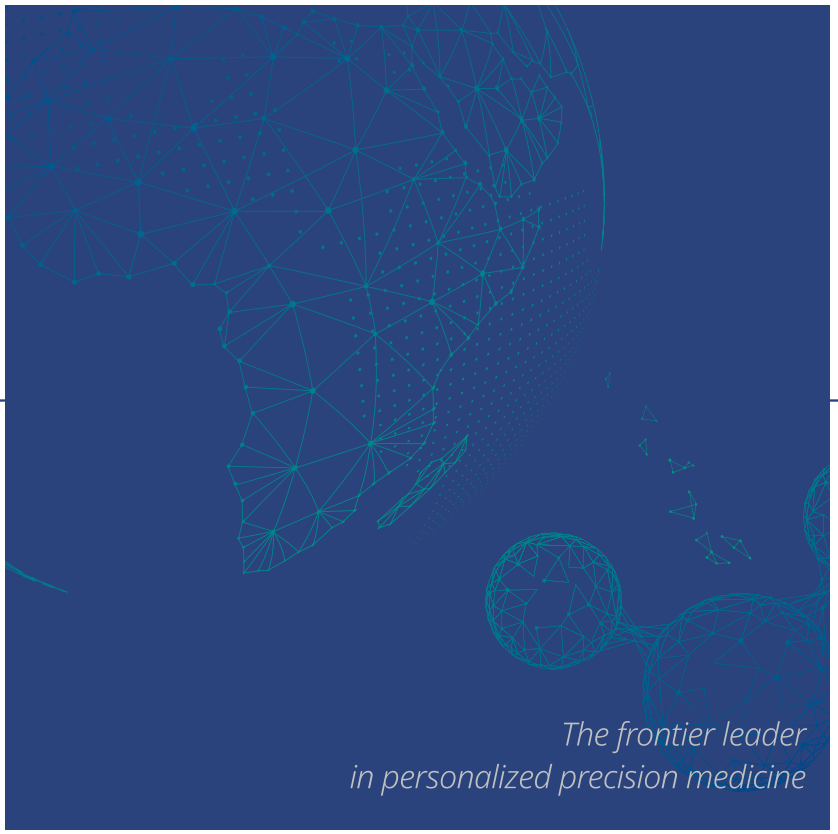
SPMED

Drug Development
Solutions



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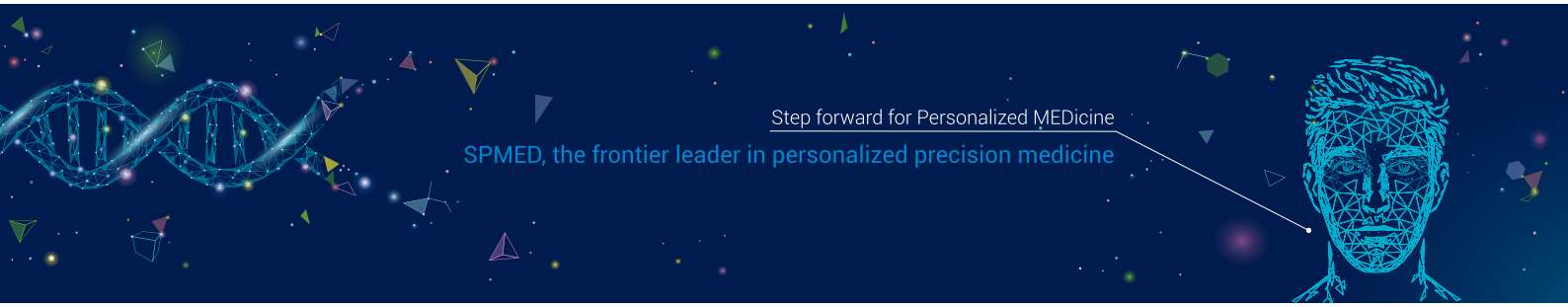

in vitro ADME service

in vitro ADME technology based on drug metabolism and transporter studies

Establishing a global level infrastructure of drug metabolism and transport systems to *in vitro* ADME/pharmacokinetics study

Evaluation of potential as new drug of candidates

Supporting the assessment of drug candidates development/Decreasing the time required for the development

Materials

Human recombinant drug metabolizing enzymes for drug development and bio-medical research (commercial/customized)

Genetic

Genotype-based research support and personalized services

Assessment of drugs absorption, distribution, metabolism and excretion (ADME) are required for verification and approve of the drugs safety and efficacy.

US FDA Guidance

- Check for issues of drug metabolism and drug transporter
- Check for issues of the PK /DDI

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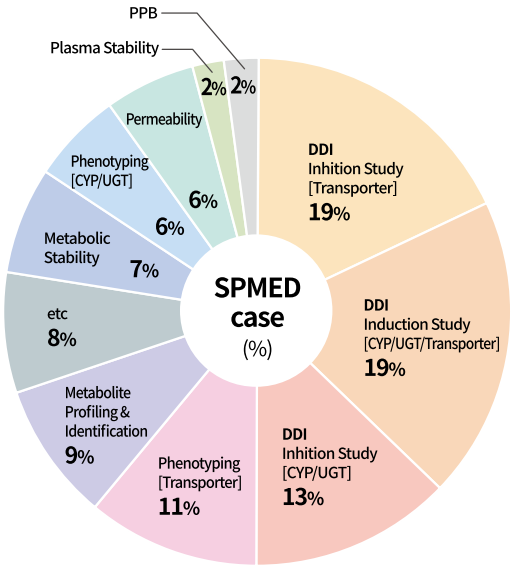
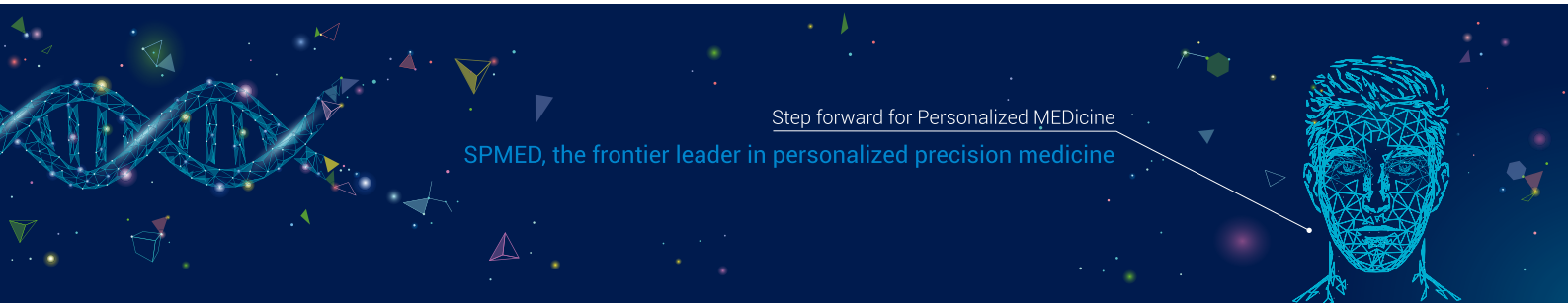
- *in vitro* ADME Testing according to US FDA guidance (2017)
- Extensive ADME technology platform related to drug metabolism and transporter
- Global networks of highly qualified and experienced professional researchers with expertise in drug metabolism, transporter as well as pharmacokinetics
- Customized services according to clients needs



Pharmaceutical company sponsored *in vitro* ADME service in SPMED
(> 40 projects, 13 companies, 2018~present)

- ▶ Permeability test
- ▶ *in vitro* Transporter Study
- ▶ Plasma Protein Binding
- ▶ *in vitro* Drug Drug Interaction (DDI)
- ▶ *in vitro* Metabolism Study
- ▶ *in vitro* ADME package[SPMED]



in vitro ADME service

Advantage

- *in vitro* ADME Testing according to US FDA recommendation
- Extensive ADME based technology for drug metabolizing enzymes and drug Transporter
- Real time communication

Service

- Step-by- step deliberation for securing accuracy and expertise in testing
- Project management services to coordinate all aspects of a client's needs
- Quality assurance to ensure enhanced reliability

Experimental items		
Permeability	▶Caco-2 permeability (LLC-PK1/ MDCK)	P_{app} , Efflux ratio
Protein binding	▶Plasma protein binding (Equilibrium dialysis)	Equilibrium dialysis
Metabolism	▶Metabolic stability / Species comparison	$T_{1/2}$, CL_{int}
	▶Metabolic Reaction phenotyping	CYPs, UGTs, non-CYPs : Kinetic studies [K_m, V_{max}, CL_{int}]
	Pharmacogenetics metabolism study	Genetic based functional study
	▶Metabolites profiling / Metabolites identification	
Transporter	▶Uptake transport screening : SLC family (overexpression cells / oocytes)	OCTs, OATs, OATPs, MATEs : Kinetic studies [K_m, V_{max}, CL_{int}]
	▶Efflux transport screening : ABC family (overexpression cells / oocytes)	MDR1, BCRP, MRP1, MRP2 Kinetic studies [K_m, V_{max}, CL_{int}]
	Cryopreserved Hepatocytes uptake	Kinetic studies [K_m, V_{max}, CL_{int}]
	Pharmacogenetics transport study	Genetic based functional study
Drug Drug Interaction	▶Screening of inhibitory potential	CYPs, UGTs, Transporters : IC_{50}, K_i
	▶Time-dependent inhibition	IC_{50} shift, k_{inact}/K_i
	▶Induction study	CYPs, UGTs, Transporters : mRNA
	in vitro to *in vivo* prediction	IVIVE prediction

Research group who have undertaken pre-clinical and clinical assignments for a number of new drug development projects
'▶' *in vitro* ADME package^{SPMED} : *in vitro* ADME Testing according to US FDA recommendation/ Comprehensive analysis

in vitro Metabolism Study

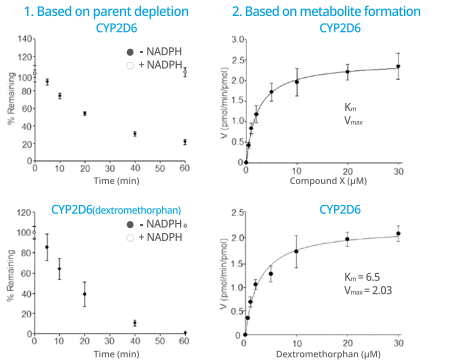
in vitro CYP study

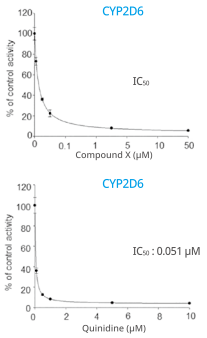
• Our *in vitro* metabolism studies include CYP/UGT Reaction phenotyping, CYP/Transporter Induction and CYP/UGT Inhibition/Time-dependent inhibition assay recommended by US.FDA guidance. These studies will help to understand about the metabolism pathway and drug-drug interaction potency of your compound.

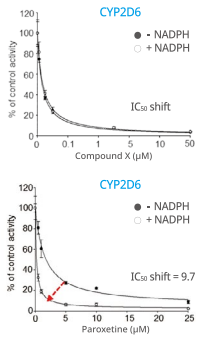
in vitro substrates and inhibitors for CYPs metabolism study

Enzyme	Substrate	Inhibitor	Enzyme	Substrate	Inhibitor
CYP1A2	Phenacetin	Furafylline	CYP2C19	S-Mephenytoin	Benzylnirvanol
CYP2A6	Coumarin	8-Methoxypsoralen	CYP2D6	Dextromethorphan	Quinidine, Paroxetine
CYP2B6	Bupropion	Ticlopidine,Thio-TEPA	CYP2E1	Chlorzoxazone	DETC
CYP2C8	Rosiglitazone	Montelukast	CYP3A	Midazolam	Ketoconazole
CYP2C9	Diclofenac	Sulfaphenazole		Testosterone	

in vitro CYPs metabolism study system

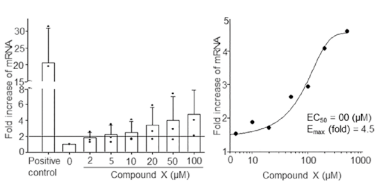
Test	Phenotyping
Enzyme	CYPs , UGTs, non-CYPs
Materials	Liver microsome, Recombinant Enzymes
Dose	Single or Multiple dose
Time	Single or Multiple time point
Data	$T_{1/2}$, % Remaining, K_m, V_{max}, Cl_{int}
Results	

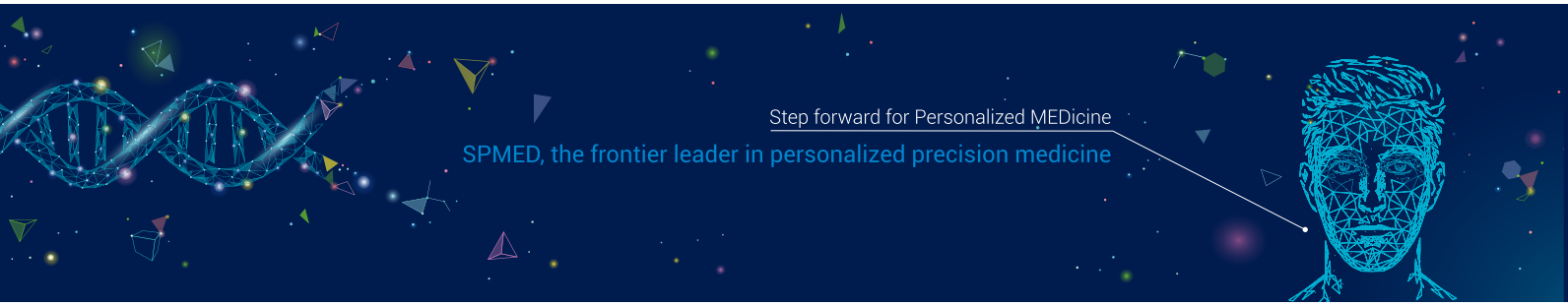
Test	Inhibition Study
Enzyme	CYPs , UGTs, non-CYPs
Materials	Liver microsome, Recombinant Enzymes
Dose	Multiple dose
Time	Single time point
Data	IC_{50} (or K_i)
Results	

Test	Time-dependent inhibition Study
Enzyme	CYPs
Materials	Liver microsome, Recombinant Enzymes
Dose	Multiple dose (± NADPH)
Time	Single time point
Data	IC_{50} shift (or K_I, k_{inact})
Results	

in vitro Induction Study

in vitro Enzyme/Transporter induction study

Category	CYPs	UGTs	Transporters	Results
Isotype	CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, 3A5	UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15	MDR1 (P-gp), MRP2, BCRP, OATP1B1, BSEP, OCT1	
Positive control	Omeprazole, Rifampin	-	Rifampin	
Materials	Hepatocytes (3 donors)	Hepatocytes (3 donors)	Hepatocytes (3 donors)	
Dose	Multiple dose	Multiple dose	Multiple dose	
Time	Single Time point (48 hr)	Single Time point (48 hr)	Single Time point (48 hr)	
Data	Fold increase, EC_{50}, E_{max}	Fold increase	Fold increase	



in vitro Transporter Study

in vitro Transporter study

• Our *in vitro* transporter studies include Phenotyping (Substrate identification), Transporter Induction and Inhibition assay for ABC/SLC transporters recommended by US.FDA guidance. These studies will help to understand about the transport activity and drug-drug interaction potency of your compound.

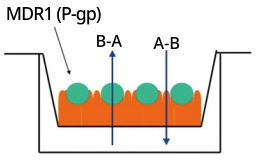
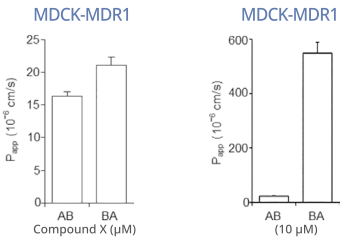
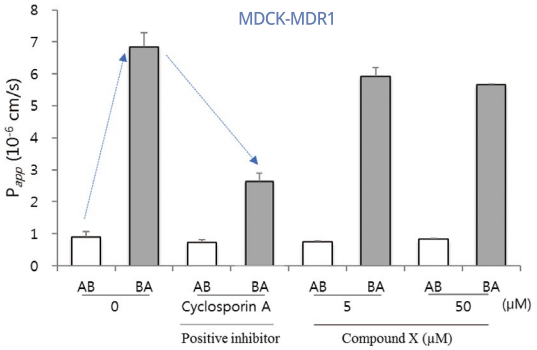
in vitro substrates and inhibitors for ABC transporter study

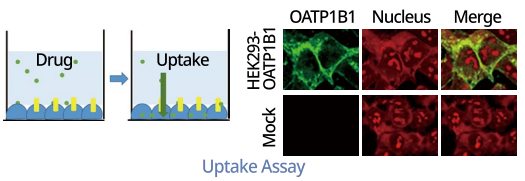
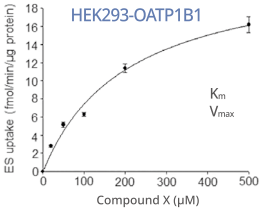
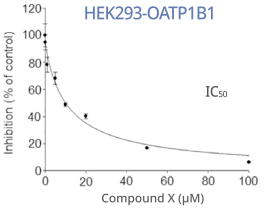
Transporters	*in vitro* system	Substrate	Inhibitor
MDR1	MDCKII-MDR1	Digoxin	Cyclosporin A
BCRP	MDCKII-BCRP	Rhodamine123	Cyclosporin A
MRP1	MDCKII-MRP1	Calcein AM	MK-571
MRP2	MDCKII-MRP2	CDFDA	Cyclosporin A

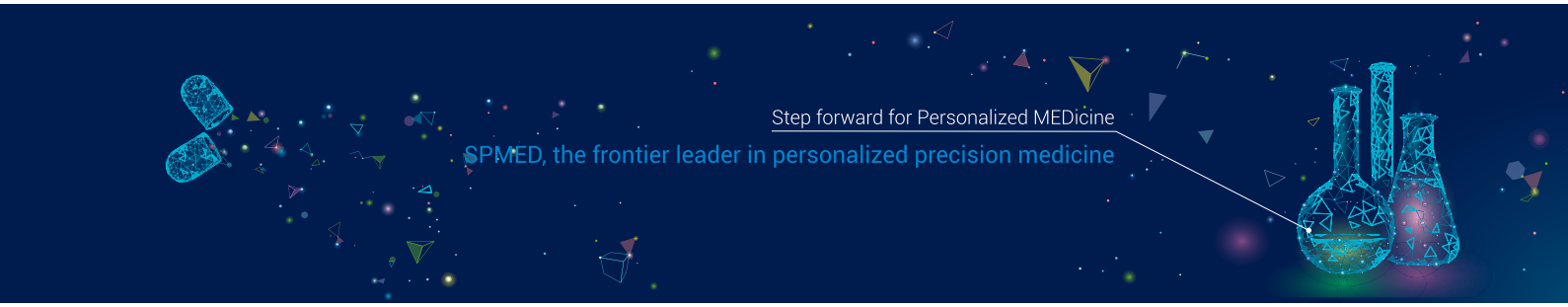
in vitro substrates and inhibitors for SLC transporter study

Transporters	*in vitro* system	Substrate	Inhibitor
OATP1B1	HEK293-OATP1B1	[^{3}H]Estrone sulfate	Cyclosporin A
OATP1B3	HEK293-OATP1B3	[^{3}H] Estradiol-17β-G	Cyclosporin A
OAT1	HEK293-OAT1	[^{3}H]*para*-Aminohippuric acid	Probenecid
OAT3	HEK293-OAT3	[^{3}H]Estrone sulfate	Diclofenac
OCT2	HEK293-OCT2	[^{14}C]Metformin	Verapamil
MATE1	HEK293-MATE1	[^{14}C]Metformin	Qunidine
MATE2K	HEK293-MATE2K	[^{14}C]Metformin	Qunidine

in vitro Transport study system

Class	*in vitro* ABC Transporter system
Assay	 Bidirectional Transport Assay
Transporters	MDR1, BCRP, MRP1, MRP2, etc.
Dose	Multiple dose
Time	Single time point
Data	P_{app}, Efflux Ratio ($P_{app\ B\ to\ A}$ / $P_{app\ A\ to\ B}$)
Phenotyping Study Results	
Inhibition Study Results	

Class	*in vitro* SLC Transporter system
Assay	 Uptake Assay
Transporters	OATP1B1/1B3/2B1, OCT1/2, OAT1/3, MATE1/2K, etc.
Dose	Multiple dose
Time	Single Time point
Data	Uptake Ratio (Transporter-expressing uptake vs. control) K_m, V_{max}, CL_{int}, IC_{50}, K_i
Phenotyping Study Results	
Inhibition Study Results	



SPMED™ Human Recombinant Enzymes

SPMED™ Human Recombinant Enzymes customized drug metabolism enzymes for drug development and bio-medical research

Introducing SPMED™ Human Recombinant Enzymes

SPMED™ Human Recombinant Enzymes can be used in essential assays (substrate identification, inhibition study, time dependent inhibition, induction study, metabolic stability, etc.) across a variety of pharmaceutical fields, especially new drug development.

These enzymes are prepared from insect cells with recombinant baculovirus containing cDNA for a human cytochrome P450 (CYPs) isoenzymes with reductase (in some cases cytochrome b_5), or a human UDP-glucuronosyltransferase (UGTs) isoenzymes.

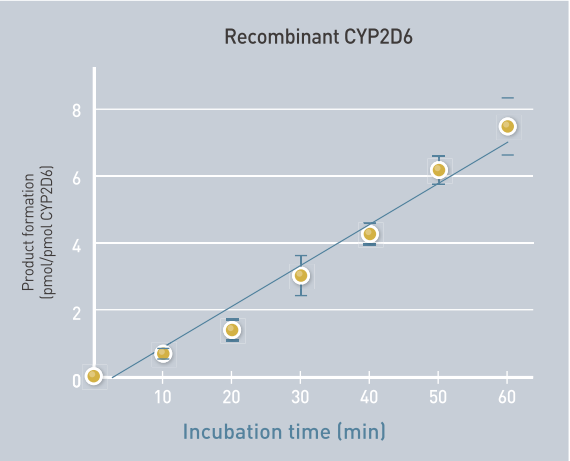
These are the full complete enzyme list of CYPs, UGTs and more, which recommended by the US FDA for drug development and drug interaction study.

SPMED can help your research providing high-quality products.

High Activity and Linearity

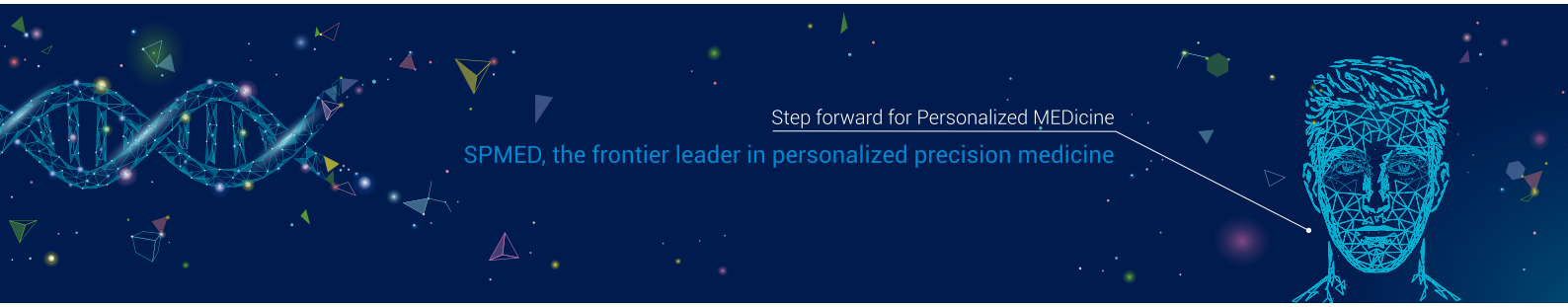
SPMED™ Human Recombinant Enzymes show excellent linearity with time.

These products provide efficient metabolite production with long linear metabolite formation with typical times of over 30 minutes.



Features & Benefits

- Higher catalytic activities than the native enzymes from human liver microsomes (HLMs)
- High-expression system and quality control: Providing excellent quality products in high activity
- Guaranteed reliability by providing performance results including activity, kinetic assay, etc.
- Customized metabolic enzyme production considering genetic variant
- Reduction of time and cost by mass production within Korea



SPMED™ Human Recombinant Enzymes

Customized orders are also available for other enzymes according to the requests, other than the existing items.

Human P450 Enzymes

Description	P450 concentration	Qty
Human CYP1A2 + reductase	0.5 nmol	0.5 mL
Human CYP2A6 + reductase + b5	0.5 nmol	0.5 mL
Human CYP2B6 + reductase + b5	0.5 nmol	0.5 mL
Human CYP2C8 + reductase + b5	0.5 nmol	0.5 mL
Human CYP2C9 + reductase + b5	0.5 nmol	0.5 mL
Human CYP2C19 + reductase + b5	0.5 nmol	0.5 mL
Human CYP2D6 + reductase	0.5 nmol	0.5 mL
Human CYP2E1 + reductase + b5	0.5 nmol	0.5 mL
Human CYP2J2 + reductase + b5	0.5 nmol	0.5 mL
Human CYP3A4 + reductase + b5	0.5 nmol	0.5 mL
Human CYP3A5 + reductase + b5	0.5 nmol	0.5 mL
Human CYP4F2 + reductase + b5	0.5 nmol	0.5 mL

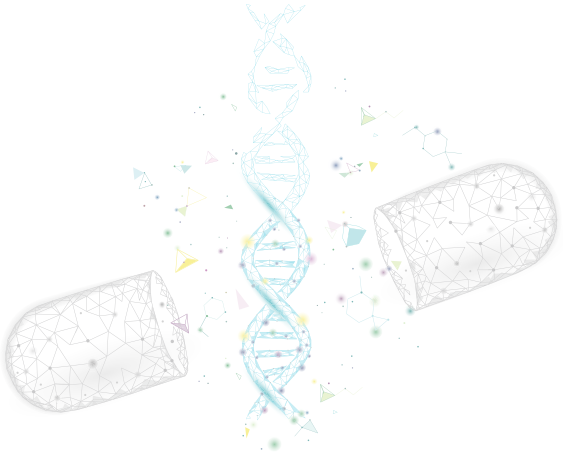
Other Human Metabolic Enzymes

The products listed will be made after your order is received. Please contact us with the details of your project and we will provide timeline and quote.

Description	Protein concentration	Qty
Human FMO1	5 mg/ml	0.5 mL
Human FMO3	5 mg/ml	0.5 mL
Human FMO5	5 mg/ml	0.5 mL
Human CES1	5 mg/ml	0.5 mL
Human CES2	5 mg/ml	0.5 mL
Human Monoamine Oxidase A (MAO-A)	5 mg/ml	0.5 mL
Human Monoamine Oxidase A (MAO-B)	5 mg/ml	0.5 mL
Human NAT1	5 mg/ml	0.5 mL
Human NAT2	5 mg/ml	0.5 mL

Human UGT Enzymes

Description	Protein concentration	Qty
Human UGT1A1	5 mg/ml	0.5 mL
Human UGT1A3	5 mg/ml	0.5 mL
Human UGT1A4	5 mg/ml	0.5 mL
Human UGT1A6	5 mg/ml	0.5 mL
Human UGT1A9	5 mg/ml	0.5 mL
Human UGT2B4	5 mg/ml	0.5 mL
Human UGT2B7	5 mg/ml	0.5 mL
Human UGT2B15	5 mg/ml	0.5 mL



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