ToxBank Integrated Data Analysis

ToxBank Public Forum
Wellcome Collection
London, United Kingdom

Barry Hardy (Douglas Connect)

26th October 2015

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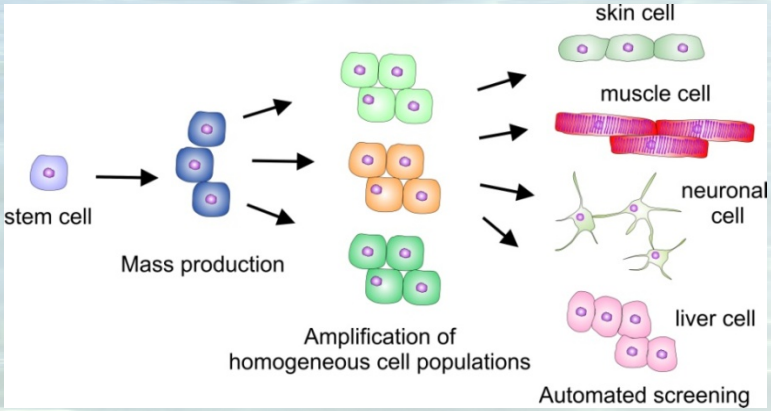
ToxBank

Cosmetics Europe
the personal care association

SEVENTH FRAMEWORK PROGRAMME

Building block 1: Scr&Tox

- Stem cell differentiation for providing human-based organ specific target cells



Coordinator:
Marc Peschanski
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France

website:
www.scrtox.eu

The cell factory

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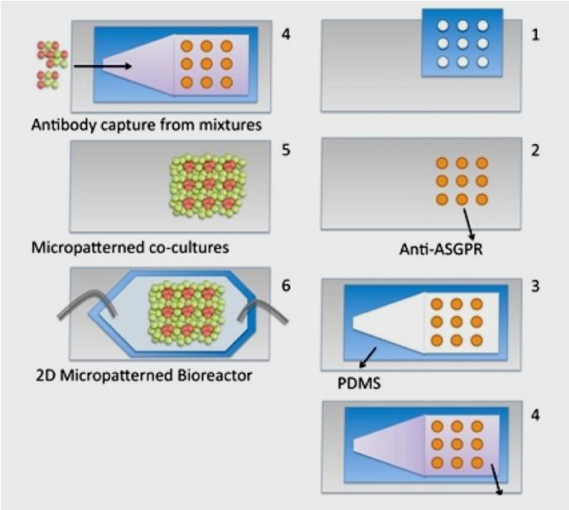
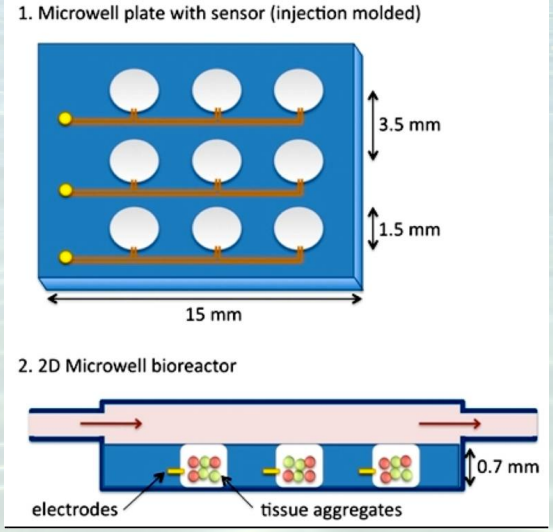
SEVENTH FRAMEWORK PROGRAMME

Building block 2: HeMiBio

- Development of a hepatic microfluidic bioreactor





Coordinator:
Catherine Verfaillie
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website:
www.hemibio.eu

The *in vitro* liver

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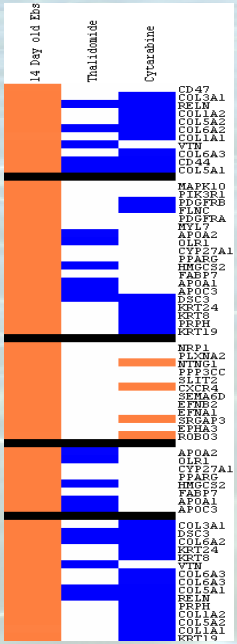
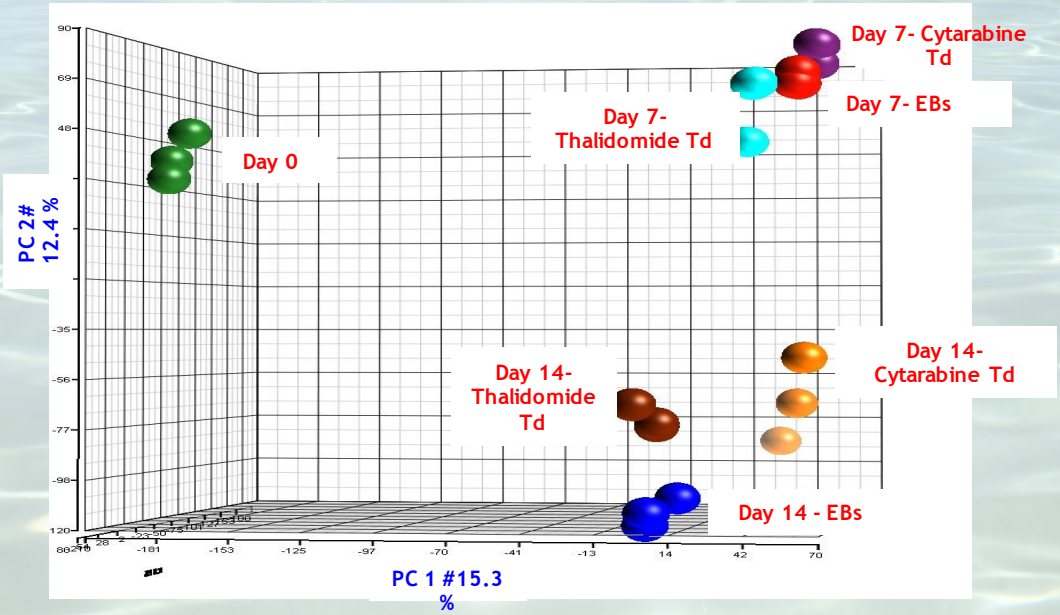
DETECTIVE

- Identification of biomarkers for prediction of toxicity in humans

DETECTIVE
Detection of Endpoints and Biomarkers for Repeated Dose Toxicity Using In Vitro Systems





Coordinator:
Jürgen Hescheler
Klinikum der Universität Köln, Germany

website:
www.detect-iv-e.eu

Biomarkers and functional assays

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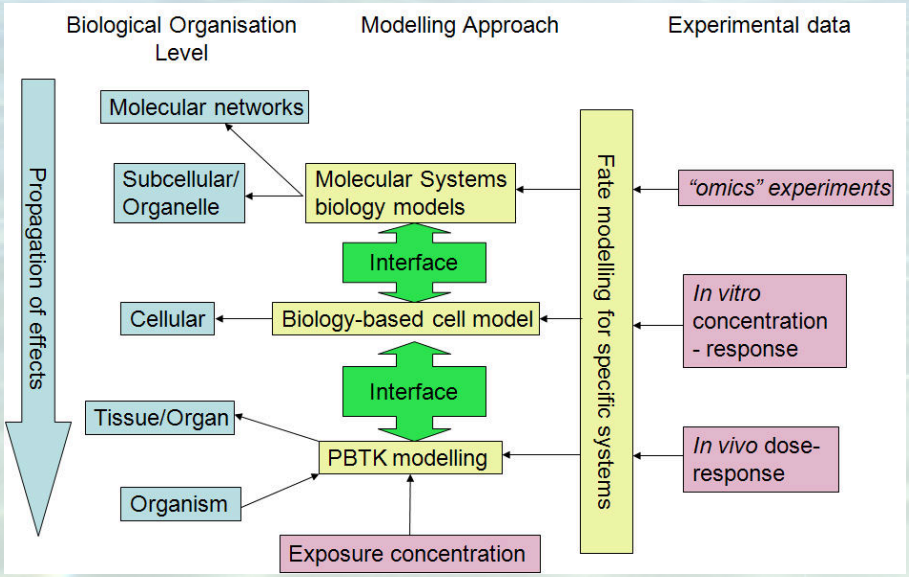
SEVENTH FRAMEWORK PROGRAMME

Building block 4: COSMOS

- Delivery of computational tools to predict the effects of chemicals based on *in silico* calculations and estimation techniques



Coordinator:
Mark Cronin
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website:
www.cosmos-tox.eu

***In silico* toxicology**

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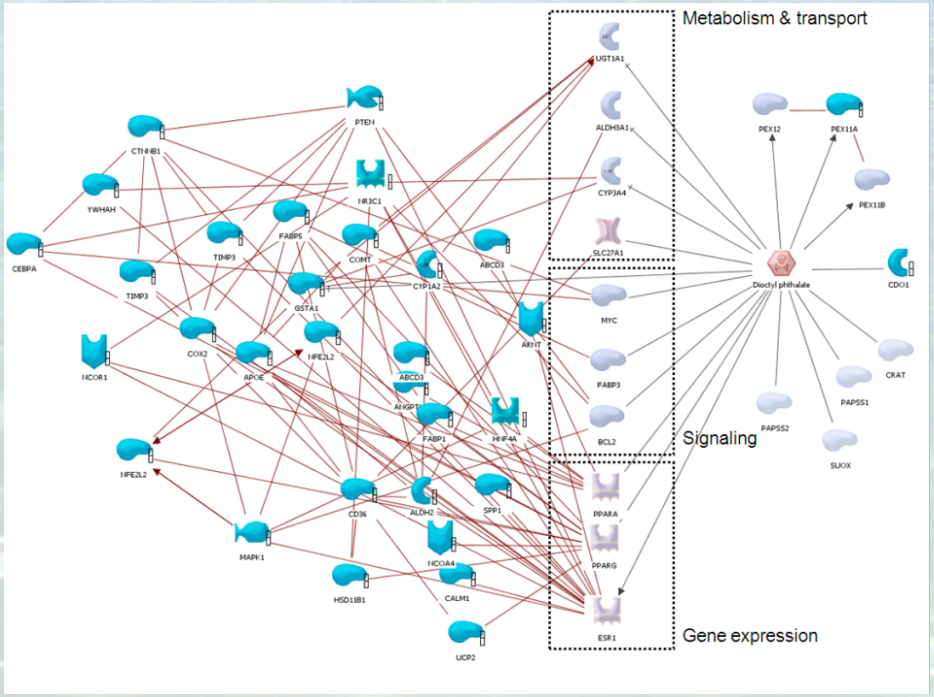
NOTOX

- Development of systems biological tools for organotypic human cell cultures



Coordinator:
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www. notox-sb.eu

Thinking in systems

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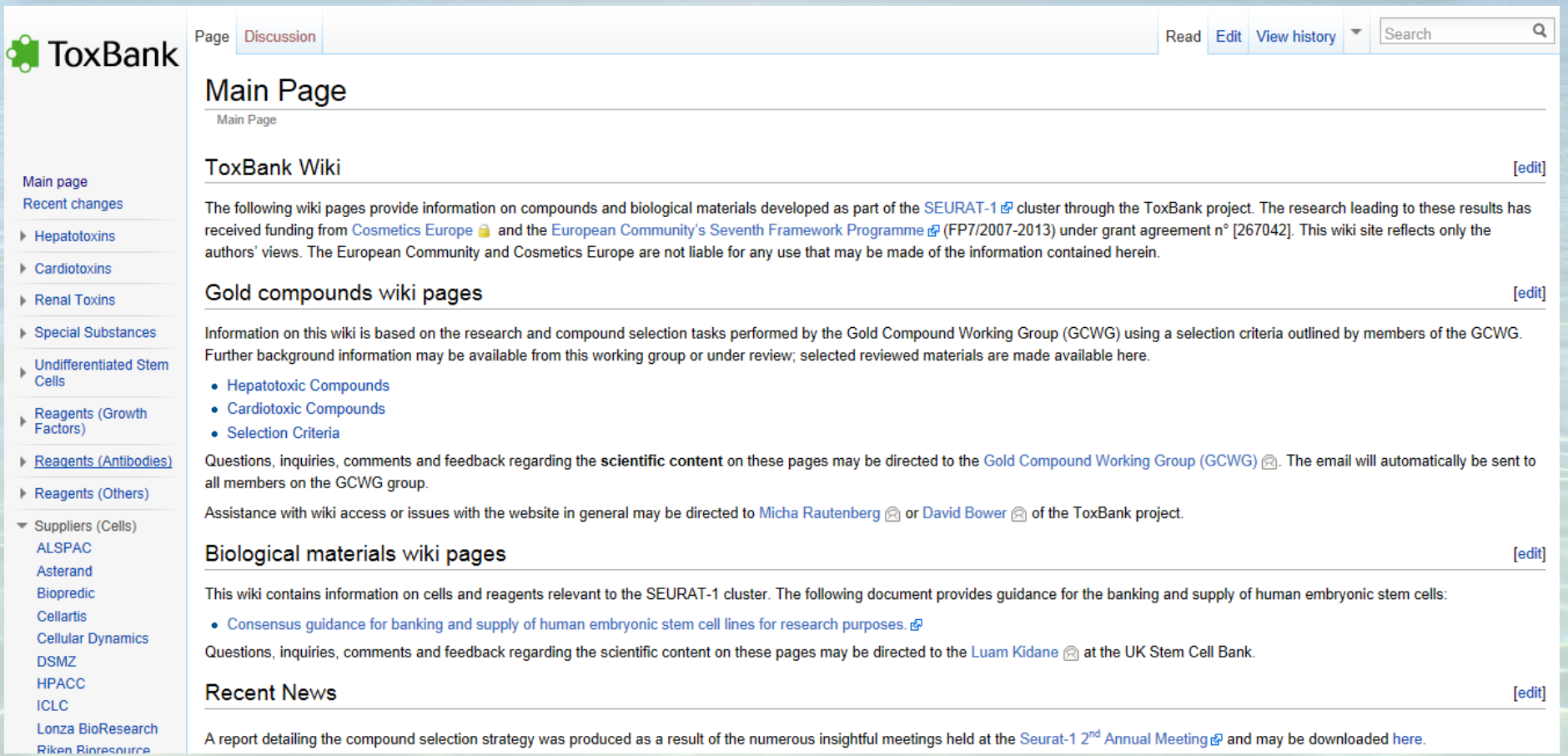
ToxBank Wiki Development



ToxBank

wiki.toxbank.net

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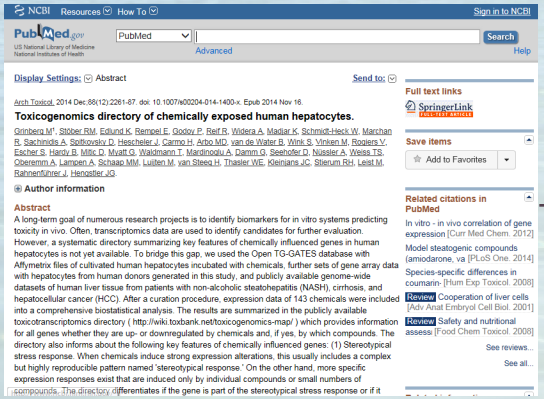
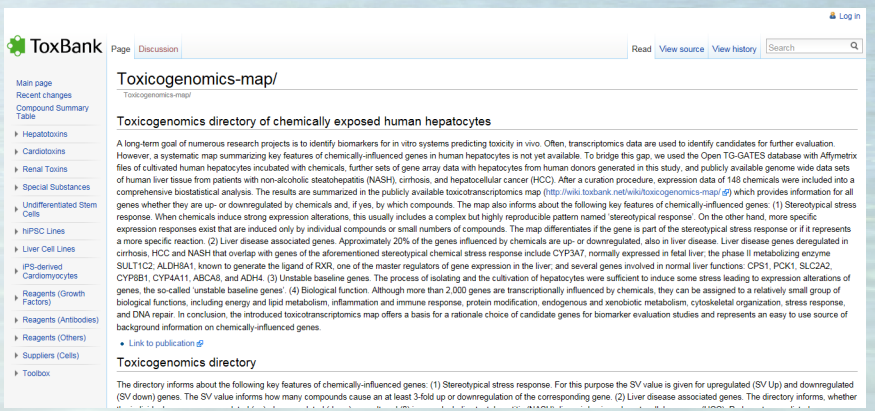
Toxicogenomics map

Toxicogenomics map publication



Links to

wiki.toxbank.net/wiki/Toxicogenomics-map/



Links to

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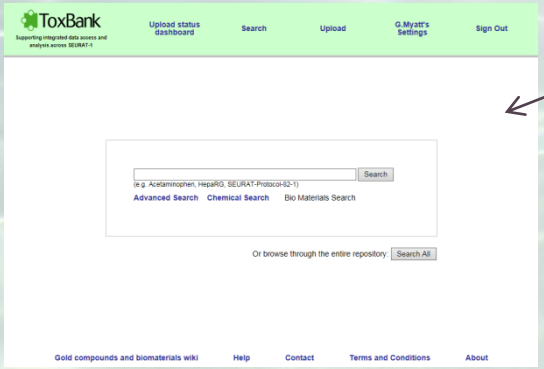

Gene Symbo	Gene Name	SV Up	Compounds	SV Down	Compounds	Deregulated in human liver disease: NASH	Cirrhosis	HCC	CS	Unstable baseline genes: Probeset	Entrez ID	Ensemble ID
NA	NA	0	-	0	-	NA	NA	NA	NA	1007_s_at	NA	NA
RFC2	replication factor C (activator 1) 2, 40kDa	0	-	2	VLF,DAPM	0	0	up	0	1053_at	5982	ENSG00000049541,ENSG0000002619
HSPA6	heat shock 70kDa protein 6 (HSP70B')	16	AA,NFT,BH	4	PM2,HY2,E	0	0	0	down	117_at	3310	ENSG00000173110
PAX8	paired box 8	0	-	0	-	0	0	up	0	121_at	7849	ENSG00000125618
GUCA1A	guanylate cyclase activator 1A (retina)	0	-	0	-	0	0	0	0	1255_s_at	2978	ENSG00000048545
UBA7	ubiquitin-like modifier activating enzyme 7	0	-	0	-	0	0	0	0	1294_at	7318	ENSG00000182179
THRA	thyroid hormone receptor, alpha	0	-	0	-	0	up	0	0	1316_at	7067	ENSG00000126351
PTPN21	protein tyrosine phosphatase, non-receptor type 21	0	-	0	-	0	0	down	0	1320_at	11099	ENSG00000070778
CCL5	chemokine (C-C motif) ligand 5	0	-	0	-	up	up	0	0	1405_i_at	6352	ENSG00000161570,ENSG0000027150
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	8	PAP,NZD,P	0	-	down	down	0	down	1431_at	1571	ENSG00000130649
EPHB3	EPH receptor B3	0	-	0	-	0	0	0	0	1438_at	2049	ENSG00000182580
ESRRA	estrogen-related receptor alpha	0	-	0	-	0	0	0	0	1487_at	2101	ENSG00000173153
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6	6	PAP,MNU,N	0	-	up	0	down	0	1494_f_at	1548	ENSG00000255974,ENSG0000019
SCARB1	scavenger receptor class B, member 1	0	-	0	-	down	0	0	0	1552256_a_	949	ENSG00000073060
TTLL12	tubulin tyrosine ligase-like family, member 12	0	-	0	-	0	0	0	0	1552257_a_	23170	ENSG00000100304
LINC00152	long intergenic non-protein coding RNA 152	0	-	0	-	0	0	up	0	1552258_at	112597	ENSG00000222041,ENSG0000017294

Toxicogenomics directory

Data are protocols in ToxBank (formatted data currently being tested)

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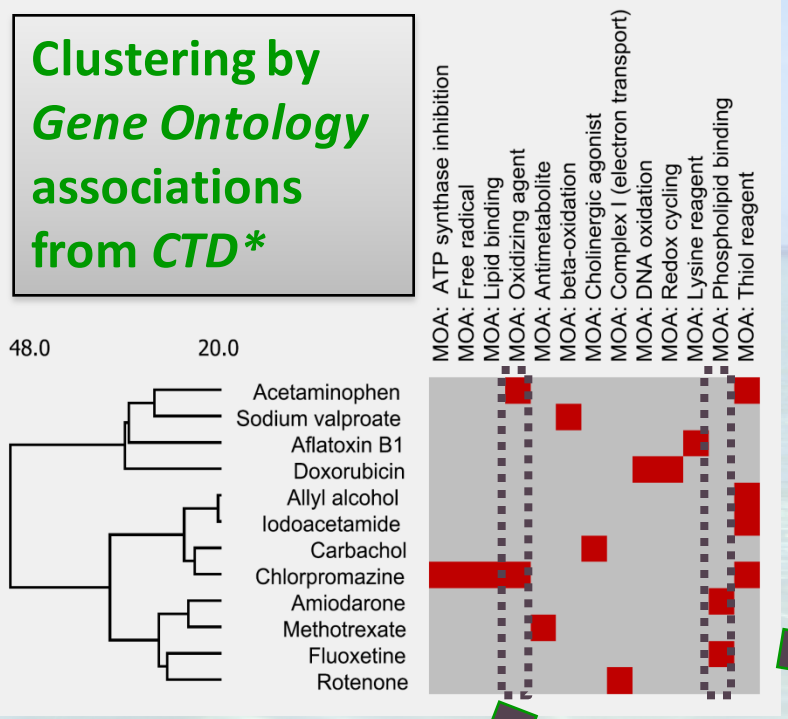
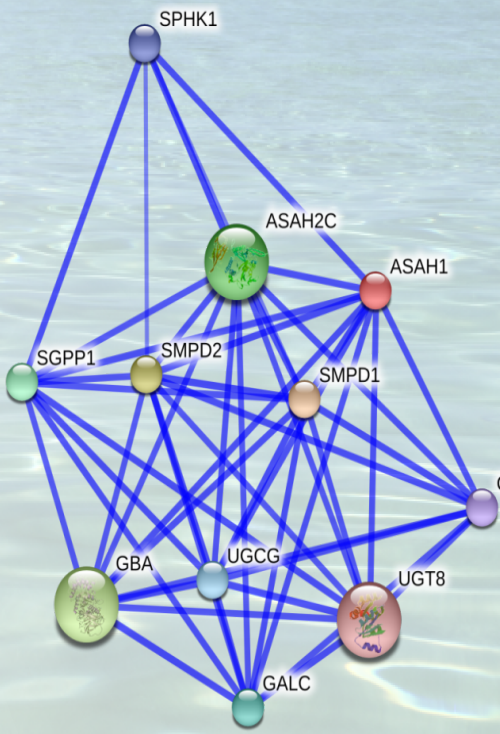
Public Data Analysis

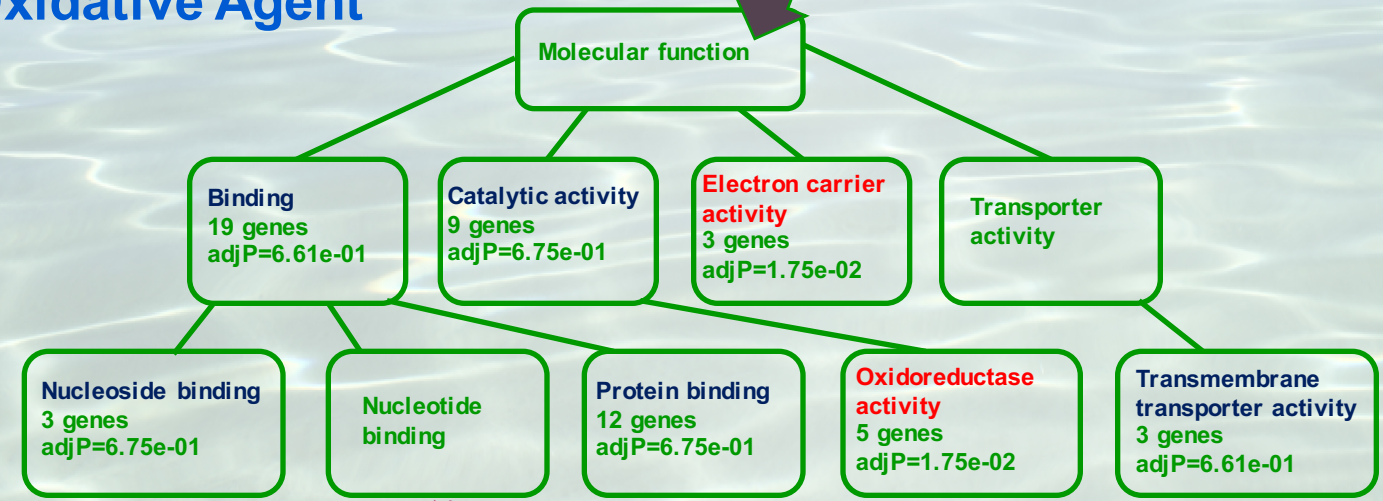
Clustering by *Gene Ontology* associations from *CTD**



Phospholipid Binding



Oxidative Agent



**CTD = Comparative Toxicogenomics Database (www.ctd.org)*

ToxBank

Karolinska Institutet

Kohonen P. et al. The ToxBank Data Warehouse: Supporting the Replacement of In Vivo Repeated Dose Systemic Toxicity Testing. Mol. Inf. 17 JAN 2013.

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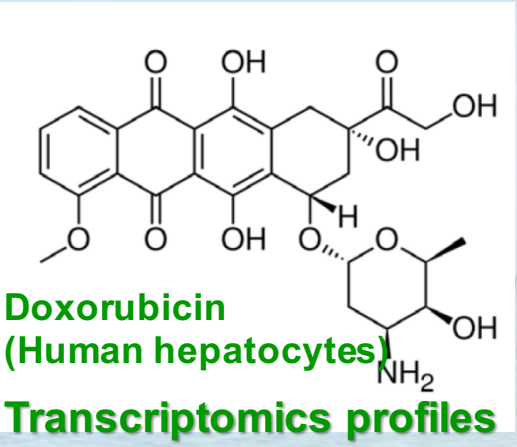
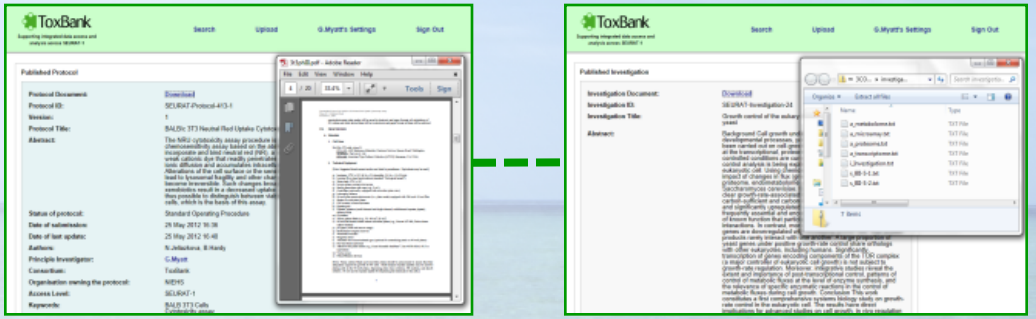
ToxBank Data Warehouse (data curation and retrieval)



Doxorubicin
(Human hepatocytes)

Transcriptomics profiles

A



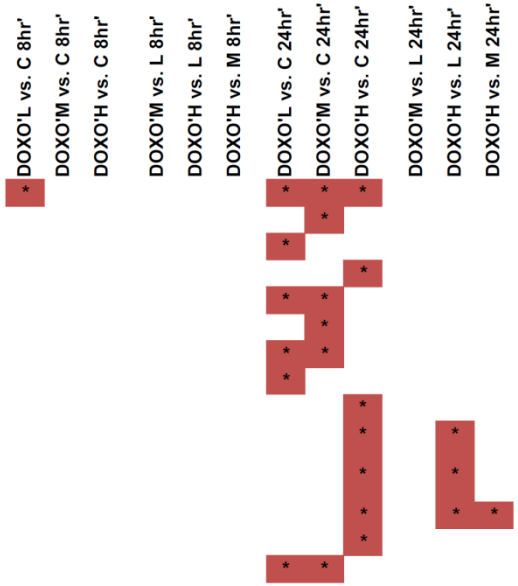
Protocols and SOPs, upload investigation data in ISA-TAB format

C

Differentially expressed genes (R/Bioconductor)

B

Pathway meta-analysis using KEGG pathways (InCroMap) software)



Pathways

1. Cell cycle
2. p53 signaling pathway
3. Oocyte meiosis
4. TNF signaling pathway
5. DNA replication
6. Mismatch repair
7. Fanconi anemia pathway
8. Viral carcinogenesis
9. Rheumatoid arthritis
10. Influenza A
11. Chagas disease (American trypanosomiasis)
12. Hepatitis B
13. Herpes simplex infection
14. Pyrimidine metabolism

Significance: *=FDR q-value < 0.05
Doses: C=Control, L=Low, M=Middle, H=High; Time: 8hr=8 hours, 24hr=24 hours

Connectivity Map (MCF7, PC-3 cell lines; p < 0.01)

1. Doxorubicin (0.999) *
2. H-7 (0.999) *
3. Mitoxantrone (0.998) *
4. Alsterpaullone (0.997) *
5. Camptothecin (0.991)
6. Ronidazole (0.87)
7. Medrysone (0.817)
8. Gliclazide (0.777)
9. Ginkgolide A (0.776)
10. Ellipticine (0.746) *
11. Etamsylate (0.746)
12. Trioxysalen (0.744)
13. Ethaverine (0.739)
14. Doxazosin (0.738)
15. Amiodarone (0.719)
16. Morantel (0.687)
17. Phthalylsulfathiazole (0.684)
18. Dipyridamole (0.672)
19. Demeclocycline (0.645)
20. Famprofazone (0.643)

*= topoisomerase II inhibitor (Mantra 2.0)

D

Comparative Toxicogenomics Database (q-value < 0.01)

Disease Name	Disease ID
1. Cardiovascular Diseases	MESH:D002318
2. Digestive System Diseases	MESH:D004066
3. Neoplasms	MESH:D009369
4. Neoplasms by Histologic Type	MESH:D009370

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Kohonen P, Ceder R, Smit I, Hongisto V, Myatt G, Hardy B, Spjuth O, Grafström R. Basic Clin Pharmacol Toxicol. 2014 Jul;115(1):50-8.

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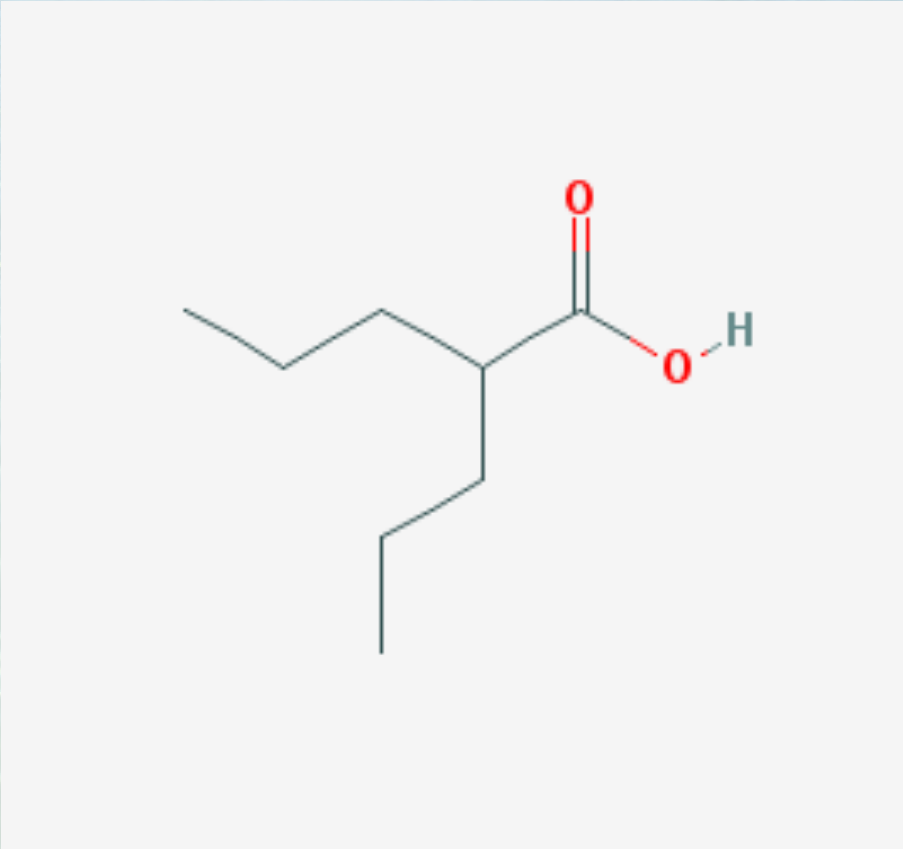
VPA – Mechanistic Analysis (Steatosis)



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VPA – Background Knowledge

VPA –background knowledge.

References

ToxBank http://wiki.toxbank.net/wiki/Valproic_Acid

Wikipedia http://en.wikipedia.org/wiki/Valproic_acid

PubChem https://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3121

VPA – ToxBank Wiki

wiki.toxbank.net/wiki/Valproic_Acid

ToxBank

Page | Discussion | Read | View source | View history | Search

- Main page
- Recent changes
- Compound Summary Table
- Hepatotoxins
  - Summary Page
  - Acetaminophen
  - Aflatoxin B1
  - Allyl Alcohol
  - Amiodarone
  - Beta-Naphthoflavone
  - Bosentan
  - CCl4
  - Chlorpromazine
  - Dimethoxy-naphthoquinone (DMNQ)
  - Dirlotapide
  - FCCP
  - Fluoxetine
  - Iodoacetamide
  - Methotrexate
  - Oligomycin A
  - Rifampicin
  - Rotenone
  - Tamoxifen
  - TO901317

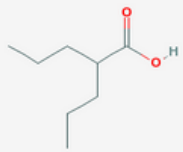
Valproic Acid

Valproic Acid

Executive Summary Information

Compound	Valproic Acid
Toxicities	Steatosis, cytotoxicity
Mechanisms	As a fatty acid analogue, the compound is a competitive inhibitor of fatty acid metabolism, which accounts for steatosis. The parent compound is also hepatotoxic by a mechanism that has not been resolved; however, this hydrophobic compound is used at very high concentrations and its promiscuous activity at these concentrations is likely due to disruption of membrane integrity. P450 ω-oxidation produces a reactive alkylating and free radical-propagating agent that adds to the toxicity profile.
Comments	This compound was selected as a reference standard for steatosis via inhibition of β-oxidation.
Feedback Contact	Gold Compound Working Group (GCWG)

Valproic Acid



In Vivo Data | LIINTOP Data | PK-ADME Data | 'Omics and IC_{50} Data | Physical Properties | Recommended Product and Source

In Vivo Data ?	Compound Assessment
Adverse Events ?	"The foremost and most severe concern for anyone taking valproic acid is its potential for sudden and severe, possibly fatal, fulminating impairments in liver, hematopoietic and/or pancreatic function, especially in those just starting the medication. This particular warning is the first one listed on any drug adverse effect listing when one receives the drug at the pharmacy."

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VPA – background knowledge profile

wiki.toxbank.net/wiki/Valproic_Acid

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VPA Toxicity

As a fatty acid analogue, VPA is a competitive inhibitor of fatty acid metabolism, which accounts for steatosis. It is also hepatotoxic by a mechanism that has not been resolved; however, this hydrophobic compound is used at very high concentrations and its promiscuous activity at these concentrations is likely due to disruption of membrane integrity. P450 ω-oxidation produces a reactive alkylating and free radical-propagating agent that adds to the toxicity profile.

VPA was selected as a ToxBank reference standard for steatosis via inhibition of ß-oxidation.

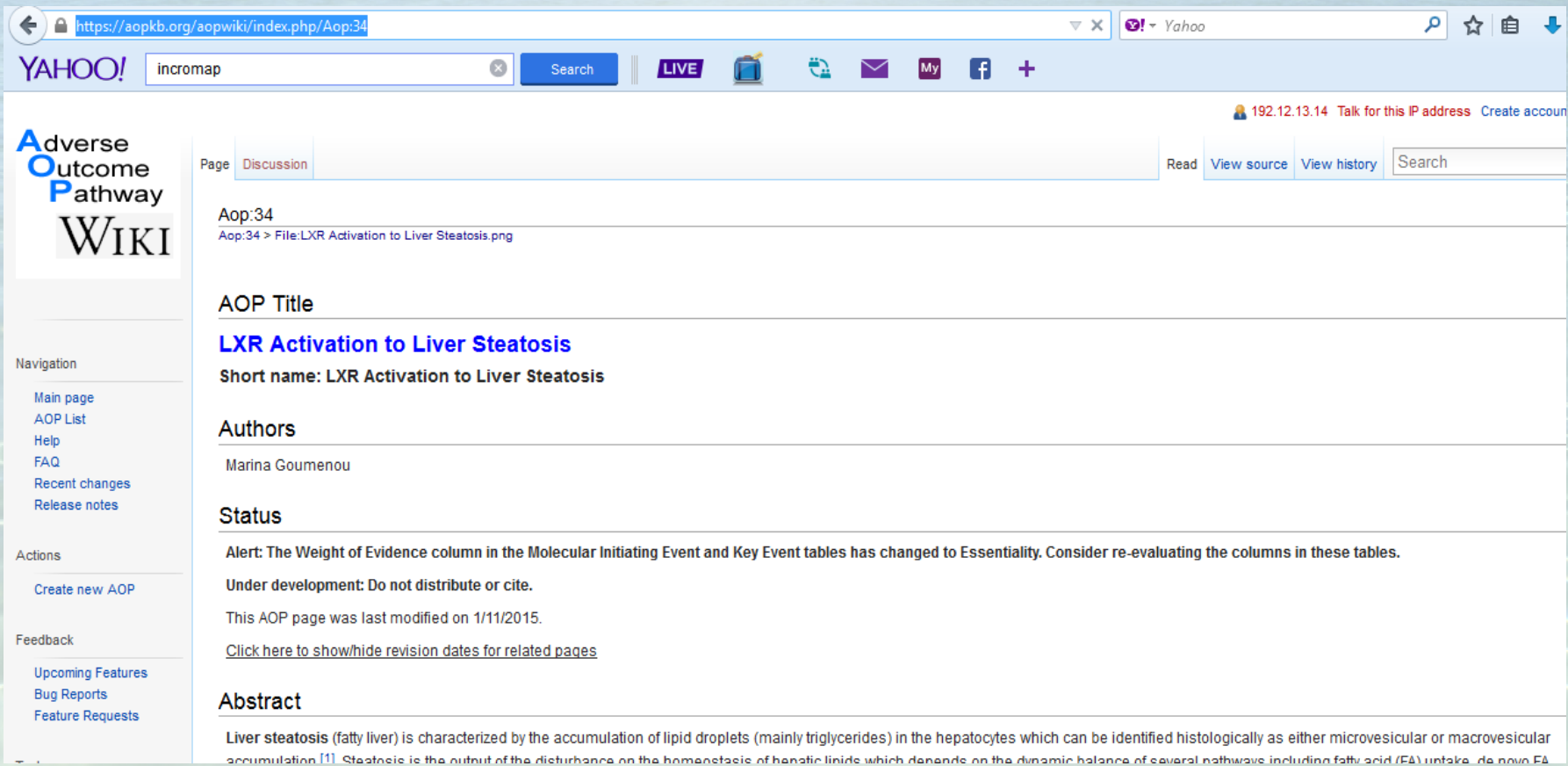
VPA Metabolism

Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30- 50% of an administered dose appears in urine as a glucuronide conjugate.

Mitochondrial -oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose.

Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

Steatosis AOP (s)



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aopkb.org/aopwiki/index.php/Aop:34

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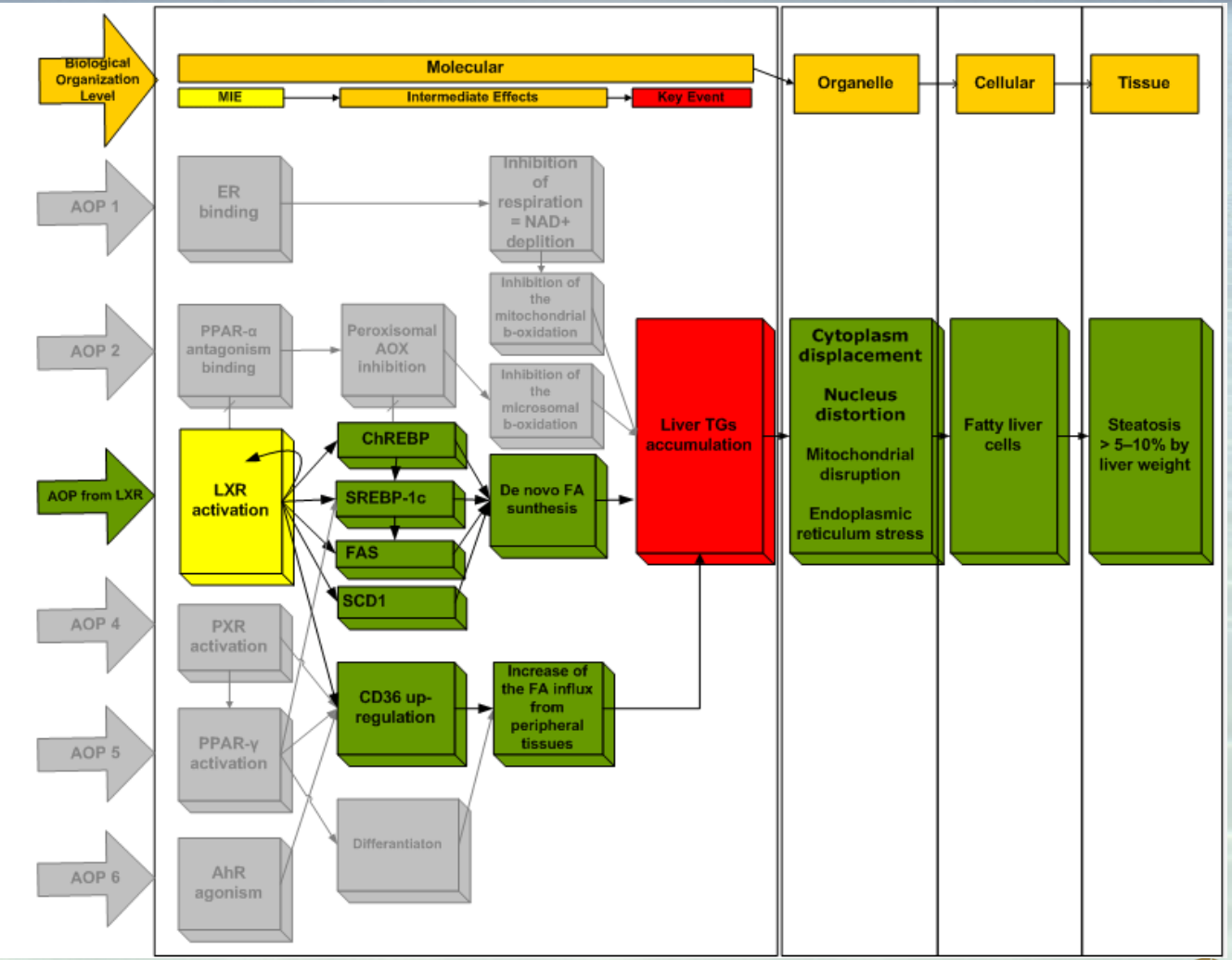
Steatosis AOP



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Source.aopkb.org/aopwiki/index.php/Aop:34

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VPA Data Analysis (Background Knowledge)

VPA

a. *Omics Enrichment Analysis (Apply enrichment to TGG ToxBank dataset using InCroMap)*

b. Include Assay Data - retrieve and examine assay data from ToxCast, PubChem and ChEMBL

c. include in multiple enrichment analysis combined with omics data)

d. Review Steatosis AOP

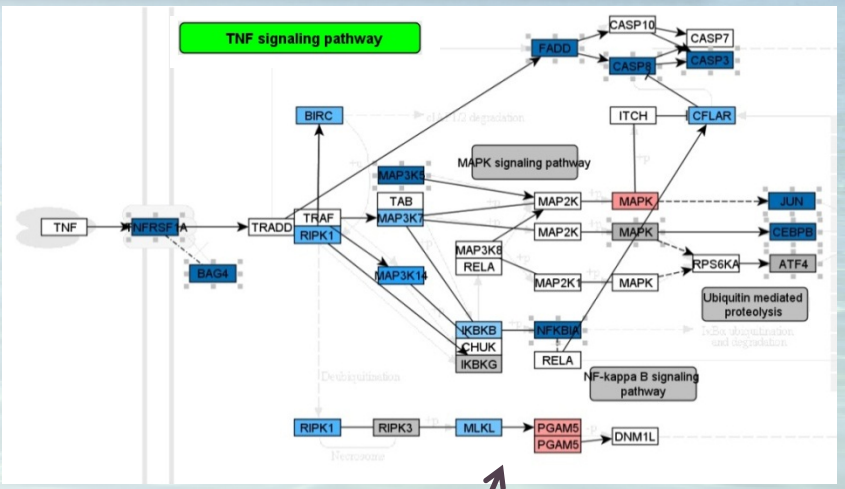
Omics analysis

Differential Expression

Ensembl	Entrez	Symbol	Log-average expression	FC'HC8hr'	FC'MC8hr'	FC'LC8hr'
ENSG00000000003	7105	TSPAN6	10.52	0.021	-0.112	0.005
ENSG00000000005	64102	TNMD	4.04	0.21	0.066	0.214
ENSG00000000419	8813	DPM1	12.31	0.168	0.316	0.184
ENSG00000000457	57147	SCYL3	7.19	-1.049	-0.206	0.101
ENSG00000000460	55732	C1orf112	5.26	-0.402	-0.497	-0.143
ENSG00000000938	2268	FGR	5.77	0.157	0.299	-0.026
ENSG00000000971	3075	CFH	10.1	0.571	0.232	0.035
ENSG00000001036	2519	FUCA2	10.46	0.036	-0.05	-0.041
ENSG00000001084	2729	GCLC	9.22	-0.377	-0.153	0.105
ENSG00000001167	4800	NFYA	6.88	-1.052	-0.966	-0.214
ENSG00000001460	90529	STPG1	6.42	0.046	0.025	0.005
ENSG00000001461	57185	NIPAL3	6.88	-0.048	0.223	0.056
ENSG00000001497	81887	LAS1L	8.9	0.303	0.129	-0.012
ENSG00000001561	22875	ENPP4	7.24	-0.059	-0.391	0.008

*InCroMAP software (http://www.ra.cs.uni-tuebingen.de/software/InCroMAP)

Pathway enrichment*



Pathway class	Pathways	FC'LC8hr'	FC'MC8hr'	FC'HC8hr'	FC'ML8hr'	FC'HL8hr'	FC'HM8hr'	FC'LC24hr'	FC'MC24hr'	FC'HC24hr'	FC'ML24hr'	FC'HL24hr'	FC'HM24hr'	FC'LC8hr24hr'	FC'MC8hr24hr'	FC'HC8hr24hr'	FC'HL8hr24hr'	FC'ML8hr24hr'	FC'HM8hr24hr'	FC'CC8hr24hr'
Cellular Processes; Cell growth and death	Cell cycle	*						*	*	*				*	*					
Cellular Processes; Cell growth and death	p53 signaling pathway								*											
Cellular Processes; Cell growth and death	Oocyte meiosis							*						*						
Environmental Information Processing; Signal transduction	TNF signaling pathway									*										
Genetic Information Processing; Replication and repair	DNA replication							*	*					*	*					
Genetic Information Processing; Replication and repair	Mismatch repair								*											
Genetic Information Processing; Replication and repair	Fanconi anemia pathway							*	*											
Human Diseases; Cancers	Viral carcinogenesis							*												
Human Diseases; Immune diseases	Rheumatoid arthritis									*										*
Human Diseases; Infectious diseases	Influenza A									*		*								
Human Diseases; Infectious diseases	Chagas disease (American trypanosomiasis)									*		*								
Human Diseases; Infectious diseases	Hepatitis B									*		*	*							
Human Diseases; Infectious diseases	Herpes simplex infection									*										
Metabolism; Nucleotide metabolism	Pyrimidine metabolism							*	*						*					
Organismal Systems; Endocrine system	Progesterone-mediated oocyte maturation													*						
Organismal Systems; Immune system	Toll-like receptor signaling pathway									*		*								

VPA Omics Data Analysis

We selected the medium concentration 24 hour TGG processed omics data set and performed an enrichment analysis with InCroMap to provide the set of processed data shown in next Table (using a filter of Fold Changes (FCs) with a log2 absolute value greater than 0.5).

Enrichment analysis of TGG data for VPA (24h, med conc)

#	ID	Name	List ratio	BG ratio	P-value	Q-value	Genes/Compounds
1	path:hsa04114	Oocyte meiosis	6/298	73/14867	2.771E-3	0.2146	CDC20, PLK1, IGF1, CCNE1, SGOL1, AURKA
2	path:hsa04110	Cell cycle	7/298	105/14867	3.948E-3	0.2146	CDC20, ORC6, PLK1, TGFB1, CCNE1, TTK, CDC25A
3	path:hsa00830	Retinol metabolism	4/298	36/14867	4.916E-3	0.2146	RDH16, CYP2C19, CYP4A11, CYP3A7
4	path:hsa00330	Arginine and proline metabolism	4/298	42/14867	8.283E-3	0.2713	ARG1, CPS1, OAT, PRODH2
5	path:hsa04975	Fat digestion and absorption	3/298	26/14867	0.0131	0.3356	MOGAT3, MOGAT2, MTTP
6	path:hsa05020	Prion diseases	3/298	29/14867	0.0173	0.3356	C6, HSPA5, C9
7	path:hsa00591	Linoleic acid metabolism	2/298	11/14867	0.0184	0.3356	CYP2C19, CYP3A7
8	path:hsa00380	Tryptophan metabolism	3/298	32/14867	0.0221	0.3356	DDC, ACMSD, KMO
9	path:hsa00140	Steroid hormone biosynthesis	3/298	33/14867	0.0238	0.3356	HSD17B2, CYP3A7, SULT1E1
10	path:hsa00590	Arachidonic acid metabolism	3/298	34/14867	0.0256	0.3356	CYP2U1, CYP2C19, CYP4A11
11	path:hsa00982	Drug metabolism - cytochrome P450	2/298	18/14867	0.0444	0.4595	CYP2C19, CYP3A7
12	path:hsa00062	Fatty acid elongation	2/298	19/14867	0.0486	0.4595	ELOVL7, ELOVL4
13	path:hsa01230	Biosynthesis of amino acids	3/298	45/14867	0.0487	0.4595	PKLR, ARG1, CPS1
14	path:hsa04621	NOD-like receptor signaling pathway	3/298	47/14867	0.0535	0.4595	CCL2, CARD6, TRIP6
15	path:hsa04918	Thyroid hormone synthesis	3/298	47/14867	0.0535	0.4595	PDIA4, HSPA5, ASGR1
16	path:hsa03430	Mismatch repair	2/298	21/14867	0.0574	0.4595	MSH6, EXO1
17	path:hsa00983	Drug metabolism - other enzymes	2/298	22/14867	0.0619	0.4595	XDH, CYP3A7
18	path:hsa04974	Protein digestion and absorption	3/298	52/14867	0.0659	0.4595	ACE2, SLC3A1, SLC7A9
19	path:hsa04141	Protein processing in endoplasmic reticulum	5/298	130/14867	0.0736	0.4595	PDIA4, CRYAB, HERPUD1, HSPA5, DDIT3
20	path:hsa00232	Caffeine metabolism	1/298	4/14867	0.0778	0.4595	XDH
21	path:hsa00980	Metabolism of xenobiotics by cytochrome P450	2/298	26/14867	0.0803	0.4595	CYP2C19, CYP3A7
22	path:hsa05204	Chemical carcinogenesis	2/298	26/14867	0.0803	0.4595	CYP2C19, CYP3A7
23	path:hsa04914	Progesterone-mediated oocyte maturation	3/298	58/14867	0.0815	0.4595	PLK1, IGF1, CDC25A
24	path:hsa04115	p53 signaling pathway	3/298	59/14867	0.0842	0.4595	IGF1, CCNE1, SESN3
25	path:hsa01200	Carbon metabolism	3/298	63/14867	0.0949	0.4972	PKLR, CPS1, G6PD
26	path:hsa05146	Amoebiasis	3/298	65/14867	0.1002	0.5051	ARG1, TGFB1, C9
27	path:hsa05215	Prostate cancer	3/298	69/14867	0.1109	0.5315	PDGFRB, IGF1, CCNE1
28	path:hsa04146	Peroxisome	3/298	70/14867	0.1136	0.5315	HAO2, XDH, ACOX2
29	path:hsa04151	PI3K-Akt signaling pathway	6/298	233/14867	0.1372	0.5952	PDGFRB, IGF1, IL7, CCNE1, TNC, EFNA1
30	path:hsa04913	Ovarian steroidogenesis	2/298	39/14867	0.1409	0.5952	HSD17B2, IGF1
31	path:hsa05218	Melanoma	2/298	39/14867	0.1409	0.5952	PDGFRB, IGF1
32	path:hsa05214	Glioma	2/298	41/14867	0.1497	0.6075	PDGFRB, IGF1
33	path:hsa05322	Systemic lupus erythematosus	2/298	42/14867	0.1541	0.6075	C6, C9
34	path:hsa05144	Malaria	2/298	43/14867	0.1583	0.6075	CCL2, TGFB1
35	path:hsa05202	Transcriptional misregulation in cancer	4/298	143/14867	0.1623	0.6075	NUPR1, TSPAN7, IGF1, DDIT3

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VPA Omics plus ToxCast Data Analysis

The ToxCast VPA data on non-gene target assays shows activities in assays involving AHR, cell cycle, mitotic arrest, and oxidative stress and are consistent with the above TGG data. Gene target assays showed activities for p53 (managing DNA repair or Apotosis if repair not feasible), FXR (controlling bile acid synthesis from cholesterol), and CYP19A1 (controlling aromatase production converting androgen male hormones to different forms of the female sex hormone estrogen).

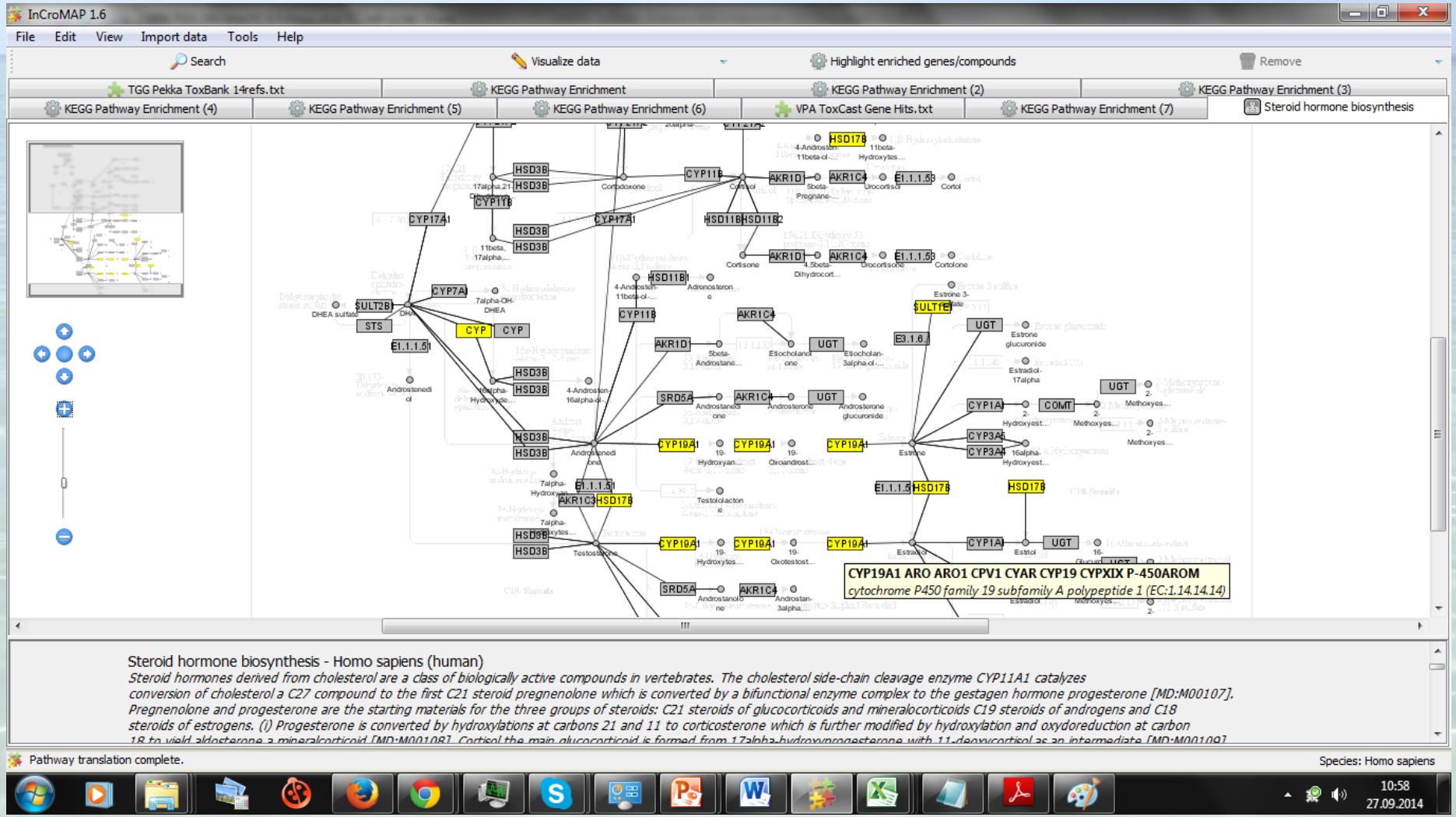
VPA Omics plus ToxCast Data Analysis

For multiple enrichment of TGG and gene target ToxCast assays we combine the two data sets in a multiple enrichment mapped to Kegg pathways. (Note that in these enrichments we apply a filter to include Homo Sapiens data only. We also repeated the analysis based on GO ontology enrichment with similar results). The addition of the CYP19A1 gene moves the steroid hormone synthesis pathway from its previous no 9 significance position with TGG omics data (3/298 genes, pv of 0.024) to its new no 2 position (4/298 genes, pv of 0.0037).

Enrichment analysis of TGG data for VPA (24h, med conc) plus ToxCast

#	ID	Name	List ratio	BG ratio	P-value	Q-value	Genes/Compounds
1	path:hsa04114	Oocyte meiosis	6/300	73/14867	2.859E-3	0.1646	CDC20, PLK1, IGF1, CCNE1, SGOL1, AURKA
2	path:hsa00140	Steroid hormone biosynthesis	4/300	33/14867	3.71E-3	0.1646	HSD17B2, CYP3A7, 1588, SULT1E1
3	path:hsa04110	Cell cycle	7/300	105/14867	4.084E-3	0.1646	CDC20, ORC6, PLK1, TGFB1, CCNE1, TTK, CDC25A
4	path:hsa00830	Retinol metabolism	4/300	36/14867	5.027E-3	0.1646	RDH16, CYP2C19, CYP4A11, CYP3A7
5	path:hsa00330	Arginine and proline metabolism	4/300	42/14867	8.464E-3	0.2218	ARG1, CPS1, OAT, PRODH2
6	path:hsa04975	Fat digestion and absorption	3/300	26/14867	0.0133	0.2902	MOGAT3, MOGAT2, MTTP
7	path:hsa05020	Prion diseases	3/300	29/14867	0.0176	0.3046	C6, HSPA5, C9
8	path:hsa00591	Linoleic acid metabolism	2/300	11/14867	0.0186	0.3046	CYP2C19, CYP3A7
9	path:hsa00380	Tryptophan metabolism	3/300	32/14867	0.0225	0.327	DDC, ACMSD, KMO
10	path:hsa00590	Arachidonic acid metabolism	3/300	34/14867	0.026	0.3409	CYP2U1, CYP2C19, CYP4A11
11	path:hsa04913	Ovarian steroidogenesis	3/300	39/14867	0.0359	0.4278	HSD17B2, IGF1, 1588
12	path:hsa00982	Drug metabolism - cytochrome P450	2/300	18/14867	0.0449	0.4295	CYP2C19, CYP3A7
13	path:hsa00062	Fatty acid elongation	2/300	19/14867	0.0492	0.4295	ELOVL7, ELOVL4
14	path:hsa01230	Biosynthesis of amino acids	3/300	45/14867	0.0494	0.4295	PKLR, ARG1, CPS1
15	path:hsa04621	NOD-like receptor signaling pathway	3/300	47/14867	0.0542	0.4295	CCL2, CARD6, TRIP6
16	path:hsa04918	Thyroid hormone synthesis	3/300	47/14867	0.0542	0.4295	PDIA4, HSPA5, ASGR1
17	path:hsa03430	Mismatch repair	2/300	21/14867	0.058	0.4295	MSH6, EXO1
18	path:hsa00983	Drug metabolism - other enzymes	2/300	22/14867	0.0625	0.4295	XDH, CYP3A7
19	path:hsa04974	Protein digestion and absorption	3/300	52/14867	0.0668	0.4295	ACE2, SLC3A1, SLC7A9
20	path:hsa04141	Protein processing in endoplasmic reticulum	5/300	130/14867	0.0748	0.4295	PDIA4, CRYAB, HERPUD1, HSPA5, DDIT3
21	path:hsa00232	Caffeine metabolism	1/300	4/14867	0.0783	0.4295	XDH
22	path:hsa00980	Metabolism of xenobiotics by cytochrome P450	2/300	26/14867	0.0811	0.4295	CYP2C19, CYP3A7
23	path:hsa05204	Chemical carcinogenesis	2/300	26/14867	0.0811	0.4295	CYP2C19, CYP3A7
24	path:hsa04914	Progesterone-mediated oocyte maturation	3/300	58/14867	0.0826	0.4295	PLK1, IGF1, CDC25A
25	path:hsa04976	Bile secretion	3/300	58/14867	0.0826	0.4295	SLC10A1, 9971, SLC22A1
26	path:hsa04115	p53 signaling pathway	3/300	59/14867	0.0852	0.4295	IGF1, CCNE1, SESN3
27	path:hsa01200	Carbon metabolism	3/300	63/14867	0.096	0.4659	PKLR, CPS1, G6PD
28	path:hsa05146	Amoebiasis	3/300	65/14867	0.1014	0.4745	ARG1, TGFB1, C9
29	path:hsa05215	Prostate cancer	3/300	69/14867	0.1122	0.5015	PDGFRB, IGF1, CCNE1
30	path:hsa04146	Peroxisome	3/300	70/14867	0.1148	0.5015	HAO2, XDH, ACOX2
31	path:hsa04151	PI3K-Akt signaling pathway	6/300	233/14867	0.1385	0.5814	PDGFRB, IGF1, IL7, CCNE1, TNC, EFNA1
32	path:hsa05218	Melanoma	2/300	39/14867	0.142	0.5814	PDGFRB, IGF1
33	path:hsa05214	Glioma	2/300	41/14867	0.1509	0.5952	PDGFRB, IGF1
34	path:hsa05322	Systemic lupus erythematosus	2/300	42/14867	0.1553	0.5952	C6, C9

Enrichment analysis of TGG data for VPA (24h, med conc) plus ToxCast



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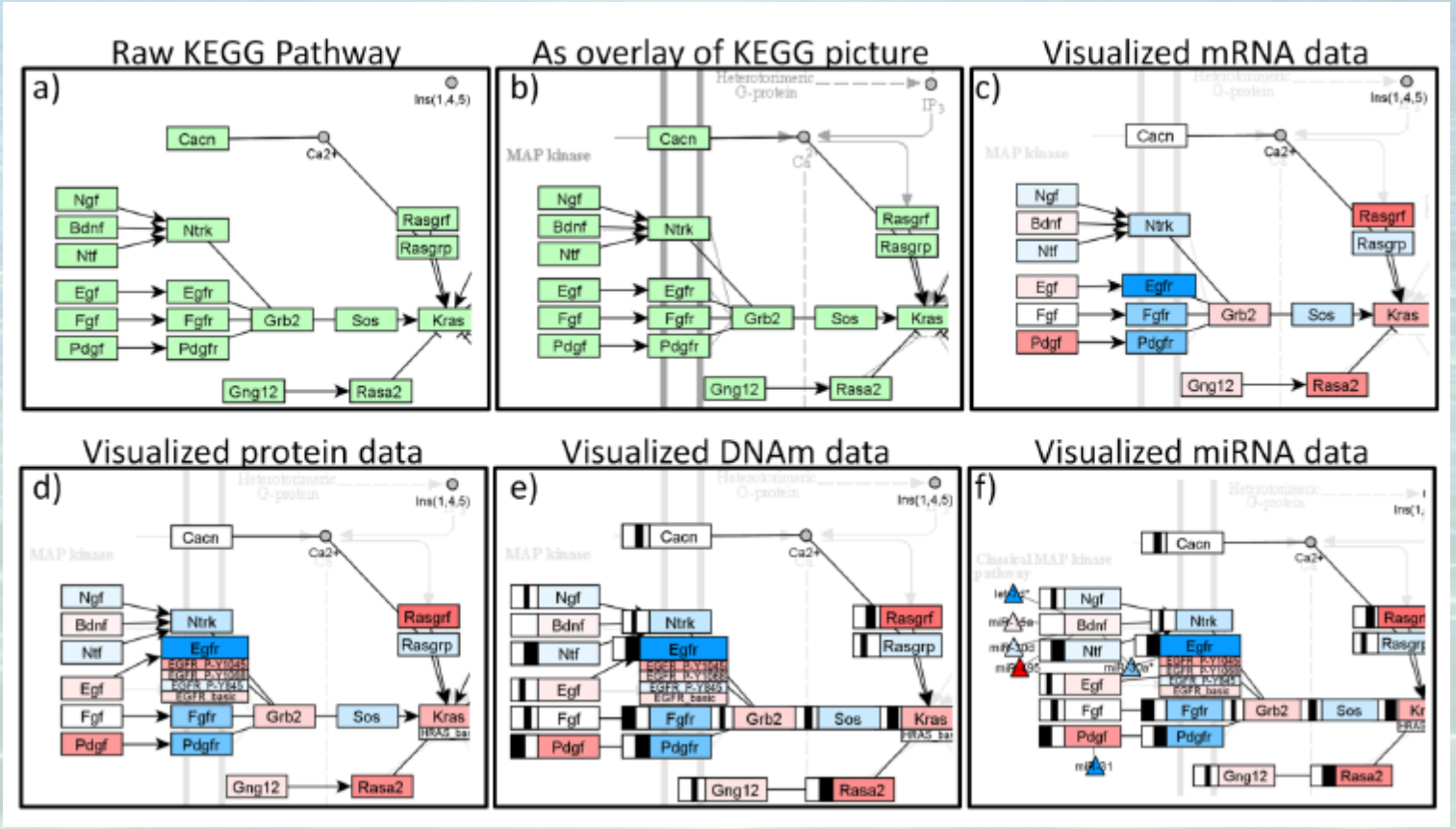
Understanding multiple omics datasets



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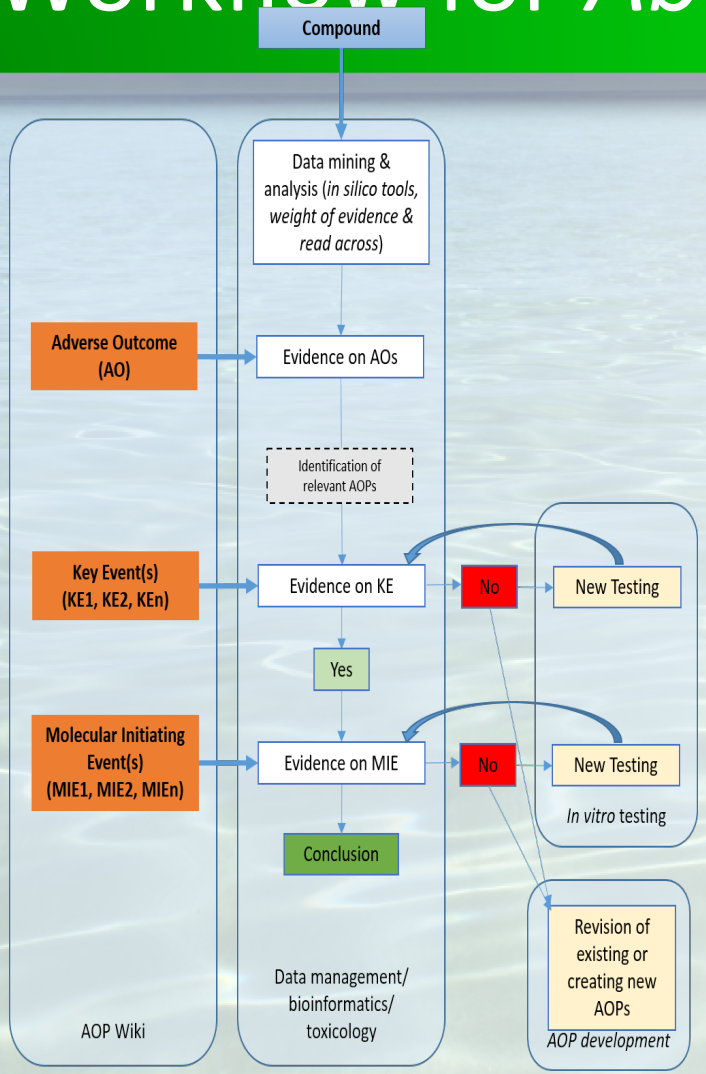
Workflow for *Ab Initio* Risk Assessment



- Identification of Adverse Effects
- Validation of Regions of Concern
- Mode of Action
  - Mechanism
  - New Test
  - Revision of AOP

Identification of Adverse Effects

- H

Transcriptomics data of the liver cell line HepaRG (AN-DIXA-012 - CarcinoGENOMICS)	EPI-T4-PPX5-24h-R-1-1	EPI-T3-PPX5-24h-R-1-1	EPI-T2-PPX5-24h-R-1-1	EPI-T4-PPX5-72h-R-1-1	EPI-T3-PPX5-72h-R-1-1	EPI-T2-PPX5-72h-R-1-1	EPI-T4-PPX10-24h-R-1-1	EPI-T3-PPX10-24h-R-1-1	EPI-T2-PPX10-24h-R-1-1	EPI-T4-PPX10-72h-R-1-1	EPI-T3-PPX10-72h-R-1-1	EPI-T2-PPX10-72h-R-1-1
Piperonyl Butoxide (PBO, PPX)	1.6 µM	1.6 µM	1.6 µM	1.6 µM	1.6 µM	1.6 µM	3.2 µM	3.2 µM	3.2 µM	3.2 µM	3.2 µM	3.2 µM
KEGG pathway (Q<0.05)	24h	24h	24h	72h	72h	72h	24h	24h	24h	72h	72h	72h
Drug metabolism - cytochrome P450							•	•		•	•	•
Retinol metabolism							•			•		•
Metabolism of xenobiotics by cytochrome P450							•	•		•	•	•
Chemical carcinogenesis							•	•		•	•	•
PI3K-Akt signaling pathway										•		
ECM-receptor interaction										•		
Proteoglycans in cancer										•		
Focal adhesion										•		
Rheumatoid arthritis											•	
Chemokine signaling pathway											•	
TNF signaling pathway											•	

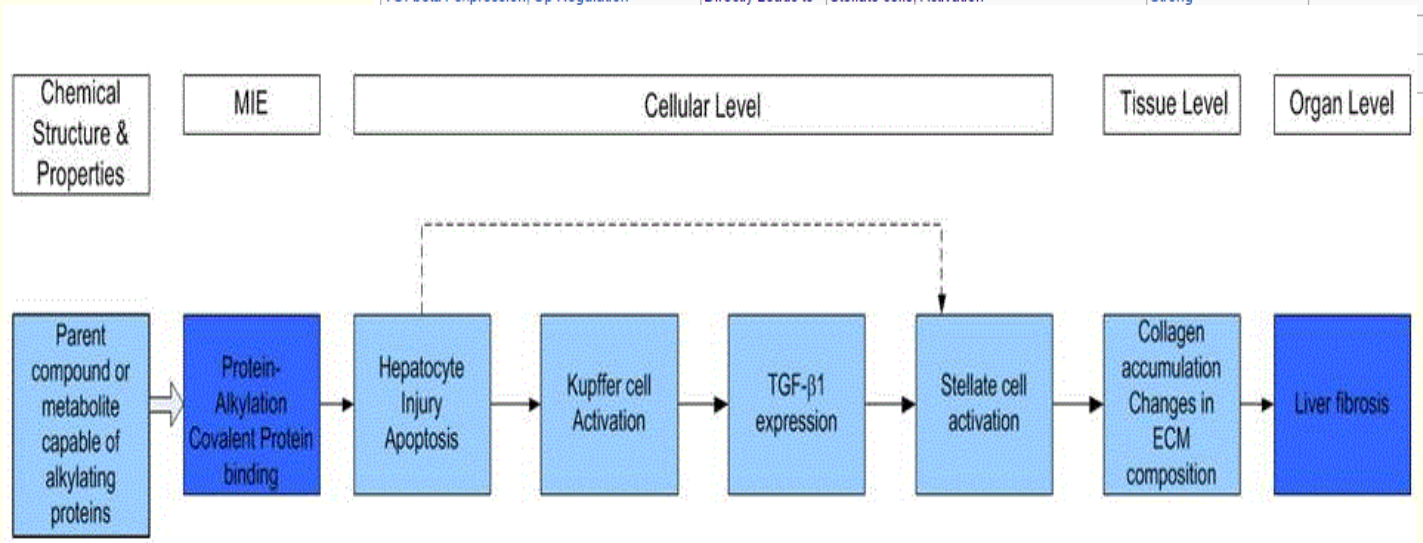
http://www.ra.cs.uni-tuebingen.de/software/InCroMAP

Validation of Regions of Concern

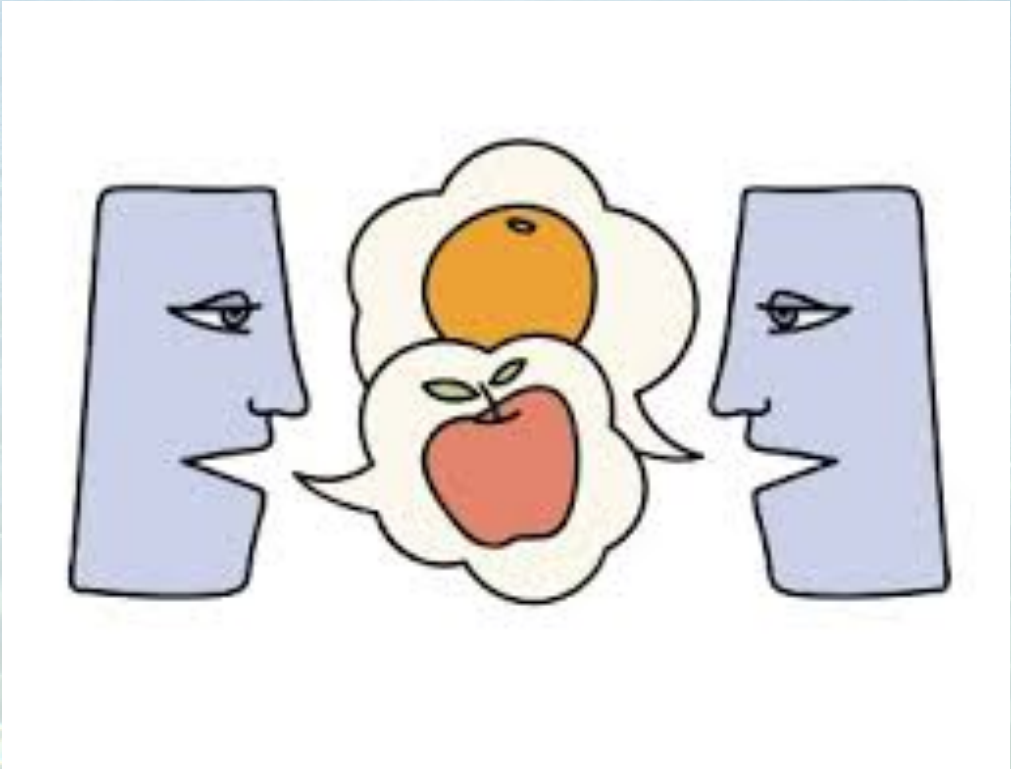
- Including information from AOPs
- AOP38:

Relationships Among Key Events and the Adverse Outcome

Event	Description	Triggers	Weight of Evidence	Quantitative Understanding
Protein, Alkylation	Directly Leads to	Cell death, N/A	Strong	
Cell death, N/A	Directly Leads to	Hepatic macrophages (Kupffer Cells), Activation	Strong	
Cell death, N/A	Indirectly Leads to	Stellate cells, Activation	Strong	
Hepatic macrophages (Kupffer Cells), Activation	Directly Leads to	TGFbeta1 expression, Up Regulation	Strong	
TGFbeta1 expression, Up Regulation	Directly Leads to	Stellate cells, Activation	Strong	



Common Language



Source: sheezaredhead.wordpress.com/2011/01/12/use-common-language-please/

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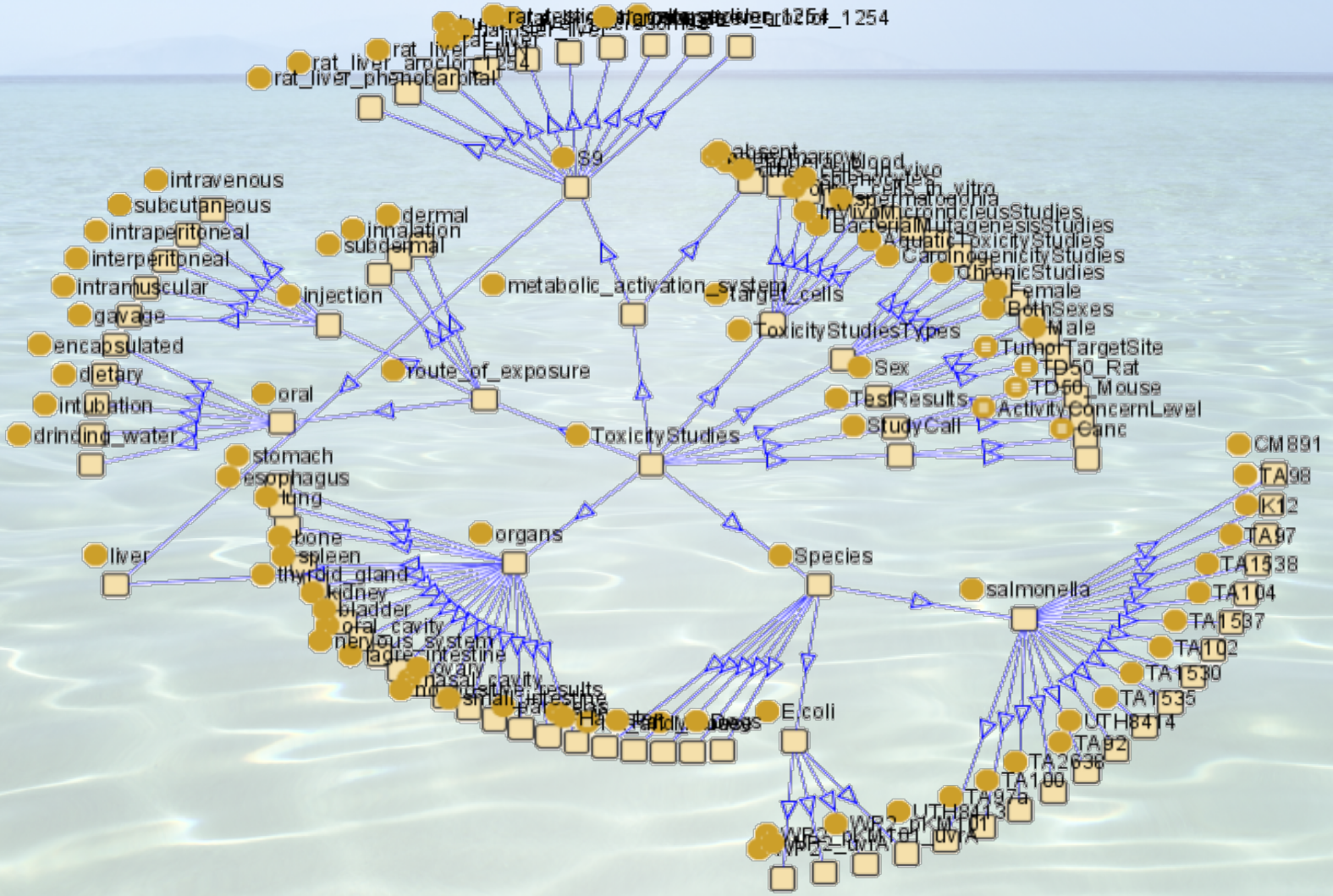
SEVENTH FRAMEWORK PROGRAMME

Toxicological Ontology: graphical representation



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A Toxicology Ontology Roadmap

- See perspectives and roadmap published in A Toxicology Ontology Roadmap ALTEX 29(2), 129- 137 and Toxicology Ontology Perspectives 139 - 156 (2012)
- Available online in Open Access mode from www.altex.ch
- Barry Hardy (Douglas Connect and OpenTox), Gordana Apic (Cambridge Cell Networks), Philip Carthew (Unilever), Dominic Clark (EMBL-EBI), David Cook (AstraZeneca), Ian Dix (AstraZeneca & Pistoia Alliance), Sylvia Escher (Fraunhofer Institute for Toxicology & Experimental Medicine), Janna Hastings (EMBL-EBI), David J. Heard (Novartis), Nina Jeliazkova (Ideaconsult), Philip Judson (Lhasa Ltd.), Sherri Matis-Mitchell (AstraZeneca), Dragana Mitic (Cambridge Cell Networks), Glenn Myatt (Leadscope), Imran Shah (US EPA), Ola Spjuth (University of Uppsala), Olga Tcheremenskaia (Istituto Superiore di Sanità), Luca Toldo (Merck KGaA), David Watson (Lhasa Ltd.), Andrew White (Unilever), Chihae Yang (Altamira)

*Based on Proceedings from the **Toxicology Ontology Roadmap Workshop***
EMBL-EBI Industry Programme Workshop
16 -17th November 2010, Hinxton, UK

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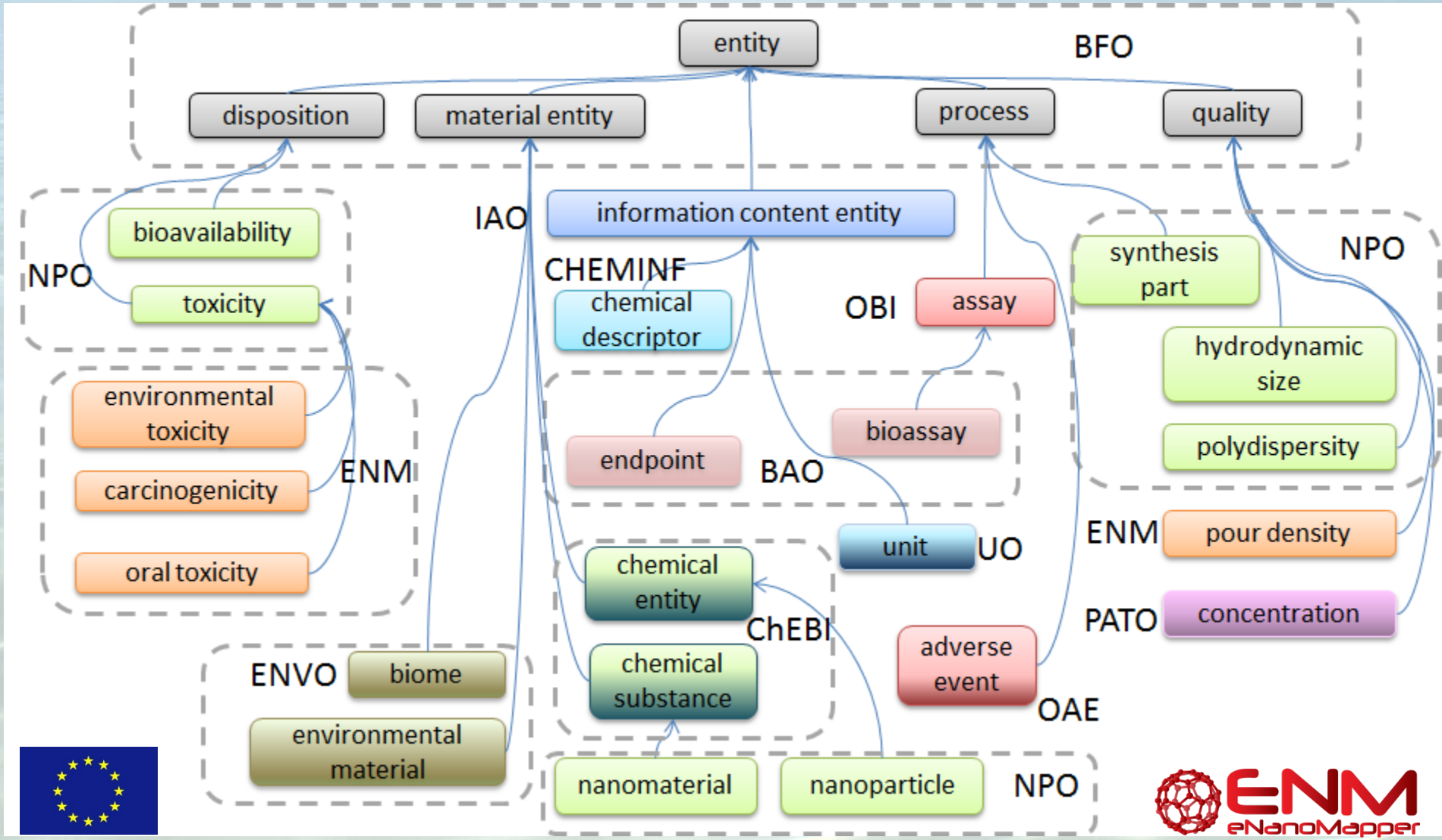
Ontology assembled from multiple sources



OpenTox and Open Components and Standards

<-New API addition from ToxBank

Investigation (Study, Assay)
GET
POST
PUT
DELETE

Authorisation & Authentication
GET
POST
PUT
DELETE

AppDomain
GET
POST
PUT
DELETE

Report
GET
POST
PUT
DELETE

Dataset
GET
POST
PUT
DELETE

Validation
GET
POST
PUT
DELETE

Feature
GET
POST
PUT
DELETE

Compound
GET
POST
PUT
DELETE

Model
GET
POST
PUT
DELETE

Ontology
GET
POST
PUT
DELETE

Algorithm
GET
POST
PUT
DELETE

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OpenTox

www.opentox.org/dev/apis/api-1.2

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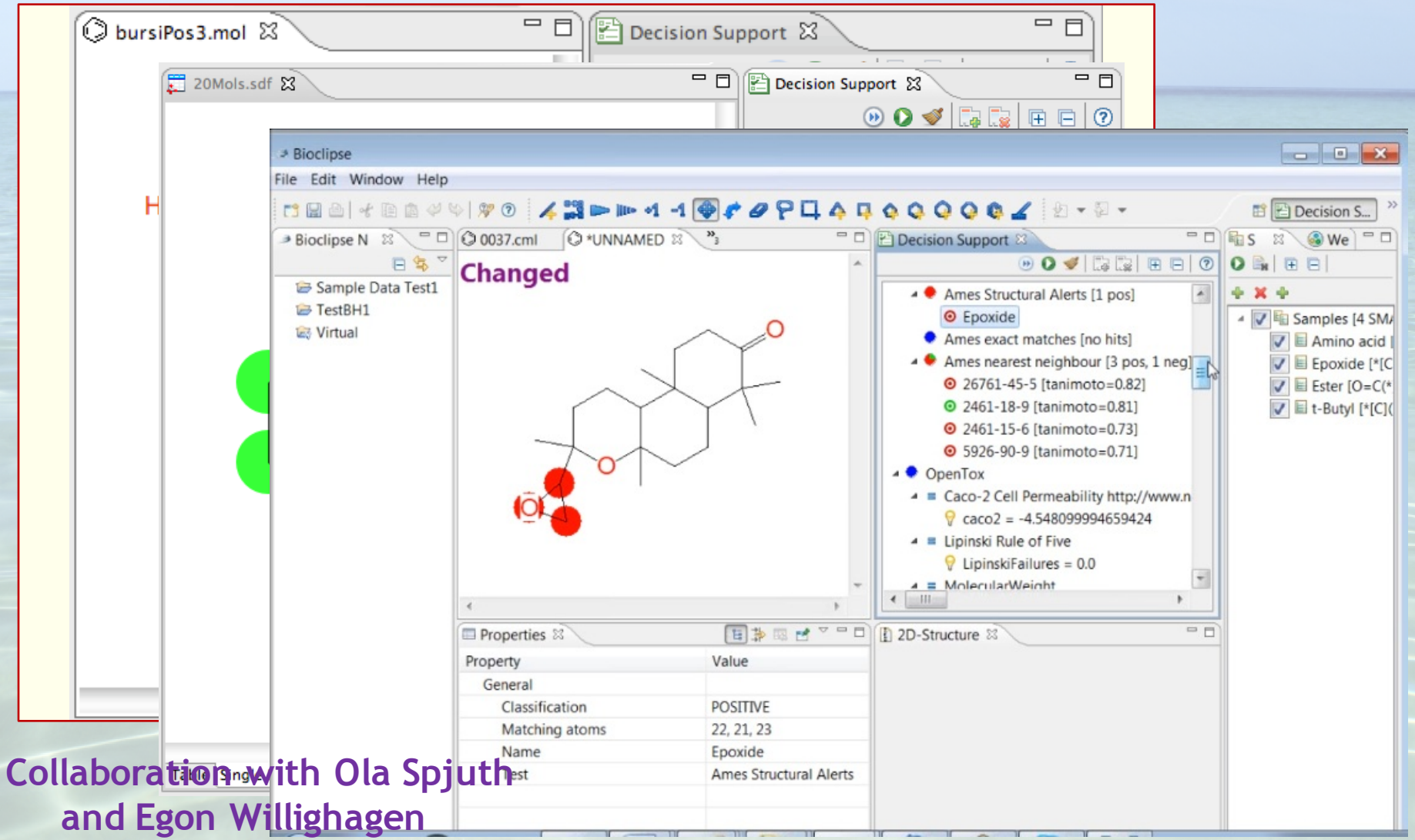
SEVENTH FRAMEWORK PROGRAMME

Bioclipse Visualisation Workbench - OpenTox



Collaboration with Ola Spjuth and Egon Willighagen

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Bioclipse-OpenTox Integration – See Application example in Chapter in **Open Source Software in Life Science Research: Practical Solutions to Common Challenges in the Pharmaceutical Industry and Beyond (Woodhead Publishing Series in Biomedicine) edited by Lee Harland and Mark Forster (30 Oct 2012)**

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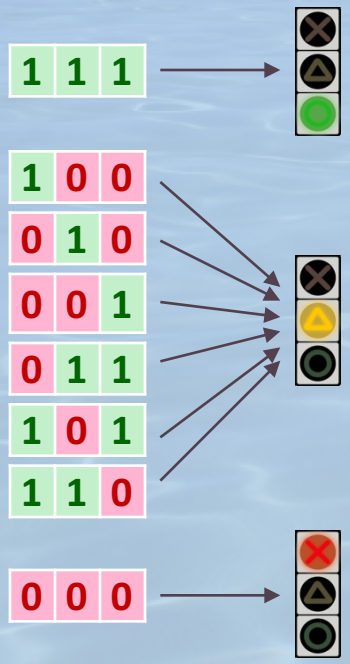
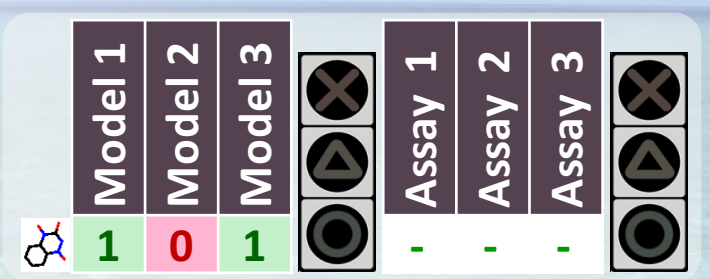
Event Driven Weight of Evidence

collaboration MODERATOR

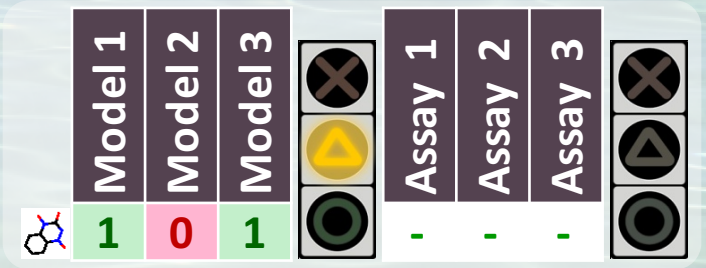
Consensus Rule Editor

Recommendation Rules:





Synergy



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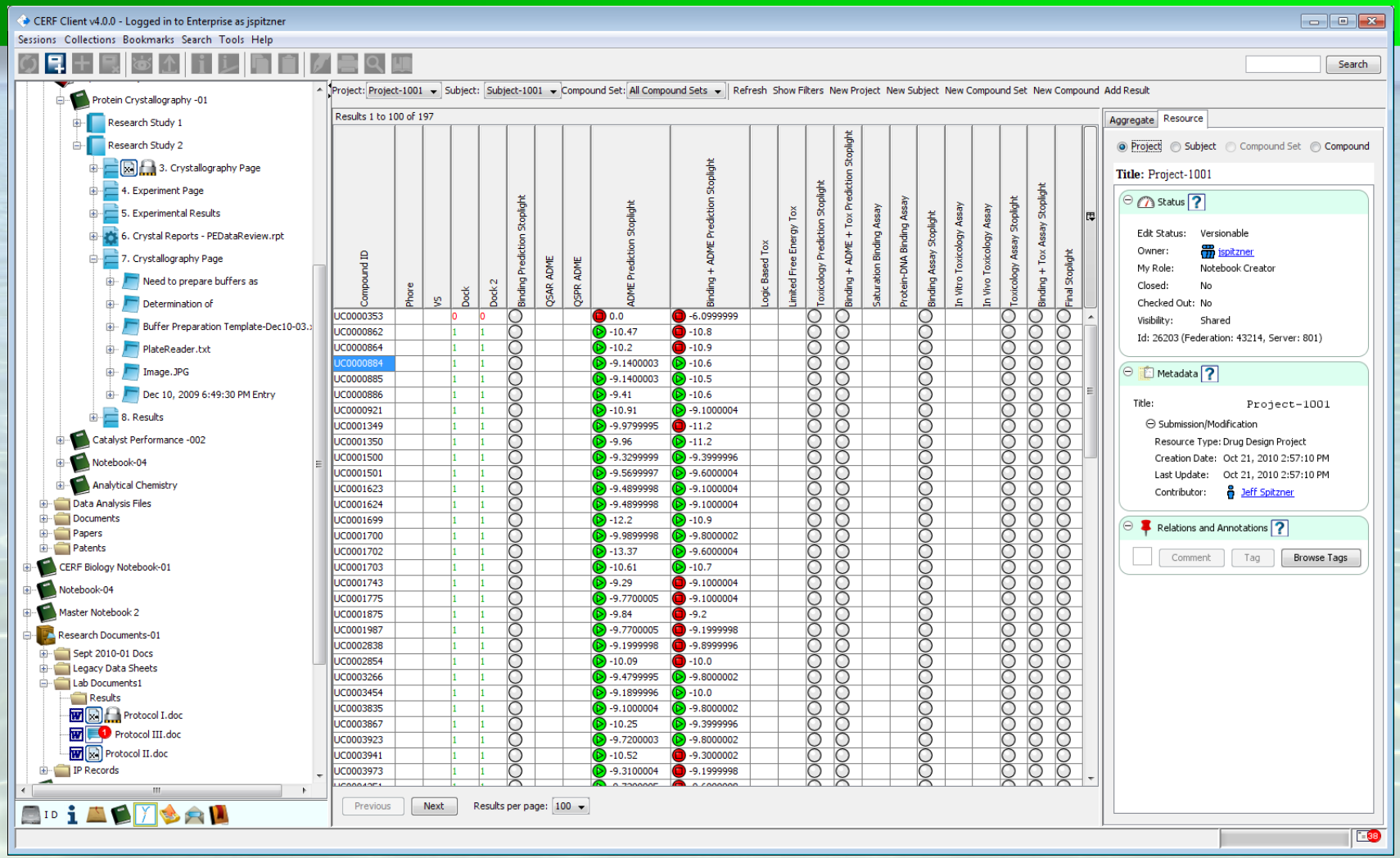
Event-driven Weight of Evidence



[Hardy and Affentranger, Drug Discovery Today. 2013 Jul;18(13-14):681-6.]

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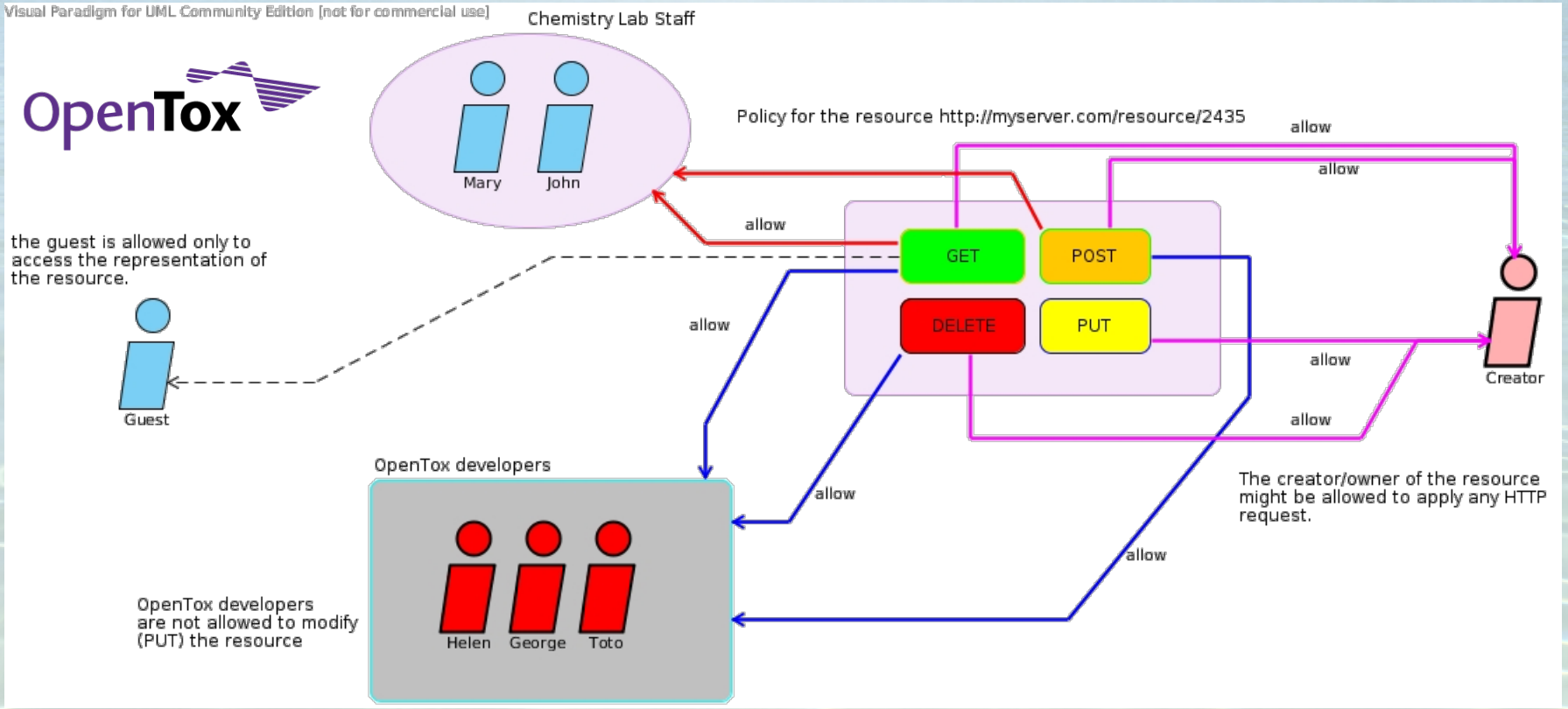
Integrating public and confidential data



Use Open Standards on Resources but with extensive Authorisation and Authentication facilities accompanied by confidential data policies. e.g. *Validation against Confidential Data Case implemented by OpenTox Spring 2011*

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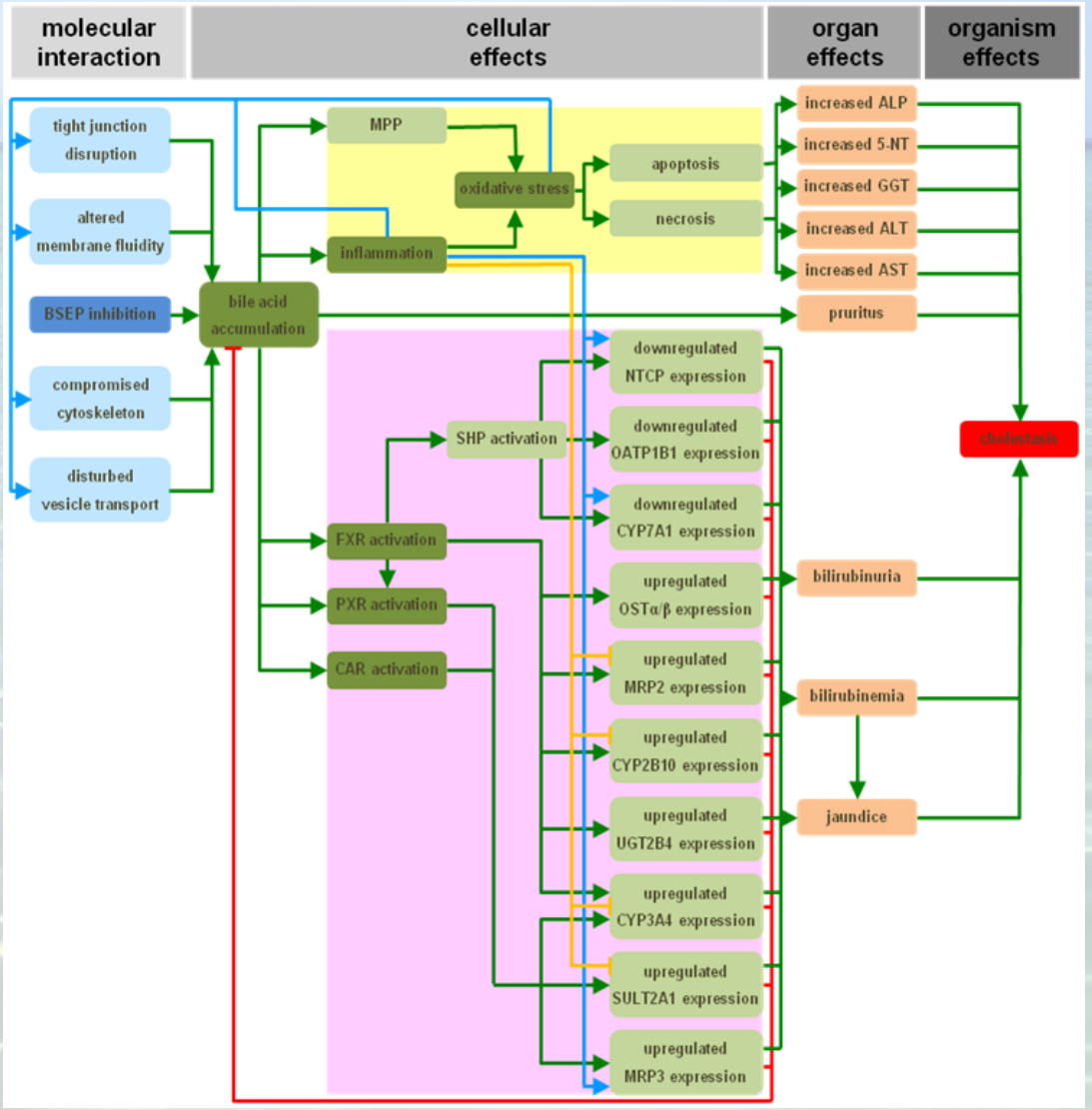
Adverse outcome pathway (AOP) : drug-induced cholestasis



Vinken M., Landesmann B., Goumenou M., Vinken S., Shah I., Jaeschke H., Willett C., Whelan M., Rogiers V. (2013) Development of an adverse outcome pathway from drug-mediated bile salt export pump inhibition to cholestatic liver injury. *Archives of Toxicology*: submitted .

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OpenTox Purpose – from the Articles of Association

The purpose of OpenTox is to promote the community-based exchange and use of open knowledge, methods, tools, reference resources, data and standards in the scientific activities of predictive toxicology, safety assessment and risk management, including the “3Rs” goal of the Reduction, Refinement and Replacement of Animal Testing.

OpenTox Working Groups

Working Groups

a. Application Programming Interfaces (APIs), *Christoph Helma (in silico toxicology)*
b. Data, Metadata and Ontology Standards, *Thomas Exner (Douglas Connect GmbH)*
c. Adverse Outcome Pathway (AOP) development, *Stephen Edwards (US EPA) & Clemens Wittwehr (EC JRC)*
d. Deployment, *Tim Dudgeon (Informatics Matters)*

OpenTox and AOPs

OpenTox

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WG2: MAPPING DATA RESOURCES TO AOPS

AOPS (ADVERSE OUTCOME PATHWAYS): COLLECTION AND DISSEMINATION WITH AOP KNOWLEDGE BASE (AOP-KB) AND POSSIBLE SYNERGIES WITH OPENTOX

An AOP is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect. AOPs are the central ele ment of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning. AOPs portray existing knowledge concerning the linkage between two anchor points - the Molecular Initiating Event (MIE), and an Adve rse Outcome (AO), connected by a chain of Key Events (KE) and the relationships between them (KER).

To enable the scientific community, in one central location, to share, develop and discuss their AOP - related knowledge, the "Adverse Outcome Pathway Knowl edge Base" (AOP - KB , http://aop - kb.org) was created. AOP - KB is a crowdsourcing platform managed by the Organisation for Economic Co - operation and Development (OECD): Everyone across the stakeholder community (research, indu stry, regulatory bodies etc.) is invited to contribute their AOP knowledge

OPENTOX EURO 2015

- PROGRAM AND ABSTRACT BOOKLET
- OPENTOX EURO 2015 MEETING
- OPENTOX EURO 2015 PROGRAM
- DUBLIN ACCOMMODATIONS & TRAVEL
- SUBMIT ABSTRACT, POSTER
- REGISTER ONLINE
- ABOUT OPENTOX EVENTS

SESSIONS EURO 2015

- ALL SESSIONS
- KNOWLEDGE CAFE SESSION
- POSTER SESSION
- S.1: INFORMATION REQUIREMENTS
- S.2: CHARACTERISATION OF SYSTEMS
- S.3: EXPERIMENTAL DATA GENERATION
- S.4: METABOLISM

OpenTox and AOPs

Working Group S ession 2 will raise awareness of the data requirements and their implementation in the AOP - KB on the one hand and data services and format standards proposed by Open Tox on the other. Short presentations of both will set the scene for a discussion on the possible synergy between the OpenTox Framework and its resources and standards, esp. the OpenTox Ontology effort and the OpenTox Data Warehouse (Toxbank). Potential in corporation of other standards like the OECD Harmonized Templates (OHTs) for chemical hazard properties (e.g. the upcoming OHT 201 on "Intermediate Effects") will be covered. Use of OpenTox warehouse data in the AOP - KB to underpin chemical - agnostic AOP kno wledge with real - life chemical data will be discussed . Embracing an open standard approach and third parties that might benefit and potentially use the emerging standard will be identified. Creating a common vision for the use of shared tools and data for the prediction of toxicity is a goal.

The result of Working Group S ession 2 will be an agreement on a way forward to re - use, where possible, OpenTox deliverables in the AOP - KB with a view to cross - fertilization between both areas, especially in the creation of a jointly supported ontology of terms used in both projects.

Workshop Leader: Clemens Wittwehr, Project Co-ordinator at European Commission - Joint Research Centre (JRC)

Clemens Wittwehr is responsible for the Data2Knowledge project in the Systems Toxicology Unit of the JRC's Institute for Health and Consumer Protection (IHCP). Data2Knowledge bridges the gap between Information Technology and Life Sciences by enabling res earchers to capture, manage, publish and share their data in a global stakeholder community from science, industry and regulatory bodies. This JRC activity underpins the

www.opentox.net/events/opentox-euro-2015/wg/mapping-data-resources-aops

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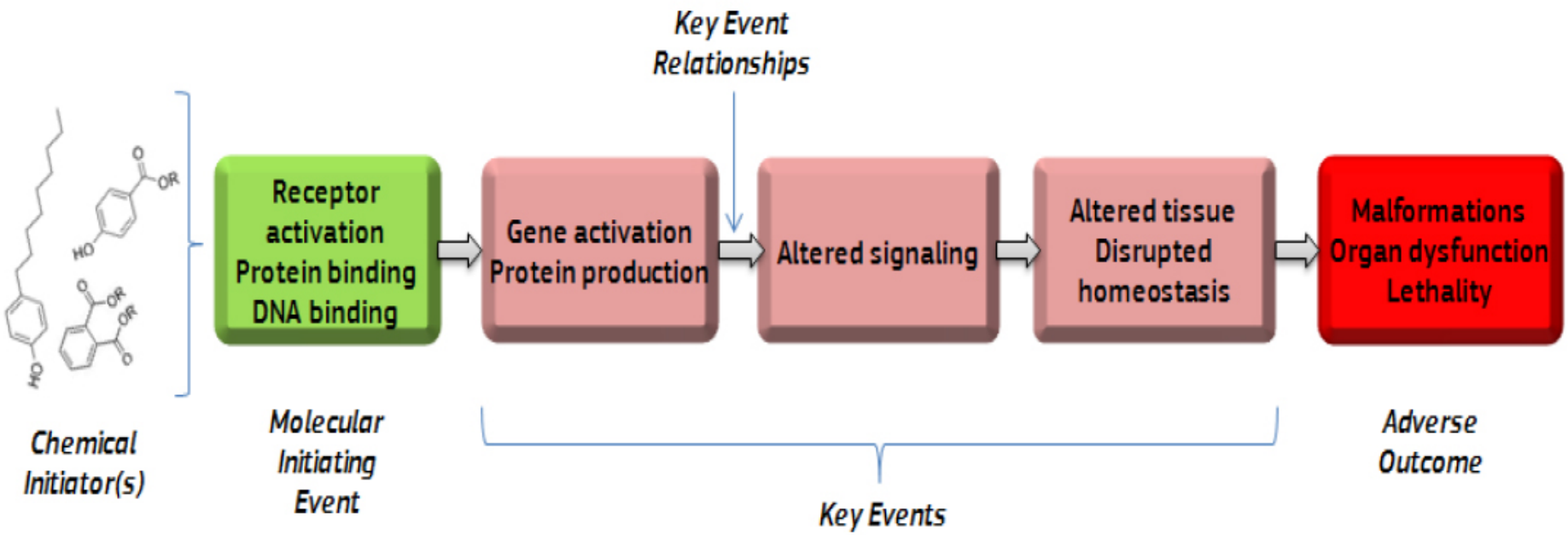
SEVENTH FRAMEWORK PROGRAMME

Key Events and AOPs



www.opentox.net/events/opentox-euro-2015/wg/mapping-data-resources-aops

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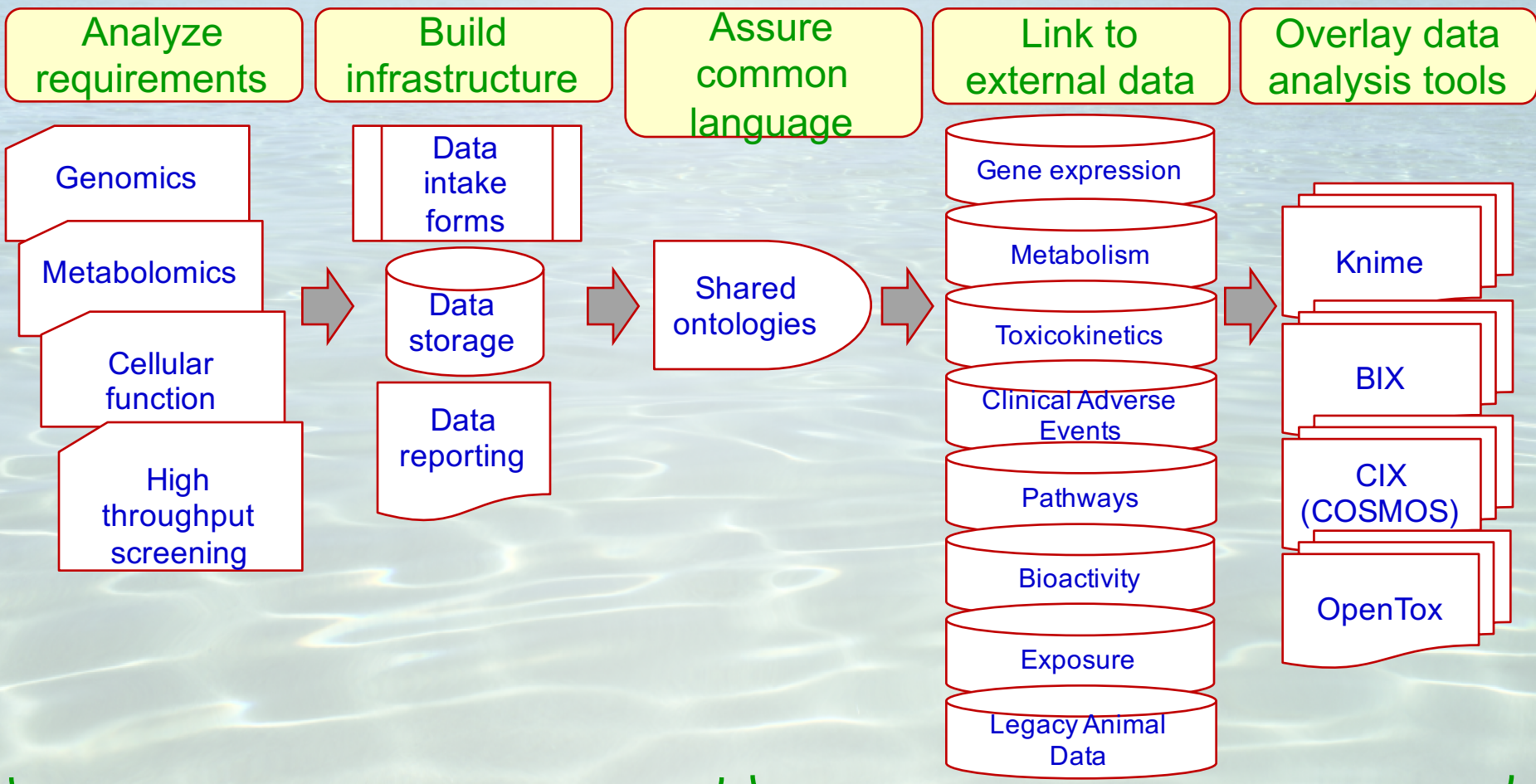
Structure of a Knowledge Management System for Toxicity Prediction



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ToxBank Analysis

2014 Lush Science Prize Winners: Roland Grafström and Pekka Kohonen

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Barcelona highlight

Messi scores winner on rebound - www.youtube.com/watch?v=5wlTvdBfhfw

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