Clarivate Cortellis™

VtR INC 法德利科技

# Clarivate MetaCore/MetaDrug在癌症和藥物相關研究

賴亦溱(Irene Lai) 產品經理

法德利科技股份有限公司

# Agenda

- 法德利科技及科睿唯安簡介
- MetaCore & MetaDrug介紹
- 案例分享
- 總結及Q&A

VtR INC 法德利科技

# 法德利：專注於產業數位轉型的專業團隊

Harnessing the Power of
Virtual Technology to
transform the
Real World!

SIMULATION - INNOVATION - QUALITY - COMPLIANCE - INTELLIGENCE

# 法德利 資訊產品

標的選定與確認
模型建構與模擬

新配方新製程之發現、
尋找、設計、與優化

毒性與安全
性試驗

製程放大與優
化

前臨床與臨床試驗
品管品保測試

製造、商品化、
銷售、與市場情
報

## 效率與合規

- 工作流程設計、協力廠商工具整合、客製化功能開發 (Dassault Systèmes 3DEXPERIENCE, BIOVIA Foundation, Pipeline Pilot)
- 合規、品質、與文檔管理系統：含文件、教育訓練、偏差、矯正預防、變更管制等管理 (Sparta Systems TrackWise; QUMAS EDMS & EQMS; Navitas pharmaREADY DMS; EXTEDO eDOCSmanager)
- 合規電子文件提交系統 (EXTEDO eCTDmanager; Navitas pharmaREADY; Certara Pinnacle 21E, PK Submit)
- 實驗室資訊管理系統：含庫存、樣品規格、儀器調校、安定性測試、環境監控等管理 (BIOVIA Inventory, Samples, EM, CISPro, Instrument, Task Plan)
- 電子實驗記錄簿 (BIOVIA Workbook & Notebook)
- 實驗執行系統 (BIOVIA Compose & Capture)
- 發展與製造資料之分析研判 (BIOVIA Discoverant; Tableau BI)

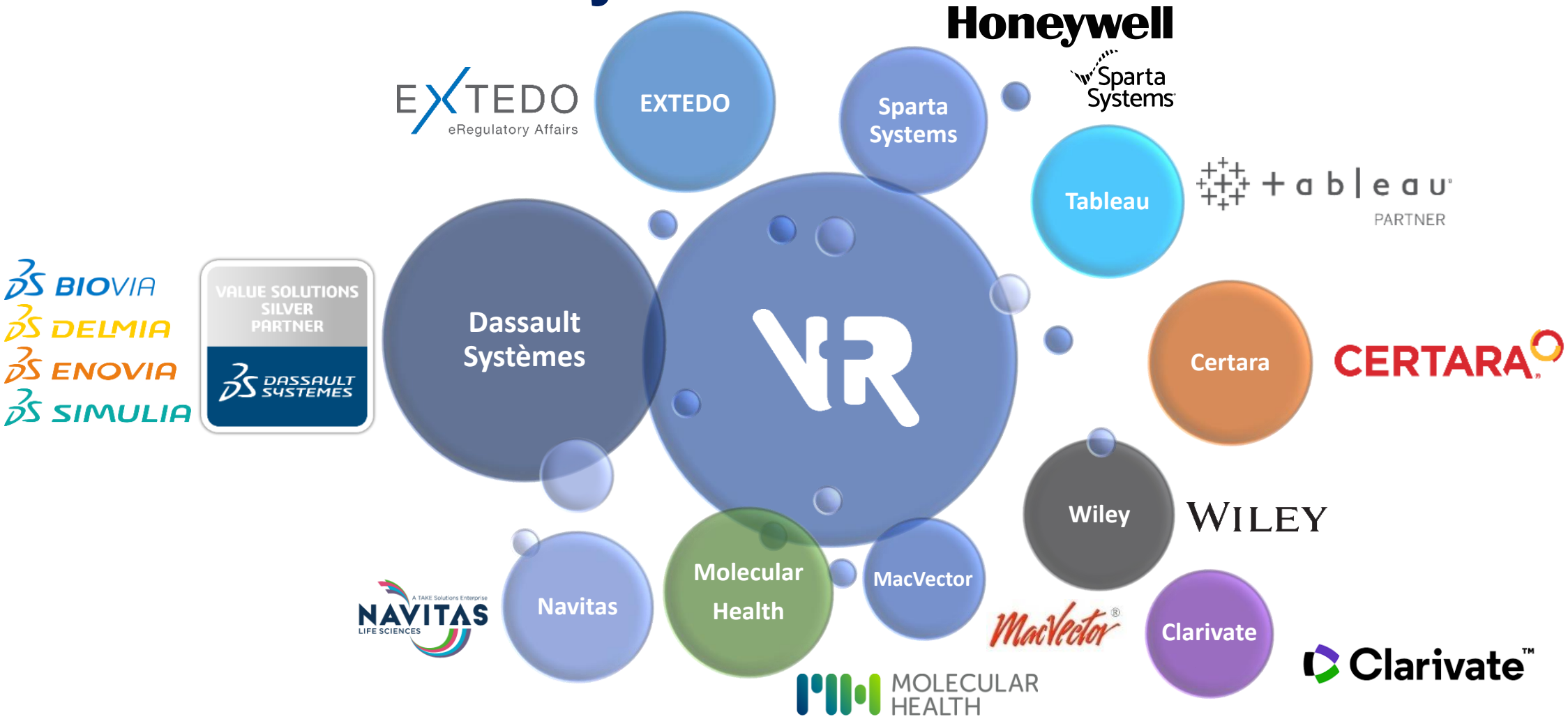
## 創新與研發

- 化合物合成設計 (BIOVIA MS)
- 材料設計與模擬 (BIOVIA MS)
- 智慧製造與運營與管理系統 (DELMIA Apriso MOM)
- 小分子與大分子新藥開發設計 (BIOVIA DS)
- 代謝、活性、與毒性分析 (BIOVIA DS)
- 藥代、藥動分析 (BIOVIA DS, Certara Phoenix, WinNonlin, NLME)
- 生物序列資料分析 (BIOVIA PP; MacVector)
- 動態3D人體數位心臟模型 (Dassault Systèmes Living Heart Project)
- 基因體學、蛋白質體學、及系統生物學 (BIOVIA DS & PP; Cortellis MetaCore/MetaDrug)
- 生命科學建模與模擬 (BIOVIA DS)
- 高速高通量藥物篩選 (BIOVIA DS)
- 全方位電磁模擬 (SIMULIA CST)

## 資料與知識

- 生物實體與化學物質註冊系統 (BIOVIA Registration)
- 基因健康診斷系統 (Molecular Health MH Guide, MH Guide BRCA)
- 化學物質分析與管理系統 (BIOVIA Insight, CISPro)
- 藥品安全警戒與監控 (EXTEDO SafetyEasy PV; Navitas safetyREADY)
- 化合物資料庫 (BIOVIA ACD, SCD)
- 臨床試驗設計及結果預測、分析、與管理 (Medidata; Certara Simcyp, Trial Simulator)
- 最新產業全方位數據及情報收集、整理、分析、報告 (Clarivate WebOfScience, Cortellis, Derwent Innovation, Medtech 360)
- 精準醫療與臨床醫學資料倉儲、人工智慧、與大數據應用 (Dassault Systèmes 3DEXPERIENCE, BIOVIA PP; Wiley Current Protocol; Tableau; Certara D360)

# VtR Partner Ecosystem 2023



# 科睿唯安是專業研發及市場情報的提供者，專業傳承超過150年

**1864**
倫敦動物學會及英國博物館建立用於動物學記錄的動物生物學資料庫

**1926**
細菌學家及植物學會創建BIOSIS生物學資料庫

**1955**
尤金•加菲爾德博士發明了引文索引和引文檢索

**1957**
美國科學資訊研究所（ISI）成立

**1963**
專利家族之父Monty Hyams開始製作發行Derwent專利摘要

**1986**
商標檢索公司Thomson & Thomson 及CompuMark加入

**1997**
Web of Science正式發佈

**2003**
Techstreet加入

**2011**
Cortellis正式發佈

**2012**
功能變數名稱與品牌保護服務商MarkMonitor 加入

**2016**
原湯森路透智慧財產權與科技業務出售，正式成立科睿唯安公司並在全球獨立運營

Clarivate Analytics

**2017**
全球同行评议Publons 加入

publons

**2018**
Kopernio 和TrademarkVision加入

Kopernio

TrademarkVision

**2019**
科睿唯安与Churchill资本合并，在纽约交易所上市

**2020**
CPA Global 加入

CPA GLOBAL

**2020**
DRG 加入

DRG Part of Clarivate

**2020**
合享智慧(IncoPat) 加入

incoPat

# 相互連結創造更大價值

## 我們了解您的需求並提供容易上手的產品及整體解決方案

**科學研究概覽**
最新研究概況及全球研究網路、專家人員及研究機構

**臨床試驗**
基於全球臨床及整合數據分析，做出明智的臨床試驗決策

**監管法規情報**
熟習全球法規況，提升上市申請核准率並成功進入全球市場

**進階分析釋出洞見**
解鎖數據間隱藏的產業見解，對可見的未來有更深的瞭解及做出信心決策

**醫療器材及數位醫療**
納入專家意見，獲取業界最全面的市場數據加速創新工作

**市場准入、權限及價值**
制定全球發展戰略，最大化售價、市場准入及保險支付

**早期發現及臨床前**
運用生物學、化學及藥理學數據，成功定位研究並避免後期失敗

**產品組合策略**
基於全球藥物研發及交易情報，趨動併購、戰略合作、產品組合選擇等經營策略

**深入市場**
優化業務拓展及行銷策略提昇整體商業績效，並在快速發展的市場中保持領先地位

# 藥物早期開發金三角

## 藥物早期研發情報 (CDDI)

- CDDI 一站收集14大類臨床前試驗數據與情報 。
- 資料來源豐富，絕非一般免費資料庫可以比擬
- 內容皆經由專家驗證、整理

## 藥物活性預測 (MetaDrug)

- 針對靶點的藥物活性預測
- 化合物代謝網絡建構與代謝體學分析
- 藥物化合物與疾病關聯性

## 藥物靶點分子路徑分析(MetaCore)

- 深度知識挖掘及檢索
- 靶點與生物標記的識別與驗證
- 交互作用機制與研究假設建構

Clarivate™

# What Is MetaCore?

# MetaCore Can Help

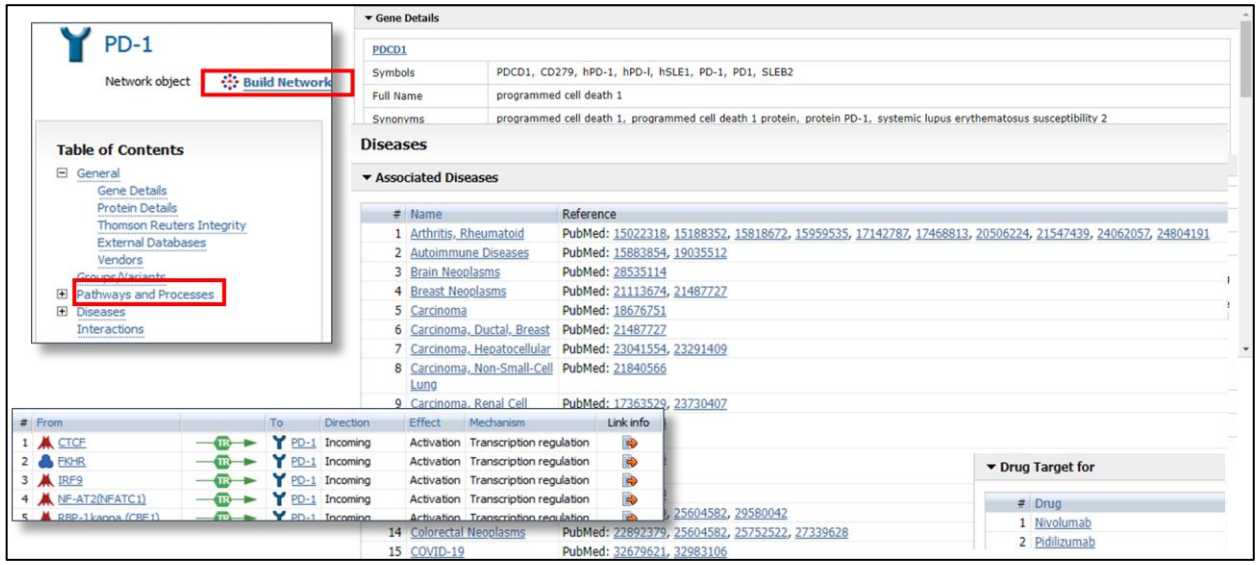
## After enter keyword or upload data, it would find out

① Deep information mining

② Pathway Map

③ Build Network

❶

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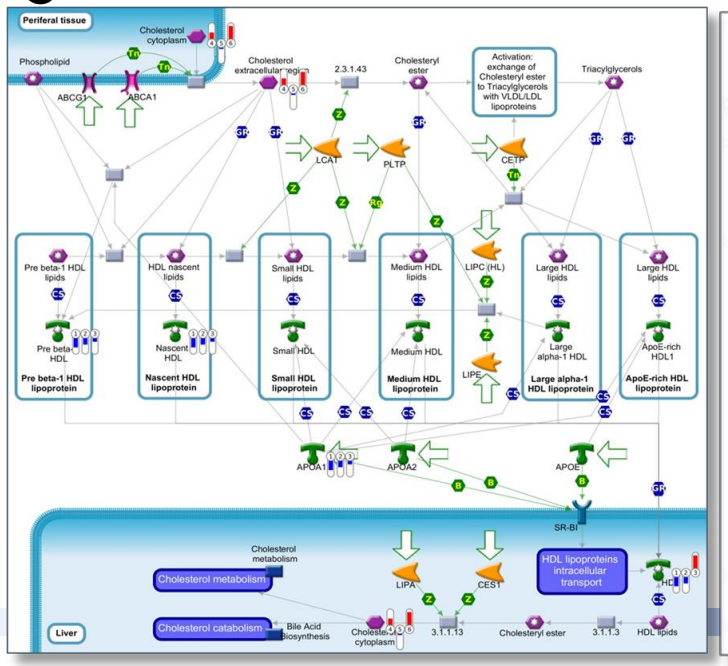


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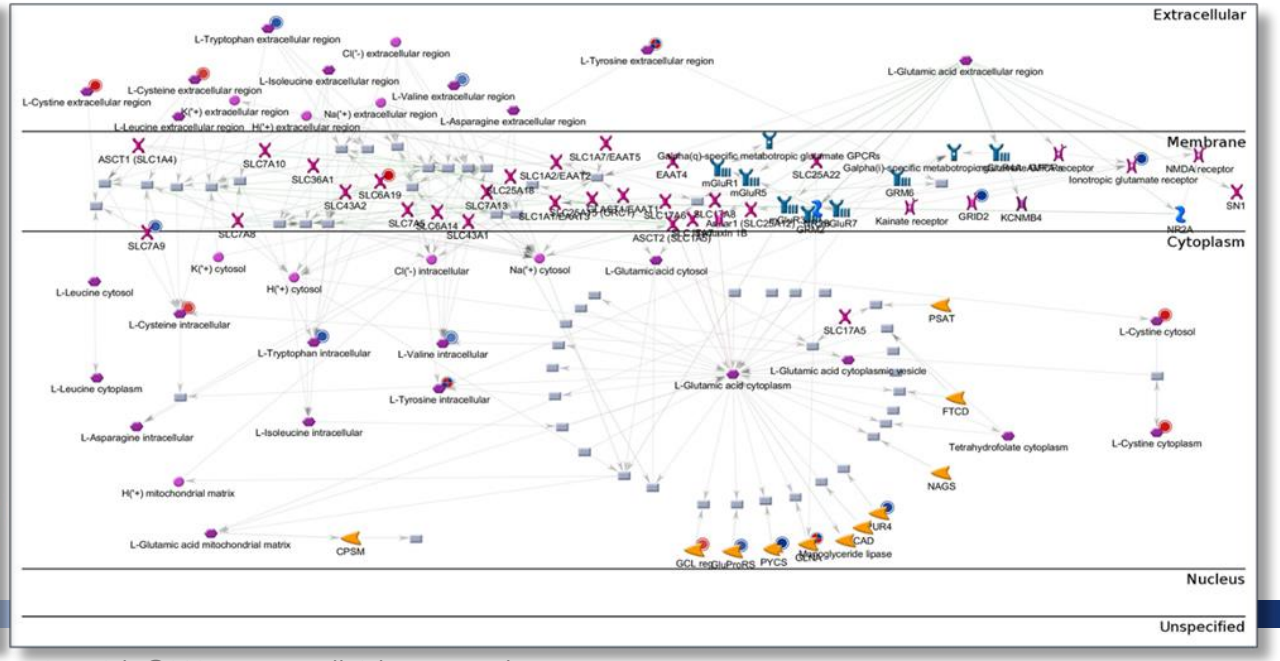
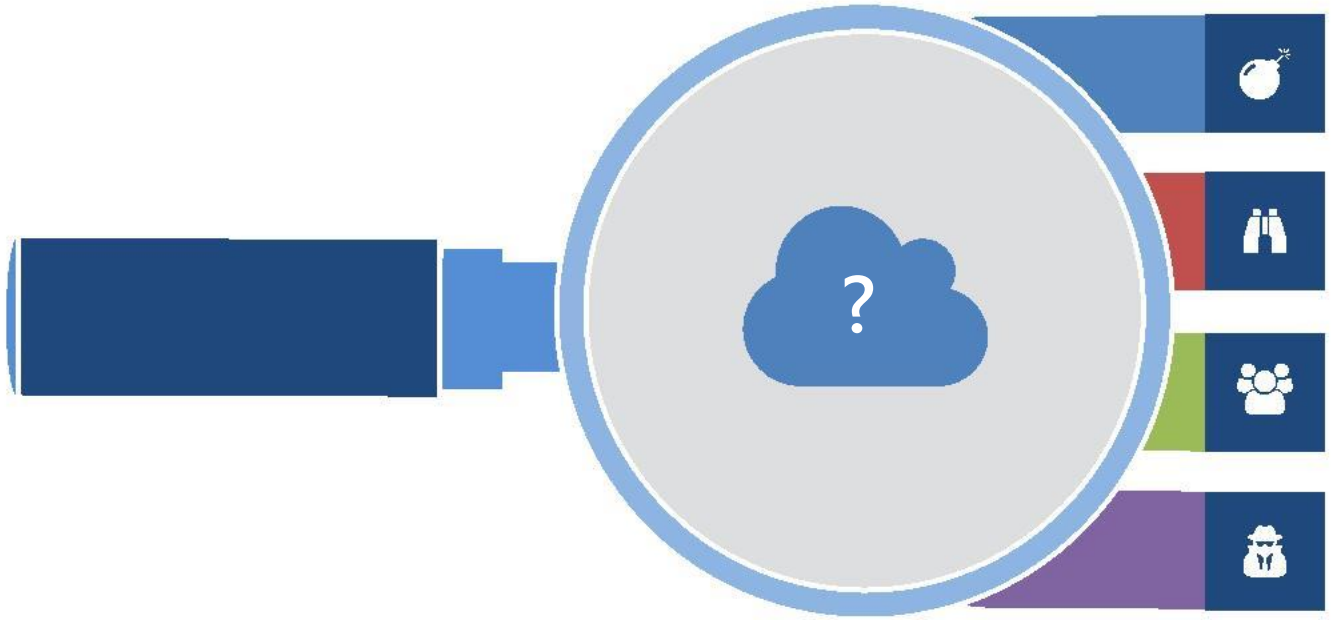


# 藥物早期開發分子路徑分析的重要性




瞭解疾病的發病機制（通過知識挖掘和多體學資料的分析）

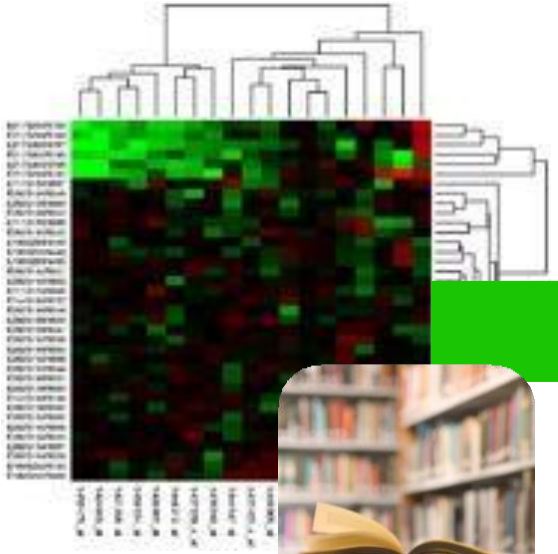
在您感興趣的治療領域裡發現潛力的藥物靶點

發現藥物的作用機制並預測它的毒性

確定生物標記，可以說明您加速臨床前，轉化醫學及臨床研究進展

# MetaCore: 來自科睿唯安的先進路徑分析平台

- 基於準確的基層內容進行體學試驗資料分析
- 提出關於生物標記、標的、作用機制的假設或者對已有的結果進行驗證

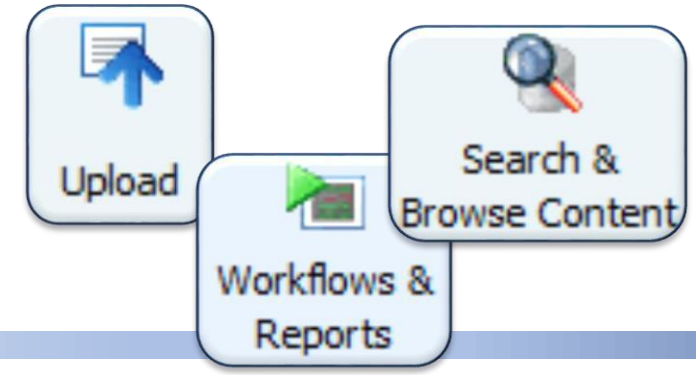


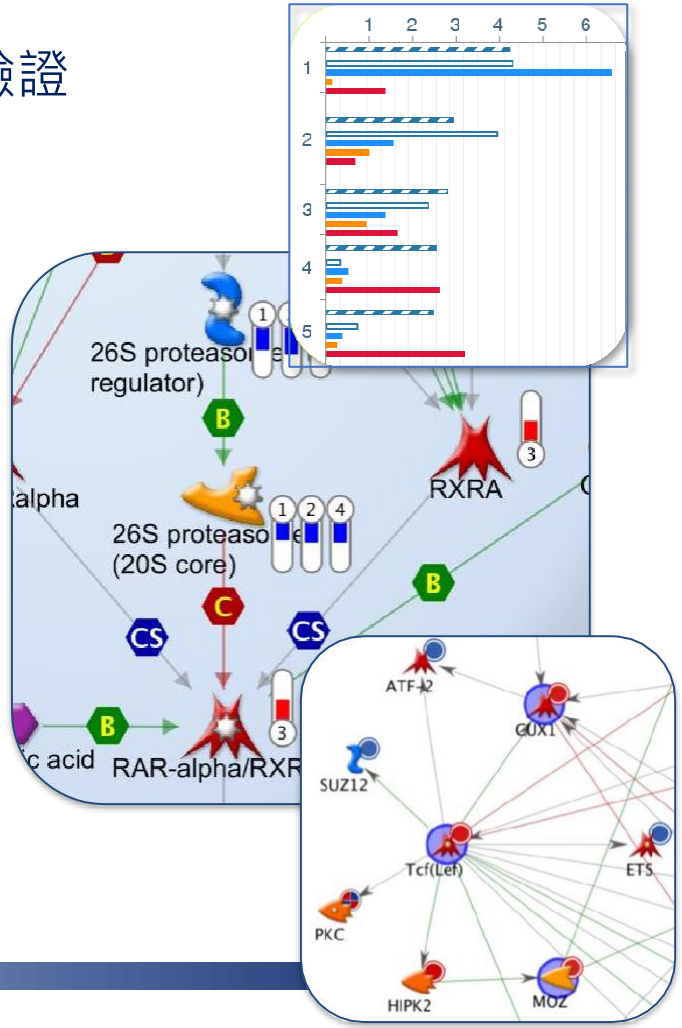
‘Omics’ Data Analysis

Knowledge Mining

MetaCore

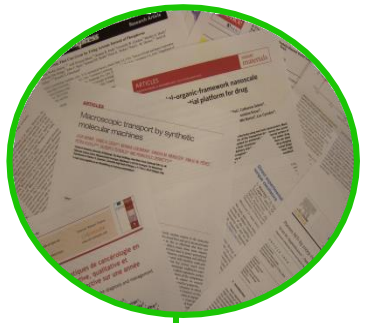
Pathway Analysis Platform

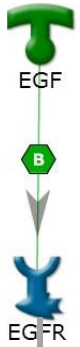


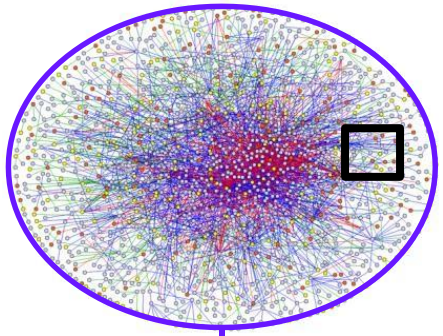



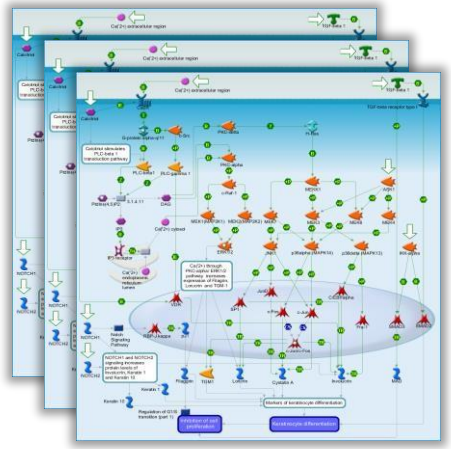
# MetaCore 全、準、新——高品質的底層內容和演算法

- 全面、準確、詳細的分子生物學資料加速疾病研究和藥物標的的發現





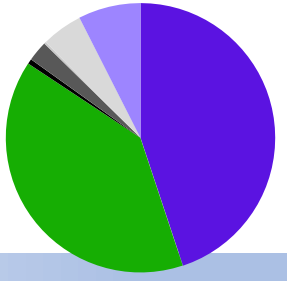





**Publications** → **Molecular Interaction** → **Global Network** → **Pathway maps**

**Manual annotation from publications**
- Team of PhDs, MDs
- More than 10 years

**3 million interactions**



- Protein-Protein
- Compound - Portein
- Compound -Compound
- Metabolic enzyme - Reaction
- Transporter - Reaction
- Substrate, Product - Reaction
- RNA - Protein

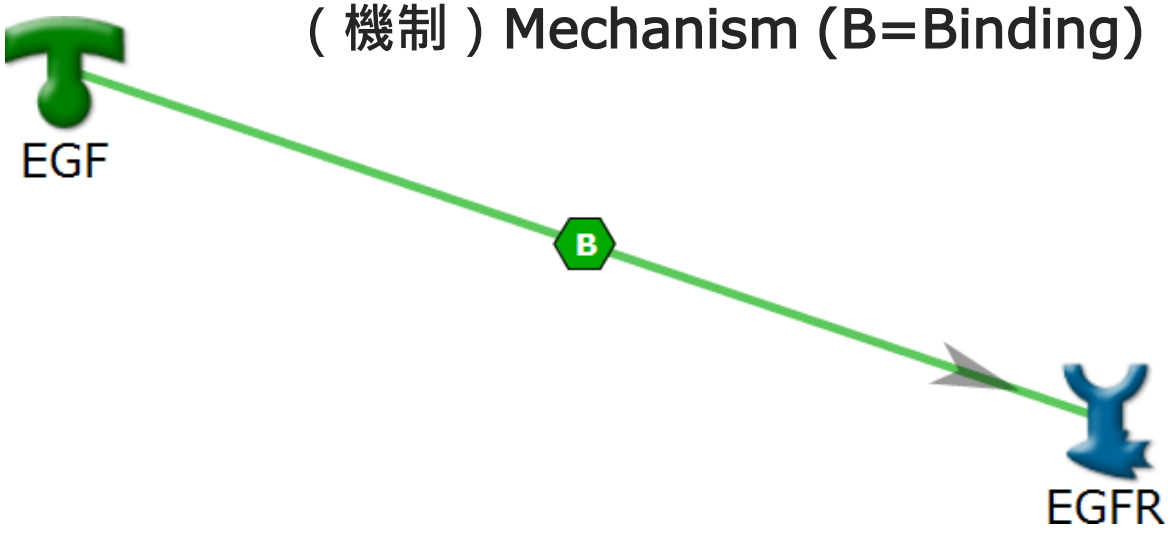
**1500+ canonical and disease signaling pathways**

# MetaCore 中的分子相互作用資料——包含：方向、效應、機制

（方向）Directionality (→)

（效應）Effect

（機制）Mechanism (B=Binding)




通過這樣三個方面的資訊，我們建立起連續完整的路徑圖

# MetaBase和MetaCore的底層資料內容

| MetaBase | number |
|---|---|
| Human Genes | 108665 |
| Human SwissProt proteins | 20384 |
| Mouse genes | 73077 |
| Mouse SwissProt proteins | 17112 |
| Rat genes | 42936 |
| Rat SwissProt proteins | 8154 |
| Compounds | 1032629 |
| Compounds with structure | 1016012 |
| Endogenous compounds | 5518 |
| Nutritional compounds | 126 |
| Metabolites of xenobiotic | 40495 |
| Drugs | 9116 |
| - Biologics | 1360 |
| - Small Molecules | 7756 |
| - Approved drugs | 2290 |
| - Withdrawn drugs | 261 |
| - Clinical trial drugs | 4992 |
| - Discontinued drugs | 1187 |
| - Preclinical drugs | 250 |
| - Unknown | 136 |
| - Drug combination regimens | 8445 |

| MetaCore | number |
|---|---|
| Human genes in network | 30838 |
| Mouse genes in network | 29299 |
| Rat genes in network | 18627 |
| Chemical compounds | 584362 |
| Drugs | 4972 |
| Endogenous compounds | 3554 |
| Metabolic reactions | 52940 |
| Transport reactions | 4976 |
| Processing Reactions | 4515 |
| Pubmed journals | 3785 |
| Pubmed records | 4250392 |
| Pubmed articles (unique) | 331133 |
| Total amount of interactions | 3717953 |
| - Protein – Protein | 1647674 |
| - Compound – Protein | 1087375 |
| - Compound – Compound | 12869 |
| - Metabolic enzyme -Reaction | 64097 |
| - Transporter – Reaction | 5529 |
| - Substrate, Product – Reaction | 141439 |
| - RNA – Protein | 758970 |
| Pathway maps | 1594 |
| - Human genes in maps | 8292 |
| - Mouse genes in maps | 7565 |
| - Rat genes in maps | 7339 |
| - Interactions in maps | 36979 |

- Q1-2023

# 可信任的，高品質的內容——全、準、新

| Percentage of statistically significant intersections with gold standards | Transcription factor/ Gold standard ID# |
|---|---|
| 16% | Ingenuity (Transcription) |
| 36% | Ingenuity (All) |
| 32% | TransPath |
| 16% | TransFac |
| 16% | Biocarta |
| 24% | KEGG |
| 8% | Wikipathways |
| 16% | Cell Signaling Technology |
| 16% | GeneSpring (Expression or Binding) |
| 4% | GeneSpring (Expression and Binding) |
| 28% | PathwayStudio |
| **84%** | **MetaCore** |

Systematic study of transcription factors and their targets identified through *"gold standard experiments"* and intersection with transcriptional regulatory interactions in free and commercially available databases

Assessing quality and completeness of human transcriptional regulatory pathways on a genome-wide scale *Biol. Direct* 2011, 6:15

# 介面介紹

# 登入首頁

MetaCore
A Cortellis solution

Clarivate Analytics

Home Support Training About Us


*"Something that I do with **MetaCore** in one afternoon now, would have taken a week before."*

**Dr. Charles Lecellier**
Principal Investigator
**IGMM**

## Your GPS in Pathway Analysis

Whether you want to reduce the risk in your OMICs analysis, realize the potential of your biomarkers, or establish a target's mechanism of action, Clarivate has the right solution for you.

### MetaCore

High quality biological systems content in context, giving you essential data and analytical tools to accelerate your scientific research.

### MetaMiner Partnerships

A series of industry-academy partnerships on systems biology of common human diseases and stem cells, led by Clarivate.

### MetaDrug

A leading systems pharmacology solution that incorporates extensive manually curated information on biological effects of small molecule compounds.

LOGIN

Username

Password

Remember me

LOGIN

Forgot your password?

使用者帳號

密碼

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Clarivate

Products weichun

MetaCore HOME APPLICATIONS

設定及工具列

搜尋列

Search for genes, drugs, diseases, p...

File Edit View Tools Help

Activate/Deactivate

Home ▸ My Data

| Name | Type | Date |
|---|---|---|
| My Data | | |
| EXPERIMENTS | | 06/08/2022 01:08:55 |
| STRUCTURES | | 06/08/2022 01:10:25 |
| VARIANT DATASETS | | 06/22/2022 01:53:33 |
| VARIANT EXPERIMENTS | | 06/22/2022 01:54:25 |
| GENE LISTS | | 06/22/2022 08:29:28 |
| FILTER PRESETS | | 10/25/2022 08:47:58 |
| WORKFLOWS | | 11/07/2022 09:02:51 |
| SAVED NETWORKS | | 11/22/2022 02:56:44 |
| ENRICHMENTS | | 11/22/2022 03:45:32 |
| Shared Data | | |
| Lost&Found | | |

檔案管理區

Home ▸ Active Data

| Name | Type | Date |
|---|---|---|
| [..] Active Data | | |

檔案狀態管理

Activate

Deactivate

Please, drag one or more experiments from the upper frame and drop it here.

Get Started | Genomic Analysis | Upload | Workflows & Reports | One-click Analysis | Build Network | Custom Content | Predict Compound Activity (MetaDrug) | Search & Browse Content

**Search**

Quick Search

Advanced search

Search/Browse Pathway Maps

**Upload**

Upload Your Data

Pre-process Omics Data

**Analyze (activate your experimental data first)**

Pathway Map Analysis

Enrichment Analysis

Compare Experiments

工作及分析操作區

Hide Description

**Get Started**

Follow the links to start making the most of MetaCore:

**Search**

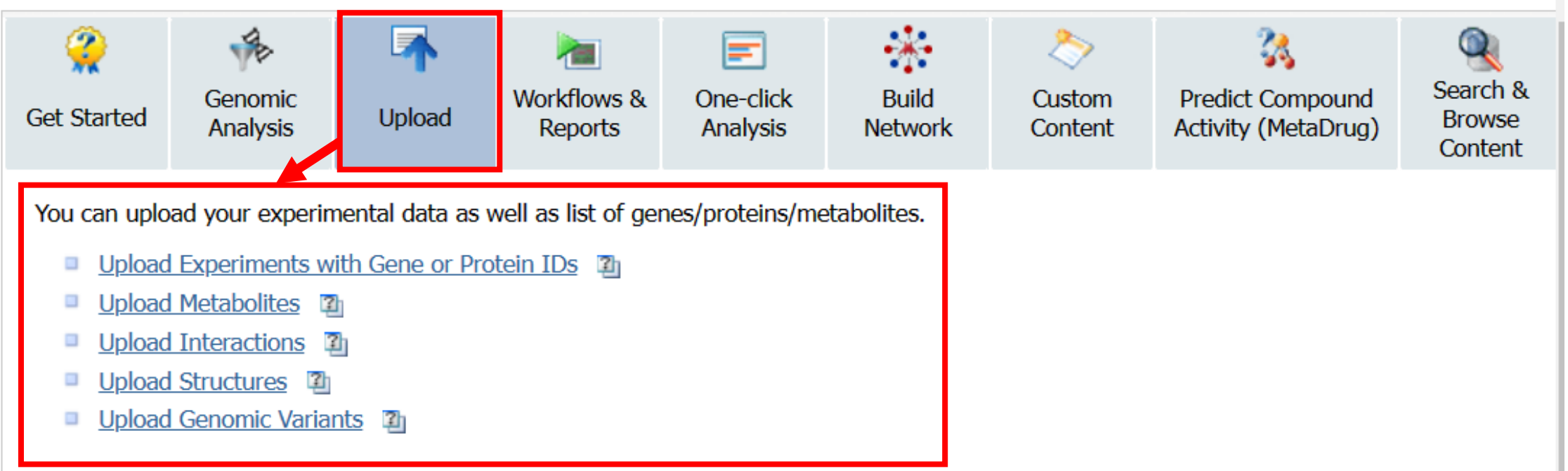
- Quickly retrieve expertly curated information on genes, proteins, diseases, and interactions among others.
- Construct more complex queries to extract specific subsets of genes, proteins, and interactions among others.
- Find and explore interactive pathway maps, built by Clarivate experts based on thorough review of the literature.

導引及解說



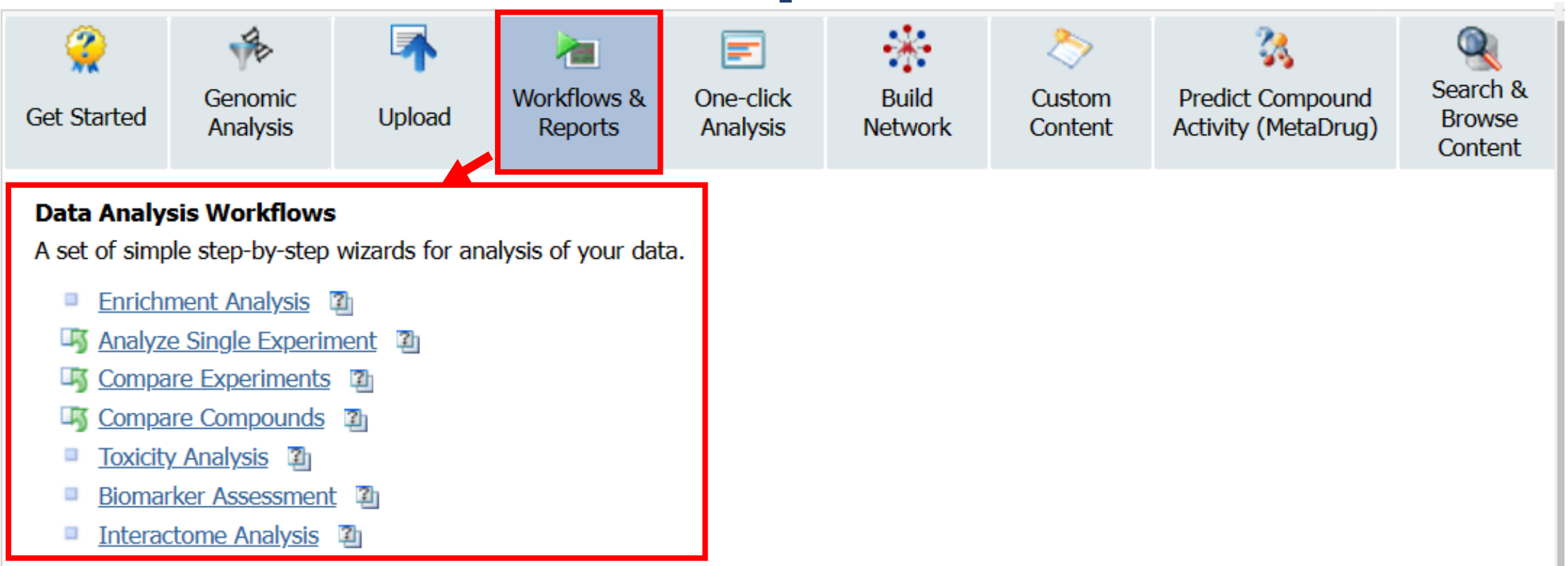
**Upload**

# Upload



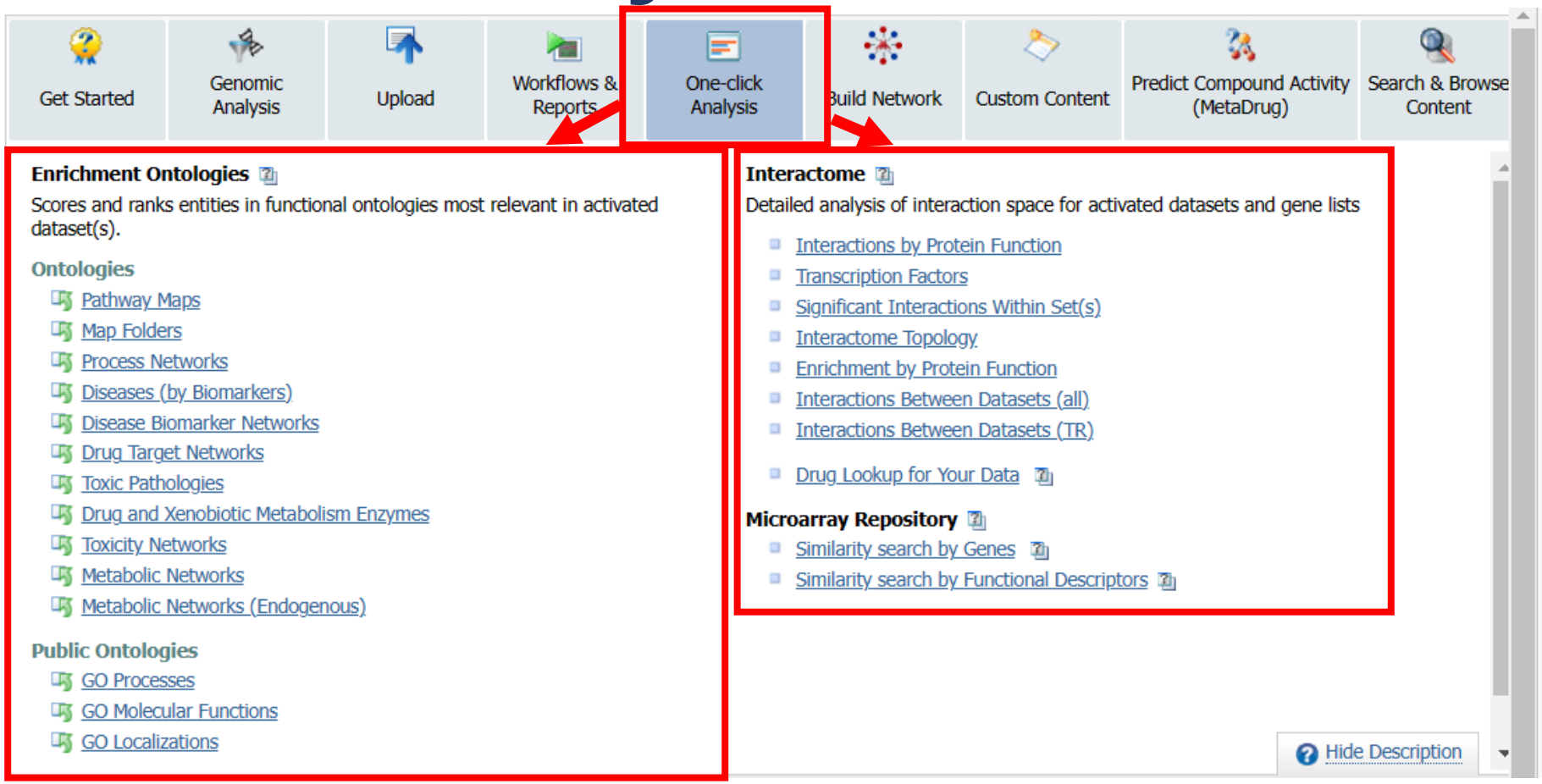

- 上傳資料，包含轉錄體學、蛋白體學、代謝體學、化合物結構等

# Workflows and Reports




- 選擇想進行的分析分法，依照提醒，依序設定工作流程，完成分析

# One-click analysis




- 提供多種分析方法，包含Pathway maps和Networks，一鍵分析上傳的實驗數據

# Build network


- 依照資料類型和目的，選擇合適的演算法進行Network的建立

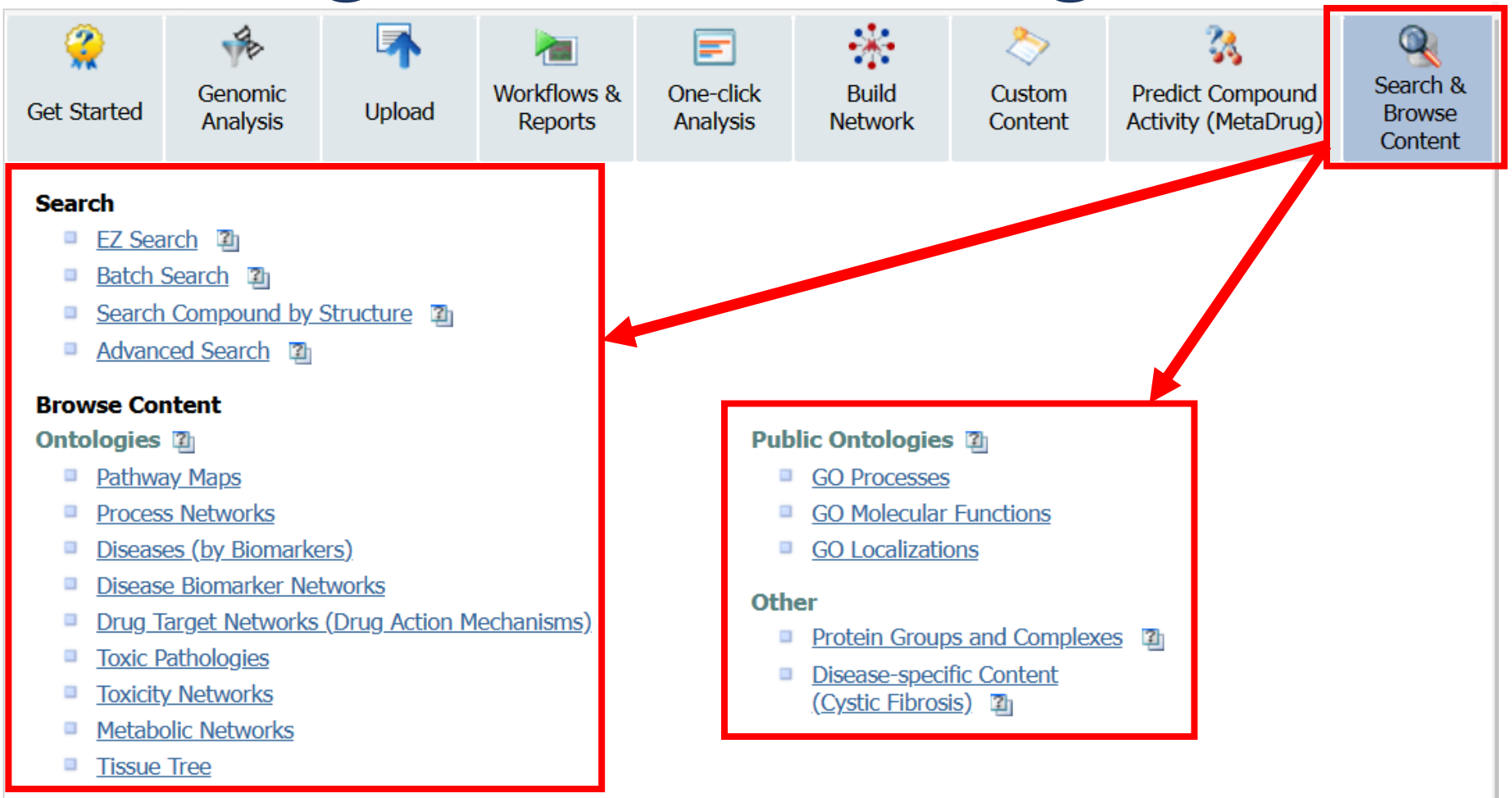
# Custom content


- 建立使用者自己的資料，像是使用map編輯器繪製使用者自己的map

# MetaDrug Compound activity prediction

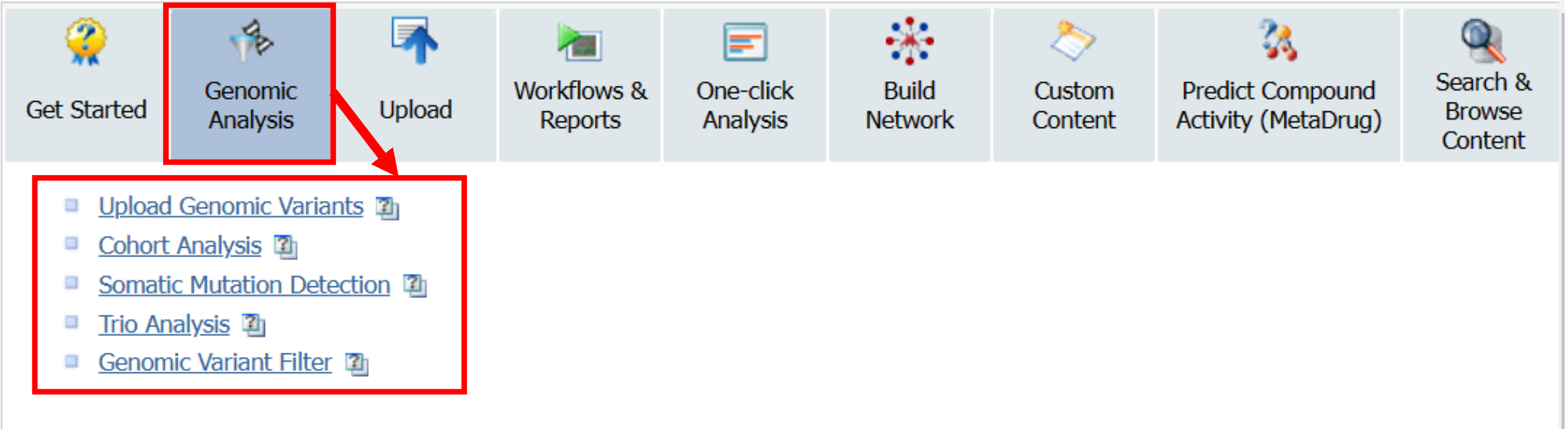

- 依照化合物的結構，進行多種活性預測分析，包含代謝產物、相似物尋找、可能的作用目標以及多種QSAR Models的預測

# Searching and Browsing



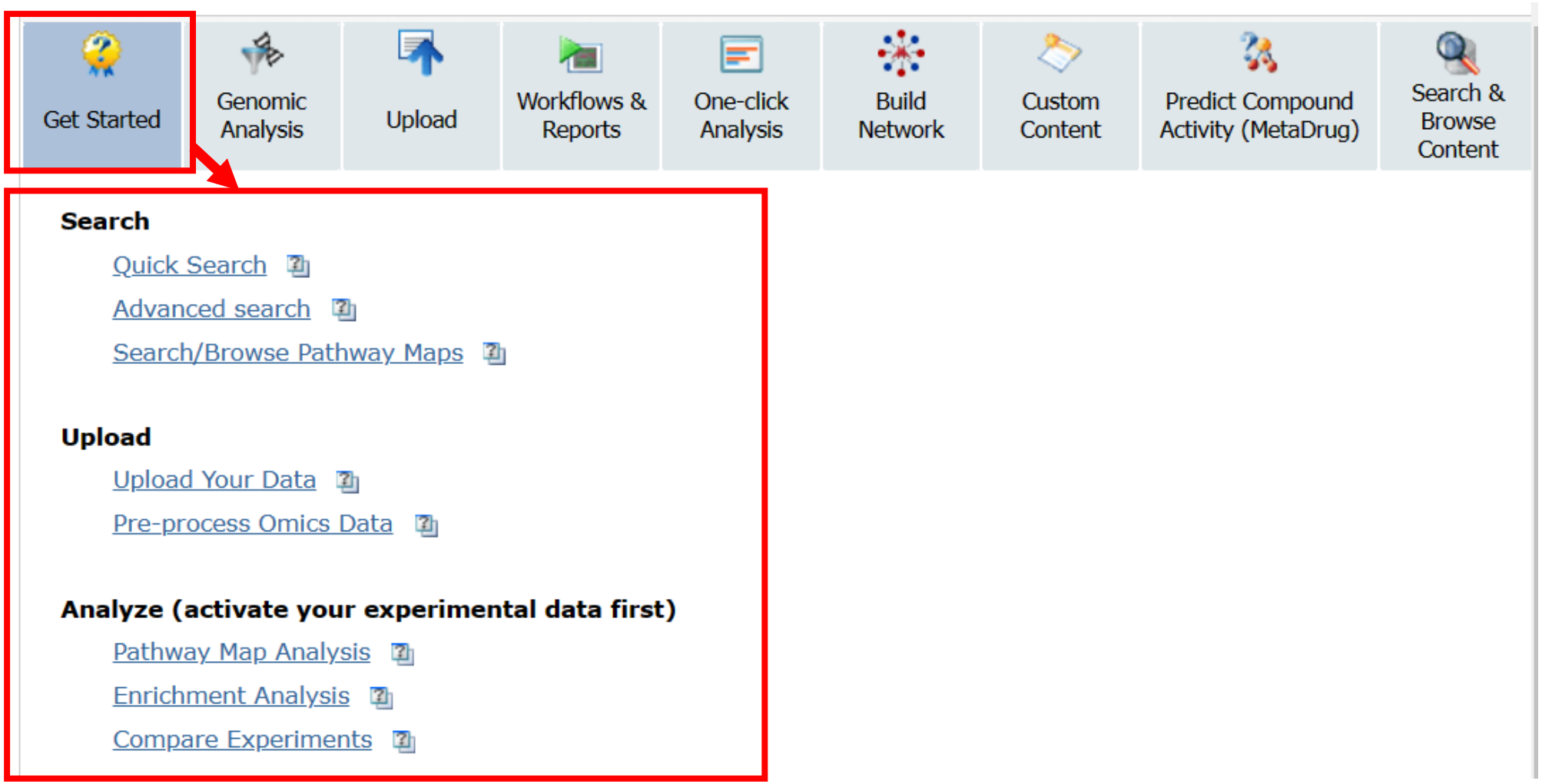

- 檢索功能，包含簡易檢索、批次檢索、結構檢索和進階檢索

# Genomic Analysis

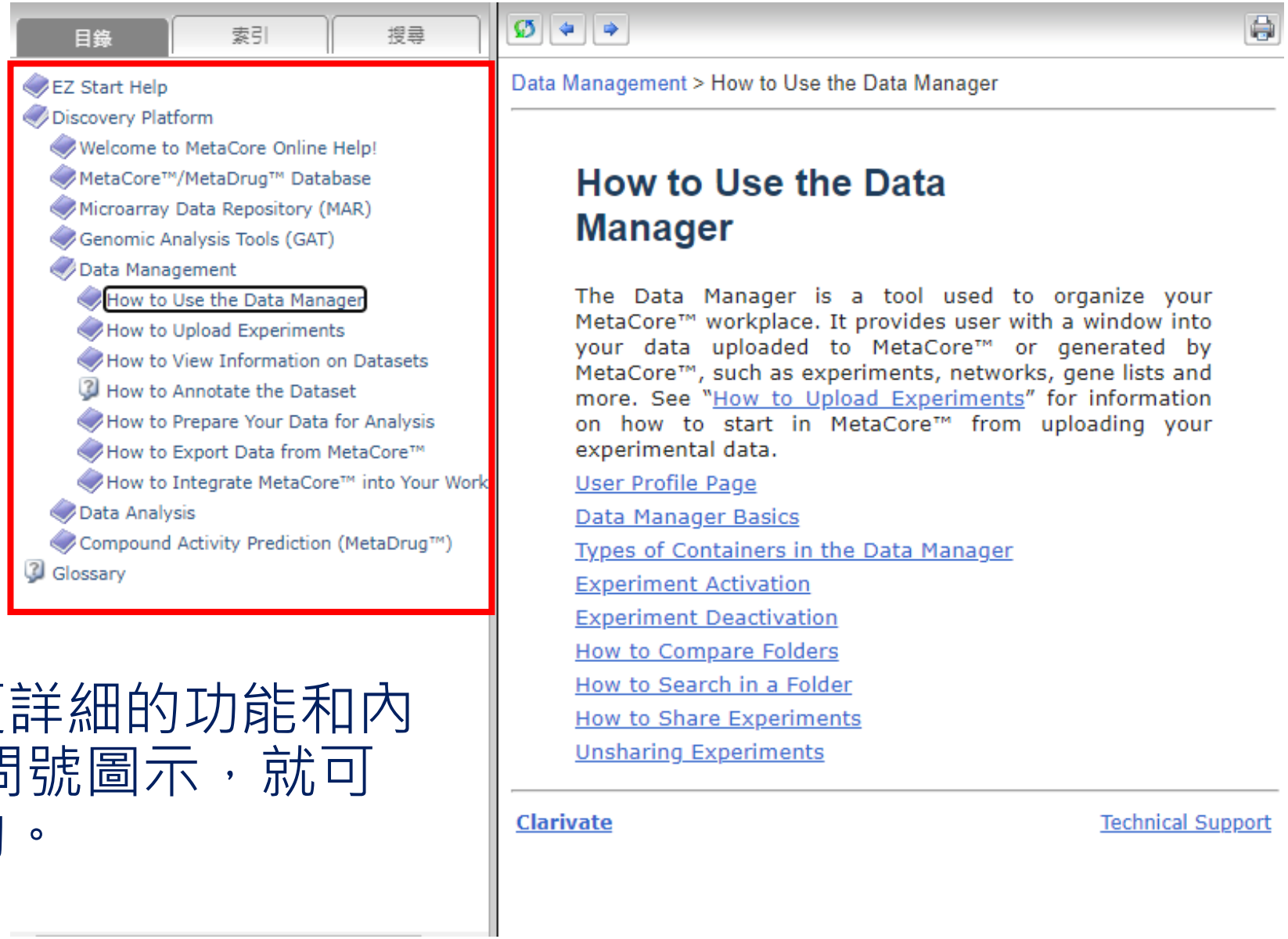



- 做基因體序列變化的分析，只能上傳VCF檔，會將上傳的VCF檔轉換成分析用的VD檔或VX檔。可做病患間的分析、正常組織和病組織間分析以及父母和後代間的分析。

# Get Started



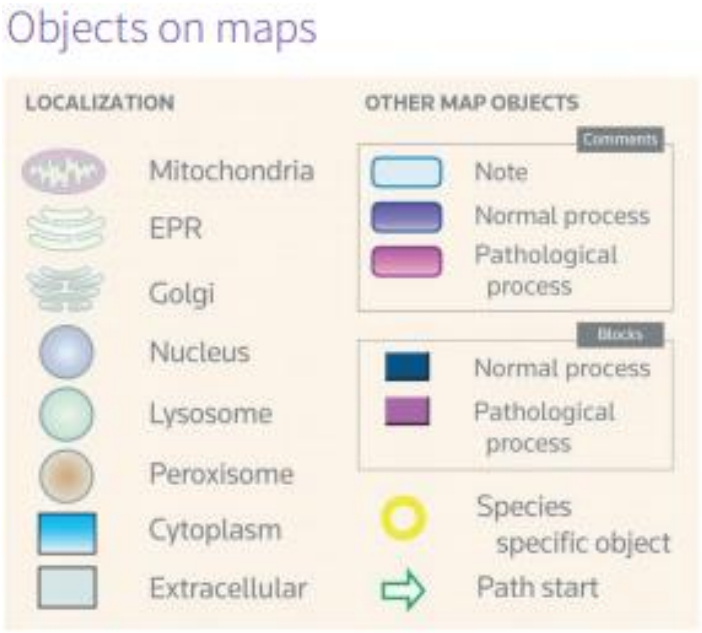
# 使用說明

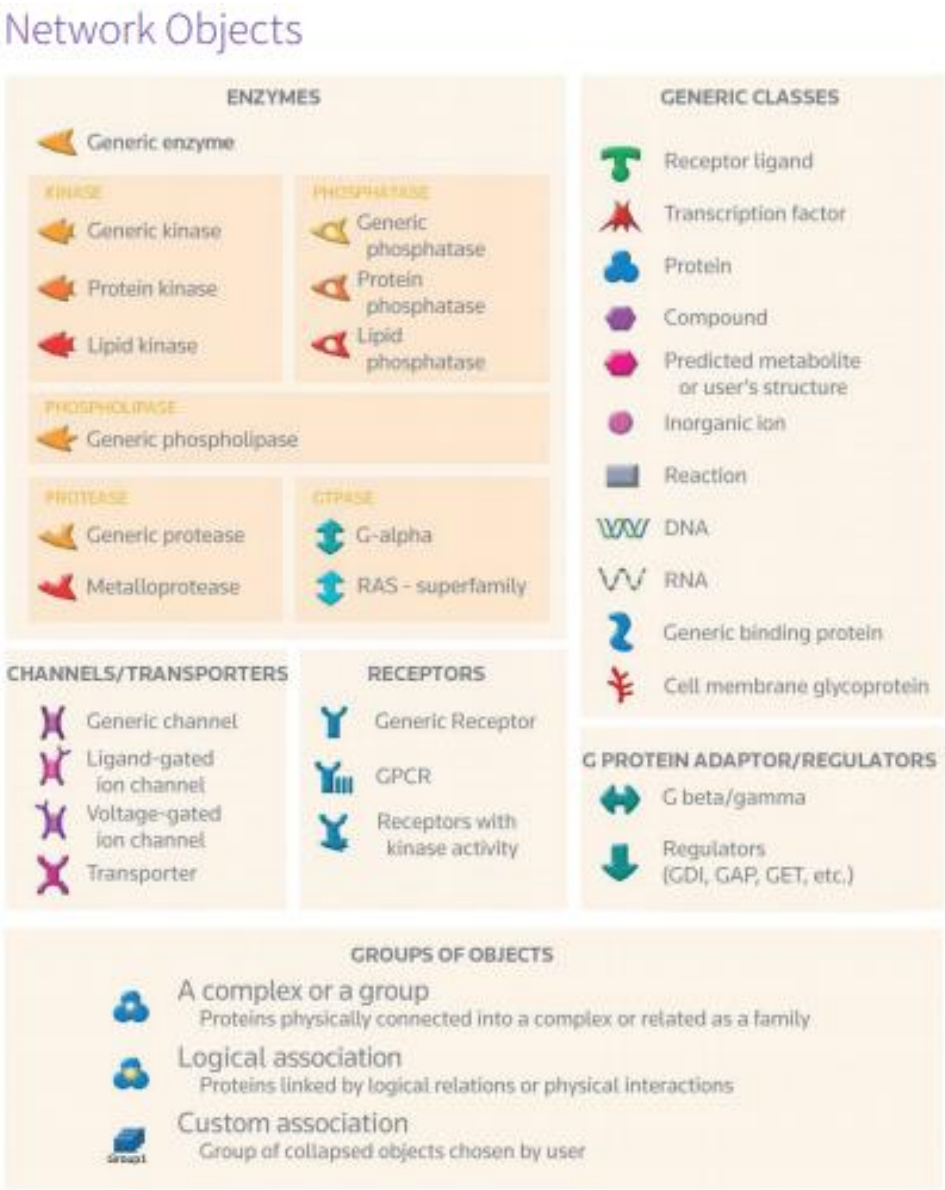


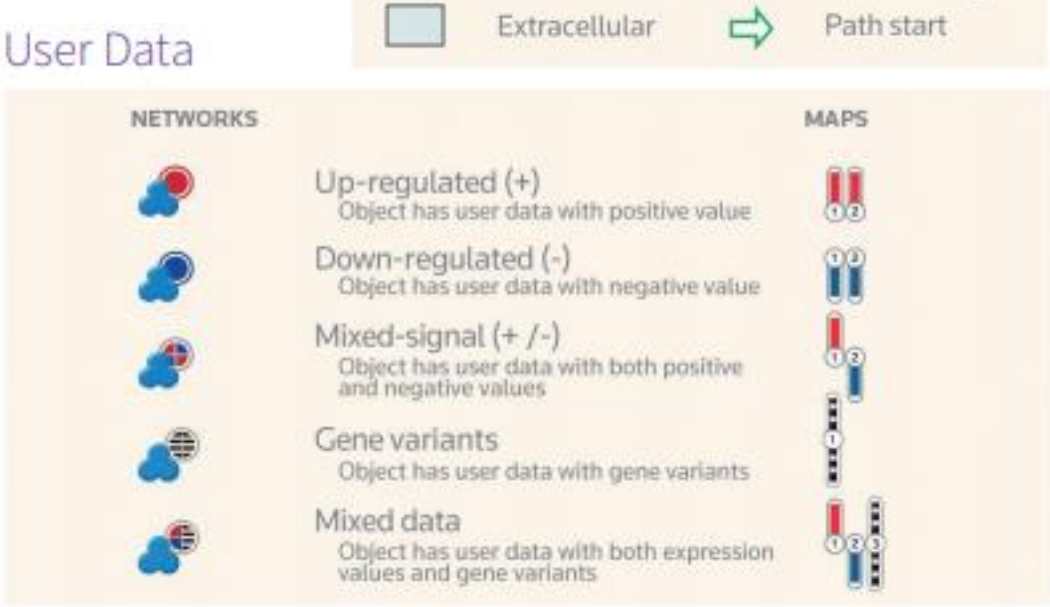

- Help中有更多更詳細的功能和內容解釋。點擊問號圖示，就可進入Help做查詢。

# 圖示及註解

- Help中的legend，可以顯示圖示說明



# Interactions between objects

### EFFECTS

- Positive / activation
- Negative / inhibition
- Unspecified

### LINKS ON NETWORKS

- **Incoming interaction**
  When the mouse is over object, yellow link indicates direction to object
- **Outgoing interaction**
  Cyan link indicates direction FROM the object

INTERACTIONS FROM CUSTOM LIST (MetaLink™)

- **Interaction is in the network**
  Interaction is represented by a thin solid line and is highlighted in blue
- **Interaction is in the base, but not in network**
  Interaction is highlighted in yellow
- **Interaction is in the network**
  Interaction is highlighted in magenta

CANONICAL PATHWAYS

- **Canonical pathway**
  The link is highlighted in a thick cyan or magenta line

### LINKS ON MAPS

- Disrupts in disease
- Weakens in disease
- Emerges in disease
- Enhances in disease
- Species specific interactions

### MECHANISMS

PHYSICAL INTERACTIONS

- **B — Binding**
  Physical interaction between molecules
- **C — Cleavage**
  Cleavage of a protein at a specific site yielding distinctive peptide fragments. Proteolytic cleavage can be carried out by both enzymes and compounds
- **CM — Covalent modifications**
  Covalent binding of a small chemical groups to protein amino acids or DNA/RNA nucleotides.
- **+P — Phosphorylation**
  Protein activity is altered via addition of a phosphate group
- **- P — Dephosphorylation**
  Protein activity is altered via removal of a phosphate group
- **T — Transformation**
  Protein activity regulation by binding & hydrolysis of GTP
- **Tn — Transport**
  Transport of a protein or a compound between organelles
- **Z — Catalysis**
  Catalysis of an enzymatic reaction
- **Tr — Transcription regulation**
  Physical binding of a transcription factor to target gene's promoter
- **cRT — Co-regulation of transcription**
  Influences on gene expression by direct binding with transcription machinery or by chromatin remodelling
- **Rg — Regulation**
  Influence on the biochemical reaction by changing its composition
- **M — MicroRNA binding**
  Regulation of gene expression by binding of microRNA to target mRNA

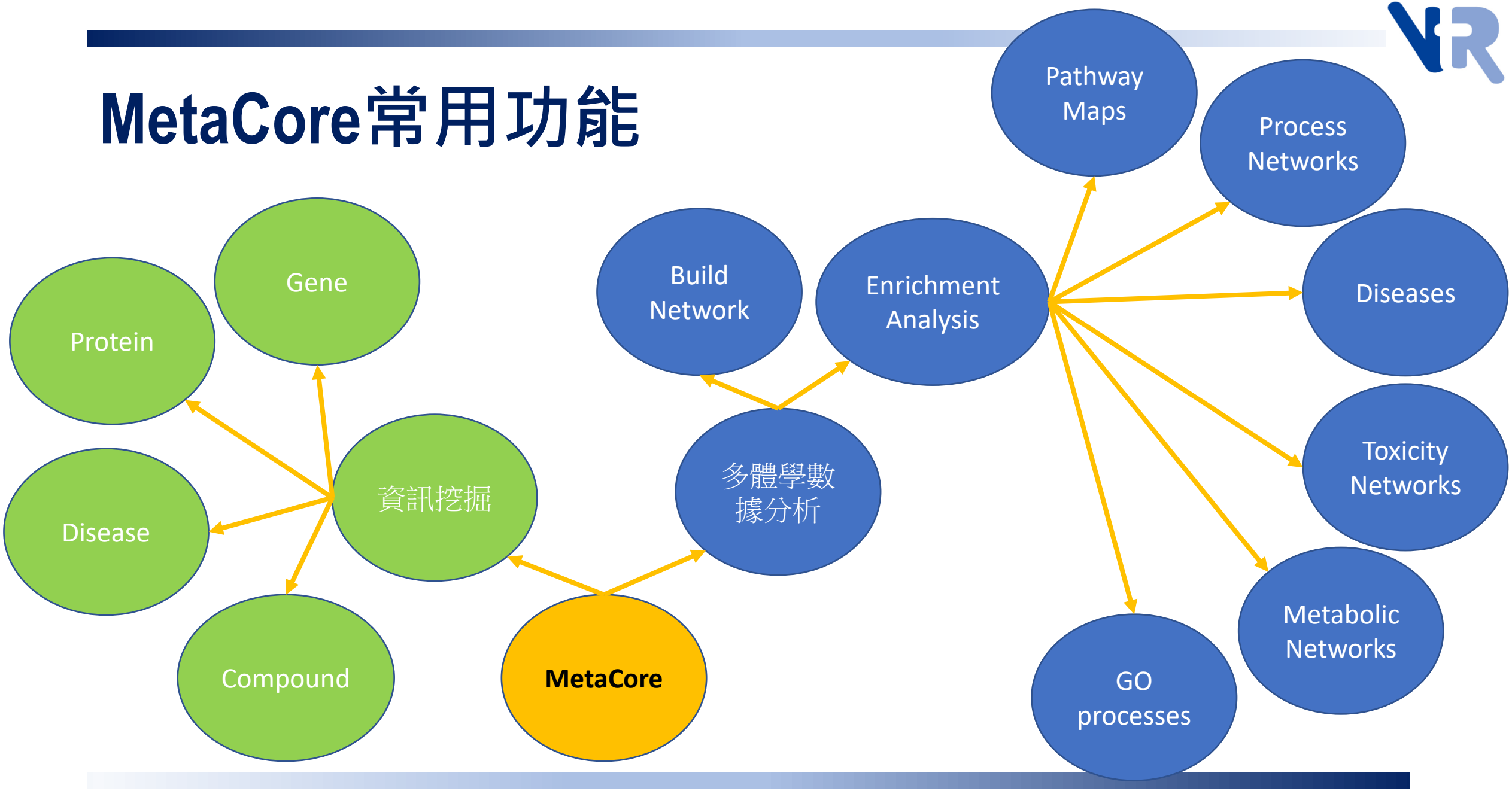
FUNCTIONAL INTERACTIONS

- **IE — Influence on expression**
  Indirect influence of chemical compound or protein on the amount of another protein
- **Cn — Competition**
  When two molecules compete for the interaction with the third molecule
- **? — Unspecified interactions**
  Influence on activity of protein or RNA without determined mechanism
- **PE — Drug-Drug interactions. Pharmacological effect**
  Drugs change pharmacological effects of other drugs, for instance by competing for drug metabolism enzymes or organic transporters
- **TE — Drug-Drug interactions. Toxic effect**
  Drugs change toxic effects of other drugs, for instance by competing for drug metabolism enzymes or organic transporters

LOGICAL RELATIONS

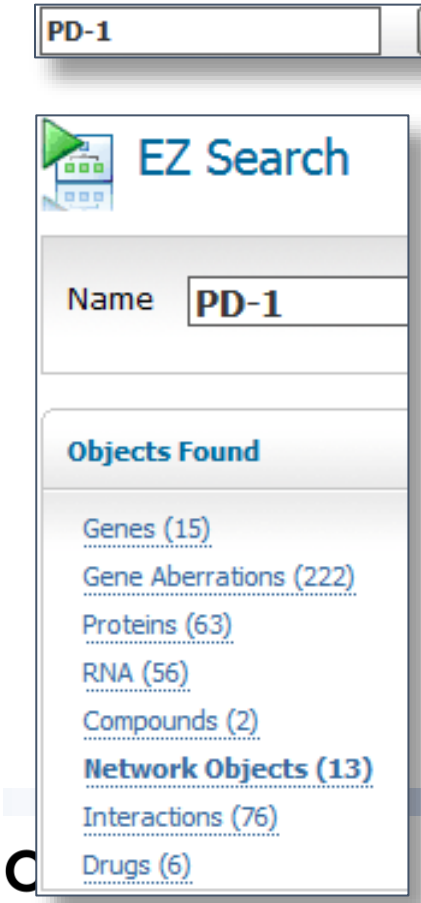
- **GR — Group relation**
  Object belongs to a generic group of related objects
- **CS — Complex subunit**
  Protein is a subunit of a protein complex
- **SR — Similarity relation**
  Chemically similar compounds with chosen Tanimoto similarity score

# MetaCore常用功能

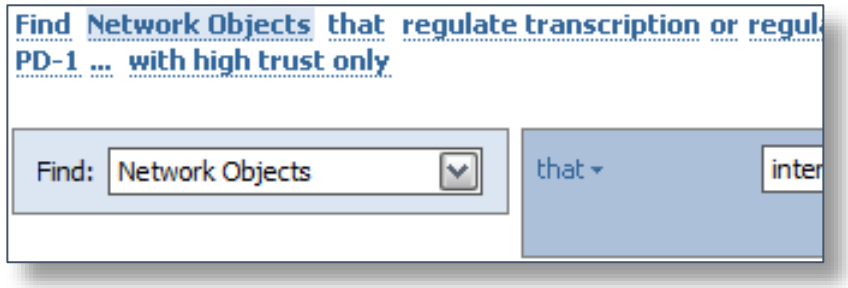


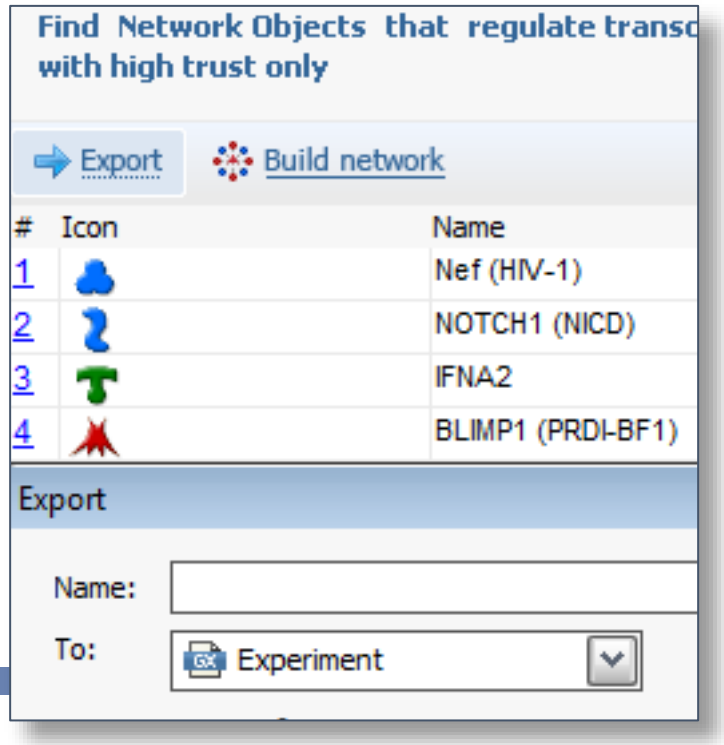
# Knowledge mining 知識挖掘

EZ Search → Advanced Search → Export to MetaCore




- 通過知識挖掘瞭解腫瘤免疫標的：以PD-1為例



# 我們能檢索到關於PD-1的哪些資訊

## PD-1

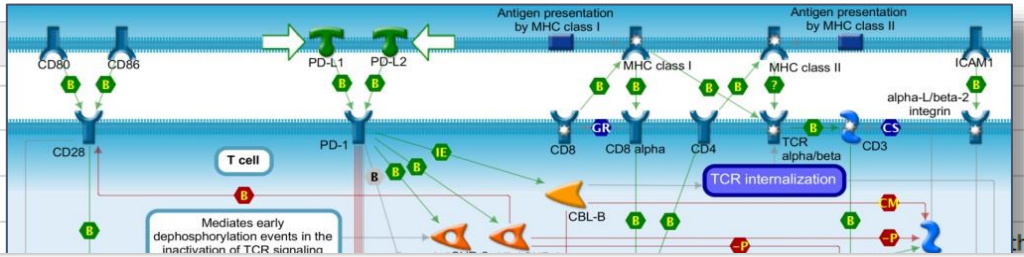
Network object | Build Network

### Table of Contents



### Gene Details

| | |
|---|---|
| PDCD1 | |
| Symbols | |
| Full Name | |
| Synonyms | |




...hematosus susceptibility 2

### Diseases

#### Associated Diseases

| # | Name | Reference |
|---|---|---|
| 1 | Arthritis, Rheumatoid | PubMed: 15022318, 15188352, 15818672, 15959535, 17142787, 17468813, 20506224, 21547439, 24062057, 24804191 |
| 2 | Autoimmune Diseases | PubMed: 15883854, 19035512 |
| 3 | Brain Neoplasms | PubMed: 28535114 |
| 4 | Breast Neoplasms | PubMed: 21113674, 21487727 |
| 5 | Carcinoma | PubMed: 18676751 |
| 6 | Carcinoma, Ductal, Breast | PubMed: 21487727 |
| 7 | Carcinoma, Hepatocellular | PubMed: 23041554, 23291409 |
| 8 | Carcinoma, Non-Small-Cell Lung | PubMed: 21840566 |
| 9 | Carcinoma, Renal Cell | PubMed: 17363529, 23730407 |
| | | ..., 25604582, 29580042 |
| 14 | Colorectal Neoplasms | PubMed: 22892379, 25604582, 25752522, 27339628 |
| 15 | COVID-19 | PubMed: 32679621, 32983106 |

| # | From | | To | Direction | Effect | Mechanism | Link info |
|---|---|---|---|---|---|---|---|
| 1 | CTCF | TR → | PD-1 | Incoming | Activation | Transcription regulation | |
| 2 | FKHR | TR → | PD-1 | Incoming | Activation | Transcription regulation | |
| 3 | IRF9 | TR → | PD-1 | Incoming | Activation | Transcription regulation | |
| 4 | NF-AT2(NFATC1) | TR → | PD-1 | Incoming | Activation | Transcription regulation | |
| 5 | RBP-J kappa (CBF1) | TR → | PD-1 | Incoming | Activation | Transcription regulation | |

### Drug Target for

| # | Drug |
|---|---|
| 1 | Nivolumab |
| 2 | Pidilizumab |

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# 哪些蛋白可以調節和影響PD-1的表現?

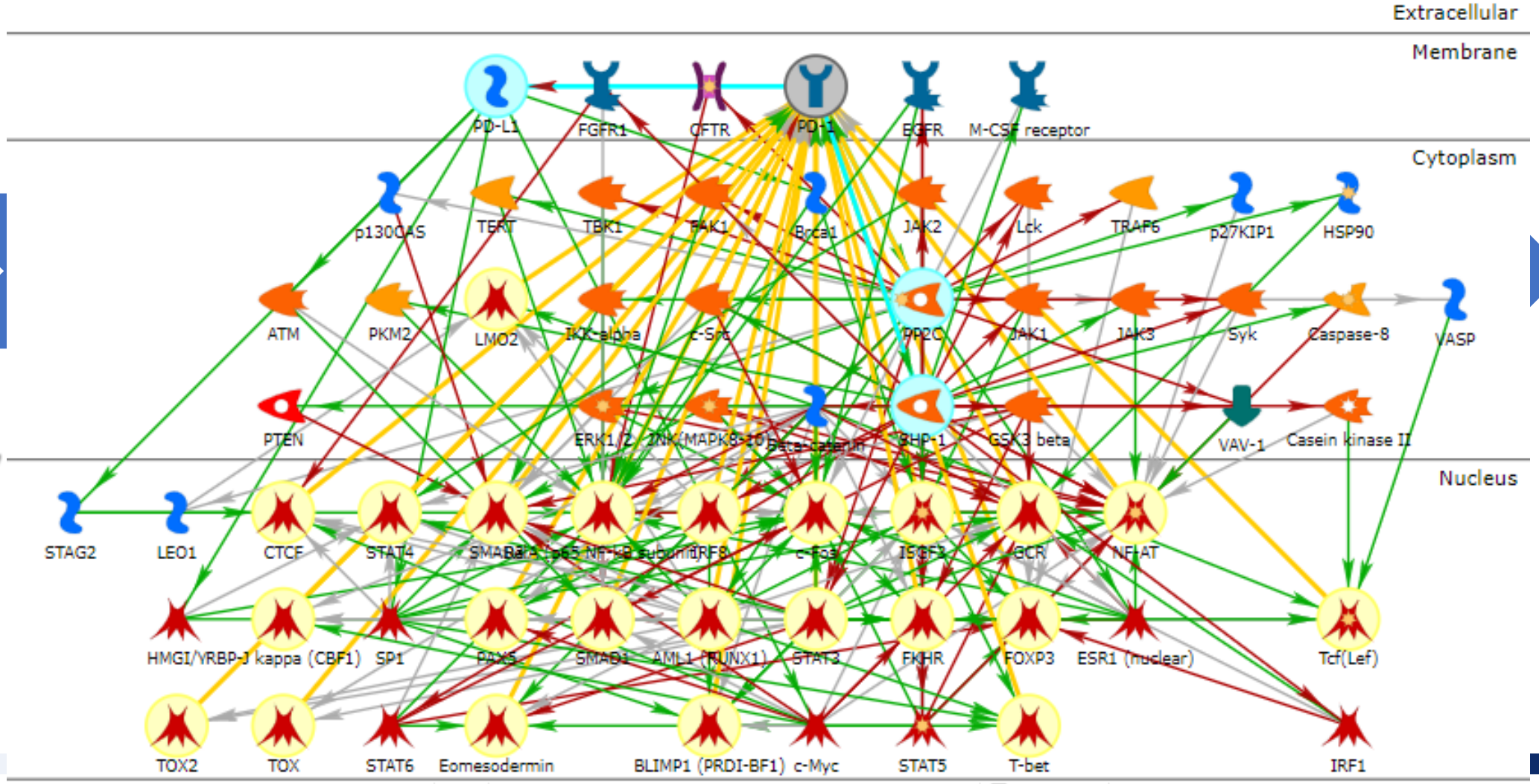
## Activation

| # | From | | To |
|---|---|---|---|
| 1 | PD-L1 | B | PD-1 |
| 2 | PD-L2 | B | PD-1 |
| 3 | KIF5B | B | PD-1 |
| 4 | CTCF | TR | PD-1 |
| 5 | FKHR | TR | PD-1 |
| 6 | GCR | TR | PD-1 |
| 7 | IRF9 | TR | PD-1 |
| 8 | NF-AT2(NFATC1) | TR | PD-1 |
| 9 | RBP-J kappa (CBF1) | TR | PD-1 |
| 10 | STAT1 | TR | PD-1 |
| 11 | STAT2 | TR | PD-1 |
| 12 | STAT3 | TR | PD-1 |
| 13 | STAT4 | TR | PD-1 |
| 14 | TOX2 | TR | PD-1 |
| 15 | NOTCH1 (NICD) | R | PD-1 |
| 16 | p300 | R | PD-1 |

## Inhibition

| # | From | | To |
|---|---|---|---|
| 1 | Cemiplimab | B | PD-1 |
| 2 | KLHL22 | B | PD-1 |
| 3 | MoKA | B | PD-1 |
| 4 | Nivolumab | B | PD-1 |
| 5 | Pembrolizumab | B | PD-1 |
| 6 | Pidilizumab | B | PD-1 |
| 7 | c-Cbl | CN | PD-1 |
| 8 | BLIMP1 (PRDI-BF1) | TR | PD-1 |
| 9 | FOXP3 | TR | PD-1 |
| 10 | PAX5 | TR | PD-1 |
| 11 | T-bet | TR | PD-1 |
| 12 | LSD1 | R | PD-1 |
| 13 | HMGB1 | TE | PD-1 |

# 建立一個網絡來推測哪些路徑可以影響PD-1的表現



# Live demo

資料查詢與檢索
建構網絡及分子路徑

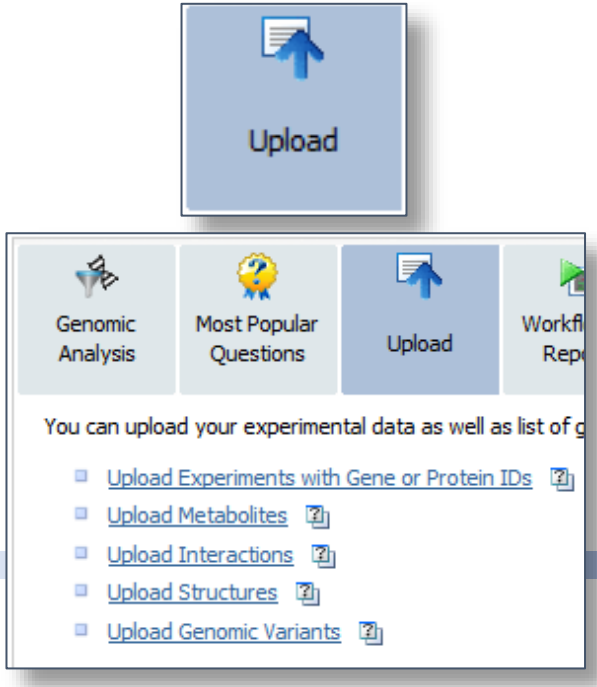
- 以Lung Cancer為例。

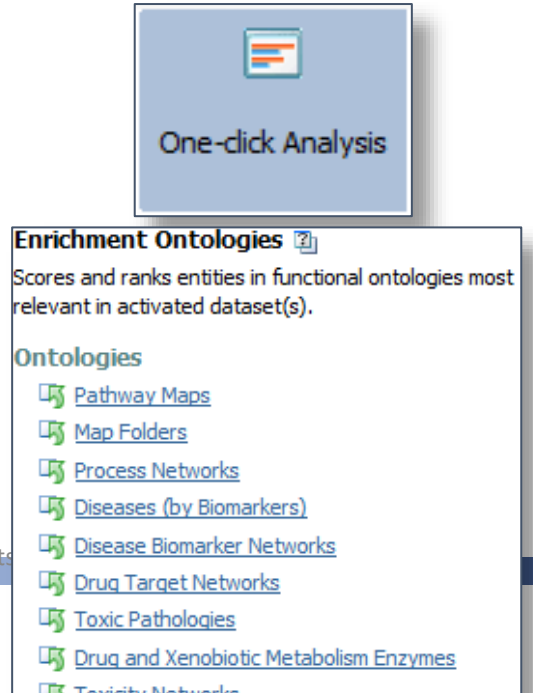
# 多體學數據分析

- 通過代謝體學、蛋白質體學和RNA-seq數據分析，發現腎功能退化患者的生物標記



**Upload metabolomic data** → **Metabolic Networks (Endogenous) Enrichment**



## Data Analysis Wizard (General parser)

**Step 1**

Next >>

### Click "browse" to select file(s) to upload:

選擇檔案 沒有選擇檔案

### Data format

**Warning:** do not mix IDs in the same column.

Excel or plain text with tab separated fields formats are supported.

The file has to be in the following format:

| Gene id * | Exp 1 | Exp 2 | ... |
|---|---|---|---|
| [name 1] | [value 1.1] | [value 2.1] | ... |
| ... | ... | ... | ... |
| [name n] | [value 1.n] | [value 2.n] | ... |

**OR**

| Gene id * | Exp 1 | P-value 1 | Exp 2 | P-value 2 | ... |
|---|---|---|---|---|---|
| [name 1] | [value 1.1] | [P-value 1.1] | [value 2.1] | [P-value 2.1] | ... |
| ... | ... | ... | ... | ... | ... |
| [name n] | [value 1.n] | [P-value 1.n] | [value 2.n] | [P-value 2.n] | ... |

**Required fields marked with (*)**

Most files are of «General» type. The following identifiers are recognized:

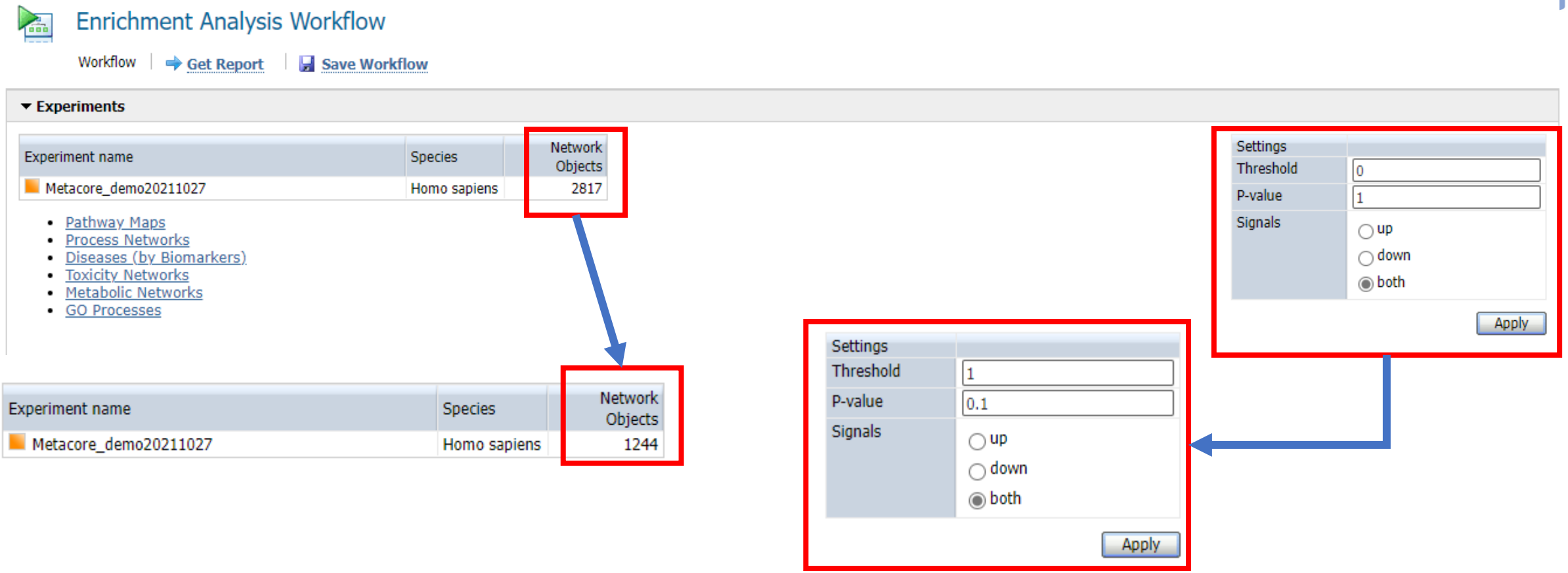
# 上傳數據格式

Most files are of «General» type. The following identifiers are recognized:

- EntrezGene (LocusLink) IDs — Mouse, Rat, Bovine, Chimpanzee, Dog, Zebra fish, Chicken, Fly, Mosquito, Worm, Arabidopsis, Rice, Blast of rice, Macaca mulatta, Mold, Bread mold, Candida sphaerica, Fission yeast and Baker's yeast IDs are supported as well (via orthologs)
- Gene symbol (e.g. TP53, etc.)
- Affymetrix tag ID (expression)
- Affymetrix tag ID (exon)
- Affymetrix tag IDs (SNP)
- Illumina tag IDs (expression)
- Agilent tag IDs (expression)
- Codelink tag IDs (expression)
- OMIM IDs
- RefSeq IDs
- Unigene IDs
- ENSEMBL IDs (including Sus scrofa)
- rsSNP IDs
- SwissProt IDs
- IPI IDs
- GeneBank IDs
- miRBase IDs
- Panther IDs
- MetaCore gene IDs

**All entries in one column should have same type of IDs. Mixed IDs are not supported.**

- 可辨識的Gene和Protein ID類型很多，包含常見的資料庫或是高通量分析工具所使用的ID



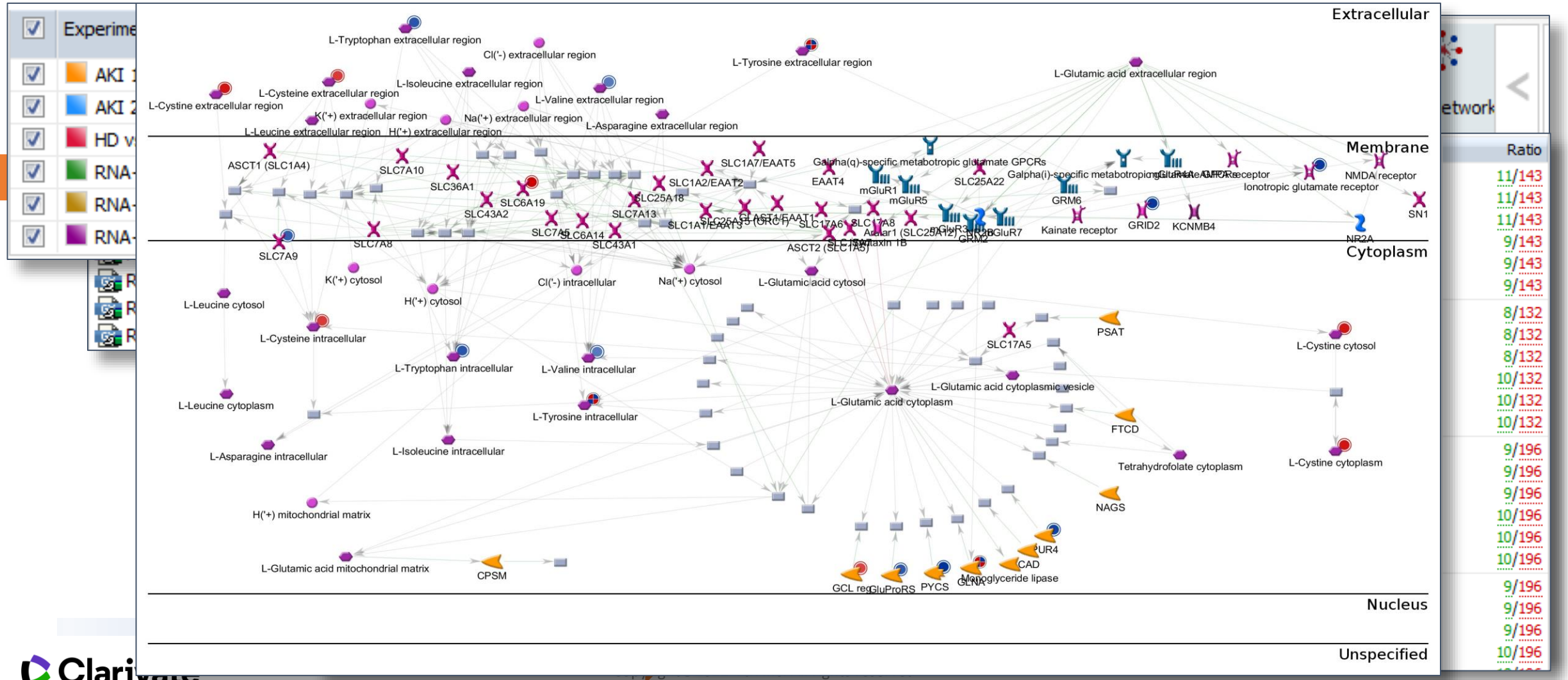

- MetaCore分析多體學數據的方式，主要是比對達到我們設定的表現量變化的物件，我們可以藉由Threshold和P-value的設定，來調整用於分析的物件

# 多體學數據分析的小技巧

- 在比較不同的體學數據時，我們需要想一想他們是怎樣相互關聯的？

1. 代謝體學、轉錄體學的分析可以幫助我們找到引起代謝變化的路徑和酶
2. 蛋白體學、轉錄體學的分析可以有助於找到與轉譯水準相關的表現
3. 代謝體學、蛋白體學的分析可以有助於找到生物標記

# 通過代謝體學和基因體學的分析，我們能發現怎樣的代謝關係？

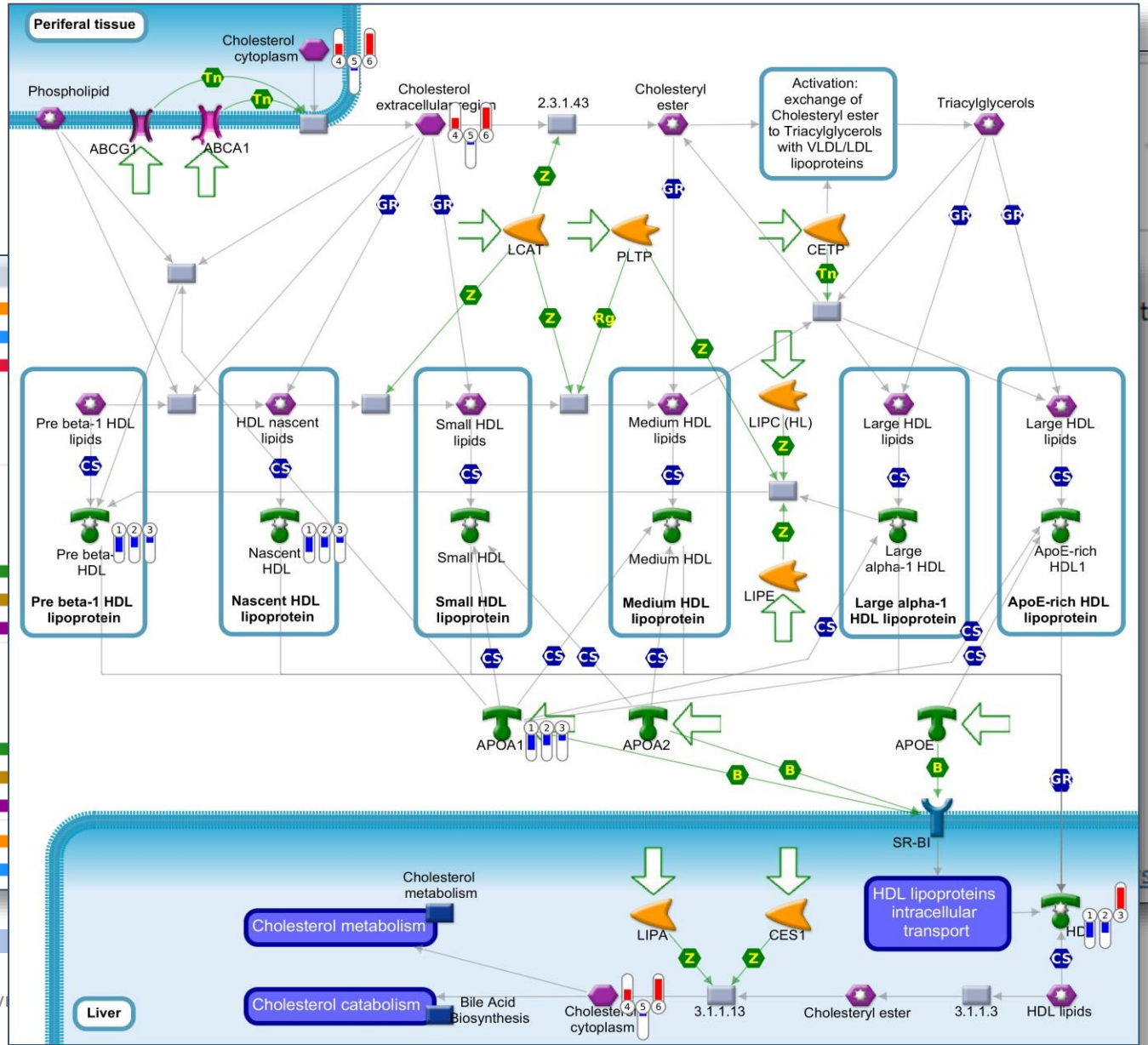


# 患者血漿中哪些代謝物和蛋白質濃度的變化可以作為生物標記?

Home ▸ Active Data

| # | Maps | 0 | 1 | 2 |
|---|---|---|---|---|
| 1 | Transport_Intracellular cholesterol transport | | | |
| 2 | Immune response_Alternative complement pathway | | | |
| 3 | Transport_HDL-mediated reverse cholesterol transport | | | |
| 4 | Cholesterol and Sphingolipid transport / Recycling to plasma membrane in lung (normal and CF) | | | |

1



# Live demo

## 上傳實驗數據及富集分析

# Demo内容

- MetaCore-GSE1122 (emphysema)

**An integrative analysis to distinguish between emphyse (EML) and alpha-1 antitrypsin deficiency related emphysem**

**Series GSE1122** Query DataSets for GSE1122

| | |
|---|---|
| Status | Public on Jun 01, 2004 |
| Title | Emphysema Lung Tissue Gene Expression Profiling |
| Organism | Homo sapiens |
| Experiment type | Expression profiling by array |
| Summary | Gene expression profiling of lung tissue from undiseased (NML), 'usual' emphysema (EML), and Alpha-1 Antitrypsin Deficiency-related emphysema (ADL).<br>Keywords = Emphysema<br>Keywords = COPD<br>Keywords = Alpha-1 Antitrypsin Deficiency<br>Keywords: ordered |

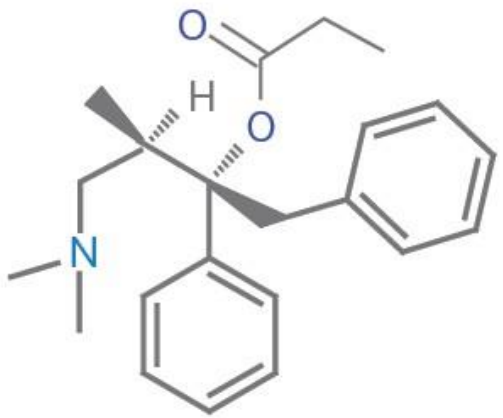
| | |
|---|---|
| Platforms (1) | GPL80 [Hu6800] Affymetrix Human Full Length HuGeneFL Array |
| Samples (15)<br>Less... | GSM18403 01_NML<br>GSM18404 02_NML<br>GSM18405 03_NML<br>GSM18406 04_NML<br>GSM18407 05_NML<br>GSM18408 02_ADL<br>GSM18409 03_ADL<br>GSM18410 04_ADL<br>GSM18411 05_ADL<br>GSM18412 06_ADL<br>GSM18413 01_EML<br>GSM18414 02_EML<br>GSM18415 03_EML<br>GSM18416 04_EML<br>GSM18417 05_EML |
| **Relations** | |
| BioProject | PRJNA87235 |

Analyze with GEO2R

# What Is MetaDrug?

# MetaDrug 預測工具：
## — 5 分鐘內你能對你的化合物了解多少？

| | 資料庫挖掘 | 代謝產物預測 | 毒性預測 | 標靶預測 | 適應症預測 | 受影響的路徑 | 體學數據分析 |
|---|---|---|---|---|---|---|---|
| METADRUG | ● | ● | ● | ● | ● | ● | ● |
| 化合物資料庫 | ● | | | | | | |
| 代謝預測工具 | | ● | | | | | |
| 毒性預測工具 | | | ● | | | | |
| 標靶/適應症預測工具 | | | | ● | ● | ● | ● |

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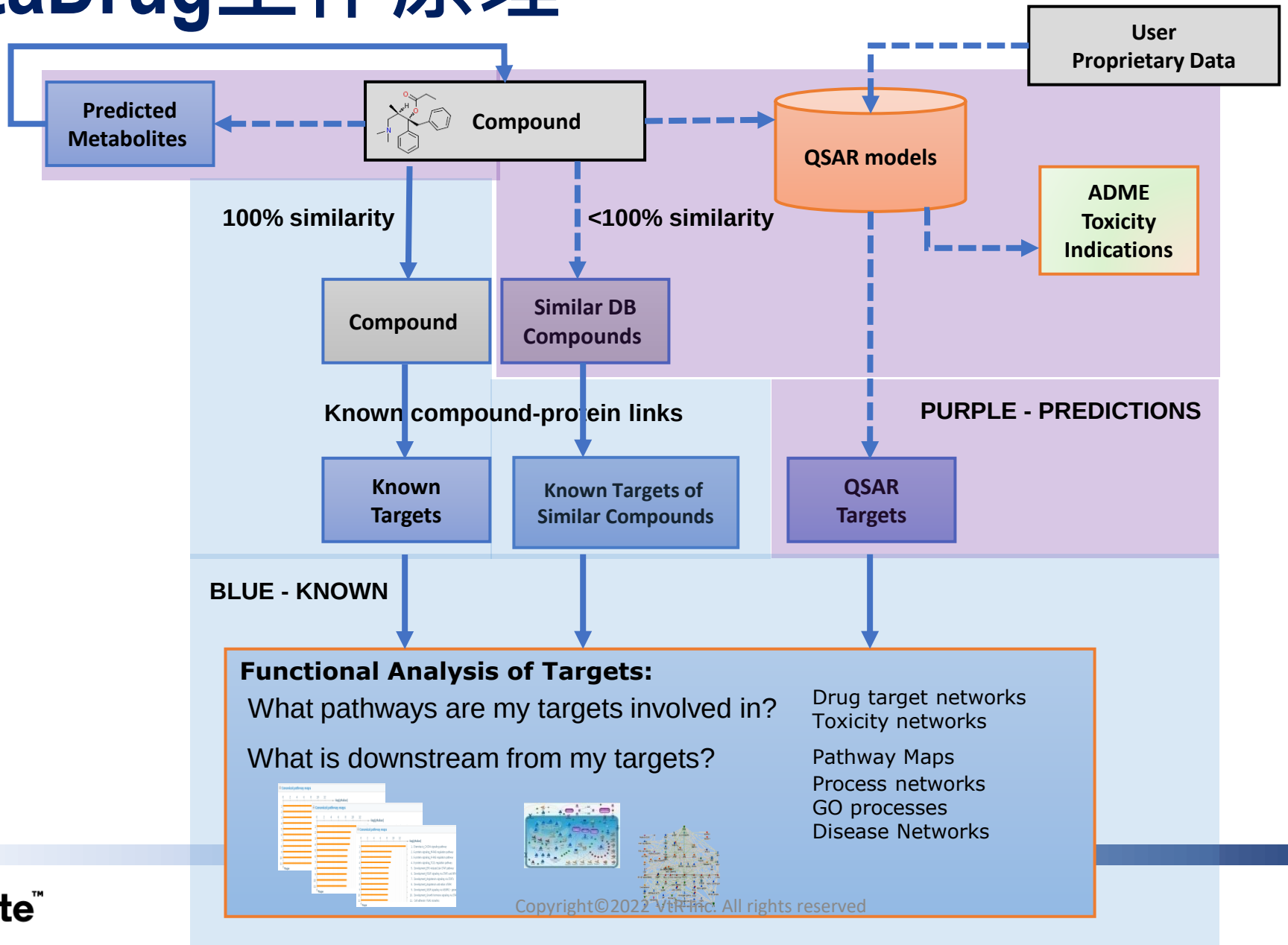
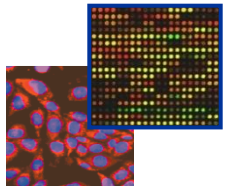
# MetaDrug工作原理




**User**
**Experimental Data**
**(Optional)**
Import and overlay
any experimental data





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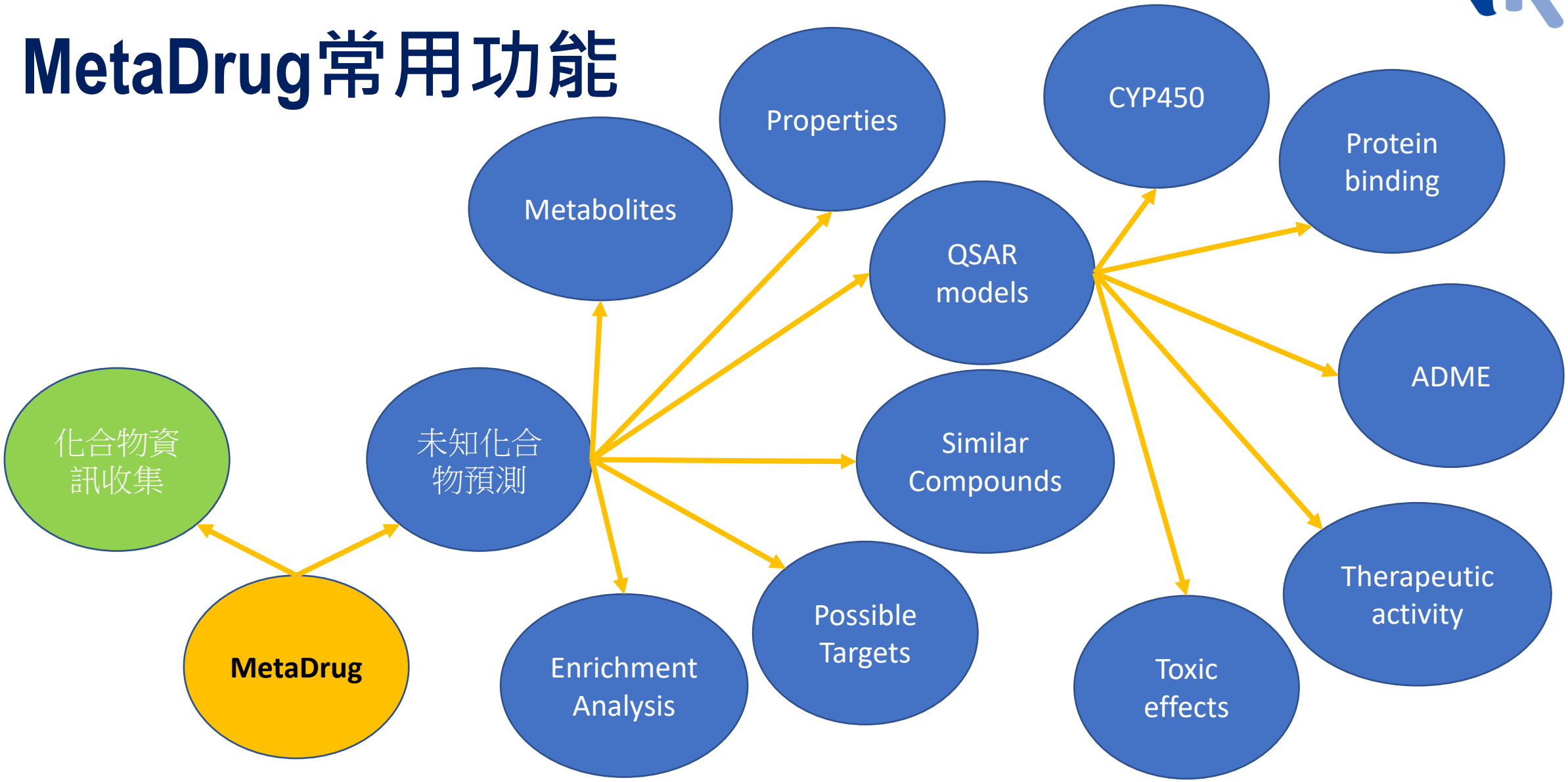
# MetaDrug 的底層資料

- > 70 QSAR 模型，用於預測化合物毒性、藥代動力學特徵、治療活性
- > 160 種代謝規則，用於代謝產物預測
- > 1,600 個經典範式路徑圖，涵蓋近200,000 個人類、小鼠、大鼠代謝和信號通路 (基於文獻報導的一致性)
- > 1,800,000 個蛋白與蛋白、DNA、RNA、代謝物、外源物相互作用
- 數千種疾病生物標記 (Biomarker)
- > 800,000 個化合物及其標靶與生物活性資料
- > 5,000 個代謝反應
- > 9,100 個藥物
- > 30,000 個內源代謝產物
- 上百萬個基因、蛋白和化合物的別稱 (同種異名)
- 人、小鼠、大鼠的蛋白複合物和蛋白家族

# MetaDrug常用功能



# 化合物的相關資訊分類

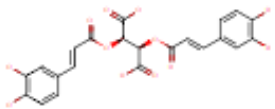
## L-Chicoric acid

Compound | Build Network | Predict Compound Activity (MetaDrug) | Download structure

### Table of Contents



### Structure



### ADMETox Properties

#### ADMETox Information

| | |
|---|---|
| Biotransformation | L-Chicoric acid undergoes reduction glucuronide and trans-caffeic acid r acetoxy-desalkyl-chicoric acid, 4-ac dihydro-chicoric acid. |

#### Toxic Pathologies

Toxic Agents for

| # | Toxic Pathology | Drug |
|---|---|---|
| 1 | Pancreas-necrosis | L-Chicoric acid |
| | | Streptozocin |
| 2 | Heart-relative weight gain ... | L-Chicoric acid |
| | | Streptozocin |
| 3 | Pancreas lesions | L-Chicoric acid |
| | | Streptozocin |
| 4 | Liver-relative weight gain (... | L-Chicoric acid |
| | | Streptozocin |

### Therapeutic Properties

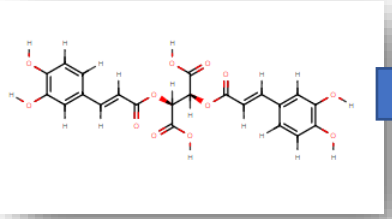
#### Therapeutic Information

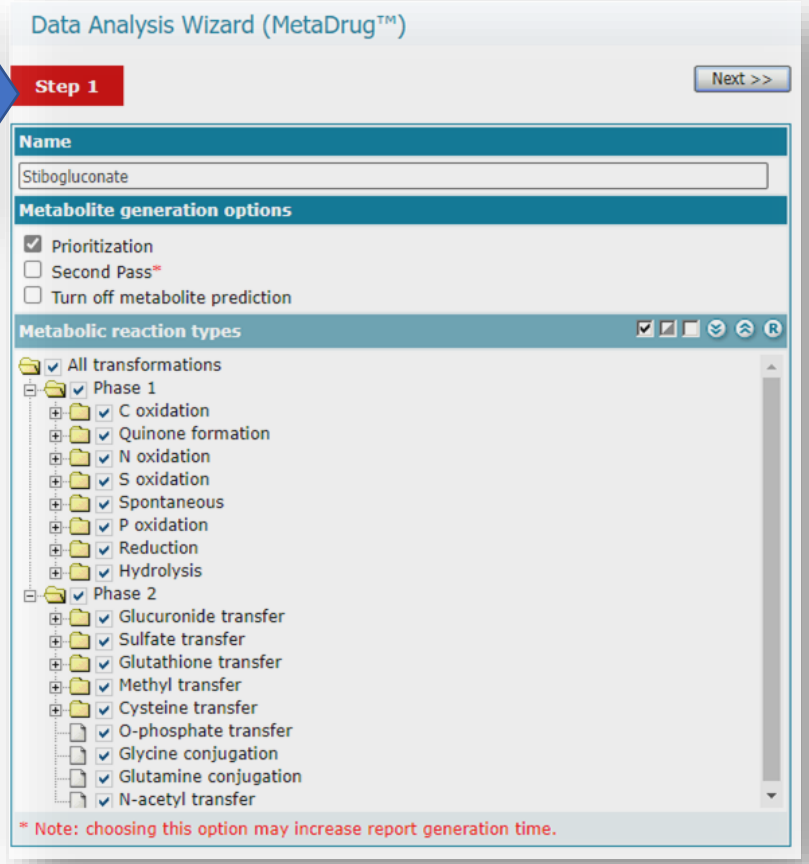
| L-Chicoric acid | |
|---|---|
| Pharmacology | HIV infection |
| Pharmacology | AIDS |

#### External Databases

| | |
|---|---|
| CAS registry | 70831-56-0 |
| ChEBI ID | CHEBI:3594 |
| ChemIDplus | 006537800, 070831560 |
| ChemSpider | 4445078 |
| DTP/NCI | 699173 |
| KEGG | C10437 |
| NIAID | 029768 |
| PubChem_Compound | 5281764 |

# Chicoric acid 的藥物活性預測






- Metabolites — 代謝物預測
- Models
  - Properties
  - CYP450 QSAR models — CYP450 代謝預測
  - Protein binding QSAR models — 蛋白質結合預測
  - ADME QSAR models — ADME預測
  - Prediction of therapeutic activity — 適應症治療活性預測
  - Prediction of toxic effects — 毒性影響預測
- Similar Compounds
- Possible Targets
- Enrichment Analysis

# 以QSAR model 進行20+種適應症治療活性預測

**Prediction of therapeutic activity**

| # | Property | Model description | Value/(TP) |
|---|---|---|---|
| 16 | Mycosis | Potential antifungal activity. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs. Model description: Training set N=172, Test set N=47, Sensitivity= 0.90, Specificity=0.88, Accuracy=0.89, MCC=0.79. Reference: Clarivate Analytics. | 0.60 (39.56) |
| 17 | Obesity | Potential activity against obesty. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Model description: Training set N=472, Test set N=75, Sensitivity= 0.89, Specificity=0.97, Accuracy=0.93, MCC=0.87. Reference: Clarivate Analytics. | 0.93 (31.64) |
| 18 | Osteoporosis | Potential anti-osteoporosis activity. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Model description: Training set N=595, Test set N=86, Sensitivity= 0.84, Specificity=0.85, Accuracy=0.85, MCC=0.70. Reference: Clarivate Analytics. | 0.67 (39.66) |
| 19 | Pain | Potential analgetic activity. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs. Model description: Training set N=525, Test set N=84, Sensitivity= 0.92, Specificity=0.67, Accuracy=0.79, MCC=0.60. Reference: Clarivate Analytics. | 0.10 (38.89) |
| 20 | Parkinson | Potential activity against Parkinson's disease. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Model description: Training set N=298, Test set N=49, Sensitivity= 0.96, Specificity=0.96, Accuracy=0.96, MCC=0.92. Reference: Clarivate Analytics. | 0.08 (35.89) |
| 21 | Psoriasis | Potential activity against psoriasis. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Model description: Training set N=199, Test set N=32, Sensitivity= 0.93, Specificity=0.82, Accuracy=0.89, MCC=0.74. Reference: Clarivate Analytics. | 0.14 (50.63) |
| 22 | Schizophrenia | Potential activity against schizophrenia. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Model description: Training set N=616, Test set N=93, Sensitivity= 0.89, Specificity=0.91, Accuracy=0.90, MCC=0.80. Reference: Clarivate Analytics. | 0.71 (53.33) |
| 23 | Skin Diseases | Potential activity against skin diseases. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs. Model description: Training set N=255, Test set N=36, Sensitivity= 1.00, Specificity=0.76, Accuracy=0.86, MCC=0.76. Reference: Clarivate Analytics. | 0.64 (41.76) |

Clarivate™

# 以QSAR model 進行20+種毒性預測

**Prediction of toxic effects**

| # | Property | Model description | Value/(TP) |
|---|---|---|---|
| 1 | AMES | Potential to be mutagenic (AMES positive), range from 0 to 1. A value of 1 is AMES positive (mutagenic), and a value of 0 is AMES negative (non-mutagenic). Cutoff is 0.5. Values close to zero are preferable. The AMES assay is based upon the reversion of mutations in the histidine operon in the bacterium Salmonella enterica sv Typhimurium. Reference: Young, Gombar, et al., 2002 (DOI: 10.1016/S0169-7439(01)00181-2). Model description: N=1780, R2=0.69, RMSE=0.29. | 0.22 (74.85) |
| 2 | Anemia | Potential for causing anemia. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing anemia in vivo. Model organisms: human. Model description: Training set N=324, Test set N=51, Sensitivity= 0.82, Specificity=0.90, Accuracy=0.86, MCC=0.72. Reference: Clarivate Analytics. | 0.22 (36.32) |
| 3 | Carcinogenicity | Potential for inducing carcinogenicity in rats and mice. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: mouse, rat. Reference: ISSCAN data. Model description: Training set N=1210, Test set N=185, Sensitivity= 0.96, Specificity=0.90, Accuracy=0.93, MCC=0.86. | 0.10 (53.33) |
| 4 | Carcinogenicity Mouse Female | Potential for inducing carcinogenicity in female mice. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: female mice. Reference: ISSCAN data. Model description: Training set N=640, Test set N=94, Sensitivity= 0.90, Specificity=0.93, Accuracy=0.92, MCC=0.83. | 0.16 (53.33) |
| 5 | Carcinogenicity Mouse Male | Potential for inducing carcinogenicity in male mice. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: mouse male. Reference: ISSCAN data. Model description: Training set N=584, Test set N=93, Sensitivity= 0.91, Specificity=0.88, Accuracy=0.89, MCC=0.78. | 0.20 (53.33) |
| 6 | Carcinogenicity Rat Female | Potential for inducing carcinogenicity in female rats. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: female rat. Reference: ISSCAN data. Model description: Training set N=667, Test set N=120, Sensitivity= 0.90, Specificity=0.96, Accuracy=0.93, MCC=0.86. | 0.07 (39.56) |

# Live demo

以化合物進行活性分析及預測

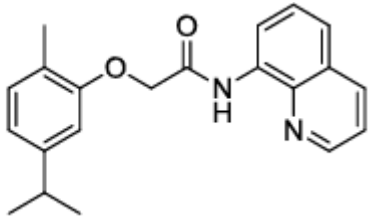
# Demo内容

- Carvacrol derivative 5v (Alzheimer's disease)

**Synthesis, Anticholinesterase Activity and Molecular Modeling Studies of Novel Carvacrol Substituted Amide Derivatives**

Belma Zengin Kurt[1,*], Serdar Durdagi[2,*], Gulsen Celebi[3], Ramin Ekhteiari Salmas[2], Fatih Sonmez[4]

5v




*J. Biomol. Struct. Dyn*. 2020, 38(3):841-859

Mol. Nutr. Food Res. 2008, *52*, 789–798 DOI 10.1002/mnfr.200700113

Review

## A critical evaluation of drug interactions with *Echinacea* spp.

**Camille Freeman [1,3] and Kevin Spelman [2,3]**

[1] Department of Physiology and Biophysics (MS candidate), Georgetown University, Washington, DC, USA
[2] Department of Chemistry and Biochemistry, University of North Carolina, Greensboro, NC, USA
[3] Department of Herbal Medicine, Tai Sophia Institute, Laurel, MD, USA

Another isoform of the CYP 450 system, CYP2D6, is known to play a primary role in the metabolism of pharmaceuticals used to treat psychiatric disorders (attention deficit/hyperactivity disorders, bipolar disorder, depression, schizophrenia) as well as cardiovascular disorders (β-block-

紫錐花萃取物可能透過 cytochrome P450 活性抑制，影響精神失調相關的治療。

## Analysis of the inhibitory potential of Ginkgo biloba, Echinacea purpurea, and Serenoa repens on the metabolic activity of cytochrome P450 3A4, 2D6, and 2C9

Steven H Yale [1], Ingrid Glurich

Affiliations + expand

PMID: 15992226 DOI: 10.1089/acm.2005.11.433

**Results:** S. repens showed potent inhibition of the metabolic activity of all three CYPs tested. The effects of G. biloba and E. purpurea varied. E. purpurea demonstrated mild inhibition of CYP3A4 activity with 7- benzyloxy-4-trifluoromethylcoumarin (BFC) as the model substrate, but mild inducing effects in the presence of the model substrate resorufin benzyl ether (BzRes). Little effect on CYP2D6 and moderate inhibition of CYP2C9 was seen with both E. purpurea and G. biloba. G. biloba also showed mild-to-moderate inhibition of CYP3A4 depending on the model substrate.

# 案例分享

IVYSPRING INTERNATIONAL PUBLISHER

*International Journal of Medical Sciences*

2021; 18(1): 256-269. doi: 10.7150/ijms.48123

Research Paper

# Upregulation of peroxisome proliferator-activated receptor-α and the lipid metabolism pathway promotes carcinogenesis of ampullary cancer

Chih-Yang Wang[1,2], Ying-Jui Chao[3,4], Yi-Ling Chen[5], Tzu-Wen Wang[3], Nam Nhut Phan[6], Hui-Ping Hsu[3,7]✉, Yan-Shen Shan[3], Ming-Derg Lai[8,9,10]

*Int. J. Med. Sci.* 2021, 18(1):256-269

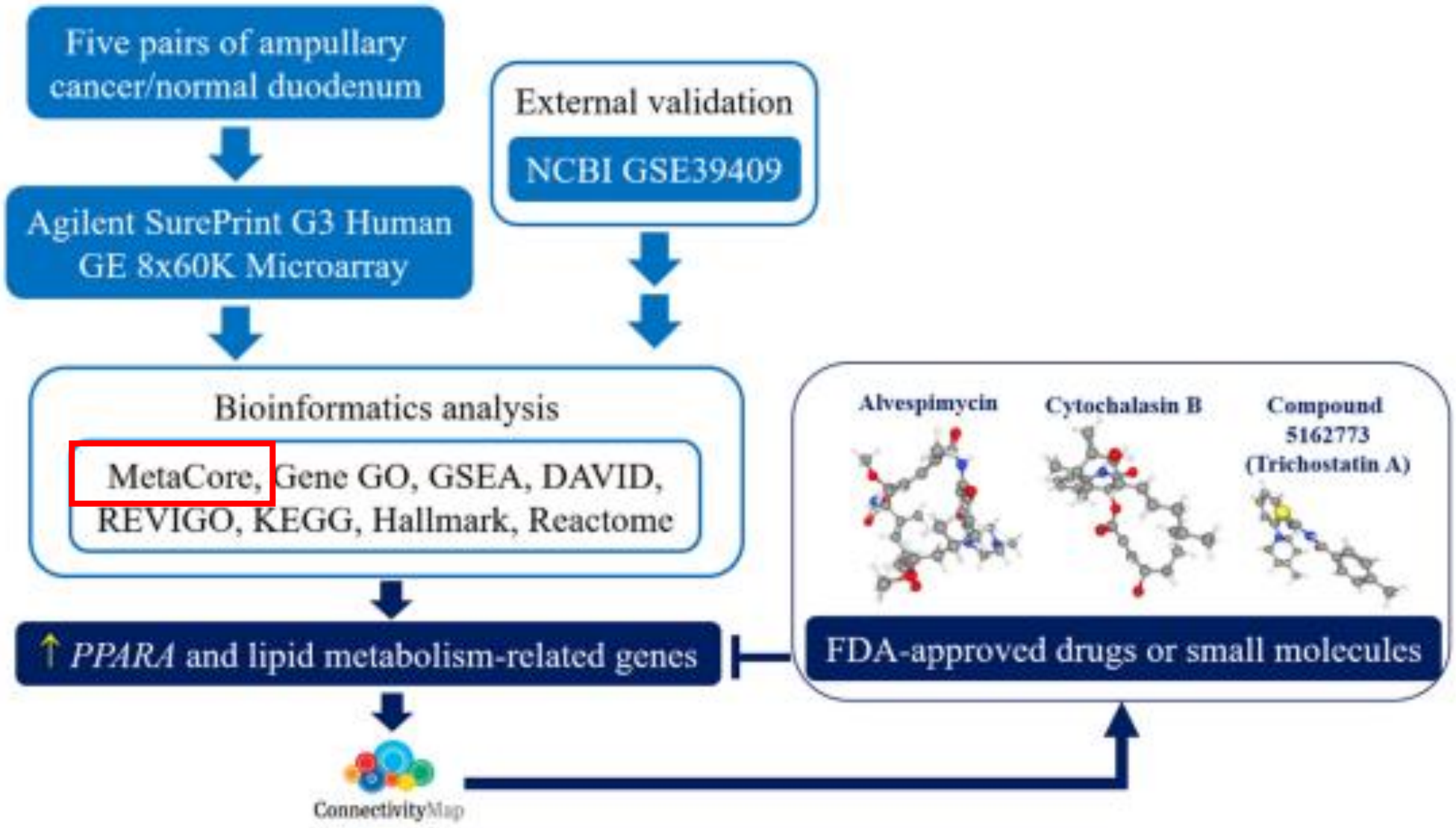
# Ampullary cancer

- Ampullary cancer is a rare type of cancer with an incidence of 0.0004%~0.0006% in the general population and 0.5% among total gastrointestinal cancer cases
- The 5-year survival rate of ampullary cancer patients ranges 30%~50%, and adjuvant chemotherapy or radiotherapy fails to improve survival
- Genetic polymorphisms of lipid metabolism-related genes were correlated with the development of biliary tract cancer and ampullary cancer
- Peroxisome proliferator-activated receptor (PPAR) and its related lipid metabolism pathway were involved in the development of ampullary cancer

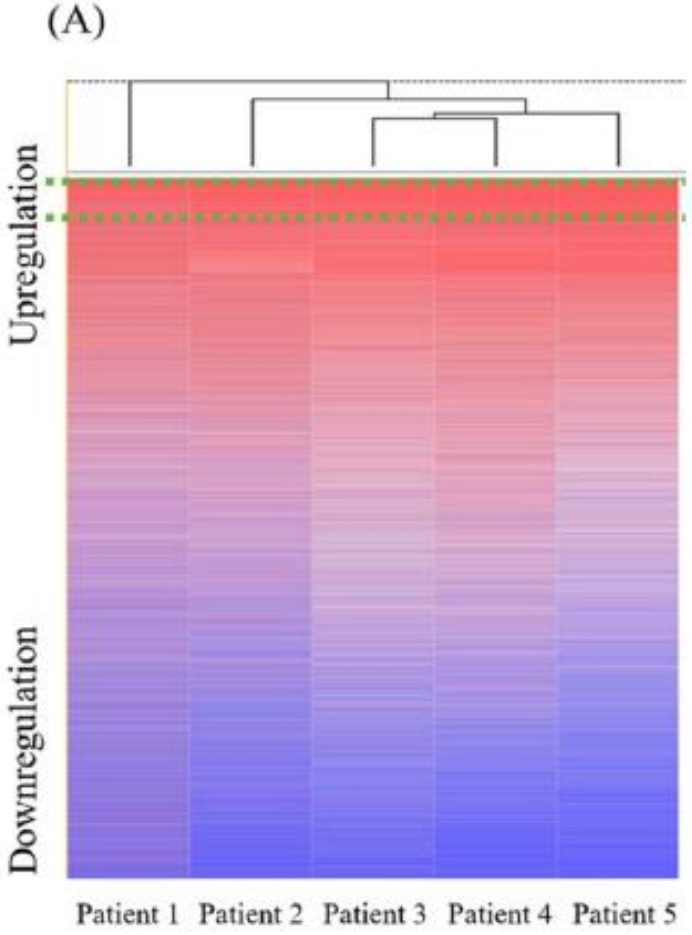
# Peroxisome proliferator-activated receptor (PPAR)

- The PPAR family protein, known as ligand-inducible transcription factors, comprises three members: PPAR-α, PPAR-β, and PPAR-γ (*PPARA*, *PPARD*, and *PPARG* gene, respectively).
- PPAR-α acts as a key factor of tumorigenesis, its role in ampullary cancer is unknown
- Exploring the function of PPAR-α in ampullary cancer from our dataset and public databases, followed by a search for potential drugs using Connectivity Map (CMap)

Connectivity Map (cmap)資料庫最初建立是為了連結生物學、化學和臨床情況，幫助發現疾病-藥物-基因的關係，包含超過1300種美國FDA核准的藥物和小分子。



# Complementary (c)DNA microarray

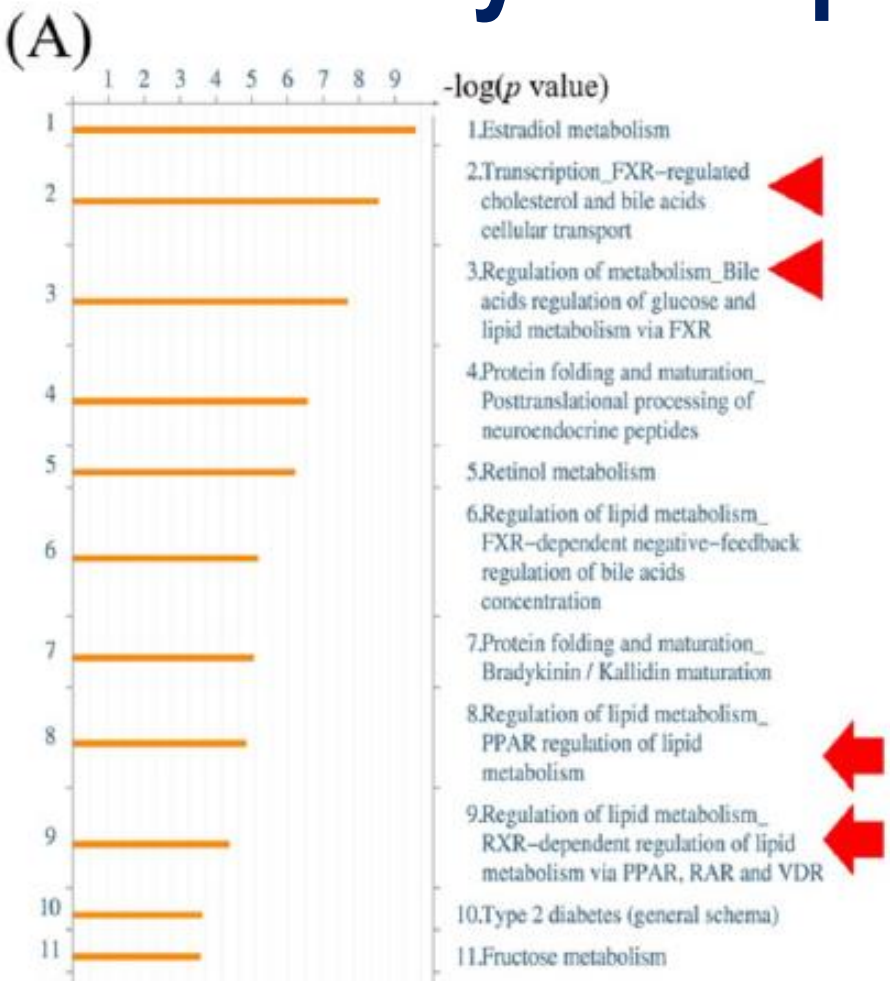


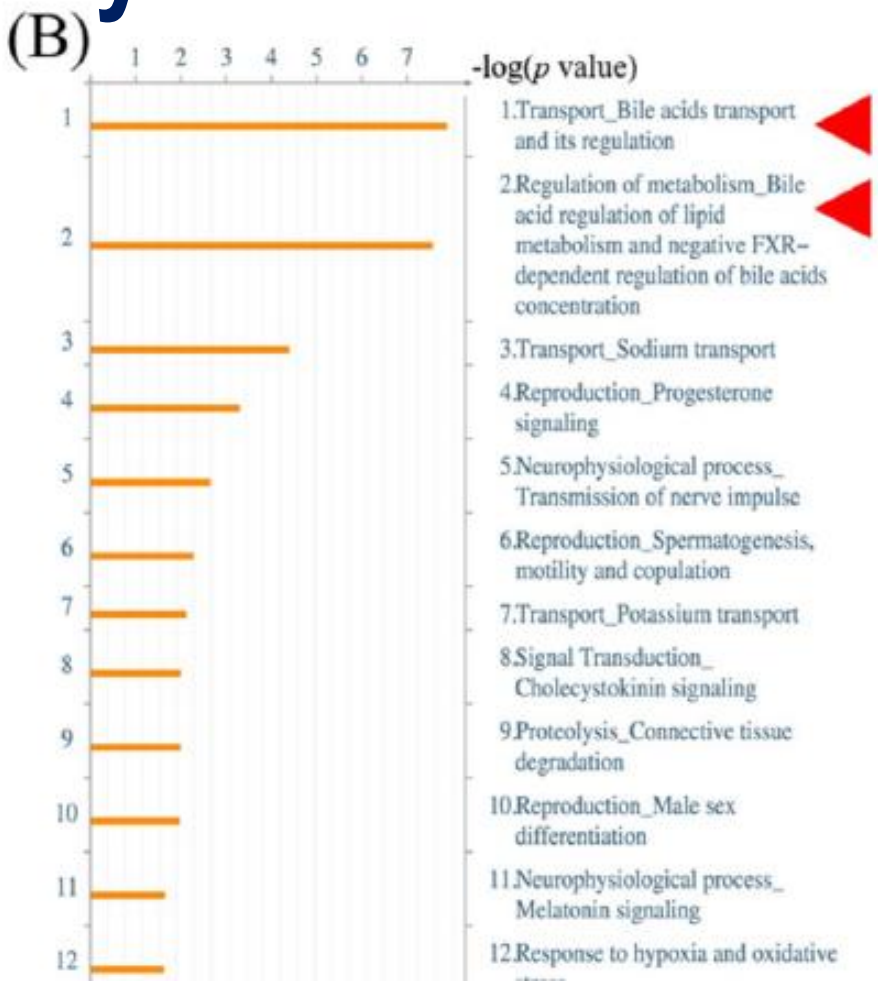

| KEGG_PATHWAY | *p* value |
|---|---|
| PPAR signaling pathway | 2.05E-11 |
| Retinol metabolism | 2.78E-10 |
| Drug metabolism | 4.65E-09 |
| Metabolism of P450 | 1.61E-08 |
| Steroid hormone biosynthesis | 2.24E-06 |
| Fatty acid metabolism | 2.27E-06 |
| Linoleic acid metabolism | 1.34E-05 |
| Arachidonic acid metabolism | 2.79E-05 |
| Arginine and proline metabolism | 6.70E-05 |
| Pentose and glucuronate interconversions | 1.50E-04 |
| Drug metabolism | 1.63E-04 |
| Maturity onset diabetes of the young | 2.43E-04 |
| Starch and sucrose metabolism | 6.03E-04 |
| Valine, leucine and isoleucine degradation | 8.94E-04 |
| Alanine, aspartate and glutamate metabolism | 1.21E-03 |
| Glycine, serine and threonine metabolism | 1.21E-03 |
| Fructose and mannose metabolism | 2.30E-03 |
| Glycolysis / Gluconeogenesis | 3.20E-03 |
| ABC transporters | 3.48E-03 |
| Androgen and estrogen metabolism | 4.04E-03 |
| Nitrogen metabolism | 4.71E-03 |
| Sulfur metabolism | 8.22E-03 |
| Histidine metabolism | 1.54E-02 |
| Pantothenate and CoA biosynthesis | 1.91E-02 |
| Tryptophan metabolism | 2.23E-02 |

# MetaCore analysis of a complementary (c)DNA microarray of ampullary cancer

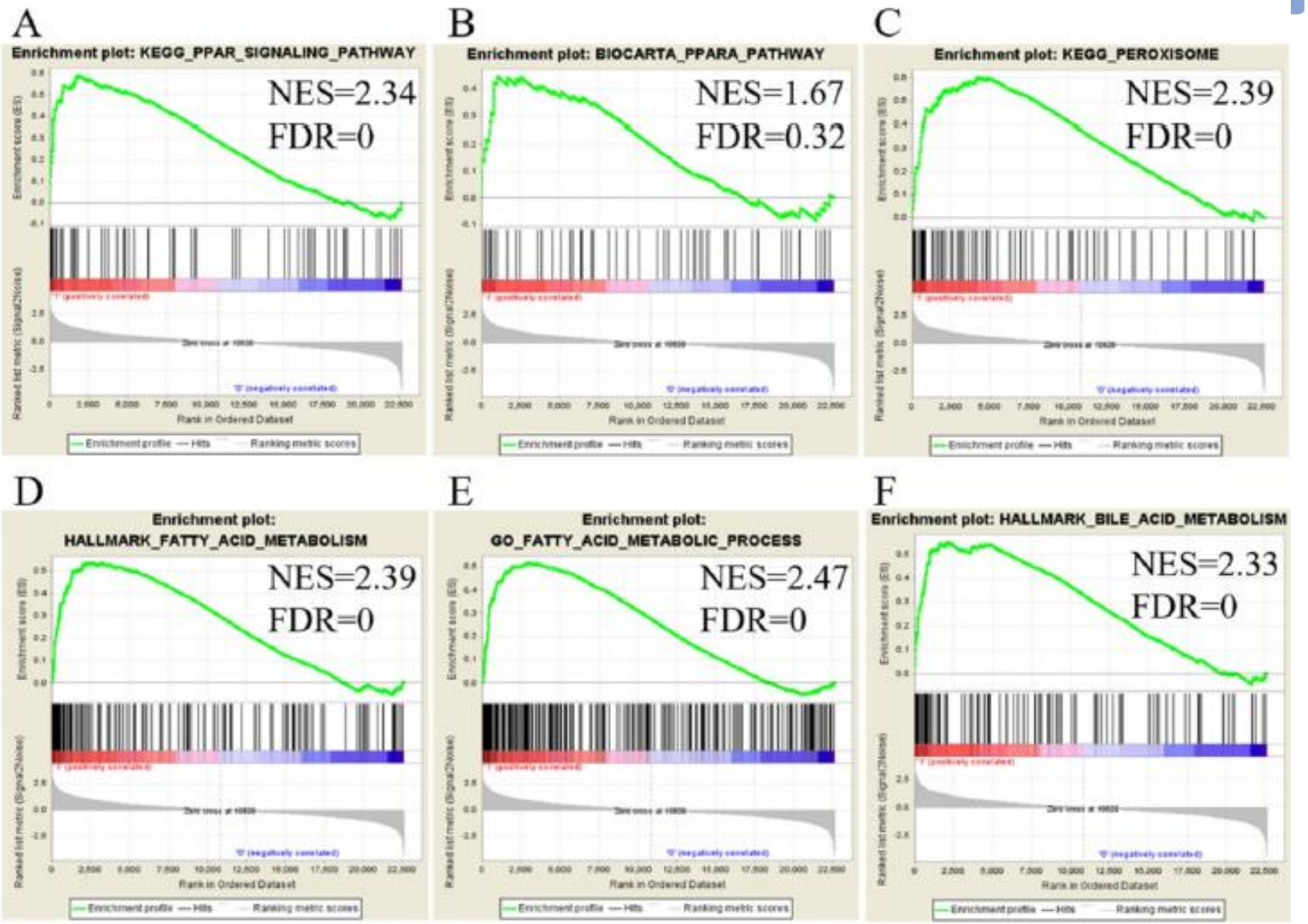
膽汁酸相關的路徑

脂質代謝相關路徑

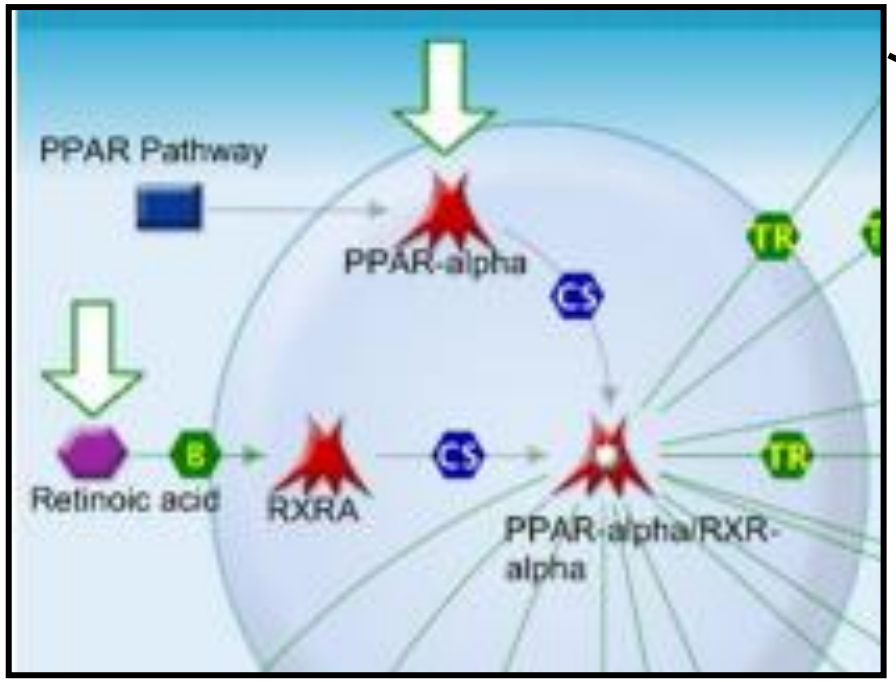


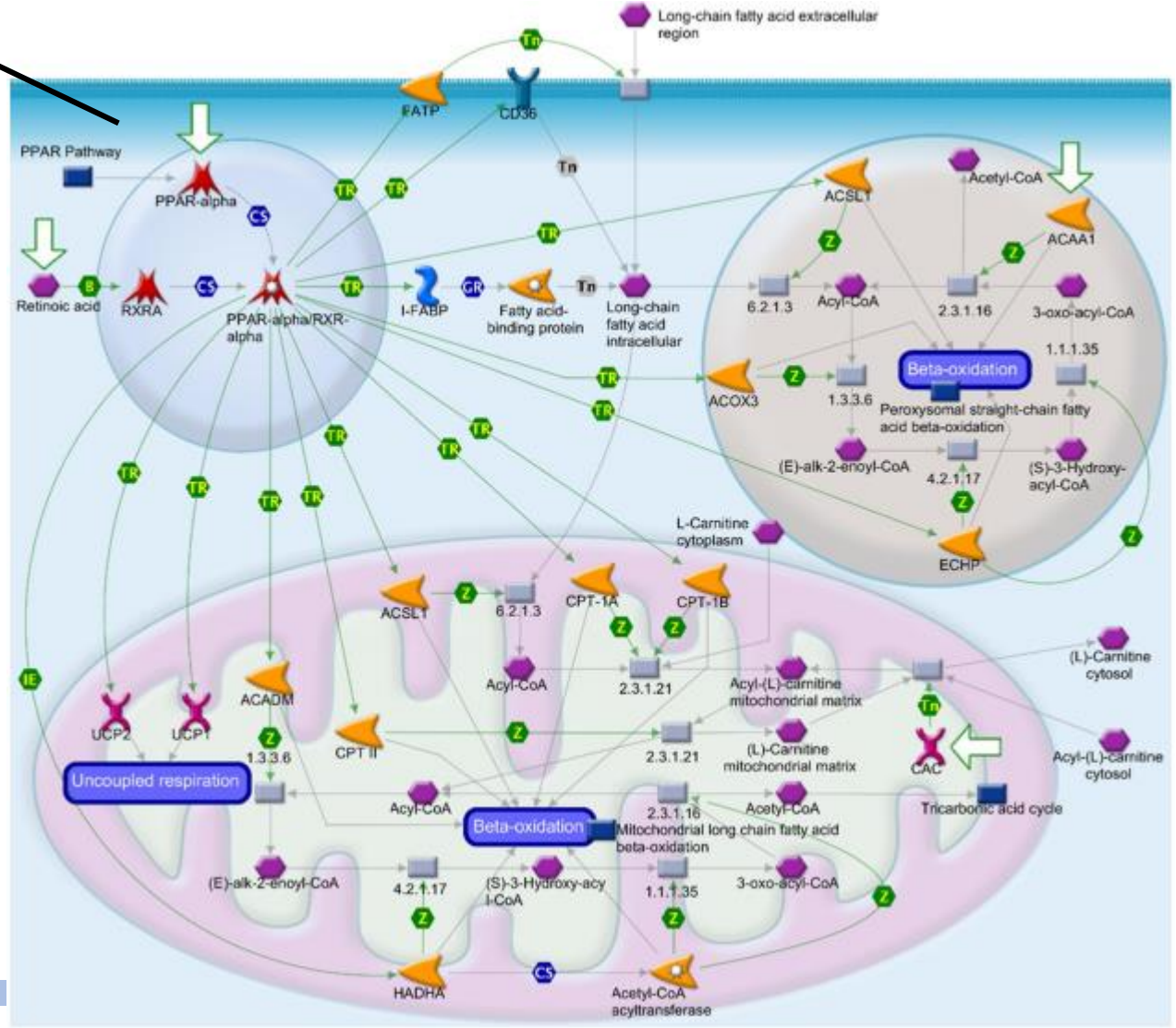



# GSEA



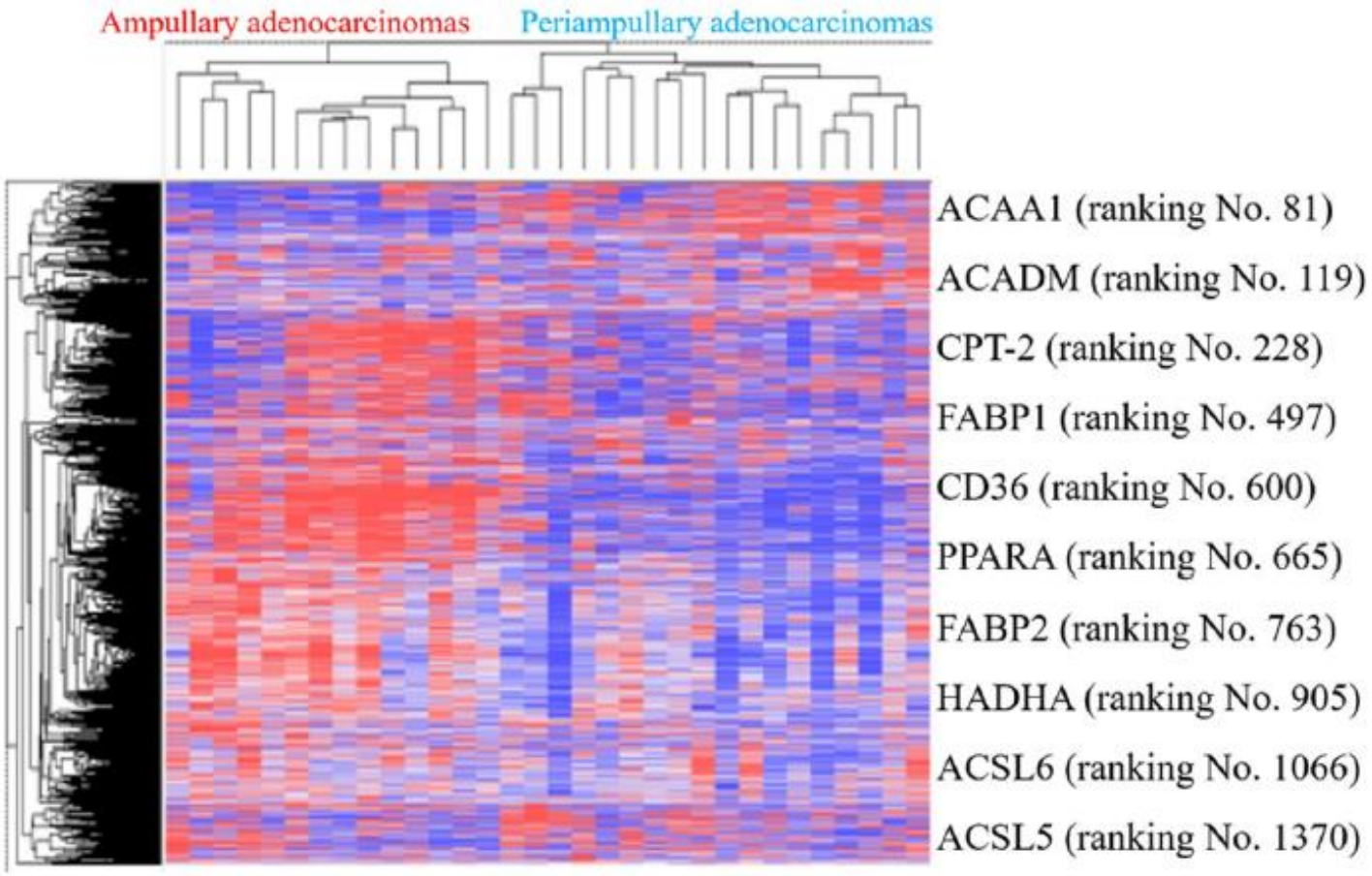
# PPAR signaling pathway in the MetaCore analysis



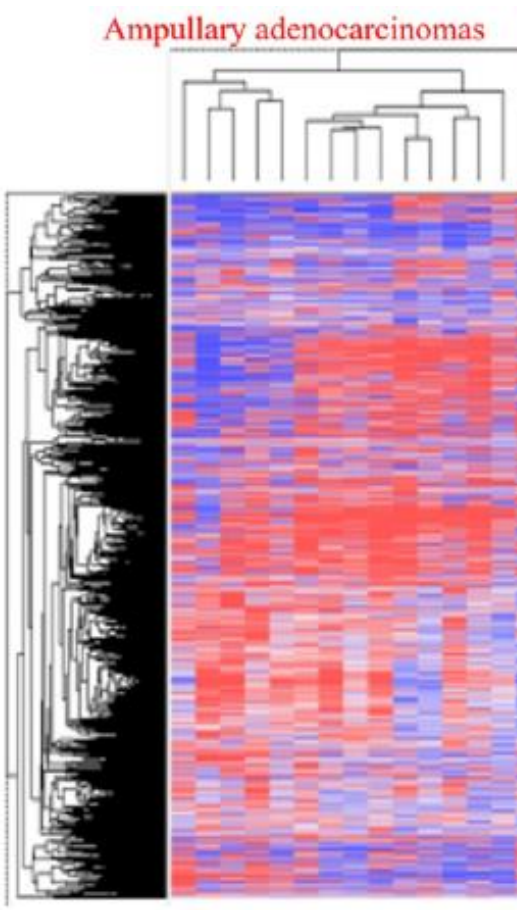



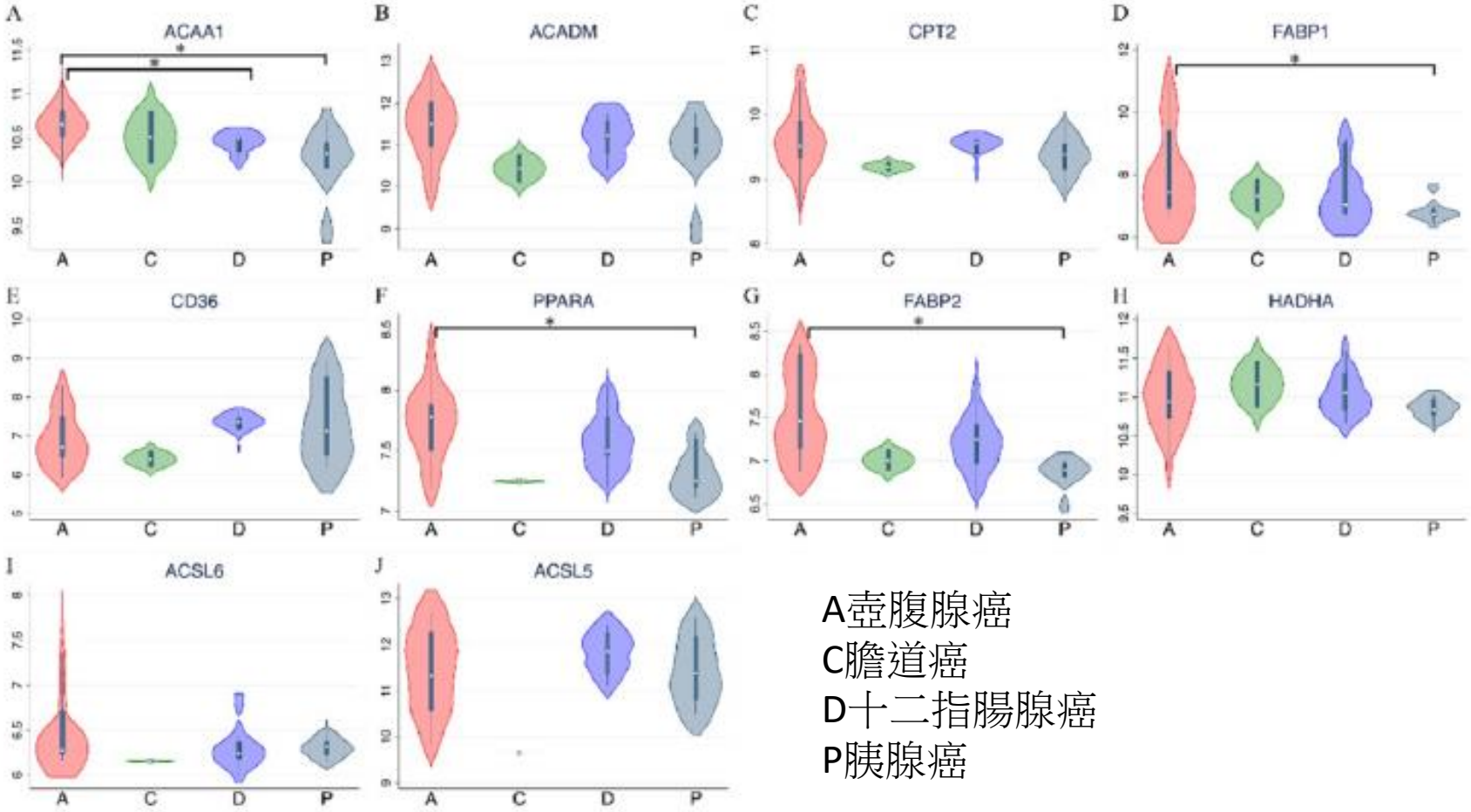

PPAR alpha跟RXRA形成complex
The PPAR-α訊號和脂質代謝相關路徑
被選擇作為壺腹癌致癌機制的研究

# Heatmap of expression (cancer/normal) ratios in the GSE39409 dataset



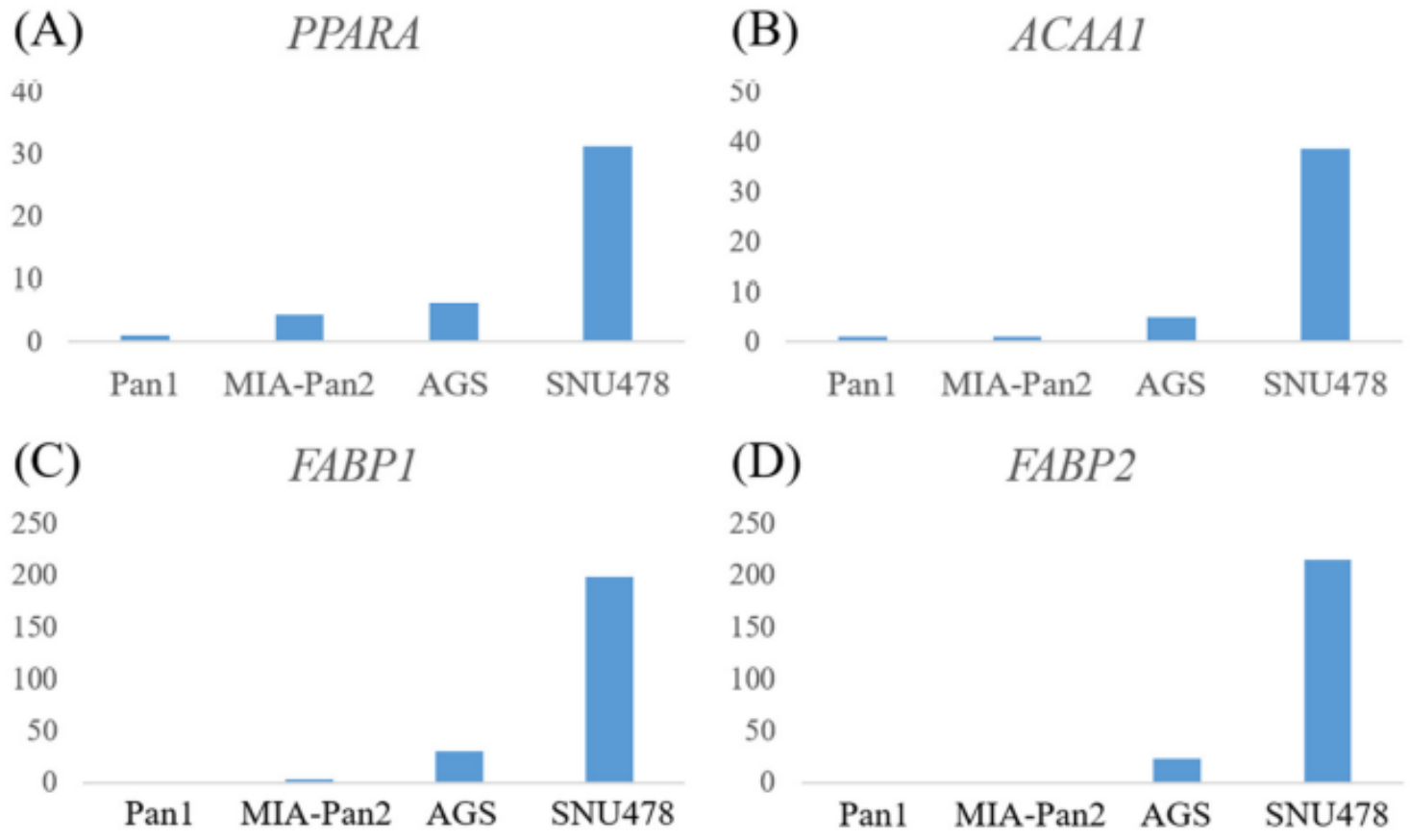
# Heatmap of expression (cancer/normal) ratios in the GSE39409 dataset

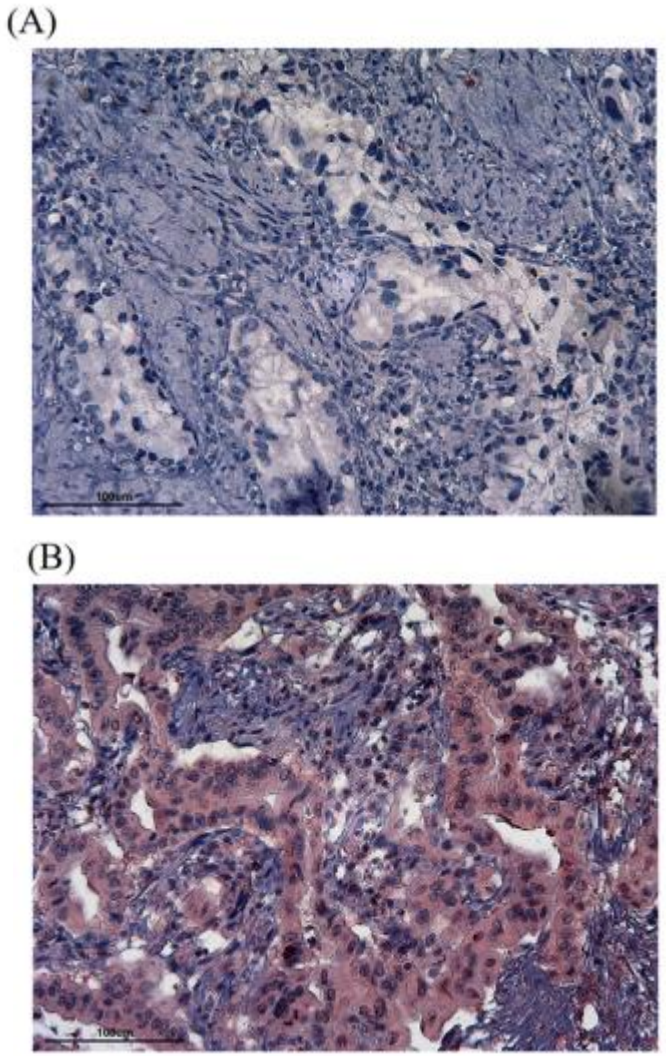



A壺腹腺癌
C膽道癌
D十二指腸腺癌
P胰腺癌

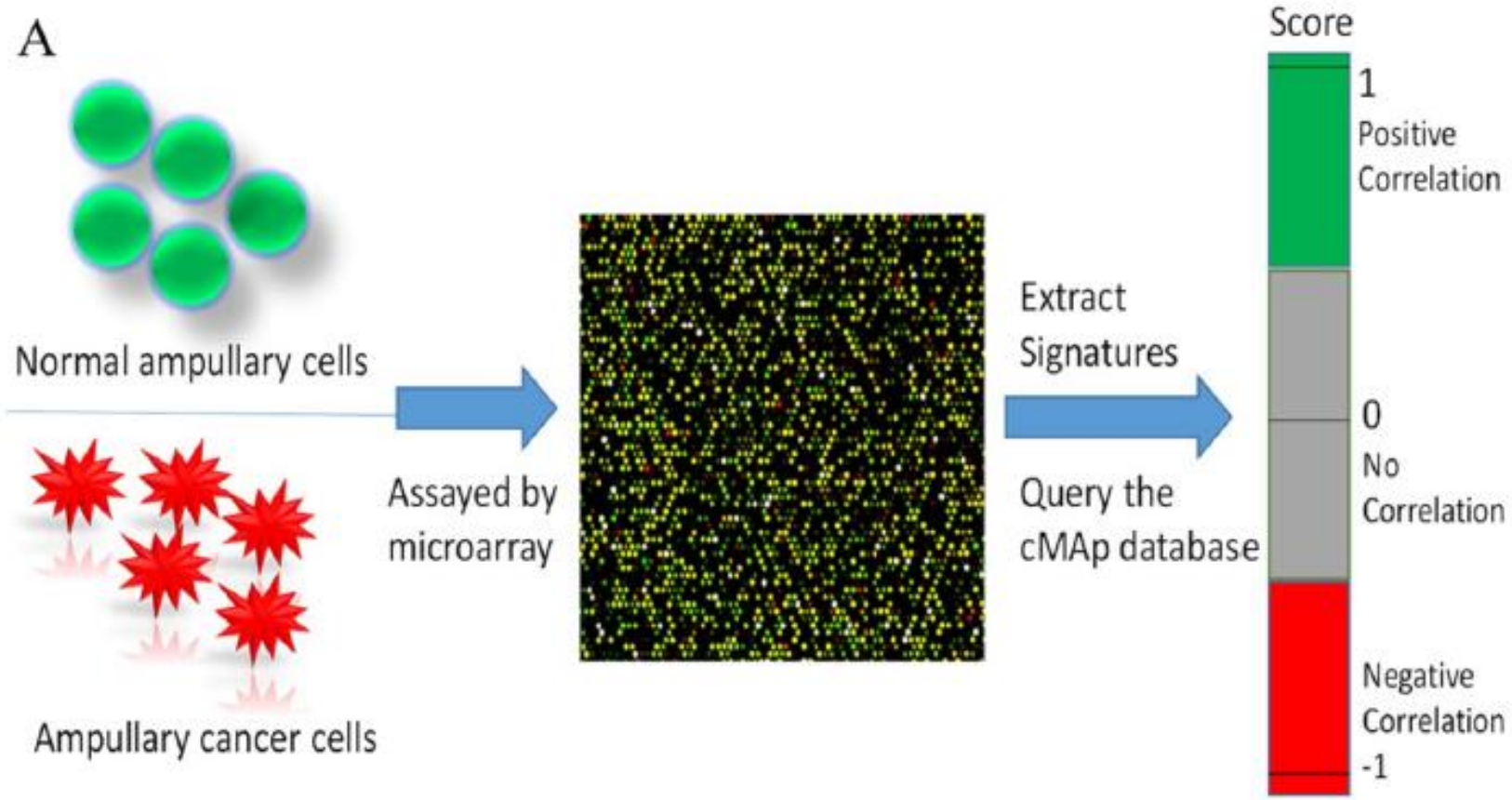
# PPARA mRNA在壺腹癌細胞株的表現量高於其他癌症的細胞(胰臟癌、結腸癌、胃癌)



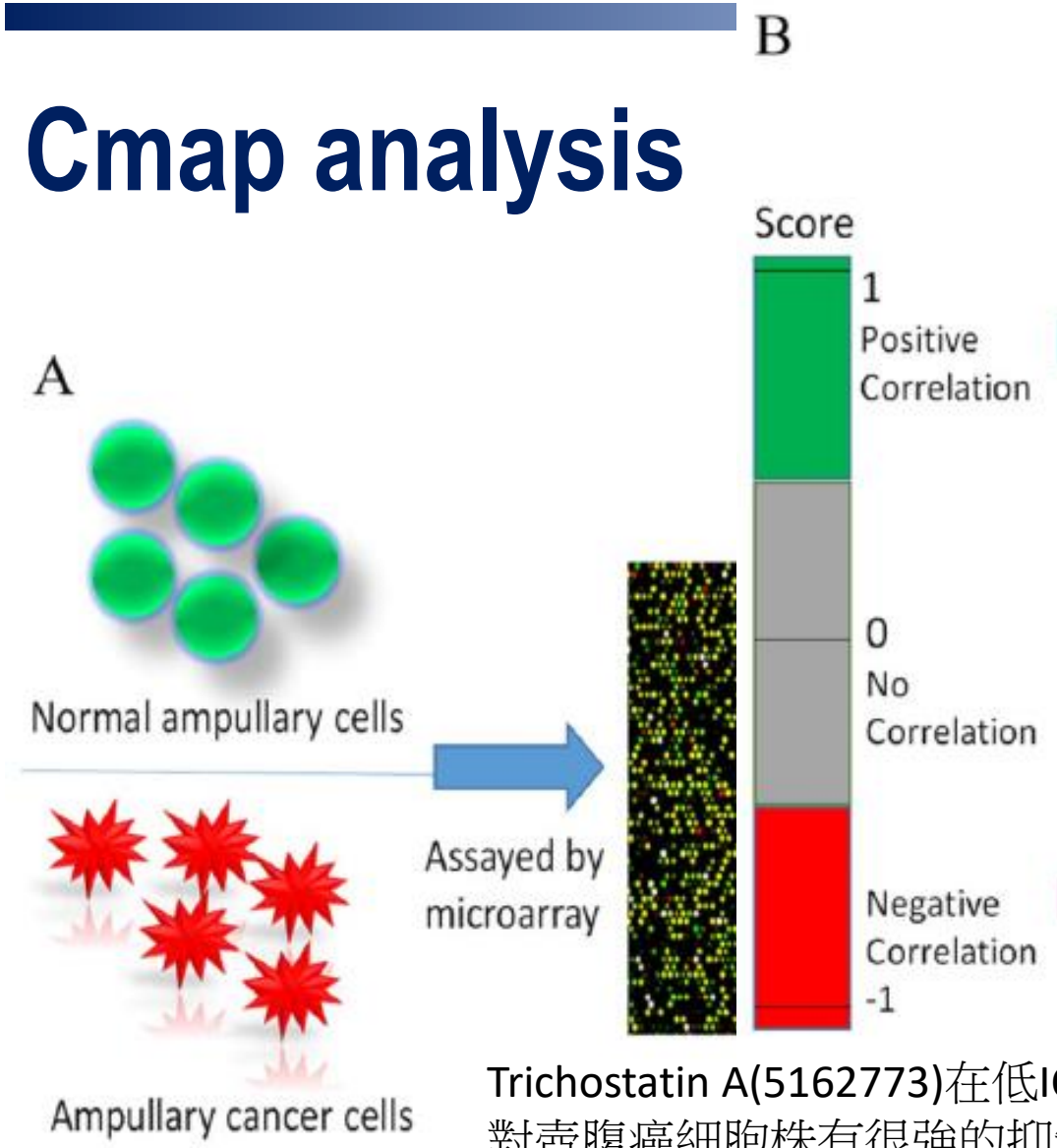




壺腹癌細胞株: SNU-478.
胃癌細胞株: AGS.
胰臟癌細胞株: Pan1 and MIA-Pan2.

# Cmap analysis



# Cmap analysis



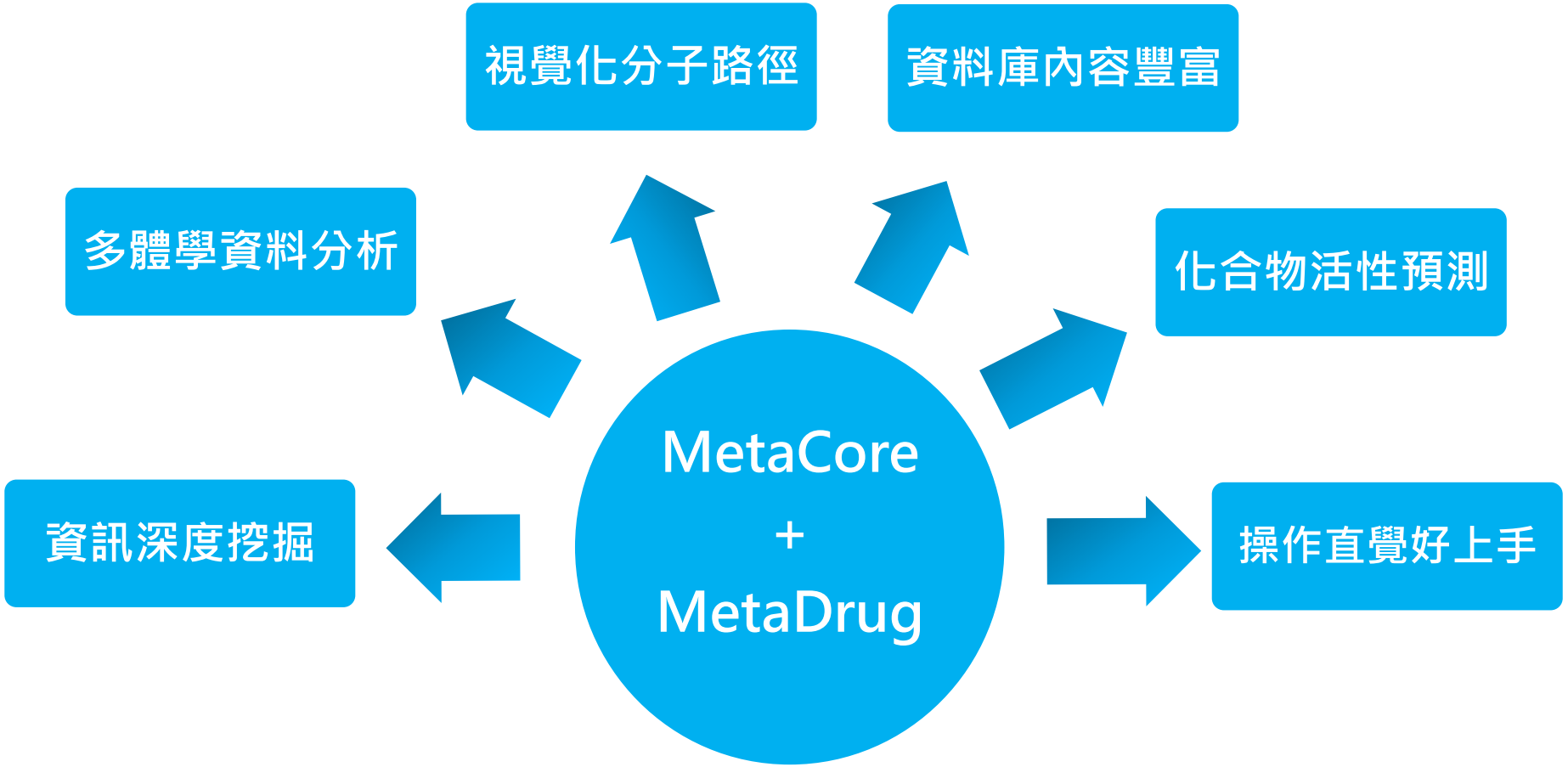

| rank | cmap name | dose | cell | score |
|---|---|---|---|---|
| 1 | vorinostat | 10 μM | HL60 | 1 |
| 2 | trichostatin A | 1 μM | HL60 | 0.961 |
| 3 | LY-294002 | 10 μM | MCF7 | 0.957 |
| 7 | aminoglutethimide | 17 μM | MCF7 | 0.889 |
| 9 | sirolimus | 100 nM | MCF7 | 0.874 |
| 10 | 5151277 | 14 μM | MCF7 | 0.87 |
| 11 | pepstatin | 6 μM | HL60 | 0.869 |
| 12 | nordihydroguaiaretic acid | 1 μM | MCF7 | 0.866 |
| 13 | zoxazolamine | 24 μM | HL60 | 0.859 |
| 16 | quercetin | 1 μM | MCF7 | 0.847 |
| 17 | valproic acid | 1 mM | HL60 | 0.843 |
| 18 | fluphenazine | 10 μM | HL60 | 0.842 |
| 19 | zardaverine | 15 μM | MCF7 | 0.839 |
| 20 | diflorasone | 8 μM | HL60 | 0.837 |
| 21 | buflomedil | 12 μM | HL60 | 0.837 |
| 22 | thiamazole | 35 μM | MCF7 | 0.831 |
| 24 | orlistat | 10 μM | MCF7 | 0.823 |
| 26 | cefalonium | 9 μM | MCF7 | 0.82 |

| rank | cmap name | dose | cell | score |
|---|---|---|---|---|
| 6084 | monorden | 100 nM | HL60 | -0.884 |
| 6085 | demecolcine | 12 μM | MCF7 | -0.885 |
| 6086 | 15-delta prostaglandin J2 | 10 μM | MCF7 | -0.887 |
| 6087 | sulfaphenazole | 13 μM | MCF7 | -0.895 |
| 6088 | SR-95531 | 11 μM | HL60 | -0.897 |
| 6089 | thioridazine | 10 μM | HL60 | -0.898 |
| 6090 | nitrofural | 20 μM | MCF7 | -0.91 |
| 6091 | cytochalasin B | 21 μM | MCF7 | -0.917 |
| 6092 | cinnarizine | 11 μM | MCF7 | -0.938 |
| 6093 | N-acetylmuramic acid | 14 μM | HL60 | -0.946 |
| 6094 | 5162773 | 7 μM | MCF7 | -0.947 |
| 6095 | dihydroergotamine | 3 μM | PC3 | -0.949 |
| 6096 | bucladesine | 2 μM | MCF7 | -0.958 |
| 6097 | N-acetyl-L-aspartic acid | 23 μM | HL60 | -0.958 |
| 6098 | aminoglutethimide | 17 μM | MCF7 | -0.96 |
| 6099 | alvespimycin | 100 nM | HL60 | -0.963 |
| 6100 | digoxin | 5 μM | MCF7 | -1 |

Trichostatin A(5162773)在低IC50下對壺腹癌細胞株有很強的抑制增殖能力

# Summary

# MetaCore+MetaDrug 分子路徑與藥物活性預測平台
## 讓研究員看的到分子路徑，快速了解分子間複雜的交互關係
## 是探討致病機制、藥物作用的一大利器



# 可信任的，高品質的內容——全、準、新

| Percentage of statistically significant intersections with gold standards | Transcription factor/ Gold standard ID# |
|---|---|
| 16% | Ingenuity (Transcription) |
| 36% | Ingenuity (All) |
| 32% | TransPath |
| 16% | TransFac |
| 16% | Biocarta |
| 24% | KEGG |
| 8% | Wikipathways |
| 16% | Cell Signaling Technology |
| 16% | GeneSpring (Expression or Binding) |
| 4% | GeneSpring (Expression and Binding) |
| 28% | PathwayStudio |
| **84%** | **MetaCore** |

Systematic study of transcription factors and their targets identified through *"gold standard experiments"* and intersection with transcriptional regulatory interactions in free and commercially available databases

Assessing quality and completeness of human transcriptional regulatory pathways on a genome-wide scale *Biol. Direct* 2011, 6:15



聆聽完本資料庫介紹，請撥空掃描QC code，填寫資料庫的問卷回饋，非常感謝您的支持!