MetaCore+MetaDrug 教育訓練

法德利科技
李尚樫 博士

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Instructor

李尚樫 Kenneth Lee

- 國立台灣大學 理學博士
- **經歷**

農委會科技計畫
陽明大學微生物與免疫學 計畫研究
台灣大學生命科學院 動物實驗 講師
法德利科技股份有限公司　　產品管理部
(負責產品 : Clarivate Cortellis MetaDrug+MetaCore, Cortellis CDDI, BIOVIA Pipeline Pilot)

- **專長**

生理學、內分泌學、分子內分泌、生物資訊

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VtR Inc 法德利科技

法德利：專注於產業數位轉型的專業團隊

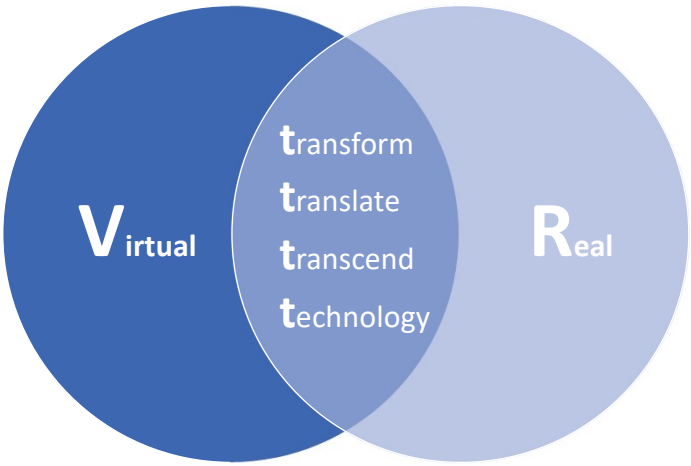
Harnessing the Power of
Virtual Technology to
transform the
Real World!



SIMULATION - INNOVATION - QUALITY - COMPLIANCE - INTELLIGENCE

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What VtR means



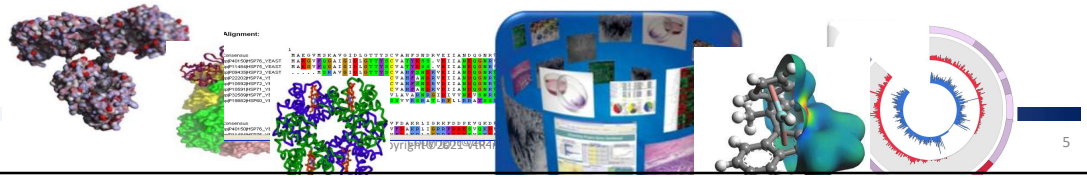
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法德利科技 科學資訊事業

VtR Incorporated
法德利科技股份有限公司

- 法德利科技是提供完整**高端科學資訊服務**的在地團隊。
- 法德利服務以科技產業為主，包含生技藥業、醫療服務業、電子半導體產業、能源石化業等，提供從R、D、Q、到M (**研究、發展、品質、製造**)一貫之資訊解決方案。
- 法德利的產品及服務項目涵括**生物資訊**、**化學資訊**、**生命科學**、**奈米與材料科學**、**電子化臨床與實驗室管理**、**製程監控分析**、及**企業品質管理系統**等。
- 法德利除提供先進之軟體及資料庫外，更包含安裝調校、合規**電腦系統確效**(CSV)、委託研究、系統客製開發、使用者教育訓練等服務，客戶遍及產、官、學、研各界。



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產業資訊與合規之完整解決方案

符合法規之電子系統確效與整合實驗研究成果之資訊解決方案



實驗室合規管理系統
電腦系統確效服務
系統整合維護與硬體資源提供





合規的文檔及品質管理與臨床資訊解決方案

企業品質及文檔管理系統
電腦系統確效服務
電子送件提交系統
系統整合維護

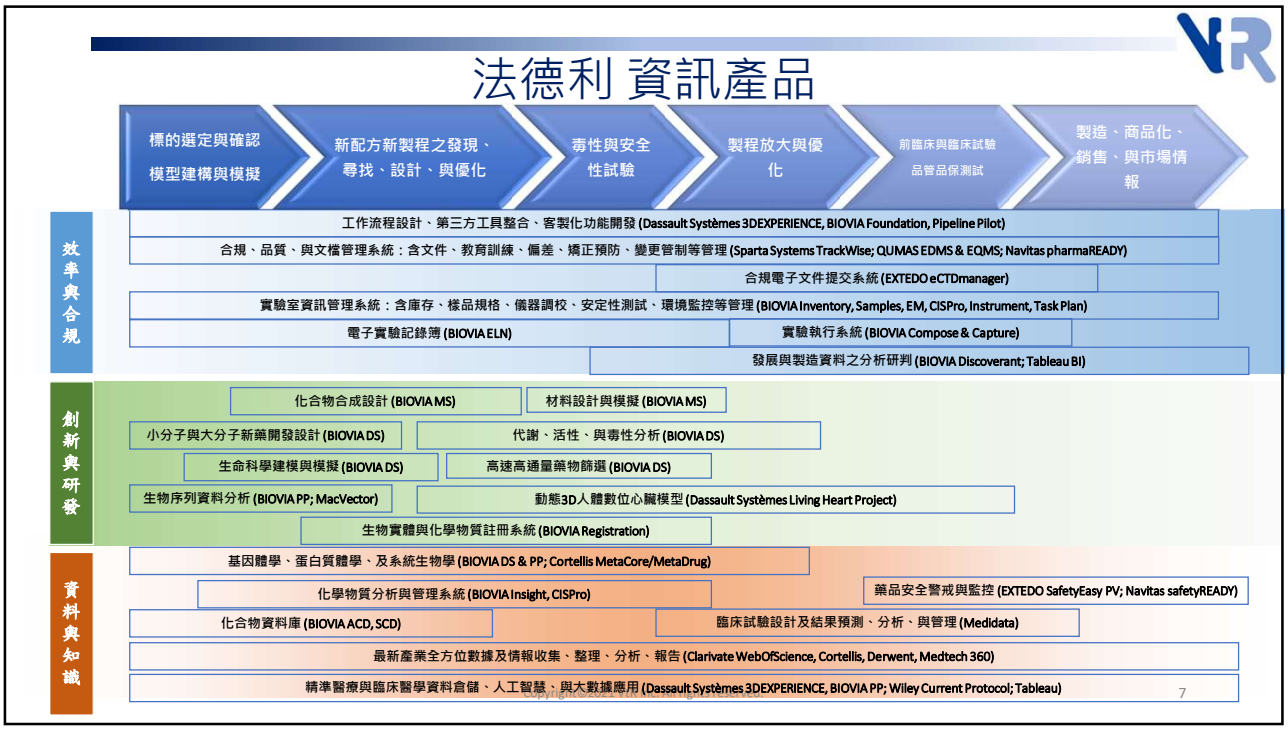
製程、化學品配方之研發解決方案



生命與材料科研軟體及資料庫
委託研究
實驗室合規管理系統
系統整合維護與硬體資源提供

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Outline

- ➢Introduction
- ➢What is MetaCore?
  - ◆ 介面介紹
  - I. 知識挖掘
  - ● Exercise I
  - II. 建構網絡及分子路徑圖
  - ● Exercise II
  - III. 體學數據上傳及分析
  - ● Case study
- ➢What is MetaDrug?
  - IV. 化合物活性預測
  - ● 針對靶點的藥物活性預測
  - ● Metadrug預測工具
- ➢Summary

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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



2020 darts-ip Part of Clarivate

London, UK, Philadelphia, US, & Brussels, Belgium, December 2, 2019— Clarivate Analytics plc (NYSE:CCC;CCC.WS), a global leader in providing trusted insights and analytics to accelerate the pace of innovation, today announced it has acquired Darts-ip, a leading provider of case law data and analytics for intellectual property (IP) professionals. Recently awarded best legal tech company by Trends Legal Awards in Belgium, Darts-ip's case law data and supporting analytics solutions will be offered alongside Clarivate's trusted patent, trademark and domain data and solutions, across Derwent™, CompuMark™ and MarkMonitor™, to help companies make smarter, faster decisions.

2020 DRG Part of Clarivate

London, UK, & Philadelphia, US, March 2, 2020– Clarivate Analytics plc (NYSE:CCC; CCC.WS) ("Clarivate"), a global leader in providing trusted insights and analytics to accelerate the pace of innovation, today announced it has completed its acquisition of Decision Resources Group ("DRG"). Previously, Clarivate announced on January 17, 2020 its intent to acquire DRG from Piramal Enterprises Limited ("PEL", NSE: PEL, BSE: 500302), part of global business conglomerate Piramal Group.

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科睿唯安和您一起走在加速創新到市場實踐的進展

持續助力基於數據做出的自信決策

科學研究及發現 → 研發及上市申請 → 上市監控及優化

學術機構　生技公司　醫療器材　政府監管　法規政策　醫療支付

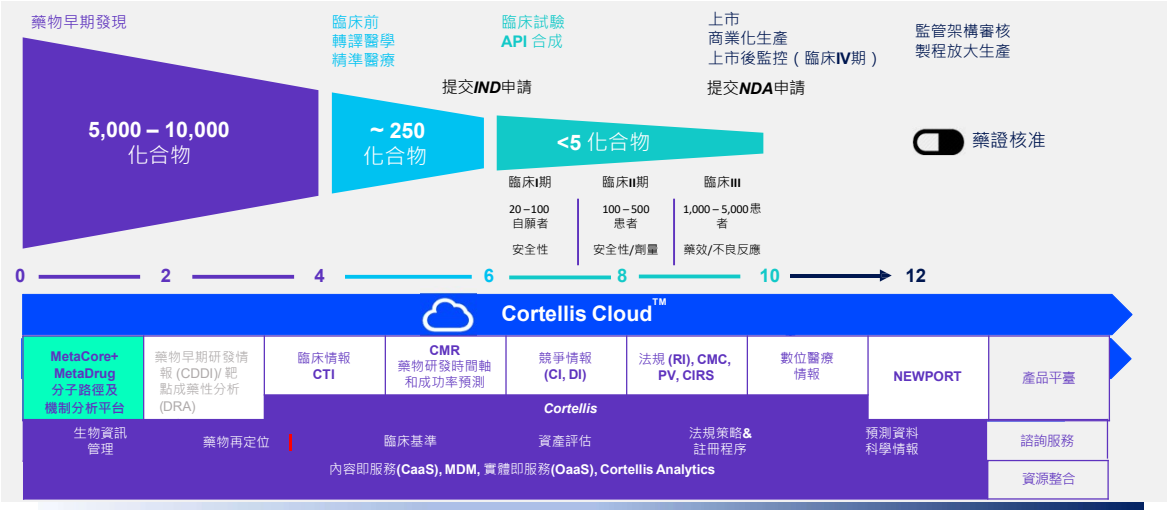
從專業觀點出發引領生命科學產業

Institute for Scientific Information	The Centre for Medicines Research	The Centre for Innovation in Regulatory Science

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科睿唯安產品全線支撐整個藥品開發生命週期



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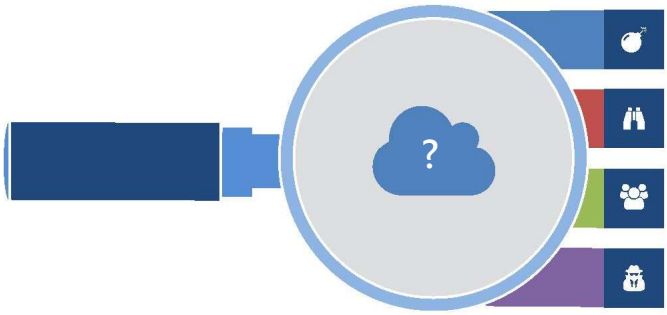
What is MetaCore?

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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

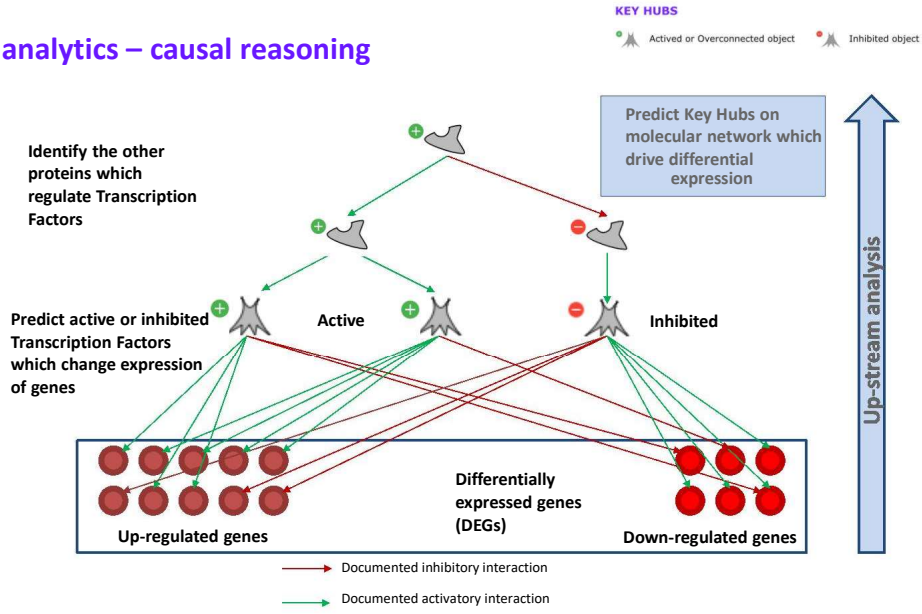
發現藥物的作用機制並預測它的毒性

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

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Powerful analytics – causal reasoning



1. Chindelevitch L, Ziemek D, Enayetallah A, Randhawa R, Sidders B, et al. (2012) Causal reasoning on biological networks: interpreting transcriptional changes. Bioinformatics 28: 1114-1121.
2. Pollard J Jr, Butte AJ, Hoberman S, Joshi M, Levy J, Pappo J. (2005) A computational model to define the molecular causes of type 2 diabetes mellitus. Diabetes Technol Ther. 2005 Apr;7(2):323-36.

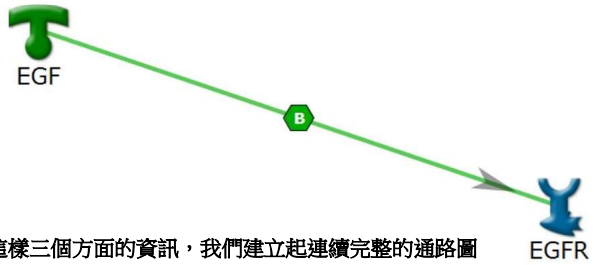
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MetaCore 中的分子相互作用資料——包含：方向，效應，機制

（方向）Directionality

（效應）Effect

（機制）Mechanism (B=Binding)



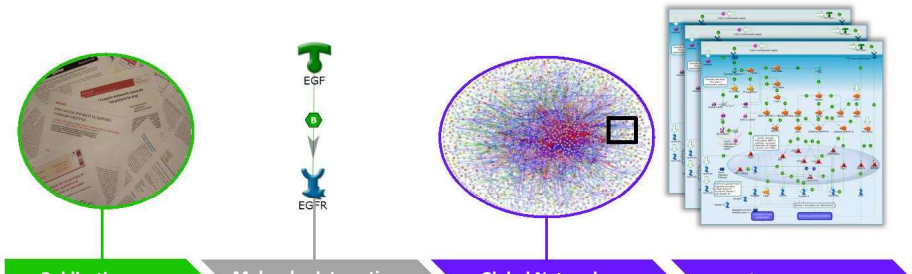
通過這樣三個方面的資訊，我們建立起連續完整的通路圖

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Metacore 全、準、新——高品質的底層內容和演算法

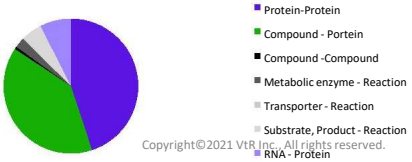
全面、準確、詳細的分子生物學資料加速疾病研究和藥物靶點的發現



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

2 million interactions

1600+ canonical and disease signaling pathways



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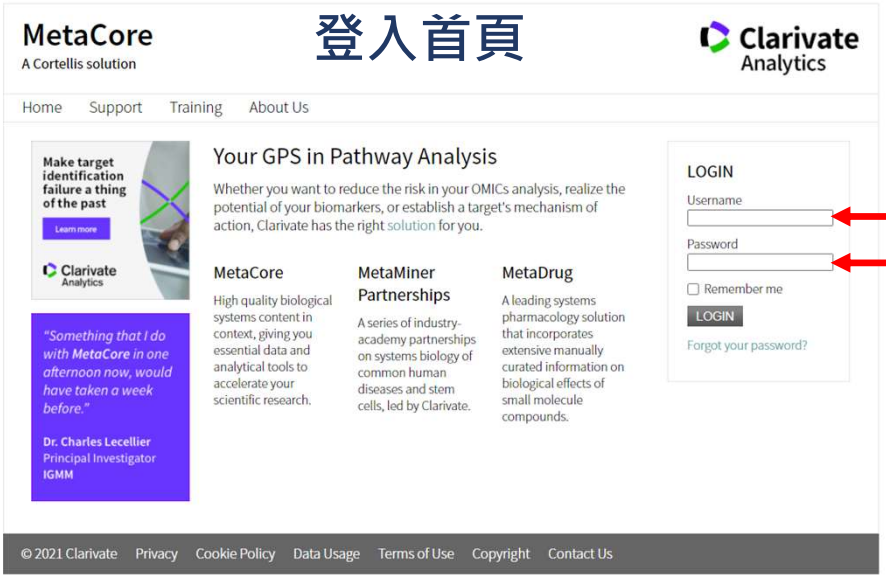
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介面介紹

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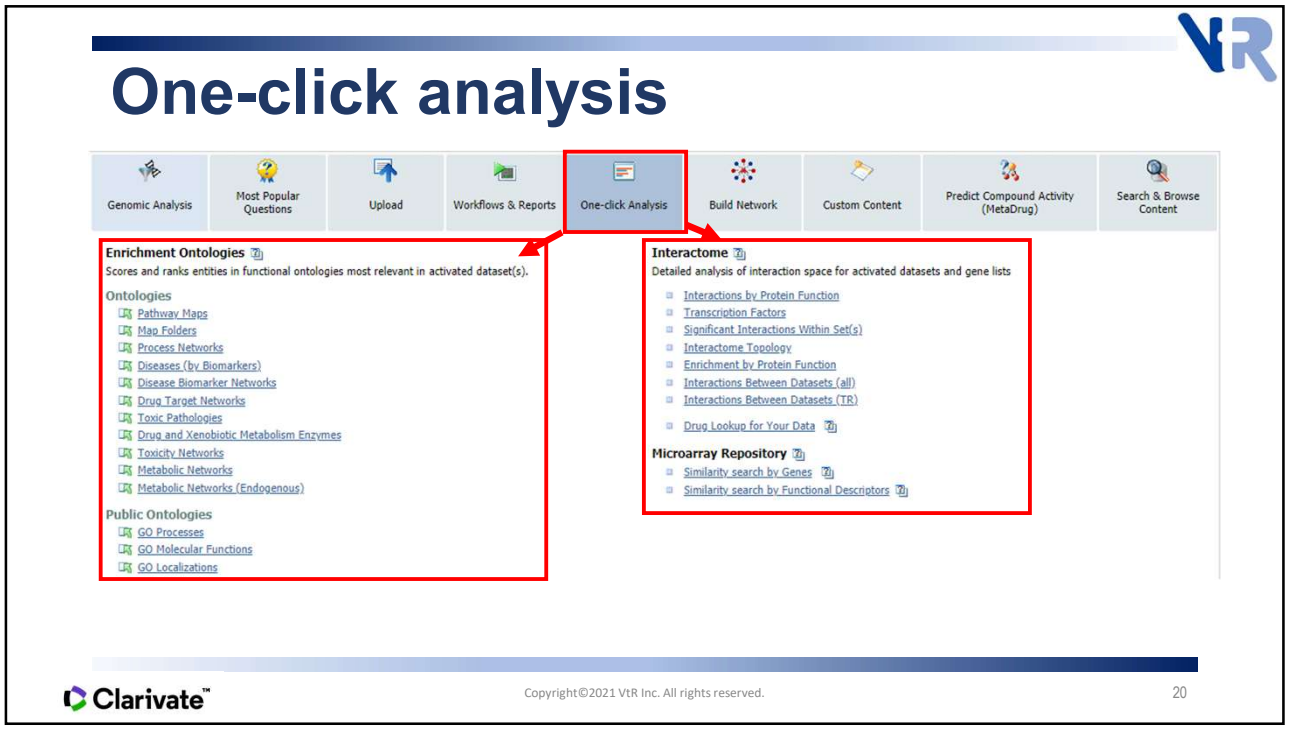
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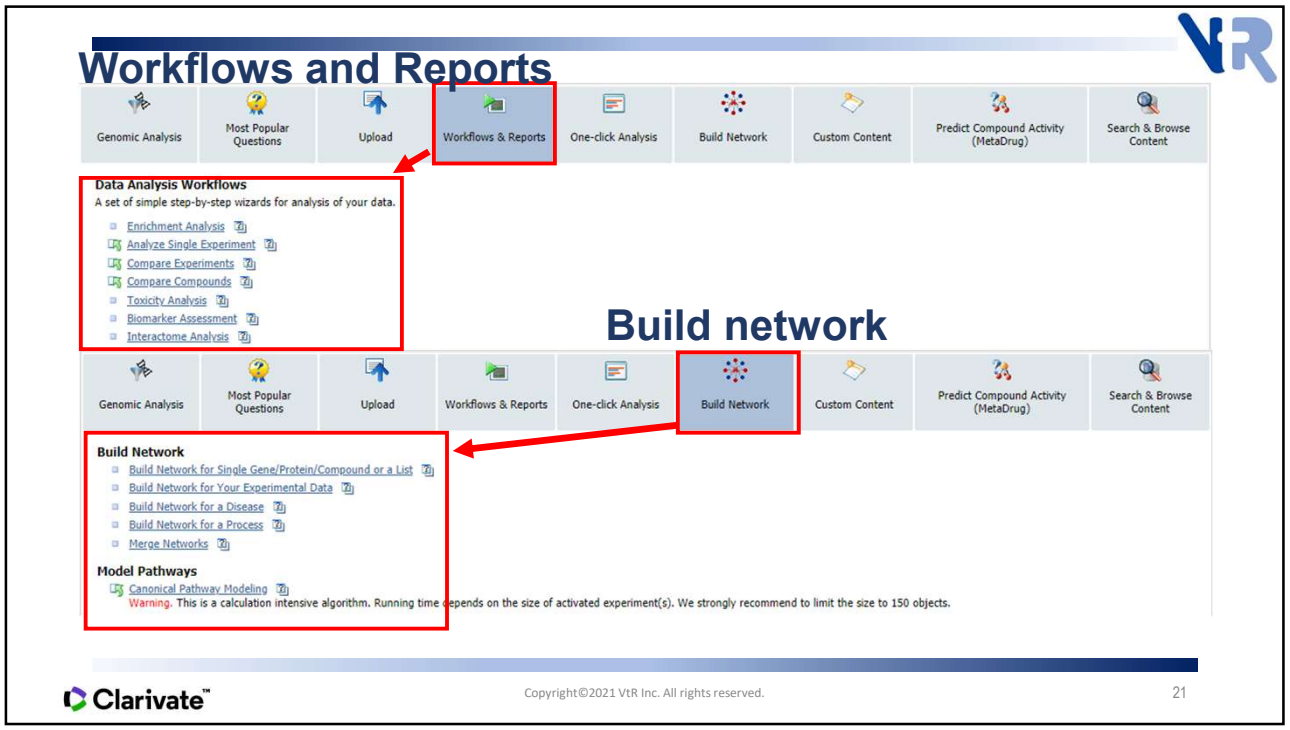
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設定及工具列
數據管理指令
搜尋列
檔案管理區
工作及分析操作區
檔案狀態管理
導引及解說
更新及教育訓練
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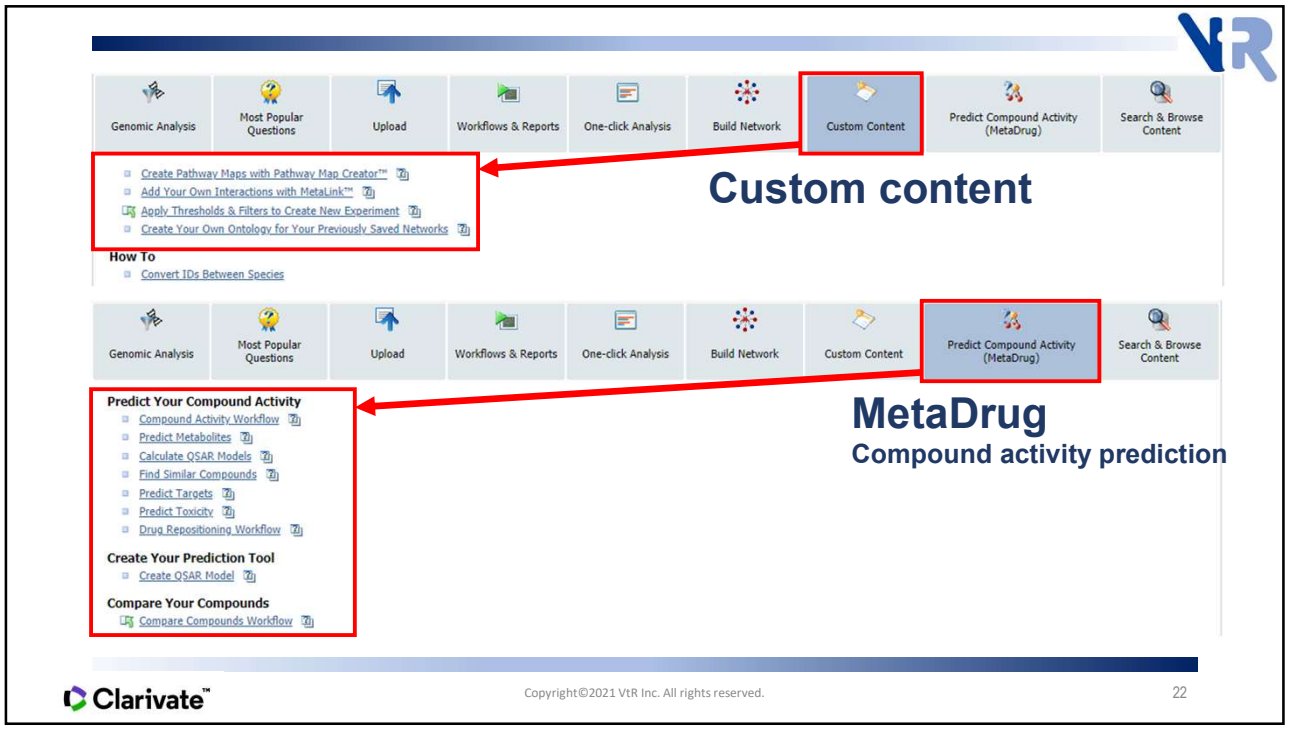
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One-click analysis
Genomic Analysis
Most Popular Questions
Upload
Workflows & Reports
One-click Analysis
Build Network
Custom Content
Predict Compound Activity (MetaDrug)
Search & Browse Content
Enrichment Ontologies
Scores and ranks entities in functional ontologies most relevant in activated dataset(s).
Ontologies
Pathway Maps
Map Folders
Process Networks
Diseases (by Biomarkers)
Disease Biomarker Networks
Drug Target Networks
Toxic Pathologies
Drug and Xenobiotic Metabolism Enzymes
Toxicity Networks
Metabolic Networks
Metabolic Networks (Endogenous)
Public Ontologies
GO Processes
GO Molecular Functions
GO Localizations
Interactome
Detailed analysis of interaction space for activated datasets and gene lists
Interactions by Protein Function
Transcription Factors
Significant Interactions Within Set(s)
Interactome Topology
Enrichment by Protein Function
Interactions Between Datasets (all)
Interactions Between Datasets (TR)
Drug Lookup for Your Data
Microarray Repository
Similarity search by Genes
Similarity search by Functional Descriptors
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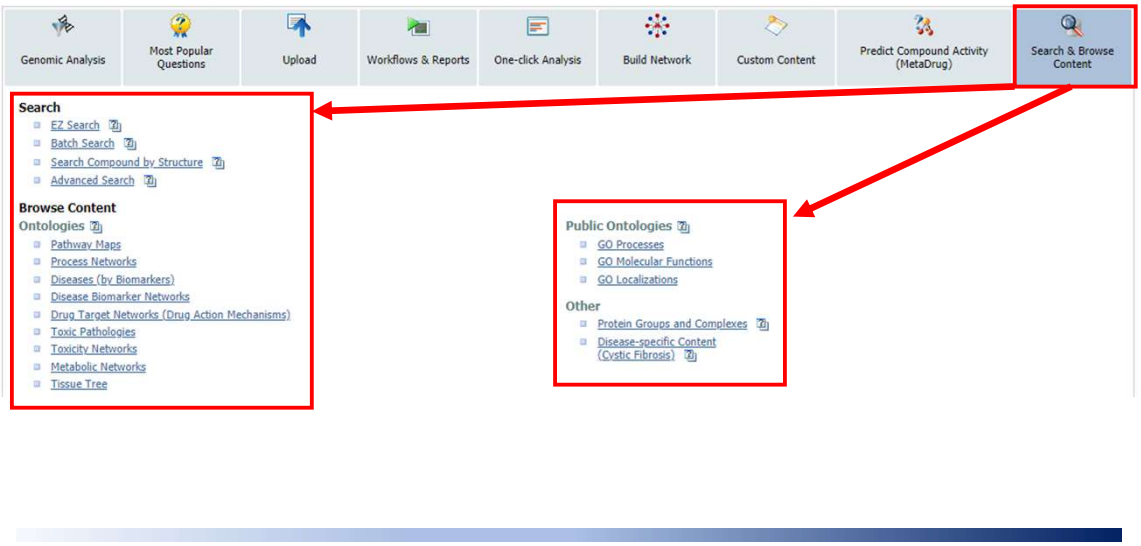

Workflows and Reports
Genomic Analysis
Most Popular Questions
Upload
Workflows & Reports
One-click Analysis
Build Network
Custom Content
Predict Compound Activity (MetaDrug)
Search & Browse Content
Data Analysis Workflows
A set of simple step-by-step wizards for analysis of your data.
Enrichment Analysis
Analyze Single Experiment
Compare Experiments
Compare Compounds
Toxicity Analysis
Biomarker Assessment
Interactome Analysis
Build network
Build Network
Build Network for Single Gene/Protein/Compound or a List
Build Network for Your Experimental Data
Build Network for a Disease
Build Network for a Process
Merge Networks
Model Pathways
Canonical Pathway Modeling
Warning. This is a calculation intensive algorithm. Running time depends on the size of activated experiment(s). We strongly recommend to limit the size to 150 objects.
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Genomic Analysis
Most Popular Questions
Upload
Workflows & Reports
One-click Analysis
Build Network
Custom Content
Predict Compound Activity (MetaDrug)
Search & Browse Content
Create Pathway Maps with Pathway Map Creator™
Add Your Own Interactions with MetaLink™
Apply Thresholds & Filters to Create New Experiment
Create Your Own Ontology for Your Previously Saved Networks
How To
Convert IDs Between Species
Custom content
Predict Your Compound Activity
Compound Activity Workflow
Predict Metabolites
Calculate QSAR Models
Find Similar Compounds
Predict Targets
Predict Toxicity
Drug Repositioning Workflow
Create Your Prediction Tool
Create QSAR Model
Compare Your Compounds
Compare Compounds Workflow
MetaDrug
Compound activity prediction
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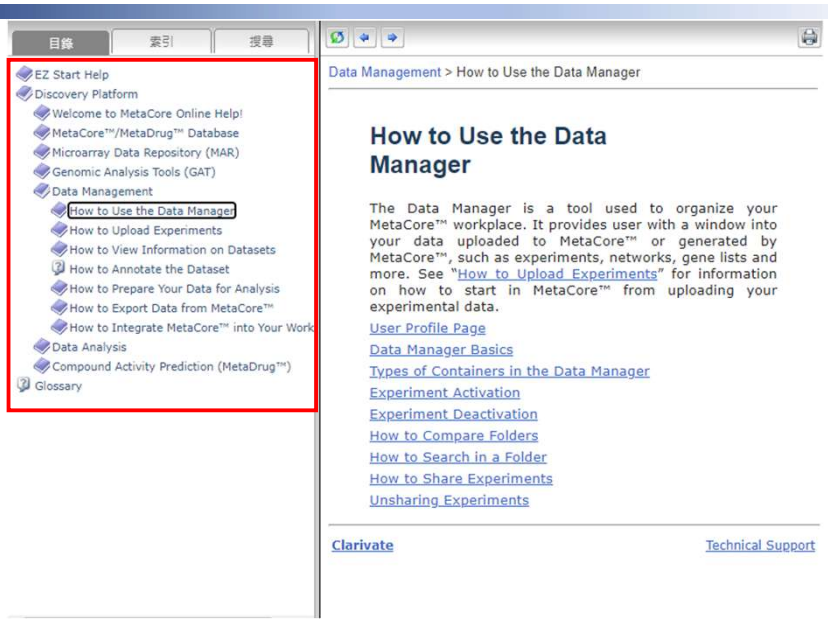
Searching and Browsing



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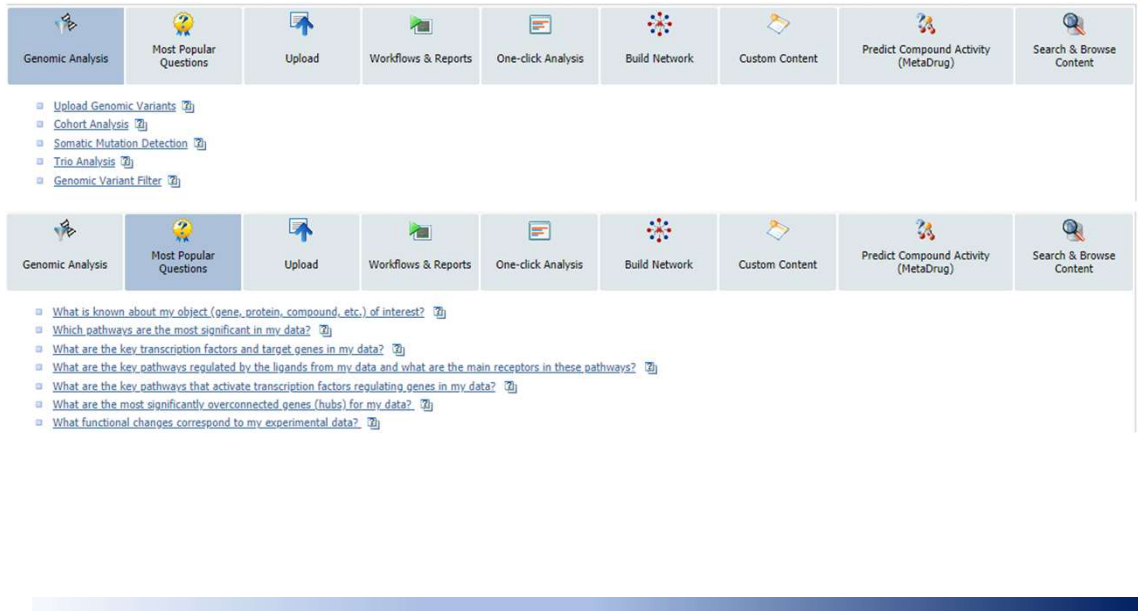
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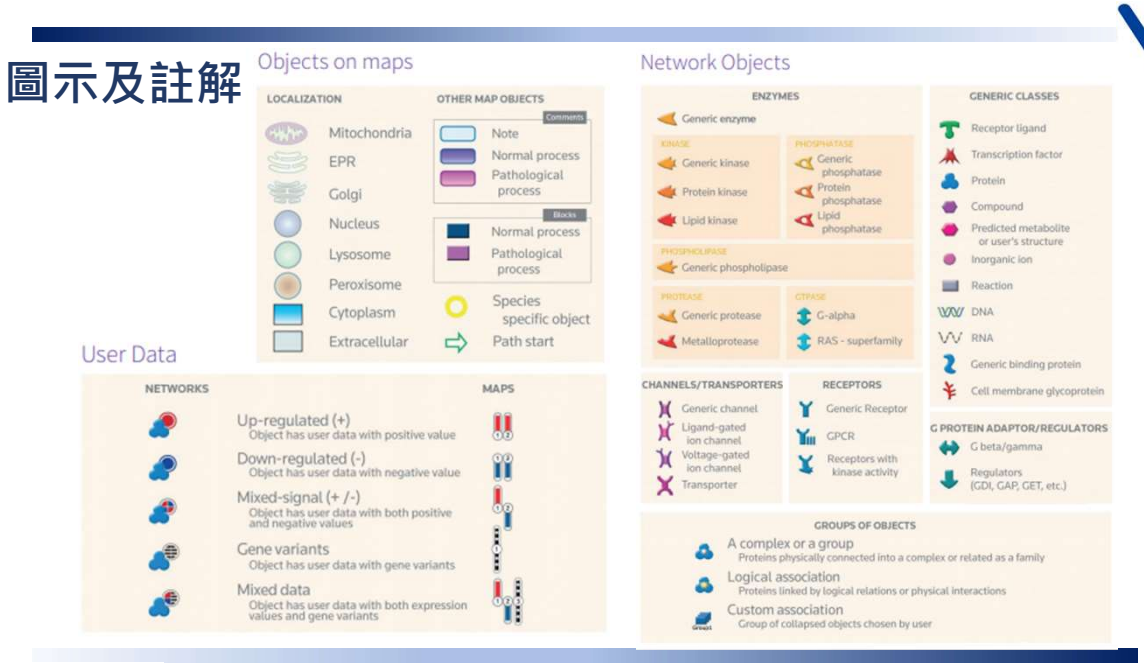
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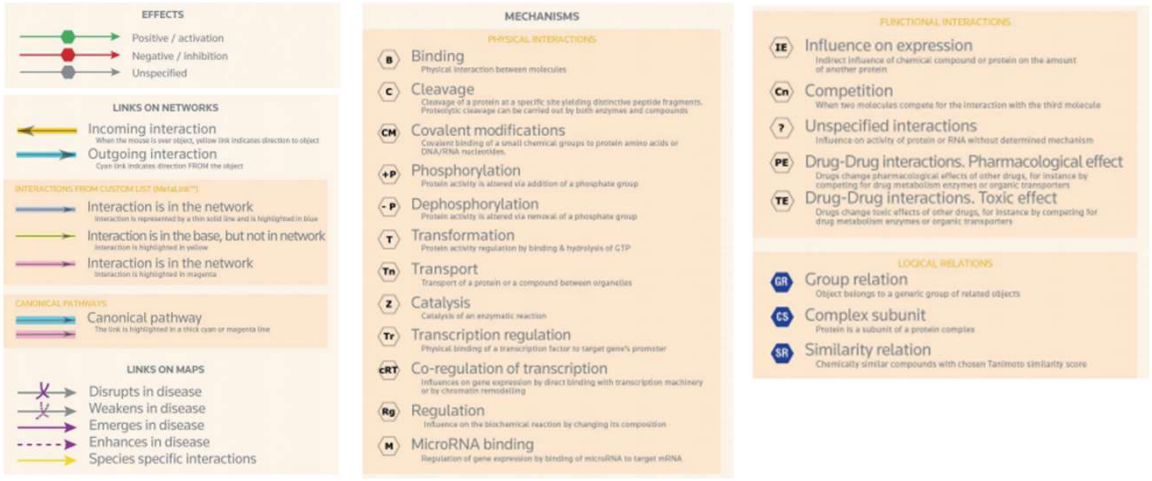
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Interactions between objects



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Live demo

MetaCore + MetaDrug 介面介紹

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I. 知識挖掘

- Understanding immuno-oncology targets through knowledge mining: a PD-1 use case
- 通過知識挖掘瞭解腫瘤免疫標的：以PD-1為例

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Questions:

- 我們能檢索到PD-1的哪些資訊？
- 哪些蛋白質可以調節PD-1的表現？
- 哪些訊息傳導路徑可以調節PD-1的表現？
- 哪些訊息傳導路徑可能成為患者分級的良好生物標記以及潛在的治療標的？

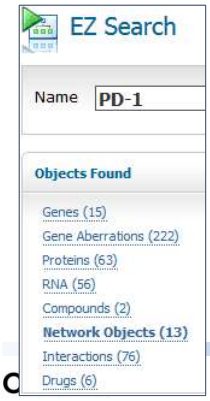
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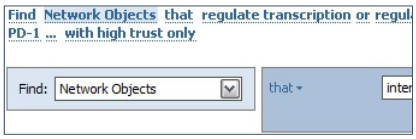
以PD-1進行檢索，並匯出相關資訊

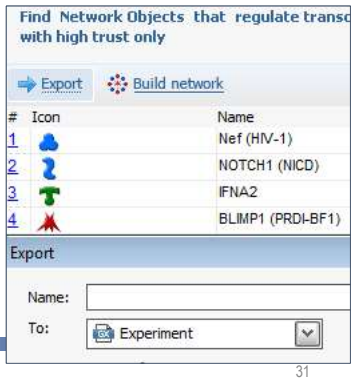
EZ Search → Advanced Search → Export to MetaCore





- Questions:
  - 我們能檢索到關於PD-1的哪些資訊
  - 哪些蛋白可以調節和影響PD-1的表現？

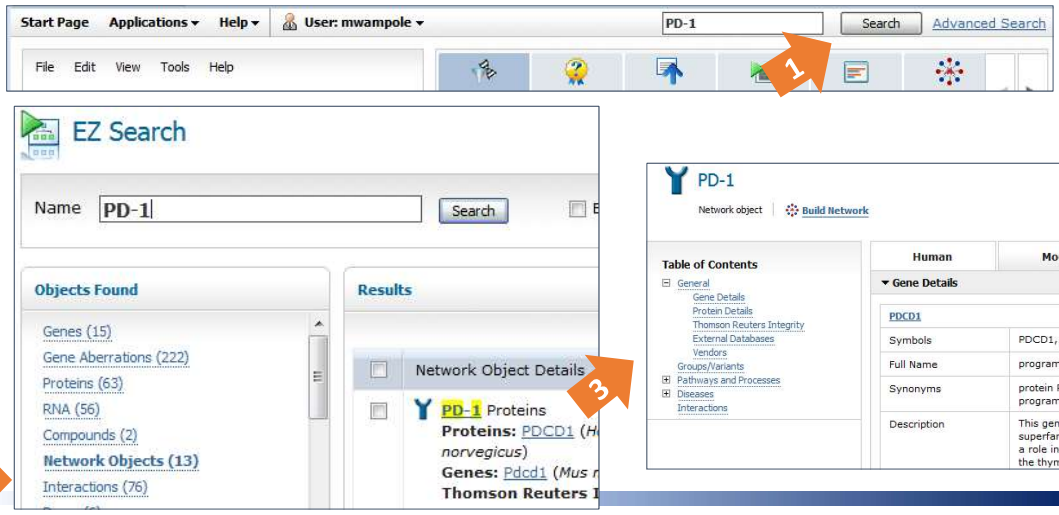




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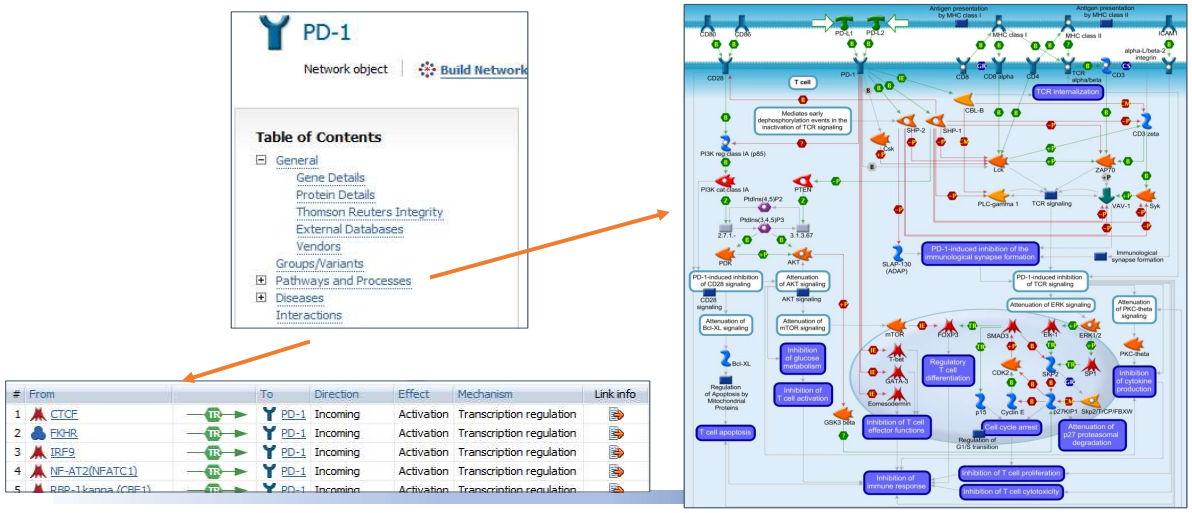
以簡單檢索找到PD-1的相關資訊



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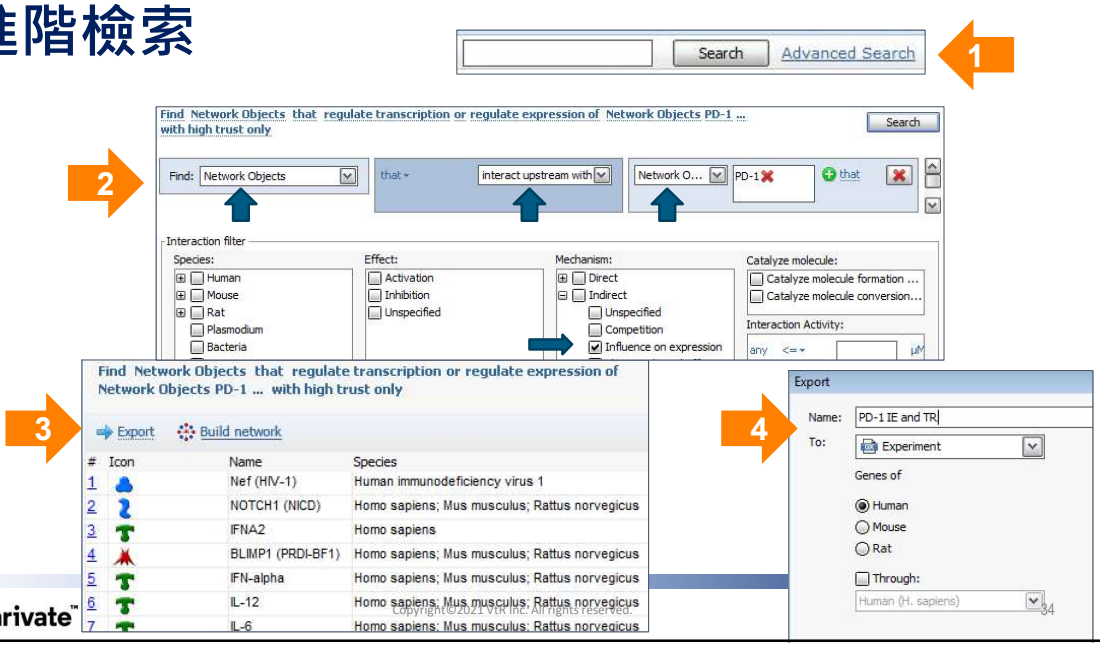
我們能檢索到PD-1的哪些資訊?



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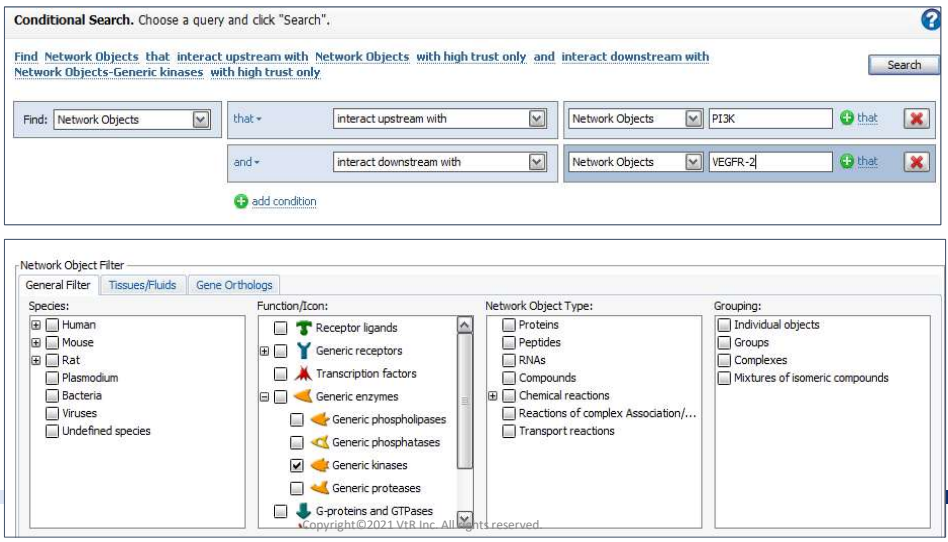
進階檢索



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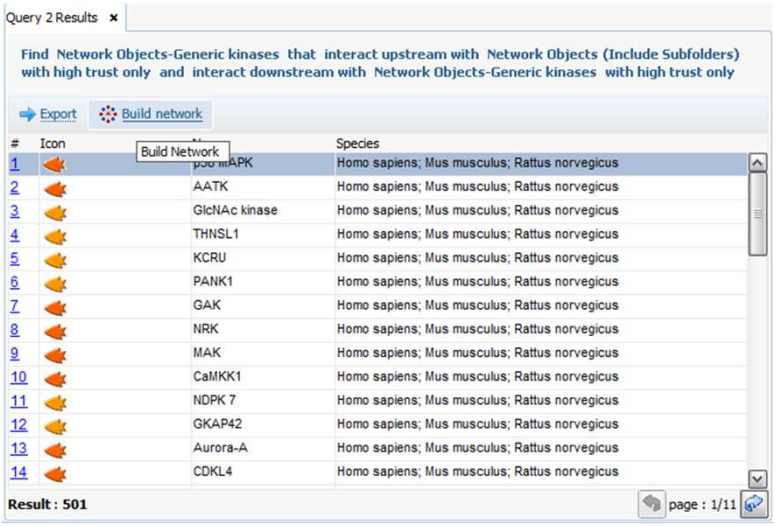
舉例: VEGFR-2 的下游與PI3K的上游，相互(共同)作用的激酶 (Kinases) 都有哪些？



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VEGFR-2 下游與PI3K上游具作用的 Kinases



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Live demo
資料查詢與檢索

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Exercise I
資料查詢與檢索

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實作練習

以EZ search 進行關鍵字搜尋

- 基因、蛋白質
- 適應症、疾病
- 藥物標的、化合物
- Pathway maps

選擇想進一步了解的分子

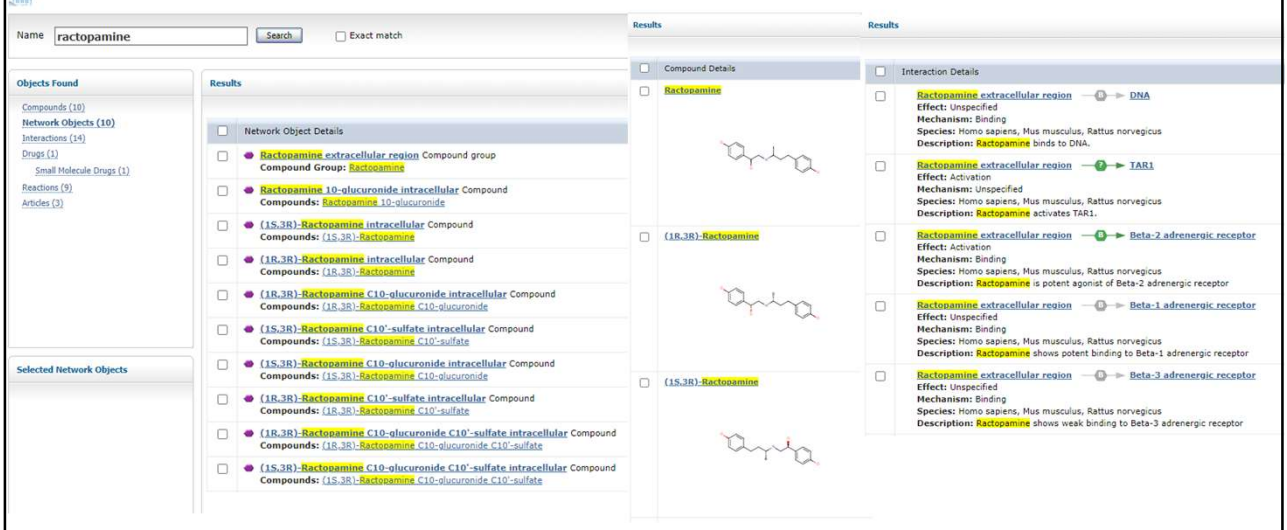
以 Advanced search 搜尋分子間相互作用的機制

- 藥物標的
- 分子路徑
- 機制
- 作用物件
- 聚焦搜尋

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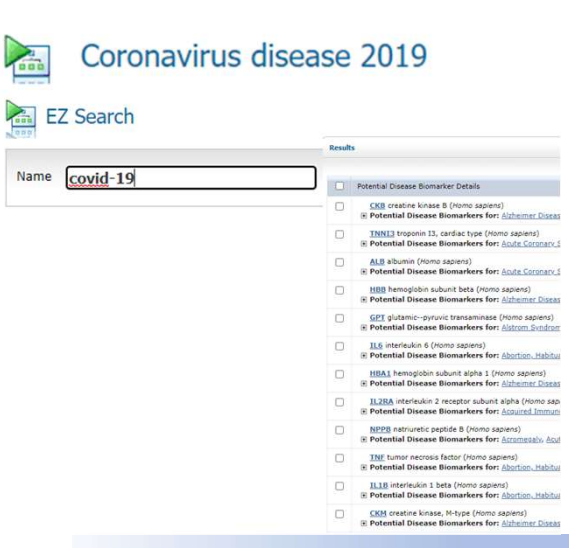
時事題: 查詢 “Ractopamine”

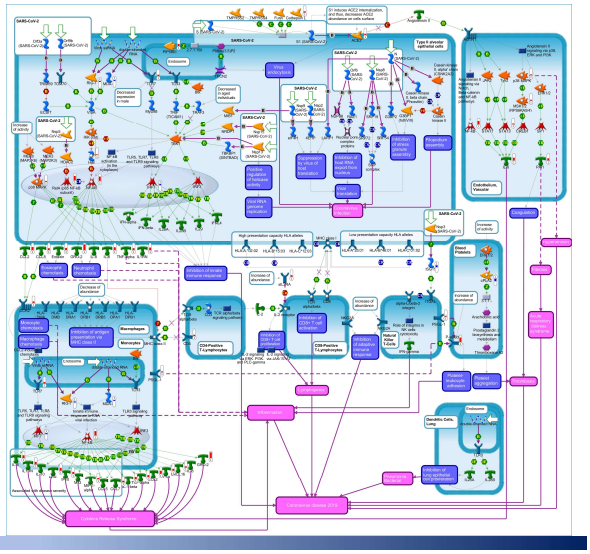


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時事題: 查詢 “COVID-19”與挖掘資訊





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II. 建構網絡及分子路徑圖

- 在這些蛋白中，哪些訊息路徑可以調節PD-1的表現?
- 哪些訊息路徑可能成為患者分級的良好生物標記以及潛在的治療標的?

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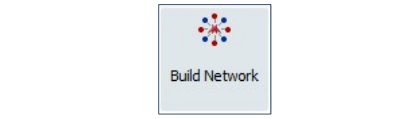
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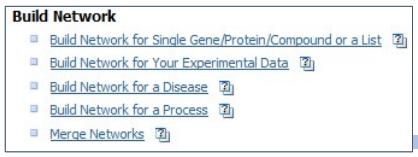
42

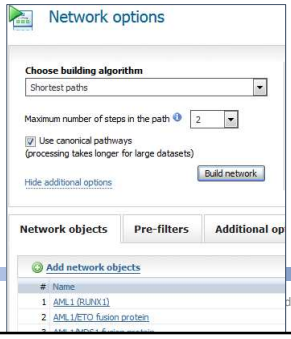
建立一個網路來推測哪些路徑可以影響PD-1的表現

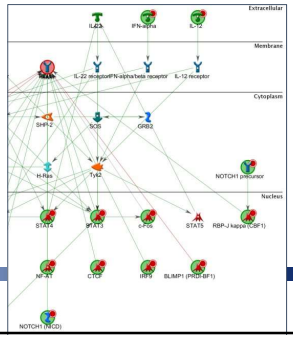
- Questions:
  - 在這些蛋白中，哪些訊息路徑可以調節PD-1的表現?
  - 哪些訊息路徑可能成為患者分級的良好生物標記以及潛在的治療標的?

Build network from experiment → **Set network building options** → **Arrange Layout**









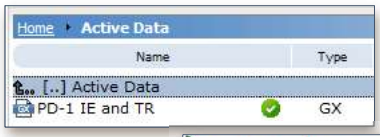
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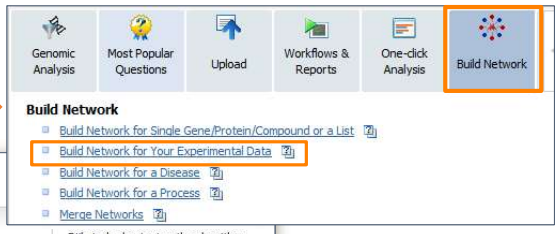
43

利用演算法構建網路 1

1



2

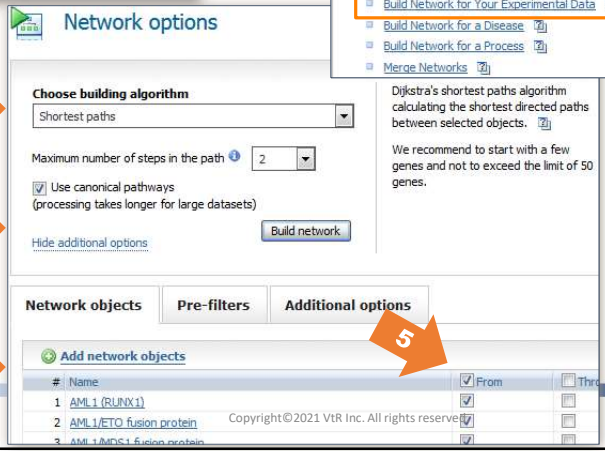


選擇 'Shortest paths' 演算法 — 3

Click 'Show additional options' — 4

Click 'Add network objects' — 6

5 — Select 'From' for all initial seed nodes



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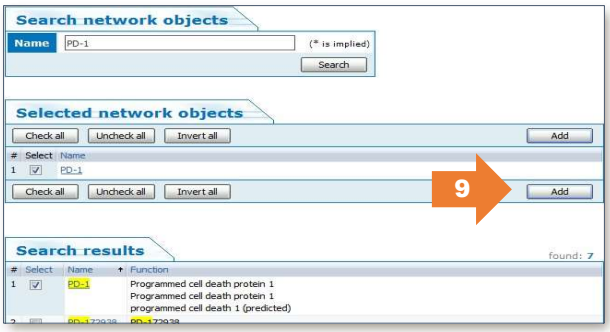
44

44

利用演算法構建網路 2

Type PD-1 into search

7



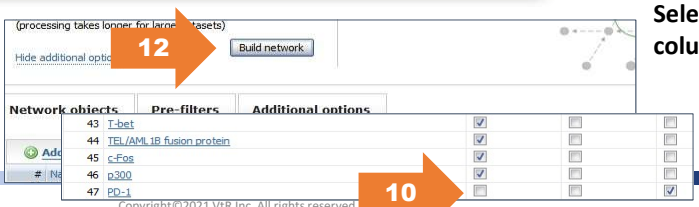
9

Add to seed list

Select the correct PD-1

8

12



Select PD-1 in 'To' column

11

Deselect PD-1 in 'From' column

10

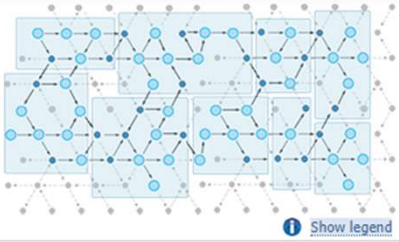
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Analyze network

Generates sub-networks enriched with seed nodes (nodes from root list = activated experiments). Sub-networks are ranked by a P-value and G-Score and interpreted in terms of Gene Ontology processes.

We recommend 300-600 genes in input list for this algorithm. Analysis of larger datasets (>2,000 genes) is possible but calculation will take longer.



Network options

Show legend

Choose building algorithm

Analyze network

Number of nodes in a network 50

Use canonical pathways (processing takes longer for large datasets)

Hide additional options

Build network

Initial (seed) node included in network

Other objects included in network

Object not included in network

Link included in network

Link not included in network

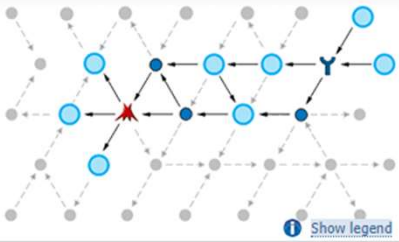
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Analyze network (TF)

For every transcription factor (TF) with direct target(s) in the root list, this algorithm generates a sub-network consisting of all shortest paths to this TF from the closest receptor with direct ligand(s) in the root list.

We recommend 300-600 genes in input list for this algorithm. Analysis of larger datasets (>2,000 genes) is possible but calculation will take longer.



Choose building algorithm

Analyze network (transcription factors)

Add ligands and TF targets

Use canonical pathways (processing takes longer for large datasets)

Build network

Hide additional options

Initial (seed) node included in network
Other objects included in network
Object not included in network
Transcription factor
Receptor
Link included in network
Link not included in network

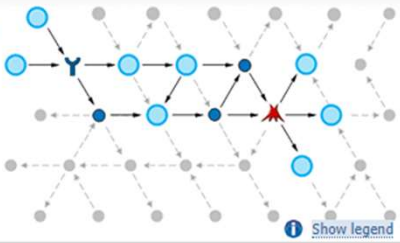
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Analyze network (Receptors)

For every receptor with direct ligand(s) in the root list, this algorithm generates a sub-network consisting of all shortest paths from that receptor to the closest TF with direct target(s) in the root list.

We recommend 300-600 genes in input list for this algorithm. Analysis of larger datasets (>2,000 genes) is possible but calculation will take longer.



Choose building algorithm

Analyze network (receptors)

Add ligands and TF targets

Use canonical pathways (processing takes longer for large datasets)

Build network

Hide additional options

Initial (seed) node included in network
Other objects included in network
Object not included in network
Transcription factor
Receptor
Link included in network
Link not included in network

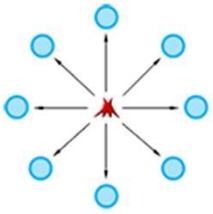
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Transcription regulation

Generates sub-networks centered on transcription factors. Sub-networks are ranked by a P-value and interpreted in terms of Gene Ontology.

We recommend 300-600 genes in input list for this algorithm. Analysis of larger datasets (>2,000 genes) is possible but calculation will take longer.



Choose building algorithm

Transcription regulation

Number of nodes in a network 50

Use canonical pathways (processing takes longer for large datasets)

Build network

Hide additional options

Show legend

Initial (seed) node included in network

Transcription factor

Link included in network

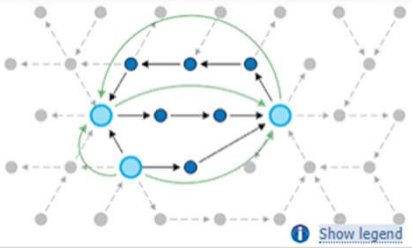
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Shortest paths

Dijkstra's shortest paths algorithm calculating the shortest directed paths between selected objects.

We recommend to start with a few genes and not to exceed the limit of 50 genes.



Show legend

Choose building algorithm

Shortest paths

Maximum number of steps in the path 2

Use canonical pathways (processing takes longer for large datasets)

Build network

Hide additional options

Initial (seed) node included in network

Other objects included in network

Object not included in network

Link included in network

Link not included in network

Pathway direction when it matters

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Direct interactions

Draws direct interactions between selected objects. No additional objects are added to the network.

We recommend not to exceed the limit of 100 genes per network.



Choose building algorithm

Direct interactions

Use canonical pathways (processing takes longer for large datasets)

Build network

Hide additional options

Initial (seed) node included in network

Object not included in network

Link included in network

Link not included in network

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Self regulation

Choose building algorithm

Self regulation

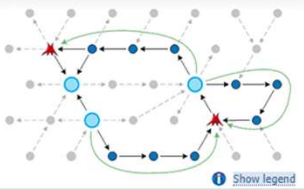
Maximum number of steps in the path 2

Use canonical pathways (processing takes longer for large datasets)

Hide additional options

Finds the shortest directed paths containing transcription factors between the selected objects.

We recommend to start with a few genes and not to exceed the limit of 50 genes.



Through | To | Avoid

Initial (seed) node included in network

Other objects included in network

Object not included in network

Transcription factor

Link included in network

Link not included in network

Pathway direction when it matters

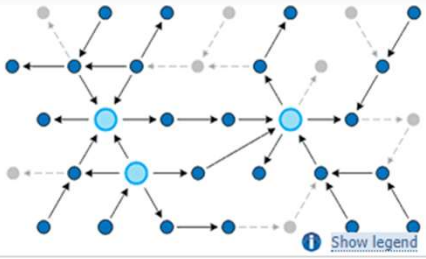
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Auto expand

Draws sub-networks around the selected objects. Expansion halts when the sub-networks intersect.

We recommend to select one to several genes (1-3) for this algorithm.



Choose building algorithm

Auto expand

Number of nodes in a network 50

Use canonical pathways (processing takes longer for large datasets)

Build network

Hide additional options

Initial (seed) node included in network
Other objects included in network
Object not included in network
Link included in network
Link not included in network

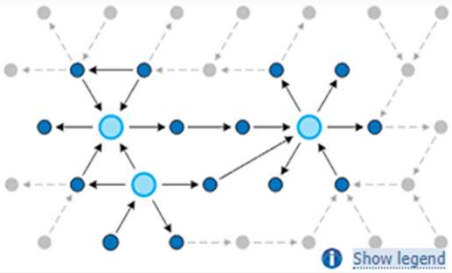
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Expand by one interaction

Draws all the one step interactions around the selected objects.

We recommend to select one to several genes (1-3) for this algorithm.



Choose building algorithm

Expand by one interaction

Directions Upstream Downstream Both

Use canonical pathways (processing takes longer for large datasets)

Build network

Hide additional options

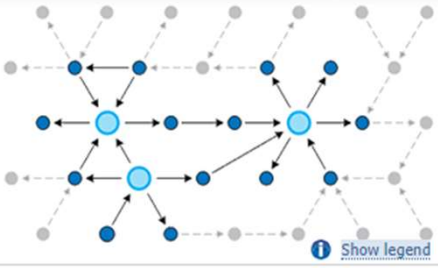
Initial (seed) node included in network
Other objects included in network
Object not included in network
Link included in network
Link not included in network

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Manual expand

"Neighborhood" analysis. Expand network manually around selected objects.



Choose building algorithm

Manual expand

Maximum number of steps 2

Use canonical pathways (processing takes longer for large datasets)

Build network

Hide additional options

Initial (seed) node included in network

Other objects included in network

Object not included in network

Link included in network

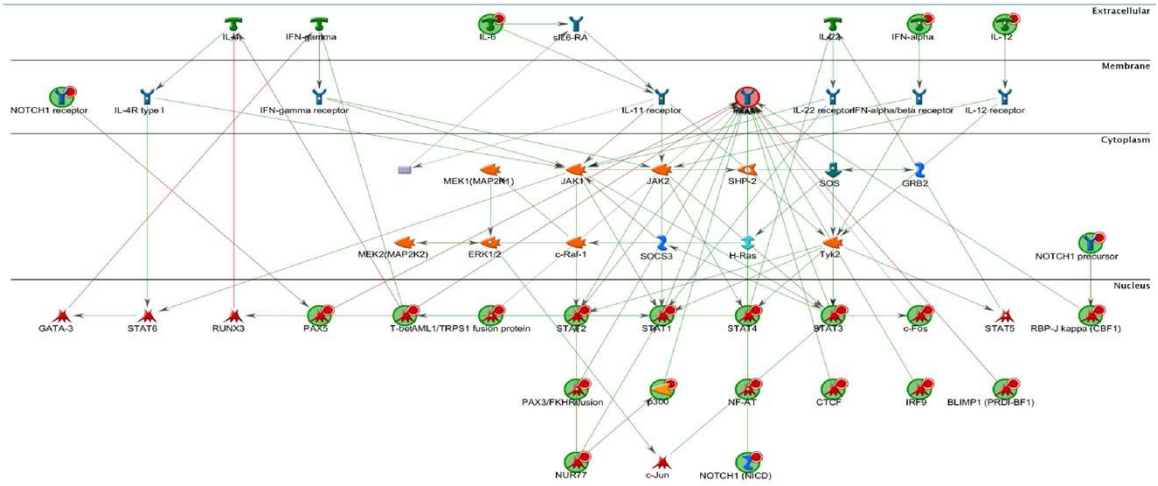
Link not included in network

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調節PD-1表現的訊息傳導路徑有哪些?



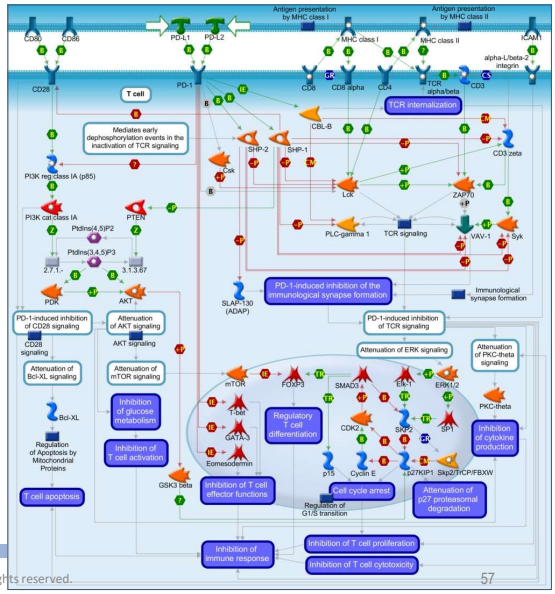
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SUMMARY

- PD-1通過與PD-L1或PD-L2結合而活化，可以抑制T細胞活化的重要訊息路徑，影響重要轉錄因子的表現。
- PD-1的表現主要集中在JAK/STAT路徑的啟動上。
- 患者分級生物標記或聯合用藥標的包括IFN- gamma、NOTCH1、STATs



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Live demo

建構網絡及分子路徑

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Exercise II
建構網絡及分子路徑

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實作練習

選擇實作 1 搜尋後感興趣的分子或物件

- 基因、蛋白質
- 藥物標的、化合物

以1-2種 model 建立分子網絡

解釋分子間相互作用的機制及可能的功能

- 藥物標的
- 分子路徑
- 機制
- 適應症、疾病

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III. 體學數據上傳及分析

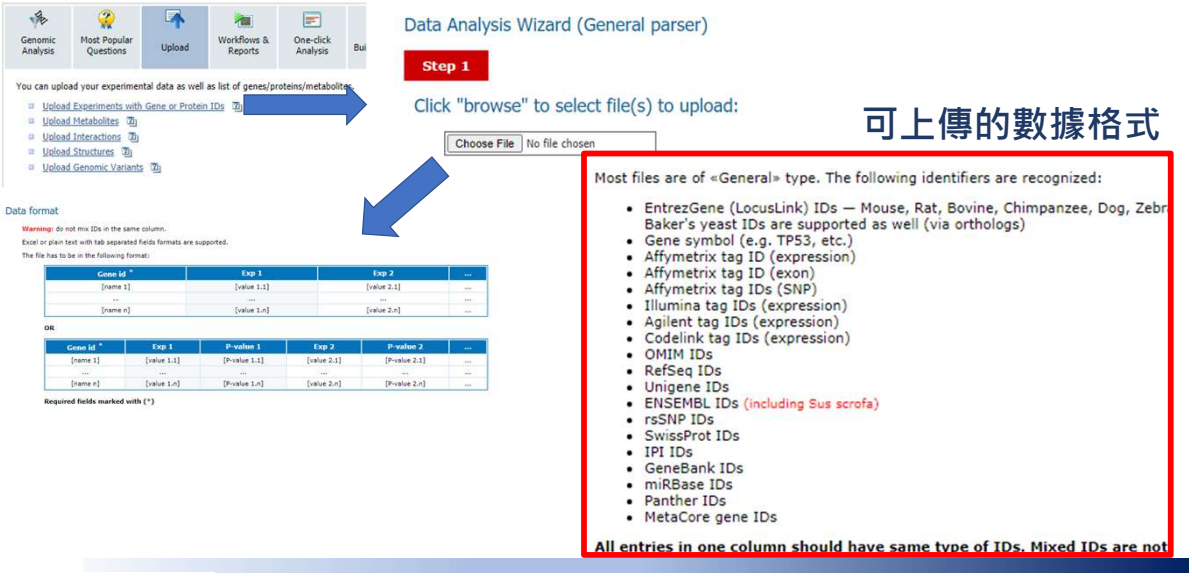
- Biomarker discovery in patients with degraded kidney function through the analysis of metabolomic, proteomic, and RNA-seq data
- 通過代謝體學、蛋白質體學和RNA-seq數據分析，發現腎功能退化患者的生物標記

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上傳體學數據



可上傳的數據格式

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

- EntrezGene (LocusLink) IDs — Mouse, Rat, Bovine, Chimpanzee, Dog, Zebr
  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

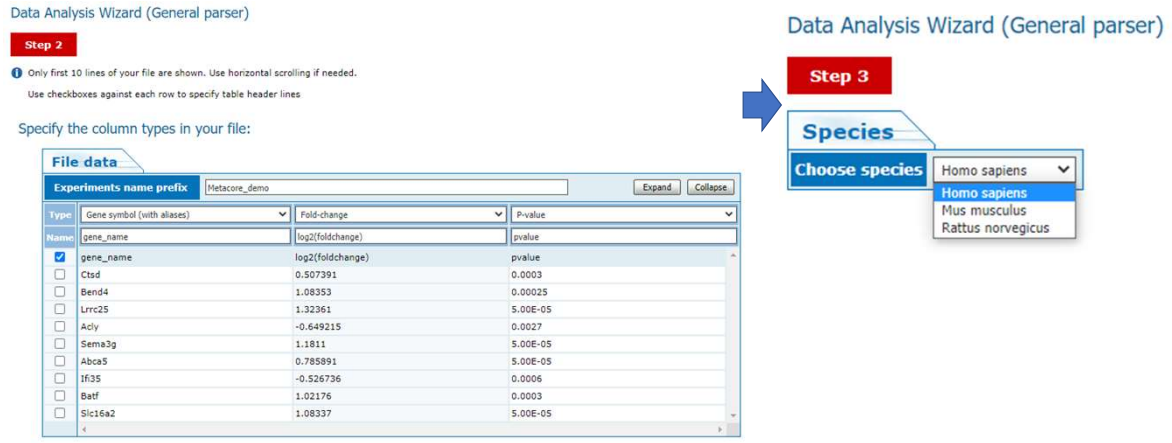
All entries in one column should have same type of IDs. Mixed IDs are not

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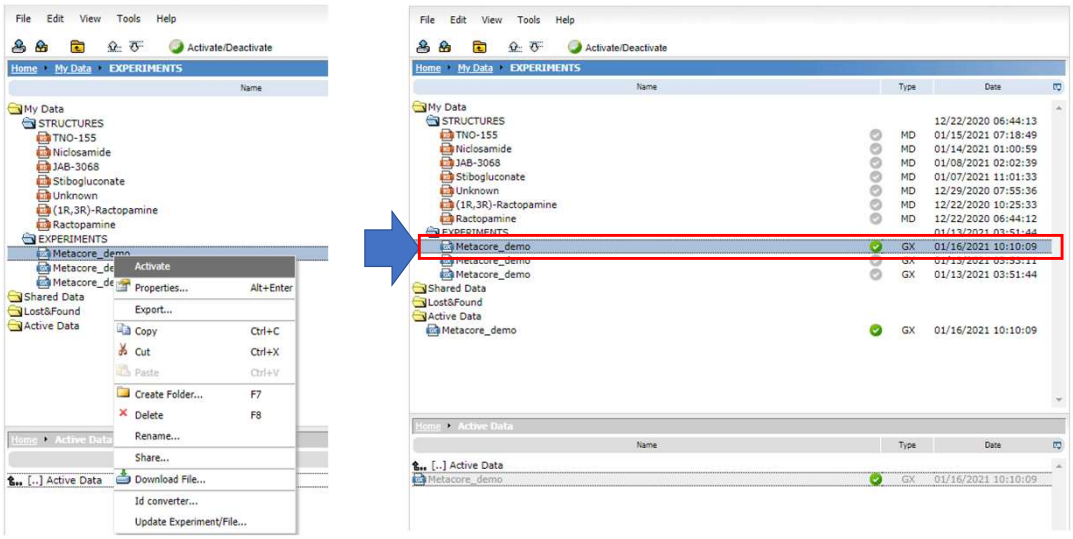
上傳體學數據的欄位對應



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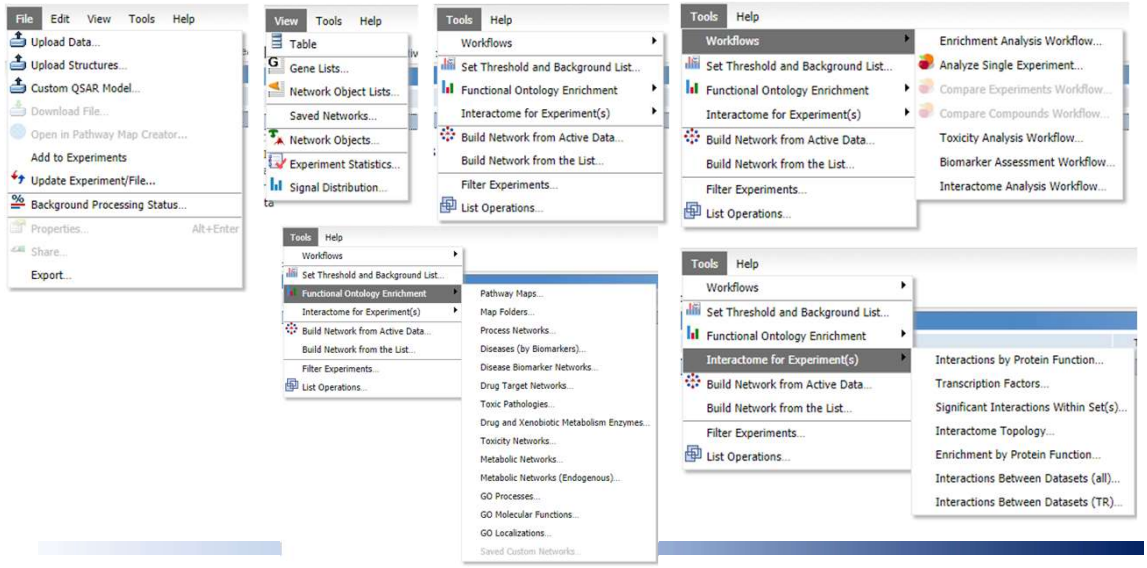
開始分析體學數據



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開始分析體學數據 (可選擇的分析工具及數據呈現方式)

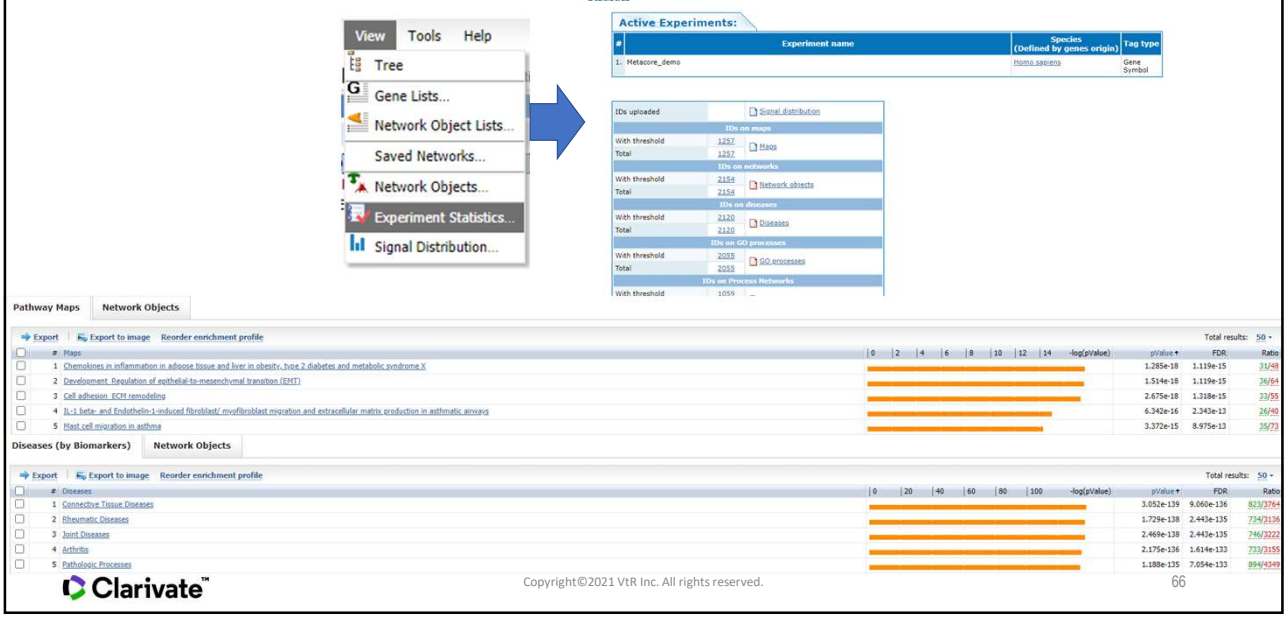


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透過統計分析，進入挖掘機制與網絡分析結果

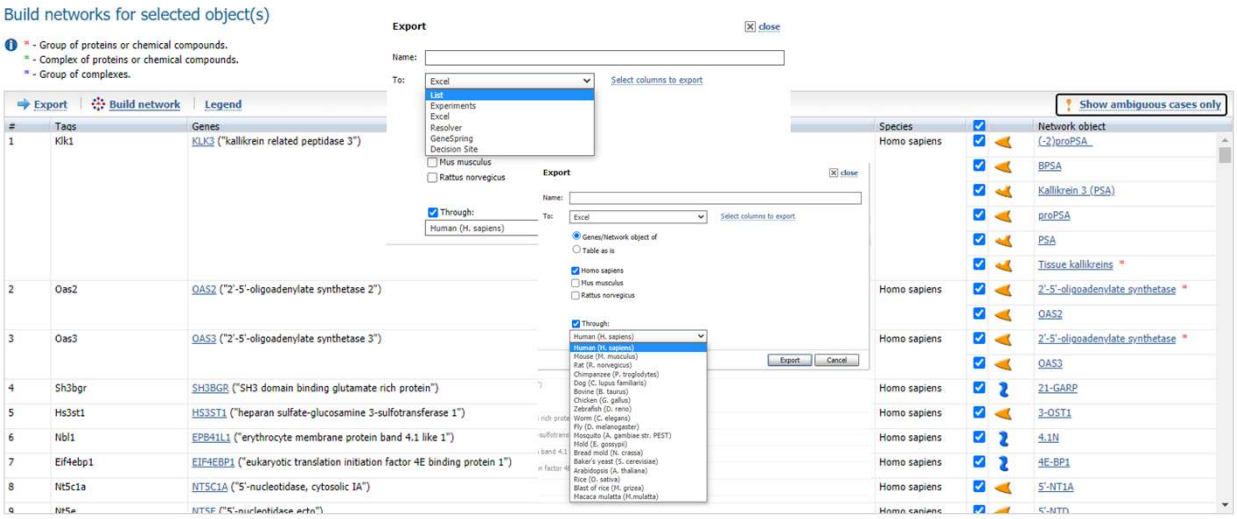


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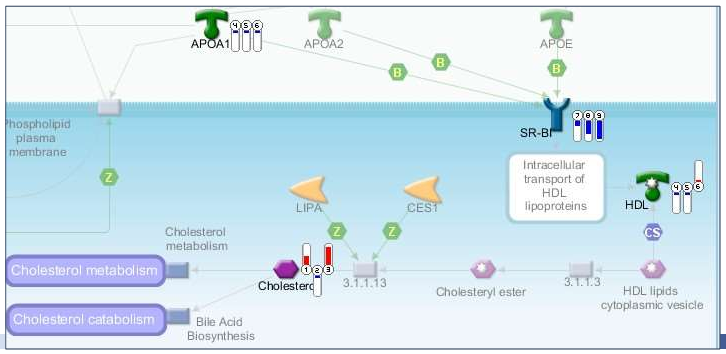
輸出網絡分析結果



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Questions:

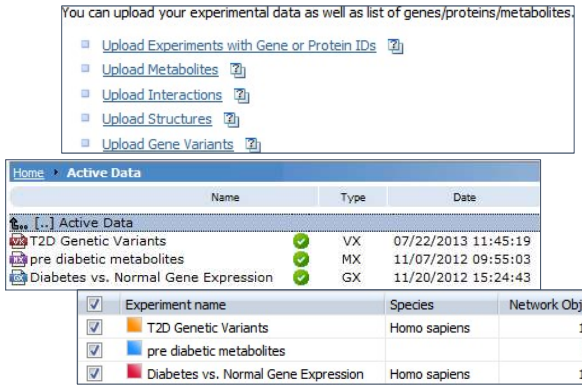
- 我們能在代謝體學和轉錄體學資料之間找到什麼代謝關係?
- 患者血漿中哪些代謝物和蛋白質濃度的變化可以作為疾病進程的生物標記？

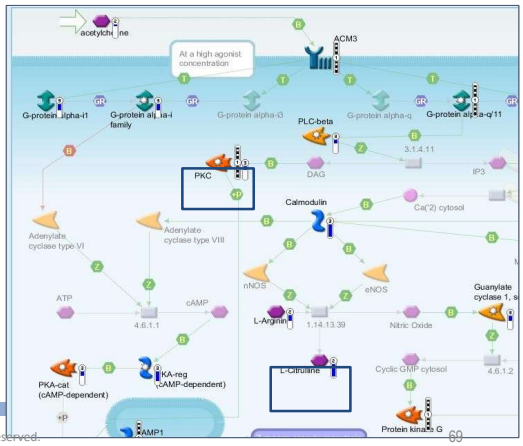


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多體學數據同時分析

- Combining metabolomic, transcriptomic and gene variants for side by side – omics enrichment analysis





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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

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數據背景

- Cohort of 150 patients from CAPSOD study with varying renal dysfunction in patients with sepsis or pneumonia.
- Renal dysfunction was classified using the Acute Kidney Injury Network (AKIN) criteria.

AKI0 (no significant increase in serum creatinine) n=65
AKI1 (serum creatinine increase of ≥ 0.3 mg/dl, or 150% to 200% above baseline) n=41
AKI2/3 (serum creatinine increase more that 200% above baseline, or ≥ 4.0 mg/dl with an acute increase of at least 0.5 mg/dl) n=20
Chronic hemodialysis (HD) n=2

HHS Public Access
Author manuscript
Kidney Int. Author manuscript; available in PMC 2016 April 01.

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Kidney Int. 2015 October ; 88(4): 804–814. doi:10.1038/ki.2015.150.

Renal systems biology of patients with systemic inflammatory response syndrome

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Dataset

- Mass spectrometry was used to measure the levels of 370 plasma metabolites.
  - 241 metabolites were annotated
  - Clinical assays of serum creatine, capillary lactate, and serum glucose was used to validate the
- use of the MS data in a semiquantitative fashion.
  - 138 annotated metabolites were significantly different from the AKI0 control group using ANOV with 1% false discovery rate correction.
- Mass spectrometry was used to measure the levels of plasma proteins.
  - 164 proteins were identified using peptide sequences
  - 46 were significantly different from the AKI0 control group using ANOVA with 5% false discover rate correction.
- RNA-seq was used to measure the blood transcriptome.
  - 133 out of 150 patients were used due to poor insufficient quality.
  - 1,997 genes were significantly differentially expressed across all groups using ANOVA with 1% false discovery rate correction.

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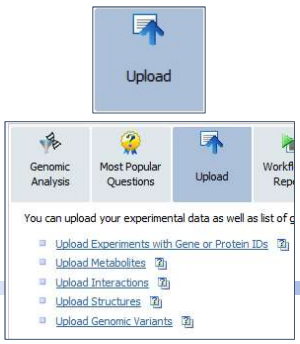
72

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用內源代謝網路來分析代謝體學和轉錄體學

- Question: 我們能在代謝體學和轉錄體學資料之間找到什麼代謝關係?

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





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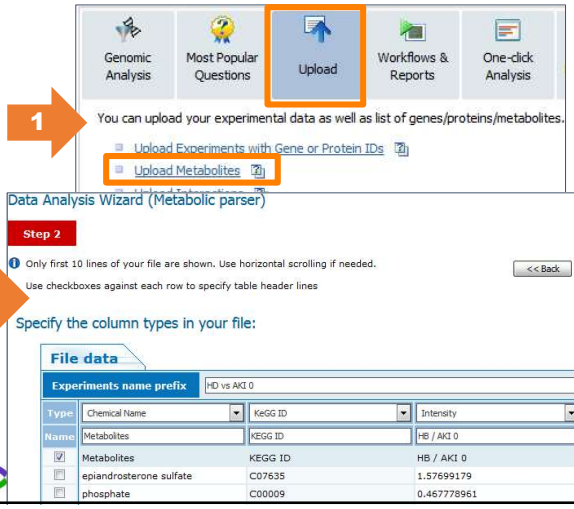
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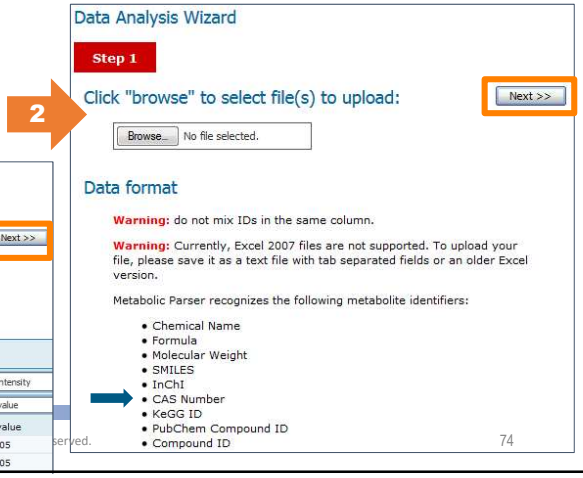
73

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上傳代謝體學數據到MetaCore中

- Tip: You can include multiple identifiers when uploading metabolites



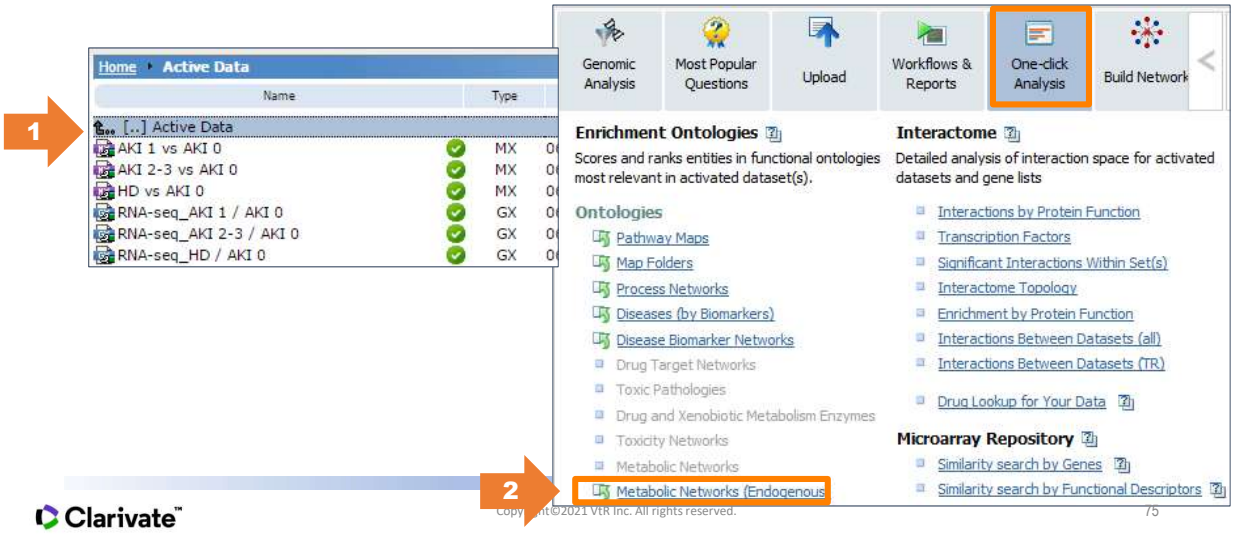


served.

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透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？



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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？

- Top 10 networks involved amino acid metabolism and glutamic acid processes.

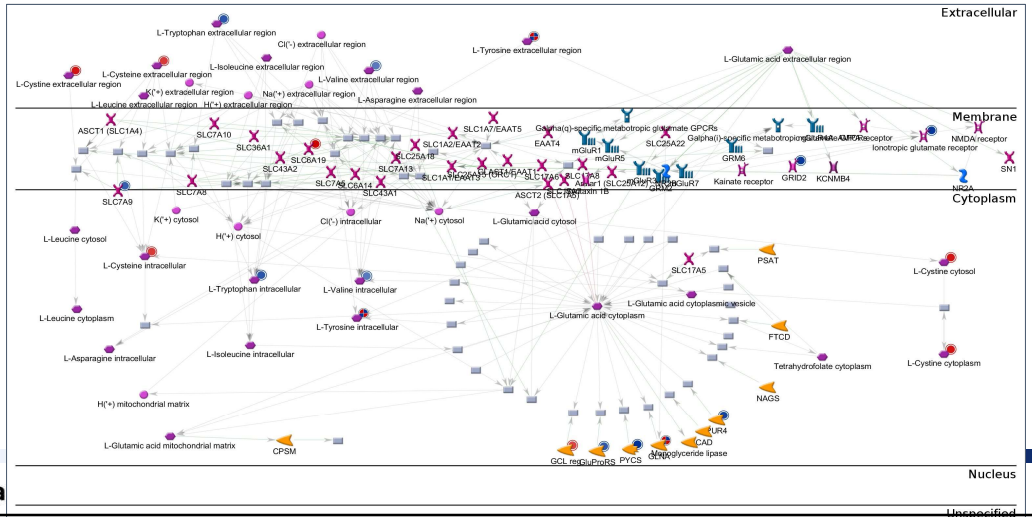


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麩胺酸訊息傳導路徑是如何被影響的？SLC7A9和SLC6A19的表達變化可能影響胺基酸濃度的失調

Glutamic acid pathways and transport



代謝體學和蛋白體學資料都涉及到的訊息傳導路徑有哪些？

- Question:
  - 患者血漿中哪些代謝物和蛋白濃度的變化可能是疾病進程的生物標記

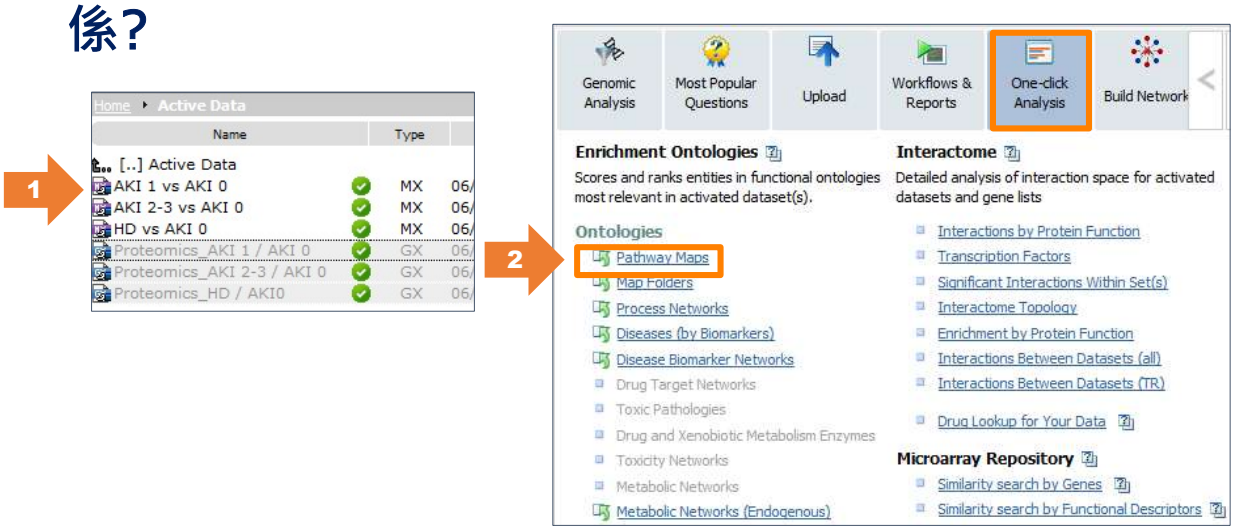
Pathway Map Enrichment





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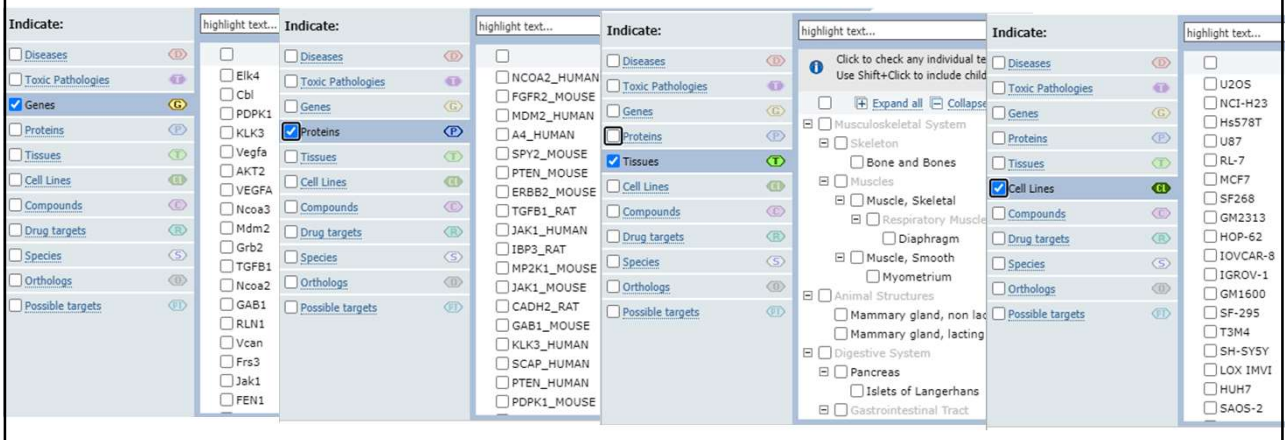
在代謝和表現數據之間我們能找到什麼代謝關係?



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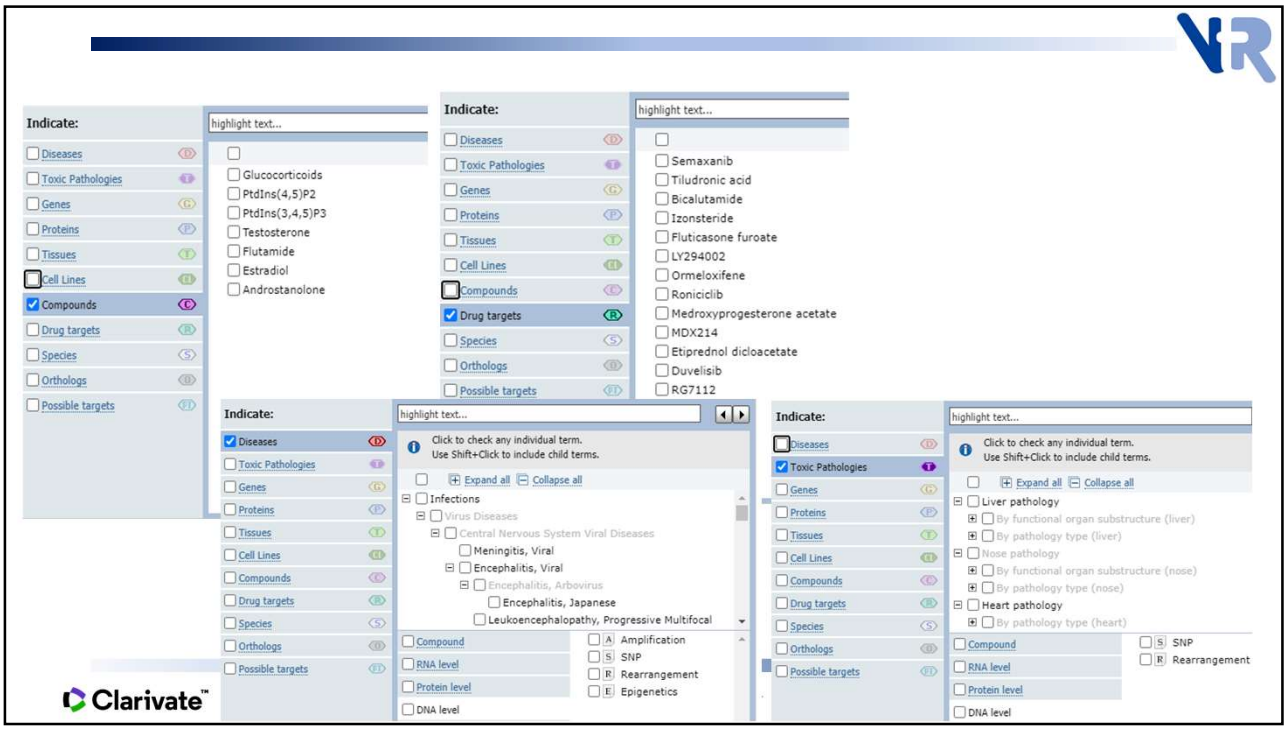
79

網絡建構時，可選擇想了解的資訊進行分析。

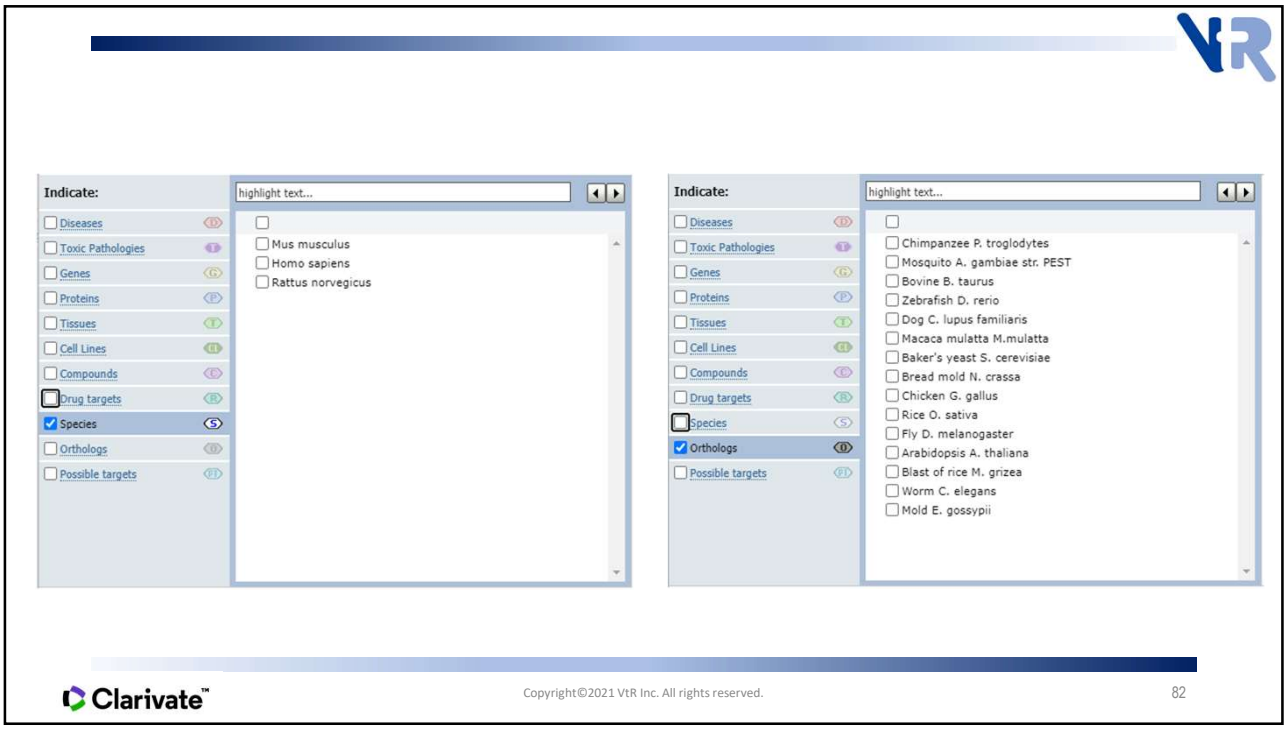


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Indicate:
highlight text...
Diseases
Toxic Pathologies
Genes
Proteins
Tissues
Cell Lines
Compounds
Drug targets
Species
Orthologs
Possible targets
Glucocorticoids
PtdIns(4,5)P2
PtdIns(3,4,5)P3
Testosterone
Flutamide
Estradiol
Androstanolone
Semaxanib
Tiludronic acid
Bicalutamide
Izonsteride
Fluticasone furoate
LY294002
Ormeloxifene
Roniciclib
Medroxyprogesterone acetate
MDX214
Etiprednol dicloacetate
Duvelisib
RG7112
Click to check any individual term.
Use Shift+Click to include child terms.
Expand all
Collapse all
Infections
Virus Diseases
Central Nervous System Viral Diseases
Meningitis, Viral
Encephalitis, Viral
Encephalitis, Arbovirus
Encephalitis, Japanese
Leukoencephalopathy, Progressive Multifocal
Liver pathology
By functional organ substructure (liver)
By pathology type (liver)
Nose pathology
By functional organ substructure (nose)
By pathology type (nose)
Heart pathology
By pathology type (heart)
Compound
RNA level
Protein level
DNA level
Amplification
SNP
Rearrangement
Epigenetics
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Indicate:
highlight text...
Diseases
Toxic Pathologies
Genes
Proteins
Tissues
Cell Lines
Compounds
Drug targets
Species
Orthologs
Possible targets
Mus musculus
Homo sapiens
Rattus norvegicus
Chimpanzee P. troglodytes
Mosquito A. gambiae str. PEST
Bovine B. taurus
Zebrafish D. rerio
Dog C. lupus familiaris
Macaca mulatta M.mulatta
Baker's yeast S. cerevisiae
Bread mold N. crassa
Chicken G. gallus
Rice O. sativa
Fly D. melanogaster
Arabidopsis A. thaliana
Blast of rice M. grizea
Worm C. elegans
Mold E. gossypii
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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?

- 膽固醇相關路徑和補體路徑都與這些體學數據變化有關。

#	Maps	-log(pValue)	pValue	min(pValue)	FDR	Ratio
1	Transport_Intracellular cholesterol transport		1.279e-9	1.279e-9	5.287e-8	9/83
			1.279e-9		5.287e-8	9/83
			1.279e-9		5.287e-8	9/83
			3.962e-2		1.657e-1	2/83
			5.015e-2		1.894e-1	2/83
			5.015e-2		1.894e-1	2/83
2	Immune response_Alternative complement pathway		2.750e-1	1.514e-6	3.667e-1	1/53
			2.750e-1		3.667e-1	1/53
			2.750e-1		3.667e-1	1/53
			1.514e-6		6.966e-5	5/53
			2.947e-6		1.503e-4	5/53
			2.947e-6		1.503e-4	5/53
3	Transport_HDL-mediated reverse cholesterol transport		2.315e-3	2.163e-5	2.609e-2	3/44
			2.315e-3		2.609e-2	3/44
			2.315e-3		2.609e-2	3/44
			2.163e-5		4.975e-4	4/44
			3.656e-5		9.324e-4	4/44
			3.656e-5		9.324e-4	4/44
4	Cholesterol and Sphingolipid transport / Recycling to plasma membrane in lung (normal and CF)		3.853e-4	3.853e-4	5.308e-3	3/24
			3.853e-4		5.308e-3	3/24

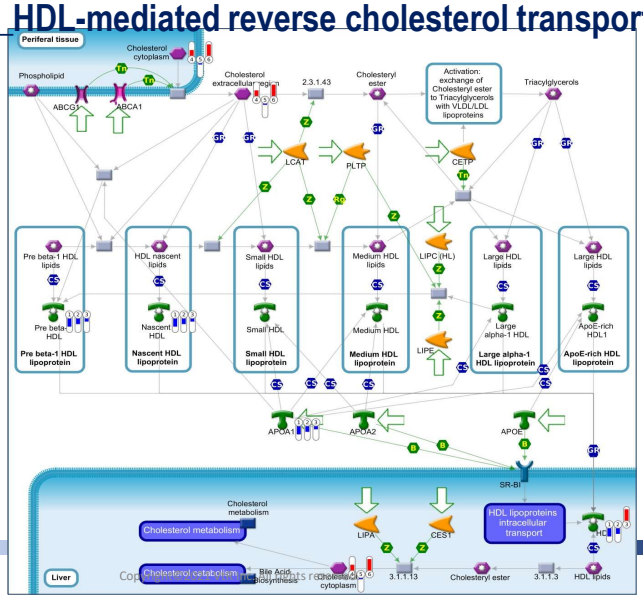
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高密度脂蛋白和膽固醇與腎衰竭有關

Transport_HDL-mediated reverse cholesterol transport

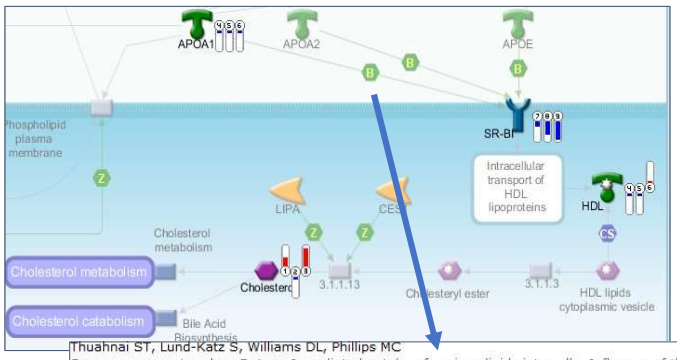


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參考文獻的資訊一目了然



- SR-B1 expression appears to decrease as kidney injury worsens and could be indicative of cholesterol metabolism dysregulation.

Thuahnai ST, Lund-Katz S, Williams DL, Phillips MC
Scavenger receptor class B, type I-mediated uptake of various lipids into cells. Influence of the nature of the donor particle interaction with the receptor.
The Journal of biological chemistry 2001 Nov 23;276(47):43801-8
PMID: 11564739

▾ Experiment Details

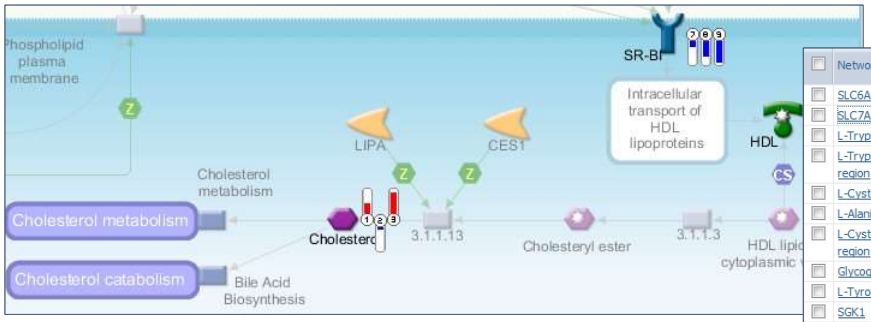
Note	APOA1 state	Mechanism	Effect	SR-BI state	Methods	Cell line/Tissue
APOA1 increases HDL binding to SRBI and selective uptake of Cholesterol ester.	APOA1_HUMAN	Binding	Activation	SCRB1_HUMAN	3h radiolabel, 125I radiolabel, transfection, binding assay, transport activity determination	COS7

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Summary

- 麩胺酸和胺基酸相關的代謝和轉運途徑包含代謝體學和RNA-seq數據
- SLC7A9和SLC6A19等路徑可能在胺基酸進出細胞的過程中發揮作用。
- 血液中APOC3和膽固醇的增加可能與肝細胞SR-B1表現的減少有關。



Network Objects	# of Networks containing Network Object
SLC6A19	18
SLC7A9	16
L-Tryptophan intracellular	15
L-Tryptophan extracellular region	14
L-Cysteine intracellular	10
L-Alanine intracellular	8
L-Cysteine extracellular region	8
Glycogen phosphorylase	8
L-Tyrosine intracellular	7
SGK1	7
L-Alanine extracellular region	7
SHMT1	7
PLC-beta	7
Urea intracellular	6

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Live demo

上傳體學數據進行分析

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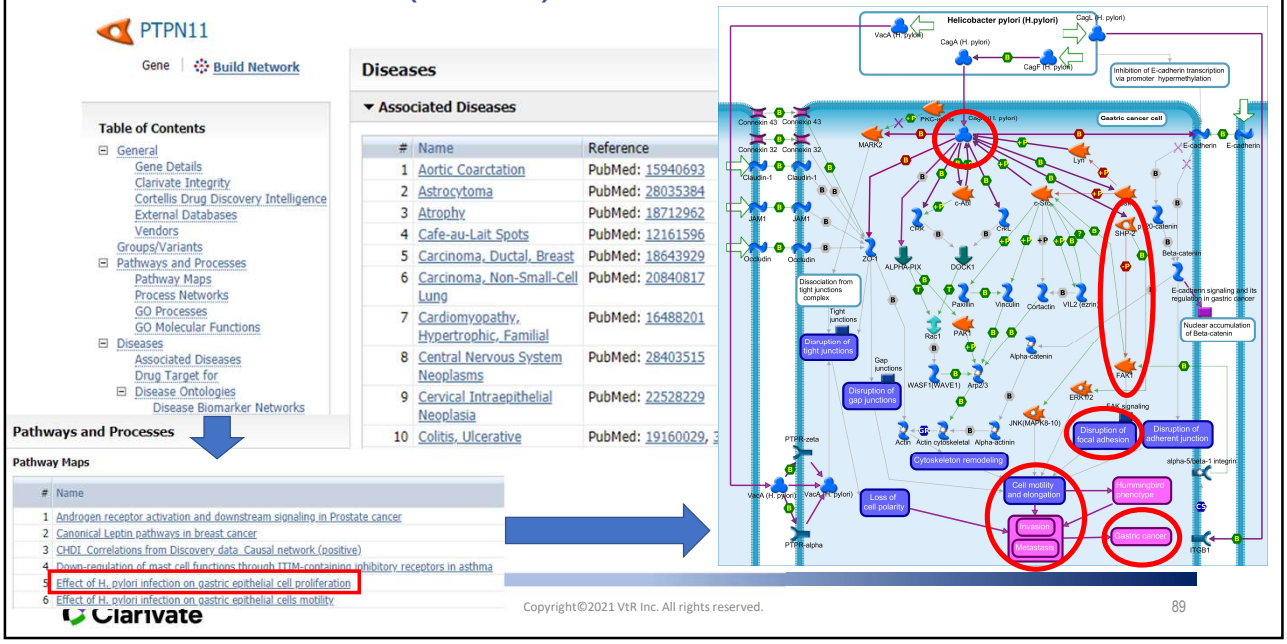
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由分子路徑分析找到藥物標靶，
並進一步了解相關藥物的活性預測。

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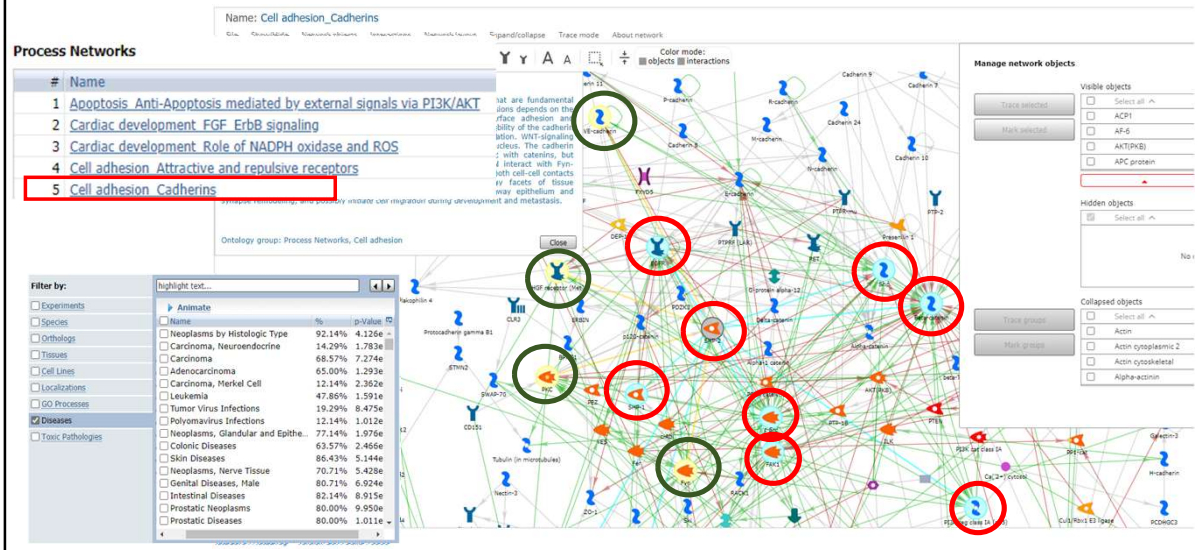
癌症轉移重要標靶 SHP2 (PTPN11) 的深度知識挖掘及檢索，及資訊收集



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以 SHP2 (PTPN11) 建構靶點與生物標記的識別與驗證



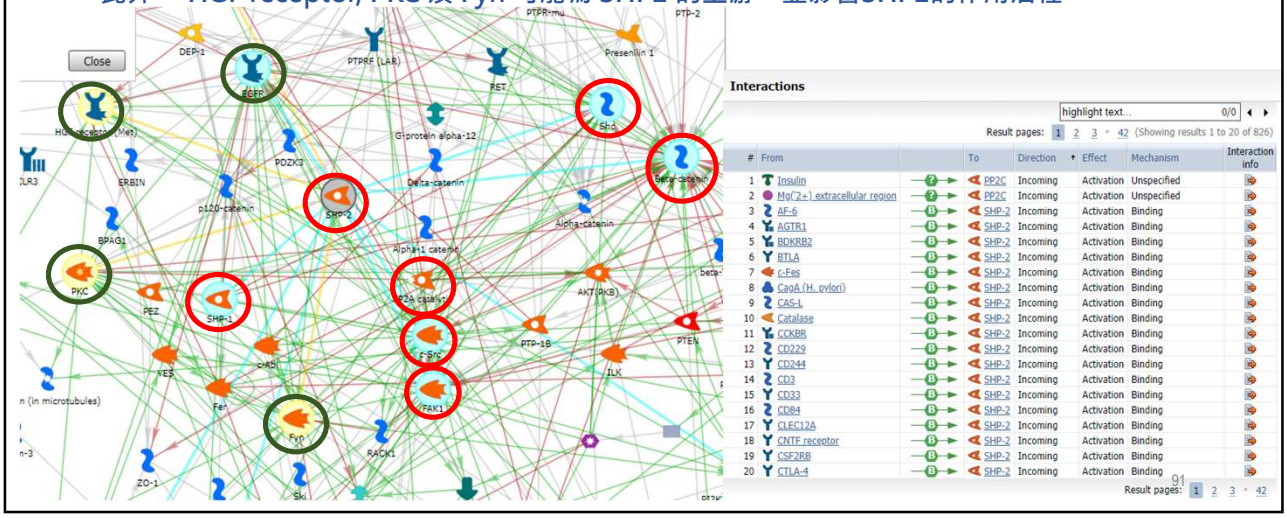
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以 SHP2 (PTPN11) 建構靶點與生物標記的識別與驗證

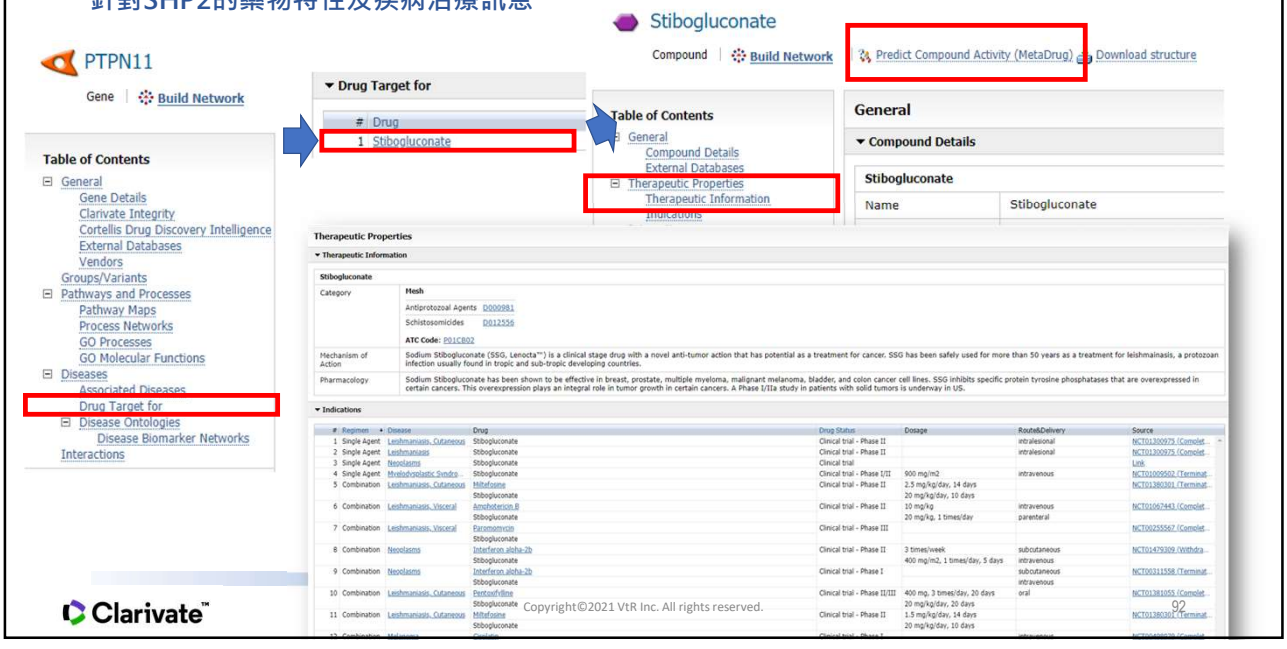
在 Cell adhesion 的過程中。

- SHP2 透過去磷酸化作用影響 SHP1, EGFR, c-Src, FAK1 及 beta catenin 的蛋白質作用活性。
- 此外， HGF receptor, PKC 及 Fyn 可能為 SHP2 的上游，並影響SHP2的作用活性。



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針對SHP2的藥物特性及疾病治療訊息



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What is MetaDrug?

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Metadrug預測工具

數據庫挖掘 代謝產物預測 毒性預測 標靶預測 適應症預測 影響到的通路 體學數據分析

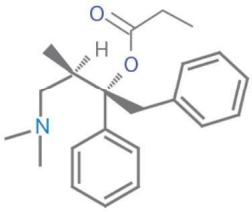
MetaDrug

化合物數據庫

代謝預測工具

毒性預測工具

標靶/
適應症預測



在五分鐘內，
可了解一個化合物
多少訊息?

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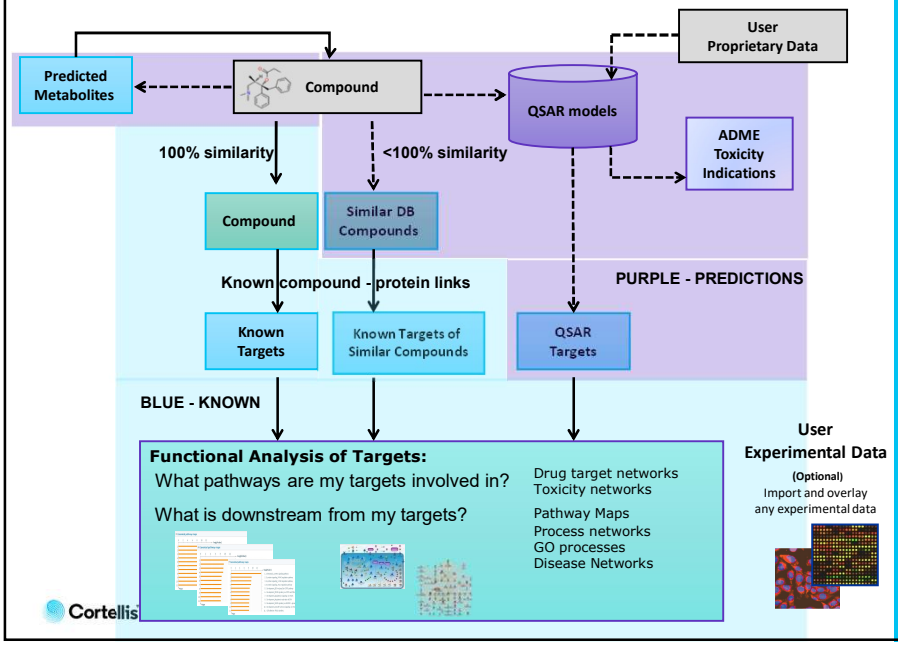
Metadrug的底層資料

- >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 個經典範式通路圖，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物（Biomarker）
- >800,000 個化合物及其靶標與生物活性資料
- > 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

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How does MetaDrug work?

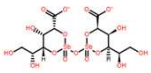


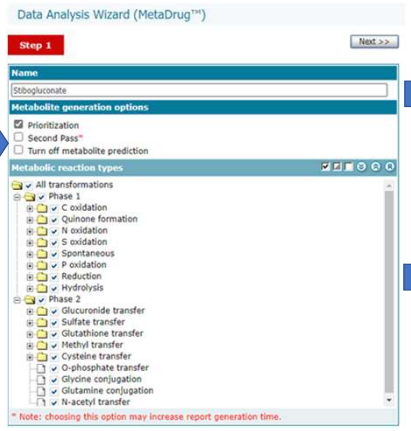
- **A systems pharmacology platform for predicting bioactivity of small molecules.**
- Provides structure-based assessment of compound activity and liability.
- Predict metabolites, ADME Tox, targets and **affected pathways and processes.**

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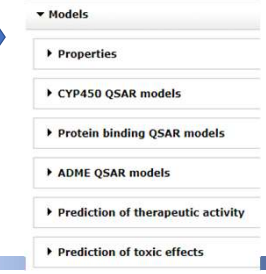
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針對SHP2的藥物活性預測









代謝物活性預測

CYP450 代謝預測

蛋白質結合活性預測

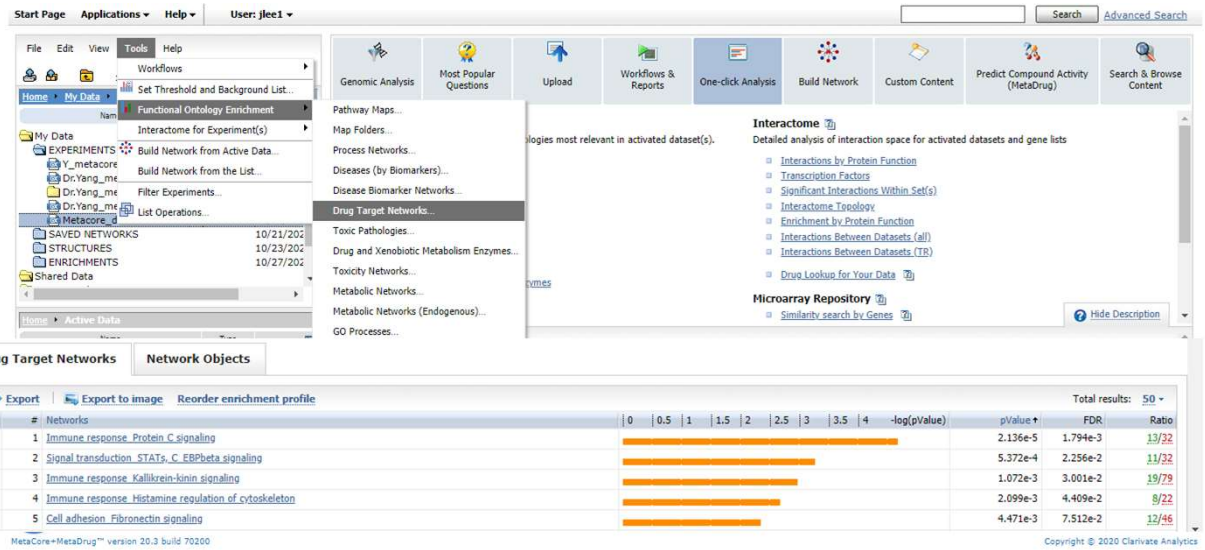
身體代謝吸收活性預測

適應症治療活性預測

毒性影響預測

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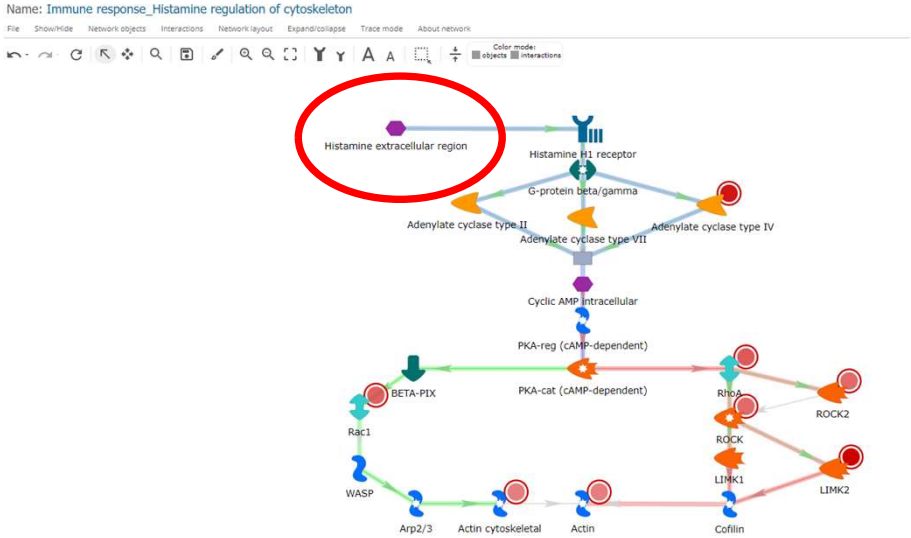
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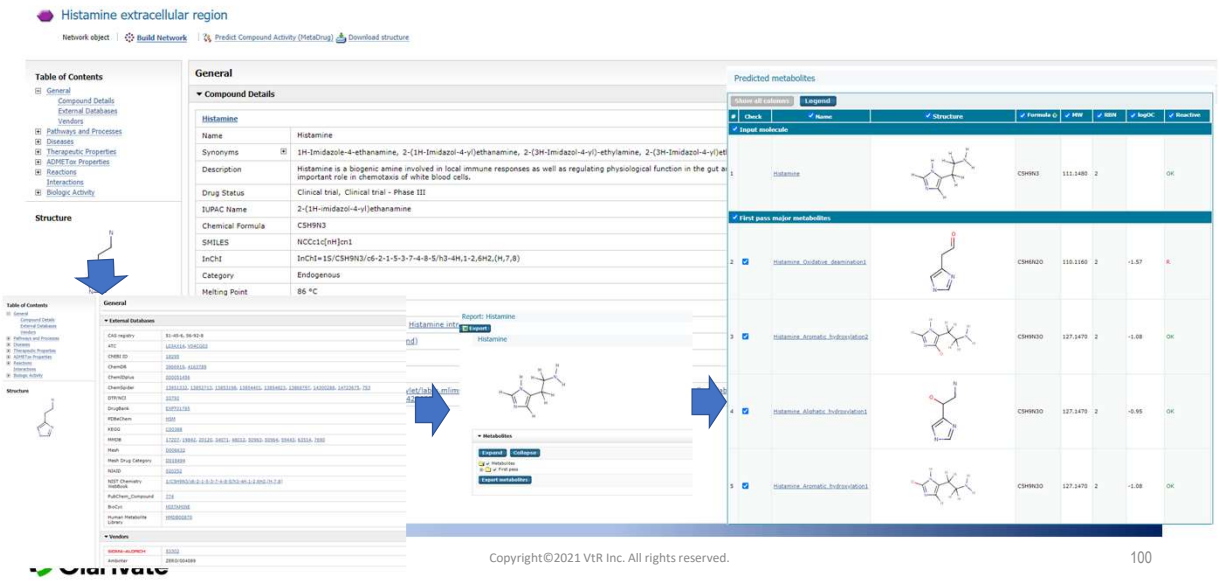
透過已建立網絡尋找化合物相關資訊



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查看化合物基本資料及代謝物預測



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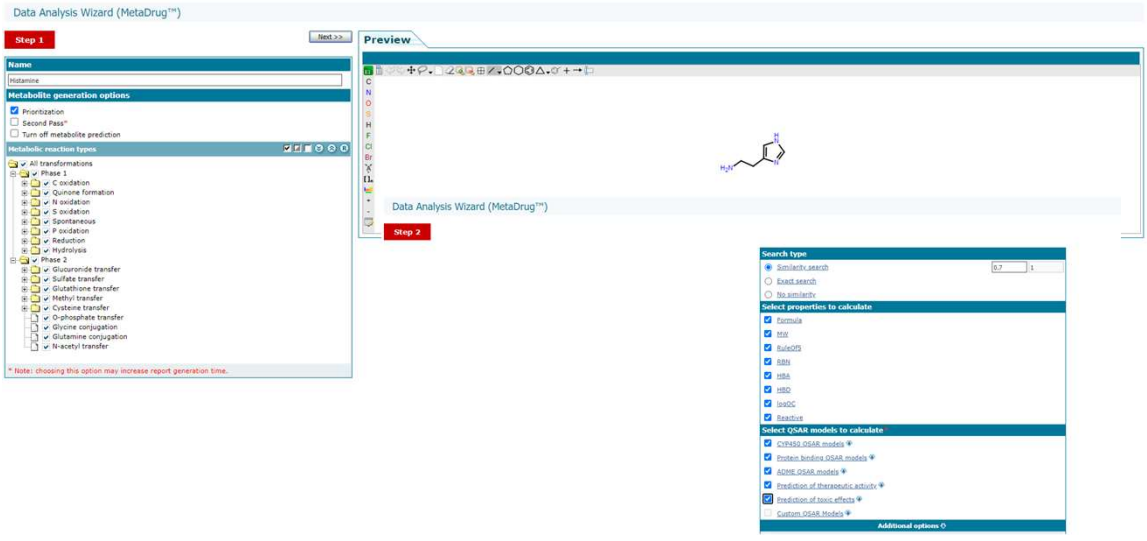
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IV. 化合物活性預測

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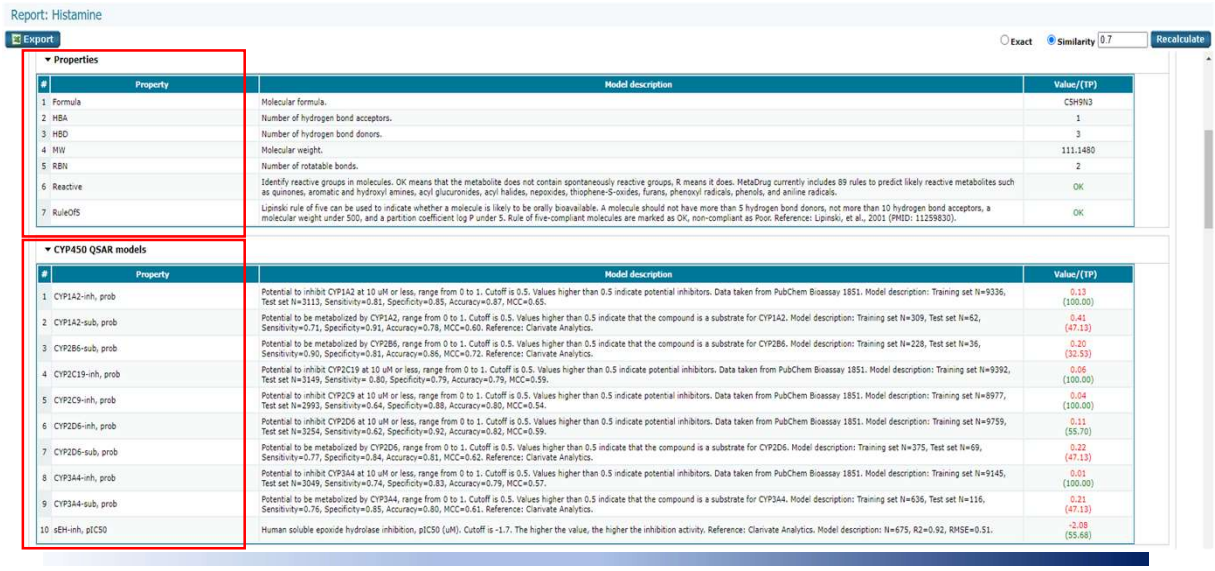
上傳化合物結構式進行預測



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以QSAR model 進行CYP450代謝預測



Report: Histamine

Export

Exact Similarity 0.7 Recalculate

▾ Properties

#	Property	Model description	Value/(TP)
1	Formula	Molecular formula.	C5H9N3
2	HBA	Number of hydrogen bond acceptors.	1
3	HBD	Number of hydrogen bond donors.	3
4	MW	Molecular weight.	111.1480
5	RBN	Number of rotatable bonds.	2
6	Reactive	Identify reactive groups in molecules. OK means that the metabolite does not contain spontaneously reactive groups, R means it does. MetaDrug currently includes 89 rules to predict likely reactive metabolites such as quinones, aromatic and hydroxyl amines, acyl glucuronides, acyl halides, nepoxides, thiophene-S-oxides, furans, phenoxyl radicals, phenols, and aniline radicals.	OK
7	RuleOf5	Lipinski rule of five can be used to indicate whether a molecule is likely to be orally bioavailable. A molecule should not have more than 5 hydrogen bond donors, not more than 10 hydrogen bond acceptors, a molecular weight under 500, and a partition coefficient log P under 5. Rule of five-compliant molecules are marked as OK, non-compliant as Poor. Reference: Lipinski, et al., 2001 (PMID: 11259830).	OK

▾ CYP450 QSAR models

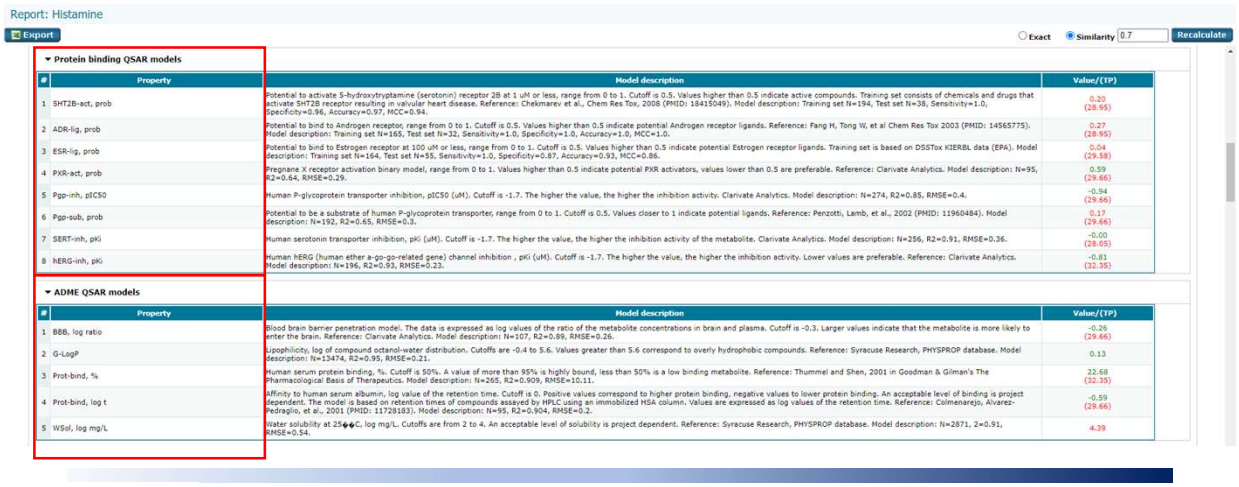
#	Property	Model description	Value/(TP)
1	CYP1A2-inh, prob	Potential to inhibit CYP1A2 at 10 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential inhibitors. Data taken from PubChem Bioassay 1851. Model description: Training set N=9336, Test set N=3113, Sensitivity=0.81, Specificity=0.85, Accuracy=0.87, MCC=0.65.	0.13 (100.00)
2	CYP1A2-sub, prob	Potential to be metabolized by CYP1A2, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate that the compound is a substrate for CYP1A2. Model description: Training set N=309, Test set N=62, Sensitivity=0.71, Specificity=0.91, Accuracy=0.78, MCC=0.60. Reference: Clarivate Analytics.	0.41 (47.13)
3	CYP2B6-sub, prob	Potential to be metabolized by CYP2B6, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate that the compound is a substrate for CYP2B6. Model description: Training set N=228, Test set N=36, Sensitivity=0.90, Specificity=0.81, Accuracy=0.86, MCC=0.72. Reference: Clarivate Analytics.	0.20 (32.53)
4	CYP2C19-inh, prob	Potential to inhibit CYP2C19 at 10 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential inhibitors. Data taken from PubChem Bioassay 1851. Model description: Training set N=9392, Test set N=3149, Sensitivity= 0.80, Specificity=0.79, Accuracy=0.79, MCC=0.59.	0.06 (100.00)
5	CYP2C9-inh, prob	Potential to inhibit CYP2C9 at 10 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential inhibitors. Data taken from PubChem Bioassay 1851. Model description: Training set N=8977, Test set N=2993, Sensitivity=0.64, Specificity=0.88, Accuracy=0.80, MCC=0.54.	0.04 (100.00)
6	CYP2D6-inh, prob	Potential to inhibit CYP2D6 at 10 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential inhibitors. Data taken from PubChem Bioassay 1851. Model description: Training set N=9759, Test set N=3254, Sensitivity=0.62, Specificity=0.92, Accuracy=0.82, MCC=0.59.	0.11 (55.70)
7	CYP2D6-sub, prob	Potential to be metabolized by CYP2D6, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate that the compound is a substrate for CYP2D6. Model description: Training set N=375, Test set N=69, Sensitivity=0.77, Specificity=0.84, Accuracy=0.81, MCC=0.62. Reference: Clarivate Analytics.	0.22 (47.13)
8	CYP3A4-inh, prob	Potential to inhibit CYP3A4 at 10 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential inhibitors. Data taken from PubChem Bioassay 1851. Model description: Training set N=9145, Test set N=3049, Sensitivity=0.74, Specificity=0.83, Accuracy=0.79, MCC=0.57.	0.01 (100.00)
9	CYP3A4-sub, prob	Potential to be metabolized by CYP3A4, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate that the compound is a substrate for CYP3A4. Model description: Training set N=636, Test set N=116, Sensitivity=0.76, Specificity=0.85, Accuracy=0.80, MCC=0.61. Reference: Clarivate Analytics.	0.21 (47.13)
10	sEH-inh, pIC50	Human soluble epoxide hydrolase inhibition, pIC50 (uM). Cutoff is -1.7. The higher the value, the higher the inhibition activity. Reference: Clarivate Analytics. Model description: N=675, R2=0.92, RMSE=0.51.	-2.08 (55.68)

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Report: Histamine

Export

Exact Similarity 0.7 Recalculate

▾ Protein binding QSAR models

#	Property	Model description	Value/(TP)
1	5HT2B-act, prob	Potential to activate 5-hydroxytryptamine (serotonin) receptor 2B at 1 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate active compounds. Training set consists of chemicals and drugs that activate 5HT2B receptor resulting in valvular heart disease. Reference: Chekmarev et al., Chem Res Tox, 2008 (PMID: 18415049). Model description: Training set N=194, Test set N=38, Sensitivity=1.0, Specificity=0.96, Accuracy=0.97, MCC=0.94.	0.20 (28.95)
2	ADR-lig, prob	Potential to bind to Androgen receptor, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential Androgen receptor ligands. Reference: Fang H, Tong W, et al Chem Res Tox 2003 (PMID: 14565775). Model description: Training set N=165, Test set N=32, Sensitivity=1.0, Specificity=1.0, Accuracy=1.0, MCC=1.0.	0.27 (28.95)
3	ESR-lig, prob	Potential to bind to Estrogen receptor at 100 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential Estrogen receptor ligands. Training set is based on DSSTox KIERBL data (EPA). Model description: Training set N=164, Test set N=55, Sensitivity=1.0, Specificity=0.87, Accuracy=0.93, MCC=0.86.	0.04 (29.58)
4	PXR-act, prob	Pregnane X receptor activation binary model, range from 0 to 1. Values higher than 0.5 indicate potential PXR activators, values lower than 0.5 are preferable. Reference: Clarivate Analytics. Model description: N=95, R2=0.64, RMSE=0.29.	0.59 (29.66)
5	Pgp-inh, pIC50	Human P-glycoprotein transporter inhibition, pIC50 (uM). Cutoff is -1.7. The higher the value, the higher the inhibition activity. Clarivate Analytics. Model description: N=274, R2=0.85, RMSE=0.4.	-0.94 (29.66)
6	Pgp-sub, prob	Potential to be a substrate of human P-glycoprotein transporter, range from 0 to 1. Cutoff is 0.5. Values closer to 1 indicate potential ligands. Reference: Penzotti, Lamb, et al., 2002 (PMID: 11960484). Model description: N=192, R2=0.65, RMSE=0.3.	0.17 (29.66)
7	SERT-inh, pKi	Human serotonin transporter inhibition, pKi (uM). Cutoff is -1.7. The higher the value, the higher the inhibition activity of the metabolite. Clarivate Analytics. Model description: N=256, R2=0.91, RMSE=0.36.	-0.00 (28.05)
8	hERG-inh, pKi	Human hERG (human ether a-go-go-related gene) channel inhibition , pKi (uM). Cutoff is -1.7. The higher the value, the higher the inhibition activity. Lower values are preferable. Reference: Clarivate Analytics. Model description: N=196, R2=0.93, RMSE=0.23.	-0.81 (32.35)

▾ ADME QSAR models

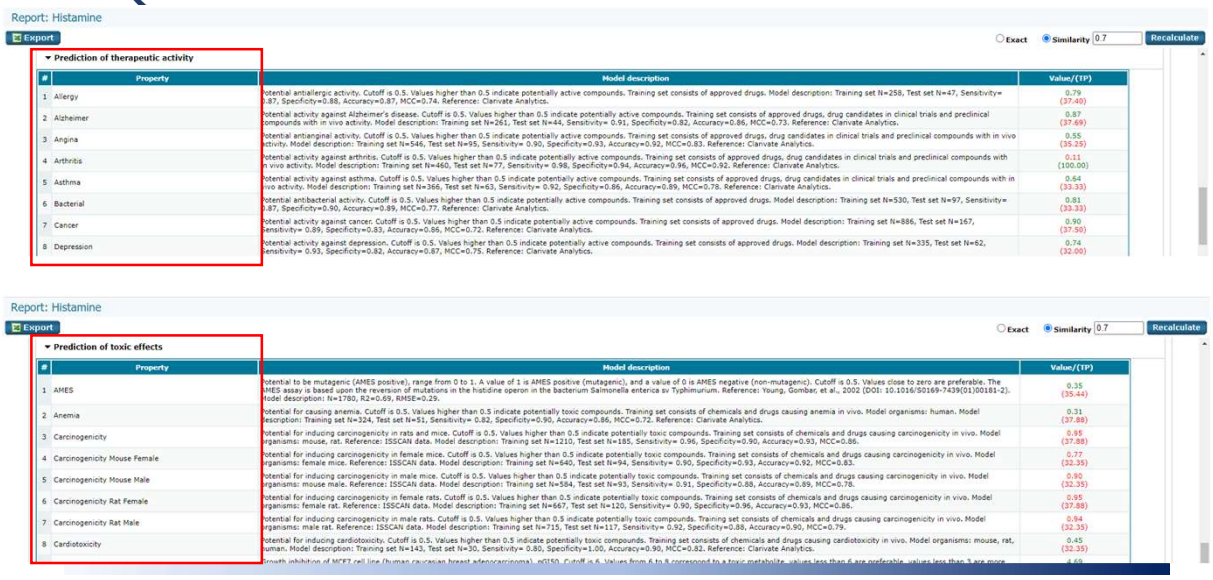
#	Property	Model description	Value/(TP)
1	BBB, log ratio	Blood brain barrier penetration model. The data is expressed as log values of the ratio of the metabolite concentrations in brain and plasma. Cutoff is -0.3. Larger values indicate that the metabolite is more likely to enter the brain. Reference: Clarivate Analytics. Model description: N=107, R2=0.89, RMSE=0.26.	-0.26 (29.66)
2	G-LogP	Lipophilicity, log of compound octanol-water distribution. Cutoffs are -0.4 to 5.6. Values greater than 5.6 correspond to overly hydrophobic compounds. Reference: Syracuse Research, PHYSPROP database. Model description: N=13474, R2=0.95, RMSE=0.21.	0.13
3	Prot-bind, %	Human serum protein binding, %. Cutoff is 50%. A value of more than 95% is highly bound, less than 50% is a low binding metabolite. Reference: Thummel and Shen, 2001 in Goodman & Gilman's The Pharmacological Basis of Therapeutics. Model description: N=265, R2=0.909, RMSE=10.11.	22.68 (32.35)
4	Prot-bind, log t	Affinity to human serum albumin, log value of the retention time. Cutoff is 0. Positive values correspond to higher protein binding, negative values to lower protein binding. An acceptable level of binding is project dependent. The model is based on retention times of compounds assayed by HPLC using an immobilized HSA column. Values are expressed as log values of the retention time. Reference: Colmenarejo, Alvarez-Pedraglio, et al., 2001 (PMID: 11728183). Model description: N=95, R2=0.904, RMSE=0.2.	-0.59 (29.66)
5	WSol, log mg/L	Water solubility at 25◆◆C, log mg/L. Cutoffs are from 2 to 4. An acceptable level of solubility is project dependent. Reference: Syracuse Research, PHYSPROP database. Model description: N=2871, 2=0.91, RMSE=0.54.	4.39

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以QSAR model 進行適應症及毒性預測



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再回到分子及路徑機制分析



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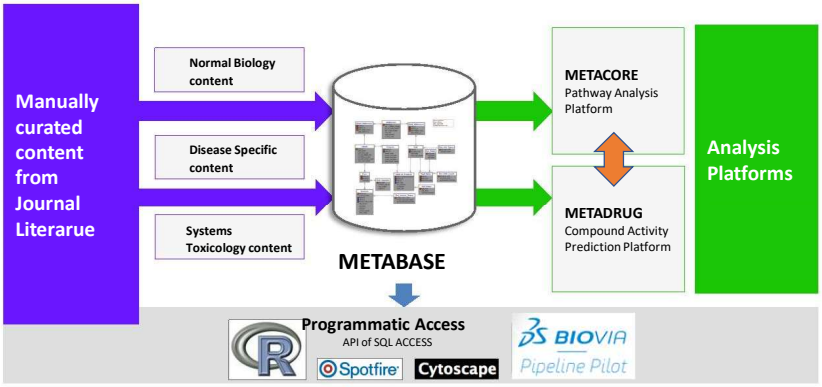
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Live demo

以化合物進行活性分析及預測

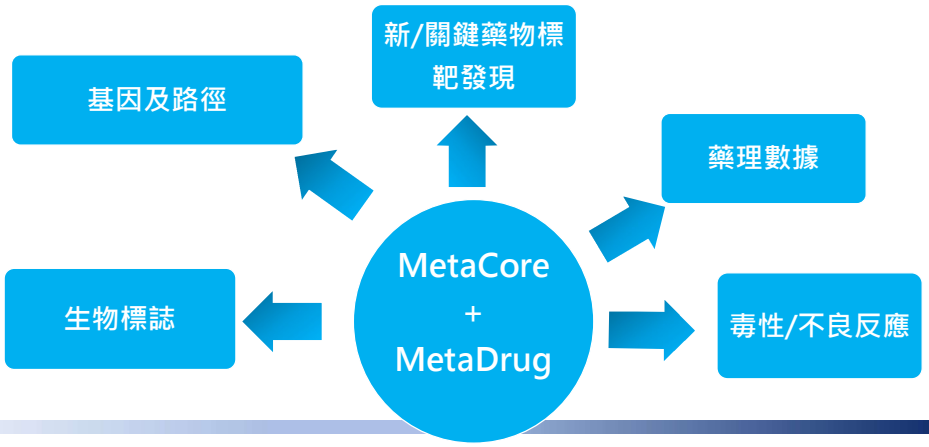
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科學研究及再發現



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