PBPK modeling of renal impairment – what is missing?

Aleksandra Galetin

Centre for Applied Pharmacokinetic Research,
University of Manchester, UK

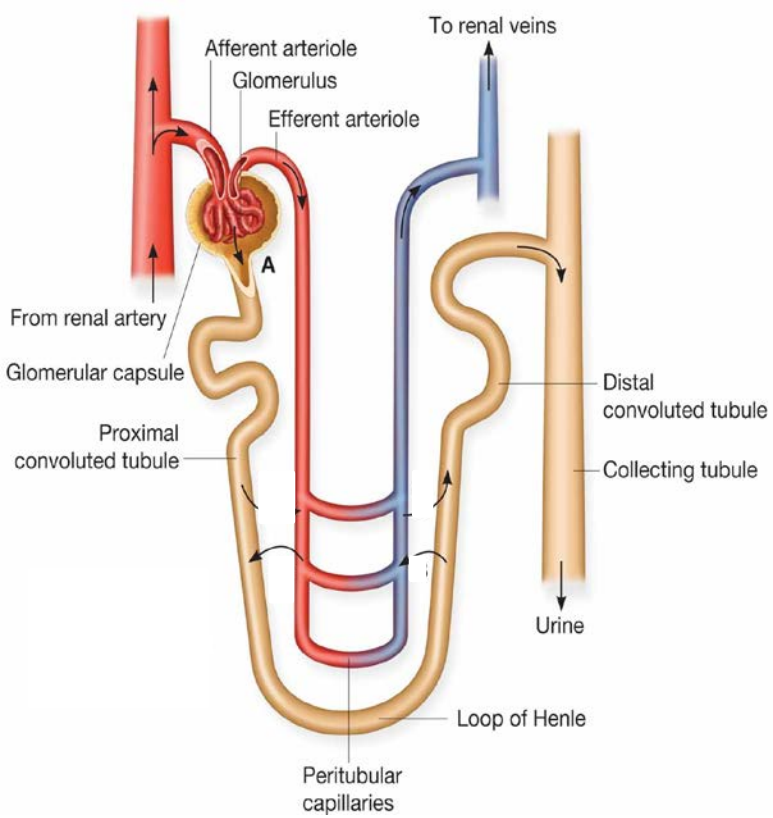
Outline of the presentation

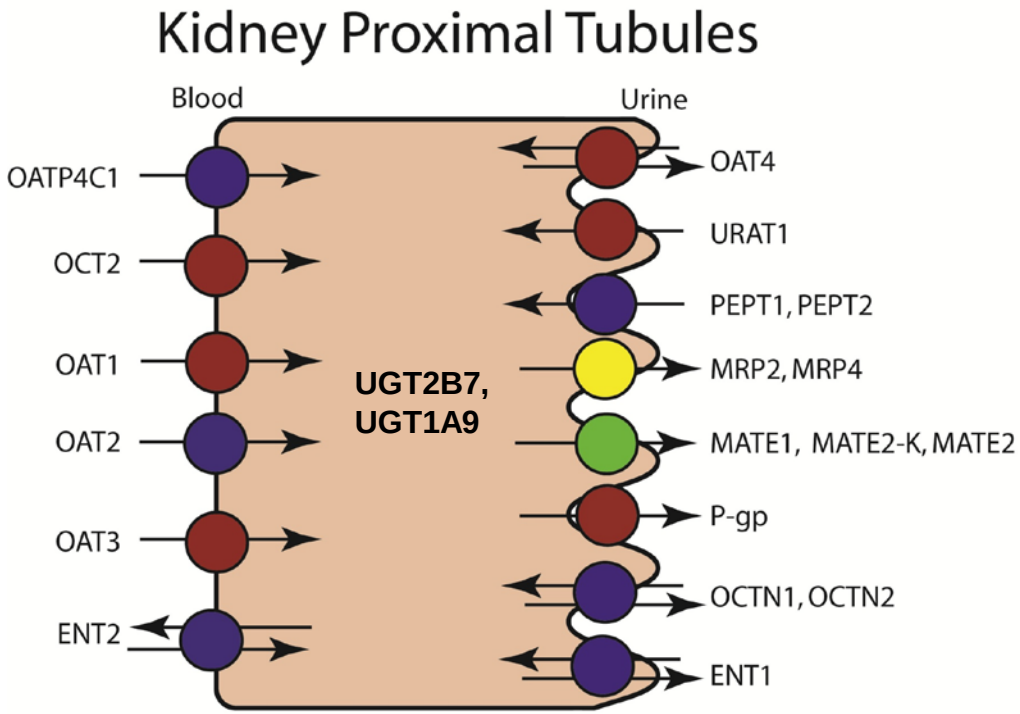
- Physiological changes in renal impairment
- PBPK modelling of RI

A. Nonrenally cleared drugs

B. Renally eliminated drugs
   - System data needed for mechanistic kidney models
   - Drug-transporter interaction in renal impairment - digoxin example

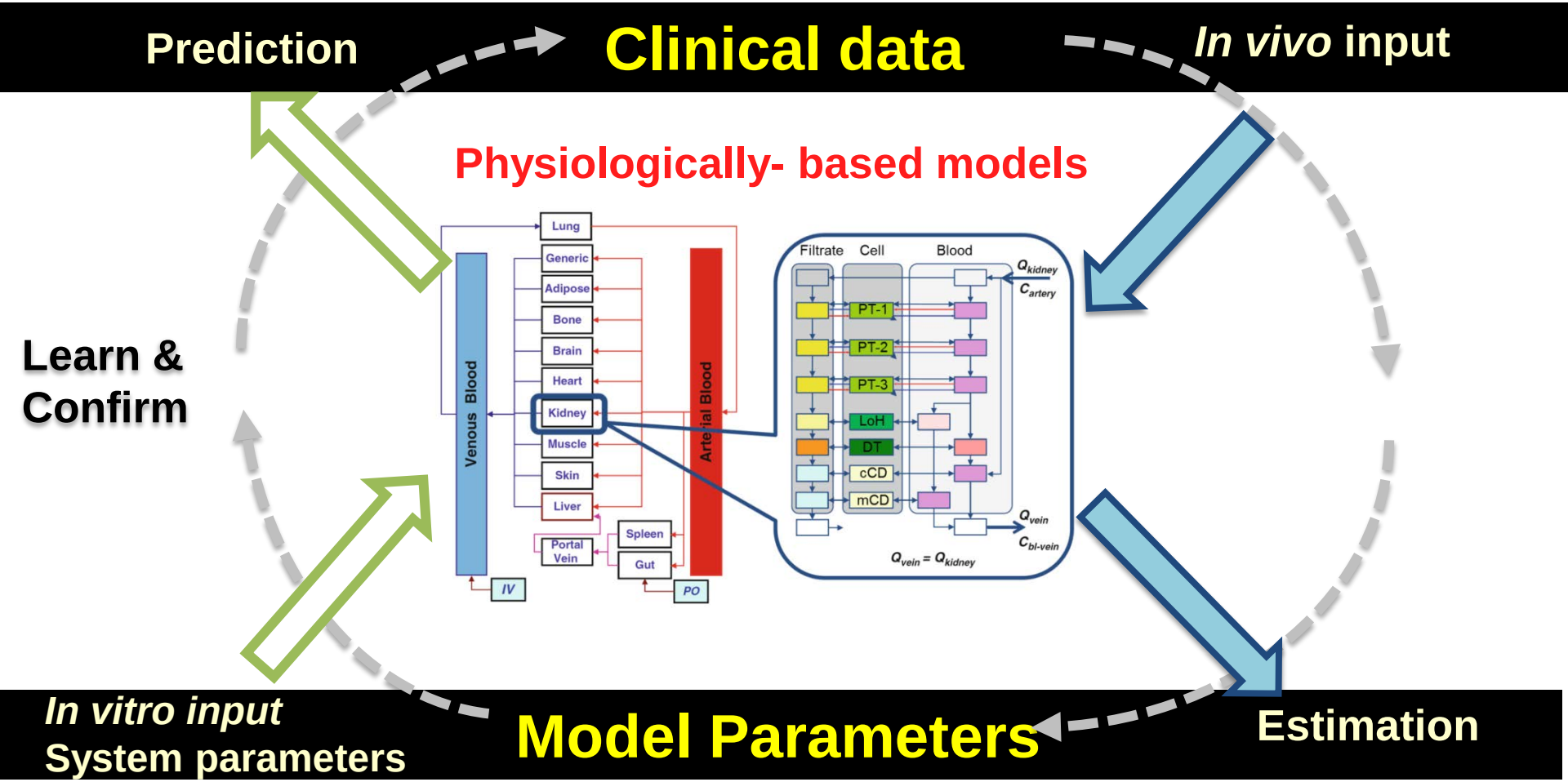
Renal elimination of drugs





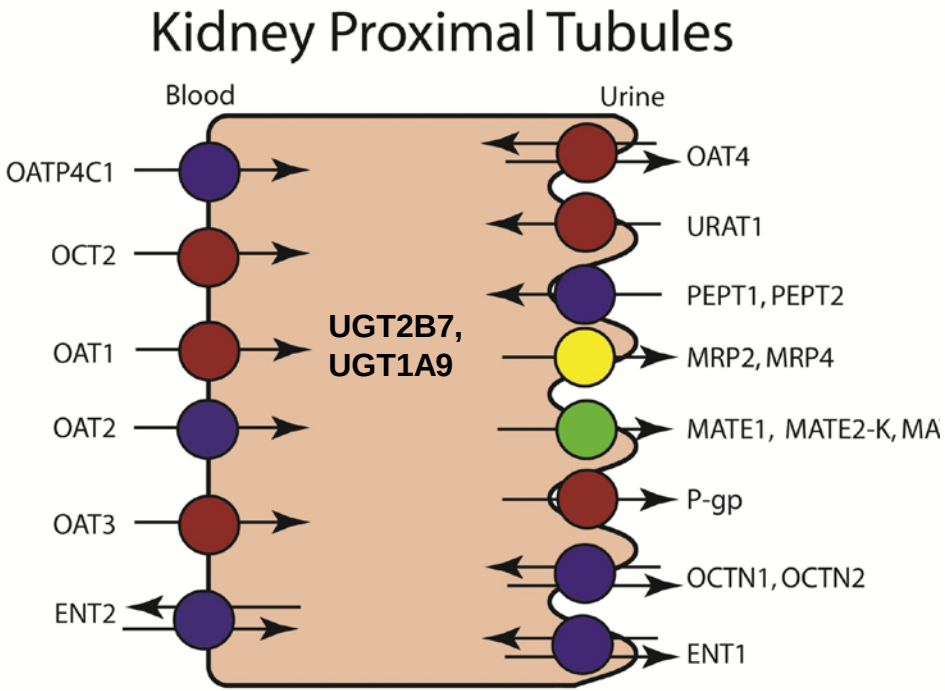
- **Active uptake via OAT1/3, OCT2 paired with efflux transporters MRP2/4, MATEs**
- **Proximal tubule cells also express drug metabolising enzymes**
- **Reabsorption - generally passive, active reabsorption via OAT4, PEPT1/2**

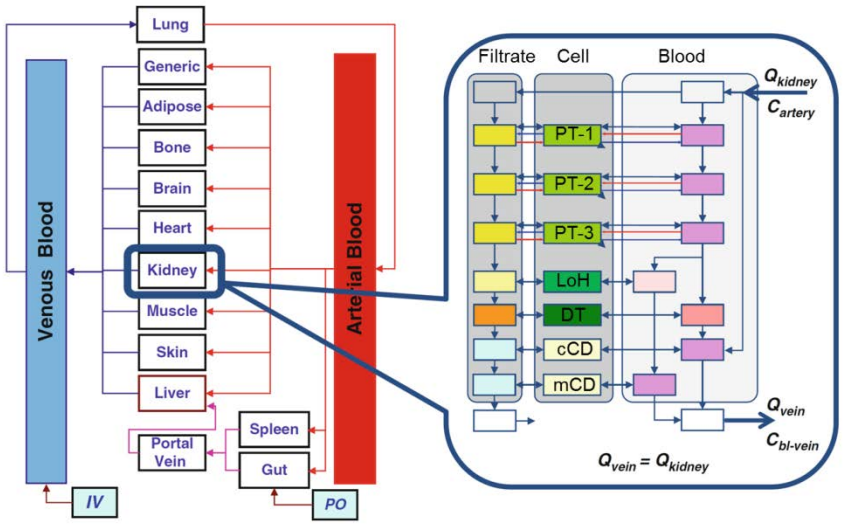
Integrated bottom up and top down approach for mechanistic prediction of CL_R



Neuhoff S, Gaohua L, Burt H, Jamei M, Li L, Tucker G, et al. Accounting for Transporters in Renal Clearance: Towards a Mechanistic Kidney Model (Mech KiM). In: Sugiyama Y, Steffansen B, editors. Transporters in Drug Development: Springer New York; 2013. p. 155-77.

Prediction of renal tDDIs and nephrotoxicity



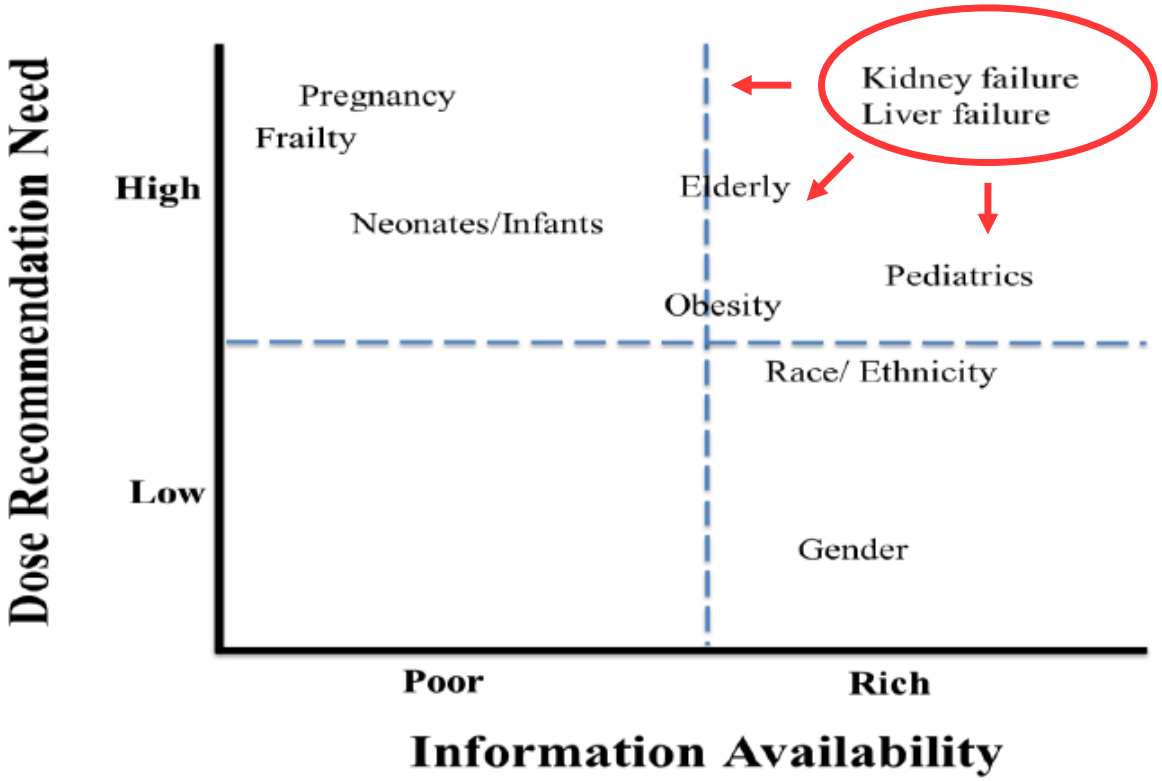


- **Recent examples – cidofovir, rivaroxaban, metformin, lesinurad[1-3]**
- ***In vitro* transporter kinetic data and certain system parameters still sparse[4]**

[1]Hsu Clin Pharmacokinet 2014, [2]Grillo BDD 2012, [3]Burt EJPS 2016, [4]Scotcher AAPS J 2016

Where we can expect PBPK modelling to inform drug labelling in the future?

- **Large % of drug labels for FDA approved drugs in 2013-14 lack dose recommendations in RI**



Utility of Model Based Approaches for Informing Dosing Recommendations in Specific Populations: Report from the Public AAPS Workshop

Islam R. Younis, PhD[1], J. Robert Powell, PharmD[2], Amin Rostami -Hodjegan, PharmD, PhD[3], Brian Corrigan, PhD[4], Norman Stockbridge, MD, PhD[5], Vikram Sinha, PhD[6], Ping Zhao, PhD[1], Pravin Jadhav, PhD, MPH[7], Bruno Flamion, MD, PhD[8], Jack Cook, PhD[4]

Jadhav J Clin Pharmacol 2015
Younis J Clin Pharmacol 2016

Changes in system parameters in CKD

KIDNEY[1-5] ↓ CL_R

↓ Q_R and kidney weight

↓ GFR

Stages 1-5: ≥ 90 to <15 mL/min/1.73m^2

Changes in tubular surface area?

↓ Tubular secretion

- ↓ Transporter expression/activity
- Inhibitory effect of uremic solutes
- ↓ Proximal tubule cell number

↓ Renal metabolism – UGT?

LIVER[2,6-8]

↓ CL_H for nonrenally cleared drugs

- Downregulation or inhibition of CYPs
- ↓ activity OATP (SN-38)
- ↓ UGT1A9, -2B7

GI[2]

- ↑Gastric emptying time
- ↑ pH
- Expression of CYPs?

[1]FDA Renal impairment Guidance [2]Rowland Yeo Expert Rev Clin Pharmacol 2011 [3]Nolin Am J Kidney Dis 2003 [4]Scotcher AAPS J 2016 [5]Hsueh Mol Pharm 2016 [6] Fujita Pharm Res 2014 [7]Zhao J Clin Pharmacol 2012 [8]Barnes Eur J Clin Pharmacol. 2014

Changes in plasma protein binding in CKD

Parameter		Heathy	GFR <30 mL/min/1.73m^2
Albumin (g/L)	**M**	44.9	37.6
	F	41.8	35.0
Hematocrit (%)	**M**	43.0	39.7
	F	38.0	33.2

- **Other factors that may affect protein binding:**
  - Conformational changes in albumin structure/binding sites
  - Competition for binding sites by uremic solutes
  - Limited data suggest elevated α-acid glycoprotein

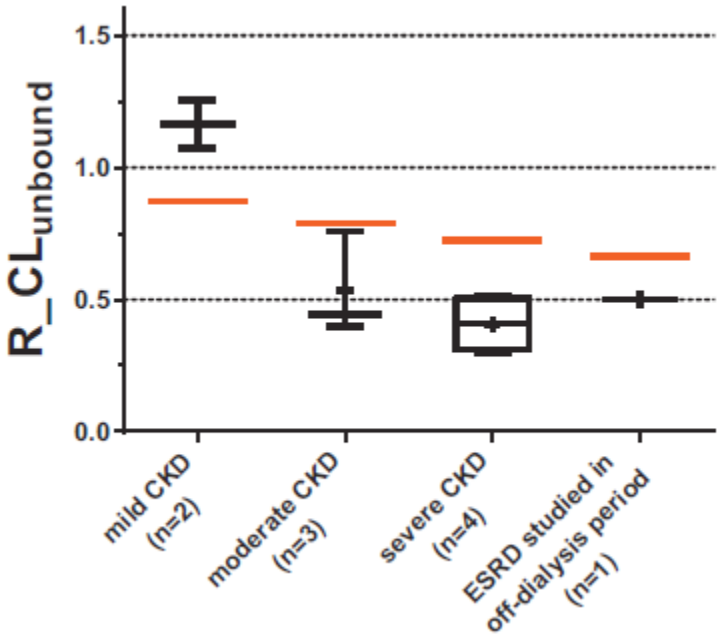
- **Important to measure fu in RI population for highly bound drugs**

$$fu_i = \frac{1}{1 + \frac{(1 - fu) \times [P]_i}{[P] \times fu}}$$

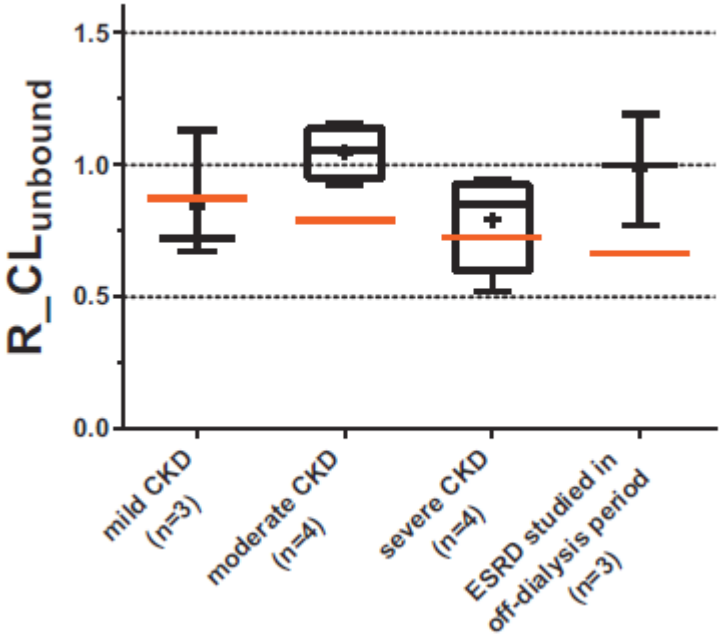
[1] Rowland Yeo Expert Rev Clin Pharmacol 2011

Systematic evaluation of the CKD effect on CYPs

CYP2D6



CYP3A4/3A5



- **CYP2D6-mediated clearance decreased in parallel with the severity of CKD**
- **No apparent relationship between the severity of CKD and CYP3A4/5-clearance**

Effect on CYP1A2, CYP2C8, CYP2C9 and CYP2C19 – Poster Tan et al.

Yoshida Clin Pharmacol Ther 2016

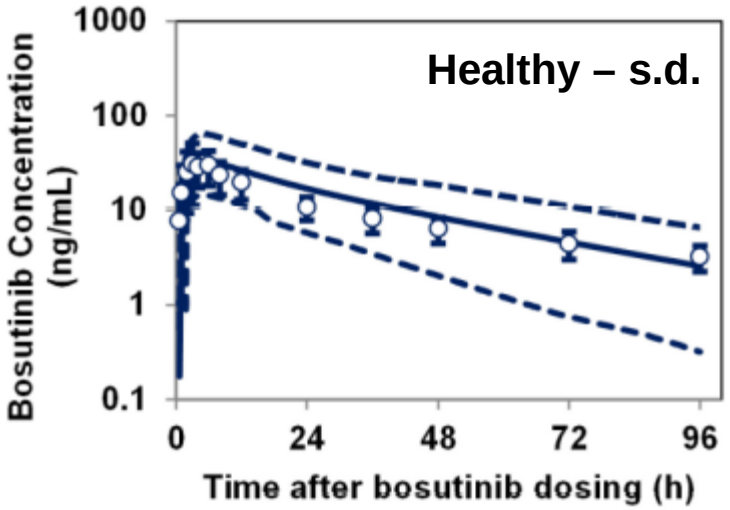
PBPK modelling of RI - nonrenal CYP-mediated clearance

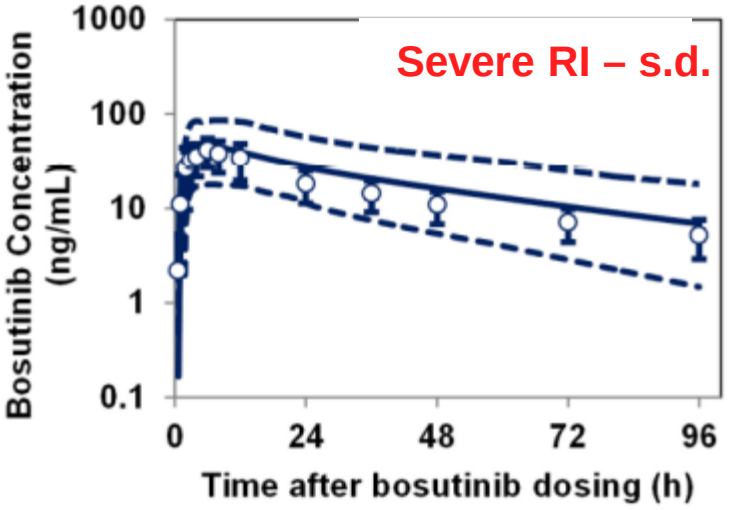
- **Retrospective analysis[1] –** repaglinide, telithromycin, slidenafil
- CYP abundance in RI extrapolated from clinical data

Bosutinib PBPK[2]

- **Step wise PBPK model development and verification**
- **RI Virtual population:**

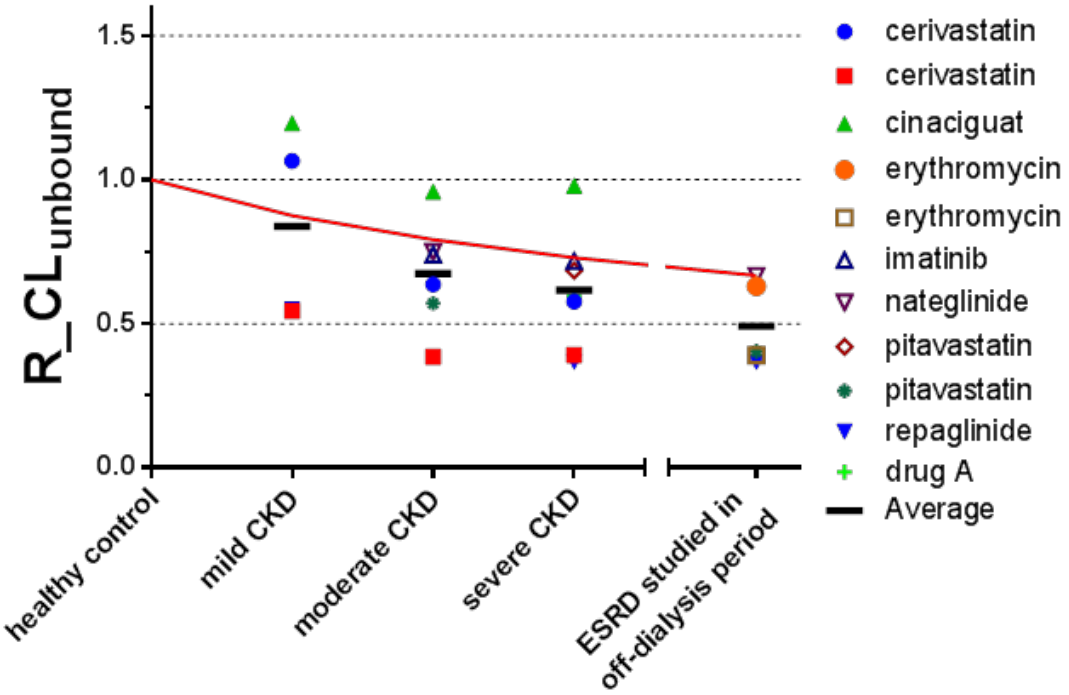
i. Reduced GFR, kidney weight and Q_R
ii. Reduced hepatic CYP3A4 expression
iii. Reduced serum albumin and hematocrit





[1]Zhao J Clin Pharmacol 2012 [2]Ono DMD 2017

Effect of CKD on OATP

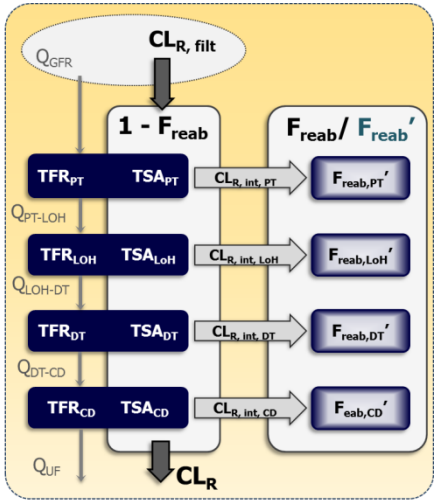


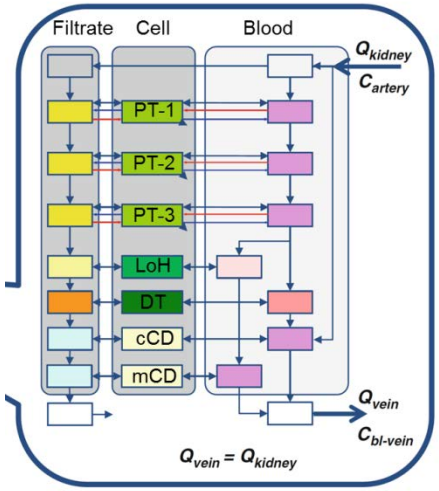
- Decrease in clearance in parallel with CKD severity
- Challenges:
  - Lack of binding data in RI subjects
  - Overlap between CYP2C8 and OATP drugs

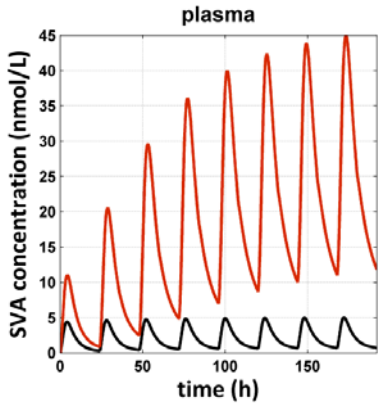
Poster Tan et al. - ITCW and ASCPT PT-020

PBPK modelling of RI – renally eliminated drugs

System parameters for mechanistic kidney models - healthy *vs.* RI?







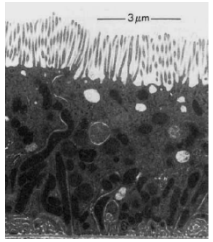
Tubular surface area – accounting for microvilli

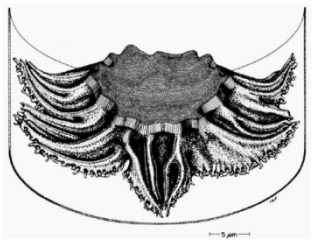
$$\underset{\text{(mL/ min)}}{CL_{R,int,reab,i}} = \underset{\text{(cm/ min)}}{P_{app}} \times \underset{\text{(cm}^2\text{)}}{TSA_i}$$

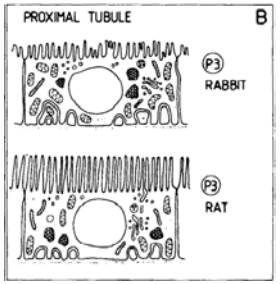
Nephron tubule considered as a cylinder

Area = $2\pi r h$
x number nephrons

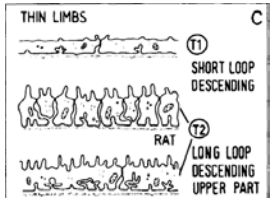
Both PT cells and **Caco-2** cells have extensive microvilli (apical membrane) - ↑surface area.

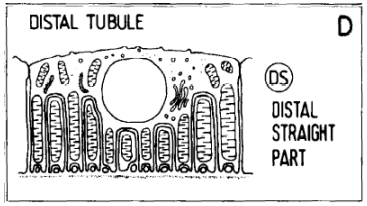


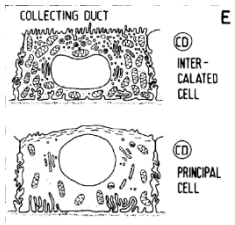




LoH, **DT** and **CD** cells - sparse/ negligible microvilli



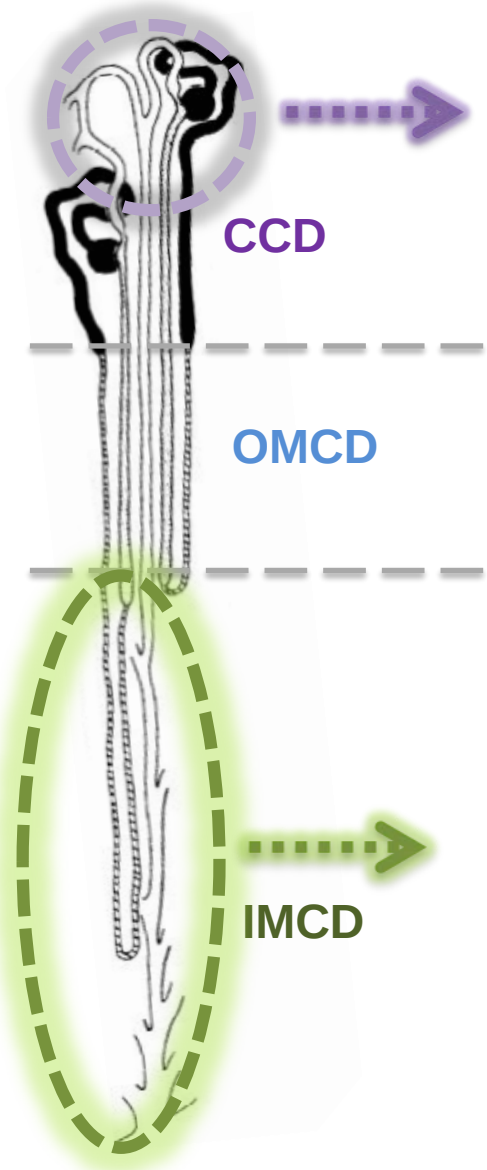




Kriz (1981).The Am. J. Physiol. 241(1):R3.

Welling and Welling (1988) J. Electron. Micr. Tech. 9; 171-85

Tubular surface area - collecting duct requires special consideration!



Cortical Collecting Ducts formed by **merging** of app. 10 tubules

(i.e. 900,000 nephrons/ kidney → 90,000 CCD/ kidney)

No merging in Outer Medulla Collecting Ducts

(i.e. 90,000 OMCD/ kidney)

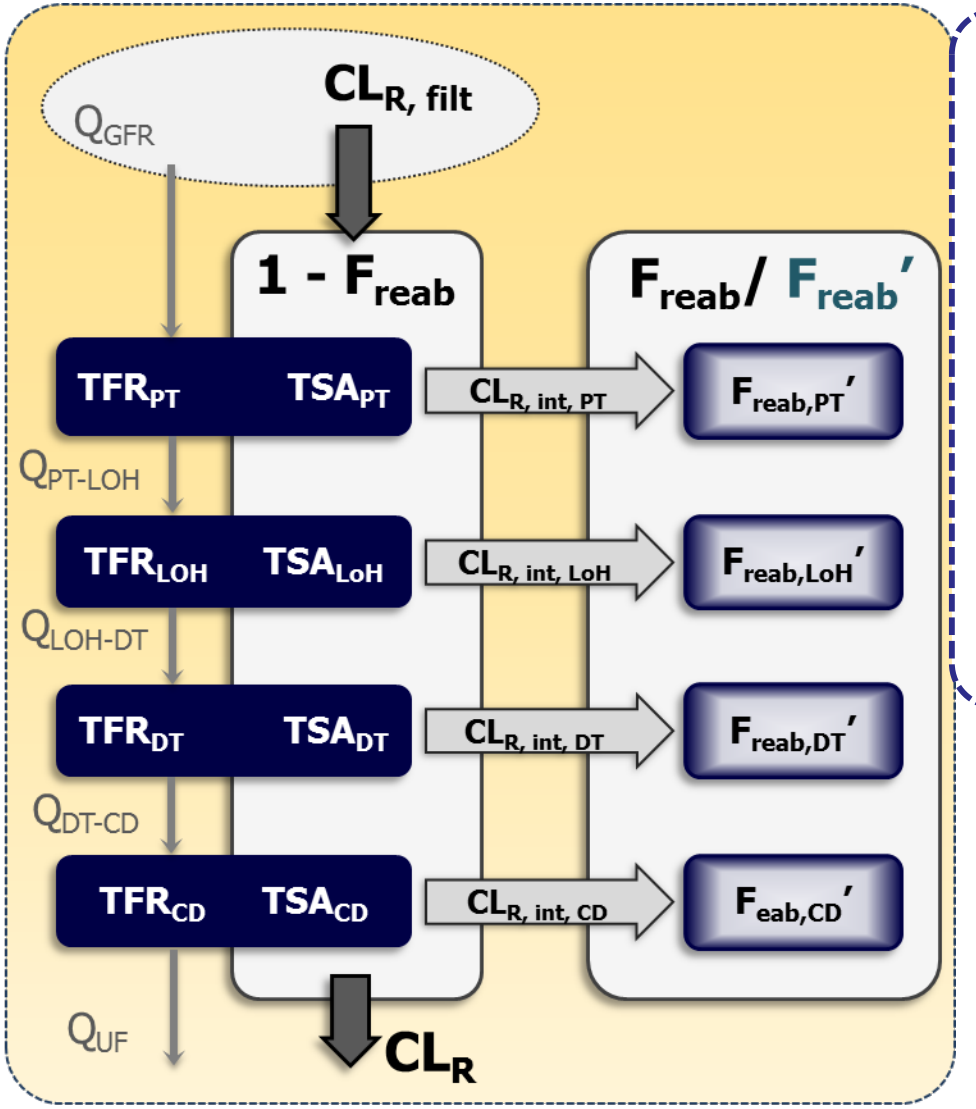
Inner Medulla Collecting Ducts undergo successive dichotomous fusions

(i.e. 90,000 IMCD/ kidney → 360 Ducts of Bellini/ kidney)

$$C_x = (d_0 \times NCD_0 \times \pi) e^{\left(\left(\frac{x \times F}{n}\right) \times \ln\left(\frac{2}{\frac{d_0}{d_n}^{\frac{1}{F}}}\right)\right)}$$

Scotcher, Eur J Pharm Sci 2016

Minimal tubular reabsorption model



IVIVE – Scaling P_{app} to $CL_{R,int}$

- pH gradient (6.5 - 7.4)
- Transporter inhibitor cocktail

$$CL_{R,int,i} = P_{app} \times TSA_i$$

Regional differences in TSA and tubular flow

Scotcher, Eur J Pharm Sci 2016

Performance of the mechanistic tubular reabsorption model – *in vivo* data from healthy

	gmfe (% predicted within 3-fold of observed)		
	Proximal tubule only	**No correction for microvilli**	**Reabsorption model**
All drugs (n = 45)	2.17 (76%)	5.35 (27%)	1.96 (87%)
Low F_{reab} (n = 17)	1.59 (94%)	5.02 (35%)	1.97 (88%)
Medium F_{reab} (n=12)	1.44 (92%)	8.52 (17%)	1.90 (92%)
High F_{reab} (n = 16)	4.11 (44%)	4.03 (25%)	2.01 (81%)

- **Proximal tubule can be used as surrogate for low-med F_{reab} (<75%)**
- **Consideration of correct tubular surface area of key relevance**

In vitro-in vivo extrapolation of active renal secretion

Increasing system complexity

Transfected cells
HEK, HeLa

Immortalised cells
LLC-PK1, ciPTEC, HK-2

Primary cultured renal tubule cells

Kidney slices

Kidney-on-a-chip

Scaling of kinetic parameters

REF (V_{max} /CL_{int})
ft IC_{50}/Ki

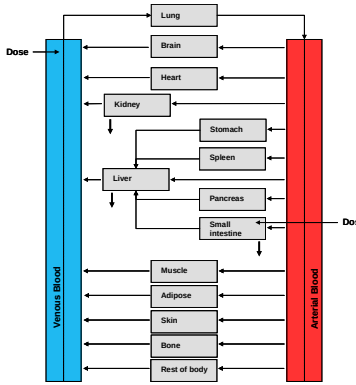
Tubular surface area (P_{app})

Proximal tubule cell number
(V_{max} /CL_{int})
30 – 209 million PTC/ g kidney

Kidney weight (CL_{int})

?

PBPK model



Scotcher et al , AAPS J, part I 2016

Implementation of transporter expression data in PBPK models

Relative expression factor =

OAT3 expression $_{\text{in vivo}}$ / OAT3 expression $_{\text{in vitro}}$

- **Emerging proteomic data for renal transporters/UGTs**
- **Missing data:**
  - Large cohort of individuals and special populations
  - Regional and species differences
  - Expression vs. functional activity
- **Current REFs – estimated using plasma or urinary excretion data**
  - 5.3 - HEK-OAT3 (pemetrexed)
  - 2.3 - HEK-OCT2 (metformin)
  - 3 - HEK-MATE1 (metformin)

Scotcher AAPS J 2016 Part II; Prasad Drug Metab Dispos 2016; Knights Br J Clin Pharmacol 2016; Posada Drug Metab Dispos 2015; Burt EJPS 2016

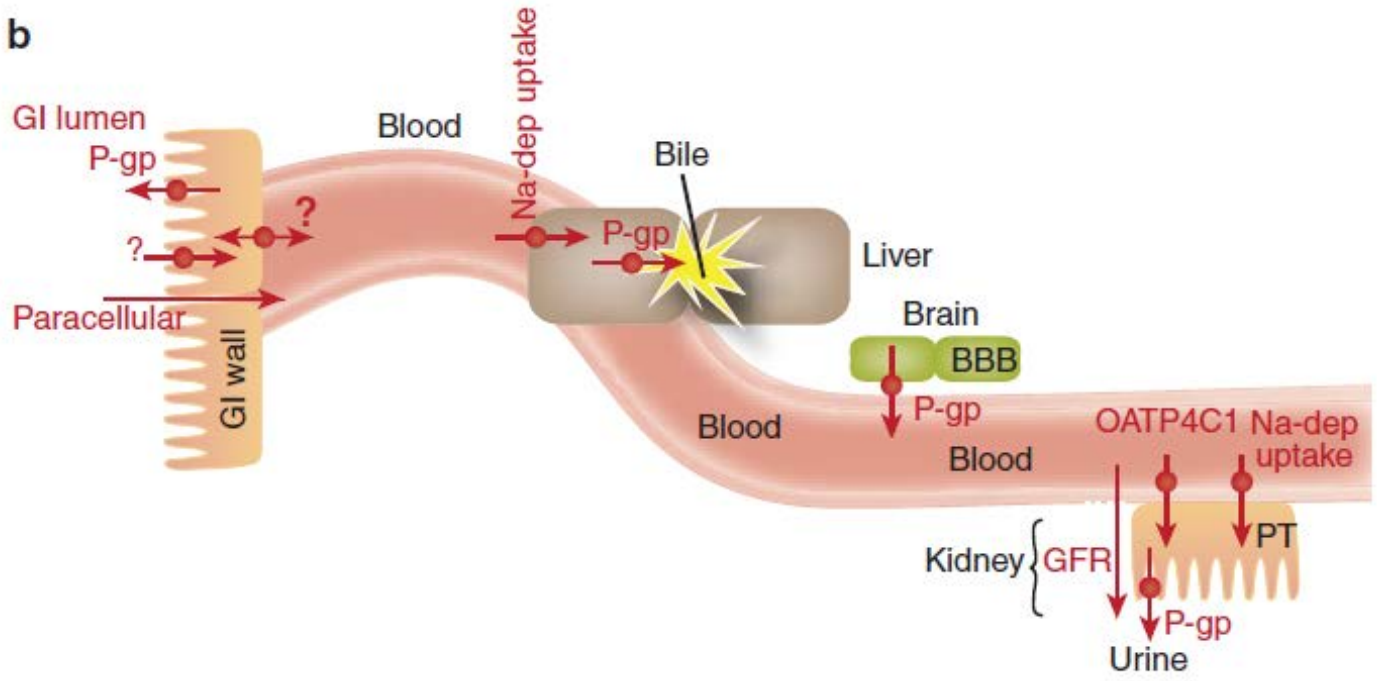
Renal PBPK models – special populations

System Parameters	Populations			
	Young adults	Paediatrics	Elderly	Renal impairment
Kidney weight/ volume	✓	✓	✓	✓
Renal blood flow	✓	✓	✓	✓/✗
GFR	✓	✓	✓ Inter-study variability	✓
Nephron number	✓ Highly variable	✓ No change after birth	✓	✓/✗ ‡
Regional tubule length/ diameter	✓ Variability within and between studies	✓/✗ Proximal tubule only (1 study)	✓/✗ Mainly proximal tubule	✗ Limited reports (qualitative)
PTCPGK	✗ Rat data only	✗	✗ Limited reports (qualitative)	✗ Limited reports (qualitative)
Transporter abundance *	✓/✗ 1 study human (pooled HKM) 1 study rat	✗ Mouse/ rat data	✗	✗ Limited rat data

✓ Data available (quantitative, human) ✓/✗ Limited or conflicting data

Scotcher et al AAPS J 2016

Mechanistic digoxin kidney model: prediction of CL_R in moderate to severe renal impairment



Lee et al, CPT (2014)

- **Existing PBPK model for digoxin incorporates transport by P-gp in liver and intestine (Neuhoff et al, J Pharm Sci, 2013)**
- **Consider role of P-gp and OATP4C1 (uptake) in kidney**
- **Availability of clinical data in healthy, elderly and different stages of RI**

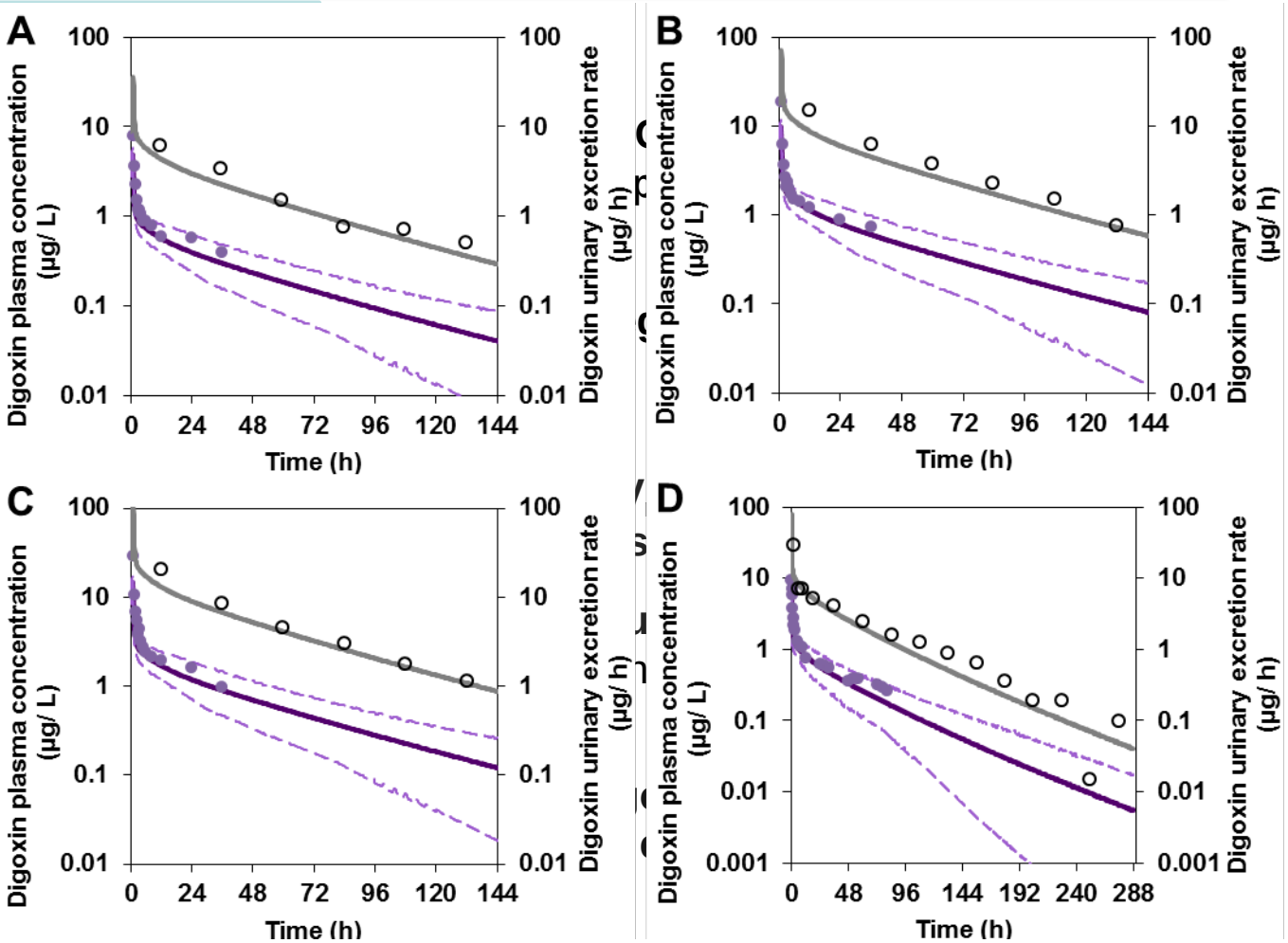
Development, verification and application of digoxin mechanistic kidney model

Model development

- Glomerular filtration
- CL_{PD}
- Transporter kinetics

Model verification

Model application



- Elderly
- Renal impairment

Scotcher et al, JPET 2017

Mechanistic digoxin kidney model: prediction of CL_R in renal impairment

Scenarios tested in digoxin model:

1. **Reduction in GFR alone**

2. **Modification of both GFR and active secretion**

   a. **↓OATP4C1 expression per million proximal tubule cells***

   b. **↓P-gp expression per million proximal tubule cells***

   c. **↓ proximal tubule cellularity (PTCPGK)**

   d. **↓OATP4C1 expression or proximal tubule cellularity proportional to changes in GFR**

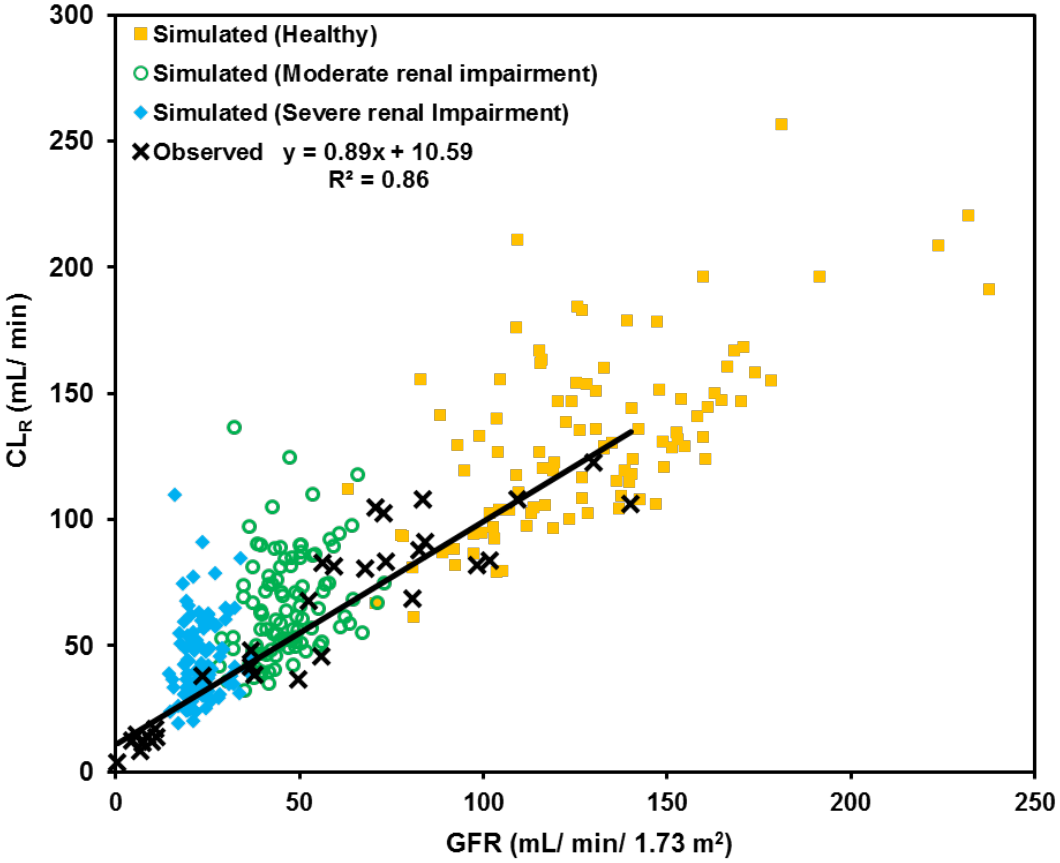
* Reflects also ↓ transporter activity due to inhibition by uremic solutes

Scotcher et al, JPET 2017, ASCPT – Quantitative Pharmacology, PII-122

Prediction of digoxin CL_R in moderate to severe renal impairment – reduction in GFR

Assumption:

- **NO changes in active secretion in renal impairment**

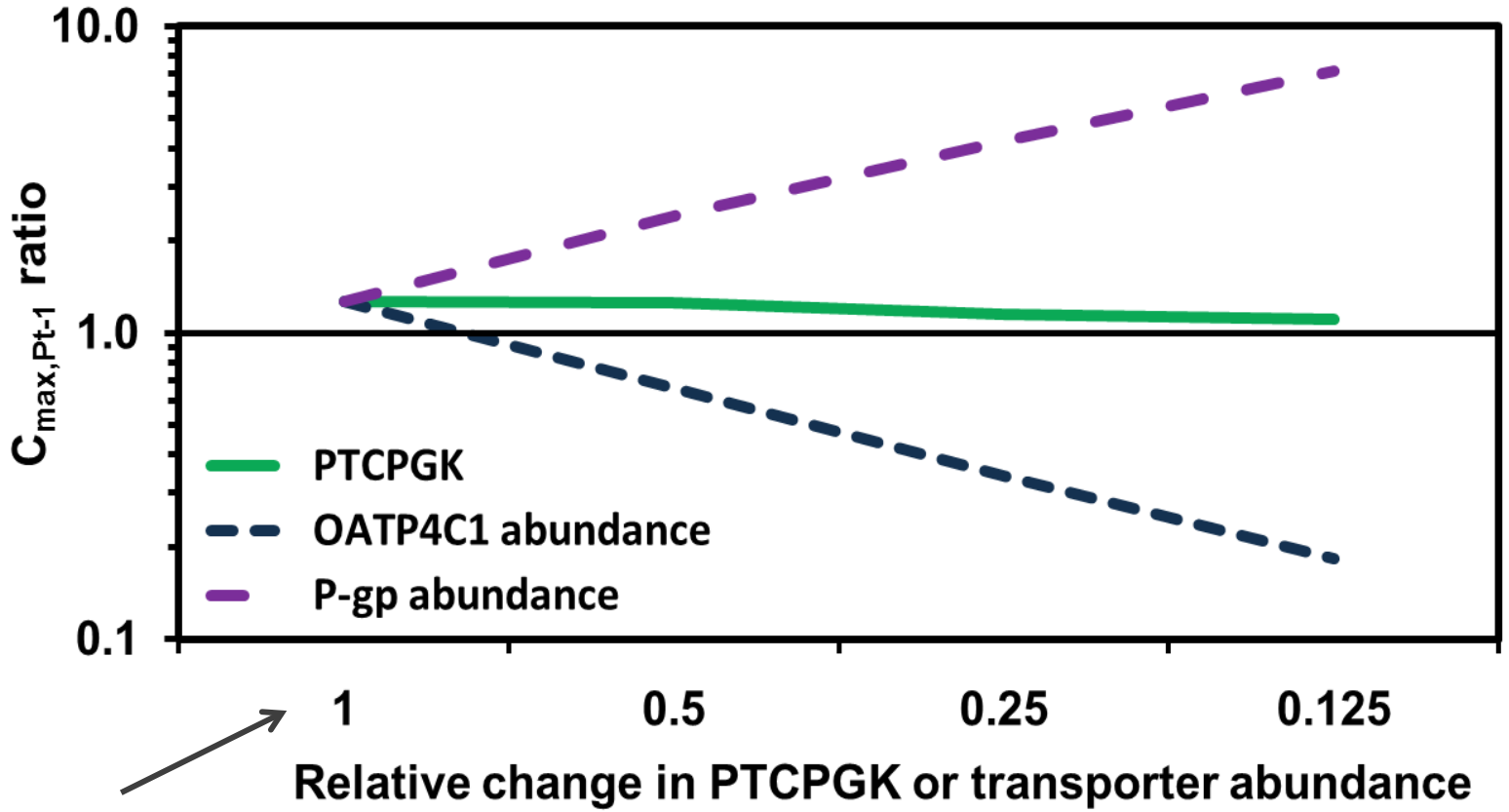


Over-estimation of CL_R in RI

Scotcher et al, JPET 2017

Mechanistic digoxin kidney model: prediction of CL_R in severe renal impairment

Additional mechanisms considered: i) ↓ transporter expression or ii) ↓ number of tubular cells

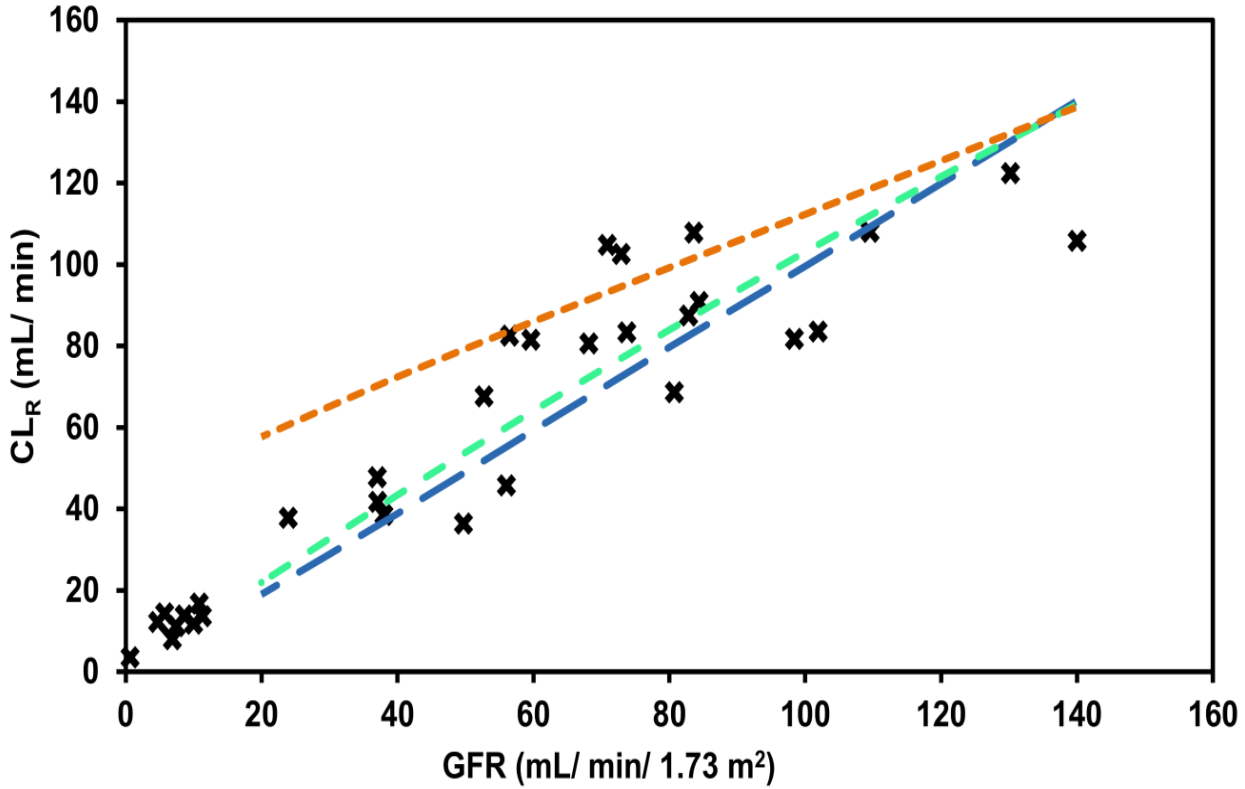


Change in GFR only
(severe renal impairment;
GFR = 15 – 30 mL/ min)

$$\text{CL}_\text{R}\ \text{ratio} = \frac{\text{CL}_\text{R}\ (\text{renal impairment})}{\text{CL}_\text{R}\ (\text{healthy subjects})}$$

Mechanistic kidney model for digoxin: renal impairment

- **OATP4C1 abundance and PTCPGK parameters changed proportionally to the change in GFR from the population representative**



Scotcher et al, JPET 2017

Take home message

- **Assumption that secretion does not change in renal impairment over-estimated digoxin CL_R**

- **Different mechanisms considered for active secretion in RI-PBPK model**
  - **Comparable NET effect on the predicted systemic exposure and CL_R**
  - **Predicted dynamics inside proximal tubule cells different – implications for nephrotoxicity or transporter-mediated DDIs**

- **Integrated bottom up-top down approaches important for step-wise RI-PBPK model development and verification**
  - **Enhanced clinical trial design/adequate clinical data**

Acknowledgements

MANCHESTER 1824
The University of Manchester

Daniel Scotcher
Andres Olivares-Morales
Hitesh Mistry

Amin Rostami
Leon Aarons
Malcolm Rowland

AstraZeneca

Chris Jones

FDA

Shiew-Mei Huang, Ping Zhao, Lei Zhang
Mingliang Tan

Genentech
A Member of the Roche Group

Kenta Yoshida

BBSRC
bioscience for the future

Lilly

Maria Posada, Stephen Hall

CAPKR consortium

http://research.bmh.manchester.ac.uk/capkr/