Bridging Drug Efficacy and Safety to the Obese: Considerations and Scientific Approaches
November 9th, 2022

How a Systems Approach May Help Drug Development Cater for Better Dose Adjustment in Obese Patients

Amin Rostami, Ph.D., FCP, FAAPS, FJSSX, FBPS

Professor of Systems Pharmacology
Director of Centre for Applied Pharmacokinetics Research, University of Manchester, UK

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

1

Declaration of Conflict of Interest

As the Director of CAPKR (Centre for Applied Pharmacokinetics Research my research is sponsored by a group of pharmaceutical companies (currently AbbVie, Amgen, Eli Lily, EMD Serono, Genentech, GSK, J&J, Servier, Takeda) in addition to grants from non-for-profit organizations, governments and research councils.

As the Chief Scientific Officer and SVP of R&D at Certara, I have been involved in overseeing the development of software tools which are used by a large group of pharmaceutical companies during drug discovery and development; particularly in the area of physiologically-based pharmacokinetics (PBPK) and quantitative systems pharmacology (QSP).

Disclaimer

This presentation is prepared in my *personal capacity* as a scientist engaged with clinical pharmacology and pharmaceutical science for over 30 years.
The opinions expressed herein are my own and do not reflect the views, policies, and strategies of any of the organisations I am affiliated with.

2

Reality of Special Populations in Clinic

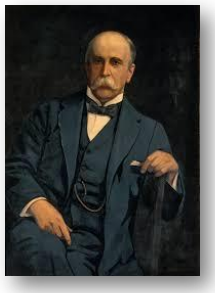
100 Years Old

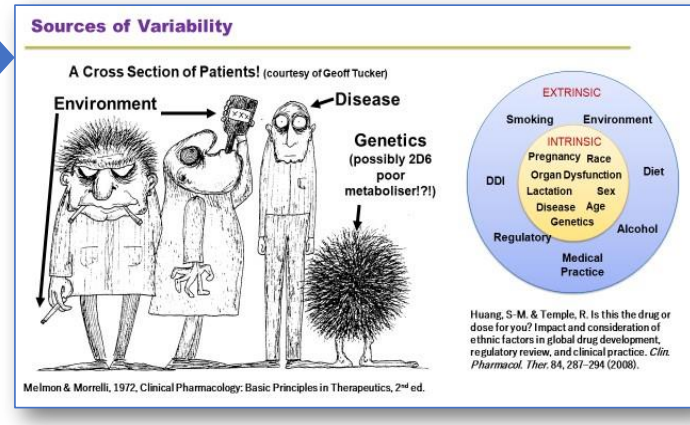
Problem

Known within Modern Medicine.

Sir William Osler (1849-1919)

Professor of Medicine Oxford, England





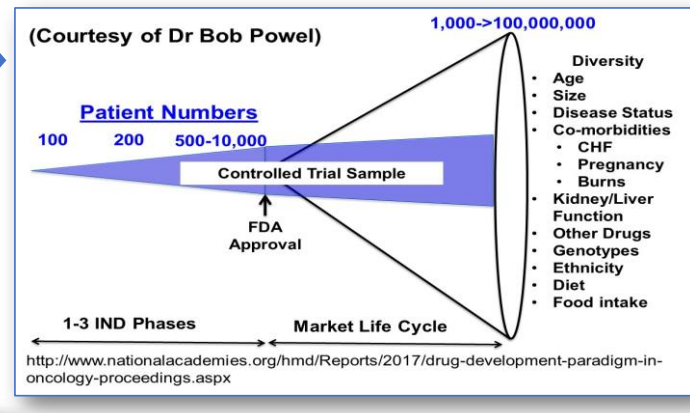
"*Variability is the law of life*, and as no two faces are the same, so no two bodies are alike, and no individuals react alike and behave alike under the abnormal conditions which we know as disease"

3

Issues with Current Drug Development

- **Regulators,**
- **Professional Associations, and**
- **Patient Advocacy Groups**

Are asking for more diversity in the clinical drug trials.



Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry

FDA Guidance for Industry

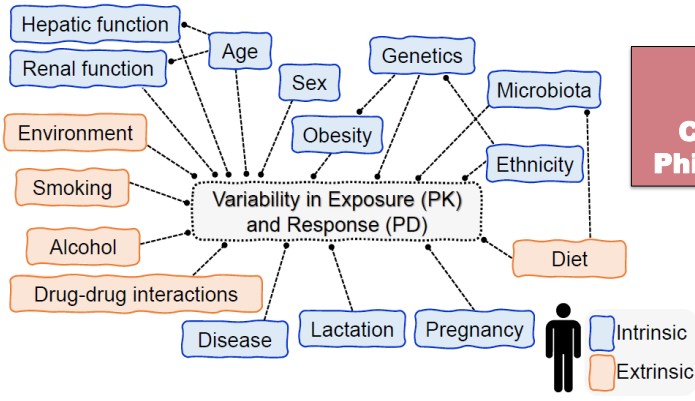
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

Clinical/Medical
November 2020
April 2022

4

Book Chapter:
A Rostami-Hodjegan and B Achour, in "Advances in Pharmacokinetics and Pharmacodynamics" by P Macheras, Springer 2023

On the Verge of Impossibility:
Caring for All Permutations of Comorbidities Influencing the Fate of Drugs



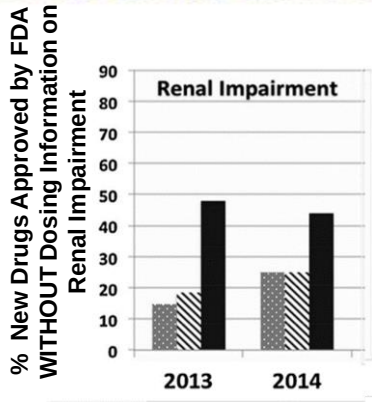
Time to Change Philosophy

5

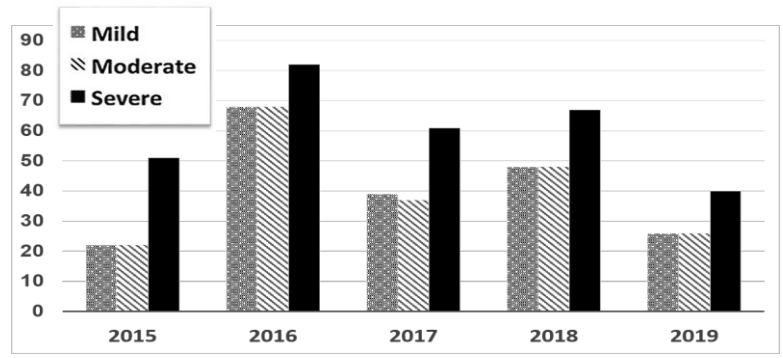
AAPS Workshop on

Specific Population Drug Dosing Recommendations: Shifting from Clinical Studies to Predict and Confirm

October 24-25, 2015
Orange County Convention Center • Orlando, Fl.



Jadhav et al., 2015



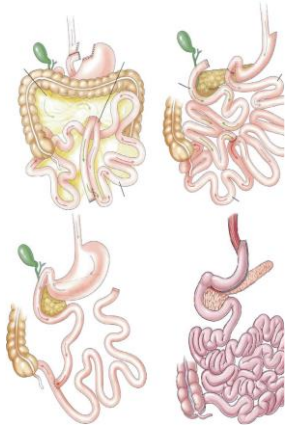
AL-Qassabi J, *Unpublished Survey*

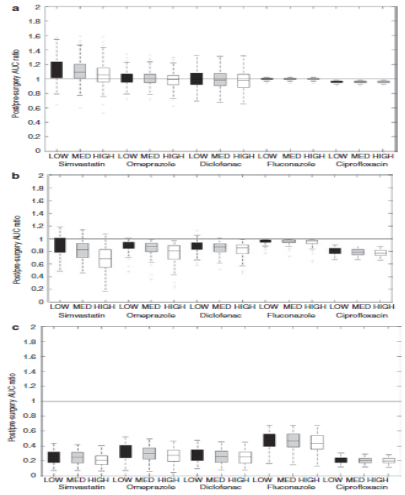
6

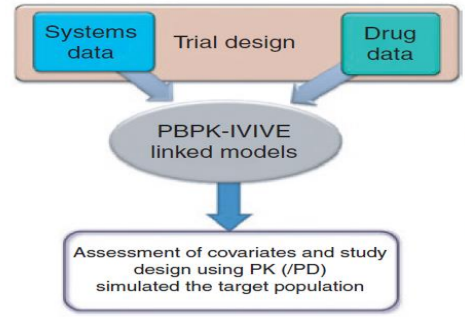
STATE OF THE ART
Clin Pharm Ther 2012 - 92 (1): 50-61
nature publishing group

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]



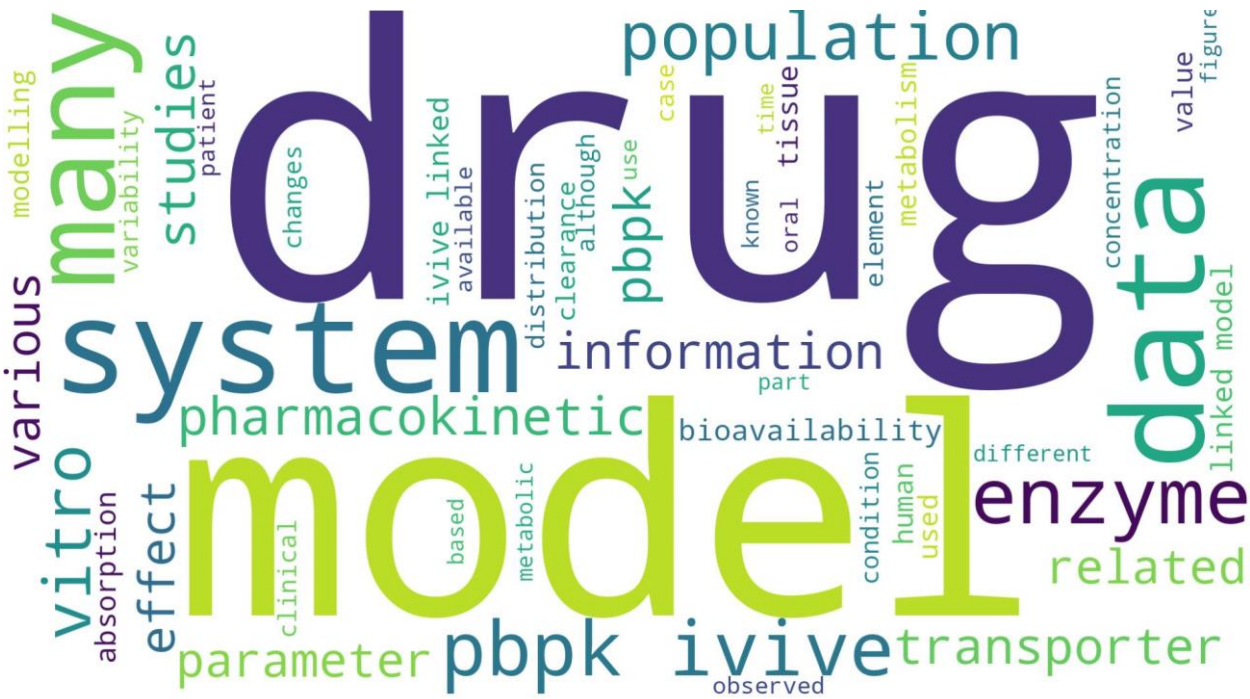




Simulated postsurgical/presurgical AUC ratio over **a range of selected drugs** at LOW, MED, and HIGH therapeutic doses: Simvastatin Immediate Release (IR), Omeprazole Enteric Coated (EC), Diclofenac EC, Fluconazole IR, and Ciprofloxacin IR for :

(a) Roux-en-Y gastric bypass surgery (RY)
(b) Biliopancreatic Diversion with Duodenal Switch (BDDS)
(c) Jejunoileal Bypass (JI-B)

7



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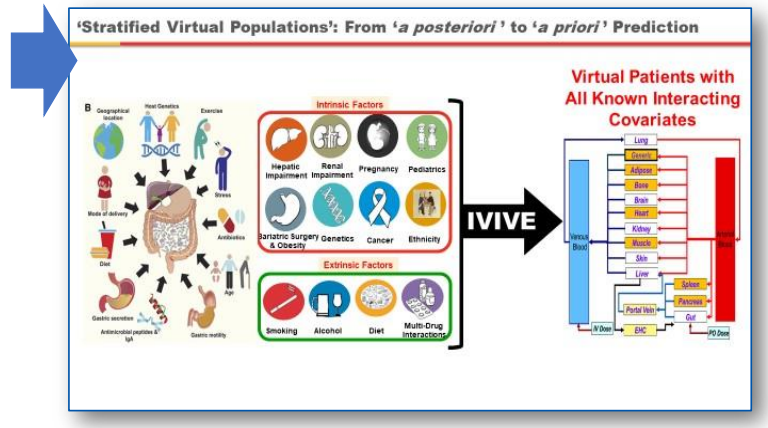
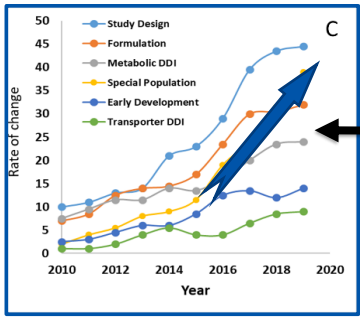
A Potential Solution to Address the Problem

Focusing on SYSTEMS rather than DRUG





Special/Disease Populations Is the Fastest Growing Area of PBPK-IVIVE Applications!

El-Khateeb et al. (2021) Physiological-based pharmacokinetic modeling trends in pharmaceutical drug development over the last 20-years; In-depth analysis of applications, organizations, and platforms. *Biopharm. Drug Dispos. 42:107–117.*

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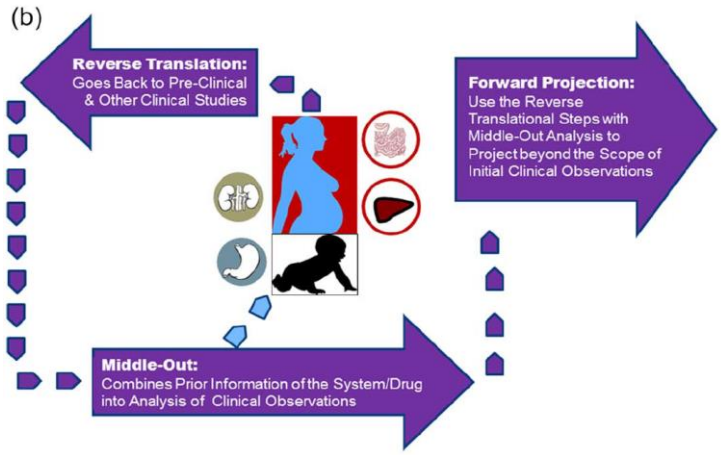
STATE OF THE ART

Clin Pharm Ther 2018 - 103 (2): 224-232

Reverse Translation in PBPK and QSP: Going Backwards in Order to Go Forward With Confidence

Amin Rostami-Hodjegan[1,2]



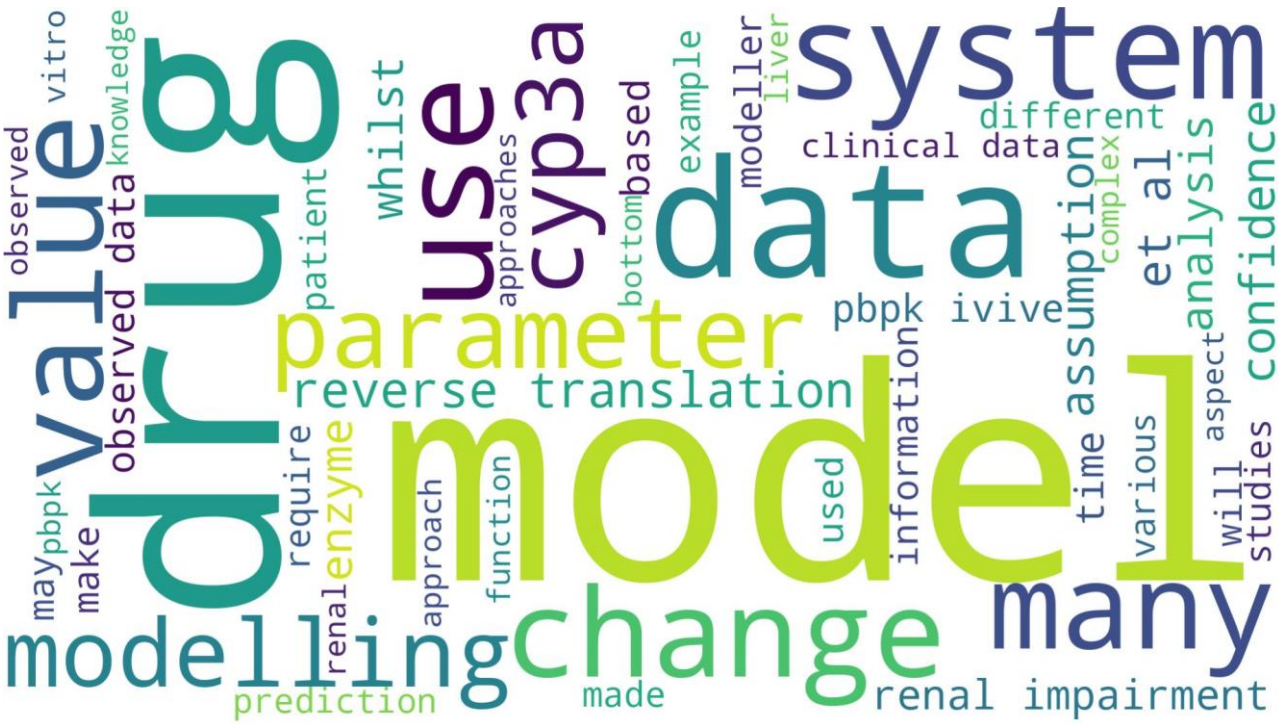
Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data

Nikolaos Tsamandouras,[1] Amin Rostami-Hodjegan[1,2] & Leon Aarons[1]

Br J Clin Pharmacol 2014 -79 (1): 48-55

Clarifying Common Philosophical Misconceptions

10



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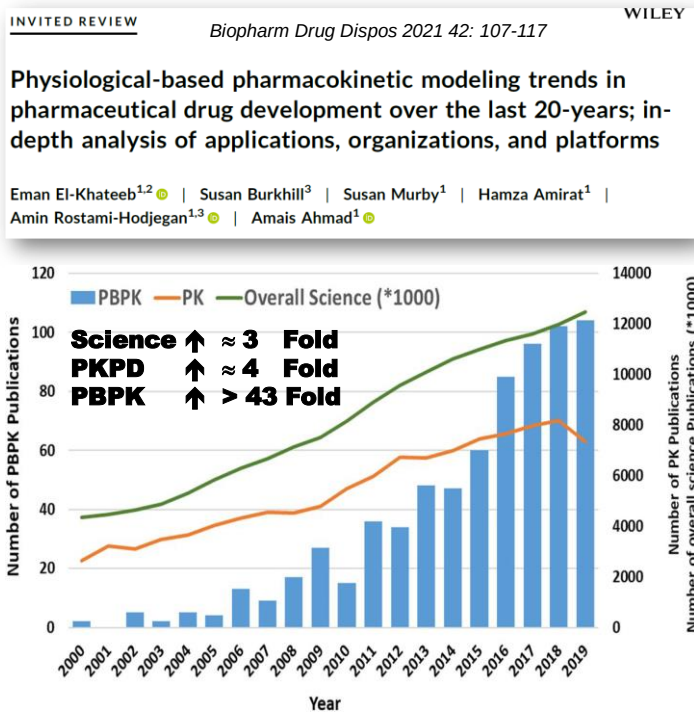

INVITED REVIEW

WILEY

Biopharm Drug Dispos 2021 42: 107-117

Physiological-based pharmacokinetic modeling trends in pharmaceutical drug development over the last 20-years; in-depth analysis of applications, organizations, and platforms

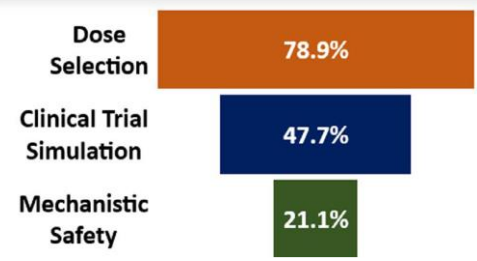
Eman El-Khateeb[1,2] | Susan Burkhill[3] | Susan Murby[1] | Hamza Amirat[1] | Amin Rostami-Hodjegan[1,3] | Amais Ahmad[1]

PERSPECTIVES

CPT ; 110 (5); 2021

Industrial Perspective on the Benefits Realized From the FDA's Model-Informed Drug Development Paired Meeting Pilot Program

Gerald R. Galluppi[1,*], Satjit Brar[2], Luzelena Caro[3], Yuan Chen[4], Nicolas Frey[5], Hans Peter Grimm[5], Deanne Jackson Rudd[3], Chi-Chung Li[6], Mindy Magee[7], Arnab Mukherjee[8], Lee Nagao[9], Vivek S. Purohit[10], Amit Roy[11], Ahmed Hamed Salem[12,13], Vikram Sinha[3,†], Ahmed A. Suleiman[14], Kunal S. Taskar[15], Vijay V. Upreti[16], Benjamin Weber[17] and Jack Cook[18,*]



12

Biopharmaceutics & Drug Disposition

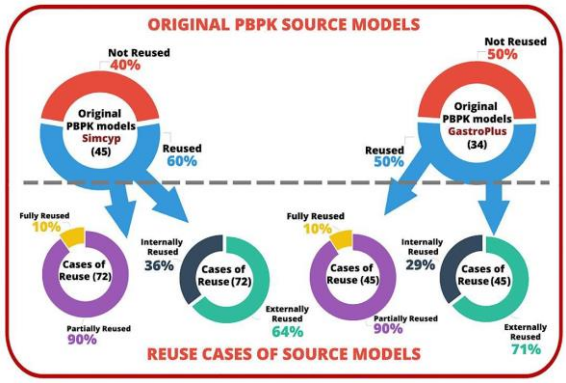
Biopharm Drug Dispos 2023 – UNDER REVIEW

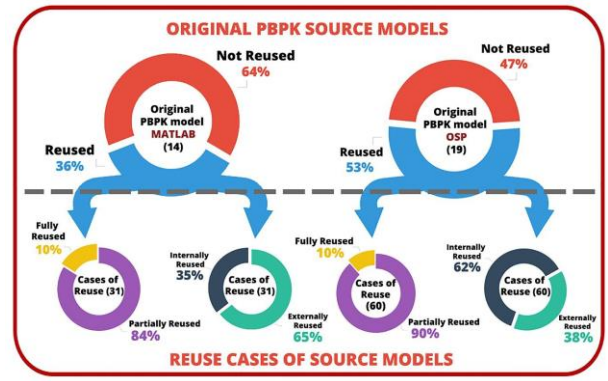
Another Philosophical Change

In-Depth Analysis of Patterns in Selection of Different Physiologically-Based Pharmacokinetic Modeling Tools:

Part I - Applications and Rationale Behind the Use of Open Source-Code Software

Part II - Assessment of Model Reusability and Comparison Between Open and Non-Open Source-Code Software





13

Reusability Concept for Models

A computational model is considered **entirely reusable** if it may be **utilised** as a simulation component **within other mathematical models**, with its physical scope being the sole constraint

Rodrigues Matos T, *et al.* (2013) On a reusable and multilevel methodology for modeling and simulation of pharmacokinetic-physiological systems: a preliminary study. *Comput Biol Med.* 43(10):1512-22.

Definitions - Current Analysis by the University of Manchester for PBPK Models Reusability

Term	Definition
Reusability	The reutilisation of (I) the model in its entirety, (II) the systems components, (III) the drug-dependent components, (IV) the modelling strategy, or (V) Leveraging the aforementioned
Partial Reusability	(II), (III), (IV) or (V) above
Full Reusability	(I) above
External Reusability	Reusability by researchers outside the organisations affiliated to original model development
Internal Reusability	Reusability of involving researchers from the same institution involved in the development of original model

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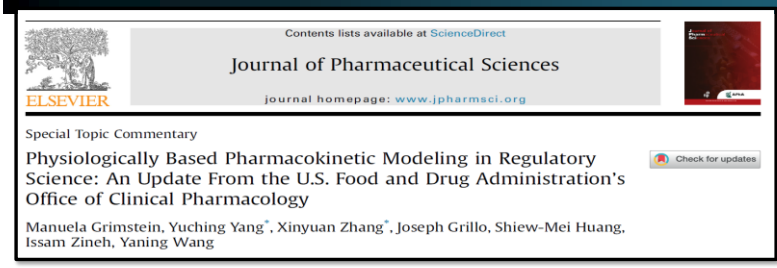
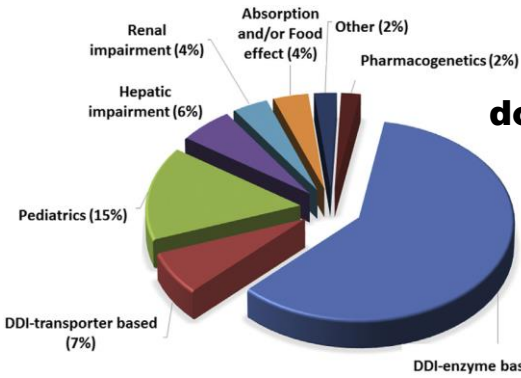
Regulatory Picture: A Dynamic Scene

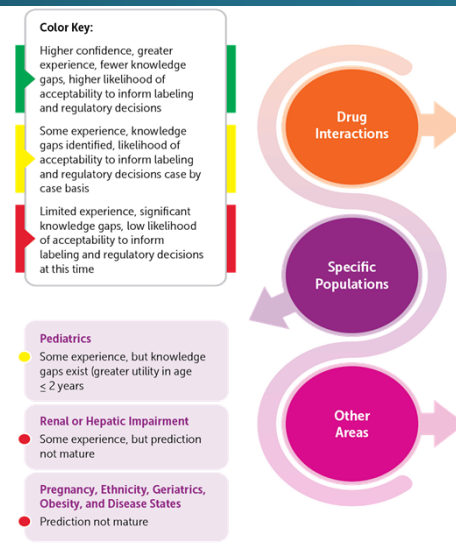

Contents lists available at ScienceDirect
Journal of Pharmaceutical Sciences
journal homepage: www.jpharmsci.org
ELSEVIER
Special Topic Commentary

Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration's Office of Clinical Pharmacology

Manuela Grimstein, Yuching Yang*, Xinyuan Zhang*, Joseph Grillo, Shiew-Mei Huang, Issam Zineh, Yaning Wang



DDI still dominates the submissions

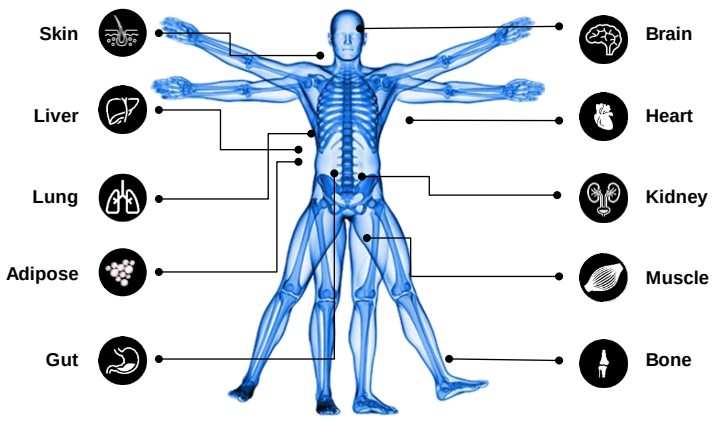


Adapted from:
Wagner *et al.*, CPT:PSP, 2015 & Joe Grillo's Slide at PKUK (2018)

15

Virtual Patients to Conduct In Silico Trials

Biosimulation to predict how the attributes of body affect the drug fate in each population:



Possible Applications:

- First-in-Human Dosing
- Drug-Drug Interactions
- Clinical Study Design
- Pediatric Dosing
- Bioequivalence
- Formulation
- Renal Impairment
- Hepatic Impairment
- Reduced Cardiac Output
- Food Effect

Reusability for 25 Virtual Patient Populations & >100 Compound Files

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Areas of Significant Impact: PBPK-IVIVE Approach

Clinical Trial Waivers

Extrapolation to Special Populations

Reduction in Study Patients

17

Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-022-01169-4

SYSTEMATIC REVIEW

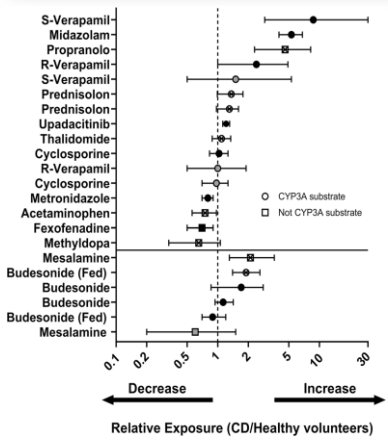
Check for updates

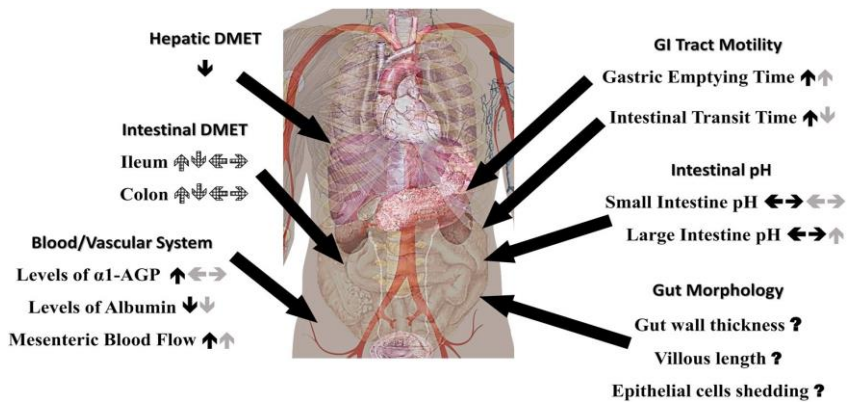
Altered Bioavailability and Pharmacokinetics in Crohn's Disease: Capturing Systems Parameters for PBPK to Assist with Predicting the Fate of Orally Administered Drugs

Sarah Alrubia[1,2] · Jialin Mao[3] · Yuan Chen[3] · Jill Barber[1] · Amin Rostami-Hodjegan[1,4]

(1) Integration of Existing Data;

(2) Creation Non-Existent Data

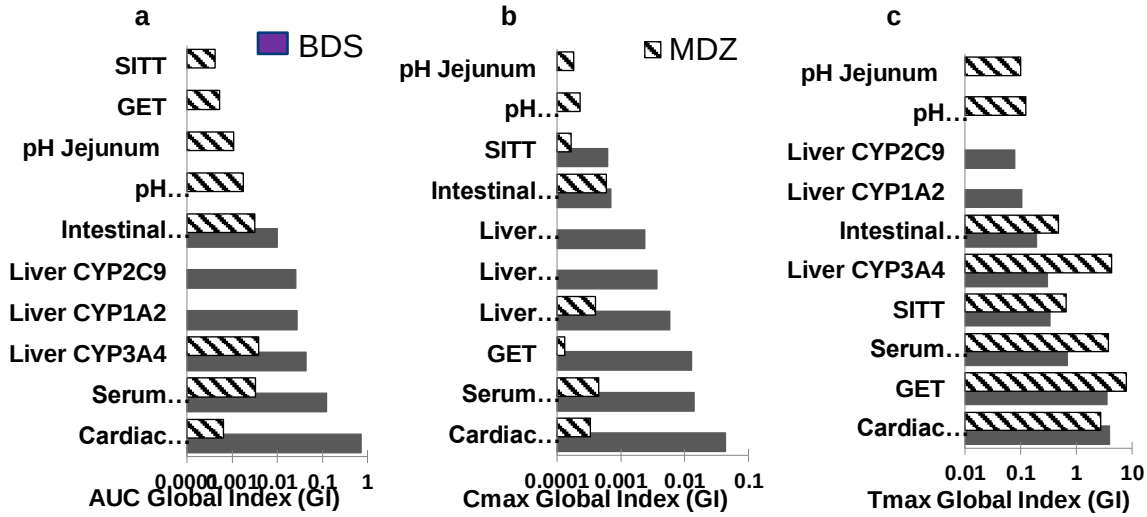




18

Model Verification/Credibility Requires Multiple Drugs & Formulations

Same Changes in Physiology: Varying Impact on Different Drugs (Midazolam [MDZ] vs Budesonide [BDS])



19

What Does Validation Mean in This Context? e.g. DDI & RI

Effect of ketoconazole on the pharmacokinetics and safety of telithromycin and clarithromycin in older subjects with renal impairment

J. Shi[1], S. Chapel[1], G. Montay[2], P. Hardy[2], J.S. Barrett[1], D. Sica[3], S.K. Swan[4], R. Noveck[5], B. Leroy[1] and V.O. Bhargava[1]

INT J CLIN PHARM THER 2005

Renal Impairment (Clinical Study)

Renal Impairment (IVIVE/PBPK)

Predicting Drug Interaction Potential With a Physiologically Based Pharmacokinetic Model: A Case Study of Telithromycin, a Time-Dependent CYP3A Inhibitor

Biopharm Drug Dispos 2012

MdLT Vieira[1,2], P Zhao[1], EG Berglund[3,4], KS Reynolds[1], L Zhang[1], LJ Lesko[1] and S-M Huang[1]

Utility of a physiologically–based pharmacokinetic (PBPK) modeling approach to quantitatively predict a complex drug–drug–disease interaction scenario for rivaroxaban during the drug review process: implications for clinical practice

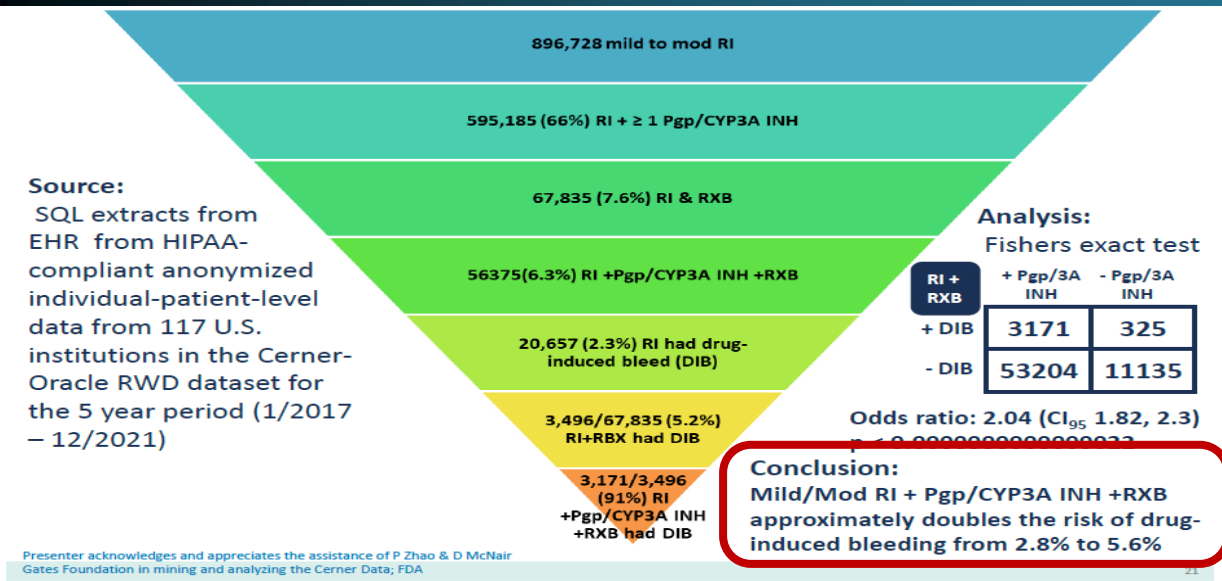
CLIN PHARM THER 2012

Drug Label Case (DDI in Renal Impairment ✓

Joseph A. Grillo[a], Ping Zhao[a,*], Julie Bullock[a], Brian P. Booth[a], Min Lu[b], Kathy Robie-Suh[b], Eva Gil Berglund[c], K. Sandy Pang[d], Atiqur Rahman[a], Lei Zhang[a], Lawrence J. Lesko[a], and Shiew-Mei Huang[a]

20

Ten Years Later and with the Help of RWDA (Real World Data Analysis)



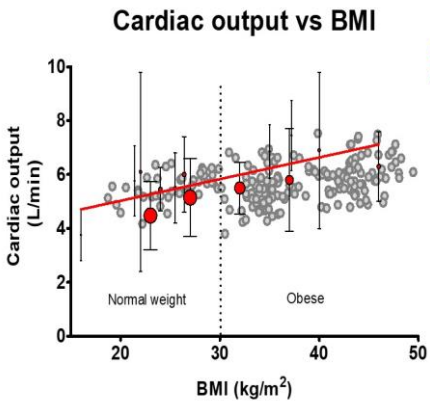
21

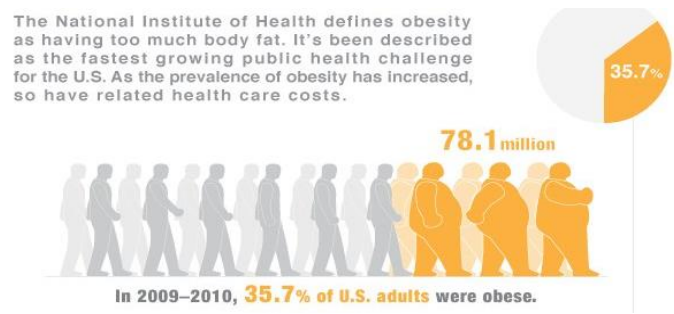
Application of a Systems Approach to the Bottom-Up Assessment of Pharmacokinetics in Obese Patients

Expected Variations in Clearance

Cyrus Ghobadi,[1] Trevor N. Johnson,[1] Mohsen Aarabi,[1] Lisa M. Almond,[1] Aurel Constant Allabi,[1] Karen Rowland-Yeo,[1] Masoud Jamei[1] and Amin Rostami-Hodjegan[1,2]

Clin Pharmacokinet 2011; 50 (12): 809-822





(ASMBS 2012; finance.yahoo.com 2012; Picot *et al*. 2009)

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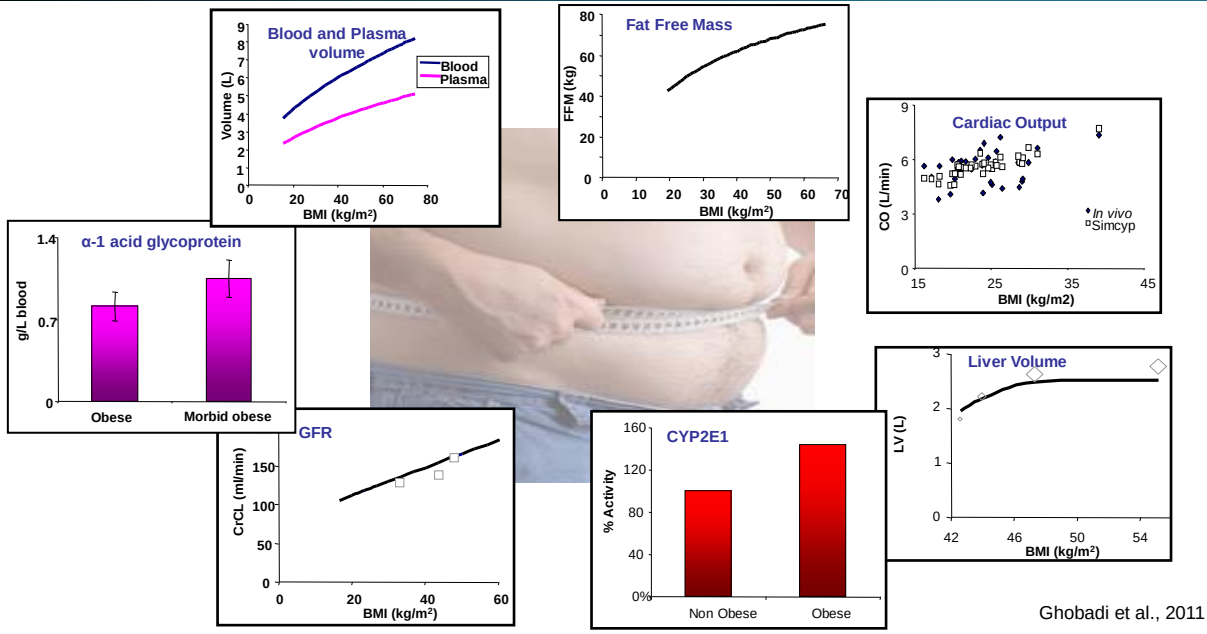
Obesity: Key 'Known' Physiological Changes Then



Ghobadi et al., 2011

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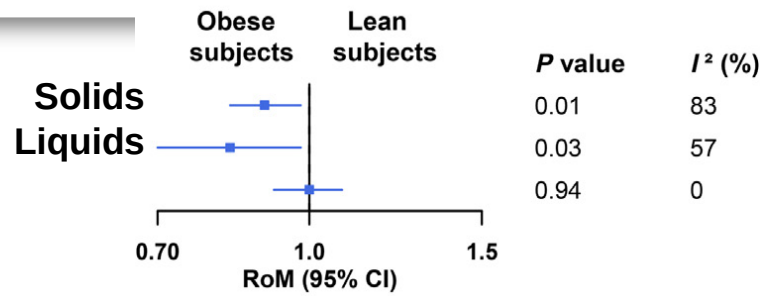
Clinical Therapeutics/Volume 43, Number 10, 2021

Pooled Analysis of Gastric Emptying in Patients With Obesity: Implications for Oral Absorption Projection

Chen-Xi Lu, BSc[1,*]; Xiao-Xiao An, MSc[1,*]; Yichao Yu, PhD[2,5]; Li-Rong Jiao, BSc[1,3]; Daniele Canarutto, MD[4]; Guo-Fu Li, PhD[1]; and Guo Yu, PhD[1]

GI Physiological Differences in Obesity Known Since Then

Gastric Emptying:
$T_{1/2}$ Is Shorter in Obese



Small Intestine in Obese:

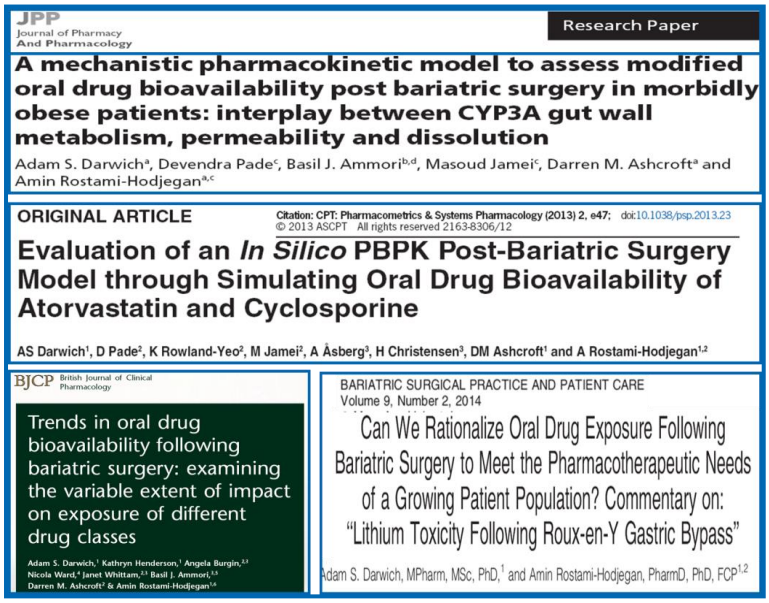
- **Higher Contractility**
- **Shorter Transit Time**
- **Lower Median pH**

Effect of obesity on gastrointestinal transit, pressure and pH using a wireless motility capsule

N. Steenackers[a], L. Wauters[b], B. Van der Schueren[a,c], P. Augustijns[d], G. Falony[e,f], M. Koziolek[g], M. Lannoo[h], A. Mertens[a,c], A. Meulemans[a,c], J. Raes[e,f], R. Vangoitsenhoven[a,c], S. Vieira-Silva[e,f], W. Weitschies[g], C. Matthys[a,c,*], T. Vanuytsel[b,i,*,1]

24

Trends: Bariatric Surgery


JPP Journal of Pharmacy And Pharmacology

Research Paper

A mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: interplay between CYP3A gut wall metabolism, permeability and dissolution

Adam S. Darwich[a], Devendra Pade[c], Basil J. Ammori[b,d], Masoud Jamei[c], Darren M. Ashcroft[a] and Amin Rostami-Hodjegan[a,c]

ORIGINAL ARTICLE

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e47; doi:10.1038/psp.2013.23
© 2013 ASCPT All rights reserved 2163-8306/12

Evaluation of an *In Silico* PBPK Post-Bariatric Surgery Model through Simulating Oral Drug Bioavailability of Atorvastatin and Cyclosporine

AS Darwich[1], D Pade[2], K Rowland-Yeo[2], M Jamei[2], A Åsberg[3], H Christensen[3], DM Ashcroft[1] and A Rostami-Hodjegan[1,2]

BJCP British Journal of Clinical Pharmacology

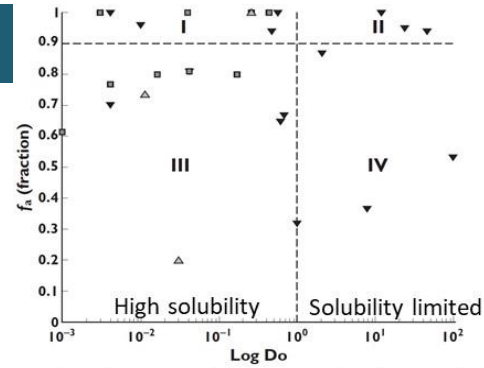
Trends in oral drug bioavailability following bariatric surgery: examining the variable extent of impact on exposure of different drug classes

Adam S. Darwich,[1] Kathryn Henderson,[1] Angela Burgin,[2,3] Nicola Ward,[4] Janet Whittam,[2,3] Basil J. Ammori,[1,5] Darren M. Ashcroft[2] & Amin Rostami-Hodjegan[1,6]

BARIATRIC SURGICAL PRACTICE AND PATIENT CARE
Volume 9, Number 2, 2014

Can We Rationalize Oral Drug Exposure Following Bariatric Surgery to Meet the Pharmacotherapeutic Needs of a Growing Patient Population? Commentary on: "Lithium Toxicity Following Roux-en-Y Gastric Bypass"

Adam S. Darwich, MPharm, MSc, PhD,[1] and Amin Rostami-Hodjegan, PharmD, PhD, FCP[1,2]



have bariatric surgery

BY: SUE DUNLEVY NATIONAL HEALTH CORRESPONDENT
FROM: NEWS LIMITED NETWORK
SEPTEMBER 19, 2013 4:26PM

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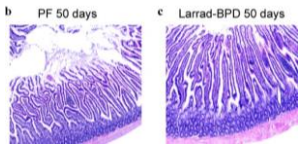
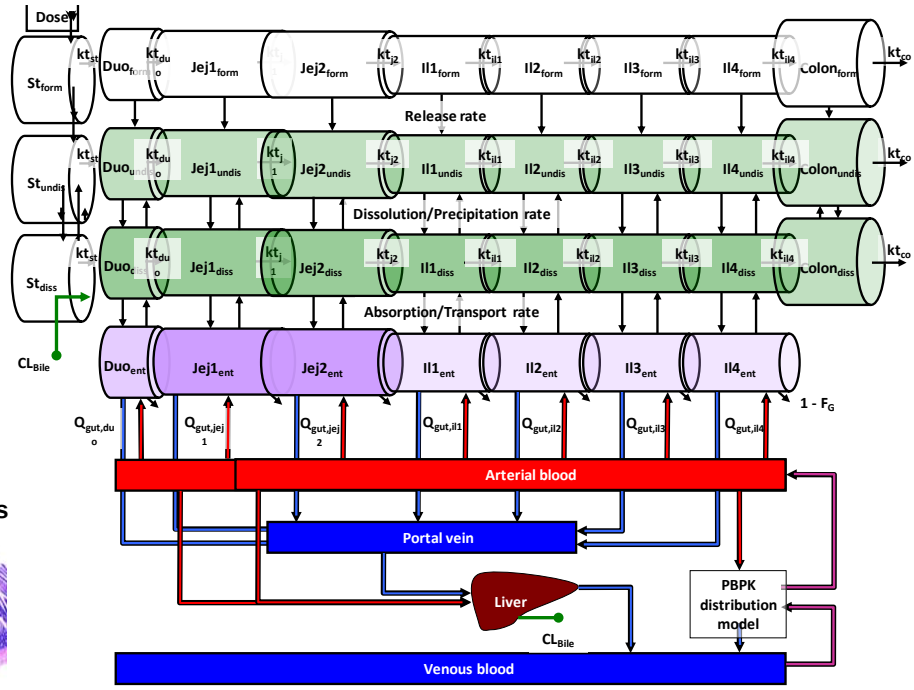
Conduct of *in Silico* Bariatric Surgery

Not Just Anatomy:

Bariatric Surgery induces villi elongation in rats



(Mendieta, et al. 2012)



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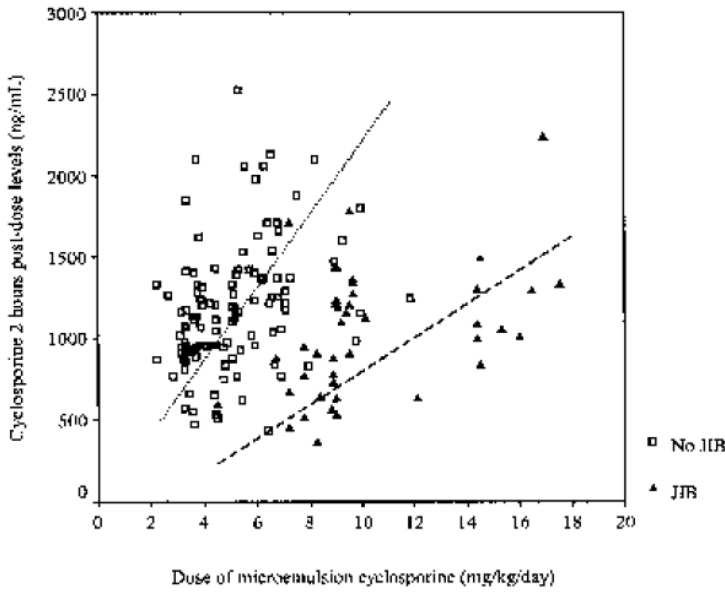
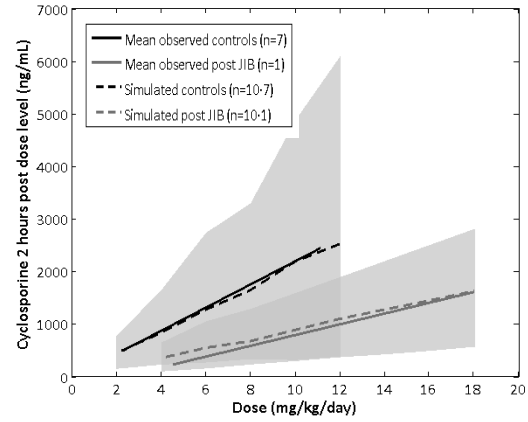
Exposure/Dose Ratio ↓ after JI-Bypass: Cyclosporine





↑ PBPK Predictions

← Actual Observations

(Chenhsu et al 2006)

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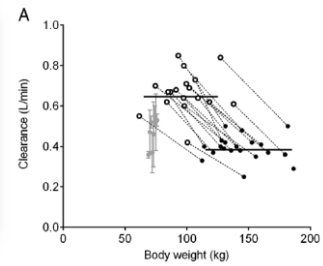
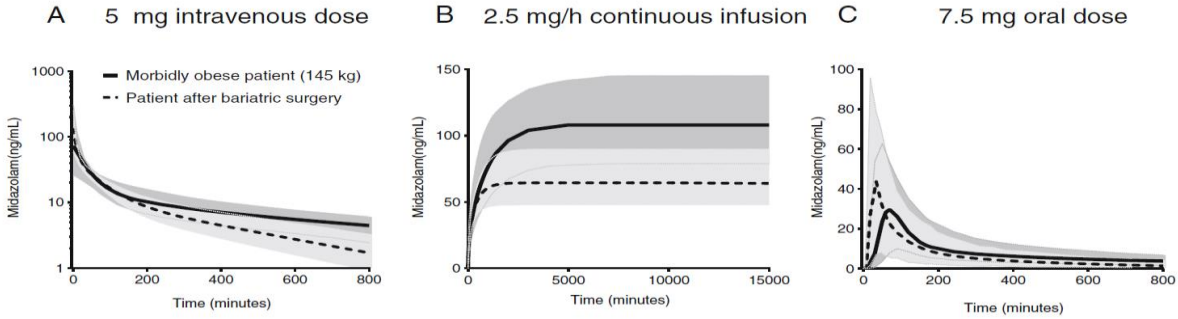
Predicted ↑ AUC for MDZ but … De-Supression of CL Post-Surgery?

The Pharmacokinetics of the CYP3A Substrate Midazolam in Morbidly Obese Patients Before and One Year After Bariatric Surgery

Margreke J. Brill[1,2] • Anne van Rongen[1,2] • Eric P. van Dongen[3] • Bert van Ramshorst[4] • Eric J. Hazebroek[4] • Adam S. Darwich[5] • Amin Rostami-Hodjegan[5] • Catherijne A. Knibbe[1,2]





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LETTER TO THE EDITOR

2018

Author's Reply to Reith: "Higher Midazolam Clearance in Obese Adolescents Compared with Morbidly Obese Adults"

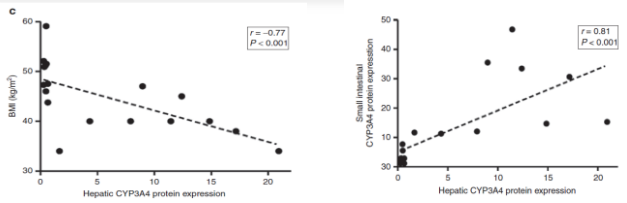
Anne van Rongen[1] · Johannes N. van den Anker[2,3,4] · Catherijne A. J. Knibbe[5,6]

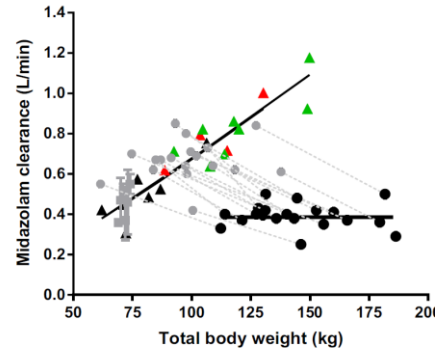
Suppression of CYP3Aactivity as a Result of Prolonged Inflammation and Prolonged Obesity in Adults (as opposed to Adolescents)

Impact of OATP1B1, MDR1, and CYP3A4 Expression in Liver and Intestine on Interpatient Pharmacokinetic Variability of Atorvastatin in Obese Subjects

2013

M Ulvestad[1,2], IB Skottheim[1], GS Jakobsen[3], S Bremer[4], E Molden[1], A Åsberg[1], J Hjelmesæth[3], TB Andersson[2], R Sandbu[3] and H Christensen[1]





Estimates MDZ CL of 19 Obese Adolescents (*red triangles* represent orthopedic surgery patients, *green triangles* represent bariatric/laparoscopic surgery patients, *black triangles* represent other patients, i.e. tonsillectomy) vs BW. CL MDZ CL are reported for 20 morbidly obese patients (*black dots*) and 18 of these 1 year after bariatric surgery (*grey dots*, with *dotted lines* for corresponding values and healthy volunteer studies (*grey squares*). *Black lines* represent population mean estimates.

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molecular pharmaceutics

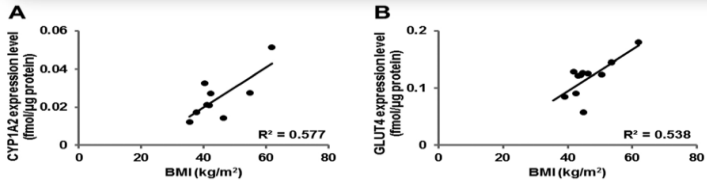
Article

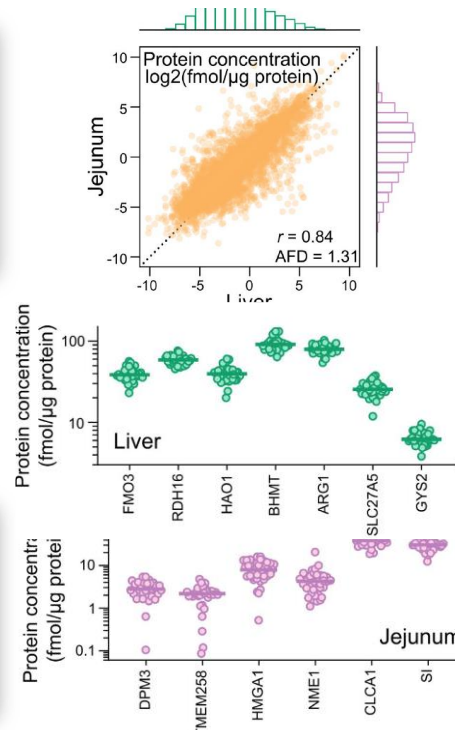
pubs.acs.org/molecularpharmaceutics

2016

Quantitative Atlas of Cytochrome P450, UDP-Glucuronosyltransferase, and Transporter Proteins in Jejunum of Morbidly Obese Subjects

Eisuke Miyauchi,[†] Masanori Tachikawa,[*,†] Xavier Declèves,[‡,§] Yasuo Uchida,[†] Jean-Luc Bouillot,[∥] Christine Poitou,[⊥] Jean-Michel Oppert,[⊥] Stéphane Mouly,[‡,#] Jean-François Bergmann,[‡,#] Tetsuya Terasaki,[†] Jean-Michel Scherrmann,[‡] and Célia Lloret-Linares[‡,#]





Drug Disposition Protein Quantification in Matched Human Jejunum and Liver From Donors With Obesity

2022

Christine Wegler[1,2], Jacek R. Wiśniewski[3], Ida Robertsen[4], Hege Christensen[4], Jens Kristoffer Hertel[5], Joran Hjelmesæth[5,6], Rasmus Jansson-Löfmark[2], Anders Åsberg[4,7], Tommy B. Andersson[2] and Per Artursson[1,*]

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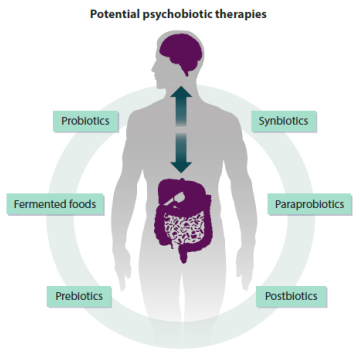
ANNUAL REVIEWS

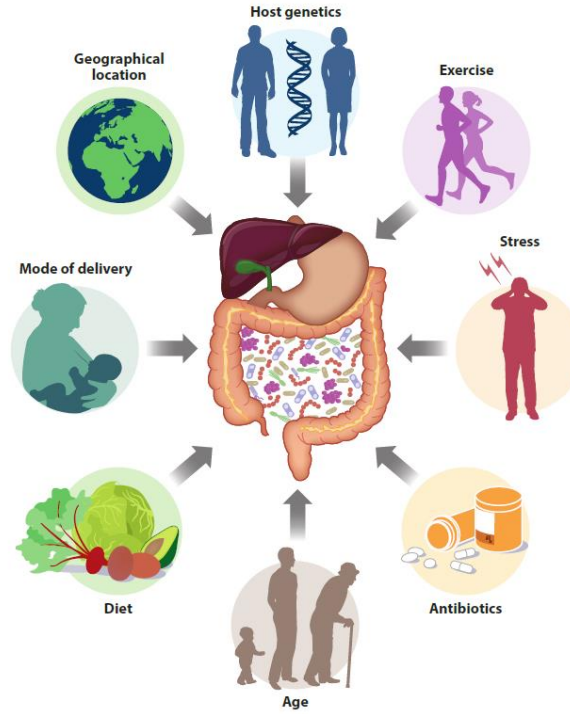
Annual Review of Pharmacology and Toxicology

Microbiota-Gut-Brain Axis: New Therapeutic Opportunities

Caitríona Long-Smith,[1] Kenneth J. O'Riordan,[1] Gerard Clarke,[1,2] Catherine Stanton,[1,3] Timothy G. Dinan,[1,2] and John F. Cryan[1,4]

2020. 60:477–502





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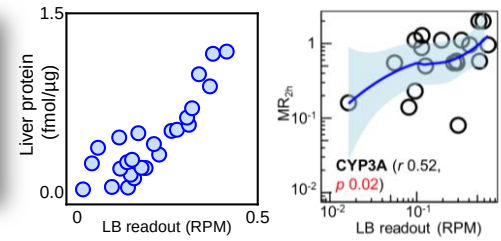
'Liquid Biopsy' for ADME: Abundance & Activity

Liquid Biopsy Enables Quantification of the Abundance and Interindividual Variability of Hepatic Enzymes and Transporters

Brahim Achour[1,*], Zubida M. Al-Majdoub[1], Agnieszka Grybos-Gajniak[2], Kristi Lea[3], Peter Kilford[4], Mian Zhang[4], David Knight[5], Jill Barber[1], Jeoffrey Schageman[3] and Amin Rostami-Hodjegan[1,6]



Liquid Biopsy for Patient Characterization in Cardiovascular Disease: Verification against Markers of Cytochrome P450 and P-Glycoprotein Activities

Brahim Achour[1,9,*,†], Pauline Gosselin[2,3,†], Jean Terrier[2,3,4], Yvonne Gloor[4], Zubida M. Al-Majdoub[1], Thomas M. Polasek[5,6,7], Youssef Daali[3,4,8], Amin Rostami-Hodjegan[1,5,†] and Jean-Luc Reny[2,3,†]

- In addition to several other enzymes, transporters and PD targets.

MR = metabolic ratio;
LB = liquid biopsy;
RPM = reads per million

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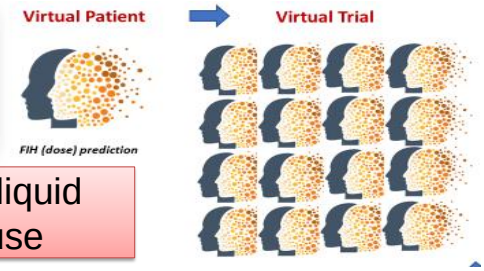
Liquid Biopsy: Quantitative Grade for Virtual Twins

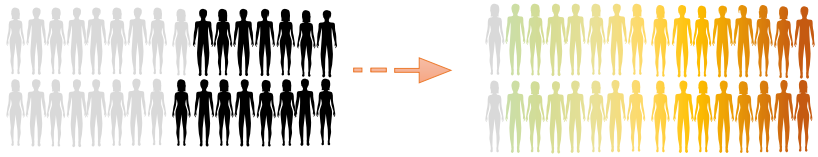
Liquid Biopsy Enables Quantification of the Abundance and Interindividual Variability of Hepatic Enzymes and Transporters

Brahim Achour[1,*], Zubida M. Al-Majdoub[1], Agnieszka Grybos-Gajniak[2], Kristi Lea[3], Peter Kilford[4], Mian Zhang[4], David Knight[5], Jill Barber[1], Jeoffrey Schageman[3] and Amin Rostami-Hodjegan[1,6]



Traditional cancer diagnostic tests

Proposed liquid biopsy use



Is the disease marker expressed?

- No
- Yes

Graded

- High expression
- Medium expression
- Low expression

'Liquid Biopsy'

A Game Changer for Handling Variability

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Going Forward: PD Variability using Liquid Biopsy

PK Variability *versus* PD Variability

- Can we address PD variability using liquid biopsy?
- 362 PD targets in plasma (23 as protein in liver), enzymes/receptors involved in inflammation, cancer, immune response and cirrhosis
- Established correlations for several PD targets: biomarkers of change in response to drugs & disease progression

The Link Between Pharmacodynamics and Physiologically Based Pharmacokinetic Models

V Perera[1], MA Elmeliegy[1], G Rao[1] and A Forrest[1]

Response to "The Link Between Pharmacodynamics and Physiologically Based Pharmacokinetic Models"

A Rostami-Hodjegan[1,2]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 93 NUMBER 2 | FEBRUARY 2013

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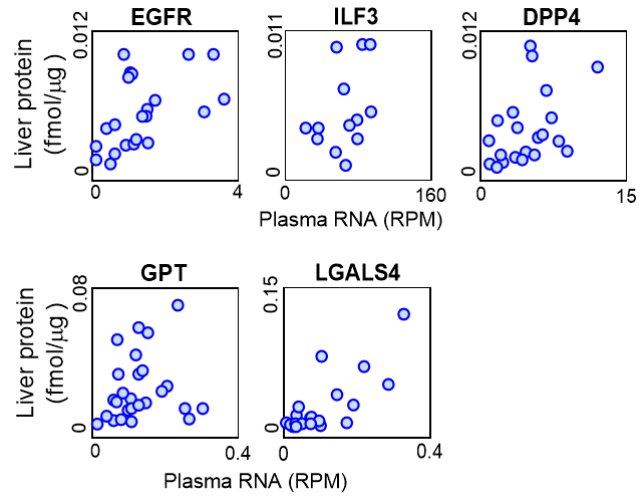
Correlations with Tissue Expression

PD/Disease Targets

- 362 PD targets in plasma:
- **81 FDA-approved drug targets**
- 202 with established link with disease
- **Examples:** EGFR (drug target of anti-cancer TKIs and mABs); DPP4 (target of the anti-diabetics gliptins); GPT (marker of liver function); LGALS4 (cancer prognosis marker)



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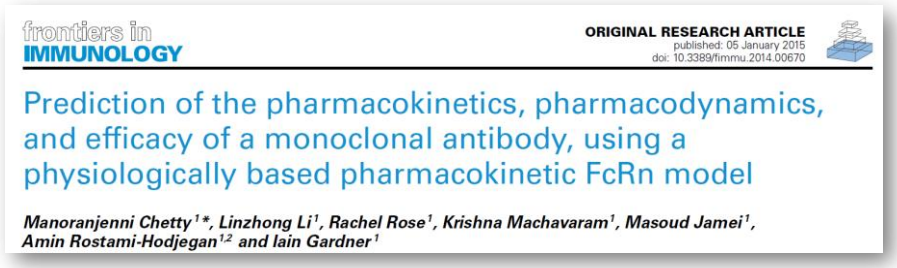

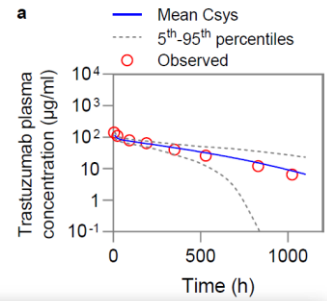

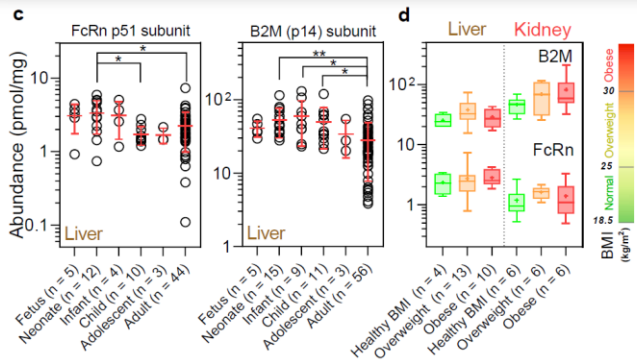

Toward Systems-Informed Models for Biologics Disposition: Covariates of the Abundance of the Neonatal Fc Receptor (FcRn) in Human Tissues and Implications for Pharmacokinetic Modelling

Jill Barber, Zubida M. Al-Majdoub, Narciso Couto, Martyn Howard, Yasmine Elmorsi, Daniel Scotcher, Naved Alizai, Saskia de Wildt, Felix Stader, Armin Sepp, Amin Rostami-Hodjegan, Brahim Achour

Under Review for Publication in 2023

Hepatic & Renal FcRn Expression in Overweight/Obese Donors > Donors with Normal BMI

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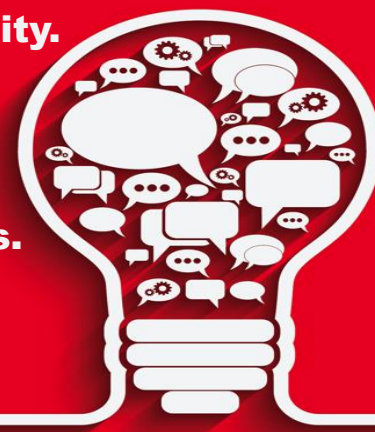
Conclusion:

- Systems Approach Can Help with (*a priori*) Dose Adjustment in Obesity.
- However, Systems Data Are Required to Build Robust Population Models and Apply to Large Sets of Verification Cases.



Thanks for Listening

Questions?

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