About OMICS Group

OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

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OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

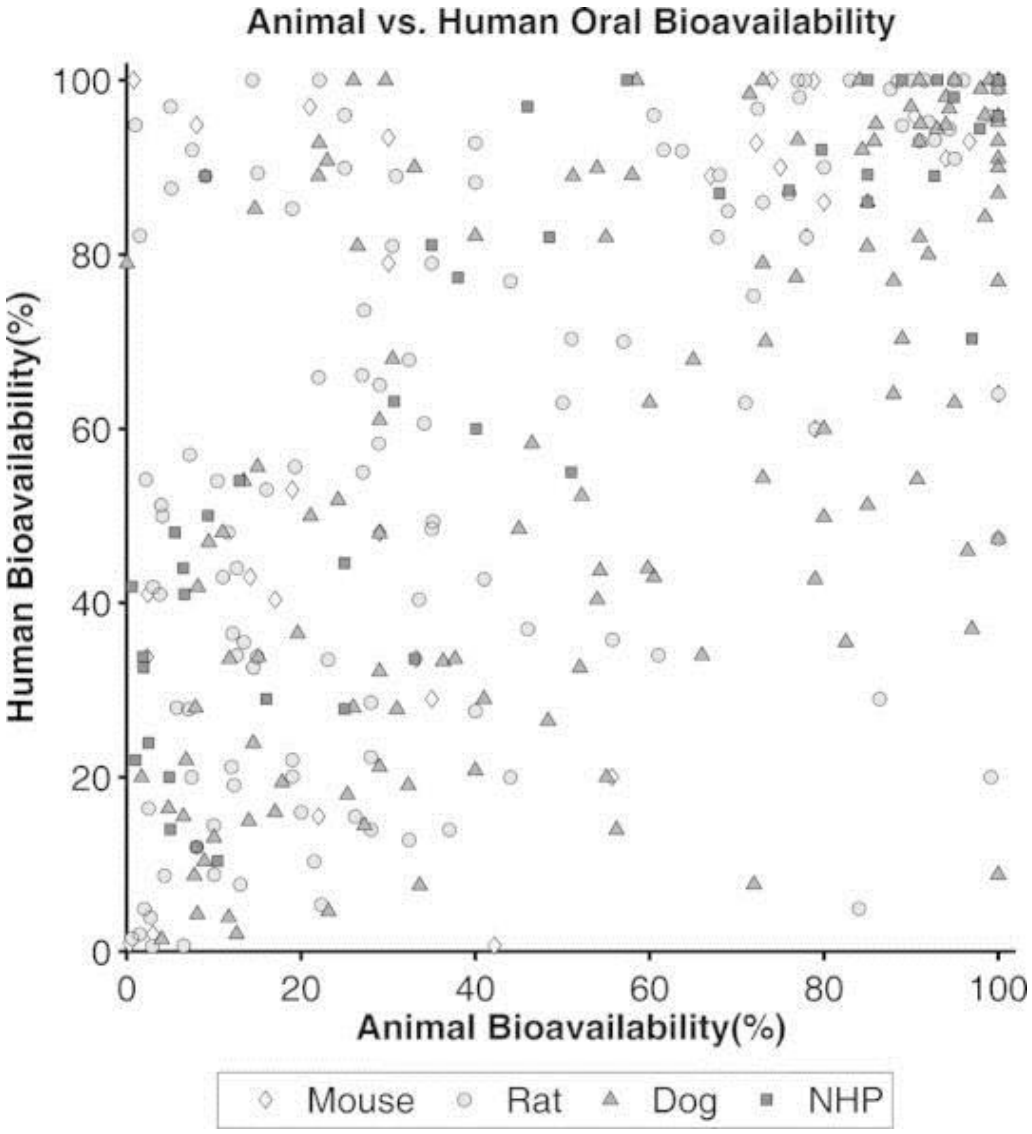
OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Prediction of *in-vivo* permeability, solubility, BCS-classing, food interactions, fraction absorbed and oral bioavailability using new *in-silico* methods and algorithms

Urban Fagerholm
Associate Professor
CEO at PROSILICO, Sweden
urban.fagerholm@prosilico.com
http://prosilico.com/

How well are fraction absorbed, oral bioavailability, solubility/dissolution, food interactions and BCS-class in humans *in-vivo* predicted using lab methods?

BIOAVAILABILITY



Musther et al. *Eur J Pharm. Sci., 2014*

BIOAVAILABILITY

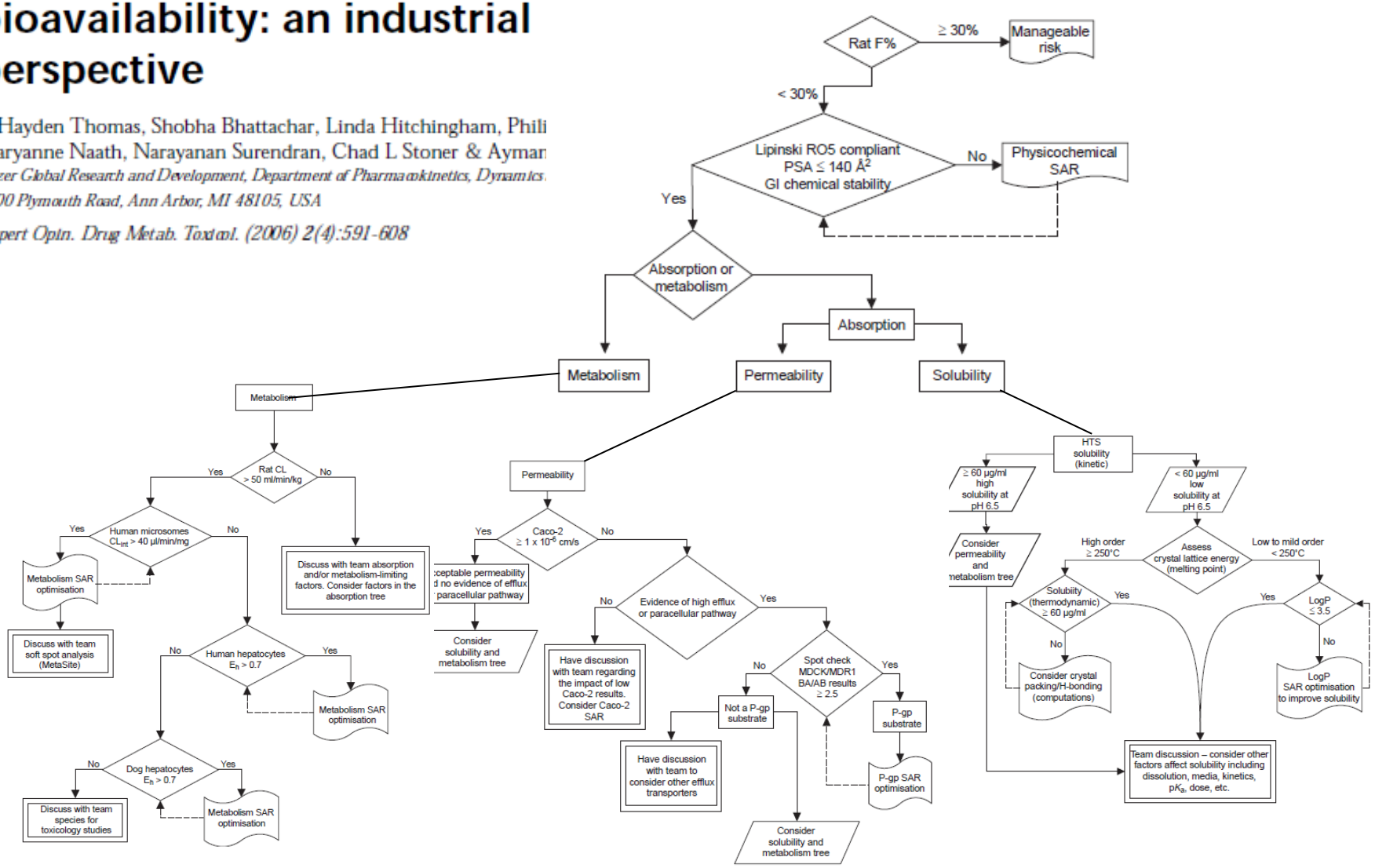
In-vitro to in-vivo

?

The road map to oral bioavailability: an industrial perspective

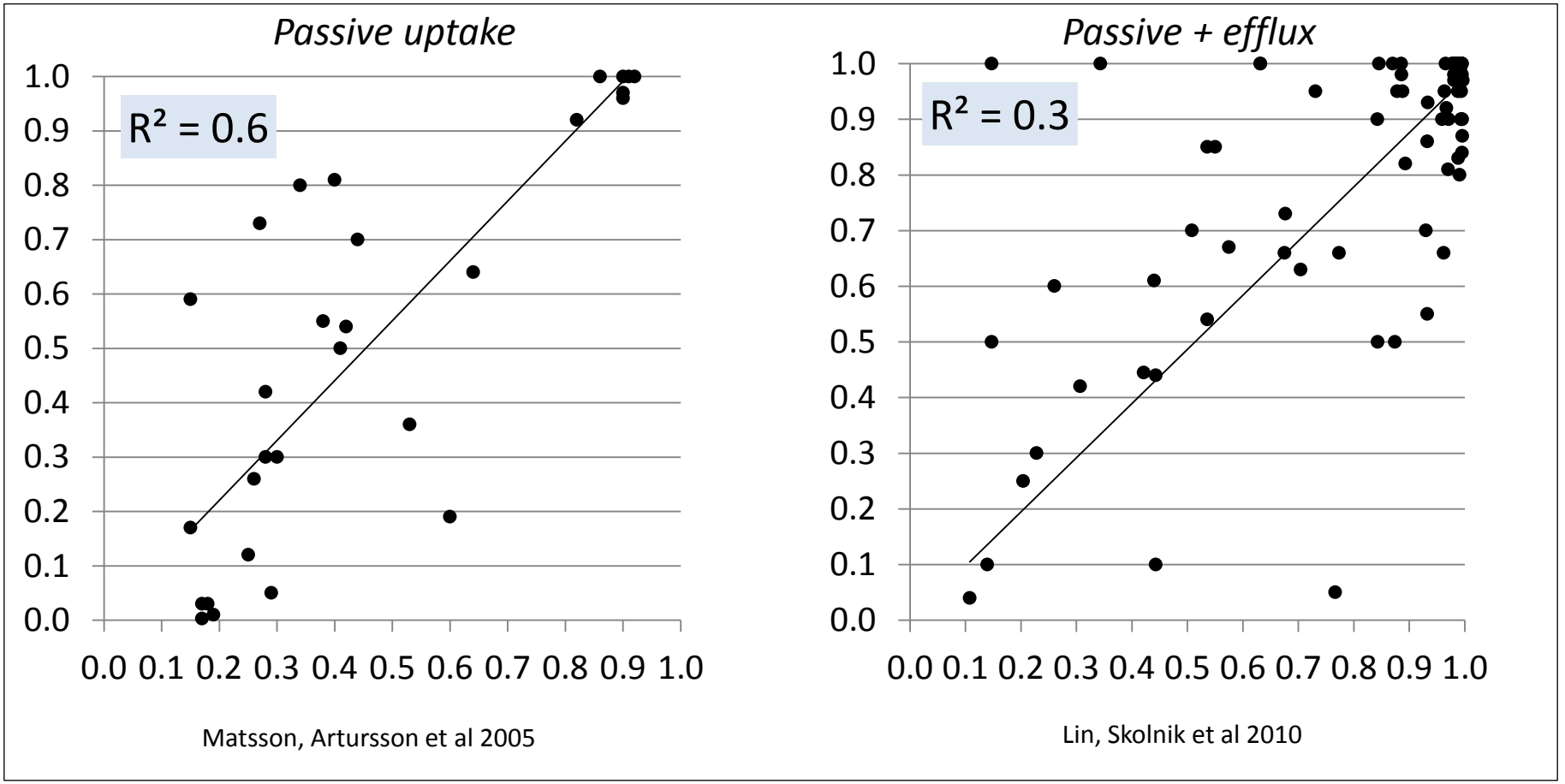
V Hayden Thomas, Shobha Bhattachar, Linda Hitchingham, Phili
Maryanne Naath, Narayanan Surendran, Chad L Stoner & Ayman
Pfizer Global Research and Development, Department of Pharmacokinetics, Dynamics
2800 Plymouth Road, Ann Arbor, MI 48105, USA

Expert Opin. Drug Metab. Toxicol. (2006) 2(4):591-608

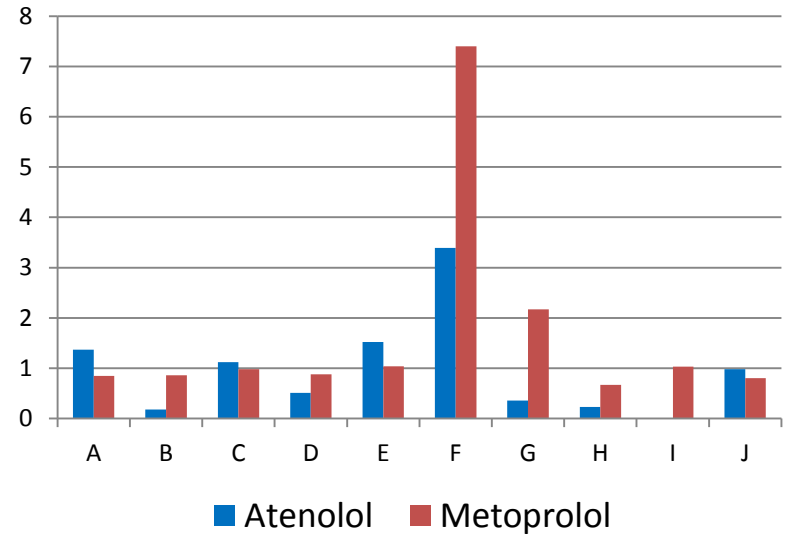


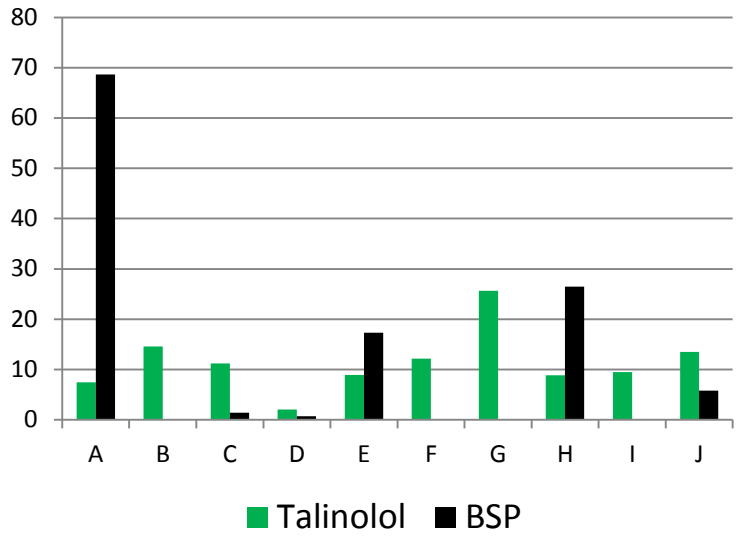
FRACTION ABSORBED

Caco-2



Caco-2 – issues with efflux



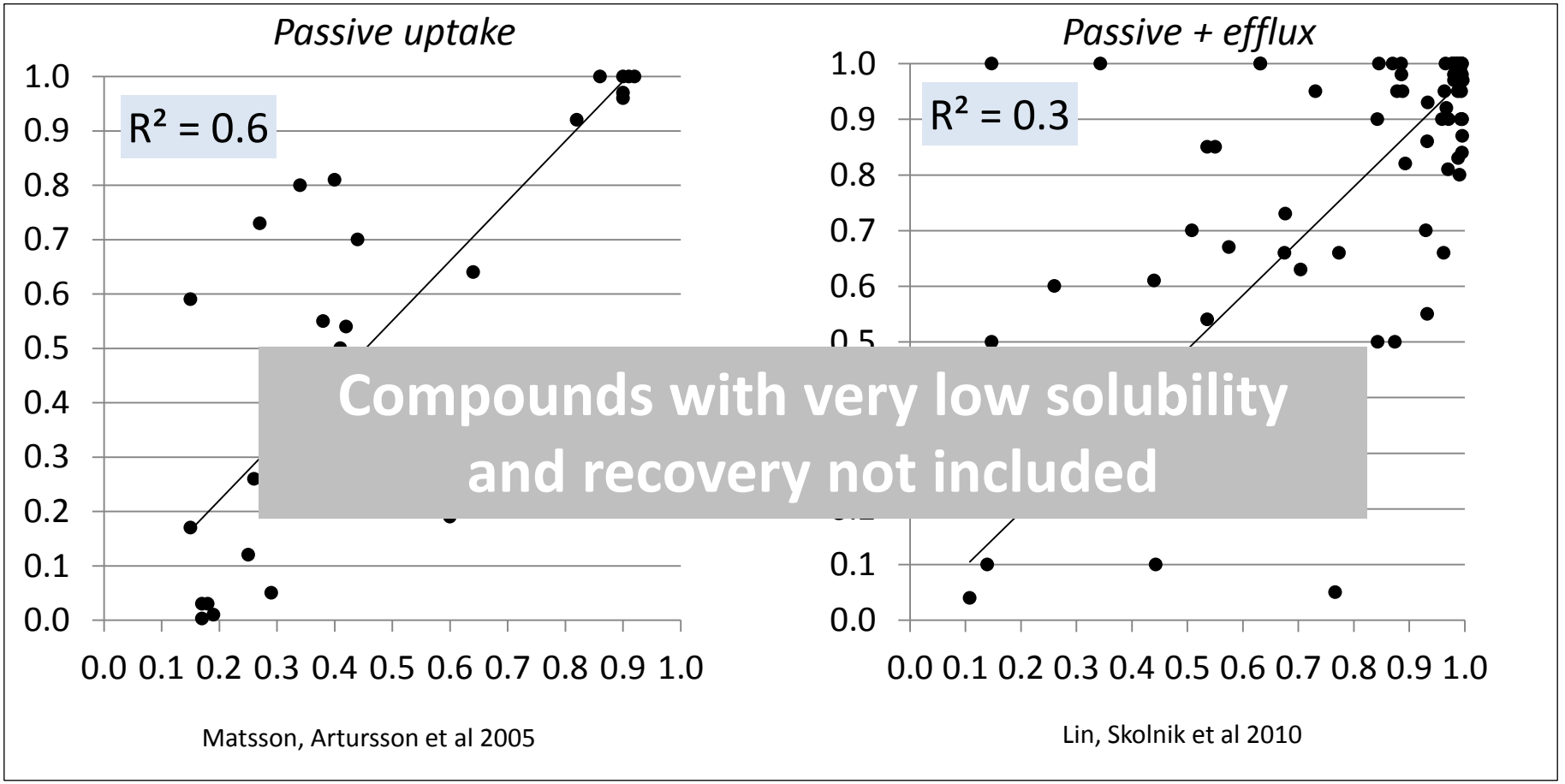


11 to 93-fold difference between labs

Poor reproducibility

Ungell et al

Caco-2 – issues with low solubility and recovery



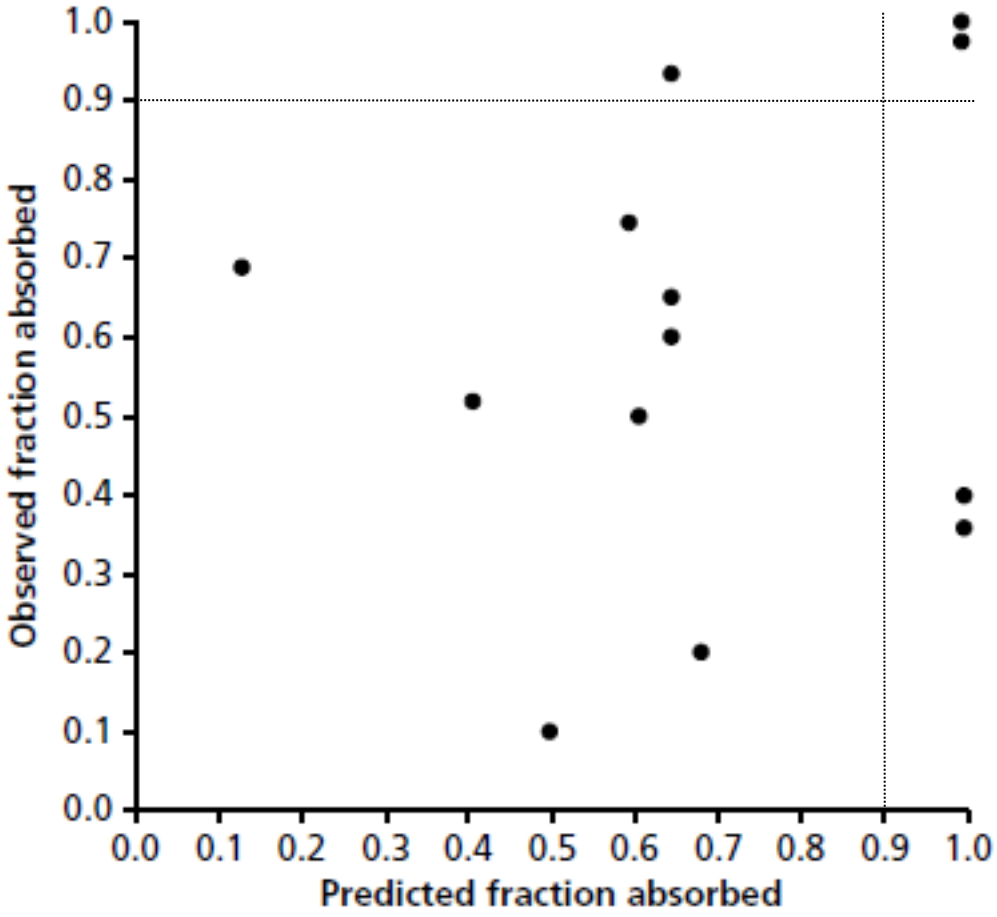
Caco-2 – issues with low solubility and recovery

”Estimated that 40% of all newly developed drugs are poorly soluble or insoluble in water.” / Naseem et al. *Int. J. Pharm*., 2004.

“1/8 of Novartis compounds (44% of low solubility cmpds) were subject to low recovery (<30%) in Caco-2 screen”.

“Poor recovery (due to nonspecific drug binding to plastic devices and cells; in particular for lipophilic compounds) is often seen and also neglected in data interpretation.” / Skolnik et al *J Ph Sci* 2010.

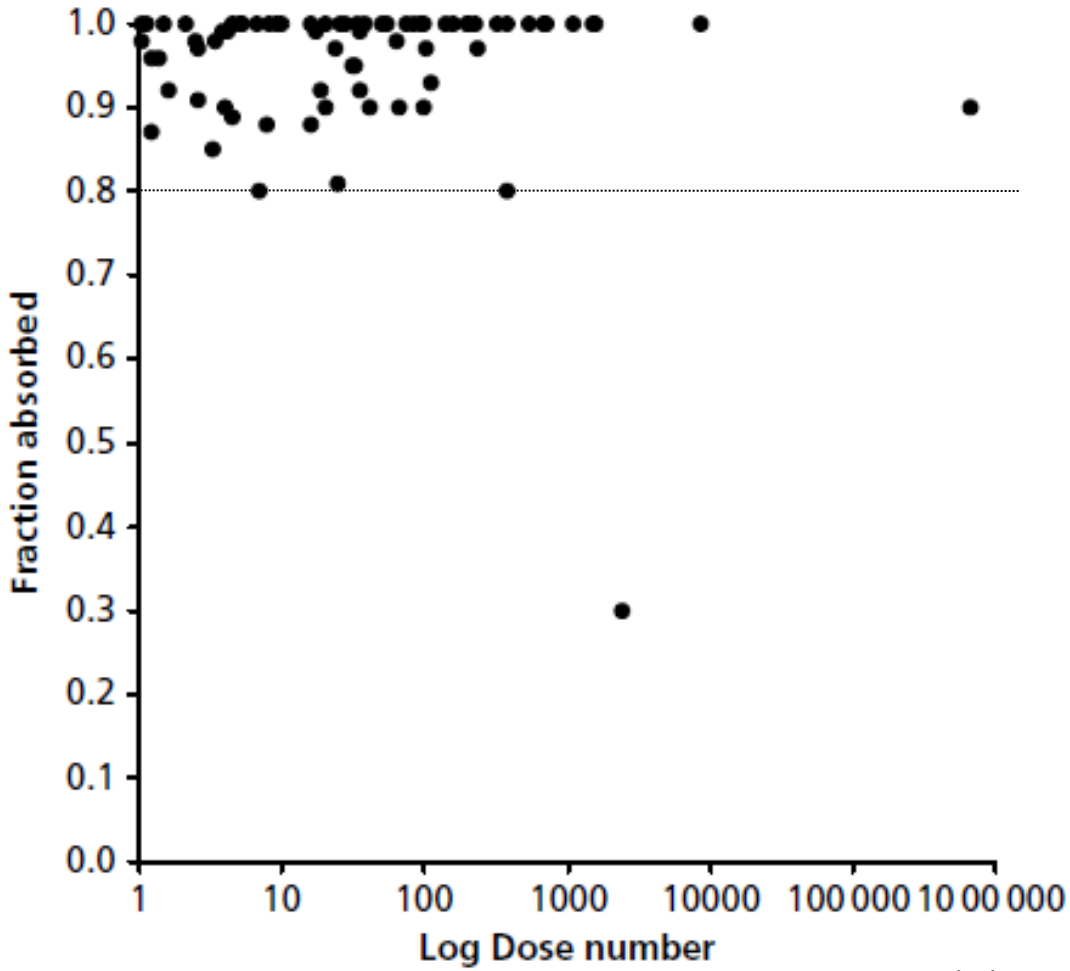
Human intestinal in-vivo Pe *(Loc-I-Gut measurements)*



Fagerholm, J Pharm Pharmacol 2007

IN-VIVO SOLUBILITY/DISSOLUTION

In-vitro aq. solubility *(Dose number=highest GI conc. / solubility)*



Fagerholm, J Pharm Pharmacol 2007

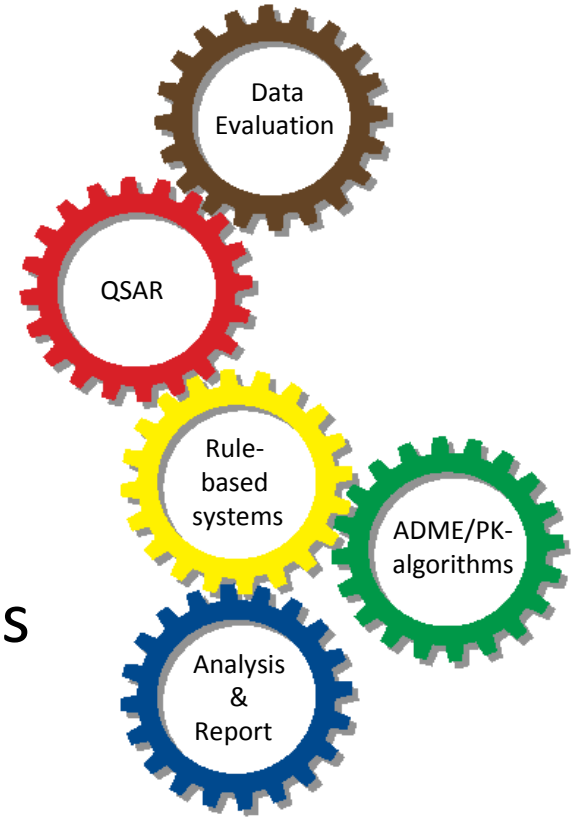
BCS-CLASSIFICATION

- Difficult to predict based on *in-vitro* and *in-vivo* permeability unless it is very low or very high
- Difficult to predict based on *in-vitro* solubility (underprediction potential when low solubility)
- Many cases of *in-vitro* BCS II-compounds belonging to *in-vivo* BCS I

Yazdanian et al, Pharm Res, 2004
Fagerholm, J Pharm Pharmacol 2007

PROSILICO

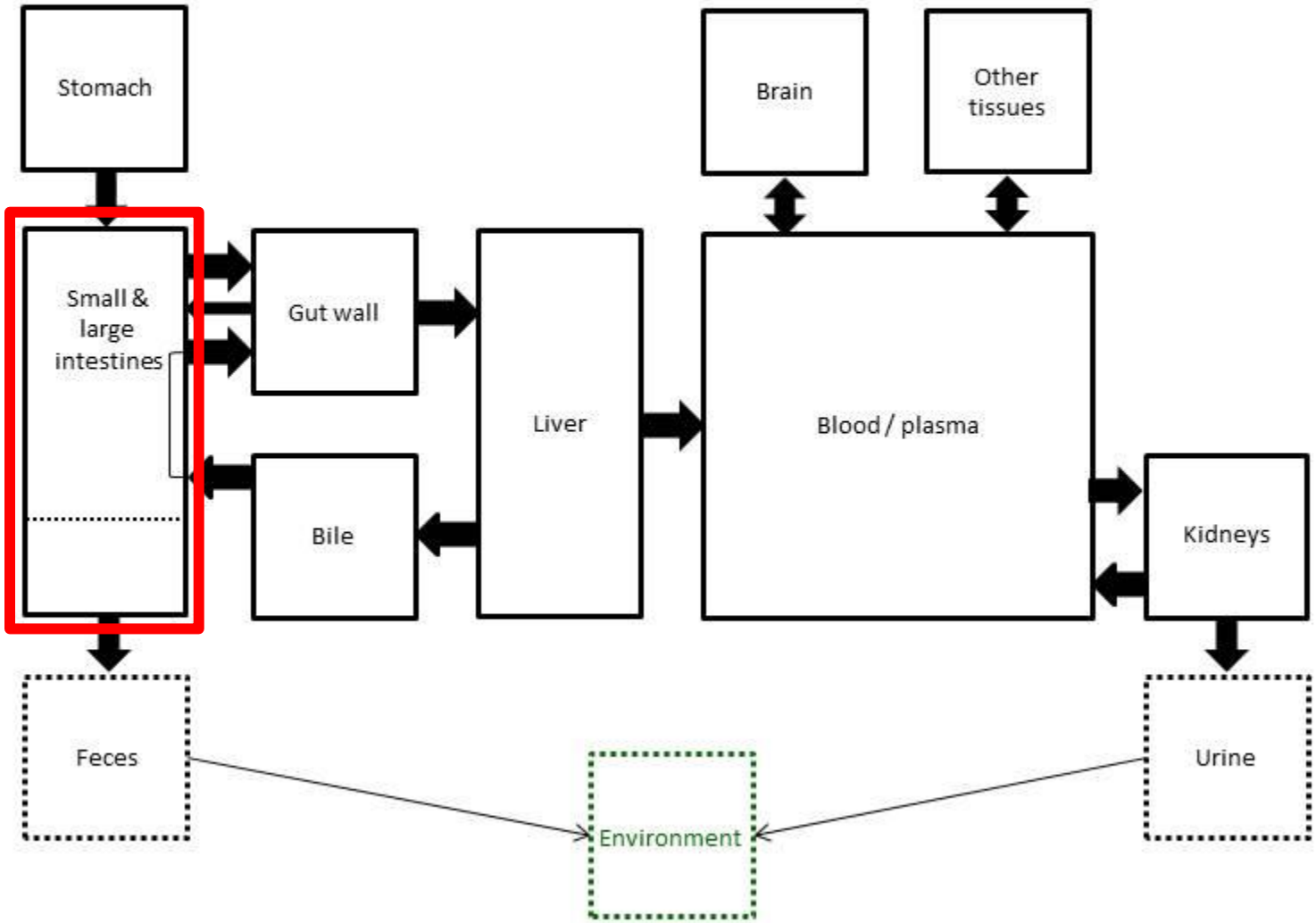
LEADER IN ADMET-PREDICTIONS



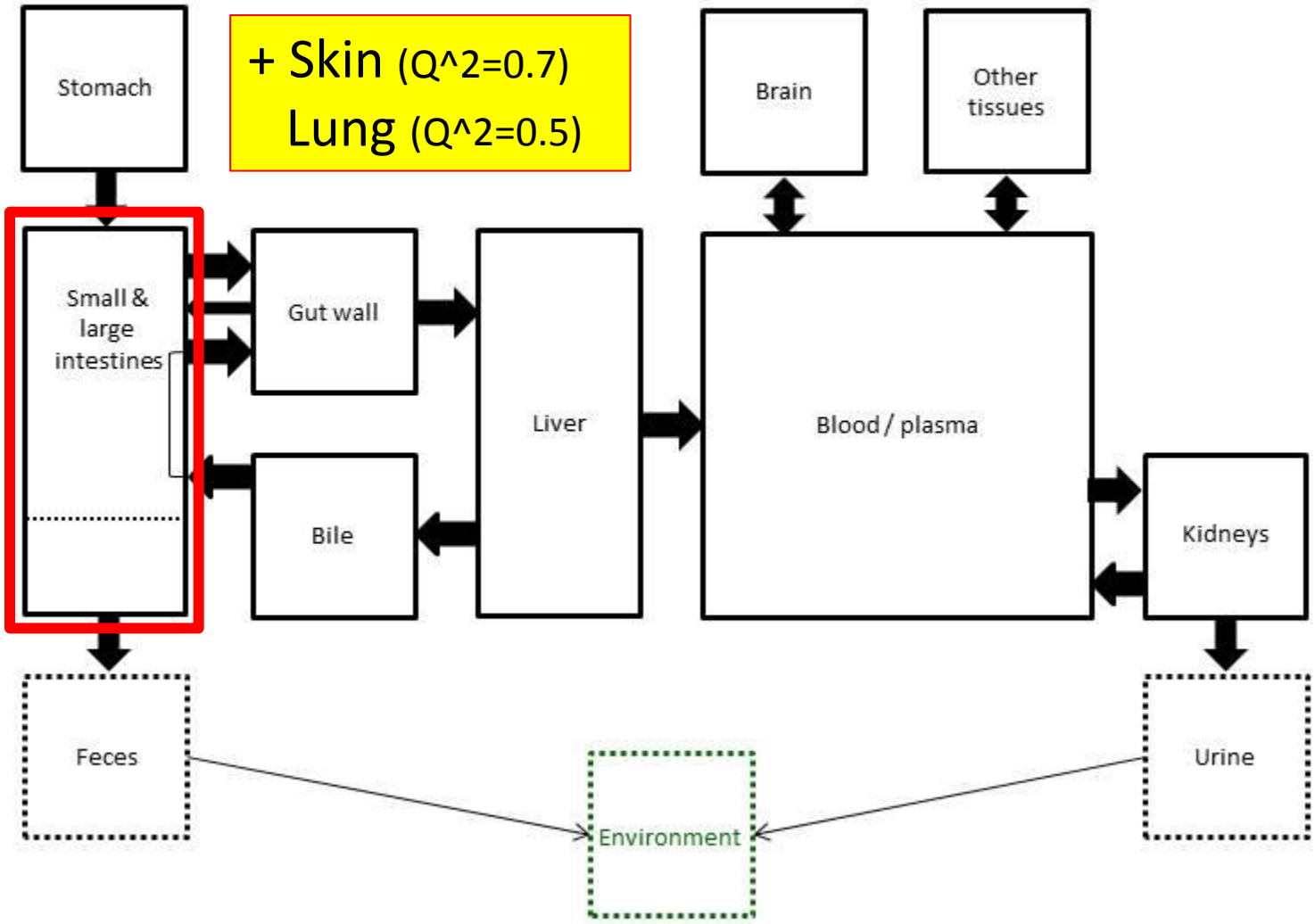
- New, unique, true, validated *in-silico* methods and algorithms for prediction of human and animal ADME/PK
- Directly from molecular structure to *in-vivo*

  O=C2/N=C(\Nc1n(cnc12)COCCO)N
- Outperforms lab methods

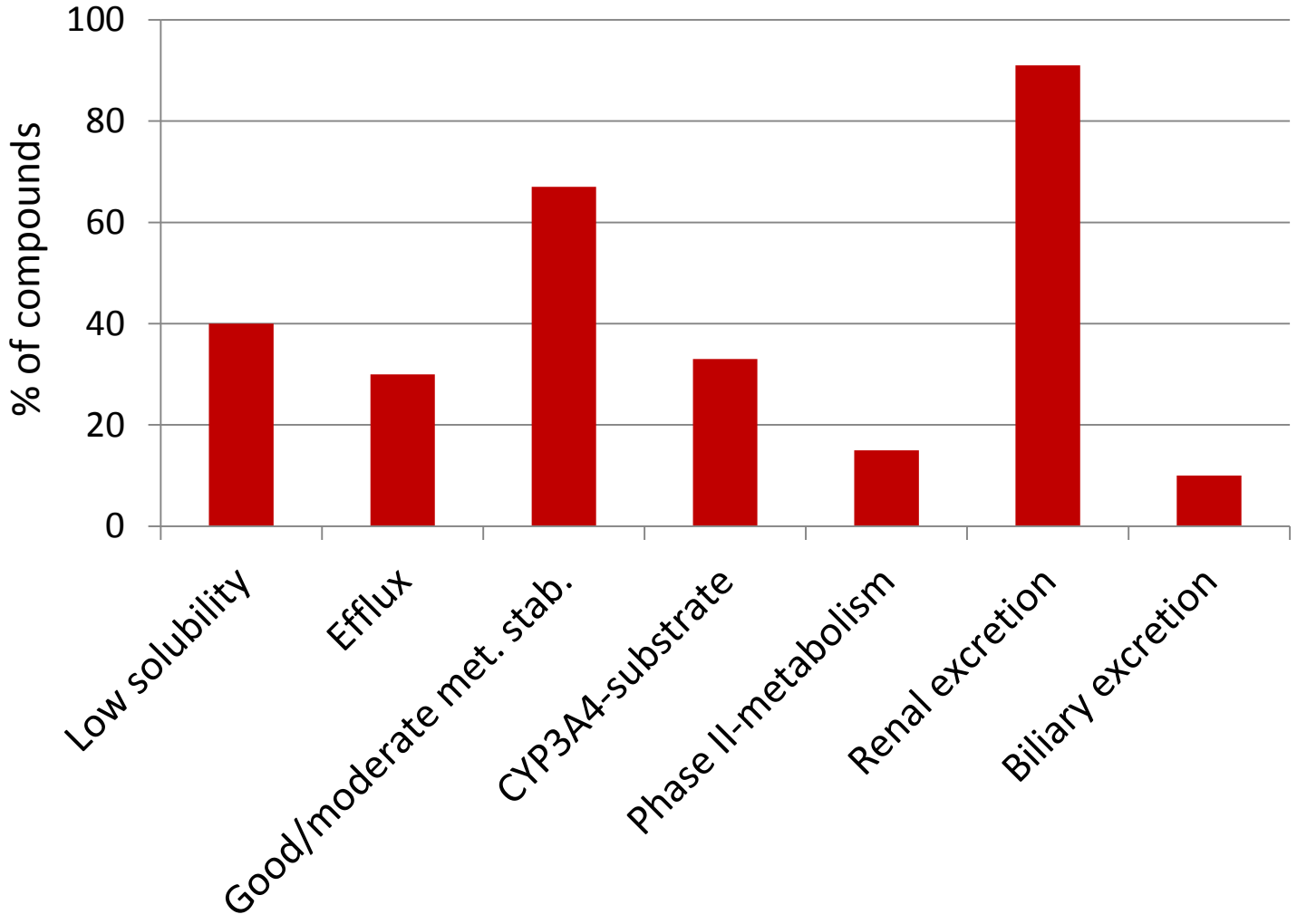
NEW, UNIQUE PBPK-MODEL



NEW, UNIQUE PBPK-MODEL



HANDLES CHALLENGING COMPOUNDS



PERFORMANCE

- >3500 human predictions
- 1.5-fold median error
  Animal models ~1.5-3 fold median errors
- Q^2 = 0.4 to 0.8 (true predictions)
- Class models 70 to 86 % correct classing
- 11/11 successful external validations by customers

POSITIONING

BEST-IN-TESTS – *vs in-vitro*

AUCpo (systemic exposure after po adm.)

		Mean error	Median error	%<2-fold error	%<3-fold error	%<10-fold error	n
PROSILICO™	*in-silico* + new algorithms	6	3	36	50	85	151
PHRMA	*in-vitro*-based	8;11	7;7.5	11;21	28;30	61;64	18;33

PHRMA CPCDC Initiative on Predictive Models of Human Pharmacokinetics, Part 5: Prediction of Plasma Concentration–Time Profiles in Human by Using the Physiologically-Based Pharmacokinetic Modeling Approach

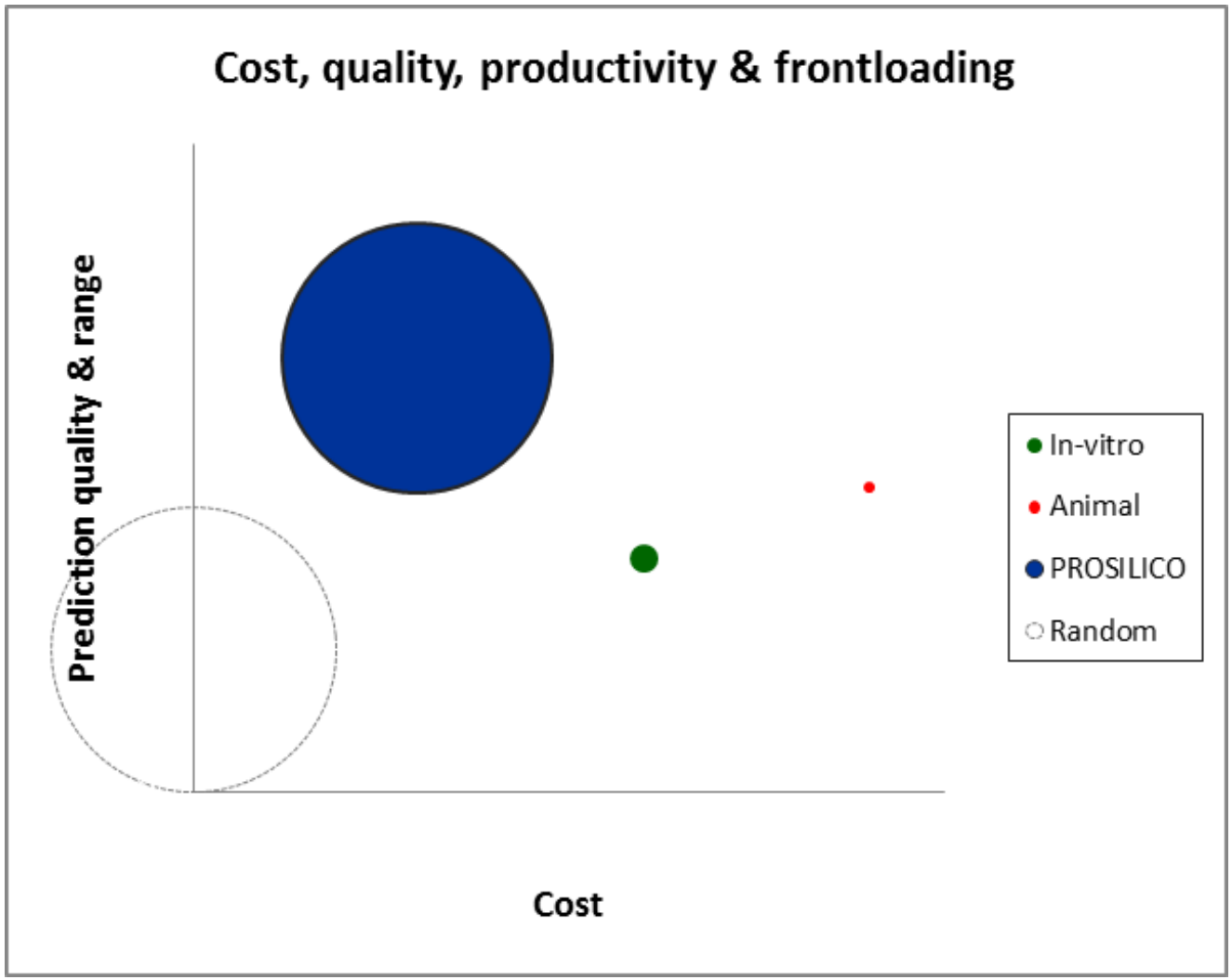
PATRICK POULIN,[1] RHYS D. O. JONES,[2] HANNAH M. JONES,[3] CHRISTOPHER R. GIBSON,[4] MALCOLM ROWLAND,[5] JENNY Y. CHIEN,[6] BARBARA J. RING,[7] KIMBERLY K. ADKISON,[8] M. SHERRY KU,[9] HANDAN HE,[10] RAGINI VUPPUGALLA,[11] PUNIT MARATHE,[11] VOLKER FISCHER,[12] SANDEEP DUTTA,[13] VIKASH K. SINHA,[14] THORIR BJÖRNSSON,[15] THIERRY LAVÉ,[16] JAMES W. T. YATES[2]

JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 100, NO. 10, OCTOBER 2011

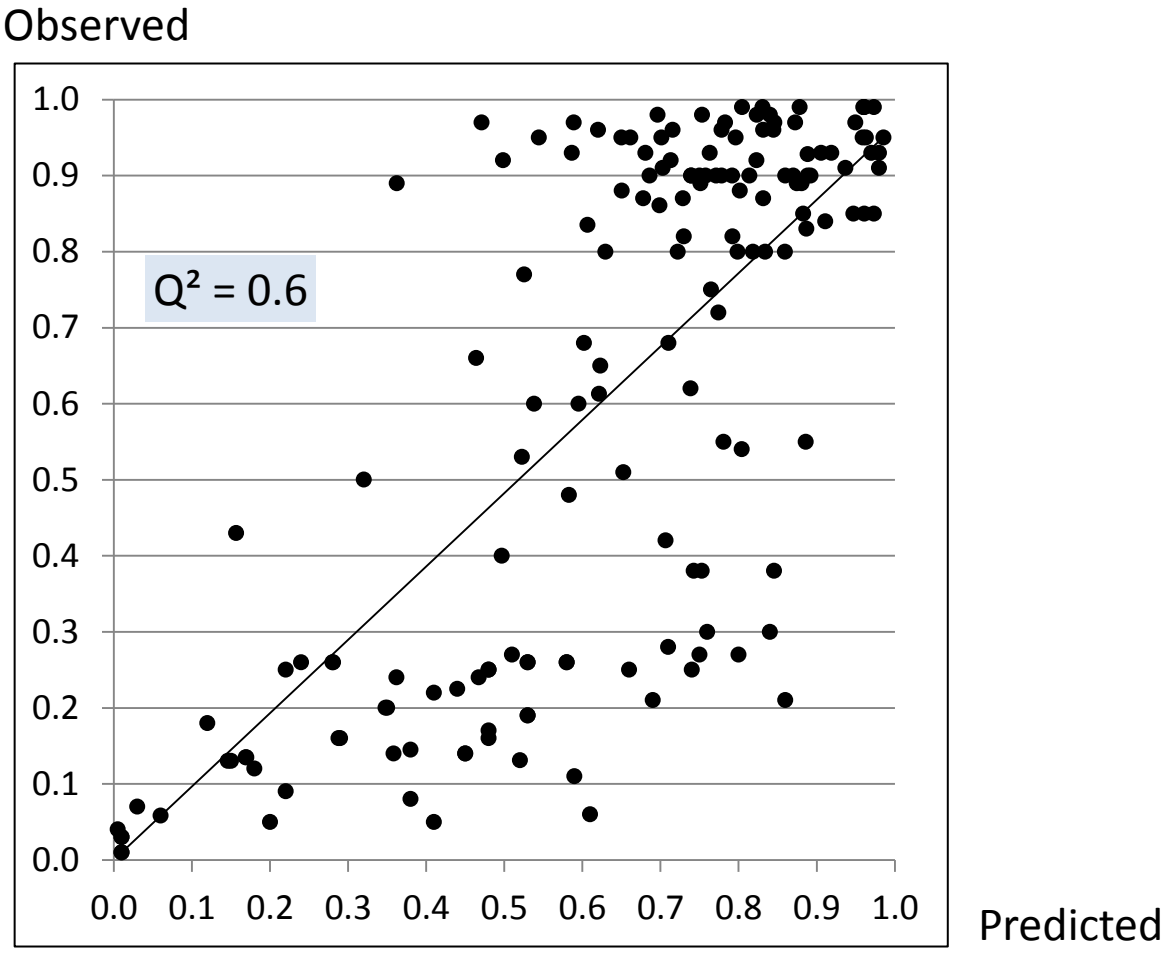
BEST-IN-TESTS – *vs allometry*

AUCpo (F/CL)
9-fold smaller prediction error range than allometry

CL
2800-fold smaller prediction error range than allometry

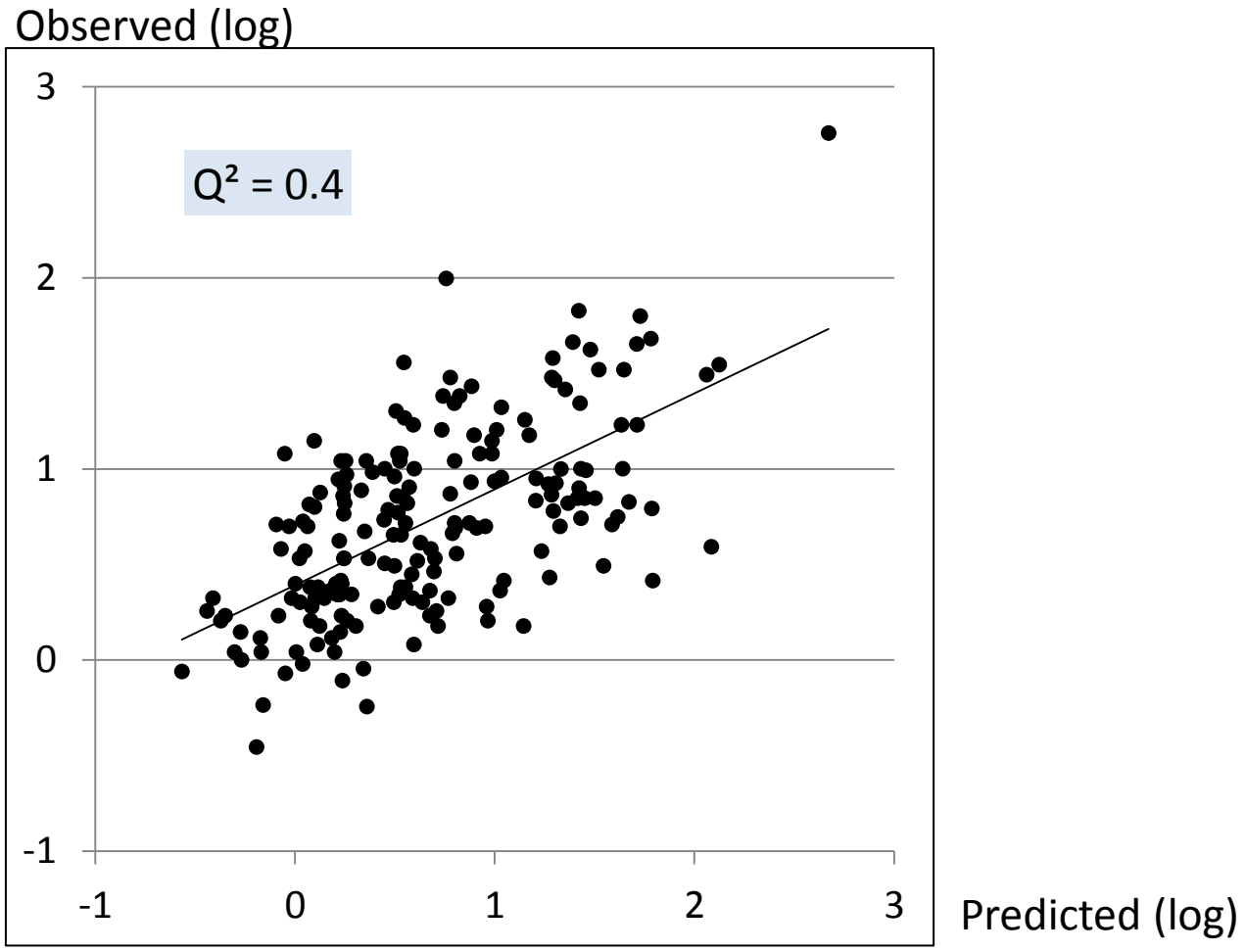

Cost, quality, productivity & frontloading
Prediction quality & range
Cost
In-vitro
Animal
PROSILICO
Random

BIOAVAILABILITY



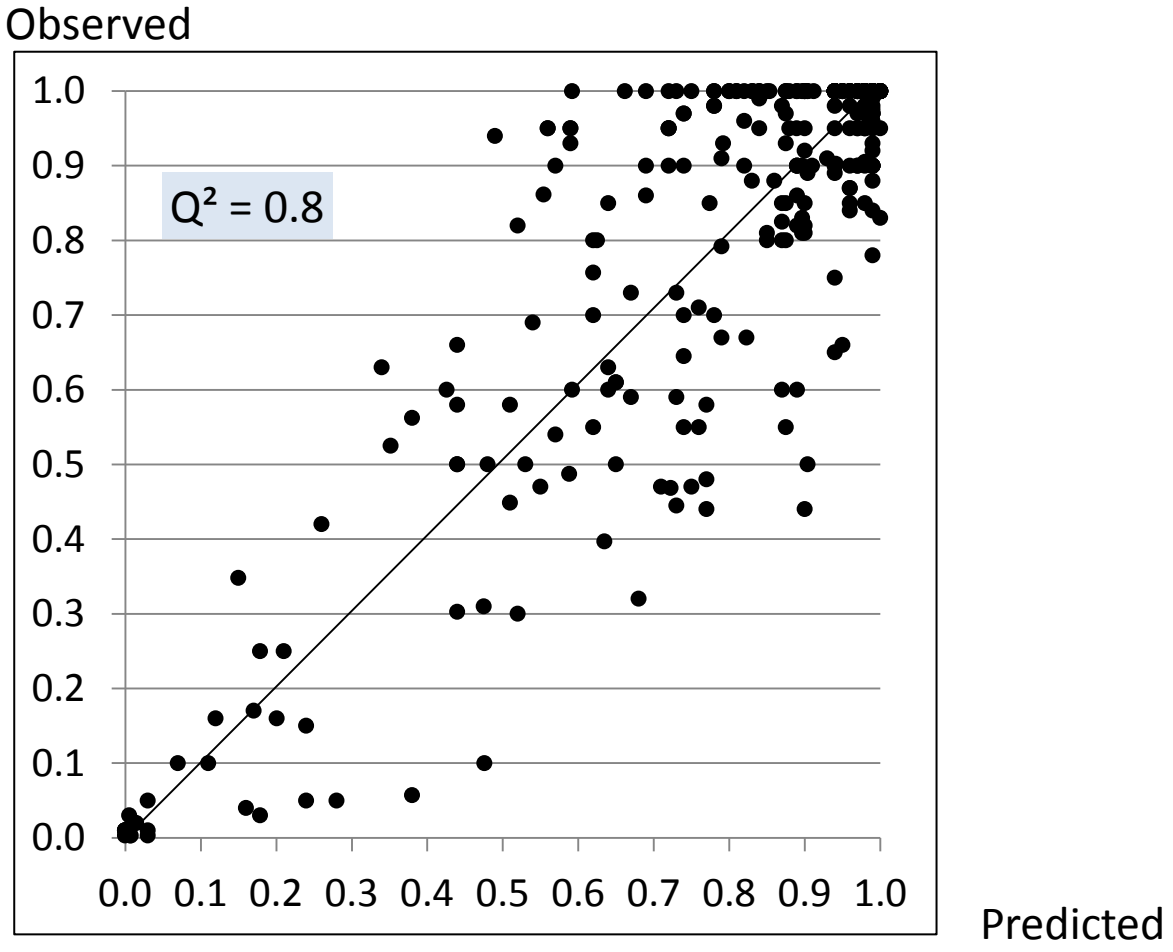
Delivered together with confidence intervals

t½



Delivered together with confidence intervals

FRACTION ABSORBED



Including very low solubility and strong efflux cmpds

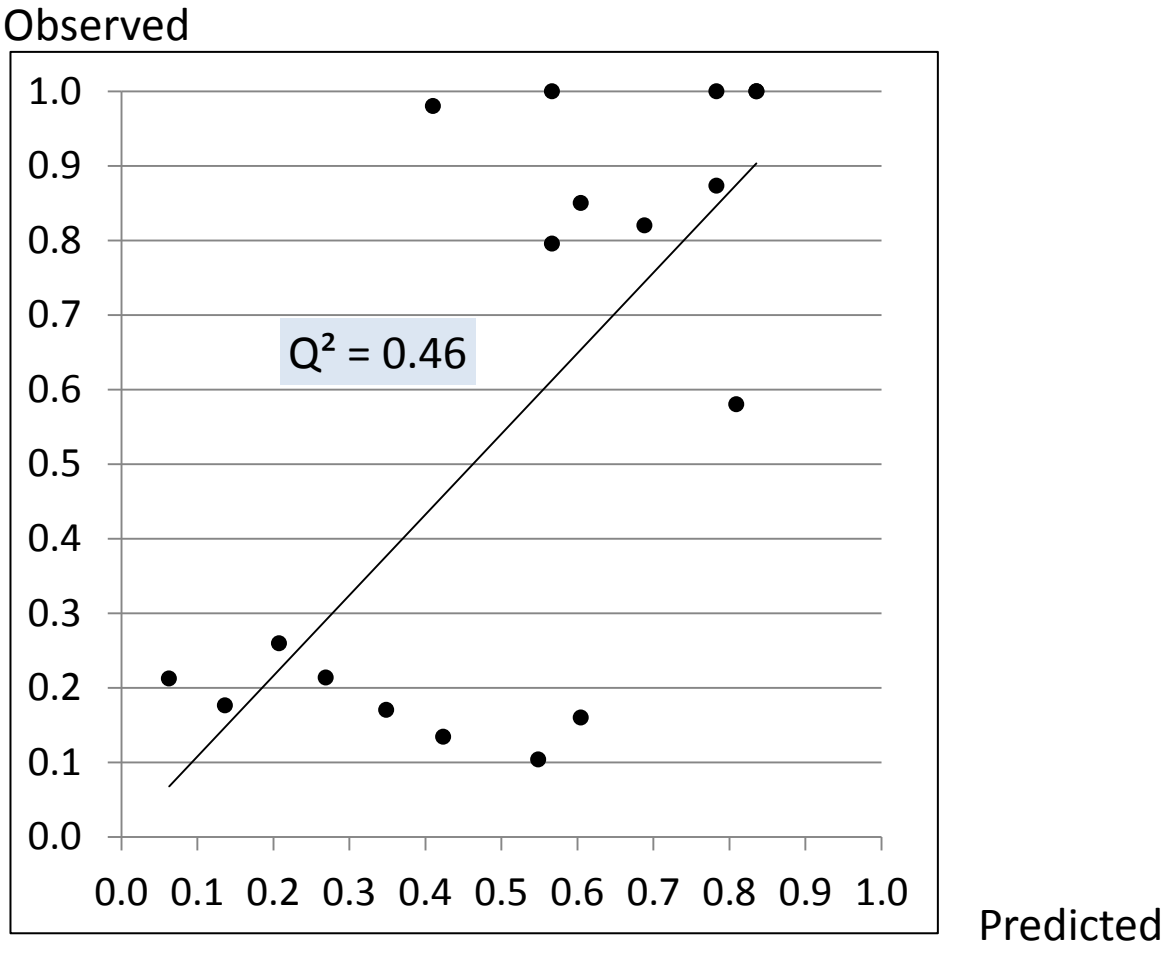
Excluding antibiotics, prodrugs and MW>700

PRODRUG ABSORPTION

Prodrugs	fraction absorbed			
	Intact prodrug		Metabolite drug	
	predicted	observed	predicted	observed
Bambuterol	0,57	0,50	0,57	0,50
Midodrine	0,47-1,00	0,93	0,47-1,00	0,93
Mycophenolate mofetil	few %	few %	0,69	0,90
AZD3582 (naproxcinod)	0,70	0,20-0,90	0,90	0,94
Ximelagatran	0,15-0,55	0,40-0,70	-	-
Metabolites				
Terbutaline	-	-	0,78	0,73
Desglymidodrine	-	-	0,84	>0,5
Mycophenolic acid	-	-	0,69	>0,4
Naproxen	-	-	0,91	0,99
Melagatran	-	-	0,08-0,33	0,1-0,2

*added *in-vitro* GI stab data

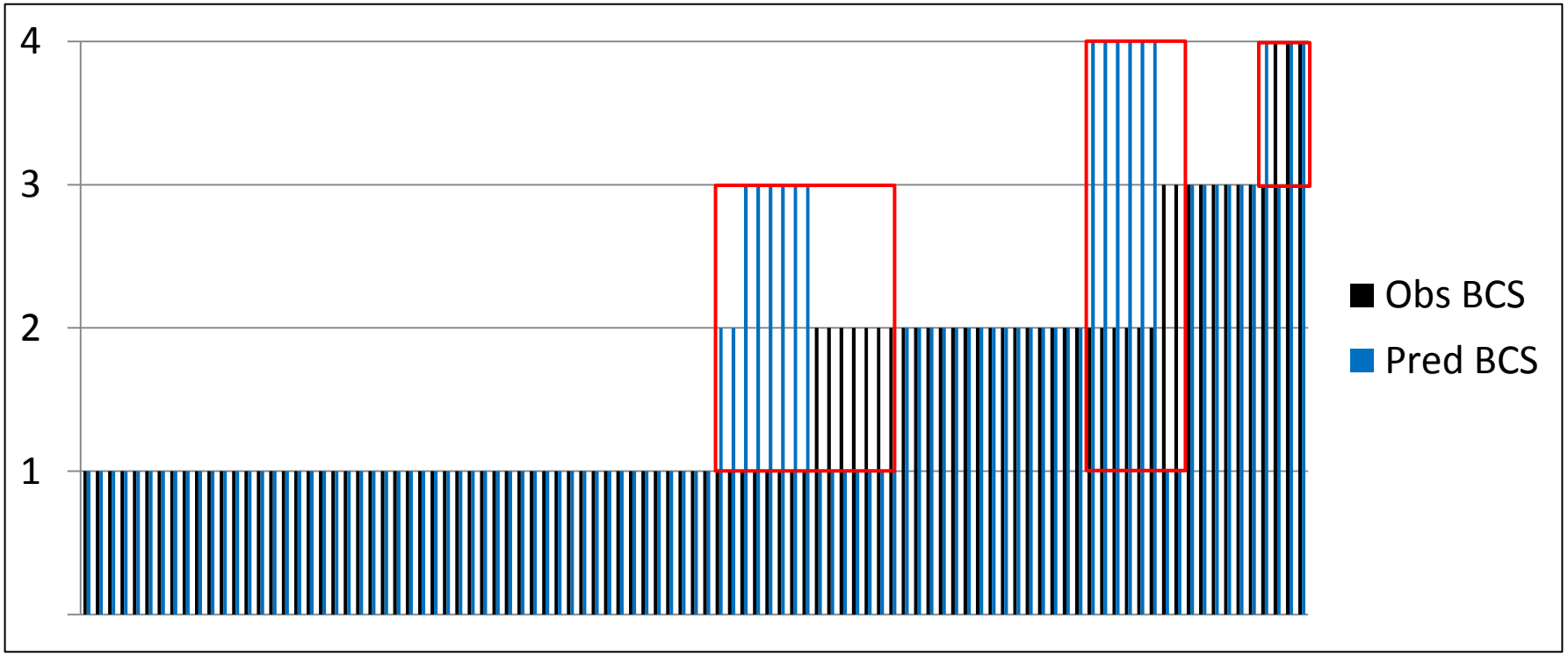
FRACTION ABSORBED FROM COLON



BCS-CLASSING OF COMPOUNDS WITH VERY LOW SOLUBILITY

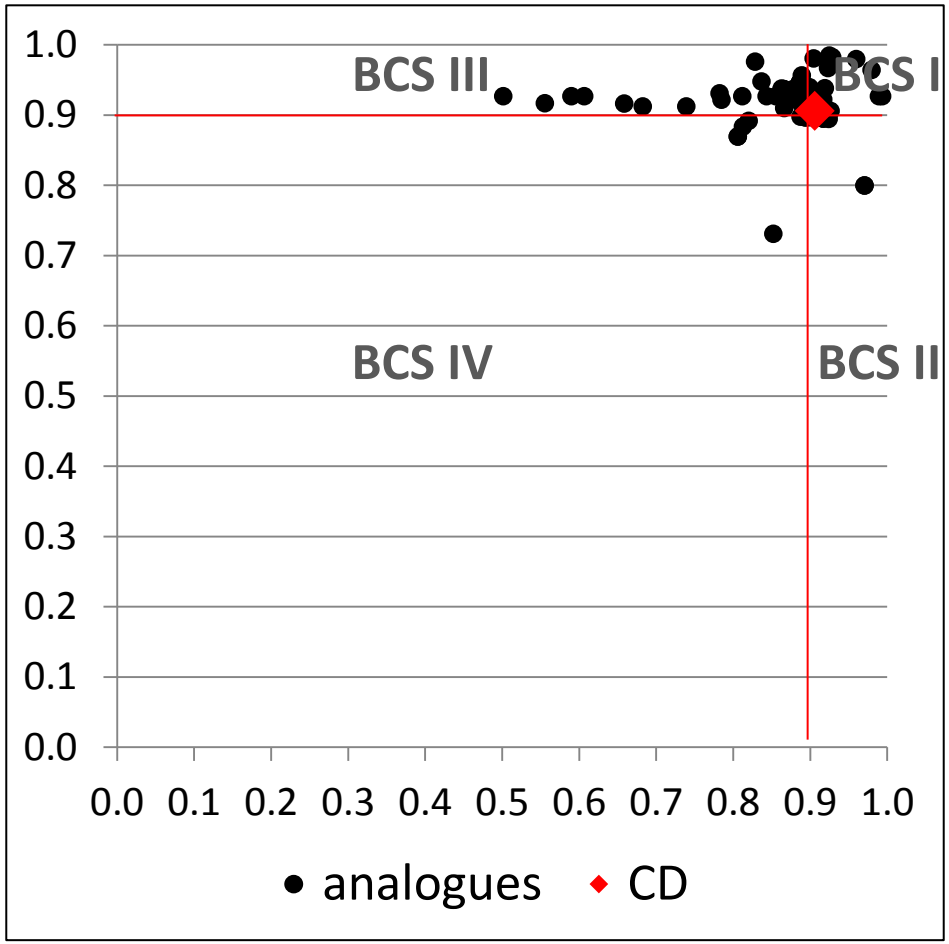
100 most insoluble cmpds with available absorption data
incl. atavaquone, danazol, dipyramidole, felodipine, itraconazole, griseofulvin, lovastatin

74 % correct BCS-classing (12 % abs. error for fa)



UPTAKE OF 275 VIRTUAL KINASE INHIBITOR ANALOGUES

Predicted *in-vivo* solubility/dissolution-based maximum uptake



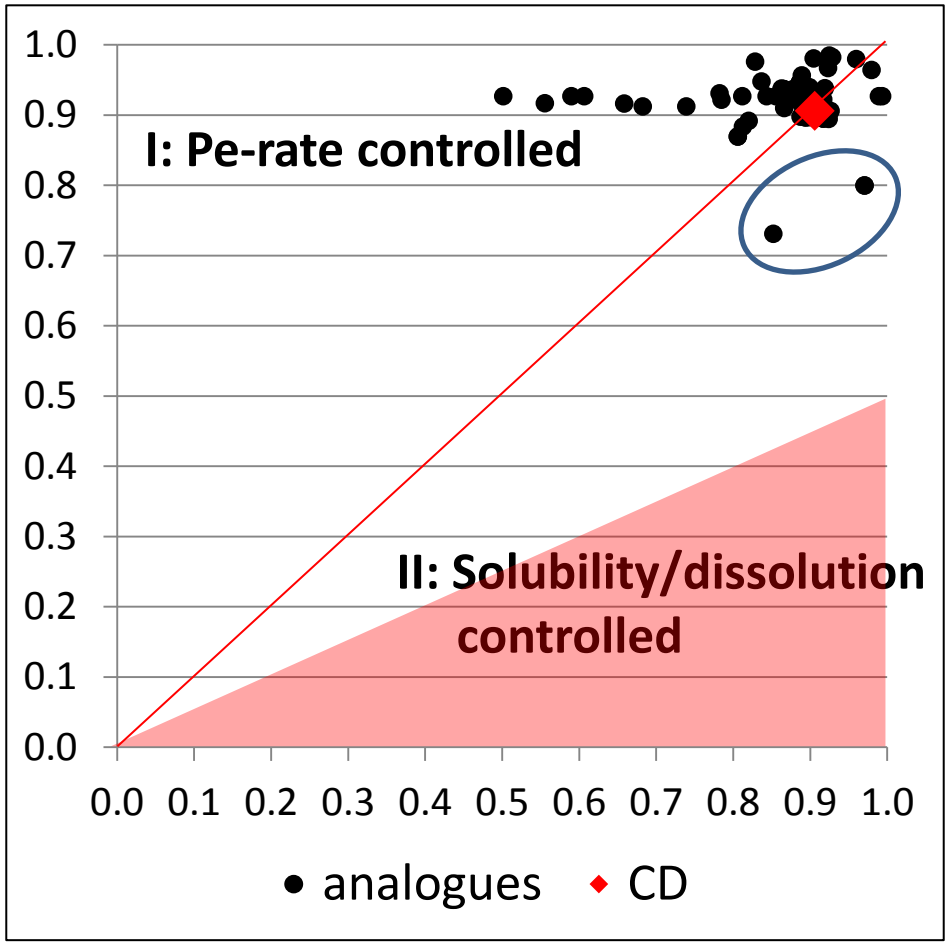
Predicted *in-vivo* permeability-based uptake

in collaboration with

CHEMNOTIA

A DIFFERENT BCS-PERSPECTIVE

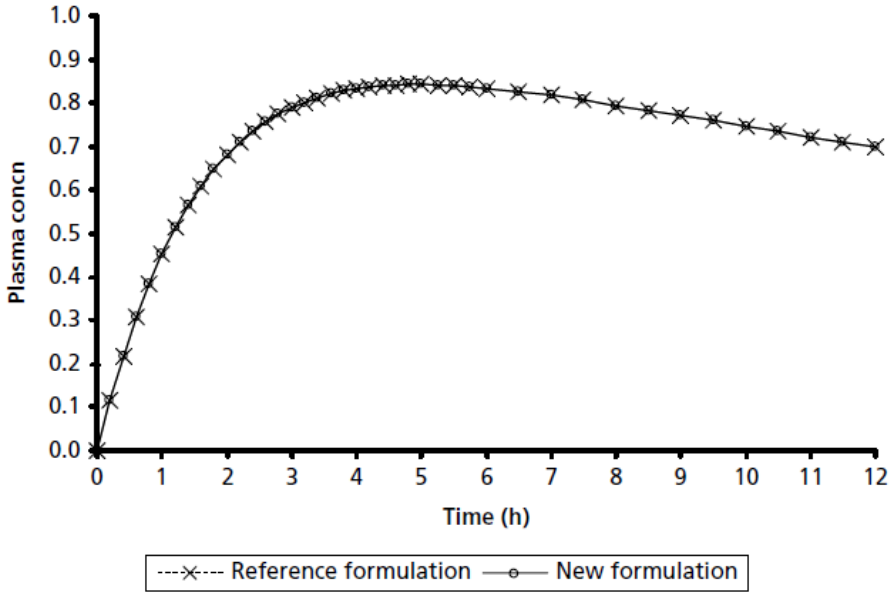
Predicted *in-vivo* solubility/dissolution-based maximum uptake



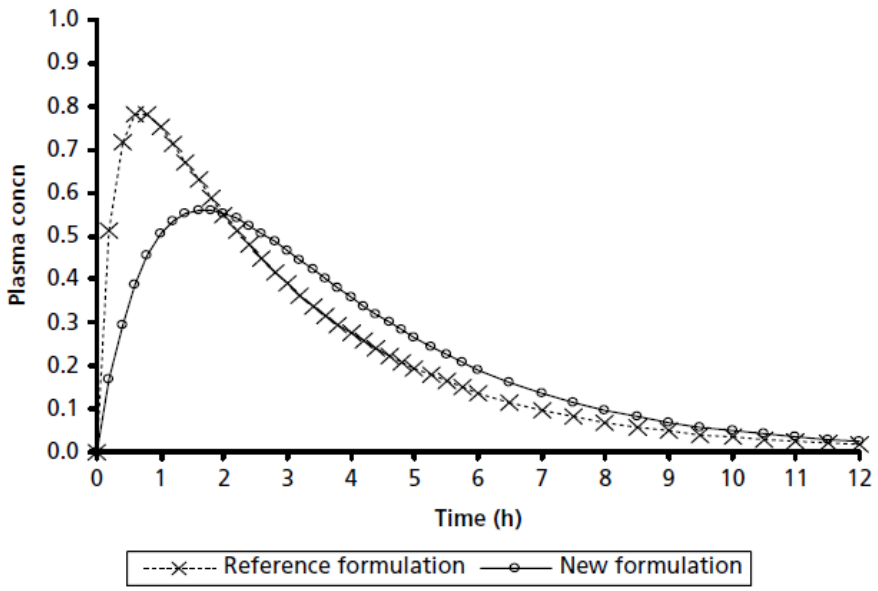
Predicted *in-vivo* permeability-based uptake

The role of t½

Simulated plasma conc *vs* time profiles for two formulations with 4-fold different dissolution rates



High Pe, long t½

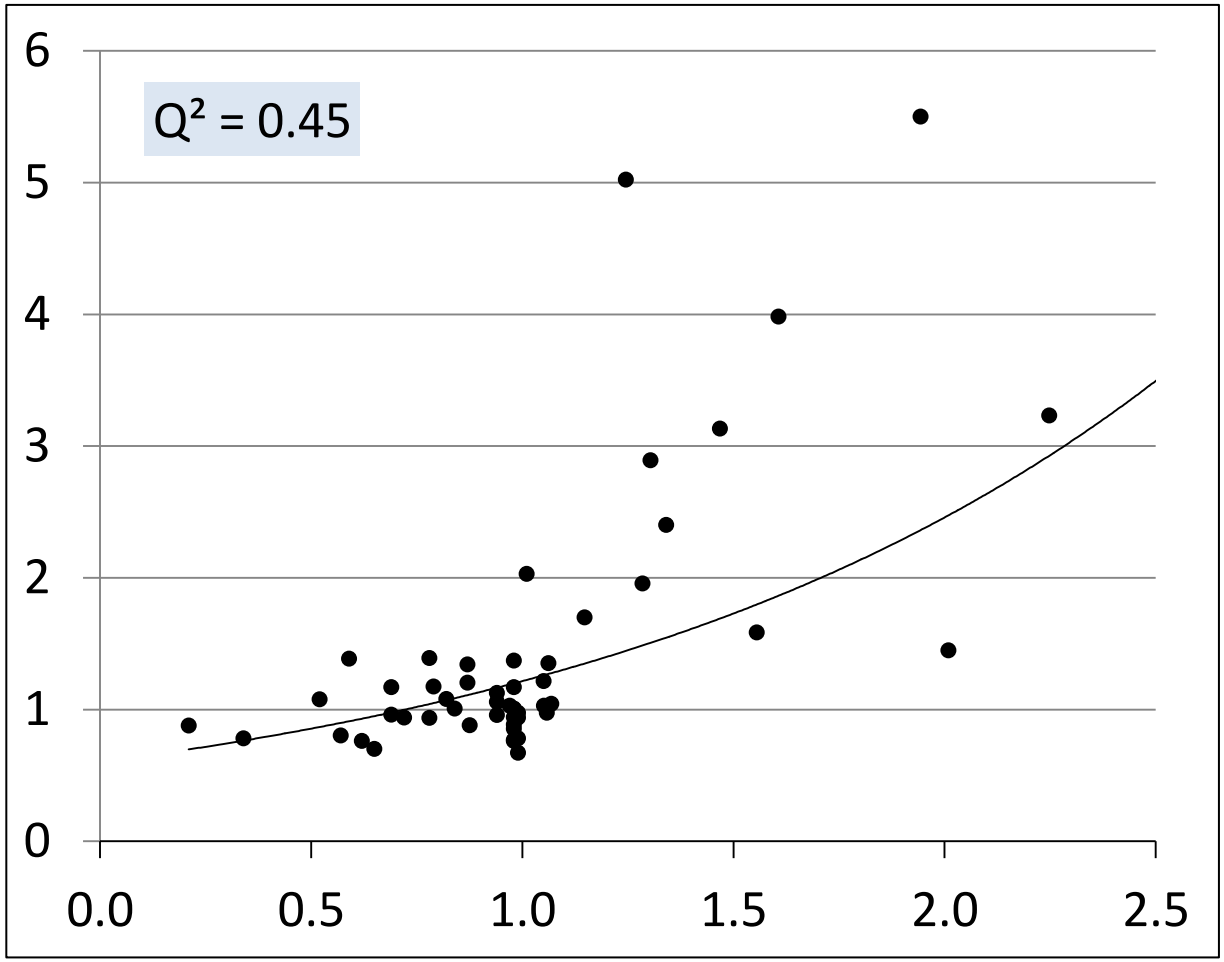


High Pe, short t½

Fagerholm, J Pharm Pharmacol 2007

FOOD INTERACTION

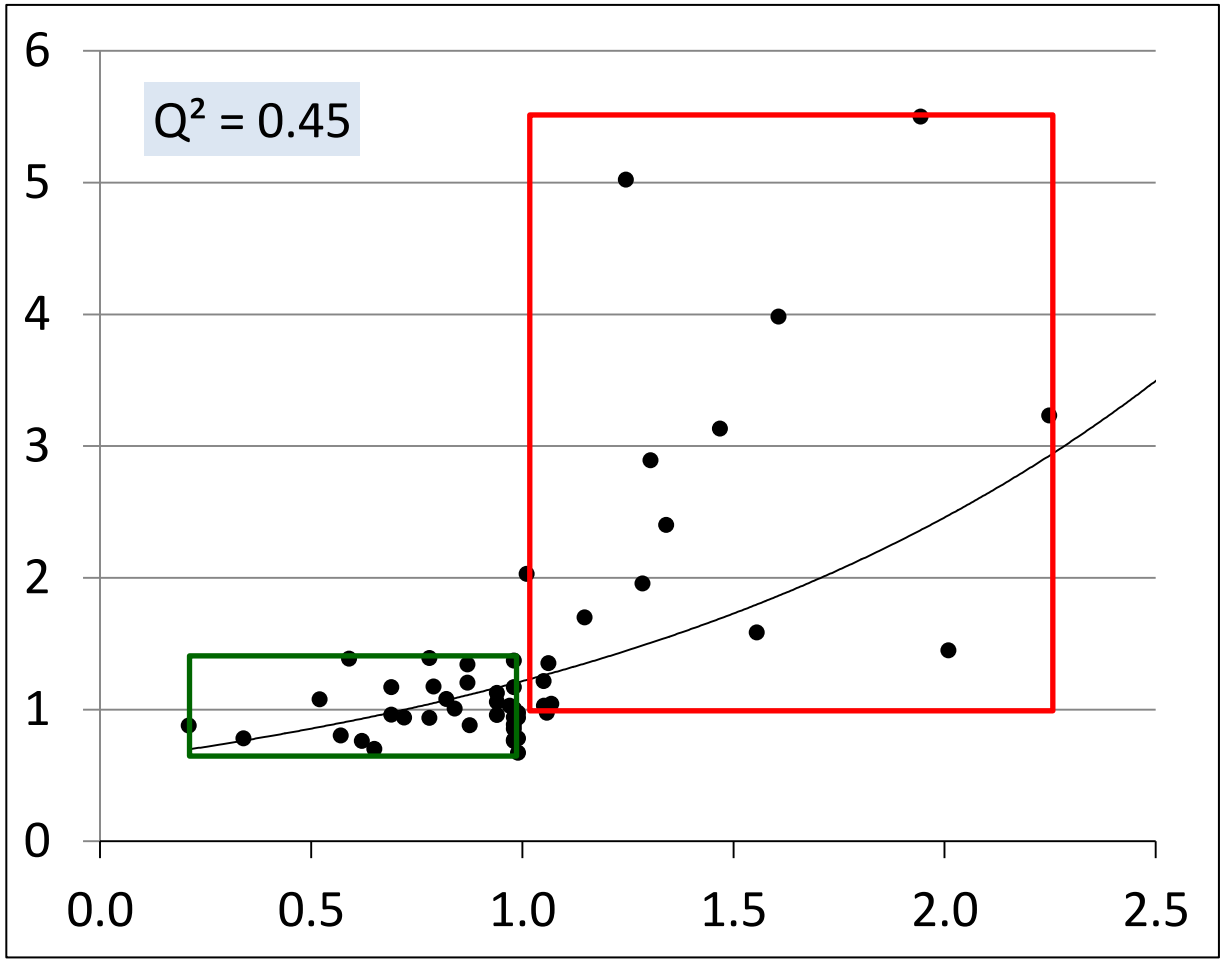
Observed AUCfed/fast



Predicted food interaction index

FOOD INTERACTION

Observed AUCfed/fast



Predicted food interaction index

SUMMARY

- Exaggerated *in-vivo* solubility limitations?!
- Adjustments of BCS needed?!
- Significant advances in predictions of absorption, bioavailability, BCS-classing and food interactions with new *in-silico* methodology
- Uptake optimization enabled with the new methodology

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http://prosilico.com/

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QureTechBio
Defeats bacterial virulence


Noviga Research

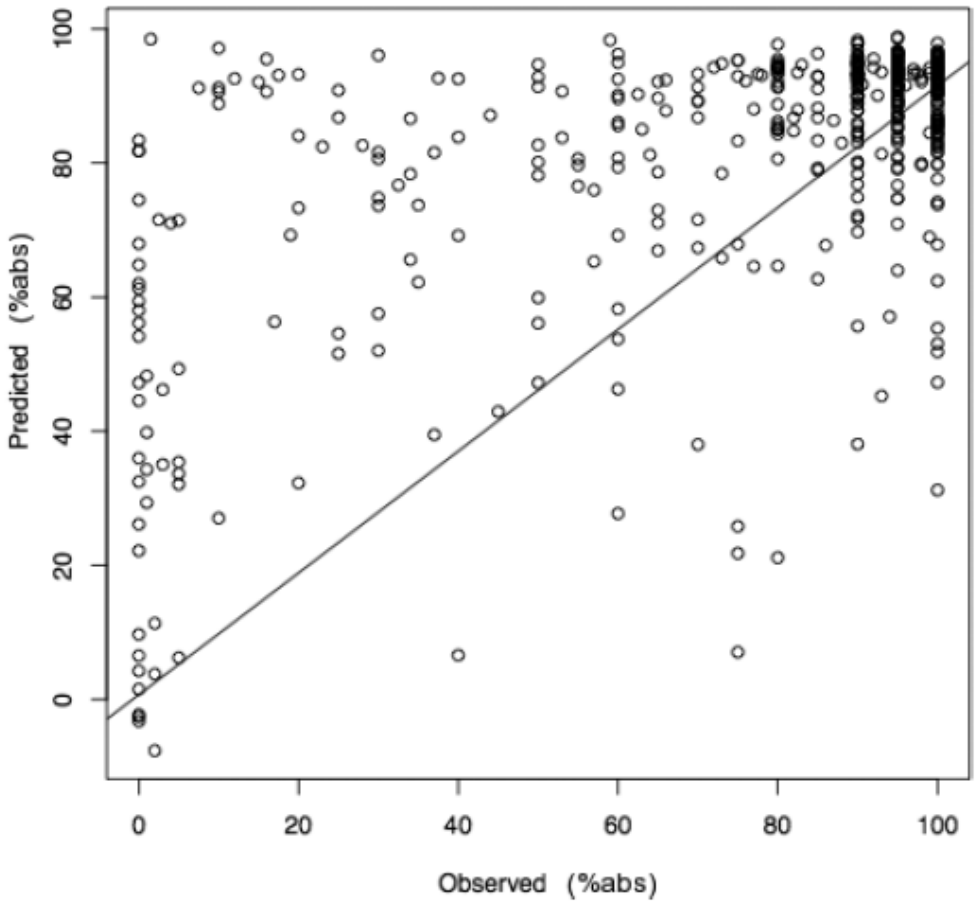

redoxis


Umecrine
cognition


CHEMNOTIA


UIC
UPPSALA INNOVATION CENTRE

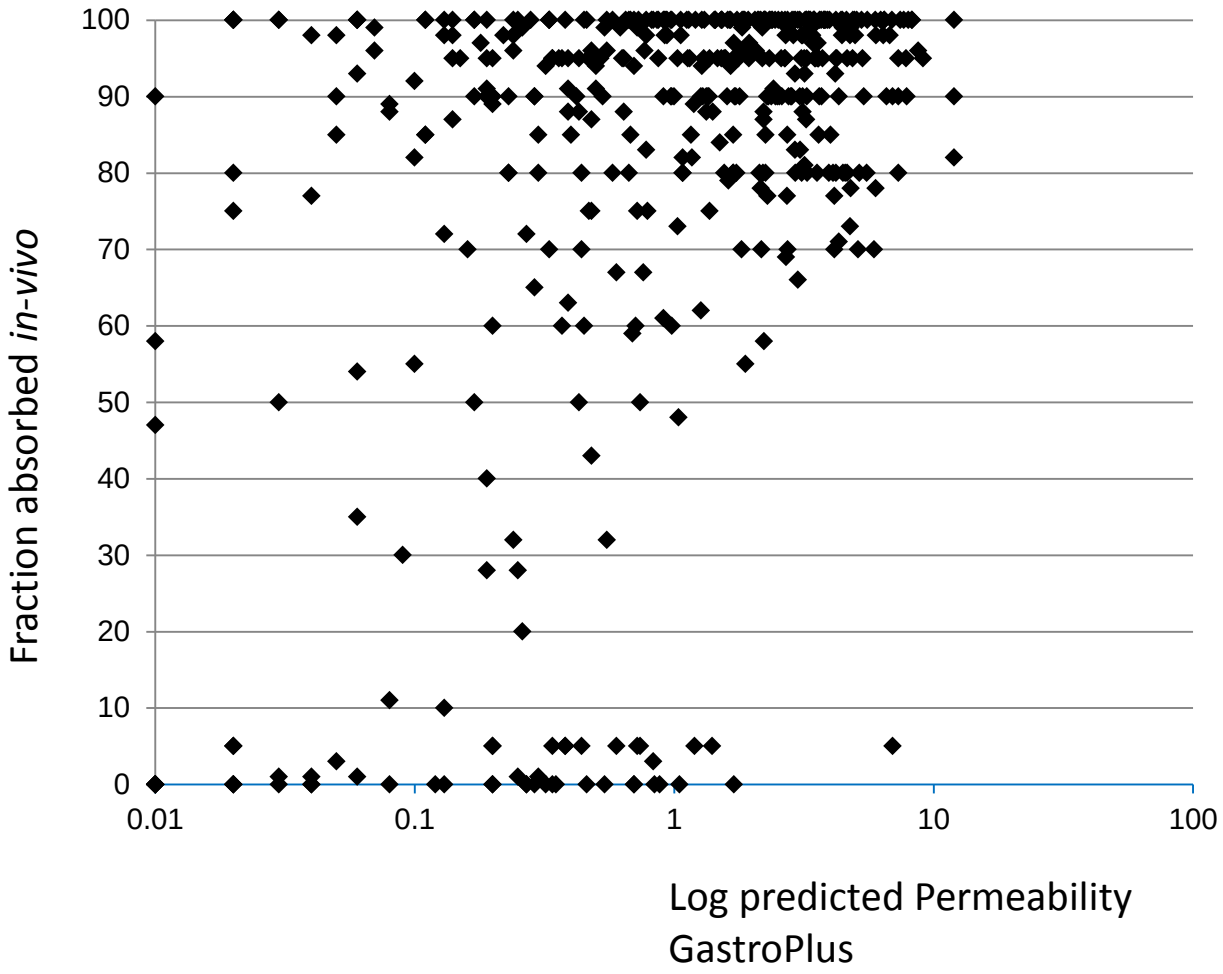
BACK-UPS



Combinatorial QSAR Modeling of Human Intestinal Absorption

Claudia Suenderhauf,[†] Felix Hammann,[†] Andreas Maunz,[‡] Christoph Helma,[‡,§] and Jörg Huwyler*[,†]

BACK-UPS


100
90
80
70
60
50
40
30
20
10
0
0.01
0.1
1
10
100
Fraction absorbed *in-vivo*
Log predicted Permeability
GastroPlus

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On

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