In Vitro In Vivo Extrapolation (IVIVE):

Why It Is Not As Easy As You May Think

Amin Rostami

Professor of Systems Pharmacology
University of Manchester, UK

&

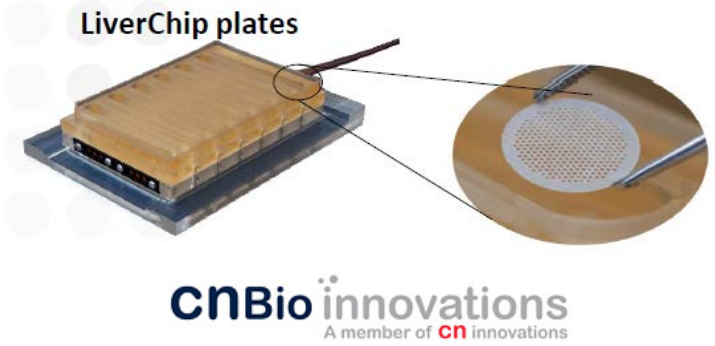
Chief Scientific Officer & Senior Vice President of R&D
Certara , Princeton, USA

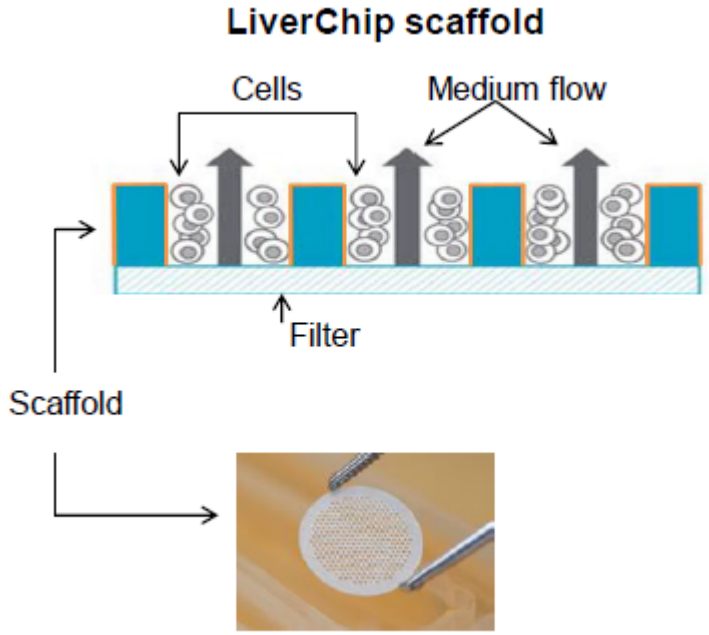
Our Experience with MPS:
(**Ayşe** Ufuk, Tom De Bruyn)

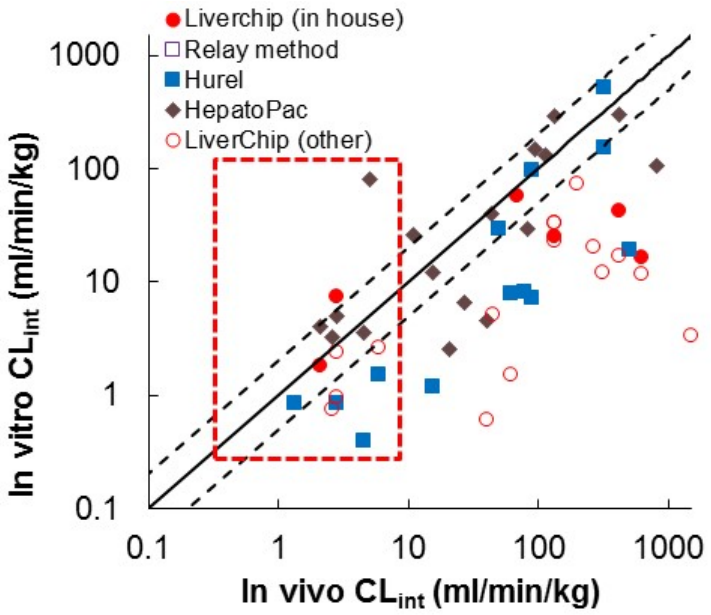
LiverChip™

MANCHESTER 1824

- Perfusion culture plate incorporates integrated scaffold permitting **formation of 3D liver microtissues** that resembles the architecture of a liver sinusoid







In vitro system	No	In vivo CL_{int} fold range	GMFE
LiverChip (in house)	6	296	4.36
Relay method	11	129	2.00
Hurel	13	379	4.60
HepatoPac	17	392	2.57
LiverChip (other)	16	568	10.7

Initial LiverChip Optimisation Studies

- ✓ **Albumin** secretion in hepatocytes cultured in LiverChip™ is stable for up to 9 days of culture time
- ✓ **Urea** medium concentrations are higher compared to static 2D cultures
  - ✓ Urea synthesis decreases with time
- ✓ Effect of **culture time** on enzyme activity was evaluated
  - ✓ CYP2C9 activity stable – no significant difference in tolbutamide depletion and 4OH-tolbutamide formation on day 3-4 and days 6-7
- ✓ Inter-day variability based on tolbutamide depletion as a marker was evaluated
  - ✓ Approximately 40% variation in tolbutamide clearance was observed

Ufuk et al, manuscript in preparation

Other Team Members:

Tom De Bruyn, Michiharu Kageyama, Alex Galetin, Brian Houston, David Hallifax

The AAPS Journal, Vol. 19, No. 5, September 2017 (© 2017)
DOI: 10.1208/s12248-017-0122-4

Research Article

Integrated Gut and Liver Microphysiological Systems for Quantitative *In Vitro* Pharmacokinetic Studies

Nikolaos Tsamandouras,[1] Wen Li Kelly Chen,[1] Collin D. Edington,[1] Cynthia L. Stokes,[2] Linda G. Griffith,[1] and Murat Cirit[1,3]

1521-0103/360/1/95–105$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

http://dx.doi.org/10.1124/jpet.116.237495
J Pharmacol Exp Ther 360:95–105, January 2017

Quantitative Assessment of Population Variability in Hepatic Drug Metabolism Using a Perfused Three-Dimensional Human Liver Microphysiological System[S]

N. Tsamandouras,[1] T. Kostrzewski, C. L. Stokes, L. G. Griffith, D. J. Hughes, and M. Cirit

Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts (N.T., L.G.G., M.C.); CN Bio Innovations, Hertfordshire, United Kingdom (T.K., D.J.H.); and Stokes Consulting, Redwood City, California (C.L.S.)

Received August 30, 2016; accepted October 17, 2016

PhysioMimetics

Human Physiome on a Chip

Ask Better Questions

Translational Applications of Organ-on-a-Chip Technologies

Murat Cirit, PhD

Director of Translational Center of Tissue Chip Technologies

Massachusetts Institute of Technology

Massachusetts Institute of Technology

July 13, 2017

DARPA

PhysioMimetics Team

Core Investigators
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- Pete Wishnok (MIT)
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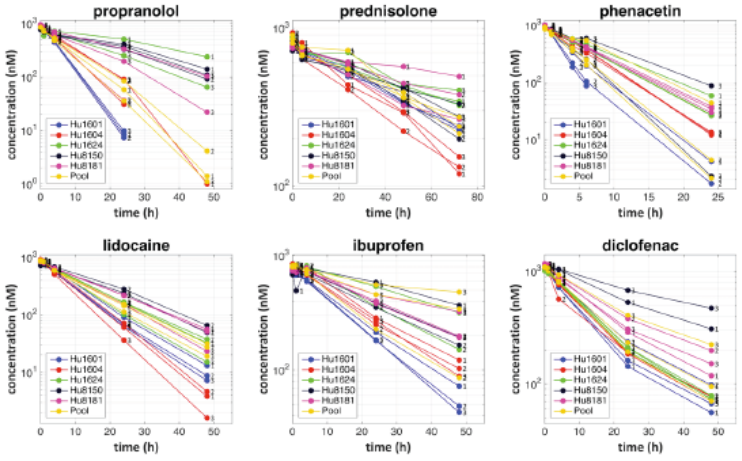
- Xin Wang

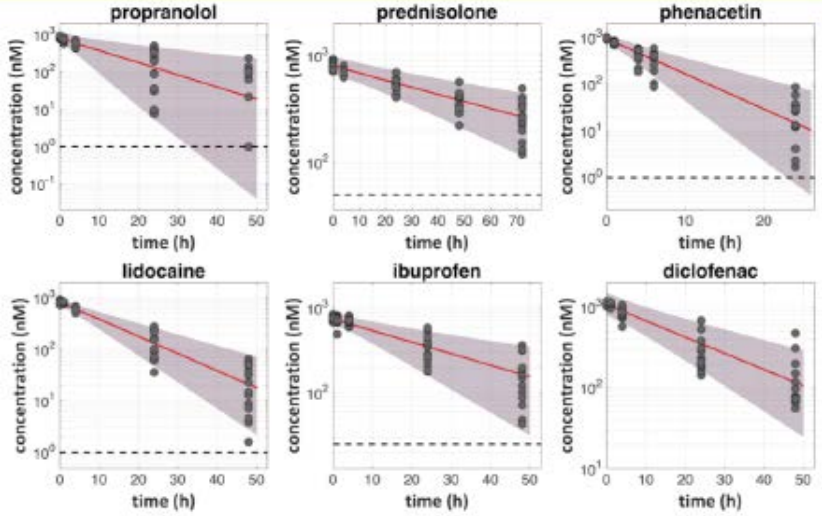
Funding: DARPA Microphysiological Systems Program (W911NF-12-2-0039), the NIH Microphysiological Systems Program (4-UH3-TR000496-03)

Quantitative assessment of donor-to-donor variability in the LiverChip

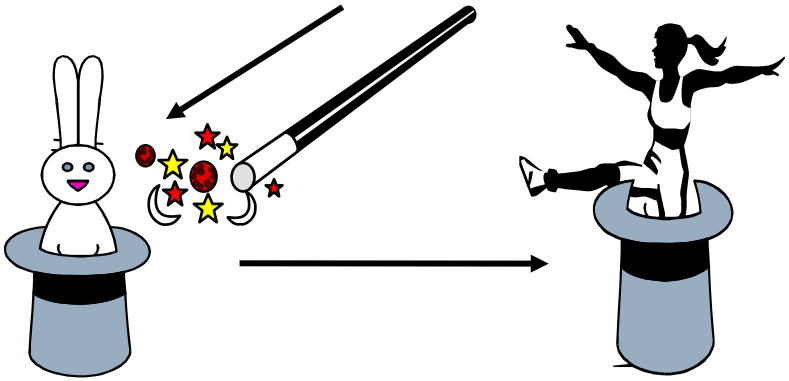


Tsamandouras & Kostrzewski et al, JPET 2017

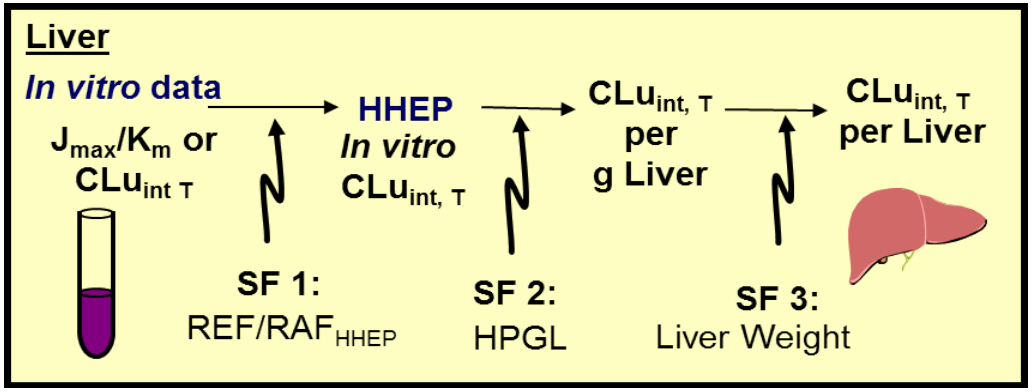
Mixed-effects modeling of drug depletion data



IVIVE: Major Input for PBPK (and any other QSP) Models



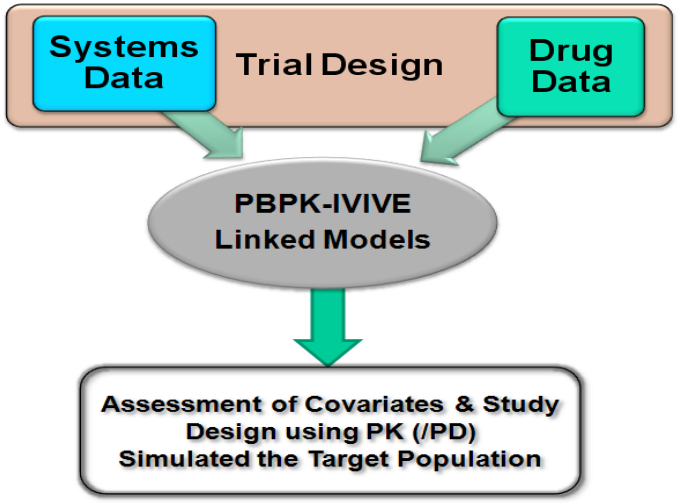
In Vitro to *In Vivo* Extrapolation



STATE OF THE ART — nature publishing group

Physiologically Based Pharmacokinetics Joined With *In Vitro–In Vivo* Extrapolation of ADME: A Marriage Under the Arch of Systems Pharmacology

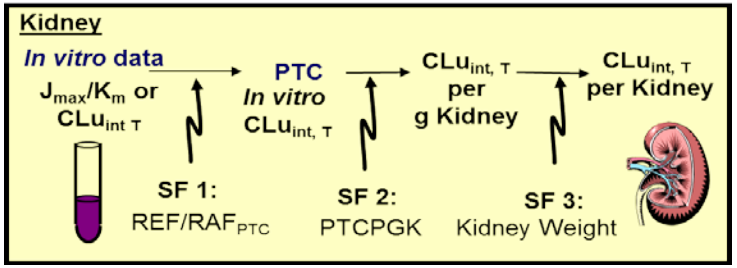
A Rostami-Hodjegan[1,2]

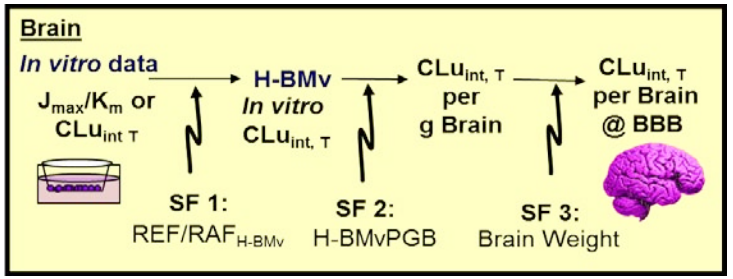


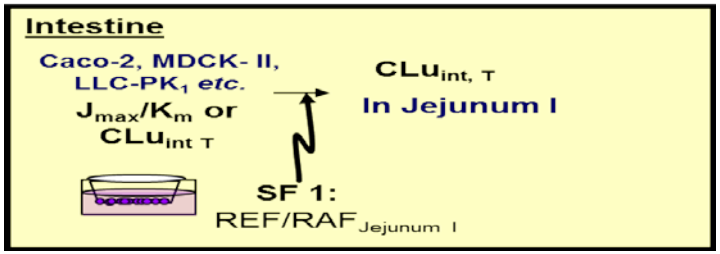
Input Data:
- Population Library
- Compound File
- Project (Workspace)

Integrated Models
- Simulation Tool
- Simulation Environment

Output
- Raw Output Data
- Output Environment
- Data Analysis



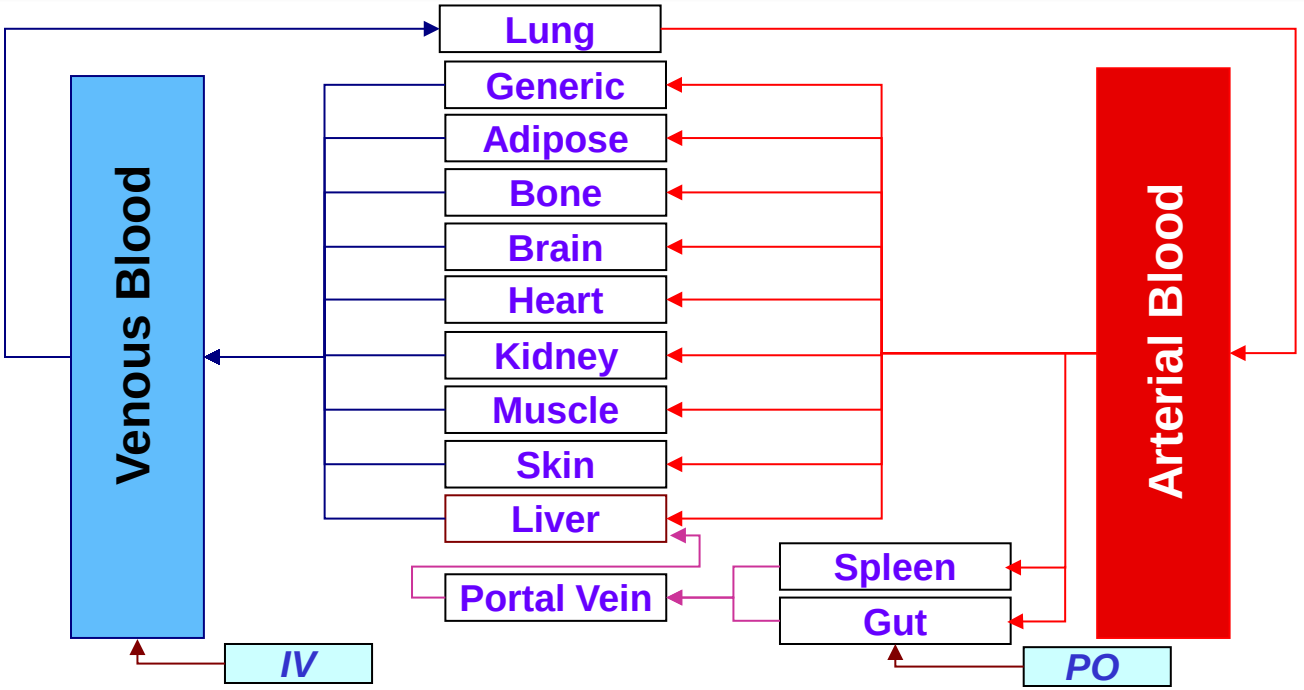




PBPK: Typical View = Nothing New!

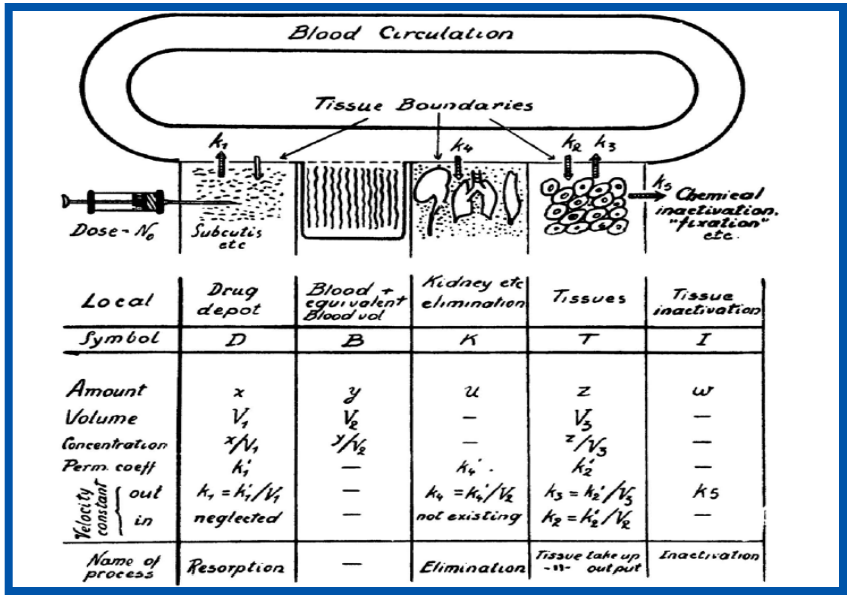
Typical View:

Describing the C-T profiles based on physiological knowledge of the flows and partitions

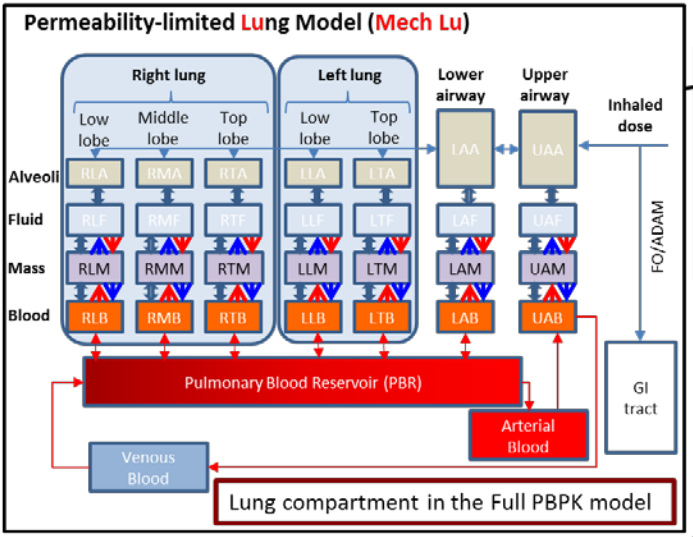


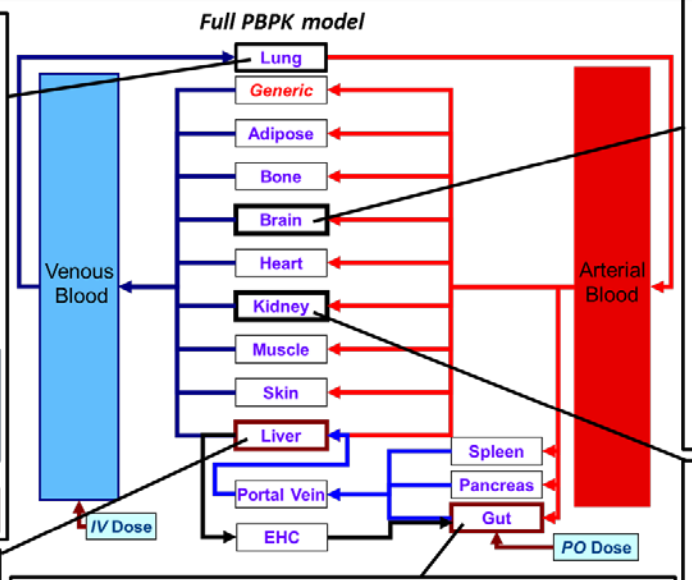
Nothing New:

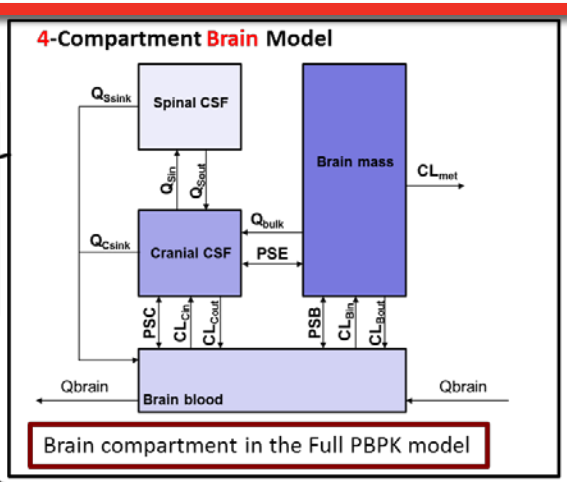
Teorell, T. Studies on the diffusion effect upon ionic distribution: II. experiments on ionic accumulation. *J. Gen. Physiol. 21, 107–122* ***(1937)***

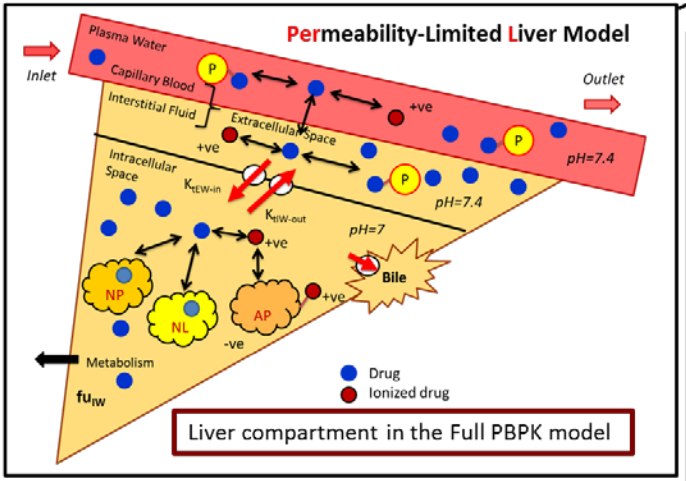


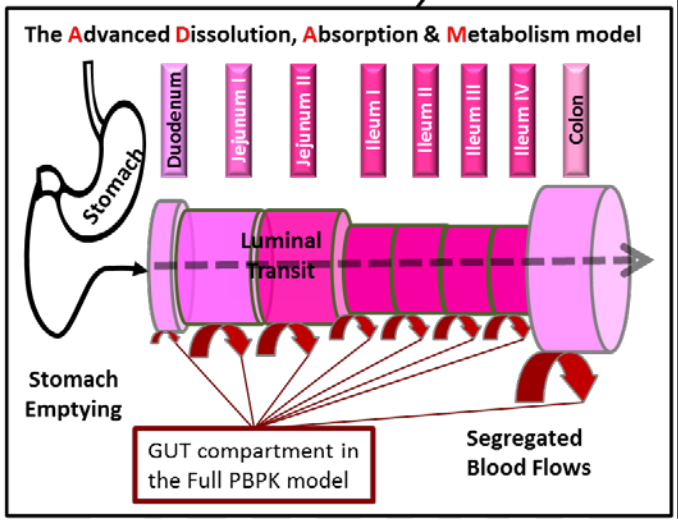
How it is done? Integrating system information

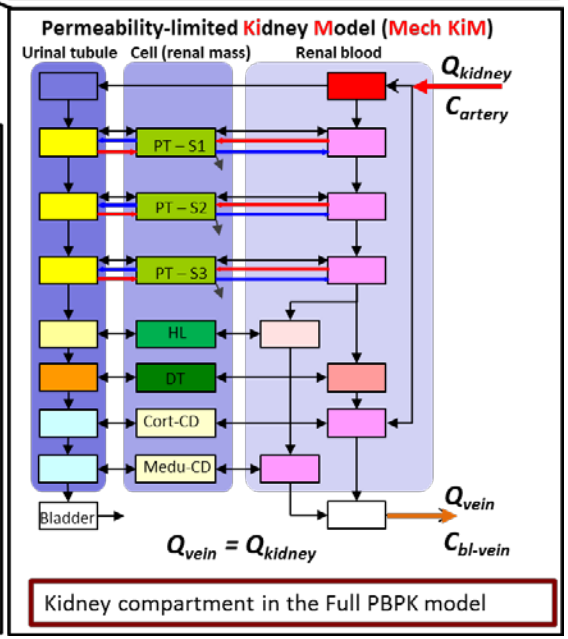












- Replacement and additional organ

Permeability-limited models are available for the intestine, liver, kidney, brain and lung.

- Transport across a membrane is often defined as Perfusion Limited
- But we now define uptake/efflux into/out of selected organs as Permeability Limited

Adoption in Industrial Scale

From Academic Nicety to Industrial Necessity

Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation

T Shepard[1]*, G Scott[2], S Cole[1], A Nordmark[3] and F Bouzom[4]

MHRA (PSP 2015)

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

C Wagner[1], P Zhao[1]*, Y Pan[2], V Hsu[1], J Grillo[1], SM Huang[1] and V Sinha[1]*

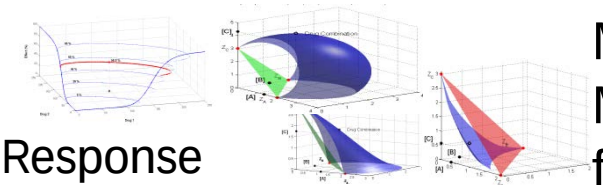
FDA (PSP 2015)

EDITORIAL

Physiologically Based Pharmacokinetics Is Impacting Drug Development and Regulatory Decision Making

M Rowland[1,2], LJ Lesko[3] and A Rostami-Hodjegan[1,4]*

PBPK under the Umbrella of Systems Pharmacology



Direct Dose Response

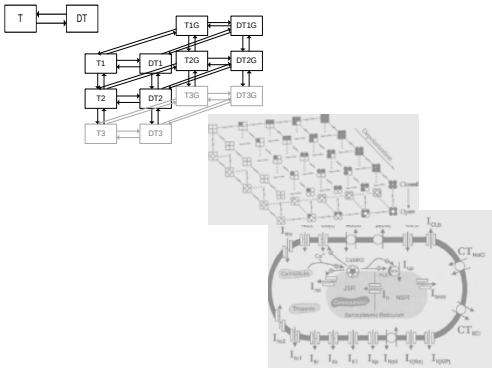
PD-DDI, Finney, Loewe, Bliss, Hewlett&Plackett., Greco, Vølund.....
Response surfaces
Generalized Linear models (GLM)

PKPD...

Hill, Indirect Physiological Response,
Disease Progression,
Cell Growth/Death
GLM, Survival Analysis, PKPD-DDI

Receptor binding...in vitro...system response

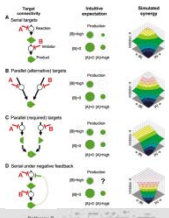
Equilibrium binding, specific receptors, Operational Agonism
Receptor states, G-Proteins & ternary complexes ... signalling
Ion channel kinetic models ...

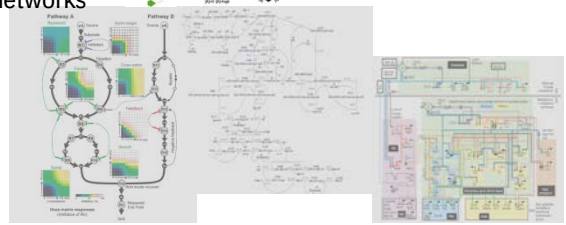


Specific Diseases, ...safety ....QTc...or

Systems Biology X-fertilization ..

Network response motifs,
Combinatorial targets
Hill in genetic regulatory networks

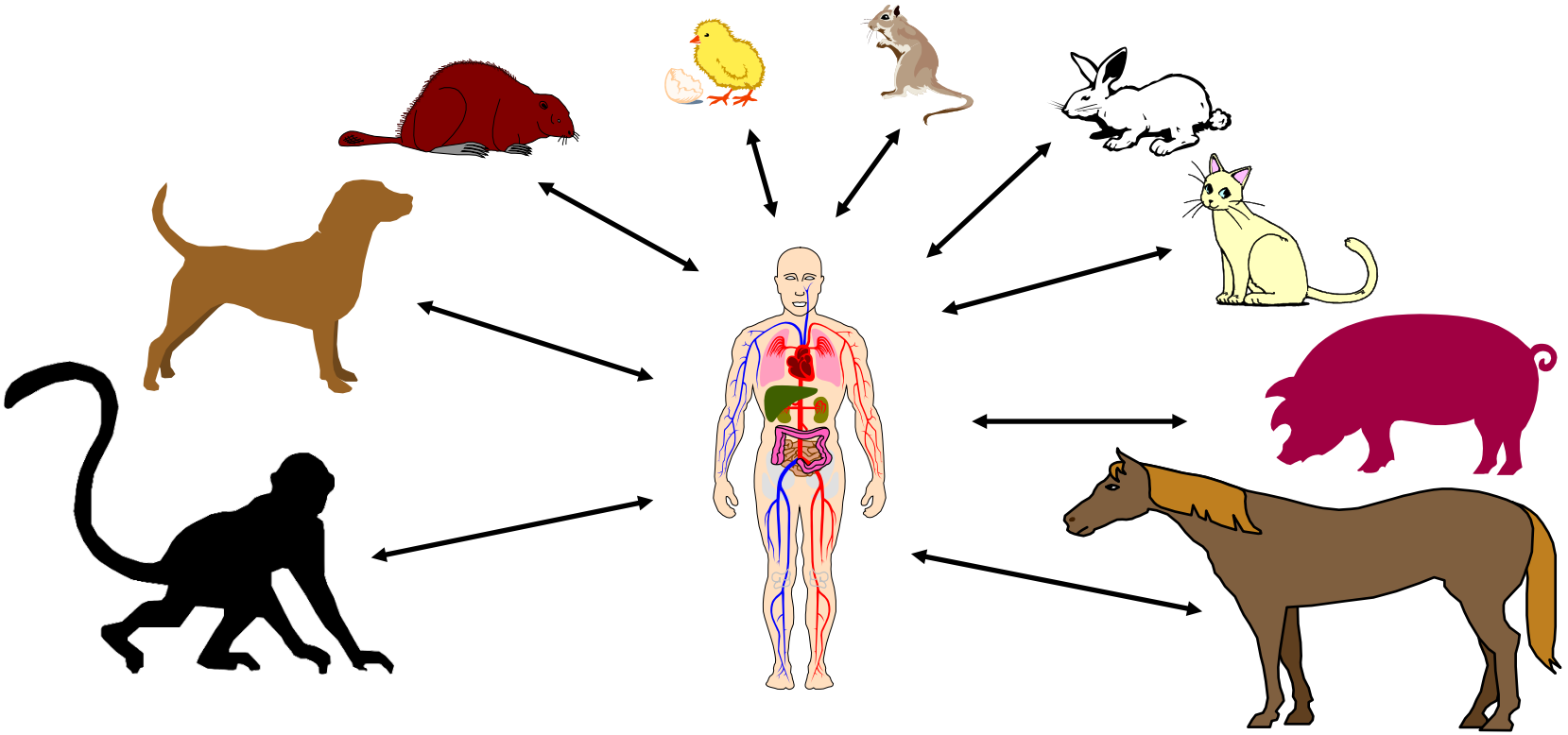




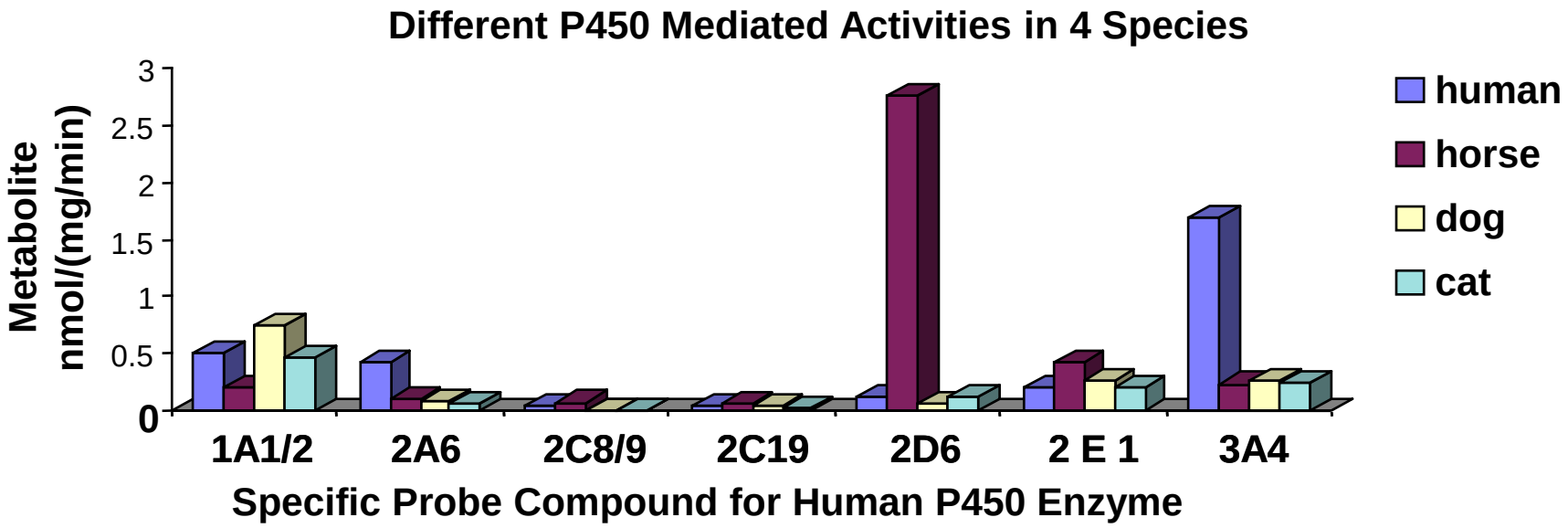
Multi-Level Hybrid Models: The Framework for Capturing, Retaining & Re-using the Available Systems Knowledge at a Given Time

Reduction in Traditional Use of Animal

One for Man, Two for Horse, G. Carson, Bramhall House, New York, 1961



A major component of PBPK is information on metabolism.



Chauret *et al*., 1997

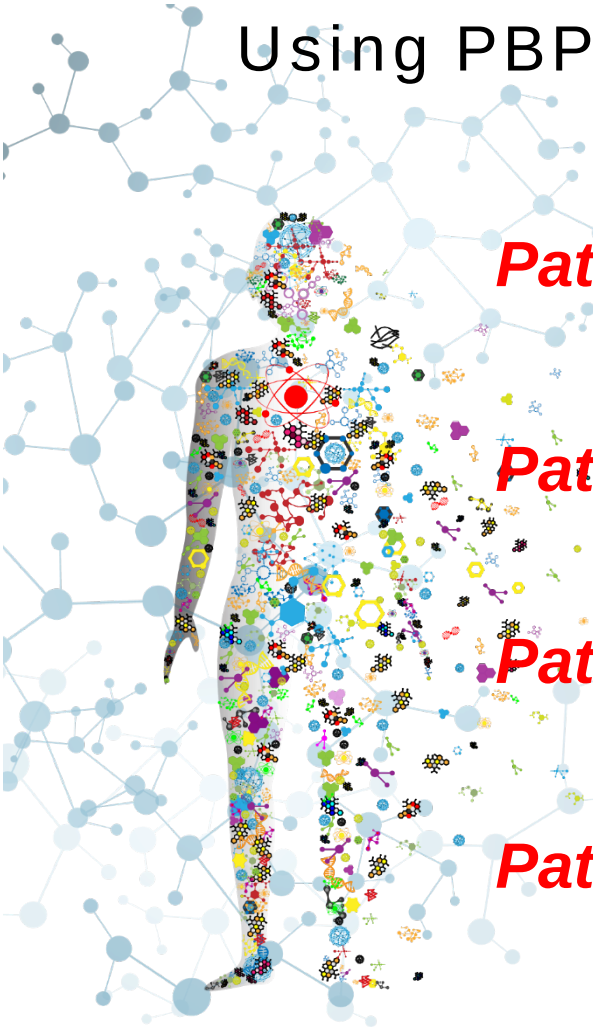
Catalyzing the Critical Path Initiative: FDA's Progress in Drug Development Activities

A Parekh[1], S Buckman-Garner[1], S McCune[1], R ONeill[1], M Geanacopoulos[1], S Amur[1], C Clingman[1], R Barratt[1], M Rocca[1], I Hills[1] and J Woodcock[2]

Modelling and Simulation

A related area in ***modernizing clinical trials*** has been the development and application of quantitative pharmacometric predictive models to support regulatory decision making. Modeling and simulation (M/S) tools for drug exposure and its response have been useful in both pre- and postmarket settings when questions related to safety and efficacy of therapeutic products arise. Some recent examples where M/S has served as a useful predictive tool include dose selection for pivotal trials, dosing in select populations such as pediatrics, optimization of dose and dosing regimen in a subset patient population, prediction of efficacy and dosing in an unstudied patient population in clinical trials, characterizing exposure and dose-related QT interval prolongation, and ***using physiologically based pharmacokinetic***

Path to Success
in
Using PBPK-IVIVE and Virtual Humans



Path (I)➔➔➔

Refining In Vitro Tests for Quantitative IVIVE

Path (II)➔➔➔

Providing & Integrating System Information

Path (III)➔➔➔

Transparent Methods and Case Examples

Path (IV) ➔➔➔

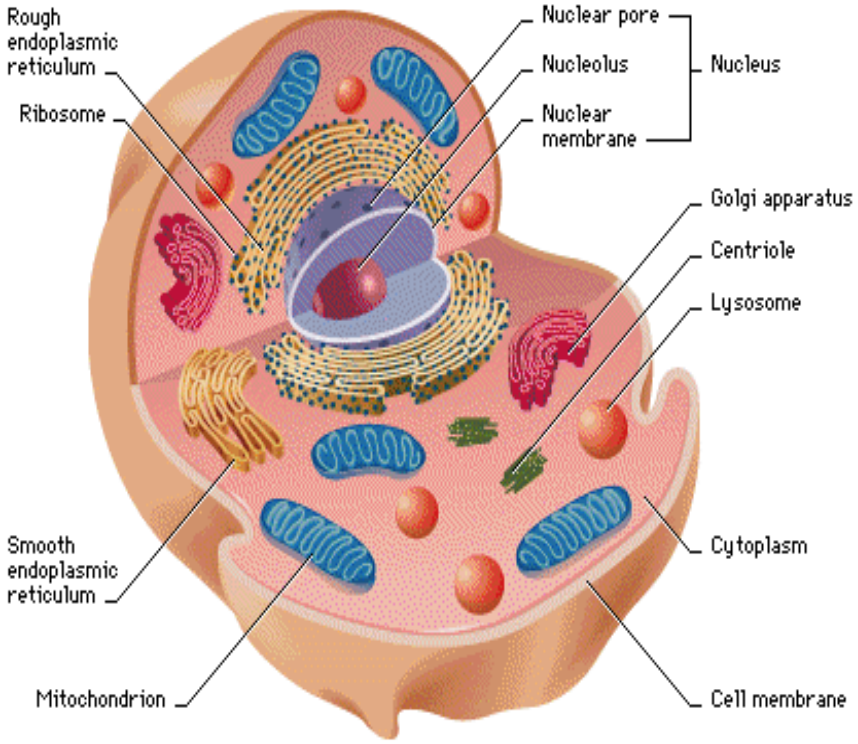
Showing Value & Re-Engineering Practices

The Debate at the Time: Which In Vitro System to Use?

Human Liver Microsomes (HLM)

Recombinantly expressed system (rhCYP)

Hepatocytes



Fractionation & Isolation of Enriched Organelles

Differences in intrinsic activity between rhCYP & HLM

Intact cells containing full complement of drug metabolising enzymes

Infrequent supply / cost

Donor variability

How Representative Is My HLM/Hepatocyte?

BD UltraPool HLM 150

BD

- **High degree of lot-to-lot consistency for CYP and UGT activity**
- **Representation of the "average patient" and known CYP polymorphisms**

XENOTECH

Uncommon Science | Uncommon Service

DATA SHEET

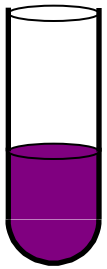
XTreme 200

Lot No. 0810413

Human Liver Microsomes
Pool of 200 (100 Male and 100 Female)
Suspension medium: 250 mM sucrose

H2610	0.5 mL at 20 mg/mL
H2620	1.0 mL at 20 mg/mL
H2630	5.0 mL at 20 mg/mL
H2640	50.0 mL at 20 mg/mL

Determination of Intrinsic Clearance: Right Units



In vitro system

In Vitro CLu_{int}

µl / min / **per functional unit of system**

$$CLu_{int} = \frac{CL_{int}}{fu_{inc}}$$

HLM

$$\frac{\text{[dA/dt] (pmol/min/mg microsomal protein)}}{\text{[S] (nmol/ml)}}$$

HHEP

$$\frac{\text{[dA/dt] (pmol/min/}10^6\text{ cells)}}{\text{[S] (nmol/ml)}}$$

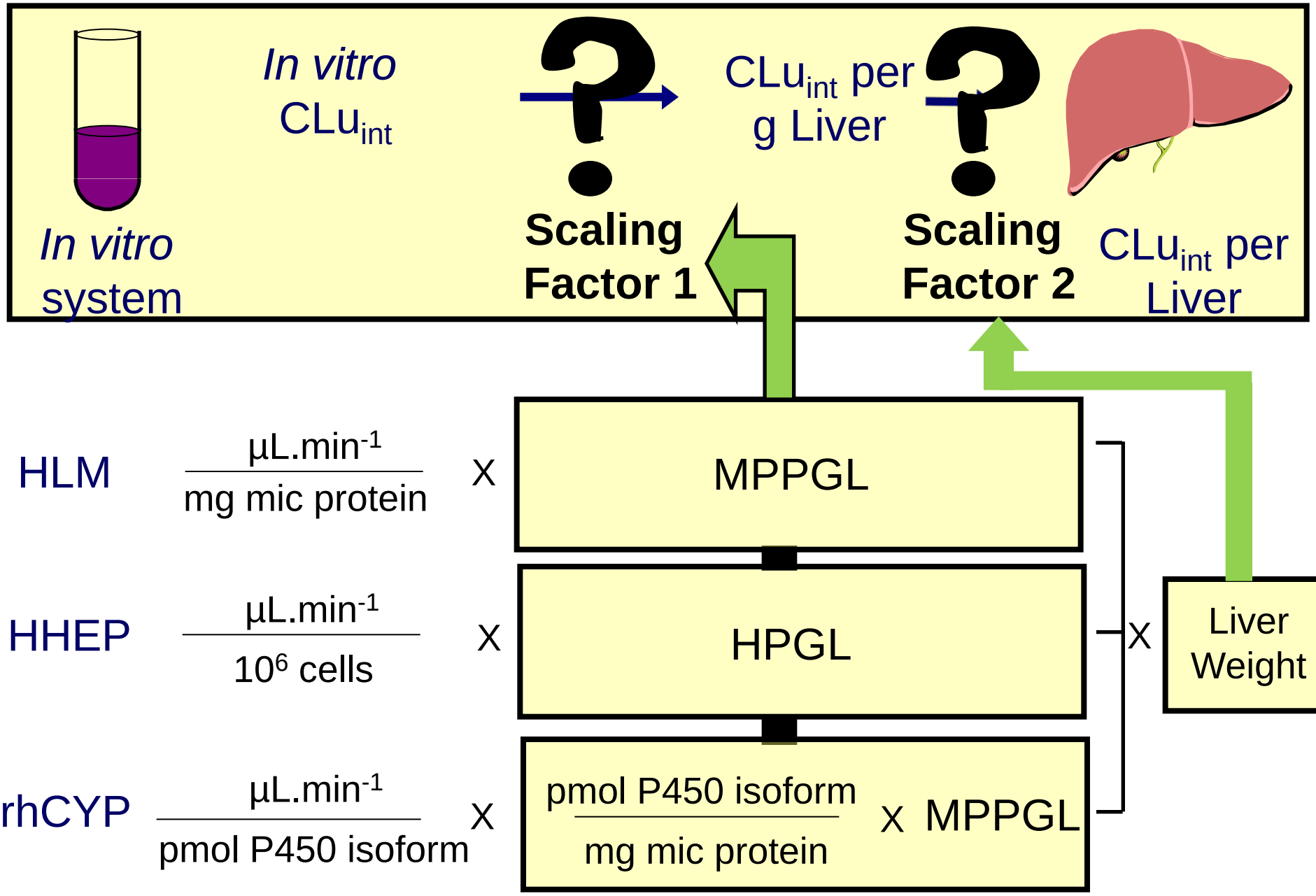
rhCYP

$$\frac{\text{[dA/dt] (pmol/min/pmol CYP isoform)}}{\text{[S] (nmol/ml)}}$$

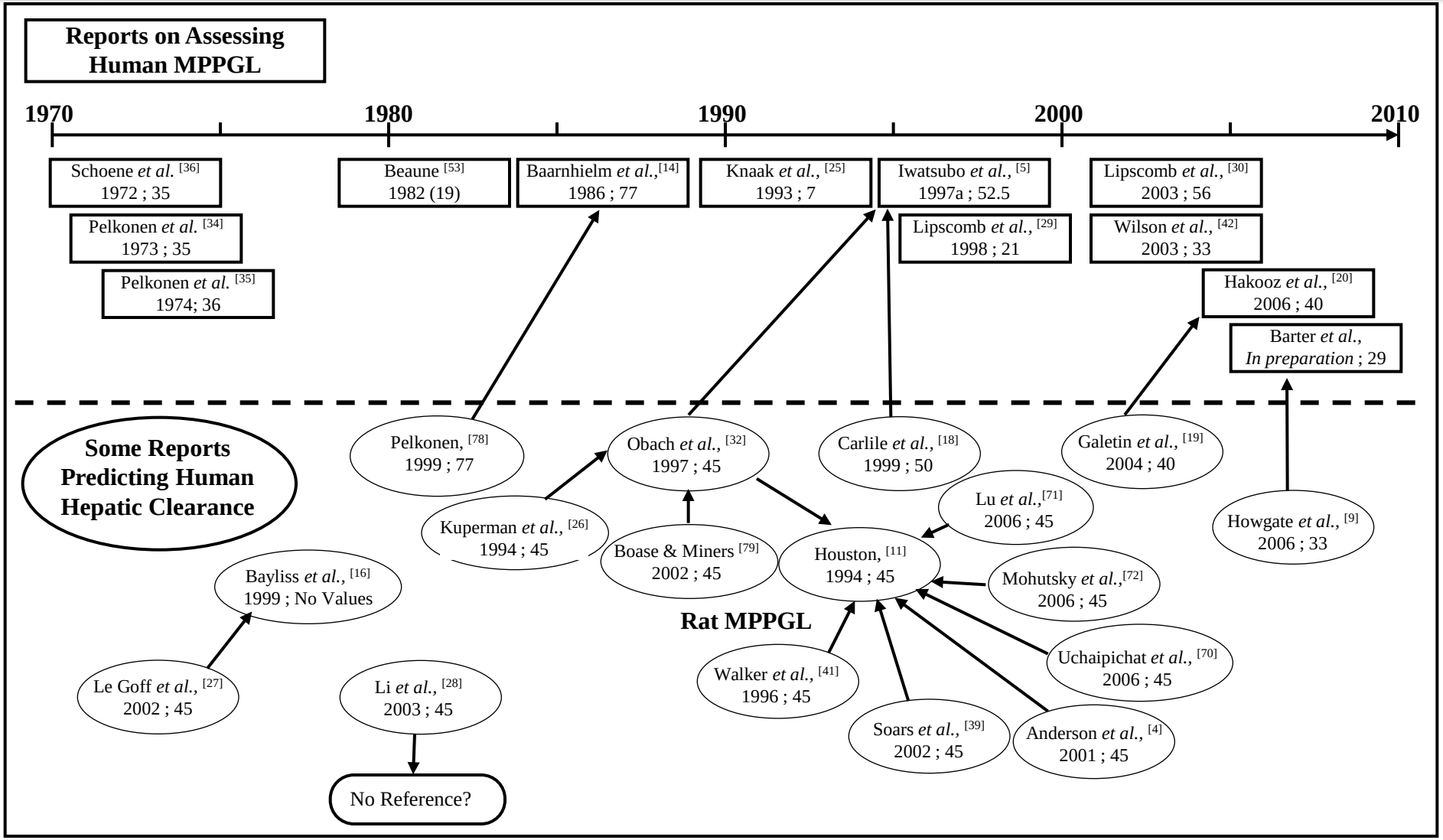
[S] = Free Substrate Concentration

[S] << Km (hopefully!)

Applying Appropriate Scaling Factors in Human IVIVE



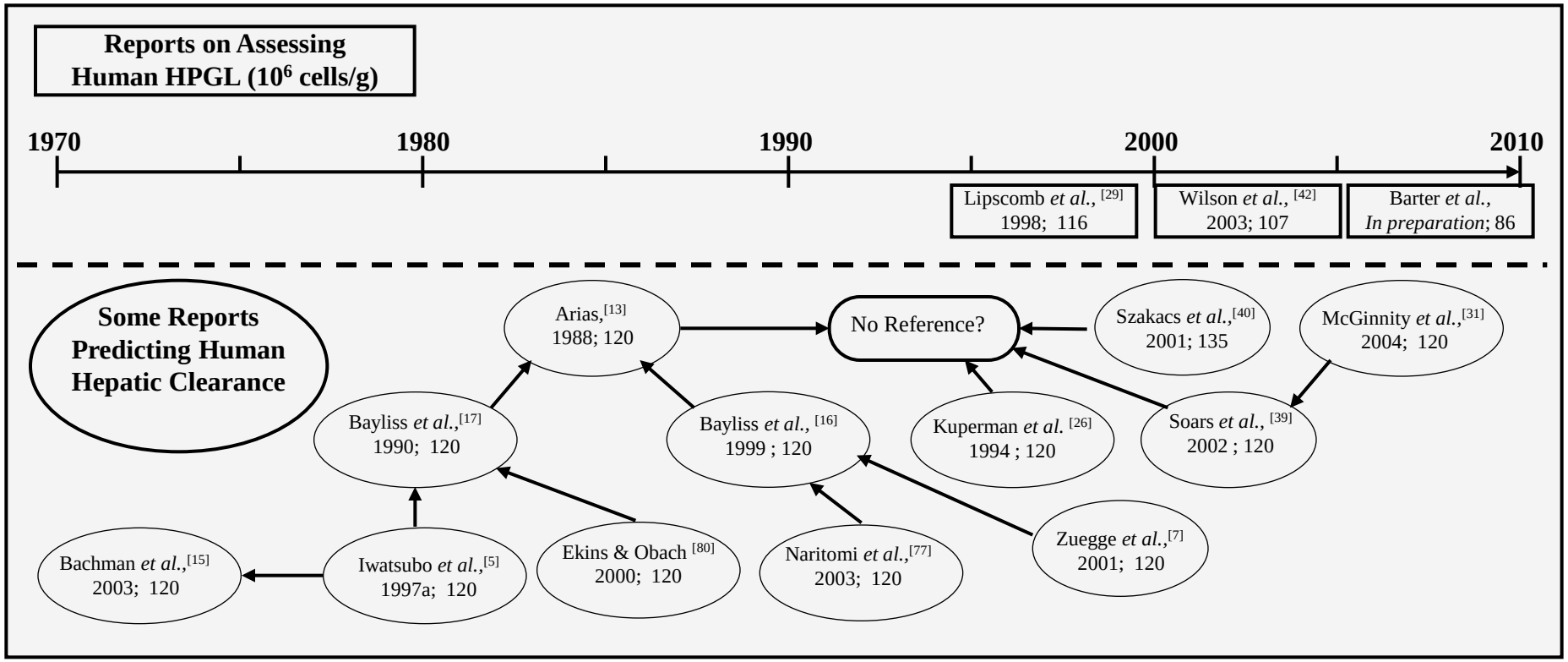
Literature Values: Human Microsomal Protein per Gram of Liver



Barter *et al.* (2007) *Current Drug Metabolism*

Scaling factors for the extrapolation of in vivo metabolic drug clearance from in vitro data: Reaching a consensus on values of human microsomal protein and hepatocellularity per gram of liver

Literature Values: Number of Human Hepatocytes per Gram of Liver



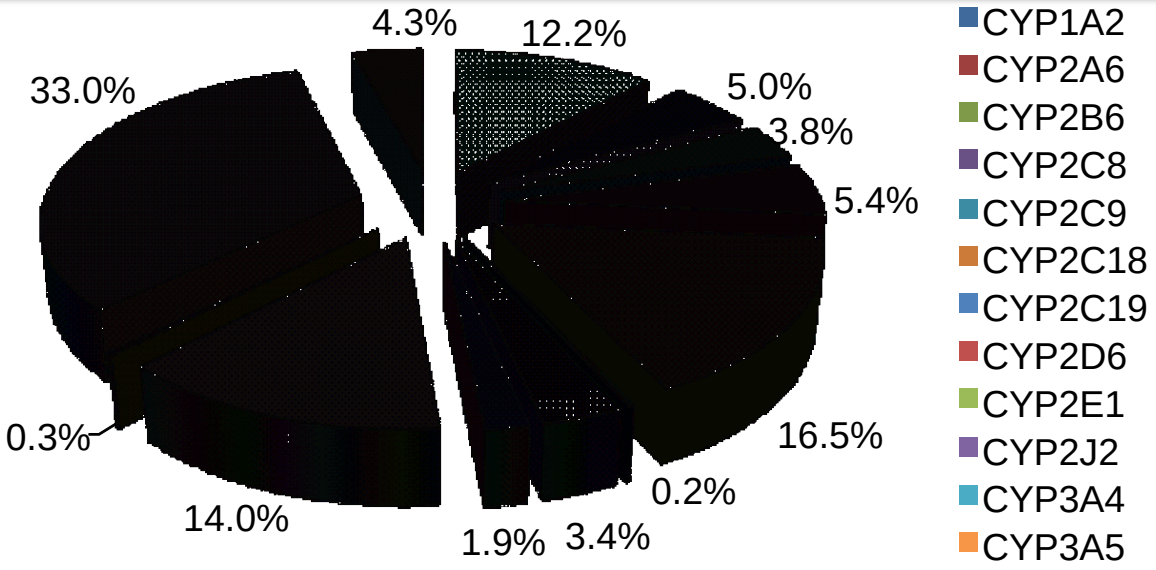
Barter *et al.* (2007) *Current Drug Metabolism*

Scaling factors for the extrapolation of in vivo metabolic drug clearance from in vitro data: Reaching a consensus on values of human microsomal protein and hepatocellularity per gram of liver

Scaling of rhCYP Data

CYP isoform abundance:

pmols CYP isoform
per
mg of microsomal protein

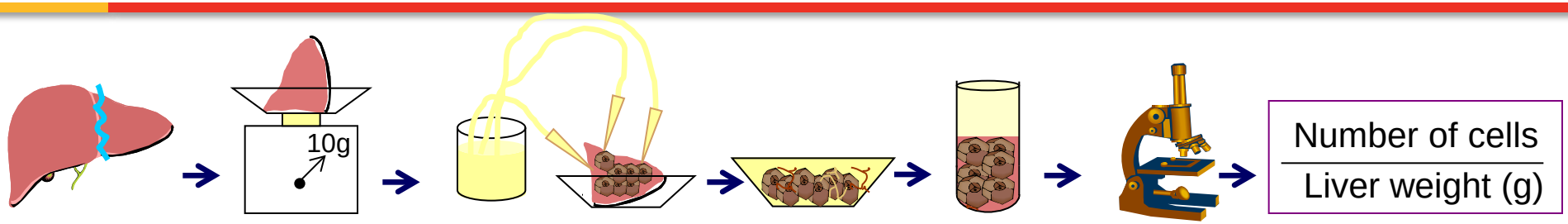


- Many groups use Shimada *et al.* (1994) values
  Don't differentiate between Japanese and Caucasian

- Literature review for papers reporting enzyme abundance values – Caucasian population
  30-40 papers reviewed; 19-27 used for meta-analysis

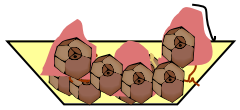
- Calculated weighted means, CVs and tested for homogeneity

HPGL Determination: Study by Simcyp Group (Sheffield)



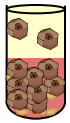
Human Liver Sample → Weight recorded → Perfusion of liver sample with digestion media to produce a homogenous suspension of hepatocytes → Centrifugation @ 50g to isolate hepatocytes → Counting of cells → Calculation of HPGL

Problem 1



Incomplete digestion leading to incomplete release of hepatocytes into suspension

Problem 2

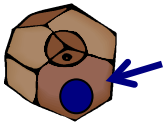


Incomplete recovery of cells following centrifugation

→ Loss of Hepatocytes → UNDERESTIMATION IN HPGL

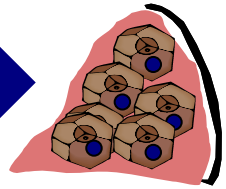
Determination of HPGL: Study by Simcyp Group (Sheffield)

Hepatocyte Specific Marker:

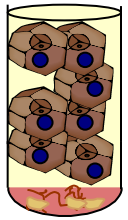


e.g. Cytochrome P450

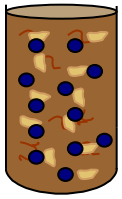
Liver tissue sample of known mass (g)

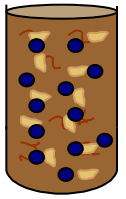


Hepatocyte Suspension of known cell concentration (x 10^6 cells)



HOMOGENISATION





CYP450 MEASUREMENT

$$\frac{\text{nmols CYP450}}{\text{g}} \qquad \frac{\text{nmols CYP450}}{10^6 \text{ cells}}$$

HPGL
10^6 cells per g

Known Issues with rhCYP Systems

- Differences in activity per unit enzyme (Crespi, 1995)
- Optimisation of rhCYP systems to mimic conditions observed in human liver (Iwatsubo *et al.*, 1997)
- Variable K_m (Nakajima *et al.*, 1999)
  - Differences in microsomal binding
- Effect of levels of accessory proteins on activity (Venkatakrishnan *et al.*, 2000)
  - NADPH cytochrome P450 reductase
  - Cytochrome b5

Accounting for Differences: ISEF

- Background information on the use of ISEFs

XENOBIOTICA, FEBRUARY 2004, VOL. 34, NO. 2, 151–178

Taylor & Francis
healthsciences

Predicting drug clearance from recombinantly expressed CYPs: intersystem extrapolation factors

N. J. PROCTOR, G. T. TUCKER and A. ROSTAMI-HODJEGAN

Molecular Pharmacology and Pharmacogenetics, Clinical Sciences Division (South), University of Sheffield, The Royal Hallamshire Hospital, Sheffield S10 2JF, UK

- Application of approach

Current Drug Metabolism, 2005, *6*, 503-517 503

Utility of Recombinant Cytochrome P450 Enzymes: A Drug Metabolism Perspective

Wei Tang[1,*], Regina W. Wang[1] and Anthony Y.H. Lu[2]

[1]Department of Drug Metabolism, Merck Research Laboratories, Rahway, New Jersey and [2]Department of Chemical Biology, College of Pharmacy, Rutgers University, Piscataway, New Jersey, USA

IVIVE Using rhCYP Systems

pmol/min/mg microsomal protein

Rate of Metabolism
pmol/min/pmol rhCYP$_j$

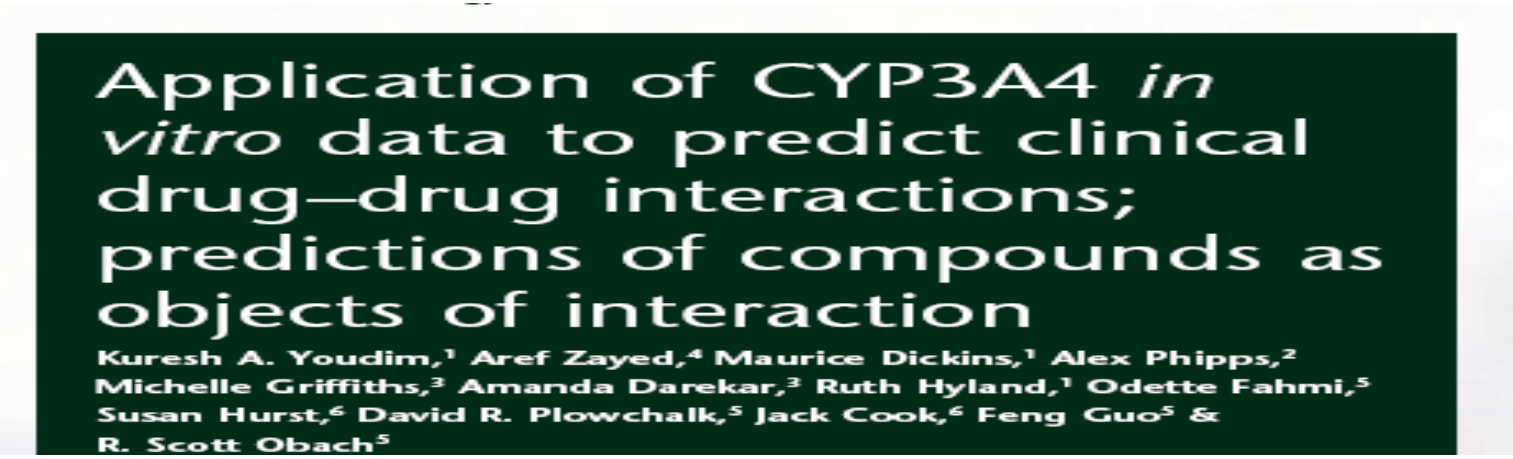
CYP abundance in
the Target Population
(pmol CYP$_j$/mg microsomal protein)

$$CL_{int}\ (L/h) = \left[\sum_{j=1}^{n}\left(\sum_{i=1}^{n}\frac{ISEF_{ji}\times Vmax\,(rhCYP_j)_i \times X_j}{K_m(rhCYP_j)_i}\right)\right]\times MPPGL \times \text{Liver weight}$$

j CYP isoforms

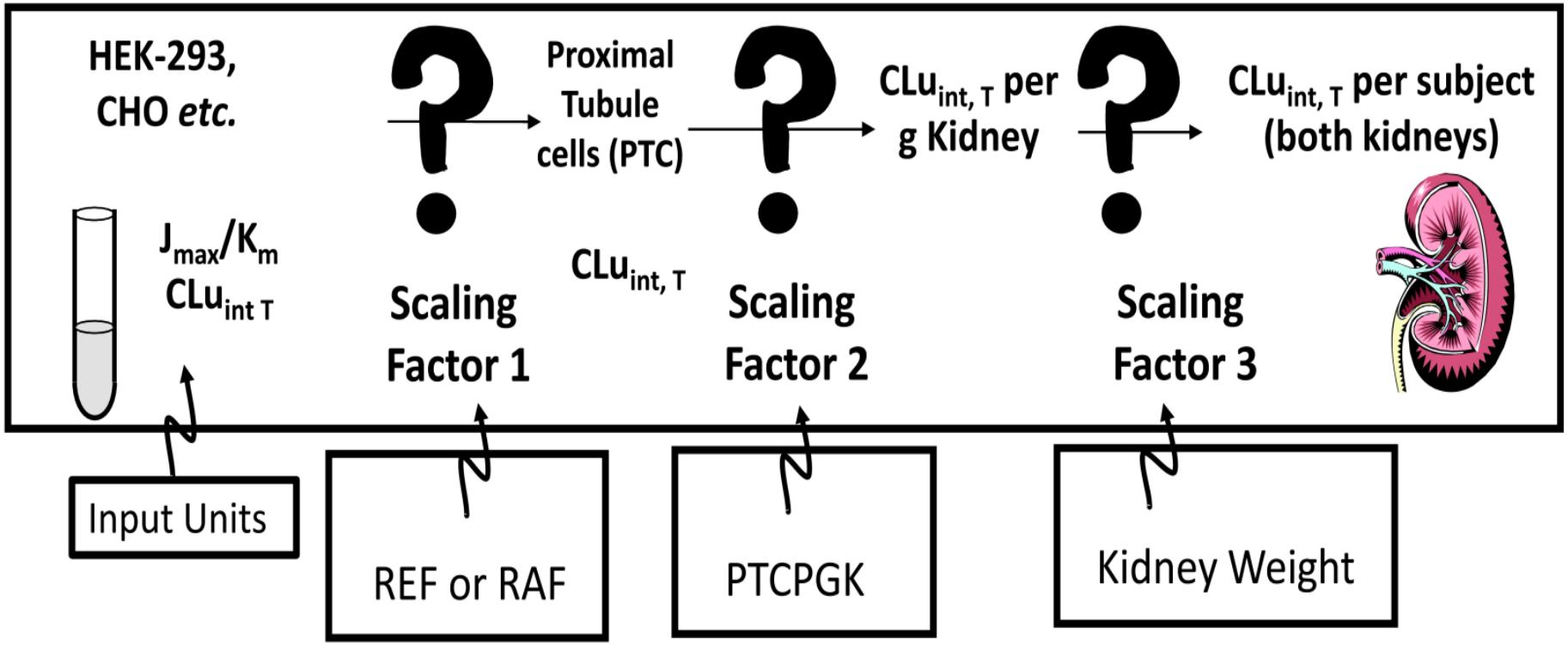
i metabolic pathways

amount of microsomal protein per gram of liver



Youdim et al Br J Clin Pharmacol, 2008

Same Issues Different Tissue: *In Vitro* Measurements



$$CL_{int,T}\left[\frac{\mu L.min^{-1}}{10^6\ CellsOfSystem1}\right] * REF\left[\frac{\frac{pmolTransporter_J\ PTC}{10^6\ PTC}}{\frac{pmolTransporter_J\ System1}{10^6\ CellsOfSystem1}}\right] * PTCPGK\left[\frac{10^6\ PTC}{gKidney}\right] * KW[gKidney]$$

$\Rightarrow$ [µL/min] or [L/h]

The AAPS Journal, Vol. 18, No. 5, September 2016 (© 2016)
DOI: 10.1208/s12248-016-9942-x

Review Article

Key to Opening Kidney for *In Vitro–In Vivo* Extrapolation Entrance in Health and Disease: Part I: *In Vitro* Systems and Physiological Data

Daniel Scotcher,[1] Christopher Jones,[2] Maria Posada,[3] Amin Rostami-Hodjegan,[1,4] and Aleksandra Galetin[1,5]

The AAPS Journal, Vol. 18, No. 5, September 2016 (© 2016)
DOI: 10.1208/s12248-016-9959-1

Review Article

Key to Opening Kidney for *In Vitro-In Vivo* Extrapolation Entrance in Health and Disease: Part II: Mechanistic Models and *In Vitro-In Vivo* Extrapolation

Daniel Scotcher,[1] Christopher Jones,[2] Maria Posada,[3] Aleksandra Galetin,[1] and Amin Rostami-Hodjegan[1,4,5]

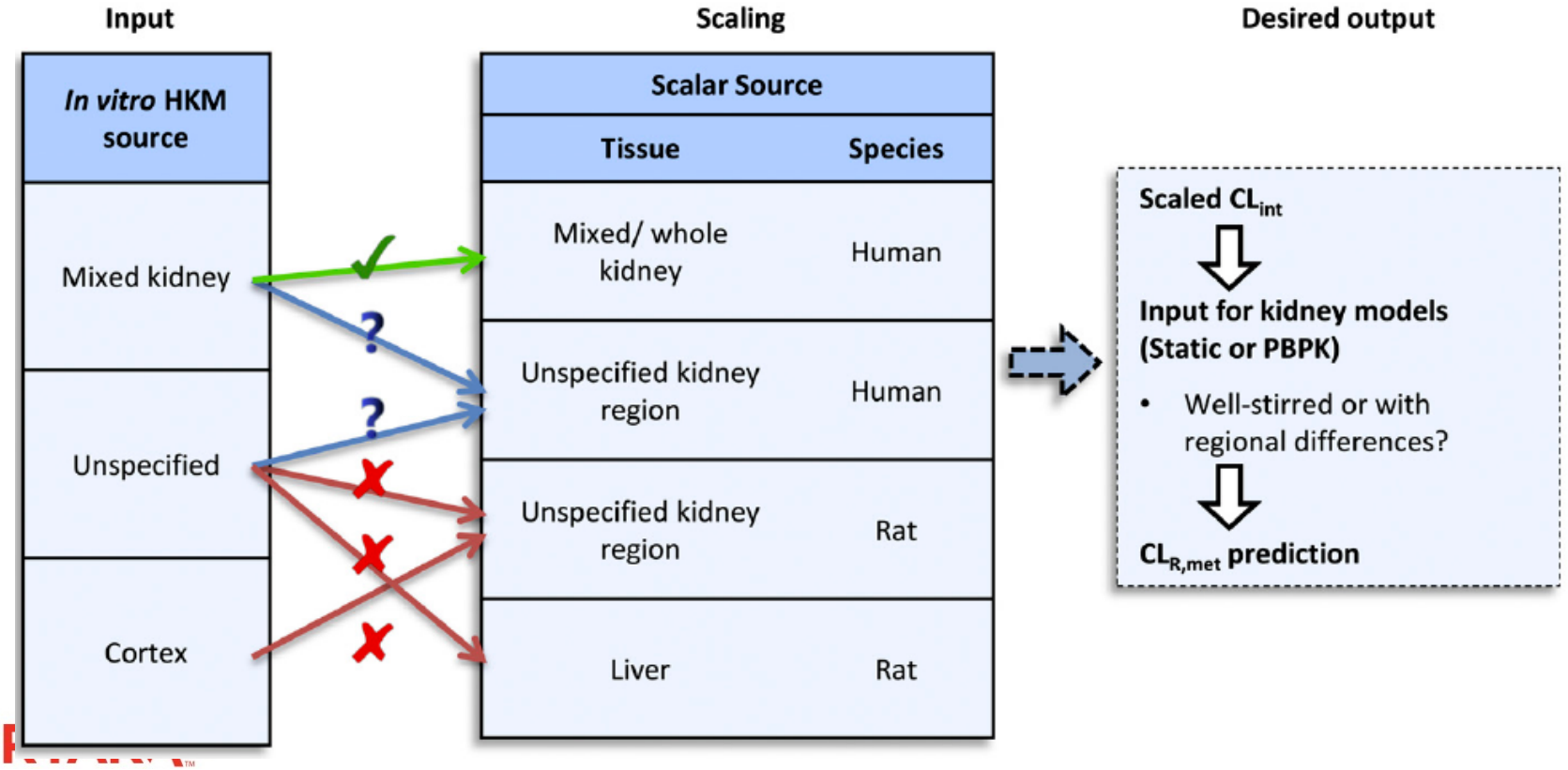
1521-009X/45/5/556–568$25.00
Drug Metabolism and Disposition

https://doi.org/10.1124/dmd.117.075242
Drug Metab Dispos 45:556–568, May 2017

Microsomal and Cytosolic Scaling Factors in Dog and Human Kidney Cortex and Application for In Vitro-In Vivo Extrapolation of Renal Metabolic Clearance[S]

Daniel Scotcher, Sarah Billington, Jay Brown, Christopher R. Jones, Colin D. A. Brown, Amin Rostami-Hodjegan, and Aleksandra Galetin

Centre for Applied Pharmacokinetic Research, University of Manchester, Manchester (D.S., A.R.-H., A.G.); Newcastle University, Newcastle (S.B., C.D.A.B.); Biobank, Central Manchester University Hospitals NHS Foundation Trust, Manchester (J.B.); DMPK, Oncology iMed, AstraZeneca R&D, Alderley Park, Macclesfield (C.R.J.); and Simcyp Limited (a Certara Company), Blades Enterprise Centre, Sheffield (A.R.-H.), United Kingdom



PBPK Modelling to Assess Patient Variability

Eur J Clin Pharmacol (1999) 55: 559–565

SPECIAL ARTICLE

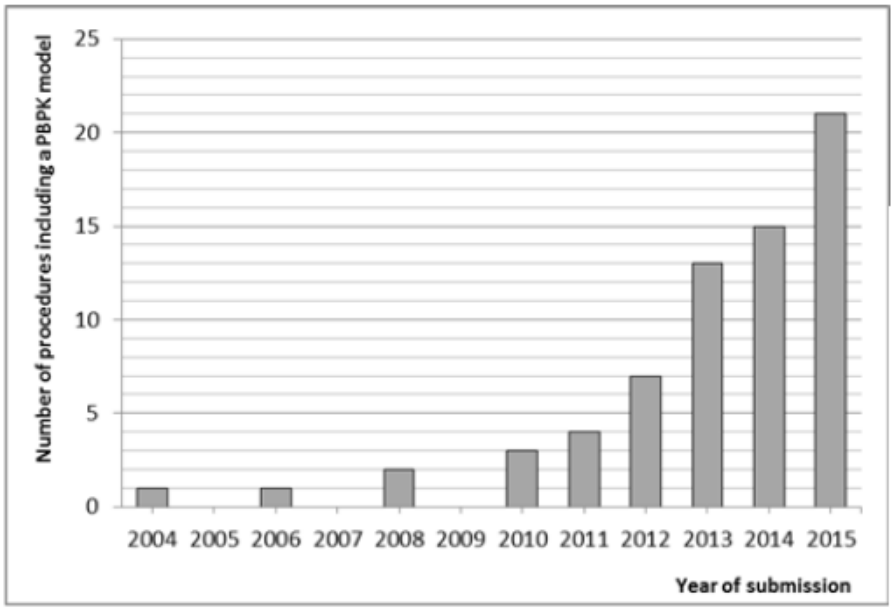
J. C. Krayenbühl · S. Vozeh
M. Kondo-Oestreicher · P. Dayer

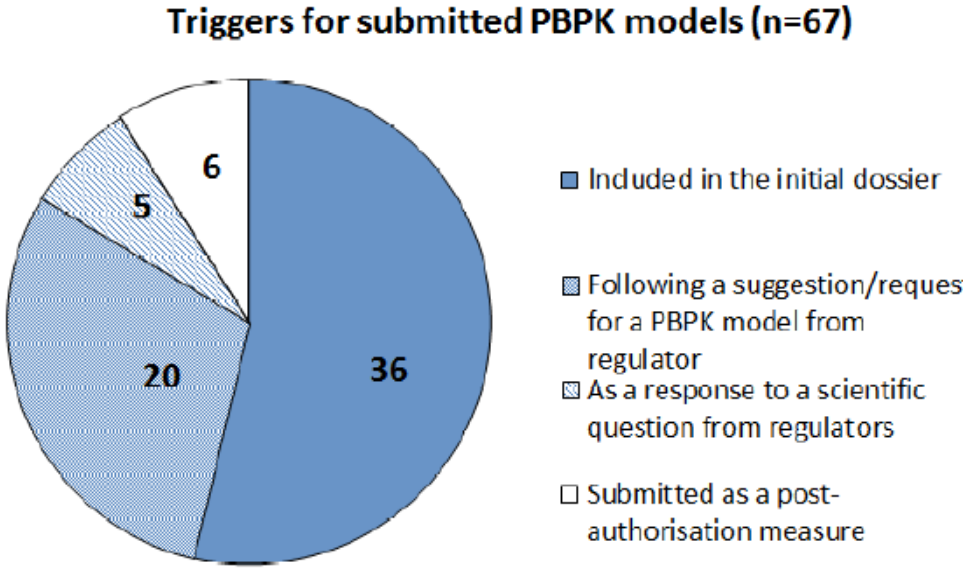
Drug–drug interactions of new active substances: mibefradil example

J.C. Krayenbühl · S. Vozeh
Swiss Intercantonal Office for the Control of Medicines,
Berne, Switzerland

Interpretation of interaction studies should focus **not only on mean** effect but also **the observed and theoretically conceivable extremes.**

Increase in PBPK submission to EMA





Luzon *et al* 2016 CPT

Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 413–415; doi:10.1002/psp4.12203

PERSPECTIVE

Quantitative Modeling and Simulation in PMDA: A Japanese Regulatory Perspective

M Sato*, Y Ochiai, S Kijima, N Nagai, Y Ando, M Shikano and Y Nomura

In Japan in October 2016, the Pharmaceuticals and Medical Devices Agency (PMDA) began to receive electronic data in new drug applications (NDAs). These electronic data are useful to conduct regulatory assessment of sponsors' submissions and contribute to the PMDA's research. In this article, we summarize the number of submissions of quantitative modeling and simulation (M&S) documents in NDAs in Japan, and we describe our current thinking and activities about quantitative M&S in PMDA.

CPT Pharmacometrics Syst. Pharmacol. (2017) **6**, 413–415; doi:10.1002/psp4.12203; published online 1 June 2017.

Physiologically based pharmacokinetic model analysis, including simulations
• Files that contain information on the model structure used for the analysis, the set values of drug and physiological parameters, analysis procedures, and sensitivity analysis of the results. The file format is optional.
• Clinical study datasets, including blood concentration data. If the datasets were created or modified to be analyzed using a specific software for PBPK model analysis, the electronic files of the created or modified datasets should be submitted in the format for the specific software (Simcyp PE Data Files (xml format), etc.). If the datasets were not created or modified for a specific software for PBPK model analysis, the datasets can be submitted in an optional file.

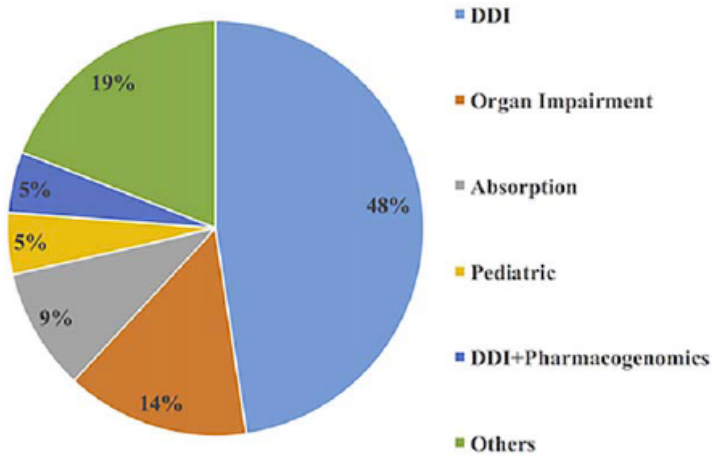
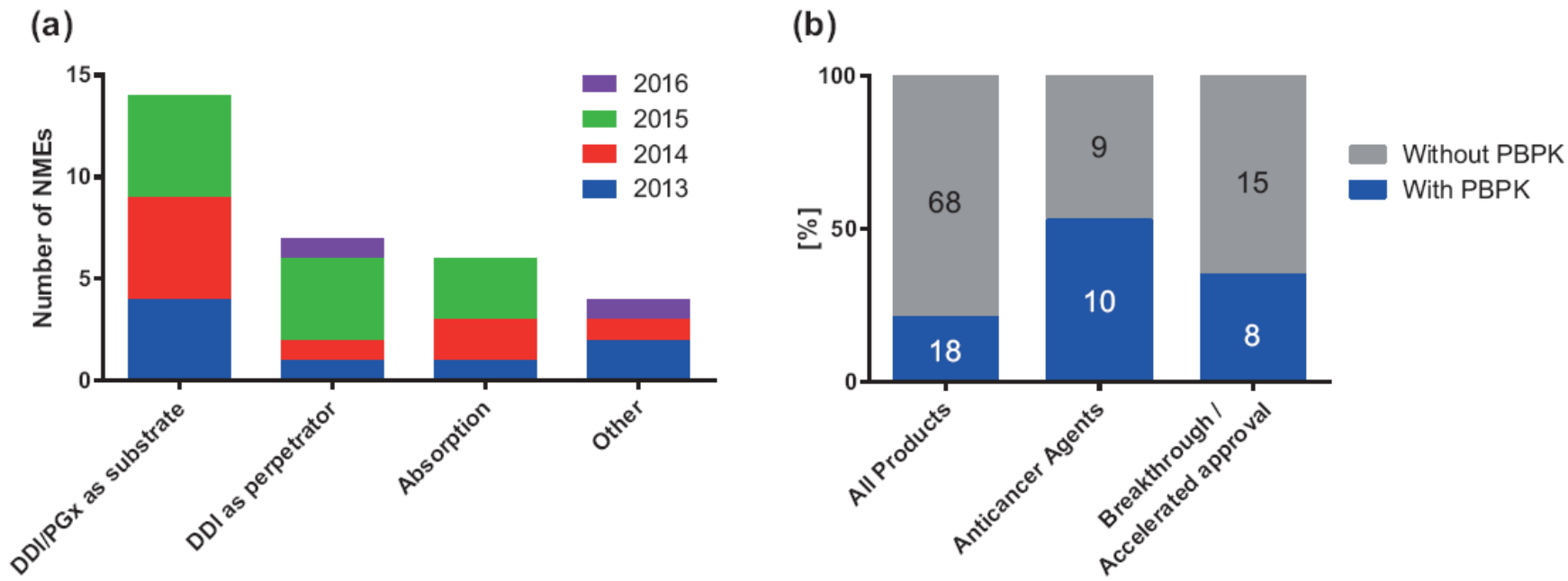


Figure 1 PBPK application in the 17 submissions in NDAs of NMEs received by the PMDA from 2014 to 2016. In some cases, multiple PBPK M&S reports were included in one submission.

Impact of Physiologically Based Pharmacokinetic Models on Regulatory Reviews and Product Labels: Frequent Utilization in the Field of Oncology

K Yoshida[1], N Budha[1] and JY Jin[1]



CERTARA

July 2016

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft

Language Barrier

“Prediction” vs “Retrodiction” vs “Post-diction”

Predictive = Relating to or having the effect of predicting an event or result

Predict = Pronunciation: /prɪˈdɪkt/
Say or estimate that (a specified thing) will happen **in the future** or will be a consequence of something
Latin origin = 'made known **beforehand**, declared', from the verb praedicere, from prae- 'beforehand' + dicere 'say'.

Postdiction is an **explanation after the fact**. In skepticism, it is considered an effect of hindsight bias that explains claimed predictions of significant events
https://en.wikipedia.org/wiki/Postdiction

Retrodiction : is the act of **making a "prediction" about the past**.
https://en.wikipedia.org/wiki/Retrodiction

Same when it comes to the use of:

Qualification vs Verification vs Validation

Qualification

Verification

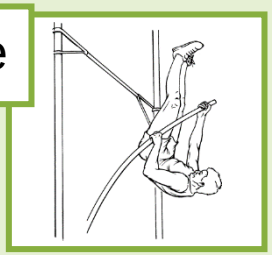
Validation

Framework for M&S in Regulatory Review

High impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +++

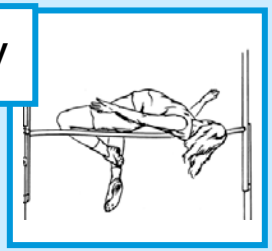
Replace



Medium impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } ++

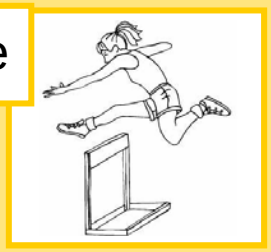
Justify



Low impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +

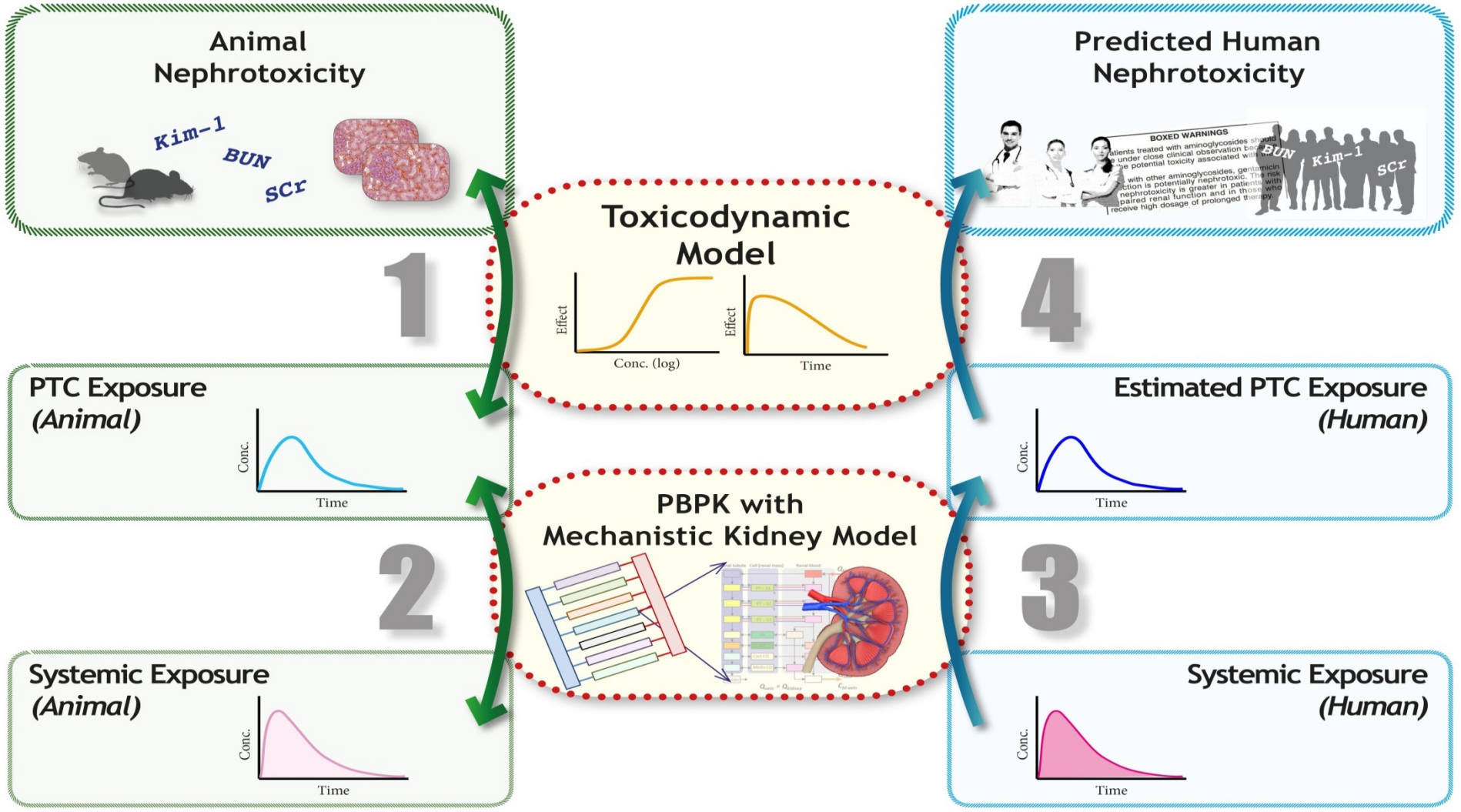
Describe



Impact on regulatory decision

From EMA-EFPIA Modelling and Simulation Workshop, December 2011

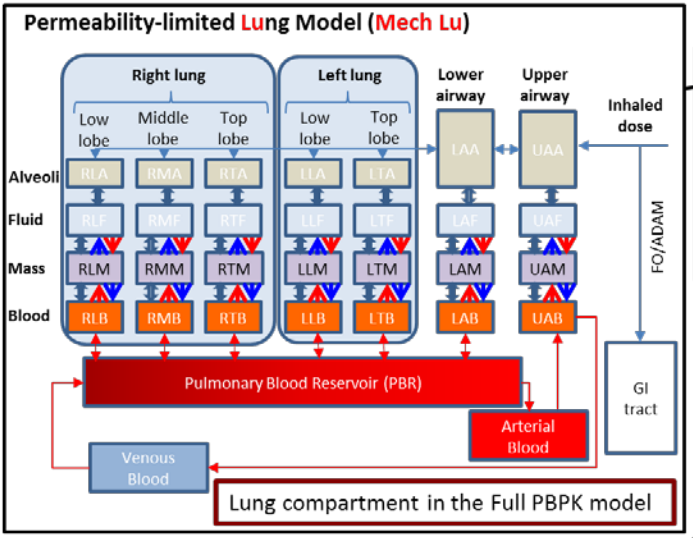
Translation from Animals to Humans

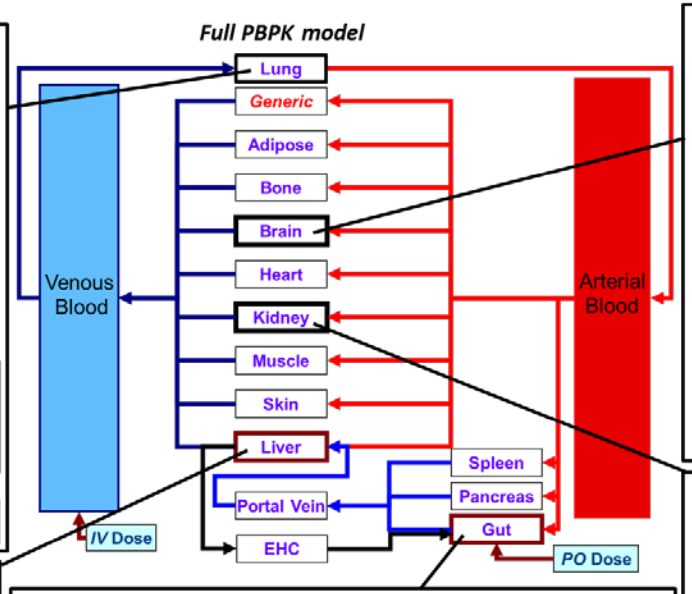


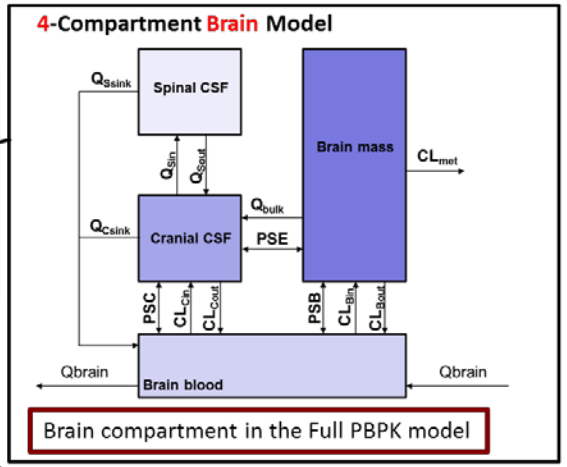
Scotcher et al 2016 AAPS J, *in press*

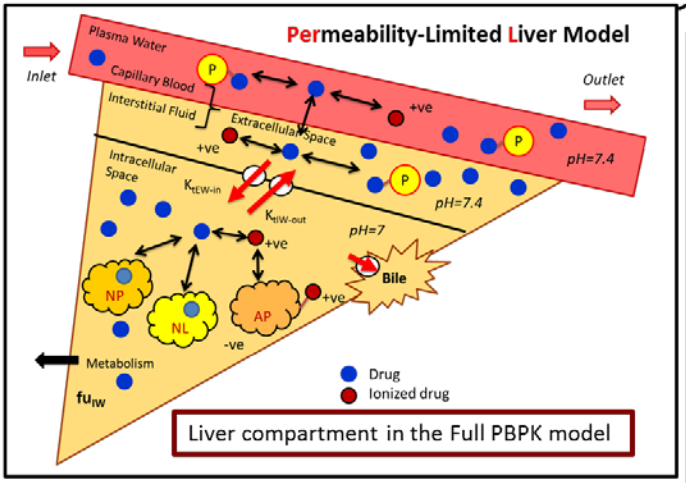
Key to Opening Kidney for *In Vitro-In Vivo* Extrapolation Entrance in Health and Disease: Part II Mechanistic Models and *In Vitro-In Vivo* Extrapolation

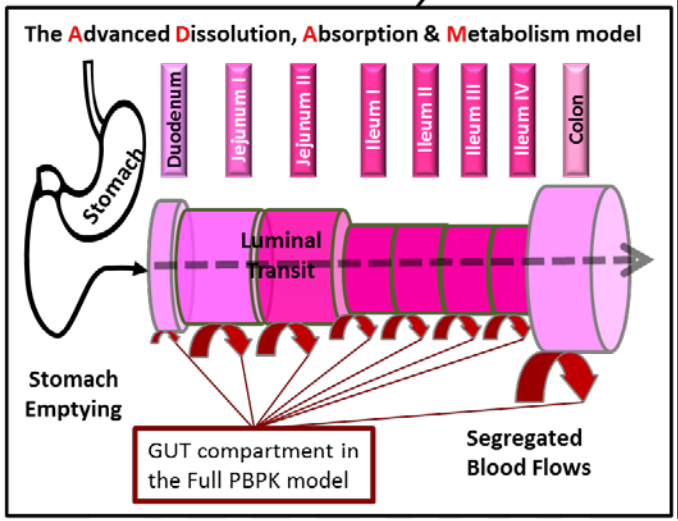
Integrating Organs within MPS: Proportionality?

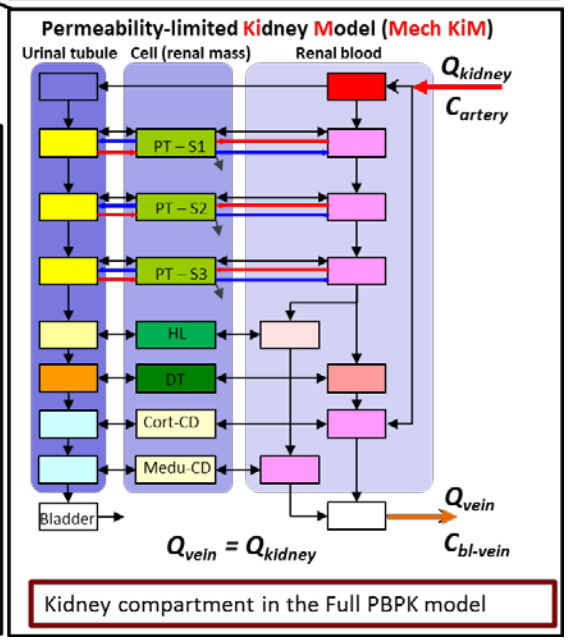












- Replacement and additional organ

Contents lists available at SciVerse ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

Evaluation of the novel *in vitro* systems for hepatic drug clearance and assessment of their predictive utility

J. Brian Houston [a,*], Karen Rowland-Yeo [b], Ugo Zanelli [c]

[a] *Centre for Applied Pharmacokinetic Research, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Oxford Road, Manchester M13 9PT, United Kingdom*
[b] *Simcyp Limited, Blades Enterprise Centre, John Street, Sheffield S2 4SU, United Kingdom*
[c] *Met Profiling, Department of Screening and Technologies, Siena Biotech S.p.A., via del Petriccio e Belriguardo 35, 53100 Siena, Italy*

Integrating Organs within MPS:

What is the INTENDED USE?