DRUG TRANSPORTERS AND DRUG INTERACTIONS

Issam Hamadeh, PharmD, BCOP

09/15/2026

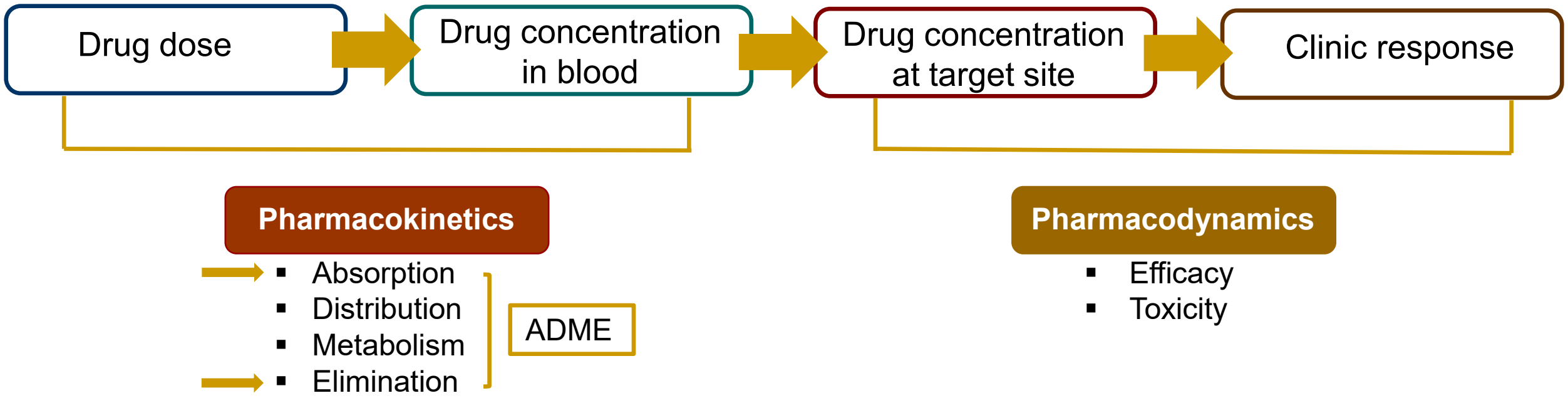


OBJECTIVES

- Describe the types of drug transporters, their function and role in drug disposition.
- Define substrates, inducers and inhibitors of drug transporters as well as the clinical implications of drug-transporter interactions.
- Understand the impact of genetic polymorphisms in drug-transporters on response to therapy.

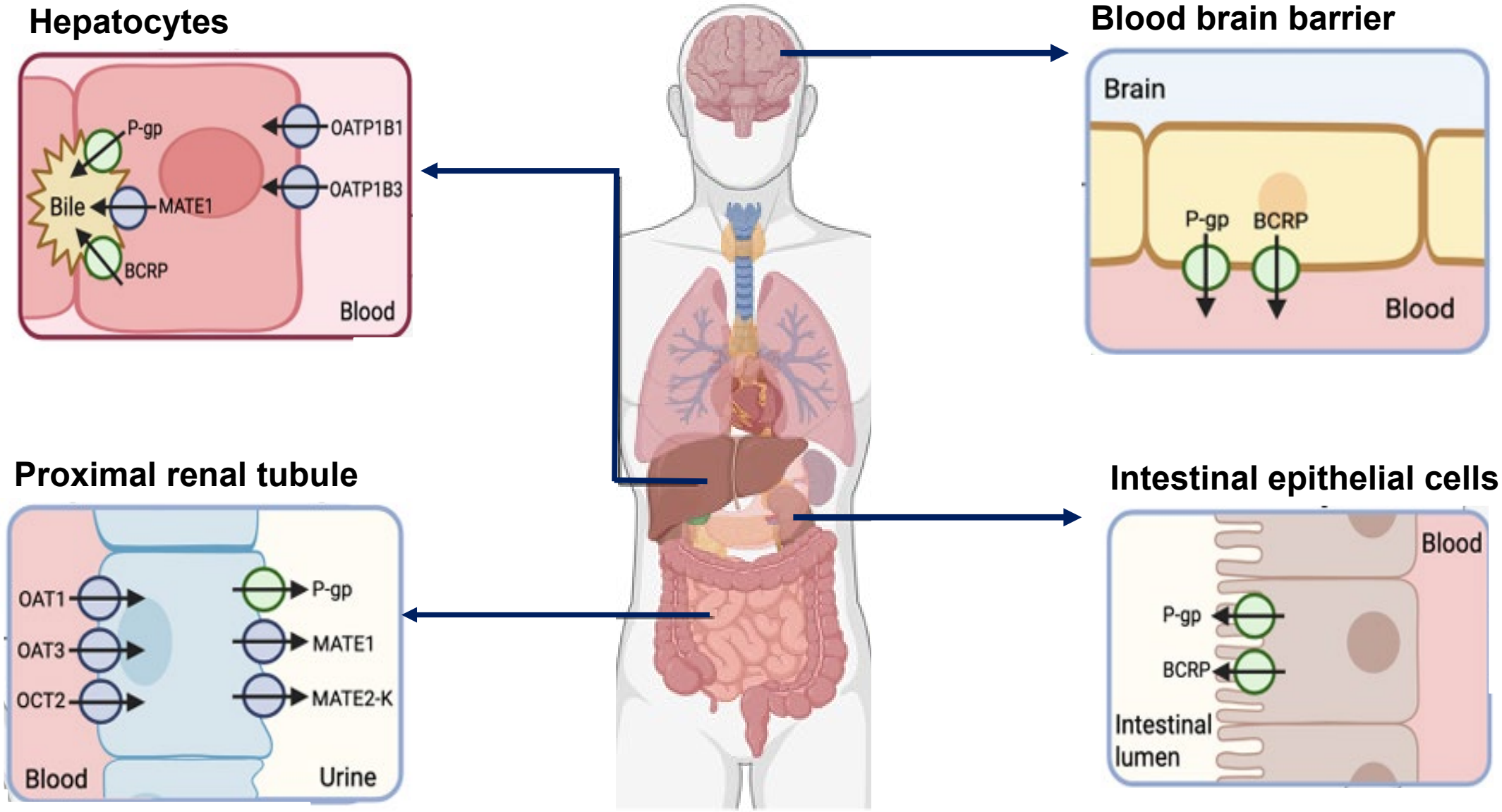


RELATIONSHIP BETWEEN PHARMACOKINETICS AND PHARMACODYNAMICS



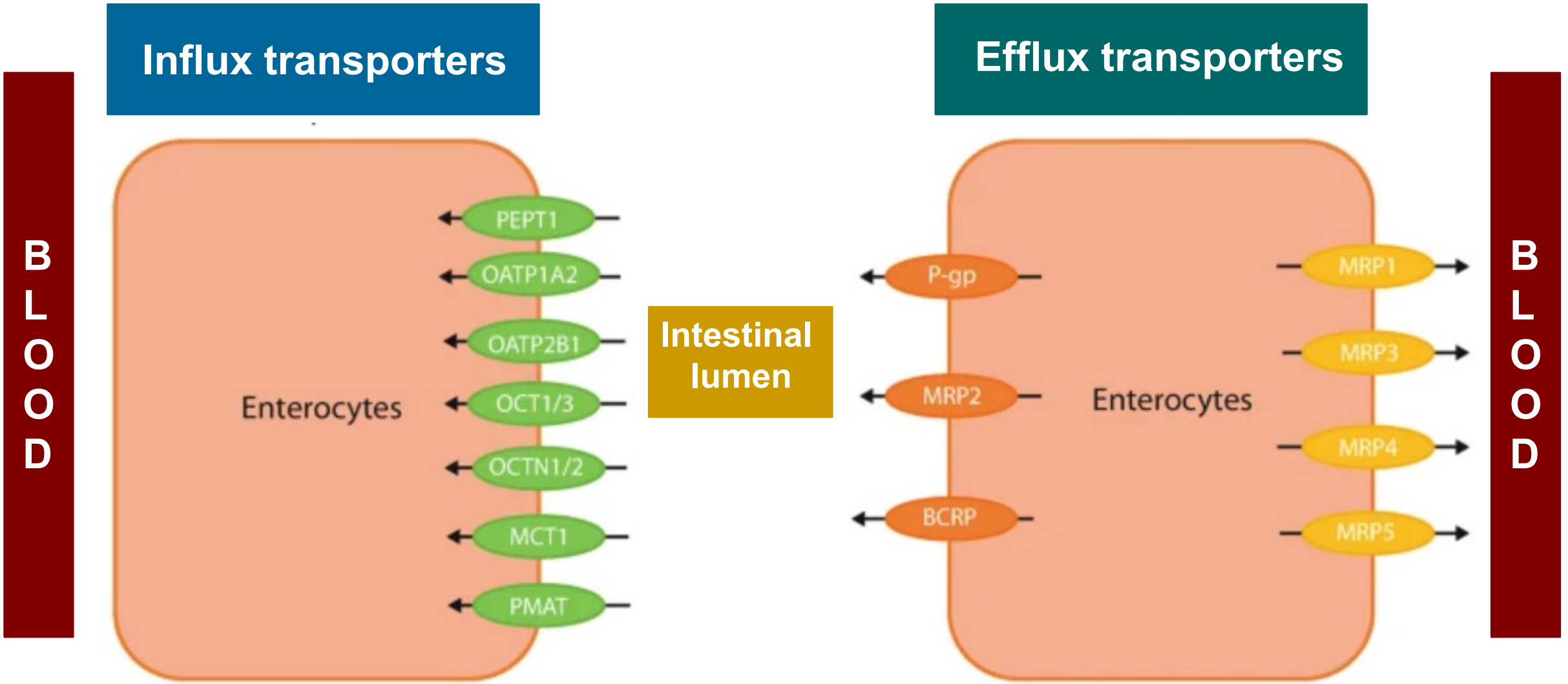
Andreotti F, et al. *Eur Heart J*. 2015;36(46):3238-3249.

DISTRIBUTION OF DRUG TRANSPORTERS



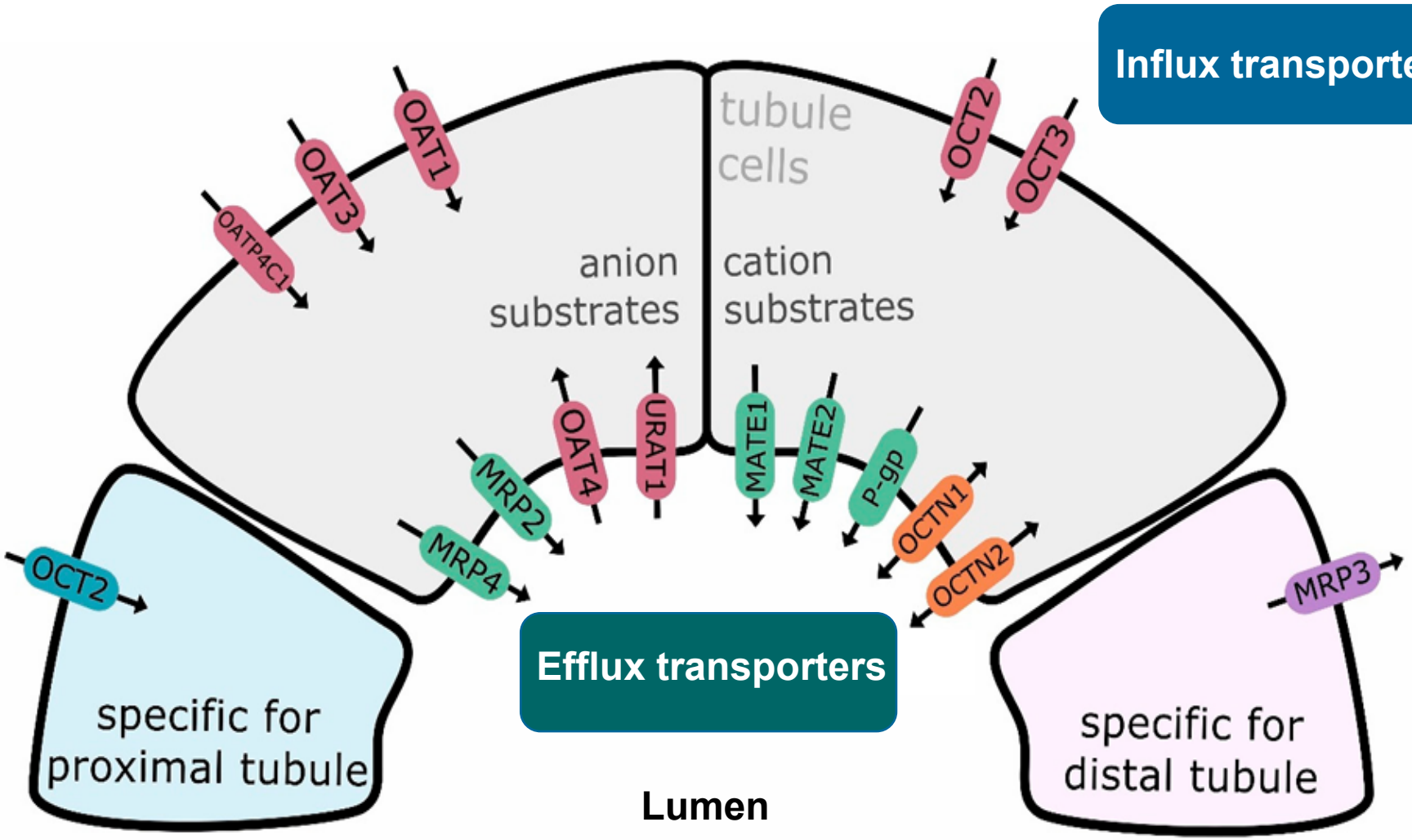
Blaze C, et al. *Pharmaceutics*. 2025;17(685):1-27

DRUG TRANSPORTERS IN INTESTINES



Drozdzik M, et al. *Pharmacol Rep*. 2020;72:1173-1194

MAJOR TRANSPORTERS IN THE KIDNEYS



- SLC carriers are more abundantly expressed than the ABC transporter family.
- Drug transporters function as a site for clinically significant drug interactions.
- They can be implicated in nephrotoxicity of certain drugs.

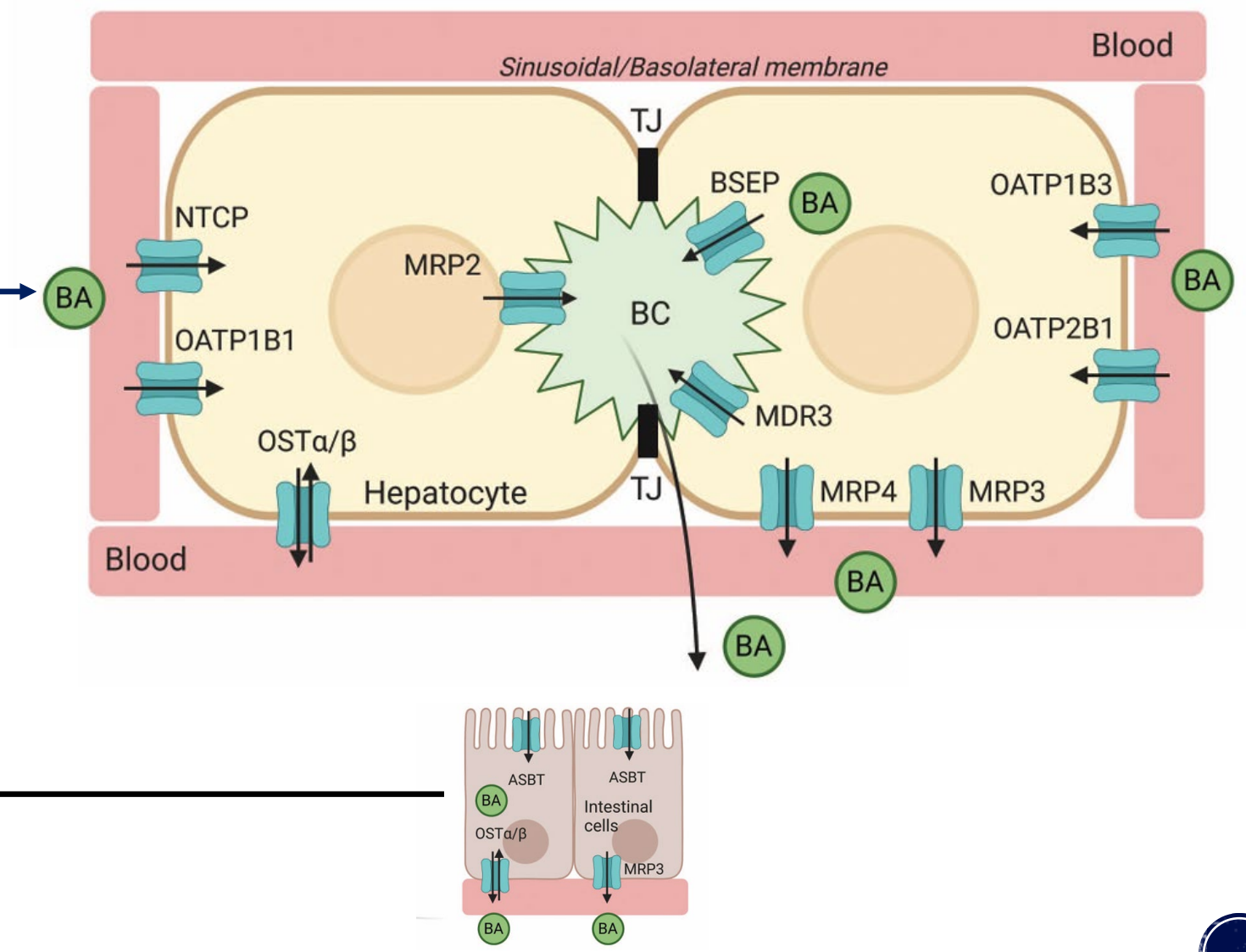
Romanska JL, et al. *Int. J Mol Sci.* 2023;24(3):1-17

MAIN TRANSPORTERS IN THE LIVER

Enterohepatic circulation

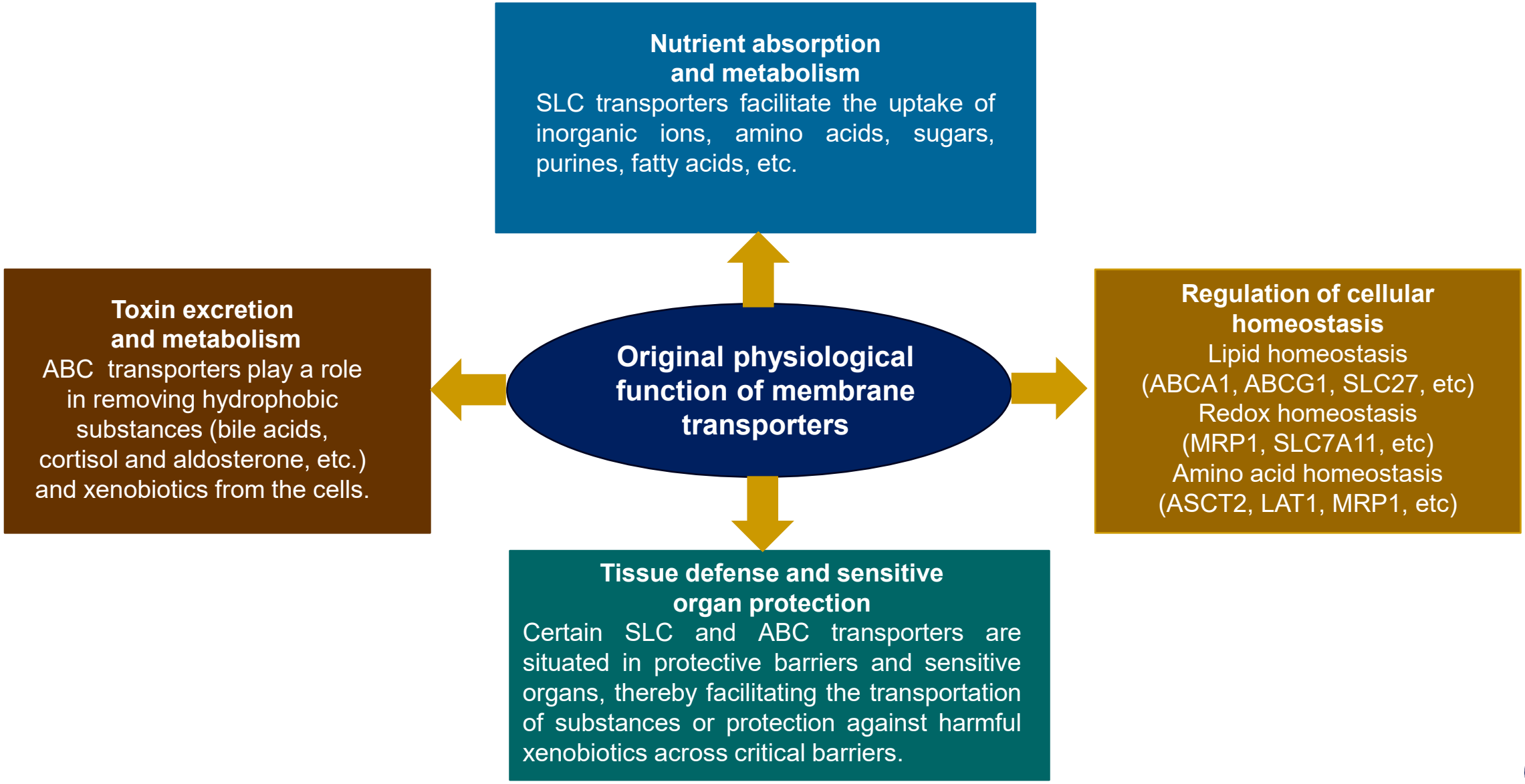
Drugs/metabolites excreted in bile:

- Cephazolin
- Digoxin
- Irinotecan
- Methotrexate
- Mycophenolic acid
- Valproic acid.
- Paclitaxel
- Vincristine



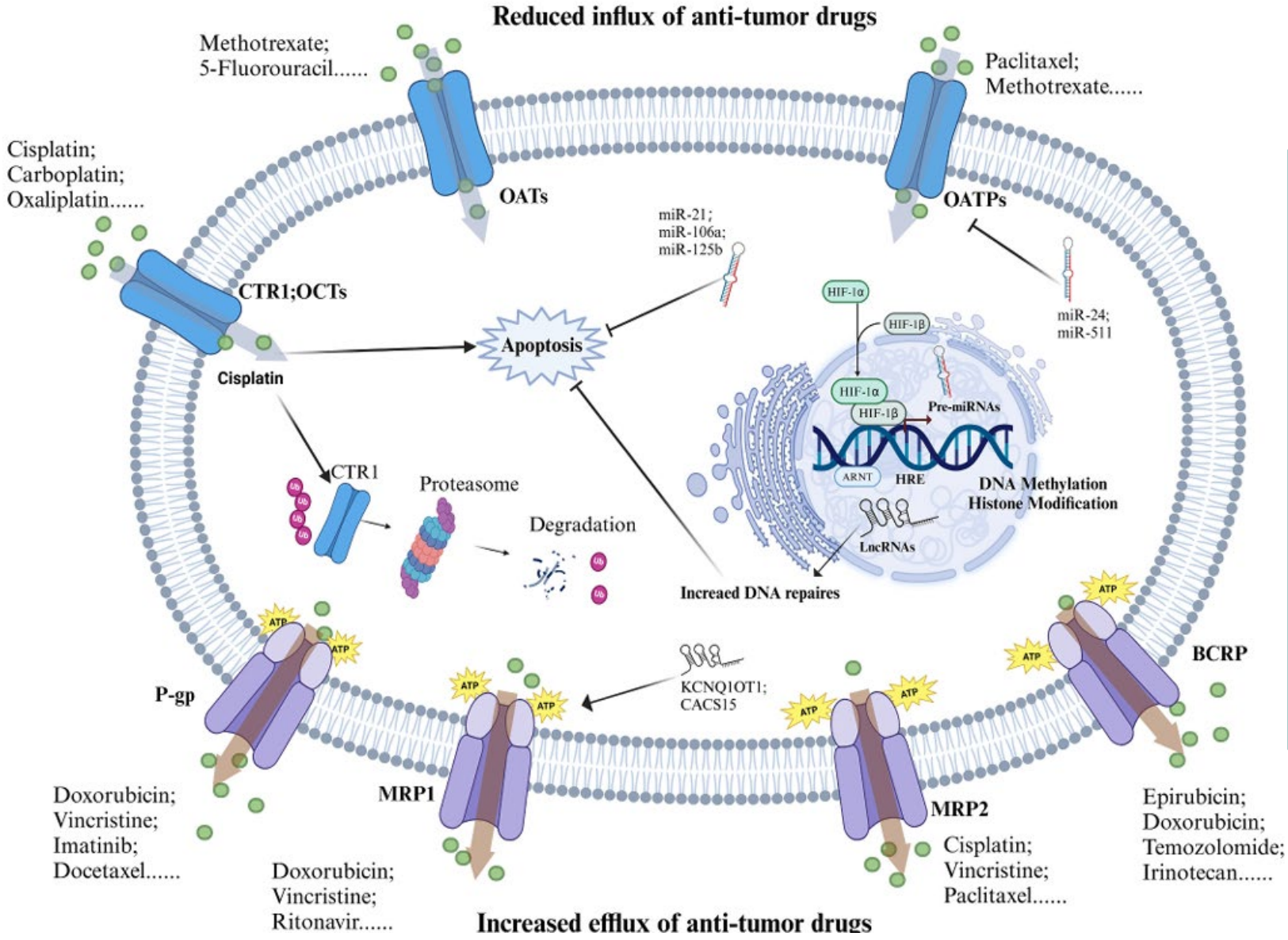
Saran C, et al. *Toxicol Pathol*. 2023;51:405-413

PHYSIOLOGIC ROLE OF TRANSPORTERS



Pan C, et al. *Biochem Biphys Acta Rev Cancer*. 2025.1880(2):1-17

DRUG TRANSPORTERS AND RESISTANCE

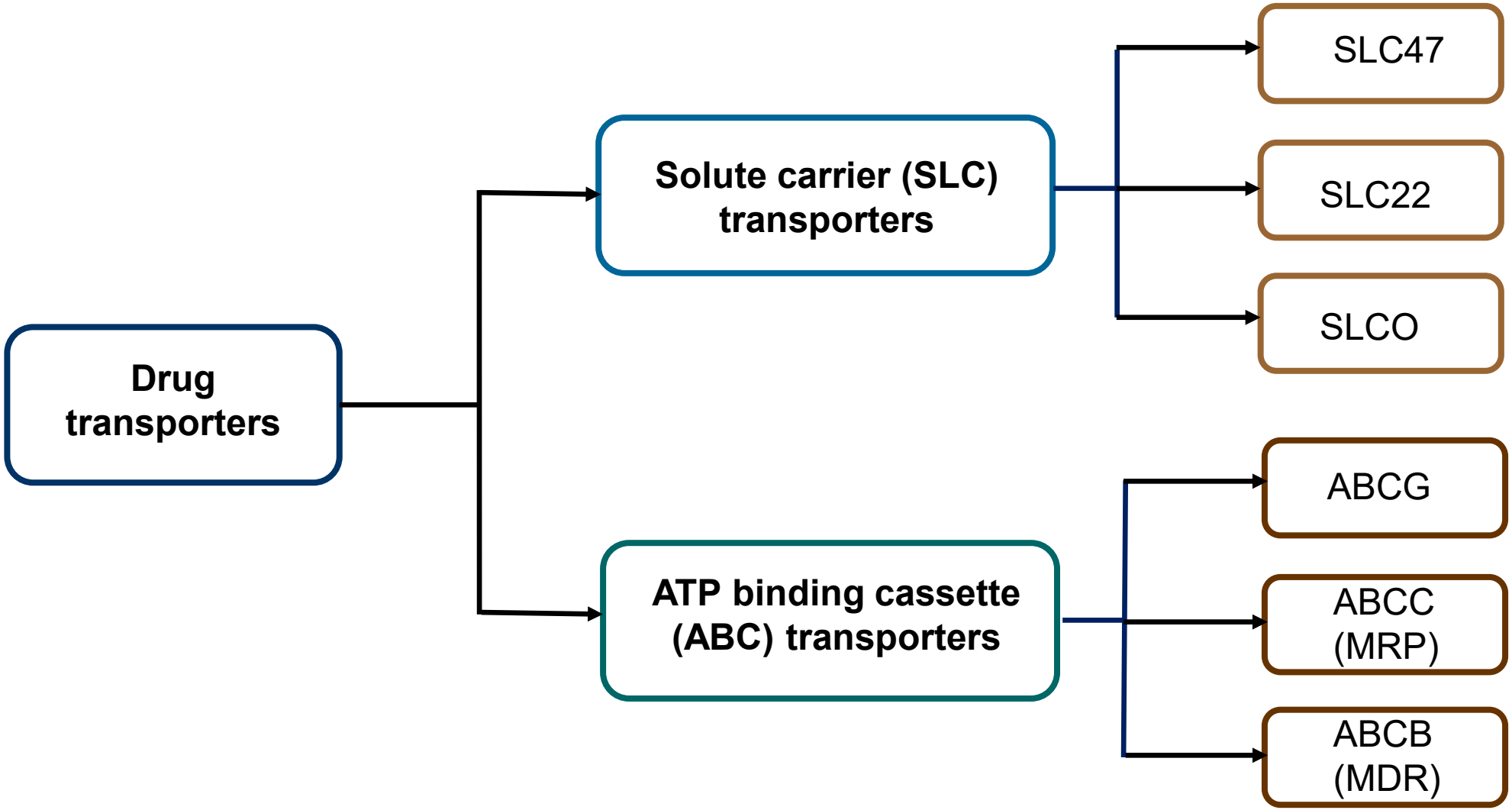


Mechanisms mediating chemoresistance:

- Epigenetic factors such as DNA methylation and histone modification influence the expression of ABC and SLC transporters.
- Specific microRNAs involved in the regulation of transporter expression.
- Proteasome degradation due to chemotherapy exposure.

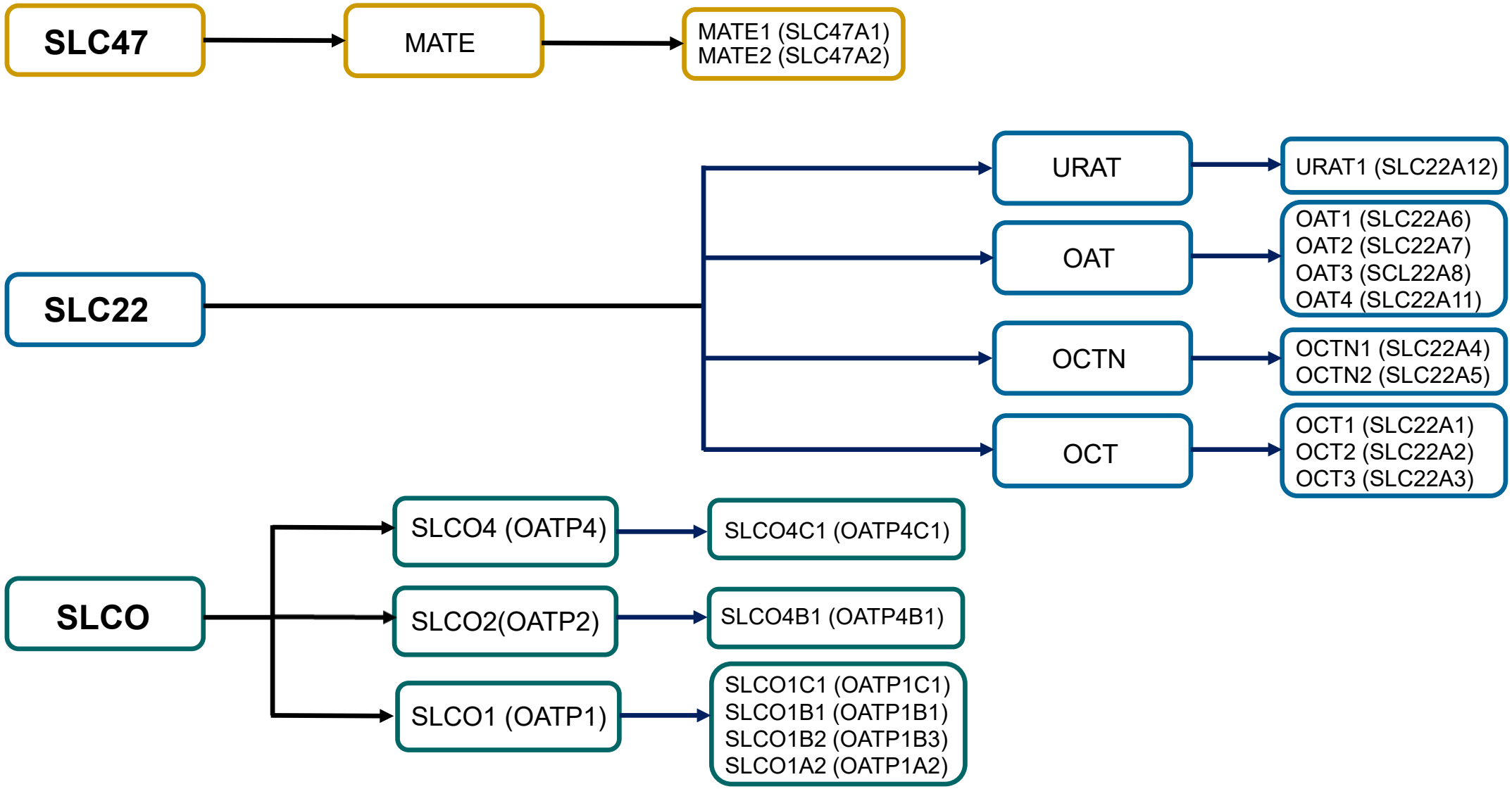
Pan C, et al. *Biochem Biphys Acta Rev Cancer*. 2025.1880(2):1-17

CLASSIFICATION OF DRUG TRANSPORTERS



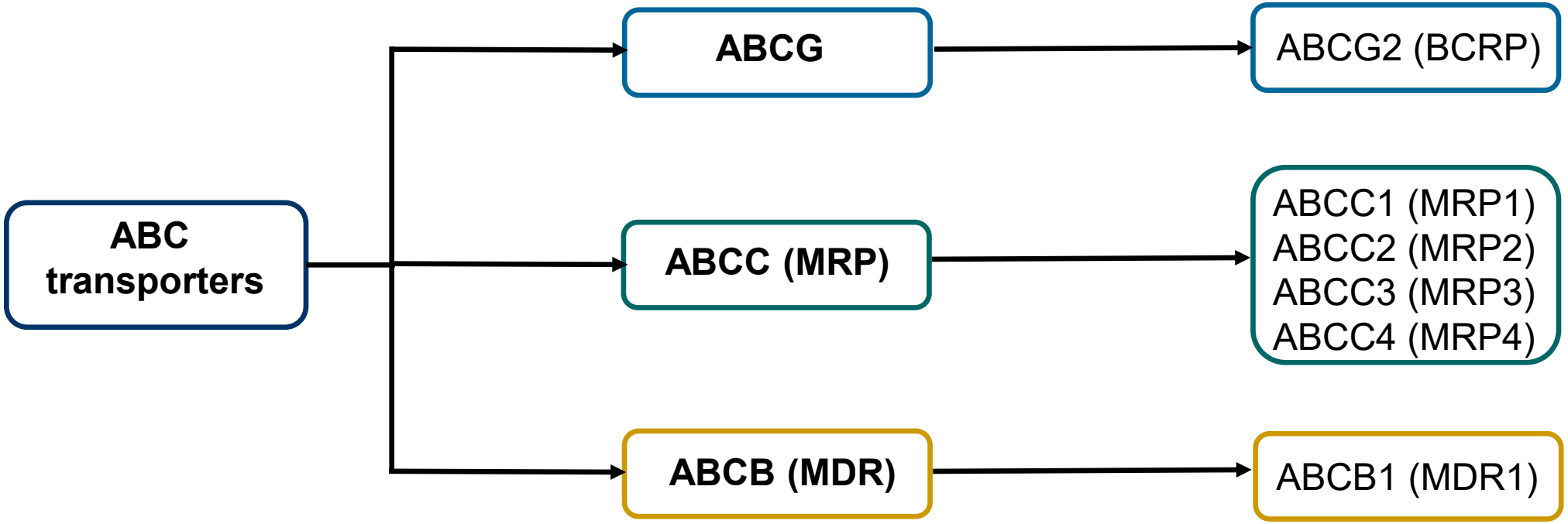
Nigam S, et al. *Nat Rev Drug Discov*.2015;14(1):29-44

SOLUTE CARRIER TRANSPORTERS CLASSIFICATION



Nigam S, et al. *Nat Rev Drug Discov*.2015;14(1):29-44

CLASSIFICATION OF ATP BINDING CASSETTE TRANSPORTERS



Nigam S, et al. *Nat Rev Drug Discov*.2015;14(1):29-44

SUBSTRATES OF ABC TRANSPORTERS

Gene	Protein	Substrate	Tissue expression
ABCB1	P-gp	Cisplatin, methotrexate, docetaxel, doxorubicin, paclitaxel, tamoxifen, vincristine, imatinib, vinblastine, etoposide, daunorubicin, mitoxantrone, epirubicin, mitomycin C, topotecan, venetoclax	Intestine, hepatic biliary epithelium, kidney, placenta, blood brain barrier
ABCC1	MRP1	Methotrexate, irinotecan, doxorubicin, daunorubicin, vincristine, vinblastine, SN-38, etoposide, mitoxantrone,	Blood brain barrier, testes, lung, ovaries, placenta
ABCC2	MRP2	Vincristine, irinotecan, cisplatin, paclitaxel, methotrexate	Hepatocytes, kidney proximal tubules, intestine
ABCC3	MRP3	Methotrexate, etoposide	Intestinal epithelium, hepatocytes
ABCG2	BCRP	Mitoxantrone, SN-38, methotrexate, topotecan, tamoxifen, doxorubicin, etoposide, irinotecan, daunorubicin, talazoparib.	Kidney, intestine, mammary glands, liver, placenta



Pan C, et al. *Biochem Biophys Acta Rev Cancer*. 2025;1880(2):1-17

SUBSTRATES OF SLC TRANSPORTERS

Gene	Protein	Substrate	Tissue expression
SLCO1A2	OATP1A2	Methotrexate, imatinib, doxorubicin, docetaxel, paclitaxel	Liver, kidney, intestine, blood brain barrier
SLCO1B1	OATP1B1	SN-38, belzutifan, etoposide, cisplatin, sorafenib, regorafenib	Liver
SLCO1B3	OATP1B3	Docetaxel, SN-38, sorafenib, paclitaxel, nilotinib	Liver
SLC22A6	OAT1	Methotrexate, bleomycin	Kidney
SLC22A7	OAT2	6-Fluorouracil, paclitaxel	Liver, kidney
SLC22A8	OAT3	Methotrexate, topotecan, pemetrexed	Kidney



Pan C, et al. *Biochem Biophys Acta Rev Cancer*. 2025;1880(2):1-17

SUBSTRATES OF SLC TRANSPORTERS

Gene	Protein	Substrate	Tissue expression
SLC22A1	OCT1	Cisplatin, dasatinib, oxaliplatin, imatinib, irinotecan, paclitaxel, mitoxantrone	Liver
SLC22A2	OCT2	Cisplatin, oxaliplatin	Kidney
SLC22A3	OCT3	Oxaliplatin, melphalan, vincristine, irinotecan, cisplatin	Kidney, adrenal glands, brain, heart, skeletal muscle, small intestine
SLC31A1	CTR1	Cisplatin, carboplatin, oxaliplatin	Liver, lung
SLC22A4	OCTN1	Mitoxantrone, imatinib, doxorubicin, oxaliplatin	Kidney, placenta, brain
SLC22A5	OCTN2	Etoposide, imatinib, oxaliplatin	Skeletal muscle, kidney
SLC22A16	OCT6	Cisplatin, oxaliplatin	Hematopoietic tissues



Pan C, et al. *Biochem Biophys Acta Rev Cancer*. 2025;1880(2):1-17

INHIBITORS AND INDUCERS OF DRUG TRANSPORTERS

Inhibitors of drug transporters	Inhibitors of drug transporters	Inducers of drug transporters
▪ Adagrasib ▪ Amiodarone ▪ Azithromycin ▪ Belumosudil ▪ Capmatinib ▪ Carvedilol ▪ Clarithromycin ▪ Cobicistat ▪ Cyclosporine ▪ Daclatasvir ▪ Dronedarone ▪ Enzalutamide ▪ Fostamatinib ▪ Isavuconazole ▪ Lapatinib ▪ Neratinib	▪ Osimertinib ▪ Pirtobrutinib ▪ Posaconazole ▪ Propafenone ▪ Ranolazine ▪ Ritonavir ▪ Rolapitant ▪ Selpercatinib ▪ Simeprevir ▪ Sotagliflozin ▪ Sotorasib ▪ Tepotinib ▪ Ticagrelor ▪ Tucatinib ▪ Vemurafenib ▪ Verapamil	▪ Apalutamide ▪ Carbamazepine ▪ Fosphenytoin ▪ Phenytoin ▪ Rifampin (rifampicin) ▪ St. John's wort



US Food and Drug Administration. Drug development and drug interactions: Table of substrates, inhibitors and inducers



IMPACT OF DRUG TRANSPORTER INTERACTIONS

INTERACTION BETWEEN TUCATINIB AND DIGOXIN

Inclusion criteria

- Adult patients aged 18-65 years of age with a body mass index of 18.0-32.0 kg/m^2.
- Exclusion criteria: use of tobacco or other nicotine containing products within 3 months; consumption of alcohol within 48 hours.

Study design

- Digoxin 0.5 mg administered orally on days 1 and 15.
- Tucatinib 300 mg administered twice daily on day 8-21.
- On day 15, morning tucatinib dose was administered immediately after digoxin.

Pharmacokinetic assessment

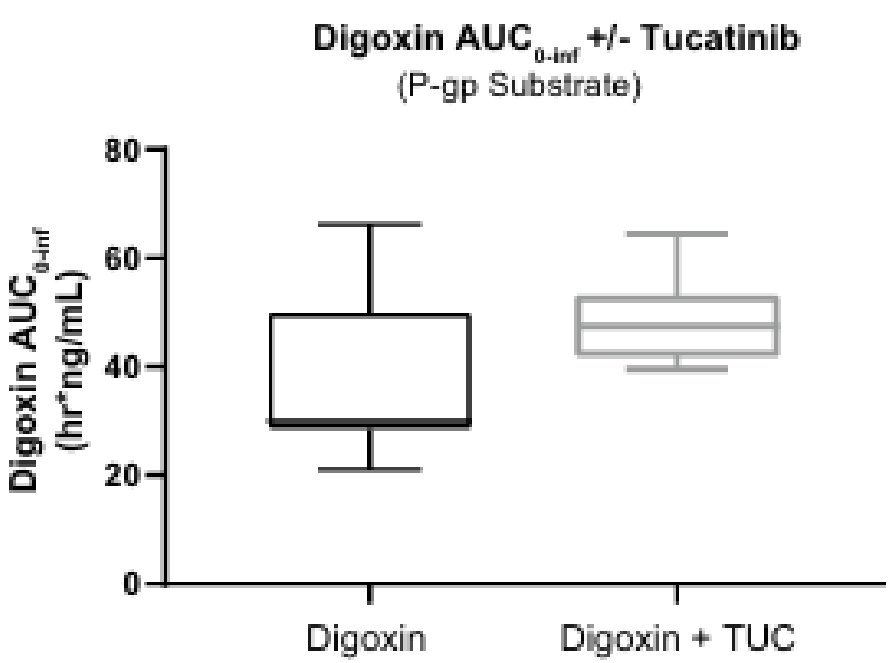
- Blood samples for determination of plasma concentrations of digoxin were collected at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96,120, 144 and168 hours post-dose on days 1 and 15.



Topletz-Erickson, et al. *Clin Pharmacokinet.* 2022;61(10):1417-1426

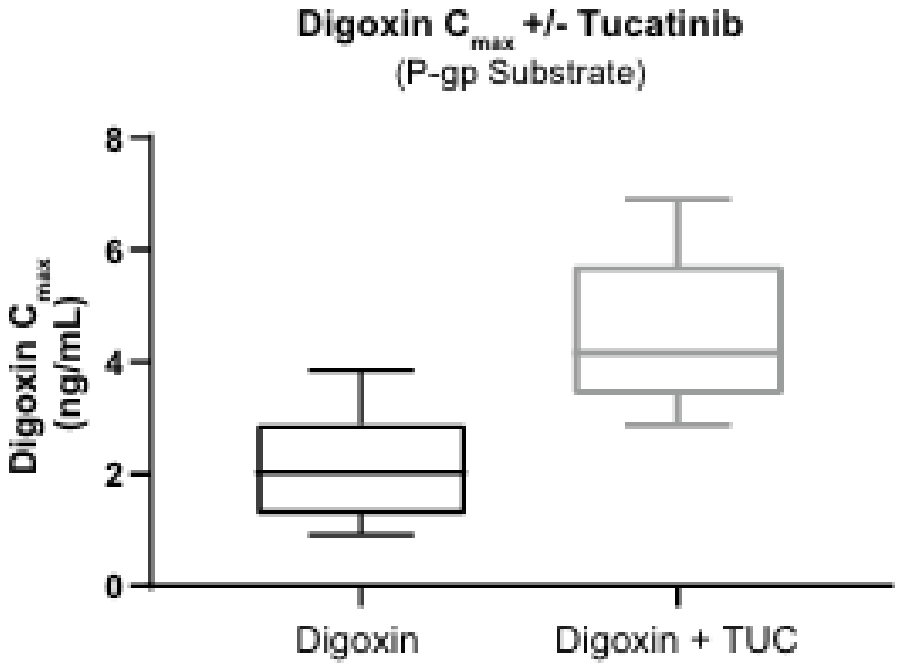
IMPACT OF TUCATINIB ON DIGOXIN EXPOSURE

Digoxin area under curve



Tucatinib increased digoxin exposure by 1.5-fold

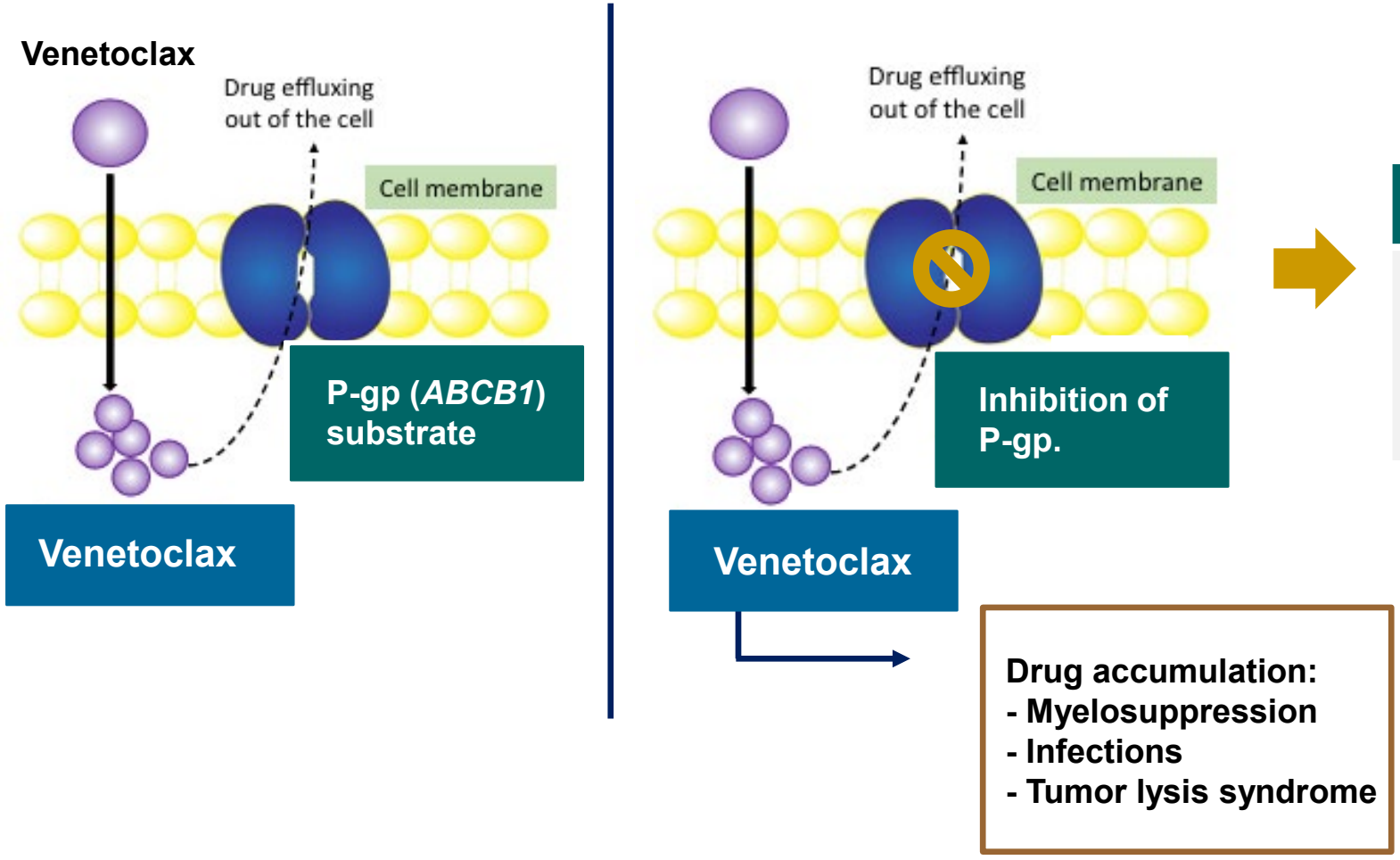
Digoxin peak plasma concentration



Tucatinib increased peak level by 2.4-fold

Topletz-Erickson, et al. *Clin Pharmacokinet*. 2022;61(10):1417-1426

VENETOCLAX INTERACTION WITH P-GP INHIBITORS

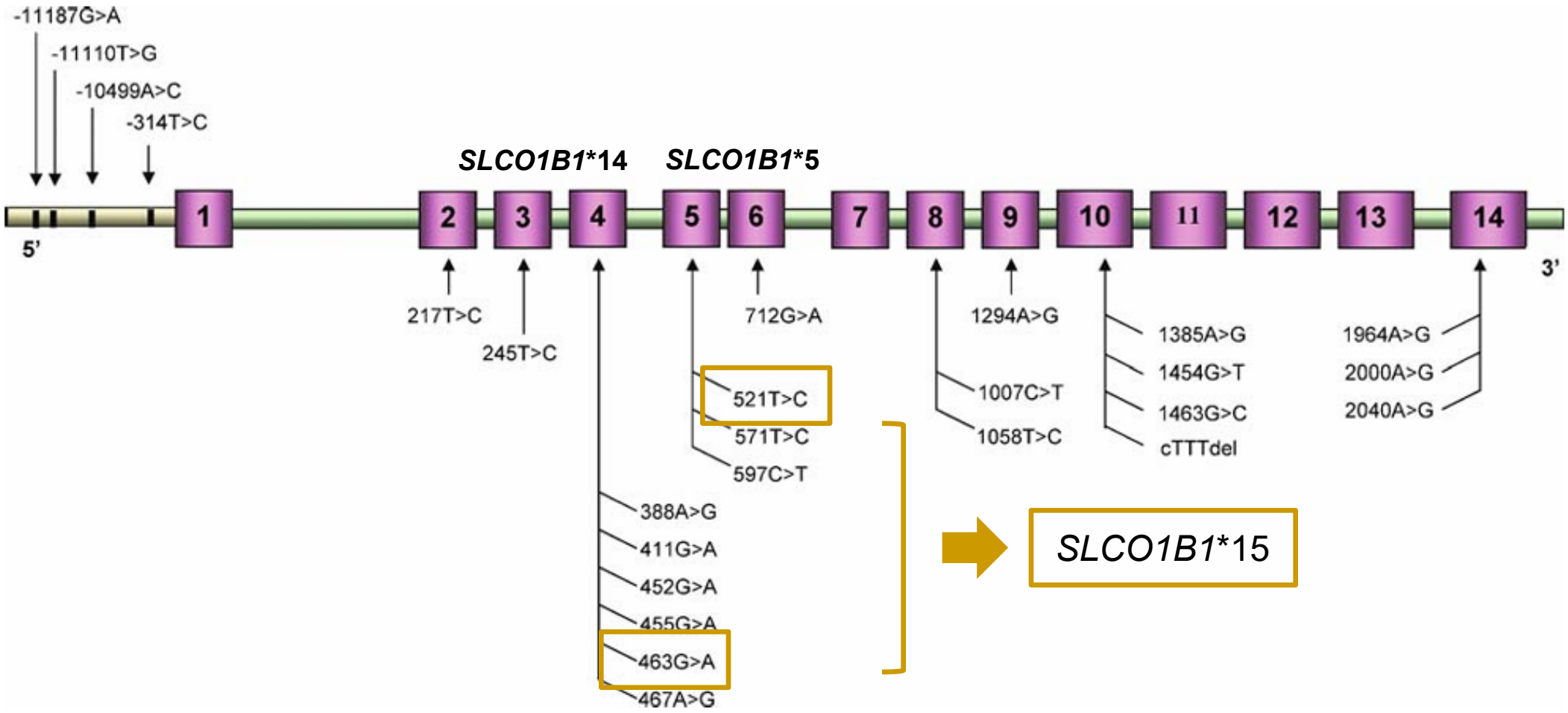


P-gp inhibitors	Recommendation
Amiodarone, cyclosporine, dronedarone, ranolazine, verapamil, carvedilol	Reduce the dose by at least 50%

Shah D, et al. *J Cancer Res Clin Oncol*. 2023;149:367-391

GENETIC POLYMORPHISMS OF DRUG TRANSPORTERS

SLCO1B1 POLYMORPHISMS



Rao Jada S et al. *Eur J Pharmacol.* 2007;63:555-563

PREDICTED *SLCO1B1* PHENOTYPES BASES ON GENOTYPES

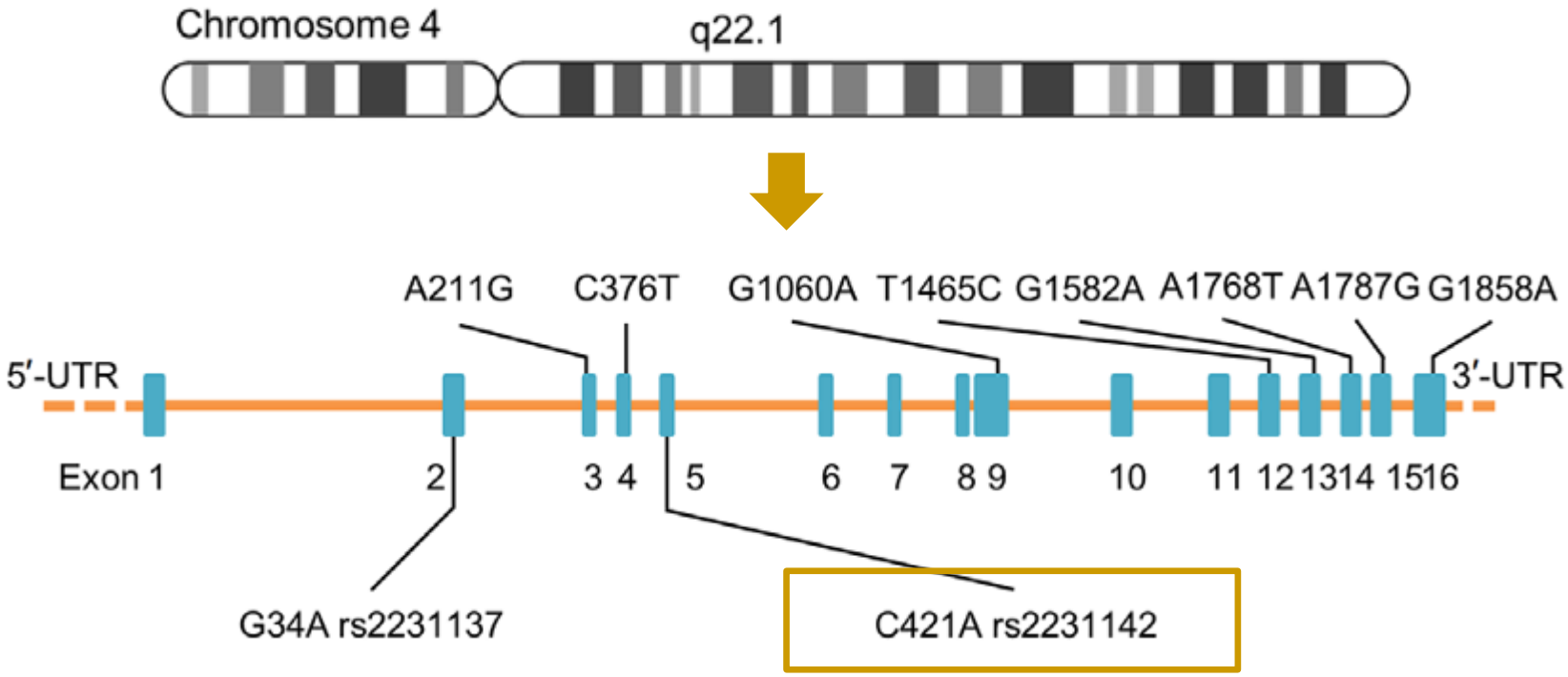
Gene	Phenotype	Genotype	Examples
SLCO1B1	Increased function	An individual carrying two increased function alleles	*14/*14
	Normal function	An individual carrying two normal function alleles or one normal plus one increased function allele	*1/*1, *1/*14
	Decreased function	An individual carrying one normal or increased function allele plus one no function allele	*1/*5, *1/*15,
	Poor function	An individual carrying two no function alleles	*5/*5, *5/*15, *15/*15

SLCO1B1 variants of unknown function: *6, *10, *43 and *7



Ramsey LB, et al. *Clin Pharmacol Ther*. 2014;96(4):423-428

ABCG2 POLYMORPHISMS



Race	rs2231142 (C421A)	rs2231137 (G34A)
Caucasian	11-17%	2-6%
African	5%	4-9%
Asian	34-45%	29-38%

Chin L, et al. *Acta Pharmaceutica Sinica B*. 2019;9(4):659-674

PREDICTED *ABCG2* PHENOTYPES BASES ON GENOTYPES

Gene	Phenotype	Genotype	Examples
ABCG2	Normal function	An individual carrying two normal function alleles	c.421 C/C (rs2231142)
	Decreased function	An individual carrying one normal function allele plus one decreased function allele	c.421 C/A (rs2231142)
	Poor function	An individual carrying two decreased function alleles	c.421 A/A (rs2231142)



Ramsey LB, et al. *Clin Pharmacol Ther*. 2014;96(4):423-428

ABCB1 POLYMORPHISMS INFLUENCE PLASMA LEVELS AND RESPONSE TO IMATINIB

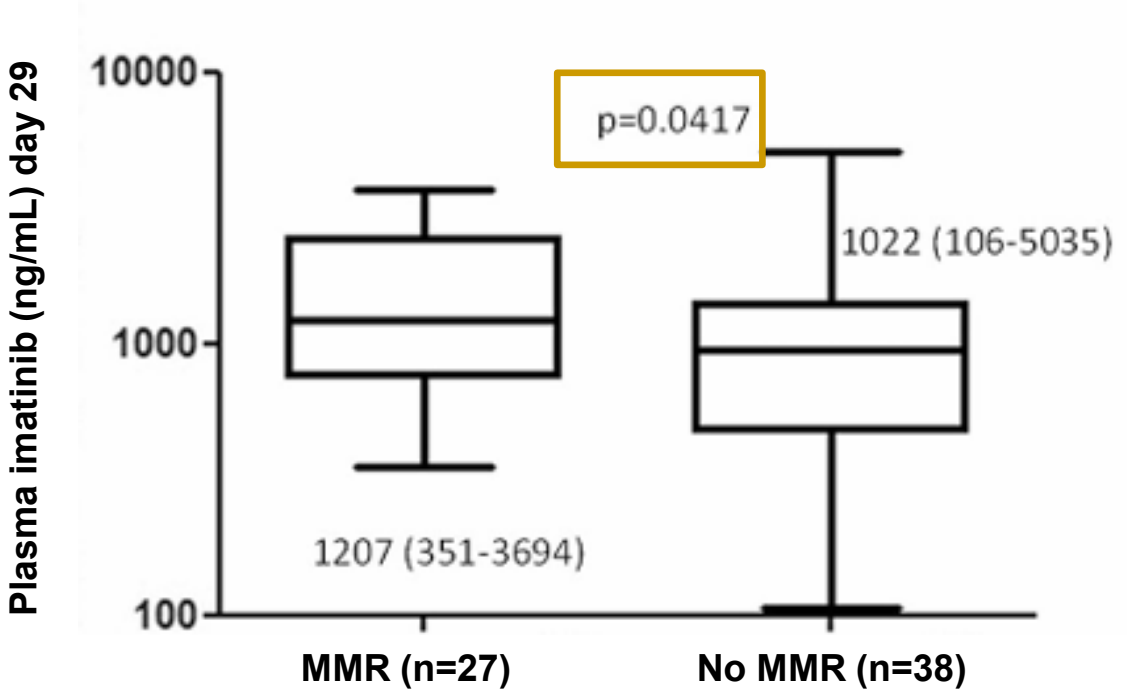
Inclusion criteria	• Adult patients with chronic myeloid leukemia (chronic phase). • No prior imatinib exposure (imatinib naïve).
Plasma imatinib levels	• Blood samples were collected day 29 post imatinib therapy. • Trough imatinib concentration was assessed using high performance liquid chromatography.
Detection of polymorphisms in transporters	• Genomic DNA was extracted from peripheral blood. • Genotyping for polymorphisms in *ABCB1*, *ABCG2*, and *SLC22A4.*
Detection of polymorphisms in transporters	Peripheral blood was collected at 3, 6, 12 and 18 months to measure BCL-ABL transcript levels using quantitative reverse transcriptase PCR.



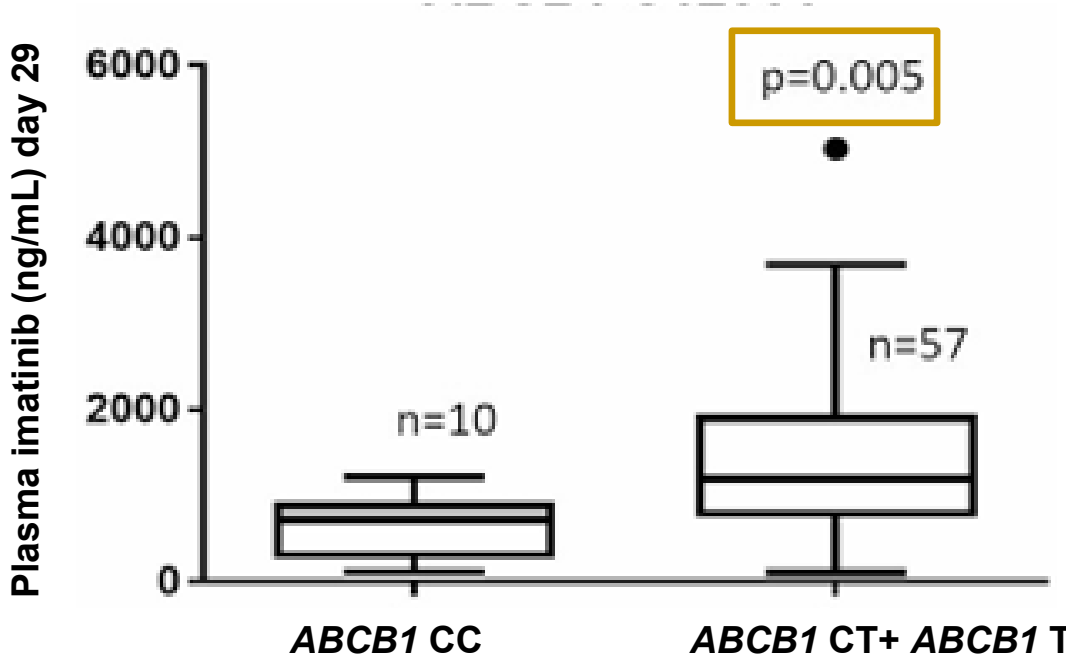
Rajamani B, et al. *Sci Rep*. 2020;10(1):1-11

ABCB1 POLYMORPHISMS INFLUENCE PLASMA LEVELS AND RESPONSE TO IMATINIB

Plasma concentration and response



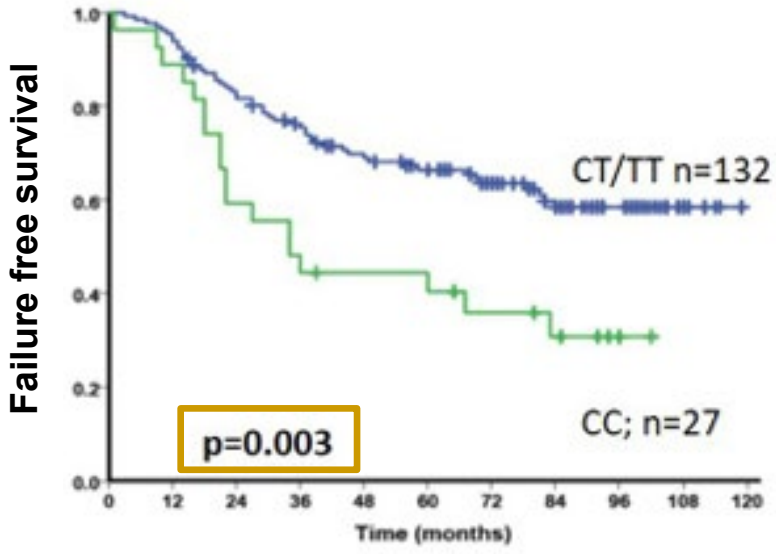
ABCB1 polymorphisms and imatinib levels

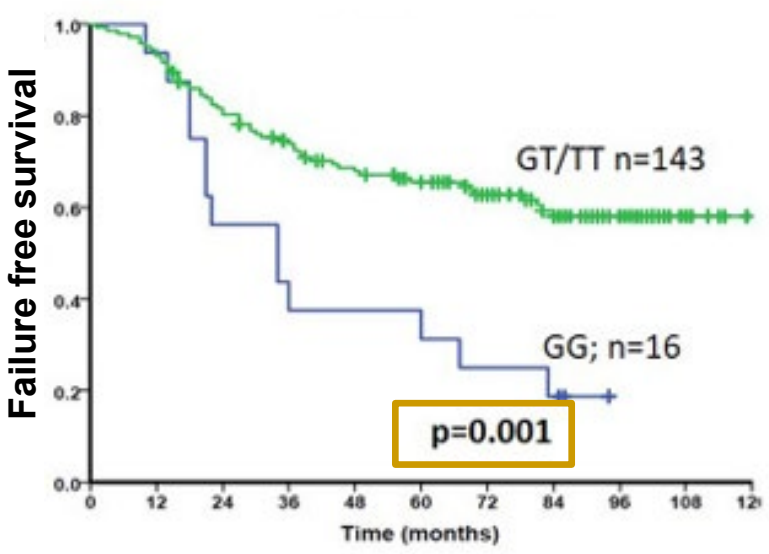


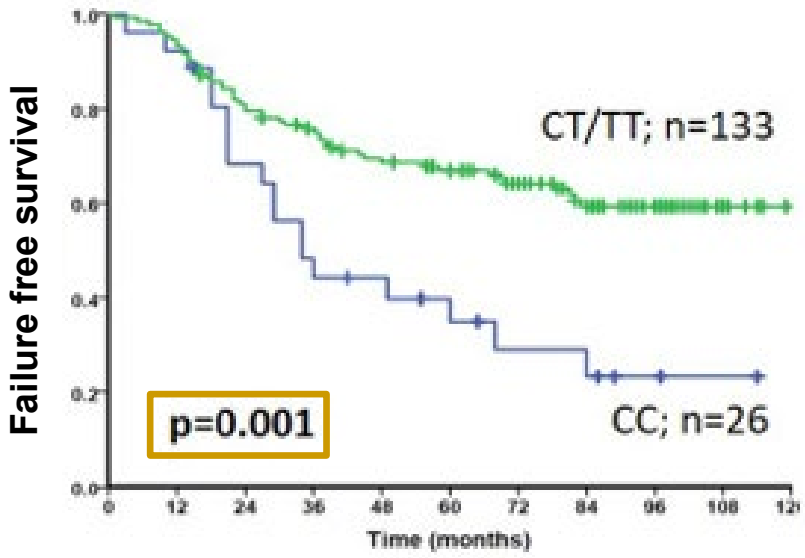
Rajamani B, et al. *Sci Rep.* 2020;10(1):1-11

ABCB1 POLYMORPHISMS INFLUENCE PLASMA LEVELS AND RESPONSE TO IMATINIB

ABCB1 C1236T	*ABCB1* G2677T	*ABCB1* C3435T







Rajamani B, et al. *Sci Rep*. 2020;10(1):1-11

ABCC2 POLYMORPHISMS AND RESPONE TO PLATINUM BASED THERAPY IN LUNG CANCER

Inclusion criteria

- Adult patients with stage III-IV non small cell lung cancer (inoperable).
- First line treatment with cisplatin or carboplatin-based therapy.

Response assessment

- Response assessment after 2 cycles using the RECIST criteria.
- Incidence of grade 2 or 3 toxicity using NCI common toxicity criteria.

***ABCC2* genotyping**

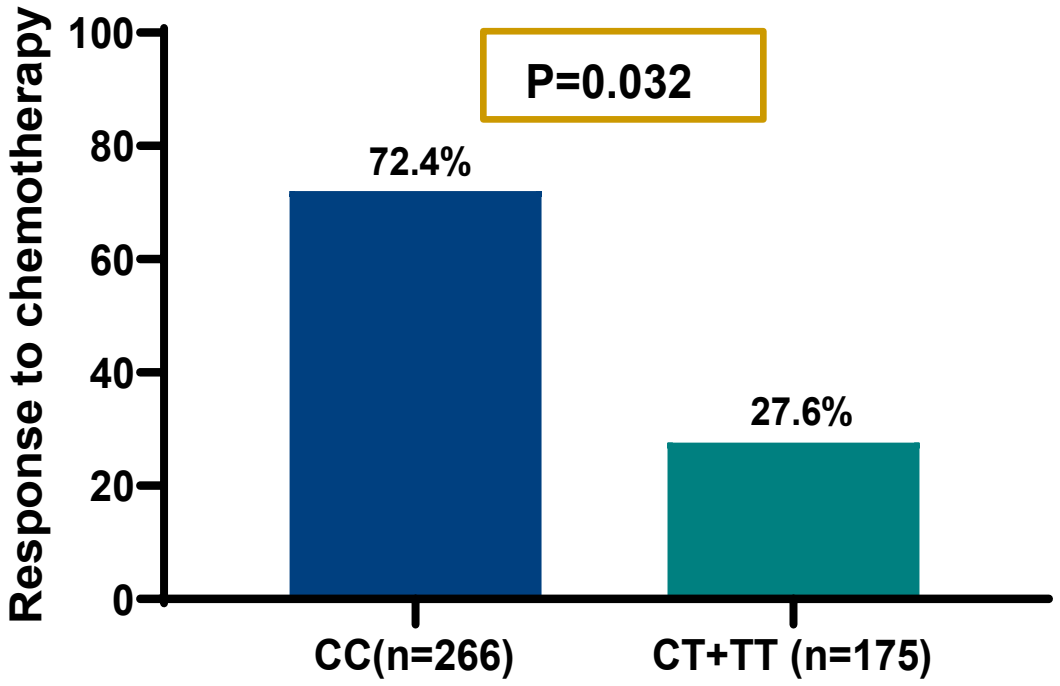
- Genomic DNA was extracted from peripheral leucocytes.
- Polymorphisms in *ABCC2* (C-24T, G1249T, C3972T) were identified through mass array (Sequenom).



Han B, et al. *Lung Cancer*;72(2):238-243

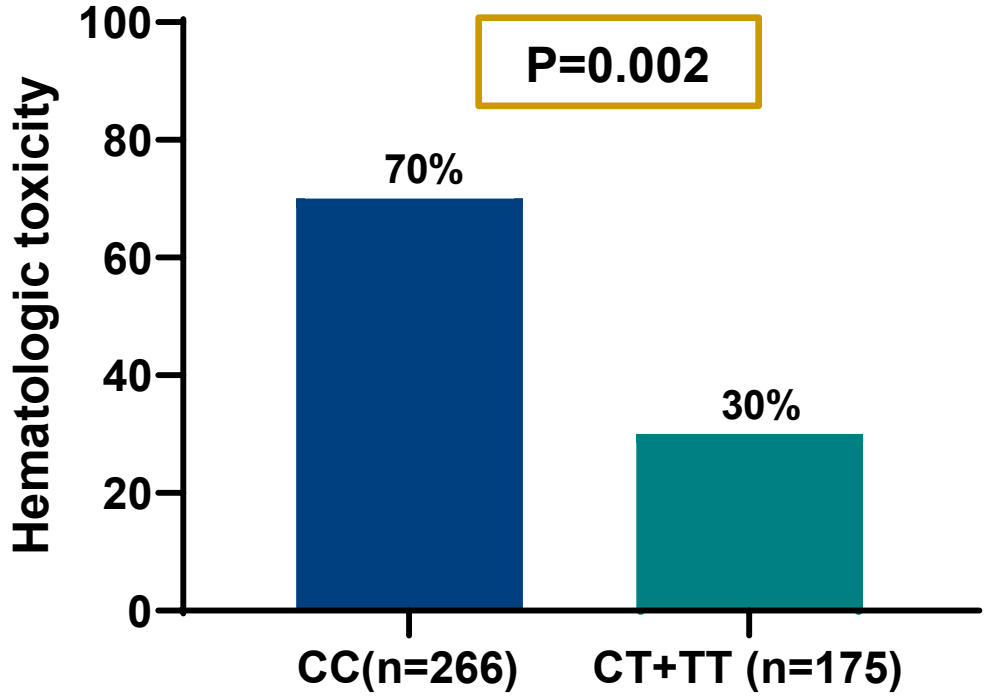
ABCC2 POLYMORPHISMS AND RESPONE TO PLATINUM BASED THERAPY IN LUNG CANCER

ABCC2 -24C>T and response



OR: 3.8 (95% CI: 1.62-8.87)

ABCC2 -24C>T and hematologic toxicity



OR: 3.8 (95% CI: 1.62-8.87)

Han B, et al. *Lung Cancer*;72(2):238-243



QUESTIONS