PATIENT SAFETY THROUGH INDIVIDUALISED THERAPY

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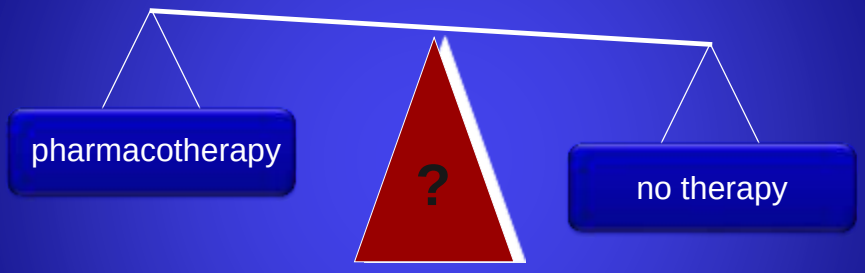
Declaration Conflict of interest:

Nothing to disclose

- Is molecular polymorphism of drug-metabolizing enzymes responsible for the rate of drug metabolism? Yes/No
- Is possible to evaluate pharmacokinetic profile of patient by genotyping? Yes/No
- Is genotyping invasive method for the patient? Yes/No

Individual decision on therapy



Requirement for the balance between pharmacotherapeutic benefit and risk of adverse effects

Rationalization of the pharmacotherapy

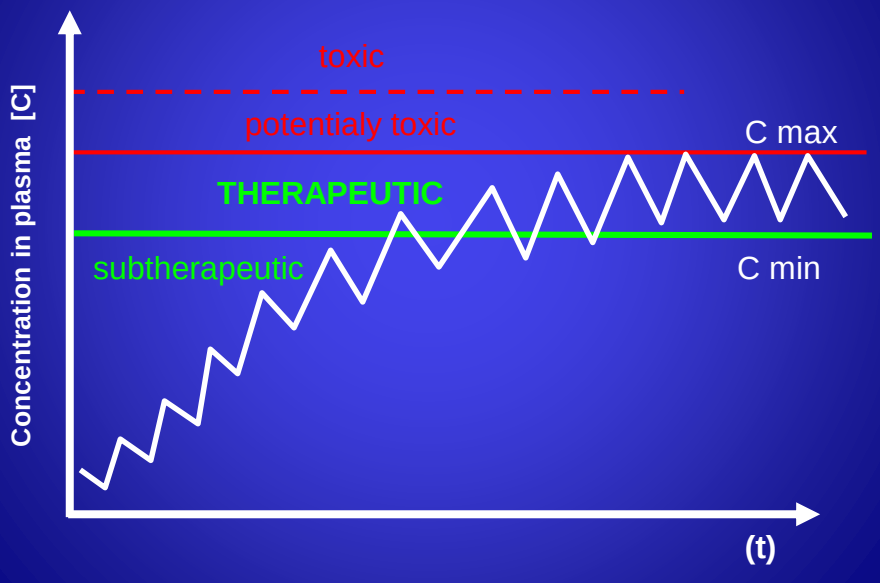
1. Simplify the treatment regimen
2. Minimize medication
3. Rate the possibility of drug-free treatment
4. First, consider the possibility of using drugs without a prescription
5. Start treatment with low doses of the drug
6. Monitor the effects of the drug

Biopharmaceutical Aspects of Pharmacotherapy

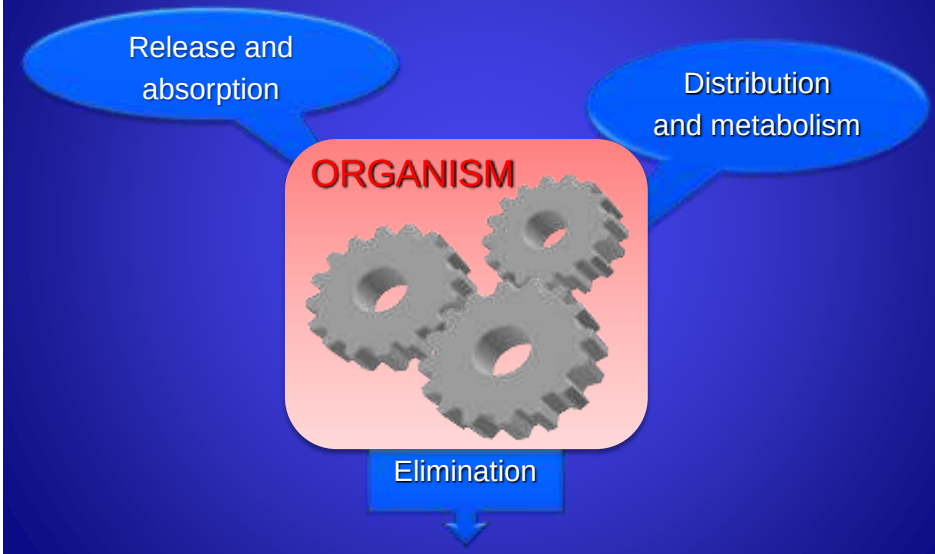



Effectivenees and Safety
of pharmacotherapy depends
on actual drug concentration
in circulation and tissues

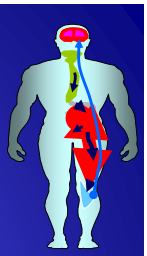
The relationship between dose -
effect of the drug



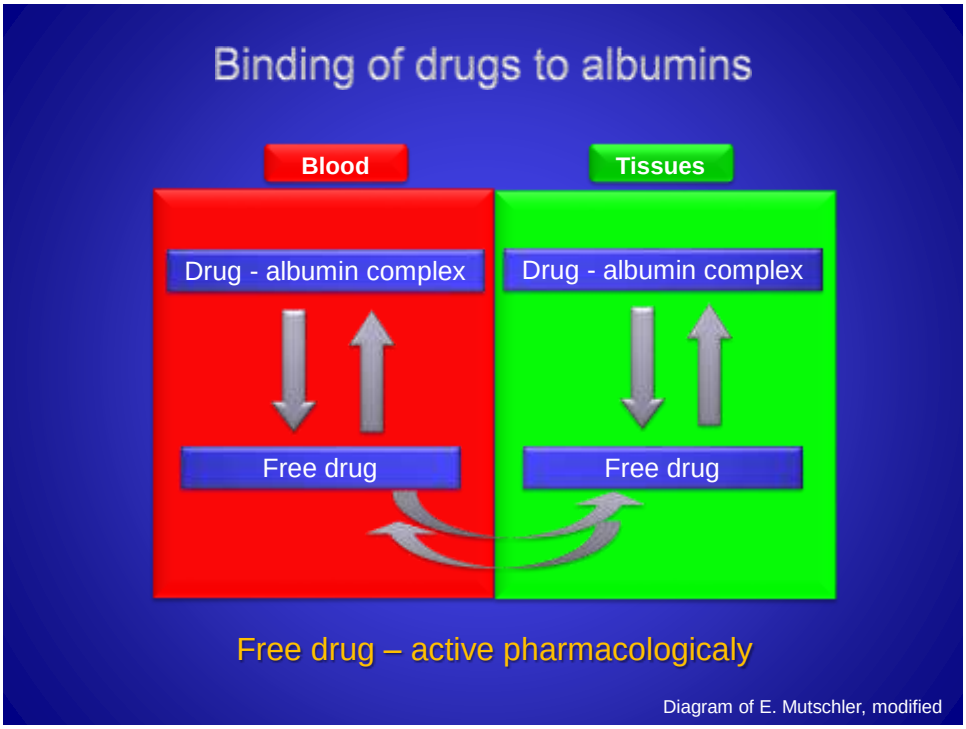
Actual drug concentration depends on the several processes

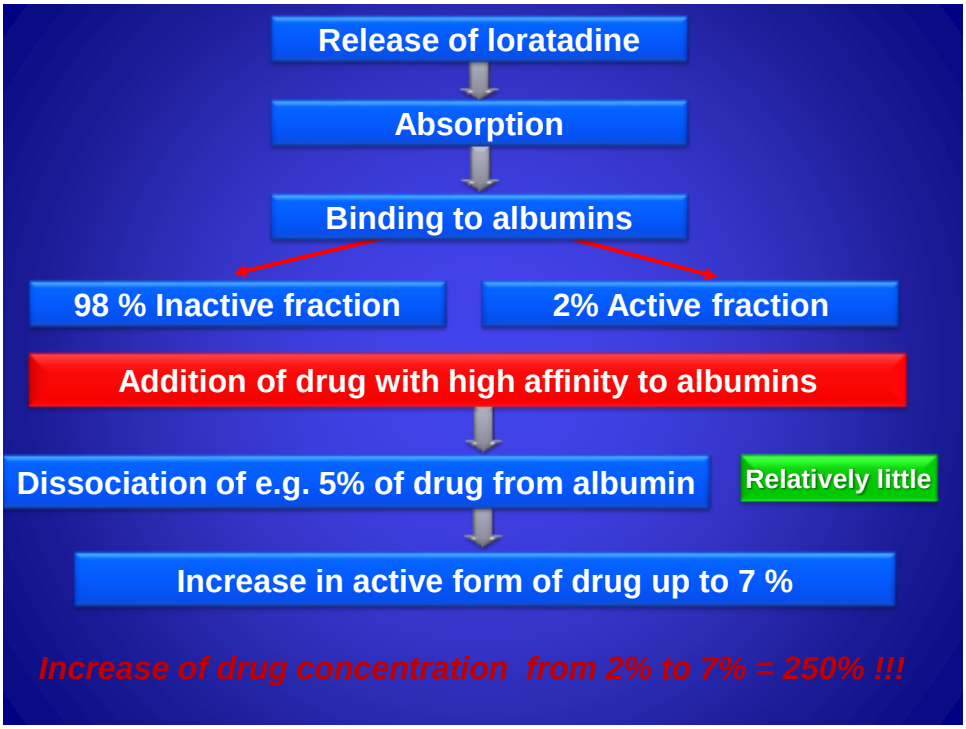


Absorption, distribution and binding to albumins



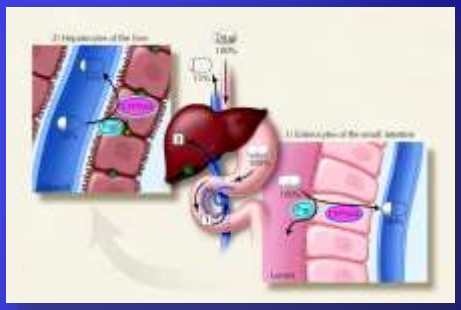
- **Absorption** (way of administration, dosage form, physico-chemical properties, food)
- **Distribution** (flow rate of blood through the tissue, rate of transport through biological membranes, lipophilicity, binding to albumins)
- **Metabolism** (genetic factors, sex, age, pathology of organs, way of administration, interactions)
- **Elimination/excretion** (urine, bile, feces, saliva, sweat: depends on pH, blood supply, amount of tissue fat)


Binding of drugs to albumins
Blood
Tissues
Drug - albumin complex
Drug - albumin complex
Free drug
Free drug
Free drug – active pharmacologicaly
Diagram of E. Mutschler, modified


Release of loratadine
Absorption
Binding to albumins
98 % Inactive fraction
2% Active fraction
Addition of drug with high affinity to albumins
Dissociation of e.g. 5% of drug from albumin
Relatively little
Increase in active form of drug up to 7 %
Increase of drug concentration from 2% to 7% = 250% !!!

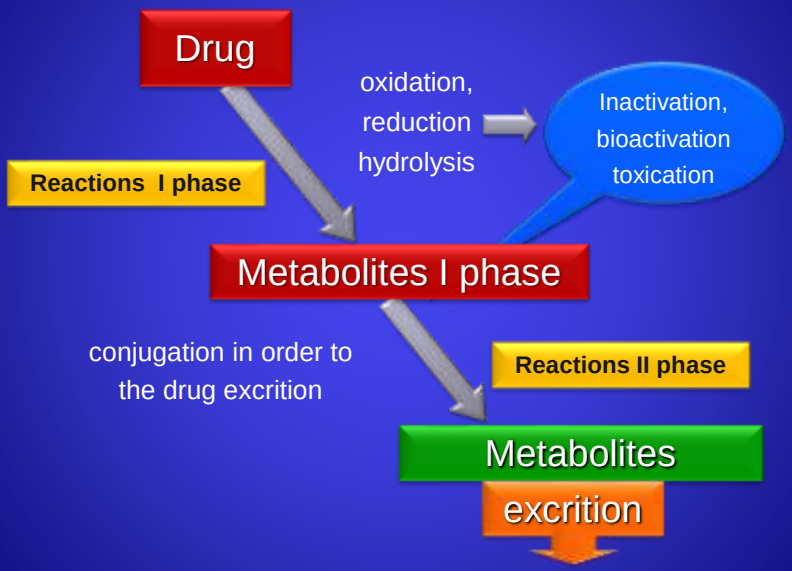
Metabolism

The effect of „the first pass" through the liver depends on functional state of the organ



- **Phase I of drug metabolism**
- **Phase II of drug metabolism**

Metabolism



Metabolism in the liver – risks

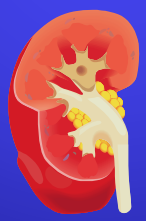
Liver dysfunction → Accumulation of the drug in circulation and tissues

Requirement for dose reduction

Drug interactions → Competition of drugs for the same cytochrom P-450, e.g.: ketoconazole, erythromycine

Excrition

- Creatinine clearance
- Kidney physiology and pathology
- Nefrotoxic drugs (e.g. aminoglicosides)
- Drugs eliminated mainly by kidney (e.g. cardenolides)



Parameters that affect pharmacokinetics

	Parameter	Effects
Absorption	State of gastric mucosa intestinal motility Blood supply to the viscera enzyme secretion	Insufficient treatment *per os*
Distribution	Amount of plasma albumins Amount of fat in the body mass amount of water in the body mass	Ineffective treatment/adverse effects, changed volume of distribution of hydrophylic/lypophylic drugs
Metabolism	Blood flow through liver (decreases 0.3-1.0% every year after 25 year of age) cytochrom P450 activity (mainly CYP3A4, CYP1A2)	Adverse effects or ineffective treatment in case of drugs that require metabolic activation (e.g. taxanes, cyclophosphamid, anthracyclines, etoposide)
Excretion	Renal filtration (decreases GRF 1ml/min/year after 40 year of age), kidney mass	Affect plasma drug concentration and adverse effects. Requirement for correction of dose of drug depending on renal filtration

Polypragmasy/Polypharmacy: risks

Drug interactions
- Ineffectiveness of therapy, adverse effects, toxicity

Weakness of „pharmacovigilance”
- Adverse effects, ineffectiveness of therapy, toxicity

Weakness of „compliance”
- Adverse effects, ineffectiveness of therapy, toxicity

Cancer Pharmacotherapy

Dose correction of chemotherapy according to renal filtration (Lichtman et al.)

Chemotherapeutic drug	Dose adjusted to renal filtration (creatinine clearance)			
	90-60 ml/min	**60-30 ml/min**	**30-15 ml/min**	**<15 ml/min**
ifosfamid *(single dose)*	*Daily dose (24h): 1,5-3 g/m2; dose per cycle: 5-10 g/m^2	-	-	Daily dose (24h): 1,13-2,25 g/m^2; Dose per cycle: 3,75-7,5 g/m^2
ifosfamid *(infusion)*	*Daily dose: 5-8 g/m^2	-	-	Daily dose: 3,75-6 g/m^2
carboplatin	Adjustment according to formula by Calvert			
cisplatin	50-120 mg/m^2 every 3-6 weeks	Contraindicated, if necessary: 25-60 mg/m^2 every 3-6 weeks		contraindicated
oksaliplatin	85 or 100 mg/m^2 every 2 weeks or 130 mg/m^2 every 3 weeks			contraindicated
fludarabine *(intravenous)*	25 mg/m^2/day	20 mg/m^2/day	15 mg/m^2/day	15 mg/m^2/day
metotrexat	30-50 mg/m^2	24-40 mg/m^2	15-25 mg/m^2	contraindicated

* >15 ml/min

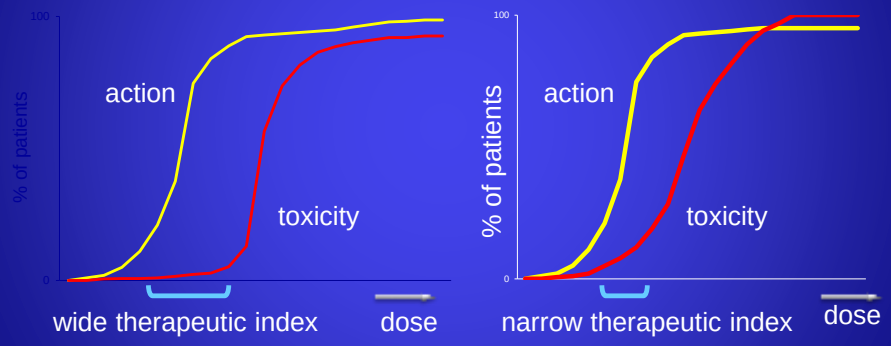
Dose correction of chemotherapy according to renal filtration (Lichtman et al.)

Chemotherapeutic drug	Dose adjusted to renal filtration (creatinine clearance)			
	90-60 ml/min	60-30 ml/min	30-15 ml/min	<15 ml/min
Bisphosphonates				
ibandroniate	6 mg every 3-4 weeks	6 mg every 3-4 weeks	6 mg every 3-4 weeks	2 mg every 3-4 weeks
pamidroniate	90 mg every 4 weeks	90 mg every 4 weeks	contraindicated	contraindicated
zoledroniate	4 mg every 3-4 weeks	60-50 ml/min: 3,5 mg every 3-4 weeks; 50-40 ml/min: 3,3 mg every 3-4 weeks; 40-30 ml/min: 3 mg every 3-4 weeks		

Individual therapy

http://www.londoncentreforpsychodrama.org/individual-therapy.php

Individual therapy is important in the case of drugs with a narrow therapeutic index



penicillin

Safe rate> 90% of the population

cyclosporin A

Difficult to predict a safe dose

Therapeutic drug monitoring (TDM), the optimal way to select an appropriate dose of drugs with a narrow therapeutic index, is indicated:

- In the case of drugs whose small changes in concentrations cause significant differences in the pharmacodynamic response
- When a slight decrease in the blood concentration reflects the ineffective therapy or if a small increase in concentration responsible for adverse reactions
- When 20% or less change in dose causes clinically significant and unexpected pharmacodynamic changes
- In the case of drugs characterized by at least 10-fold interindividual variability in the therapeutic range

Most immunosuppressive drugs meet the above criteria!

- Benet LZ, *Transpl Proc* 1999 -

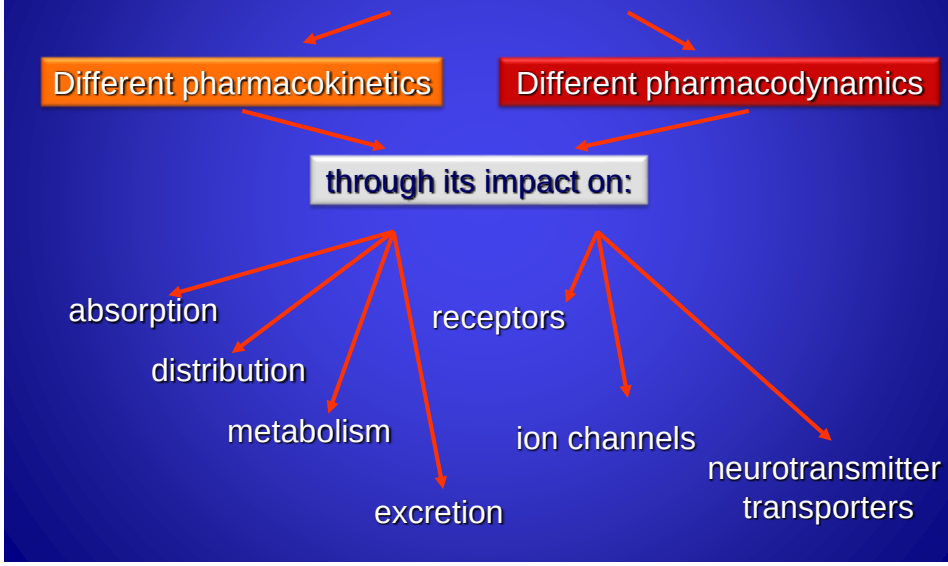
Pharmacogenetics or pharmacogenomics?

The influence of individual genes on pharmacotherapy

The impact of the entire genome for pharmacotherapy

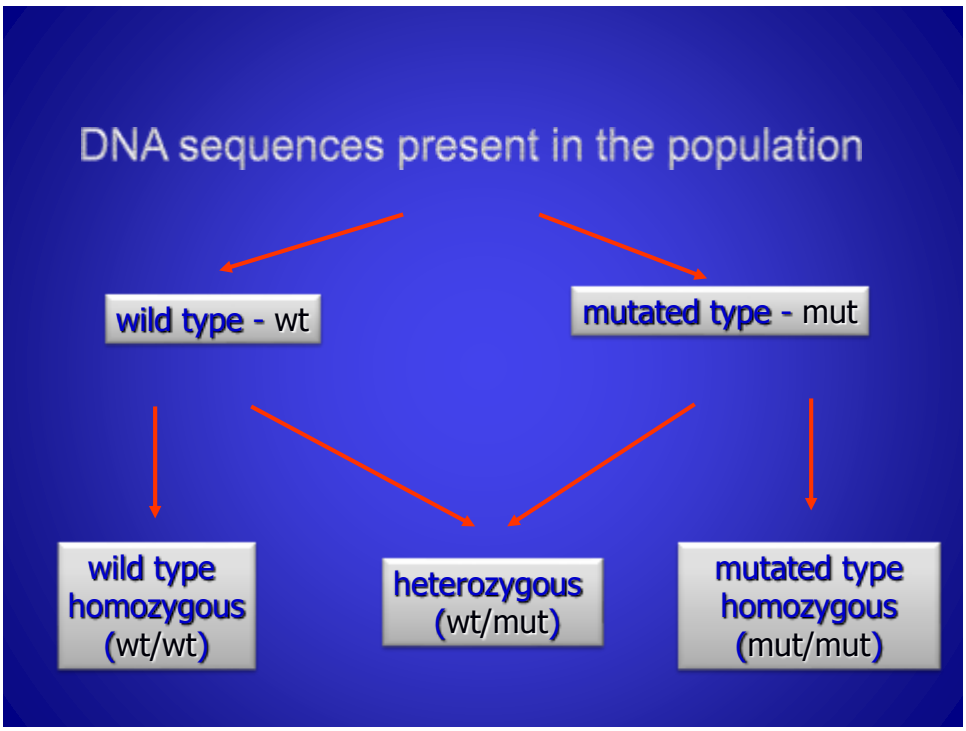
- Pharmacogenetics assesses the impact of a single gene on the effect of each drug
- Pharmacogenomics examines the impact of the whole genome (all genes), the operation of each drug, as well as assess the impact of gene-gene interactions in medicine response

Consequenses of pharmacogenetic differences



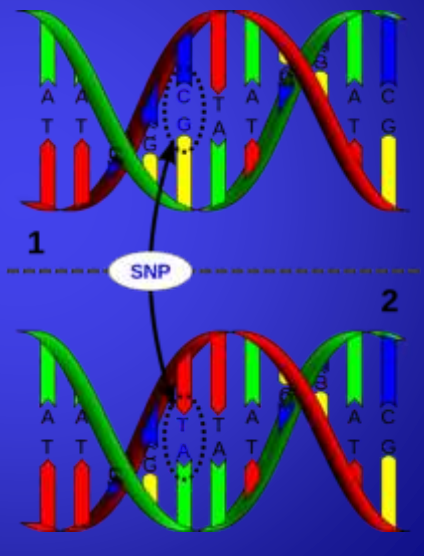
Molecular mechanisms of genetic polymorphism

- Single nucleotide mutations (Single Nucleotide Polymorphism - SNP)
- Mutation in the gene



Single Nucleotide Polymorphism (SNP)

A **Single-nucleotide polymorphism** is a DNA sequence variation occurring when a Single Nucleotide — A, T, C or G — in the genome (or other shared sequence) differs between members of a biological species or paired chromosomes



Evaluate the pharmacokinetic profile - Determination of the genotype

Frequently used:

- the method of polymerase chain reaction (*Polymerase Chain Reaction* - PCR)

in combination with

- method of analysis restriction fragment length polymorphism (*Restriction Fragment Length Polymorphism* - RFLP)

Evaluate the pharmacokinetic profile - Determination of the genotype

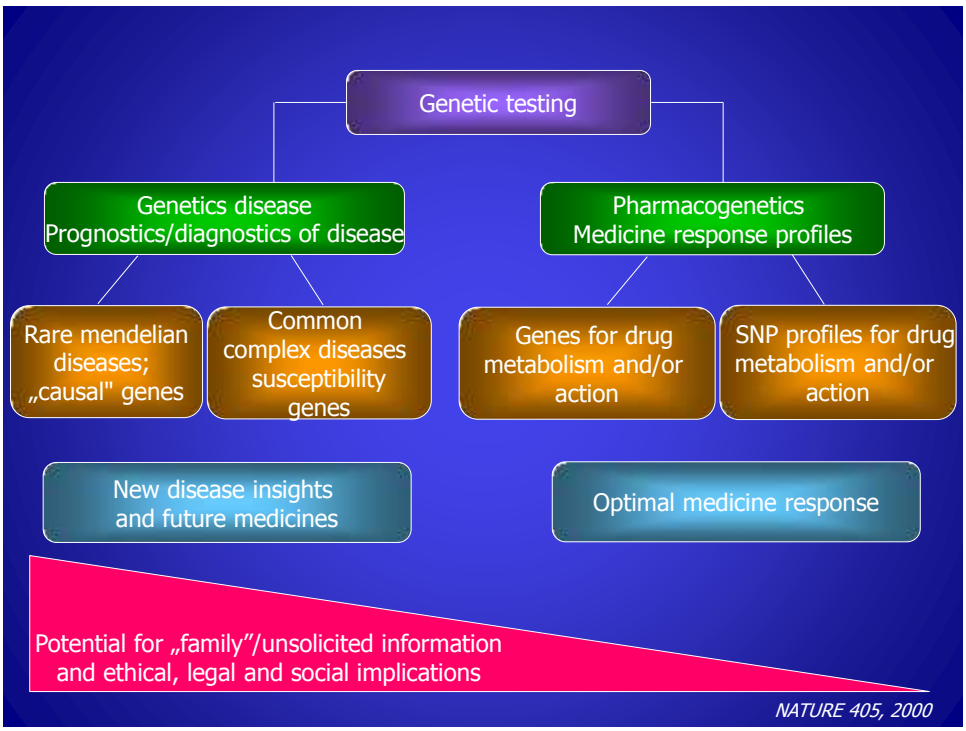
Modern method of genotyping using gene chips

(gene array)

allows the quickly determine:

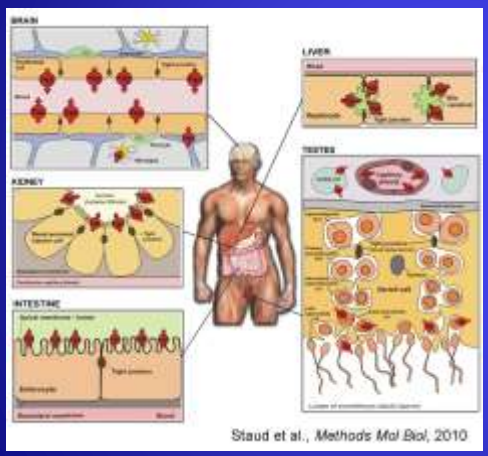
many mutations
in one individual

one mutation
in many subjects



The role of genetics in drug absorption – P-glycoprotein

Expression, localization and function of ABC transporters



Staud et al., *Methods Mol Biol*, 2010

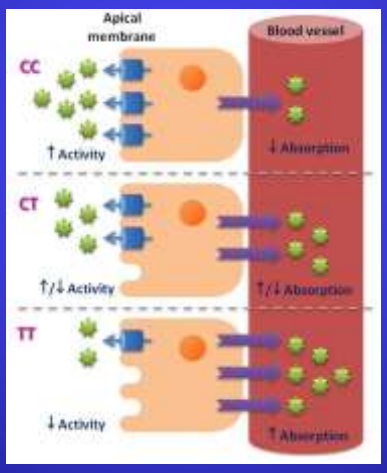
P-gp is extensively distributed and expressed in:

- the intestinal epithelium,
- liver cells,
- the cells of the proximal tubular of the kidney,
- the capillary endothelial cells and blood-testis barrier

Examples of Glycoprotein P Substrates, Inhibitors and Inducers

Substrate	Inhibitor	Inducer
aliskiren	amiodarone	avasimibe
ambrisentan	azithromycin	carbamazepine
colchicine	captopril	phenytoin
digoxin	carvedilol	rifampin
everolimus	clarithromycin	St John's Wort
fexofenadine	conivaptan	tipranavir
imatinib	cyclosporine	ritonavir
lapatinib	diltiazem	
maraviroc	erythromycin	
nilotinib	felodipine	
posaconazole	itraconazole	
ranolazine	ketoconazole	
saxagliptin	lopinavir	
sirolimus	ritonavir	
sitagliptin	quercetin	
tacrolimus	quinidine	
tolvaptan	ranolazine	
topotecan	verapamil	

Influence of the functional activity of glycoprotein-P (transporter in apical membrane) in the transport of tacrolimus (green stars) in the intestine epithelium



3435 TT variant

"Current Issues and Future Direction in Kidney Transplantation"

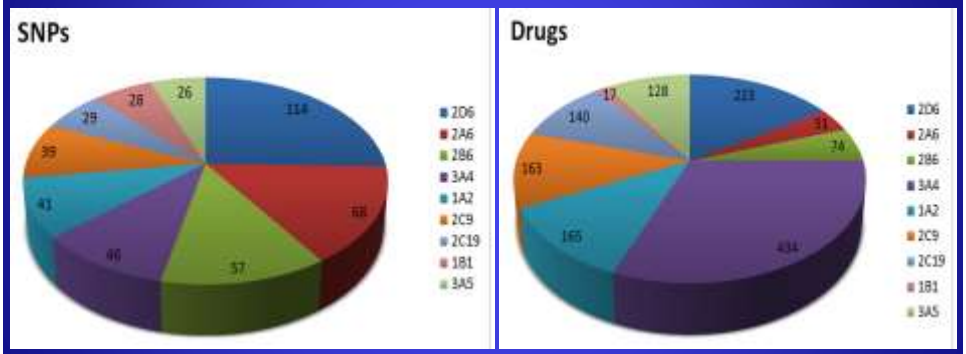
Effect of polymorphism on the transport and drug action

Transporter or target	Drug	Effect
ABCB1 (MDR1)	Digoxin, HIV protease inhibitors	↓ The bioavailability of digoxin, ↓ CD_4 response in patients with HIV
β_1-adrenergic receptor	β_1-antagonists	↓ Response of the cardiovascular system
β_2-adrenergic receptor	β_2-agonists	↓ The ability of bronchodilation
Serotonin transporter (5-HTT)	Fluoxetine	↓ Antidepressant action

- *NATURE*, 2004 -

The role of genetics in drug metabolism – cytochrome P450

SNPs and cytochrome P450



http://www.plosone.org/article/info:doi/10.1371/journal.pone.0082562

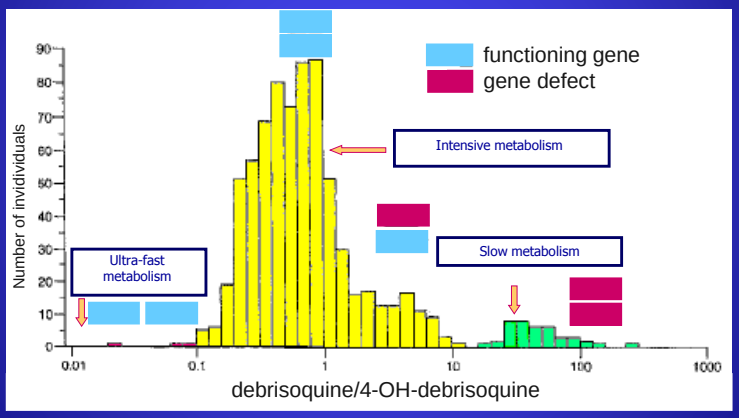
Examples of in vivo substrate, inhibitor, and inducer of specific CYP enzymes for evaluation (oral administration)

CYP	Substrate	Inhibitor	Inducer
1A2	theophylline caffeine	fluvoxamine	smokers versus non-smokers
2B6	efavirenz		rifampin
2C8	repaglinide rosiglitazone	gemfibrozil	rifampin
2C9	warfarin tolbutamide	fluconazole amiodarone	rifampin
2C19	omeprazole esoprazole lansoprazole pantoprazole	omeprazole fluvoxamine moclobemide	rifampin

Examples of in vivo substrate, inhibitor, and inducer of specific CYP enzymes for evaluation (oral administration)

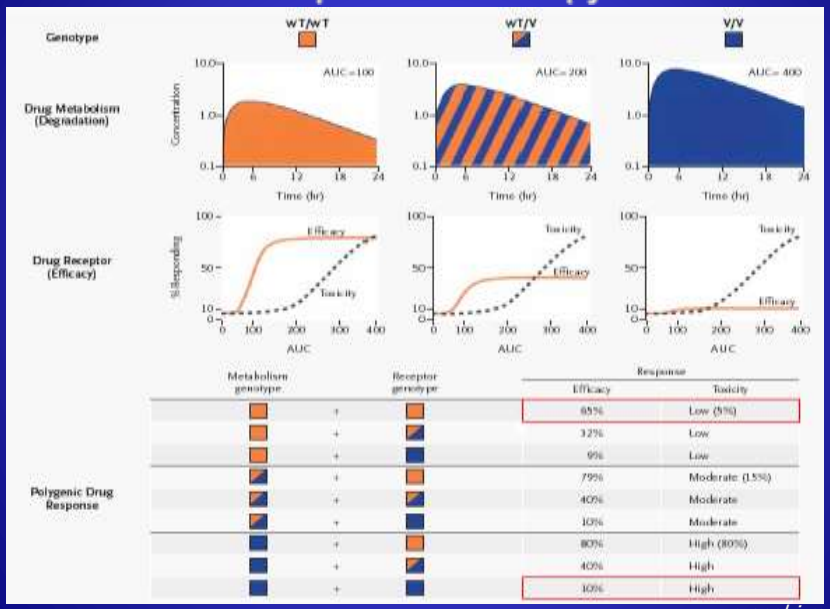
CYP	Substrate	Inhibitor	Inducer
2D6	desipramine, dextromethorphan, atomoxetine	paroxetine, quinidine, fluoxetine	none identified
2E1	chlorzoxazone	disulfirum	ethanol
3A4/ 3A5	midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, triazolam	atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin	rifampin, carbamazep

Effect of CYP2D6 polymorphism on drug metabolism



Bertilsson, *Clin Pharmacol Ther* 1992 -

Genetic variation and the effectiveness of pharmacotherapy



- *n engl j med* 2003 -

Effect of polymorphism on the phase I metabolism

Metabolizing enzyme	The incidence of slow metabolizing phenotype	Drug	Effect of SNP
Cytochrome P 450 2D6 (CYP2D6)	6.8% of Swedes 1% of the Chinese	Codeine	↓ Therapeutic effect
Cytochrome P 450 2C9 (CYP2C9)	3% of the British	Warfarin Phenytoin	↑ Therapeutic effect
Cytochrome P 450 2C19 (CYP2C19)	2.7% of white Americans 3.3% of Swedes 14.6% of the Chinese 18% of Japanese people	Omeprazole	↑ Therapeutic effect
Dihydropyrimidine dehydrogenase	1% of the world's population is heterozygous	Fluorouracil	↑ Therapeutic effect
Butyrylocholino-esterase (pseudocholino-esteraze)	1 on the 3500 Europeans	Succinylcholine	↑ Therapeutic effect

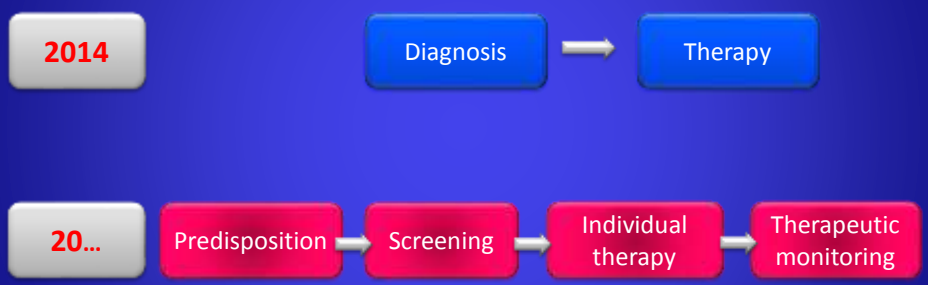
- *N Engl J Med.*, 2003 -

Effect of polymorphism on the phase II metabolism

Metabolizing enzyme	The incidence of slow metabolizing phenotype	Drug	Effect of SNP
N-acetyltransferase 2	52% of white Americans 17% of Japanese people	Isoniazid Hydralazine Procainamide	↑ Therapeutic effect
Uridine diphospho-glucuronosyltran-sferases 1A1	10.9% of the population of white 4% of the Chinese 1% of Japanese people	Irinotecan Bilirubin	↑ Therapeutic effect
S-thiopurine methyltransferase	1 in 300 white 1 2500 Asians	Mercaptopurine Azathioprine	↑ Therapeutic effect
Catechol-O-methyltransferase	25% of the white population	Levodopa	↑ Therapeutic effect

- *N Engl J Med.*, 2003 -

Today's diagnosis and the prospect for tomorrow



NATURE, 429, 2004

- Is molecular polymorphism of drug-metabolizing enzymes responsible for the rate of drug metabolism? Yes/No
- Is possible to evaluate pharmacokinetic profile of patient by genotyping? Yes/No
- Is genotyping invasive method for the patient? Yes/No

Contributors

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Dr. Arkadiusz Surazynski

Proper answers to the questions

1. YES
2. YES
3. NO