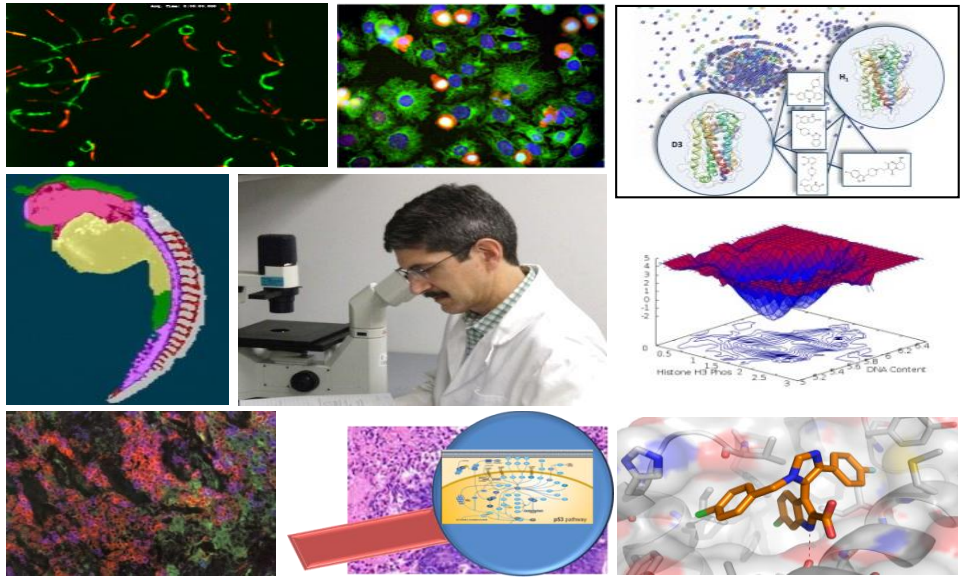
University of Pittsburgh Drug Discovery Institute

The Microphysiology Systems Database (MPS-Db): A platform for aggregating, analyzing, sharing and modeling of in vitro and in vivo safety and efficacy data

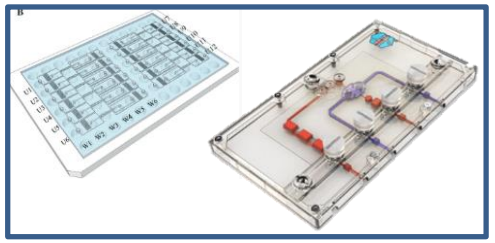
https://mps.csb.pitt.edu/



Mark Schurdak, PhD
Director of Operations, University of Pittsburgh Drug Discovery Institute,
Associate Professor, Computational and Systems Biology

The MPS-Db Is an Internet-Based Platform That Integrates External Databases, to Provide Tools for Data Management, Analysis, and Computational Modeling

Preclinical Data



MPS Data

Output

PubChem

MPS DB

Proprietary Databases and Tools

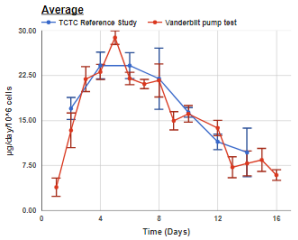
ChEMBL, Unichem, DrugBank

OpenFDA, NAMCS/NHAMCS

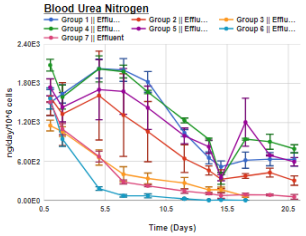
EMA, CT.gov, Health Canada

LiverTox

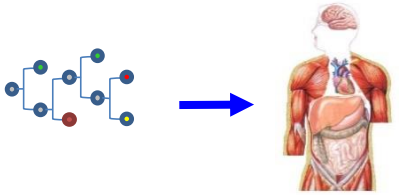
Clinical Data



Reproducibility



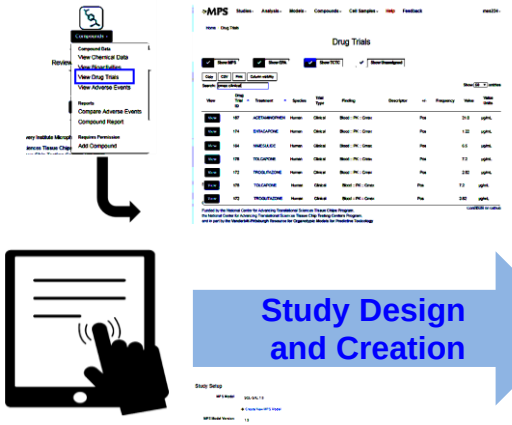
Safety and Efficacy



Computational Models of ADME/Tox & Disease

The MPS-Db Is a Single Entry System Guiding Users Along a Simple, Streamlined Workflow to Design, Create, Implement, Analyze, and Document MPS Studies

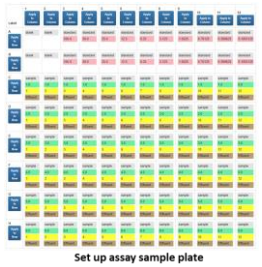
Drug Trials
Adverse Events, …



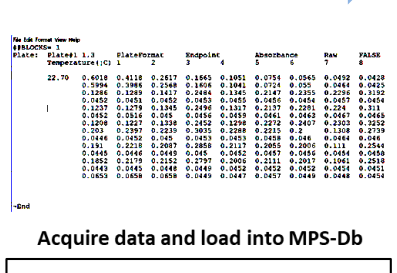
Study Design and Creation

Simple menus facilitate metadata entry for study details

Setting up chips or plates

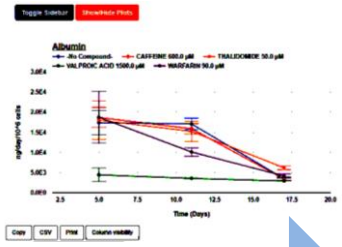


Study Implementation and Data Import

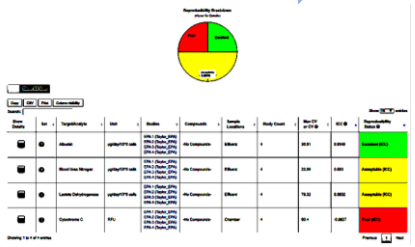


Data import, calibration and review tools

Graphing and Analysis

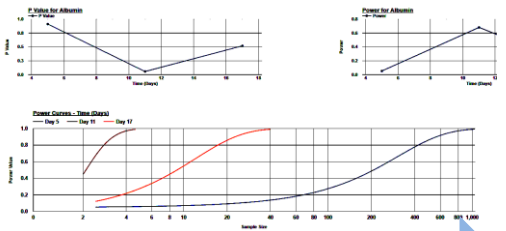


Data Normalization And Analysis

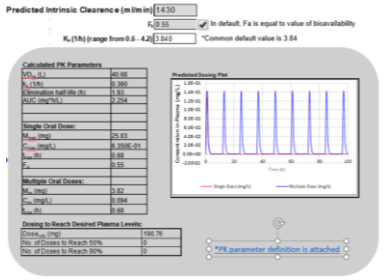


Intra- & Inter-Reproducibility Analysis

One and Two sample Power Analysis

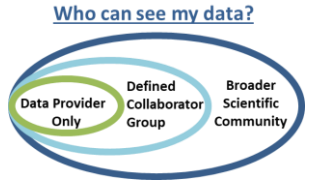


Statistics and Data Modeling



PBPK Computational Modeling

Non-Profit sharing options.



Sharing Data

For-profit sharing options.

The MPS-Db Development Has Evolved to Serve Two Types of Data Sharing Applications

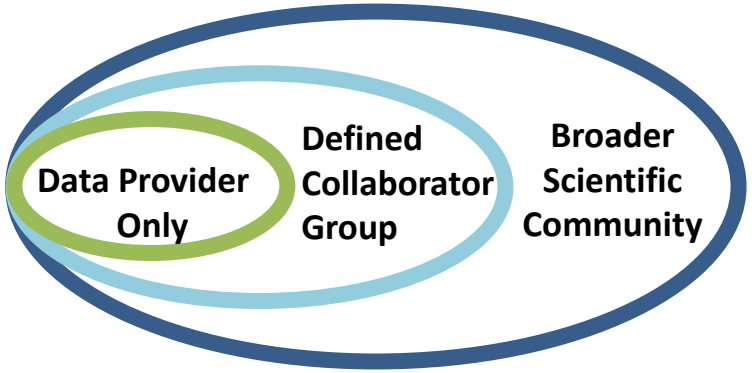
Non-Profit: Academic version

Tissue Chip Consortium, academic institutions, etc.

Provider controls sharing of data & data analyses with:

- Data Provider personnel only
- Defined group(s) of collaborators
- And optionally with the public

Who can see my data?



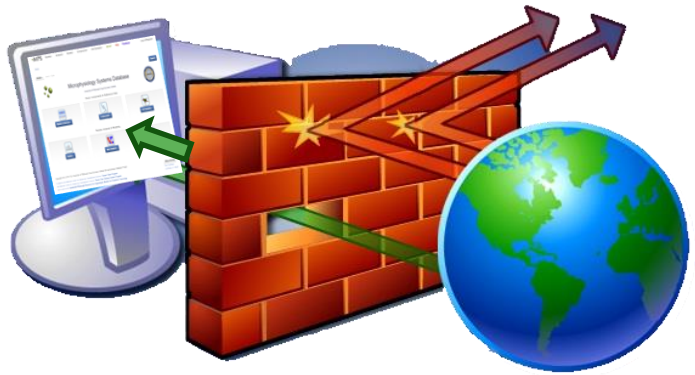
For-Profit: Commercial version

Companies using MPS experimental models

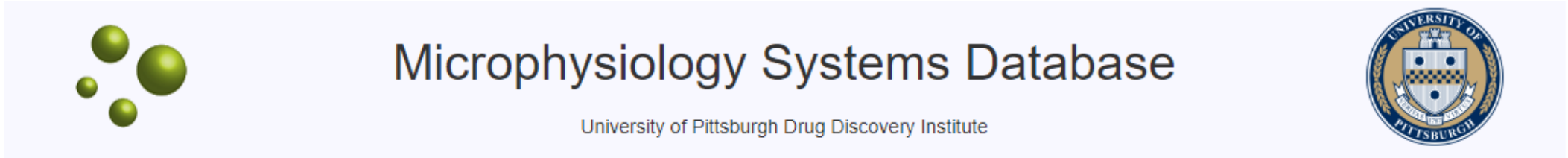
For proprietary company projects:

- Installation behind the **company firewall**
- Integration with **company databases**
- Development of **custom features**

The company can easily copy selected data to the public MPS-Db for sharing with collaborators or the general public.

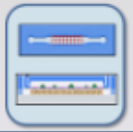


The MPS-Db Is Organized Based on Workflow

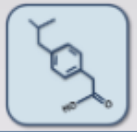


Study Design

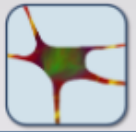
Study Components & Reference Data



Models & Devices



Compounds



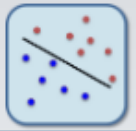
Cell Samples

Study Implementation and Analysis

Review, Analysis & Modeling

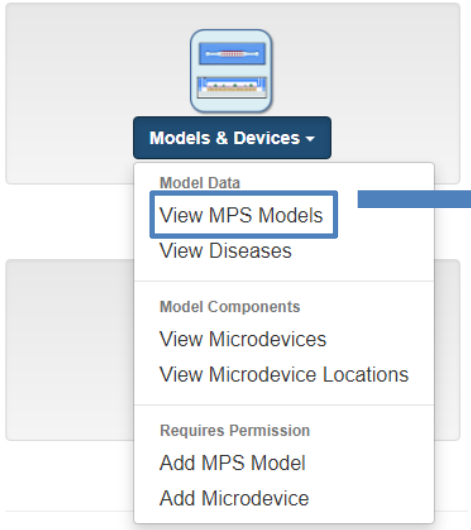
Studies

Data Analysis



Computational Modeling

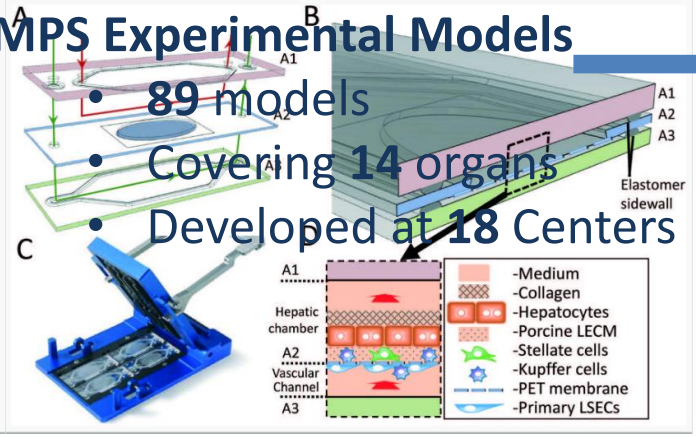
The MPS-Db Provides Convenient Access to Information on a Variety of MPS Models



vLAMPS

vLiver (UPDDI)

Center	University of Pittsburgh Drug Discovery Institute (UPDDI)
Institution	University of Pittsburgh
Device	Micronit OOC
Organ	Liver
Model Image	



MPS Experimental Models

- **89** models
- Covering **14** organs
- Developed at **18** Centers

Locations

Location	Description
Effluent-Vascular	Sampling Location - for samples from the media flowing out of the vascular chamber.
Vascular	Addition Location - for cells. Sampling Location - for images.
Hepatic	Addition Location - for cells. Sampling Location - for images.
Effluent-Hepatic	Sampling Location - for samples from the media flowing out of the hepatic chamber.
Influent-Hepatic	Addition Location - for compounds and some settings.
Zone 1	Imaging zone; The area closest to the influent port with the highest oxygen tension, analogous to Zone 1 in the liver acinus
Zone 2	Imaging zone: the area halfway between the influent port and effluent port, with reduced oxygen tension analogous to Zone 2 in the liver acinus
Zone 3	Imaging zone; The area closest to the effluent port with the lowest oxygen tension, analogous to Zone 3 in the liver acinus
Influent-Vascular	Addition Location - for media, compounds, circulating immune cells, and some settings.

MPS Model Version

MPS Model	vLAMPS
Name	NCATS Oct 2019 Demo
Description	A model version for demoing MPS features at the NCATS NextGen October 2019 meeting
Protocol Details	Protocol Details

MPS Model Versions

View	Name	Description	Protocol
View	6-27-18 ver1.0		Protocol Details
View	7-12-18 ver1.1b		Protocol Details
View	NCATS Oct 2019 Demo	A model version for demoing MPS features at the NCATS NextGen October 2019 meeting	Protocol Details
View	12-15-2019 ver 3.0		Protocol Details

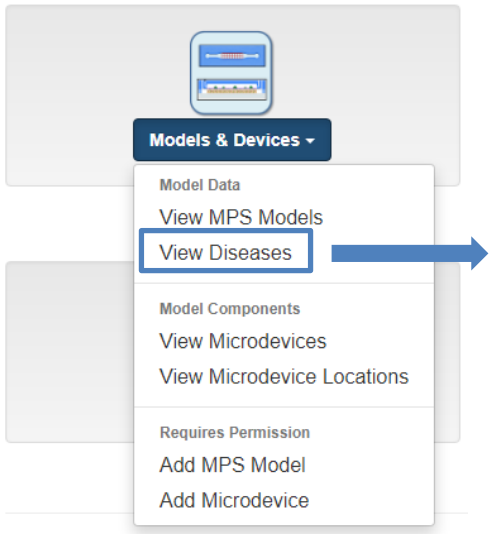
Cells

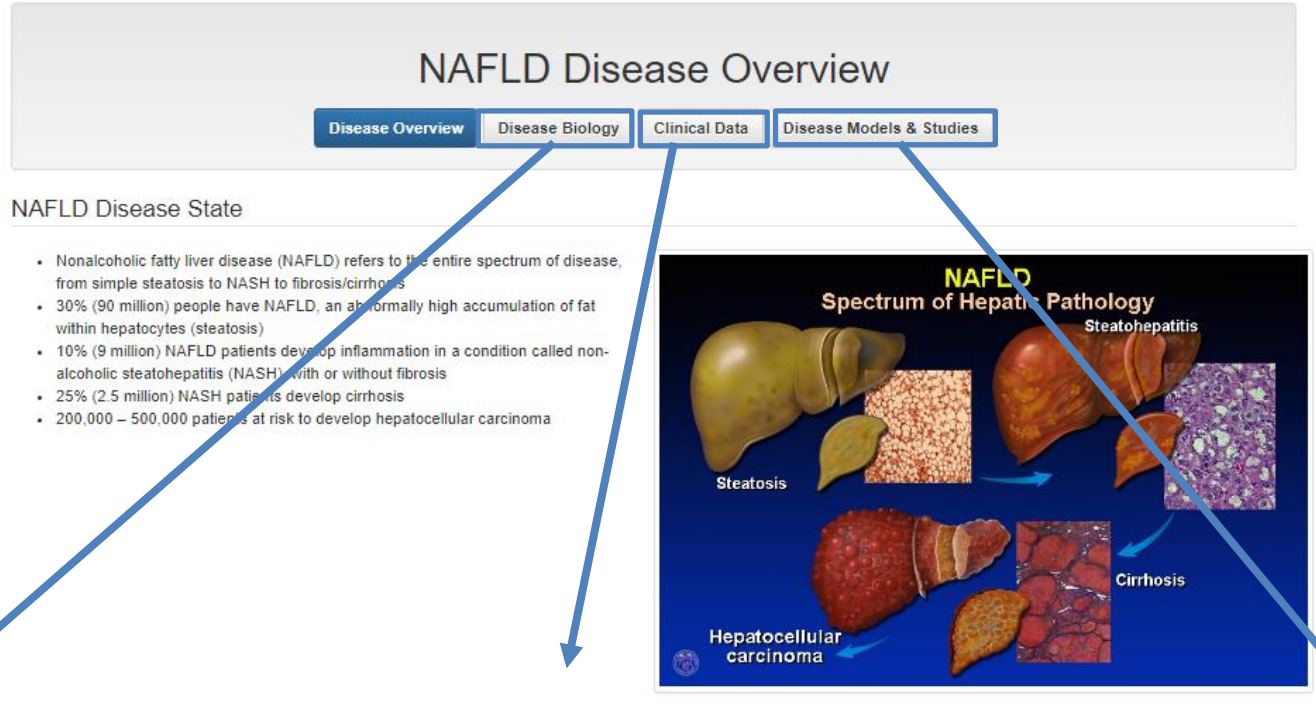
Cell Sample	Cell Biosensor	Density	Unit	Passage#	Addition Time	Addition Location
primary-cryopreserved endothelial (Human Liver) (Samsara-HL160019)	naive (none)	100,000.0	cells / chip		D-3 H00 M00	Vascular
LX2 stellate (Human Liver) (UPDDI)	naive (none)	36,000.0	cells / chip		D-2 H00 M00	Hepatic
THP1 monocyte (Human Immune) (University of Pittsburgh)	naive (none)	15,000.0	cells / chip		D-2 H00 M00	Hepatic
primary-cryopreserved hepatocyte (Human Liver) (Thermo Fisher-Hu1838)	naive (none)	100,000.0	cells / chip		D00 H-22 M00	Hepatic

Settings

Setting	Value	Unit	Addition Time	Duration	Addition Location
Flow Rate	150	µL/hour	D00 H00 M00	D21 H00 M00	Influent-Vascular
Flow Rate	50	µL/hour	D00 H00 M00	D21 H00 M00	Influent-Hepatic

MPS Disease Model Development Is Assisted With Information Obtained Through the Disease Portal





Pre-Queried links to databases:

- Genomic data
- KEGG
- Proteomic data
- Metabolomic data
- DrugBank

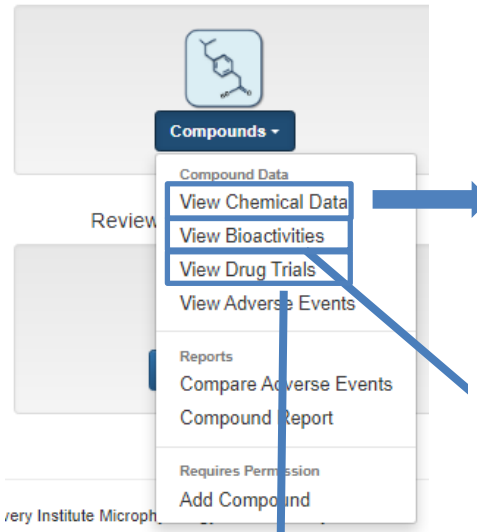
Clinical data:

- Manually curated clinical data
- Pre-Queried links to Clinical Trials.gov
  - Completed studies with results

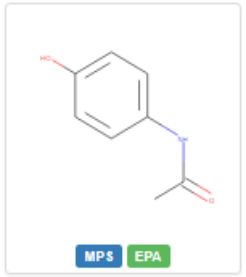
Direct links to

- Other models of the disease
- Studies using these models

The MPS-Db Links to Information to Aid in the Identification of Compounds for Model Validation



ACETAMINOPHEN



ChEMBL ID	
PubChem ID	
DrugBank ID	
ClinicalTrials	
Molecular Formula	
Inchikey	

Class	Anilides
Smiles	CC(=O)Nc1ccc(O)cc1
Synonyms	APAP, SID11112253, Acetaminophen, Infar SID26747171, SID124882135, Injectapap,

Compound Properties

Drug/Drug-like Properties	
Known Drug	✔
Medchem Alerts	
Passes of Rule of 3	✔
Rule of 5 Violations	0
Molecular Species	NEUTRAL
Protein Binding	25%
Half Life	1-4 hours

Summaries

Absorption	Rapid and almost complete
PK/Metabolism	Bioavail=75%, T1/2=3 hr, Excr=95% kidney, Met=25% first pass clearance, glucuronide & sulfation, reactive metabolite
Pre-clinical Findings	Rat Study 1:↑ ALT, AST, AP, TB female onlyRat 28 day tox study:Kidney, liver toxicity Reactive Intermediate
Clinical Findings	7.5-15 g single dose fatal: centrilobular necrosis4g/day ↑ ATL,AST > 3X ULN

Targets

Copy | CSV | Print | Column visibility

Show 100 entries

Search:

Previous 1 Next

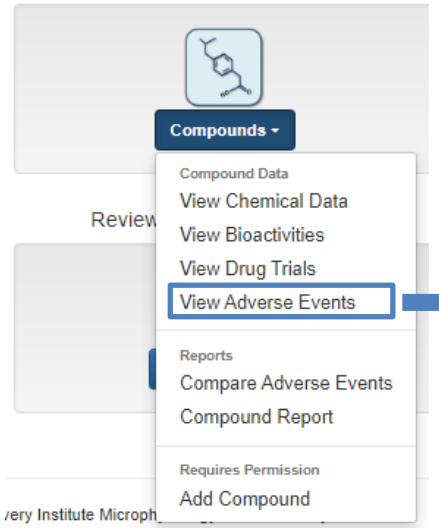
Showing 1 to 23 of 23 entries

Name	Uniprot ID	Type	Organism	Pharmacological Action	Actions
Prostaglandin G/H synthase 1	P23219	Target	Human	yes	inhibitor
Prostaglandin G/H synthase 2	P35354	Target	Human	yes	inhibitor
Arylamine N-acetyltransferase 2	P11245	Enzyme	Human	unknown	inhibitor
Bile salt sulfotransferase	Q06520	Enzyme	Human	unknown	substrate
Cytochrome P450 1A1	P04798	Enzyme	Human	unknown	substrate
Cytochrome P450 1A2	P05177	Enzyme	Human	unknown	substrate
Cytochrome P450 2A6	P11509	Enzyme	Human	unknown	substrate
Cytochrome P450 2C8	P10632	Enzyme	Human	unknown	substrate
Cytochrome P450 2C9	P11712	Enzyme	Human	unknown	substrate
Cytochrome P450 2D6	P10635	Enzyme	Human	unknown	substrate

Links to human and animal data

- Manually curated literature da
- Links to completed clinical tria

Linking to FAERS and CDC Databases Enables Identification of Test Compounds Based on Normalized Reported Adverse Events



Adverse Events

Copy | CSV | Print | Column visibility

Show 50 entries

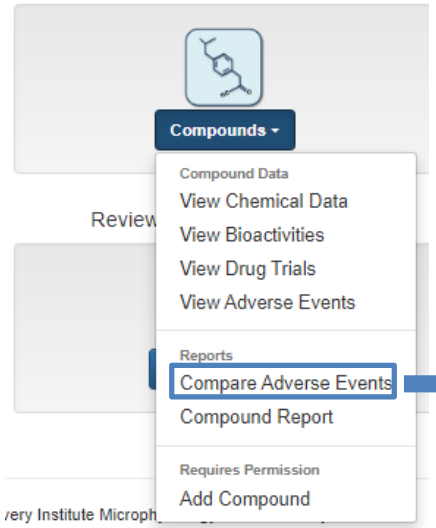
Search: capone liver

Previous 1 Next

Showing 1 to 10 of 10 entries (filtered from 9,280 total entries)

View	Compound	Event	Number of Reports	Normalized # of Reports	Estimated Usage	Organ	Black Box Warning
View	ENTACAPONE	ASPARTATE AMINOTRANSFERASE INCREASED	43	2.46	174,449	Liver	
View	ENTACAPONE	ALANINE AMINOTRANSFERASE INCREASED	36	2.06	174,449	Liver	
View	ENTACAPONE	HEPATIC FUNCTION ABNORMAL	27	1.55	174,449	Liver	
View	ENTACAPONE	GAMMA-GLUTAMYLTRANSFERASE INCREASED	19	1.09	174,449	Liver	
View	ENTACAPONE	LIVER DISORDER	17	0.97	174,449	Liver	
View	TOLCAPONE	ALANINE AMINOTRANSFERASE INCREASED	8	7.85	10,195	Liver	
View	TOLCAPONE	ASPARTATE AMINOTRANSFERASE INCREASED	5	4.90	10,195	Liver	
View	TOLCAPONE	BLOOD BILIRUBIN INCREASED	4	3.92	10,195	Liver	
View	TOLCAPONE	LIVER FUNCTION TEST ABNORMAL	4	3.92	10,195	Liver	
View	TOLCAPONE	AMMONIA INCREASED	3	2.94	10,195	Liver	

Compare Adverse Event Tool Shows Relative Clinical Activity of Compounds



Save Selections | Load Selections | Clear Current Selections

Search: liver Show 10 entries

Select	Adverse Event	Reports Among Top	Organ
☑	ALANINE AMINOTRANSFERASE INCREASED	54,634	Liver
☑	ASPARTATE AMINOTRANSFERASE INCREASED	48,550	Liver
☑	HEPATIC ENZYME INCREASED	35,914	Liver
☐	LIVER FUNCTION TEST ABNORMAL	24,688	Liver
☐	LIVER DISORDER	13,079	Liver
☑	HEPATIC FAILURE	11,323	Liver
☐	HEPATIC FUNCTION ABNORMAL	10,241	Liver
☐	BLOOD BILIRUBIN INCREASED	9,821	Liver
☐	METASTASES TO LIVER	7,716	Liver
☐	HEPATIC STEATOSIS	5,215	Liver

Showing 1 to 10 of 60 entries (filtered from 701 total entries)

Previous 1 2 3 4 5 6 Next

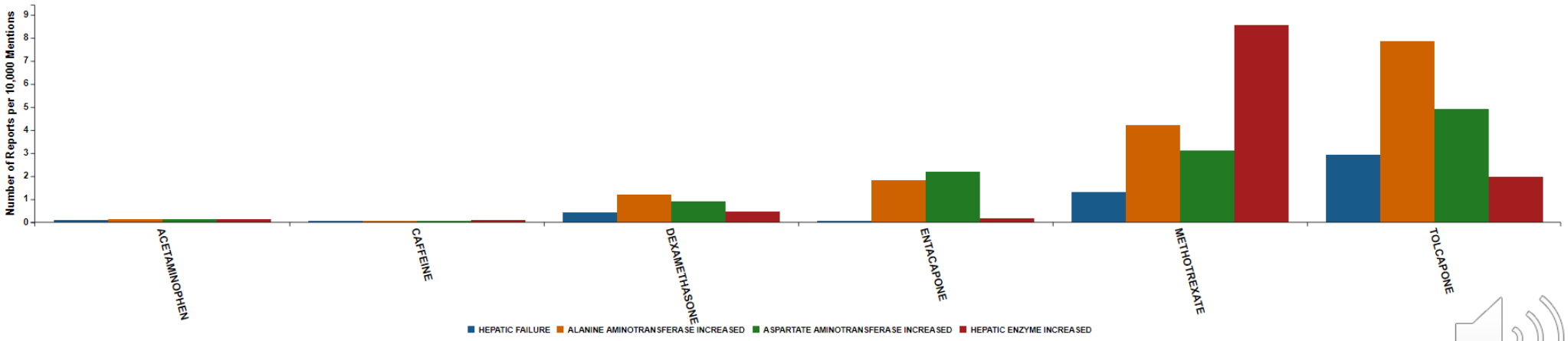
Search: Show 10 entries

Select	Compound	Reports Among Top	Estimated Usage
☑	ACETAMINOPHEN	349,149	127,412,556
☐	ASPIRIN	332,464	84,412,791
☐	LEVOTHYROXINE	298,191	52,046,110
☑	METHOTREXATE	282,977	5,105,489
☐	METFORMIN	266,182	
☐	FUROSEMIDE	248,613	31,355,113
☐	METOPROLOL	219,386	44,749,206
☐	GABAPENTIN	215,877	16,212,570
☐	DIPHENHYDRAMINE	206,026	14,608,776
☐	LISINOPRIL	205,828	64,222,855

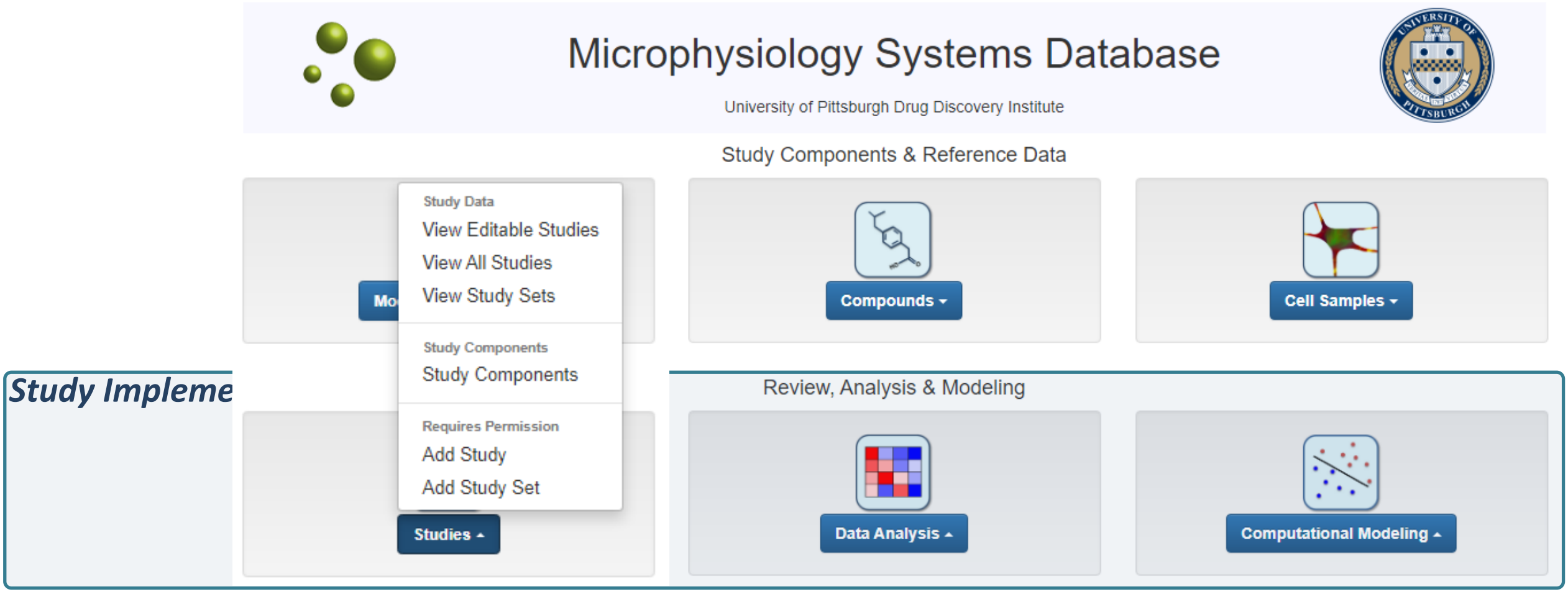
Showing 1 to 10 of 231 entries (filtered from 251 total entries)

Previous 1 2 3 4 5 … 24 Next

Show Raw Counts

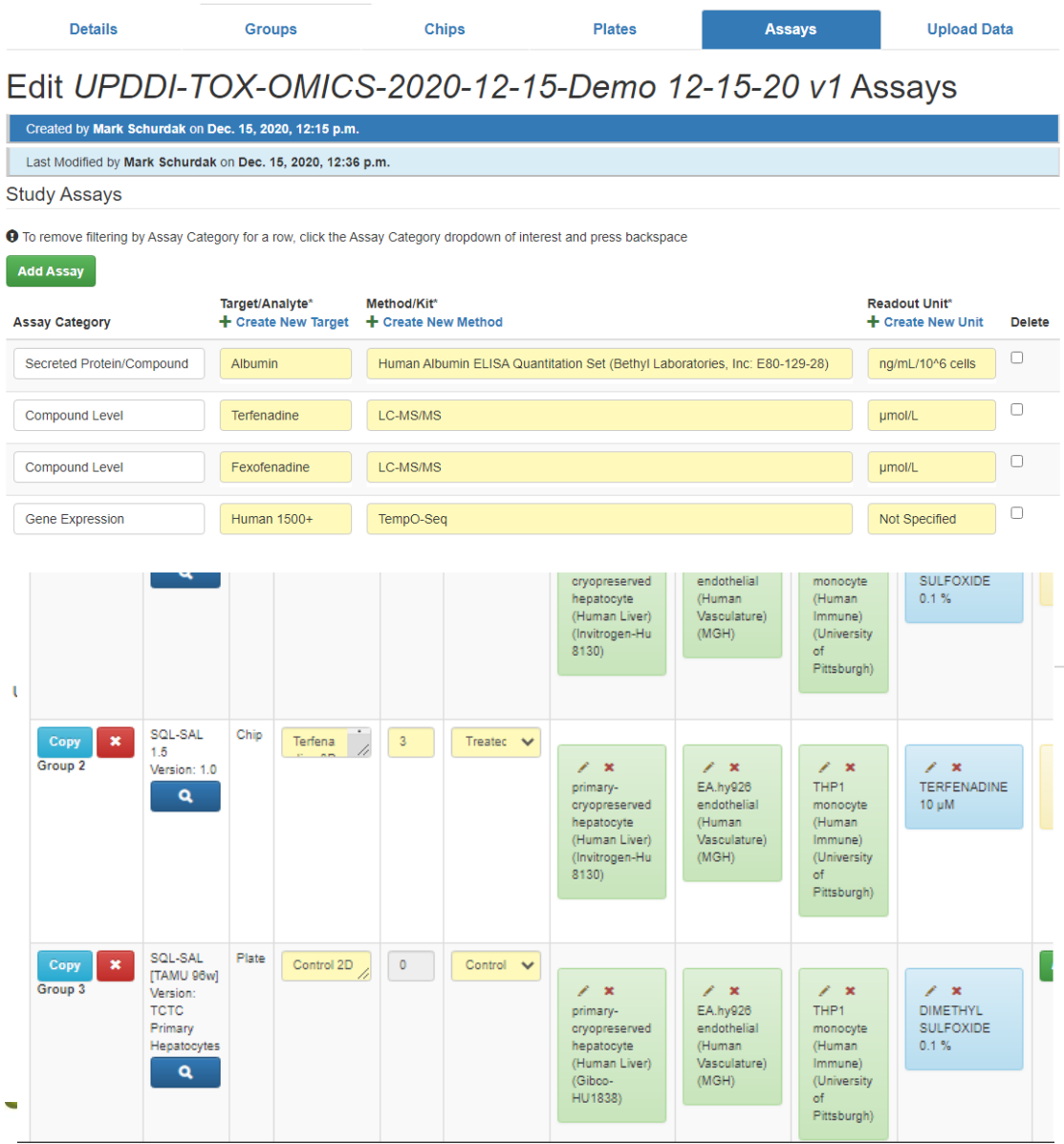


The MPS-Db Is Organized Based on Workflow



Study Impleme

A Streamlined Workflow Facilitates Study Creation Directly in the MPS-Db

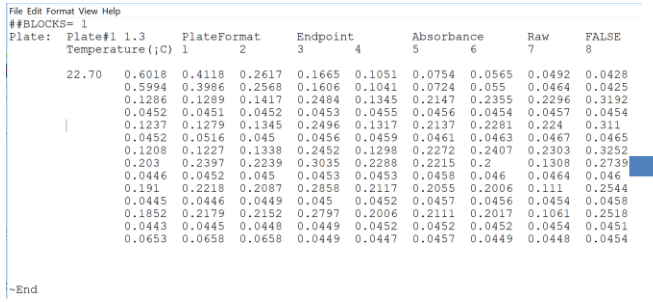


- Simple menus facilitate metadata entry for study details

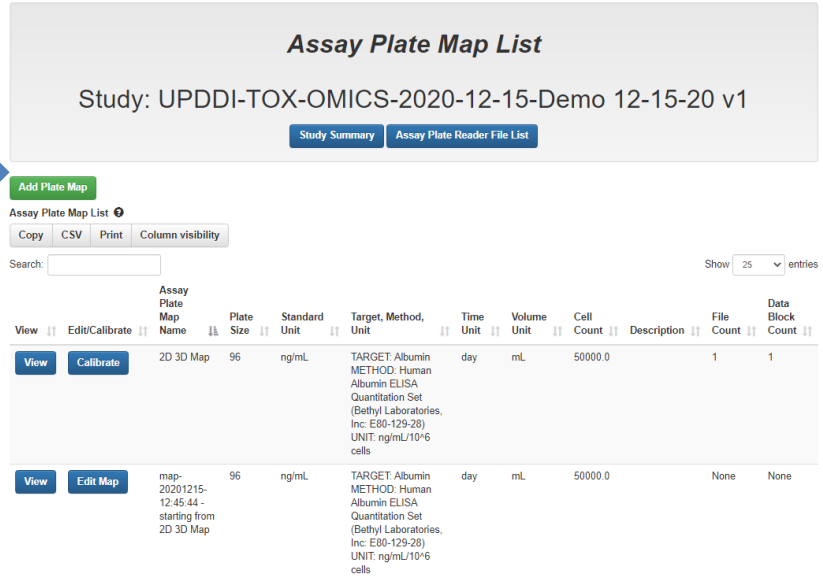
- MPS model component information is automatically entered when setting up a study
- Entering in information as groups facilitates Study Setup

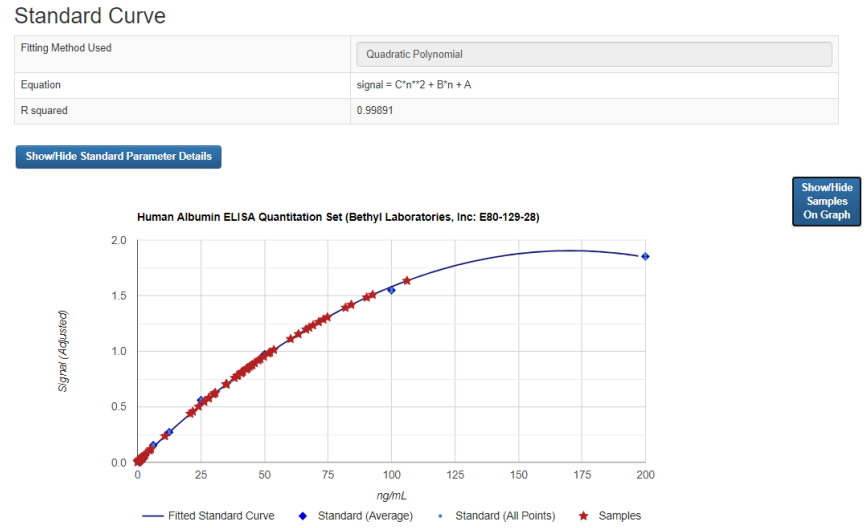
- Assay category dropdowns expedite selection of Target/Analyte and Method Kits used in the study

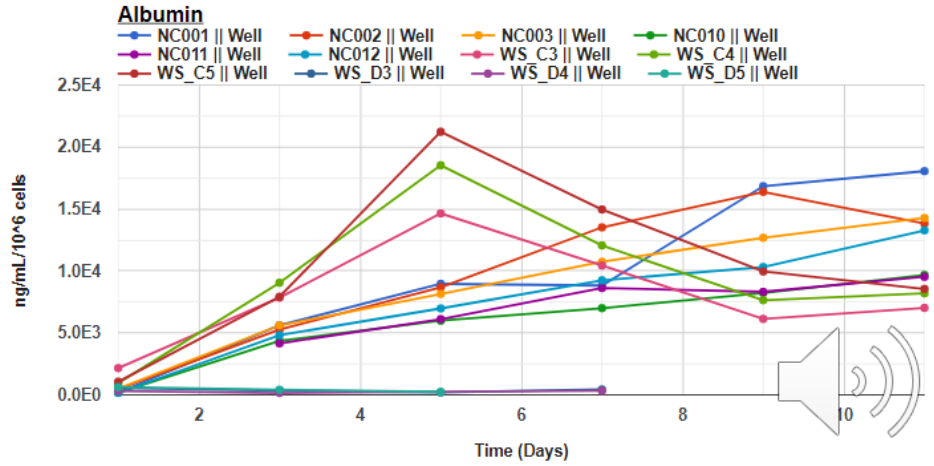
Study Data Are Easily Imported Into the MPS-Db



Acquire data and load into MPS-Db



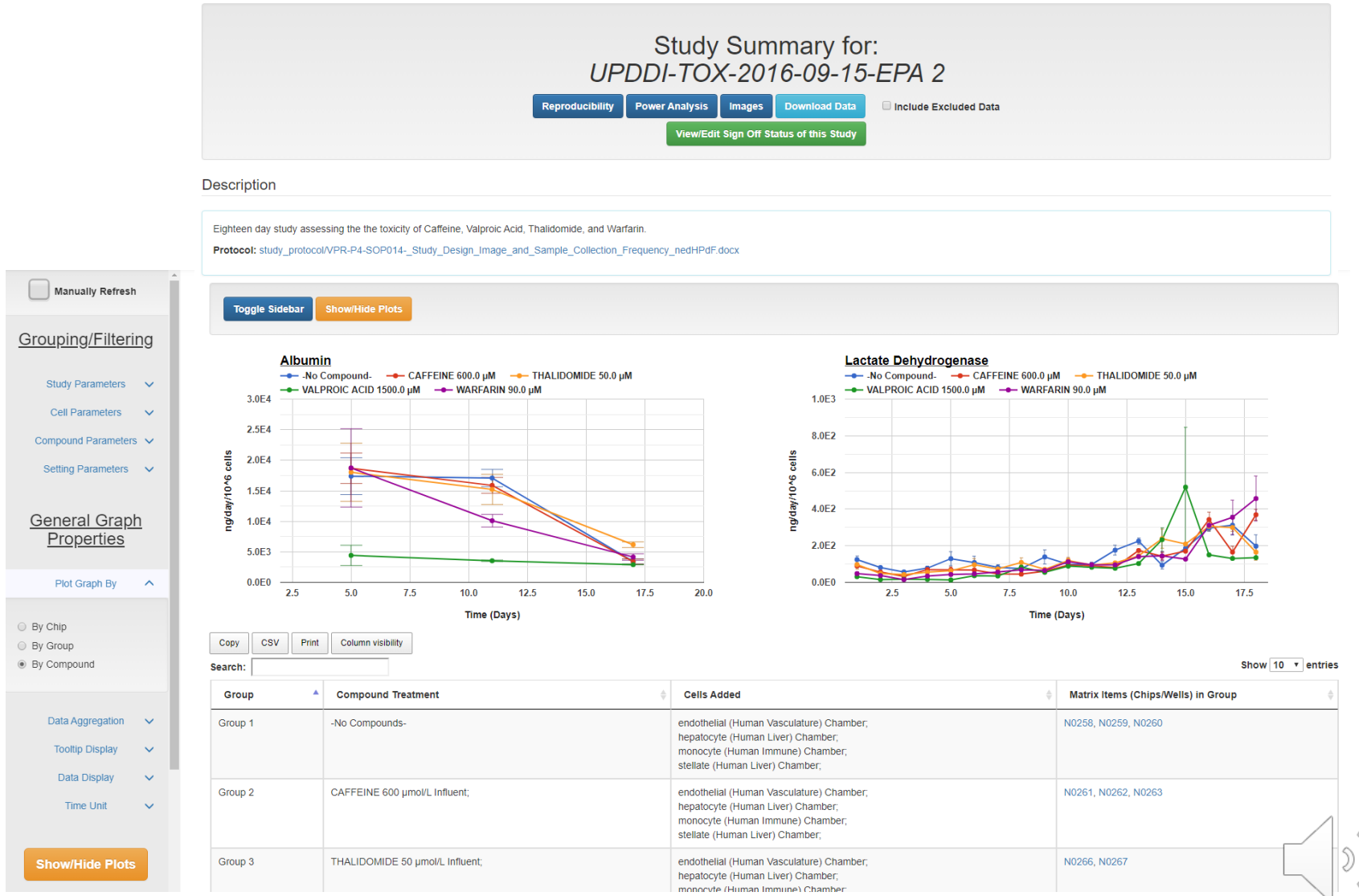




- Integrated tools allow for importing raw data directly from a variety of plate readers.
- Sample data are calibrated and normalized against standards in the MSP-Db
- Results are reviewed prior to submitting to the Db

Visualization Tools Enable Flexible Analysis of Study Data

- A **Grouping/Filtering** sidebar menu provides filters to select and group samples by specific study parameters to narrow down or expand the results set for analysis.
- A **General Graph Properties** menu provides options for customization of plots and selection of plots to display.
- Functionality is enabled to convert individual plots to show percent control, and convert from time series to dose response

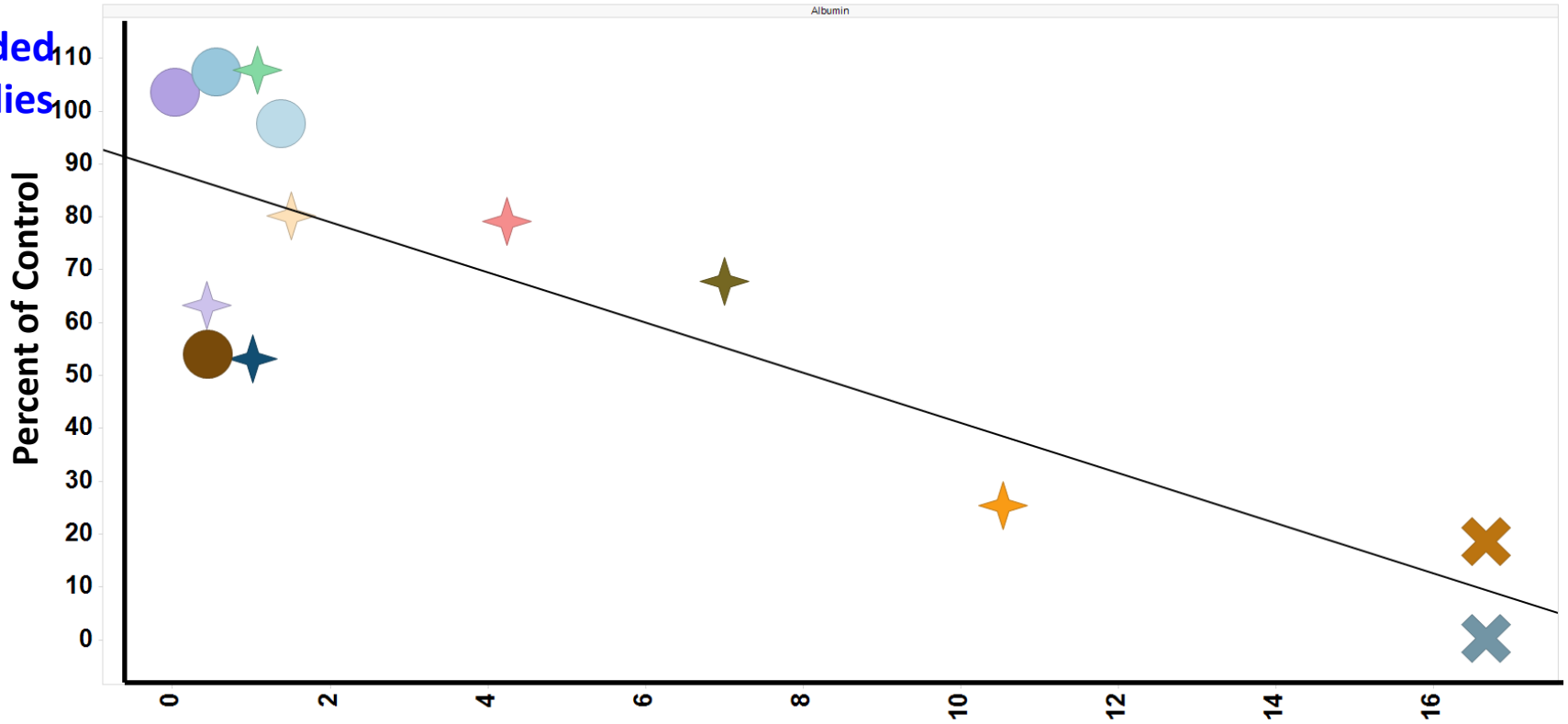


Data Can Be Easily Exported From the MPS-Db for Analysis in Other Software

Data Table_Straight line

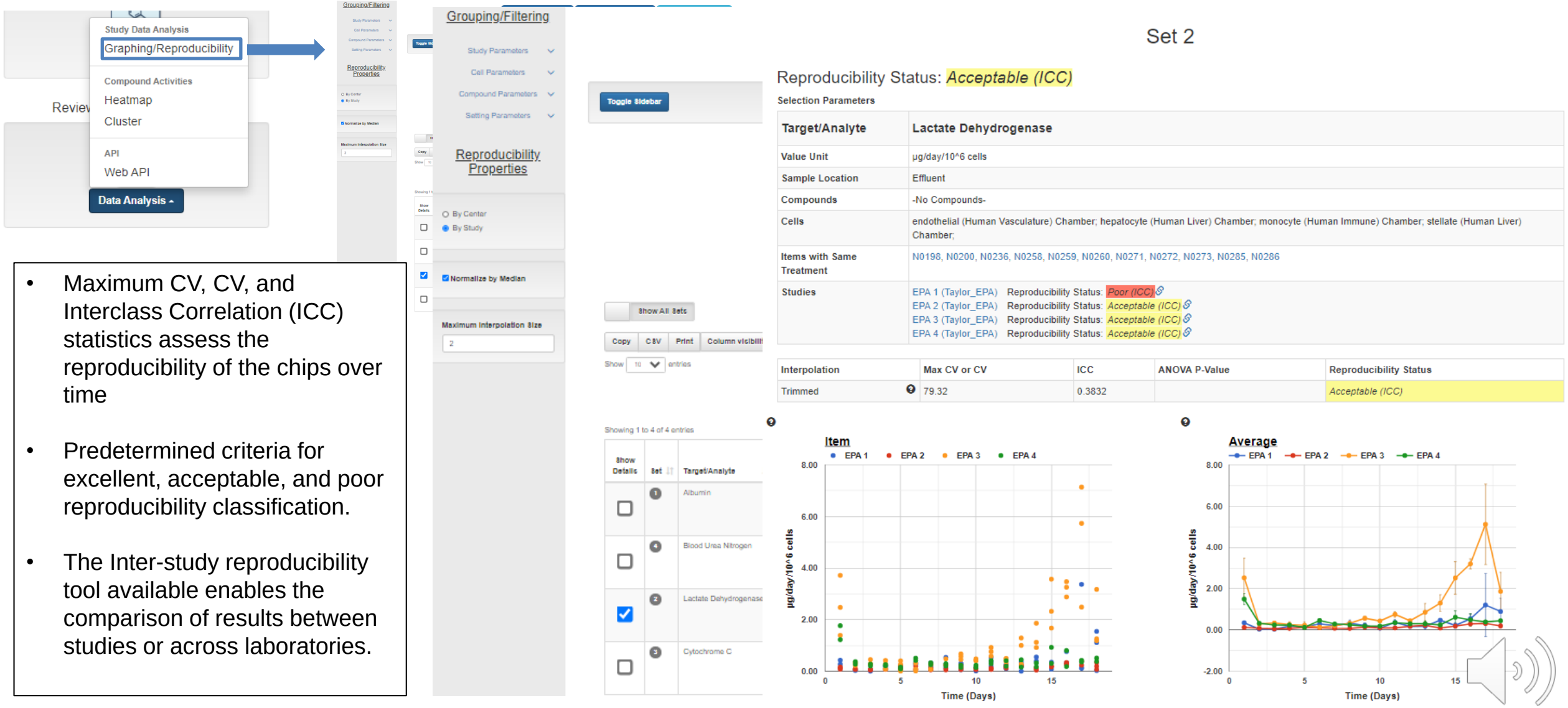
Target/Analyte	b	a	r2	Notes
Albumin	-4.74	88.50	0.68	

Data downloaded from MPS studies



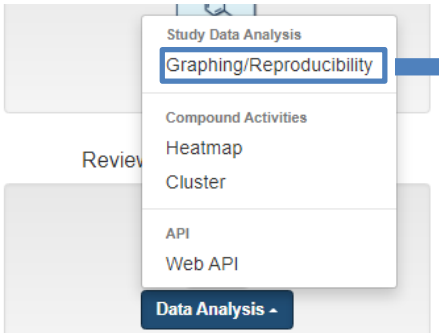
Data downloaded from Adverse Events tables

Integrated Reproducibility Analysis Statistics Facilitates Inter-Study Reproducibility Assessment



- Maximum CV, CV, and Interclass Correlation (ICC) statistics assess the reproducibility of the chips over time
- Predetermined criteria for excellent, acceptable, and poor reproducibility classification.
- The Inter-study reproducibility tool available enables the comparison of results between studies or across laboratories.

Graphing/Reproducibility Feature Allows Easy Comparison of Study Sets



Manually Refresh

Grouping/Filtering

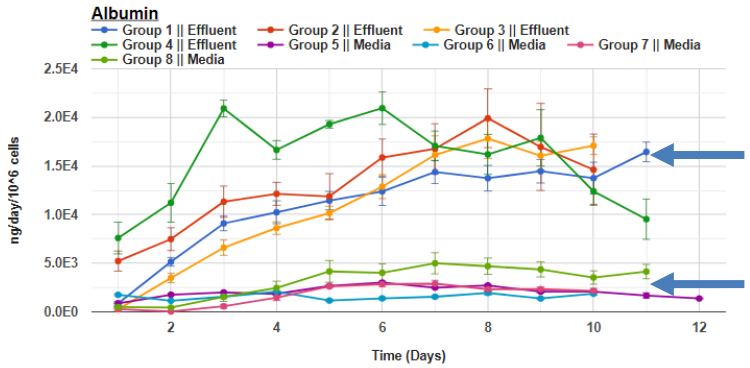
- Study Parameters
- Cell Parameters
- Compound Parameters
- Setting Parameters

General Graph Properties

- Plot Graph By
- Data Aggregation
- Tooltip Display
- Data Display
- Time Unit

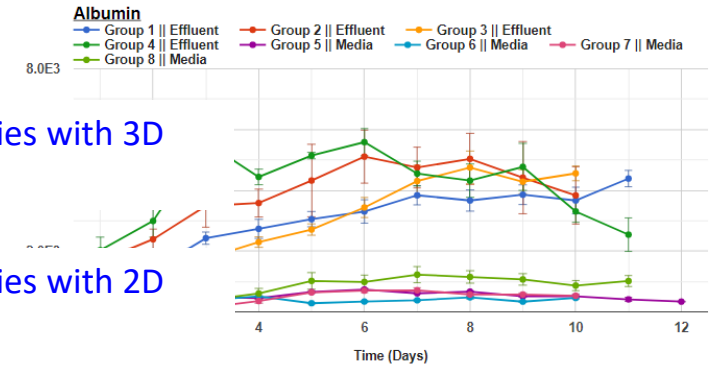
Show/Hide Plots

Toggle Sidebar | Show/Hide Plots



4 Studies with 3D model

4 Studies with 2D model



Copy | CSV | Print | Column visibility

Show 10 entries

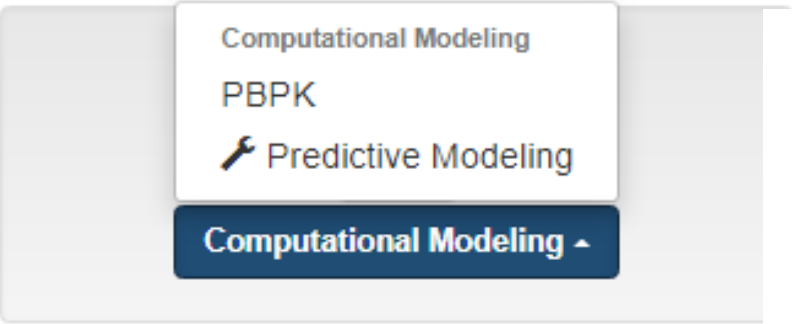
Search:

Previous 1 Next

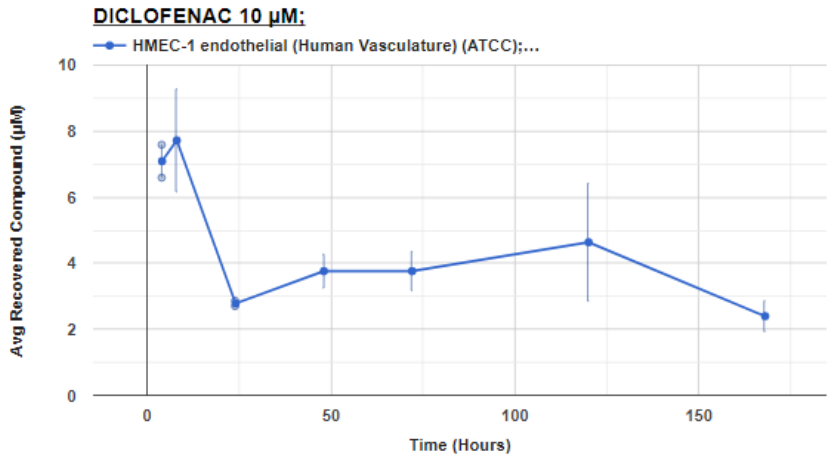
Showing 1 to 8 of 8 entries

Group	MPS Model	Study	Compound Treatment	Cells Added	Matrix Items (Chips/Wells) in Group
Group 1	SQL-SAL 1.5	UPLiver_Tier2a2b_3D	-No Compounds-	hepatocyte (Human Liver) Chamber; endothelial (Human Vasculature) Chamber; monocyte (Human Immune) Chamber; stellate (Human Liver) Chamber;	L051, L052, L053, L054, L055
Group 2	SQL-SAL 1.5	Tier1c_Upitt_3D	-No Compounds-	hepatocyte (Human Liver) Chamber; endothelial (Human Vasculature) Chamber; monocyte (Human Immune) Chamber; stellate (Human Liver) Chamber;	L015, L016, L027, L028, L039, L040
Group 3	SQL-SAL 1.5	UPLiver_Tier2c_3D	-No Compounds-	hepatocyte (Human Liver) Chamber; endothelial (Human Vasculature) Chamber; monocyte (Human Immune) Chamber; stellate (Human Liver) Chamber;	L064, L065, L066

Integration of Computational Modeling Tools



- Physiologically-based PK tools estimate blood levels based on hepatic clearance calculated from liver MPS experimental models.



Include Cell-free Data

Start / End Times (Hours)

Steady State Start Time	24
Steady State End Time	168

Model Parameters

No. of Cells in Chip (for Calculations)	80,000

Compound Physicochemical Parameters

Compound	DICLOFENAC
MW	296.15
logD	1.44
pKa	4.18
f_u	0.01
F_a	0.927
K_a (1/h)	3.84

Acidic Basic Calculate Clearance

Predicted MPS Model Physiological Parameter

CL_H (mL/min)	371.550

Species Parameters

Species	Human
Organ	Liver
Body Mass (kg)	70
Total Organ Weight (g)	1,400
Organ Tissue (Cells/g)	130,000,000
Blood Volume (L)	5
V_p (L/kg)	0.0436
V_E (L/kg)	0.151
$R_{E/I}$	1.4
V_R (L/kg)	0.38
Absorptive Surface Area (m^2)	200
K_I (1/h)	0.302

References:

Lombardo F, Obach RS, Shalaeva MY, Gao F. Prediction of human volume of distribution values for neutral and basic drugs. 2. Extended data set and leave-class-out statistics.. J Med Chem.. 2004. doi:10.1021/jm[illegible]0408h. PMID:14971904

Usansky HH, Sinko PJ. Estimating human drug oral absorption kinetics from Caco-2 permeability using an absorption-disposition model: model development and evaluation and derivation of analytical solutions for k(a) and F(a).. J Pharmacol Exp Ther.. 2005. doi:10.1124/jpet.104.076182. PMID:15833900

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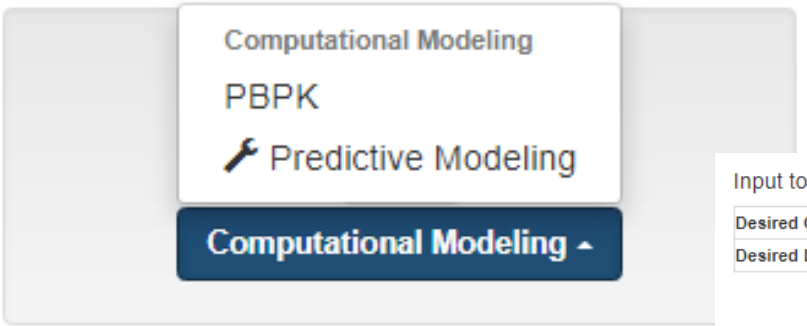
Integration of Computational Modeling Tools



Predict dose regimen

Predict plasma levels

Input to Estimate Dosing

Desired Cp (μM)	0.25
Desired Dose Interval (h)	6

Input to Predict Plasma Levels

Dose (mg)	50
Dose Interval (h)	6

Run PBPK Predictions

- Physiologically-based PK tools estimate blood levels based on hepatic clearance calculated from liver MPS experimental models.
- Computational models are being integrated into the MPS-Db that will utilize omics data to understand disease pathways and networks, and drug mechanism of action.

Predicted Results

Calculated PK Parameters

VD_{ss} (L)	40.683
k_e (1/h)	0.548
Elimination Half-life (h)	1.265
AUC (mg*h/L)	2.079

Single Oral Dose

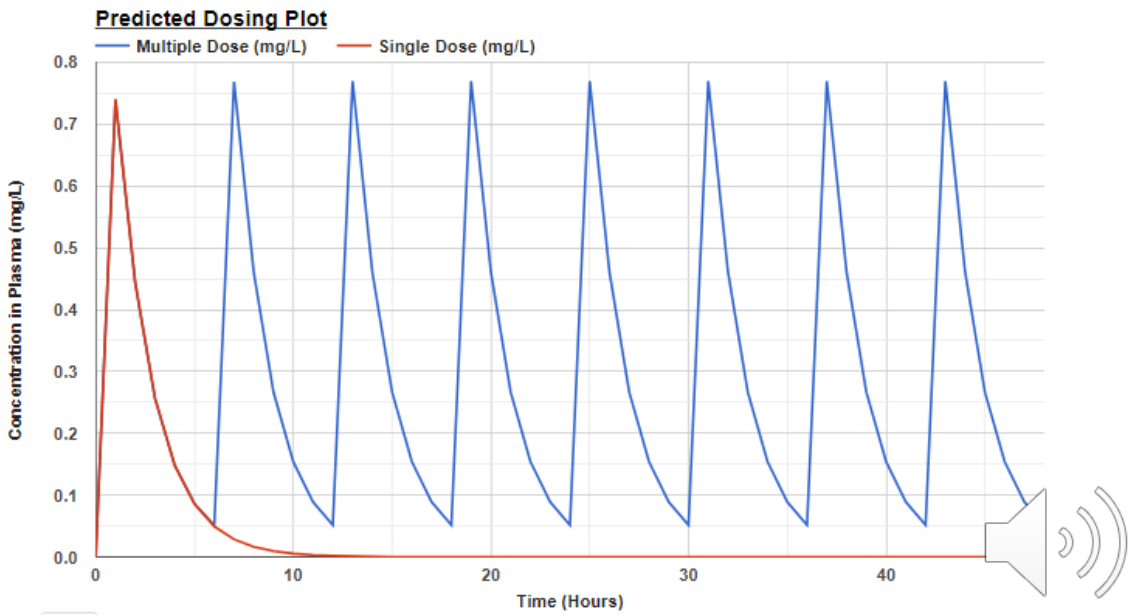
M_{max} (mg)	33.520
C_{max} (mg/L)	0.824
t_{max} (h)	0.591

Multiple Oral Doses

M_{ss} (mg)	14.098
C_{ss} (mg/L)	0.347
t_{max} (h)	0.580

Dosing to Reach Desired Plasma Levels

$Dose_{calc}$ (mg)	10.683
No. of Doses to Reach 50%	0.211
No. of Doses to Reach 90%	0.700



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We Continue to Develop the MPS-Db

Currently in development

- Integration of Genomic data and tools for visualization (Phase II)
- Enhancements to the Coronavirus **Covid-19 Disease Portal**

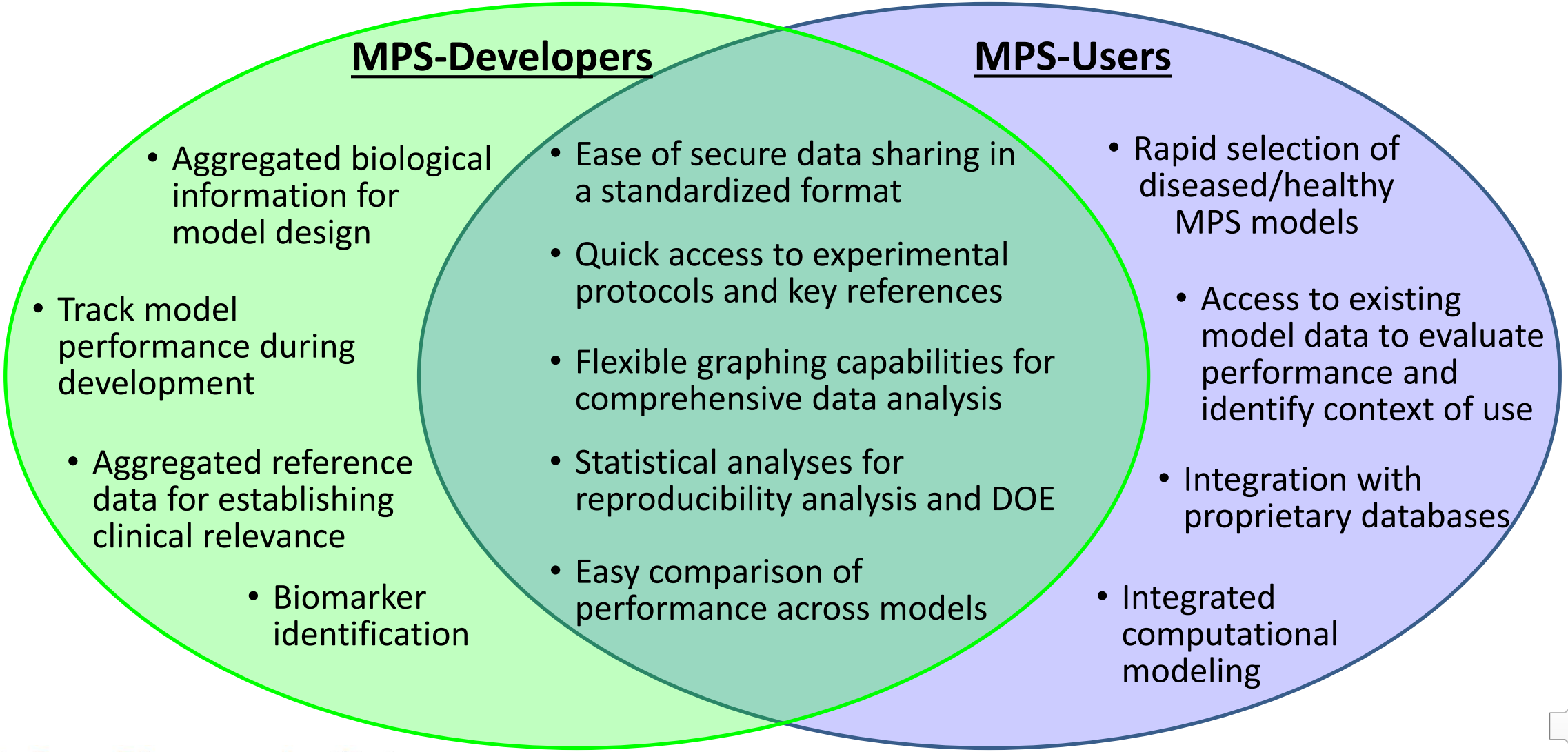
Next up in development

- Enhance preclinical and clinical reference data, and optimize data concordance analysis
  - Integrate *in vivo* data
- Computational pathway modeling using Genomic data

Developing commercialized version

- Enable full MPS-Db functionality behind data provider's firewall
- Enable interfacing with private company databases for their proprietary use
- Provide links to MPS device, cell, and reagent vendors.

Summary: The MPS-Db Provides Value for All MPS Developers and Users



Webinar Series in Progress

- ✓ **Introduction to the Microphysiology Systems Database (MPS-Db) - A Critical Tool for Managing, Analyzing, and Modeling MPS Experimental Data** (October 6, 2020)
  - ✓ A video recording of the webinar is available on the MPS-Db help page https://mps.csb.pitt.edu/help/
- ✓ **Designing studies and choosing test compounds in the MPS-Db** (November 10, 2020)
  - ✓ A video recording of the webinar is available on the MPS-Db help page https://mps.csb.pitt.edu/help/
- ✓ **Study workflow and data entry** (December 8, 2020)-(December 15,2020)
  - ✓ A video recording of the webinar is available on the MPS-Db help page https://mps.csb.pitt.edu/help/

- **Data analysis in the MPS-Db** (January 26, 2021)- registration link coming soon

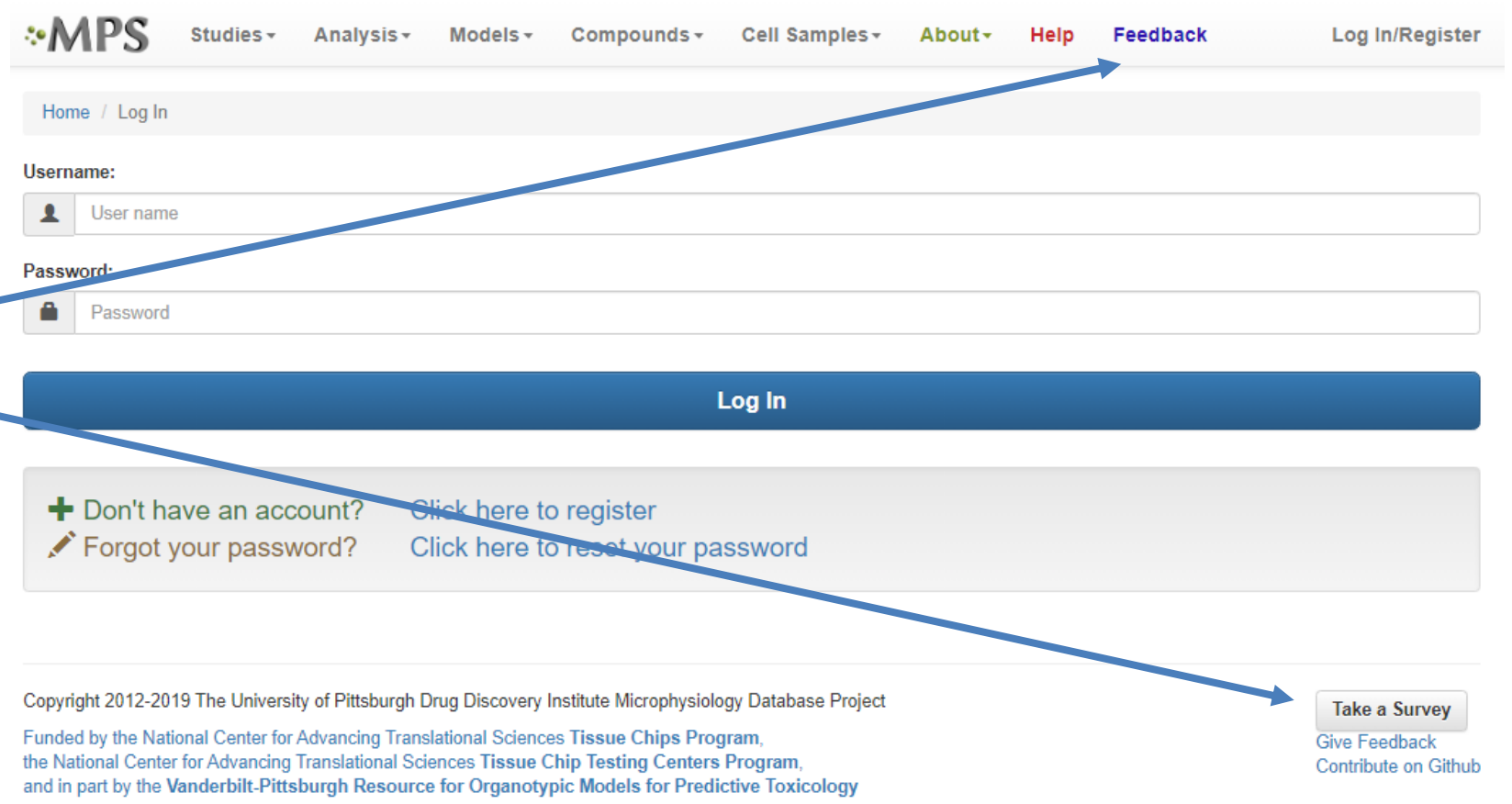
Login, Explore, and Provide Feedback on the MPS-Db

Login/Register

- https://mps.csb.pitt.edu

Please provide feedback,

- Feedback function
- email to
  - MPSHELP@pitt.edu
  - gough@pitt.edu



Schedule an Individual Interactive Online Training:

- Feedback function
- email to

  MPSHELP@pitt.edu

  gough@pitt.edu

The MPS-Db Team

Core Development Team

Mark Schurdak –Multi-PI
Bert Gough – Multi-PI
Lans Taylor- Multi-PI

Celeste Reese –Project Manager
Luke Bergenthal – Database Developer
Quinn Wolter– Database Developer
Sandra Karcher – Data Analyst/Modeler
Mike Castiglione – Data Analyst
Dillon Gavlock – Data Analyst
Tongying Shun – Lead Statistician, DBA

Applications Development and Support Team

Lawrence Vernetti– Toxicologist, Database Applications
Jan Beumer– Collaborating Toxicologist
Joe Maggiore – Clinical and Commercialization
Harold Takyi – Information Systems Manager
A**manda Maleski** – Administration Manager

Database Publications

1. Gough A et al. Appl In Vitro Toxicol. 2016;2(2):103-17. PMID: 28781990.
2. Schurdak M et al. Lab Chip. 2020;20(8):1472-92. PMID: 32211684
3. Sakolish C et al., Toxicology, 2020:152651. PMID: 33307106

Thank You for Your Attention

Questions??

https://mps.csb.pitt.edu/