real solutions from virtual populations

Have you designed your clinical PK studies with adequate power?

What we do

The Simcyp Population-based ADME Simulator

Simcyp provides a platform for modelling and simulation of drug absorption, distribution, metabolism and excretion (ADME) in virtual populations. The Simulator is licensed to our Consortium member clients for use in drug discovery and development.

Currently, 9 of the top 10 pharmaceutical companies worldwide have access to Simcyp expertise through Consortium membership. The Consortium helps guide scientific development at Simcyp, ensuring that our products continue to meet, and exceed, industry needs.

Simcyp maintains strong academic links and our science team conducts internationally recognised cutting-edge research and development. We also offer consultancy services and run education programmes around the world.

see more

Latest News | Workshops

New study investigates covariates influencing the amount of human microsomal protein per gram of liver
03 Nov 2008
more

Medical Products Agency, Sweden, renews Simcyp licenses
30 Oct 2008

Simcyp confirms additional speaker for Tokyo seminar day
29 Oct 2008

Wyeth joins the Simcyp Consortium
23 Oct 2008

all news

Consortium members and associates include:

SERVIER | Flinders University | biovitrum. | Pfizer | J & J PRD | Universitätsklinikum Heidelberg | Otsuka

Background to Simcyp: Current Members (Feb 2007)

Commercial Organisations:

Amgen	F Hoffmann-La Roche	Novartis	Sanofi-Aventis
AstraZeneca	GlaxoSmithKline	Novo Nordisk	Servier
Biovitrum	Lundbeck	Nycomed(Altana)	Takeda
Daiichi-Sankyo	Neurocrine	Pfizer	UCB

Regulatory/Governmental Organisations:

MPA - Medical Product Agency (Sweden)
NAM - National Agency for Medicines (Finland)
ECVAM - EU Centre for Validation of Alternative Methods (Italy)
FDA (USA) [negotiations in final stages for renewal of their License]
MEB - Medicines Evaluation Board (Holland) [under negotiations]
etc.

Universities:

e.g. Manchester (UK); Uppsala (Sweden); Aberdeen (UK); Lisbon (Portugal); Showa (Japan); Buffalo (USA); Göteborg (Sweden); China Pharmceutical (China); Missouri (USA); Méditerranée (France), Groningen (Holland), Malta University, ….

Background: Consortium was FORMED in 2000 !

Primary aims included:

- Integrate new science in IVIVE area into the regulatory process of assessing mDDI

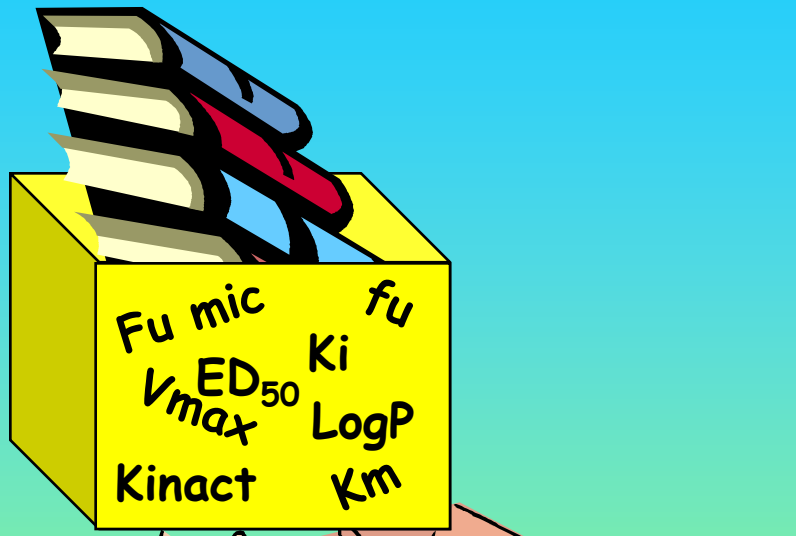
- Focus on "toolkit" development rather than being product-specific

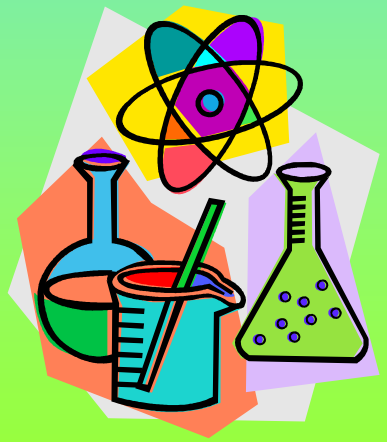
- Provide opportunity to work in a consortia involving industry, academia, and government agencies

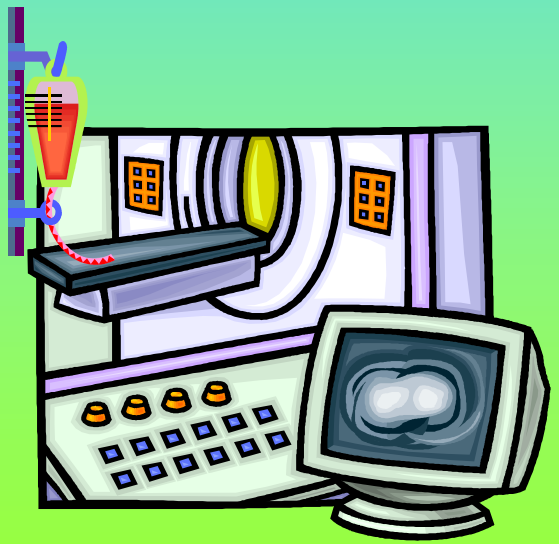
Background: IVIVE as Starting Point (not the endpoint)

PRE-CLINICAL

CLINICAL

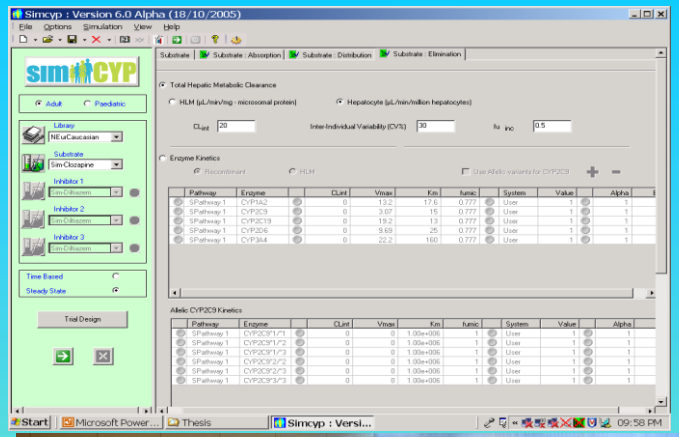






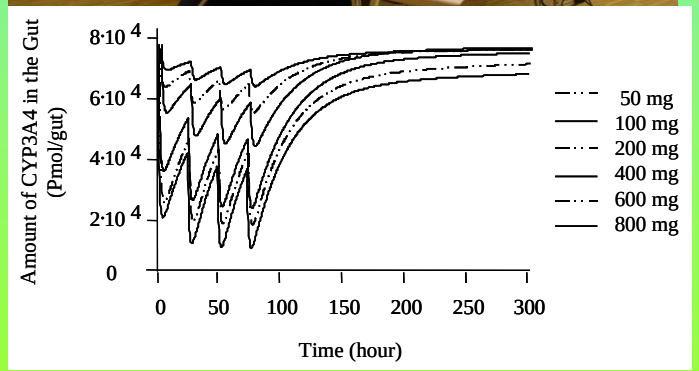
Background: Activities to Achieve the Objectives

Continual Development and Update of a User Friendly, Comprehensive, Mechanistic Platform for Integration of ADME Models & Databases
(simulation of candidate drugs in virtual populations)



Regular Worldwide Workshops and Seminars on PK & IVIVE for Key Players on the Drug Development Scene
(e.g. scientists in regulatory agencies and different sections of industry – as internal or open meeting)

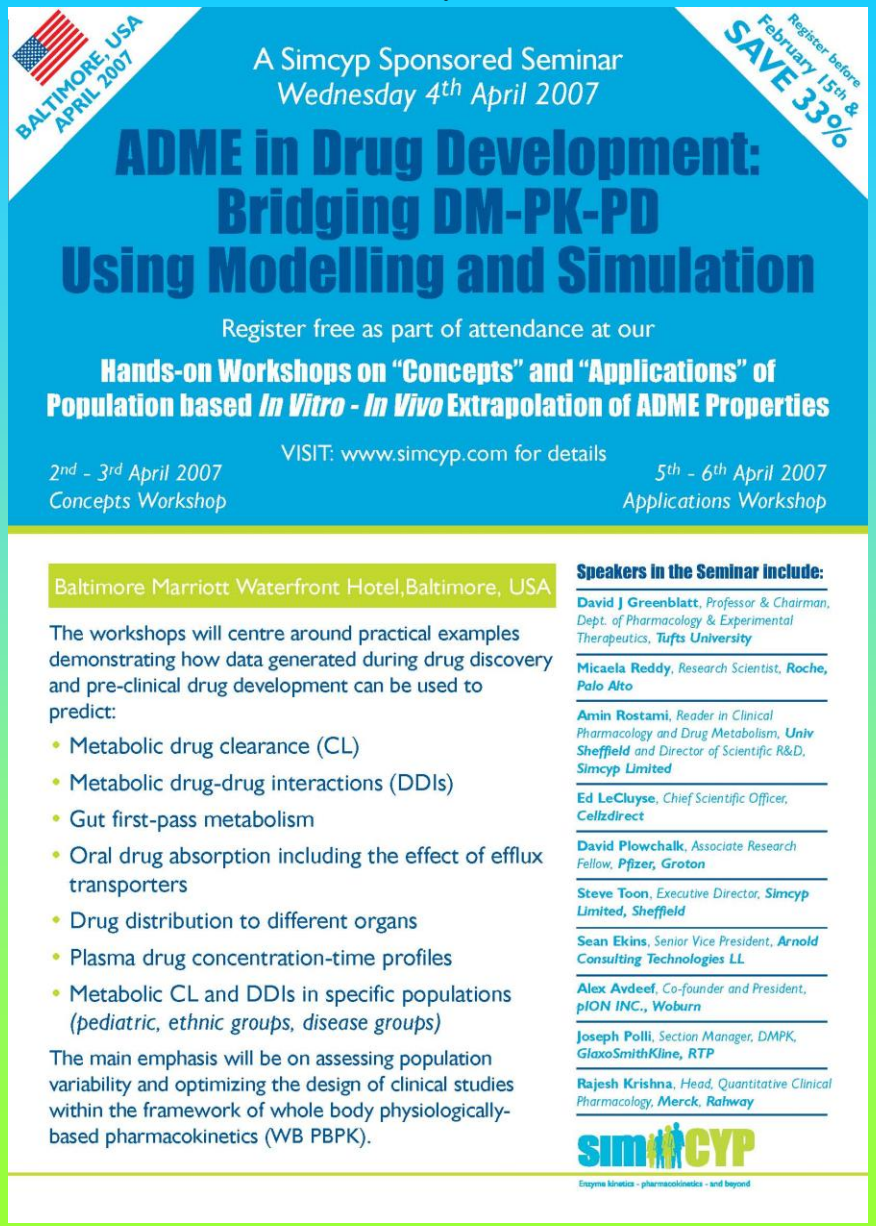
Gathering Advice / Reaching Consensus on Common IVIVE & ADME Issues / Identifying Areas of Further Research
(defining common or specific projects in the form of focus groups)



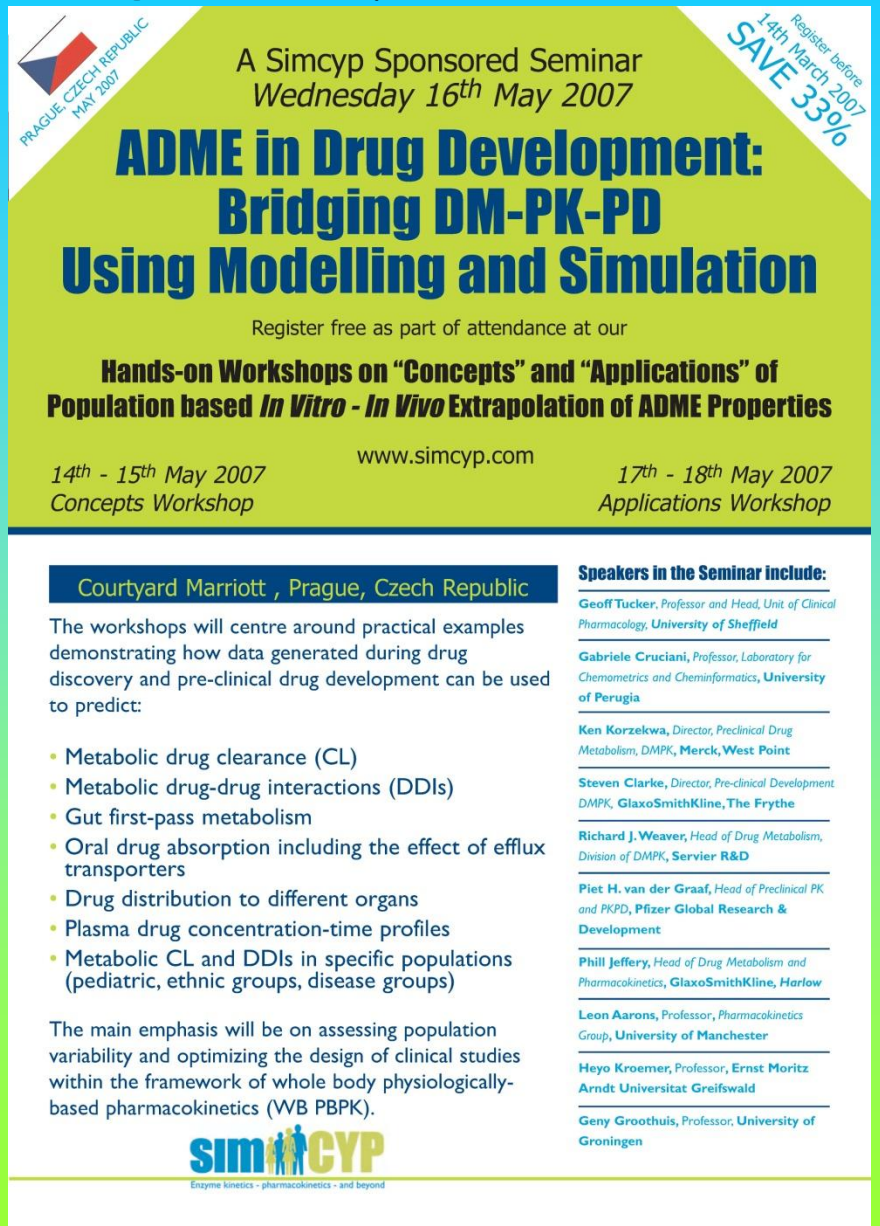
Activities: Hands-On IVIVE Workshops (2005 - 2006)

Activities: Finalised IVIVE Workshops & Seminars (2007)

Baltimore - April



Prague - May



Agenda: Lectures Reinforced with Workshops

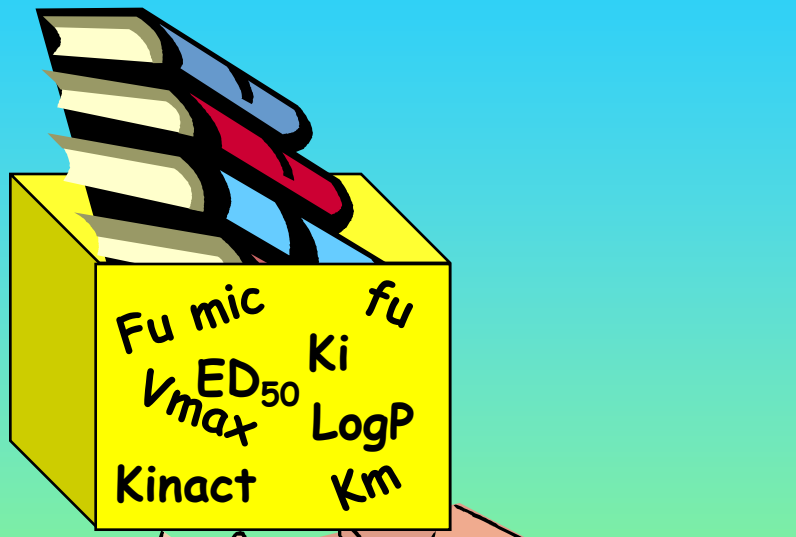
- Introduction to Simcyp IVIVE Course
- IVIVE - Prediction of Clearance & Issues related to Quality Assurance
- Hands on Workshop – Prediction of Clearance

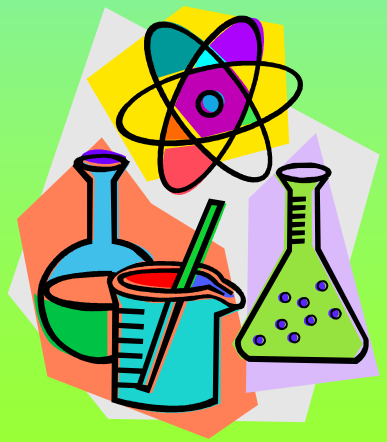
- IVIVE - Prediction of Gut First-Pass
- Hands on Workshop – Gut First-Pass
- IVIVE - Incorporating Biological Variability
- Hands on Workshop – Incorporating Interindividual Variability
- IVIVE - Prediction of Age & Ethnicity Related Changes
- Hands on Workshop - Predicting Clearance in Neonates & Japanese
- IVIVE - Prediction of Metabolic Drug-Drug Interactions
- Hands on Workshop – Metabolic Drug-Drug Interactions
- Liver Models & the Case for Sensitivity Analysis
- Hands on Workshop- Sensitivity Analysis

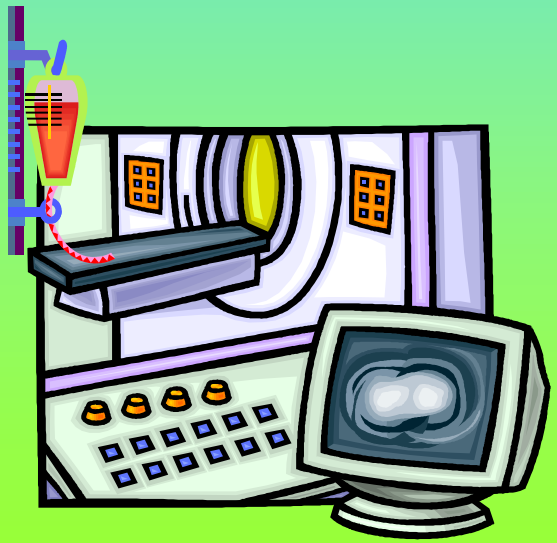
The Need for Better Communications on IVIVE

PRE-CLINICAL

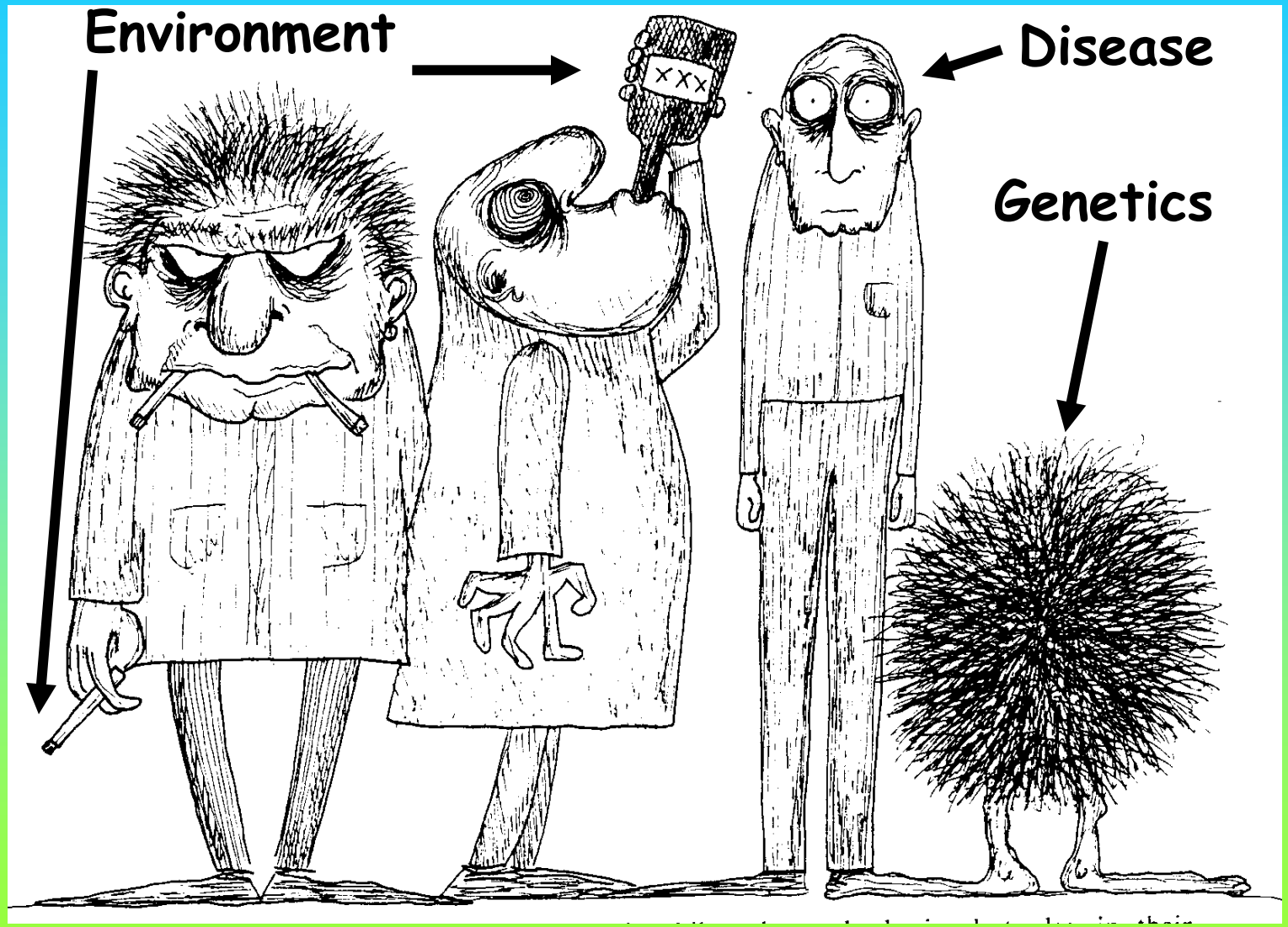
CLINICAL



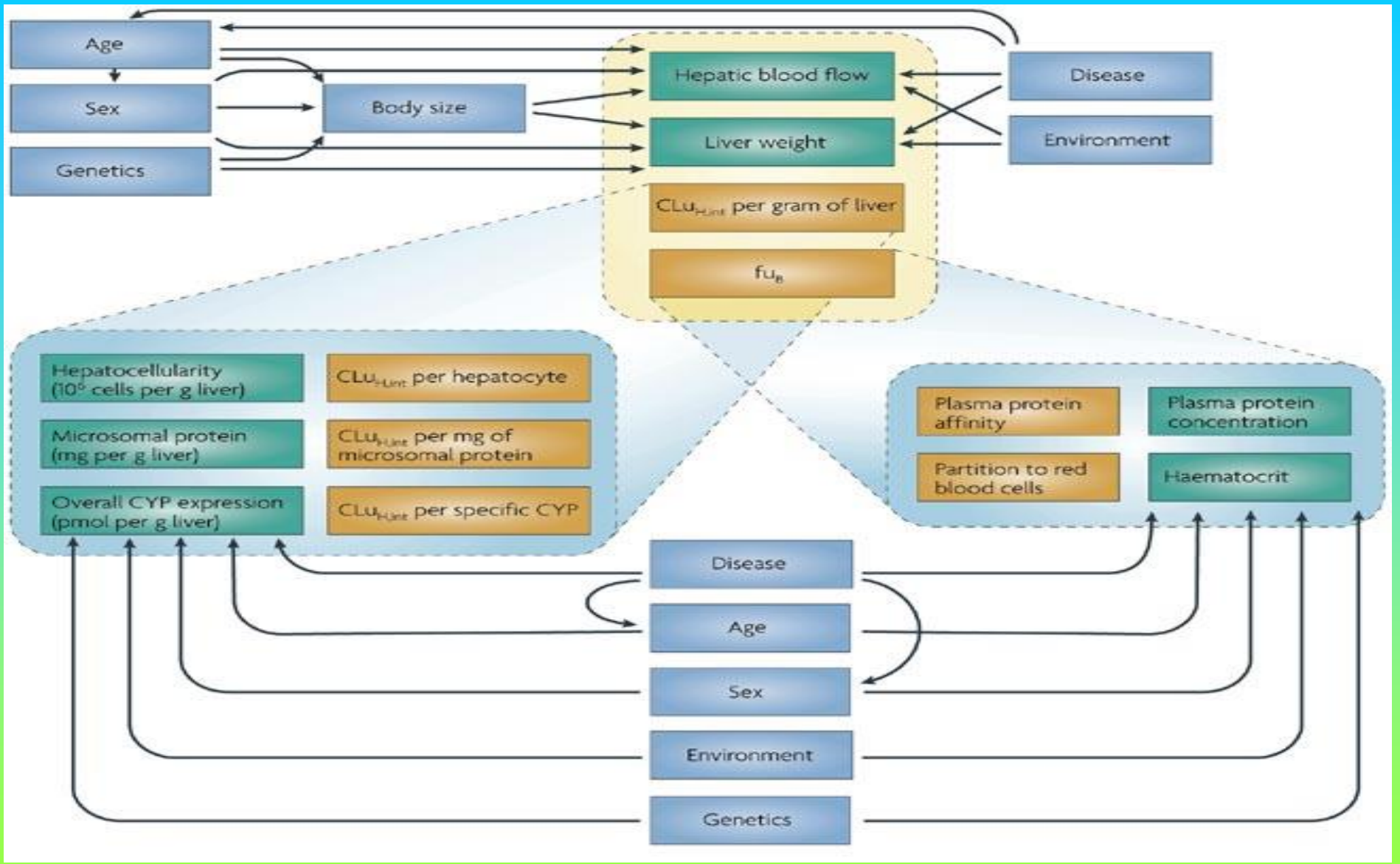




The Challenge of Population Variability



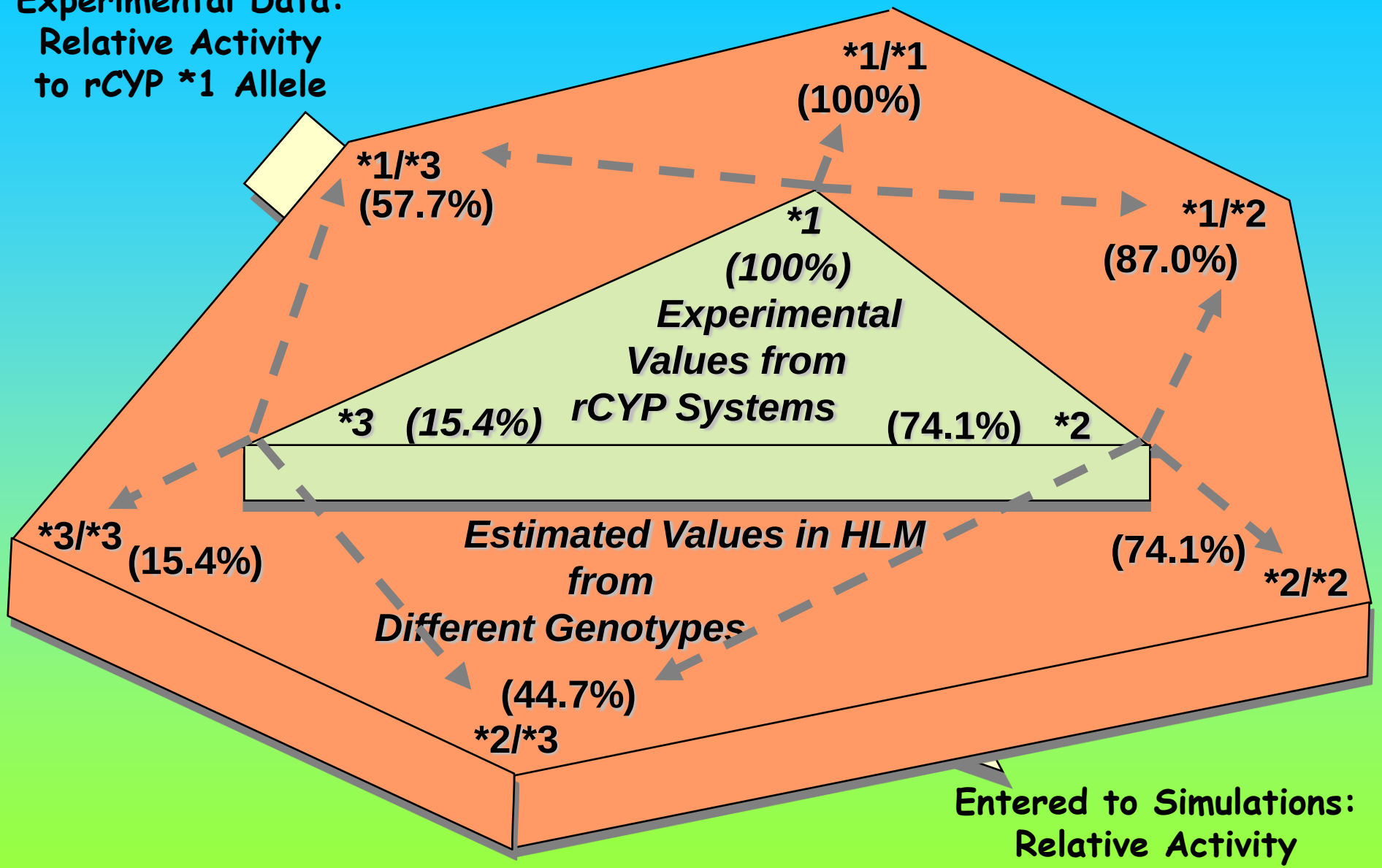
The Complexity of Covariate Effects



Rostami-Hodjegan and Tucker *Nature Reviews Drug Discovery* 6, 140–148 (February 2007) |

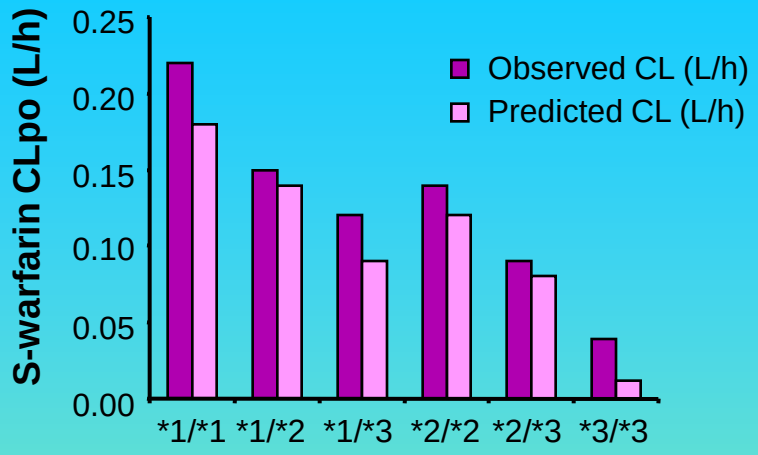
nature REVIEWS DRUG DISCOVERY

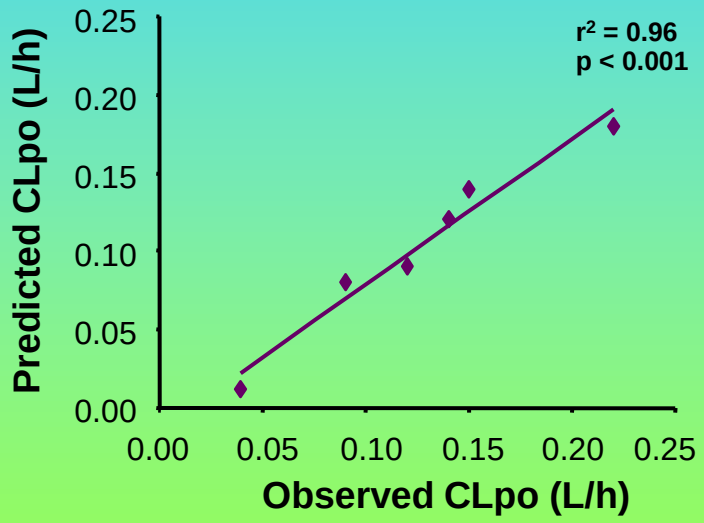
Use of rCYP to Assess Effects of Genetics



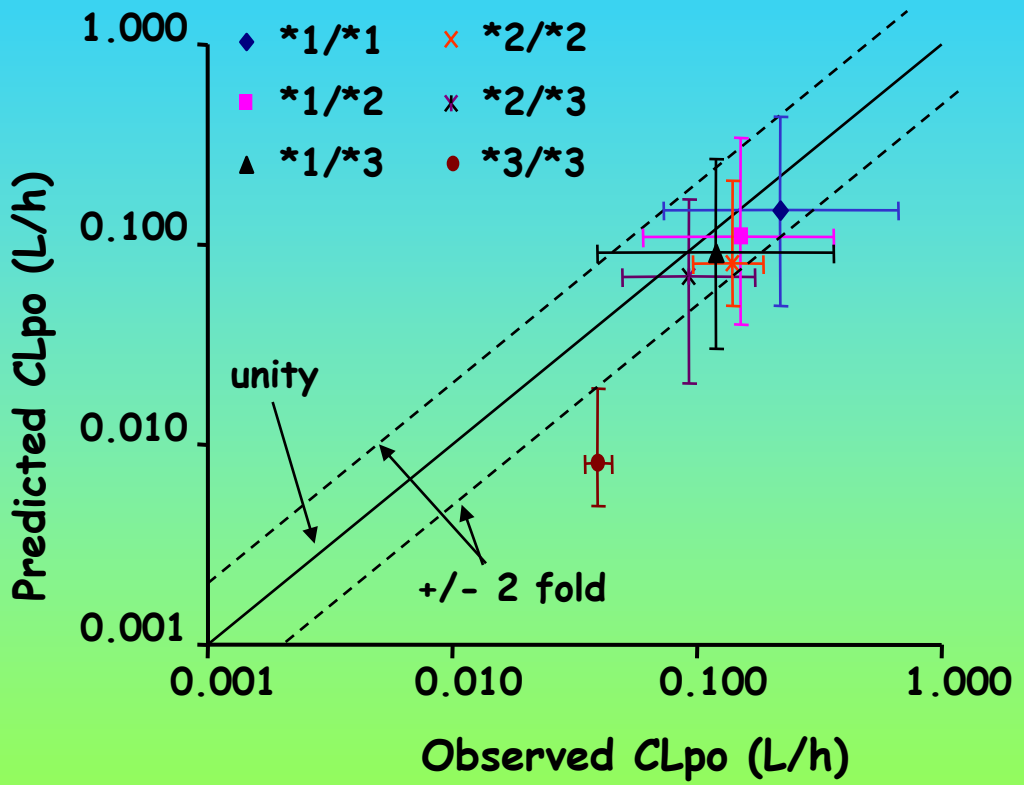
Predicted vs Observed CLpo: CYP2C9 Genotypes

S-Warfarin - Lisa Almond (ISSX Manchester 2006)





Not just central tendency (mean or median) but also variability:

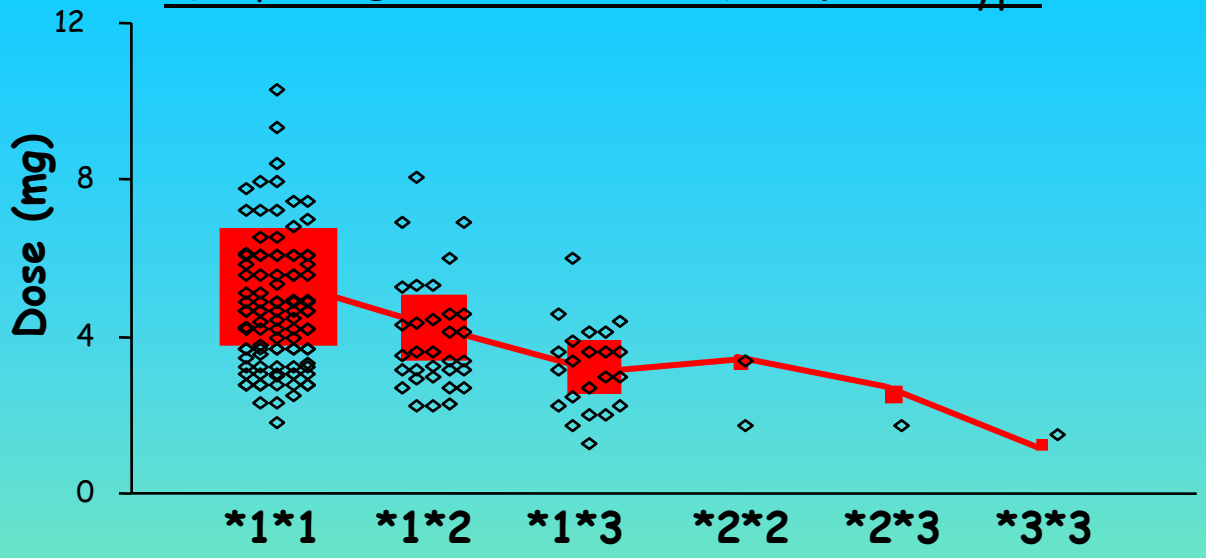


The Propagation of Genetic Polymorphism in CYP2C9 into Tolbutamide Pharmacokinetics: Assessment Using an Integrated Model

Dickinson et al. (ISSX Manchester 2006)

Difficulties with Retrospective Studies

Warfarin Dose in Clinic vs CYP2C9 Genotype



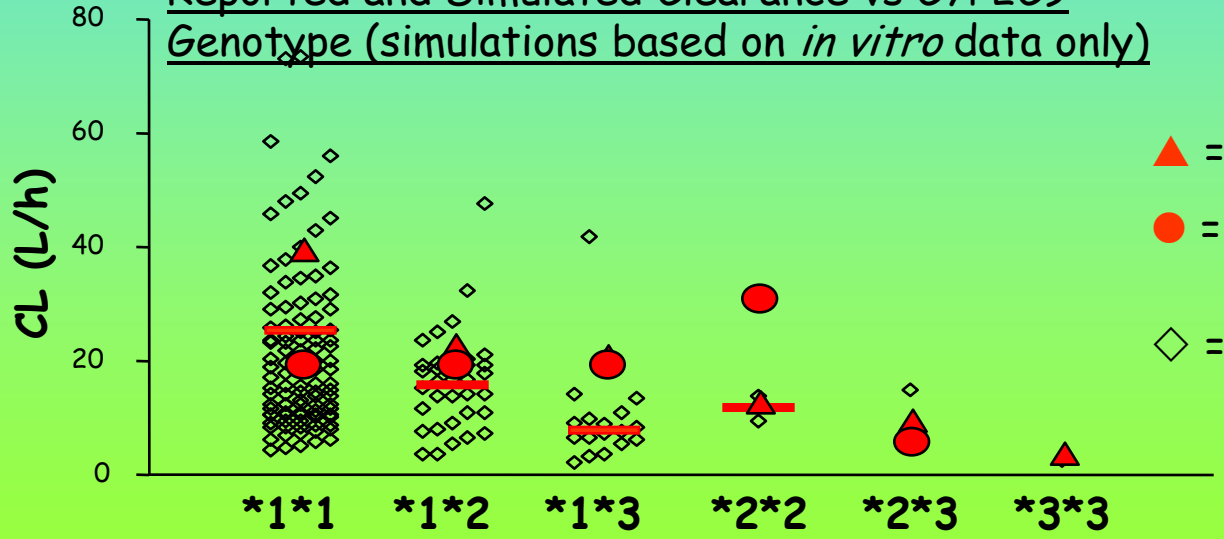
■= Meta-analysis (literature)

Siguret et al, 2004; n = 126 -
Kamali et al, 2004; n = 121
King et al, 2004; n = 159
Aithal et al, 1999; n = 52
Taube et al, 2000; n = 561
Hillman et al, 2004; n = 453
Scordo et al, 2002; n = 93
Loebstein et al, 2001; n = 156
Higashi et al, 2002; n = 185
Margaglione et al, 2000; n = 180

◇= Individual data

Daly et al, 2005 (n = 159)

Reported and Simulated Clearance vs CYP2C9 Genotype (simulations based on *in vitro* data only)



▲ = Scordo et al, 2002; n=93

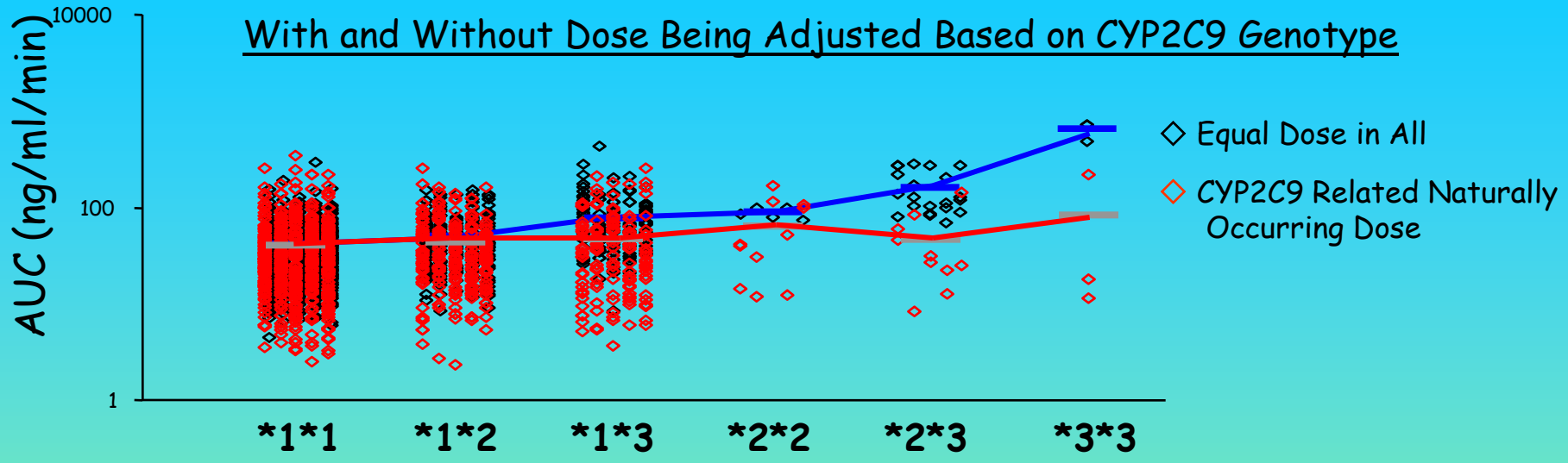
● = Takahashi et al, 2003; n = 47

◇ = Simulated CL Values (n = 159)

Propagation of CYP2C9 Effects on PK/PD

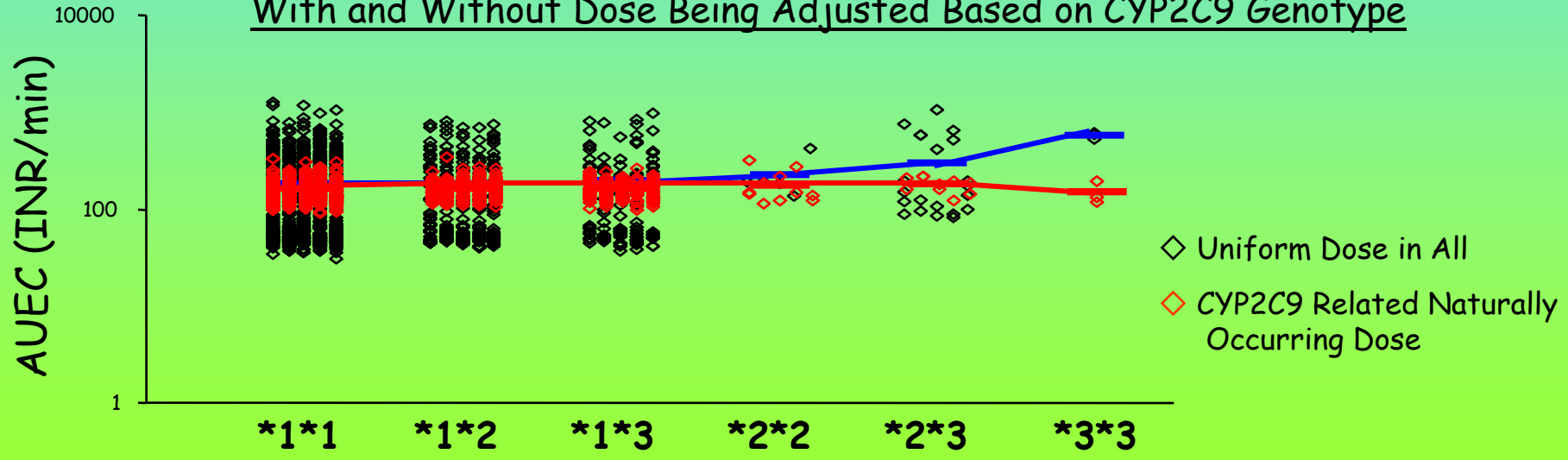
Simulated Exposure (AUC ; n = 1000)

With and Without Dose Being Adjusted Based on CYP2C9 Genotype

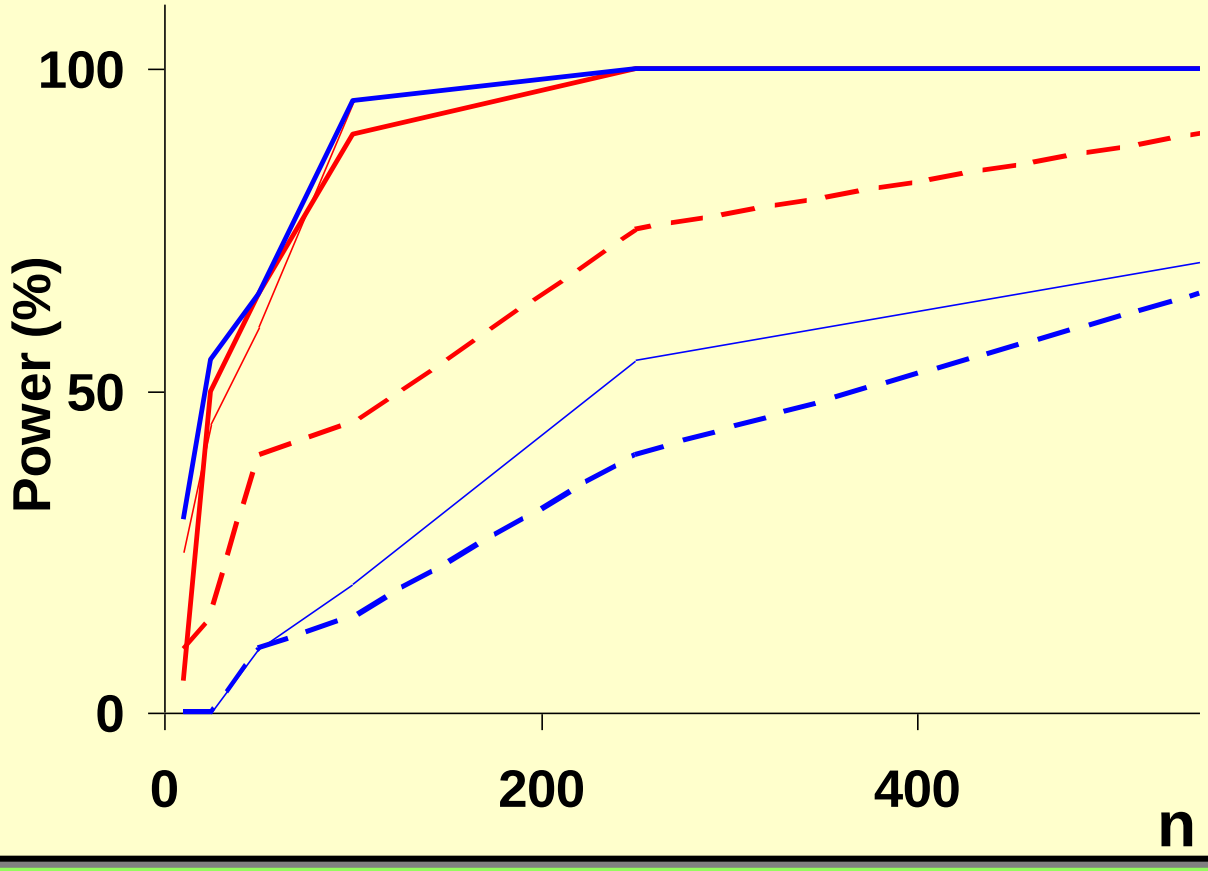


Simulated Effects (AUEC of INR ; n = 1000)

With and Without Dose Being Adjusted Based on CYP2C9 Genotype



Helping with Study Design: Power



PK (CL)
PK (AUC)
PD (AUEC)
PK (CL) dose adjusted
PK (AUC) dose adjusted
PD (AUEC) dose adjusted

FDA's Draft Guidance (Sept 2006):

Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling

II. BACKGROUND

Identifying metabolic differences in patient groups based on **genetic polymorphism, or on other readily identifiable factors, such as age, race, and gender**, can aid in interpreting results. **The extent of interactions may be defined by these variables (e.g., CYP2D6 genotypes).** Further, in subjects who lack the major clearance pathway, remaining pathways become important and should be understood and examined.

III. GENERAL STRATEGIES

To the extent possible, drug development should follow a sequence in which **early *in vitro* and *in vivo* investigations** can either **fully address a question of interest or provide information to guide further studies.**

III. GENERAL STRATEGIES

(A) *IN VITRO* STUDIES

In vitro studies can frequently serve as a screening mechanism to rule out the importance of a metabolic pathway and the drug-drug interactions that occur through this pathway **so that subsequent *in vivo* testing is unnecessary.**

SECTION IV. DESIGN OF *IN VIVO* DRUG-DRUG INTERACTION STUDIES

(A) STUDY POPULATION

Performance of **phenotype or genotype determinations to identify genetically determined metabolic polymorphisms** is important in evaluating effects on enzymes with polymorphisms, notably CYP2D6, CYP2C19, and CYP2C9. Subjects lacking the major clearance pathway, for example, cannot show metabolism and **remaining pathways can become important and should be understood and examined.**

FDA's Draft Guidance (Sept 2006):

Rference to **SIMULATIONS**

SECTION III – GENERAL STRATEGIES
***(A) IN VITRO* STUDIES**
(B) SPECIFIC IN VIVO CLINICAL INVESTIGATIONS
(C) POPULATION PHARMACOKINETIC SCREENS

The results from such analyses can be informative and ***sometimes conclusive when the clinical studies are adequately designed*** *to detect significant changes in drug exposure due to drug-drug interactions.* ***Simulations can provide valuable insights into optimizing the study design.***

SECTION IV. DESIGN OF *IN VIVO* DRUG-DRUG INTERACTION STUDIES
(A) STUDY DESIGN

The inhibiting/inducing drugs and the substrates should be dosed so that the exposures of both drugs are relevant to their clinical use, including the highest doses likely to be used. **Simulations can be helpful in selecting an appropriate study design.** The following considerations may be useful: [1] - **attainment of steady state (SUB/INHIB)** ; [2] - **time to achieve maximum effect (INDUCERS/MBI/ACCUMULATION OF METABOLITES)** ; [3] - ….

SECTION IV. DESIGN OF IN VIVO DRUG-DRUG INTERACTION STUDIES
(C) CHOICE OF SUBSTRATE AND INTERACTING DRUGS (NID as Substrate of CYPs)

Evaluation of multiple CYP inhibitors if: (1) the drug exhibits blood concentration-dependent safety concerns; (2) multiple CYP enzymes are responsible for the metabolic clearance of the drug; (3) the residual or non-inhibitable drug clearance is low.

Before investigating the impact of multiple inhibitors on drug exposure, it is important to first characterize the individual effects of the CYP inhibitors and to estimate the combined effect of the inhibitors based on computer simulation.

FDA's view (examples):

General Aim of DDI Studies

In some instances, understanding **how to adjust dose or dosage regimen** in the presence of an interacting drug, or how to avoid interactions, **may allow marketing of a drug that would otherwise have been associated with an unacceptable level of toxicity.**

When a drug-drug interaction of potential importance is clearly present, the sponsor should provide specific **recommendations regarding the clinical significance of the interaction based on what is known about the dose-response and/or PK/PD relationship** for either the investigational agent or the approved drugs used in the study. ….. FDA recognizes that dose-response and/or PK/PD information can sometimes be incomplete or unavailable, especially for an older approved drug used as substrate.

Useful Simulations vs Accurate Predictions

Accumulation of Information on Compound (as Substrate)

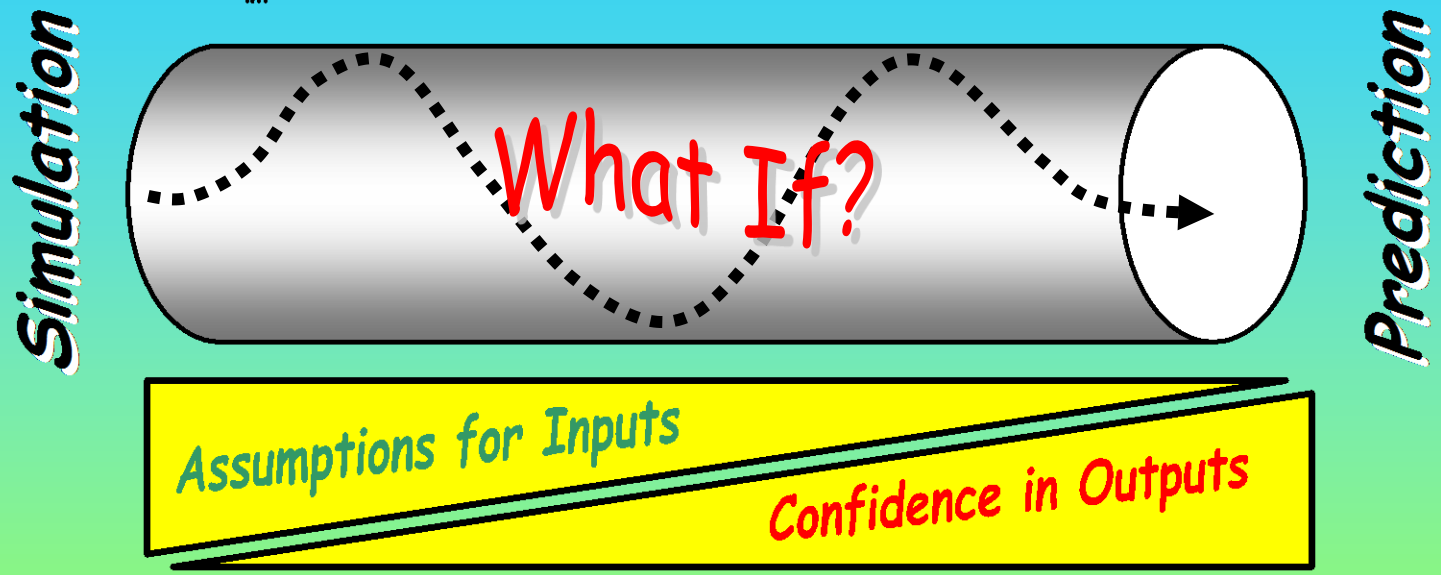
fm *via* each route in average subject → Population distribution of fm

Estimates of microsomal/plasma binding → Actual fu and fu_{mic}

Estimates of gut absorption (e.g.Caco-2) → fa from Phase I

Estimate of CL_R → CL_R from mass balance

Estimate of CLu_{int} → Km and Vmax



Single concn simulations → Full conc profile

Possible effects on transporters → Characterised effects on transporters

Likely mechanism of inhibition → Confirmed mechanism of inhibition

Estimate of inhibitory potency (IC50) → Ki

Accumulation of Information on Compound (as Inhibitor)

Rostami-Hodjegan & Tucker, *Drug Discovery Today: Technologies*, V4, Dec 2004

Conclusions

PRE-CLINICAL

CLINICAL