Contribution of Drug Metabolism Research to New Drug development

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COI disclosure information

Authors : Eiji Kashiyama

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

- Employees : Eiji Kashiyama
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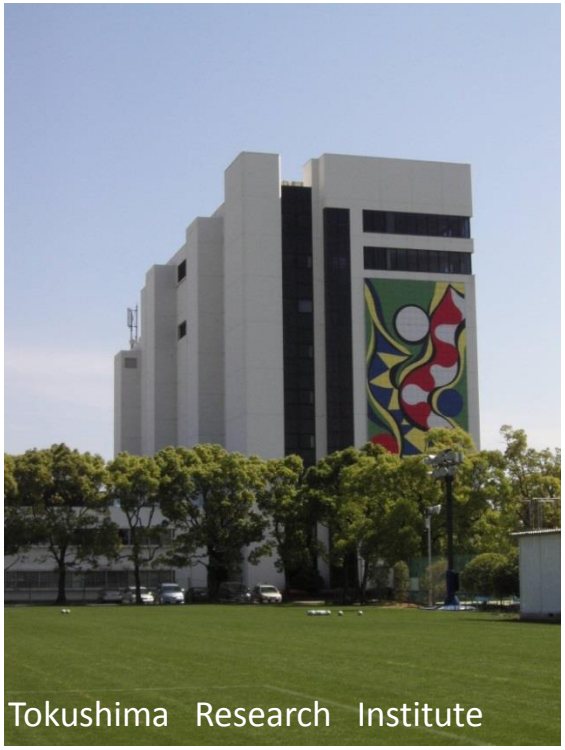
Other many researchers


Tokushima Research Institute

History of drug Development at Otsuka

Otsuka
Otsuka-people creating new products for better health worldwide

Otsuka Original New Drugs

- 1980

Carteolol (1980)
Procaterol (1980)

← Joined Otsuka (1983)

- Aripiprazole Synthesized (1987)

- 1990

←

↓

- 2000

Approval (2002, US)
(Schizophrenia)

Mozavaptan (2006)
Tolvaptan (2009)

- 2010

Delamanid (2014)
Brexpiprazole (2015)

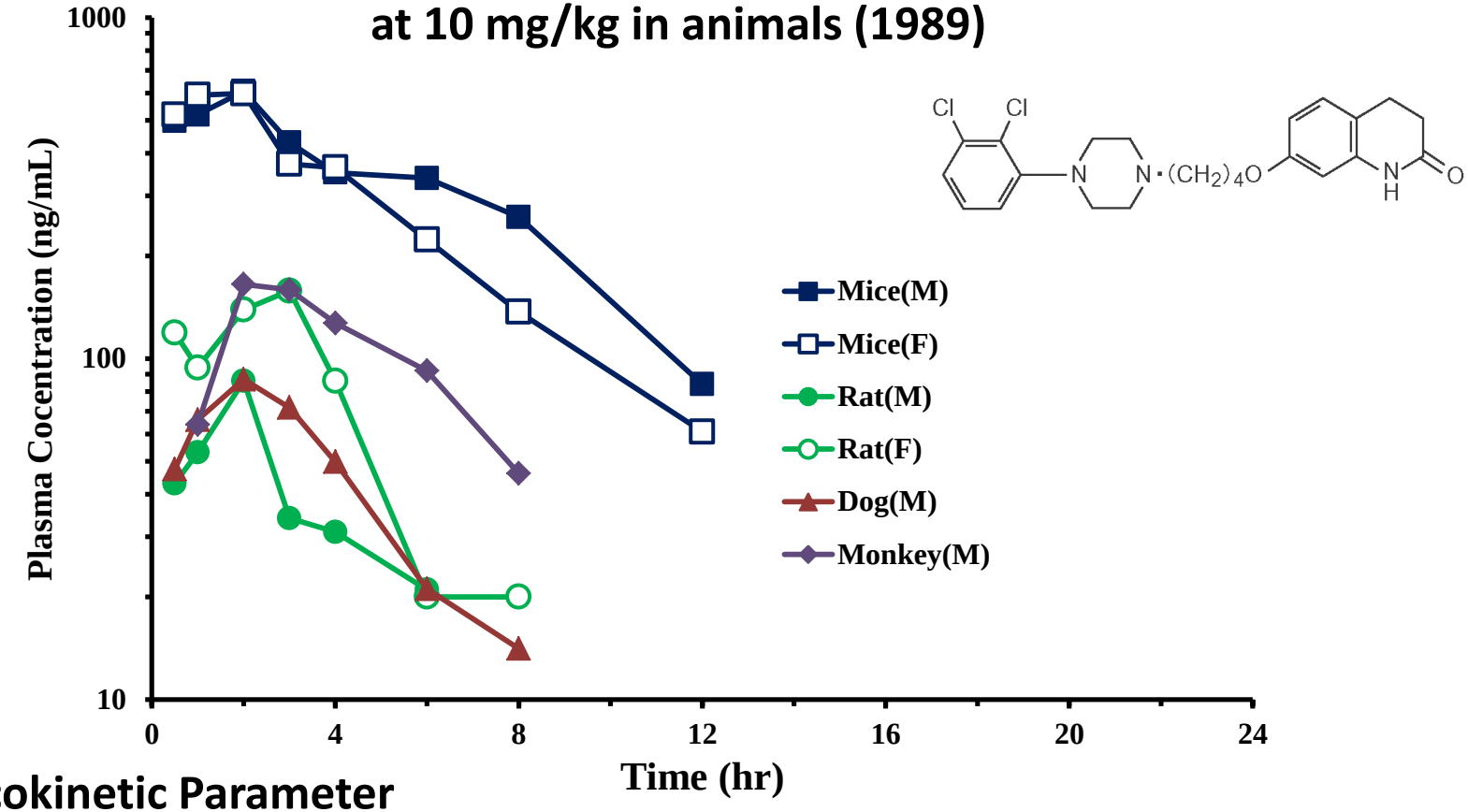
Progress of drug metabolism research

- Purification of P450 proteins
- P450 cDNA cloning (1982)
- P450 Nomenclature (1987)
- Crystal structure of P450cam (1987)
- Gene polymorphism of CYP2D6 (1990)
- Drug Interaction –sorivudine- (1993)

1995: Recombinant P450s were available.
1996: Human liver microsomes were available.

Aripiprazole : Pharmacokinetics (Animals)

Plasma Concentration of Aripiprazole after an Oral Administration at 10 mg/kg in animals (1989)



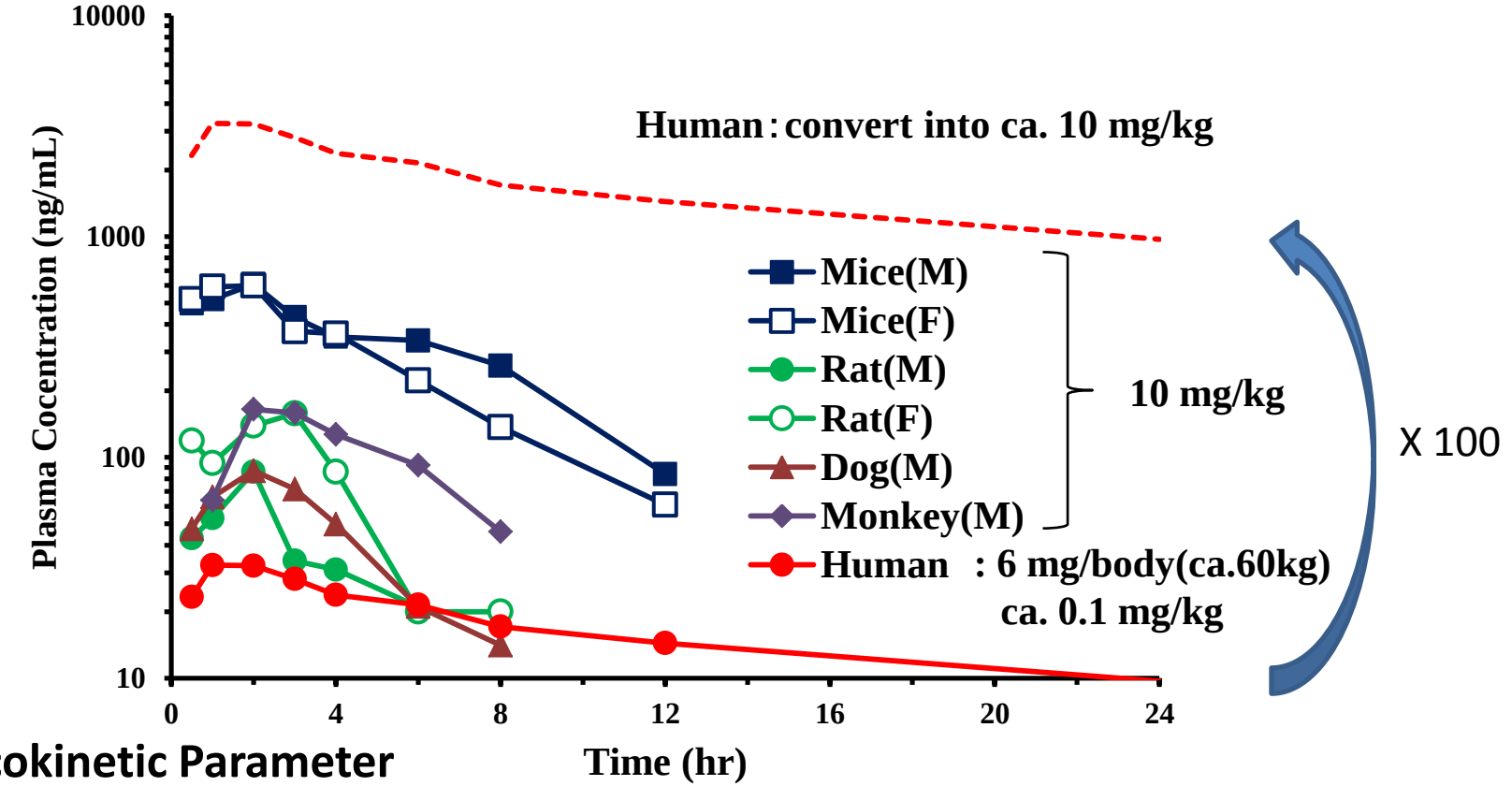
Pharmacokinetic Parameter

	Mouse(M)	Mouse(F)	Rat(M)	Rat(F)	Dog(M)	Monkey(M)	Human
Vd (L/kg)	5.6	5.7	8.1	7.1	5.5	4.6	??
CL(mL/min/kg)	19.4	24.2	103	83.3	28.7	14.1	??
BA (%)	51.1	50.4	19.1	32.2	6.4	6.8	??

CL and Vd: intravenous administration

Aripiprazole : Pharmacokinetics (Human)

Plasma Concentration of Aripiprazole after an Oral Administration to Human

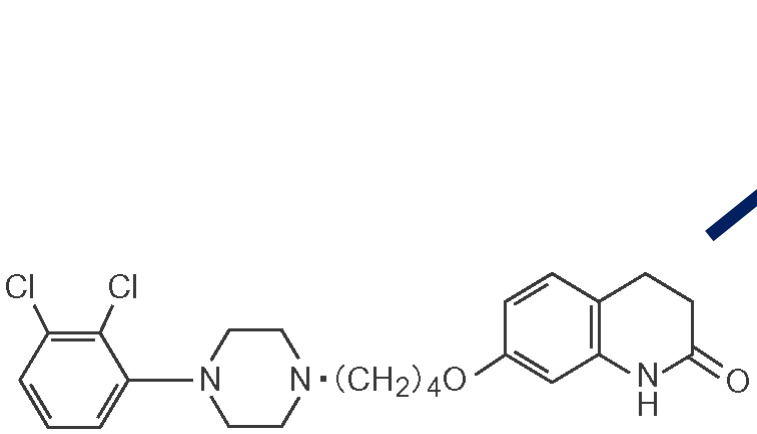


Pharmacokinetic Parameter

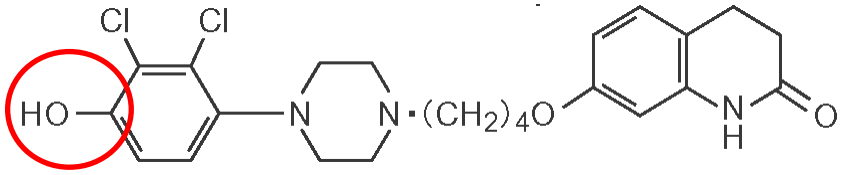
	Mouse(M)	Mouse(F)	Rat(M)	Rat(F)	Dog(M)	Monkey(M)	Human
Vd (L/kg)	5.6	5.7	8.1	7.1	5.5	4.6	5.0
CL(mL/min/kg)	19.4	24.2	103	83.3	28.7	14.1	0.72
BA (%)	51.1	50.4	19.1	32.2	6.4	6.8	77.8

CL and Vd: intravenous administration

Aripiprazole : Metabolism

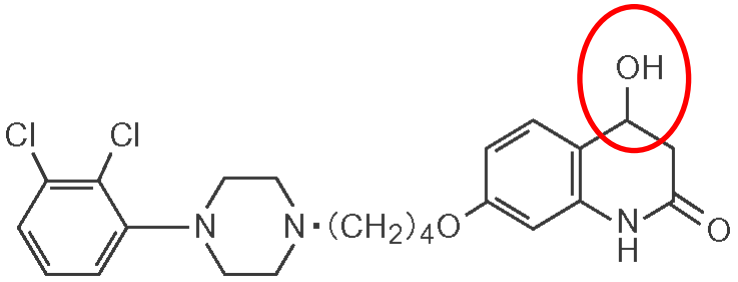


Aripiprazole

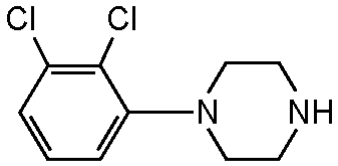


M1

Glucuronide and Sulfate

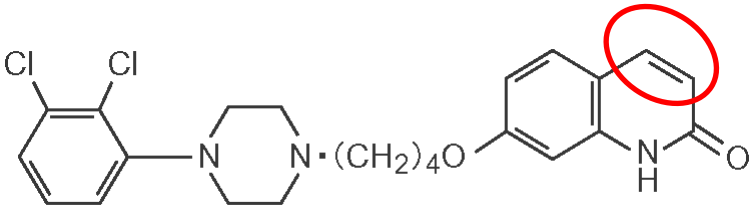


M2



+ R

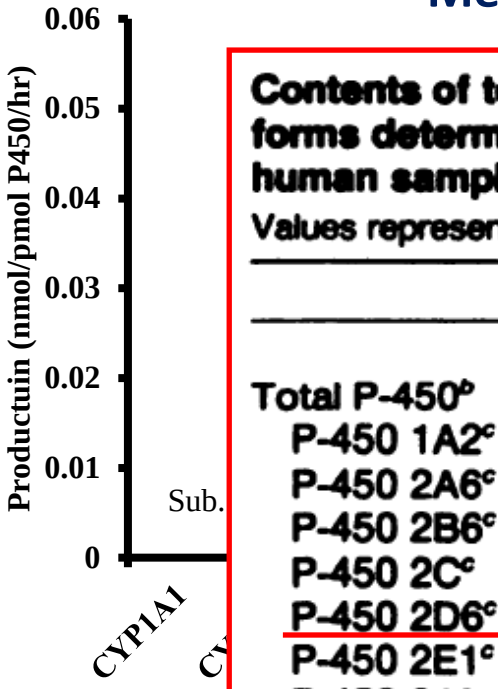
M4



M3 (Active metabolite)

Aripiprazole: Metabolizing Enzymes

Metabolized by Recombinant P450s (1995)



Contents of total P-450 determined spectrally and individual P-450 forms determined immunochemically in liver microsomes from 60 human samples

Values represent mean ± S.D. from 60 human samples.

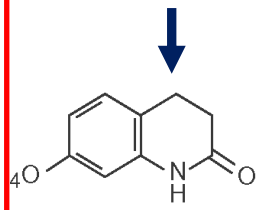
	P-450 content in liver microsomes	
	nmol/mg protein	% of total P-450[a]
Total P-450[b]	0.344 ± 0.167	
P-450 1A2[c]	0.042 ± 0.023	12.7 ± 6.2
P-450 2A6[c]	0.014 ± 0.013	4.0 ± 3.2
P-450 2B6[c]	0.001 ± 0.002	0.2 ± 0.3
P-450 2C[c]	0.060 ± 0.027	18.2 ± 6.7
P-450 2D6[c]	0.005 ± 0.004	1.5 ± 1.3
P-450 2E1[c]	0.022 ± 0.012	6.6 ± 2.9
P-450 3A[c]	0.096 ± 0.051	28.8 ± 10.4
Total[d]	0.240 ± 0.100	72.0 ± 15.3

[a] Percentage of total P-450.
[b] Determined spectrally.
[c] Determined immunochemically.
[d] Sum of individual forms of P-450 determined immunochemically.

T Snimada *et al*. JEPET, 270(1) 414-423 (1994)

D6 > CYP3A4

M2 and M3



Kinetic Par

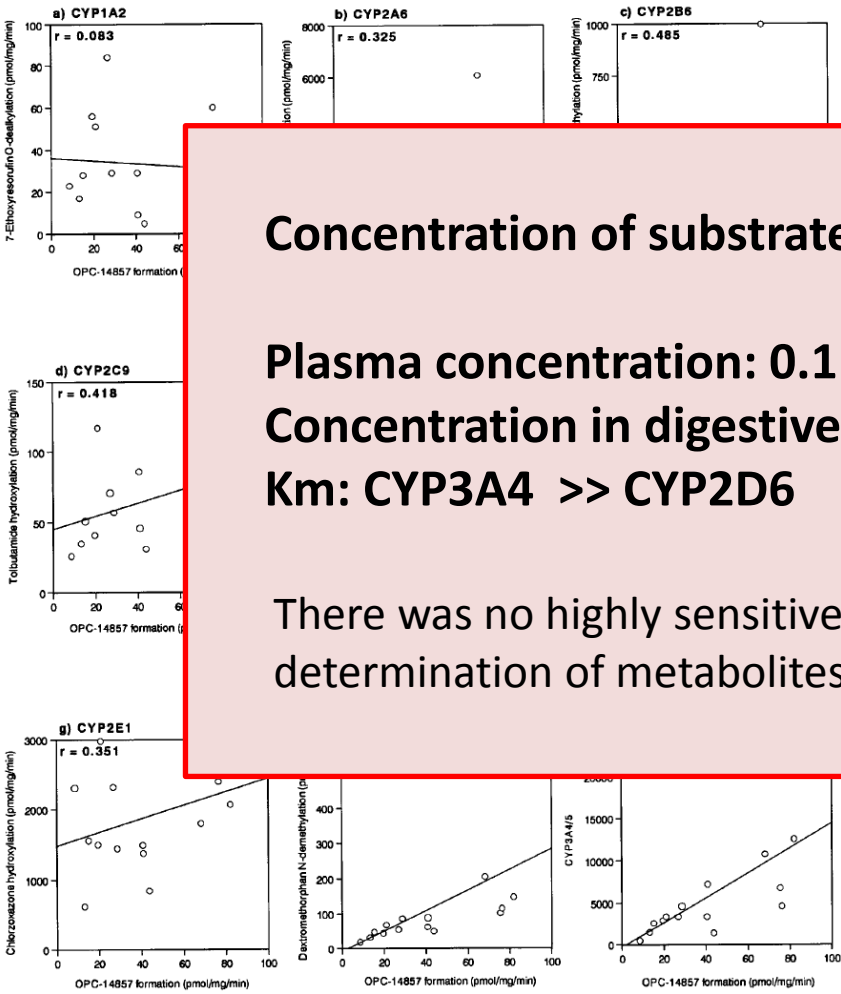
Param					M4
Km (μ					IC
					–
Vmax/					IC
(L/n					–

NC: Not calculated

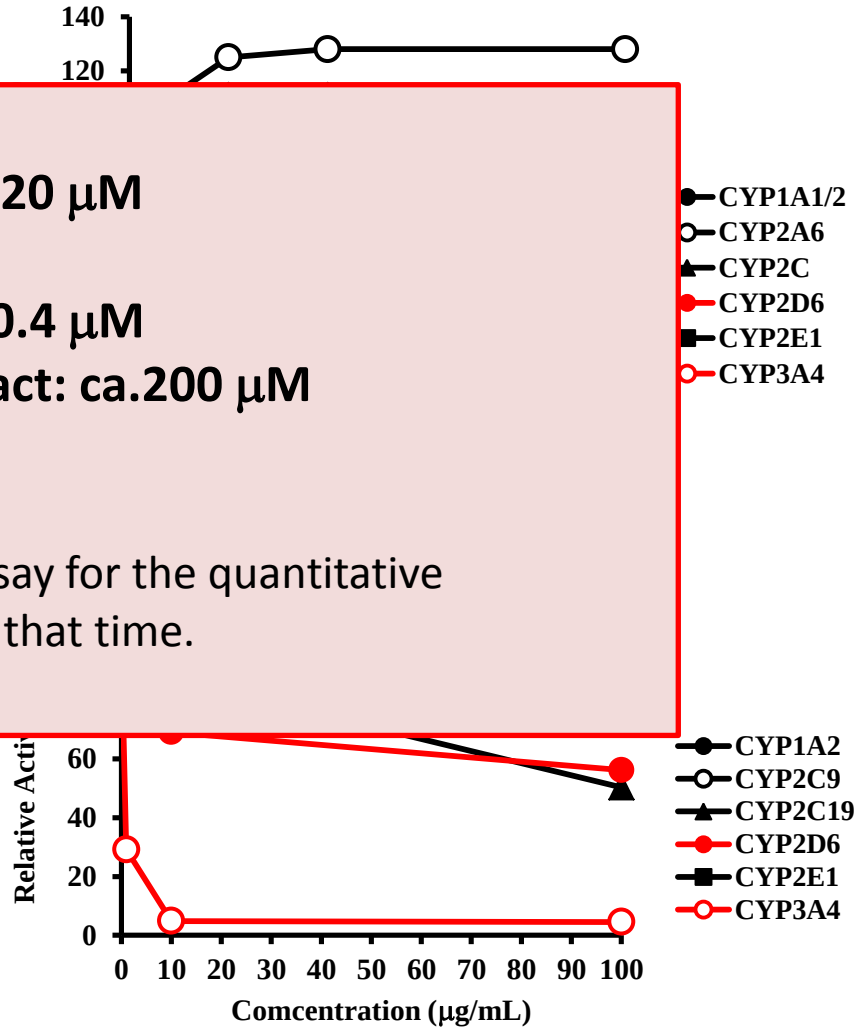
Aripiprazole: Metabolizing Enzymes

Metabolized by Human Liver Microsomes (EX: Aripiprazole ⇒ M3), 1996

- Correlation analysis



- Inhibition by Anti-P450s



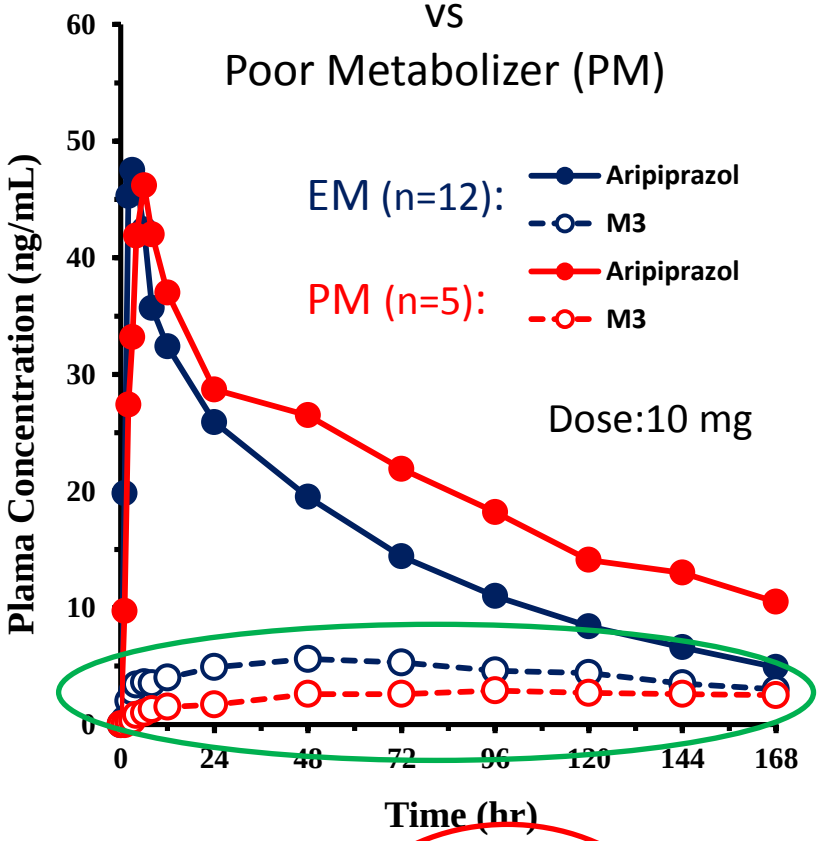
Concentration of substrate : 20 μM

Plasma concentration: 0.1～0.4 μM
Concentration in digestive tract: ca.200 μM
Km: CYP3A4 >> CYP2D6

There was no highly sensitive assay for the quantitative determination of metabolites at that time.

Aripiprazole: Clinical Studies

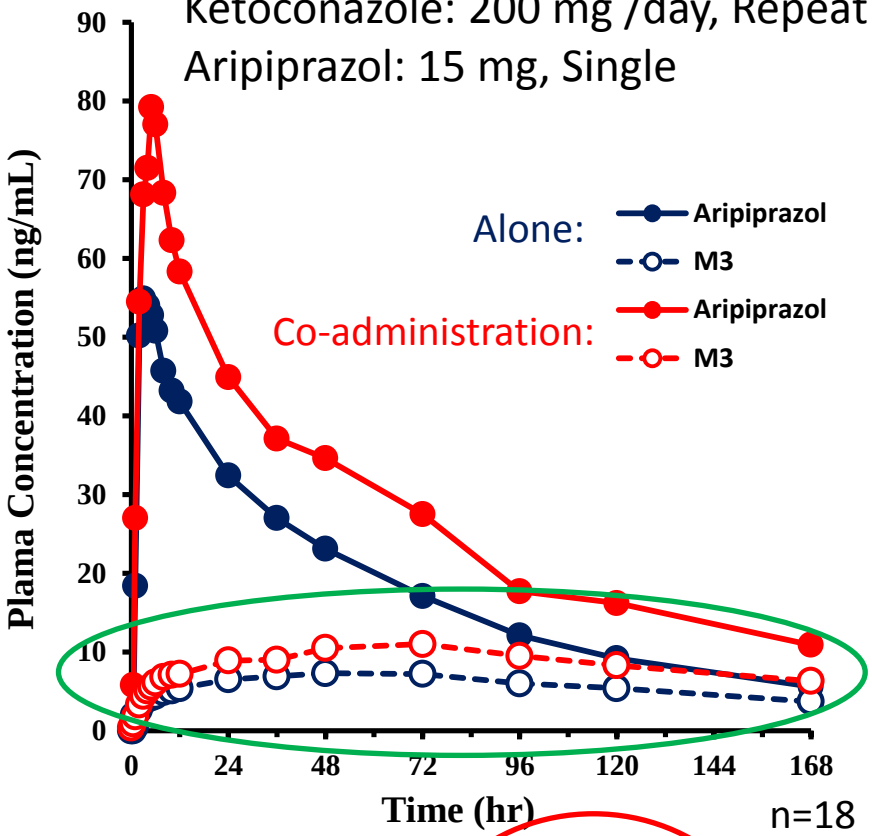
CYP2D6 Extensive Metabolizer (EM) vs Poor Metabolizer (PM)



Genotype	Cmax (ng/mL)	AUC (ng·hr/mL)	CL/F/BW (mL/hr/kg)	T1/2 (hr)
Extensive metabolizer	53.5	3221	50	85
Poor Metabolizer	49.1 (92%)	5698 (177%)	31 (62.8%)	146 (171%)

CYP3A4

Ketoconazole: 200 mg /day, Repeat
Aripiprazol: 15 mg, Single



n=18

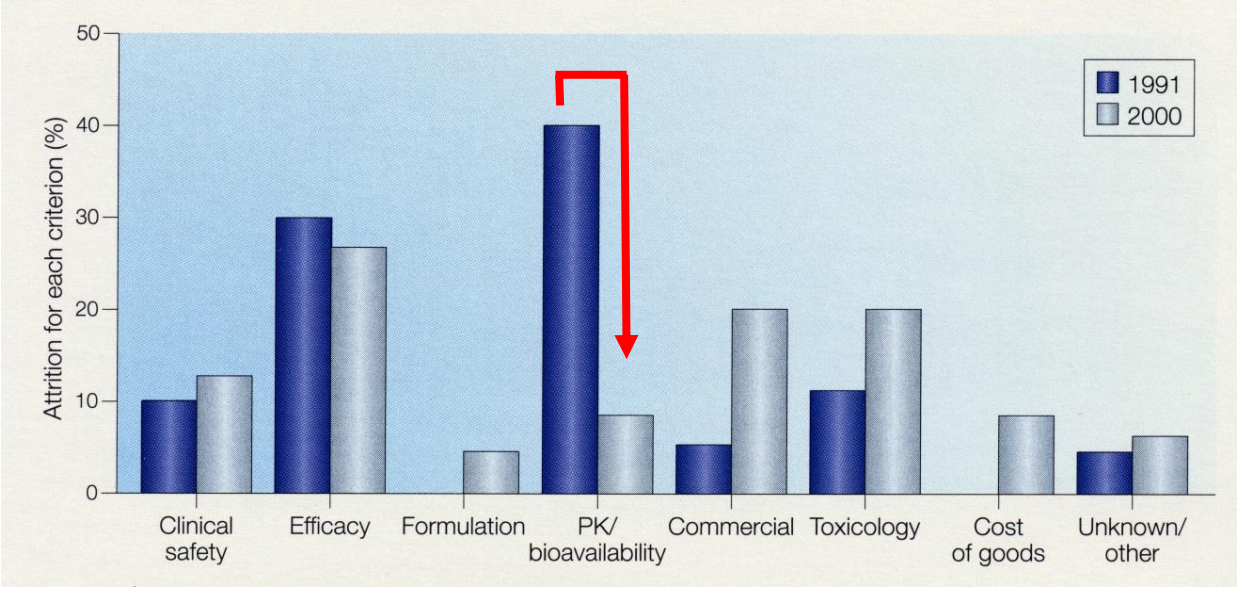
Drugs	Cmax (ng/mL)	AUC (ng·hr/mL)	CL/F/BW (mL/hr/kg)	T1/2 (hr)
Aripiprazol	61.3	3750	65	83
Aripiprazol + Ketoconazole	85.3 (139%)	6803 (181%)	40 (61.5%)	100 (120%)

Turning Pont of DMPK Study in Industry

Aripiprazole has not only a good pharmacokinetic profile but also a new action mechanism and high safety. It was approved by the US, EU and Japan in 2002, 2004 and 2006, respectively.

However a lot of candidates were withdraw during clinical development stage.

- In the 1980's, compounds for development were selected for efficacy and safety. The DMPK studies were initiated after candidate compounds were selected.
- Since late 1990, DMPK research has provided important information to selection of candidate compounds for development.



Nat Rev Drug Discov 3: 711-715 (2004)

History of drug Development at Otsuka

Otsuka-people creating new products for better health worldwide

Otsuka Original New Drugs

- 1980 **Carteolol (1980)**
Procaterol (1980)

Cilostazol (1988)

- 1990 **Rebamipide (1990)**
Vesnarinone (1990)
Nadifloxacin (1993)

- 2000 • **Delamanid**
Synthesized (2001)

↓

Approval (2014, EU and JP)
(Anti-Tuberculosis)

- 2010 **Brexpiprazole (2015)**

～2000

DMPK studies in Discovery Stage

- Animal PK
- In Silico
- Membrane permeability
- Metabolic stability
- P450 inhibition and induction
- Transporter
- Reactive metabolite
- etc

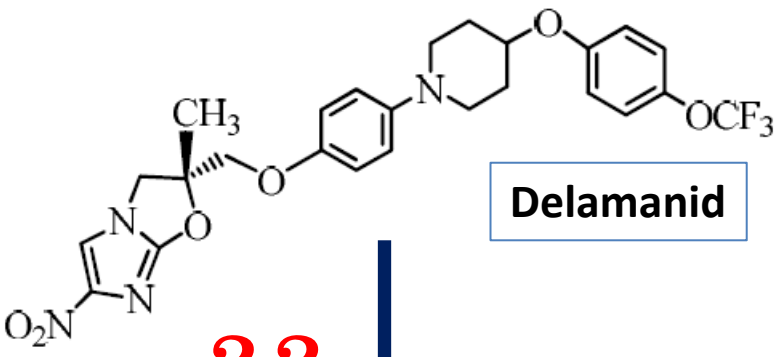
↓

Prediction of human Pharmacokinetics

Delamanid: Metabolism

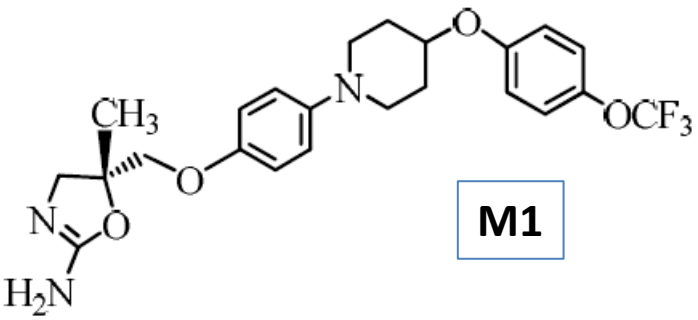
This compound was relatively stable by human liver microsomes in discovery stage.

In vivo Metabolites in Animals

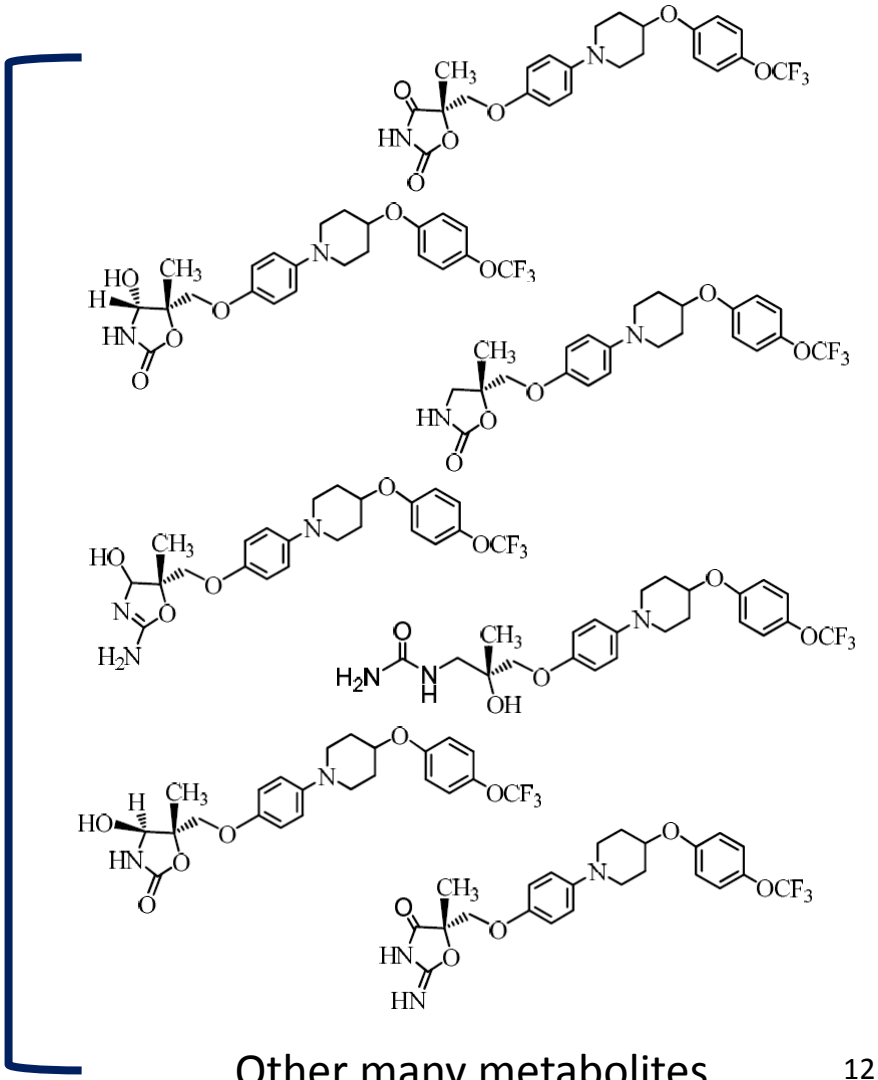


Delamanid

? ?



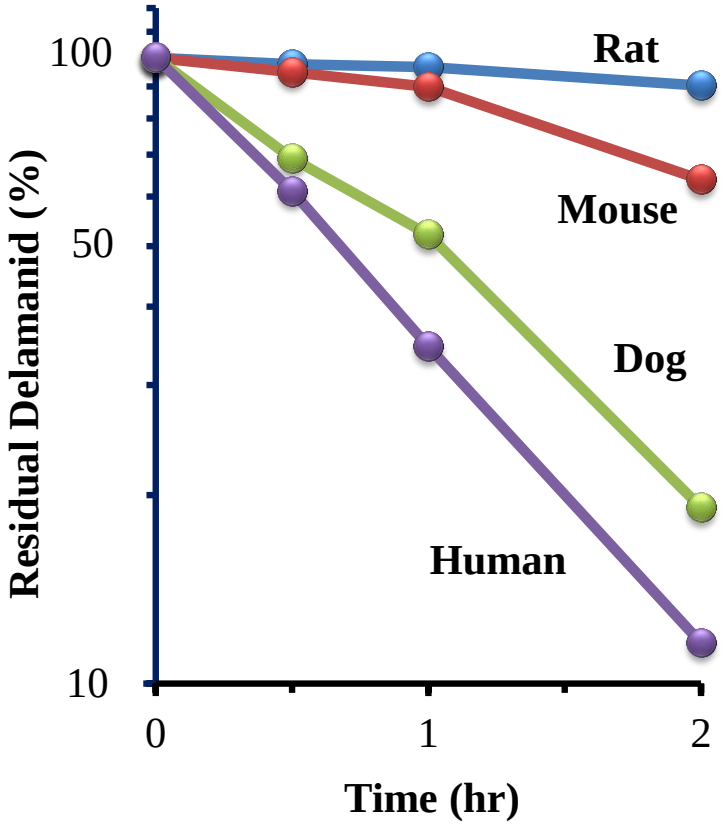
M1



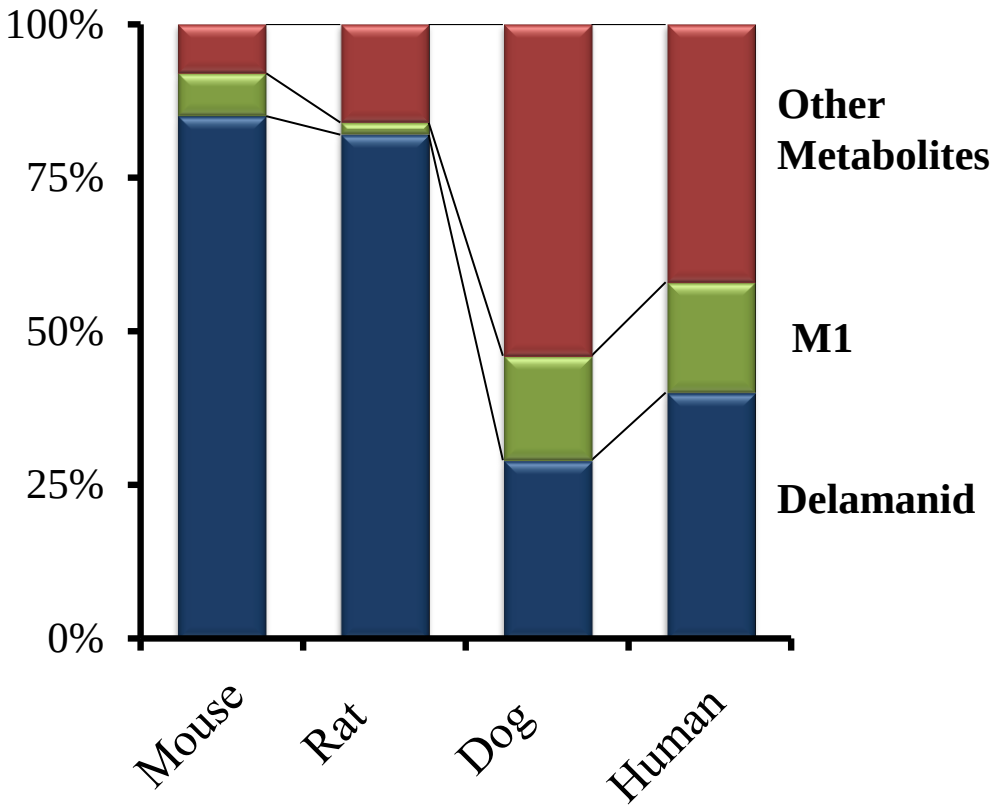
Other many metabolites

Delamanid : Metabolism in Plasma

Stability in Plasma (*in vitro*)



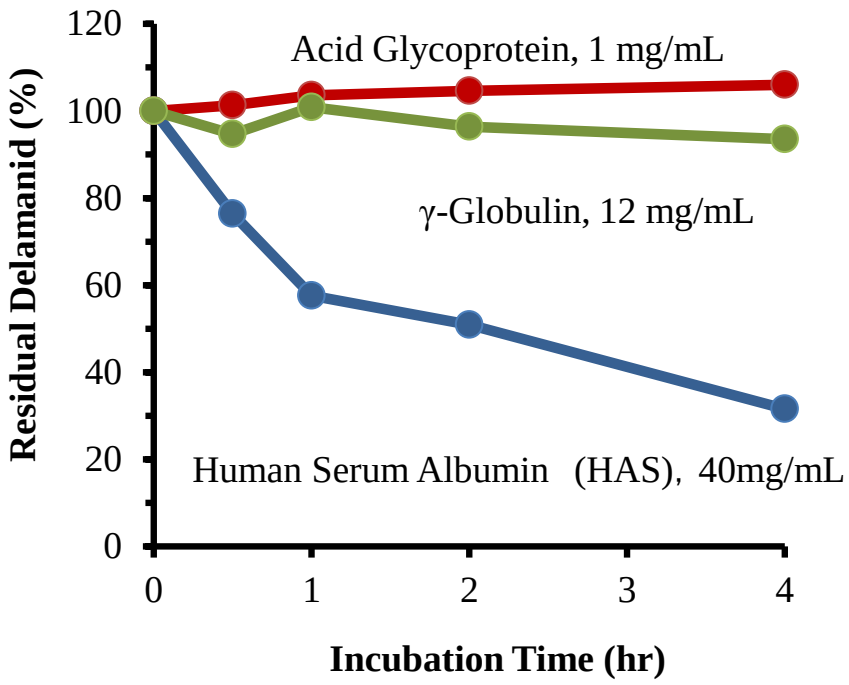
AUC Ratio after Oral Dosing (*in vivo*)



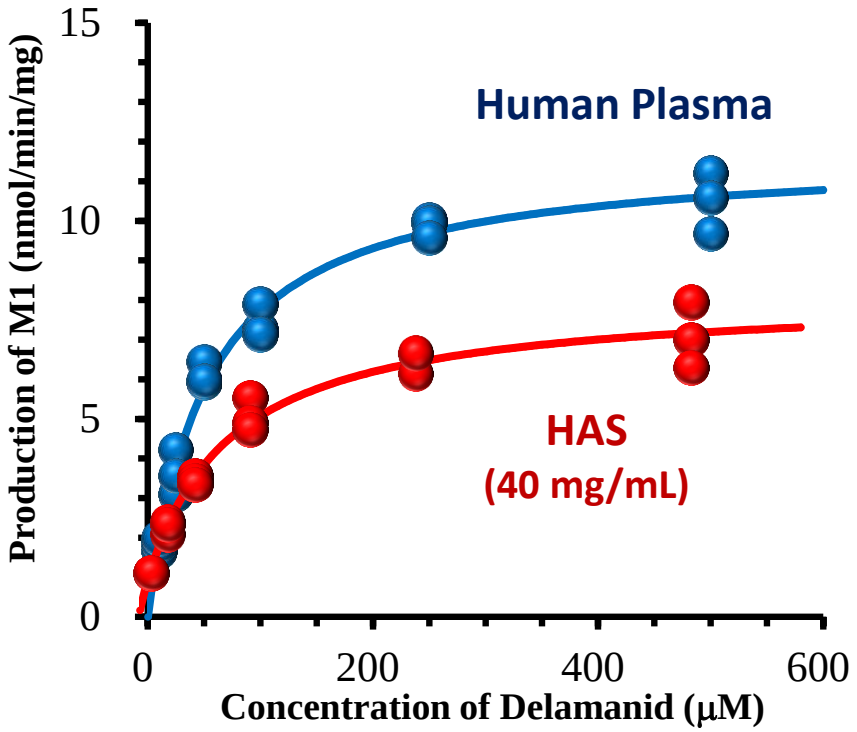
Delamanid is metabolized in Plasma.

Delamanid : Metabolizing Enzyme

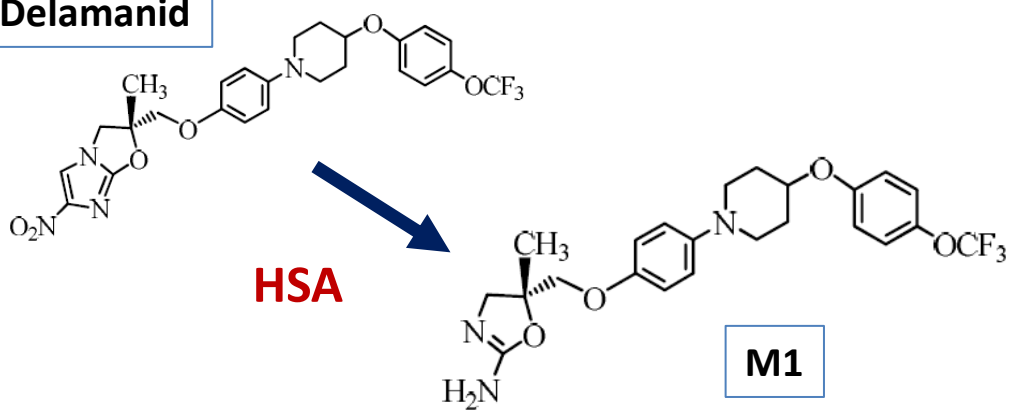
Reaction by purified protein



Kinetic Analysis



Delamanid



Parameter	Plasma	HSA
Km (μM)	68	52
Vmax (pmol/min/mg)	7.6	12
Vmax/Km (μL/min/mg)	0.11	0.23

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Otsuka-people creating new products for better health worldwide

To Researchers in Industries

Drug discovery will become more difficult in the future.

Our mission is to create innovative new medicines for patients in the world.

Let’s create useful medicines.

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I learned many useful things as well as about drug metabolism.
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Otsuka

Otsuka-people creating new products for better health worldwide

Thank you for Your Attention