Chemistry for Medicine 1

医用化学１

(1st period, Friday)

November 16th, 2018

(Next time: Nov. 22nd)

- **Interaction of particles and biointerface**
  ~For control of cellular uptake~ (continued)
- **Introduction to pharmacokinetics and pharmacodynamics**

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Introduction to Drug Delivery System (from the engineering viewpoint)

5	Nov 2nd	**Why size matters? ~ From the anatomic viewpoint** (人体の構造とサイズ感)
6	Nov 9th	**Interaction of particles and biointerface ~ For control of cellular uptake** (微粒子のバイオ界面との相互作用)
7	Nov 16th	**Introduction to pharmacokinetics and pharmacodynamics (PK/PD入門)**
8	Nov 22th	**Formulation design based on nanotechnology** (ナノ剤形の設計と疾患治療)

Teaching material：Open access on BookRoll（e-learning system）
教材 - 教材一覧 - Others - 公開資料（岸村顕広）
(Contents - List Contents - Others - 公開資料（岸村顕広）)

Pattern recognition by macrophage

Macrophages or dendritic cells often recognize pathogens or foreign materials by "pattern recognition receptors (PRRs)". This is a primitive part of the immune system to know "nonself".

Pathogen-associated molecular patterns (PAMPs)

"Common sign" of bacteria (microbe-specific molecules) can be recognized by PAMPs.

1) Toll-like receptor (TLR) (membrane-bound)

ex.) TLR2 : bacterial lipopeptides etc.
TLR4 : lipopolysaccharide of gram-negative bacteria etc.

2) C-type lectin receptors (CLR) (membrane-bound)

ex.) Mannose receptor : the recognition motif for many viruses, fungi and mycobacteria
DC-SIGN : Binding to HIV and hepatitis C (to promote to infect T-cell).
Dectin-1 : β-glucans of fungi and bacteria

3) RIG-I-like receptors (Intracellular)

Recognition of viral double-stranded (ds) and single stranded RNA

4) NOD-like receptors

ex.) NOD1, NOD2 : peptidoglycan motifs from bacterial cell

Scavenger receptors

- A group of receptors that recognize modified (or oxidized) low-density lipoprotein, apoptotic cells, and pathogens.
- Many kinds. Mainly, they recognize negatively charged materials.

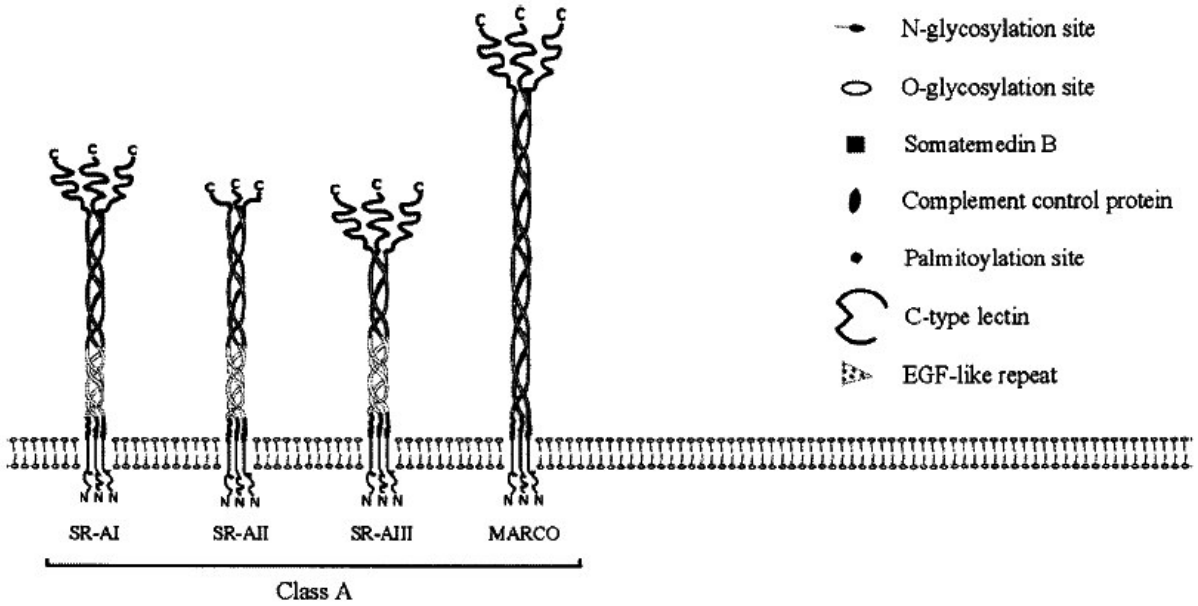


TABLE 1. Hepatic and Extrahepatic Expression of SRs

Class	Hepatic Expression	Extrahepatic Expression
Class A		
SR-AI SR-AII SR-AIII	Kupffer cells, sinusoidal endothelial cells	Tissue macrophages, foam cells
MARCO	Kupffer cells under inflammatory conditions	Macrophages in marginal zone of the spleen and lymph nodes

TABLE 2. SRs and Their Proposed Ligands

Class	Ligands
Class A	
SR-AI SR-AII	AcLDL (1–5 μg/mL[160]), OxLDL (10 μg/mL[160]), AGE-modified proteins (1–5 μg/mL[35]); M-BSA, LPS (for ReLPS, 50–250 μg/mL[5]), LTA, whole bacteria, polyinosinic acid, polyguanosinic acid
SR-AIII	?
MARCO	AcLDL, LPS, whole bacteria

Transport across the membrane

Type	Carrier	Energy
a. Passive transport		
1) Simple diffusion		
i) Dissolution-diffusion	No	No
ii) Restricted diffusion (filtration)	No (By pore or intercellular gap)	No
iii) Solvent drag	No (By pore or intercellular gap)	No
2) Facilitated diffusion	Need	No
b. Active transport		
1) Primary active transport (Pump, ATPase)	Need	Need (直接的)
2) Secondary active transport		
i) Symport	Need	Need (間接的)
ii) Antiport	Need	Need (間接的)
iii) Uniiport (Charged compound)	Need	Need (間接的)

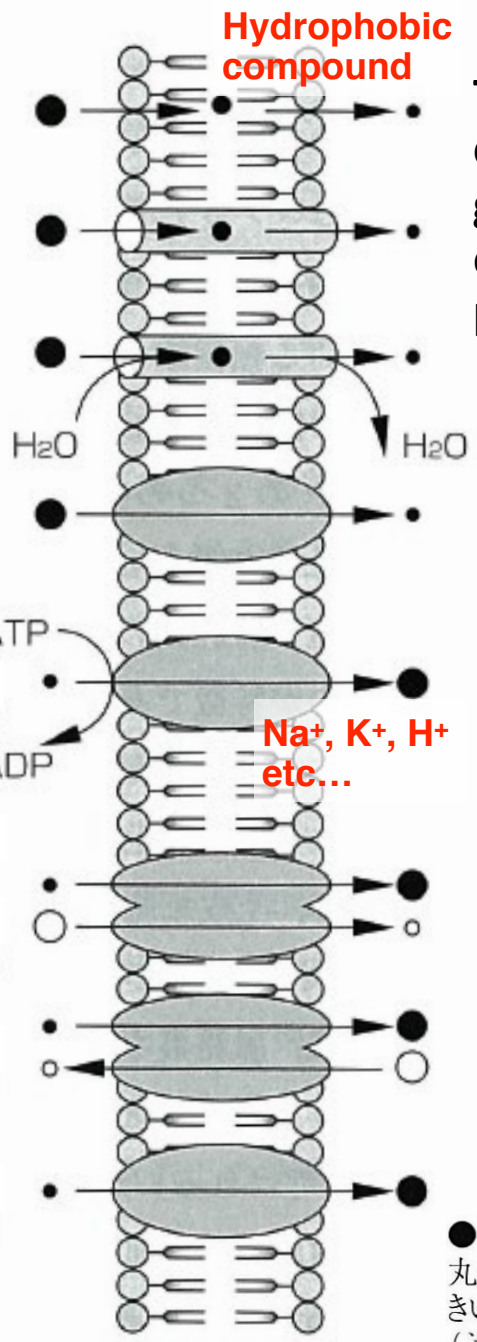


図 I-1-3. 物質輸送の機構

●は透過する物質,○は物質と共役して透過するイオン(Na^+, H^+など)を示す.丸の大きさはそれぞれ化学ポテンシャルの高さを表す.例えば,小さい丸から大きい丸への移行は濃度勾配に逆らった輸送(上り坂輸送)を意味する.
(辻　彰:"わかりやすい生物薬剤学(第2版)", 辻　彰(編), p. 14, 廣川書店, 1997より)

Passive transport

The thermodynamic process driven by concentration gradient, and/or electrochemical gradient (down-hill transport). It involves no energy consumption; but it is dependent on the potential.

1-i): Only for hydrophobic small compounds, and gasses.

Facillitated transport: Protein channels or carriers are required.

Active transport

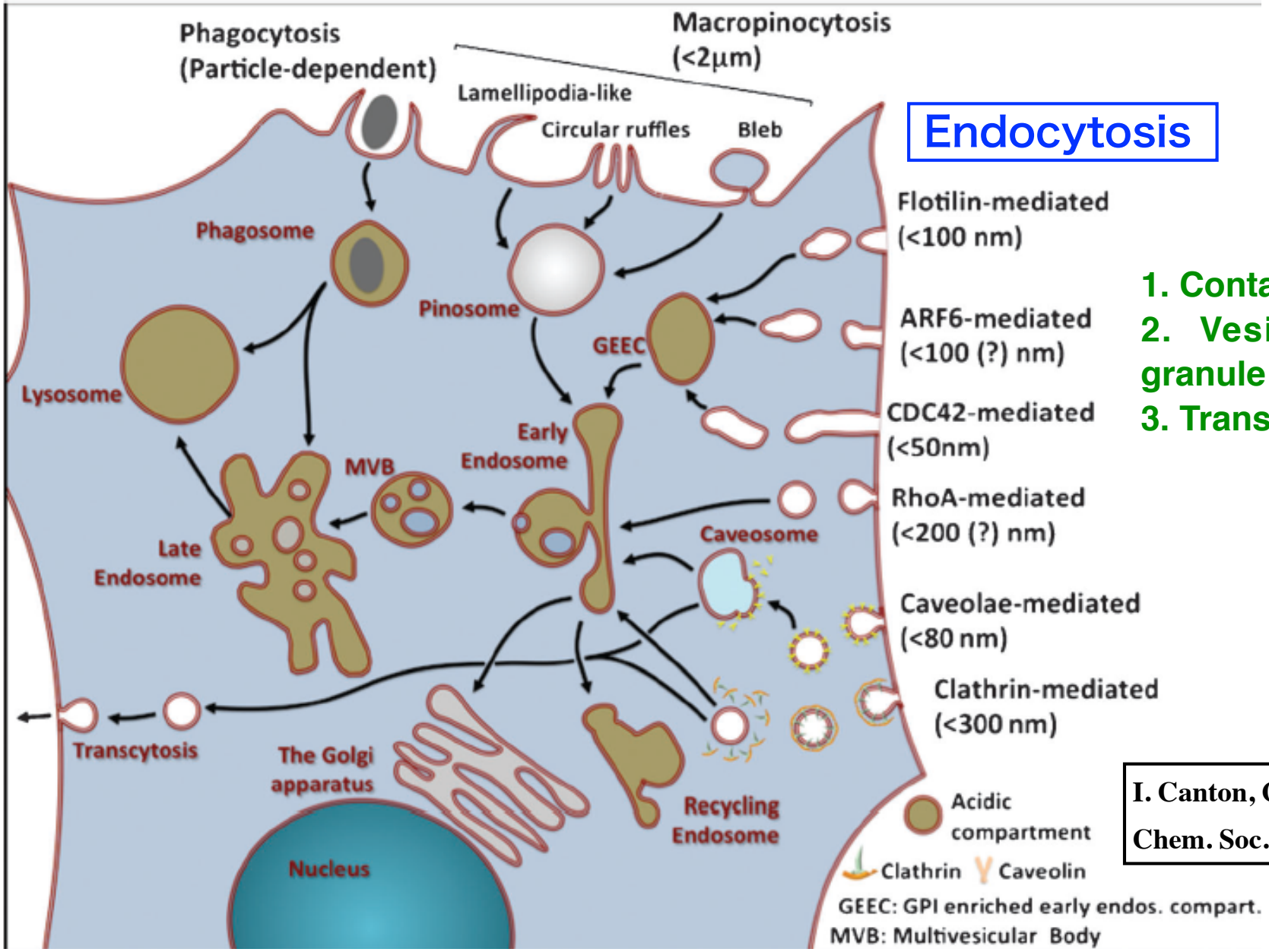
Energy-dependent process. Up-hill transport. Specific protein carries/transporters are required.

Primary: Directly utilizes ATP, GTP.

Secondary: The up-hill transport coupled with the down-hill transport using concentration gradient produced by primary active transports (Na^+, H^+ gradient, etc..) (Symport, antiport). Uniport: Driven by membrane potential created by primary active transports.

Cellular uptake and transportation by vesicles

Invagination or budding of cell membrane results in formation of vesicles.



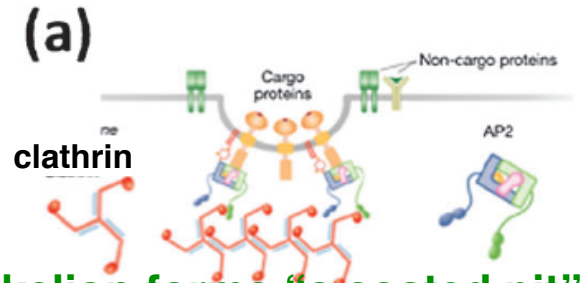
1. Contact to cell surface
2. Vesicle formation & granule release
3. Transportation

I. Canton, G. Battaglia,
Chem. Soc. Rev. 41 (2012) 2718–2739.

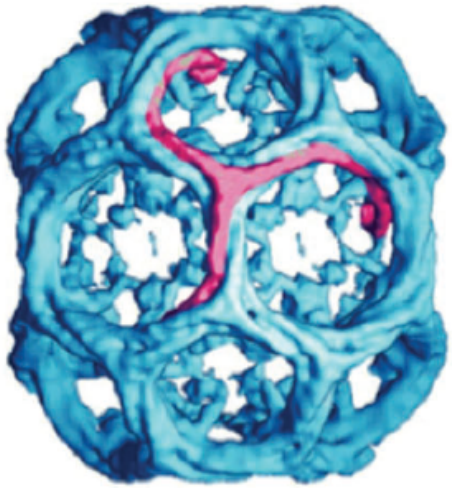
→ After endocytosis, materials may escape from endosome to cytosol, if needed.

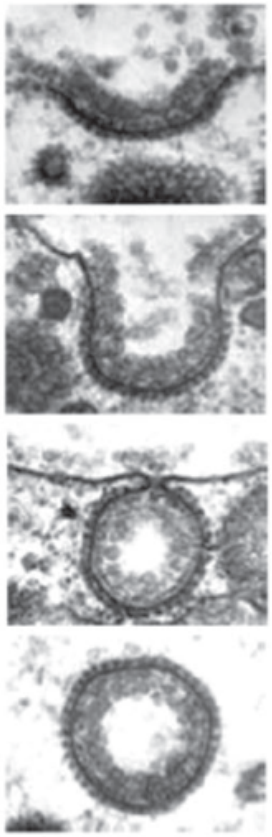
Cathrin-mediated endocytosis

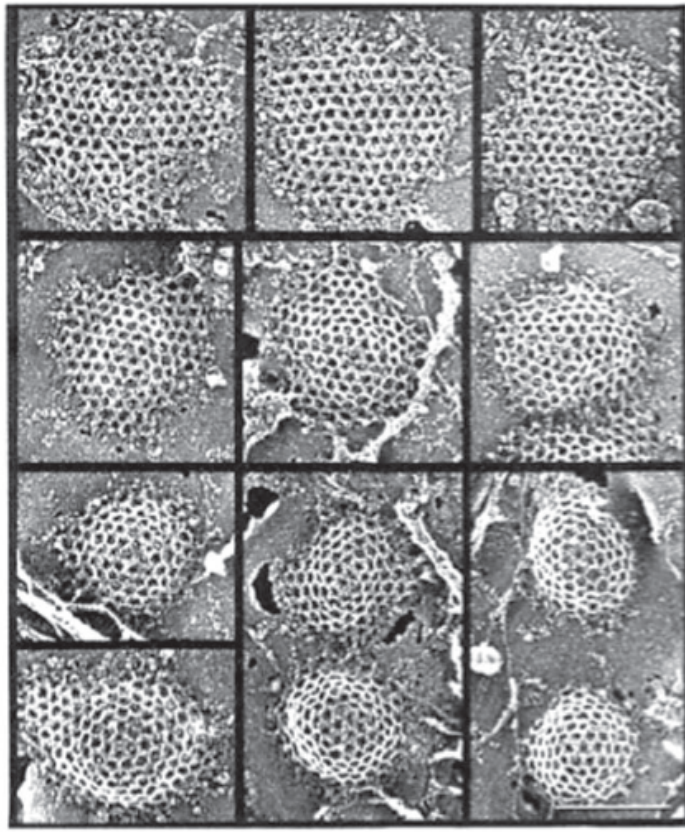
Firstly, material interact with some receptors.



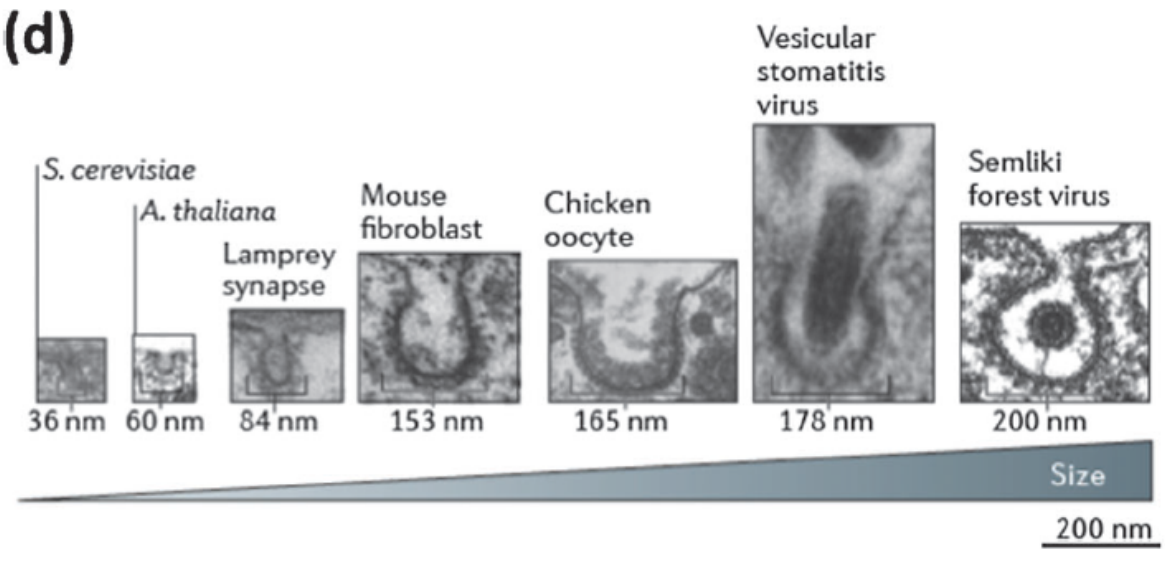
Triskelion forms "a coated pit".

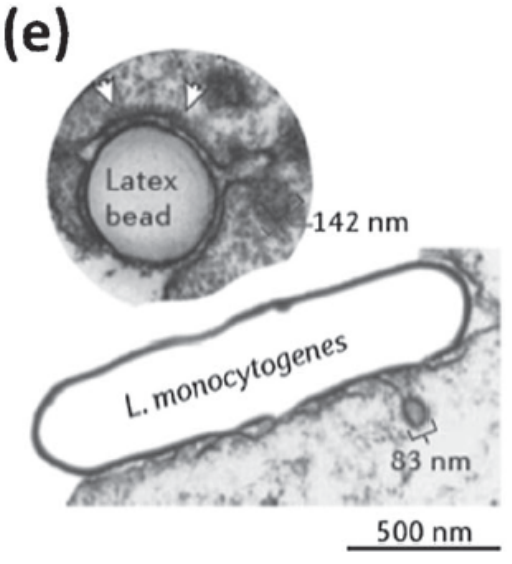






Upper limit for efficient endocytois is [redacted]. But, some cells internalize larger paricles (< 300 nm).





Caveolae-mediated endocytosis

An invaginated pit with [redacted] in size finally allows for endosome formation.

Lipid raft (the plasma membranes of cells contain combinations of glycosphingolipids and protein receptors organized in glycolipoprotein microdomains) forms a flask-shaped invagination with help of caveolin.

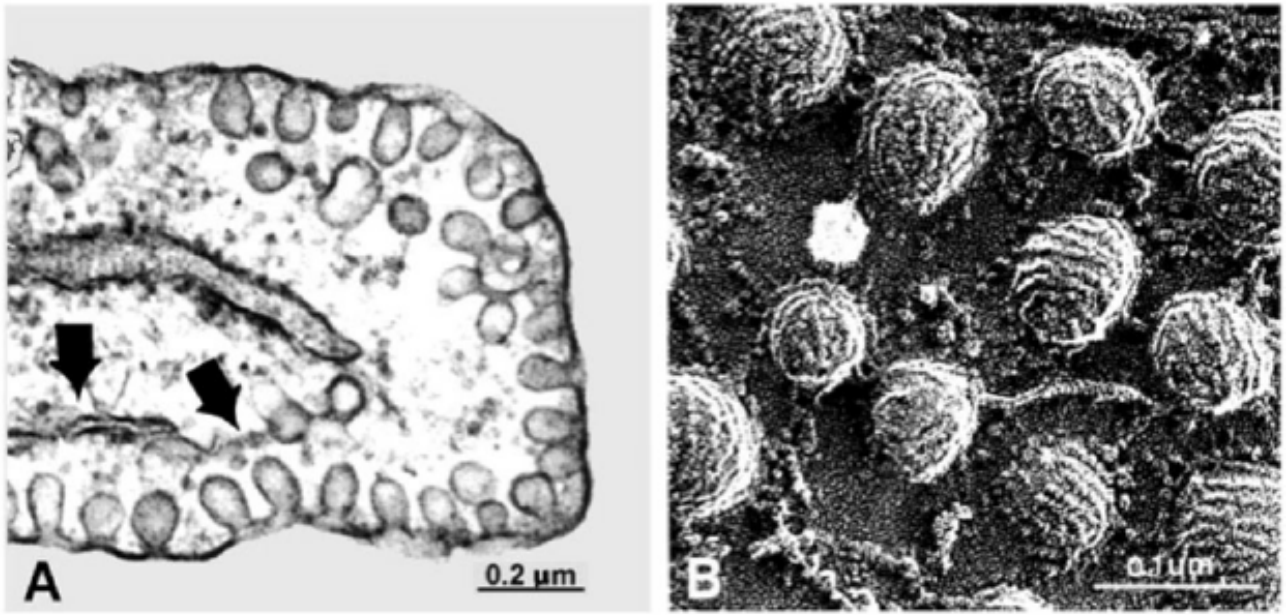


Fig. 3 (a) Thin-section electron microscopy (EM) image and (b) rapid-freeze deep-etch image of fibroblast caveolae. Arrows point to endoplasmic reticulum near invaginated caveolae.[43]

Other types of endocytosis

RhoA-mediated

細胞内骨格であるアクチンの制御に関わるRhoAの関与する経路。詳細は明らかでない部分が多いが、ある種のサイトカイン受容体の内在化に関連する。アクチンはエンドサイトーシスの機構に関わる重要な因子であるので、関連性は深いと思われる。

CDC42(cell division cycle42)-mediated

幅は< 50 nmチューブ状200-600 nm（長さ）に陥入する。
CDC42は、細胞の成長、分化、アポトーシスなどに関与し、アクチンや細胞ストレスの制御因子であるため、関係が深いものと思われる。GTP結合性。

ARF6-mediated

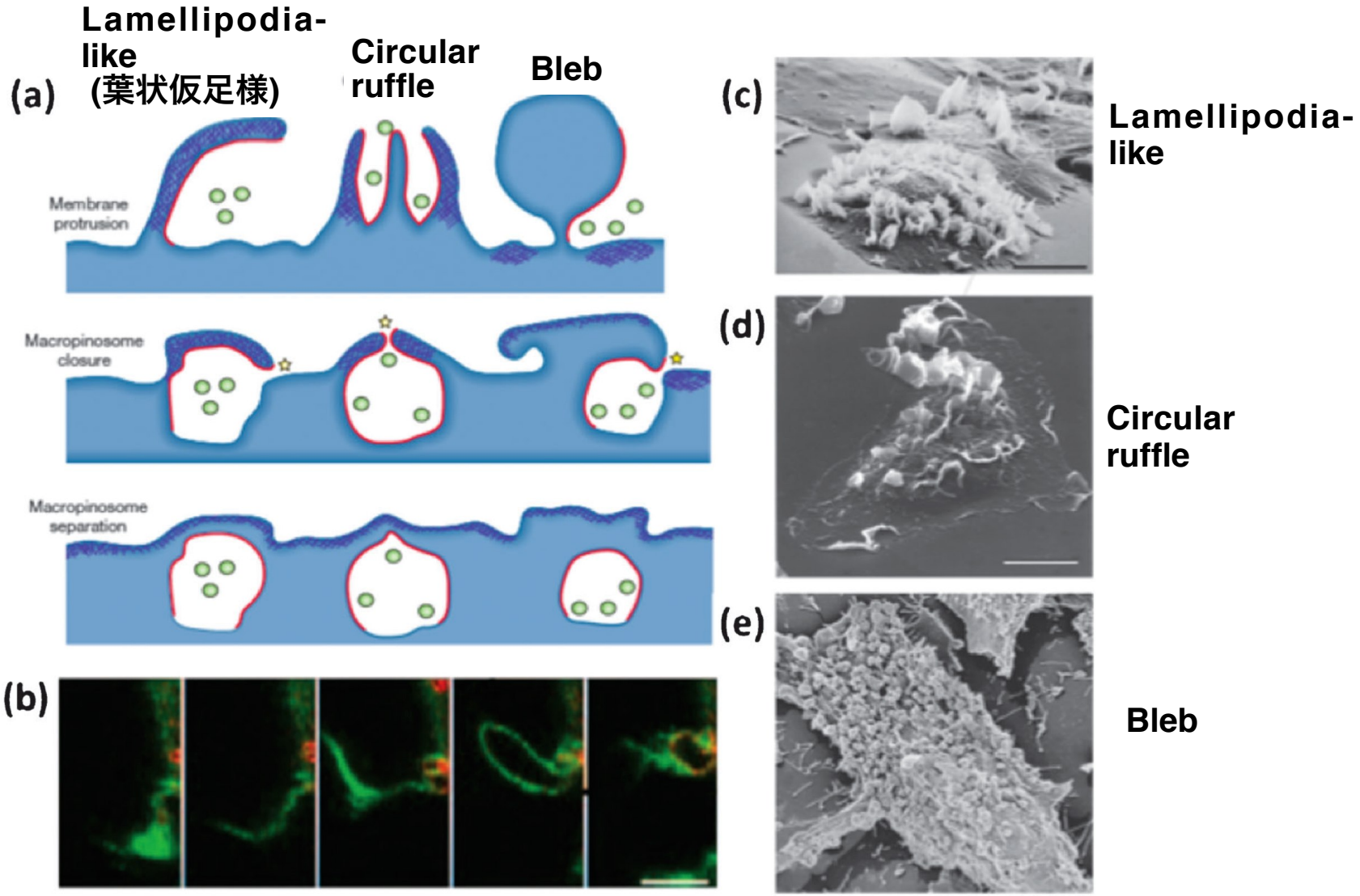
こちらもチューブ状に陥入する。発見から日が浅く、詳細は不明。ARF6は膜の曲率制御に関連があるとも言われる。（GTPと結合して曲率が上がり、くびれる。）

Flotilin-mediated

カベオリンと類似のコンフォメーションを持つタンパク質であるが、カベオラ型とは独立してエンドサイトーシスを起こすらしい。

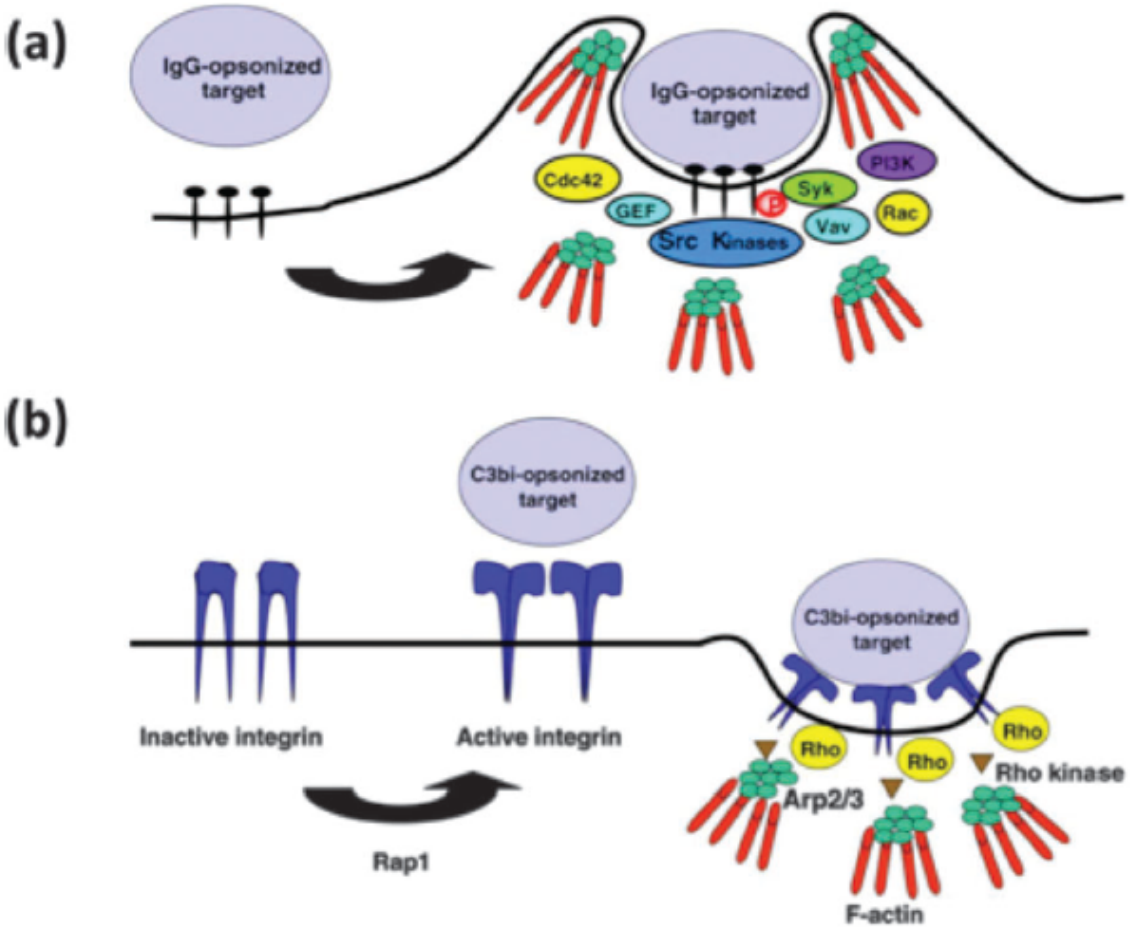
Macropinocytosis

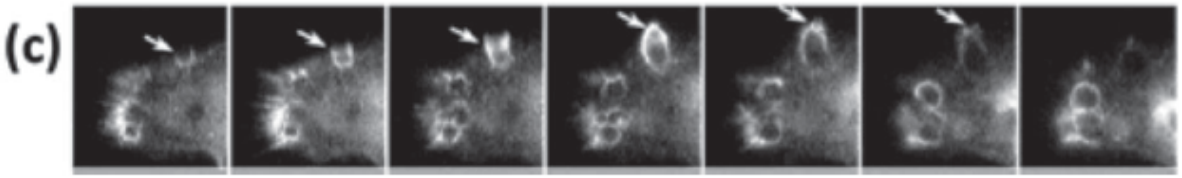
Engulfment of a large quantity of external fluid by the formation of waving sheet-like extensions of the plasma membrane that close, thus forming large organelles called macropinosomes. Polymerization of actin is a key step for engulfment.



Phagocytosis

Endocytosis performed by immune cells, e.g., macrophages, dendritic cells, mast cells, neutrophils and so on. Rather large (~μm?).



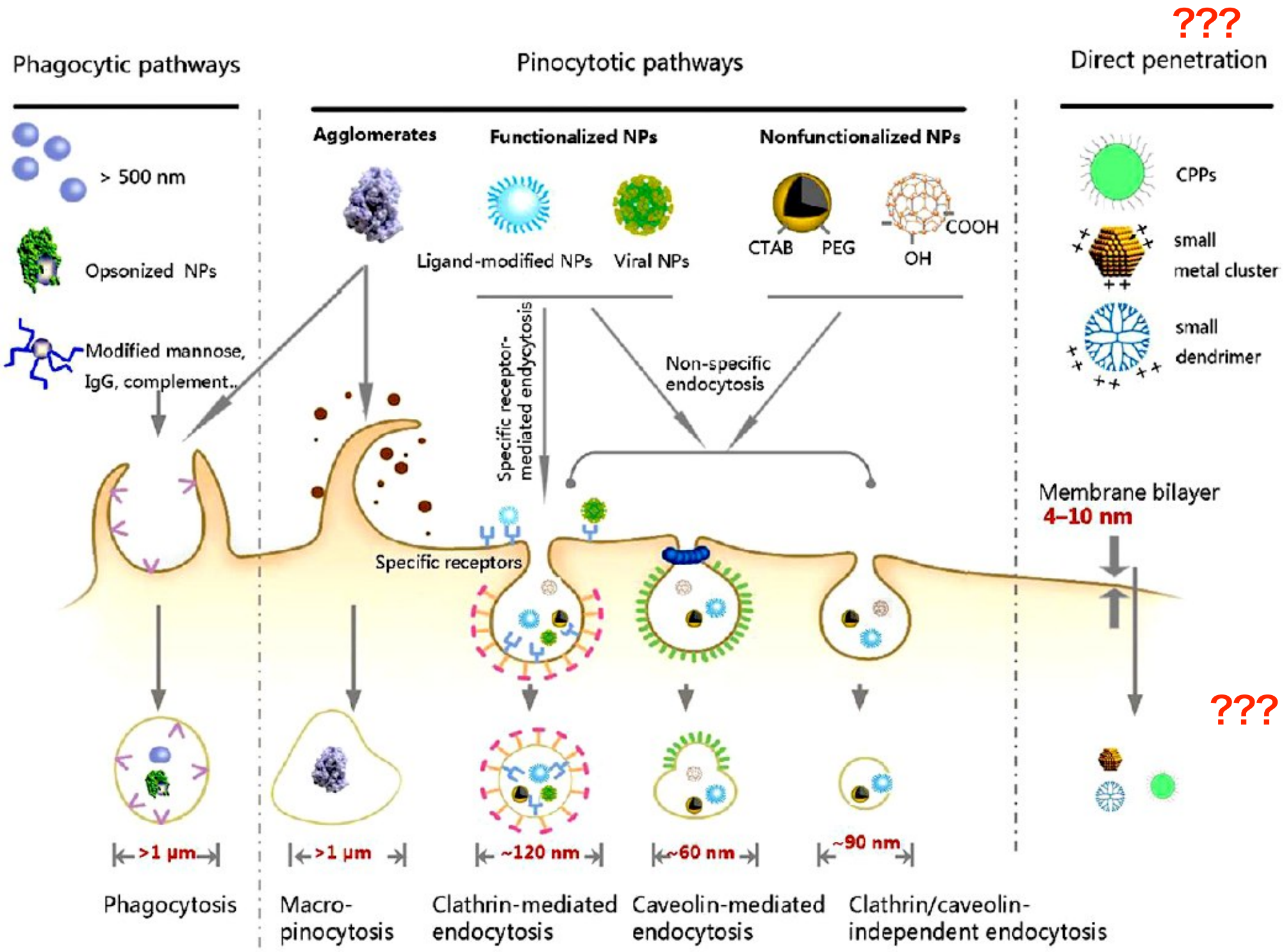


For opsonized matreials

(a) For IgG, recognition by Fcγ receptor results in phagocytosis.

(b) For C3b, recognition by CR3 (complement receptor 3) results in phagocytosis.

(c) Engulfment of opsonized RBC. Actin filaments were labeled by FL proteins.



M. Zhu, et al., Acc. Chem. Res. 46 (2013) 622–631. Fig. 3

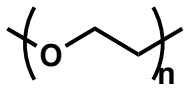
Surface chemistry & cellular uptake

- Usual cell surface is negatively charged due to glyco-chains and lipid head group. => Cationic particles are favorable, but sometimes lead to high cytotoxicity.
- In *in vivo* conditions, cationic surface often induces adsorption of proteins. (low biocompatibility)

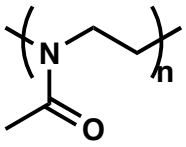
Biocompatible polymer

→ Suppression of non-specific uptake.
but, may result in low cellular uptake.
"PEG dillenma"

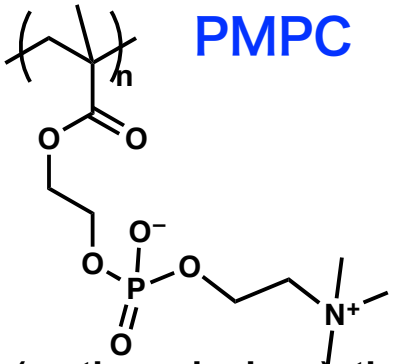
Poly(ethylene glycol) (PEG)



Poly(2-methyloxazoline)

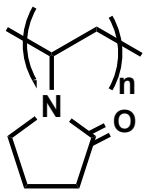


PMPC

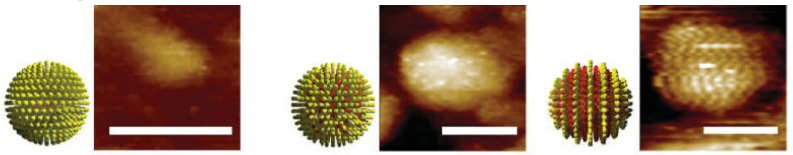


Poly(2-(methacryloyloxy)ethyl phosphorylcholine)

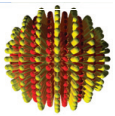
Poly(*N*-vinyl pyrrolidone) (PVP)



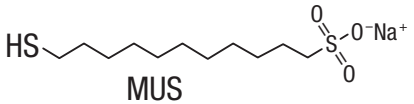
homogeneous random structured

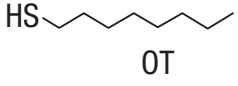


Surface structure



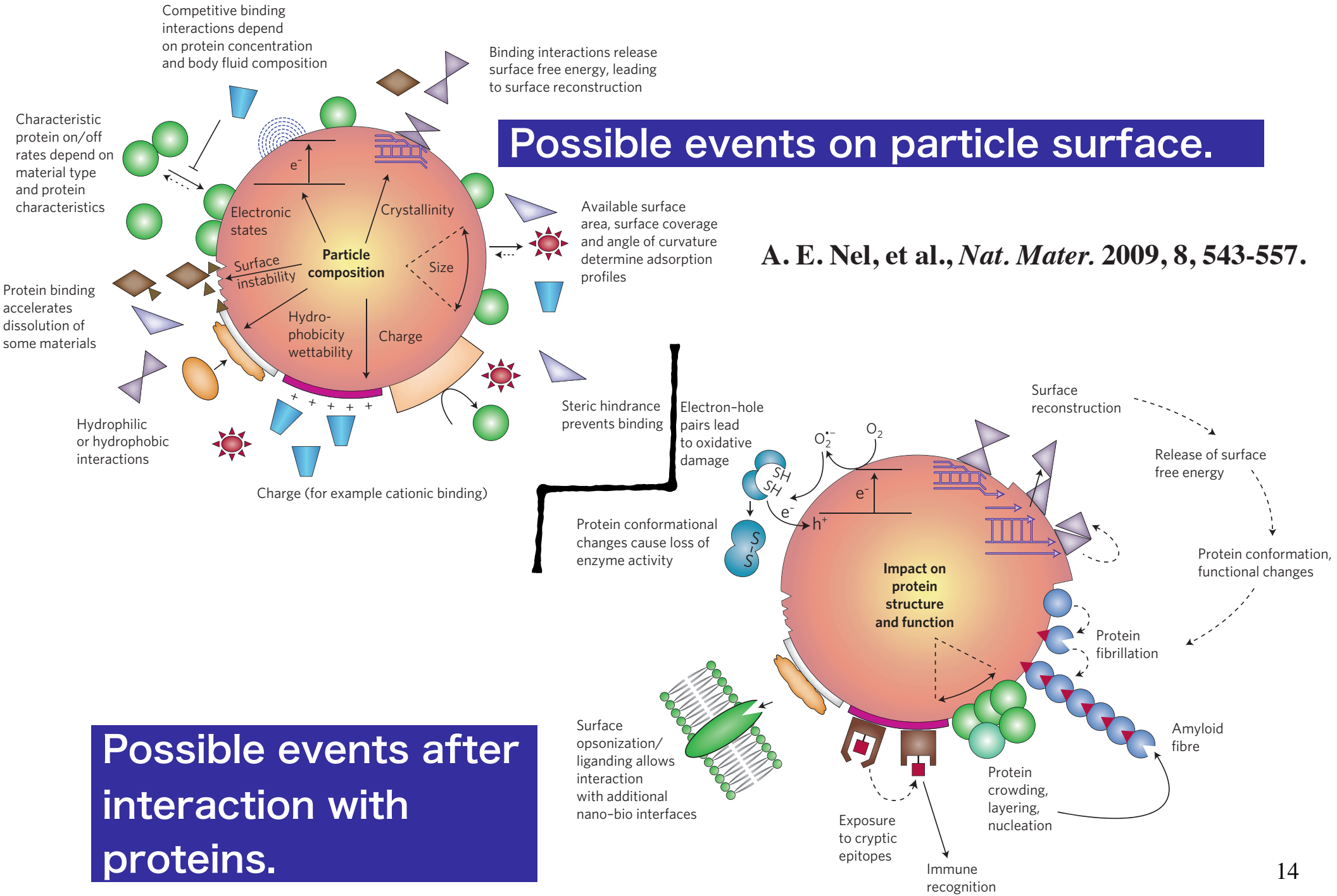
Structured





A. Verma, et al., *Nat. Mater.* 2008, 7, 588.

Surface of the particle

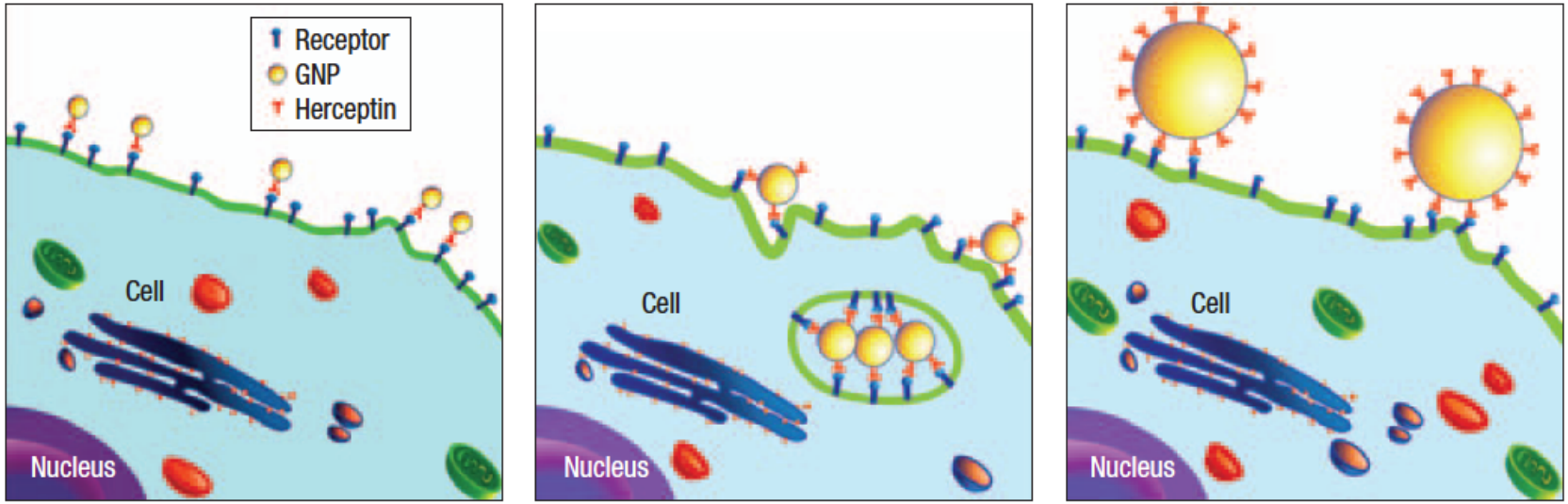


A. E. Nel, et al., *Nat. Mater.* 2009, 8, 543-557.

Effect of Size on cellular uptake

➡**Size-dependency** of interaction between antibody-functionalized gold nanoparticles (GNPs) and cells: Different internalization and signaling.

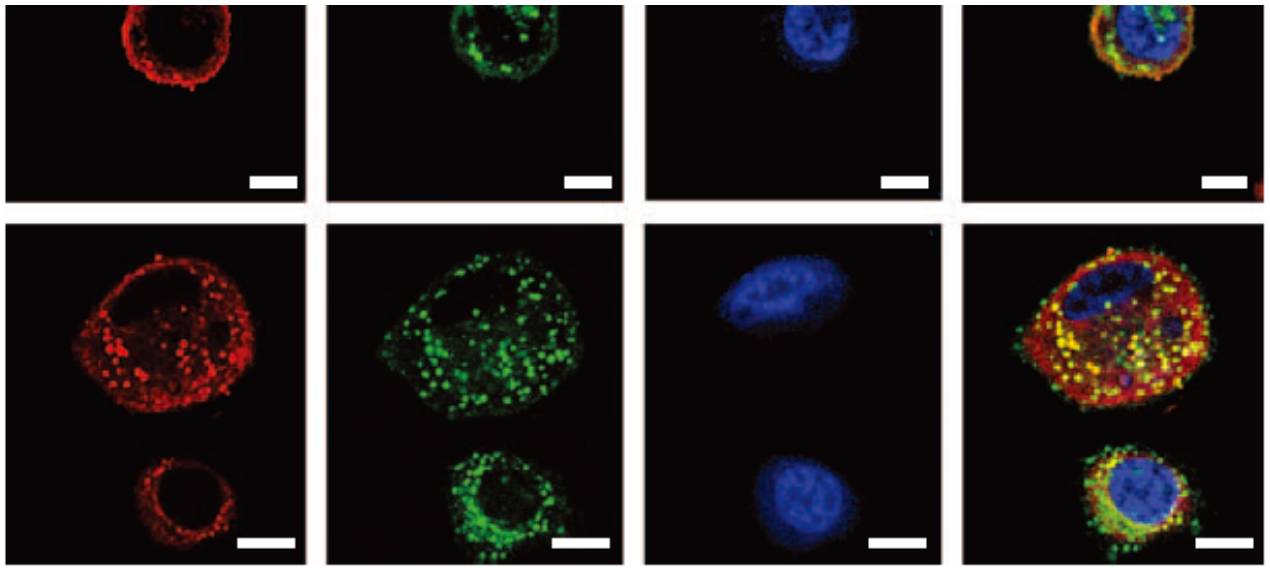
2 nm GNPs **40 nm GNPs** **70 nm GNPs**



vesicle 核 重ね合わせ

10 nm

40 nm

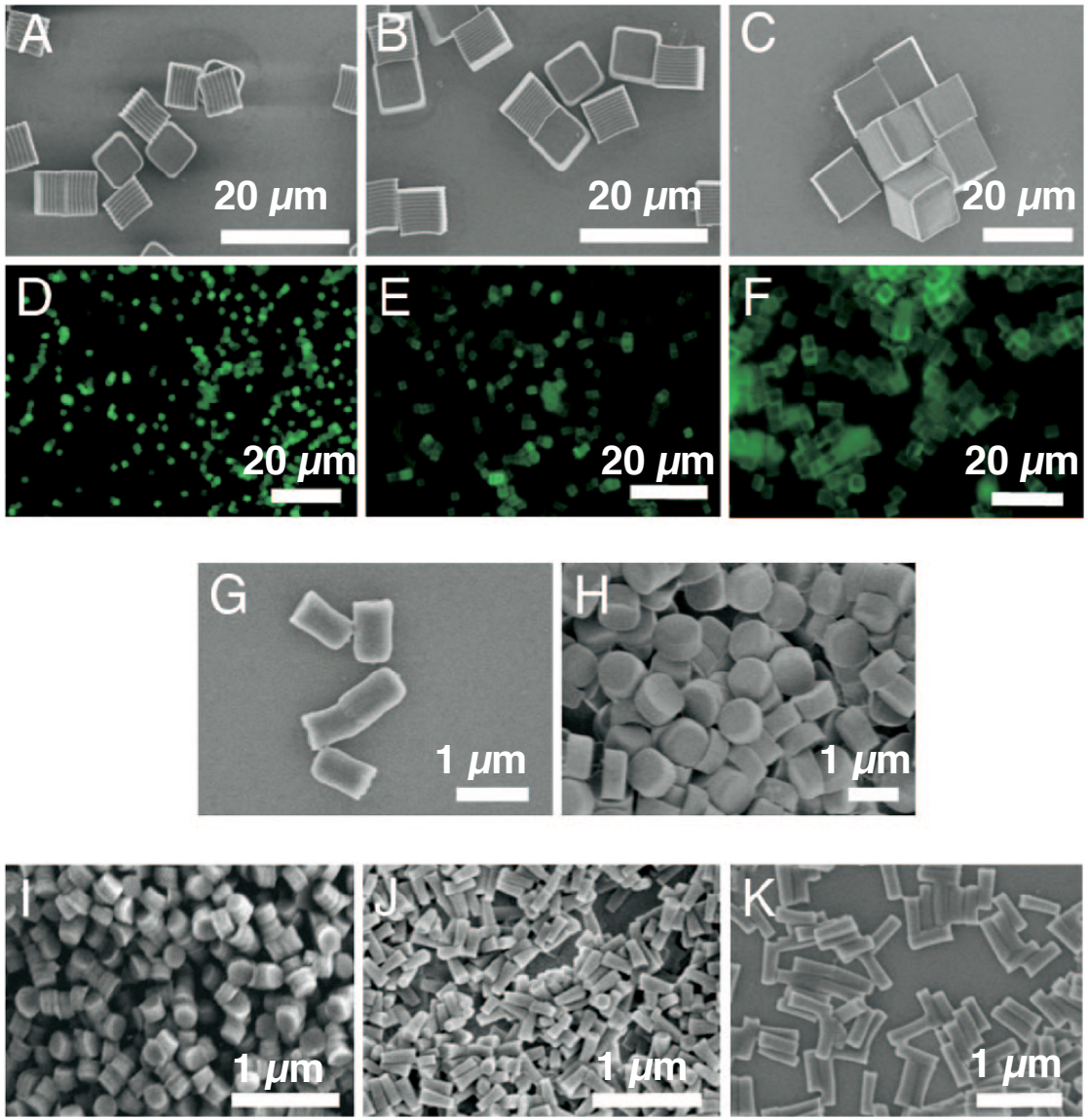


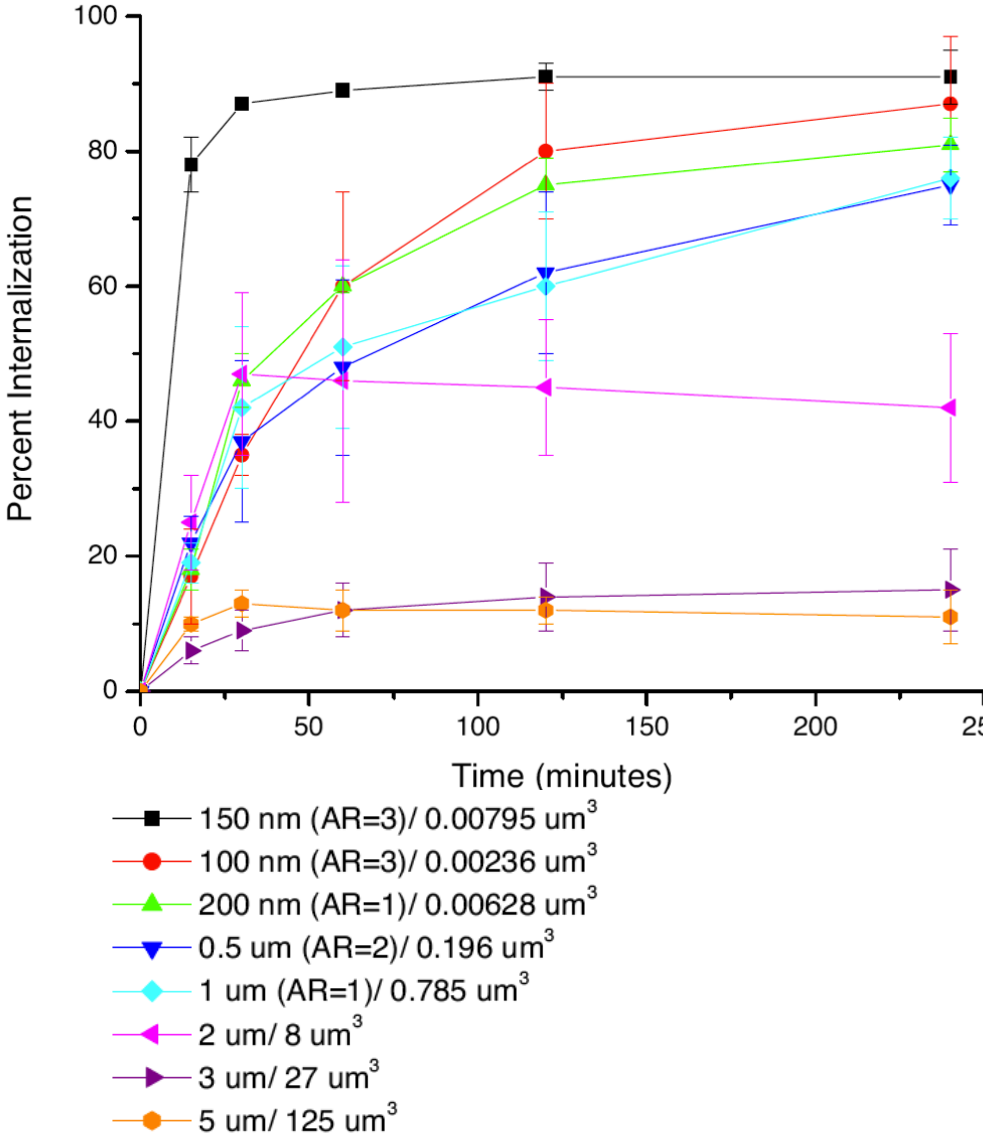
W. Jiang et al. *Nat. Nanotechnol.* 2008, 3, 145.

Effect of shape on cellular uptake (1)

Nano-/micro-hydrogels with various sizes and shapes were prepared, and cellular uptake was examined.

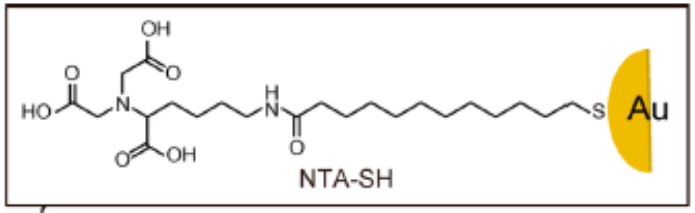
➡Internalization into HeLa cells is dependent on the size and aspect ratios.

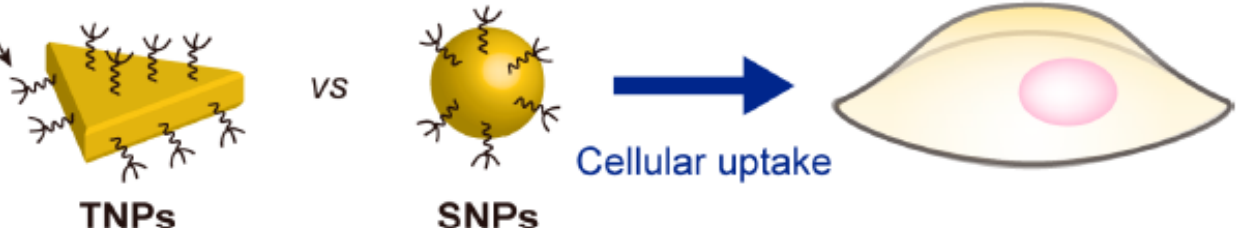




J. M. DeSimone et al., *PNAS*, 2008, 105, 11613.

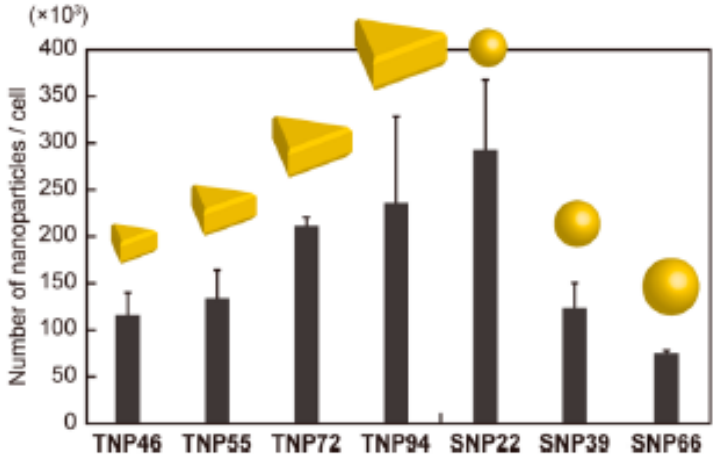
Effect of shape on cellular uptake (2)



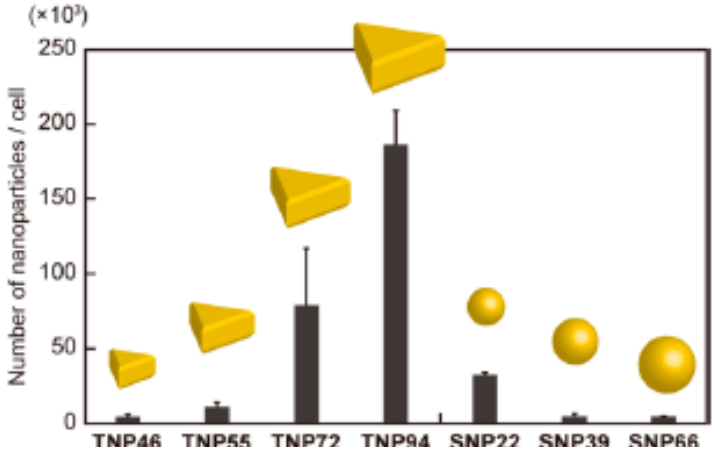


- Macrophages (RAW264.7)
- Cervical cancer cells (HeLa)

(A) RAW264.7 cells

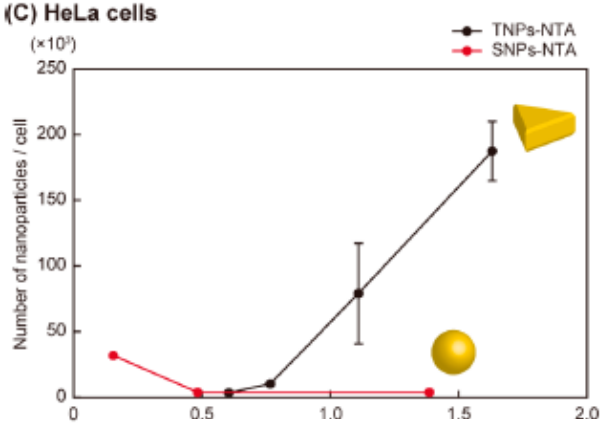


(B) HeLa cells

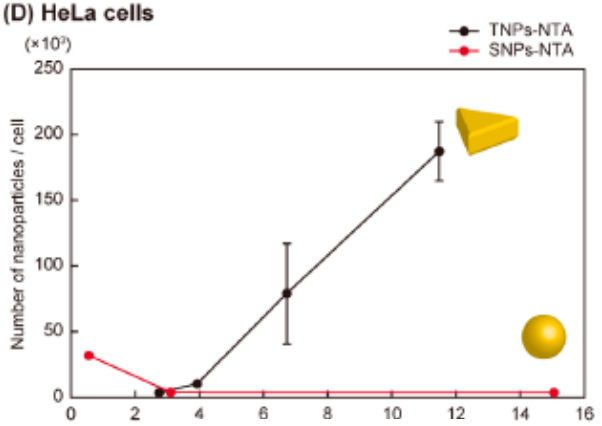


- More flat & bigger AuNP showed higher cellular uptake.
- Longer retention time on the cell surface effectively contributes…?

(C) HeLa cells

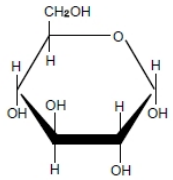
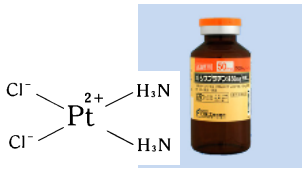
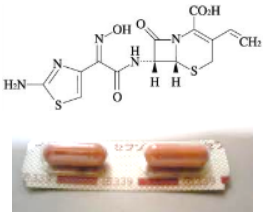
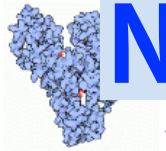
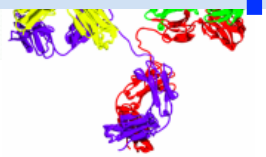
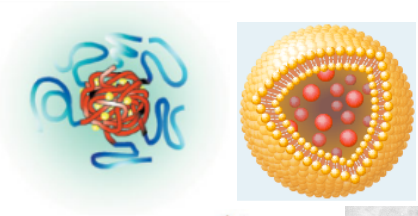
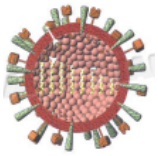
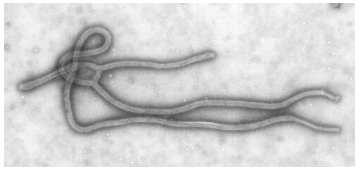
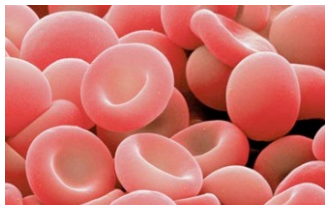


(D) HeLa cells



K. Nambara, K. Niikura, et al., *Langmuir*, 2016, *32*, 12559.

Transport from capillary

Molecular weight	Size	Substances	Type of transport
32		Oxygen 	- Diffusion
180		Glucose 	- Protein carrier
300-1,000		Low-molecular-weight drug  	
70,000	15 nm	Albumin, etc 	Nano-physiology
170,000		Ig （Antibody） 	
	20-150 nm	Nano-medicine 	- Only leaking?
	tens–hundreds of nm	Viruses (Influenza, Ebola…)  	Exosome 
7 µm		Red Blood Cell 	- Bleeding

Low Molecular Weight

Organic chemistry

Nano-scale Objects

Polymer/colloid sciences

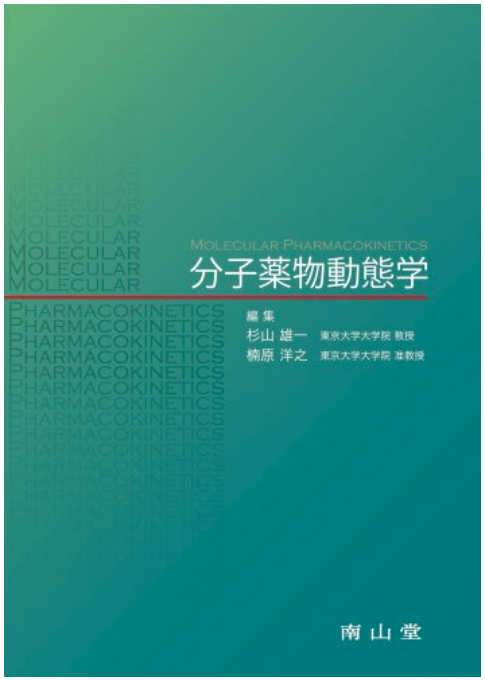
血球

参考文献

『図解で学ぶDDS』(じほう)

『分子薬物動態学』(南山堂)

pharmacokinetics



『総合製剤学』(南山堂)

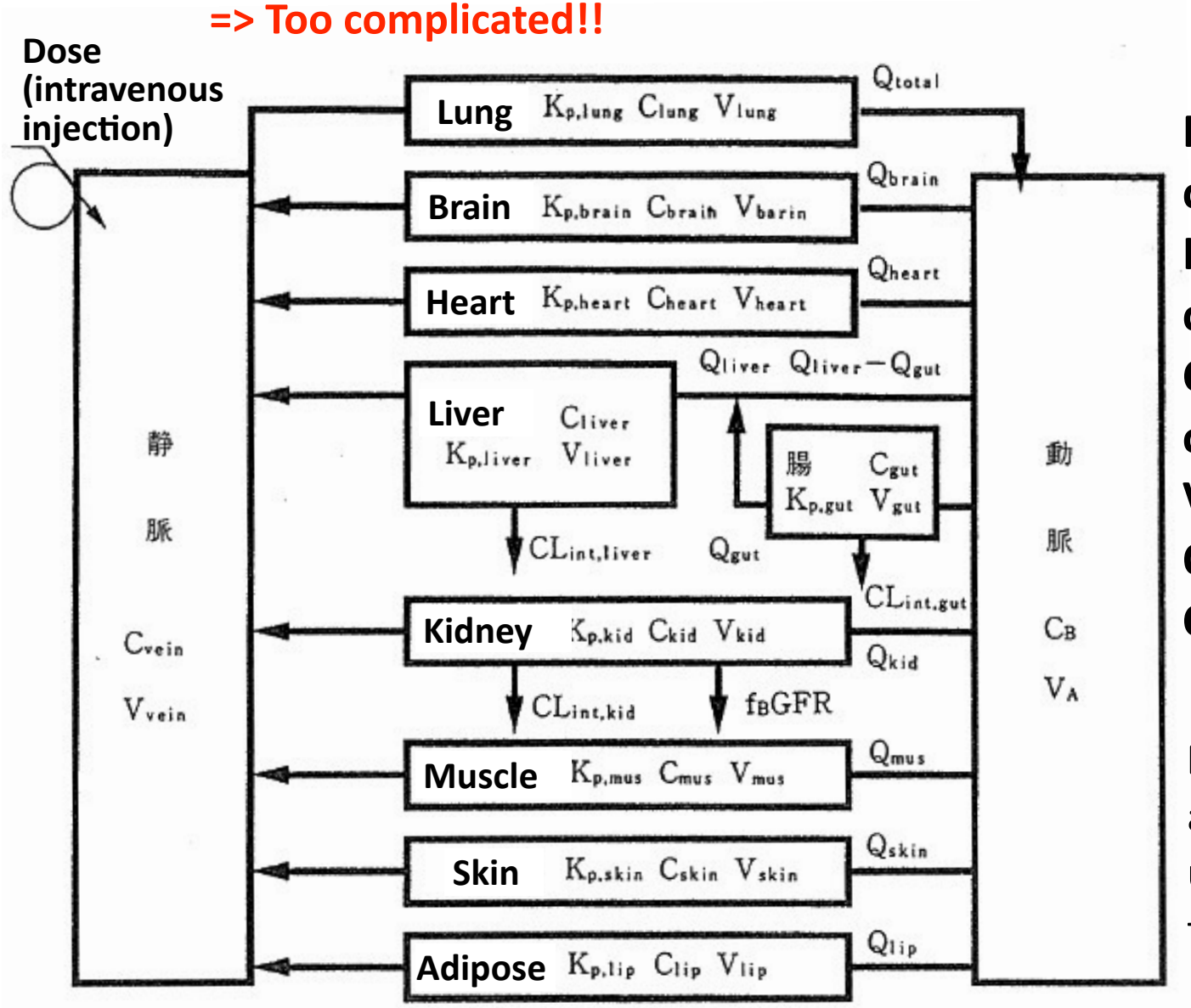
Formulation sciences

『生体内薬物送達学』 (基礎生体工学講座)
橋田 充, 高倉 喜信 (著) (産業図書, 1994年)

総説 加藤将夫、杉山雄一、薬毒物のわかりやすい体内動態、中毒研究, 7, 395–403 (1994); 8, 85–97 & 163–178 (1995).

Pharmacokinetics &

- For clear description of the movement of drug into, through, and out of the body, we consider the time course of its absorption, distribution, metabolism, excretion, and bioavailability. (Pharmacokinetics)
- Modeling by connecting organs (as compartments) with the bloodstream (as a pipeline)
  => Too complicated!!



For each compartment, we can set some parameters:

K_p: tissue to blood concentration ratio

C: drug concentration at the organ

V: volume of the organ

Q: Blood flow rate

CL: Clearance

Bioavailability: the fraction of an administered dose of unchanged drug that reaches the systemic circulation

Virtual Clinical Study based on “model & simulation”

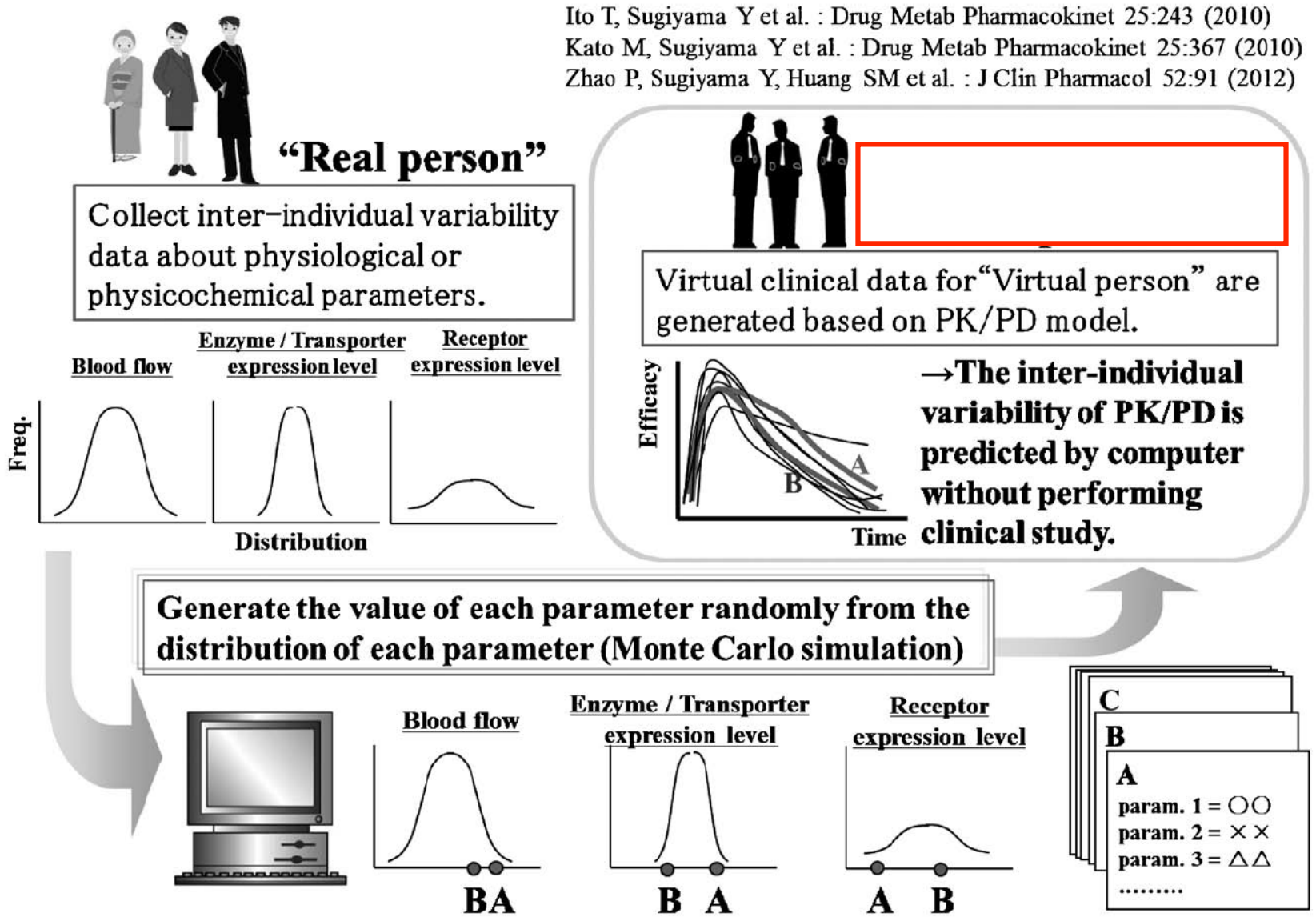


Fig. 4. Prediction of Inter-individual Variability Using Virtual Clinical Trial (VCT)

杉山雄一、リバーストランスレーショナルリサーチの重要性、

YAKUGAKU ZASSHI, 137, 673-679 (2017).

Virtual Clinical Study

Simulation of clinical studies to explore the relationships between pharmacokinetics and markers of efficacy and/or safety

=>Optimization of clinical study design, by simulating the study in advance considering inter-individual variability

- Dose-response relationships
- Optimal dosage regimen to get good balance of safety and efficacy
- Impact of genotypes
- Impact of ethnic difference

=>General information, such as physiology, pharmacokinetics including activities of metabolic enzymes and transporters, pharmacology, and disease progressing, can be integrated into models and contribute to future drug development of new drug candidates.

Fig. 5. Understanding Variability in Pharmacokinetics for Drug Development and Optimal Dosage Regimen

杉山雄一、リバーストランスレーショナルリサーチの重要性、

YAKUGAKU ZASSHI, 137, 673-679 (2017).

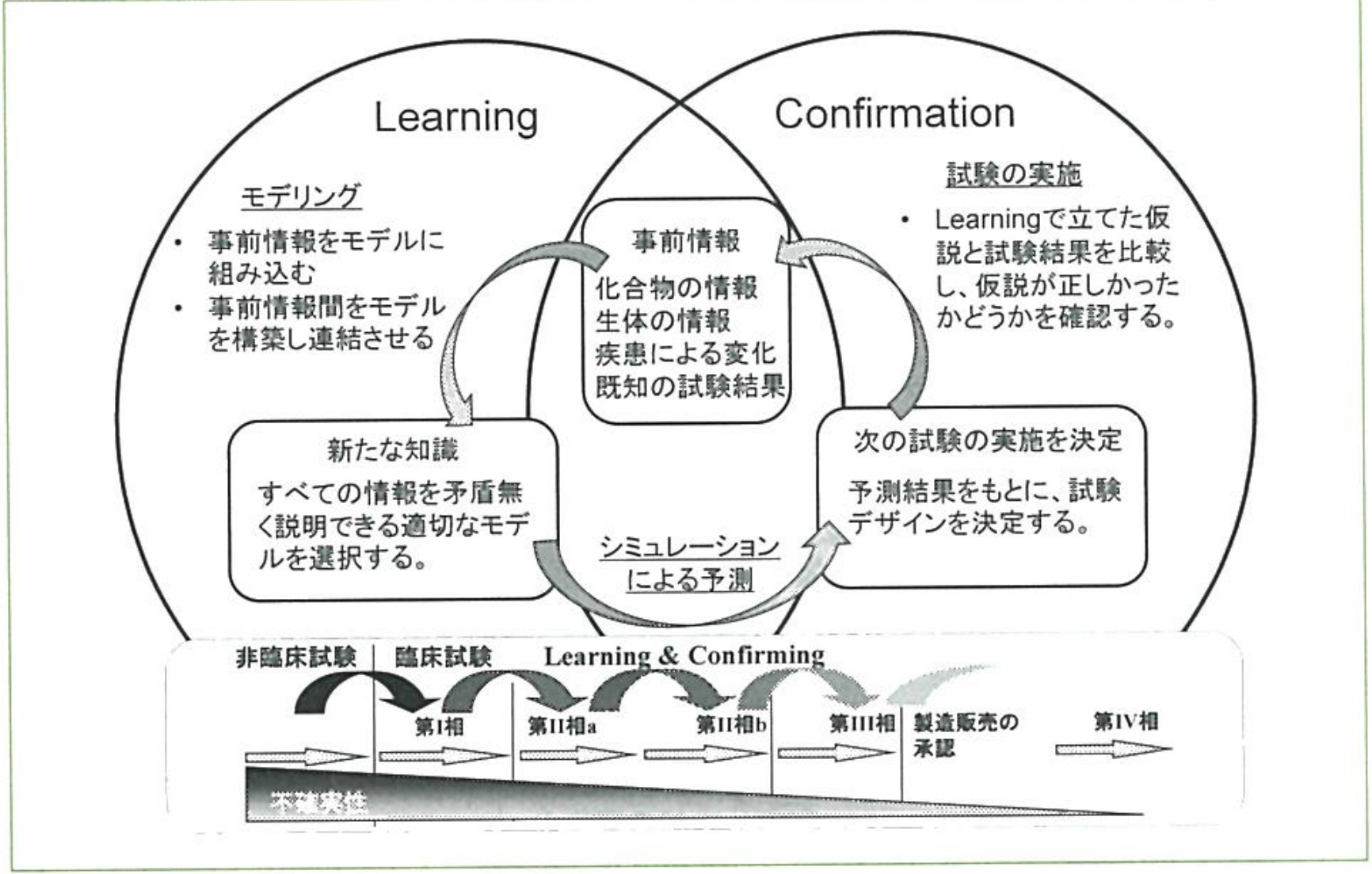


図１　医薬品開発における VCS の位置づけ

様々な情報は VCS のためのモデル上で統合され(下矢印)，そのモデルにより臨床試験の結果をシミュレーションして最適な試験計画が立案される(右矢印)．得られた予測結果と実際の臨床試験の結果を比較・確認し(上矢印)，異なる点は次の VCS で修正される.[2] これを医薬品開発の各段階で繰り返し，医薬品開発の不確実性を下げていく(図下部).[6]

ファルマシア Vol.54 No.5 2018, 402-406.

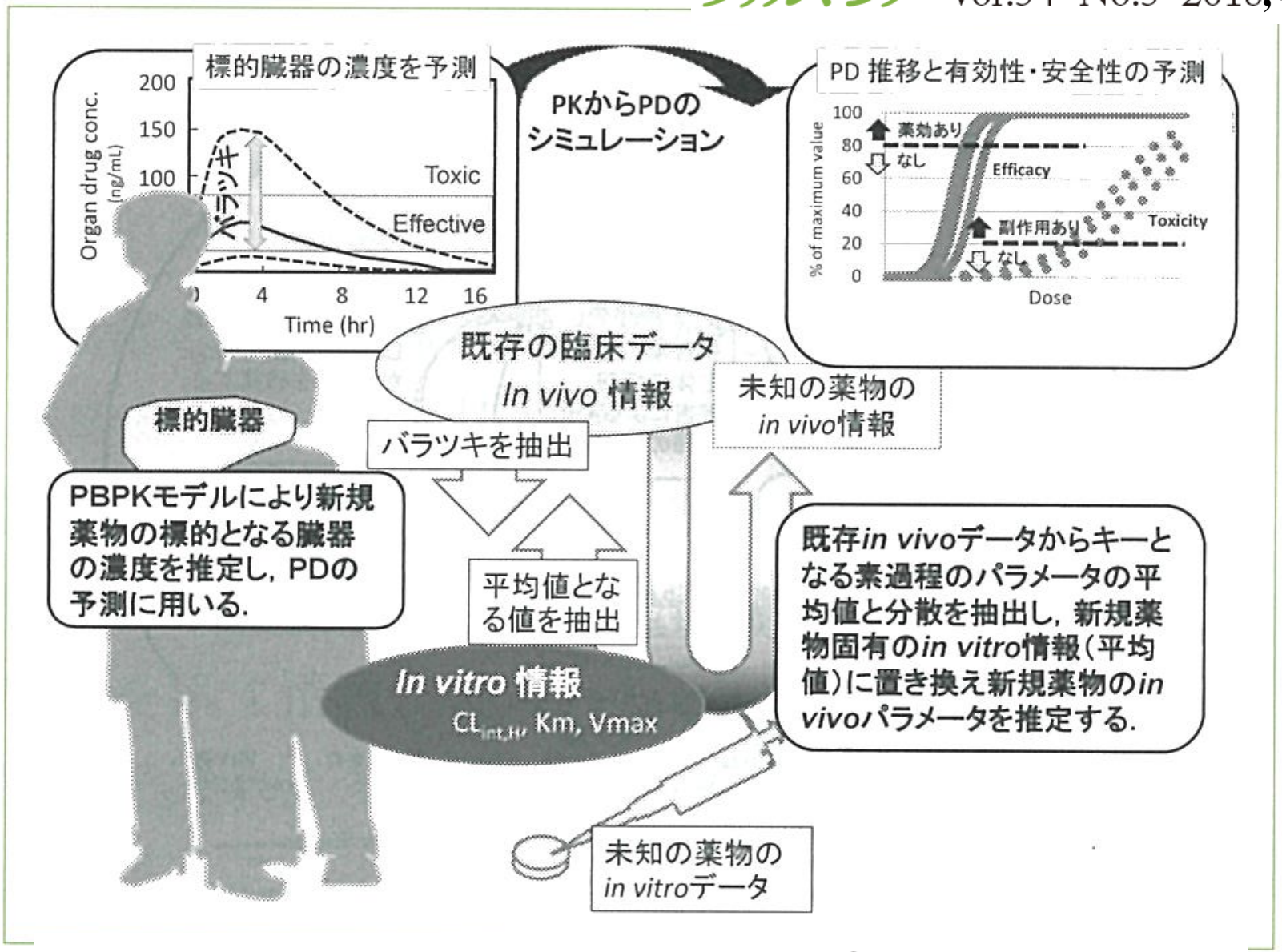


図 2　VCS のコンセプト

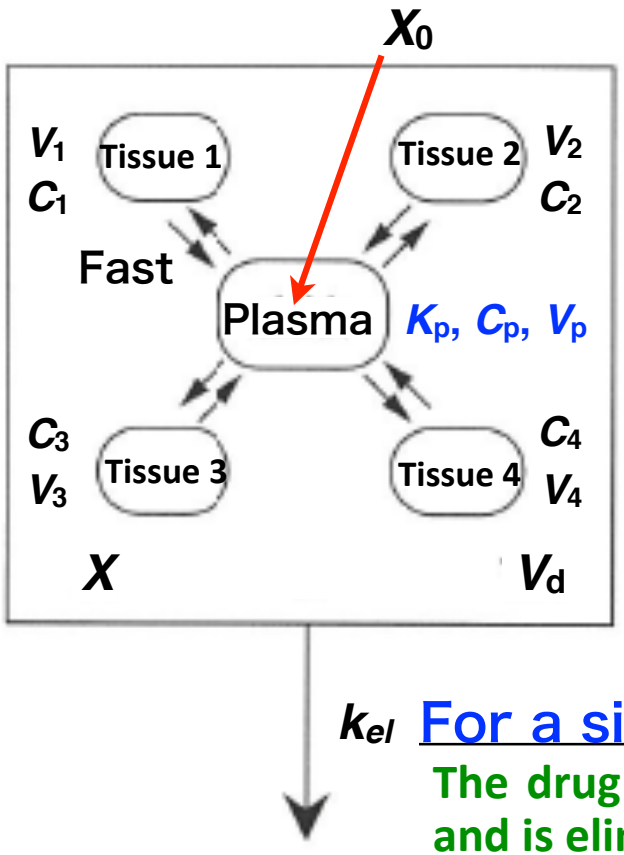
医薬品開発の早期段階では，*in vitro* データから $CL_{int,H}$ などの情報を組み込むが，臨床第 I 相が始まり実測値が得られると，*in vitro* と *in vivo* との乖離の原因を明らかにし，これらの情報をさらにモデルに組み込むことにより予測精度を高める.

Compartmental analysis

Simple models based on several compartments.
=> Useful for prediction of drug concentration at any time.

1-compartment model

a rapid intravenous injection (IV bolus)



For drugs to be effective, they need to be able to move rapidly from blood plasma to other body fluids and tissues.

X: Total amount of drug
C_i: drug concentration at the tissue
V_i: volume of the tissue
K_i: tissue to plasma concentration ratio = C_i/C_p
(i = 1–4)

"p" stands for plasma.

$$X = \boxed{\quad} = (V_p + \sum V_i K_i) C_p$$

This term should be small, if the drug shows slow clearance. *Ideally, V_iK_i for the target tissue should be maximized.*

V_d (Distribution volume) $\equiv V_p + \sum V_i K_i = X/C_p$

For a single bolus IV injection

The drug concentration is uniform in the body compartment at all times and is eliminated by a first order process

$dX/dt = -k_{el}X$ (k_{el} : elimination rate constant)

$X = X_0 \cdot \exp(-k_{el}t)$ (X_0 : Dose)

$C_p = C_0 \cdot \exp(-k_{el}t)$ (C_0 : initial plasma concentration)

The integral of $1/x$ is $\ln(x)$.

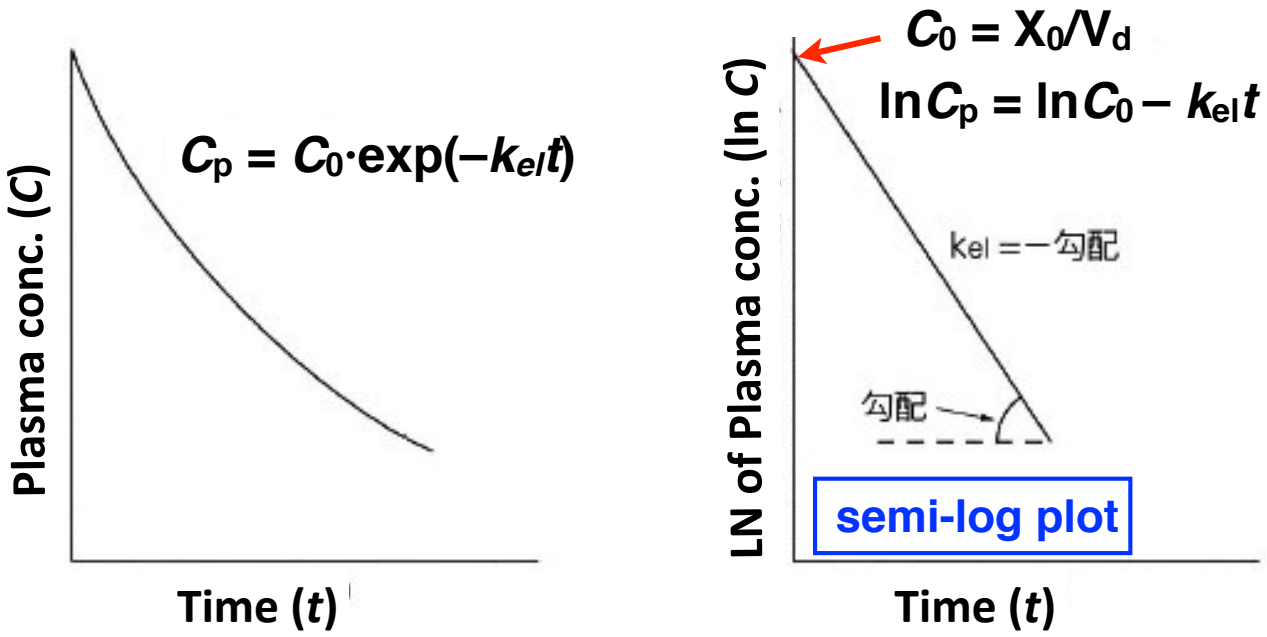


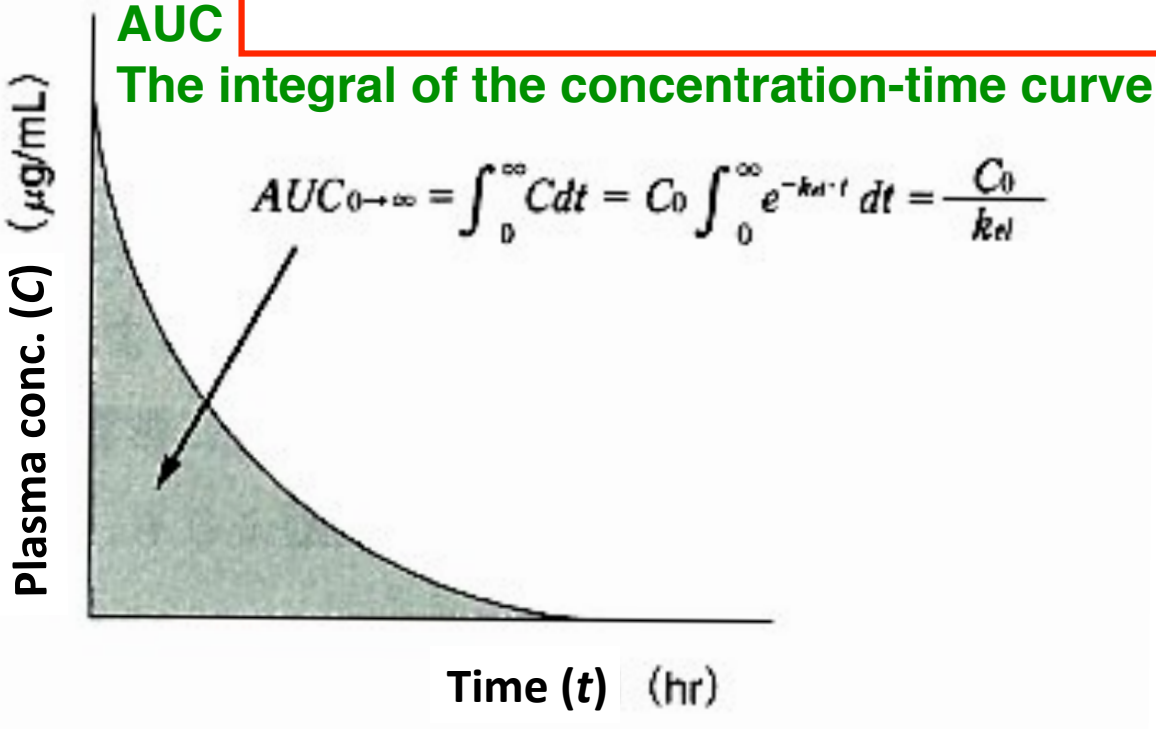
図 I -6-2. 1-コンパートメントモデルにおける静脈内瞬時投与後の血漿中濃度推移

Elimination half-life ($t_{1/2}$): The time required for the concentration of the drug to reach half of its original value.

$$t_{1/2} = \ln(2)/k_{el}$$

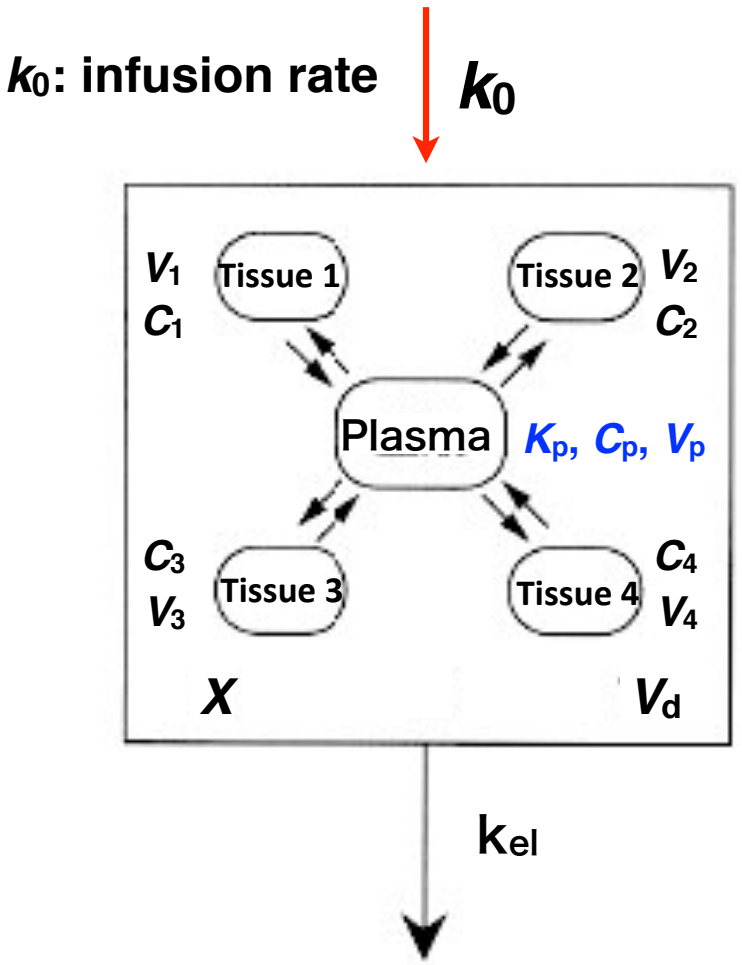
AUC

The integral of the concentration-time curve (after a single dose or in steady state).



Assignment (Due date: Nov 22nd)

1-Compartment model (for constant-rate IV infusion)



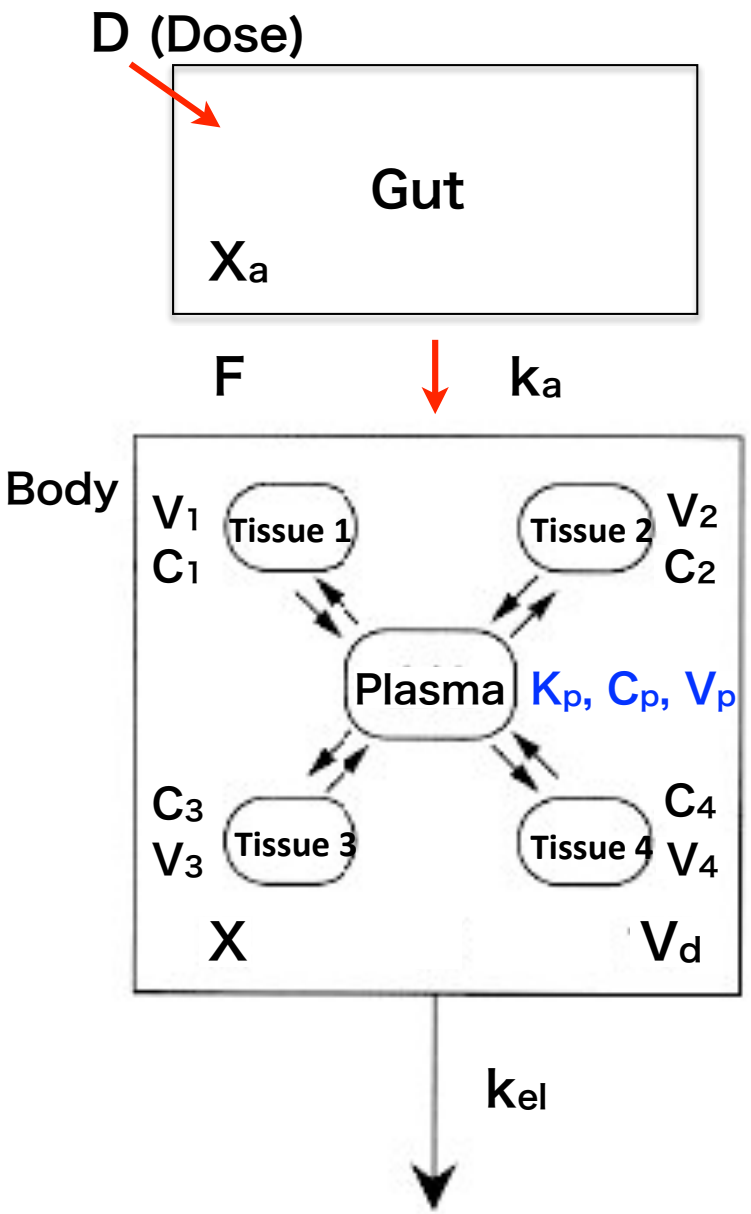
Problems)

i) Express the total amount of drug *X* as a function of *t*.
ii) From the equation of $C_p = X/V_d$, find the C_p at the steady state using k_{el}, k_0, and V_d.
iii) Briefly describe the time course of drug concentration in plasma.

Hints :

- Express the mass balance regarding *X* using a differential equation.
- differential of ln(*x*) is 1/*x*; integral of 1/*x* is ln(*x*); integral of 1/(a*x*+b) is (1/a)ln(a*x*+b)

1-Compartment model (for gut absorption)



e.g., Single oral administration & absorbed from the gut

$$\frac{dXa}{dt} = -k_a Xa$$

$$\frac{dX}{dt} = k_a Xa - k_{el} X$$

***Xa*: drug conc. in gut**
k_a: Absorption rate constant
***F*: Absorbed fraction**
***D*: Dose**

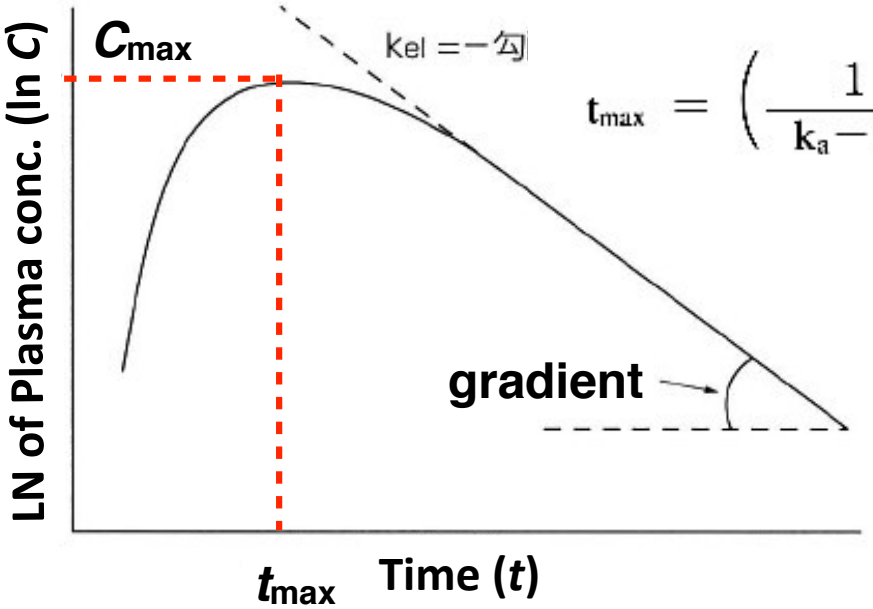
$$X = \frac{F D k_a}{k_a - k_{el}} \{\exp(-k_{el} t) - \exp(-k_a t)\}$$

Use the Laplace transform

$$C_p = \frac{F D k_a}{Vd(k_a - k_{el})} \{\exp(-k_{el} t) - \exp(-k_a t)\}$$

$$C_{max} = \frac{F D}{Vd} \left(\frac{k_a}{k_{el}}\right)^{\frac{k_{el}}{k_{el}-k_a}}$$

$$t_{max} = \left(\frac{1}{k_a - k_{el}}\right) \ln \left(\frac{k_a}{k_{el}}\right)$$



k_{el} = –(gradient)

（Appendix）Laplace transform

1．ラプラス変換の定義

式（22）のような線形微分方程式は，ラプラス変換を用いることにより簡単に解くことができる．ラプラス変換は，次式によって定義される．

$$F(s)=\int_0^{\infty} e^{-st} f(t)\,dt \qquad (27)$$

ここで f(t) を原関数または表関数，F(s) を像関数または裏関数と呼ぶ．式（27）から，表 I-6-1 に示すような公式が導かれる．

表 I-6-1. ラプラス変換の公式

式番号	f(t)	F(s)
公式 1	$f_1(t)+f_2(t)$	$F_1(s)+F_2(s)$
公式 2	$af(t)$	$aF(s)$
公式 3	$\frac{df(t)}{dt}$	$sF(s)-f(0)$
公式 4	e^{-kt}	$\frac{1}{s+k}$
公式 5	a	$\frac{a}{s}$
公式 6	δ（t＝0 のときのみ 1，その後ゼロの関数）	1

$$sxa-Xa(0)=-k_a x_a \qquad (28)$$

$$sx-X(0)=k_a xa-k_{el}\,x \qquad (29)$$

ここで，xa，x はそれぞれ Xa, X をラプラス変換したものである．経口投与直後の初期値は Xa(0)＝D，X(0)＝0 となるので，以下の式が導かれる．

$$(s+k_a)xa=D \qquad (30)$$

$$-k_a xa+(s+k_{el})x=0 \qquad (31)$$

この連立方程式を解くと，次のようになる．

$$xa=\frac{D}{s+k_a} \qquad (32)$$

$$xb=\frac{D\,k_a}{(s+k_{el})(s+k_a)} \qquad (33)$$

式（32）を表 I-6-1 の公式を使って逆変換すると，式（34）が得られる．

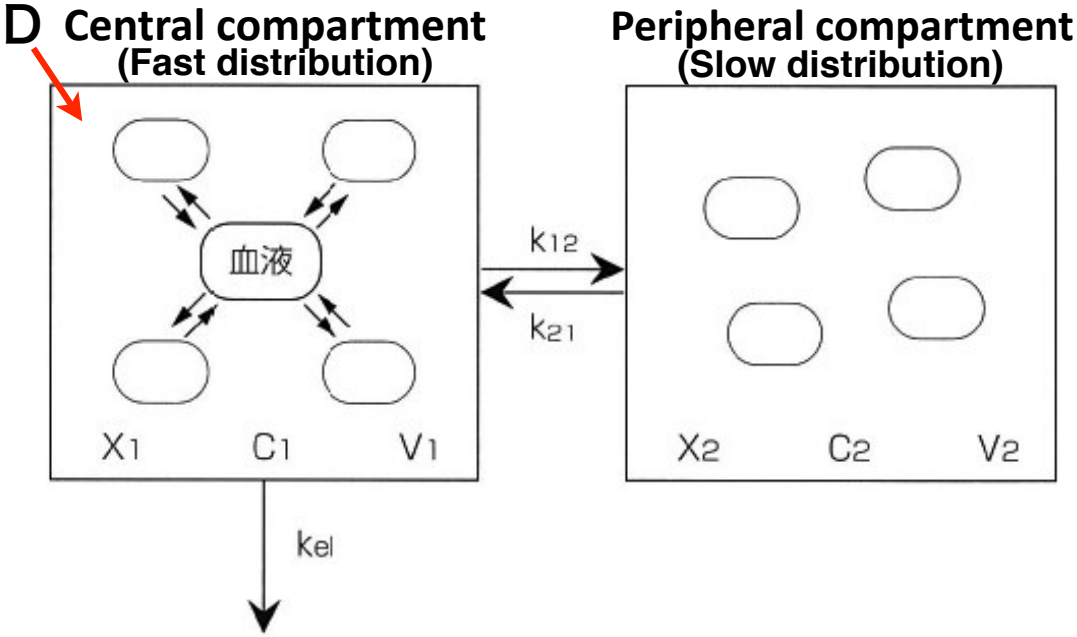
$$Xa=D\exp(-k_a t) \qquad (34)$$

また，式（33）を逆変換し，さらに吸収率を考慮することにより式（11）が得られる．

2-Compartment model

http://www.gatewaycoalition.org/files/hidden/deliv/ch3/3_5f.htm

Often drug does not distribute evenly amongst all the organs. To account for this a two compartment model is used in which drug disposition is biexponential. The drug is assumed to distribute into a second compartment but be eliminated from the first compartment only.



$$dX_1/dt = -(k_{el} + k_{12})X_1 + k_{21}X_2$$

$$dX_2/dt = -k_{21}X_2 + k_{12}X_1$$

Solved using the Laplace transform

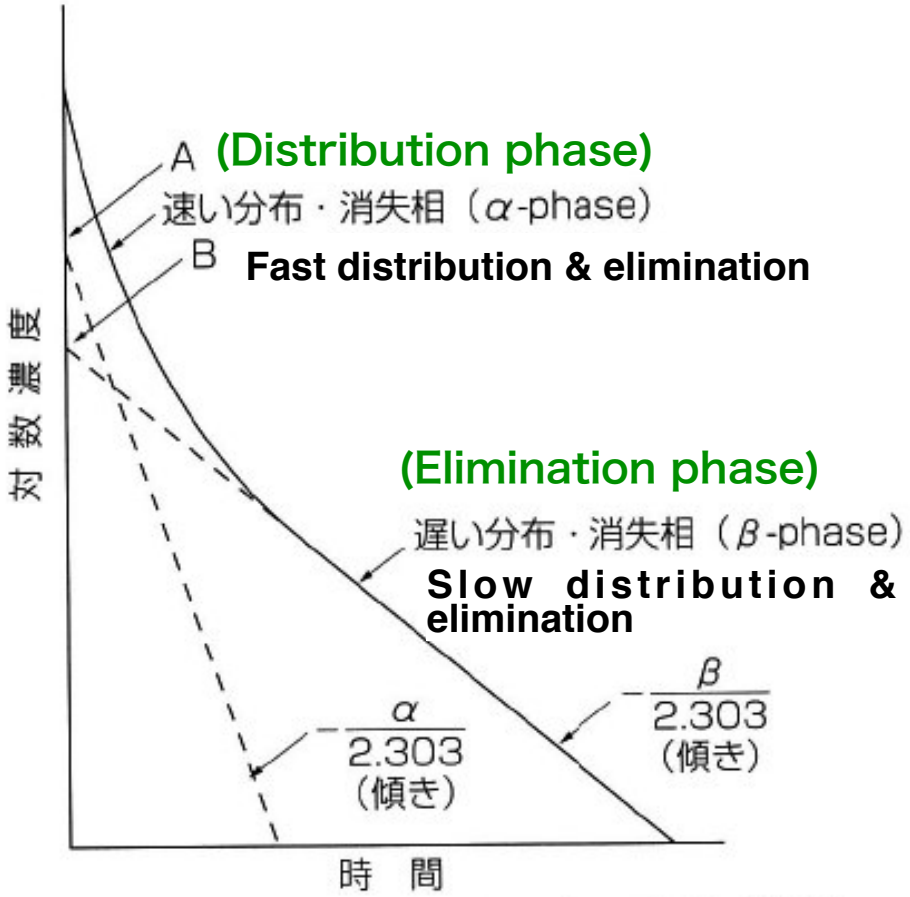
$$C_1 = X_1/V_1 = A\cdot\exp(-\alpha t) + B\cdot\exp(-\beta t) \quad (\alpha > \beta)$$

$$A = D(\alpha - k_{21})/\{V_1(\alpha - \beta)\}$$

$$B = D(k_{21} - \beta)/\{V_1(\alpha - \beta)\}$$

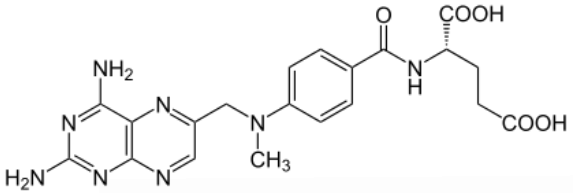
$$V_1 = D/(A + B),\ V_2 = k_{12}\cdot V_1/k_{21}$$

$$V_{ss} = V_1 + V_2$$



図Ⅰ-6-7. 2-コンパートメントモデルにおける静脈内瞬時投与後の血漿中濃度推移

Example of 2-compartment model



Methotrexate: Antimetabolite (antifolate type).
Used to treat cancers, autoimmune diseases etc.
Protein binding: -50%, Urine excretion：48% (1 h)

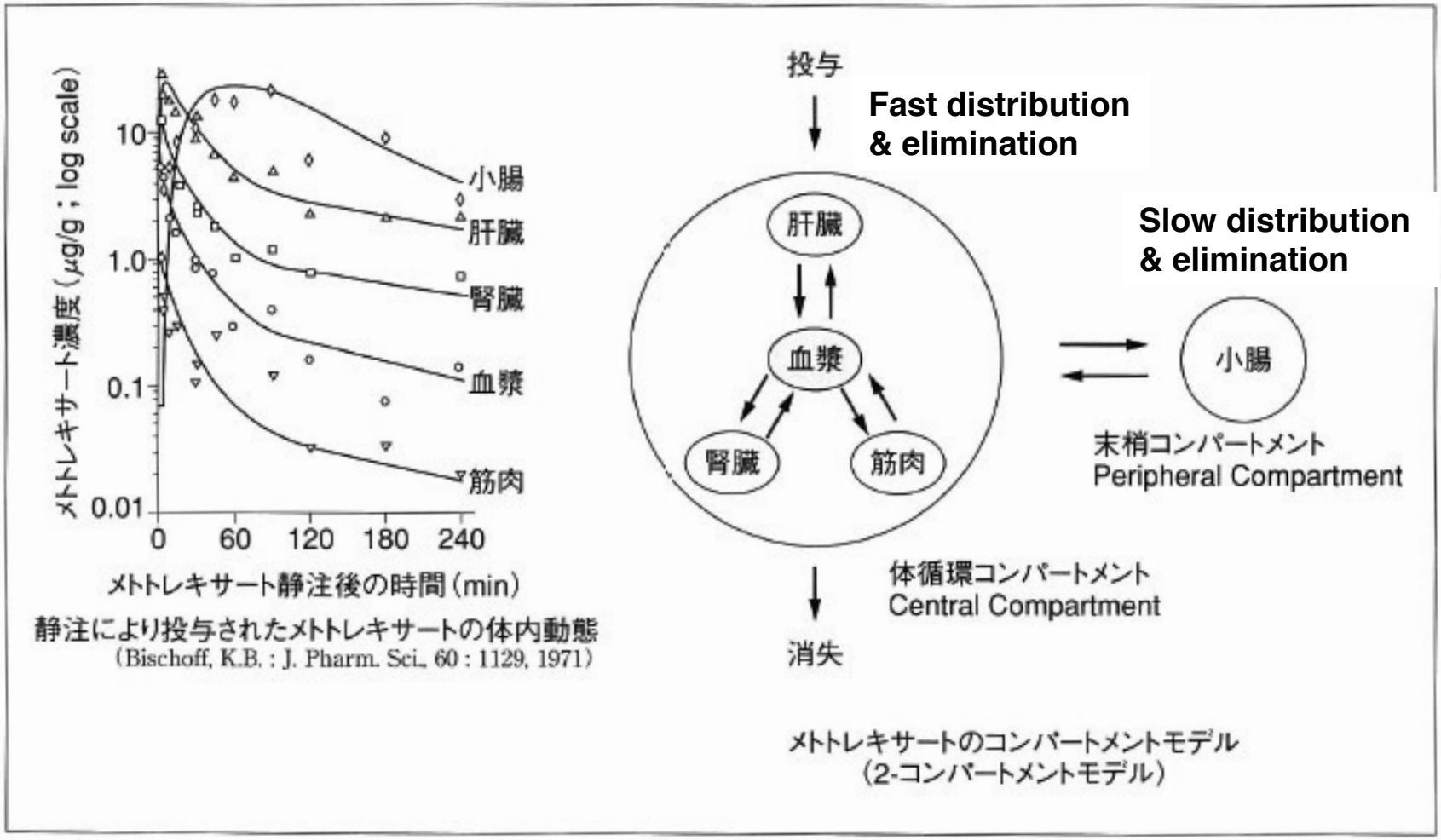


図 3-1　コンパートメントモデルの考え方

左のグラフはメトトレキサートを静脈内投与後の血漿および各組織中薬物濃度の時間推移を示している．コンパートメントモデルを構築する場合，血液と常に平衡が成立している組織をまとめて1つのコンパートメント（体循環コンパートメント）とし，この例の小腸のような組織は別のコンパートメント（末梢コンパートメント）とした2-コンパートメントモデルを考える．

Model-independent approach (moment analysis)

It gives us characteristic properties of drugs, but it's not useful for predicting its time course.

Zero moment

$$AUC = \int_0^\infty C_p(t)\,dt$$

First moment

Mean residence time

$$MRT = \frac{\int_0^\infty t \cdot C_p(t)\,dt}{\int_0^\infty C_p(t)\,dt}$$

Second moment

Variance of residence time

$$VRT = \frac{\int_0^\infty (t - MRT)^2 C_p(t)\,dt}{\int_0^\infty C_p(t)\,dt}$$

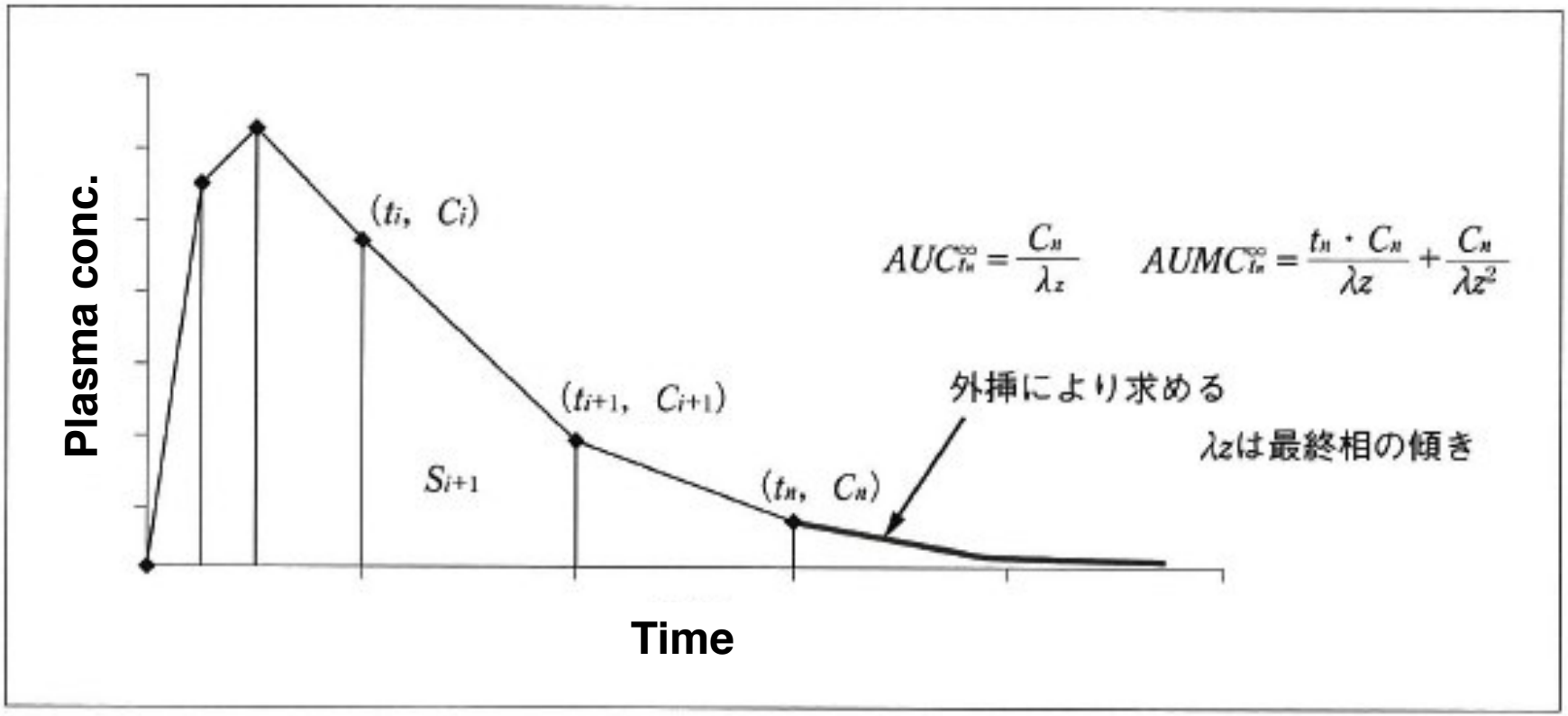
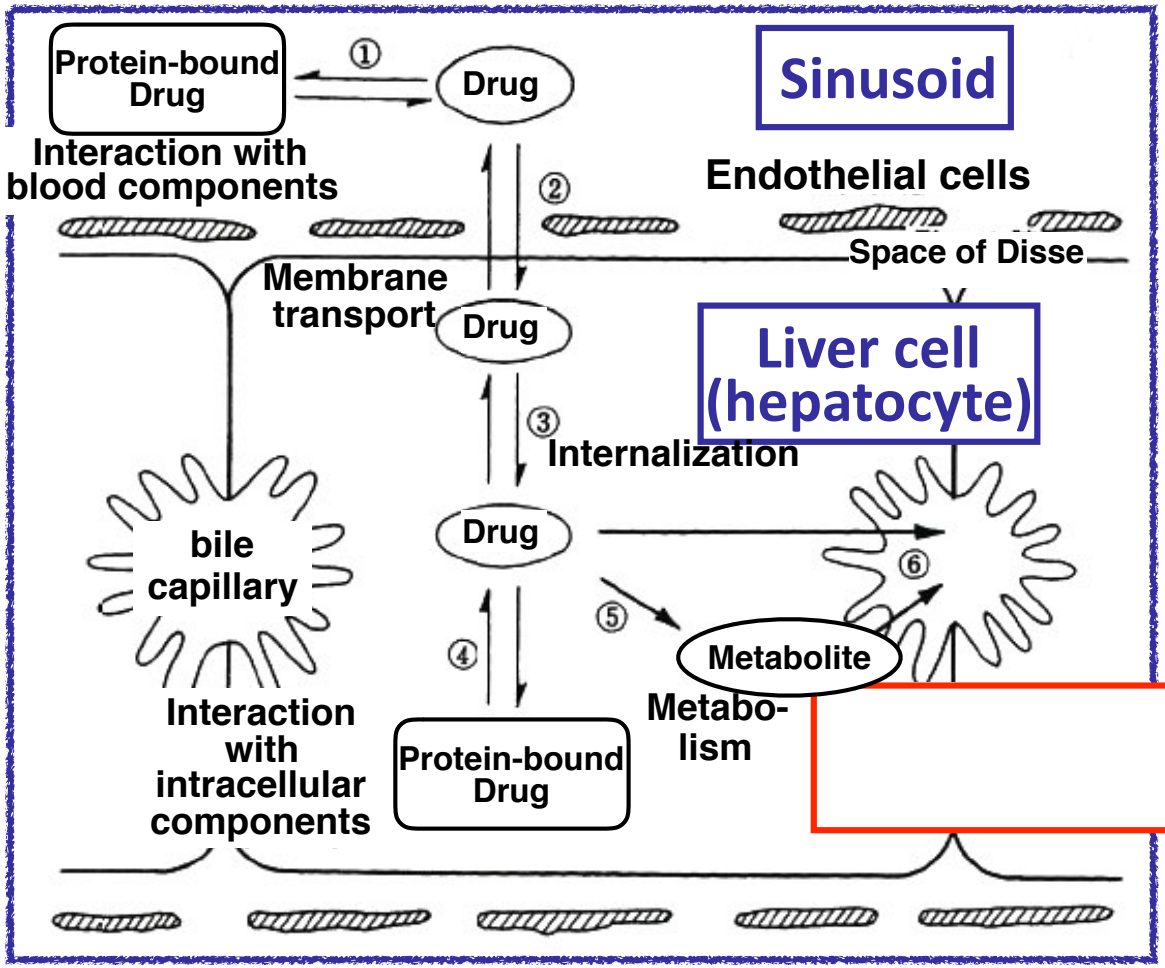


図 4-2　血（血漿）中濃度推移からのAUCの計算

AUC，AMUCは最終測定点までを台形公式により求め，それ以降は外挿して求める．

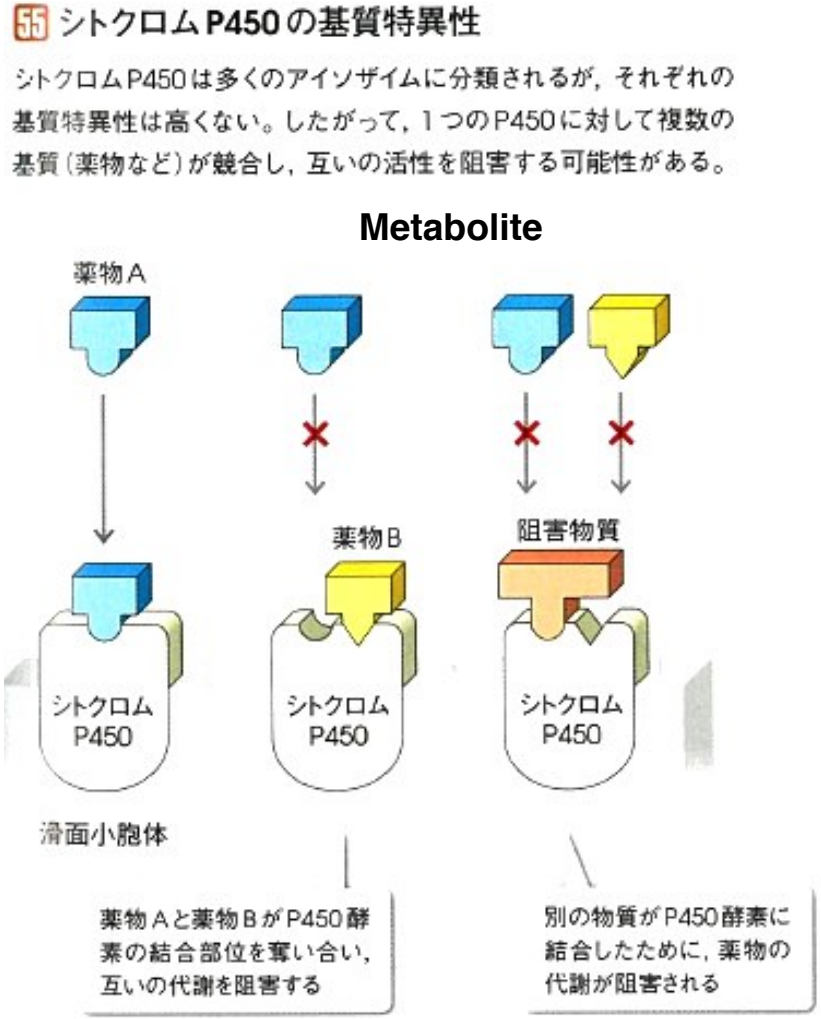
Liver metabolism



『生体内薬物送達学』p. 130 を英訳

✓Liver metabolizes toxic compounds, such as alcohol, drugs, etc. for detoxification or elimination.

→ Excreted in urine or bile



- Lipophilic drugs are converted into hydrophilic compounds.
- Main route is oxidation by cytochrome P450. (P450 has a lot of isozymes (57 types) having many variants.)

→ Drug efficacy is dependent on personal difference.

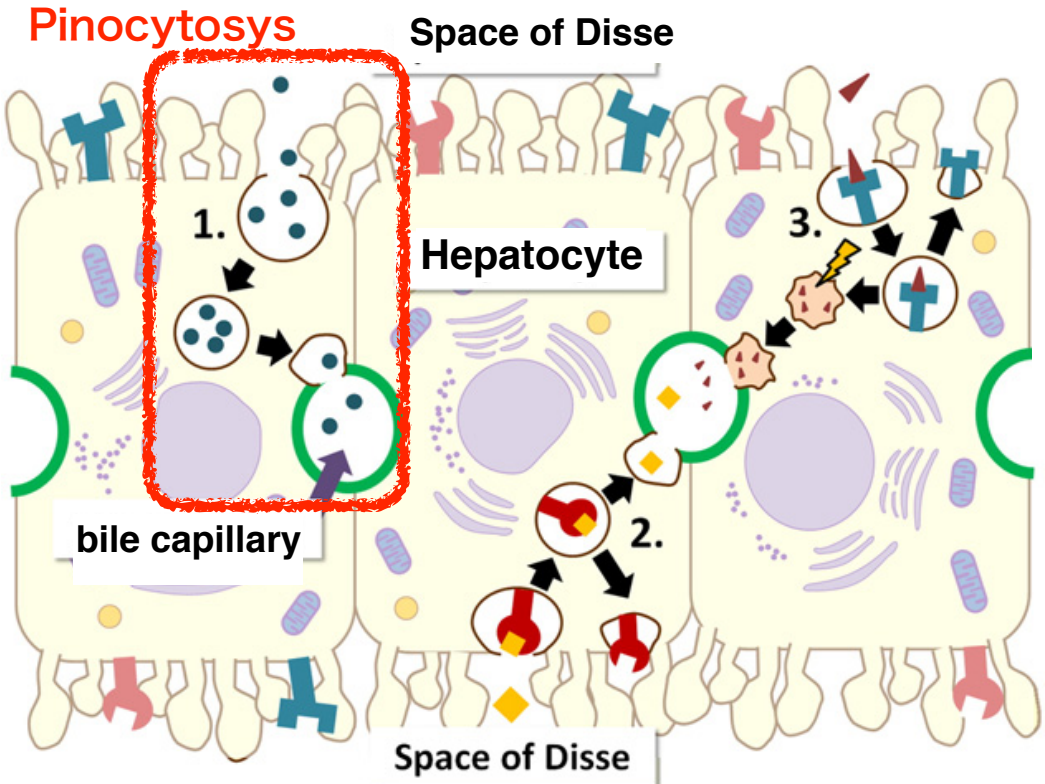
Bile excretion/Gallbladder

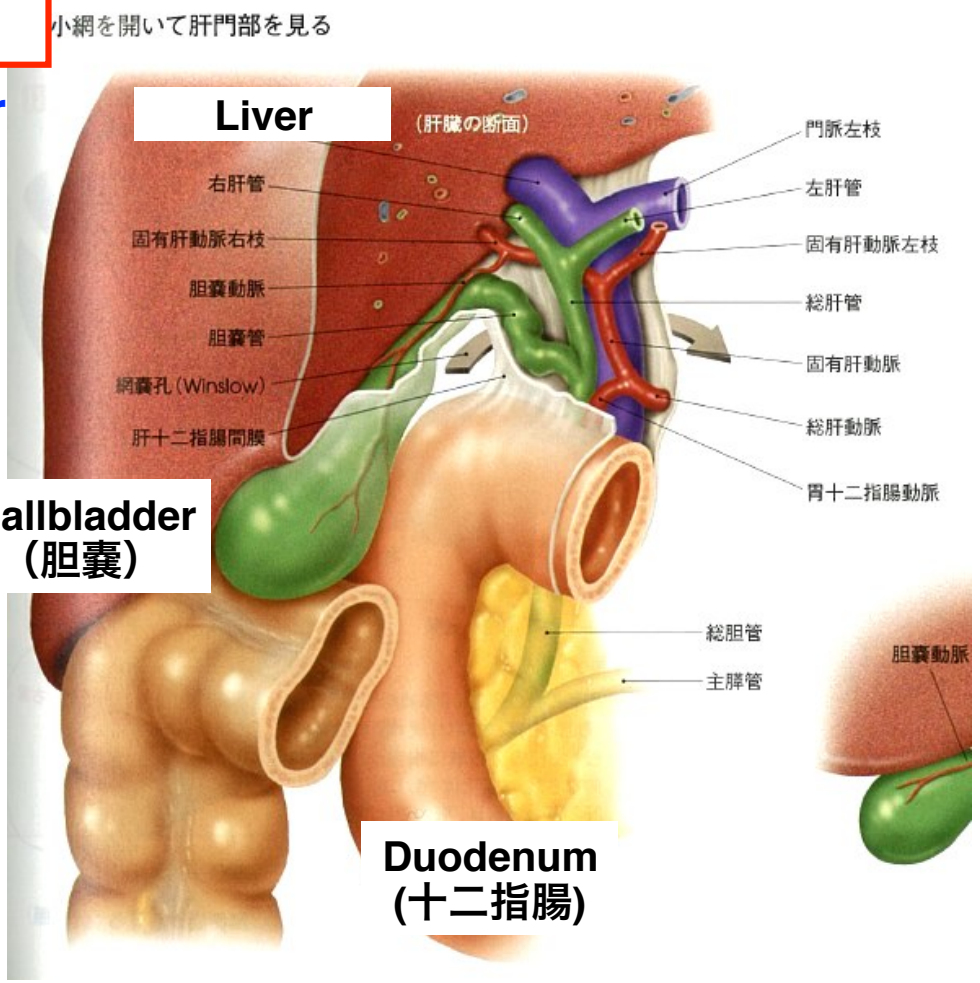
→ The materials passing through fenestrations of sinusoids (size <) be internalized by liver cells, unless they encounter Kupffer cells.

→ Main internalization pathway is pinocytosis. Then, bile excretion occurs.

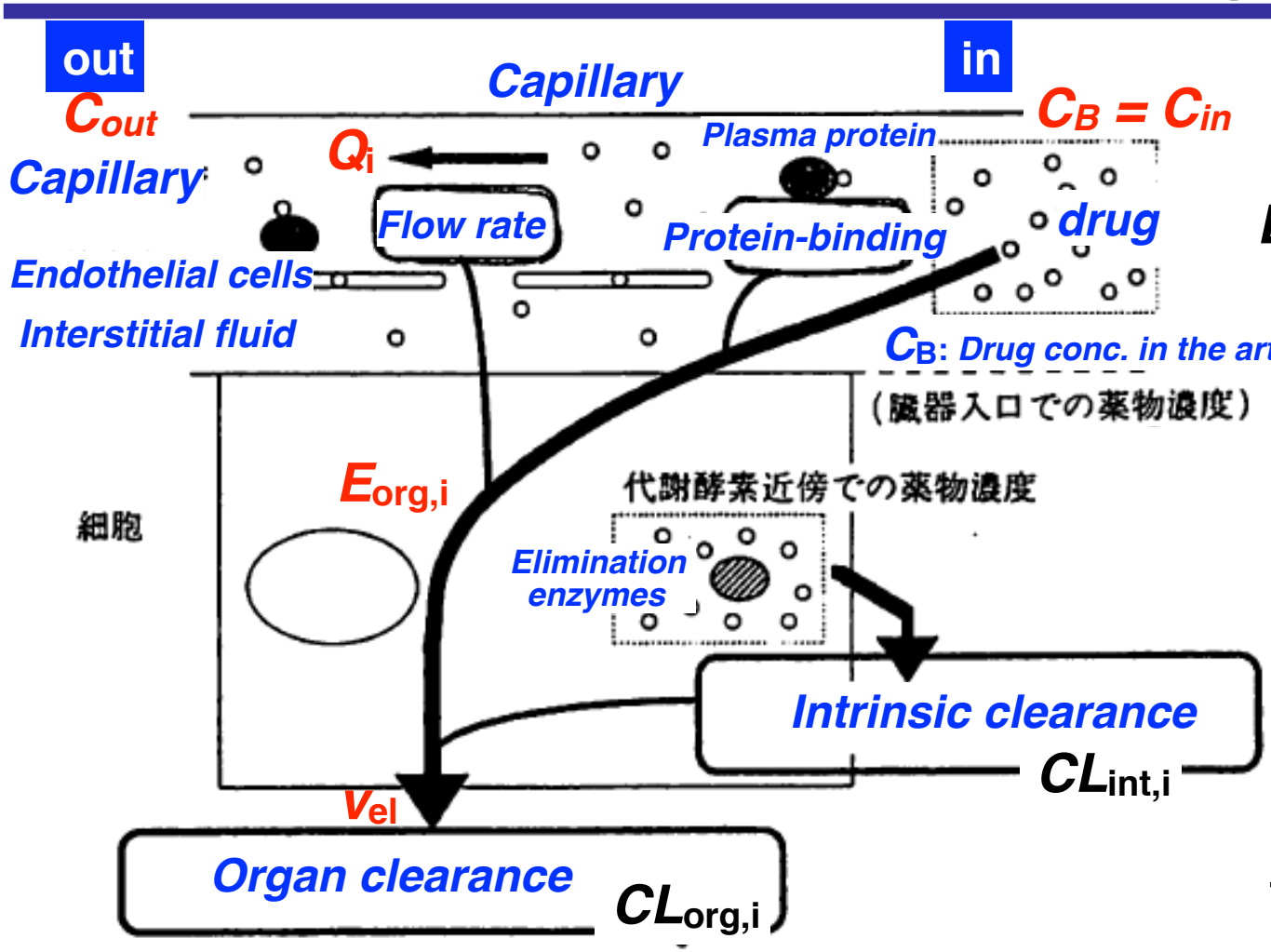
→ Bile excretion is the only elimination path of non-biodegradable materials with size > Cationic materials show higher uptake. But, excretion process is very slow (< 48 h for 5-10% of dose).

Bile: bile is produced by the liver, and stored and concentrated in the **gallbladder**. After eating, the stored bile is discharged into the duodenum for the digestion of lipids in the small intestine. Main component of gallbladder bile is bile salts and fats (cholesterol, fatty acids, and lecithin), which can work as an emulsifier.





(Advanced contents) Organ clearance



Organ extraction ratio $E_{org,i}$:

$$E_{org,i} = (Q_i C_{in} - Q_i C_{out,i})/Q_i C_{in}$$

C_B: Drug conc. in the artery (臓器入口での薬物濃度)

Elimination rate at organ *i* $v_{el,i}$:

$$v_{el,i} = CL_{org,i} \cdot C_B$$
$$= Q_i C_{in} - Q_i C_{out,i}$$
$$= E_{org,i} Q_i C_{in}$$

From $C_B = C_{in}$

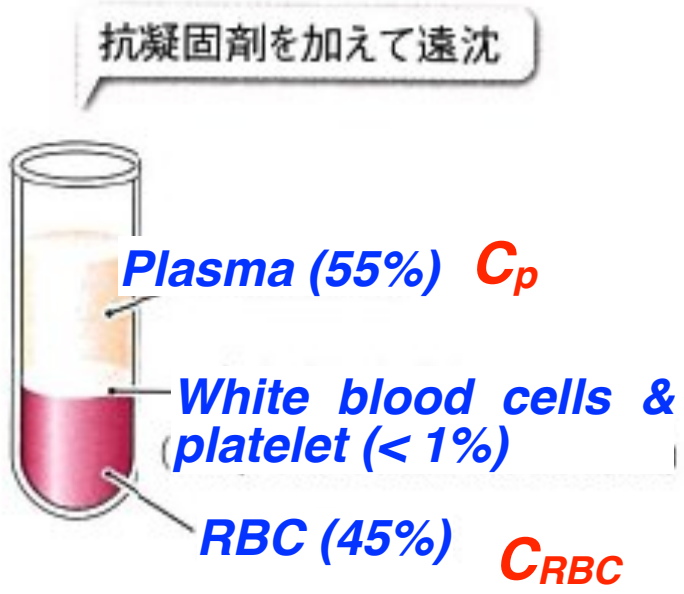
$$CL_{org,i} = E_{org,i} \cdot Q_i$$

$$1 - E_{org,i} \equiv F_{org,i}$$

F: Availability

- Both Organ extraction ratio & avialabilry can be determined only by organ clearance $CL_{org,i}$ & Blood flow rate Q_i.
- Upper limit of the *E value is* 1. Therefore, the upper limit of $CL_{org,i}$ can be determined by the upper limit value of Q_i. (Particularly for rapid elimination cases.)

(Advanced contents) Drug distribution to blood cells



H_{ct}: Hematocrit
(Volume ratio of red blood cells to the total volume of blood)

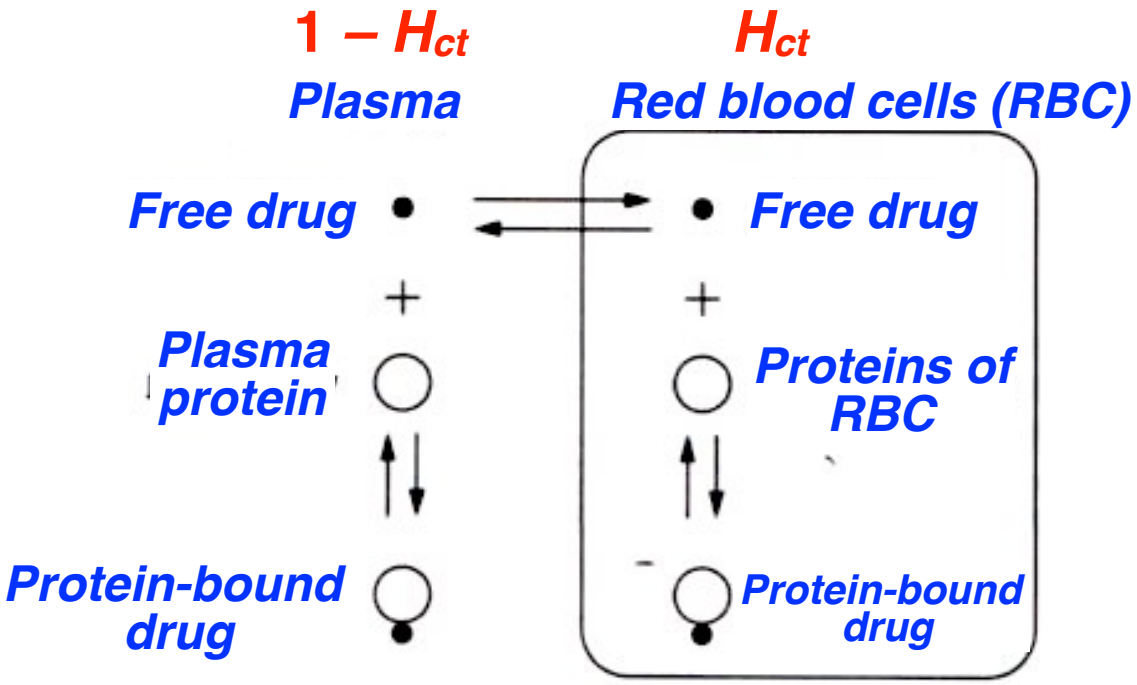


図 I-6-9. 薬物の血球への分配

Drug cocn. in blood cell components (R_b)

$R_b = C_B/C_p$ (BC distribution ratio)

$C_B = (1 - H_{ct})C_p + H_{ct}C_{RBC}$

Therefore,

$R_b = C_B/C_p = (1 - H_{ct}) + H_{ct}C_{RBC}/C_p$

In the case of $C_{RBC} = 0$, $R_b = 1 - H_{ct}$

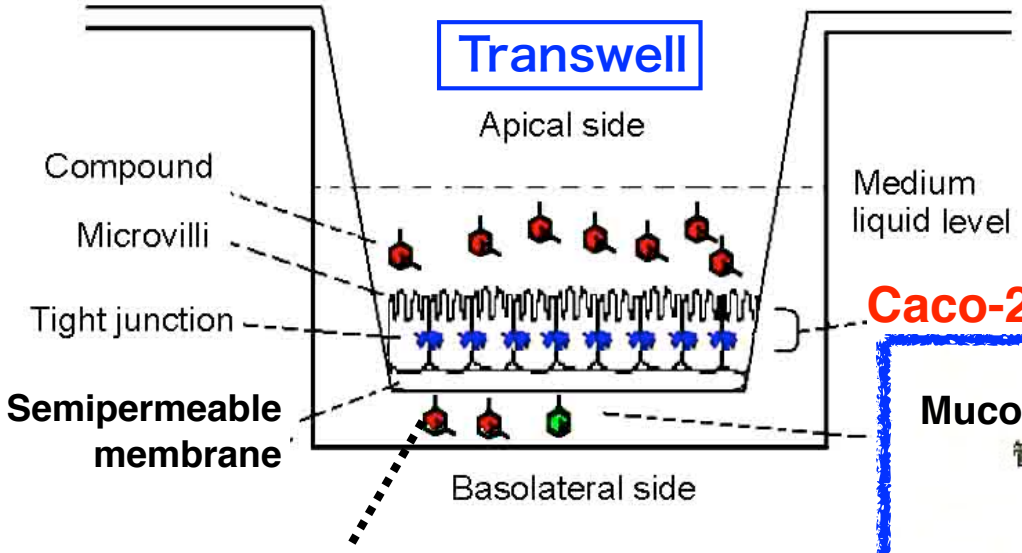
You do not need to consider the RBC distribution, when you use drug carriers or water soluble drug.

Model system for evaluation of PK

As an alternative for animal experiments.

Ex.1) To estimate liver clearance, microsomes prepared from human liver cells are used.（細胞を破砕してできる小胞体が細分化した小胞で、肝細胞由来だと代謝酵素であるシトクロムP450を含む）

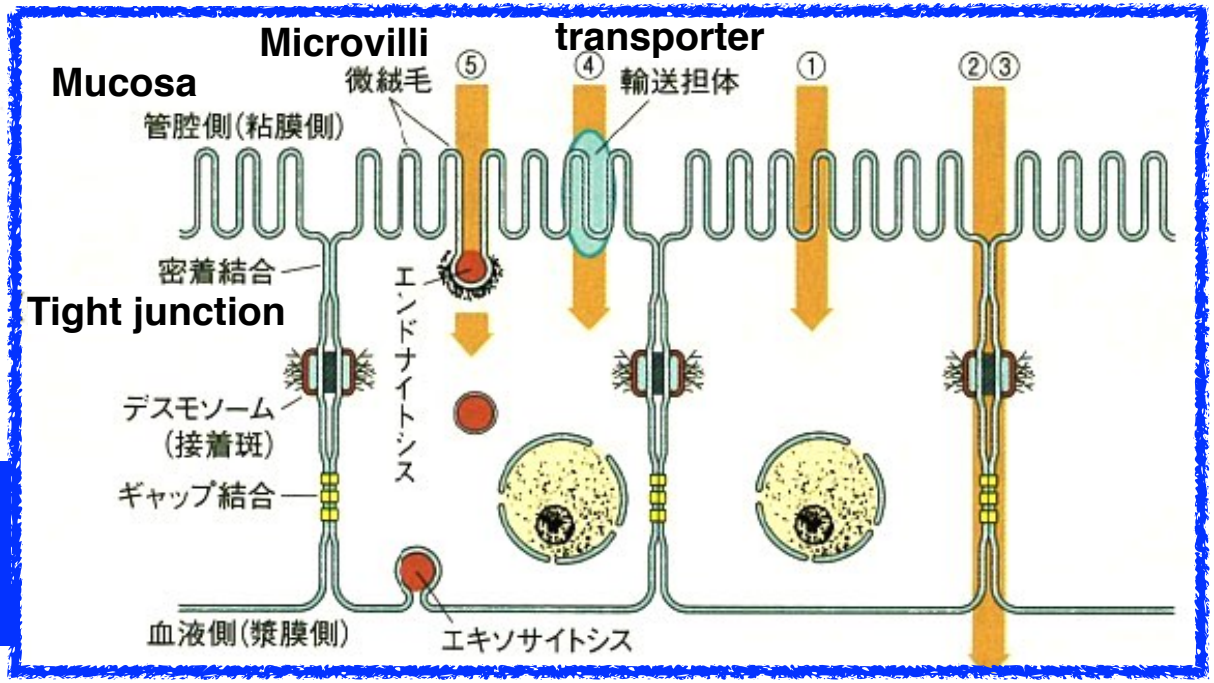
Ex.2) To estimate intestinal absorption behavior, Caco-2 cell layer system is often used. (to evaluate drug permeation, function of transporter, etc…)



Drug passing through the epithelial cell layer

X.-W. Yang, et al. Journal of Chinese Integrative Medicine: Volume 5, 2007, p. 637.

Caco-2 cells

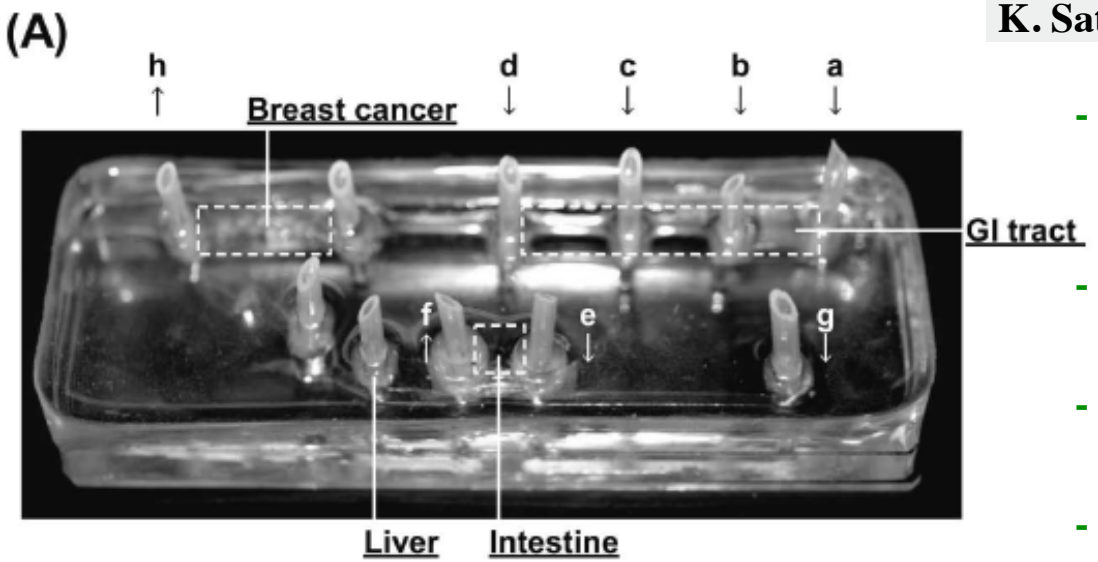


Drug absorption mechanism at intenstinal epithelia.

消化管粘膜部位での薬物吸収機構

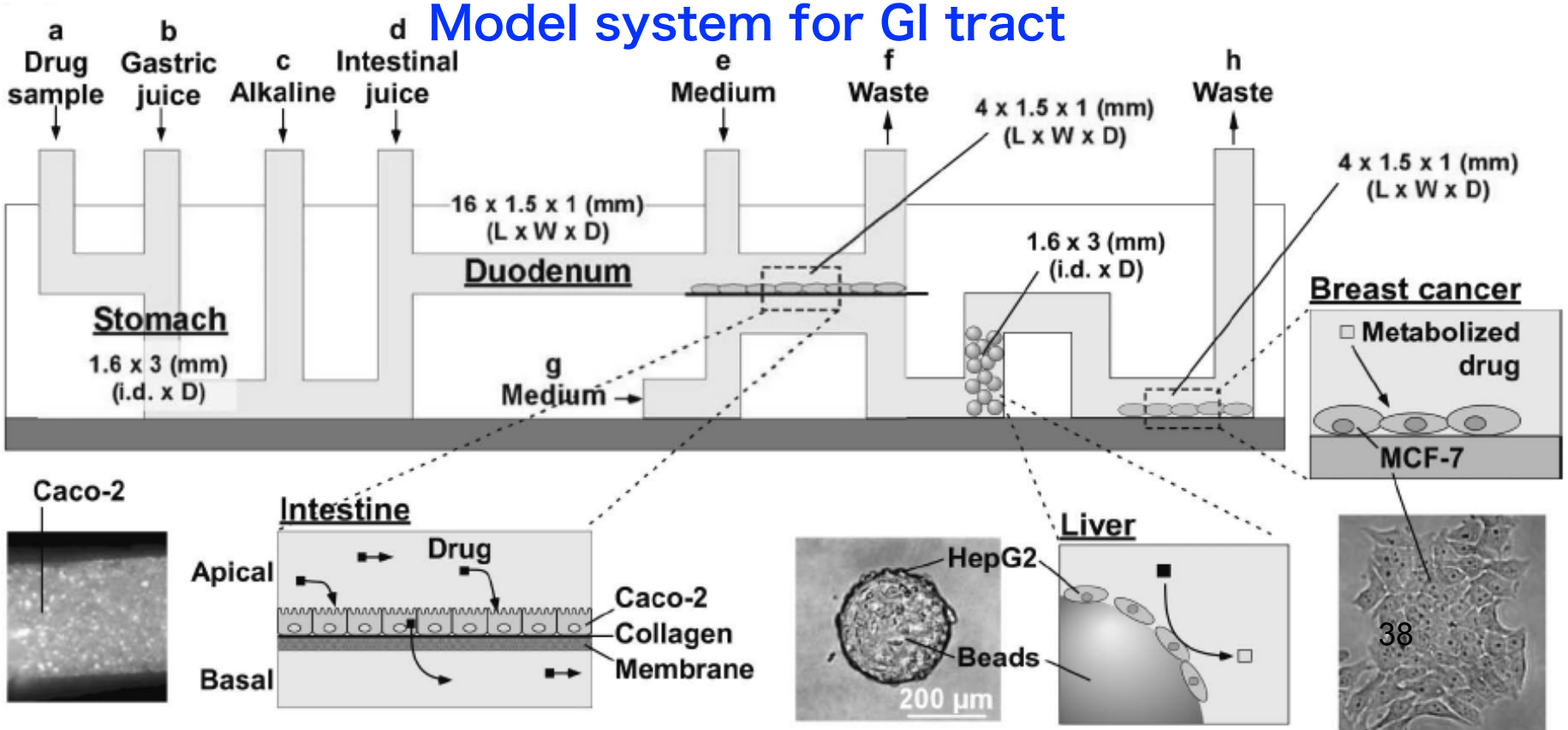
Application of microfluidic devices as a model system

K. Sato, et al., ANALYTICAL SCIENCES, 2012, 28, 197–199.



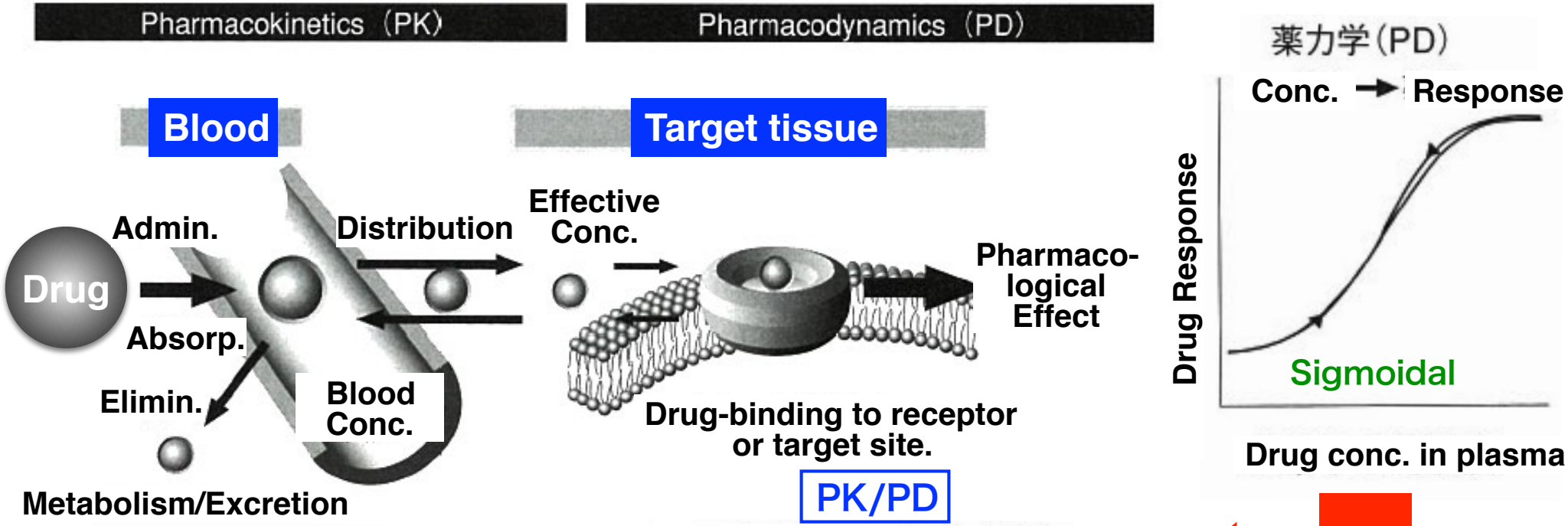
- PDMS-based （シリコンゴム） microfluidic device（1.5 mm-wide）
- GI tract model system + liver metabolism model
- Final target: breast cancer by systemic circulation
- Useful for estimation of PK/PD

Model system for GI tract

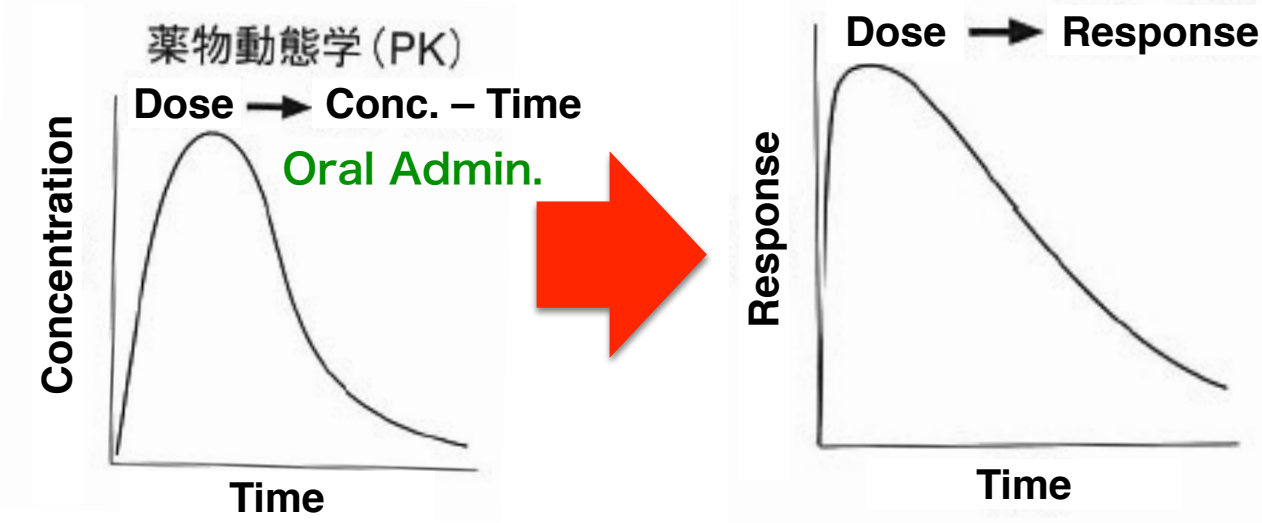


Pharmacodynamics (PD)

Pharmacodynamics (PD) is the study of how a drug affects an organism, whereas pharmacokinetics (PK) is the study of how the organism affects the drug. PD places particular emphasis on dose–response relationships, that is, the relationships between drug concentration and effect.



PK/PD

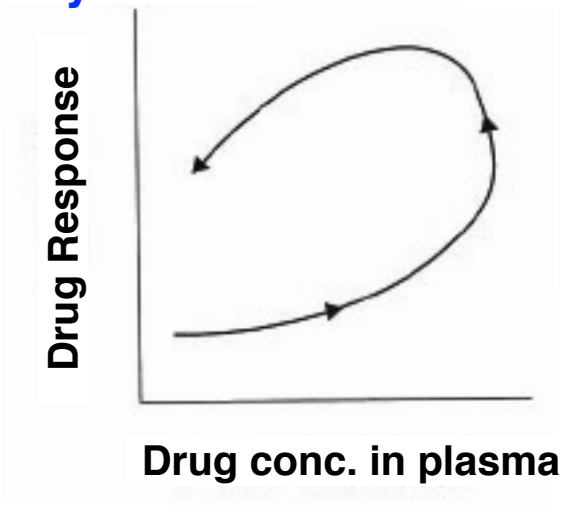


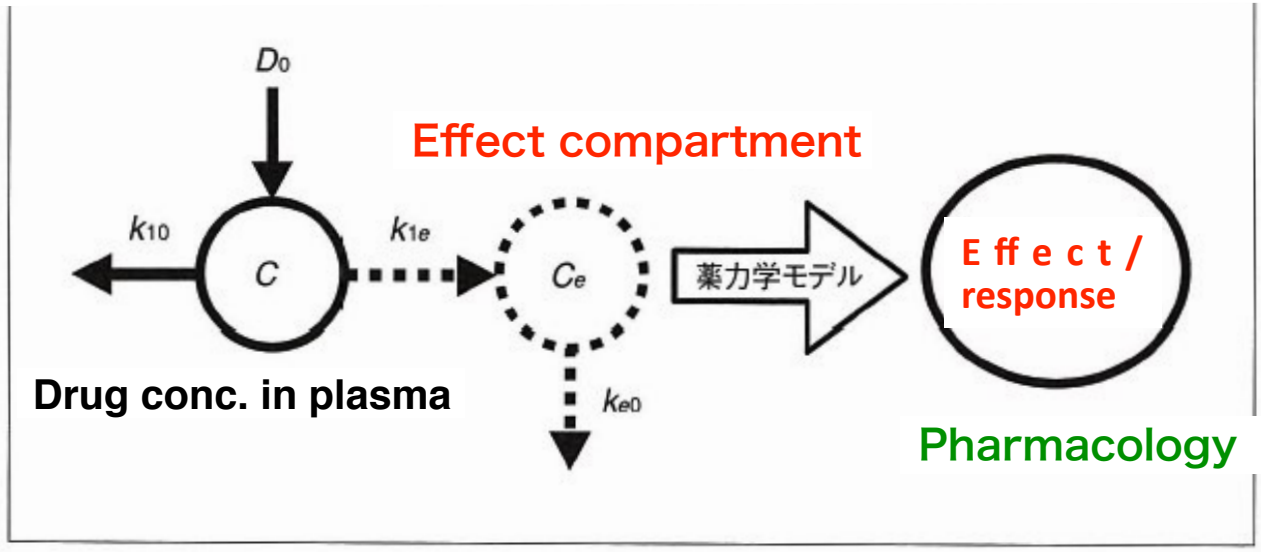
PK/PD解析の目的：

薬効発現に関わる生物学的なプロセス込みでの速度論的考察を可能にし、最も安全かつ有効な薬物・剤形、投与計画の設計につなげる。

Effect compartment model

Sometimes, drug response is delayed.



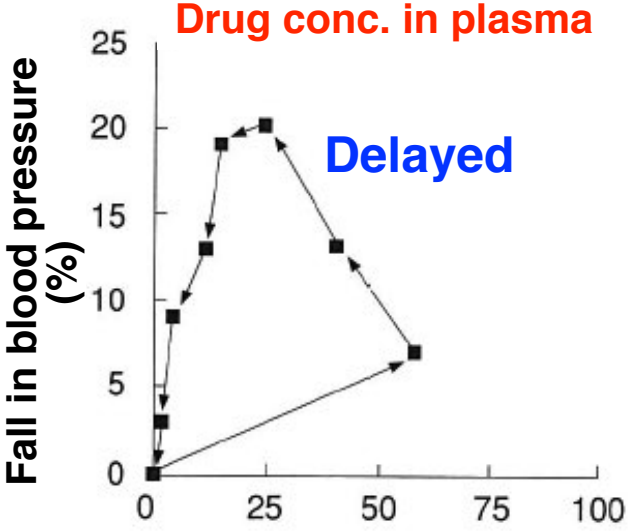


＊各コンパートメントは１次の速度論で結合され、薬効コンパートメントの分布容積は小さく、全体の濃度変化に影響を与えないと仮定。

Drug conc. in plasma

(A) **x-axis：**

Drug conc. in plasma

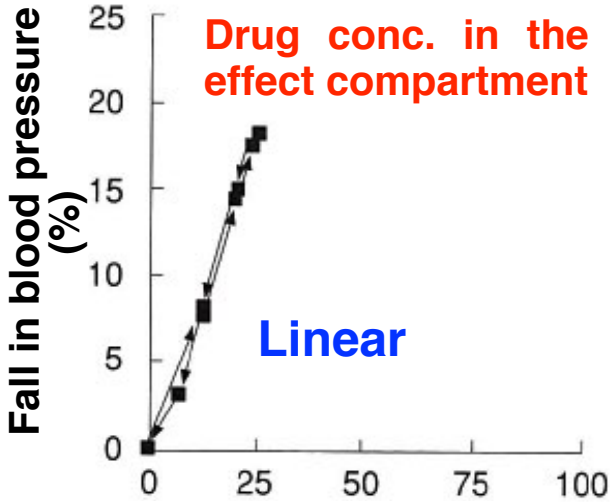


Drug conc. in plasma (ng/mL)

(B)

x-axis：

Drug conc. in the effect compartment



Drug conc. in effect compartment (ng/mL)

Bunazosin：an alpha 1 antagonist.

Bunazosin was initially developed to treat benign prostatic hyperplasia (BPH).