MetaCore利用事例

A biomarker-assisted systems biology approach to explore host-microbiome-drug metabolomics

MetaCoreユーザー会
2019年6月5日

クラリベイト・アナリティクス
ライフサイエンス・ジャパン
ソリューションコンサルタント
門岡　桂史

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WHAT IS THE HUMAN MICROBIOME?

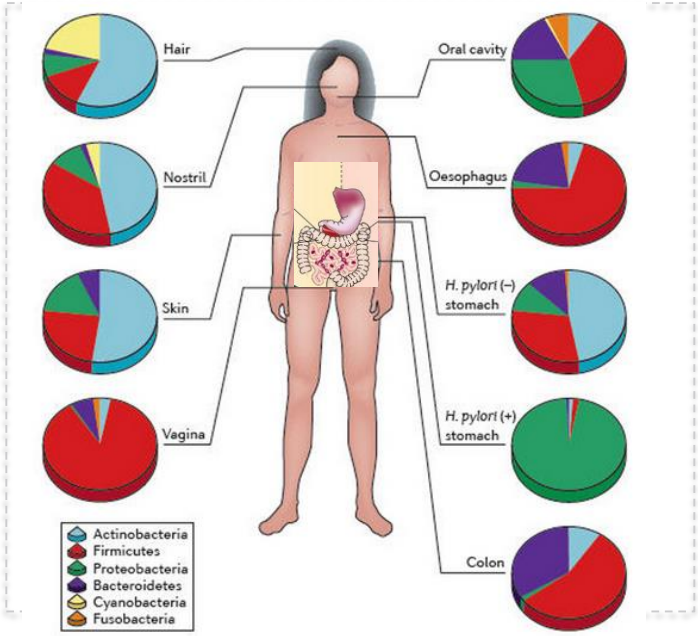
The collection of microbes (**microbiota**) - that inhabits the human body, and their genomes.

100 trillion symbiotic microbes (**10 X)**

2-20 million unique genes (**100 X)**

99.9 % Percentage individual humans are identical to one another in terms of host genomes.

80-90 % Percentage individual humans are different from one another in terms of microbiome.



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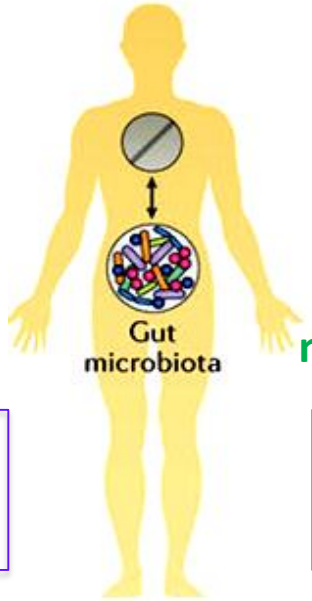
MICROBIOME-HOST-DRUG INTERACTIONS

Direct mechanisms

Drug metabolism by microbiota

Activated drugs
Deactivated drugs
Toxic metabolites

Drug effects on microbiota



Indirect mechanisms

Microbial metabolites

Microbiota- modified host metabolites

Altered host xenobiotic metabolism

Based on concepts reported in Nature Reviews Microbiology14, 273–287(2016)

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MICROBIOME-HOST-DRUG INTERACTIONS

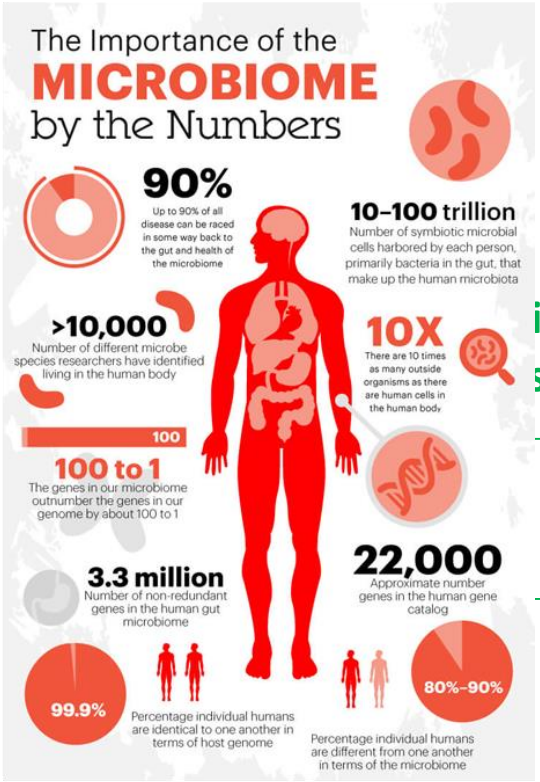
Microbiome and the immune system

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

V. Gopalakrishnan[1,2,*], C. N. Spencer[2,3,*], L. Nezi[3,*], A. Reuben[1], M. C. Andrews[1], T. V. Karpinets[3], P. A. Prieto[1,†], D. Vicente[1]...
+ See all authors and affiliations

Science 02 Nov 2017:
eaan4236
DOI: 10.1126/science.aan4236

- Gut microbiome is being extensively studied to understand it's impact in gastric and metabolic diseases.
- Further studies have looked into its importance in the immune systems and neurological diseases.
- This recent study from scientists at MD Anderson explored the relationship between anti-PD-1 therapies and microbiome colonies in melanoma patients.
  - Higher diversity and higher abundance of the Ruminococcaceae family bacteria was associated with longer progression-free survival.
  - Low diversity and higher abundance of the Bacteroidales order bacteria was associated with shorter progression-free survival.



METHODS FOR MINING THE MICROBIOME

TAXONOMIC APPROACHES

METAGENOMICS

- **Sequencing methods**
- The study of the genomes in a microbial community.
- Metagenomic shotgun sequencing studies are used (e.g., 16S rRNA gene amplicon sequencing).
- Suggested that dysbiosis of the gut microbiota may be a key risk factor for many diseases.
- Problems: Poor taxonomic resolution & absence of adequate functional insight.
- Metagenome-wide association studies (MWAS). Study design largely modeled on GWAS to identify taxa and function.

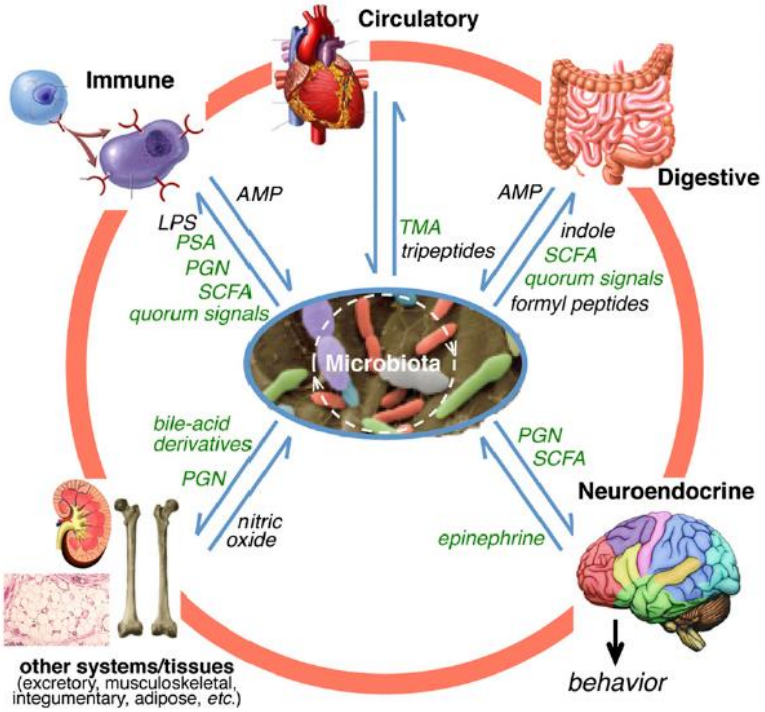
METATRANSCRIPTOMICS

- **Sequencing methods**
- The study of what genes are expressed by the entire microbial community.
- Sheds light on the *active* functional profile of a microbial community.
- Limitations because of the reference genomes needed for alignment approaches, and limitations in the ability of software programs to assemble contigs and supercontigs correctly from short reads data for de novo assembly approaches.

METHODS FOR MINING THE MICROBIOME

METABOLOMICS

- **Chromatography, Spectrometry, Magentic Resonance**
- Metabolomics is the comprehensive analysis by which all metabolites of a sample (small molecules released by the organism into the immediate environment) are identified and quantified.
- The metabolome is considered the most direct indicator of the health of an environment or of the alterations in homeostases (i.e., dysbiosis).
- Variation in the production of signature metabolites are related to changes in activity of metabolic routes, and therefore, metabolomics represents an applicable approach to pathway analysis.



*Signals in green promote body's homeostasis

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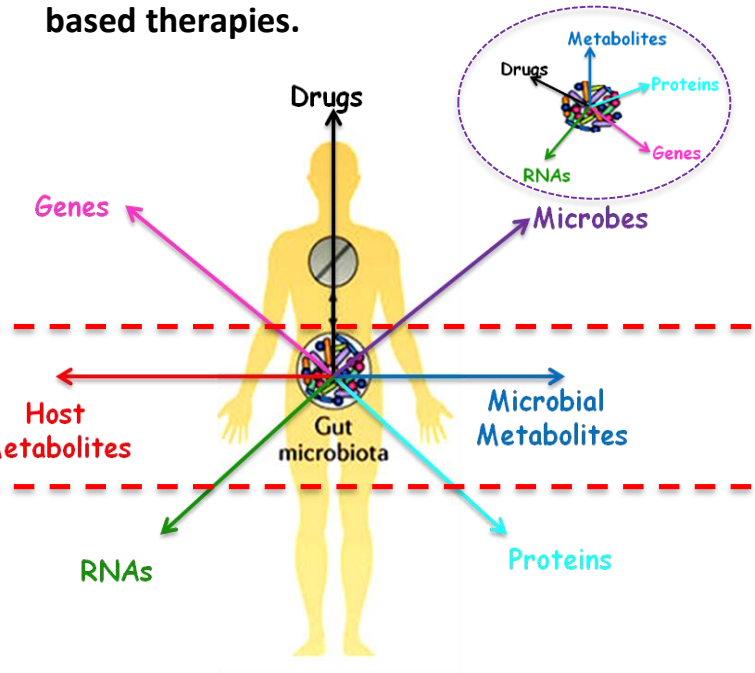
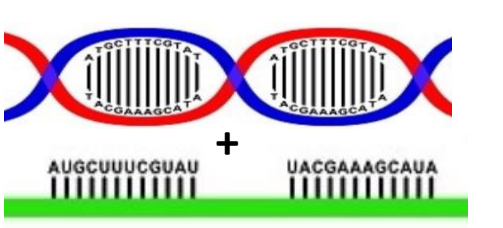
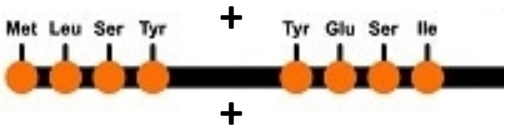
A BIOMARKER-ASSISTED SYSTEMS BIOLOGY APPROACH TO METABOLOMICS

Drug discovery space for microbiome-based therapies.

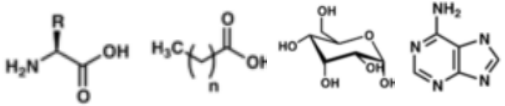




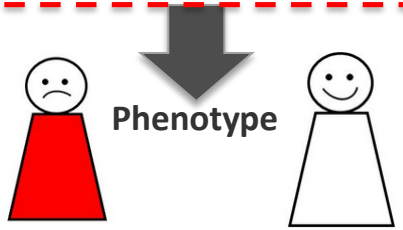
Integrity
Genomic Biomarkers



Integrity
Proteomic Biomarkers



Integrity
Biochemical Biomarkers



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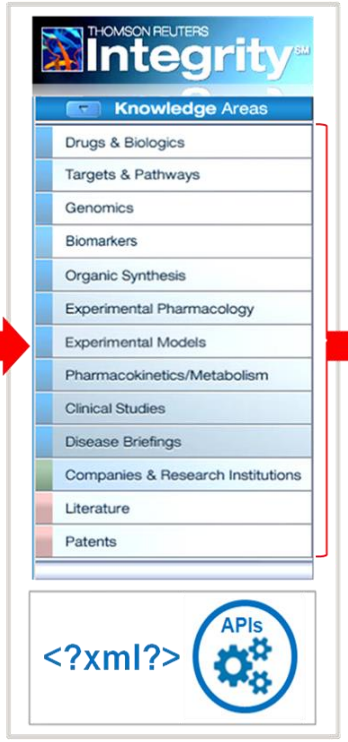
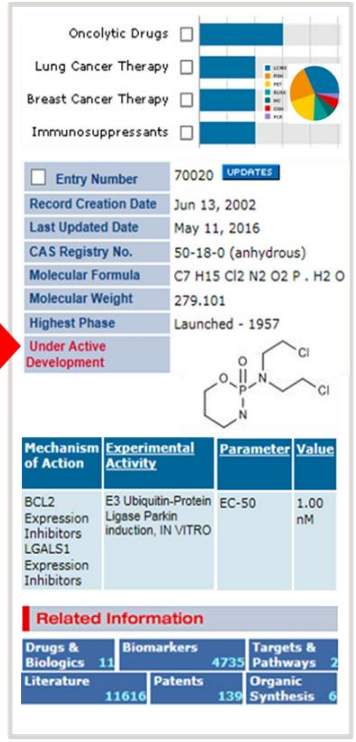
INTEGRITY: DRUG R&D PIPELINE DATABASE, CREATED BY SCIENTISTS FOR SCIENTISTS

Drug pipeline and competitive intelligence database





Number of records in each knowledge area

572,661	drugs & biologics
6,966	targets
48,008	genomic records
42,560	biomarkers
35,375	synthetic routes
2,620,311	pharmacology records
130,833	experimental models
1,007,355	PK/metabolism records
379,976	clinical studies references
161	disease briefings
31,550	companies & research institutions
2,604,039	references
437,410	patents

**As of 2019/06/03*

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WHY INTEGRITY BIOMARKERS?

42,560 biomarkers
~ 2.5 million biomarker uses

Biomarker's "ROLE"

- Disease/Toxicity Profiling
- Risk Factor
- **Predicting Treatment Efficacy** / Tox.
- Screening
- **Monitoring Treatment Efficacy** / Tox.
- Staging
- Prediction of Drug Resistance
- Prognosis
- Prediction of Drug Resistance
- Diagnosis, Differential Diagnosis
- Monitoring Disease Progression

Biomarker's "VALIDITY"

1) Emerging
2) Experimental
3) Early studies in humans
4) Late studies in human or observational studies
5) Recommended/approved

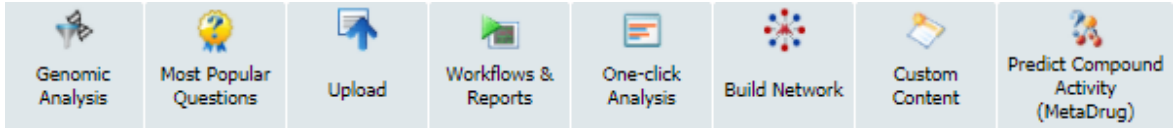
Biomarker's "TYPE"

1) Genomic
2) Proteomic
3) Biochemical
4) Other

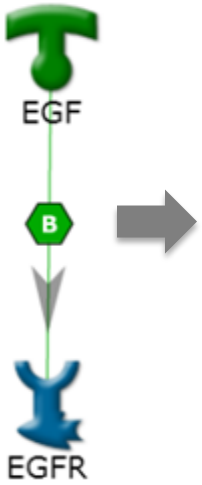
Analytics

METACORE: YOUR SYSTEMS BIOLOGY GPS

TRUSTED, HIGH QUALITY, MANUALLY-CURATED CONTENT (ERACTIONS, NETWORKS, AND PATHWAY MAPS

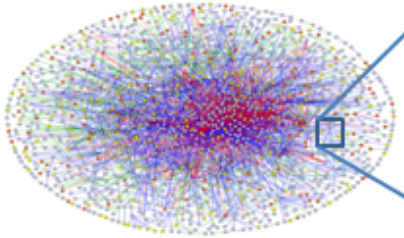


Molecular Interaction



Extracted from scientific papers and patents

Global Interaction Network

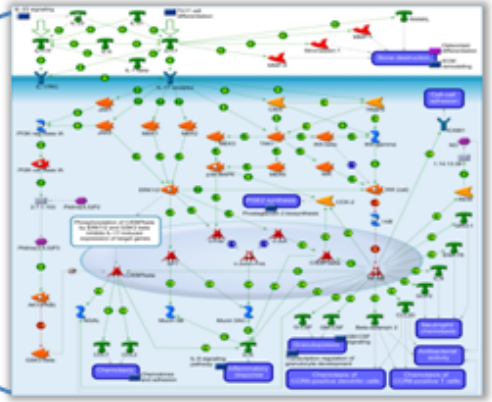


>2.3 million interactions

Process Networks

Global view of a process
(typically 100s of network objects)

Canonical Pathway Maps



Focused view on a subset of interactions or processes
(typically 50-60 network objects)

> 1,550 Pathway maps
> 220,000 Gene-disease associations

CASE STUDY

"Exploring Host-Microbiome-Metformin Metabolomics in Type 2 Diabetes"

MICROBIOME-HOST METFORMIN INTERACTIONS

Nat Med. 2017 Jul;23(7):850-858. doi: 10.1038/nm.4345. Epub 2017 May 22.

Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug.

Wu H[1], Esteve E[2,3,4], Tremaroli V[1], Khan MT[1], Caesar R[1], Mannerås-Holm L[1], Ståhlman M[1], Olsson LM[1], Serino M[5], Planas-Fèlix M[6], Xifra G[2,3,4], Mercader JM[6], Torrents D[6,7], Burcelin R[8,9], Ricart W[2,3,4], Perkins R[1], Fernàndez-Real JM[2,3,4], Bäckhed F[1,10,11].

Author information

Abstract

Metformin is widely used in the treatment of type 2 diabetes (T2D), but its mechanism of action is poorly defined. Recent evidence implicates the gut microbiota as a site of metformin action. In a double-blind study, we randomized individuals with treatment-naive T2D to placebo or metformin for 4 months and showed that metformin had strong effects on the gut microbiome. These results were verified in a subset of the placebo group that switched to metformin 6 months after the start of the trial. Transfer of fecal samples (obtained before and 4 months after treatment) from metformin-treated donors to germ-free mice showed that glucose tolerance was improved in mice that received metformin-altered microbiota. By directly investigating metformin-microbiota interactions in a gut simulator, we showed that metformin affected pathways with common biological functions in species from two different phyla, and many of the metformin-regulated genes in these species encoded metalloproteins or metal transporters. Our findings provide support for the notion that altered gut microbiota mediates some of metformin's antidiabetic effects.

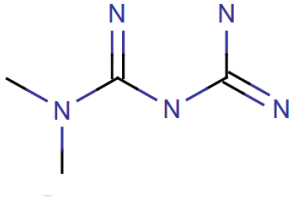
MICROBIOME-HOST METFORMIN INTERACTIONS

nature medicine

Type 2 Diabetes:

- Butyrate producing bacterial Taxa ↓
- Butyrate is the major energy source for microbiome and colonocytes.
- Colonocytes depend on butyrate for energy production.

Metformin Treatment:



- Gamma-proteobacteria (Gram-negative ↑, LPS ↑)
- Fermicutes Gram-positive ↓
- Many of the metformin-regulated genes in these species encoded **metalloproteins or metal transporters.**

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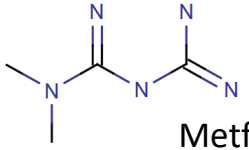
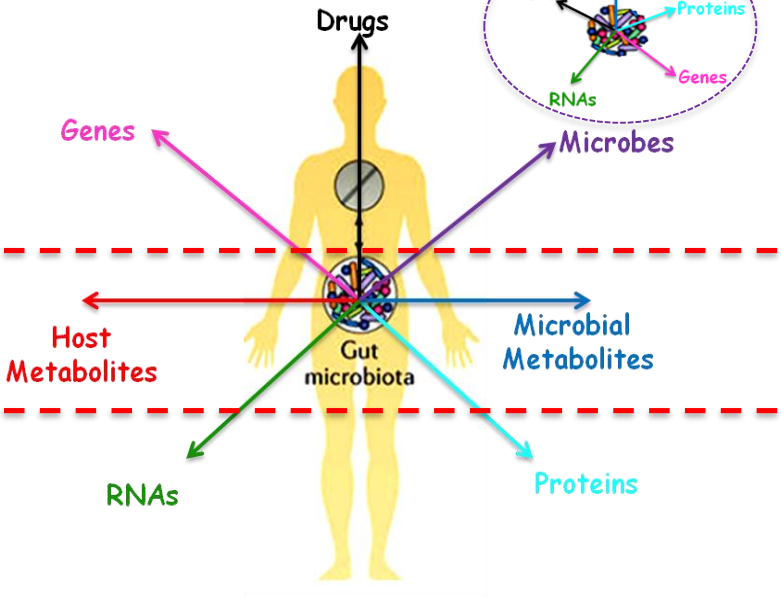
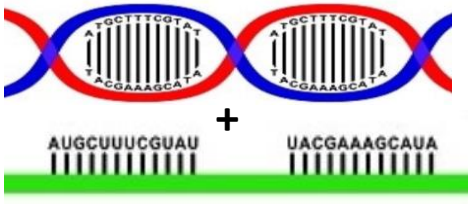
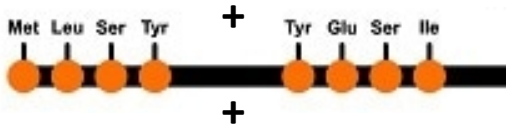
A BIOMARKER-ASSISTED SYSTEMS BIOLOGY APPROACH TO METABOLOMICS

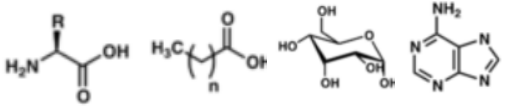


Metformin





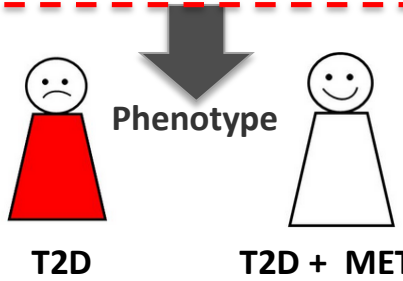




Integrity
Genomic Biomarkers

Integrity
Proteomic Biomarkers

Integrity
Biochemical Biomarkers



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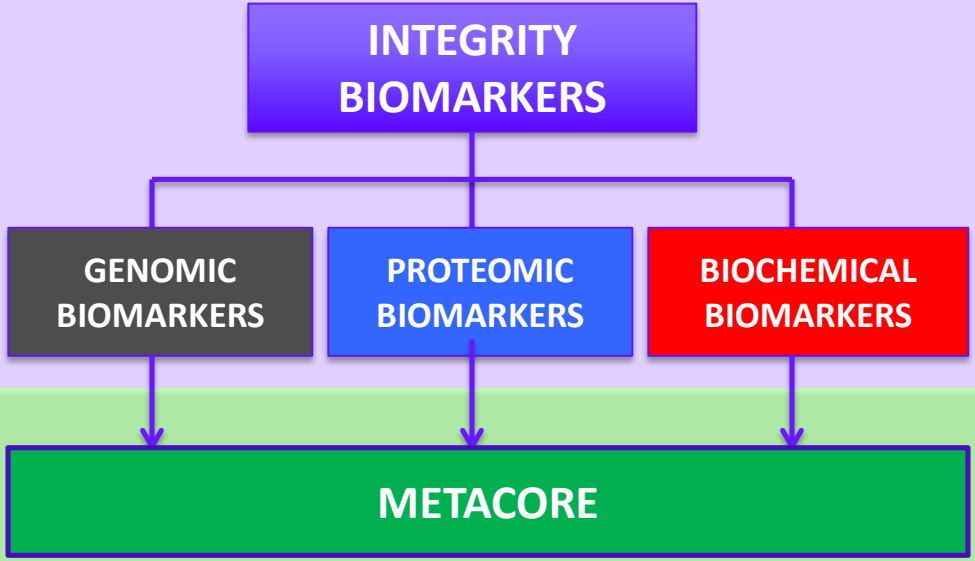
WORKFLOW



Derive

"genomic"
"proteomic"
"metabolomic"
signatures representative of biology/pharmacology

- Identify enriched pathways
- Identify enriched metabolic processes
- Understand the relationships between metabolites, genes/proteins and drugs.

Analyze

the underlying biology and metabolic processes on a "systems" level.

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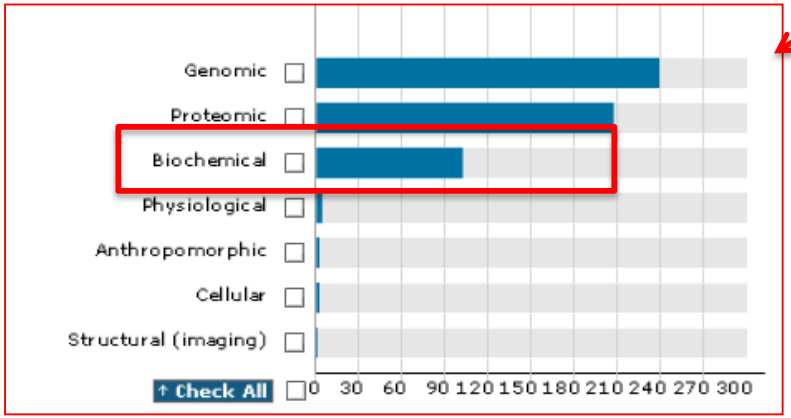
BIOMARKERS TO MONITOR /PREDICT TREATMENT EFFICACY OF METFORMIN

Biomarkers

Advanced Search | Session History | Clear Form | Start

Biomarker

Product Name	Metformin	Index	AND
Condition (Indication)	"Diabetes"	Index	AND
Role	"Monitoring Treatment Efficacy" or "Predicting Treatment Efficacy"	Index	AND



Filter by Statistics

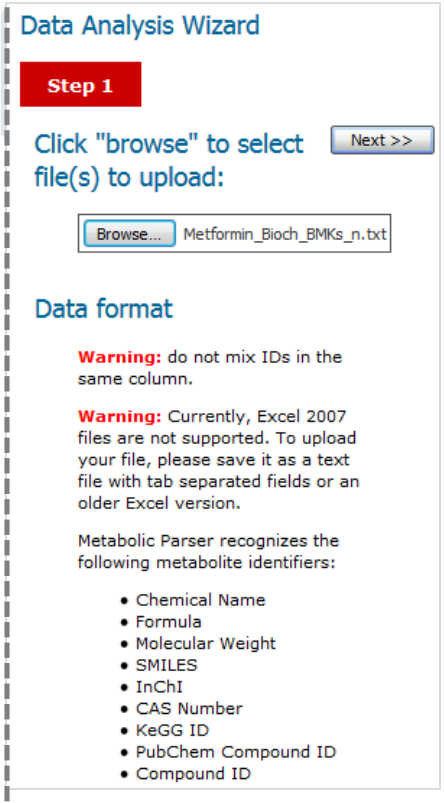
BIOMARKER
- Biomarker Type
- Highest Validity
- Combination Type
- Component Biomarker
- Component Of
- Biological Process
- Product Modifier
- Mechanism Modifier
- Method Papers (Y/N)

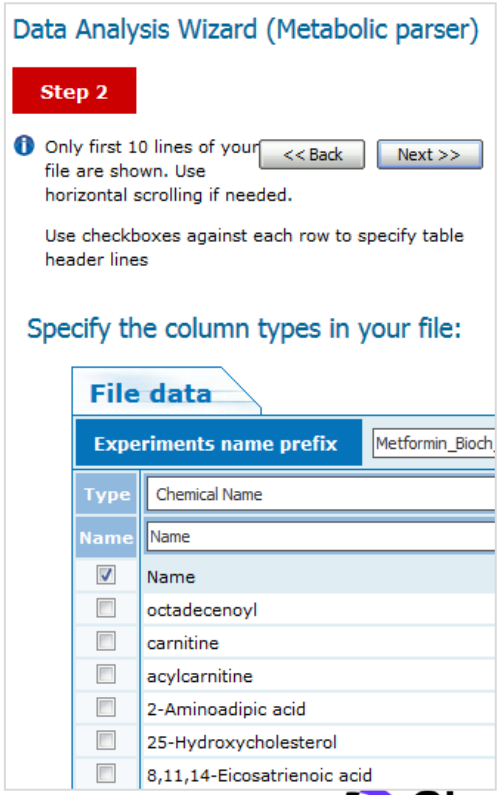
BIOMARKER USE
- Indication Type
  - Major Condition
  - Condition
  - Safety/Tox
  - Experimental Pathology
- Population
- Role
- Technique
- Substrate
- Genetic Variation Type
- Parameter
- Validity
- Scientific Authority
- Source Evidence

BIOMARKER KIT
- Kit Name
- Organization
- Status
- Country / Area
- Regulatory Authority

UPLOAD METABOLIC DATA

- Upload Experiments with Gene or Protein IDs
- Upload Metabolites
- Upload Interactions
- Upload Structures
- Upload Genomic Variants





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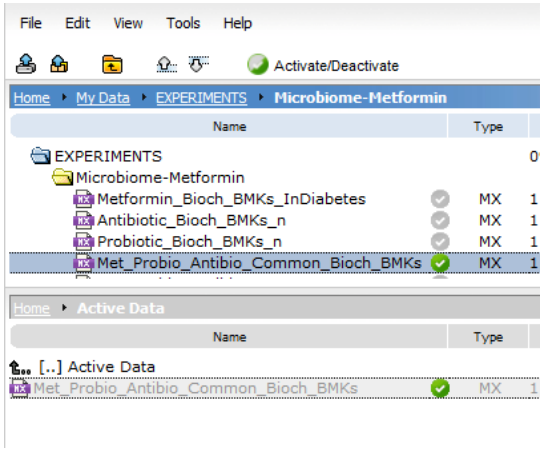
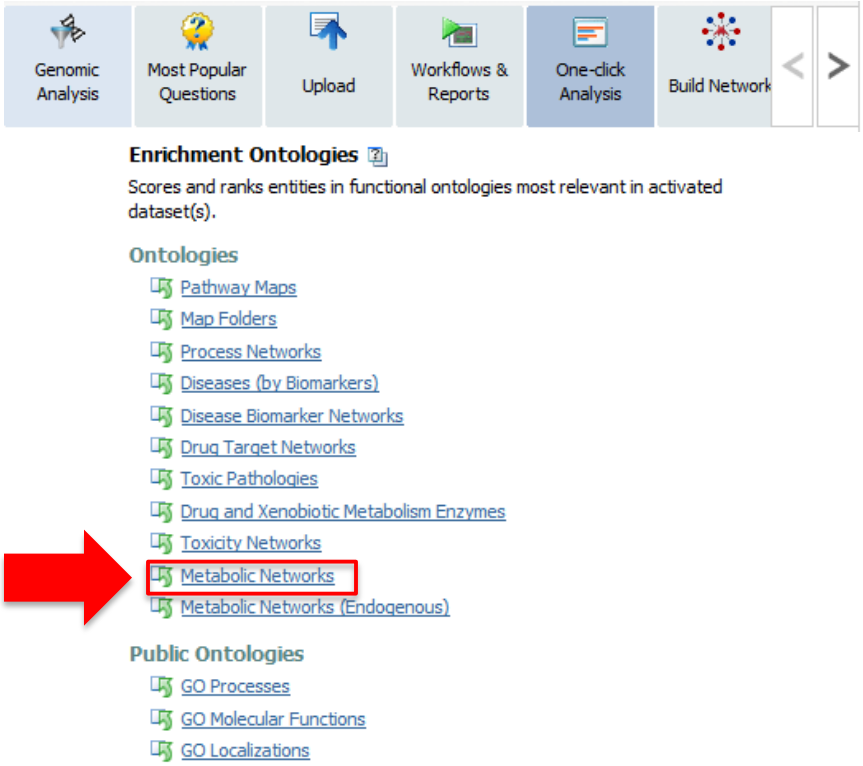
ENRICHMENT ANALYSIS IN METABOLIC NETWORKS





To explore linked series of chemical reactions

The reactants, products, and intermediates of an enzymatic reaction are known as metabolites, which are modified by a sequence of chemical reactions catalyzed by enzymes.

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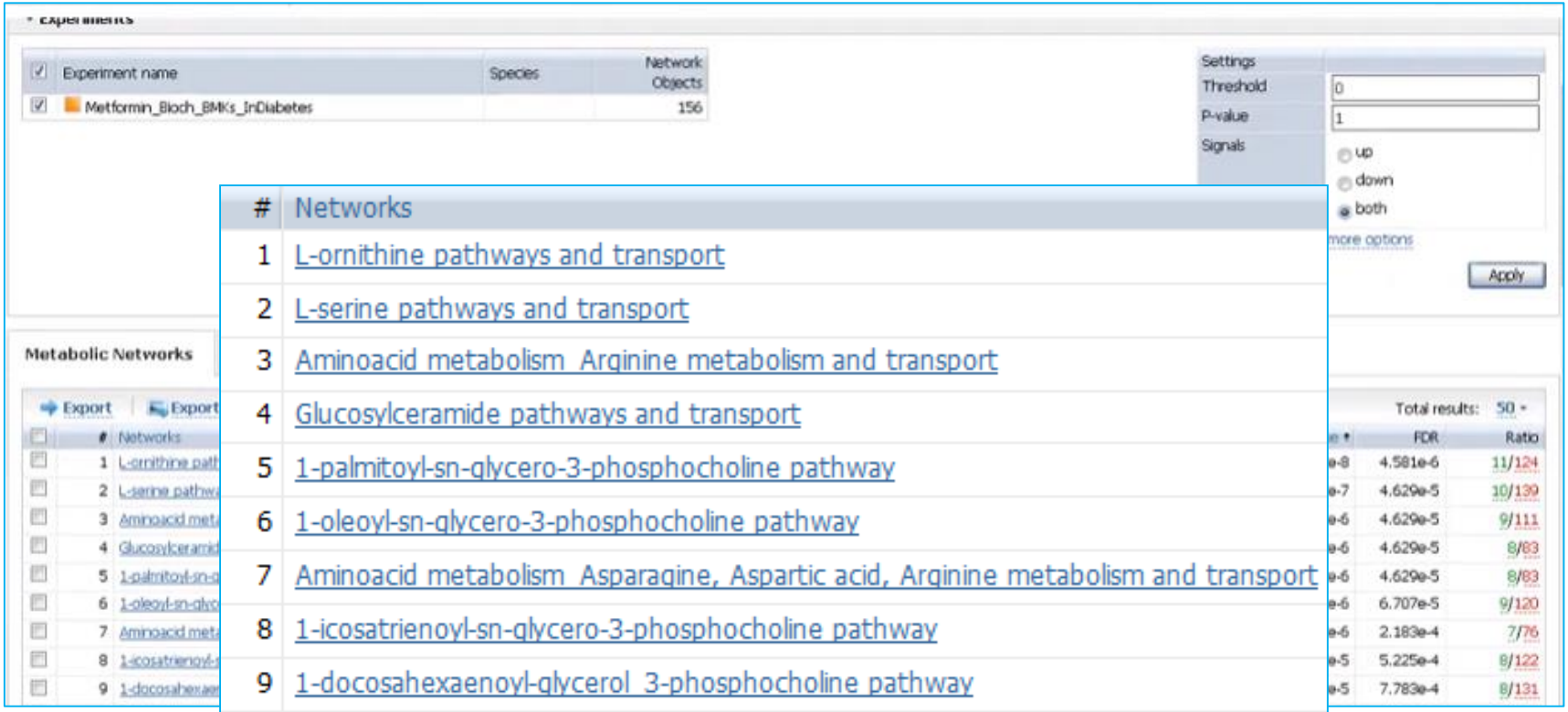
TOP ENRICHED METABOLIC NETWORKS



#	Networks
1	L-ornithine pathways and transport
2	L-serine pathways and transport
3	Aminoacid metabolism_Arginine metabolism and transport
4	Glucosylceramide pathways and transport
5	1-palmitoyl-sn-glycero-3-phosphocholine pathway
6	1-oleoyl-sn-glycero-3-phosphocholine pathway
7	Aminoacid metabolism_Asparagine, Aspartic acid, Arginine metabolism and transport
8	1-icosatrienoyl-sn-glycero-3-phosphocholine pathway
9	1-docosahexaenoyl-glycerol_3-phosphocholine pathway
10	Glutamic acid pathways and transport

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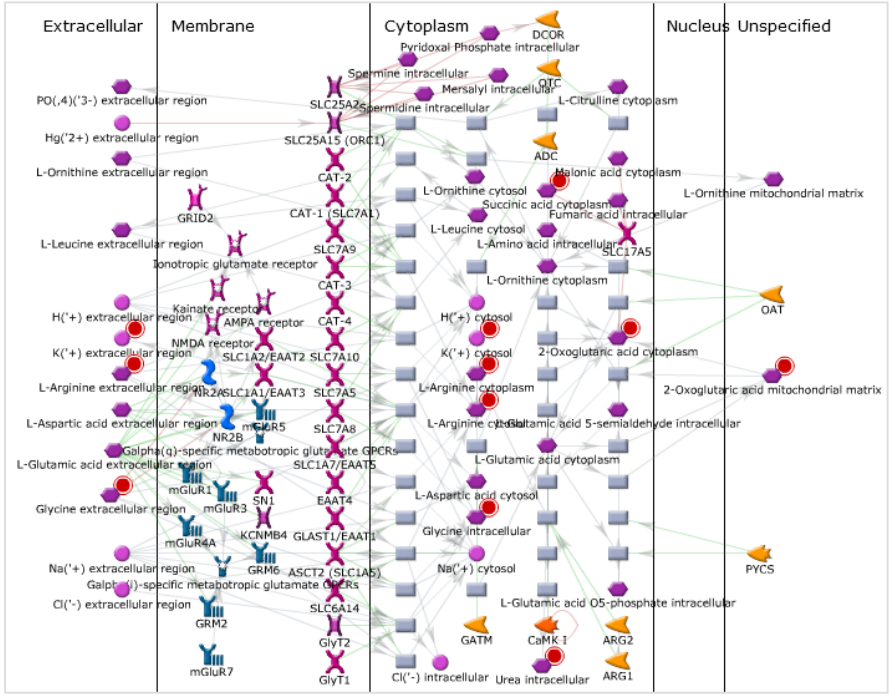
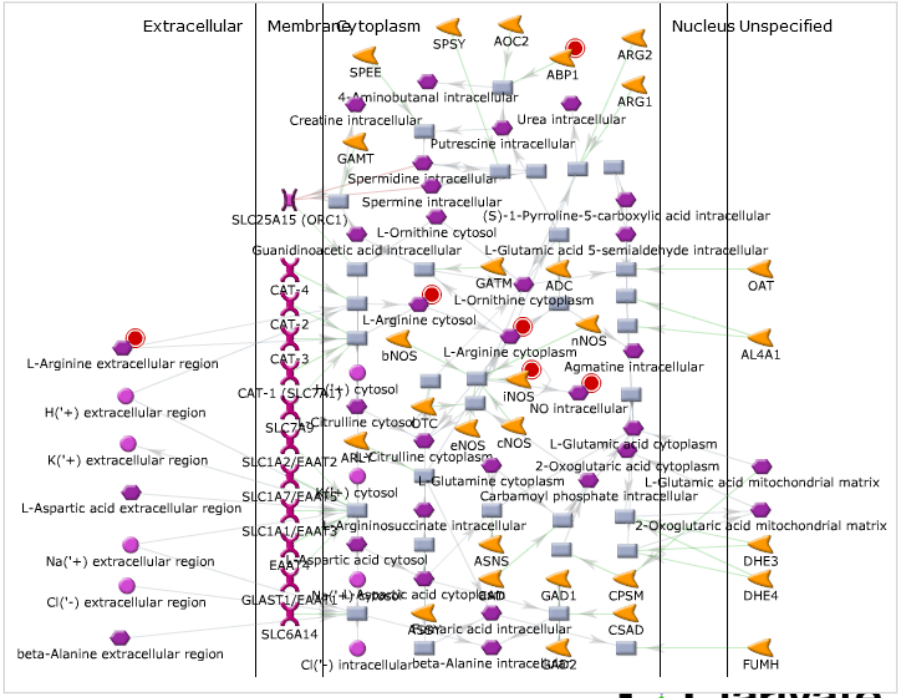
ENRICHED METABOLIC NETWORKS: AMINOACID METABOLISM

L-ornithine pathways and transport



Arginine metabolism and transport



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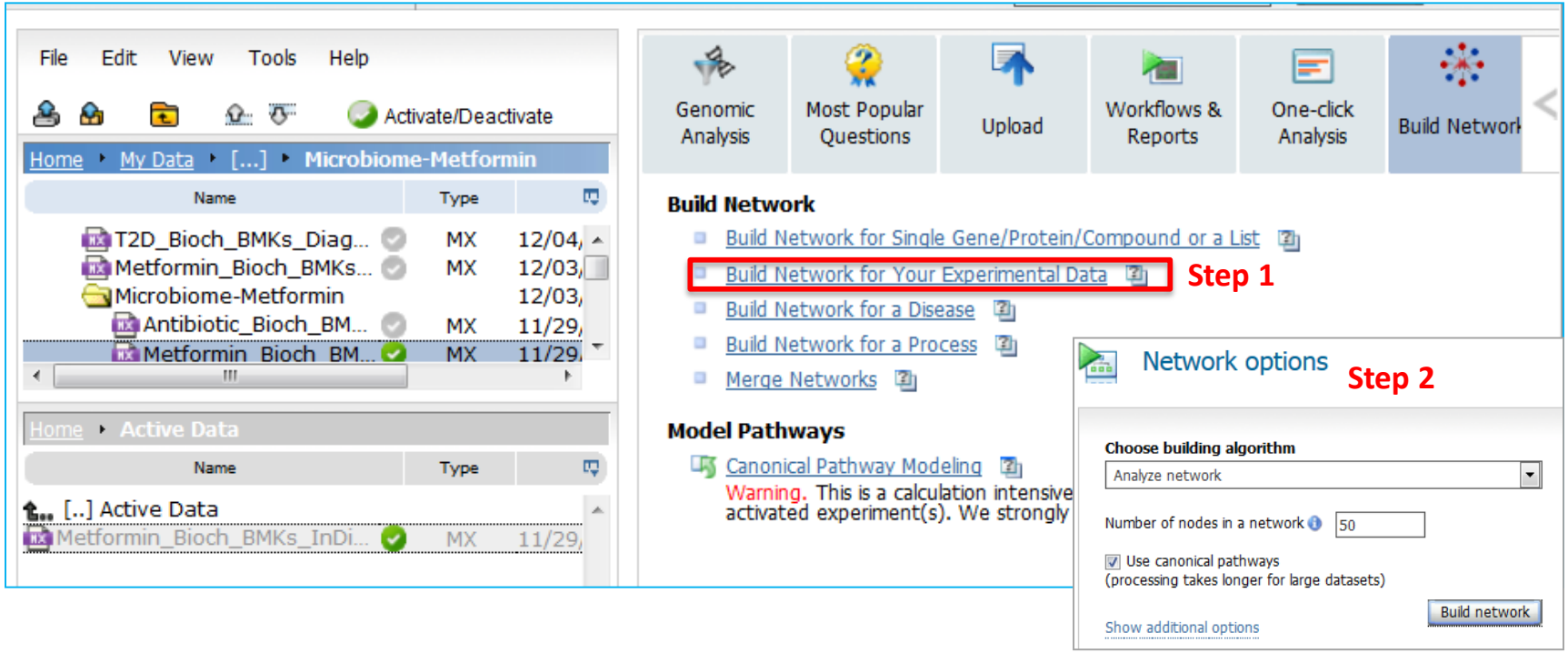
BUILD NETWORK FOR YOUR BIOMARKERS/EXPERIMENTAL DATA



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ANALYZE RESULTS

Networks in List with 30 networks List

Save list | Get report | Export | Delete | Merge | P-value for networks | Show excluded objects | Rebuild

#	Name	GO processes	# Nodes Total	# Nodes Seed	Pathways	p-Value	zScore	gScore	Edit
1	NO(.2)('-) intracellular, L-Tryptophan intracellular, L-Tyrosine intracellular, Tetrahydrobiopterin intracellular, iNOS	response to oxygen-containing compound (93.3%; 3.759e-24), response to hormone (80.0%; 3.300e-23), response to endogenous stimulus (83.3%; 1.234e-20), response to organonitrogen compound (76.7%; 6.007e-20), response to organic cyclic compound (76.7%; 1.019e-19)	50	9	0	1.15e-19	46.78	46.78	
2	Arachidonic acid extracellular region, Eicosapentaenoic acid intracellular, D-Glucose intracellular, 25-Hydroxycholesterol intracellular, Ca('2+) cytosol	response to organic cyclic compound (77.1%; 4.631e-23), cellular response to endogenous stimulus (77.1%; 5.358e-23), response to lipid (74.3%; 2.280e-22), response to endogenous stimulus (80.0%; 4.869e-22), cellular response to organic substance (88.6%; 9.240e-22)	50	8	0	4.29e-17	41.12	41.12	
3	Cholesterol cytoplasm, Triacylglycerols intracellular, Cholesterol Golgi apparatus, Cholesterol lysosome, Cholesterol endoplasmic reticulum		50	5	0	3.45e-14	59.54	59.54	
4	Cholesterol mitochondrion, Cholesterol		50	5	0	1.26e-13	53.84	53.84	

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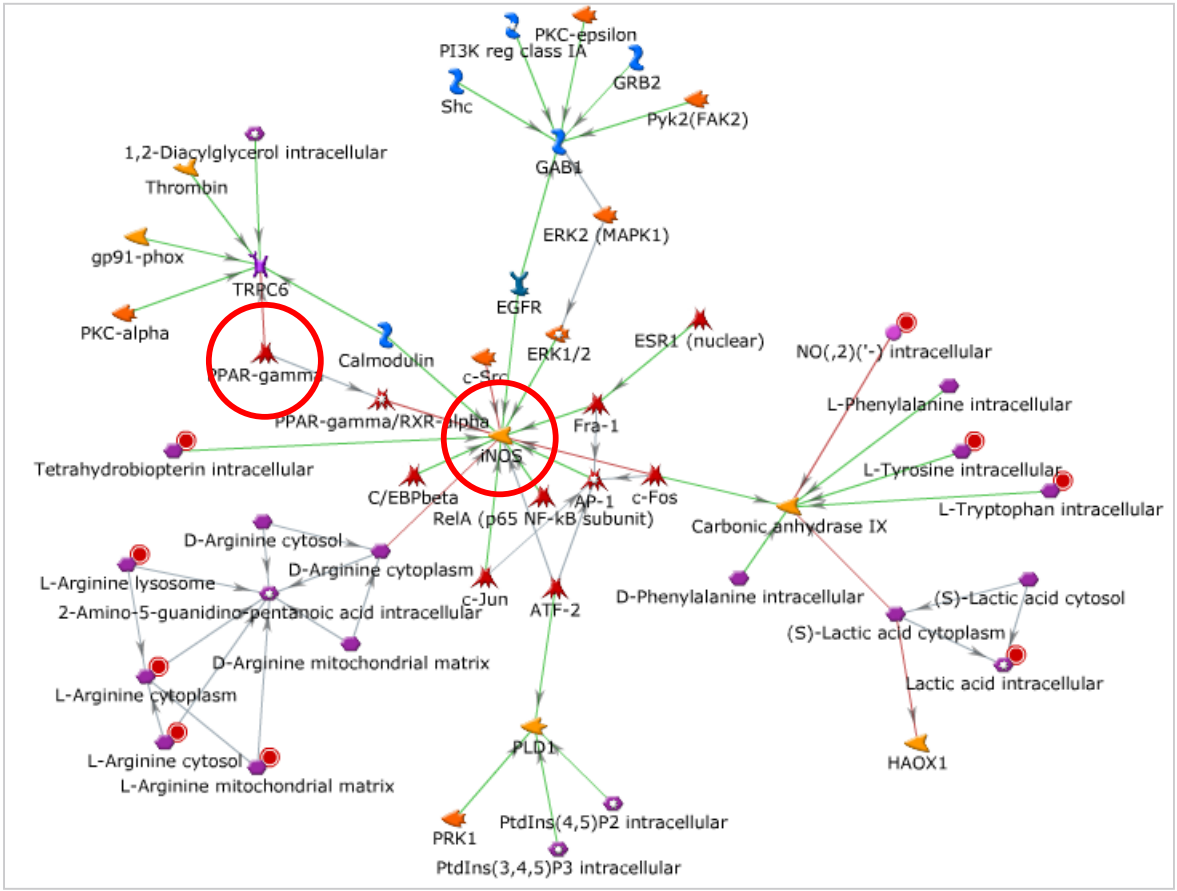
ANALYZING GENERATED NETWORKS



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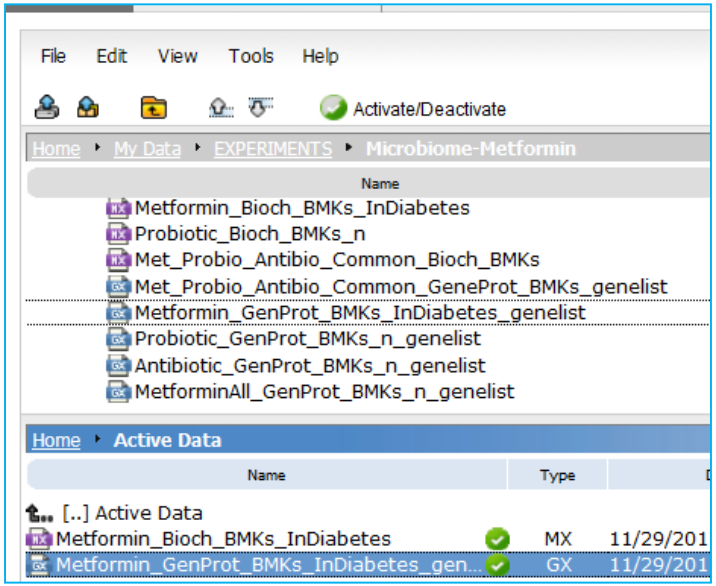
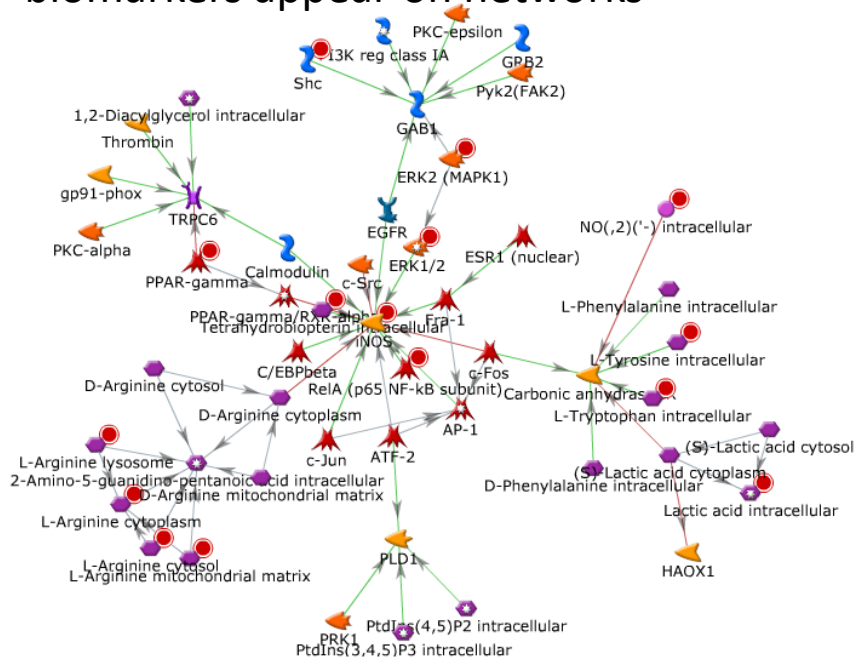
ACTIVATE GENOMICS /PROTEOMICS BIOMARKER DATA



Look which genomic and proteomic biomarkers appear on networks



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FINDINGS

Wu *et al*

Type 2 Diabetes:

- Butyrate producing bacterial Taxa ↓
- Butyrate is the major energy source for microbiome and colonocytes.
- Colonocytes depend on butyrate for energy production.

Metformin Rx:

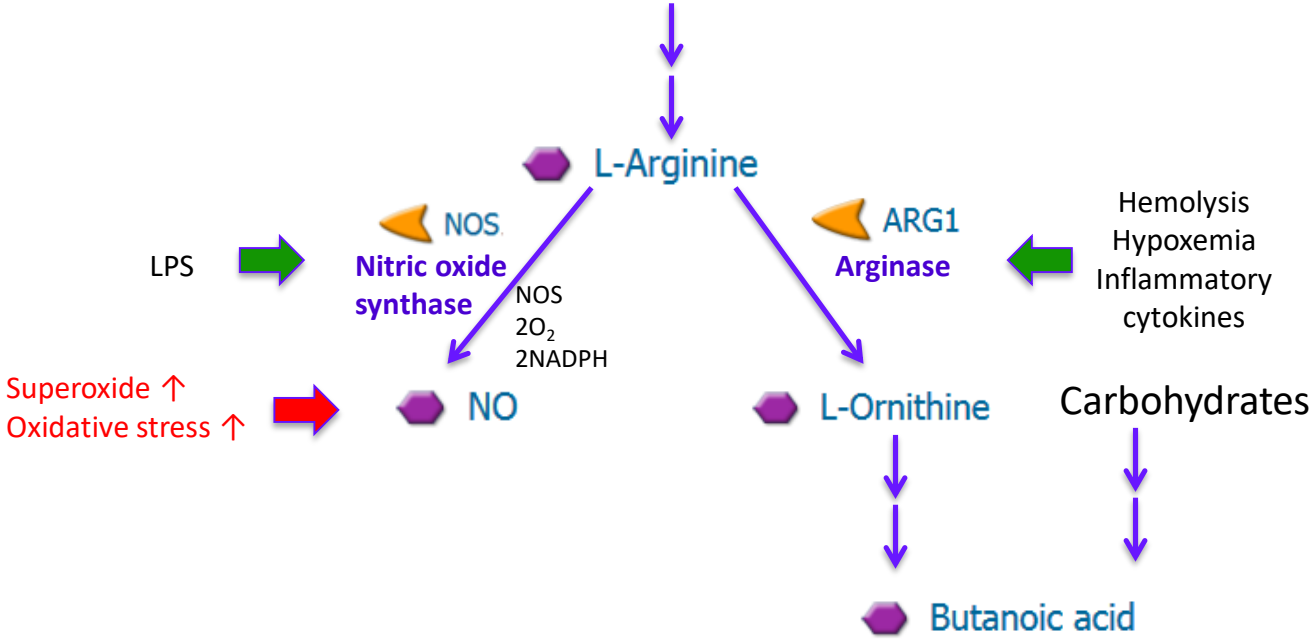
- Gram-negative ↑ , LPS ↑
- Gram-positive ↓

Study Findings

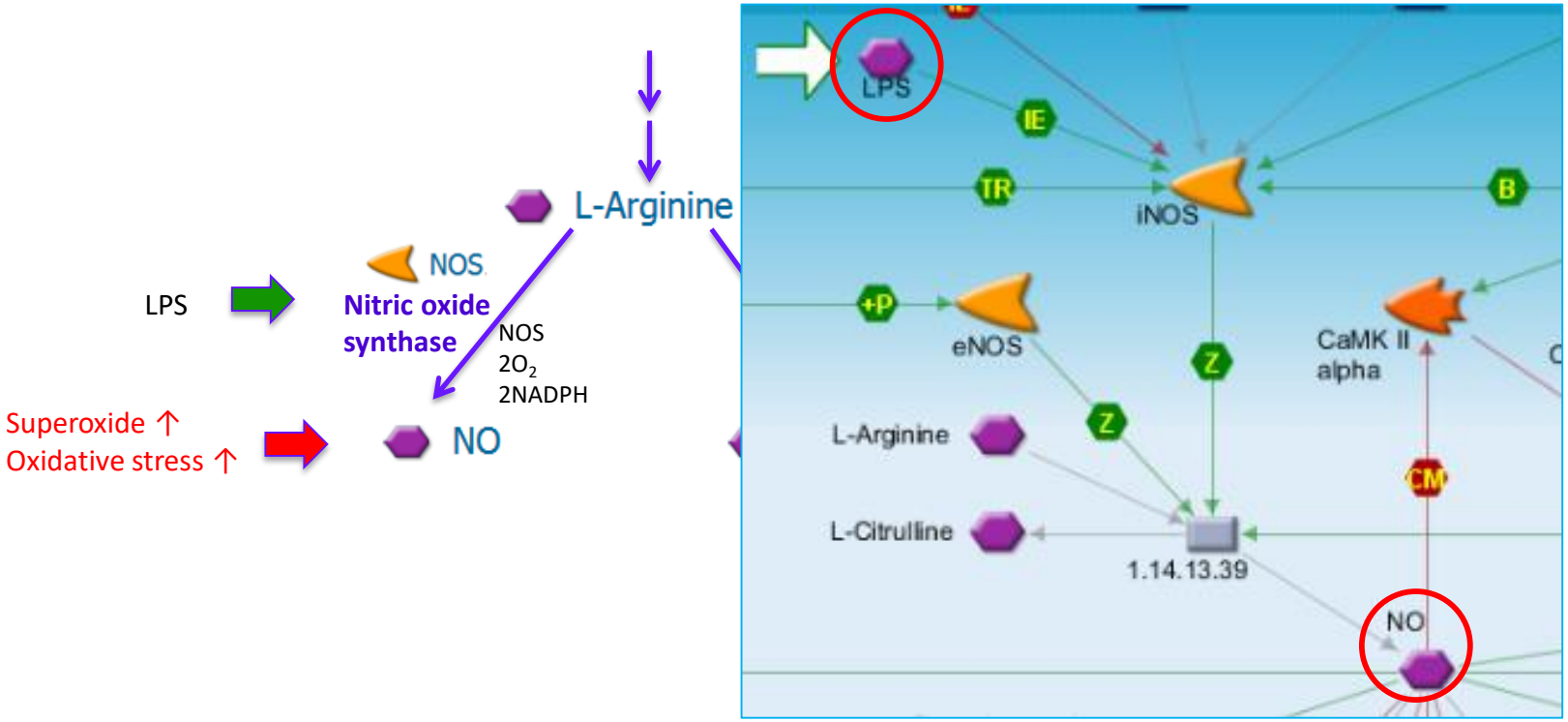
Prioritized metabolic processes of interest:

- Arginine and ornithine metabolism and transport.
- NO metabolism
- Fatty acid metabolism
- Amino acid metabolism

HIGHLIGHTED PATHWAYS, ENZYMES, METABOLITES AND REACTIONS



HIGHLIGHTED PATHWAYS, ENZYMES, METABOLITES AND REACTIONS



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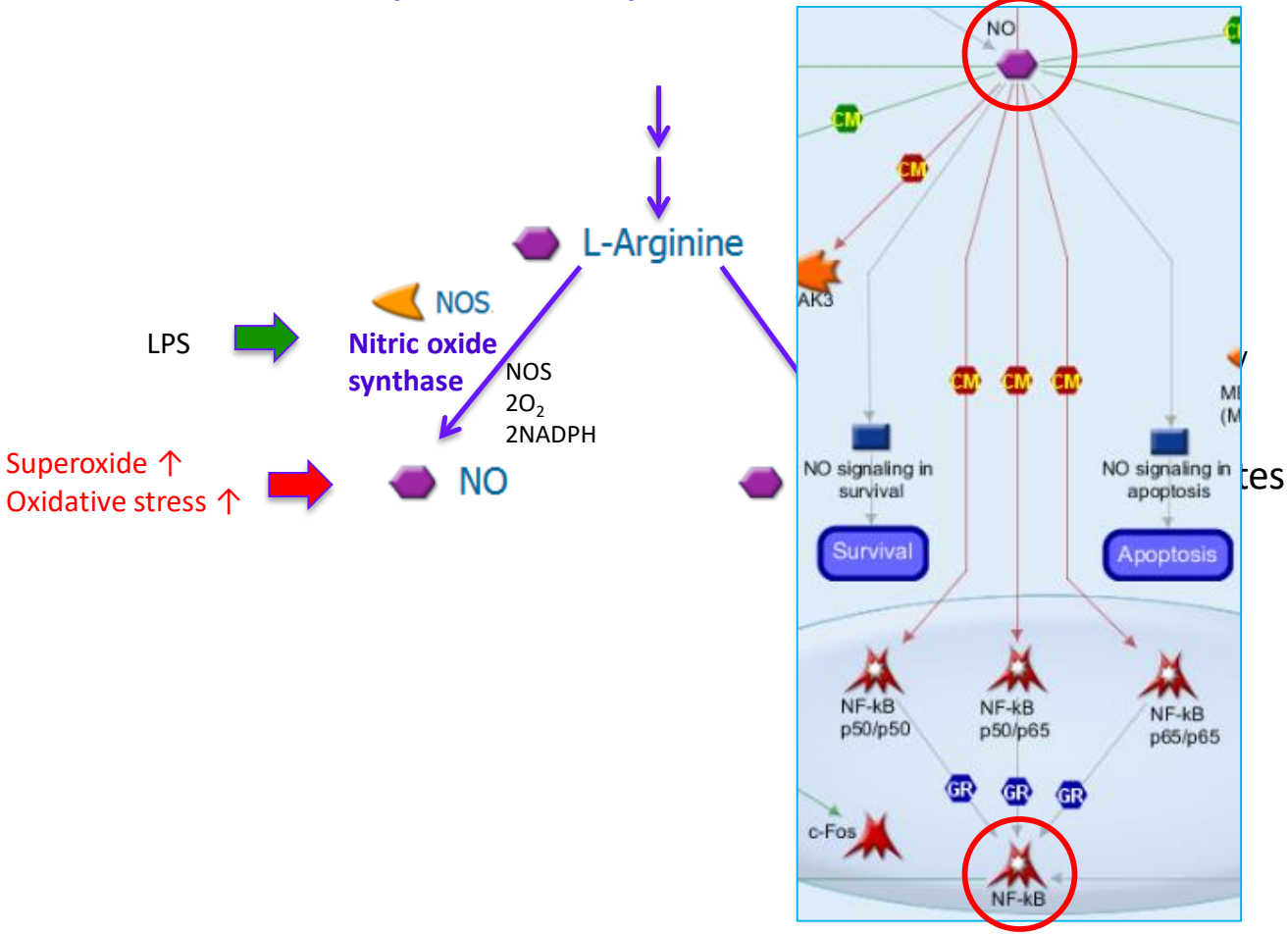
HIGHLIGHTED PATHWAYS, ENZYMES, METABOLITES AND REACTIONS



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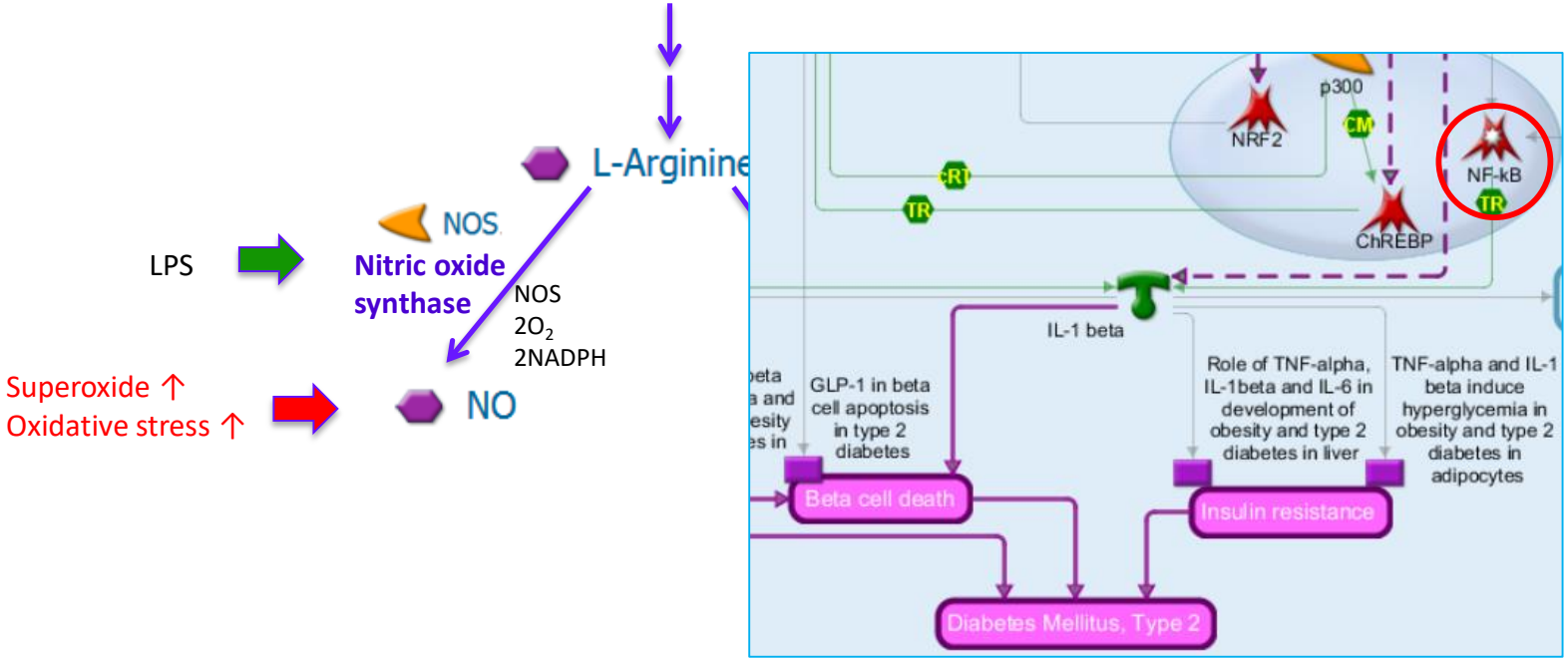
HIGHLIGHTED PATHWAYS, ENZYMES, METABOLITES AND REACTIONS



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CONCLUSIONS

Network Analysis Using A Biomarkers Approach

- Arginine and ornithine metabolism and transport
- NO metabolism
- Fatty acid metabolism
- Amino acid metabolism

Testable hypothesis: Metformin maybe normalized NO and butyrate production through affect bacterial colonization in the gut.

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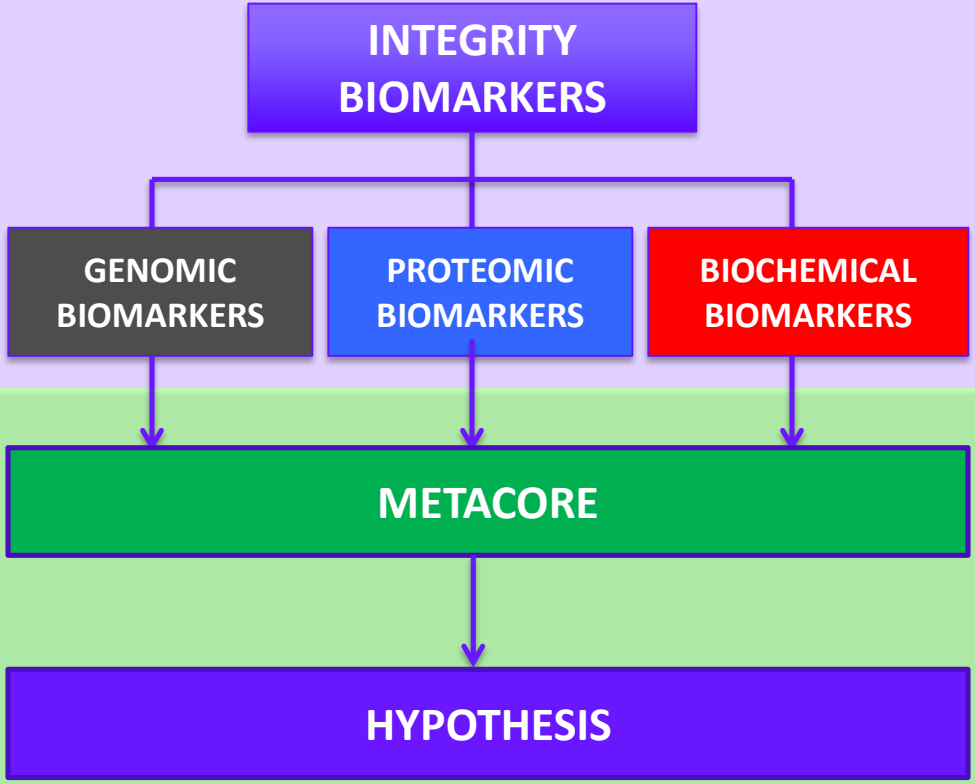
CONCLUTIONS



Derive

"genomic"
"proteomic"
"metabolomic"
signatures representative of biology/pharmacology

Analyze

the underlying biology and metabolic processes on a "systems" level.

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Analytics