P-gp (P-glycoprotein) active transporter

Dr. Shashi Kiran Misra
Assistant professor
School of Pharamaceutical Sciences

P-glycoproteins

- belonging to the super family of adenosine triphosphate (ATP)-binding cassette (ABC) transporters.

❖ ABC efflux transporters in cancer cells such as :

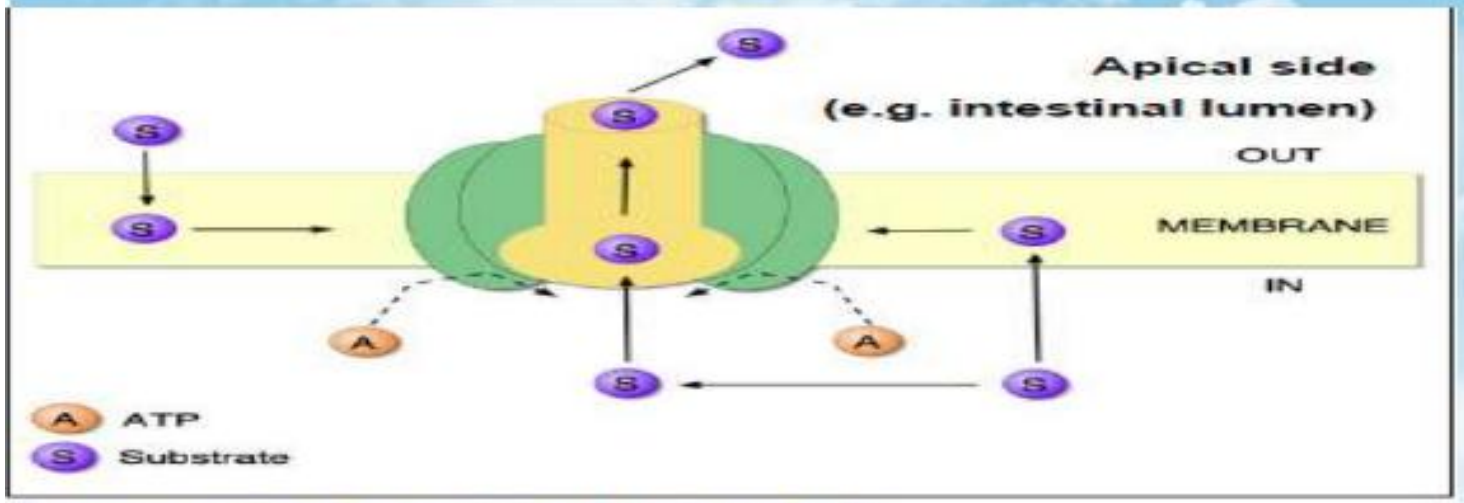
- P-glycoprotein (P-gp/MDR1/ABCB1)
- multidrug resistance-associated protein 2 (MRP2/ABCC2)
- breast cancer resistance protein (BCRP/ABCG2)

limits the prolonged and effective use of chemotherapeutic drugs .

- P-gp is the most importent efflux transporter in the body.

Structure of transporters

- P-Gp is an integral membrane protein, about 170–180 kDa encoded by the MDR1 gene in humans and contains 12 putative transmembrane domains and two ATP binding sites.



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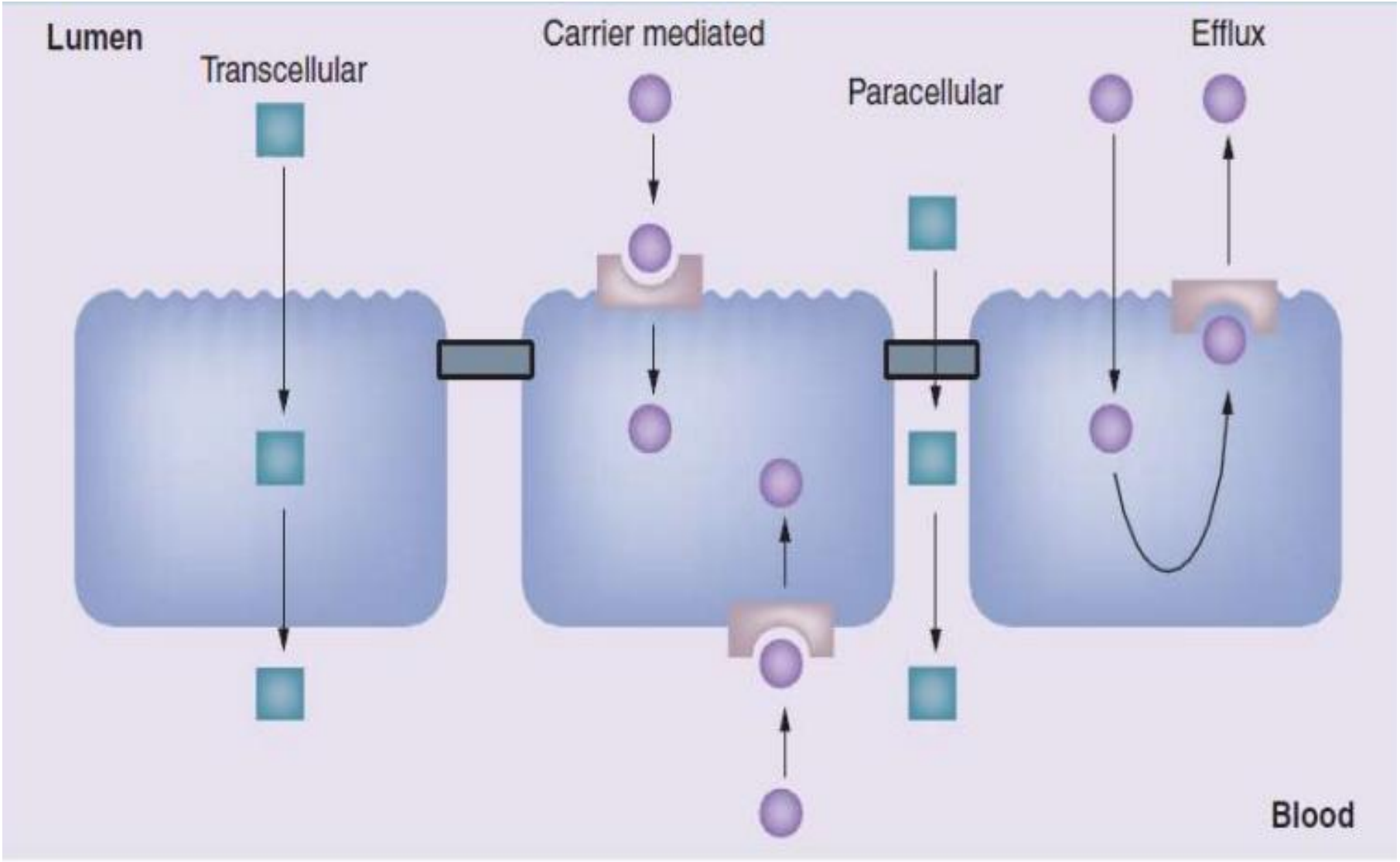


Figure 1. Passive (transcellular and paracellular) and active (carrier-mediated uptake, efflux) mechanisms of drug absorption across the intestinal epithelium. The outlined bars represent the tight junctions between the cells.

Site of transportation	Function
Liver – Bile	Elimination
Kidney - Urine	Excretion
Placenta – Maternal blood	Protect fetal from drug exposure
Intestine – Intestinal lumen	Reduce drug absorption into the blood
Brain – Blood	Monitor drug access to the brain

Necessity of p-glycoproteins

- responsible for pumping substances out of cells
- Lypophilic substances are the substrates of efflux system .
- P-gp is an apical membrane transporter that is abundantly expressed on the intestine mucosal membrane, kidney proximal tubule epithelia, liver,placenta, and luminal blood–brain barrier, where it functions to protect against xenobiotics and cellular toxicants.

Substrate specificity of P-glycoprotein and nature of the drug-binding site

- Most preferred substrates are amphipathic and relatively hydrophobic.

- Many substrates, but not all, contain planar aromatic rings and positively-charged tertiary N atoms.

Substrates of p-glycoproteins

- Neutral or cationic compounds form the substrates
- **Anticancer drugs**: Actinomycin, cyclosporine-A, cisplatin,
- **Cardiovascular drugs**: Atorvastatin, lovastatin, digitoxin, losartan,
- **Antiviral drugs**: amprenavir, indinavir, saquinavir, nelfinavir, and ritonavir
- **Antibacterial agents**: erythromycin, rifampin, sparfloxacin, levofloxacin
- **GIT drugs**: Cimetidine,domperidone, loperamide and ondansetron

Mechanism of p-glycoprotein

- The efflux action of the protein follows a carrier mediated primary active transport mechanism.

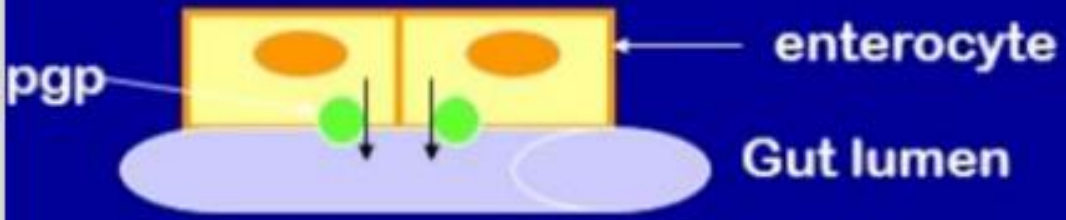
- In this process, the protein pump export needs direct ATP requirement and the energy released from the ATP hydrolysis gives the driving force for extrusion process.

- The efflux takes place unidirectionally (out of the cells into the extracellular space) and transfers only one molecule at a time. Thus, P-gp is a uniporter carrier protein.

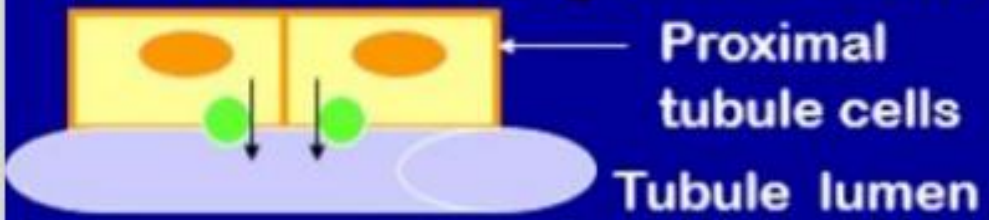
Consequence of the Efflux Transporter P-glycoprotein

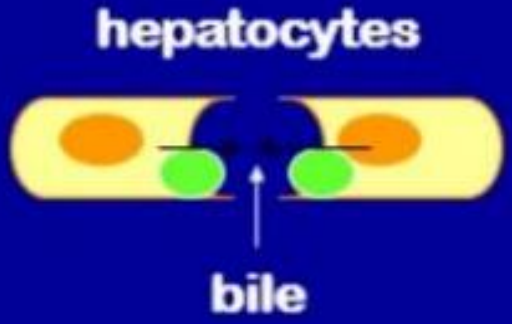
Adapted from: Fromm MF. *Trends in Pharmacol Sci* 25:423, 2004

1) Limited drug absorption

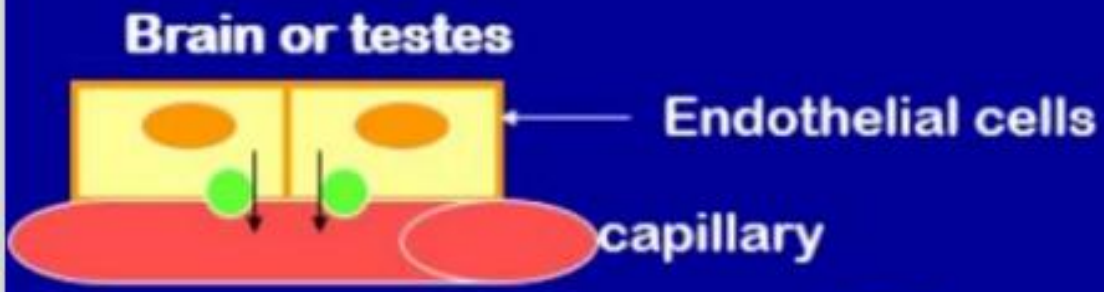


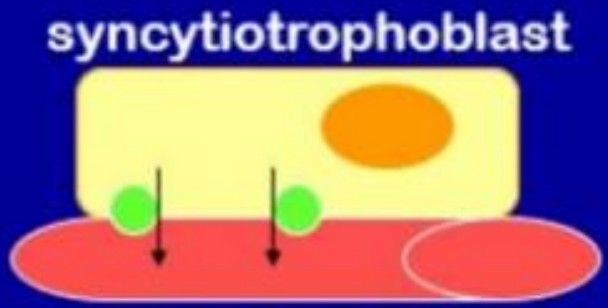
2) Enhanced drug elimination





3) Limited distribution



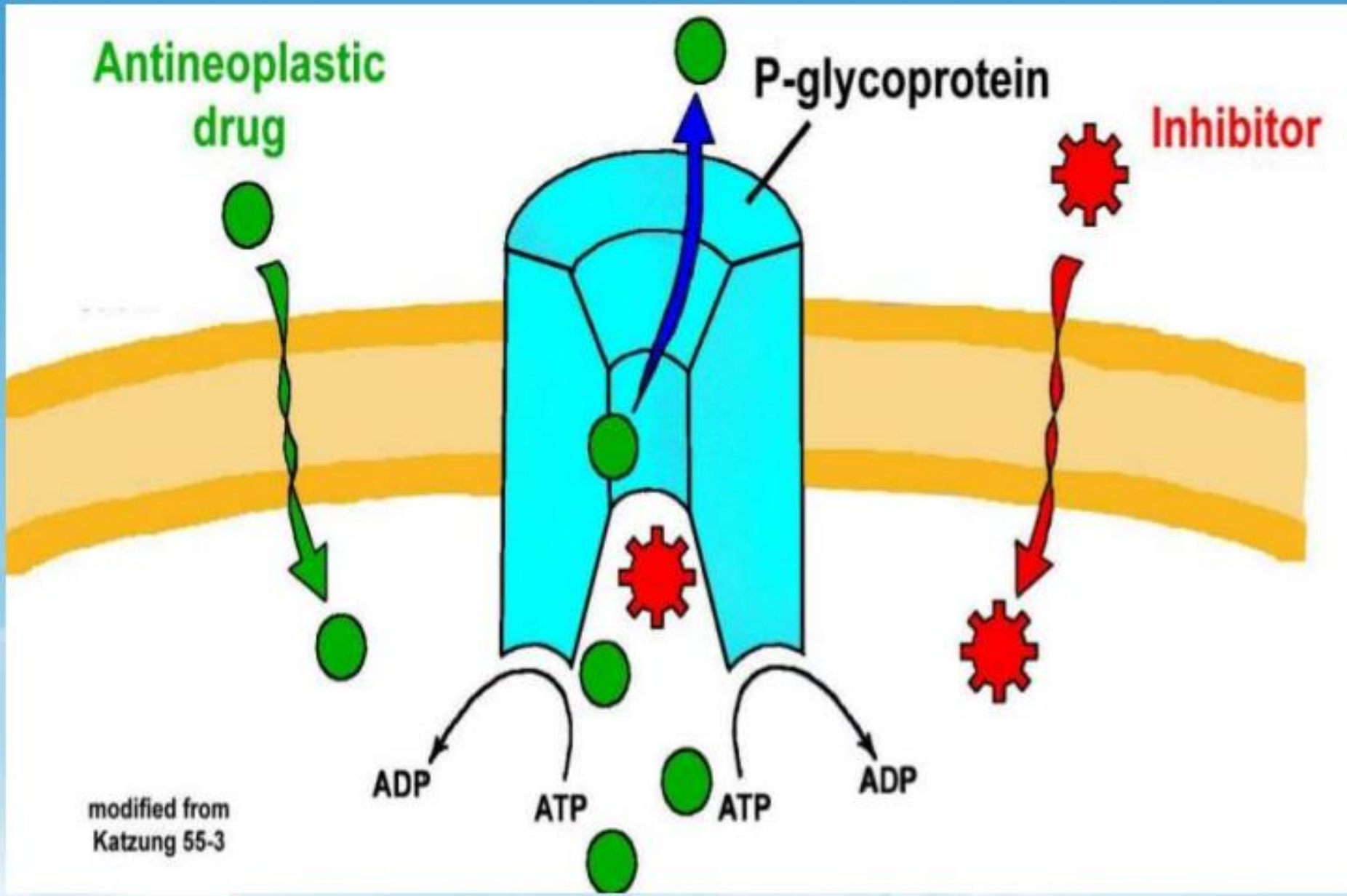


inhibitors

- P-gp inhibitors were explored for overcoming multidrug resistance and poor bioavailability problems of the therapeutic P-gp substrates .

- competitive and non-competitive (non-transported) inhibitors apart from the P-gp efflux kinetics .

- competitive inhibitors compete with the substrate drugs for extrusion and occupy all the available protein transport sites leaving no space for the P-gp and substrate interaction.


Antineoplastic drug
P-glycoprotein
Inhibitor
ADP
ATP
ATP
ADP
modified from Katzung 55-3