JSSX 2017

消化管薬物間相互作用と抗体の動態制御に関する研究

Intestinal drug-drug interaction of small molecule drugs and improvement of PK profile of antibody drugs

Tatsuhiko Tachibana, Ph.D
Pre-Clinical Research Dept.
CHUGAI PHARMACEUTICAL CO., LTD.

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Contents

1. Intestinal drug-drug interaction of small molecule drugs
2. Improvement of PK profile of antibody drugs

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1. Intestinal drug-drug interaction of small molecule drugs

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PKPD seminar members

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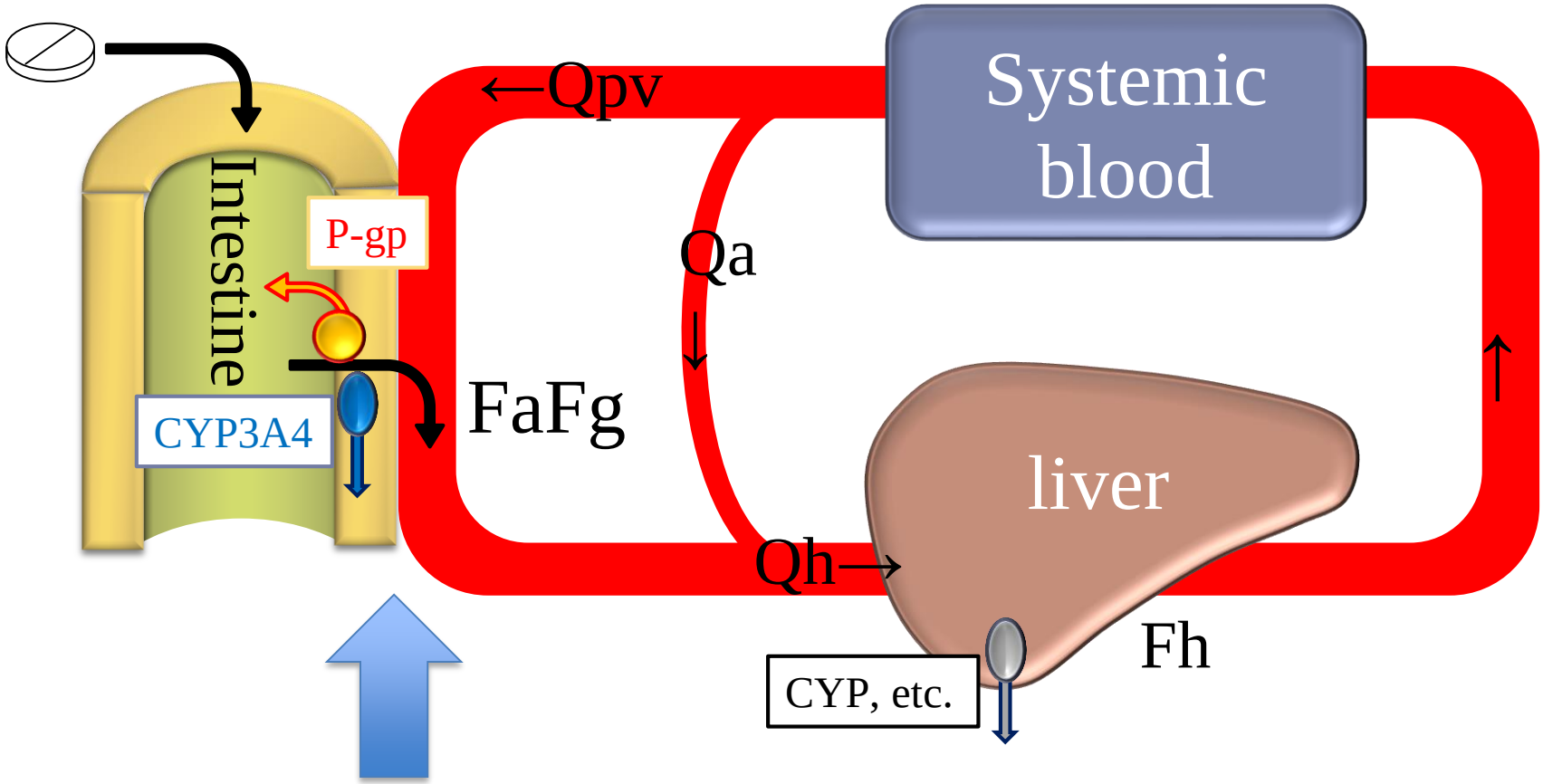
The intestinal absorption and the hepatic metabolism of drugs.



Intestinal drug-drug interaction

AUC of CYP3A4/P-gp substrates will be increased when intestinal CYP3A4/P-gp are inhibited

Definition of DIN

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Direct exposure of the inhibitor may cause DDI with the lower dose compared with hepatic DDI.

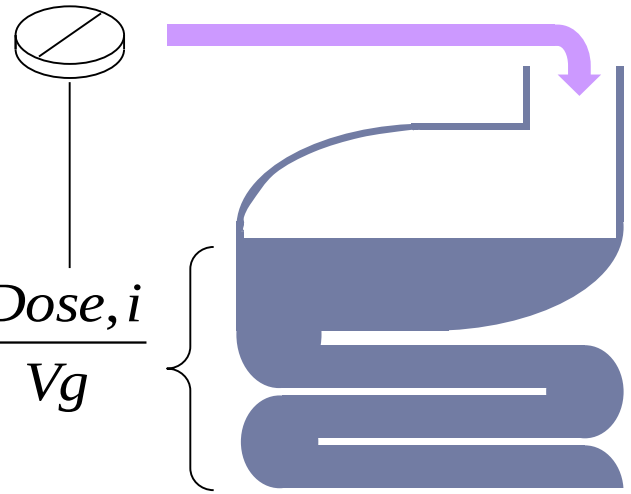
How can the intestinal inhibitor concentration be estimated?

Drug Interaction Number (DIN)

$$DIN = \frac{dose, i}{Ki}$$

$$\left(= \frac{I}{Ki} Vg \right)$$

$$I = \frac{Dose, i}{Vg}$$



DIN can be used for predicting intestinal DDI.

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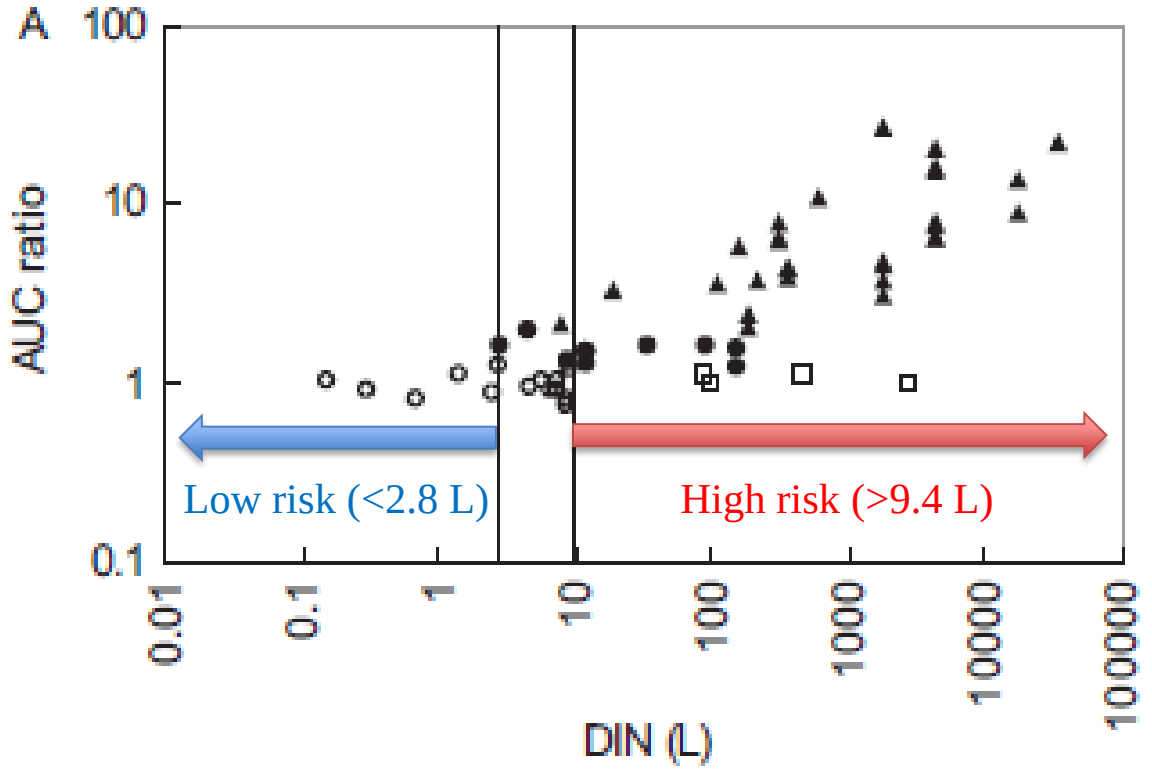
The relationship between AUC ratio and DIN

CYP3A4 substrates (felodipine, midazolam, triazolam)



AUC ratio ≤1.25

○ high solubility

□ low solubility

AUC ratio >1.25

● AUCratio ≤1/FaFg (intestine)

▲ AUCratio >1/FaFg (intestine＋liver)

DDI risk of CYP3A4 substrates can be predicted by DIN.

Xenobiotica 39(6):430-43, (2009)

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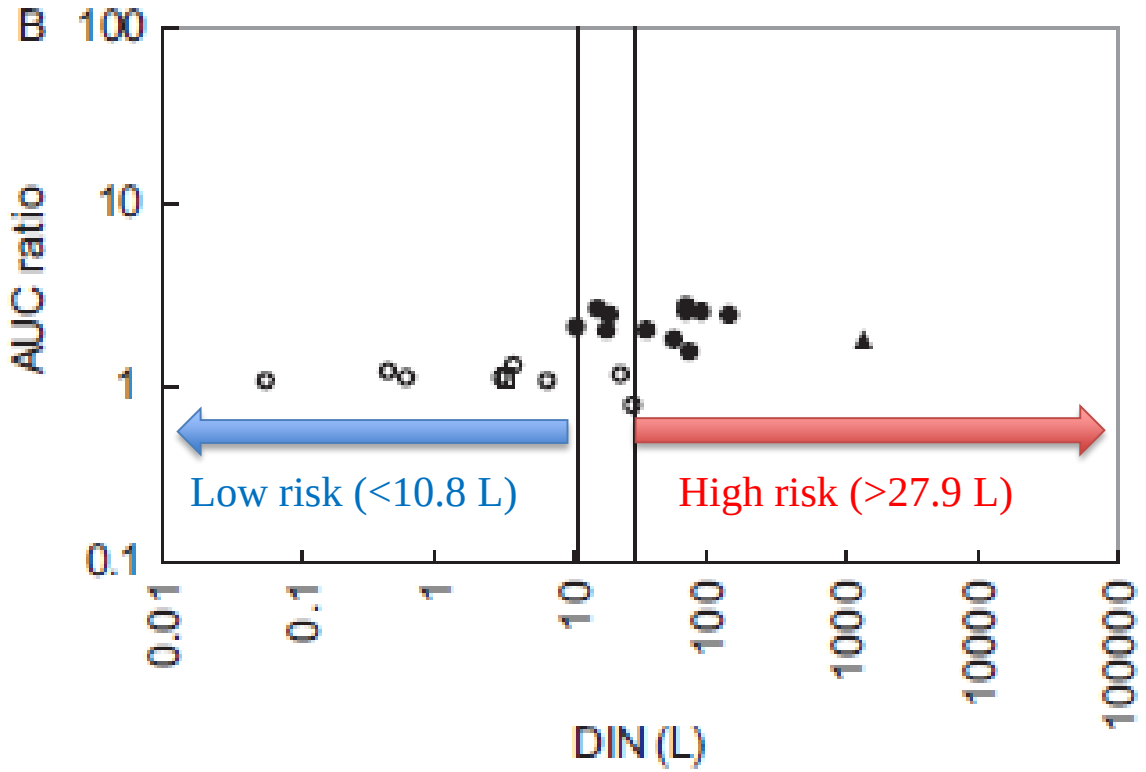
The relationship between AUC ratio and DIN

P-gp substrates (digoxin, fexofenadine, talinolol)



AUC ratio ≤1.25

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AUC ratio >1.25

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DDI risk of P-gp substrates can be predicted by DIN.

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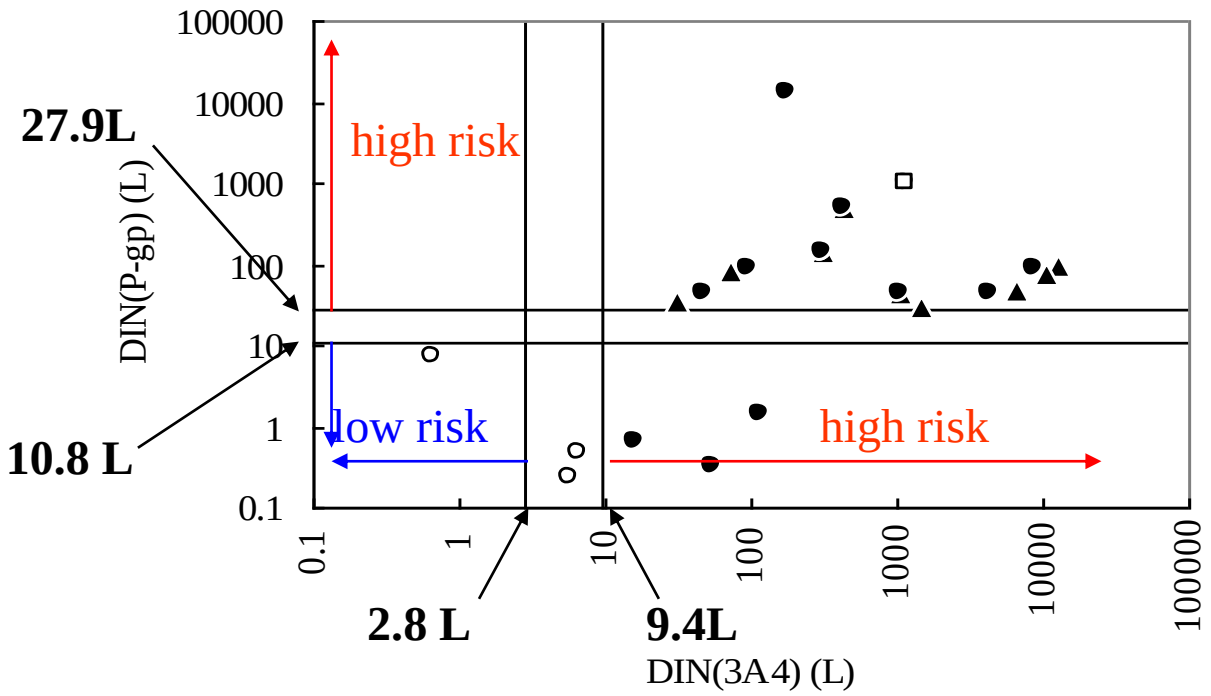
The relationship between AUC ratio and DIN

CYP3A4/P-gp dual substrates



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DDI risk of CYP3A4/P-gp dual substrates can be predicted by DIN.

Xenobiotica 39(6):430-43, (2009)

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Referred by U.S. FDA's Draft Guidance

In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2017
Clinical Pharmacology

Figure 1: Equations to Calculate the Predicted Ratio of Victim Drug's AUC in the Presence and Absence of an Inhibitor for Basic Models of Reversible Inhibition

$$R_1 = 1 + (I_{max,u} / K_i)$$

$$R_{1,gut} = 1 + (I_{gut} / K_i)$$

R_1 or $R_{1,gut}$ is the predicted ratio of the victim drug's AUC in the presence and absence of an inhibitor for basic models of reversible inhibition.
$I_{max,u}$ is the maximal unbound plasma concentration of the interacting drug.*
I_{gut} is the intestinal luminal concentration of the interacting drug calculated as the dose/250 mL.
K_i is the unbound inhibition constant determined in vitro.

Note: I and K_i need to be expressed in the same unit (e.g., in a molar concentration unit).

*Considering uncertainties in the protein binding measurements, the unbound fraction in plasma should be set to 1% (fraction unbound in the plasma ($f_{u,p}$) = 0.01) if experimentally determined to be < 1%.

If $R_1 \geq 1.02$, $R_2 \geq 1.25$ (Vieira, Kirby et al. 2014) or the $R_{1,gut} \geq 11$ (Tachibana, Kato, et al. 2009; Vieira, Kirby, et al. 2014), the sponsor should further investigate the DDI potential by either using mechanistic models (see the appendix, section VII.C) or conducting a clinical DDI study with a sensitive index substrate. If the predicted AUC ratio (AUCR) of a sensitive index substrate in the presence and absence of an investigational drug is ≥ 1.25 based on static mechanistic models or dynamic mechanistic models (e.g., PBPK models) (see appendix, section VII.C), the sponsor should conduct a clinical DDI study using a sensitive index substrate.

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2. Improvement of PK profile of antibody drugs

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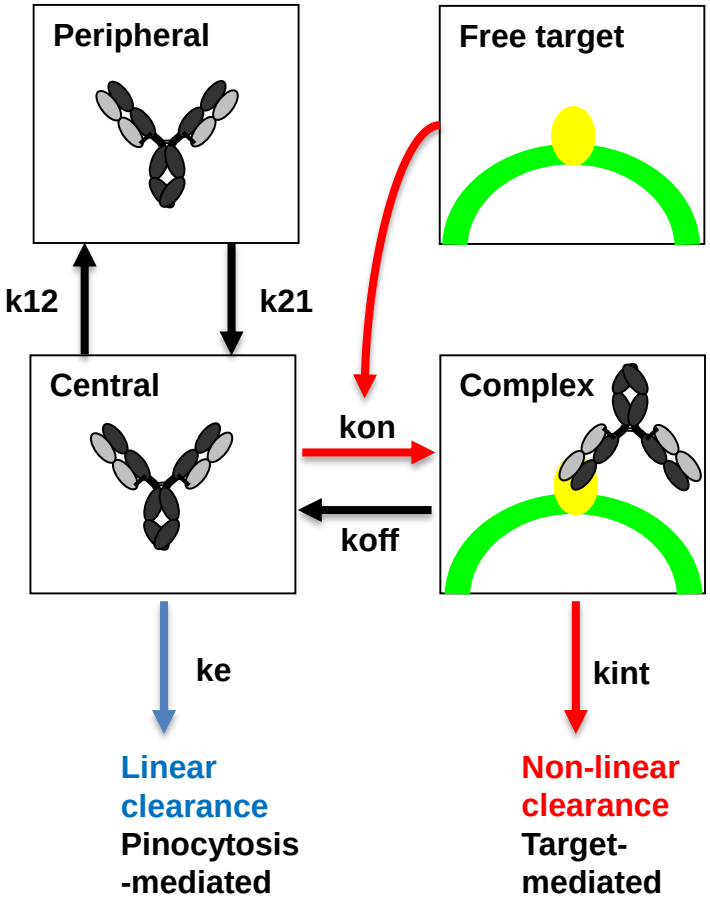
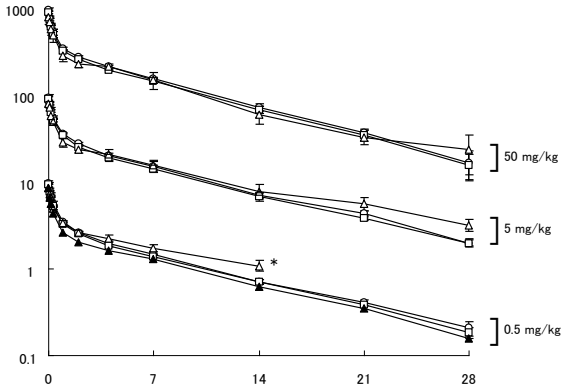
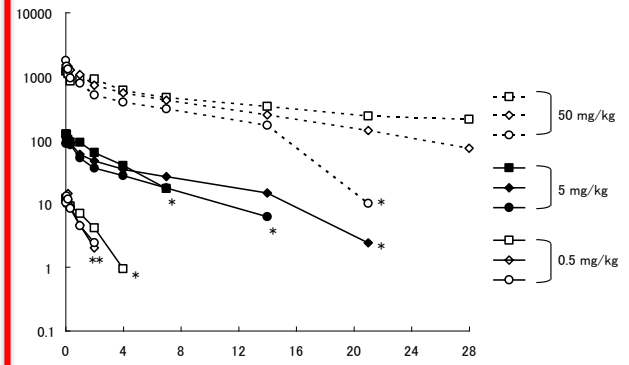
Target mediated drug disposition model for antibody drugs



PK profile of anti-human IL-6R antibody in rats



PK profile of anti-human IL-6R antibody in monkeys



pI engineering

Recycling technology

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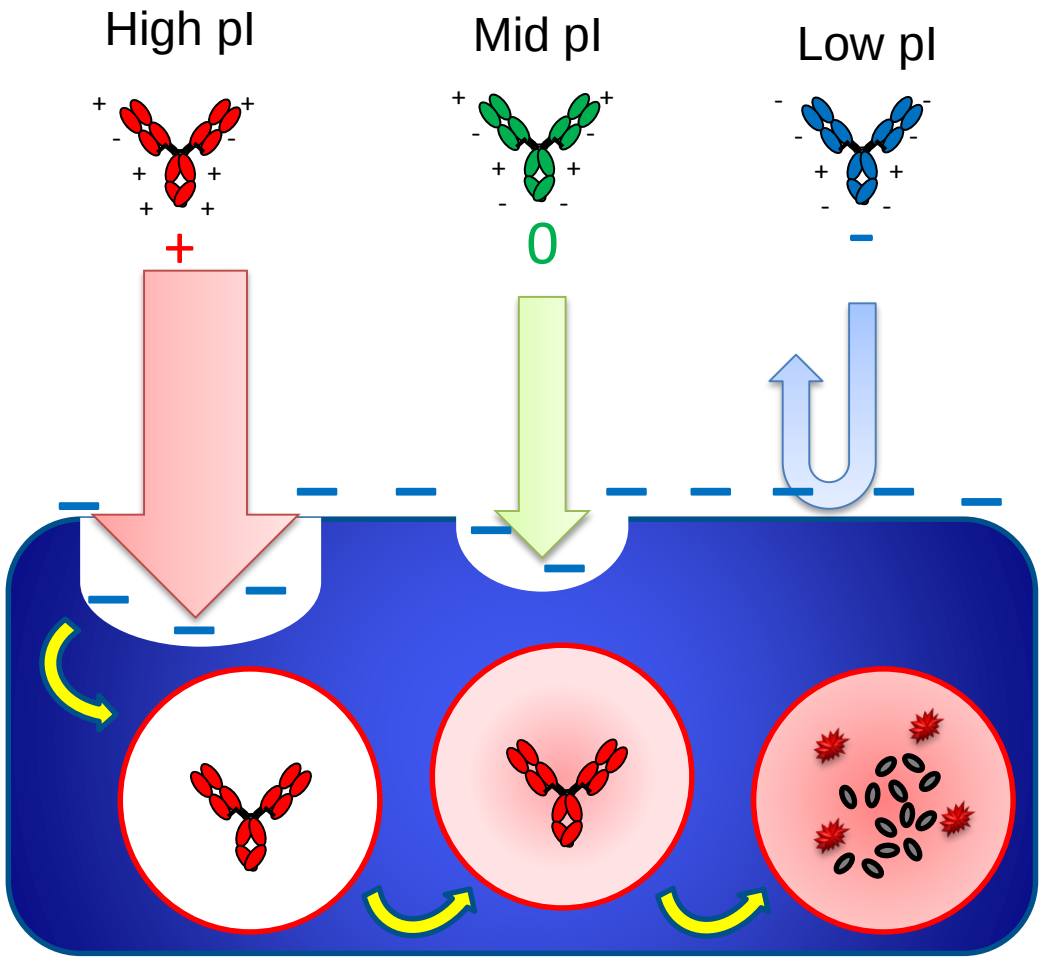
Concept of reduced elimination of IgG by pI engineering

isoelectric point (pI)



Cell surface is negatively charged

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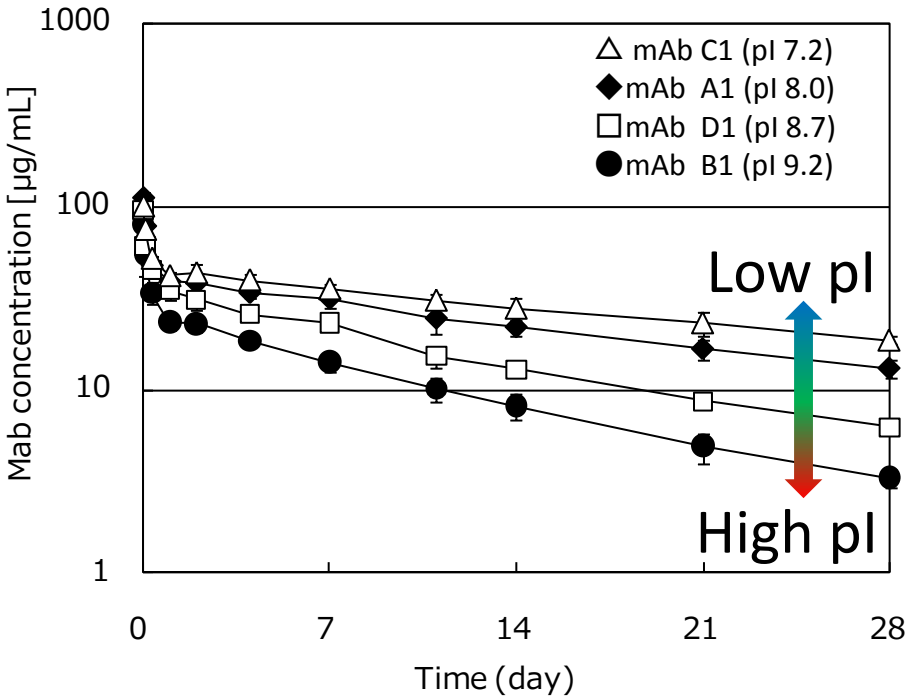
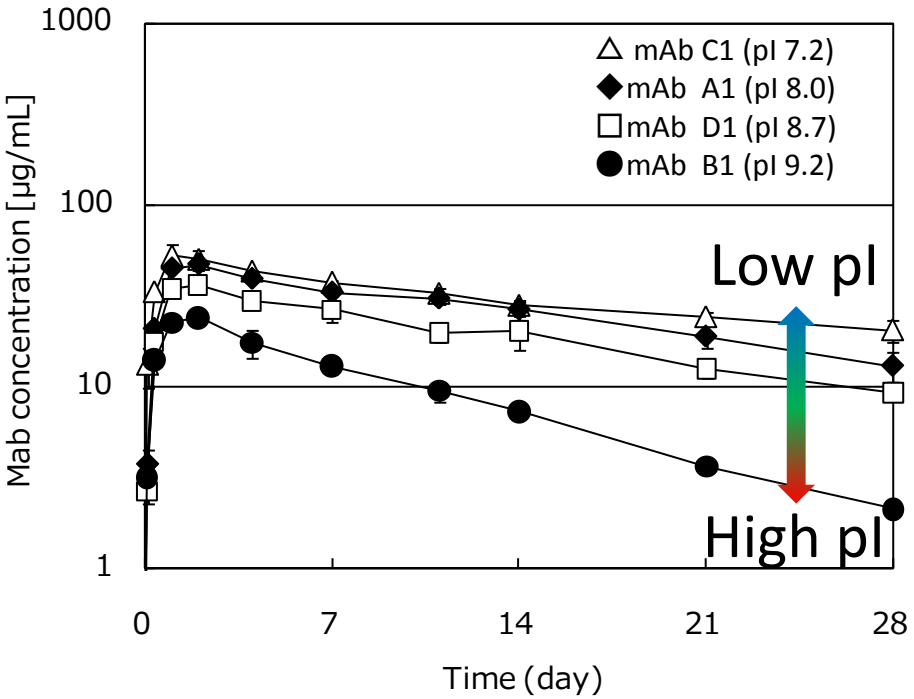
PK profile of antibodies with different pI in mice





Antibodies with lower pI showed reduced elimination

Protein Eng Des Sel 23(5):385-92, (2010)

Concept of recycling antibody technology

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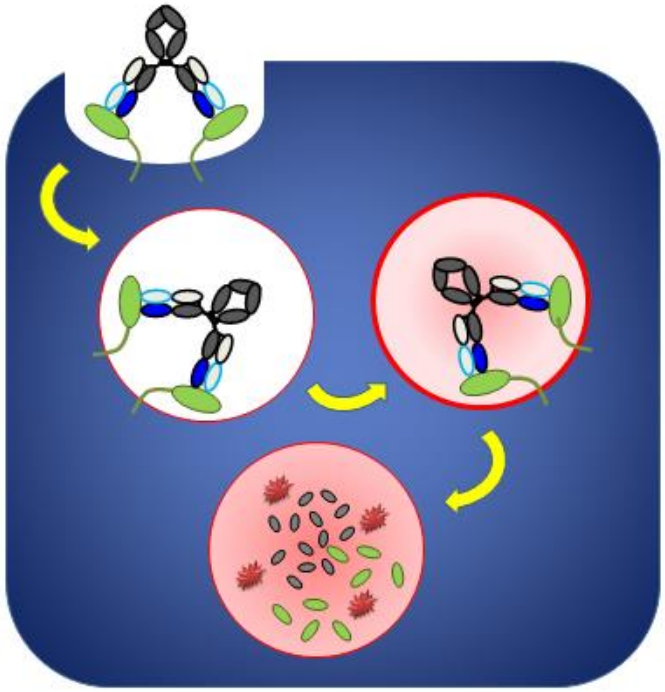
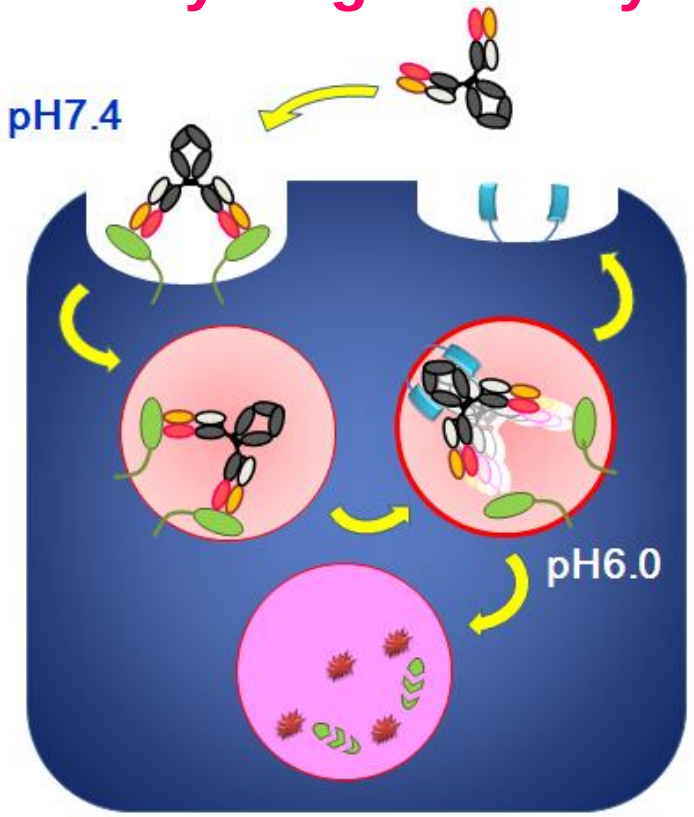
Conventional antibody



Antibody cleared rapidly by antigen-mediated internalization

Recycling antibody



Antibody is recycled back to plasma via FcRn

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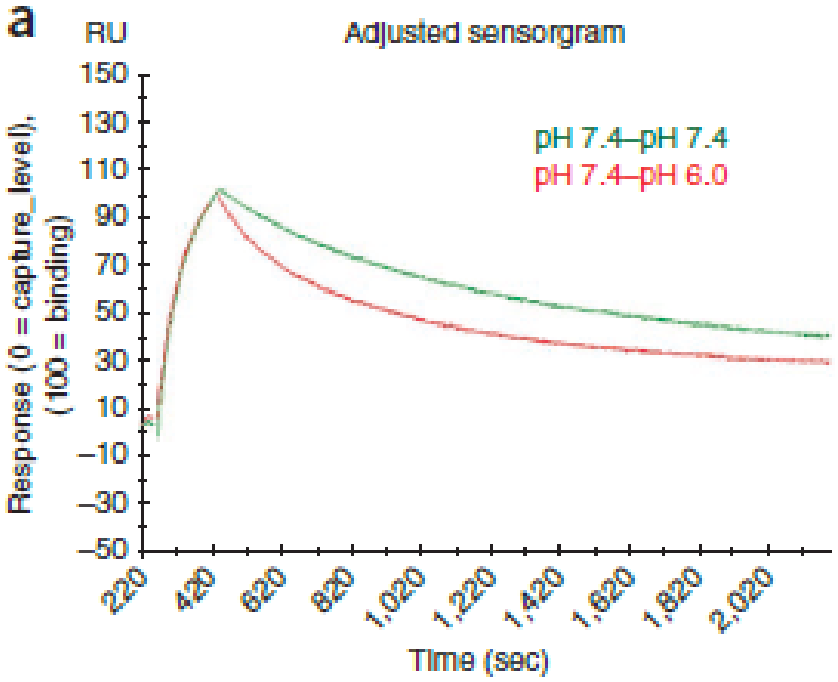
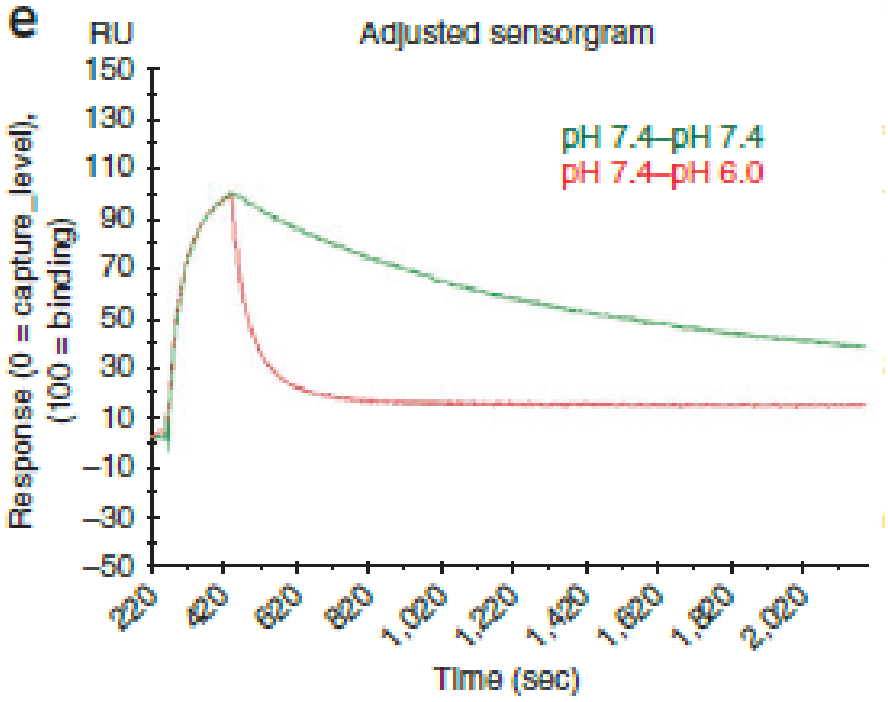
Surface plasmon resonance (SPR) sensorgrams

Conventional antibody (tocilizumab)



Recycling antibody



Nat Biotechnol 28(11):1203-7, (2010)

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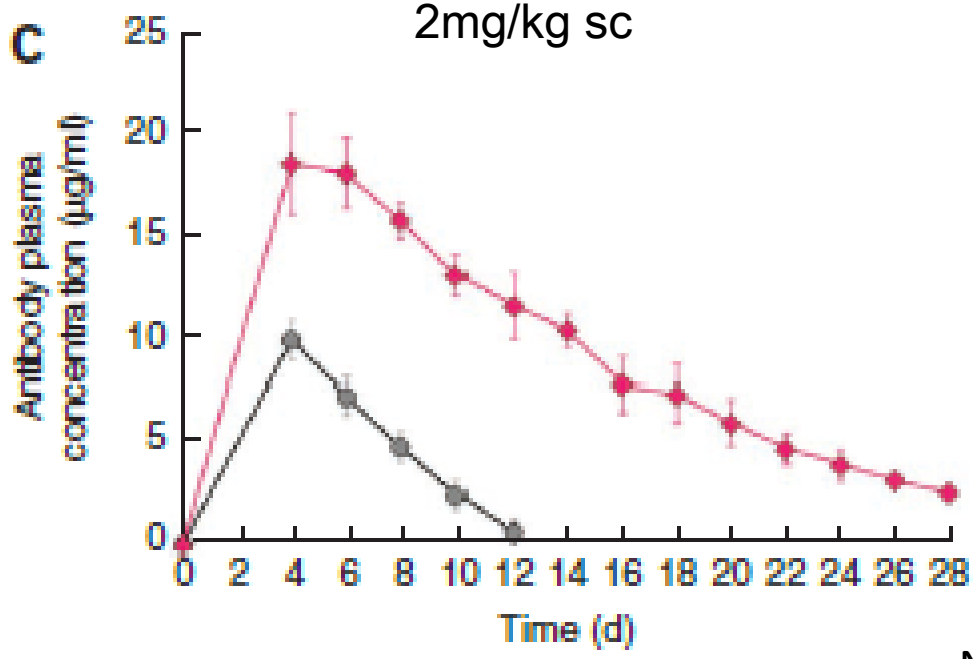
Pharmacokinetic result of tocilizumab and Recycling antibody in monkey



Recycling antibody

Conventional antibody (tocilizumab)

Nat Biotechnol 28(11):1203-7, (2010)

- The PK profile of recycling antibody was greatly improved compared to tocilizumab.

TMDD + Recycling model

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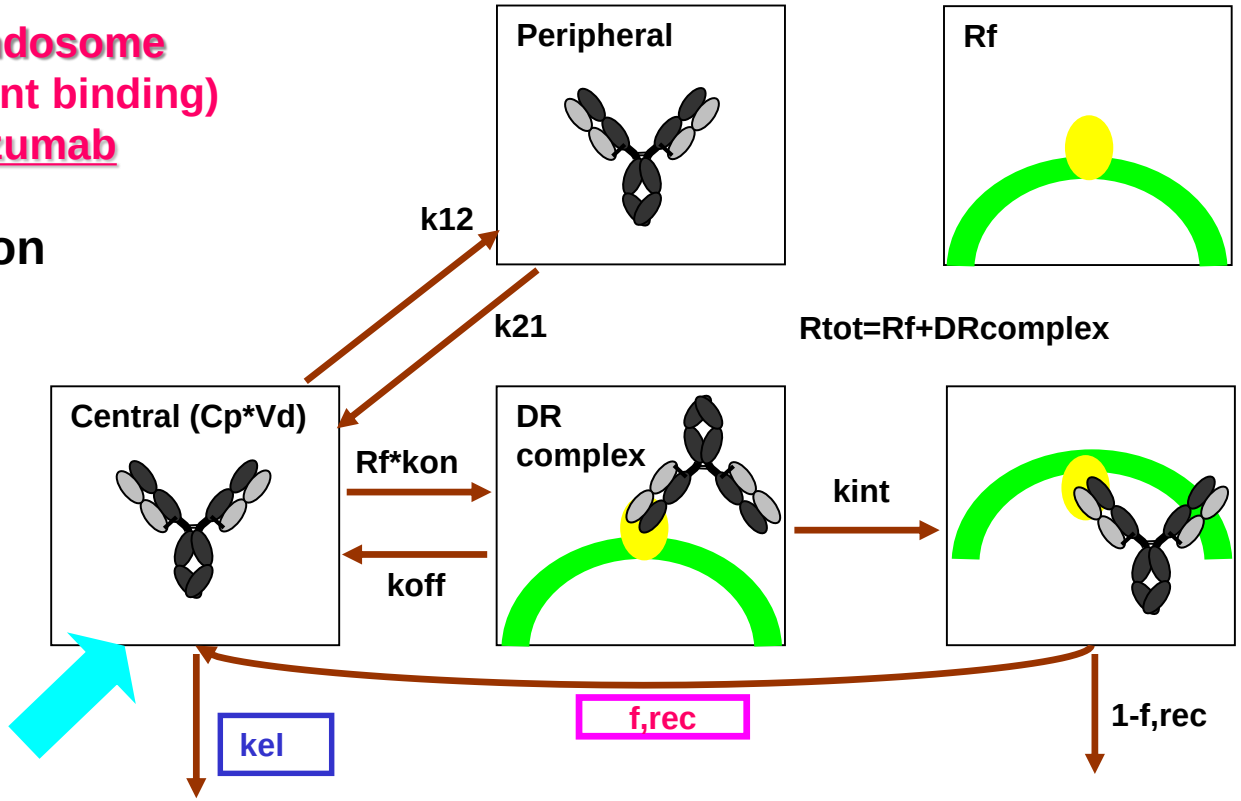
Rtot, total membrane IL-6R; Rf, free membrane IL-6R;
DR, Ab - mIL-6R complex; kint, internalization rate constant of mIL-6R
kel: elimination rate constant

f,rec: fraction recycled from endosome (recycling ratio by pH dependent binding)

Presumption :f,rec=0 for tocilizumab

Target mediated degradation was reduced to 25% by recycling technology

		tocilizumab	recycling antibody
f,rec		0	0.753
Rtot	nmol/kg	0.130	0.130
Vd	L/kg	0.0456	0.0363
k12	1/h	0.0143	0.0328
k21	1/h	0.0101	0.0515
kel	1/h	0.00378	0.00312



Nat Biotechnol 28(11):1203-7, (2010)

- Non-linear PK profiles of tocilizumab and recycling antibody were analyzed using target-mediated drug disposition and recycling model

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Conclusion

1. Criteria for intestinal drug-drug interaction of small molecule drugs were established.

   The criteria were referred by U.S. FDA's draft guidance in 2017

2. Two technologies to improve PK profile of antibody drugs were developed and evaluated.

   Non-specific elimination of antibody was reduced by pI engineering.

   Target-mediated elimination of antibody was reduced by recycling technology

3. Both studies contribute to drug discovery and development.

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