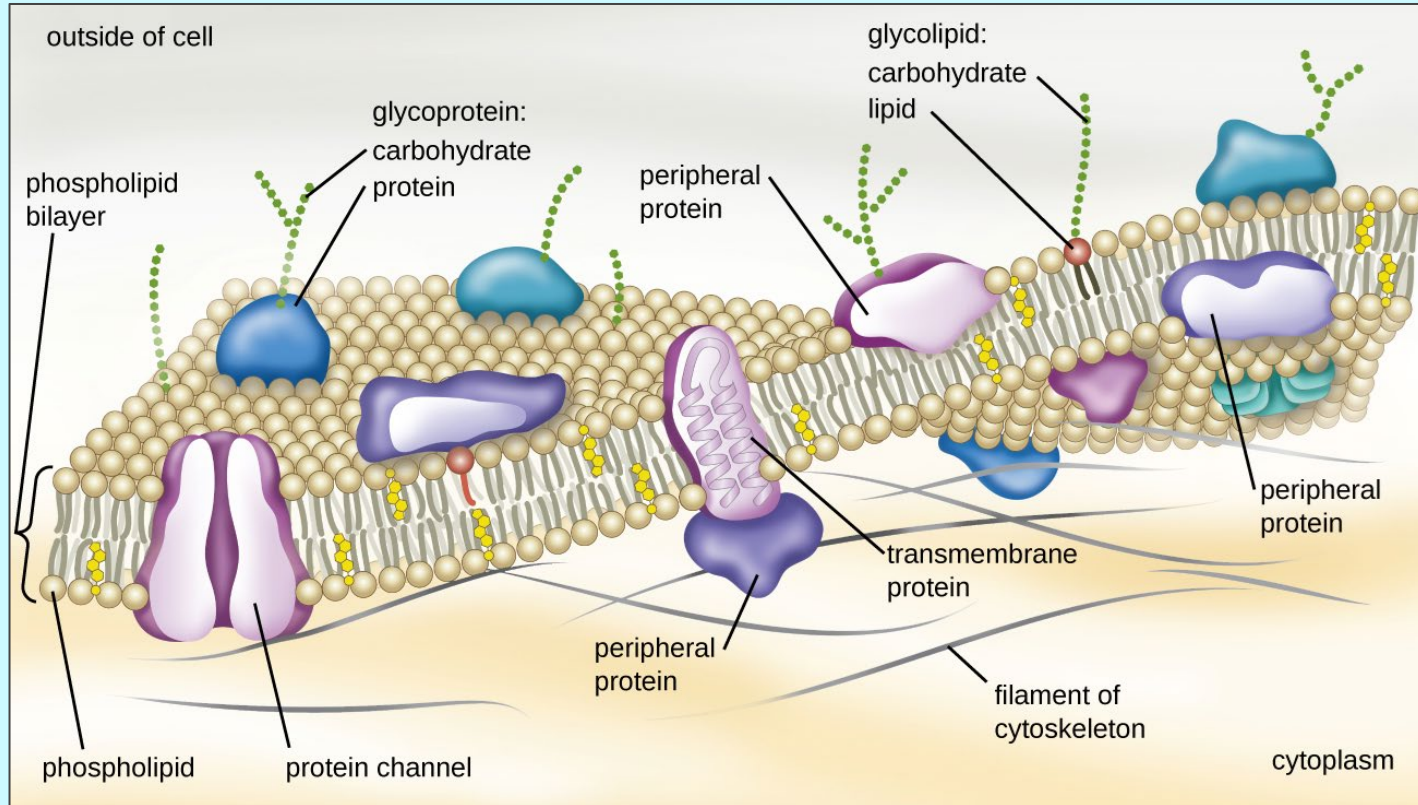


Phospholipid Bilayer

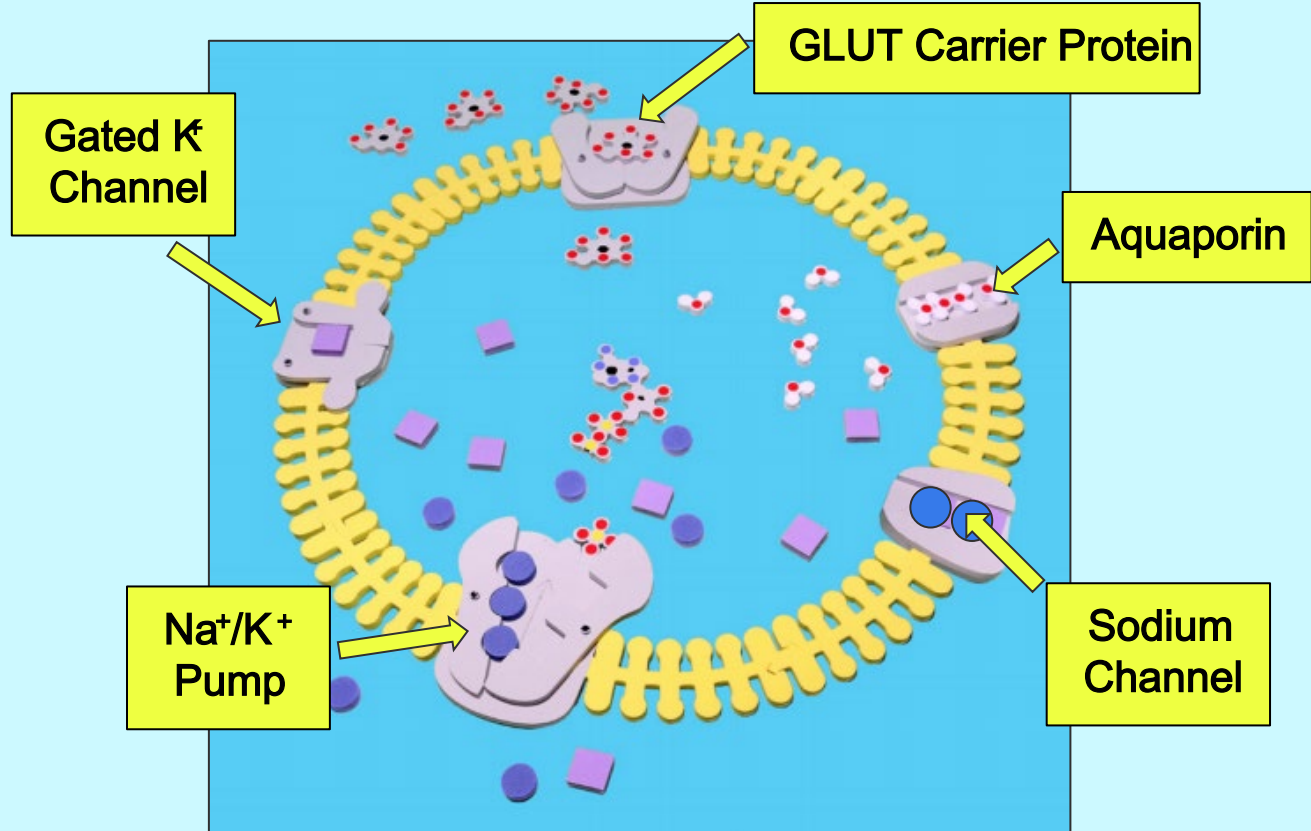
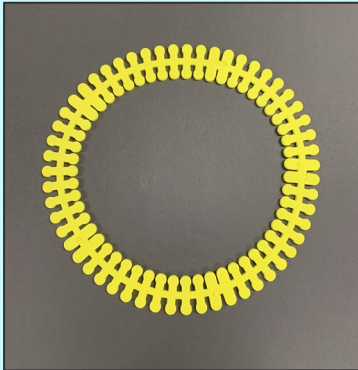




Components of the Cell Membrane



Let's Model the Cell Membrane!



Membrane Transport Proteins

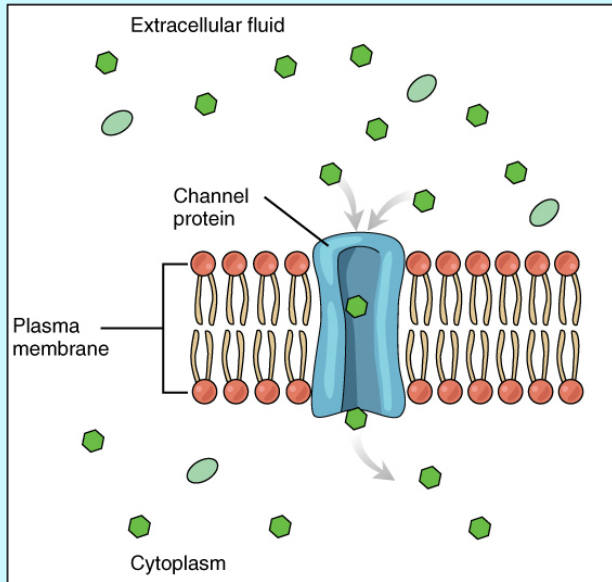
Channel Proteins

- Voltage-gated ion channel
- Ligand-gated ion channel
- Aquaporins
- Cl^- , Na^+ , K^+ , Ca^{2+}

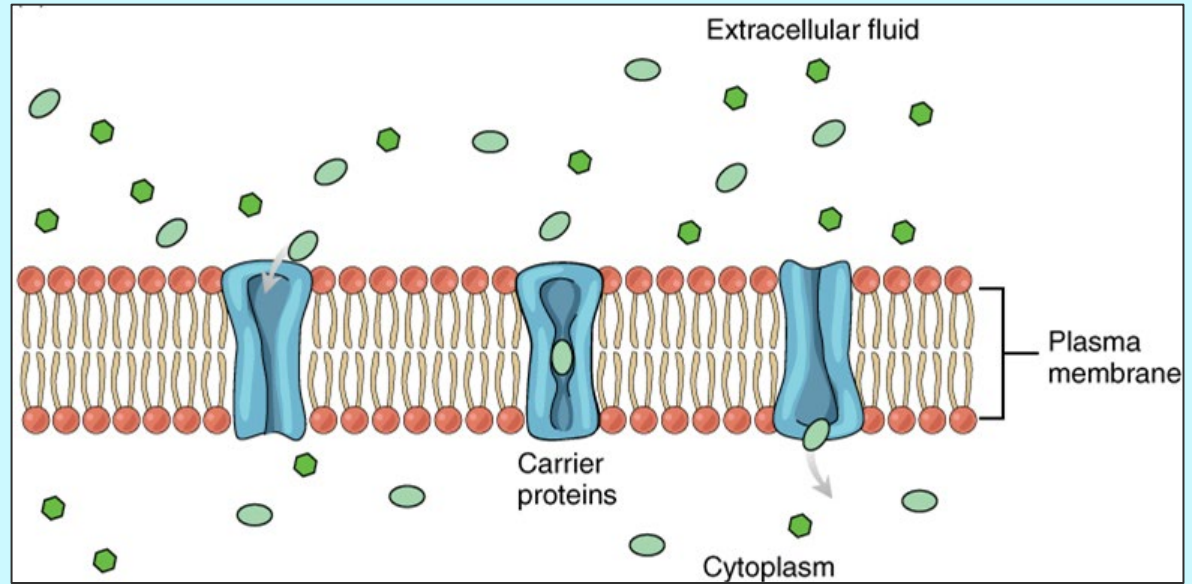
Carrier Proteins

- Electrochemical potential-driven
- Passive transport (facilitated diffusion) - large polar molecules and charged ions
- Active transport
 - Na^+/K^+ pump
 - Proton pump

Channel Proteins

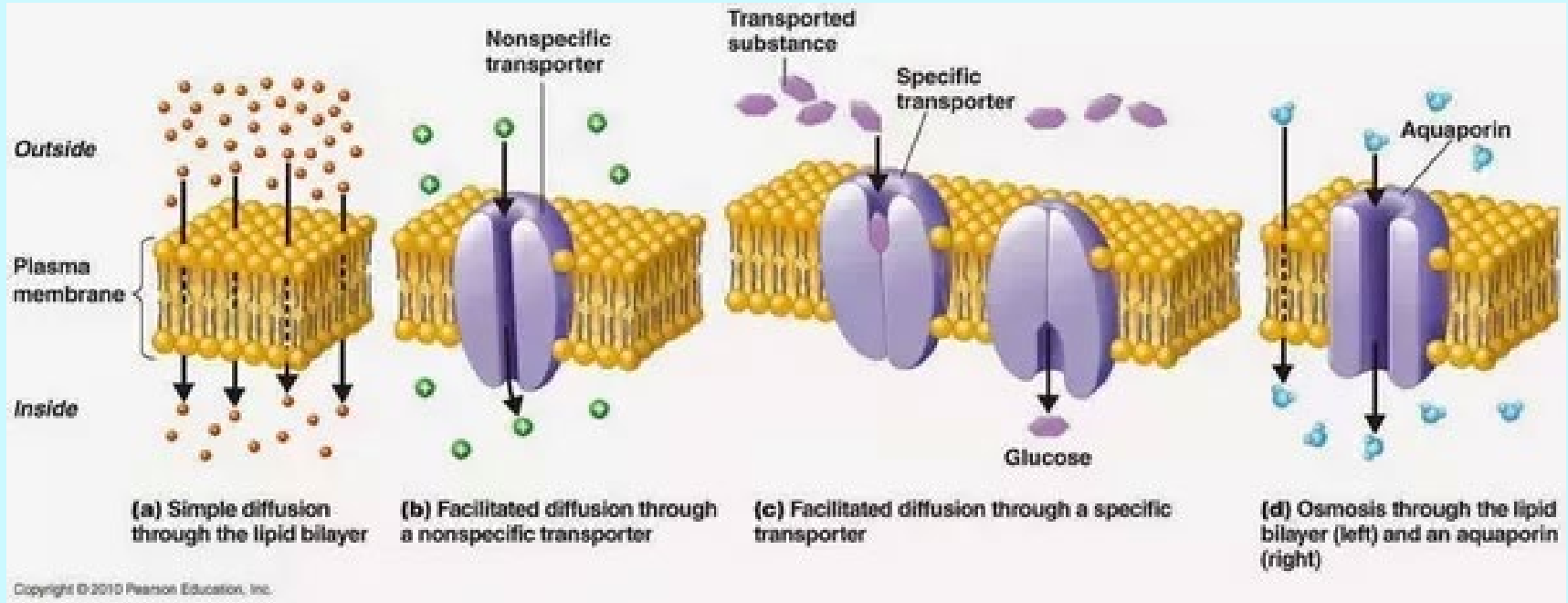


Carrier Proteins



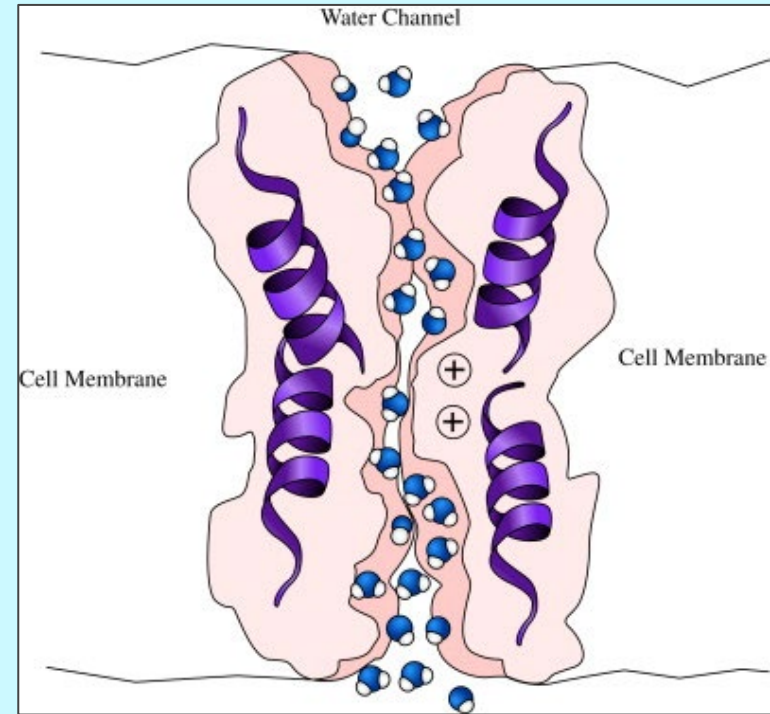
Passive Transport

Passive Transport



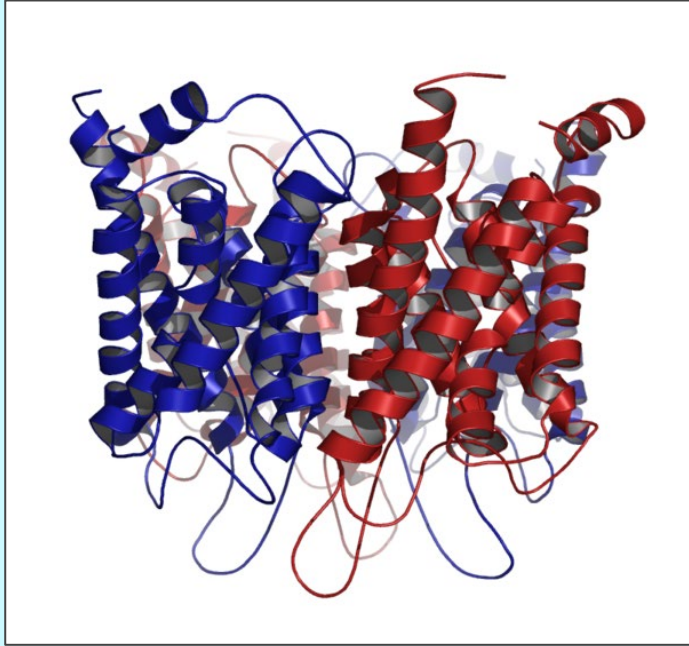
Aquaporins (AQPs)

- Transport water and small, uncharged molecules (gases, glycerol, ammonia, urea)
- Fluid transport
- Homeostatic maintenance
- Leak ion channel
 - Selective
 - Always open
 - Bidirectional
- Water molecules pass through pore in single-file

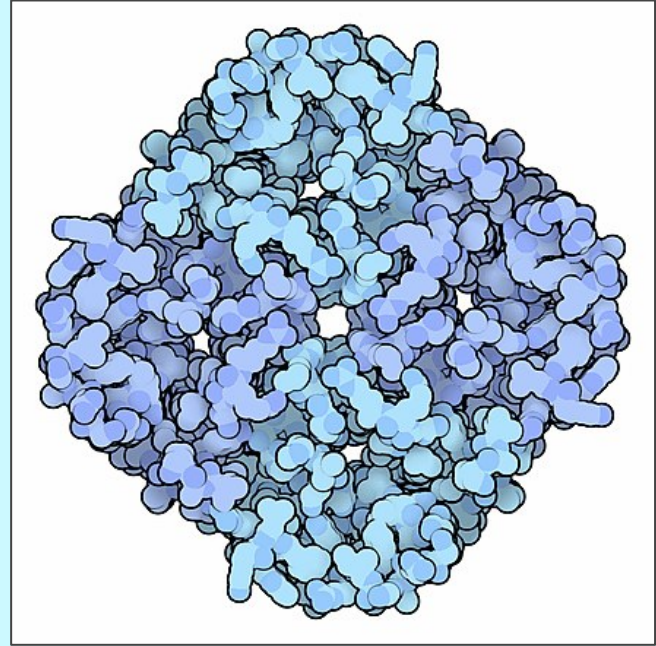


<https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/aquaporin>

Aquaporin Tetramer



PDB ID: 1J4N

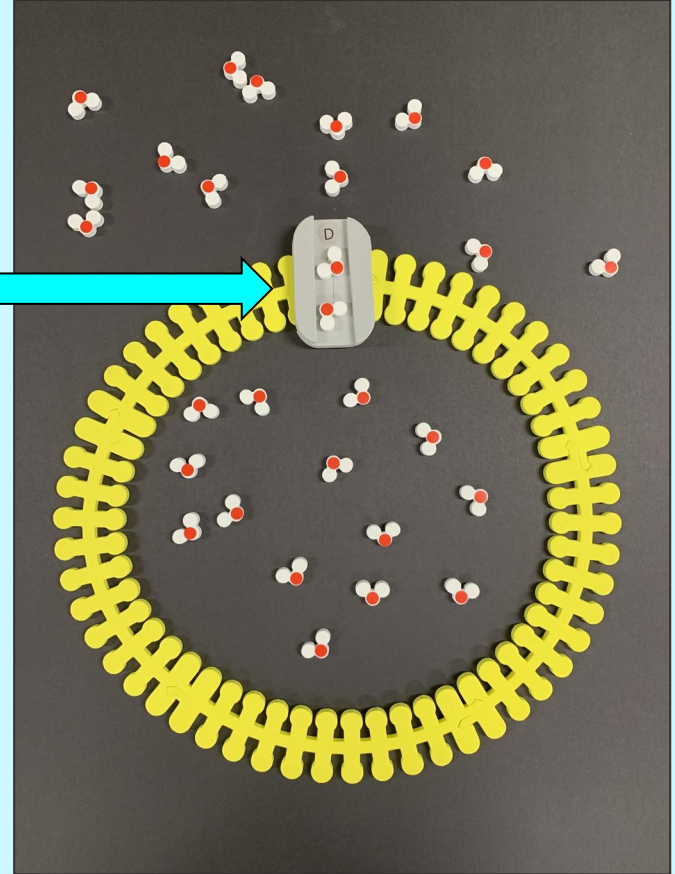


David Goodsell, PDB Molecule of the Month, PDB ID 1FQY



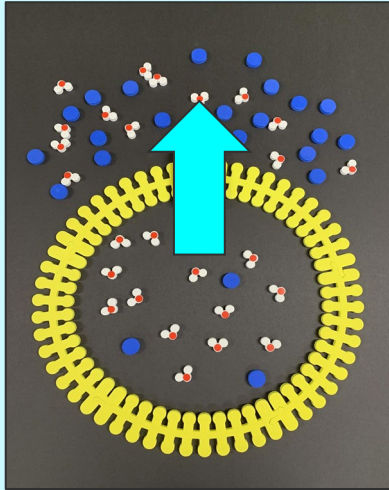
Let's Model Osmosis!

Aquaporin

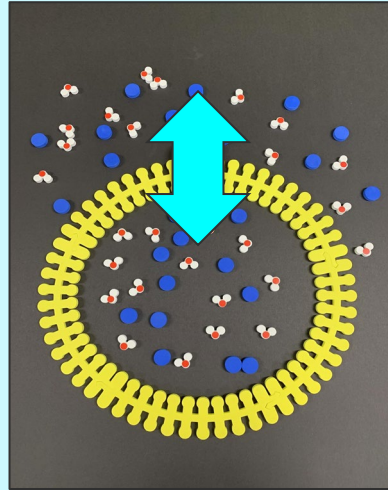


Let's Model!

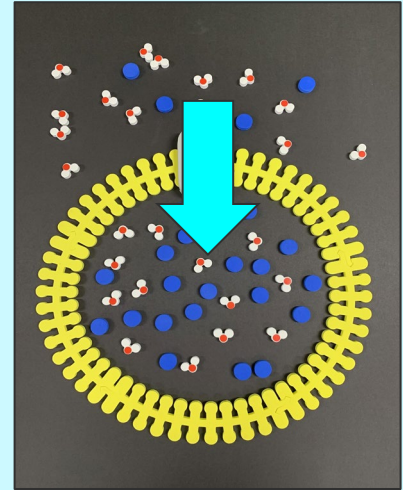
**Hypertonic
Solution**



**Isotonic
Solution**



**Hypotonic
Solution**



Which direction will water flow?

Case Study #1

A patient is admitted to the emergency room with severe vomiting and diarrhea. An intravenous (IV) solution is administered to restore fluid loss. Shortly after, the patient experiences a dramatic loss in blood pressure.

A blood sample is sent to the lab. Under the microscope, the patient's red blood cells appear very swollen.



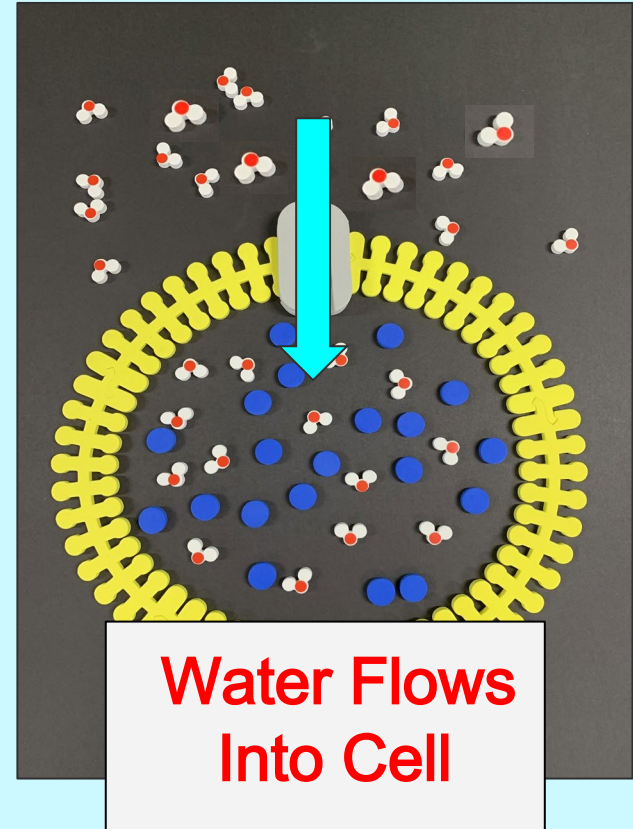
Using the membrane model, **explain** what you think happened at the hospital.

Case Study #1

A patient is admitted to the emergency room with severe vomiting and diarrhea. An intravenous (IV) solution is administered to restore fluid loss. Shortly after, the patient experiences a dramatic loss in blood pressure.

A blood sample is sent to the lab. Under the microscope, the patient's red blood cells appear very swollen.

Hypotonic Solution
(Distilled Water)

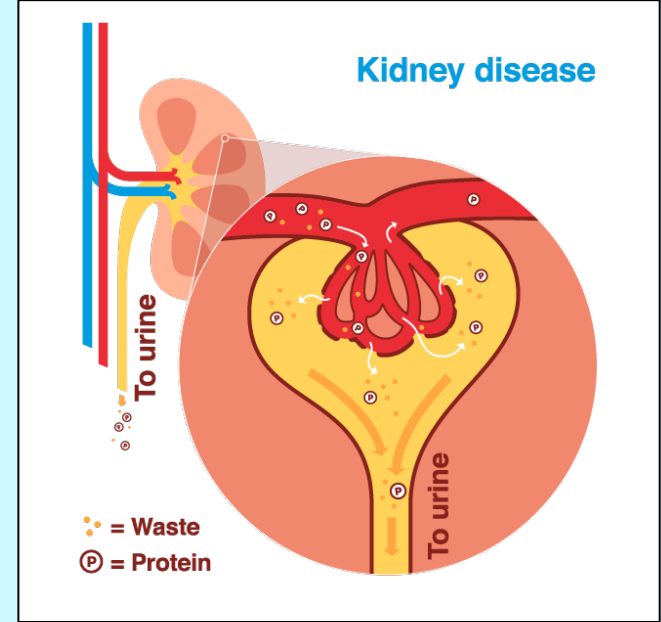


Case Study #2

A couple takes their 7-year-old young son to the doctor. Their child has been complaining of being thirsty all the time and has been getting up several times during the night to urinate.

The doctor orders tests and finds high levels of glucose in the patient's urine. She suspects her patient may have Type 1 Diabetes.

Using your understanding of osmosis and diffusion, **create** a model to explain why diabetics can experience frequent urination and increased thirst.

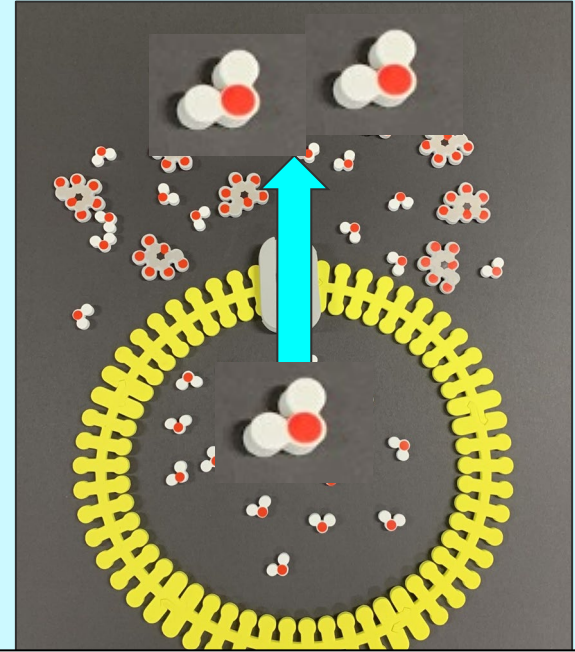


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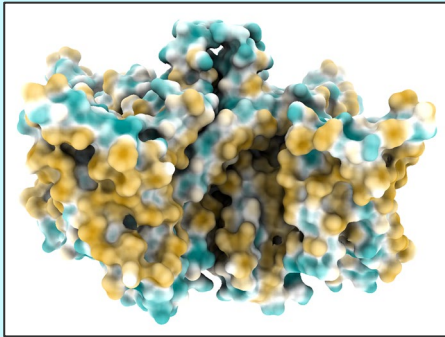
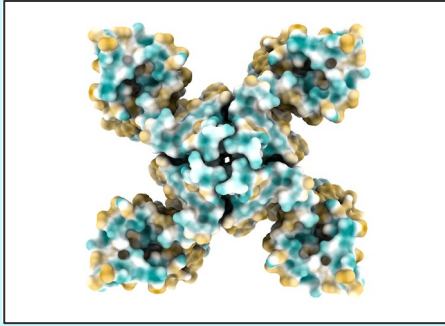
The doctor orders tests and finds high levels of glucose in the patient's urine. She suspects her patient may have Type 1 Diabetes.

Hypertonic Solution

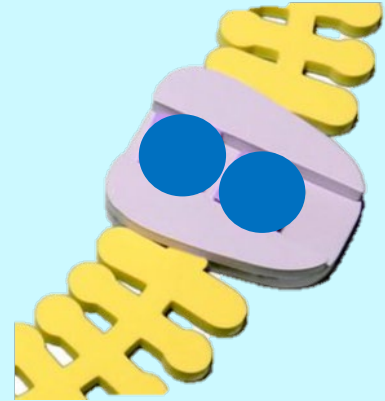


**Water Flows Out of Cell
(↑ urine production)**

Sodium Channel



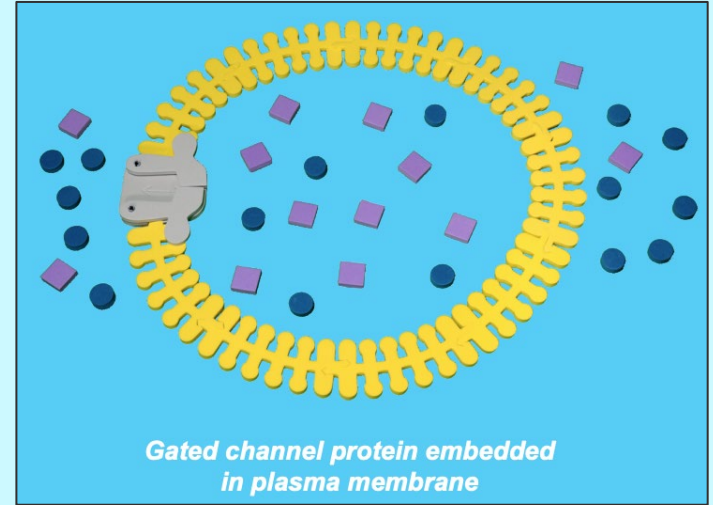
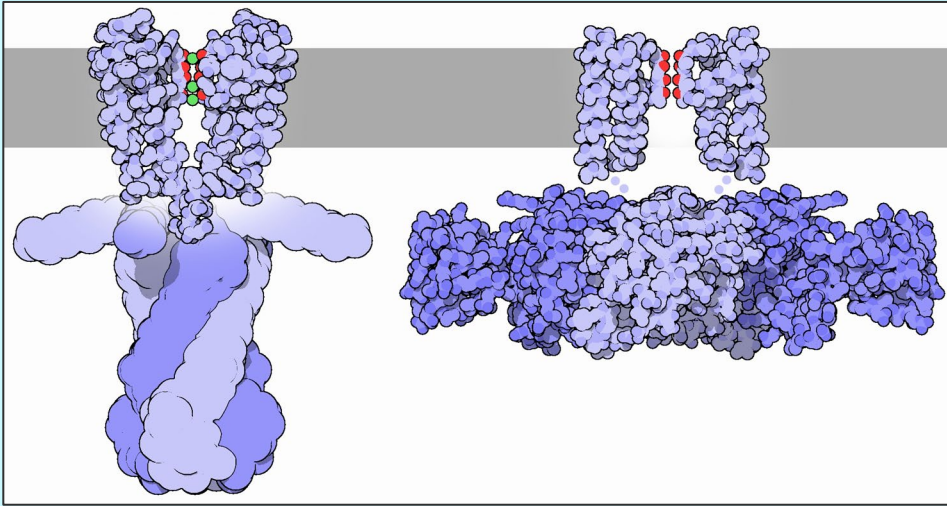
PDB ID: 6P6W



Gated Potassium Channel

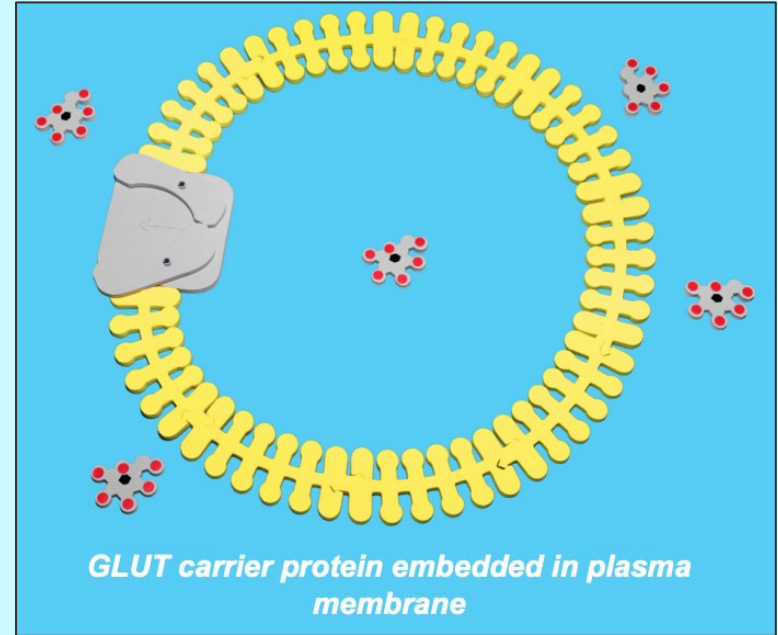
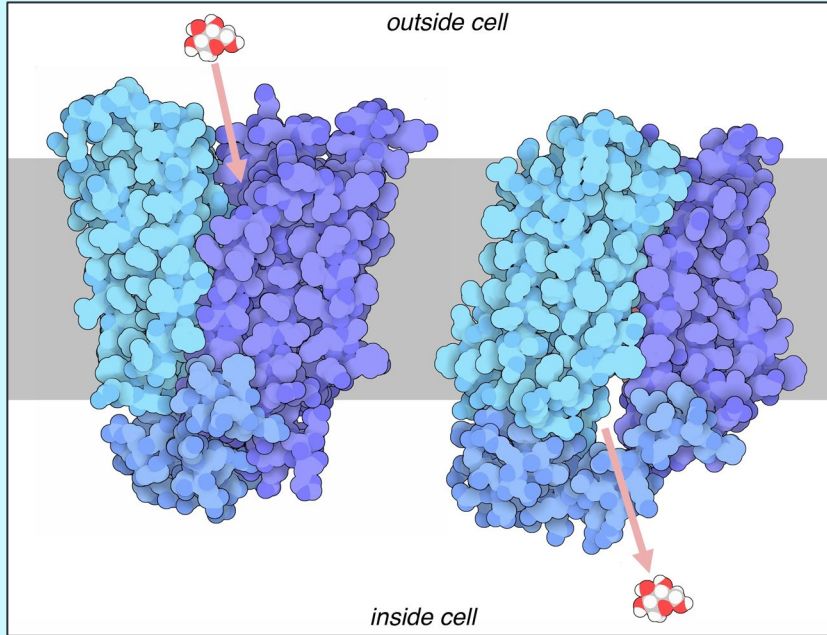
“Closed” Channel

“Open” Channel



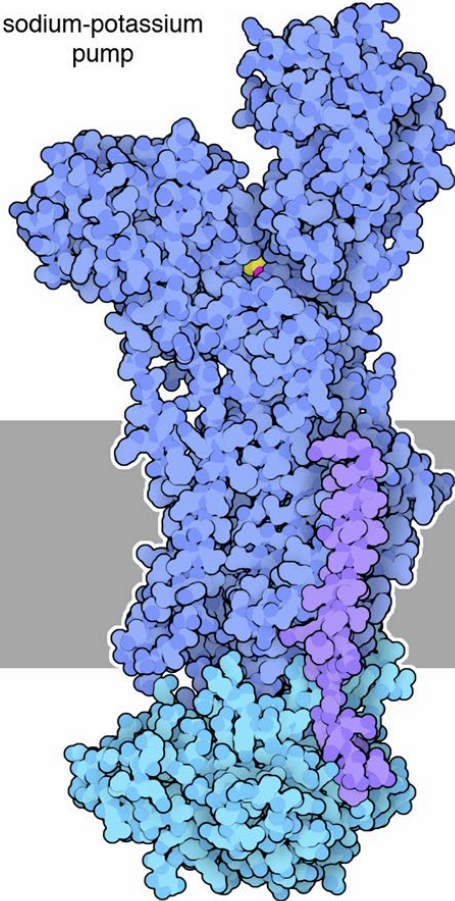
<http://pdb101.rcsb.org/motm/38>

GLUT: Glucose Transporter / Carrier Protein

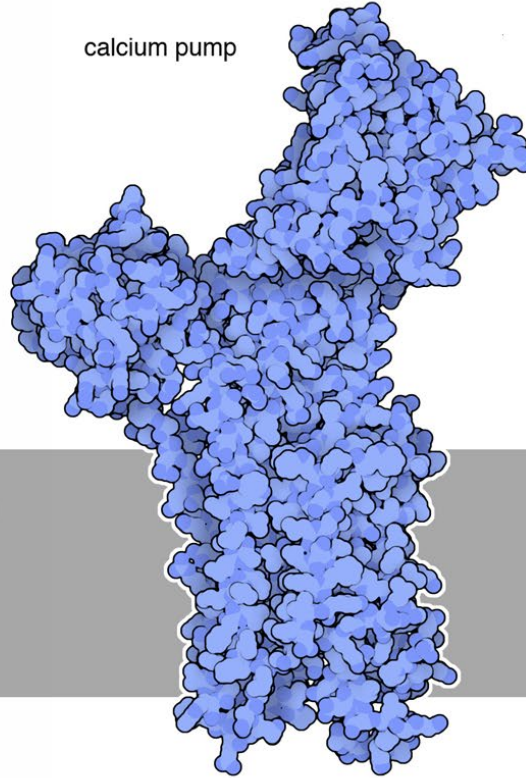


Active Transport

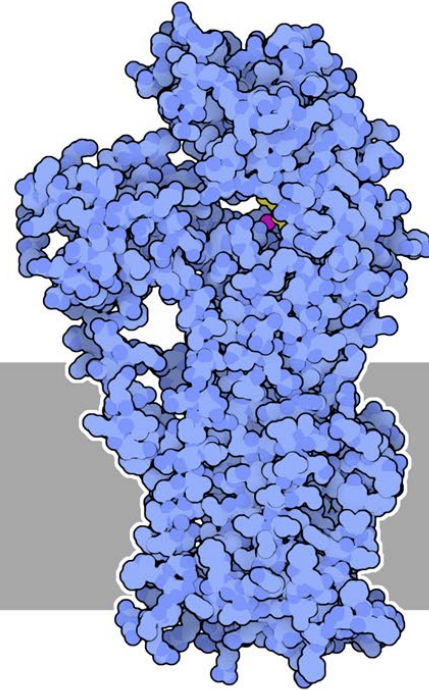
sodium-potassium
pump



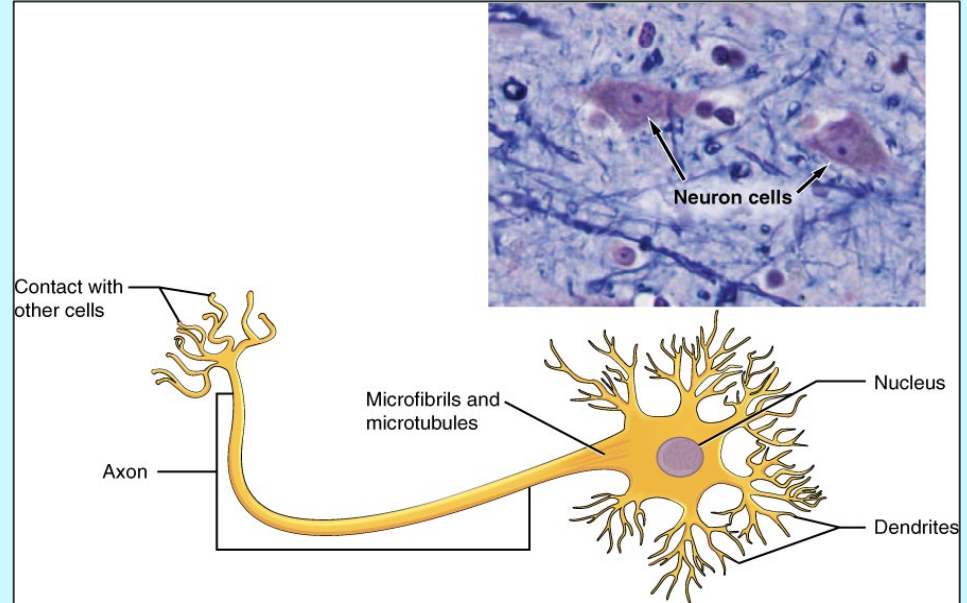
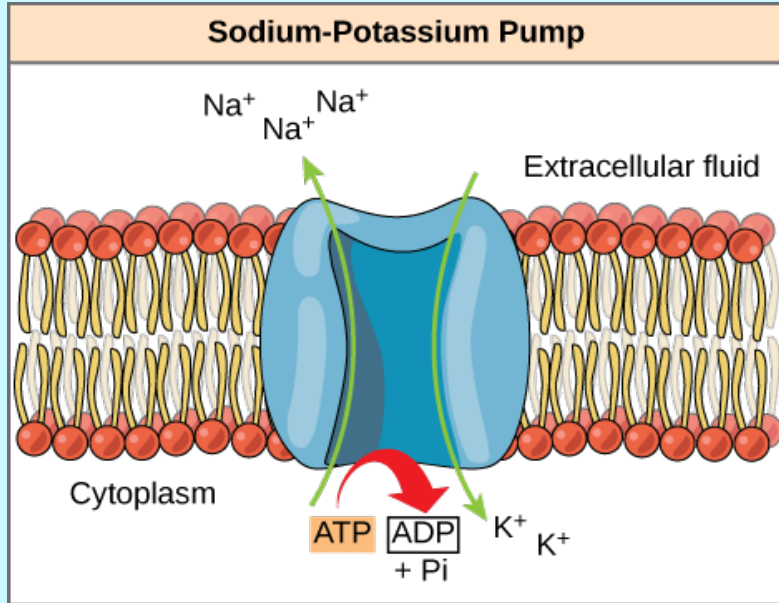
calcium pump



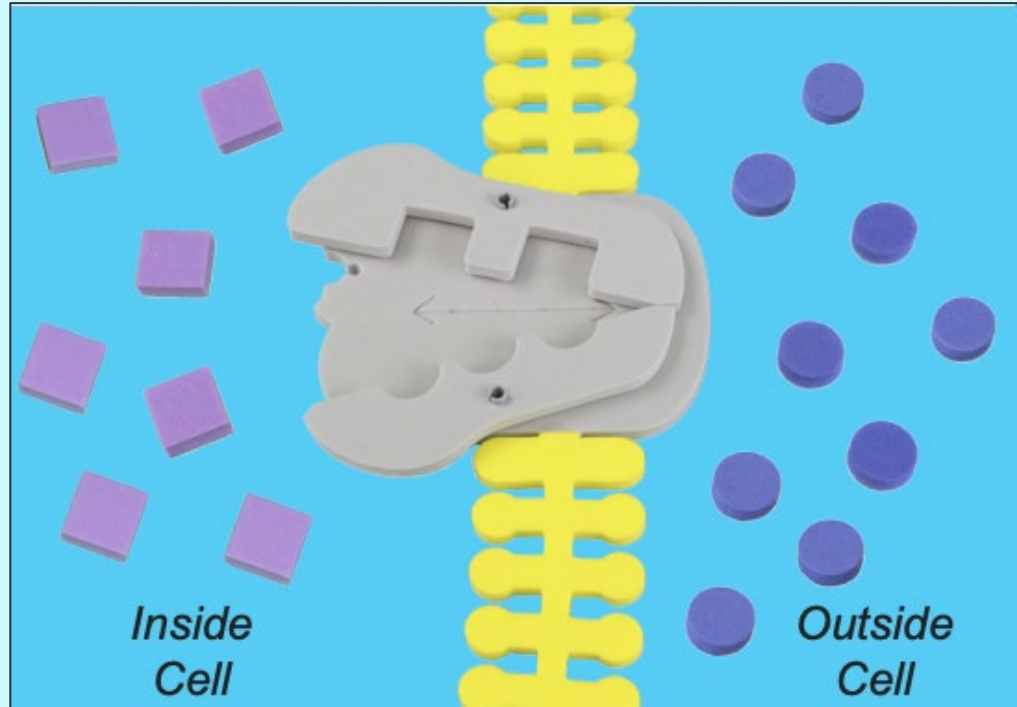
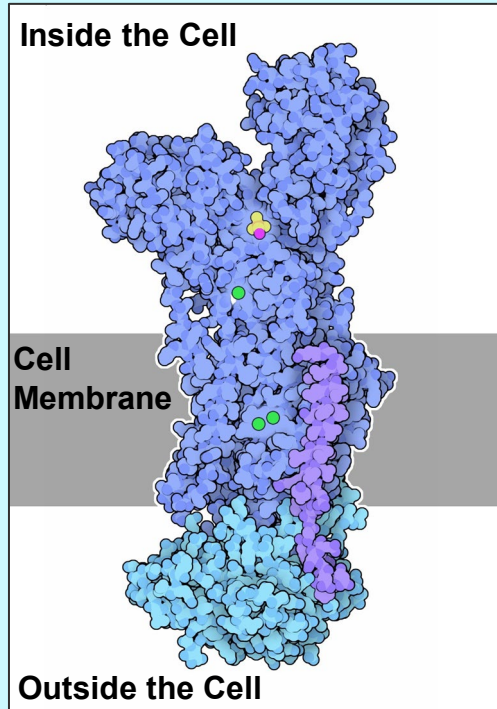
proton pump



Sodium-Potassium Pump

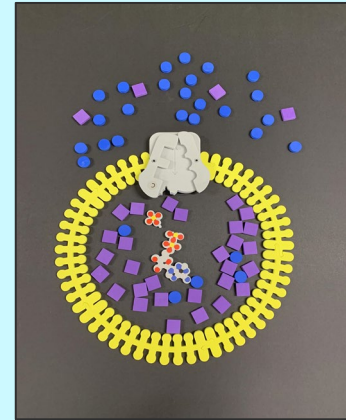
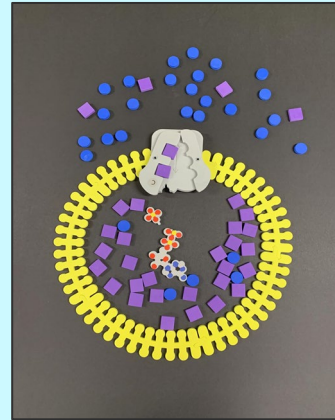
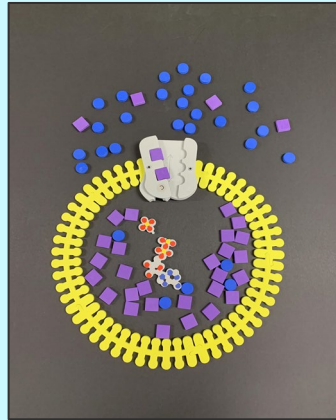
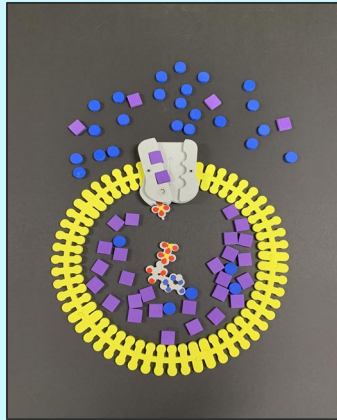
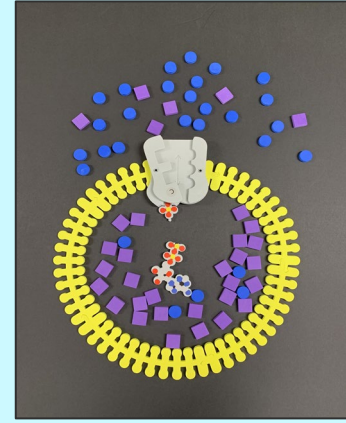
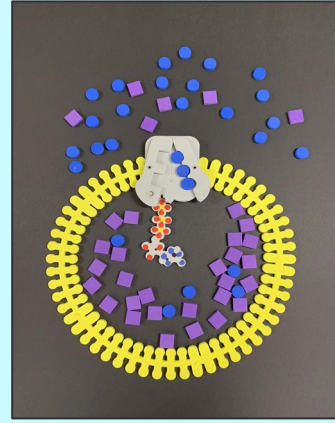
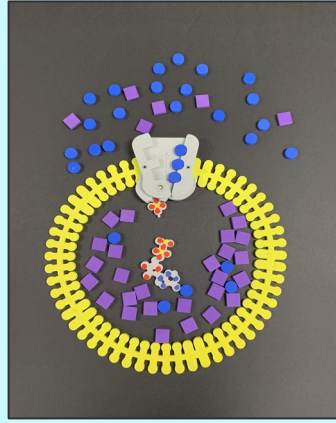
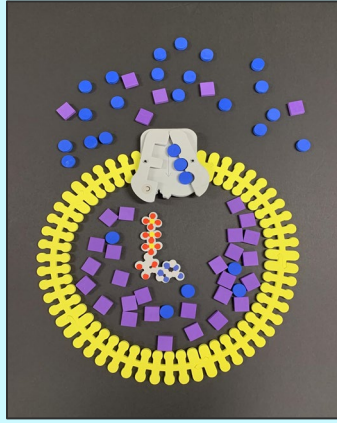


Sodium-Potassium Pump



<http://pdb101.rcsb.org/motm/118>

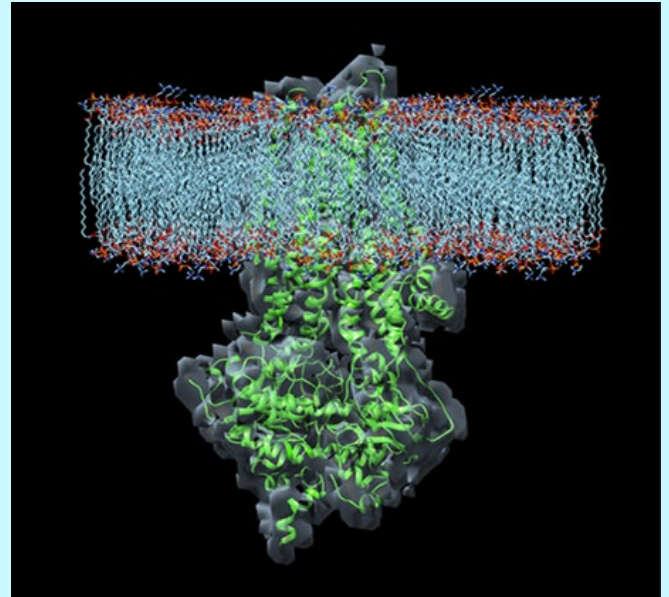
Let's Model the Sodium/Potassium Pump!



CFTR Protein

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Protein

- CFTR gene located on chromosome 7
- CFTR protein = 1480 amino acids
- Gated chloride ion channel: movement of Cl^- from inside to outside of cell
- 2 ATP-binding sites
- Involved in production of sweat, digestive fluids and mucus



Jue Chen, Rockefeller University

How is CFTR made?

DNA in the cell nucleus provides instructions to make proteins. The CFTR gene contains instructions to make the cystic fibrosis transmembrane conductance regulator (CFTR) protein.



RNA acts as a template to make proteins. RNA is created by matching the coded instructions in the DNA. This process is called **transcription**.



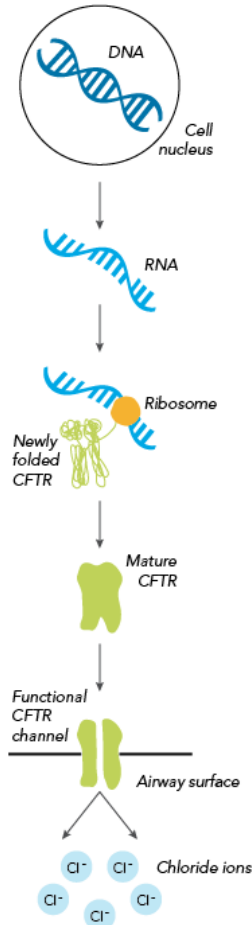
Ribosomes are tiny molecular machines that read the instructions in the RNA and use them to make the CFTR protein. This process is called **translation**.



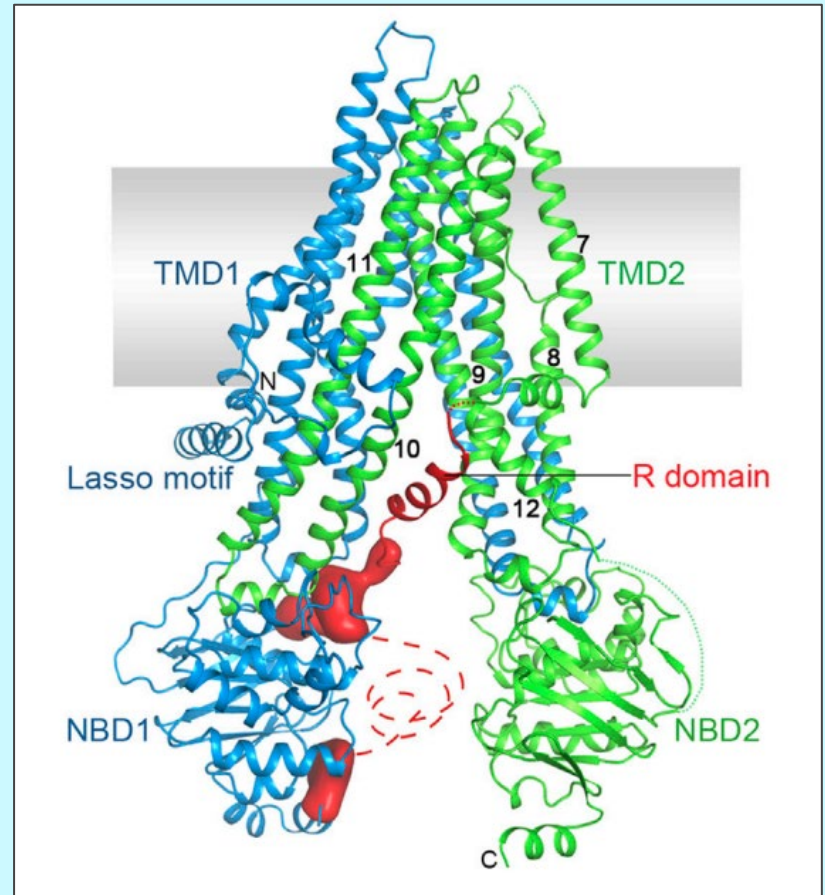
Once complete, the CFTR protein moves through the cell to the cell surface. This process is called **trafficking**.



Once at the cell surface, the CFTR protein functions as a chloride channel. This channel helps maintain the right balance of fluid in the airways.

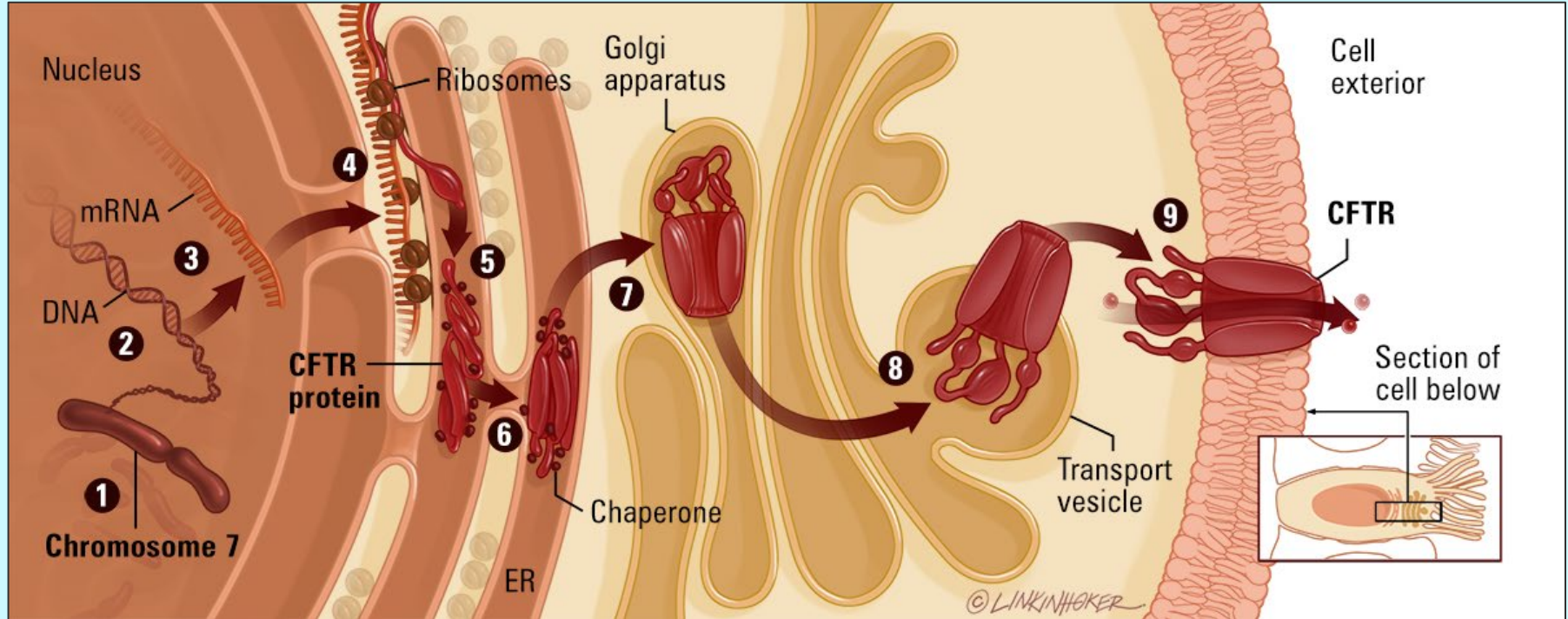


WHAT'S HAPPENING IN THE CELL



Liu, Zhang, Csanady, Gadsby, Chen, 2017, *Cell*.

CFTR Cellular Processing



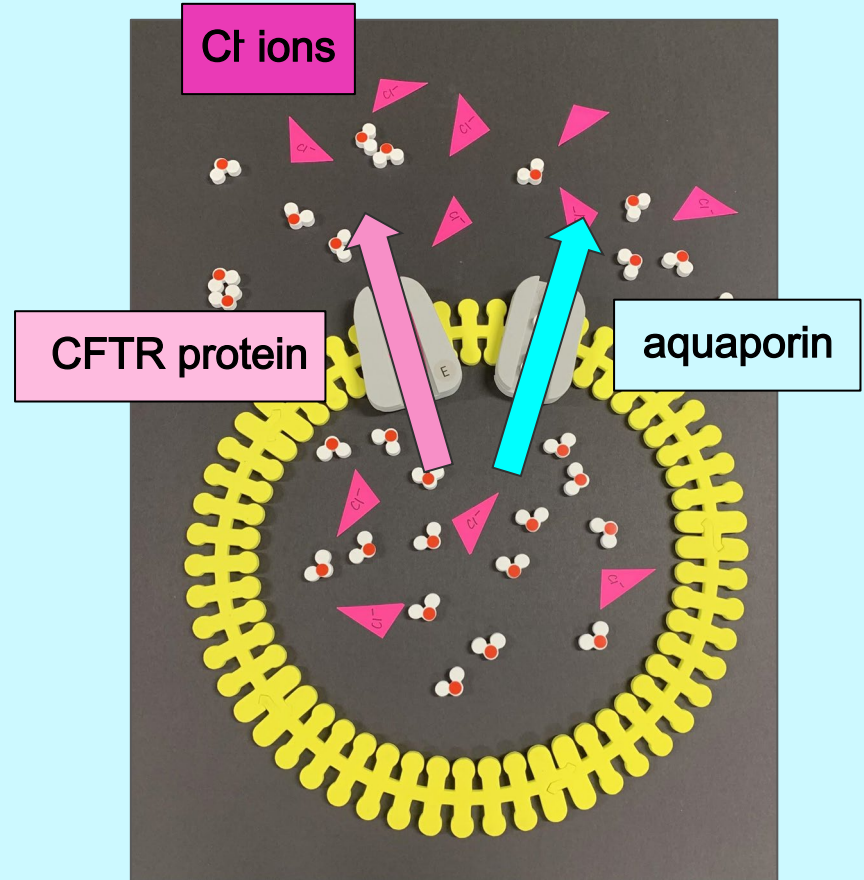
Let's Model!

Model the role of the CFTR protein in the transport of chloride ions and water across the cell membrane.

Let's Model!

Cl^- transported out of
epithelial cell

water diffuses out of cell
(mucus membrane)

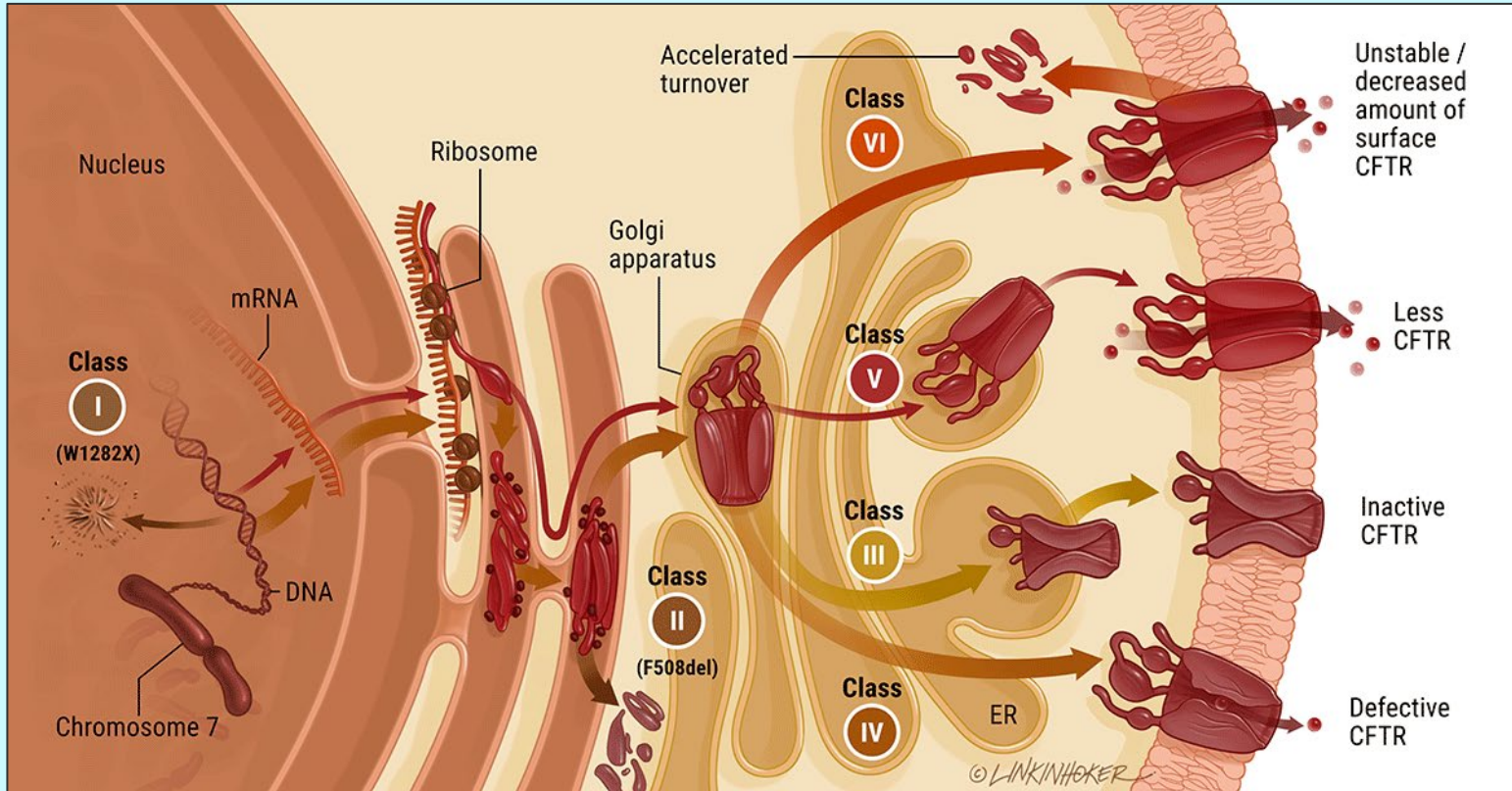


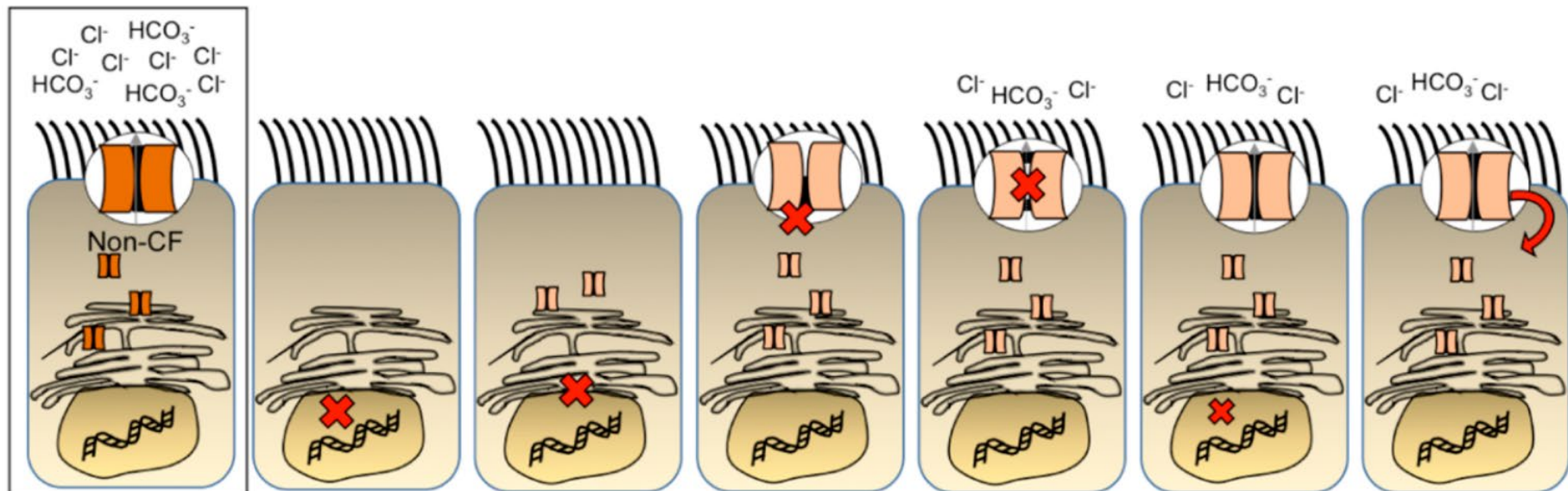


Cystic Fibrosis

- Mutation in CFTR gene
 - 2000+ identified mutations; F508del most common ($\frac{2}{3}$ cases worldwide; 90% cases in US)
- Secretions become thick; affects mostly the lungs, but also the pancreas, liver, kidneys, and intestine
- Signs and symptoms: difficulty breathing, coughing up mucus, sinus infections, poor growth, fatty stool, clubbing of fingers and toes, infertility in most males
- Diagnosed by sweat test and genetic testing (infant screening at birth)
- CF most common among people of Northern European ancestry (1:3000 newborns; 1:25 is carrier); least common in Africans and Asians
- Average life expectancy: 42-50 years in developed world

CFTR Mutations

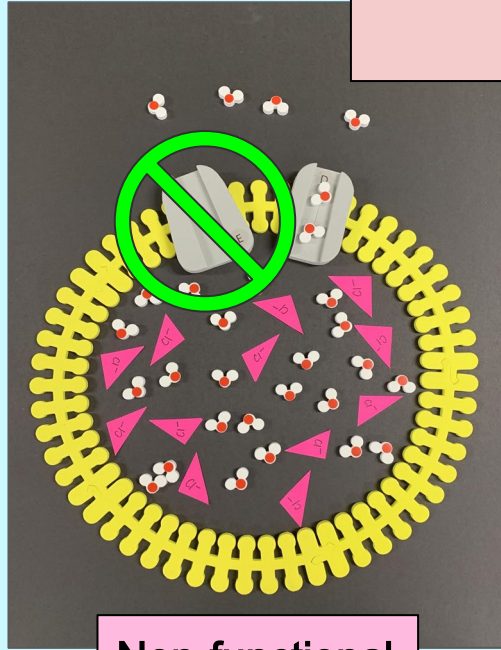




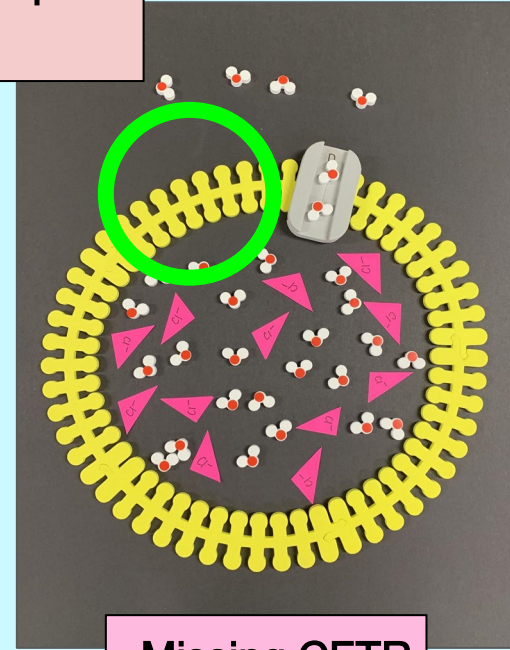
Class of CFTR mutation	I	II	III	IV	V	VI
Protein output	No synthesis	Block in processing	Block in regulation	Reduced conductance	Reduced synthesis	Reduced half-life
Mutation example	G542X	F508	G551D	R117H	3489+10kb C>T	4326delTC
% of people with CF who have at least one mutation*	22%	88%	6%	6%	5%	5%

Let's Model!

Less water in extracellular space
→ thicker mucous



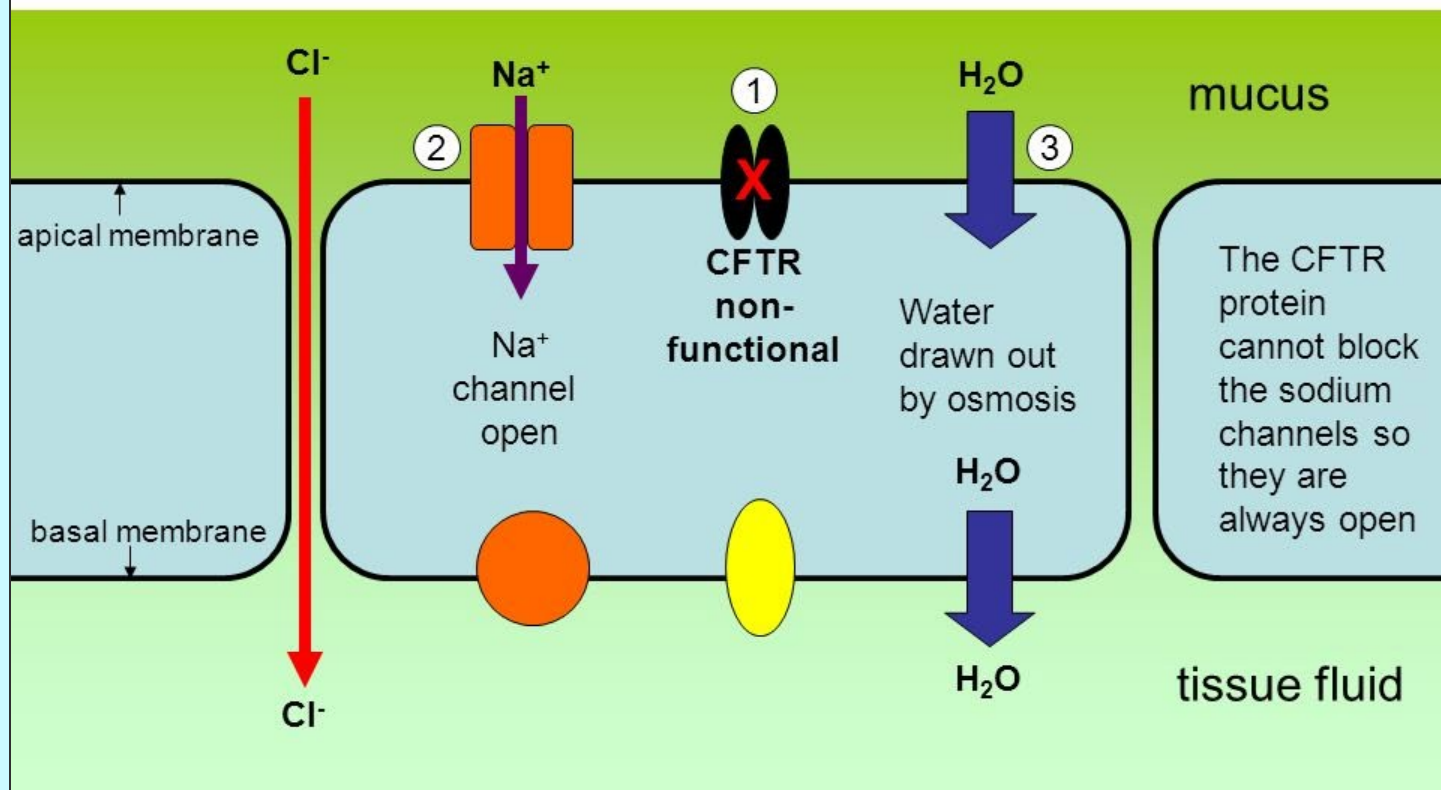
Non-functional
CFTR protein



Missing CFTR
protein

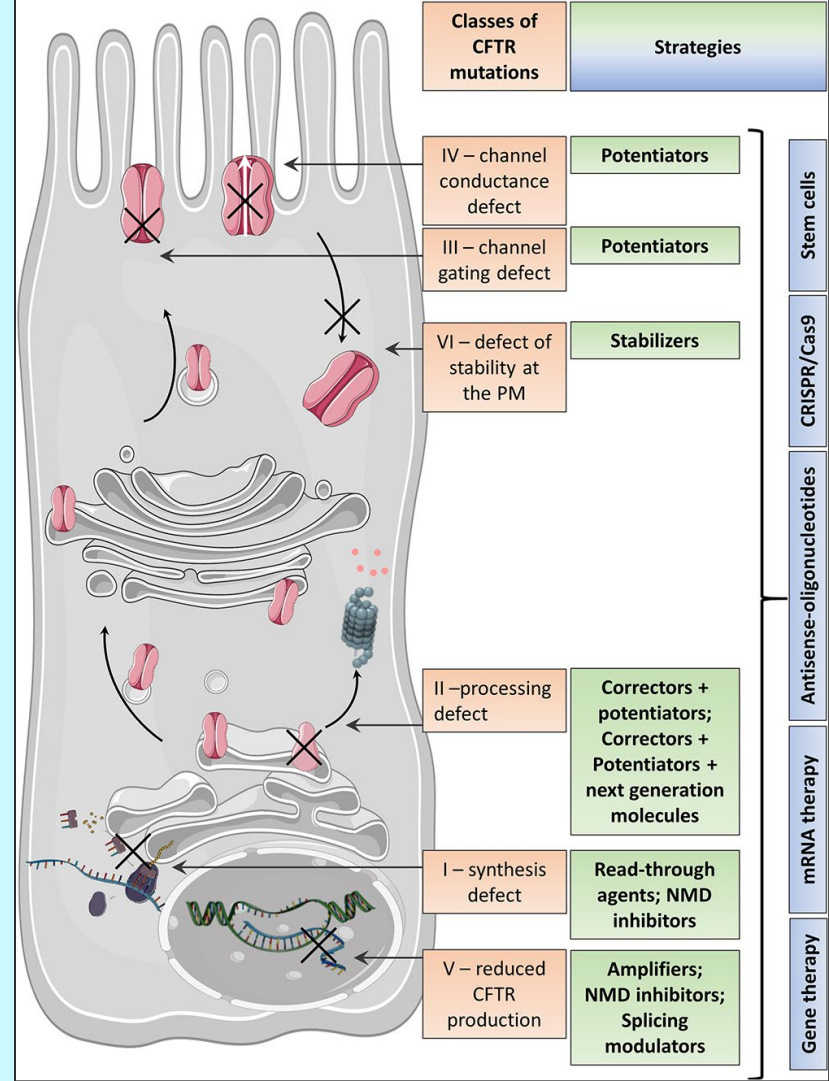
With cystic fibrosis

The mucus becomes very thick and sticky

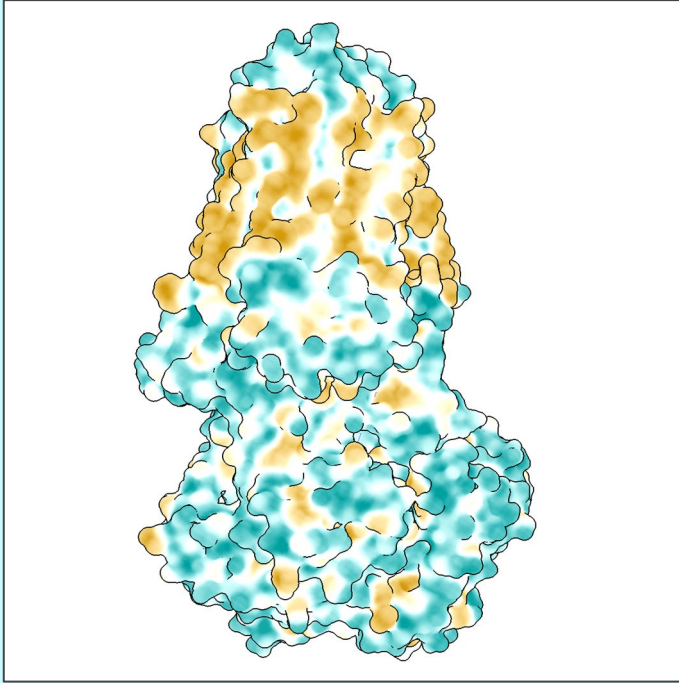


Cystic Fibrosis Treatment Options

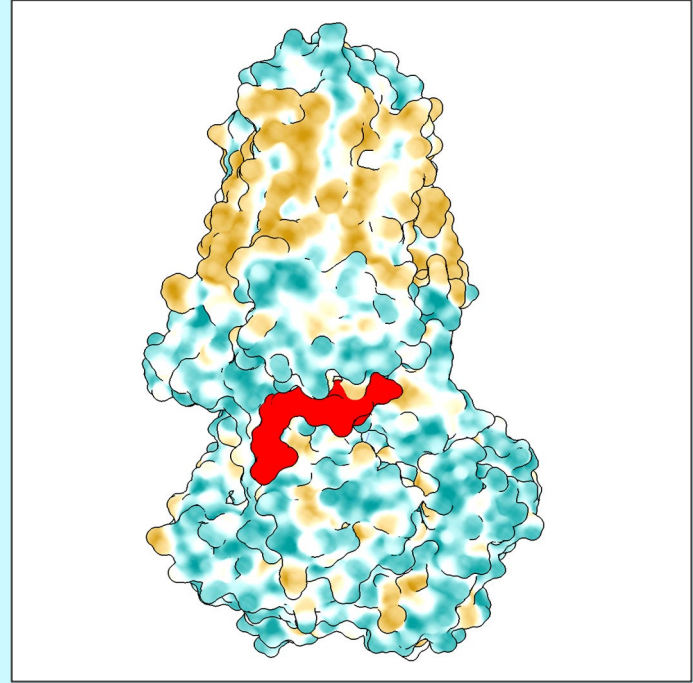
Front. Pharmacol., 27 February 2019 |
<https://doi.org/10.3389/fphar.2019.00121>



Ivacaftor: CFTR Modulator Therapy for G551D Mutation

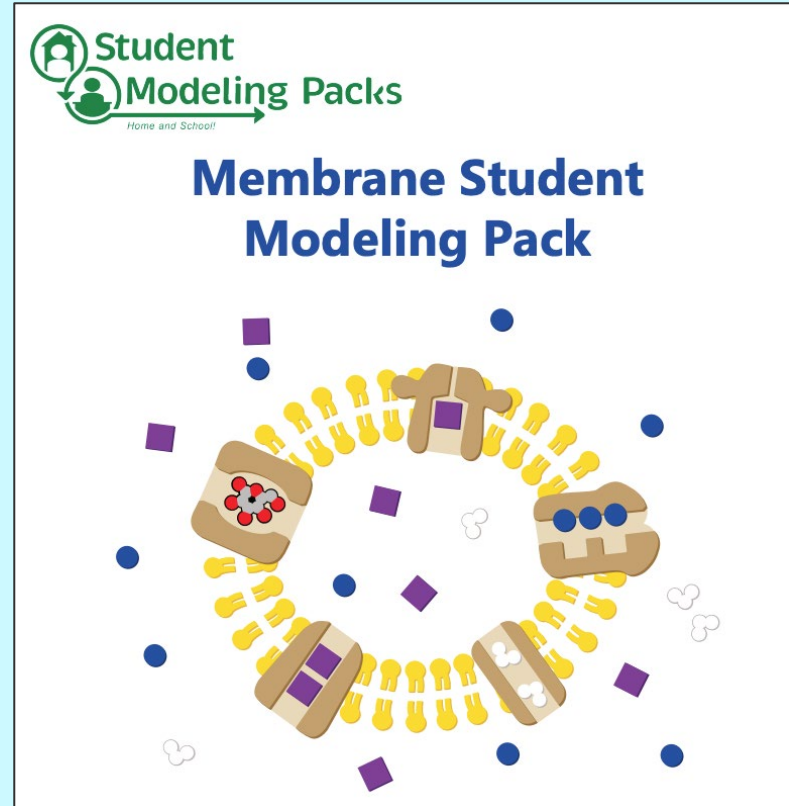
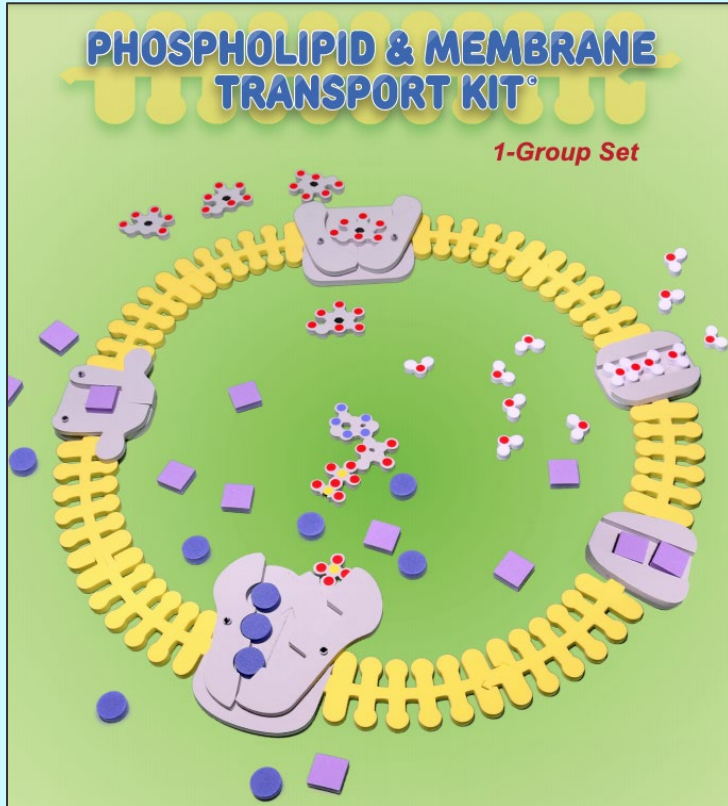


PDB ID: 6O2P



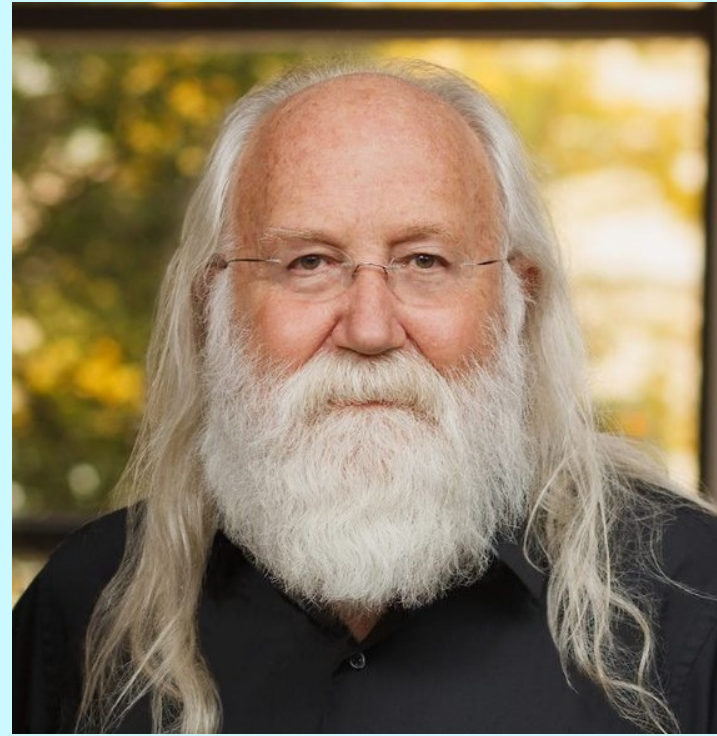
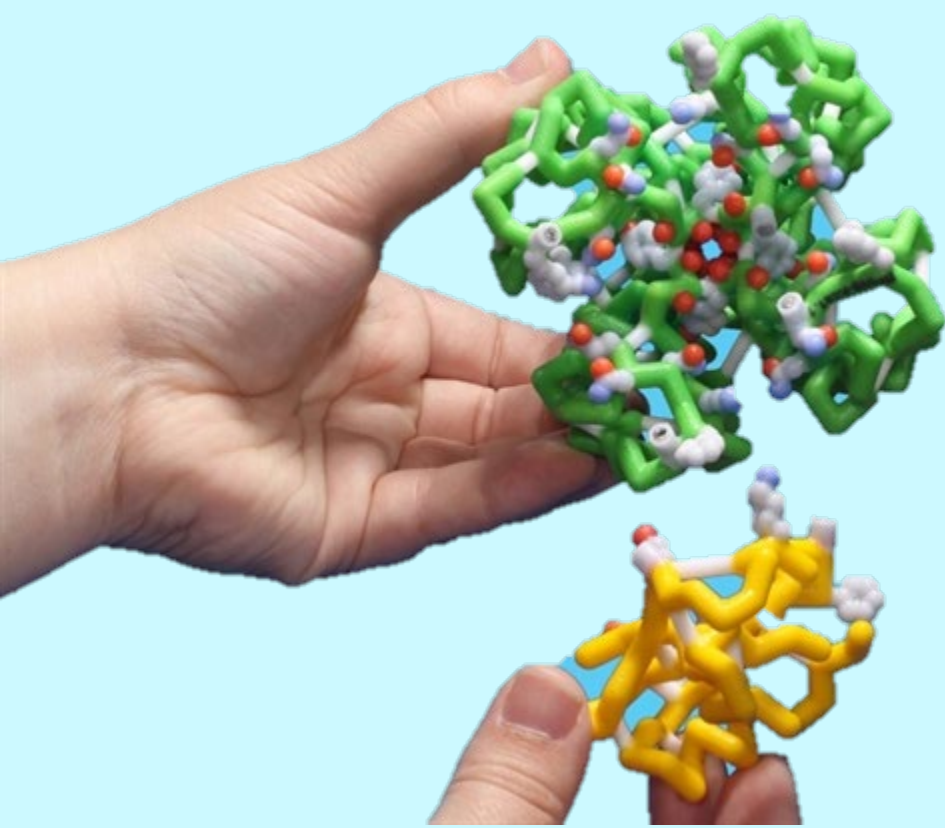
Ivacaftor (red) bound to CFTR protein

Classroom Kit vs. Student Modeling Pack





Questions?

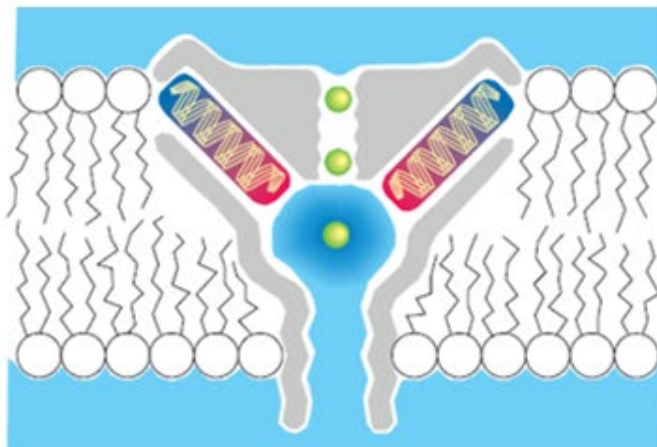


Potassium Channels & Scorpion Toxins

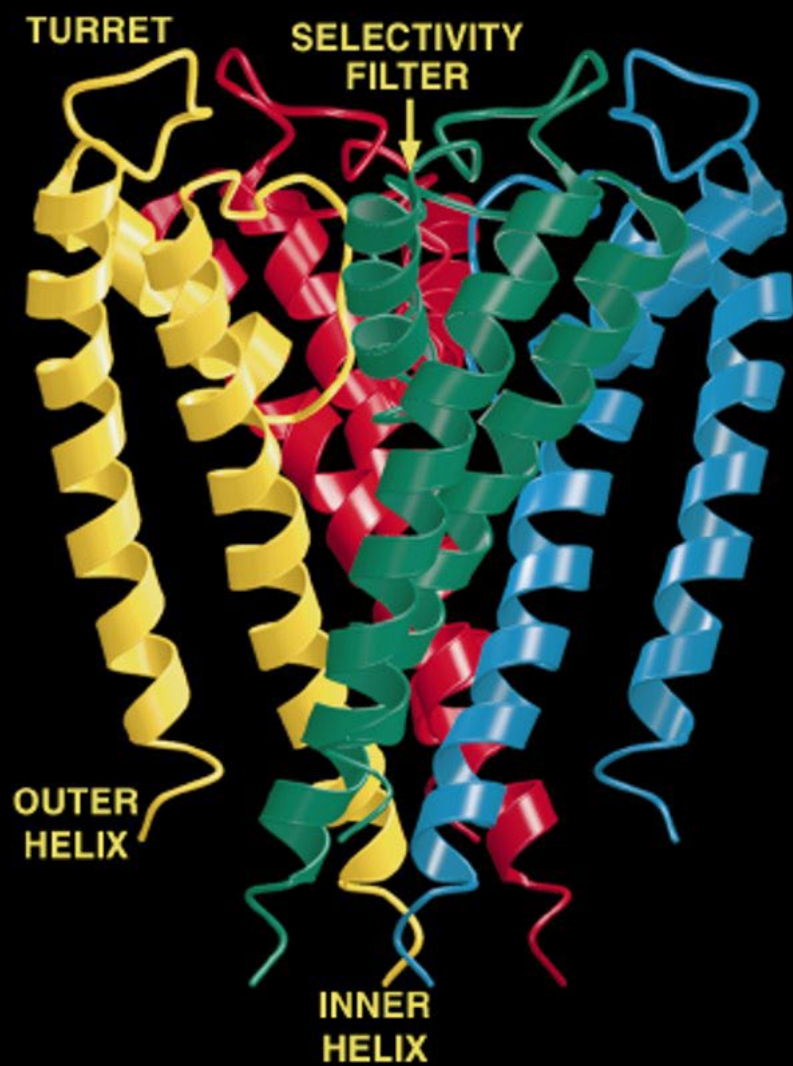
Channel: Molecular Basis of K^+ Conduction and Selectivity

Declan A. Doyle, João Morais Cabral, Richard A. Pfuetzner,
Anling Kuo, Jacqueline M. Culbis, Steven L. Cohen,
Brian T. Chait, **Roderick MacKinnon**

The potassium channel from *Streptomyces lividans* is an integral membrane protein with sequence similarity to all known K^+ channels, particularly in the pore region. X-ray analysis with data to 3.2 angstroms reveals that four identical subunits create an inverted teepee, or cone, cradling the selectivity filter of the pore in its outer end. The narrow selectivity filter is only 12 angstroms long, whereas the remainder of the pore is wider and lined with hydrophobic amino acids. A large water-filled cavity and helix dipoles are positioned so as to overcome electrostatic destabilization of an ion in the pore at the center of the bilayer. Main chain carbonyl oxygen atoms from the K^+ channel signature sequence line the selectivity filter, which is held open by structural constraints to coordinate K^+ ions but not smaller Na^+ ions. The selectivity filter contains two K^+ ions about 7.5 angstroms apart. This configuration promotes ion conduction by exploiting electrostatic repulsive forces to overcome attractive forces between K^+ ions and the selectivity filter. The architecture of the pore establishes the physical principles underlying selective K^+ conduction.



SCIENCE, VOL. 280 **3 APRIL 1998**



PORE
HELIX



PORE
HELIX



Thank you for attending!

For a Certificate of Participation

Click the link in the chat

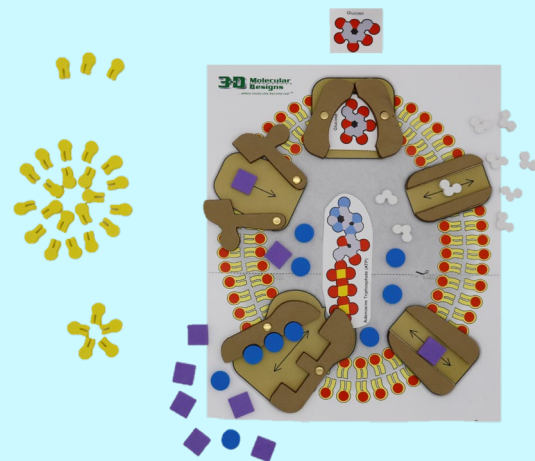
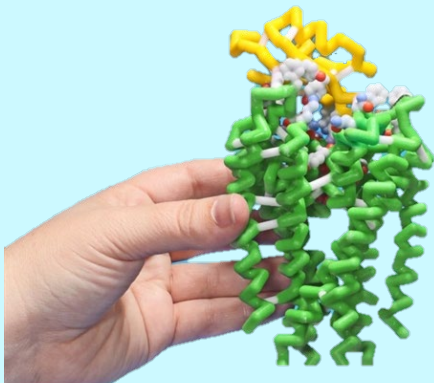
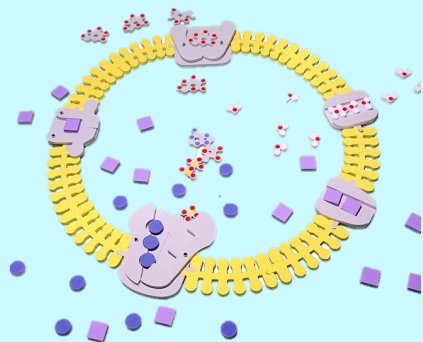
Purchase Kits and Models at
3dmoleculardesigns.com.

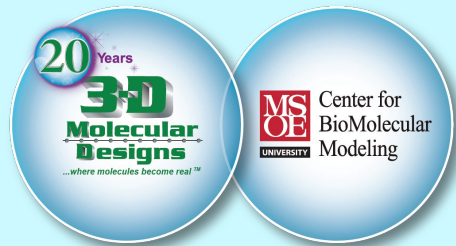
Discount code: **WEBINAR20**

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Contact us at: Ask3DMD@3DMoleculardesigns.com





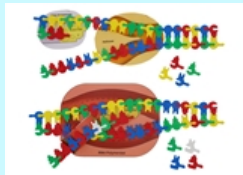
Invite your colleagues to register!



DNA Structure & Function

Inspiring Student Questions with a TWIST in DNA Modeling

Wednesday, April 21, 2021 at 6:00 PM Central



Biotechnology & Coronavirus

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