Two-Axis Recognizing Material World

Involvement with human beings and society

Span of Integration·Application

Komiyama

Toriumi

Koseki

Sugiyama

Iye

Kojima

Komamiya

Suto

Komamiya

Span of Scientific(Physical·Chemical) Exploration

10^{-10} 10^{-6} 10^{-2} 10^{2} 10^{6} 10^{10} (m)

Size

Material World

The Search for,and Creation of Matter with Desirable Properties — Discoveries from the Field of Pharmaceutical Science

- Why Do Drugs Work?

- Drug Transporters

- Drugs and Compatibility with Humans

Yuichi Sugiyama

Professor, Department of Molecular Pharmacokinetics,
The University of Tokyo

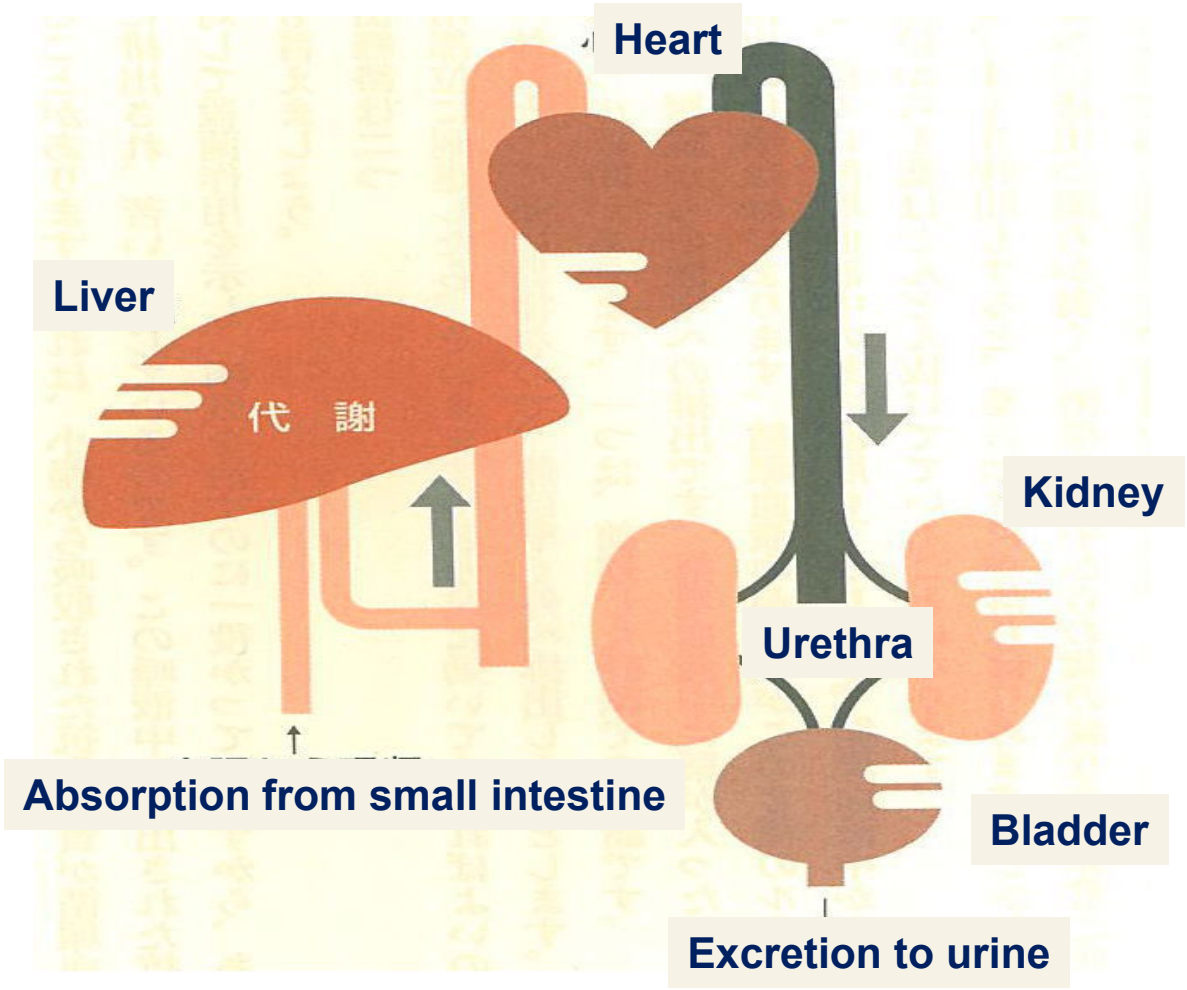
GFK, Global Focus on Knowledge
The University of Tokyo
Bldg. 18 Hall, Komaba Campus

Why do drugs take effect?

Why do drugs develop adverse effects?

Drugs Are Metabolized in the Liver and Excreted from the Kidneys

[肝腎要：Kan・Jin・Kaname (liver/kidney/bottom line): Bottom line like liver and kidneys in the body; Essential bottom line; Essential]



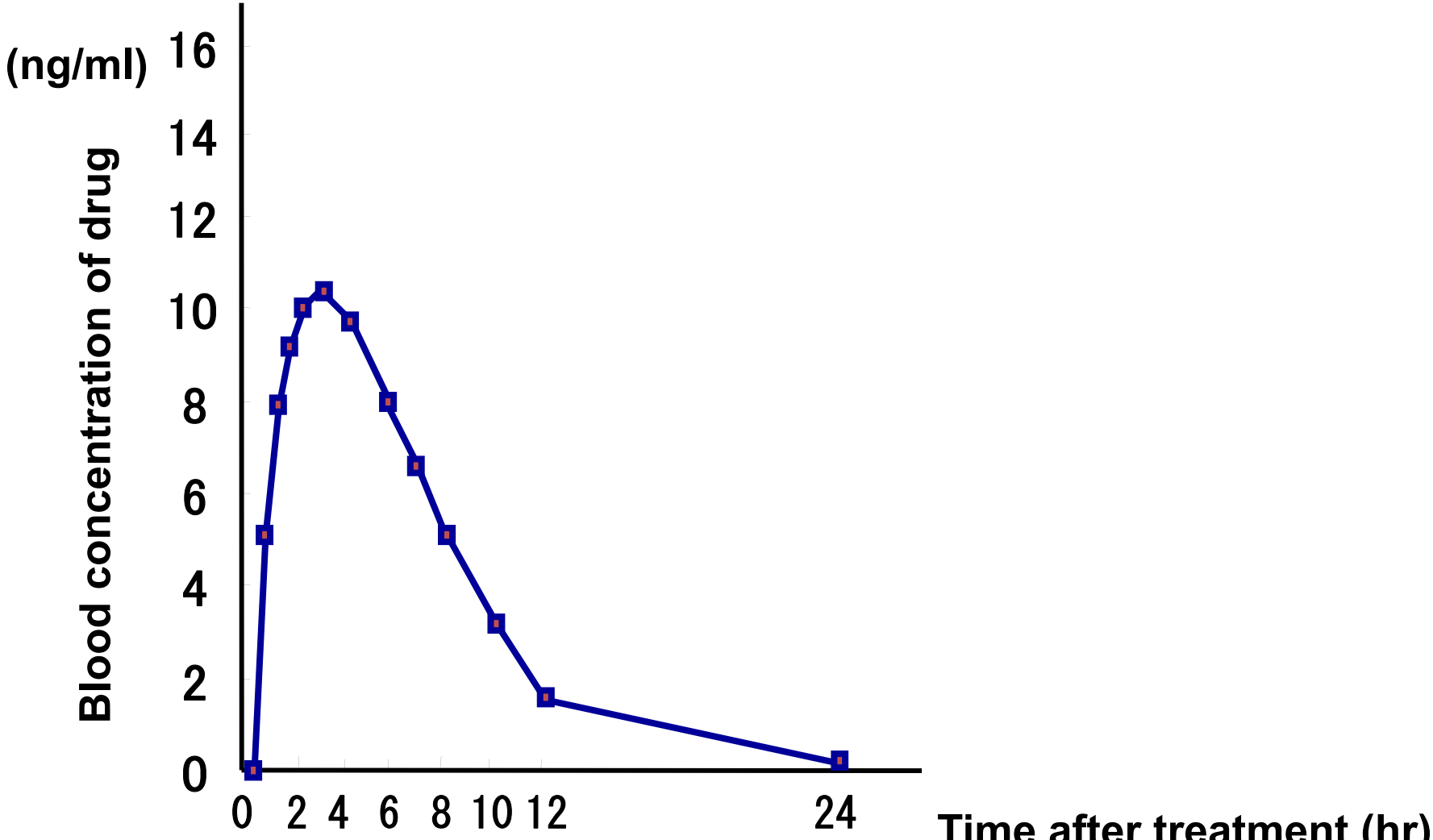
Drugs transported to the liver are metabolized by drug metabolizing enzymes.Drugs that escape from metabolism are transported through the hepatic vein and aorta to the heart, from where they are further transported to the whole body.

When they have circulated through the whole body, the drugs are excreted from the kidney to the urine.

‡ Source: K. Takada, 'My Medicine, Your Poison! ', HOME-SHA, Tokyo, 2000

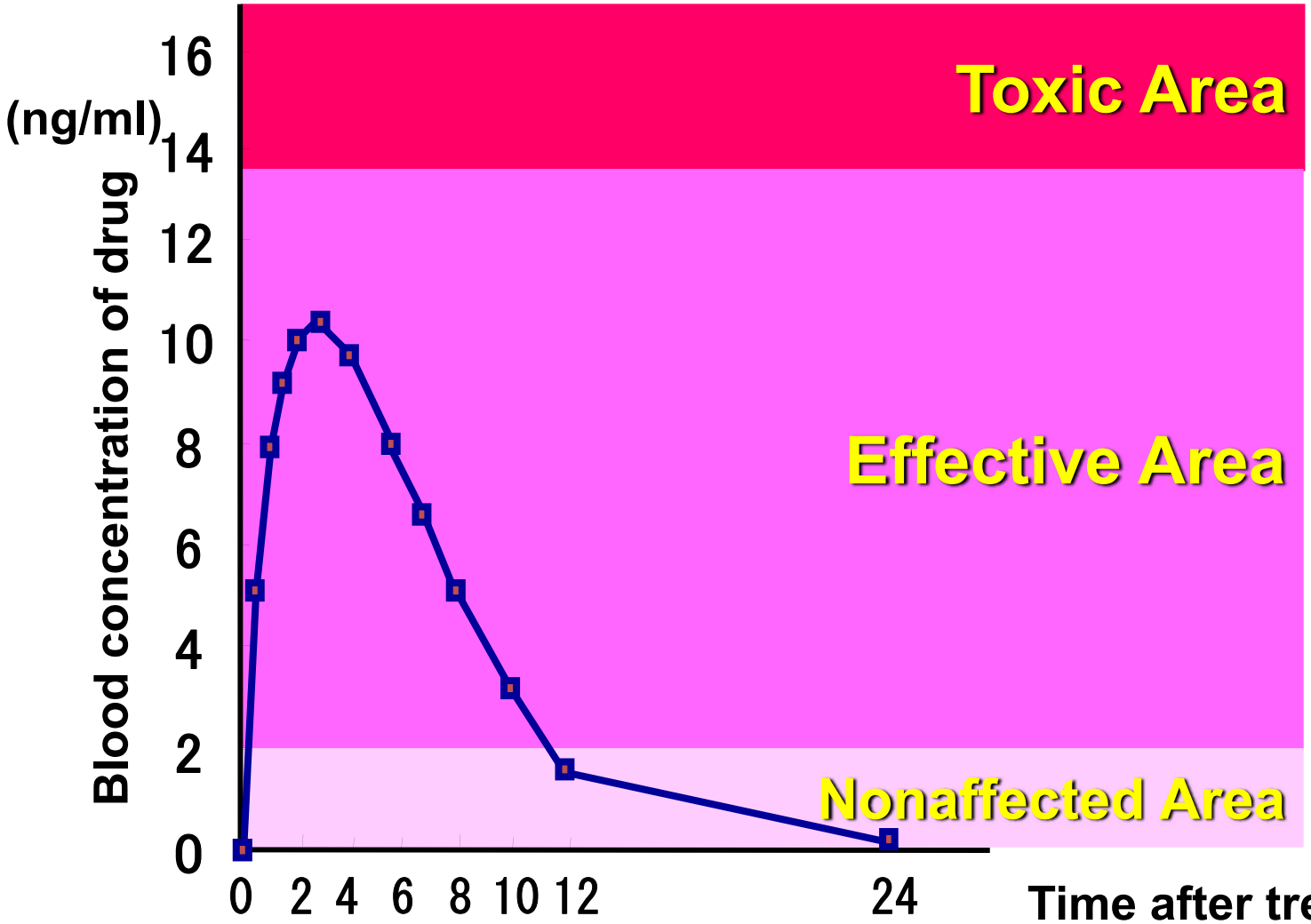
Effective and Toxic Concentrations of Drugs

Individual Differences of Blood level



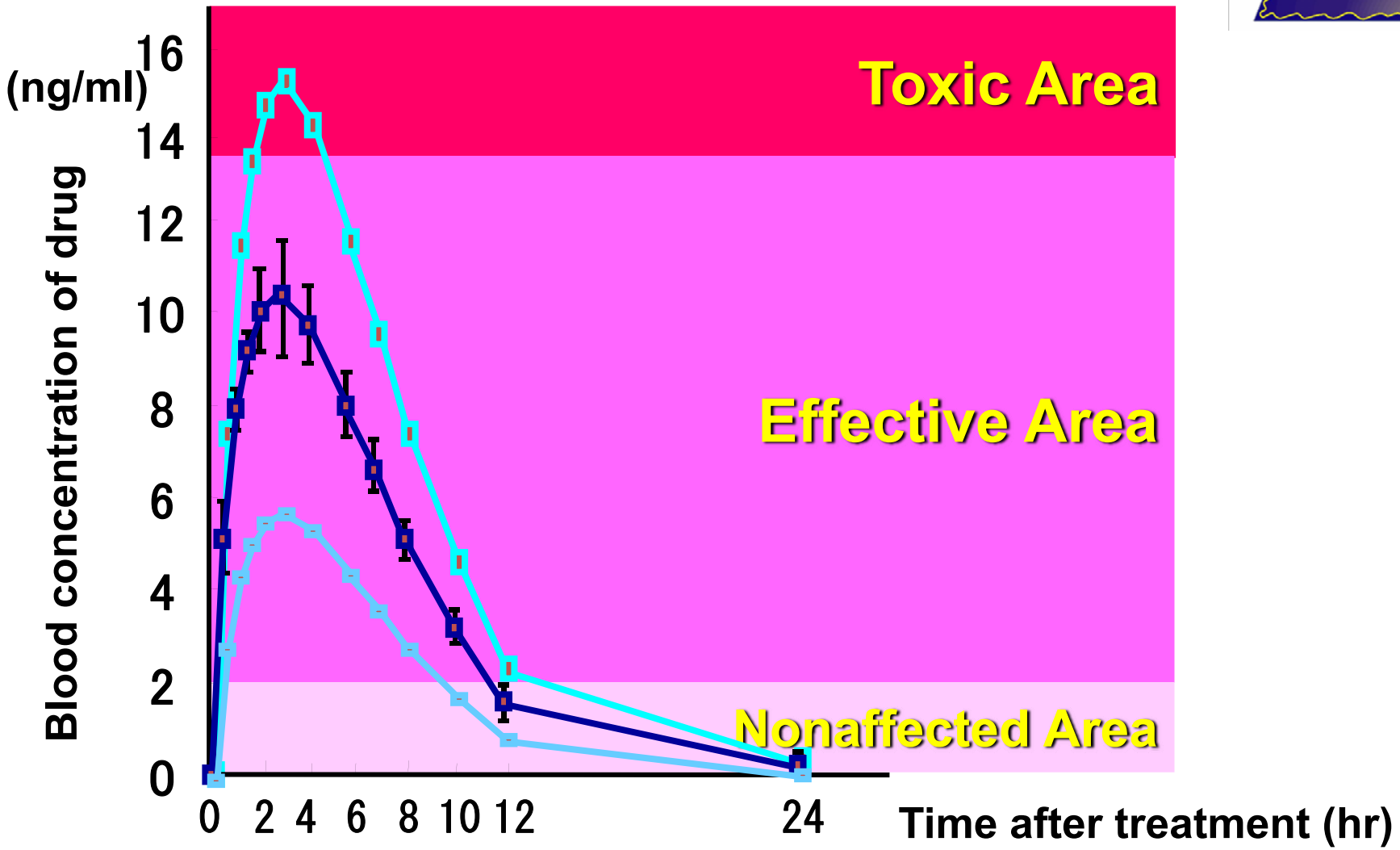
Effective and Toxic Concentration of Drugs

Individual Differences of Blood level



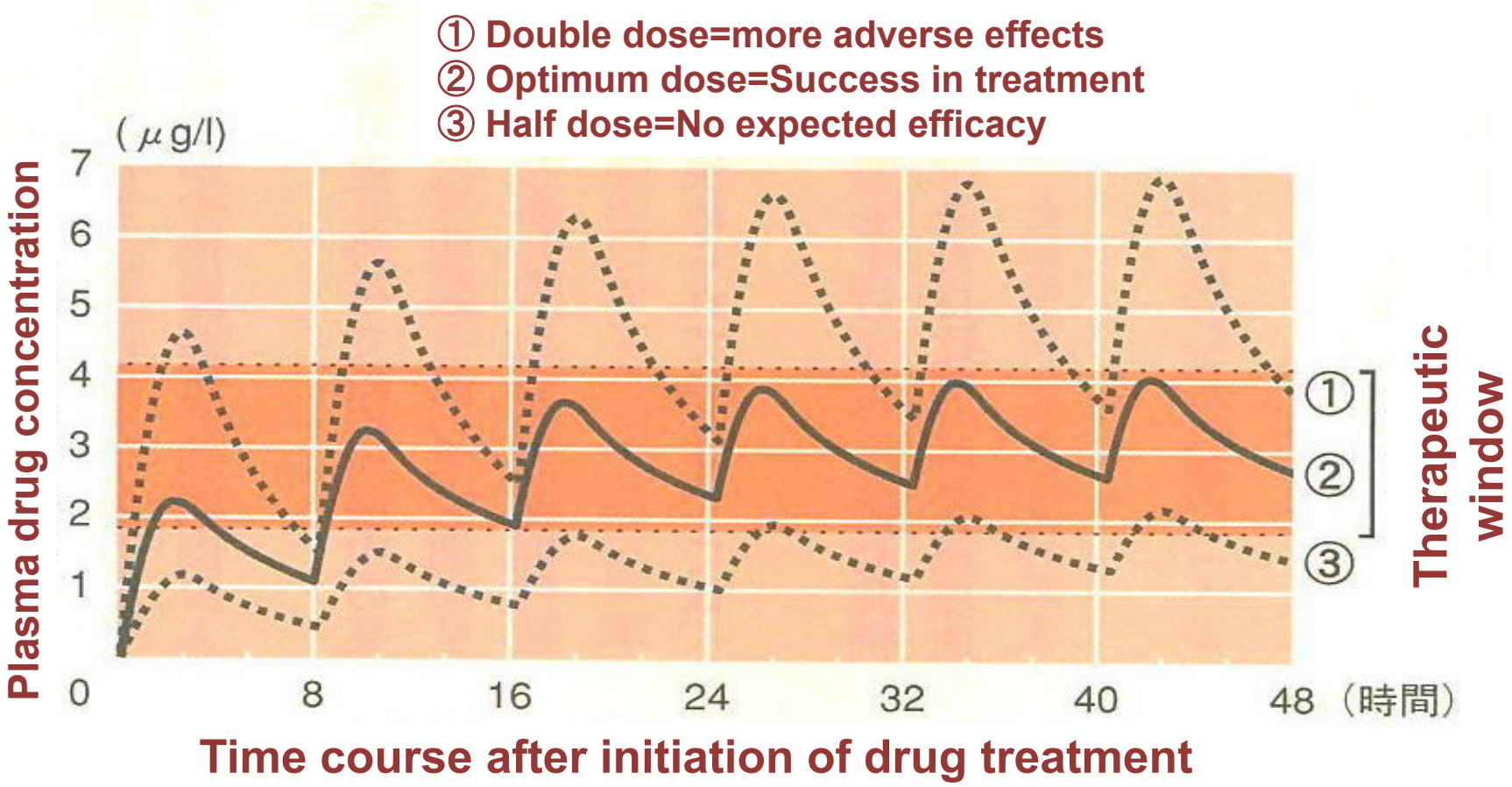
Effective and Toxic Concentration of Drugs

Individual Differences of Blood level



Drug Efficacy Depends on Dose and Treatment Intervals

B. A cases of either two-fold or half dose in the same treatment time

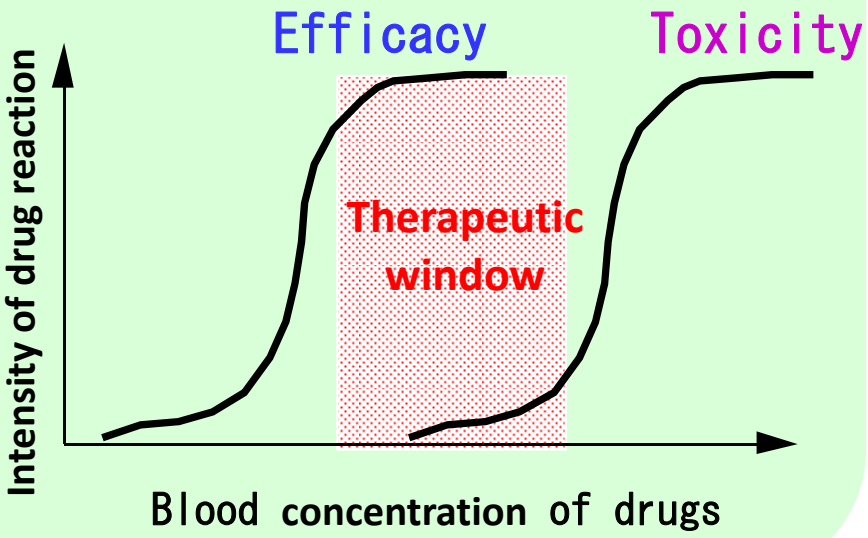


‡ Source: K. Takada, 'My Medicine, Your Poison! ', HOME-SHA, Tokyo, 2000

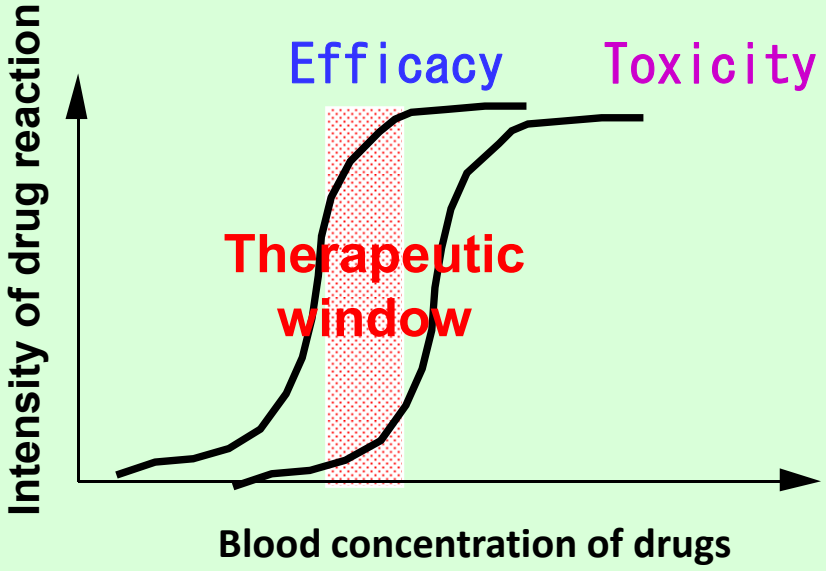
Drug and Risk- Benefit-Relationship -

Every excellent drug is potentially poisonous！

Generic drugs (e.g. cold medicine)



Anti-cancer drugs, etc



What is Pharmacokinetics?

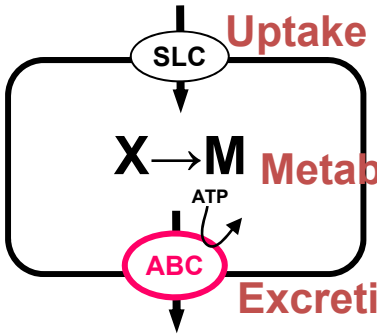
Pharmacokinetics: The discipline to precisely study the fate of externally administered drugs; absorption into the body, distribution throughout the tissues, metabolism in the liver to transform into metabolites, and finally, excretion into bile or urine.

Commonly referred to as the ADME.

Absorption, Distribution, Metabolism & Excretion

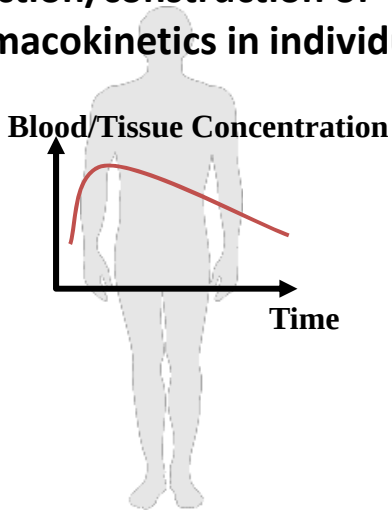
（**Drug Metabolism and Pharmacokinetics**）

Cellular biology method
Molecular Biology Method

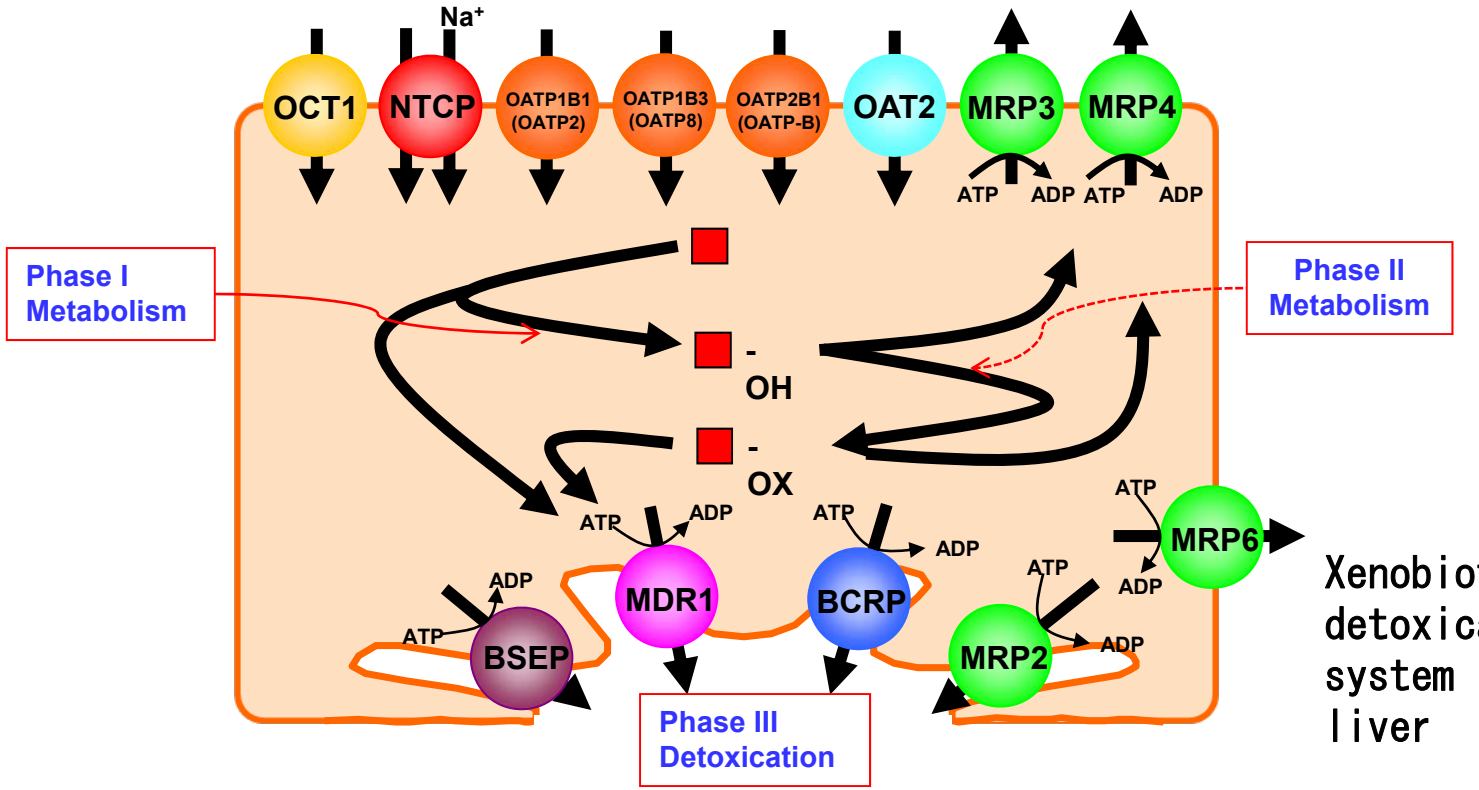


Construction of mathematical model

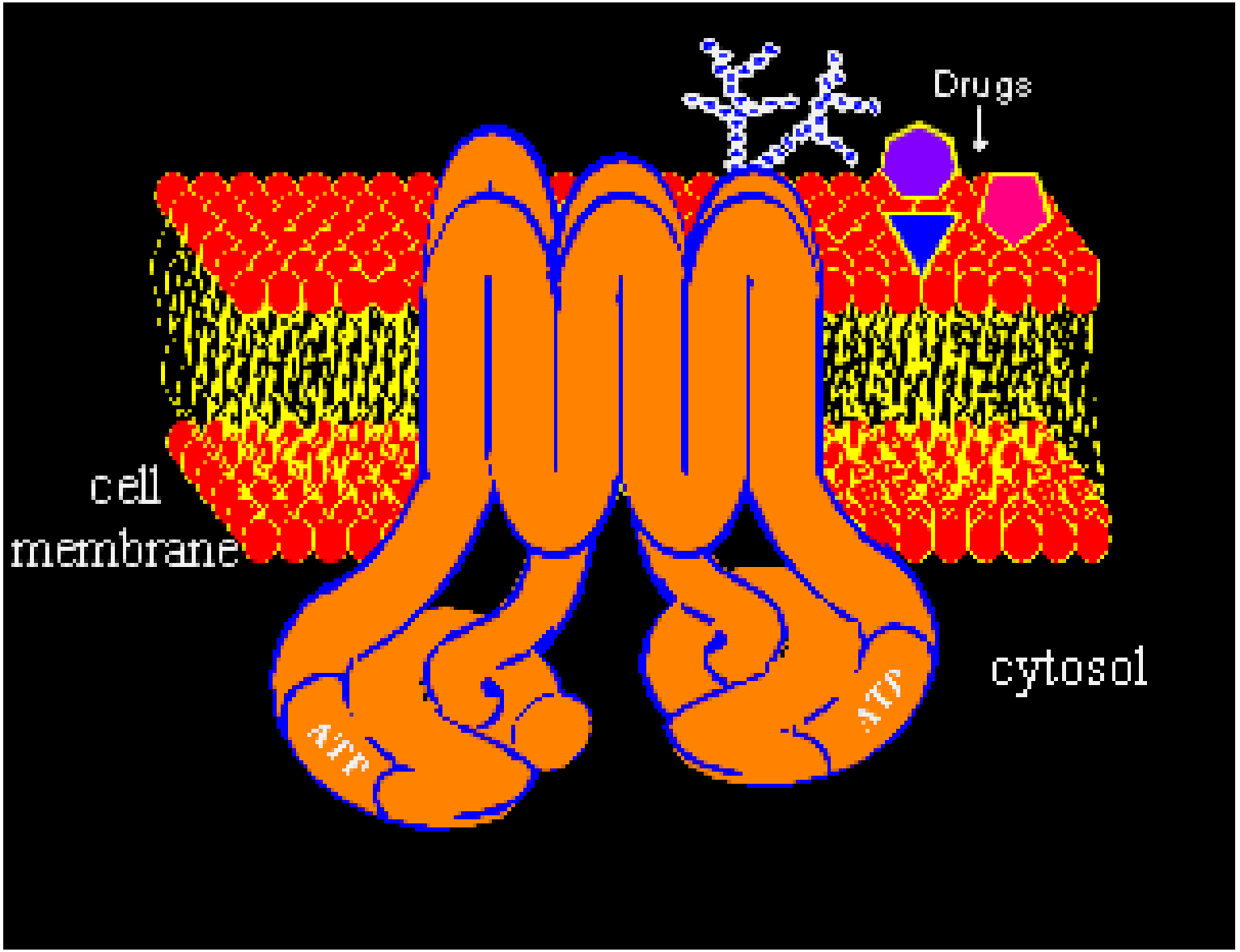
Prediction/construction of Pharmacokinetics in individual (*in vivo*)



Elucidation of xenobiotic detoxication mechanism and estimation of pharmacokinetic parameters

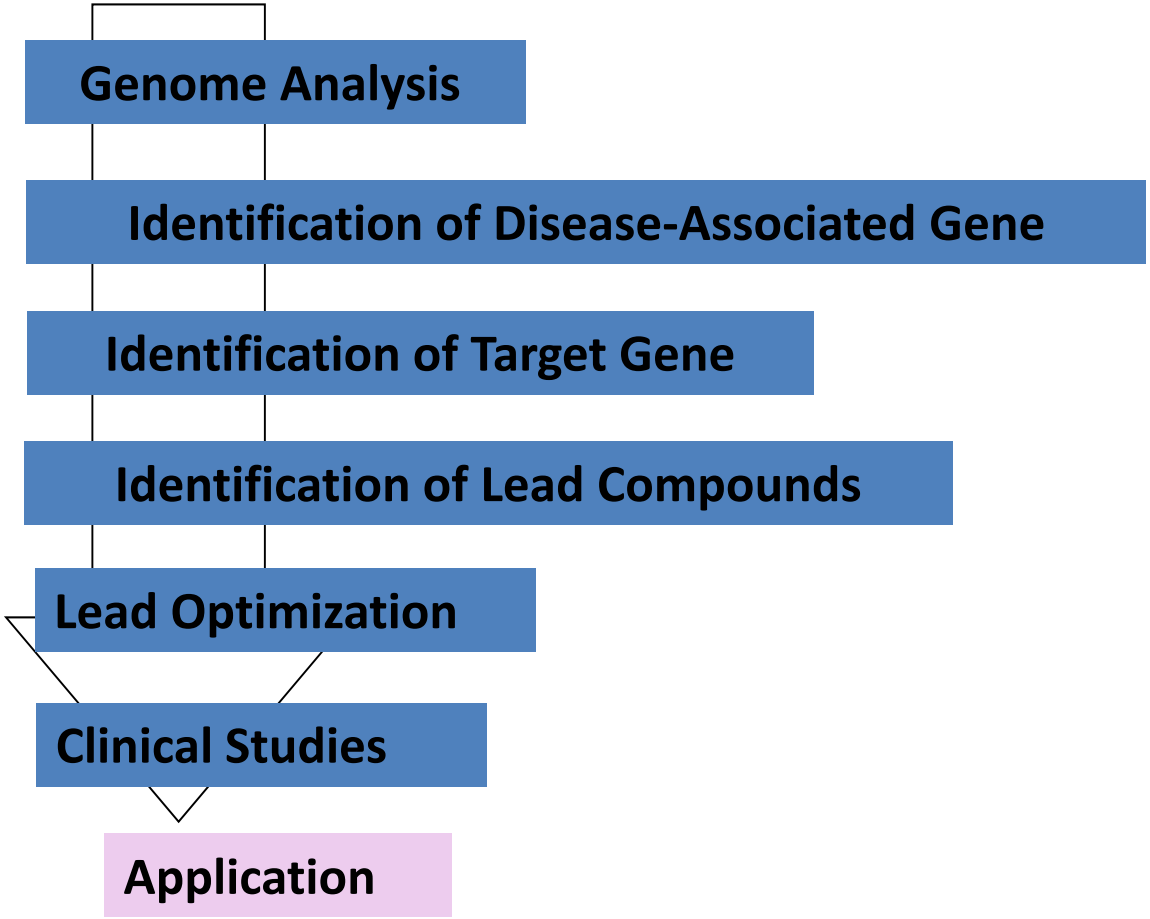


Xenobiotic detoxication system in human liver

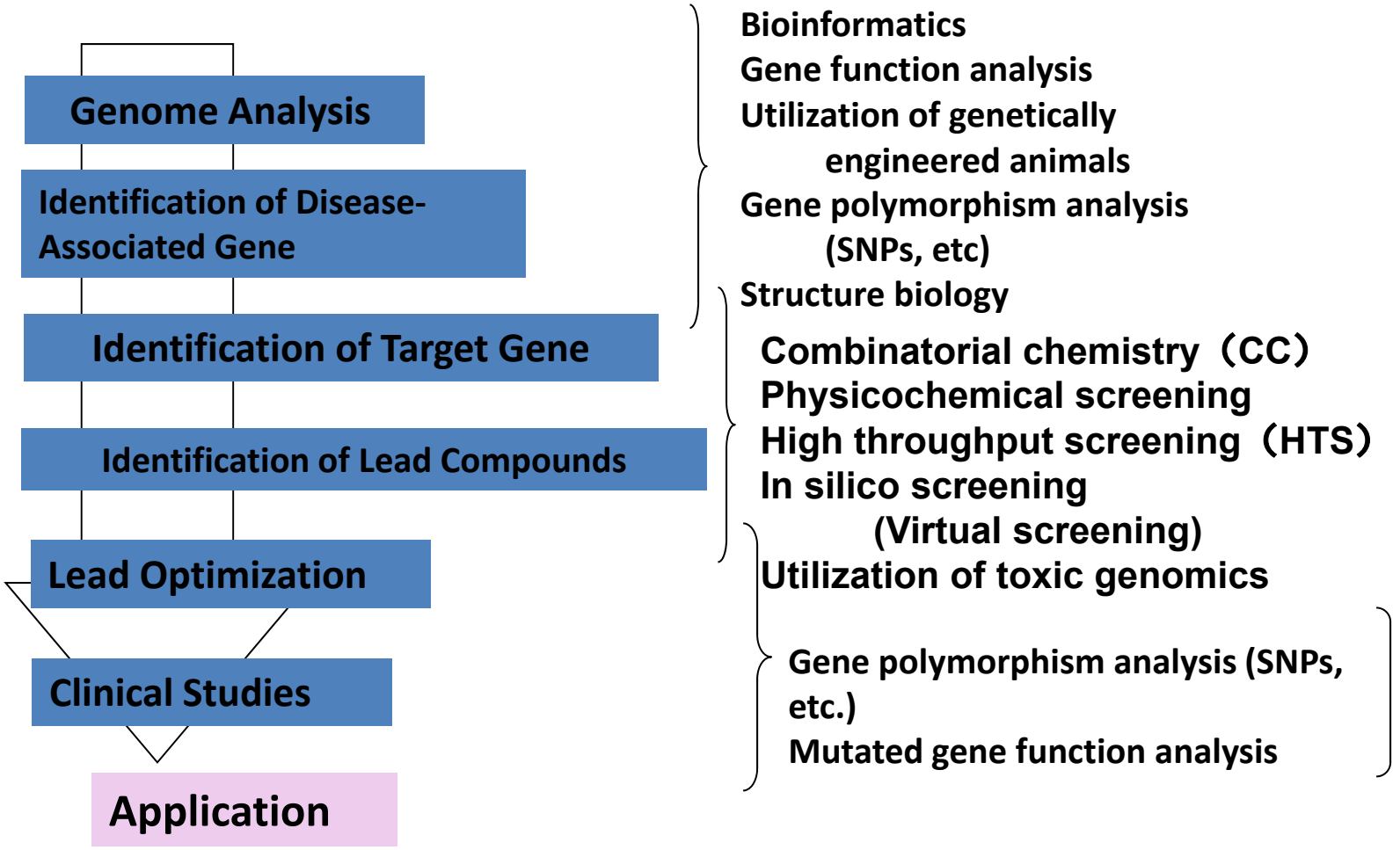


[Provided by Dr. Sonia De Morais, Pfizer]

Flow of Current Drug Discovery and Development



Flow of Current Drug Discovery and Development



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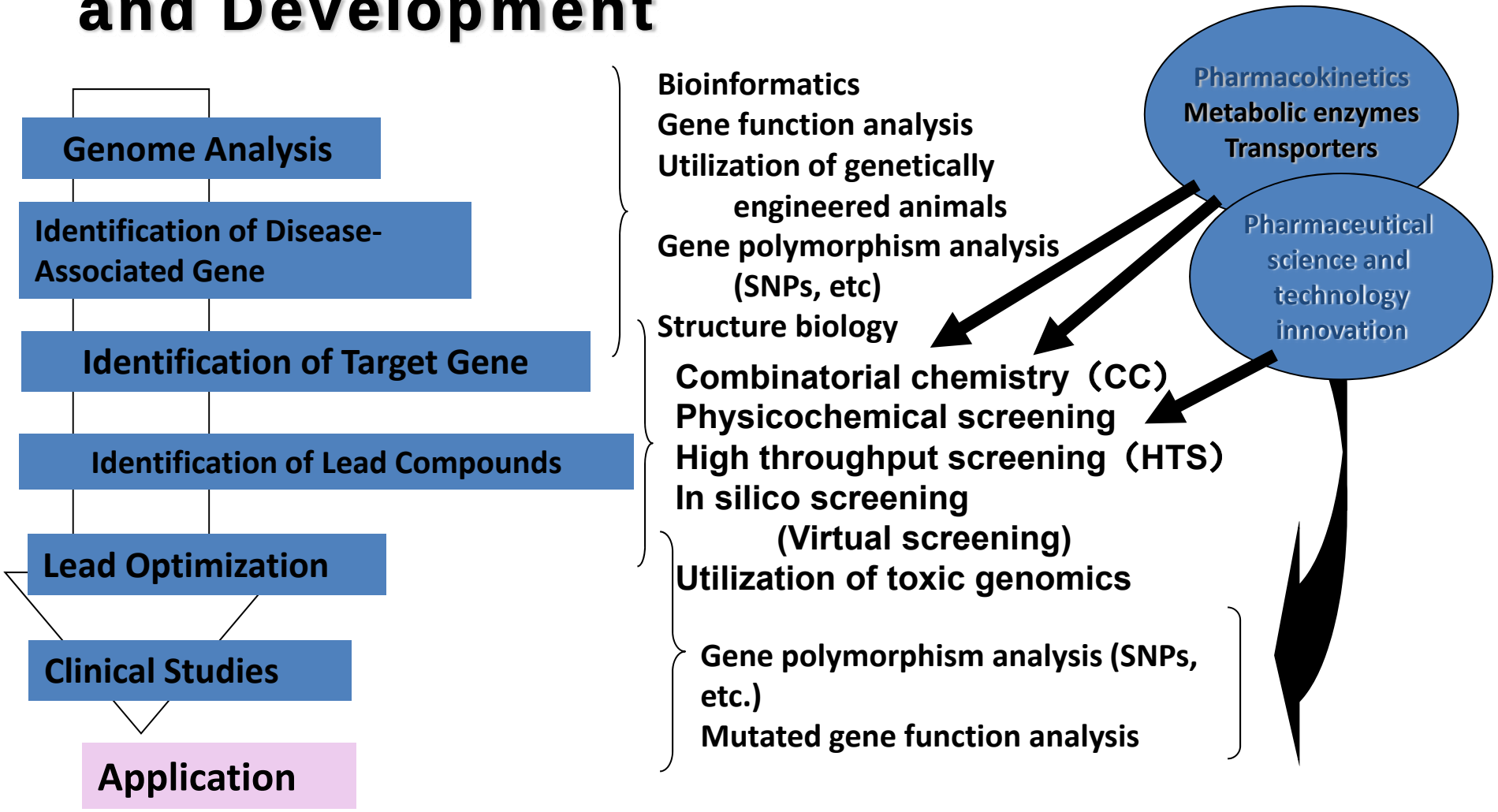


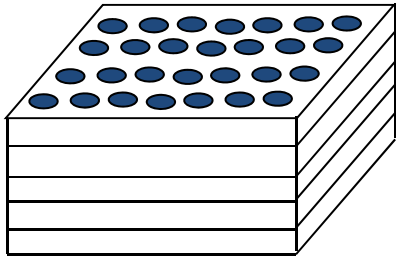
Conventional Drug Discovery & Development: 12 - 15 years

Current Drug Discovery & Development: 5 – 8 years

Prediction of Phamacokinetic & Pharmacodynamic Parameters Based on In silico Approach

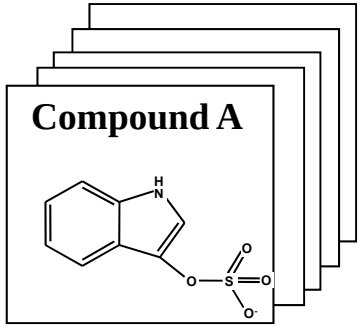
Chemical library

"real" library



"virtual" library

Calculation with computer



In silico Analysis

QSAR approach

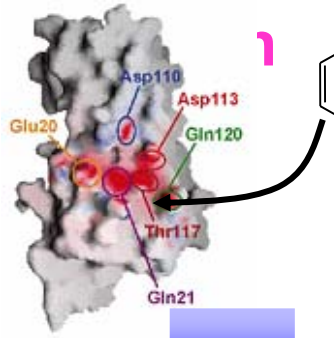
Parameter group with compound characteristics

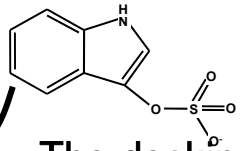
(PSA, Charge, Function numbers, etc.)

↓

Characteristics extraction by multiple regression analysis, neural network, etc.

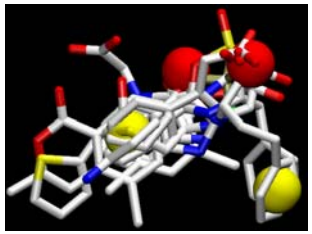
Structure-based drug





The docking of the compound with the protein structure.

Ligand-based drug design



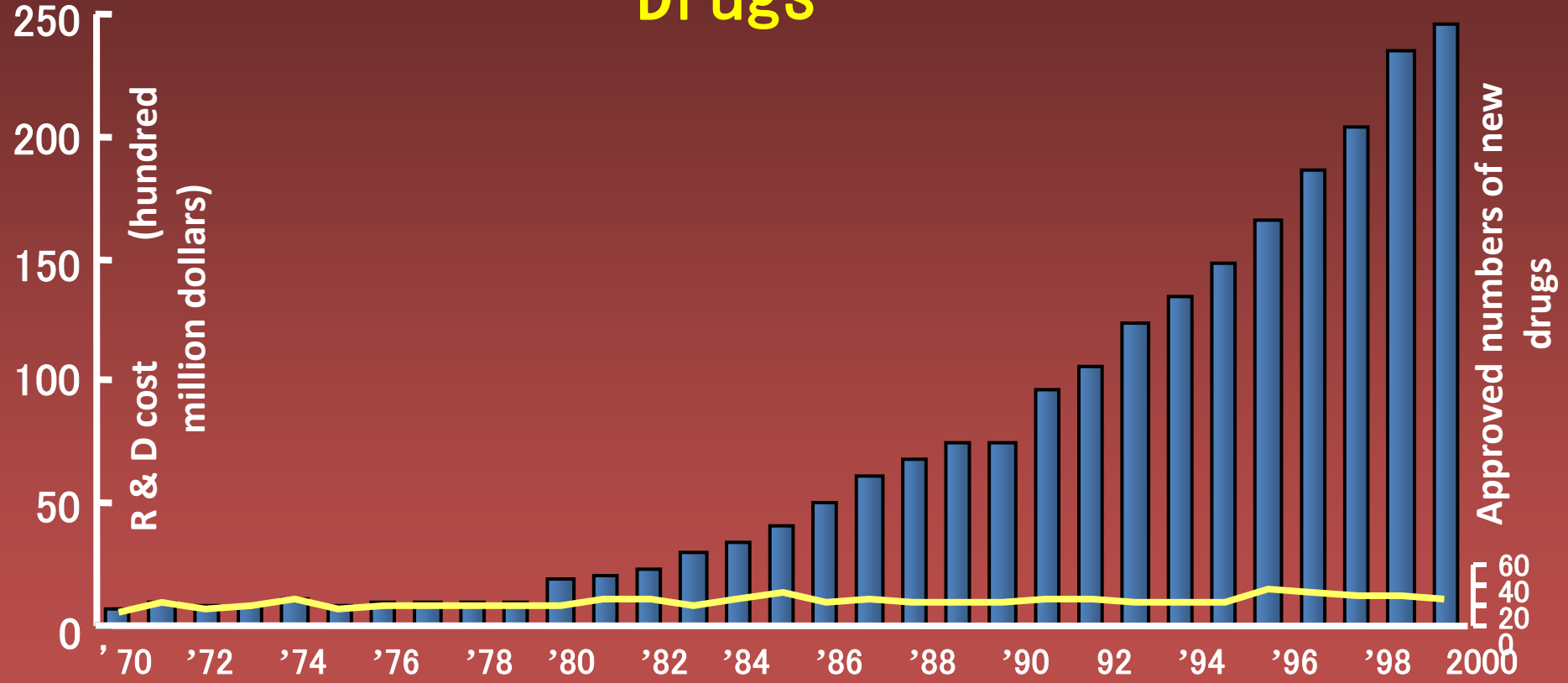
Extraction of common structural characteristics by the superposition of substrate molecule group.

Estimation of various parameters related to phamacokinetics/phamacodynamics (target/protein binding, identification/clearance estimation of molecular species in metabolic enzymes, etc)

→

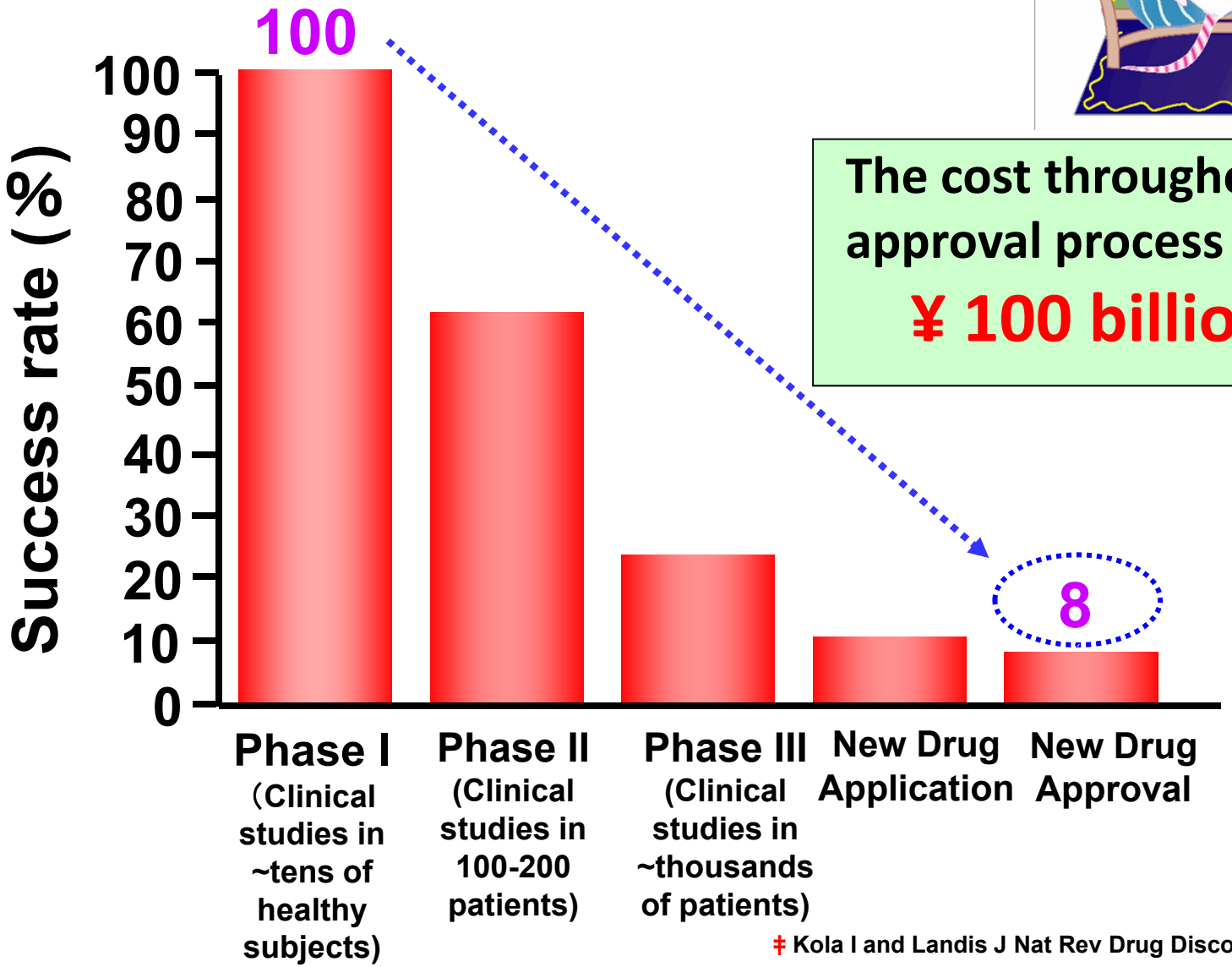
Simulation prediction is available by using them as the input data of mathematical models.

Transition in R & D Cost and Approved Numbers for New Drugs



PhRMA annual survey, 2000

Process to Approval of New Drugs



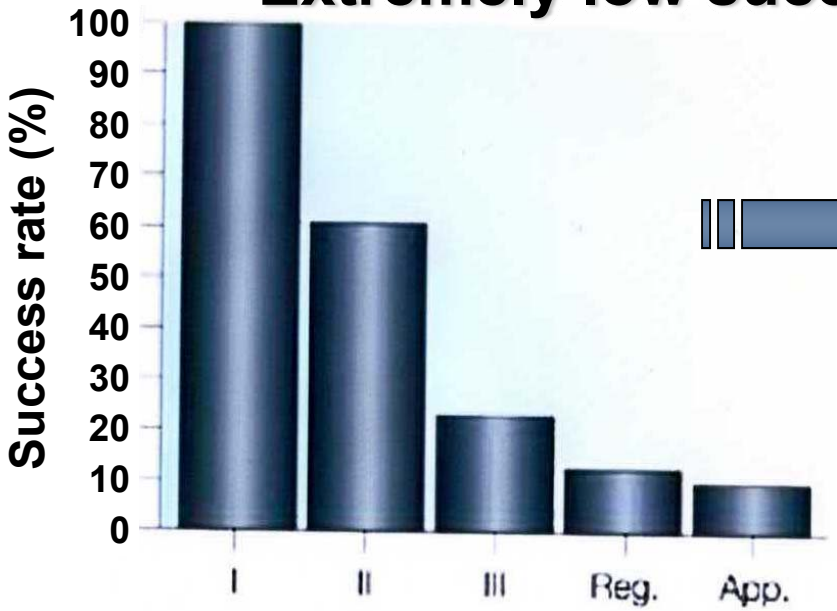
The cost throughout the approval process

¥ 100 billion ！

‡ Kola I and Landis J Nat Rev Drug Discov 3(8), 711-5 (2004)

Current Status of Drug Development

Extremely low success rate in clinical trials



Stages of Clinical Trials

Selection of drug candidates with higher probability in creating finally approved drugs need to be made on the stage for entry to clinical trials.

‡ Kola I and Landis J., Nat Rev Drug Discov. 2004 3(8):711-5.

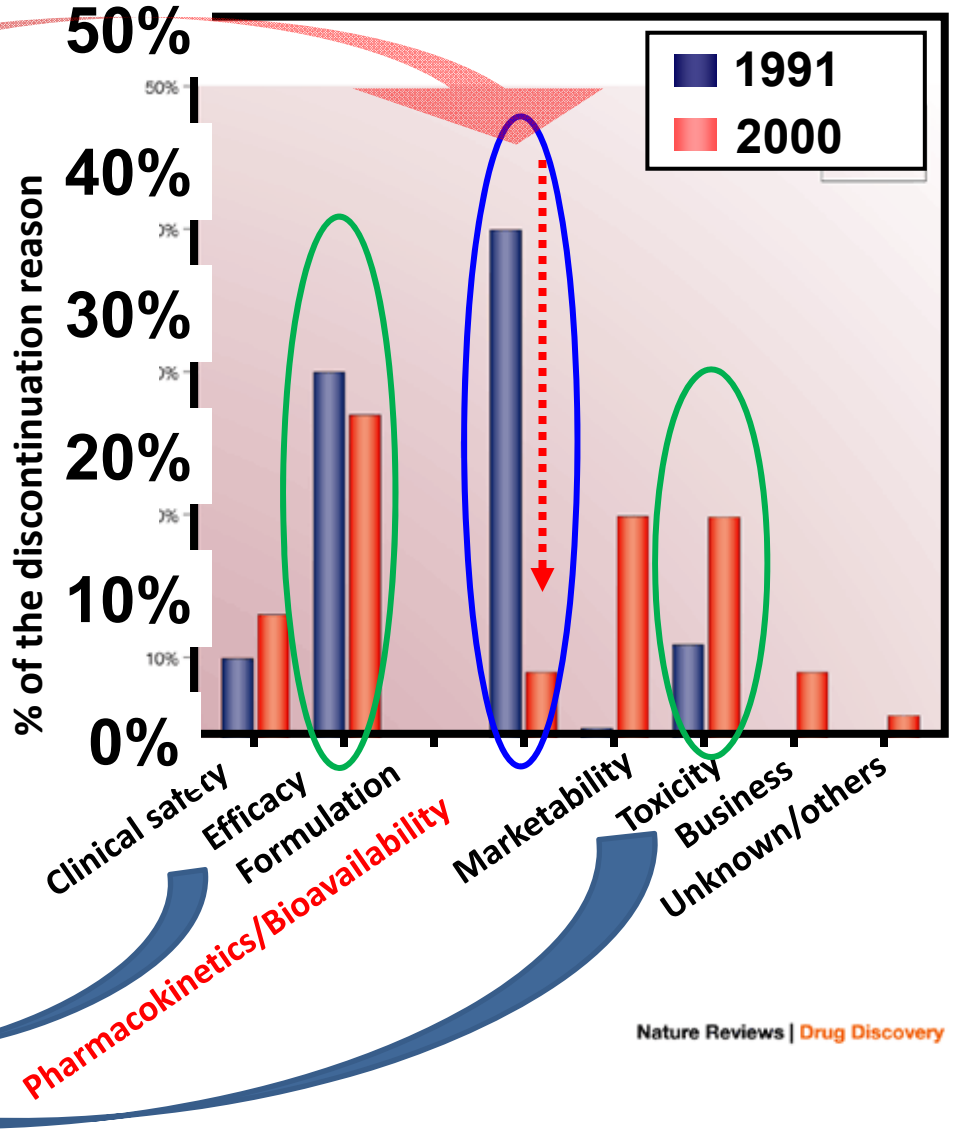
- A few compounds among new chemical entities in Phase I clinical trials have been actually approved as new drugs (approx. 8%).
- The cost of creating an approved new drug are ¥ 80-100 billion.

Pharmaceutical companies in Japan have faced an especially difficult situation compared with pharmaceutical mega-industries in US and Europe.

Need for Quantitative Estimation of Phamacokinetics in Humans

- Diversity
- Ethnic difference
- Gene polymorphism
- Broad range of substrate specificities (Interaction)

Issues of efficacy and toxicity are potentially due to those of pharmacokinetics (distribution to tissues, formation of reactive metabolite.

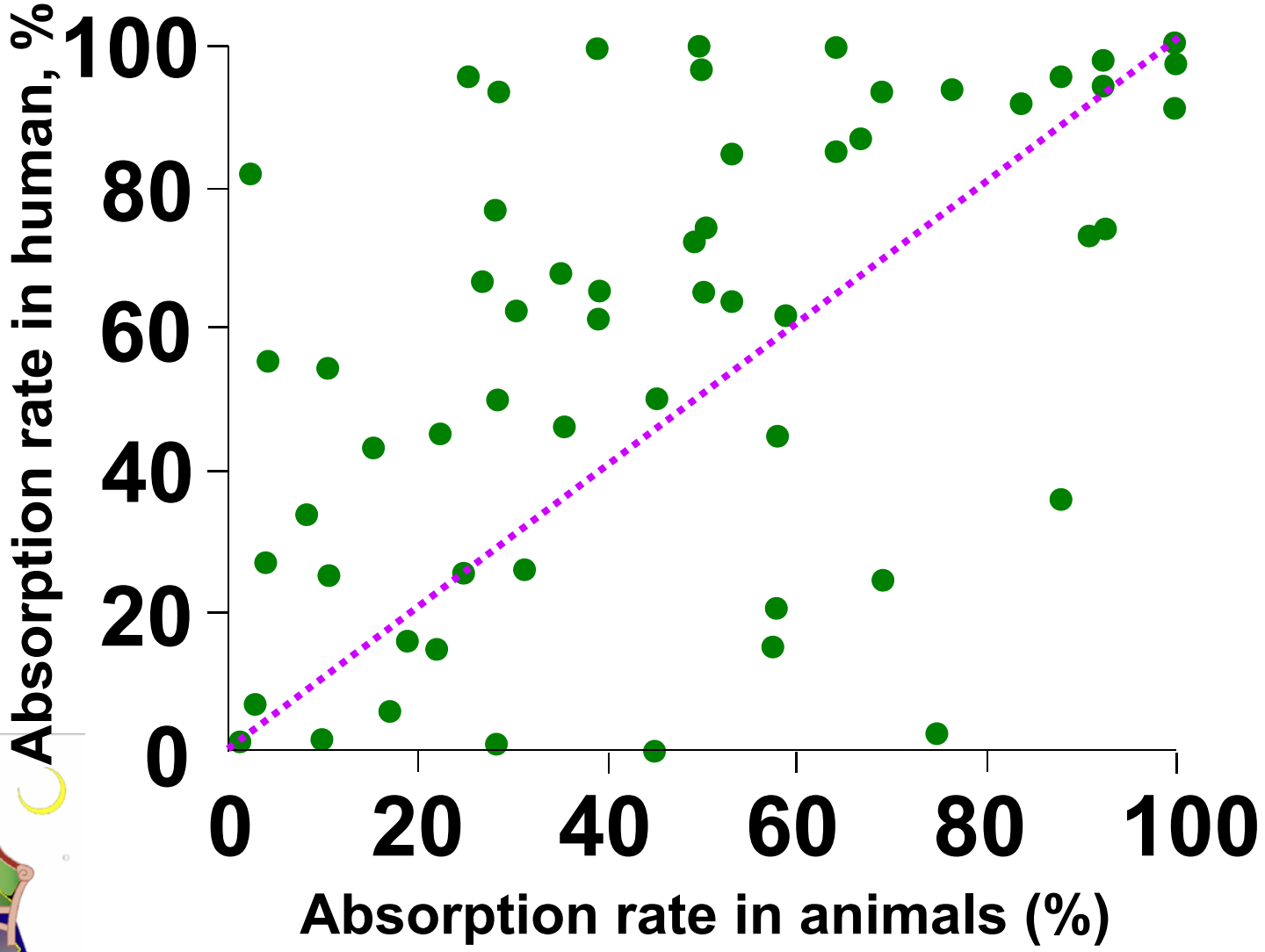


Reasons for discontinuation during new drug development

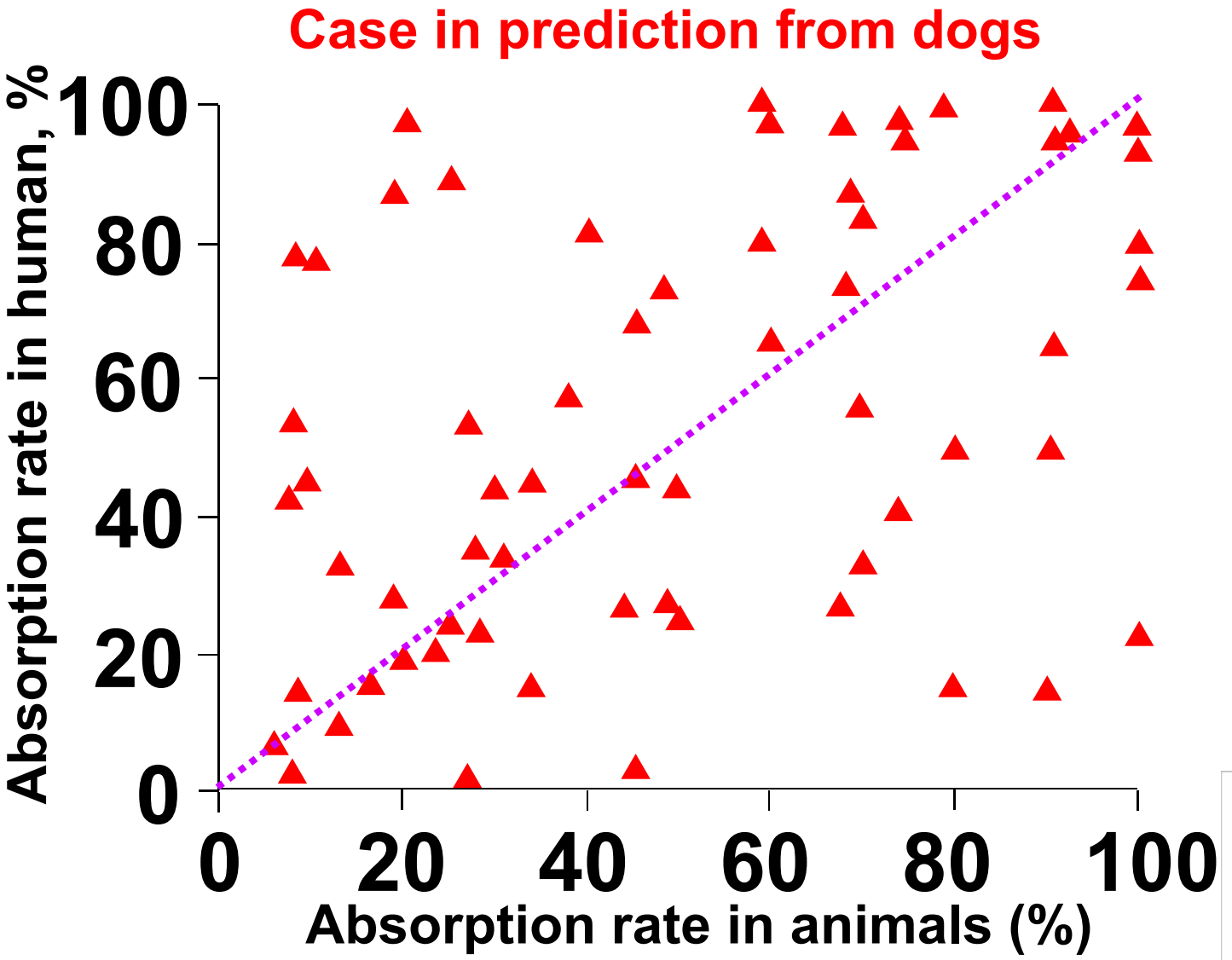
‡ *Frank, R. and Hargreaves, R., Nat Rev Drug Discov 2: 566-580 (2003)*

Difficulty in Predicting Human Pharmacokinetics from Animal Data

Case in prediction from murinae (rat/mouse)



Difficulty in Predicting Human Pharmacokinetics from Animal Data



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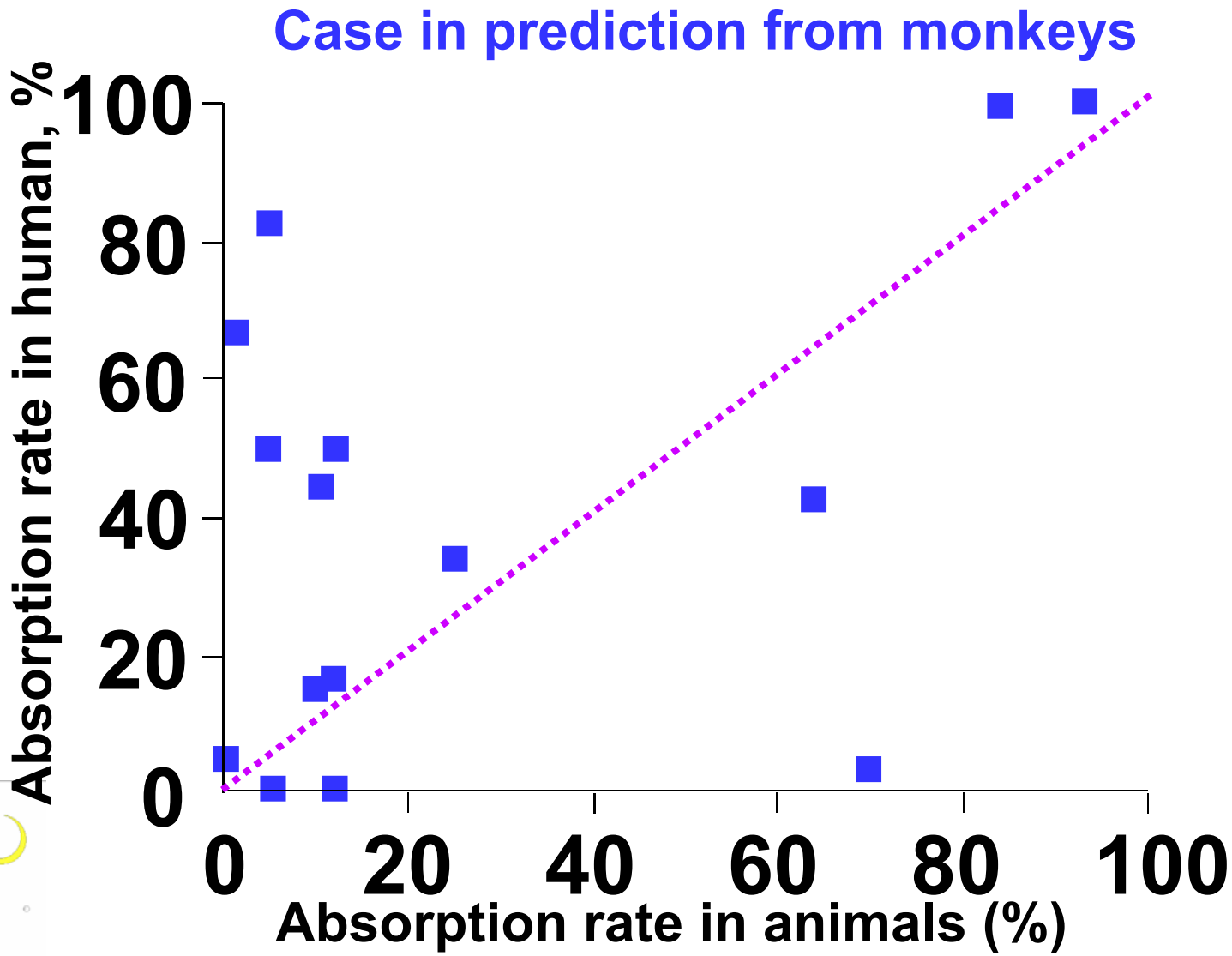

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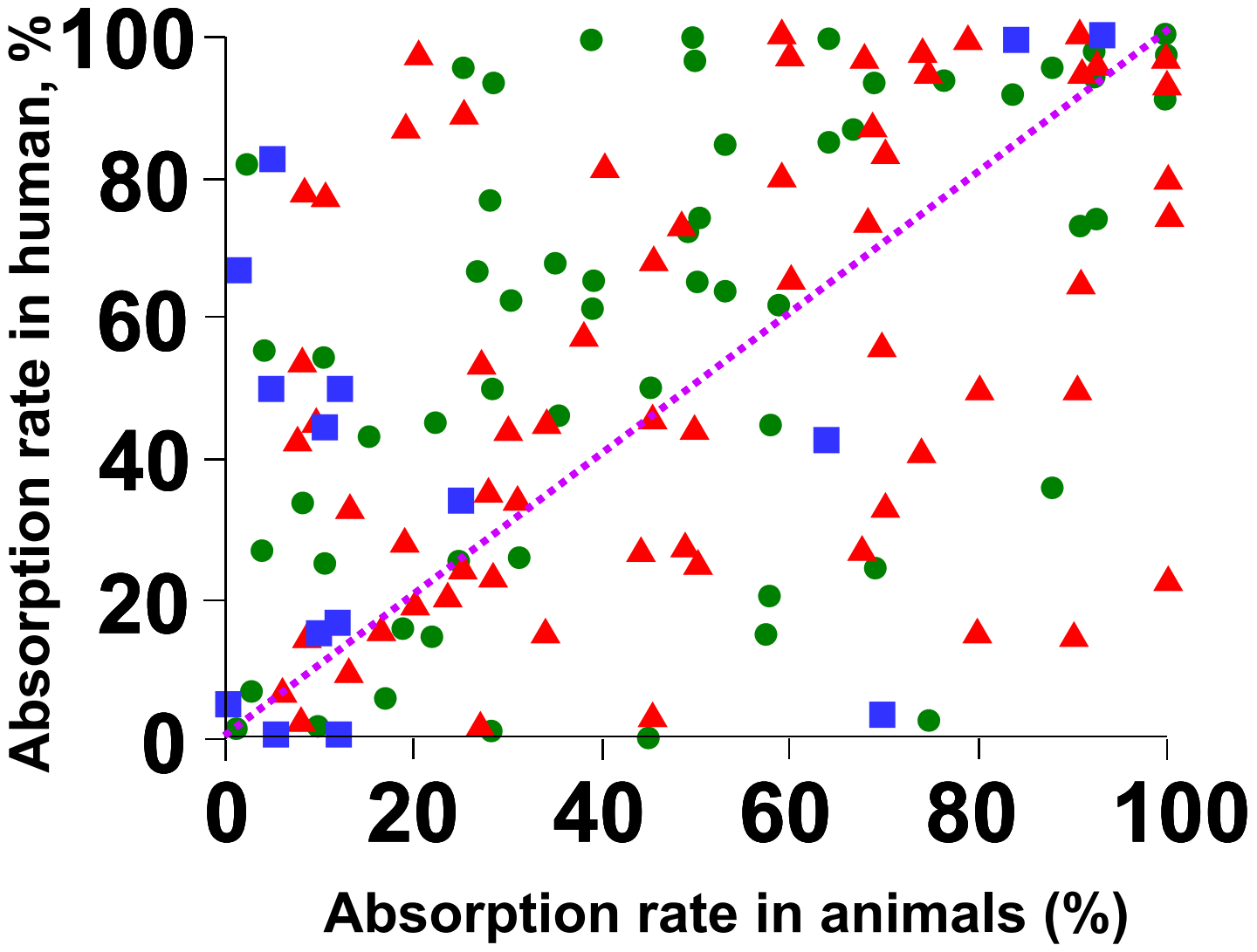
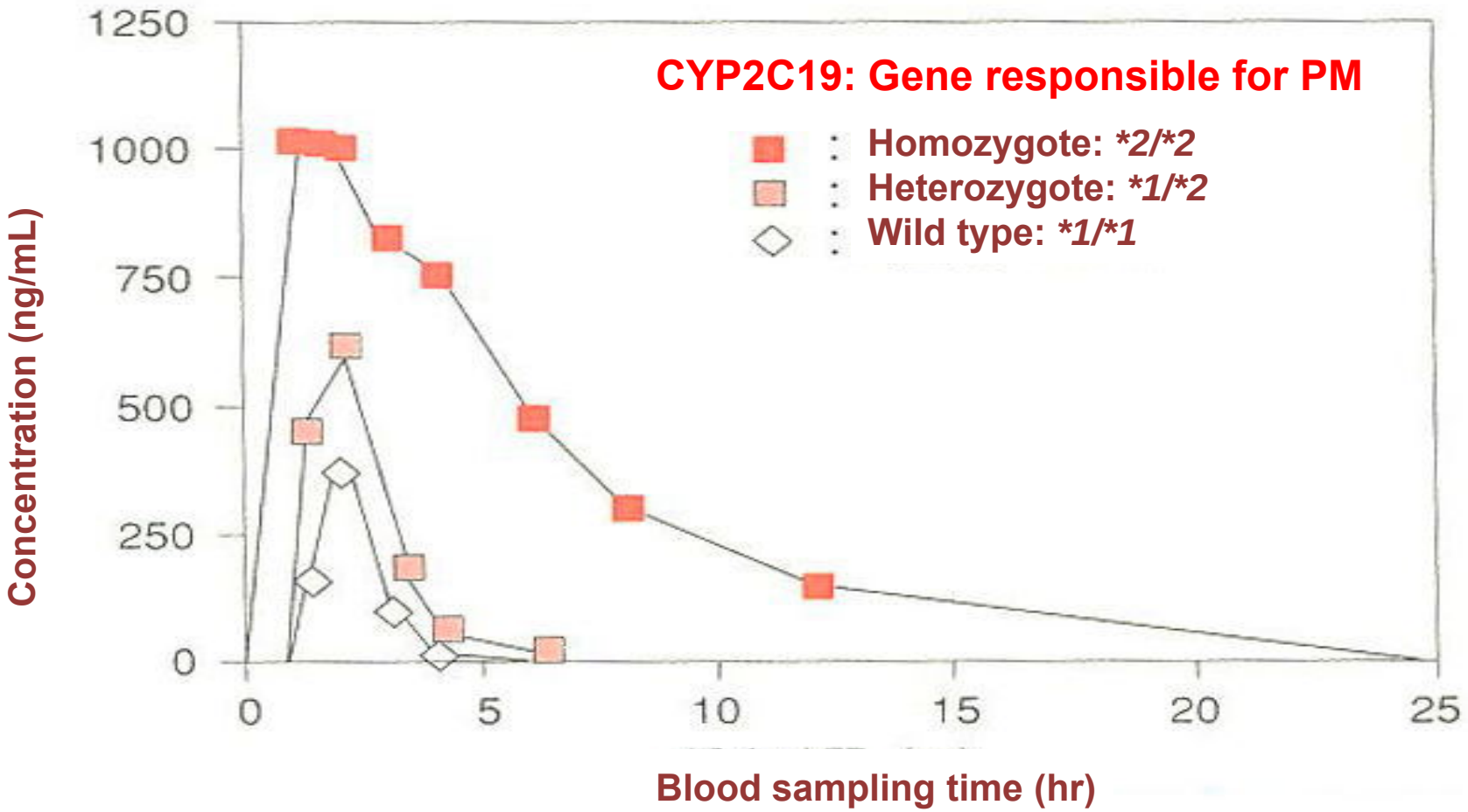
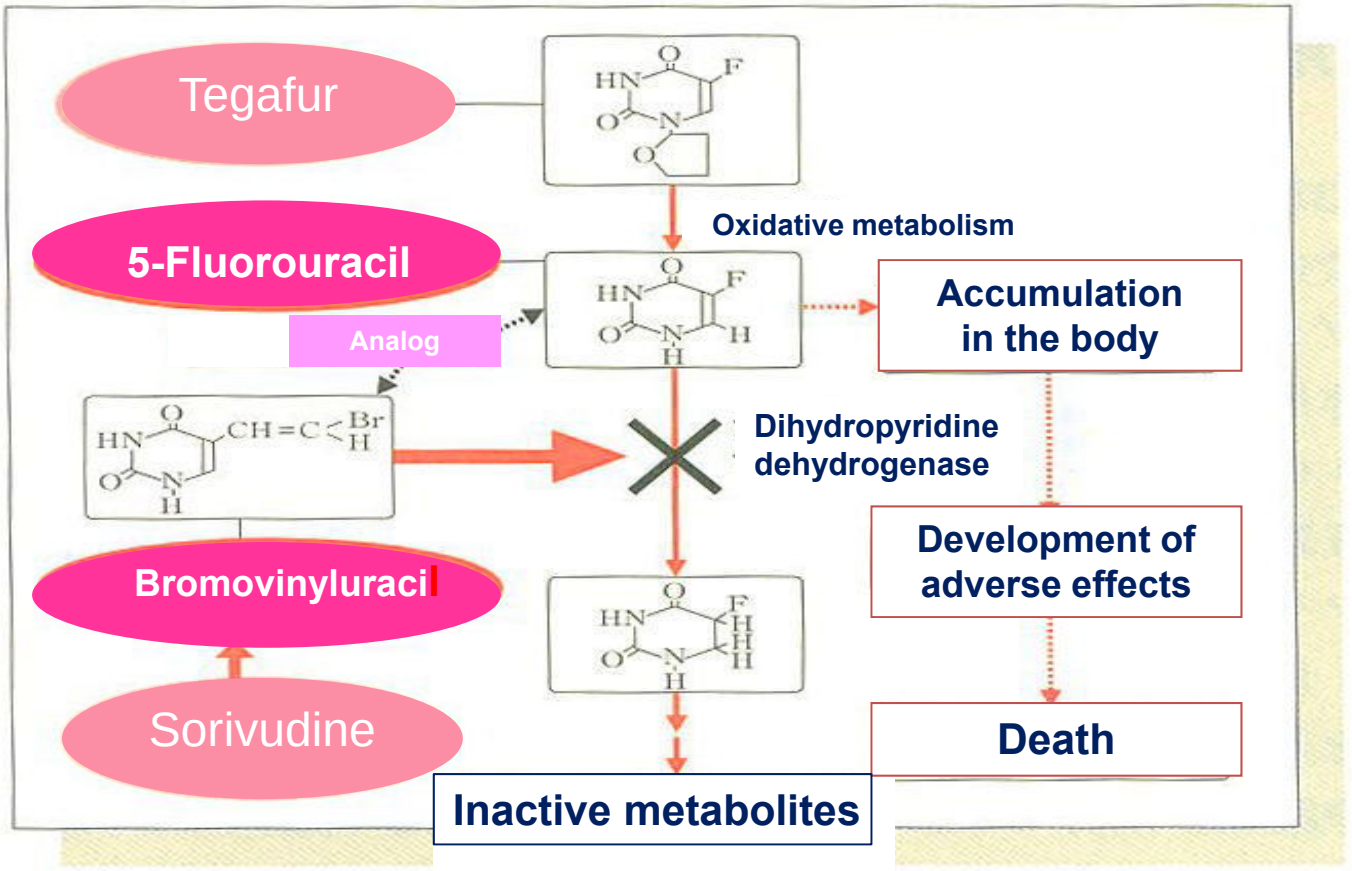


Time Course of Blood Omeprazole Concentration



‡ Source: J. Azuma: 「「クスリに弱いヒト」と「困ったクスリ」たち」 (Individual Difference of Reactivity to Drug),Jiho, Inc., Tokyo, 2001

Interaction between 5-FU and Sorivudine



‡(Modified figure from J. Azuma: 「「クスリに弱いヒト」と「困ったクスリ」たち」 (Individual Difference of Reactivity to Drug),Jiho, Inc., Tokyo, 2001

Adverse Effects of Cerivastatin - Drug-Drug Interaction with Gemfibrozil -

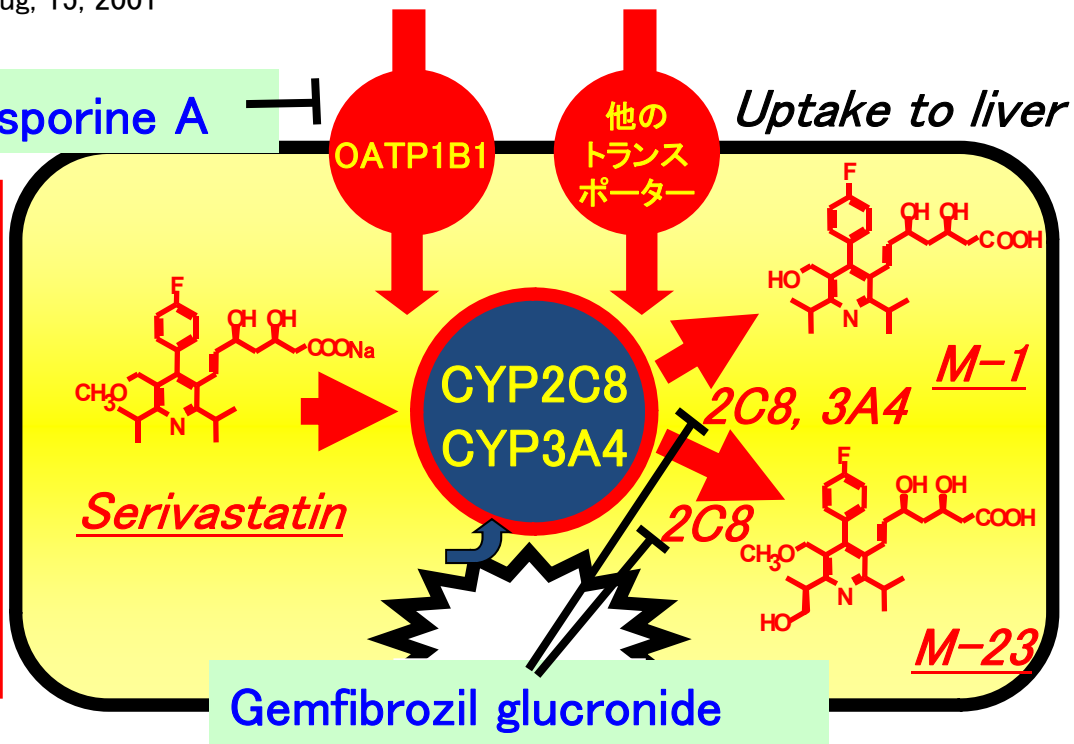
In Japan, the drug maker initiated voluntary recall of cerivastatin due to serious adverse effects.

Yakuji Nippo, Aug. 27, 2001

Yakuji Nippo, Aug, 15, 2001

There have been 52 deaths (31 in the US) from the adverse effect rhabdomyolysis in patients taking serivastatin.
Twelve of the 31 patients in the US were confirmed to take concomitant fibrate group ant-hyperlipidemic agents.
[from British Medical Journal 323, 359 (2001) & British Medical Journal 323, 415 (2001)]

Low risk of interaction has been considered in Serivastatin due to its multiple metabolic pathways .



Shitara, Y. et al.
J Pharmacol Exp Ther,
304(2): 610-6 (2003)

Shitara, Y. et al.
J Pharmacol Exp Ther, 311(1): 228-36 (2004)

Shitara, Y. and Sugiyama, Y.
Pharmacol Ther,
112(1): 71-105 (2006)

Elucidation of Primary Action Point in the Interacting Drug and Detoxification of Cerivastatin in Liver

Metabolism of Alcohol

What is low tolerance for alcohol?:
Is it due to sensitivity or metabolism?

(Ethanol) CH_3CH_2OH **Cause one to get drunk**

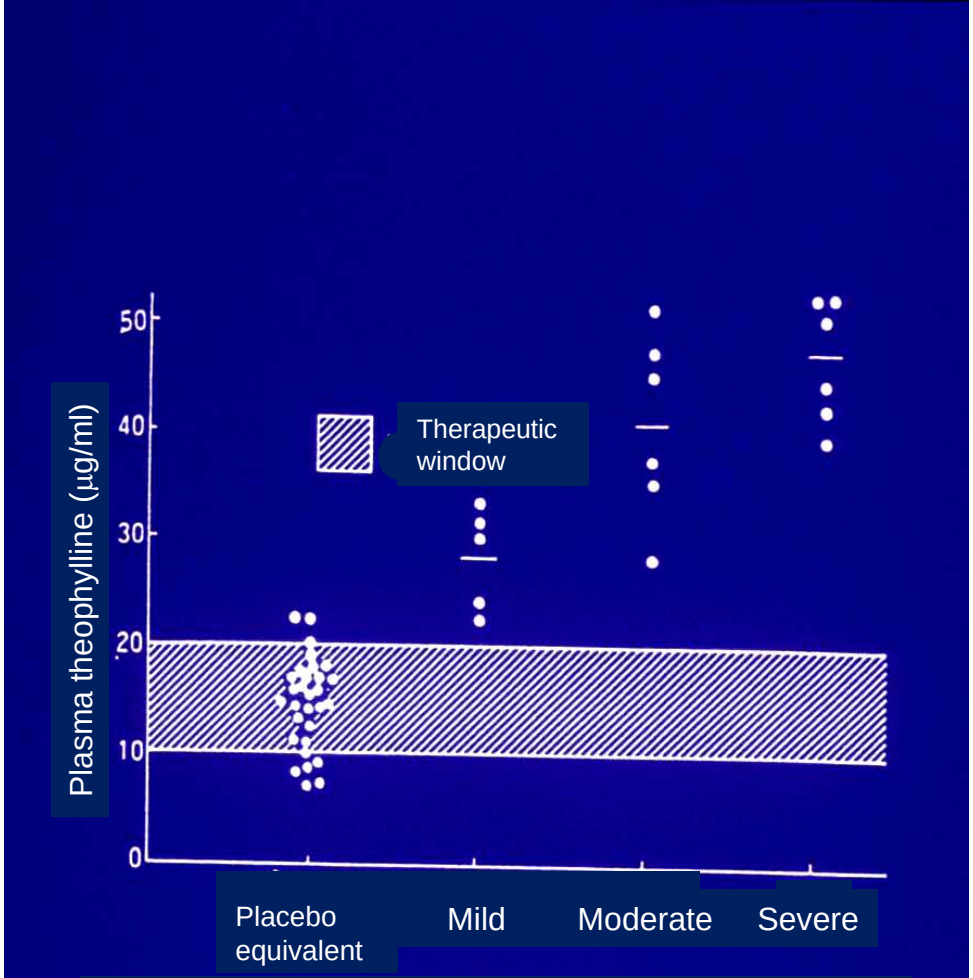
↓ Alcohol dehydrogenase（ADH）

↓ CYP2E1 (A Drug-metabolizing enzyme)

(Acetoaldehyde) CH_3CHO **Cause one to get sick after drinking**

↓ **Aldehyde dehydrogenase (ALDH)**

(Acetic acid) CH_3COOH **Some Japanese have little or extremely low activity of this enzyme.**



Relationship between adverse effects and plasma theophylline concentration in 50 adult patients
(Hendeles, et al., 1973)

Mild: vomiting, headache, tremor
Moderate: mild arrhythmias
Severe: Life-threatening arrhythmias, tremor

R. Kato, 1998, 臨床薬物動態学(Clinical Pharmacokinetics), Nankodo

Idiosyncratic drug toxicity and its prevention

Drug-induced hepatotxicity

Withdrawal of Troglitazone (Noscar) from Market Due to Hepatotoxicity

‡

01/12/1997, Released by Ministry of Health, Welfare & Labor (MHLW)

糖尿病治療薬トログリタゾン投与に伴う重篤な
肝障害に関する緊急安全性情報の配布について

平成9年12月1日

糖尿病治療薬トログリタゾン投与に伴う重篤な
肝障害に関する緊急安全性情報の配布について

1. 対象となる医薬品

一般名: トログリタゾン
ノスカール錠100, ノスカール錠200
販売名: (承 認 :平成7年9月)
(販売開始:平成9年3月)
製造: 三共株式会社 (本社:東京都中央区)
販売実績: 販売開始以後約60億円(約15万人に使用)

2. 経緯

(1)トログリタゾンは、三共株式会社が開発した糖尿病治療薬であり、我が国では平成9年3月から販売されている。また、海外ではこれまでに米国、英国などで承認されている。

(2)トログリタゾンの肝障害については治験段階では認められていなかったが、本年10月30日に米国において、肝障害についての添付文書改定が行われたことを受けて、我が国でも三共から医療機関に対して情報提供が行われた。

また、本年11月21日に開催された中央薬事審議会副作用第一・第二合同調査会において、これまでに報告された我が国の肝障害症

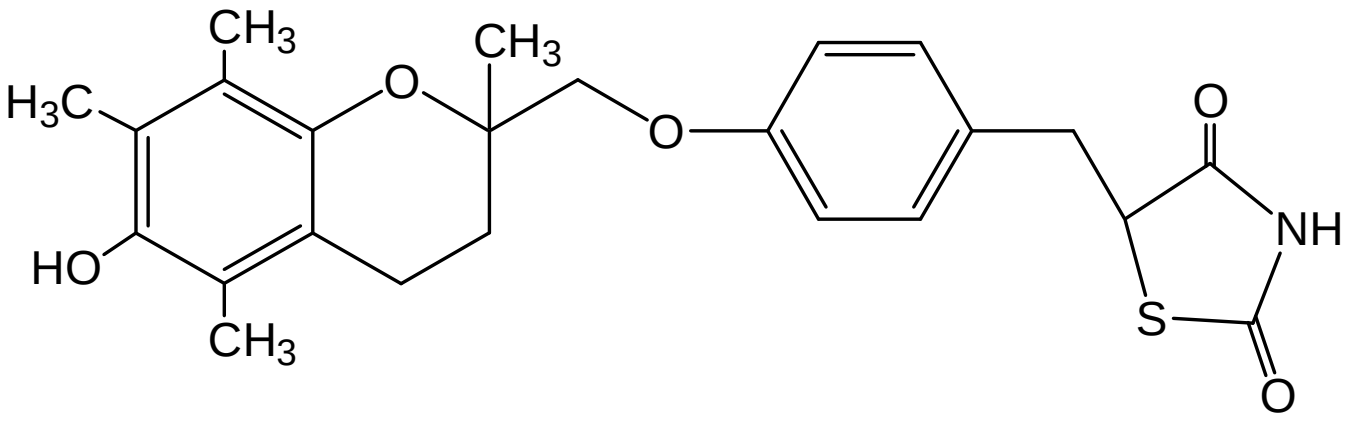
22/03/2000, Release by Sankyo

Figure removed due to copyright restrictions

○03/1997: Noscal was launched in Japan
○1998
・Prescribed in 200 thousand pts. in Japan
→Severe hepatotoxicity pts. (hospitalized or equivalent to): 74 pts. (1/2700 cases)
→ Death: 4 patients（1/50000 cases)
・Prescribed in approx. 600 thousand pts. in the US
→Hepatotoxicity: 165 pts (~1/3600 pts.)

○12/1997: Voluntary withdrawal from market in UK
MHLW distributed Dear Dr. Safety Letter
○05/1999
・US: Prescription to approx. 1.6 million pts.
→Death,155 pts (~1/10000 pts.）
→Sever hepatotoxicity, 1/1200-1800 pts.
○21/03/2000 Withdrawal from market in the US
○22/03/2000 Voluntary recall by Sankyo

The Antidiabetic Agent Troglitazone and Liver Toxicity



March, 1997 **Launched as the first antidiabetic agent for the treatment of type II diabetes mellitus.**

December, 1997 **"Dear doctor" safety letter was released concerning severe liver toxicity despite rare cases (1/100 thousand patients).**

March, 2000 **Voluntary withdrawal from the market**

Characteristics of Liver Toxicity by Troglytazone

1. **No relation to gender, age, dose, and co-medication.**
2. **Hepatotoxicity onset 3-5 months after treatment.**
3. **No hepatotoxicity observed in animal experiments**
4. **Diagnosed as idiosyncratic hepatopathic hepatotoxicity.**

Gene Analysis in Patients with Hepatotoxicity

I. Watanabe and T. Koga *et al. Clin. Pharm. Ther*. 73, 435-455 (2003)

Control diabetic patients: 85 patients
Diabetic patients with troglitazone induced hepatotoxicity: 25 patients

Analysis of 51 genes

Fifty-one genes were analyzed.
CYP1A1, CYP2C9, CYP2C19, CYP2E1, CYP3A
MAOB, Cytochrome C oxidase, UGT1A1, GSTT1, GSTM1,
Nitric oxide synthase 2A (NOS2A), NOS3,
MRP2, GLUT1, GLUT2,
Glutathione peroxidase 1(GPX1), GPX3, GPX4,
Catalase, SOD1, DT-diaphorase
TNFα, TNFR1, TNFR2, PPARγ2, HGFf, ADRB3, UCP1
TPMT, CASP9, FAS antigen, CTLA4, RDH5,
Leptin, Leptin receptor, Albumin,
APOA1, APOC3, LPL, CD36, SEP,
Insulin receptor, IGF1, IGF2, IGF receptor 2, IRS1, IRS2,
IRS4, GYS1, GYS2

Glutathione-conjugating enzyme

Next

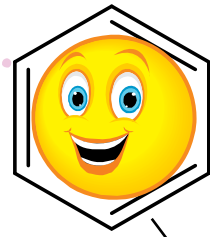
Genotypes of GSTT1 and GSTM1

I. Watanabe and T. Koga *et al. Clin. Pharm. Ther*. 73, 435-455 (2003)

GST gene		Patients tolerant to troglytazone		Patient with troglytazone hepatotoxicity	
GSTT1	*GSTM1*	Numbers	(%)	Numbers	(%)
Wild	Wild	25	(29)	3	(12)
Wild	Deficient	27	(32)	7	(28)
Deficient	Wild	20	(24)	5	(20)
Deficient	Deficient	13	(15)	10	(40)
Sum		85	(100%)	25	(100%)

$p = 0.043$

Pathogenic Mechanism of Drug-Induced Hepatotoxicity



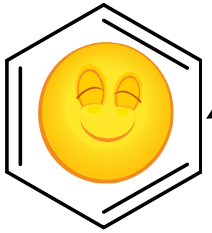
Drugs

Metabolism（highest activity in liver)

Reactive (toxic) metabolites

Hepatotoxicity

Glutathione-conojugating detoxification enzyme (GST)

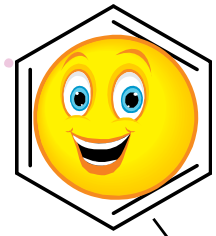


Detoxification

Covalent binding to DNA and proteins

Cellular dysfunction

Pathogenic Mechanism of Drug-Induced Hepatotoxicity



Drugs

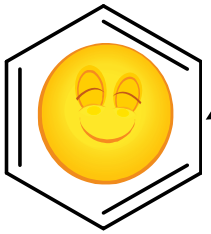
Metabolism
(highest activity in liver)

Reactive (toxic)
metabolites

Hepatotoxicity

Decreased activities

Glutathione-conojugating
detoxification enzyme (GST)



Detoxification

Covalent binding to
DNA and proteins

Cellular
dysfunction

Idiosyncratic Drug Toxicity
And Its Prevention

1) Individuals with a low detoxification activity (glutathione-conjugating enzyme) of toxic metabolites →Identifiable from gene analysis

Is more sensitive method available for detecting individuals with idiosyncrasy?

↓

How about HLA (Human Leukocyte Antigen, human leukocyte antigen)?
The transplant without compatibility of HLA types between donors and recipients is difficult due to the rejection response.

Ideal Drug from Pharmacokinetic Perspectives

- ✓ High absorbability (Bioavailability)
- ✓ Low variability in blood concentration
- ✓ Blood concentration without nonlinearity
- ✓ Distribution to target organs at the required concentration and time.
- ✓ No accumulation with repeated administrations
- ✓ No induction and inhibition of metabolic enzyme
- ✓ Multiple metabolized and excreted pathways
- ✓ No formation of active (toxic) metabolites
- ✓ No gene polymorphism

from T. Suwa, 126th Annual Meeting of Pharmaceutical Society of Japan, 2006