

SUPPLEMENTARY DATA

APPENDICES III - V

Appendix III

Data Associated with Information
Detailed in Chapter 3

A3.1:

Search strategy for the identification of epidemiological studies for PB

Search Engines Used:

- PubMed
- EMBASE
- Cochrane library
- Toxline
- Web of Science

Search Strategy:

- ((“Phenobarbital” or “primidone”) OR (“epilepsy”)) AND (“Liver Neoplasms”/liver cancer”)

Limits:

- Only studies in English
- Human studies only (Observational studies: these included: case series, cross sectional, cohort, case-control or nested case control studies)
- All years (from 1970)

Synonyms Used as Key Words in Search:

All words kept in quotation marks and separated by “OR”

Phenobarbital and Primidone:

"primidone"
"Desoxyphenobarbital"
"Misodine"
"Liskantin"
"Desitin Brand of Primidone"
"Resimatil"
"Sanofi-Synthelabo Brand of Primidone"
"Primidon Holsten"
"Holsten Brand of Primidone"
"Mizodin"
"Mysoline"
"Astra Brand of Primidone"
"AstraZenecaBrand of Primidone"
"Draxis Brand of Primidone"
"Xcel Brand of Primidone"
"Zeneca Brand of Primidone"

"Mylepsinum"
"Apo-Primidone"
"Apotex Brand of Primidone"
"Primaclone"
"Sertan"
"Phenobarbital"
"Phenobarbitone"
"Phenemal"
"Phenylbarbital"
"Phenylethylbarbituric Acid"
"Acid, Phenylethylbarbituric"
"Gardenal" "Hysteps"
"Luminal"
"Phenobarbital Sodium"
"Sodium, Phenobarbital"
"Phenobarbital, Monosodium Salt"
"Monosodium Salt Phenobarbital"

Epilepsy:

Epileptic Seizure"
"Seizure, Epileptic"
"Seizure Disorder"
"Seizure Disorders"
"Seizures, Epileptic"
"Single Seizure"
"Seizure, Single"
"Seizures, Single"
"Single Seizures"
"Aura"
"Auras"
"Awakening Epilepsy"
"Epilepsy, Awakening"
"Epilepsy, Cryptogenic"
"Cryptogenic Epilepsies"
"Cryptogenic Epilepsy"
"Epilepsies, Cryptogenic"
"seizures"
"seizure"
"patients with epilepsy"
"epileptic patients"
"people with epilepsy"

Liver /liver cancer

"Experimental Liver Neoplasm"
"Liver Neoplasm, Experimental"
"Experimental Liver Neoplasms"
"Neoplasms, Experimental Liver"
"Experimental Hepatoma"
"Experimental Hepatomas"
"Hepatoma, Experimental"
"Hepatomas, Experimental"
"Hepatoma, M ris"
"M ris Hepatoma"
"Hepatoma, Novikoff"
"Novikoff Hepatoma"
"Hepatocellular Carcinoma"
"Carcinomas, Hepatocellular"
"Hepatocellular Carcinomas"
"Hepatoma" "Hepatomas"
"Hepatic Neoplasms"
"Hepatic Neoplasm"
"Neoplasm, Hepatic"
"Neoplasms, Hepatic"
"Neoplasms, Liver"
"Liver Neoplasm"
"Neoplasm, Liver"
"Cancer of Liver"
"Cancer of the Liver"
"Hepatic Cancer"
"Cancer, Hepatic"
"Cancers, Hepatic"
"Hepatic Cancers"
"Liver Cancer"
"Cancer, Liver"
"Cancers, Liver"
"Liver Cancers"
"liver tumor "
"liver tumors"
"liver tumour"
"liver tumours"
"Adenomas, Liver Cell"
"Liver Cell Adenoma"
"Liver Cell Adenomas"
"Adenoma, Hepatocellular"
"Adenomas, Hepatocellular"
"Hepatocellular Adenoma"
"Hepatocellular Adenomas"
"Hepatoma, Benign"
"Benign Hepatoma"
"Benign Hepatomas"

"Hepatomas, Benign"
"Liver"
"Livers"
"Liver failure"
"liver failures"
"Chemically induced liver failure"
"liver diseases"
"liver disease"
"Neoplasm"
"Tumours"
"Tumour "
"Tumors"
"Tumor"
"Benign Neoplasms"
"Neoplasms, Benign"
"Benign Neoplasm"
"Neoplasm, Benign"
"Cancer"
"Cancers"
"Carcinogenicity"
"Carcinogen"
"Carcinogens"
"Cancer incidence"
"Incidence of cancer"

Appendix IV

Data Associated with Information
Detailed in Chapter 4

A4.1: Summary of experiments from which the microarray data were obtained. The microarray data generated from the studies were exported from the public microarray repository, Gene Expression Omnibus.

Study Series: GSE 6721					
Authors/ Data contributors	Study Title	Study Summary	Species	Platform for Analysis	Mode of PB administration and dose
Rezen et al [143]	High cholesterol diet and phenobarbital affect cholesterol homeostasis and drug metabolism	Study was designed to investigate the effects of a high cholesterol diet and xenobiotic treatment on cholesterol homeostasis and drug metabolism. Three groups of C57BL/6 strain of male mice were fed for 7 days with a high cholesterol diet, treated with Phenobarbital or injected with the vehicle only (control). The animals treated with PB were injected i.p. 50 mg/kg of phenobarbital in vehicle (5% DMSO in corn oil). After 10h they were sacrificed and the total RNA was isolated from the liver. The affymetrix scan data (.cel files) for the samples collected from PB treated animals and the controls were imported into Rosetta Resolver for analysis.	Mouse	GPL339 Affymetrix GeneChip Mouse Expression Array 430A and Mouse Genome 430A 2.0 Array	Intraperitoneal injection. 50mg/kg in vehicle (5% DMSO in corn oil)

Study Series: GSE 9387					
Author/ Data contributors	Study Title	Study Summary	Species	Platform for Analysis	Mode of PB administration and dose
Dix DJ, Goetz AK No publication available from this study. Study contact: dix.david@epa.gov	Triazole Antifungal Toxicogenomics: rat_primary_hepatocyte_CellzDirect	Phenobarbital was used as a positive control in this in vivo study set up to investigate the role of 3 different triazole antifungals (myclobutanil, propiconazole and triadimefon) on the disruption of steroid hormone homeostasis. Microarray data for 35 samples were submitted by the study investigators to the Gene Expression Omnibus (GEO) repository for microarray data. The affymetrix scan data (.cel files) provided for the 3 biological replicates for the controls (DMSO 0.1%) and 3 biological replicates for positive control Phenobarbital were imported into Rosetta Resolver for analysis.	Rat primary hepatocytes	GPL 1355 Affymetrix GeneChip Rat Genome 230 2.0 Array	In vitro exposure, 72 hour exposure via medium. PB 200μM .

Study Series: GSE16777					
Author/ Data contributors	Study Title	Study Summary	Species	Platform for Analysis	Mode of PB administration and dose
Nesnow et al [144]	Discrimination of Tumorigenic Triazole Conazoles from Phenobarbital by Transcriptional Analyses of Mouse Liver	Phenobarbital was used as a main component in this comparative transcriptional analysis study to differentiate the transcriptional profile of mouse hepatic tissues treated with PB and 2 triazole conazole fungicides (propiconazole and triadimefon). Male CD-1 mice were administered with tumorigenic levels of PB (850 ppm) in the feed and control feed for periods of 2, 4 and Day 30. The latter resulted in an average daily intake of ± 5.9 mg/kg/day of Phenobarbital. The microarray samples available for 4 and Day 30 were obtained from the Gene Express Omnibus gene repository. The data for Day 2 was obtained by personal communication from one of the study contributors, Dr Susan Hester. The affymetrix scan data (.cel files) for the PB and control samples from the 3 different time points were imported into Rosetta Resolver for analysis.	Mouse	GPL1261 [Mouse430_2] Affymetrix Mouse Genome 430 2.0 Array	Administered in diet. PB ± 5.9 mg/kg/day

Study Series: GSE 10410					
Author/ Data contributors	Study Title	Study Summary	Species	Platform for Analysis	Mode of PB administration and dose
Goetz et al [146]	Transcription profiling of human primary hepatocytes after treatment with variable doses OF triazole antifungals to assess toxicity	This transcriptional study was carried out to investigate the hepatic toxicity effects of triazole antifungals (myclobutanil, propiconazole and triadimefon) on human primary hepatocytes. The study investigators set out to explore gene expressions similarities and differences between in vitro data obtained from rodents and humans. Among the 43 samples analysed by the study investigators included 4 biological replicates for phenobarbital as the positive control and 4 biological replicates for controls (DMSO 0.1%). The affymetrix scan data (.cel files) for the latter samples were imported into Rosetta Resolver for analysis.	Human primary hepatocytes	GPL570 Affymetrix [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array	In vitro exposure, 72 hour exposure via medium. PB 1000µM

Study Series: GSE 14712					
Author/ Data contributors	Study Title	Study Summary	Species	Platform for Analysis	Mode of PB administration and dose
Ren et al [145]	Xenobiotic-responsive Nuclear Receptors in Transcriptional Effects Upon Perfluoroalkyl Acid Exposure in Diverse Species	Phenobarbital was used as a positive control as a prototypical activator of CAR in this expression profiling study to investigate the role of on nuclear receptors such as CAR/PXR in rat livers. Male and female Sprague-Dawley rats were dosed orally by gavage with PB (100 mg/kg) or vehicle (0.5% aqueous methylcellulose with 1% Tween 80). The Livers were collected at 6 and 24 h after a single dose or 24 h after 5 consecutive days of dosing (n = 5 animals per sex per time point), immediately flash frozen in liquid N2, and stored at approximately -70 C. The affymetrix scan data (.cel files) provided for the 5 biological samples for the PB and control samples at the 3 different time points were imported into Rosetta Resolver for further analysis.	Rat	GPL85 [RG_U34A] Affymetrix Rat Genome U34 Array	Administered by gavage. PB 100 mg/kg

A4.2:
Gene Biomarkers Identified By Fielden et al. (2007) For Non-Genotoxic Carcinogenicity

Unigene Accession	Gene Symbol		
	Rat	Human	Mouse
BF553500	Cited4	Cited4	Mrg2; AU019445; AW742964; Cited4
L20900	Ica1; Ica69	ICA69; ICAp69; ICA1	69kDa; ICA69; Ica1
AW533663	PRODH	PRODH POX; PIG6; SCZD4; HSPOX2; PRODH1; PRODH2; TP53I6; FLJ33744; MGC148078; MGC148079; PRODH	Pro1; Pro-1; Ym24d07; MGC159030; Prodh
D88666	Pspla1; Ps-pla1; Pla1a	PSPLA1; PS-PLA1; PLA1A	Pspla1; Ps-pla1; AA986889; Pla1a
AW919277	Caps; Caps1; Caps2; Cadps	CAPS; CAPS1; CADPS1; KIAA1121; CADPS	CAPS; CAPS1; AU067781; MGC90712; mKIAA1121; Cadps
AI407719	MGC93284; Usp2	USP9; UBP41; USP2	Ubp41; B930035K21Rik; Usp2
U53184	Pig7; EET-1; Litaf	PIG7; SIMPLE; TP53I7; FLJ38636; MGC116698; MGC116700; MGC116701; MGC125274; MGC125275; MGC125276; LITAF	TBX1; C85531; N4WBP3; 3222402J11Rik; Litaf
AI232085	MGC124985; Trnt1	CCA1; MtCCA; CGI-47; TRNT1	C76540; CGI-47; mt-Trat; AA408384; 2410043H24Rik; 2610044E04Rik; 9830143O18Rik; Trnt1
AW915076	RGD1560731; Gpr146	PGR8; GPR146	PGR8; GPR146
AW143696	-	P; CAF; PCAF; P/CAF; KAT2B	Pcaf; AI461839; AW536563; A930006P13Rik; Kat2b
M19651	Fra-1; fra-1; Fosl1	FRA; FRA1; fra-1; FOSL1	Fra1; fra-1; AW538199; Fosl1
AI454466	Gng13	h2-35; G(gamma)13; GNG13	AB030194; Ggamma13; 1500031D04Rik; Gng13
BF397229	NOT FOUND	-	-
AI230591	RGD1565540; Ctla2a	-	Ctla-2b; AW545568; Ctla2b
BF282574	NOT FOUND	-	-

Biomarkers identified by Fielden et al (2007) continued:

Unigene Accession	Gene Symbol		
	Rat	Human	Mouse
AW917064	Exod1; Eri2	EXOD1; KIAA1504; MGC16943; ERI2	Exod1; mKIAA1504; 4933424N09Rik; Eri2
AF163477	-	-	-
AB011534	Egfl4; Megf8	SBP1; EGFL4; C19orf49; FLJ22365; MGC120684; MGC138147; MEGF8	Egfl4; AW049492; mKIAA0817; Megf8
D38292	Pcptp1; Ptprr	PTPRQ; EC-PTP; PCPTP1; PTP-SL; PTPBR7; FLJ34328; MGC131968; MGC148170; DKFZp781C1038; PTPRR	Gmcp1; PTP-SL; PTPBR7; RPTPRR; mPTP213; Ptprr
AA955786	-	-	-
AF135115	Cul5	VACM1; VACM-1; CUL5	VACM1; VACM-1; AI852817; 4921514I20Rik; 8430423K24Rik; C030032G03Rik; C330021I08Rik; Cul5
L16532	CNPF; CNPI; Cnp1; CNPII; Cnp	CNP1; CNP	Cnp1; Cnp-1; CNPase; Cnp
AA850509	Trip13	16E1BP; TRIP13	D13Erd328e; 2410002G23Rik; Trip13
AB043892	Csen; Dream; rKChIP3; Kcnip3	CSEN; DREAM; KCHIP3; MGC18289; KCNIP3	Csen; DREAM; KChIP3; R74849; AI413860; 4933407H12Rik; Kcnip3
NM_019203	Tsx	-	AV207184; Tsx
D50694	MSS1; Psmc2	S7; MSS1; MGC3004; Nbla10058; PSMC2	Psmc2
AA892240	H2-T24; RT1-T24-1	-	-
AI408727	MGC109234; RGD1308059	-	-
AA851239	Extl2	EXTR2; EXTL2	AW146439; 3000001D04Rik; Extl2
BF413176	NOT FOUND	-	-
AF009329	NOT FOUND	-	-
BF543356	Hrc	MGC133236; HRC	HRC
NM_012857	LGP120; Lamp1	LAMPA; CD107a; LGP120; LAMP1	CD107a; Lamp-1; AI196048; Lamp1

Biomarkers identified by Fielden et al (2007) continued:

Unigene Accession	Gene Symbol		
	Rat	Human	Mouse
NM_013197	Alas2	ASB; ANH1; XLSA; ALASE; XLDPP; ALAS-E; FLJ93603; ALAS2	ALAS; ALASE; ALAS-E; Alas- 2; Alas2
AA859585	MGC95014; RGD1359443; Fam100a	PP11303; FLJ31223; FLJ32185; FAM100A	BC013706; 1500031H01Rik; Fam100a

A4.3:**Signature Genes Identified by Nie et al (2006) To Predict Nongenotoxic Carcinogenicity**

Unigene Accession	Gene Symbol			
	Gene Name	Rat	Human	Mouse
NM_012860	methionine adenosyltransferase I, alpha	SAS; SADE; AdoMet; MGC108563; Mat1a	Mat1a	Ams; MAT; SAMS; MATA1; SAMS1; AdoMet; AI046368; Mat1a
NM_138826	metallothionein 1A	Mt; Mt1; Mt1a	MT1; MTC; MT1S; MGC32848; MT1A	-
BC061569	nuclear transport factor 2	NTF2; MGC72930; Nutf2	NTF2; PP15; NUTF2	Ntf2; Ntf3; PP15; AI115459; AI413596; AW546000; MGC102015; 2700067I02Rik; Nutf2
NM_021766	progesterone receptor membrane component 1	MPR; 25Dx; VEMA; 25-Dx; Pgrmc1	MPR; HPR6.6; PGRMC1	PPMR; Vema; HPR6.6; AA415812; Pgrmc1
NM_177933	Sel1 (suppressor of lin-12) 1 homolog (C. elegans)	Sel1h; Sel1l	IBD2; SEL1L1; PRO1063; SEL1-LIKE; SEL1L	Sel1h; AW493766; KIAA4137; mKIAA4137; Sel1l
NM_173295	UDP glucuronosyltransferase 2 family, polypeptide B1	2B1; Udpgr2; Ugt2b17; Ugt2b1	-	1300012D20Rik; Ugt2b1

A4.4:**Reference Genes: Genes Identified By Pei et al. (2009) To Have Been Highlighted In Hepatocellular Carcinoma Microarray Studies**

Gene name	Gene Symbol		
	RAT	human gene symbol	MOUSE
alpha-fetoprotein	Afp	FETA; HPAFP; AFP	Afp
retinoblastoma 1	Rb1	RB; pRb; OSRC; pp110; p105-Rb; RB1	Rb; pRb; Rb-1; Rb1
mitogen-activated protein kinase 1	Erk2; Mapk1	ERK; p38; p40; p41; ERK2; ERT1; MAPK2; PRKM1; PRKM2; P42MAPK; p41mapk; MAPK1	ERK; Erk2; MAPK2; PRKM2; Prkm1; C78273; p41mapk; p42mapk; AA407128; AU018647; 9030612K14Rik; Mapk1
transcription elongation factor A (SII)-like 1	MGC105656; Tceal1	p21; SIIR; pp21; TCEAL1	P21; SIIR; pp21; BC011290; MGC18752; MGC102312; 0610011M09Rik; Tceal1
vimentin	Vim	FLJ36605; VIM	MGC102095; Vim
periostin, osteoblast specific factor	Postn	PN; OSF2; OSF-2; PDLPOSTN; MGC119510; MGC119511; periostin; RP11-412K4.1; POSTN	PN; PLF; Osf2; peri; OSF-2; AI747096; Periostin; Postn
v-akt murine thymoma viral oncogene homolog 1	Akt; Akt1	AKT; PKB; RAC; PRKBA; MGC99656; PKB-ALPHA; RAC-ALPHA; AKT1	Akt; PKB; Rac; PKB/Akt; PKBalpha; Akt1
glypican 3	OCI-5; MGC93606; Gpc3	SGB; DGSX; MXR7; SDYS; SGBS; OCI-5; SGBS1; GTR2-2; GPC3	OCI-5; Gpc3
insulin-like growth factor binding protein 3	IGF-BP3; MGC156773; Igfbp3	IBP3; BP-53; IGFBP3	IGFBP-3; IGgfbp3; AI649005; Igfbp3
midkine	Mdk	MK; NEGF2; FLJ27379; MDK	MK; Mek; Mdk
paternally expressed 10	Peg10; LOC678843	EDR; HB-1; Mar2; MEF3L; Mart2; RGAG3; KIAA1051; PEG10	Edr; HB-1; Mar2; MEF3L; Mart2; MyEF-3; AA407948; Peg10

Reference genes identified by Pei et al. (2009) continued:

Gene name	Gene Symbol		
	RAT	human gene symbol	MOUSE
secreted phosphoprotein 1	OSP; Spp1	OPN; BNSP; BSPI; ETA-1; MGC110940; SPP1	OP; Bsp; Eta; Opn; Ric; BNSP; BSPI; Opnl; Apl-1; ETA-1; Spp-1; AA960535; AI790405; Spp1
epithelial cell adhesion molecule	Egp314; Tacstd1; Epcam	ESA; KSA; M4S1; MK-1; DIAR5; EGP-2; EGP40; KS1/4; MIC18; TROP1; EGP314; HNPCC8; GA733-2; TACSTD1; EPCAM	EGP; Ly74; gp40; CD326; EGP-2; TROP1; Egp314; EpCAM; Tacsdl; GA733-2; Tacstd1; Epcam
annexin A2	ANX2; Anxa2	P36; ANX2; LIP2; LPC2; CAL1H; LPC2D; ANX2L4; PAP-IV; ANXA2	Cal1h; AW215814; Anxa2
fibrinogen-like 1	Frep1; Lfire1; MGC108569; Fgl1	HFREP1; HP-041; LFIRE1; MGC12455; FGL1	Mfire1; MGC37822; Fgl1

Appendix V

Data Associated with Information
Detailed In Chapter 5

A5.1: Toxicity Lists

The tables below show the direction of expression for the genes identified as part of the different Tox Lists across the different studies investigated.

Where more than one gene symbol is provided the tables below, the gene orthologs for the different species are listed in the order of Human: Rat: Mouse

[\[Link to the full list of genes involved in all the IPA Tox Lists\]](#)

A5.1.1: CAR/ RXR Activation

Symbol	Rat				Mouse				Human	Family
	6hrs	1d	3d	5d	10hrs	2d	4d	30d	3d	
Pvalue:	7.81E-3	2.58E-10	2.9E-2	7.13E-17	3.8E-09	7.7E-16	2E-07	2.54E-10	2.58E-11	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	2/28	8/29	1/28	12/28	7/26	20/26	11/26	12/26	10/29	
ABCC3* (ABC3)		+		+	+	+	+	+		transporter
ABCB1									+	transporter
ABCC2* (ABC2)				+	+	+			+	transporter
ABCC4* (ABC4)						+	+	+		transporter
ALDH1A1		+		+		+	+	+		enzyme
CYP2B6* (CYP2B2/ CYP2B10)	+	+		+	+	+	+	+	+	enzyme
CYP2C18* (CYP2C55)					+	+	+	+		enzyme
CYP2C19									+	enzyme
CYP2B7P1									+	enzyme
CCND1						+				other
CES1 (includes EG:1066)						+				enzyme
CYP2C19* (CYP2C37)					+	+	+	+		enzyme
CYP2C8* (CYP2C66)						+	+	+		enzyme
GADD45B						+	+	+		enzyme

GSTA1		+		+					+	enzyme
GSTA3		+		+		+			+	enzyme
GSTA5		+		+		+	+			other
MCL1						-				transporter
MDM2										transcription regulator
NR1I3						-				ligand-dependent nuclear receptor
PAPSS2					+	+				enzyme
PCK1						-	-	-		kinase
RXRA						-		+	-	ligand-dependent nuclear receptor
SULT1A1		-		-					+	enzyme
SULT1B1				+						enzyme
SULT2A1				-						enzyme
UGT1A1				+					+	enzyme
UGT2B4	+	+	+	+		+	+	+		enzyme

A5.1.2: PXR/RXR Activation

Symbol	Rat				Mouse				Human	Family
	6hrs	1d	3d	5d	10hrs	2d	4d	30d	3d	
Pvalue	2.25E-4	5.01E-10	6.4E-2	1.83E-13	1.4E-11	4.6E-13	8.1E-05	4.43E-13	4.99E-11	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	4/63	10/63	1/63	13/63	11/60	28/60	13/60	20/60	13/63	
ABCB1									+	transporter
ABCC2* (ABC2)				+	+	+			+	transporter
ABCC3		+		+						transporter
ABCB11* (ABC16)								+		transporter
ABCC3* (ABC3)					+	+	+	+		transporter
ALAS1	+	+		+	+	+		+	+	enzyme
ALDH1A1		+		+	+	+	+	+		enzyme
ALDH1A7	+		+	+	+	+	+	+		enzyme
ALDH3A2						+			+	enzyme
CES3						-				enzyme
CPT1A						-				enzyme
CYP1A2* (CP12)						+	+	+		enzyme
CYP3A7* (CYP3A13)							+			enzyme
CYP2B1	+			+						enzyme
CYP2B6* (CYP2B2/ CYP2B10)	+	+		+	+	+	+	+	+	enzyme
CYP2C19* (CYP2C37)					+	+	+	+	+	enzyme
CYP2C8* (CYP2C66)						+	+	+		enzyme
CYP3A4* (CYP3A1/ CYP3A)		+		+		+			+	enzyme
CYP3A5									+	enzyme
CYP3A7		+		+					+	transcription regulator
CYP7A1 (CYP7A)		-								enzyme
FOXO1						-		-		transcription regulator
GSTA1		+		+					+	enzyme
GSTM1				-	+	+	+	+		enzyme

G6PC								-		phosphatase
HNF4A							-	-		transcription regulator
HMGCS2						-		-		enzyme
IGFBP1					-	-	-			other
INSR						-		-		kinase
NR1I2							+			ligand- dependent nuclear receptor
NR1I3						-				ligand- dependent nuclear receptor
NR3C1		-				-				ligand- dependent nuclear receptor
PAPSS2					+	+		+		enzyme
PPARA						-		-		ligand- dependent nuclear receptor
PPARGC1A						-				transcription regulator
PRKACA						+	+			kinase
PRKAR1A						-	-	-		kinase
PRKAR2A						+				kinase
PRKAR2B								-		kinase
RXRA						-			-	ligand- dependent nuclear receptor
SLCO1B3						+				transporter
SCD		-						-	-	enzyme
SULT2A1				-						enzyme
UGT1A1				-					+	enzyme

A5.1.3: PPAR α /RXR Activation

Symbol	Rat		Mouse				Human	Family
	1d	5d	10hrs	2d	4d	30d	3d	
	Pvalue	Pvalue	Pvalue	Pvalue	Pvalue	Pvalue	Pvalue	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	3/152	2/157	7/160	42/160	19/160	24/160	6/152	
ABCA1					-	-	-	Transporter
ACAA1	+			+		-	-	Enzyme
ACOX1						-		Enzyme
APOA1			-					Transporter
APOA2		+						Transporter
ADIPOQ				-		-		Other
CHUK				-		-		Kinase
CKAP5				+	+			Other
CYP2C18* (CYP2C55)			+	+	+	+		Enzyme
CYP2C19* (CYP2C37)			+	+	+	+	+	Enzyme
CYP2C29* (CYP2C)			+	+	+	+		Enzyme
CYP2C8* (CYP2C66)				+	+	+		Enzyme
CYP2C70* (CYP2C22)						+		Enzyme
FASN				+				Enzyme
GHR				-	-	-		transmembrane receptor
GK				-	-	-		Kinase
GRB2					-			Other
GNAQ				+				Enzyme
GPD1				-			-	Enzyme
GPD2				+				Enzyme
GRB2				+				Other
HRAS				+				Enzyme

HSP90AA1	+		+	+				Other
HSP90AB1	+							Other
IKBKE				+	+			Kinase
IKBKG			+	+		+	+	Kinase
INSR				-		-		Kinase
IRS1				+		+		Other
ITGB5					-			Other
LPL					+			Other
JUN				+				transcription regulator
MAP2K1				+		+		Kinase
MAP2K2				+	+	+		Kinase
MAP2K3				+				Kinase
MAP2K7				-				Kinase
MAPK8				+				Kinase
NCOA3				+				transcription regulator
NFKBIA				-				Other
NR2C2				+				ligand-dependent nuclear receptor
PDIA3					+			Peptidase
PLCE1				-		-		Enzyme
PPARA				-		-		ligand-dependent nuclear receptor
PPARGC1A				-				transcription regulator
PRKACA				+	+			Kinase
PRKAR1A				-	-	-		Kinase
PRKAR2A				+				Kinase
PRKAR2B						-		Kinase
RAF1		+	-	-		-		Kinase
RRAS				+				Enzyme
RRAS2				-	-	-		Enzyme
RXRA				-		-	-	ligand-dependent nuclear receptor
SMAD4					-			transcription regulator

STAT5B				-				transcription regulator
TGFBR2				+	+	+		Kinase

A5.1.4: Mechanism of Gene Regulation by Peroxisome Proliferators via PPAR α

Symbol	Rat		Mouse				Human	Family
	1d	5d	10hrs	2d	4d	30d	3d	
Pvalue	3.26E-4	8.85E-2	0.0185	0.00025	0.333	6.05E-4	4.97E-1	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	6/94	3/93	4/94	23/94	8/94	13/94	2/94	
APOA1			-					transporter
APOA2		+						transporter
ACOX1						-		enzyme
CHUK				-		-		kinase
CITED2	-				+			transcription regulator
CPT1B	-							enzyme
DUSP1	-							phosphatase
EHHADH						-		enzyme
GRB2				+	-			other
HRAS				+				enzyme
HSD17B4						-		enzyme
HSP90AA1* (HSP86)	-		+	+				other
HSP90AB1	+							other
IKBKE				+	+	+		kinase
IKBKG			+	+			+	kinase
LPL					+			enzyme
INSR				-		-		kinase
JUN				+				transcription regulator
MAP2K1* (MAPKK1)				+		+		kinase
MAP2K2* (MAPKK2)				+	+	+		kinase

ME1	+	+		+				enzyme
MRPL11					-			other
MYC				+		+		transcription regulator
NFKBIA				-				other
PDGFA				+				growth factor
PPARA				-		-		ligand-dependent nuclear receptor
PPARG					+			ligand-dependent nuclear receptor
PPARGC1A				-				transcription regulator
PRKAR1A				-	-	-		kinase
PRKAR2A				+				kinase
PRKAR2B						-		kinase
RAF1		+	-	-		-		kinase
RXRA				-			-	ligand-dependent nuclear receptor
SRA1				-				transcription regulator
STAT5A				+				transcription regulator
STAT5B				-				transcription regulator

A5.1.5: Oxidative Stress Mediated by NrF2

Symbol	Rat			Mouse				Human	Family
	6hrs	1d	5d	10hrs	2d	4d	30d	3d	
	Pvalue	5.89E-2	3.38E-13	1.68E-15	7.3E-09	0.0016	2.3E-10	4.04E-9	4.52E-9
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	3/186	18/188	9/56	14/191	64/191	39/191	30/191	18/88	
ACTB				-	-				Other
ACTG2 (includes EG:72)						+			Other
ACTG1					+				Other
AKR1A1					+	+	+		Enzyme
AKR7A2						+			Enzyme
AKR7A3		+	+						Enzyme
AOX1					+	+			Enzyme
ATF4					-	-	-		transcription regulator
BACH1								+	transcription regulator
CAT		-					-		Enzyme
CBR1				+	+		+	+	Enzyme
CCT7					+	+			Other
CDC34 (includes EG:997)					+	+	+		Enzyme
CYP1A2* (CP12)					+	+	+		Enzyme
CYP4A11 (CYP4A1)* (CYP4A)							-		Enzyme
CYP2A13* (CYP2A5)				+	+	+	+		Enzyme
CYP2C18* (CYP2C55)				+	+	+	+		Enzyme
CYP2C19* (CYP2C37)				+	+	+	+	+	Enzyme
CYP2C29* (CYP2C)*				+	+	+	+		Enzyme
CYP2C8* (CYP2C66)					+	+	+		Enzyme
CYP2C70* (CYP2C22)							+		Other
CYP3A7* (CYP3A13)				+					Enzyme
CYP3A43								+	Enzyme
CYP3A4		+	+		+			+	Enzyme

CYP3A5			+					+	Enzyme
CYP3A7		+						+	Enzyme
CYP4A11 (CYP4A1)			-						Enzyme
CYP4A22 (CYP4A12)			+						Enzyme
DNAJA1					+	+			Other
DNAJA2					+		-		Other
DNAJA3				+		+			Other
DNAJC3						+			Other
DNAJC5			+						Other
DNAJC6						-			Other
DNAJC7						-			Other
DNAJC8						-			Other
DNAJB1				+	+				Other
DNAJB12					+				Other
DNAJB4					+				Other
DNAJB9	+								Other
DNAJC10					+				Enzyme
DNAJC17					+				Other
DNAJC9					+				Other
EIF2AK3					+				Kinase
EPHX1		+	+		+	+	+	+	peptidase
ERP29			+		+				transporter
FKBP5					-			-	Enzyme
FTH1					+	+			Enzyme
GCLC							-		Enzyme
FTL		+		+	+				Other
FMO1	-	-	-						Enzyme
GCLM								+	Enzyme
GSR		+	+		+	+			Enzyme
GPX2								+	Enzyme
GSTA1		+	+					+	Enzyme

GSTA3		+	+		+			+	Enzyme
GSTA4		+	+		+	+	+		Enzyme
GSTA5		+	+		+	+	+		Enzyme
GSTK1			+						Enzyme
GSTM1			+	+	+	+	+		Enzyme
GSTM4					+	+	+		Enzyme
GSTM6					+				Enzyme
GSTO1					-		-		Enzyme
GSTT1						+	+		Enzyme
GSTT2	-				+	+			Enzyme
HMOX1								+	Enzyme
HSPB8							+		Kinase
HRAS					+				Enzyme
HSP90AA1* (HSP86)		+		+	+				Other
HSP90AB1		+							Other
JUN					+				transcription regulator
KEAP1					+	+	+		transcription regulator
MAF					-				transcription regulator
MAFG								+	transcription regulator
MAP2K1* (MAPKK1)					+		+		Kinase
MAP2K2* (MAPKK2)					+	+	+		Kinase
MAP2K3* (MAPKK3)					+				Kinase
MAP2K7* (MAPKK7)					-				Kinase
MAPK8* (JNK1)(JNK1)					+				Kinase
MGST1						+			Enzyme
MGST2		+	+						Enzyme
NFE2L2					+			+	transcription regulator
NQO1		+	+		+				Enzyme
NQO2					+				Enzyme
PIK3C2A					+				Kinase
PIK3C3					-				Kinase
PIK3CD					-				Kinase

PPIB			+						Enzyme
PRDX1			+		+	+			Enzyme
PTPLAD1							-		Other
RAF1			+	-	-		-		Kinase
RRAS					+		-		Enzyme
RRAS2					-	-	-		Enzyme
SCARB1				-	-				transporter
SLC35A2					-	-			transporter
SQSTM1						+		+	transcription regulator
TXN					+	+			Enzyme
TXNRD1					+			+	Enzyme
UBE2K					+				transcription regulator
UBB		+				+			Other
USP14						-			peptidase
VCP		+			+	+	+		Enzyme

A5.1.6: Oxidative Stress

Symbol	Rat		Mouse				Human	Family
	1d	5d	10hrs	2d	4d	30d	3d	
Pvalue	6.83E-8	1.13E-8	0.453	0.00216	0.0117	4.3E-3	2.61E-3	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	8/56	9/56	1/54	14/54	9/54	8/54	3/35	
CAT	-					-		enzyme
CYP2E1 (CYP2PE)		-					-	enzyme
DUSP1	-							phosphatase
GPX4				+	+	+		enzyme
GCLC						-		enzyme
GCLM							+	enzyme
GSR	+	+		+	+			enzyme
GSTA1	+	+					+	enzyme
GSTA4	+	+		+	+	+		enzyme
GSTA5	+	+		+	+	+		enzyme
GSTM1		-	+	+	+	+		enzyme
GSTM6				+				enzyme
GPX2							+	enzyme
JUN				+				transcription regulator
MGST1					+			enzyme
ME1	+	+		+				enzyme
NFE2L2				+			+	transcription regulator
NQO1	+	+		+				enzyme
PRDX1		+		+	+			enzyme
PRDX3					+			enzyme

PRDX4				+	-	-		enzyme
PRDX6				+		+		enzyme
STAT3				+				transcription regulator

A5.1.7: Aryl Hydrocarbon Receptor Signalling

Symbol	Rat			Mouse				Human	Family
	6hrs	1d	5d	10hrs	2d	4d	30d	3d	
Pvalue	4.9E-1	1.19E-7	6E-9	1.7E-05	4.1E-15	0.00064	1.39E-4	2.85E-5	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	1/140	11/139	13/140	9/144	51/144	21/144	18/144	11/139	
AHR				+	+	+	+		ligand-dependent nuclear receptor
ALDH1A1		+	+	+	+	+	+		Enzyme
ALDH3A2					+			+	Enzyme
ALDH6A1					-				Enzyme
ALDH7A1			+						Enzyme
ALDH9A1					-				Enzyme
ALDH1L1			+						Enzyme
ARNT					-	-			transcription regulator
ATR (includes EG:545)					+		+		Kinase
BAX					+				Other
CCNA2					+	+			Other
CCND1					+				Other
CCND3					+				Other
CCNE2					+				Other
CDK4					+				Kinase
CHEK1					+				Kinase
CHEK2					+				Kinase

CTSD					+				Peptidase
CYP1A2* (CP12)					+	+	+		Enzyme
CYP2C18* (CYP2C55)				+	+	+	+		Enzyme
CYP2C19* (CYP2C37)				+	+	+	+	+	Enzyme
CYP2C29* (CYP2C)				+	+	+	+		Enzyme
CYP2C70* (CYP2C22)							+		Enzyme
CYP2C8* (CYP2C66)					+	+	+		Enzyme
CYP3A43								+	Enzyme
CYP3A4		+	+		+			+	Enzyme
CYP3A5								+	Enzyme
CYP3A7* (CYP3A13)		+	+	+				+	Enzyme
DHFR								-	Enzyme
E2F1					+				transcription regulator
ESR1						-			ligand-dependent nuclear receptor
FASN					+				Enzyme
GSTA1		+	+					+	Enzyme
GSTA3		+	+		+			+	Enzyme
GSTA4		+	+		+		+		Enzyme
GSTA5		+	+		+	+	+		Enzyme
GSTK1			+						Enzyme
GSTM1			-	+	+	+	+		Enzyme
GSTM4					+	+	+		Enzyme
GSTM6					+	+			Enzyme
GSTO1					-		-		Enzyme
GSTT1						+	+		Enzyme
GSTT2	-				+	+			Enzyme
HSP90AA1		+		+	+				Other
HSP90AA2		+							Other
JUN					+				transcription regulator
MAPK8					+				Kinase
MCM7					+				Enzyme

MGST1						+			Enzyme
MGST2		+	+						Enzyme
MDM2					+				transcription regulator
MYC					+		+		transcription regulator
NCOA2					-				transcription regulator
NCOA3					+				transcription regulator
NFE2L2					+			+	transcription regulator
NFIA						-			transcription regulator
NFIB					-		-		transcription regulator
NFIX				+	+				Enzyme
NQO1		+	+		+				Enzyme
NQO2					+				Enzyme
POLA1					+				Enzyme
RARB					+		+		ligand-dependent nuclear receptor
RXRA					-			-	ligand-dependent nuclear receptor
SLC35A2					-	-			Transporter
SRC					+	+			Kinase
TGM2					+	+			Enzyme

A5.1.8: P53 Signalling

Symbol	Mouse			Family
	2 d	4 d	30 d	
Pvalue	7.74E-06	5.87E--2	5.68E-01	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	24/83	10/83	4/83	
ATR (includes EG:545)	+		+	kinase
BAX	+			other
BIRC5	+	+		other
C12ORF5* (C79710)	+			enzyme
CASP6	-			peptidase
CCNG1		+		other
CCND1	+			other
CDK4	+			kinase
CHEK1	+			kinase
CHEK2	+			kinase
CSNK1D	-	+		kinase
E2F1	+			transcription regulator
FASN	+			enzyme
GADD45A	+	+	+	other
GADD45B	+	+	+	other
HIPK2			-	kinase
JUN	+			transcription regulator
KAT2B	-	-		transcription regulator
MAPK8	+			kinase
MDM2	+			transcription regulator
PCNA	+			other

PERP		-		other
PLAGL1		+		transcription regulator
PTEN		-		phosphatase
PIK3C2A	+			kinase
PIK3C3	-			kinase
PIK3CD	-			kinase
PRKDC	+			kinase
SIRT1	-	-		transcription regulator

A5.1.9: G1/S Transition of the Cell Cycle

Symbol	Mouse		Family
	2d	30d	
Pvalue	1E-04	1.83E-1	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	15/47	4/47	
ATR (includes EG:545)	+	+	kinase
CCND1	+		other
CCND3	+		other
CCNE2	+		other
CDC25A	-		phosphatase
CDK4	+		kinase
E2F1	+		transcription regulator
E2F2	+	+	transcription regulator
E2F3	+	+	transcription regulator
E2F4	+		transcription regulator
E2F6	+		transcription regulator
MYCq	+	+	transcription regulator
RBL1	+		other
RBL2	-		other
SUV39H1	+		enzyme

A5.1.10: G2/M Transition of the Cell Cycle

Symbol	Mouse			Family
	2d	4d	30d	
Pvalue	1.2E-07	1.9E-1	4.81E-1	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	16/34	4/34	2/34	
ATR (includes EG:545)	+		+	kinase
CCNB1	+			other
CCNB2	+			other
CDC2	+	+		kinase
CDC25C	+			phosphatase
CHEK1	+			kinase
CHEK2	+			kinase
GADD45A	+	+	+	other
KAT2B	-	-		transcription regulator
MDM2	+			transcription regulator
PLK1	+			kinase
PRKDC	+			kinase
TOP2A	+	+		enzyme
TOP2B	-			enzyme
WEE1	+			kinase
YWHAE	-			other

A5.1.11: Mitochondrial Dysfunction

Symbol	Rat			Mouse				Family
	6hrs	1d	5d	10hrs	2d	4d	30d	
Pvalue	9.67E-2	7.34E-3	1.29E-1	0.0268	0.00035	0.483	2.71E	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	2/110	5/123	3/110	4/119	25/119	8/119	7/119	
APH1B					+			peptidase
APP		+	+					other
BACE1					-			peptidase
CASP3					+			peptidase
CAT		-					-	enzyme
COX15					+	+		enzyme
COX4I1								enzyme
COX5A	-			-	-			enzyme
COX6A2					+			enzyme
COX6C				-	-			enzyme
COX7A1							-	enzyme
COX8C						+		enzyme
CPT1A					-			enzyme
CPT1B		-						enzyme
CYB5R3					+			enzyme
GPD2					+			enzyme
GPX4					+	+	+	enzyme
GPX7					+			enzyme
GSR		-	+		+	+		enzyme
MAOA							-	enzyme
MAPK8					+			kinase
NDUFA4						+		enzyme
NDUFA6	-	-	-	-				enzyme
NDUFA12					-			enzyme

NDUFA8					+			enzyme
NDUFAF1					-		-	other
NDUFB3					+			enzyme
NDUFB5					-			enzyme
NDUFB6				-	-			enzyme
NDUFB9					+			enzyme
PARK7						+	+	other
PDHA1 (includes EG:5160)					+	+		enzyme
PSEN1					+		+	peptidase
PRDX3						+		enzyme
SDHA					-			enzyme
SDHC					-			enzyme

A5.1.12: Pro-Apoptosis

Symbol	Rat	Mouse			Human	Family
	5d	2d	4d	30d	3 d	
Pvalue	3.59E-1	0.144	2.88E-1	1.19E-1	5.27E-1	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	1/39	7/40	4/40	4/40	1/42	
BAX		+				other
BAD			-			other
BAK1			+			other
BIK			+		+	other
BID				+		other
BNIP3L	+			+		other
BOK		-				other
CASP3		+				peptidase
CASP6		-				peptidase
DAPK2 (includes EG:23604)		+				kinase
ERCC3		+	+	+		enzyme
FAS				+		transmembrane receptor
TRAF3		+				other

A5.1.13: Anti-Apoptosis

Symbol	Mouse			Family
	2d	4d	30d	
Pvalue	0.0389	3.31E-1	4.15E-1	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	7/30	3/30	2/30	
BAG3	+			other
BAG4	-			other
BIRC5	+	+		other
BIRC6		-		other
BNIP2	-	-		other
MCL1	-			transporter
TMX1	+		+	enzyme
XIAP	-		-	other

A5.1.14: Hepatic Cholestasis

Symbol	Rat		Mouse				Human	Family
	1d	5d	10hrs	2d	4d	30d	3d	
Pvalue	9.83E-3	4.26E-1	0.0457	0.00209	1.11E-1	3.75E-3	5.72E-5	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	5/132	2/128	4/131	26/131	13/131	14/131	9/132	
ABCB1							+	Transporter
ABCB4* (ABCB1A)				-		-	+	Transporter
ABCC2* (ABC2)		+	+	+			+	Transporter
ABCC3* (ABC3)	+	+	+	+	+	+		Transporter
ABCG5				-	-			Transporter
ABCB11* (ABC16)						+		Transporter
ATP8B1				-	-	-		Transporter
CHUK				-		-		Kinase
CD14							+	transmembrane receptor
ESR1					-			ligand-dependent nuclear receptor
CYP7A1 (CYP7A)	-							Enzyme
CYP7B1* (CYP7B)				-			-	Enzyme
GCGR	-							G-protein coupled receptor
FGFR4				-	-			Kinase
HNF4A					-	-		transcription regulator
IKBKE				+	+	+		Kinase
IKBKG			+	+			+	Kinase
IL1RN				+				Cytokine
INSR				-		-		Kinase
IRAK1				+	-	+		Kinase
IRAK2					+	+		kinase

IRAK3							-	kinase
JUN				+				transcription regulator
LY96						+		other
MAPK8				+				kinase
MYD88							-	other
NFKBIA				-				other
NR1I2					+			ligand-dependent nuclear receptor
PPARA				-			-	ligand-dependent nuclear receptor
PRKACA				+	+			kinase
PRKAR1A				-	-	-		kinase
PRKAR2A				+				kinase
PRKAR2B							-	kinase
RXRA				-			-	ligand-dependent nuclear receptor
SLC10A1	+			+				transporter
SLC10A2			+	+				transporter
SLCO1B3				+				transporter
SLCO1C1				+				transporter
SREBF1	-							transcription regulator
TAP1					+			transporter
TJP2				+				kinase

A5.1.15: LPS/IL-1 Mediated Inhibition of RXR Function

Symbol	Rat			Mouse				Human	Family
	6hrs	1d	5d	10hrs	2d	4d	30d	3d	
Pvalue	1.02E-2	1.18E-14	3.16E-18	1.5E-07	2.8E-09	1.94E-6	6.28E-12	8.26E-17	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	4/178	4/178	23/178	12/176	47/176	30/176	33/176	26/180	
ABCA1						-	-	-	transporter
ABCB1								+	transporter
ABCC2* (ABC2)		+	+	+	+			+	transporter
ABCC3* (ABC3)			+	+	+	+	+		transporter
ABCC4* (ABC4)					+	+	+		transporter
ABCG5					-	-			transporter
ABCB11* (ABC16)							+		transporter
ACSL1			-		-				enzyme
ACSL3						-			enzyme
ACSL4						-	-		enzyme
ACSL5						-	-	+	enzyme
ACOX1							-		enzyme
ALAS1	+	+		+	+		+	+	enzyme
ALDH1A1		+		+	+	+	+		enzyme
ALDH3A2					+			+	enzyme
ALDH6A1					-				enzyme
ALDH7A1			+						enzyme
ALDH9A1					-				enzyme
ALDH1L1			+						enzyme
APOC4					-				transporter
CAT		+					-		enzyme
CD14								+	transmembrane receptor
CHST13								-	enzyme

CPT1A					-				enzyme
CPT1B		-							enzyme
CYP2A13* (CYP2A5)				+	+	+	+		enzyme
CYP2B6* (CYP2B2/ CYP2B10)	+	+	+	+	+	+	+	+	enzyme
CYP2C19* (CYP2C37)				+	+	+	+	+	enzyme
CYP2C8* (CYP2C66)					+	+	+		enzyme
CYP3A4		+	+		+			+	enzyme
CYP3A5								+	enzyme
CYP3A7* (CYP3A13)		+	+	+				+	enzyme
CYP4A11 (CYP4A1)			-				-		enzyme
CYP7A1 (CYP7A)		-							enzyme
EG629219									enzyme
FABP5						-	-		transporter
FMO1	-	-	-						transporter
FMO2					-				enzyme
FMO4					+		+	-	enzyme
FMO5					+	+			enzyme
GAL3ST1			-					+	enzyme
GSTA1		+	+					+	enzyme
GSTA3		+	+		+	+		+	enzyme
GSTA4		+	+		+	+	+		enzyme
GSTA5		+	+		+	+	+		enzyme
GSTK1			+						enzyme
GSTT1						+	+		enzyme
GSTT2	-					+			enzyme
GSTM1			-	+	+		+		enzyme
GSTM4					+	+	+		enzyme
GSTM6					+				enzyme
GSTO1					-		-		enzyme
GSTT2					+				enzyme
HMGCS2					-		-		enzyme

IRAK1					+	-	+		kinase
JUN					+				transcription regulator
LIPC		-			-				enzyme
LY96							+		other
MAP2K7					-				kinase
MAPK8					+				kinase
MGST1		+				+			enzyme
MGST2			+						enzyme
MAOA							-	-	enzyme
MYD88								-	other
NDST1					-	-	-	-	enzyme
NR1I2						+			ligand-dependent nuclear receptor
NR1I3					-				ligand-dependent nuclear receptor
PAPSS2				+	+		+		enzyme
PPARA					-		-		ligand-dependent nuclear receptor
PLTP							-		other
RXRA					-			-	ligand-dependent nuclear receptor
SCARB1				-	-				transporter
SLCO1A2				+					transporter
SLC10A1		+			+				transporter
SLC27A2								+	transporter
SLC27A4					+	+			transporter
SLC27A5						-			transporter
SLC35A2					-	-			transporter
SLCO1B3					+				transporter
SULT1A1		-	-					+	enzyme
SULT2A1			-						enzyme
SULT1A2								+	enzyme
SULT1A3								-	enzyme
SULT1B1			+						enzyme
SULT1C2					+	+	+	+	enzyme
SULT1D1					+	+	+		enzyme

SREBF1		-						transcription regulator
UST					-			Enzyme
XPO1						+		Transporter

A5.1.16: Negative Acute Phase Response Proteins

Symbol	Rat		Mouse				Human	Family
	1d	5d	10hrs	2d	4d	30d	3d	
Pvalue	7.61E-2	2.57E-3	0.0854	0.0521	1.03E-1	5.43E-2	8.13E-3	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	1/8	2/7	1/8	3/8	2/8	2/8	2/8	
AHSG				-			-	other
ALB							-	transporter
APOA1			-					transporter
APOA2		+						transporter
ITIH2				-	-	-		other
ITIH3	-	-		-	-	-		other

A5.1.17: Positive Acute Phase Response Proteins

Symbol	Rat			Mouse		Human	Family
	1d	3d	5d	2d	30d	3d	
Pvalue	2.61E-4	3.11E-2	2.9E-1	0.13	3.35E-3	9.89E-2	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	4/32	1/30	1/30	6/32	6/32	2/32	
A2M				-			transporter
APCS				+	+		other
CP	-						enzyme
CRP	+	+		+	+		other
FGA			+				other
FGB				-			other
HP					+		peptidase
HMOX1						+	enzyme
MBL2						+	other
ORM1				+	+		other
ORM2					+		other
SAA2					+		other
SERPINA3	-						other
SERPING1	-			-			other

A5.1.18: TGF- β Signalling

Symbol	Rat		Mouse				Family
	1d	5d	10hrs	2d	4d	30d	
Pvalue	5.34E-1	2.17E-1	0.553	0.0483	1.12E-1	1.17E-1	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	1/77	2/77	1/77	14/77	8/77	6/77	
BMP2				-			growth factor
BMPR2				-			kinase
GRB2				+	-		other
HRAS				+			enzyme
HNF4A					-	-	transcription regulator
JUN				+			transcription regulator
MAP2K1				+		+	kinase
MAP2K2				+	+	+	kinase
MAPK8				+			kinase
RAF1		+	-	-		-	kinase
RRAS				+			enzyme
RRAS2				-	-	-	enzyme
SMAD1				+	-		transcription regulator
SMAD4					-		transcription regulator
TFE3				+			transcription regulator
TGFBR2				+	+	+	kinase
UBB	+				+		other
VDR		+					enzyme

A5.1.19: Hepatic Fibrosis

Symbol	Rat							Family
	6hrs	1d	5d	10hrs	4d	30d	Human	
Pvalue	6.08E-2	2E-1	1.51E-2	0.231	1.12E-2	3.68E-1	6.16E-2	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	2/84	2/84	4/84	2/83	12/83	5/83	4/84	
AGT					-			other
COL1A1					+			other
COL1A2					+			other
COL3A1	-				+			other
COL4A1					+	-		other
CYP2E1 (CYP2PE)			-				-	enzyme
DCN					-			other
FGF1					-	-		other
FN1		-	-					enzyme
HGF	-	-	-					growth factor
IGF1					-	-	-	growth factor
IGFBP1				-	-			growth factor
IGFBP7				-				other
MMP13					+			peptidase
SDC1			-		-	-	-	other
SMAD4					-			other
TGFA						+		transcription regulator
VTN							-	other

A5.1.20: Hepatic Stellate Cell Activation

Symbol	Rat	Mouse			Human	Family
	5d	2d	4d	30d	3d	
Pvalue	3.21E-1	0.338	4.27E-1	2.28E-1	2.36E-2	
Ratio (Genes from dataset/ total genes involved in IPA pathway/Tox List)	1/34	7/35	3/35	3/35	3/35	
AGT		-	-			other
CD14					+	transmembrane transporter
CYP2E1 (CYP2PE)	-				-	enzyme
IGF1		-	-	-	-	growth factor
PDGFA		+				growth factor
TGFA				+		growth factor
TGFBR2		+	+	+		kinase
TGFBR3		-				kinase

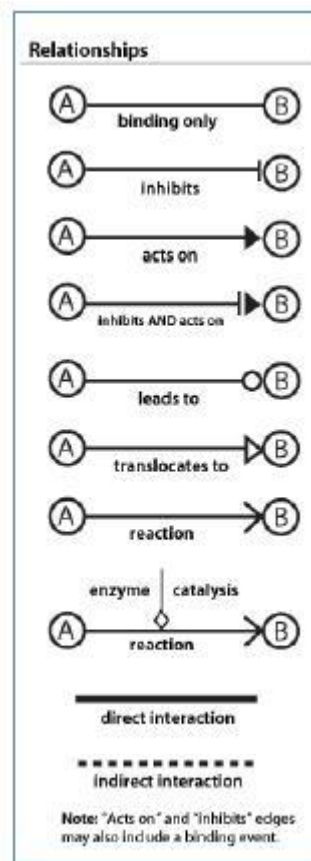
A5.2: Toxicity Functions (Networks Generated using Data Obtained from the Tox Function Analysis).
The genes were selected on the basis of their association with Key events for a hepatocarcinogenesis MOA).

General IPA Legend:

Molecule Shapes

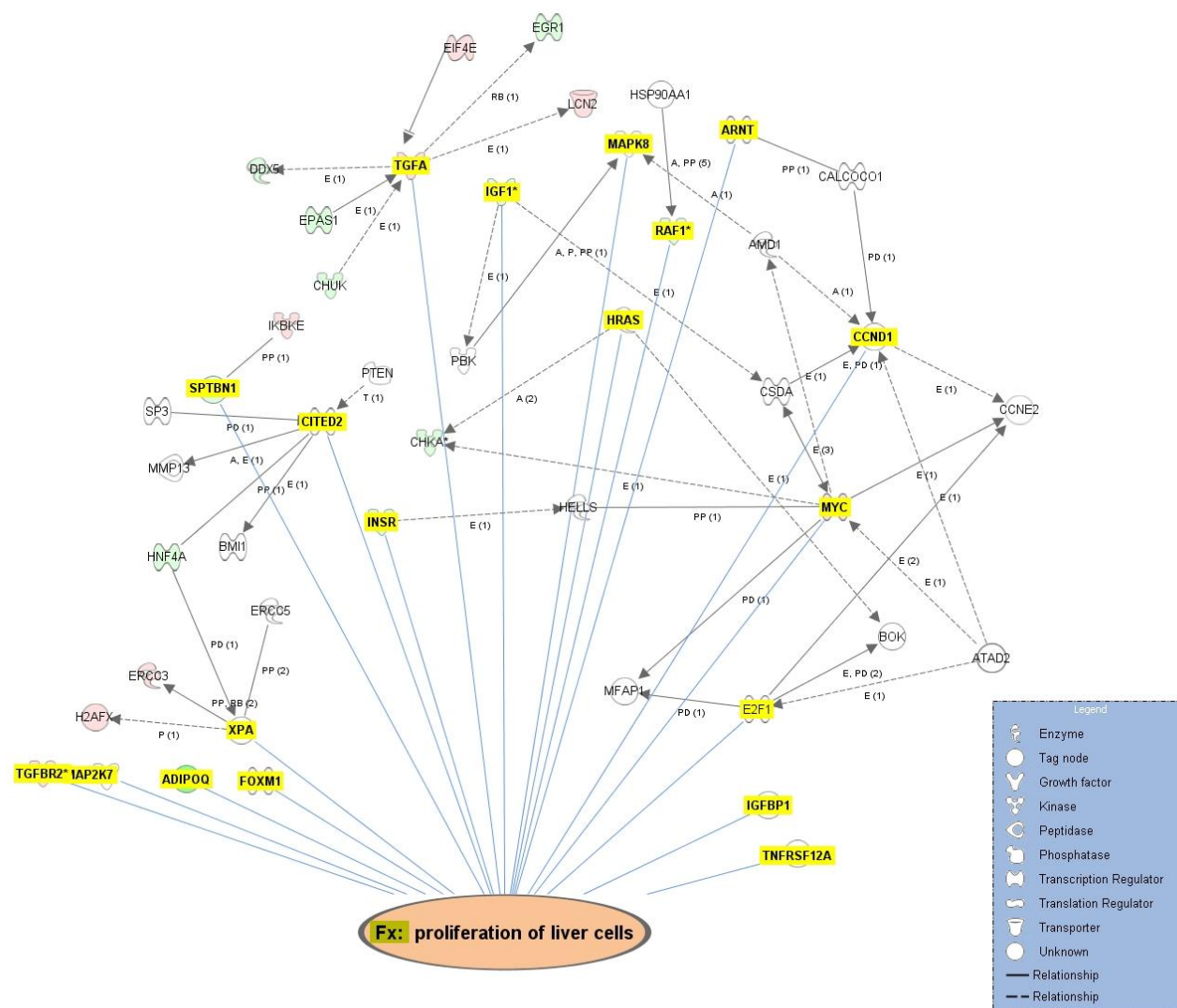
Network Shapes	
	Cytokine
	Growth Factor
	Chemical / Drug/ Toxicant
	Enzyme
	G-protein Coupled Receptor
	Ion Channel
	Kinase
	Ligand-dependent Nuclear Receptor
	Peptidase
	Phosphatase
	Transcription Regulator
	Translation Regulator
	Transmembrane Receptor
	Transporter
	microRNA
	Complex / Group
	Other

Path Designer Shapes	
	Cytokine / Growth Factor
	Drug
	Chemical / Toxicant
	Enzyme
	G-protein Coupled Receptor
	Ion Channel
	Kinase
	Ligand-dependent Nuclear Receptor
	Peptidase
	Phosphatase
	Transcription Regulator
	Translation Regulator
	Transmembrane Receptor
	Transporter
	microRNA
	Complex / Group
	Other



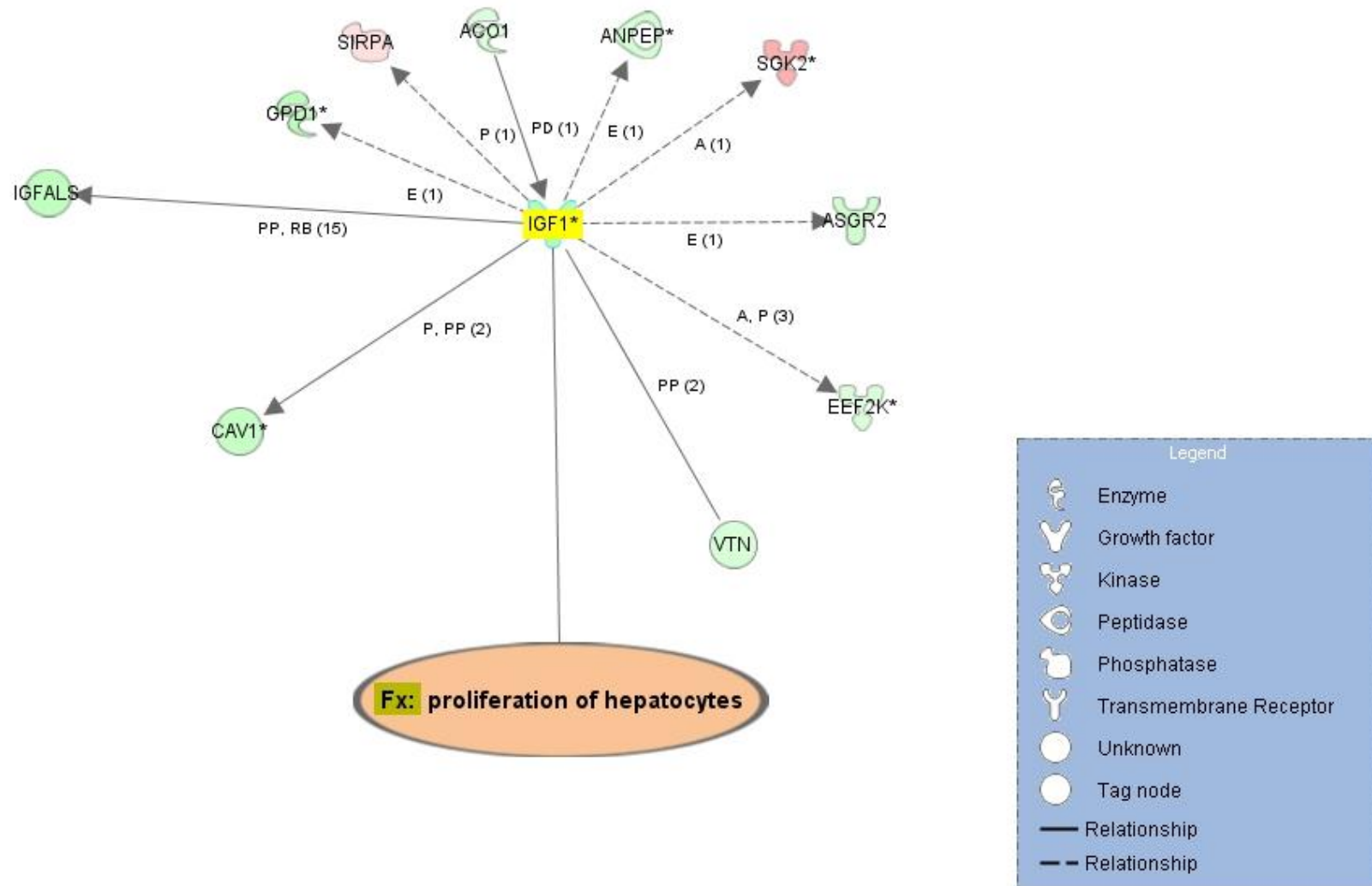
A5.2.1:

Toxicity Function (Mouse data): Liver Proliferation



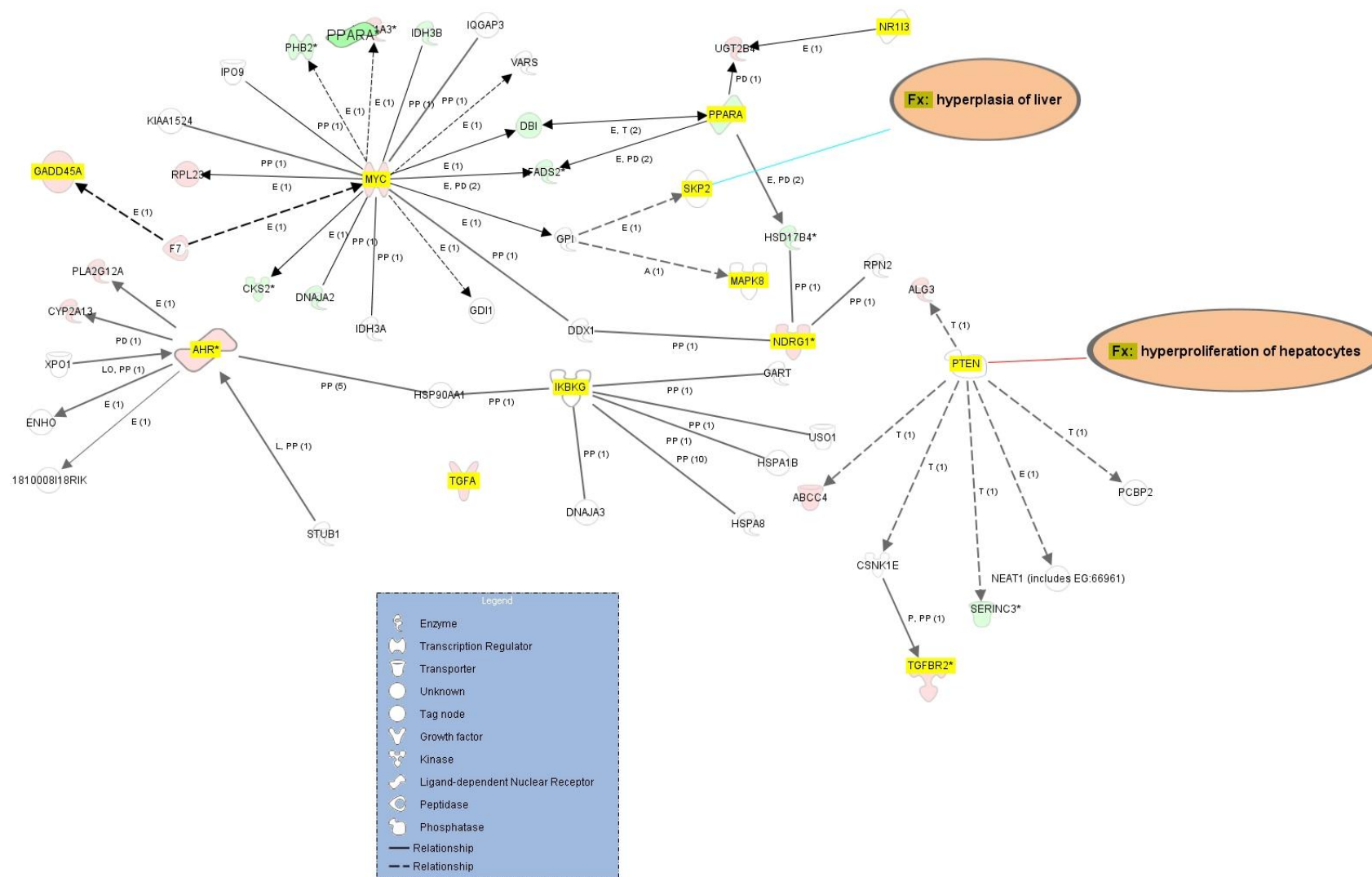
A5.2.2:

Toxicity Function (Human Data): Liver Proliferation



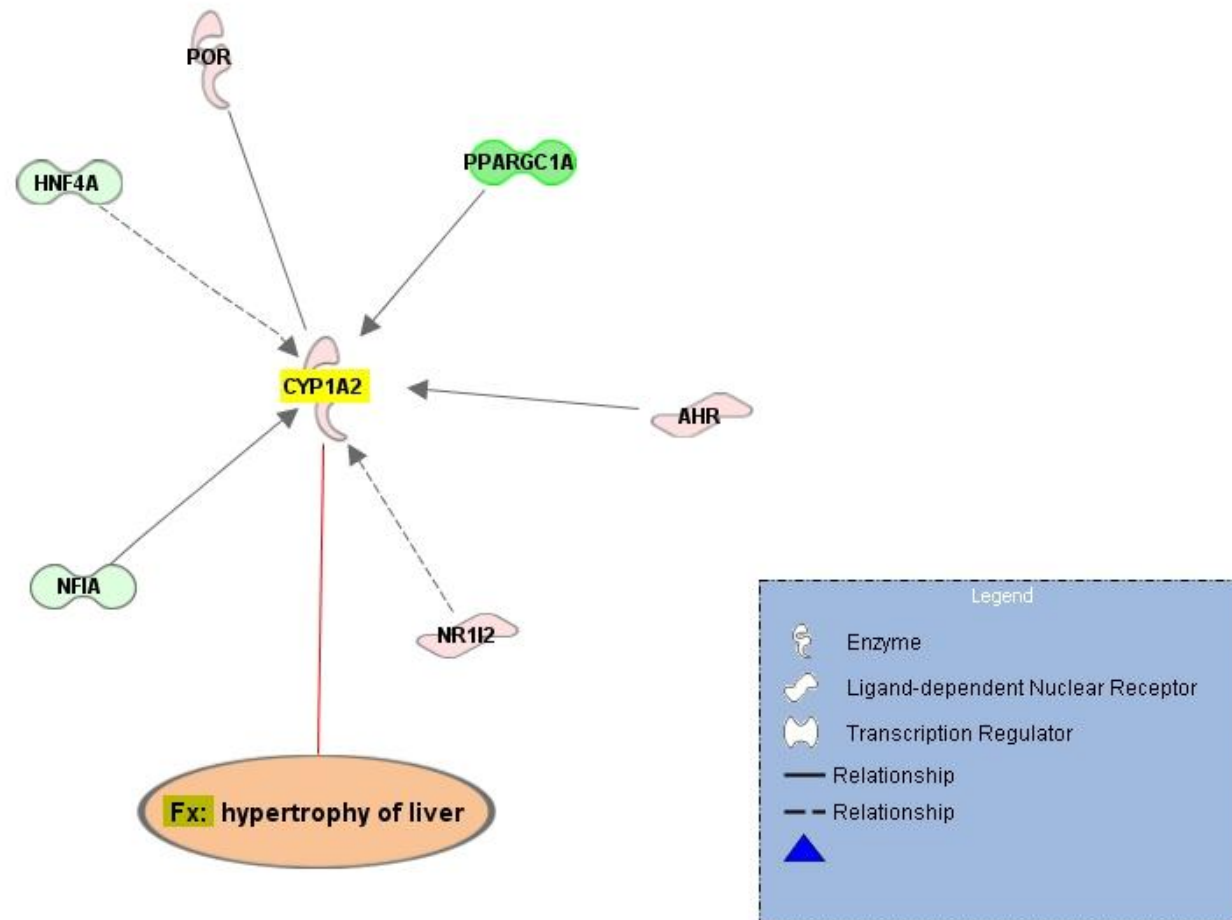
A5.2.3:

Toxicity Function (Mouse Data): Liver Hyperplasia/ Hyperproliferation



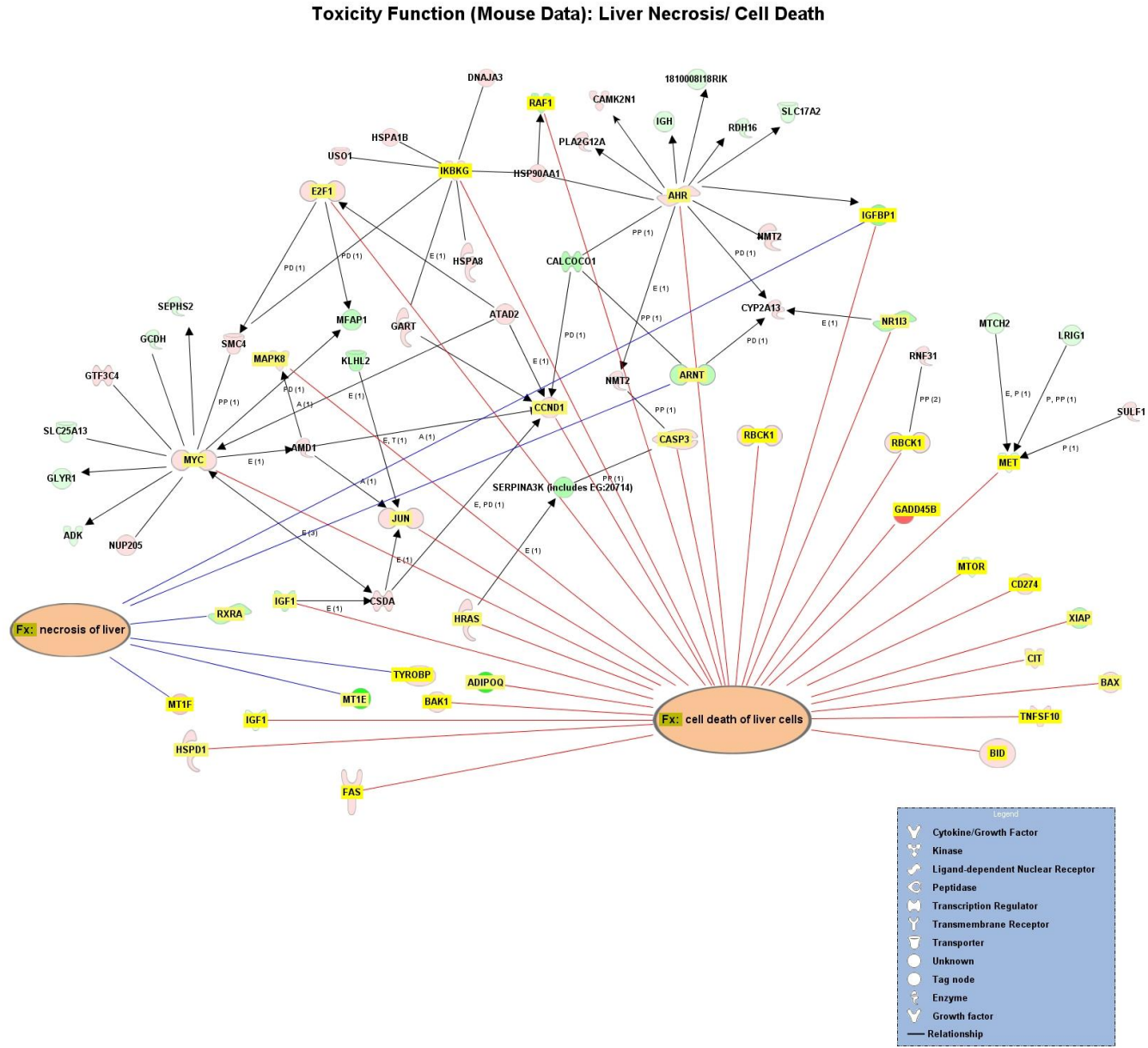
A5.2.4:

Toxicity Function (Mouse Data): Liver Hypertrophy



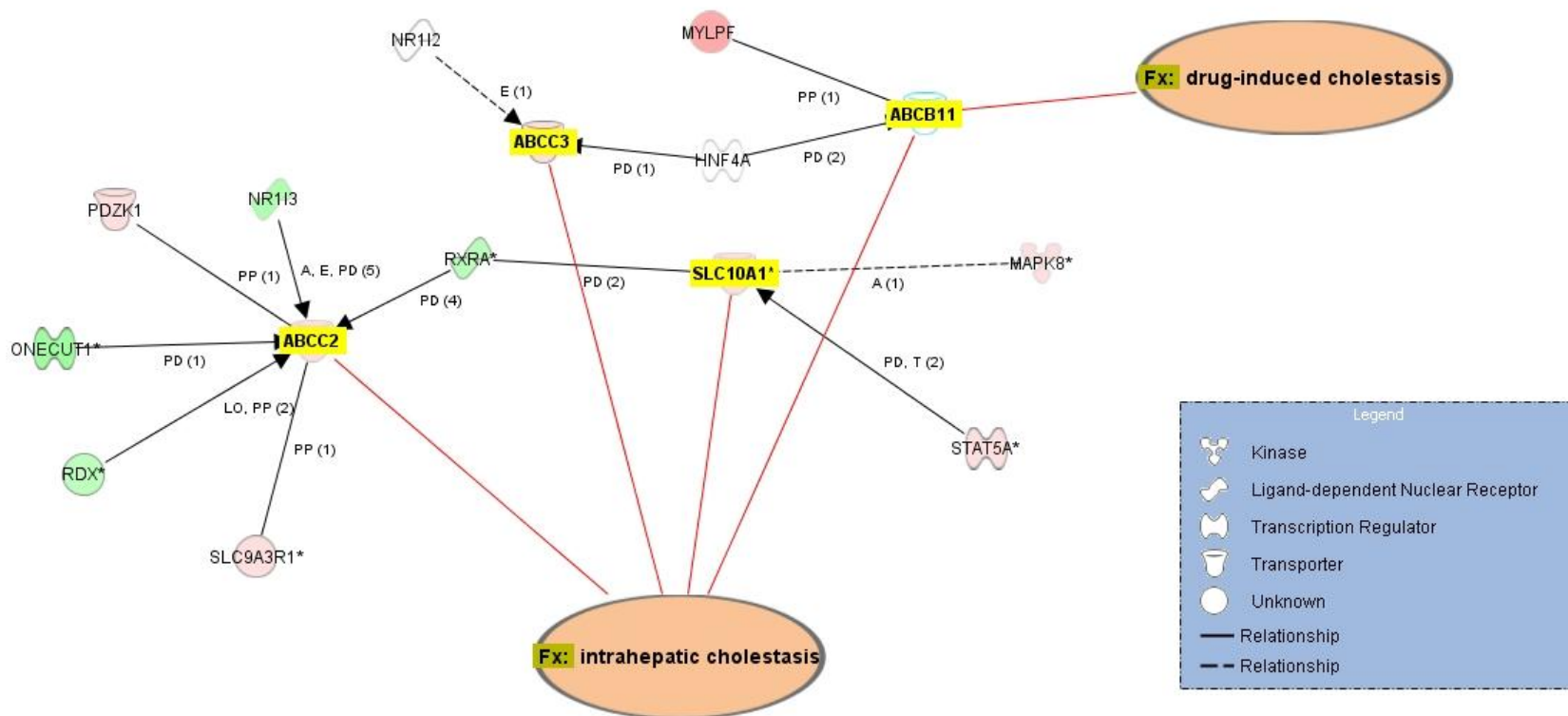
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A5.2.5:



A5.2.6:

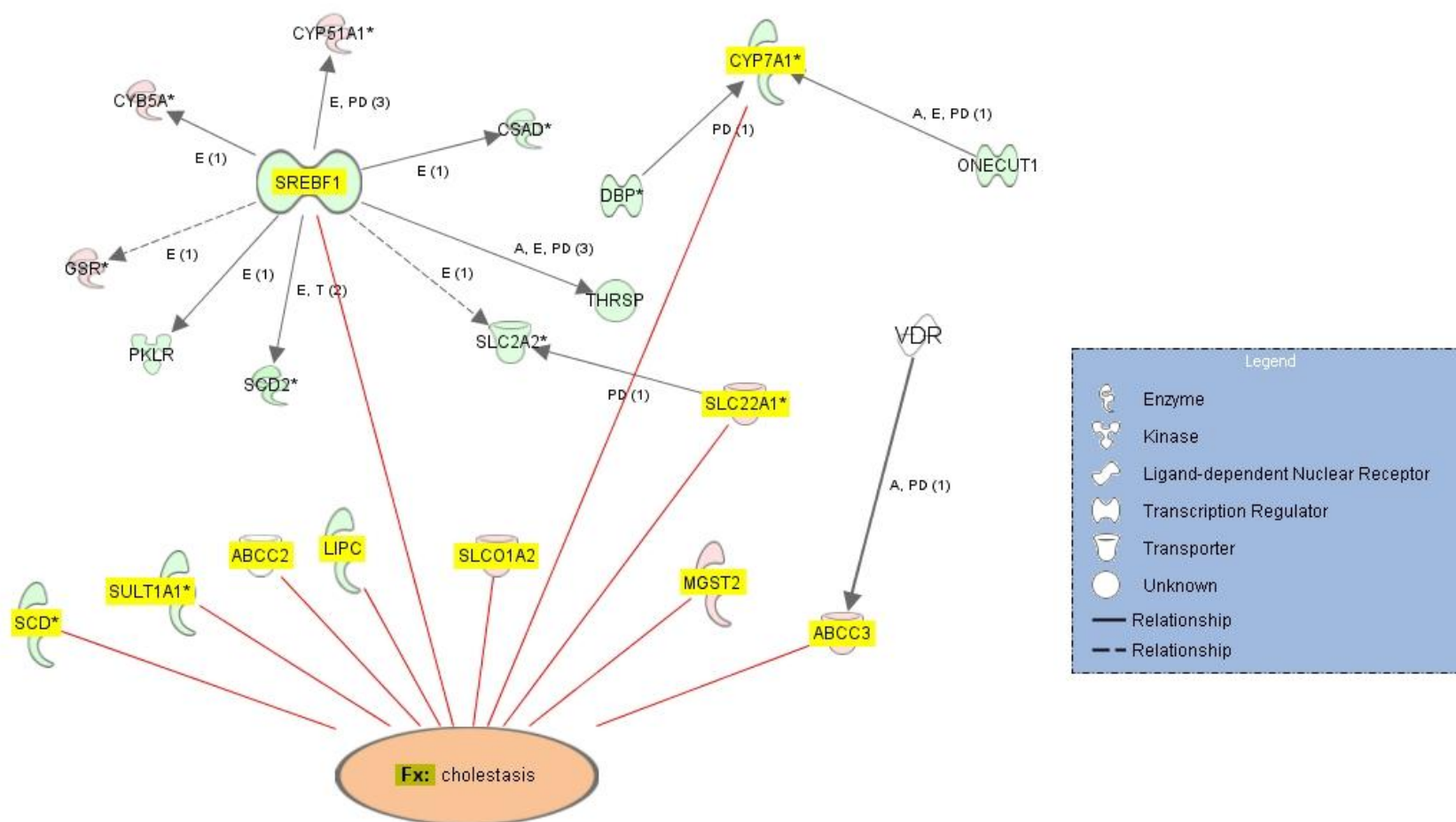
Toxicity Function (Mouse Data): Liver Cholestasis



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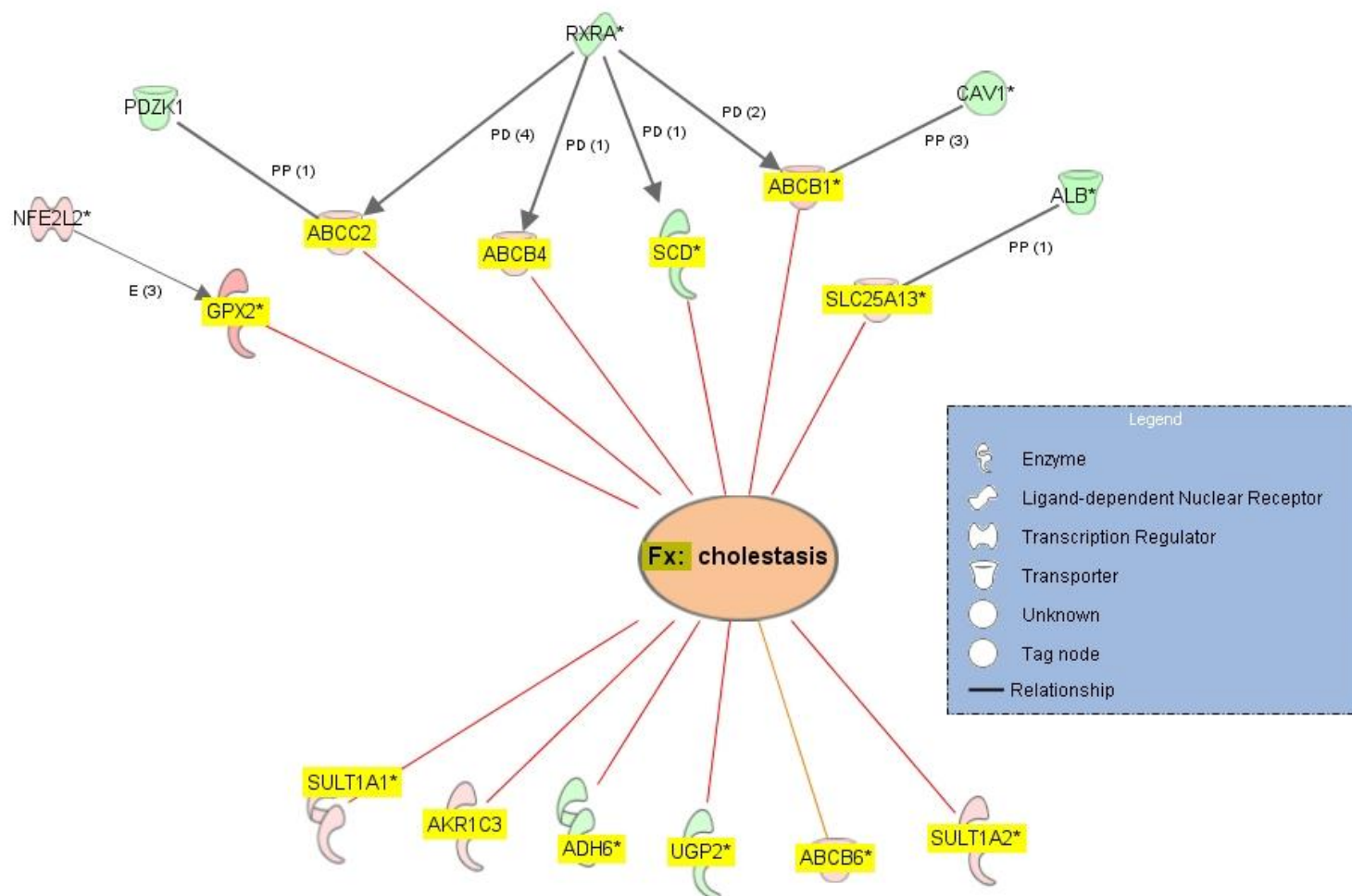
A5.2.7:

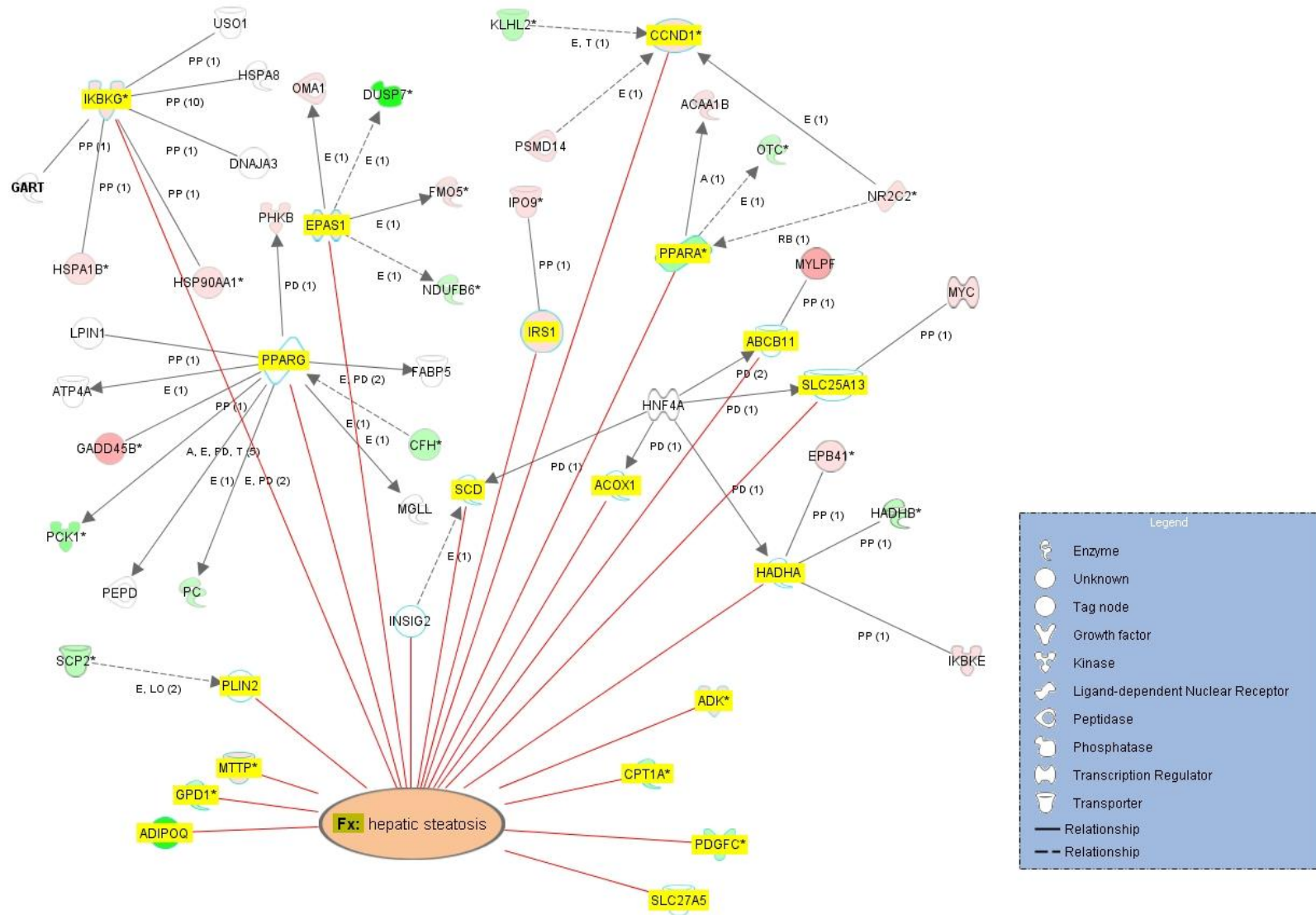
Toxicity Function For Rat Data: Liver Cholestasis



A5.2.8:

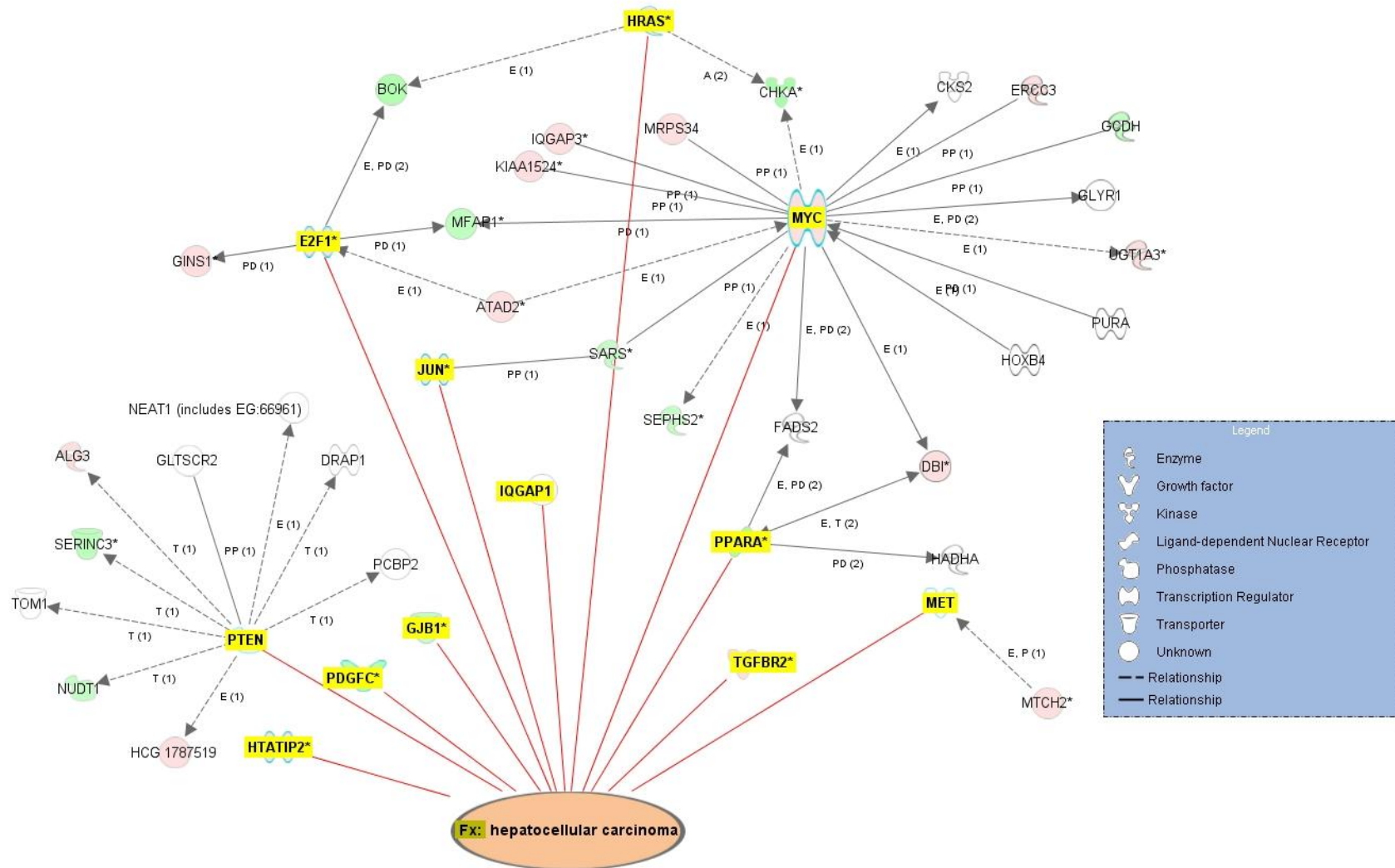
Toxicity Function (Human Data): Liver Cholestasis





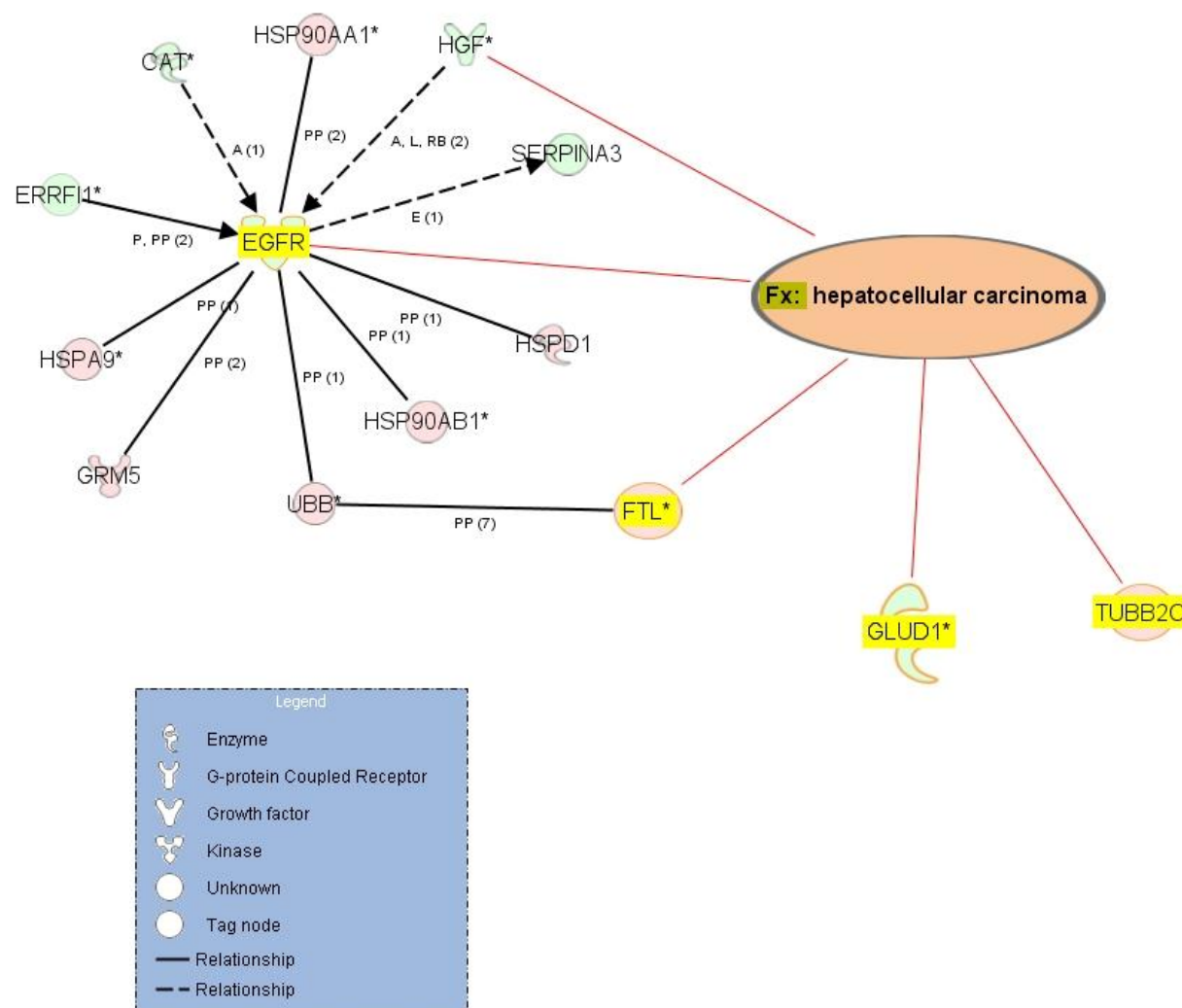
A5.2.10:

Toxicity Function (Mouse Data): Hepatocellular Carcinoma



A5.2.11:

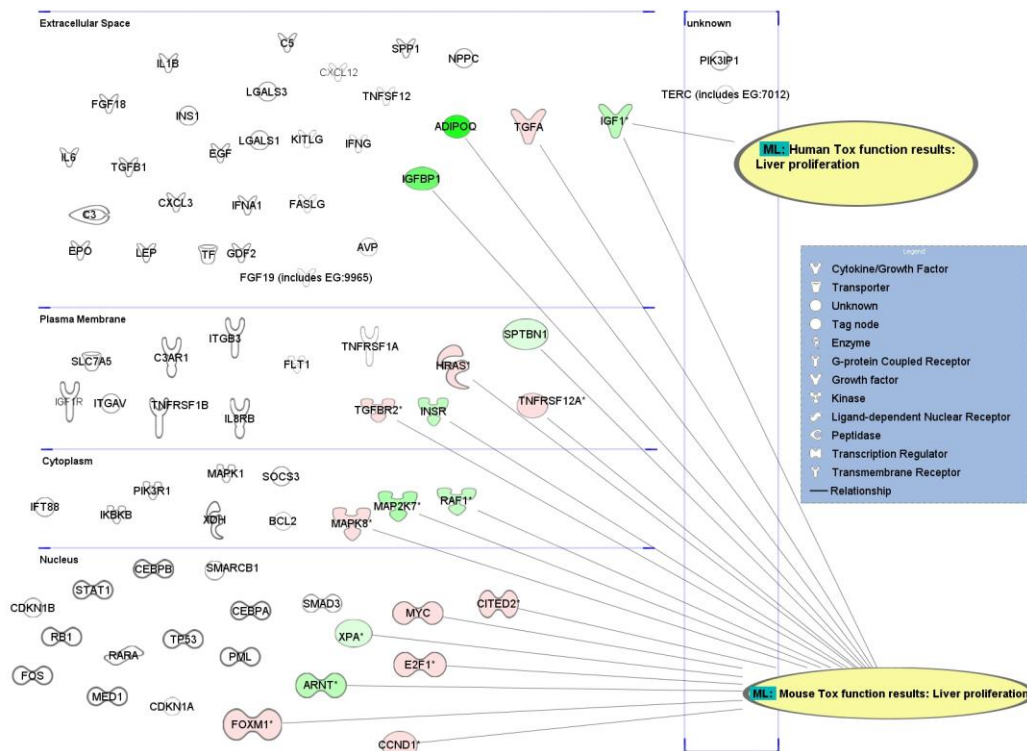
Toxicity Function (Rat Data): Hepatocellular Carcinoma



A5.3: Comparison of selected Tox Function genes with genes from IPA Knowledgebase Known to be associated with Key Events for Hepatocarcinogenesis.

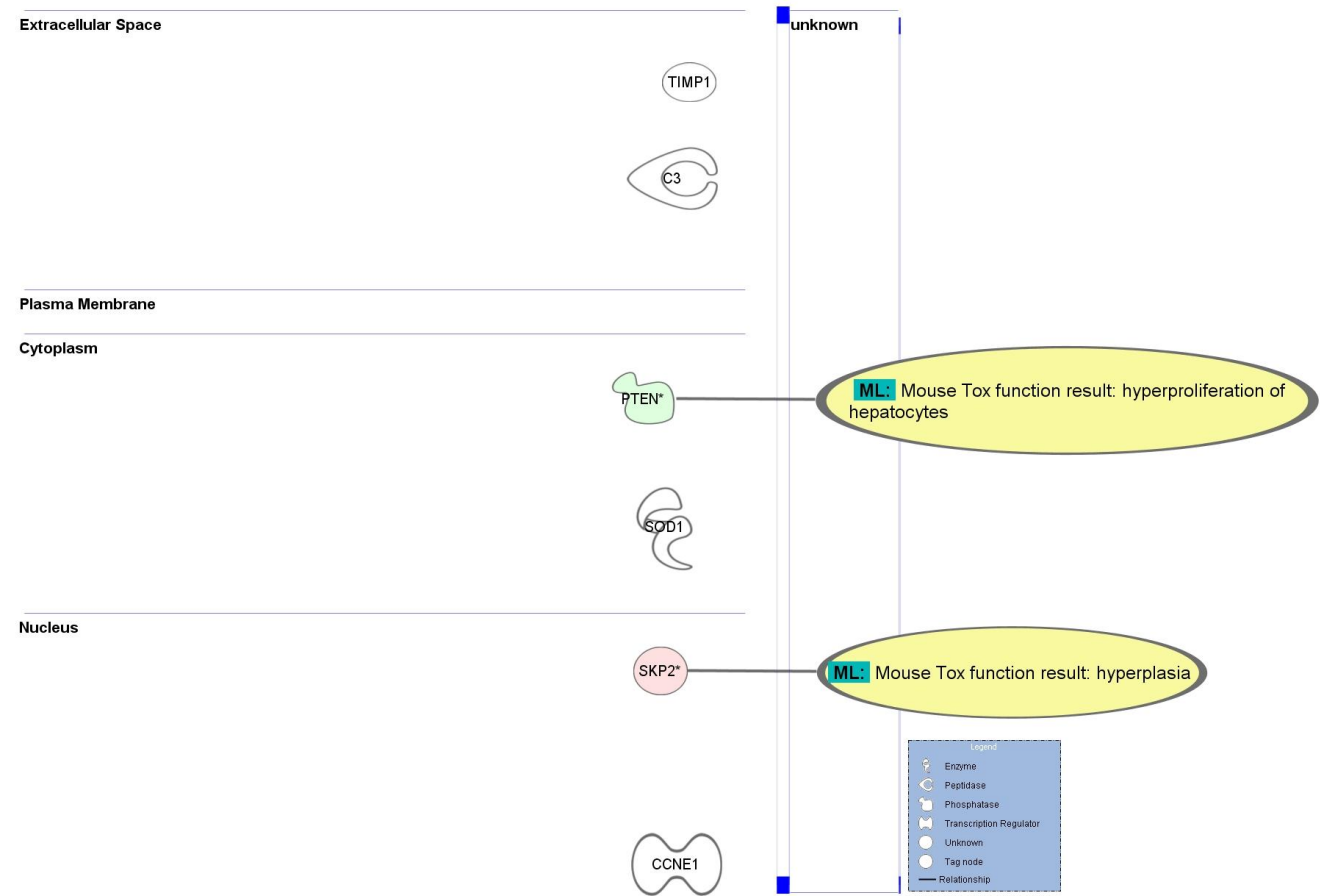
A5.3.1:

Genes from IPA Knowledge Base associated with Liver Proliferation



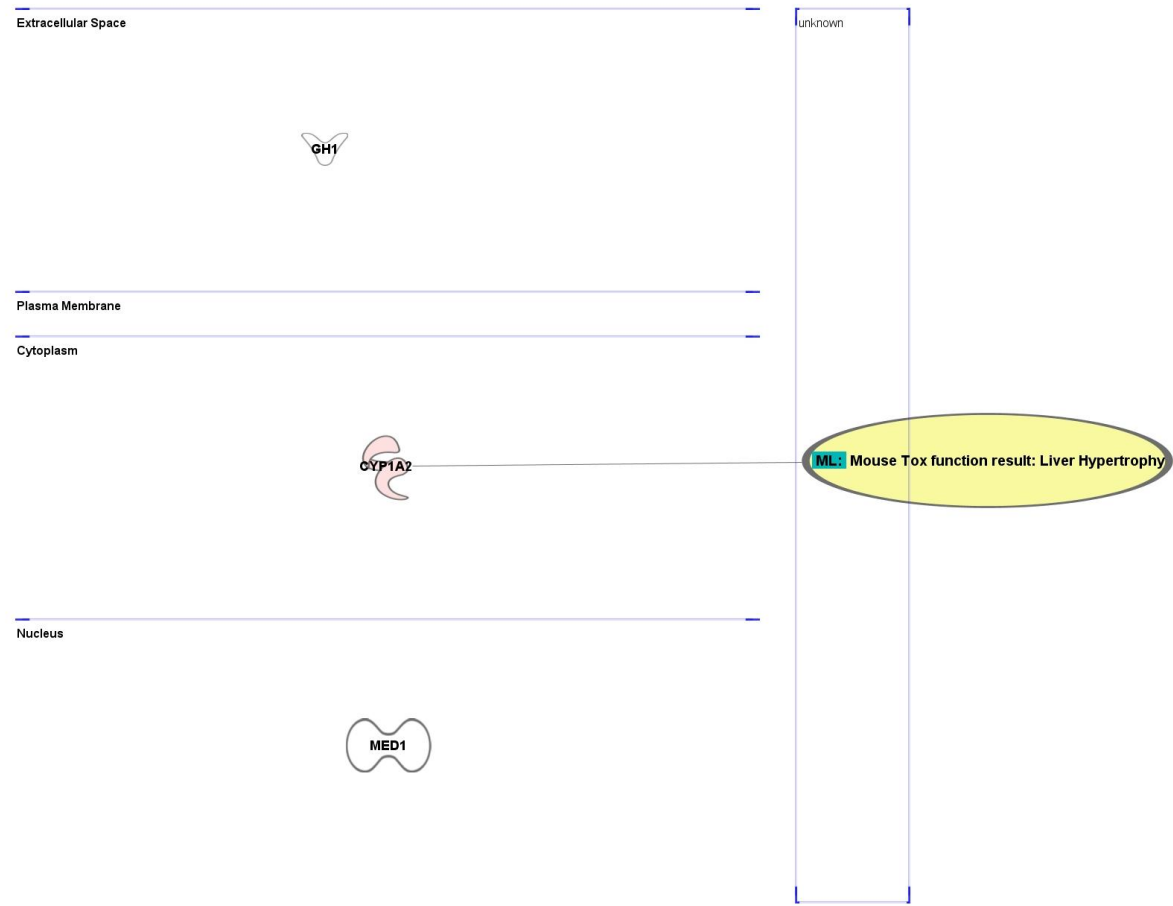
A5.3.2:

Genes from IPA Knowledge Base Associated with Liver Hyperplasia/ Hyperproliferation



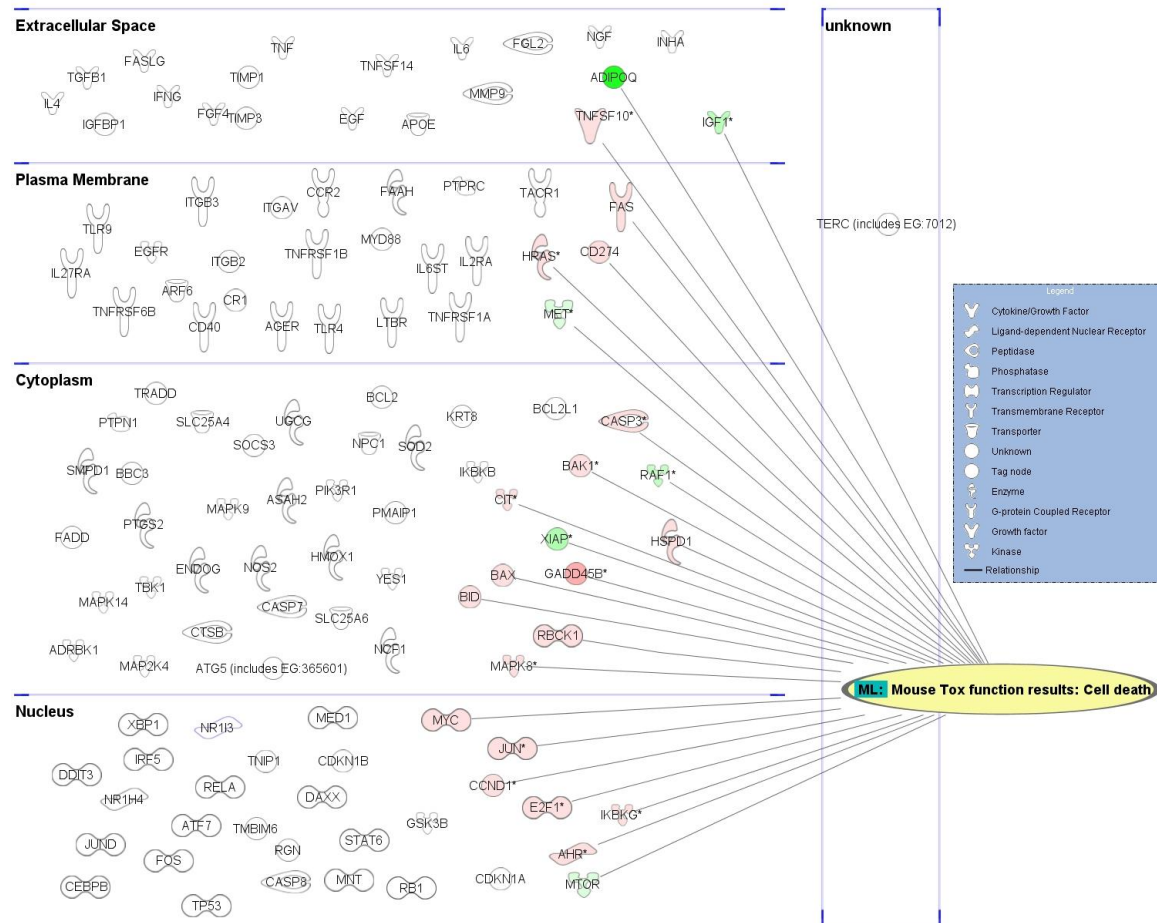
A5.3.3:

Genes from IPA Knowledge Base Associated with Liver Hypertrophy



A5.3.4:

Genes from IPA Knowledge Base Associated with Cell Death



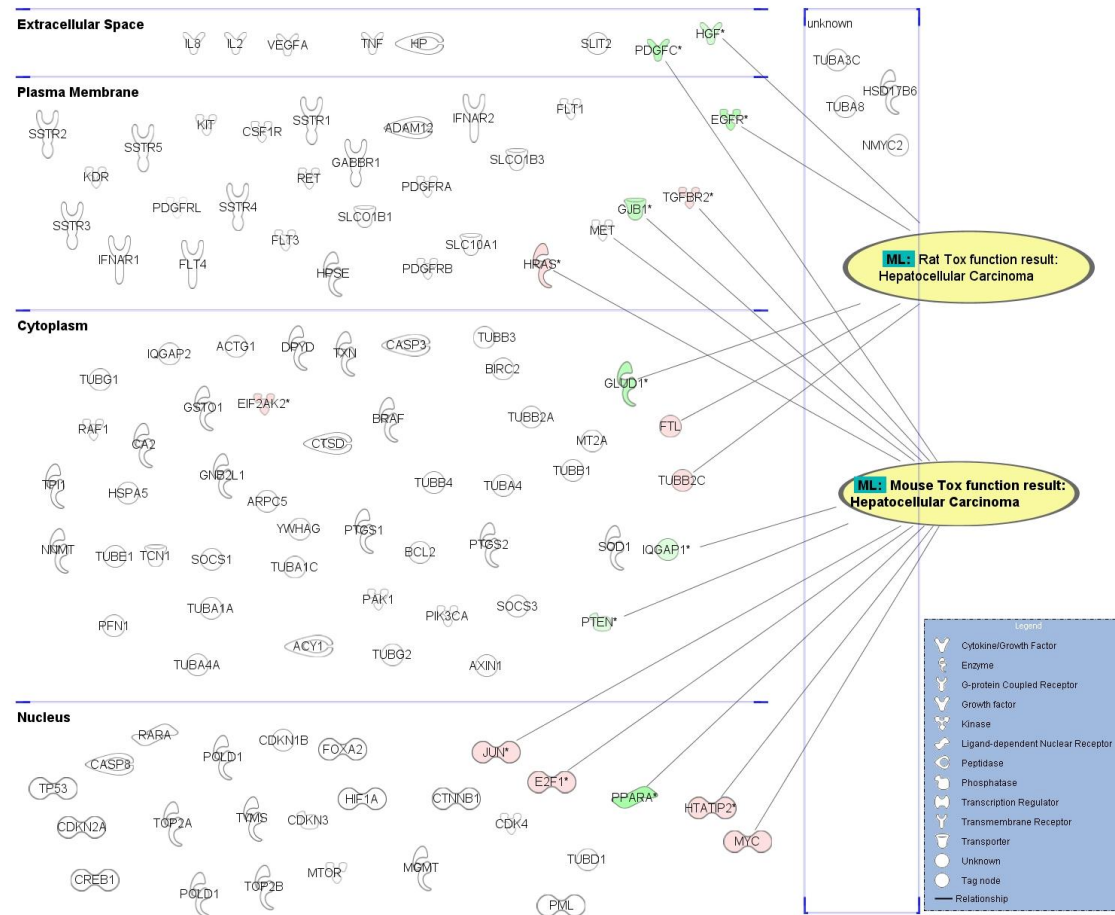
A4.3.5:

Genes from IPA Knowledge Base Associated with Liver Cholestasis



A5.3.6:

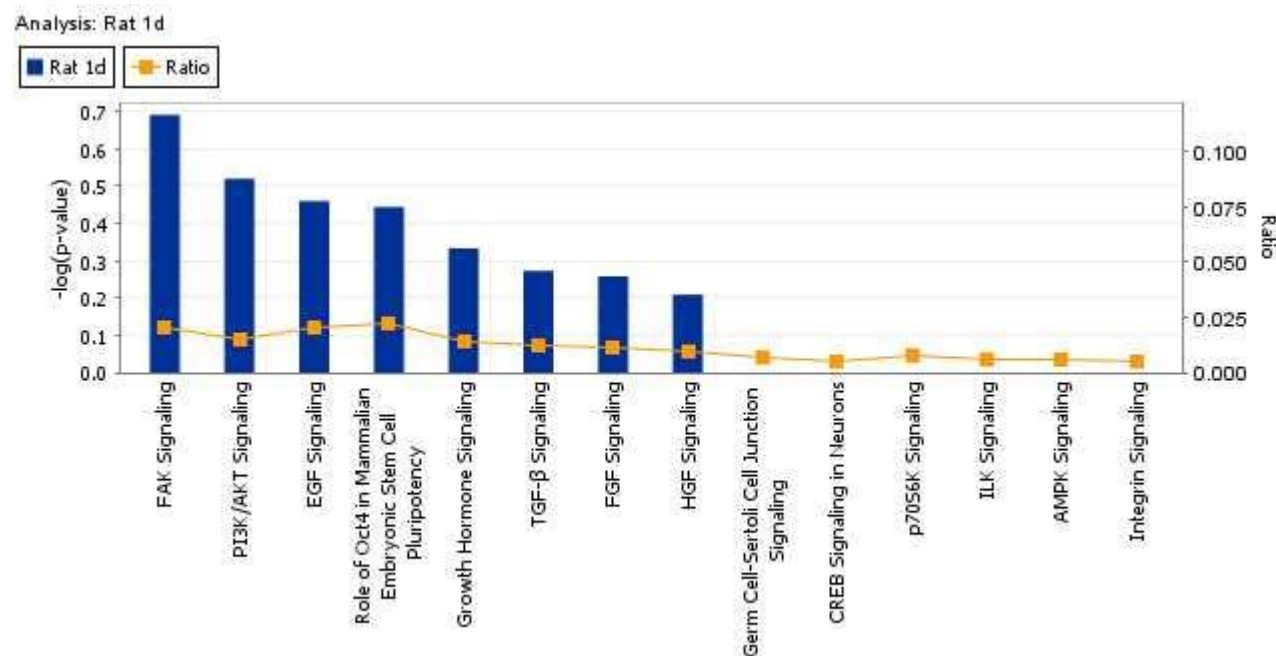
Genes from IPA Knowledge Base Associated with Hepatocellular Carcinoma



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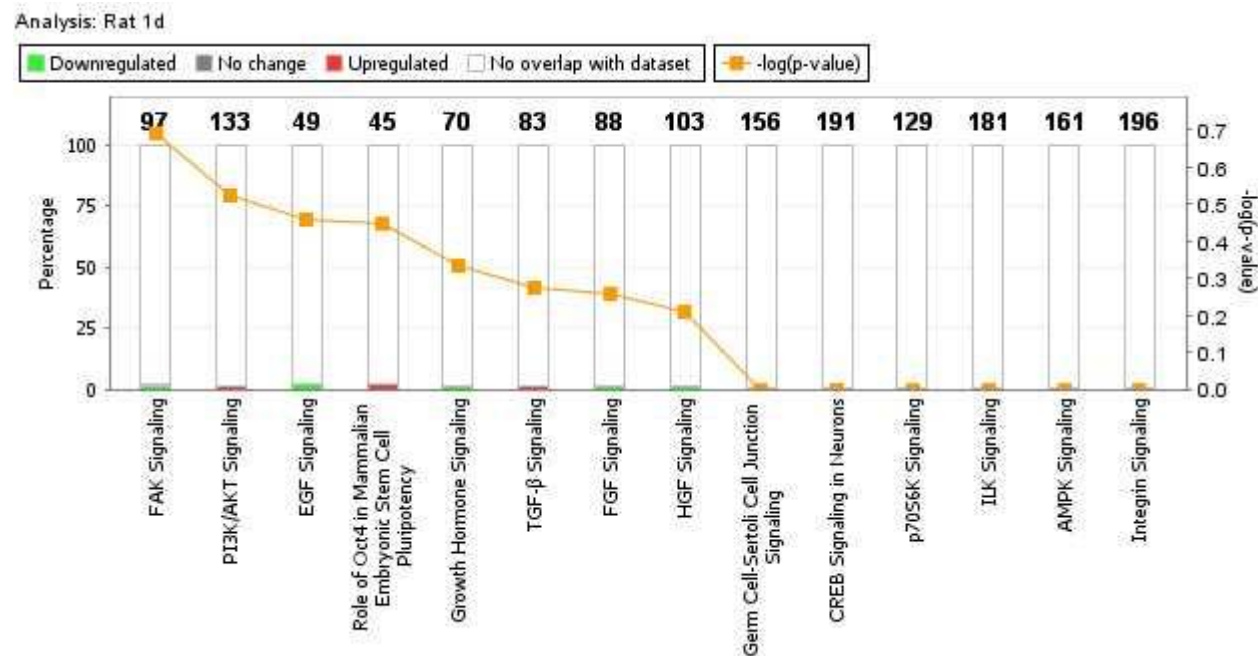
A5.4: MOA Related Signalling Pathways for Cellular Growth, Proliferation and Development, Apoptosis, Cellular Stress and Injury. The Graphs below Illustrate the Results obtained for the Datasets from the Rat Day 1, Mouse 2days and Human Day 3.

A5.4.1: Signalling pathway: Cellular growth, proliferation and development (represented as a bar chart)-Rat Day 1



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A5.4.2: Signalling pathway: Cellular growth, proliferation and development (represented as a stacked bar chart)- Rat Day 1

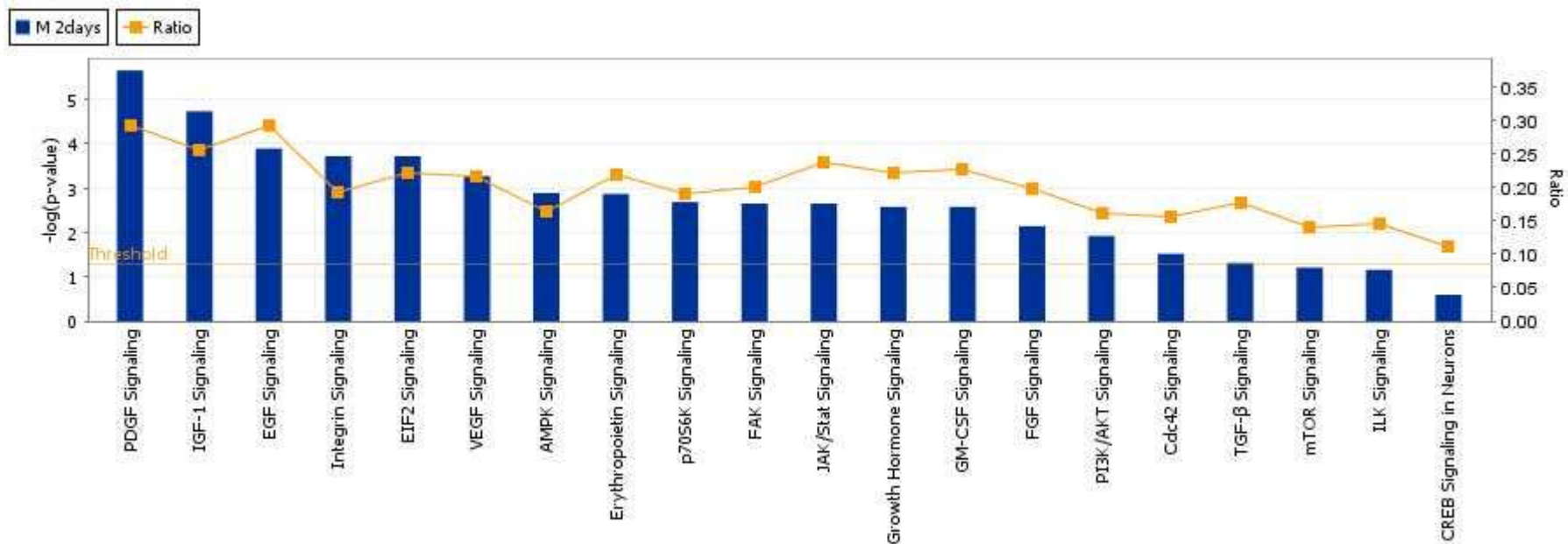


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N.B: The pathways represented by stacked bar charts show the number of up-regulated (red), down regulated (green), and unchanged molecules (grey) in each Canonical Pathway. The selected canonical pathways involved in the analysis are shown on the x-axis. The y-axis on the left shows the percentage of genes within the dataset that are involved in the relevant pathway, while the right y-axis shows the level of significance (P-value = 0.05). The total number of genes that make up the individual IPA pathway is displayed above each bar chart.

A5.4.3: Signalling pathway: Cellular growth, proliferation and development (represented as a bar chart)- Mouse Day 2

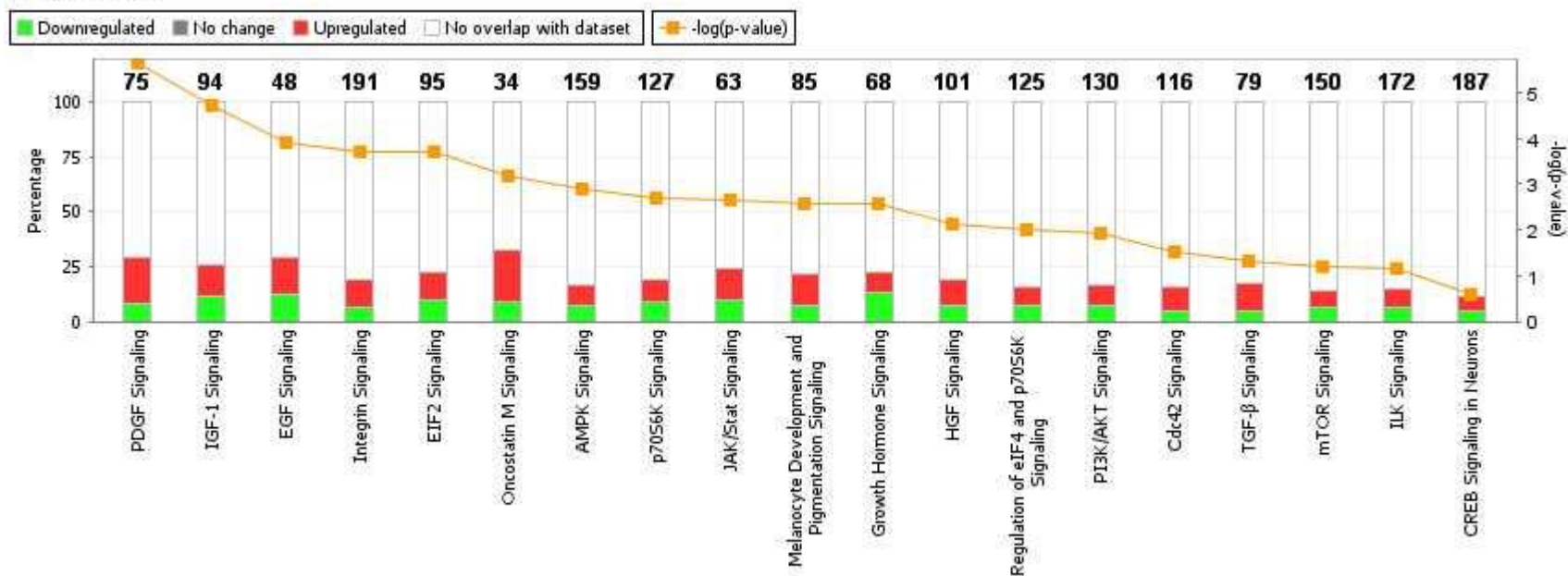
Analysis: M 2days



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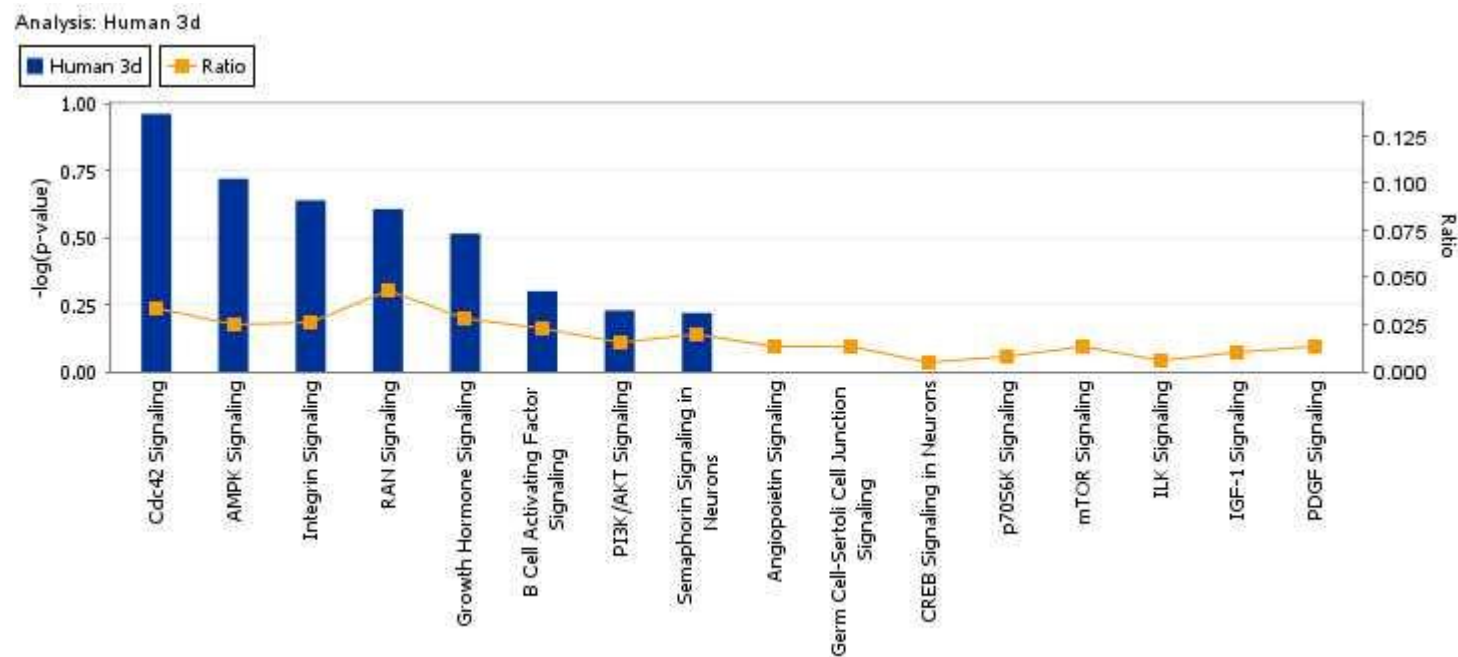
A5.4.4: Signalling pathway: Cellular growth, proliferation and development (represented as a stacked bar chart)- Mouse Day 2

Analysis: M 2 days



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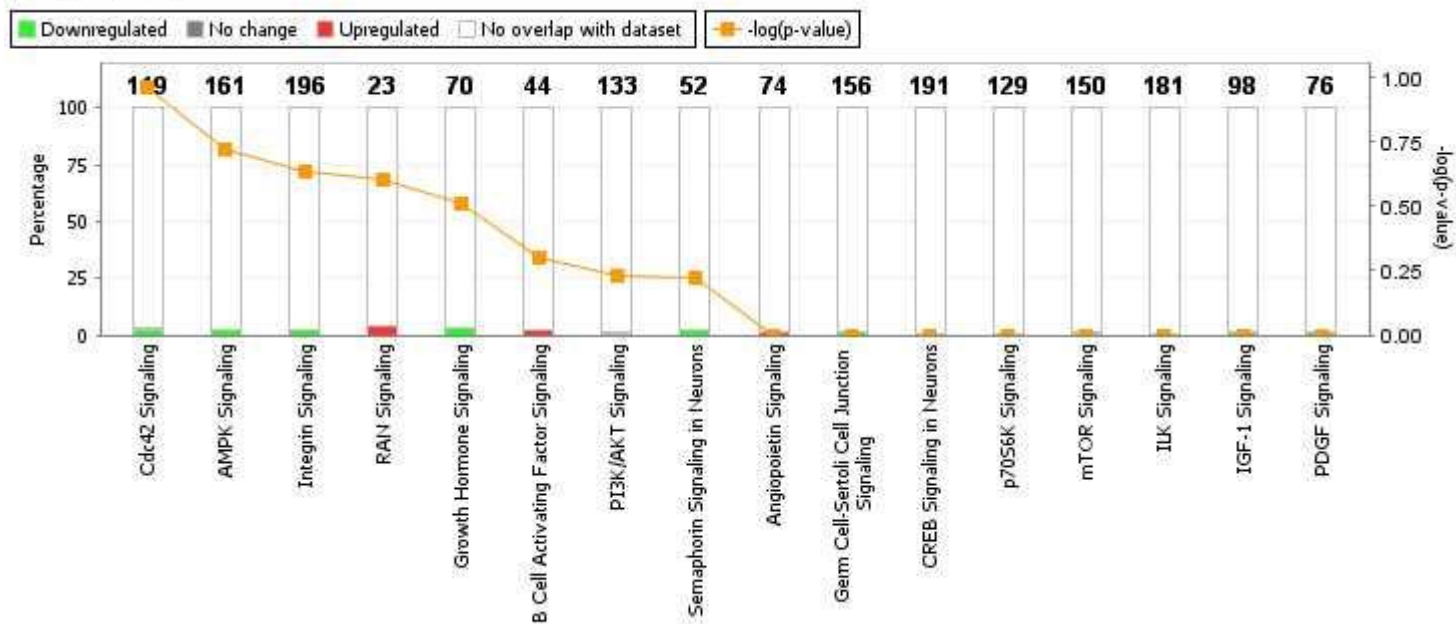
A5.4.5: Signalling pathway: Cellular growth, proliferation and development (represented as a bar chart)- Human Day 3



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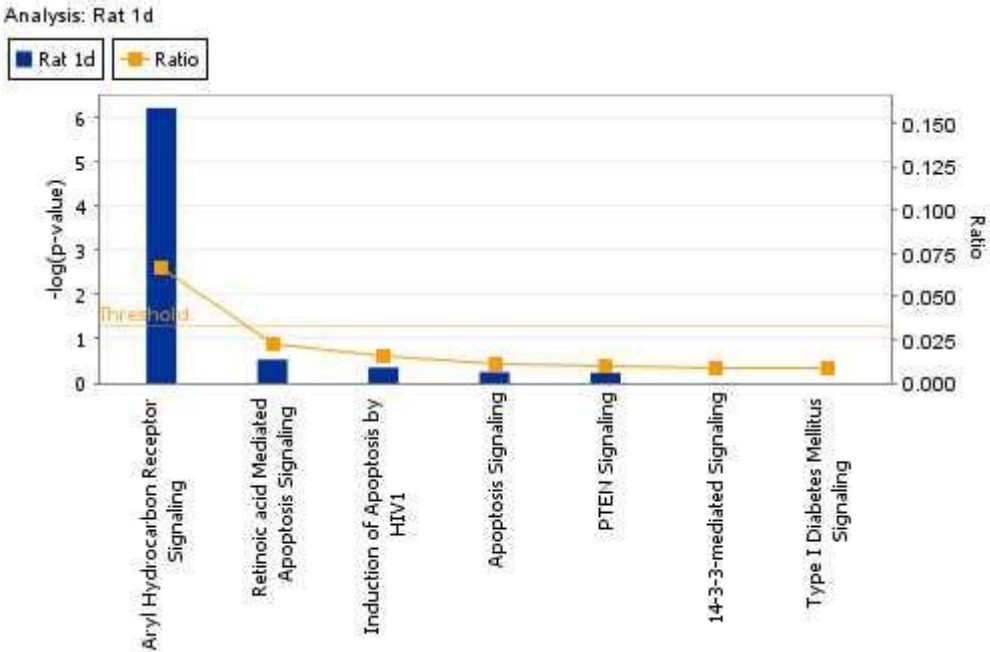
A5.4.6: Signalling pathway: Cellular growth, proliferation and development (represented as a stacked bar chart)- Human Day 3

Analysis: Human 3d



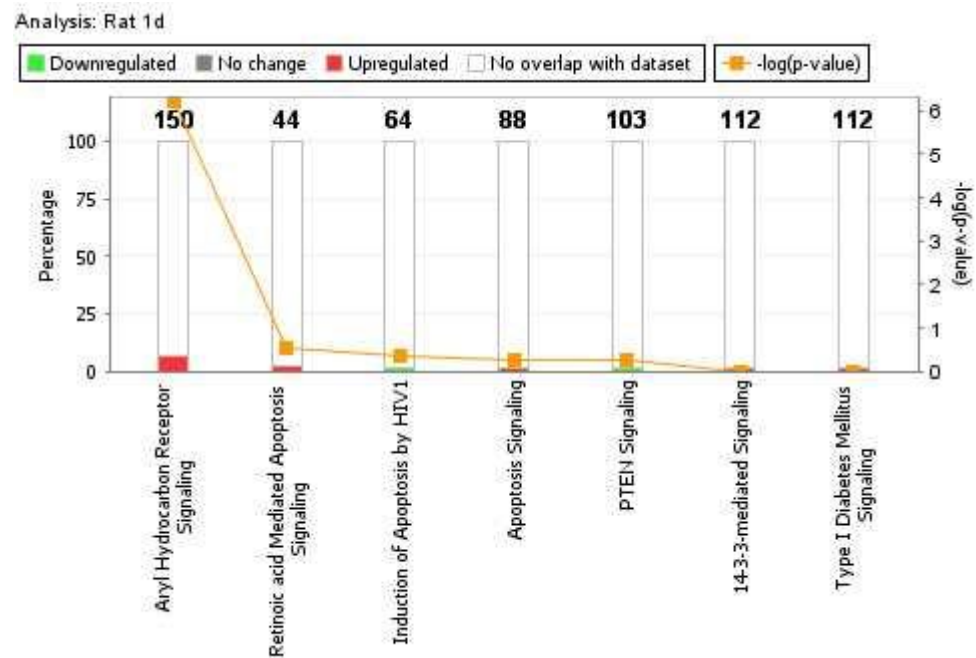
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A5.4.7: Signalling pathway: Apoptosis (represented as a bar chart) - Rat Day 1



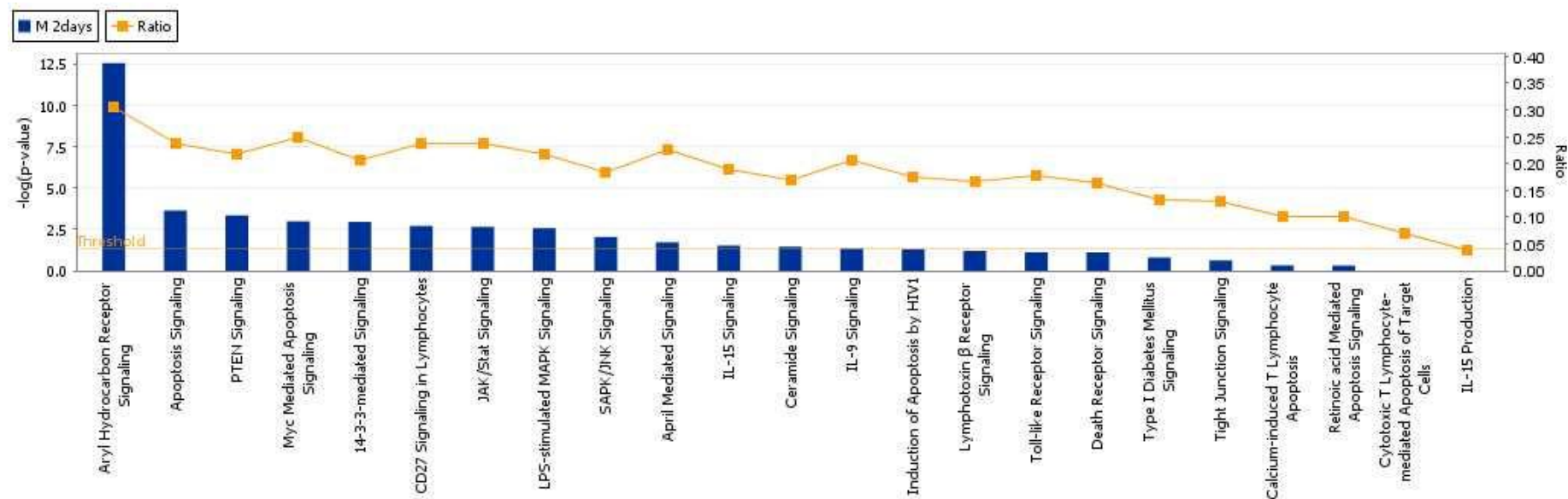
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A5.4.8: Signalling pathway: Apoptosis (represented as a stacked bar chart) - Rat Day 1



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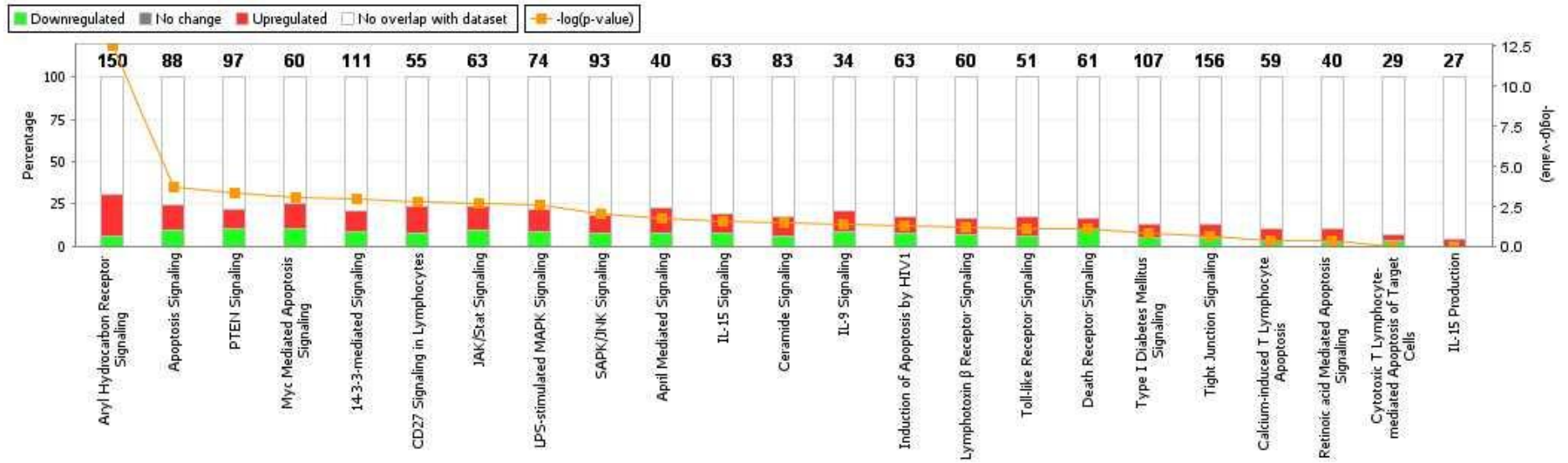
A5.4.9: Signalling pathway: Apoptosis (represented as a bar chart) - Mouse Day 2



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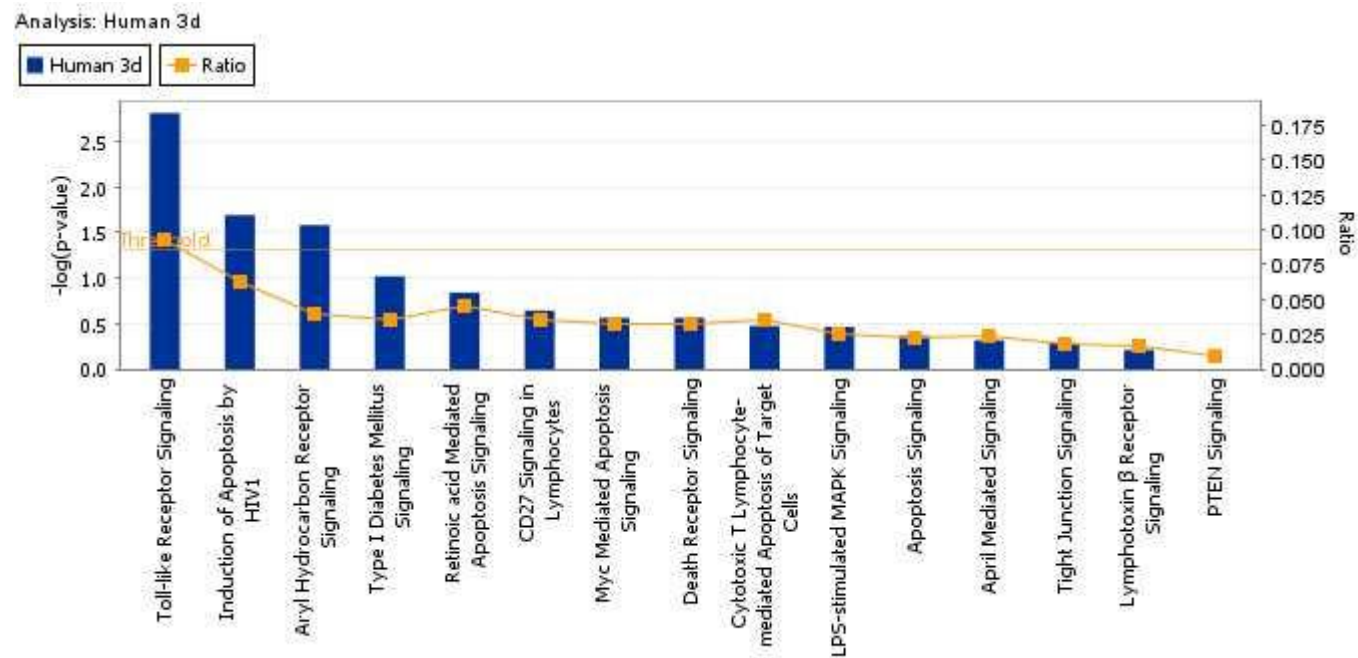
A5.4.10: Signalling pathway: Apoptosis (represented as a stacked bar chart) - Mouse Day 2

Analysis: M 2days



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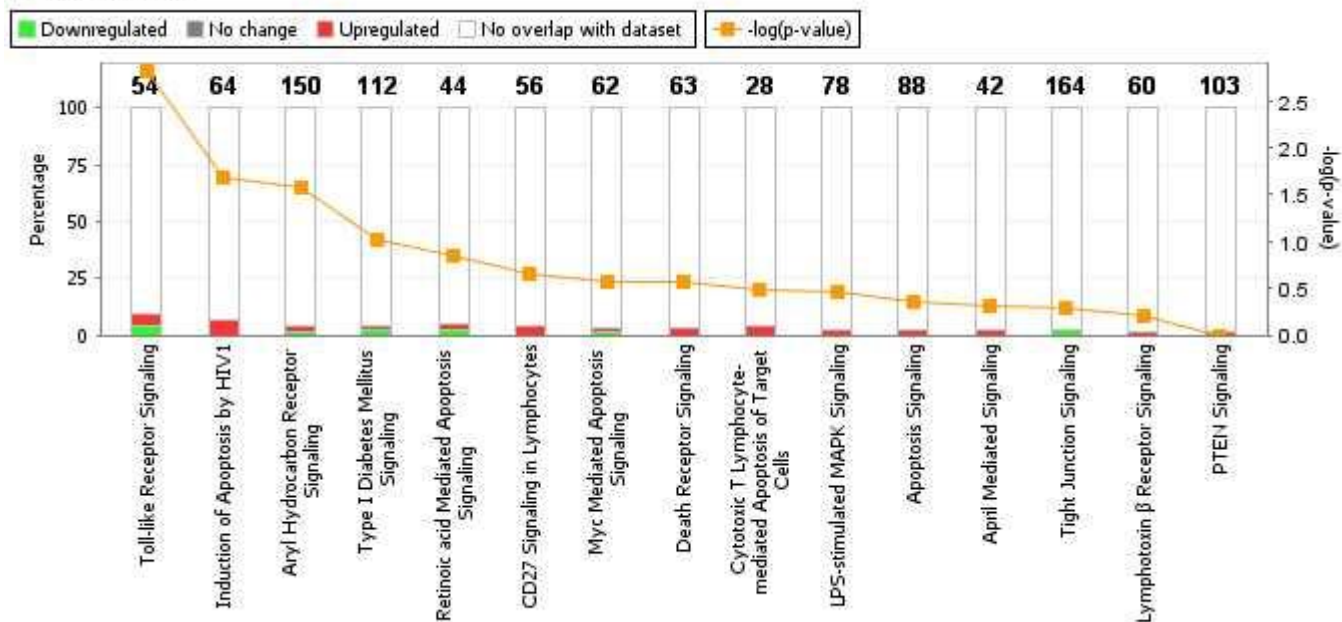
A5.4.11: Signalling pathway: Apoptosis (represented as a bar chart) - Human Day 3



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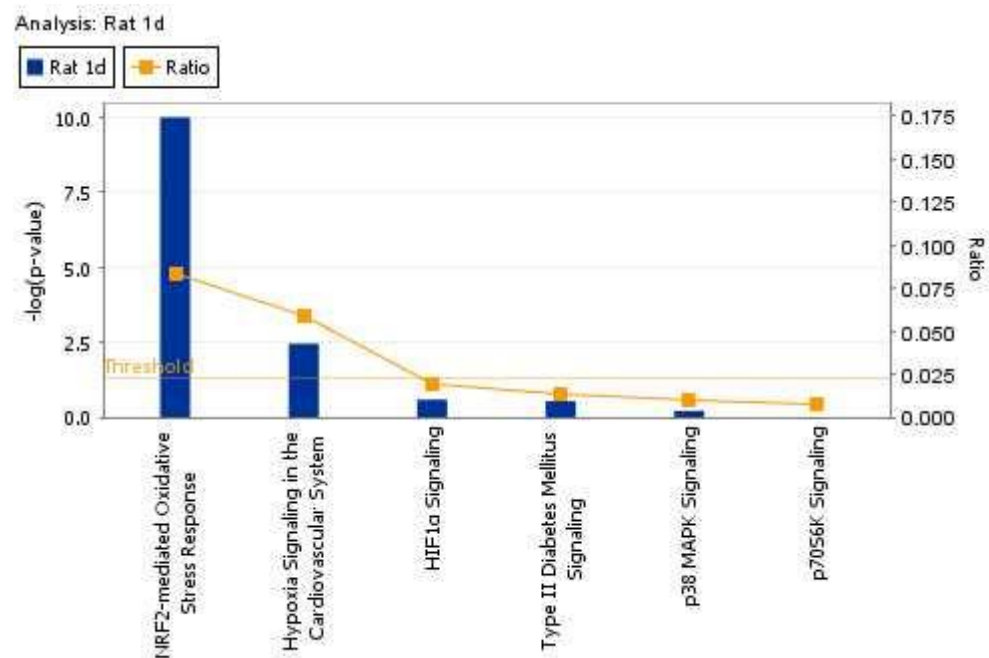
A5.4.12: Signalling pathway: Apoptosis (represented as a stacked bar chart)- Human Day 3

Analysis: Human 3d



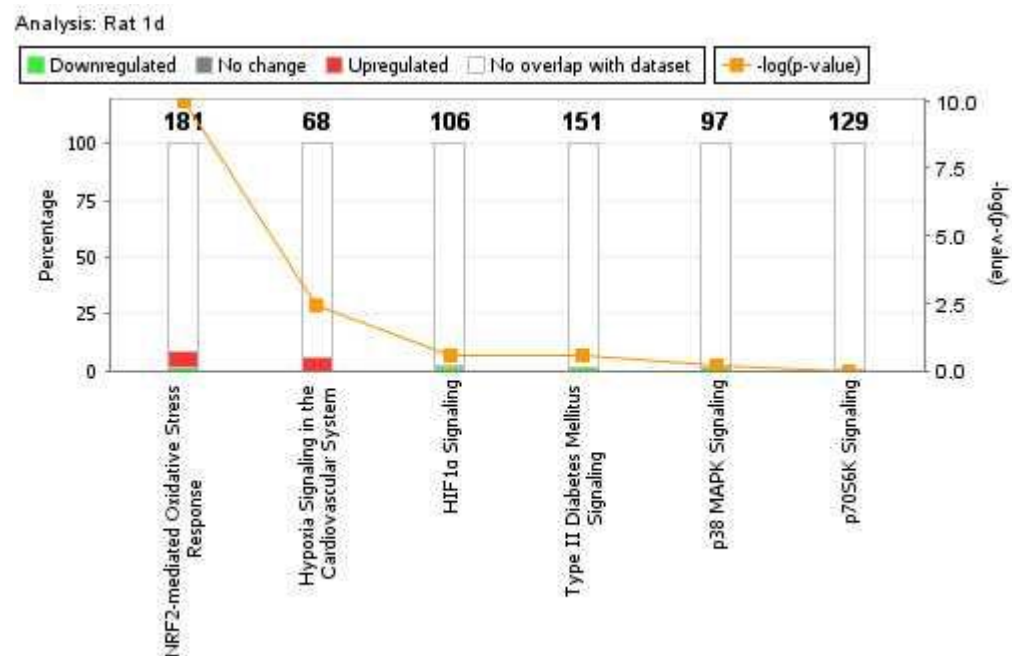
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A5.4.13: Signalling pathway: Cellular Stress and Injury (represented as a bar chart)- Rat Day 1



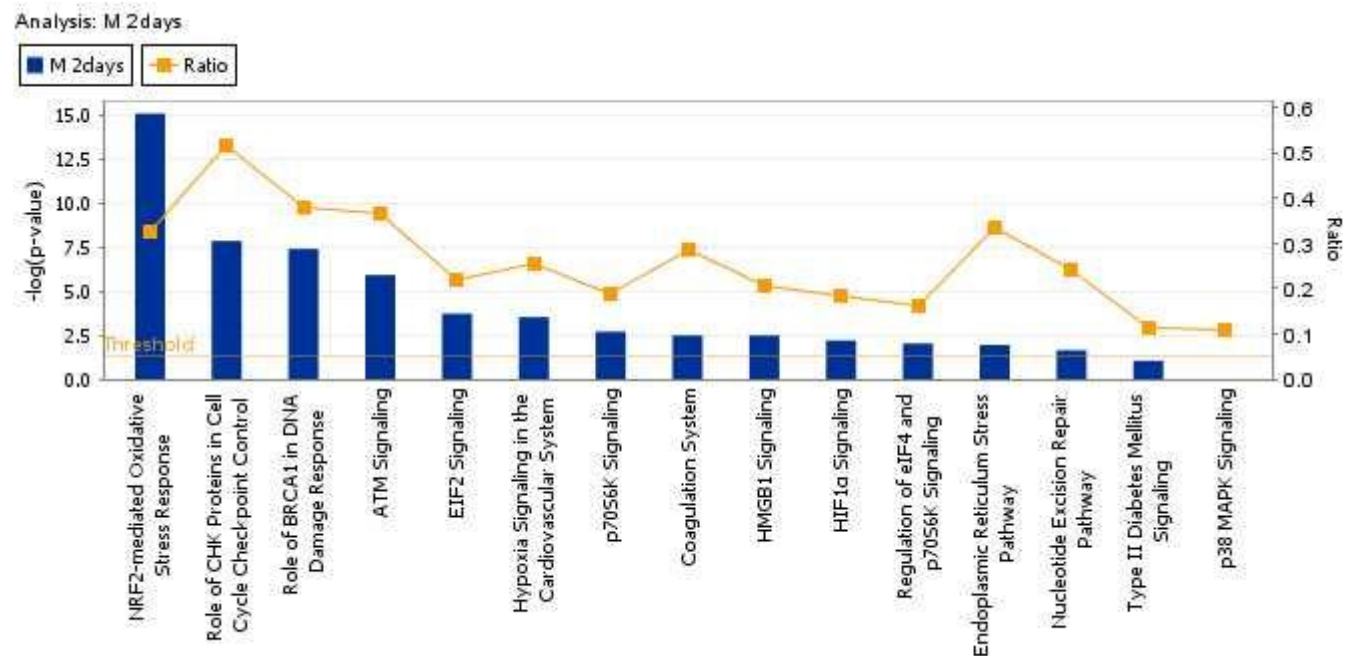
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A5.4.14: Signalling pathway: Cellular Stress and Injury (represented as a stacked bar chart)- Rat Day 1



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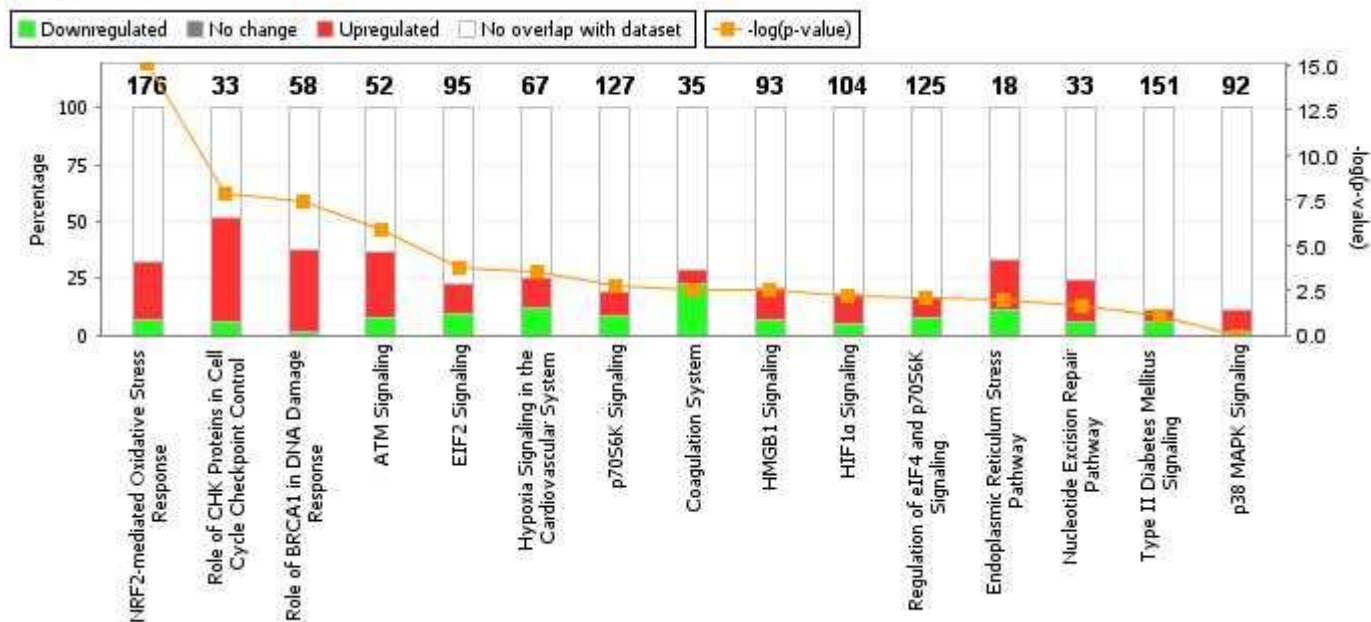
A5.4.15: Signalling pathway: Cellular Stress and Injury (represented as a bar chart)- Mouse Day 2



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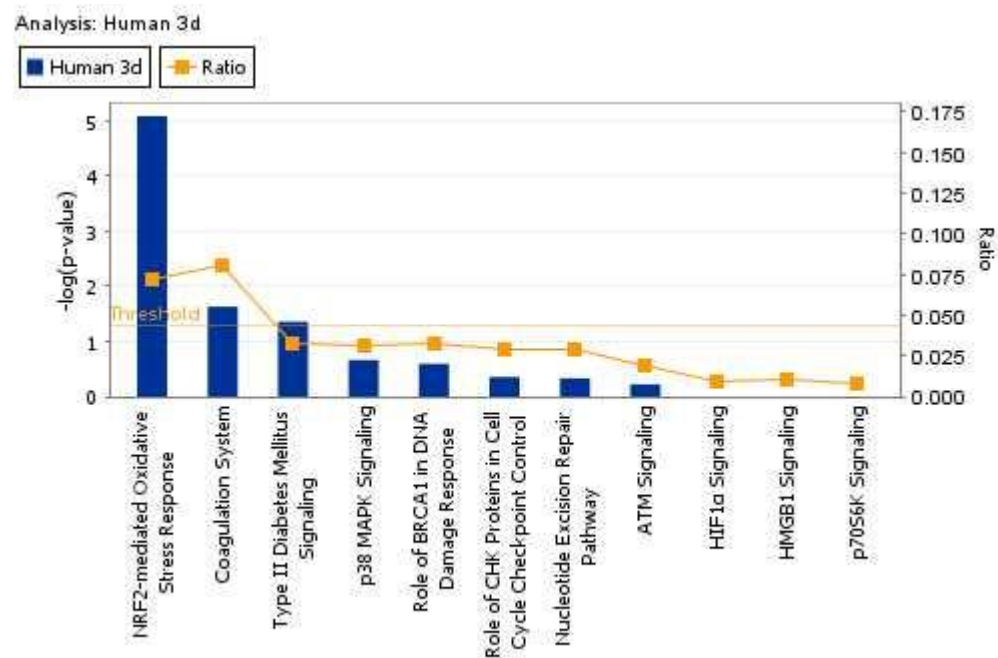
A5.4.16: Signalling pathway: Cellular Stress and Injury (represented as a stacked bar chart)- Mouse Day 2

Analysis: M 2 days



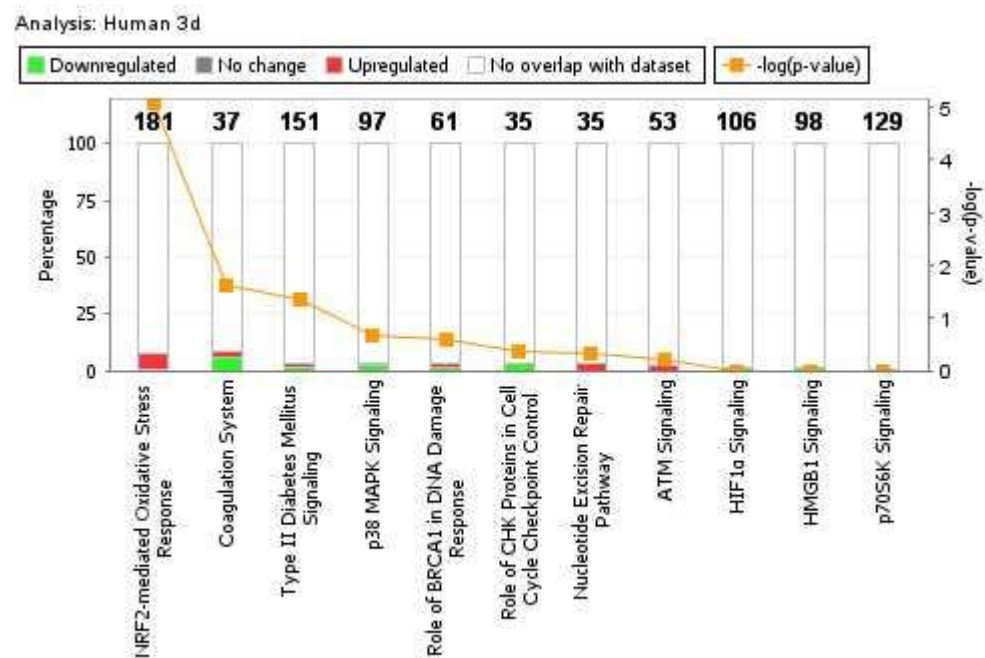
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A5.4.17: Signalling pathway: Cellular Stress and Injury (represented as a bar chart)- Human Day 3



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A5.4.18: Signalling pathway: Cellular Stress and Injury (represented as a stacked bar chart)- Human Day 3



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A5.5:

Genes Found to Be Common across the Different Mouse Datasets Investigated
(Mouse datasets: 10hrs, Days 2, 4 and 30).

Symbol	Entrez Gene Name	Type(s)
ABCC3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	transporter
AHR	aryl hydrocarbon receptor	ligand-dependent nuclear receptor
ALDH1A1	aldehyde dehydrogenase 1 family, member A1	enzyme
ALDH1A7	aldehyde dehydrogenase family 1, subfamily A7	enzyme
ARHGEF5	Rho guanine nucleotide exchange factor (GEF) 5	other
CCL9	chemokine (C-C motif) ligand 9	cytokine
CEACAM1	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)	transmembrane receptor
CES6	carboxylesterase 6	enzyme
CYB5A	cytochrome b5 type A (microsomal)	enzyme
CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	enzyme
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6	enzyme
CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18	enzyme
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19	enzyme
Symbol	Entrez Gene Name	Type(s)
CYP2C29	cytochrome P450, family 2, subfamily c, polypeptide 29	enzyme
DDX5	DEAD (Asp-Glu-Ala-Asp) box polypeptide 5	enzyme
DDX17	DEAD (Asp-Glu-Ala-Asp) box polypeptide 17	enzyme
DSP	desmoplakin	other
ENTPD5	ectonucleoside triphosphate diphosphohydrolase 5	enzyme
GSTM1	glutathione S-transferase mu 1	enzyme
GSTM3 (includes EG:14864)	glutathione S-transferase, mu 3	enzyme
GSTT3	glutathione S-transferase, theta 3	enzyme
HMGN1	high-mobility group nucleosome binding domain 1	transcription regulator
IL1RAP	interleukin 1 receptor accessory protein	transmembrane receptor

KAT2A	K(lysine) acetyltransferase 2A	enzyme
KDELR2	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 2	transporter
NADK (includes EG:65220)	NAD kinase	kinase
NRP1	neuropilin 1	transmembrane receptor
PDXDC1	pyridoxal-dependent decarboxylase domain containing 1	other
PHB2	prohibitin 2	transcription regulator
Symbol	Entrez Gene Name	Type(s)
PLA2G12A	phospholipase A2, group XIA	enzyme
POR	P450 (cytochrome) oxidoreductase	enzyme
RDX	radixin	other
SGPP1	sphingosine-1-phosphate phosphatase 1	phosphatase
SRXN1	sulfiredoxin 1 homolog (S. cerevisiae)	enzyme
UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10	enzyme

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