JSSX Award Lecture, Nov. 8, 2022
The 37th JSSX Annual Meeting
in Yokohama

薬物動態及び安全性に関する予測評価法及びそのための分析法に関する研究

Studies on prediction of drug pharmacokinetics and safety by biomarkers and their bioanalytical evaluation

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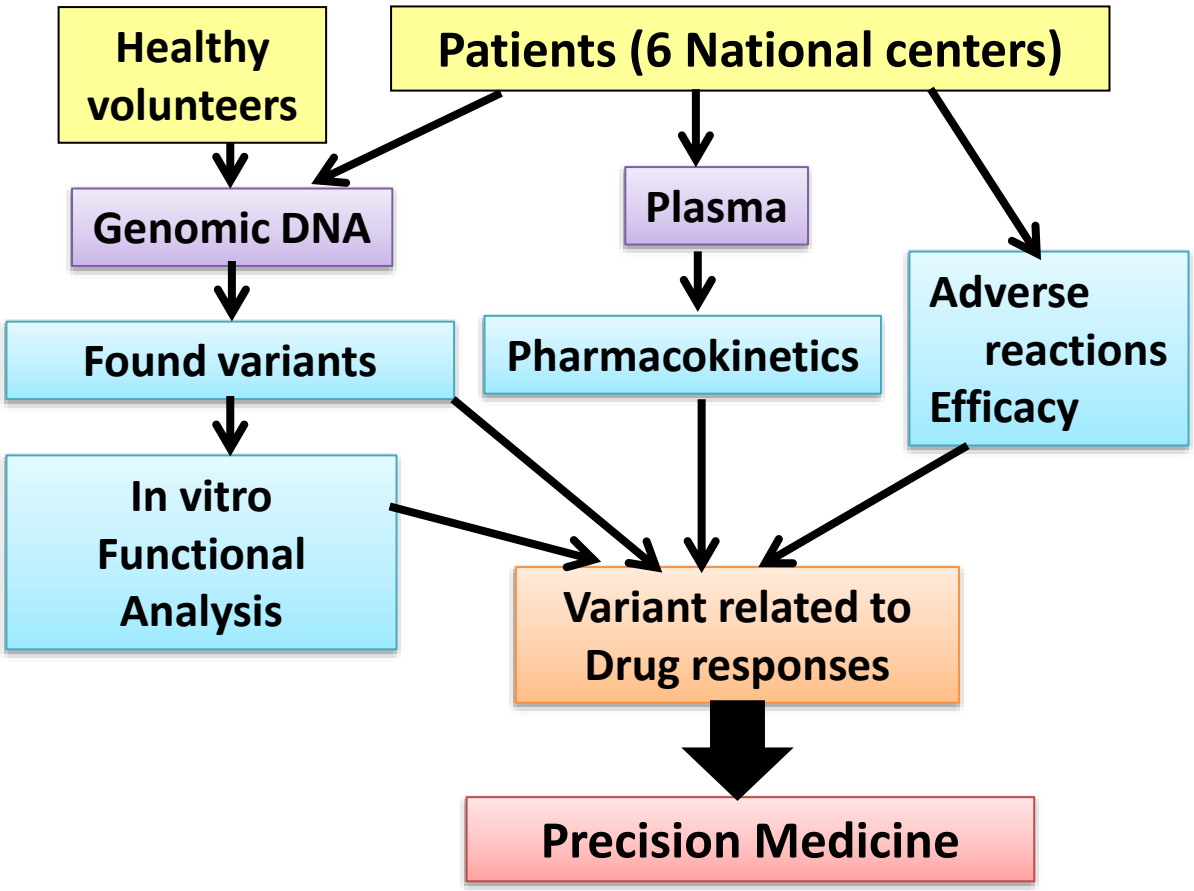
Millennium genome project (MPJ-6/05-25)

Dec. 19, 1999, Prime minister determination

Purpose: To realize tailor-made medical care based on the pharmacogenomics for major diseases of the elderly such as cancer, diabetes, and hypertension.



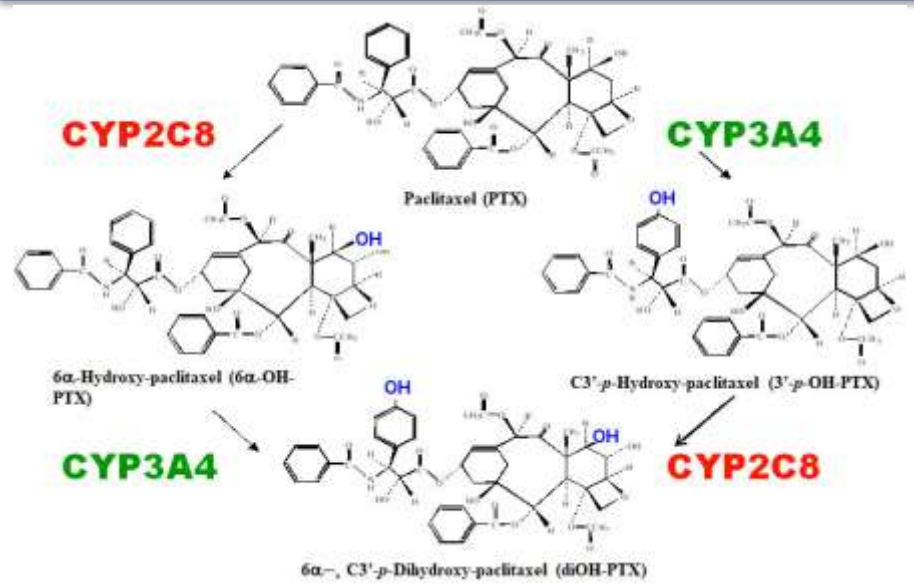
Anti-cancer drugs
  Irinotecan, 5-FU
  Paclitaxel, Oxaliplatin,
  Gemcitabine
Anti-arrhysmic drugs
  Mexiletine,
  Amiodarone
  β-blockers
Anti-diabetic drug
  Glimepiride
Anti-epileptic drug
  Carbamazepine
Anti-inflammatory drug
  Beclomethasone
  Dexamethasone

Genetic variants and haplotype analysis

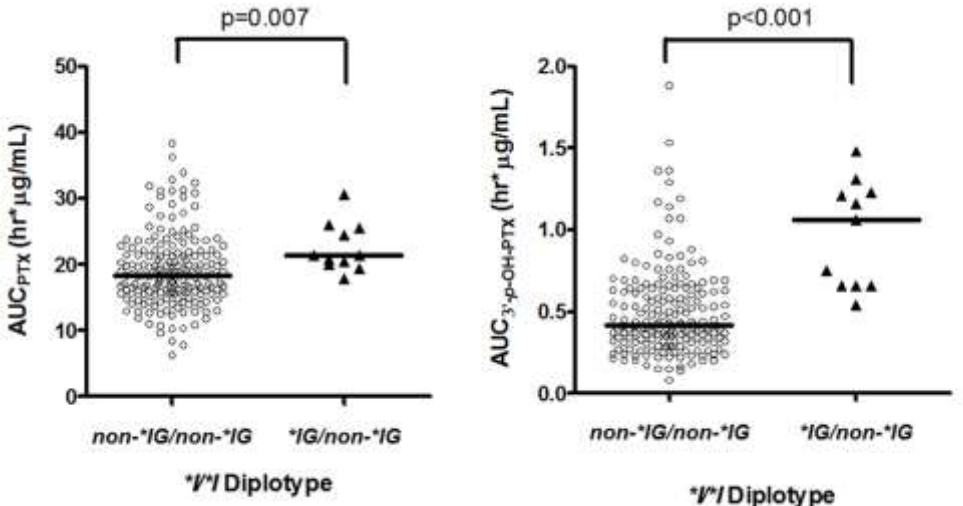
Cytochrome P450s	*CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, POR*
UGTs	*UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10,UGT2B4, UGT2B7*
	EPHX1, CDA, DCK, DPYD, CES1, CES2
Other enzymes	*ABCC1/MRP1, ABCC2/MRP2, ABCC3/MRP3,*
Drug transporters	*ABCG2/BCRP, ABCB11/BSEP, SLC22A1/OCT1, SLC22A2/OCT2, SLCO1B1, SLC29A1/ENT1, ATP7A, ATP7B*
Transcriptional factors/receptors	*NR1I1/VDR, NR3C1/GR, ABCC8/SUR1 AHR, KCNJ11, NFE2L2/Nrf2, KEAP1, HNF4A,*
Oxidative stress	*GSTM1, GSTT1, GSTP1, GSTA1, GSTA2*
Antibody DMPK	*FCGRT, FCGR2A, FCGR3A*

Reported in *Drug Metabolism and Pharmacokinetics*

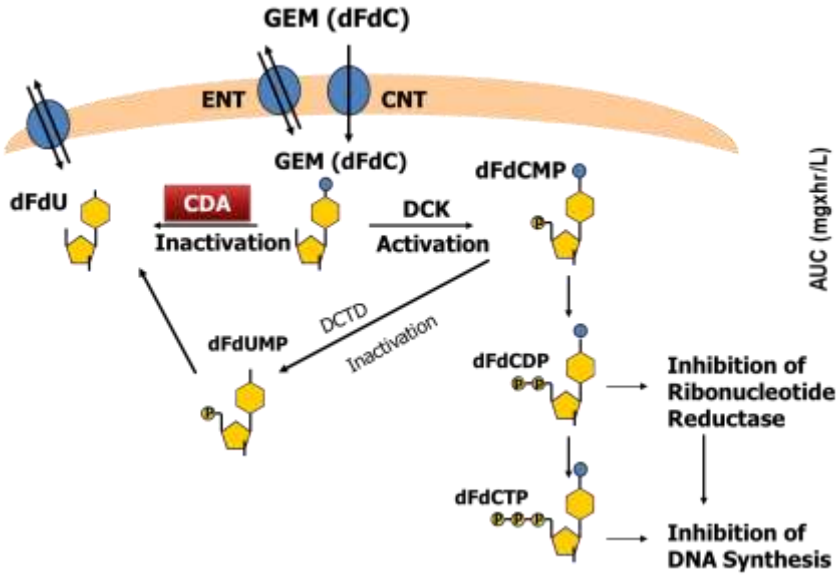
Millennium genome project



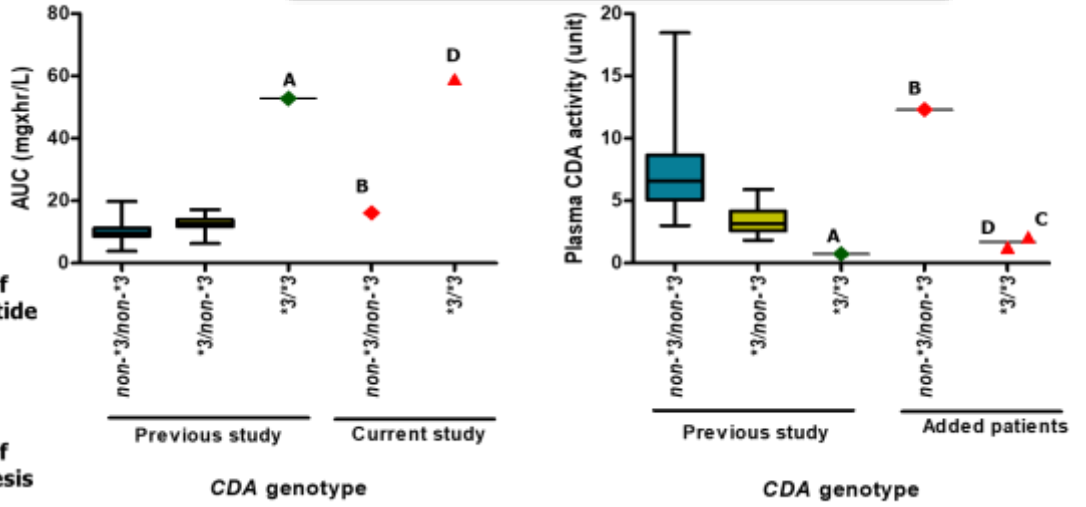
PK effect of *CYP2C8*IG*



Saito et al., ***Pharmacogenet. Genomics*, 17: 461-471 (2007)**



PK and adverse effect of *CDA*3*

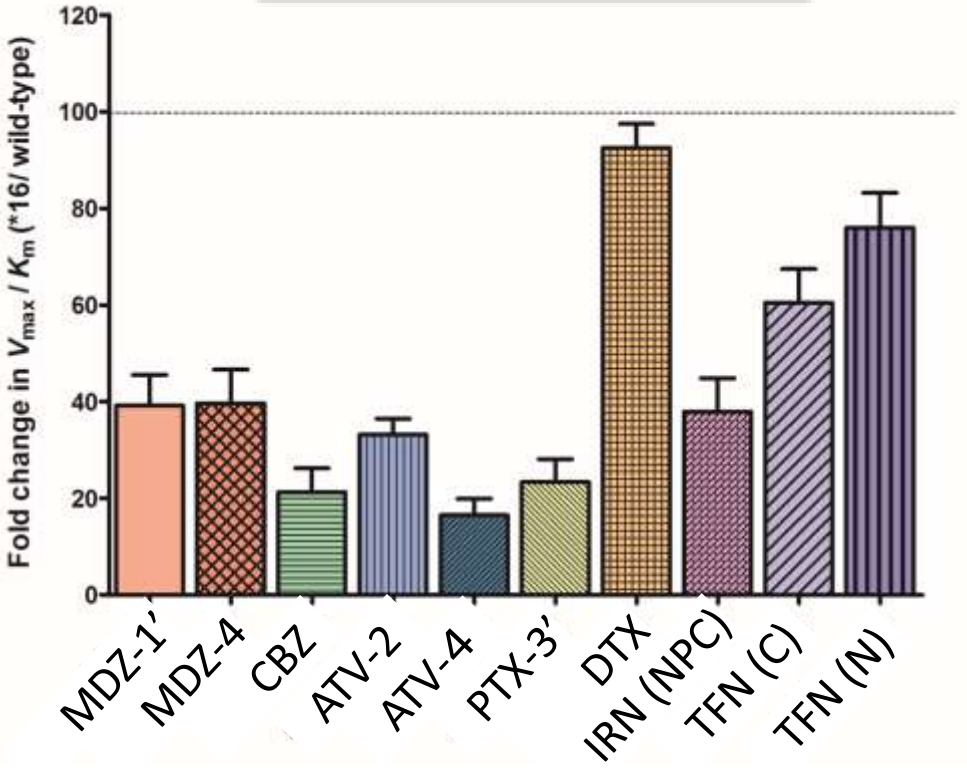


Ueno *et al.*, *Br. J. Cancer*、100: 870-873 (2009)

Millennium genome project

Substrate-dependent functional alterations with genetic variants

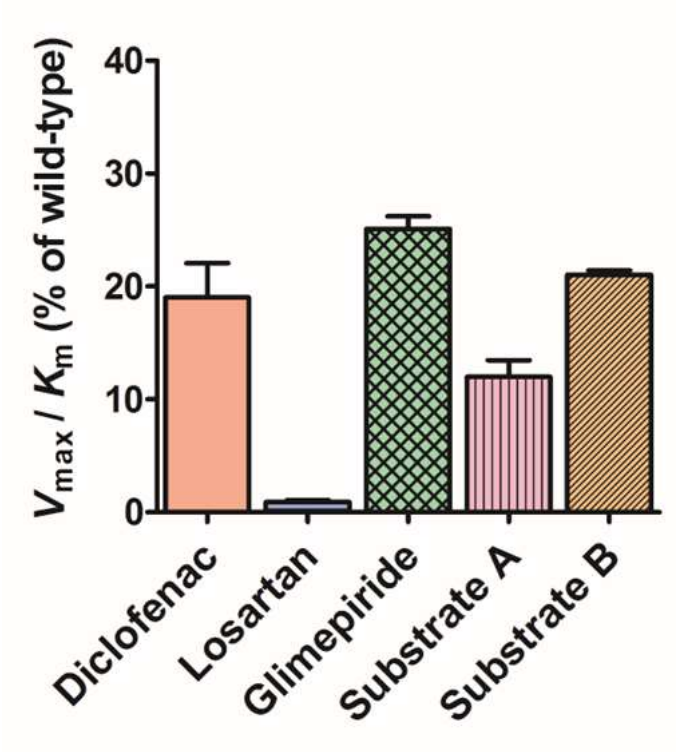
CYP3A4.16 enzyme



Docetaxel>Terfenadinne>Midazolam, Irinotecan >Atorvastatin, Carbamazepine

Maekawa et al., *Drug Metab. Dispos*. 38:2100-2104. (2010)

CYP2C9.30 enzyme



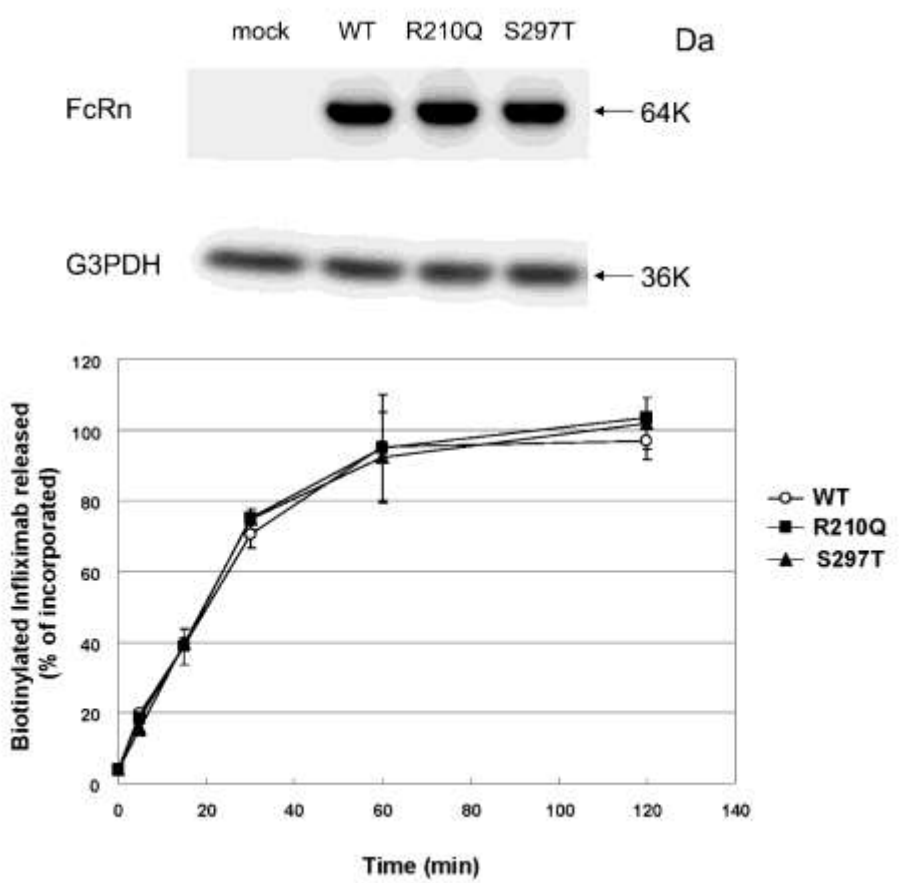
Glimepiride, Diclofenac>Losartan

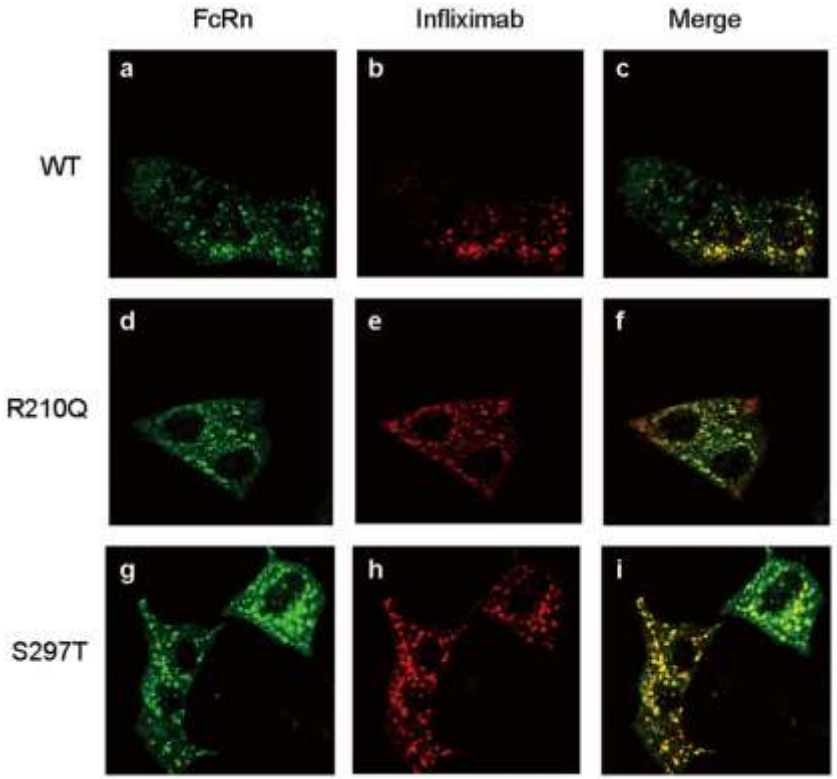
Maekawa et al., *Drug Metab. Dispos*. 37, 895-903 (2009)

Millennium genome project

Pharmacogenetics of FcRn (FCGRT): Related to recycling of antibody drugs

- Screened variants for 5'-flanking region, all exons and their flanking introns from 126 Japanese subjects Found novel variants: **629G>A (R210Q)** and **889T>A (S297T)**





No common functional variant was detected in *FCGRT* in Japanese

Ishii-Watabe et al., *Drug Metab Pharmacokinet*. 2010;25(6):578-87.

Collaboration project with Tohoku Univ.

Points-to-consider documents: Scientific information on the evaluation of genetic polymorphisms during non-clinical studies and phase I clinical trials in the Japanese population

Scientific information on the evaluation of genetic polymorphisms, mainly on DMPK-related genes, during non-clinical studies and phase I clinical trials in Japanese subjects/patients.

Major genetic polymorphisms of drug-metabolizing enzymes and transporters in Japanese populations.

Gene	Allele	Locations		Activity	Allele frequencies			References
		Nucleotide changes	Amino acid changes		Japanese	Caucasian	African American	
CYP2A6	*4	gene deleted		None	0.19	0	0.009	[15,95,96]
	*7	1412T > C, gene conversion in the 3′ flanking region	I471T	Decrease	0.098	0	0	[15,95,96]
	*9	−1013A > G, −48T > G	TATA box	Decrease	0.19	0.08	0.085	[15,95,96]
CYP2B6	*4	785A > G	K262R	Change	0.093	0.040	0.000	[33,35]
	*5	1459C > T	R487C	Decrease?	0.011	0.109	0.01–0.04	[33,35]
	*6	516G > T, 785A > G	Q172H, K262R	Change	0.164	0.256	0.33–0.50	[33,35]
CYP2C9	*3	1075A > C	I359L	Decrease	0.029	0.064	0.018	[12,97]
CYP2C19	*2	681G > A, 991A > G	Splicing defect, I331V	None	0.267–0.29	0.050–0.250	0–0.330	[12,98,99]
	*3	636G > A, 991A > G	W212Stop, I331V	None	0.108–0.128	0–0.004	0–0.060	[12,98,100]
	*17	−806C > T; 99C > T	I331V	Increase	0.011	0.188	0.235	[12]
CYP2D6	*5	gene deleted		None	0.041–0.072	0.016–0.082	0.028–0.107	[101–103]
	*10	100C > T, 1661G > C, 4180G > C	P34S, S486T	Decrease	0.333–0.408	0.001–0.080	0.019–0.086	[101–103]
	*41	−1584C, −1235A > G, −740C > T, −678G > A, CYP2D7 gene conversion in intron 1, 1661G > C, 2850C > T, 2988G > A, 4180G > C	R296C, Splicing defect, S486T	Decrease	0–0.016	0.031–0.150	0.004–0.149	[102–104]
CYP3A4	*16	554C > G	T185S	Decrease	0.014	0	0	[105–107]
CYP3A5	*3	219-237A > G	Splicing defect	Decrease	0.71–0.85	0.9	0.27–0.5	[108–110]
UGT1A1	*6	211G > A	G71R	Decrease	0.13–0.19	0.001–0.03	0	[12,111,112]
	*28	−54_-39A $(TA)_6TAA > A (TA)_7TAA$		Decrease	0.09–0.13	0.30–0.39	0.36–0.45	[12,111,112]
	*60	−3279T > G		Decrease	0.14–0.26	0.45–0.55	0.79–0.85	[112–114]
	*93	−3156G > A		Decrease	0.12	0.28–0.33	0.28–0.32	[112,113,115]
NAT2	*5	341T > C	I114T	Decrease	0.014	0.448	0.342	[12,60,61]
	*6	590G > A	R197Q	Decrease	0.205	0.283	0.213	[12,60,61]
	*7	857G > A	G286E	Decrease	0.088	0.018	0.063	[12,60,61]
GSTM1	*0 (null)	gene deleted		None	0.501	0.529	0.266	[6,12]
GSTT1	*0 (null)	gene deleted		None	0.496	0.197	0.231	[6,12]
TPMT	*3C	719A > G	Y240C	Decrease	0.008–0.028	0.017–0.080	0.024–0.076	[65,68,116]
ALDH2	*2	1510G > A	E504K	None	0.267	0	0.002	[69,72,73]
SLCO1B1	*1b	388A > G	N130D	Increase	0.469	0.246	0.763	[79,117]
	*5,*15,*17	521T > C	V174A	Decrease	0.139	0.161	0.048	[12,77,78]
ABCG2(BCRP)		421C > A	Q141K	Decrease	0.313	0.105	0.027	[12,118,119]
		376C > T	Gln126Stop	None	0.009–0.017	0	0	[83,118]

Hiratsuka et al., *Drug Metab Pharmacokinet*. 2018; 33:141-149.

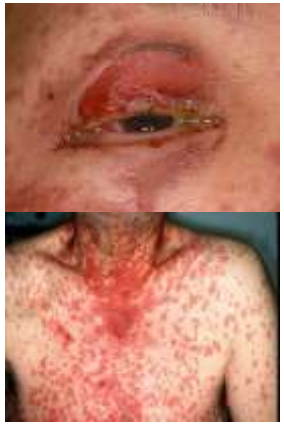
Drug-induced severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS)/ Toxic epidermal necrolysis (TEN)

◆ Symptoms:

- Wide-spread blistering exanthema, fever (with mucosal impairment in SJS)
- Classification by skin detachment/blistering area of the epidermis

<10% of body surface area (BSA): SJS
10%~30% of BSA : SJS/TEN overlap
≥30% of BSA : TEN
(SJS/TEN overlap is included in TEN in Japanese diagnostic criteria)



From manual for handling disorders due to ADRs

◆ Characteristics:

- Very rare（1-5 cases/year/1 million subjects）
- Developed within several days to weeks
- Caused by ≥ 100 kinds of drugs
- Hospitalization needed（Systemic administration of corticosteroids）
- High mortality（SJS: 1~5%, TEN: 20-30%）
- Sequela (*e.g.*, Visual and pulmonary defects)

HLAs associated with SCARs in Japanese

Allele	Healthy	SJS/TEN patients		Odds ratio (95% confidence interval)	P-value
	Allele frequency	Carrier frequency	Allele frequency		
Carbamazepine（anti-epileptic）					
*B*15:11* [1]	1.0%	5/21 (23.8%)	5/42 (11.9%)	12.2 (4.6-32.1)	0.0001
*A*31:01* [2]	8.7%	9/21 (42.9%)	10/42 (23.8%)	3.72 (1.56-8.88)	0.004
Phenobarbital（anti-epileptic）					
*B*51:01* [3]	7.87%	6/8 (75.0%)	7/16 (43.8%)	16.71 (3.66-83.06)	0.0003
Zonisamide (anti-epileptic）					
*A*02:07* [3]	3.49%	5/12（41.7%)	5/24 (20.8%)	9.77 (3.07-31.1)	0.0008
Alloprurinol (anti-uricemic)					
*B*58:01* [4]	0.6%	10 /18 (55.6%)	10/36 (27.8%)	62.8 (21.2-185.8)	5.4×10^{-12}
Phenytoin (anti-epileptic)					
*CYP2C9*3* [5]	5.33%（保有者）	3/9（33.3%)		8.88 (2.20-35.83)	0.003
NSAIDs with severe ocular involvement					
*A*02:06* [6]	13.6%（保有者）	9/20 (45.0%)		5.18 (1.98 – 13.56)	0.0014
*B*44:03* [6]	13.6%（保有者）	8/20 (40.0%)		4.22 (1.59 – 11.19)	0.0058
Sulfonamides					
*A*11:01* [7]	16.9%	10/15 (67%)		9.84 (3.4-28.9)	2.7×10^{-5}

Association of *CYP2C9*3* and phenytoin-related SJS/TEN

Phenytoin: **Anticonvulsant drug (Inhibition of Na^+ channel for neurotransmission.)**

	Cases of Phenytoin-Related SJS/TEN, Number		Population Controls, Number		
Subgroup	***CYP2C9*3* Carriers**	**Total Participants**	***CYP2C9*3* Carriers**	**Total Participants**	**OR (95%CI)**
Han Chinese	**20**	**48**	**20**	**412**	**14.00 (6.75–29.02)**
Japanese	**3**	**9**	**153**	**2869**	**8.88 (2.20–35.83)**
Malay	**1**	**4**	**21**	**374**	**5.60 (0.56–56.20)**
Subtotal		**61**		**3655**	**11.96 (6.42–22.28)**

Chung et al., JAMA, 312: 525-534 (2014)

	Cases of Phenytoin-Related SJS/TEN, Number		Tolerant Controls, Number		
Subgroup	***CYP2C9*3* Carriers**	**Total Participants**	***CYP2C9*3* Carriers**	**Total Participants**	**OR (95%CI)**
Thai	**9**	**39**	**6**	**92**	**4.30 (1.41-13.09)**

Tassaneeyakul et al., Pharmacogenet Genomics, 26: 225-234 (2016)

Clearance impairment of phenytoin in SCAR patients

Association with *CYP2C9*3*

	Tolerant controls		Cases		Cases	
	Continued	Dis-continued	SJS/TEN	DRESS	*CYP2C9*3*	
					-	+
During	11.8 μg/mL					
Before Conc.		11 μg/mL (n=23)	34 μg/mL (n=4)	11 μg/mL (n=5)	11 μg/mL (n=2)	24 μg/mL (n=7)
p-value			0.02	0.86	0.96	0.12
1-5 d After withdrawal Conc.		62h 2.5 μg/mL (n=62)	65h 12 μg/mL (n=65)	79h 5.5 μg/mL (n=79)	72h 4.9 μg/mL (n=72)	70h 17 μg/mL (n=70)
p-value			4.0×10^{-4}	0.029	0.015	2.0×10^{-4}
>5 d After withdrawal Conc.		168 h 0.3 μg/mL (n=62)	278h 3.3 μg/mL (n=65)	255h 0.7 μg/mL (n=79)	267h 0.6 μg/mL (n=72)	259h 4.7 μg/mL (n=70)
p-value			0.33	0.44	0.54	0.16

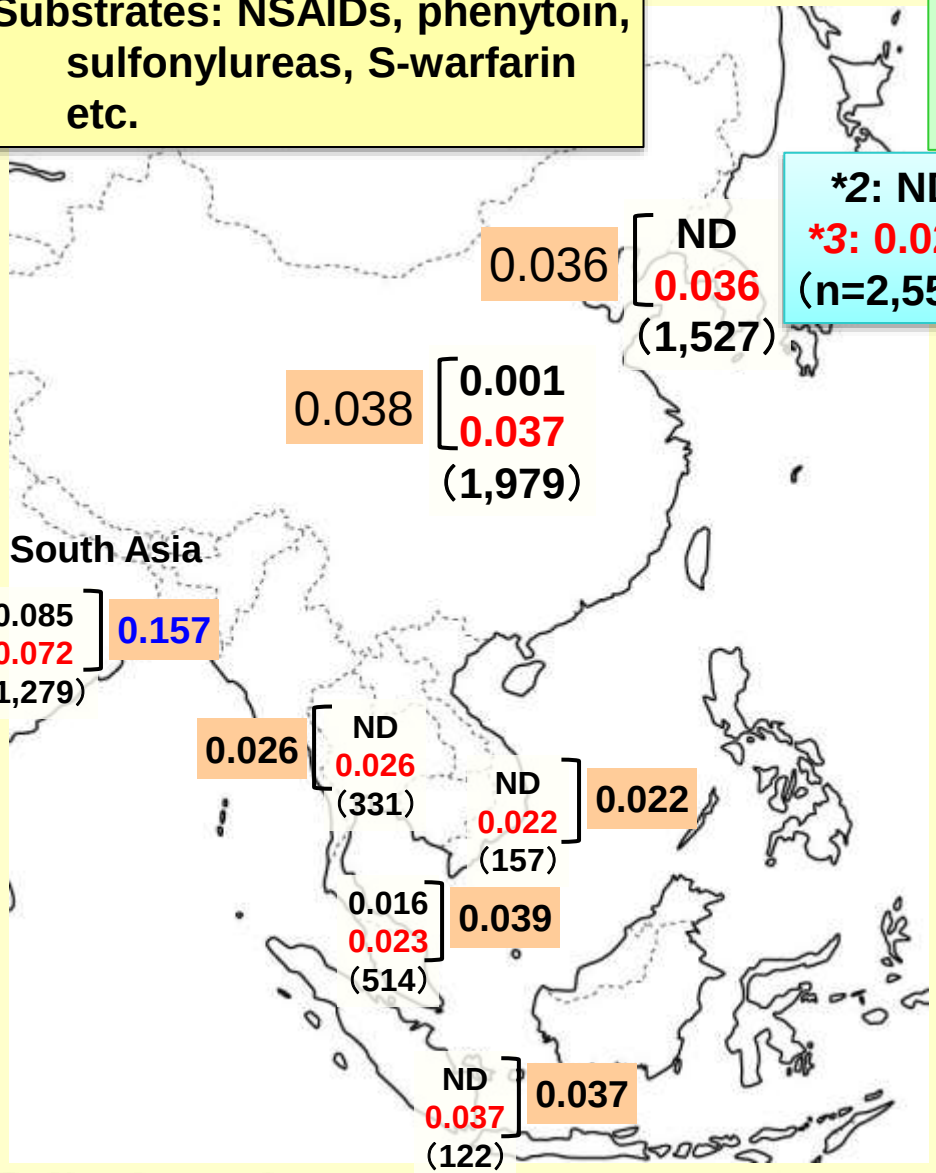
DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

Chung et al., JAMA, 312: 525-534 (2014)

Cytochrome P450: CYP2C9

Substrates: NSAIDs, phenytoin, sulfonylureas, S-warfarin etc.

***2* : 430C>T, Arg144Cys (Reduced activity)**
***3* : 1075A>C, Ile359Leu (Reduced activity)**
(Number of subjects in parenthesis)



ND: Not detected, *Kurose et al., Drug Metab. Pharmacokinet., 27:9-54 (2012).*

Biomarker evaluation

- **Clinical (& non-clinical) significance and usefulness**

  Sufficient diagnostic or therapeutic significance and usefulness, such as improvement of efficacy or safety of the drug, by measuring the biomarker.

Requirement that necessary validation is done

- **Analytical method validation: analytical validity**

  The process of establishing that a measurement is acceptable on sensitivity, specificity, accuracy, precision, stability, and other necessary performance characteristics using specific technical procedures to ensure the usefulness of a biomarker.

- **Clinical validation: clinical utility**

  Validation that the selected biomarker can adequately assess the clinical concept of interest (Context of Use)

Points to consider document on biomarker assay validation

Scope: close to Critical-Path Institute document (2019.6)

Molecules : Endogenous metabolites, peptides, proteins

Methods: LC/GC-MS、LBA（Exc. IHC, flow cytometry, genomics, MS imaging）

- ◆ Biomarkers as drug developmental tools (excluding CDx, clinical chemistry)
- ◆ Biomarkers used for regulatory decision

(At first, excluding ones for exploration and decision making in a company)

Biomarkers: to be used for drug efficacy and/or adverse reactions,
as a part of 1) endpoints for clinical evaluations
2) supporting the post-marketing evaluation

Their analytical methods should be fully assessed and validated

Principle for biomarker assay validation (BAV):

- ➢ Necessary validation parameters should be selected by the sponsor and performed based on the fit-for-purpose principle.
- ➢ Pre-determined acceptance criteria should be described in validation protocol according to biomarker's Context of Use (COU).

Examples of the validation levels for situations (biomarker screening and internal decision) are also listed in the accompanying table.

Points to consider document on biomarker assay validation

1. Introduction
2. Scope and Basic Principle
3. Matrices
4. Full validation
   - 4-1) Reference Standards, Internal Standards, and Critical Reagents
   - 4-2) Selectivity
   - 4-3) Specificity
   - 4-4) Calibration Curve
   - 4-5) Matrix Effect
   - 4-6) Accuracy and Precision
   - 4-7) Parallelism
   - 4-8) Dilution Linearity
   - 4-9) Stability
   - 4-10) Carryover
   - 4-11) MRD (minimum required dilution)
5. Partial validation
6. Cross Validation
7. Study Sample Analysis
   - 7-1) Calibration Curve
   - 7-2) QC Samples
   - 7-3) ISR
8. Point to Note
   - 8-1) Commercial Kits
   - 8-2) Reanalysis
   - ■ Addendum: Evaluation of analytical methods for purposes other than inclusion in an application dossier
   - ■ References
   - ■ Glossary

http://www.nihs.go.jp/mss/PTC%20document-Biomarker%20Assay%20Validation.pdf

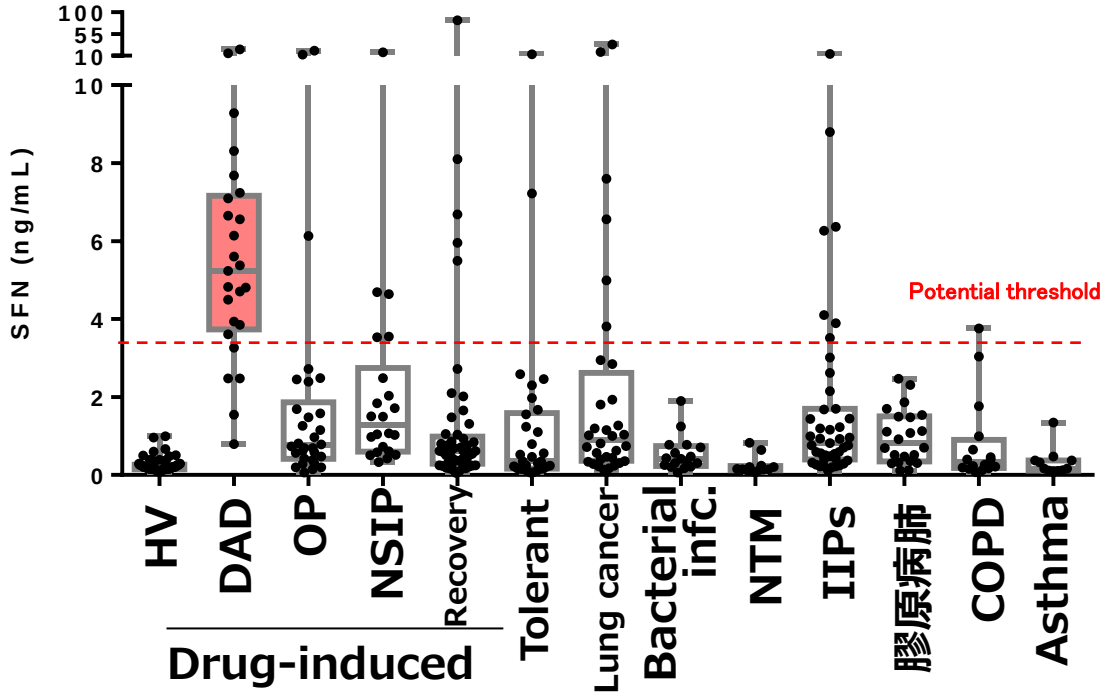
Ohtsu et al., Bioanalysis.13(18):1379-1389 (2021)

Other ADR –related biomarker studies

Stratifin: Diffused alveolar damage (DAD)-type Intestinal lung disease

Parameter	Results
Range	0.117 - 30 ng/mL
LLOQ	0.2 ng/mL
Linearity	x1 to x256
Recovery	≤± 20%
Same batch	Relative accuracy ≤±20%, Precision ≤15%
Intra-day	Relative accuracy ≤±20%, Precision ≤15%
Inter-day	Relative accuracy ≤±20%, Precision ≤15%

Parameter	Results
Selectivity	Not affected by bilirubin C, bilirubin F, hemolytic hemoglobin, lactobacillus, ascorbic acid, heterophilic antibodies (HAMA), human rheumatoid factor, albumin, lipids, human IgG.
Specificity	Not reactive with other 14-3-3 isoforms
Stability	Stable (relative accuracy ≤±20%) 4℃ x 72 hrs, 37℃ x 6 hrs, -80℃ x 2.5 yrs, Freeze-thaw x 5 times



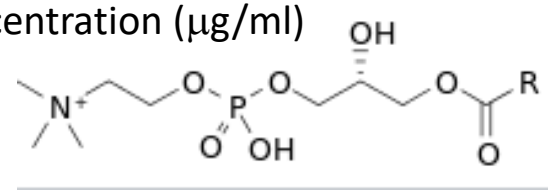
DAD: DAD + DAD-mixed
OP: Organizing pneumonia
NSIP：Non-specific interstitial lung disease
NTM：nontuberculous mycobacteria
IIPs：idiopathic interstitial pneumonia
COPD：Chronic Obstructive Pulmonary Disease

Arakawa et al., *Nat Commun*. 2022: 13; 5854

Fundamental studies on metabolite biomarkers

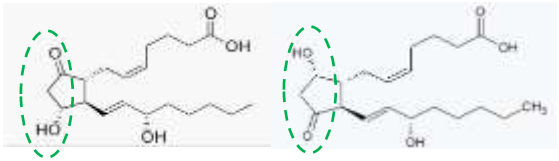
Bioanalysis of model biomarkers in the multiple laboratories for future regulation

- Lysophosphatidylcholine (LPC)
  - ❖ The major lysophospholipids in blood
  - ❖ Reported as marker for hapatocarcinoma and diabetes
  - ❖ High blood concentration (μg/ml)



- Prostaglandin E_2 (PGE_2)
  - ❖ A prostaglandin associated with inflammatory response
  - ❖ Reported as marker for chronic inflammation
  - ❖ Low blood concentration (pg/ml)

PGE_2 PGD_2



LPC(16:0)*	Lab A	Lab B	Lab C	Lab D	Lab E	Lab F
Carry over	6.7%	0%	1.9%	17.4%	2.6%	0%
Parallelism	98.1%	102.2%	98.4%	100.0%	98.3%	96.6%
Precision	< 5.3%	< 10.2%	< 2.4%	< 4.8%	< 4.0%	< 1.9%
Accuracy	< ±4.8%	< ±6.0%	< ±5.4%	< ±10.2%	< ±4.7%	< ±15.9%
Unknown sample deviation**	6.2 – 13.7%	-39.1 – -2.3%	-1.4 – 8.3%	-9.0 – 11.6%	-14.7 – -3.5%	12.7 – 17.3%

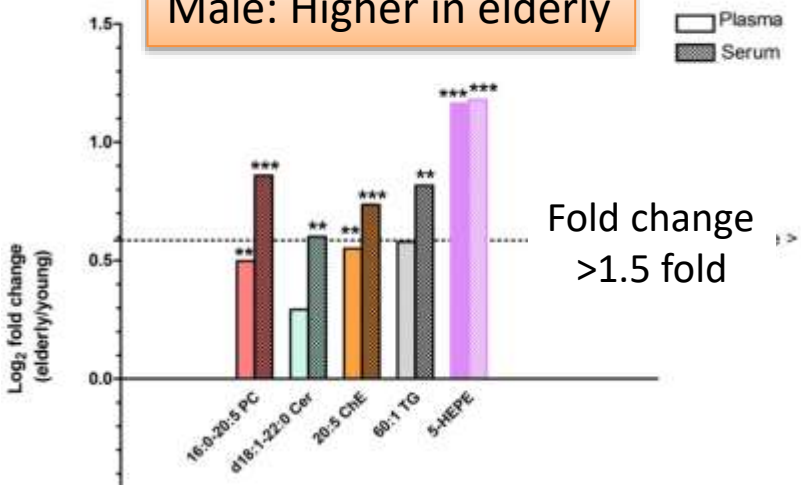
PGE_2	Lab A	Lab B	Lab C	Lab D	Lab E	Lab F
Carry over	0%	0%	0%	0%	NA	0%
Parallelism	97.4%	89.6%	99.8%	103.1%	NA	88.4%
Precision	< 3.6%	< 5.6%	< 2.0%	< 2.5%	NA	< 7.9%
Accuracy	< ±14.7%	< ±12.7%	< ±5.4%	< ±24.7%	NA	< ±12.0%
Unknown sample deviation**	-52.9 – -12.4%	-68.0 – -23.4%	-52.2 – 29.2%	-13.5 – 195.9%	NA	-24.0 – -28.4%

Ishikawa R, et al., *Bioanalysis*. 2021;13: 1533-1546.

Fundamental studies on biomarker candidates

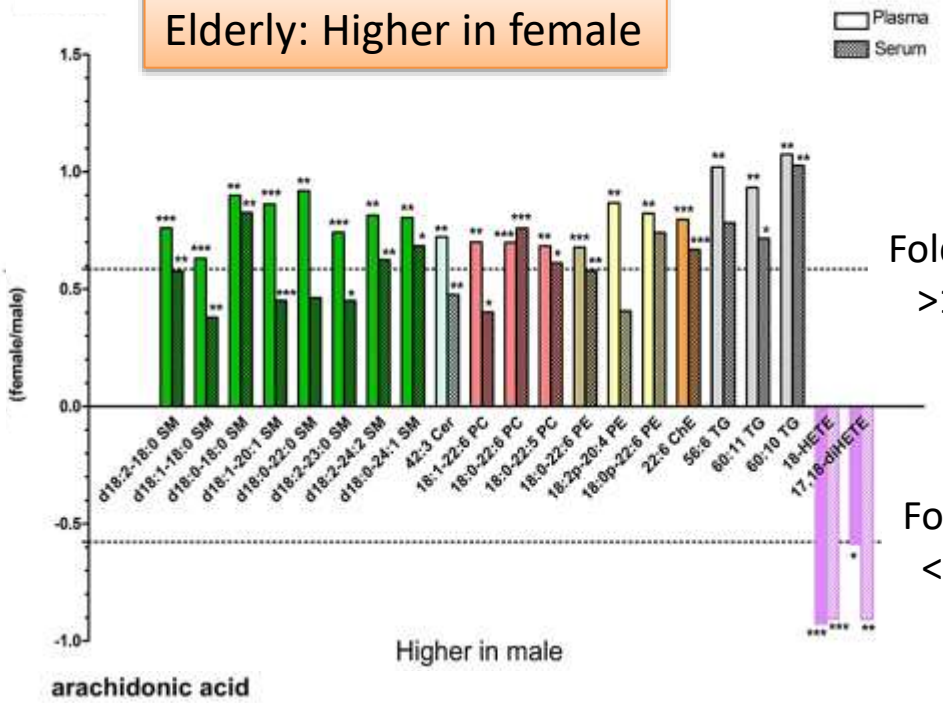
Age and sex differences of miRNA, proteins and metabolites in human serum/plasma

Male: Higher in elderly



Fold change >1.5 fold

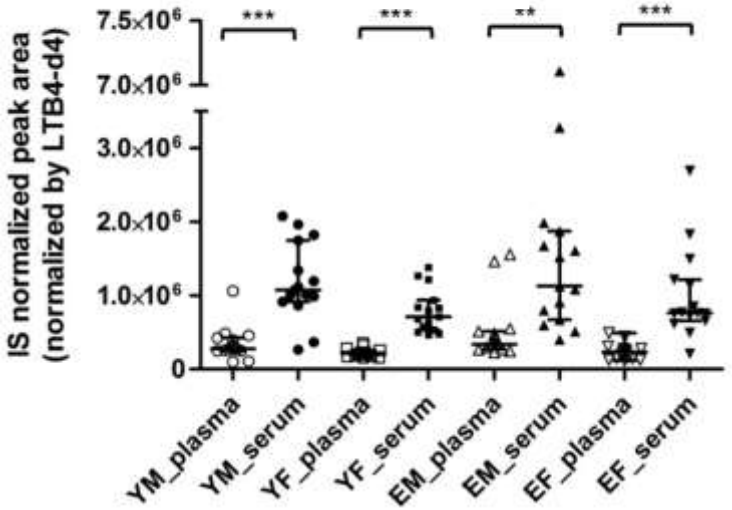
Elderly: Higher in female

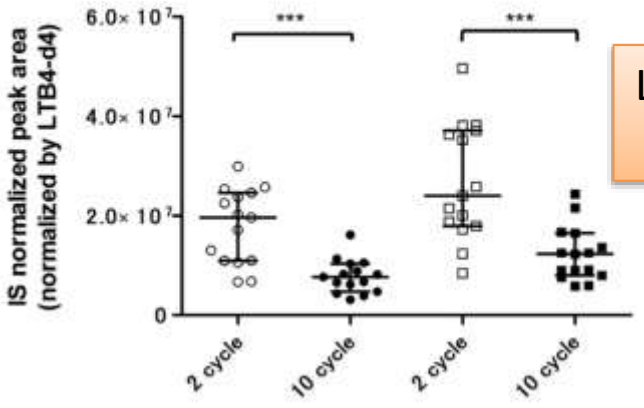


Fold change >1.5 fold

Fold change <0.67 fold

Serum>Plasma (5.6-diHEtrE)





Labile by freeze-thaw (Arachidonic acid)

Ishikawa et. Al., *PLoS One*. 2014; 9: e91806.

Bioanalytical studies on new modality drugs

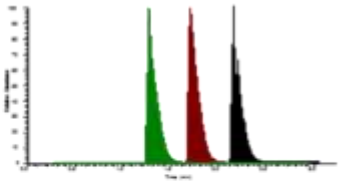
Development of LC/MS-based bioanalytical methods on oligonucleotide therapeutics for future regulation

Oligonucleotide therapeutics
(Antisense oligonucleotide[ASO]
・siRNA)

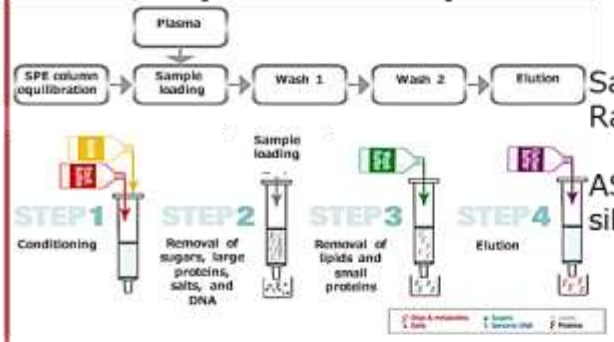
What is the best sample extraction method ?

LC/MS

What is the best separation & detection condition ?

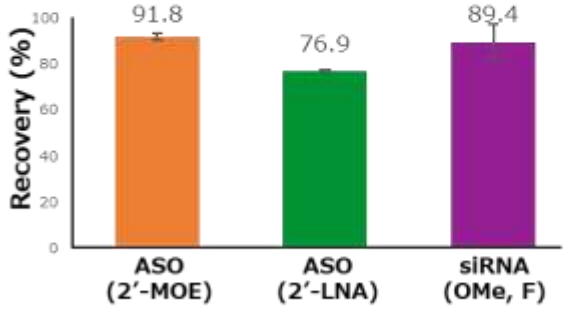


Clarity OTX solid phase extraction



Sample:
Rat plasma

ASO; mipomernsen
siRNA; fitusiran



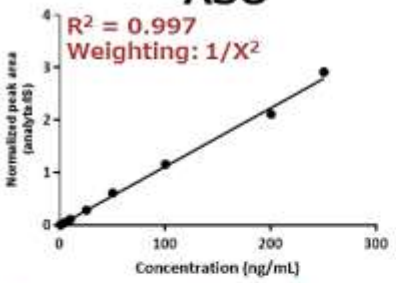
We established an extraction method for ASOs and siRNA with high recovery rate (>80%).

Performance of the developed methods

LC : Ion-pairing reverse phase chromatography (Triethylamine/hexafluoro-2-propanol)

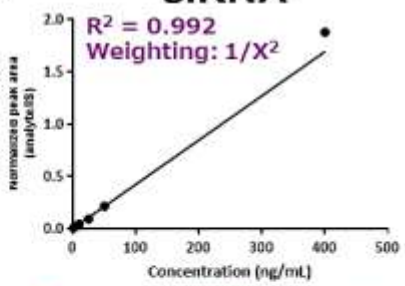
MS: Orbitrap-based high accurate MS

ASO



Range ; 1-250 ng/mL
Accuracy ; 102.8-116.5%
Precision; 4.2-8.0%

siRNA



Range ; 1-400 ng/mL
Accuracy ; 87.6-115.6%
Precision; 4.9-12.7%

We developed highly sensitive bioanalytical methods for an ASO and siRNA.

Sun Y. et al., Bioanalysis. 2020 Dec;12(24):1739-1756.

Bioanalytical studies on new modality drugs

Results of multicenter validation study of the triple quadrupole MS-based bioanalytical method for mipomersen

	Lab A	Lab B	Lab C	Lab D	Lab E	Lab F	Lab G
Calibration range	1 ng/mL – 500.0 ng/mL						
Linearity (R^2)	0.991	0.993	0.997	0.995	0.999	0.993	0.999
Weighting factor	$1/X^2$	$1/X^2$	$1/X^2$	$1/X^2$	$1/X^2$	$1/X^2$	$1/X$
LLOQ	1 ng/mL						
Carry-over	**214.8%** (mipomersen) N.D. (IS)	N.D. (mipomersen、IS)	<20% (mipomersen、IS)	**34.7%** (mipomersen) N.D. (IS)	N.D. (mipomersen、IS)	**122%** (mipomersen) <20% (IS)	<20% (mipomersen) N.D. (IS)
No. of wash needed to remove carry-over peaks	Twice	-	-	Once	-	-	-
Accuracy	88.1% - 101.2%	89.0% - 103.0%	95.5% - 101.3%	96.7% - 110.7%	85.5% - 92.3%	97.3% - 110.0%	87.8% - 99.0%
Precision	0.2% - 8.9%	0.3% - 9.4%	0.8% - 11.8%	3.1% - 8.7%	0.3% - 2.4%	1.9% - 19.0%(LLOQ)	3.4% - 12.8%
Selectivity	No interfering signals	No interfering signals	<20% LLOQ <5% IS	No interfering signals	No interfering signals	<20% LLOQ <5% IS	No interfering signals

The results of validation tests demonstrate that our method could be applied as a standardized bioanalytical method for ASOs, although the occurrence of carry-over should be carefully monitored.

Sun Y, et al., *Bioanalysis*. in press.

On-going research on bioanalysis of new modality drugs

Goal

Standardized method for analyzing drug concentrations in biological samples necessary for PK evaluation of 4 new modalities, including resolution of issues, with companies.

Outline

Principal Investigator: Yoshiro Saito

- Oligonucleotide drug (Yuchen Sun)
- Antibody-drug conjugate (Noritaka Hashii)
- Gene therapy (Yoichi Tanaka)
- Non-natural peptide, peptide-antibody drugs (Kosuke Saito)
- Intracellular peptide drug distribution by Raman spectrometry (Yosuke Demizu)
- Standardization by multi-center evaluation

Participation: 7 Pharma, 6 CRO, 2 Machine and 2 other companies

Efficient drug evaluation and novel regulatory guideline

Reduce time and costs, Efficient drug evaluation

Involved regulatory guidelines on DMPK

- ✓ **Guideline on drug interaction studies for drug development and appropriate information provision (July, 2018, MHLW)**
  - **Evaluation of PK-related drug interaction and inclusion of their information in the drug labels**
  - **Contributed to the overall revision as secretariat/member**

- ✓ **ICH S3A Q&A: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies Focus on Microsampling (November, 2017, ICH)**
  - **Q&A on microsampling for toxicokinetic animal studies**
  - **Contributed as the Rapporteur and Topic leader of MHLW**

- ✓ **ICH M10: Bioanalytical Method Validation and Study Sample Analysis (May, 2022, ICH)**
  - **Bioanalysis of drugs using LC(GC)/MS and ligand binding assay**
  - **Contributed as Topic leader of MHLW**

- ✓ **ICH M12: Drug interaction studies (ICH)**
  - **Contributed as domestic secretariat**

New Modality/New Technology

There still be many issues to be researched in DMPK

DMPK researchers should be centered in the drug development

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(Kihara Mem. Fouda.)

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Thank you for your kind attention

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