• Genetic polymorphism in drug transport:

• P-glycoprotein is an ATP-dependent efflux pump that contributes to the protection of the body from environment toxins, p-glycoprotein is involved in limiting absorption of xenobiotics from the gut lumen in protection of sensitive tissues (brain) and in biliary and urinary excretion of its substrates.

• P-glycoprotein can be inhibited or induced by xenobiotics, thereby contributing to variable drug disposition and drug interactions. Recently several SNPs (Single nucleotide polymorphism) have been identified in the MDR1 gene, some of which can affect p-glycoprotein expression and function.

• Transporter pharmacogenetics is concerned with drug uptake and efflux into or through tissues Significant problems in the clinical application of drugs result from poor or variable oral drug

bioavailability, and high intra and interindividual variation in pharmacokinetics. Several membrane transporter proteins are involved in the absorption of drugs from the intestinal tract into the body, into nonintestinal tissues, or into specific target sites of action.

. Drug efflux is an important cause of drug resistance in certain types of cells.

In cytotoxic chemotherapy for several human cancerous diseases, drugs are generally very effective, but in case of intrinsic or acquired multidrug resistance, usually highly effective antineoplastic compounds eg: Vincristine, Vinblastine fail to produce cures.

. One of the major causes of such multidrug resistance is the appearance of special integral membrane proteins the P-glycoprotein

multidrug transporter or MDR1 which is one of the major causes of low drug level in targeted cells.

- The multidrug resistance-associated proteins (MRPs) are members of the ATP-binding cassette (ABC) superfamily with six members currently of which MRP1, MRP2, MRP3 are commonly known to affect drug disposition.

- Genetic polymorphism in drug targets:

In the future, proteins involved in disease will become identified as important biomarkers for pharmacodynamic studies. Proteins can be used as probe for drug discovery or as biomarker for drug safety such as cell surface protein (eg: cox-2, D-2R), intracellular proteins (eg: troponin I) and secreted proteins.

- The physiologic response of the body to a drug is generally the result of interaction of the drug at a specific target site in the body.
- Many of genes encoding these target proteins exhibit polymorphisms that may alter drug response.
- For example the B-2 adrenergic receptor and its common mutation of Arg, Gly at amino acid 16 greatly reduces the bronchodilator response of albuterol.
- The response to clonazepine in patients with schizophrenia appears to involve genetic polymorphisms in the 5-hydroxytryptamine (serotonin) receptor, HTR2A finally, mutations in five genes involved in the cardiac ion channels affect the risk of drug-induced long QT syndrome, a potential cause of sudden

cardiac death in young individuals without structural heart disease

Clinically important genetic polymorphism of drug targets and drug transporters:

Gene	frequency	Drug	Drug effect
MDR1	24%	Digoxin	Incre conc
2AR$_{16}$-Gly	37%	Albuterol	Dec response
SUR1	2-3%	Tolbutamide	Dec insulin response
Five genes coding	1-2%	Antiarrythmatics	Sudden cardiac death

- Pharmacogenetics enable clinicians to make reliable assessments of an individual's risk of acquiring a particular disease be more specific in targeting drugs, and account for individual variation of therapeutic response and toxicity of drugs.
- Genomics is providing the information and technology needed to analayse the complex multifactorial situations involved in drug therapy.

P-glycoprotein and its role in drug-drug interactions

- Efflux transporters such as P-glycoprotein play an important role in drug transport in many organs. In the gut, P-glycoprotein pumps drugs back into the lumen, decreasing their absorption.
- Drugs which induce P-glycoprotein, such as rifampicin, can reduce the bioavailability of some other drugs. Inhibitors of p-glycoprotein, such as verapamil, increase the bioavailability of susceptible drugs.
- Many, but not all, of the drugs which are transported by P-glycoprotein are also metabolised by cytochrome P4503A4.
- Important substrates of P-glycoprotein include calcium channel blockers, cyclosporine, digoxin etc. Predicting clinically important interactions is difficult because of interindividual differences in drug transport.

• Introduction:

P-glycoprotein is one of the drug transporters that determine the uptake and efflux of a range of drugs. This process affects their plasma and tissue concentrations and ultimately their final effects. P-glycoprotein functions as a transmembrane efflux pump, pumping its substrates from inside to outside the cell. Drugs which induce or inhibit P-glycoprotein can interact with other drugs handled by the pump.

Pharmacology

• P-glycoprotein was first described in tumour cells. These cells had over-expression of P-glycoprotein which reduced the access of cytotoxic drugs. As this made the tumours resistant to various anticancer drugs, P-gp

was also known as multidrug resistance protein 1. P-glycoprotein is also expressed in a variety of normal, non-tumorous tissues with excretory functions (small intestine, liver and kidney) and at blood-tissue barriers (BBB, blood-testis barrier and placental).

- Along with the cytochrome P-450 (CYP) family of enzymes, concomitant expression of P-glycoprotein is believed to be an important evolutionary adaptation against potentially toxic substances. As an efflux transporter it limits the bioavailability of orally administered drugs by pumping them back into the lumen. This promotes drug elimination into the bile and urine and protects a number of tissues such as the brain, testis, placenta and lymphocytes. The substrates for P-glycoprotein are a broad variety of

structurally diverse compounds.

Drug absorption:

- The epithelial cell lining of the small intestine is not just a site for drug absorption, but also an important barrier to the absorption of xenobiotics. P-glycoprotein is found in the apical (luminal) membrane of the entire intestine from duodenum to rectum, with a high expression in the enterocytes of the small intestine. It reduces the oral availability of drugs that are its substrates.
- Like the enzymes involved in drug metabolism, substrates of P-glycoprotein can potentially act as inhibitors or inducers of its function. Inhibition of P-glycoprotein can result in increased bioavailability of the susceptible

drug. Induction of P-glycoprotein reduces the bioavailability.

- Drug elimination:

P-glycoprotein has a modest role in drug elimination. It is expressed in the luminal membrane of proximal tubule cells in the kidneys. P-glycoprotein pumps drugs into the urine.

Drug distribution:

Once a drug has reached the systemic circulation, P-glycoprotein further limits penetration into a number of sensitive tissues. P-glycoprotein is also important for the blood-brain barrier as a defence against the penetration of toxins and drugs into the CNS.

∘Drug interactions:

P-glycoprotein is an important mediator of drug -drug interactions. The pharmacokinetics of a drug may be altered when co-administered with compounds which inhibitor or induce P-glycoprotein.

∘ Inhibitors include clarithromycin, erythromycin, ritonavir and verapamil.

∘ Inducers include rifampicin.

∘ It is involved in the transport of drugs from different drug classes including:

→ antineoplastic drugs eg: Vincristine

→ Calcium channel blockers e.g: Amlodipine

→ Macrolide antibiotics eg Clarithromycin

Conclusion:

P-glycoprotein is an efflux transporter pump

present in many organs and plays an important role in drug transport.

Expression of P-glycoprotein can have important effects on drug absorption, distribution and elimination. Although interactions with drug transporters can be clinically insignificant, an awareness of potential transporter-related drug-drug interactions is important. CNS depression, undertreated HIV infection and transplant rejection can help ensure the provision of safe and effective treatment.