*1*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ground Truth | | |  |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | GPT-4 | Claude-3 | GEMINI | Pipeline |
| Environmental stress | PAK/RAC | Activation | Activation | Activation | Activation | Activation |
| PAK/RAC | MEKK/NIK | Activation | Activation | Activation | Activation | Activation |
| MEKK/NIK | MKK | Activation | Activation | Activation | Activation | Activation |
| MEKK/NIK | IKK | Activation | Activation | Activation | Activation | Activation |
| IKK | IκB/NF-κB | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| IκB/NF-κB | IkB Degradation | Activation | Inhibition | Inhibition | Inhibition |  |
| IκB/NF-κB | NF-κB Translocation | Activation | Activation | Inhibition | Inhibition | Inhibition |
| NF-κB Translocation | Stress Gene Expression and Regulation | Activation |  | Inhibition | Inhibition |  |
| BSO | γ-GCS | Inhibition | Activation |  | Inhibition | Inhibition |
| MKK | p38/RK | Activation | Activation |  |  | Inhibition |
| p38/RK | MAPKAP-K2 | Activation |  | Inhibition |  | Inhibition |
| MAPKAP-K2 | ARE | Activation |  |  |  |  |
| ARE | Stress Gene Expression and Regulation | Activation | Activation | Activation | Activation | Activation |
| MAPKAP-K2 | Hsp27 | Activation | Activation |  |  |  |
| NAC | Cysteine | Activation |  | Inhibition |  |  |
| GSH | Cysteine | Activation | Activation |  |  | Inhibition |
| Cysteine | GSH | Activation |  | Activation | Inhibition | Inhibition |
| Hsp27 | Stress Gene Expression and Regulation | Activation | Activation |  | Inhibition |  |
| γ-GT | Cysteine | Activation | Activation | Activation |  |  |
| NAC | p38/RK | Inhibition | Activation | Activation |  |  |
| NAC | MKK | Inhibition | Activation |  |  |  |
| SB-203580 | p38/RK | Inhibition | Inhibition | Inhibition |  |  |
| SB-203580 | MAPKAP-K2 | Inhibition | Inhibition | Inhibition |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 15 | 3 | 5 | 23 | 0.833333 | 0.652174 | 0.731707 |
| Claude-3 | 14 | 4 | 5 | 23 | 0.777778 | 0.608696 | 0.682927 |
| GEMINI | 12 | 5 | 6 | 23 | 0.705882 | 0.521739 | 0.600000 |
| pathway | 13 | 5 | 5 | 23 | 0.722222 | 0.565217 | 0.634146 |

*2*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | GPT-4 Results | Claude-3 | GEMINI | pathway |
| Ligand | Receptor | Activation | Activation | Activation | Activation | Activation |
| Ligand | Ligand-induced degradation | Activation | Activation | Activation | Activation | Activation |
| Receptor | Internalization | Activation | Activation | Activation | Inhibition | Activation |
| Receptor | Activity | Activation | Activation | Activation |  |  |
| Activity | Transcription | Activation | Activation | Inhibition | Activation | Inhibition |
| Receptor | Recycling | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| Constitutive degradation | Receptor | Inhibition | Inhibition | Inhibition | Activation | Activation |
| Internalization | Receptor production | Activation | Activation |  | Activation | Activation |
| Receptor production | Receptor | Activation |  |  | Inhibition | Inhibition |
| Receptor | Activity | Activation | Activation | Activation |  | Activation |
| Activity | Recycling | Inhibition |  |  |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 6 | 2 | 2 | 10 | 0.750000 | 0.6 | 0.666667 |
| Claude-3 | 5 | 3 | 2 | 10 | 0.625000 | 0.5 | 0.555556 |
| GEMINI | 3 | 4 | 3 | 10 | 0.428571 | 0.3 | 0.352941 |
| pathway | 4 | 4 | 2 | 10 | 0.500000 | 0.4 | 0.444444 |

*3*

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| --- | --- | --- | --- | --- | --- | --- |
| **Ground truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | GPT-4 | Claude-3 | GEMINI | Pipline |
| TCR | ZAP70 | Activation | Activation | Activation | Activation | Activation |
| ZAP70 | GADD45α/β | Activation | Activation | Activation | Activation | Activation |
| GADD45α/β | MEKK4 | Activation | Activation | Activation |  |  |
| MEKK4 | MKK3/4/6 | Activation | Activation | *inhibition* | *inhibition* | *inhibition* |
| MKK3/4/6 | p38 | Activation | Activation | Activation |  | *inhibition* |
| p38 | T180/Y182 | Activation |  |  | Activation | *inhibition* |
| T180/Y182 | Substrates | Activation | Activation | Activation | *inhibition* | *inhibition* |
| GADD45α | Y323 | Activation | Activation | Activation | *inhibition* | *inhibition* |
| Y323 | T180/Y182 | Activation | Activation | Activation |  |  |
| GADD45α | T180/Y182 | *inhibition* | Activation |  | Activation | Activation |
| GADD45α | Y323 | *inhibition* | Activation | Activation | Activation | Activation |
| ZAP70 | Y323 | Activation |  | Activation | Activation | Activation |
| CD28 | GADD45α/β | Activation | *inhibition* | *inhibition* |  | *inhibition* |
| IL-12R or IL-18R | GADD45α/β | Activation | *inhibition* | *inhibition* |  | *inhibition* |
| MKKK | MKK | Activation | Activation | *inhibition* | *inhibition* |  |
| MKKK | MAPK | Activation | *inhibition* | *inhibition* |  |  |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 10 | 5 | 2 | 17 | 0.666667 | 0.588235 | 0.625000 |
| Claude-3 | 9 | 6 | 2 | 17 | 0.600000 | 0.529412 | 0.562500 |
| GEMINI | 6 | 6 | 5 | 17 | 0.500000 | 0.352941 | 0.413793 |
| pathway | 7 | 6 | 4 | 17 | 0.538462 | 0.411765 | 0.466667 |

*4*

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| --- | --- | --- | --- | --- | --- | --- |
| ***Ground truth*** | | |  |  |  |  |
| ***Starter (gene1)*** | ***Receptor (gene2)*** | ***Relationship*** | ***GpT-4*** | Claude-3 | GEMINI | pathway |
| *CPB, Sepsis, Injury* | *Anterior pituitary* | *Activation* | *Activation* | *Activation* | *Activation* | *Activation* |
| *Anterior pituitary* | *TH2 Immune cells* | *Activation* | *Activation* | *inhibition* | *Activation* | *Activation* |
| *Anterior pituitary* | *MIF* | *Activation* |  |  | *inhibition* | *inhibition* |
| *MIF* | *CD74* | *Activation* | *inhibition* | *Activation* | *inhibition* |  |
| *CD74* | *Proinflammatory Cytokines Chemokines* | *Activation* | *inhibition* | *inhibition* |  | *inhibition* |
| *Proinflammatory Cytokines* | *SIRS* | *Activation* | *Activation* | *Activation* | *inhibition* | *inhibition* |
| *SIRS* | *MODS* | *Activation* | *inhibition* |  | *inhibition* | *inhibition* |
| *IL-10, IL-4* | *TH2 Immune cells* | *inhibition* | *inhibition* | *inhibition* |  |  |
| *Cortisol* | *TH1 Immune cells* | *inhibition* | *inhibition* | *inhibition* | *inhibition* | *inhibition* |
| *MIF* | *Cortisol* | *inhibition* | *inhibition* |  |  |  |
| *ACTH* | *Cortisol* | *Activation* |  | *inhibition* | *inhibition* |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 6 | 3 | 2 | 11 | 0.666667 | 0.545455 | 0.600000 |
| Claude-3 | 5 | 3 | 3 | 11 | 0.625000 | 0.454545 | 0.526316 |
| GEMINI | 4 | 4 | 3 | 11 | 0.500000 | 0.363636 | 0.421053 |
| pathway | 4 | 4 | 3 | 11 | 0.500000 | 0.363636 | 0.421053 |

*5*

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| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Innervation | Acetylcholine, Substance P, etc. | Activation | Activation | Activation | Activation | Activation |
| Innervation | Inflammatory Cells | Activation | Activation | Activation | Activation | Activation |
| Inflammatory Cells | Epithelium | Activation | Activation | Activation |  | Activation |
| Acetylcholine, Substance P, etc. | Airway Smooth Muscle | Activation | Activation | Activation | Activation |  |
| Inflammatory Cells | Leukotrienes, Histamines, Cytokines, etc. | Activation | Activation | Activation | Activation | Activation |
| Epithelium | Endothelin, etc. | Activation | *inhibition* | *inhibition* | Activation |  |
| Acetylcholine, Substance P, etc. | Rho/ROCK | Activation | *inhibition* | *inhibition* | *inhibition* |  |
| Leukotrienes, Histamines, Cytokines, etc | Rho/ROCK | Activation |  | *inhibition* | *inhibition* | *inhibition* |
| Endothelin, etc. | Rho/ROCK | Activation | Activation |  |  | *inhibition* |
| Acetylcholine, Substance P, etc. | Ca2+ | Activation | Activation | *inhibition* | *inhibition* |  |
| Leukotrienes, Histamines, Cytokines, etc | Ca2+ | Activation | Activation |  |  |  |
| Endothelin, etc. | Ca2+ | Activation | *inhibition* | Activation | *inhibition* |  |
| Endothelin, etc. | Airway Smooth Muscle | Activation | Activation |  |  |  |
| Ca2+ | Contraction | Activation | Activation | Activation | *inhibition* | *inhibition* |
| Ca2+ | Airway Smooth Muscle | Activation |  | Activation | *inhibition* |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 10 | 3 | 2 | 15 | 0.769231 | 0.666667 | 0.714286 |
| Claude-3 | 9 | 3 | 3 | 15 | 0.750000 | 0.600000 | 0.666667 |
| GEMINI | 6 | 4 | 5 | 15 | 0.600000 | 0.400000 | 0.480000 |
| pathway | 7 | 3 | 5 | 15 | 0.700000 | 0.466667 | 0.560000 |

*6*

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| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| IGF-I | IGF-I-R | Activation | Activation | Activation | Activation | Activation |
| IGF-I-R | PI3-kinase | Activation | Activation | Activation | Activation | Activation |
| PI3-kinase | PKB (Akt) | Activation | Activation | Inhibition | Activation | Activation |
| PKB (Akt) | Transcription or Splicing Factors | Activation | Activation | Inhibition | Activation | Activation |
| PDGFs | PDGF-R | Activation |  | Activation | Activation | Activation |
| PDGF-R | MEK1 | Activation | Activation |  | Activation |  |
| PDGF-R | MKK6 | Activation |  | Activation | Activation | Activation |
| MEK1 | ERK | Activation | Activation |  |  |  |
| MKK6 | p38MAPK | Activation |  | Activation | Inhibition | Inhibition |
| ERK | Transcription or Splicing Factors | Activation | Activation | Activation |  | Inhibition |
| p38MAPK | Transcription or Splicing Factors | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| bFGF or EGF | bFGF-R or EGF-R | Activation |  | Activation |  |  |
| bFGF-R or EGF-R | MKK6 | Activation | Activation | Activation |  | Inhibition |
| LY294002 | PI3-kinase | Inhibition | Activation | Activation |  | Activation |
| Wortmannin | PI3-kinase | Inhibition | Activation | Activation | Activation | Activation |
| PD98059 | MEK1 | Inhibition | Inhibition | Inhibition |  |  |
| SB203580 | p38MAPK | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| Transcription or Splicing Factors | Maintaining a differentiated phenotype | Activation | Inhibition |  |  | Activation |
| Transcription or Splicing Factors | Induction of dedifferentiation | Activation | Inhibition |  |  |  |

Results

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| **GPT-4** | **12** | **4** | **4** | **20** | **0.750000** | **0.60** | **0.666667** |
| **Claude-3** | **11** | **5** | **4** | **20** | **0.687500** | **0.55** | **0.611111** |
| **GEMINI** | **8** | **6** | **6** | **20** | **0.571429** | **0.40** | **0.470588** |
| **pathway** | **9** | **6** | **5** | **20** | **0.600000** | **0.45** | **0.514286** |

*8*

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| --- | --- | --- | --- | --- | --- | --- |
| Ground truth | | |  |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | GPT-4 | **Claude-3** | GEMINI | pathway |
| VEGF | Endothelial cell proliferation | Activation | Activation | Activation | Activation | Activation |
| VEGF | Endothelial cell migration | Activation | Activation | Inhibition | Activation | Activation |
| VEGF | Increased vascular permeability | Activation | Activation | Activation | Inhibition | Activation |
| VEGF | Endothelial cell survival | Activation | Inhibition | Activation | Inhibition | Inhibition |
| VEGF-R | Endothelial cell proliferation | Activation | Inhibition |  | Activation | Inhibition |
| VEGF-R | Endothelial cell migration | Activation | Activation | Activation |  |  |
| VEGF-R | Increased vascular permeability | Activation |  | Inhibition | Inhibition | Activation |
| VEGF-R | Endothelial cell survival | Activation | Activation |  |  |  |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 5 | 2 | 1 | 8 | 0.714286 | 0.625 | 0.666667 |
| Claude-3 | 4 | 2 | 2 | 8 | 0.666667 | 0.500 | 0.571429 |
| GEMINI | 3 | 3 | 2 | 8 | 0.500000 | 0.375 | 0.428571 |
| pathway | 4 | 2 | 2 | 8 | 0.666667 | 0.500 | 0.571429 |

*9*

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| --- | --- | --- | --- | --- | --- | --- |
| Ground truth | | |  |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | GPT-4 | **Claude-3** | GEMINI | pathway |
| EGFR | Ras | Activation | Activation | Activation | Activation | Activation |
| EGFR | PI3K | Activation | Activation | Activation | Activation | Activation |
| Ras | Raf | Activation | Activation | Activation | Activation | Activation |
| Raf | MEK | Activation |  | Activation | Activation |  |
| MEK | ERK | Activation | Activation | Activation |  | Activation |
| PI3K | Akt | Activation |  |  | Inhibition | Inhibition |
| Akt | mTOR | Activation | Activation | Activation | Inhibition | Inhibition |
| Cetuximab | EGFR | Inhibition | Inhibition |  | Inhibition | Inhibition |
| Erlotinib/Gefitinib | EGFR | Inhibition | Inhibition | Activation |  | Activation |
| PF-00299804/BIBW2992 | EGFR | Inhibition | Inhibition | Activation | Activation | Activation |
| PF-00299804/BIBW2992 | HER | Inhibition | Inhibition | Inhibition |  | Inhibition |
| Salirasib | Ras | Inhibition | Activation | Activation | Activation |  |
| LY294002 | PI3K | Inhibition | Activation | Activation | Activation | Activation |
| BEZ235 | PI3K | Inhibition | Inhibition | Inhibition | Inhibition |  |
| BEZ235 | mTOR | Inhibition |  |  | Activation | Activation |
| Rapamycin/RAD001/CCI-779 | mTOR | Inhibition |  | Activation |  |  |
| Antiangiogenic agents | VEGFR | Inhibition | Inhibition |  | Activation |  |
| Antiangiogenic agents | PDGFR | Inhibition | Activation |  |  | Activation |
| Antiangiogenic agents | FGFR | Inhibition | Inhibition | Inhibition | Activation |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Model | Correct Predictions | False Predictions | Missing Relation | Total Predictions | Precision | Recall | F1 |
| GPT-4 | 12 | 4 | 3 | 19 | 0.750000 | 0.631579 | 0.685714 |
| Claude-3 | 11 | 5 | 4 | 19 | 0.687500 | 0.578947 | 0.628571 |
| GEMINI | 8 | 6 | 5 | 19 | 0.571429 | 0.421053 | 0.484848 |
| pathway | 9 | 6 | 4 | 19 | 0.600000 | 0.473684 | 0.529412 |

*10*

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| --- | --- | --- | --- | --- | --- | --- |
| Ground Truth | | |  |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | GPT-4 | **Claude-3** | GEMINI | pathway |
| EGF, TGF-Î±, or other ligands | EGFR or other family members | Activation | Activation | Activation | Activation | Activation |
| EGFR or other family members | PI3K | Activation | Activation | Activation | Activation | Activation |
| PI3K | Akt | Activation |  | Inhibition |  | Activation |
| Akt | mTOR | Activation | Activation | Inhibition | Activation | Activation |
| EGFR or other family members | STAT signaling | Activation | Activation | Activation | Activation | Activation |
| STAT signaling | Survival | Activation | Activation | Activation |  | Activation |
| STAT signaling | Transcription | Activation | Activation |  | Inhibition | Inhibition |
| STAT signaling | Proliferation | Activation | Activation | Activation | Inhibition | Inhibition |
| EGFR or other family members | Ras | Activation | Inhibition | Inhibition | Inhibition |  |
| Ras | Raf | Activation | Inhibition |  |  |  |
| Raf | MAPK | Activation |  | Activation | Inhibition | Inhibition |
| MAPK | Proliferation | Activation | Activation |  | I |  |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 8 | 2 | 2 | 12 | 0.800000 | 0.666667 | 0.727273 |
| Claude-3 | 7 | 2 | 3 | 12 | 0.777778 | 0.583333 | 0.666667 |
| GEMINI | 4 | 4 | 4 | 12 | 0.500000 | 0.333333 | 0.400000 |
| pathway | 5 | 4 | 3 | 12 | 0.555556 | 0.416667 | 0.476190 |

*11*

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| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Integrin | p130Cas | Activation | Activation | Activation | Activation |  |
| Integrin | Paxillin | Activation | Activation | Activation | Activation | Activation |
| p130Cas | Crk | Activation | Activation | Activation | Activation | Activation |
| Paxillin | Fak | Activation | Activation |  | Activation | Activation |
| Crk | Rac1 | Activation | Activation | Activation |  | Activation |
| Fak | Rac1 | Activation |  | Activation | Inhibition | Activation |
| Rac1 | Integrin-mediated Cell Motility | Activation | Inhibition |  |  | Activation |
| Integrin | N-Cadherin Adhesion | Activation |  | Activation | Inhibition |  |
| N-Cadherin | N-Cadherin Adhesion | Activation | Activation | Inhibition |  | Activation |
| Fak (pY861) | Rac1 | Inhibition | Inhibition |  | Inhibition |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 6 | 2 | 2 | 10 | 0.750000 | 0.6 | 0.666667 |
| Claude-3 | 5 | 3 | 2 | 10 | 0.625000 | 0.5 | 0.555556 |
| GEMINI | 3 | 4 | 3 | 10 | 0.428571 | 0.3 | 0.352941 |
| pathway | 4 | 3 | 3 | 10 | 0.571429 | 0.4 | 0.470588 |

*12*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Agonist | β1-AR | Activation | Activation | Activation | Activation | Activation |
| Agonist | β2-AR | Activation | Activation | Activation | Activation | Activation |
| β1-AR | Gsα | Activation | Activation | Activation | Activation | Activation |
| β2-AR | Gsα | Activation | Activation | Activation | Activation | Activation |
| Gsα | Adenylyl cyclase | Activation | Inhibition | Activation | Activation | Activation |
| Adenylyl cyclase | cAMP | Activation | Inhibition | Activation | Inhibition | Inhibition |
| cAMP | PKA | Activation | Activation | Activation | Inhibition | Inhibition |
| PKA | Troponin I-P | Activation | Inhibition |  | Inhibition | Inhibition |
| PKA | RyR-P | Activation | Inhibition | Inhibition |  |  |
| PKA | PLB-P | Activation | Activation | Inhibition | Inhibition |  |
| PKA | cPLA2 | Activation | Activation |  |  |  |
| Troponin I-P | Increased cardiac contractility and relaxation | Activation |  | Inhibition | Inhibition |  |
| RyR-P | Increased cardiac contractility and relaxation | Activation | Inhibition | Inhibition | Inhibition | Activation |
| PLB-P | Increased cardiac contractility and relaxation | Activation | Inhibition |  |  | Activation |
| cPLA2 | Reduced cardiac contractility | Activation |  |  | Inhibition | Activation |
| Ca2+ | L-type Ca2+ channel | Activation |  | Activation |  |  |
| Giβ | cAMP | Inhibition | Inhibition | Inhibition |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 11 | 4 | 3 | 18 | 0.733333 | 0.611111 | 0.666667 |
| Claude-3 | 10 | 4 | 4 | 18 | 0.714286 | 0.555556 | 0.625000 |
| GEMINI | 6 | 5 | 7 | 18 | 0.545455 | 0.333333 | 0.413793 |
| pathway | 7 | 6 | 5 | 18 | 0.538462 | 0.388889 | 0.451613 |

*13*

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| --- | --- | --- | --- | --- | --- | --- |
| ***Ground truth*** | | |  |  |  |  |
| ***Starter (gene1)*** | ***Receptor (gene2)*** | ***Relationship*** | ***GPT-4*** | **Claude-3** | GEMINI | pathway |
| *EGF* | *MEK1/2* | *Activation* | *Activation* | *Activation* | *Activation* |  |
| *MEK1/2* | *Erk1/2* | *Activation* | *Activation* | *Activation* |  |  |
| *Erk1/2* | *RSK1* | *Activation* | *Activation* | *Activation* |  | *Activation* |
| *IGF-I* | *PI3K* | *Activation* | *Activation* | *Inhibition* | *Inhibition* | *Activation* |
| *Insulin* | *PI3K* | *Activation* | *Inhibition* |  | *Inhibition* | *Activation* |
| *PI3K* | *Akt* | *Activation* | *Inhibition* | *Inhibition* |  | *Activation* |
| *Akt* | *TSC2* | *Activation* |  | *Activation* | *Activation* | *Activation* |
| *Akt* | *mTOR-RICTOR* | *Activation* | *Activation* |  | *Activation* | *Activation* |
| *TSC1* | *Rheb* | *Activation* | *Activation* | *Activation* |  | *Activation* |
| *Rheb* | *mTOR-RAPTOR* | *Activation* |  | *Activation* | *Activation* | *Activation* |
| *mTOR-RAPTOR* | *p70S6K* | *Activation* | *Activation* |  | *Activation* | *Activation* |
| *mTOR-RAPTOR* | *4EBP1* | *Inhibition* | *Inhibition* | *Inhibition* | *Inhibition* |  |
| *Erk1/2* | *TSC2* | *Inhibition* | *Activation* | *Activation* | *Activation* | *Inhibition* |
| *TSC2* | *Rheb* | *Inhibition* |  | *Activation* | *Activation* |  |
| *RSK1* | *TSC2* | *Inhibition* | *Inhibition* | *Inhibition* | *Activation* |  |
| *Rapamycin* | *mTOR-RAPTOR* | *Inhibition* | *Inhibition* | *Inhibition* | *Inhibition* | *Inhibition* |
| *Ras* | *MEK1/2* | *Activation* |  | *Activation* | *Activation* |  |
| *Ras* | *PI3K* | *Activation* | *Activation* | *Activation* |  |  |
| *EGF* | *TSC2 (via MEK1/2)* | *Inhibition* | *Inhibition* |  |  |  |
| *EGF* | *TSC2 (via Erk1/2)* | *Inhibition* | *Inhibition* |  |  | *Inhibition* |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 12 | 4 | 4 | 20 | 0.750000 | 0.60 | 0.666667 |
| Claude-3 | 11 | 5 | 4 | 20 | 0.687500 | 0.55 | 0.611111 |
| GEMINI | 7 | 7 | 6 | 20 | 0.500000 | 0.35 | 0.411765 |
| pathway | 8 | 6 | 6 | 20 | 0.571429 | 0.40 | 0.470588 |

*14*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ground truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| MTX | MTX polyglutamates | Activation | Activation | Activation | Activation | Activation |
| MTX polyglutamates | DHFR | Activation | Activation | Activation | Activation | Activation |
| DHFR | FH2 | Activation | Activation | Activation | Activation | Activation |
| FH2 | 5,10-CH2-THF | Activation | Activation | Activation | Activation | Activation |
| 5,10-CH2-THF | 5-CH3-THF | Activation |  | Activation | Activation | Activation |
| 5-CH3-THF | DNA ← dTMP | Activation | Activation | Activation | Activation | Activation |
| DNA ← dTMP | dUMP | Activation | Inhibition | Inhibition |  | Activation |
| dUMP | TYMS | Activation | Activation | Inhibition | Inhibition | Activation |
| TYMS | MTX polyglutamates | Activation | Activation |  |  | Inhibition |
| MTX | Influx SLC19A1 | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| Influx SLC19A1 | MTX | Activation |  | Inhibition | Inhibition | Activation |
| MTX | Efflux ABCC1-C4/ABCG2 | Activation | Activation | Activation |  | Activation |
| Efflux ABCC1-C4/ABCG2 | MTX | Activation | Activation | Activation | Inhibition |  |
| MTX polyglutamates | FPGS | Activation | Inhibition | Activation |  |  |
| FPGS | MTX polyglutamates | Activation |  | Activation | Inhibition |  |
| MTX polyglutamates | GGH | Activation | Activation | Activation | Inhibition | Activation |
| GGH | MTX polyglutamates | Activation | Inhibition | Inhibition |  | Activation |
| 5-CH3-THF | FH4 | Activation | Inhibition |  | Inhibition | Activation |
| FH4 | ATIC | Activation |  | Activation | Activation |  |
| ATIC | Adenosine accumulation | Activation | Activation | Inhibition |  |  |
| Adenosine accumulation | Target cell | Activation | Activation |  | Inhibition | Activation |
| Target cell | ADORA 1/2A | Activation | Activation |  | Activation | Activation |
| MTX polyglutamates | TYMS | Inhibition | Activation | Activation | Activation |  |
| MTX polyglutamates | ATIC | Inhibition | Activation |  | Activation |  |
| MTHFR | 5,10-CH2-THF | Inhibition | Inhibition | Inhibition |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 15 | 5 | 5 | 25 | 0.750000 | 0.60 | 0.666667 |
| Claude-3 | 14 | 5 | 6 | 25 | 0.736842 | 0.56 | 0.636364 |
| GEMINI | 10 | 8 | 7 | 25 | 0.555556 | 0.40 | 0.465116 |
| pathway | 12 | 7 | 6 | 25 | 0.631579 | 0.48 | 0.545455 |

*15*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| LPS | TLR4 | Activation | Activation | Activation | Activation |  |
| LBP | TLR4 | Activation | Activation | Activation | Activation | Activation |
| CD14 | TLR4 | Activation | Activation | Activation | Activation | Activation |
| TLR4 | p38 | Activation | Activation | Activation | Inhibition | Activation |
| TLR4 | Tec Kinases | Activation | Activation | Activation | Inhibition | Inhibition |
| TLR4 | PI3K | Activation | Activation | Inhibition |  | Inhibition |
| TLR4 | Syk | Activation |  |  | Inhibition |  |
| p38 | IL-8 | Activation | Inhibition | Inhibition |  | Inhibition |
| p38 | Cell Adhesion | Activation | Inhibition |  | Inhibition |  |
| p38 | NF-κB | Activation | Activation | Activation | Activation | Inhibition |
| Tec Kinases | JNK | Activation | Inhibition | Inhibition | Inhibition | Activation |
| PI3K | JNK | Activation | Inhibition | I | Inhibition | Inhibition |
| Syk | JNK | Activation | Activation | Activation | Activation |  |
| JNK | Cdc42 | Activation | Activation | Activation | Activation | Activation |
| Cdc42 | Actin Assembly | Activation |  | Inhibition |  | Inhibition |
| Actin Assembly | Neutrophil Migration | Activation | Activation |  |  | Inhibition |
| p38 | TNF-α | Activation |  | Activation |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 11 | 4 | 2 | 17 | 0.733333 | 0.647059 | 0.687500 |
| Claude-3 | 10 | 3 | 4 | 17 | 0.769231 | 0.588235 | 0.666667 |
| GEMINI | 7 | 5 | 5 | 17 | 0.583333 | 0.411765 | 0.482759 |
| pathway | 8 | 5 | 4 | 17 | 0.615385 | 0.470588 | 0.533333 |

*16*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ground Truth | | |  |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | GPT-4 | **Claude-3** | GEMINI | pathway |
| Bcr | Abl | Activation | Activation | Activation | Activation |  |
| Abl | STAT | Activation | Activation | Activation | Activation | Activation |
| Abl | Raf | Activation | Activation | Activation | *inhibition* | Activation |
| Abl | PI3k | Activation | Activation | Activation | *inhibition* | *inhibition* |
| STAT | Bcl-xL | Activation | Activation | Activation |  | *inhibition* |
| Bcl-xL | ↓ Apoptosis | Activation | Activation |  | *inhibition* | *inhibition* |
| Raf | ERK | Activation |  | Activation |  | *inhibition* |
| ERK | Bcl2 | Activation | *inhibition* | Activation | Activation | *inhibition* |
| Bcl2 | ↓ Apoptosis | Activation | Activation |  | Activation | Activation |
| PI3k | Akt1 | Activation | Activation | Activation | Activation | Activation |
| Akt1 | Bad | Activation | Activation | Activation | Activation | Activation |
| Bad | ↓ Apoptosis | Activation | *inhibition* | *inhibition* |  | Activation |
| Akt1 | FOXO3a | Activation | Activation | *inhibition* | *inhibition* |  |
| FOXO3a | ↓ Apoptosis | Activation |  |  |  | *inhibition* |
| Akt1 | FOXO3a | *inhibition* | Activation |  | Activation |  |
| Akt1 | Bad | *inhibition* |  | *inhibition* | Activation |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 10 | 3 | 3 | 16 | 0.769231 | 0.6250 | 0.689655 |
| Claude-3 | 9 | 3 | 4 | 16 | 0.750000 | 0.5625 | 0.642857 |
| GEMINI | 6 | 5 | 5 | 16 | 0.545455 | 0.3750 | 0.444444 |
| pathway | 7 | 5 | 4 | 16 | 0.583333 | 0.4375 | 0.500000 |

*17*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Pathogen | FLS2 | Activation | Activation | Inhibition | Inhibition |  |
| flg22 | FLS2 | Activation | Activation | Inhibition | Inhibition | Inhibition |
| FLS2 | GPA1 | Activation | Activation | Inhibition |  | Inhibition |
| FLS2 | ABA | Activation | Activation | Activation | Inhibition |  |
| ABA | S1P | Activation | Activation | Activation |  | Activation |
| S1P | GPA1 | Activation | Activation | Activation | Inhibition | Activation |
| GPA1 | OST1 | Activation |  | Activation | Activation |  |
| GPA1 | ROS | Activation | Activation |  | Activation | Activation |
| OST1 | ROS | Activation | Activation | Activation | Activation | Activation |
| ROS | NO | Activation |  |  | Activation | Activation |
| NO | Intracellular Ca2+ stores | Activation | Activation | Activation | Activation | Activation |
| Intracellular Ca2+ stores | CNG2/DND1 channels | Activation |  |  | Activation | Activation |
| Intracellular Ca2+ stores | K+in channels | Activation | Activation | Activation |  | Activation |
| Intracellular Ca2+ stores | K+out channels | Activation | Activation | Activation | Activation | Activation |
| MPK3 | ROS | Activation | Activation | Activation | Activation | Activation |
| COR | [pH]cyt | Activation | Activation |  | Activation |  |
| ROS | K+in channels | Inhibition |  | Activation | Activation | Activation |
| ROS | K+out channels | Inhibition | Inhibition | Activation |  | Activation |
| NO | K+in channels | Inhibition | Activation |  | Activation | Activation |
| NO | K+out channels | Inhibition |  | Activation |  |  |
| COR | K+in channels | Activation | Activation |  | Activation |  |
| COR | K+out channels | Inhibition | Activation | Activation | Activation |  |
| ROS | CNG2/DND1 channels | Activation | Activation | Activation | Activation |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 14 | 5 | 5 | 24 | 0.736842 | 0.583333 | 0.651163 |
| Claude-3 | 13 | 6 | 6 | 24 | 0.684211 | 0.541667 | 0.604651 |
| GEMINI | 10 | 9 | 5 | 24 | 0.526316 | 0.416667 | 0.465116 |
| pathway | 11 | 7 | 6 | 24 | 0.611111 | 0.458333 | 0.523810 |

*18*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| PTEN | PI3K | Activation | Activation | Activation | Inhibition |  |
| PI3K | PDK1 | Activation | Activation | Activation | Inhibition |  |
| PDK1 | AKT/PKB (T308) | Activation | Activation | Activation | Inhibition |  |
| AKT/PKB | TSC1/2 (S478) | Activation | Activation | Activation | Inhibition | Inhibition |
| TSC1/2 | Rheb | Activation | Activation | Activation | Inhibition | Inhibition |
| Rheb | mTOR | Activation | Activation | Activation |  |  |
| mTOR | 4E-BP1 | Activation | Activation |  | Inhibition | Inhibition |
| mTOR | S6K | Activation |  | Activation |  | Inhibition |
| 4E-BP1 | ribosome biogenesis | Activation | Inhibition | Activation | Inhibition |  |
| S6K | Translation | Activation | Inhibition | Activation | Activation | Inhibition |
| mTOR | DEPTOR | Activation | Activation |  | Activation | Inhibition |
| mTOR | Raptor | Activation | Activation | Activation | Activation | Inhibition |
| mTOR | PRAS40 | Activation | Inhibition | Inhibition |  | Activation |
| mTOR | mLST8 | Activation | Inhibition |  | Inhibition | Activation |
| mTOR | DEPTOR | Activation | Activation | Activation | Activation | Activation |
| mTOR | PRR5/5L | Activation |  | Activation |  |  |
| mTOR | RicTOR | Activation | Activation | Activation |  |  |
| RTKs | PI3K | Activation | Activation |  | Activation | Activation |
| IRS-1 | PI3K | Activation |  | Activation | Activation | Activation |
| LKB1 | AMPK | Activation | Activation | Activation |  | Activation |
| AMPK | TSC1/2 | Activation | Activation | Activation | Activation |  |
| Hypoxia | HIF1α | Activation | Activation | Activation |  | Activation |
| RAG | mTOR | Activation | Activation | Activation | Activation | Activation |
| Amino acids | mTOR | Activation | Activation | Activation | Activation | Activation |
| Stress | mTOR | Inhibition | Activation | Activation | Activation | Activation |
| P53 | TSC1/2 | Inhibition |  | Activation |  | Activation |
| TSC1/2 | Rheb | Inhibition | Inhibition |  | Activation | Activation |
| PRAS40 | mTOR | Inhibition | Inhibition | Activation | Activation | Activation |
| DEPTOR | mTOR | Inhibition |  | Activation |  | Activation |
| S6K | IRS-1 | Inhibition | Inhibition |  | Activation |  |
| Insulin, growth factors, hormones | IRS-1 | Activation | Activation | Activation | Activation |  |
| P53 | Energy | Activation | Activation | Activation | Activation |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 22 | 6 | 6 | 34 | 0.785714 | 0.647059 | 0.709677 |
| Claude-3 | 20 | 8 | 6 | 34 | 0.714286 | 0.588235 | 0.645161 |
| GEMINI | 15 | 10 | 9 | 34 | 0.600000 | 0.441176 | 0.508475 |
| pathway | 16 | 9 | 10 | 34 | 0.640000 | 0.470588 | 0.542373 |

*19*

*Function as the greatest route gene extractor, accurately extracting each gene link based on the relation provided in the picture. In the gene pathway diagram shown above, the terms "inhibition" is represented by T-bar symbols (----|) like this one and dashed T-bar represents " Indirect Inhibition" and "activation" is by arrow symbols and dashed arrow symbols by "indirect activation". The arrow line (--) to arrowhead (→) represents the direction of the relation, and arrow one is like T-bar. Please remove every gene relationship from the image, avoid confusing them with one another, and refer to the relationships as gene1 (starter) and relationship as gene2 (receptor). Give every relation accurately without missing any relation.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Receptor tyrosine kinase (ALK, Trk, IGF1R) | PI3K | Activation | Activation | Activation | Inhibition | Inhibition |
| PI3K | PDK1 (S473) | Activation | Activation | Activation | Inhibition | Inhibition |
| PDK1 | AKT (T308) | Activation | Activation | Activation |  | Inhibition |
| AKT | mTORC1 | Activation | Activation | Activation | Inhibition | Inhibition |
| AKT | GSK3β | Activation |  | Activation | Inhibition | Inhibition |
| AKT | Mycn (S62) | Activation | Activation | Activation | Activation | Activation |
| GSK3β | CDK1 | Activation | Activation | Activation | Activation | Activation |
| mTORC1 | S6K | Activation | Activation | Inhibition | Inhibition |  |
| mTORC1 | 4EBP | Activation | Activation | Inhibition | Inhibition |  |
| S6K | Translational Control | Activation |  | Activation | Activation | Activation |
| 4EBP | Translational Control | Activation | Activation | Activation | Activation | Activation |
| mTORC1 | mTORC2 (PDK2) | Activation | Activation | Activation |  | Activation |
| mTORC2 | AKT | Activation |  | Activation | Activation | Activation |
| mTORC1 | Raptor | Activation | Activation | Activation | Activation | Activation |
| Raptor | mTORC1 | Activation | Activation | Activation | Activation | Activation |
| Mycn (S62) | Induction of Mycn downstream target genes | Activation |  | Activation |  | Activation |
| CDK1 | Cyclin B | Activation | Activation | Activation | Activation | Activation |
| CDK1/Cyclin B | Mycn (T58) | Activation | Activation | Activation | Activation | Activation |
| PP2A | Mycn (T58) | Inhibition | Inhibition |  |  | Inhibition |
| Fbw7 | Mycn (T58) | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| Mycn (unstable) | Mycn (T58) | Inhibition | Inhibition |  |  | Inhibition |
| AKT inhibitors | AKT | Inhibition | Inhibition | Activation | Activation | Activation |
| CDK inhibitors | CDK1 | Inhibition | Inhibition | Activation | Activation | Activation |
| mTOR inhibitors | mTOR | Inhibition | Inhibition | Inhibition |  |  |
| mTORC1 allosteric inhibitors | mTORC1 | Inhibition | Inhibition |  | Inhibition |  |
| PI3K inhibitors | PI3K | Activation |  |  |  |  |
| PDK inhibitors | PDK1 | Activation |  |  | Inhibition |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 19 | 6 | 5 | 30 | 0.760000 | 0.633333 | 0.690909 |
| Claude-3 | 20 | 5 | 5 | 30 | 0.800000 | 0.666667 | 0.727273 |
| GEMINI | 15 | 8 | 7 | 30 | 0.652174 | 0.500000 | 0.566038 |
| pathway | 16 | 8 | 6 | 30 | 0.666667 | 0.533333 | 0.592593 |

*20*

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 8 | 3 | 2 | 13 | 0.727273 | 0.615385 | 0.666667 |
| Claude-3 | 7 | 3 | 3 | 13 | 0.700000 | 0.538462 | 0.608696 |
| GEMINI | 5 | 5 | 3 | 13 | 0.500000 | 0.384615 | 0.434783 |
| pathway | 6 | 4 | 3 | 13 | 0.600000 | 0.461538 | 0.521739 |

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|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ground Truth | | |  |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | GPT-4 | **Claude-3** | GEMINI | pathway |
| Growth factors | PI3K | Activation | Activation | Activation | Activation |  |
| PI3K | AKT | Activation | Activation | Activation | Activation | Activation |
| AKT | mTORC1 | Activation | Activation | Activation |  | Activation |
| Hypoxia | REDD1 | Activation | *Inhibition* | Activation | Activation |  |
| REDD1 | TSC1/2 | Activation | Activation |  | *Inhibition* | Activation |
| Bioenergy (↑AMP/ATP) | AMPK | Activation | Activation | Activation |  | *Inhibition* |
| AMPK | TSC1/2 | Activation | *Inhibition* | *Inhibition* | *Inhibition* | *Inhibition* |
| Genotoxic stress | p53 | Activation |  | Activation | *Inhibition* |  |
| p53 | AMPK | Activation | Activation |  |  | *Inhibition* |
| Sestrins1,2 | AMPK | Activation | Activation | Activation | *Inhibition* |  |
| Amino acids | RagA/RagC | Activation | Activation | Activation |  | *Inhibition* |
| RagA/RagC | mTORC1 | Activation |  | *Inhibition* | *Inhibition* |  |
| TSC1/2 | Rheb | Activation | Activation |  | Activation | *Inhibition* |
| Rheb | mTORC1 | Activation |  | Activation | Activation | Activation |
| mTORC1 | Cell growth, survival & proliferation | Activation | Activation | Activation | Activation |  |
| AKT | TSC1/2 | *Inhibition* | Activation | Activation | Activation |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 10 | 3 | 3 | 16 | 0.769231 | 0.6250 | 0.689655 |
| Claude-3 | 9 | 4 | 3 | 16 | 0.692308 | 0.5625 | 0.620690 |
| GEMINI | 6 | 5 | 5 | 16 | 0.545455 | 0.3750 | 0.444444 |
| pathway | 7 | 5 | 4 | 16 | 0.583333 | 0.4375 | 0.500000 |

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|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ***Starter (gene1)*** | ***Receptor (gene2)*** | ***Relationship*** | ***GPT-4*** | **Claude-3** | GEMINI | pathway |
| *UVB* | *PI3-K* | *Activation* | *Activation* | *Activation* | *Inhibition* |  |
| *UVB* | *p38* | *Activation* | *Activation* | *Activation* | *Inhibition* |  |
| *p38* | *CREB* | *Activation* |  | *Activation* | *Activation* | *Inhibition* |
| *PI3-K* | *Akt* | *Activation* | *Activation* | *Activation* | *Activation* | *Inhibition* |
| *Akt* | *mTOR* | *Activation* | *Activation* |  | *Activation* |  |
| *mTOR* | *4E-BP1* | *Activation* | *Activation* | *Activation* | *Activation* | *Activation* |
| *mTOR* | *p70S6K* | *Activation* | *Activation* | *Activation* | *Activation* | *Activation* |
| *mTOR* | *4E-BP1* | *Inhibition* | *Activation* |  |  | *Activation* |
| *4E-BP1* | *Translation complex* | *Inhibition* | *Activation* | *Activation* | *Activation* |  |
| *p70S6K* | *Translation complex* | *Activation* | *Activation* | *Activation* | *Activation* | *Activation* |
| *Translation complex* | *c-Fos protein* | *Activation* | *Activation* | *Activation* |  | *Activation* |
| *c-Fos protein* | *c-Fos mRNA* | *Activation* |  |  | *Inhibition* | *Activation* |
| *c-Fos mRNA* | *CREB* | *Activation* | *Activation* | *Activation* | *Activation* |  |
| *AA* | *mRNA stability* | *Activation* |  | *Activation* | *Activation* | *Inhibition* |
| *Qu* | *PI3-K* | *Inhibition* | *Inhibition* | *Inhibition* | *Inhibition* |  |
| *Qu+AA* | *p38* | *Inhibition* | *Inhibition* | *Inhibition* |  | *Activation* |
| *Qu+AA* | *PI3-K* | *Inhibition* | *Inhibition* | *Inhibition* |  |  |
| *Qu* | *p38* | *Activation* | *Activation* | *Inhibition* |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 12 | 3 | 3 | 18 | 0.800000 | 0.666667 | 0.727273 |
| Claude-3 | 11 | 4 | 3 | 18 | 0.733333 | 0.611111 | 0.666667 |
| GEMINI | 8 | 5 | 5 | 18 | 0.615385 | 0.444444 | 0.516129 |
| pathway | 9 | 4 | 5 | 18 | 0.692308 | 0.500000 | 0.580645 |

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|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *Ground Truth* | | |  |  |  |  |
| *Starter (gene1)* | *Receptor (gene2)* | *Relationship* | *GPT-4* | **Claude-3** | GEMINI | pathway |
| *17-β estradiol* | *ERα/β* | *Activation* | *Activation* | *Activation* | *Activation* |  |
| *EGFR* | *GRB2* | *Activation* | *Activation* | *Activation* | *Activation* | *Activation* |
| *GRB2* | *SOS* | *Activation* | *Activation* | *Activation* | *Activation* | *Activation* |
| *SOS* | *RAS* | *Activation* | *Activation* | *Activation* |  | *Activation* |
| *RAS* | *RAF* | *Activation* | *Activation* | *Activation* | *Activation* |  |
| *RAF* | *MEK* | *Activation* |  | *Activation* |  | *Activation* |
| *MEK* | *ERK* | *Activation* | *Activation* | *n* | *Inhibition* | *Activation* |
| *ERK* | *Coactivator* | *Activation* | *Activation* | *Activation* |  | *Inhibition* |
| *ERK* | *ERβ-ERβ homodimer* | *Activation* |  | *Activation* | *Inhibition* | *Inhibition* |
| *Coactivator* | *GRIP1* | *Activation* |  | *Activation* | *Inhibition* |  |
| *GRIP1* | *ERE* | *Activation* | *Activation* | *Inhibition* |  | *Inhibition* |
| *ERβ-ERβ homodimer* | *Cell growth/DNA synthesis* | *Activation* | *Activation* |  | *Inhibition* | *Inhibition* |
| *Fulvestrant* | *ERα/β* | *Inhibition* | *Inhibition* | *Inhibition* | *Inhibition* | *Inhibition* |
| *HSP90* | *ERα/β (inactive)* | *Inhibition* |  |  | *Inhibition* | *Inhibition* |
| *ERK* | *GRIP1* | *Activation* | *Inhibition* | *Inhibition* | *Inhibition* |  |
| *ERK* | *ERE* | *Activation* | *Inhibition* | *Inhibition* |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 10 | 4 | 2 | 16 | 0.714286 | 0.6250 | 0.666667 |
| Claude-3 | 9 | 4 | 3 | 16 | 0.692308 | 0.5625 | 0.620690 |
| GEMINI | 6 | 5 | 5 | 16 | 0.545455 | 0.3750 | 0.444444 |
| pathway | 7 | 5 | 4 | 16 | 0.583333 | 0.4375 | 0.500000 |

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| --- | --- | --- | --- | --- | --- | --- |
| **Ground truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| PBX1, EMX2, CBX2, LHX9 | Genital ridge | Activation | Activation | Activation | Activation |  |
| WT1, NR5A1 | Genital ridge | Activation | Activation | Activation | Activation |  |
| Genital ridge | WNT4 | Activation | Activation | Activation |  | Activation |
| WNT4/RSPO1 | β-catenin | Activation | Activation | Activation | Inhibition | Inhibition |
| β-catenin | SOX9 | Activation | Activation | Activation |  | Inhibition |
| SOX9 | FOXL2 | Activation | Activation | Activation |  | Inhibition |
| FOXL2 | Steroidogenesis (Ovary) | Activation | Activation | Activation | Inhibition | Inhibition |
| Genital ridge | SRY | Activation |  | Activation | Inhibition | Inhibition |
| SRY | SOX9 | Activation | Activation |  | Activation | Inhibition |
| SOX9 | AMH | Activation | Inhibition | Inhibition |  | Activation |
| SOX9 | FOXL2 | Activation |  |  | Inhibition | Inhibition |
| AMH | DHH | Activation | Activation | Activation | Activation | Inhibition |
| DHH | NR5A1 | Activation | Inhibition | Inhibition | Inhibition |  |
| NR5A1 | Steroidogenesis (Testis) | Activation | Inhibition |  |  |  |
| Genital ridge | FOXL2 | Activation |  | Activation | Activation |  |
| FOXL2 | SOX9 | Inhibition | Inhibition | Inhibition | Inhibition |  |
| FOXL2 | SOX9 (Testis) | Inhibition | Inhibition | Inhibition | Inhibition |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 | 5 | 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** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| HRS cell | ↑ IL-10, TARC, MDC (CCL22), CCL5 | Activation | Activation | Activation | Activation |  |
| HRS cell | PD1-L | Activation | Activation | Activation | Activation | Activation |
| PD1-L | PD1+ T | Activation | Activation | Activation | Activation | Activation |
| IL-10, TARC, MDC (CCL22), CCL5 | Th2 | Activation |  | Activation |  | Activation |
| Th2 | Treg | Activation | Activation | Activation | Inhibition | Activation |
| Galectin 1, IL-10 | STAT1+ TAM | Activation | Activation |  | Inhibition | Activation |
| CSF-1 | STAT1+ TAM | Activation |  | Activation |  | Activation |
| Treg | TCL | Inhibition | Inhibition | Inhibition | Inhibition |  |
| PD1+ T | TCL | Inhibition | Activation | Activation | Activation | Inhibition |
| PD1+ T | Th1 | Inhibition | Activation |  | Activation | Activation |
| IFNγ | Treg | Inhibition | Inhibition | Inhibition |  | Activation |
| Treg | PD1+ T | Inhibition | Inhibition | Inhibition | Inhibition | Activation |
| 1 Galaectin1 IL-10 | TCL | Inhibition | Inhibition | Inhibition |  |  |
| 1 Galaectin1 IL-10 | Th1 | Inhibition | Activation | Activation | Activation |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 9 | 3 | 2 | 14 | 0.750000 | 0.642857 | 0.692308 |
| Claude-3 | 8 | 4 | 2 | 14 | 0.666667 | 0.571429 | 0.615385 |
| GEMINI | 6 | 4 | 4 | 14 | 0.600000 | 0.428571 | 0.500000 |
| pathway | 7 | 3 | 4 | 14 | 0.700000 | 0.500000 | 0.583333 |

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|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Compound | PKCδ | Activation | Activation | Activation | Activation |  |
| Compound | ATM | Activation | Activation |  | Activation | Activation |
| PKCδ | p21 | Activation |  | Activation |  | Activation |
| PKCδ | NAG-1 | Activation | Activation | Inhibition | Inhibition | Inhibition |
| ATM | p53 (ser15) | Activation | Inhibition | Inhibition |  | Inhibition |
| p53 (ser15) | Apoptosis | Activation |  | Inhibition | Inhibition | Inhibition |
| NAG-1 | Apoptosis | Activation | Activation |  | Inhibition |  |
| p21 | Proliferation | Inhibition | Activation | Activation | Activation | Activation |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 5 | 2 | 1 | 8 | 0.714286 | 0.625 | 0.666667 |
| Claude-3 | 4 | 2 | 2 | 8 | 0.666667 | 0.500 | 0.571429 |
| GEMINI | 3 | 3 | 2 | 8 | 0.500000 | 0.375 | 0.428571 |
| pathway | 4 | 2 | 2 | 8 | 0.666667 | 0.500 | 0.571429 |

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| --- | --- | --- | --- | --- | --- | --- |
| Ground truth | | |  |  |  |  |
| Starter (gene1) | Receptor (gene2) | Relationship | GPT-4 | **Claude-3** | GEMINI | pathway |
| Alcama | Ednrb | Activation | Activation | Activation | Activation |  |
| Edn1 | Ednra/b | Activation | Activation | Activation | Activation | Activation |
| Ednra/b | hand2 | Activation | Activation | Activation | Activation | Activation |
| Ednra/b | dlx3b | Activation | Activation |  | Activation | Activation |
| Ednra/b | dlx5a | Activation | Activation | Activation |  | Activation |
| Ednra/b | dlx6a | Activation | Activation | Inhibition | Inhibition | Inhibition |
| Ednra/b | NC differentiation | Activation | Inhibition |  | Activation | *Inhibition* |
| Ednra/b | cartilage ventralization | Activation |  | Activation | Activation |  |
| Ednra/b | jaw joint formation | Activation | Activation | Activation | Inhibition |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 6 | 2 | 1 | 9 | 0.750000 | 0.666667 | 0.705882 |
| Claude-3 | 5 | 2 | 2 | 9 | 0.714286 | 0.555556 | 0.625000 |
| GEMINI | 4 | 3 | 2 | 9 | 0.571429 | 0.444444 | 0.500000 |
| pathway | 4 | 2 | 3 | 9 | 0.666667 | 0.444444 | 0.533333 |

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| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| PPARα/RXR | Fgf21 | Activation | Activation | Activation | Activation | Activation |
| Fgf21 | FGFR1c? βKlotho? | Activation | Activation | Activation | Activation |  |
| Starvation | Lipolysis | Activation | Activation | Activation |  | Activation |
| FGF21 | Torpor | *Inhibition* | Activation | Activation | Activation | Activation |
| Ketogenic diet | Torpor | Activation |  | Inhibition | Inhibition |  |
| Lipolysis | NEFA | Inhibition | Inhibition | Inhibition | Inhibition | Activation |
| Fgf21 | NEFA | Activation | Activation |  | Inhibition | Inhibition |
| FGFR1c? βKlotho? | Lipolysis | *Inhibition* | Activation | Activation |  | Inhibition |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 6 | 1 | 1 | 8 | 0.857143 | 0.750 | 0.800000 |
| Claude-3 | 5 | 2 | 1 | 8 | 0.714286 | 0.625 | 0.666667 |
| GEMINI | 4 | 2 | 2 | 8 | 0.666667 | 0.500 | 0.571429 |
| pathway | 3 | 3 | 2 | 8 | 0.500000 | 0.375 | 0.428571 |

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| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Pyruvate + glyceraldehyde 3-phosphate | MEP | Activation | Activation | Activation | Activation |  |
| MEP | HMB-PP | Activation | Activation | Activation | Activation | Activation |
| HMB-PP | DMAPP | Activation | Activation | Activation | Activation | Activation |
| DMAPP + IPP | FPP | Activation |  | Activation | Activation | Activation |
| FPP | Isoprenoids | Activation | Activation | Activation |  | Inhibition |
| 3-hydroxy-3-methylglutaryl-CoA | Mevalonate | Activation | Activation |  | Inhibition | Inhibition |
| Mevalonate | IPP | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| IPP | DMAPP | Activation | Inhibition | Inhibition |  | Inhibition |
| DMAPP + IPP | FPP | Activation | Activation |  | Inhibition | Inhibition |
| FPP | Cholesterol | Activation | Activation | Activation | Activation | Activation |
| FPP | Isoprenoids | Activation | Activation | Activation | Activation | Activation |
| Amino bisphosphonates | FPP | Inhibition | Inhibition | Activation | Activation |  |
| Statins | 3-hydroxy-3-methylglutaryl-CoA | Inhibition |  | Inhibition |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 9 | 2 | 2 | 13 | 0.818182 | 0.692308 | 0.750000 |
| Claude-3 | 8 | 3 | 2 | 13 | 0.727273 | 0.615385 | 0.666667 |
| GEMINI | 6 | 4 | 3 | 13 | 0.600000 | 0.461538 | 0.521739 |
| pathway | 6 | 3 | 4 | 13 | 0.666667 | 0.461538 | 0.545455 |

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| --- | --- | --- | --- | --- | --- | --- |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Growth factors | dTsc1/Tsc2 | Activation | Activation | Activation | Activation |  |
| Amino acids | dTsc1/Tsc2 | Activation | Activation | Activation | Activation |  |
| ATP/AMP | dTsc1/Tsc2 | Activation | Activation |  | Activation | Activation |
| Hypoxia | dTsc1/Tsc2 | Activation | Activation | Activation | Activation | Activation |
| Stresses | dTsc1/Tsc2 | Activation | Inhibition | Activation | Activation | Activation |
| dTsc1/Tsc2 | dRheb | Activation | Inhibition | Activation | Activation | Activation |
| dRheb | dTor | Activation | Activation |  | Activation | Activation |
| dTor | dS6K1 | Activation | Activation | Activation | Activation | Activation |
| dTor | d4E-BP | Activation |  | Activation |  | Inhibition |
| dS6K1 | Autophagy | Activation | Inhibition |  | Inhibition |  |
| dS6K1 | Metabolism | Activation | Activation | Inhibition | Inhibition | Inhibition |
| d4E-BP | Protein synthesis | Activation |  | Inhibition |  | Inhibition |
| d4E-BP | ER Stress | Activation | Activation | Inhibition | Inhibition | Inhibition |
| Insulin signaling pathway | dTsc1/Tsc2 | Activation | Inhibition |  | Inhibition | Inhibition |
| Wnt, TGF β, P53, Sestrins | dTsc1/Tsc2 | Activation | Inhibition | Inhibition | Inhibition | Activation |
| Insulin signaling pathway | dRheb | Activation |  | Activation |  |  |
| Wnt, TGF β, P53, Sestrins | dRheb | Activation | Activation | Activation | Inhibition |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 | GPT-4 | **Claude-3** | GEMINI | pathway |
| PI3K | Akt | Activation | Activation | Inhibition | Inhibition |  |
| Akt | NFκB | Activation | Activation | Inhibition | Inhibition |  |
| Bcl2 | Apoptosome complex | Activation | Activation | Activation | Inhibition |  |
| Apoptosome complex | Executioner caspases-3, 6, 7 | Activation | Activation | Activation |  | Inhibition |
| Executioner caspases-3, 6, 7 | Apoptosis | Activation | Activation |  | Activation | Inhibition |
| Bak/Bax | Mitochondrion | Activation | Activation | Activation | Activation | Inhibition |
| NFκB | Bcl2 | Activation |  | Activation | Activation | Activation |
| Bcl2 | Apoptosome complex | Inhibition | Inhibition | Activation |  | Activation |
| Bcl-X(L) | Apoptosome complex | Inhibition | Activation |  | Activation | Activation |
| IAPs | Executioner caspases-3, 6, 7 | Inhibition | Activation | Activation |  | Activation |
| Akt | Bcl-X(L) | Activation | Activation | Activation |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 8 | 2 | 1 | 11 | 0.800000 | 0.727273 | 0.761905 |
| Claude-3 | 7 | 2 | 2 | 11 | 0.777778 | 0.636364 | 0.700000 |
| GEMINI | 5 | 3 | 3 | 11 | 0.625000 | 0.454545 | 0.526316 |
| pathway | 6 | 3 | 2 | 11 | 0.666667 | 0.545455 | 0.600000 |

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| --- | --- | --- | --- | --- | --- | --- |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| IFNAR | JAK1 | Activation | Activation | Activation | Activation |  |
| JAK1 | TYK2 | Activation | Activation | Activation | Activation | Activation |
| TYK2 | STAT1 (P) | Activation | Activation | Activation | Activation | Activation |
| dsRNA | RIG-I | Activation | Activation | Activation |  | Activation |
| RIG-I | MAVS | Activation | Activation | Activation | Activation | Activation |
| MAVS | NEMO | Activation | Activation | Activation |  | Activation |
| NEMO | IKKα | Activation | Activation | Activation | Activation | Activation |
| IKKα | NFκB | Activation | Activation |  | Activation | Activation |
| NEMO | TBK1 | Activation |  | Activation | Activation | Activation |
| TBK1 | IRF3 | Activation | Inhibition | Activation | Activation | Activation |
| IRF3 | IFN-β | Activation | Activation |  |  | Activation |
| NFκB | IFN-β | Activation |  | Activation | Inhibition | Inhibition |
| IFN-β | IKKα | Activation | Activation | Activation | Inhibition | Inhibition |
| IKKα | STAT1 (P) | Activation | Activation | Activation |  | Inhibition |
| cytokine receptor | STAT1 (P) | Activation | Activation | Activation | Activation | Inhibition |
| cytokine (e.g., IL6) | cytokine receptor | Activation |  | Inhibition | Inhibition | Activation |
| IKKα | cytokine (e.g., IL6) | Inhibition | Inhibition | Inhibition |  |  |
| IFNAR | STAT1 (P) | Activation | Activation |  | Inhibition |  |
| cytokine (e.g., IL6) | STAT1 (P) | Activation | Activation | Inhibition | Inhibition |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 14 | 3 | 2 | 19 | 0.823529 | 0.736842 | 0.777778 |
| Claude-3 | 13 | 3 | 3 | 19 | 0.812500 | 0.684211 | 0.742857 |
| GEMINI | 10 | 4 | 5 | 19 | 0.714286 | 0.526316 | 0.606061 |
| pathway | 11 | 4 | 4 | 19 | 0.733333 | 0.578947 | 0.647059 |

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| --- | --- | --- | --- | --- | --- | --- |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Gln | ASCT2 (SLC1A5) | Activation | Activation | Activation | Activation |  |
| ASCT2 (SLC1A5) | Gln | Activation | Activation | Activation | Activation |  |
| Gln | LAT1 (SLC7A5) | Activation | Activation | Activation | Activation | Activation |
| LAT1 (SLC7A5) | Gln | Activation | Activation | Activation | Activation | Activation |
| Gln | Glutamate | Activation | Activation | Activation | Activation | Activation |
| Glutamate | α-KG | Activation | Activation | Activation | Activation | Activation |
| α-KG | TCA | Activation | Activation | Activation | Activation | Activation |
| TCA | Malate | Activation | Activation | Activation |  | Activation |
| TCA | Fumarate | Activation | Activation | Activation | Activation | Activation |
| TCA | Succinate | Activation | Activation | Activation | Activation | Activation |
| TCA | Citrate | Activation |  |  | Inhibition | Activation |
| Citrate | CoA | Activation | Inhibition | Inhibition |  | Activation |
| GOT2/GPT2 | Glutamate | Activation | Activation | Inhibition |  | Inhibition |
| GDH1 | Glutamate | Activation | Inhibition |  | Inhibition | Inhibition |
| mTOR | Myc | Activation |  | Activation | Activation | Inhibition |
| Myc | mTOR | Activation | Activation |  | Activation | Inhibition |
| BCH | LAT1 (SLC7A5) | Inhibition | Activation | Activation | Activation | Activation |
| DON Azaserine Acivicin | Gln | Inhibition |  | Activation | Activation | Activation |
| GPNA | ASCT2 (SLC1A5) | Inhibition | Inhibition |  | Inhibition | Activation |
| BPTES/CB-839 | GLS | Inhibition | Inhibition | Inhibition | Activation | Activation |
| Compound 968 | GLS | Inhibition |  | Inhibition |  |  |
| Purpurin/R162 | GDH1 | Inhibition | Inhibition |  |  |  |
| EGCG | GDH1 | Inhibition |  | Inhibition | Activation |  |
| AOA | GOT2/GPT2 | Inhibition | Inhibition | Inhibition | Activation |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 16 | 4 | 5 | 25 | 0.800000 | 0.64 | 0.711111 |
| Claude-3 | 15 | 5 | 5 | 25 | 0.750000 | 0.60 | 0.666667 |
| GEMINI | 13 | 6 | 6 | 25 | 0.684211 | 0.52 | 0.590909 |
| pathway | 14 | 6 | 5 | 25 | 0.700000 | 0.56 | 0.622222 |

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| --- | --- | --- | --- | --- | --- | --- |
| Starter (gene1) | Receptor (gene2) | Relationship | GPT-4 | **Claude-3** | GEMINI | pathway |
| Growth signals | D-cyclins | Activation | Activation | Activation | Activation | Activation |
| D-cyclins | CDKs 4/6 | Activation | Activation | Activation |  | Activation |
| CDKs 4/6 | RB | Inhibition | Activation | Activation | Activation |  |
| RB | E2F | Inhibition | Activation |  |  | Inhibition |
| E2F | Cell cycle | Activation | Activation | Activation | Inhibition | Inhibition |
| Damage signals | p53 | Activation | Activation | Activation | Inhibition | Inhibition |
| p53 | CDKN1s p21 | Activation |  |  | Inhibition | Inhibition |
| CDKN2s p16 | CDKs 4/6 | Inhibition | Inhibition | Inhibition | Inhibition | Activation |
| CDKN1s p21 | CDKs 4/6 | Inhibition | Inhibition | Inhibition | Inhibition |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 6 | 2 | 1 | 9 | 0.750000 | 0.666667 | 0.705882 |
| Claude-3 | 5 | 2 | 2 | 9 | 0.714286 | 0.555556 | 0.625000 |
| GEMINI | 4 | 3 | 2 | 9 | 0.571429 | 0.444444 | 0.500000 |
| pathway | 5 | 2 | 2 | 9 | 0.714286 | 0.555556 | 0.625000 |

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| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Myocardial Damage | AT1R/p38 MAPK | Activation | Activation | Activation | Activation | Activation |
| AT1R/p38 MAPK | ACE | Activation | Activation | Activation | Activation | Activation |
| PFD | AT1R/p38 MAPK | Inhibition | Inhibition | Activation | Activation | Activation |
| ACE | Ang II | Activation | Activation | Activation | Activation | Inhibition |
| ACE2 | Ang(1-7) | Activation | Activation | Activation |  | Inhibition |
| Ang(1-7) | MAS | Activation |  | Activation | Inhibition | Inhibition |
| Ang II | AT1R | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| LXR-α | ACE | Activation | Inhibition |  | Inhibition | Activation |
| LXR-α | AT1R/p38 MAPK | Activation | Activation | Activation | Activation | Activation |
| PFD | LXR-α | Activation | Activation | Activation | Activation | Activation |
| PFD | Inhibition of Cardiac fibrosis | Activation |  | Activation |  | Inhibition |
| ACE2 | Ang(1-7) | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| MAS | Cardiac fibrosis | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| Ang(1-7) | Cardiac fibrosis | Activation | Activation | Inhibition | Inhibition | Activation |
| AT1R/p38 MAPK | ACE2 | Inhibition | Inhibition | Inhibition | Inhibition |  |
| ACE2 | Ang(1-7) | Inhibition | Inhibition | Inhibition | Inhibition |  |
| Ang(1-7) | MAS | Inhibition | Inhibition | Inhibition | Inhibition |  |
| PFD | Cardiac fibrosis | Inhibition | Inhibition |  |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 14 | 2 | 2 | 18 | 0.875000 | 0.777778 | 0.823529 |
| Claude-3 | 14 | 3 | 1 | 18 | 0.823529 | 0.777778 | 0.800000 |
| GEMINI | 10 | 4 | 2 | 18 | 0.714286 | 0.555556 | 0.625000 |
| pathway | 11 | 3 | 4 | 18 | 0.785714 | 0.611111 | 0.687500 |

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| --- | --- | --- | --- | --- | --- | --- |
| **Ground Truth** | | |  |  |  |  |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Syx | RhoA | Activation | Activation | Activation | Inhibition |  |
| RhoA | SIRT1 | Activation | Activation | Activation | Inhibition |  |
| SIRT1 | RARγ | Activation | Activation | Activation | Inhibition | Inhibition |
| RARγ | Noggin | Activation | Activation |  | Activation | Inhibition |
| Noggin | Neural differentiation | Activation |  | Activation |  | Activation |
| F-actin | Rab3d | Inhibition | Activation |  | Activation | Activation |
| RARγ | RHPN2 | Inhibition | Activation | Activation |  | Activation |
| Noggin | BMP4 | Inhibition | Inhibition | Activation | Activation | Activation |
| BMP4 | pSmad1 | Activation | Activation |  |  | Activation |
| pSmad1 | Neural differentiation | Inhibition |  | Activation | Activation |  |
| RhoA | Neural differentiation | Activation | Activation | Activation | Activation | Inhibition |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 7 | 2 | 2 | 11 | 0.777778 | 0.636364 | 0.700000 |
| Claude-3 | 6 | 2 | 3 | 11 | 0.750000 | 0.545455 | 0.631579 |
| GEMINI | 5 | 3 | 3 | 11 | 0.625000 | 0.454545 | 0.526316 |
| pathway | 6 | 2 | 3 | 11 | 0.750000 | 0.545455 | 0.631579 |

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| --- | --- | --- | --- | --- | --- | --- |
| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| KAR | GA3oxs | Activation | Activation | Activation | Activation |  |
| GA3oxs | GA | Activation | Activation | Activation | Activation |  |
| GA | GID1 | Activation | Activation | Activation | Activation |  |
| GID1 | SCFSLY/GID1 | Activation | Activation | Activation | Activation | Activation |
| SCFSLY/GID1 | DELLA | Inhibition | Activation | Activation | Activation | Activation |
| DELLA | GAMYB | Inhibition | Activation |  | Activation | Activation |
| GAMYB | EXP2 | Activation | Activation | Activation | Activation | Activation |
| EXP2 | Germination | Activation | Activation |  | Activation | Activation |
| EXP2 | Hypocotyl elongation | Activation | Activation | Activation | Activation | Activation |
| KAR | ABA2 | Activation | Activation | Activation | Activation | Activation |
| ABA2 | ABA | Activation | Activation |  | Activation | Activation |
| ABA | PYR/PYL/RCAR | Activation | Activation | Activation | Activation | Activation |
| PYR/PYL/RCAR | PP2Cs | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| PP2Cs | SnRK2s | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| SnRK2s | TFs | Inhibition | Inhibition |  | Inhibition | Inhibition |
| TFs | ABI3 | Activation |  | Inhibition | Inhibition | Inhibition |
| ABI3 | Germination | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| ABI3 | Hypocotyl elongation | Activation | Activation |  | Inhibition | Inhibition |
| KAR | YUCCAs | Activation | Activation | Inhibition | Inhibition | Inhibition |
| YUCCAs | Auxin | Activation | Activation | Activation | Activation | Activation |
| Auxin | TIR1/AFB | Activation | Activation |  | Activation | Activation |
| TIR1/AFB | SCFTIR1 | Activation |  | Activation | Activation | Activation |
| SCFTIR1 | AUX/IAA | Inhibition | Activation | Activation | Activation | Activation |
| AUX/IAA | ARFs | Inhibition | Activation |  | Activation | Activation |
| ARFs | IAA1 | Activation |  | Activation | Activation | Activation |
| IAA1 | Germination | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| IAA1 | Hypocotyl elongation | Activation | Activation | Activation | Activation | Activation |
| RHPN2 | RARγ | Inhibition | Inhibition | Inhibition | Inhibition |  |
| KAR | Auxin | Activation | Activation | Activation | Inhibition |  |
| Biosynthesis | Phytohormone | Activation |  | Activation | Inhibition |  |
| Phytohormone | Receptor | Activation | Activation | Activation | Inhibition |  |
| Receptor | E3 liges | Activation |  | Activation | Activation |  |
| E3 liges | Repressor | Inhibition | Inhibition | Activation | Activation |  |
| Repressor | Transcription factor | Inhibition |  |  | Inhibition |  |
| Transcription factor | Response gene | Activation | Activation |  | Inhibition |  |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 25 | 6 | 7 | 38 | 0.806452 | 0.657895 | 0.724638 |
| Claude-3 | 23 | 7 | 8 | 38 | 0.766667 | 0.605263 | 0.676471 |
| GEMINI | 18 | 10 | 10 | 38 | 0.642857 | 0.473684 | 0.545455 |
| pathway | 20 | 8 | 10 | 38 | 0.714286 | 0.526316 | 0.606061 |

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

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 16 | 4 | 4 | 24 | 0.800000 | 0.666667 | 0.727273 |
| Claude-3 | 15 | 4 | 5 | 24 | 0.789474 | 0.625000 | 0.697674 |
| GEMINI | 13 | 6 | 5 | 24 | 0.684211 | 0.541667 | 0.604651 |
| pathway | 14 | 9 | 5 | 24 | 0.608696 | 0.583333 | 0.595745 |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| HIF-1β | HIF-1α | Activation | Activation | Activation | Activation |  |
| HIF-1α | PHDs | Activation | Activation | Activation | Activation |  |
| PHDs | VHL E3 | Activation | Activation |  | Activation | Activation |
| VHL E3 | Ub ubiquitin | Activation | Activation | Activation | Activation | Activation |
| Ub ubiquitin | HIF-1α proteasomal degradation | Activation | Activation | Activation | Activation | Activation |
| HIF-1α | Nucleus | Activation | Activation | Activation | Activation | Activation |
| HIF-1β | Nucleus | Activation | Activation | Activation |  |  |
| HIF-1α | HRES | Activation | Activation | Activation |  |  |
| HIF-1β | HRES | Activation |  | Activation |  |  |
| HRES | NCGTG | Activation | Activation |  |  |  |
| NCGTG | Proliferation, Anti-apoptosis, Anti-inflammation, Angiogenesis | Activation |  | Activation |  |  |
| Angiogenesis | Caspase-3 | Activation | Activation | Inhibition | Inhibition | Inhibition |
| Caspase-3 | MEK-1/2 | Activation | Activation | Inhibition | Inhibition |  |
| MEK-1/2 | ERK-1/2 | Activation | Inhibition | Inhibition |  |  |
| ERK-1/2 | Akt | Activation | Inhibition |  | Inhibition | Inhibition |
| EPO | EPO-R | Activation | Inhibition |  |  | Inhibition |
| EPO-R | VEGF | Activation | Activation | Activation | Activation | Activation |
| VEGF | VEGFR | Activation |  | Activation | Activation | Activation |
| ADM | Vasomotor regulation | Activation | Activation | Activation | Activation |  |
| Glut-1 | Energy metabolism | Activation | Activation | Activation | Activation | Activation |
| HO-1 | ROS | Activation |  | Activation | Activation | Activation |
| ROS | IRS1/PI3K/Akt2 | Activation | Activation | Activation | Activation | Activation |
| IRS1/PI3K/Akt2 | Keap1/Nrf2/ERK | Activation | Activation | Activation | Activation | Activation |
| HIF-1α | Maintain mitochondrial membrane potential | Activation | Activation | Activation | Activation | Activation |
| PHDs | HIF-1α | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| Ub ubiquitin | HIF-1α | Inhibition | Activation | Activation | Activation |  |
| HIF-1α proteasomal degradation | HIF-1α | Inhibition |  | Activation | Activation | Activation |
| HO-1 | ROS | Inhibition | Inhibition | Activation | Activation | Activation |
| EPO-R | Hormone effect | Activation | Activation | Activation | Activation | Activation |
| VEGF | Proliferation, Anti-apoptosis, Anti-inflammation, Angiogenesis | Activation |  | Activation | Activation | Activation |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 25 | 5 | 5 | 35 | 0.833333 | 0.714286 | 0.769231 |
| Claude-3 | 24 | 6 | 5 | 35 | 0.800000 | 0.685714 | 0.738462 |
| GEMINI | 20 | 8 | 7 | 35 | 0.714286 | 0.571429 | 0.634921 |
| pathway | 22 | 7 | 6 | 35 | 0.758621 | 0.628571 | 0.687500 |

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| Starter (gene1) | Receptor (gene2) | Relationship | GPT-4 | **Claude-3** | GEMINI | GEMINI | pathway |
| Egr-1 | PDGFC | Activation | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| Sp1 | PDGFC | Activation | Activation | Inhibition | Inhibition |  | Inhibition |
| PDGFC | PDGF-CC | Activation | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| tPA | inactive PDGF-CC | Activation | Activation | Activation | Inhibition |  | Inhibition |
| inactive PDGF-CC | active PDGF-CC | Activation |  | Activation | Inhibition | Inhibition |  |
| active PDGF-CC | PDGFR-α | Activation | Activation |  | Activation |  | Inhibition |
| PDGFR-α | PI3K | Activation | Activation | Activation | Activation | Inhibition | Inhibition |
| PDGFR-α | Ras MAPK | Activation | Activation | Activation | Activation | Activation | Activation |
| PDGFR-α | p38 MAPK | Activation | Activation | Activation | Activation | Activation | Activation |
| PDGFR-α | PLC-γ | Activation | Activation | Activation | Activation | Activation | Activation |
| PAI-1 | tPA | Inhibition | Activation |  | Activation | Activation |  |
| Neuroserpin | tPA | Inhibition | Activation | Activation | Activation | Activation |  |
| LRP1 | PDGFR-α | Activation | Activation | Activation | Activation | Activation |  |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 10 | 2 | 1 | 13 | 0.833333 | 0.769231 | 0.800000 |
| Claude-3 | 9 | 2 | 2 | 13 | 0.818182 | 0.692308 | 0.750000 |
| GEMINI | 7 | 3 | 3 | 13 | 0.700000 | 0.538462 | 0.608696 |
| pathway | 8 | 2 | 3 | 13 | 0.800000 | 0.615385 | 0.695652 |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Growth factor | Growth factor receptor | Activation | Activation | Activation | Activation | Activation |
| Growth factor receptor | IRS | Activation | Activation | Activation | Activation | Activation |
| IRS | PIP2 | Activation | Activation | Activation | Activation | Activation |
| PIP2 | PI3K | Activation | Activation | Activation |  | Activation |
| PIP2 | PTEN | Activation |  | Activation | Activation | Activation |
| PI3K | PIP3 | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| PIP3 | PDK1 | Activation | Inhibition |  | Inhibition | Inhibition |
| PDK1 | AKT (Thr308) | Activation | Activation | Activation | Activation | Activation |
| mTORC2 | AKT (Ser473) | Activation | Activation | Activation | Activation | Activation |
| AKT | mTORC1 | Activation | Activation |  | Activation |  |
| mTORC1 | S6K1/2 | Activation | Activation | Activation | Activation | Activation |
| mTORC1 | 4EBP1 | Inhibition |  | Inhibition |  | Inhibition |
| AKT | FOXG1 (phosphorylation) | Activation | Activation | Activation | Activation | Activation |
| FOXG1 (phosphorylation) | Reelin | Activation | Activation | Activation | Activation | Activation |
| PTEN | PI3K | Inhibition | Activation | Activation | Activation | Activation |
| Rapamycin | mTORC1 | Inhibition | Activation | Activation |  |  |
| FOXG1 | Reelin | Inhibition | Inhibition | Inhibition | Inhibition |  |
| PIP3 | AKT | Activation | Activation | Inhibition | 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 | GPT-4 | **Claude-3** | GEMINI | pathway |
| Rab7 | Lysosome | Activation | Activation | Activation | Activation | Activation |
| Lysosome | Endolysosome/Autolysosome | Activation | Activation | Activation | Activation | Activation |
| Endolysosome/Autolysosome | Lysosomal digestion | Activation | Activation | Activation | Activation |  |
| Lysosome | Lysosome reformation | Activation |  | Activation | Activation | Activation |
| VapA | Lysosomal digestion | Inhibition | Activation |  |  |  |
| VapA | Membrane retrieval | Inhibition | Activation | Activation | Activation | Activation |
| VapA | Lysosome reformation | Inhibition | Inhibition | Activation | Activation | Activation |
| VapA | TFEB Signalling | Inhibition | Inhibition | Activation |  |  |

Results

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 6 | 1 | 1 | 8 | 0.857143 | 0.750 | 0.800000 |
| Claude-3 | 5 | 2 | 1 | 8 | 0.714286 | 0.625 | 0.666667 |
| GEMINI | 4 | 2 | 2 | 8 | 0.666667 | 0.500 | 0.571429 |
| pathway | 5 | 1 | 2 | 8 | 0.833333 | 0.625 | 0.714286 |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| SDHDv | ROS | Activation | Activation | Activation |  |  |
| ROS | Oxi PTEN | Activation | Activation | Activation | Activation | Activation |
| Oxi PTEN | Mono-Ub PTEN | Activation | Activation | Activation | Activation | Activation |
| Mono-Ub PTEN | PTEN nuclear Localization | Activation | Activation | Activation | Activation | Activation |
| PTEN nuclear Localization | Mono-Ub PTEN p-Akt | Activation | Activation | Activation | Activation | Activation |
| PTEN nuclear Localization | Acetylation-FOXO3a | Activation |  |  | Inhibition |  |
| Acetylation-FOXO3a | p-FOXO3a | Activation | Inhibition | Inhibition |  | Inhibition |
| p-FOXO3a | ATG12, Beclin 1 transcription | Activation | Inhibition |  | Inhibition | Inhibition |
| FOXO3a-14-3-3 | Degradation | Activation | Activation | Inhibition | Inhibition | Inhibition |
| ATG12, Beclin 1 transcription | Autophagy | Activation | Activation | Inhibition |  |  |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 6 | 1 | 1 | 8 | 0.857143 | 0.750 | 0.800000 |
| Claude-3 | 5 | 1 | 2 | 8 | 0.833333 | 0.625 | 0.714286 |
| GEMINI | 4 | 2 | 2 | 8 | 0.666667 | 0.500 | 0.571429 |
| pathway | 5 | 1 | 2 | 8 | 0.833333 | 0.625 | 0.714286 |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Lm | c-di-AMP | Activation | Activation | Activation | Activation | Activation |
| c-di-AMP | STING | Activation | Activation | Activation | Activation | Activation |
| STING | DDX41 | Activation | Activation | Activation | Activation |  |
| DDX41 | p38 | Activation |  | Activation |  | Activation |
| DDX41 | TBK1 | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| p38 | IRF3 | Activation | Activation |  | Activation | Activation |
| TBK1 | IRF3 | Activation | Activation | Activation | Activation | Activation |
| IRF3 | Ifnb1 | Activation | Activation |  | Activation |  |
| BTK | DDX41 | Inhibition | Activation | Activation |  | Activation |
| BTK | STING | Inhibition | Activation | Activation | Activation | Activation |
| C3a | BTK | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| C5a | BTK | Inhibition | Inhibition | Activation |  |  |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| Model | Correct Predictions | False Predictions | Missing Relation | Total Predictions | Precision | Recall | F1 |
| GPT-4 | 9 | 2 | 1 | 12 | 0.818182 | 0.750000 | 0.782609 |
| Claude-3 | 8 | 2 | 2 | 12 | 0.800000 | 0.666667 | 0.727273 |
| GEMINI | 6 | 3 | 3 | 12 | 0.666667 | 0.500000 | 0.571429 |
| pathway | 7 | 2 | 3 | 12 | 0.777778 | 0.583333 | 0.666667 |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| EtOH | FoxO1 | Activation | Activation | Activation | Activation | Activation |
| FoxO1 | AMPK | Activation | Activation | Activation | Activation | Activation |
| AMPK | ULK1 (S555) | Activation | Activation | Activation | Activation | Activation |
| AMPK | PIK3C3 (S164) | Activation | Activation | Activation | Activation | Activation |
| AMPK | BECN1 (S93) | Activation | Activation |  | Activation |  |
| AMPK | BECN1 (S14) | Activation |  | Activation |  | Activation |
| ULK1 (S555) | BECN1 (S93) | Activation | Activation | Activation | Activation | Activation |
| ULK1 (S555) | PIK3C3 (S164) | Activation | Activation | Activation | Activation | Activation |
| PIK3C3 | 14-3-3Θ | Activation | Activation | Activation | Activation | Activation |
| PIK3C3 | ATG14 | Activation |  | Activation |  | Activation |
| PIK3C3 | AMBRA1 | Activation | Activation | Activation | Activation | Activation |
| PIK3C3 | BECN1 | Activation | Activation |  | Activation |  |
| BECN1 | SQSTM1 | Activation | Activation | Activation | Activation | Activation |
| BECN1 | LC3B | Activation | Inhibition | Inhibition | Inhibition |  |
| BECN1 | ATG7 | Activation | Activation | Inhibition | Inhibition | Inhibition |
| mTORC1 | ULK1 (S757) | Activation | Activation | Inhibition |  |  |
| mTORC1 | AMPK | Inhibition | Activation | Inhibition |  |  |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 13 | 2 | 2 | 17 | 0.866667 | 0.764706 | 0.812500 |
| Claude-3 | 12 | 3 | 2 | 17 | 0.800000 | 0.705882 | 0.750000 |
| GEMINI | 10 | 4 | 3 | 17 | 0.714286 | 0.588235 | 0.645161 |
| pathway | 10 | 3 | 4 | 17 | 0.769231 | 0.588235 | 0.666667 |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| Wnt | Frizzled | Activation | Activation | Activation | Activation | Activation |
| PDGF | PDGFR | Activation | Activation | Activation | Activation | Activation |
| GLP-1 | GLP-1R | Activation | Activation | Activation |  | Activation |
| BTC | ErbB1 | Activation | Activation | Activation |  | Activation |
| BTC | ErbB2 | Activation | Activation | Activation | Activation | Activation |
| IGF-1 | IGF-1R | Activation | Activation | Activation | Activation |  |
| Frizzled | Dsh | Activation | Activation | Activation |  | Activation |
| Dsh | cAMP | Activation |  | Activation |  | Activation |
| cAMP | MEK | Activation | Activation | Activation | Activation |  |
| cAMP | PKA | Activation | Activation | Activation |  | Activation |
| MEK | ERK1/2 | Activation | Activation | Activation | Activation |  |
| PKA | ERK1/2 | Activation |  | Activation |  | Activation |
| ERK1/2 | EZH2 | Activation | Activation | Activation | Activation | Activation |
| EZH2 | ErbBR | Activation | Activation | Activation | Activation |  |
| ErbBR | P16LINK4 | Activation |  | Activation |  | Activation |
| P16LINK4 | Tcf7L2 | Activation | Activation | Activation | Activation | Activation |
| Dsh | GS3Kβ | Activation | Activation | Activation |  | Activation |
| GS3Kβ | β-catenin | Activation |  | Activation | Activation |  |
| β-catenin | APC | Activation | Activation | Activation |  | Activation |
| APC | Axin | Activation | Activation | Activation | Activation | Activation |
| Axin | Tcf7L2 | Activation | Activation | Activation |  | Activation |
| Tcf7L2 | CyclinD1-2, cMyc, cdk4 | Activation | Activation |  | Activation |  |
| CyclinD1-2, cMyc, cdk4 | Proliferation | Activation | Activation | Activation | Activation | Activation |
| PDGFR | IRS | Activation |  | Inhibition | Inhibition | Inhibition |
| IRS | PI3K | Activation | Inhibition |  |  | Inhibition |
| PI3K | PDK1 | Activation | Activation | Activation | Activation | Activation |
| PDK1 | AKT/PKB | Activation | Activation | Activation |  | Activation |
| AKT/PKB | TSC1/2 | Activation | Activation |  | Activation |  |
| TSC1/2 | GTP | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| GTP | Rheb | Activation | Inhibition |  | Inhibition | Inhibition |
| Rheb | mTORC1 | Activation | Activation | Activation | Activation | Activation |
| mTORC1 | 4E-BPs | Activation | Activation |  | Activation |  |
| 4E-BPs | S6K1 | Activation | Activation | Activation | Activation | Activation |
| S6K1 | Proliferation | Activation | Activation |  | Activation | Activation |
| AKT/PKB | MDM2/P53 | Activation | Inhibition | Activation | Activation | Activation |
| MDM2/P53 | P21cip1 | Activation | Inhibition |  | Activation | Activation |
| P21cip1 | Proliferation | Activation | Activation | Inhibition |  |  |
| AKT/PKB | FOXO1 | Activation | Activation | Inhibition |  |  |
| FOXO1 | P27kip1 | Activation | Activation | Inhibition |  |  |
| P27kip1 | Pdx1, GSK3 | Activation | Activation |  |  |  |
| Pdx1, GSK3 | mTORC1 | Activation | Activation | Inhibition |  |  |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 30 | 10 | 5 | 45 | 0.750000 | 0.666667 | 0.705882 |
| Claude-3 | 25 | 10 | 10 | 45 | 0.714286 | 0.555556 | 0.625000 |
| GEMINI | 20 | 10 | 15 | 45 | 0.666667 | 0.444444 | 0.533333 |
| pathway | 22 | 10 | 13 | 45 | 0.687500 | 0.488889 | 0.571429 |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| IGF-I | IGF-I-R | Activation | Activation | Activation | Activation | Activation |
| IGF-I-R | PI3-kinase | Activation | Activation | Activation | Activation | Activation |
| PI3-kinase | PKB (Akt) | Activation | Activation | Activation | Activation | Activation |
| PKB (Akt) | Transcription or Splicing factors | Activation | Activation | Activation | Activation | Activation |
| PDGFs | PDGF-R | Activation | Activation | Activation | Activation |  |
| PDGF-R | MEK1 | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| MEK1 | ERK | Activation | Inhibition | Inhibition | Inhibition | Inhibition |
| ERK | Transcription or Splicing factors | Activation | Activation | Activation | Activation | Activation |
| bFGF or EGF | bFGF-R or EGF-R | Activation |  |  | Inhibition | Inhibition |
| bFGF-R or EGF-R | MKK6 | Activation | Inhibition | Inhibition |  | Inhibition |
| MKK6 | p38MAPK | Activation | Activation | Activation | Activation | Activation |
| p38MAPK | Transcription or Splicing factors | Activation |  | Activation | Activation | Activation |
| LY294002 or Wortmannin | PI3-kinase | Inhibition | Activation |  | Activation | Activation |
| PD98059 | MEK1 | Inhibition | Activation | Activation | Activation | Activation |
| SB203580 | p38MAPK | Inhibition |  | Inhibition | Inhibition | Inhibition |
| IGF-I-R | PKB (Akt) | Activation | Activation | Activation | Activation | Activation |
| PI3-kinase | Transcription or Splicing factors | Activation | Activation |  | Activation | Activation |
| ERK | Induction of dedifferentiation | Activation | Activation | Activation |  |  |
| p38MAPK | Induction of dedifferentiation | Activation | Activation | Activation |  |  |
| PI3-kinase | Maintaining of a differentiated phenotype | Inhibition | Inhibition | Activation |  |  |

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| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 15 | 3 | 2 | 20 | 0.833333 | 0.750 | 0.789474 |
| Claude-3 | 14 | 3 | 3 | 20 | 0.823529 | 0.700 | 0.756757 |
| GEMINI | 12 | 4 | 4 | 20 | 0.750000 | 0.600 | 0.666667 |
| pathway | 13 | 3 | 5 | 20 | 0.812500 | 0.650 | 0.722222 |

*48*

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| EGFR | Ras | Activation | Activation | Activation |  |  |
| Ras | Raf | Activation | Activation | Activation | Activation | Activation |
| Raf | MEK | Activation | Activation | Activation | Activation | Activation |
| MEK | ERK | Activation | Activation | Activation |  | Activation |
| EGFR | PI3K | Activation | Activation | Activation | Activation | Activation |
| PI3K | Akt | Activation | Activation |  | Activation |  |
| Akt | mTOR | Activation | Activation | Activation |  | Activation |
| mTOR | Proliferation / Survival / Angiogenesis | Activation |  | Activation | Activation | Activation |
| Cetuximab | EGFR | Inhibition | Inhibition | Activation | Activation | Activation |
| Erlotinib / Gefitinib | EGFR | Inhibition | Activation |  | Activation | Activation |
| Salirasib | Ras | Inhibition | Activation | Activation | Activation |  |
| LY294002 | PI3K | Inhibition | Inhibition | Inhibition |  | Activation |
| BEZ235 | PI3K | Inhibition | Inhibition | Inhibition | Inhibition | Inhibition |
| Rapamycin / RAD001 / CCI-779 | mTOR | Inhibition |  | Inhibition |  | Inhibition |
| PF-00299804 / BIBW2992 | HER | Inhibition | Inhibition |  | Inhibition | Inhibition |
| Antiangiogenic agents | VEGFR / PDGFR / FGFR | Inhibition | Inhibition | Inhibition |  |  |

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| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 12 | 2 | 2 | 16 | 0.857143 | 0.7500 | 0.800000 |
| Claude-3 | 11 | 2 | 3 | 16 | 0.846154 | 0.6875 | 0.758621 |
| GEMINI | 9 | 3 | 5 | 16 | 0.750000 | 0.5625 | 0.642857 |
| pathway | 10 | 2 | 4 | 16 | 0.833333 | 0.6250 | 0.714286 |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| RTK | Ras | Activation | Activation | Inhibition | Inhibition | Inhibition |
| Ras | Raf | Activation | Activation | Inhibition | Inhibition | Inhibition |
| Raf | MEK | Activation | Activation | Activation |  |  |
| MEK | ERK1/2 | Activation | Inhibition |  | Activation | Activation |
| TRAF | MEKK1/ASK1/TAK1 | Activation | Inhibition | Activation | Activation |  |
| MEKK1/ASK1/TAK1 | MKK3/6 | Activation |  | Activation |  | Activation |
| MKK3/6 | p38 α/β/γ/δ | Activation | Activation | Activation | Activation | Activation |
| RAC1 | MEKK/MUK | Activation | Activation | Activation | Activation | Activation |
| MEKK/MUK | MKK4/7 | Activation | Activation | Activation |  | Activation |
| MKK4/7 | JNK1/2/3 | Activation | Activation | Activation | Activation | Activation |
| Shp2 | RTK | Inhibition | Activation | Activation |  |  |

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| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 8 | 2 | 1 | 11 | 0.800000 | 0.727273 | 0.761905 |
| Claude-3 | 7 | 2 | 2 | 11 | 0.777778 | 0.636364 | 0.700000 |
| GEMINI | 5 | 2 | 4 | 11 | 0.714286 | 0.454545 | 0.555556 |
| pathway | 6 | 2 | 3 | 11 | 0.750000 | 0.545455 | 0.631579 |

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| **Starter (gene1)** | **Receptor (gene2)** | **Relationship** | **GPT-4** | **Claude-3** | GEMINI | pathway |
| c-MET | Ras | Activation | Activation | Activation | Activation | Activation |
| c-MET | PI3K | Activation | Activation | Activation | Activation | Activation |
| EGFR | Ras | Activation | Activation | Activation | Activation |  |
| EGFR | PI3K | Activation | Activation | Activation |  | Activation |
| IGFR1 | Ras | Activation | Activation | Activation |  | Activation |
| IGFR1 | PI3K | Activation | Activation |  | Activation | Activation |
| AXL | Ras | Activation |  | Activation | Activation | Activation |
| AXL | PI3K | Activation | Activation | Activation | Activation |  |
| Fyn | Ras | Activation |  | Activation |  | Activation |
| Fyn | PI3K | Activation | Activation |  | Activation | Activation |
| Ras | Raf | Activation | Activation | Activation |  | Activation |
| Raf | MEK | Activation | Activation | Activation | Activation |  |
| MEK | ERK | Activation | Activation |  | Activation | Activation |
| Rho | PAK | Activation | Activation | Activation | Activation | Activation |
| PAK | Cell motility and invasion | Activation | Activation | Activation |  | Activation |
| ERK | Cell cycle progression and proliferation | Activation | Activation | Activation | Activation | Activation |
| PI3K | AKT | Activation | Activation |  | Activation | Activation |
| AKT | mTOR | Activation | Activation | Activation | Activation | Activation |
| mTOR | Protein synthesis and cell growth | Activation | Activation | Activation | Activation | Activation |
| AKT | Survival | Activation | Activation | Activation | Activation |  |
| PTEN | AKT | Inhibition | Inhibition | Activation | Activation |  |
| miR-125a-3p | Fyn | Inhibition | Inhibition | Activation | Activation |  |
| miR-7 | FAK | Inhibition | Activation |  | Activation | Inhibition |
| miR-7, miR-23b, miR-145 | PAK | Inhibition | Activation | Activation | Activation | Inhibition |
| miR-302-367, miR-612 | PI3K | Inhibition |  | Activation |  | Inhibition |
| miR-99, miR-145 | mTOR | Inhibition | Activation | Activation | Activation | Inhibition |
| Fyn | Rho | Activation | Activation | Activation |  |  |
| Fyn | PAK | Activation | Activation | Activation |  |  |

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| **Model** | **Correct Predictions** | **False Predictions** | **Missing Relation** | **Total Predictions** | **Precision** | **Recall** | **F1** |
| GPT-4 | 20 | 5 | 3 | 28 | 0.800000 | 0.714286 | 0.754717 |
| Claude-3 | 18 | 5 | 5 | 28 | 0.782609 | 0.642857 | 0.705882 |
| GEMINI | 16 | 4 | 8 | 28 | 0.800000 | 0.571429 | 0.666667 |
| pathway | 18 | 4 | 6 | 28 | 0.818182 | 0.642857 | 0.720000 |

**Avg precision, recall and f1.**

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| **Model** | **Precision** | **Recall** | **F1** |
| GPT-4 | 0.7785 | 0.6645 | 0.7167 |
| Claude-3 | 0.7353 | 0.5949 | 0.6571 |
| GEMINI | 0.6113 | 0.4495 | 0.5176 |
| PIPELINE | 0.6713 | 0.5088 | 0.5783 |
| Hybrid | 0.7024 | 0.5443 | 0.6328 |