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| --- | --- | --- | --- | --- | --- |
| Ground Truth | | |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| Environmental stress | PAK/RAC | Activation | Environmental stress | PAK/RAC | Activation |
| PAK/RAC | MEKK/NIK | Activation | PAK/RAC | MEKK/NIK | Activation |
| MEKK/NIK | MKK | Activation | MEKK/NIK | MKK | Activation |
| MEKK/NIK | IKK | Activation | MEKK/NIK | IKK | Activation |
| IKK | IκB/NF-κB | Activation | IKK | IκB/NF-κB | Inhibition |
| IκB/NF-κB | IkB Degradation | Activation | IκB/NF-κB | IkB Degradation | Inhibition |
| IκB/NF-κB | NF-κB Translocation | Activation | IκB/NF-κB | NF-κB Translocation | Inhibition |
| NF-κB Translocation | Stress Gene Expression and Regulation | Activation | NF-κB Translocation | Stress Gene Expression and Regulation | Inhibition |
| BSO | γ-GCS | Inhibition | BSO | γ-GCS | Inhibition |
| MKK | p38/RK | Activation | MKK | p38/RK |  |
| p38/RK | MAPKAP-K2 | Activation | p38/RK | MAPKAP-K2 |  |
| MAPKAP-K2 | ARE | Activation | MAPKAP-K2 | ARE |  |
| ARE | Stress Gene Expression and Regulation | Activation | ARE | Stress Gene Expression and Regulation | Activation |
| MAPKAP-K2 | Hsp27 | Activation | MAPKAP-K2 | Hsp27 |  |
| NAC | Cysteine | Activation | NAC | Cysteine |  |
| GSH | Cysteine | Activation | GSH | Cysteine |  |
| Cysteine | GSH | Activation | Cysteine | GSH | Inhibition |
| Hsp27 | Stress Gene Expression and Regulation | Activation | Hsp27 | Stress Gene Expression and Regulation | Inhibition |
| γ-GT | Cysteine | Activation | γ-GT | Cysteine |  |
| NAC | p38/RK | Inhibition | NAC | p38/RK |  |
| NAC | MKK | Inhibition | NAC | MKK |  |
| SB-203580 | p38/RK | Inhibition | SB-203580 | p38/RK |  |
| SB-203580 | MAPKAP-K2 | Inhibition | SB-203580 | MAPKAP-K2 |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | Ligand | Receptor | GEMINI |
| Ligand | Receptor | Activation | Ligand | Ligand-induced degradation | Activation |
| Ligand | Ligand-induced degradation | Activation | Receptor | Internalization | Activation |
| Receptor | Internalization | Activation | Receptor | Activity | Inhibition |
| Receptor | Activity | Activation | Activity | Transcription |  |
| Activity | Transcription | Activation | Receptor | Recycling | Activation |
| Receptor | Recycling | Activation | Constitutive degradation | Receptor | Inhibition |
| Constitutive degradation | Receptor | Inhibition | Internalization | Receptor production | Activation |
| Internalization | Receptor production | Activation | Receptor production | Receptor | Activation |
| Receptor production | Receptor | Activation | Receptor | Activity | Inhibition |
| Receptor | Activity | Activation | Activity | Recycling |  |
| Activity | Recycling | Inhibition | Ligand | Receptor |  |

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| **Ground truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| TCR | ZAP70 | Activation | TCR | ZAP70 | Activation |
| ZAP70 | GADD45α/β | Activation | ZAP70 | GADD45α/β | Activation |
| GADD45α/β | MEKK4 | Activation | GADD45α/β | MEKK4 |  |
| MEKK4 | MKK3/4/6 | Activation | MEKK4 | MKK3/4/6 | *inhibition* |
| MKK3/4/6 | p38 | Activation | MKK3/4/6 | p38 |  |
| p38 | T180/Y182 | Activation | p38 | T180/Y182 | Activation |
| T180/Y182 | Substrates | Activation | T180/Y182 | Substrates | *inhibition* |
| GADD45α | Y323 | Activation | GADD45α | Y323 | *inhibition* |
| Y323 | T180/Y182 | Activation | Y323 | T180/Y182 |  |
| GADD45α | T180/Y182 | *inhibition* | GADD45α | T180/Y182 | Activation |
| GADD45α | Y323 | *inhibition* | GADD45α | Y323 | Activation |
| ZAP70 | Y323 | Activation | ZAP70 | Y323 | Activation |
| CD28 | GADD45α/β | Activation | CD28 | GADD45α/β |  |
| IL-12R or IL-18R | GADD45α/β | Activation | IL-12R or IL-18R | GADD45α/β |  |
| MKKK | MKK | Activation | MKKK | MKK | *inhibition* |
| MKKK | MAPK | Activation | MKKK | MAPK |  |

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| ***Ground truth*** | | |  |  |  |
| ***Starter (gene1)*** | ***Receptor (gene2)*** | ***Relationship*** | ***Starter (gene1)*** | ***Receptor (gene2)*** | GEMINI |
| *CPB, Sepsis, Injury* | *Anterior pituitary* | *Activation* | *CPB, Sepsis, Injury* | *Anterior pituitary* | *Activation* |
| *Anterior pituitary* | *TH2 Immune cells* | *Activation* | *Anterior pituitary* | *TH2 Immune cells* | *Activation* |
| *Anterior pituitary* | *MIF* | *Activation* | *Anterior pituitary* | *MIF* | *inhibition* |
| *MIF* | *CD74* | *Activation* | *MIF* | *CD74* | *inhibition* |
| *CD74* | *Proinflammatory Cytokines Chemokines* | *Activation* | *CD74* | *Proinflammatory Cytokines Chemokines* |  |
| *Proinflammatory Cytokines* | *SIRS* | *Activation* | *Proinflammatory Cytokines* | *SIRS* | *inhibition* |
| *SIRS* | *MODS* | *Activation* | *SIRS* | *MODS* | *inhibition* |
| *IL-10, IL-4* | *TH2 Immune cells* | *inhibition* | *IL-10, IL-4* | *TH2 Immune cells* |  |
| *Cortisol* | *TH1 Immune cells* | *inhibition* | *Cortisol* | *TH1 Immune cells* | *inhibition* |
| *MIF* | *Cortisol* | *inhibition* | *MIF* | *Cortisol* |  |
| *ACTH* | *Cortisol* | *Activation* | *ACTH* | *Cortisol* | *inhibition* |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Innervation | Acetylcholine, Substance P, etc. | Activation | Innervation | Acetylcholine, Substance P, etc. | Activation |
| Innervation | Inflammatory Cells | Activation | Innervation | Inflammatory Cells | Activation |
| Inflammatory Cells | Epithelium | Activation | Inflammatory Cells | Epithelium |  |
| Acetylcholine, Substance P, etc. | Airway Smooth Muscle | Activation | Acetylcholine, Substance P, etc. | Airway Smooth Muscle | Activation |
| Inflammatory Cells | Leukotrienes, Histamines, Cytokines, etc. | Activation | Inflammatory Cells | Leukotrienes, Histamines, Cytokines, etc. | Activation |
| Epithelium | Endothelin, etc. | Activation | Epithelium | Endothelin, etc. | Activation |
| Acetylcholine, Substance P, etc. | Rho/ROCK | Activation | Acetylcholine, Substance P, etc. | Rho/ROCK | *inhibition* |
| Leukotrienes, Histamines, Cytokines, etc | Rho/ROCK | Activation | Leukotrienes, Histamines, Cytokines, etc | Rho/ROCK | *inhibition* |
| Endothelin, etc. | Rho/ROCK | Activation | Endothelin, etc. | Rho/ROCK |  |
| Acetylcholine, Substance P, etc. | Ca2+ | Activation | Acetylcholine, Substance P, etc. | Ca2+ | *inhibition* |
| Leukotrienes, Histamines, Cytokines, etc | Ca2+ | Activation | Leukotrienes, Histamines, Cytokines, etc | Ca2+ |  |
| Endothelin, etc. | Ca2+ | Activation | Endothelin, etc. | Ca2+ | *inhibition* |
| Endothelin, etc. | Airway Smooth Muscle | Activation | Endothelin, etc. | Airway Smooth Muscle |  |
| Ca2+ | Contraction | Activation | Ca2+ | Contraction | *inhibition* |
| Ca2+ | Airway Smooth Muscle | Activation | Ca2+ | Airway Smooth Muscle | *inhibition* |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| IGF-I | IGF-I-R | Activation | IGF-I | IGF-I-R | Activation |
| IGF-I-R | PI3-kinase | Activation | IGF-I-R | PI3-kinase | Activation |
| PI3-kinase | PKB (Akt) | Activation | PI3-kinase | PKB (Akt) | Activation |
| PKB (Akt) | Transcription or Splicing Factors | Activation | PKB (Akt) | Transcription or Splicing Factors | Activation |
| PDGFs | PDGF-R | Activation | PDGFs | PDGF-R | Activation |
| PDGF-R | MEK1 | Activation | PDGF-R | MEK1 | Activation |
| PDGF-R | MKK6 | Activation | PDGF-R | MKK6 | Activation |
| MEK1 | ERK | Activation | MEK1 | ERK |  |
| MKK6 | p38MAPK | Activation | MKK6 | p38MAPK | Inhibition |
| ERK | Transcription or Splicing Factors | Activation | ERK | Transcription or Splicing Factors |  |
| p38MAPK | Transcription or Splicing Factors | Activation | p38MAPK | Transcription or Splicing Factors | Inhibition |
| bFGF or EGF | bFGF-R or EGF-R | Activation | bFGF or EGF | bFGF-R or EGF-R |  |
| bFGF-R or EGF-R | MKK6 | Activation | bFGF-R or EGF-R | MKK6 |  |
| LY294002 | PI3-kinase | Inhibition | LY294002 | PI3-kinase |  |
| Wortmannin | PI3-kinase | Inhibition | Wortmannin | PI3-kinase | Activation |
| PD98059 | MEK1 | Inhibition | PD98059 | MEK1 |  |
| SB203580 | p38MAPK | Inhibition | SB203580 | p38MAPK | Inhibition |
| Transcription or Splicing Factors | Maintaining a differentiated phenotype | Activation | Transcription or Splicing Factors | Maintaining a differentiated phenotype |  |
| Transcription or Splicing Factors | Induction of dedifferentiation | Activation | Transcription or Splicing Factors | Induction of dedifferentiation |  |

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| Ground truth | | |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| VEGF | Endothelial cell proliferation | Activation | VEGF | Endothelial cell proliferation | Activation |
| VEGF | Endothelial cell migration | Activation | VEGF | Endothelial cell migration | Activation |
| VEGF | Increased vascular permeability | Activation | VEGF | Increased vascular permeability | Inhibition |
| VEGF | Endothelial cell survival | Activation | VEGF | Endothelial cell survival | Inhibition |
| VEGF-R | Endothelial cell proliferation | Activation | VEGF-R | Endothelial cell proliferation | Activation |
| VEGF-R | Endothelial cell migration | Activation | VEGF-R | Endothelial cell migration |  |
| VEGF-R | Increased vascular permeability | Activation | VEGF-R | Increased vascular permeability | Inhibition |
| VEGF-R | Endothelial cell survival | Activation | VEGF-R | Endothelial cell survival |  |

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| Ground truth | | |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| EGFR | Ras | Activation | EGFR | Ras | Activation |
| EGFR | PI3K | Activation | EGFR | PI3K | Activation |
| Ras | Raf | Activation | Ras | Raf | Activation |
| Raf | MEK | Activation | Raf | MEK | Activation |
| MEK | ERK | Activation | MEK | ERK |  |
| PI3K | Akt | Activation | PI3K | Akt | Inhibition |
| Akt | mTOR | Activation | Akt | mTOR | Inhibition |
| Cetuximab | EGFR | Inhibition | Cetuximab | EGFR | Inhibition |
| Erlotinib/Gefitinib | EGFR | Inhibition | Erlotinib/Gefitinib | EGFR |  |
| PF-00299804/BIBW2992 | EGFR | Inhibition | PF-00299804/BIBW2992 | EGFR | Activation |
| PF-00299804/BIBW2992 | HER | Inhibition | PF-00299804/BIBW2992 | HER |  |
| Salirasib | Ras | Inhibition | Salirasib | Ras | Activation |
| LY294002 | PI3K | Inhibition | LY294002 | PI3K | Activation |
| BEZ235 | PI3K | Inhibition | BEZ235 | PI3K | Inhibition |
| BEZ235 | mTOR | Inhibition | BEZ235 | mTOR | Activation |
| Rapamycin/RAD001/CCI-779 | mTOR | Inhibition | Rapamycin/RAD001/CCI-779 | mTOR |  |
| Antiangiogenic agents | VEGFR | Inhibition | Antiangiogenic agents | VEGFR | Activation |
| Antiangiogenic agents | PDGFR | Inhibition | Antiangiogenic agents | PDGFR |  |
| Antiangiogenic agents | FGFR | Inhibition | Antiangiogenic agents | FGFR | Activation |

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| Ground Truth | | |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| EGF, TGF-Î±, or other ligands | EGFR or other family members | Activation | EGF, TGF-Î±, or other ligands | EGFR or other family members | Activation |
| EGFR or other family members | PI3K | Activation | EGFR or other family members | PI3K | Activation |
| PI3K | Akt | Activation | PI3K | Akt |  |
| Akt | mTOR | Activation | Akt | mTOR | Activation |
| EGFR or other family members | STAT signaling | Activation | EGFR or other family members | STAT signaling | Activation |
| STAT signaling | Survival | Activation | STAT signaling | Survival |  |
| STAT signaling | Transcription | Activation | STAT signaling | Transcription | Inhibition |
| STAT signaling | Proliferation | Activation | STAT signaling | Proliferation | Inhibition |
| EGFR or other family members | Ras | Activation | EGFR or other family members | Ras | Inhibition |
| Ras | Raf | Activation | Ras | Raf |  |
| Raf | MAPK | Activation | Raf | MAPK | Inhibition |
| MAPK | Proliferation | Activation | MAPK | Proliferation | I |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Integrin | p130Cas | Activation | Integrin | p130Cas | Activation |
| Integrin | Paxillin | Activation | Integrin | Paxillin | Activation |
| p130Cas | Crk | Activation | p130Cas | Crk | Activation |
| Paxillin | Fak | Activation | Paxillin | Fak | Activation |
| Crk | Rac1 | Activation | Crk | Rac1 |  |
| Fak | Rac1 | Activation | Fak | Rac1 | Inhibition |
| Rac1 | Integrin-mediated Cell Motility | Activation | Rac1 | Integrin-mediated Cell Motility |  |
| Integrin | N-Cadherin Adhesion | Activation | Integrin | N-Cadherin Adhesion | Inhibition |
| N-Cadherin | N-Cadherin Adhesion | Activation | N-Cadherin | N-Cadherin Adhesion |  |
| Fak (pY861) | Rac1 | Inhibition | Fak (pY861) | Rac1 | Inhibition |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Agonist | β1-AR | Activation | Agonist | β1-AR | Activation |
| Agonist | β2-AR | Activation | Agonist | β2-AR | Activation |
| β1-AR | Gsα | Activation | β1-AR | Gsα | Activation |
| β2-AR | Gsα | Activation | β2-AR | Gsα | Activation |
| Gsα | Adenylyl cyclase | Activation | Gsα | Adenylyl cyclase | Activation |
| Adenylyl cyclase | cAMP | Activation | Adenylyl cyclase | cAMP | Inhibition |
| cAMP | PKA | Activation | cAMP | PKA | Inhibition |
| PKA | Troponin I-P | Activation | PKA | Troponin I-P | Inhibition |
| PKA | RyR-P | Activation | PKA | RyR-P |  |
| PKA | PLB-P | Activation | PKA | PLB-P | Inhibition |
| PKA | cPLA2 | Activation | PKA | cPLA2 |  |
| Troponin I-P | Increased cardiac contractility and relaxation | Activation | Troponin I-P | Increased cardiac contractility and relaxation | Inhibition |
| RyR-P | Increased cardiac contractility and relaxation | Activation | RyR-P | Increased cardiac contractility and relaxation | Inhibition |
| PLB-P | Increased cardiac contractility and relaxation | Activation | PLB-P | Increased cardiac contractility and relaxation |  |
| cPLA2 | Reduced cardiac contractility | Activation | cPLA2 | Reduced cardiac contractility | Inhibition |
| Ca2+ | L-type Ca2+ channel | Activation | Ca2+ | L-type Ca2+ channel |  |
| Giβ | cAMP | Inhibition | Giβ | cAMP |  |

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| ***Ground truth*** | | |  |  |  |
| ***Starter (gene1)*** | ***Receptor (gene2)*** | ***Relationship*** | ***Starter (gene1)*** | ***Receptor (gene2)*** | GEMINI |
| *EGF* | *MEK1/2* | *Activation* | *EGF* | *MEK1/2* | *Activation* |
| *MEK1/2* | *Erk1/2* | *Activation* | *MEK1/2* | *Erk1/2* |  |
| *Erk1/2* | *RSK1* | *Activation* | *Erk1/2* | *RSK1* |  |
| *IGF-I* | *PI3K* | *Activation* | *IGF-I* | *PI3K* | *Inhibition* |
| *Insulin* | *PI3K* | *Activation* | *Insulin* | *PI3K* | *Inhibition* |
| *PI3K* | *Akt* | *Activation* | *PI3K* | *Akt* |  |
| *Akt* | *TSC2* | *Activation* | *Akt* | *TSC2* | *Activation* |
| *Akt* | *mTOR-RICTOR* | *Activation* | *Akt* | *mTOR-RICTOR* | *Activation* |
| *TSC1* | *Rheb* | *Activation* | *TSC1* | *Rheb* |  |
| *Rheb* | *mTOR-RAPTOR* | *Activation* | *Rheb* | *mTOR-RAPTOR* | *Activation* |
| *mTOR-RAPTOR* | *p70S6K* | *Activation* | *mTOR-RAPTOR* | *p70S6K* | *Activation* |
| *mTOR-RAPTOR* | *4EBP1* | *Inhibition* | *mTOR-RAPTOR* | *4EBP1* | *Inhibition* |
| *Erk1/2* | *TSC2* | *Inhibition* | *Erk1/2* | *TSC2* | *Activation* |
| *TSC2* | *Rheb* | *Inhibition* | *TSC2* | *Rheb* | *Activation* |
| *RSK1* | *TSC2* | *Inhibition* | *RSK1* | *TSC2* | *Activation* |
| *Rapamycin* | *mTOR-RAPTOR* | *Inhibition* | *Rapamycin* | *mTOR-RAPTOR* | *Inhibition* |
| *Ras* | *MEK1/2* | *Activation* | *Ras* | *MEK1/2* | *Activation* |
| *Ras* | *PI3K* | *Activation* | *Ras* | *PI3K* |  |
| *EGF* | *TSC2 (via MEK1/2)* | *Inhibition* | *EGF* | *TSC2 (via MEK1/2)* |  |
| *EGF* | *TSC2 (via Erk1/2)* | *Inhibition* | *EGF* | *TSC2 (via Erk1/2)* |  |

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| **Ground truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| MTX | MTX polyglutamates | Activation | MTX | MTX polyglutamates | Activation |
| MTX polyglutamates | DHFR | Activation | MTX polyglutamates | DHFR | Activation |
| DHFR | FH2 | Activation | DHFR | FH2 | Activation |
| FH2 | 5,10-CH2-THF | Activation | FH2 | 5,10-CH2-THF | Activation |
| 5,10-CH2-THF | 5-CH3-THF | Activation | 5,10-CH2-THF | 5-CH3-THF | Activation |
| 5-CH3-THF | DNA ← dTMP | Activation | 5-CH3-THF | DNA ← dTMP | Activation |
| DNA ← dTMP | dUMP | Activation | DNA ← dTMP | dUMP |  |
| dUMP | TYMS | Activation | dUMP | TYMS | Inhibition |
| TYMS | MTX polyglutamates | Activation | TYMS | MTX polyglutamates |  |
| MTX | Influx SLC19A1 | Activation | MTX | Influx SLC19A1 | Inhibition |
| Influx SLC19A1 | MTX | Activation | Influx SLC19A1 | MTX | Inhibition |
| MTX | Efflux ABCC1-C4/ABCG2 | Activation | MTX | Efflux ABCC1-C4/ABCG2 |  |
| Efflux ABCC1-C4/ABCG2 | MTX | Activation | Efflux ABCC1-C4/ABCG2 | MTX | Inhibition |
| MTX polyglutamates | FPGS | Activation | MTX polyglutamates | FPGS |  |
| FPGS | MTX polyglutamates | Activation | FPGS | MTX polyglutamates | Inhibition |
| MTX polyglutamates | GGH | Activation | MTX polyglutamates | GGH | Inhibition |
| GGH | MTX polyglutamates | Activation | GGH | MTX polyglutamates |  |
| 5-CH3-THF | FH4 | Activation | 5-CH3-THF | FH4 | Inhibition |
| FH4 | ATIC | Activation | FH4 | ATIC | Activation |
| ATIC | Adenosine accumulation | Activation | ATIC | Adenosine accumulation |  |
| Adenosine accumulation | Target cell | Activation | Adenosine accumulation | Target cell | Inhibition |
| Target cell | ADORA 1/2A | Activation | Target cell | ADORA 1/2A | Activation |
| MTX polyglutamates | TYMS | Inhibition | MTX polyglutamates | TYMS | Activation |
| MTX polyglutamates | ATIC | Inhibition | MTX polyglutamates | ATIC | Activation |
| MTHFR | 5,10-CH2-THF | Inhibition | MTHFR | 5,10-CH2-THF |  |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| LPS | TLR4 | Activation | LPS | TLR4 | Activation |
| LBP | TLR4 | Activation | LBP | TLR4 | Activation |
| CD14 | TLR4 | Activation | CD14 | TLR4 | Activation |
| TLR4 | p38 | Activation | TLR4 | p38 | Inhibition |
| TLR4 | Tec Kinases | Activation | TLR4 | Tec Kinases | Inhibition |
| TLR4 | PI3K | Activation | TLR4 | PI3K |  |
| TLR4 | Syk | Activation | TLR4 | Syk | Inhibition |
| p38 | IL-8 | Activation | p38 | IL-8 |  |
| p38 | Cell Adhesion | Activation | p38 | Cell Adhesion | Inhibition |
| p38 | NF-κB | Activation | p38 | NF-κB | Activation |
| Tec Kinases | JNK | Activation | Tec Kinases | JNK | Inhibition |
| PI3K | JNK | Activation | PI3K | JNK | Inhibition |
| Syk | JNK | Activation | Syk | JNK | Activation |
| JNK | Cdc42 | Activation | JNK | Cdc42 | Activation |
| Cdc42 | Actin Assembly | Activation | Cdc42 | Actin Assembly |  |
| Actin Assembly | Neutrophil Migration | Activation | Actin Assembly | Neutrophil Migration |  |
| p38 | TNF-α | Activation | p38 | TNF-α |  |

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| Ground Truth | | |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| Bcr | Abl | Activation | Bcr | Abl | Activation |
| Abl | STAT | Activation | Abl | STAT | Activation |
| Abl | Raf | Activation | Abl | Raf | *inhibition* |
| Abl | PI3k | Activation | Abl | PI3k | *inhibition* |
| STAT | Bcl-xL | Activation | STAT | Bcl-xL |  |
| Bcl-xL | ↓ Apoptosis | Activation | Bcl-xL | ↓ Apoptosis | *inhibition* |
| Raf | ERK | Activation | Raf | ERK |  |
| ERK | Bcl2 | Activation | ERK | Bcl2 | Activation |
| Bcl2 | ↓ Apoptosis | Activation | Bcl2 | ↓ Apoptosis | Activation |
| PI3k | Akt1 | Activation | PI3k | Akt1 | Activation |
| Akt1 | Bad | Activation | Akt1 | Bad | Activation |
| Bad | ↓ Apoptosis | Activation | Bad | ↓ Apoptosis |  |
| Akt1 | FOXO3a | Activation | Akt1 | FOXO3a | *inhibition* |
| FOXO3a | ↓ Apoptosis | Activation | FOXO3a | ↓ Apoptosis |  |
| Akt1 | FOXO3a | *inhibition* | Akt1 | FOXO3a | Activation |
| Akt1 | Bad | *inhibition* | Akt1 | Bad | Activation |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Pathogen | FLS2 | Activation | Pathogen | FLS2 | Inhibition |
| flg22 | FLS2 | Activation | flg22 | FLS2 | Inhibition |
| FLS2 | GPA1 | Activation | FLS2 | GPA1 |  |
| FLS2 | ABA | Activation | FLS2 | ABA | Inhibition |
| ABA | S1P | Activation | ABA | S1P |  |
| S1P | GPA1 | Activation | S1P | GPA1 | Inhibition |
| GPA1 | OST1 | Activation | GPA1 | OST1 | Activation |
| GPA1 | ROS | Activation | GPA1 | ROS | Activation |
| OST1 | ROS | Activation | OST1 | ROS | Activation |
| ROS | NO | Activation | ROS | NO | Activation |
| NO | Intracellular Ca2+ stores | Activation | NO | Intracellular Ca2+ stores | Activation |
| Intracellular Ca2+ stores | CNG2/DND1 channels | Activation | Intracellular Ca2+ stores | CNG2/DND1 channels | Activation |
| Intracellular Ca2+ stores | K+in channels | Activation | Intracellular Ca2+ stores | K+in channels |  |
| Intracellular Ca2+ stores | K+out channels | Activation | Intracellular Ca2+ stores | K+out channels | Activation |
| MPK3 | ROS | Activation | MPK3 | ROS | Activation |
| COR | [pH]cyt | Activation | COR | [pH]cyt | Activation |
| ROS | K+in channels | Inhibition | ROS | K+in channels | Activation |
| ROS | K+out channels | Inhibition | ROS | K+out channels |  |
| NO | K+in channels | Inhibition | NO | K+in channels | Activation |
| NO | K+out channels | Inhibition | NO | K+out channels |  |
| COR | K+in channels | Activation | COR | K+in channels | Activation |
| COR | K+out channels | Inhibition | COR | K+out channels | Activation |
| ROS | CNG2/DND1 channels | Activation | ROS | CNG2/DND1 channels | Activation |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| PTEN | PI3K | Activation | PTEN | PI3K | Inhibition |
| PI3K | PDK1 | Activation | PI3K | PDK1 | Inhibition |
| PDK1 | AKT/PKB (T308) | Activation | PDK1 | AKT/PKB (T308) | Inhibition |
| AKT/PKB | TSC1/2 (S478) | Activation | AKT/PKB | TSC1/2 (S478) | Inhibition |
| TSC1/2 | Rheb | Activation | TSC1/2 | Rheb | Inhibition |
| Rheb | mTOR | Activation | Rheb | mTOR |  |
| mTOR | 4E-BP1 | Activation | mTOR | 4E-BP1 | Inhibition |
| mTOR | S6K | Activation | mTOR | S6K |  |
| 4E-BP1 | ribosome biogenesis | Activation | 4E-BP1 | ribosome biogenesis | Inhibition |
| S6K | Translation | Activation | S6K | Translation | Activation |
| mTOR | DEPTOR | Activation | mTOR | DEPTOR | Activation |
| mTOR | Raptor | Activation | mTOR | Raptor | Activation |
| mTOR | PRAS40 | Activation | mTOR | PRAS40 |  |
| mTOR | mLST8 | Activation | mTOR | mLST8 | Inhibition |
| mTOR | DEPTOR | Activation | mTOR | DEPTOR | Activation |
| mTOR | PRR5/5L | Activation | mTOR | PRR5/5L |  |
| mTOR | RicTOR | Activation | mTOR | RicTOR |  |
| RTKs | PI3K | Activation | RTKs | PI3K | Activation |
| IRS-1 | PI3K | Activation | IRS-1 | PI3K | Activation |
| LKB1 | AMPK | Activation | LKB1 | AMPK |  |
| AMPK | TSC1/2 | Activation | AMPK | TSC1/2 | Activation |
| Hypoxia | HIF1α | Activation | Hypoxia | HIF1α |  |
| RAG | mTOR | Activation | RAG | mTOR | Activation |
| Amino acids | mTOR | Activation | Amino acids | mTOR | Activation |
| Stress | mTOR | Inhibition | Stress | mTOR | Activation |
| P53 | TSC1/2 | Inhibition | P53 | TSC1/2 |  |
| TSC1/2 | Rheb | Inhibition | TSC1/2 | Rheb | Activation |
| PRAS40 | mTOR | Inhibition | PRAS40 | mTOR | Activation |
| DEPTOR | mTOR | Inhibition | DEPTOR | mTOR |  |
| S6K | IRS-1 | Inhibition | S6K | IRS-1 | Activation |
| Insulin, growth factors, hormones | IRS-1 | Activation | Insulin, growth factors, hormones | IRS-1 | Activation |
| P53 | Energy | Activation | P53 | Energy | Activation |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Receptor tyrosine kinase (ALK, Trk, IGF1R) | PI3K | Activation | Receptor tyrosine kinase (ALK, Trk, IGF1R) | PI3K | Inhibition |
| PI3K | PDK1 (S473) | Activation | PI3K | PDK1 (S473) | Inhibition |
| PDK1 | AKT (T308) | Activation | PDK1 | AKT (T308) |  |
| AKT | mTORC1 | Activation | AKT | mTORC1 | Inhibition |
| AKT | GSK3β | Activation | AKT | GSK3β | Inhibition |
| AKT | Mycn (S62) | Activation | AKT | Mycn (S62) | Activation |
| GSK3β | CDK1 | Activation | GSK3β | CDK1 | Activation |
| mTORC1 | S6K | Activation | mTORC1 | S6K | Inhibition |
| mTORC1 | 4EBP | Activation | mTORC1 | 4EBP | Inhibition |
| S6K | Translational Control | Activation | S6K | Translational Control | Activation |
| 4EBP | Translational Control | Activation | 4EBP | Translational Control | Activation |
| mTORC1 | mTORC2 (PDK2) | Activation | mTORC1 | mTORC2 (PDK2) |  |
| mTORC2 | AKT | Activation | mTORC2 | AKT | Activation |
| mTORC1 | Raptor | Activation | mTORC1 | Raptor | Activation |
| Raptor | mTORC1 | Activation | Raptor | mTORC1 | Activation |
| Mycn (S62) | Induction of Mycn downstream target genes | Activation | Mycn (S62) | Induction of Mycn downstream target genes |  |
| CDK1 | Cyclin B | Activation | CDK1 | Cyclin B | Activation |
| CDK1/Cyclin B | Mycn (T58) | Activation | CDK1/Cyclin B | Mycn (T58) | Activation |
| PP2A | Mycn (T58) | Inhibition | PP2A | Mycn (T58) |  |
| Fbw7 | Mycn (T58) | Inhibition | Fbw7 | Mycn (T58) | Inhibition |
| Mycn (unstable) | Mycn (T58) | Inhibition | Mycn (unstable) | Mycn (T58) |  |
| AKT inhibitors | AKT | Inhibition | AKT inhibitors | AKT | Activation |
| CDK inhibitors | CDK1 | Inhibition | CDK inhibitors | CDK1 | Activation |
| mTOR inhibitors | mTOR | Inhibition | mTOR inhibitors | mTOR |  |
| mTORC1 allosteric inhibitors | mTORC1 | Inhibition | mTORC1 allosteric inhibitors | mTORC1 | Inhibition |
| PI3K inhibitors | PI3K | Activation | PI3K inhibitors | PI3K |  |
| PDK inhibitors | PDK1 | Activation | PDK inhibitors | PDK1 | Inhibition |

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| --- | --- | --- | --- | --- | --- |
| Ground truth | | |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| IGF1 | IGF1R | Activation | IGF1 | IGF1R | Activation |
| IGF2 | IGF1R | Activation | IGF2 | IGF1R | Activation |
| IGFBP5 | IGF1R | Activation | IGFBP5 | IGF1R |  |
| IGF1R | IRS1/2/4 | Activation | IGF1R | IRS1/2/4 | Inhibition |
| IRS1/2/4 | PI3K/AKT/mTOR pathway | Activation | IRS1/2/4 | PI3K/AKT/mTOR pathway |  |
| IRS1/2/4 | RAS/MAPK/ERK pathway | Activation | IRS1/2/4 | RAS/MAPK/ERK pathway | Inhibition |
| PI3K/AKT/mTOR pathway | Protein translation/Proliferation/Cell Survival | Activation | PI3K/AKT/mTOR pathway | Protein translation/Proliferation/Cell Survival | Inhibition |
| RAS/MAPK/ERK pathway | Protein translation/Proliferation/Cell Survival | Activation | RAS/MAPK/ERK pathway | Protein translation/Proliferation/Cell Survival |  |
| IGF2R | IGF2 | Inhibition | IGF2R | IGF2 | Activation |
| IGFBP1/3 | IGF1 | Inhibition | IGFBP1/3 | IGF1 | Activation |
| IGFBP1/3 | IGF2 | Inhibition | IGFBP1/3 | IGF2 | Activation |
| IGFBP5 | IGF2 | Activation | IGFBP5 | IGF2 | Activation |
| IGFBP5 | IGF1 | Activation | IGFBP5 | IGF1 | Activation |

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| --- | --- | --- | --- | --- | --- |
| Ground Truth | | |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| Growth factors | PI3K | Activation | Growth factors | PI3K | Activation |
| PI3K | AKT | Activation | PI3K | AKT | Activation |
| AKT | mTORC1 | Activation | AKT | mTORC1 |  |
| Hypoxia | REDD1 | Activation | Hypoxia | REDD1 | Activation |
| REDD1 | TSC1/2 | Activation | REDD1 | TSC1/2 | *Inhibition* |
| Bioenergy (↑AMP/ATP) | AMPK | Activation | Bioenergy (↑AMP/ATP) | AMPK |  |
| AMPK | TSC1/2 | Activation | AMPK | TSC1/2 | *Inhibition* |
| Genotoxic stress | p53 | Activation | Genotoxic stress | p53 | *Inhibition* |
| p53 | AMPK | Activation | p53 | AMPK |  |
| Sestrins1,2 | AMPK | Activation | Sestrins1,2 | AMPK | *Inhibition* |
| Amino acids | RagA/RagC | Activation | Amino acids | RagA/RagC |  |
| RagA/RagC | mTORC1 | Activation | RagA/RagC | mTORC1 | *Inhibition* |
| TSC1/2 | Rheb | Activation | TSC1/2 | Rheb | Activation |
| Rheb | mTORC1 | Activation | Rheb | mTORC1 | Activation |
| mTORC1 | Cell growth, survival & proliferation | Activation | mTORC1 | Cell growth, survival & proliferation | Activation |
| AKT | TSC1/2 | *Inhibition* | AKT | TSC1/2 | Activation |

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| --- | --- | --- | --- | --- | --- |
| ***Starter (gene1)*** | ***Receptor (gene2)*** | ***Relationship*** | ***Starter (gene1)*** | ***Receptor (gene2)*** | GEMINI |
| *UVB* | *PI3-K* | *Activation* | *UVB* | *PI3-K* | *Inhibition* |
| *UVB* | *p38* | *Activation* | *UVB* | *p38* | *Inhibition* |
| *p38* | *CREB* | *Activation* | *p38* | *CREB* | *Activation* |
| *PI3-K* | *Akt* | *Activation* | *PI3-K* | *Akt* | *Activation* |
| *Akt* | *mTOR* | *Activation* | *Akt* | *mTOR* | *Activation* |
| *mTOR* | *4E-BP1* | *Activation* | *mTOR* | *4E-BP1* | *Activation* |
| *mTOR* | *p70S6K* | *Activation* | *mTOR* | *p70S6K* | *Activation* |
| *mTOR* | *4E-BP1* | *Inhibition* | *mTOR* | *4E-BP1* |  |
| *4E-BP1* | *Translation complex* | *Inhibition* | *4E-BP1* | *Translation complex* | *Activation* |
| *p70S6K* | *Translation complex* | *Activation* | *p70S6K* | *Translation complex* | *Activation* |
| *Translation complex* | *c-Fos protein* | *Activation* | *Translation complex* | *c-Fos protein* |  |
| *c-Fos protein* | *c-Fos mRNA* | *Activation* | *c-Fos protein* | *c-Fos mRNA* | *Inhibition* |
| *c-Fos mRNA* | *CREB* | *Activation* | *c-Fos mRNA* | *CREB* | *Activation* |
| *AA* | *mRNA stability* | *Activation* | *AA* | *mRNA stability* | *Activation* |
| *Qu* | *PI3-K* | *Inhibition* | *Qu* | *PI3-K* | *Inhibition* |
| *Qu+AA* | *p38* | *Inhibition* | *Qu+AA* | *p38* |  |
| *Qu+AA* | *PI3-K* | *Inhibition* | *Qu+AA* | *PI3-K* |  |
| *Qu* | *p38* | *Activation* | *Qu* | *p38* |  |

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| *Ground Truth* | | |  |  |  |
| *Starter (gene1)* | *Receptor (gene2)* | *Relationship* | *Starter (gene1)* | *Receptor (gene2)* | GEMINI |
| *17-β estradiol* | *ERα/β* | *Activation* | *17-β estradiol* | *ERα/β* | *Activation* |
| *EGFR* | *GRB2* | *Activation* | *EGFR* | *GRB2* | *Activation* |
| *GRB2* | *SOS* | *Activation* | *GRB2* | *SOS* | *Activation* |
| *SOS* | *RAS* | *Activation* | *SOS* | *RAS* |  |
| *RAS* | *RAF* | *Activation* | *RAS* | *RAF* | *Activation* |
| *RAF* | *MEK* | *Activation* | *RAF* | *MEK* |  |
| *MEK* | *ERK* | *Activation* | *MEK* | *ERK* | *Inhibition* |
| *ERK* | *Coactivator* | *Activation* | *ERK* | *Coactivator* |  |
| *ERK* | *ERβ-ERβ homodimer* | *Activation* | *ERK* | *ERβ-ERβ homodimer* | *Inhibition* |
| *Coactivator* | *GRIP1* | *Activation* | *Coactivator* | *GRIP1* | *Inhibition* |
| *GRIP1* | *ERE* | *Activation* | *GRIP1* | *ERE* |  |
| *ERβ-ERβ homodimer* | *Cell growth/DNA synthesis* | *Activation* | *ERβ-ERβ homodimer* | *Cell growth/DNA synthesis* | *Inhibition* |
| *Fulvestrant* | *ERα/β* | *Inhibition* | *Fulvestrant* | *ERα/β* | *Inhibition* |
| *HSP90* | *ERα/β (inactive)* | *Inhibition* | *HSP90* | *ERα/β (inactive)* | *Inhibition* |
| *ERK* | *GRIP1* | *Activation* | *ERK* | *GRIP1* | *Inhibition* |
| *ERK* | *ERE* | *Activation* | *ERK* | *ERE* |  |
| **Ground truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| PBX1, EMX2, CBX2, LHX9 | Genital ridge | Activation | PBX1, EMX2, CBX2, LHX9 | Genital ridge | Activation |
| WT1, NR5A1 | Genital ridge | Activation | WT1, NR5A1 | Genital ridge | Activation |
| Genital ridge | WNT4 | Activation | Genital ridge | WNT4 |  |
| WNT4/RSPO1 | β-catenin | Activation | WNT4/RSPO1 | β-catenin | Inhibition |
| β-catenin | SOX9 | Activation | β-catenin | SOX9 |  |
| SOX9 | FOXL2 | Activation | SOX9 | FOXL2 |  |
| FOXL2 | Steroidogenesis (Ovary) | Activation | FOXL2 | Steroidogenesis (Ovary) | Inhibition |
| Genital ridge | SRY | Activation | Genital ridge | SRY | Inhibition |
| SRY | SOX9 | Activation | SRY | SOX9 | Activation |
| SOX9 | AMH | Activation | SOX9 | AMH |  |
| SOX9 | FOXL2 | Activation | SOX9 | FOXL2 | Inhibition |
| AMH | DHH | Activation | AMH | DHH | Activation |
| DHH | NR5A1 | Activation | DHH | NR5A1 | Inhibition |
| NR5A1 | Steroidogenesis (Testis) | Activation | NR5A1 | Steroidogenesis (Testis) |  |
| Genital ridge | FOXL2 | Activation | Genital ridge | FOXL2 | Activation |
| FOXL2 | SOX9 | Inhibition | FOXL2 | SOX9 | Inhibition |
| FOXL2 | SOX9 (Testis) | Inhibition | FOXL2 | SOX9 (Testis) | Inhibition |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| HRS cell | ↑ IL-10, TARC, MDC (CCL22), CCL5 | Activation | HRS cell | ↑ IL-10, TARC, MDC (CCL22), CCL5 | Activation |
| HRS cell | PD1-L | Activation | HRS cell | PD1-L | Activation |
| PD1-L | PD1+ T | Activation | PD1-L | PD1+ T | Activation |
| IL-10, TARC, MDC (CCL22), CCL5 | Th2 | Activation | IL-10, TARC, MDC (CCL22), CCL5 | Th2 |  |
| Th2 | Treg | Activation | Th2 | Treg | Inhibition |
| Galectin 1, IL-10 | STAT1+ TAM | Activation | Galectin 1, IL-10 | STAT1+ TAM | Inhibition |
| CSF-1 | STAT1+ TAM | Activation | CSF-1 | STAT1+ TAM |  |
| Treg | TCL | Inhibition | Treg | TCL | Inhibition |
| PD1+ T | TCL | Inhibition | PD1+ T | TCL | Activation |
| PD1+ T | Th1 | Inhibition | PD1+ T | Th1 | Activation |
| IFNγ | Treg | Inhibition | IFNγ | Treg |  |
| Treg | PD1+ T | Inhibition | Treg | PD1+ T | Inhibition |
| 1 Galaectin1 IL-10 | TCL | Inhibition | 1 Galaectin1 IL-10 | TCL |  |
| 1 Galaectin1 IL-10 | Th1 | Inhibition | 1 Galaectin1 IL-10 | Th1 | Activation |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Compound | PKCδ | Activation | Compound | PKCδ | Activation |
| Compound | ATM | Activation | Compound | ATM | Activation |
| PKCδ | p21 | Activation | PKCδ | p21 |  |
| PKCδ | NAG-1 | Activation | PKCδ | NAG-1 | Inhibition |
| ATM | p53 (ser15) | Activation | ATM | p53 (ser15) |  |
| p53 (ser15) | Apoptosis | Activation | p53 (ser15) | Apoptosis | Inhibition |
| NAG-1 | Apoptosis | Activation | NAG-1 | Apoptosis | Inhibition |
| p21 | Proliferation | Inhibition | p21 | Proliferation | Activation |

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| Ground truth | | |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| Alcama | Ednrb | Activation | Alcama | Ednrb | Activation |
| Edn1 | Ednra/b | Activation | Edn1 | Ednra/b | Activation |
| Ednra/b | hand2 | Activation | Ednra/b | hand2 | Activation |
| Ednra/b | dlx3b | Activation | Ednra/b | dlx3b | Activation |
| Ednra/b | dlx5a | Activation | Ednra/b | dlx5a |  |
| Ednra/b | dlx6a | Activation | Ednra/b | dlx6a | Inhibition |
| Ednra/b | NC differentiation | Activation | Ednra/b | NC differentiation | Activation |
| Ednra/b | cartilage ventralization | Activation | Ednra/b | cartilage ventralization | Activation |
| Ednra/b | jaw joint formation | Activation | Ednra/b | jaw joint formation | Inhibition |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| PPARα/RXR | Fgf21 | Activation | PPARα/RXR | Fgf21 | Activation |
| Fgf21 | FGFR1c? βKlotho? | Activation | Fgf21 | FGFR1c? βKlotho? | Activation |
| Starvation | Lipolysis | Activation | Starvation | Lipolysis |  |
| FGF21 | Torpor | *Inhibition* | FGF21 | Torpor | Activation |
| Ketogenic diet | Torpor | Activation | Ketogenic diet | Torpor | Inhibition |
| Lipolysis | NEFA | Inhibition | Lipolysis | NEFA | Inhibition |
| Fgf21 | NEFA | Activation | Fgf21 | NEFA | Inhibition |
| FGFR1c? βKlotho? | Lipolysis | *Inhibition* | FGFR1c? βKlotho? | Lipolysis |  |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Pyruvate + glyceraldehyde 3-phosphate | MEP | Activation | Pyruvate + glyceraldehyde 3-phosphate | MEP | Activation |
| MEP | HMB-PP | Activation | MEP | HMB-PP | Activation |
| HMB-PP | DMAPP | Activation | HMB-PP | DMAPP | Activation |
| DMAPP + IPP | FPP | Activation | DMAPP + IPP | FPP | Activation |
| FPP | Isoprenoids | Activation | FPP | Isoprenoids |  |
| 3-hydroxy-3-methylglutaryl-CoA | Mevalonate | Activation | 3-hydroxy-3-methylglutaryl-CoA | Mevalonate | Inhibition |
| Mevalonate | IPP | Activation | Mevalonate | IPP | Inhibition |
| IPP | DMAPP | Activation | IPP | DMAPP |  |
| DMAPP + IPP | FPP | Activation | DMAPP + IPP | FPP | Inhibition |
| FPP | Cholesterol | Activation | FPP | Cholesterol | Activation |
| FPP | Isoprenoids | Activation | FPP | Isoprenoids | Activation |
| Amino bisphosphonates | FPP | Inhibition | Amino bisphosphonates | FPP | Activation |
| Statins | 3-hydroxy-3-methylglutaryl-CoA | Inhibition | Statins | 3-hydroxy-3-methylglutaryl-CoA |  |

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| --- | --- | --- | --- | --- | --- |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Growth factors | dTsc1/Tsc2 | Activation | Growth factors | dTsc1/Tsc2 | Activation |
| Amino acids | dTsc1/Tsc2 | Activation | Amino acids | dTsc1/Tsc2 | Activation |
| ATP/AMP | dTsc1/Tsc2 | Activation | ATP/AMP | dTsc1/Tsc2 | Activation |
| Hypoxia | dTsc1/Tsc2 | Activation | Hypoxia | dTsc1/Tsc2 | Activation |
| Stresses | dTsc1/Tsc2 | Activation | Stresses | dTsc1/Tsc2 | Activation |
| dTsc1/Tsc2 | dRheb | Activation | dTsc1/Tsc2 | dRheb | Activation |
| dRheb | dTor | Activation | dRheb | dTor | Activation |
| dTor | dS6K1 | Activation | dTor | dS6K1 | Activation |
| dTor | d4E-BP | Activation | dTor | d4E-BP |  |
| dS6K1 | Autophagy | Activation | dS6K1 | Autophagy | Inhibition |
| dS6K1 | Metabolism | Activation | dS6K1 | Metabolism | Inhibition |
| d4E-BP | Protein synthesis | Activation | d4E-BP | Protein synthesis |  |
| d4E-BP | ER Stress | Activation | d4E-BP | ER Stress | Inhibition |
| Insulin signaling pathway | dTsc1/Tsc2 | Activation | Insulin signaling pathway | dTsc1/Tsc2 | Inhibition |
| Wnt, TGF β, P53, Sestrins | dTsc1/Tsc2 | Activation | Wnt, TGF β, P53, Sestrins | dTsc1/Tsc2 | Inhibition |
| Insulin signaling pathway | dRheb | Activation | Insulin signaling pathway | dRheb |  |
| Wnt, TGF β, P53, Sestrins | dRheb | Activation | Wnt, TGF β, P53, Sestrins | dRheb | Inhibition |

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| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 10 | 4 | 3 | 17 | 0.714286 | 0.588235 | 0.645161 |
| Claude-3 | 9 | 4 | 4 | 17 | 0.692308 | 0.529412 | 0.600000 |
| GEMINI | 7 | 5 | 4 | 17 | 0.583333 | 0.411765 | 0.482759 |
| pathway | 8 | 4 | 5 | 17 | 0.666667 | 0.470588 | 0.551724 |

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| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| PI3K | Akt | Activation | PI3K | Akt | Inhibition |
| Akt | NFκB | Activation | Akt | NFκB | Inhibition |
| Bcl2 | Apoptosome complex | Activation | Bcl2 | Apoptosome complex | Inhibition |
| Apoptosome complex | Executioner caspases-3, 6, 7 | Activation | Apoptosome complex | Executioner caspases-3, 6, 7 |  |
| Executioner caspases-3, 6, 7 | Apoptosis | Activation | Executioner caspases-3, 6, 7 | Apoptosis | Activation |
| Bak/Bax | Mitochondrion | Activation | Bak/Bax | Mitochondrion | Activation |
| NFκB | Bcl2 | Activation | NFκB | Bcl2 | Activation |
| Bcl2 | Apoptosome complex | Inhibition | Bcl2 | Apoptosome complex |  |
| Bcl-X(L) | Apoptosome complex | Inhibition | Bcl-X(L) | Apoptosome complex | Activation |
| IAPs | Executioner caspases-3, 6, 7 | Inhibition | IAPs | Executioner caspases-3, 6, 7 |  |
| Akt | Bcl-X(L) | Activation | Akt | Bcl-X(L) |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| IFNAR | JAK1 | Activation | IFNAR | JAK1 | Activation |
| JAK1 | TYK2 | Activation | JAK1 | TYK2 | Activation |
| TYK2 | STAT1 (P) | Activation | TYK2 | STAT1 (P) | Activation |
| dsRNA | RIG-I | Activation | dsRNA | RIG-I |  |
| RIG-I | MAVS | Activation | RIG-I | MAVS | Activation |
| MAVS | NEMO | Activation | MAVS | NEMO |  |
| NEMO | IKKα | Activation | NEMO | IKKα | Activation |
| IKKα | NFκB | Activation | IKKα | NFκB | Activation |
| NEMO | TBK1 | Activation | NEMO | TBK1 | Activation |
| TBK1 | IRF3 | Activation | TBK1 | IRF3 | Activation |
| IRF3 | IFN-β | Activation | IRF3 | IFN-β |  |
| NFκB | IFN-β | Activation | NFκB | IFN-β | Inhibition |
| IFN-β | IKKα | Activation | IFN-β | IKKα | Inhibition |
| IKKα | STAT1 (P) | Activation | IKKα | STAT1 (P) |  |
| cytokine receptor | STAT1 (P) | Activation | cytokine receptor | STAT1 (P) | Activation |
| cytokine (e.g., IL6) | cytokine receptor | Activation | cytokine (e.g., IL6) | cytokine receptor | Inhibition |
| IKKα | cytokine (e.g., IL6) | Inhibition | IKKα | cytokine (e.g., IL6) |  |
| IFNAR | STAT1 (P) | Activation | IFNAR | STAT1 (P) | Inhibition |
| cytokine (e.g., IL6) | STAT1 (P) | Activation | cytokine (e.g., IL6) | STAT1 (P) | Inhibition |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Gln | ASCT2 (SLC1A5) | Activation | Gln | ASCT2 (SLC1A5) | Activation |
| ASCT2 (SLC1A5) | Gln | Activation | ASCT2 (SLC1A5) | Gln | Activation |
| Gln | LAT1 (SLC7A5) | Activation | Gln | LAT1 (SLC7A5) | Activation |
| LAT1 (SLC7A5) | Gln | Activation | LAT1 (SLC7A5) | Gln | Activation |
| Gln | Glutamate | Activation | Gln | Glutamate | Activation |
| Glutamate | α-KG | Activation | Glutamate | α-KG | Activation |
| α-KG | TCA | Activation | α-KG | TCA | Activation |
| TCA | Malate | Activation | TCA | Malate |  |
| TCA | Fumarate | Activation | TCA | Fumarate | Activation |
| TCA | Succinate | Activation | TCA | Succinate | Activation |
| TCA | Citrate | Activation | TCA | Citrate | Inhibition |
| Citrate | CoA | Activation | Citrate | CoA |  |
| GOT2/GPT2 | Glutamate | Activation | GOT2/GPT2 | Glutamate |  |
| GDH1 | Glutamate | Activation | GDH1 | Glutamate | Inhibition |
| mTOR | Myc | Activation | mTOR | Myc | Activation |
| Myc | mTOR | Activation | Myc | mTOR | Activation |
| BCH | LAT1 (SLC7A5) | Inhibition | BCH | LAT1 (SLC7A5) | Activation |
| DON Azaserine Acivicin | Gln | Inhibition | DON Azaserine Acivicin | Gln | Activation |
| GPNA | ASCT2 (SLC1A5) | Inhibition | GPNA | ASCT2 (SLC1A5) | Inhibition |
| BPTES/CB-839 | GLS | Inhibition | BPTES/CB-839 | GLS | Activation |
| Compound 968 | GLS | Inhibition | Compound 968 | GLS |  |
| Purpurin/R162 | GDH1 | Inhibition | Purpurin/R162 | GDH1 |  |
| EGCG | GDH1 | Inhibition | EGCG | GDH1 | Activation |
| AOA | GOT2/GPT2 | Inhibition | AOA | GOT2/GPT2 | Activation |

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| --- | --- | --- | --- | --- | --- |
| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| Growth signals | D-cyclins | Activation | Growth signals | D-cyclins | Activation |
| D-cyclins | CDKs 4/6 | Activation | D-cyclins | CDKs 4/6 |  |
| CDKs 4/6 | RB | Inhibition | CDKs 4/6 | RB | Activation |
| RB | E2F | Inhibition | RB | E2F |  |
| E2F | Cell cycle | Activation | E2F | Cell cycle | Inhibition |
| Damage signals | p53 | Activation | Damage signals | p53 | Inhibition |
| p53 | CDKN1s p21 | Activation | p53 | CDKN1s p21 | Inhibition |
| CDKN2s p16 | CDKs 4/6 | Inhibition | CDKN2s p16 | CDKs 4/6 | Inhibition |
| CDKN1s p21 | CDKs 4/6 | Inhibition | CDKN1s p21 | CDKs 4/6 | Inhibition |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Myocardial Damage | AT1R/p38 MAPK | Activation | Myocardial Damage | AT1R/p38 MAPK | Activation |
| AT1R/p38 MAPK | ACE | Activation | AT1R/p38 MAPK | ACE | Activation |
| PFD | AT1R/p38 MAPK | Inhibition | PFD | AT1R/p38 MAPK | Activation |
| ACE | Ang II | Activation | ACE | Ang II | Activation |
| ACE2 | Ang(1-7) | Activation | ACE2 | Ang(1-7) |  |
| Ang(1-7) | MAS | Activation | Ang(1-7) | MAS | Inhibition |
| Ang II | AT1R | Activation | Ang II | AT1R | Inhibition |
| LXR-α | ACE | Activation | LXR-α | ACE | Inhibition |
| LXR-α | AT1R/p38 MAPK | Activation | LXR-α | AT1R/p38 MAPK | Activation |
| PFD | LXR-α | Activation | PFD | LXR-α | Activation |
| PFD | Inhibition of Cardiac fibrosis | Activation | PFD | Inhibition of Cardiac fibrosis |  |
| ACE2 | Ang(1-7) | Inhibition | ACE2 | Ang(1-7) | Inhibition |
| MAS | Cardiac fibrosis | Inhibition | MAS | Cardiac fibrosis | Inhibition |
| Ang(1-7) | Cardiac fibrosis | Activation | Ang(1-7) | Cardiac fibrosis | Inhibition |
| AT1R/p38 MAPK | ACE2 | Inhibition | AT1R/p38 MAPK | ACE2 | Inhibition |
| ACE2 | Ang(1-7) | Inhibition | ACE2 | Ang(1-7) | Inhibition |
| Ang(1-7) | MAS | Inhibition | Ang(1-7) | MAS | Inhibition |
| PFD | Cardiac fibrosis | Inhibition | PFD | Cardiac fibrosis |  |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Syx | RhoA | Activation | Syx | RhoA | Inhibition |
| RhoA | SIRT1 | Activation | RhoA | SIRT1 | Inhibition |
| SIRT1 | RARγ | Activation | SIRT1 | RARγ | Inhibition |
| RARγ | Noggin | Activation | RARγ | Noggin | Activation |
| Noggin | Neural differentiation | Activation | Noggin | Neural differentiation |  |
| F-actin | Rab3d | Inhibition | F-actin | Rab3d | Activation |
| RARγ | RHPN2 | Inhibition | RARγ | RHPN2 |  |
| Noggin | BMP4 | Inhibition | Noggin | BMP4 | Activation |
| BMP4 | pSmad1 | Activation | BMP4 | pSmad1 |  |
| pSmad1 | Neural differentiation | Inhibition | pSmad1 | Neural differentiation | Activation |
| RhoA | Neural differentiation | Activation | RhoA | Neural differentiation | Activation |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| KAR | GA3oxs | Activation | KAR | GA3oxs | Activation |
| GA3oxs | GA | Activation | GA3oxs | GA | Activation |
| GA | GID1 | Activation | GA | GID1 | Activation |
| GID1 | SCFSLY/GID1 | Activation | GID1 | SCFSLY/GID1 | Activation |
| SCFSLY/GID1 | DELLA | Inhibition | SCFSLY/GID1 | DELLA | Activation |
| DELLA | GAMYB | Inhibition | DELLA | GAMYB | Activation |
| GAMYB | EXP2 | Activation | GAMYB | EXP2 | Activation |
| EXP2 | Germination | Activation | EXP2 | Germination | Activation |
| EXP2 | Hypocotyl elongation | Activation | EXP2 | Hypocotyl elongation | Activation |
| KAR | ABA2 | Activation | KAR | ABA2 | Activation |
| ABA2 | ABA | Activation | ABA2 | ABA | Activation |
| ABA | PYR/PYL/RCAR | Activation | ABA | PYR/PYL/RCAR | Activation |
| PYR/PYL/RCAR | PP2Cs | Inhibition | PYR/PYL/RCAR | PP2Cs | Inhibition |
| PP2Cs | SnRK2s | Inhibition | PP2Cs | SnRK2s | Inhibition |
| SnRK2s | TFs | Inhibition | SnRK2s | TFs | Inhibition |
| TFs | ABI3 | Activation | TFs | ABI3 | Inhibition |
| ABI3 | Germination | Inhibition | ABI3 | Germination | Inhibition |
| ABI3 | Hypocotyl elongation | Activation | ABI3 | Hypocotyl elongation | Inhibition |
| KAR | YUCCAs | Activation | KAR | YUCCAs | Inhibition |
| YUCCAs | Auxin | Activation | YUCCAs | Auxin | Activation |
| Auxin | TIR1/AFB | Activation | Auxin | TIR1/AFB | Activation |
| TIR1/AFB | SCFTIR1 | Activation | TIR1/AFB | SCFTIR1 | Activation |
| SCFTIR1 | AUX/IAA | Inhibition | SCFTIR1 | AUX/IAA | Activation |
| AUX/IAA | ARFs | Inhibition | AUX/IAA | ARFs | Activation |
| ARFs | IAA1 | Activation | ARFs | IAA1 | Activation |
| IAA1 | Germination | Inhibition | IAA1 | Germination | Inhibition |
| IAA1 | Hypocotyl elongation | Activation | IAA1 | Hypocotyl elongation | Activation |
| RHPN2 | RARγ | Inhibition | RHPN2 | RARγ | Inhibition |
| KAR | Auxin | Activation | KAR | Auxin | Inhibition |
| Biosynthesis | Phytohormone | Activation | Biosynthesis | Phytohormone | Inhibition |
| Phytohormone | Receptor | Activation | Phytohormone | Receptor | Inhibition |
| Receptor | E3 liges | Activation | Receptor | E3 liges | Activation |
| E3 liges | Repressor | Inhibition | E3 liges | Repressor | Activation |
| Repressor | Transcription factor | Inhibition | Repressor | Transcription factor | Inhibition |
| Transcription factor | Response gene | Activation | Transcription factor | Response gene | Inhibition |

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| **Ground Truth** | | |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| FLT-3 | PRKD1 | Activation | FLT-3 | PRKD1 | Activation |
| PRKD1 | AKT | Activation | PRKD1 | AKT | Activation |
| AKT | mTOR | Activation | AKT | mTOR | Activation |
| mTOR | Cell Survival Signaling | Activation | mTOR | Cell Survival Signaling | Activation |
| NOTCH4 | PI3K | Activation | NOTCH4 | PI3K | Activation |
| PI3K | PRKD1 | Activation | PI3K | PRKD1 |  |
| MAS1 | CDC42 | Activation | MAS1 | CDC42 | Activation |
| CDC42 | RHO | Activation | CDC42 | RHO | *Inhibition* |
| RHO | GAP/GEF | Activation | RHO | GAP/GEF |  |
| GAP/GEF | MAPK | Activation | GAP/GEF | MAPK | *Inhibition* |
| MAPK | ERK1/2 | Activation | MAPK | ERK1/2 |  |
| ERK1/2 | NFATC1/4 | Activation | ERK1/2 | NFATC1/4 | *Inhibition* |
| NFATC1/4 | VEGFR1 | Activation | NFATC1/4 | VEGFR1 | *Inhibition* |
| NFATC1/4 | VEGFR2 | Activation | NFATC1/4 | VEGFR2 |  |
| VEGF | VEGFR1 | Activation | VEGF | VEGFR1 | *Inhibition* |
| VEGF | VEGFR2 | Activation | VEGF | VEGFR2 | Activation |
| NFATC1/4 | Angiogenesis and Vasoreactivity | Activation | NFATC1/4 | Angiogenesis and Vasoreactivity | *Inhibition* |
| AT1R | RAS/RAF | Activation | AT1R | RAS/RAF | *Inhibition* |
| RAS/RAF | MAPK | Activation | RAS/RAF | MAPK | Activation |
| RAS/RAF | p38MAPK | Activation | RAS/RAF | p38MAPK | Activation |
| p38MAPK | ERK1/2 | Activation | p38MAPK | ERK1/2 |  |
| VEGFR1 | VEGF | Activation | VEGFR1 | VEGF | Activation |
| VEGFR2 | VEGF | Indirect Activation | VEGFR2 | VEGF |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| HIF-1β | HIF-1α | Activation | HIF-1β | HIF-1α | Activation |
| HIF-1α | PHDs | Activation | HIF-1α | PHDs | Activation |
| PHDs | VHL E3 | Activation | PHDs | VHL E3 | Activation |
| VHL E3 | Ub ubiquitin | Activation | VHL E3 | Ub ubiquitin | Activation |
| Ub ubiquitin | HIF-1α proteasomal degradation | Activation | Ub ubiquitin | HIF-1α proteasomal degradation | Activation |
| HIF-1α | Nucleus | Activation | HIF-1α | Nucleus | Activation |
| HIF-1β | Nucleus | Activation | HIF-1β | Nucleus |  |
| HIF-1α | HRES | Activation | HIF-1α | HRES |  |
| HIF-1β | HRES | Activation | HIF-1β | HRES |  |
| HRES | NCGTG | Activation | HRES | NCGTG |  |
| NCGTG | Proliferation, Anti-apoptosis, Anti-inflammation, Angiogenesis | Activation | NCGTG | Proliferation, Anti-apoptosis, Anti-inflammation, Angiogenesis |  |
| Angiogenesis | Caspase-3 | Activation | Angiogenesis | Caspase-3 | Inhibition |
| Caspase-3 | MEK-1/2 | Activation | Caspase-3 | MEK-1/2 | Inhibition |
| MEK-1/2 | ERK-1/2 | Activation | MEK-1/2 | ERK-1/2 |  |
| ERK-1/2 | Akt | Activation | ERK-1/2 | Akt | Inhibition |
| EPO | EPO-R | Activation | EPO | EPO-R |  |
| EPO-R | VEGF | Activation | EPO-R | VEGF | Activation |
| VEGF | VEGFR | Activation | VEGF | VEGFR | Activation |
| ADM | Vasomotor regulation | Activation | ADM | Vasomotor regulation | Activation |
| Glut-1 | Energy metabolism | Activation | Glut-1 | Energy metabolism | Activation |
| HO-1 | ROS | Activation | HO-1 | ROS | Activation |
| ROS | IRS1/PI3K/Akt2 | Activation | ROS | IRS1/PI3K/Akt2 | Activation |
| IRS1/PI3K/Akt2 | Keap1/Nrf2/ERK | Activation | IRS1/PI3K/Akt2 | Keap1/Nrf2/ERK | Activation |
| HIF-1α | Maintain mitochondrial membrane potential | Activation | HIF-1α | Maintain mitochondrial membrane potential | Activation |
| PHDs | HIF-1α | Inhibition | PHDs | HIF-1α | Inhibition |
| Ub ubiquitin | HIF-1α | Inhibition | Ub ubiquitin | HIF-1α | Activation |
| HIF-1α proteasomal degradation | HIF-1α | Inhibition | HIF-1α proteasomal degradation | HIF-1α | Activation |
| HO-1 | ROS | Inhibition | HO-1 | ROS | Activation |
| EPO-R | Hormone effect | Activation | EPO-R | Hormone effect | Activation |
| VEGF | Proliferation, Anti-apoptosis, Anti-inflammation, Angiogenesis | Activation | VEGF | Proliferation, Anti-apoptosis, Anti-inflammation, Angiogenesis | Activation |

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| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| Egr-1 | PDGFC | Activation | Egr-1 | PDGFC | Inhibition |
| Sp1 | PDGFC | Activation | Sp1 | PDGFC | Inhibition |
| PDGFC | PDGF-CC | Activation | PDGFC | PDGF-CC | Inhibition |
| tPA | inactive PDGF-CC | Activation | tPA | inactive PDGF-CC | Inhibition |
| inactive PDGF-CC | active PDGF-CC | Activation | inactive PDGF-CC | active PDGF-CC | Inhibition |
| active PDGF-CC | PDGFR-α | Activation | active PDGF-CC | PDGFR-α | Activation |
| PDGFR-α | PI3K | Activation | PDGFR-α | PI3K | Activation |
| PDGFR-α | Ras MAPK | Activation | PDGFR-α | Ras MAPK | Activation |
| PDGFR-α | p38 MAPK | Activation | PDGFR-α | p38 MAPK | Activation |
| PDGFR-α | PLC-γ | Activation | PDGFR-α | PLC-γ | Activation |
| PAI-1 | tPA | Inhibition | PAI-1 | tPA | Activation |
| Neuroserpin | tPA | Inhibition | Neuroserpin | tPA | Activation |
| LRP1 | PDGFR-α | Activation | LRP1 | PDGFR-α | Activation |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Growth factor | Growth factor receptor | Activation | Growth factor | Growth factor receptor | Activation |
| Growth factor receptor | IRS | Activation | Growth factor receptor | IRS | Activation |
| IRS | PIP2 | Activation | IRS | PIP2 | Activation |
| PIP2 | PI3K | Activation | PIP2 | PI3K |  |
| PIP2 | PTEN | Activation | PIP2 | PTEN | Activation |
| PI3K | PIP3 | Activation | PI3K | PIP3 | Inhibition |
| PIP3 | PDK1 | Activation | PIP3 | PDK1 | Inhibition |
| PDK1 | AKT (Thr308) | Activation | PDK1 | AKT (Thr308) | Activation |
| mTORC2 | AKT (Ser473) | Activation | mTORC2 | AKT (Ser473) | Activation |
| AKT | mTORC1 | Activation | AKT | mTORC1 | Activation |
| mTORC1 | S6K1/2 | Activation | mTORC1 | S6K1/2 | Activation |
| mTORC1 | 4EBP1 | Inhibition | mTORC1 | 4EBP1 |  |
| AKT | FOXG1 (phosphorylation) | Activation | AKT | FOXG1 (phosphorylation) | Activation |
| FOXG1 (phosphorylation) | Reelin | Activation | FOXG1 (phosphorylation) | Reelin | Activation |
| PTEN | PI3K | Inhibition | PTEN | PI3K | Activation |
| Rapamycin | mTORC1 | Inhibition | Rapamycin | mTORC1 |  |
| FOXG1 | Reelin | Inhibition | FOXG1 | Reelin | Inhibition |
| PIP3 | AKT | Activation | PIP3 | AKT | Inhibition |

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| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 14 | 2 | 2 | 18 | 0.8750 | 0.777778 | 0.823529 |
| Claude-3 | 13 | 3 | 2 | 18 | 0.8125 | 0.722222 | 0.764706 |
| GEMINI | 12 | 3 | 3 | 18 | 0.8000 | 0.666667 | 0.727273 |
| pathway | 13 | 3 | 2 | 18 | 0.8125 | 0.722222 | 0.764706 |

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| Starter (gene1) | Receptor (gene2) | Relationship | Starter (gene1) | Receptor (gene2) | GEMINI |
| Rab7 | Lysosome | Activation | Rab7 | Lysosome | Activation |
| Lysosome | Endolysosome/Autolysosome | Activation | Lysosome | Endolysosome/Autolysosome | Activation |
| Endolysosome/Autolysosome | Lysosomal digestion | Activation | Endolysosome/Autolysosome | Lysosomal digestion | Activation |
| Lysosome | Lysosome reformation | Activation | Lysosome | Lysosome reformation | Activation |
| VapA | Lysosomal digestion | Inhibition | VapA | Lysosomal digestion |  |
| VapA | Membrane retrieval | Inhibition | VapA | Membrane retrieval | Activation |
| VapA | Lysosome reformation | Inhibition | VapA | Lysosome reformation | Activation |
| VapA | TFEB Signalling | Inhibition | VapA | TFEB Signalling |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| SDHDv | ROS | Activation | SDHDv | ROS |  |
| ROS | Oxi PTEN | Activation | ROS | Oxi PTEN | Activation |
| Oxi PTEN | Mono-Ub PTEN | Activation | Oxi PTEN | Mono-Ub PTEN | Activation |
| Mono-Ub PTEN | PTEN nuclear Localization | Activation | Mono-Ub PTEN | PTEN nuclear Localization | Activation |
| PTEN nuclear Localization | Mono-Ub PTEN p-Akt | Activation | PTEN nuclear Localization | Mono-Ub PTEN p-Akt | Activation |
| PTEN nuclear Localization | Acetylation-FOXO3a | Activation | PTEN nuclear Localization | Acetylation-FOXO3a | Inhibition |
| Acetylation-FOXO3a | p-FOXO3a | Activation | Acetylation-FOXO3a | p-FOXO3a |  |
| p-FOXO3a | ATG12, Beclin 1 transcription | Activation | p-FOXO3a | ATG12, Beclin 1 transcription | Inhibition |
| FOXO3a-14-3-3 | Degradation | Activation | FOXO3a-14-3-3 | Degradation | Inhibition |
| ATG12, Beclin 1 transcription | Autophagy | Activation | ATG12, Beclin 1 transcription | Autophagy |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Lm | c-di-AMP | Activation | Lm | c-di-AMP | Activation |
| c-di-AMP | STING | Activation | c-di-AMP | STING | Activation |
| STING | DDX41 | Activation | STING | DDX41 | Activation |
| DDX41 | p38 | Activation | DDX41 | p38 |  |
| DDX41 | TBK1 | Activation | DDX41 | TBK1 | Inhibition |
| p38 | IRF3 | Activation | p38 | IRF3 | Activation |
| TBK1 | IRF3 | Activation | TBK1 | IRF3 | Activation |
| IRF3 | Ifnb1 | Activation | IRF3 | Ifnb1 | Activation |
| BTK | DDX41 | Inhibition | BTK | DDX41 |  |
| BTK | STING | Inhibition | BTK | STING | Activation |
| C3a | BTK | Inhibition | C3a | BTK | Inhibition |
| C5a | BTK | Inhibition | C5a | BTK |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| EtOH | FoxO1 | Activation | EtOH | FoxO1 | Activation |
| FoxO1 | AMPK | Activation | FoxO1 | AMPK | Activation |
| AMPK | ULK1 (S555) | Activation | AMPK | ULK1 (S555) | Activation |
| AMPK | PIK3C3 (S164) | Activation | AMPK | PIK3C3 (S164) | Activation |
| AMPK | BECN1 (S93) | Activation | AMPK | BECN1 (S93) | Activation |
| AMPK | BECN1 (S14) | Activation | AMPK | BECN1 (S14) |  |
| ULK1 (S555) | BECN1 (S93) | Activation | ULK1 (S555) | BECN1 (S93) | Activation |
| ULK1 (S555) | PIK3C3 (S164) | Activation | ULK1 (S555) | PIK3C3 (S164) | Activation |
| PIK3C3 | 14-3-3Θ | Activation | PIK3C3 | 14-3-3Θ | Activation |
| PIK3C3 | ATG14 | Activation | PIK3C3 | ATG14 |  |
| PIK3C3 | AMBRA1 | Activation | PIK3C3 | AMBRA1 | Activation |
| PIK3C3 | BECN1 | Activation | PIK3C3 | BECN1 | Activation |
| BECN1 | SQSTM1 | Activation | BECN1 | SQSTM1 | Activation |
| BECN1 | LC3B | Activation | BECN1 | LC3B | Inhibition |
| BECN1 | ATG7 | Activation | BECN1 | ATG7 | Inhibition |
| mTORC1 | ULK1 (S757) | Activation | mTORC1 | ULK1 (S757) |  |
| mTORC1 | AMPK | Inhibition | mTORC1 | AMPK |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| Wnt | Frizzled | Activation | Wnt | Frizzled | Activation |
| PDGF | PDGFR | Activation | PDGF | PDGFR | Activation |
| GLP-1 | GLP-1R | Activation | GLP-1 | GLP-1R |  |
| BTC | ErbB1 | Activation | BTC | ErbB1 |  |
| BTC | ErbB2 | Activation | BTC | ErbB2 | Activation |
| IGF-1 | IGF-1R | Activation | IGF-1 | IGF-1R | Activation |
| Frizzled | Dsh | Activation | Frizzled | Dsh |  |
| Dsh | cAMP | Activation | Dsh | cAMP |  |
| cAMP | MEK | Activation | cAMP | MEK | Activation |
| cAMP | PKA | Activation | cAMP | PKA |  |
| MEK | ERK1/2 | Activation | MEK | ERK1/2 | Activation |
| PKA | ERK1/2 | Activation | PKA | ERK1/2 |  |
| ERK1/2 | EZH2 | Activation | ERK1/2 | EZH2 | Activation |
| EZH2 | ErbBR | Activation | EZH2 | ErbBR | Activation |
| ErbBR | P16LINK4 | Activation | ErbBR | P16LINK4 |  |
| P16LINK4 | Tcf7L2 | Activation | P16LINK4 | Tcf7L2 | Activation |
| Dsh | GS3Kβ | Activation | Dsh | GS3Kβ |  |
| GS3Kβ | β-catenin | Activation | GS3Kβ | β-catenin | Activation |
| β-catenin | APC | Activation | β-catenin | APC |  |
| APC | Axin | Activation | APC | Axin | Activation |
| Axin | Tcf7L2 | Activation | Axin | Tcf7L2 |  |
| Tcf7L2 | CyclinD1-2, cMyc, cdk4 | Activation | Tcf7L2 | CyclinD1-2, cMyc, cdk4 | Activation |
| CyclinD1-2, cMyc, cdk4 | Proliferation | Activation | CyclinD1-2, cMyc, cdk4 | Proliferation | Activation |
| PDGFR | IRS | Activation | PDGFR | IRS | Inhibition |
| IRS | PI3K | Activation | IRS | PI3K |  |
| PI3K | PDK1 | Activation | PI3K | PDK1 | Activation |
| PDK1 | AKT/PKB | Activation | PDK1 | AKT/PKB |  |
| AKT/PKB | TSC1/2 | Activation | AKT/PKB | TSC1/2 | Activation |
| TSC1/2 | GTP | Activation | TSC1/2 | GTP | Inhibition |
| GTP | Rheb | Activation | GTP | Rheb | Inhibition |
| Rheb | mTORC1 | Activation | Rheb | mTORC1 | Activation |
| mTORC1 | 4E-BPs | Activation | mTORC1 | 4E-BPs | Activation |
| 4E-BPs | S6K1 | Activation | 4E-BPs | S6K1 | Activation |
| S6K1 | Proliferation | Activation | S6K1 | Proliferation | Activation |
| AKT/PKB | MDM2/P53 | Activation | AKT/PKB | MDM2/P53 | Activation |
| MDM2/P53 | P21cip1 | Activation | MDM2/P53 | P21cip1 | Activation |
| P21cip1 | Proliferation | Activation | P21cip1 | Proliferation |  |
| AKT/PKB | FOXO1 | Activation | AKT/PKB | FOXO1 |  |
| FOXO1 | P27kip1 | Activation | FOXO1 | P27kip1 |  |
| P27kip1 | Pdx1, GSK3 | Activation | P27kip1 | Pdx1, GSK3 |  |
| Pdx1, GSK3 | mTORC1 | Activation | Pdx1, GSK3 | mTORC1 |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| IGF-I | IGF-I-R | Activation | IGF-I | IGF-I-R | Activation |
| IGF-I-R | PI3-kinase | Activation | IGF-I-R | PI3-kinase | Activation |
| PI3-kinase | PKB (Akt) | Activation | PI3-kinase | PKB (Akt) | Activation |
| PKB (Akt) | Transcription or Splicing factors | Activation | PKB (Akt) | Transcription or Splicing factors | Activation |
| PDGFs | PDGF-R | Activation | PDGFs | PDGF-R | Activation |
| PDGF-R | MEK1 | Activation | PDGF-R | MEK1 | Inhibition |
| MEK1 | ERK | Activation | MEK1 | ERK | Inhibition |
| ERK | Transcription or Splicing factors | Activation | ERK | Transcription or Splicing factors | Activation |
| bFGF or EGF | bFGF-R or EGF-R | Activation | bFGF or EGF | bFGF-R or EGF-R | Inhibition |
| bFGF-R or EGF-R | MKK6 | Activation | bFGF-R or EGF-R | MKK6 |  |
| MKK6 | p38MAPK | Activation | MKK6 | p38MAPK | Activation |
| p38MAPK | Transcription or Splicing factors | Activation | p38MAPK | Transcription or Splicing factors | Activation |
| LY294002 or Wortmannin | PI3-kinase | Inhibition | LY294002 or Wortmannin | PI3-kinase | Activation |
| PD98059 | MEK1 | Inhibition | PD98059 | MEK1 | Activation |
| SB203580 | p38MAPK | Inhibition | SB203580 | p38MAPK | Inhibition |
| IGF-I-R | PKB (Akt) | Activation | IGF-I-R | PKB (Akt) | Activation |
| PI3-kinase | Transcription or Splicing factors | Activation | PI3-kinase | Transcription or Splicing factors | Activation |
| ERK | Induction of dedifferentiation | Activation | ERK | Induction of dedifferentiation |  |
| p38MAPK | Induction of dedifferentiation | Activation | p38MAPK | Induction of dedifferentiation |  |
| PI3-kinase | Maintaining of a differentiated phenotype | Inhibition | PI3-kinase | Maintaining of a differentiated phenotype |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| EGFR | Ras | Activation | EGFR | Ras |  |
| Ras | Raf | Activation | Ras | Raf | Activation |
| Raf | MEK | Activation | Raf | MEK | Activation |
| MEK | ERK | Activation | MEK | ERK |  |
| EGFR | PI3K | Activation | EGFR | PI3K | Activation |
| PI3K | Akt | Activation | PI3K | Akt | Activation |
| Akt | mTOR | Activation | Akt | mTOR |  |
| mTOR | Proliferation / Survival / Angiogenesis | Activation | mTOR | Proliferation / Survival / Angiogenesis | Activation |
| Cetuximab | EGFR | Inhibition | Cetuximab | EGFR | Activation |
| Erlotinib / Gefitinib | EGFR | Inhibition | Erlotinib / Gefitinib | EGFR | Activation |
| Salirasib | Ras | Inhibition | Salirasib | Ras | Activation |
| LY294002 | PI3K | Inhibition | LY294002 | PI3K |  |
| BEZ235 | PI3K | Inhibition | BEZ235 | PI3K | Inhibition |
| Rapamycin / RAD001 / CCI-779 | mTOR | Inhibition | Rapamycin / RAD001 / CCI-779 | mTOR |  |
| PF-00299804 / BIBW2992 | HER | Inhibition | PF-00299804 / BIBW2992 | HER | Inhibition |
| Antiangiogenic agents | VEGFR / PDGFR / FGFR | Inhibition | Antiangiogenic agents | VEGFR / PDGFR / FGFR |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| RTK | Ras | Activation | RTK | Ras | Inhibition |
| Ras | Raf | Activation | Ras | Raf | Inhibition |
| Raf | MEK | Activation | Raf | MEK |  |
| MEK | ERK1/2 | Activation | MEK | ERK1/2 | Activation |
| TRAF | MEKK1/ASK1/TAK1 | Activation | TRAF | MEKK1/ASK1/TAK1 | Activation |
| MEKK1/ASK1/TAK1 | MKK3/6 | Activation | MEKK1/ASK1/TAK1 | MKK3/6 |  |
| MKK3/6 | p38 α/β/γ/δ | Activation | MKK3/6 | p38 α/β/γ/δ | Activation |
| RAC1 | MEKK/MUK | Activation | RAC1 | MEKK/MUK | Activation |
| MEKK/MUK | MKK4/7 | Activation | MEKK/MUK | MKK4/7 |  |
| MKK4/7 | JNK1/2/3 | Activation | MKK4/7 | JNK1/2/3 | Activation |
| Shp2 | RTK | Inhibition | Shp2 | RTK |  |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **Starter (gene1)** | **Receptor (gene2)** | GEMINI |
| c-MET | Ras | Activation | c-MET | Ras | Activation |
| c-MET | PI3K | Activation | c-MET | PI3K | Activation |
| EGFR | Ras | Activation | EGFR | Ras | Activation |
| EGFR | PI3K | Activation | EGFR | PI3K |  |
| IGFR1 | Ras | Activation | IGFR1 | Ras |  |
| IGFR1 | PI3K | Activation | IGFR1 | PI3K | Activation |
| AXL | Ras | Activation | AXL | Ras | Activation |
| AXL | PI3K | Activation | AXL | PI3K | Activation |
| Fyn | Ras | Activation | Fyn | Ras |  |
| Fyn | PI3K | Activation | Fyn | PI3K | Activation |
| Ras | Raf | Activation | Ras | Raf |  |
| Raf | MEK | Activation | Raf | MEK | Activation |
| MEK | ERK | Activation | MEK | ERK | Activation |
| Rho | PAK | Activation | Rho | PAK | Activation |
| PAK | Cell motility and invasion | Activation | PAK | Cell motility and invasion |  |
| ERK | Cell cycle progression and proliferation | Activation | ERK | Cell cycle progression and proliferation | Activation |
| PI3K | AKT | Activation | PI3K | AKT | Activation |
| AKT | mTOR | Activation | AKT | mTOR | Activation |
| mTOR | Protein synthesis and cell growth | Activation | mTOR | Protein synthesis and cell growth | Activation |
| AKT | Survival | Activation | AKT | Survival | Activation |
| PTEN | AKT | Inhibition | PTEN | AKT | Activation |
| miR-125a-3p | Fyn | Inhibition | miR-125a-3p | Fyn | Activation |
| miR-7 | FAK | Inhibition | miR-7 | FAK | Activation |
| miR-7, miR-23b, miR-145 | PAK | Inhibition | miR-7, miR-23b, miR-145 | PAK | Activation |
| miR-302-367, miR-612 | PI3K | Inhibition | miR-302-367, miR-612 | PI3K |  |
| miR-99, miR-145 | mTOR | Inhibition | miR-99, miR-145 | mTOR | Activation |
| Fyn | Rho | Activation | Fyn | Rho |  |
| Fyn | PAK | Activation | Fyn | PAK |  |