High-throughput prediction of fraction absorbed and bioavailability *in silico*

Robert D. Clark, Pankaj Daga and Robert Fraczkiewicz
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Lancaster CA, USA

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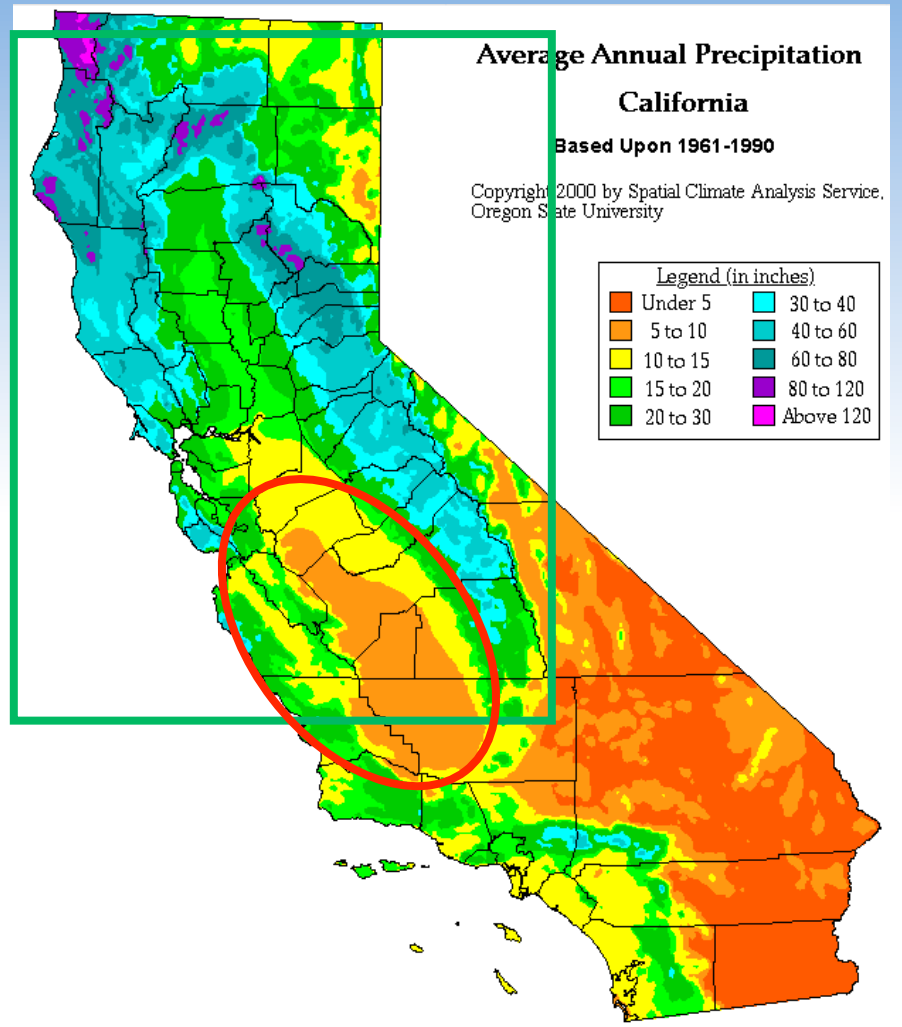
Motivation

- Late-stage attrition due to obviously bad physicochemical properties has been reduced by application of rules-of-thumb like Lipinski's Rule of Five.
- Failure due to lack of efficacy remains a major issue. This can be due to a poor choice of target, but can also reflect poor pharmacokinetics (PK).
- *Combinations* of physicochemical properties may be problematic even when each individual property seems acceptable.
- This can make it hard to know which property to modify next, e.g., decreasing hydrophobicity to try to address problems with solubility and metabolism is likely to decrease absorption as well.

➢ *Is there a way to explore the pharmacokinetic landscape before enough compound has been synthesized to assess its PK behavior in vivo?*



http://www.geosci.sfsu.edu/Geosciences

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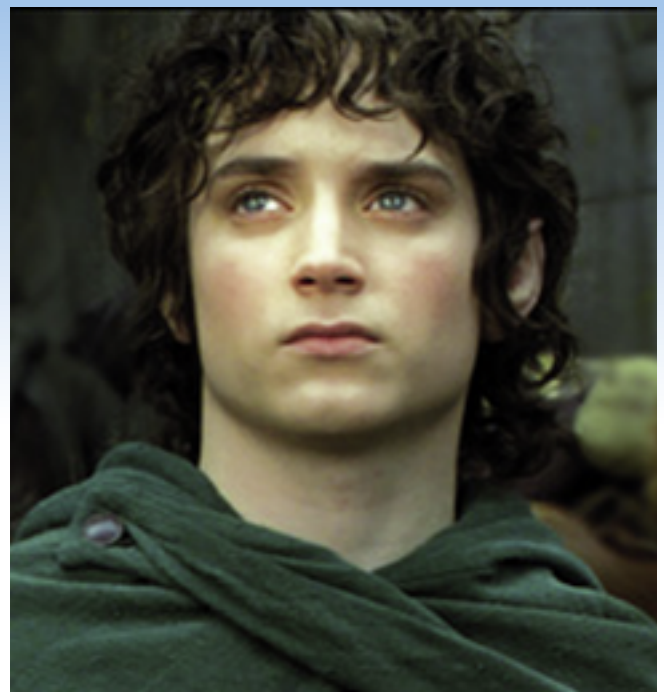
Many Key Properties Can be Estimated Individually *in silico*

- Acid/base dissociation constants (pK_a's) & ionization
- Solubility and tendency to supersaturate
- Lipophilicity
- Intestinal permeability
  - quantitative: passive permeability & local models
  - qualitative: susceptibility to active uptake or efflux on transporters
- Metabolism
  - quantitative: cytochrome P450 (CYP) clearance & local models
  - qualitative: glucuronidation & glutathione conjugation
- Binding to plasma proteins, to red blood cells & within tissues



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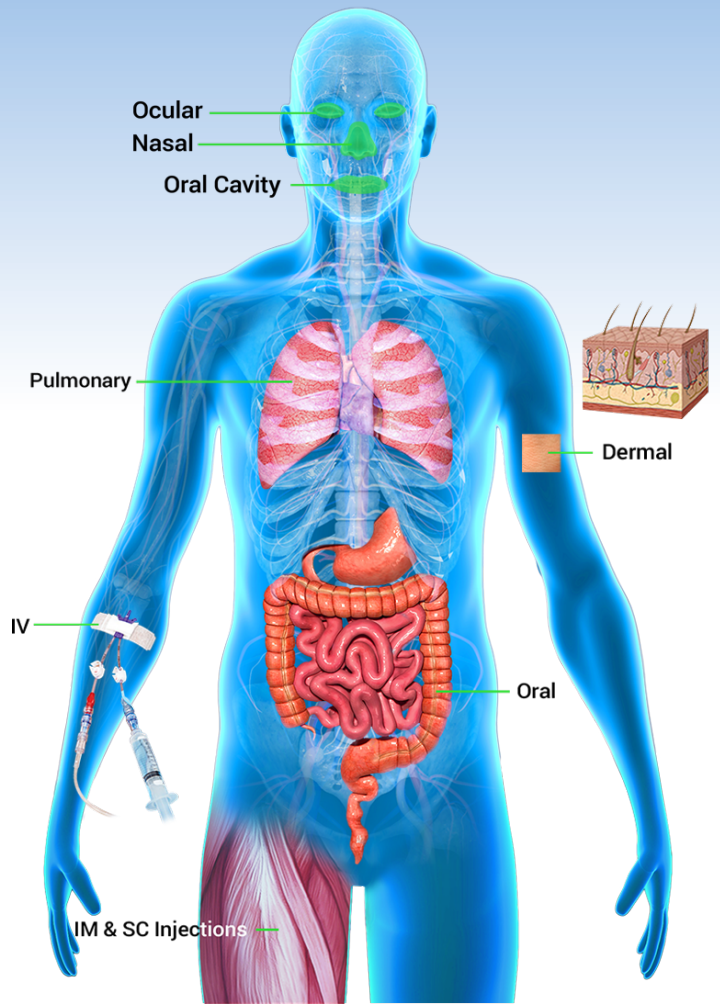
➢ *It takes Physiologically-Based Pharmacokinetic (PBPK) simulation to bind them all.*

Full-blown PBPK Simulation Takes *Everything* Into Account



GastroPlus(TM): Bioavails-rat-50.mdb (C:\Users\Bob\Desktop\9.x\SIMz ..\Rat e..\)

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound | Gut Physiology-Rat | Pharmacokinetics | Simulation | Graph

Compartmental Parameters

CPD-65I-1 — Reset All Values

☐ Excrete all un-absorbed drug at the end of gut transit time

☐ Zero-order gastric emptying

Compartment Data

Compartment	Peff	ASF	pH	Transit Time (h)	Volume (mL)	Length (cm)	Radius (cm)	SEF	Bile Salt (mM)
Stomach	0	0.0	3.90	0.25	3.360	1.07	1.00	1.000	0.0
Duodenum	0	15.20	5.89	0.19	0.578	9.50	0.22	3.363	20.00
Jejunum 1	0	14.22	6.13	0.83	2.494	45.00	0.21	2.982	17.29
Jejunum 2	0	11.78	6.13	0.75	2.262	45.00	0.20	2.353	6.980
Ileum 1	0	10.64	5.93	0.02	0.045	1.00	0.19	2.032	2.820
Ileum 2	0	11.16	5.93	0.01	0.041	1.00	0.18	2.018	1.300
Ileum 3	0	11.73	5.93	0.01	0.036	1.00	0.17	2.004	1.240
Caecum	0	10.38	6.58	4.29	0.884	5.00	0.75	1.550	0.0
Asc Colon	0	18.70	6.23	7.71	0.308	9.00	0.33	1.660	0.0

Enzyme and Transporter Regional Distributions

C1-C4: 0.06944 | 0.43028 | 0.12147 | 0.46632

Qh (L/min): 0.0118

Physiology: Rat - Physiological - Fasted

Percent Fluid in SI: 40 Colon: 10

ASF Model: Opt logD Model SA/V 6.1

Experimental or user defined values used for properties:; Vc=S+rVd_PBPK; Rbp=RBP_rat; Fup=rat_fup%; Dose=Dose
All remaining properties are predictions from ADMET Predictor v8.1.0.0
Tendency Supersaturate=SupSat; Likelihood of BBB Penetration=High; Pgp-Inhibitor=Yes (97%); Pgp-Substrate=Yes (91%); OATP1B1-Inhibitor=No (63%);

pKa Table | logD: Struct-6.1 | Diss Model: Johnson | PartSize-Sol: ON | BileSalt-Sol: ON | Diff: ON | ConstRad: OFF | Precip: Time | Ppara: Zhim | EHC: OFF

Graph

20 21 22 23 24

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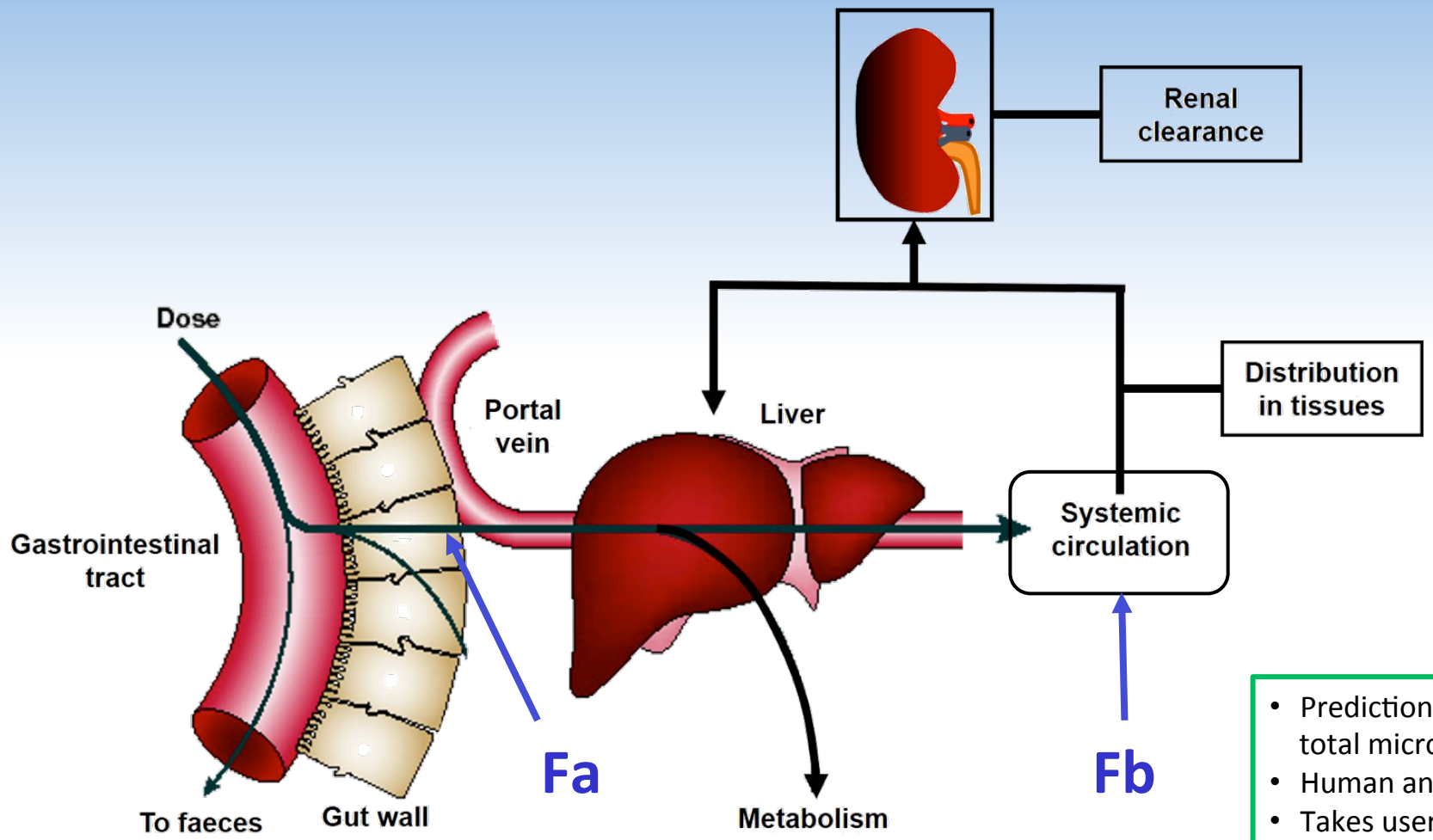
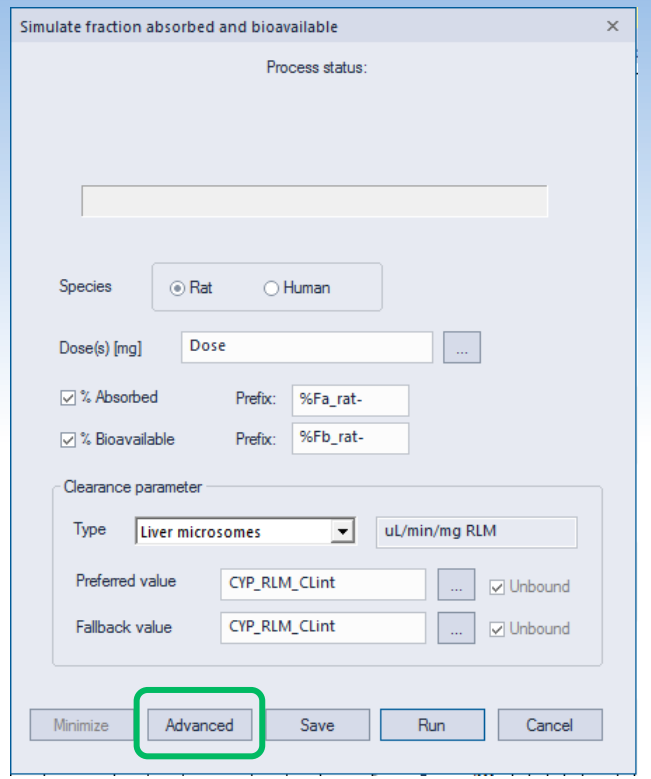
The HTPK Simulation Module in ADMET Predictor™ is Simpler…





- Predictions provided for physicochemical properties and total microsomal CYP clearance
- Human and rat both supported
- Takes user specified data or predictions where available

"A thing should be made as simple as possible, but no simpler."
- Albert Einstein

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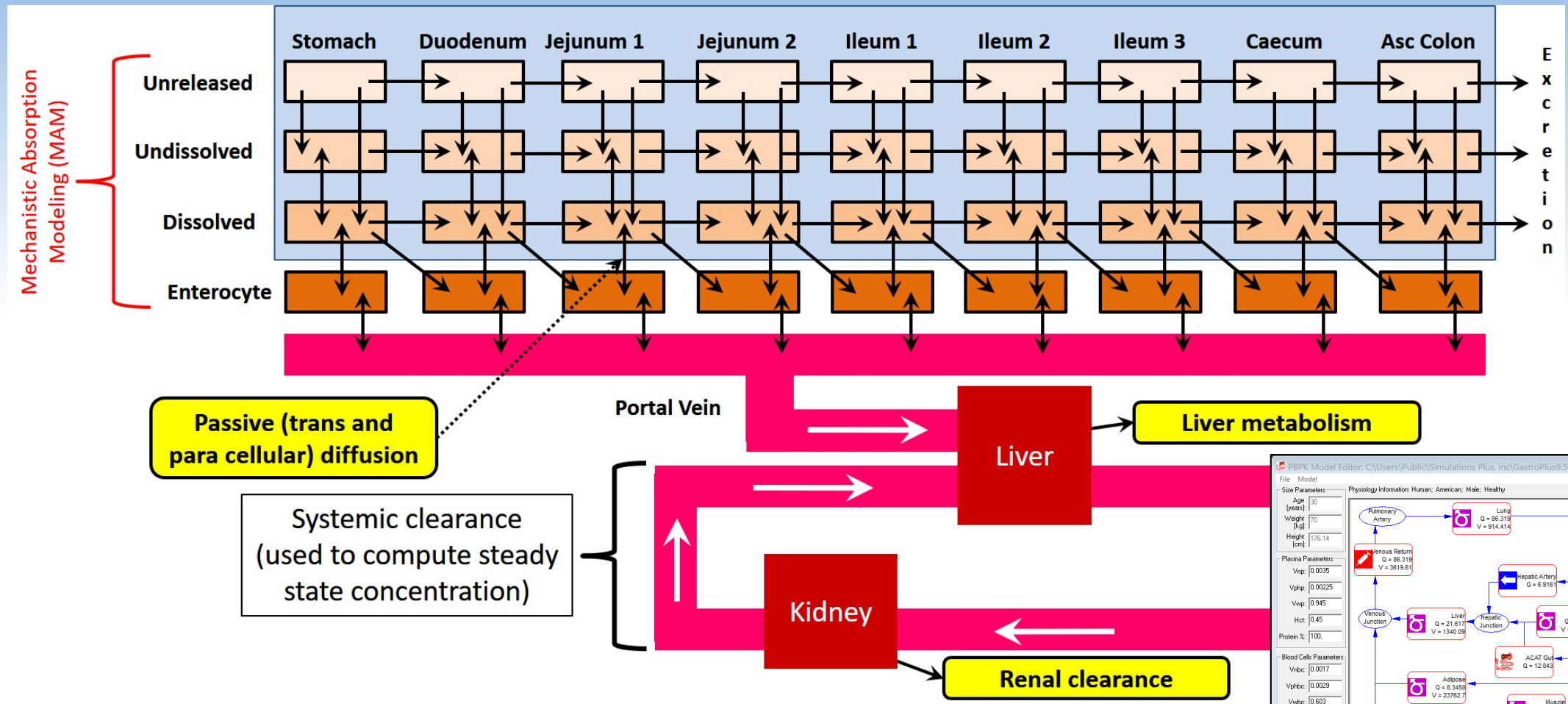
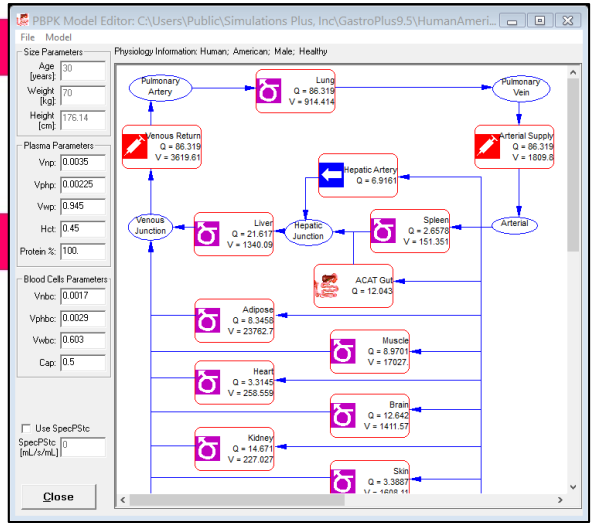
…But Is Complicated Enough to Get the Job Done

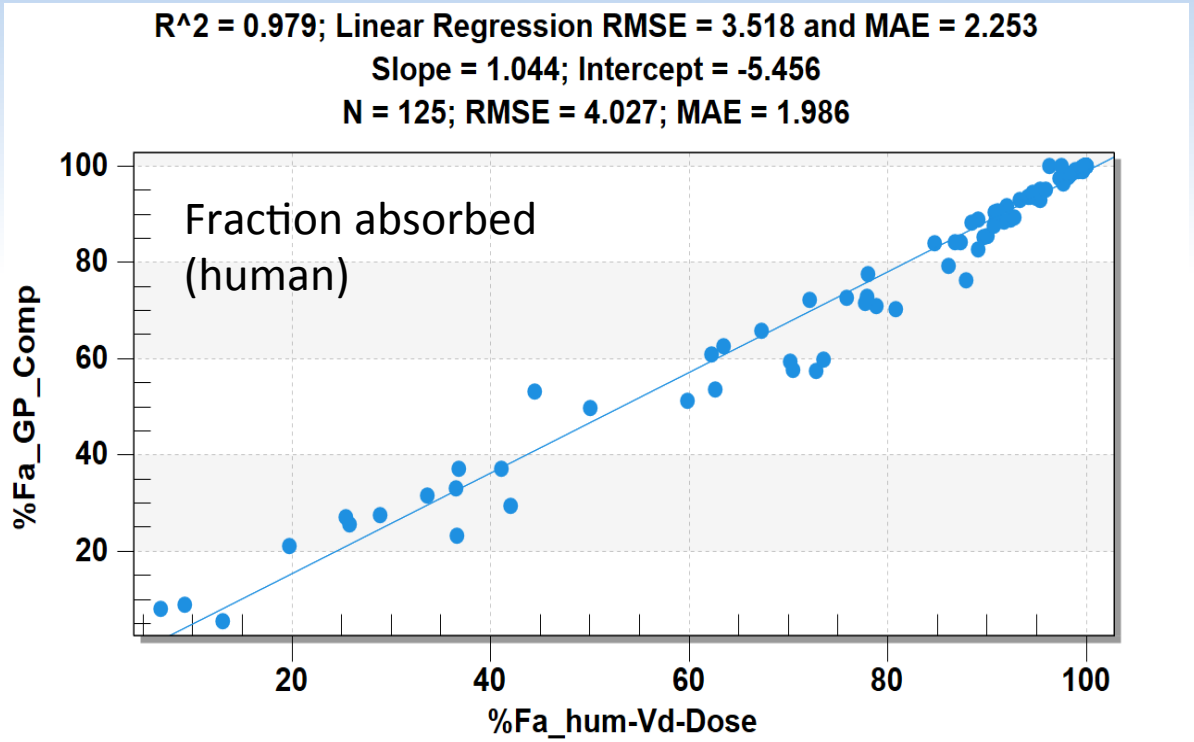


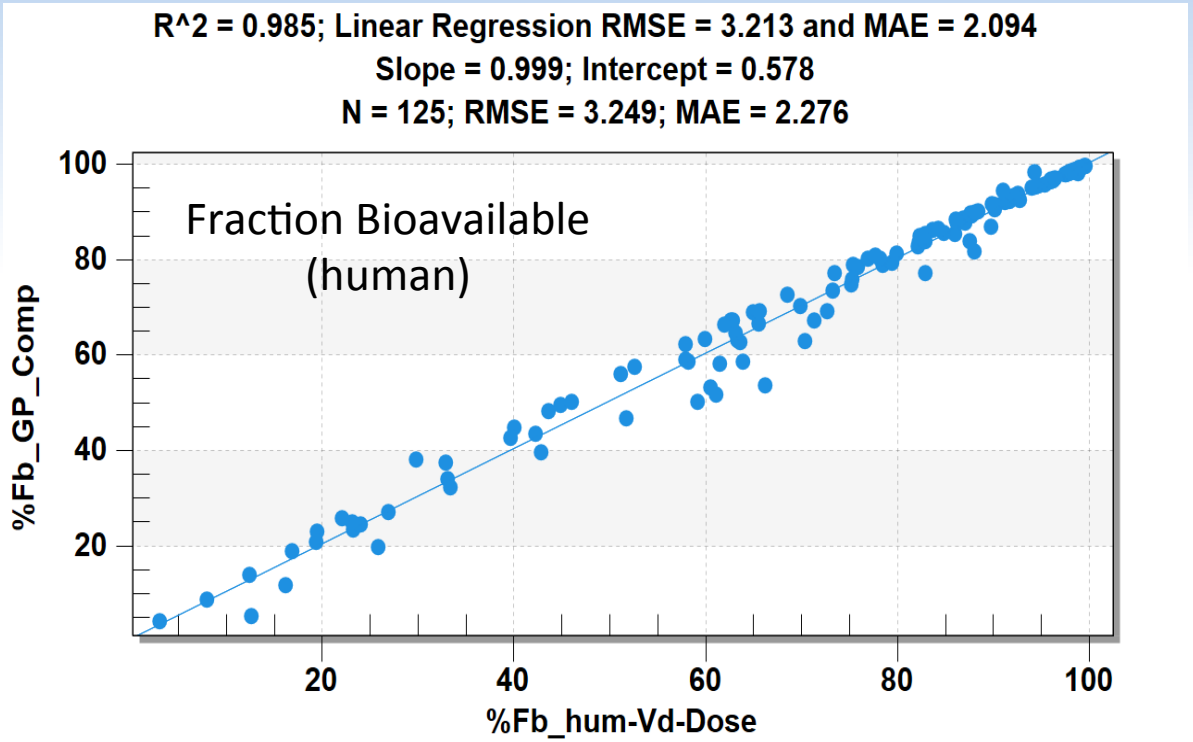


Uses the Advanced Compartmental Absorption and Transit (ACAT™) Model from GastroPlus™, lumps everything else other than first-pass liver and kidney into a single central compartment.

The Streamlined System Produces Similar Results*

125 passively absorbed compounds from Zhao et al., *J. Pharm. Sci.* **2001**, 90:749





*GastroPlus was run using a compartmental model with ACAT absorption.

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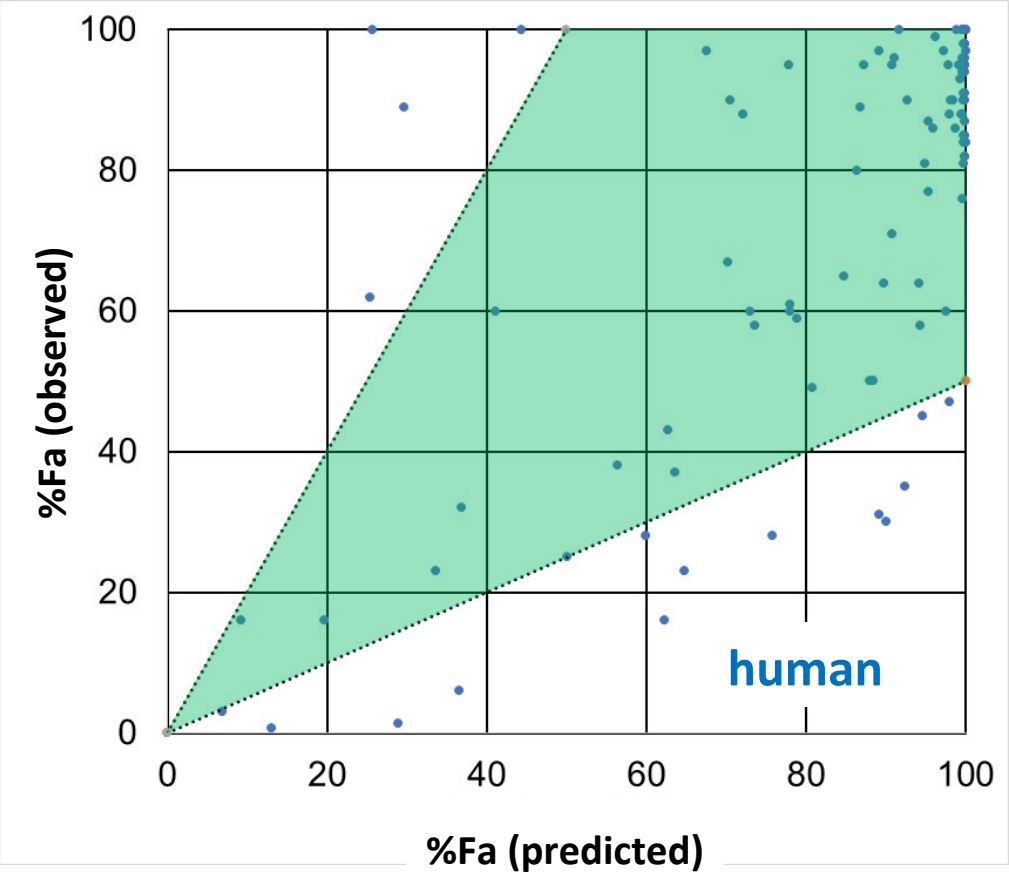
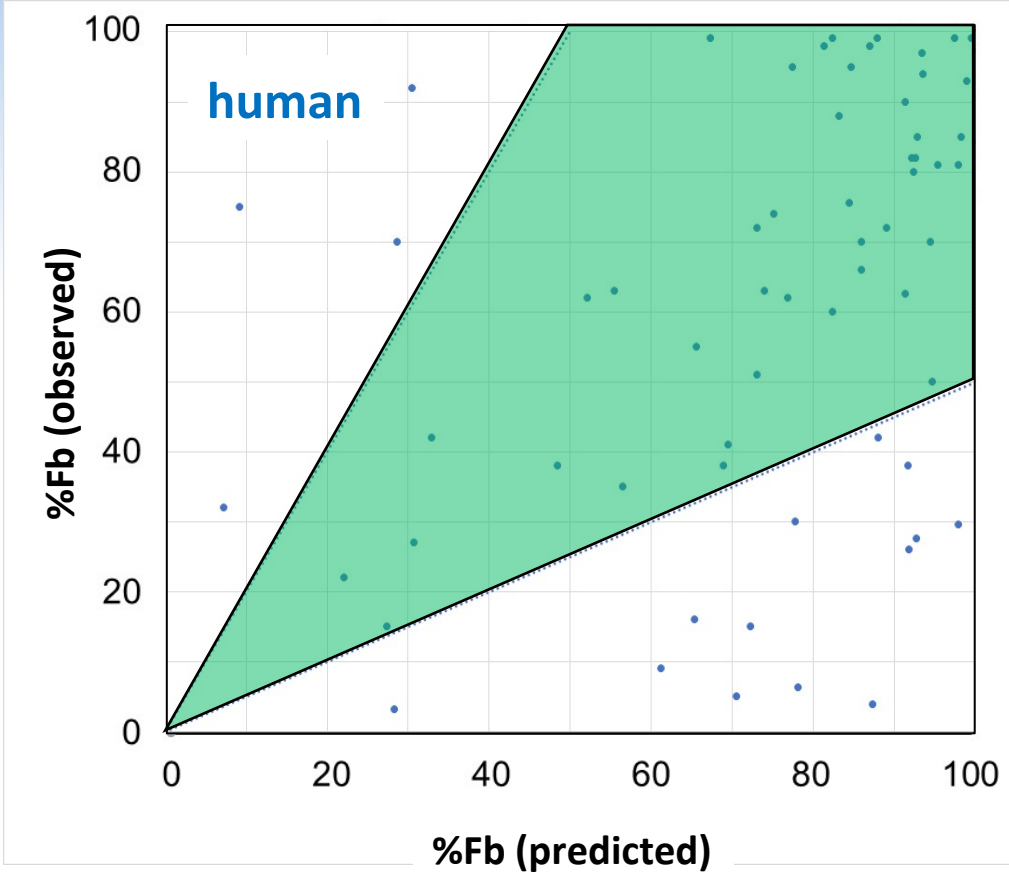
Does HTPK Give Good Enough Answers?

125 passively-absorbed compounds from Zhao et al.
(*J. Pharm. Sci.*, **2001**, 90: 749)



86% predicted within 2-fold of the reported value.
80% predicted within 1.5-fold.

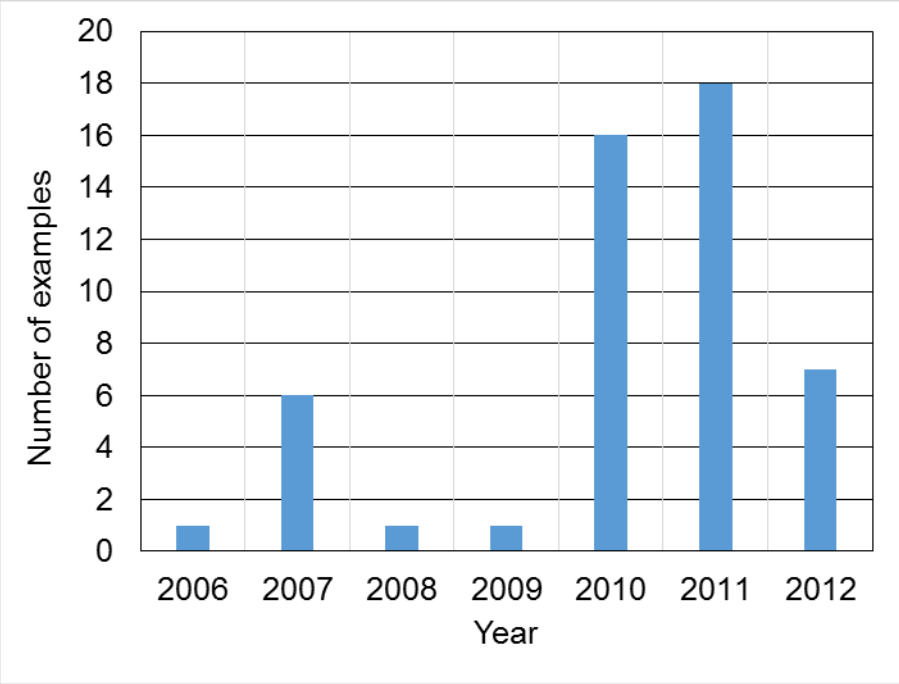
62 CYP-metabolized compounds from the Toshimoto et al.
(*Drug Metab. Dispos.* **2014**, 42:1811)

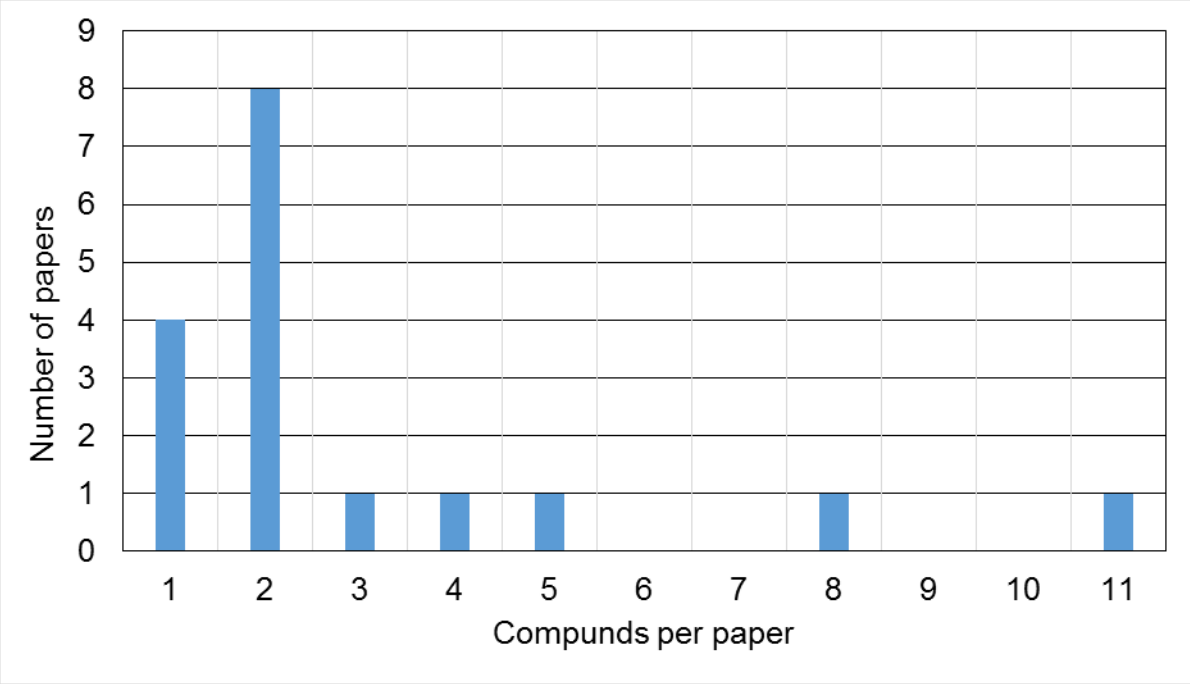


73% predicted within 2-fold of the reported value.
65% predicted within 1.5-fold

Rat Bioavailability Data Set 1

- Data taken from drug design and development papers published in the *Journal of Medicinal Chemistry* between 2006 and 2012 that report oral bioavailability in rats for one or more analogs
  - rat bioavailabilities for 51 compounds with many different targets
  - 1-11 examples from 17 papers
  - many also include other experimental PK data and results from *in vitro* assays





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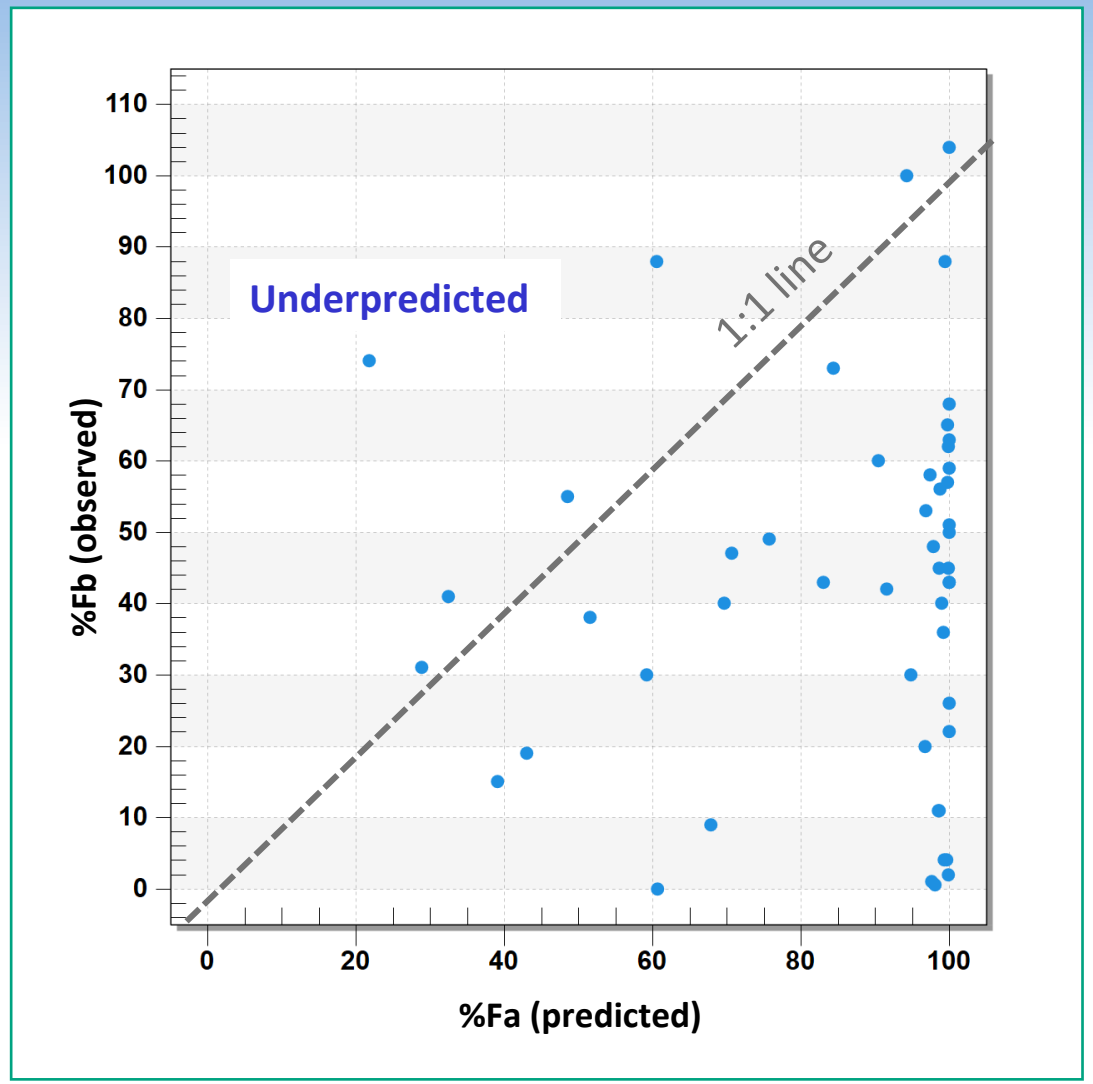
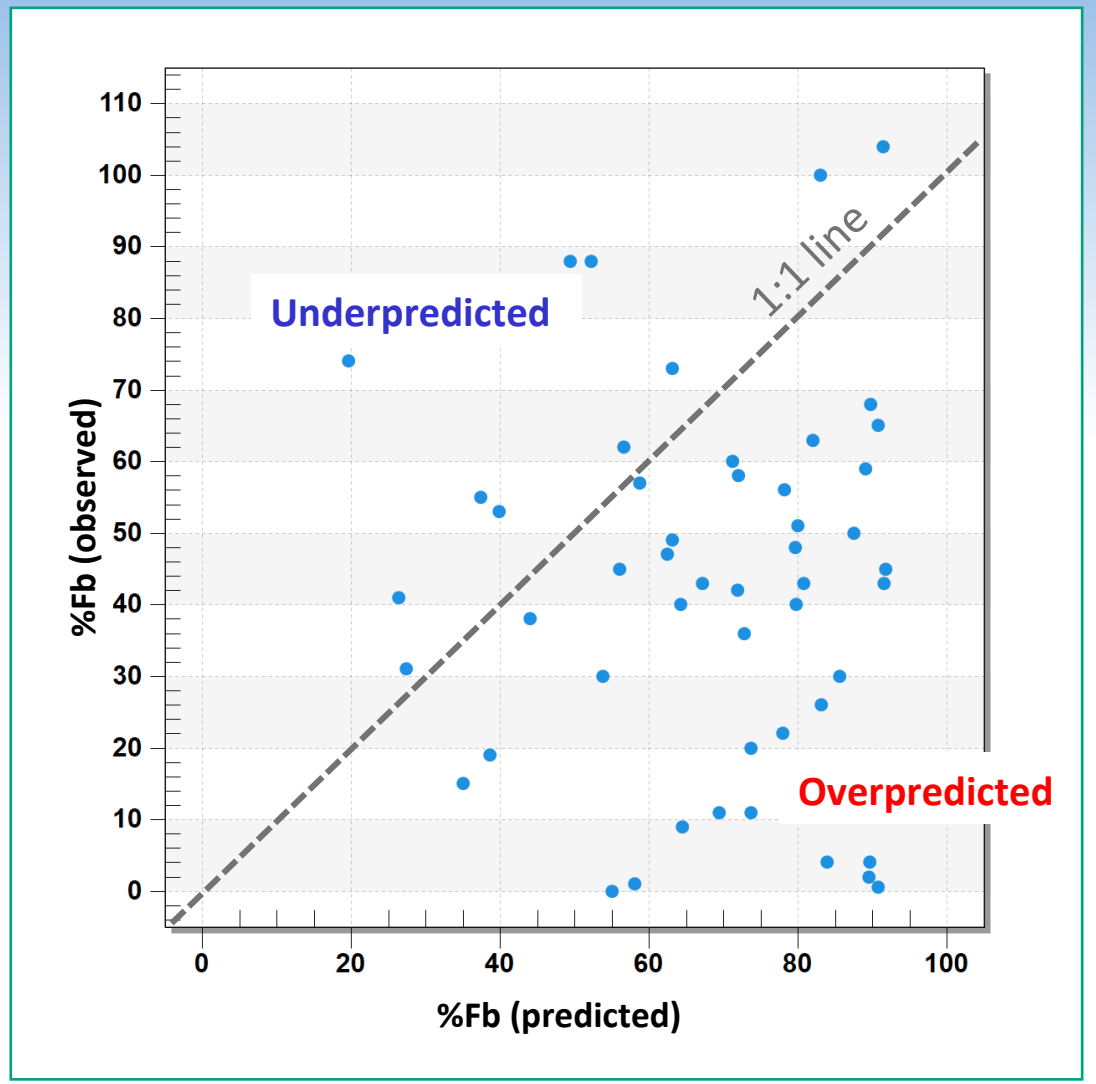
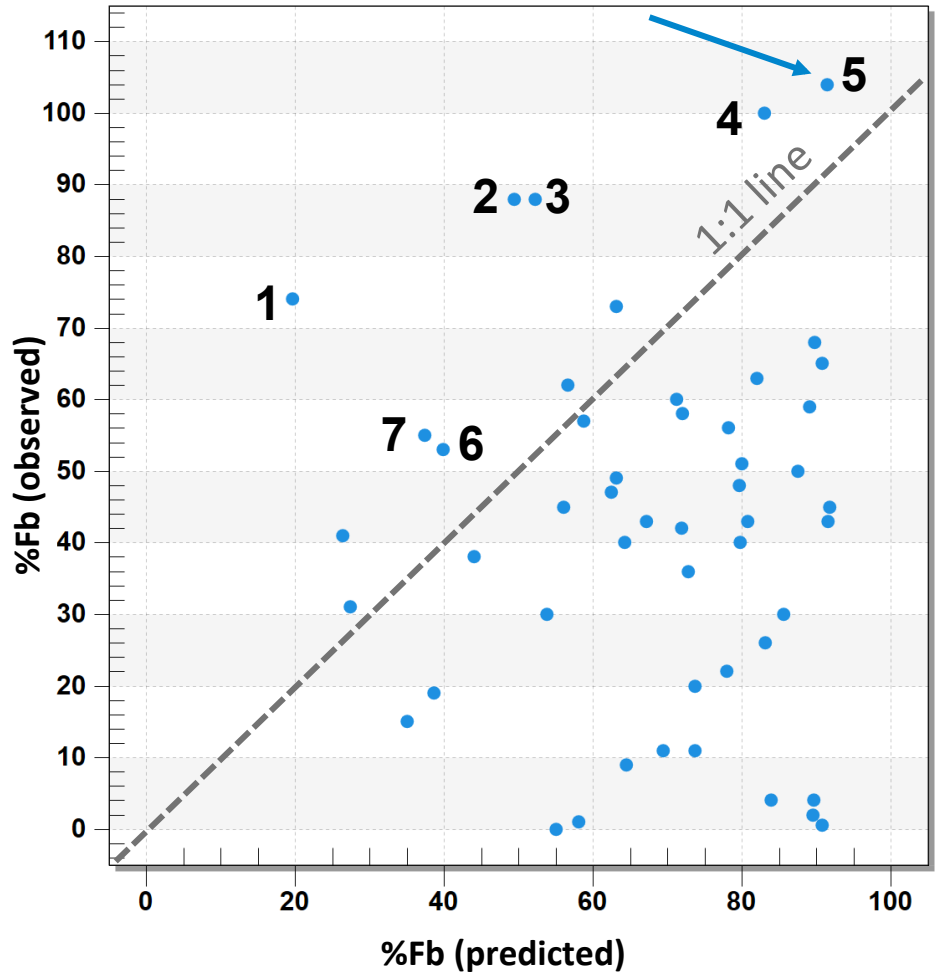
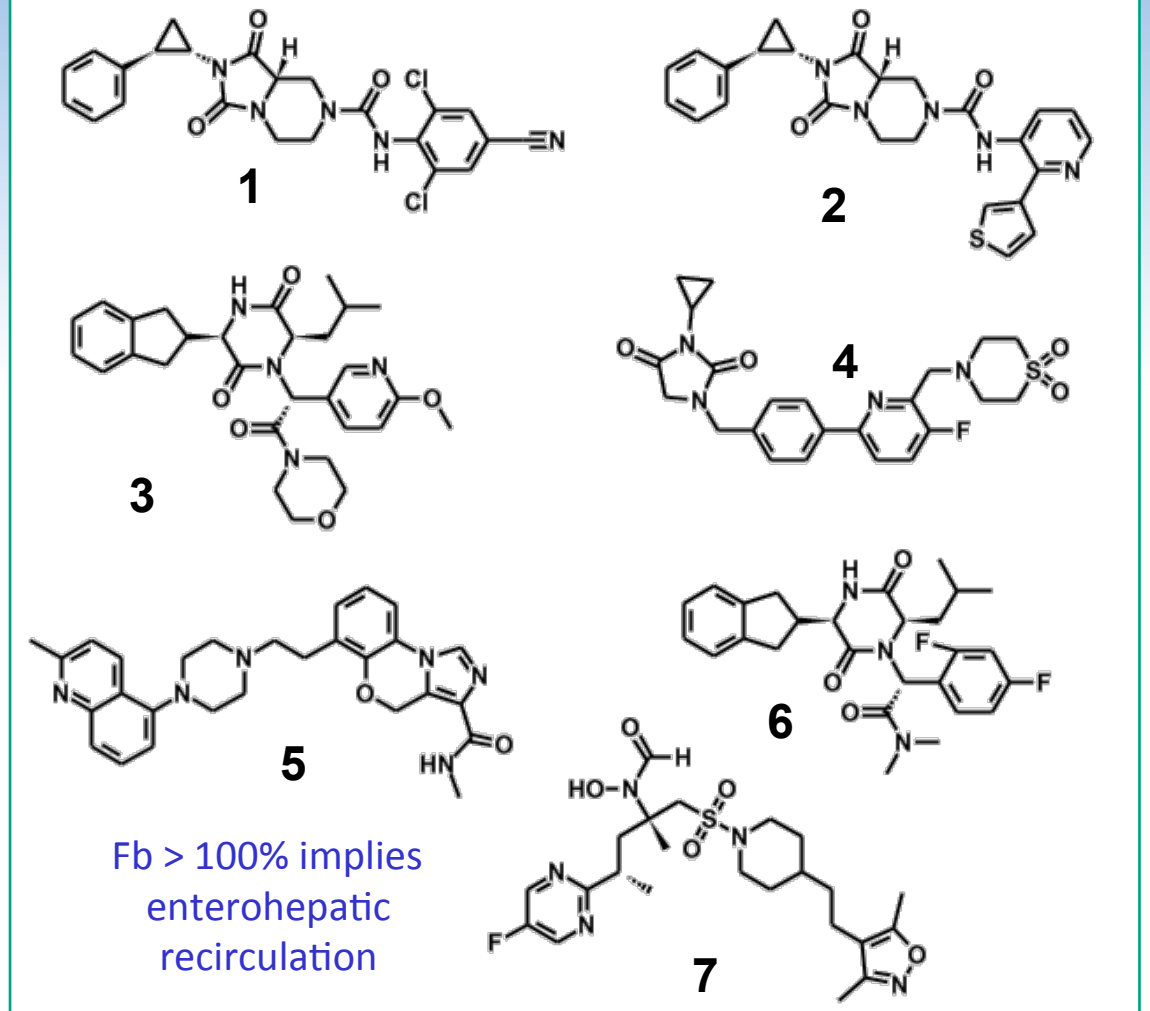
Experimental Fa and Fb vs. *in silico* Predictions





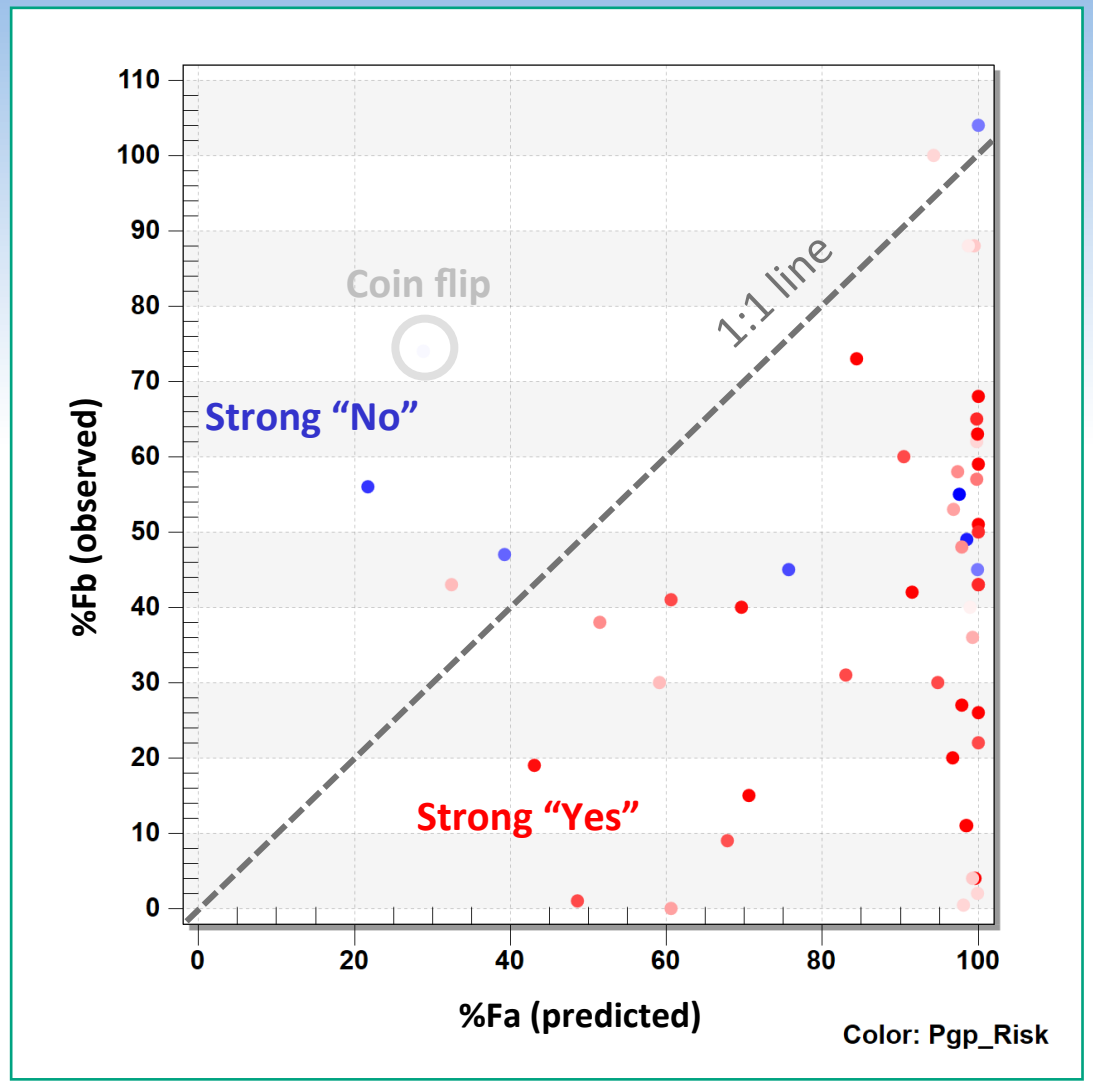
Why Are Some Bioavailabilities Underpredicted?

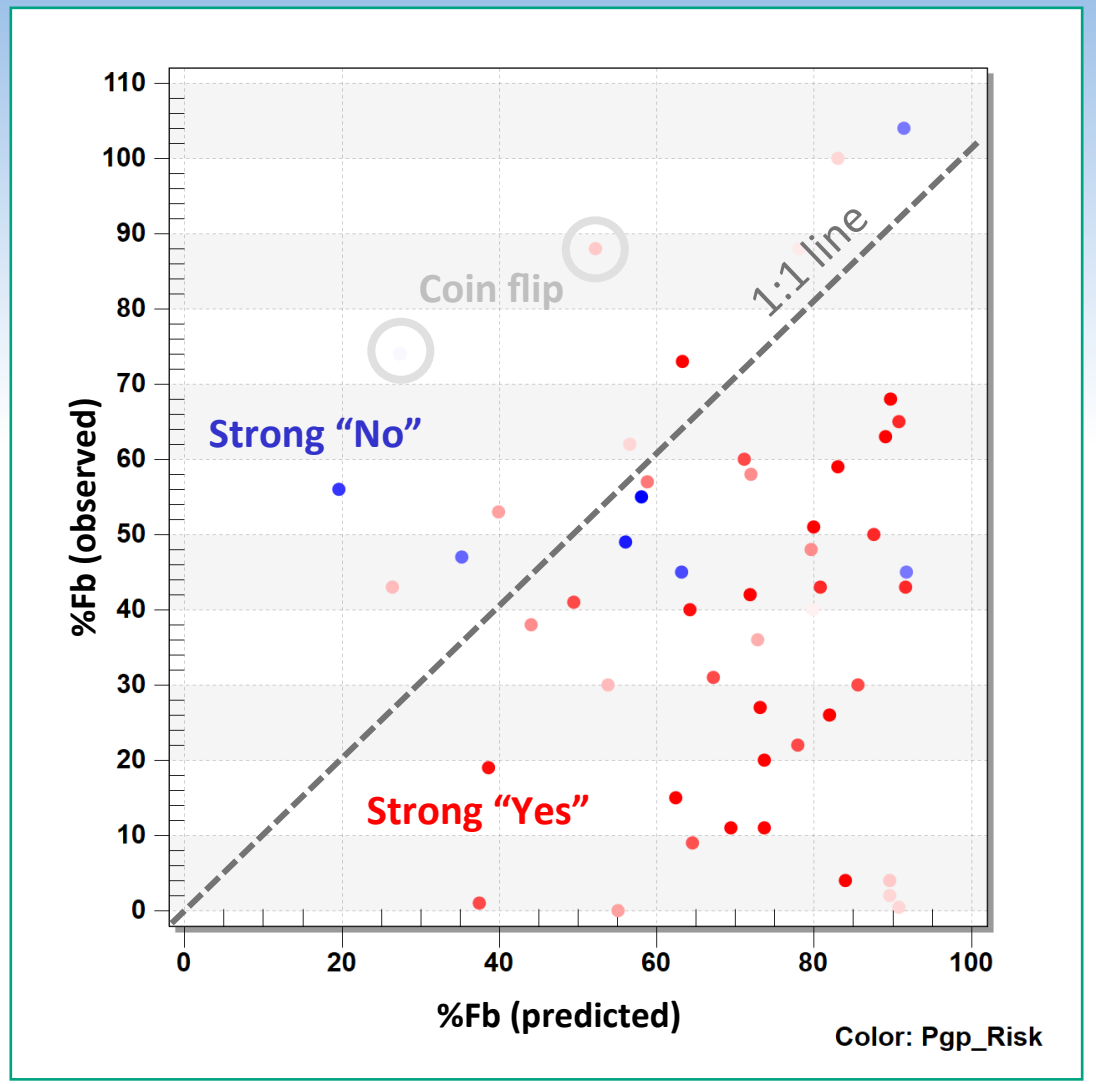




Fb > 100% implies enterohepatic recirculation

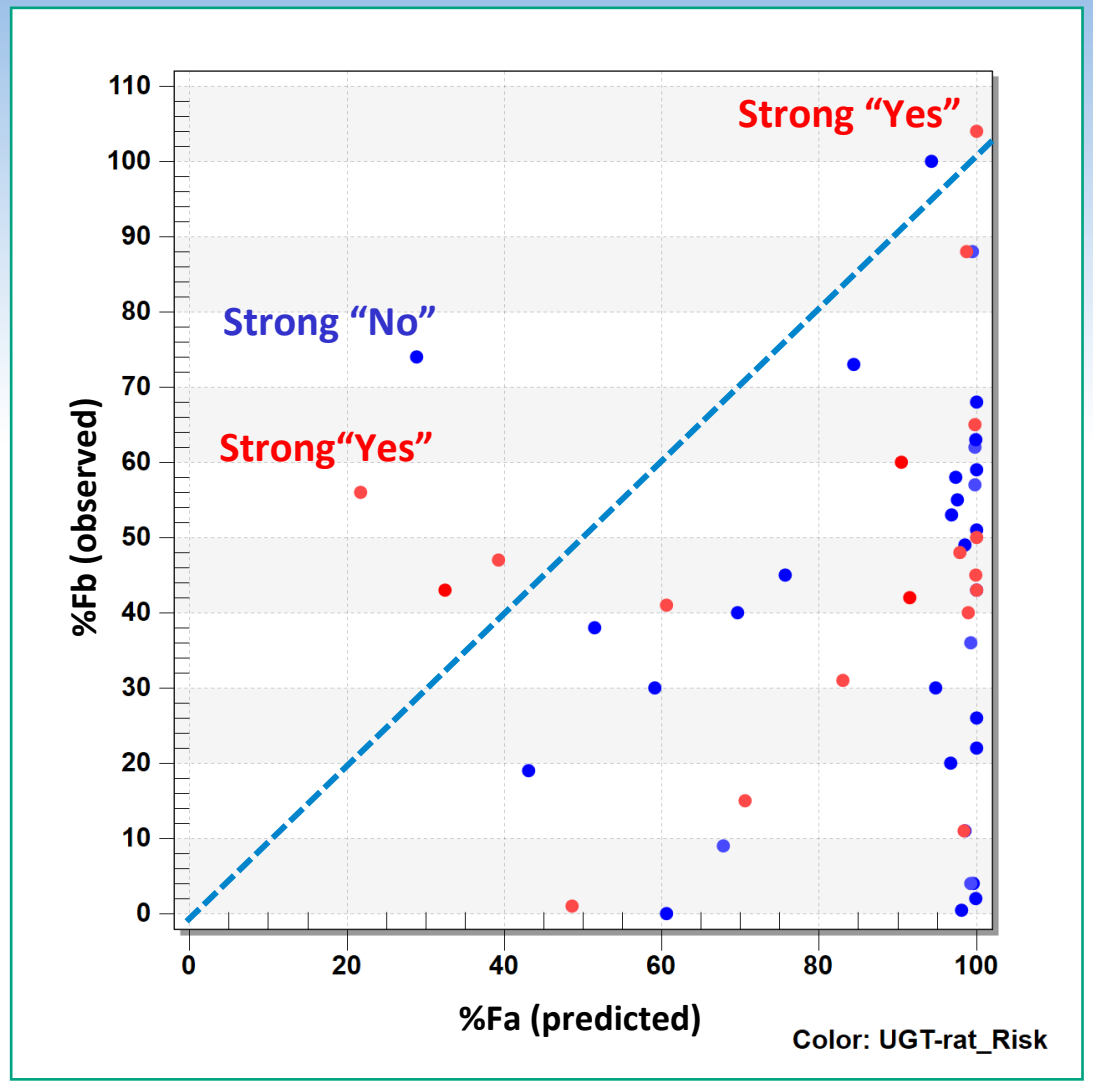
Effect of Being a P-gp Substrate* on Predicted Rat PK

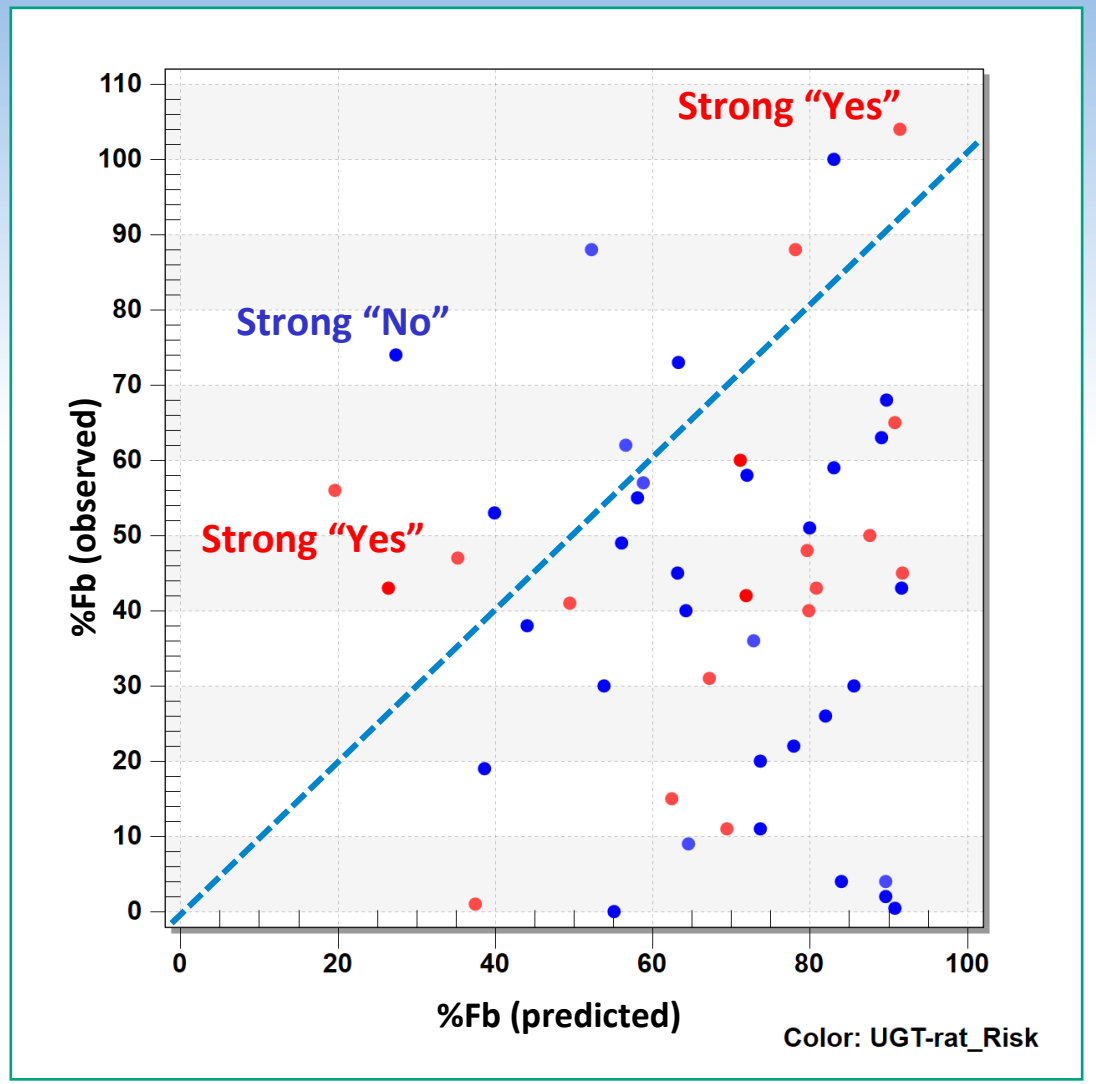




*Based on confidence in human P-gp substrate classification

Effect of Being a UGT Substrate* on Predicted Rat PK





*Based on expression levels of rat orthologs of human UGTs and hUGT substrate classifications

Rat Bioavailability Data Set 2

- Data taken from a survey of all bioavailability enhancement studies published in the *Journal of Medicinal Chemistry* between September 2001 and September 2002
  - rat bioavailabilities for 89 compounds with 20 different targets
  - 1-12 examples from 40 papers

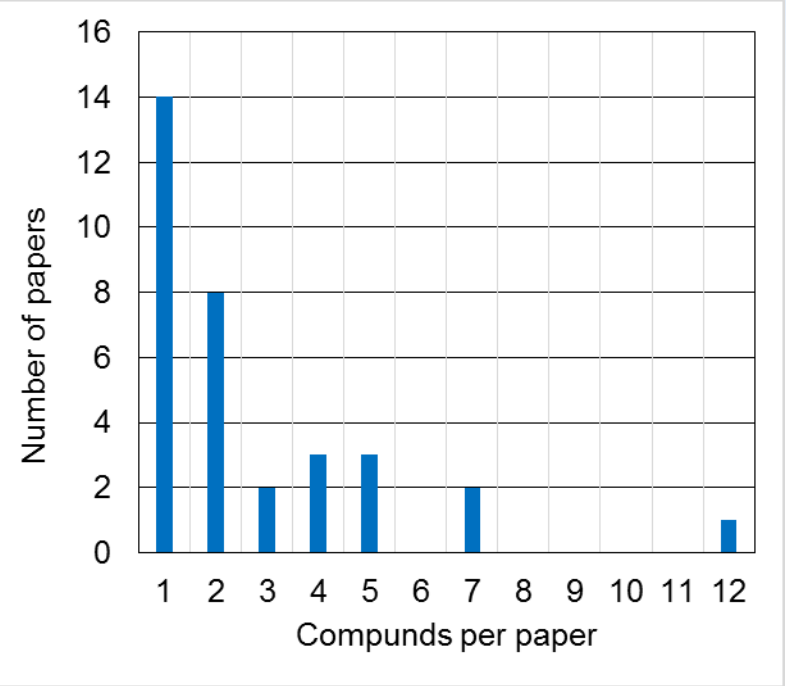
Current Topics in Medicinal Chemistry 2003, *3*, 1269-1288

Molecular Design and Bioavailability

Robert D. Clark* and Philippa R.N. Wolohan

Tripos, Inc., 1699 S. Hanley Road, St. Louis MO 63144 USA

Abstract: A "snapshot" of current medicinal chemistry work on bioavailability is drawn from issues of *J. Med. Chem.* covering the time period between September 2001 and September 2002. An exhaustive compilation of reported absolute oral bioavailability (*F*) values for this period is included, covering 34 structural series and 107 distinct compounds, with data for multiple species in many cases. This is supplemented with a discussion of more qualitative oral bioavailability results, and with illustrative examples addressing clearance, prodrug design, and blood/brain barrier penetration problems. Papers discussing predictions pertaining to one or another aspect of bioavailability are also discussed, and some thoughts on future directions of work on *in silico* prediction in this area are presented.



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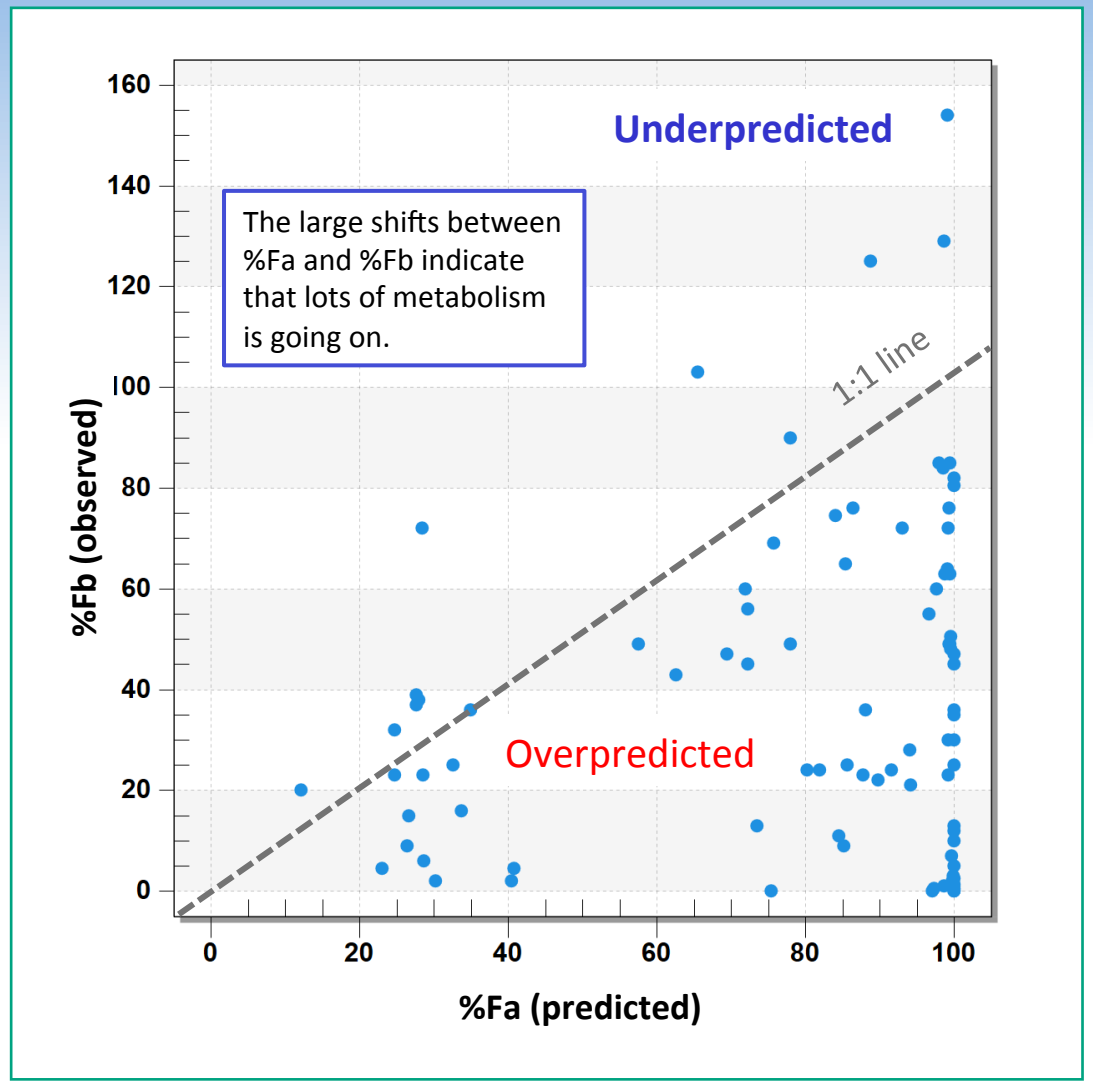

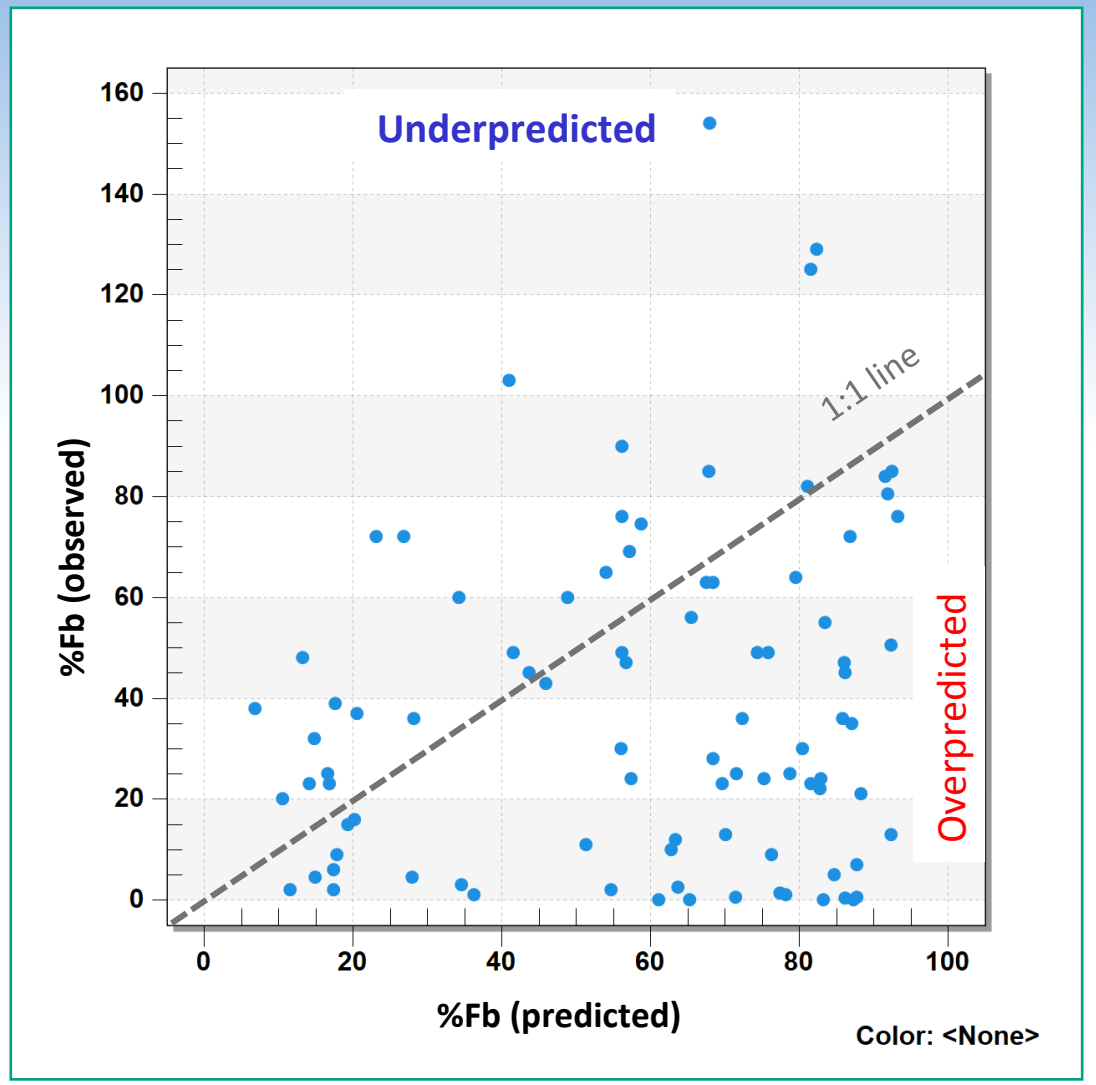

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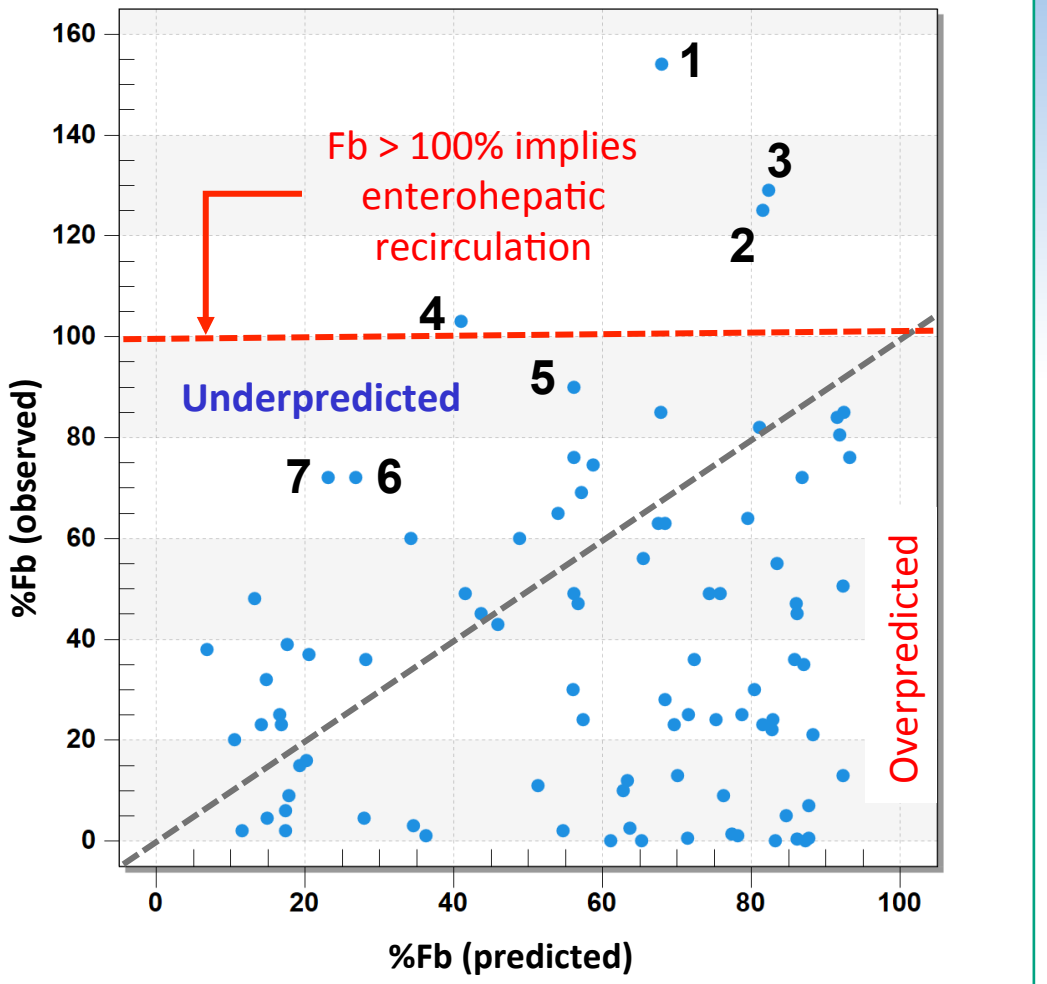
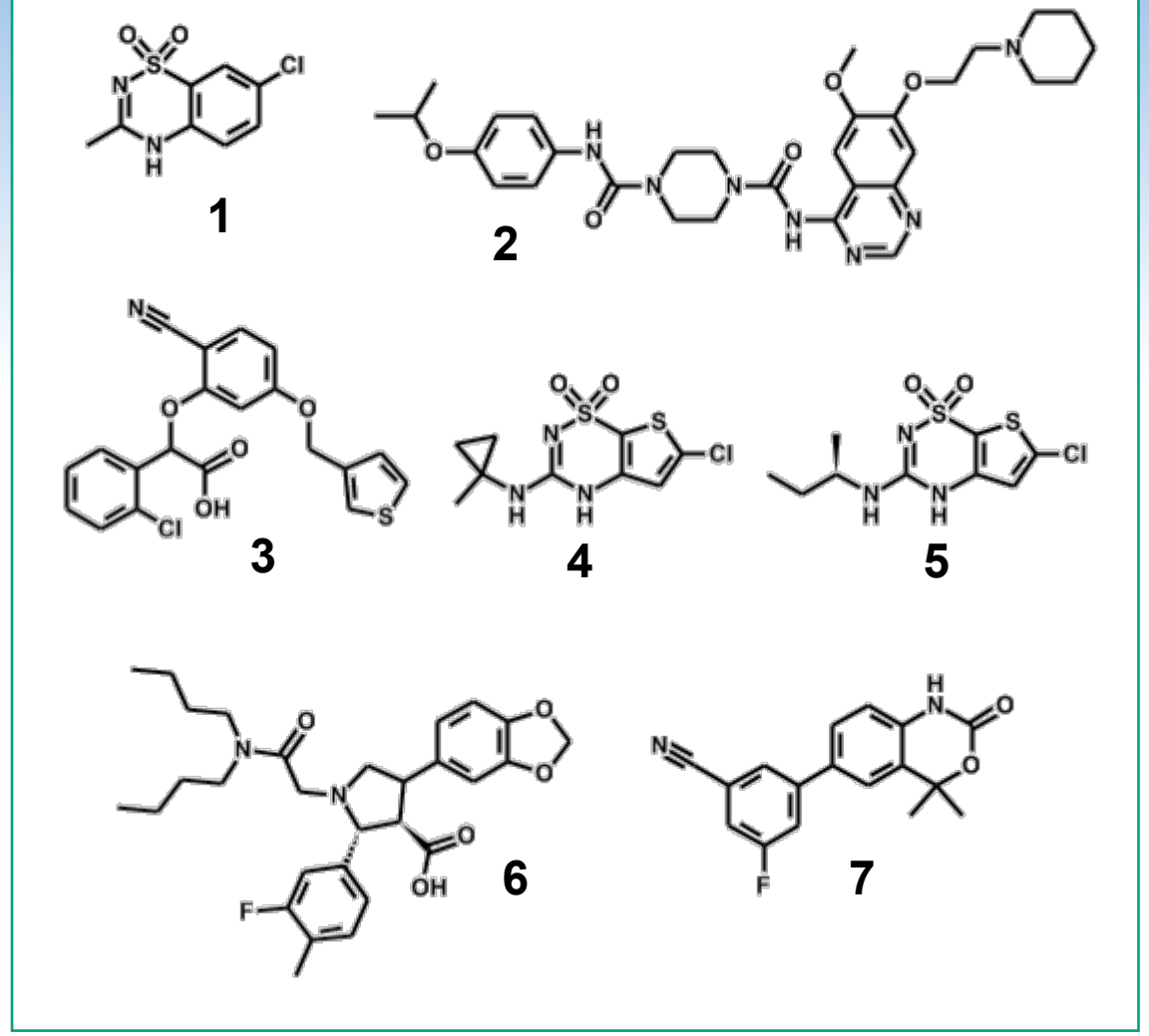
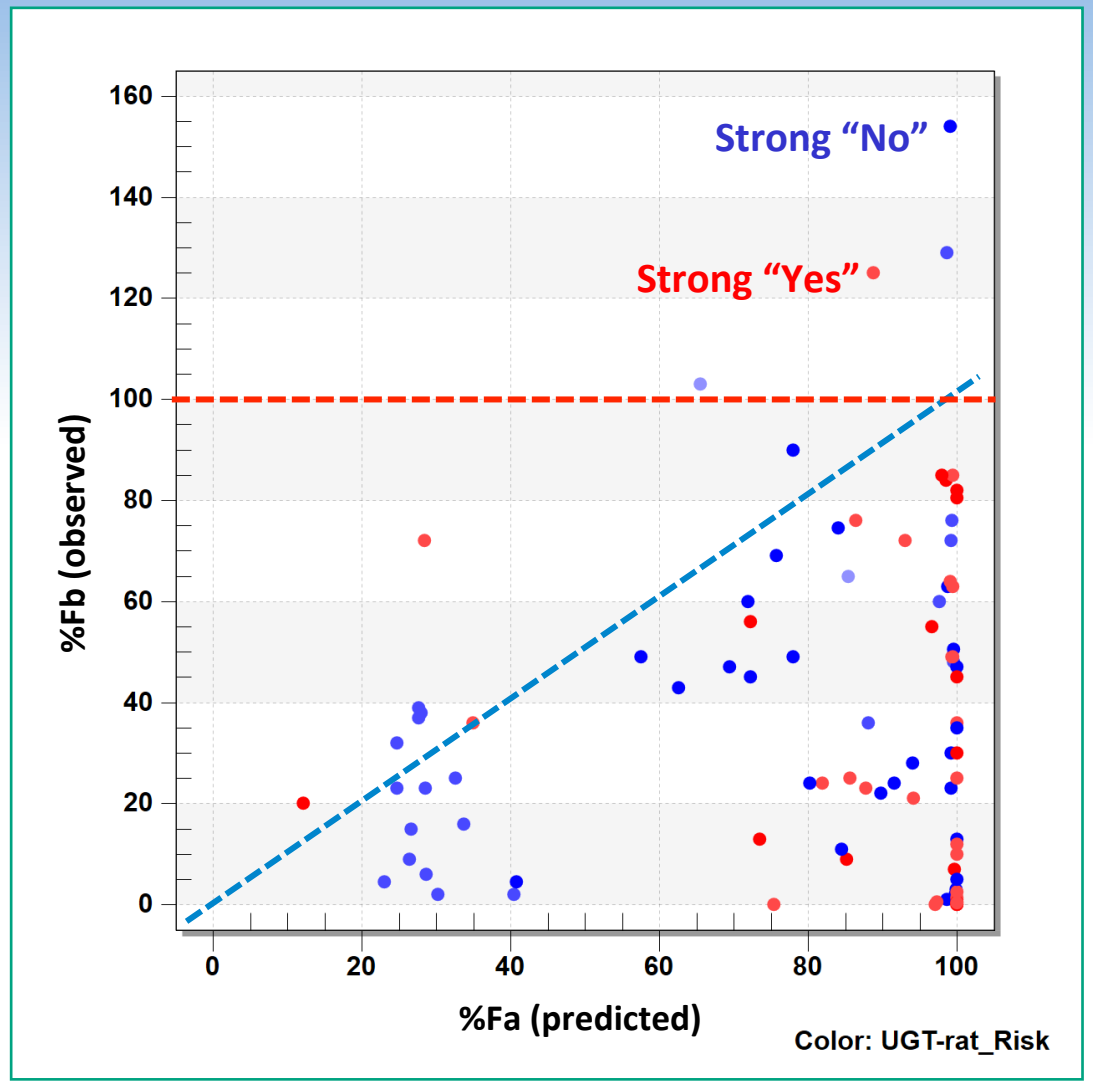
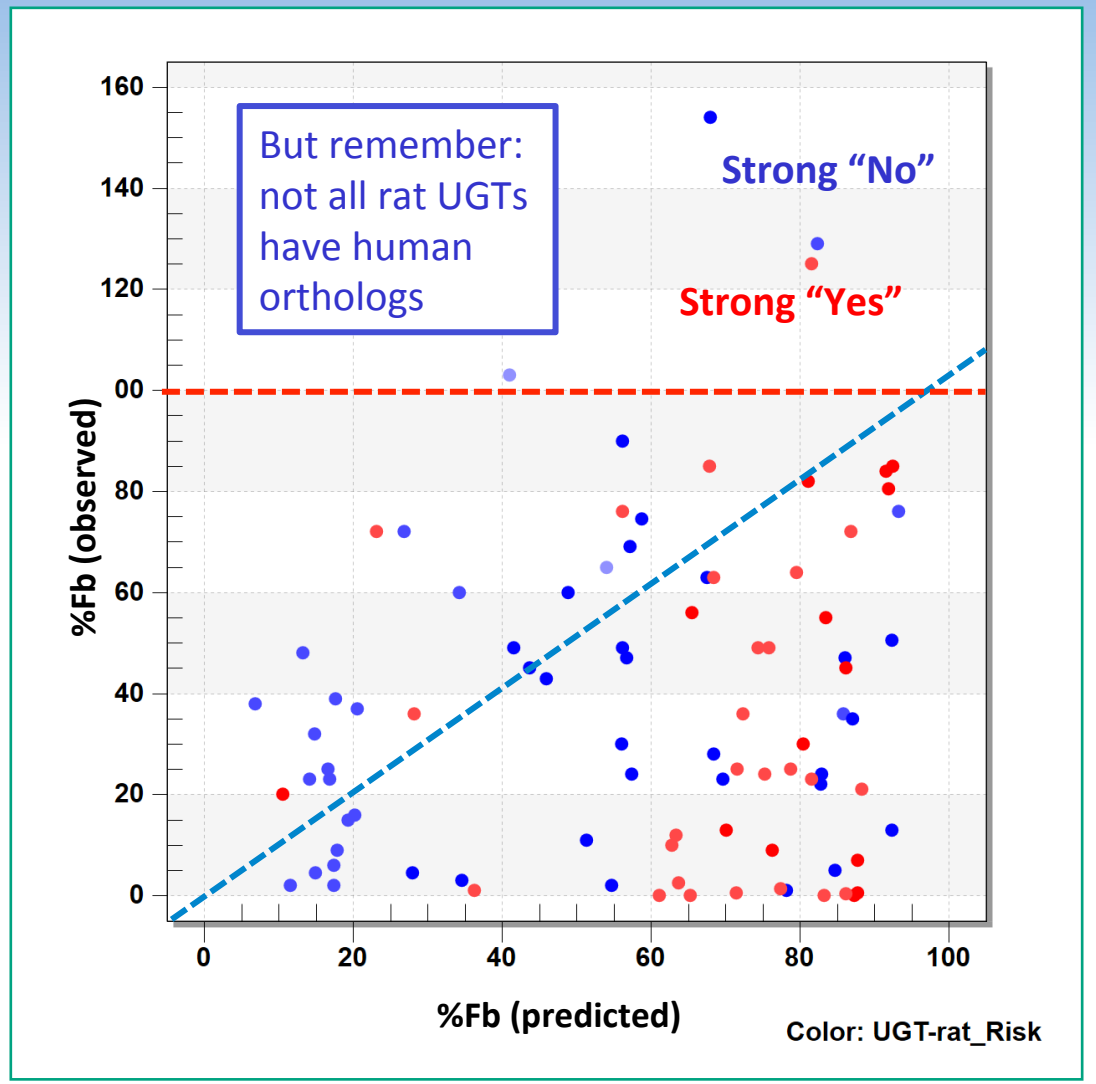




Effect of Being a UGT Substrate* on Predicted Rat PK





*Based on expression levels of rat orthologs of human UGTs human UGTs and hUGT substrate classifications

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Physiologically Based Pharmacokinetic Modeling in Lead Optimization. 2. Rational Bioavailability Design by Global Sensitivity Analysis To Identify Properties Affecting Bioavailability

Pankaj R. Daga,[†,‡] Michael B. Bolger,[§] Ian S. Haworth,[∥] Robert D. Clark,[§] and Eric J. Martin*[,†]

[†]Novartis Institute of Biomedical Research, Emeryville, California 94608, United States

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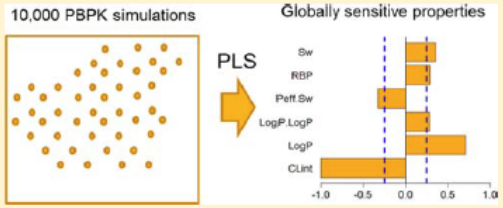
Supporting Information

ABSTRACT: When medicinal chemists need to improve oral bioavailability (%F) during lead optimization, they systematically modify compound properties mainly based on their own experience and general rules of thumb. However, at least a dozen properties can influence %F, and the difficulty of multiparameter optimization for such complex nonlinear processes grows combinatorially with the number of variables. Furthermore, strategies can be in conflict. For example, adding a polar or charged group will generally increase solubility but decrease permeability. Identifying the 2 or 3 properties that most influence %F for a given compound series would make %F optimization much more efficient. We previously reported an adaptation of physiologically based pharmacokinetic (PBPK) simulations to predict %F for a lead series from purely computational inputs within a 2-fold average error. Here, we run thousands of such simulations to generate a comprehensive "bioavailability landscape" for the series. A key innovation was recognition that the large and variable number of pK_a's in drug molecules could be replaced by just the two straddling the isoelectric point. Another was use of the ZINC database to cull out chemically inaccessible regions of property space. A quadratic partial least squares regression (PLS) accurately fits a continuous surface to these thousands of bioavailability predictions. The PLS coefficients indicate the globally sensitive compound properties. The PLS surface also displays the %F landscape in these sensitive properties locally around compounds of particular interest. Finally, being quick to calculate, the PLS equation can be combined with models for activity and other properties for multiobjective lead optimization.



KEYWORDS: *PBPK, lead optimization, lead series, local model, global sensitivity analysis, PLS, multiobjective optimization*

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molecular pharmaceutics

Article

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Physiologically Based Pharmacokinetic Modeling in Lead Optimization. 1. Evaluation and Adaptation of GastroPlus To Predict Bioavailability of Medchem Series

Pankaj R. Daga,[†,‡] Michael B. Bolger,[§] Ian S. Haworth,[∥] Robert D. Clark,[§] and Eric J. Martin*[,†]

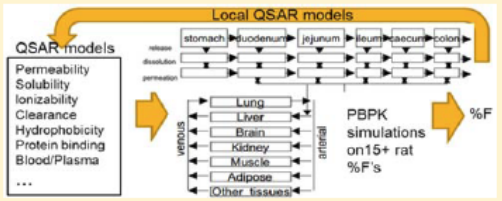
[†]Novartis Institute of Biomedical Research, Emeryville, California 94608, United States

[§]Simulations Plus, Inc., 42505 10th Street West, Lancaster, California 93534, United States

[∥]Department of Pharmacology and Pharmaceutical Sciences, University of Southern California, Los Angeles, California 90089, United States

Supporting Information

ABSTRACT: When medicinal chemists need to improve bioavailability (%F) within a chemical series during lead optimization, they synthesize new series members with systematically modified properties mainly by following experience and general rules of thumb. More quantitative models that predict %F of proposed compounds from chemical structure alone have proven elusive. Global empirical %F quantitative structure−property (QSPR) models perform poorly, and projects have too little data to train local %F QSPR models. Mechanistic oral absorption and physiologically based pharmacokinetic (PBPK) models simulate the dissolution, absorption, systemic distribution, and clearance of a drug in preclinical species and humans. Attempts to build global PBPK models based purely on calculated inputs have not achieved the <2-fold average error needed to guide lead optimization. In this work, local GastroPlus PBPK models are instead customized for individual medchem series. The key innovation was building a local QSPR for a numerically fitted effective intrinsic clearance (CL_{loc}). All inputs are subsequently computed from structure alone, so the models can be applied in advance of synthesis. Training CL_{loc} on the first 15−18 rat %F measurements gave adequate predictions, with clear improvements up to about 30 measurements, and incremental improvements beyond that.



KEYWORDS: *PBPK, lead optimization, lead series, local model, intrinsic clearance*

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Conclusions

- The high-throughput implementation of PBPK simulation in ADMET Predictor yields results in good agreement with analogous analyses in GastroPlus.
- HTPK simulations run using purely *in silico* property estimates are in reasonable but imperfect agreement with experimental results in humans and rats.
- Most experimental bioavailabilities for lead-type compounds in rat fall near or below the predicted fraction absorbed, which suggests that %Fa estimates are accurate.
- Increasing the accuracy of bioavailability estimation using *in silico* property estimates will require quantitative accounting for transporters and non-CYP metabolism.
- Measuring absorption and bioavailability is hard, as is modeling them. Validating the models designed to estimate them may be even harder.

My thanks to:

- My co-authors
- David Miller
- Michael Lawless
- Eric Martin & Ben Madej (Novartis)
- Mike Bolger
- Viera Lukacova
- John DiBella
- Karen Webster

…and to you for your kind attention.

bob@simulations-plus.com

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