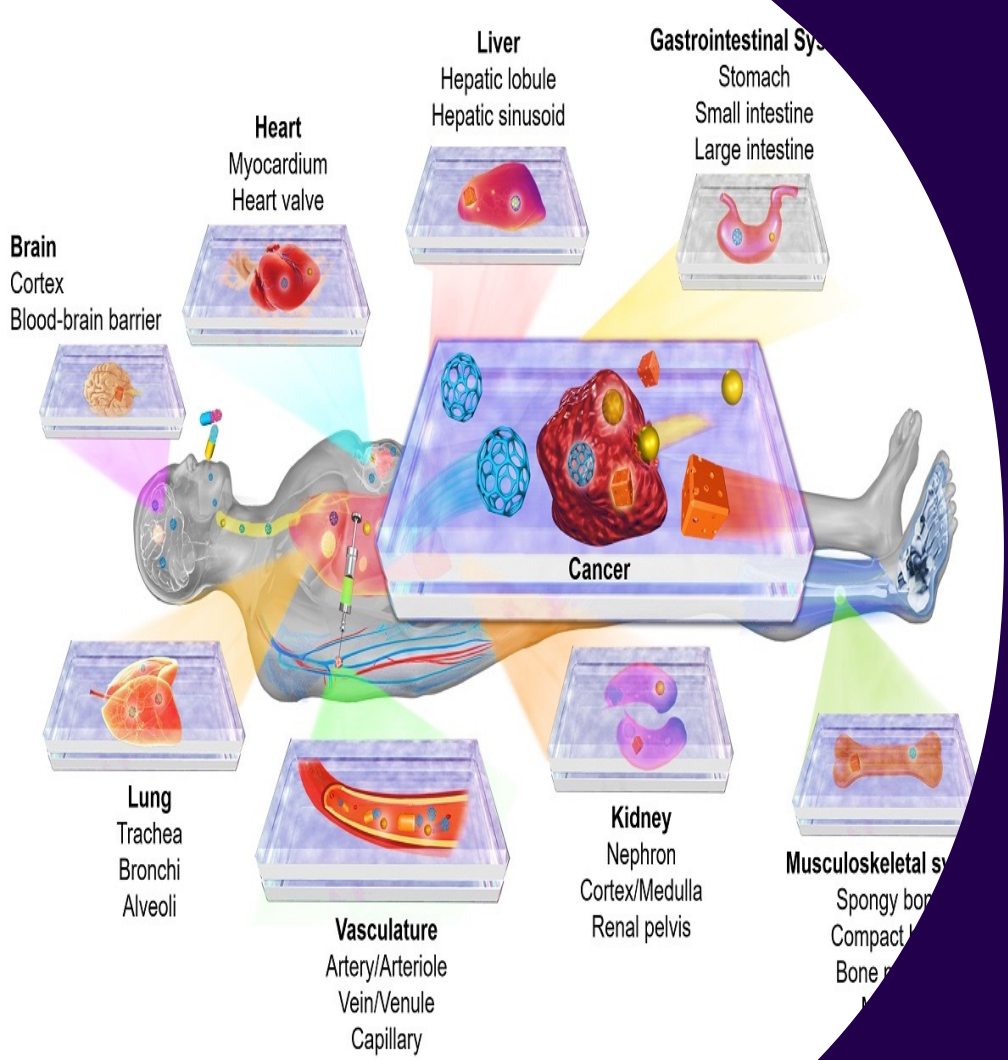

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Organ-on-a-Chip (OoC) Mechanistic Model for Estimating Small Molecules' Human Hepatic Clearance and PK Profiles

Siak-Leng, Choi

Sanofi DMPK, Global M&S

OSP Community Conference 2024

7th October, 2024

FDA Modernization Act, 2022 – Reduce Animals Use in Drug Testing

Congress Approves Landmark Measure to Reduce Animal Testing

FDA Modernization Act promises to spare animals, bring safer and better treatments to patients, and drive down drug prices

December 23, 2022 18:48 ET| Source: Animal Wellness Action Follow

https://www.globenewswire.com/news-release/2022/12/23/2579295/0/en/Congress-Approves-Landmark-Measure-to-Reduce-Animal-Testing.html

3Rs Principle – guiding principles for ethical use of animals

First described by W. M. S. Russell and R. L. Burch in 1959.[1]

The 3Rs are:

Using In-vitro Data and In-silico Method

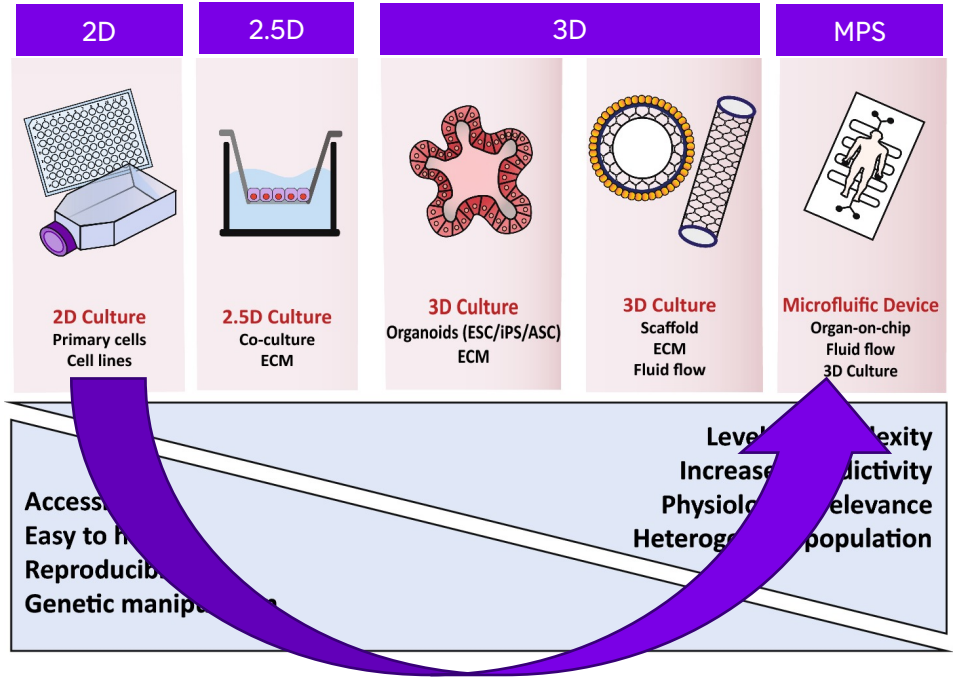
1.Replacement: **alternative** methods which avoid or replace the use of animals in research
2.Reduction: use of methods that enable researchers to obtain comparable levels of information from **fewer animals**, or to obtain more information from the same number of animals.
3.Refinement: use of methods that **alleviate or minimize** potential pain, suffering or distress, and enhance animal welfare for the animals used.

[1] Russell, W.M.S. and Burch, R.L., (1959)

Advancements of In-vitro System

Benefits
- Established protocols
- Cost-effective

Disadvantages
- Limited complexity
- Static environment
- Frequently inaccurate in predicting human responses
- Low relevance to human physiology



Benefits
- Physiological Relevance
- Dynamic environment
- Reduced animal testing
- Real-time monitoring

Disadvantages
- High cost
- Technical complexity

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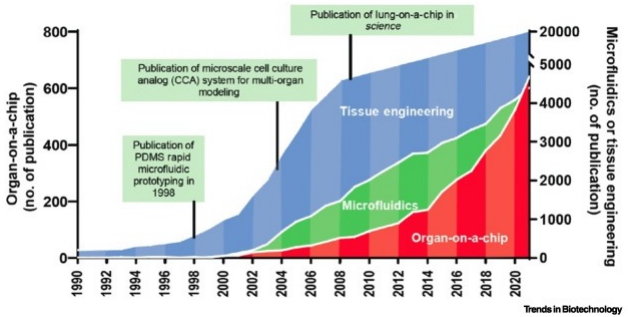
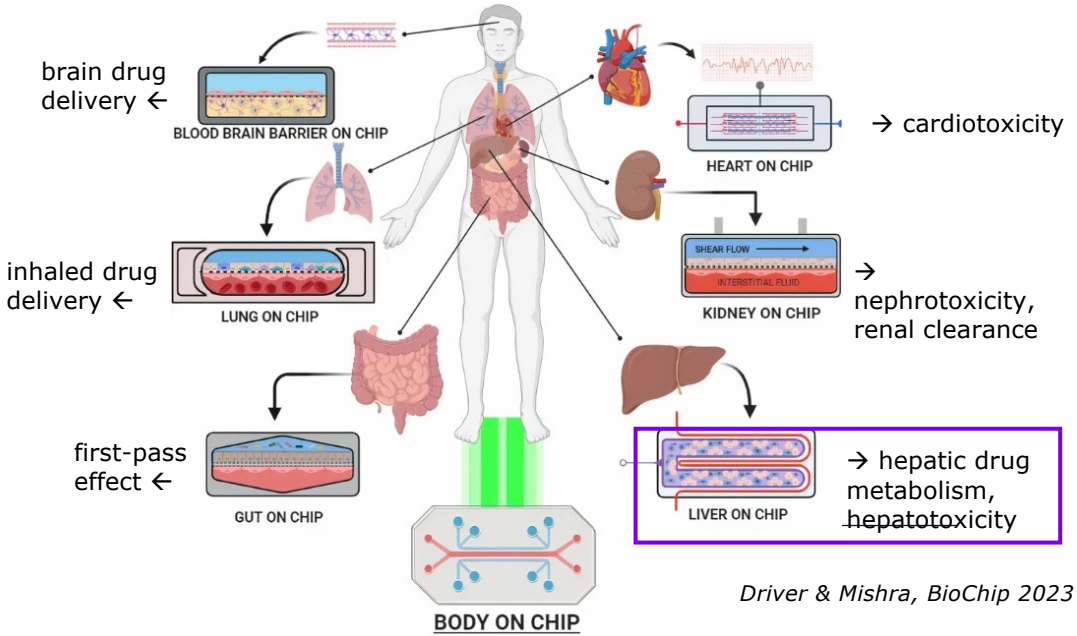
Increasing interest of Organ-on-a-Chip (OoC) technology for ADME



Wide development of OoC since 2010 with progress on polymers, microfluidics and tissue engineering

Various organ-on-a-chip systems and applications



Driver & Mishra, BioChip 2023

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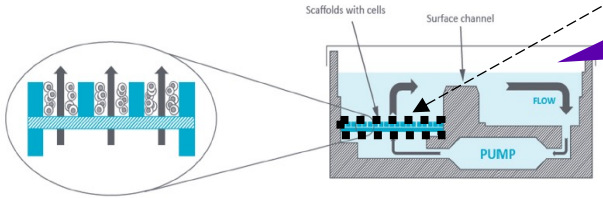
Liver-chip: Example of the PhysioMimix® Platform Liverchip

"Mimicking as close as possible the haemodynamic and 3D architecture of the liver"

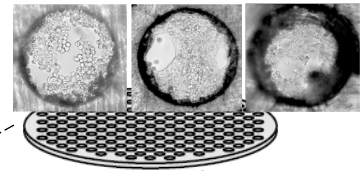
Controller with three 12-well plates

Multi-well plate with 12 culture chambers



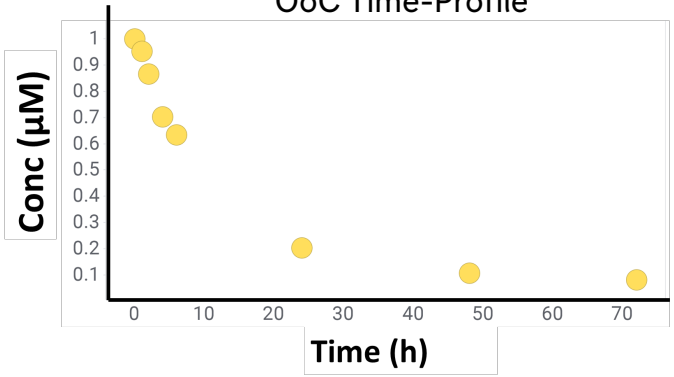
Scheme of one chamber of the plate with 1 scaffold

Collagen-coated 3D scaffold



Sampling

OoC Time-Profile



The applied medium flow is controlled very carefully, thereby mimicking blood flow and vessels

300 channels/scaffold and flow rate at 1 µL/sec, governed by physiological flow and shear stress observed in vivo

- Channel width: ~ 0.3 mm, governed by tissue morphogenesis
- Channel depth: ~ 0.2 mm, governed by oxygen transport limitation

Non-PDMS-based chip

Vivares et al., Xenobiotica

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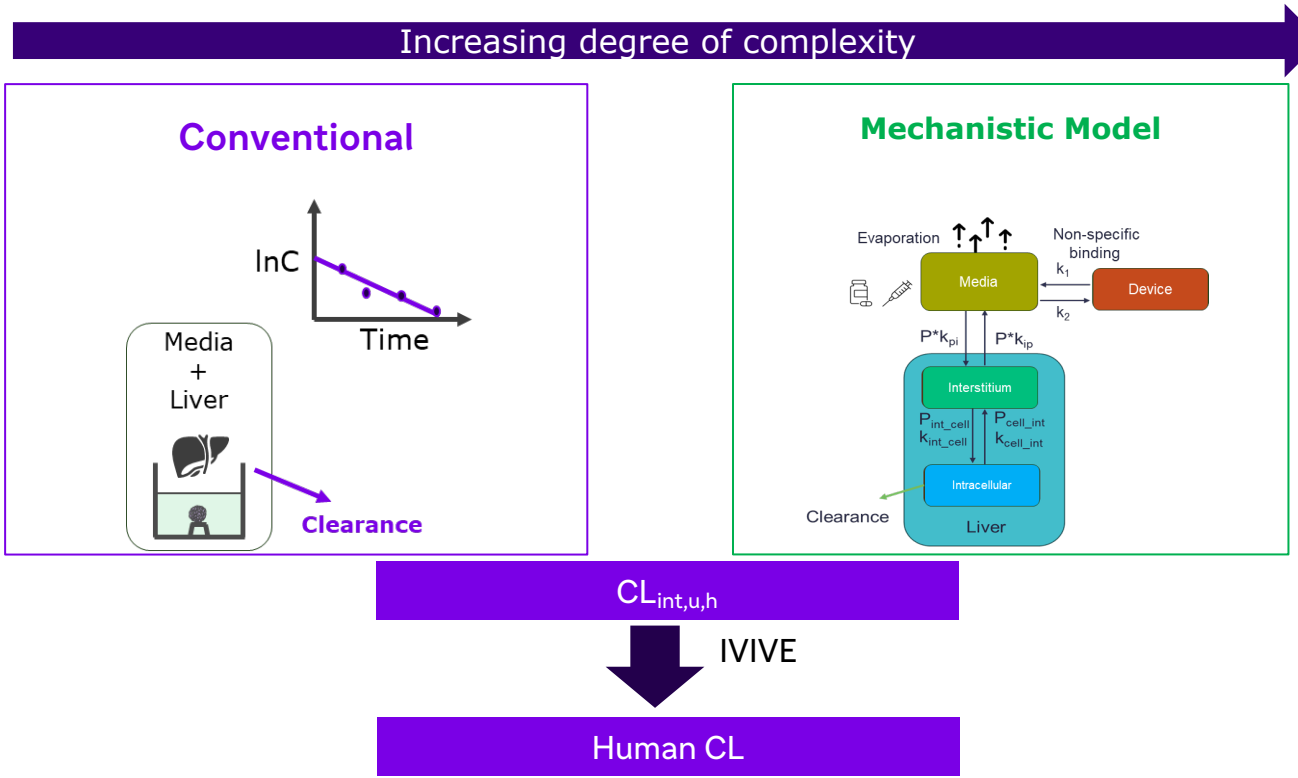
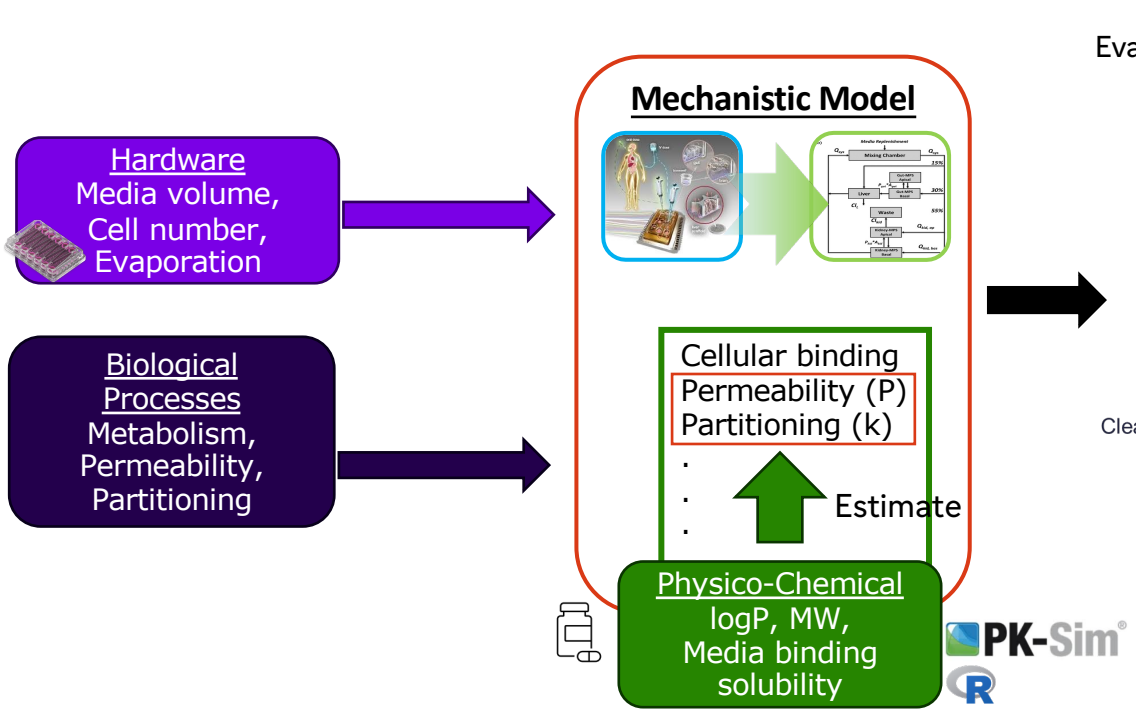
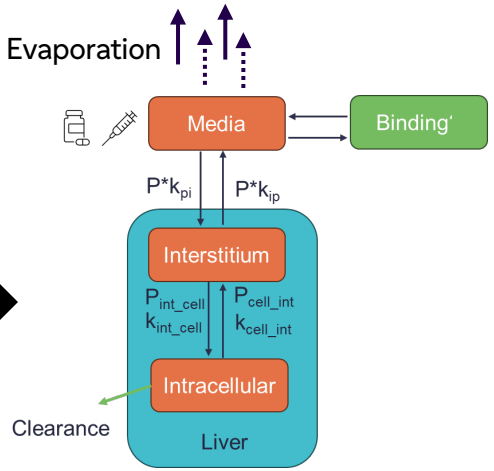
Which in-silico method is Superior for Human Hepatic CL Estimation?



Mechanistic Modeling Approach

- Model mapping hardware (OoC conditions) and biological Processes





1. Maximal information used to develop mathematical model
2. Deconvolute active and passive processes
    1. Metabolism
    2. Partitioning, permeability

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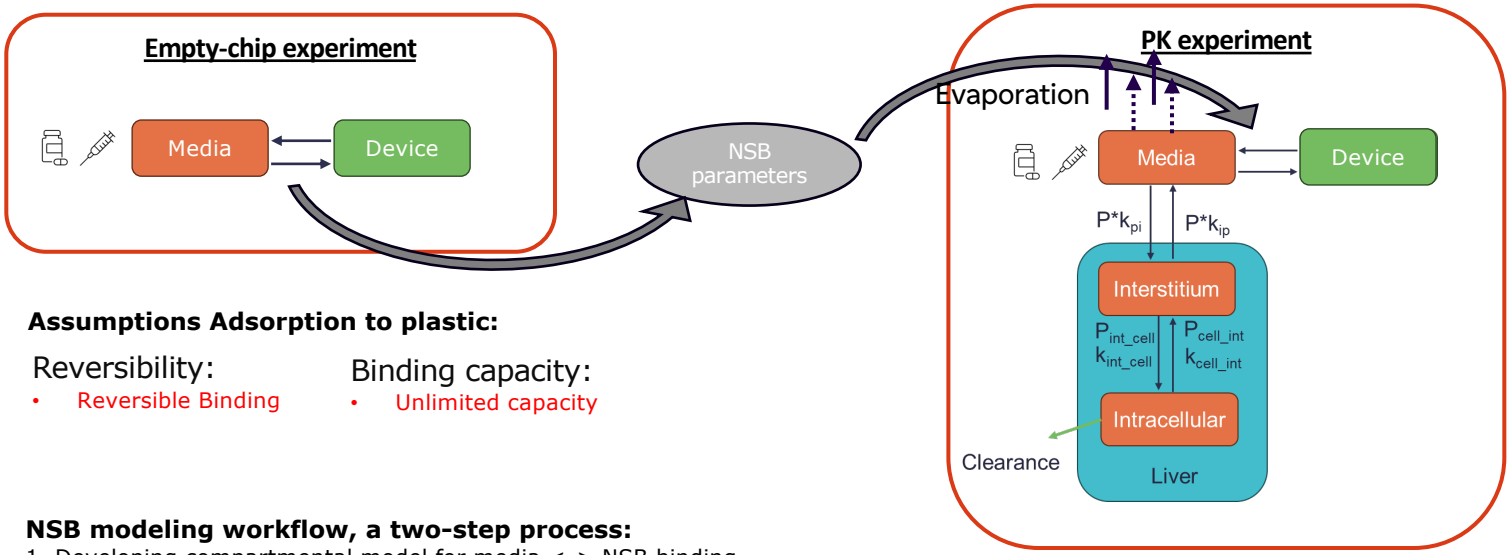
Non-Specific Binding (NSB) Modeling



Assumptions Adsorption to plastic:

Reversibility:
- Reversible Binding

Binding capacity:
- Unlimited capacity

NSB modeling workflow, a two-step process:

1. Developing compartmental model for media <-> NSB binding
   Fitting parameters/rates/% binding → NSB parameters

2. Expanding liver Mechanistic Model with NSB binding
   Implementing parameters from step 1 and re-fit clearance
   Comparing predictions with and without NSB

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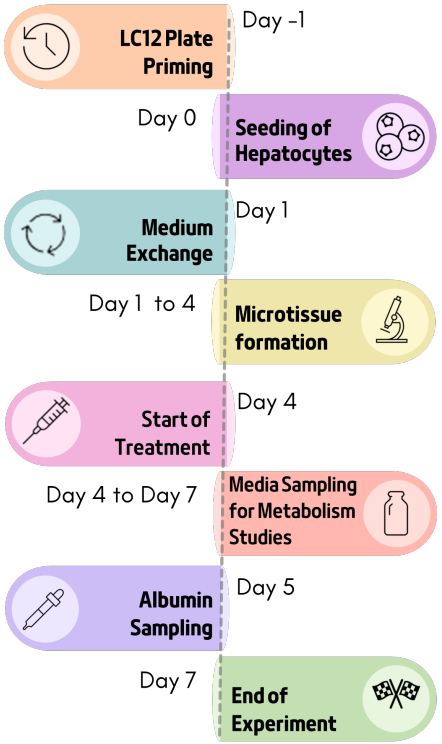
Experimental Design

- Set of different hepatic predominant cleared small molecular drugs (N=11)
  - Diverse hepatic enzymes involved
  - Assuming negligible non-hepatic metabolism
  - High/Mod/Low extraction with clinical PK data available

Compound	pKa	logP	fu_p	RBP	fu_{inc}	Observed Plasma CL (mL/min/kg)	Metabolizing Enzymes
Dextromethorphan	8.85	3.47	0.5	1.76	0.84	8.6	CYP2D6, CYP3A4
Diclofenac	4.2	4.5	0.010	0.55	0.09	7.6	CYP2C9
Midazolam	6.04	3.27	0.017	0.55	0.076	10	CYP3A4, UGT2B7
Tolbutamide	5.27	2.34	0.04	0.75	0.56	0.21 – 0.38	CYP2C9
Repaglinide	3.68 (most acid) /4.82 (most basic)	5.9	0.015	0.85	0.034	7.8	
Lidocaine	7.75	2.44	0.302	0.84	0.863	10.6	
Pioglitazone	5.19	3.53	0.01	0.67	0.14	0.8 – 1.7	
Troglitazone	10.8	3.7	0.026	0.55	0.02	6.6 – 11.8 – 15 (Cl/F)	
Propranolol	9.1	3.6	0.13	0.83	0.73	15	UGT
Compound A	12.1	3.42	0.01	0.75	0.47	14 - 17	
Compound B	4.1	5.5	0.0003	0.60	0.012	1.4 – 1.9	UGT1A4, CYP2C8

- Different biological donors: RAS (n=2), S1610T (n=2), S1682T (n=2)
- Control for assessing Non-specific binding kinetic



fu_p: fraction of drug unbound in plasma
R_{BP}: blood-to-plasma concentration ratio
fu_{inc}: unbound fraction of drug investigated in the medium

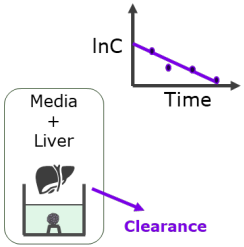
Compare Predictable Performance of Conventional Approach vs. Mechanistic Model

Reported CL

Conventional approach

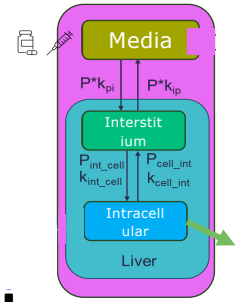
Mechanistic model

Literature Reported
Total hepatic clearance



IVIVE

Conventional Approach
Total hepatic clearance



IVIVE

Mechanistic model
Total hepatic clearance

CL Pred Accuracy

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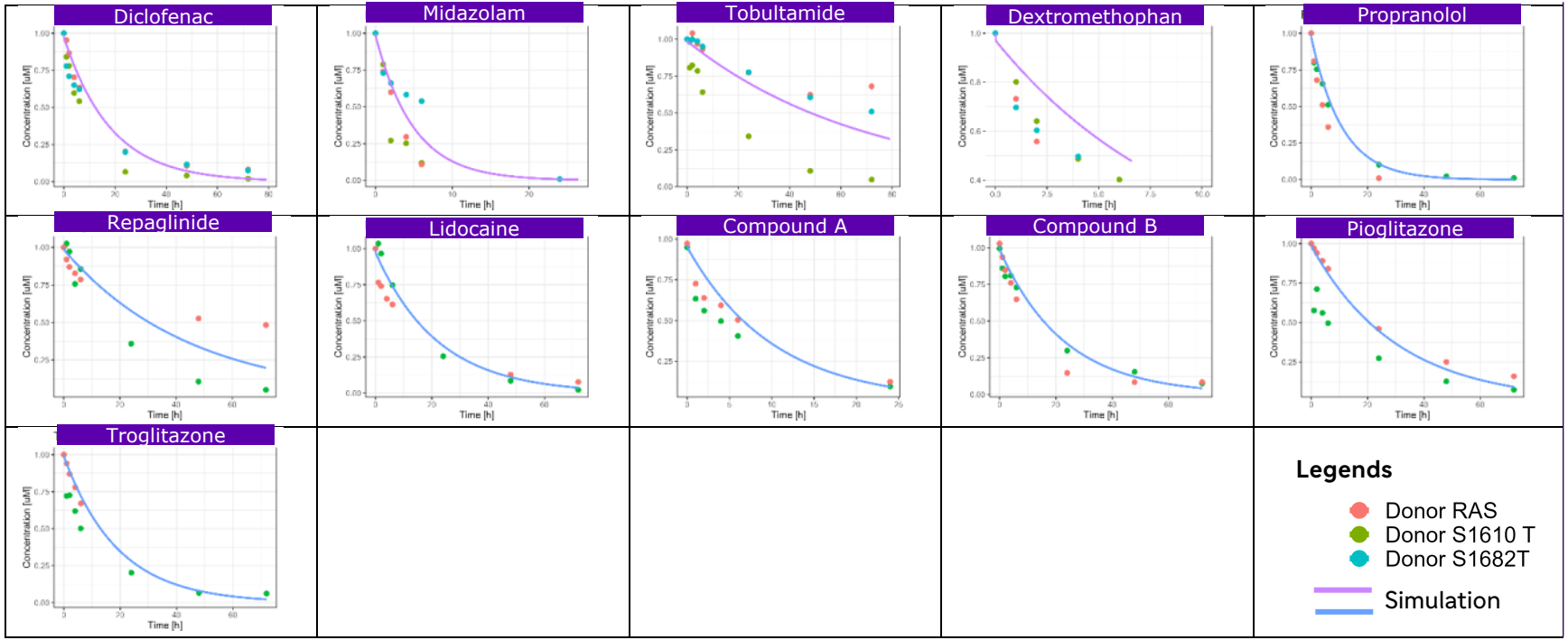
Mechanistic Model Fits (On-chip PK)



Model fits On-chip PK were adequately fitted using Mechanistic Model

* Compounds A&B logP was calibrated with OoC data

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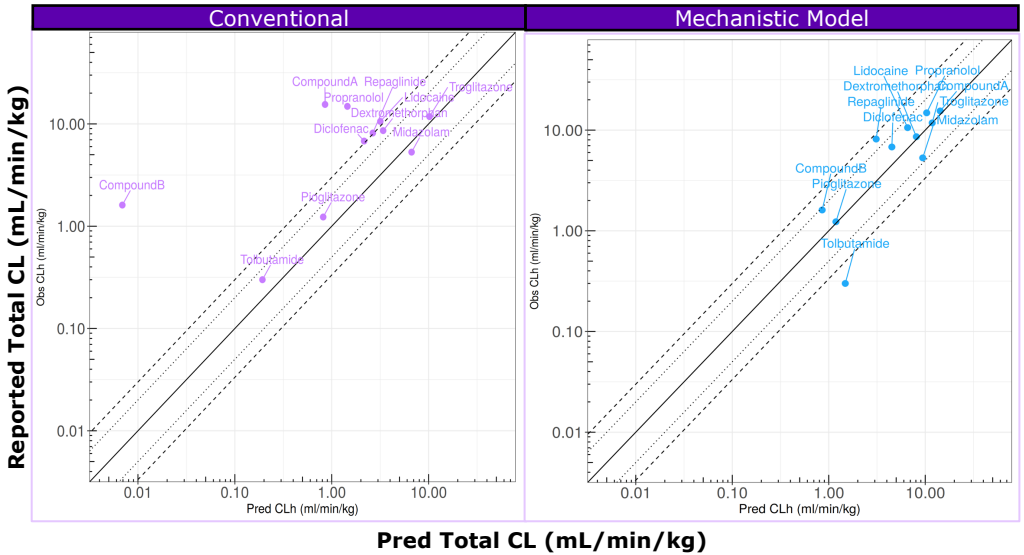
Mechanistic Modeling Approach is superior in Estimating Human Total CL

Human total plasma heaptic clearance (CLh) : Reported CL vs Pred



Note: Dotted and dashed lines are boundaries of 2- and 3-fold change, respectively.

Summary of Predictability of Human CL; n(%)

% of compounds (N=11)	Conventional	Mechanistic Model
Within 2-fold	4 (36%)	9 (82%)
Within 3-fold	1 (9%)	1 (9%)
Outside	6 (55%)	1 (9%)

* Compounds A&B logP was calibrated with OoC data

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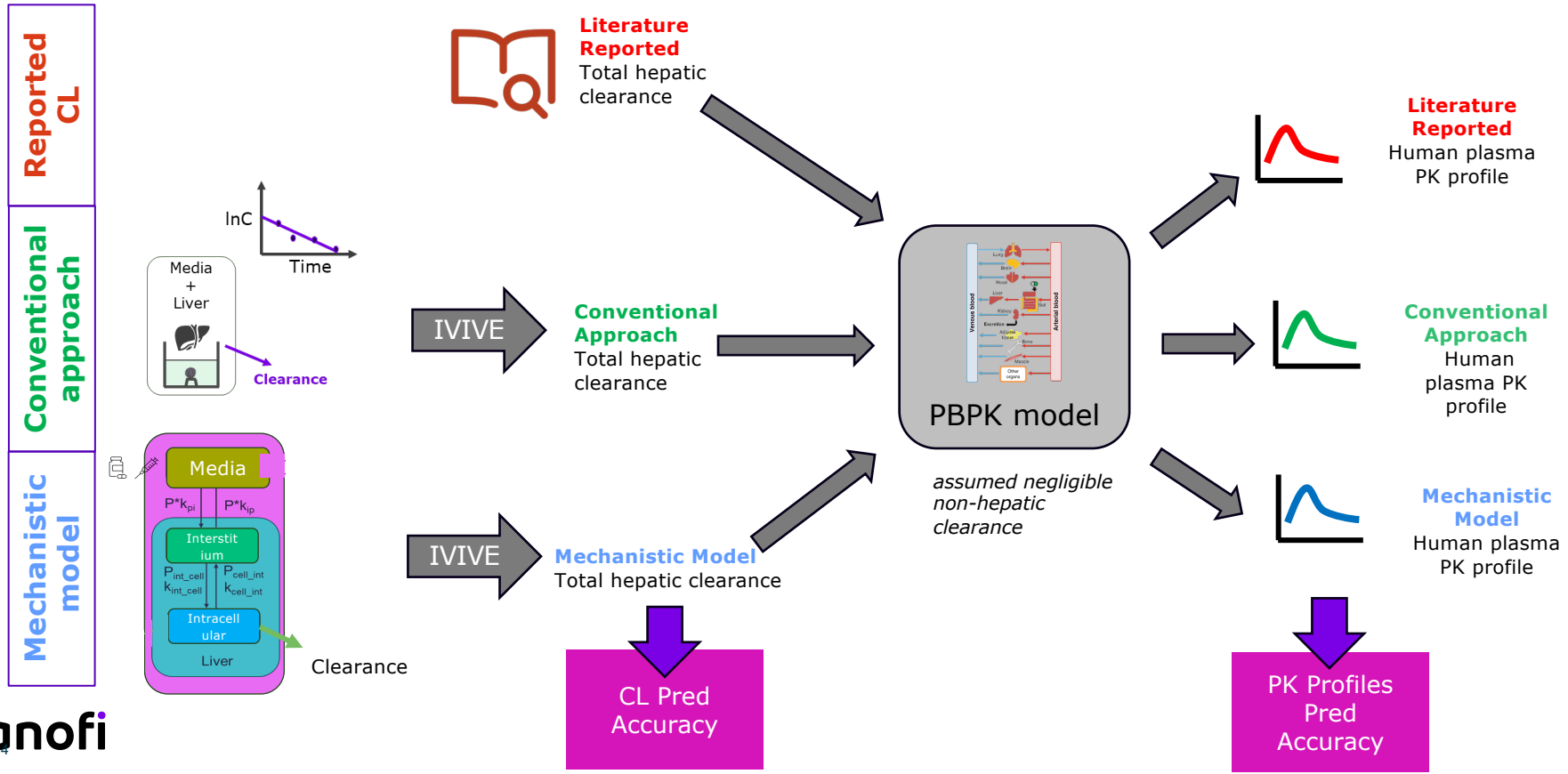
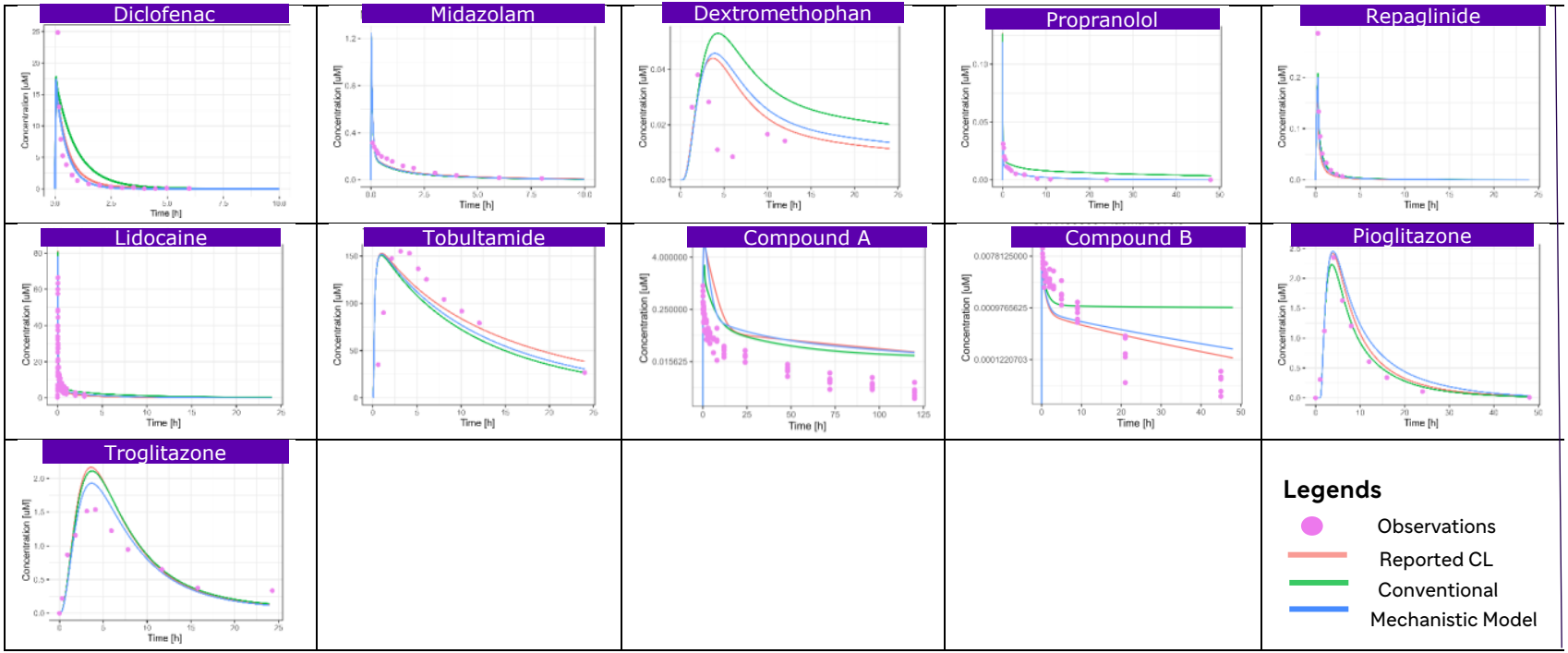
Compare Predictable Performance of Conventional Approach vs. Mechanistic Model



Comparison of PBPK Human Plasma PK Profiles Predictions with Human Total Clearance Estimations from Different Sources

Reported CL vs. Conventional vs. Mechanistic Model



Human PBPK model plasma PK predictions, based on total clearance (CL) estimations from both mechanistic model simulations and literature, are comparable

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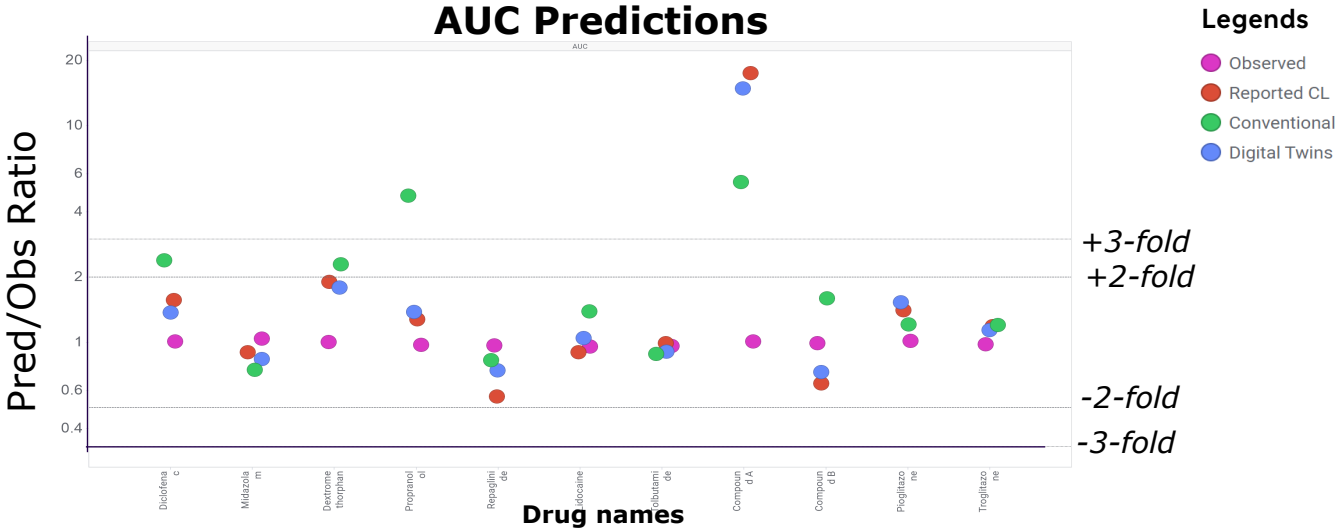
Superior Accuracy of Human Plasma PBPK AUC Predictions using Mechanistic Model Total CL Estimation



Summary of Predictability of Human AUC; n(%)

% of compounds (N=11)	Reported CL	Conventional	Mechanistic Model
Within 2-fold	10 (91%)	7 (63%)	10 (91%)
Within 3-fold	0 (0%)	2 (18%)	0 (0%)
Outside	1 (9%)	2 (18%)	1 (9%)

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Key Take Home Messages

- Analyzing OoC data using mechanistic model is superior to conventional method in the accuracy of human CL estimations because:
  - Mechanistic Model can describe:
    - Experiments conditions/phenomenon (media evaporation, non-specific binding to OoC material)
    - Biological processes (drug distribution between media, interstitium and intracellular)
- Integrating mechanistic model total human CL estimation in PBPK model, allowing adequate human PK profiles prediction
- This approach could be adopted for routine small molecules' PK evaluations for human translation in drug discovery phase

Acknowledgement

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