IPA用户培训

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邮箱：liya@tri-ibiotech.com

源资科技 Biotech(Shanghai) Ltd.

2022年3月2日

源资科技 Biotech(Shanghai) Ltd.

创新信息技术与整合资讯管理的知识领航者

源资信息科技（上海）有限公司成立于2008年5月，目前公司主要经营和研发生命科学与材料科学类学术专业软件、信息化管理系统和质量管理系统，同时提供从药物发现到药物开发的完整解决方案。

人数 110
30% 硕士以上学历
50% 5年以上项目经验

科研计算模拟解决方案
智能信息化业务
临床电子化业务

注册资金200万美金
ISO9001认证
高新技术企业
客户数量超过1000

为国内医药、化工、材料等高科技领域客户提供高附加价值的优质服务

http://www.tri-ibiotech.com/

计算模拟类产品

01 材料科学

VASP materials design

材料基因组计划
材料模拟
VASP计算

02 计算化学

Q-CHEM

量子化学
分子模拟

OpenEye SCIENTIFIC

03 化学信息学

波谱解析
实验信息管理
电子实验记录ELN

ACD/Labs

dotmatics knowledge solutions

04 生命科学

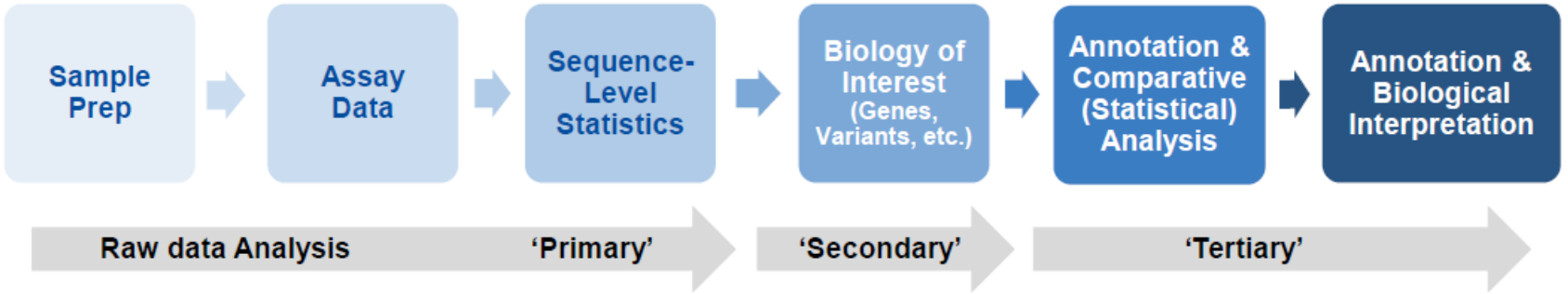
CERTARA

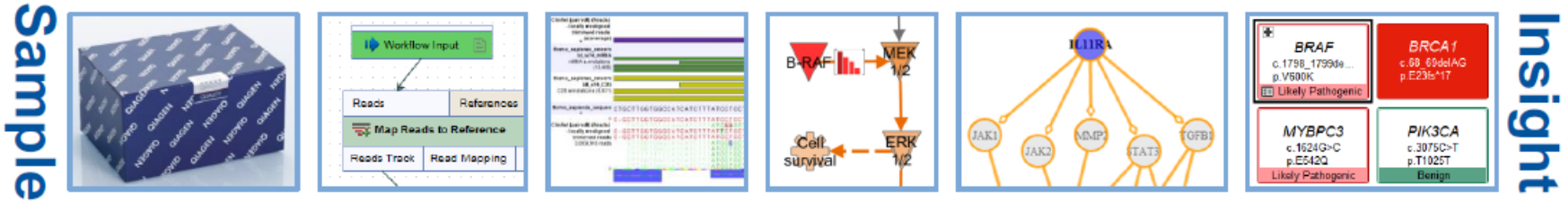
QIAGEN

PK/PD
临床试验
生物信息学

生物信息学软件和数据库的应用

QIAGEN Digital Insight Total Solution





CLC Genomics Workbench

QIAGEN Clinical Insight

Content

PART

1

IPA软件基本信息

IPA登录

- 安装完成后，桌面会出现图标：
- 双击图标，软件进入加载界面，加载界面之后为登录界面。

- 在登录界面中输入申请IPA账号使用的Email及密码即可进入软件

License类型

IPA with Advanced Analytics LCL

Advanced Analytics: Causal Network Analysis, BioProfiler, IsoProfiler, Relationship Export, and Phosphoproteomics Analysis

交大IPA预约：登陆时间规定**工作日上午8点到下午5点**（寒暑假登陆时间为上午9点半到下午4点）

地点：医学院图书馆一楼电子阅览室IPA专用电脑系统，IPA操作系统绑定在指定电脑上，使用者建议提前2到3周预约使用，每人每次使用时间不得超过4小时。

注意：

- 对于轮流申请使用的账号，请协调好不同用户登入登出的时间。自己的数据可以导出保存（.qipa文件）或删除以便下一位用户使用IPA。
- 数据上传以后超过180天，凯杰将从IPA永久删除这些老数据，注意导出保存重要数据。
- 如果要更换锁定的电脑，请联系技术支持工程师。注意不要频繁更换。

系统要求

Windows Operating Systems:
•Windows 10
•Windows 8
•Windows 7
•Windows XP SP2 or later*

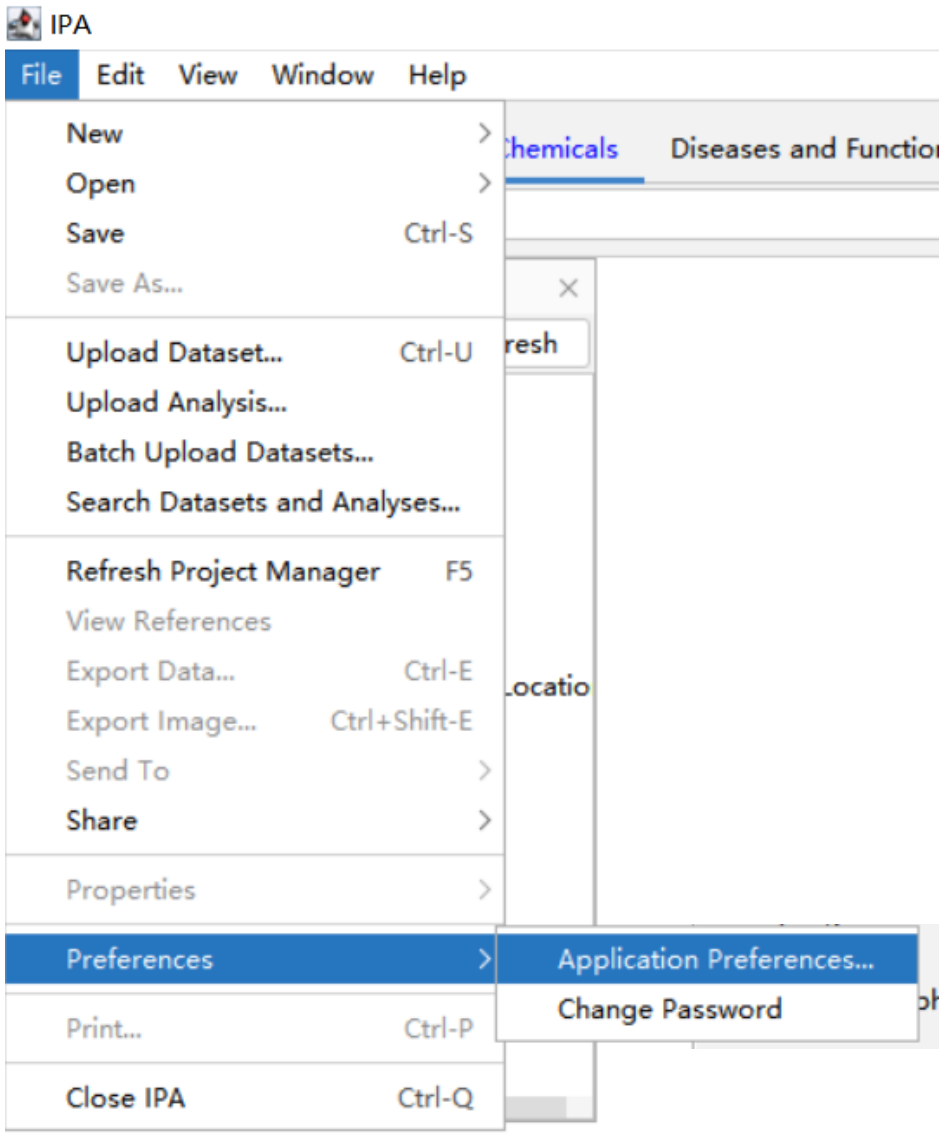
Windows Internet Browsers:
•Microsoft Edge 87 or later
•Firefox 5 or later
•Chrome 10 or later
•Safari 5.05 or later

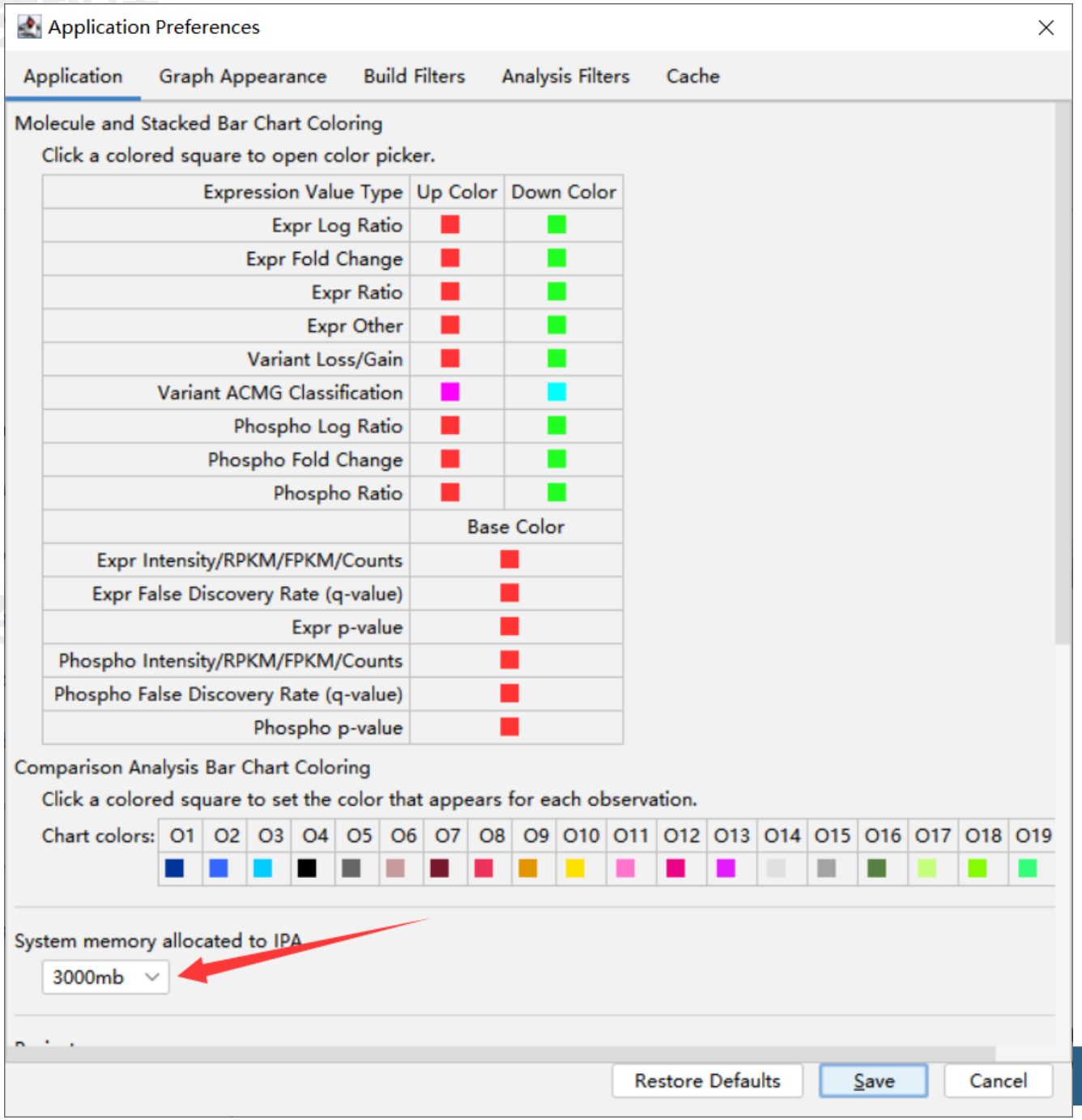
Java Runtime Environment (JRE).
Not needed if using the installed version of the QIAGEN IPA client **:
•JRE 1.8.0_xx or higher

Minimum Hardware Requirements:
•CoreTM i5 processor or equivalent running at 2 GHz or higher with 64 bit OS and Java
•Minimum at least 3 GB RAM free for Java
•Minimum Screen resolution of 1280×800

Mac用户见：https://digitalinsights.qiagen.com/products-overview/discovery-insights-portfolio/analysis-and-visualization/qiagen-ipa/

调高IPA的系统内存

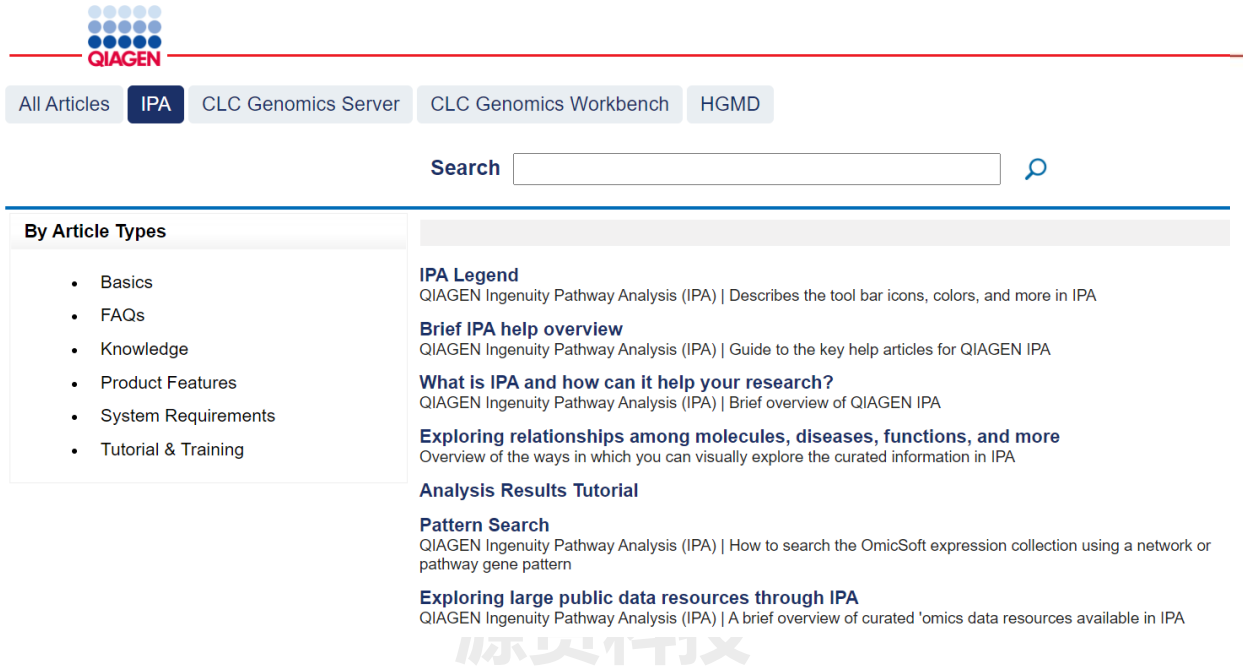

IPA
File
Edit
View
Window
Help
New
Open
Save Ctrl-S
Save As...
Upload Dataset... Ctrl-U
Upload Analysis...
Batch Upload Datasets...
Search Datasets and Analyses...
Refresh Project Manager F5
View References
Export Data... Ctrl-E
Export Image... Ctrl+Shift-E
Send To
Share
Properties
Preferences
Application Preferences...
Change Password
Print... Ctrl-P
Close IPA Ctrl-Q
Chemicals
Diseases and Functio
resh
Locatio

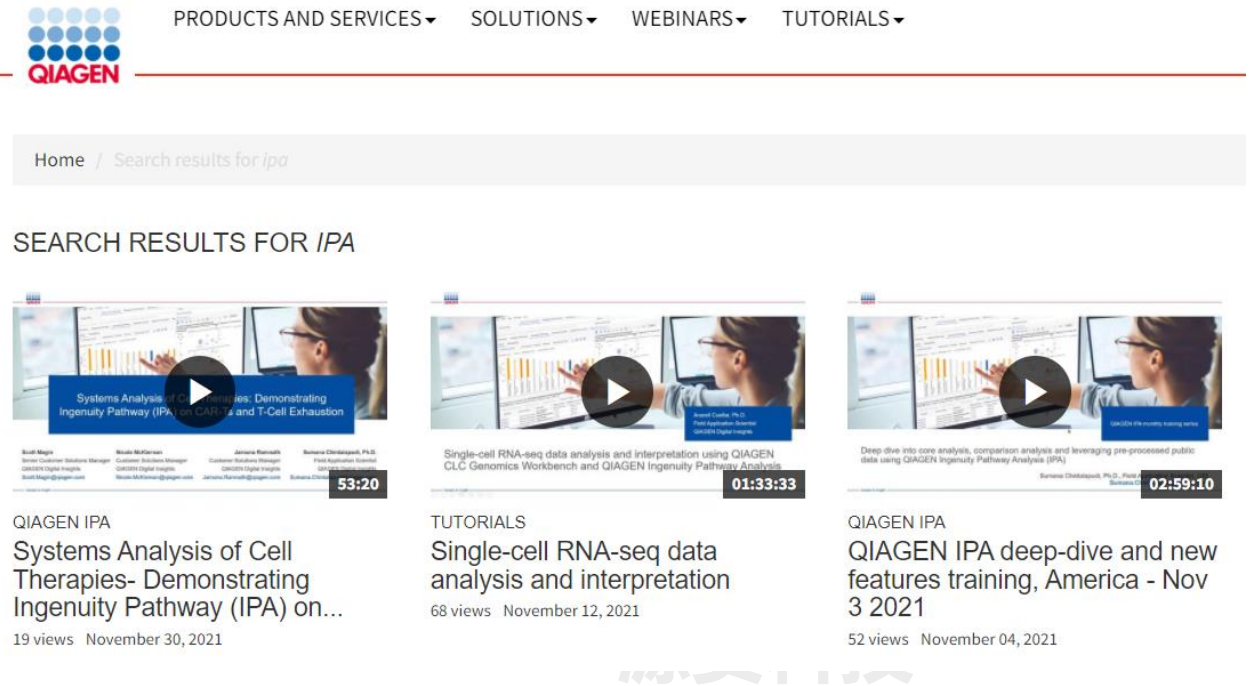

Application Preferences
Application
Graph Appearance
Build Filters
Analysis Filters
Cache
Molecule and Stacked Bar Chart Coloring
Click a colored square to open color picker.
Expression Value Type
Up Color
Down Color
Expr Log Ratio
Expr Fold Change
Expr Ratio
Expr Other
Variant Loss/Gain
Variant ACMG Classification
Phospho Log Ratio
Phospho Fold Change
Phospho Ratio
Base Color
Expr Intensity/RPKM/FPKM/Counts
Expr False Discovery Rate (q-value)
Expr p-value
Phospho Intensity/RPKM/FPKM/Counts
Phospho False Discovery Rate (q-value)
Phospho p-value
Comparison Analysis Bar Chart Coloring
Click a colored square to set the color that appears for each observation.
Chart colors: O1 O2 O3 O4 O5 O6 O7 O8 O9 O10 O11 O12 O13 O14 O15 O16 O17 O18 O19
System memory allocated to IPA
3000mb
Restore Defaults
Save
Cancel

有用的官网在线资源（英文）

IPA指南: https://qiagen.secure.force.com/KnowledgeBase/KnowledgeIPAPage

视频教程、讲座等：https://tv.qiagenbioinformatics.com/search/perform?search=ipa



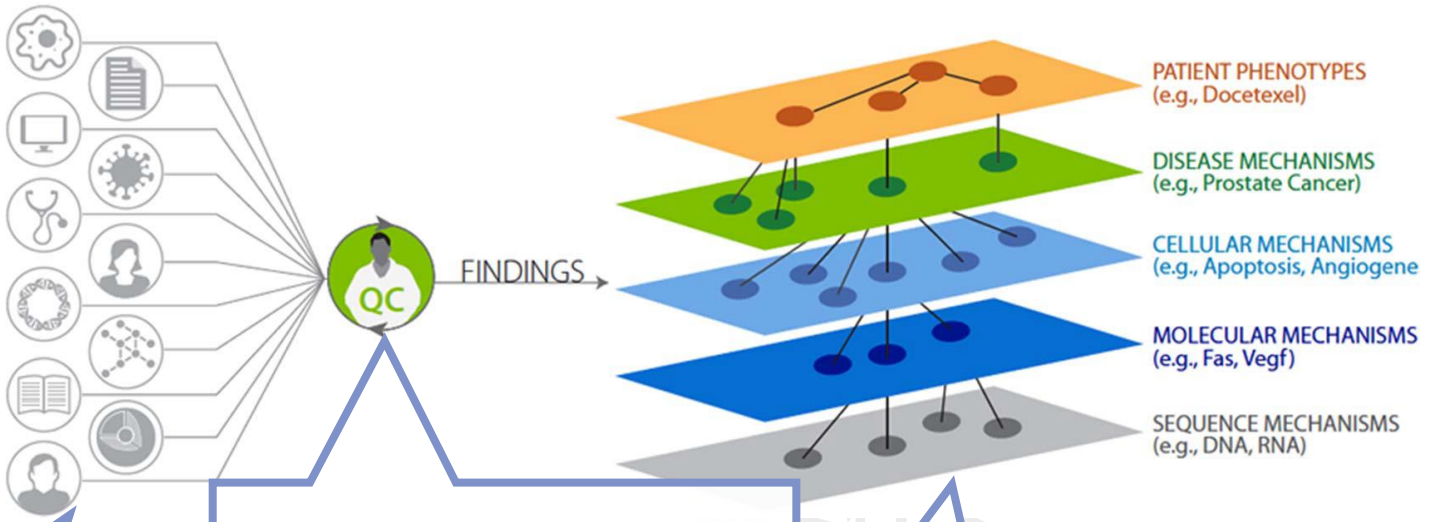


PART

2

查询功能

Ingenuity Knowledge Base



500多名专家多轮质控

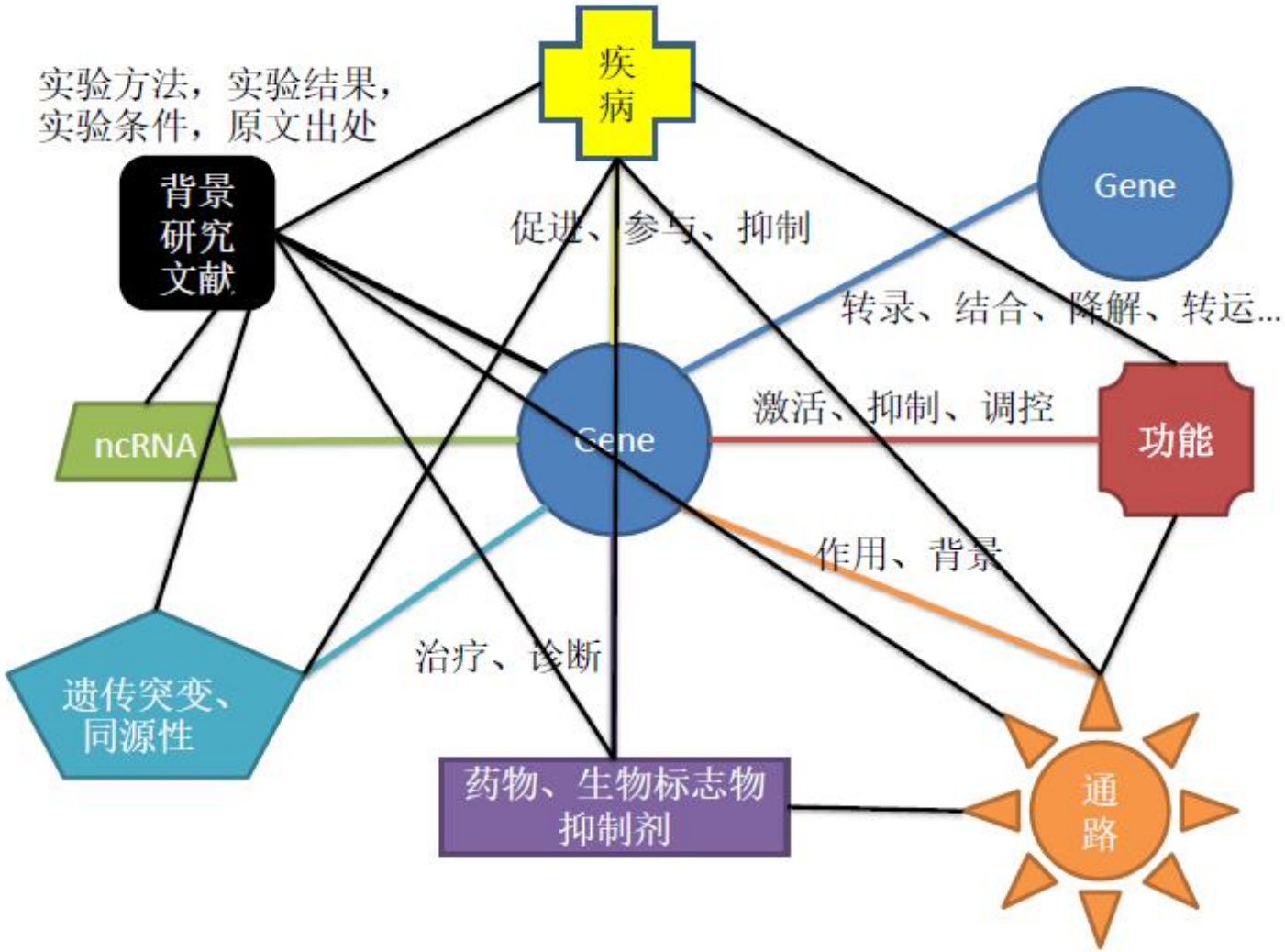
300多种顶尖杂志全文
3000多种生物学杂志摘要
30多种公共数据库
850多万条生物学知识

人、小鼠、大鼠等物种
3万多种基因、化合物
近1万种生物学功能、疾病本体论分类
超过130万种相互作用

高质量，严把关的系统生物学数据库

IPA

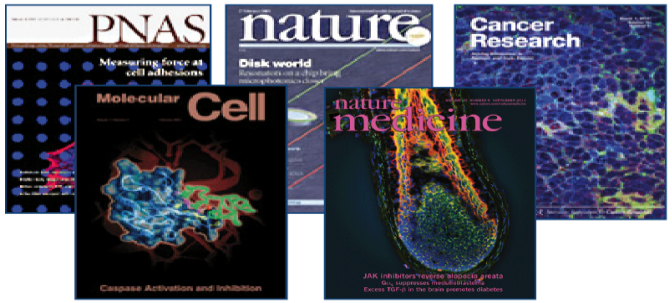
IPA：立体整合多组学系统的强力工具

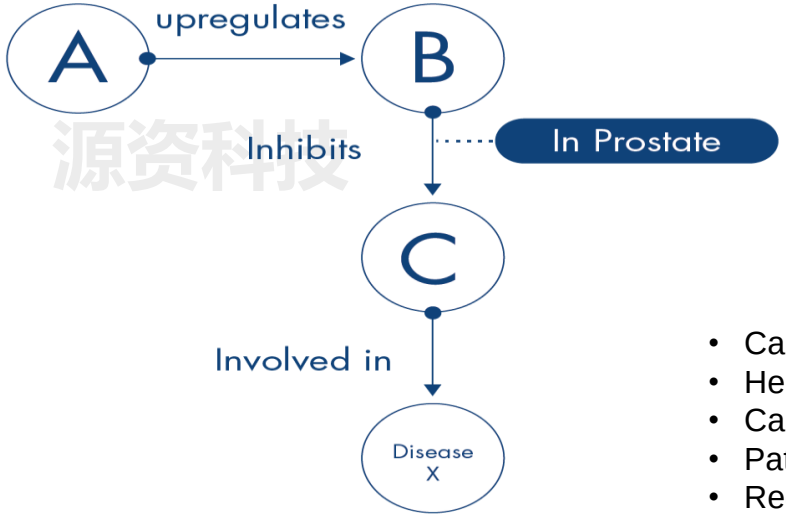


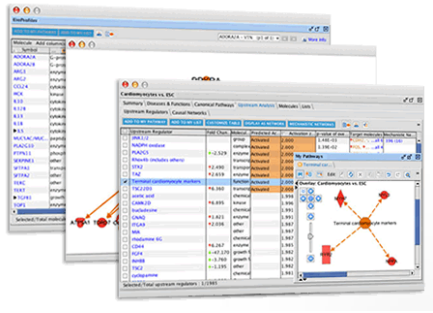
IPA 整合的第三方数据库

Entrez Gene
RefSeq
OMIM
ClinVAR
GWAS Database
Gene Ontology (GO)
Human Metabolome Database (HMDB)
GNF Tissue Expression Body Atlas
NCI-60 Cell Line Expression Atlas
HumanCyc metabolic pathway information
BIND, DIP, MINT, MIPS, BioGRID, IntAct, Cognia protein-protein interactions
Clinicaltrials.gov
Drugs@FDA
Mosby's Drug Consult
Goodman & Gilman's Pharmacological Basis of Therapeutics
DrugBank
Hazardous Substance Database (HSDB)
Chemical Carcinogenesis Research Information System Database (CCRIS)
TargetScan
miRBase
miRecords
TarBase
COSMIC
The Mouse Genome Database (MGD) from The Jackson Laboratory (JAX)

IPA：知其然知其所以然



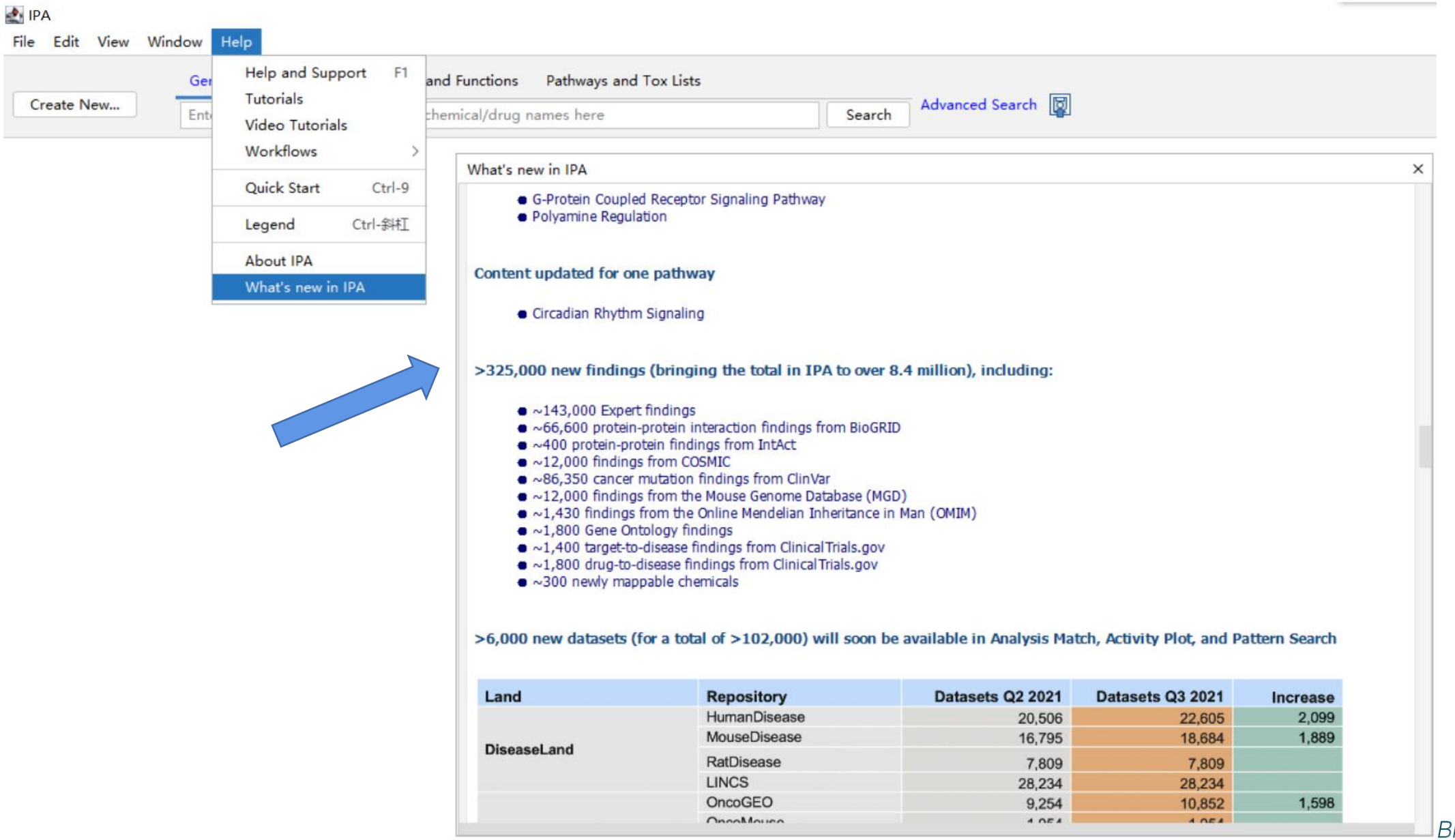




- Cancer Scoring
- Hereditary Disease Scoring
- Causal Network Analysis
- Pathway Activity Analysis
- Regulator Effects

整合　　组织　　分析

查看findings统计数值



Land	Repository	Datasets Q2 2021	Datasets Q3 2021	Increase
DiseaseLand	HumanDisease	20,506	22,605	2,099
	MouseDisease	16,795	18,684	1,889
	RatDisease	7,809	7,809	
	LINCS	28,234	28,234	
	OncoGEO	9,254	10,852	1,598

IPA具有独一无二的数据库和人性化的操作界面

	公共软件	IPA
数据来源	表达谱芯片、人工上传、同源比较、自动提取文献摘要	高质量论文人工全文阅读取证 权威数据库 具备临床信息
数据组成	GO：基因注释 KEGG：信号通路 SRING：相互作用 Transfac：转录因子 mirBase：miRNA信息 Nexbio：疾病信息	亚细胞定位，生理过程，分子功能 生物通路，转录调控 药物靶标，生物标志物 疾病表型，遗传突变
易用性	单一的结果 无详细的参考文献信息 每种数据库都要从头学习	各类分析在同一界面完成 所有结果包含参考文献资料 界面简洁，易学易用
准确性	数据来源、更新速度、数据提取算法均各不相同，无法保证一致性 大多数工具不支持个性化需求 大部分数据来源于表达谱芯片，志愿上传，无验证结果	每周更新文献资料，每季度更新软件分析模块 支持个性化分析需求，构建非经典调控途径 多轮专家质控搜索结果 参考数据库、杂志、数据均为高影响力资源

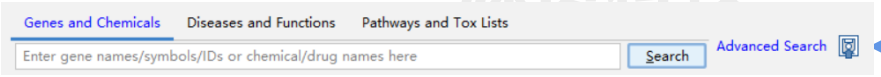
Quantifiable benefits of IPA

- **Quick to provide insights**
  - Upload and get analysis results in minutes. One upload, many ways to look at the data.
- **Trustworthy**: Cited frequently in publications by the top 10 academic and top 10 pharma
  - ~1400 citations in the last 5 years from institutions like Harvard, University of Cambridge, MIT, Stanford, Johns Hopkins, Pfizer, Merck, GSK, JNJ and only ~270 from MetaCore.
  - IPA cited 7x more than top competitor MetaCore since 2004.
- **Up to date:** Weekly content updates and four major software releases per year– other software is updated much less often, and some can go years without content updates.
- **Great customer support:** 1-day turnaround on customer support cases from scientists

IPA：打开方式

生物学问题

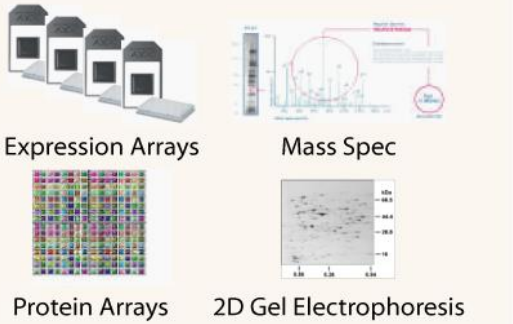
搜索



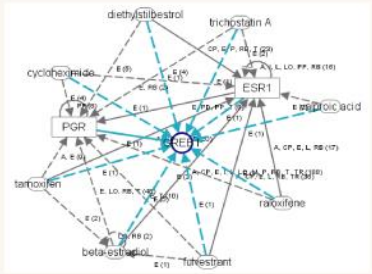
BioProfiler

- Core
- IPA- Biomarkers
- IPA-Tox
- IPA- Metabolomics

实验数据

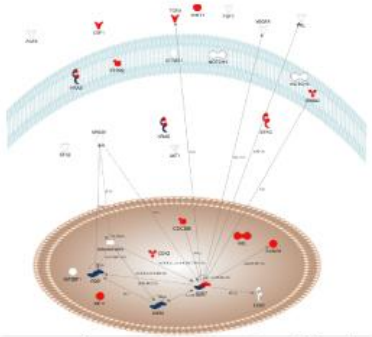


定制路径



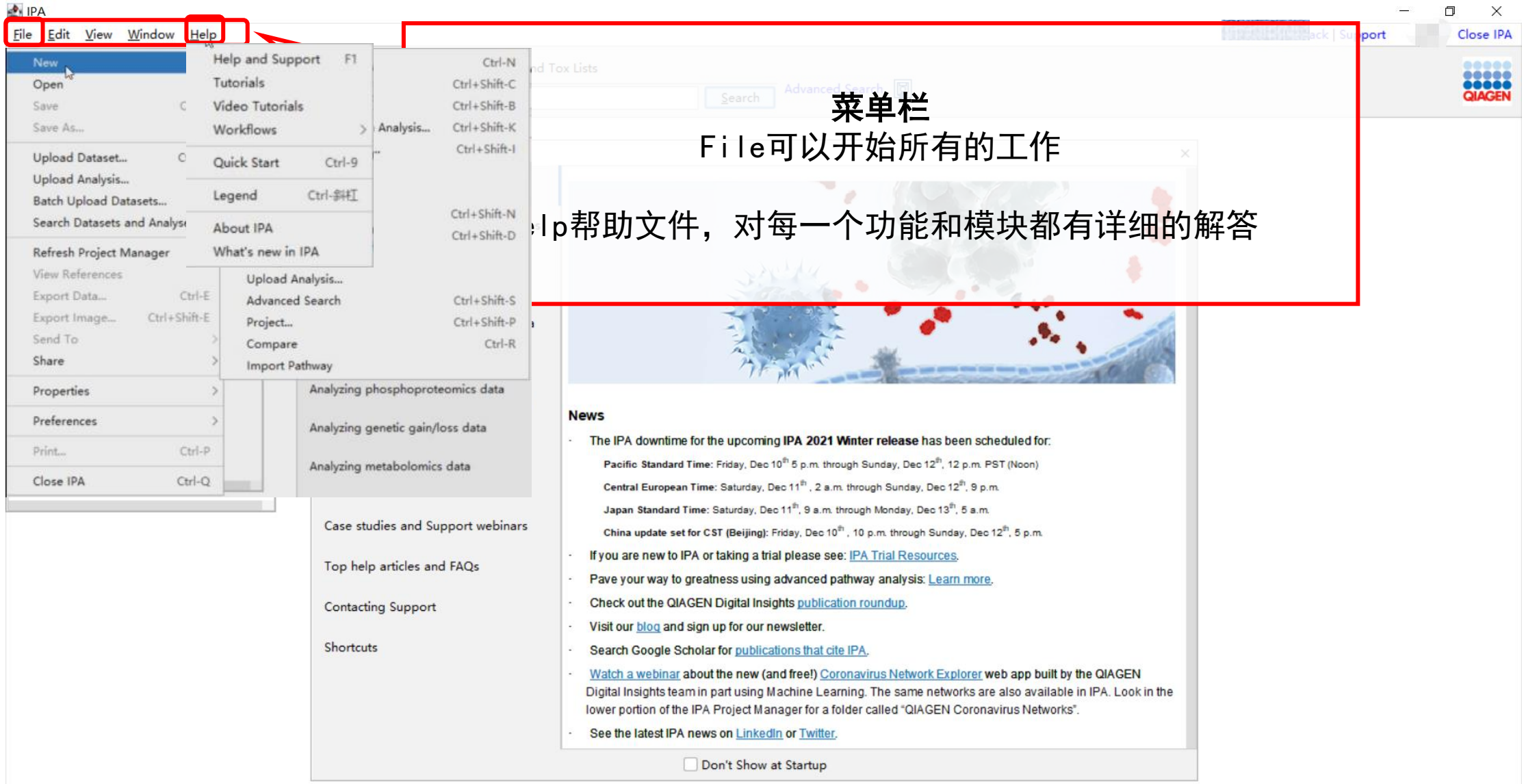
- 模拟下游效应
- 理解基因表达变化的原因
- 解释预测的调控子如何导致预测的功能效应
- 鉴定可能的新调控子网络等

对比分析



Communicate & Collaborate

软件打开界面——菜单栏



菜单栏

File可以开始所有的工作

lp帮助文件，对每一个功能和模块都有详细的解答

软件打开界面——Create New

Create New：

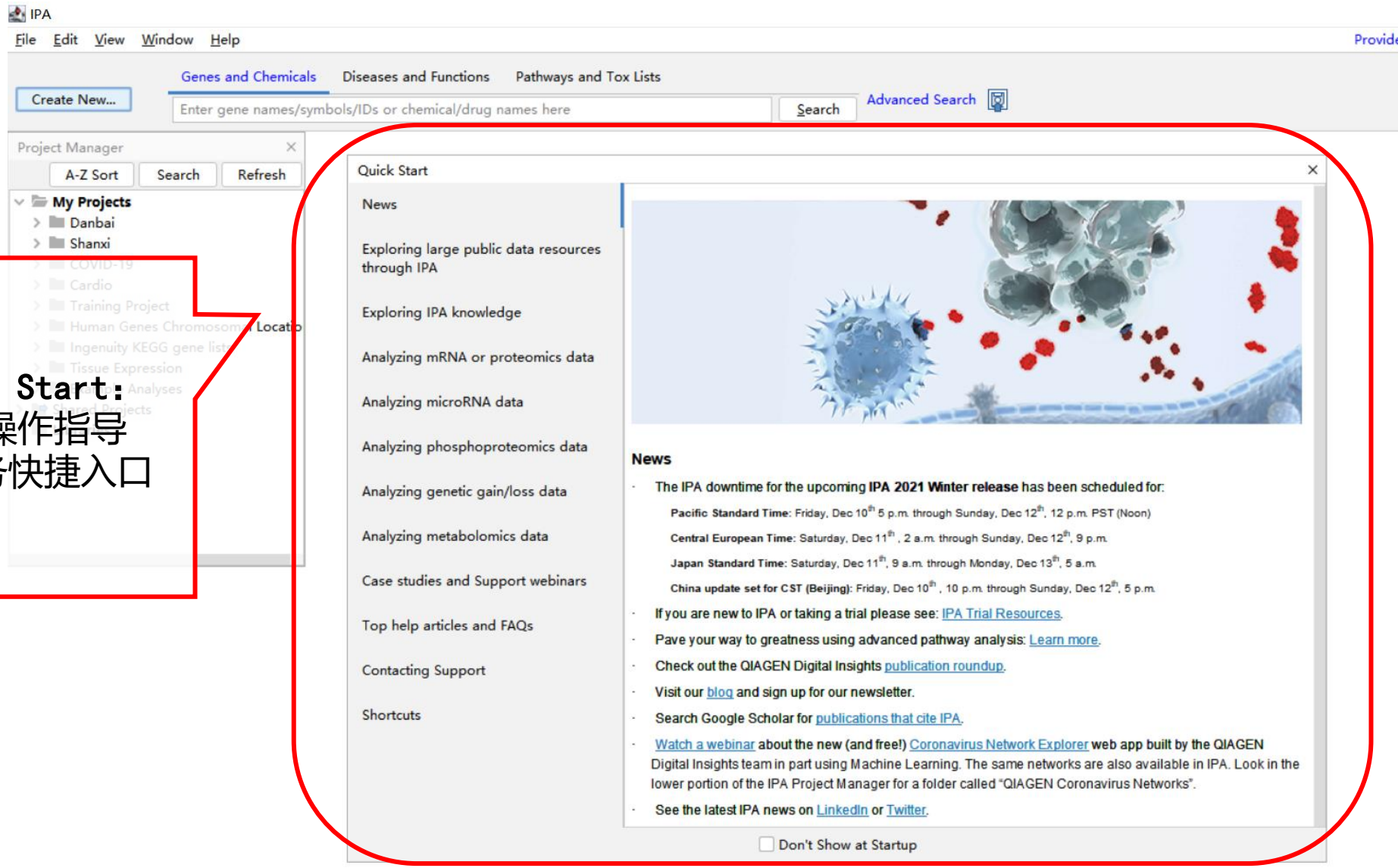
操作的快捷键，能够开始多种操作命令和数据分析

软件打开界面——Project Manager

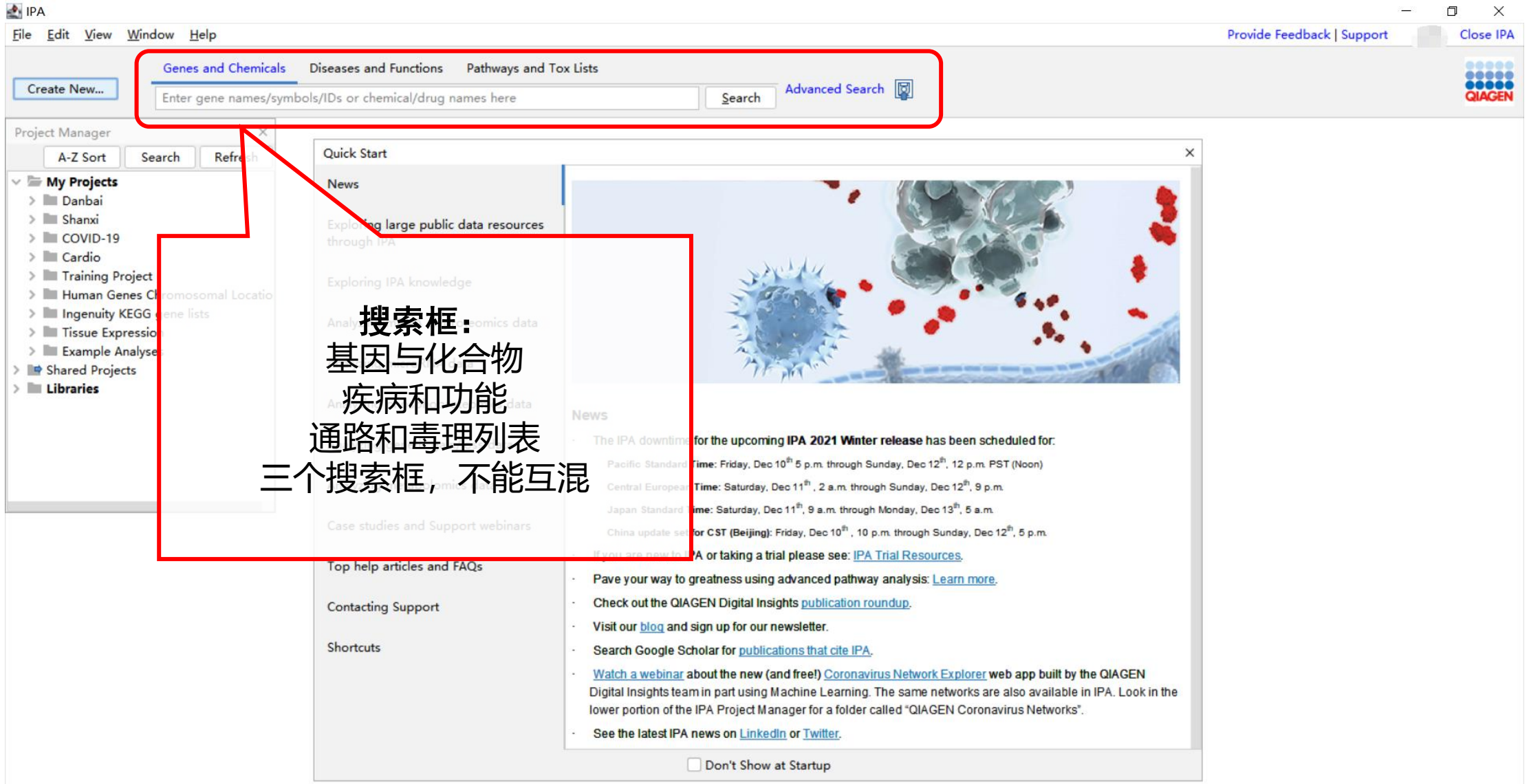
Project Manager：
所有上传的数据、分析的结果
收集整理的分子列表、通路
与其他科学家共享的结果

软件打开界面——Quick Start

Quick Start:
IPA操作指导
新任务快捷入口



软件打开界面——搜索框

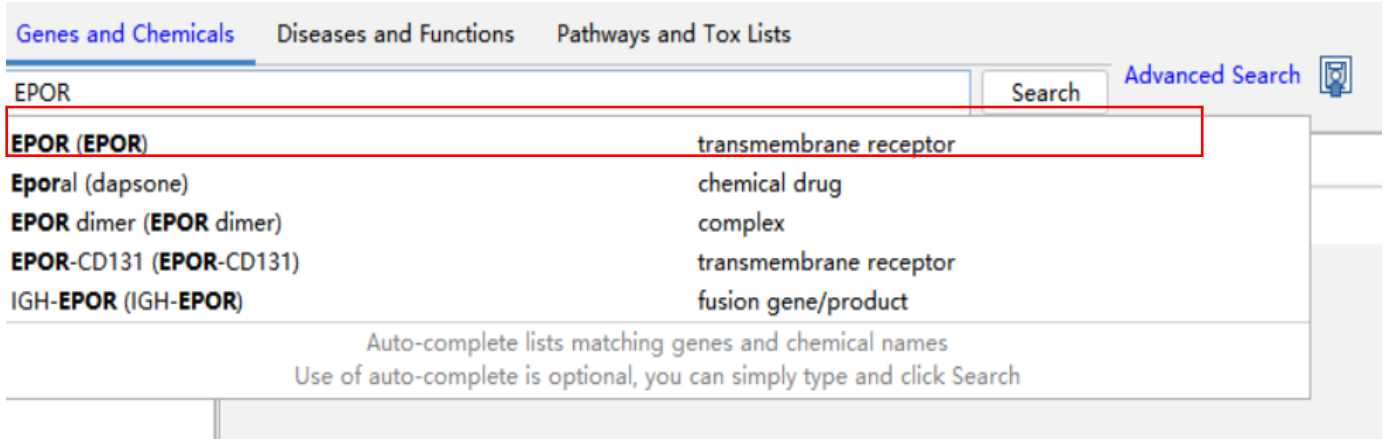


IPA搜索功能——全方位的信息梳理

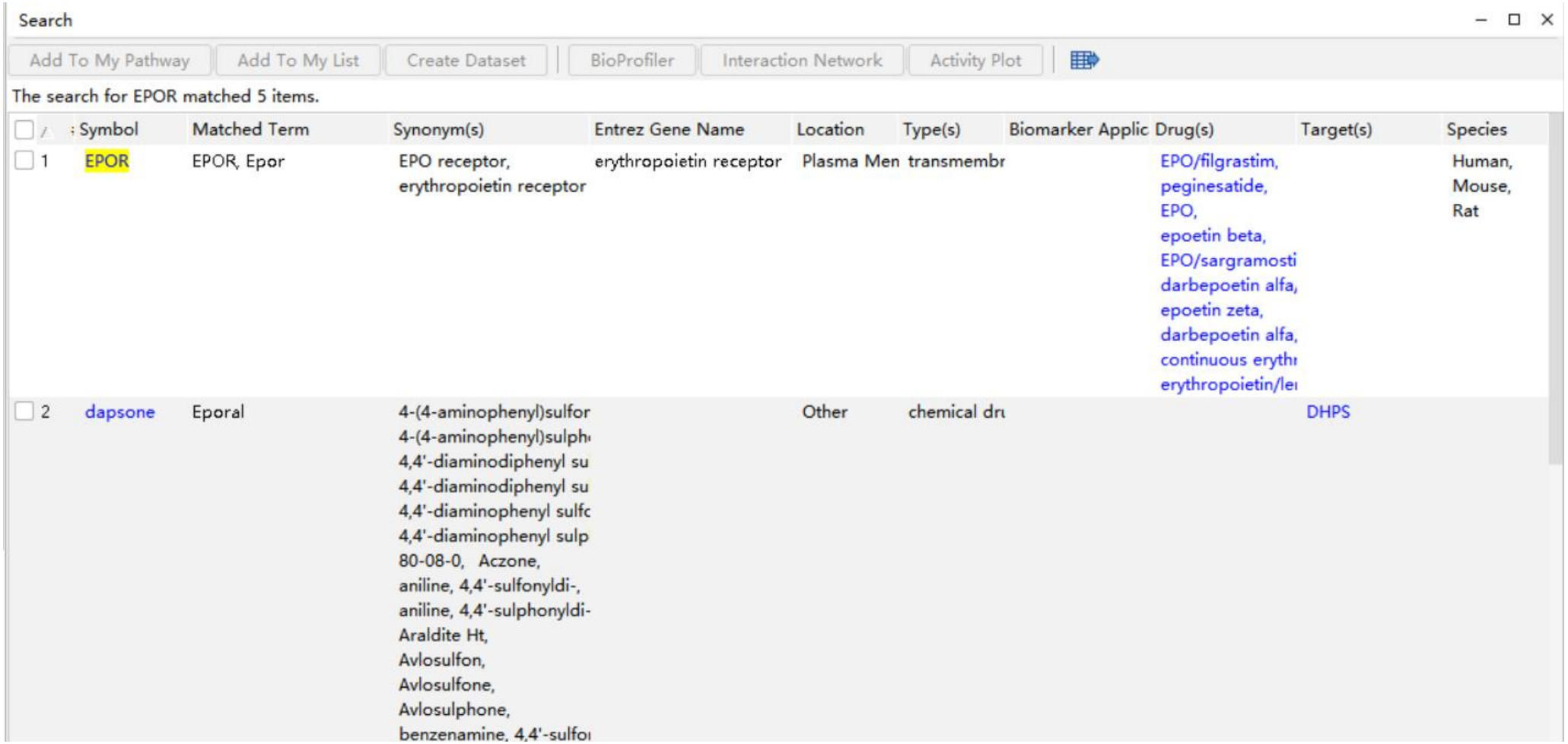
基因搜索	• EPOR是什么，其分子类型，表达位置，分子功能，参与通路等基本信息有哪些？与它相互作用的分子有哪些？上游有哪些对它进行调控的分子？在它的上游有什么可以对它进行激活的激活因子？
靶标基因与已知药物关系	• 靶标基因HDAC • 药物TamiFlu作用信息 • TamiFlu与靶标基因HDAC是否有作用关系
疾病与功能基因搜索（BioProfiler）	• 研究发现了与两千多个与肺癌相关的基因，其中哪些基因与肺癌生长和发展有关？

IPA搜索功能——举例EPOR基因

EPOR是什么，其分子类型，表达位置，分子功能，参与通路等基本信息有哪些？与它相互作用的分子有哪些？上游有哪些对它进行调控的分子？在它的上游有什么可以对它进行激活的激活因子？



IPA搜索功能——举例EPOR基因



Search

Add To My Pathway | Add To My List | Create Dataset | BioProfiler | Interaction Network | Activity Plot

The search for EPOR matched 5 items.

	Symbol	Matched Term	Synonym(s)	Entrez Gene Name	Location	Type(s)	Biomarker Applic	Drug(s)	Target(s)	Species
1	EPOR	EPOR, Epor	EPO receptor, erythropoietin receptor	erythropoietin receptor	Plasma Men	transmembr		EPO/filgrastim, peginesatide, EPO, epoetin beta, EPO/sargramosti darbepoetin alfa, epoetin zeta, darbepoetin alfa, continuous erythr erythropoietin/le		Human, Mouse, Rat
2	dapsone	Eporal	4-(4-aminophenyl)sulfor 4-(4-aminophenyl)sulph 4,4'-diaminodiphenyl su 4,4'-diaminodiphenyl su 4,4'-diaminophenyl sulfc 4,4'-diaminophenyl sulp 80-08-0, Aczone, aniline, 4,4'-sulfonyldi-, aniline, 4,4'-sulphonyldi- Araldite Ht, Avlosulfon, Avlosulfone, Avlosulphone, benzenamine, 4,4'-sulfo		Other	chemical dr			DHPS	

EPOR总结性信息

IPA Gene View: EPOR (Mammalian)

Review the categorized literature findings and database information for this node.

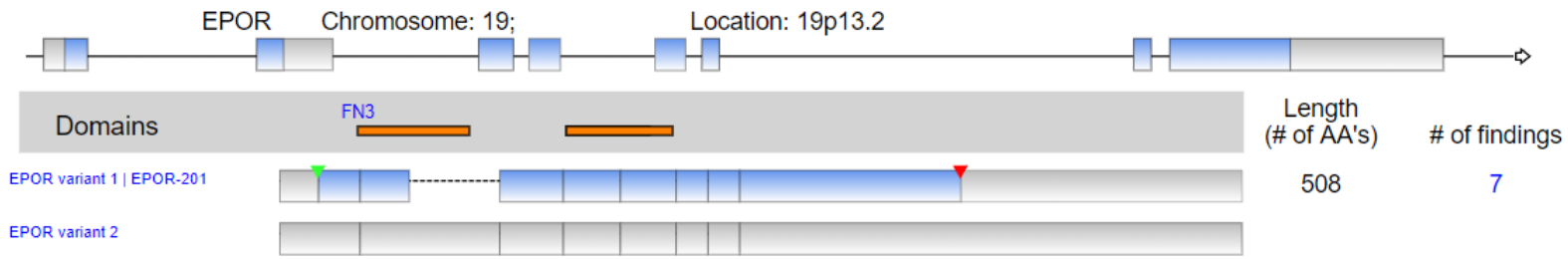
Member Of:	EPOR-CD131, EPOR dimer, IGH-EPOR
Entrez Gene Name:	erythropoietin receptor
Synonym(s):	EPO receptor, erythropoietin receptor
NCBI CDD Domains (Superfamilies / Multi-Domains):	Fibronectin type 3 domain, FN3
Protein Functions / Functional Domains:	Box I domain, Box II domain, cytoplasmic domain, dimerization domain, ectodomain, erythropoietin receptor, extracellular domain, identical protein binding, intracellular domain, Jak2 binding domain, negative regulatory domain, phosphotyrosine motif, PI3K binding domain, protein binding, Shp1 binding domain, Sh Ptp1 binding domain, signaling domain, Src-homology 2 binding domain, Stat5 binding domain, transmembrane/cytoplasmic domain, transmembrane domain, transmembrane receptor, tyrosine phosphorylation site, YXXP domain
Subcellular Location:	cell surface, cellular membrane, Cytoplasm, dendrites, Endoplasmic Reticulum, intracellular space, membrane fraction, nuclear speckles, perikaryon, plasma, Plasma Membrane, plasma membrane extracellular face, presynaptic terminals, rod inner segments
Canonical Pathway:	Erythropoietin Signaling Pathway; Role of JAK2 in Hormone-like Cytokine Signaling
Targeted By miRNA Functional Cluster: (showing 50 out of 109) show all	miR-10400-3p (and other miRNAs w/seed UGGGCUC), miR-1179 (miRNAs w/seed AGCAUUC), miR-1184 (miRNAs w/seed CUGCAGC), miR-1188-3p (and other miRNAs w/seed GAGGCUC), miR-1199-5p (and other miRNAs w/seed CUGAGCC), miR-1200 (miRNAs w/seed UCCUGAG), miR-12185-3p (and other miRNAs w/seed CAGCCAC), miR-12192-5p (and other miRNAs w/seed GUGGGGU), miR-12204-5p (and other miRNAs w/seed UGAGUCU), miR-125b-5p (and other miRNAs w/seed CCCUGAG), miR-1264 (and other miRNAs w/seed AAGUCUU), miR-1284 (and other miRNAs w/seed CUAUACA), miR-1285-3p (and other miRNAs w/seed CUGGGCA), miR-1343-3p (and other miRNAs w/seed UCCUGGG), miR-1587 (and other miRNAs w/seed UGGGCUG), miR-17-2-3p (and other miRNAs w/seed CUGCACU), miR-188-5p (and other miRNAs w/seed AUCCCUU), miR-1896 (and other miRNAs w/seed GGUGGGU), miR-1909-3p (and other miRNAs w/seed GCAGGGG), miR-198 (miRNAs w/seed GUCCAGA), miR-2117 (miRNAs w/seed GUUCUCU), miR-2276-3p (miRNAs w/seed CUGCAAG), miR-2392 (miRNAs w/seed AGGAUGG), miR-2681-3p (miRNAs w/seed AUCAUGG), miR-296-3p (miRNAs w/seed AGGGUUG), miR-3064-5p (and other miRNAs w/seed GGCUGUU), miR-3065-3p (miRNAs w/seed CAGCACC), miR-3070-5p (and other miRNAs w/seed GCCCCUG), miR-3083-5p (and other miRNAs w/seed GGCUGGG), miR-3104-5p (and other miRNAs w/seed AGGGGGC), miR-3127-5p (miRNAs w/seed UCAGGGC), miR-3160-3p (miRNAs w/seed GAGCUGA), miR-3179 (miRNAs w/seed GAAGGGG), miR-3199 (and other miRNAs w/seed GGGACUG), miR-324-3p (and other miRNAs w/seed CACUGCC), miR-324-3p (miRNAs w/seed CCACUGC), miR-328-5p (and other miRNAs w/seed GGGGGGC), miR-342-5p (and other miRNAs w/seed GGGGUGC), miR-3473h-5p (and other miRNAs w/seed AGGGGCU), miR-3594-5p (and other miRNAs w/seed CCAGGGC), miR-3605-3p (miRNAs w/seed CUCCGUG), miR-361-3p (miRNAs w/seed CCCCCAG), miR-3614-3p

Top findings from Ingenuity Knowledge Base (show all 3727 categorized literature findings)

regulates:	JAK2, STAT3, STAT5a/b, STAT5A, EPOR, ERK1/2, PIM1, JAK1, STAT5B, STAT1, AKT1, BCL2L1, LYN, SHC1, CSN2
regulated by:	EPO, KITLG, EPOR, JAK2, beta-estradiol, GATA1, ESR1, lenalidomide, CSF2, darbepoetin alfa, TFR2, Gp55, HIPK2, trans-hydroxytamoxifen, megakaryocytes
binds:	EPO, JAK2, CISH, PIK3R1, PTPN6, SOCS2, STAT5A, GRB2, SOCS3, CRKL, SYK, LYN, CSF2RB, STAT5a/b, PLCG2
role in cell:	proliferation, growth, differentiation, apoptosis, development, number, tyrosine phosphorylation in, phosphorylation in, mitogenesis in, survival
disease:	erythrocytosis, anemia, chronic kidney disease, chemotherapy-induced anemia, chronic renal failure, myelodysplastic syndrome, chronic hepatitis C, polycythemia, stage V chronic kidney disease, renal failure, stage III chronic kidney disease, lymphoma, venous thrombosis, solid tumor, delayed graft function, hip fracture, hypoxic-ischemic encephalopathy, acute mountain sickness, fatigue, optic neuritis, end stage renal disease, thoracic aortic dissection, lower-risk myelodysplastic syndrome, cancer anemia, zidovudine induced anemia, hemolytic uremic syndrome, stage IV chronic kidney disease, traumatic brain injury, plasma cell myeloma, out of hospital cardiac arrest, myelodysplastic syndrome with ring sideroblasts, preterm birth, refractory anemia, non-myeloid cancer, congestive heart failure, neonatal anemia, chronic renal impairment, cognitive impairment, chronic myelomonocytic leukemia, refractory anemia with excess blasts, renal anemia, short-term memory impairment, acute myocardial infarction, osteoarthritis, HIV infection, left ventricular hypertrophy, diabetic nephropathy, heart failure, kidney disease, renal impairment, secondary hyperparathyroidism, diabetes mellitus, acute kidney injury, unclassifiable myelodysplastic syndrome, myelodysplastic syndrome with multilineage dysplasia, hypoplasia, leukemia, ventricular dysfunction, hypoplastic anemia, chronic obstructive pulmonary disease, cardiovascular disorder, acute renal failure, contrast induced nephropathy, familial erythrocytosis, cerebral malaria, edema, neoplasia, mature T-cell neoplasia, peripheral T-cell lymphoma, endometriosis, infection, Philadelphia-like B-lymphoblastic leukemia/lymphoma, global developmental delay, neoplastic cell transformation, Philadelphia-like acute lymphoblastic leukemia, benign erythrocytosis, neurodegeneration, natural killer cell neoplasia, T-cell non-Hodgkin disease, natural killer/T-cell lymphoma, primary familial congenital polycythemia, Philadelphia-like B-cell acute lymphoblastic leukemia, familial polycythemia

EPOR其他信息

Human **Isoforms From** RefSeq | View GTEx human tissue expression (Land Explorer) | More Info



Descriptions from External Databases

Entrez Gene Summary: This gene encodes the erythropoietin receptor which is a member of the cytokine receptor family. Upon erythropoietin binding, this receptor activates Jak2 tyrosine kinase which activates different intracellular pathways including: Ras/MAP kinase, phosphatidylinositol 3-kinase and STAT transcription factors. The stimulated erythropoietin receptor appears to have a role in erythroid cell survival. Defects in the erythropoietin receptor may produce erythroleukemia and familial erythrocytosis. Dysregulation of this gene may affect the growth of certain tumors. Alternate splicing results in multiple transcript variants.[provided by RefSeq, May 2010]

GO Annotations

Molecular Function: cytokine receptor activity; erythropoietin receptor activity; identical protein binding; protein binding; transmembrane signaling receptor activity

Biological Process: aging; brain development; cardiac muscle tissue morphogenesis; decidualization; elevation of cytosolic calcium ion concentration; embryo development; erythropoietin-mediated signaling pathway; heart development; heart morphogenesis; negative regulation of neuron apoptotic process; negative regulation of nitric oxide biosynthetic process; positive regulation of cell proliferation; positive regulation of ERK1 and ERK2 cascade; positive regulation of neuron projection development; positive regulation of phosphatidylinositol 3-kinase cascade; positive regulation of Ras protein signal transduction; response to hypoxia; signal transduction; vasculogenesis involved in coronary vascular morphogenesis; ventricular cardiac muscle tissue morphogenesis; viral reproduction; visceral serous pericardium development

Cellular Component: cytoplasm; external side of plasma membrane; extracellular region; integral to membrane; integral to plasma membrane; membrane; nuclear speck; plasma membrane

Drug Information

Targeting Drug	Drug Brand Name(s)	Action
darbepoetin alfa/filgrastim		agonist,stimulator
EPO/filgrastim		stimulator,agonist
EPO/sargramostim		agonist,stimulator
erythropoietin/lenalidomide		binder,agonist
EPO	Abseamed; Binocrit; E.P.O.; Epogen; Epogen/Procrit; Eprex; Erythropoietin; Procrit; Retacrit	binder,stimulator,agonist
darbepoetin alfa	Aranesp; Aranest; Nesp	agonist,stimulator
continuous erythropoietin receptor activator	Mircera	activator
epoetin beta	NeoRecormon; Recormon	binder
peginesatide	Omontys; Omontys Preservative Free	stimulator
epoetin zeta	Silapo	binder

与EPOR相关的信息总结（Findings）

3727 Categorized Literature Findings (show details)

3727 Categorized Literature Findings (hide details)

Functional Roles | Mutant Information | Modifications and Regulation | Disease | Expression and Localization | Physical Interactions | Toxicology | Additional Findings | Isoform Specific Findings

Functional Roles

Molecular Processes

activation of (100) A2M, AKT1 TYK2 ... STAT1, STAT2, STAT3, STAT5A, STAT5B, STAT5a/b,

expression of (55) BCL2L1, C STAT5a/b, ... MYC, OAS2, PIM1, SIGLEC1, SLC40A1, SOCS1, SOCS3,

Findings: Functional Roles

Review the information that supports the gene-to-f

PlainText | Export references

Findings 1 - 20 of 100

<< Previous 20 | Next 20 >> Show Findings 1 - 20

In Cho cells, mutant **EPOR protein** (deletion 469-475) d

Experiment Type: immunoblot

12538595 Guillard C, Chré Chem. 2003 Ma

Source: Ingenuity Expert Findings

PRL protein in cell culture **causes little or no change i** protein fragment (substitution Y401F;Y429F;Y431F;Y4

Experiment Type: anti-phosphores

16407271 Um M, Lodish H Jan 4.

Source: Ingenuity Expert Findings

In Cho cells, mutant **EPOR protein** (deletion 469-475) d

Experiment Type: immunoblot

12538595 Guillard C, Chré Chem. 2003 Ma

Source: Ingenuity Expert Findings

ceptor via a G(i)protein beta gamma-subunit-initiated pathway. J Biol

ent containing a **extracellular domain** from **PRLR protein** and of a mutant SY5Y cells.

naling pathways. J Biol Chem. 2006 Mar 03;281(9):5648-56. Epub 2006

ceptor via a G(i)protein beta gamma-subunit-initiated pathway. J Biol

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5.157 点这里更新 J Biol Chem. 2006 Mar 3;281(9):5648-56. doi: 10.1074/jbc.M510943200. Epub 2006 Jan 4.

Antiapoptotic effects of erythropoietin in differentiated neuroblastoma SH-SY5Y cells require activation of both the STAT5 and AKT signaling pathways

Moonkyoung Um [1], Harvey F Lodish

Affiliations + expand

PMID: 16407271 DOI: 10.1074/jbc.M510943200

Free article

Abstract

The hematopoietic cytokine erythropoietin (Epo) prevents neuronal death during ischemic events in

FULL TEXT LINKS

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ACTIONS

Cite

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ENDNOTE

ENDNOTE

EPOR参与的经典通路

Canonical Pathways

Erythropoiet...

Edit: | Build | Overlay | Path Designer | Pattern Search | View: | Zoom: | Export:

IPA Ge

Review t

Summary

NCE

Pr

T

Ingenuity Pathway Analysis

Canonical Pathway

Report Date: 2021-10-20
Report Version:
Content Version: 68752261 (Release Date: 2021-09-06)

Provide Feedback | Contact Support | Download Report (PDF)

Canonical Pathway: **Erythropoietin Signaling Pathway**

Description: Erythropoietin (Epo) elicits cell-specific responses upon interacting with its receptor EpoR. Activation of EpoR by Epo results in receptor homodimerization, which induces a cascade of signaling events.

Epo is a major activator of the Ras/MAPK pathway. This activation is achieved via signaling through GRB2, SHC, GAB2 and the PTB domain containing proteins. GRB2 constitutively associates with SOS and binds to EpoR either via an interaction with GAB2 or by binding to EpoR-associated tyrosine-phosphorylated SHC. SHC recruits the GRB2-SOS complex to the plasma membrane, thereby promoting Ras activation. PKC, a potent activator of Ras and c-Raf, plays an important role in the Epo-induced activation of MAPK. Raf1 inhibits the activity of VDAC and functions as an important Anti-apoptotic factor. Activated c-Raf phosphorylates the dual functional protein kinases MEKs, which then phosphorylate and activate ERK/MAPKs. Activated ERKs in turn enhance transcriptional activity of Elk1 and CREB, which regulate the early gene expression in erythroid cells.

Epo activates MAPK through a novel pathway dependent on Gi association to EpoR. Following Epo stimulation, Gi is released from the receptor, resulting in subsequent activation of MAPKs. The tyrosine kinase JAK2 contributes to this pathway by acting downstream of GNβ-γ and upstream of Ras and PI3K. Epo signaling also activates the Ras/MAPK/ERK pathway by the use of a third group of interacting partners other than the SHC/GRB2/SOS complex or the Gi proteins. The adaptor protein CrkL, interacts with and recruits C3G to the activated EpoR. C3G independently initiates Epo-mediated MAPK signaling via the activation of Ras. Activated Ras then stimulates the Raf/MEK/ERK signalling cascade leading to the activation of Elk1, which enhances transcriptional activity of immediate early factors c-Fos and c-Jun through the serum response element. CrkL and C3G are also implicated in c-Raf activation via a Ras/PI3K-dependent mechanism involving the activation of Rac.

The transcriptional activation and stability of c-Jun is accomplished by JNK1, CKII and PPtase, whereas in case of c-Fos, ERK phosphorylates c-Fos, resulting in its increased transcriptional activity. PIN1 regulates AP-1-mediated transcription. As a consequence, the mitogenic action of Epo is directly linked to transcriptional regulatory events utilizing Ras as a molecular switch relaying upstream tyrosine kinase signals to a serine/threonine kinase cascade. Active ERKs also activate Cyclin D1, the critical regulator of the cell-cycle clock apparatus directing the G1-S phase progression during the cell cycle.

Activated EpoR ensures its control over this trail via Src tyrosine kinase. JAK2-activated FAK1 activates PI3K in a Syk-dependent manner. Activated PI3K phosphorylates membrane-bound PIP2 to generate PIP3, and PTEN acts as a negative regulator of this phosphorylation event. As a result, PI3K triggers the phosphorylation of Akt via PDK-1. Akt phosphorylates various signaling molecules such as GSK3, BAD and FkhR to promote cell survival. Akt prevents the nuclear translocation of FoxO3A, which inhibits apoptosis. BAD phosphorylation also stimulates certain anti-apoptotic signals that facilitate inhibition of Cytochrome C release and inactivation of caspase 1, 3, 8 and 9. Optimal function of GATA1 is essential for the biological function of Epo, and GATA1 plays a role at a number of steps of the erythroid differentiation program. (Upgraded 07/2020)

Signaling Pathway Categories: Cellular Growth, Proliferation and Development; Growth Factor Signaling

Top Functions & Diseases: Cell Death and Survival; Cell Cycle; Cellular Function and Maintenance

Molecules: show all — 1-phosphatidyl-D-myo-inositol 4,5-bisphosphate, Akt, Angiogenesis, Ap1, APAF1, Apoptosis, BAD, BCL2L1, BIRC2, BIRC3, Ca2+, CCND1, CCND2, Cell cycle progression, Cellular infiltration by granulocytes, CSF2RB, CTNNB1, diacylglycerol, Differentiation of erythroid precursor cells, ELK1, EPO, EPOR, EPOR dimer, EPOR-CD131, ERK1/2, FOS, FOXO3, GATA1, GRB2, Grb2-Shc1-Sos, GSK3B, hemoglobin, Hif1, Hypoxia of kidney, Ikb, IkB-NfkB, Inflammation, inositol triphosphate, IRS2, ITPR, JAK2, JUN, MACROH2A2, MAP2K1/2, Maturation of erythroid cells, MDM2, MTOR, Neuroprotection, NFkB (complex), nitric oxide, NOS3

Back to top >>

Drug Summary - Overview of drugs targeting molecules in Canonical Pathway

Showing 3 of 656 row(s) of Drug data. (Show All)

Drug Name	Targets	Actions	Brand Names	Indications/Status
1-(3-(1,4-dihydroimidazo[4,5-c]pyrazol-5-yl)-4-methylphenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)urea	RAF1	inhibitor		
1-(5-isoquinolinesulfonyl)piperazine	Pkc(s)	inhibitor		
1-o-hexadecyl-2-o-methyl-rac-glycerol	Pkc(s)	inhibitor		

Back to top >>

Target Information - Overview of known drug targets in Canonical Pathway

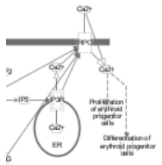
Showing 3 of 86 row(s) of Target data. (Show All)

Target (Gene Symbol)	Entrez Gene Name	Location	Type	Drug(s)	Species
Akt		Cytoplasm	group	afuresertib, Akt inhibitor XI, AT13148, ipatasertib, MSC2363318A, ONC-201, SR-13668, TAS-117, TAS0612	Human, Mouse, Rat
AKT1	AKT serine/threonine kinase 1	Cytoplasm	kinase	A-443654, AKT inhibitor XIII, archexin, ARQ 751, BAY1125976, capivasertib, CCT129524, enzastaurin, GSK690693, ipatasertib, LY2780301, miransertib, MK2206, MPT0E028, perifosine, triciribine, triciribine phosphate, uprosertib	Human, Mouse, Rat
AKT2	AKT serine/threonine kinase 2	Cytoplasm	kinase	AKT inhibitor XIII, BAY1125976, CCT129524, enzastaurin, GSK690693, triciribine, triciribine phosphate	Human, Mouse, Rat

Back to top >>

Supporting References (Show details) - References from which the Canonical Pathway was derived

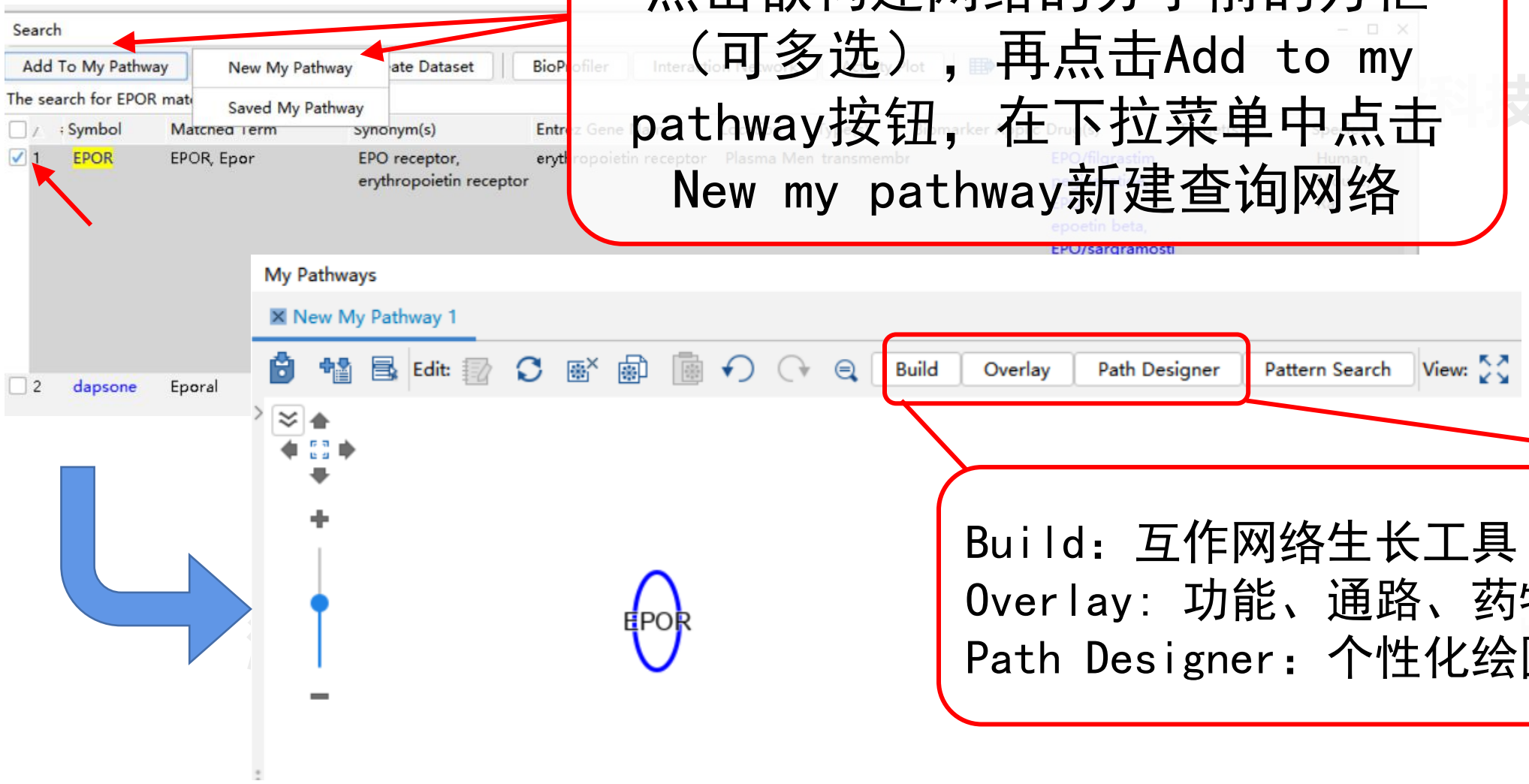
Back to top >>



5GGG), miR-198 (miRNAs w/seed GUCCAGA), miR-2117 (miRNAs w/seed
d AUCAUGG), miR-296-3p (miRNAs w/seed AGGGUUG), miR-3064-5p (and other
, miR-3083-5p (and other miRNAs w/seed GGCUGGG), miR-3104-5p (and other
9 (miRNAs w/seed GAAGGGG), miR-3199 (and other miRNAs w/seed GGGACUG),
w/seed GGGGGGC), miR-342-5p (and other miRNAs w/seed GGGGUGC), miR-
s w/seed CUCCGUG), miR-361-3p (miRNAs w/seed CCCCCAG), miR-3614-3p
niR-378g (miRNAs w/seed CUGGGCU), miR-3921 (and other miRNAs w/seed
s w/seed UAGGGGG)...(more)

EPOR相互作用的分子

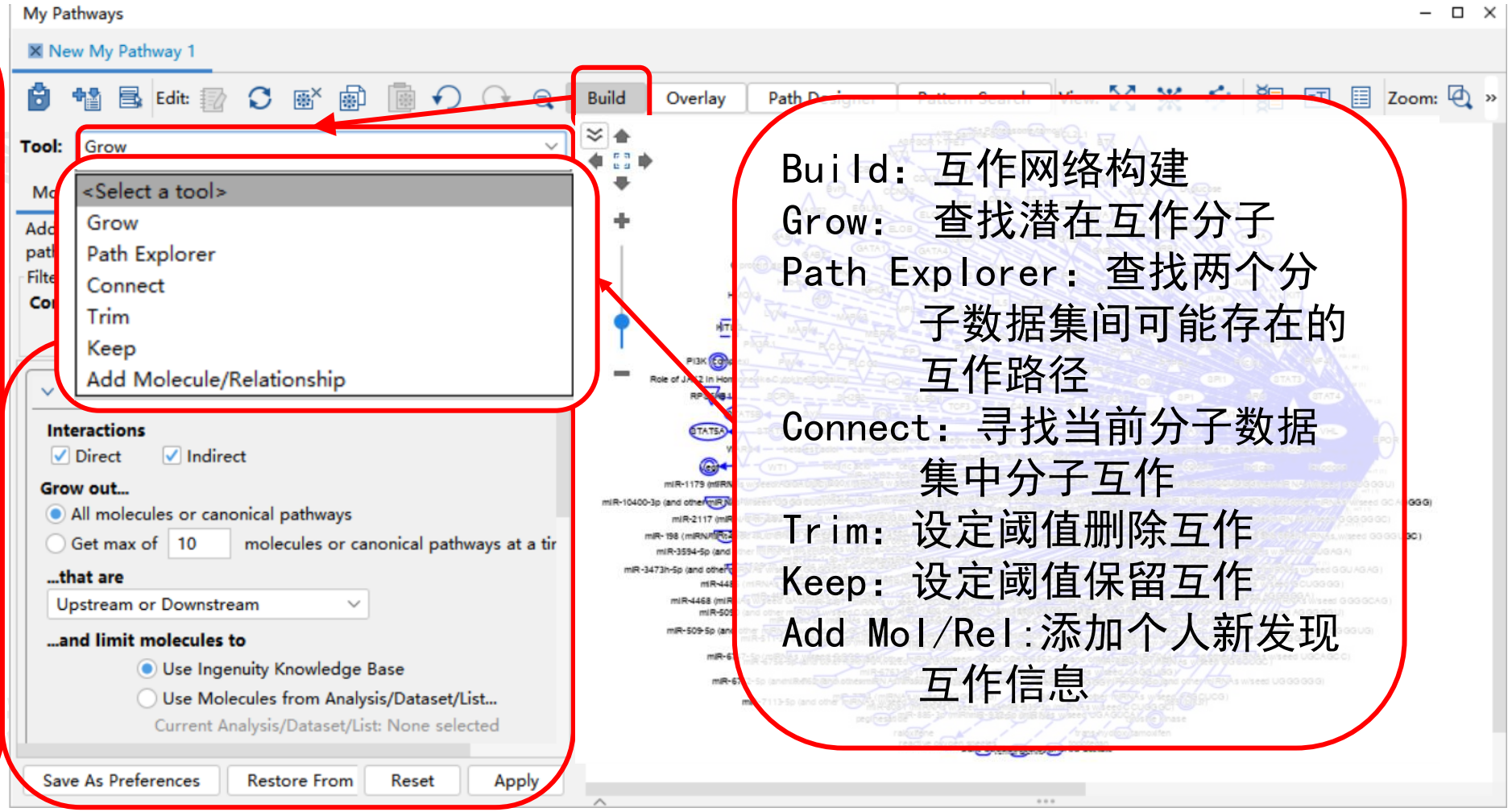
点击欲构建网络的分子前的方框（可多选），再点击Add to my pathway按钮，在下拉菜单中点击New my pathway新建查询网络



Build：互作网络生长工具
Overlay：功能、通路、药物等关联
Path Designer：个性化绘图工具

EPOR相互作用的分子

通过Build构建分子互作网络：
采用Grow即可寻找与EPOR直接间接相互作用的10个分子，也可以设定过滤参数，得到最合适的分子网络。过滤参数包括：查询数量限制；数据库；互作置信度；物种；器官组织；突变；互作类型；互作实验时限；互作分子类型等



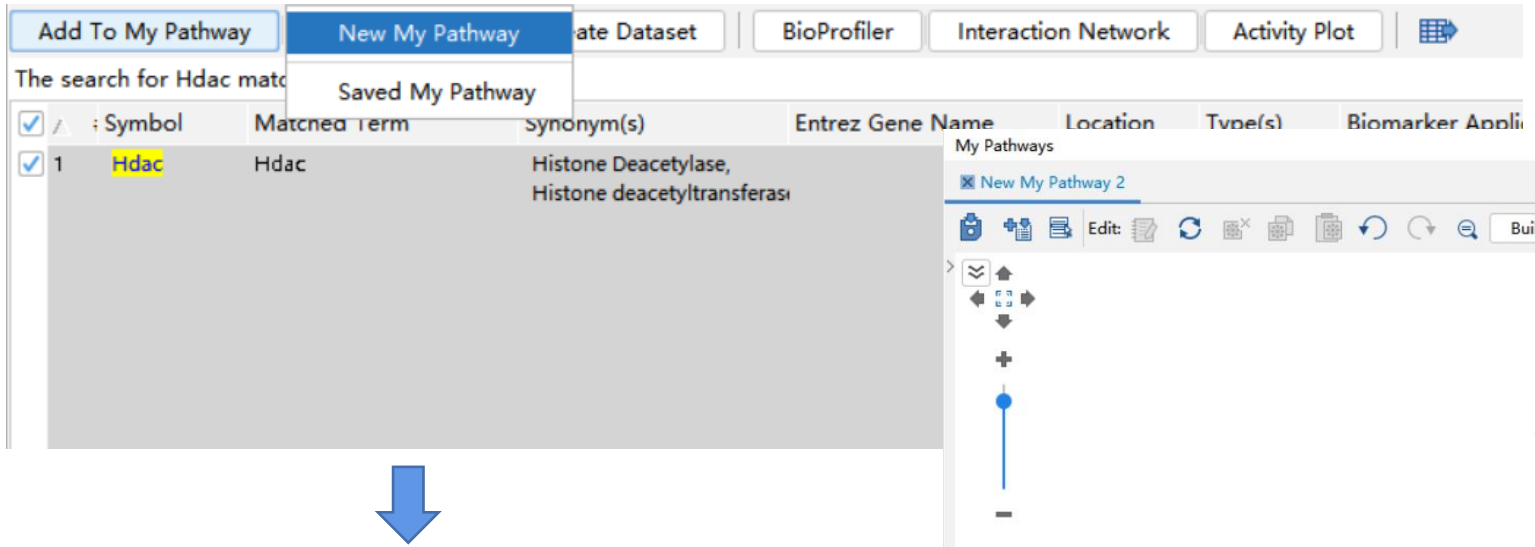
Build：互作网络构建
Grow：查找潜在互作分子
Path Explorer：查找两个分子数据集间可能存在的互作路径
Connect：寻找当前分子数据集中分子互作
Trim：设定阈值删除互作
Keep：设定阈值保留互作
Add Mol/Rel：添加个人新发现互作信息

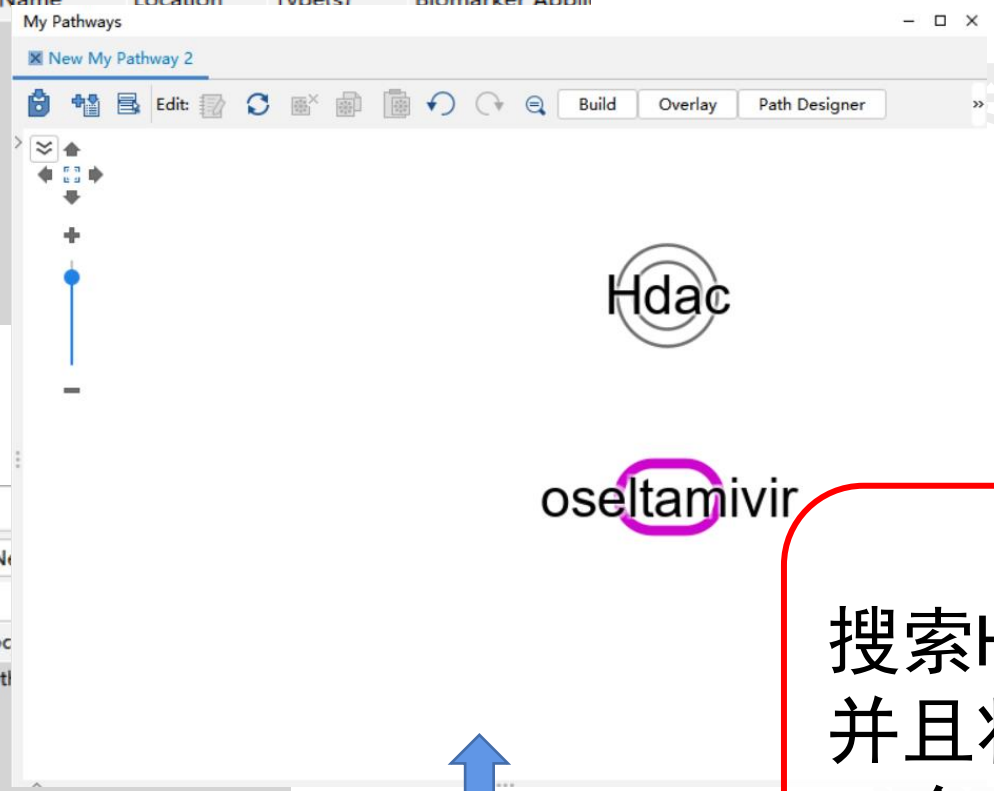
上游调控EPOR的分子

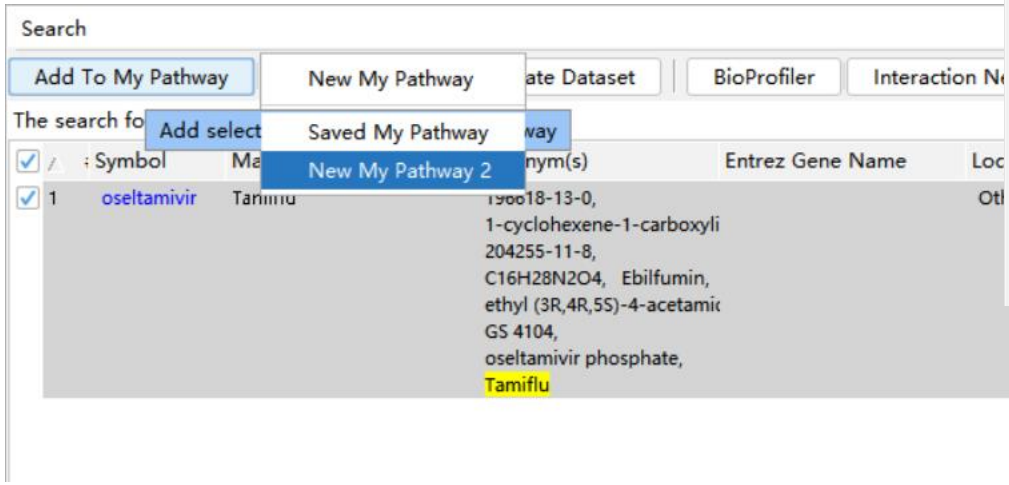
如果双击分子与分子之间的连接线，则能看到分子间相互作用的总结，点击上方链接既可以打开IPA内部的findings

靶标基因与已知药物关系——举例HDAC基因

TamiFlu与靶标基因HDAC是否有作用关系?

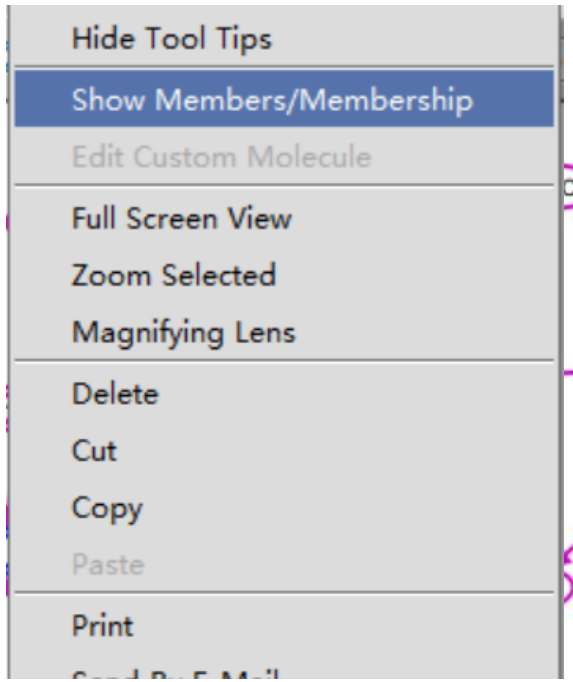




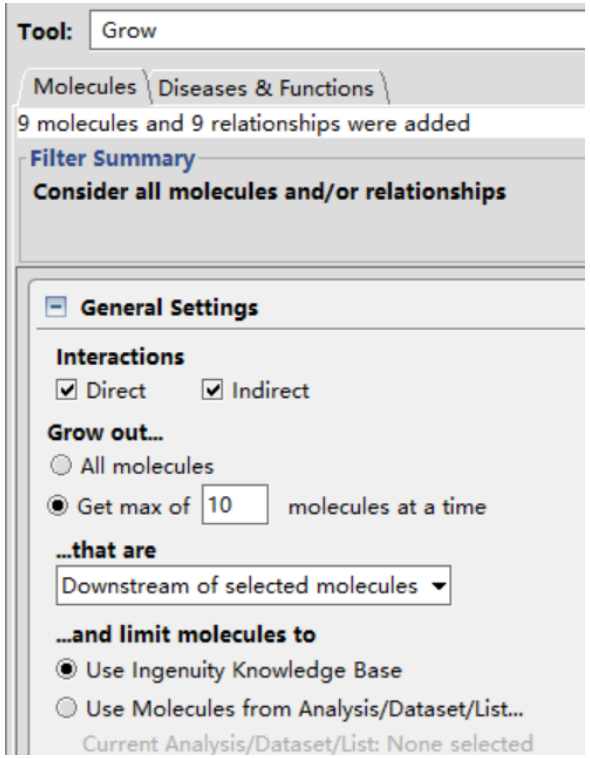


搜索HDAC与TamiFlu，并且将他们放入同一个My Pathway中。

靶标基因HDAC与已知药物TamiFlu的关系

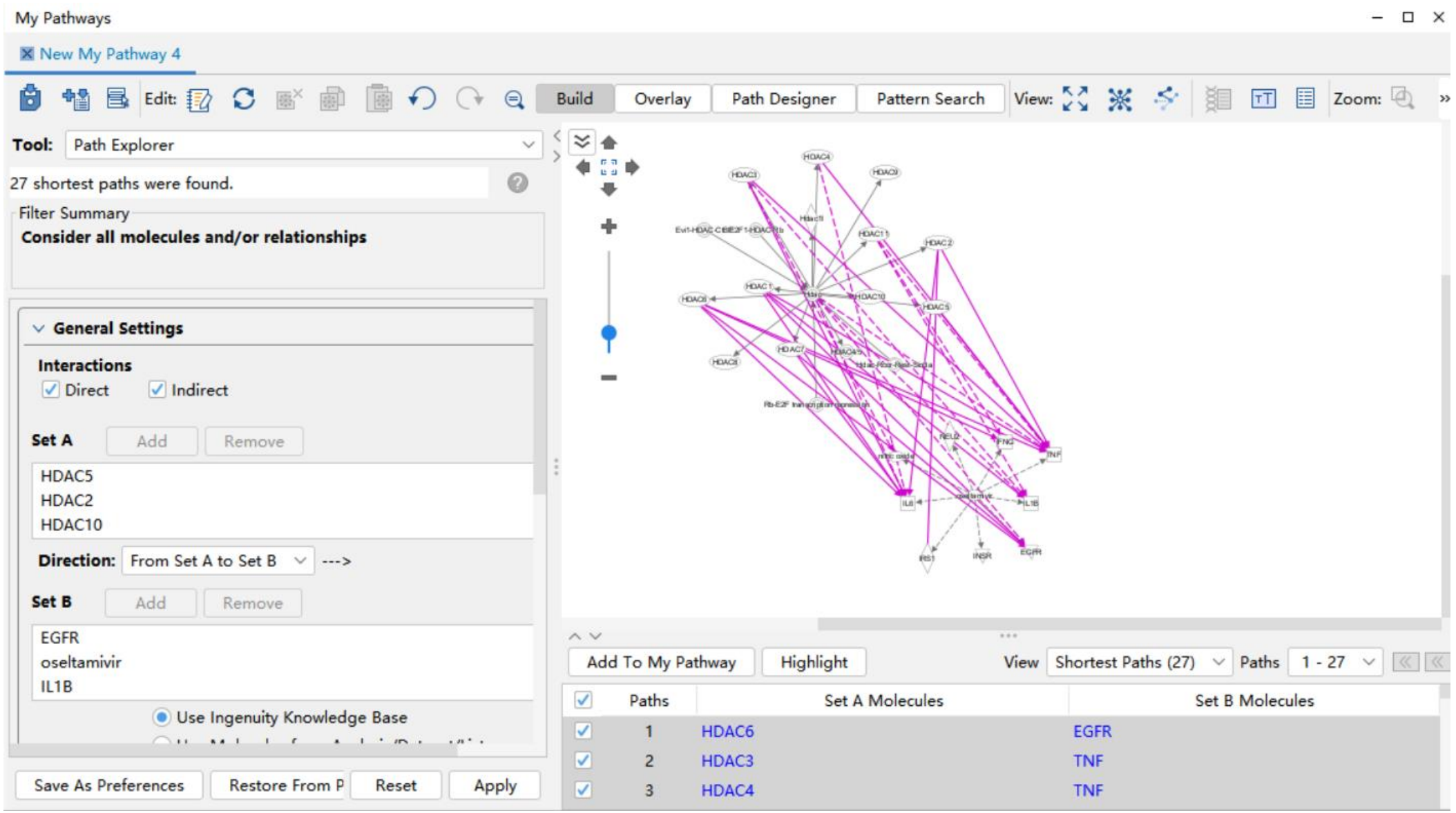


左键单击oseltamivir，选择Build——Grow工具，关联性选择Downstream of selected molecules



右键单击HDAC，点击Show Members/Membership显示所有家族分子

靶标基因HDAC与已知药物TamiFlu的关系



靶标基因HDAC与已知药物TamiFlu的关系

My Pathways

New My Pathway 4

Edit:

Tool: Grow

Molecules & Canonical Pathways | Diseases & Functions

Grow from selected molecules to selected diseases & functions

Indicate diseases or functions related to Any

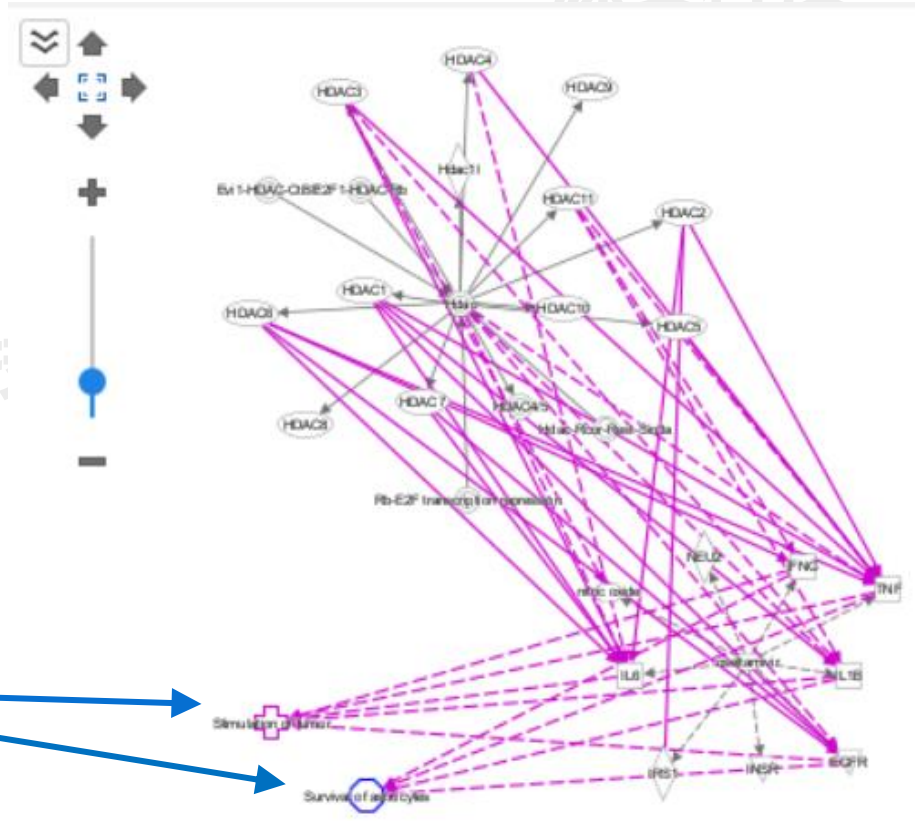
Consider all functions

Recalculate

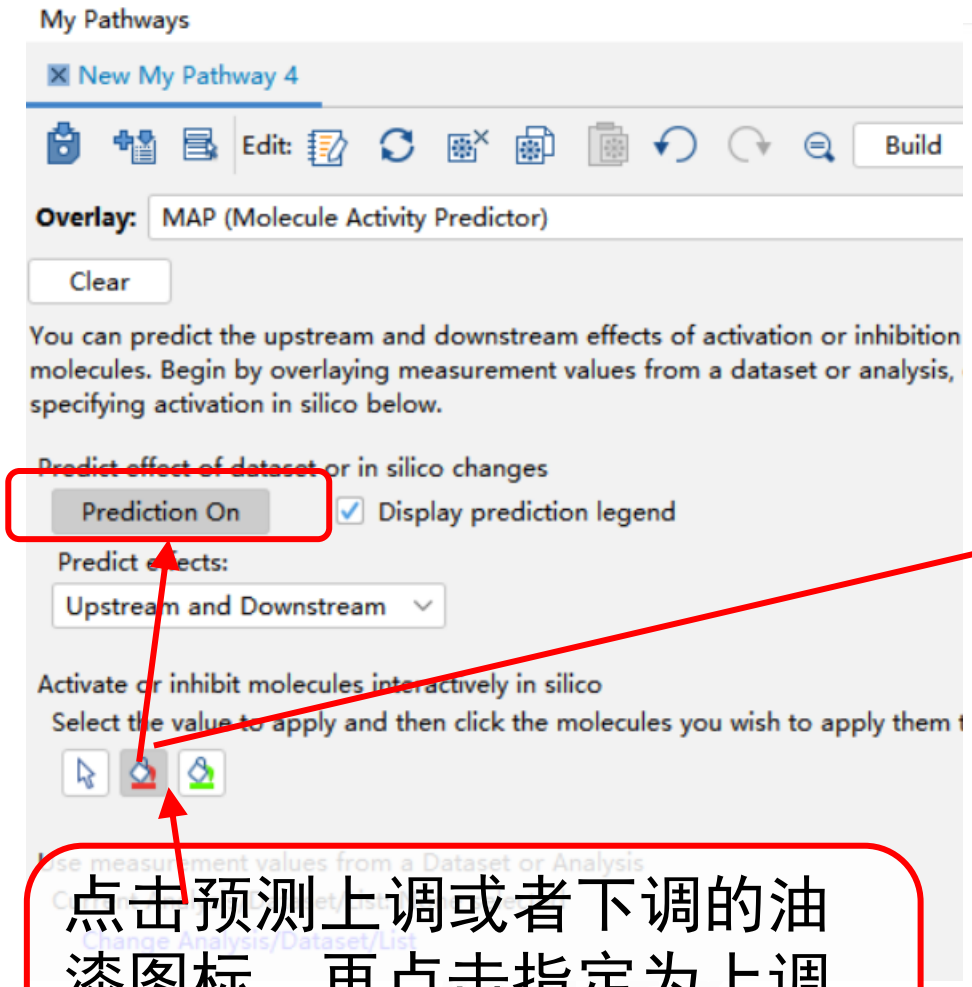
Diseases an...	p-value	Molecules
Synthesis of extracellu	7.60E-10	IL6, IFNG, IL1B, ...all 4
Synthesis of DNA	1.21E-09	EGFR, IFNG, IL... ...all 9
Synthesis of ATP	8.03E-09	INSR, IRS1, IL6, ...all 6
Swelling of joint	1.05E-08	IL6, IFNG, IL1B, ...all 4
Susceptibility to coron	1.75E-03	IRS1 ...all 1
Survival of organism	8.73E-09	EGFR, IFNG, ...all 12
Survival of astrocytes	3.97E-09	EGFR, IFNG, IL... ...all 4
Stimulation of tumor	5.32E-09	EGFR, IL6, IFNG, ...all 5
Stimulation of smooth	2.85E-11	IL6, IL1B, IFNG, ...all 4
Stimulation of hepato	3.02E-12	IL6, IL1B, IFNG, ...all 4
Stimulation of airway	6.87E-10	IL1B, IFNG, TNF ...all 3

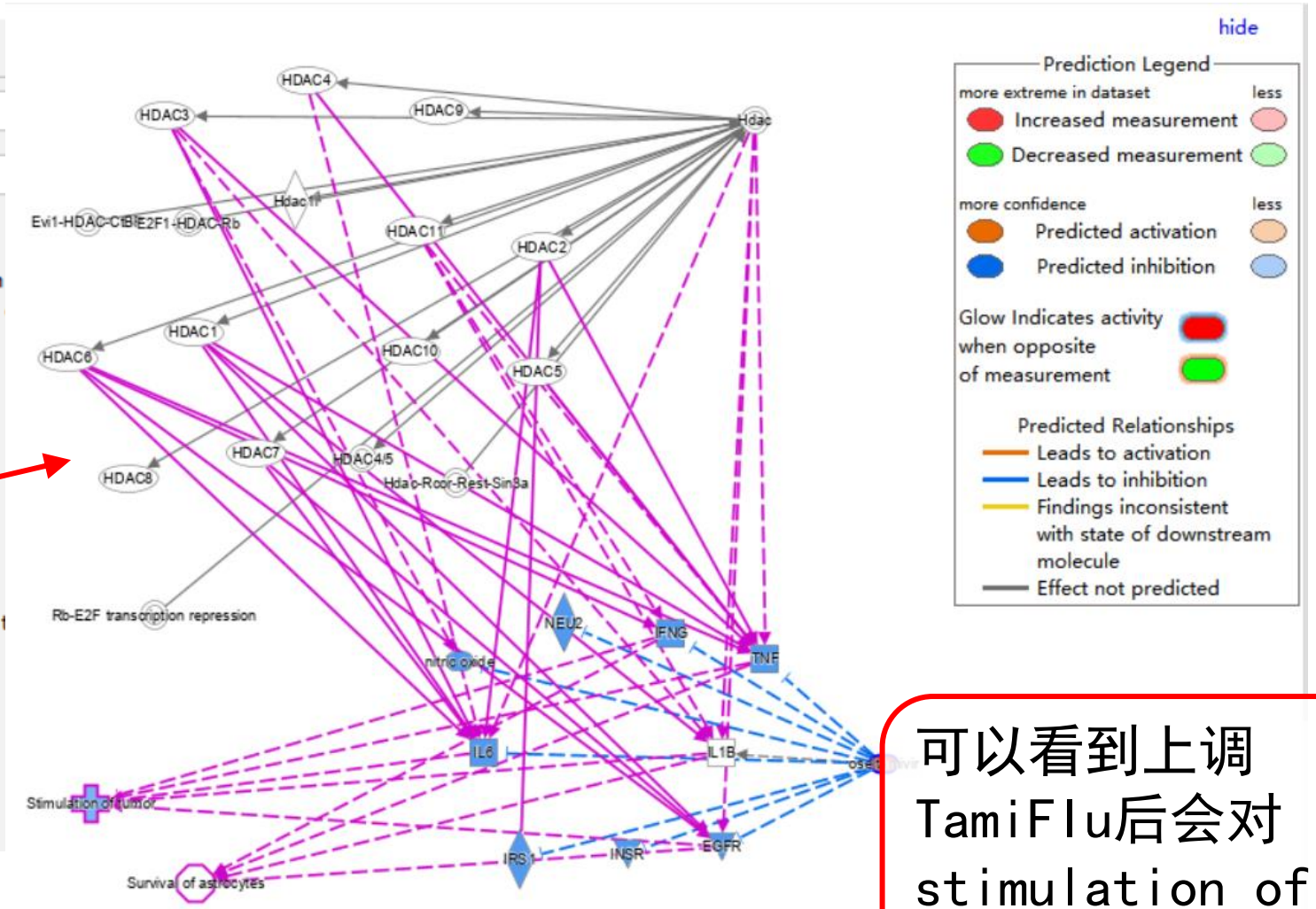
2/476 Reset Apply

全选所有需要聚类分子



靶标基因HDAC与已知药物TamiFlu的关系





点击预测上调或者下调的油漆图标，再点击指定为上调的节点，最后点击Start Prediction进行预测

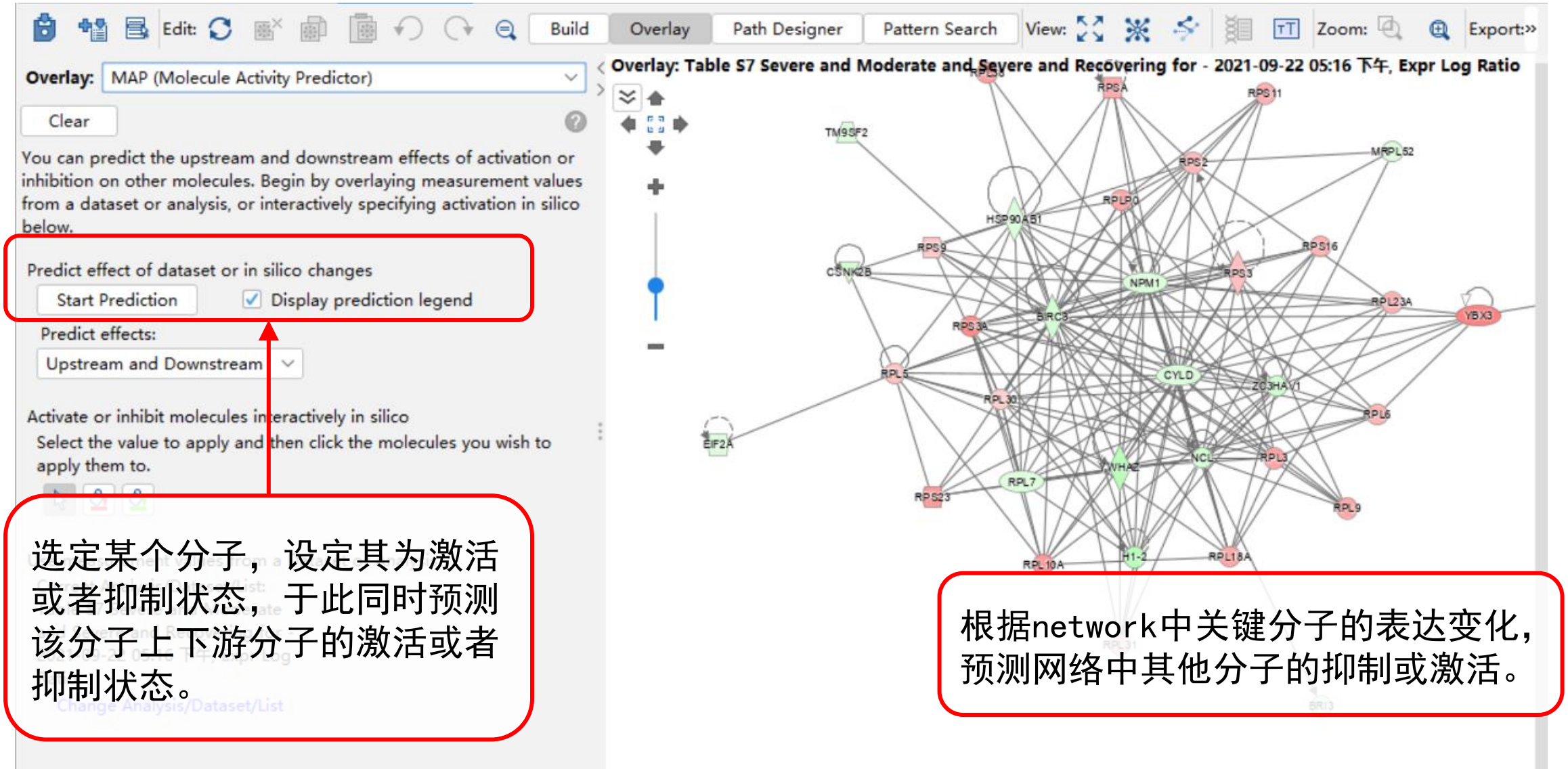
可以看到上调TamiFlu后会对stimulation of tumor有抑制作用。

PART

3

分子活性预测功能

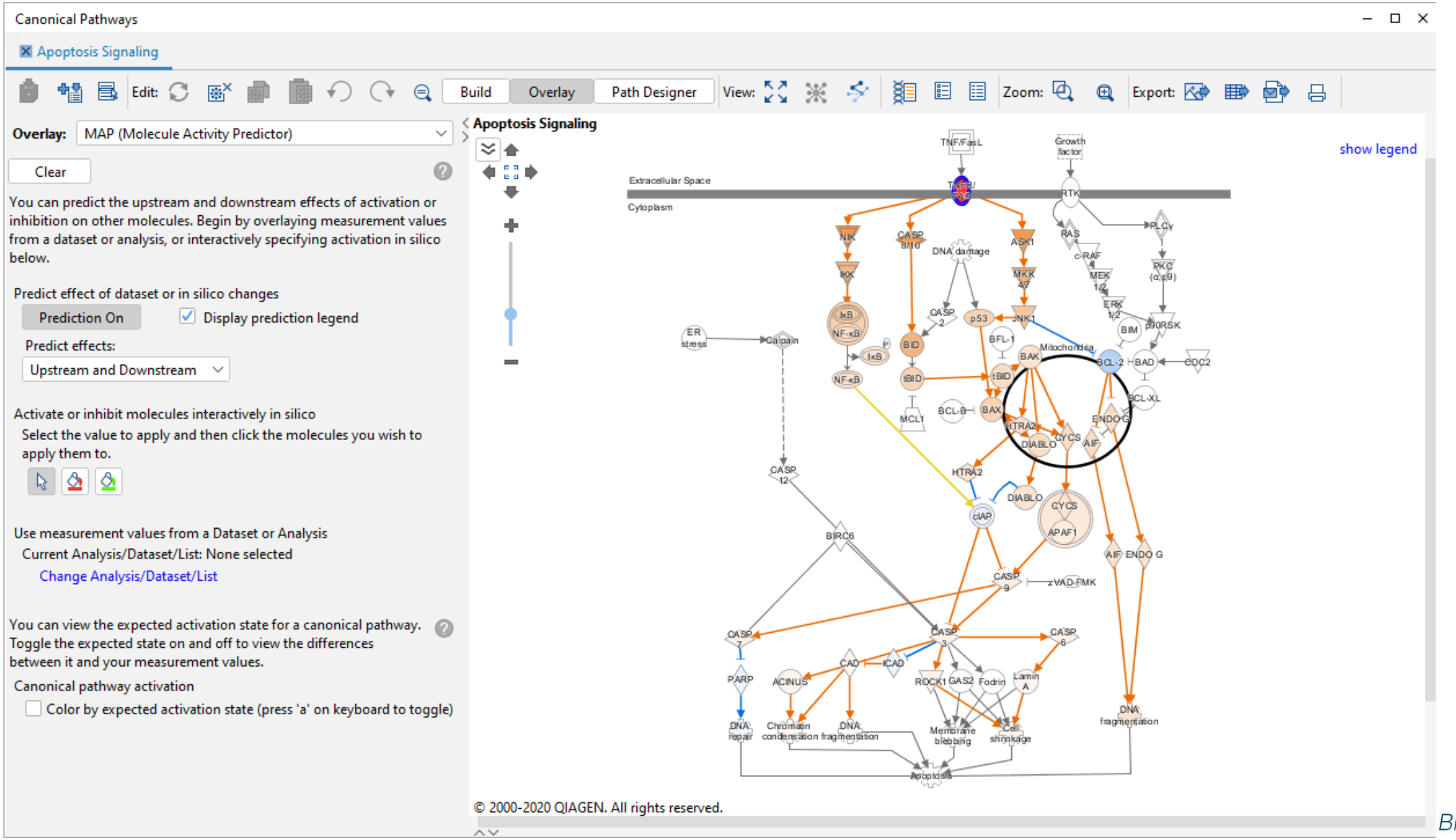
Overlay——MAP（Molecule Activity Predictor）



选定某个分子，设定其为激活或者抑制状态，于此同时预测该分子上下游分子的激活或者抑制状态。

根据network中关键分子的表达变化，预测网络中其他分子的抑制或激活。

Overlay——MAP（Molecule Activity Predictor）



PART

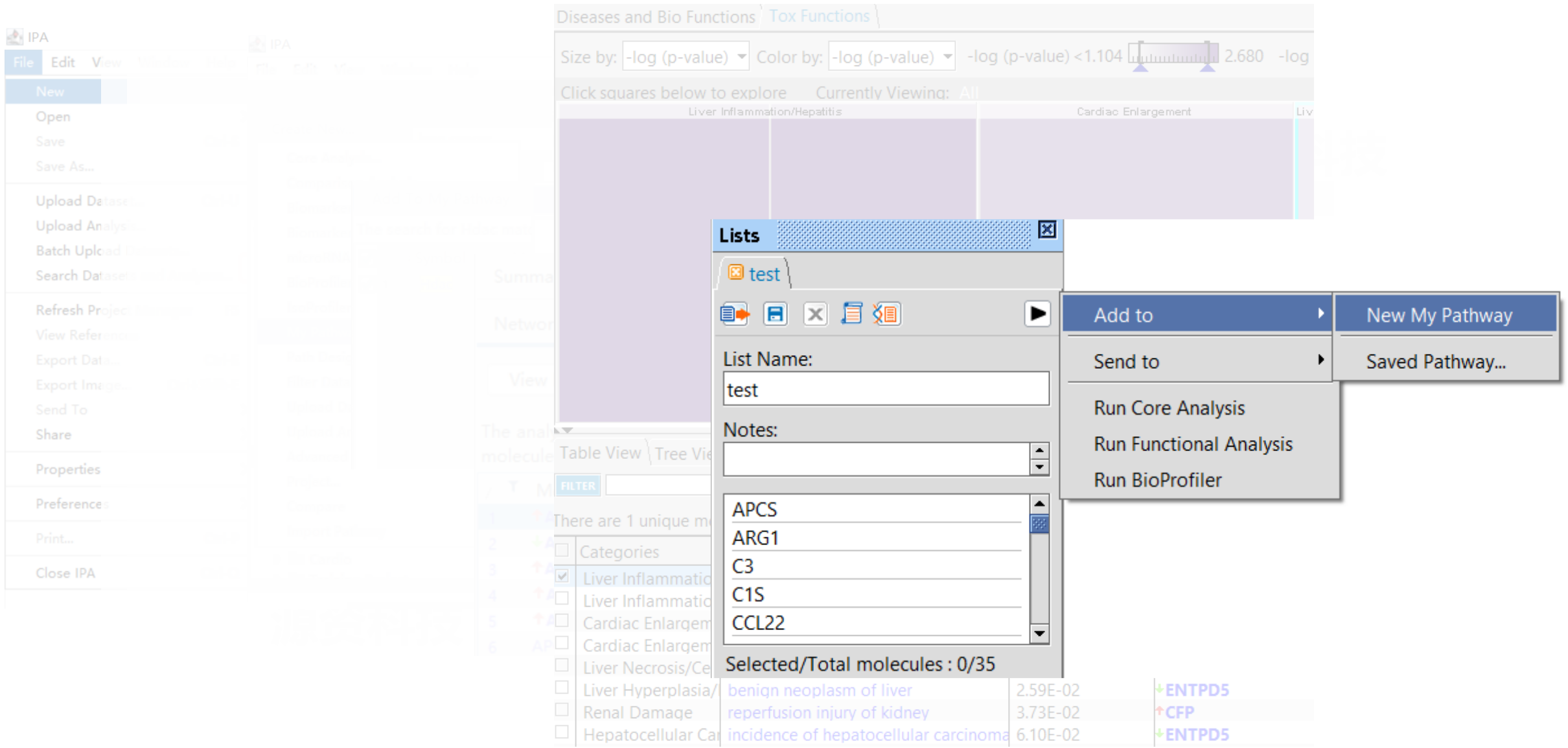
4

Pathway构建

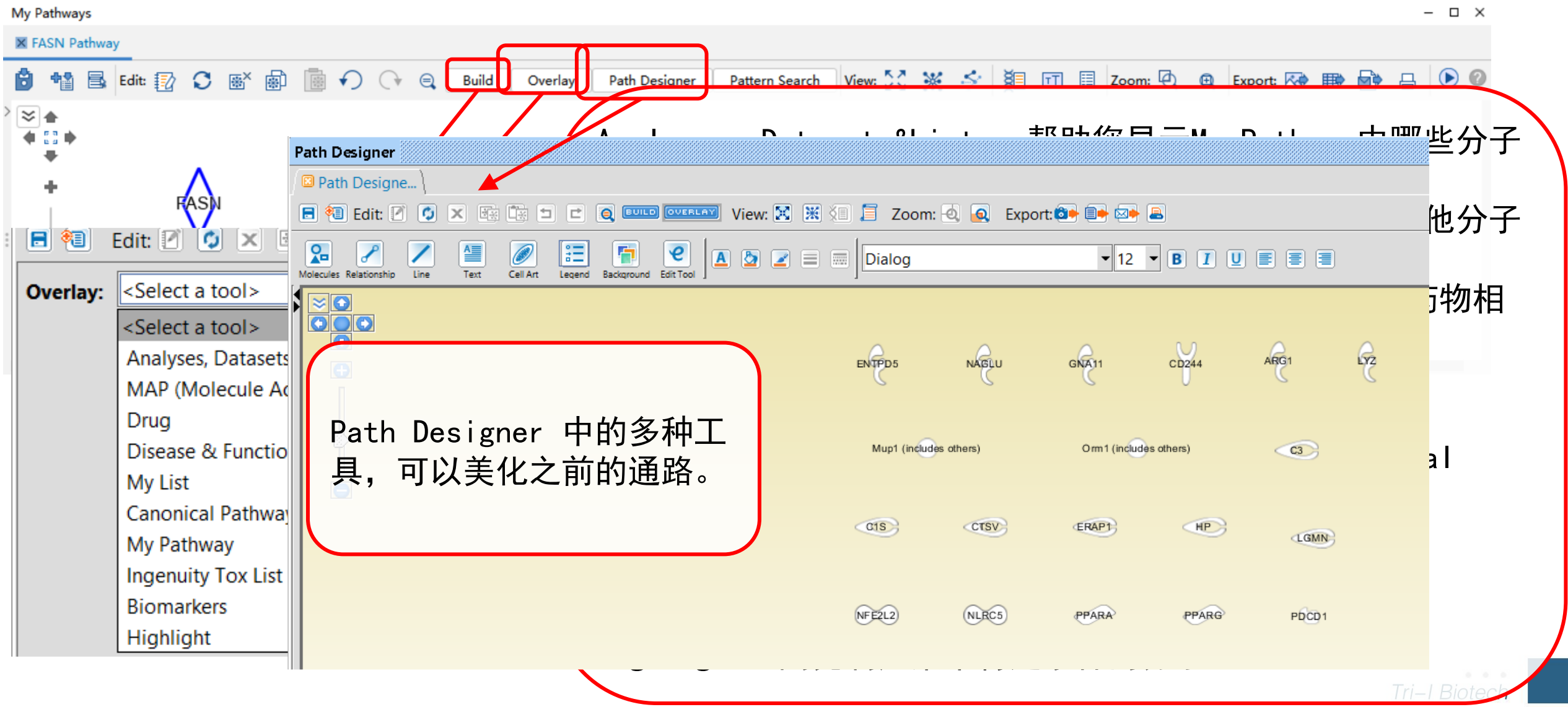
My Pathway是什么?

- 创建个性化通路
- 界面友好，易操作
- 功能强大，灵活
- 不受固有的经典通路限制

创建My Pathway



My Pathway功能



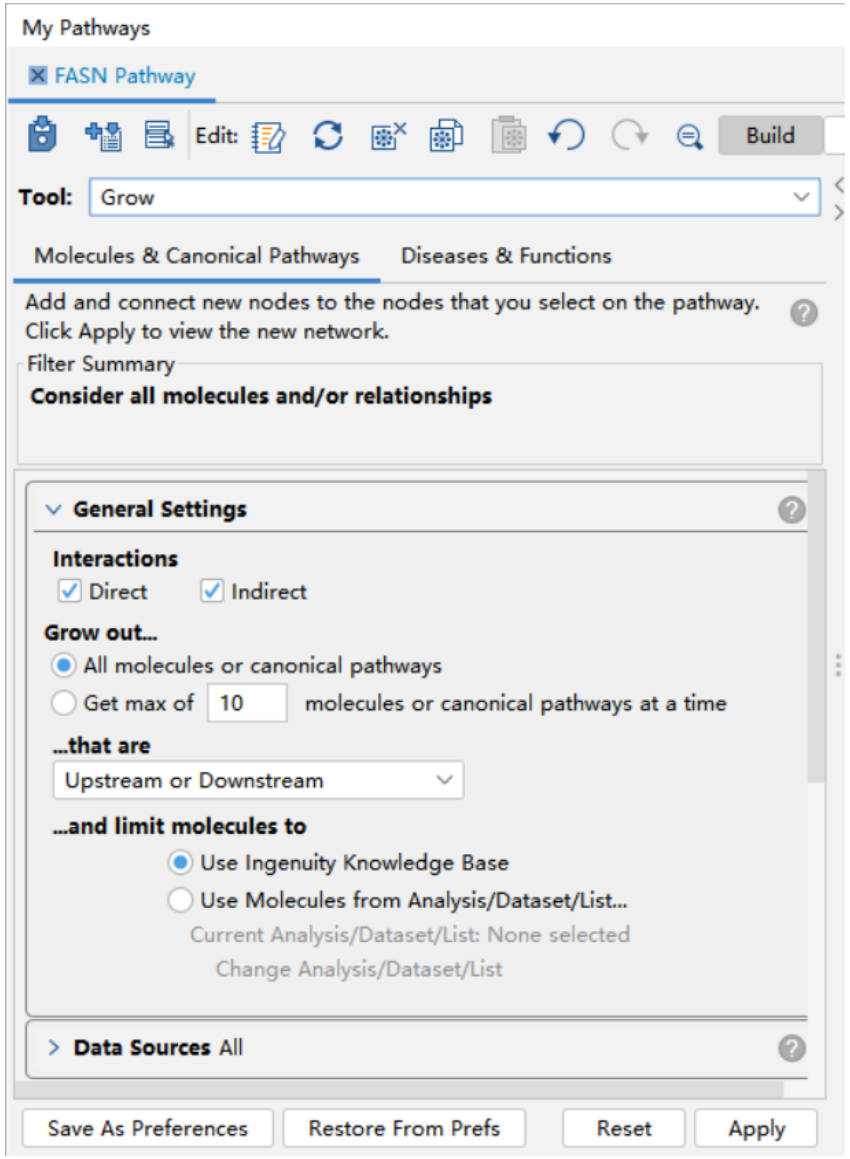
些分子

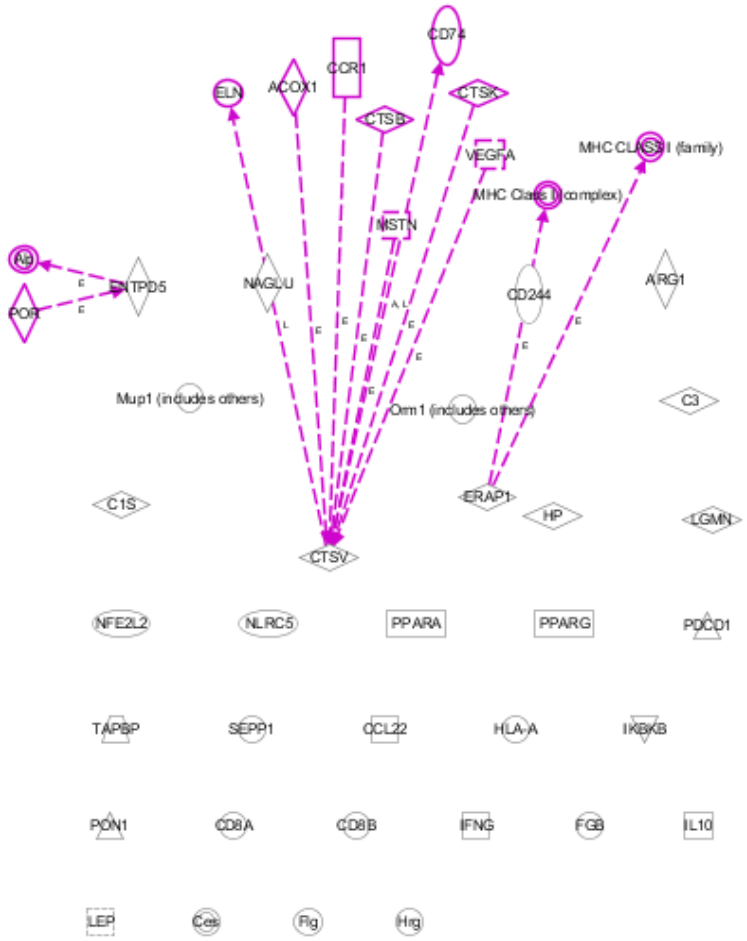
他分子

物相

al

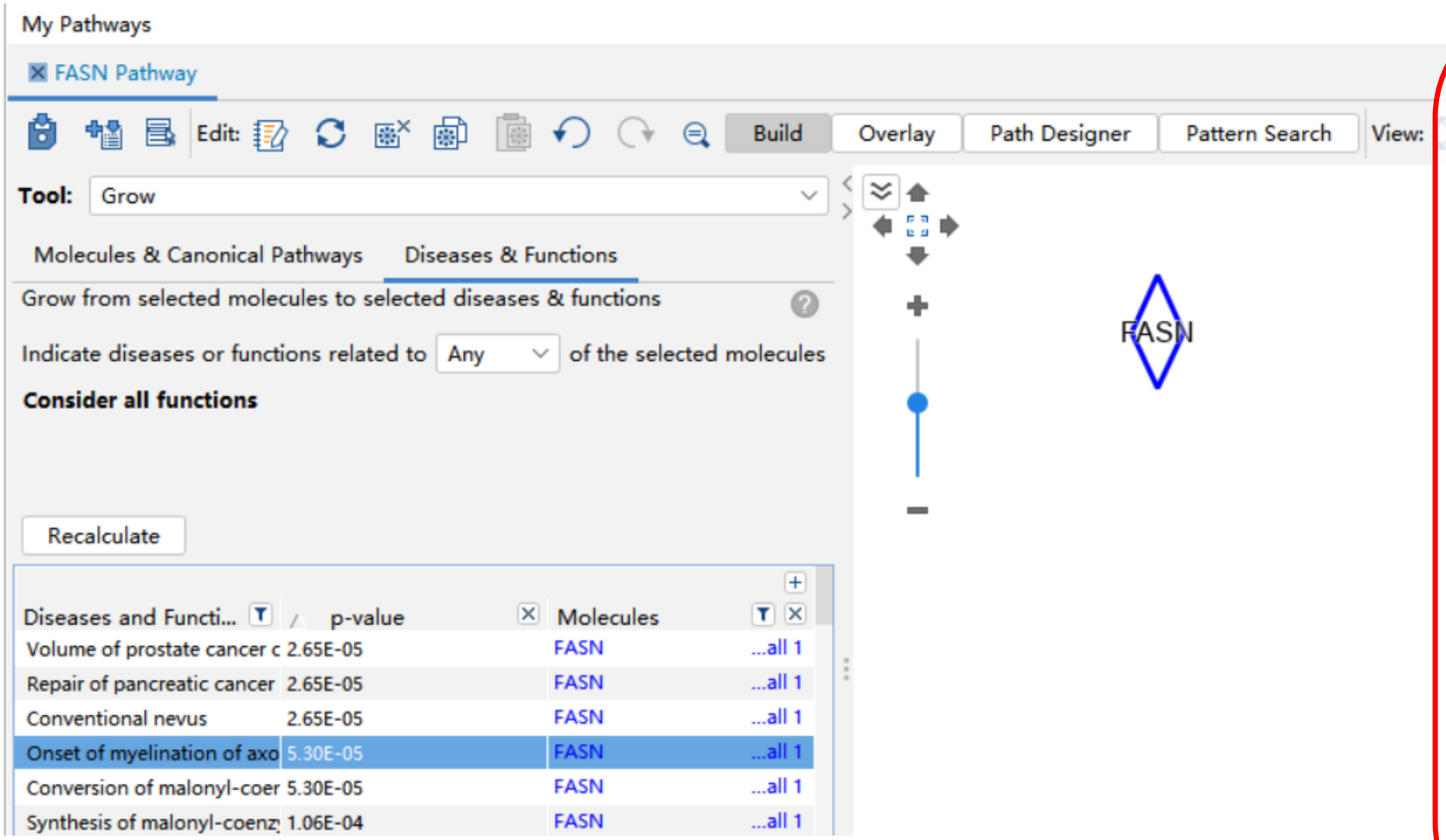
Build——Grow——Molecular





选择My Pathway 中一个或多个感兴趣的分子，通过Grow 工具找出与此分子相互作用的其他分子。可以设定相互作用分子数，分子来源，相互作用关系类型等参数来达到最优的结果。

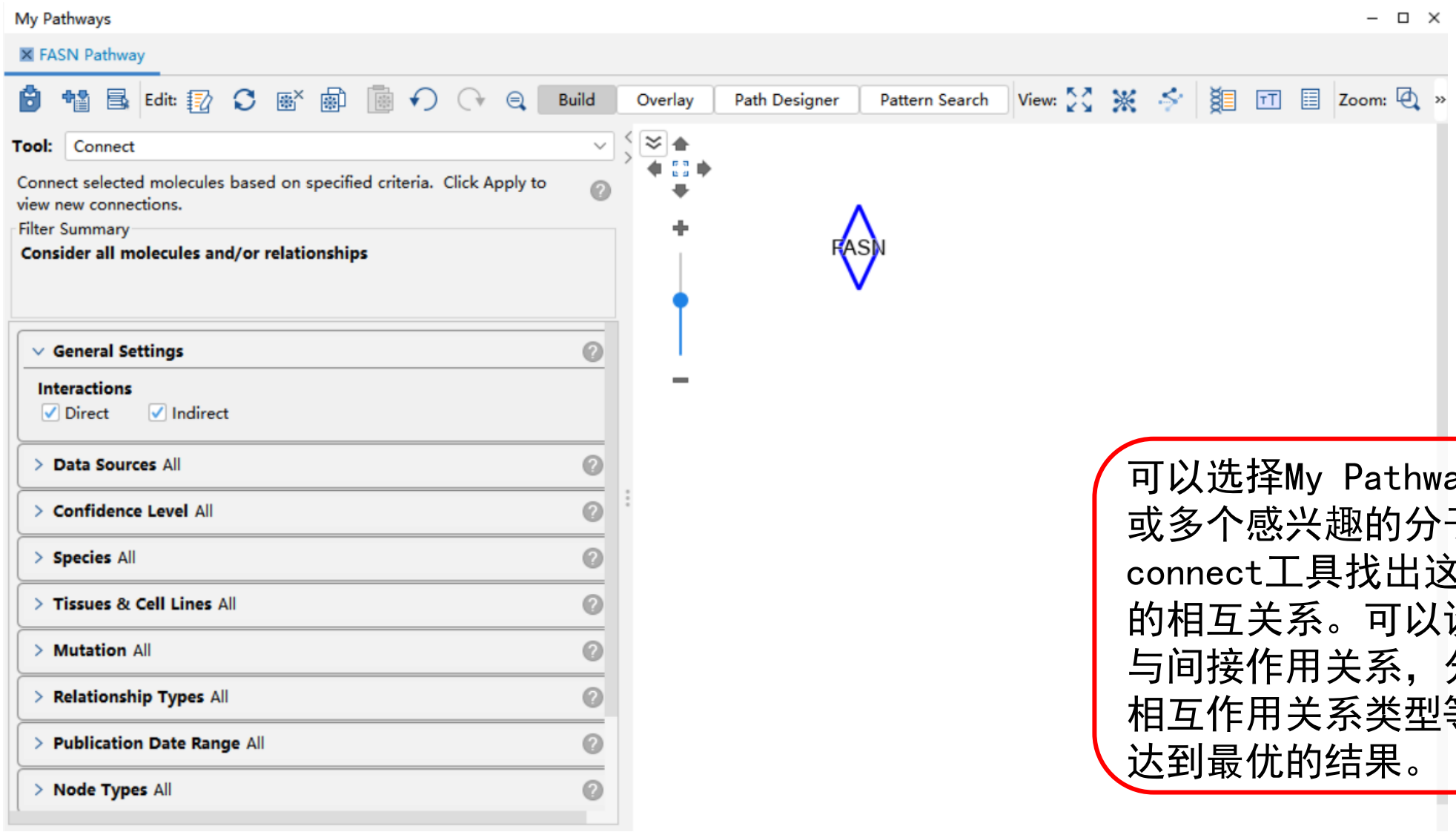
Build——Grow——Disease & Functions



Grow 中的Disease & Functions 功能可以构建所选分子与疾病间的关系。选中一个或多个分子，左侧高亮显示了该分子所参与的疾病。如果想知道选中的多个分子共同参与的疾病，可以将“Any”改成“All”。选中疾病，当点击“Apply”后，疾病就会关联到所选择的分子上。

也可以通过“Filter”工具来聚焦想关注的疾病或分子。

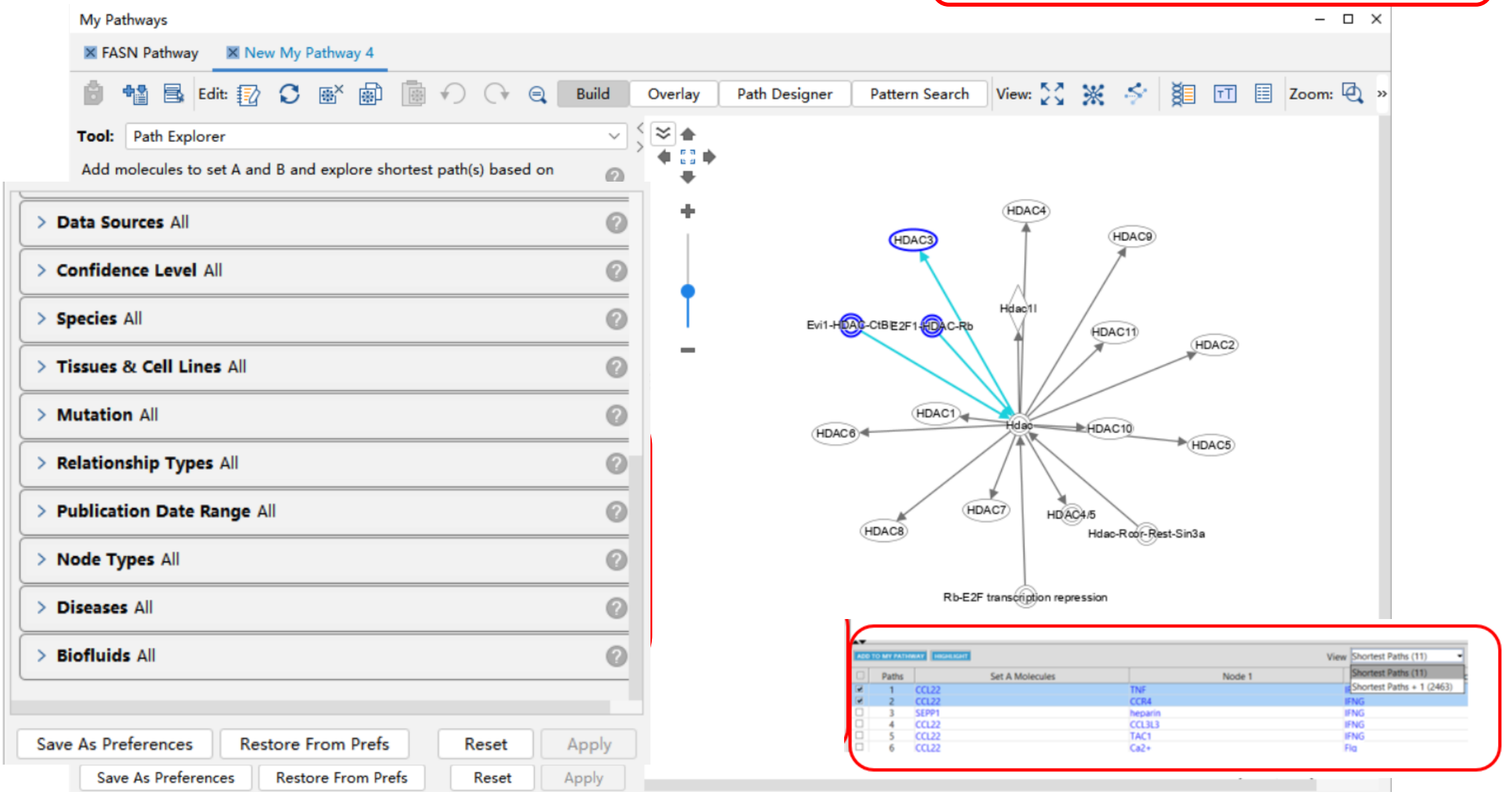
Build——Connect



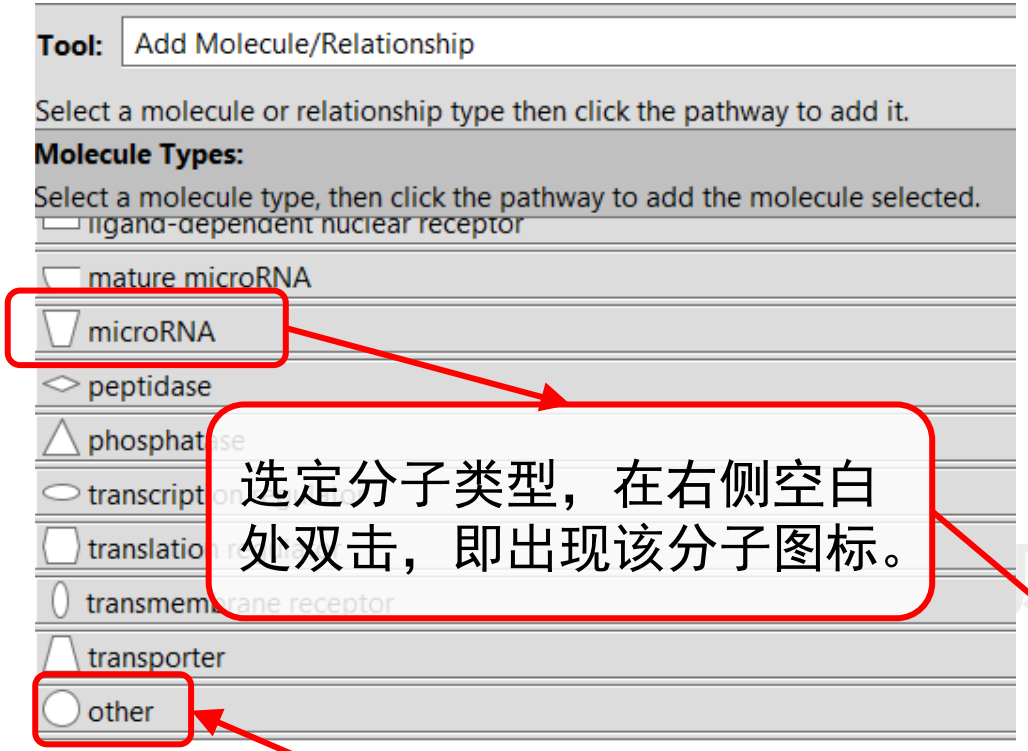
可以选择My Pathway 中两个或多个感兴趣的分子，通过connect工具找出这些分子间的相互关系。可以设定直接与间接作用关系，分子来源，相互作用关系类型等参数来达到最优的结果。

Build——Path Explorer

两个/组分子间作用的最短路径。

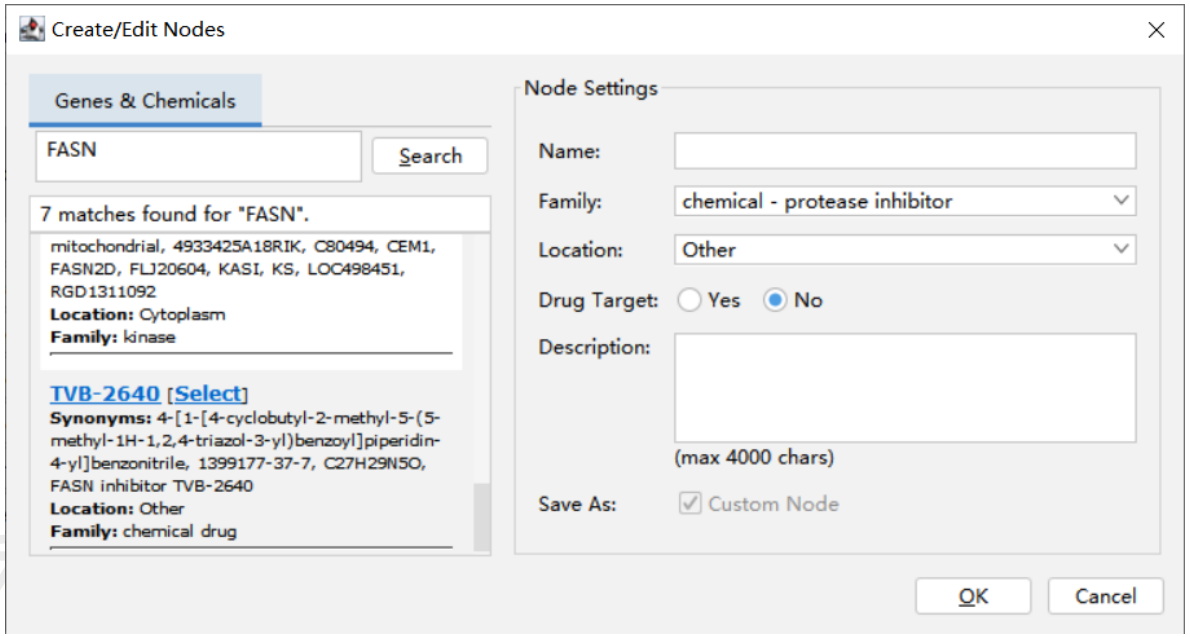


Build——Add Molecular/Relationship



选定分子类型，在右侧空白处双击，即出现该分子图标。

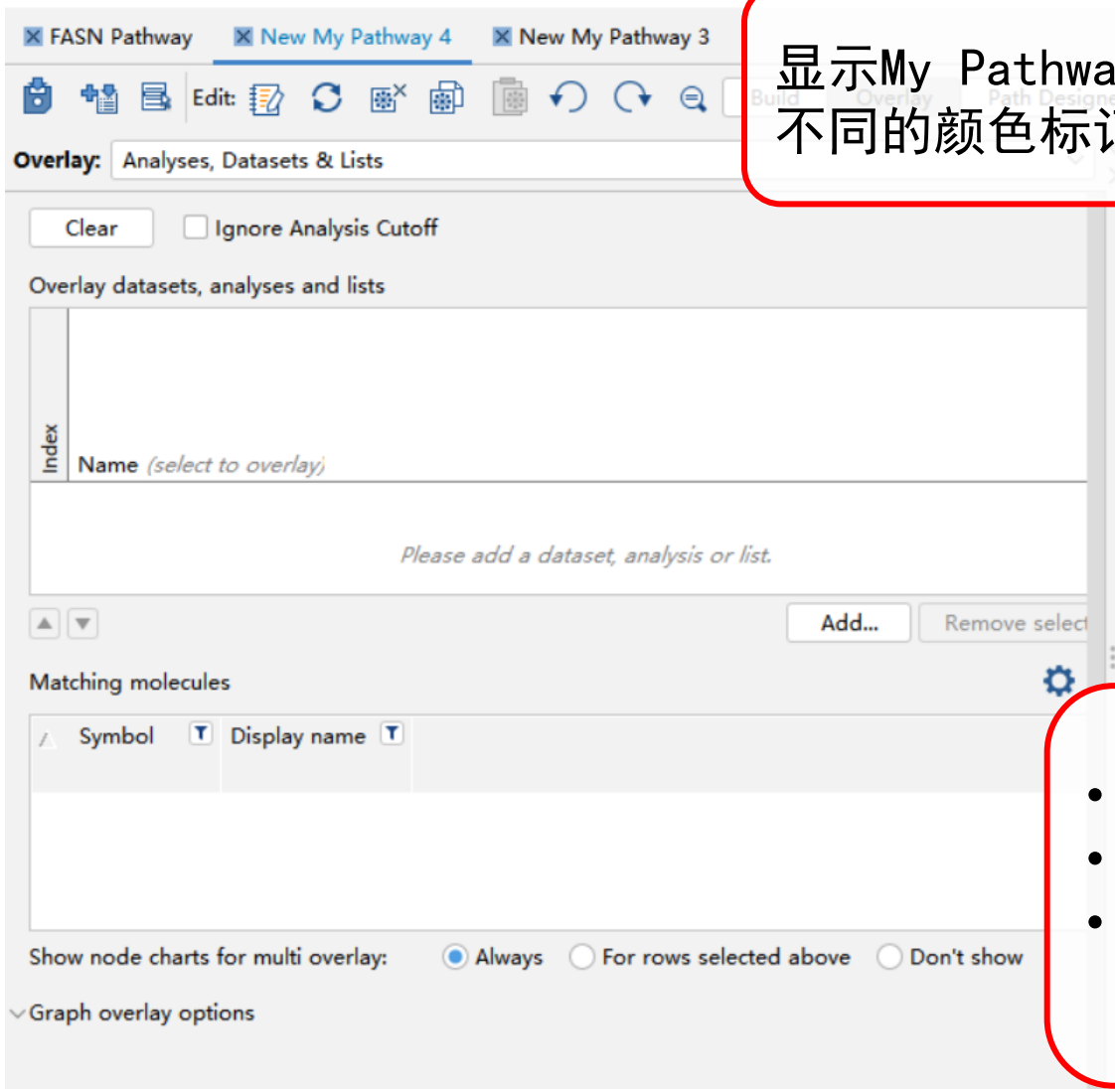
如果不知道分子的类型，可以直接点other

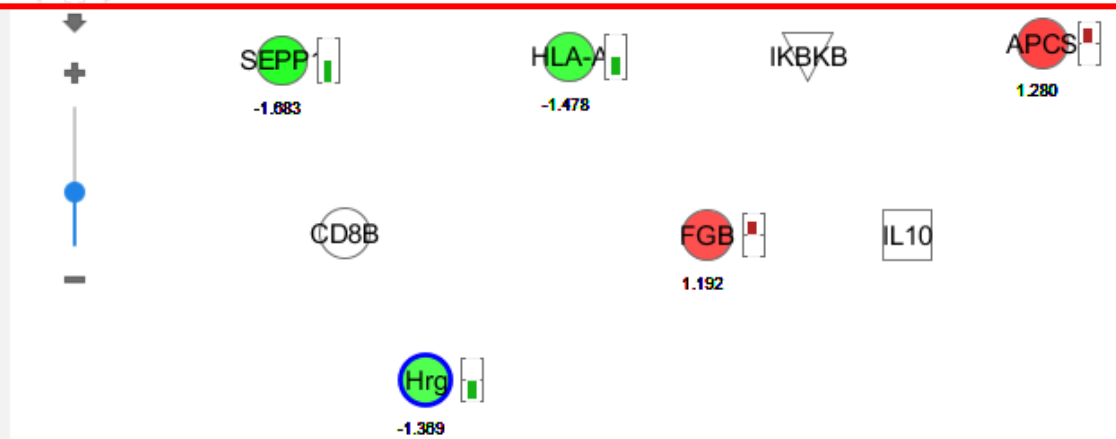


双击分子图标，即可弹出分子注释对话框，搜索想要插入的分子名，找到需要的分子，点击select，分子及类型会自动编辑好。

Overlay——Analyses, Dataset & Lists

显示My Pathway中哪些分子在某个特定的network中出现，并且以不同的颜色标记这些分子表达的变化以及表达量。



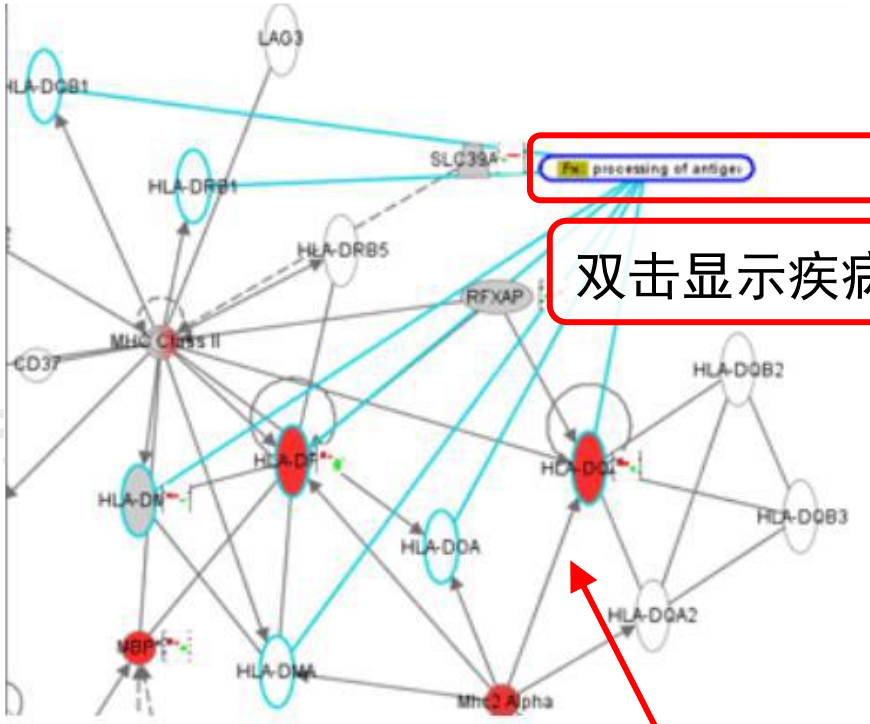


- 选择一组或多组观察值的分析结果。
- 在分析结果中的出现的分子会高亮显示
- 显示表达值，表达量与bar图表示。红色为上调，绿色为下调。

Overlay—— Disease & Function

显示网络或通路中参与的疾病。

选中某个疾病过程，右侧显示网络中参与的分子。



双击显示疾病信息

双击作用关系，显示相关文献

Overlay——My Pathway、My list & Toxlist

加入自定义通路、列表或毒性列表。确定分子之间是否有重叠，或者通路是否参与了任何分子毒理过程

Overlay: My List

REFRESH

Select list labels from table to be displayed on pathway.

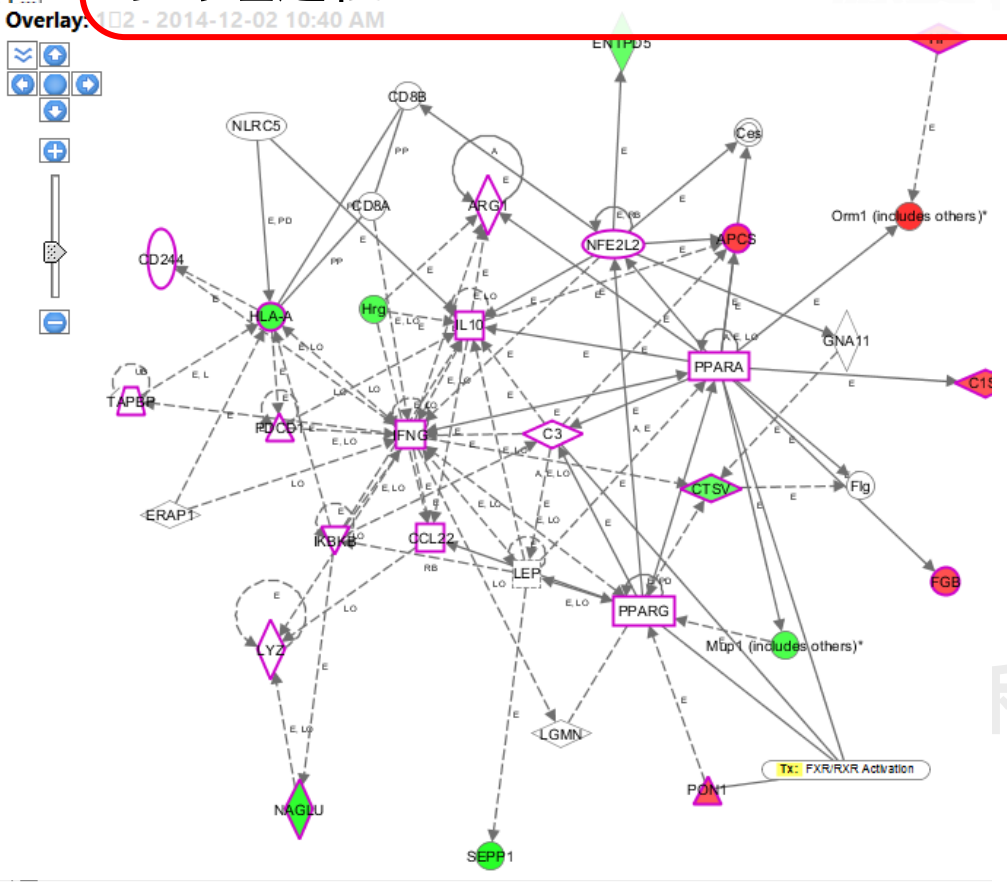
List Name	# Mole...	Molecule(s)
test	35	APCS, ARG1, C3, C1S*, CCL22, C...
stat	8	ARG1, C3, FGB, HP, IFNG, IL10, I...
New My		
New My		
Patient 2		
Patient 1		
TFIID AP		
CNV Ge		

Overlay: Ingenuity Tox List

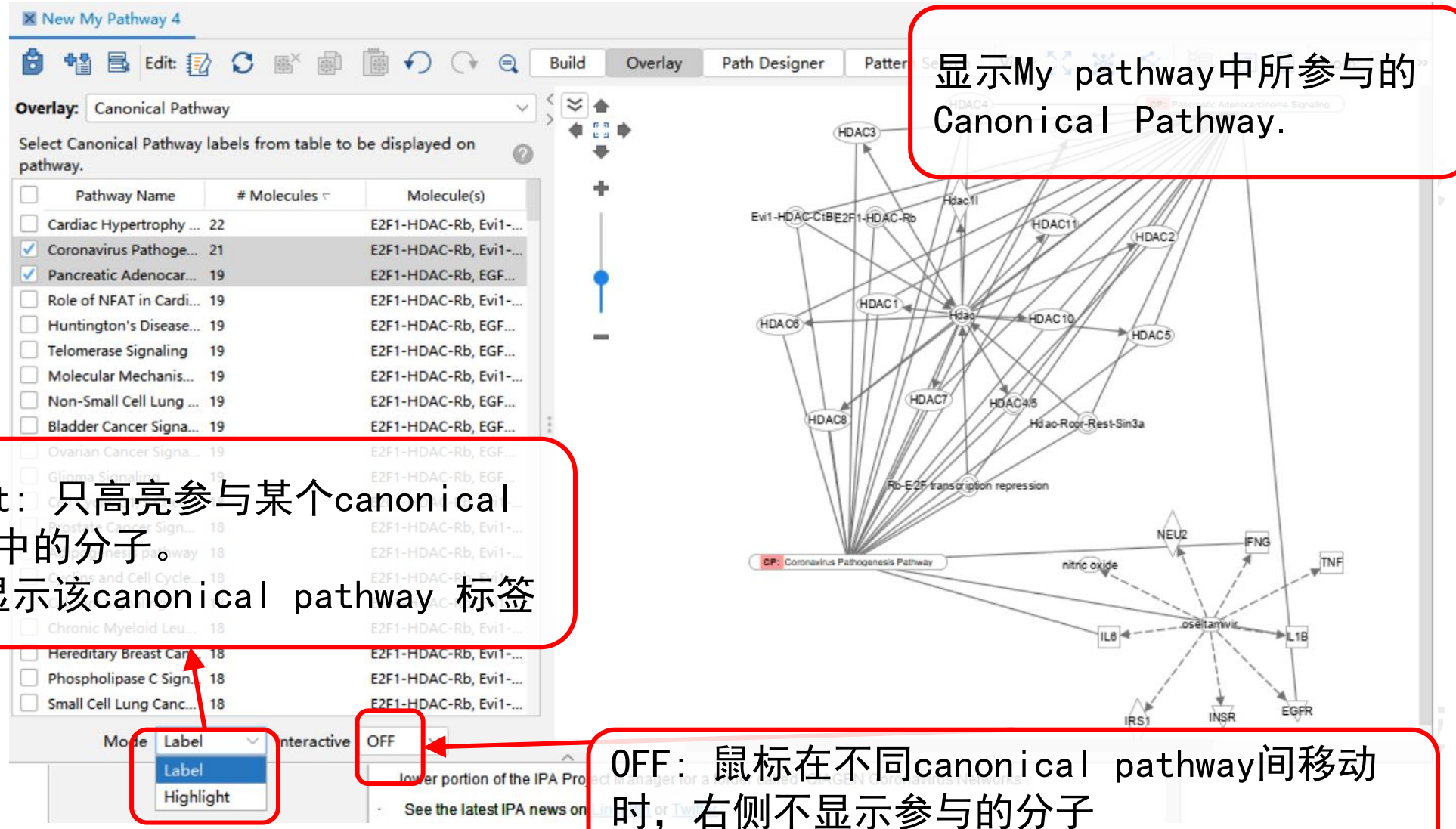
Select Ingenuity Tox List labels from table to be displayed on pathway.

Ingenuity Tox Name	# Mole...	Molecule(s)
Liver Proliferation	8	C3, ENTPD5, IFNG, IKBKB, LEP,...
Liver Necrosis/Cell Death	8	C3, ENTPD5, IFNG, IKBKB, IL10...
Increases Liver Damage	5	C3, IFNG, IKBKB, PDCD1, PPARA
Positive Acute Phase Respons...	4	APCS, C3, FGB, HP
Increases Liver Hepatitis	4	IFNG, IKBKB, IL10, LEP
FXR/RXR Activation	4	C3, PON1, PPARA, PPARG
Cardiac Hypertrophy	4	GNA11, IKBKB, LEP, PPARA
Increases Renal Nephritis	3	IFNG, IL10, LEP
Cardiac Necrosis/Cell Death	3	IFNG, IKBKB, LEP
Hepatic Cholestasis	3	IFNG, IKBKB, PPARA
Mechanism of Gene Regulatio...	3	IKBKB, PPARA, PPARG
Cardiac Fibrosis	3	IFNG, PDCD1, PPARA
Increases Liver Hyperplasia/H...	3	IKBKB, LEP, PPARA
Renal Necrosis/Cell Death	3	IFNG, NFE2L2, PPARG
Hepatic Fibrosis	3	IFNG, IL10, LEP
LXR/RXR Activation	3	C3, LYZ, PON1
PPARα/RXRα Activation	3	GNA11, IKBKB, PPARA
Hepatic Stellate Cell Activation	2	IFNG, IL10
Increases Liver Steatosis	2	C3, PPARG
Oxidative Stress	2	IL10, NFE2L2
LPS/IL-1 Mediated Inhibition ...	2	Ces, PPARA
Increases Glomerular Injury	2	C3, CCL22
Xenobiotic Metabolism Signal...	2	Ces, NFE2L2
PXR/RXR Activation	2	Ces, PPARA
Persistent Renal Ischemia-Rep...	2	C3, LYZ
Increases Transmembrane Pot...	1	PPARG
Increases Cardiac Dysfunction	1	PPARA
Increases Cardiac Dilation	1	IFNG
NF-κB Signaling	1	IKBKB
NRF2-mediated Oxidative Str...	1	NFE2L2

Mode: Label Interactive: OFF



Overlay——Canonical Pathways

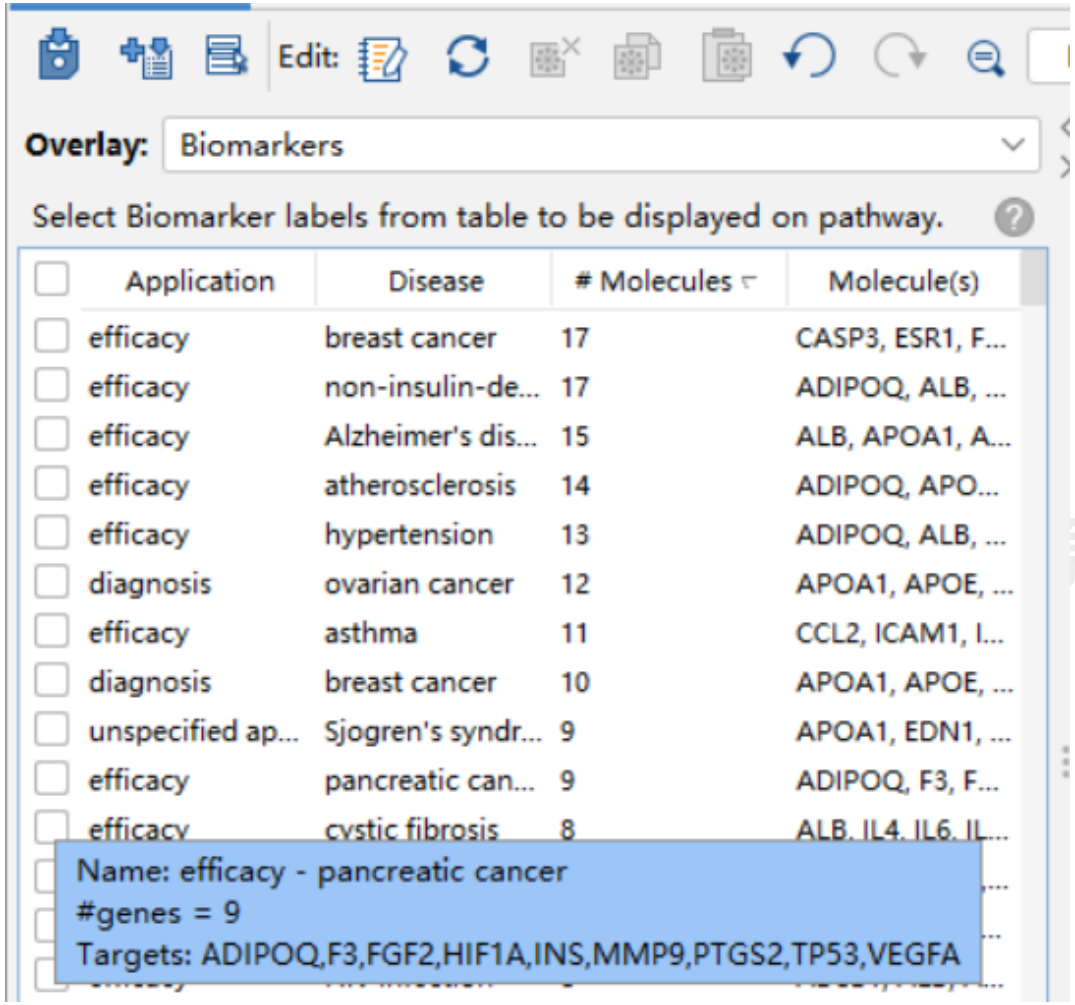


显示My pathway中所参与的Canonical Pathway.

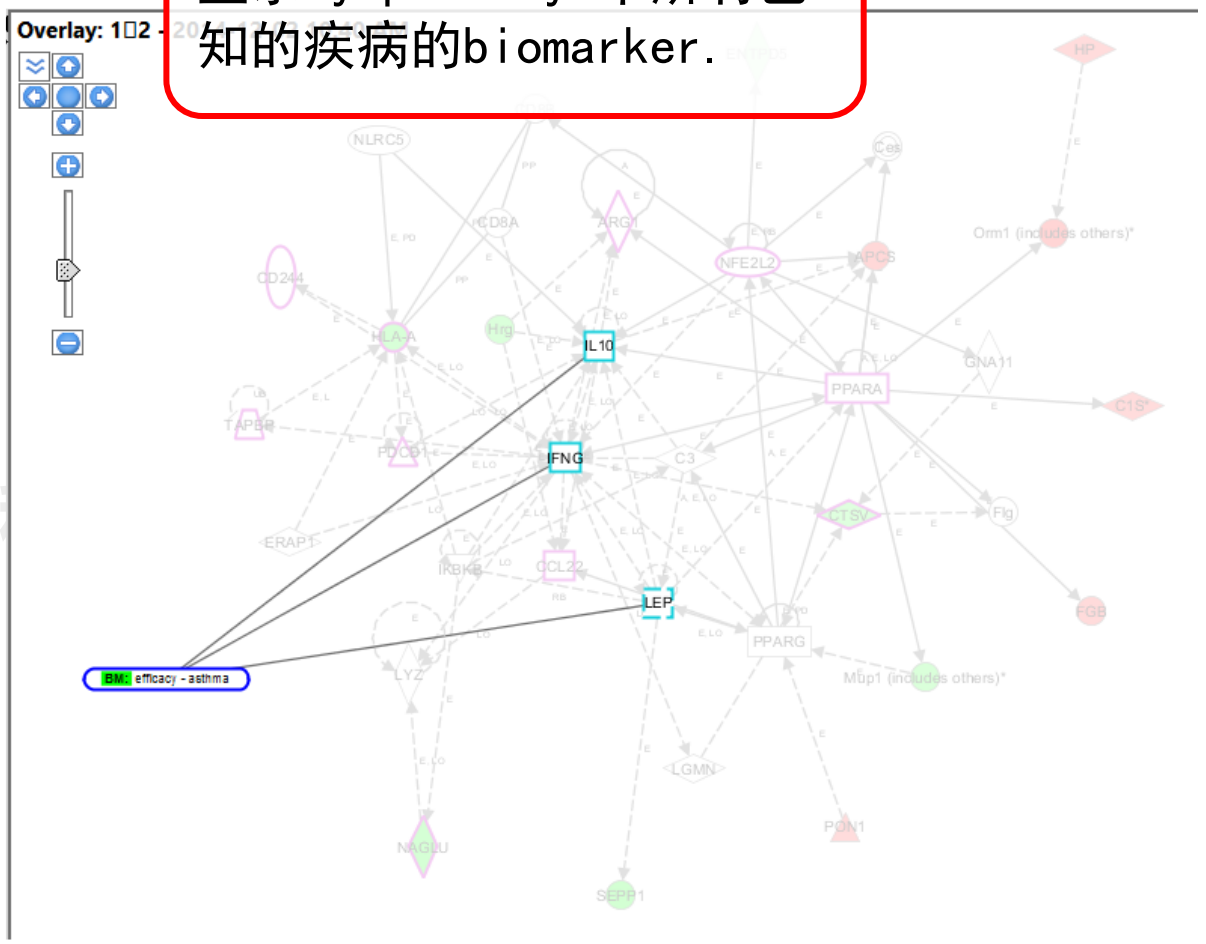
Highlight：只高亮参与某个canonical pathway 中的分子。
Label：显示该canonical pathway 标签

OFF：鼠标在不同canonical pathway间移动时，右侧不显示参与的分子
On：与OFF 功能相反。

Overlay——Biomarker

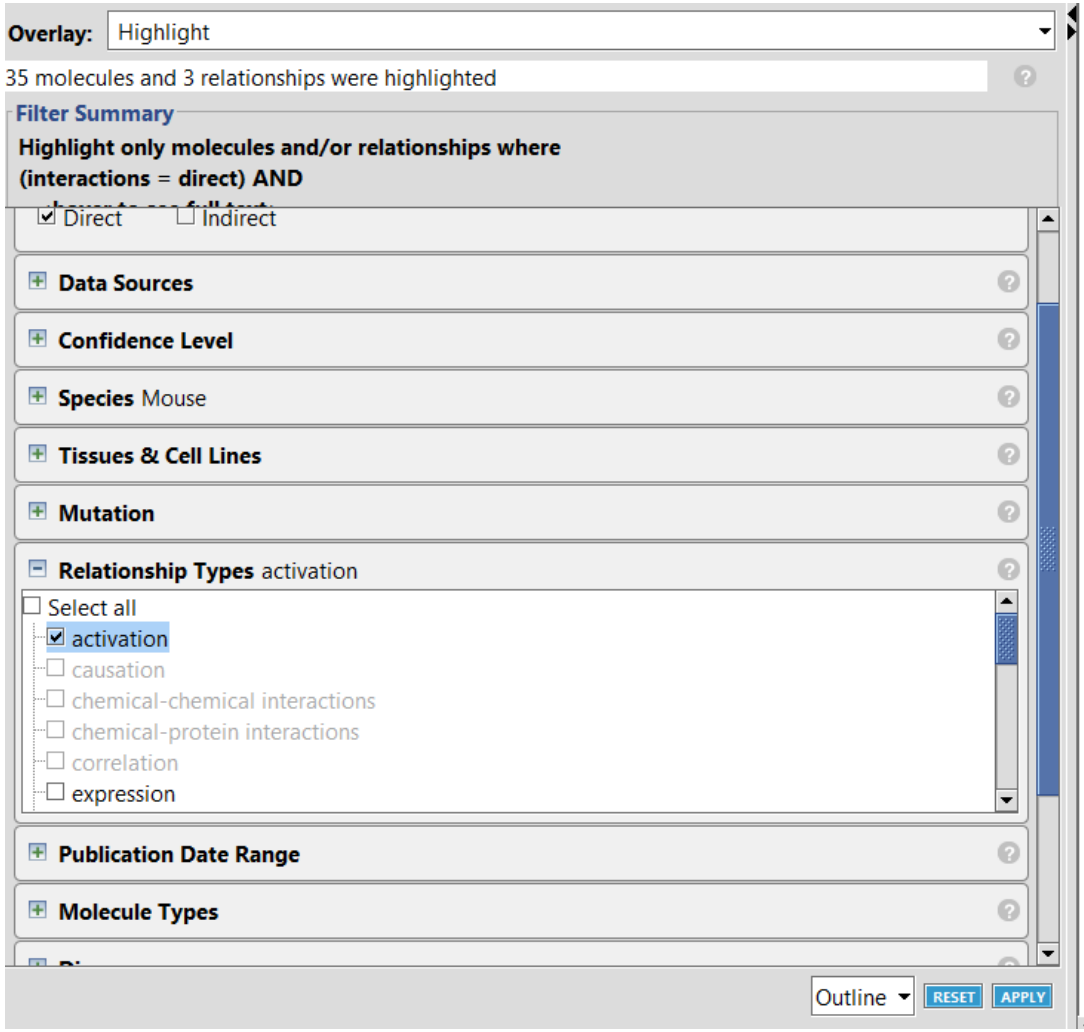


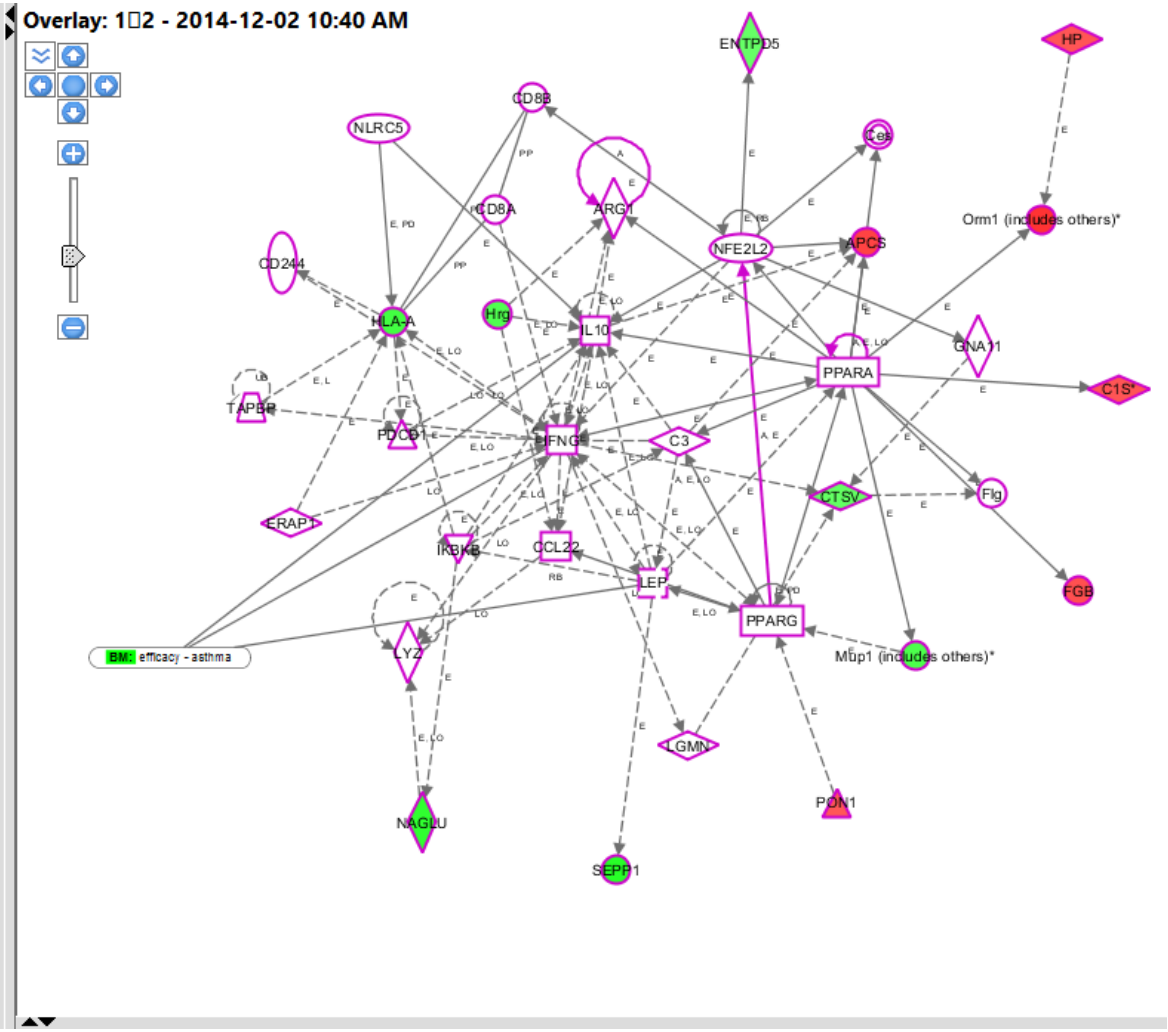
显示My pathway 中所有已知的疾病的biomarker.



Overlay——Highlight

高亮满足某个特定条件的分子





Overlay——Drug

显示My Pathway 与FDA 批准的I，II，III期临床药物相互作用的分子

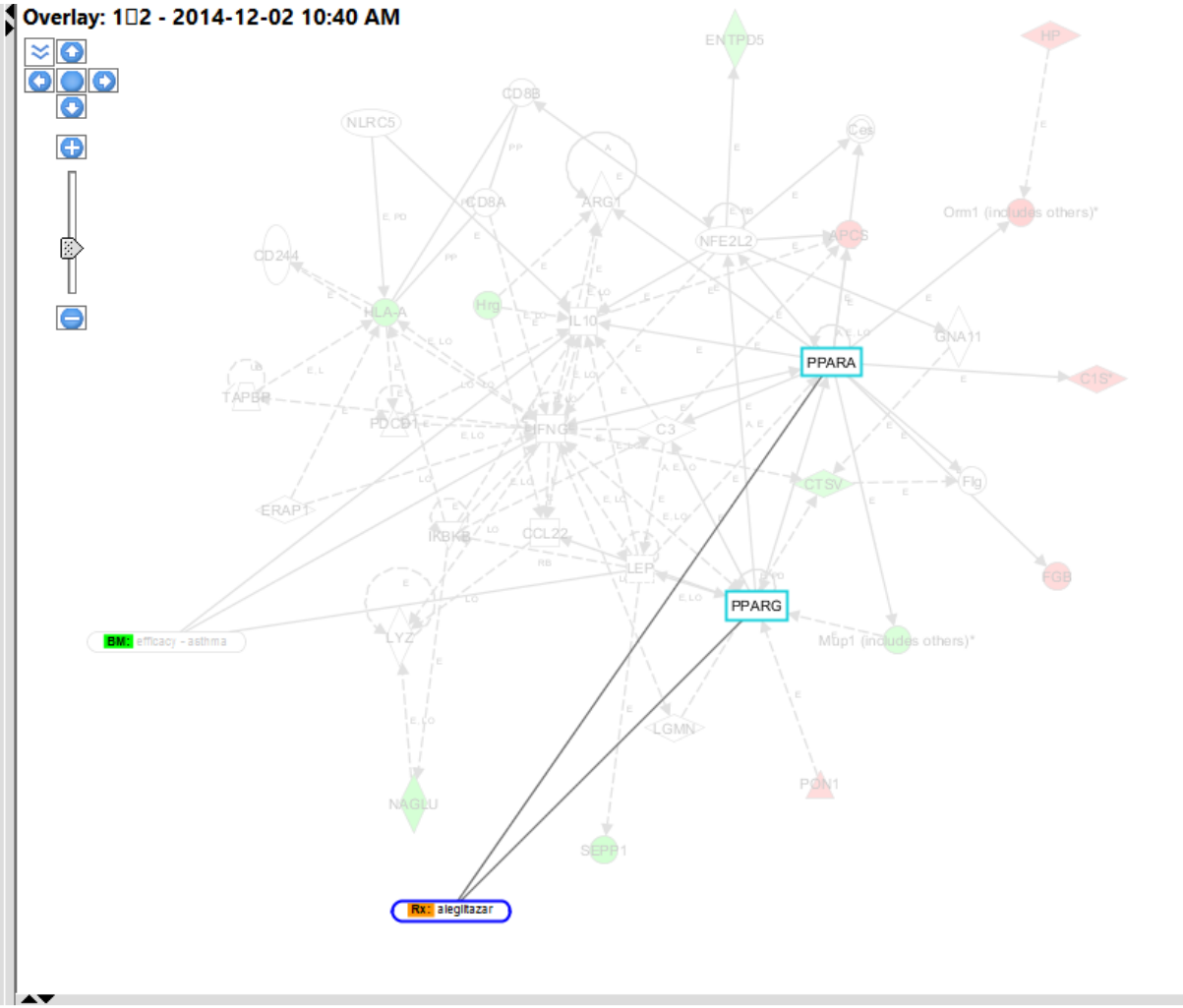
Overlay: Drug

DRUG SUMMARY

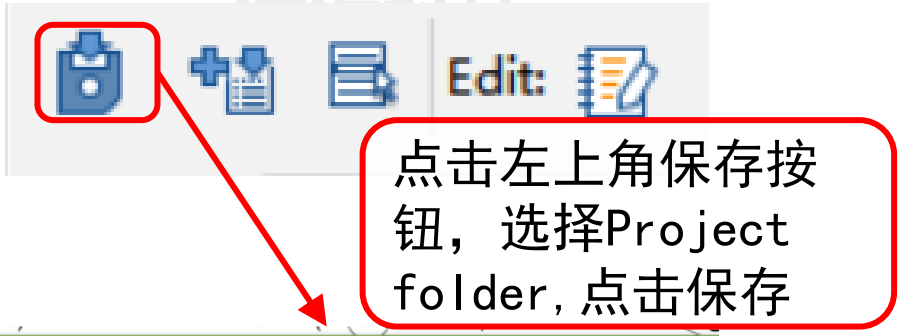
Select drug labels from table to be displayed on pathway.

Drug Name	# Mole...	Target(s)
aleglitazar	2	PPARA, PPARG
bezafibrate	2	PPARA, PPARG
tesaglitazar	2	PPARA, PPARG
aspirin/dipyridamole/telmisartan	1	PPARG
nicotinic acid/pioglitazone	1	PPARG
clopidogrel/telmisartan	1	PPARG
rosiglitazone	1	PPARG
hydrochlorothiazide/telmisartan	1	PPARG
NS-220	1	PPARA
F2	1	FGB
icosapent	1	PPARG
fenofibrate	1	PPARA
nivolumab	1	PDCD1
pembrolizumab	1	PDCD1
balsalazide	1	PPARG
SERPING1	1	C1S*
glimepiride/rosiglitazone	1	PPARG
amlodipine/telmisartan	1	PPARG
telmisartan	1	PPARG
gemfibrozil	1	PPARA
choline fenofibrate/simvastatin	1	PPARA
alogliptin/pioglitazone	1	PPARG
clofibrate	1	PPARA
auranofin	1	IKBKB
mesalamine	1	PPARG
sulfasalazine	1	PPARG
docosahexaenoic acid	1	PPARA
ezetimibe/fenofibrate	1	PPARA
IgG	1	C3
pioglitazone	1	PPARG
troglitazone	1	PPARG
farglitazar	1	PPARG
choline fenofibrate	1	PPARA

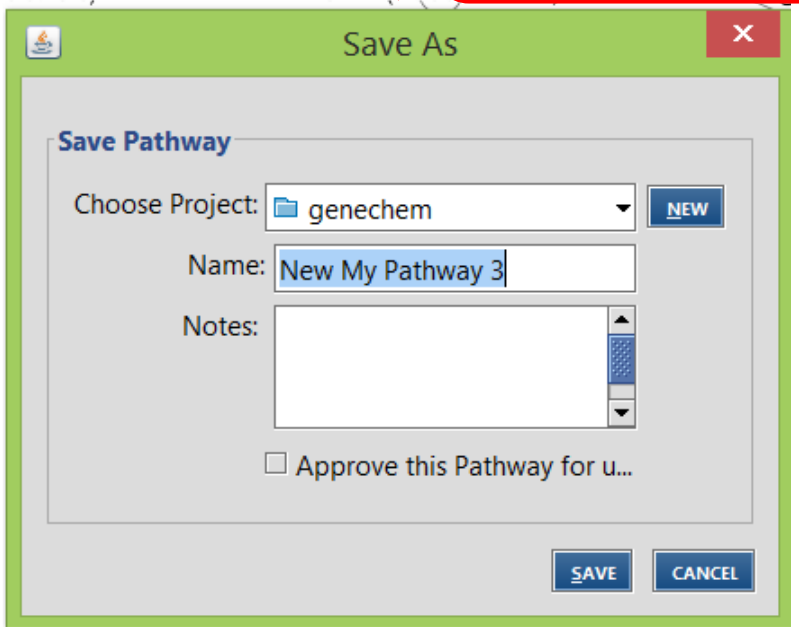
Mode Label Interactive OFF

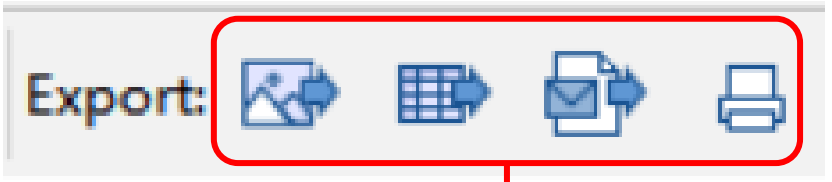


My Pathway的保存和输出



点击左上角保存按钮，选择Project folder，点击保存

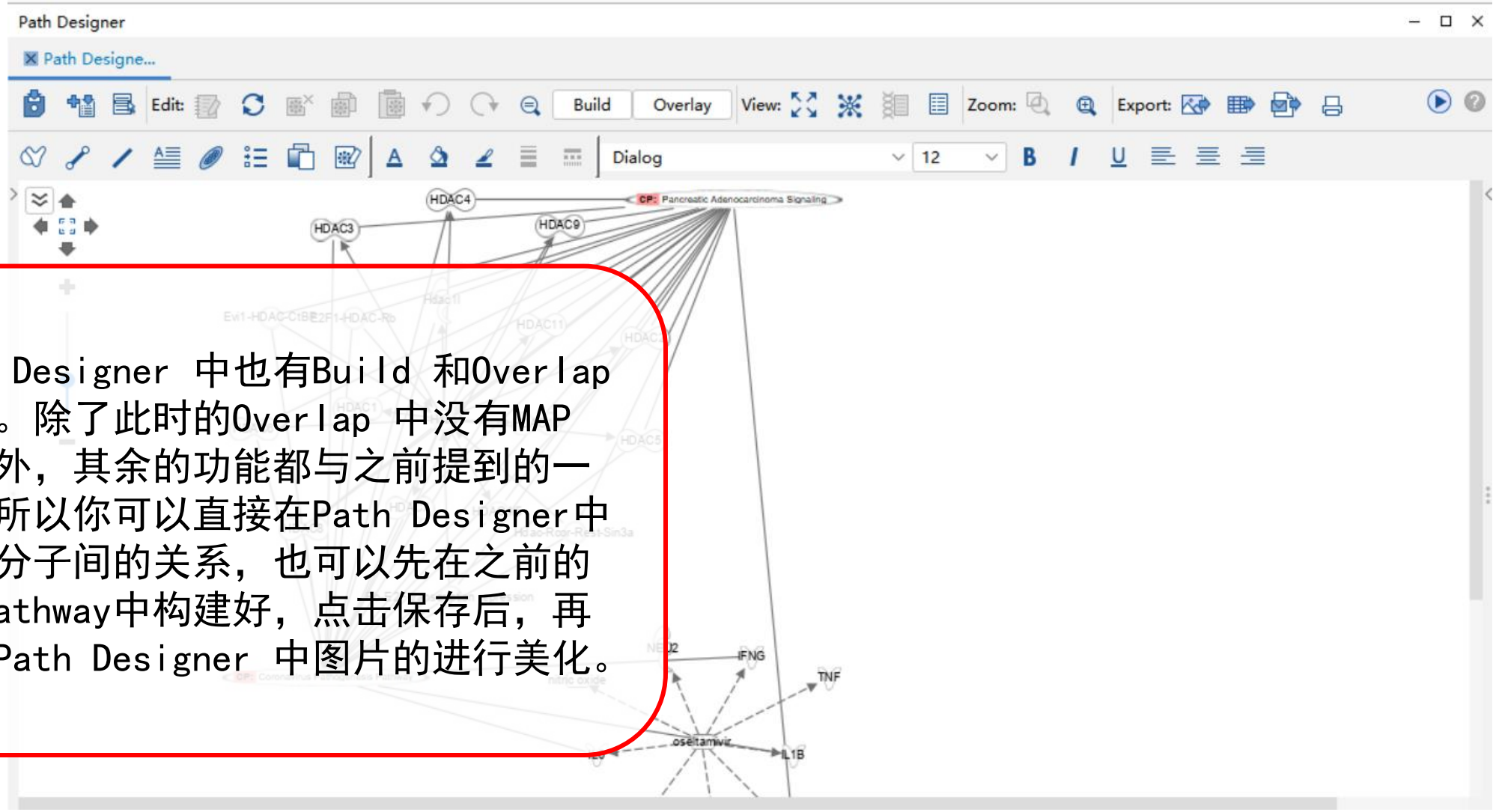




My Pathway 的结果可以以图片格式，文件格式输出，也可以通过邮件发送给同事，或者打印输出。

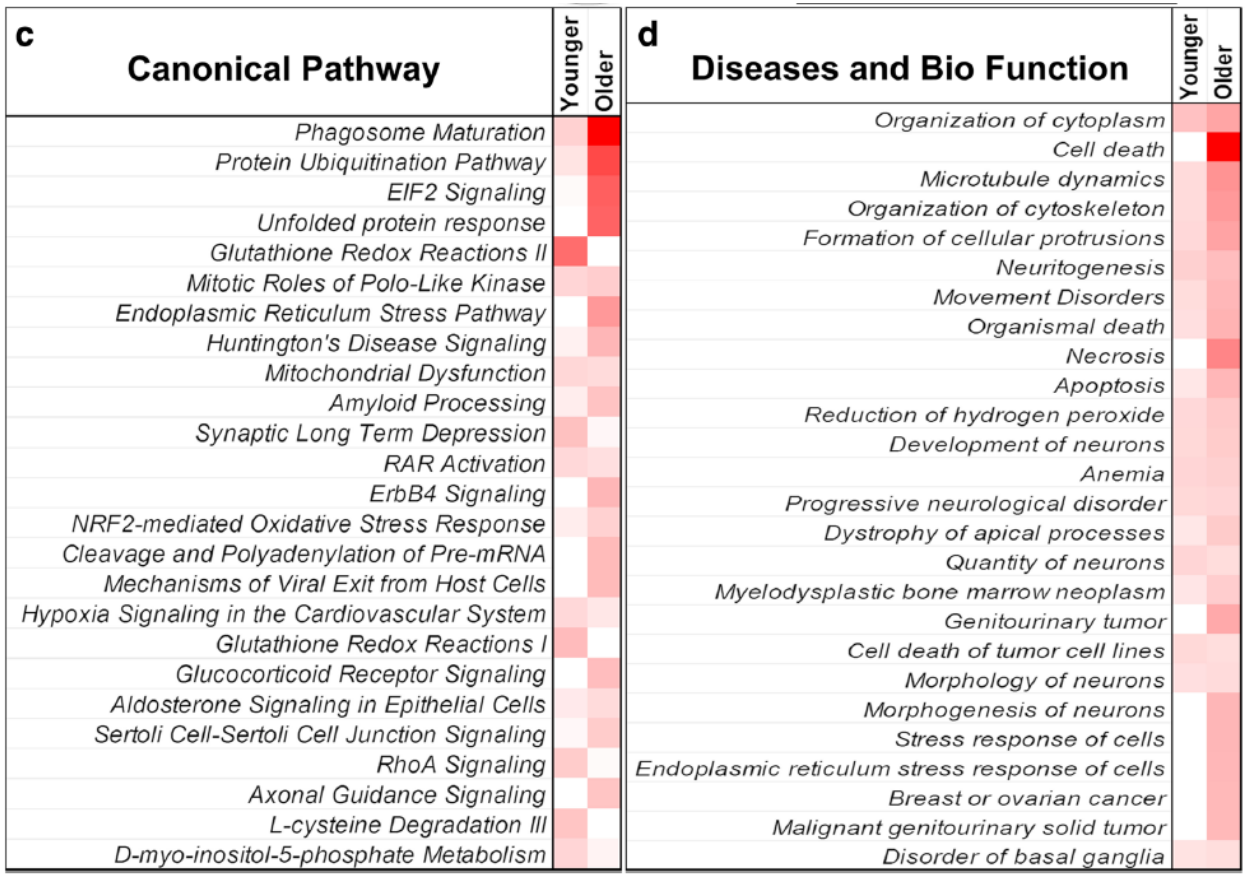
Path Designer

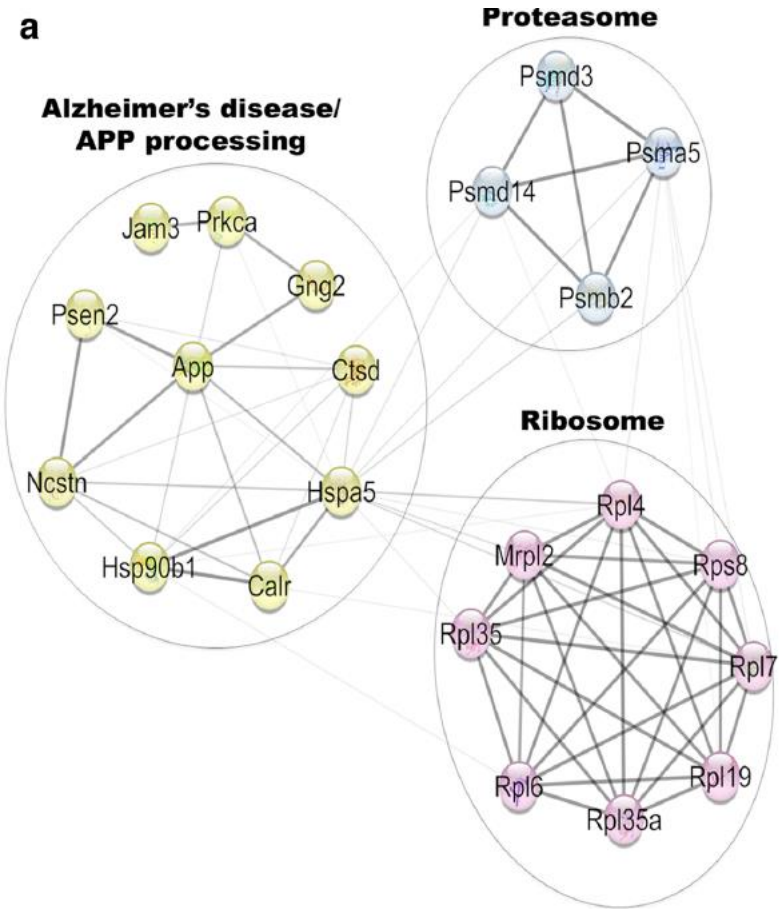
描绘个性化彩图Pathway 、可用于发表



Path Designer 中也有Build 和Overlap功能。除了此时的Overlap 中没有MAP功能外，其余的功能都与之前提到的一样。所以你可以直接在Path Designer中分析分子间的关系，也可以先在之前的My Pathway中构建好，点击保存后，再进入Path Designer 中图片的进行美化。

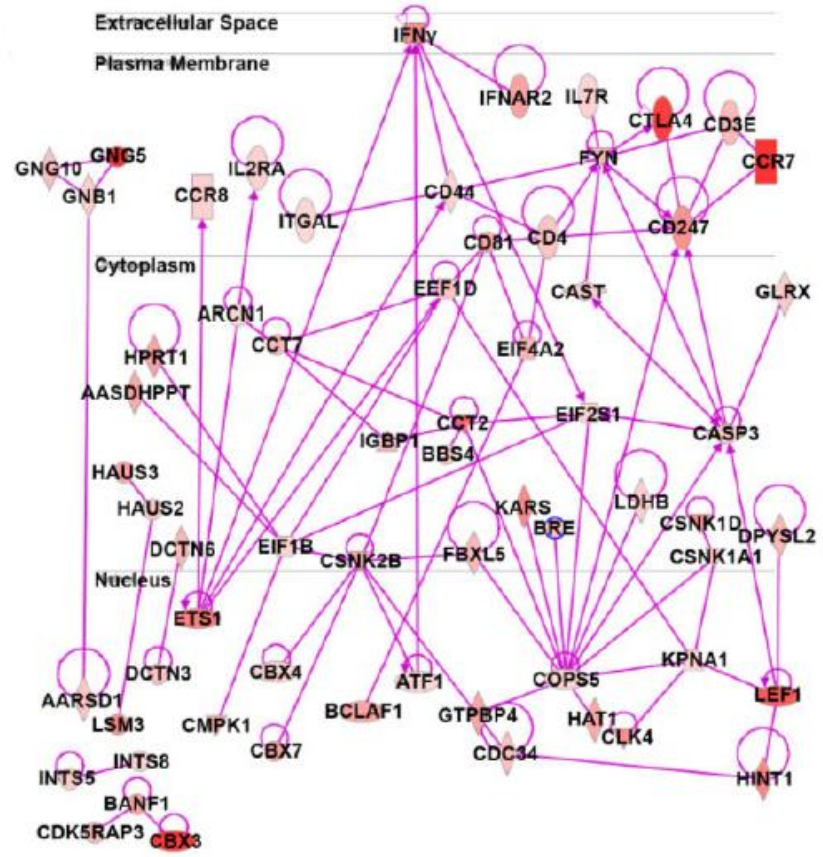
普通的分子网络图表



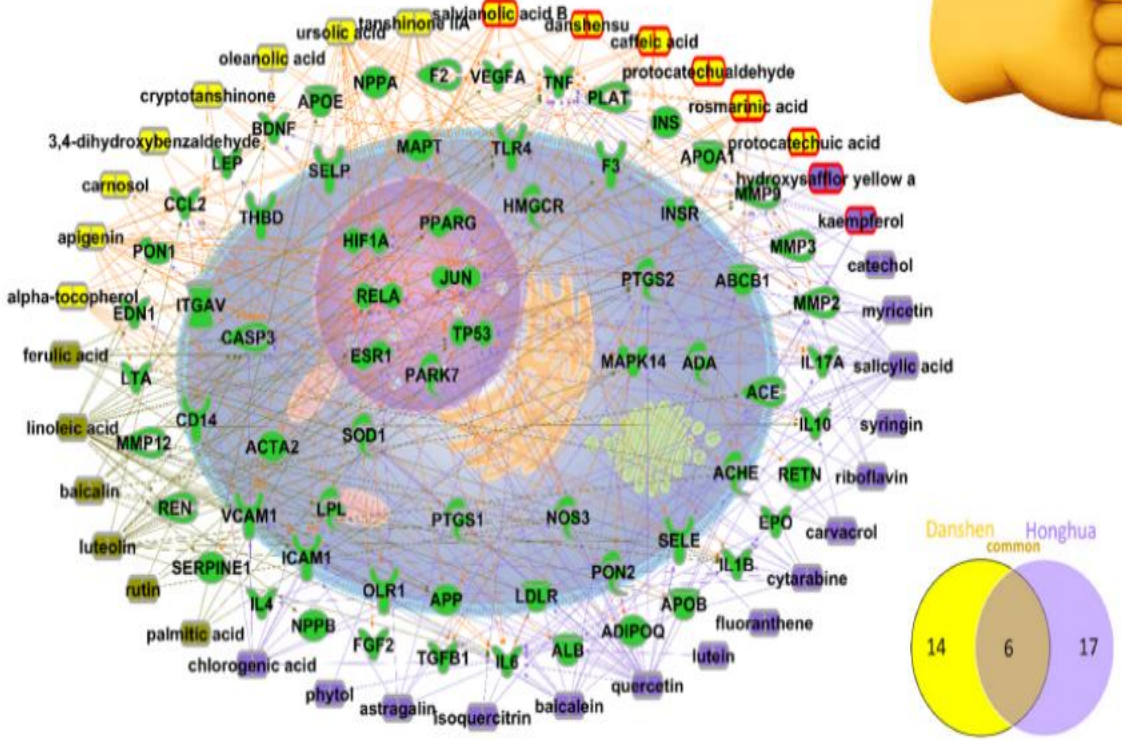


Mirzaei M , Pushpitha K , Deng L , et al. Upregulation of Proteolytic Pathways and Altered Protein Biosynthesis Underlie Retinal Pathology in a Mouse Model of Alzheimer′ s Disease[J]. Molecular Neurobiology, 2019.

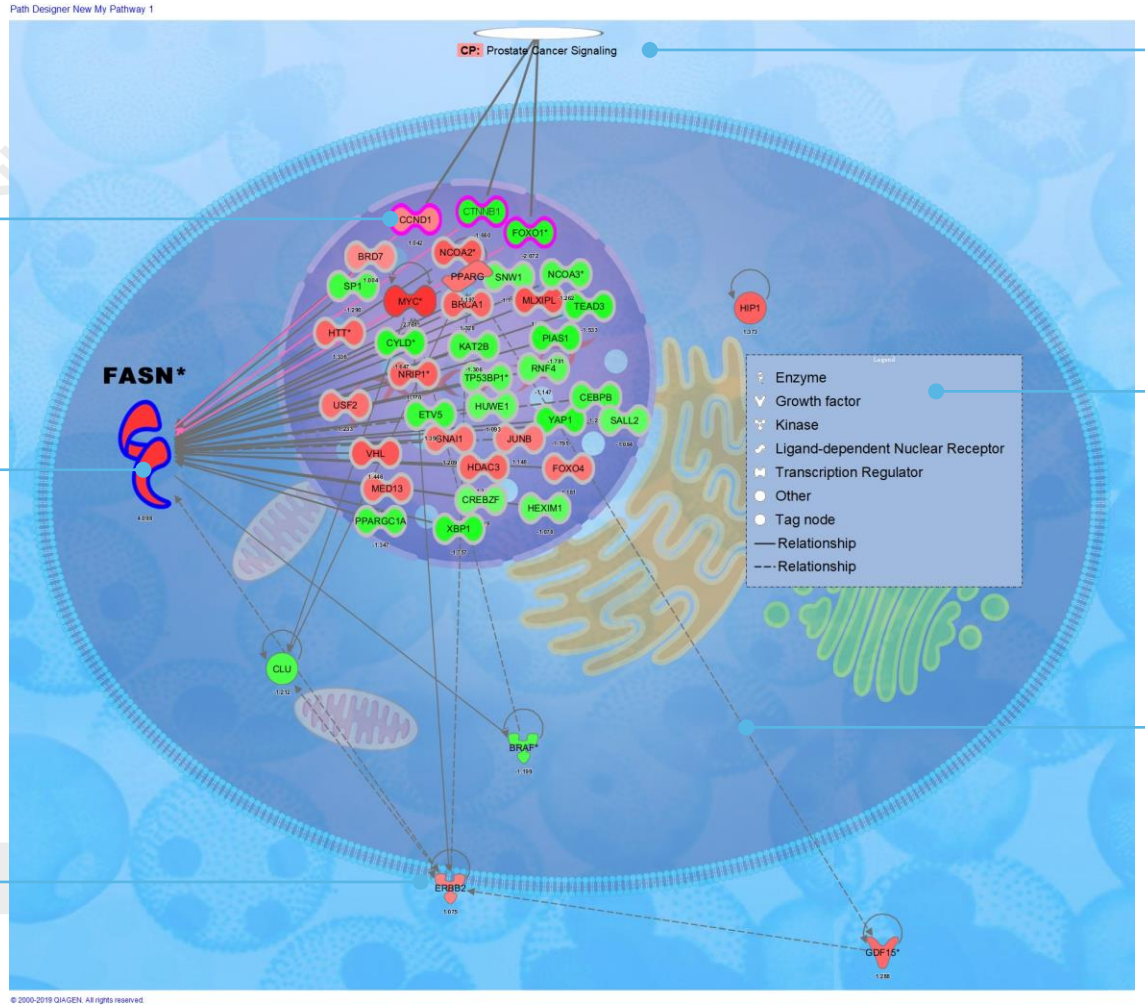
优秀的分子网络图



Butcher M J , Filipowicz A R , Waseem T C , et al. Atherosclerosis-Driven Treg Plasticity Results in Formation of a Dysfunctional Subset of Plastic IFNγ + Th1/Tregs[J]. Circulation Research, 2016, 119(11):CIRCRESAHA.116.309764.



Lyu, M.; Yan, C.L.; Liu, H.X.; Wang, T.Y.; Shi, X.H.; Liu, J.P.; Orgah, J.; Fan, G.W.; Han, J.H.; Wang, X.Y., et al. Network pharmacology exploration reveals endothelial inflammation as a common mechanism for stroke and coronary artery disease treatment of danhong injection. Scientific reports 2017, 7, 15427.



实验数据中的表达值

重点突出目标分子

精确的亚细胞定位

经典通路

图例：按分子类型区分

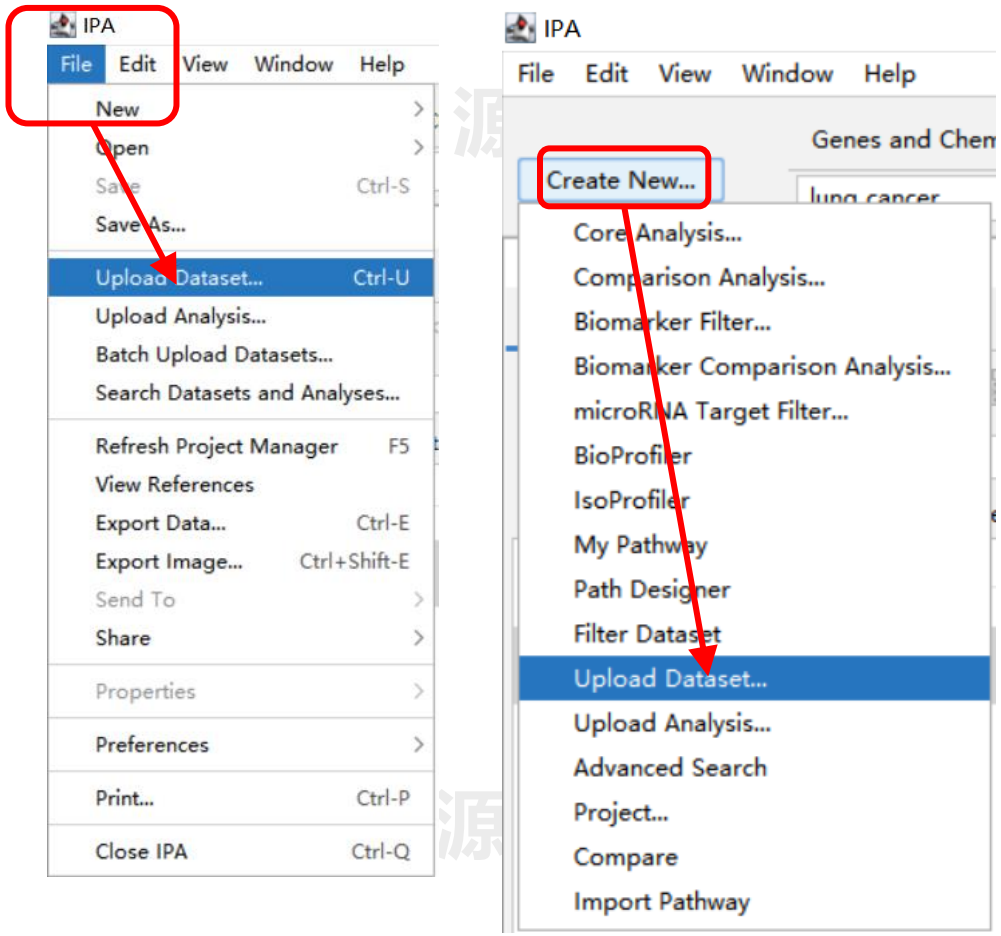
清晰分子调控关系

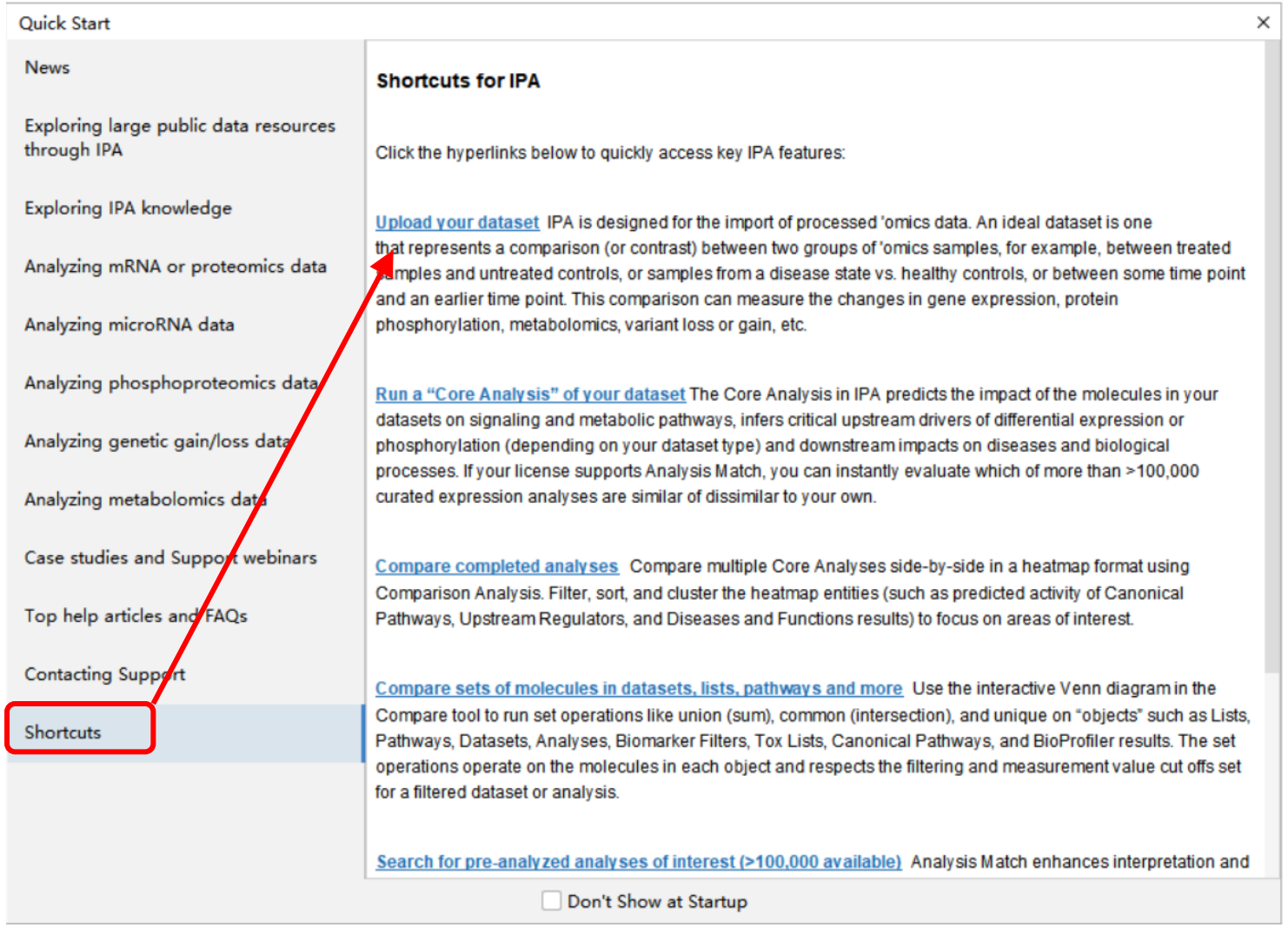
PART

5

Causal Networks

将数据上传到IPA中





数据上传——基本名词概念

Observation

- 一组分子以及它们所对应的某个实验条件下的表达量定义为一个观察组；
- 一组分子以及它们对应的不同实验条件下（比如时间系列，剂量响应实验）的表达量，构成了多个观察组；

Identifier

- 分配给某个基因，蛋白或者化学物的特定的注释。IPA会从数据文件中的Identifier column 一栏找到每个identifier,然后将其匹配到Ingenuity Knowledge Base中具体的分子信息

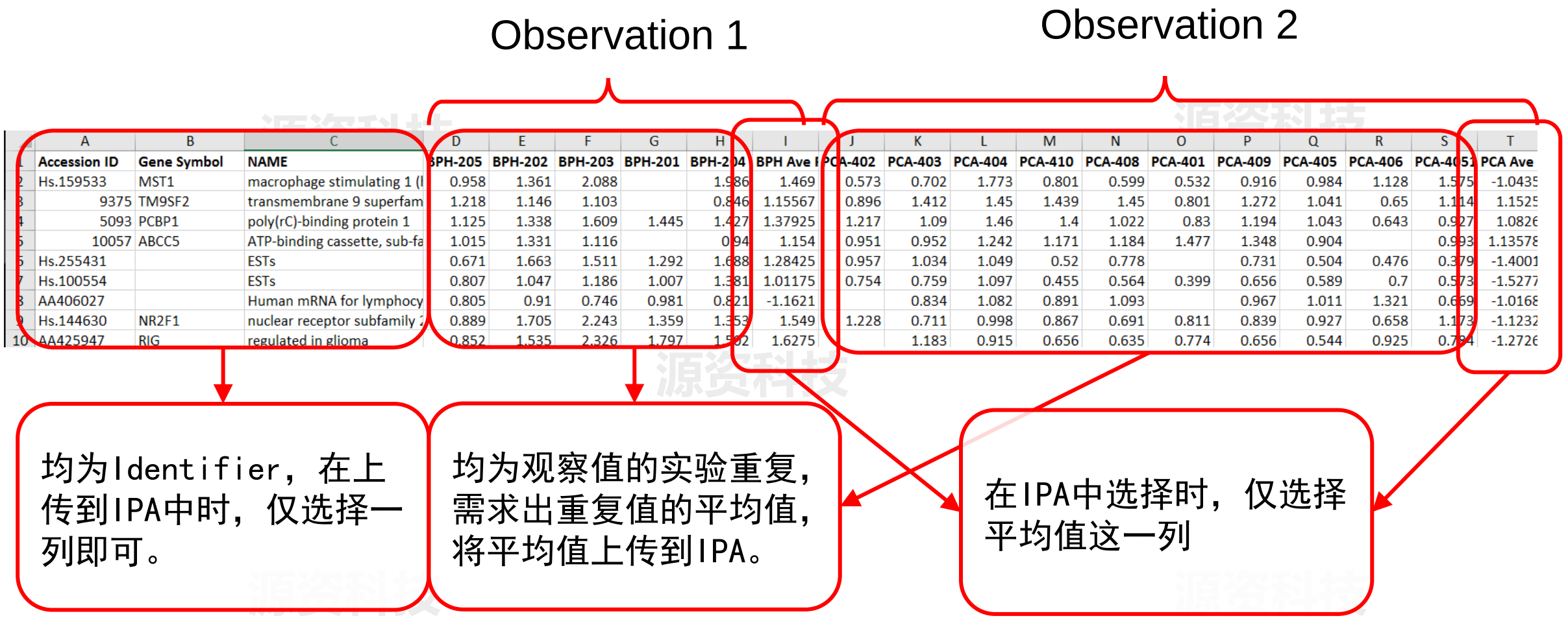
Expression Value

- 代表某个分子活性程度或者重要性程度的数字。IPA 可以识别不同类型的表达量
- 选择的表达量要符合IPA数据值范围

IPA 支持的数据类型

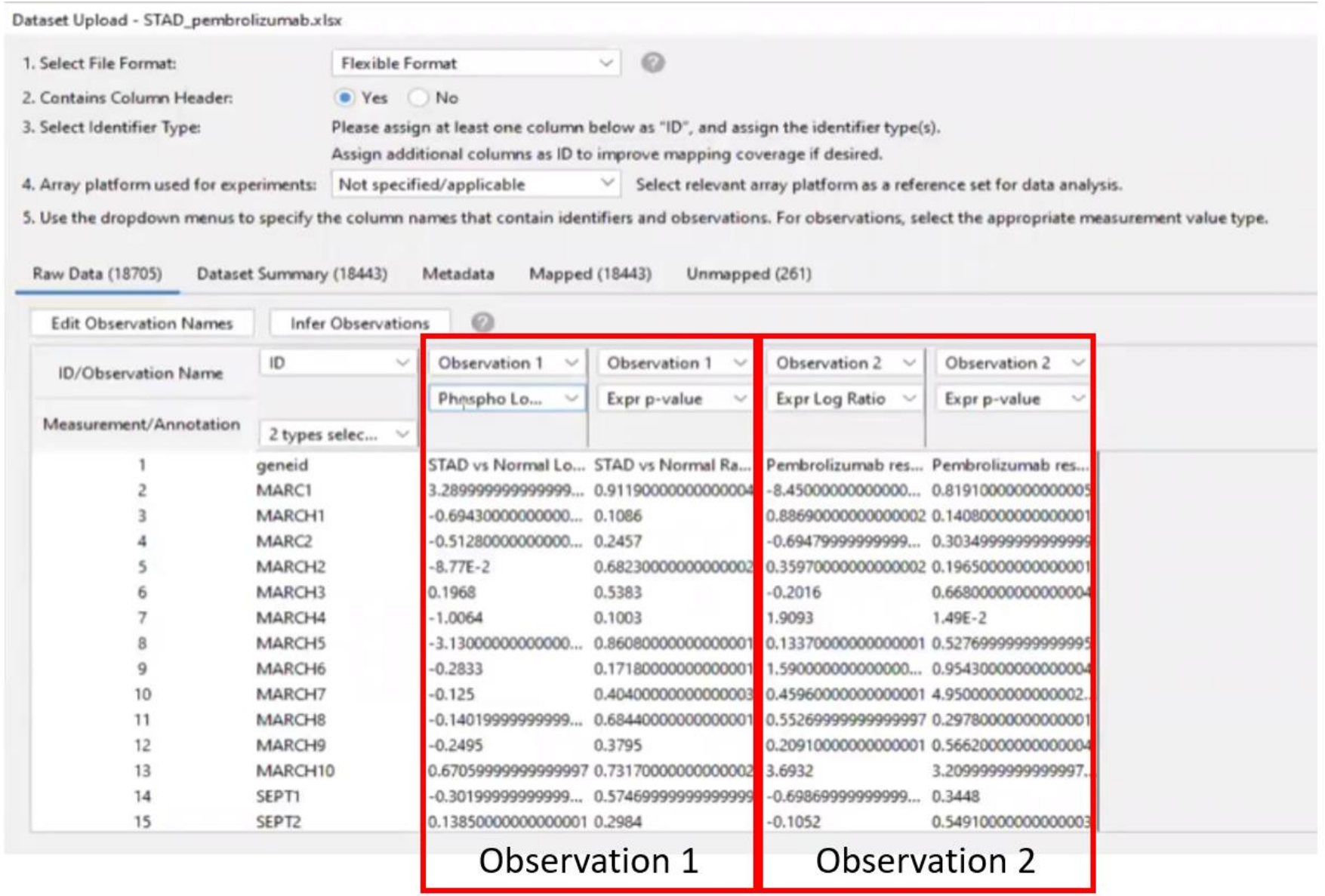
Affymetrix®
Affymetrix SNP ID
Agilent®
CAS Registry Number
CodeLink
dbSNP
Ensembl
Entrez Gene
GenBank
Gene Symbol – mouse (Entrez Gene)
Gene Symbol – rat (Entrez Gene)
Gene Symbol – human (Hugo/HGNC)
GenPept
GI Number
Human Metabolome Database (HMDB)
Illumina
Ingenuity
International Protein Index
KEGG
Life Technologies (Applied Biosystems®)
miRBase (mature)
miRBase (stemloop)
PubChem CID
Refseq
UCSC (hg18)
UCSC (hg19)
Unigene
Uniprot/Swiss-Prot Accession
Species-specific Identifiers supported in IPA
Human
Mouse
Rat
Additional species via ortholog mapping

上传数据样例



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
1	Accession ID	Gene Symbol	NAME	BPH-205	BPH-202	BPH-203	BPH-201	BPH-204	BPH Ave I	PCA-402	PCA-403	PCA-404	PCA-410	PCA-408	PCA-401	PCA-409	PCA-405	PCA-406	PCA-40	PCA Ave
2	Hs.159533	MST1	macrophage stimulating 1 (l	0.958	1.361	2.088		1.986	1.469	0.573	0.702	1.773	0.801	0.599	0.532	0.916	0.984	1.128	1.575	-1.0435
3	9375	TM9SF2	transmembrane 9 superfam	1.218	1.146	1.103		0.846	1.15567	0.896	1.412	1.45	1.439	1.45	0.801	1.272	1.041	0.65	1.114	1.1525
4	5093	PCBP1	poly(rC)-binding protein 1	1.125	1.338	1.609	1.445	1.427	1.37925	1.217	1.09	1.46	1.4	1.022	0.83	1.194	1.043	0.643	0.927	1.0826
5	10057	ABCC5	ATP-binding cassette, sub-fa	1.015	1.331	1.116		0.94	1.154	0.951	0.952	1.242	1.171	1.184	1.477	1.348	0.904		0.993	1.13578
6	Hs.255431		ESTs	0.671	1.663	1.511	1.292	1.688	1.28425	0.957	1.034	1.049	0.52	0.778		0.731	0.504	0.476	0.379	-1.4001
7	Hs.100554		ESTs	0.807	1.047	1.186	1.007	1.381	1.01175	0.754	0.759	1.097	0.455	0.564	0.399	0.656	0.589	0.7	0.573	-1.5277
8	AA406027		Human mRNA for lymphocy	0.805	0.91	0.746	0.981	0.821	-1.1621		0.834	1.082	0.891	1.093		0.967	1.011	1.321	0.669	-1.0168
9	Hs.144630	NR2F1	nuclear receptor subfamily 2	0.889	1.705	2.243	1.359	1.353	1.549	1.228	0.711	0.998	0.867	0.691	0.811	0.839	0.927	0.658	1.173	-1.1232
10	AA425947	RIG	regulated in glioma	0.852	1.535	2.326	1.797	1.502	1.6275		1.183	0.915	0.656	0.635	0.774	0.656	0.544	0.925	0.784	-1.2726

将数据上传到IPA中



Dataset Upload - STAD_pembrolizumab.xlsx

1. Select File Format: Flexible Format
2. Contains Column Header: Yes No
3. Select Identifier Type: Please assign at least one column below as "ID", and assign the identifier type(s).
   Assign additional columns as ID to improve mapping coverage if desired.
4. Array platform used for experiments: Not specified/applicable — Select relevant array platform as a reference set for data analysis.
5. Use the dropdown menus to specify the column names that contain identifiers and observations. For observations, select the appropriate measurement value type.

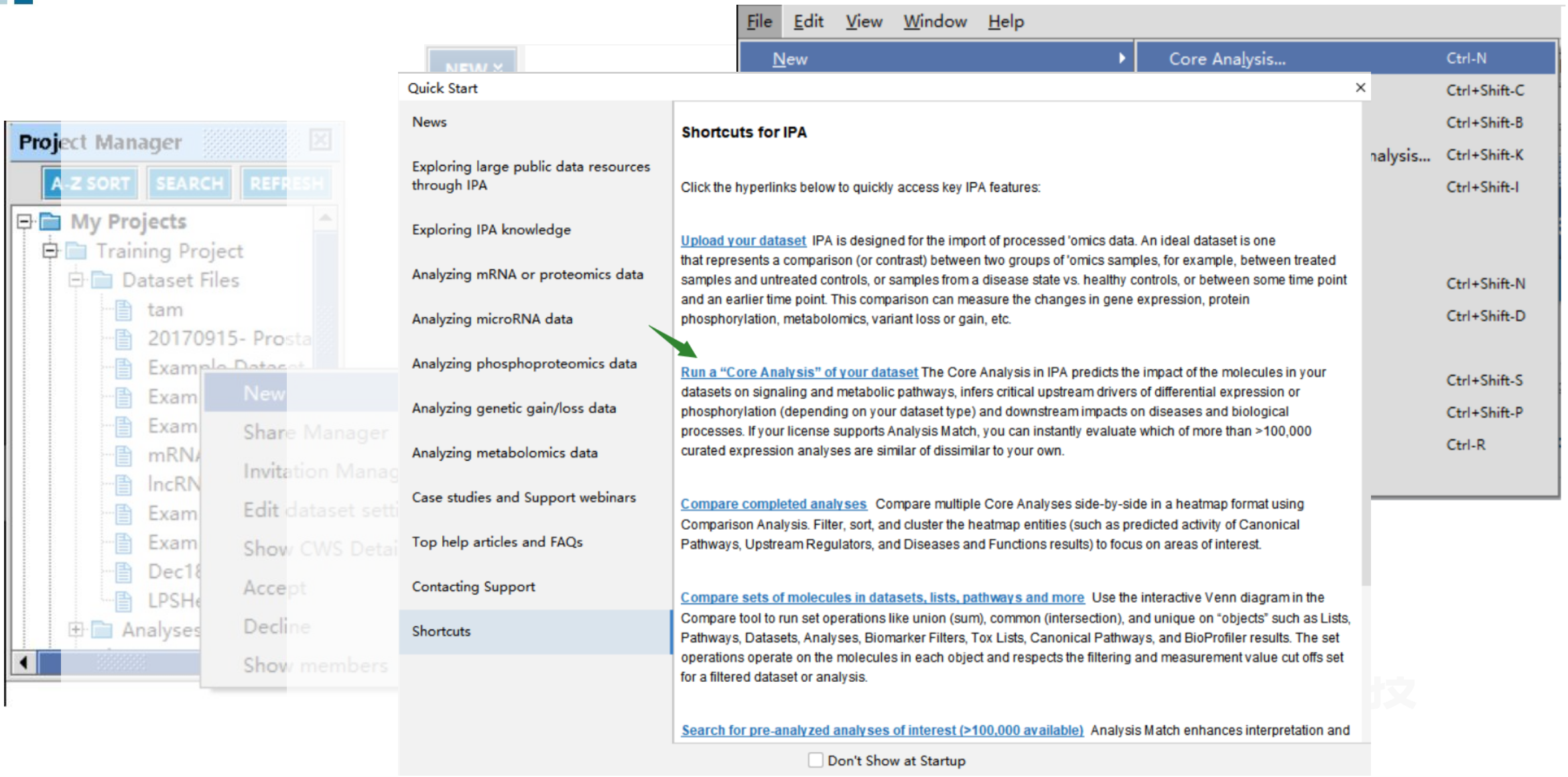
Raw Data (18705) | Dataset Summary (18443) | Metadata | Mapped (18443) | Unmapped (261)

Edit Observation Names | Infer Observations

ID/Observation Name	ID	Observation 1	Observation 1	Observation 2	Observation 2
Measurement/Annotation	2 types selec...	Phospho Lo...	Expr p-value	Expr Log Ratio	Expr p-value
1	geneid	STAD vs Normal Lo...	STAD vs Normal Ra...	Pembrolizumab res...	Pembrolizumab res...
2	MARC1	3.289999999999999...	0.911900000000000...	-8.45000000000000...	0.819100000000000...
3	MARCH1	-0.69430000000000...	0.1086	0.886900000000000...	0.140800000000000...
4	MARC2	-0.51280000000000...	0.2457	-0.69479999999999...	0.303499999999999...
5	MARCH2	-8.77E-2	0.682300000000000...	0.359700000000000...	0.196500000000000...
6	MARCH3	0.1968	0.5383	-0.2016	0.668000000000000...
7	MARCH4	-1.0064	0.1003	1.9093	1.49E-2
8	MARCH5	-3.130000000000000...	0.860800000000000...	0.133700000000000...	0.527699999999999...
9	MARCH6	-0.2833	0.171800000000000...	1.590000000000000...	0.954300000000000...
10	MARCH7	-0.125	0.404000000000000...	0.459600000000000...	4.950000000000000...
11	MARCH8	-0.140199999999999...	0.684400000000000...	0.552699999999999...	0.297800000000000...
12	MARCH9	-0.2495	0.3795	0.209100000000000...	0.566200000000000...
13	MARCH10	0.670599999999999...	0.731700000000000...	3.6932	3.209999999999999...
14	SEPT1	-0.301999999999999...	0.574699999999999...	-0.698699999999999...	0.3448
15	SEPT2	0.138500000000000...	0.2984	-0.1052	0.549100000000000...

Observation 1 | Observation 2

开始Core analysis



设置Core Analysis参数

确认参考数据和分析的分子背景一致

设置构建互作网络或上游调控因子是否考虑间接作用。互作网络寻找的最为相关的，或有分子结合作用相关的关系。

点击按钮应用过滤阈值，并查看用于分析的分子数量

设置数据过滤阈值

数据量在100-2000之间为佳，范围外的数据也能进行分析

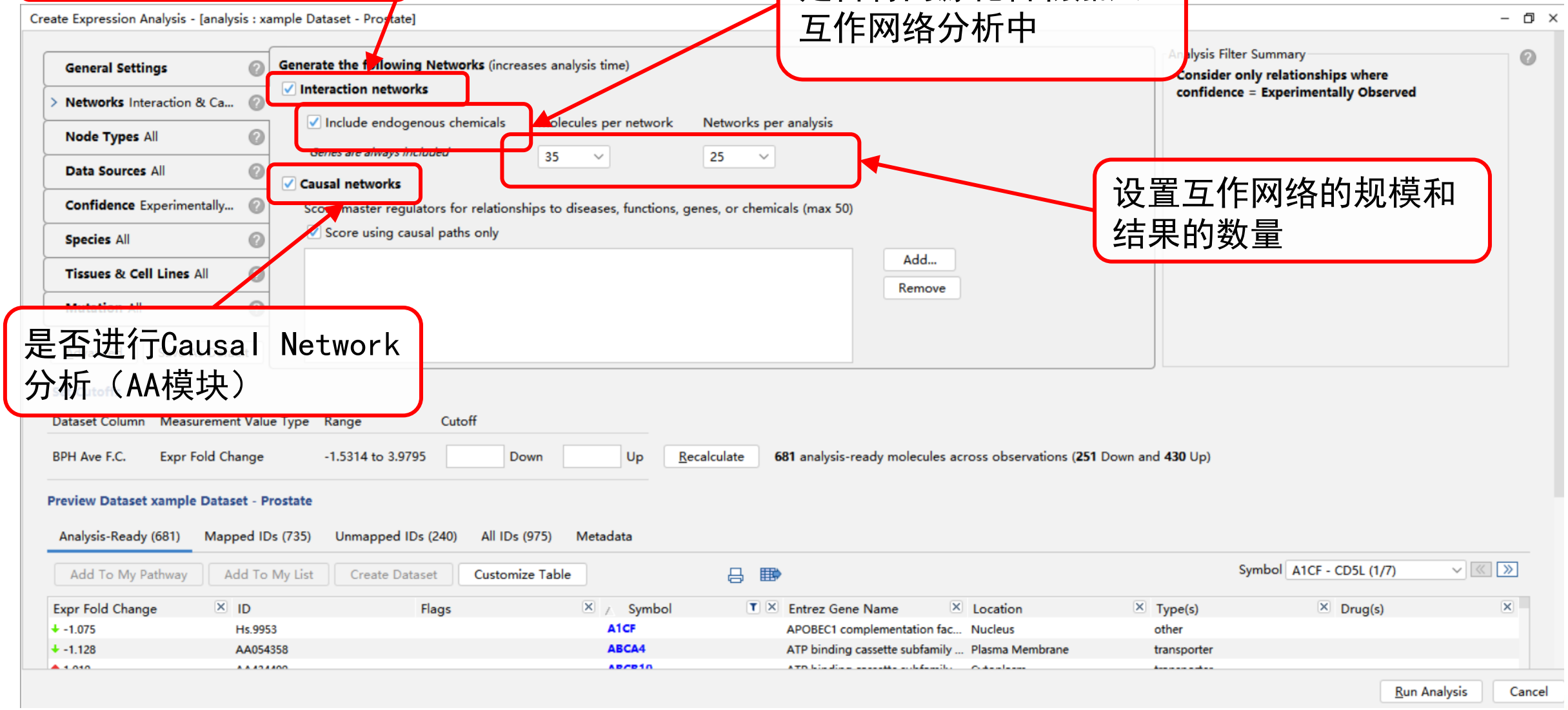
设置Core Analysis参数

是否进行互作网络分析

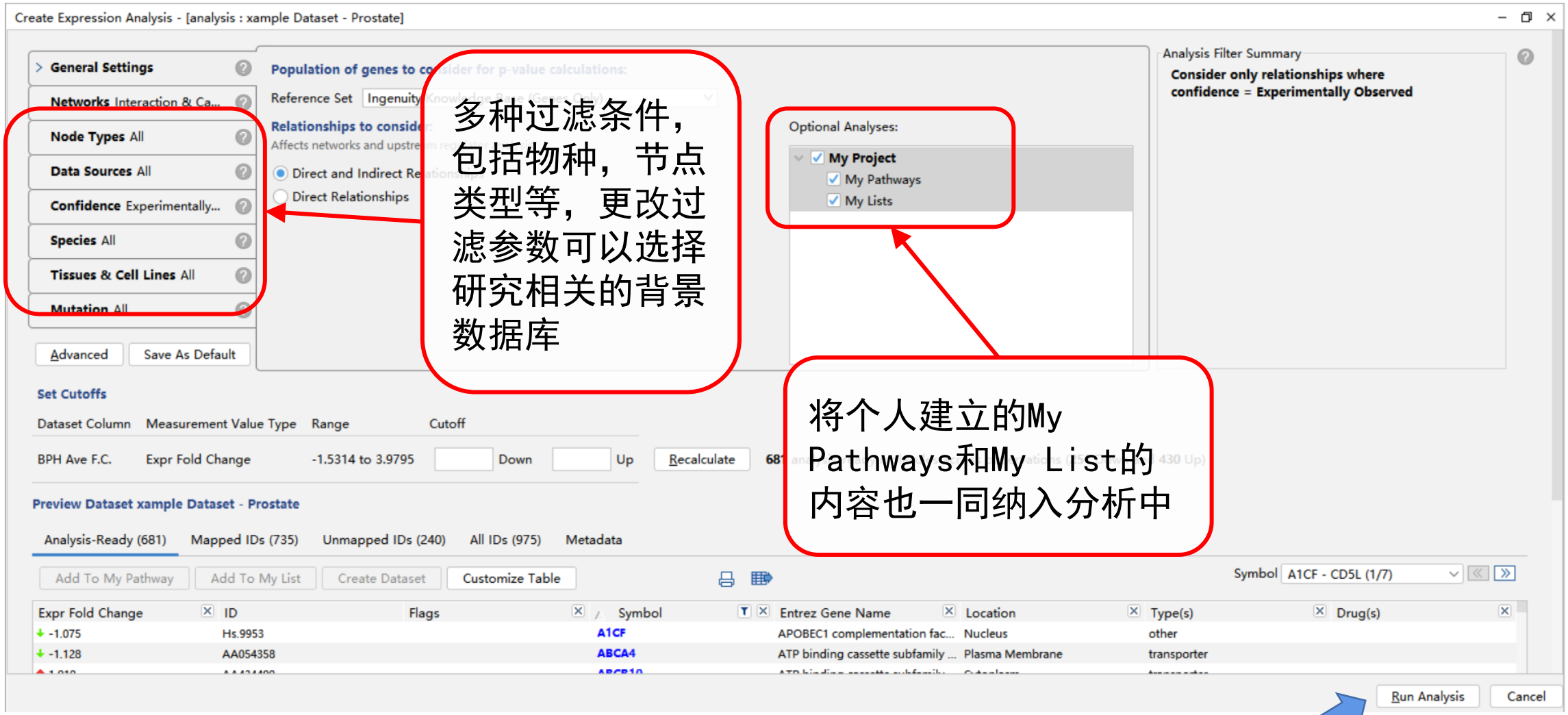
是否将内源化合物加入互作网络分析中

设置互作网络的规模和结果的数量

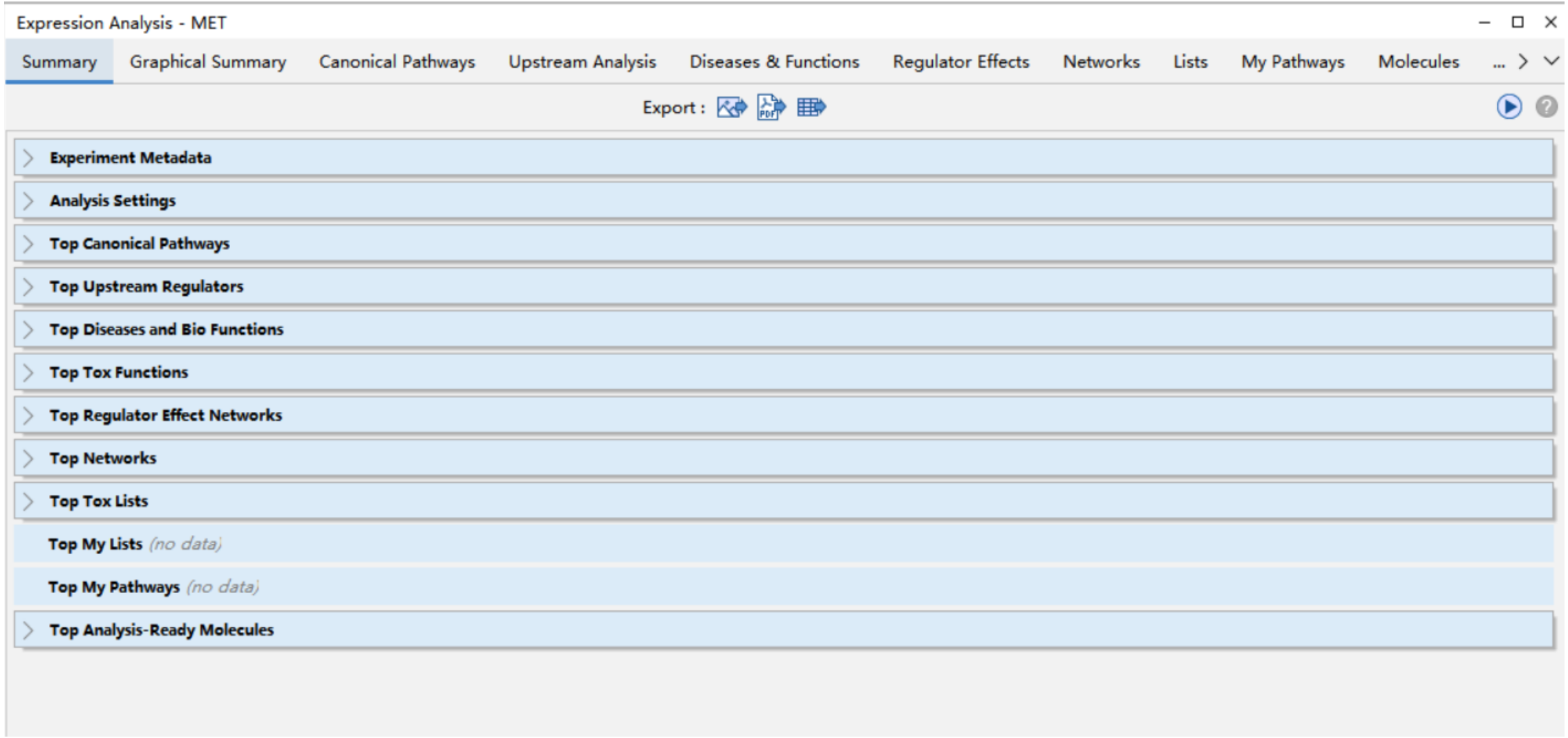
是否进行Causal Network分析（AA模块）



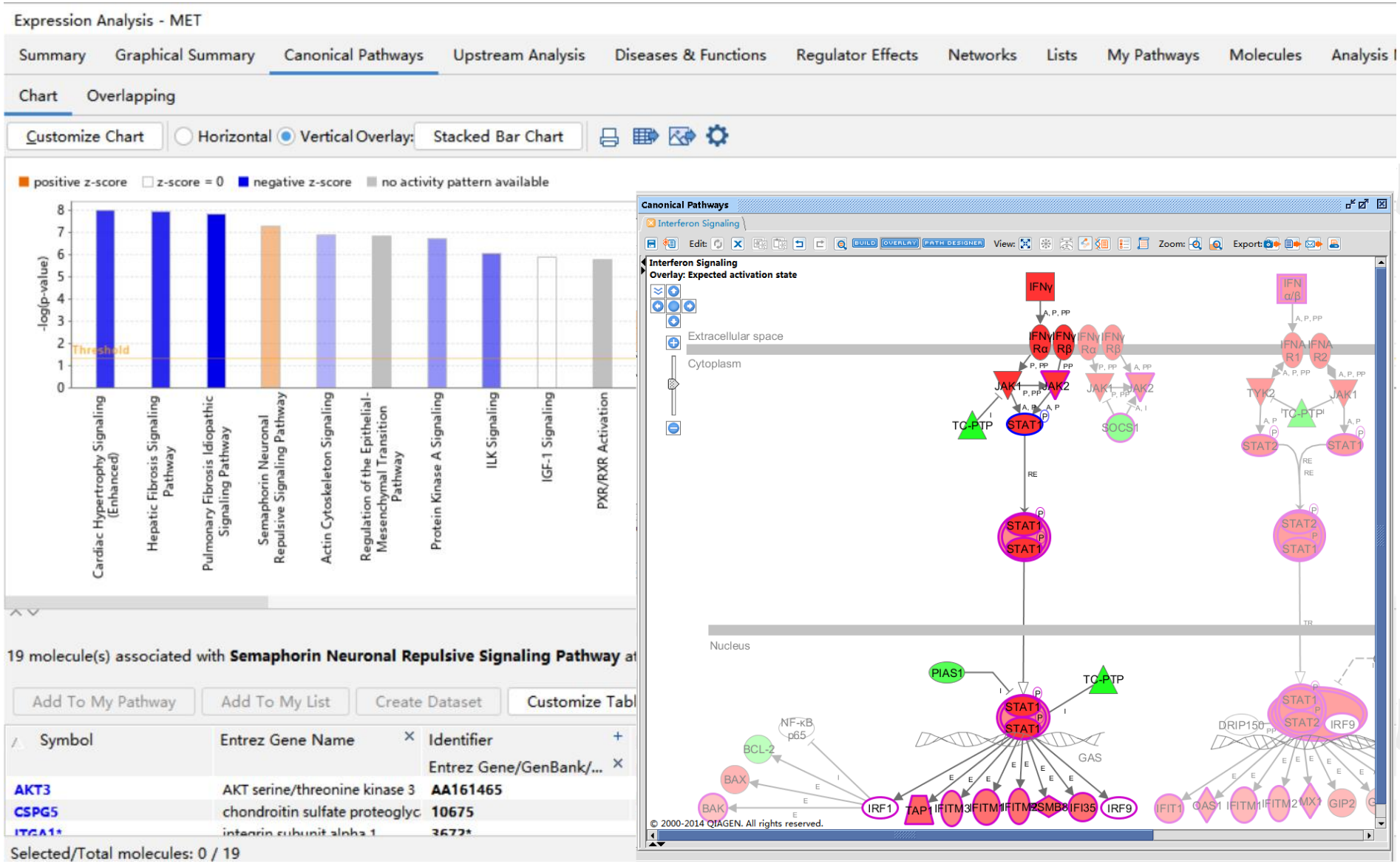
设置Core Analysis参数



获得Core Analysis分析结果



Canonical Pathway



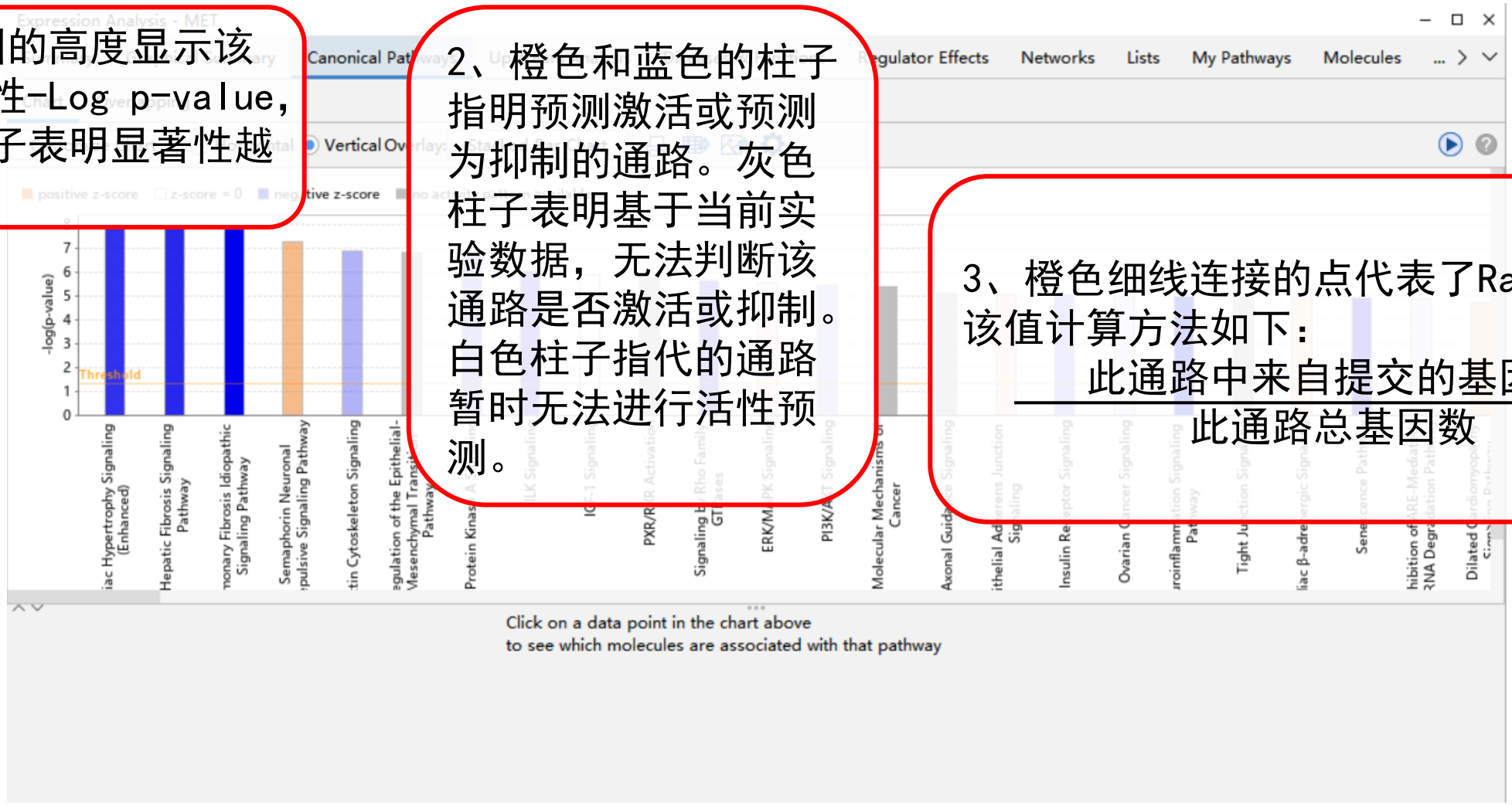
IPA的Canonical Pathways 是由科学家们人工摘取并构建的代谢和细胞信号通路数据库。

Canonical Pathways中的信息来自于特定的杂志文章、综述、教科书和一些其它权威数据库。

Canonical Pathway

1、柱状图的高度显示该通路显著性-Log p-value，越高的柱子表明显著性越高。

2、橙色和蓝色的柱子指明预测激活或预测为抑制的通路。灰色柱子表明基于当前实验数据，无法判断该通路是否激活或抑制。白色柱子指代的通路暂时无法进行活性预测。

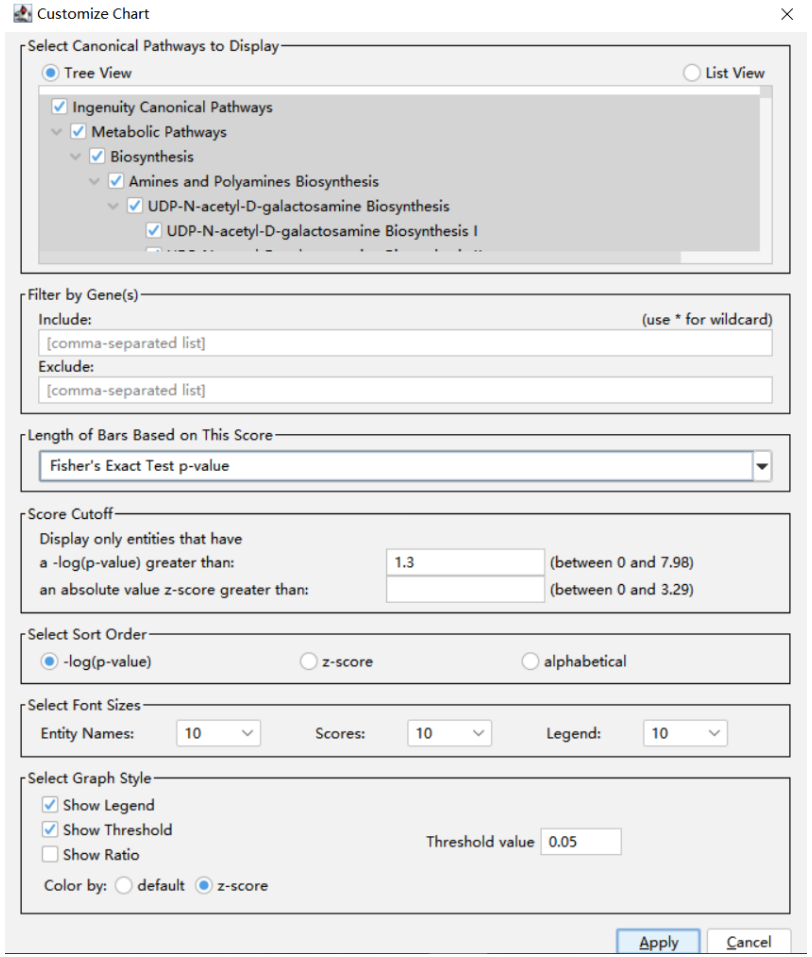


3、橙色细线连接的点代表了Ratio值，该值计算方法如下：

$$\frac{\text{此通路中来自提交的基因数}}{\text{此通路总基因数}}$$

Canonical Pathway

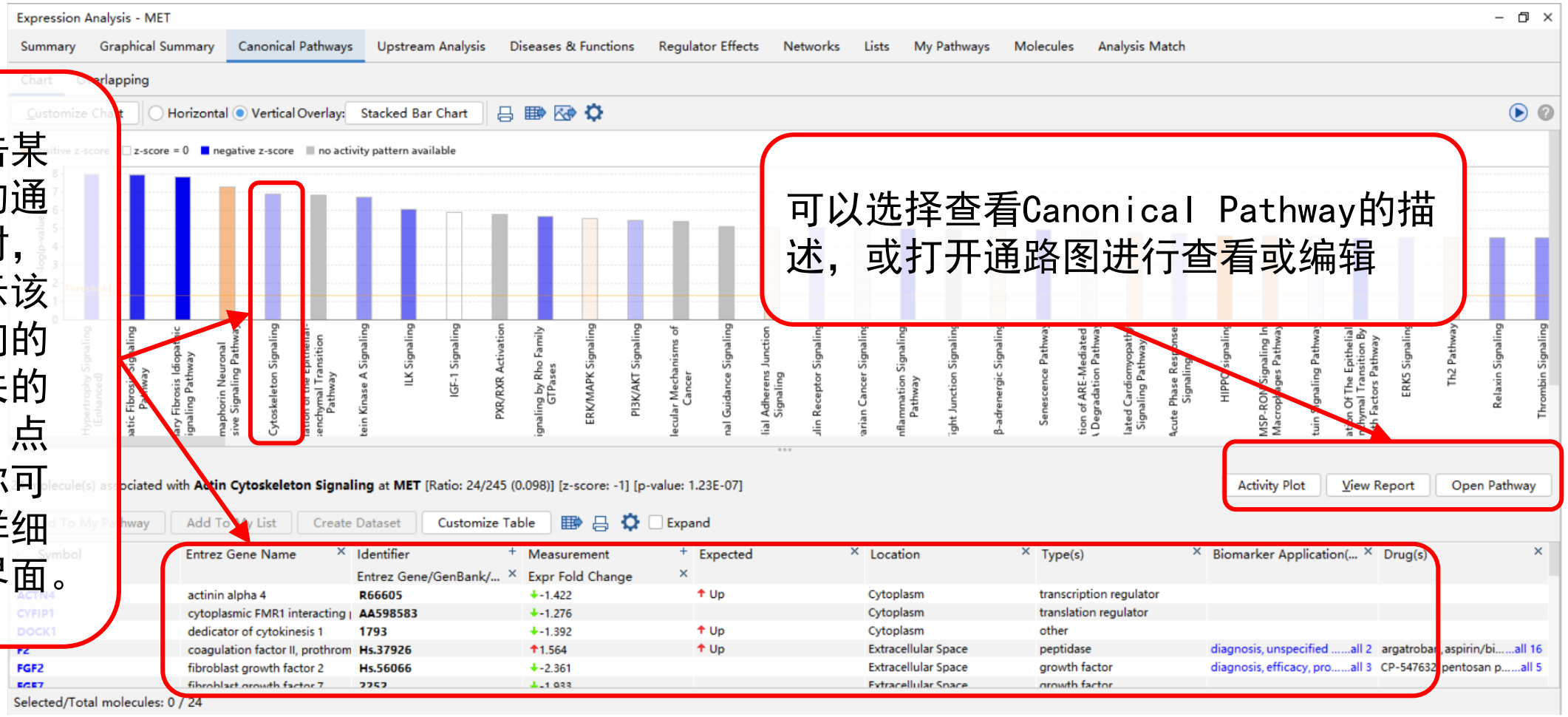
点击Customize Chart按钮将弹出定制对话框。您通过该对话框可以去除柱状图中不想显示的通路，也可以使用P-Value Cutoff设置通路可信度最低阈值（默认值是-Log P=1）来去掉不想显示的低相关性结果。



单击Stacked Bar Chart按钮显示各个通路中上调(红色)，下调(绿色)和未发生差异表达的分子(灰色)的数量。

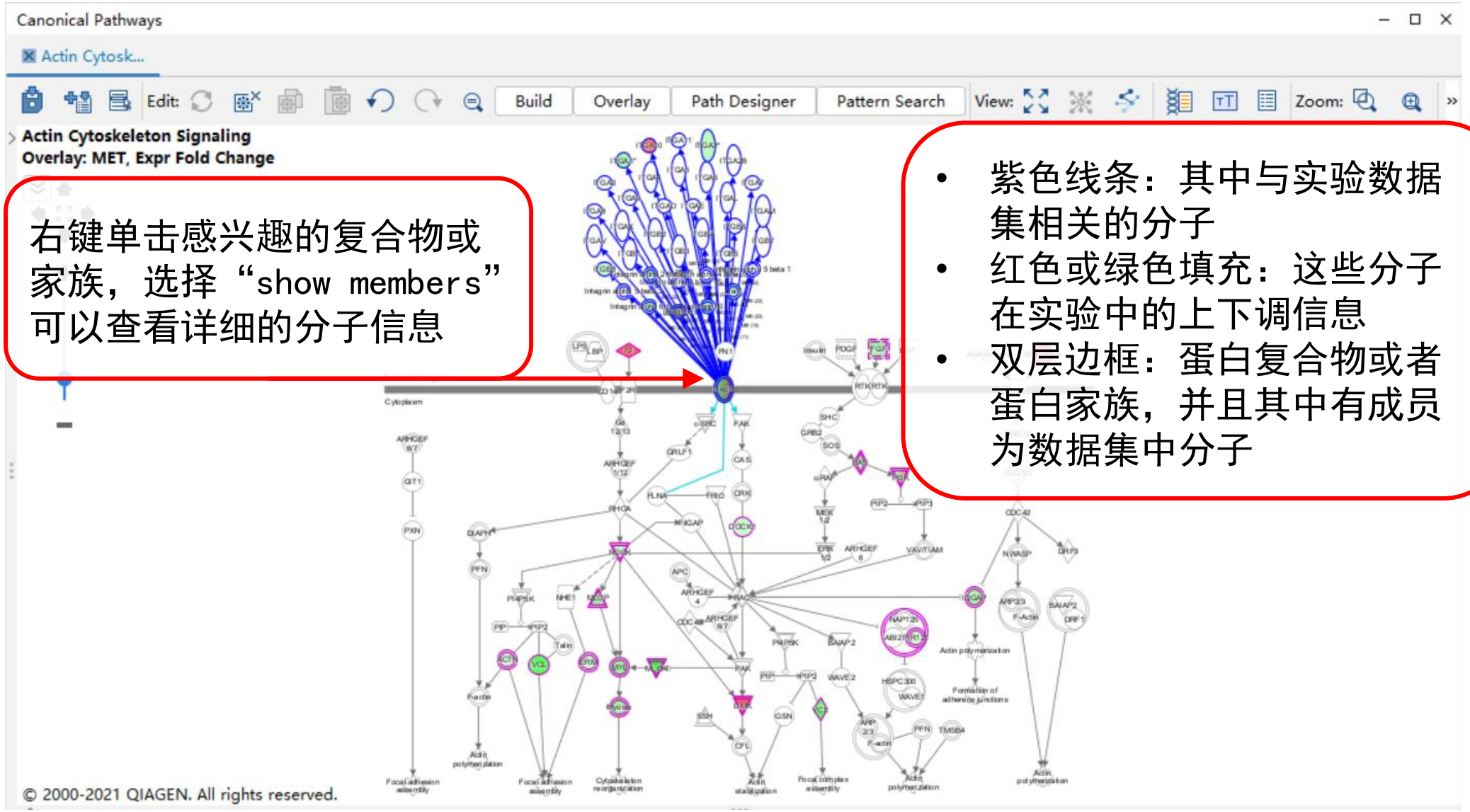
查看感兴趣的Canonical Pathway

当我们单击某个感兴趣的通路的柱子时，下方会显示该通路与我们的数据集相关的分子信息。点击基因名称可以打开其详细注释网页界面。



可以选择查看Canonical Pathway的描述，或打开通路图进行查看或编辑

通路图查看与编辑



右键单击感兴趣的复合物或家族，选择“show members”可以查看详细的分子信息

- 紫色线条：其中与实验数据集相关的分子
- 红色或绿色填充：这些分子在实验中的上下调信息
- 双层边框：蛋白复合物或者蛋白家族，并且其中有成员为数据集中分子

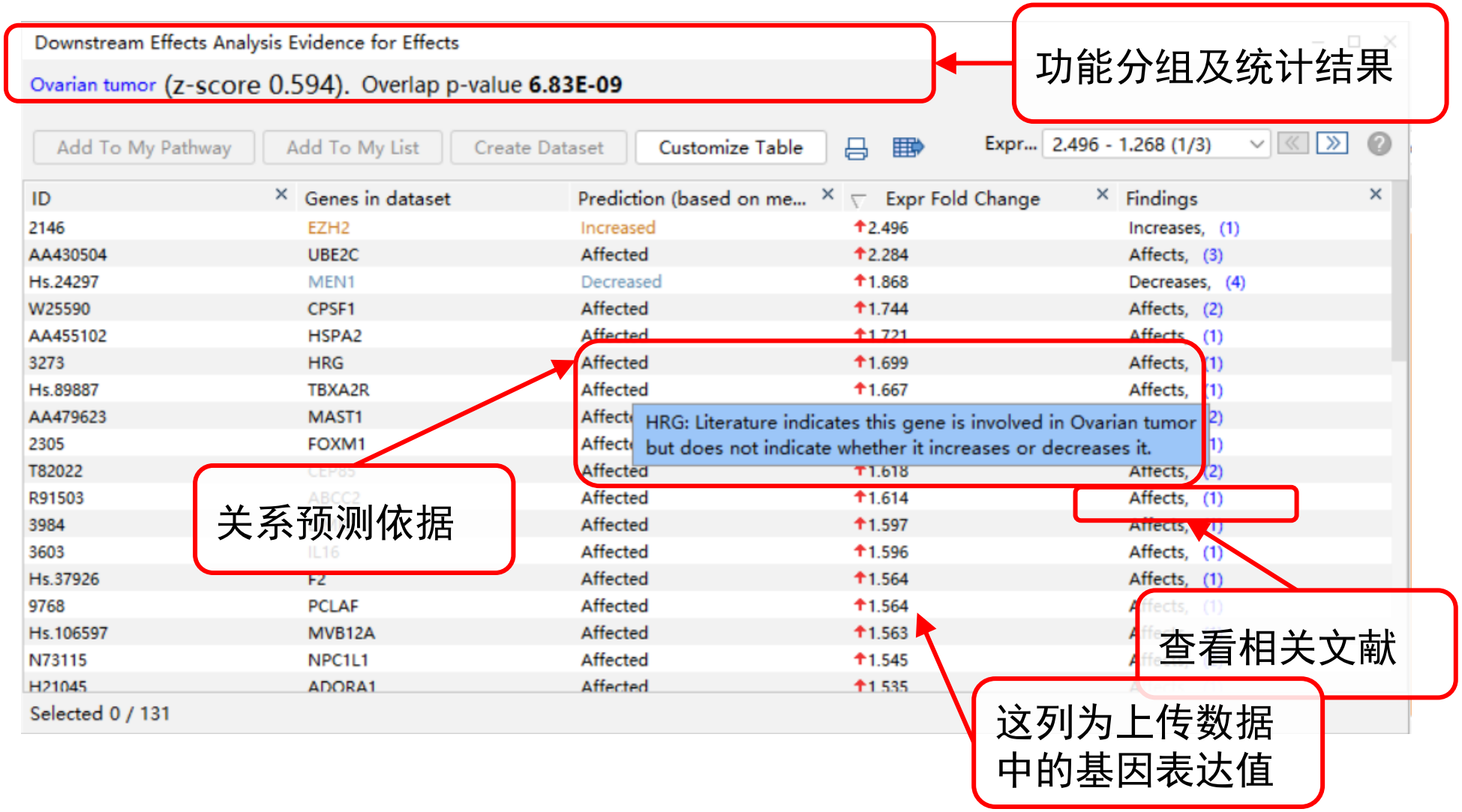
Downstream Effect分析

热图大小排序依据

热图颜色依据

改为柱状图视图

与疾病和功能相关的基因及文献



获得感兴趣的功能列表

点击Customize Chart可以选择感兴趣的功能，改变阈值，改变视图类型等

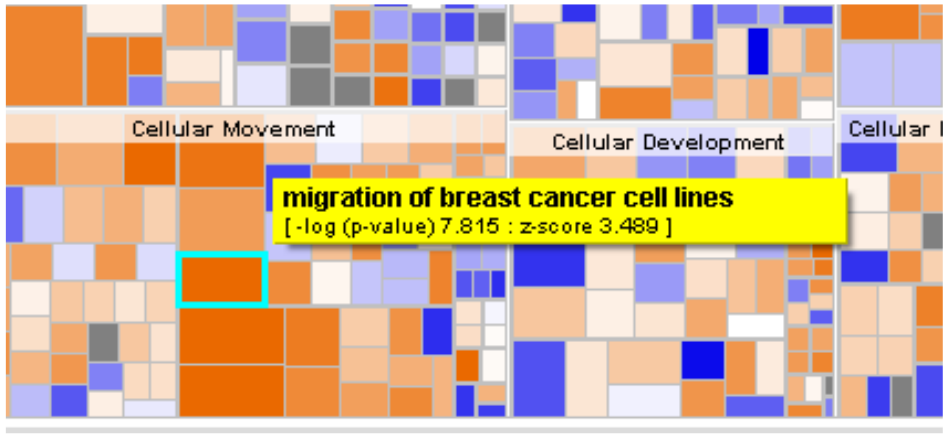
点击该按钮切换到热图界面

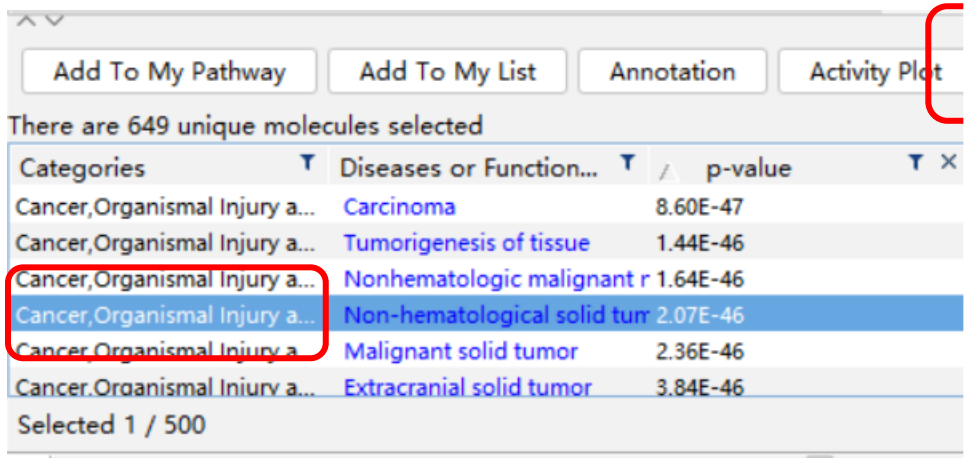
此处以柱状图显示高层级的功能分类结果。点击感兴趣的高层级功能后会在下方窗口显示其包好的低层级功能分类信息

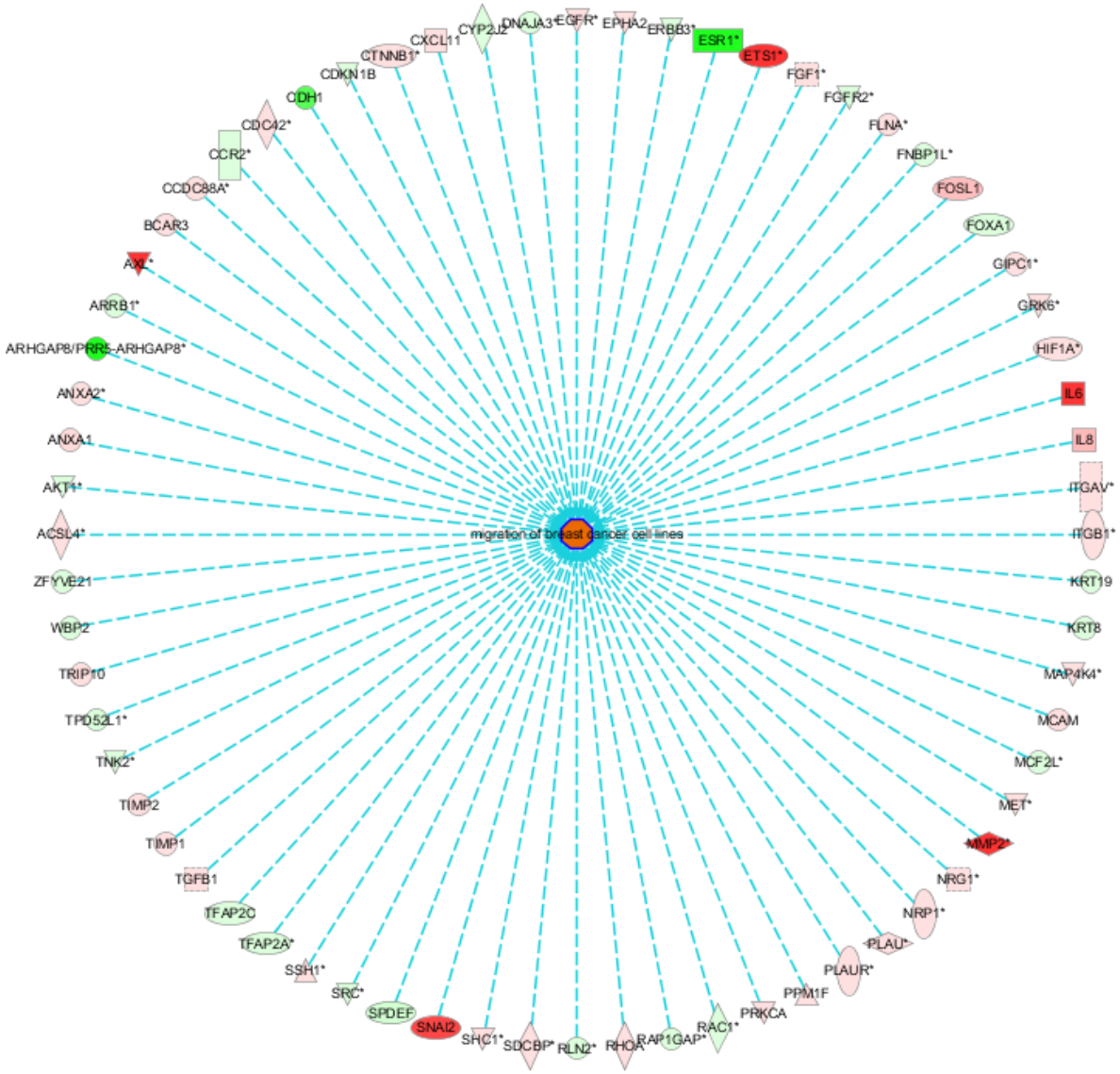
选择感兴趣的分类功能并点击add to my pahtway或add to my list可以将它们添加到My Pathway模块中进行进一步的网络构建

每一种低层级功能分类的p-value

将疾病和功能以通路图显示





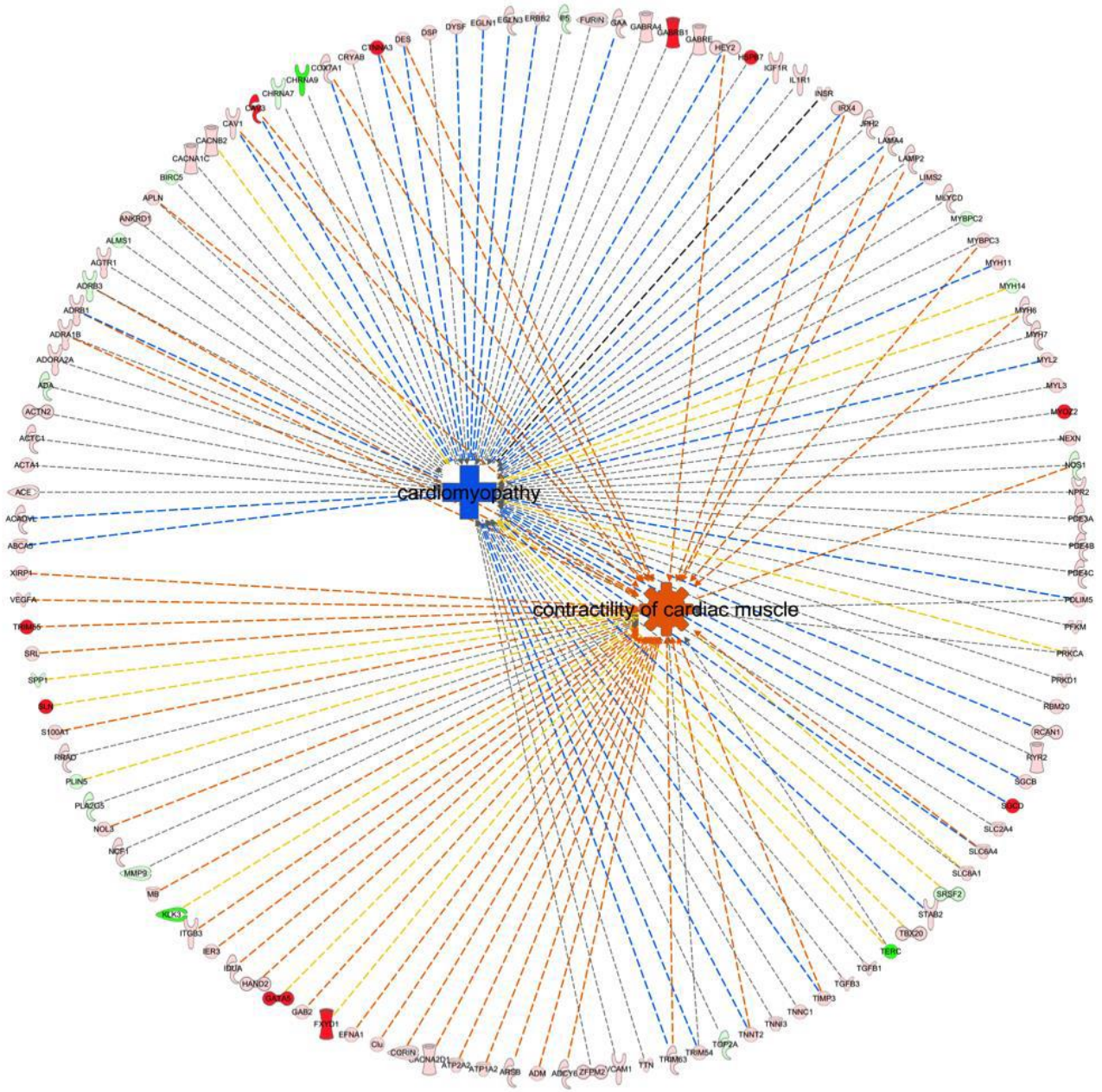


方便查看分子与疾病和功能的关系

关注趋势相反的功能/疾病:

- 抑制
- 激活

查看和两者均有关的分子



Upstream Analysis简介

- Upstream regulator analysis 是基于Ingenuity® Knowledge Base中记录的transcriptional regulators (TR)及其target genes间先验的互作关系进行分析的工具。

- 该分析工具告知在您的数据集中有多少**已知的靶基因及其转录调控子**，并通过和文献比对转录调控子及其靶基因可能的作用关系来预测本实验中它们的作用方向（如实验样本相对于对照组的表达量变化

- IPA对转录调控子的定义非常宽泛–任何能够影响其他分子表达量变化的均可成为转录调控子，如转录因子、microRNA、激酶、化合物或药物等。

Upstream Regulators 结果查看

选择特定的转录因子及其靶

点击以筛选分子类型

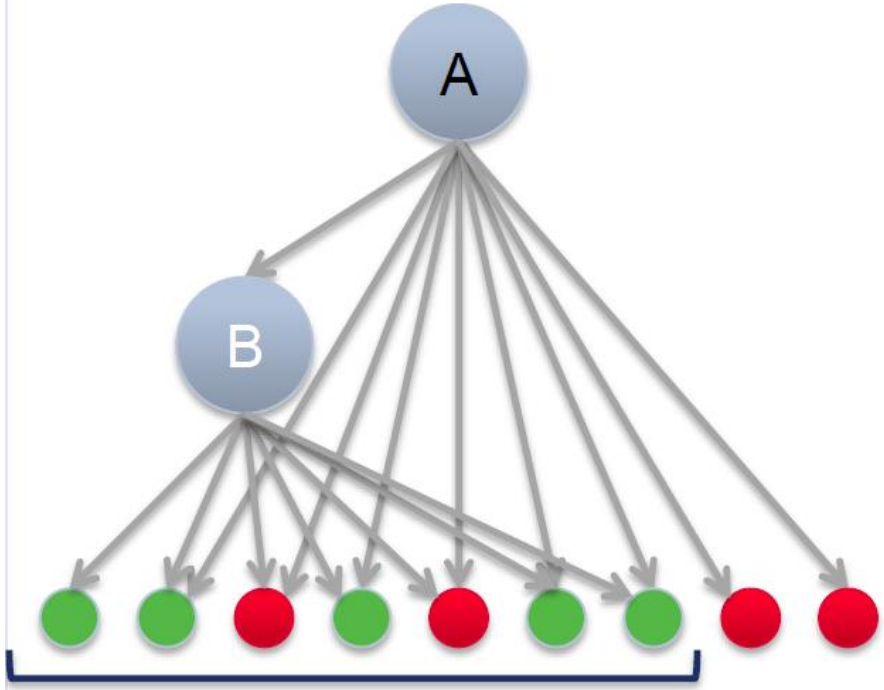
转录调节因子参考文献

点击基因名称开该基因背景可以查看该转子的所有文献信息

鼠标置于Prediction 列上方可以查看预测该TR会激活或抑制对应基因判断依据

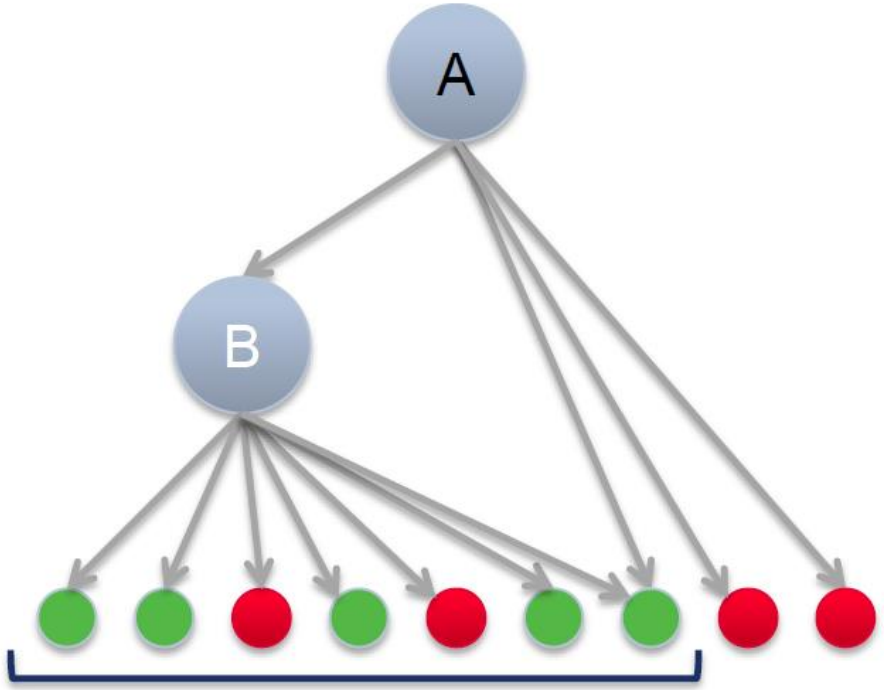
机制网络预测的原理

上游分子**可能**会通过其下游的调控子进行调控



共享 **7个**更下游靶基因**中的6个**

上游分子**不太可能**会通过其下游的调控子进行调控

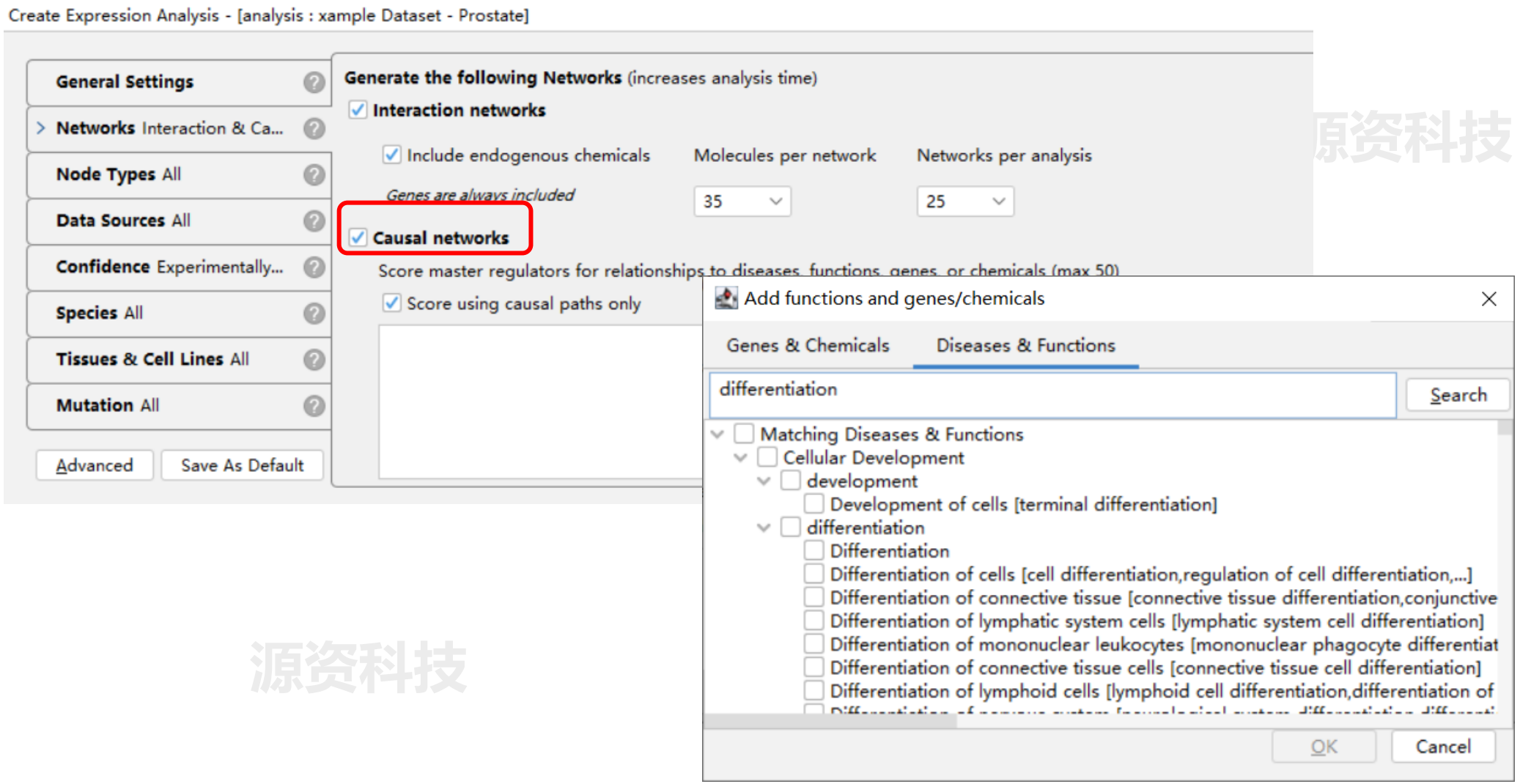


共享 **7个**更下游靶基因**中的1个**

Causal Network Analysis?

- Causal Network Analysis（因果网络分析）可识别控制您数据集中基因表达的上游分子，可视化您正在评估的疾病和功能，了解主调节因子对该疾病或功能的影响，并深入了解支持这些关系的证据。此外，还可以通过干预分子或功能，将假设与评估的标准联系起来，提高预测能力。

建立一个Causal Network Analysis（即Core Analysis中）



Expression Analysis - BPH

Summary | Graphical Summary | Canonical Pathways | Upstream Analysis | Diseases & Functions | Regulator Effects | Networks | Lists | My Pathways | Molecules | Analysis Match

Upstream Regulators | Causal Networks

Add To My Pathway | Add To My List | Activity Plot | Customize Table

Customize columns displayed in the table

Click on the link to access the Causal Network diagram

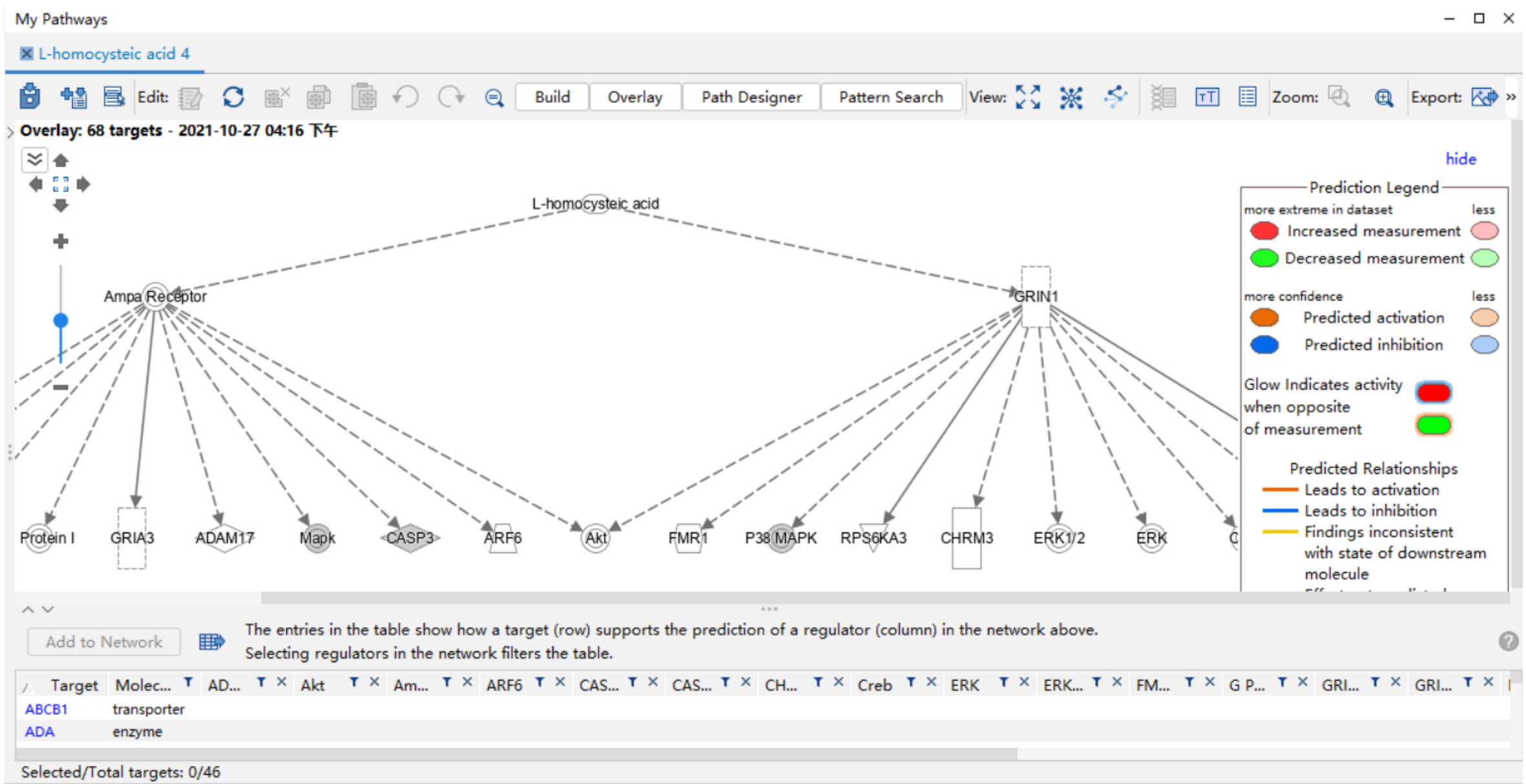
Master ...	Expr...	Mol...	Part...	Depth	Pre...	Note	Net...	Target...	Causal network	Targ...	Incr...	Dec...
PTPRM		phosphatase	Akt, ...all 43	3	Inhibited		1.00E-04	AB... ...all 159	159 (43)	42	HNF1B ...all 3	topo... ...all 1
SPN		transmemb...	AGT ...all 57	3	Activated		1.00E-04	AB... ...all 205	205 (57)	55	beta-... ...all 1	HNR... ...all 3
FCN-159		chemical dr...	AMPK...all 43	3			1.00E-04	AD... ...all 159	159 (43)			
TSC22D1		transcriptio...	AKT1, ...all 50	3			6.24E-23	1.00E-04	AB... ...all 191	191 (50)		...all 5
trichosanthin		chemical dr...	AKT1, ...all 55	3			1.86E-22	1.00E-04	AB... ...all 187	187 (55)		
miR-96-5p (ar		mature micr...	Akt, ...all 25	3			3.03E-22	1.00E-04	AB... ...all 153	153 (25)		
SMARCA4		transcriptio...	AR, B... ...all 8	2			4.11E-22	1.00E-04	AB... ...all 153	153 (8)	8	FN1, ...all 5
KRAS		enzyme	Akt, ...all 24	2			6.07E-22	2.00E-04	AB... ...all 152	152 (24)	24	5-fl... ...all 21 DGCR8 ...all 7
SVIL		other	APEX1...all 47	3			1.30E-21	6.00E-04	AB... ...all 195	195 (47)	46	ERG ...all 1 doxo... ...all 1
PFDN5		transcriptio...	Ap1, ...all 27	3			1.91E-21	5.00E-04	AB... ...all 166	166 (27)	26	
Arf		group	AKT1, ...all 50	3			2.98E-21	7.00E-04	AB... ...all 182	182 (50)	45	
XRCC6	↑1.273	enzyme	AHR, ...all 59	3			3.97E-21	6.00E-04	AB... ...all 198	198 (59)	54	CD40... ...all 3 5-aza... ...all 3
Jmy-p300		complex	AKT1, ...all 44	3			4.55E-21	5.00E-04	AB... ...all 182	182 (44)	43	
Scf		complex	AR, ...all 49	3			4.97E-21	1.00E-04	AD... ...all 152	152 (49)	42	
TMF1		transcriptio...	AKT1, ...all 43	3			5.03E-21	1.20E-03	AB... ...all 160	160 (43)	42	beta-... ...all 2 ESR1 ...all 1
cobalt		chemical to...	APEX1...all 45	3			6.33E-21	1.30E-03	AB... ...all 186	186 (45)	43	
TRIM29		transcriptio...	AKT1, ...all 49	3			7.59E-21	3.30E-03	AB... ...all 185	185 (49)	48	TP63 ...all 1 miR-... ...all 1
bendamustin		chemical dr...	AKT1, ...all 49	3			7.97E-21	2.10E-03	AB... ...all 182	182 (49)	46	
SAFB		other	Ap1, ...all 20	3			1.70E-20	3.00E-04	AB... ...all 153	153 (20)	20	MMP3 ...all 1
SAFB2		other	Ap1, ...all 20	3			3.23E-20	3.00E-04	AB... ...all 152	152 (20)	20	MAPK1...all 2
tucatinib		chemical dr...	Akt, ...all 44	3			3.36E-20	9.00E-04	AB... ...all 170	170 (44)	43	
LAMTOR5		other	AKT1, ...all 65	3			4.00E-20	9.00E-04	AB... ...all 215	215 (65)	62	HOT... ...all 1 miR-... ...all 1
harmine		chemical - e...	2-a... ...all 58	3			4.15E-20	4.10E-03	AB... ...all 194	194 (58)	56	
AG 1433		chemical - k...	AG ... ...all 49	3			4.85E-20	3.60E-03	AB... ...all 181	181 (49)	47	
USP36		peptidase	Akt, ...all 43	3			6.78E-20	2.90E-03	AB... ...all 164	164 (43)	42	PRKCD ...all 2
RCHY1		enzyme	APEX1...all 44	3			7.05E-20	9.00E-04	AB... ...all 186	186 (44)	43	Breas... ...all 1 decit... ...all 3
SYVN1		transporter	26s ... ...all 52	3		0.509	7.80E-20	4.60E-03	AB... ...all 189	189 (52)	52	XBP1 ...all 1
HEXIM1		transcriptio...	AJU... ...all 55	3	Inhibited	-2.392	8.12E-20	2.90E-03	AB... ...all 202	202 (55)	54	5-aza... ...all 1
OXSR1		kinase	APEX1...all 42	3		1.313	8.43E-20	6.40E-03	AB... ...all 188	188 (42)	40	Breas... ...all 4

Customize Table

Select column(s) to be displayed in table.

- [ ] Select/Deselect all
- [x] Master Regulator
- [x] Expr Fold Change
- [x] Molecule Type
- [x] Participating regulators
- [x] Depth
- [x] Predicted Activation
- [x] Notes
- [x] Activation z-score
- [x] p-value of overlap
- [ ] B-H corrected p-value
- [x] Network bias-corrected p-value
- [x] Target Molecules in Dataset
- [x] Causal network
- [x] Target-connected regulators
- [x] Increases/Downstream

OK | Cancel


My Pathways
L-homocysteic acid 4
Edit:
Build
Overlay
Path Designer
Pattern Search
View:
Zoom:
Export:
Overlay: 68 targets - 2021-10-27 04:16 下午
hide
L-homocysteic acid
Ampa Receptor
GRIN1
Protein I
GRIA3
ADAM17
Mapk
CASP3
ARF6
Akt
FMR1
P38 MAPK
RPS6KA3
CHRM3
ERK1/2
ERK
Prediction Legend
more extreme in dataset
less
Increased measurement
Decreased measurement
more confidence
less
Predicted activation
Predicted inhibition
Glow Indicates activity when opposite of measurement
Predicted Relationships
Leads to activation
Leads to inhibition
Findings inconsistent with state of downstream molecule
Add to Network
The entries in the table show how a target (row) supports the prediction of a regulator (column) in the network above.
Selecting regulators in the network filters the table.
Target
Molec...
AD...
Akt
Am...
ARF6
CAS...
CAS...
CH...
Creb
ERK
ERK...
FM...
G P...
GRI...
GRI...
ABCB1
transporter
ADA
enzyme
Selected/Total targets: 0/46

PART

6

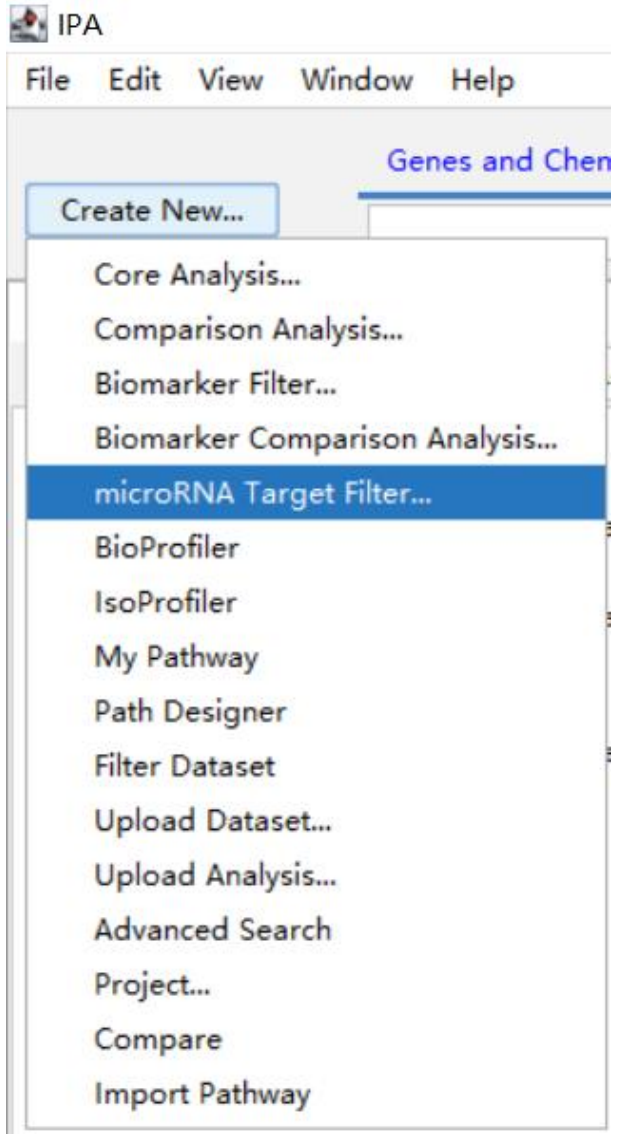
MicroRNA Target Filter

MicroRNA Target Filter功能

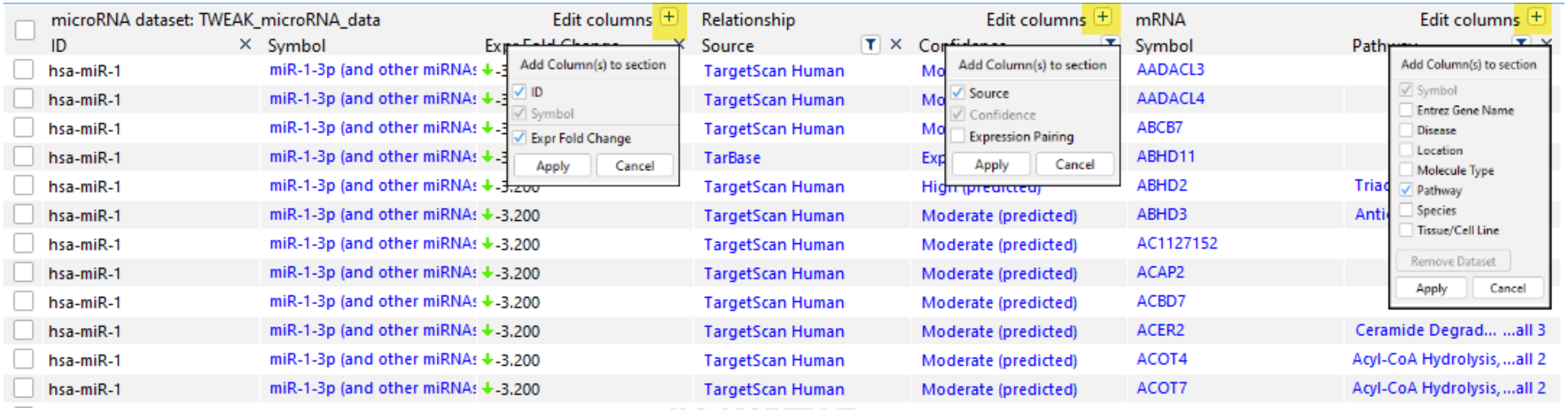
IPA中的microRNA Target Filter通过target的一组mRNAS来探索数据集中microRNA的生物学特性。

使用该功能需要构建一个表格，该表格将数据集中的microRNA与实验观察和预测的mRNA target相关联，且用户可使用实验结果和Ingenuity知识库提供的信息对target进行优先排序。

注意：MicroRNA Target Filter的数据集必须至少包含一个microRNA。



丰富的筛选功能



寻找潜在的生物学效应、导出筛选结果并保存过滤内容

Add to my pathway→用做图Build和overlay绘制个性化的通路图

Create Data→保存搜索结果后进行core analysis

Add to my List→保存为列表，也可以进行core analysis

PART

7

IsoProfiler

IsoProfiler功能

IsoProfiler可对RNA-seq数据集中的转录本和异构体进行筛选，找到关键异构体。

IsoProfiler主要有以下三方面用途：

1. 从人类或小鼠数据集中发现具有特殊表达模式的异构体基因：

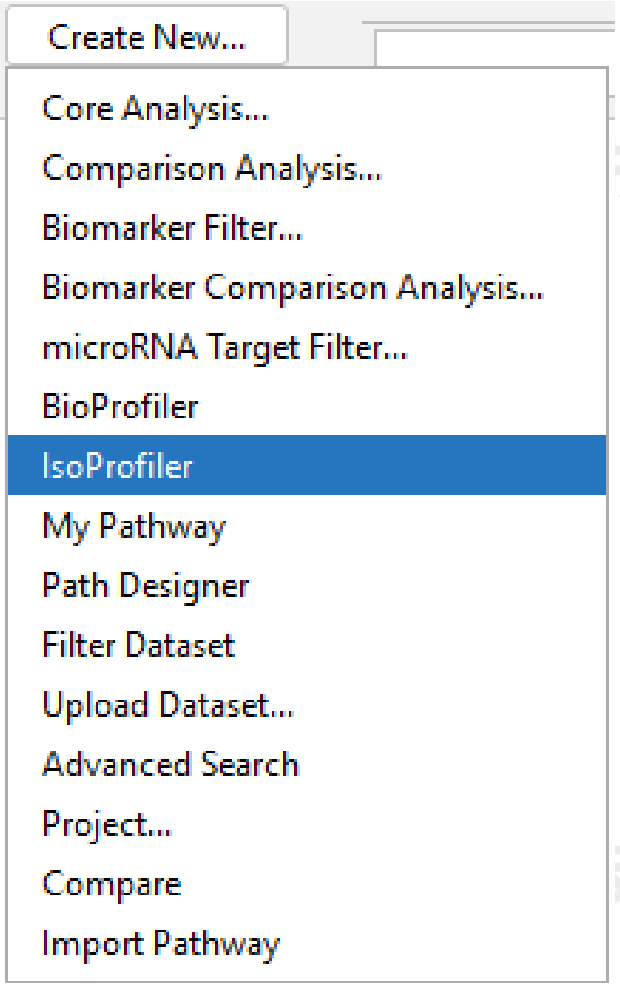
- 同时具有上调和下调亚型的基因
- 异构体转换——当一个基因最高丰度（例如，最高FPKM或RPKM）的异构体在数据集的实验组和对照组之间不同时
- 转录本仅在某些组织中表达的人类基因（基于人类GTEx数据）

2. 关注数据集中异构体的重要属性，例如：

- Fold change、p值和丰度（强度）截止值（cutoff）
- 与已知疾病或功能相关的亚型
- 蛋白质编码亚型
- APPRIS注释的主要亚型

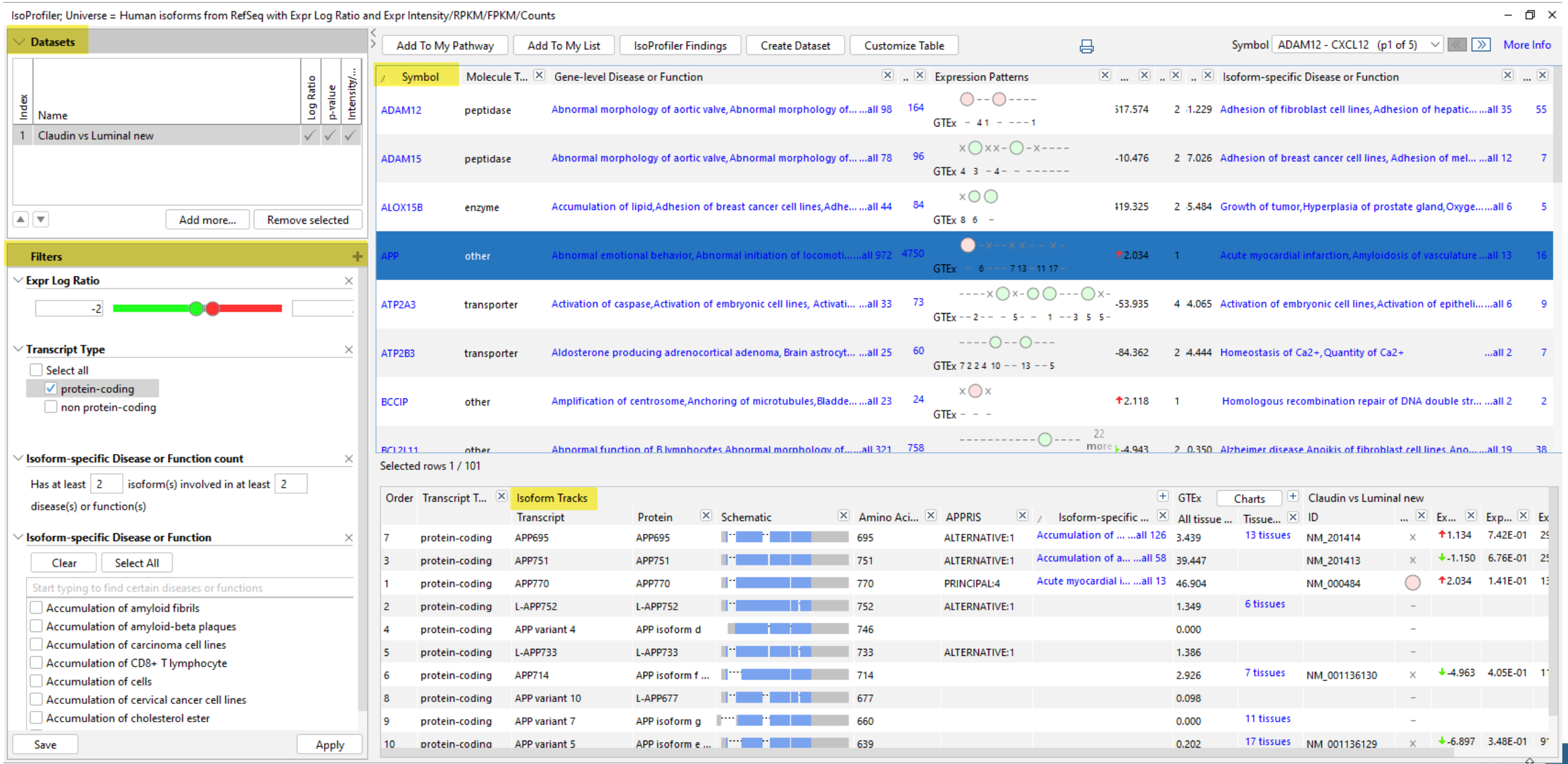
3. 在一个（或多个）数据集中可视化异构体级别的表达

新建IsoProfiler



1. 上传异构体（即转录或剪接变体）RNA-seq数据集。
2. 数据**必须来自人类或小鼠**，并使用RefSeq、Ensembl或UCSC进行比对。不能使用基因名称或基因级ID来比对，必须使用转录本ID。例如，对于人类CDC16基因，比对的转录本ID包括NM_001078645（RefSeq）、ENST0000360383（Ensembl）或uc001vuk（UCSC）。
3. 数据集必须只有一个来源，即只有Ensembl或只有RefSeq，不能混用。因为每个来源可能对每个基因的转录本有不同的“模型”，因此不能混用。
4. **不建议使用UCSC ID**，因为蛋白质编码过滤器不适用于UCSD ID。
5. 可以直接上传CuffDiff Isoform .diff数据文件（以及随附的跟踪文件）。

IsoProfiler界面



IsoProfiler界面

Expression Patterns（表达模式）列中的虚线表示数据集中不存在基因的已知转录本。

Add To My Pathway | Add To My List | IsoProfiler Findings | Create Dataset | Customize Table | Symbol ABCG1 - ATP2A3 (p1 of 20) | More Info

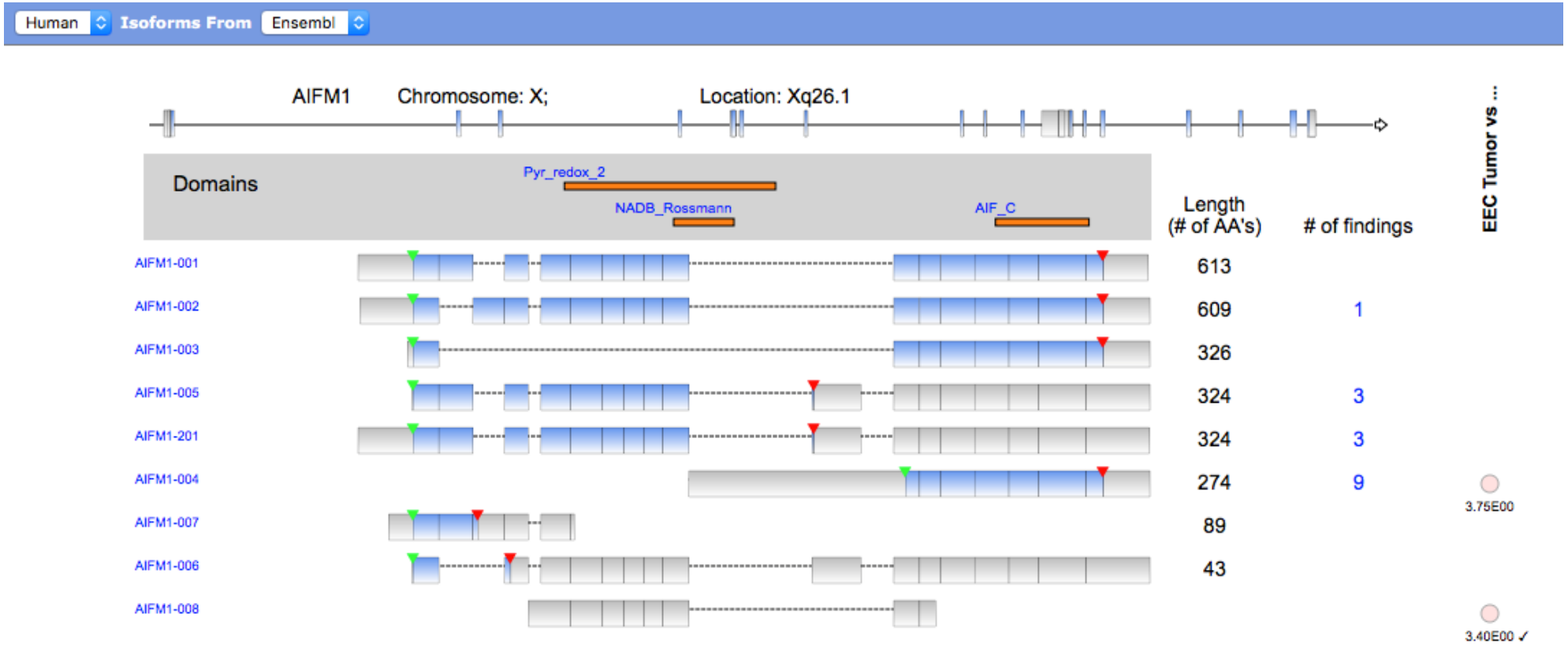
Symbol	...	Isoform-specific Disease or Function	Expression Patterns	Max Expression Change	Transcript count	Range	Isoform-specific Findings
AGAP2	enzy...	Apoptosis,Apoptosis of cancer cells,Apoptosis of tumor cel... ...all 11	GTEx 14 – 10 15 8	-4.366	1		10
AHI1	other	Chronic phase chronic myeloid leukemia ...all 1	GTEx 4 – – 2 – – – – 1 – 1 – – 1 – 3 – 1 2 (10 more)	2.163	1		5
AIFM1	enzy...	Production of reactive oxygen species ...all 1	GTEx – 8 – – –	6.640	1		1
ALOX15B	enzy...	Growth of tumor,Hyperplasia of prostate gland, Oxygenatio... ...all 6	GTEx 8 6 –	-5490.053	3	5416.212	6
AMOT	other	Enlargement of endosomal compartment ...all 1	GTEx 1 – – 7 – –	-4.191	1		1
AMPH	other	Replication of Semliki Forest virus, Replication of Sindbis virus ...all 2	GTEx 2 1 – – – 12 1 –	22.959	1		2

Selected rows 1 / 498

Order	Transcript Type	Isoform Tracks: Transcript	Protein	Schematic	Amino Aci...	APPRIS	Isoform-specific Disease or Funct...	GTEx Charts: All tissue media...	Claudin vs Luminal new: ID	Expr...	Expr ...	Exp...	Expr ...
1	protein-coding	AIFM1 variant 1	AIFM1 isoform AIF precu...		613	PRINCIPAL:4		9.072	NM_004208	×	-1.018	9.71E-01	23548.855
4	protein-coding	PDCD8-short	PDCD8-short		274		Cell death of cervical cancer cell.....all 3	0.464	NM_001130846	×	-1.093	8.54E-01	2227.456
2	protein-coding	AIFM1 variant 2	AIFM1 isoform AIF-exB p...		609	ALTERNATIV...		0.136	NM_145812	×	1.988	4.40E-01	315.051
3	protein-coding	AIFSH2	AIFSH2		324		Production of reactive oxygen s... ...all 1	0.000	NM_001130847	○	6.640	1.38E-01	529.458
5	non protein-coding	AIFM1 variant 6						0.000		–			

IsoProfiler界面

- 点击蓝色超链接AIFM1基因，即可显示Isoform视图中有重叠的数据集。
- IsoProfiler中的转录本顺序与Isoform视图中的顺序相同。如果亚型为非蛋白质编码，则排序顺序为从最长到最短的蛋白质编码区，然后是从最长到最短的核苷酸长度。



PART

8

IPA文献

文献一

期刊： Cell

影响因子： 41.58

关键词： metastasis tumor, microenvironment, pre-metastatic niche, cancer immunology, immune suppression, stem cell niche, immunotherapy...

目的： 探索癌症转移过程中的关键生态位调节信号特征

实验对象： 基因工程髓样细胞（GEMys）

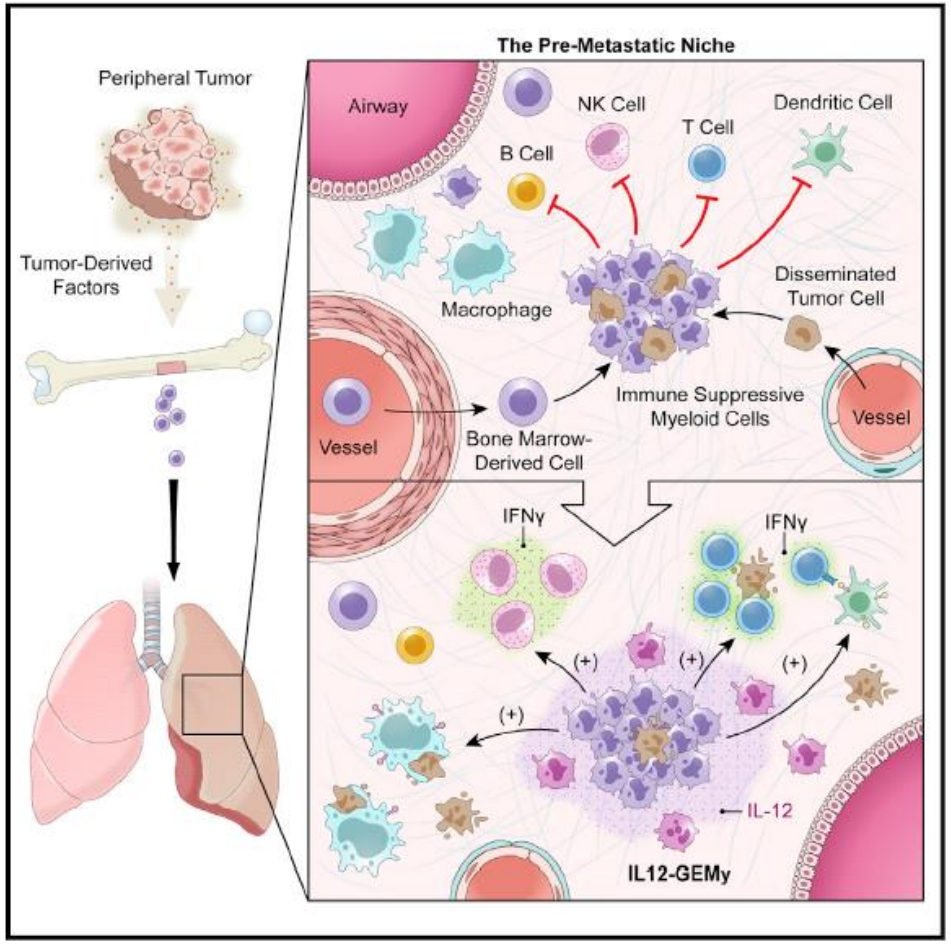
IPA分析： Ingenuity pathway analysis (IPA) indicated a significant enrichment in multiple **pathways** of myeloid cell-mediated immune suppression

Cell

Article

Genetically engineered myeloid cells rebalance the core immune suppression program in metastasis

Graphical abstract



Authors

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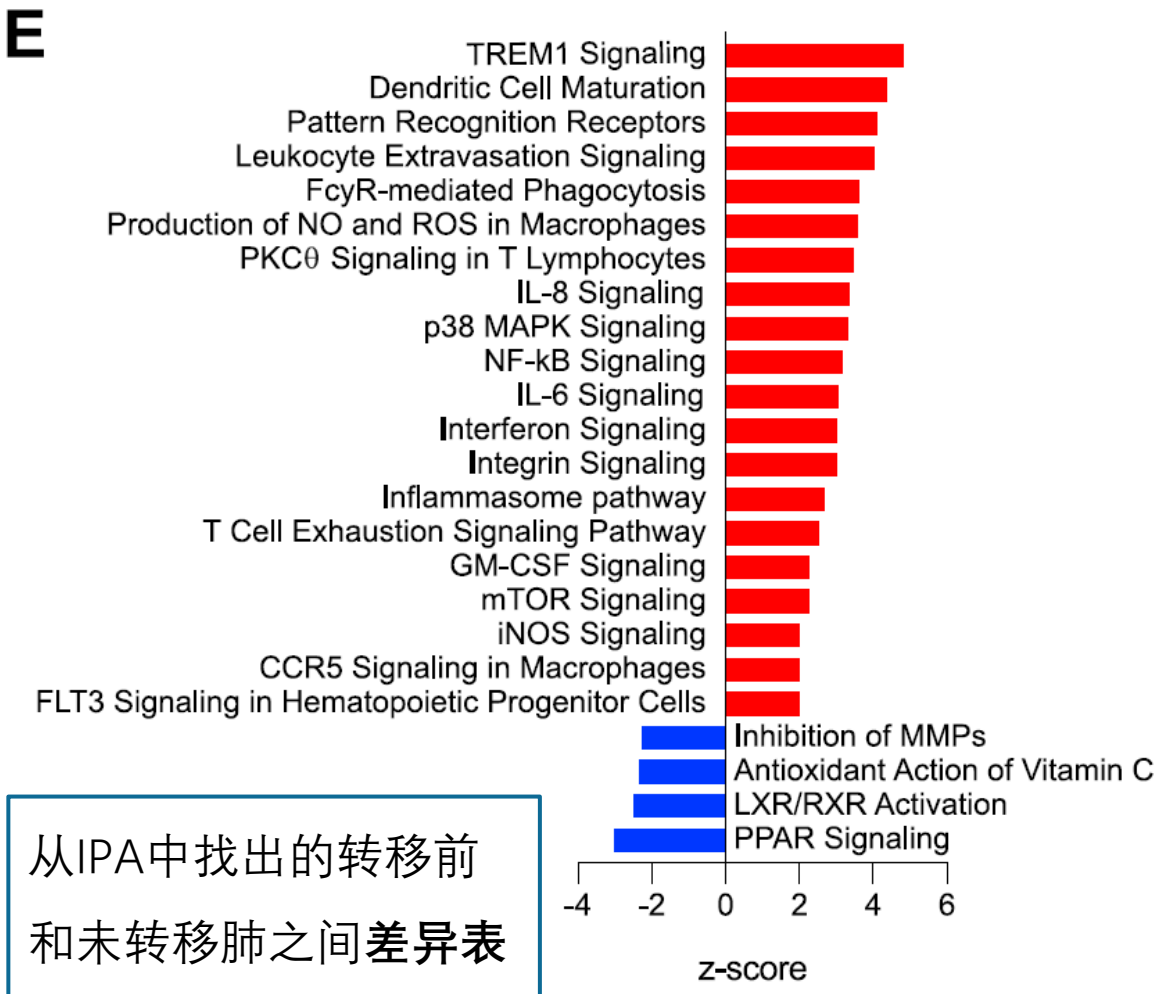
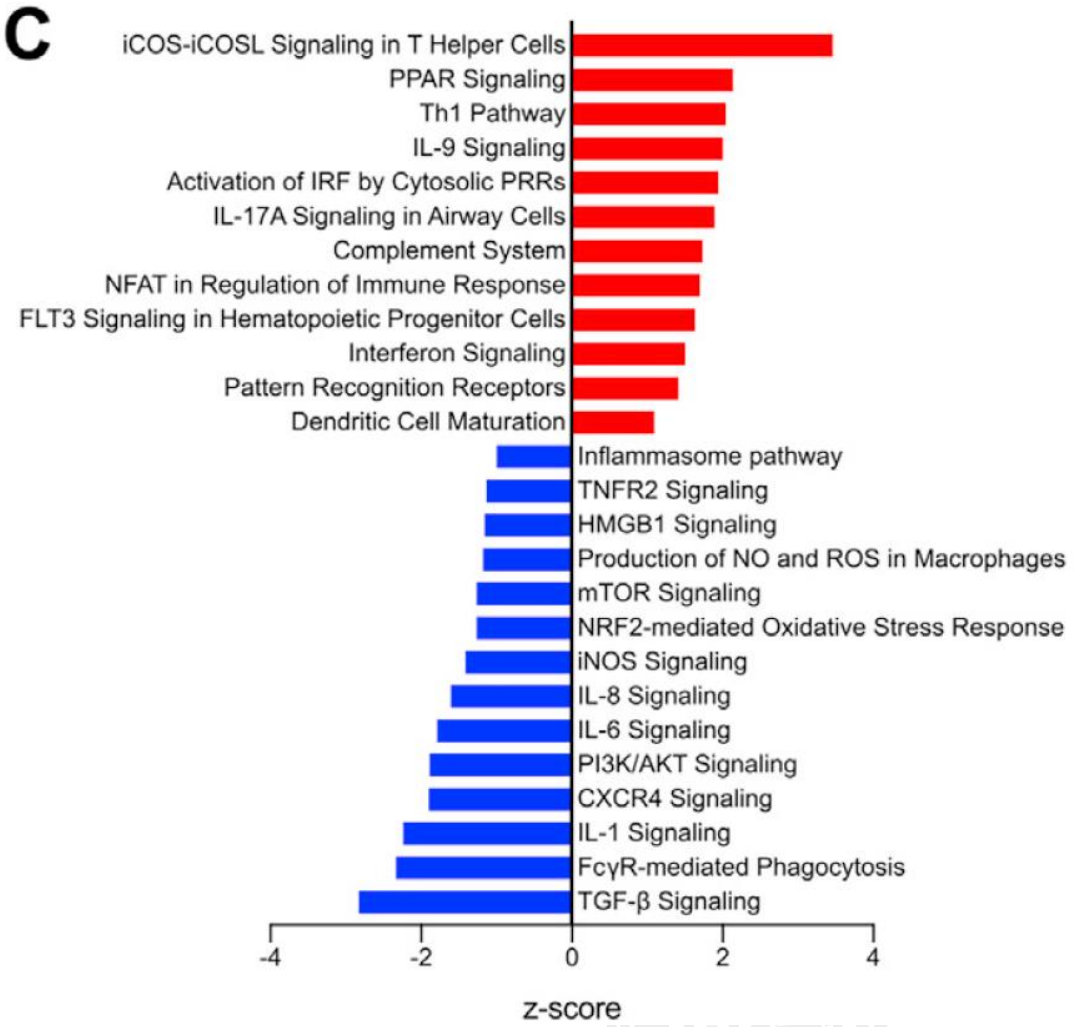
In brief

Genetically engineered myeloid cells expressing IL-12 can reverse the immunosuppressive environment developed during metastatic progression by augmenting T cell responses and reducing metastatic burden in preclinical models.



从IPA中找出的转移前和未转移肺之间**差异表达基因的通路**。



通过IPA找出的IL12-GEMy治疗小鼠中显著**上调和下调的通路**。

文献二

期刊： Cell

影响因子： 41.58

关键词： proteomics, metabolomics, COVID-19, serum, severity

研究对象： COVID-19患者血清46份，正常对照53份

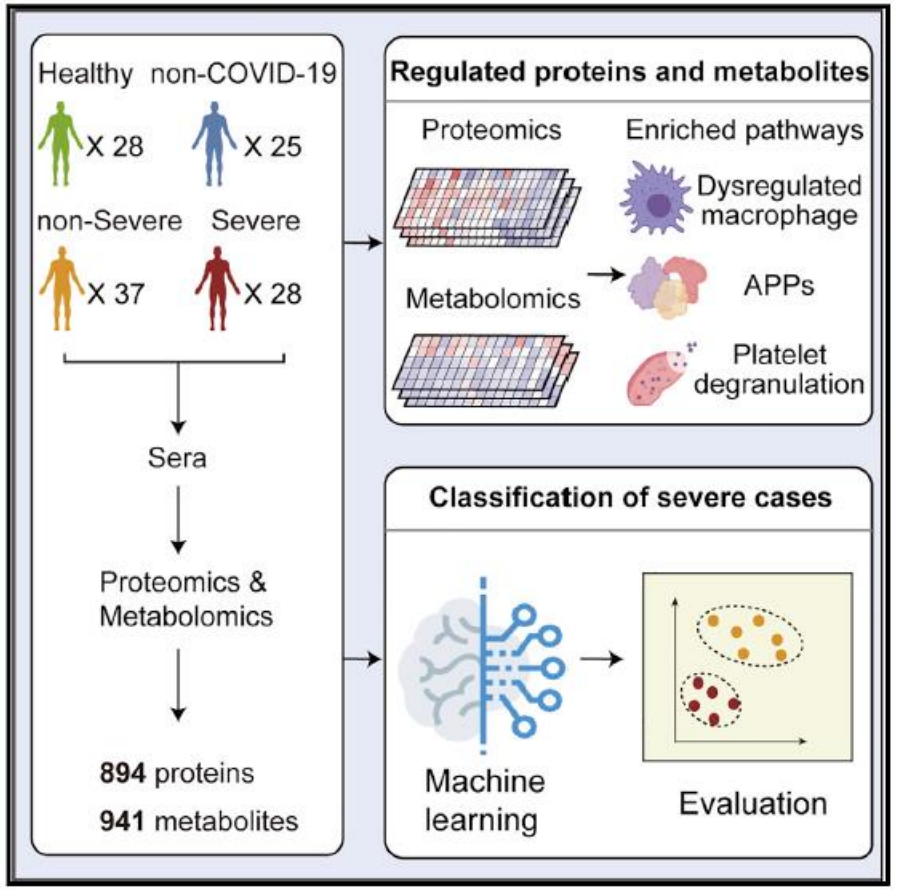
IPA分析： Ingenuity pathway analysis (Kramer et al., 2014) of the regulated proteins identifies most **significantly relevant pathways** with p value of determined based on right-tailed Fisher's Exact Test with the overall activation or inhibition states of enriched pathways were predicted by z-score.

Cell

Article

Proteomic and Metabolomic Characterization of COVID-19 Patient Sera

Graphical Abstract



Authors

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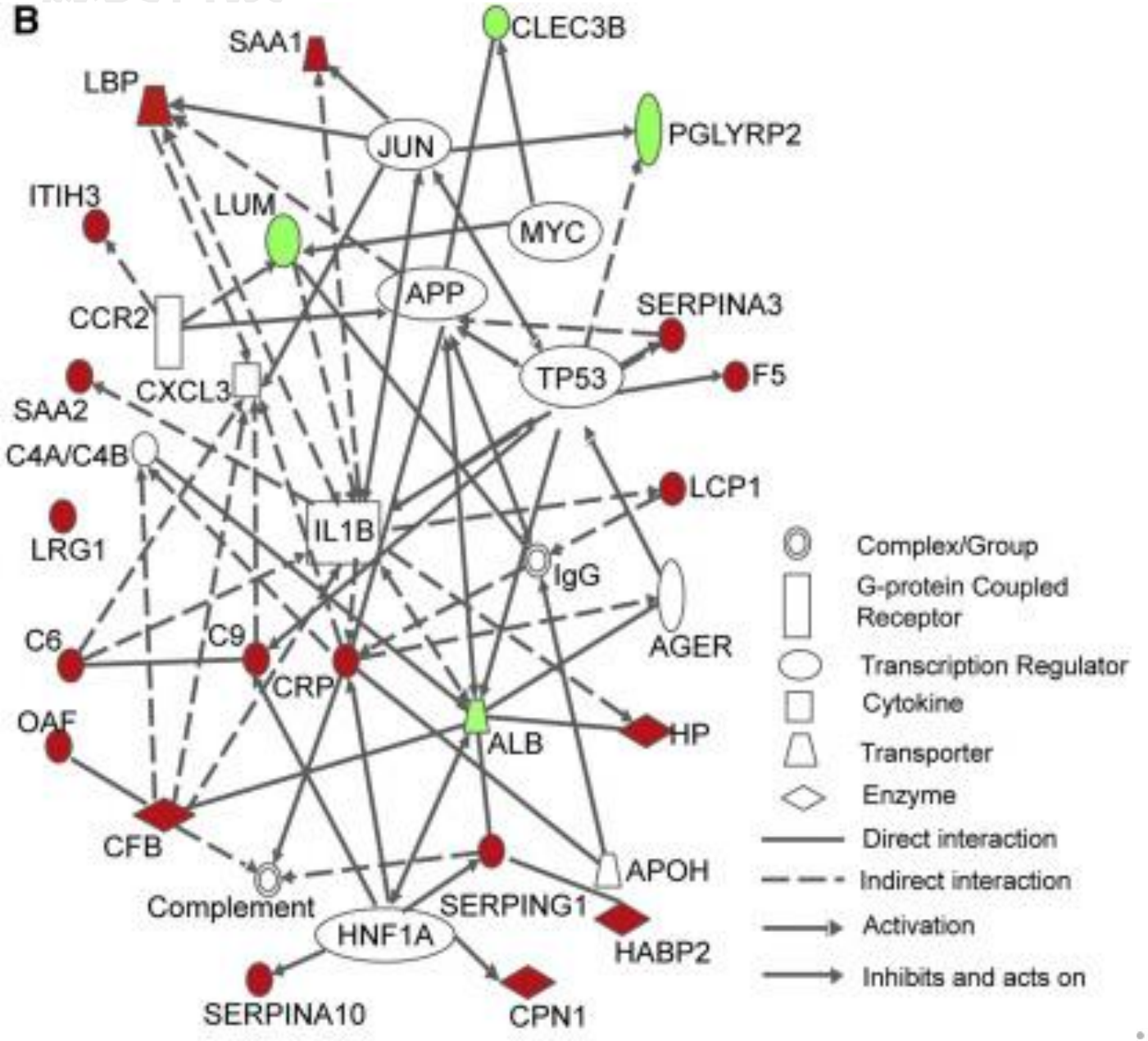
In Brief

Proteomic and metabolomic analysis of COVID-19 sera identifies differentially expressed factors that correlate with disease severity and highlights dysregulation of multiple immune and metabolic components in clinically severe patients.

文献二

研究者基于18名非重症患者和13名重症患者的蛋白质组学和代谢组学数据建立了一个随机森林机器学习模型，从而对29个重要变量进行了排序，包括22个蛋白质和7个代谢物。

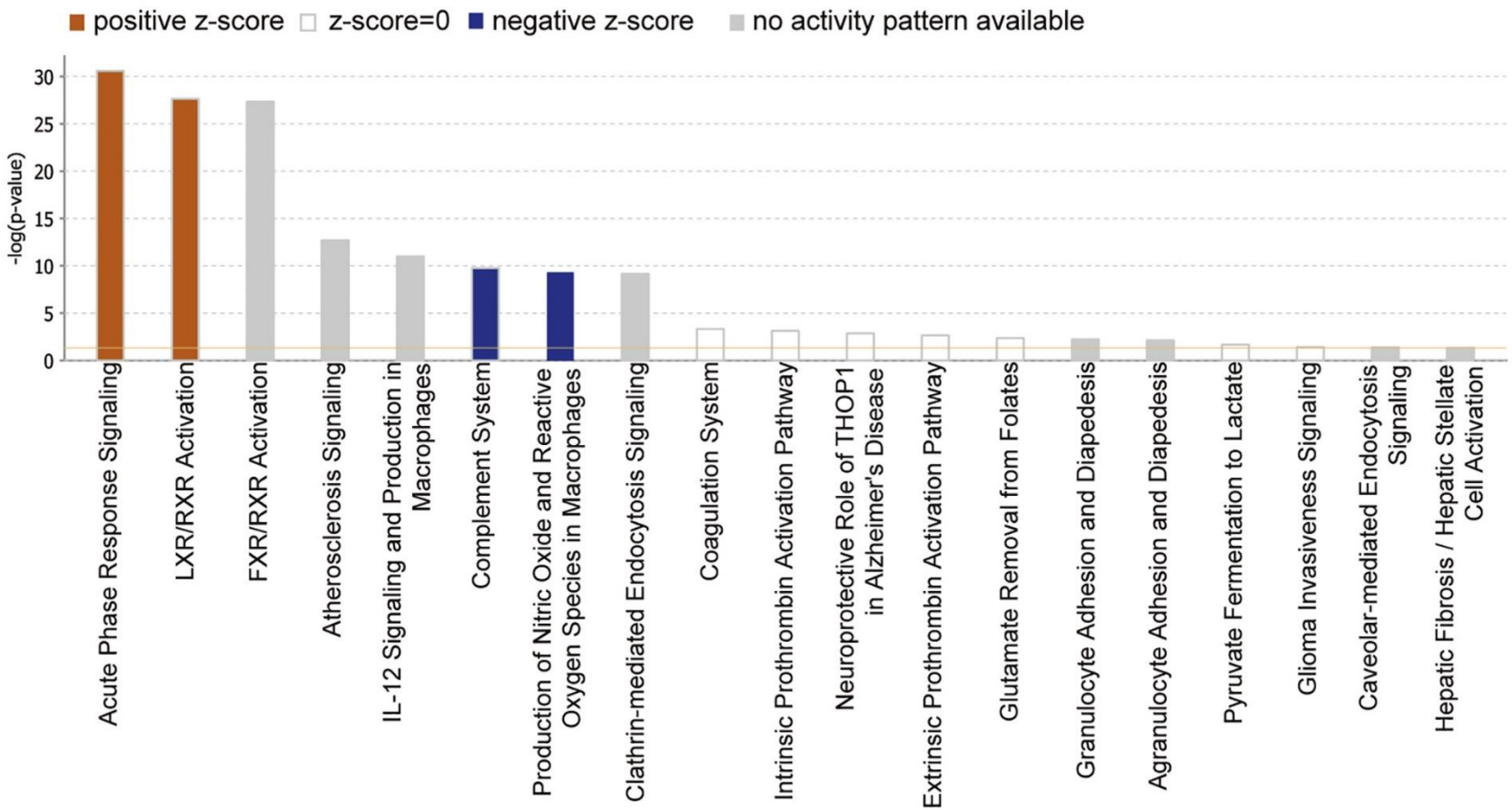
如图为优先的**蛋白质网络**。红色和绿色节点分别表示上调和下调的分子。白色节点表示数据集中未检测到的分子。



文献二

COVID-2019 93种差异表达蛋白的通路分析

IPA预测的最显著相关通路的激活或抑制状态。



文献三

期刊： Cancer Cell

影响因子： 31.74

关键词： tumor microenvironment, cancer-associated fibroblast lineages, pancreatic cancer, CyTOF, tumor-restrictive fibroblast...

目的： 完善成纤维细胞异种细胞关系的功能注释和表征

研究对象： 18个小鼠组织和5个自发性肿瘤模型

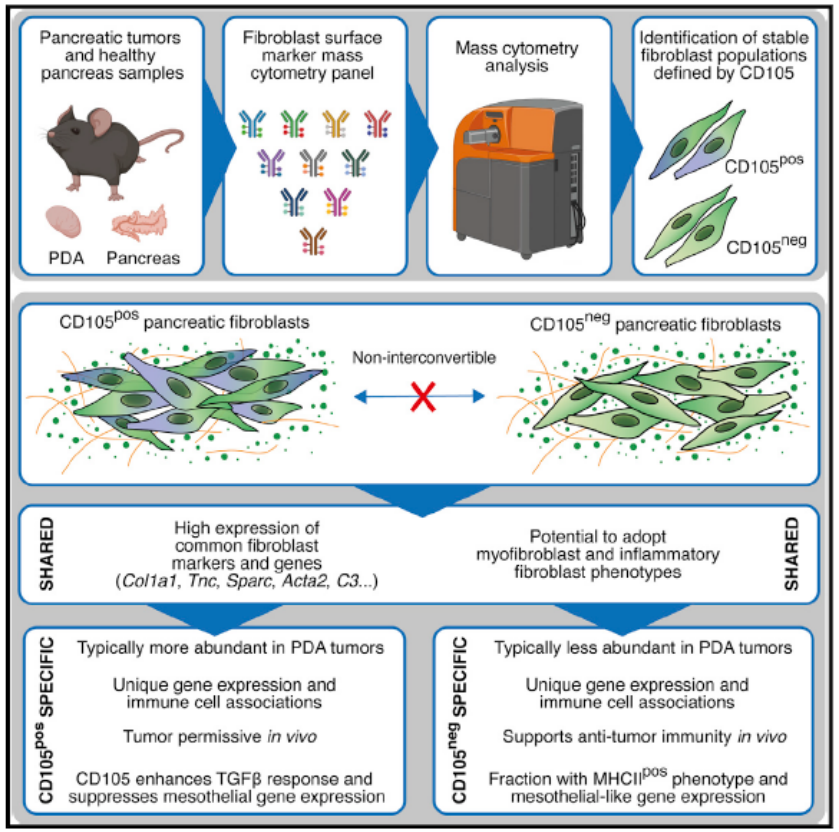
IPA分析： Ingenuity Pathway Analysis (IPA) highlighted several differentially engaged **upstream regulators and pathways**. IPA revealed engagement of pathways and upstream regulators with established roles in productive anti-tumor immune responses.

Article

Cancer Cell

Single-cell analysis defines a pancreatic fibroblast lineage that supports anti-tumor immunity

Graphical abstract



Authors

Colin Hutton, Felix Heider, Adrian Blanco-Gomez, ..., Santiago Zelenay, Jennifer P. Morton, Claus Jørgensen

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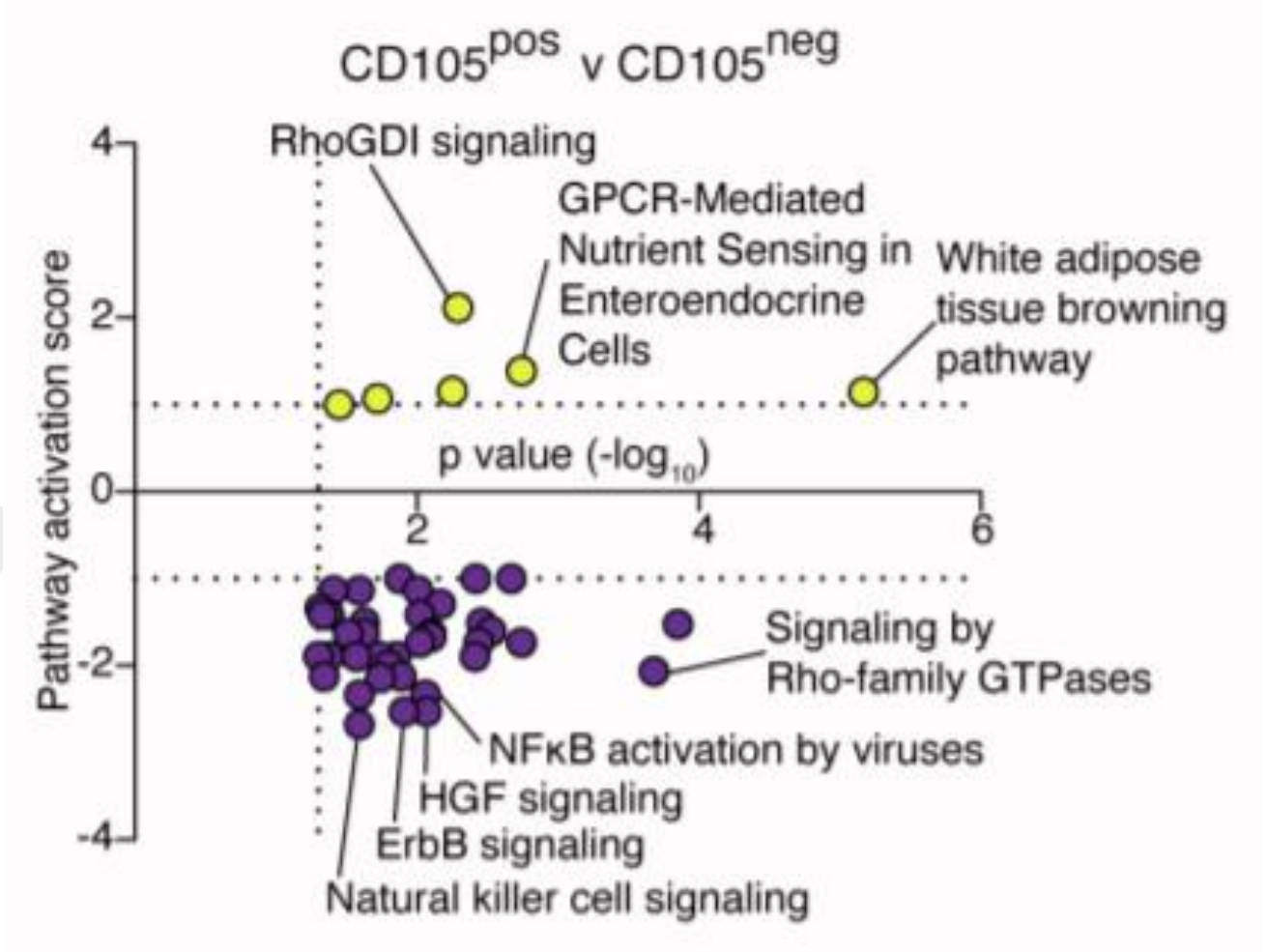
In brief

Hutton et al. use mass cytometry to chart stromal cells and describe mesenchymal states and lineages in pancreatic ductal adenocarcinoma. CD105 (*Eng*) expression distinguishes two pancreatic fibroblast lineages with distinct functions. $CD105^{pos}$ fibroblasts are tumor permissive, whereas $CD105^{neg}$ fibroblasts suppress tumor growth in a manner dependent on adaptive immunity.

文献三

对分离的PDA（胰腺导管腺癌）CAF基因表达进行IPA分析，得到**通路激活评分**。如图为正富集（CD105pos中的富集，黄色）和负富集（CD105neg中的富集，紫色）的图。



文献三

Table S3. Isolation and analysis of CD105pos and CD105neg CAFs, related to Figure 3

IPA Pathway analysis of RNAseq of KPC CD105pos (n=6) and CD105neg CAFs

Ingenuity Canonical	-log(p-value)	z-score	Molecules
RhoGDI Signaling	2'29	2'111	ARHGAP4,ARHGDIB,ARHGEF15,ARHGEF6,CDH2,CDH23,EZR,GNA14,GNG1
GPCR-Mediated Nutrient	2'74	1'387	ADCY2,ADCY7,CACNA1D,CACNA1H,CACNB2,CACNG7,CACNG8,GNA14,GNC
P2Y Purigenic Receptor S	2'25	1'155	ADCY2,ADCY7,CREB3L3,GNG11,ITGA2B,P2RY1,P2RY6,PIK3CB,PIK3R3,PIK
White Adipose Tissue Bro	5'17	1'147	ADCY2,ADCY7,ADRB3,ANGPT2,BMP7,CACNA1D,CACNA1H,CACNB2,CACNG
Adrenomedullin signaling	1'72	1'069	ADCY2,ADCY7,CALCRL,CTH,GNA14,GUCY1A2,GUCY1B1,IL18,KCNH2,KCNC
Role of p14/p19ARF in Tu	1'45	1	CDKN2A,PIK3CB,PIK3R3,PIK3R5
Osteoarthritis Pathway	2'67	-1	ALPL,ANKH,BMP2,CASQ1,COL10A1,CREB3L3,GREM1,IL18RAP,IL1RAPL1,IL

Table S3. Isolation and analysis of CD105pos and CD105neg CAFs, related to Figure 3

IPA upstream regulator analysis of RNAseq of KPC CD105pos (n=6) and CD105neg CAFs

Upstream Regulator	Expr Log Ratio	Molecule Type	Activation z-score	p-value of overlap	-log10pvalue	Target Molecules in Dataset	Mechanistic Network
Bvht		other	2'496	0'000043	4'366531544	ALDH1A3,ALX4,CYGB,EBF1,FO	
Tgf beta		group	2'449	0'002	2'698970004	CCL11,CSF3,CXCL3,IL10,IL16,M64 (5)	
C3AR1		G-protein coupled receptor	2'385	0'00538	2'269217724	C5,CD40,CD80,CSF3,IL10,LTBF	
TP53		transcription regulator	2'308	0'0168	1'774690718	Abcb1b,ABCB4,ACE,ADRB3,AH(	
EBF2	1'834	transcription regulator	2'236	0'00308	2'511449283	DIO2,ENTPD2,MEOX1,QPRT,RI	
DMD	1'114	other	2'176	0'00128	2'89279003	CASQ1,Cmah,COL23A1,DMD,G	

Table S6. In vivo analysis, related to Figure 6

IPA canonical pathway analysis of bulk RNAseq of co-transplantd tumours

Ingenuity Canonical Pathways	-log(p-value)	Ratio	z-score	Molecules
PD-1, PD-L1 cancer immunotherapy pathway	4'69	0'0645	2'449	HLA-DMA,HLA-DMB,HLA-DQB1,IL2RB,LCK,ZAP70
Fcγ Receptor-mediated Phagocytosis in Macropha	2'64	0'0435	-2	FCGR3A/FCGR3B,FYB1,PLD4,RAC2
IL-15 Production	2'29	0'0348	-2	CSF1R,LCK,MERTK,ZAP70
Th1 Pathway	3'31	0'0463	-2'236	CD3D,HLA-DMA,HLA-DMB,HLA-DQB1,TBX21
Dendritic Cell Maturation	2'55	0'0312	-2'236	FCGR3A/FCGR3B,HLA-DMA,HLA-DMB,HLA-DQB1,TREM2
Natural Killer Cell Signaling	2'46	0'0298	-2'236	FCGR3A/FCGR3B,IL2RB,LCK,RAC2,ZAP70

IPA upstram regulators analysis of bulk RNAseq of co-transplantd tumours

Upstream Regulator	Molecule Type	Activation z-score	p-value of overlap	-log10p-value	Target Molecules in Dataset
IL10RA	transmembrane rece	2'891	0'0000404	4'393618635	CALHM6,CLEC12A,CYFIP2,CYP2S1,ECM1,ERO1A,GHR,HGFAC,Ly6a (includes others),Serpina
PIK3CG	kinase	2'449	0'000228	3'642065153	AIF1,CTSW,FCGR3A/FCGR3B,IL2RB,LCK,SOX9
RHO	G-protein coupled re	2'236	0'000231	3'63638802	C1QA,CD74,CSF1R,NCAM1,NT5E
NCSTN	peptidase	2'219	0'0000173	4'761953897	CSF1R,CSF2RB,GRN,Ly6a (includes others),SPI1
ATF4	transcription regulato	2'2	0'00111	2'954677021	ERO1A,NDRG1,NUPR1,PRRX2,TNFRSF12A,VEGFA

文献四

期刊： Cancer Cell

影响因子： 31.74

关键词： rectal cancer, neoadjuvant therapy, cancer-associated fibroblasts, IL-1 signalling, senescence, IL1RN SNP

目的： 探索炎症成纤维细胞介导直肠癌对新辅助治疗的耐药性

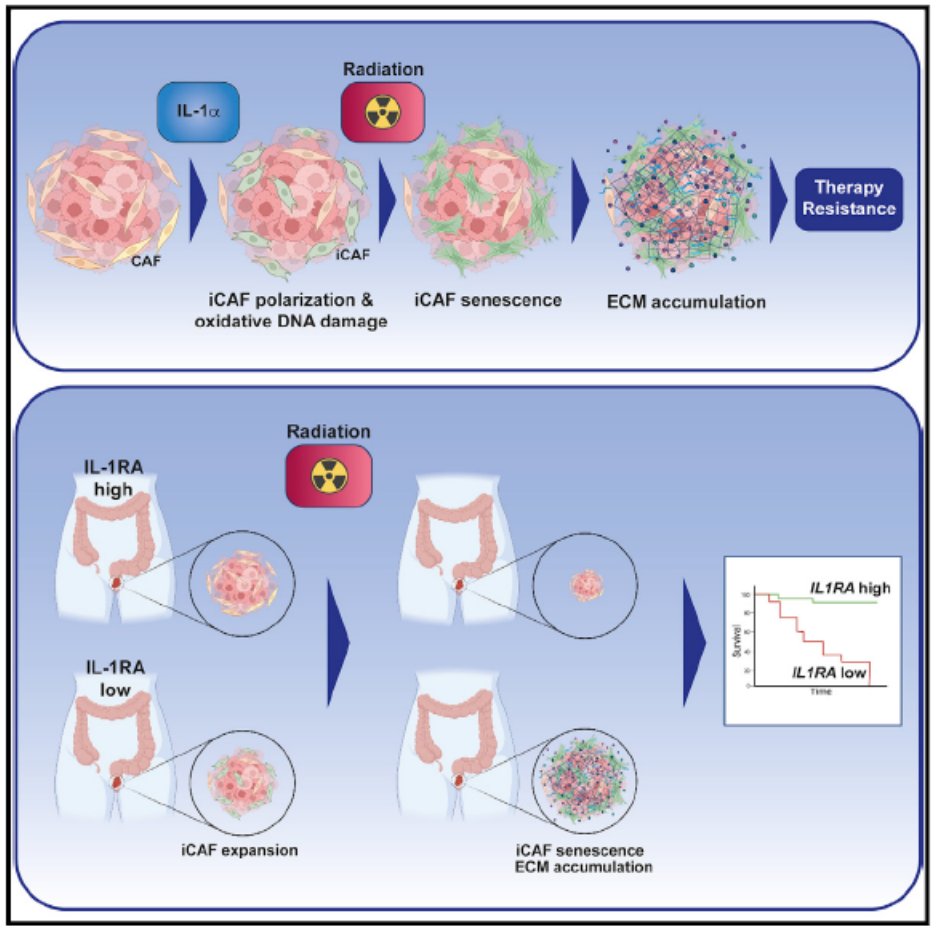
IPA分析： Analyses of each cluster **signature upstream regulators** and generation of mechanistic **network** maps were performed using ingenuity pathway analysis software

Cancer Cell

Article

Inflammatory fibroblasts mediate resistance to neoadjuvant therapy in rectal cancer

Graphical abstract



Authors

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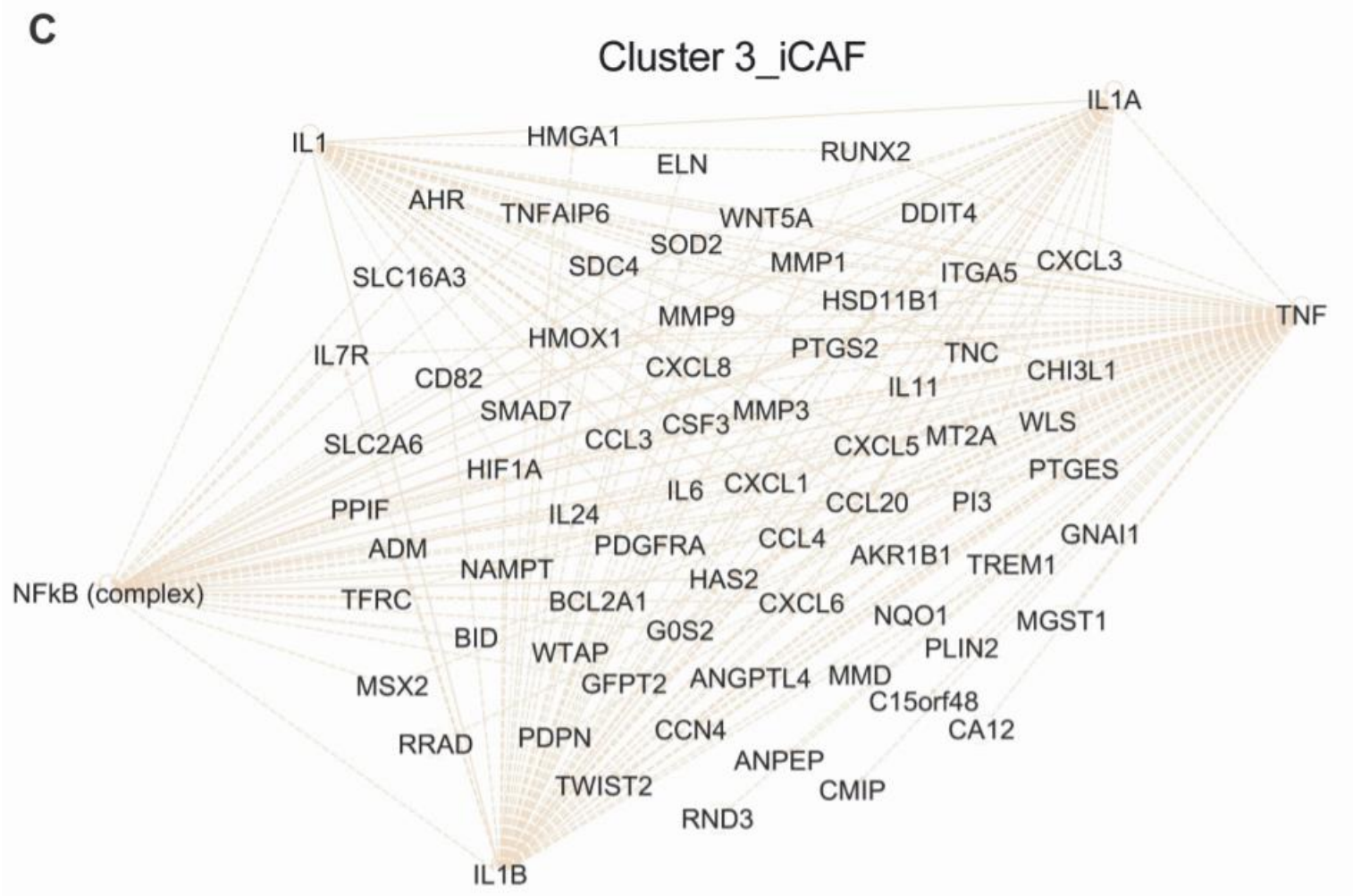
In brief

Nicolas et al. highlight the important role of inflammatory cancer-associated fibroblasts (iCAFs) for therapy response of rectal cancer patients. They demonstrate that IL-1-dependent signaling elevates oxidative DNA damage in iCAFs, which upon irradiation undergo senescence. This causes tissue remodeling and therapy resistance that can be overcome by inhibiting IL-1.

文献四

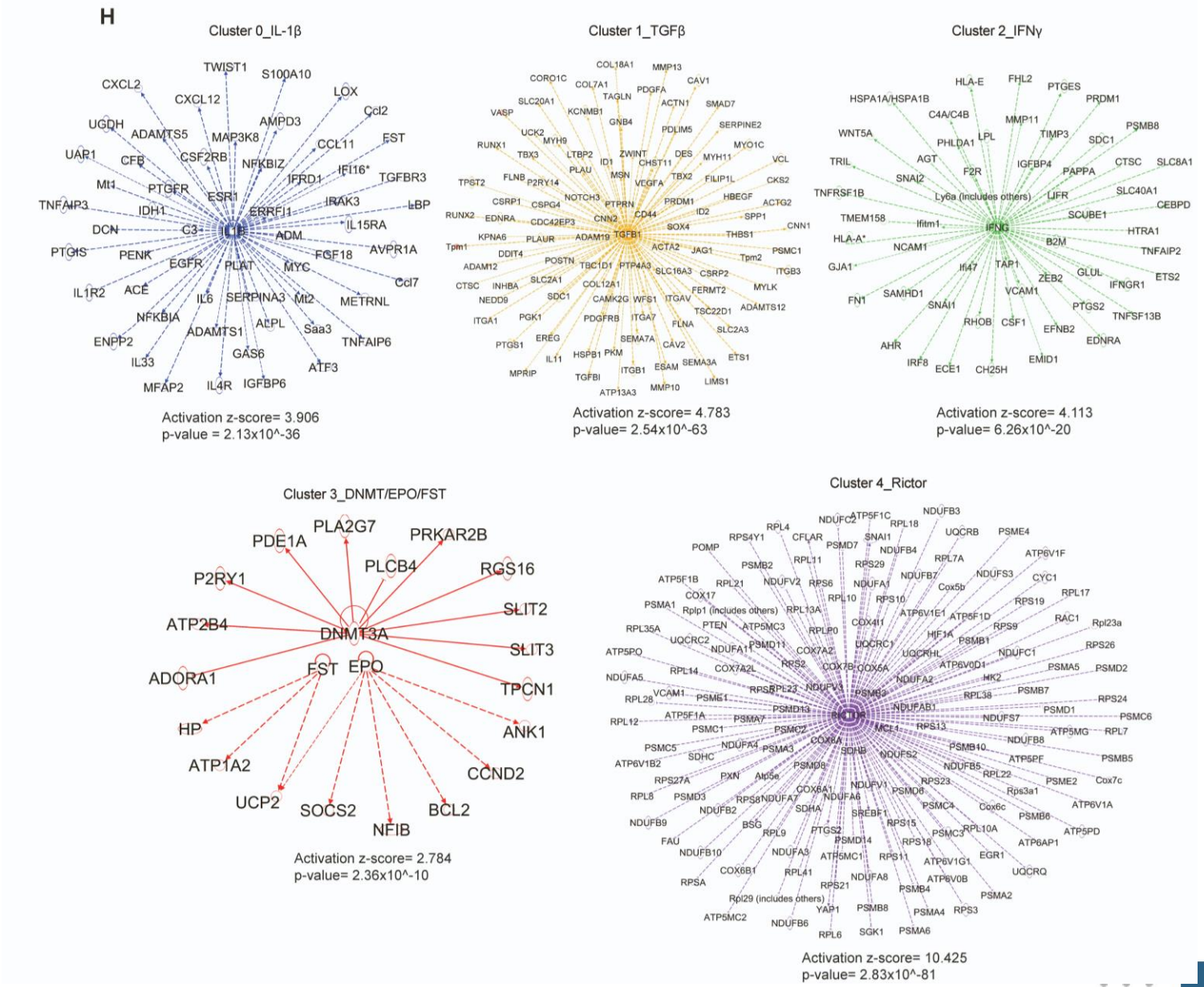
炎症性CAF Cluster C3的**机制网络图**，预测**上游调节因子**及其**差异表达基因的变化**(Log2FoldChange ⩾ 1，adjusted p-value threshold为0.05)。TNF、IL-1β、IL-1α、IL-1和NFκB激活z-score分别为：6.178、6.047、4.617、4.575和4.506。 p-value <0.0001。



文献四

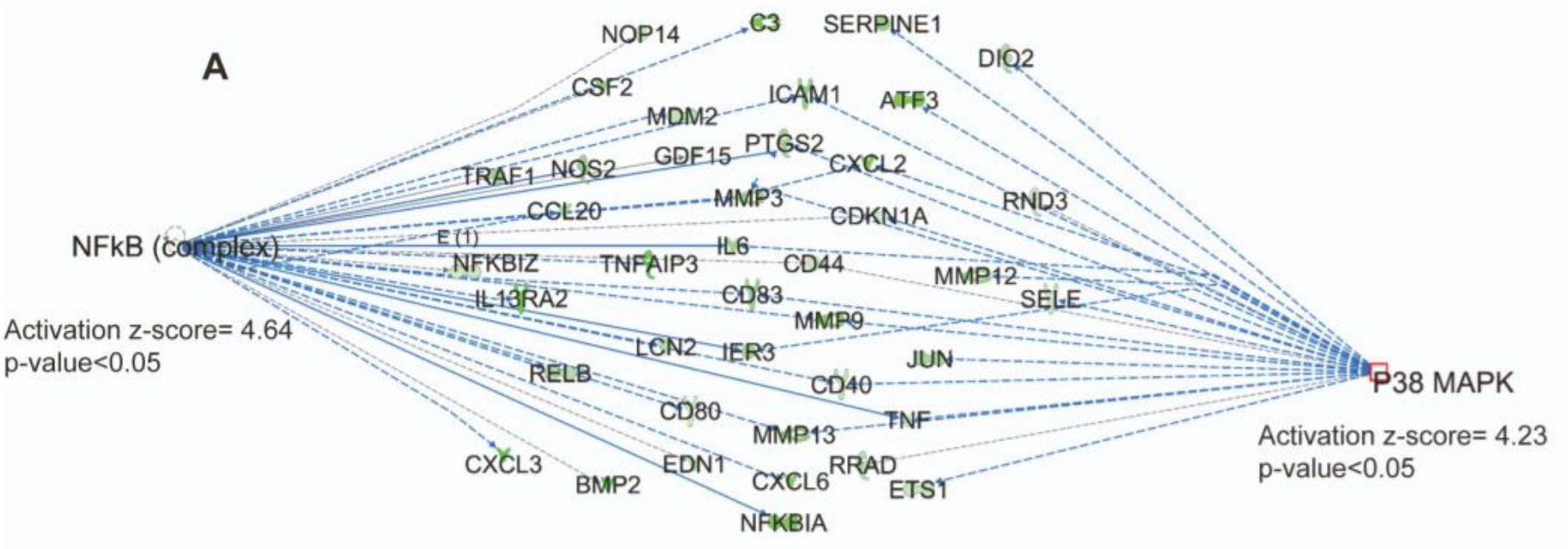
直肠癌原位肿瘤类器官小鼠模型中的CAF分子异质性

Cluster 0_IL-1β、 Cluster 1_TGFβ、 Cluster 2_IFNɣ和Cluster 3_DNMT/EPO/FST中CAF**上游调节因子**及其相关差异**上调基因**的机制网络图，以及Cluster 4_Rictor CAF**上游调节因子**及其相关的显著**下调基因**。单细胞测序数据代表了从APTKA原位肿瘤（n=4只小鼠）中分离的624个CAF，通过IPA软件进行分析。激活z-score>2，p-value of overlap<0.0001。



IPA表明NF-B和p38激活是负责炎症基因表达谱的主要信号通路

如图为APTKA条件培养基处理的成纤维细胞上游调节因子及其差异表达基因的**机制网络图**（Log2FoldChange≥ 1，adjusted p-value threshold为0.05）。NF-κB和p38激活z-score分别为4.64和4.23。p-value of overlap<0.05。

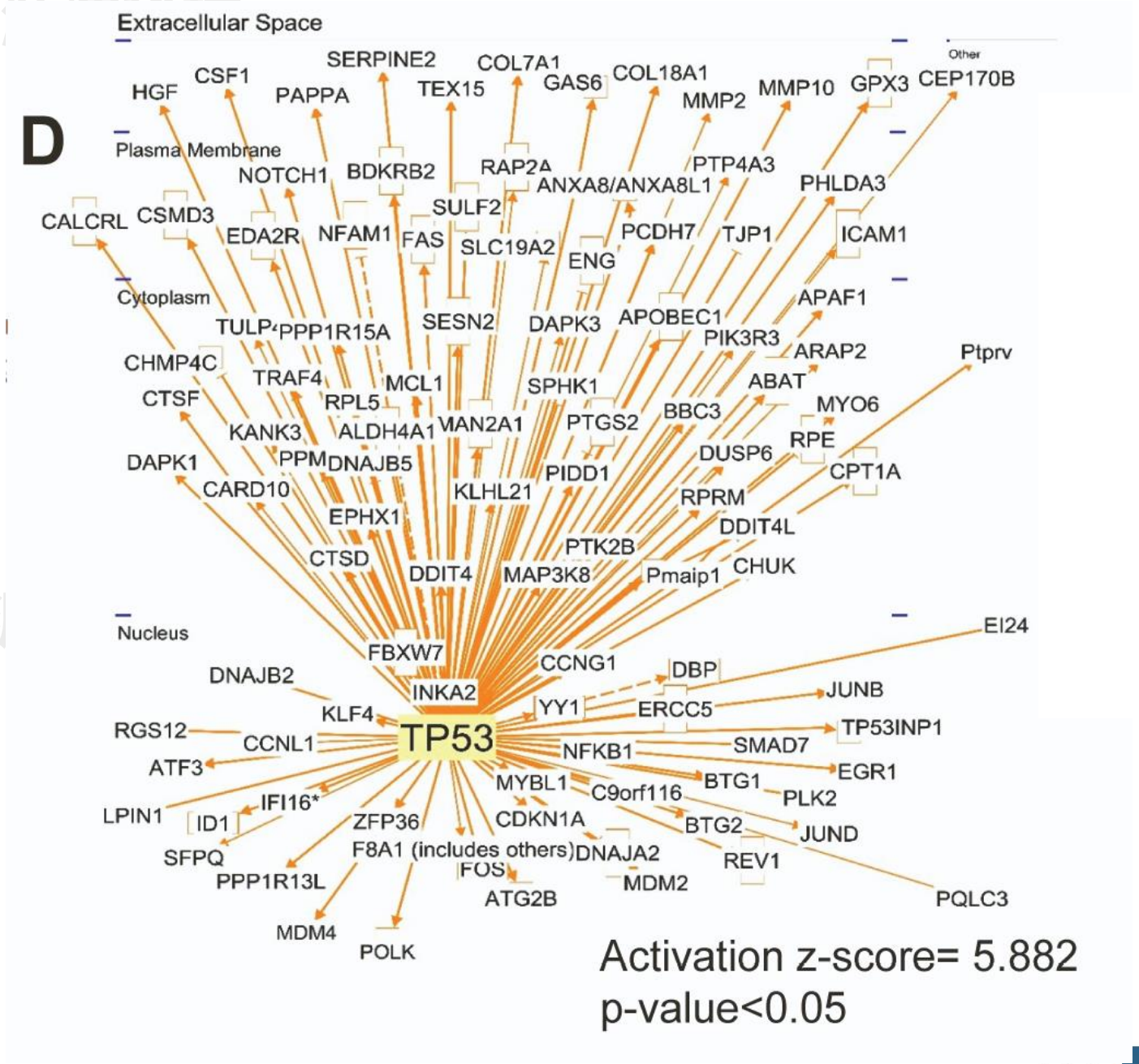


文献四

p53信号网络图

辐照后APTKA成纤维细胞及其差异表达基因的**上游调节因子**（adjusted p-value threshold为0.05）。

IPA表明，我们在matrisome分析中发现的许多诱导基因，包括编码各种分泌因子（细胞外蛋白：胶原蛋白、蛋白多糖、生长因子、ECM调节因子、ECM相关蛋白）的基因，以及细胞周期抑制剂Cdkn1a，均以p53依赖的方式调节。



文献五

Inherent hepatocytic heterogeneity determines expression and retention of edited *F9* alleles post-AAV/CRISPR infusion

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影响因子： 11

关键词： gene therapy, hemophilia B, AAV/CRISPR, liver immunity

目的： 探索AAV/CRISPR介导肝脏基因编辑的应用范围、潜在机制和潜在局限性

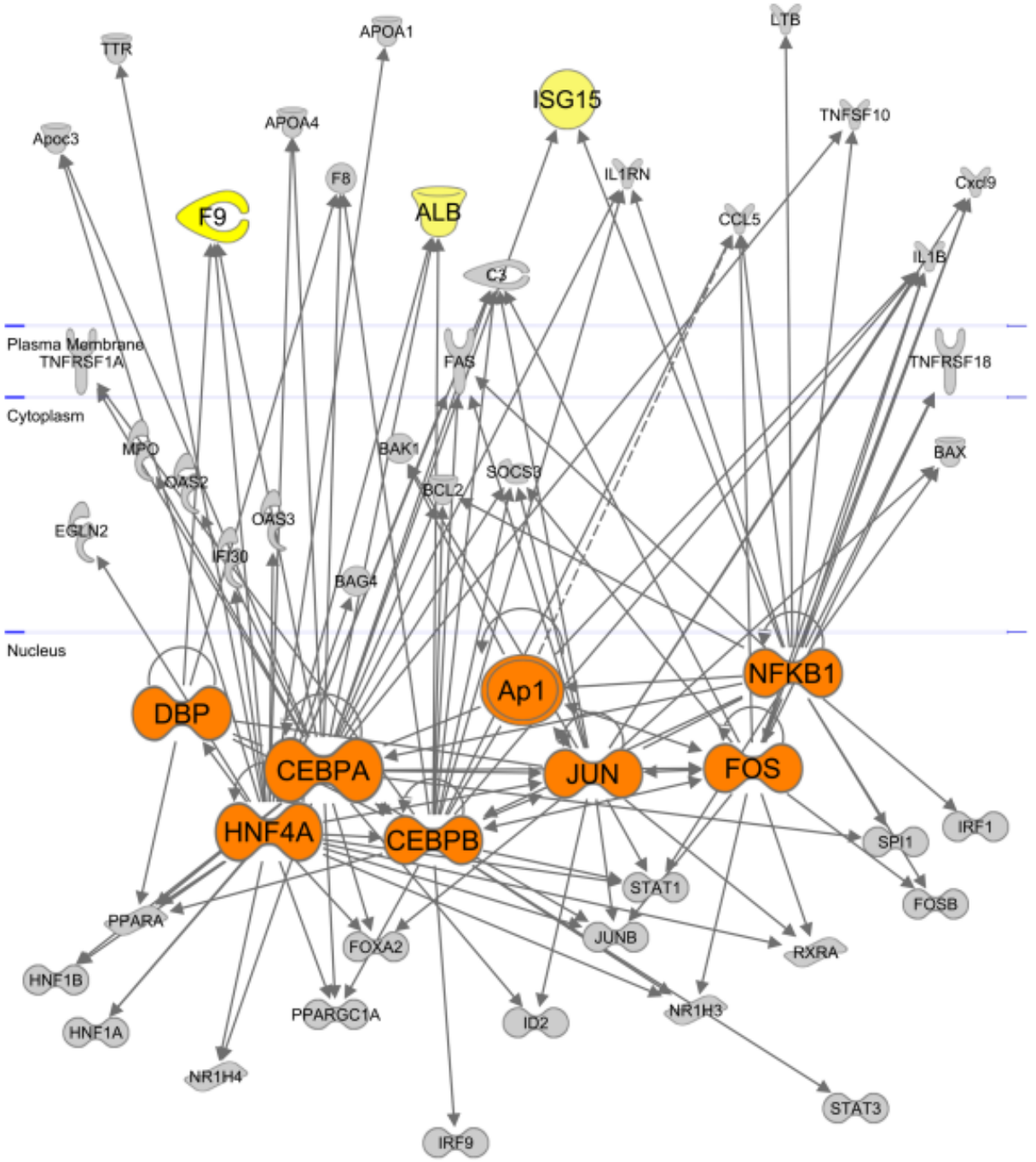
研究对象： C57BL/6背景的HB小鼠（因子IX启动子和外显子1至3敲除[F9-KO]）

IPA分析： IPA analysis was used to **determine pathways** or **gene networks** that may be altered across clusters based on scRNA-seq results. Via Qiagen Digital Insights (https://www.qiagenbioinformatics.com), we uploaded each cluster marker gene to IPA, and used the "**core analysis**" function to analyze **upstream transcriptional regulators and gene networks**.

文献五

发现：炎症信号通过调节离散的LETF（肝脏富集转录因子），以肝细胞亚群依赖的方式，调节P2驱动的F9表达

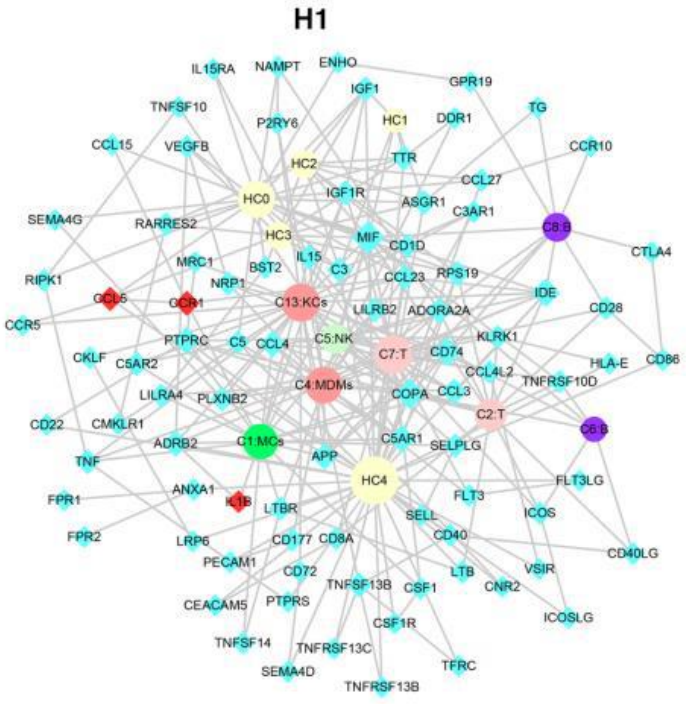
IPA图中显示了Alb派生的P2序列中专门针对I类LEFT和II类LEFT的大量响应元素的分布。

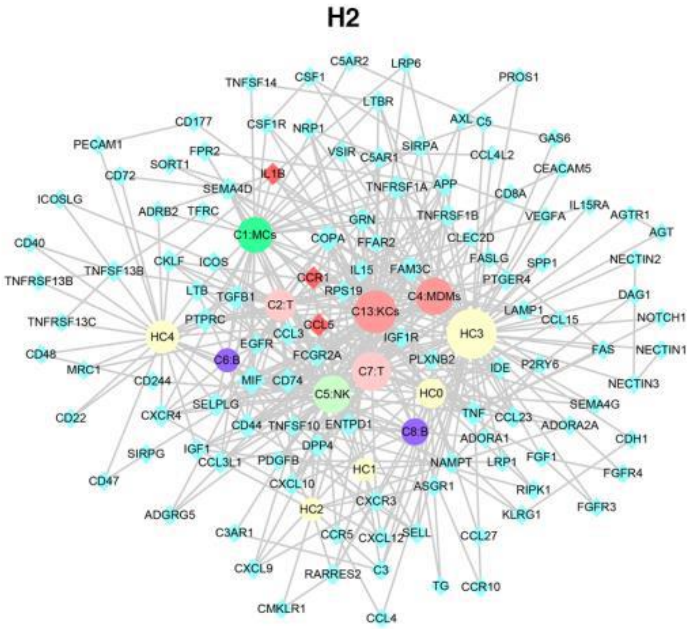


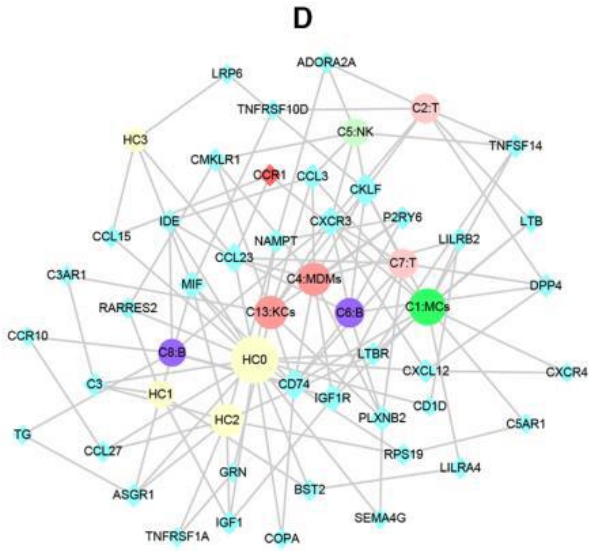
文献五

各种类型的免疫细胞和炎症因子之间相互作用的特征

IPA图中显示了在H1（injected with PBS）、H2（dual AAVs without DXM treatment）和D（dual AAVs treated with DXM）条件下，主要免疫细胞和肝细胞亚群之间的细胞因子**通讯网络**所构成的肝脏炎症簇。





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