メカニズムに基づいたモデル解析の創薬研究への活用

Application of mechanistic model analysis in drug discovery research

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Mechanistic PK model usage in drug discovery and development at pre-clinical stage

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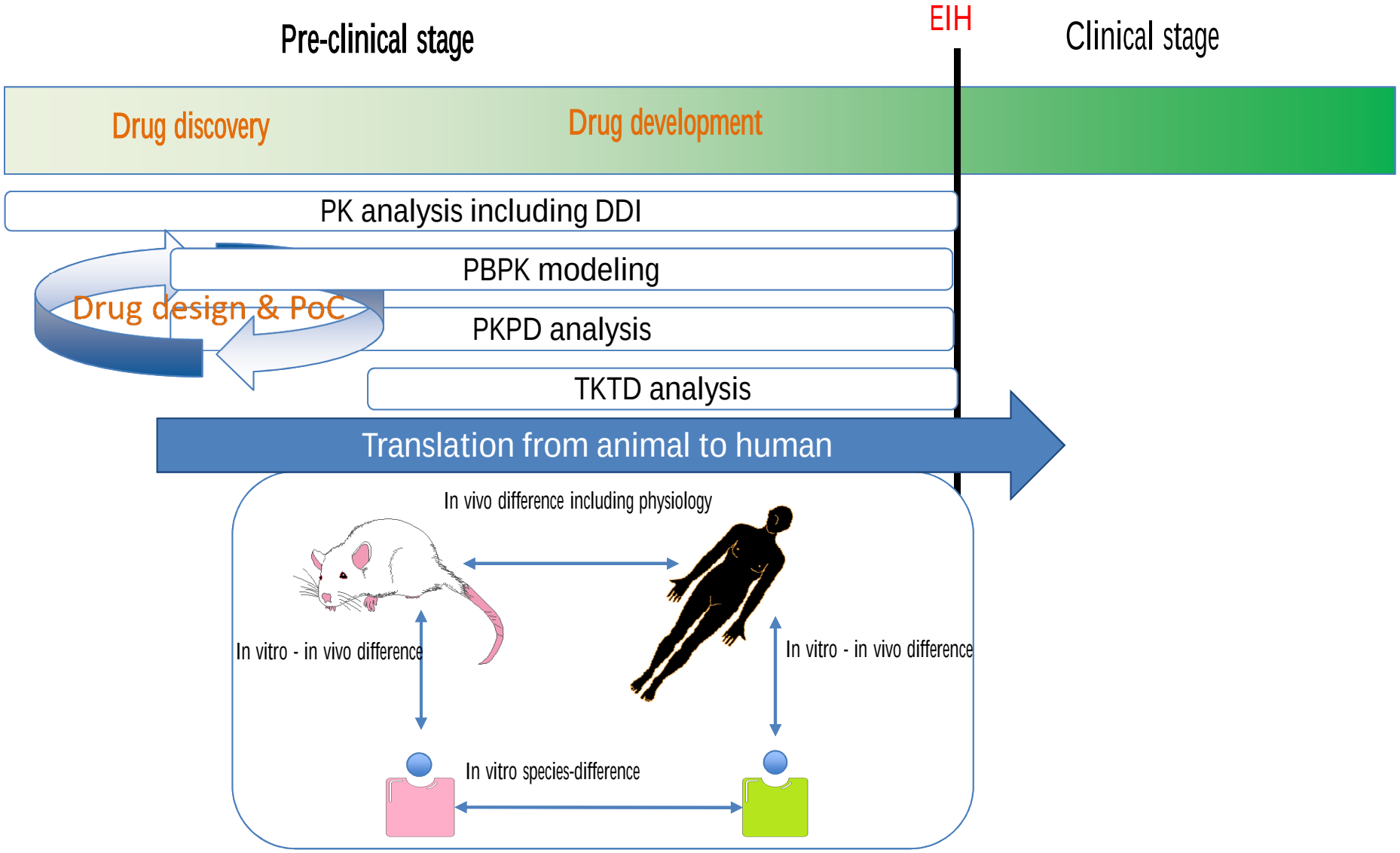

Contents

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- A diffusion model analysis considering skin metabolism
  - Transdermal vitamin D_3 analogues
- PKPD analysis
  - An SGLT2 inhibitor, tofogliflozin

A diffusion model analysis considering skin metabolism

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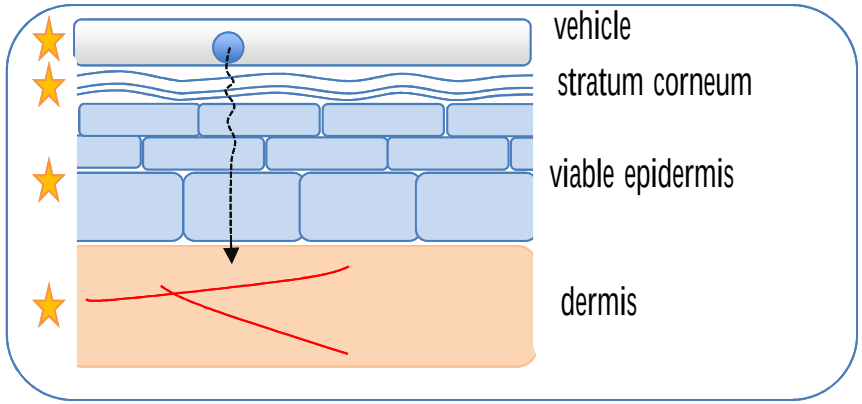
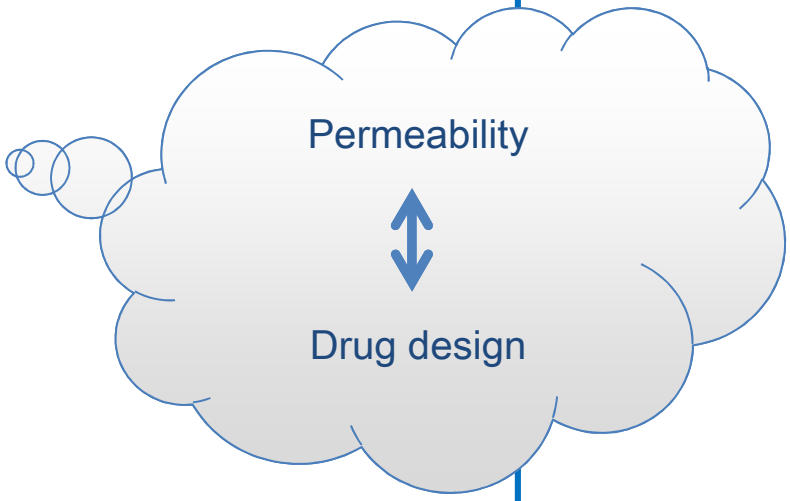
Drug: transdermal vitamin D3 analogues

- **Disease area:** psoriasis
- **Target organ:** viable epidermis (skin)
- **MOA:** 'induction of cell differentiation' and 'inhibition of keratinocyte proliferation'
- **Ideal PK property:**
  - ✓ **Eliminate rapidly before penetrated into blood circulation** to avoid side effect





Rat skin permeation profile of Maxacalcitol

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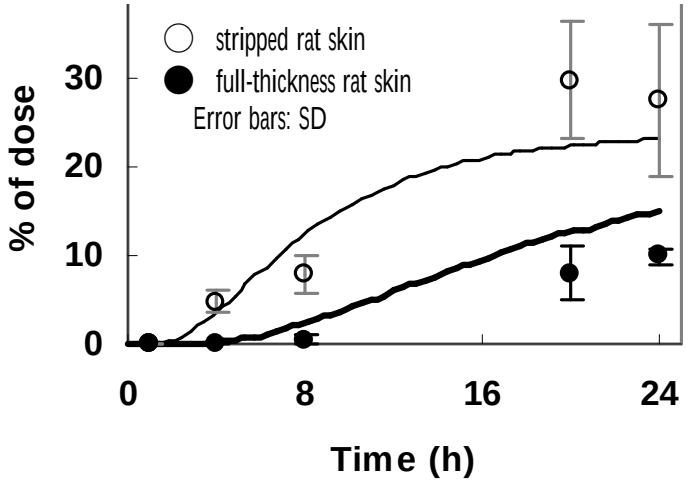
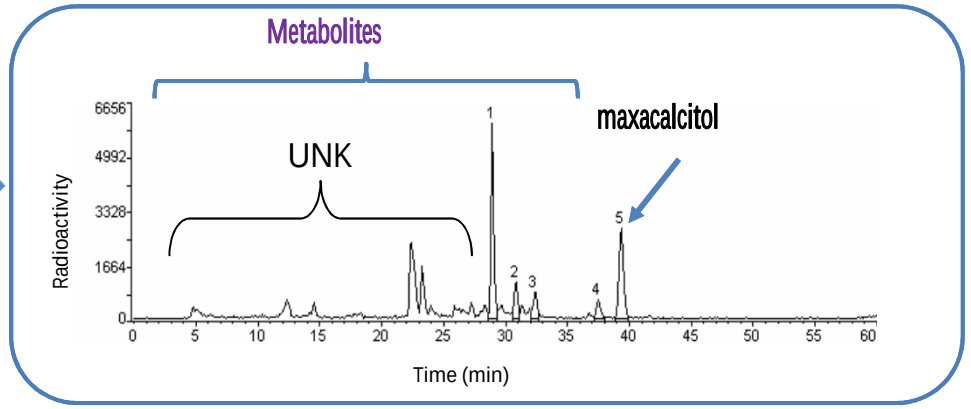
Permeated unchanged maxacalcitol through Skin



Metabolic profile in receptor fluid



- ✓ Maxacalcitol was highly metabolized in skin.
- ✓ Skin metabolism might affect apparent permeability of a drug.

Yamaguchi et al., ***Pharm Res*** 23: 680–688, 2006

Diffusion model analysis considering skin metabolism

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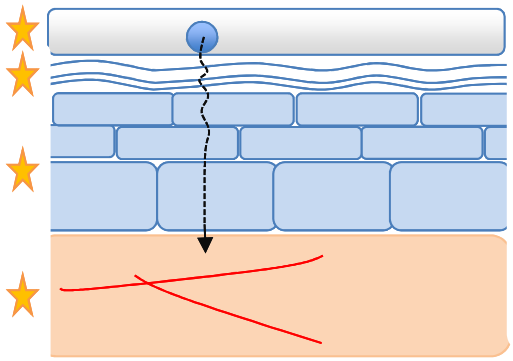
Divide permeation factors into 'diffusivity' and 'metabolic rate'



Vehicle [partitioning]

Stratum corneum [diffusivity]

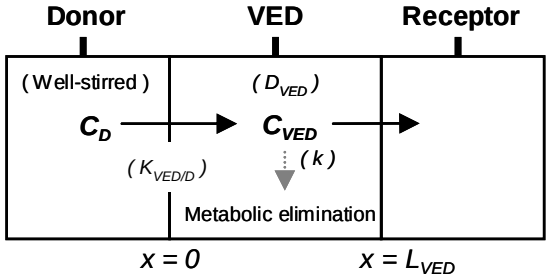
Viable epidermis [diffusivity, metabolism]

Dermis [diffusivity]

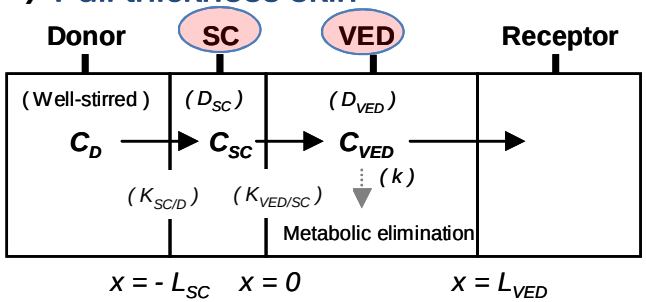
VED
(viable epidermis and dermis)

Modeling

a) Stripped skin



b) Full thickness skin



Low diffusivity in VED blocks permeation of highly lipophilic compounds

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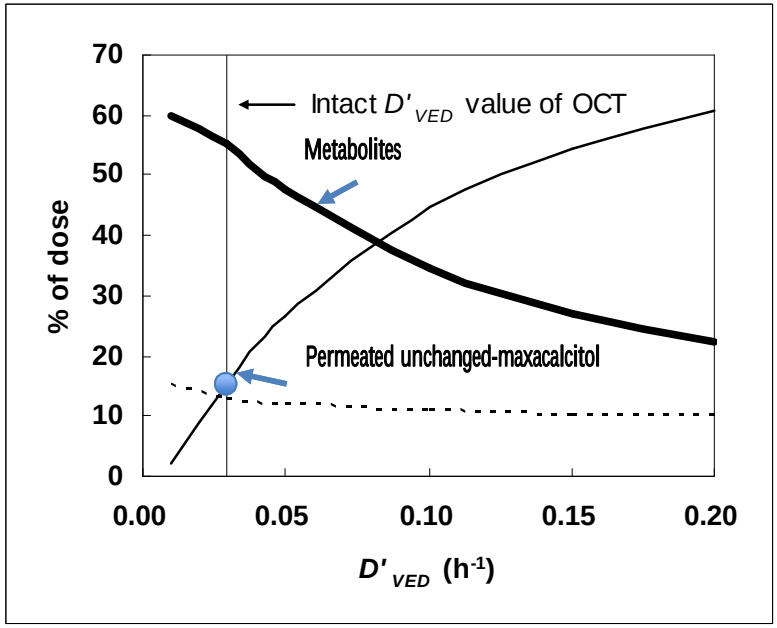
Structure-permeability relationship analysis using 10 drugs (log P: – 0.89 to 5.34)

$$\log D_{VED} = -0.0715 \bullet (\log K_{o/w})^2 + 0.142 \bullet (\log K_{o/w}) - 2.63$$

D_{VED} decreases when log P > 2.

Simulation study to understand diffusivity in VED on skin metabolism of a drug



Low diffusivity in VED of lipophilic drugs would increase the probability of drug metabolism in skin.

Yamaguchi et al., ***Pharm Res*** 23: 680–688, 2006; Yamaguchi et al., ***J Pharm Sci*** 97: 4391–4403, 2008

Highly lipophilic vitamin D3 analogues showed low permeability because of low diffusivity in VED

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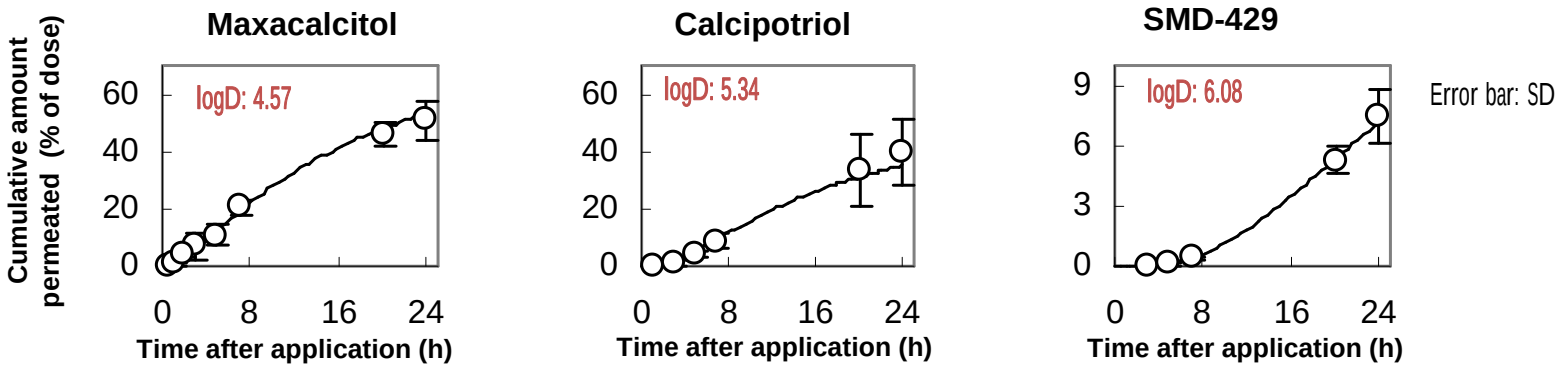
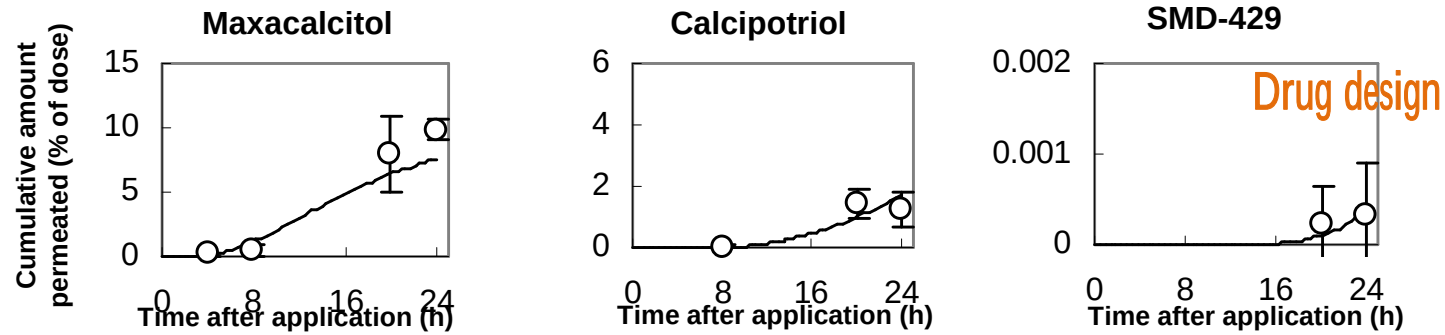
- A three-dimensional cultured human skin



- Excised rat skin



Low — Lipophilicity — High

High — Permeability — Low

Yamaguchi et al., ***Int J Pharm*** 353: 105–112, 2008

Conclusion 1

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- VED (viable epidermis and dermis) acts as a permeation barrier for highly lipophilic compounds due to low diffusivity in VED.
- Low diffusivity in VED contributes to increase the probability of drug metabolism in skin, which would reduce penetration of unchanged drug.

➢ A new vitamin D3 analogue with high lipophilicity was developed, which showed low skin permeability and low adverse event.

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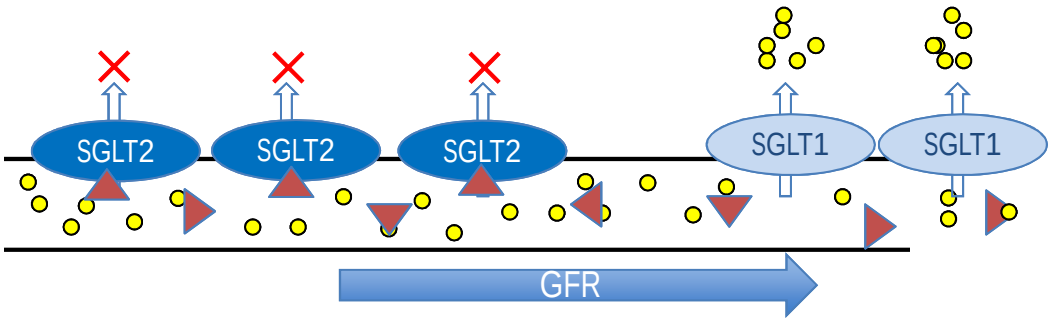
PKPD analysis

Drug: a highly selective SGLT2 inhibitor, tofogliflozin

- **Disease area:** type II diabetes mellitus
- **Target organ:** kidney
- **MOA:** Blood Glucose reduction caused by SGLT2 inhibition expressed in the proximal tubule
- **Ideal Drug property:**

  High selectivity toward SGLT2 to avoid hypoglycemia risk caused by SGLT1 inhibition

Glucose reabsorption and its inhibition at proximal tubule



- A drug affects only kidney?
- In vitro selectivity is reflected in in vivo?
- Highly selective SGLT2 inhibitor show sufficient efficacy?

Blood glucose lowering effect can be explained only by accelerated renal glucose clearance (db/db mice)

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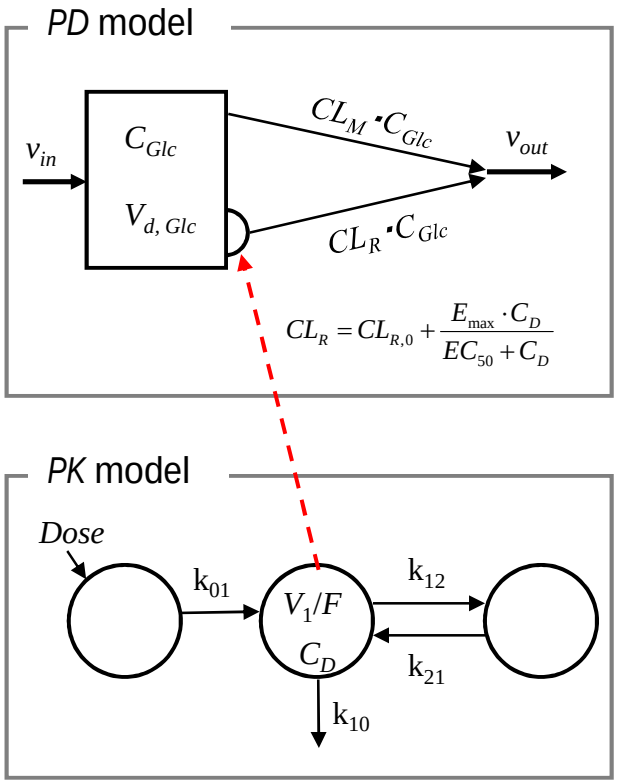
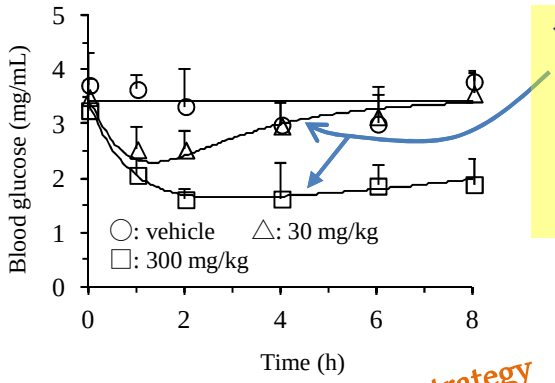
Indirect response model



Blood glucose



Drug design and regimen

✓ Effective time is controlled by saturation of SGLT inhibition and T1/2 of a drug

PoC: confidence for strategy

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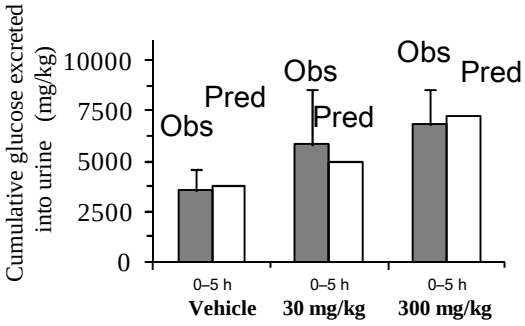
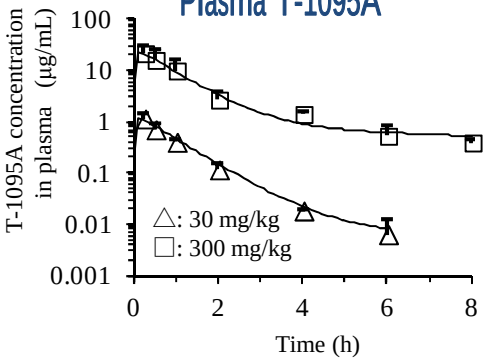
Urinary glucose



Plasma T-1095A



Yamaguchi et al., ***J Pharm Sci*** 101: 4347–4356, 2012

Effect of an SGLT1/SGLT2 inhibitor, phlorizin, on renal glucose excretion in rat

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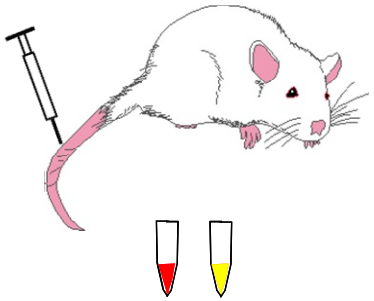
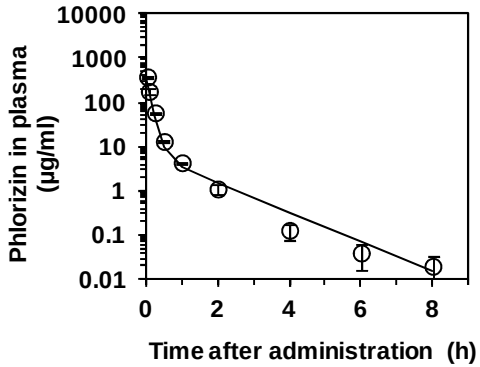
IV injection

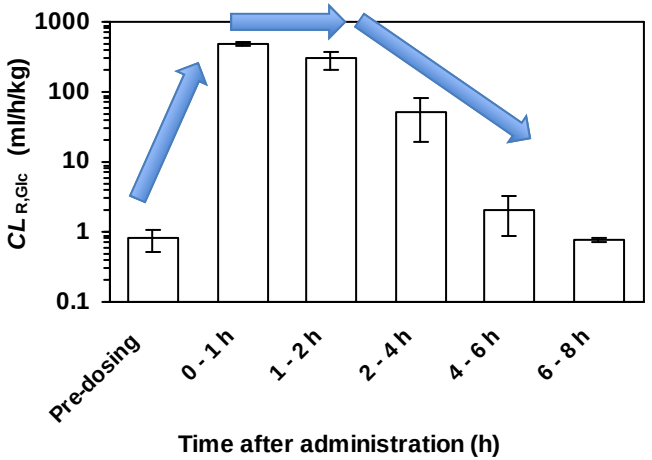


Plasma, Urine sampling

Plasma phlorizin



Renal glucose clearance



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Yamaguchi et al., ***Drug Metab Dispos*** 39: 1801–1807, 2011

PK/PD analysis for the effect of SGLT inhibitors on renal glucose clearance in rat

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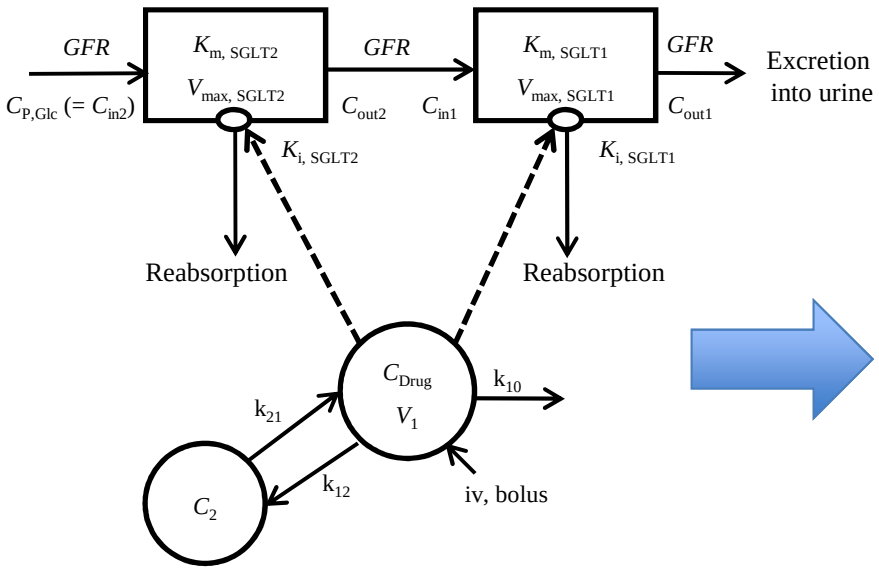
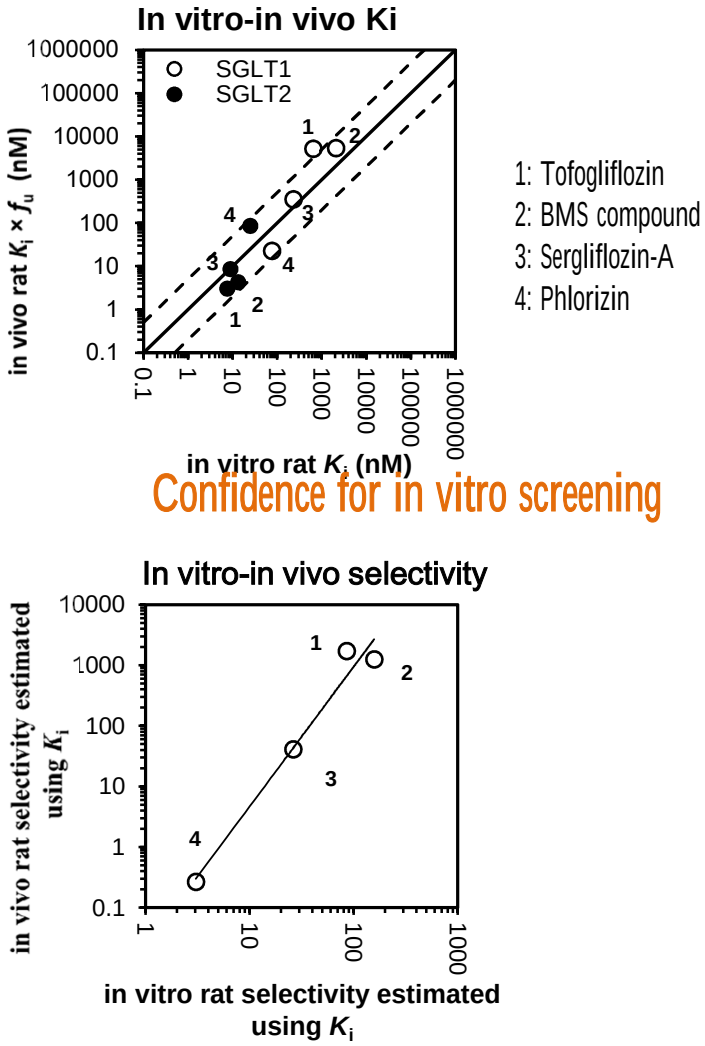
A nonlinear parallel tube model considering GFR and SGLT1, 2-mediated glucose reabsorption





Yamaguchi et al., ***J Pharmacol Exp Ther*** 345: 52–61, 2013

Relationship between selectivity and maximal in vivo efficacy on renal glucose excretion

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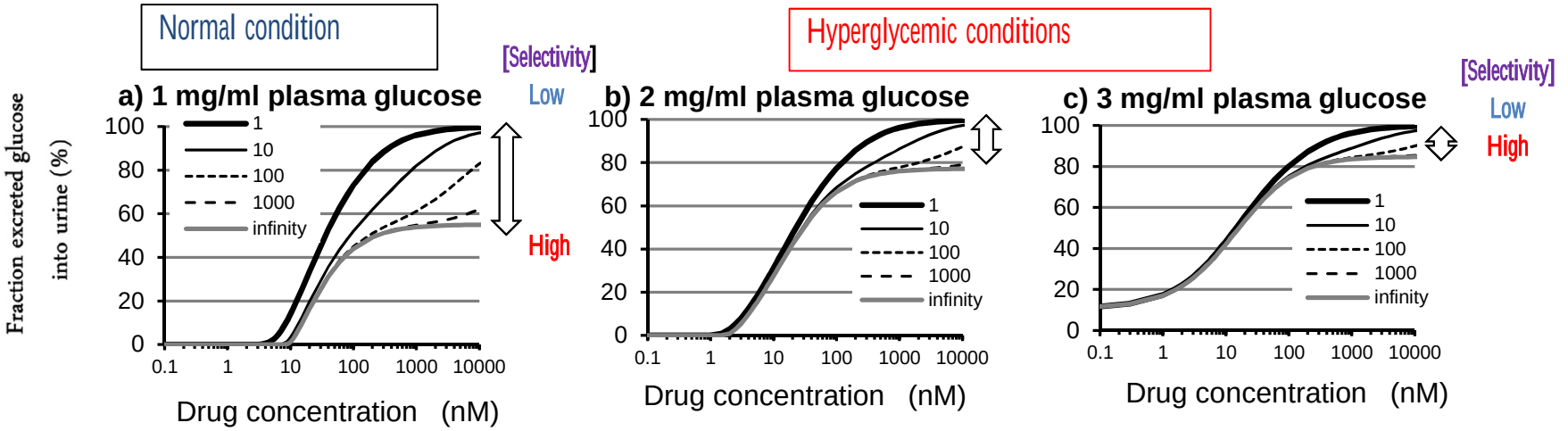

* 1 nM Ki for SGLT2 was assumed for the simulation

Confidence for clinical efficacy and safety

Simulation study indicated that

1. a highly selective SGLT2 inhibitor show comparable efficacy to SGLT1/2 dual inhibitor under hyperglycemic condition.
2. however, the maximal effect was lower than dual inhibitor under normal plasma glucose level.

➢ This suggests that a highly selective SGLT2 inhibitor, tofogliflozin, would show sufficient efficacy for hyperglycemia and low risk of hypoglycemia.

Yamaguchi et al., ***J Pharmacol Exp Ther*** 345: 52–61, 2013

Conclusion 2

- Blood glucose lowering effect could be explained only by accelerated renal glucose clearance with no consideration of other mechanism (PoC).
- Efficacy of SGLT inhibitor can be controlled by saturation of SGLT inhibition and T1/2 of a drug.
- In vivo PD prediction from in vitro seemed to be possible, that increased the confidence for in vitro screening.
- Simulation study suggested that highly selective SGLT2 inhibitor would show comparable efficacy to dual inhibitor under hyperglycemic condition but low risk of hypoglycemia. That gave us confidence for our strategy.

Mechanistic PK model usage in drug discovery

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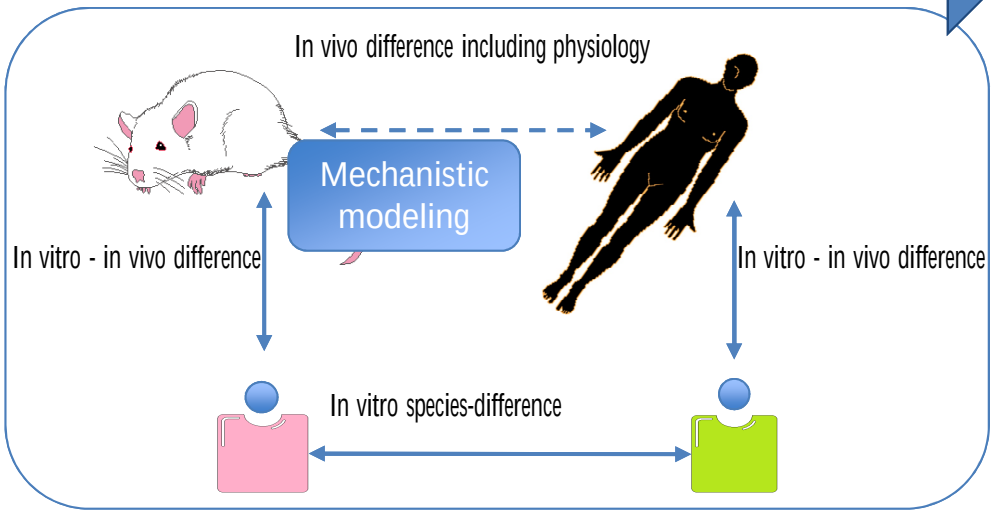
Pre-clinical stage

Drug discovery → Drug development

- PK analysis including DDI
- PBPK modeling
- PKPD analysis
- TKTD analysis

Translation from animal to human

- Drug design
- PoC in non-clinical
- Preferable Regimen design
- in vitro – in vivo correlation
- Human prediction of PK, PD, TD



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