14th Residential Course on Clinical Pharmacology of Antiretrovirals
16th January 2019

Before Liverpool site: how to evaluate a potential DDI

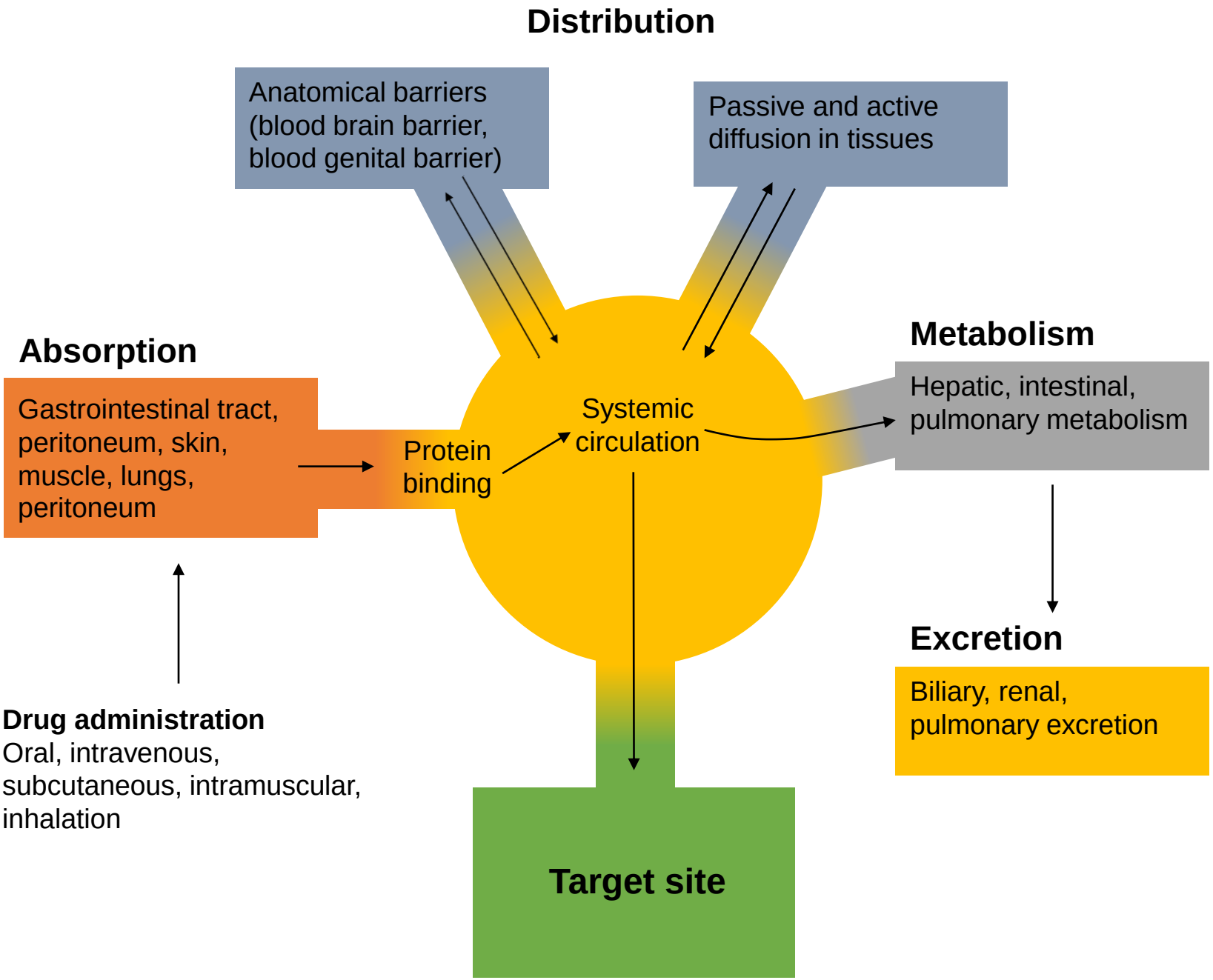
Marco Siccardi

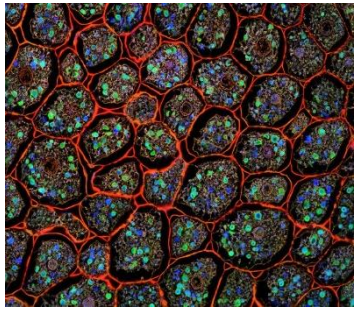
UNIVERSITY OF LIVERPOOL

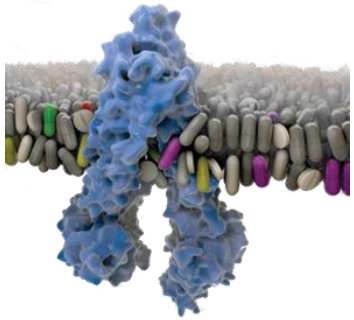
Can we predict magnitude and relevance of DDIs?

Why are DDIs complex?

- Variety of different mechanisms underpinning DDIs
- Effects on efficacy and potential toxicity
- Effect of comorbidities on drug disposition
- Aging population of HIV patients
- Other special populations
- Increasing frequency of polypharmacy
- Complex therapies
- Constant “flow” of new agents


Distribution
Anatomical barriers (blood brain barrier, blood genital barrier)
Passive and active diffusion in tissues
Absorption
Gastrointestinal tract, peritoneum, skin, muscle, lungs, peritoneum
Protein binding
Systemic circulation
Metabolism
Hepatic, intestinal, pulmonary metabolism
Excretion
Biliary, renal, pulmonary excretion
Drug administration
Oral, intravenous, subcutaneous, intramuscular, inhalation
Target site





Patients

Volunteers

Transgenic animals

Animals

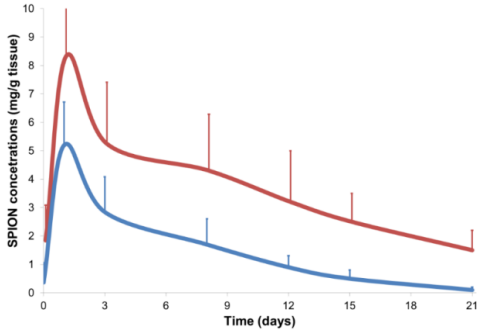
Tissue/Cells

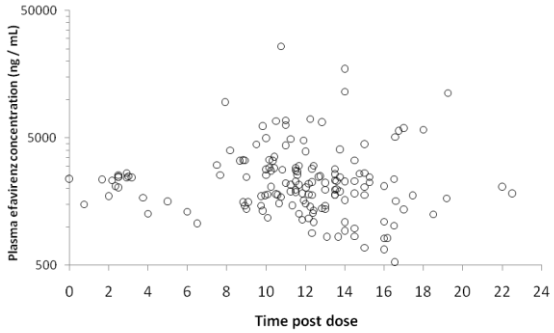
Subcellular fractions

Proteins

RELEVANCE

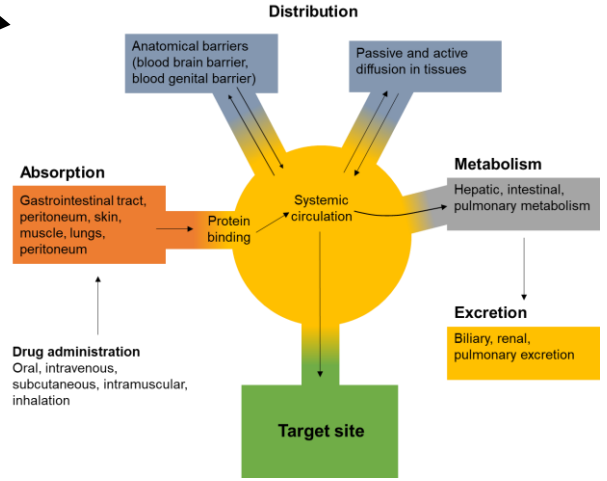
MECHANISMS





BOTTOM-UP

TOP-DOWN



Analysis of Clinical Drug-Drug Interaction Data To Predict Magnitudes of Uncharacterized Interactions between Antiretroviral Drugs and Comedications

Felix Stader,[a,b,c] Hannah Kinvig,[d] Manuel Battegay,[a,c] Saye Khoo,[d] Andrew Owen,[d] Marco Siccardi,[d] Catia Marzolini[a,c]

July 2018 Volume 62 Issue 7 Antimicrobial Agents and Chemotherapy

Good understanding of ADME

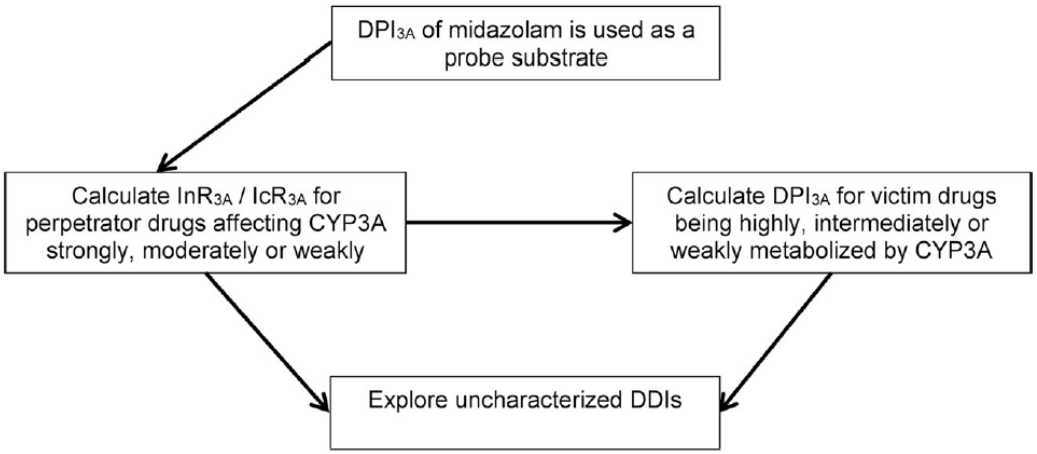
Existing clinical data

Victim

fraction of the disposition pathway mediated by CYP3A [DPI_{3A}]

Perpetrator

CYP3A inhibitor or inducer ratios [InR_{3A}/IcR_{3A}])



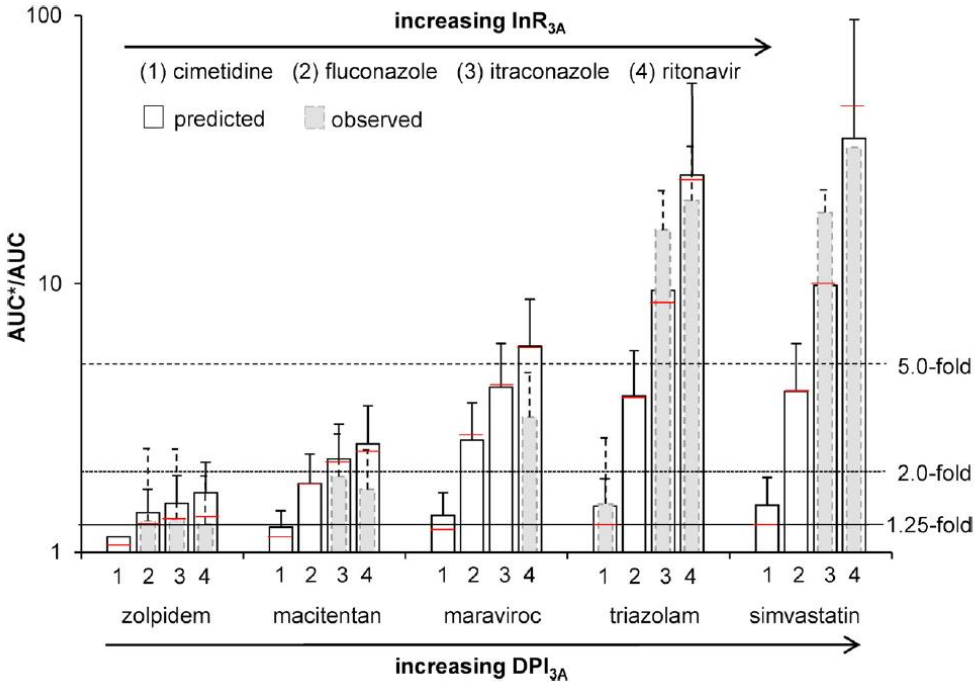
Workflow of the study. DPI_{3A}, fraction of disposition pathway mediated by CYP3A; InR_{3A}, inhibitor ratio; IcR_{3A}, inducer ratio.

$$InR_x = \frac{1 - \frac{AUC}{AUC^*}}{DPI_x}$$

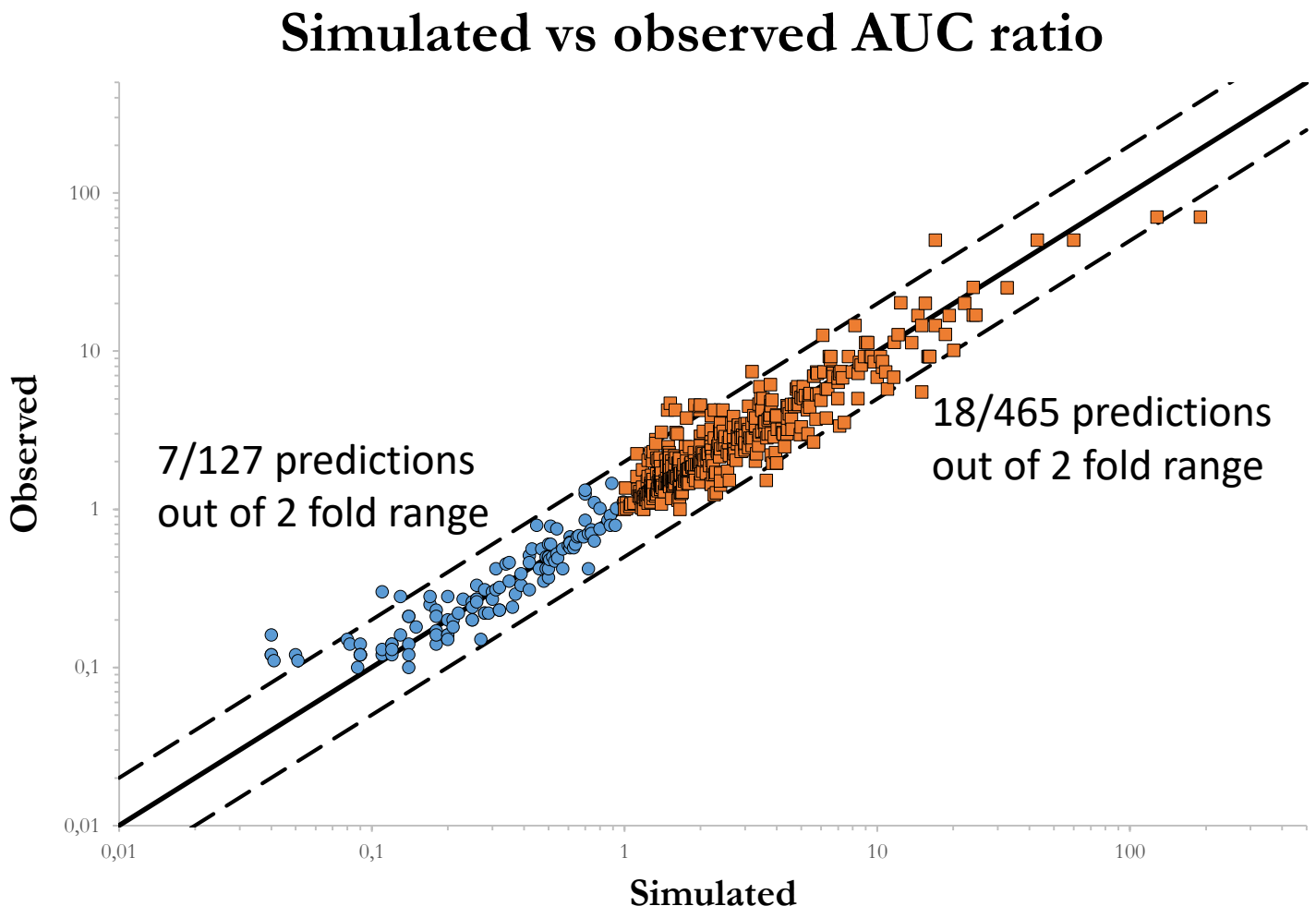
$$DPI_x = \frac{1 - \frac{AUC}{AUC^*}}{InR_x}$$

TABLE 1 Calculated fraction of the disposition pathway mediated by CYP3A (DPI_{3A}) of victim drugs sorted by their CYP3A sensitivities[b]

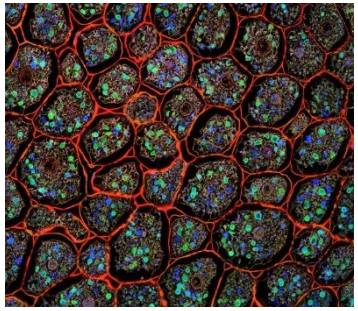
	DPI_{3A}			Predicted AUC*/AUC with:			
				Ritonavir (inhibitor)		Etravirine (inducer)	
Drug	Single calculation	Monte Carlo simulation	Reference(s)[a]	Single calculation	Monte Carlo simulation	Single calculation	Monte Carlo simulation
Simvastatin	0.978	0.979 [0.916, 1.0]	12	45.97	34.54 [5.33, 100.0]	0.34	0.31 [0.12, 0.44]
Triazolam	0.959	0.966 [0.898, 1.0]	30, 31	24.39	24.97 [4.91, 100.0]	0.35	0.31 [0.12, 0.44]
Midazolam	0.940	0.940 [0.909, 0.971]	32–35	16.67	12.36 [5.40, 20.64]	0.35	0.32 [0.13, 0.45]
Quetiapine	0.896	0.845 [0.645, 1.0]	37	9.66	7.97 [2.42, 62.46]	0.36	0.34 [0.14, 0.47]
Tacrolimus	0.875	0.831 [0.531, 1.0]	36	8.03	10.20 [1.97, 100.0]	0.37	0.34 [0.14, 0.48]
Maraviroc	0.828	0.792 [0.559, 0.998]	38	5.80	5.85 [1.98, 31.26]	0.38	0.35 [0.14, 0.49]
Saquinavir	0.638	0.580 [0.258, 0.849]	39	2.76	2.88 [1.31, 6.04]	0.44	0.42 [0.18, 0.57]
Darunavir	0.602	0.543 [0.215, 0.817]	40	2.51	2.62 [1.26, 5.19]	0.46	0.43 [0.18, 0.59]
Macitentan	0.585	0.524 [0.200, 0.810]	41	2.41	2.55 [1.24, 4.98]	0.47	0.43 [0.19, 0.59]
Amlodipine	0.468	0.464 [0.117, 1.0]	16	1.88	2.75 [1.12, 30.13]	0.52	0.46 [0.19, 0.64]
Etravirine	0.340	0.336 [0.077, 0.701]	42	1.52	1.79 [1.08, 3.18]	0.60	0.52 [0.24, 0.71]
Rilpivirine	0.324	0.334 [0.079, 0.656]	43	1.48	1.73 [1.08, 2.84]	0.61	0.53 [0.24, 0.71]
Zolpidem	0.268	0.303 [0.065, 0.661]	44, 45	1.37	1.66 [1.06, 2.79]	0.66	0.55 [0.25, 0.73]
Ritonavir	0.156	0.231 [0.038, 0.552]	46	1.19	1.46 [1.04, 2.19]	0.77	0.60 [0.29, 0.78]

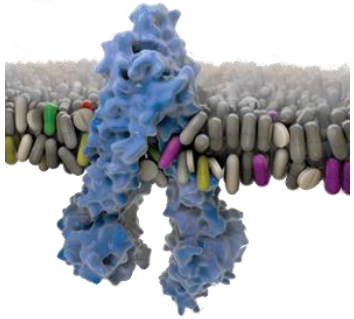


Is this approach working?



Goutelle et al 2013
Ohno et al 2008
Castellan et al 2013
Yamashita et al 2013
Tod et al 2016
Ohno et al 2006





RELEVANCE

Patients

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Transgenic animals

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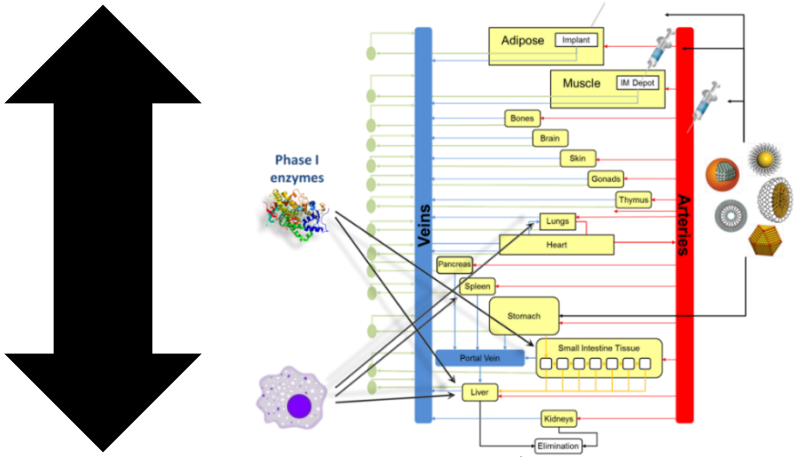
Tissue/Cells

Subcellular fractions

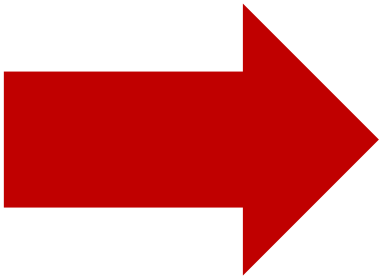
Proteins



MECHANISMS

PERPETRATOR

VICTIM



INHIBITORY POTENTIAL

INDUCTION POTENTIAL

PHASE I METABOLISM

PHASE II METABOLISM

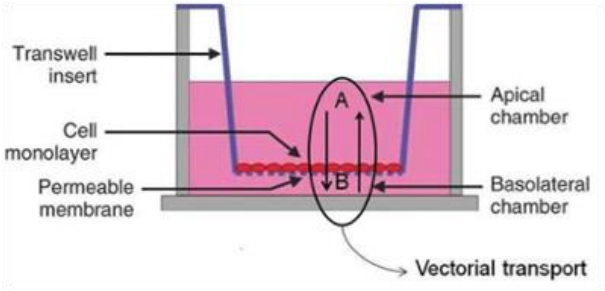
TRANSPORTERS

ALTERED SOLUBILITY

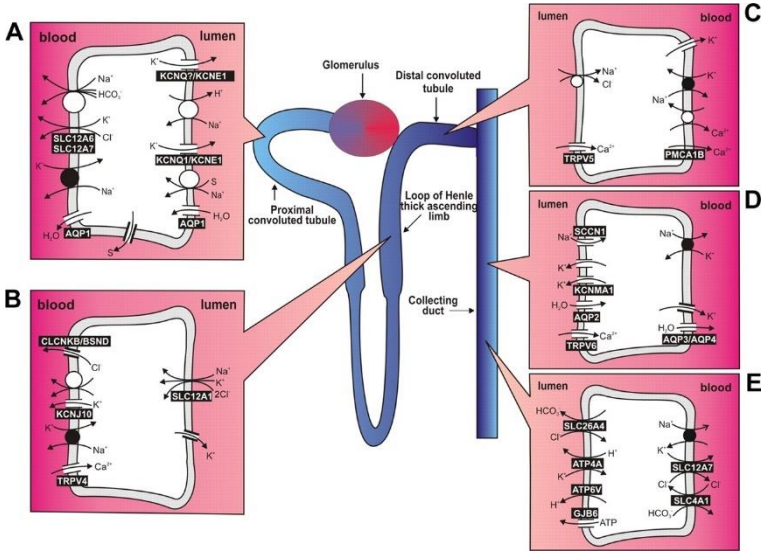
PROTEIN BINDING

Experimental methods to characterise drug-drug interactions

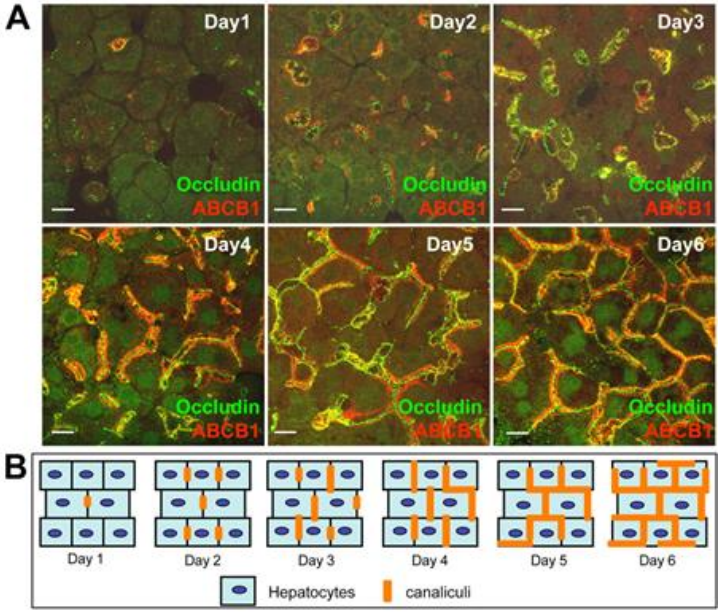
Intestinal absorption



Renal elimination

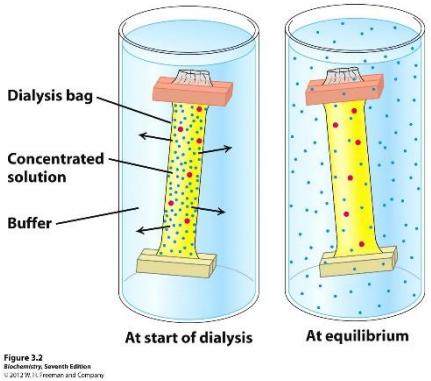


Hepatobiliary elimination

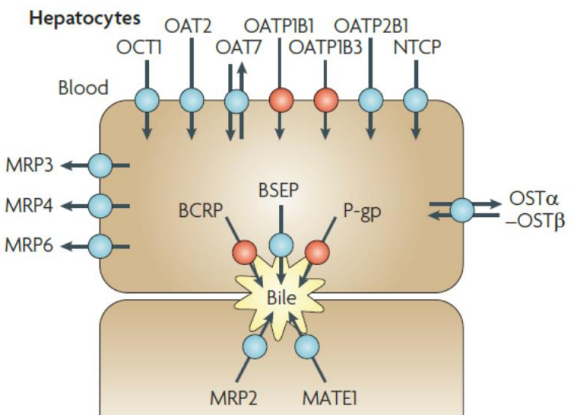


Swift et al 2010

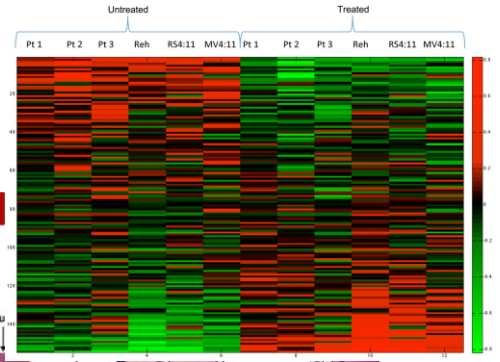
Protein binding in plasma



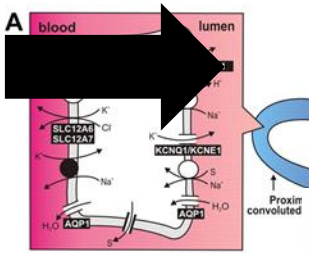
Transporter activity



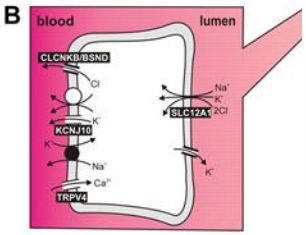
mRNA

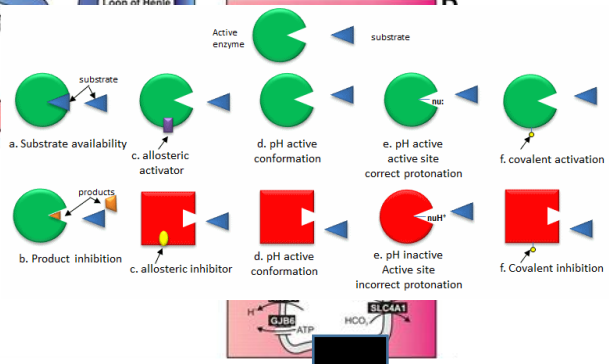


Renal el

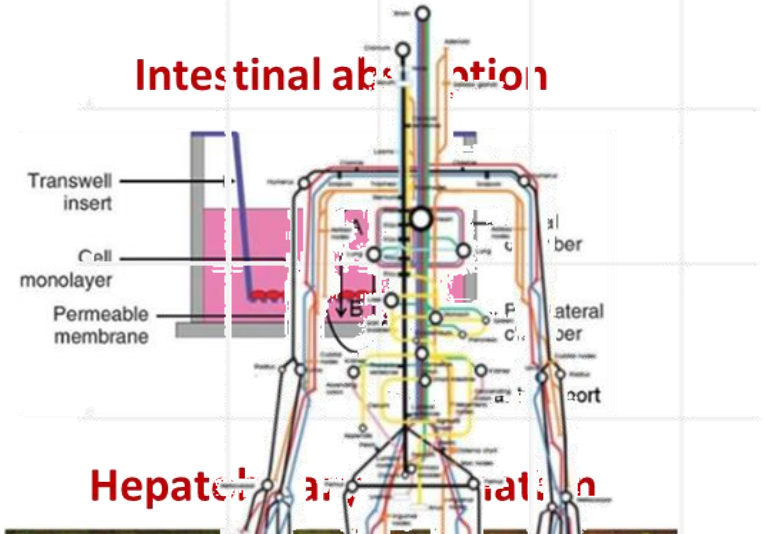


Enzymatic activity

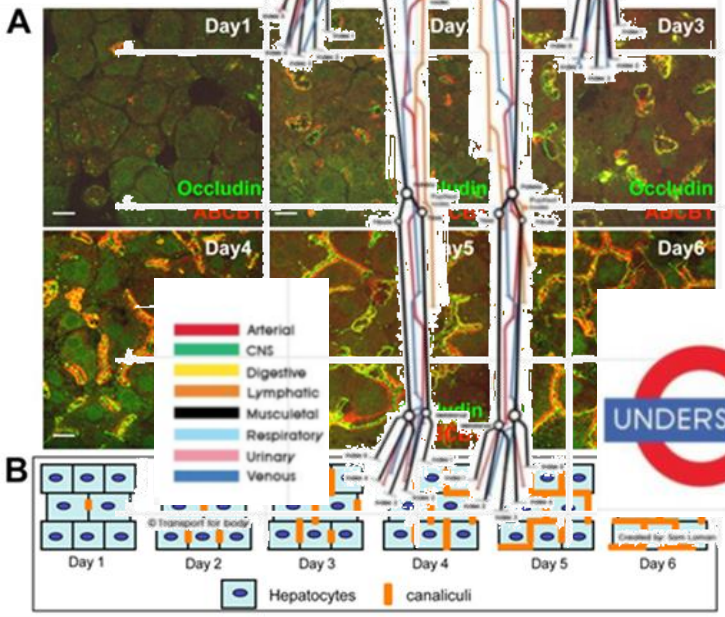




Intestinal abs tion

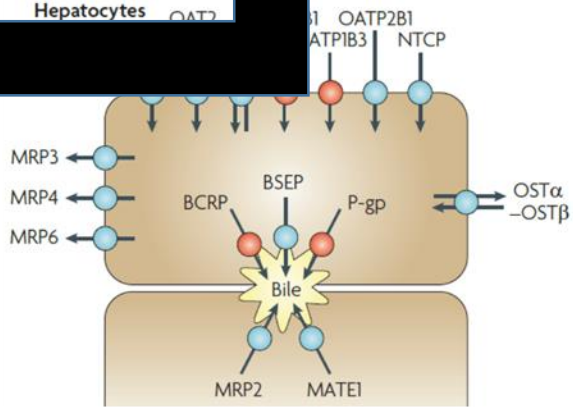


Hepate ial n

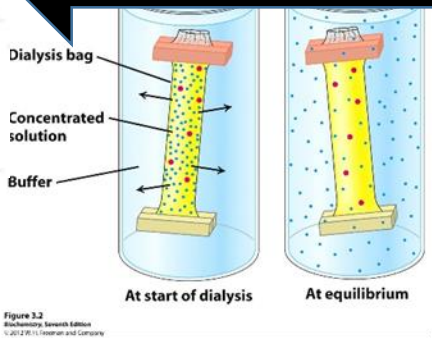


Swift et al 2010

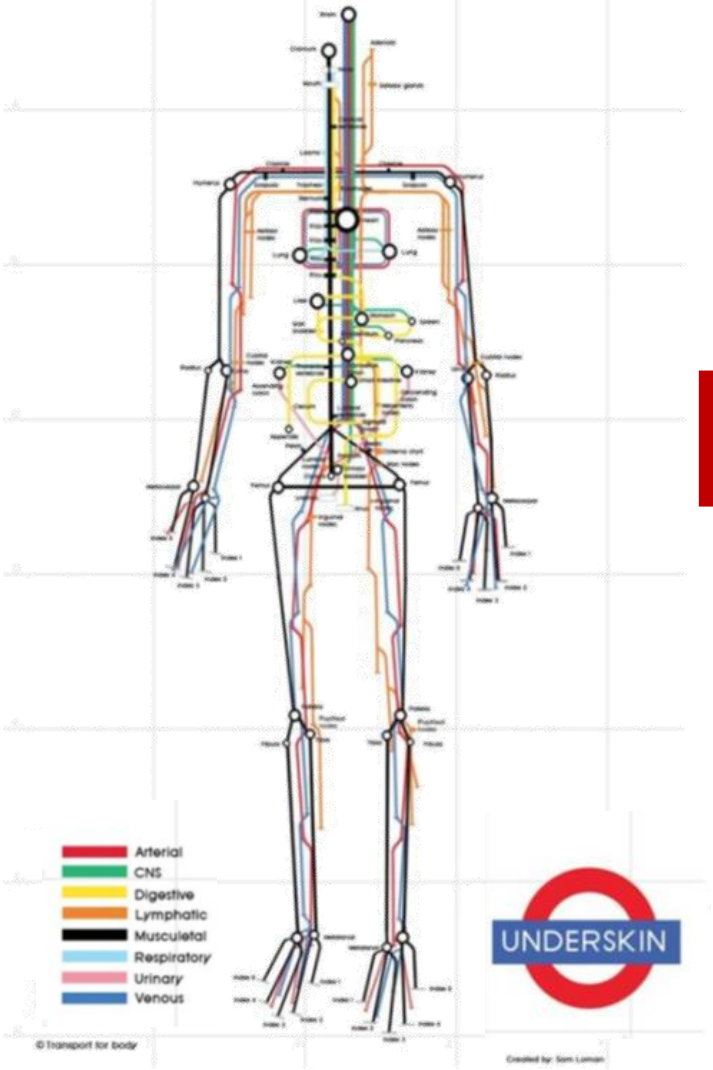
Transpo activity



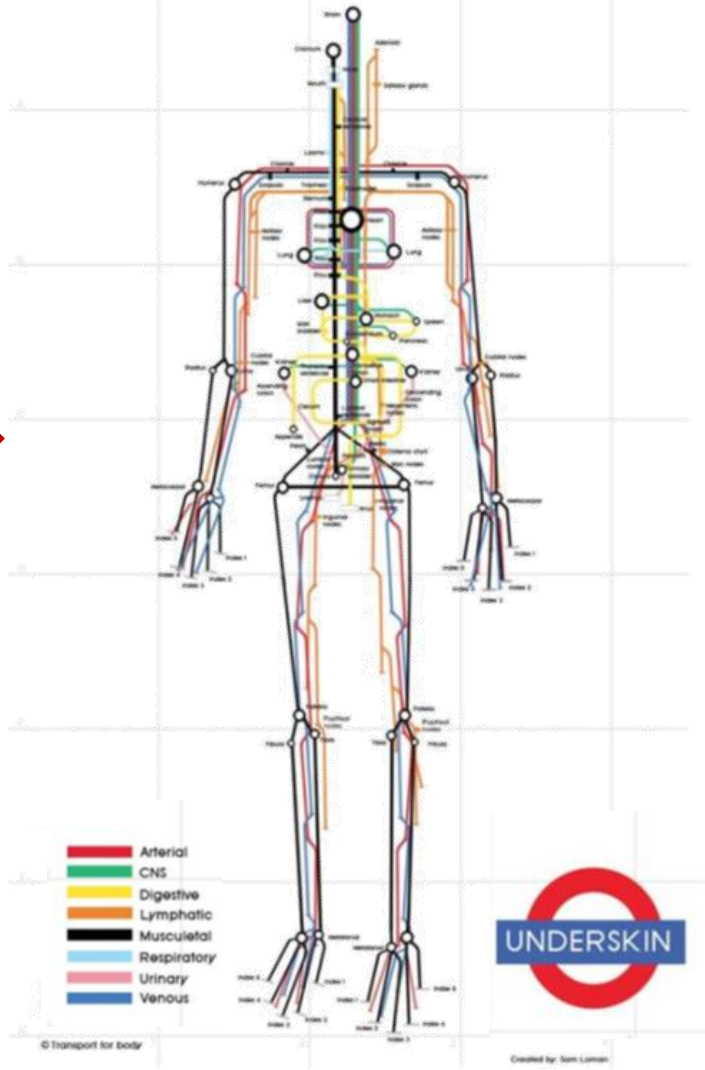
Pr ein binding in plasma

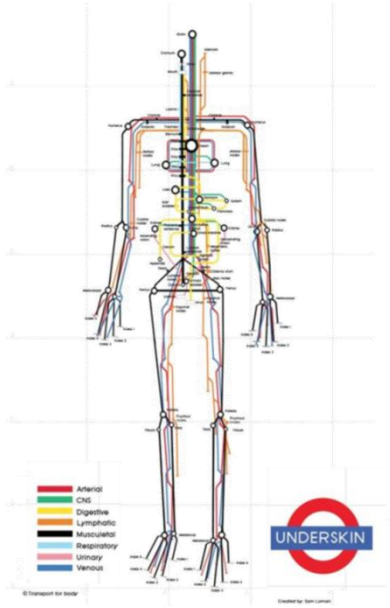


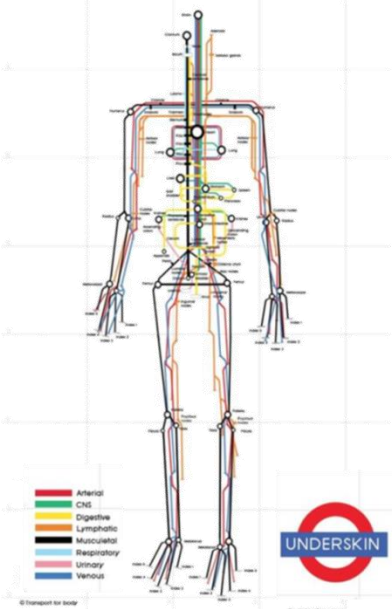
PERPETRATOR



VICTIM




Arterial
CNS
Digestive
Lymphatic
Musculetal
Respiratory
Urinary
Venous
UNDERSKIN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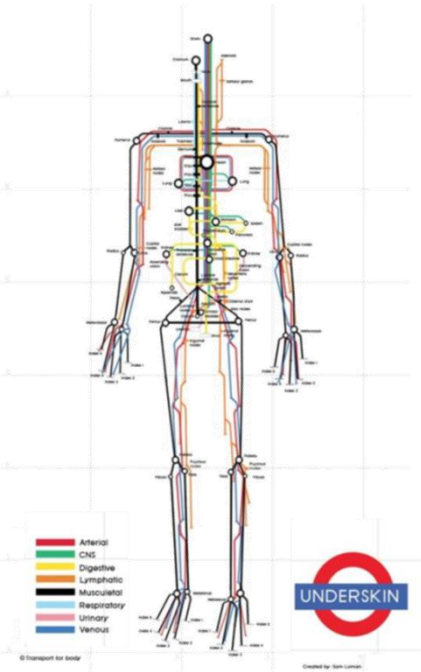
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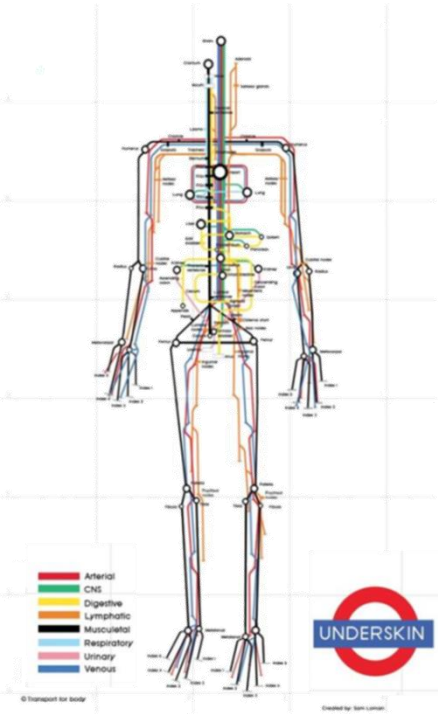
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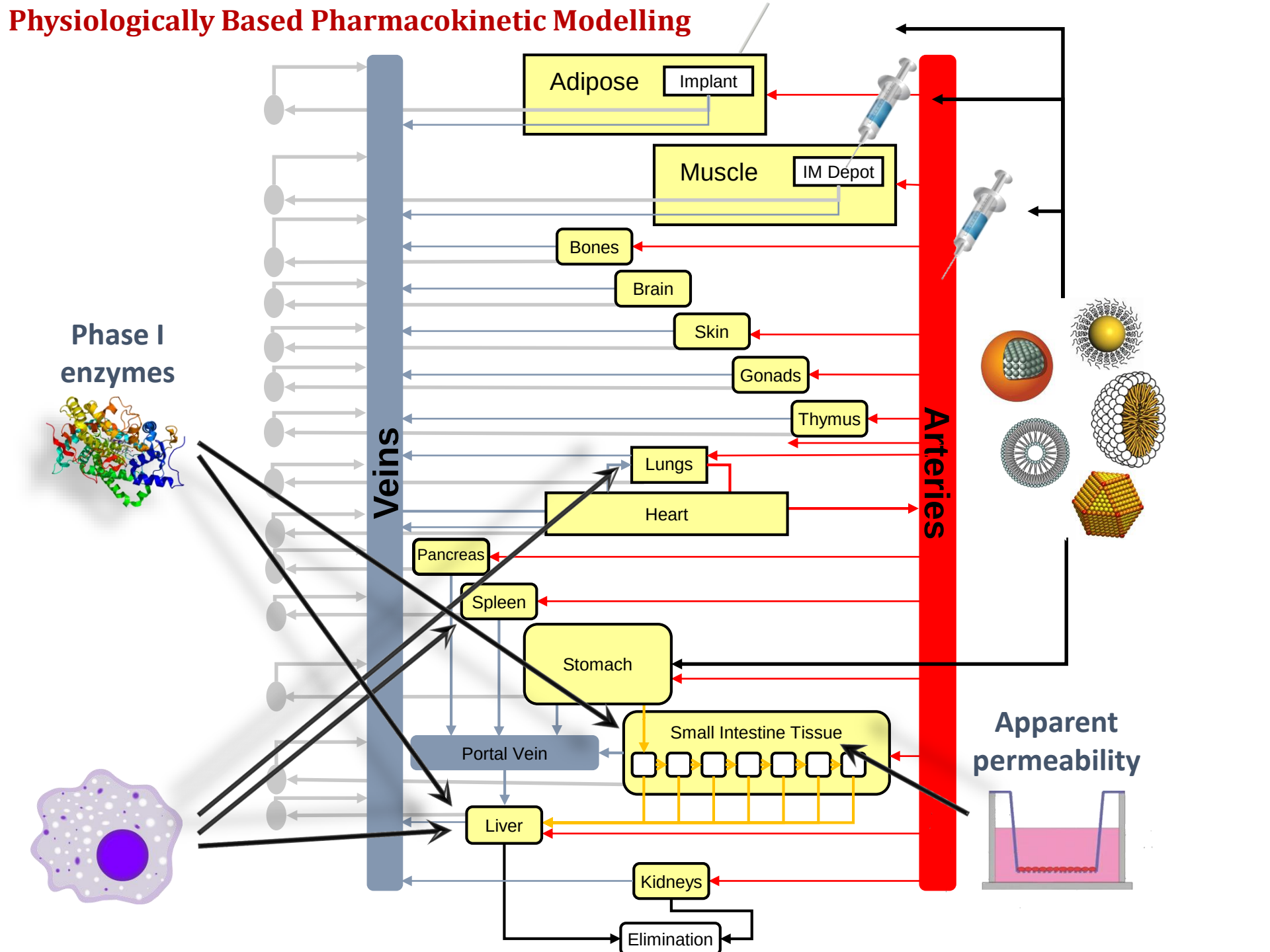
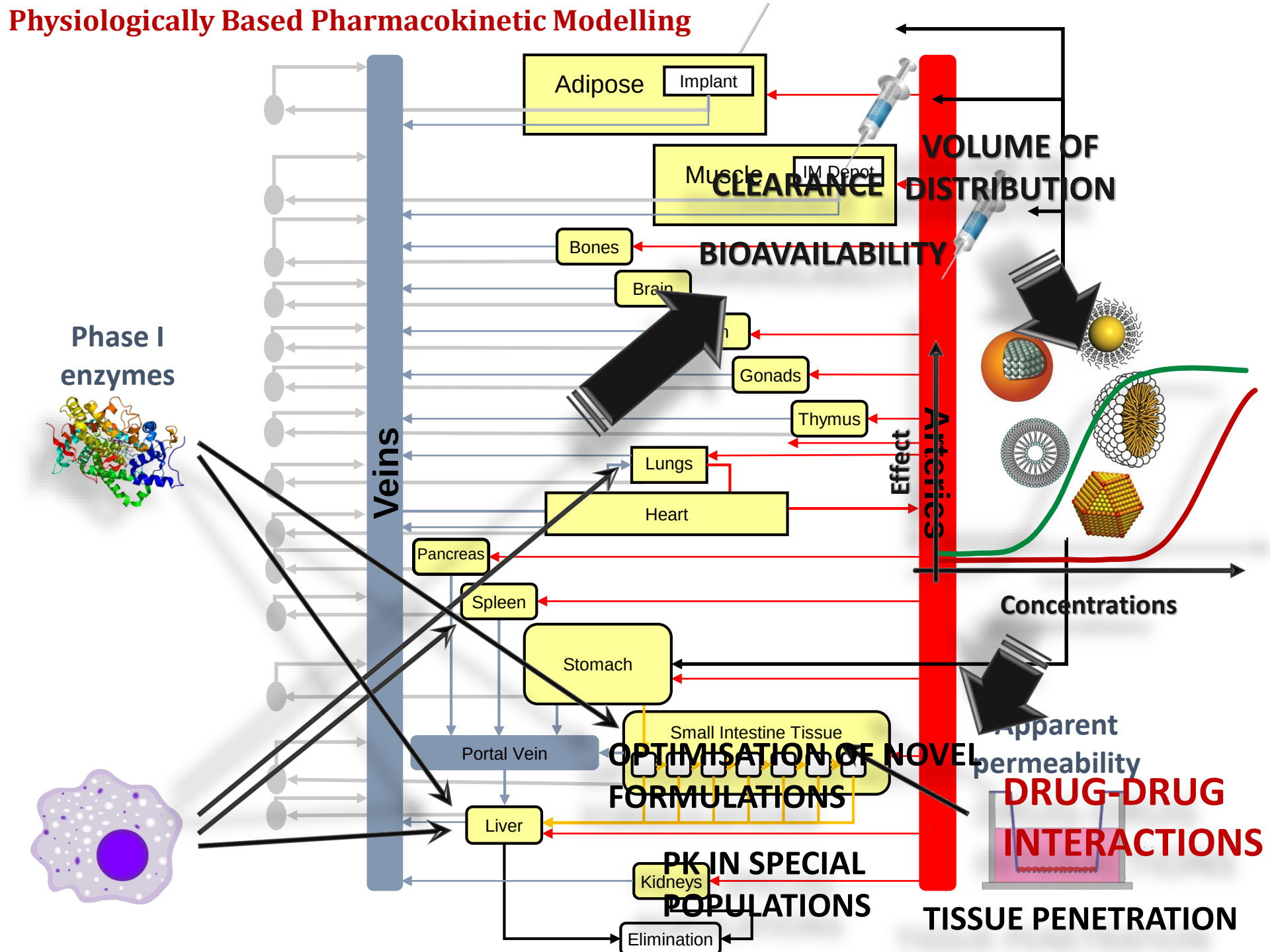
Physiologically Based Pharmacokinetic Modelling



Physiologically Based Pharmacokinetic Modelling

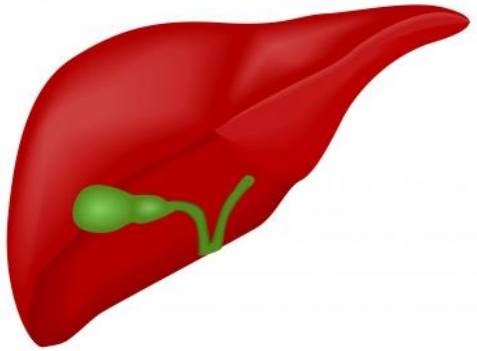


In vitro CL_{int}

CL_{int} x gram of liver

AMOUNT OF ENZYME x GRAM OF LIVER

LIVER WEIGHT



CL_{int} x whole liver

AGE

WEIGHT

GENDER

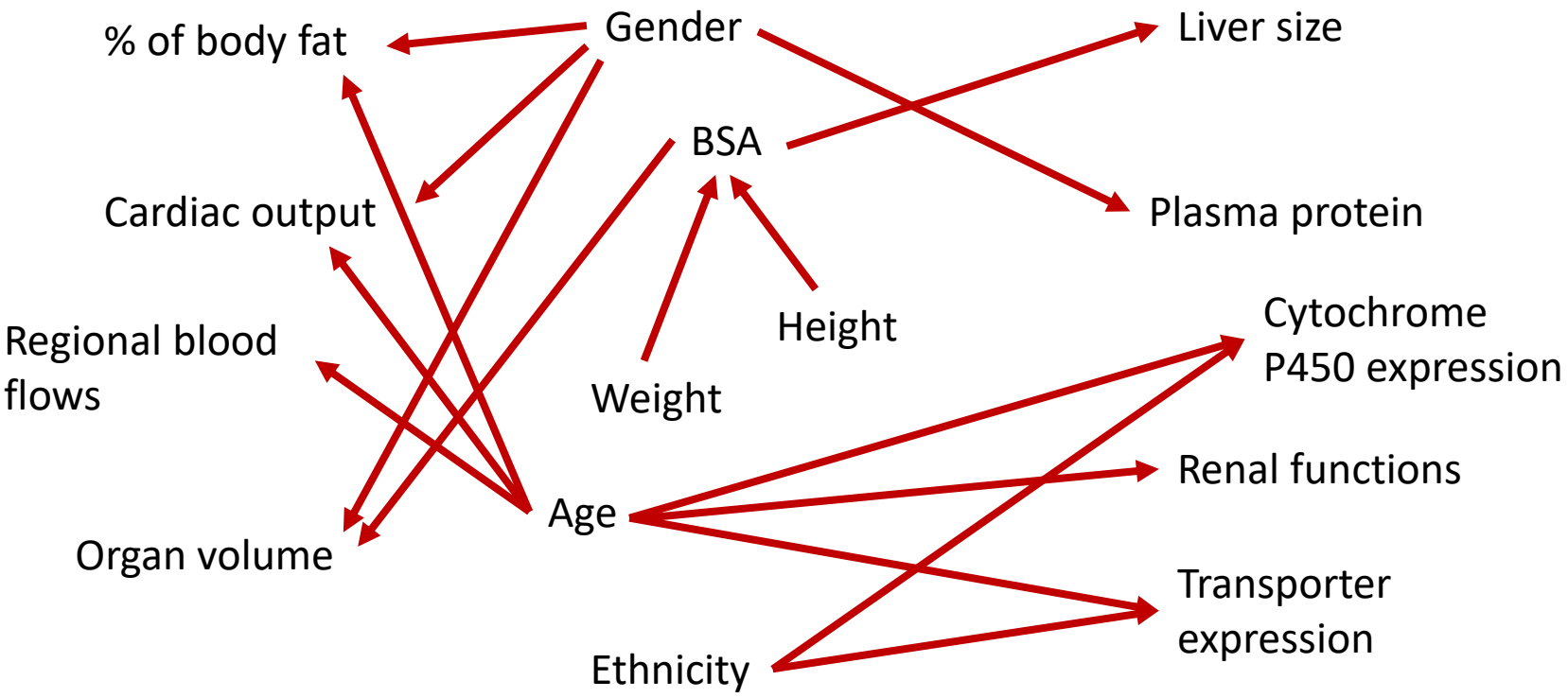
ETHNICITY

DISEASES

GENETICS

COMEDICATIONS

Population Variability



Physiologically Based Pharmacokinetic Modeling to Predict Drug–Drug Interactions with Efavirenz Involving Simultaneous Inducing and Inhibitory Effects on Cytochromes

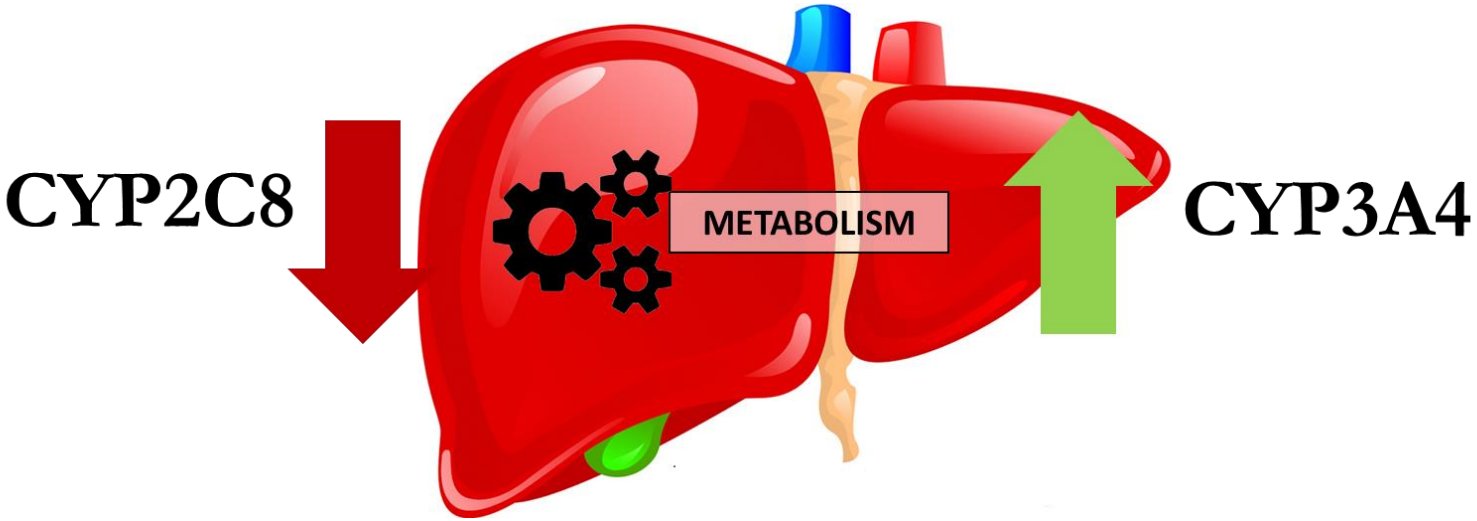
Catia Marzolini[1,2] · Rajith Rajoli[3] · Manuel Battegay[1,2] · Luigia Elzi[4] · David Back[3] · Marco Siccardi[3]

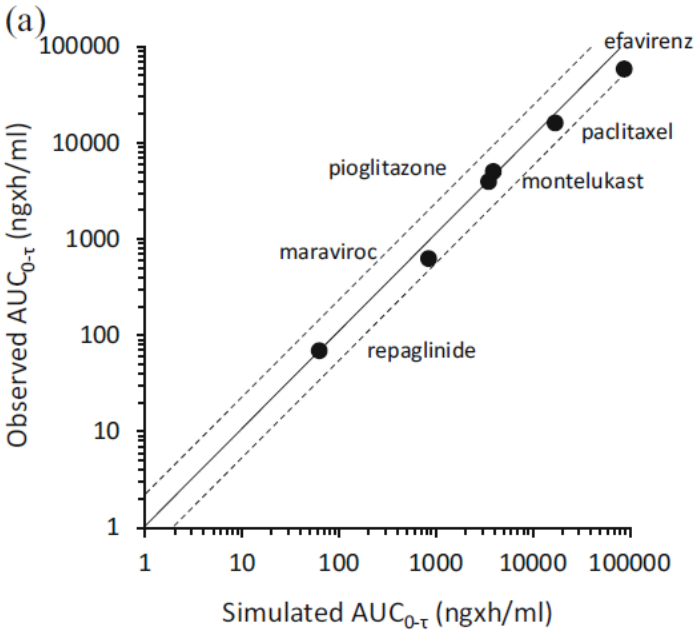
Clin Pharmacokinet
DOI 10.1007/s40262-016-0447-7

Repaglinide, pioglitazone, montelukast and paclitaxel = **substrates CYP2C8 + CYP3A4**

Efavirenz = **inducer CYP3A4** and **inhibitor CYP2C8**

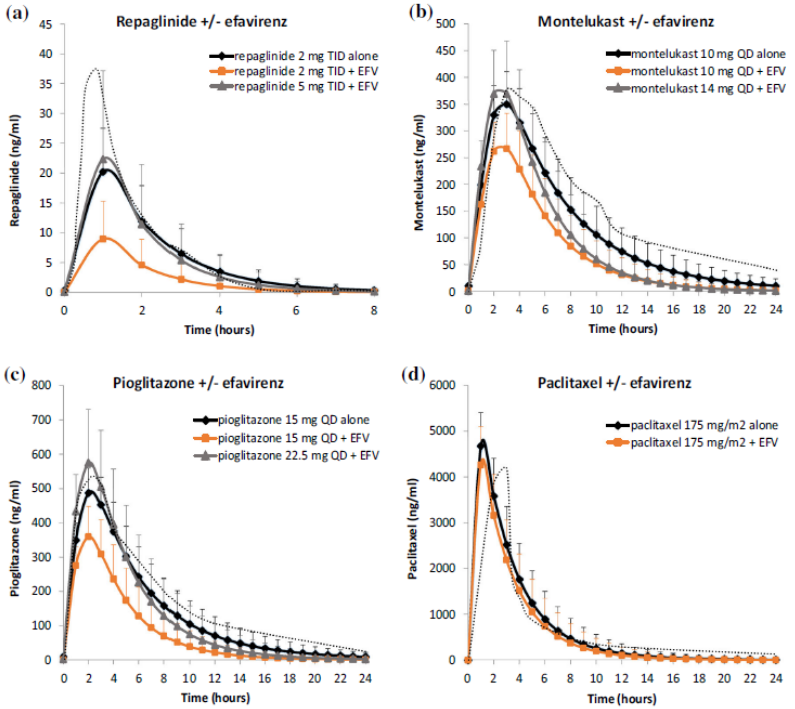
Aim = to predict PK and relative DDIs and to simulate potential dose adjustment to overcome DDI

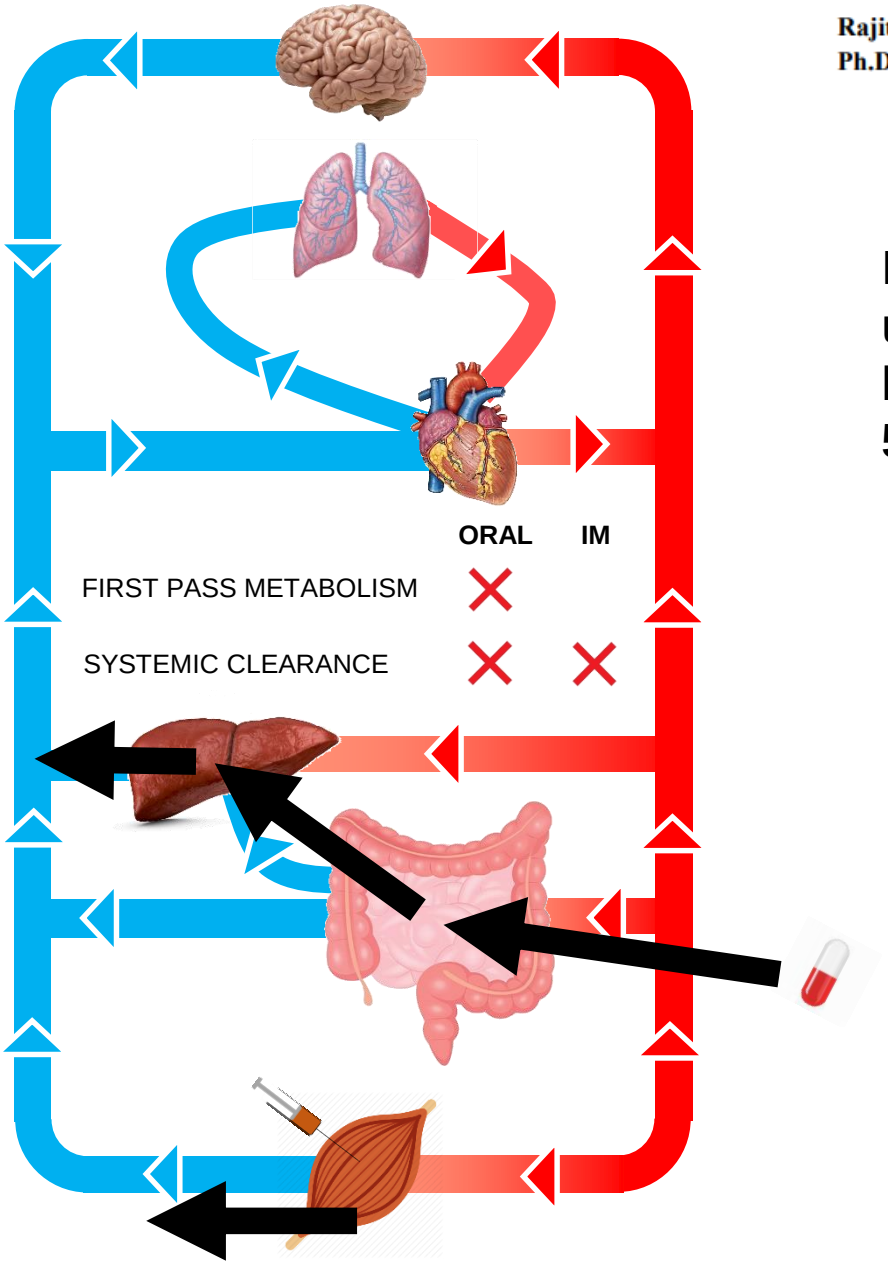




Parameter	AUC_τ GMR (90 % CI)	C_{max} GMR (90 % CI)
Repaglinide (2 mg tid) + EFV / Repaglinide (2 mg tid) alone	0.35 (0.30–0.42)	0.40 (0.35–0.46)
Repaglinide (5 mg tid) + EFV / Repaglinide (2 mg tid) alone	1.01 (0.83–1.20)	1.11 (0.95–1.29)
Montelukast (10 mg od) + EFV / Montelukast (10 mg od) alone	0.60 (0.53–0.68)	0.77 (0.72–0.82)
Montelukast (14 mg od) + EFV / Montelukast (10 mg tid) alone	0.79 (0.70–0.89)	1.07 (1.00–1.14)
Pioglitazone (15 mg od) + EFV / Pioglitazone (15 mg od) alone	0.55 (0.48–0.63)	0.73 (0.68–0.77)
Pioglitazone (22.5 mg od) + EFV / Pioglitazone (15 mg od) alone	0.91 (0.81–1.05)	1.15 (1.07–1.23)
Paclitaxel (175 mg/m^2) + EFV / Paclitaxel (175 mg/m^2) alone	0.86 (0.76–0.96)	0.91 (0.86–0.96)

AUC_τ area under the plasma concentration–time curve over a dosing interval, *CI* confidence interval, *C_{max}* maximum plasma concentration, *EFV* efavirenz, *GMR* geometric mean ratio, *od* once daily, *tid* three times daily





Predicting drug-drug interactions between rifampicin and long-acting cabotegravir and rilpivirine using PBPK modelling

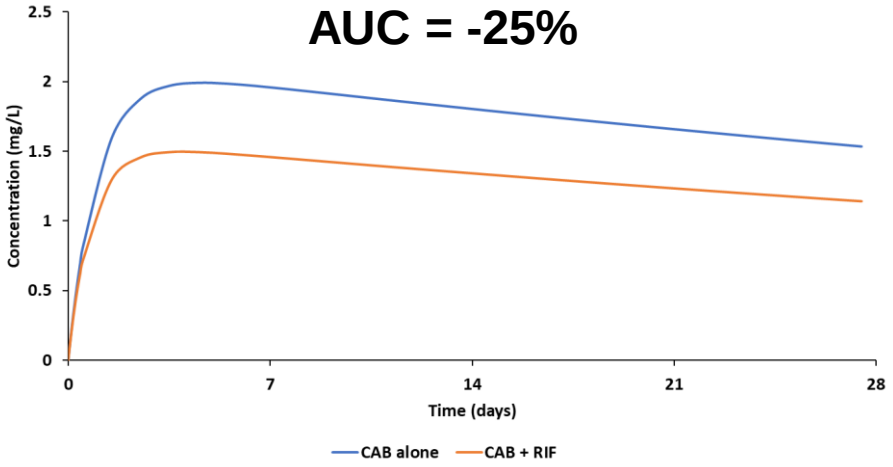
Rajith KR Rajoli, Ph.D.[1], Paul Curley, Ph.D.[1], Justin Chiong, MBA[1], Prof David Back, Ph.D.[1], Prof Charles Flexner, M.D.[2], Prof Andrew Owen, Ph.D.[1], Marco Siccardi, Ph.D.[1]

Oral cabotegravir

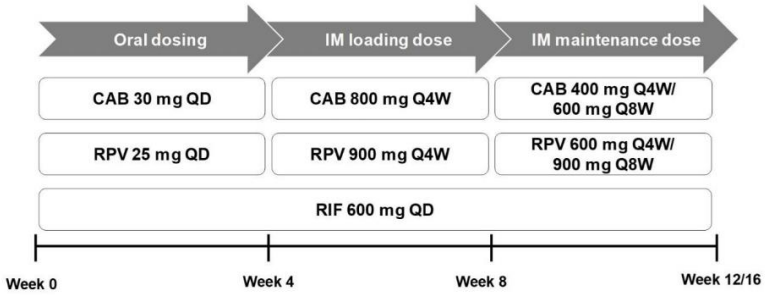
Rifampin decreased the cabotegravir area under the concentration-time curve from 0 h to infinity and the half-life by **59% and 57%**

Long-acting cabotegravir

AUC = -25%



Pharmacokinetic IM cabotegravir (800 mg IM) with and without rifampicin (600 mg OD oral)



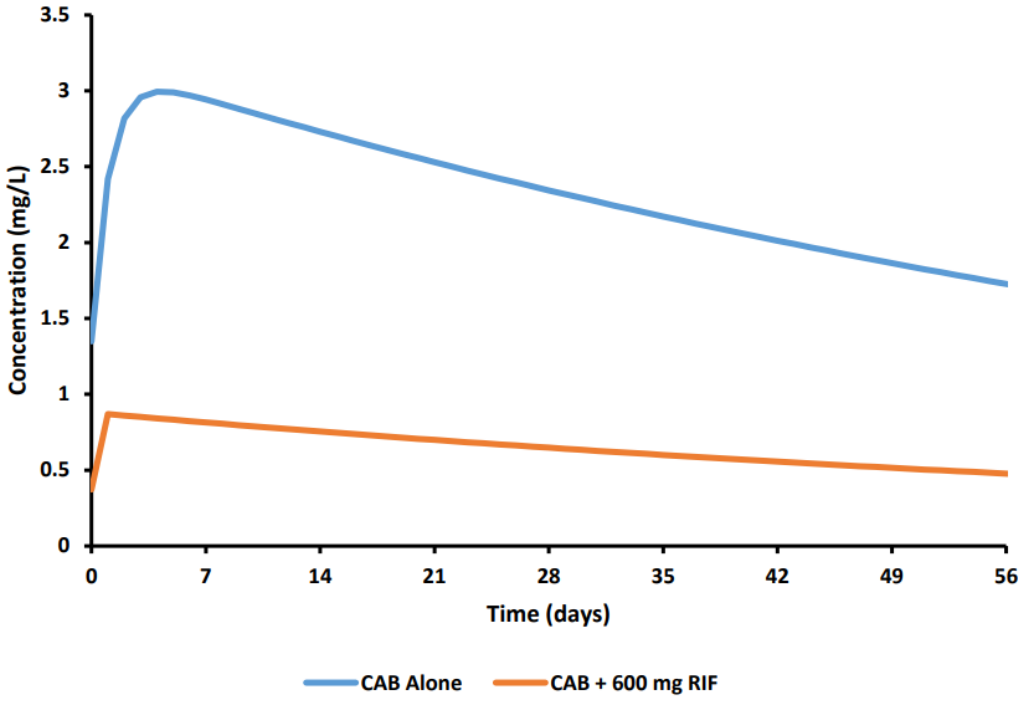


Table 4 Pharmacokinetic summary of drug alone and drug-drug interaction between cabotegravir, rilpivirine long-acting intramuscular formulation vs. 600 mg oral rifampicin

Drug	Drug Alone		Drug + 600 mg OD Rifampin		% difference (alone vs. DDI)		Half-life	
	AUC	C_{trough}	AUC	C_{trough}	AUC	C_{trough}	Alone	Drug + Rif
Cabotegravir 400 mg MD (4-weekly)	1340 ± 295	1.40 ± 0.31	794 ± 186	0.8 ± 0.2	-40.7%	-40.7%	68	65
Cabotegravir 600 mg MD (8-weekly)	2291 ± 541	1.42 ± 0.33	1,247 ± 319	0.77 ± 0.2	-45.6%	-45.8%	69	64
Rilpivirine 600 mg MD (4-weekly)	39,313 ± 22,724	37.3 ± 22.3	7,128 ± 3,128	6.7 ± 2.9	-81.9%	-82.1%	62	59
Rilpivirine 900 mg MD (8-weekly)	59,219 ± 28,134	37.4 ± 17.9	10,175 ± 4,464	6.6 ± 2.9	-82.8%	-82.4%	62	59

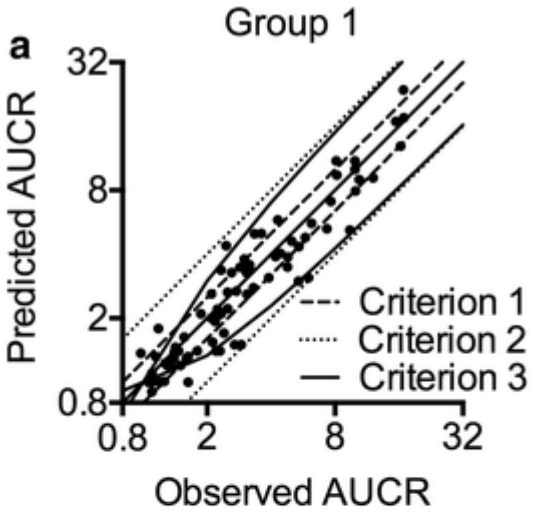
MD – maintenance dose. Cabotegravir C_{max}, C_{trough} are expressed as mg/L and AUC in mg.h/L; Rilpivirine C_{max}, C_{trough} are expressed as ng/ml and AUC in ng.h/ml. Half-life is expressed in days. Intramuscular maintenance dose was preceded by 4-weeks of daily oral dose (30 mg- cabotegravir, 25 mg – rilpivirine) and 4-weeks of intramuscular loading dose (800 mg – cabotegravir and 900 mg rilpivirine)

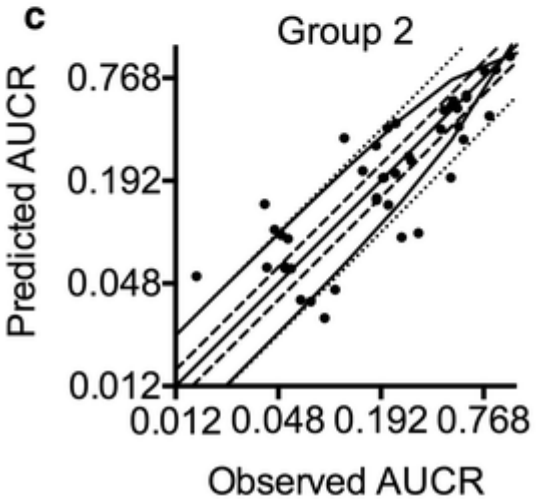
Clin Pharmacokinet (2018) 57:1337–1346
https://doi.org/10.1007/s40262-018-0635-8

ORIGINAL RESEARCH ARTICLE

Predictive Performance of Physiologically-Based Pharmacokinetic Models in Predicting Drug–Drug Interactions Involving Enzyme Modulation

Chia-Hsiang Hsueh[1,2] · Vicky Hsu[1] · Yuzhuo Pan[1,3] · Ping Zhao[1,4]





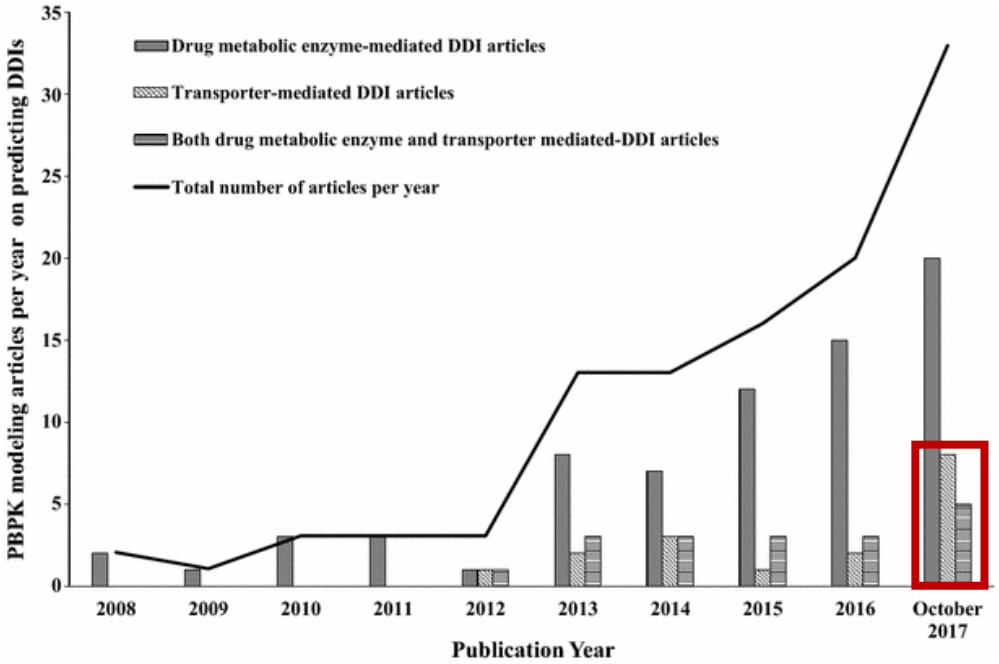
For Groups 1, 2, 3, and 4, **62, 50, 44, and 43%** of model-predicted AUCRs, respectively, were within a predefined threshold of **1.25-fold of observed values** (0.8–1.25x)

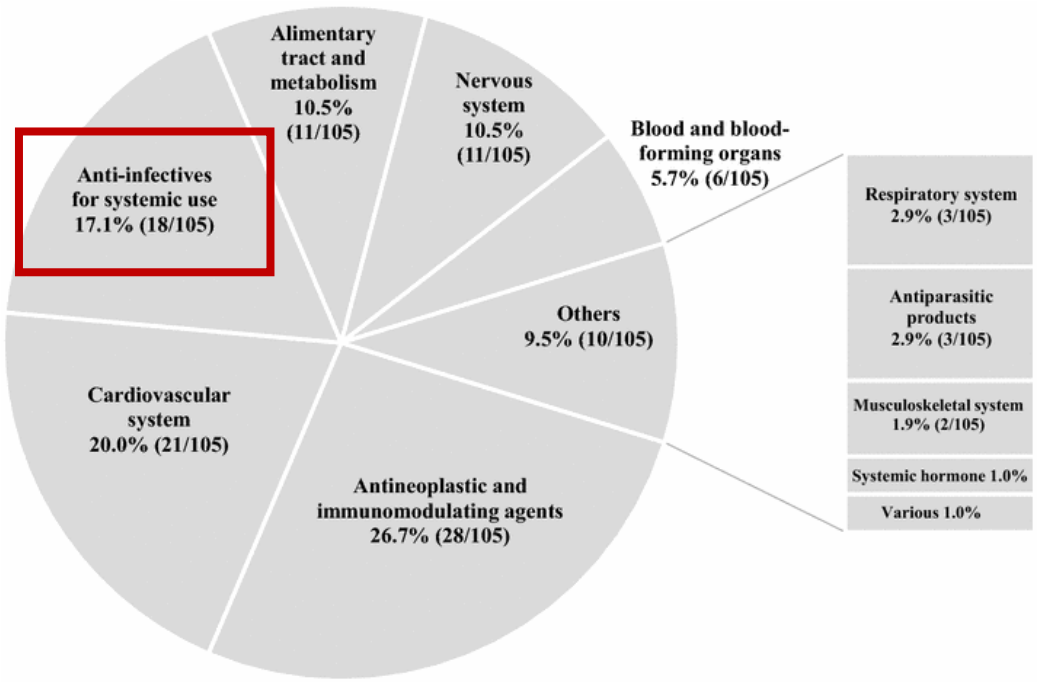
When the threshold was widened to **twofold**, the values increased to **100, 80, 81, and 86%** (0.5–2.0x).

Prediction of drug–drug interaction potential using physiologically based pharmacokinetic modeling

Jee Sun Min[1] · Soo Kyung Bae[1]

Arch. Pharm. Res. (2017) 40:1356–1379





Is this approach relevant?

“Drug interactions” + PBPK results in around 260 hits on NCBI

Extracts from FDA/EMA guidelines:

PBPK has **great potential value to support benefit–risk evaluations**

PBPK provides **a mechanistic basis for extrapolation beyond the clinical trial population**, reducing uncertainty, and **enabling better labeling** around drug–drug interactions and in special populations

“PBPK-thinking” in drug development is encouraged, as it leads to a mechanistic understanding of the processes mediating drug disposition

Relevance of DDI magnitude

Sensitive substrates: increase in AUC of ≥5-fold with strong inhibitors
Moderate sensitive substrates: increase in AUC of ≥2 to <5-fold with strong inhibitors

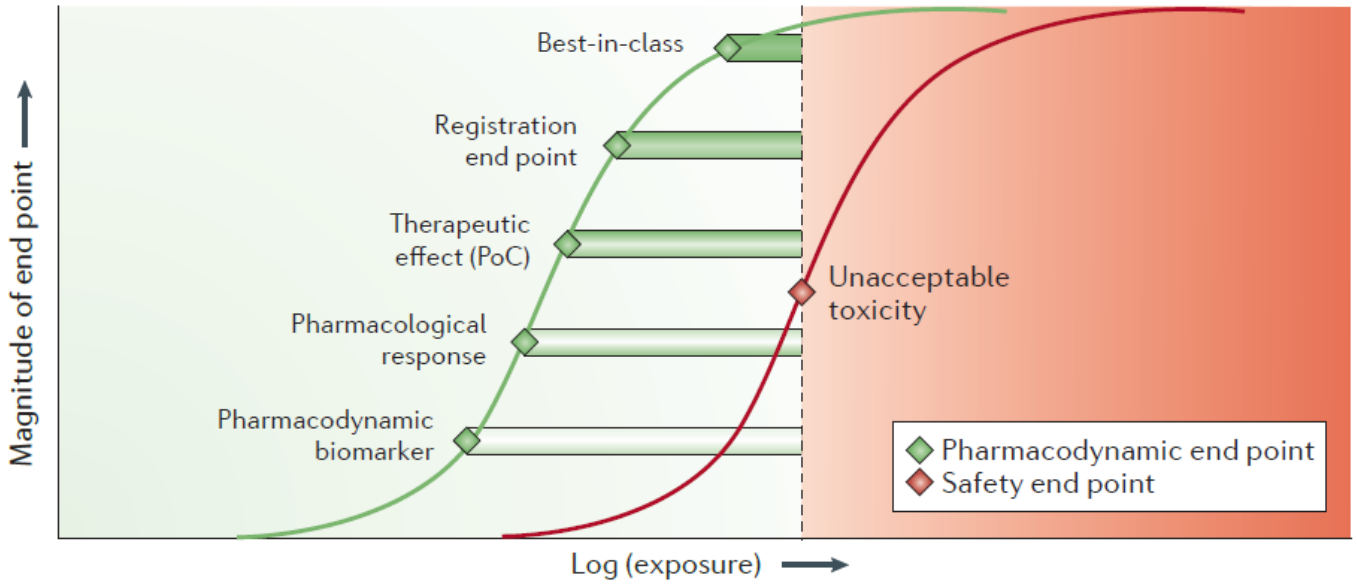
Strong and moderate inhibitors are drugs that increase the AUC of sensitive substrates ≥5-fold and ≥2 to <5-fold.

Strong and moderate inducers decreases the AUC of sensitive substrates by ≥80% and ≥50% to <80%.

Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications - Food and Drug Administration - October 2017

PK/PD and therapeutic index

The therapeutic index (TI) — which is typically considered as the ratio of the highest exposure to the drug that results in no toxicity to the exposure that produces the desired efficacy

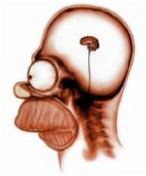


Integration in clinical scenarios

Age related changes/special populations

Polypharmacy and complex therapies

Pharmacogenetics

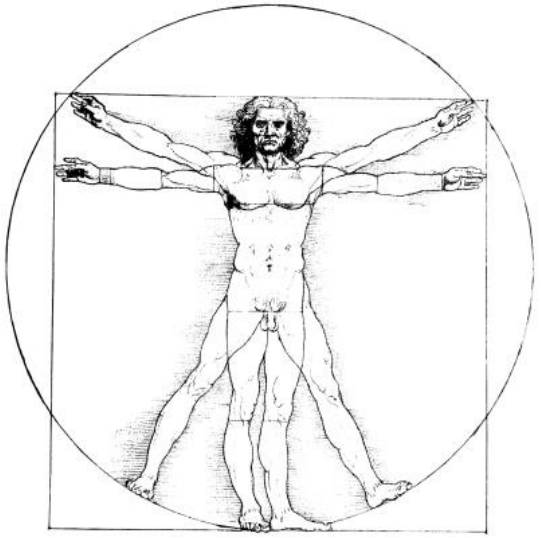


Penetration through barriers

Pregnancy and brestfeeding

Blood flows
Organ volume

Plasma protein binding
CYPs expression
GI physiology



Blood flows
Organ volume
Organ function

CYPs expression
GI physiology
Blood flows
Organ volume
Organ function

Pharmaceutical Research, Vol. 25, No. 6, June 2008 (© 2008)
DOI: 10.1007/s11095-008-9546-y

Research Paper

A Physiological Model to Evaluate Drug Kinetics in Patients with Hemorrhagic Shock Followed by Fluid Resuscitation

Michel Tod,[1,2,3,9,10] Franck Lagneau,[4] Vincent Jullien,[5,6] and Olivier Mimoz[7,8]

COMORBIDITIES

RENAL IMPAIRMENTS

Prediction of the Disposition of Midazolam in Surgical Patients by a Physiologically Based Pharmacokinetic Model

SVEN BJÖRKMAN,[1] D. RUSSELL WADA,[2] BRITT-MARIE BERLING,[3] GÖRAN BENONI[4]

[1]Hospital Pharmacy, Malmö University Hospital, S-205 02 Malmö, Sweden

[2]Pharsight Corporation, Mountain View, California

Anesthesia, Malmö University Hospital

Orthopedics, Malmö University Hospital

Acta Pharmacologica Sinica (2012) 33: 1359–1371

1671-4083/12 $32.00
www.nature.com/aps

Original Article

Simulation of the pharmacokinetics of bisoprolol in healthy adults and patients with impaired renal function using whole-body physiologically based pharmacokinetic modeling

Guo-fu LI[1, 2], Kun WANG[1, *], Rui CHEN[2], Hao-ru ZHAO[3], Jin YANG[2], Qing-shan ZHENG[1, *]

PREGNANCY

BJCP British Journal of Clinical Pharmacology

A pregnancy physiologically based pharmacokinetic (p-PBPK) model for disposition of drugs metabolized by CYP1A2, CYP2D6 and CYP3A4

Lu Gaohua,[1*] Khaled Abduljalil,[1*] Masoud Jamei,[1] Trevor N. Johnson[1] & Amin Rostami-Hodjegan[1,2]

AGE

The AAPS Journal, Vol. 15, No. 4, October 2013 (© 2013)
DOI: 10.1208/s12248-013-9505-3

Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-018-0709-7

ORIGINAL RESEARCH ARTICLE

Repository Describing an Aging Population to Inform Physio Based Pharmacokinetic Models Considering Anatomical, Phy and Biological Age-Dependent Changes

Felix Stader[1,2,3] · Marco Siccardi[4] · Manuel Battegay[1,3] · Hannah Kinvig[4] · Melissa A. Penny[2,3] · Catia Marzolini[1,3]

Research Article

A Simplified PBPK Modeling Approach for Prediction of Pharmacokinetics of Four Primarily Renally Excreted and CYP3A Metabolized Compounds During Pregnancy

Binfeng Xia,[1] Tycho Heimbach,[1,4] Rakesh Gollen,[2] Charvi Nanavati,[3] and Handan He[1]

Regulatory guidelines

Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1601, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Office of Clinical Pharmacology, at 301-796-5008 or OCPt@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

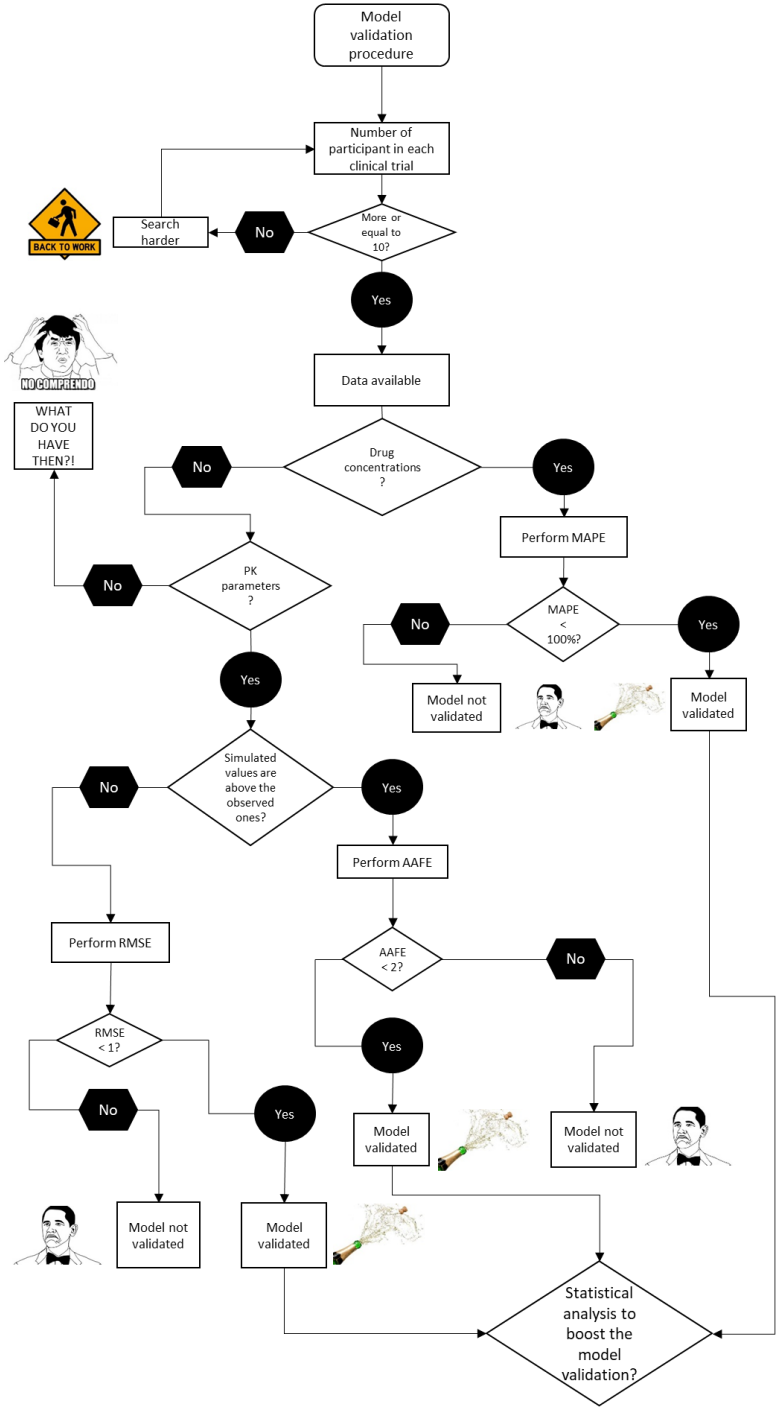
December 2016
Clinical Pharmacology

5. Software

The FDA does not require the use of a particular PBPK modeling software. Because of substantive differences in software models and versions, sponsors should include information on the PBPK modeling software. Table 1 below highlights the information that should be included regarding commercial PBPK modeling software (commercial PBPK platform) versus custom modeling software (e.g., commercial software that has been modified with custom codes or otherwise revised for the purpose of PBPK modeling).

Table 1. Software Information for PBPK Modeling

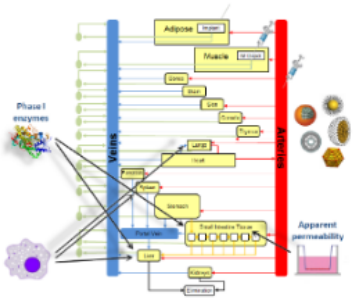
Suggested Software Information	PBPK Models	
	Custom Modeling Software	Commercial PBPK Platform
Name and version of the software	Yes	Yes
Schematic view of model structure and differential equations based on established theoretical or biological basis	Yes	Optional
Parameterization of system information and sources of parameter values	Yes	Optional
Table of drug-dependent parameters for the investigational drug of interest, including names, values, units, and sources of the parameters, prediction algorithms, and assumptions being made	Yes	Yes
Literature references and the sponsor's prior experience/knowledge in using the software for PBPK modeling (to help the reviewer understand how PBPK models are coded using the modeling software that was tested)	Yes	Yes
Manuals on model implementation of the software (to be provided as supporting documents)	Yes	Optional
Library system models (e.g., virtual population), including justifications for any modifications made to the model's physiological parameters by the sponsor	Not applicable	Yes
Library drug models, including justifications for any modifications to the model made by the sponsor and information on model verification	Not applicable	Yes


Model validation procedure
Number of participant in each clinical trial
More or equal to 10?
No
Search harder
BACK TO WORK
Yes
Data available
NO COMPRENDO
WHAT DO YOU HAVE THEN?!
Drug concentrations ?
No
Yes
Perform MAPE
PK parameters ?
No
MAPE < 100%?
No
Yes
Model not validated
Model validated
Yes
Simulated values are above the observed ones?
No
Yes
Perform AAFE
Perform RMSE
AAFE < 2?
No
RMSE < 1?
Yes
No
Model validated
Model not validated
Yes
No
Model not validated
Model validated
Statistical analysis to boost the model validation?

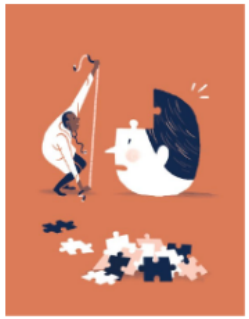
Challenges and limitations

- Reliability of input data (clinical & experimental)
- Full understanding of molecular mechanisms underpinning DDIs
- Qualification and refinement of the modelling approach
- Assumptions and structure of the computational environment
- Model reproducibility
- Special populations
- New routes of administration

Experimental approaches



Computational models



Clinical studies

ADME UNDERSTANDING

Predict DDI magnitude

Identification of dose adjustments

Rational design of future studies

PK-PD analysis

Prescription tools

Acknowledgements

The Liverpool Team

Andrew Owen
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Andrea Calcagno

Basel
Catia Marzolini
Manuel Battegay
Felix Stader

IDI - Kampala
Mohammed Lamorde

Cape Town
Paolo Denti
Gary Maartens