

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₫ | × |
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| 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

| | | | | | | <u> </u> | | | | |
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| 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)

Click ADD TO MY LIST

| 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 | | | |
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| | Entities Comparison Results | | | |
| | Nodes common in all Entity (2) | | | |
| | Nodes common in all Endey (2) | | | |
| | EGFR | | | -1 |
| | I GFB1 | | | -1 |
| | | | | |
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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 |
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| Wnt/β-catenin Signaling |
| whit/p-catenin Signation |
| Dathway Papart |
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| 🤤 🚟 Protein of interest is highlighted. |
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| (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 |
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Grow Downstream

My Pathways



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്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 |
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| 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





| Path D | esigner 👯 | | | | | | | | | | | | | | | | |
|----------|--------------------|------------------|-----------|----------|--------|------------|----------------|------------|----------|----------|------|---|--|----------------------------|------|------|---|
| 😢 Pat | h Designe) | 1 | | | | | | | | | | | | | | | |
| 8 | 📔 Edit: 🗙 | | * 5 | | BUILD | OVERLAY | View: | * 1 | Zoom: | • | 0 | 0 | a, 🞑 | | Ехро | t 🚺 | • |
| Molecule | s Relations | / Line | A Text | Cell Art | Leaend | Background | e Edit Tool | | D | | | |) | | | ▼ 12 | • |
| | Plasminogr PLAT | n Activity | PAU | | | | SP1 | | | FIR | Chem | Group/Co Ligand-dey Peptidase Transmen Unknown ical reagen Relations Relations | Légend mplex/Other pendent Nucl tion Regulate | lear Recept ar aptar | tor | | |
| | | | | | | | 10000 | | | | | | | | | | |


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)





📄 📲 Edit: 📝 🥥 🗙 🙀 🏗 🛨 🖻 🕲 EUILD OVERLAY PATH DESIGNER

View: 🛞 🐹 🌾 📄 📄 Zoom: 🖭 💽 🔍 🔍 🔍 🔍 Export: 🍑 📑 📨 🛋

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