Novel lead optimization strategy using Quantitative Structure-Activity Relationship (QSAR) and Physiologically-Based Pharmacokinetics (PBPK) modeling

Predicting Human PK/ADME/Dose (FIH and beyond) for the First-In-Class or Best-In-Class Drug Candidates by extrapolating from in-silico/in-vitro/in-vivo preclinical study data

early discovery → candidate nomination

- 'cold' ADME studies
- cassette IV PK
- HTS CLint
- HTS PPB
- Papp

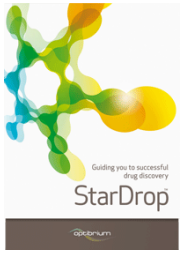
- establish mechanism of elimination
- look for IVIVC
- follow up on cases where IVIVC 'should' work but is not

E.g., ABT or BDC Studies

- single dose PK in preclinical species
- Tier 2 PPB
- Tier 2 CLint
- in silico (fu,mic, Log P/D, pKa, etc.)
- initial PK-PD studies
- in vitro and in vivo met ID

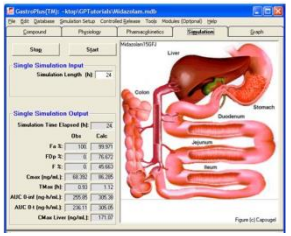
- continual refinement of human PK prediction
- Initial human dose estimate (if early PK-PD are available)
- IVIVC/E refinement

- radiolabeled ADME in preclinical species
- measured blood:plasma and fu,mic
- reaction phenotyping
- quantitative rCYP data
- FaSSIF/FeSSIF on developable drug forms
- transporter information
- in vitro CYP DDI
- Dose proportionality



Phoenix®
WinNonlin®

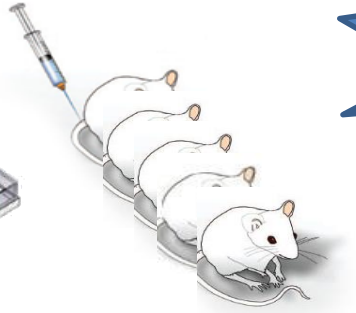
- translational PK-PD model-based human dose and DDI/PGx prediction



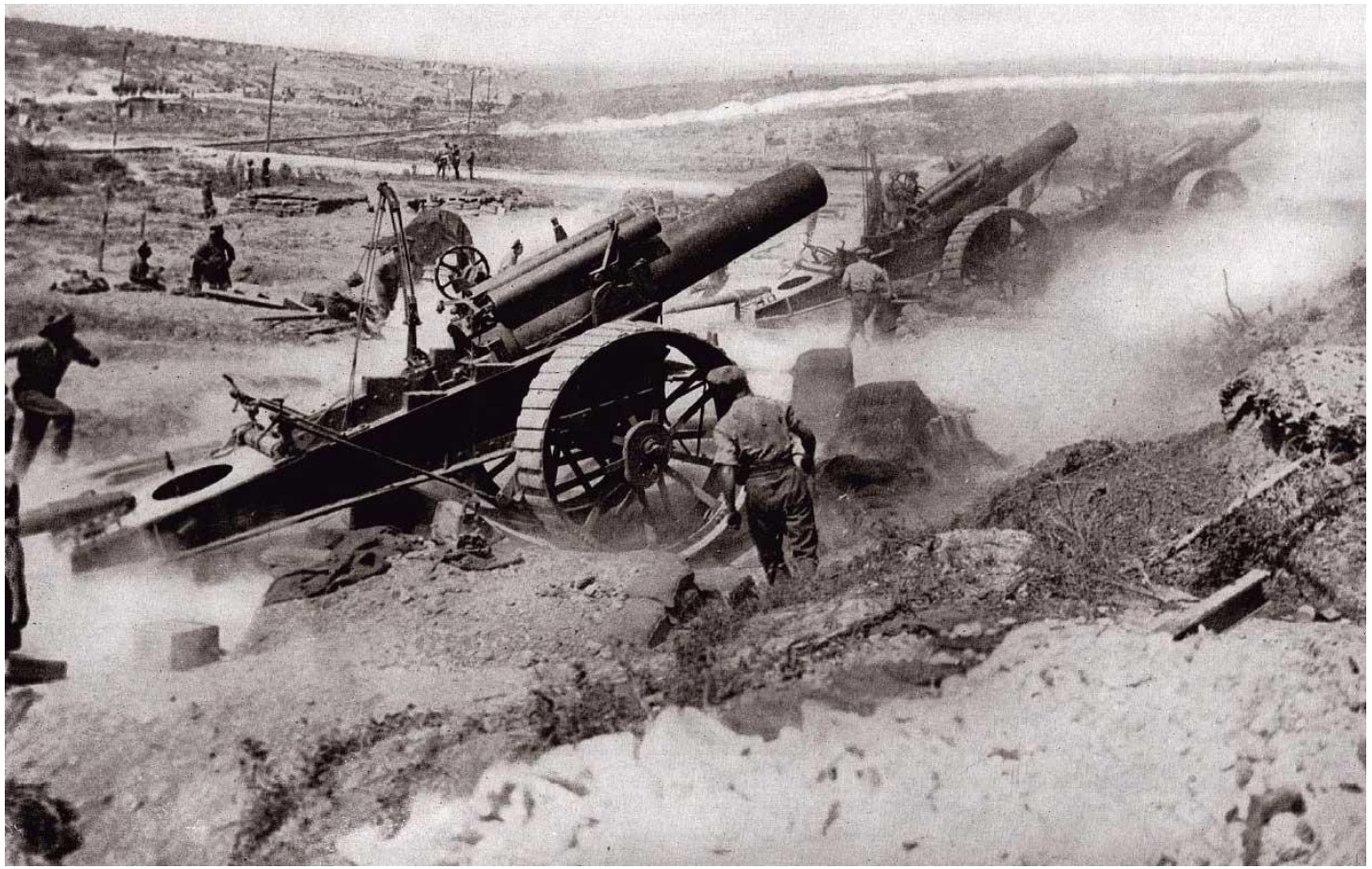
이전의 신약개발 전략

Hit compounds → Tremendous In vitro assay → Tremendous In vivo assay → Candidate

If not appropriate



- ✓ Tremendous cost
- ✓ Many animal sacrifice
- ✓ High labor intensity
- ✓ Much time
- ✓ Uncertainty



Tomahawk cruise missile

These missiles can be launched from U.S. Navy ships and U.S. and British submarines and can carry conventional or nuclear warheads. The U.S. has used them in every major combat operation since Operation Desert Storm in 1991.

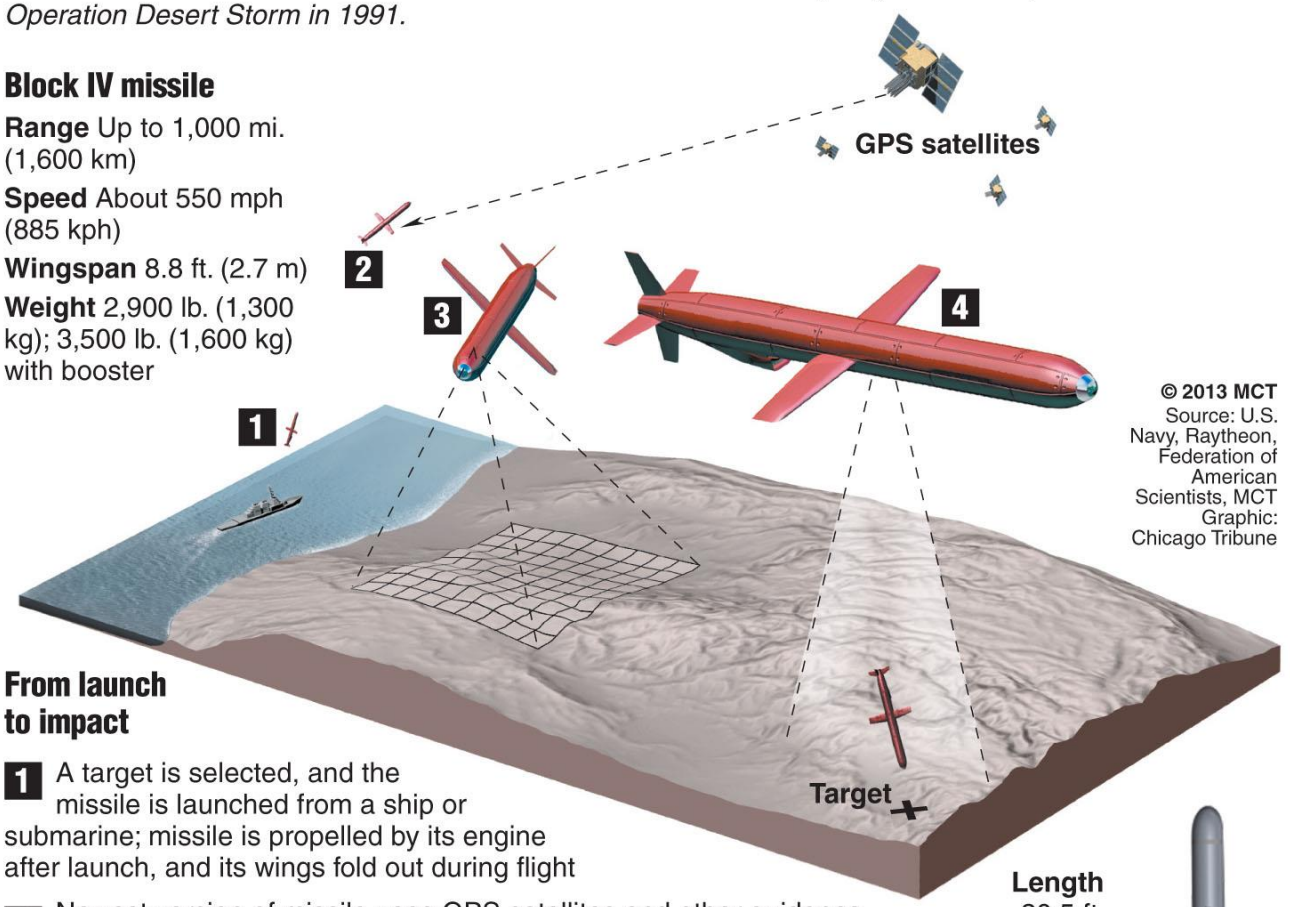
Block IV missile

Range Up to 1,000 mi. (1,600 km)

Speed About 550 mph (885 kph)

Wingspan 8.8 ft. (2.7 m)

Weight 2,900 lb. (1,300 kg); 3,500 lb. (1,600 kg) with booster



Source: U.S. Navy, Raytheon, Federation of American Scientists, MCT

Graphic: Chicago Tribune

From launch to impact

1 A target is selected, and the missile is launched from a ship or submarine; missile is propelled by its engine after launch, and its wings fold out during flight

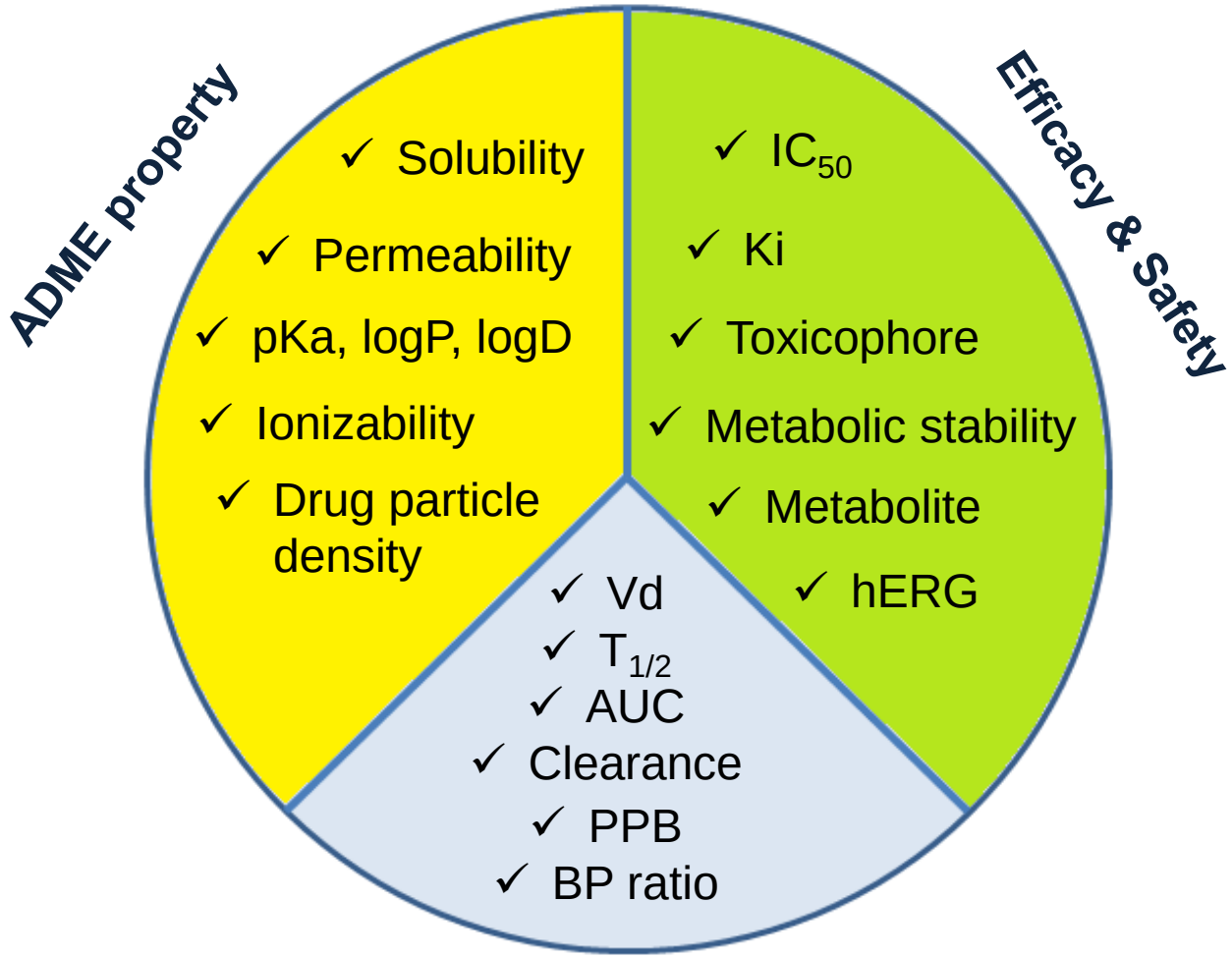
2 Newest version of missile uses GPS satellites and other guidance systems for navigation; can be redirected to new target while in flight

3 Missile can take image of target or other areas of interest during flight and "loiter" near target before striking

4 The missile can strike a fixed or moving target

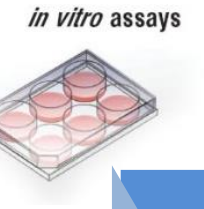
Length 20.5 ft. (6.2 m) (with solid-fuel booster used at launch)

Lead optimization과정에서 고려할 것



ADME property, PK parameter, Efficacy&Safety가 균형을 이룰 때 신약개발로의 발전이 가능

Novel strategy using in silico tools in drug discovery



Hit compounds &

Improved derivatives

ADME property

& Efficacy

& Ranking order

Human PK

prediction

& Candidate

QSAR

QSAR

ADMET Design Suite™

MedChem Studio™

MedChem Designer™

StarDrop™

SIMCYP

real solutions from virtual populations

ADMET Predictor™

MembranePlus™

StarDrop™

GastroPlus™

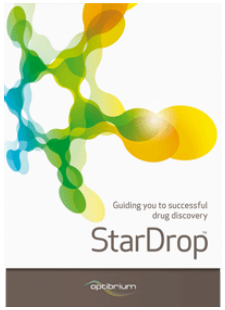
SIMCYP

real solutions from virtual populations

QSAR (Quantitative Structure-Activity Relationship)

✓ QSAR (Quantitative Structure-Activity Relationship) 란?

- 정량적 구조-활성 상관관계.
- Lead compound와 이에 대한 derivatives에 QSAR를 적용하면 화합물의 분자 구조가 갖는 물리화학적 특성에 따른 생물학적 활성 변화를 정량적으로 분석할 수 있음.

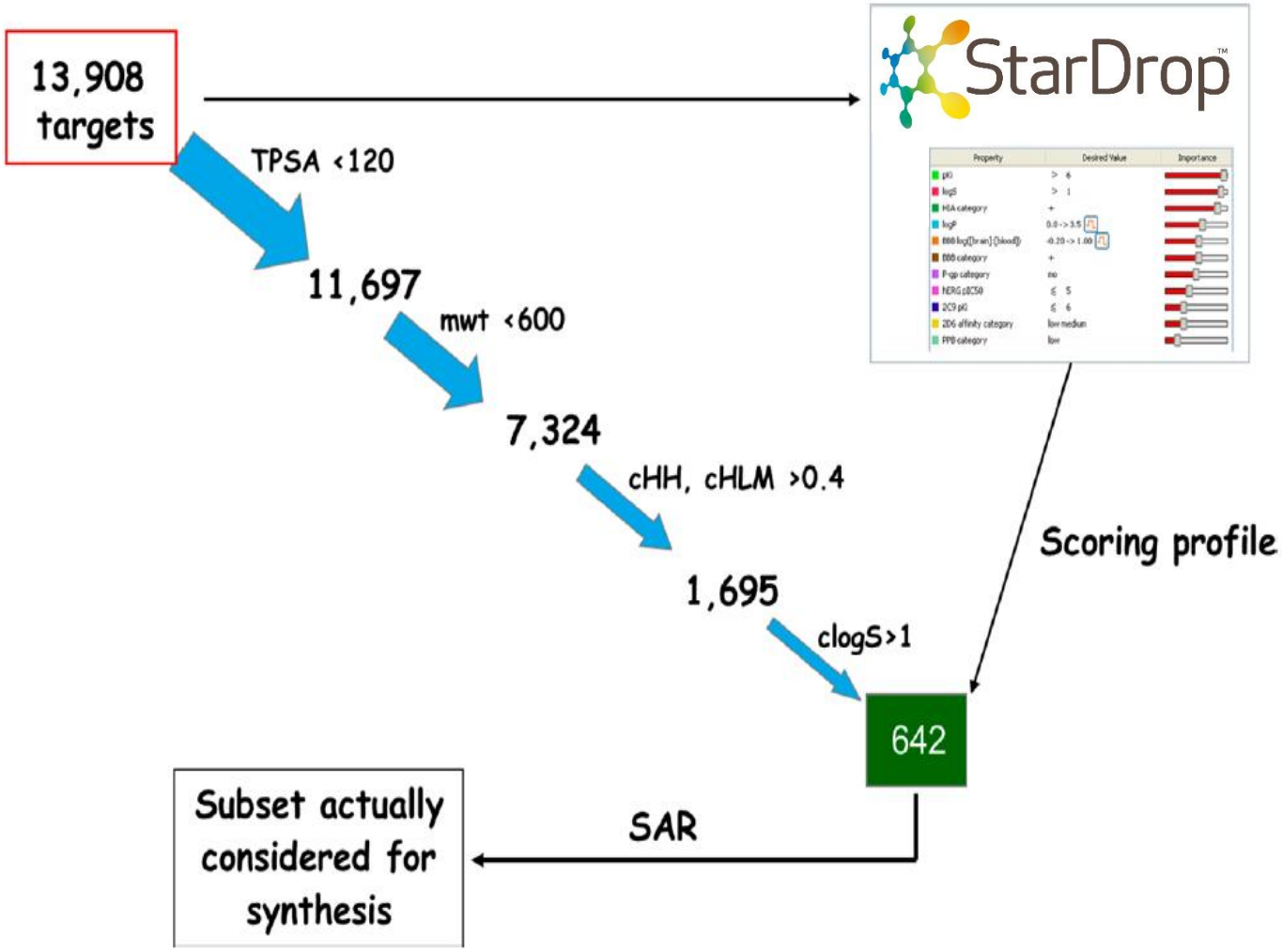


QSAR modeling을 통해 compound의 efficacy, ADME properties를 예측 가능

QSAR modeling을 이용하여 더 나은 compound를 가상으로 합성 가능

QSAR modeling 결과를 이용하여 수 많은 화합물들을 ranking order 가능.

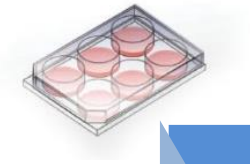
QSAR (Quantitative Structure-Activity Relationship)



Ortwine DF et al., Physicochemical and DMPK In Silico Models: Facilitating Their Use by Medicinal Chemists, *Molecular Pharmaceutics*, 2013, **10**, 1153-1161.

Novel strategy using in silico tools in drug

discovery *in vitro* assays



in vivo assays

Hit compounds &

Improved derivatives

ADME property

& Efficacy

& Ranking order

Human PK

prediction

& Candidate

PBPK

ADMET Design Suite™

MedChem Studio™

MedChem Designer™

StarDrop™

SIMCYP real solutions from virtual populations

ADMET Predictor™

MembranePlus™

StarDrop™

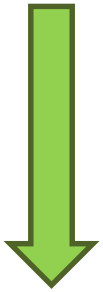
GastroPlus™

SIMCYP real solutions from virtual populations

PBPK (Physiologically-based Pharmacokinetics)

✓ PBPK (Physiologically-based Pharmacokinetics) 란?

- 생리학적 특성을 고려한 약물동태학.
- 약물의 체내 동태를 정확하게 예측하기 위해 생리학적 특성을 고려하여 생체를 구성하는 각 조직 및 장기를 혈류와 연결하여 모델링.



즉, 생리학적 특징, 약물의 특징, 약물과 생체반응의 특징을 modeling에 도입하면 다양한 조건에 따른 혈중농도 및 표적 장기에서 약물농도를 예측가능.

PBPK (Physiologically-based Pharmacokinetics)

Physiologically based pharmacokinetic model (Gastroplus in this case)

SOLUBILITY

PAMPA / CACO 2

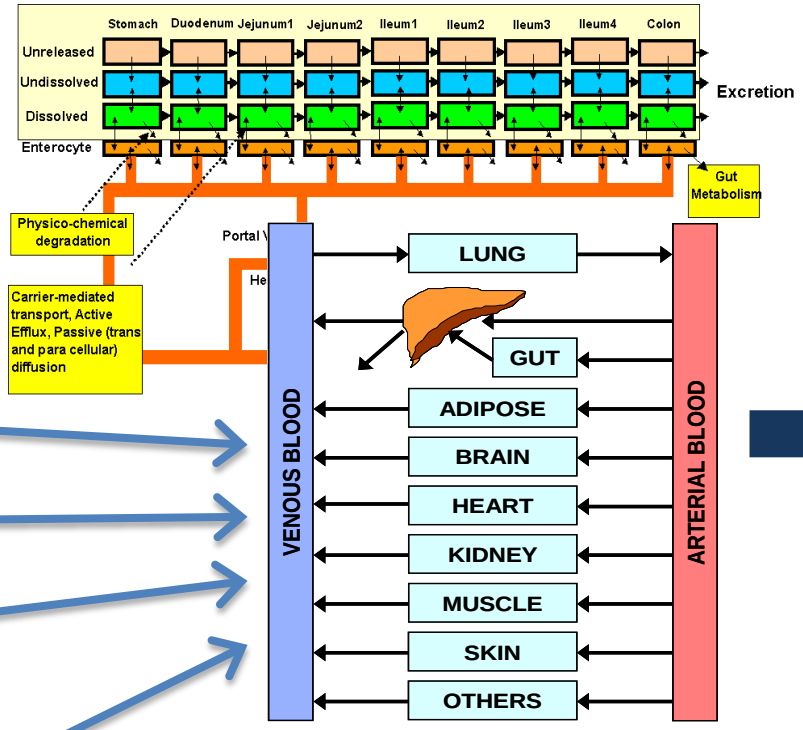
MOL WEIGHT

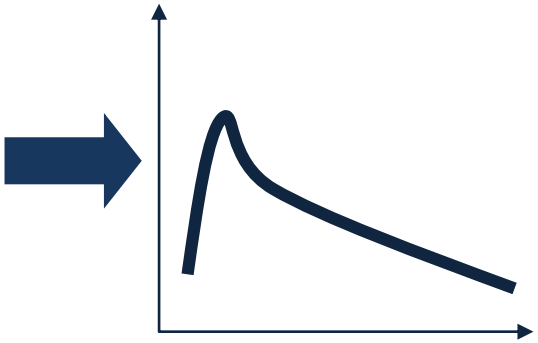
pKa / LOG D / P

PLASMA BINDING

B:P RATIO

MICROSOMAL Clint or In Vivo CL





Advantages for using computational simulation in drug discovery

- ✓ 비용대비, 보다 효율적으로 결과 예측
- ✓ In vitro/in vivo resource의 효율적 활용 가능
- ✓ Prospective analysis를 통해 예측 성공률 재고
- ✓ Retrospective analysis를 통해 모델 재평가, 오류 발견 시 원인 분석
- ✓ 보다 나은 시뮬레이션 모델 확립
- ✓ Early human PK/metabolism read-out을 통해 보다 효율적으로 신약후보물질 도출 가능

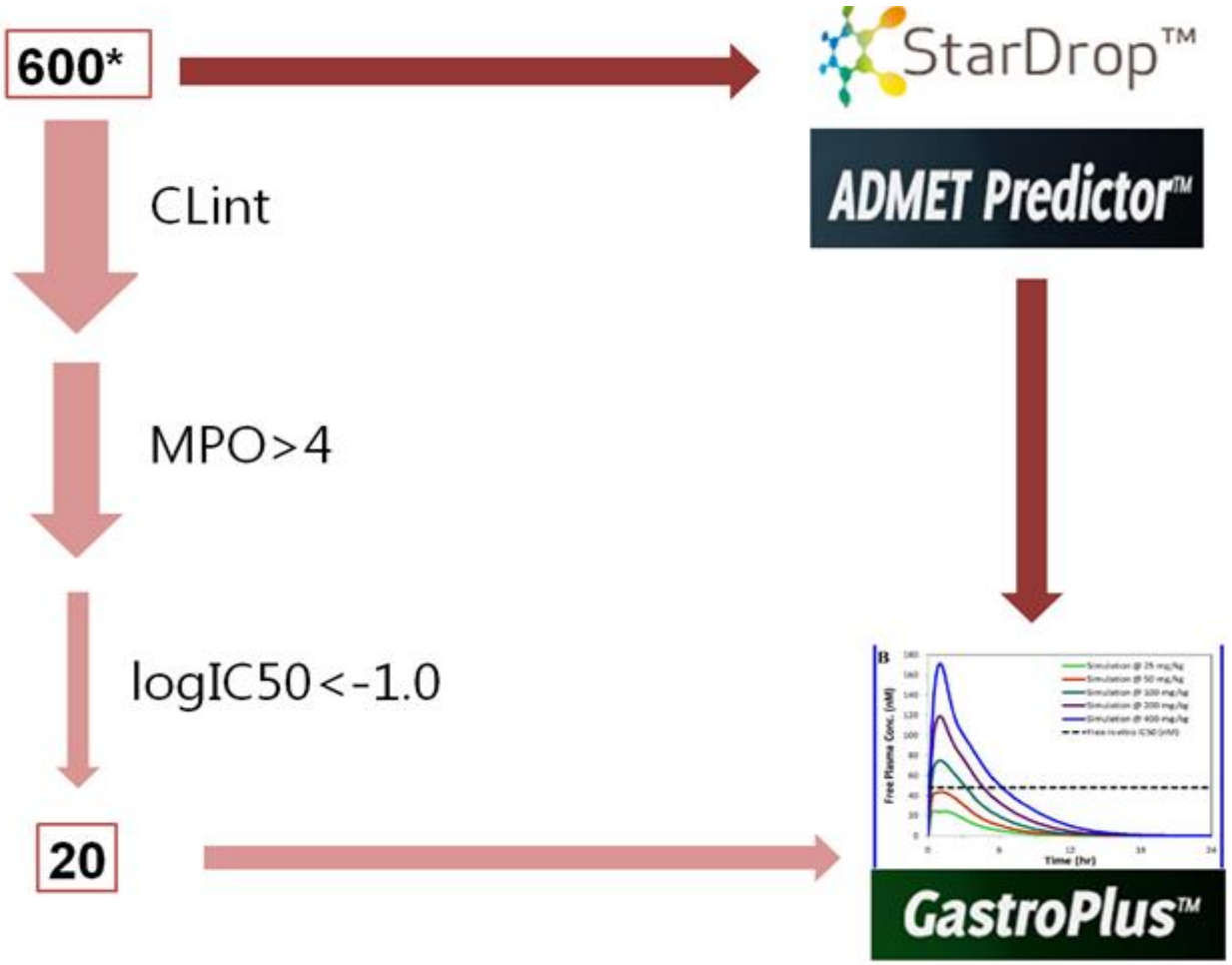
Applications : using StarDrop™ and GastroPlus®

- ✓ 'Discovery of Cyclic Sulfone Hydroxyethylamines as Potent and Selective β-Site APP-Cleaving Enzyme I (BACEI) Inhibitors: Structure-Based Design and in Vivo Reduction of Amyloid β-Peptides' 논문을 참고.

- ✓ 이는 Alzheimer's disease (AD)의 특징인 amyloid-β (Aβ) peptide의 생성을 줄이기 위해 β-Site APP-Cleaving Enzyme I (BACEI) 에 대한 inhibitor를 AD의 치료제로서 제안한 문헌임.

- ✓ 위의 논문에 제시된 화합물과 in vitro efficacy값을 이용하여 StarDrop™을 통해 QSAR모델링을 소개하고, 위의 논문 중 in vivo 결과가 존재하는 화합물을 기반으로 GastroPlus®를 통해 PBPK 모델링을 소개하고자 함.

Applications : using StarDrop™ and GastroPlus®



*over 100,000 compounds can be synthesized using virtual library synthesis

Innovative CNS drug discovery strategy using in silico tools

Applications : using StarDrop™ and GastroPlus®

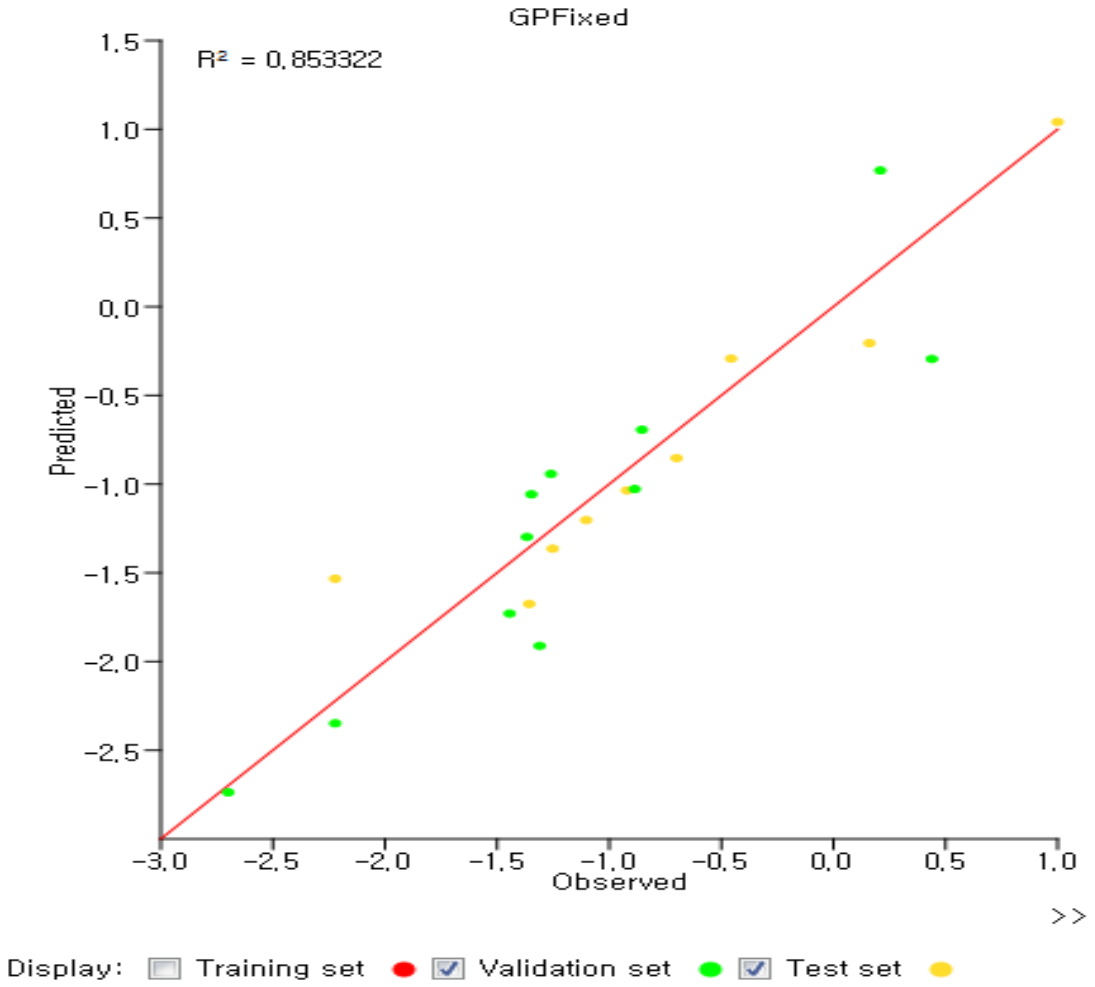


Figure 1. Development of an user-defined QSAR model for IC_{50} prediction using StarDrop Auto-Modeller™. The best predicted model was produced by the GPFixed algorithm. (R^2=0.85 ; validation set and test set).

Applications : using StarDrop™ and GastroPlus®

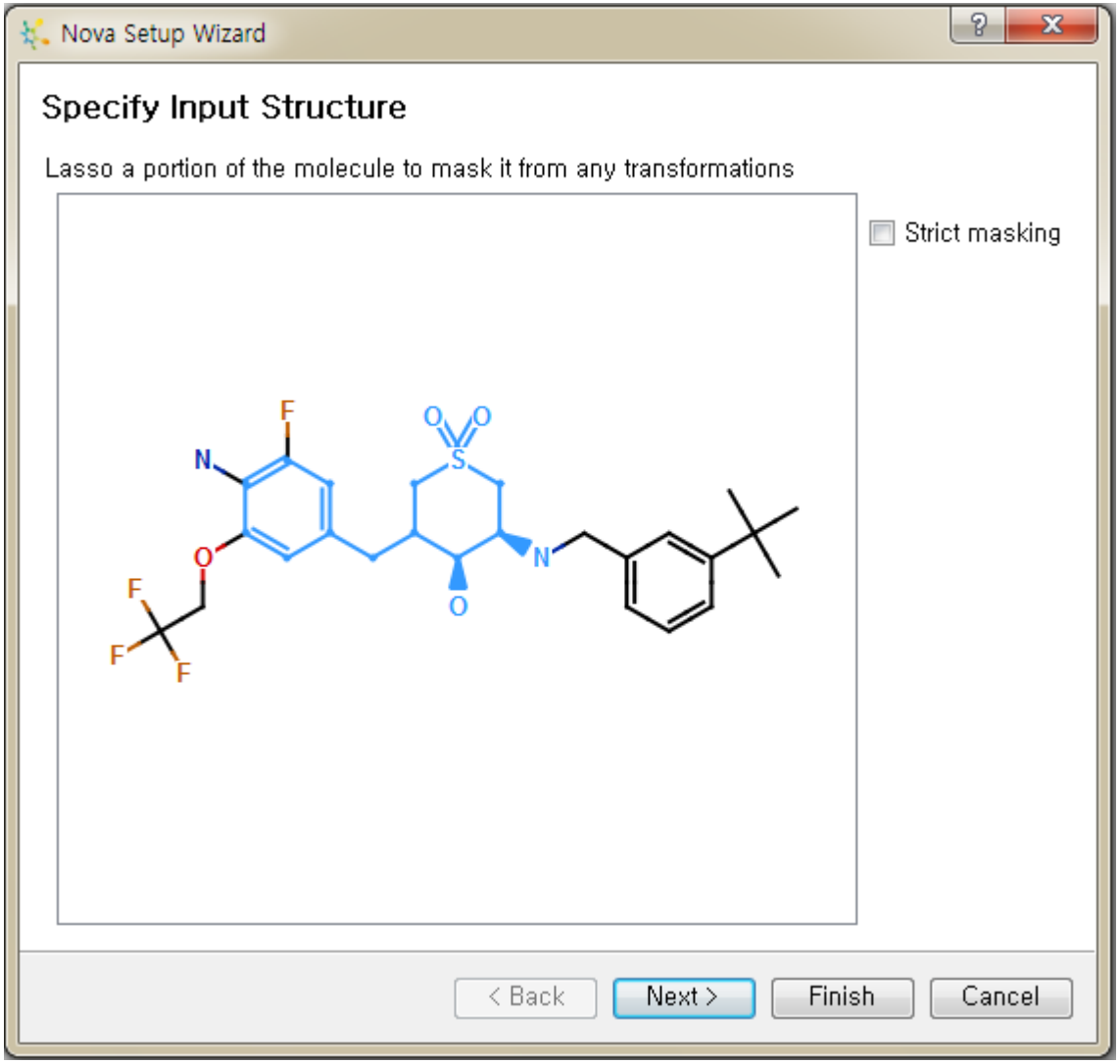


Figure 2. In silico generation of new library compounds using StarDrop Nova™

Applications : using StarDrop™ and GastroPlus®

MPO = ∑Score (clogP + clogD + PSA + MW + HBD + pKa)

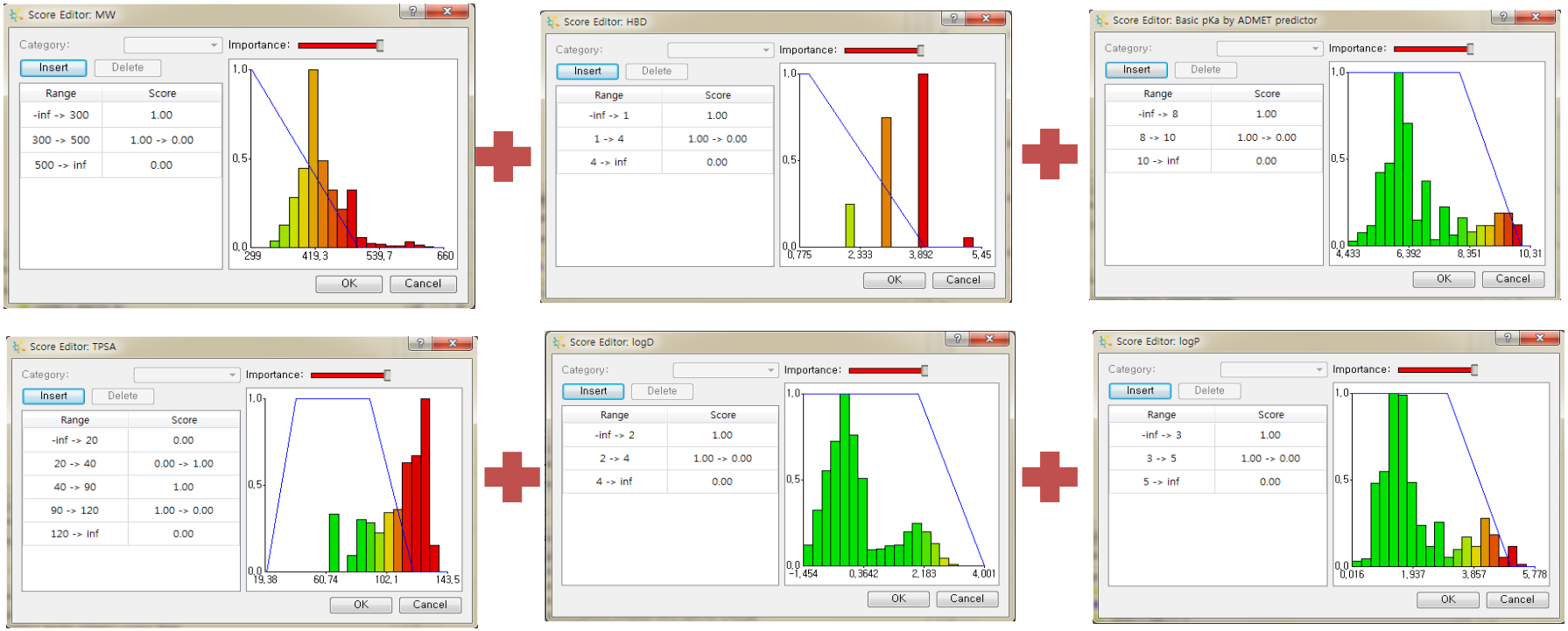


Figure 3. Production process of CNS Multi-Parameter Optimization(MPO) score.

Applications : using StarDrop™ and GastroPlus®

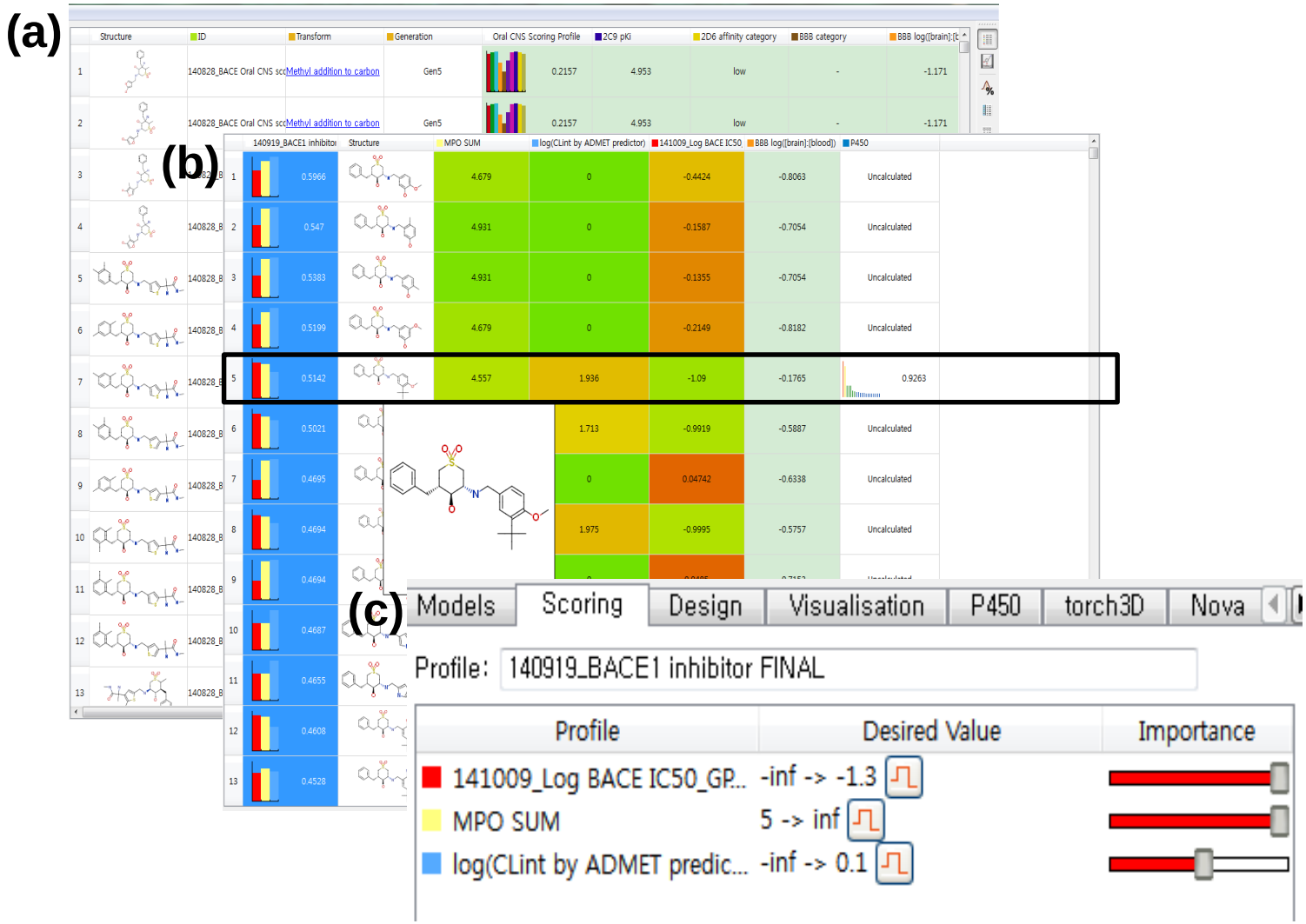


Figure 4. (a) 626 compounds virtually generated using StarDrop Nova™. (b) Compounds rank-ordered based on the composite scores. (c) The composite scoring rule used for BACE-1 inhibitors.

Applications : using StarDrop™ and GastroPlus®

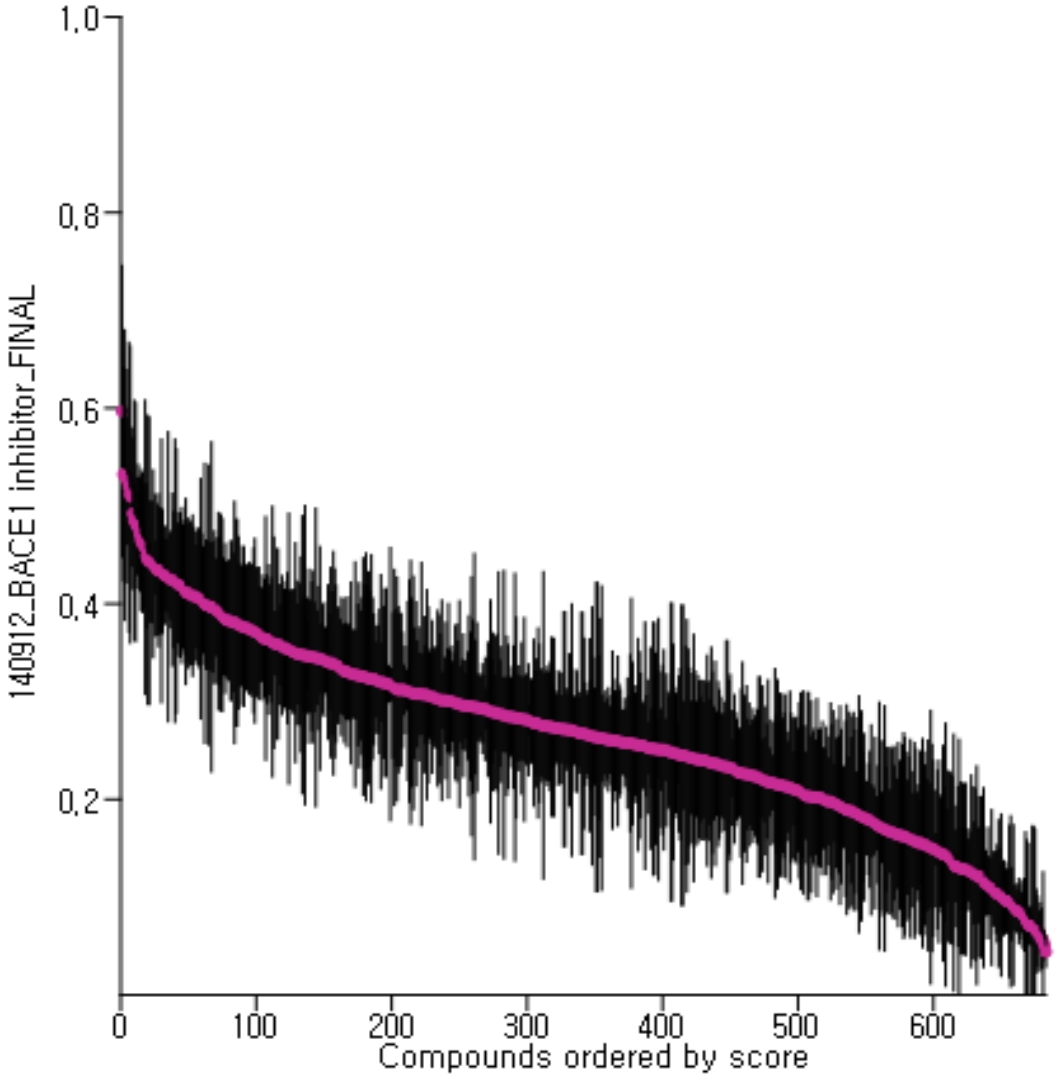


Figure 5. Score distribution of all compounds tested by user-defined scoring rule and global ADME/CNS models.

Applications : using StarDrop™ and GastroPlus®

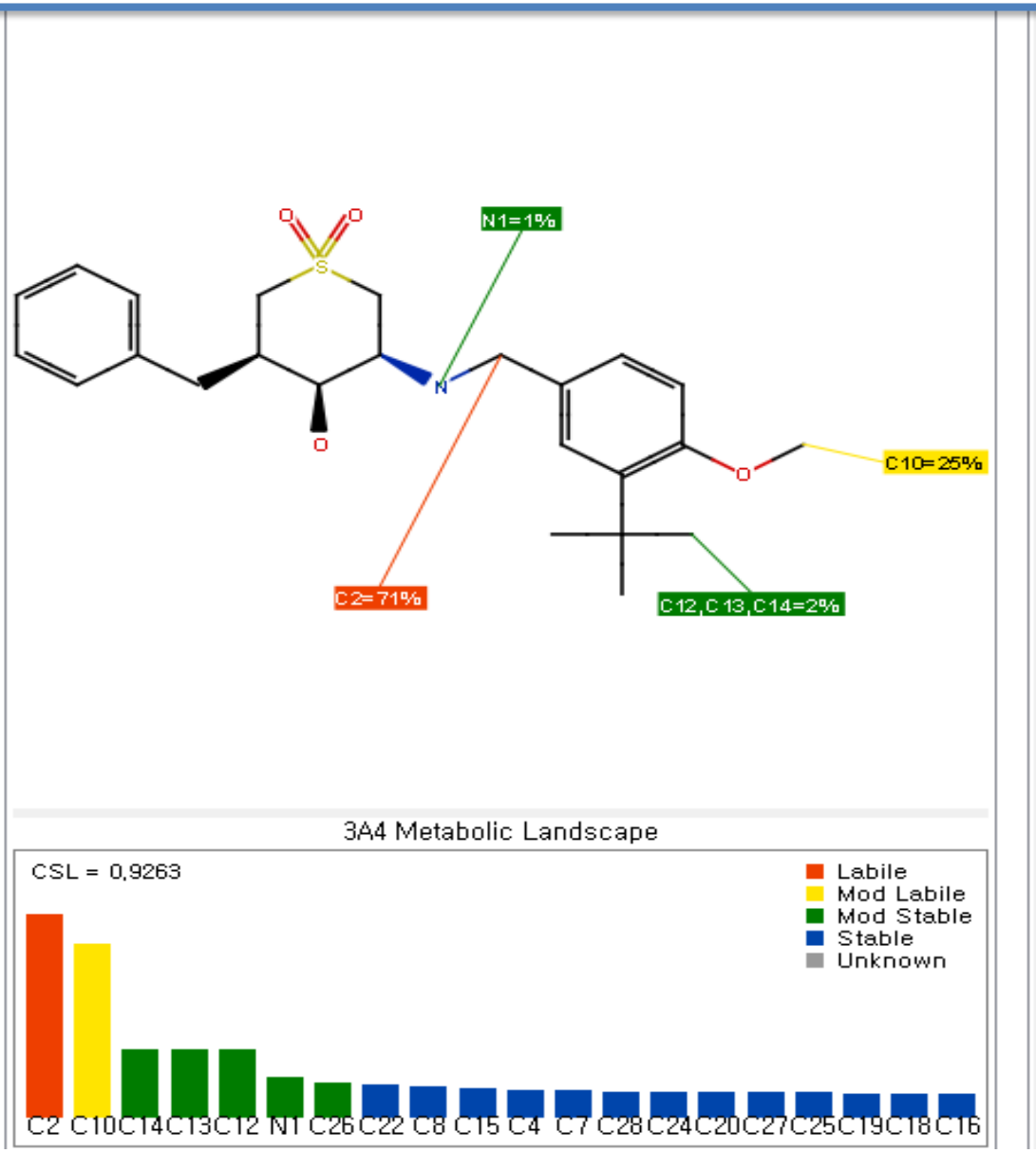
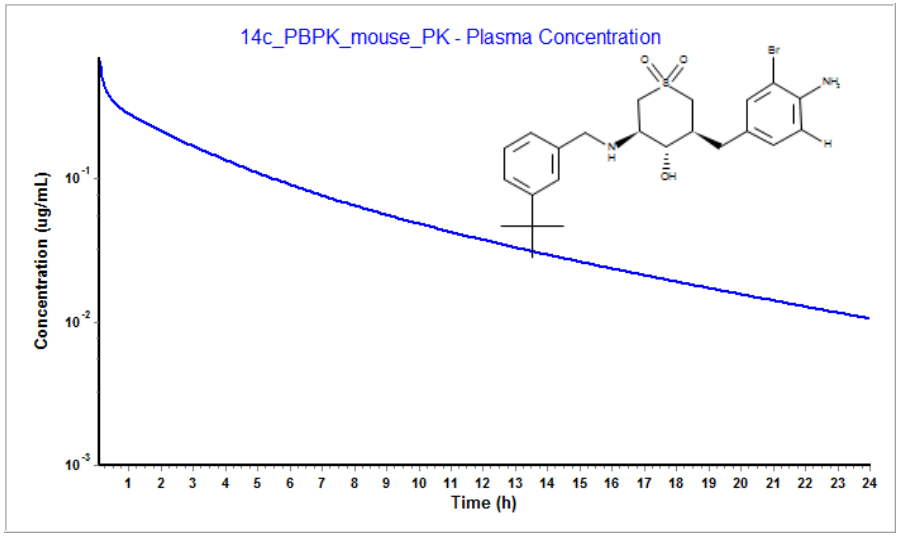
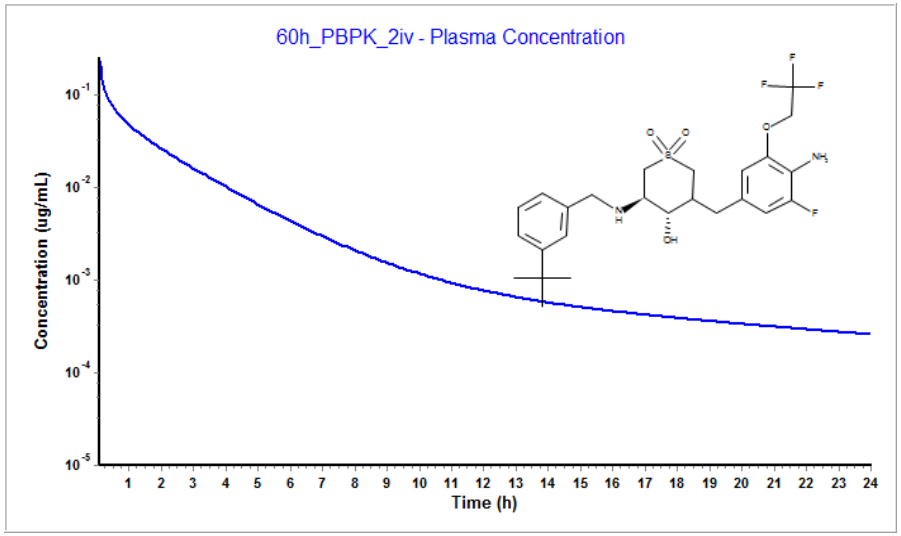
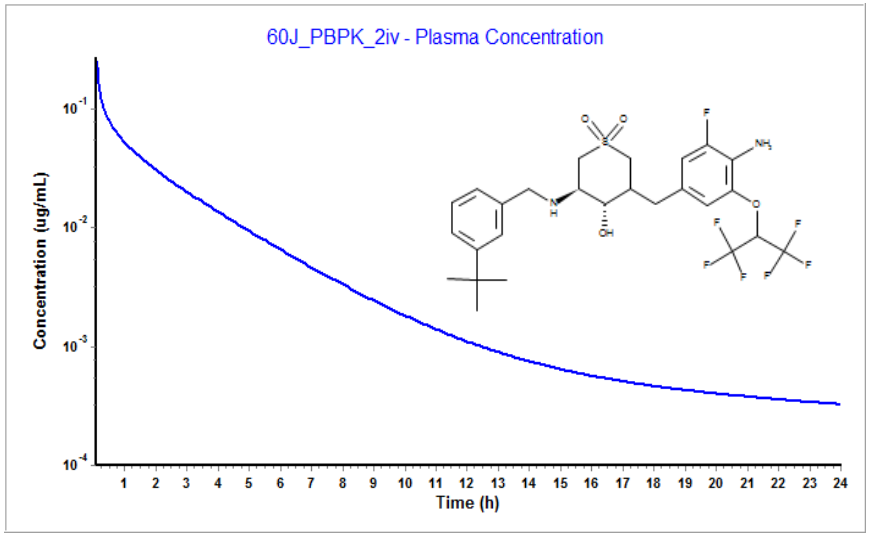


Figure 6. Metabolic soft spot analysis of selected compound using StarDrop P450™.

Applications : using StarDrop™ and GastroPlus®







Result	14c		60h		60j	
	Obs.*	Sim.*	Obs.*	Sim.*	Obs.*	Sim.*
AUC 0-t (ug·h/mL)	2.6	1.9	0.20	0.3	0.3	0.3
Vdss (L/kg)	1.6	2.8	7.2	6.4	16.3	9.5
$T_{1/2}$ (hr)	4.0	4.8	1.4	1.6	2.0	2.4

*Obs. – Observed value, *Sim. – Simulated value

Figure 7. Predictive PK profile at logarithmic scale for 3 compounds(14c, 60h, 60j) of reference.

Applications : using StarDrop™ and GastroPlus®

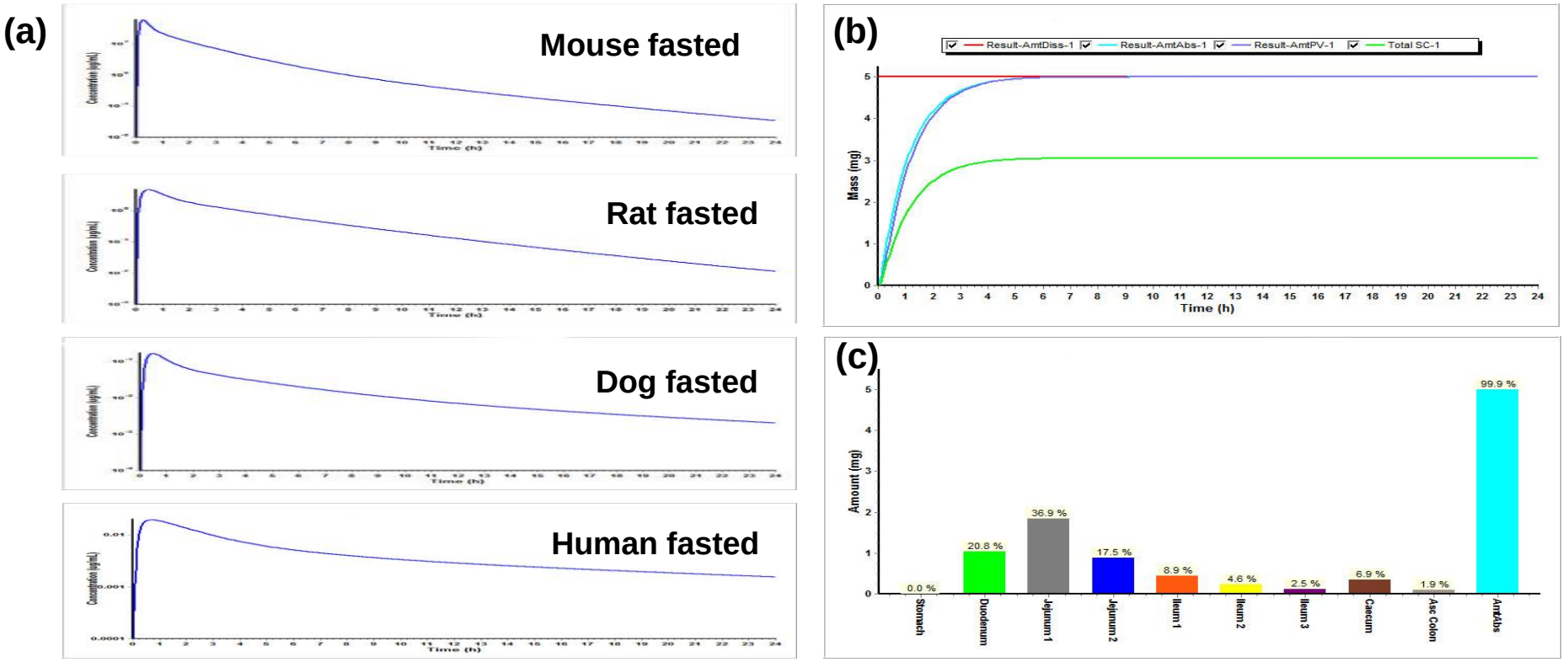
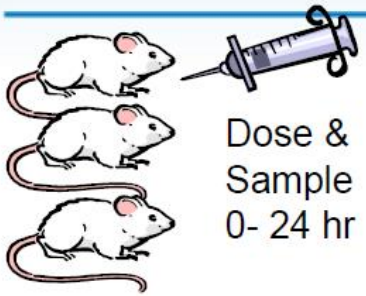


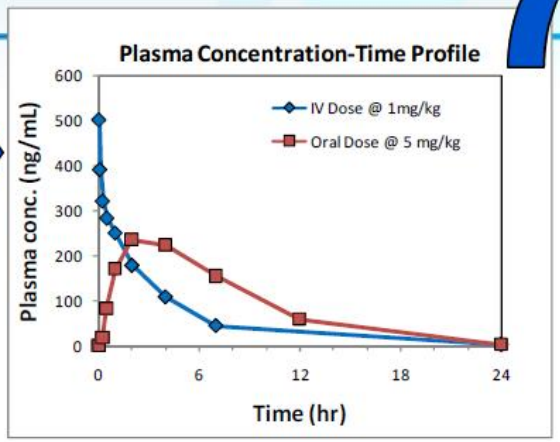
Figure 8. (a) PK profiles of compound 5 in four species (mouse, rat, dog and human) using GastroPlus ® PBPK modeling. (b) Absorption and dissolution profiles predicted in human PBPK model. (c) Relative compartmental absorption predicted in human.

Traditional Practice of Human PK Prediction

For orally administered small molecules



Dose & Sample 0- 24 hr



PK Parameter estimate

CLp = 12 mL/min/kg

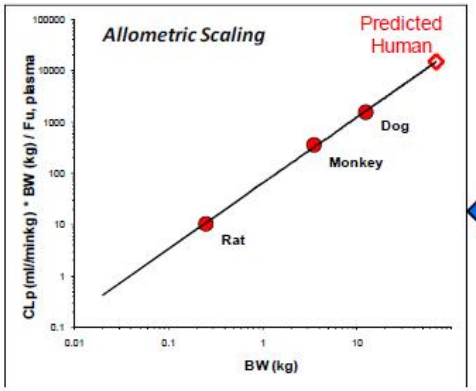
Vd_{ss}= 2.8 L/kg

$T_{1/2}$: 3.6 hrs

Bioavailability = 31%

Repeat in various species
Rat, Dog, Monkey, or GP, etc

- PK in Rat
- PK in Dog
- PK in Monkey



2 - 4 Months Later!

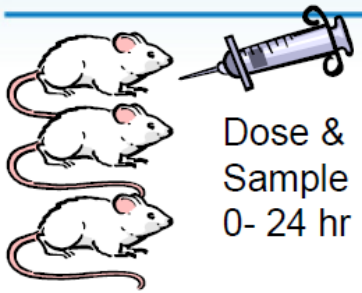
Predicted Human PK Available!

Natilie Hosea - Pfizer

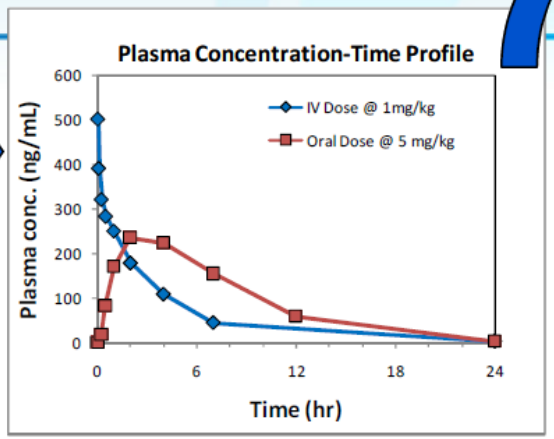
Traditional Practice of Human PK Prediction

For orally administered small molecules

PDM
•PHARMACOKINETICS•
DYNAMICS & METABOLISM



Dose & Sample 0- 24 hr



PK Parameter estimate

CLp = 12 mL/min/kg

Vd_{ss}= 2.8 L/kg

$T_{1/2}$: 3.6 hrs

Bioavailability = 31%

~~***Repeat in various species Rat, Dog, Monkey, or GP, etc***~~

PK in Rat

OR PK in Dog

OR PK in Monkey

Single Species Scaling to Human

Weeks later

Predicted Human PK Available!

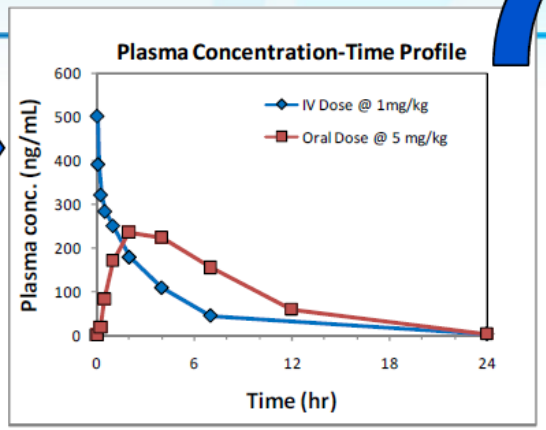
Ward & Smith 2004, DMD 32; pg 603 & 612
Tang et al. 2007, DMD 35; pg 1886
Hosea et al. 2009, J Clin Pharm 49; pg 513
Hu & Chiu 2009; J Med Sci 29; pg 331

Non-Traditional Practice of Human PK Prediction

For orally administered small molecules

PDM
•PHARMACOKINETICS•
DYNAMICS & METABOLISM

Dose & Sample 0 - 24 hr



PK Parameter estimate

CLp = 12 mL/min/kg

Vd_{ss} = 2.8 L/kg

$T_{1/2}$: 3.6 hrs

Bioavailability = 31%

~~***Repeat in various species Rat, Dog, Monkey, or GP, etc***~~

~~PK in Rat~~

~~PK in Dog~~

~~PK in Monkey~~

~~***Single Species Scaling to Human***~~

In Vitro

Days Later

Predicted Human PK Available!

In Silico

Same Day?

Question: Can we predict without in vivo PK?

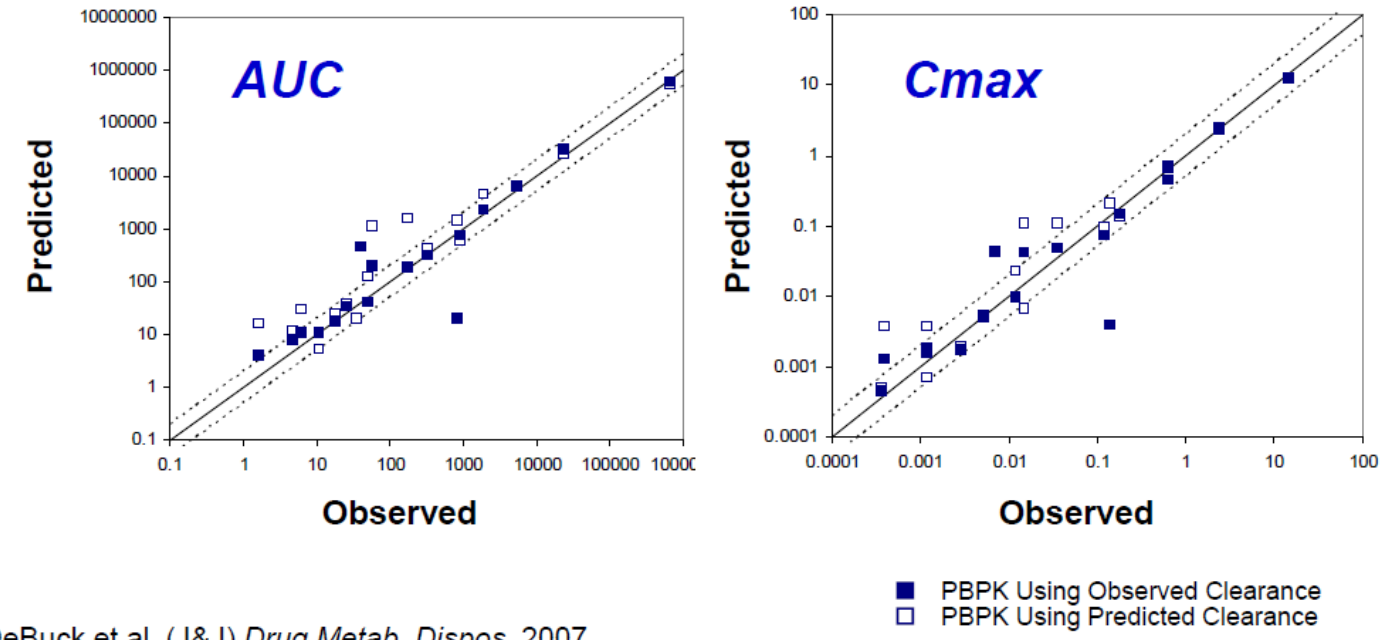
Natilie Hosea - Pfizer

Retrospective Validation of PBPK Approach Using GastroPlus™

PDM
•PHARMACOKINETICS• DYNAMICS & METABOLISM

Retrospective evaluation of the prediction of human PK using PBPK methodology with 21 Pfizer compounds

Jones et al. (Pfizer) Clinical Pharmacokinetics 2011, 50: 331



DeBuck et al. (J&J) *Drug Metab. Dispos.* 2007
Jones et. al. (Roche) *Clinical Pharmacokinetics* 2006

DD I prediction by SIMCYP : CYP3A4 reversible inhibition

Clinical DDI

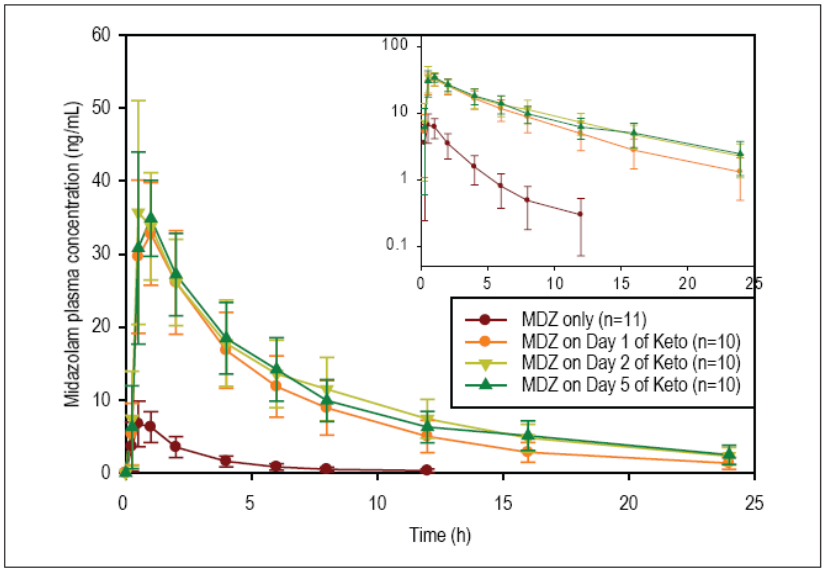
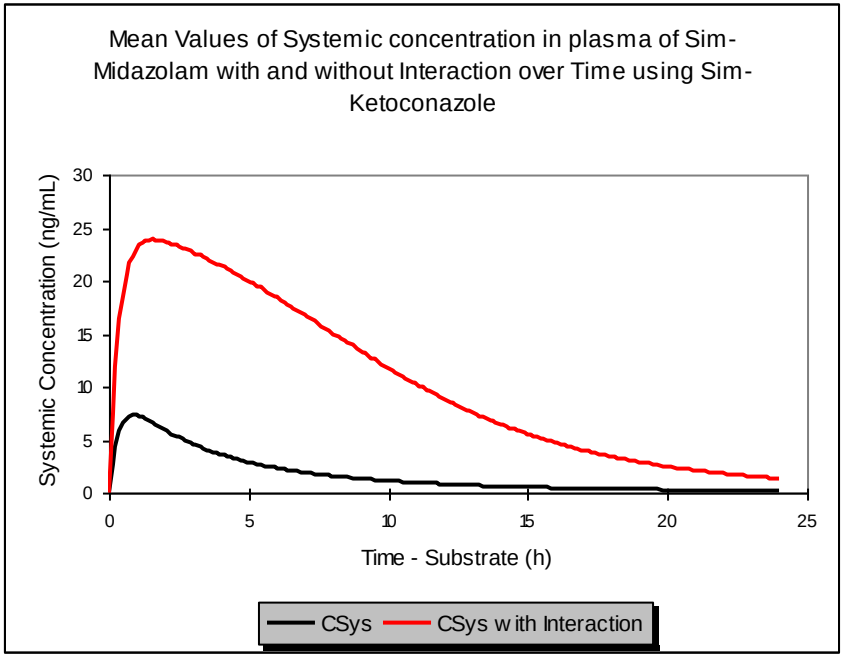


Figure 1. Mean midazolam plasma concentration (ng/mL) versus time following single-dose administration of 2 mg midazolam with and without 400 mg ketoconazole in the fasted state to young, healthy male participants.

Simcyp simulated DDI



PK parameters (mean) of **midazolam** in the absence and presence of **ketoconazole**

	AUC (ng/ml.h)	Cmax (ng/ml)	t1/2 (h)
Control	19	7.2	2.6
+ ketoconazole	196	36.1	4.9
fold change	10.3		

PK parameters (mean and 90% CI) of midazolam in the absence and presence of ketoconazole

	AUC (ng/ml.h)	Cmax (ng/ml)
Control	41 (6 - 106)	7.5 (2 - 15)
+ ketoconazole	254 (80 – 487)	25 (10 – 40)
fold change	10.3 (3.2 - 24.1)	

Single dose 2 mg PO midazolam + 400 mg PO ketoconazole

Stoch *et al.*, 2009 *J Clin Pharmacol* 49:393-406

Case study: FDA review of ibrutinib

- Predominantly metabolized by CYP3A
- Clinical drug interaction studies:
  - *With strong CYP3A inhibitor ketoconazole: AUC increased by ~24 fold*
  - *With strong CYP3A inducer rifampin: AUC decreased by >90%*

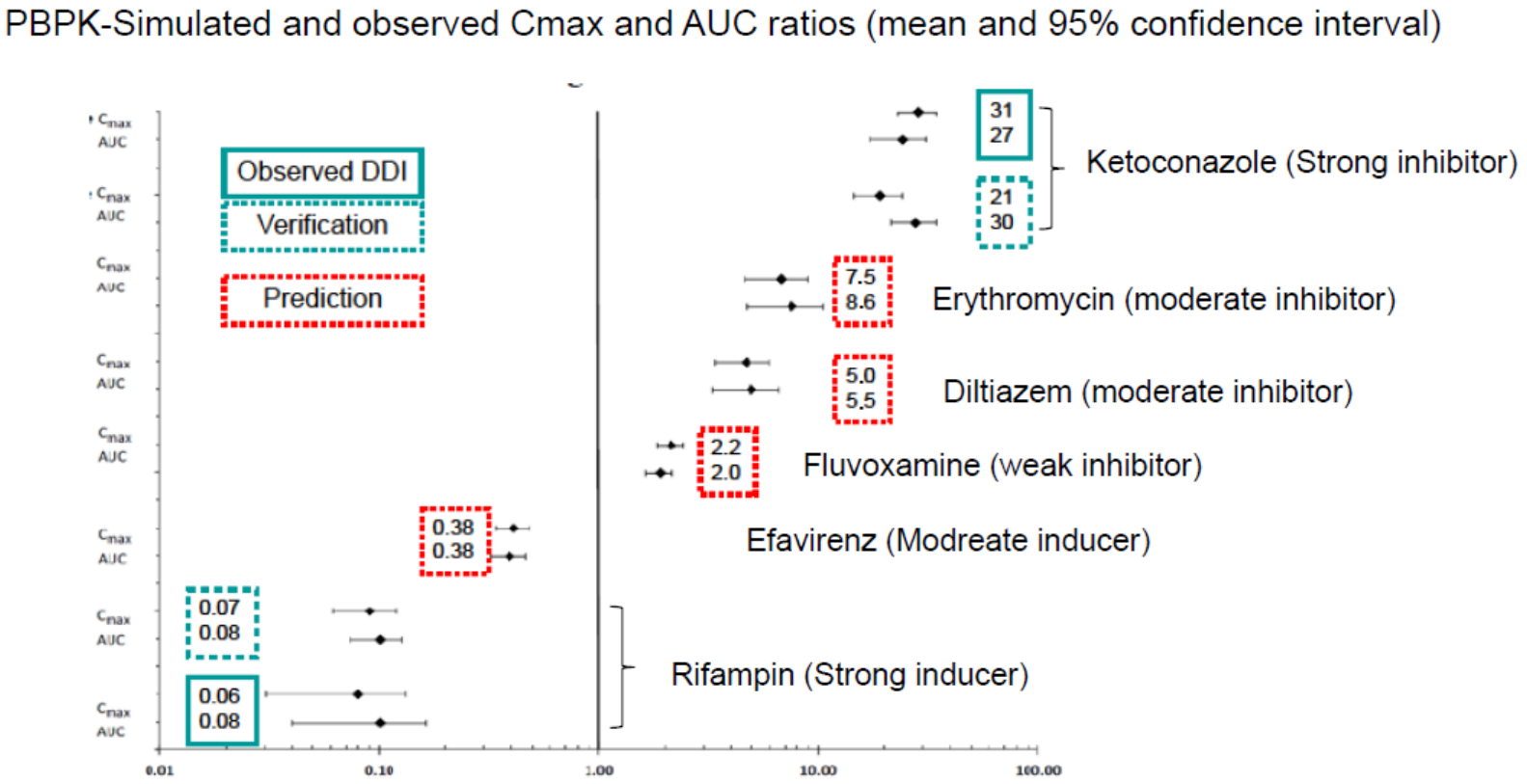
- **What are expected exposure changes with other CYP3A inhibitors or inducers?**

- **What is dosing recommendation in patients who have to take CYP3A inhibitor/inducer?**

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

What are expected exposure changes with other CYP3A inhibitors or inducers?

PBPK-Simulated and observed Cmax and AUC ratios (mean and 95% confidence interval)



What is dosing recommendation in patients who have to take CYP3A inhibitor/inducer?

FDA analysis using sponsor's model to support dosing strategy for the coadministration of ibrutinib with CYP3A perpetrators: dose-staggering with Strong CYP3A inhibitors

CYP3A inhibitor and dosing regimen	Inhibition mechanism	Ibrutinib dosing in relation to inhibitor dosing				**Does dose staggering have effect?**
		Scenario 1 2 hrs. before inhibitor		Scenario 2 Co-administration		
		Ibrutinib exposure ratio (with/without inhibitor)				
		AUC	Cmax	AUC	Cmax	
Ketoconazole 400 mg QD	Strong, reversible	6.5	3.7	29	21	**Yes**
Ritonavir 100 mg BID	Strong, Time-dependent	39	23	40	24	**No**

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

Simulations supporting dose optimization (FDA in house analyses)

CYP3A modulators	CYP3A interaction mechanisms of co-medications	Ibrutinib dosing
Inhibitors	Strong, reversible, minimal accumulation (e.g. ketoconazole)	**Reduce to 140 mg and give 2 hours before inhibitor**
	Strong, time-dependent (e.g. ritonavir)	**Do not use**
	Moderate	**Reduce to140 mg**
Inducers	Moderate	**No dose adjustment**
	Strong	**Do not use**

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

성공적인 PBPK modeling 사례
Ibrutinib Package Insert: What are expected exposure changes with other CYP3A inhibitors or inducers?

Drug Interactions

Coadministration of Ibrutinib with CYP3A Inhibitors

In a sequential design trial of 18 healthy volunteers, a single dose of 120 mg of IMBRUVICA was administered alone on Day 1 and a single dose of 40 mg of IMBRUVICA was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 - 9). Ketoconazole increased ibrutinib dose-normalized C_{max} and AUC 29-fold and 24-fold, respectively.

Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that moderate CYP3A inhibitors (diltiazem and erythromycin) may increase the AUC of ibrutinib 6 to 9-fold in fasted condition.

Coadministration of Ibrutinib with CYP3A Inducers

PK data from a dedicated drug interaction trial showed that rifampin (a strong CYP3A inducer) decreases ibrutinib C_{max} and AUC by more than 13- and 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib by up to 3-fold.

Thank you


IF YOU WANT TO GO FAST, GO ALONE.
IF YOU WANT TO GO FAR, GO TOGETHER
AFRICAN PROVERB