創薬貢献:北川賞　受賞講演

# A Pursuit of New Drug Discovery and Development

# -　新薬創製の夢を追って -

BRAIZON THERAPEUTICS, Inc.

Masato Chiba, Ph.D.

# Introduction - My Overall Profile


Ph.D.
Japan → Canada/US


## University of Toronto

Post-doctoral Fellow in College of Pharmacy, University of Toronto, ONT, Canada (1991-1993)

Academia → Industry

After graduated Chiba University, worked as a Research Assistant in Biopharmaceutics at Faculty of Pharmaceutical Science (1983-1991)

## Merck Research Laboratories

BANYU


Japan ← U.S.

MERCK

Senior Research Fellow in Drug Metabolism, Merck Research Laboratories, West Point, PA, USA (1993-2000)

TAIHO 大鵬薬品

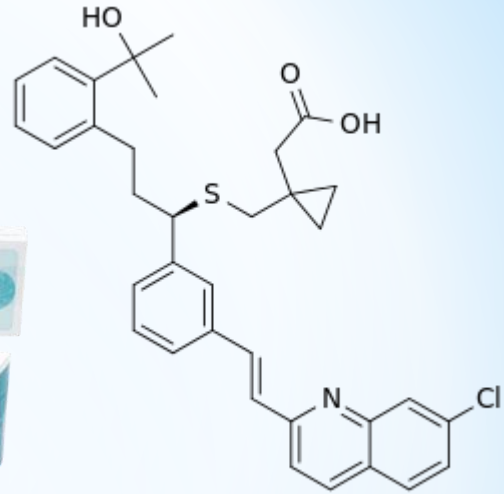
Director for Pre-clinical Drug Metabolism at Banyu (MSD) Research Institute (2000-2009), and the facility acquired by Taiho Pharmaceutical Company (2009), Head of Pharmacokinetics Research Laboratories (- June, 2018).

# Two Products which I was in the development at Merck

## Montelukast (SINGULAIR®)

Leukotriene D4 receptor antagonist
For the treatment of Asthma
1998.2. FDA approved.

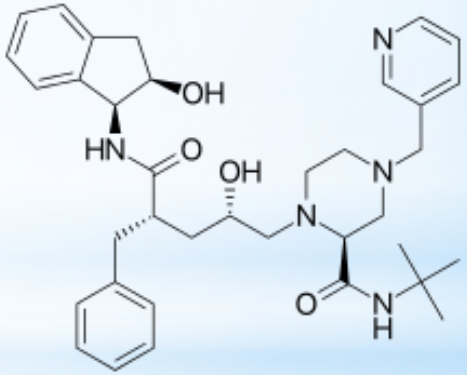
10 mg Once Daily


## Indinavir (CRIXIVAN®)

HIV protease inhibitor
For the treatment of AIDS
1996.3. FDA approved.

800 mg THREE times a day


**Regimen for the other HIV PIs were also OUTRAGEOUS at that time:**

- Saquinavir (Fortovase®);
  **1200 mg, three times a day.**
- Ritonavir (Norvir®);
  **600 mg, twice daily.**

Project was started (in 1994) to discover and optimize the follow-on candidate for HIV protease inhibitor with gentler regimen (fewer frequency of dosing with less dosage) by simultaneous assessments of metabolic stability, metabolic "soft" spot and P450 (CYP3A) inhibition potency (for the first time at Merck Research Laboratories then).

# In the revolutionary times for the change of DMPK roles

MERCK Research Laboratories
Sponsored by Merck Research Laboratories – Boston

## - The dramatic Change of Non-clinical DMPK Roles in the Discovery in 1990' -

Non-clinical DMPK used to mainly collect the excretion/mass balance data, ARG and metabolite profiling in safety animals for IND at the pharmaceutical company ~ 1980 with minimal contribution to the structure optimization…….

Jiunn H. Lin, Ph.D
Senior Director,
Non-clinical DMPK
MRL, Merck

Established Human Liver Bank (microsomes and hepatocytes) at MRL in 1993, and screening flow to optimize DMPK properties such as metabolic stability and CYP inhibition potential by structure modification.

Tadanobu Inaba, Ph.D
Professor, Pharmacology
University of Toronto

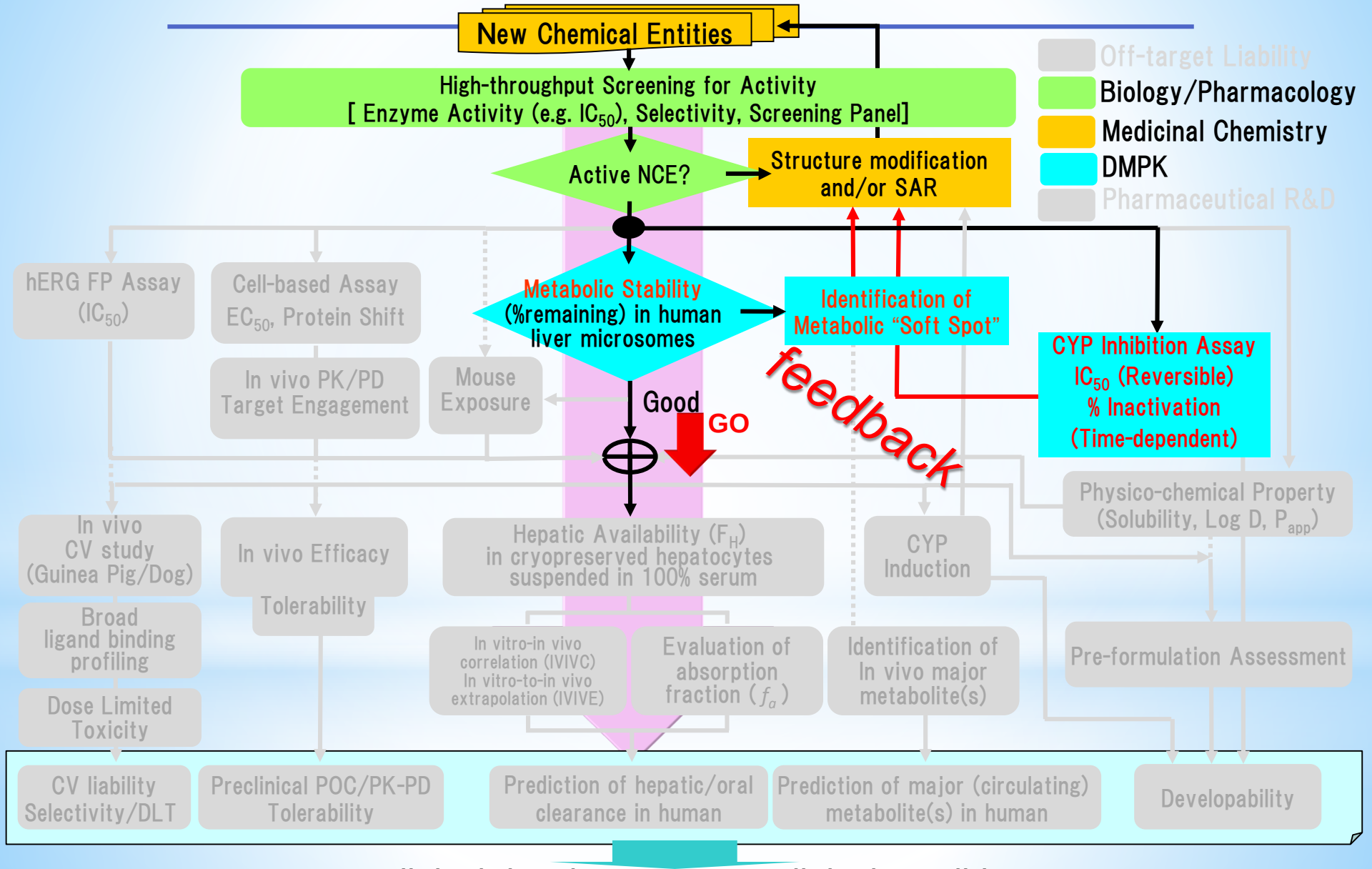
However, almost the same time, commercial supplies of human liver microsomes, cryopreserved human hepatocytes and recombinant CYPs was started at IIAM, Gentest and IVT etc……

Thomas A. Baillie, Ph.D
Vice President,
Drug Metabolism
MRL, Merck

Albert P. Li, Ph.D
Director, St. Louis University
School of Medicine

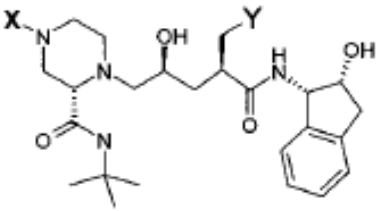
Non-clinical DMPK became a big player in the drug discovery at early optimization stage as it is today !

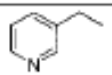
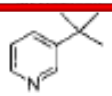
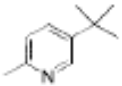
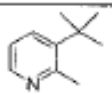
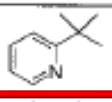
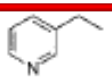
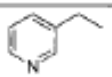
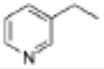
# DMPK Screenings in the Lead Optimization/Profiling Strategy for Clinical Development Candidate

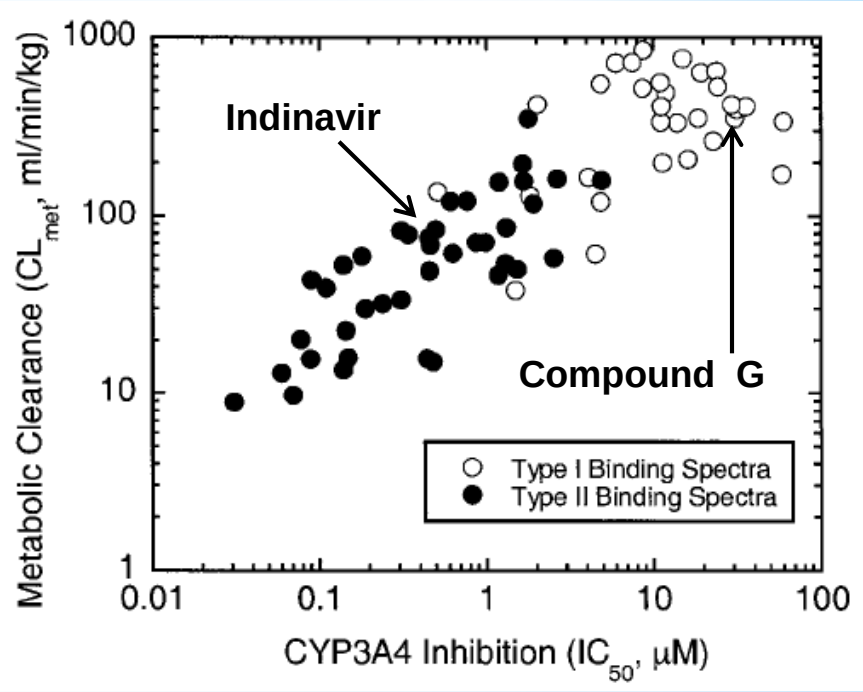



Pre-clinical development as a clinical candidate

# Relationship between Metabolic Stability and CYP3A Inhibition found in the DMPK Screening for HIV Protease Inhibitor Backup

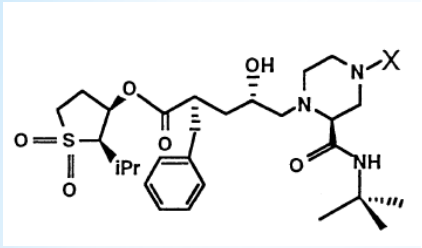


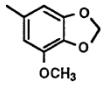
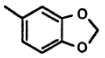
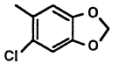

| No. | X | Y | P450 Binding Spectra | Metabolic Clearance (ml/min/kg) | $IC_{50}$ (μM) |
|---|---|---|---|---|---|
| Indinavir |  |  | II | 75.0 | 0.451 |
| I |  |  | II | 71.0 | 0.873 |
| II |  |  | I | 763 | 15.1 |
| III |  |  | I | 854 | 8.70 |
| IV |  |  | I | 636 | 19.3 |
| V |  | H | II | 53.7 | 1.32 |
| VI |  |  | II | 70.7 | 0.990 |
| VII |  |  | II | 61.2 | 0.625 |

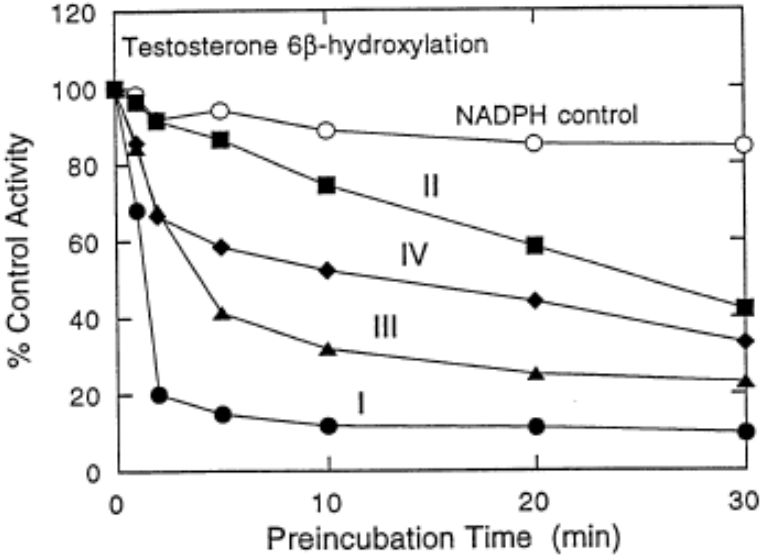


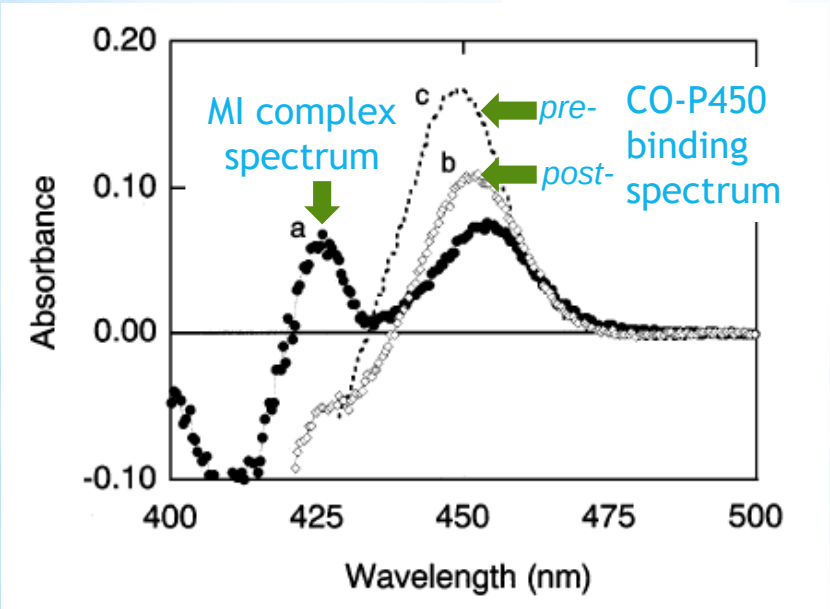

**Chiba M**, Jin L, Neway W, Vacca JP, Tata, JR, Chapman K and Lin JH (2001) P450 Interaction with HIV Protease Inhibitors: Relationship between Metabolic Stability, Inhibitory Potency, and P450 Binding Spectra, *Drug Metab.Dispos.*, **29**: 1-3.

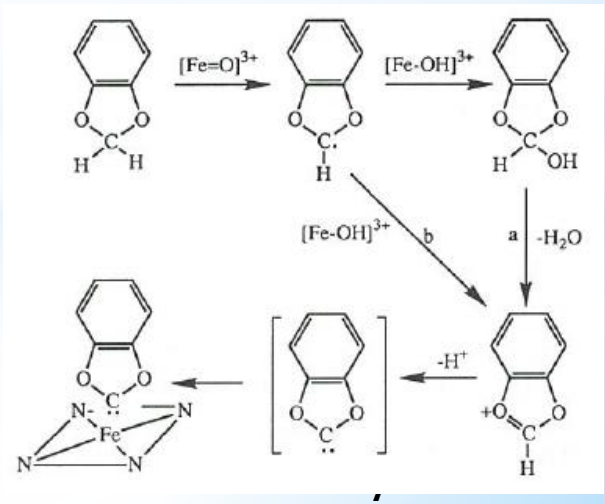
# Quasi-irreversible CYP3A inhibition (MI Complex) by Methylenedioxyphenyl HIV PI Backup found in the DMPK Screening




| X | Compound# |
|---|---|
|  | I |
|  | II |
|  | III |
|  | IV |

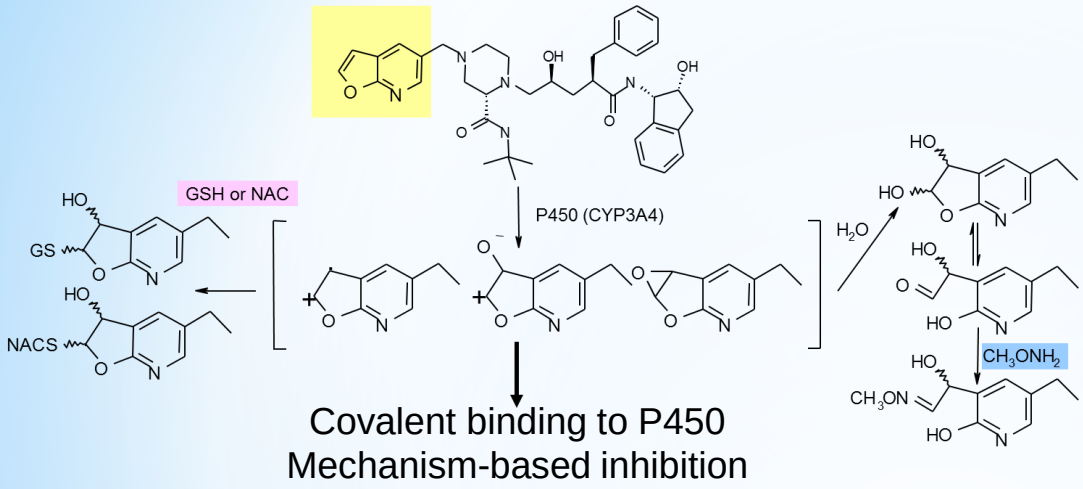


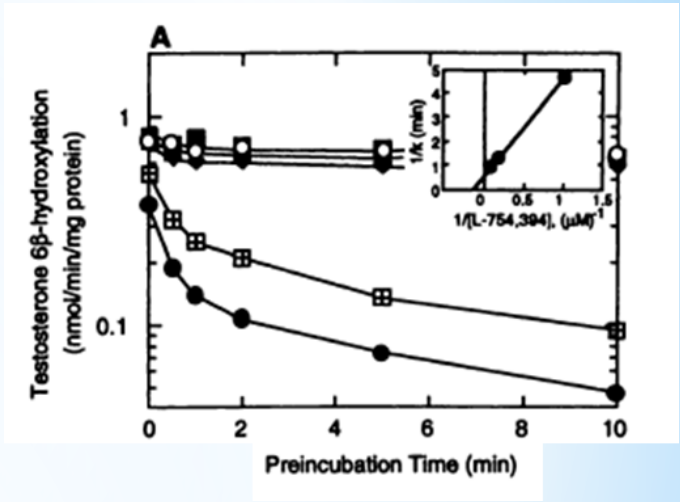




**Chiba M**, Nishime JA, Chen IW, Vastag KJ, Sahly YS, Kim BM, Dorsey BD, Vacca JP, Lin JH (1998) Metabolite-P450 Complex Formation by Methylenedioxyphenyl HIV protease inhibitors in rat and human liver microsomes, *Biochem. Pharmacol.* **56**:223-230.

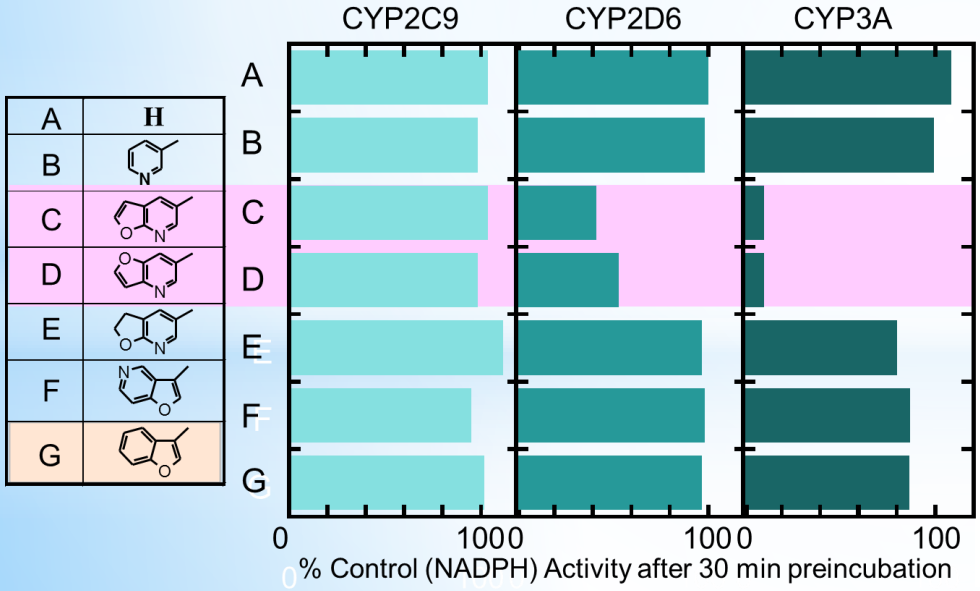
# Mechanism-based P-450 Inhibition – Covalent binding to CYP3A - found in the DMPK Screening for HIV Protease Inhibitor Backup

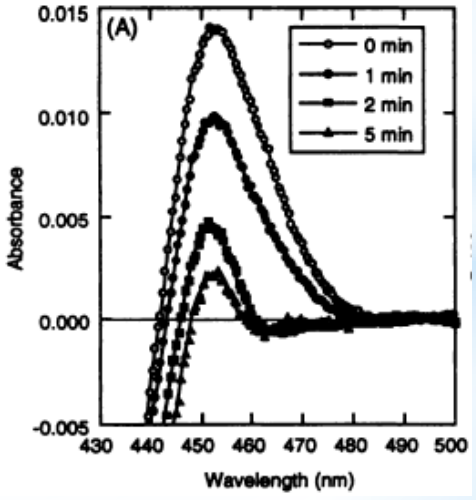


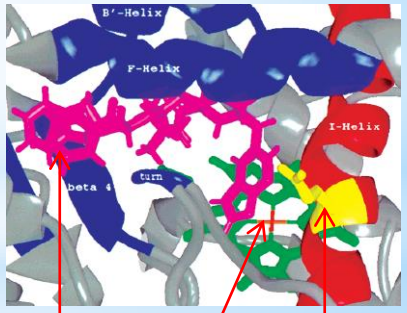

Covalent binding to P450
Mechanism-based inhibition




Lightning LK et al. (2000)
*Biochemistry*., **39**, 4276-4287.



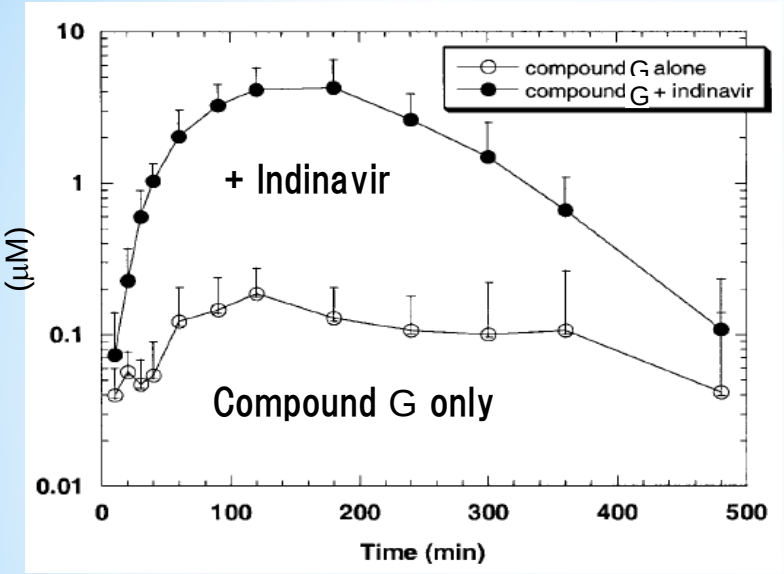

Compound C

**Heme-Iron**

Glu residue (307)

**Chiba M**, Nishime J, Lin JH (1995) Potent and selective inactivation of human liver microsomal cytochrome P-450 isoforms by L-754394, an investigational human deficiency virus protease inhibitor. *J. Pharmacol. Exp. Ther.*, **275**, 1527-1534.

# Combination Regime of HIV Protease Inhibitor with Indinavir as a Plasma Concentration "Booster" by Competitive CYP3A Inhibition in Patients




It was almost impossible to identify the compound which showed a good balance of efficacy (against mutated HIV), and metabolic stability....

| $IC_{50}$ (μM) | Indinavir on G | G on Indinavir |
|---|---|---|
| Rat | 0.10 | 21 |
| Dog | 0.13 | 36 |
| Monkey | 0.16 | 21 |
| Human | 0.17 | 30 |

Compound G metabolically very unstable, but had little inhibition potency for CYP3A. Then, by using high inhibition potential of indinavir to the metabolism of compound G, it was hypothesized that the co-administration of indinavir could boost plasma concentration of compound G.

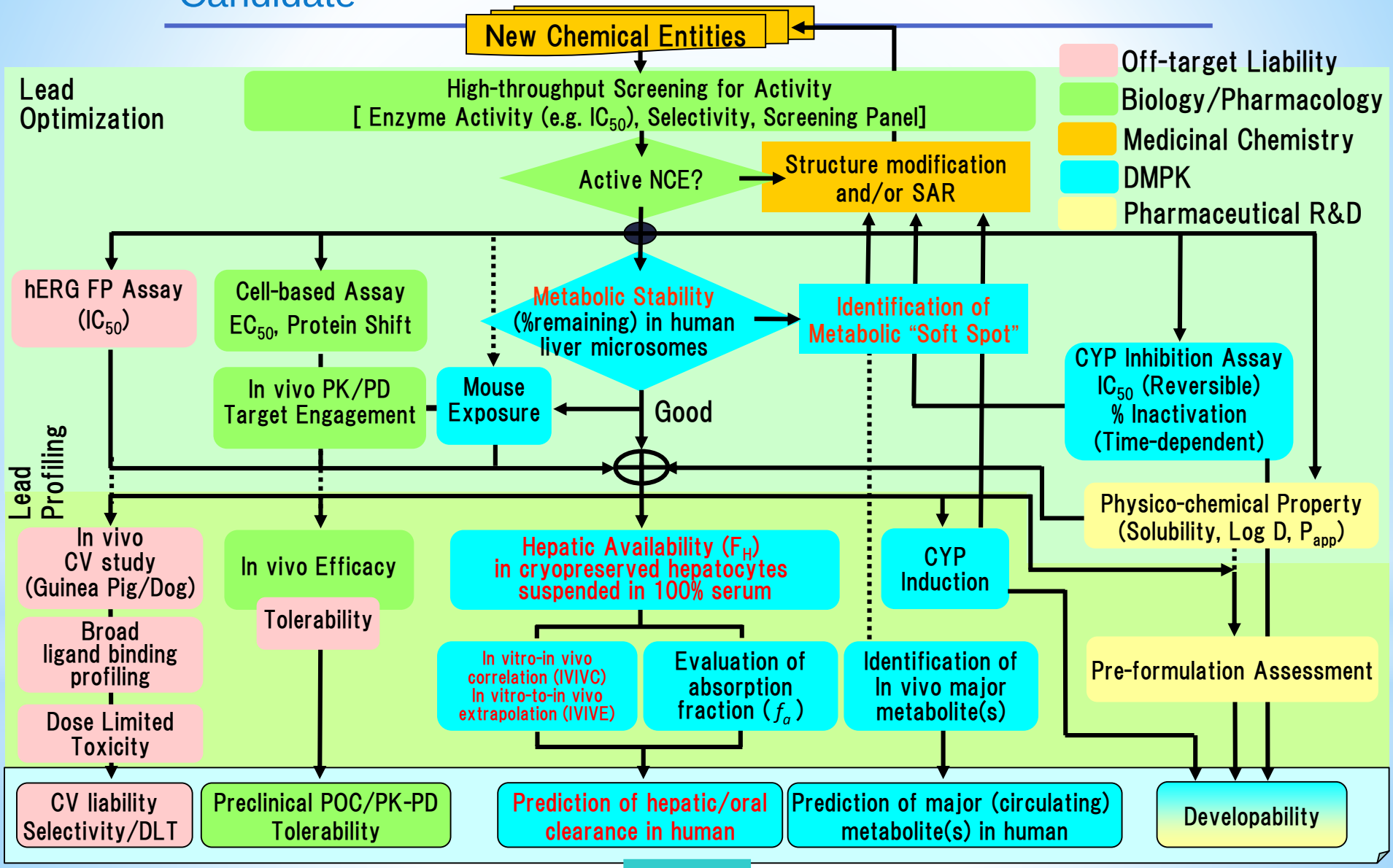
| | Combination | Cmax (nM) | fold | AUC (μMxhr) | fold |
|---|---|---|---|---|---|
| Rat | Compound G (40 mg/kg) | 240 | 19 | 0.9 | 18 |
| | + Indinavir (40 mg/kg) | 4560 | | 15.9 | |
| Dog | Compound G (5 mg/kg) | 7600 | 3 | 19 | 7 |
| | + Indinavir (20 mg/kg) | 21500 | | 133 | |
| Monkey | Compound G (10 mg/kg) | < 30 | 60 | - | - |
| | + Indinavir (20 mg/kg) | 1800 | | 5.9 | |
| Human | Compound G (200mg) | 85 | 24 | 0.24 | 31 |
| | + Indinavir (800 mg) | 1576 | | 7.45 | |

It was confirmed that the boosting effect was observed in clinical as well as in non-clinical studies (rat, dog, monkey).

Gentle regimen (**Compound G**/Indinavir: 200 mg/800 mg once daily) was established in Phase II (POC study) !!

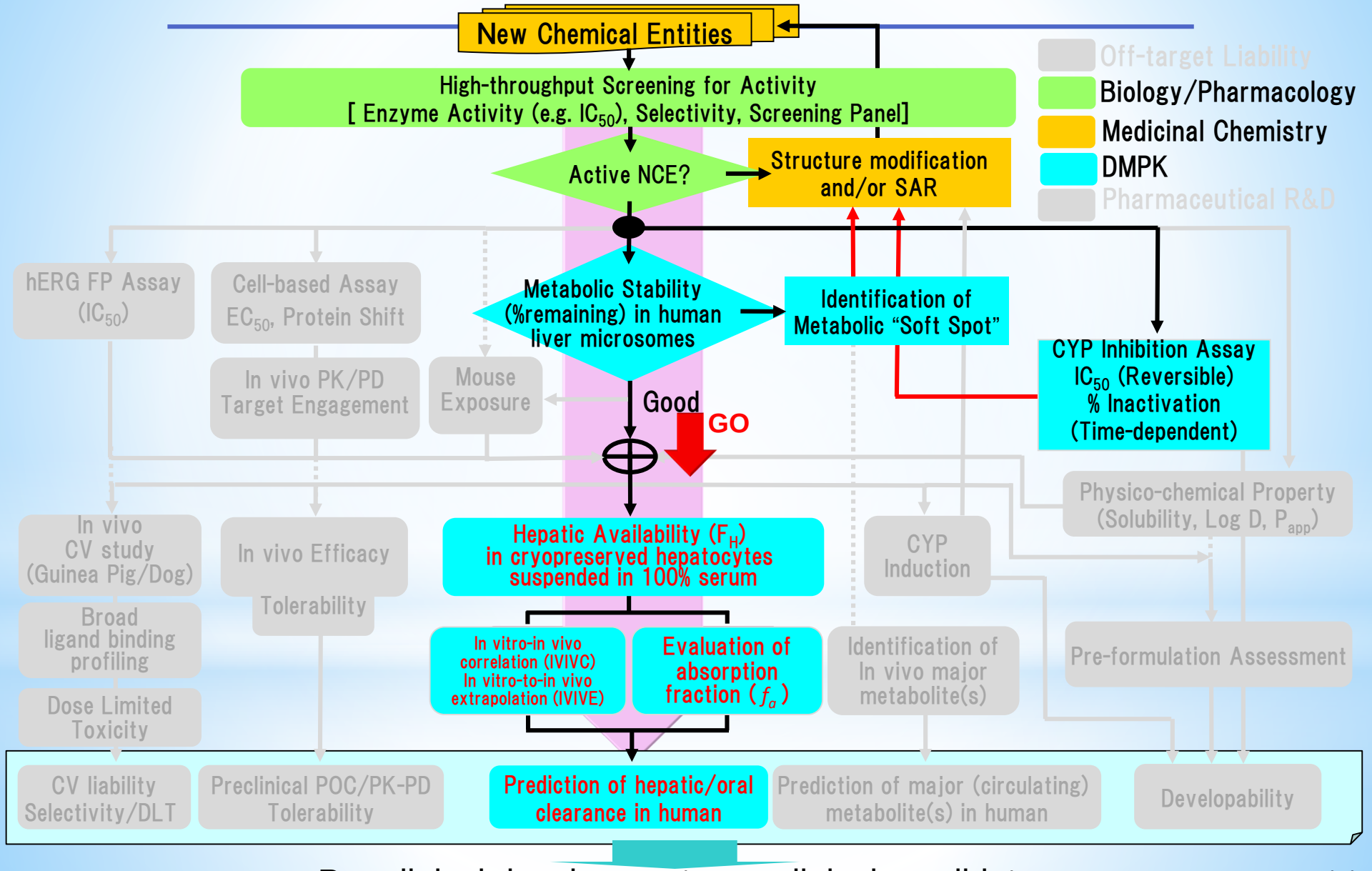

Jin L, Chen I-W, **Chiba M,** Lin JH (2003): Interaction with indinavir to enhance systemic exposure of an investigational HIV protease inhibitor in rats, dogs and monkeys. *Xenobiotica* **33**, 643-654.

# Lead Optimization/Profiling Strategy for Clinical Development Candidate



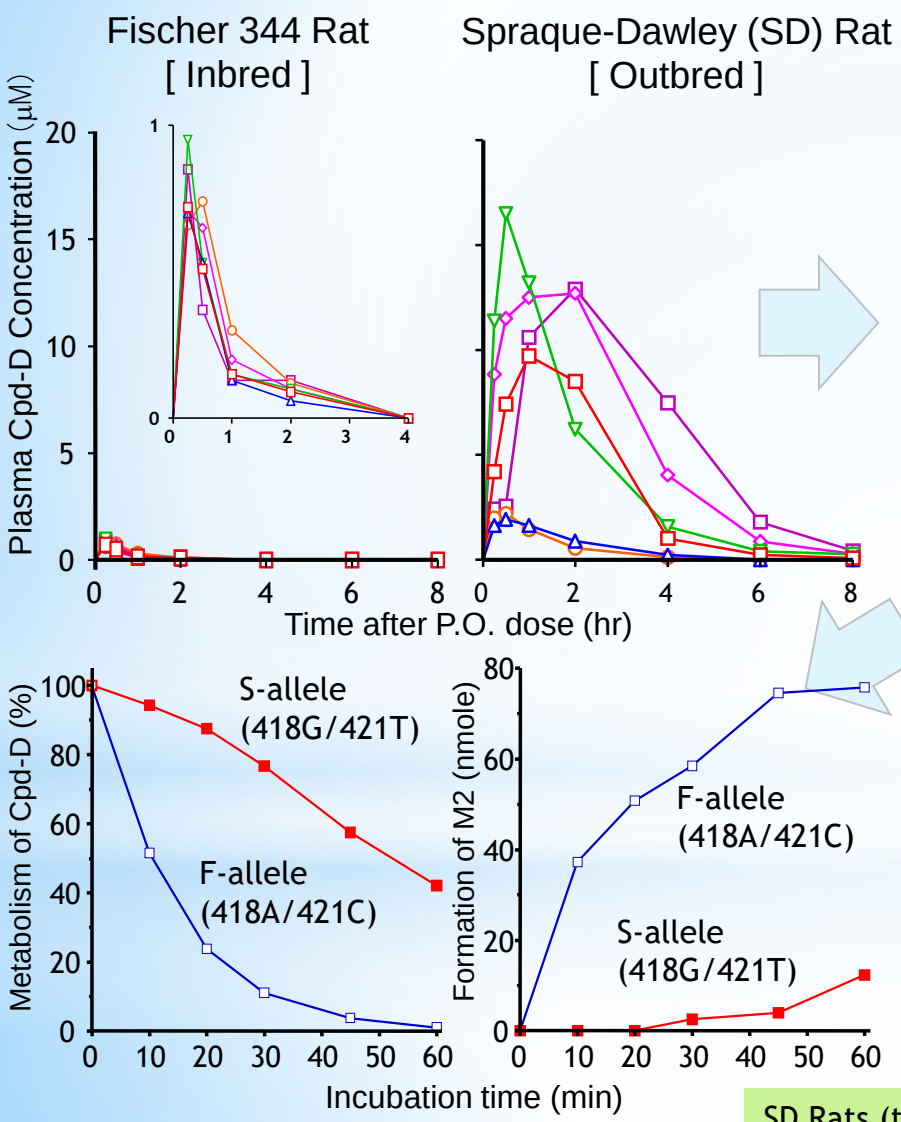

Pre-clinical development as a clinical candidate

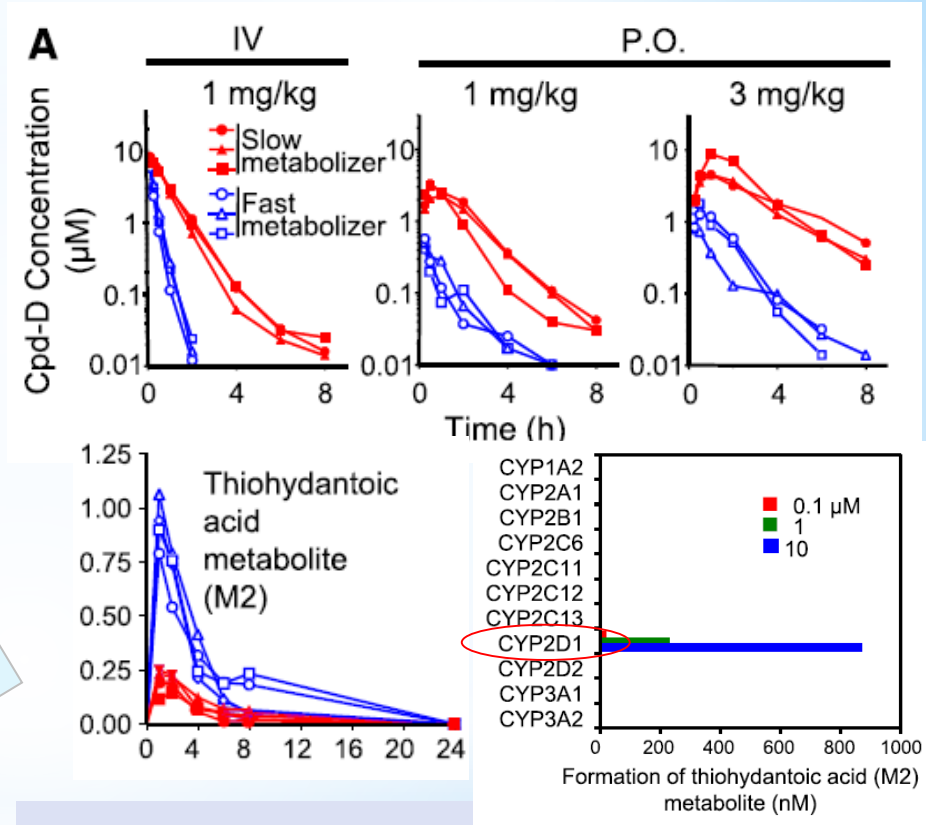
# DMPK Screenings in the Lead Optimization/Profiling Strategy for Clinical Development Candidate




Pre-clinical development as a clinical candidate

# CYP2D1 Polymorphism caused by Nucleotide Substitutions (418A/421C vs. 418G/421T) In Rats




418 421
ATCC
G/ATCT/C } Fast Metabolizer (27%) — IID1v (Matsunaga,1990) db1 (Gonzalez, 1987)

GTCT → Slow Metabolizer (73%) — IID1 (Matsunaga,1989)

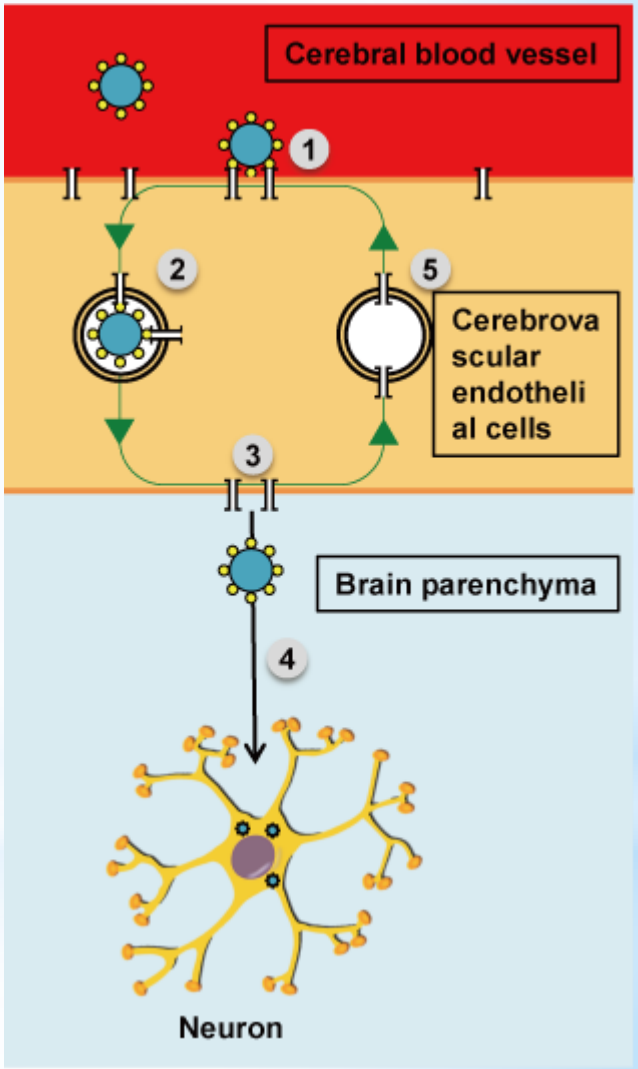
SD Rats (total 476 rats) were genotyped prior to the safety studies of Cpd-D.

Hasegawa T., Eiki J.and **Chiba M.** (2014) *Drug Metab. Dispos.* **42**:1548-1555 (2014).

# My Passion to the Discovery/Development has never died…

BRAIZON THERAPEUTICS

is a bio-venture firm originating from the University of Tokyo and Tokyo Medical and Dental University with the aim of bringing about a paradigm shift in the fields of medicine and life science through the application and implementation of our own innovative technology for the delivery of drugs to the brain.



# Acknowledgement


**千葉大学薬学部 生物薬剤学教室**

鈴木徳治 先生
藤田正一 先生
桝渕泰宏 先生

**トロント大学薬学部**

K.S. Pang 教授

**モントリオール総合病院**

A.J. Schwab 博士
C.A. Goresky 博士

**メルク医薬研究所**

J. H. Lin 博士
L. Jin 博士
D.C. Dean 博士
T.A. Baillie 博士

**トロント大学医学部薬理学**

稲葉忠信 先生

**セントルイス大学医学部**

Albert P. Li 博士

**万有製薬(株) つくば研究センター**

石井康行 博士
D. Schmatz 博士

**大鵬薬品工業(株) 研究本部**

吉末訓弘 博士
北村龍一 博士
山谷英利 博士

岩沢善一 博士

そして共に研究させていただいた皆さんに！