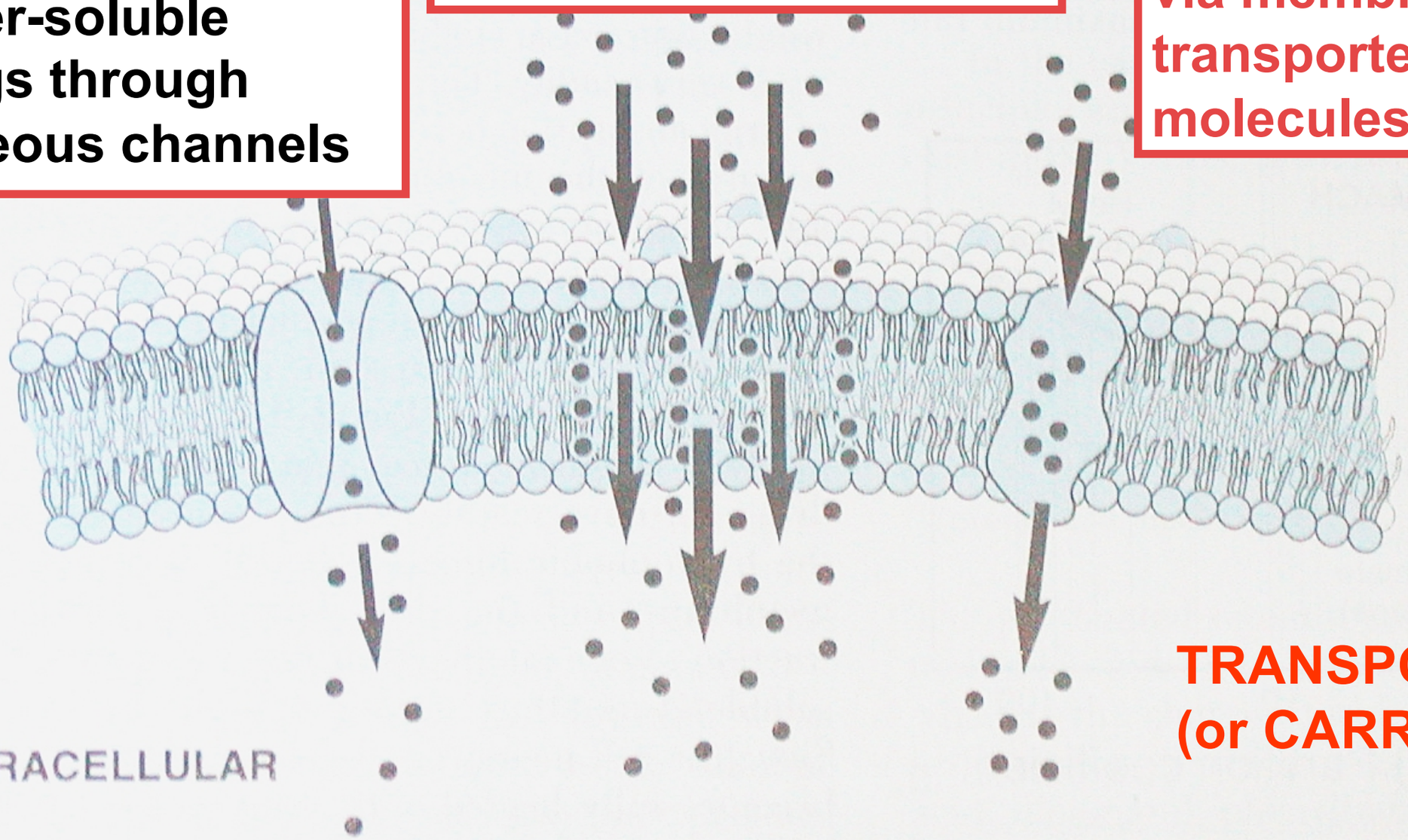
# Mechanisms of Absorption

**Passive diffusion of lipid-soluble drugs via hydrophobic bonding with membrane lipids**

**Active transport and facilitated diffusion via membrane transporters molecules**

EXTRACELLULAR

**Passive diffusion of water-soluble drugs through aqueous channels**

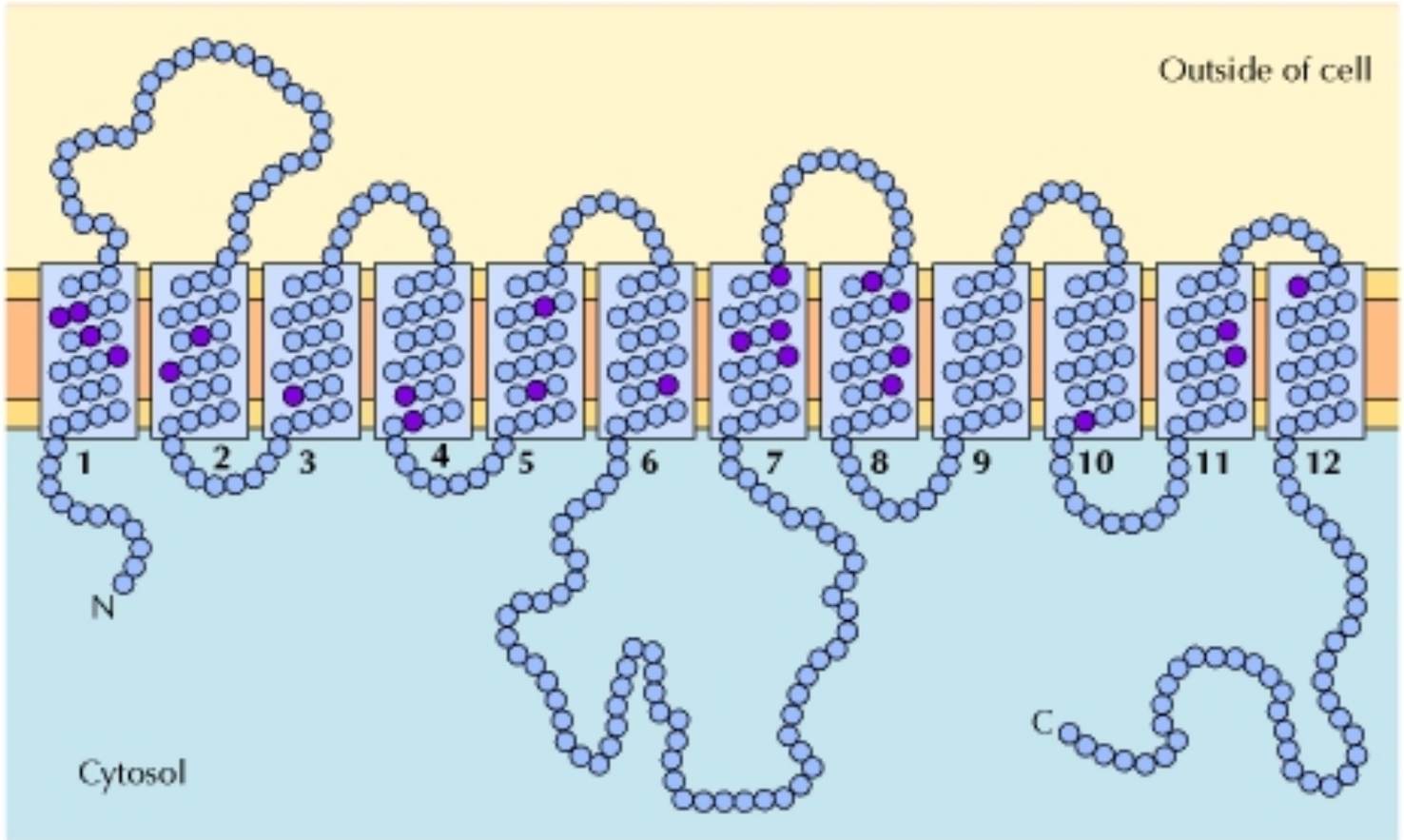


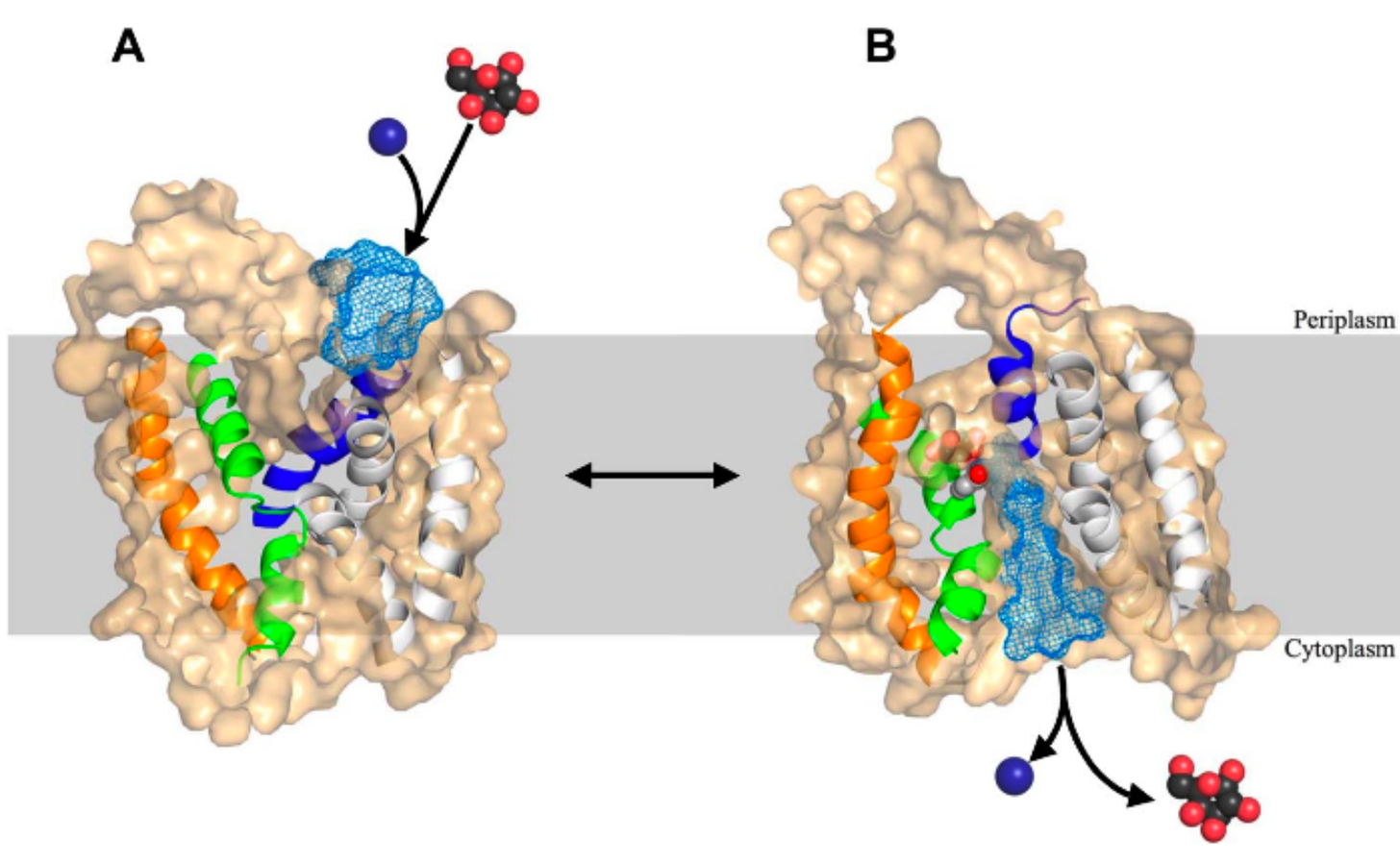
INTRACELLULAR

**TRANSPORTERS (or CARRIERS)**

# TRANSPORTERS

**A transporter is a transmembrane protein which binds stereoselectively one or more molecules or ions, undergoes to a conformation change and releases them on the other side of the membrane**



# TRANSPORTERS

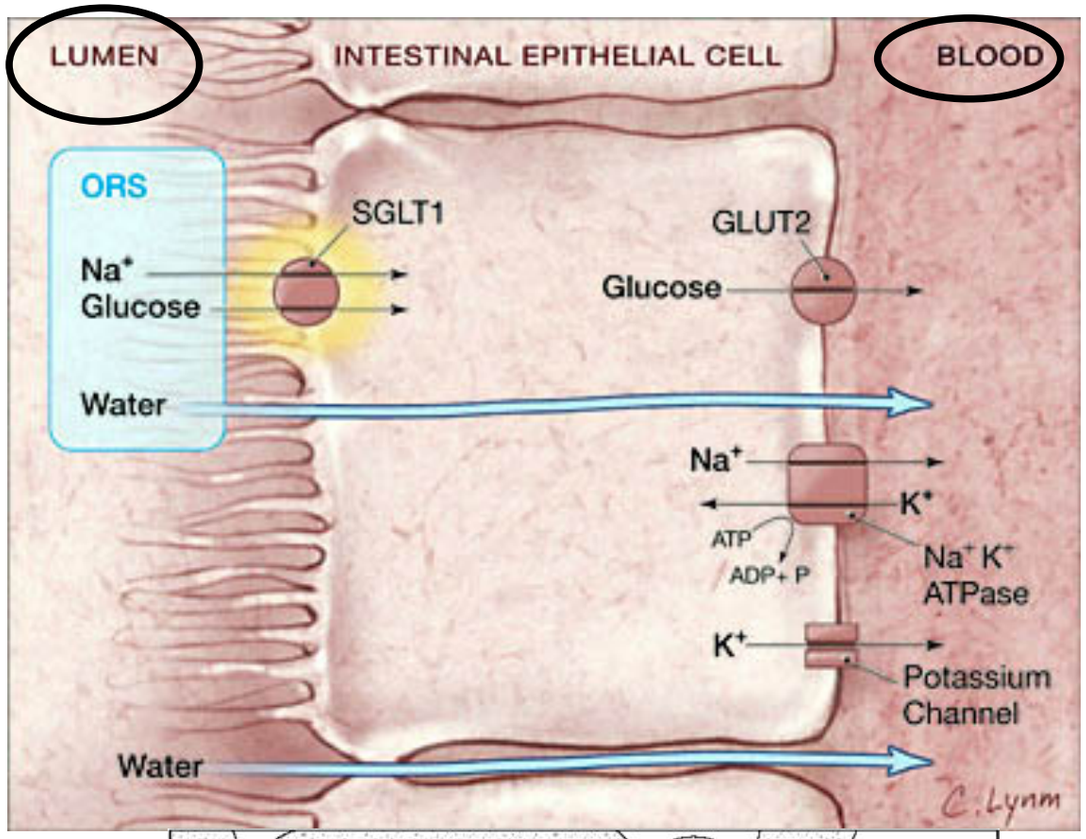
**Subcellular orientation:**

apical (luminal) o basolateral (abluminal)

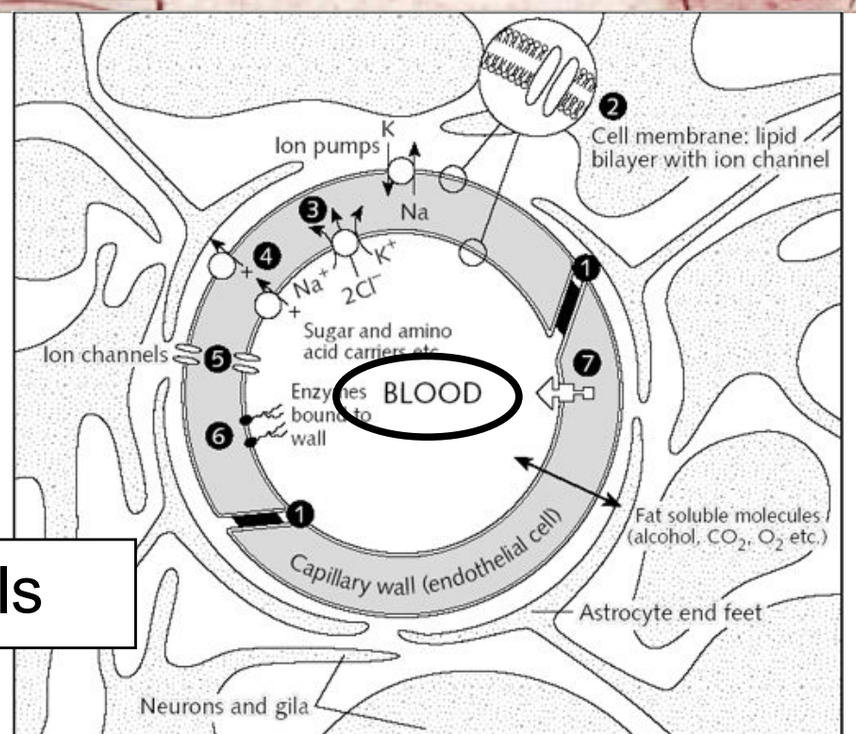
**Substrate direction:**

Uptake (into the cell) or efflux (outside the cell)

Epithelial cells (gut, kidney, lung)




Endothelial cells



# TRANSPORTERS

Facilitated diffusion

Electrochemical potential-driven transporters

SLC Superfamily
(Solute Carrier):
65 families
386 genes

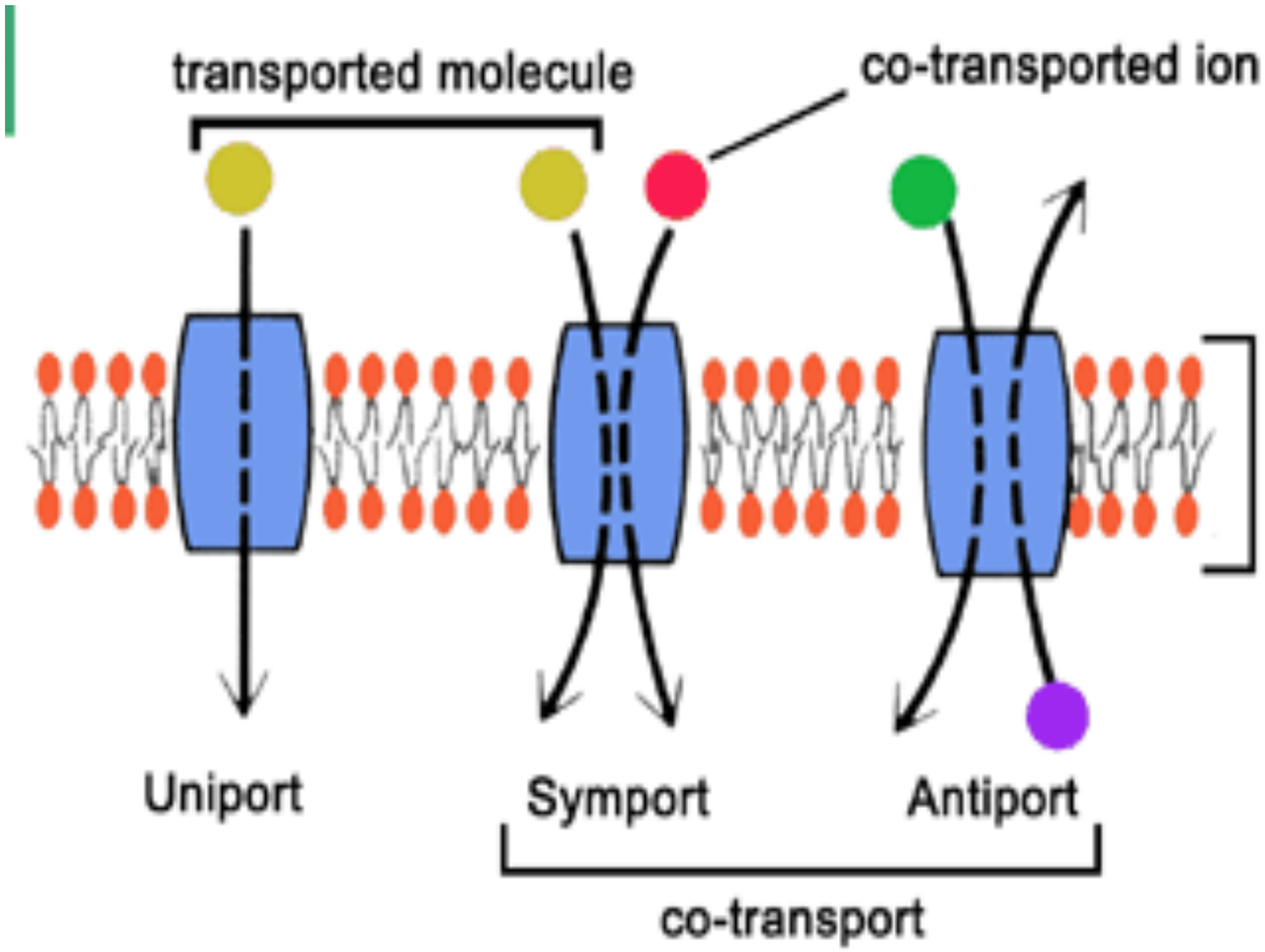
Active transport

Primary active transporters

ABC Superfamily
(ATP Binding Cassette):
8 families
49 genes

# Facilitated Diffusion

**Carrier molecules facilitate entry and exit of physiologically important polar and charged molecules, such as sugars, amino acids, neurotransmitters and metal**




- **No external energy source is needed**
- **Down concentration/electro chemical gradient**
- **Transport is saturable (is mediated by a limited number of proteins) and selective**

# Facilitated Diffusion

Neurotransmitter Transporters Family:

Sodium NT T (SLC6A1-20)
DAT – NET - 5-HTT
GLUT (SLC1A1-7)

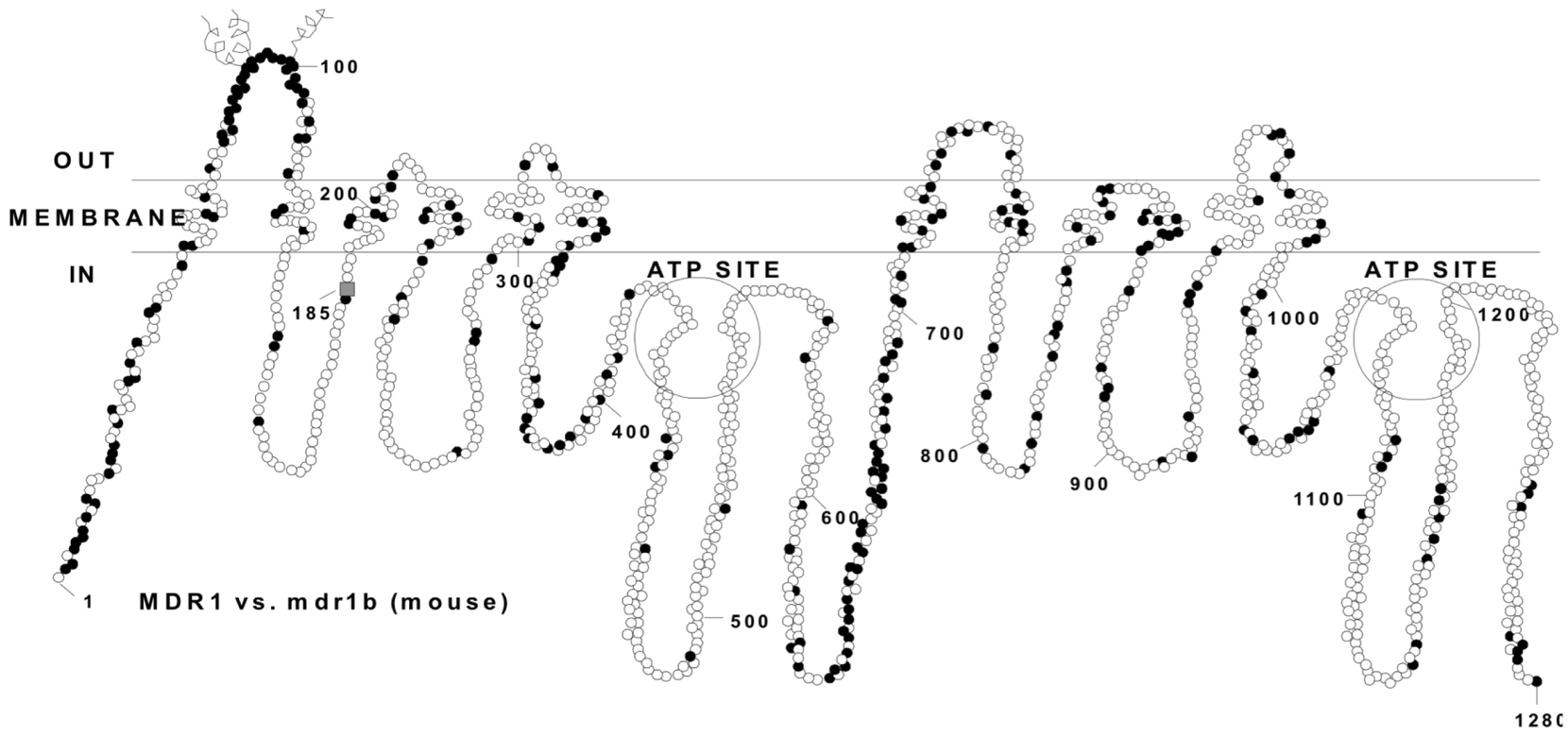
Major Facilitator Superfamily

**ORGANIC CATION TRANSPORTER - OCT**

**ORGANIC ANION TRANSPORTERS – OAT**

# Active Transport

- **Directly coupled to energy source (ATPase)**
- **Against concentration gradient**
- **Transport is saturable (is mediated by a limited number of proteins) and selective**



# Active Transport

P-ATPase Superfamily

SERCA

ATP Binding Cassette (ABC) Superfamily

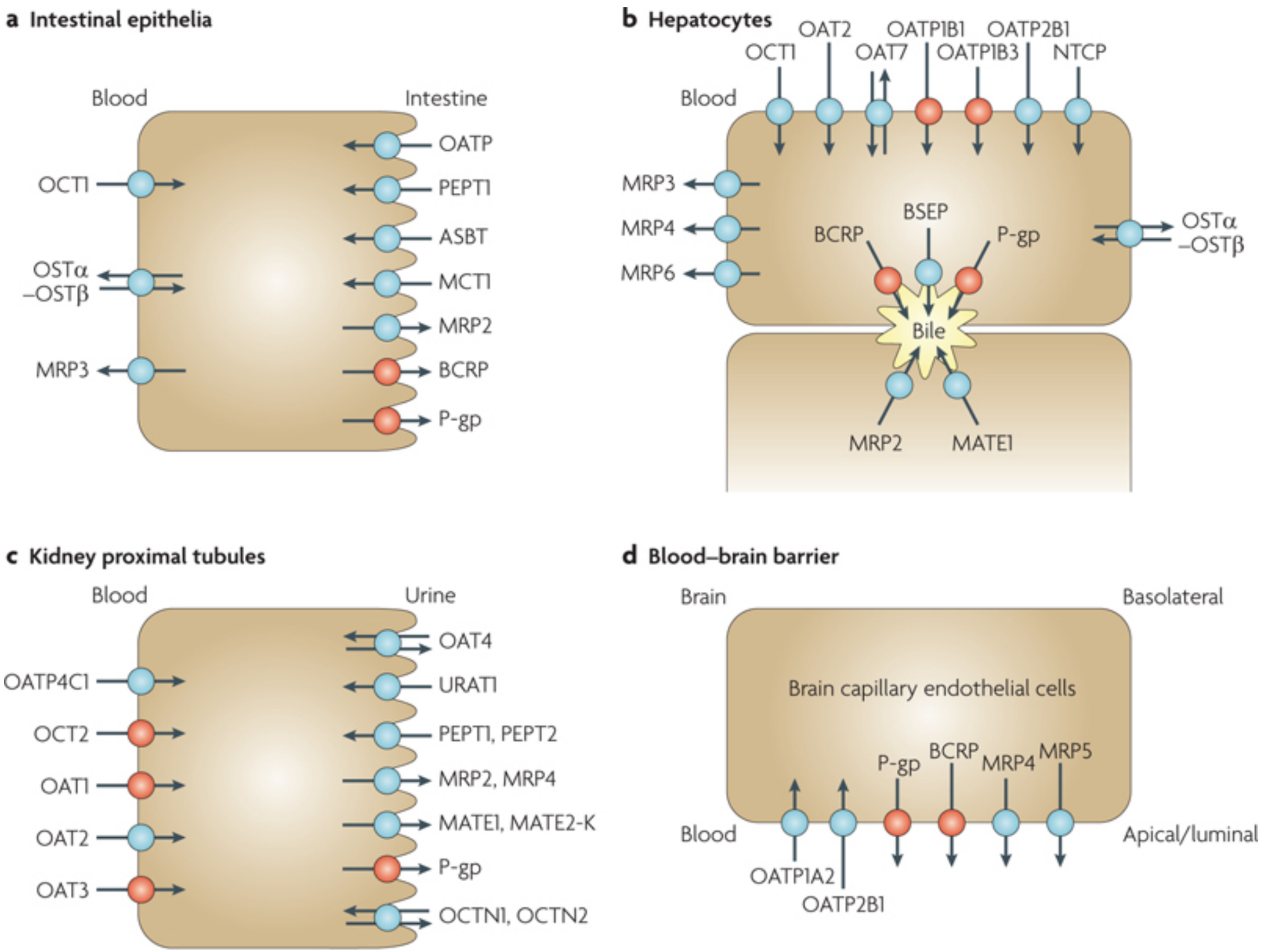
- **Large gene family**
- **Defined by sequence homology**
- **Critical for moving a wide range of substances**
- **Approximately 1000 ABC proteins have been identified, 49 in humans**

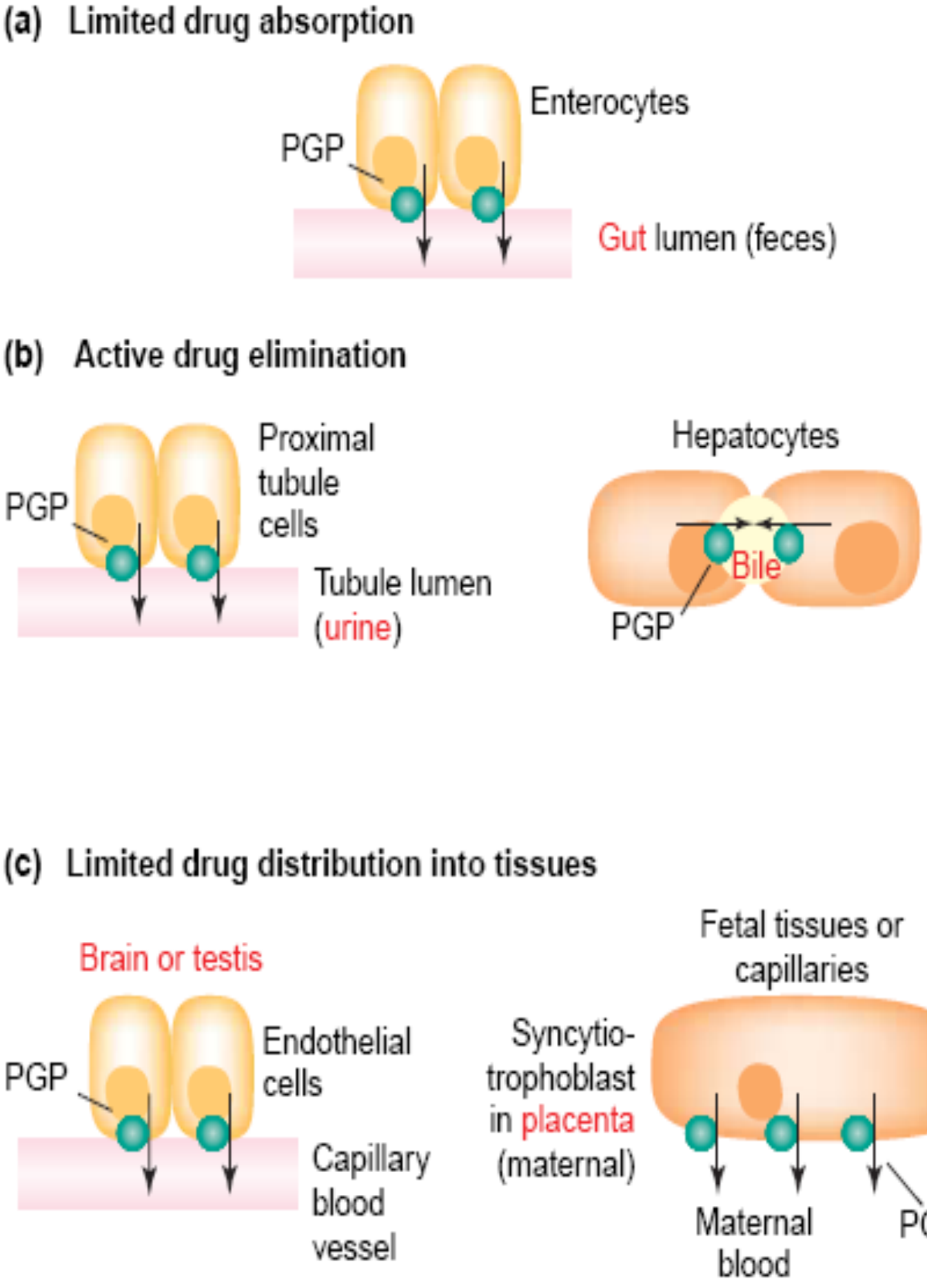
**MDR (Multi Drug Resistance) family**
**e.g. P-glycoprotein**

# P-glycoprotein

- **Encoded by the MDR1 gene, is an efflux pump responsible for the resistance of tumor cells to multiple chemotherapeutic agents**
- **Expressed on the apical membrane of epithelial cells in the intestine, liver, kidney, testes, blood-brain barrier and adrenals**
- **Plays a role in the absorption, distribution and elimination of numerous drugs**

# TRANSPORTERS LOCALIZATION

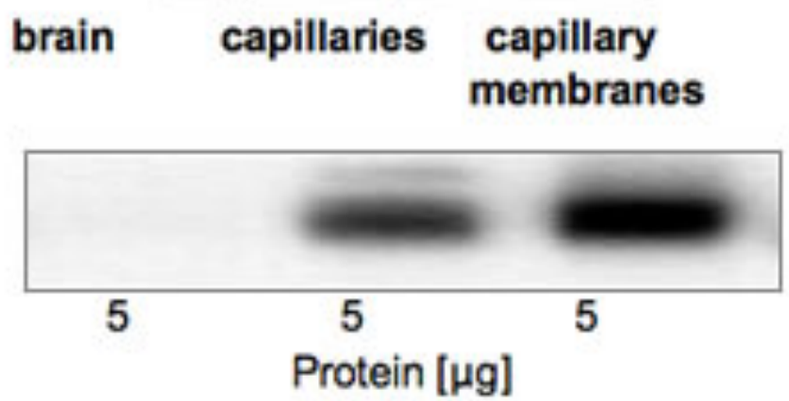




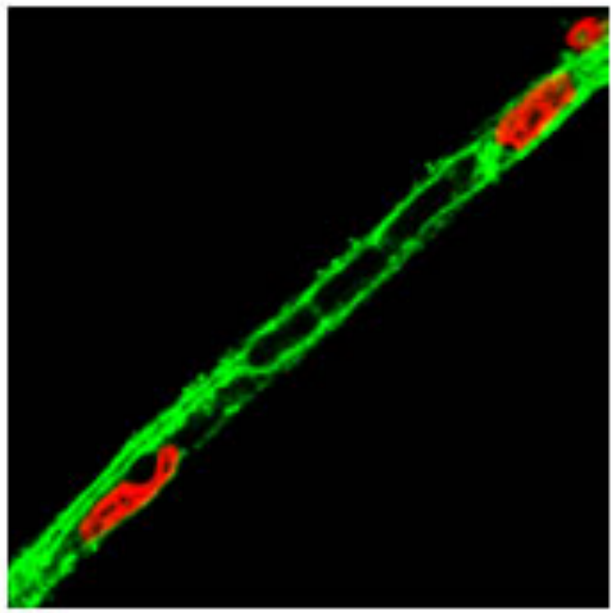

# How P-glycoproteins expression affects ADME

# Why is p-Glycoprotein the 800-lb Gorilla of the Blood-Brain Barrier?

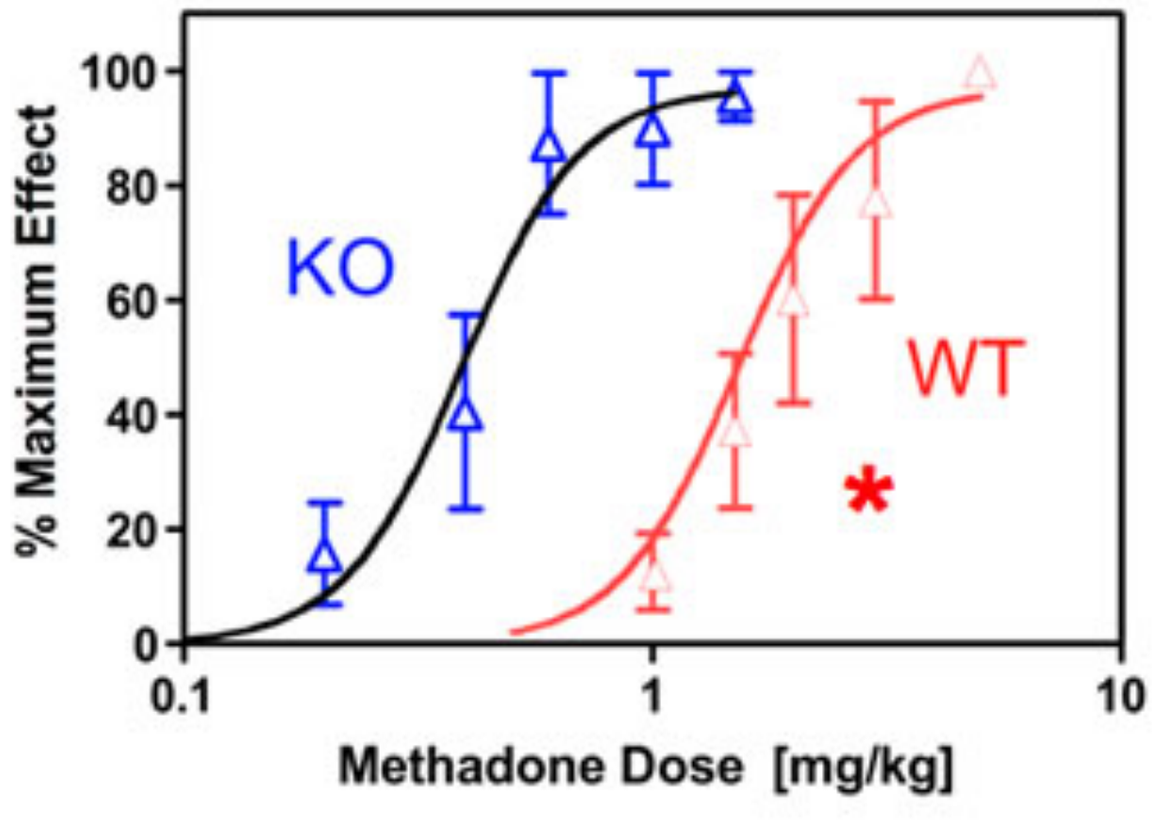
## High Expression



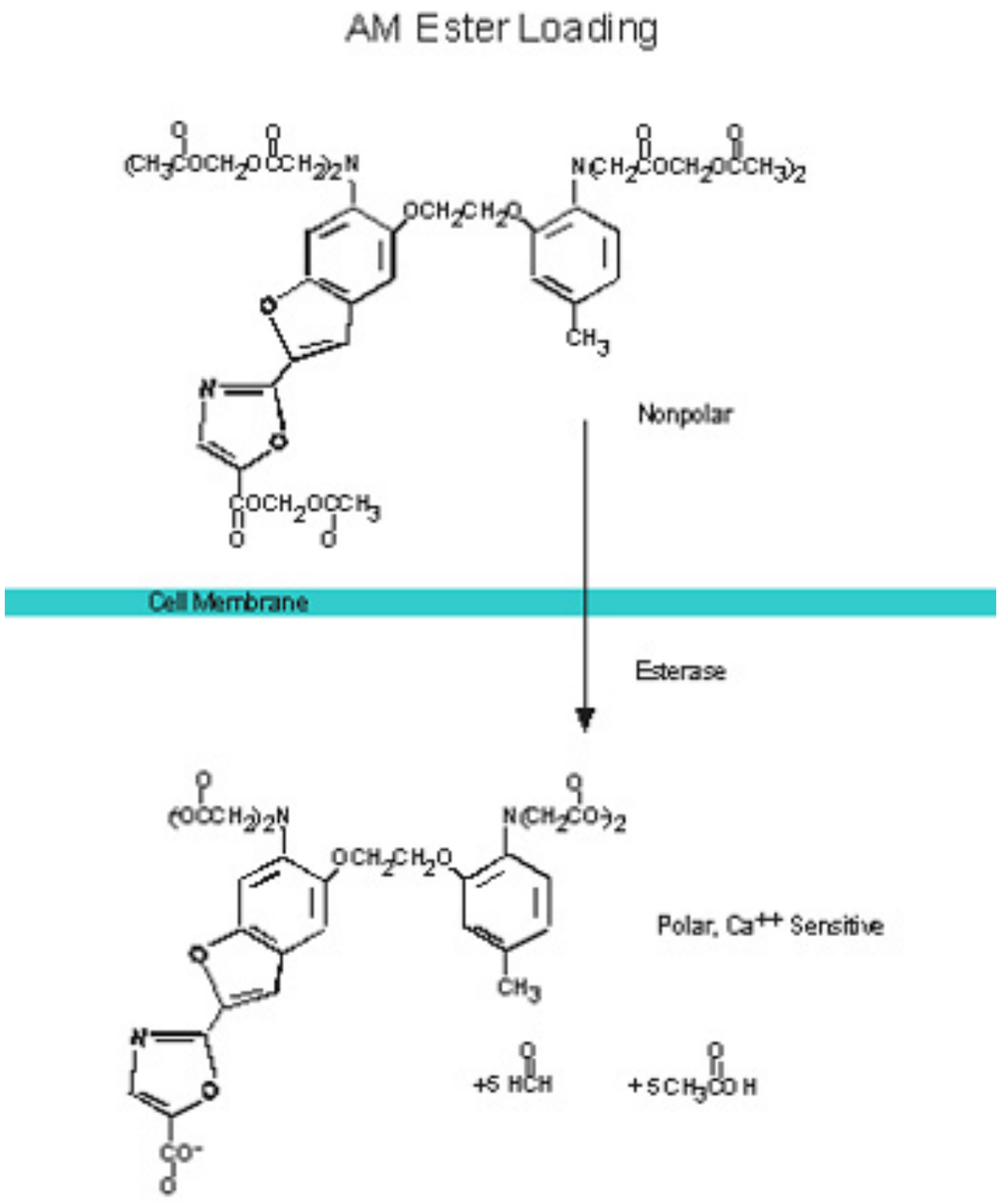

## Right Location



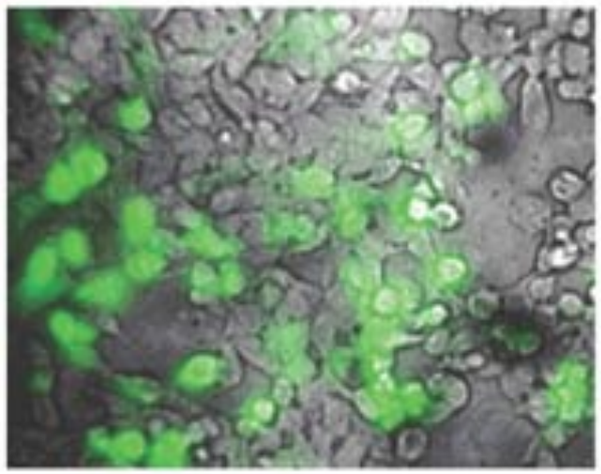
KO for p-Gp



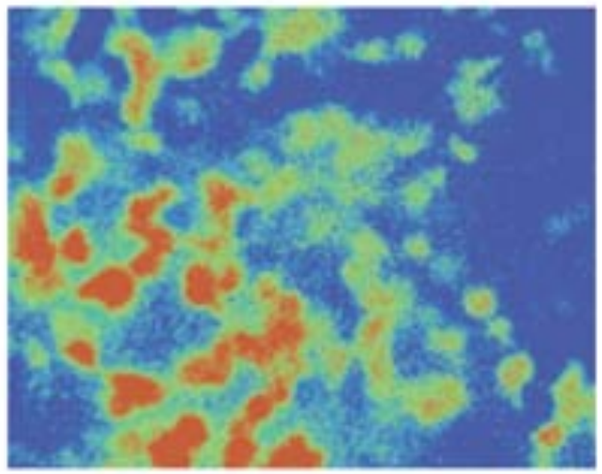
# Fura-2



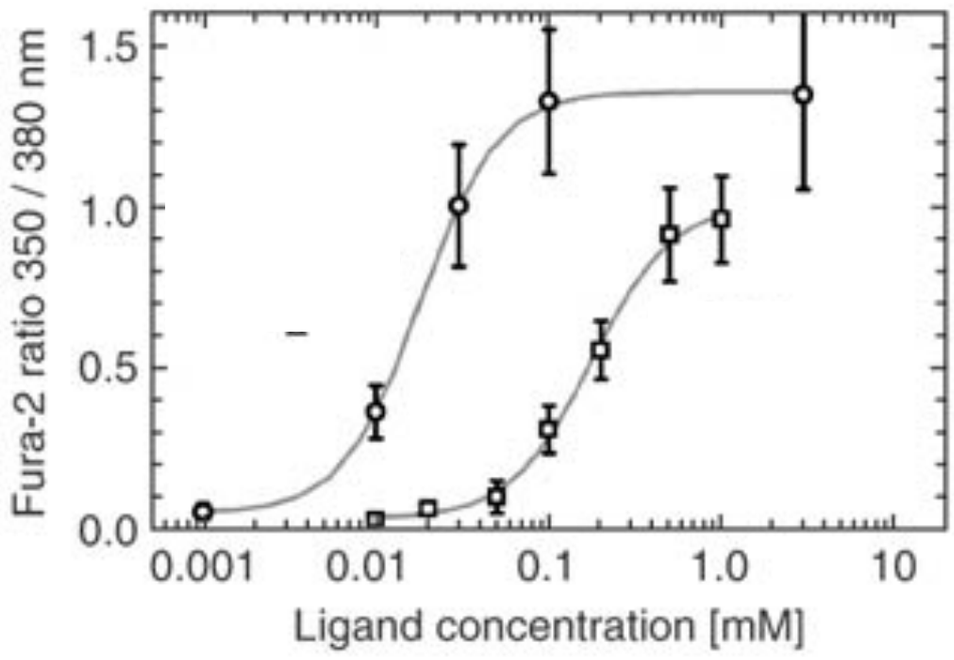

a no p-gp blocker (square)



b plus p-gp blocker (circle)



d



# Vesicle-mediated transport