

Ingenuity Pathways Analysis (IPA)

Using the Ingenuity Knowledgebase understand genes and disease



- What does my gene/protein/compound of interest do?
- What other compounds bind my target of interest?
- If I inhibit or activate a target protein, what cellular processes are likely to be affected that are beneficial or lead to adverse side effects?
- What are the upstream activators or downstream targets of my protein of interest?
- What can my microarray data tell me about changes in cellular functions, pathways, and toxicology?
- What genes are implicated in my disease of interest?
- What proteins might act as good biomarkers for drug efficacy?



Basic gene and chemical search

Finding curated information about a gene/gene-product or drug, reagent or biochemical



Enter a gene or protein name in the search box

	Genes and Chemical	s Functions and Diseases Pathways and Tox Lists		
	serpine1			Adversed Seconds (C)
	a company of		<u>SEARCH</u>	Advanced Search
	SERPINE1	other N		
hà	g	Auto-complete lists matching genes and chemical nother		
		Use of auto-complete is optional, you can simply type and click search		

Enter a drug or chemical name in the search box





More than one search term can be entered at once

- Comma delimited
- Copy a column of IDs from MS Excel and past directly into the search box
- Search terms can be any IPA supported identifier.
- Genbank, SwissProt, Affy probe ID, RefSeq, etc.
- See Help Manuel, "Data Upload Definitions" for complete list
- Wildcard symbol should be used with searching with a partial gene name
- When searching or expecting protein isoforms or related IDs, append a wildcard "*"
- Example: "SERPINE*" will find all gene and protein names that begin with SERPINE



Search results return as a list of entities that have a name or synonym that closely matches the search term





		Reagent View
Gene View: SERPINE1	Mammalian) > Interaction Network > View Reagents (61) Provide Feedback	
Review the categorized literatu	re Findings and satabase information for this node.	Summary tab, partial view
animary manet House ka		Species specific information
Entrez Gene Name:	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	Opecies specific information
Synonym(s):	Pailaa, Planh, PLANH1, PLASMINOGEN ACTIVATOR INHIBITOR 1, RATPAILA	a and physical characteristics from
Source Id:	INdille	e and physical characteristics norm
Protein Family, Domain:	public	c domain
Subcellular Location:	alpha granules, cell membrane leading edge, cell surface, Extracellular Space, Golgi Apparatus, intracellular space, pla polyribosome fractions, ribosome	
Canonical Pathway:	Acute Phase Response Signaling; Coagulation System; Glucocorticoid Receptor Signaling; HMGB1 Signaling; TGF-β Signaling	Links to IPA Canonical Pathway
Top Findings from Ingenui	y Knowledge Base (show all 2653 categorized literature Findings)	
regulates:	PLAT, PLAU, PLAUR, VTN, PLG, SERPINE1, F2, TGFB1, PLASMINOGEN ACTIVATOR, ITGAV, LRP1, ITGB3, FN1, Laminin, FLT1	
regulated by:	TGFB1, TNF, AGT, phorbol myristate acetate, Tgf beta, SMAD3, F2, lipopolysaccharide, troglitazone, SMAD4, TGFBR2, D- glucose, actinomycin D, dexamethasone, LDL	
binds:	VTN, PLAT, SMAD4, PLAU, SMAD3, LRP1, VLDLR, PLAUR, PLASMINOGEN ACTIVATOR, Lrp, Fibrin, F2, PROC, ORM1, IGFBP5	Summary of Indenuity curated
role in cell:	nigration, proliferation, growth, adhesion, matility, apoptosis, binding, formation, phosphorylation in, activation in	
disease:	thrombosis, obesity, fibrosis, severe sepsis, hypotension, stroke, sepsis, heart failure, colorectal cancer, acute respiratory distress syndrome, bacterial meningitis, proteinuria, dengue shock syndrome, bone cancer, giant cell tumor of bone, brain neoplasm, colorectal carcinoma, liver cancer, liver metastases, preeclampsia, colon cancer, brain cancer, edema, cardiac fibrosis, acute lung injury, head and neck cancer, hypertrophy, bleeding, vascular dementia, non-insulin-dependent diabetes mellitus, cancer, tumorigenesis, neoplasia	Description
Descriptions from Externa	Databases	Description
Entrez Gene Summary:	This gene encodes a member of the serine proteinase inhibitor (servin) superiamily. This member is the principal inhibitor of tissue plasminogen activator (tPA) and urokinase (uPA), and hence is an inhibitor of fibrinolysis. Defects in this gene are the cause of plasminogen activator inhibitor-1 deficiency (PAI-1 deficiency), and high concentrations of the gene product are associated with thrombophilia. Alternatively spliced transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq]	Gene Ontology information
GO Annotations		from public domain
Molecular Function:	protease binding; serine-type endopeptidase activity, online type endopeptidase inhibitor activity; protein binding; peptidase inhibitor activity	
Biological Process:	response to reactive oxygen species; chronological cell aging; negative regulation of plasminogen activation; positive regulation of blood coagulation; positive regulation of interleukin-8 production; regulation of cell proliferation; tissue regeneration; glucose homeostasis; regulation of angiogenesis; negative regulation of fibrinolysis; negative regulation of vascular wound healing; cellular response to chemical stimulus; cellular response to lipopolysaccharide; positive regulation of monocyte chemotaxis	Drug Information
Cellular Component:	extracellular region; soluble fraction; plasma membrane; extracellular matrix	
Drug Information		Recently Added Findings
Targeting [rug Drug Band Name(s)	recorning / ladea / intailige
drotrecogin alfa	Xigris inhibitor	
53 Recently Added Finding	s (show Findings)	Link to full content
2653 Categorized Literatur	e Findings (show details)	



2613 Categorized Literature Fin	dinas (hide details)	
Biomarker Information Toxicology	Functional Roles Mutan	t Information Modifications and Regulation Disease Expression and Localization Physical
Interactions Additional Findings		Lineder Linke for novinction to point of
efficacy (10)	atherosclerosis, atrial fibr	illation, non-small cell lung cancer, breast cancer, non-insur
	small cell lung cancer	interest.
safety (3)	hypertension, breast can	
diagnosis (2)	abdominal obesity-metab	olic syndrome, coronary artery disease
disease progression (2)	benign prostatic hyperpla	sia, melanoma
prognosis (2)	acute respiratory distrem	Findings: Functional Roles
		Review the information that supports the gene-to-function relationship. Click the plus icon to view the reference information.
Toxicology (hide details)		PlainText EXPORT REFERENCES
Cardiotoxicity		Findings 1 - 9 of 9
fibrosis (2)	heart, myocardium	
rupture (2)	heart, myocardium	Plasminogen activator inhibitor type 1 [SERPINE1] increases inhibition of tissue-type plasminogen activator [PLAT].
dilation (1)	left ventricle	8180342 Reilly TM, Mousa SA, Seetharam R, Racanelli AL. Recombinant plasminogen activator inhibitor type 1: a review of
dysfunction (1)	left ventricle	structural, functional, and biological aspects. Blood Coagul Fibrinolysis 1994 Feb 1;5(1):73-81.
hypertrophy (1)	cardiomyocytes	Source: Ingenuity curated modings
		tissue-type plasminogen activator inhibitor type 1 (PAI-1), a member of the serpin family of serine procease inhibitors, inhibits both tissue-type plasminogen activator (t-PA) and urokinase type plasminogen activator (u-PA).
Functional Roles (hide details)	\sim	Human PAI-1 [SERPINE1] protein increases in Reference can be viewed by clicking the
Molecular Processes		Plasminogen activator inhibitor-1 [SERPINE1] Dlus-sign or "Expand All"
expression of (44)	CASP3, G/P43, TGF31,	In cytoplasm, SERPINE1 protein increases inhib
inhibition of (22	TGFBR2, CALR, CASP9,	In a cell-free system, Pai1 [SERPINE1] protein in Fibringgen.
	PLAT, PLAU, PZ, PLASMI	Pubmed ID links to abstract.
activity of (26)	PLAT, IGFBI, PLAU, CI:	PAT-1 [SEPPINE1] increases inhibition of t-PA [PLAT]
binding of (26)	Laminin, SHC1, Sos	PAT-1 [SEPDINE1] protein increases inhibition of T-DA [DI AT] protein
activation of (13)	TGFB1, Erk1/2, PLG, AK	Placminogen activator inhibitor 1 [SEPDINE1] increases inhibition of tDA [DI AT]
generation of (11)	PLG, F2	
adhesion of (9)	FN1, VTN, Collagen Typ	Findings 1 - 9 of 9
phosphorylation of (8)	Akt, SMAD2, EGFR, Erk	
localization of (6)	HGF, ITGAV, ITGB3, PLAU	JR, Smad2/3





Ingenuity Findings

Ingenuity® Expert Findings – Manually curated Findings that are reviewed, from the full-text, rich with contextual details, and are derived from top journals.

Ingenuity® ExpertAssist Findings –

Automated text Findings that are reviewed, from abstracts, timely, and cover a broad range of publications.

Ingenuity Modeled Knowledge

Ingenuity[®] Expert Knowledge – Content we model such as pathways, toxicity lists, etc.

Ingenuity[®] Supported Third Party

Information – Content areas include Protein-Protein, miRNA, biomarker, clinical trial information, and others



- Synonyms, Protein Family, Domains GO, Entrez Gene, Pfam
- Tissue and Biofluid Expression & Location GNF, Plasma Proteome
- Molecular Interactions BIND, DIP, MIPS, IntAct, Biogrid, MINT, Cognia, etc.
- miRNA/mRNA target databases TarBase, Argonaut 2
- Gene to Disease Associations
 OMIM, GWAS databases
- Exploratory Clinical Biomarkers
- Clinical Trial information
 clinical trials.gov





• Enter a drug or chemical name in the search box

NEW > Sense or Chemicals Functions and Disease Genes targeted by Drugs	<u>F</u> ile	<u>E</u> dit	<u>W</u> indow	Help
	NE	N ×		Concesor Chemicals Functions and Disease Genes targeted by Drugs VIOXX SEARCH







If the chemical is a drug, there will be additional information such as manufacturer, clinical trail status, target(s), and action

Drug Information									
Brand Name(s	s): Vioxx								
Manufacturer(s): MERCK									
Therapeutic Categorie	es: non-narcotic analge	sic; NSAID							
Indication	FDA Approval Status	Trial Status	Clinical Trial Sponsor(s)	NCT#	Last Updated				
malignant tumor of stomach	Phase III	Active, not recruiting	Chinese University of Hong Kong	NCT00164892	2005-11-16				
osteoarthritis	Phase III	Completed	Novartis	NCT00637949	2008-03-17				
brain tumor	Phase I	Terminated	M.D. Anderson Cancer Center	NCT00038389	2005-06-23				
rheumatoid arthritis	Withdrawn								
osteoarthritis	Phase III	Completed	Novartis	NCT00637949	2008-03-17				
colorectal cancer	Phase III	Active, not recruiting	Cancer Research Campaign Clinical Trials Centre	NCT00031863	2007-12-15				
dysmenorrhea	Withdrawn								
prostatic carcinoma	Phase III	Completed	Merck	NCT00060476	2008-07-31				
glioma	Phase I	Terminated	M.D. Anderson Cancer Center	NCT00038389	2005-06-23				
prostate cancer	Phase III	Completed	Merck	NCT00060476	2008-07-31				
malignant tumor of stomach	Phase III	Active, not recruiting	Chinese University of Hong Kong	NCT00164892	2005-11-16				
pain	Phase II	Completed	National Institute of Dental and Craniofacial Research (NIDCR)	NCT00026819	2006-07-10				
	Target		Action						
PTGS2			inhibitor						
715 Categorized Litera	ture Findings (show deta	ils)							



- IPA Search retrieves a wealth of experimental evidence for genes and proteins on the Gene View page, and Drug and Chemicals on the Chem View page.
- Gene and Chem pages display information that is explicitly known about a gene or molecule; there is no inferred or hypothetical information (this is done through custom pathway building).
- Gene and Chem View information is based primarily on literature findings taken from the full-text of journal articles but may come from other defined sources with references.



Function & Disease to Gene search

Finding gene and chemical entities associated with biological functions, processes, and diseases



One can also find molecules (gene/chemicals) associated with a biological process or disease. Results are listed in a tree or list format.

Genes and Chemicals Functions and Diseases Pathways and Tox Lists	
ovarian cancer	SEARCH Advanced Search
Search	- [⊭] ⊠ 12
ADD TO MY PATHWAY ADD TO MY LIST ANNOTATIONS AN SHOW FUNCTIONS EX	PAND FUNCTIONS
The search for ovarian cancer matched 104 functions and diseases.	
Functions & Diseases	
Matching Functions & Diseases	704
	457
ovarian cancer	435
ovarian cancer	435
ovarian cancer of humans [ovarian cancer of Homo sapiens (human)]	4
ovarian cancer of primate	4
ovarian cancer of mammalia	4
epithelial ovarian cancer	54
epithelial ovarian cancer	54
endometrioid carcinoma	25
endometrioid carcinoma [endometrioid ovarian cancer,endometrioid ovarian carcinoma,]	25
clear-cell ovarian carcinoma	24
└────────────────────────────────────	24
│	19



Genes and Chemicals Function	is and Diseases Pathways and Tox Lists			
ovarian cancer		<u>S</u> EARCH	Advanced Sear	ch
Advanced Search Options	•	X	- 5 B	X
$\underline{G}ene(s)$, Chemical(s) and Identifier(s)		2?	s	»
Identifier Type(s)	All Identifiers -			g Neti
Molecule Type(s) Subcellular Location(s) <u>P</u> athways and Tox Lists Display results in a	Select all biologic drug chemical - endogenous mammalian chemical - endogenous non-mammalian chemical - other chemical - other chemical - protease inhibitor chemical - protease inhibitor chemical reagent chemical train ant	Image: Cancel	sociated Molecules	
In Cancer CNA & E taset Files alyses	compasity compasity	4 51 51		
Common with KB -	<u>R</u> ESET <u>O</u> K	24		-



Clicking the function text to see the effect-on-function and then clicking to view findings works well there are a small number of results.

Search	- d X
ADD TO MY PATHWAY ADD TO MY LIST ANNOTATIONS 📑 🗟 SHOW FUNCTIONS EXP	AND FUNCTIONS »
The search for ovarian cancer, tran matched 93 functions and diseases.	
Functions & Diseases	
Matching Functions & Diseases	471
	327
ovarian cancer	307
	307
• • • • • • • • • • • • • • • • • • •	1
et-covarian cancer of primate	1
t → _ ovarian cancer of mammalia	1
epithelial ovarian cancer	47
	47
endometrioid carcinoma	25
endometrioid carcinoma [endometrioid ovarian cancer,endometrioid ovarian carcinoma,]	25
□-□ clear-cell ovarian carcinoma	24
	24
□-□ mucinous ovarian carcinoma	19
Le transmission de la carcinoma (mucinous <mark>ovarian cancer</mark>)	19



Search	et 🗗	×	
ADD TO MY PATHWAY ADD TO MY LIST ANNOTATIONS IN SHOW FUNCTIONS EXP	AND FUNCTIONS	»	
The search for ovarian cancer, tran matched 93 functions and diseases.			
Functions & Diseases			
Click plus-sign to expand selection			
er ovarian cancer	307	333	
(p-	307		
ABCB1, ABCC5, ABL1, ABP1, ADA, AFP, AGPAT2, AGR2, AGR3, AKT1, AKT2, AKT3, ALCAM, ANXA10, APOE, AR, ASCL2, ATP6V1B1, BCR, BMP7, BRAF, BRCA1, BRCA2, C70RF68, CCL2, CCL4, CCT5, CD24, CDH1, CDKN24, CEACAM6 (includes EG:4680), CHI3L1, CLDN3, CLDN4, CLEC3B, CLU, COL18A1, COL4A1, COX5A, CP, CPP, CSF3, CSF1R, CSF3R, CTLA4, CXCL14, CXCL16, CYP19A1, CYP24A1, DACH1, DDR1, DHCR24, DHFR, DPPA2, DUSP4, DYNLRB1, E2F1, E2F3, ECT2, EEF1A2, EFNB2, EGF, EGFR, EP300, EPCAM, EPHA2, EPO, EPOR, ERBB3, ERCC1, ESR1, ESR2, EYA2, F10, FABP4, FAM720, FDF11, FGF1, FGF2, FGFR1, FGFR3, FIGF, FLT1, FLT3, FLT4, ENTA FNTA FOLR1 FOST FOST FOST FOST FOST			
GHRH, GSK38, GSTM1, GTF2A1, H19, HDAC1, HDAC2, HDA HDAC8, HDAC10, HDAC11, HDAC9 (includes EG:9734), HGF HDAC8, HDAC41, HDAC11, HDAC9 (includes EG:9734), HGF	d to Gene	Vie	w pages
 IDOAB, HOARS, HOARS, HOARS, HOARS, HOARS, HOARS, H., HARSWART, HARSWART, HARSWARS, HARS			
ovarian cancer of humans [ovarian cancer of Homo sapiens (human)]	1		
	.1		



Search		₽≝₽₹	
ADD TO MY PATHWAY ADD TO MY LIST ANNOTATIONS SHO	W FINDINGS EFFECT ON FUNCTION	D FUNCTION BIOPROFILER	
The search for ovarian cancer matched 229 diseases and function	ns.		
Diseases & Functions			
ovarian cancer		956	
e-⊡ ovarian cancer		956	
abagovomab, ABCA3, ABCA8, ABCB1, ABCC11, ABC ADCY2, ADGRG1, ADNP, ADORA2A, ADRB2, AGO4, J ALDH1A2, ALDH3A1, ALKBH1, ALKBH3, ALKBH7, alt anthracycline/carboplatin, ANXA10, ANXA8/ANXA8 ARID1A, ARID1B, ARL4C, aromatase inhibitor, arzoxii BARD1, BCL10, BCL2, BCL2L1, BCL2L11, BCR, BECN1 bevacizumab/carboplatin/paclitaxel, bleomycin, BM C2ort88, C3ort20, C4A/C4B, C5ort28, C8B, C32+, C4	C8, ABHD12B, ABL1, ABLIM2, ACP5, ADAM10, ADAM17, ADAM18, ADAMTSL: GPAT2, AGR2, AGR3, AIFM1, AKAP2, Akt, AKT1, AKT2, ALCAM, ALDH1A1, etamine, amifostine, ANG, ANGPT1, ANKRD24, ANKRD36, ANKRD36C, 1, AOC1, APBA1, APCDD1, APOA1, APOE, AQP6, AR, ARAF, ARFIP1, ARHGEF1 ene, ASCL2, ATG2B, ATIC, ATP6V1B1, ATP8B1, ATP8B2, B2M, BAHD1, BAP1, BEND5, bevacizumab, bevacizumab/carboplatin/gemcitabine, P7, BNC1, BRAF, BRCA1, BRCA2, BRIP1, BROX, BSN, BTRC, C16orf78, C2CD3, NA1A, CAB, CALB2, CALCOCC2, CAMX2B, CAMX2N2, capacitabine	2,	
carboplatin, carboplatin/chemotherapy, carboplatin	M/bat paw?		
CD24, CD274, CD40LG, CDH1, CDK1, CDK2, CDK20, C	vvnal now?		
CENPE, CEP120, CEP152, CFH, CHEK1, CHEK2, CHB	 Send to a nathway to c 	connect to	other denes or overlay
COL15A1, COL18A1, COL28A1, COL3A1, COL4A1, C			other genes of overla.
CSF2RB, CSF3, CSF3R, CTDSPL, CTNNAL1, CTNNB1,	biological criteria to sul	oset	
DDX23, DDX39A, decitabine, DEPDC5, DESI2, dexame	Cove on list		
DNAH2, DNAH5, DNAH7, DNAJA1, docetaxel, DOCK E2E2 E2E3 E2E4 E2E8 ECT2 EEE1A2 EENB1 EENB2	• Save as list.		
EPCAM, EPHB6, epirubicin, EPO, EPOR, epothilone E etoposide ETV4, everylimus, EVIS, EVI, EVA2, E2, E28	A list can be		
FAM72C/FAM72D, FANCD2, farletuzumab, FARP1, F		/ /	
FGF16, FGF18, FGF2, FGF9, FGFR1OP, filgrastim, FLII, FOXD414/FOXD415_FOXG1_FOXM1_FOXN2_FOXO4	 Used to limit Grow 	' (create pa	athway to these genes
gemcitabine, GHRH, GINS1, GLDC, GLI1, glutathione	 Used for Overlay (vicualiza i	ntoreactione)
GPATCH4, GPR132, GPR4, GPR65, GPX3, GRB7, GRIN GTF2IRD1, GTPBP4, GYG1, H19, H2AFX, H2AFY, HAS	• Used for Overlay (visualize il	
HHLA2, HIC1, HIST1H2BI, HIST2H2AA3/HIST2H2AA	 Compared to othe 	r lists (File	->New->Compare)
HOXA4, HOXA5, HOXA9, HOXB2, HOXB5, HOXB6, H HTR1F, hydralazine, Icam, IDO1, idronoxil, IFI27, IFI3			
IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGSF21, IL10, IL12B,	 Sent to a Core Ana 	alvsis	
IAK2, JUN, JUNB, KALKN, KANK3, karenitecin, KAT2 KIAA1467, KIAA1804, KIF7, KISS1, KISS1R, KIT, KLF8, K		Drofilerte	
KRT19, KRT23, KRT6B, KRTAP1-5, KX-01, LAMA5, LC	 Further analyzed in Bio 	perofiler to	SUDSET
LIG1, LMNA, Iomustine, Ionidamine, LOXHD1, LPAR	AP2K4 Mapk MCAM MCCC1 MCF2 MDM4 MECOM megestrol acetate		



Advanced Analytics

Causal Networks

BioProfiler

Advanced Analytics requires an additional subscription fee

- Sample to Insight



- Which genes when [increased] in activity [increase] [COPD]?
- Which genes when [decreased] in activity [increase] [liver cholestasis]? What types of [genetic] evidence support this?
- Which genes are potential [diagnosis OR prognosis] biomarkers of [breast cancer] and are [upregulated] in breast cancer?
- Which genes are known to both [affect OR increase] [colorectal cancer AND obesity]?



Targets of toxicity:

Which genes when [decreased] in activity [increase] [liver cholestasis]? What types of [genetic] evidence support this?

Target discovery:

- What [heterozygous knockouts] in [mouse] can [decrease] [asthma]?
- Which drugs or which targets have been in late stage clinical trials or approved to decrease [diabetes]?

Biomarker research:

Which genes are potential [diagnosis OR prognosis] biomarkers of [breast cancer] and are [upregulated] in breast cancer?

BioProfiler enables precise filtering on the "components" of Ingenuity Findings



CIAGE



Identify genes known to be causally relevant as potential targets or identify targets of toxicity, associated known drugs, biomarkers and pathways

	THWAY ADD TO MY LIST		1							
Aolecule	Ac	ld column(s) 王	Disease & Evidence		(dd column(s) 王
Symbol	Molecule Type 🛛 🔀	Disease 🗙	Disease 🛐	Mut 🝸 🔀	Effect on Diseas	e/Function 🚺 🕱	Spe 🝸 🔀	Causal or Correlated 🔳	🛚 Molecule Activity 🔳 🛛	Findings 🔀
ACE	peptidase	219	Alzheimer's disease	wild type	increases		Human	causal	increased activity	1
APBB2	other	55	Alzheimer's disease; late-onset Al	wild type	increases		Human	causal	increased activity	1
APOE	transporter	920	Alzheimer's disease	wild type	increases		Human	causal	increased activity	1
APP	other	1134	Alzheimer's disease	wild type	increases		Human	causal	increased activity	2
3LMH	peptidase	54	Alzheimer's disease	wild type	increases		Human	causal	increased activity	1
PAXIP1	other	63	Alzheimer's disease	wild type	increases		Human	causal	increased activity	1
PSEN1	peptidase	585	Alzheimer's disease	wild type	increases		Extraosikilar Space	look	urikizden (Rec tenenpit/typ/octionalite	ate wedays
PSEN2	peptidase	277	Alzheimer's disease	wild type	increases	End A d of CI CI d Avanation/or	longistlongiggide Sylveryick entrybecamete		an example to dever	
ORL1	transporter	49	Alzheimer's disease	wild type	increases		Plasma Menthrana		The /	The rest of the statements
Fili ca WI act	ter down to usally assoc nich genes v tivity increas	genes l ciated w when do se liver	known to be vith Alzheimer's ecreased in cholestasis?							
								/	APO02	



- Find molecules causally relevant to the disease or phenotype
- Filter by specific genetic evidence or species
- Explore association with other similar diseases or phenotypes/symptoms leveraging the depth of the Ingenuity Ontology and the Human Phenotype Ontology

Search for a disease, phenotype or function	Species unclassified mutation
Alzheimer's disease [Alzheimer's dementia, Alzheimer's disease-like dementia,] Search	
Select a search result to view in hierarchy	
Select asarch result to view in hierarchy (/deseer/Neurological Disesse/disess of central nervous system/resphalopathy/Dementia/Abbiemer's disesse/experimental Abbiemer's disesse/experiment	

Disease Evidence

□ functional effect

··□ knockout ··□ loss of function ··□ null mutation

inheritance mode

recessive

· □ X-linked · □ Y-linked

Select all



Molecule	Add column(s) 💽	Disease, Phenotype & Evidence Add column(s)							
📐 Symbol	Molec 🝸 🔀	Molecule Acti 🝸 🕱	Effect 🝸 💌	Disease 🔳	Mutation e 🝸 💌	Speci 🝸 🕱	Caus 🝸 🕱	Findings 🔀	
ALOX5	enzyme	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	1	
BAX	transporter	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	3	
BID	other	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	4	
CCL17	cytokine	decreased activity	decreases	ibrosis of lung	wild type	Mouse	causal	1	
CCR2	G-protein cou	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	3	
CDH11	other	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	1	
CXCL12	cytokine	decreased activity	decreases	ibrosis of lung	wild type	Mouse	causal	1	
EGR1	transcription r	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	2	
ELANE	peptidase	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	1	
FAS	transmembran	decreased activity	decreases	ibrosis of lung	homozygous, loss of	Mouse	causal	1	
► FASLG	cytokine	decreased activity	decreases	ibrosis of lung	homozygous, loss of	Mouse	causal	2	
►ICAM1	transmembran	decreased activity	decreases	ibrosis of lung	homozygous,knock	Uncategorized	causal	5	
IKBKB	kinase	decreased activity	decreases	ibrosis of lung;	homozygous,knockout	Mouse	causal	1	
IL11RA	transmembran	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	1	
▶IL12B	cytokine	decreased activity	decreases	ibrosis of lung	homozygous,knock	Mouse	causal	4	
IL13	cytokine	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	4	
IL17A	cytokine	decreased activity	decreases	ibrosis of lung	wild type	Mouse	causal	9	
IL1R1	transmembran	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	1	
IL4	cytokine	decreased activity	decreases	ibrosis of lung	homozygous,knockout	Mouse	causal	3	
IL5	cytokine	decreased activity	decreases	ibrosis of bronchia; f	homozygous,knockout	Mouse	causal	1	
ITGA5	transmembran	decreased activity	decreases	ibrosis of lung	wild type	Mouse	causal	2	

Drug targets: genes or proteins that when decreased in activity, decrease lung fibrosis



Alzheimer's Disease Identify and understand key molecules involved with the disease for potential target discovery



Genes and Chemicals Functions and Disea	ses Pathways and Tox I	Lists								
Alzheimer's disease [Alzheimer's dementia, Alzheimer's disease-like dementia,]										
DETA		BET		- 0						
Search										
ADD TO MY PATHWAY ADD TO MY LIST ANNOTATIONS SHOW FINDINGS	EFFECT ON FUNCTION		EXPAND FUNCTIONS BIO	PROFILER						
The search for Alzheimer's disease [Alzheimer's dementia, Alzheimer's disease-	ike dementia,] matched 1	functions and diseases.								
Functions & Diseases										
Matching Functions & Diseases										
□ 🗹 Neurological Disease										
□ I Alzheimer's disease										
🕀 🗹 Alzheimer's disease [Alzheimer's disease-like dementia, Alzheimer's	dementia]									
Psychological Disorders										
Alzheimer's disease										
🕀 🗹 Alzheimer's disease [Alzheimer's disease-like dementia, Alzheimer'	BioProfiler									ජ් ් ⊠
	ADD TO MY PATHWAY	ADD TO MY LIST	•			(R)-	flurbiprofen4-(2-(6-(2-(2	(p1 of 7)	🗠 💌 🔟 N	Aore Info
	Molecule		Add column(s) 🔳	Disease & Evidence	ice					
	∠ Symbol	Molecule T 🝸 💌	Tissue/Cell 🝸 💌	Molecule A 🝸 💌	Effect on Di 🝸 💌	Disease 🔳	Mutation e 🝸 💌	Biomarker 🝸 🕱	Species Evi 🝸 🚺	K Druc
	LGALS1	other	Activated CD56brigh	decreased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a 🗖
	miR-132-3p (and oth	mature microRNA		decreased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	BCL2L11	other	Activated CD56brigh	increased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	RTN3	other	Adipose, Amygdala, B	increased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	HOMER1	other	Activated helper T cel	increased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	► HMGCR	enzyme	Cerebral Cortex, Live	decreased activity	affects, decreases	Alzheimer's disease	wild type	not applicable	Human	not a
	EIF2AK2	kinase	Adipose, Amygdala, B	increased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	CRP	other	Adipose, Liver, Other C.	increased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	PRKAR2B	kinase	Activated Vd1 Gam	decreased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	acetaminophen	chemical drug		increased activity	decreases	Alzheimer's disease	wild type	not applicable	Uncategorized	phas
	mik-378a-3p (and ot	mature microkivA		increased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	EDDS	oner	Activated CD56brieb	increased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	olanzanino	chemical drug	Activated CD50blight	increased activity	decreases	Alzheimer's disease	wild type	not applicable	Uncategorized	nota
	УТАР	enzyme	Activated beloer Ticel	increased activity	affects	Alzheimer's disease	wild type	not applicable	Human	prias
	МАРК9	kinase	Activated CD56brigh	increased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	PRKAR2A	kinase	Activated CD56brigh	decreased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a
	▶ rivastigmine	chemical drug	Sectored Costonight in	increased activity	decreases	Alzheimer's disease	wild type	not applicable	Uncategorized	appr
	CXCR4	G-protein coupled re	Activated CD56brigh	increased activity	affects	Alzheimer's disease	wild type	not applicable	Human	not a



Show me only those molecules that when increased are known to increase Alzheimer's disease.

Quickly identify 9 molecules causally relevant to Alzheimer's from 682 search results

BioProfiler										
ADD TO MY PATHWAY ADD TO MY LIST 😩 📑										
Molecule		Add column(s) 王	Disease & Evidence						Add column(s) 王	
∧ Symbol	Molecule Type 🝸 🕱	Tissue/Cell 🝸 💌	Molecule Activity 🔳 🗵	Effect on Diseate 🔳 💌	Disease 🗾 🔀	Mutation e 🝸 💌	Species Evi 🔳 💌	Causal or C 🝸 💌	Findings 🛛 🗙	
APP	other	Activated CD56brigh	increased activity	increases	Alzheimer's disease	wild type	Human	causal	2	
PSEN1	peptidase	Adipose, Amygdala, B	increased activity	increases	Alzheimer's disease	wild type	Human	causal	1	
ACE	peptidase	Dorsal Root Ganglio 🧠	increased activity	increases	Alzheimer's disease	wild type	Human	causal	1	
PSEN2	peptidase	B lymphocytes not o	increased activity	increases	Alzheimer's disease	wild type	Human	causal	1	
APBB2	other	Activated CD56dim	increased activity	increases	Alzheimer's disease; I	wild type	Human	causal	1	
APOE	transporter	Activated Vd1 Gam	increased activity	increases	Alzheimer's disease	wild type	Human	causal	1	
BLMH	peptidase	Activated Vd1 Gam	increased activity	increases	Alzheimer's disease	wild type	Human	causal	1	
PAXIP1	other	Activated CD56brigh	increased activity	increases	Alzheimer's disease	wild type	Human	causal	1	
SORL1	transporter	Activated CD56brigh	increased activity	increases	Alzheimer's disease	wild type	Human	causal	1	



Molecule Activity

- Whether the finding indicates increased or decreased activity
- Calculated using various factors
 - □ Observed upregulation or downregulation
 - □ Functional effect of mutations
 - □ Etc.
- Effect on Disease/Function
- Whether the disease or function was increased or suppressed
- Species evidence and Tissue/Cell line
- Select specific species e.g. mouse, and/or specific tissues e.g. lung

Mutation evidence

Limit to certain mutation types e.g. homozygous, knockout

Causal v/s correlation



Select molecules, place on a pathway and overlay drugs





Analysis of the clinical aspect of EMT in Breast Cancer

Exploring the EMT molecules involved in breast cancer.

 Focusing on the Upstream Regulators predicted to be activated in the dataset to explore which ones if any would be of interest for therapeutic purposes.

Do any of these molecules of interest have biomarker application in breast cancer?







Genes and Chemicals Functions and Diseases Pathways and Tox Lists	
breast cancer SEARCH Advanced Search 🔽	
Search	
ADD TO MY PATHWAY ADD TO MY LIST ANNOTATIONS SHOW FINDINGS EFFECT ON FUNCTION EXPAND FUNCTIONS EXPAND FUNCTIONS	BIOPROFILER
The search for breast cancer matched 274 functions and diseases.	
Functions & Diseases	
Matching Functions & Diseases	2551
⊖ Cancer	1542
P⊡ neoplasia	1483
■ ✓ Breast Cancer and Tumors	1432
	68
in eoplasia of mammary tumor cells [neoplastic growth of breast cancer cells, neoplastic syndrome of breast cancer cells,]	13
P → breast cancer	1416
breast cancer [cancer of breast,cancer of the breast]	1416
■ ■ breast cancer of mammary gland [cancer of breast of glandula mammaria, breast cancer of lactiferous gland,]	1
□ □ carcinoma	556
□ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □	556
⊐ ductal carcinoma	118
United to the state of the stat	118
E-1 disease	116
disease of breast cancer cell lines (breast cancer cell line syndrome, disorder of breast cancer cell lines,]	70
⊕	42
	13
⊡ metastasis	65
the metastasis of breast cancer cell lines (breast cancer cell line carcinogenesis, breast cancer cell line metastasis,)	37
The metastasis of mammary tumor (metastatic cancer of breast tumor, stage IV cancer of neoplasm of the breast)	24
The metastasis of breast carcinoma [stage IV cancer of breast carcinoma, metastatic cancer of breast cancer tumor]	13
metastasis of mammary tumor cells [neoplasm metastasis of breast cancer cells stage IV cancer of breast carcinoma cell]	11
He delay in initiation of metastasis of mammary tumor (delay in initiation of stage IV ranger of breast tumor delay in initiation of metastatic	2
	65



Search		ŕ₫	×
ADD TO MY PATHWAY ADD TO MY LIST ANNOTATIONS SHOW FINDINGS EFFECT ON FUNCTION EPFECT ON FUNCTION ADD TO MY LIST	BIOPROFILER		
The search for breast cancer matched 274 functions and diseases.		<u> </u>	
Functions & Diseases		Molecul	
□ □ Cancer	1542		Ŀ
⊨ neoplasia	1483		NVN
Breast Cancer and Tumors	1432		L
 J. J. Janker, M. B. 1993 J. Janker, M. Mylestradiol, 17-hydroxyprogesterone, 2-mercaptoethanesulfonic acid, 3,3'-diindolylmethane, S-fluorouracil, 9,10-dimethyl-1,2-benzanthracene, ABAT, ABCB1, ABCB7, ABCC1, ABCC4, ABCC5, ABCC2, abiraterone acetate, ABL, ACAAI, ACACB, ACADVL, ACOT9, ACF5, ACTA2, ACRB1, ADAM15, ADAM175, ADAM175, ADAMT58, ADAMT59, ADAMT51, ADAMT510, ADAMT514, ADAMT520, ADAMT53, ADAMT54, ADAMT55, ADAMT58, ADAMT58, ADAMT59, ADCY2, ADCY3, ADIPOQ, ADK, ADRA2C, ADRM1, AE 941, AGPAT2, ACPAT6, GAC2, AIDA, AIGO, AIADOA, AIDOC, alendronic acid, ALOX15, AMSRA1, amiodipine, ampicillin/sublactam, ANAPC13, anastrozole, ANG, ANKB30A, anthracycline, ANXA1, ANXA3, ANXA9, AOC3, APSM2, APC, APLP1, APOAL, APOBEC3G, APOE, aprepitant, AR, ARAF, AREG/AREGE, ARFGEF1, ARHCAP19, ARHGAP8/PRR5-ARHGAP8, ARHGDIA, ARHGDIB, ARHGEF1, ARHGEF2, ARHGEF2, ARHGEF2, ARHGEF2, ARHGAP19, ARHGAP8, PRR5-ARHGAP8, ARHGDIA, ARHGDIB, ARHGEF1, ARHGEF2, ARHGEF5, ARHGEF7, ARMCX5, ARNTL, ARRB1, arzoxifene, ASF18, SM3L2, ASXL3, atamestane, ATF2, ATF3, ATM, ATP282, ATP22C, ATP5A1, ATP51, ATP510, ATRAD, 201KA, AURK8, AXIN11, AXIN2, BAD, BAG1, BAG4, BARD1, BAX, BCAM, BCAR1, BCL2, BCL2A1, BCL2L2, BECN1, benzyl isothiocyanate, beta-estradiol, bevacizumab, BEX1, BEX2, BHLHE40, BIRC5, BKN120, BLD, BLVRA, BMI1, BMP7, BNIPL, botulinum toxin type A, BRAF, BRCA1, BRCA2 BRF2, BRRP1, BSS, HCL2, HEX, BULHE40, BIRC5, BKN120, BLD, BLVRA, BMI1, BMP7, BNIPL, botulinum toxin type A, BRAF, BRCA1, BRCA2 BRF2, BRRP1, BCS, CASP7, CASP8, CASP9, CAT, CAV1, Cbr2, CEX3, CEX4, CCA, CANA2D2, CACNA2D3, CACMA2D4, Calcium gluconate, CALD1, CALM1 (includes others), CAT11, capecitabine, CAP2A2, carboplatin, carmustine, carvediol, CASP0, CASP2, CASP3, CASP6, CASP7, CASP8, CASP9, CAT, CAV1, Cbr2, CEX3, CEX4, CCAS, CCD14, CD44, CD45, CD54, CD54, CD54, CD54, CD52, CDC21, CCN11, CCN11, CCN12, CCN12, CCN11, CCP110, CCR2, CCR4, CCR5, CCR6, CCR7, CCT3, CD14, CD44, CD86, CD69, CD70 CD798, CD80, CDC20, CDC25A, CDC25B, CDC37, CDC42, CDC47, CD11, CD12, CD13, CD14, CD			F

- Sample to Insight


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a 🖦 All Pages **-** () More Inf 1 Molecule Add column(s) Disease & Evidence Add column(s Symbol Molecule Type **Y X** Diseas... Disease **T** M... 🝸 🔀 Biom... 🝸 🔀 Eff... 🝸 🔀 Spe... 🝸 🔀 ... 🍸 💌 Drug... 🝸 🔀 Exp... 🝸 🕱 Caus... **T** Mole... 🝸 💌 Findings Breast Cance (S)-duloxetine chemical drug 59 wild type not applicable decreases Uncategorized phase III not applicable causal increased acti.. approved, pha. 17-alpha-ethinylestradic chemical drug 155 Breast Cance wild type not applicable decreases Uncategorized not applicable causal increased acti. 12 Breast Cance chemical - endogenous... 15 wild type diagnosis affects Uncategorized not applicable 17-hydroxyprogesterone not applicable correlation increased acti. 2-mercaptoethanesulfoni chemical drug 22 Breast Cance wild type decreases Uncategorized phase III not applicable increased acti. not applicable causal Breast Cance wild type 3,3'-diindolylmethane chemical drug 97 not applicable decreases Uncategorized not applicable. not applicable causal increased acti. 3 5-fluorouracil chemical drug 355 Breast Cance wild type not applicable decreases Uncategorized approved, pha. not applicable causal increased acti. 54 9,10-dimethyl-1,2-be. chemical toxicant 258 Breast Cance wild type not applicable increases Rat,Mouse Mammary not applicable not applicable causal increased acti. Human 44 Breast Cance wild type not applicable affects upregulation correlation increased acti. ABAT enzyme not applicable 212 Breast Cance wild type diagnosis, not ABCB1 transporter affects Human not applicable not applicabl. correlation decreased act. ABCB7 transporter 36 Breast Cance wild type unspecified a. affects Mouse not applicable upregulation correlation increased acti. Breast Cance 36 not applicable affects,decr. not applicabl. ABCC11 transporter homozygou. Human not applicable correlation, ca increased acti. Breast Cance 135 unclassified. not applicable affects not applicable ABCC4 transporter Human not applicable correlation unknown chan. ABCC5 transporter 60 Breast Cance wild type not applicable affects Human not applicable upregulation correlation increased acti. 162 Breast Cance wild type diagnosis affects Human not applicable not applicable correlation increased acti. ABCG2 transporter Breast Cance abiraterone acetate chemical drug 17 wild type not applicable decreases Uncategorized phase III not applicable causal increased acti. 540 Breast Cance wild type not applicable affects Human not applicable downregulation correlation ABL1 kinase decreased act. 2 17 Breast Cance wild type affects Mouse ACAA1 enzyme unspecified a.. not applicable upregulation correlation increased acti. Breast Cance 88 wild type not applicable affects Human not applicable ACACB enzyme upregulation correlation increased acti. 4 ACADVL 53 Breast Cance wild type not applicable affects Mouse not applicable downregulation correlation decreased act. enzyme 7 ACOT9 enzyme Breast Cance wild type not applicable affects Human Other Or not applicable downregulation correlation decreased act. 2 104 Breast Cance wild type ACP5 phosphatase unspecified a... affects Human not applicable upregulation correlation increased acti. other 80 Breast Cance wild type not applicable affects Other Ce not applicable correlation ACTA2 Human upregulation increased acti. 2 Breast Cance Other Or other 7 ACTBL2 heterozygo. not applicable affects Human not applicable not applicable correlation unknown chan. peptidase 140 Breast Cance wild type not applicable affects ADAM12 Human not applicable upregulation correlation increased acti. ADAM15 peptidase 104 Breast Cance wild type not applicable affects Human not applicable upregulation correlation increased acti. ADAM17 peptidase 227 Breast Cance wild type not applicable affects not applicable upregulation correlation increased acti. Human 24 Breast Cance wild type ADAM23 peptidase not applicable affects Human not applicable not applicable correlation increased acti. peptidase 32 Breast Cance wild type not applicable affects upregulation ADAM28 Human not applicable correlation increased acti. ADAM9 peptidase 104 Breast Cance wild type not applicable affects Human not applicable upregulation correlation increased acti.. ADAMTS1 peptidase 156 Breast Cance wild type not applicable affects Human not applicable upregulation. correlation decreased act. 2 ADAMTS10 25 Rreast Cance offorte Human antidace vild two ot annlicable ot applicable lowprogulation correlatio decreased act

Selected/Total molecules : 0 / 1432

Sample to Insight

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Narrowing down to Genes, RNAs and Proteins common to Breast Cancer and EMT: 47 molecules

BioProfiler

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ADD TO MY PATH	IWAY ADD TO MY	LIST 📃 📑									ABL1 - VEGFA	(p1 of 1)	▼ ≪	💿 🧵 More	e I
Molecule	Ad	d column(s) 💽	Disease & Ev	vidence									Ad	d column(s) 💽	Π
A Symbol	Mole 🝸 🔀	Disease 💌	Disease	🝸 🛛 Vuta 🝸 💌	Biom 🝸 💌	Effec 🝸 🕱	Spec 🝸 🕱	Tiss 🝸 💌	Drug 🝸 🔀	Expr 🝸 🔀	Caus 🝸 🕱	Mole	r 🗙	Findings 🗙	Ī
ABL1	kinase	539	Breast Canc	Search for a disease	e or runction								act	5	
AKT1	kinase	896	Breast Can <mark>e</mark>	epithelial-mesench	nymal transition [[EMT]		Searc	h				act	23	
AKT2	kinase	352	Breast Can										act	3	
BMP7	growth factor	469	Breast Cance	onitholial mocon	shumal transitio	archy							ıcti	8	
CAV1	transmembra	766	Breast Cance	/process/develor	omental biology/	n epithelial-mesen	hymal transition					-	act	11	
CD44	enzyme	658	Breast Cance	epithelial-mesen	chymal transitio	on of adenocarci	noma cell lines						ıcti	5	
CDC42	enzyme	526	Breast Cance	/process/develop	omental biology/e	epithelial-mesen	chymal transition,	epithelial-meser	nchymal transitio	on of tumor cell lin	es/epithelial-me	senchym	ıcti	2	
CDH1	other	396	Breast Cance	epithelial-mesen	chymal transitio	on of atrioventri	cular canal cush	lion	eres of embry	unia tianua (dauala	n montal necesso	of atria	act	16	
CTNNB1	transcription r	708	Breast Cance	/process/develop	omental biology/	anithelial_mesen	ocess of lissue/c	levelopmental pr	nchymal transitio	onic ussue/develo	prinental process	or atriov	act	16	
EGFR	kinase	890	Breast Cance	epithelial-mesen	chymal transitio	on of bladder ca	ncer cell lines	epinienai-mesei	nenymar transitio	in or achoventricu	ar canar cusmon	-	act	19	
ERBB3	kinase	336	Breast Cance	•	3333333							•	act	3	
ESR2	ligand-depen	539	Breast Cance	Select term(s) to ac	ld to filter at righ	t			Filter or	n these terms(s)			act	34	
FBLN5	other	94	Breast Cance	🗄 🗀 endocrine	system develop	ment			•	Include any ('OP) 🔘 Include all ('AND')	act	8	
FGF1	growth factor	306	Breast Can e	🗉 🕮 entry into	differentiation of	cells					_		ıcti	3	
FGFR2	kinase	544	Breast Can	🕀 🗀 epithelial-	-mesenchymal tra	ansition			В	reast Cancer and	Tumors		act	24	
► FOXC2	transcription r	244	Breast Cane	🕀 🗀 fate deter	mination of cells				e e	pitnellal-mesencr	iymai transition		ıcti	3	
►FOXO1	transcription r	401	Breast Cance	🕀 🗀 glandular	development								ıcti	2	
FTH1	enzyme	97	Breast Cance	🕀 🗀 hematopo	biesis				<				ıcti	3	
►HEY2	transcription r	138	Breast Cance	initiation o	of differentiation (of cells							act	3	
►HGF	growth factor	924	Breast Cance	Integumen Integumen	system developr	elopment			Ex	clude (logical NO	T)		ıcti	2	
►HIF1A	transcription r	523	Breast Cance	H mornhoge	system develop	nent							ıcti	5	
HMGA2	enzyme	187	Breast Cance	muscle de	velopment								ıcti	4	
HRAS	enzyme	809	Breast Cance	🕀 🗀 onset of d	lifferentiation of o	ells							ıcti	17	
▶IGF1R	transmembra	454	Breast Cance	🕀 🗀 reproduct	tive system devel	opment			<				ıcti	4	1
►KLF8	other	18	Breast Cance	🕀 🗀 respirator	y system develop	oment			-				ıcti	7	
► KRAS	enzyme	665	Breast Cance					L					ıcti	10	
MCAM	other	102	Breast Cance	include disease	phenotype assoc	ciation					Apply	Cancel	ıcti	3	
MST1R	kinase	133	Breast Cance	··· wild type	not applicable	affects,increa	Human	Other Cells	not applicable	not applicable	. correlation,ca	increased	acti	3	1
►NFATC1	transcription r	215	Breast Cance	wild type	not applicable	affects,increa	Mouse,Uncate		not applicable	not applicable	causal	increased	acti	2	
▶NOTCH1	transcription r	539	Breast Cance	homozygous,	not applicable	affects, increa	Mouse	Heart,Mamma	not applicable	not applicable	causal	decreased	act	4	-
NOTCH2	transcription r	264	Breast Cance	homozygous,	disease progr	affects, increa	Mouse,Human		not applicable	not applicable	correlation, ca	decreased	l act	4	
Selected/Tota	l molecules : 1 / 4	47		I	1.	l	1	l		· · · ·		1.			

Sample to Insight —

QIAGEN

EMT-Breast Cancer molecules: Filter down further on molecules testable for therapeutic purposes: with interest in specific criteria and combining with previous Upstream Regulators Analysis: 17 molecules

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	1	2		3				4		
BioProfiler										# d 🛛
ADD TO MY PATH	AY ADD TO MY I						All Pa	es	_ ≪ ≫	🔝 More Info
Molecule	Add column(s) 💽	Disease, Phen	typ	& Evidence						
🔨 Symbol	Molecul 🝸 [Molecul 🝸	×	Effe 🝸	۲	Disease 🝸 M 🍸 🐹 Bio	omarker Appl 🝸 💌	S 🝸 💌	Drug t 🝸 🔀	Express 🝸
▶BMP7	growth factor	increased activ	y	affects		Breast Cancer and Tumors; wild type not	applicable	Human	not applicable	not applicable,
CAV1	transmembrane .	. increased activ	y	affects, increa		Breast Cancer and Tumors; wild type not	applicable	Human	not applicable	not applicable.
CD44	enzyme	increased activ	y	affects, increa		Breast Cancer and Tumors; wild type diag	gnosis,not applicable,.	Human	not applicable	not applicable,
CTNNB1	transcription reg.	. increased activ	y	affects		Breast Cancer and Tumors; wild type dise	ease progression,not	Human	not applicable	not applicable
EGFR	kinase	increased activ	y.	affects, increa		Breast Cancer and Tumors; wild type diag	gnosis,not applicable	Human	not applicable	not applicable,
FOXC2	transcription reg.	. increased activ	y	affects, increa		Breast Cancer and Tumors; wild type not	applicable	Human	not applicable	not applicable,
FOX01	transcription reg.	. increased activ	y	affects, increa		Breast Cancer and Tumors; wild type not	applicable,prognosis	Human	not applicable	not applicable
►HIF1A	transcription reg.	. increased activ	y	affects		Breast Cancer and Tumors; wild type not	applicable,prognosis	Human	not applicable	not applicable,
HMGA2	enzyme	increased activ	y	affects		Breast Cancer and Tumors; wild type not	applicable,prognosis	Human	not applicable	not applicable
▶IGF1R	transmembrane .	. increased activ	y	affects		Breast Cancer and Tumors; wild type diag	gnosis,not applicable	Human	not applicable	not applicable
►KLF8	other	increased activ	y	affects, increa		Breast Cancer and Tumors; wild type not	applicable	Human	not applicable	not applicable,
► MCAM	other	increased activ	y	affects, increa		Breast Cancer and Tumors; wild type diag	gnosis,not applicable	Human	not applicable	not applicable
MST1R	kinase	increased activ	y	affects, increa		Breast Cancer and Tumors; wild type not	applicable	Human	not applicable	not applicable,
SNAI2	transcription reg.	. increased activ	y	affects		Breast Cancer and Tumors; wild type dise	ease progression,not	Human	not applicable	not applicable
►TGFB1	growth factor	increased activ	y	affects, increa		Breast Cancer and Tumors; wild type dise	ease progression,not	Human	not applicable	not applicable
►TGFBR1	kinase	increased activ	y	affects		Breast Cancer and Tumors; wild type dise	ease progression,not	Human	not applicable	not applicable
►TP63	transcription reg.	. increased activ	y	affects, increa		Breast Cancer and Tumors; wild type not	applicable, prognosis	Human	not applicable	not applicable,

Sample to Insight



Upstream Regulator Analysis indicated the predicted activated regulators in the dataset: 114 UR (Z-score > 2)

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Cla	udin vs Luminal new	-2013-03-31 12:48	PM				- k 6
Su	mmary \ Functions \ Ca	nonical Pathways Ups	tream Analysis \ Netwo	rks \ Molecules \ Lists	\ My Pathways \		
Up	stream Regulators \ C	ausal Networks \					
		D TO MIT LIST COSTOM		MECHANIST			
	Upstream Regulator	Fold Change	Molecule Type	Predicted Activation	Activation z-score	p-value of overlap	Target molecules in Mechanistic Netw
	FZ	T 3.652	peptidase	Activated	4.671	1.09E-06	
		+-4.469	cytokine	Activated	4.492	1.18E-01	*ACE, *Aall 225
	SKF	T 1.483	transcription regulato	Activated	4.146	1.37E-01	
	ERK		group	Activated	3.712	6.90E-03	↑ACIN1, ↓all 42 609 (13)
✓	Vegf		group	Activated	3.698	4.60E-04	ADAMIS,all 73 766 (16)
•	SYVN1	+-2.290	transporter	Activated	3.667	9.72E-05	↑ABCC4, ↑all 36 481 (7)
✓	TGFB1	† 8.019	growth factor	Activated	3.618	9.30E-09	↑ABCE1, ▶all 302 824 (12)
✓	IL1B	† 437.671	cytokine	Activated	3.595	1.00E00	+ACPP, +all 103
✓	RHOA	† 2.137	enzyme	Activated	3.538	1.24E-01	↑ACTA1, ↑all 14
✓	SNAI1	† 1.041	transcription regulato	Activated	3.467	2.46E-04	+ADIPOQ, +all 16
~	TBX2	↓-19.612	transcription regulato	Activated	3.464	2.79E-01	↑ANLN, +Call 13
•	MKL1	+-1.728	transcription regulato	Activated	3.450	4.13E-01	↑ACTA1, ↑all 16
✓	Mek		group	Activated	3.440	4.12E-04	↑ABCE1, ↑all 34 624 (13)
~	FN1	† 43.582	enzyme	Activated	3.354	3.31E-02	↓ACE, ↑BIRC3all 28
•	P38 MAPK		group	Activated	3.246	1.00E00	↑ANXA5, ↓all 40
✓	FGF2	† 192.766	growth factor	Activated	3.232	3.28E-03	↓ACE, ↑AGall 63 628 (13)
•	EDN1	↓ -1.766	cytokine	Activated	3.191	3.52E-03	↑ACTB, ↑Aall 39 597 (12)
•	HGF	† 9.788	growth factor	Activated	3.173	1.19E-05	+ABCB4, ►all 104 587 (13)
~	ANXA7	↓ -1.436	ion channel	Activated	3,162	5.43E-01	+ALOX15, Fall 10
	REL	+-4.076	transcription regulato	Activated	3.085	4.67E-01	↑AHR, ↑B2Mall 19
	VEGFA	† 1.787	growth factor	Activated	3.056	1.47E-01	↓ACE, ↓ADall 37
	Ap1		complex	Activated	3.038	1.00E00	+ACE, ↑BAK1all 19
	NRG1	† 33.641	growth factor	Activated	2 987	8.93E-02	↑ACTN1, ↓ARall 32
	МАРКЗ	+-3.752	kinase	Activated	2.975	3.41E-01	↑CTNNB1, F.,all 10
	NUPR1	+-3,449	transcription regulato	Activated	2 946	3.99E-04	↑ABL2, ↓Aall 96 159 (3)
	PDGF BB		complex	Activated	2 909	6.67E-02	↑ACAT2, ↓all 54
	TRAF6	+-1.444	enzyme	Activated	2 903	5.50E-02	↑BIRC3, ↑all 12
m	ple to Insight	1.1.1.1	COLTING .		17 - 711 3	5.502 02	



			<u>0</u> '	×
	Entities to Compare			
	UR 114 molecules activated			
1	lev bioprofiler filtered 17 molecules			
		1	NIOL	
			NIQU	
	Entities Comparison Results			
	Nodes common in all Entity (2)			
	Nodes common in all Endey (2)			
	EGFR			-1
	I GFB1			-1



Exploring the EMT molecules involved in breast cancer.

 Focusing on the Upstream Regulators predicted to be activated in the dataset to explore which ones if any would be of interest for therapeutic purposes. 2: EGFR, TGFB1

Do any of these molecules of interest have biomarker application in breast cancer ?

- EGFR: diagnosis
- TGFB1: disease progression



BioProfiler										
ADD TO MY PATH	WAY ADD TO MY LIST	2					All	Pages	- « »	i More Inf
Molecule	Add column(s) 💽	Disease, Phenotyp	e & Evidence				\sim			
🛆 Symbol	Molecul 🝸 🔀	Molecul 👅 🔀	Effe 🝸 🔀	Disease	T	M 🝸 🔀	Biomarker Appl 🝸	🕅 S 🔳 💌	Drug t 🝸 🔀	Express
►CD44	enzyme	increased activity	affects,increa	Breast Cancer and	Tumors;	wild type	diagnosis,disease prog	r Human	not applicable	not applical
CTNNR1	transcription reg	increased activity	affects	Breast Cancer and	Tumors:	wild type	disease progression no	t Human	not applicable	not applicat
►EGFR	kinase	increased activity	affects,increa	Breast Cancer and	Tumors;	wild type	diagnosis,not applicab	e, Human	not applicable	not applica
►HIF1A	transcription reg	increased activity	affects	Breast Cancer and	Tumors;	wild type	not applicable,prognos	is Human	not applicable	not applica
►IGF1R	transmembrane	increased activity	affects	Breast Cancer and	Tumors;	wild type	diagnosis,not applicab	e, Human	not applicable	not applical
►TGFBR1	kinase	increased activity	affects	Breast Cancer and	Tumors; .	wild type	disease progression,no	t Human	not applicable	not applical
►TP63	transcription reg	increased activity	affects,increa	Breast Cancer and	Tumors;	wild type	diagnosis,not applicab	e, Human	not applicable	not applical



Ingenuity pathway search



Genes and Chemicals Functions and Diseases	Pathways and Tox Lists	
cancer]		<u>S</u> EARCH
Bladder Cancer Signaling	Signaling Pathway	
Ovarian Cancer Signaling	Signaling Pathway	
Thyroid Cancer Signaling	Signaling Pathway	
Breast Cancer Regulation by Stathmin1	Signaling Pathway	
Colorectal Cancer Metastasis Signaling	Signaling Pathway	
Endometrial Cancer Signaling	Signaling Pathway	
Estrogen-Dependent Breast Cancer Signaling	Signaling Pathway	
HER-2 Signaling in Breast Cancer	Signaling Pathway	
Hereditary Breast Cancer Signaling	Signaling Pathway	
Molecular Mechanisms of Cancer	Signaling Pathway	
Auto-complete list:	s matching pathway and toxicity list names	
Use of auto-complete is	optional, you can simply type and click Search	

Se	arch 👸				4° 🛛 🖂
A	dd to f	ATHWAY ADD TO LIST CUSTOMIZE TAB	LE 🛛 📑		
The	e search f	or O∨arian Cancer Signaling matched 1 pathways and	tox lists.		
	∠ #	Name	Action	Group	Pathway Category
	1	Ovarian Cancer Signaling	View Report Open Pathway	Signaling path	Cancer, Disease-Specific Pathways

Most common workflow will be to open pathway after search



Understanding Canonical Pathways



- Canonical pathways are constructed, curated, IPA pathway diagrams for well established signaling and metabolic pathways
 - □ Vary in size
 - □ May contain one or more pathway branches or paths
 - Shows the canonical pathway in a large context
- Canonical Pathways can be modified and saved
 - □ Genes and molecules can be added or removed
 - □ Can be converted to Path Designer
- Canonical pathways show you both key biological and molecular roles of proteins and chemicals of interest.



Gene View: MMP7 (Man	nmalian) > Neighborhood Explorer								
Review the categorized literatu	re Findings and database information for this node.								
Summary Human Mouse Ra	at								
Member Of: Mmp									
Entrez Gene Name:	matrix metallopeptidase 7 (matrilysin, uterine)								
Synonym(s):	MAT, MATRILYSIN, MPMM, MPSL1, PUMP-1								
Source Id:									
Protein Family, Domain:	catalytic domain, DNA binding, matrilysin, metalloendopeptidase, peptidase								
Subcellular Location:	apical cell surfaces, apical membrane, cell surface, Cytoplasm, endothelial basement membrane, Extracellular Space, granules								
Canonical Pathway:	Bladder Cancer Signaling; Colorectal Cancer Metastasis Signaling; HIF1α Signaling; Leukocyte Extravasation Signaling; Ovarian Cancer Signaling; Wnt/β-catenin Signaling								
Teo Findings from Inconvi	the Knowladza Raca (above all 1107 estagarized literatura Findiaga)								
Top Findings from Ingenui									
regulates:	PLG, HBEGF, CDH1, FN1, FASLG, BDNF, TNF, MMP2, ELN, DCN, Collagen Type IV, SPARC, IGFBP5, CTGF, Cryptdin								
regulated by:	TNF, IL1B, CTNNB1, Vegf, Flagellin, PLG, beta-estradiol, Il1, CD40LG, BSG, APC, Integrin, progesterone, Tgf beta, phorbol esters								
binds:	CD44, FASLG, Timp, TIMP2, BCAN, Integrin, A2M, TNFSF11, TIMP3, ELN, Scavenger receptor, TAT, HBEGF, ITGAM, heparan sulfate								
role in cell:	proliferation, apoptosis, invasion, aggregation, migration, growth, invasion by, malignancy, cell movement, invasiveness								
disease:	cancer, neoplasia, arthritis, metastasis, swelling, pulmonary fibrosis, colitis, atherosclerosis, inflammatory disorder, cardiovascular disorder, periodontal disease, cardiac hypertrophy, metaplasia, ovarian cancer, mammary neoplasm, osteoarthritis, prostatic intraepithelial neoplasia, prostatic intraepithelial neoplasm, Budd-Chiari syndrome, aortic stenosis, colon cancer, pancreatic cancer, pancreatic adenocarcinoma, skin cancer, skin neoplasm, Dupuytren contracture, prostate cancer, prostatic carcinoma, fibrosis, endometriosis, hypertension, breast cancer, biliary atresia								
Descriptions from Externa									



anonical Pathways Wnt/β-cateni \ Edit: X K K K K K K K K K K K K K K K K K K
S Wnt/β-cateni \ E elit: C X E: C C C C C C C C C C C C C C C C C C
Edit: 🔉 🗙 🗟 🗅 🖿 🍳 EUILD OVERLAY (PATH DESIGNER) View: 🔀 🛞 🤮 🗐 🗐 Zoom: 🔩 💽 🕼
Wnt/β-catenin Signaling
whit/p-catenin Signation
Dathway Papart
Castave(r(F)(P,VE) NPENNIN_LEPTING COTA
Cytoplann
🤤 🚟 Protein of interest is highlighted.
(ALVE) FYCER (TCF1) (TCF1) (TCF1) (ALVE) (ALVE) (ALVE) (CD44)
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HTML and PDF formats

Reports contain

QIAGEN

- Description
- Top functions
- Molecule list
- Drug Summary
- Target Information
- Link to references

Ovarian Can	athway Report cer Signaling				SYSTEM
Report Date: 2010-05-0 IPA Version: 8.5 (Relea Content Version: 2802	06 ise Date: 2010-02-13) (Release Date: 2010-01-16	;)			Download Report (PDF)
Description:	Ovarian cancer is the mos Ovarian epithelial carcinor endometrioid, clear cell ar	at lethal gynecological canc ma is the most common of ad mucinous. Diverse signa	er today, a predomin the ovarian malignar aling pathways are tri	ant reason for this being an abse ncies. It is classified into histologic iggered depending on the cancer	nce of early detection tests. cal subtypes: serous, subtype.
	The two pathway model h follow one of two pathway gradually from benign cys grade endometrioid and u	as been developed to expl s: Type I tumors that inclu tadenomas and borderline ndifferentiated carcinomas	ain ovarian cancer de ide low-grade serous, lesions to malignant . These tumors devel	evelopment and progression. Acco , mucinous, endometrioid and clea tumors; Type II tumors which inc lop rapidly and almost always inv	ording to this model, tumors of ar cell carcinomas. They evo clude high-grade serous, high olve the peritoneum.
	Mutations that play a signi cancer) and K-Ras, B-Raf, molecules in various DNA involved in a number of or associated with 90% of the with far-reaching consequ in the PIK3CA or PTEN ge and uncontrolled cell grow found in endometrioid ove underlying genetic and mo disease.	ficant role in pathogenesis PIK3CA, CTNNB1, PTEN a repair pathways. Hence m ther biological processes li reditary ovarian cancers, ences for cell survival and nes leading to elevated ex th. Another important mut rian cancers, leading to in olecular disorders in the dif	of ovarian cancer ind nd p53 (sporadic ova utations in these gen- ke transcriptional reg Activating mutations i angiogenesis. K-Ras pression the PI3K/PTI ation is in the CTINB creased cell adhesion ferent types of ovaria	clude BRCA1, BRCA2, MLH1 and H timin cancer). BRCA1, BRCA2, ML es leads to genomic instability an ulation and ubiquitination. Mutatio in K-Ras and B-Raf lead to actual mutations are found in low grade EN/Akt/mTOR pathway can result 1 gene that is involved in Wnt sig , migration, invasion and metastat an cancer will help in early detect	ASH2 (hereditary ovarian H1 and MSH2 are key is bRCA1 is a min BRCA1 and BRCA2 are ion of the ERK/MAPK pathwa serous carcinomas. Mutatio in malignant transformation naling. This mutation is ofter sis. An understanding of the ion and treatment of the
Signaling Pathway Categories:	Cancer; Disease-Specific	Pathways			
Top Functions &	Cell Cycle; Cancer; Tumo	r Morphology			
Molecules:	1-phosphatidyl-D-myo-inc CD44, CDK4, CDKN2A, C FGF9, Frizzled, FSH, FSHR MTOR, P110, p70 S6k, phy repression, RB1, SRC, Tof	sitol 4,5-bisphosphate, Aki TNNB1, CTNNβ-TCF/LEF, C , GJA1, GSK3B, KRAS, Lh, osphatidylinositol-3,4,5-trip /lef, TP53, Vegf, Wnt	t, APC, APC-AXIN-GS yclin D1/cdk4, Cyclor LHCGR, MAP2K1/2, N shosphate, PI3K, PI3F	SK3β, ARRB1, AXIN1, BCL2, BRAF oxygenase, DVL1L1, E2F1, EDN1, 4LH1, MLH1-MSH2-MSH6-PMS2, M < p85, Pka, PMS2, PTEN, RAD51,	, BRCA1, BRCA2, CCND1, EDNRA, EGF, EGFR, ERK1/2, MP2/9, MMP7, MSH2, MSH6, RAF1, Ras, Rb-E2F transcript
					Back to top
Drug Summary - Over	view of drugs targeting mo	lecules in Canonical Pathw	ау		
Showing 3 of 118 row(s)	of Drug data. (Show All)				
-)-gossypol -aminosalicylic acid		BCL2 PTGS1, PTGS2	inhibitor	Asacol, Asacolitin, Canasa,	chronic B-cell leukemia/Pha II follicular B-cell lymphoma/Phase II large-cell diffuse lymphoma/Phase II active ulcerative
				Claversal, Fisalamine, Lixacol, Mesasal, Pentasa, Rowasa, Salofalk	proctitis/Approved Crohn's disease/Phase III diarrhea/Phase III
eeaminophen		P1051, P1052	innibkor	Adenoi, Adensanii, Adenio, Acci Tap, Acephani, Aceta Elixi, Tap, Acephan, Aceta Elixi, Tap, Acephan, Aceta Elixi, Acetalgin, Actamin, Actimol, Acetalgin, Actamin, Actimol, Anacin, Anacin, Sanafon, Anacin, Anacin-3, Anaflon, Anapap, Anelix, Anhiba, Apacet, Apadon, Apamid, Apamide, APAP, Atasol, Banesin, Bayer Select, Bickie-mol, Butapap, Select, Bickie-mol, Butapap, Clixodyne, Conacetol, Dafalgan, Dalen AP-S, Darvocet, Datin, Dimindol, Dirox, Dispol, Dolene AP-S, Dollarone, Dolene AP-S, Dollarone, Dolene AP-S, Dollarone, Dolene AP-S, Dollarone, Bortad, Exdul, Febridol, Febrili, Cellocatil, Genapap, Genebs, Janupap, Korum, Lestemp, Janupap, Korum, Lestemp, Janupap, Korum, Lestemp, Liquagesic, Liquiprin, Lonarid, Lyteca, Momentum, Multin, NAPA, Napaen, Napap,	Cancer/Phase III fever/Aphase III



- Left-click selects (turns blue)
- Left-click-drag on nodes moves the node

Pathway Navigation

- Right-click hold-and-drag moves your view
- Right-click brings up menu for controlling
- tool tip (mouse-over node pop-up)
- copy/past
- Highlight
- selection

Node shapes indicate a protein's primary function, see Help>Legend

Relationship lines indicate the type of relationship and the mouse-over letter the type of relationship, see Help>Legend





Double-clicking a node brings up the node summary

You can navigate to the Gene/Chem View page by clicking the protein name at the top of the summary window pane.

Double-clicking a relationship line brings up the relationship summary

You can to the literature evidence findings by clicking the "<u>View relationships between:</u>..." link at the top of the summary window pane.

Groups

- Groups are represented by a double outline applicable to any molecule shape. These represent cases where findings use a general gene name to describe a gene class or group of isoforms
- Complexes of different proteins are also given a double outline
 - □ View members by left-click selecting, then right-click>Show Membership



Building Custom pathways



- What other compounds bind my target of interest?
- If I inhibit (LOF) or activate (GOF) a protein (gene), what cellular processes are likely to be affected and how will they change?
 - □ What are the upstream activators or downstream targets of my protein of interest?
 - □ Might there be adverse effects of a drug
 - □ Explain how a loss-of-function mutation results in a disease phenotype
- What proteins might act as good biomarkers for molecular drug effect?



1. Select nodes that you want to operate on

- 2. Click the BUILD button to open the build toolbox
 - Not necessary if the build window pane is already open
- 3. Choose a build tool in the pull-down
- 4. Set tool parameters and filters
 - Highly recommended to use filters
- 5. APPLY



- **Grow**: Adds new molecules and their relationships given the criteria that the user specifies
 - Disease & Functions: Adds nodes representing diseases or biological function/processes based on gene enrichment of pathway genes
- **Path Explorer**: Calculates the "Shortest Path" between 2 molecules or 2 sets of molecules
- **Connect**: Connects molecules given the criteria that the user specifies
- **Trim**: Removes molecules/relationships that meet the criteria that the user specifies
- **Keep**: Keeps molecules/relationships that meet the criteria that the user specifies
- Add Molecule/Relationship: Add a custom molecules or relationship to the current pathway that does not exist in Ingenuity's Knowledge Base as well as ones that already exist



- Adds new molecules and their relationships given the criteria that the user specifies
- Recommend growing to "All molecules" and using relationship, molecule type, or other filters to limit grow
- If specifying "Add max of 'x' molecules":
 - □ Priority is given to those molecules that have a high degree of connectivity
 - Prefers to add molecules that interact with the many molecules on the pathway instead of molecules not on the pathway
 - De-emphasis on "hub" molecules that interact promiscuously with many molecules that are not on the pathway



•Genes (proteins, chemicals) will not be added if already present somewhere on the pathway.

- Know if the molecule you are growing from already connects to others in the pathway using Connect or Path Explore
- •Newly grown out nodes do not automatically CONNECT to other nodes in a pathway.
- Use Connect or Path Explorer after Grow to see these relationships.
- •Protein-Protein (PP) relationships and other binding relationships will be added when growing either upstream, downstream, or both directions.
- Recommend as a separate Grow step.
- •If Grow is used directionally, only the specific directional interactions (edges) will be displayed.
- Select new nodes following Grow and use the connect tool to add all interactions from the Knowledge Base.



🛓 Ingenuit	y Pathway	s Analysis									
<u>F</u> ile <u>E</u> dit	<u>W</u> indow	<u>H</u> elp									
	Gene	s or Chemicals	Functions an	d Dis	sease	Genes ta	rgeted by Drugs	7			
NEW¥	SERPI	NE1								SEARCH	1 Adv
			-	Sea At The	DD TO	PATHWAY for SERPIN	ADD TO LIS	ST CUSTOMIZE TABI	E B		
					∠ #	Symbol	Matched Te	Synonym(s)	Entrez Gene Name	Location	Туре
			C)	SERPIN	E1 SERPINE1	BETA MIGRATING PLA BETA-MIGRATING PLA PAI, PAI-1, PAI1A, Pai1aa, Planh, PLANH1, PLASMINOGEN ACTIV, BATPAI1A	serpin peptidase inhibito clade E (nexin, plasminogen activator inhibitor type 1), member 1	Extracellular	other



Grow Downstream

My Pathways



്മ് 🗵



്മ് My Pathways X 🔞 New My Pathway 1 Edit: 📝 🗳 🗙 🙀 🐄 🛨 🖻 BUILD OVERLAY FATH DESIGNER View: 🔀 💥 🎒 🏭 📒 🧾 Zoom: 🤕 👩 Export: 😂 📑 🖂 Tool: Grow \approx N \mathbf{T} $\mathbf{O} \mathbf{O}$ Molecules Diseases & Functions Θ 8 molecules and 8 relationships were added θ Filter Summary Consider only relationships where (interactions = direct) AND (rel. types = activation OR causation OR chemical-chemical interactions OR... General Settings θ Interactions ✓ Direct Indirect Grow out... All molecules Get max of 10 molecules at a time ...that are Downstream of selected molecules 💌 ...and limit molecules to Use Ingenuity Knowledge Base PLG Use Molecules from Analysis/Dataset/List... Current Analysis/Dataset/List: None selected Change Analysis/Dataset/List + Data Sources All Click in white-space to deselect • + Confidence Level All · Right-click to "Reset Highlight" + Species All 6 Tissues & Cell Lines All + Mutation All 4 . RESET APPLY



<u>E</u> ile <u>E</u> dit <u>W</u> indow <u>H</u> elp		Dr. Gietzen CLOSE SESSION
Genes or Chemicals Functions and Disease Genes to	argeted by Drugs	CEARCH Advand South E
Pathways		sk ⊑k ⊠
🖸 New Pathway 1		
	TH DESIGNER View: 🎇 🐹 🎦 📰 Zoom:	🖽 💽 🕘 🧔 💽 Export: 🍽 📑 🖙 🖴
Tool: Grow		
7 molecules and 7 relationships were added		
Filter Summary		
Consider only relationships where		
(interactions = direct) AND (rel. types = activation OB chemical-chemical interactions		
General Settings	Double-click relationship	Relationship Summary
Interactione	Boable eller relationship	Sew relationships between: SEBPINE1/PLAT
Direct Indirect		
Grow out		Click Add Relationship to create a custom relationship.
All molecules		
Get max of 10 molecules at a time		
that are	PROC (Cludes D6:5624)	
Downstream of selected molecules		
and E-2 and a to		
Use Indenuity Knowledge Base		
Use Molecules from Analysis/Dataset		_
Current Analysis/Dataset: None selected	HLAUH	Ingenuity Relationships
Change Analysis/Dataset		inhibition [14]
		Plasminogen activator inhibitor-1 [SERPINE1]
		increases inhibition of <u>tissue type plasminogen</u>
		activator [PLAT].
💽 Tissues & Cell Lines All 📀		
Biofluids All (?)		
RESET	▲ ▼	QK



eview the information that supports lainText EXPORT REFERENCES	the gene-to-function relationship. Click the plus icon to view the reference information.
	Expand All
genuity Relationships	Click to view citation
ibition [14]	
Plasminogen activator inhibi	tor-1 [SERPINE1] increases inhibition of tissue type plasminogen activator [PLAT].
In a cell-free system, Pai1 [SER	PINE1] protein increases inhibition of single-chain human Tpa [PLAT] protein that involves Fibrinogen.
Plasminogen activator inhibi	tor-1 [SERPINE1] increases inhibition of tPA [PLAT].
P11 [S100A10] protein decre	ases inactivation of human TPA [PLAT] protein that is increased by PAI1 [SERPINE1] protein.
Plasminogen activator inhibi	tor-1 [SERPINE1] increases inactivation of tissue plasminogen activator [PLAT].
Human PAI-1 [SERPINE1] pro	otein increases inhibition of human T-PA [PLAT] protein.
In cytoplasm, SERPINE1 protei	n increases inhibition of PLAT protein.
Plasminogen activator inhibi	tor [SERPINE1] increases inactivation of tissue plasminogen activator [PLAT].
PAI-1 [SERPINE1] protein ind	reases inhibition of T-PA [PLAT] protein.
PAI-1 [SERPINE1] increases	inhibition of t-PA [PLAT].
A protein-protein complex [p TPA [PLAT] protein that is incre	rotein-protein] consisting of cow Annexin2 [ANXA2] and of cow S100a10 decreases inactivation of human eased by PAI1 [SERPINE1] protein.
∃ Plasminogen activator inhibi	tor type 1 [SERPINE1] increases inhibition of tissue-type plasminogen activator [PLAT].
E Plasminogen activator inhibi	tor-1 [SERPINE1] increases inactivation of tissue plasminogen activator [PLAT].
Plasminogen activator inhibi	tor 1 [SERPINE1] increases inhibition of tissue-type plasminogen activator [PLAT].



My Pathways				ት ፬ ⁻ ጀ
🗵 New My Pathway 1 🔪				
📄 🐔 Edit: 🖉 🏈 🗙 🗺		Q BUILD OVERLAY PA	H DESIGNER	View: 🔀 🔣 🌜 👔 🚼 🧮 Zoom: 🙋 👩 Export: 🚳 💷 😂
Tool: Grow				
Molecular Diseases & Functions				
Grow from selected molecules to selecte	d diseases & fi	unctions ?		
Indicate diseases or functions related to	Any T of th	e selected molecules		
indicate diseases of functions related to	Any or th	e selecteu molecules		
Consider all functions				
		Add column(s) \pm		
Diseases and Functions	🛆 р 💌	Molecules 🝸 🕱		
migration of smooth muscle cells	2.99E-14	PLG, HABP2, Pall 7		SERFINE
blister	5.15E-13	PLG, ELANE, PLall 5		
formation of blister	1.01E-12	PLG, ELANE, PLall 4		
proliferation of smooth muscle cells	3.56E-12	PLG, HABP2, ELall 7		
delay in toe-spreading reflex of hindlim	1.23E-11	PLG, PLAU, PLATall 3		
size of glomerular crescent	1.23E-11	PLG, PLAU, PLATall 3		ELANE HABP2
formation of glomerular crescent	1.49E-11	PLG, PLAU, SERall 4		
Thrombosis	4.63E-11	PLG, HABP2, Pall 6		
morphology of zona glomerulosa	4.92E-11	PLG, PLAU, PLATall 3		PLG
fibrinolysis	5.58E-11	PLG, plasminogall 5		
blood clot	7.68E-11	PLG, PROC, plaall 6		
hemostasis	9.50E-11	PLG, PROC, PLall 7		Asminogen activator
proteolysis	1.06E-10	PLG, ELANE, PLall 6		
fibrin clot	1.07E-10	PLG, PLAU, SERall 4		
development of blister	1.23E-10	PLG, PLAUR, PLall 3		Thrombosis
degradation of fibrin clot	2.46E-10	PLG, PLAU, PLATall 3		
Fibrosis	2.47E-10	PLG, PROC, ELall 7		
permeability of blood-brain barrier	3.03E-10	PLG, PROC, SEall 4		
recovery of mice	4.68E-10	PLG, PLAUR, PLall 4	•	Drag disease node to left from center
cell movement of myeloid cells	6.84E-10	PLG, PROC, ELall 7		
growth of atherosclerotic lesion	6.88E-10	PLG, PLAU, SERall 3		
1/340	15 ADE 4A	RES. APPLY		

Sample to Insight







- Analysis/ Dataset: Expression/data values that have been uploaded into IPA
- Drug: Known drugs that target the molecules on pathway
- Function & Disease: Functions and Diseases that overlap
- My List/My pathway: User created lists/pathways saved within IPA that overlap
- Canonical Pathway: Canonical Pathways that overlap
- Biomarkers: Displays the molecules that are known biomarkers for specific Applications and Diseases
- Ingenuity Tox List: Ingenuity created toxicity related lists that overlap
- Highlight: Outline molecules that match specified criteria



Use the drug overlay tool to identify drugs that target proteins on the pathway.

- Labels provide links to Chem Views
- Highlight Mode at bottom of Overlay pane provides easy visualization of drug targets
- Drug summary provides indications and clinical status of drugs that target the pathway

Pathways	ъст. 🔀
😰 New Pathway 1 🔪	
	TH DESIGNER View: 🋞 🐹 🌾 📄 📄 Zoom: 🖽 💽 💽 🧕 🔯 🔯 Export: 🚳 📑 🗠 🖴
Overlay: Drug 🗸	
DRUG SUMMART	
To display drugs labels, select a checkbox from the table.	
Drug Name # Molecules v Target	
nandrolone decan 1 AR	Plasminogen Activator
testosterone enant 1 AB	
bicalutamide 1 AR	
testosterone 1 AR	
spironolactone 1 AR	
estradiol valerate/t 1 AR	
GF1 1 IGF1R	
testosterone propi 1 AR	AR
medroxyprogester 1 AR	SERDINE
argatroban 1 F2	F2
estradiol cypionate 1 AR	
antithrombin alfa 1 F2	
enoxaparin 1 F2	
danazol 1 AB	
stanozolol 1 AB	
lepirudin 1 F2	HNF1A
oxymetholone 1 AB	PROC
dabigatran etexilate 1 F2	
desirudin 1 F2	
✓ drotrecogin alfa 1 SERPINE1	TP53
flutamide 1 AB	Rx: drotrecogin alfa
OSI-906 1 IGF1R	
oxandrolone 1 AB	
testosterone cypio 1 AB	
bivalirudin 1 F2	

✓ Interactive OFF ▼

•

Mode Label



Drug Summary:New Pathway 1

Review the details of drugs associated with a network.

Drug Name 🔺	Targets	Actions	Brand Names	Indications/Status
antithrombin alfa	F2	inhibitor	ATryn	disseminated intravascular coagulation/Phase II thromboembolism/Approved
argatroban	F2	inhibitor	Acova	heparin-induced thrombocytopenia/Approved heparin-induced thrombocytopenia/Phase III heparin-induced thrombocytopenia/Phase III coronary artery disease/Phase II
bicalutamide	AR	antiandrogen	Casodex	prostate cancer/Phase III prostate cancer/Phase III prostate cancer/Phase III prostatic carcinoma/Phase III prostatic carcinoma/Phase III prostatic carcinoma/Phase III prostate cancer/Phase III prostate cancer/Phase III prostatic carcinoma/Approved prostatic carcinoma/Phase II breast cancer/Phase II breast cancer/Phase II prostate cancer/Phase II
bivalirudin	F2	inhibitor	Angiox, Angiomax	heparin-induced thrombocytopenia/Approved hematological disorder/Phase III cardiovascular disorder/Phase III thrombosis/Phase II angioplasty/Approved



Saving a Pathway

Once a pathway is complete, make sure to save it

- 1. Using the save icon in the tool bar if you ar saving a new one
- 2. Using File>Save or File>Save As... if you edit an existing one





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Search and Explore Review



Calculates the "Shortest Path" between 2 molecules or 2 sets of molecules

If 2 molecules/sets don't have specific connections in IPA, Path Explorer will find how many and which molecules can be added to this pathway to create the shortest path

- Shortest Path (n)
- Shortest Path + 1 (n+1)
- Shortest Path + 2 (n+2)





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Tool Bar in Pathway/Network view that contains a variety of functions

- **Save:** Save molecules in the pathway as a graphic or as a list
- **Edit:** Delete, Copy, Paste, Undo, Redo, and Find
- Build: Grow, Path Explorer, Connect, Trim, Keep, and Add Molecules/Relationships
- Overlay: Analyzed Dataset, Molecule Activity Predictor, Drugs, Function & Disease, My List, Canonical Pathway, My Pathway, Ingenuity Tox List, and Highlight
- Path Designer: Make a publish/presentation quality version
- View: Auto Layout, Sub Cellular Layout, View Annotations, and Preference Settings
- Zoom: Overview, Zoom In, Zoom Out, Zoom Selected, Fit to Window, and Magnifying Lens
- **Export:** Image, Data, e-Mail, and Print





Path Explorer: Calculates the "Shortest Path" between 2 molecules or 2 sets of molecules

Connect: Connects molecules given the criteria that the user specifies

Trim: Removes molecules/relationships that meet the criteria that the user specifies

Keep: Keeps molecules/relationships that meet the criteria that the user specifies

Add Molecule/Relationship: Allows adding a custom molecules or relationship to the current pathway that does not exist in Ingenuity's KB as well as ones that already exist



Analysis/ Dataset: Expression/data values that have been uploaded into IPA

Molecule Activity Predictor (MAP): Uses expression or user-defined activation states to predict the activity of neighboring molecules

Drug: Known drugs that target the molecules on pathway

Function & Disease: Functions and Diseases that overlap

My List/My Pathway: User created lists/pathways saved within IPA that overlap

Canonical Pathway: Canonical Pathways that overlap

Biomarkers: Displays the molecules that are known biomarkers for specific Applications and Diseases

Ingenuity Tox List: Ingenuity created toxicity related lists that overlap

Highlight: Outline molecules that match specified criteria