INGENUITY PATHWAY ANALYSIS

Analysis Name: Amb_vs_Low
Analysis Creation Date: 2022-04-11
Build version: exported
Content version: 70750971 (Release Date: 2021-10-22)

Experiment Metadata

Name	Value

Analysis Settings

Reference set: User Dataset
Relationship to include: Direct and Indirect
Includes Endogenous Chemicals
Optional Analyses: My Pathways My List

Filter Summary:
Consider only molecules and/or relationships where
(species = Uncategorized OR Human OR Rat OR Mouse) AND
(confidence = Experimentally Observed) AND
(tissues/cell lines = Naive B cells OR Hep3B OR Other Macrophages OR Other Immune cell lines OR Th1 cells OR T47-D OR CCRF-CEM OR Other Macrophage Cancer Cell Lines OR KM-12 OR Leukemia Cell Lines not otherwise specified OR Cerebellum OR Cervical cancer cell line not otherwise specified OR Astrocytes OR Trachea OR HL-60 OR Mammary Gland OR Liver OR Microglia OR Bladder OR U937 OR Sciatic

Nerve OR NIH/3T3 cells OR Cartilage Tissue OR Pro-B lymphocytes OR Immune cell lines not otherwise specified OR Dorsal Root Ganglion OR Testis OR LNCaP cells OR BDCA-1+ dendritic cells OR Macrophages not otherwise specified OR Other Peripheral blood leukocytes OR U87MG OR CD4+ T-lymphocytes OR Small Intestine OR Kidney cell lines not otherwise specified OR Cortical neurons OR Crypt OR Prostate Cancer Cell Lines not otherwise specified OR MDA-MB-231 OR HeLa OR Monocyte-derived macrophage OR Epithelial cells not otherwise specified OR Melanoma Cell Lines not otherwise specified OR Adipose OR Myeloma Cell Lines not otherwise specified OR Hippocampus OR HCC-2998 OR Effector memory RA+ cytotoxic T cells OR Immature monocyte-derived dendritic cells OR Other Granulocytes OR ACHN OR Oocytes OR A498 OR Other Pheochromocytoma cell lines OR MDA-MB-361 OR Hepatocytes OR Stem cells not otherwise specified OR Neuroblastoma Cell Lines not otherwise specified OR Other Kidney Cancer Cell Lines OR Langerhans cells OR Natural T-regulatory cells OR Th17 cells OR Calvaria OR THP-1 OR Adrenal Gland OR Kidney OR Hepatoma Cell Lines not otherwise specified OR PC-12 cells OR Other T lymphocytes OR DU-145 OR Adipocytes OR U2OS OR Eosinophils OR Gray Matter OR NK cells not otherwise specified OR M14 OR NCI-H226 OR Memory B cells OR BA/F3 OR SK-MEL-5 OR Hypothalamus OR Other Epithelial cells OR Other Mononuclear leukocytes OR Other B lymphocytes OR NT2/D1 OR Other Prostate Cancer Cell Lines OR HUVEC cells OR Mature monocyte-derived dendritic cells OR Embryonic stem cells OR MEF cells OR Lung OR Cell Line not otherwise specified OR Purkinje cells OR Retina OR 786-0 OR Caudate Nucleus OR Jurkat OR Immune cells not otherwise specified OR 293 cells OR Caco2 cells OR Pre-B lymphocytes OR J774 OR Plasmacytoid dendritic cells OR Vascular smooth muscle cells OR Other Memory T lymphocytes OR Putamen OR Bone marrow-derived macrophages OR Macrophage Cancer Cell Lines not otherwise specified OR RKO OR Cerebral Ventricles OR Breast Cancer Cell Lines not otherwise specified OR Pituitary Gland OR Other CNS Cell Lines OR Other Ovarian Cancer Cell Lines OR Mesenchymal stem cells OR NCI-ADR-RES OR U266 OR HS 578T OR Peripheral blood lymphocytes OR SK-OV-3 OR Cerebral Cortex OR UACC-257 OR MDA-MB-468 OR Other Kidney cell lines OR RAW 264.7 OR HCT-15 OR Endothelial cells not otherwise specified OR Nucleus Accumbens OR MOLT-4 OR Pheochromocytoma cell lines not otherwise specified OR A2780 OR Effector memory cytotoxic T cells OR Other Osteosarcoma Cell Lines OR Other Pancreatic Cancer Cell Lines OR Other Monocytes OR Activated helper T cells OR COLO205 OR Myeloid dendritic cells OR Blood platelets OR Lung Cancer Cell Lines not otherwise specified OR Subventricular Zone OR Thyroid Gland OR SNB-75 OR EKVX OR TK-10 OR Osteoblasts OR Other Immune cells OR Smooth Muscle OR Min6 OR MG-63 OR Cornea OR Other Stem cells OR RPMI-8266 OR Trigeminal Ganglion OR PBMCs OR Mast cells OR CD34+ cells OR RXF-393 OR Epidermis OR Thymus OR BT-474 OR Pyramidal neurons OR CD56dim NK cells OR Spleen OR P19 OR Effector T cells OR Substantia Nigra OR Granulocytes not otherwise specified OR Dermis OR SK-N-SH OR Chondrocytes OR Hematopoietic progenitor cells OR Neutrophils OR Memory T lymphocytes not otherwise specified OR Murine NKT cells OR OVCAR-8 OR Th2 cells OR Vd2 Gamma-delta T cells OR Other Melanoma Cell Lines OR Stromal cells OR OVCAR-4 OR Plasma cells OR Other Dendritic cells OR NCI-H23 OR Central memory helper T cells OR Other Lymphoma Cell Lines OR Other Organ Systems OR J-774A.1 OR U251 OR SK-MEL-2 OR Pancreas OR Forestomach OR Placenta OR Large Intestine OR Monocytes not otherwise specified OR HepG2 OR Other Cells OR White Matter OR Fibroblasts OR MDA-N OR LOX

IMVI OR Corpus Callosum OR Skeletal Muscle OR Central memory cytotoxic T cells OR SN12C OR Prostate Gland OR Cos-7 cells OR Other Cell Line OR BT-549 OR Other Smooth muscle cells OR Other Endothelial cells OR Thymocytes OR Colon Cancer Cell Lines not otherwise specified OR SF-295 OR Olfactory Bulb OR Other Monocyte-derived dendritic cells OR MCF7 OR Other Breast Cancer Cell Lines OR Ovary OR Cells not otherwise specified OR Effector memory helper T cells OR CAKI-1 OR Sertoli cells OR Activated CD56dim NK cells OR A549-ATCC OR PC-3 OR Amygdala OR NB4 OR Keratinocytes OR HOP-92 OR 3T3-L1 cells OR UACC-62 OR Esophagus OR Granule cells OR Activated CD56bright NK cells OR Other Neuroblastoma Cell Lines OR Lymph node OR Peritoneal macrophages OR HT29 OR MDA-MB-435 OR Other Colon Cancer Cell Lines OR Stomach OR Lymphoma Cell Lines not otherwise specified OR Nervous System not otherwise specified OR CNS Cell Lines not otherwise specified OR Striatum OR Thalamus OR Splenocytes OR NCI-H332M OR SF-268 OR Other Tissues and Primary Cells OR Dendritic cells not otherwise specified OR WEHI-231 OR Other Neurons OR BDCA-3+ dendritic cells OR HCT-116 OR Ventricular Zone OR Fibroblast cell lines not otherwise specified OR Pancreatic Cancer Cell Lines not otherwise specified OR Microvascular endothelial cells OR Intraepithelial T lymphocytes OR Uterus OR Lymphocytes not otherwise specified OR PANC-1 OR Granule Cell Layer OR Tissues and Primary Cells not otherwise specified OR Other Leukemia Cell Lines OR SW-480 OR Swiss 3T3 cells OR Megakaryocytes OR Spinal Cord OR HOP-62 OR IGROV1 OR OVCAR-5 OR Organ Systems not otherwise specified OR HuH7 OR Other Fibroblast cell lines OR Other Lymphocytes OR Mononuclear leukocytes not otherwise specified OR Skin OR Neurons not otherwise specified OR Lens OR Other Lung Cancer Cell Lines OR Smooth muscle cells not otherwise specified OR Bone marrow cells not otherwise specified OR Other Hepatoma Cell Lines OR Other Myeloma Cell Lines OR Granulosa cells OR SR OR Bone marrow-derived dendritic cells OR NCI-H522 OR HEL OR Vd1 Gamma-delta T cells OR Osteosarcoma Cell Lines not otherwise specified OR MALME-3M OR Other NK cells OR K-562 OR H460 OR Kidney Cancer Cell Lines not otherwise specified OR Medulla Oblongata OR Activated Vd1 Gamma-delta T cells OR B lymphocytes not otherwise specified OR Other Nervous System OR Teratocarcinoma Cell Lines not otherwise specified OR Peripheral blood leukocytes not otherwise specified OR Peripheral blood monocytes OR RBL-2H3 OR Other Bone marrow cells OR Brainstem OR INS-1 OR Other Cervical cancer cell line OR Other Teratocarcinoma Cell Lines OR Brain OR Naive helper T cells OR Salivary Gland OR Choroid Plexus OR A375 OR SW-620 OR Heart OR OVCAR-3 OR Melanocytes OR SK-MEL-28 OR Monocyte-derived dendritic cells not otherwise specified OR T lymphocytes not otherwise specified OR CD56bright NK cells OR Cardiomyocytes OR HMC-1 OR Activated Vd2 Gamma-delta T cells OR UO-31 OR Ovarian Cancer Cell Lines not otherwise specified OR SF-539 OR Beta islet cells OR Cytotoxic T cells OR Parietal Lobe) AND
(mol. types = biologic drug OR canonical pathway OR chemical - endogenous mammalian OR chemical - endogenous non-mammalian OR chemical - kinase inhibitor OR chemical - other OR chemical - protease inhibitor OR chemical drug OR chemical reagent OR chemical toxicant OR complex OR cytokine OR disease OR enzyme OR function OR fusion gene/product OR G-protein coupled receptor OR group OR growth factor OR ion channel OR kinase OR ligand-dependent nuclear receptor OR mature microRNA OR microRNA OR other OR peptidase OR phosphatase OR transcription regulator OR translation regulator OR transmembrane receptor OR transporter) AND

(data sources = An Open Access Database of Genome-wide Association Results OR BIND OR BioGRID OR Catalogue Of Somatic Mutations In Cancer (COSMIC) OR Chemical Carcinogenesis Research Information System (CCRIS) OR Clinical Genome Resource (ClinGen) OR ClinicalTrials.gov OR ClinVar OR Cognia OR DIP OR DrugBank OR Gene Ontology (GO) OR GVK Biosciences OR Hazardous Substances Data Bank (HSDB) OR HumanCyc OR Ingenuity Expert Findings OR Ingenuity ExpertAssist Findings OR IntAct OR Interactome studies OR MIPS OR miRBase OR miRecords OR Mouse Genome Database (MGD) OR Obesity Gene Map Database OR Online Mendelian Inheritance in Man (OMIM) OR TarBase OR TargetScan Human)

Top Canonical Pathways

Name	p-value	Overlap
EIF2 Signaling	3.53E-16	46.2 % 49/106
Oxidative Phosphorylation	1.08E-10	61.8 % 21/34
Mitochondrial Dysfunction	2.38E-09	45.8 % 27/59
Gluconeogenesis I	2.32E-08	90.9 % 10/11
Coronavirus Pathogenesis Pathway	1.41E-07	40.0 % 26/65

Top Upstream Regulators

Upstream Regulators

Name	p-value	Predicted Activation
torin1	1.55E-25	Inhibited
LARP1	2.04E-21	Inhibited
MLXIPL	2.99E-21	Activated
YAP1	5.20E-20	

RICTOR	1.13E-15	Inhibited

Causal Network

Name	p-value	Predicted Activation
MLXIPL	2.14E-24	Activated
LARP1	2.04E-21	Inhibited
FBXW7	1.16E-17	Inhibited
NT219	5.09E-16	Inhibited
RICTOR	1.13E-15	Inhibited

Top Diseases and Bio Functions

Diseases and Disorders

Name	p-value range	# Molecules
Cancer	3.54E-02 - 5.48E-08	252
Organismal Injury and Abnormalities	3.54E-02 - 5.48E-08	458
Tumor Morphology	3.39E-02 - 5.48E-08	56
Cardiovascular Disease	3.09E-02 - 1.42E-07	91
Developmental Disorder	2.56E-02 - 1.42E-07	68

Molecular and Cellular Functions

Name	p-value range	# Molecules
RNA Damage and Repair	6.55E-21 - 6.55E-21	42
Protein Synthesis	3.35E-02 - 5.55E-17	163
Cell Death and Survival	3.39E-02 - 5.48E-08	81
Small Molecule Biochemistry	3.39E-02 - 4.46E-06	184
Energy Production	3.35E-02 - 8.85E-06	53

Physiological System Development and Function

Name	p-value range	# Molecules
Cardiovascular System Development and Function	2.56E-02 - 1.86E-04	38
Organ Morphology	2.56E-02 - 1.86E-04	55
Organismal Development	3.39E-02 - 1.86E-04	63
Embryonic Development	3.39E-02 - 1.55E-03	24
Organ Development	2.56E-02 - 1.55E-03	17

Top Tox Functions

Assays: Clinical Chemistry and Hematology

Name	p-value range	# Molecules
Increased Levels of ALT	5.19E-02 - 5.19E-02	2
Increased Levels of Hematocrit	1.59E-01 - 1.59E-01	6

Decreased Levels of Albumin	2.57E-01 - 2.57E-01	1
Increased Levels of Red Blood Cells	2.75E-01 - 2.75E-01	6
Increased Levels of Creatinine	4.48E-01 - 3.44E-01	3

Cardiotoxicity

Name	p-value range	# Molecules
Cardiac Dilation	4.48E-01 - 1.86E-04	23
Cardiac Enlargement	1.00E00 - 1.86E-04	37
Cardiac Inflammation	6.47E-01 - 1.91E-02	7
Cardiac Fibrosis	1.00E00 - 3.09E-02	13
Cardiac Congestive Cardiac Failure	1.00E00 - 5.19E-02	7

Hepatotoxicity

Name	p-value range	# Molecules
Hepatocellular carcinoma	1.00E00 - 2.91E-05	115
Liver Hyperplasia/Hyperproliferation	1.00E00 - 2.91E-05	359
Liver Steatosis	1.00E00 - 1.48E-02	35
Glutathione Depletion In Liver	5.25E-01 - 2.11E-02	7
Liver Fibrosis	5.42E-01 - 2.11E-02	20

Nephrotoxicity

Name	p-value range	# Molecules
Nephrosis	1.00E00 - 9.43E-03	10
Renal Damage	1.00E00 - 1.70E-02	19
Renal Tubule Injury	3.14E-01 - 1.70E-02	9
Renal Atrophy	2.50E-01 - 1.91E-02	2
Renal Dysplasia	1.38E-01 - 1.91E-02	4

Top Regulator Effect Networks

ID	Regulators	Disease & Functions	Consistency Score
1	DDX3X,FAAH,LARP1,Lh,MLXIPL,MYCN,RICTOR,TCR	Cell death of malignant tumor (+1 more)	34.584
2	DDX3X,LARP1,Lh,MLXIPL,MYC,MYCN,RICTOR,TCR	Cell death of malignant tumor (+2 more)	24.505
3	AHR,ARNT,CLPP,CPT1B,CSF2,DDX5,FLCN,FOXM1, HBA1/HBA2 (+16 more)	Biosynthesis of nucleoside triphosphate (+3 more)	13.291
4	AHR,CLPP,CPT1B,CSF2,FLCN,FOXM1,PSME3,RICTOR	Biosynthesis of nucleoside triphosphate (+3 more)	10.097
5	ESRRA,NR1I3	Hepatic steatosis,Metabolism of hormone (+1 more)	4.914

Top Networks

ID	Associated Network Functions	Score
1	Metabolic Disease, Organismal Injury and Abnormalities, Developmental Disorder	52

2	Post-Translational Modification, Cancer, Endocrine System Disorders	47
3	Small Molecule Biochemistry, Molecular Transport, RNA Trafficking	45
4	Cellular Movement, Hematological Disease, Immunological Disease	45
5	Post-Translational Modification, Protein Folding, Developmental Disorder	42

Top Tox Lists

Name	p-value	Overlap
Mitochondrial Dysfunction	2.38E-09	45.8 % 27/59
Oxidative Stress	6.77E-05	52.6 % 10/19
Fatty Acid Metabolism	1.13E-03	31.9 % 15/47
Aryl Hydrocarbon Receptor Signaling	3.46E-03	28.8 % 15/52
Cytochrome P450 Panel - Substrate is a Xenobiotic (Rat)	4.30E-03	66.7 % 4/6

Top My Lists

Top My Pathways

Top Analysis-Ready Molecules

Expr Log Ratio

Molecules	Expr. Value	Chart
LGMN*	6.038	
AOX1	5.112	
SLC36A3*	3.797	
GLB1*	3.730	
MALRD1*	3.233	
MRC1*	3.137	
LIPA*	2.648	
CLEC4F*	2.587	
CPA1*	2.531	
GBA*	2.445	

Expr Log Ratio

Molecules	Expr. Value	Chart
YJEFN3	-1.115	
NPC2*	-1.072	
RORA	-1.071	
FGFR1*	-1.066	
HTR1A*	-1.011	
PLIN4*	-0.928	
KIF26B	-0.885	
LRP6*	-0.859	
CCN1	-0.771	
NPTX1*	-0.724