sanofi

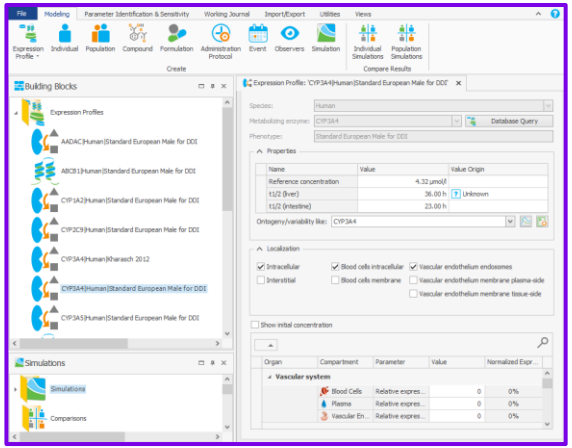
Growing a Community-built Qualified OSP-Model Library

Denise Feick, Sanofi

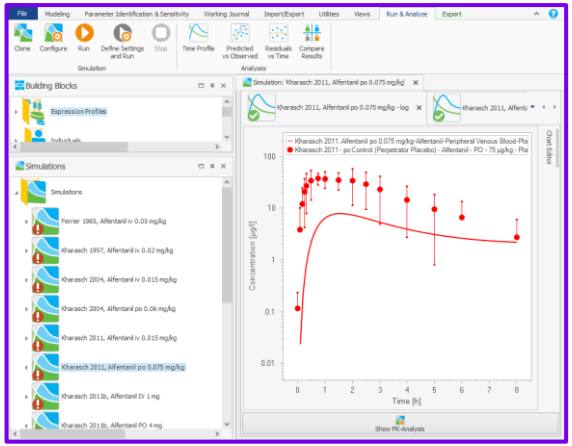
OSP Community Conference 2025, Sep 29-30, Paris, France

Challenge

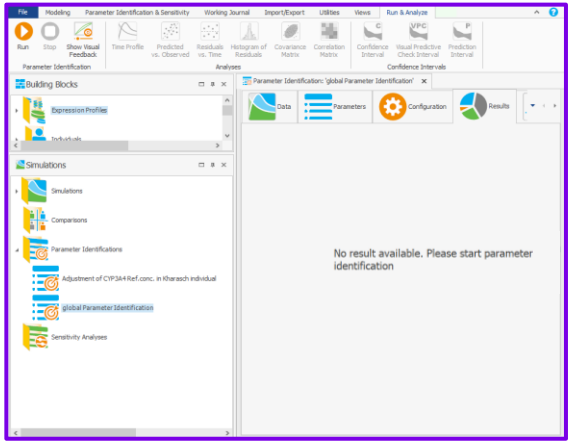
*Let's recall the steps if you need to update **one** PBPK model manually*



Change building block



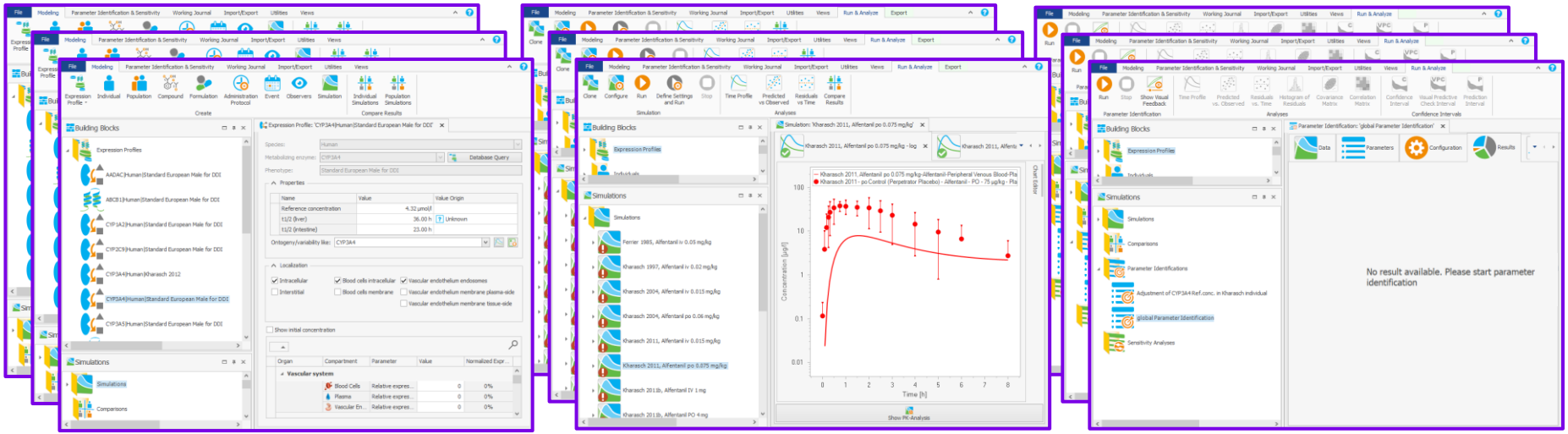
All simulations require update



Perform new parameter identification
Update all simulations
...

Challenge

*Imagine now you need to update **not one but several** PBPK models manually*



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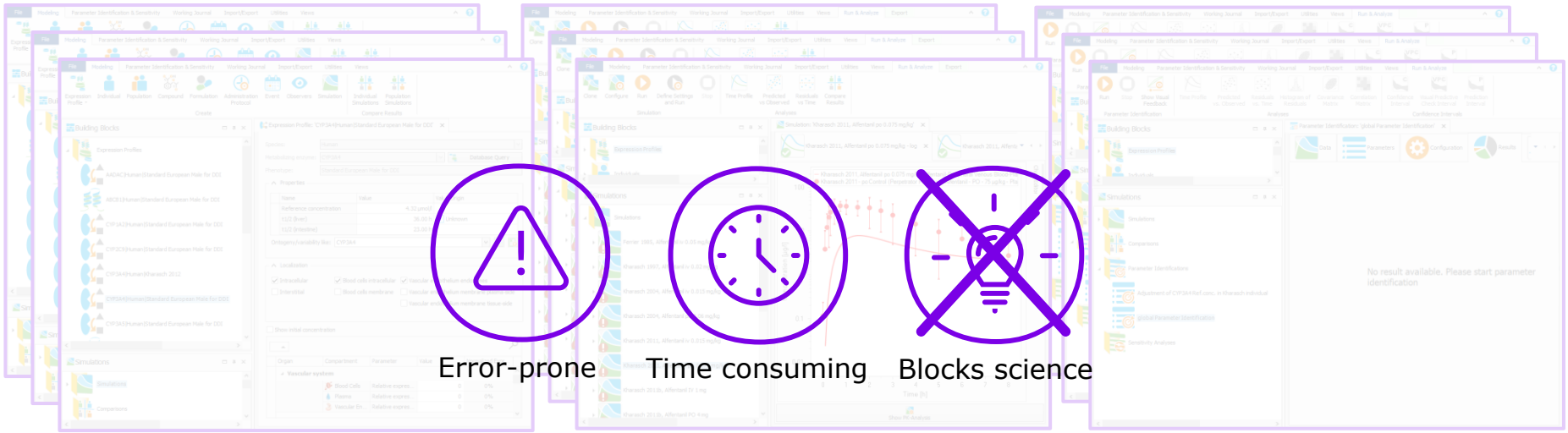


Change building block

All simulations require update

Perform new parameter identification
Update all simulations
...

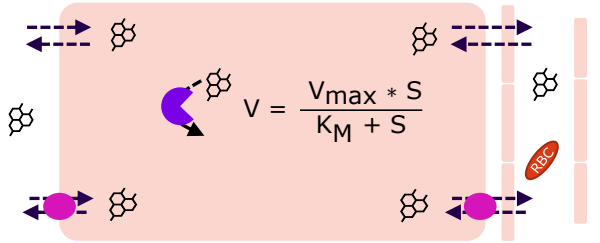
Mission

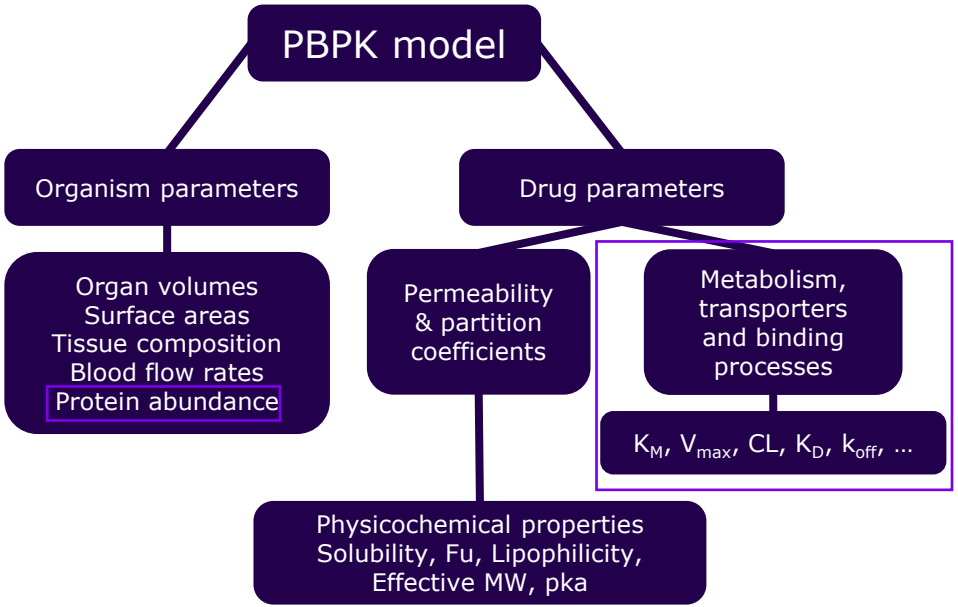
OSP Suite** is a **continuously improving** and **updated** software due to **community efforts

- Focus should lie on ***improvement*** of ***OSP Suite*** but ***not on increased workload***
- Need for ***automated*** and ***standardized workflow*** to keep models up-to-date

- We develop a workflow on the example of systematic expression database replacement in library models
- We present a functional evaluation of a new expression database

Relevance of Expression Data in PBPK





$$V_{max} = k_{cat} * E_0$$

$$V_{max}^{Organ,i} = k_{cat} * E_0^{Organ,i}$$

$$V_{max}^{Organ,i} = k_{cat}^{*} * e_{Rel}^{Organ,i}$$

V_{max}=maximum velocity

k_{cat} = catalytic rate constant

E_0= total enzyme or transporter concentration

$V_{max}^{Organ,i}$= tissue−specific maximum velocity

$E_0^{Organ,i}$= tissue−specific enzyme or transporter concentration

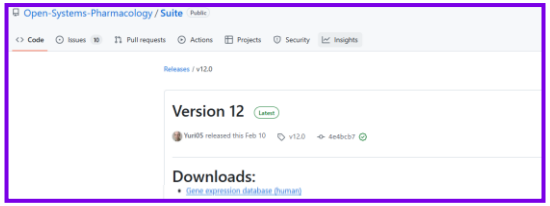
$e_{Rel}^{Organ,i}$ = relative expression (tissue−specific)

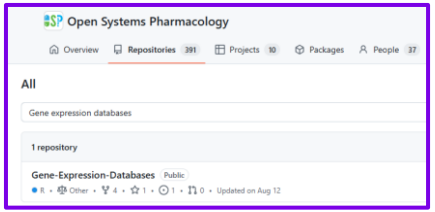
k_{cat}^{*} = apparent catalytic rate constant (global parameter)

Consideration of expression databases allows modeling of tissue-specific active ADME processes

Graphic adopted from: Kuepfer et al. CPT PSP. 2016;5(10):516-531.
Equations derived from: Meyer at al. Drug Metab Dispos. 2012;40(5):892-901

Expression Data for OSP Suite





TECHNOLOGY & SOURCE	Array	EST	RT-PCR	RNAseq
	Whole genome expression arrays from ArrayExpress[1,2]	Expressed sequence tags (EST) from UniGene[1,3]	Gene expression estimates from literature[1,4,5,6]	Data from BgeeDB database[7]

Technological progress

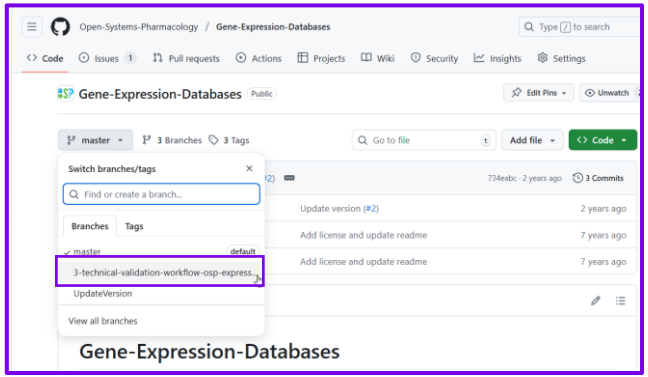
DATA	Healthy tissue, tumor, tissue samples, cell lines, etc.	Healthy, normal, and untreated primary tissue samples
SPECIES	Restricted to human expression	17 species, e.g., human, monkey, minipig, dog, rat and mouse

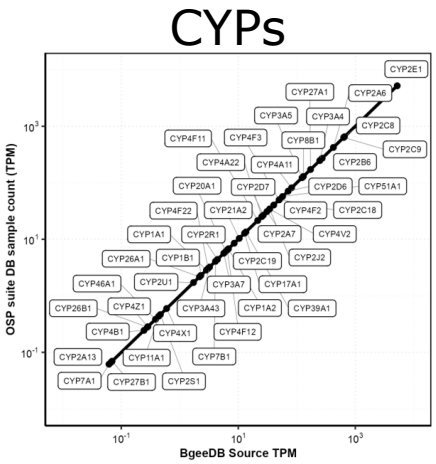
[1]Meyer at al. Drug Metab Dispos. 2012;40(5):892-901
[2]Kolesnikov et al. Nucleic Acids Res. 2015;43(Database issue):D1113-6
[3]Wheeler et al. Nucleic Acids Res. 200836(Database issue):D13-21
[4]Nishimura et al. Yakugaku Zasshi.. 2003; 123(5). 369-75
[5]Nishimura and Naito. Drug Metab Pharmacokinet. 2005;20(6). 452-77
[6]Nishimura and Naito. TDrug Metab Pharmacokinet. 2006;21(5). 357-74
[7]Cordes and Rapp. CPT PSP. 2023;12(3):311-319

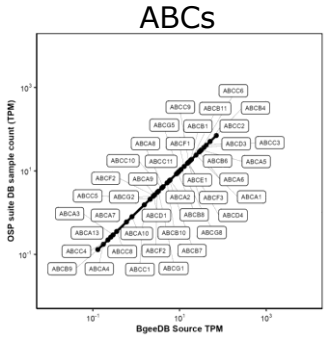
RNAseq-based Gene Expression Databases

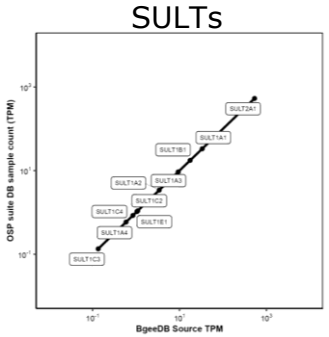
Technical validation

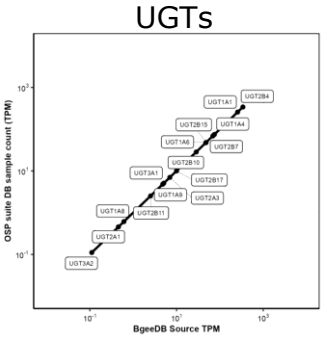
- Provide source code:
  - Data extraction & preparation
  - Constructing OSP expression databases
  - Visual inspection
  - Data comparisons



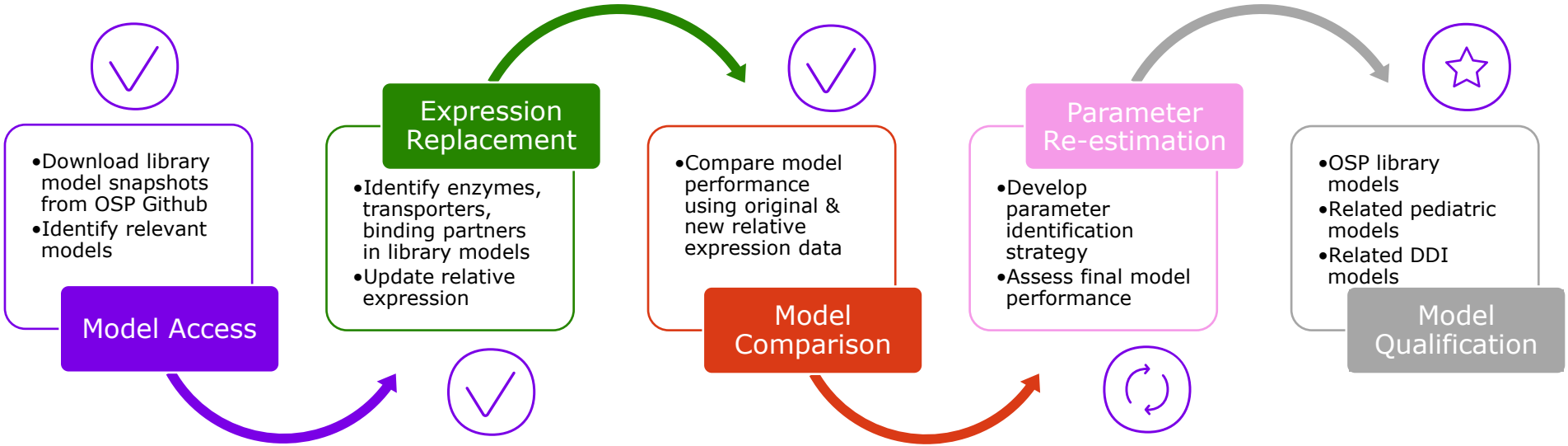








Model Update Workflow



OSP Model Library

Scientific Community

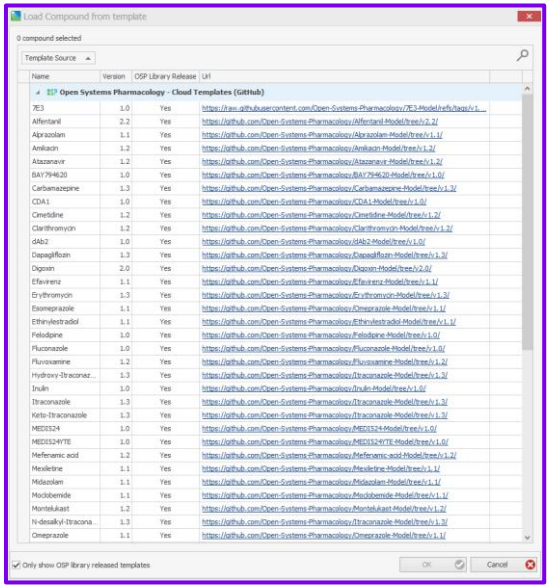
Models → Validation/Quality Assessment → Model Versioning and Evaluation Plan

Library Model

- Download library model snapshots from OSP Github
- Identify relevant models

Model Access

Access via PK-Sim GUI



Access via OSP Github

OSP Model Library

Model	Function	Model	Function	Model	Function
7E3	Antibody[1]	**Digoxin**	Substrate P-gp[2] DDI Qualification P-gp[3]	**Midazolam**	Index substrate CYP3A4[2] DDI Qualification CYP3A4[3]
Alfentanil	Substrate CYP3A4[2] DDI Qualification CYP3A4[3] Pediatric Qualification CYP3A4 Ontogeny[3]	**Efavirenz**	Moderate inducer CYP3A4, CYP2B6, CYP2C19[2] Moderate sensitive substrate CYP2B6[2] DDI Qualification CYP3A4[3]	**Moclobemide**	DDI Qualification CYP2C19[3]
Alprazolam	Substrate CYP3A[2] DDI Qualification CYP3A4[3]	**Erythromycin**	Moderate inhibitor CYP3A4[2] DDI Qualification CYP3A4[3] DDI Qualification P-gp[3]	**Montelukast**	Substrate CYP2C8[2] Pediatric Qualification CYP2C8 Ontogeny[3]
Amikacin	Pediatric Qualification GFR Ontogeny[3]	**Ethinylestradiol**	DDI Qualification CYP1A2[3]	**Omeprazole**	Index substrate CYP2C19[2] DDI Qualification CYP2C19[3]
Atazanavir	Inhibitor OATP1B1 & OATP1B3[2] DDI Qualification UGT[3]	**Felodipine**	Substrate CYP3A4*	**Raltegravir**	Pediatric modeling DDI Qualification UGT[3]
BAY794620	Antibody[1]	**Fluconazole**	Moderate inhibitor CYP3A4[2] DDI Qualification CYP3A4[3]	**Rifampicin**	Inducer (several CYPs)[2] DDI Qualification CYP3A4[3] DDI Qualification P-gp[3]
Caffeine	Index substrate CYP1A2[2] DDI Qualification CYP1A2[3]	**Fluvoxamine**	Strong inhibitor CYP1A2, 2C19[2] DDI Qualification CYP3A4[3] DDI Qualification CYP1A2[3] DDI Qualification CYP2C19[3]	**Sildenafil**	Substrate CYP3A4[2]
Carbamazepine	Strong inducer CYP3A4[2] DDI Qualification CYP3A4[3]	**Inulin**	Polysaccharide[1]	**S-Mephenytoin**	Sensitive substrate CYP2C19[2] DDI Qualification CYP2C19[3]
CDA1	Antibody[1]	**Itraconazole**	Strong inhibitor CYP3A4[2] DDI Qualification CYP3A4[3] DDI Qualification P-gp[3]	**Sufentanil**	Pediatric Qualification CYP3A4 Ontogeny[3]
Cimetidine	Weak inhibitor CYP3A4[2] Inhibitor MATE1/2-K, OCT2[2] DDI Qualification CYP3A4[3]	**MEDI524**	Antibody[1]	**Tefibazumab**	Antibody[1]
Clarithromycin	Strong inhibitor CYP3A4[2] DDI Qualification P-gp[3] DDI Qualification CYP3A4[3]	**MEDI524YTE**	Antibody[1]	**Tizanidine**	Index substrate CYP1A2[2] DDI Qualification CYP1A2[3]
dAb2	Antibody[1]	**Mefenamic acid**	DDI Qualification UGT[3]	**Triazolam**	Index substrate CYP3A4[2] DDI Qualification CYP3A4[3]
Dapagliflozin	DDI Qualification UGT[3]	**Mexiletine**	Moderate inhibitor CYP1A2[2] DDI Qualification CYP1A2[3]	**Vancomycin**	Pediatric Qualification GFR Ontogeny[3]
				Verapamil	Moderate inhibitor CYP3A4[2] DDI Qualification CYP3A4[3] DDI Qualification P-gp[3]

[1]Niederalt et al. J Pharmacokinet Pharmacodyn. 2018;45(2):235-257
[2]Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)
[3]https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports

OSP Model Library

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CDA1	Antibody[1]	Itraconazole	A4[3] DDI Qualification P-gp[3]	Sufentanil	Pediatric Qualification CYP3A4 Ontogeny[3]
Cimetidine	Weak inhibitor CYP3A4[2] Inhibitor M DDI Quali			tibody[1]	
Clarithromycin	Strong inh DDI Quali DDI Quali			ex substrate CYP1A2[2] I Qualification CYP1A2[3]	
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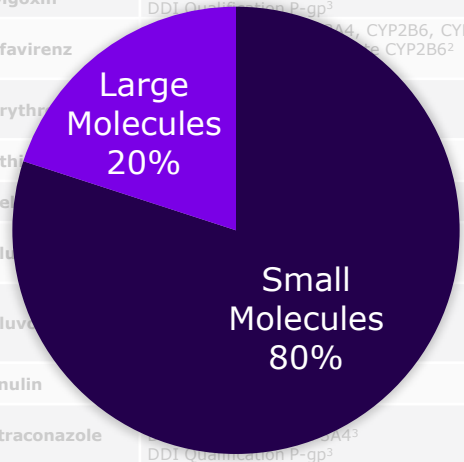


Small molecule OSP library models with defined expression profiles are relevant for replacement of expression data

[1]Niederalt et al. J Pharmacokinet Pharmacodyn. 2018;45(2):235-257
[2]Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)
[3]https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports

Expression Profiles Used in OSP Library

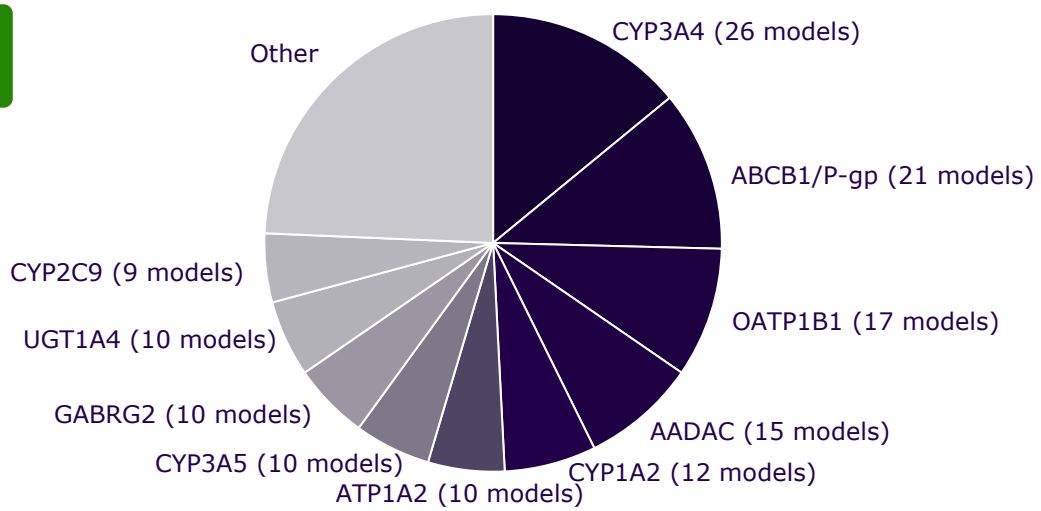
How often do respective expression profiles occur across OSP library models?

- Download library model snapshots from OSP Github
- Identify relevant models

Model Access

Expression Replacement

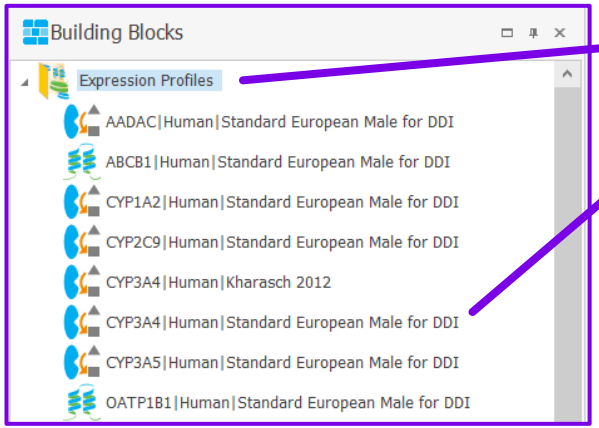
- Identify enzymes, transporters, binding partners in library models
- Replace relative expression



Replacement of Expression Profiles

PK-Sim project
Compound-Model.pksim5

Snapshot
Compound-Model.json

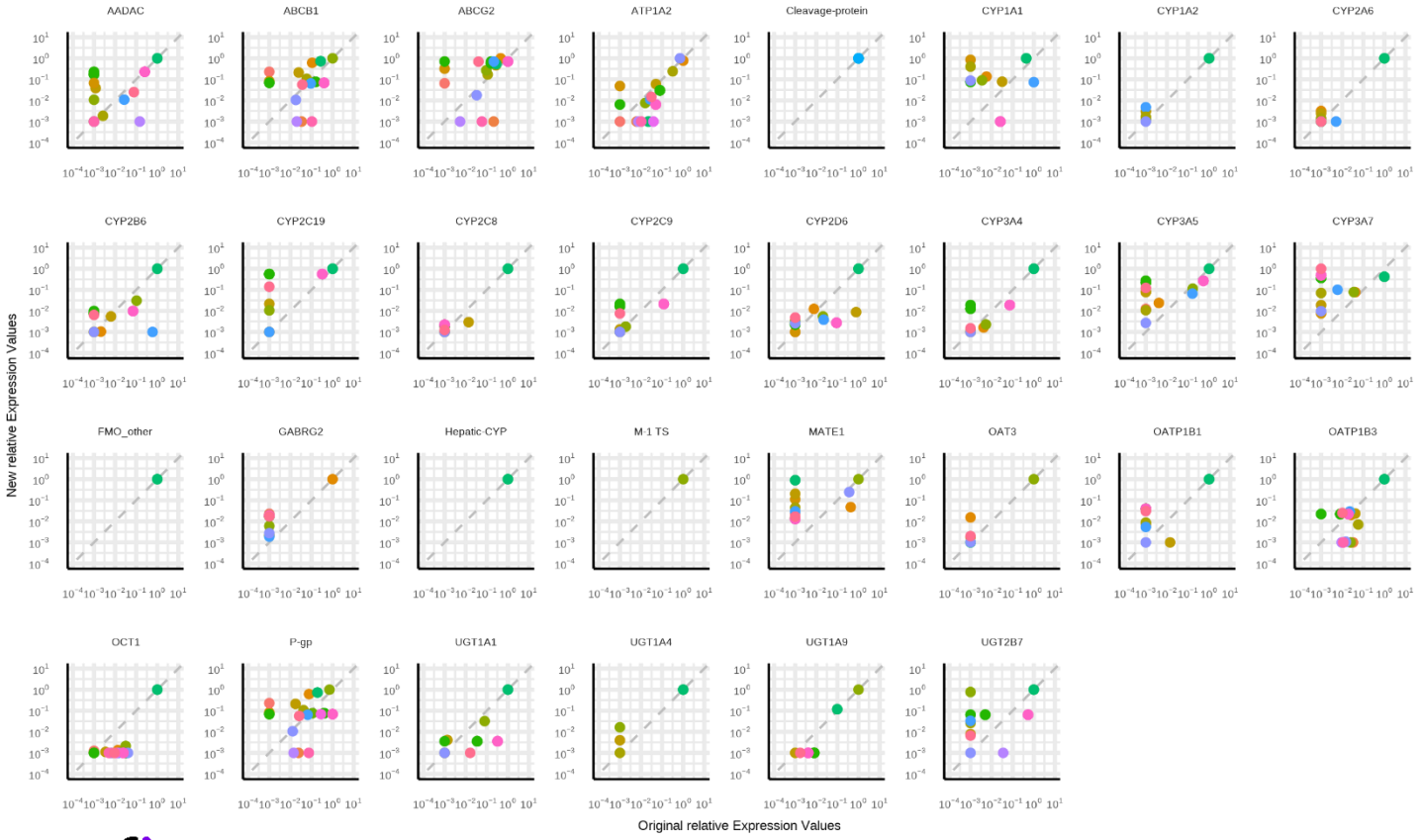


Relative expression

...

Replaced relative expression

Comparing Original & New Expression Values



Selected Meta Data Impacts Relative Expression Profile

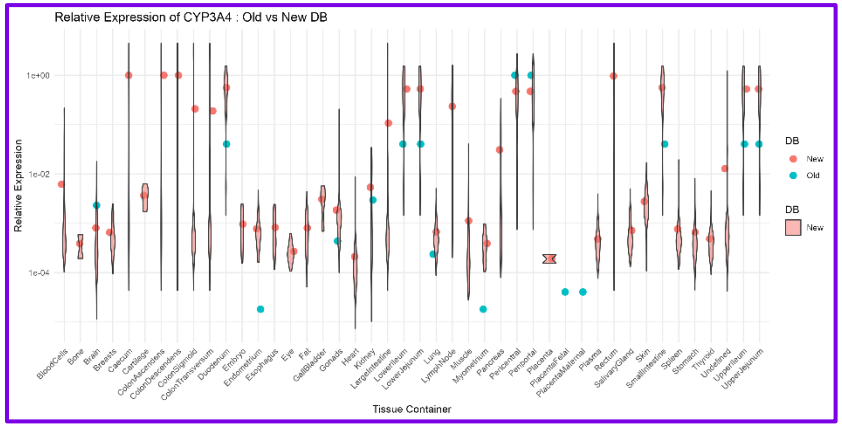
Characteristics of meta data

- Provide annotation & mapping of experimental organs to OSP containers
- Relative expression depends on:
  - Selected meta data
    (age, health state, gender, etc.)
  - Mapping of experimental organs to OSP containers (sub-tissue samples)

- ***Previous RT-PCR***
  - Based entirely on 3 literature sources[1,2,3] with usually one measurement per organ
- ***New RNAseq (for human)[4]***
  - Based on 80 independent experiments with 7390 measurements
  - Multiple measurements per organ for different ages, health state, and gender

OSP-Container	Experimental sample
Kidney	ADULT MAMMALIAN KIDNEY
Kidney	CORTEX OF KIDNEY
Kidney	HEAD KIDNEY
Kidney	KIDNEY
Kidney	KIDNEY EPITHELIAL CELL
Kidney	MESONEPHROS
Kidney	NEPHRON
Kidney	PROXIMAL TUBULE
Kidney	RENAL MEDULLA
Kidney	RIGHT KIDNEY
LowerIleum	DIGESTIVE TRACT
LowerIleum	ILEUM
LowerIleum	INTESTINE
LowerIleum	SMALL INTESTINE

OSP-Container	Experimental sample
LargeIntestine	ASCENDING COLON
LargeIntestine	CAECUM
LargeIntestine	CECAL TONSIL
LargeIntestine	COLON
LargeIntestine	COLONIC EPITHELIUM
LargeIntestine	DESCENDING COLON
LargeIntestine	DIGESTIVE TRACT
LargeIntestine	INTESTINE
LargeIntestine	LARGE INTESTINE
LargeIntestine	MUSCLE LAYER OF SIGMOID COLON
LargeIntestine	OMASUM
LargeIntestine	RECTUM
LargeIntestine	RUMEN
LargeIntestine	SIGMOID COLON
LargeIntestine	SPIRAL COLON
LargeIntestine	TRANSVERSE COLON



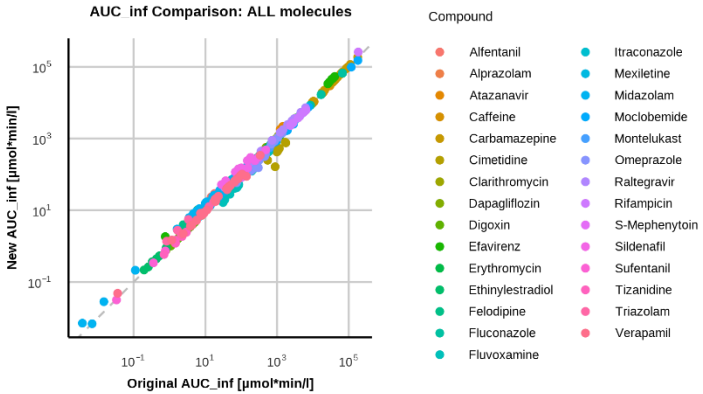
[1]Nishimura et al. Yakugaku Zasshi.. 2003; 123(5). 369-75.
[2]Nishimura and Naito. Drug Metab Pharmacokinet. 2005;20(6). 452-77
[3]Nishimura and Naito. TDrug Metab Pharmacokinet. 2006;21(5). 357-74
[4]Cordes and Rapp. CPT PSP. 2023;12(3):311-319

Comparing PK Using Original & New Expression Values

Model Access
- Download library model snapshots from OSP Github
- Identify relevant models

Expression Replacement
- Identify enzymes, transporters, binding partners in library models
- Replace relative expression

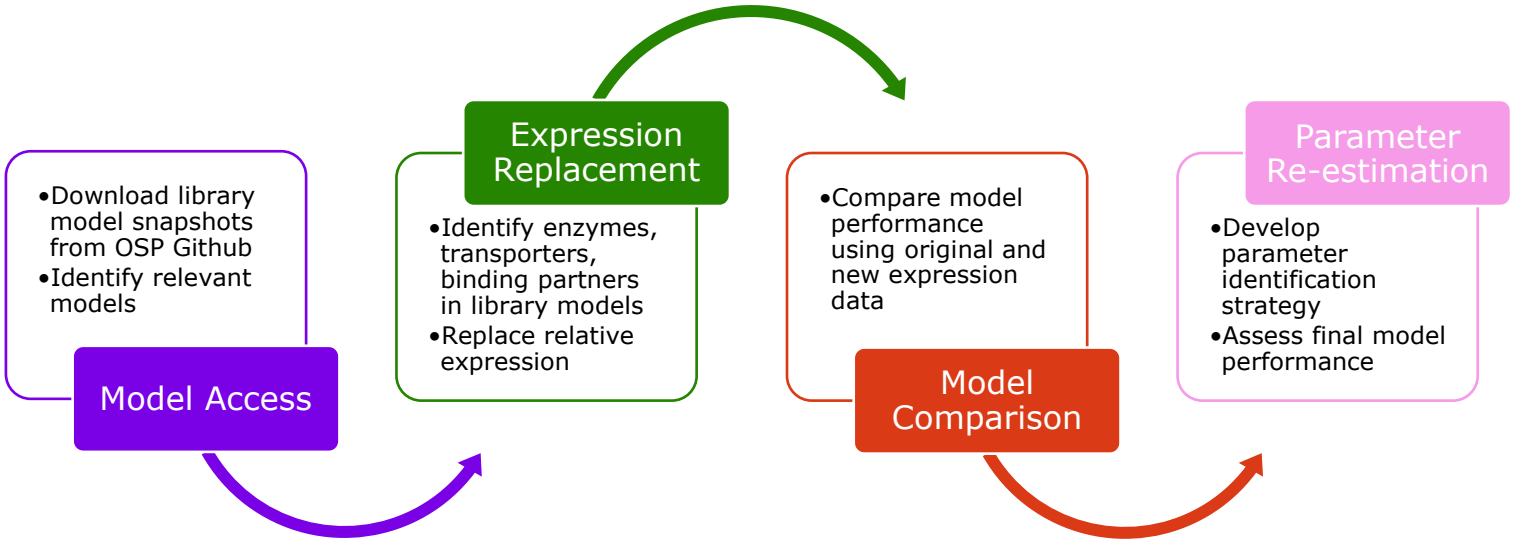
Model Comparison
- Compare model performance using original and new expression data



Changing expression profiles while maintaining original model parametrization impacts PK profiles
→ Parameter re-estimation required

Used Software: https://github.com/Open-Systems-Pharmacology/OSPSuite-R

Parameter Identification Rationale



Used Software: https://github.com/Open-Systems-Pharmacology/OSPSuite.ParameterIdentification

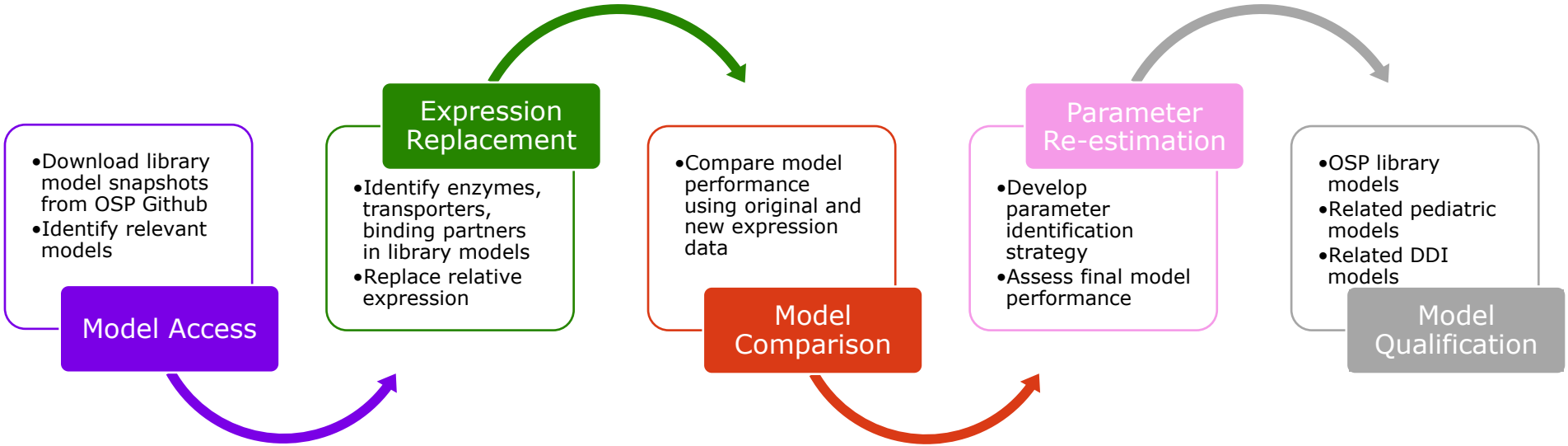
Parameter Identification Rationale

Challenge: Develop a parameter identification rationale applicable to all library models

- ***Which parameters should be estimated?***
  - Expectation: Only parameters related to the modified active processes only, e.g., k_{cat}
  - Reality: In addition parameters like lipophilicity, intestinal permeability & distribution models are impacted

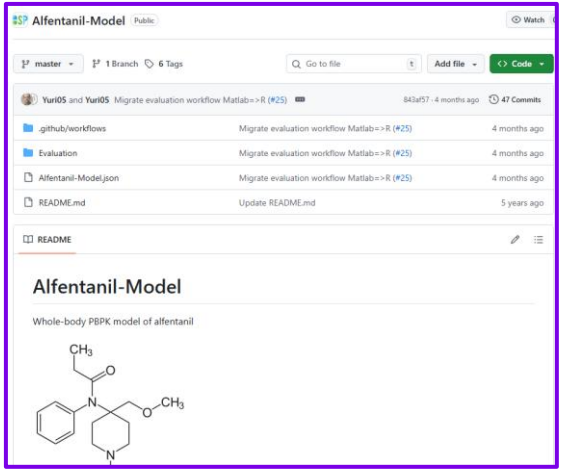
- ***Which scenarios should be considered for parameter optimization?***
  - Expectation: Utilization of all administration routes, whole dose range, fasted/fed, excretion and tissue data, metabolites, etc.
  - Reality: Handle heterogenous literature-based data
    - Mostly plasma/serum data only for limited different scenarios
    - Mostly mean profiles (with error) instead of individual measurements

Complete Model update Workflow with Qualification

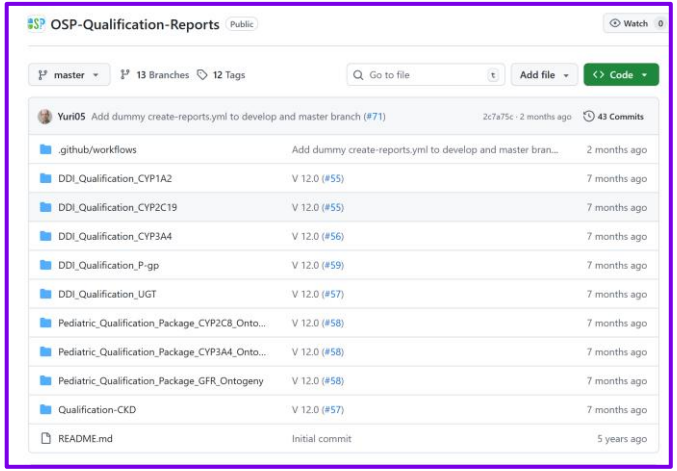


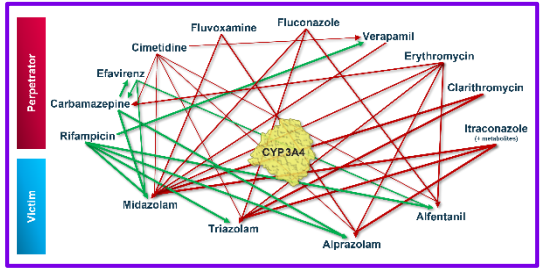
Model Qualification

OSP library models



Pediatric and DDI models





Qualification DDI CYP3A4 network

7 pediatric and >50 DDI models to be updated with new expression database for complete functional evaluation

Updating OSP library models means updating all dependent pediatric and DDI models

https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports
https://github.com/Open-Systems-Pharmacology/Qualification-DDI-CYP3A4
Frechen et al. CPT PSP. 2021;10(6):633-644

Lessons Learned

- First steps towards a script-based workflow for automated and standardized model update

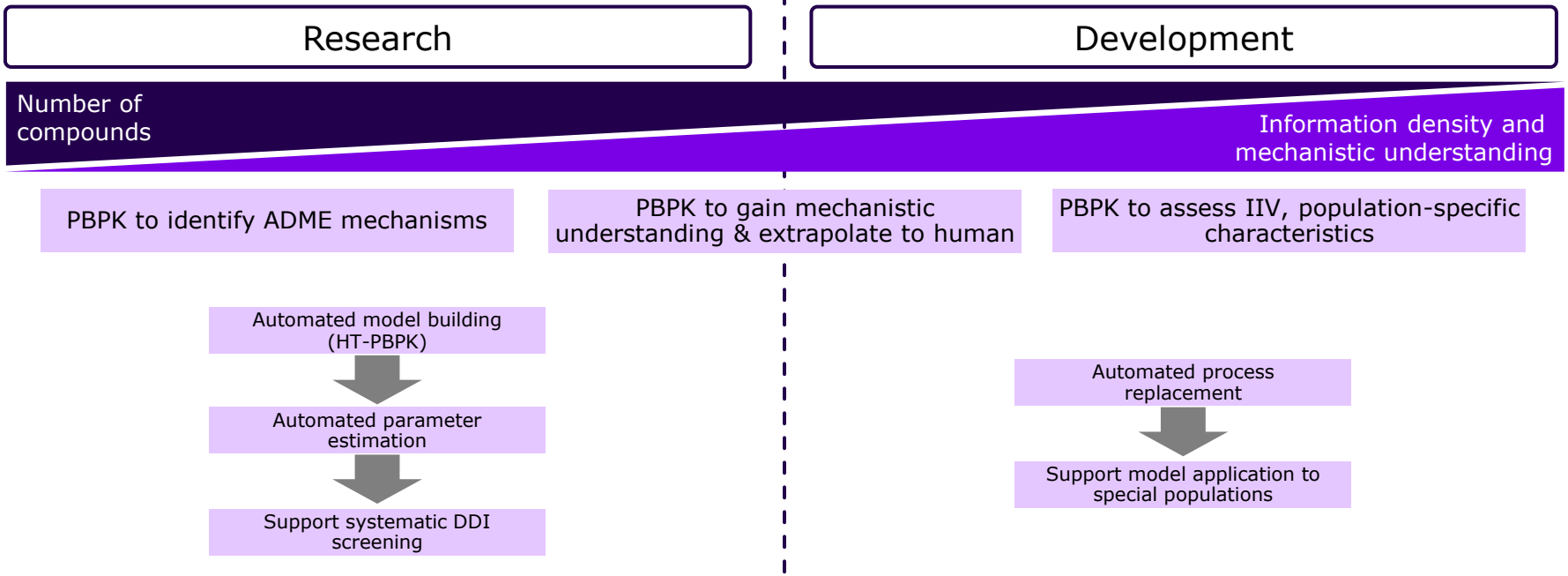
- Great exchange with OSP Community
  - User forum/feature requests
  - Discussions with peers

- R package functionalities identified which would aid automatization and standardization

  - Model snapshot → export simulation pkml → load simulation with *OSPSuite-R*
    - Read json functionality not available yet
  - No direct export from json of *DatasetCombined* objects for further analysis
  - No direct export from json of Parameter Identification to R-based PI object

Application of Workflow

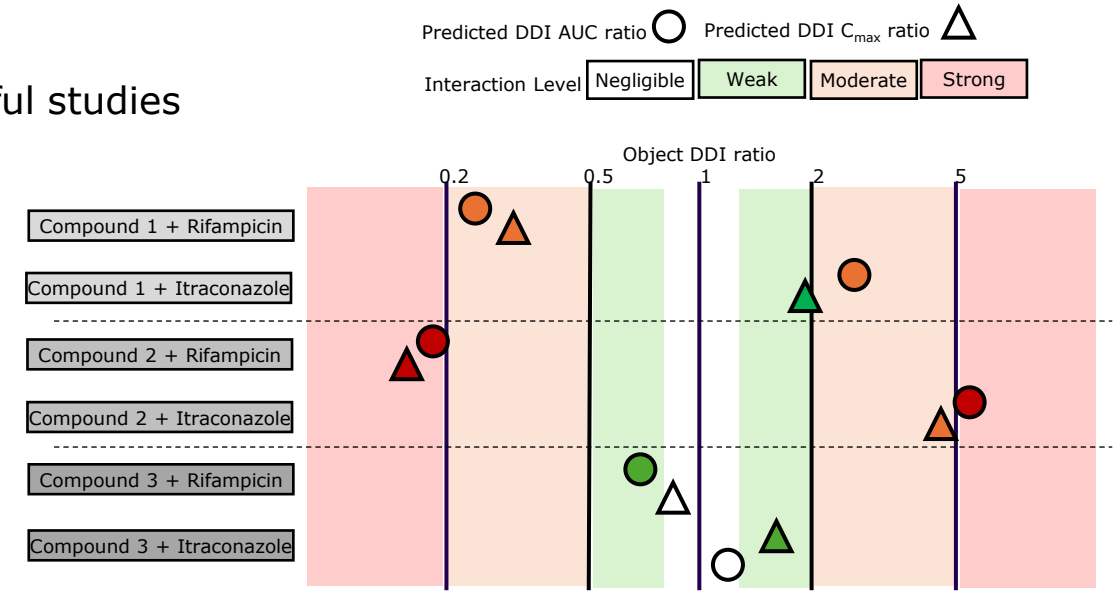
All drug R&D stages can benefit from systematic model building, parameter estimation and model updates



Application of Updated OSP Library Models

Integration in workflows to run virtual DDI trials

- Derisk candidate selection
- Planning and initiation of meaningful studies
- Assessment of co-medication
- Extrapolation of new DDI cases



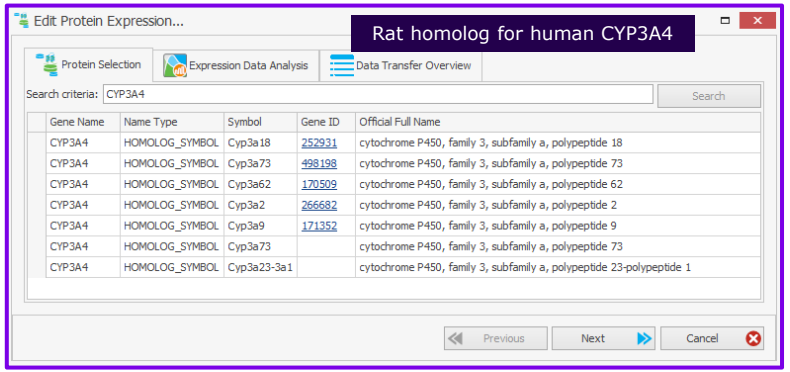
Example of systematic CYP3A4-related DDI assessment

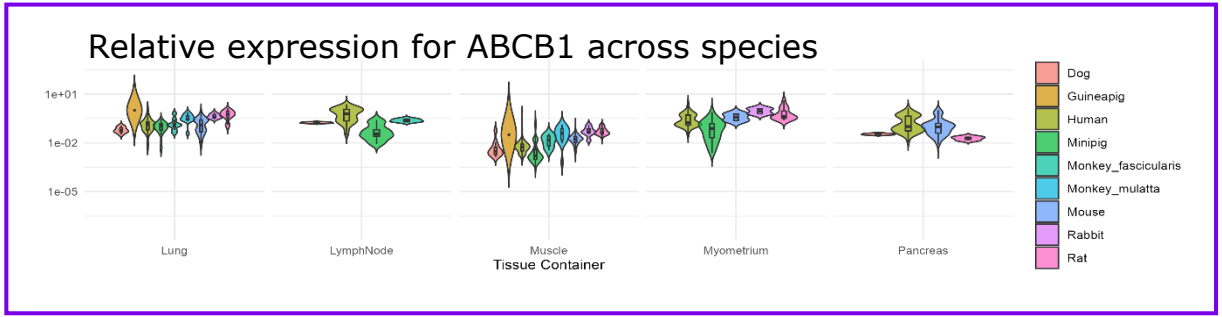
Application of Updated Expression Database

Coverage of relevant species for drug R&D

- Interspecies scaling to predict human PK
  - Information about protein homologs and expression across different species

- Enables combination with AI methods for ADME parameter prediction





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