Advanced Application of Pharmacokinetic Theory on Quantitative Systems Modeling in Drug Discovery and Development

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COI disclosure information

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I have the following financial relationships to disclose for our presentation contents.

- **Employees : Hiroyuki Sayama (Astellas Pharma Inc.)**

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Outline

1. Prediction of Pharmacokinetics in Healthy Subjects

2. Prediction of Pharmacokinetics in Disease States

3. Prediction of Pharmacological Effect in Target Patients

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1. Prediction of Pharmacokinetics in Healthy Subjects

2. Prediction of Pharmacokinetics in Disease States

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Prediction of Pharmacokinetics in Healthy Subjects

Backgrounds

- There are two different approaches.
- How to correct each approach for better predictability was big issue in pharmaceutical industry.
- More practical approach to predict PK parameters as well as plasma concentration-time (C-T) profile was strongly demanded.

Physiological Approach

CL: IVIVE
V_{ss}: tissue composition model
C-T profile: PBPK model

✓ Trend to underpredict CL
✓ Needs to clarify physiological manner of elimination/distribution

Empirical Approach

CL: Allometric Scaling
V_{ss}: Allometric Scaling
C-T profile: Dedrick approach

✓ Trend to overpredict CL
✓ Can be easily applied regardless of elimination /distribution mechanisms

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Feasible Hybrid Approaches
in drug development process in pharmaceutical industries

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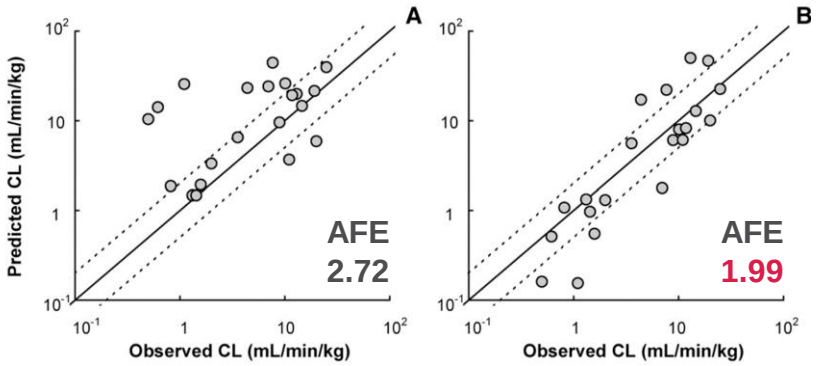
IVIVE: In Vitro-In Vivo Extrapolation

Prediction of Pharmacokinetics in Healthy Subjects

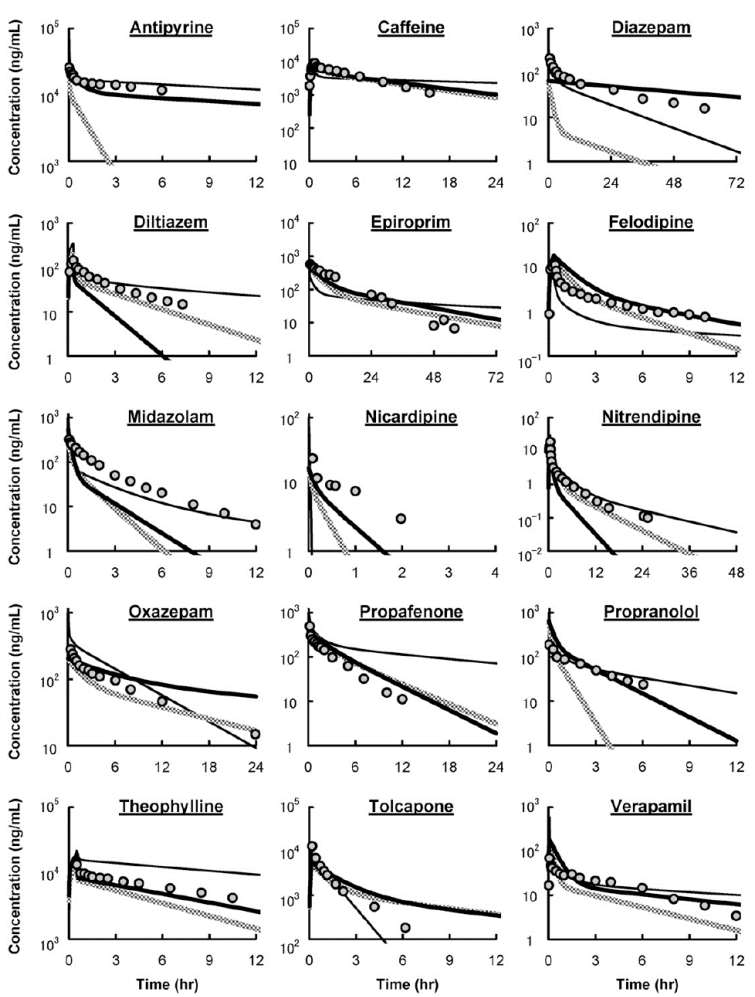
Establishment of the Hybrid Dedrick Approach

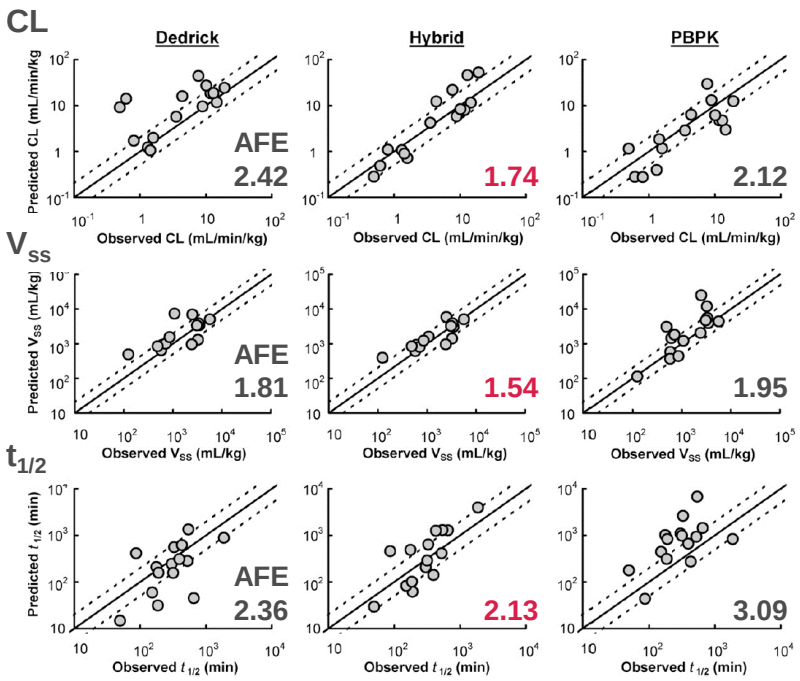
- ✓ Allometric scaling corrected with $CL_{int,vitro}$ yielded better accuracy in CL prediction.
- ✓ The same theory was applied to prediction of C-T profile by Dedrick approach (***hybrid Dedrick approach***).
- ✓ The hybrid Dedrick approach showed better prediction than conventional Dedrick and PBPK approaches.

Allometry



Allometry ($CL_{int,vitro}$ correction)





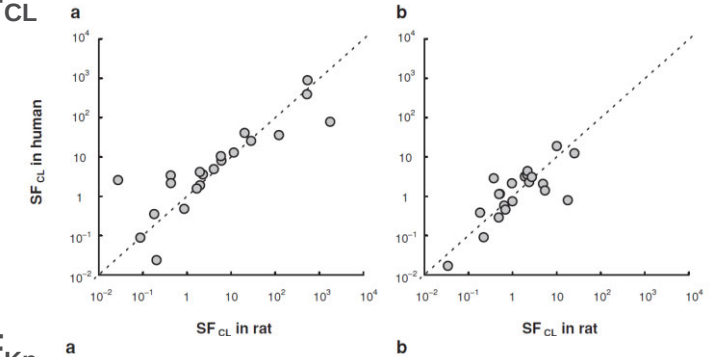
Sayama et. al., *Drug Metab Dispos*, 41:498 (2013)

Prediction of Pharmacokinetics in Healthy Subjects

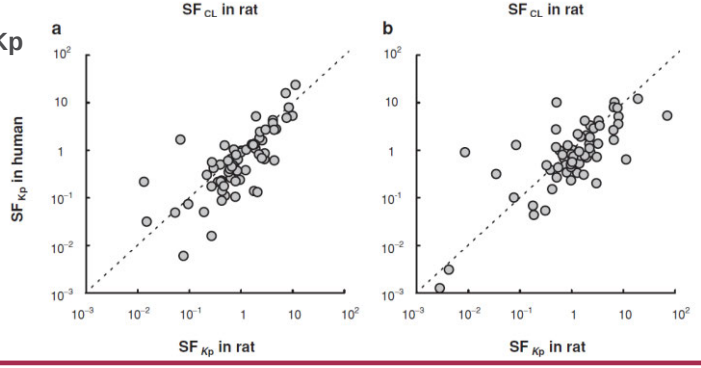
Establishment of the Hybrid PBPK Approach

- ✓ SFs were comparable between rat and human for both;
  - CL prediction by IVIVE
  - V_{ss} prediction by tissue composition model
- ✓ Prediction accuracies were improved by introducing SFs not only for CL but for V_{ss}.

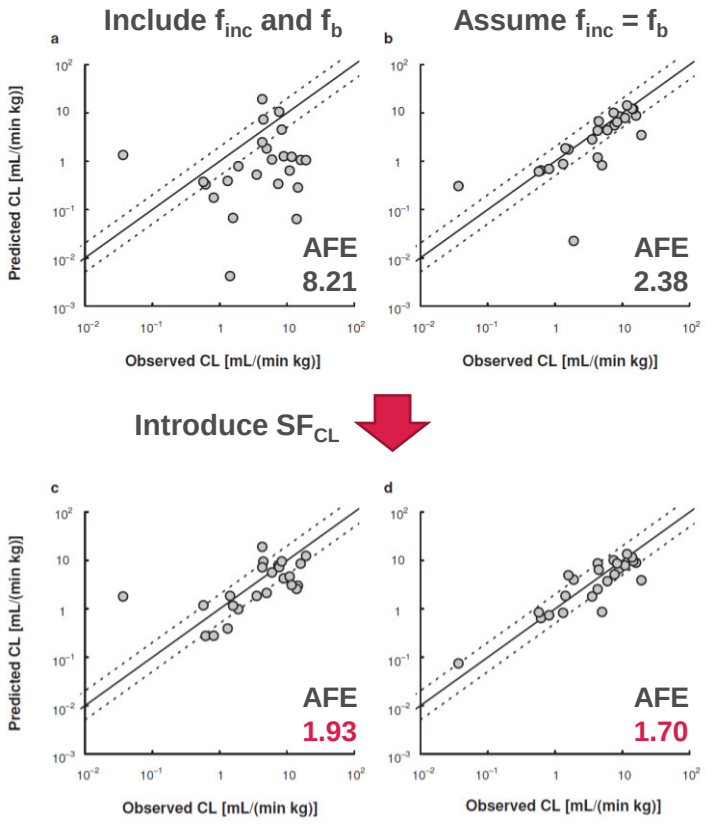
SF_{CL}



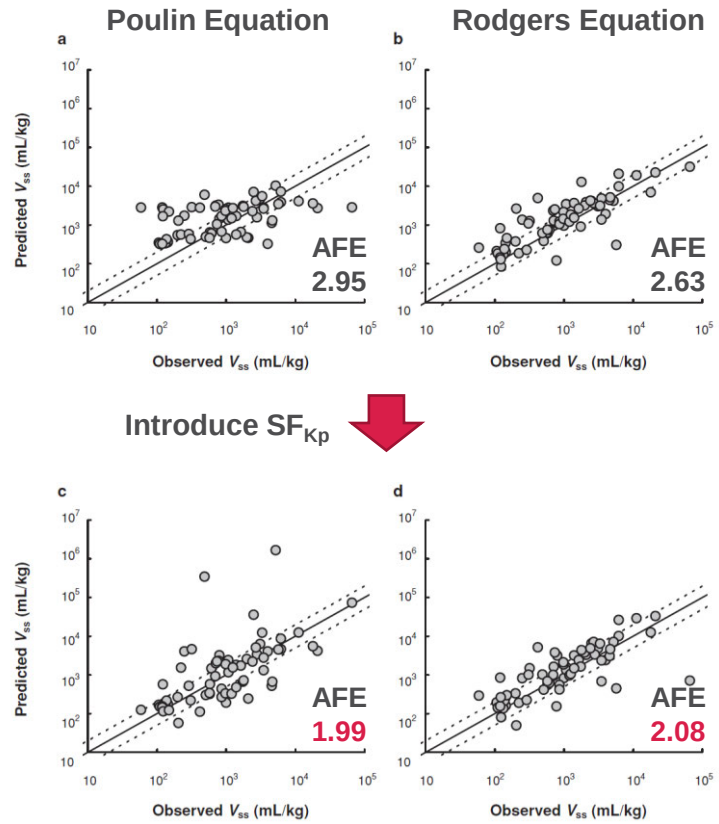
SF_{Kp}



CL Prediction



V_{ss} Prediction



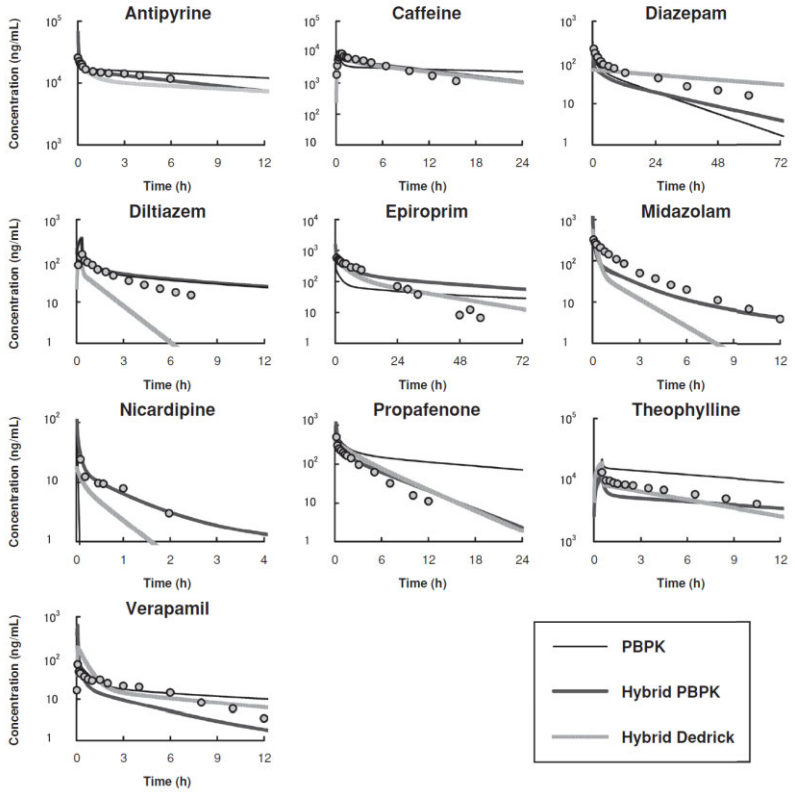
SF: Scaling Factor = difference between predictions and actual observations

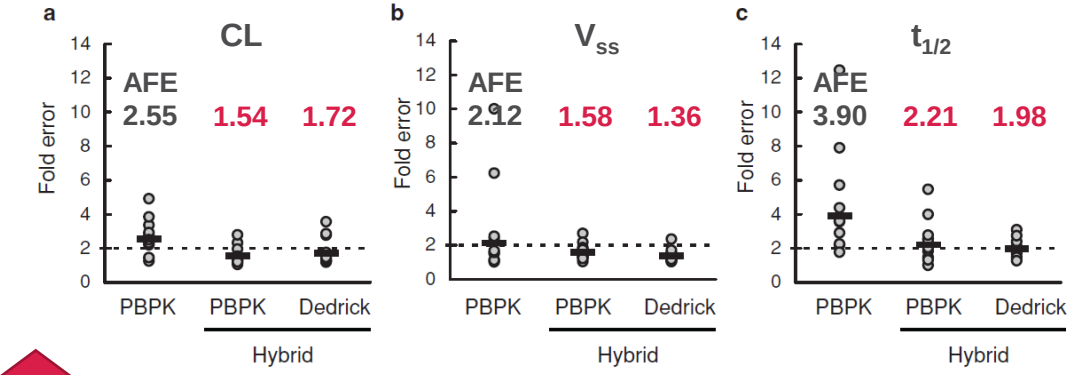
Sayama et. al., *J Pharm Sci*, 102:4193 (2013)

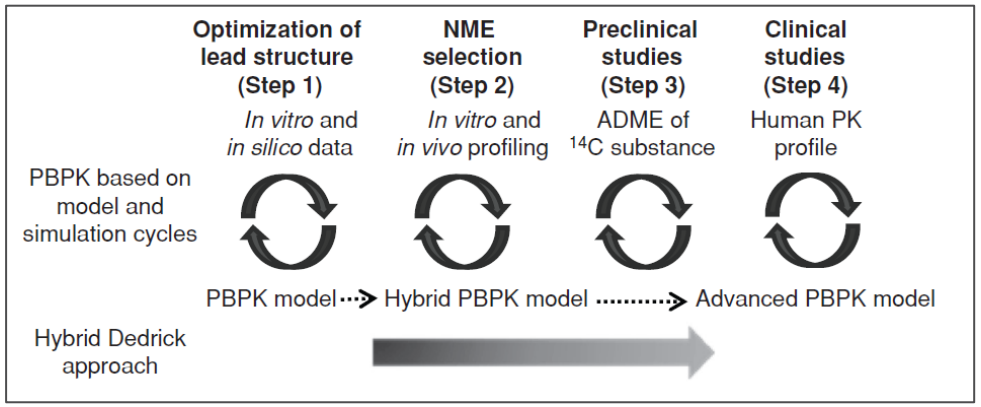
Prediction of Pharmacokinetics in Healthy Subjects

Establishment of the Hybrid PBPK Approach & Prediction Scheme

- ✓ SF_{CL} and SF_{Kp} were introduced to PBPK model to predict C-T profile (***hybrid PBPK model***).
- ✓ Both hybrid PBPK and hybrid Dedrick approaches showed higher prediction accuracy.







Feasible hybrid approaches have been established, and the process for translational PK prediction has been streamlined.

Sayama et. al., *J Pharm Sci*, 102:4193 (2013)

Outline

1. Prediction of Pharmacokinetics in Healthy Subjects

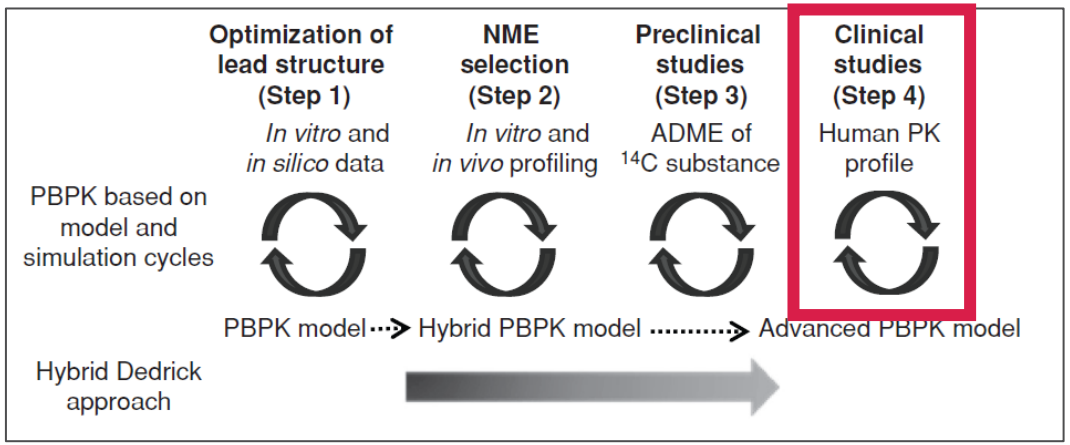
2. Prediction of Pharmacokinetics in Disease States

3. Prediction of Pharmacological Effect in Target Patients

Prediction of Pharmacokinetics in Disease States

Backgrounds

- PBPK model can be applied to prediction of effect of intrinsic/extrinsic factors on PK profile in human.
- Chronic kidney disease (CKD) is associated with multiple physiological changes and alters drug PK.
- Bottom-up approach requires labor-intensive experiments to develop PBPK model in CKD.



Bottom-Up Approach

- ✓ Predicts PK profile in patients based on preclinical data.
- ✓ Needs to clarify ADME profile for each investigated compound.

Top-Down Approach

- ✓ Predicts PK profile in patients based on available clinical information.
- ✓ Needs comprehensive survey for clinical data.

Top-down approach was applied to expand the established PBPK model to clinical application

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Prediction of Pharmacokinetics in Disease States

Establishment of the PBPK Model for CKD Patients

- ✓ PK parameters for 151 compounds in CKD patients were extensively surveyed to obtain SFs in disease conditions.
- ✓ The SFs were introduced to PBPK model to simulate C-T profile.
- ✓ The PBPK model provided good prediction in CKD patients.

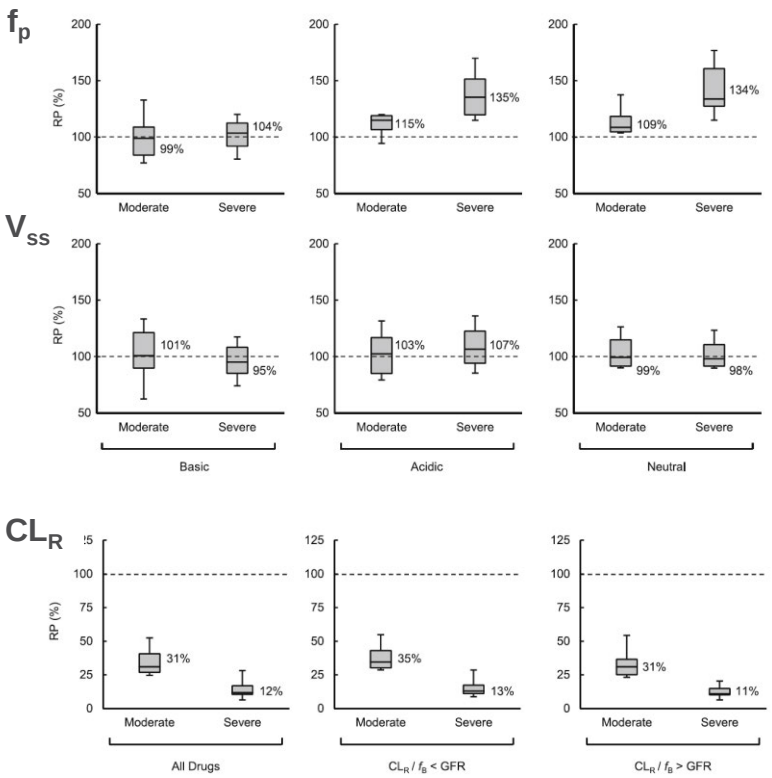
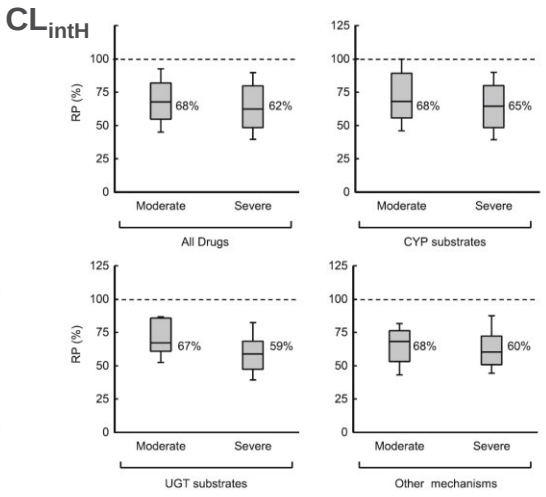
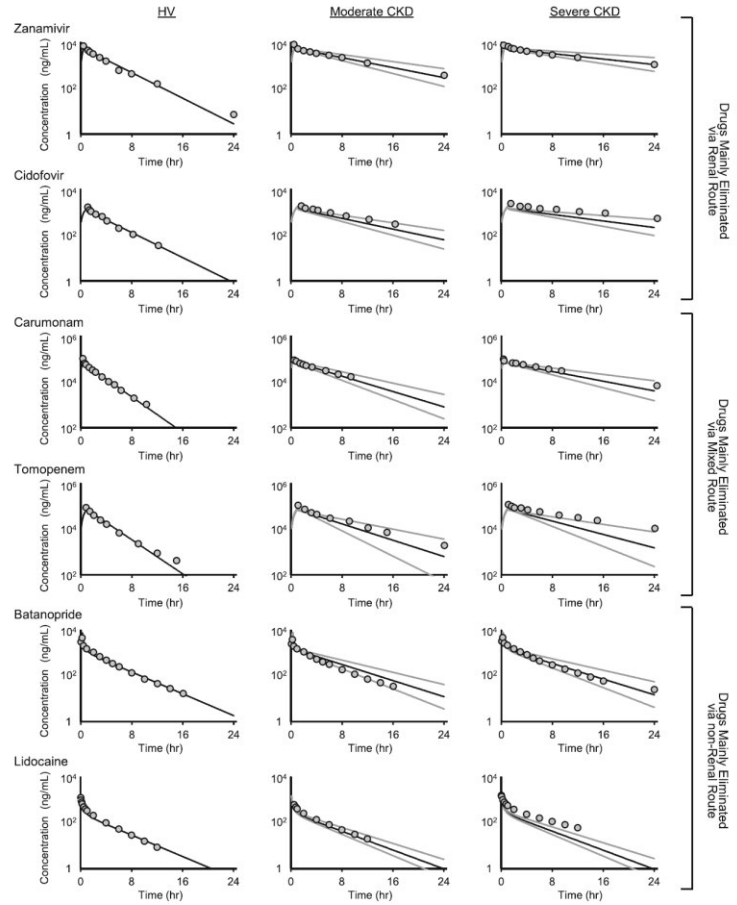


Table III. SFs for CL_R, CL_{UintH}, and f_p for the Prediction of CL and PK in CKD

Parameter	Group	Moderate CKD (%)	Severe CKD (%)
CL_R	All drugs	24–47	8–23
CL_{UintH}	All drugs	55–82	48–80
f_p	Basic	84–109	92–113
	Acidic	107–119	120–151
	Neutral	105–118	127–161





PBPK theory was successfully applied to PK prediction in disease conditions.

CKD: Chronic Kidney Disease

Sayama et. al., *AAPS J*, 16:1018 (2014)

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3. Prediction of Pharmacological Effect in Target Patients

Prediction of Pharmacological Effect in Target Patients

Backgrounds

- PK-PD relationship is sometimes too complex to be described by conventional modeling approach.
- Conventional PK-PD model alone cannot address research questions from the project team;

- ☐ *Quantitatively understand complex PK-PD response in mice*
- ☐ *Predict / compare clinical response for competitor differentiation*

Mechanistic PK-PD Model

- ✓ Describes PK-PD relationship by statistical approach.
- ✓ CAN represent drug behavior such as covalent binding to target molecule.
- ✓ CANNOT consider complex biological mechanisms such as negative feedbacks.

QSP Model

- ✓ Describes dynamic interaction between biological system and therapeutics in physiological manner.
- ✓ CAN support quantitative understanding of complex biological responses.

Mechanistic PK model was combined with QSP approach to address research questions for developing compound

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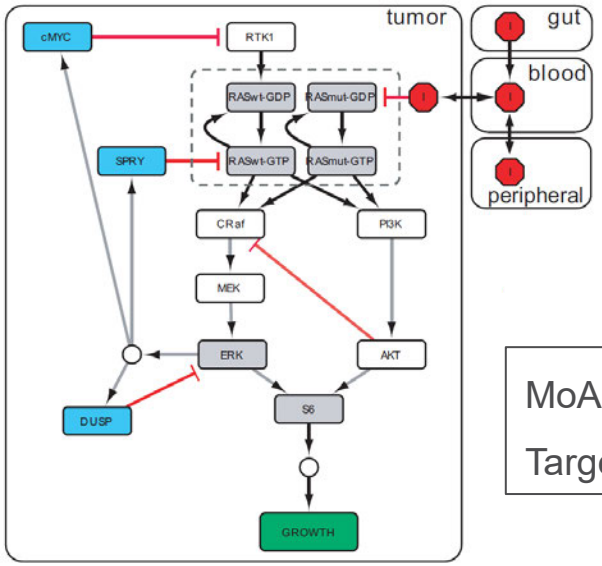
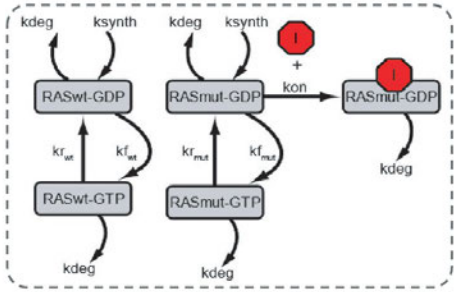
QSP: Quantitative Systems Pharmacology

Prediction of Pharmacological Effect in Target Patients

Establishment of the QSP Model for NSCLC

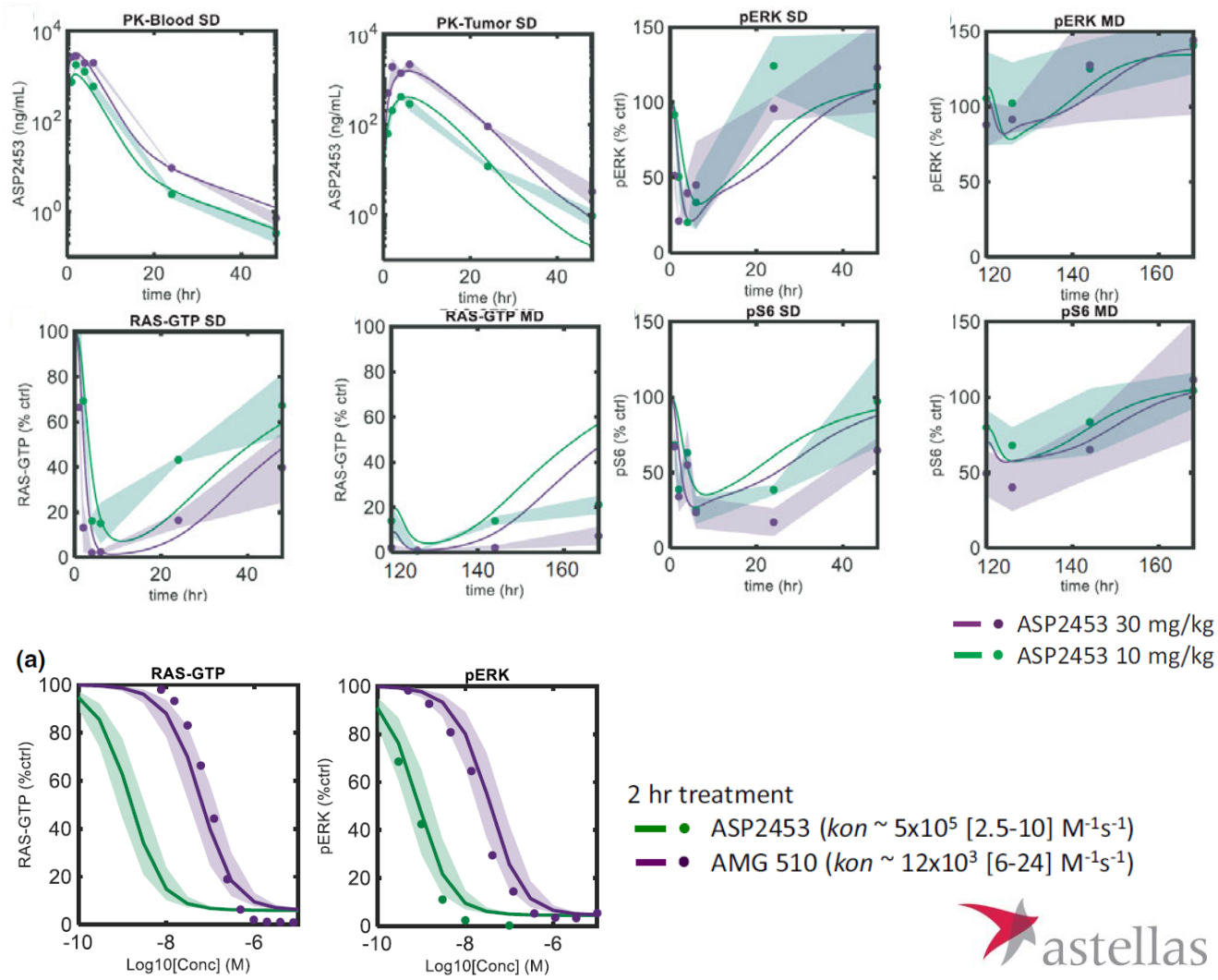
- ✓ A QSP model for MAPK pathway was constructed by considering negative feedbacks within the pathway and covalent binding of drug.
- ✓ The model was re-calibrated using PK-PD dynamics data in xenograft mouse.
  -> expanded to an advanced competitor by bridging using in vitro data.





MoA: *KRAS*^{G12C} covalent inhibitor

Target Indication: NSCLC



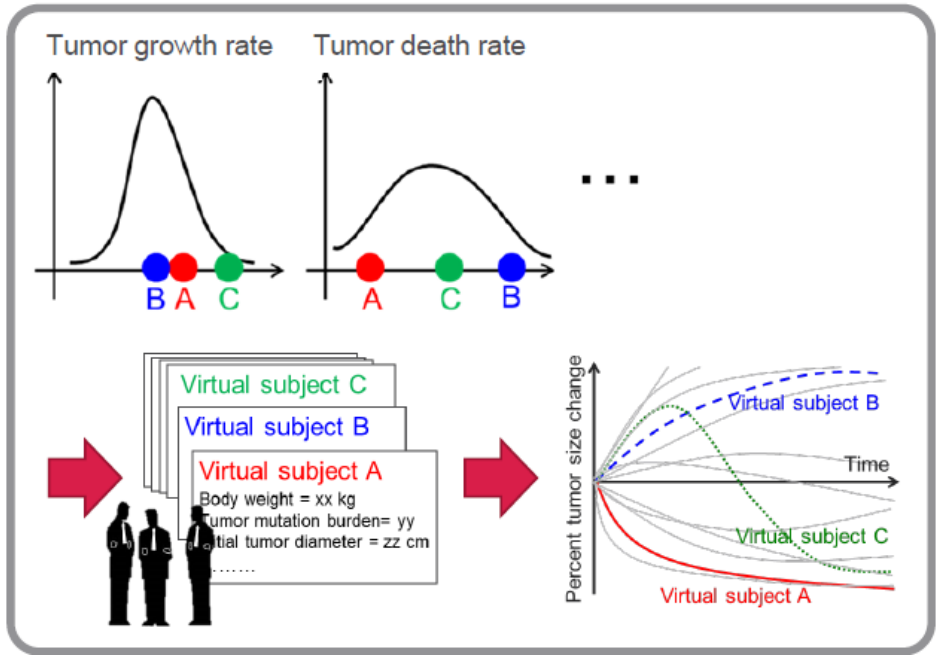
NSCLC: Non-Small Cell Lung Cancer

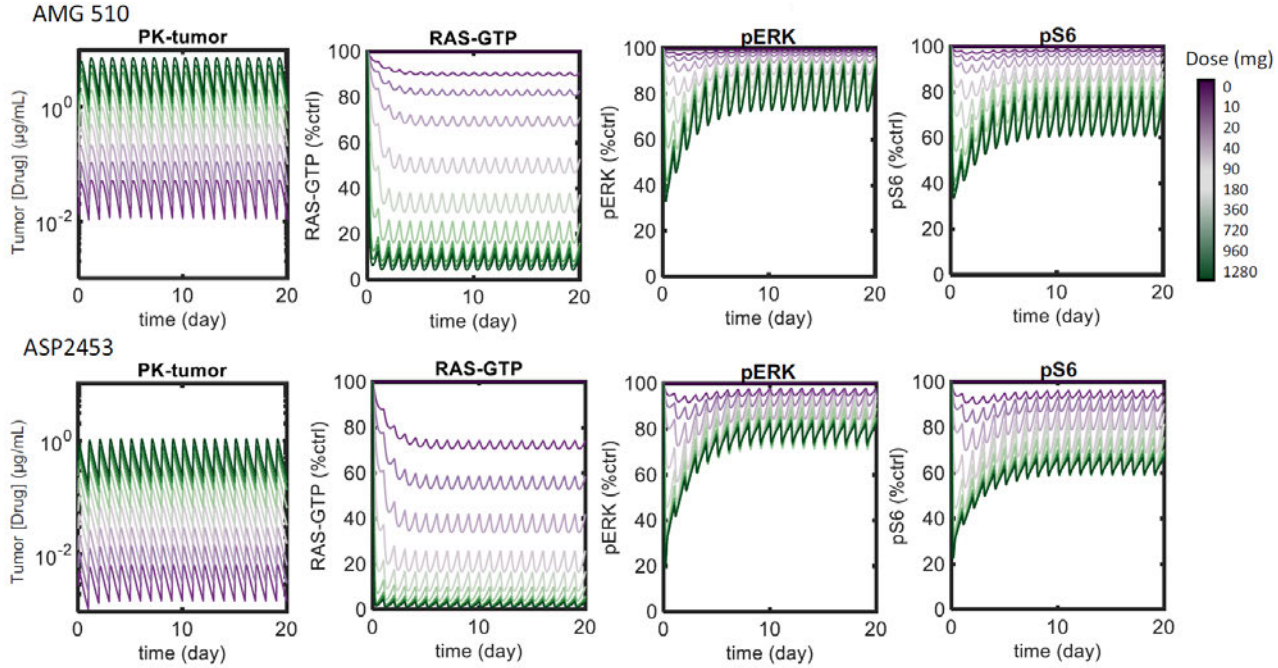
Sayama et. al., *CPT Pharmacometrics Syst Pharmacol*, 10:864 (2021)

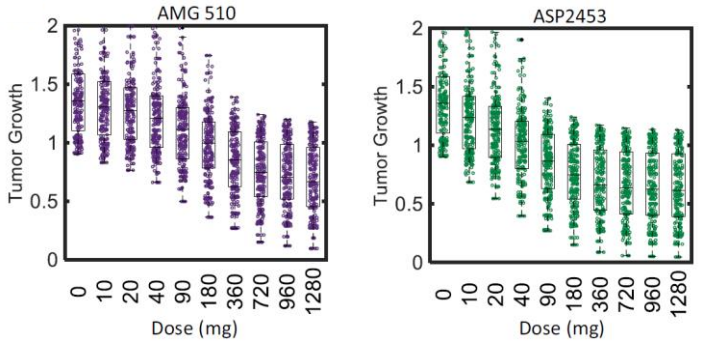
Prediction of Pharmacological Effect in Target Patients

Virtual Clinical Trial Simulation for NSCLC by QSP Model

- ✓ The mouse QSP model was translated to NSCLC patients by considering species difference in PK and available clinical information.
- ✓ Virtual clinical trial simulations were conducted to predict pharmacological effect in patients and support differentiation strategy.



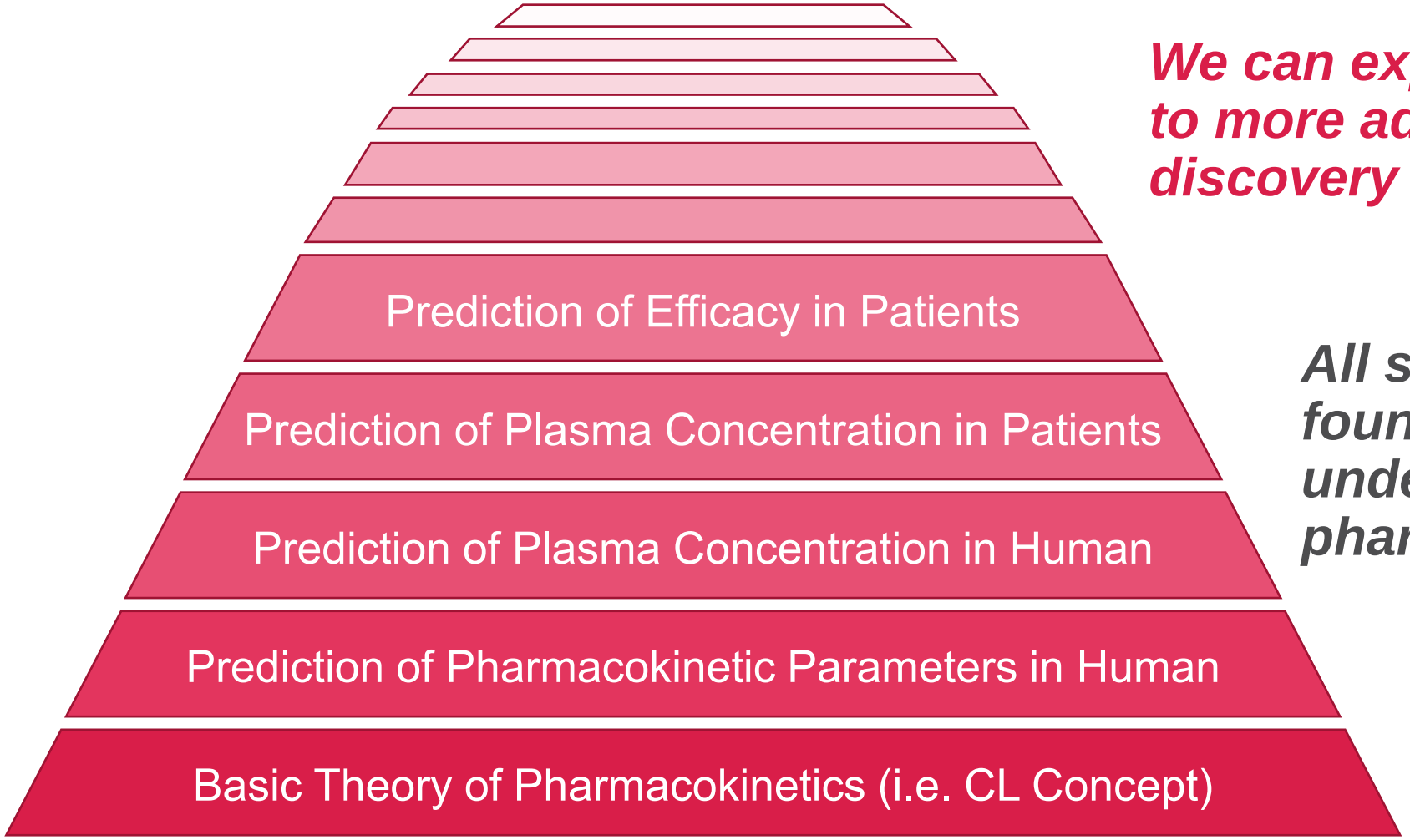




QSP approach combined with mechanistic PK model supported internal decision making.

Sayama et. al., *CPT Pharmacometrics Syst Pharmacol*, 10:864 (2021)

Expansion of Pharmacokinetic Theory and Expertise to Quantitative Systems Modeling



We can expand our expertise to more advanced field of drug discovery and development!

All system models are founded on basic understandings of pharmacokinetic theory!

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Summary

- Effectively combined / properly used M&S approaches can accelerate R&D;
  - Physiological vs empirical approaches

    Established practical hybrid approaches for translational PK prediction in human
  - Bottom-up vs top-down approaches

    Utilized the PBPK model to PK prediction in disease patients
  - Mechanistic PK-PD vs QSP models

    Applied mathematical modeling skills to prediction of pharmacological effect
- We can further expand deep understanding of PK theory and expertise for systemic modeling to various fields of drug discovery and development.

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