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Quantifying polymorphic metabolic clearance of diclofenac in CYP2C9 genotyped individuals using coupled physiology-based pharmacokinetic models

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A. Edginton[1], M. Sevestre[1], J. Kirchheiner[2], J. Brockmöller[3], S. Willmann[1]

[1] Systems Biology & Computational Solutions, Bayer Technology Services GmbH, Leverkusen, Germany

[2] Pharmacology of Natural Products & Clinical Pharmacology, University of Ulm, Ulm, Germany

[3] Clinical Pharmacology, University of Göttingen, Göttingen, Germany

Objective

- Determine the correlation between CYP2C9 genotype and intrinsic CYP2C9 metabolism for different individuals
- Determine the importance of CYP2C9-mediated clearance to total diclofenac clearance
- Understand the advantages and limitations of using the coupled PBPK model approach

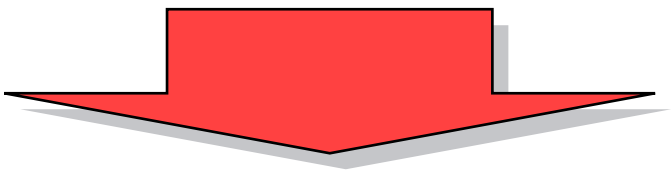
Diclofenac – What is known?

- Exclusively cleared in the liver
- Metabolism to 4'OH-diclofenac mediated by CYP2C9
- % cleared via CYP2C9 is unknown. The most recent in vitro study estimated about 25%.
- CYP2C9 is polymorphic with three alleles (**1*, **2*, **3*)
- In vitro CYP2C9 metabolism studies inconclusive on the correlation between genotype and 4'OH-dilofenac production
- In vivo oral clearance shows no CYP2C9 genotype dependence

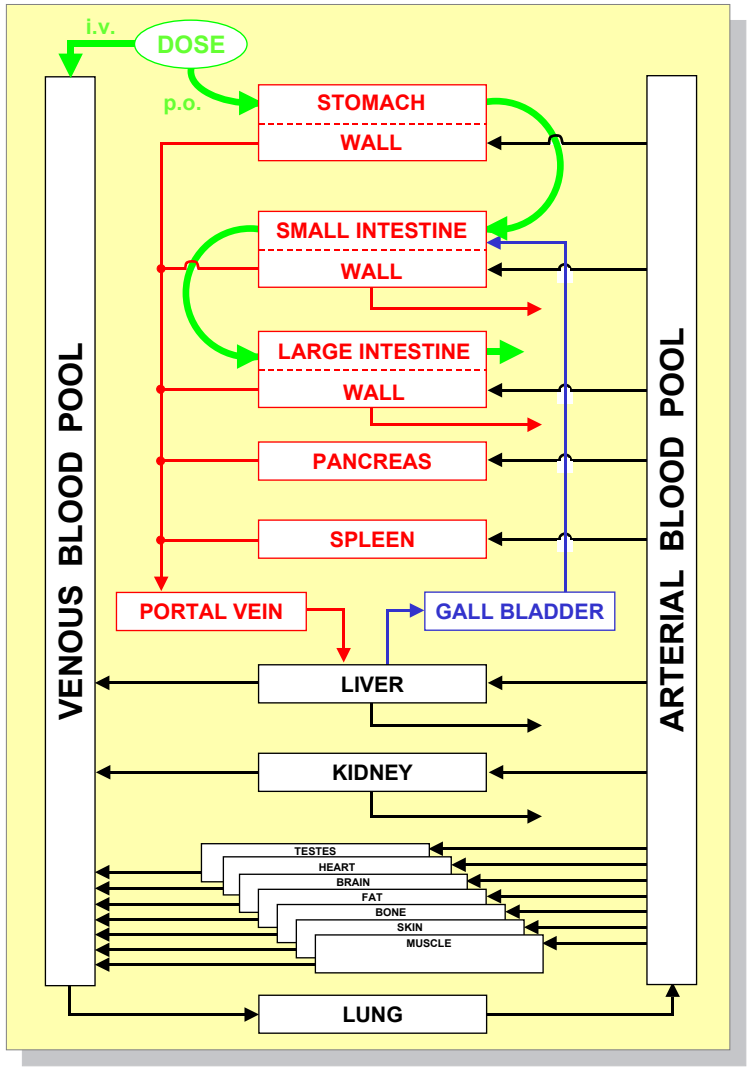
PK-Sim® Model-Structure

Integrated Whole Body Model:

- ⇨ Mathematical description of most important organs and their relationship to each other and to the blood pools
- ⇨ Organs separated into vascular (plasma + rbcs), interstitial and cellular space
- ⇨ Active processes (metabolism, transporters) can be included in every organ



Capability for treating even very sophisticated problems.



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PK-Sim® Model-Inputs

- Height, weight, gender – generates organ weights, blood flows (see PK-Pop poster Friday afternoon)
- Physico-chemistry of parent and metabolite
  - Lipophilicity
  - Molecular weight
  - Solubility
  - Acid/Base Properties

  } Tissue: plasma partition ratios
- Unbound fraction in plasma

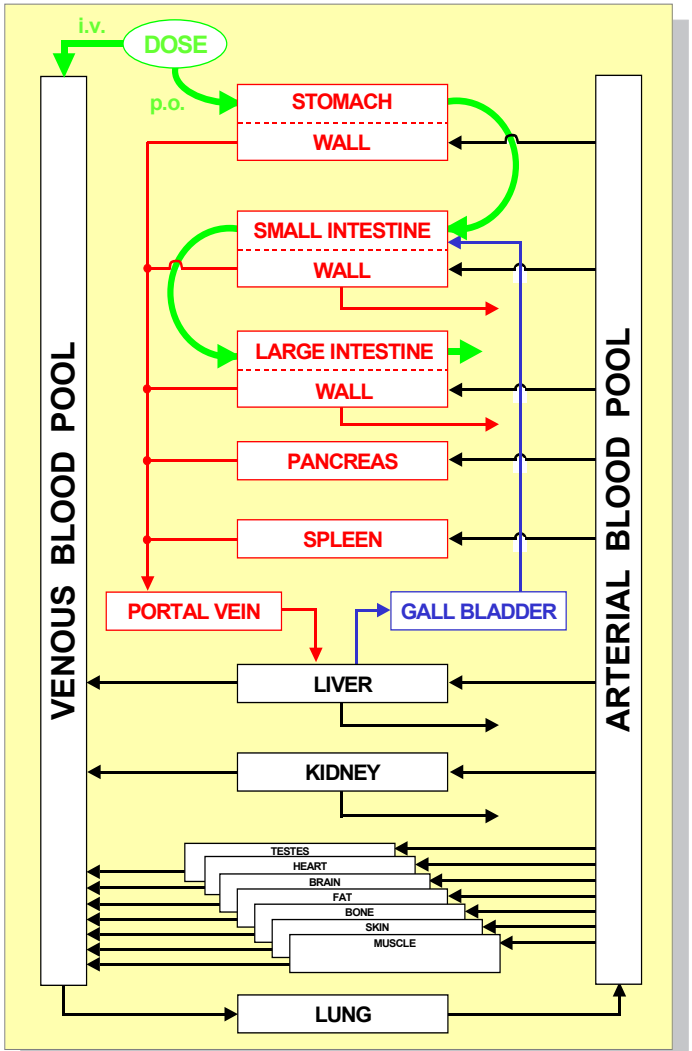
Clinical Data

- 19 CYP2C9 genotyped adult males
  - *1*1; *n* = 2
  - *1*2; *n* = 4
  - *1*3; *n* = 4
  - *2*2; *n* = 3
  - *2*3; *n* = 3
  - *3*3; *n* = 3
- Diclofenac and 4'OH-diclofenac plasma concentration time profiles over 10 hours following oral administration
- Anthropometric information of age, weight and height

Kirchheiner et al. *Br J Clin Pharmacol* 55:51-61 (2003).

Coupling Drug & Metabolite PBPK Models

Diclofenac PK-Sim Simulation



Check distribution using IV data

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Coupling Drug & Metabolite PBPK Models

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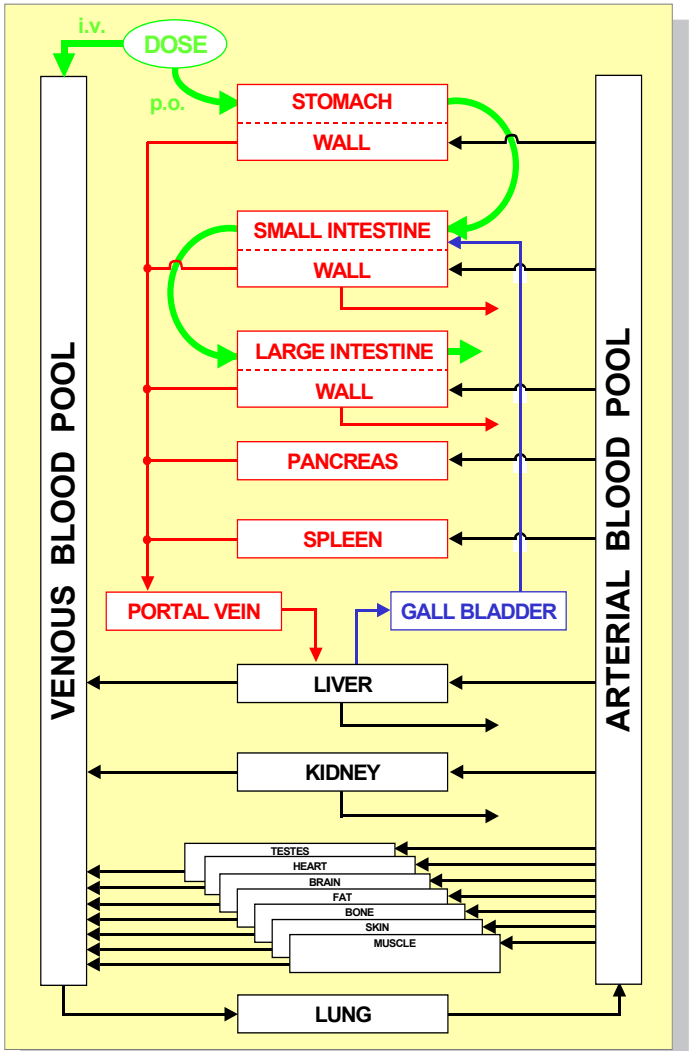

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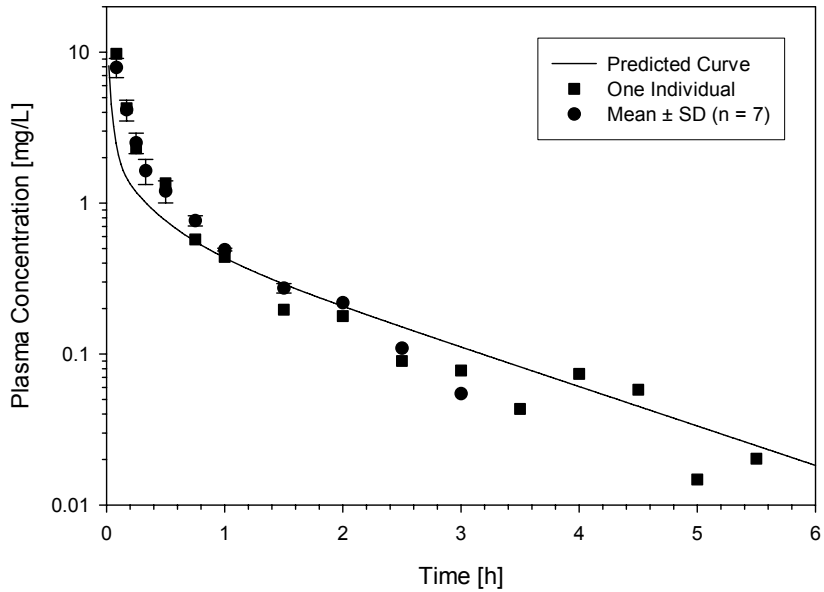

Willis et al. 1979. *Eur J Clin Pharmacol* 16:405-410.

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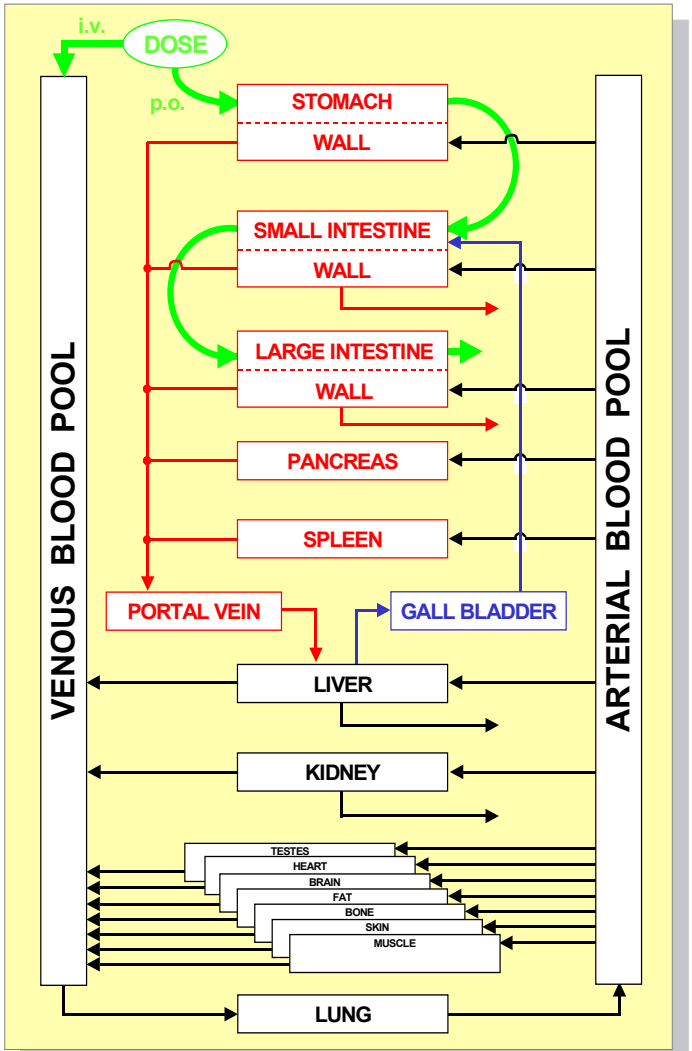
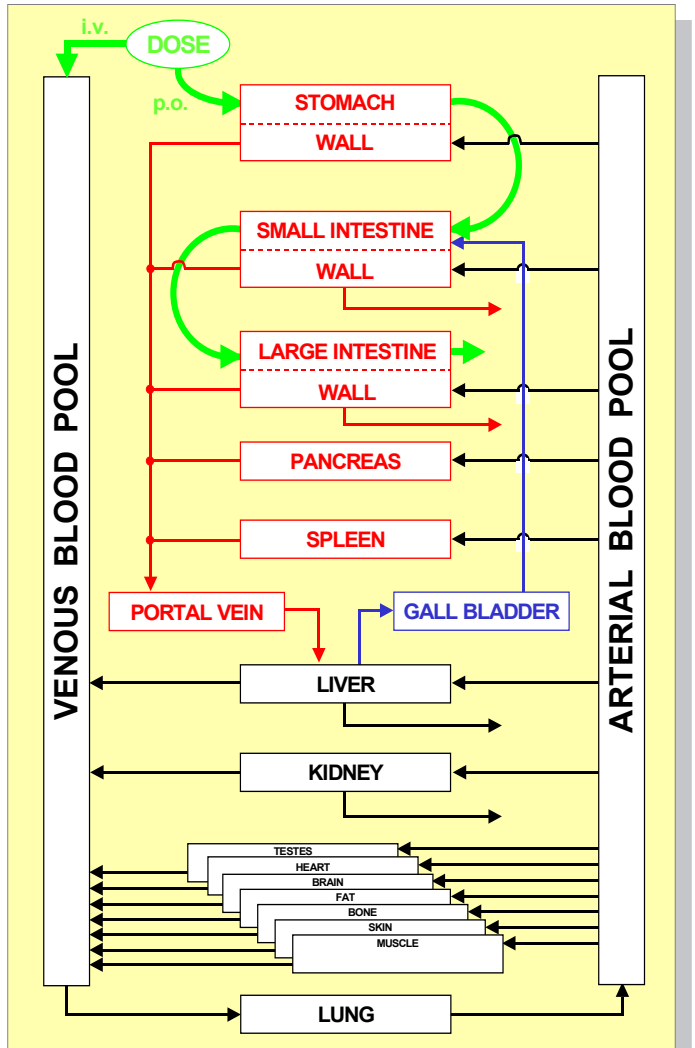
Coupling Drug & Metabolite PBPK Models

Diclofenac PK-Sim Simulation



4'OH-Diclofenac PK-Sim Simulation

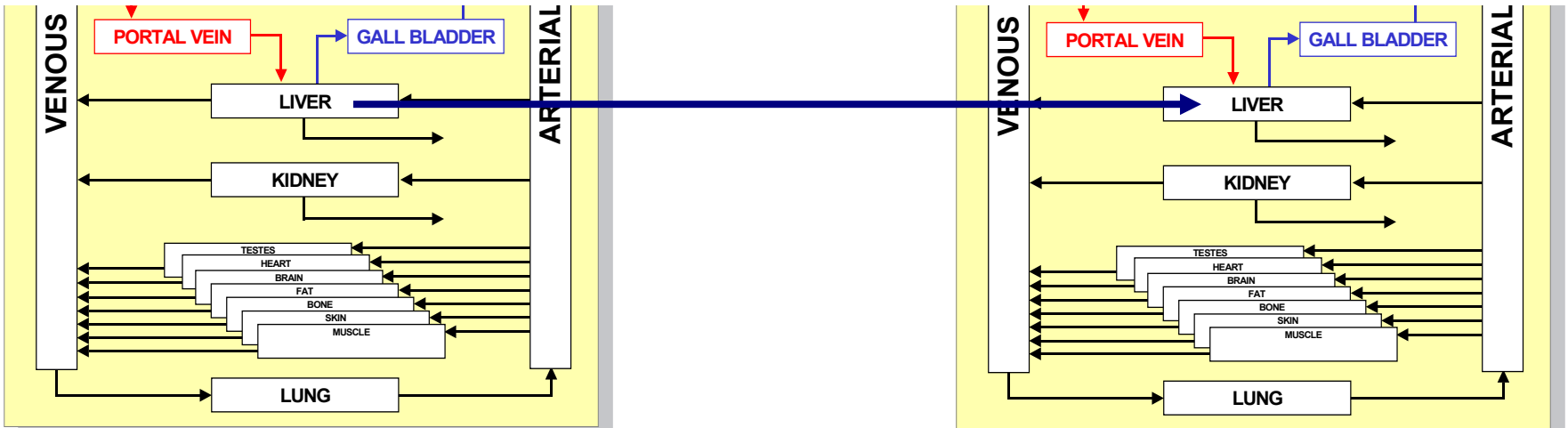


Coupling Drug & Metabolite PBPK Models

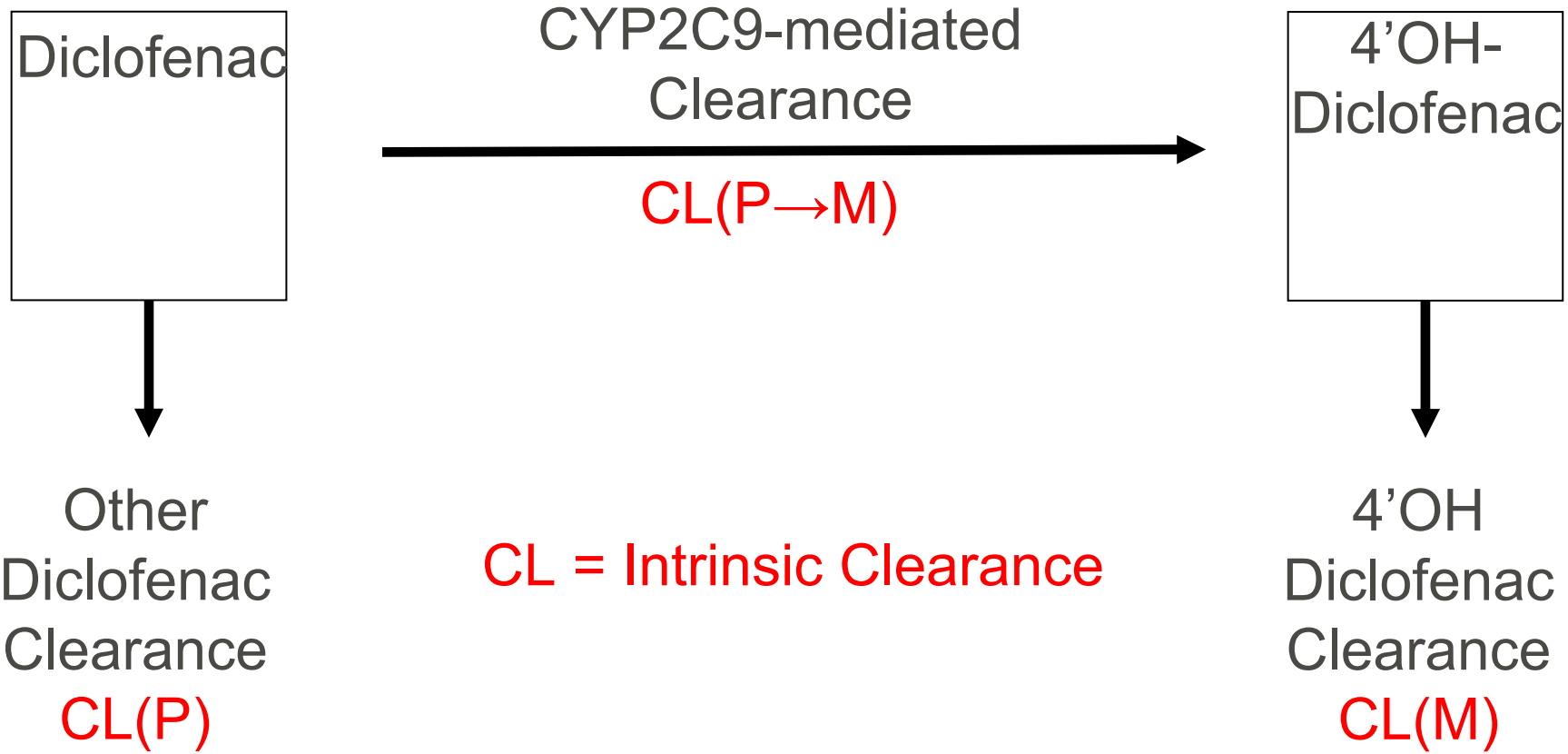
Diclofenac PK-Sim Simulation

4'OH-Diclofenac PK-Sim Simulation

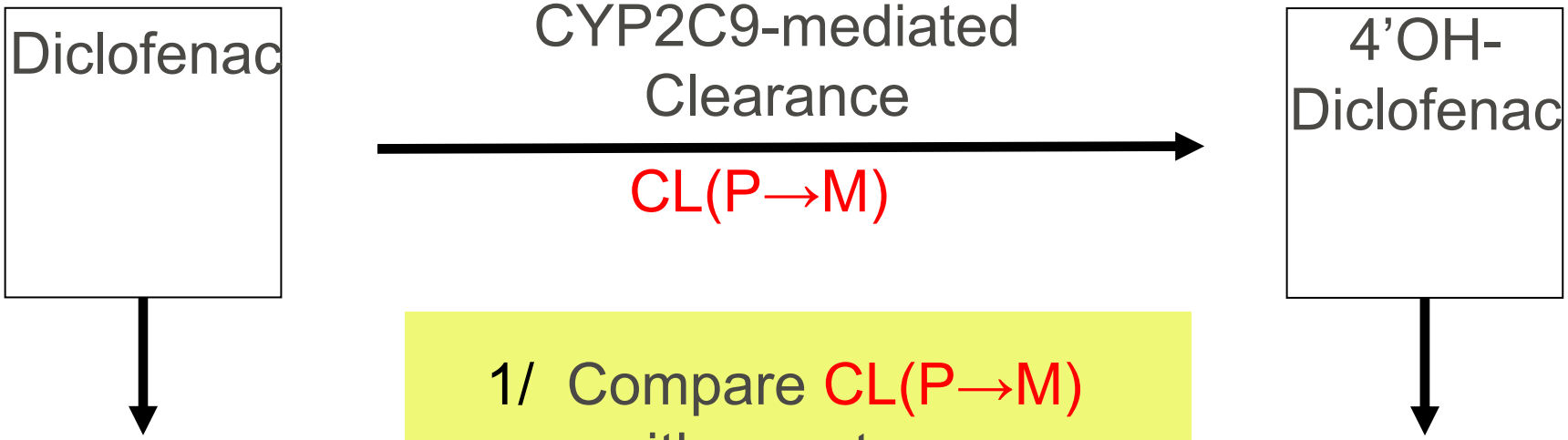
Source of 4'OH diclofenac is diclofenac CYP2C9-mediated metabolism in the liver intracellular space



Clearance Optimization



Clearance Optimization

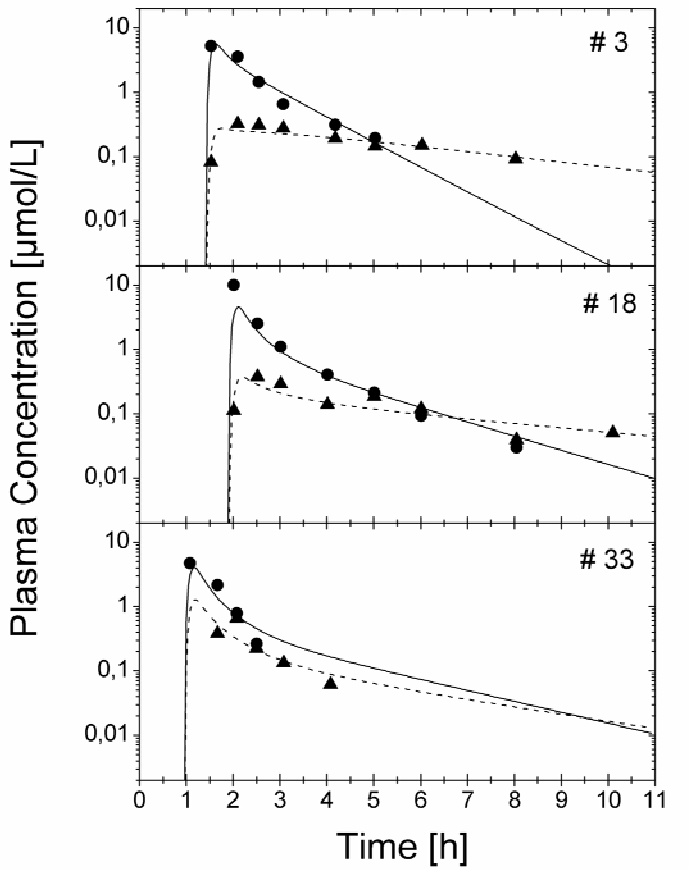


1/ Compare CL(P→M) with genotype

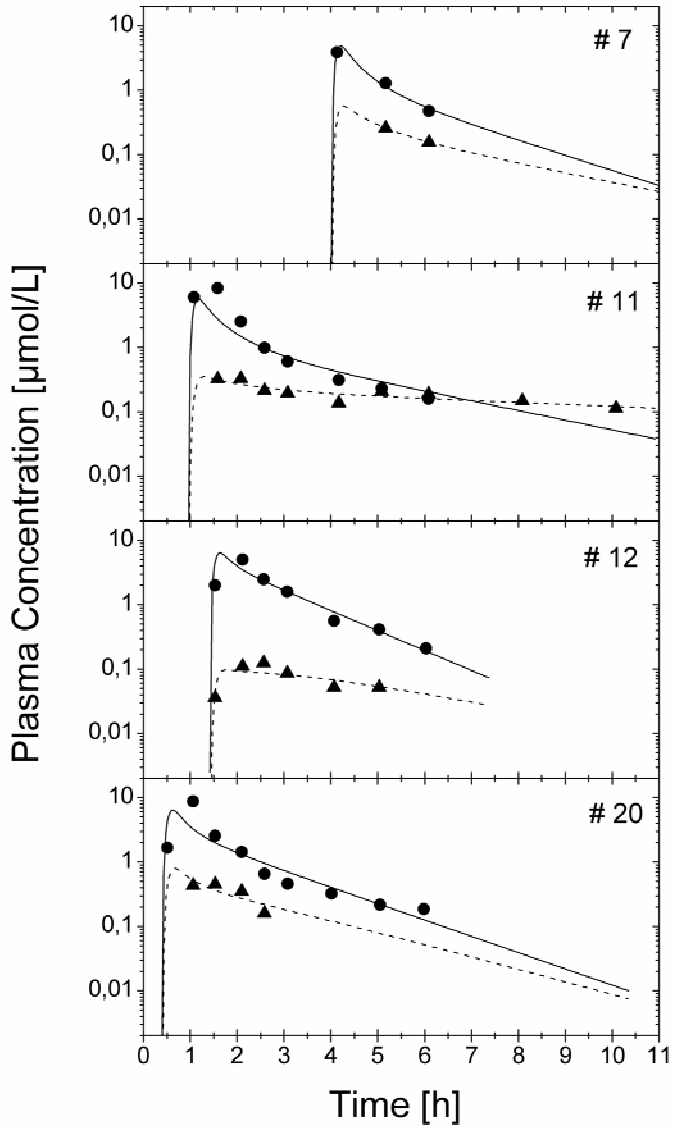
2/ $\% = \frac{CL(P \rightarrow M)}{CL(P \rightarrow M) + CL(P)}$

Diclofenac Results

CYP2C9*2*2

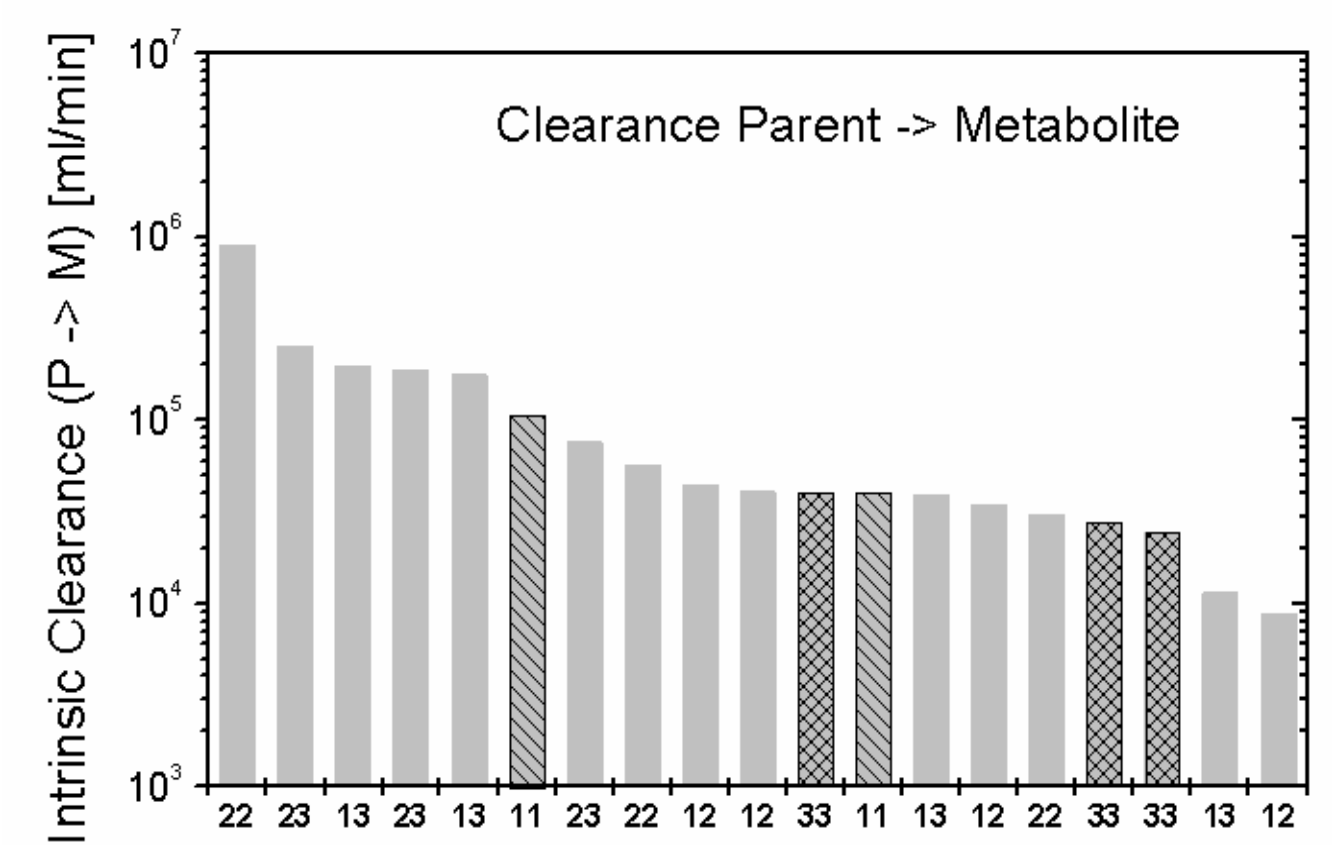


CYP2C9 *1*3



Diclofenac Results

Weak genotype-phenotype correlation!



% of Total Clearance Due to CYP2C9

- Based on optimized clearance values, CL(P→M) as a percentage of total diclofenac intrinsic clearance was:
  - **Median 7.2%**
  - **Mean 19.8%**
  - **Range 1.9 to 93.8%**

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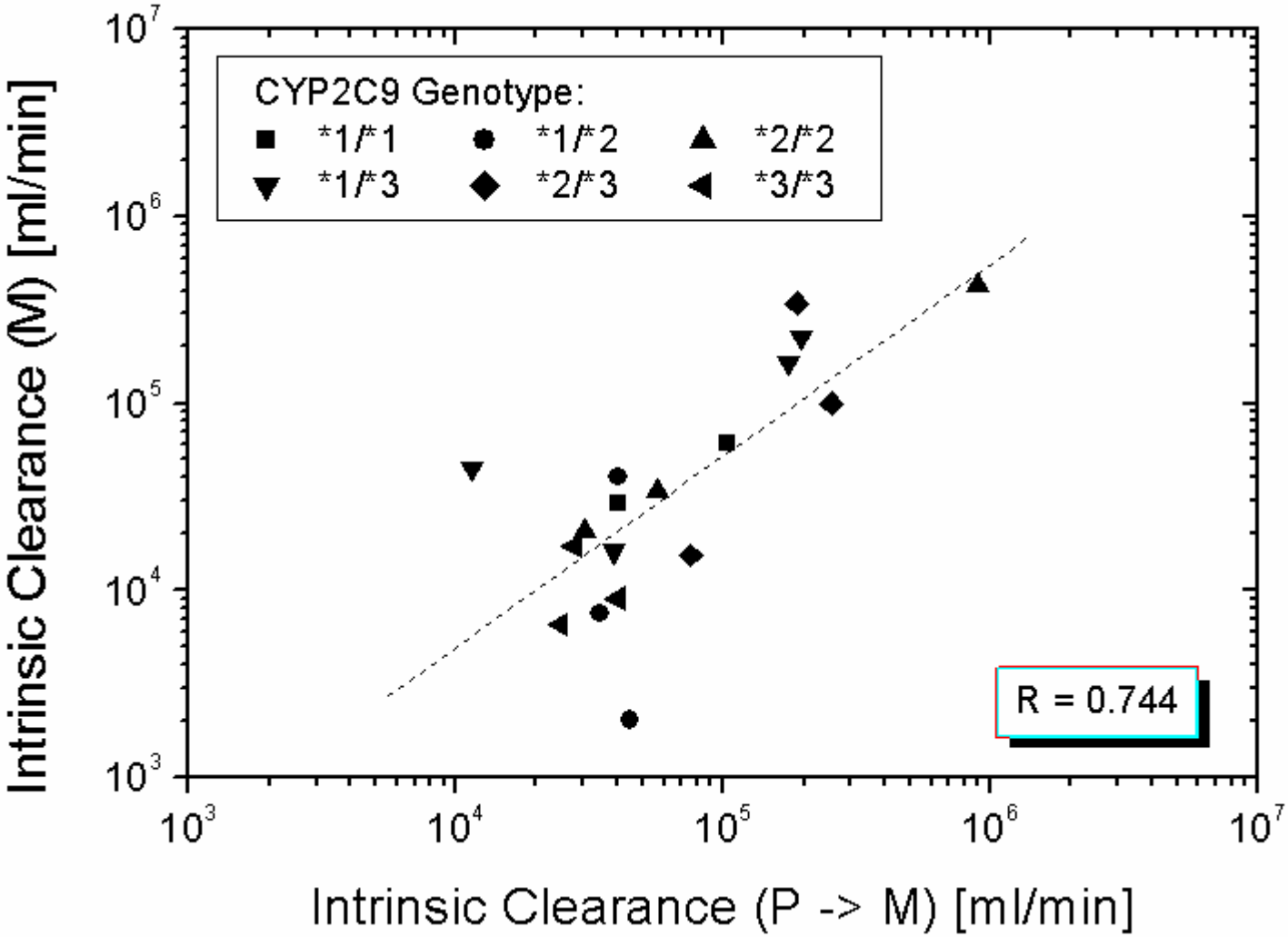
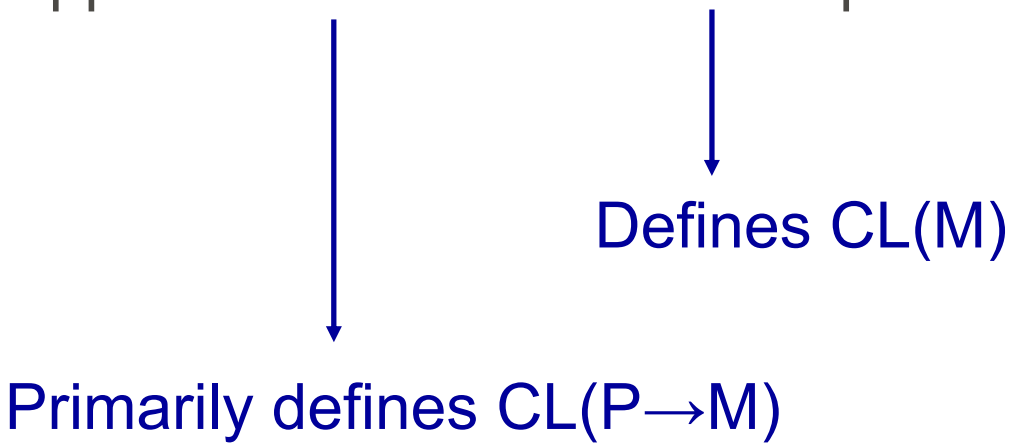
A weak pheno/genotype correlation along with a limited importance of CYP2C9 likely the reason why no in vivo correlation between oral diclofenac clearance and genotype is observed

Correlation between CL(P→M) and CL(M)



Potential Limitations

- Distribution is adequately estimated from physico-chemistry of the parent (can test) and metabolite (assumed)
- Requires a metabolite curve with observed data surrounding both the apparent Cmax and terminal phase



Uses of Method

- Determine the relative importance of the metabolite to the overall clearance of the parent
- Determine if there is an *in vivo* genotypic effect for polymorphic enzymes
- Generate a measure of the inter-individual variation in intrinsic clearances
- Examine age-related differences in metabolite production

Thank you

Acknowledgement

Thorsten Hartman from Nimbus Technology for the lipophilicity (Log MA) and serum binding measurements.

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