



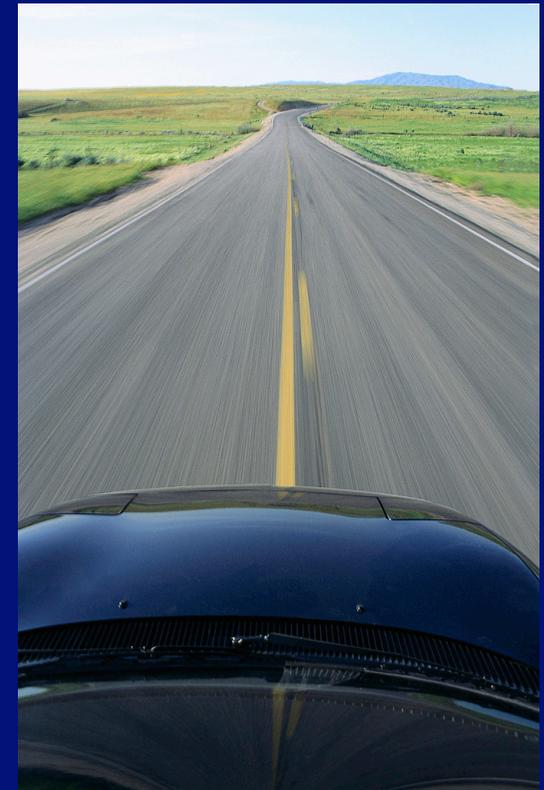
# **Metabolomics: quantifying the phenotype**



**Craig Wheelock, March 5th, 2010**  
**<http://metabolomics.se/>**

# Outline

- **Metabolomics – what is it & why do we care??**
  - **Overview of mass spectrometry**
- **Pathway mapping with the KEGG database**
  - **Tutorial on KEGG functionality**
- **Systems Biology and the Omics Cascade**
  - **How do we tie together all of these data????**



# Metabolomics Promises Quantitative Phenotyping

What can happen

**GENOME**

**Bioinformatics**

What appears to be happening

**TRANSCRIPTOME**

What makes it happen

**PROTEOME**

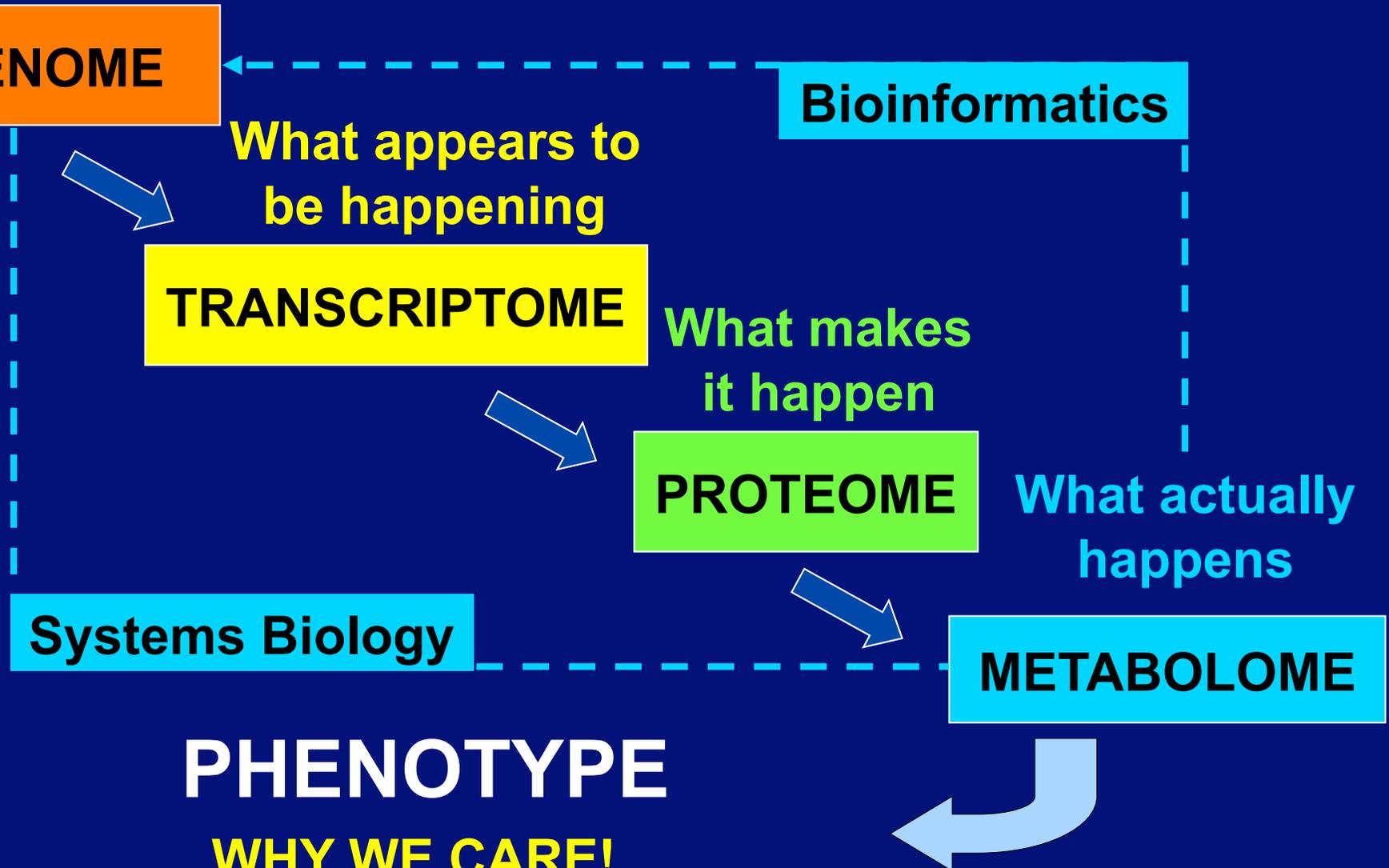
What actually happens

**Systems Biology**

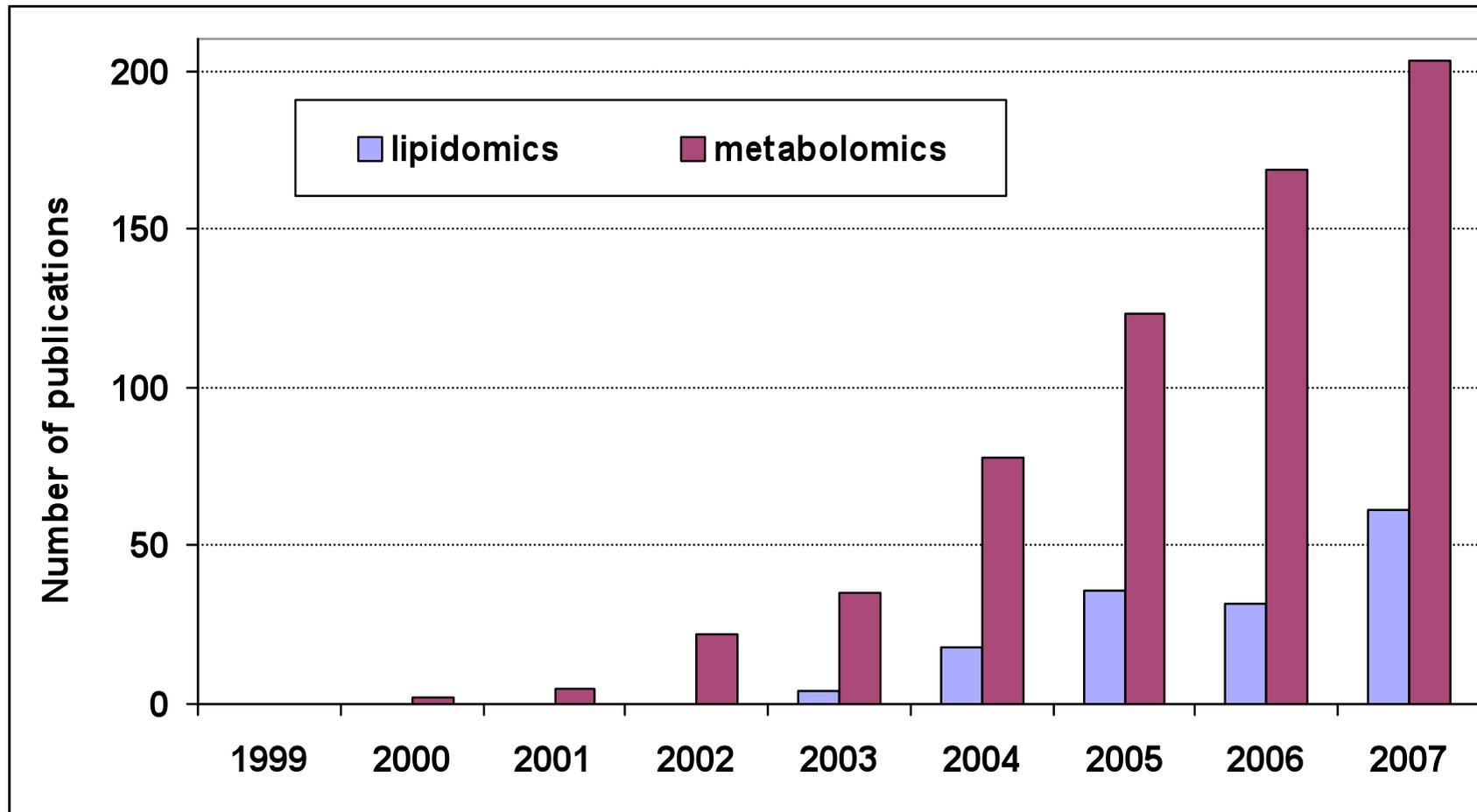
**METABOLOME**

**PHENOTYPE**

**WHY WE CARE!**



# Metabolomics publications in Pubmed



↑  
**First**  
**"metabolomics"**  
**publication**

↑  
**First**  
**"lipidomics"**  
**publication**

# History of metabolomics

## **Quantitative Analysis of Urine Vapor and Breath by Gas-Liquid Partition Chromatography**

*(orthomolecular medicine/vitamins/controlled diet)*

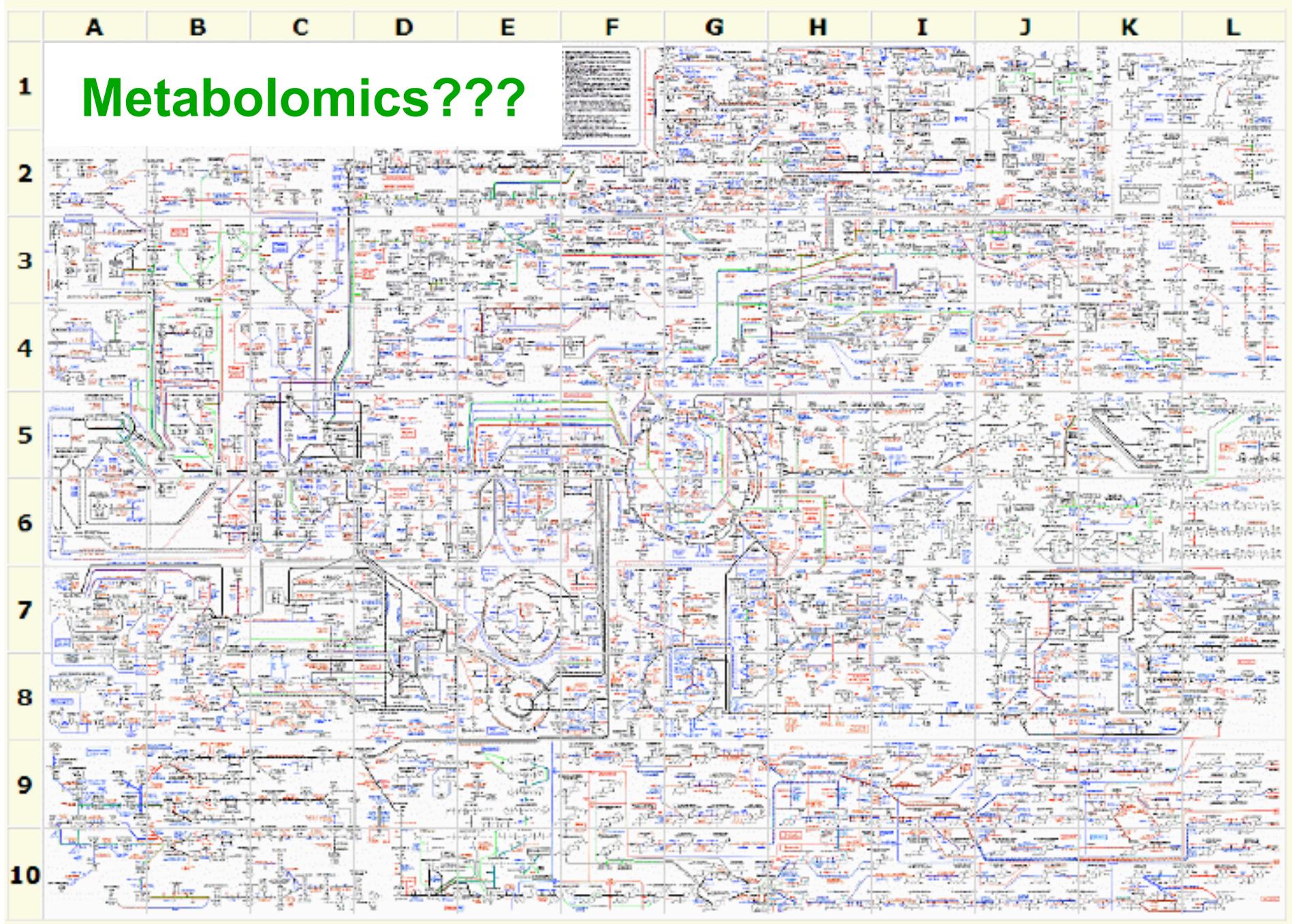
LINUS PAULING\*, ARTHUR B. ROBINSON\*, ROY TERANISHI†, AND PAUL CARY\*

\* Department of Chemistry, Stanford University, Stanford, California 94305; and † Western Regional Laboratory, U.S. Department of Agriculture

*Contributed by Linus Pauling, July 29, 1971*

- **Metabolomics “developed” by Pauling in 1970**
- **the term metabolomics first used in 1998**
  - **Oliver SG et al (1998). Trends Biotechnol 16:373**
- **Metabolomics Society founded 2004**
- **January 23rd, 2007 first draft of the human metabolome “completed”**

# Metabolomics???



# Approaches to Investigating the Metabolome

- **Metabolic Fingerprinting**

- **Pattern recognition** to classify samples by shifts in “global” metabolite composition.

---

- **Metabolic Targeting**

- **Quantification** of a small number of known compounds.

- **Metabolic Profiling**

- **Quantification** of a group of related compounds or metabolites within a specific metabolic pathway.

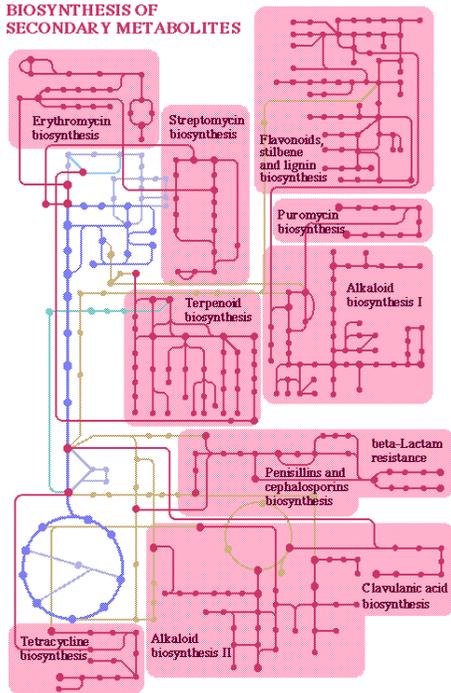


- **Metabolomics**

- **Quantification** of “all” metabolites at a defined time under specific environmental conditions.

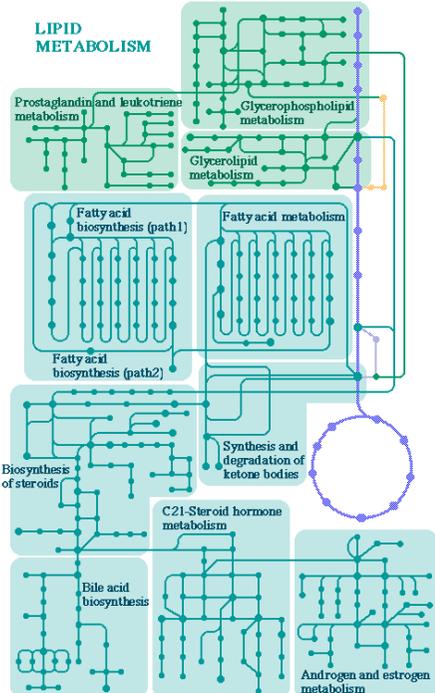


**BIOSYNTHESIS OF SECONDARY METABOLITES**



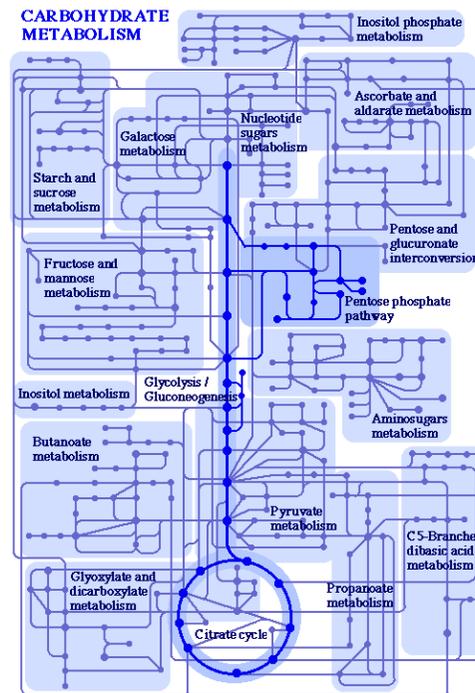
195 6/26/02

**LIPID METABOLISM**



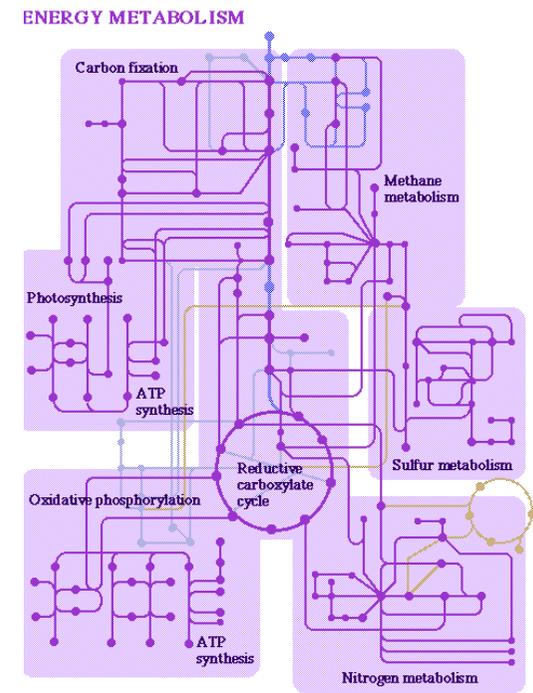
01130 2/28/05

**CARBOHYDRATE METABOLISM**



10 8/10

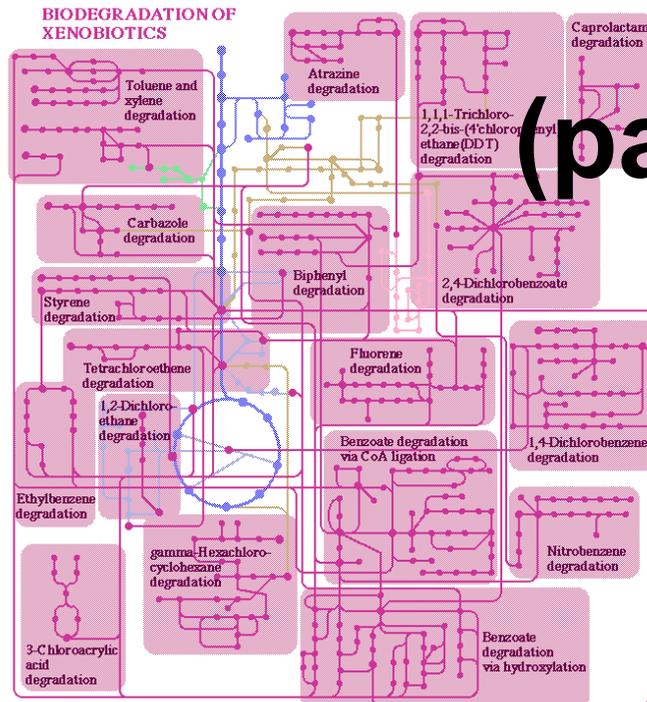
**ENERGY METABOLISM**



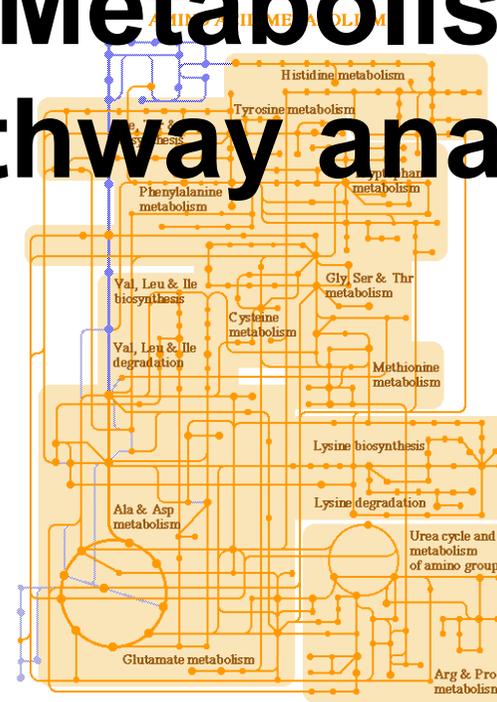
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# Metabolism (pathway analysis)

**BIODEGRADATION OF XENOBIOTICS**

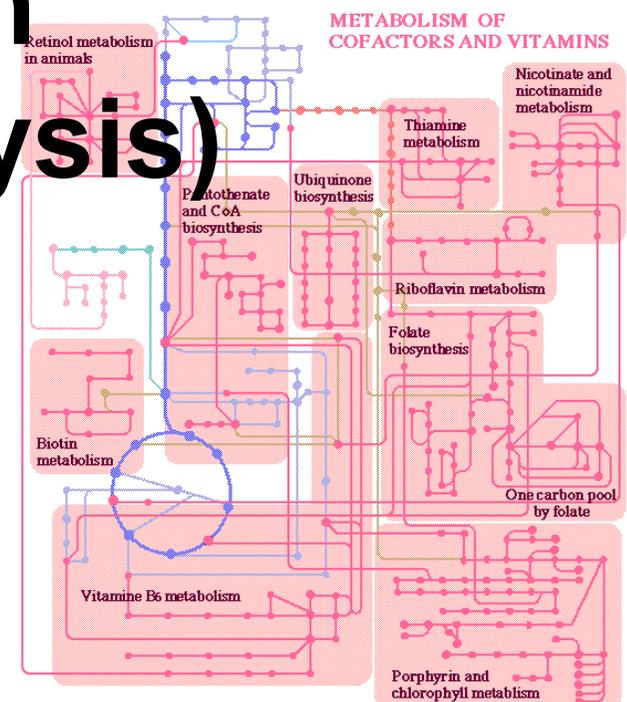


01196 6/26/02



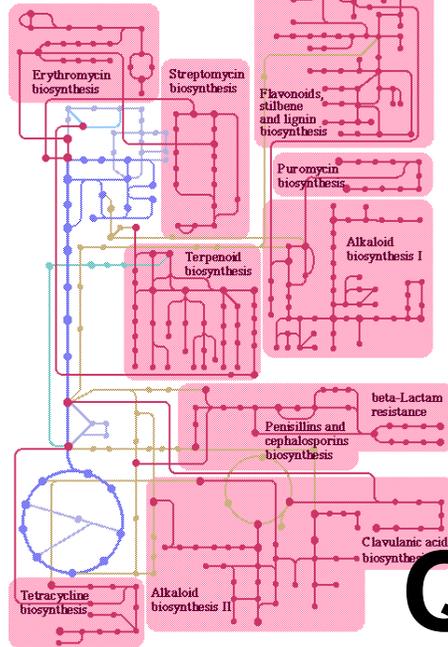
01100 3/3/05

**METABOLISM OF COFACTORS AND VITAMINS**

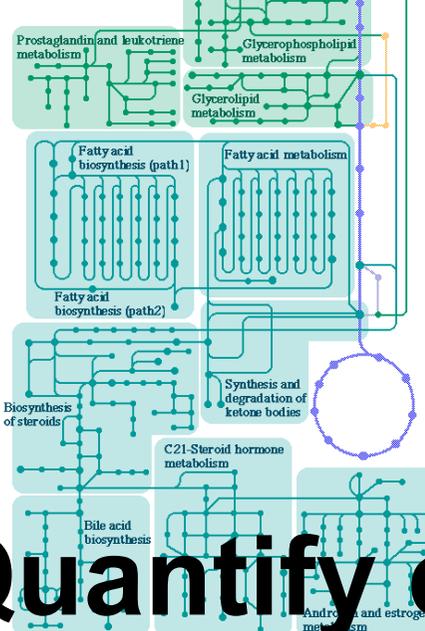


01140 5/1/00

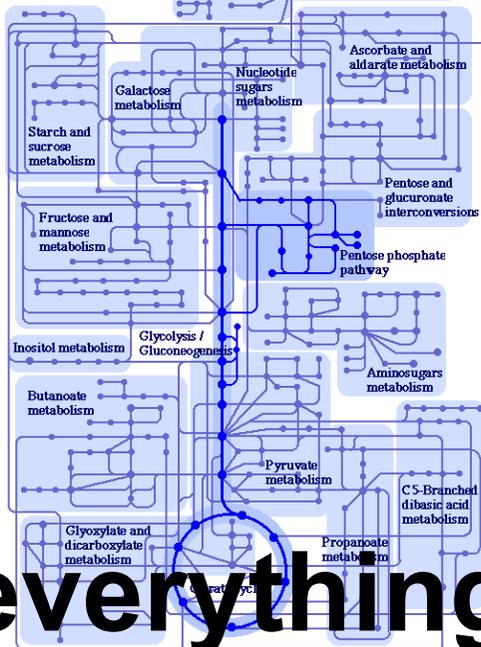
**BIOSYNTHESIS OF SECONDARY METABOLITES**



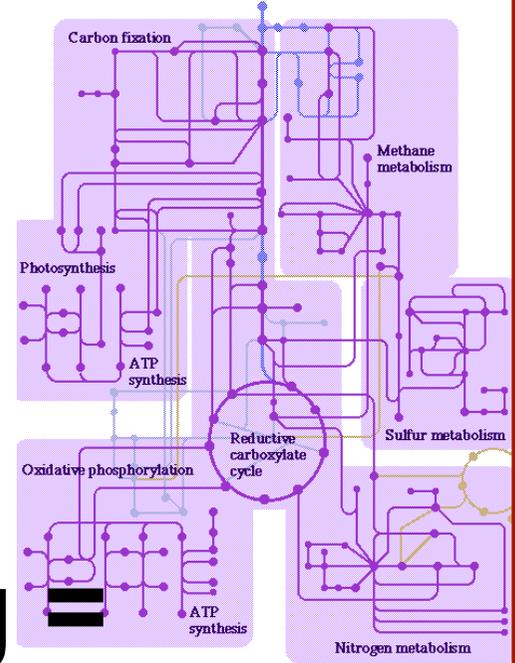
**LIPID METABOLISM**



**CARBOHYDRATE METABOLISM**



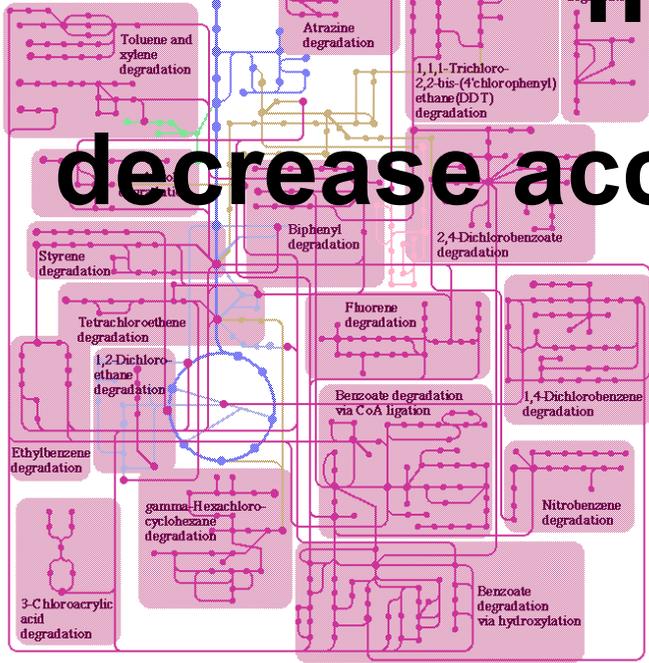
**ENERGY METABOLISM**



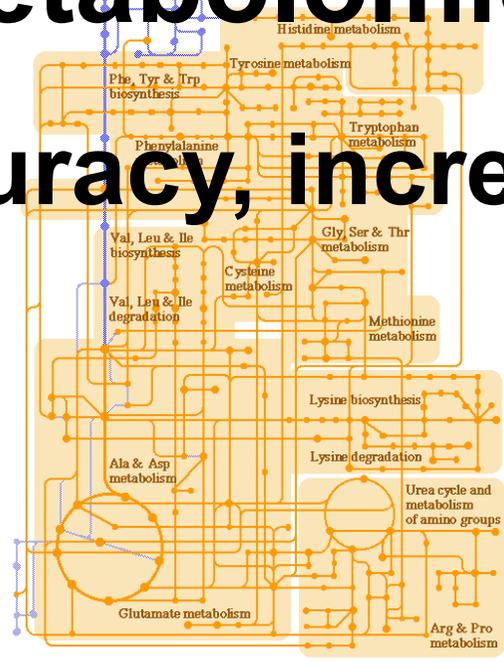
**Quantify everything = metabolomics**

**decrease accuracy, increase coverage**

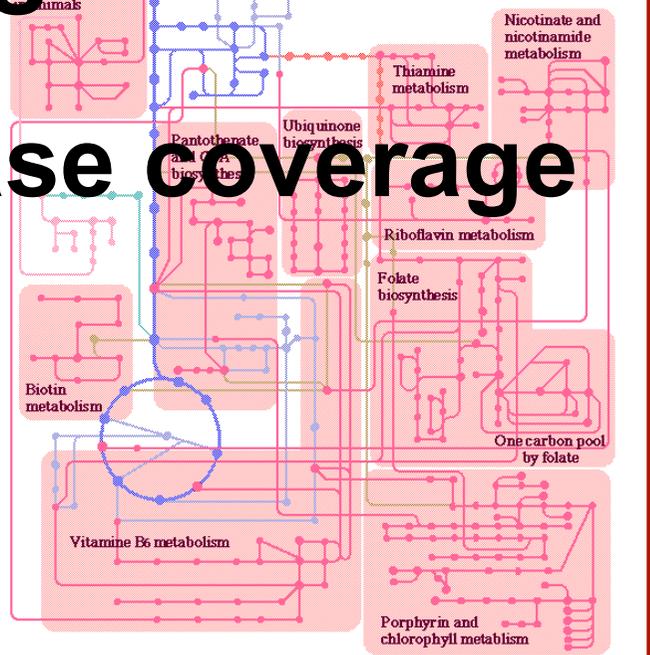
**BIODEGRADATION OF XENOBIOTICS**



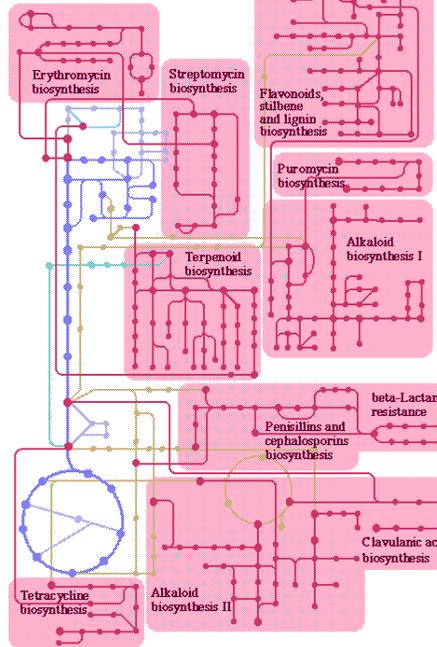
**AMINO ACID METABOLISM**



**METABOLISM OF COFACTORS AND VITAMINS**

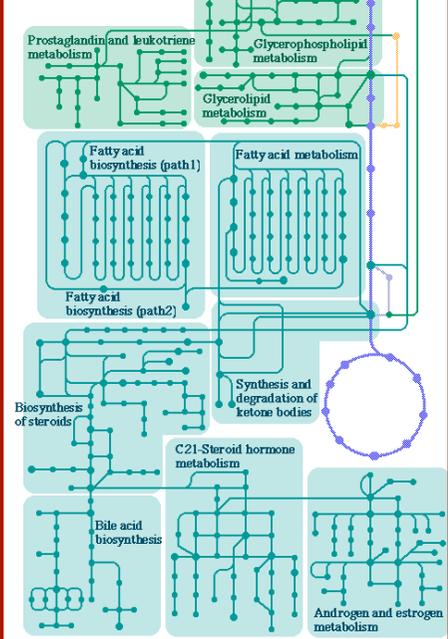


**BIOSYNTHESIS OF SECONDARY METABOLITES**



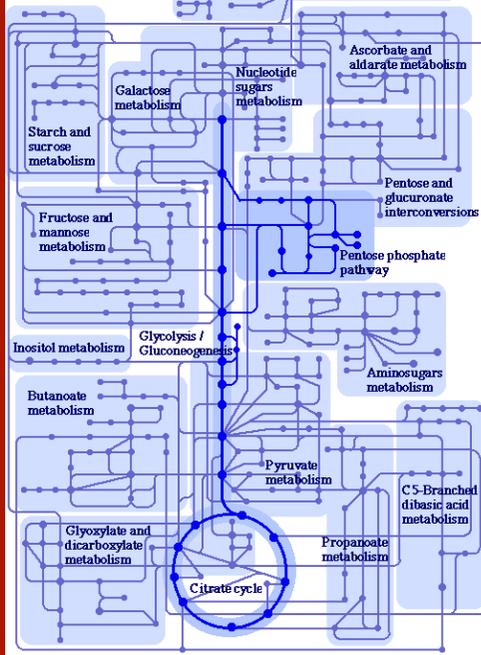
195 6/26/02

**LIPID METABOLISM**

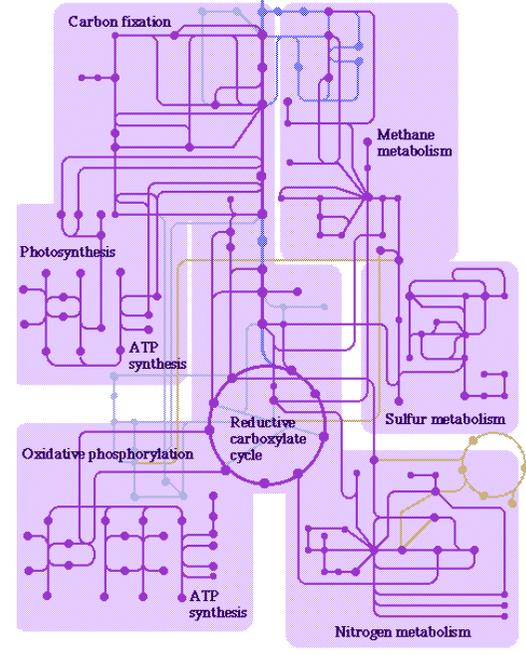


10 8/10/04

**CARBOHYDRATE METABOLISM**

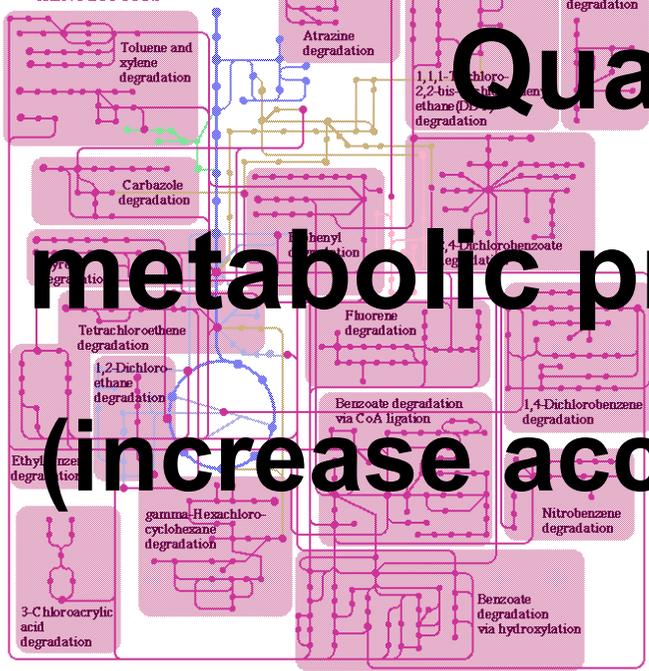


**ENERGY METABOLISM**



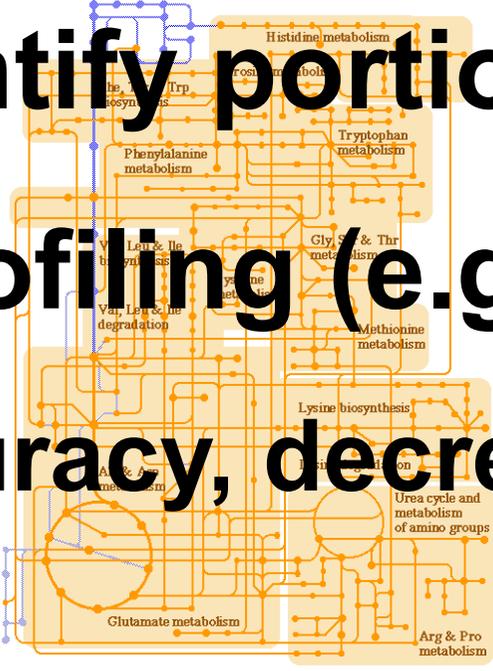
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**BIODEGRADATION OF XENOBIOTICS**



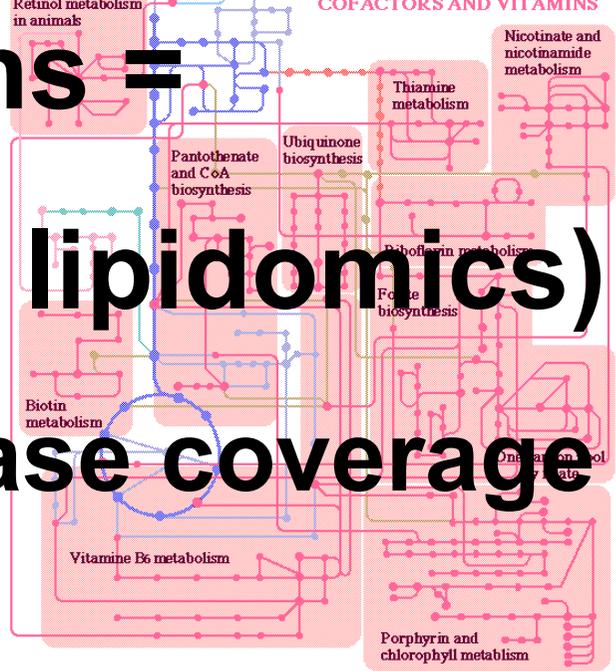
01196 6/26/02

**AMINO ACID METABOLISM**



01100 3/3/05

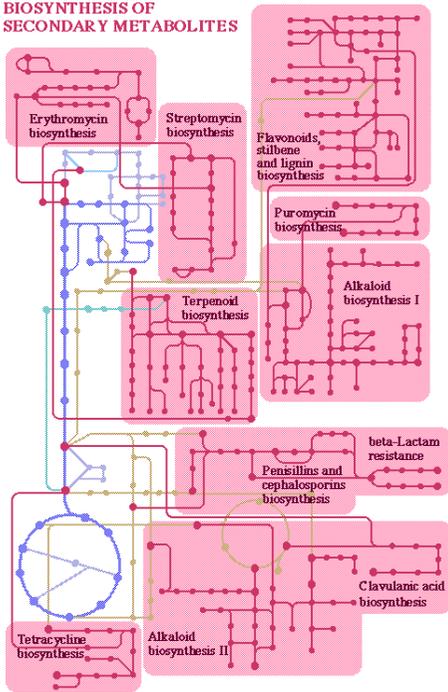
**METABOLISM OF COFACTORS AND VITAMINS**



01100 5/1/00

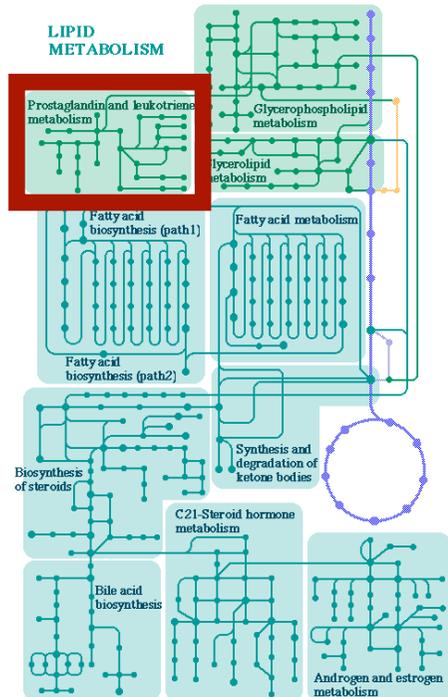
**Quantify portions = metabolic profiling (e.g. lipidomics) (increase accuracy, decrease coverage)**

**BIOSYNTHESIS OF SECONDARY METABOLITES**



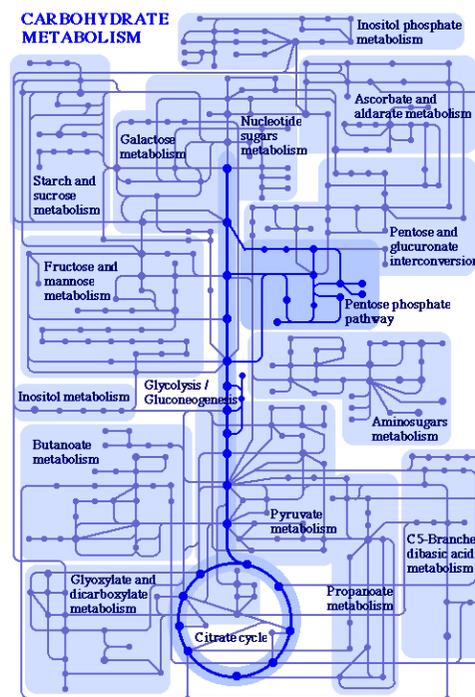
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**LIPID METABOLISM**



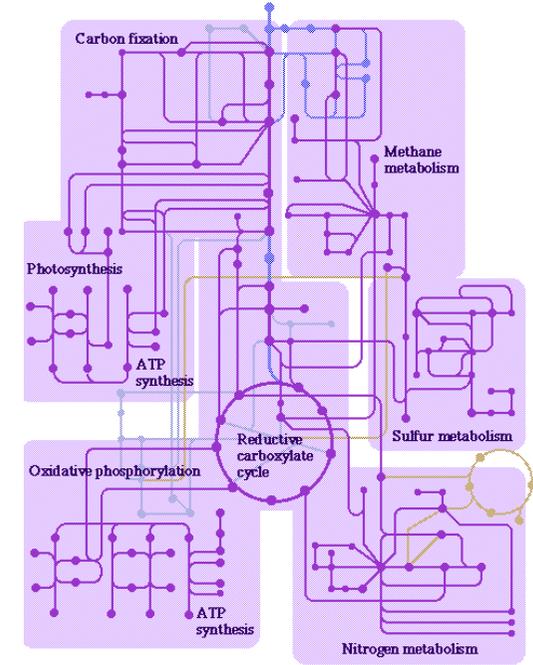
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**CARBOHYDRATE METABOLISM**



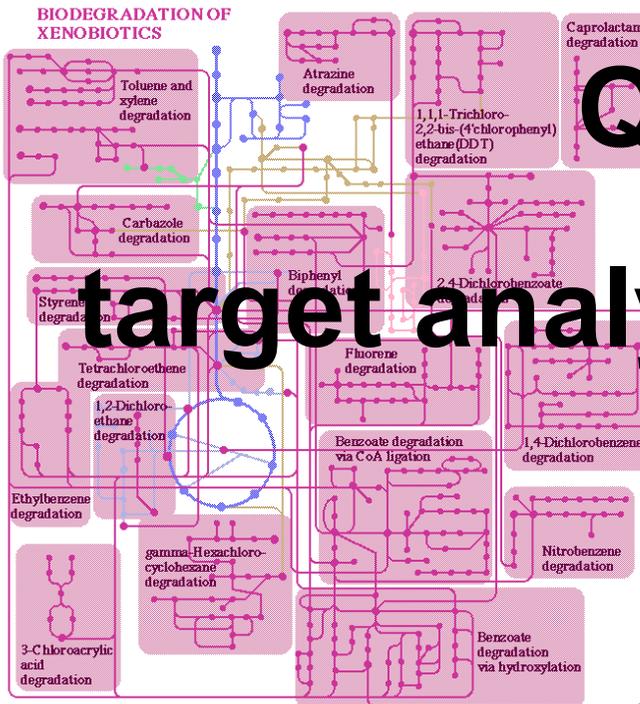
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**ENERGY METABOLISM**



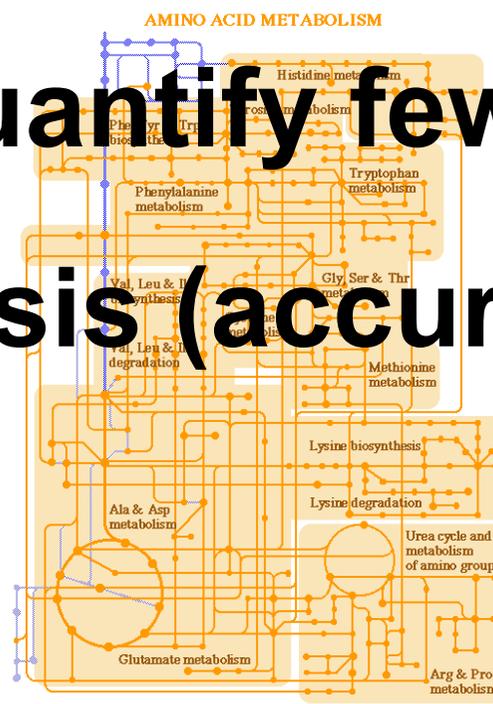
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**BIODEGRADATION OF XENOBIOTICS**



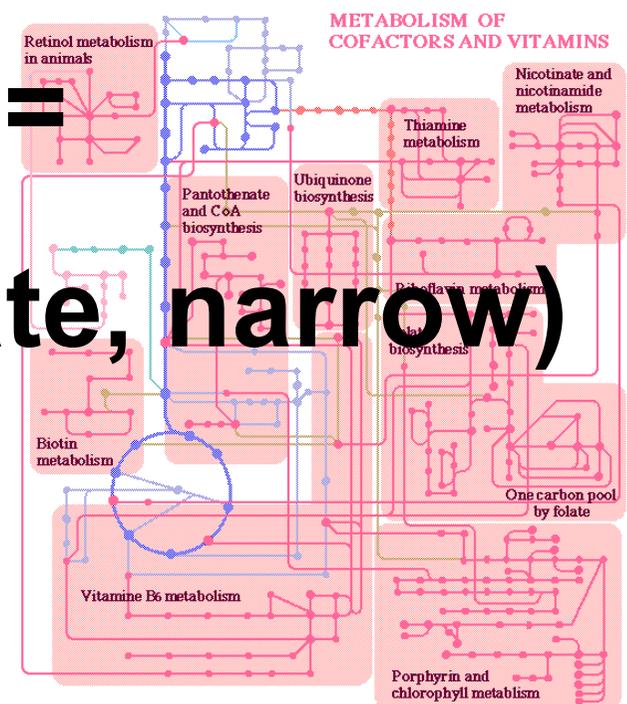
01196 6/26/02

**AMINO ACID METABOLISM**



01100 3/3/05

**METABOLISM OF COFACTORS AND VITAMINS**



01140 5/1/00

**Quantify few = target analysis (accurate, narrow)**

# Metabolomics methods

## Separation methods

- **Gas chromatography (GC)**
  - one of the most widely used and powerful methods
  - high chromatographic resolution
  - compounds must be volatile (or derivatized)
- **High performance liquid chromatography (HPLC)**
  - lower chromatographic resolution
  - wider range of analytes can be analyzed (polar)
- **Capillary electrophoresis (CE)**
  - higher theoretical separation efficiency than HPLC
  - suitable for wider range of metabolites than GC
  - most appropriate for charged analytes (electrophoretic technique)

# Metabolite detection techniques

## Physical Property

- mass
- rotation, vibration
- $h\nu$  absorbance
- $h\nu$  emittance
- spin
- volatility
- hydrophobicity
- charge
- size

## Method

- mass spectrometry
- infrared spectrometry
- ultraviolet-visible spectroscopy
- fluorescence spectroscopy
- nuclear magnetic resonance
- gas chromatography
- liquid chromatography
- capillary electrophoresis
- size-exclusion chromatography

# Gas chromatography

- **Advantages**
  - Very high chromatographic resolving power
  - Good selection of stationary phases
  - Wide dynamic range
- **Disadvantages**
  - Compounds must be sufficiently volatile (derivatized)
  - Compounds must be thermally stable
  - Limited to nonpolar and slightly polar molecules





# Liquid chromatography

- **Advantages**
  - Capable of analyzing wide range of metabolites
  - (thermally labile, polar, high molecular mass)
  - Good selection of stationary phases
- **Disadvantages**
  - Fragmentation rules not well-established
  - Few MS fragmentation libraries
  - Limited resolution (but UPLC is an improvement)





# Metabolomics methods

## Non-separation methods

### ➤ NMR (nuclear magnetic resonance)

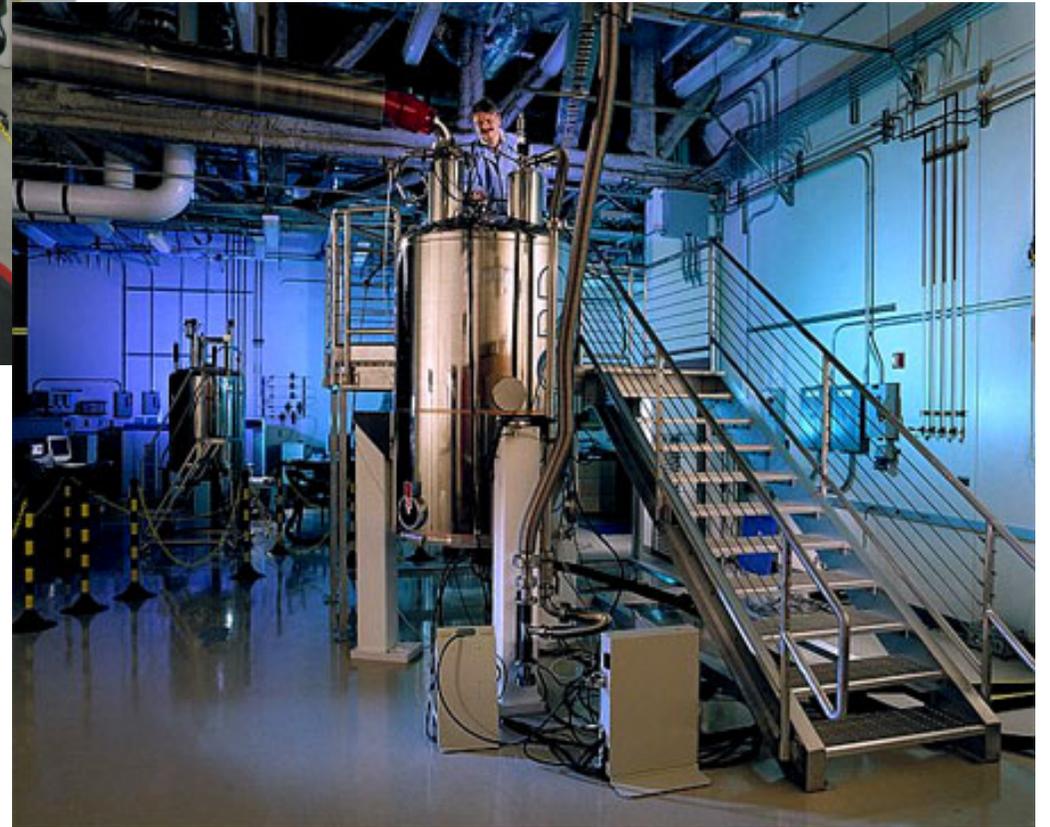
- **Advantages**

- No sample separation necessary
- Essentially universal detector
- Non-destructive

- **Disadvantages**

- Low sensitivity
- Results difficult to interpret
- Decreased quantification
- Expensive





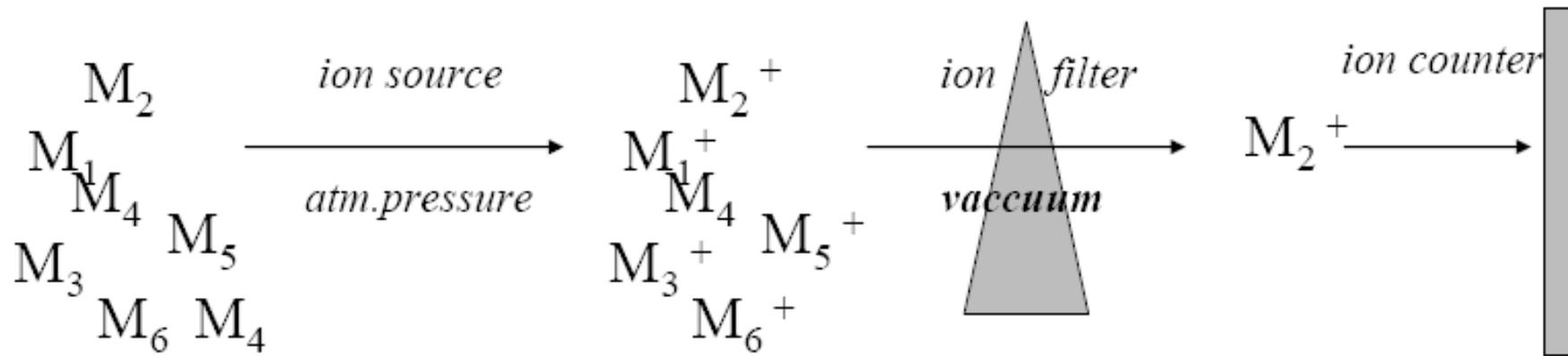
# Mass spectrometry

- *chemical analysis technique to measure the mass of molecules by ionizing, separating & detecting ions according to their mass-to-charge ratios.*
- *involves the study of ionized molecules in the gas phase with the aim of one or more of the following:*
- **Molecular weight determination**
- **Identify unknown compounds**
- **Structural characterization**
- **Qualitative and quantitative analysis of mixtures**
- **Carbon dating**

# What is ionization?

- **What is ionization?**
- producing an electrically charged molecule from a neutral molecule by adding protons or removing electrons.
  
- **Why is ionization of sample required in mass spectrometry?**
- sample to be analyzed by mass spectrometry must be ionized to separate ions according to their mass-to-charge ratio
  
- **What is the "mass-to-charge" ratio of an ion?**
- The mass of the ion divided by the charge on the ion.
- The charges on an ion are always positive integers (1, 2, 3, ...).
- Charged ions are produced by ionization.
- Ions charged by adding a proton or by removing an electron.
  
- **For example:**
  - molecule  $C_2H_6$  with mass of  $(2 \times 12) + (6 \times 1) = 30 \text{ Da}$ .
  - can acquire a charge of 1 unit in 2 ways:
    - losing an electron (mass-to-charge ratio =  $30/1 = 30$ )
    - accepting a proton (mass-to-charge ratio =  $(30+1)/1 = 31$ )

# What is mass spectrometry????



**A very very very expensive filter.....**

# Ion sources used in metabolomics

## HPLC

ESI – electrospray ionization (Nobel prize in 2002)

API – atmospheric pressure ionization

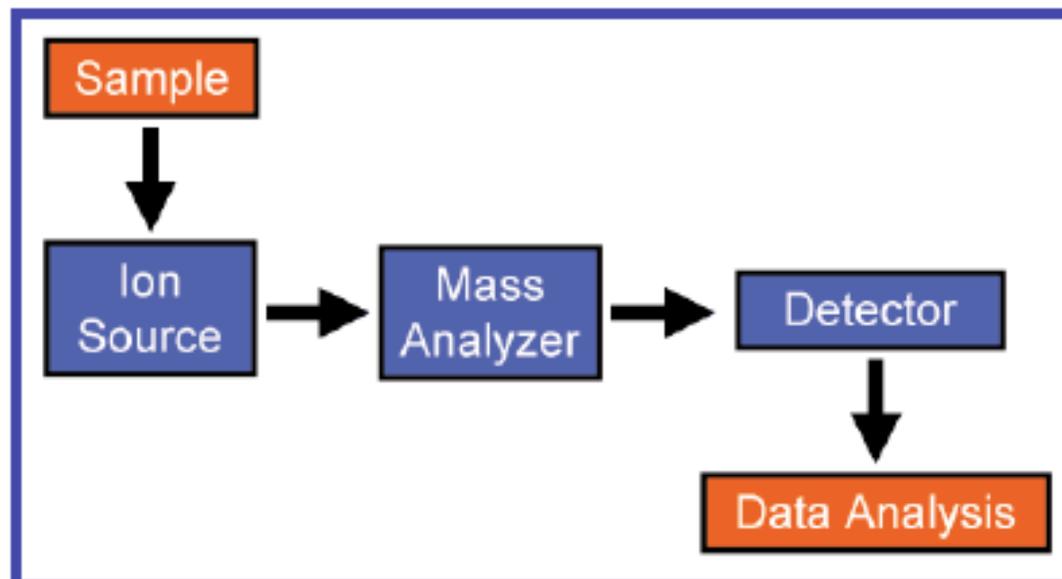
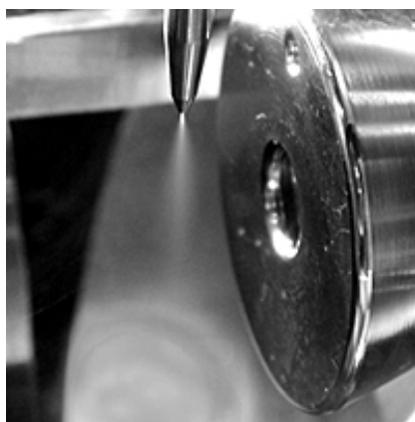
MALDI – matrix-assisted laser desorption ionization

ICP – inductively coupled plasma

## GC

EI – electron impact ionization

CI – chemical ionization



# Summary of metabolomics

- **Analytical approach to quantify the small molecule metabolites of an organism**
- **Multiple analytical methods for measuring metabolites, but none currently capable of capturing the full “metabolome”**
- **Various levels of method development depending upon biological question**
- **Mass spectrometry is the workhorse of metabolomics**
- **Mass spectrometry functions essentially as a very expensive mass filter**
- **Metabolomics is suggestive of phenotype**

# Human Metabolome Database

The screenshot shows the Human Metabolite Database (HMDB) website in a Netscape browser window. The browser title is "Metabolomics Toolbox - Netscape". The website header includes "Metaboxomics Toolbox" and navigation links: "About Us", "Project Info", "News & Events", "Related Links", "Metabolite Database", and a search box. The main content area is titled "Metabolite Database" and features a "Human Metabolite Browser" section. This section includes a navigation bar with "HMDB", "Search", "Extract", "ChemQuery", and "BLAST". Below this, a sorting control indicates "Sorted By Common Name" with dropdown menus for "Common Name", "Ascending", and "Display: 20". A pagination bar shows "Page 1 of 10:" with numbered links 1 through 10. A table displays the first entry:

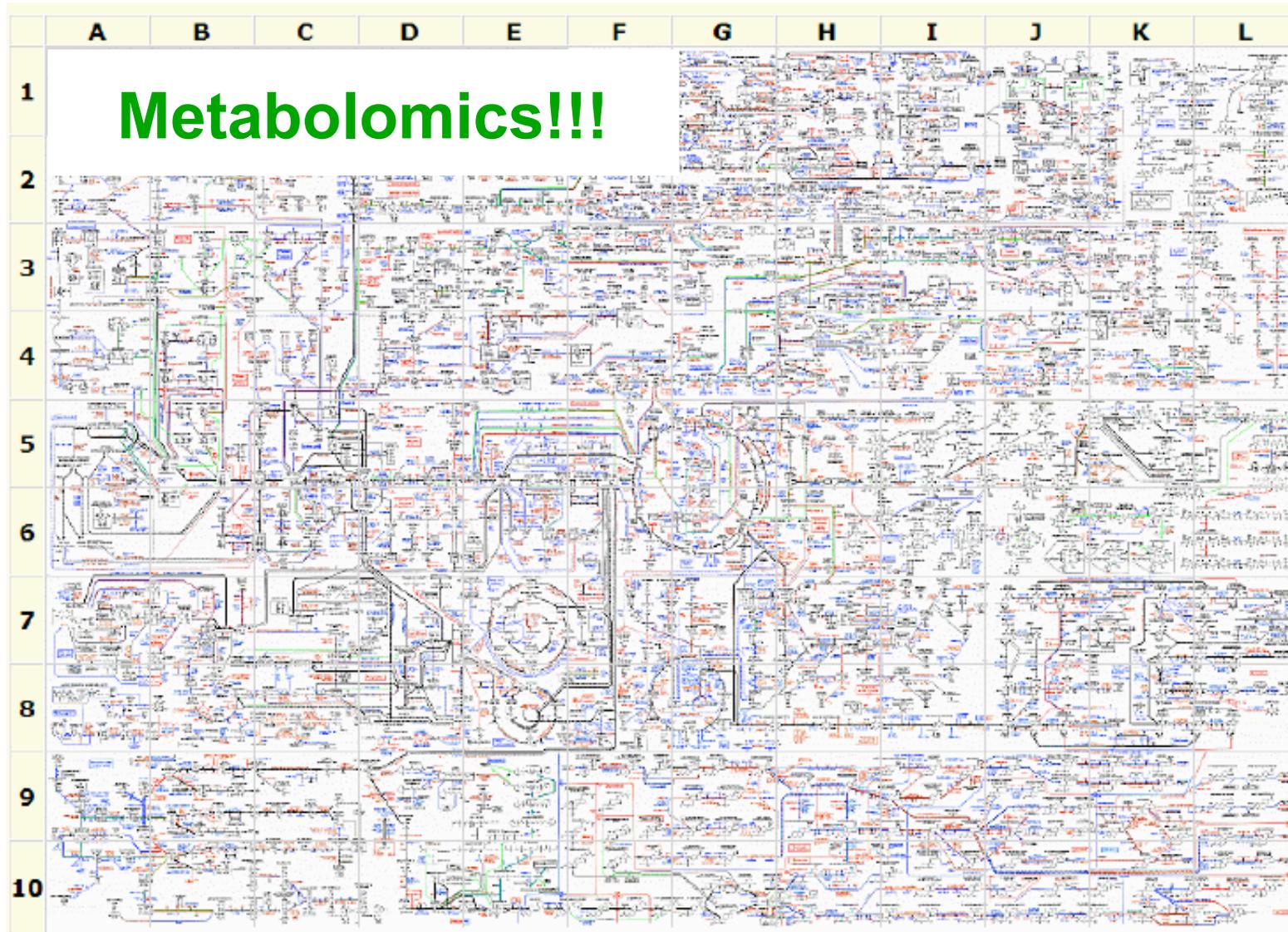
CAS REGISTRY	COMMON NAME	CHEMICAL NAME	MOLECULAR FORMULA	MOLECULAR WEIGHT
625-72-9 MetaboCard	(R)-3-Hydroxybutyric acid	(R)-3-Hydroxybutyric acid	C <sub>4</sub> H <sub>8</sub> O <sub>3</sub>	104.1045

The left sidebar contains a description of the database and a list of tools: "Metabolite Database", "Metabolite Search", "Data Extractor", "Chemical Query", and "BLAST Search". The Windows taskbar at the bottom shows the Start button, several open applications, and the system clock at 3:46 PM.

<http://www.hmdb.ca/>



# What do we do with our vast quantities of metabolomics data???

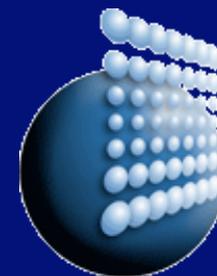


Even if we manage to capture a significant portion of the metabolome, how do we then go about analyzing it and making biological sense of the observed fluctuations??



京都大学

# Interfacing with KEGG



**KEGG – Kyoto Encyclopedia of  
Genes and Genomes**

# What is KEGG??



- **KEGG is an integrated database resource consisting of 16 main databases, broadly categorized into systems information, genomic information, and chemical information.**
- **A grand challenge in the post-genomic era is a complete computer representation of the cell, the organism, and the biosphere, which will enable computational prediction of higher-level complexity of cellular processes and organism behaviors from genomic and molecular information.**
- **KEGG was created to address this need.**

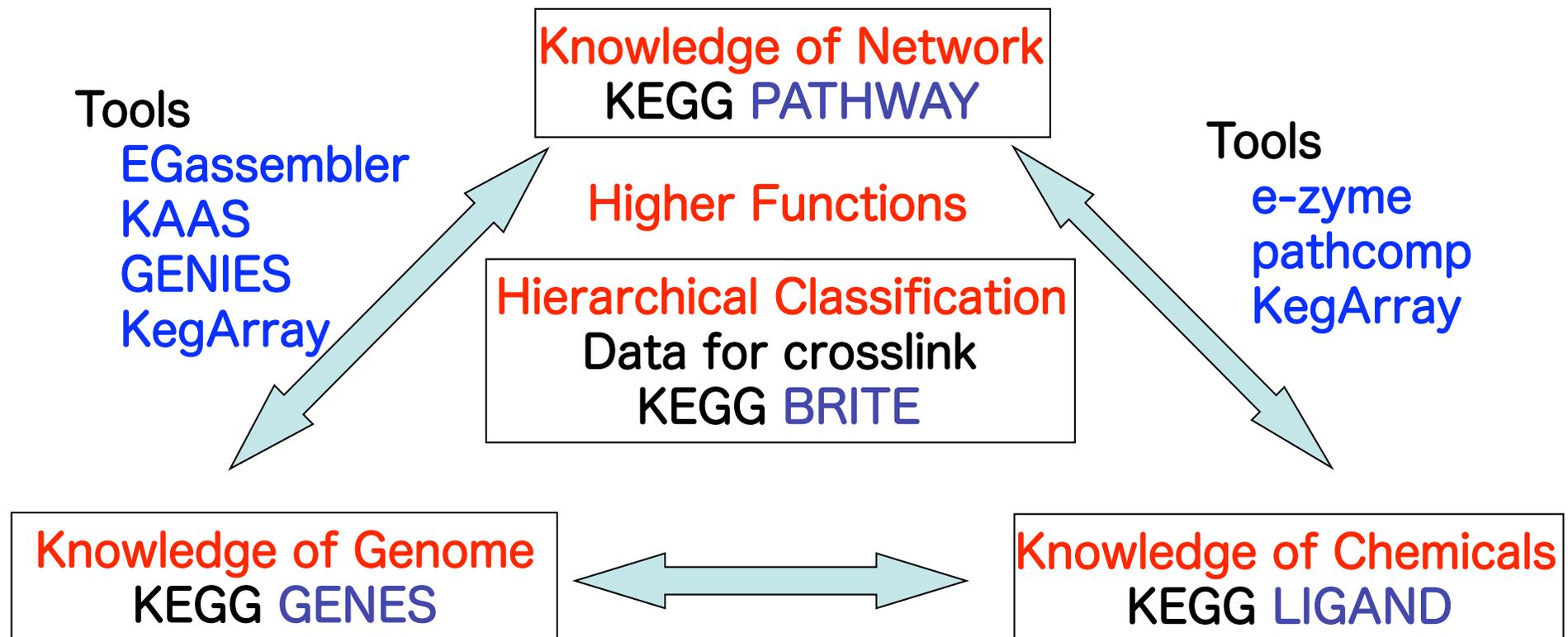
# Current KEGG Release, March 2010



- **KEGG PATHWAY**
- **103,908 pathways generated from 348 reference pathways**
- **KEGG BRITE**
- **29,812 hierarchies generated from 89 reference hierarchies**
- **KEGG GENES**
- **5,346,973 genes in 129 eukaryotes + 971 bacteria + 74 archaea**
- **KEGG LIGAND**
- **16,145 compounds, 9,258 drugs, 10,969 glycans, 8,123 reactions, 12,114 reactant pairs**

# KEGG: Kyoto Encyclopedia of Genes and Genomes

Reconstruction of various aspects of the life sciences from biological knowledge (from primary researchers) and omics data



Linking biological knowledge to “omics” data (e.g. genomics data)

# KEGG: Kyoto Encyclopedia of Genes and Genomes

KEGG: Kyoto Encyclopedia of Genes and Genomes

[KEGG Home](#)  
Introduction  
Overview  
Release notes  
Current statistics

[KEGG Identifiers](#)

[KEGG XML](#)

[KEGG API](#)

[KEGG FTP](#)

[KegTools](#)

[GenomeNet](#)

[DBGET/LinkDB](#)

[Feedback](#)

## KEGG: Kyoto Encyclopedia of Genes and Genomes

A grand challenge in the post-genomic era is a complete computer representation of the cell, the organism, and the biosphere, which will enable computational prediction of higher-level complexity of cellular processes and organism behaviors from genomic and molecular information. Towards this end we have been developing a bioinformatics resource named KEGG as part of the research projects of the Kanehisa Laboratories in the Bioinformatics Center of Kyoto University and the Human Genome Center of the University of Tokyo.

**Main entry point to the KEGG web service**  
[KEGG2](#)    KEGG Table of Contents    [Update notes](#)    [Help](#)

**Data-oriented entry points**

- [KEGG PATHWAY](#)    Pathway maps and pathway modules    [Pathway maps](#)
- [KEGG BRITE](#)    Functional hierarchies and ontologies    [Brite hierarchies](#)
- [KEGG ORTHOLOGY](#)    KO system and orthology annotation
- [KEGG GENES](#)    Genomes, genes, and proteins
- [KEGG LIGAND](#)    Chemical compounds, glycans, and reactions
- [KEGG DISEASE](#)    Human diseases    [Article in NAR DB issue](#)
- [KEGG DRUG](#)    Drugs

**Organism-specific entry points**

[KEGG Organisms](#)    Select   (example) hsa

**Other entry points**

- [KEGG Atlas](#)    New interface to navigate pathway maps
- [KEGG GLYCAN](#)    Glycome informatics resource
- [KEGG COMPOUND](#)    Knowledge base for biochemical compounds
- [KEGG REACTION](#)    Knowledge base for biochemical reactions
- [KEGG PLANT](#)    Knowledge base for plant natural products
- [KAAS](#)    KEGG automatic annotation server

Copyright 1995-2010 Kanehisa Laboratories

<http://www.genome.jp/kegg/>

KEGG Encyclopedia

## KEGG - Table of Contents

KEGG2    PATHWAY    BRITE    KO    GENES    LIGAND    DISEASE    DRUG    DBGET

Search  for

Category	Entry Point	Release Info	Search & Compute	DBGET Search
Systems information	<a href="#">KEGG PATHWAY</a> <a href="#">KEGG BRITE</a> <a href="#">KEGG Atlas</a>	New maps Map# changes Update status New hierarchies Update status	Search objects in pathways Color objects in pathways Search objects in brite Color objects in brite KEGG pathway maps KEGG pathway modules BRITE functional hierarchies	PATHWAY BRITE MODULE
	<a href="#">KEGG DISEASE</a> <a href="#">KEGG DRUG</a>		Human diseases ATC drug classification	DISEASE DRUG
	<a href="#">KEGG ORTHOLOGY</a>		KEGG Orthology (KO)	ORTHOLOGY
Genomic information	<a href="#">KEGG GENES</a> <a href="#">KEGG Organisms</a>	New organisms Update status	Map organisms to taxonomy Generate taxonomy tree KEGG organisms SSDB search BLAST search FASTA search KAAS automatic annotation	GENOME GENES DGENES EGENES
	<a href="#">KEGG LIGAND</a> <a href="#">KEGG GLYCAN</a> <a href="#">KEGG PLANT</a>	Update status	SIMCOMP search SUBCOMP search KCaM search E-zyme reaction prediction PathComp computation	COMPOUND GLYCAN REACTION RPAIR ENZYME

See Kanehisa et al. (2010) for the new features of KEGG.

**KEGG for specific organisms**

[KEGG Organisms](#) - the list of currently available organisms

Select    (examples) hsa mmu sce eco bsu syn

**KEGG as an integrated web resource**

<http://www.genome.jp/kegg/kegg2.html>

# KEGG: Kyoto Encyclopedia of Genes and Genomes



[KEGG](#) [KEGG2](#) [PATHWAY](#) [BRITE](#) [DISEASE](#) [DRUG](#)

## KEGG Home

[Introduction](#)  
[Overview](#)  
[Release notes](#)  
[Current statistics](#)

## KEGG Identifiers

### KEGG XML

### KEGG API

### KEGG FTP

### KegTools

[GenomeNet](#)

[DBGET/LinkDB](#)

[Feedback](#)

## KEGG Identifiers

### KEGG Object Identifier

**KEGG objects** are biological entities from molecular to higher levels. Each object (except for GENES) is identified by the KEGG object identifier, consisting of a five-digit number prefixed by an upper-case alphabet, such as **K05032** and **D00336**, or prefixed by a 2-4 letter code for **PATHWAY** and **BRITE**, such as **map00010** and **br08301**.

Prefix	Content	Database
K	Gene/protein ortholog group	ORTHOLOGY
C	Chemical compound	COMPOUND
D	Drug	DRUG
G	Glycan	GLYCAN
R	Reaction	REACTION
RP	Reactant pair	RPAIR
map/ko/ec/rn/(org)	Pathway map	PATHWAY
br/ko/(org)	Brite hierarchy (ontology)	BRITE
M	Pathway module	MODULE
H	Human disease	DISEASE
T	Organism	GENOME

Enter KEGG object identifiers to retrieve corresponding database entries:

(Example) R07326 R00623 R00754 R01036 R04805 R04880 R06917

## KEGG Organism Code

Each KEGG object can be uniquely identified without the database name because of the different prefix, but the general format to retrieve a database entry in KEGG and all other GenomeNet databases is:

db:entry

where "db" is the database name and "entry" is the entry name or the accession number (see [DBGET](#) for the list of database names and abbreviations). The above examples can then be written as **ko:K05032** and **drug:D00336** (or **dr:D00336**).

In addition to the internally used T number shown above, an organism in KEGG is given a three-letter **KEGG organism code** (with prefix "d" for draft genome and "e" for EST contigs), which is treated like a database name. Therefore, individual genes in an organism can be identified in the following way:

org:gene

where "org" is the KEGG organism code and "gene" is the KEGG GENES entry name (see below). The KEGG organism code is also used as a prefix to identify organism-specific pathway maps or BRITE functional hierarchies, such as **hsa04930** and **mmu04000**.

Prefix	Content
map	Reference pathway
ko	Reference pathway (KO) or Reference BRITE hierarchy (KO)
ec	Reference pathway (EC)
rn	Reference pathway (Reaction)
br	Reference BRITE hierarchy (BR)
"org"	Organism-specific pathway or BRITE hierarchy

## KEGG GENES Entry Name

Entry names of the KEGG GENES database are usually locus\_tags given by the International Nucleotide Sequence Database Collaboration (INSDC). The major sequence databases such as NCBI and UniProt/Swiss-Prot use different sets of gene/protein identifiers. In order to facilitate the use of KEGG, automatic name conversion has been implemented for these identifiers.

Enter outside DB accession numbers to convert to KEGG GENES entries:

NCBI GeneID  NCBI gi  UniProt

(Example) 3775638 3737440 3743551 3897645 3902295

# KEGG PATHWAY

Molecular interaction network diagram in biological systems

KEGG PATHWAY Database  
Wiring diagrams of molecular interactions, reactions, and relations

KEGG2 PATHWAY BRITE KO GENES LIGAND DISEASE DRUG DBGET

Select prefix: map Organism Enter keywords: [ ] Go Help

### Pathway Maps

KEGG PATHWAY is a collection of manually drawn pathway maps (see [new maps](#), [last updates](#), and [change history](#)) representing our knowledge on the molecular interaction and reaction networks for:

- 1. Metabolism**  
Carbohydrate Energy Lipid Nucleotide Amino acid Other amino acid  
Glycan PK/NRP Cofactor/vitamin Secondary metabolite Xenobiotics Overview
- 2. Genetic Information Processing**
- 3. Environmental Information Processing**
- 4. Cellular Processes**
- 5. Organismal Systems**
- 6. Human Diseases**

and also on the structure relationships (KEGG drug structure maps) in:

- 7. Drug Development**

KEGG Atlas may now be used to examine any of the KEGG pathway maps.

### Pathway Entries and Pathway Modules

Pathway entries are text representation of pathway maps, containing descriptions (for a limited number of entries, at the moment). **Pathway modules** are specification of subnetworks that correspond to tighter functional units, each represented as a list of KO identifiers (K numbers).

Search Pathway entries for [ ] Go Clear

### Pathway Mapping

KEGG PATHWAY mapping is the process to map molecular datasets, especially large-scale datasets in genomics, transcriptomics, proteomics, and metabolomics, to the KEGG pathway maps for biological interpretation of higher-level systemic functions.

- Search objects in KEGG pathways
- Color objects in KEGG pathways

### 1. Metabolism

#### 1.1 Carbohydrate Metabolism

Glycolysis / Gluconeogenesis  
Glyceraldehyde-3-phosphate (GAP) cycle

Pentose phosphate pathway  
Pentose and glucuronate interconversions  
Fructose and mannose metabolism  
Galactose metabolism  
Ascorbate and aldarate metabolism

Global metabolism map

## • Metabolism

- 12 categories
- primary, secondary, drug metabolism

## • Regulatory network

- 19 categories
- Genetic and Environment information, Cellular processes, Organismal systems

## • Human diseases

- Cancer, immune disorders, etc.

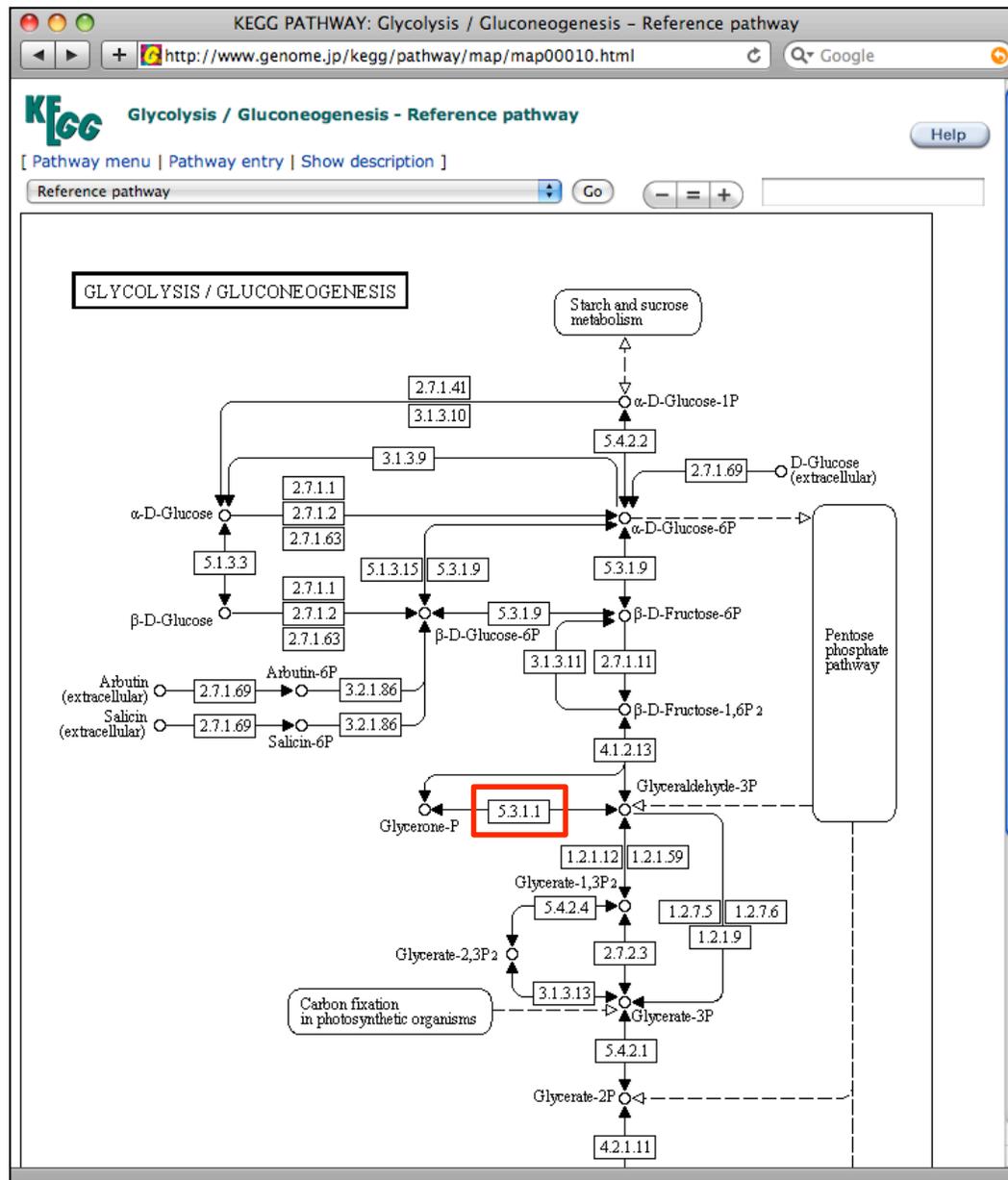
## • Drug development

- History, structure and target based design

<http://www.genome.jp/kegg/pathway.html>

# KEGG PATHWAY

An example: glycolysis



- Network of Enzymes/ Genes and Chemical compounds
- Pathway menu
  - To previous page
- Pathway entry
  - Text version of PATHWAY database
- Show description
  - Description of pathway map
- Zoom map in/out

<http://www.genome.jp/kegg/pathway/map/map00010.html>

# KEGG PATHWAY

An example: glycolysis



ORTHOLOGY: K01803

Help

<b>Entry</b>	K01803	KO
<b>Name</b>	TPI, tpiA	
<b>Definition</b>	triosephosphate isomerase (TIM) [EC:5.3.1.1]	
<b>Pathway</b>	ko00010 Glycolysis / Gluconeogenesis ko00051 Fructose and mannose metabolism ko00562 Inositol phosphate metabolism ko00710 Carbon fixation in photosynthetic organisms	
<b>Module</b>	M00001 Glycolysis (Embden-Meyerhof pathway), glucose => pyruvate M00002 Glycolysis, core module involving three-carbon compounds M00003 Gluconeogenesis, oxaloacetate => fructose-6P	
<b>Class</b>	Metabolism; Carbohydrate Metabolism; Glycolysis / Gluconeogenesis [PATH:ko00010] Metabolism; Carbohydrate Metabolism; Fructose and mannose metabolism [PATH:ko00051] Metabolism; Carbohydrate Metabolism; Inositol phosphate metabolism [PATH:ko00562] Metabolism; Energy Metabolism; Carbon fixation in photosynthetic organisms [PATH:ko00710] <a href="#">BRITE hierarchy</a>	
<b>Other DBs</b>	RN: R01015 COG: COG0149 GO: 0004807	
<b>Genes</b>	HSA: 7167(TPI1) PTR: 451799(TPI1) MCC: 706960(TPI1) 714090(TPI1) MMU: 21991(Tpi1) RNO: 246267 24849(Tpi1) 498731(RGD1563601) 500959 CFA: 477711(TPI1) BTA: 281543(TPI1) SSC: 641360(TPI1) ECB: 100052671 MDO: 100016284 OAA: 100092831 GGA: 396435(TPI1) XLA: 380168(tpi) XTR: 100038162(tpi1) DRE: 192309(tpila) 560753(tpilb) BFO: BRAFLDRAFT_282392 CIN: 100183090 SPU: 548616 DME: Dmel_CG2171(Tpi) DPO: Dpse_GA15281(Dpse_Tpi) DAN: Dana_GF16201 DER: Dere_GG11962 DPE: Dper_GL14069 DSE: Dsec_GM12179	

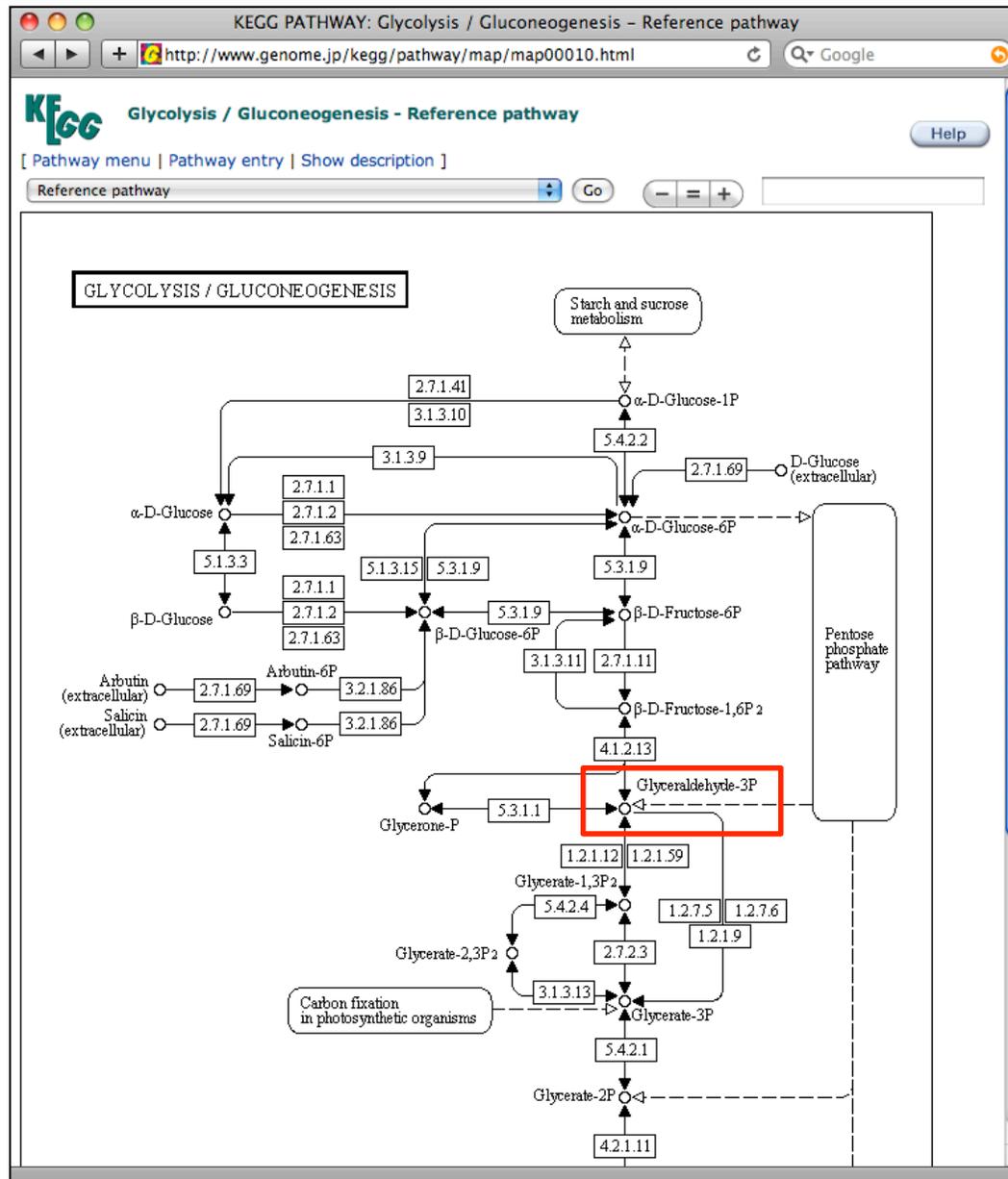
## All links

Ontology (5)  
KEGG BRITE (3)  
GO (1)  
COG (1)  
Pathway (3336)  
KEGG PATHWAY (3333)  
KEGG MODULE (3)  
Chemical reaction (2)  
KEGG ENZYME (1)  
KEGG REACTION (1)  
Gene (1843)  
KEGG GENES (1283)  
KEGG DGENES (17)  
KEGG EGENES (543)  
All databases (5186)

[http://www.genome.jp/dbget-bin/www\\_bget?K01803+5.3.1.1+R01015](http://www.genome.jp/dbget-bin/www_bget?K01803+5.3.1.1+R01015)

# KEGG PATHWAY

An example: glycolysis



- Network of Enzymes/ Genes and Chemical compounds
- Pathway menu
  - To previous page
- Pathway entry
  - Text version of PATHWAY database
- Show description
  - Description of pathway map
- Zoom map in/out

<http://www.genome.jp/kegg/pathway/map/map00010.html>

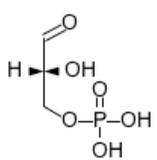
# KEGG PATHWAY

An example: glycolysis



COMPOUND: C00118

Help

<b>Entry</b>	C00118	Compound
<b>Name</b>	D-Glyceraldehyde 3-phosphate; (2R)-2-Hydroxy-3-(phosphonoxy)-propanal; Glyceraldehyde 3-phosphate	
<b>Formula</b>	C3H7O6P	
<b>Mass</b>	169.998	
<b>Structure</b>	 <p>C00118</p> <p>Mol file KCF file DB search Jmol KegDraw</p>	
<b>Reaction</b>	<a href="#">R00845</a> <a href="#">R01015</a> <a href="#">R01058</a> <a href="#">R01059</a> <a href="#">R01061</a> <a href="#">R01063</a> <a href="#">R01064</a> <a href="#">R01066</a> <a href="#">R01067</a> <a href="#">R01068</a> <a href="#">R01069</a> <a href="#">R01070</a> <a href="#">R01440</a> <a href="#">R01621</a> <a href="#">R01641</a> <a href="#">R01827</a> <a href="#">R01830</a> <a href="#">R02340</a> <a href="#">R02721</a> <a href="#">R02722</a> <a href="#">R05465</a> <a href="#">R05605</a> <a href="#">R05636</a> <a href="#">R06861</a> <a href="#">R07159</a> <a href="#">R07456</a> <a href="#">R08575</a>	
<b>Pathway</b>	PATH: <a href="#">ko00010</a> Glycolysis / Gluconeogenesis PATH: <a href="#">ko00030</a> Pentose phosphate pathway PATH: <a href="#">ko00040</a> Pentose and glucuronate interconversions PATH: <a href="#">ko00051</a> Fructose and mannose metabolism PATH: <a href="#">ko00052</a> Galactose metabolism PATH: <a href="#">ko00331</a> Clavulanic acid biosynthesis PATH: <a href="#">ko00562</a> Inositol phosphate metabolism PATH: <a href="#">ko00680</a> Methane metabolism PATH: <a href="#">ko00710</a> Carbon fixation in photosynthetic organisms PATH: <a href="#">ko00730</a> Thiamine metabolism PATH: <a href="#">ko00750</a> Vitamin B6 metabolism PATH: <a href="#">ko00900</a> Terpenoid backbone biosynthesis PATH: <a href="#">map01060</a> Biosynthesis of plant secondary metabolites PATH: <a href="#">ko01061</a> Biosynthesis of phenylpropanoids PATH: <a href="#">ko01062</a> Biosynthesis of terpenoids and steroids PATH: <a href="#">ko01063</a> Biosynthesis of alkaloids derived from shikimate pathway PATH: <a href="#">ko01064</a> Biosynthesis of alkaloids derived from ornithine, lysine and nicotinic acid PATH: <a href="#">ko01065</a> Biosynthesis of alkaloids derived from histidine and purine PATH: <a href="#">ko01066</a> Biosynthesis of alkaloids derived from terpenoid and polyketide PATH: <a href="#">ko01070</a> Biosynthesis of plant hormones PATH: <a href="#">ko01100</a> Metabolic pathways	
<b>Enzyme</b>	<a href="#">1.1.1.177</a>	<a href="#">1.2.1.9</a> <a href="#">1.2.1.12</a> <a href="#">1.2.1.13</a>

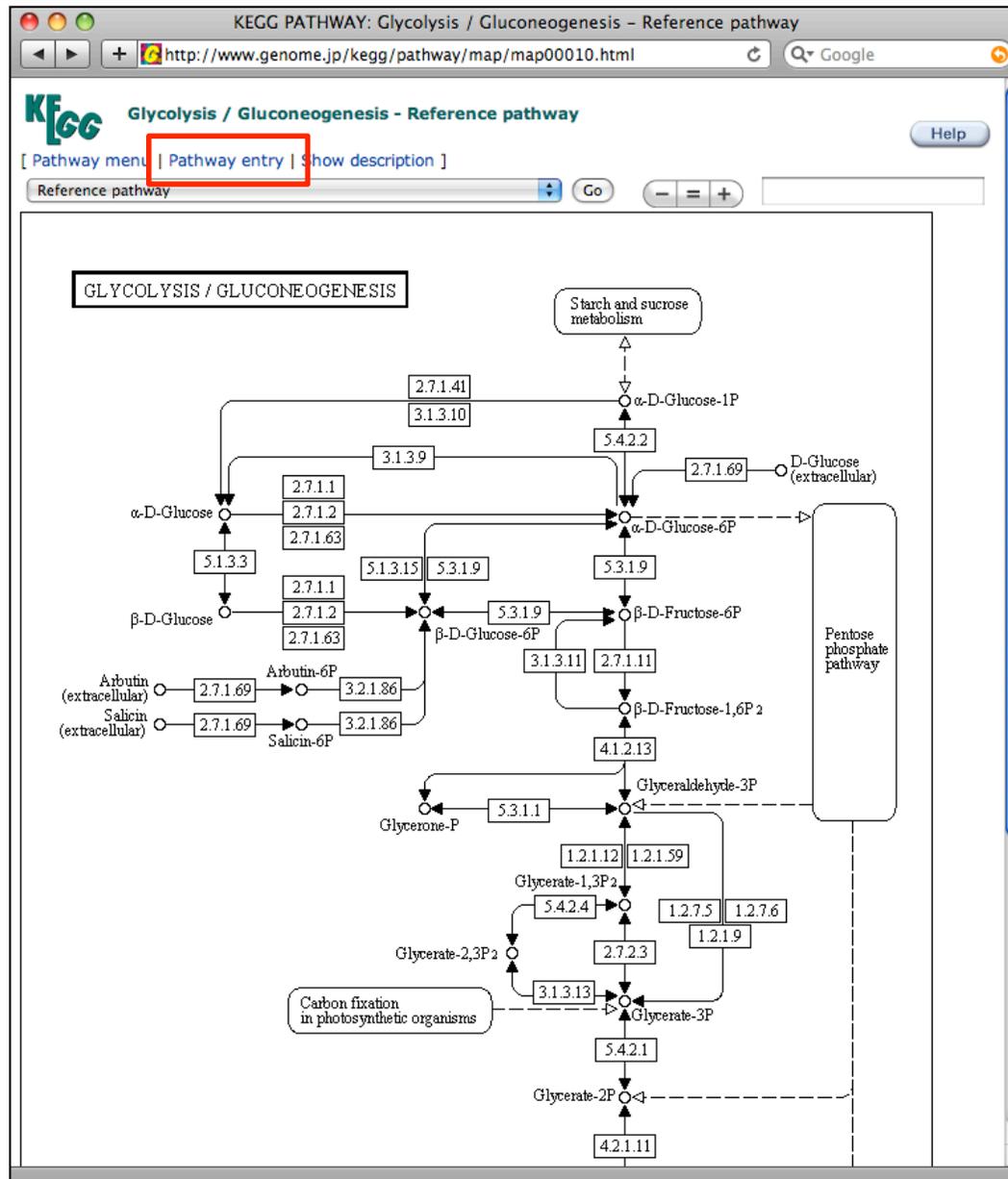
## All links

[Ontology \(1\)](#)  
[KEGG BRITE \(1\)](#)  
[Pathway \(12223\)](#)  
[KEGG PATHWAY \(12212\)](#)  
[KEGG MODULE \(11\)](#)  
[Chemical substance \(7\)](#)  
[KEGG COMPOUND \(1\)](#)  
[PubChem \(1\)](#)  
[ChEBI \(1\)](#)  
[3DMET \(1\)](#)  
[KnapSacK \(1\)](#)  
[MASSBANK \(1\)](#)  
[PDB-CCD \(1\)](#)  
[Chemical reaction \(71\)](#)  
[KEGG ENZYME \(24\)](#)  
[KEGG REACTION \(27\)](#)  
[KEGG RPAIR \(20\)](#)  
[All databases \(12302\)](#)

[http://www.genome.jp/dbget-bin/www\\_bget?C00118](http://www.genome.jp/dbget-bin/www_bget?C00118)

# KEGG PATHWAY

An example: glycolysis



- Network of Enzymes/ Genes and Chemical compounds
- Pathway menu
  - To previous page
- Pathway entry
  - Text version of PATHWAY database
- Show description
  - Description of pathway map
- Zoom map in/out

<http://www.genome.jp/kegg/pathway/map/map00010.html>

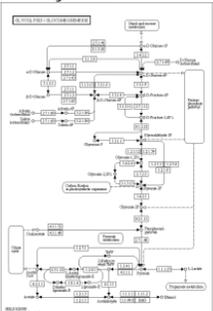
# KEGG PATHWAY

Text version

KEGG PATHWAY: map00010

http://www.genome.jp/dbget-bin/www\_bget?pathway+map00010

**PATHWAY: map00010**

<b>Entry</b>	map00010	Pathway
<b>Name</b>	Glycolysis / Gluconeogenesis	
<b>Description</b>	Glycolysis is the process of converting glucose into pyruvate and generating small amounts of ATP (energy) and NADH (reducing power). It is a central pathway that produces important precursor metabolites: six-carbon compounds of glucose-6P and fructose-6P and three-carbon compounds of glycero-3-P, glyceraldehyde-3P, glyceroate-3P, phosphoenolpyruvate, and pyruvate [MD:M00001]. Acetyl-CoA, another important precursor metabolite, is produced by oxidative decarboxylation of pyruvate [MD:M00679]. When the enzyme genes of this pathway are examined in completely sequenced genomes, the reaction steps of three-carbon compounds from glycero-3-P to pyruvate form a conserved core module [MD:M00002], which is found in almost all organisms and which often corresponds to operon structures in bacterial genomes. Gluconeogenesis is a synthesis pathway of glucose from noncarbohydrate precursors. It is essentially a reversal of glycolysis with minor variations of alternative paths [MD:M00003].	
<b>Class</b>	Metabolism; Carbohydrate Metabolism <a href="#">BRTE hierarchy</a>	
<b>Pathway map</b>	map00010 Glycolysis / Gluconeogenesis 	
<b>Module</b>	M00001 Glycolysis (Embden-Meyerhof pathway), glucose => pyruvate M00002 Glycolysis, core module involving three-carbon compounds M00003 Gluconeogenesis, oxaloacetate => fructose-6P M00239 Ascorbate biosynthesis, plants M00602 PTS system, glucose-specific II component M00603 PTS system, maltose and glucose-specific II component M00605 PTS system, arbutin-like II component M00609 PTS system, arbutin-, cellobiose-, and salicin-specific II component M00679 Pyruvate oxidation, pyruvate => acetyl-CoA	
<b>Other DBs</b>	GO: 0006096 0006094	
<b>Reference</b>	(map 1)	
<b>Authors</b>	Nishizuka Y (ed).	
<b>Title</b>	[Metabolic Maps] (In Japanese)	
<b>Journal</b>	Tokyo Kagaku Dojin (1980)	
<b>Reference</b>	(map 1)	
<b>Authors</b>	Nishizuka Y, Seyama Y, Ikai A, Ishimura Y, Kawaguchi A (eds).	

**All links**

- Pathway (44)
- KEGG PATHWAY (40)
- KEGG MODULE (4)
- Drug (2)
- KEGG DRUG (2)
- Chemical substance (31)
- KEGG COMPOUND (31)
- Chemical reaction (88)
- KEGG ENZYME (41)
- KEGG REACTION (47)
- Gene (62)
- KEGG ORTHOLOGY (62)
- All databases (227)

## • Pathway entry

### – Entry

- Map number (map|ko|ec|rn|species code+number)

### – Name, Description

- Description of pathways, including their relationship with modules

### – Class

- Functional classification

### – Pathway map / Module

- Links to the corresponding pathway diagram and modules

### – Reference

## • Module

- Functional modules considering phylogenetic conservation, complexes, and operons

[http://www.genome.jp/dbget-bin/www\\_bget?pathway+map00010](http://www.genome.jp/dbget-bin/www_bget?pathway+map00010)

# KEGG PATHWAY

Module



MODULE: M00001

Help

<b>Entry</b>	M00001 Pathway Module
<b>Name</b>	Glycolysis (Embden-Meyerhof pathway), glucose => pyruvate
<b>Definition</b>	(K00844,K00845) (K01810,K06859) K00850 (K01623,K01624) K01803 (K00134,K00150) K00927 (K01834,K01837) K01689 K00873
<b>Class</b>	Metabolism; Central metabolism; Central carbohydrate metabolism
<b>Pathway</b>	ko00010 Glycolysis / Gluconeogenesis
<b>Orthology</b>	K00844,K00845 hexokinase/glucokinase [EC:2.7.1.1 2.7.1.2] [RN:R01786] K01810,K06859 glucose-6-phosphate isomerase [EC:5.3.1.9] [RN:R02740] K00850 6-phosphofructokinase [EC:2.7.1.11] [RN:R04779] K01623,K01624 fructose-bisphosphate aldolase [EC:4.1.2.13] [RN:R01070] K01803 triosephosphate isomerase [EC:5.3.1.1] [RN:R01015] K00134,K00150 glyceraldehyde 3-phosphate dehydrogenase [EC:1.2.1.12 1.2.1.59] [RN:R01061 R01063] K00927 phosphoglycerate kinase [EC:2.7.2.3] [RN:R01512] K01834,K01837 phosphoglycerate mutase [EC:5.4.2.1] [RN:R01518] K01689 enolase [EC:4.2.1.11] [RN:R00658] K00873 pyruvate kinase [EC:2.7.1.40] [RN:R02320] <a href="#">Ortholog table</a>
<b>Reaction</b>	R01786 C00267 -> C00668 R02740 C00668 -> C05345 R04779 C05345 -> C05378 R01070 C05378 -> C00111 + C00118 R01015 C00111 -> C00118 R01061,R01063 C00118 -> C00236 R01512 C00236 -> C00197 R01518 C00197 -> C00631 R00658 C00631 -> C00074 R02320 C00074 -> C00022
<b>Compound</b>	C00267 alpha-D-Glucose C00668 alpha-D-Glucose 6-phosphate C05345 beta-D-Fructose 6-phosphate C05378 beta-D-Fructose 1,6-bisphosphate C00111 Glycerone phosphate C00118 D-Glyceraldehyde 3-phosphate C00236 3-Phospho-D-glyceroyl phosphate C00197 3-Phospho-D-glycerate C00631 2-Phospho-D-glycerate C00074 Phosphoenolpyruvate C00022 Pyruvate

## All links

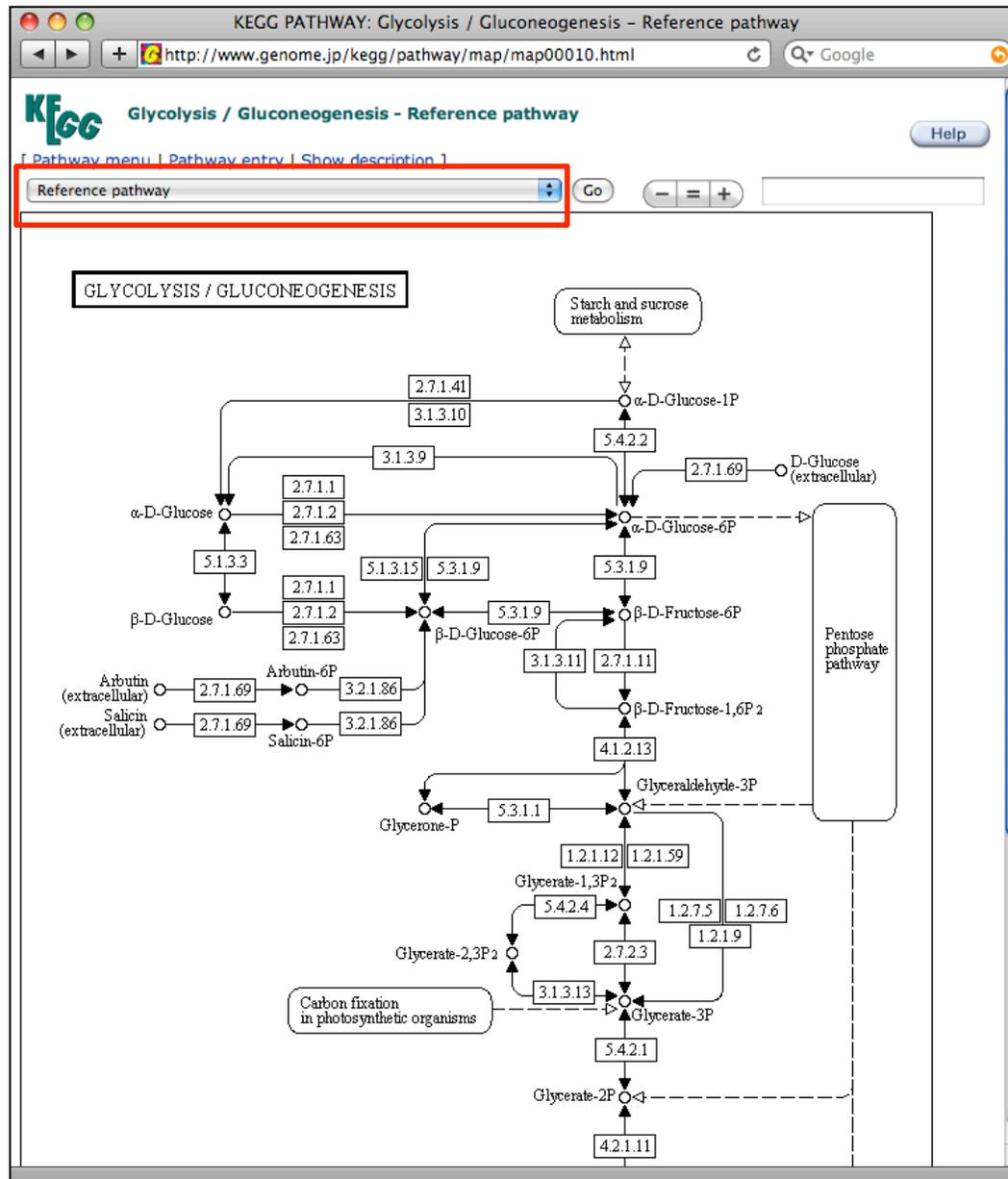
Ontology (1)  
 KEGG BRITE (1)  
 Pathway (1164)  
 KEGG PATHWAY (1164)  
 Chemical substance (11)  
 KEGG COMPOUND (11)  
 Chemical reaction (23)  
 KEGG ENZYME (12)  
 KEGG REACTION (11)  
 Gene (15)  
 KEGG ORTHOLOGY (15)  
 All databases (1214)

DBGET integrated database retrieval system

[http://www.genome.jp/dbget-bin/www\\_bget?md:M00001](http://www.genome.jp/dbget-bin/www_bget?md:M00001)

# KEGG PATHWAY

An example: glycolysis



- Network of Enzymes/ Genes and Chemical compounds
- Pathway menu
  - To previous page
- Pathway entry
  - Text version of PATHWAY database
- Show description
  - Description of pathway map
- Zoom map in/out

<http://www.genome.jp/kegg/pathway/map/map00010.html>

# KEGG PATHWAY

An example: glycolysis

KEGG PATHWAY: Glycolysis / Gluconeogenesis - Reference pathway

Reference pathway (KO)  
Reference pathway (EC) **Go** Current selection Select  
Reference pathway (Reaction)  
----- < Sort below by alphabet > -----  
Homo sapiens (human)  
Pan troglodytes (chimpanzee)  
Macaca mulatta (rhesus monkey)  
Mus musculus (mouse)  
Rattus norvegicus (rat)  
Canis familiaris (dog)  
Bos taurus (cow)  
Sus scrofa (pig)  
Monodelphis domestica (opossum)  
Ornithorhynchus anatinus (platypus)  
Gallus gallus (chicken)  
Xenopus laevis (African clawed frog)  
Xenopus tropicalis (western clawed frog)  
Danio rerio (zebrafish)  
Strongylocentrotus purpuratus (purple sea urchin)  
Nematostella vectensis (sea anemone)  
Drosophila melanogaster (fruit fly)  
Drosophila pseudoobscura pseudoobscura  
Anopheles gambiae (mosquito)  
Aedes aegypti (yellow fever mosquito)  
Tribolium castaneum (red flour beetle)  
Caenorhabditis elegans (nematode)  
Caenorhabditis briggsae  
Brugia malayi (filaria)  
Trichoplax adhaerens  
Arabidopsis thaliana (thale cress)  
Oryza sativa japonica (Japanese rice)  
Physcomitrella patens subsp. patens  
Chlamydomonas reinhardtii  
Ostreococcus lucimarinus  
Cyanidioschyzon merolae  
Saccharomyces cerevisiae  
Ashbya gossypii (Eremothecium gossypii)  
Kluyveromyces lactis  
Debaryomyces hansenii  
Pichia stipitis  
Vanderwaltozyma polyspora  
Candida albicans  
Candida glabrata  
Yarrowia lipolytica  
Schizosaccharomyces pombe  
Neurospora crassa  
Podospira anserina  
Magnaporthe grisea  
Fusarium graminearum

Starch and sucrose metabolism  
α-D-Glucose-1P  
5.4.2.2  
D-Glucose (extracellular)  
2.7.1.69  
α-D-Glucose-6P  
5.3.1.9  
β-D-Fructose-6P  
3.1.9  
e-6P  
3.1.3.11  
2.7.1.11  
β-D-Fructose-1,6P2  
4.1.2.13  
Glyceraldehyde-3P  
3.1.1  
1.2.1.12  
1.2.1.59  
Glycerate-1,3P2  
5.4.2.4  
1.2.7.5  
1.2.7.6  
2.7.2.3  
1.2.1.9  
3.1.3.13  
Glycerate-3P  
5.4.2.1  
Glycerate-2P  
4.2.1.11

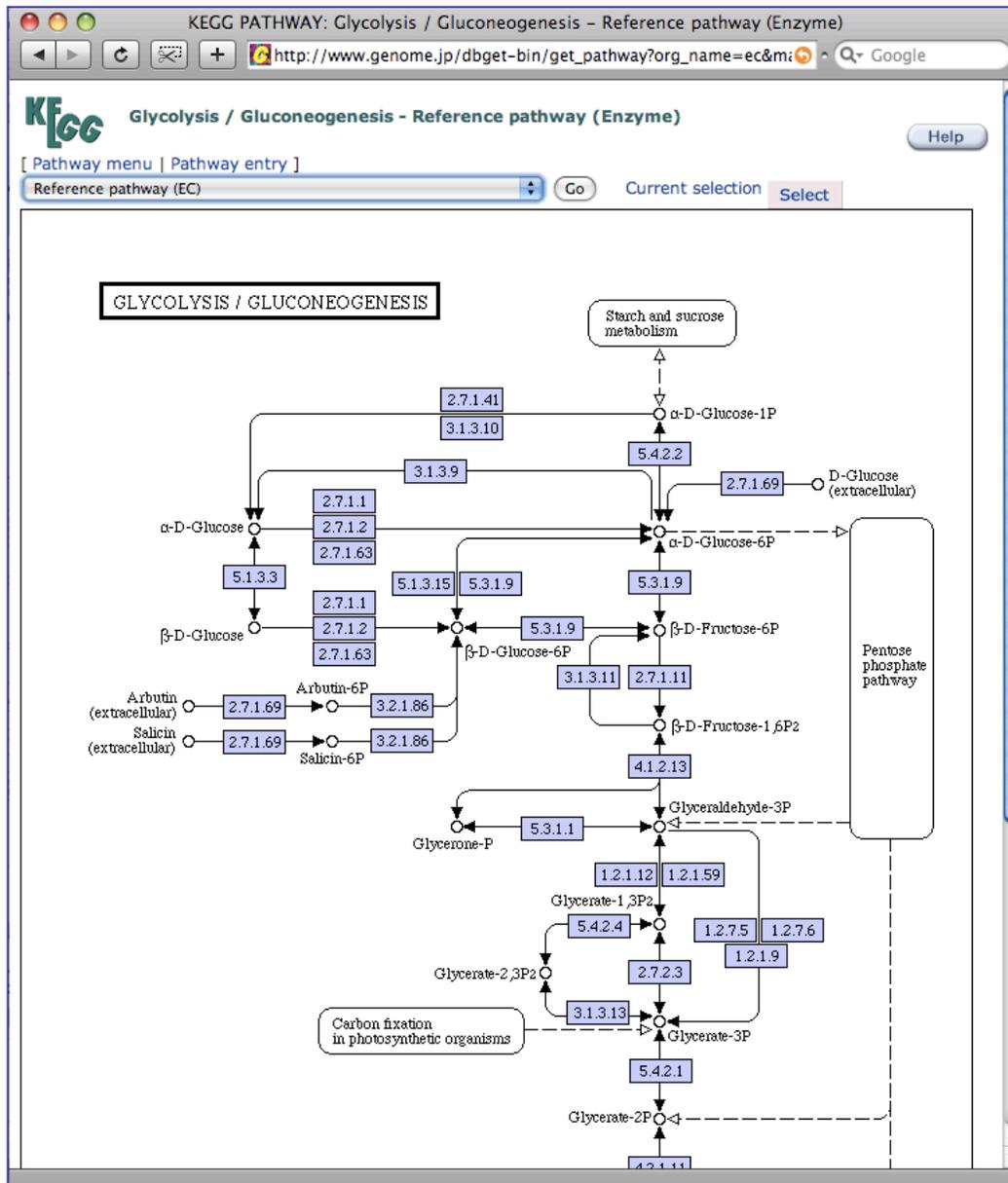
Pentose phosphate pathway

- Reference pathway
- Reference pathway (KO)
  - KEGG Ortholog
  - Links to ortholog entries
- Reference pathway (EC)
  - Enzyme Commission
  - Links to enzyme entries
- Reference pathway (RN)
  - Reaction
  - Links to reaction entries
- Organism names
  - Links to gene entries for each organism
- Sort below by...
  - Sorting organism names

<http://www.genome.jp/kegg/pathway/map/map00010.html>

# KEGG PATHWAY

An example: glycolysis (EC)



- Reference pathway (EC)

- References for the previous versions
- Colored if corresponding enzymes are defined

- Reference pathway (KO)

- Colored if corresponding orthologs are defined
- KO: KEGG Orthology defined for genes in KEGG GENES
- Some enzymes do not have ortholog info

<http://www.genome.jp/kegg/pathway/ko/ko00010.html>

# KEGG PATHWAY

## Organism selection

The screenshot shows the KEGG Pathway website interface. The main page displays the 'Glycolysis / Gluconeogenesis - Reference pathway (KO)'. A 'Select organisms' dialog box is open, allowing users to choose organisms for the pathway. The dialog box includes options for 'GENES', 'DGENES', and 'EGENES', and radio buttons for 'All organisms', 'Eukaryotes', 'Prokaryotes', 'Animals', 'Plants', 'Bacteria', 'Archaea', and 'Another category'. There is also a 'Favorites' section for entering KEGG organism codes. The background shows a metabolic pathway diagram with various enzymes and metabolites labeled, such as Glycerone-P, Glycerate-1,3P<sub>2</sub>, Glycerate-2,3P<sub>2</sub>, Glycerate-3P, and Glycerate-2P.

- Select organisms from the menu list
  - Can use category names defined in the KEGG organism list
    - Mammals, Protists, Actinobacteria, etc.
  - Organism codes are also available from KEGG organism list
    - hsa (human), mmu (mouse), eco (E. coli), etc.

[http://www.genome.jp/kegg/catalog/org\\_list.html](http://www.genome.jp/kegg/catalog/org_list.html)

# KEGG PATHWAY

## Disease pathway



KEGG PATHWAY Database

http://www.genome.jp/kegg/pathway.html#disease

**5. Human Diseases**

**5.1 Cancers**

- Colorectal cancer
- Pancreatic cancer
- Glioma
- Thyroid cancer
- Acute myeloid leukemia
- Chronic myeloid leukemia
- Basal cell carcinoma
- Melanoma
- Renal cell carcinoma
- Bladder cancer
- Prostate cancer
- Endometrial cancer
- Small cell lung cancer
- Non-small cell lung cancer

**5.2 Immune Disorders**

- Asthma
- Systemic lupus erythematosus *New!*
- Autoimmune thyroid disease
- Allograft rejection
- Graft-versus-host disease
- Primary immunodeficiency

**5.3 Neurodegenerative Diseases**

- Alzheimer's disease
- Parkinson's disease *Revised!*
- Amyotrophic lateral sclerosis (ALS)
- Huntington's disease
- Dentatorubropallidolysian atrophy (DRPLA)
- Prion diseases

**5.4 Metabolic Disorders**

- Type I diabetes mellitus
- Type II diabetes mellitus
- Maturity onset diabetes of the young

**5.5 Infectious Diseases**

- Vibrio cholerae infection
- Vibrio cholerae pathogenic cycle
- Epithelial cell signaling in Helicobacter pylori infection
- Pathogenic Escherichia coli infection

**6. Drug Development**

**6.1 Chronology: Antibiotics**

- Penicillins
- Cephalosporins - parenteral agents
- Cephalosporins - oral agents

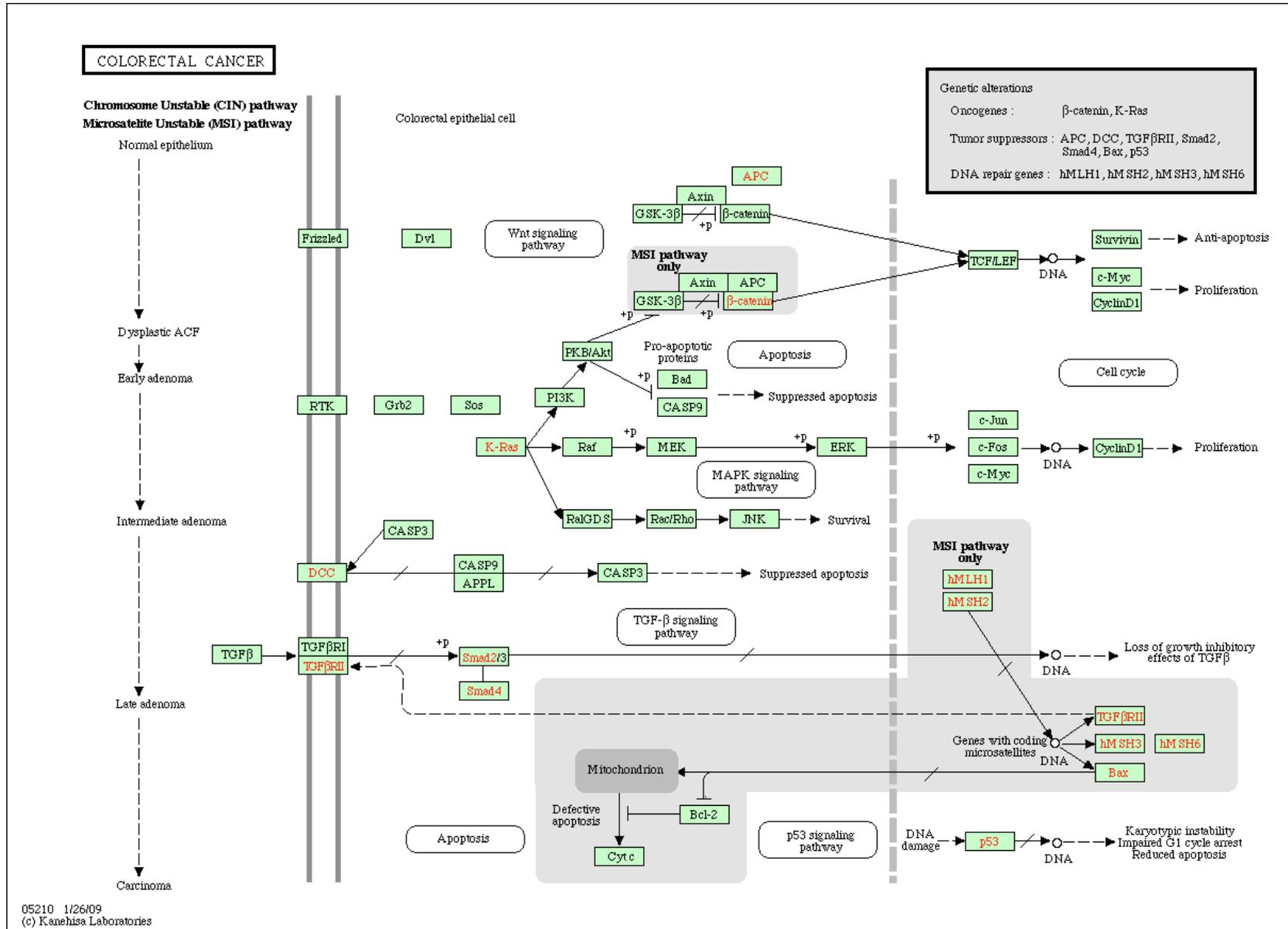
- Metabolism
  - 12 categories
  - Intermediary, secondary, drug metabolism
- Regulatory network
  - 19 categories
  - Genetic and environment information, Cellular processes
- Human diseases
  - Cancer, immune disorders, etc.
- Drug development
  - History, structure and target based design

<http://www.genome.jp/kegg/pathway.html>

# KEGG PATHWAY

## Disease pathway

### Cancer related protein interaction network



# KEGG PATHWAY

## Disease pathway

KEGG PATHWAY: hsa05210

http://www.genome.jp/dbget-bin/www\_bget?pathway+hsa05210

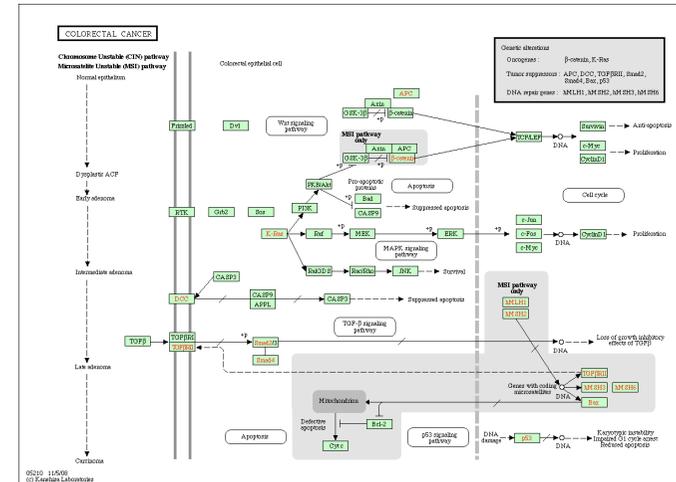
**KEGG PATHWAY: hsa05210**

Help

<b>Entry</b>	hsa05210	Pathway
<b>Name</b>	Colorectal cancer - Homo sapiens (human)	
<b>Description</b>	Classically, colorectal cancer (CRC) has been believed to develop from normal mucosa through the premalignant adenoma by the step-wise accumulation of mutations. All CRC display either microsatellite instability (MSI) or chromosome instability (CIN). MSI occurs in 15% of colon cancers and results from inactivation of the DNA mismatch repair (MMR) system by either MMR gene mutations or hypermethylation of the MLH1 promoter. MSI promotes tumorigenesis through generating mutations in target genes that possess coding microsatellite repeats, such as beta-catenin, TGFBR2 and BAX. CIN is found in the majority of colon cancers and leads to a different pattern of gene alterations that contribute to tumor formation. Genes involved in CIN are those coding for APC, K-ras, SMAD4 and p53.	
<b>Class</b>	Human Diseases; Cancers	
	<a href="#">BRITE hierarchy</a>	
<b>Pathway map</b>	hsa05210 Colorectal cancer	
	<a href="#">All organisms</a> <a href="#">Ortholog table</a>	
<b>Module</b>	M00636 MutS alpha complex M00637 MutS beta complex	
<b>Organism</b>	Homo sapiens (human) [GN:hsa]	
<b>Gene</b>	8321 FZD1 [KO:K02432] 2535 FZD2 [KO:K02235] 7976 FZD3 [KO:K02329] 8322 FZD4 [KO:K02354] 7855 FZD5 [KO:K02375] 8323 FZD6 [KO:K02376]	

**All links**

- Ontology (1)
- KEGG BRITE (1)
- Pathway (8)
- KEGG PATHWAY (8)
- Disease (1)**
- KEGG DISEASE (1)**
- Drug (8)
- KEGG DRUG (9)
- Chemical reaction (9)
- KEGG ENZYME (9)
- Genome (1)
- KEGG GENOME (1)
- Gene (149)
- KEGG ORTHOLOGY (64)
- KEGG GENES (85)
- Literature (20)
- PubMed (20)
- All databases (198)



- Pathway entry
- Description
- Links to:
  - Disease entries
  - Genes and compounds
  - References

# KEGG DISEASE

## Disease pathway

KEGG DISEASE: H00020

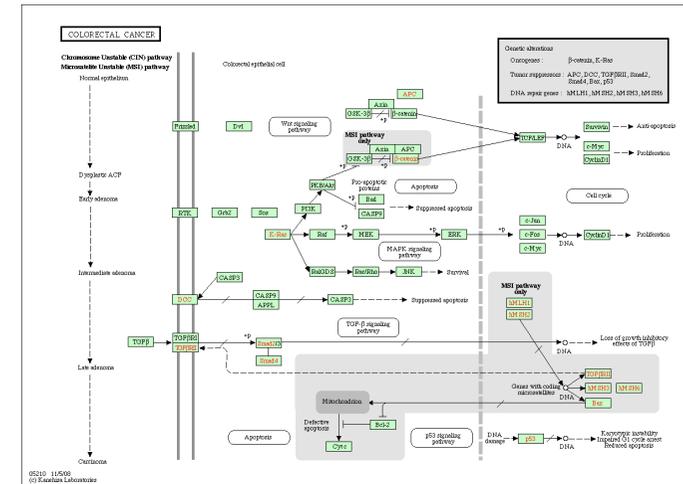
http://www.genome.jp/dbget-bin/www\_bget?ds:H00020

**DISEASE: H00020**

<b>Entry</b>	H00020	Disease
<b>Name</b>	Colorectal cancer	
<b>Description</b>	Colorectal cancer (CRC) is the second largest cause of cancer-related deaths in Western countries. CRC arises from the colorectal epithelium as a result of the accumulation of genetic alterations in defined oncogenes and tumor suppressor genes (TSG). Two major mechanisms of genomic instability have been identified in sporadic CRC progression. The first, known as chromosomal instability (CIN), results from a series of genetic changes that involve the activation of oncogenes such as K-ras and inactivation of TSG such as p53, DCC/Smad4, and APC. The second, known as microsatellite instability (MSI), results from inactivation of the DNA mismatch repair genes MLH1 and/or MSH2 by hypermethylation of their promoter, and secondary mutation of genes with coding microsatellites, such as transforming growth factor receptor II (TGF-RII) and BAX. Hereditary syndromes have germline mutations in specific genes (mutation in the tumor suppressor gene APC on chromosome 5q in FAP, mutated DNA mismatch repair genes in HNPCC) that greatly increase the lifetime risk of developing colorectal cancer (more than 80 per cent in HNPCC) compared with the general population.	
<b>Category</b>	Cancer	
<b>Pathway</b>	hsa05210 Colorectal cancer	
<b>Gene</b>	beta-Catenin (mutation) [HSA:1499] [KO:K02105] K-ras (mutation) [HSA:3845] [KO:K07827] APC (germline mutation (FAP), somatic mutation) [HSA:10297] [KO:K02085] TGF-betaRII (mutation) [HSA:7048] [KO:K04388] Smad2 (mutation) [HSA:4087] [KO:K04500] Smad4 (deletion) [HSA:4089] [KO:K04501] BAX (mutation) [HSA:581] [KO:K02159] p53 (deletion) [HSA:7157] [KO:K04451] MLH1 (germline mutation (HNPCC), LOH, promoter hypermethylation) [HSA:4292] [KO:K08734] MSH2 (germline mutation (HNPCC), LOH, somatic mutation) [HSA:4293] [KO:K08735] MSH3 (somatic frameshift mutation) [HSA:4437] [KO:K08736] MSH6 (germline mutation (HNPCC), LOH, somatic frameshift mutation) [HSA:2956] [KO:K08737]	
<b>Carcinogen</b>	Mineral oils, untreated and mildly treated X- and gamma-radiation	
<b>Marker</b>	Hemoglobin [HSA:3039 3040 3043] K-ras (mutation) [HSA:3845] p53 (mutation) [HSA:7157] APC (mutation) [HSA:10297] BAT-26 (mutation)	
<b>Drug</b>	Oxaliplatin [DR:D01790] 5-Fluorouracil (5-FU) [DR:D00594]	

**All links**

- Ontology (2)
- KEGG BRTE (2)
- Pathway (1)
- KEGG PATHWAY (1)
- Drug (8)
- KEGG DRUG (8)
- Gene (27)
- KEGG ORTHOLOGY (12)
- KEGG GENES (15)
- Literature (8)
- PubMed (8)
- All databases (46)



Pathway map

KEGG PATHWAY: hsa05210

http://www.genome.jp/dbget-bin/www\_bget?pathway+hsa05210

**PATHWAY: hsa05210**

<b>Entry</b>	hsa05210	Pathway
<b>Name</b>	Colorectal cancer - Homo sapiens (human)	
<b>Description</b>	Classically, colorectal cancer (CRC) has been believed to develop from normal mucosa through the premalignant adenoma by the step-wise accumulation of mutations. All CRC display either microsatellite instability (MSI) or chromosome instability (CIN). MSI occurs in 15% of colon cancers and results from inactivation of the DNA mismatch repair (MMR) system by either MMR gene mutations or hypermethylation of the MSH1 promoter. MSI promotes tumorigenesis through generating mutations in target genes that possess coding microsatellite repeats, such as beta-catenin, TGFBR2 and BAX. CIN is found in the majority of colon cancers and leads to a different pattern of gene alterations that contribute to tumor formation. Genes involved in CIN are those coding for APC, K-ras, SMAD4 and p53.	
<b>Human Diseases:</b>	Cancers	
<b>BRTE hierarchy</b>	hsa05210 Colorectal cancer	

**All links**

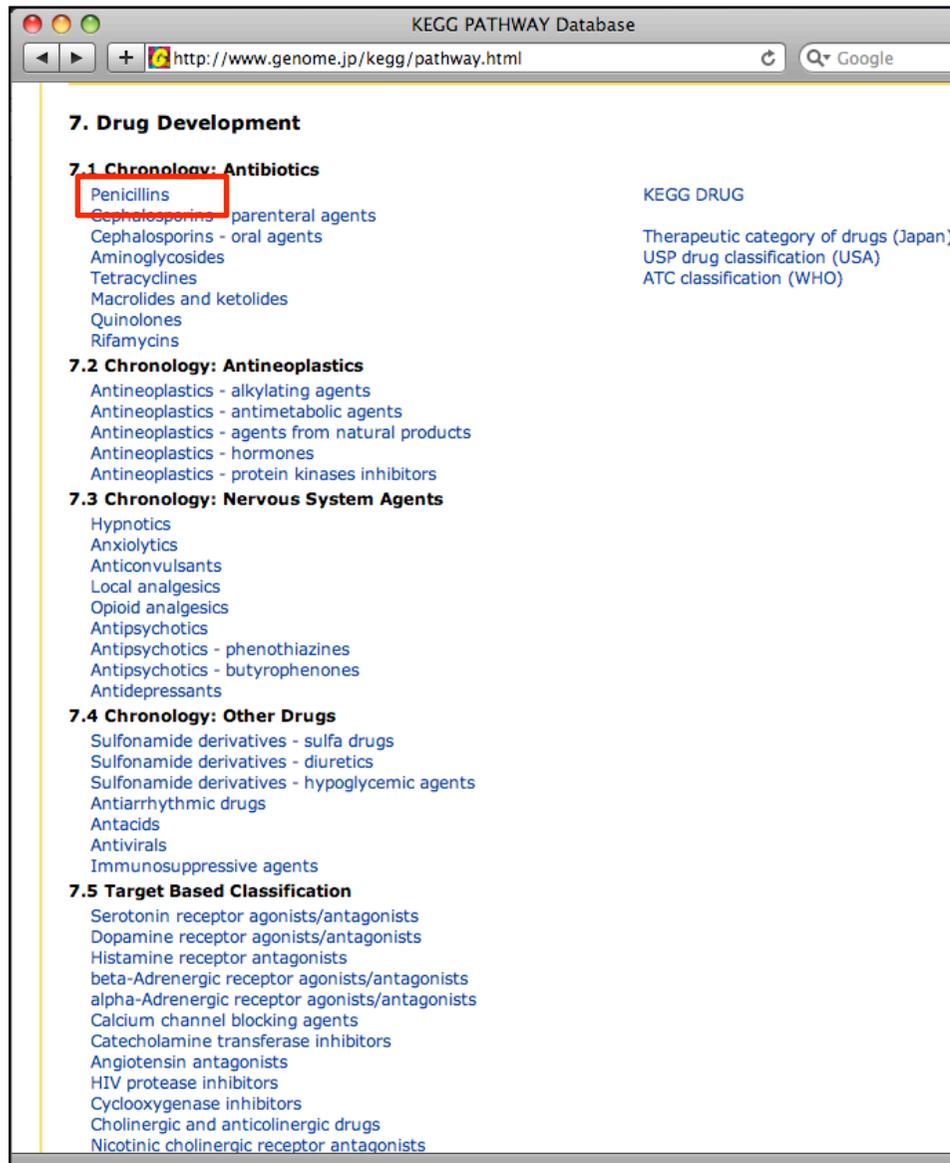
- Ontology (1)
- KEGG BRTE (1)
- Pathway (8)
- Disease (1)
- KEGG PATHWAY (8)
- Drug (9)
- KEGG DRUG (9)
- Chemical reaction (9)
- KEGG ENZYME (9)
- Gene (149)
- KEGG GENE (149)
- KEGG ORTHOLOGY (64)
- KEGG GENES (85)
- Literature (20)
- PubMed (20)
- All databases (198)

Pathway entry

Disease entry  
Responsible genes  
Marker, Drug  
References

# KEGG DRUG

## Drug pathway



KEGG PATHWAY Database

http://www.genome.jp/kegg/pathway.html

**7. Drug Development**

**7.1 Chronology: Antibiotics**

Penicillins

Cephalosporins - parenteral agents

Cephalosporins - oral agents

Aminoglycosides

Tetracyclines

Macrolides and ketolides

Quinolones

Rifamycins

**7.2 Chronology: Antineoplastics**

Antineoplastics - alkylating agents

Antineoplastics - antimetabolic agents

Antineoplastics - agents from natural products

Antineoplastics - hormones

Antineoplastics - protein kinases inhibitors

**7.3 Chronology: Nervous System Agents**

Hypnotics

Anxiolytics

Anticonvulsants

Local analgesics

Opioid analgesics

Antipsychotics

Antipsychotics - phenothiazines

Antipsychotics - butyrophenones

Antidepressants

**7.4 Chronology: Other Drugs**

Sulfonamide derivatives - sulfa drugs

Sulfonamide derivatives - diuretics

Sulfonamide derivatives - hypoglycemic agents

Antiarrhythmic drugs

Antacids

Antivirals

Immunosuppressive agents

**7.5 Target Based Classification**

Serotonin receptor agonists/antagonists

Dopamine receptor agonists/antagonists

Histamine receptor antagonists

beta-Adrenergic receptor agonists/antagonists

alpha-Adrenergic receptor agonists/antagonists

Calcium channel blocking agents

Catecholamine transferase inhibitors

Angiotensin antagonists

HIV protease inhibitors

Cyclooxygenase inhibitors

Cholinergic and anticholinergic drugs

Nicotinic cholinergic receptor antagonists

KEGG DRUG

Therapeutic category of drugs (Japan)

USP drug classification (USA)

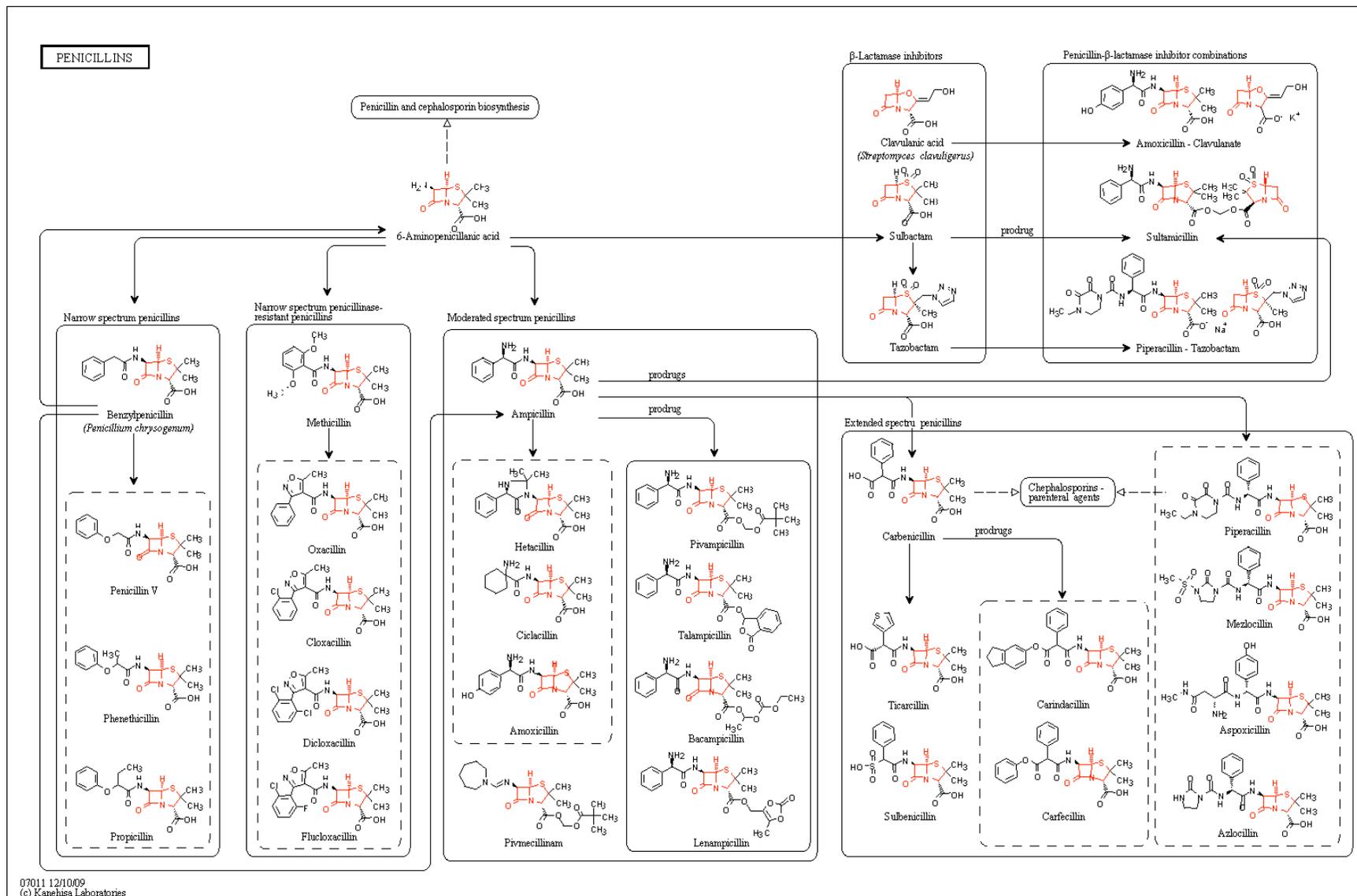
ATC classification (WHO)

- Metabolism
  - 12 categories
  - Intermediary, secondary, drug metabolism
- Regulatory network
  - 19 categories
  - Genetic and environment information, Cellular processes
- Human diseases
  - Cancer, immune disorders, etc.
- Drug development
  - History, structure and target based design

<http://www.genome.jp/kegg/pathway.html>

# KEGG PATHWAY

## Drug pathway



# PATHWAY search

The screenshot shows the KEGG Encyclopedia website. The browser address bar displays <http://www.genome.jp/kegg/kegg2.html>. The page title is "KEGG - Table of Contents". The navigation menu includes KEGG2, ATLAS, PATHWAY, BRITE, KO, GENES, SSDB, LIGAND, and DBGET. A search bar is present with a dropdown menu set to "KEGG" and buttons for "Go" and "Clear". Below the search bar is a table with columns: Category, Entry Point, Release Info, Search & Compute, and DBGET Search. The "Search & Compute" column is highlighted with a red box, and the "DBGET Search" column is highlighted with a blue box. The table lists various search options for Systems information, Genomic information, and Chemical information. At the bottom, there is a section for "KEGG for specific organisms" with a search bar and a "Select" button.

Category	Entry Point	Release Info	Search & Compute	DBGET Search
Systems information	<a href="#">KEGG PATHWAY</a> <a href="#">KEGG BRITE</a>	New maps Update status New hierarchies Update status	Search objects in pathways Color objects in pathways Search objects in Brite <i>New!</i> KEGG pathway modules KEGG Orthology (KO)	PATHWAY BRITE MODULE DISEASE
Genomic information	<a href="#">KEGG ORTHOLOGY</a> <a href="#">KEGG GENES</a>	New organisms Update status	SSDB search BLAST search FASTA search EGassembler for ESTs KAAS automatic annotation	ORTHOLOGY GENES GENOME EGENES VGENES / OGENES VGENOME
Chemical information	<a href="#">KEGG LIGAND</a>	Update status	SIMCOMP compound search KCaM glycan search e-zyme reaction prediction PathComp computation	COMPOUND DRUG GLYCAN REACTION RPAIR ENZYME

- Keyword search

- DBGET system
- For Entry, Name, Description fields

- Keywords

- Glycolysis, Cancer, etc.

- Object search

- Search by objects (genes, orthologs, reactions, compounds) in pathway diagrams

- Keywords: gene names, IDs

- GPI, C00236, etc.

<http://www.genome.jp/kegg/kegg2.html>

# Keyword search for PATHWAY

KEGG PATHWAY Database

Wiring diagrams of molecular interactions, reactions, and relationships

KEGG2 PATHWAY BRITe KO GENES LIGAND DISEASE DRUG

Select prefix:  Organism:  Enter keywords:   [help](#)

### Pathway Maps

KEGG PATHWAY is a collection of manually drawn pathway maps (see [new maps](#), [last update change history](#)) representing our knowledge on the molecular interaction and reaction network.

- Metabolism**  
Carbohydrate Energy Lipid Nucleotide Amino acid Other amino acid Glycan PK/NRP Cofactor/vitamin Secondary metabolite Xenobiotics Overview
- Genetic Information Processing**
- Environmental Information Processing**
- Cellular Processes**
- Organismal Systems**
- Human Diseases**

and also on the structure relationships (KEGG drug structure maps) in:

- Drug Development**

KEGG Atlas may now be used to examine any of the KEGG pathway maps.

### Pathway Entries and Pathway Modules

Pathway entries are text representation of pathway maps, containing descriptions (for a limited entries, at the moment). **Pathway modules** are specification of subnetworks that correspond functional units, each represented as a list of KO identifiers (K numbers).

for

### Pathway Mapping

KEGG PATHWAY mapping is the process to map molecular datasets, especially large-scale data genomics, transcriptomics, proteomics, and metabolomics, to the KEGG pathway maps for biological interpretation of higher-level systemic functions.

- Search objects in KEGG pathways

Pathway Search Result

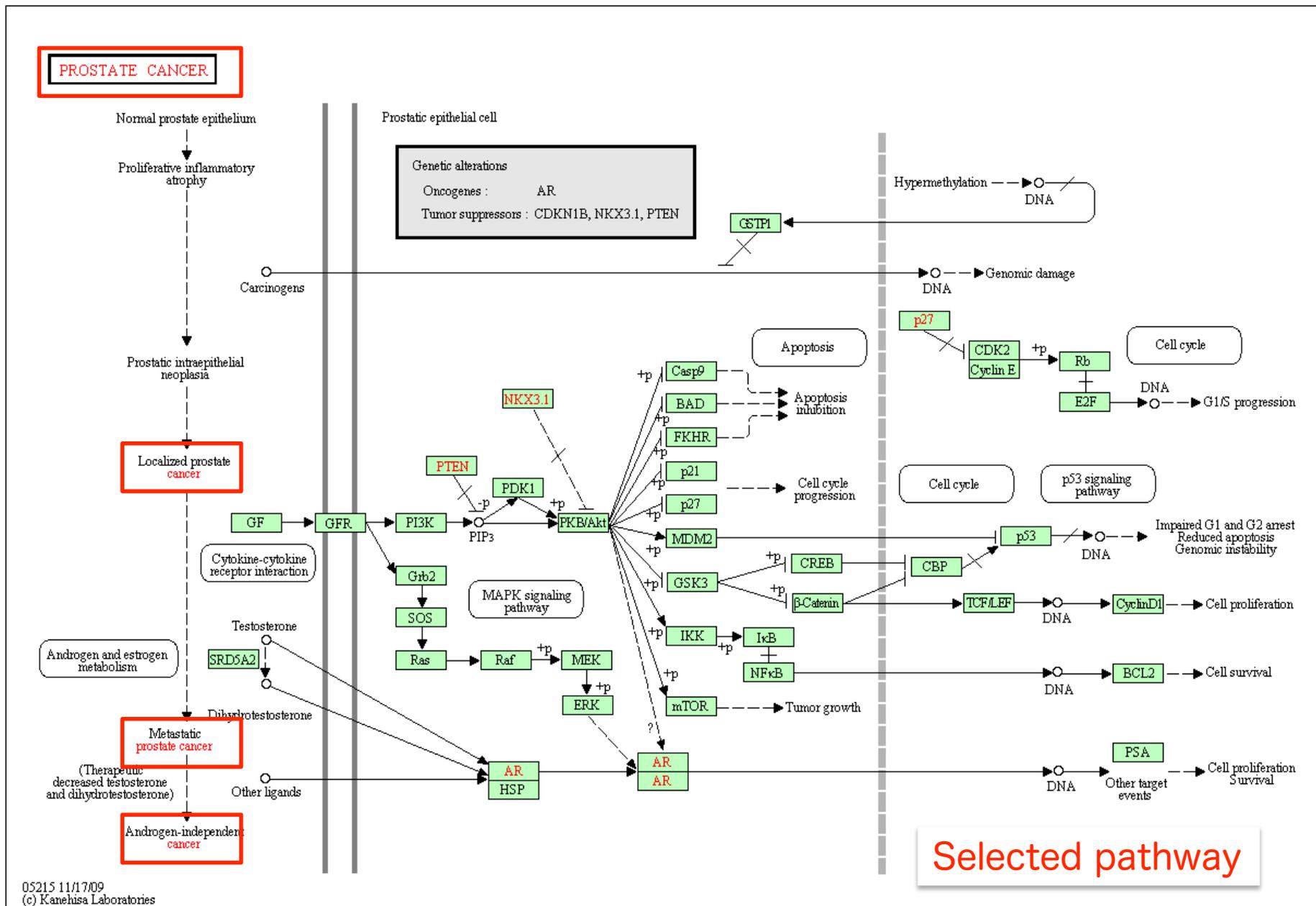
Pathway Text Search

Number of entries in a page: 20

Items: 1 - 14 of 14

Entry	Thumbnail Image	Name	Description	Object	Legend
hsa05215		Prostate cancer - Homo sapiens (human)	...ation of key molecular alterations in prostate-cancer cells implicates carcinogen defenses (GSTP1), ...	C00951 (Estradiol-17beta), C00410 (Progesterone), C07653 (Flutamide), C01227 (3beta-Hydroxyandrost-5...	...signaling pathway PKB/Akt PI3K GSTP1 PROSTATE CANCER Cell cycle ERK MEK Raf Normal prostate epithel...
hsa05210		Colorectal cancer - Homo sapiens (human)	Classically, colorectal cancer (CRC) has been believed to develop from normal mucosa through the pr...	11211 (FZD10), 2535 (FZD2), 7855 (FZD5), 7976 (FZD3), 8321 (FZD1), 8322 (FZD4), 8323 (FZD6), 8324 (F...	...nes : hMLH1, hMSH2, hMSH3, hMSH6 COLORECTAL CANCER DNA DNA DNA DNA 05210 11/17/09
hsa05223		Non-small cell lung cancer - Homo sapiens (human)	Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer and represents a he...	C00777 (Retinoate), C15493 (9-cis-Retinoic acid) C00076 (Calcium) C00165 (Diacylglycerol) C01245 (D-...	...1 p16 PKB/Akt PI3K FHIT NON-SMALL CELL LUNG CANCER ERK MEK Raf K-ras INK4a Alveolar and bronchiol...
hsa05216		Thyroid cancer - Homo sapiens	...thelium, accounts for about 80% of all thyroid cancers. Chimeric	3265 (HRAS), 3845 (KRAS), 4893 (NRAS) 5468 (PPARG) 673 (BRAF) 673 (BRAF)	...MEK PFPF p53 RXR beta-catenin c-Myc ECAD THYROID CANCER FRK

# Keyword search for PATHWAY



# Object search for PATHWAY

The screenshot shows the KEGG PATHWAY Database homepage. At the top, there is a navigation bar with tabs for KEGG2, PATHWAY, BRITE, KO, GENES, LIGAND, DISEASE, DRUG, and DBGET. Below this is a search bar with a 'map' button and a 'Go' button. The main content area is titled 'Pathway Maps' and contains a list of categories: 1. Metabolism, 2. Genetic Information Processing, 3. Environmental Information Processing, 4. Cellular Processes, 5. Organismal Systems, 6. Human Diseases, and 7. Drug Development. A red box highlights the 'Search objects in KEGG pathways' link in the 'Pathway Mapping' section.

The screenshot shows the 'Search Objects in KEGG Pathways' tool. It features a search bar with a dropdown menu set to 'Reference pathway (KO)'. Below the search bar is a text input field containing the example search string: 'ko:K01803 cpd:C00111 cpd:C00118 K00134 C00236'. To the right of the input field are examples for Reference pathway (KO), Reference pathway (EC), and Homo sapiens pathway. Below the input field is a checkbox labeled 'Display objects NOT found in the search' which is checked. At the bottom of the search area are 'Exec' and 'Clear' buttons, with the 'Exec' button highlighted by a red box.

## • Object search

- Genes, orthologs, reactions, compounds in pathway diagrams
- Keywords: gene names, IDs GPI, C00236, etc.
- Try yourself by copying & pasting from the example

<http://www.genome.jp/kegg/pathway.html>

# Object search for PATHWAY

Search PATHWAY  
http://www.genome.jp/kegg-bin/search\_pathway\_object

### Pathway Search Result

Sort by the pathway list

Show all objects

- ko00010 Glycolysis / Gluconeogenesis (5)
- ko01100 Metabolic pathways (5)
- ko00710 Carbon fixation in photosynthetic organisms (4)
- ko00562 Inositol phosphate metabolism (3)
- ko01062 Biosynthesis of terpenoids and steroids (3)
- ko01061 Biosynthesis of phenylpropanoids (3)
- ko01063 Biosynthesis of alkaloids derived from shikimate pathway (3)
- ko00051 Fructose and mannose metabolism (3)
- ko00040 Pentose and glucuronate interconversions (2)
- ko00052 Galactose metabolism (2)
- ko01065 Biosynthesis of alkaloids derived from histidine pathway (2)
- ko01066 Biosynthesis of alkaloids derived from terpenoid pathway (2)
- ko01064 Biosynthesis of alkaloids derived from ornithine pathway (2)
- ko01070 Biosynthesis of plant hormones (2)
- ko00730 Thiamine metabolism (1)
- ko05010 Alzheimer's disease (1)
- ko00750 Vitamin B6 metabolism (1)
- ko00760 Nicotinate and nicotinamide metabolism (1)
- ko00680 Methane metabolism (1)
- ko00900 Terpenoid backbone biosynthesis (1)
- ko00030 Pentose phosphate pathway (1)
- ko00620 Pyruvate metabolism (1)
- ko00561 Glycerolipid metabolism (1)
- ko00564 Glycerophospholipid metabolism (1)
- ko00331 Clavulanic acid biosynthesis (1)

Search PATHWAY  
http://www.genome.jp/kegg-bin/search\_pathway\_object

### Pathway Search Result

Sort by the pathway list

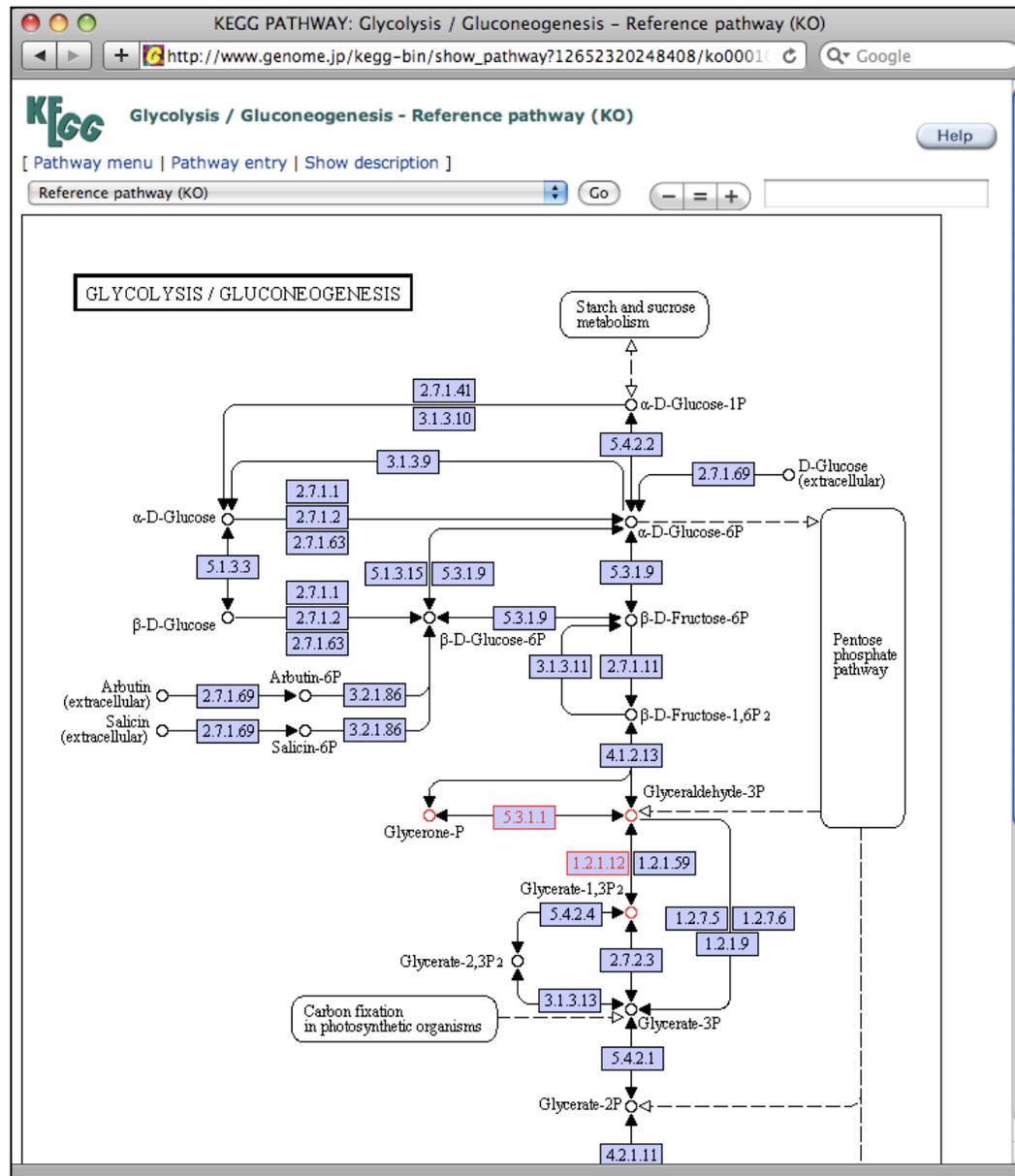
Hide all objects

- ko00010 Glycolysis / Gluconeogenesis (5)
  - cpd:C00111 Glycerone phosphate; Dihydroxyacetone phosphate
  - cpd:C00118 D-Glyceraldehyde 3-phosphate; (2R)-2-Hydroxy-3-(phosphonoxy)-propanal; Glyceraldehyde 3-phosphate
  - cpd:C00236 3-Phospho-D-glyceroyl phosphate; 1,3-Bisphospho-D-glycerate; (R)-2-Hydroxy-3-(phosphonoxy)-propanal
  - ko:K00134 GAPDH, gapA; glyceraldehyde 3-phosphate dehydrogenase [EC:1.2.1.12]
  - ko:K01803 TPI, tpiA; triosephosphate isomerase (TIM) [EC:5.3.1.1]
- ko01100 Metabolic pathways (5)
  - cpd:C00111 Glycerone phosphate; Dihydroxyacetone phosphate
  - cpd:C00118 D-Glyceraldehyde 3-phosphate; (2R)-2-Hydroxy-3-(phosphonoxy)-propanal; Glyceraldehyde 3-phosphate
  - cpd:C00236 3-Phospho-D-glyceroyl phosphate; 1,3-Bisphospho-D-glycerate; (R)-2-Hydroxy-3-(phosphonoxy)-propanal
  - ko:K00134 GAPDH, gapA; glyceraldehyde 3-phosphate dehydrogenase [EC:1.2.1.12]
  - ko:K01803 TPI, tpiA; triosephosphate isomerase (TIM) [EC:5.3.1.1]
- ko00710 Carbon fixation in photosynthetic organisms (4)
  - cpd:C00111 Glycerone phosphate; Dihydroxyacetone phosphate
  - cpd:C00118 D-Glyceraldehyde 3-phosphate; (2R)-2-Hydroxy-3-(phosphonoxy)-propanal; Glyceraldehyde 3-phosphate
  - cpd:C00236 3-Phospho-D-glyceroyl phosphate; 1,3-Bisphospho-D-glycerate; (R)-2-Hydroxy-3-(phosphonoxy)-propanal
  - ko:K00134 GAPDH, gapA; glyceraldehyde 3-phosphate dehydrogenase [EC:1.2.1.12]
  - ko:K01803 TPI, tpiA; triosephosphate isomerase (TIM) [EC:5.3.1.1]
- ko00562 Inositol phosphate metabolism (3)
  - cpd:C00111 Glycerone phosphate; Dihydroxyacetone phosphate
  - cpd:C00118 D-Glyceraldehyde 3-phosphate; (2R)-2-Hydroxy-3-(phosphonoxy)-propanal; Glyceraldehyde 3-phosphate
  - ko:K01803 TPI, tpiA; triosephosphate isomerase (TIM) [EC:5.3.1.1]
- ko01062 Biosynthesis of terpenoids and steroids (3)
  - cpd:C00111 Glycerone phosphate; Dihydroxyacetone phosphate
  - cpd:C00118 D-Glyceraldehyde 3-phosphate; (2R)-2-Hydroxy-3-(phosphonoxy)-propanal; Glyceraldehyde 3-phosphate
  - cpd:C00236 3-Phospho-D-glyceroyl phosphate; 1,3-Bisphospho-D-glycerate; (R)-2-Hydroxy-3-(phosphonoxy)-propanal
  - ko:K00134 GAPDH, gapA; glyceraldehyde 3-phosphate dehydrogenase [EC:1.2.1.12]
  - ko:K01803 TPI, tpiA; triosephosphate isomerase (TIM) [EC:5.3.1.1]
- ko01061 Biosynthesis of phenylpropanoids (3)
  - cpd:C00111 Glycerone phosphate; Dihydroxyacetone phosphate
  - cpd:C00118 D-Glyceraldehyde 3-phosphate; (2R)-2-Hydroxy-3-(phosphonoxy)-propanal; Glyceraldehyde 3-phosphate
  - cpd:C00236 3-Phospho-D-glyceroyl phosphate; 1,3-Bisphospho-D-glycerate; (R)-2-Hydroxy-3-(phosphonoxy)-propanal
  - ko:K00134 GAPDH, gapA; glyceraldehyde 3-phosphate dehydrogenase [EC:1.2.1.12]
  - ko:K01803 TPI, tpiA; triosephosphate isomerase (TIM) [EC:5.3.1.1]
- ko01063 Biosynthesis of alkaloids derived from shikimate pathway (3)
  - cpd:C00111 Glycerone phosphate; Dihydroxyacetone phosphate
  - cpd:C00118 D-Glyceraldehyde 3-phosphate; (2R)-2-Hydroxy-3-(phosphonoxy)-propanal; Glyceraldehyde 3-phosphate
  - cpd:C00236 3-Phospho-D-glyceroyl phosphate; 1,3-Bisphospho-D-glycerate; (R)-2-Hydroxy-3-(phosphonoxy)-propanal
  - ko:K00134 GAPDH, gapA; glyceraldehyde 3-phosphate dehydrogenase [EC:1.2.1.12]
  - ko:K01803 TPI, tpiA; triosephosphate isomerase (TIM) [EC:5.3.1.1]
- ko00051 Fructose and mannose metabolism (3)
  - cpd:C00111 Glycerone phosphate; Dihydroxyacetone phosphate
  - cpd:C00118 D-Glyceraldehyde 3-phosphate; (2R)-2-Hydroxy-3-(phosphonoxy)-propanal; Glyceraldehyde 3-phosphate
  - cpd:C00236 3-Phospho-D-glyceroyl phosphate; 1,3-Bisphospho-D-glycerate; (R)-2-Hydroxy-3-(phosphonoxy)-propanal
  - ko:K00134 GAPDH, gapA; glyceraldehyde 3-phosphate dehydrogenase [EC:1.2.1.12]
  - ko:K01803 TPI, tpiA; triosephosphate isomerase (TIM) [EC:5.3.1.1]

## • Search results by objects

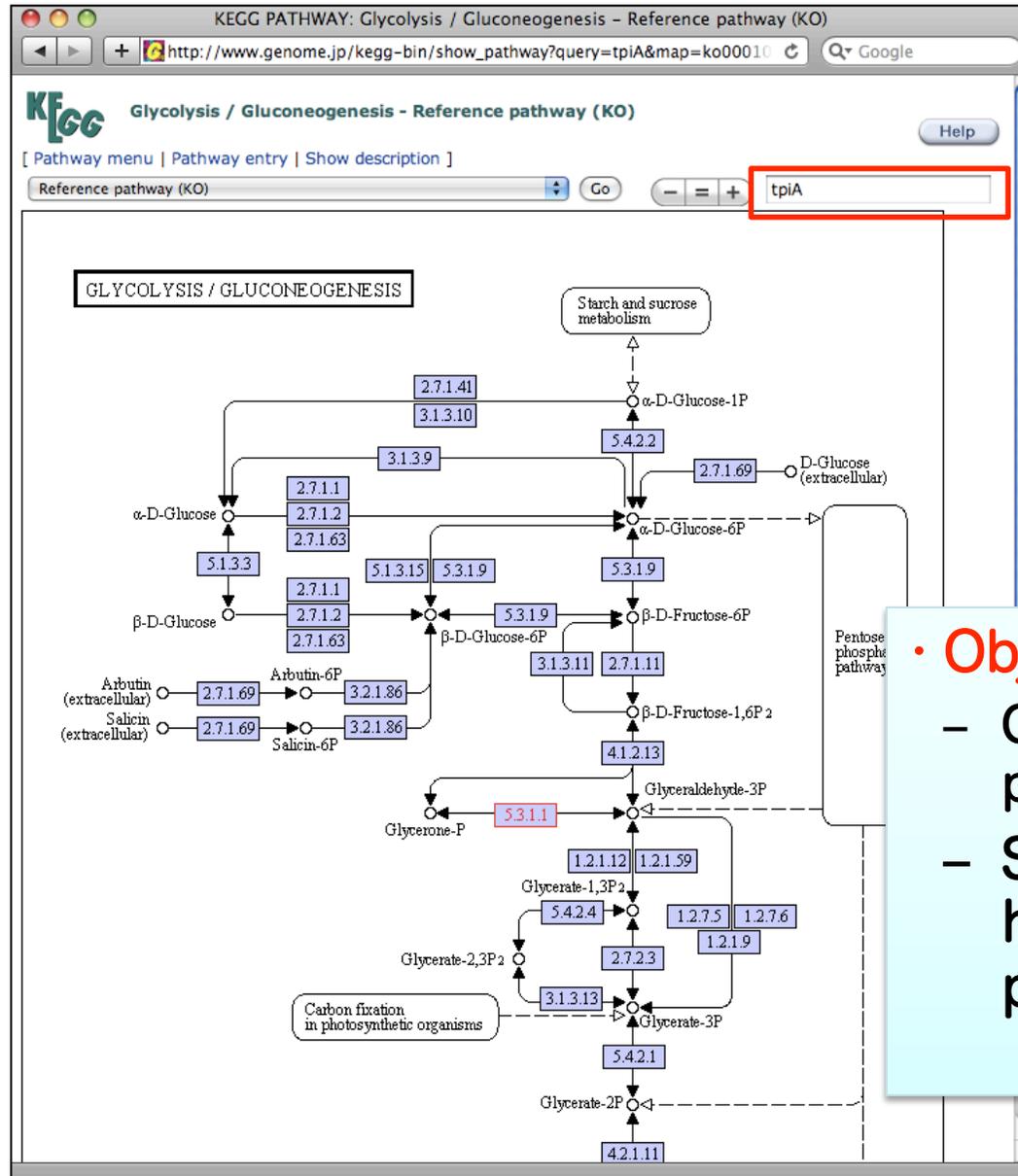
- List of hit pathways & input objects
- For unique IDs in KEGG databases such as C numbers for compounds, K numbers for orthologies, database name can be omitted

# Object search for PATHWAY



Selected pathway resulting from the object search, with inputted objects colored according to default parameters

# Object search for PATHWAY



## • Object search

- Can search within the selected pathway
- Selected objects will be highlighted within the target pathway

# Specify colors for objects in PATHWAY

The screenshot shows the KEGG PATHWAY Database homepage. The main navigation bar includes links for KEGG2, PATHWAY, BRITE, KO, GENES, LIGAND, DISEASE, DRUG, and DBGET. Below this is a search area with a 'Select prefix' dropdown (set to 'map') and an 'Enter keywords' input field. The 'Pathway Maps' section describes the database and lists categories: 1. Metabolism, 2. Genetic Information Processing, 3. Environmental Information Processing, 4. Cellular Processes, 5. Organismal Systems, 6. Human Diseases, and 7. Drug Development. A 'Pathway Mapping' section is also visible, with a red box highlighting the link 'Color objects in KEGG pathways'.

The screenshot shows the 'Color Objects in KEGG Pathways' tool interface. It features a search area with a 'Search against:' dropdown (set to 'Reference pathway (KO)') and an input field for 'Enter objects one per line followed by bgcolor, fgcolor:'. A red box highlights the input text: 'K01803 red,blue' and 'C00118 pink'. To the right, 'Examples:' are provided for both 'Reference pathway (KO)' and '(Homo sapiens pathway)'. Below the input field is a file selection button and a 'Default bgcolor' dropdown (set to 'pink'). A red box highlights the 'Exec' button. A light blue callout box is overlaid on the right side of the screenshot.

- Same as before for object search
- Can specify colors for each object (html acceptable color names)
- Try copying & pasting from the examples

<http://www.genome.jp/kegg/pathway.html>

# Specify colors for objects in PATHWAY

Search PATHWAY

http://www.genome.jp/kegg-bin/color\_pathway\_object

### Pathway Search Result

Sort by the pathway list

Show all objects

- ko00562 Inositol phosphate metabolism (2)
- ko00010 Glycolysis / Gluconeogenesis (2)**
- ko01100 Metabolic pathways (2)
- ko00710 Carbon fixation in photosynthetic organisms (2)
- ko00051 Fructose and mannose metabolism (2)
- ko00730 Thiamine metabolism (1)
- ko00040 Pentose and glucuronate interconversions (1)
- ko01062 Biosynthesis of terpenoids and steroids (1)
- ko01061 Biosynthesis of phenylpropanoids (1)
- ko00750 Vitamin B6 metabolism (1)
- ko01063 Biosynthesis of alkaloids derived from shikimate pathway (1)
- ko00680 Methane metabolism (1)
- ko00900 Terpenoid backbone biosynthesis (1)
- ko00030 Pentose phosphate pathway (1)
- ko00052 Galactose metabolism (1)
- ko01065 Biosynthesis of alkaloids derived from histidine and purine (1)
- ko01066 Biosynthesis of alkaloids derived from terpenoid and polyketide (1)
- ko00331 Clavulanic acid biosynthesis (1)
- ko01064 Biosynthesis of alkaloids derived from ornithine, lysine and nicotinic acid (1)
- ko01070 Biosynthesis of plant hormones (1)

KEGG PATHWAY: Glycolysis / Gluconeogenesis - Reference pathway (KO)

http://www.genome.jp/kegg-bin/show\_pathway?126523305312876/ko00010

### Glycolysis / Gluconeogenesis - Reference pathway (KO)

[ Pathway menu | Pathway entry | Show description ]

Reference pathway (KO)

Starch and sucrose metabolism

α-D-Glucose-1P

α-D-Glucose

β-D-Glucose

Arbutin (extracellular)

Salicin (extracellular)

Arbutin-6P

Salicin-6P

α-D-Glucose-6P

β-D-Glucose-6P

β-D-Fructose-6P

β-D-Fructose-1,6P2

Glycerone-P

Glyceraldehyde-3P

Glycerate-1,3P2

Glycerate-2,3P2

Glycerate-3P

Glycerate-2P

Pentose phosphate pathway

Carbon fixation in photosynthetic organisms

# Specify colors for objects in PATHWAY

Use sample microarray data

<http://metabolomics.se/Courses/test.txt>

The screenshot shows a web browser window with the URL [http://www.genome.jp/kegg/tool/color\\_pathway.html](http://www.genome.jp/kegg/tool/color_pathway.html). The page title is "Color Objects in KEGG Pathways". The interface includes a navigation menu with "KEGG2", "KEGG Atlas", "Search Pathway", "Color Pathway", "Search Brite", and "Color Brite". The "Color Pathway" tab is active. Below the menu, there is a "Search against:" dropdown menu set to "Mus musculus (mouse)". A text input field contains the following text: "19156 red", "18946 red", "109791 red", "20250 red", "20397 red", "21991 red", "20249 red", "71780 red", "110611 red", "56703 red". To the right of this field, there are "Examples:" showing "Reference pathway (KO)" with "K01803 red,blue" and "C00118 pink", and "Homo sapiens pathway" with "7167 red,blue" and "C00118 pink". Below the input field, there is a section "Alternatively, enter the file name containing the data:" with a file selection button and the text "ファイルを選択 ファイルが選択されていません". There is also a field "If necessary, change default bgcolor:" with the value "pink". Checkboxes for "Include aliases" (checked), "Use uncolored diagrams" (unchecked), and "Display objects not found in the search" (checked) are present. "Exec" and "Clear" buttons are at the bottom. A note at the bottom states: "(Note) The mapping is based on the KEGG identifiers for molecular objects shown below." Below the note is a table:

Prefix Type	KEGG identifier	Alias
map	Reference pathway - metabolic	K/R/EC numbers, C/G/D numbers
map	Reference pathway - non-metabolic	K number, C/G/D numbers
ko	Reference pathway (KO)	K number, C/G/D numbers
ec	Reference pathway (EC)	EC number, C/G/D numbers

Specify an organism (mouse in this example)

Copy & paste data, or access the data from the test file test.txt

Specify colors for genes not in the input list.



# Specify colors for objects in PATHWAY

Search PATHWAY

http://www.genome.jp/kegg-bin/color\_pathway\_object

### Pathway Search Result

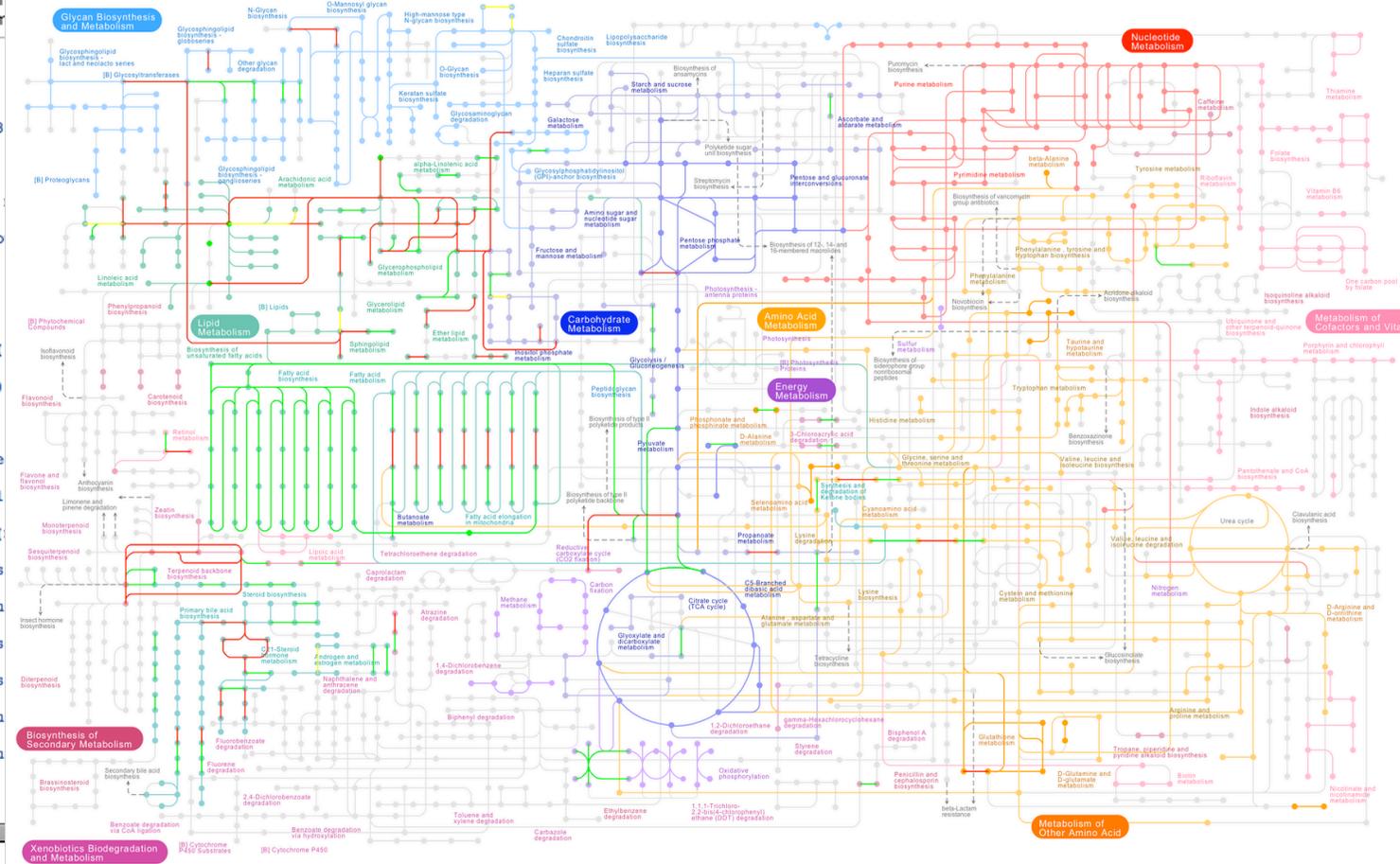
Following object(s) was/were not found cpd:C01712 cpd:C08322 mmu:100102 mmu:100273 mmu:109791 mmu:110611 mmu:114874 mmu:11576 mmu:11813 mmu:12007 mmu:12683 mmu:12686 mmu:12908 mmu:13863 mmu:14149 mmu:14245 mmu:14422 mmu:16181 mmu:16795 mmu:16922 mmu:170459 mmu:170461 mmu:170789 mmu:17777 mmu:18391 mmu:20186 mmu:20388 mmu:20845 mmu:20865 mmu:22229 mmu:22359 mmu:22428 mmu:226856 mmu:228983 mmu:230101 mmu:233549 mmu:234407 mmu:237320 mmu:23801 mmu:239759 mmu:240633 mmu:241230 mmu:241447 mmu:269437 mmu:30924 mmu:320581 mmu:329910 mmu:51798 mmu:52123 mmu:54325 mmu:56351 mmu:56453 mmu:56794 mmu:59045 mmu:64291 mmu:65107 mmu:66776 mmu:67260 mmu:67331 mmu:67618 mmu:67815 mmu:68177 mmu:70568 mmu:71720 mmu:71949 mmu:74032 mmu:74114 mmu:79196 mmu:83603 mmu:85031 mmu:93898 mmu:99031 mmu:

Can perform global mapping

Sort by the pathway list

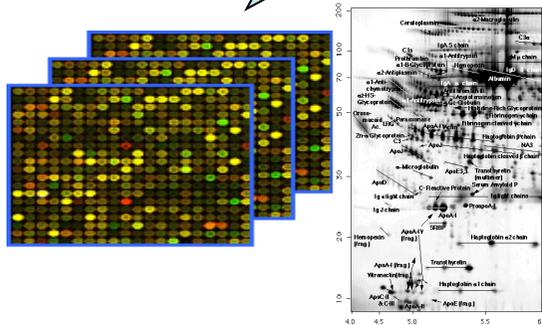
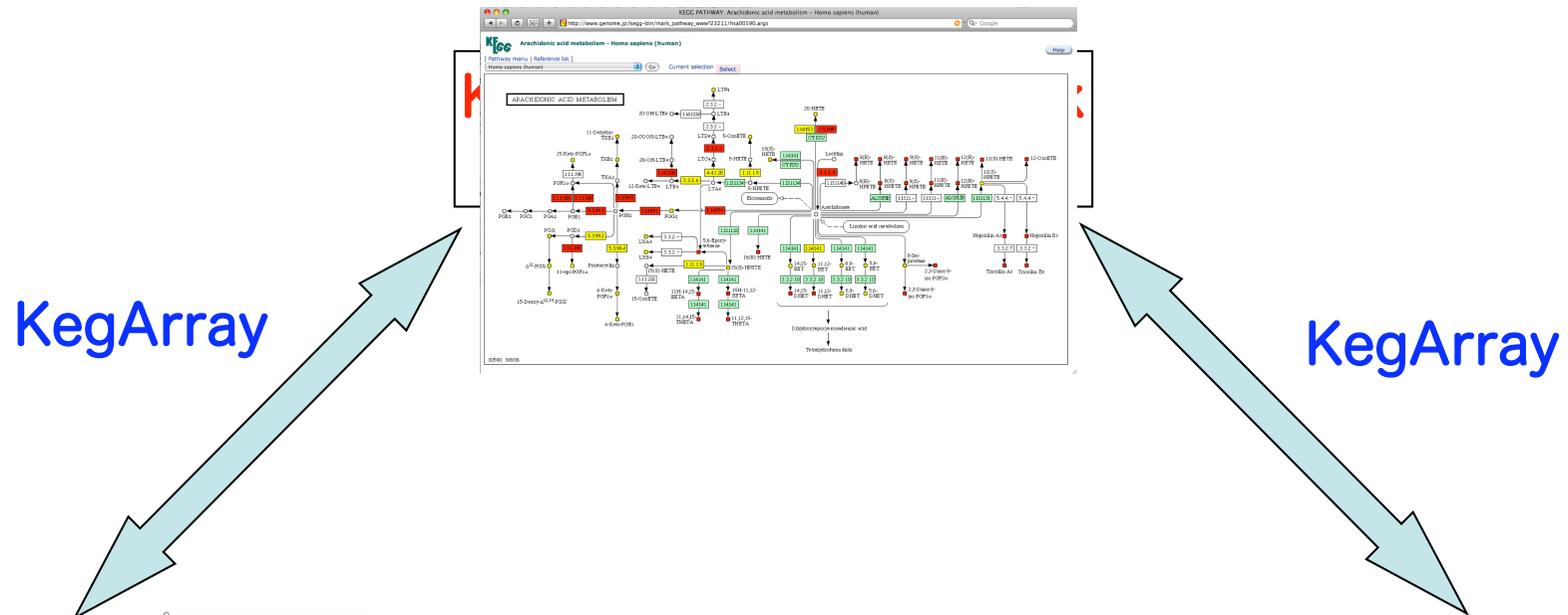
Show all objects

- mmu01100 Metabolic pathways - Mus musculus (mouse) 133
- mmu00564 Glycerophospholipid metabolism - Mus musculus
- mmu01040 Biosynthesis of unsaturated fatty acids - Mus musculus
- mmu00590 Arachidonic acid metabolism - Mus musculus (mouse)
- mmu03320 PPAR signaling pathway - Mus musculus (mouse)
- mmu00565 Ether lipid metabolism - Mus musculus (mouse)
- mmu00071 Fatty acid metabolism - Mus musculus (mouse)
- mmu00600 Sphingolipid metabolism - Mus musculus (mouse)
- mmu04912 GnRH signaling pathway - Mus musculus (mouse)
- mmu00591 Linoleic acid metabolism - Mus musculus (mouse)
- mmu04730 Long-term depression - Mus musculus (mouse)
- mmu00562 Inositol phosphate metabolism - Mus musculus (mouse)
- mmu04664 Fc epsilon RI signaling pathway - Mus musculus (mouse)
- mmu04070 Phosphatidylinositol signaling system - Mus musculus (mouse)
- mmu00592 alpha-Linolenic acid metabolism - Mus musculus (mouse)
- mmu04920 Adipocytokine signaling pathway - Mus musculus (mouse)
- mmu04270 Vascular smooth muscle contraction - Mus musculus (mouse)
- mmu04666 Fc gamma R-mediated phagocytosis - Mus musculus (mouse)
- mmu04370 VEGF signaling pathway - Mus musculus (mouse)

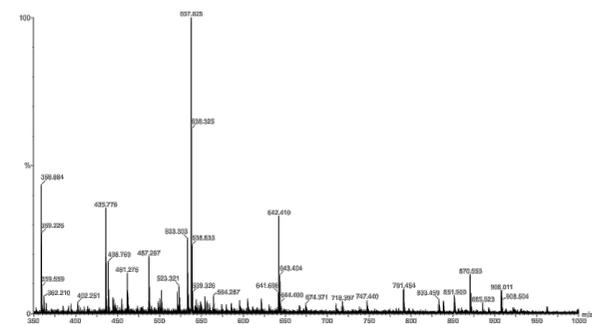


# Omic data and PATHWAY

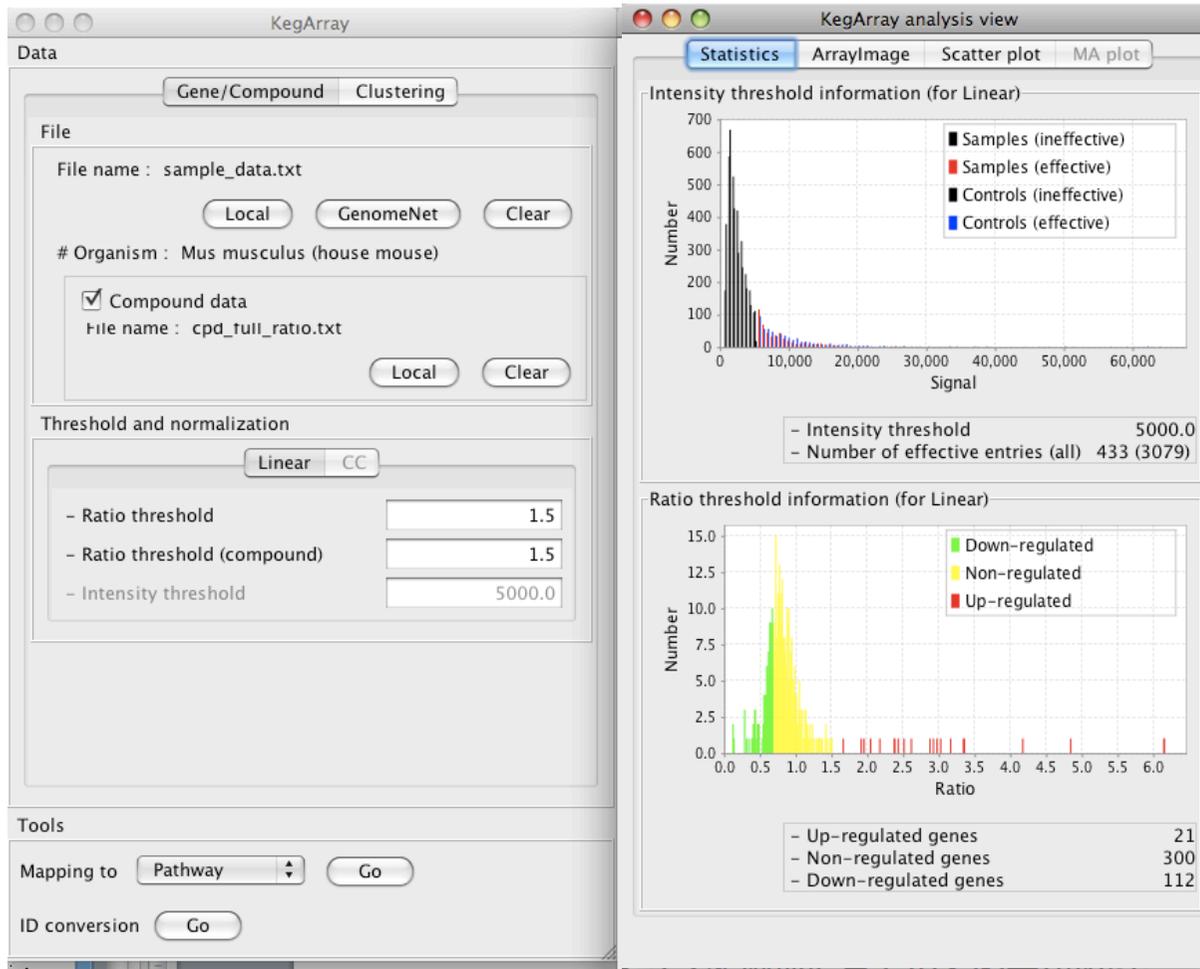
Linking biological knowledge to omics data



Transcriptome  
Proteome  
Metabolome



# KegArray



- Java application linking KEGG and omics data
- Genes / Proteins
  - Ratio, Intensity
- Chemical compounds
  - Ratio
- Distribution map for setting threshold values
  - Color code setting

## ID Conversion

Gene ID : GenBank, ENSEMBL -> KEGG ID

Protein ID : UniProt, IPI -> KEGG ID

- Links to **PATHWAY**
- Links to functional classifications

# KegArray



# Downloading KegArray

KEGG: Kyoto Encyclopedia of Genes and Genomes

<http://www.genome.jp/kegg/>

Search KEGG Get Entry

**KEGG: Kyoto Encyclopedia of Genes and Genomes**

A grand challenge in the post-genomic era is a complete computer representation of the cell, the organism, and the biosphere, which will enable computational prediction of higher-level complexity of cellular processes and organism behaviors from genomic and molecular information. Towards this end we have been developing a bioinformatics resource named KEGG as part of the research projects of the Kanehisa Laboratories in the Bioinformatics Center of Kyoto University and the Human Genome Center of the University of Tokyo.

- Main entry point to the KEGG web service**
  - [KEGG2](#) KEGG Table of Contents Update notes Help
- Data-oriented entry points**
  - [KEGG Atlas](#) Global maps of cell/organism functions
  - [KEGG PATHWAY](#) Pathway maps and pathway modules
  - [KEGG BRITE](#) Functional hierarchies and ontologies
  - [KEGG GENES](#) Genomes, genes, proteins, and orthologs
  - [KEGG LIGAND](#) Chemical compounds, drugs, glycans, and reactions
- Organism-specific entry points**
  - [KEGG Organisms](#) Select   (example) [hsa](#)
- Subject-specific entry points**
  - [KEGG DISEASE](#) Gene/molecule based disease information resource
  - [KEGG DRUG](#) Chemical structure based drug information resource
  - [KEGG GLYCAN](#) Glycome informatics resource
  - [KEGG COMPOUND](#) Knowledge base for biochemical compounds
  - [KEGG REACTION](#) Knowledge base for biochemical reactions
  - [KAAS](#) KEGG automatic annotation server

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KEGG - Software

<http://www.genome.jp/kegg/download/kegtools.html>

Search KEGG Get Entry

**KEGG Software for Distribution**

**KegTools**

**KegTools** are desktop applications that run on the Mac OS X, Windows, and Linux platforms. Currently, the following three applications are available.

- KegHier** for browsing and searching functional hierarchies in KEGG BRITE as well as for manipulating locally created hierarchical text files
- KegArray** for analysis of transcriptome data (gene expression profiles) and metabolome data (compound profiles) in conjunction with KEGG pathway maps and genome maps
- KegDraw** for drawing chemical compound structures and glycan structures with capabilities to search against the KEGG databases

Both academic and non-academic users may download the applications for personal use.

<http://www.genome.jp/download/>

**iKeg Server**

**iKeg server** is a commercial product distributed by [Pathway Solutions](#). It allows local implementation and customization of KEGG, as well as synchronization with the KEGG web server at GenomeNet. iKeg runs on Linux and Mac OS X. Contact [Pathway Solutions](#) for more details.

Last updated: July 7, 2007

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<http://www.genome.jp/kegg/>

<http://www.genome.jp/kegg/download/kegtools.html>

# KegArray



## Downloading KegArray

The screenshot shows the download page for KegHier, KegArray, and KegDraw. The KegArray section is highlighted with a red box around the download link for Mac OS X [dmg].

**KegHier**  
Java application for browsing hierarchical text files

- KegHier 0.4.0beta (May 1, 2008) for Mac OSX [dmg] Windows (exe) [zip] Windows (jar/bat) [zip] Linux [tar.gz]
- ReadMe file
- About KegHier

Please send your comments and suggestions through the [feedback form](#).

---

**KegArray**  
Java application for microarray data analysis

- KegArray 1.2.0 (November 11, 2008) for Mac OSX [dmg] Windows (exe) [zip] Windows (jar/bat) [zip] Linux [tar.gz]
- ReadMe file

Please send your comments and suggestions through the [feedback form](#).

---

**KegDraw**  
Java application for drawing compound and glycan structures

- KegDraw 0.1.9beta (September 22, 2008) for Mac OSX [dmg] Windows (exe) [zip] Windows (jar/bat) [zip] Linux [tar.gz]
- ReadMe file

Please send your comments and suggestions through the [feedback form](#).

[ [KEGG](#) | [GenomeNet](#) ]



Just double click the icon

The screenshot shows the KegArray application interface. The 'Load data from EXPRESSION' dialog box is open, showing a list of entry IDs. The entry ID 'ex0000143' is selected. The dialog box displays the following information:

entry ID : ex0000143

- Organism: Synechocystis
- Definition: Synechocystis PCC6803 acclimation, exposed to high light...
- Control: WT (GT), incubated to OD730=0.679 at 20 uEm-2s-1
- Target: WT (GT), incubated for 15 minutes at 300 uEm-2s-1

The 'load' button is visible at the bottom of the dialog box.

<http://www.genome.jp/download/>

# KegArray



The screenshot displays the KegArray software interface, divided into two main windows: 'KegArray' and 'KegArray analysis view'.

**KegArray Window:**

- Data:** Includes tabs for 'Gene/Compound' and 'Clustering'. The 'File' section shows 'File name: ex:ex0000143' with 'Local' and 'GenomeNet' buttons. The '# Organism' is 'Synechocystis sp. PCC 6803'. A 'Compound data' section is checked, with a 'File name' field and 'Local'/'Clear' buttons.
- Threshold and normalization:** Features 'Linear' and 'CC' tabs. The 'Linear' tab is active, showing:
  - Ratio threshold: 1.5
  - Ratio threshold (compound): 1.5
  - Intensity threshold: 5000.0'Cancel' and 'Apply' buttons are present.
- Tools:** Includes 'Mapping to' (set to 'Pathway') and 'ID conversion' (set to 'Go') buttons.

**KegArray analysis view Window:**

- Statistics:** Shows 'Intensity threshold information (for Linear)' with a histogram of 'Number' vs 'Signal'. The legend includes:
  - Samples (ineffective)
  - Samples (effective)
  - Controls (ineffective)
  - Controls (effective)Summary statistics:
  - Intensity threshold: 5000.0
  - Number of effective entries (all): 276 (3079)
- Ratio threshold information (for Linear):** Shows a histogram of 'Number' vs 'Ratio'. The legend includes:
  - Down-regulated
  - Non-regulated
  - Up-regulatedSummary statistics:
  - Up-regulated genes: 11
  - Non-regulated genes: 188
  - Down-regulated genes: 77
- ArrayImage, Scatter plot, MA plot:** These tabs are visible at the top of the analysis view window.

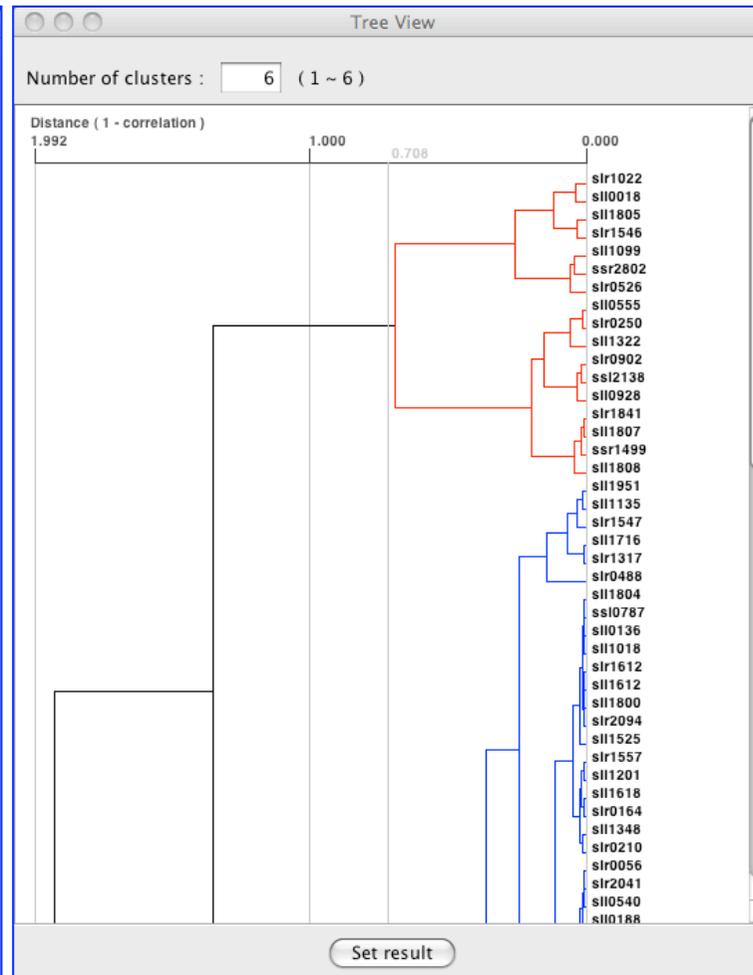
- Read array data
- Set threshold by examining Analysis view
- Set color codes
  - KegArray -> Preferences -> Color
- See related PATHWAY, BRITE, and GENOME data by Mapping Tools
- ID conversions

# KegArray



Simple clustering for arrays

The screenshot shows the 'KegArray' application window. It has a 'Data' section with 'Gene/Compound' and 'Clustering' tabs. Under 'Files', there are buttons for 'Local', 'GenomeNet', and 'Clear'. A list of files is shown: ex0000142, ex0000143, ex0000144, ex0000145, and ex0000146. A 'Clustering' button is at the bottom of this section. Below is 'Information of selected entries' showing '- Organism: Synechocystis sp. PCC 6803' and '- Number of files: 5'. The 'Parameters' section includes '- Intensity threshold: 5000' and '- Clustering algorithm: Complete linkage'. At the bottom, there are 'Tools' for 'Mapping to Pathway' and 'ID conversion'.



1. Read array data by GenomeNet or Local button
2. Clustering
3. Specify the number of clusters
4. Set result, then can map it to PATHWAY, etc

# KegArray



Also accepts metabolomics data

Use sample data

[http://metabolomics.se/Courses/sample\\_data.txt](http://metabolomics.se/Courses/sample_data.txt)

[http://metabolomics.se/Courses/sample\\_cpd.txt](http://metabolomics.se/Courses/sample_cpd.txt)

File -> Save as -> save on the desktop

Read sample\_data.txt by Local button

Ignore errors by selecting No (skip error lines)

Read sample\_cpd.txt by Local button in Compound data

Set threshold values, then

Pathway -> Go

# KegArray



Search PATHWAY

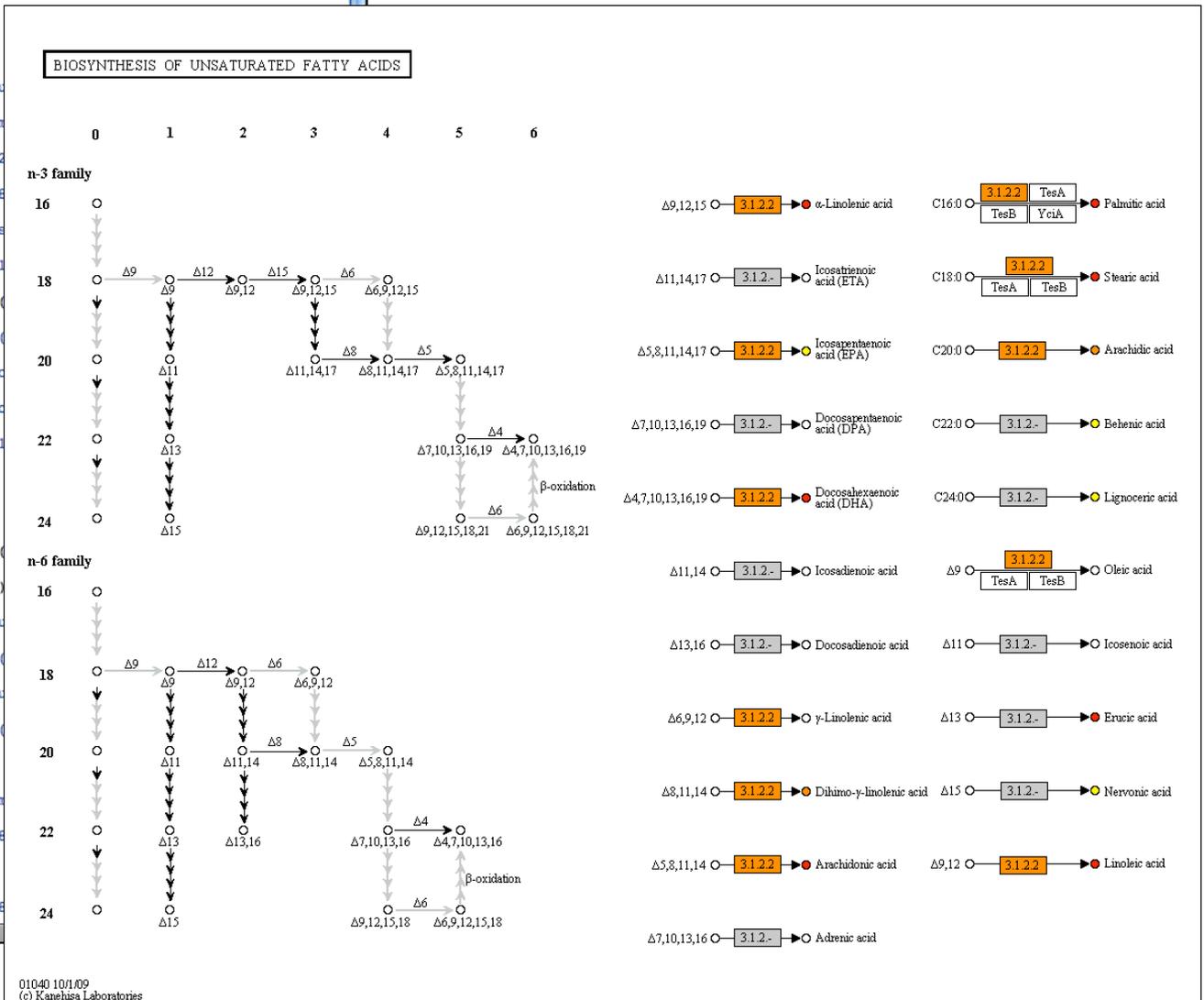
http://www.genome.jp/kegg-bin/color\_pathway\_object?org\_name=mm

### Pathway Search Result

Sort by the pathway list

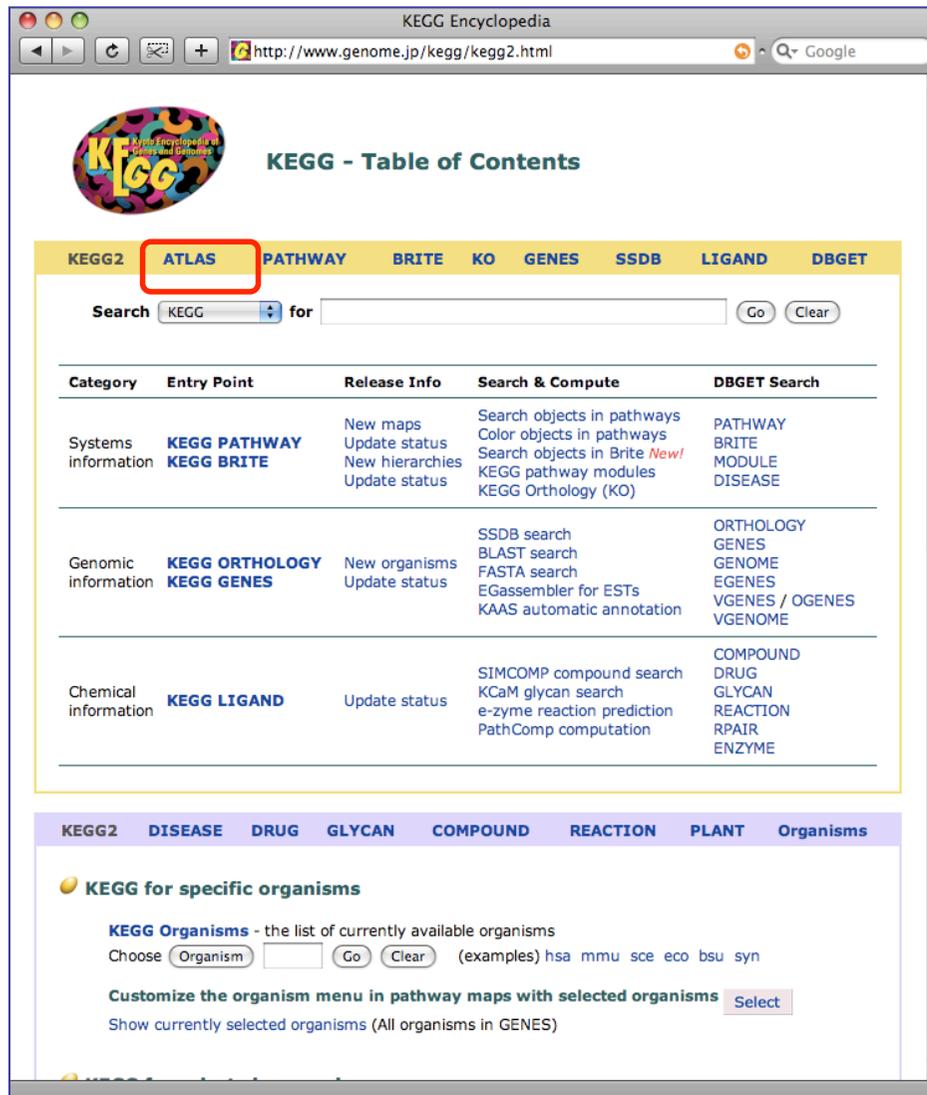
Show all objects

- mmu01100 Metabolic pathways - Mus musculus (mouse) (122)
- mmu01040 Biosynthesis of unsaturated fatty acids - Mus musculus (mouse) (12)
- mmu00564 Glycerophospholipid metabolism - Mus musculus (mouse) (12)
- mmu03320 PPAR signaling pathway - Mus musculus (mouse) (2)
- mmu00071 Fatty acid metabolism - Mus musculus (mouse) (18)
- mmu00590 Arachidonic acid metabolism - Mus musculus (mouse) (12)
- mmu00565 Ether lipid metabolism - Mus musculus (mouse) (2)
- mmu00600 Sphingolipid metabolism - Mus musculus (mouse) (12)
- mmu04920 Adipocytokine signaling pathway - Mus musculus (mouse) (12)
- mmu00562 Inositol phosphate metabolism - Mus musculus (mouse) (12)
- mmu04070 Phosphatidylinositol signaling system - Mus musculus (mouse) (12)
- mmu04912 GnRH signaling pathway - Mus musculus (mouse) (12)
- mmu00591 Linoleic acid metabolism - Mus musculus (mouse) (12)
- mmu04666 Fc gamma R-mediated phagocytosis - Mus musculus (mouse) (12)
- mmu00561 Glycerolipid metabolism - Mus musculus (mouse) (12)
- mmu04730 Long-term depression - Mus musculus (mouse) (11)
- mmu00140 Steroid hormone biosynthesis - Mus musculus (mouse) (12)
- mmu00592 alpha-Linolenic acid metabolism - Mus musculus (mouse) (12)
- mmu04270 Vascular smooth muscle contraction - Mus musculus (mouse) (12)
- mmu04664 Fc epsilon RI signaling pathway - Mus musculus (mouse) (12)
- mmu00100 Steroid biosynthesis - Mus musculus (mouse) (9)
- mmu00120 Primary bile acid biosynthesis - Mus musculus (mouse) (12)
- mmu04010 MAPK signaling pathway - Mus musculus (mouse) (8)
- mmu00650 Butanoate metabolism - Mus musculus (mouse) (8)
- mmu04370 VEGF signaling pathway - Mus musculus (mouse) (8)



# KEGG Atlas

## Graphical interface for global maps



KEGG Encyclopedia

http://www.genome.jp/kegg/kegg2.html

**KEGG - Table of Contents**

KEGG2 **ATLAS** PATHWAY BRITE KO GENES SSDB LIGAND DBGET

Search  for

Category	Entry Point	Release Info	Search & Compute	DBGET Search
Systems information	<a href="#">KEGG PATHWAY</a> <a href="#">KEGG BRITE</a>	New maps Update status New hierarchies Update status	Search objects in pathways Color objects in pathways Search objects in Brite <i>New!</i> KEGG pathway modules KEGG Orthology (KO)	PATHWAY BRITE MODULE DISEASE
Genomic information	<a href="#">KEGG ORTHOLOGY</a> <a href="#">KEGG GENES</a>	New organisms Update status	SSDB search BLAST search FASTA search EGassembler for ESTs KAAS automatic annotation	ORTHOLOGY GENES GENOME EGENES VGENES / OGENES VGENOME
Chemical information	<a href="#">KEGG LIGAND</a>	Update status	SIMCOMP compound search KCaM glycan search e-zyme reaction prediction PathComp computation	COMPOUND DRUG GLYCAN REACTION RPAIR ENZYME

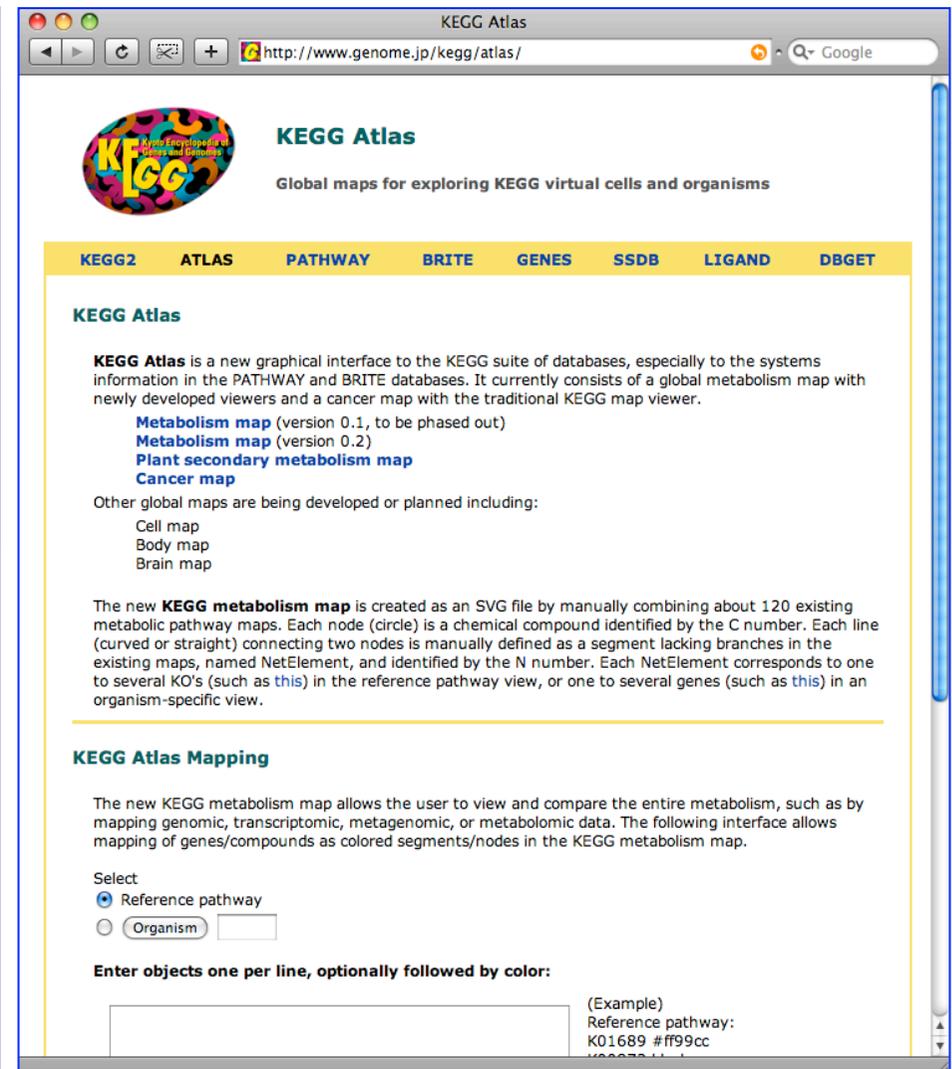
KEGG2 DISEASE DRUG GLYCAN COMPOUND REACTION PLANT Organisms

**KEGG for specific organisms**

**KEGG Organisms** - the list of currently available organisms  
Choose    (examples) hsa mmu sce eco bsu syn

**Customize the organism menu in pathway maps with selected organisms**   
Show currently selected organisms (All organisms in GENES)

<http://www.genome.jp/kegg/kegg2.html>



KEGG Atlas

Global maps for exploring KEGG virtual cells and organisms

KEGG2 **ATLAS** PATHWAY BRITE GENES SSDB LIGAND DBGET

**KEGG Atlas**

**KEGG Atlas** is a new graphical interface to the KEGG suite of databases, especially to the systems information in the PATHWAY and BRITE databases. It currently consists of a global metabolism map with newly developed viewers and a cancer map with the traditional KEGG map viewer.

- [Metabolism map](#) (version 0.1, to be phased out)
- [Metabolism map](#) (version 0.2)
- [Plant secondary metabolism map](#)
- [Cancer map](#)

Other global maps are being developed or planned including:

- Cell map
- Body map
- Brain map

The new **KEGG metabolism map** is created as an SVG file by manually combining about 120 existing metabolic pathway maps. Each node (circle) is a chemical compound identified by the C number. Each line (curved or straight) connecting two nodes is manually defined as a segment lacking branches in the existing maps, named NetElement, and identified by the N number. Each NetElement corresponds to one to several KO's (such as [this](#)) in the reference pathway view, or one to several genes (such as [this](#)) in an organism-specific view.

**KEGG Atlas Mapping**

The new KEGG metabolism map allows the user to view and compare the entire metabolism, such as by mapping genomic, transcriptomic, metagenomic, or metabolomic data. The following interface allows mapping of genes/compounds as colored segments/nodes in the KEGG metabolism map.

Select

Reference pathway

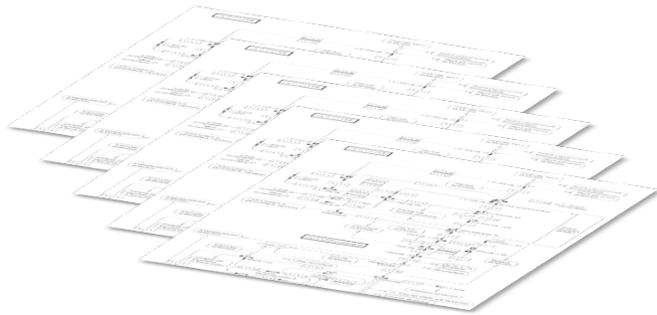
Organism

**Enter objects one per line, optionally followed by color:**

(Example)  
Reference pathway:  
K01689 #ff99cc  
K00000 #cccccc

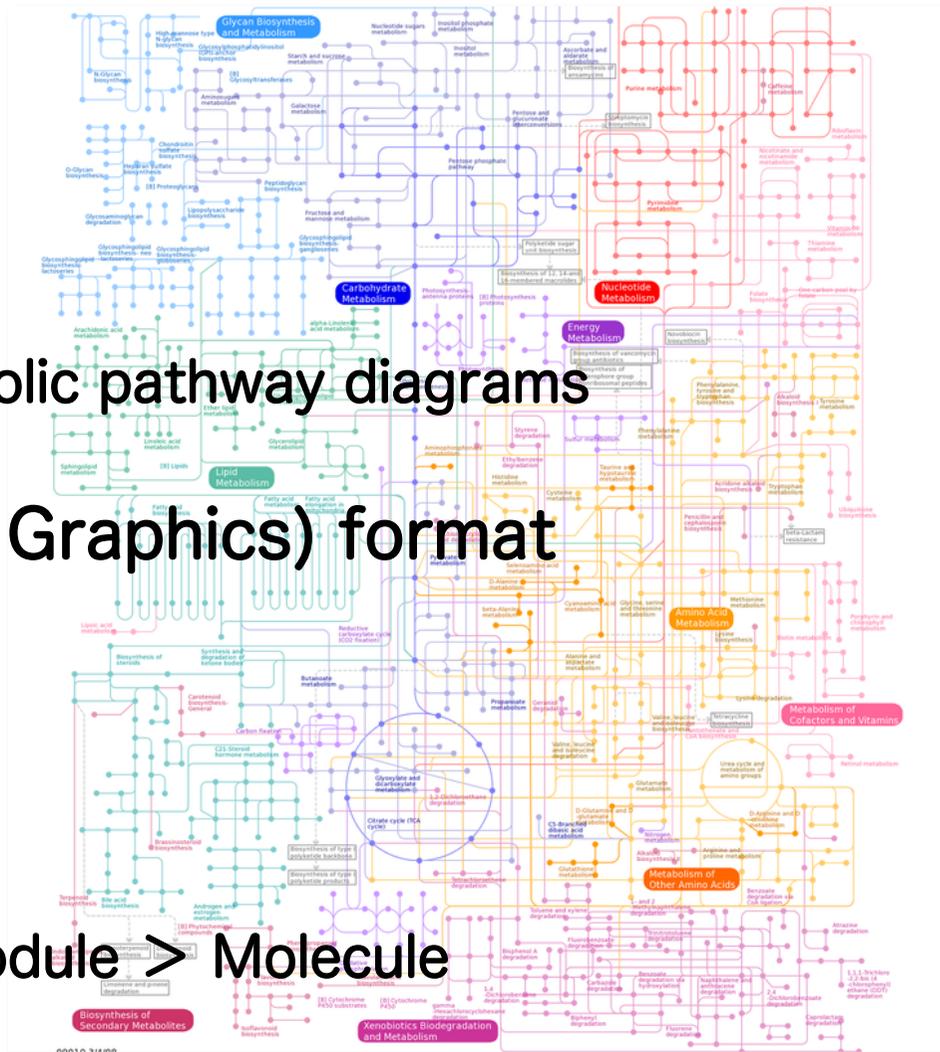
<http://www.genome.jp/kegg/atlas>

# KEGG Atlas – Metabolism

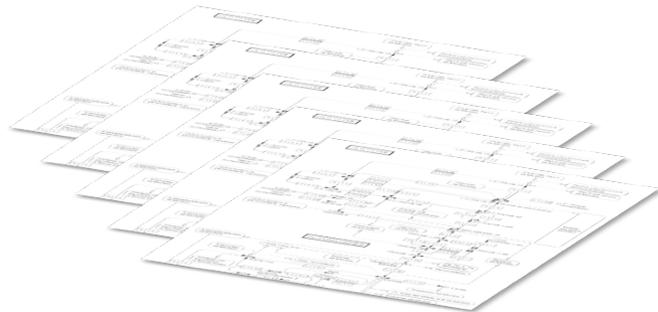


Global map for ~150 metabolic pathway diagrams

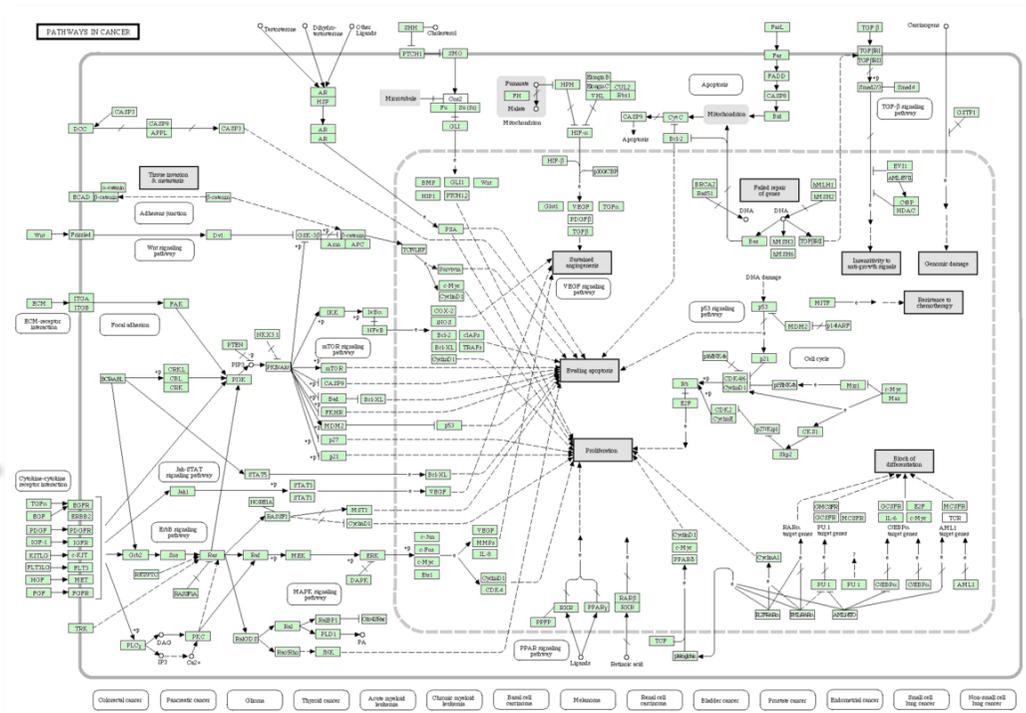
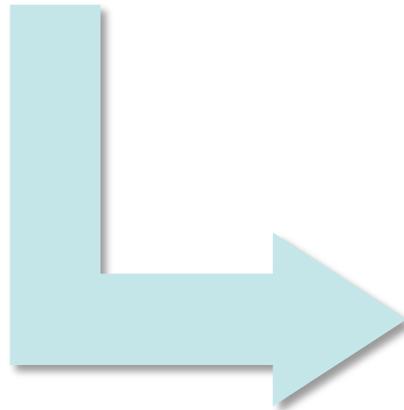
- **SVG (Scalable Vector Graphics) format**
  - Coloring for lines
  - Zooming
- **Module mapping**
  - Atlas > Diagram > Module > Molecule



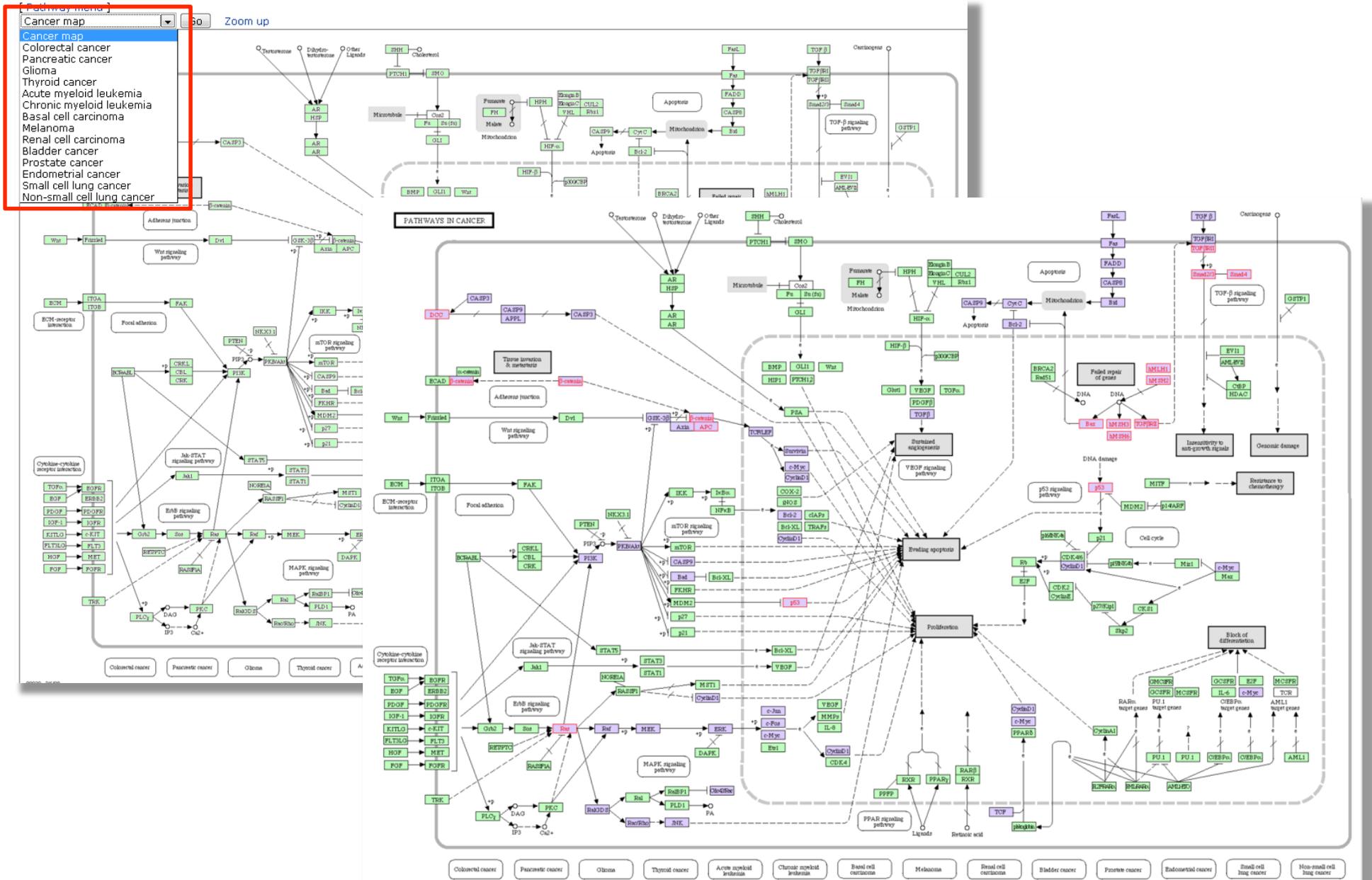
# KEGG Atlas – Cancer map



Global map for 14 cancer pathways



# KEGG Atlas – Map selection for each cancer



# KEGG Atlas – Object mapping

KEGG Atlas Mapping

The new KEGG metabolism map allows the user to view and compare the entire metabolism, such as by mapping genomic, transcriptomic, metagenomic, or metabolomic data. The following interface allows mapping of genes/compounds as colored segments/nodes in the KEGG metabolism map.

Select

Reference pathway

Organism

Enter objects one per line, optionally followed by color:

56351 red  
56386 red  
19017 green  
12894 green  
74121 yellow  
223920 green  
C00219 green  
C06429 green  
C01530 green  
C00249 green

(Example)  
Reference pathway:  
C01689 #ff99cc  
C00873 black  
C00024 yellow  
C00189

H. sapiens (hsa):  
C1101 red  
C1102 KLR #3300FF

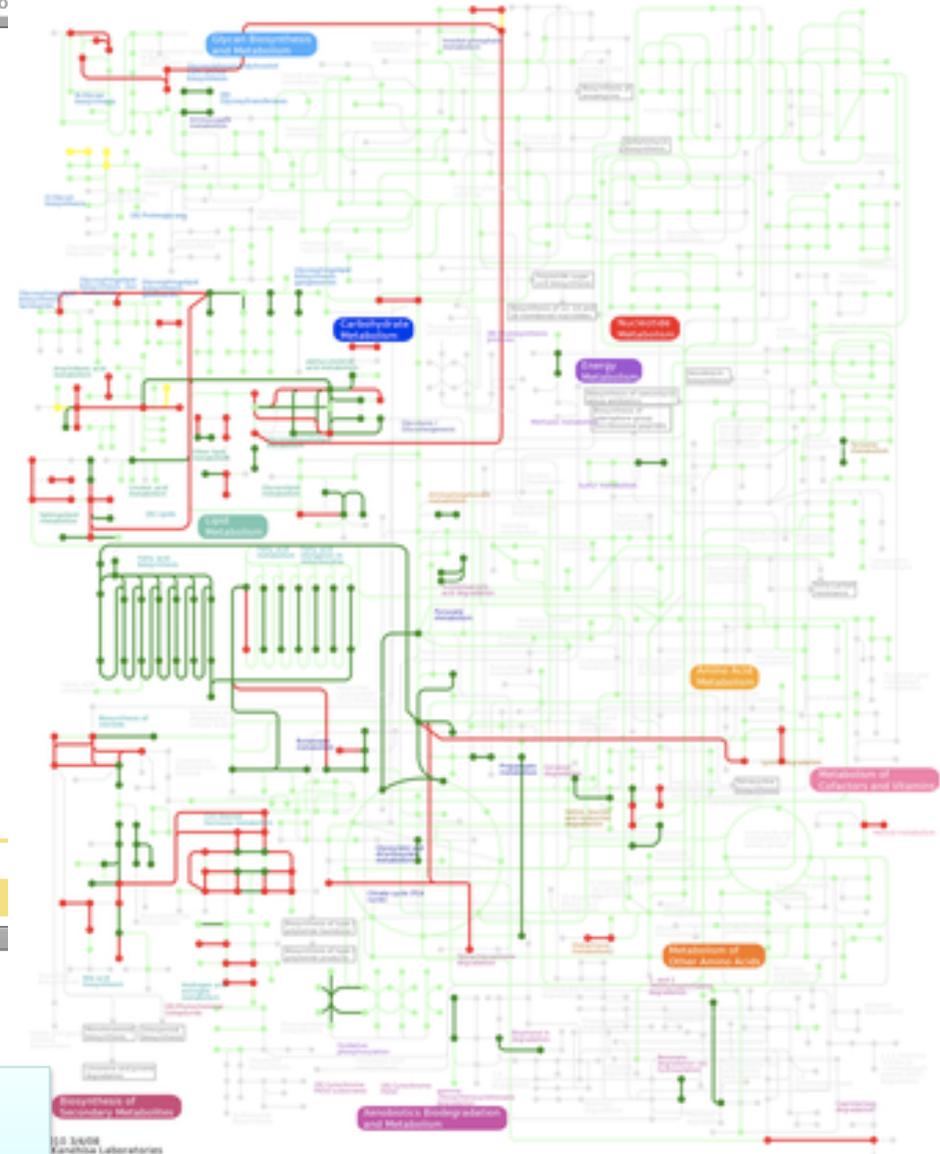
Alternatively, enter the file name containing the data:  
 ファイルが選択されていません

NetElements:  Partial match  Complete match

Default color:

Last updated: July 1, 2008

[Feedback](#) [KEGG](#) [GenomeNet](#) [Kanehisa Laboratories](#)



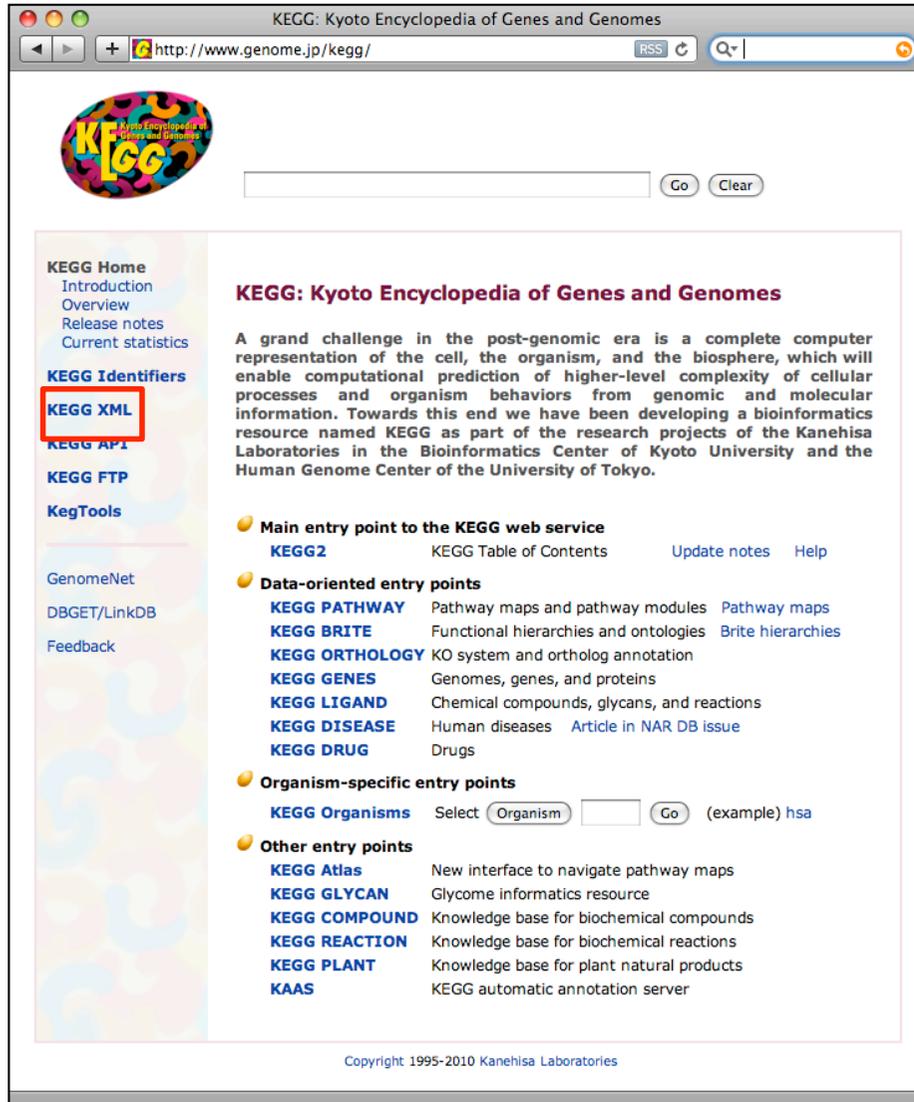
<http://www.genome.jp/kegg/atlas>

Try sample data

<http://metabolomics.se/Courses/test.txt>

# KGML: KEGG Markup Language

## XML representation for relationship between objects in pathway diagrams



KEGG: Kyoto Encyclopedia of Genes and Genomes

http://www.genome.jp/kegg/

KEGG Home  
Introduction  
Overview  
Release notes  
Current statistics

KEGG Identifiers  
**KEGG XML**  
KEGG API  
KEGG FTP  
KegTools

GenomeNet  
DBGET/LinkDB  
Feedback

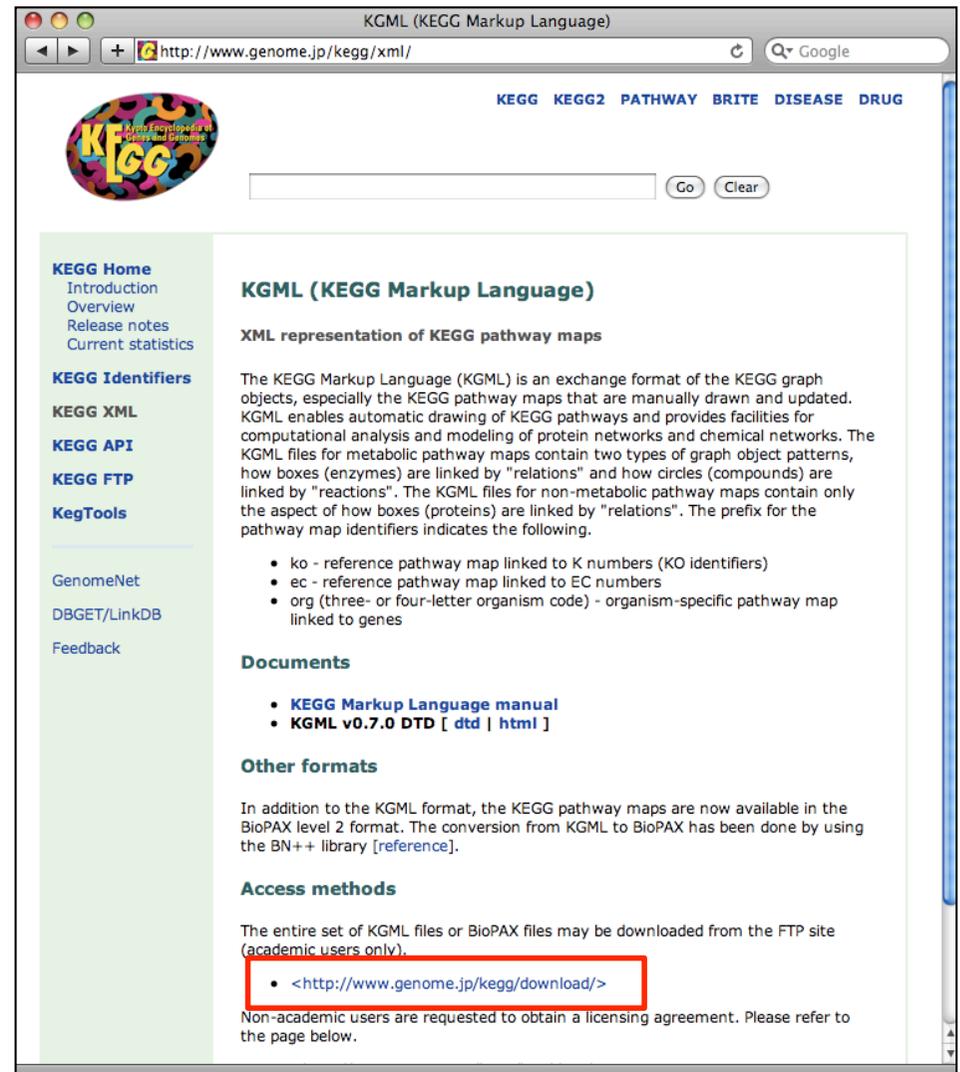
### KEGG: Kyoto Encyclopedia of Genes and Genomes

A grand challenge in the post-genomic era is a complete computer representation of the cell, the organism, and the biosphere, which will enable computational prediction of higher-level complexity of cellular processes and organism behaviors from genomic and molecular information. Towards this end we have been developing a bioinformatics resource named KEGG as part of the research projects of the Kanehisa Laboratories in the Bioinformatics Center of Kyoto University and the Human Genome Center of the University of Tokyo.

- Main entry point to the KEGG web service**
  - KEGG2** KEGG Table of Contents Update notes Help
- Data-oriented entry points**
  - KEGG PATHWAY** Pathway maps and pathway modules Pathway maps
  - KEGG BRITE** Functional hierarchies and ontologies Brite hierarchies
  - KEGG ORTHOLOGY** KO system and ortholog annotation
  - KEGG GENES** Genomes, genes, and proteins
  - KEGG LIGAND** Chemical compounds, glycans, and reactions
  - KEGG DISEASE** Human diseases Article in NAR DB issue
  - KEGG DRUG** Drugs
- Organism-specific entry points**
  - KEGG Organisms** Select   (example) hsa
- Other entry points**
  - KEGG Atlas** New interface to navigate pathway maps
  - KEGG GLYCAN** Glycome informatics resource
  - KEGG COMPOUND** Knowledge base for biochemical compounds
  - KEGG REACTION** Knowledge base for biochemical reactions
  - KEGG PLANT** Knowledge base for plant natural products
  - KAAS** KEGG automatic annotation server

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<http://www.genome.jp/kegg/>



KGML (KEGG Markup Language)

http://www.genome.jp/kegg/xml/

KEGG KEGG2 PATHWAY BRITE DISEASE DRUG

KEGG Home  
Introduction  
Overview  
Release notes  
Current statistics

KEGG Identifiers  
KEGG XML  
KEGG API  
KEGG FTP  
KegTools

GenomeNet  
DBGET/LinkDB  
Feedback

### KGML (KEGG Markup Language)

#### XML representation of KEGG pathway maps

The KEGG Markup Language (KGML) is an exchange format of the KEGG graph objects, especially the KEGG pathway maps that are manually drawn and updated. KGML enables automatic drawing of KEGG pathways and provides facilities for computational analysis and modeling of protein networks and chemical networks. The KGML files for metabolic pathway maps contain two types of graph object patterns, how boxes (enzymes) are linked by "relations" and how circles (compounds) are linked by "reactions". The KGML files for non-metabolic pathway maps contain only the aspect of how boxes (proteins) are linked by "relations". The prefix for the pathway map identifiers indicates the following.

- ko - reference pathway map linked to K numbers (KO identifiers)
- ec - reference pathway map linked to EC numbers
- org (three- or four-letter organism code) - organism-specific pathway map linked to genes

#### Documents

- KEGG Markup Language manual**
- KGML v0.7.0 DTD** [ dtd | html ]

#### Other formats

In addition to the KGML format, the KEGG pathway maps are now available in the BioPAX level 2 format. The conversion from KGML to BioPAX has been done by using the BN++ library [reference].

#### Access methods

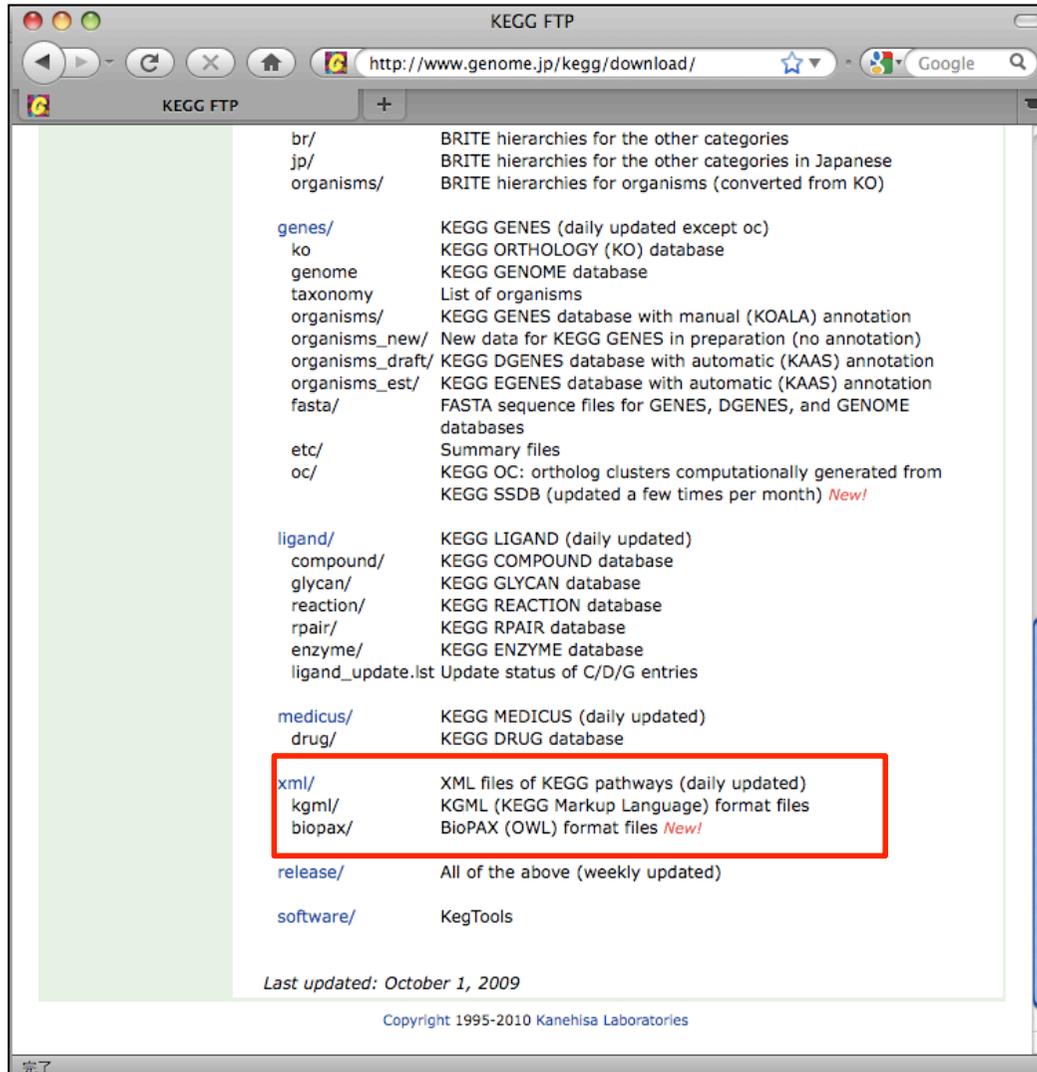
The entire set of KGML files or BioPAX files may be downloaded from the FTP site (academic users only).

- <http://www.genome.jp/kegg/download/>

Non-academic users are requested to obtain a licensing agreement. Please refer to the page below.

<http://www.genome.jp/kegg/xml>

# KGML representing protein objects as orthologs



- Information on protein interactions and chemical interactions (reaction) is provided for each diagram
- Computer friendly format for pathway analysis

- **xml**

- Direct access to XML

- **text**

- Display XML as text

- **KGML Viewer**

- Java application for graphical representation of XML

<http://www.genome.jp/kegg/download/>

# KGML contents

```
-<pathway name="path:ko00010" org="ko" number="00010" title="Glycolysis / Gluconeogenesis"
image="http://www.genome.jp/kegg/pathway/ko/ko00010.png" link="http://www.genome.jp/kegg-
bin/show_pathway?ko00010">
  -<entry id="1" name="ko:K01623 ko:K01624" type="ortholog" reaction="rn:R01070" link="http://www.kegg.jp
/dbget-bin/www_bget?K01623+K01624">
    <graphics name="K01623..." fgcolor="#000000" bgcolor="#BFBFFF" type="rectangle" x="456" y="402"
width="46" height="17"/>
  </entry>
  -<entry id="2" name="ko:K00128" type="ortholog" reaction="rn:R00710" link="http://www.kegg.jp/dbget-
bin/www_bget?K00128">
    <graphics name="K00128" fgcolor="#000000" bgcolor="#BFBFFF" type="rectangle" x="262" y="941"
width="46" height="17"/>
  </entry>
  -<entry id="3" name="ko:K01895" type="ortholog" reaction="rn:R00235" link="http://www.kegg.jp/dbget-
bin/www_bget?K01895">
    <graphics name="K01895" fgcolor="#000000" bgcolor="#BFBFFF" type="rectangle" x="119" y="909"
width="46" height="17"/>
  </entry>
  -<entry id="4" name="ko:K00129" type="ortholog" reaction="rn:R00711" link="http://www.kegg.jp/dbget-
bin/www_bget?K00129">
    <graphics name="K00129" fgcolor="#000000" bgcolor="#BFBFFF" type="rectangle" x="262" y="962"
width="46" height="17"/>
  </entry>
```

```
-<relation entry1="36" entry2="39" type="ECrel">
  <subtype name="compound" value="52"/>
</relation>
-<relation entry1="36" entry2="38" type="ECrel">
  <subtype name="compound" value="52"/>
</relation>
-<relation entry1="34" entry2="36" type="ECrel">
  <subtype name="compound" value="52"/>
</relation>
```

```
-<reaction name="rn:R00710" type="reversible">
  <substrate name="cpd:C00084"/>
  <product name="cpd:C00033"/>
</reaction>
-<reaction name="rn:R00235" type="irreversible">
  <substrate name="cpd:C00024"/>
  <product name="cpd:C00033"/>
</reaction>
```

KGML for glycolysis map ko00010

## • entry tag

- Objects in a diagram
- Proteins (enzymes), chemical compounds, maps

## • relation tag

- Relationship between proteins
- ECrel: neighboring enzymes in a diagram
- PPrel: protein-protein interaction

## • reaction tag

- Reaction representing substrates and products as appearing in a diagram with directionality

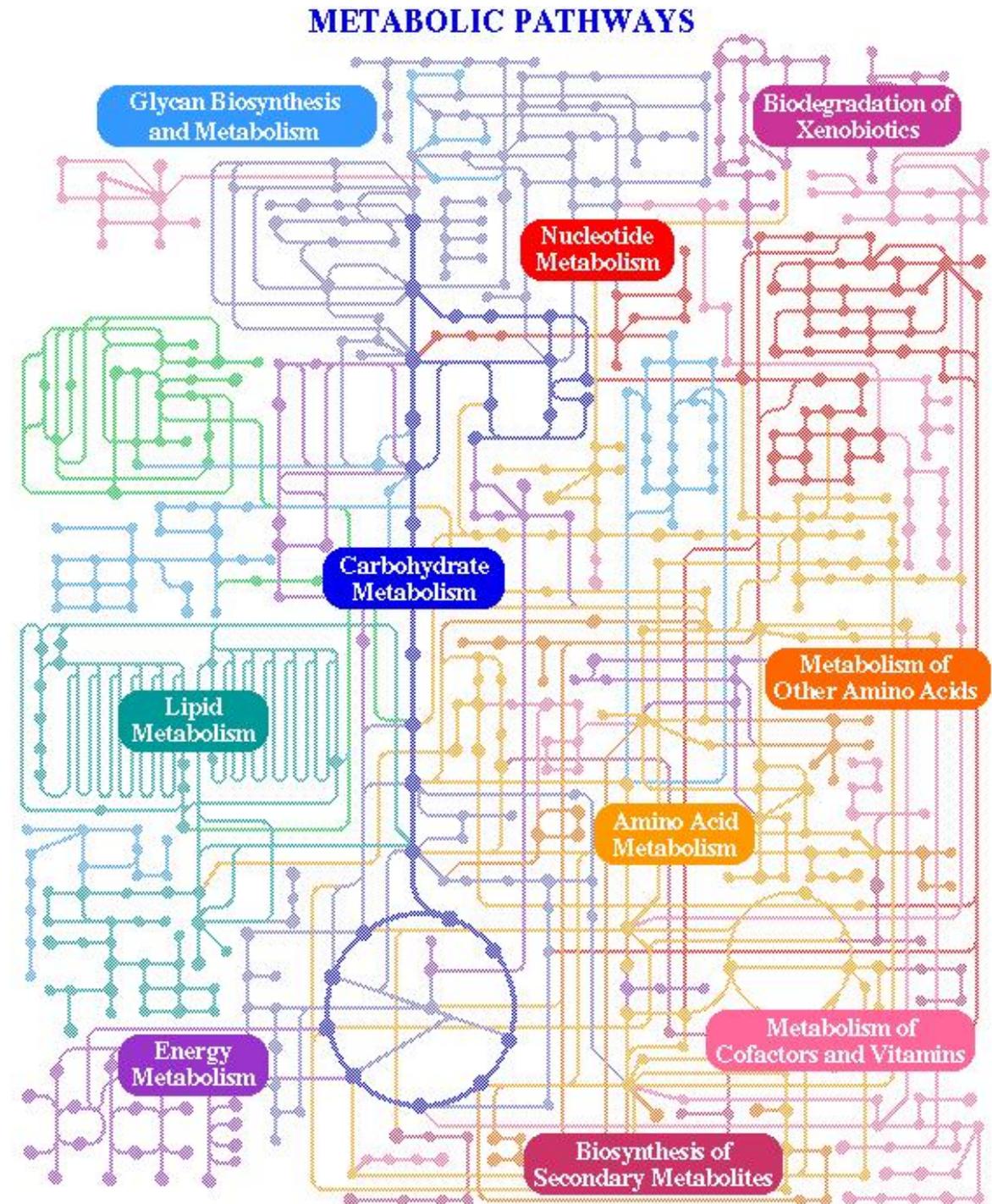




# Data contained in KEGG

	Contained	Not contained
Genome	Gene Functional annotation	cis elements variations Protein 3D structures
Pathway	Metabolism, Signaling, Disease, Drugs	Simulation parameters
Compounds	2D structures Drugs, Metabolites, Reaction (patterns)	Physicochemical properties 3D structures Kinetics
	<a href="#">Links within KEGG</a>	<a href="#">Links to external DBs</a>

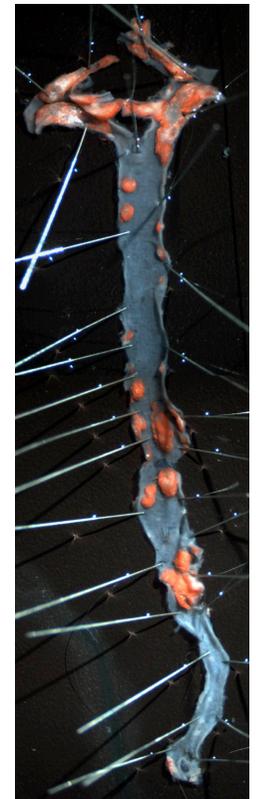
**KEGG's goal is to provide metabolic pathway maps for all biochemical processes**



# What are the applications of KegArray?

## Example:

- ApoE\*3Leiden mice fed diet of control, low cholesterol, or high cholesterol
- Investigated lipid & inflammatory component of atherosclerosis development
- Performed microarray analysis and lipidomics profiling
  - Affected 264 genes in lipid metabolism
  - Range of lipid fluctuations



Collaboration with Robert Kleemann at TNO

# Pathways in inflammatory heart disease

## Affected KEGG pathways

---

[mmu01040](#) Biosynthesis of unsaturated fatty acids

[mmu03320](#) PPAR signaling pathway

[mmu00564](#) Glycerophospholipid metabolism

[mmu00071](#) Fatty acid metabolism

[mmu04920](#) Adipocytokine signaling pathway

[mmu00565](#) Ether lipid metabolism

[mmu00590](#) Arachidonic acid metabolism

[mmu00100](#) Biosynthesis of steroids

[mmu00120](#) Bile acid biosynthesis

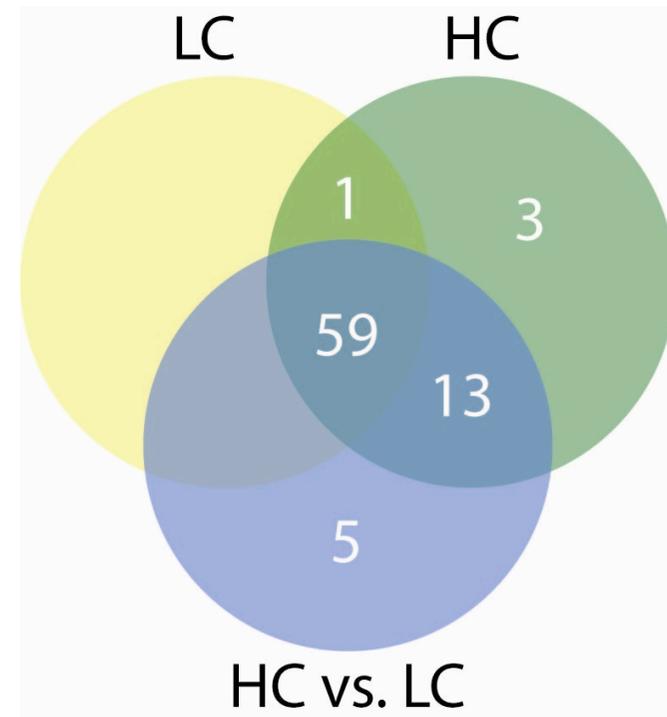
[mmu00561](#) Glycerolipid metabolism

[mmu00600](#) Sphingolipid metabolism

[mmu00591](#) Linoleic acid metabolism

[mmu00592](#) alpha-Linolenic acid metabolism

---

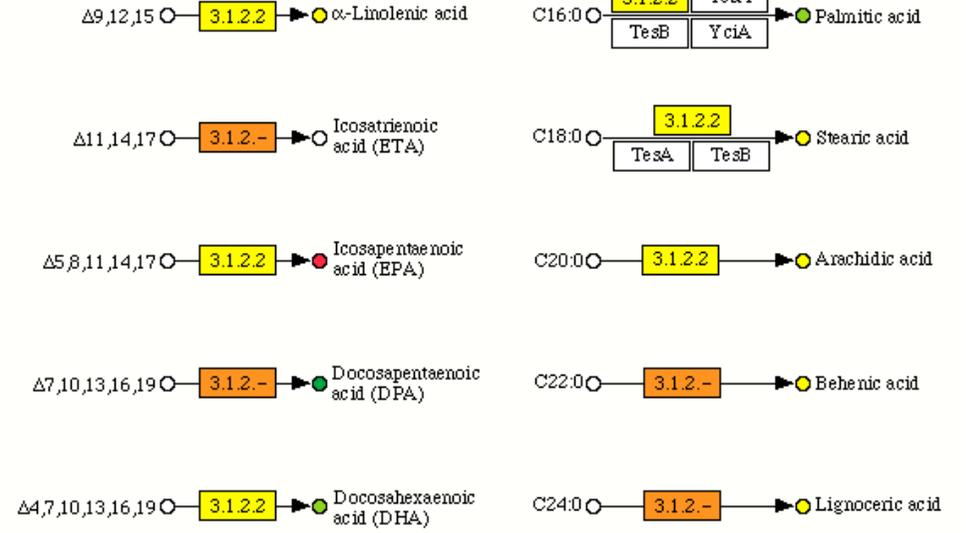
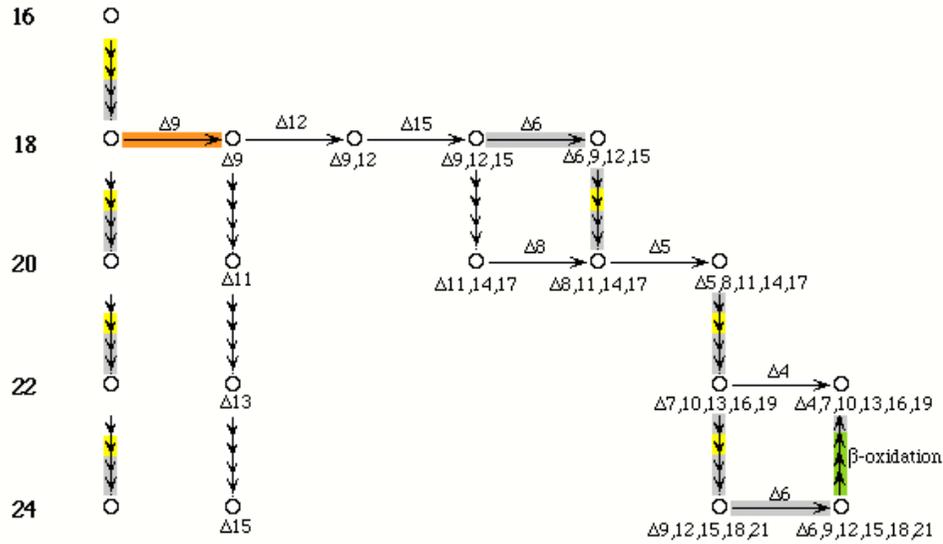


LC = low cholesterol  
HC = high cholesterol

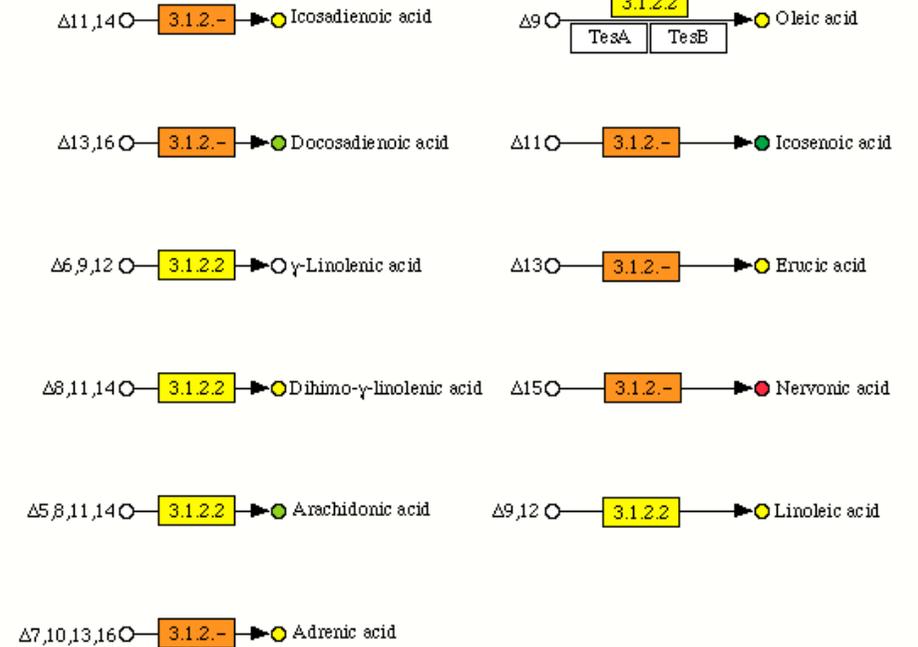
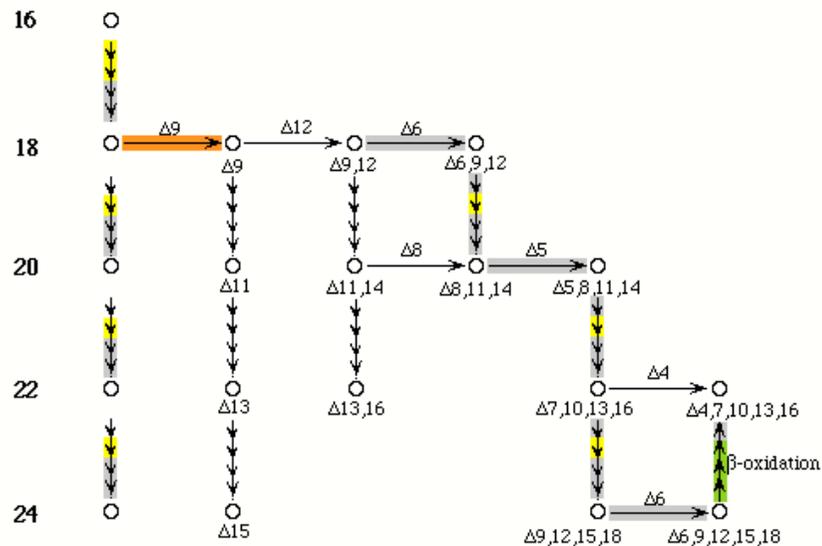
# BIOSYNTHESIS OF UNSATURATED FATTY ACIDS

0 1 2 3 4 5 6

## n-3 family



## n-6 family

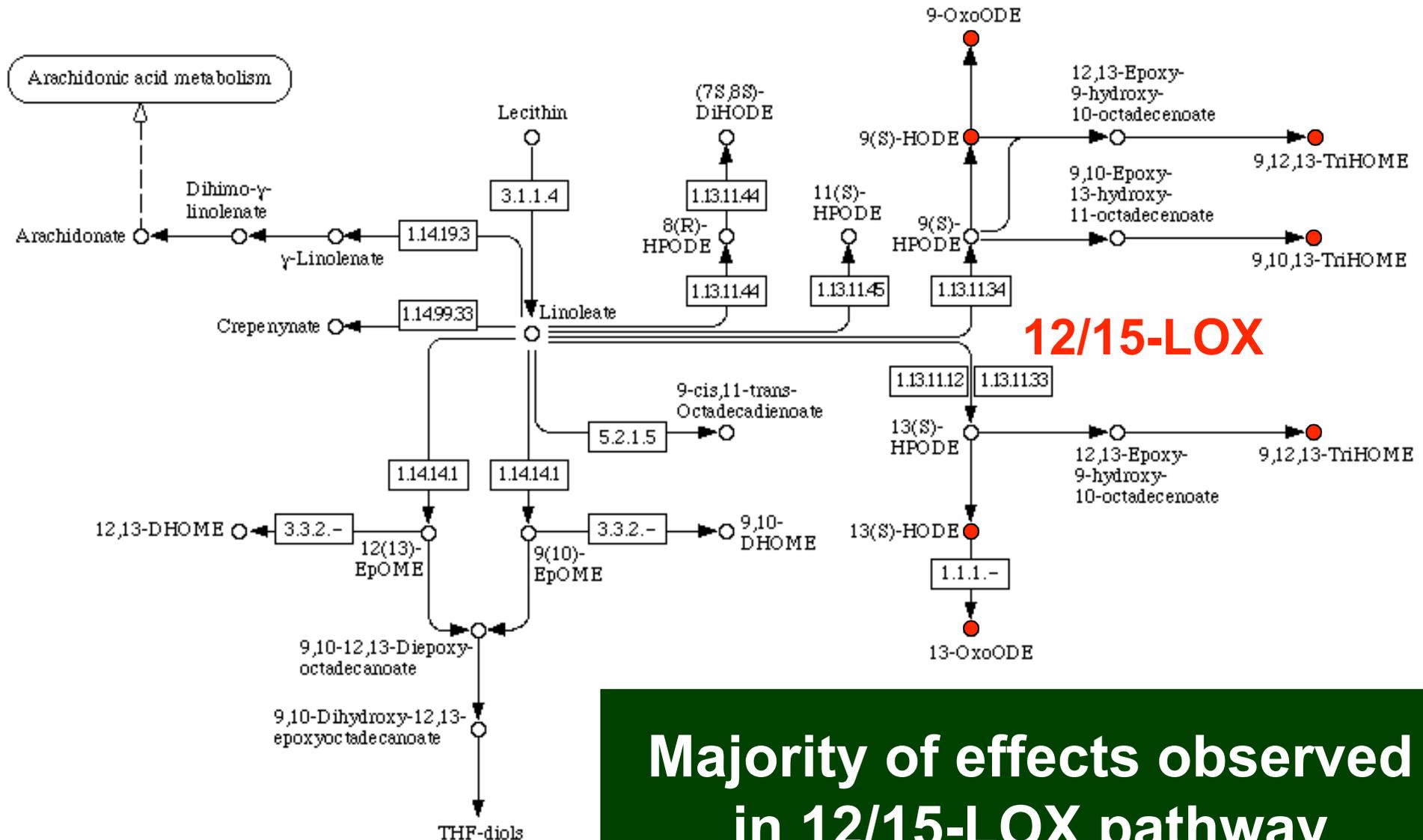






# Linoleic Acid Metabolism (KEGG)

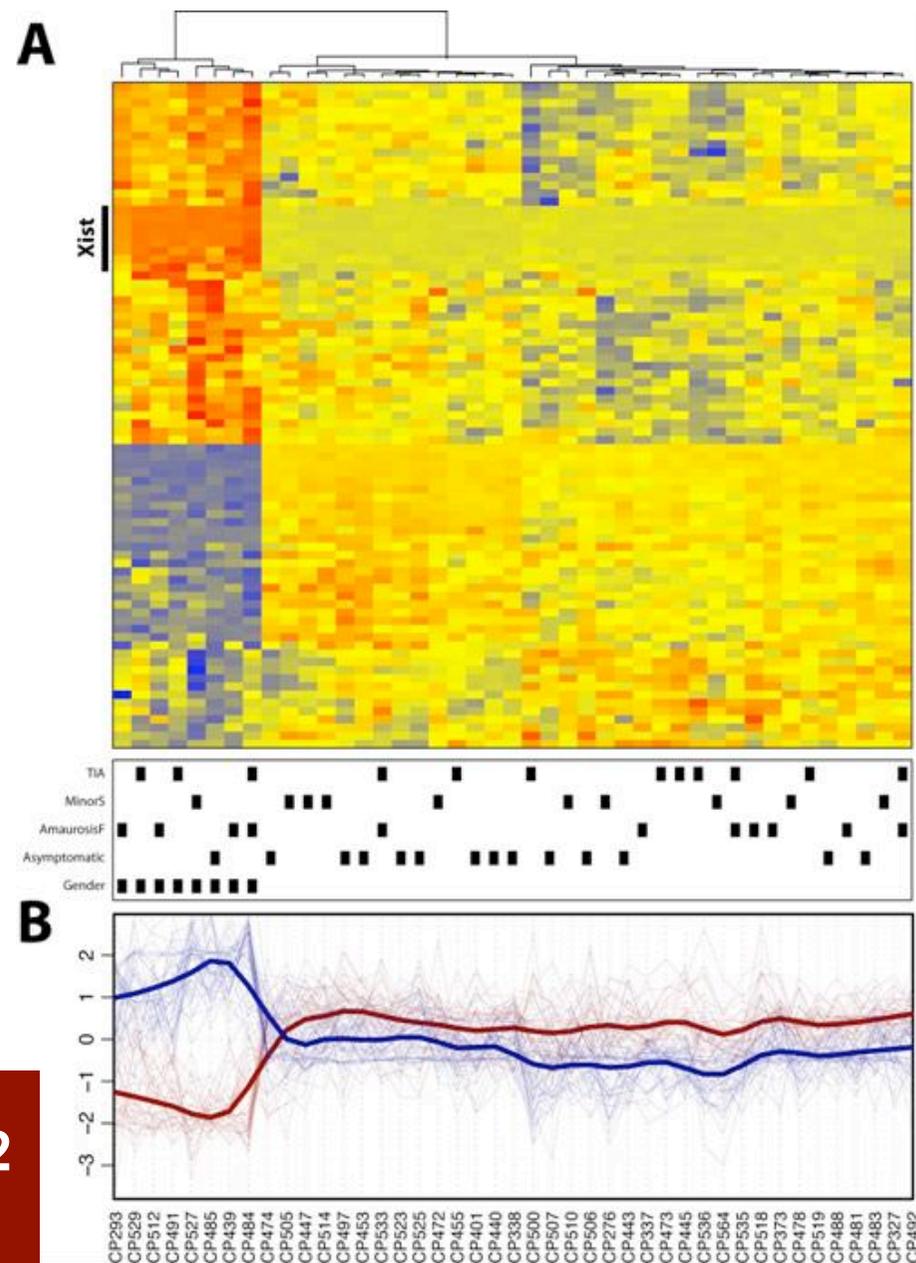
## LINOLEIC ACID METABOLISM



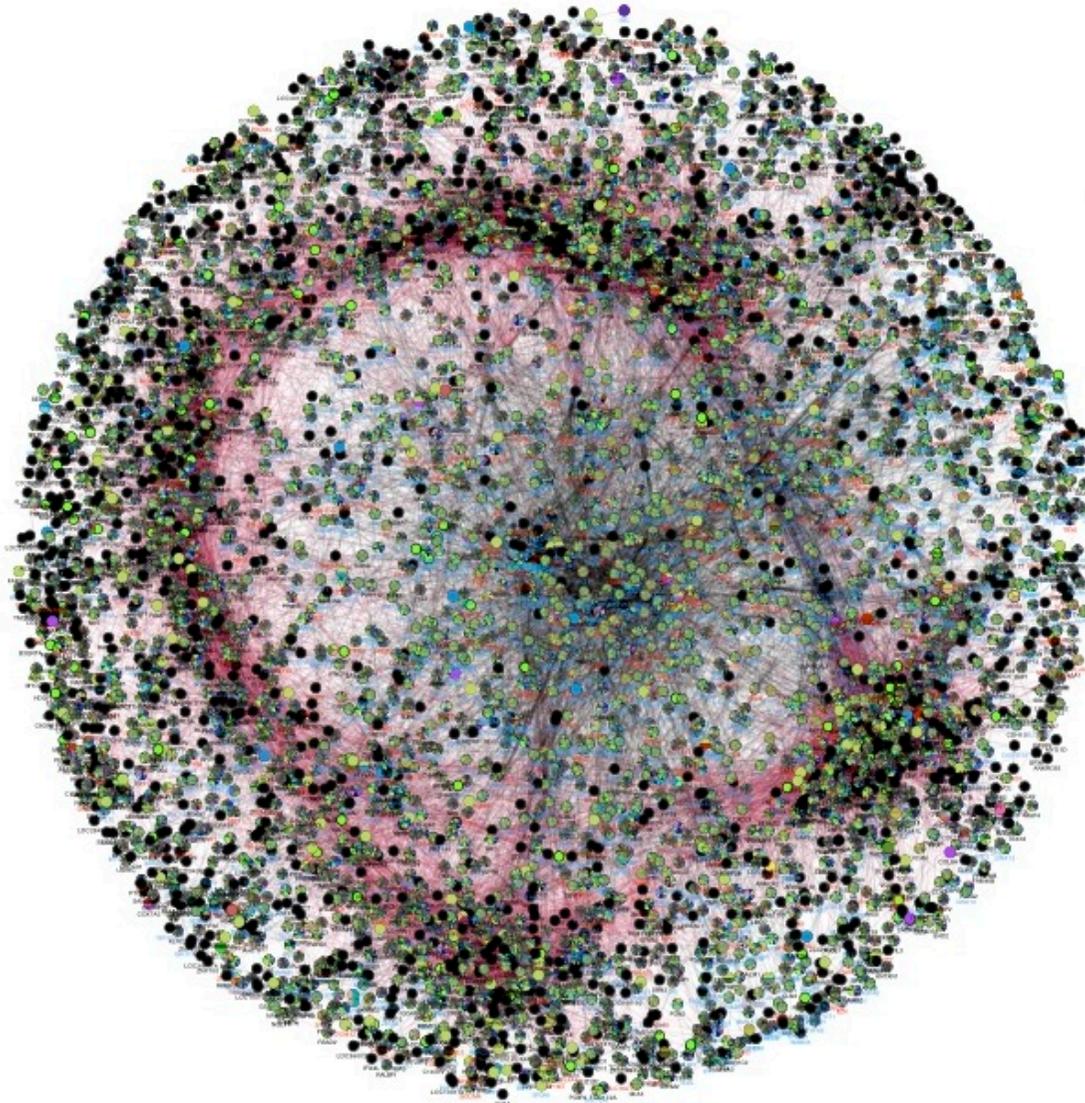
# Atherosclerosis transcriptomics analysis

- Analyzed 107 microarrays
- Focused on gender-specific fluctuations
- Identified 42 DE genes
- 23 down-regulated and 19 up-regulated in females
  - **ApoC1** 2.1-fold down-regulated in women
  - **Fabp3** 1.5-fold down-regulated in women

Profile of the intensities, showing the 2 different expression profiles identified



# Global network based upon multiple phenotypes



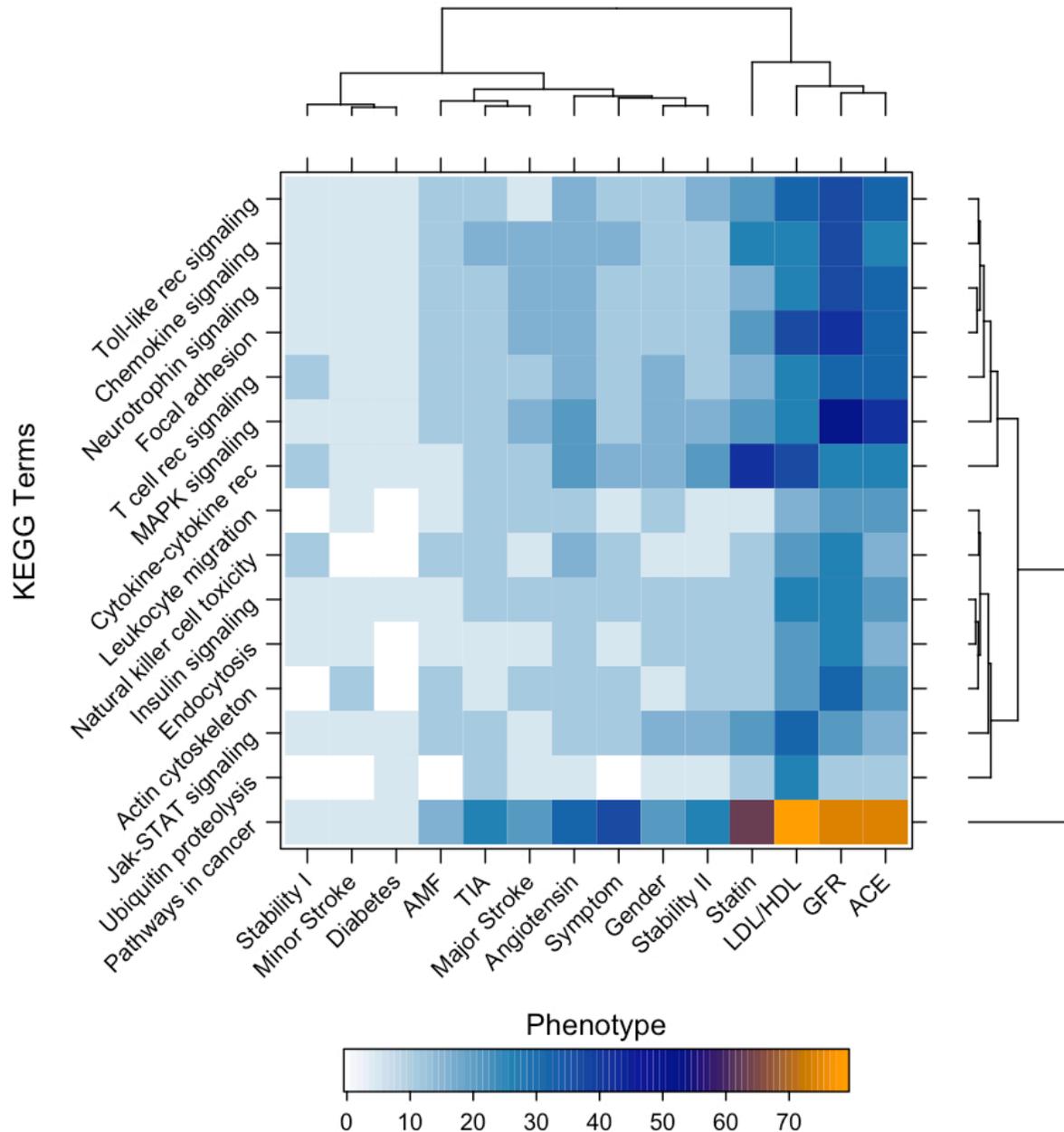
## NODES

- Orange: genes used for literature mining
- Gray: genes found in literature mining
- Black: genes from the correlation network

## EDGES

- Blue: association network
- Green: positively correlated profiles
- Red: negatively correlated profiles

# Map network terms to KEGG pathways



Provides information on the enrichment of distinct biological pathways within the constructed network

# Summary

- KEGG PATHWAY

- Pathway diagrams of biological interactions
- Can search and custom color pathway diagrams

- KegArray

- Links omics data to KEGG databases



- KEGG Atlas

- Global map of the KEGG pathway diagrams

- KGML

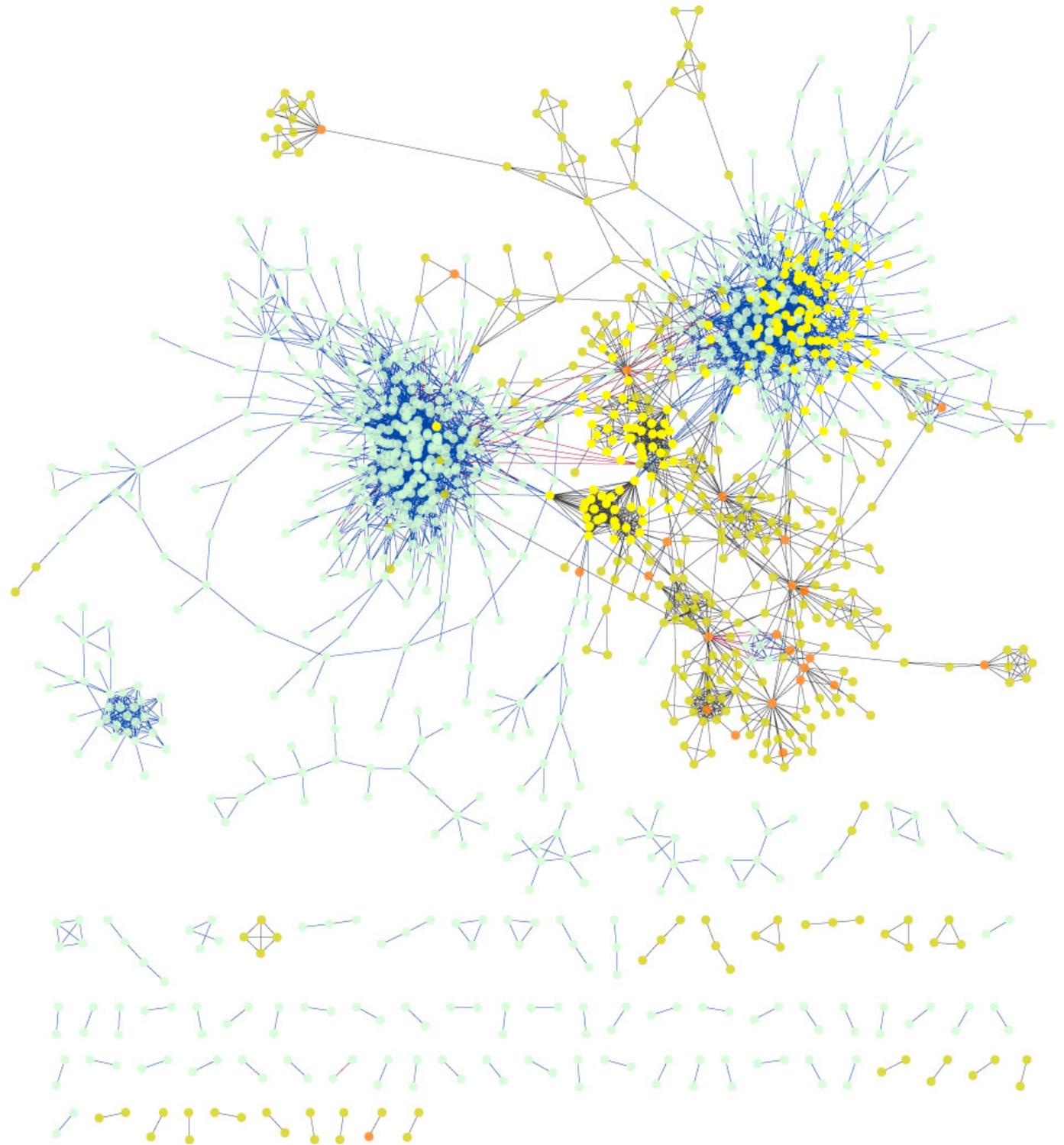
- XML format for KEGG pathway diagrams

**KEGG useful utility for visualizing relationships between multiple data structures across biological hierarchies & species**

# Systems Biology & the Omics Cascade

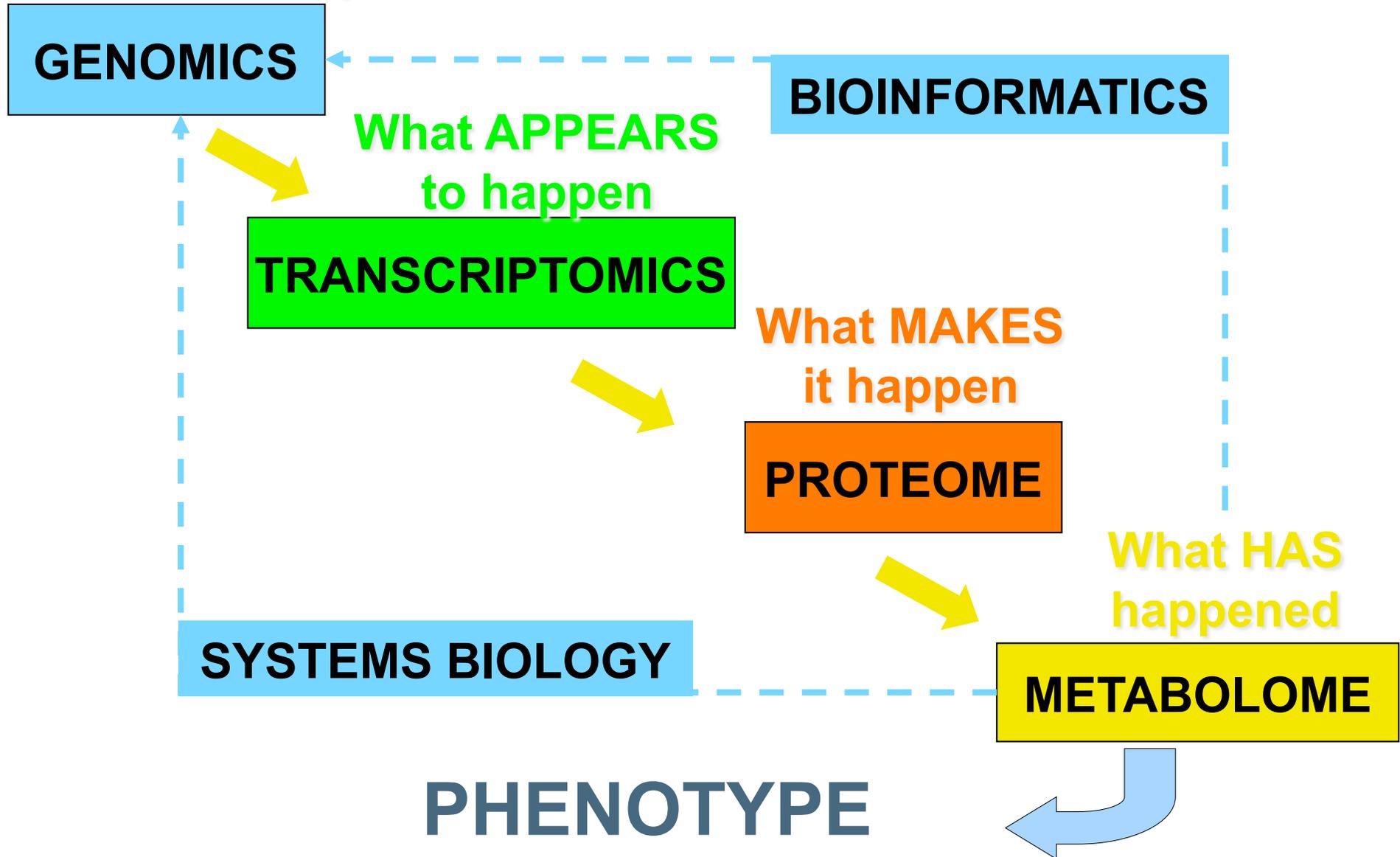
or

## How do we put it all together??



# Omics ≠ Systems Biology

What CAN happen



# Shift in Philosophy of Medicine...



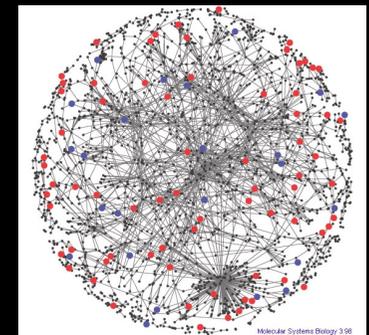
**1800s: Observational  
Disease states**



**1900s: Molecular  
Disease states**



**2000s: Integration  
Healthy state  
Systems biology**

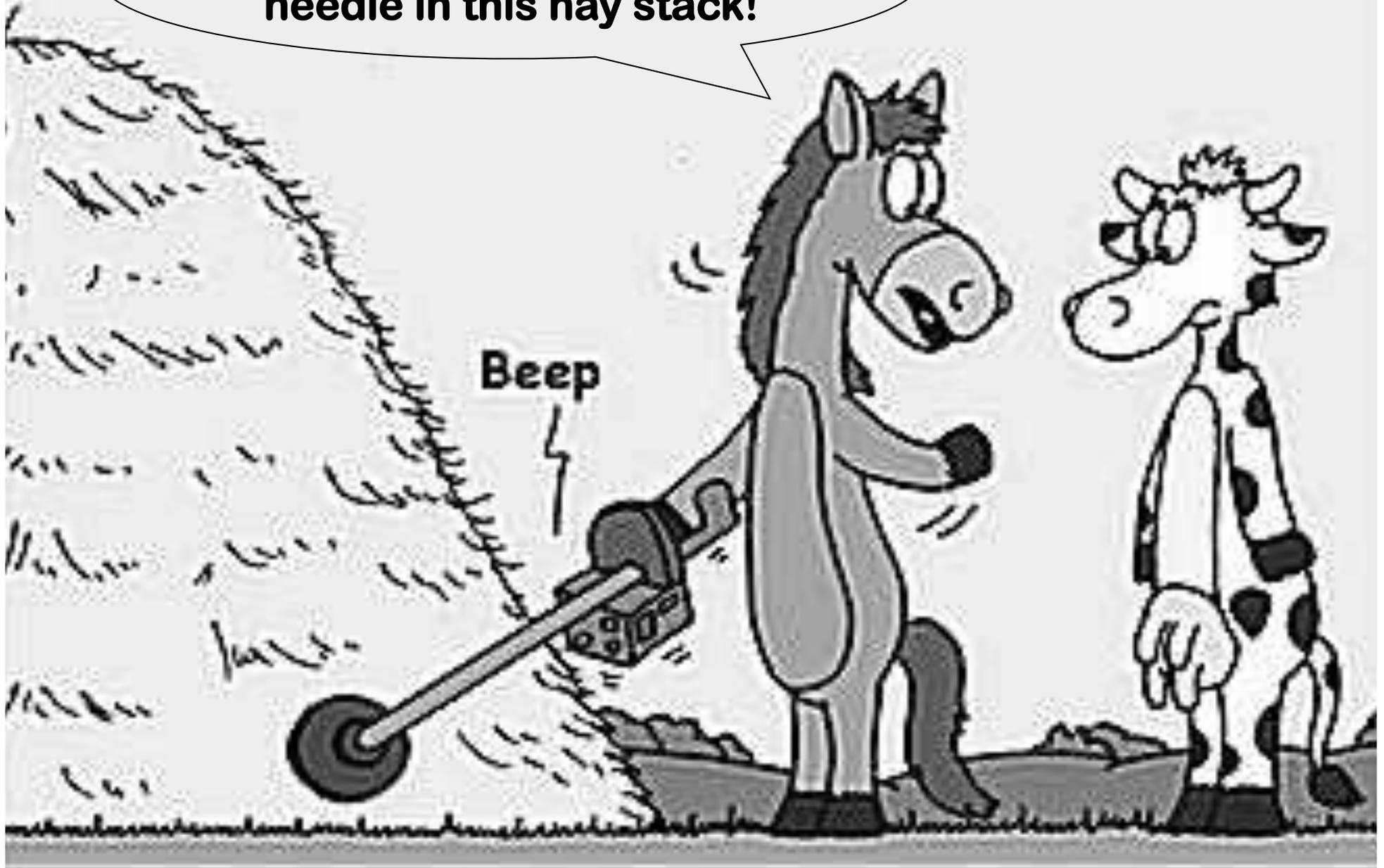


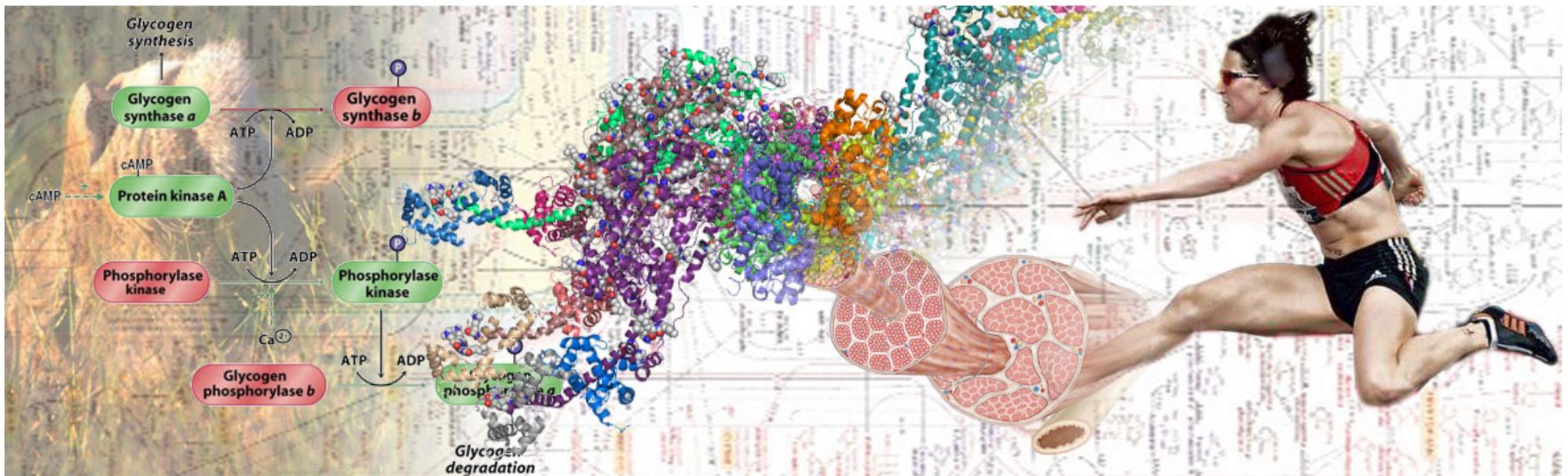






**You were right, there is a  
needle in this hay stack!**





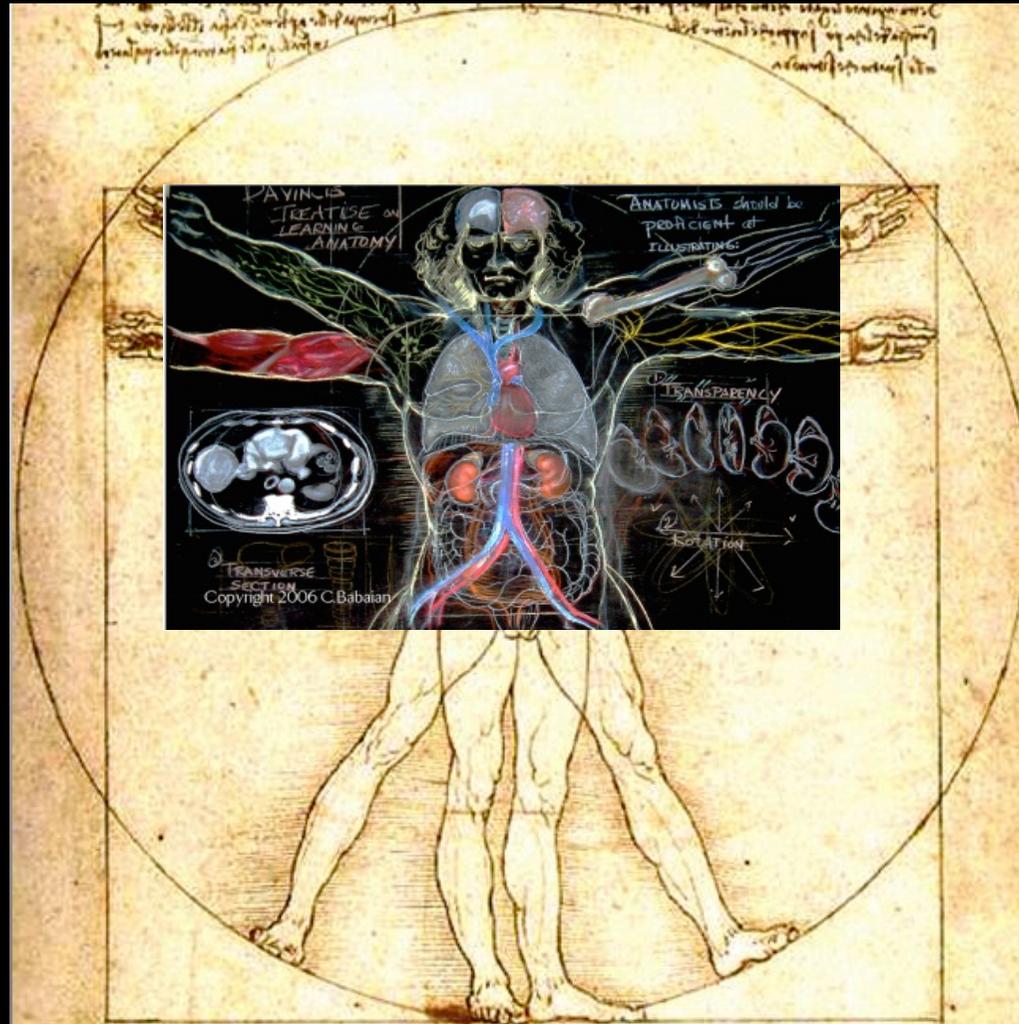
# What is systems biology?



**“Organisms function in an integrated manner - our senses, our muscles, our metabolism and our mind work together seamlessly. But biologists have historically studied organisms part by part and celebrated the modern ability to study them molecule by molecule, gene by gene. Systems biology is devoted to a new science, a critical science of the future that seeks to understand the integration of the pieces to form biological systems.”**

**-David Baltimore, Nobel Laureate**

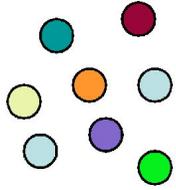
# Renaissance in Biology



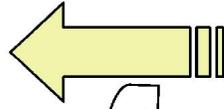
**Systems Biology is about putting together rather than taking apart, integration rather than reduction**

*- Denis Noble*

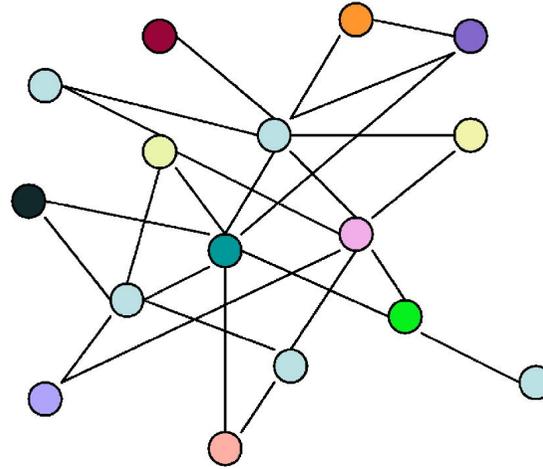
## Reductionism



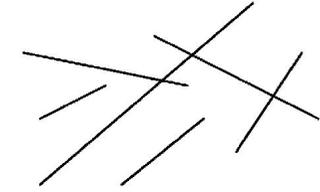
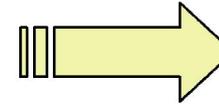
**Components**



Time  
Space  
Context



## Systems Science



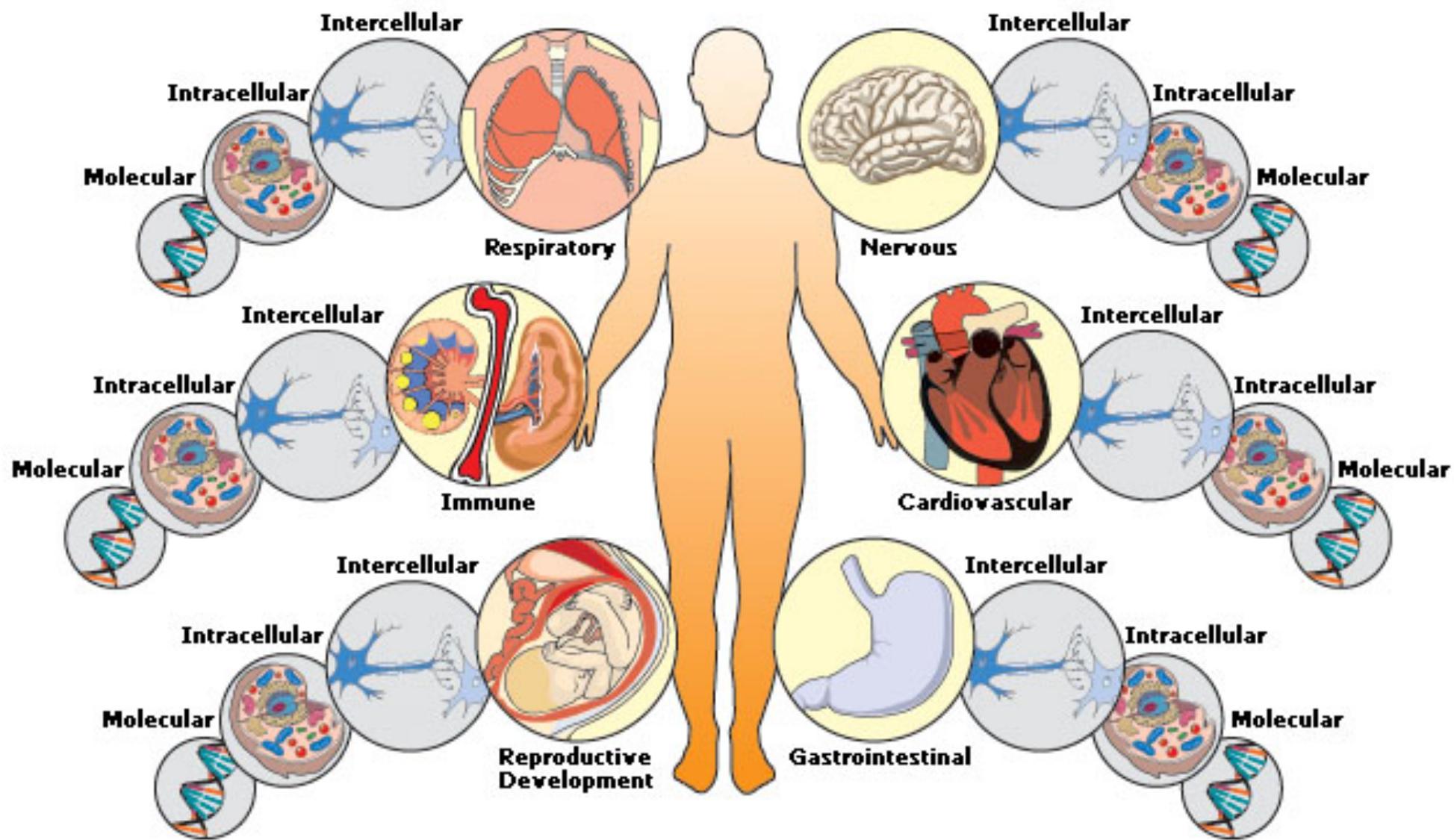
**Interrelationships,  
Dynamics**

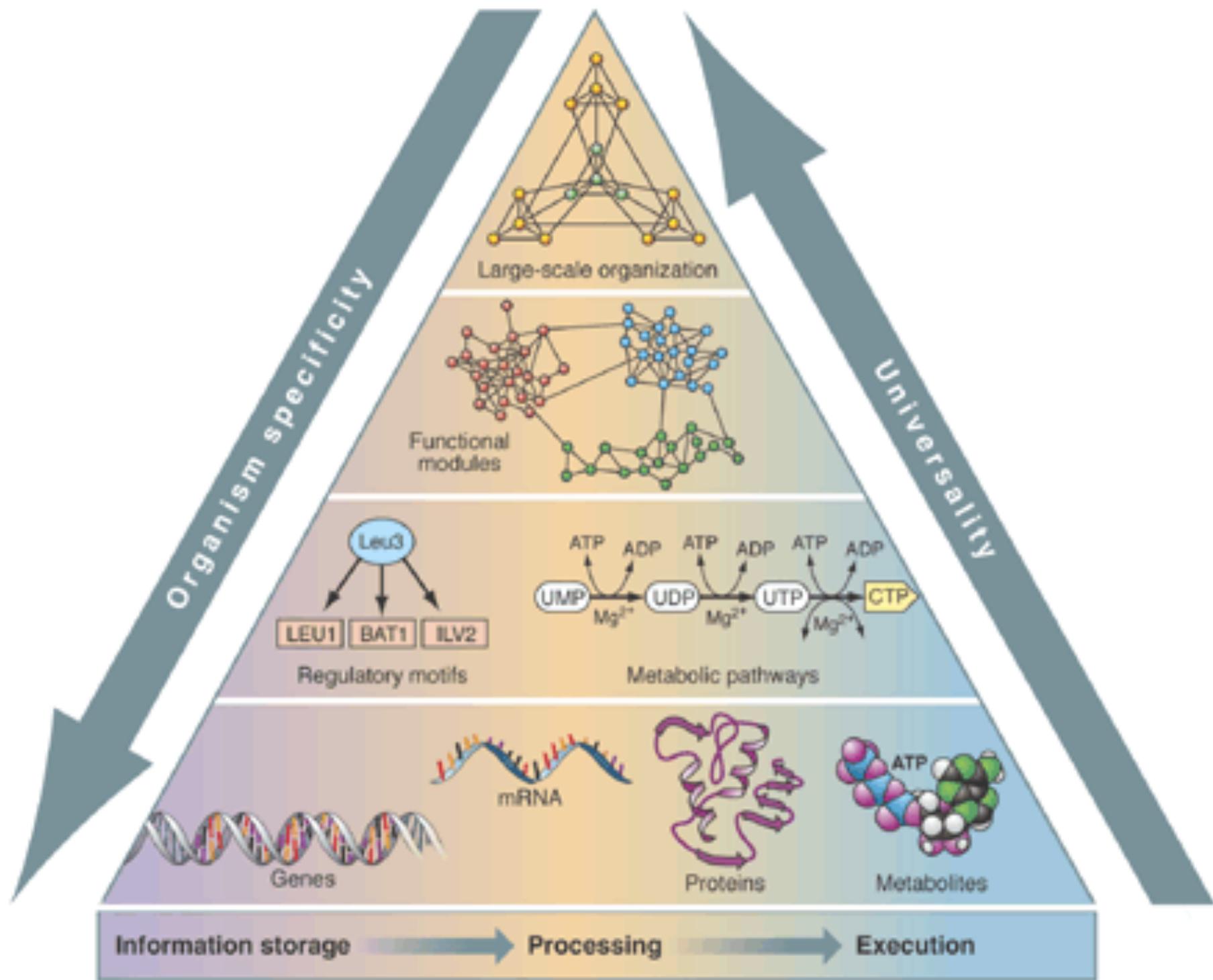
## Medical Treatments

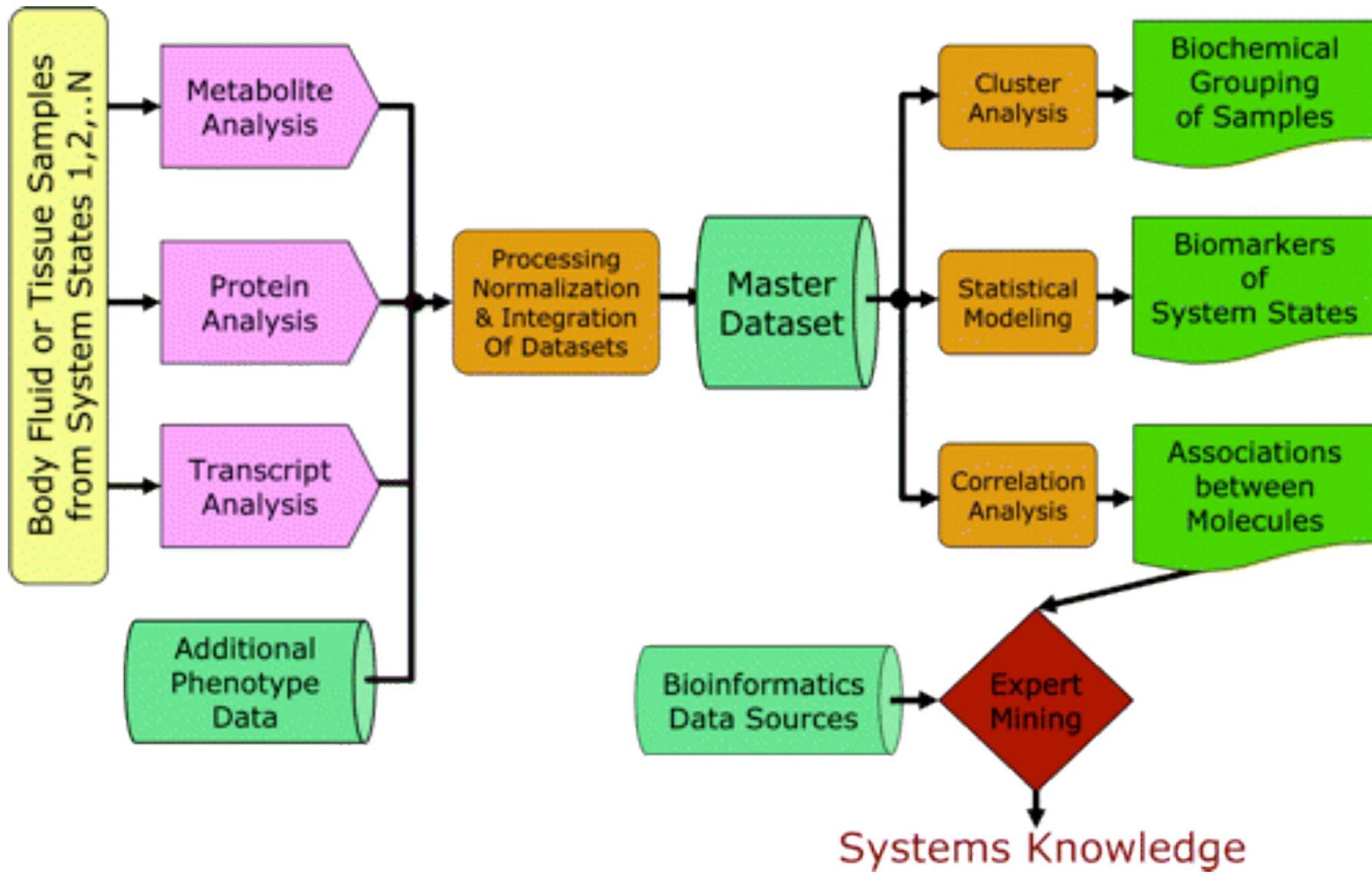
Disease-driven  
Aimed for normalcy (normal range)  
Additive

## Medical Treatments

Individualized  
Multidimensional use of drugs  
Time-sensitive  
Space-sensitive  
Synergistic

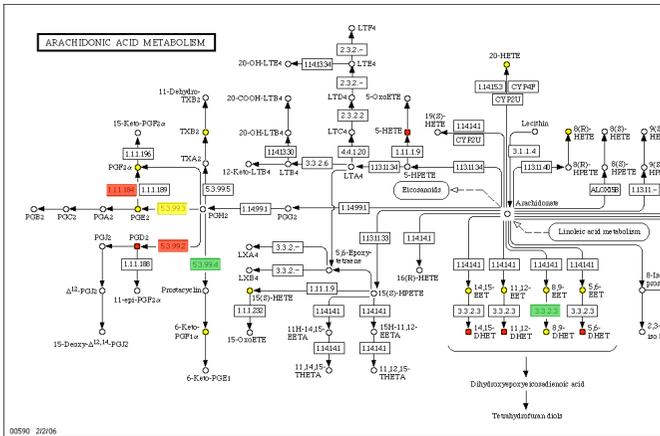




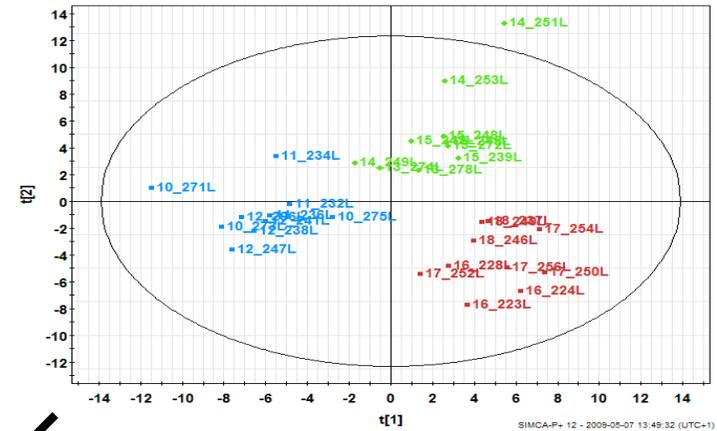


# Data analysis & integration are vital

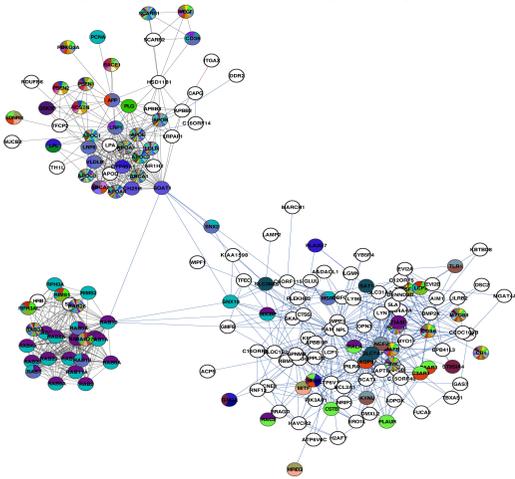
## Pathway mapping (KegArray)



## Statistics (multivariate)

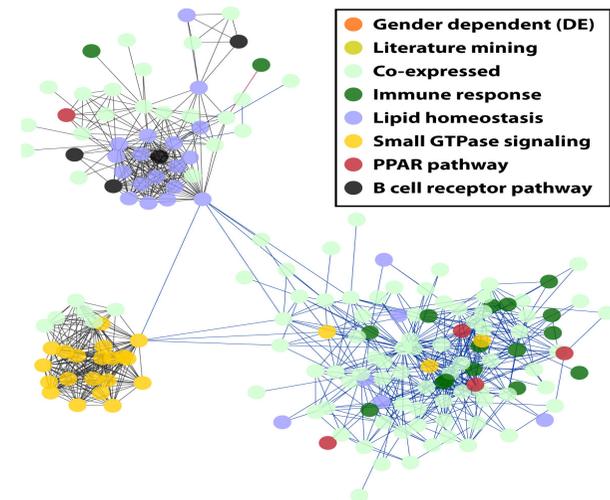


## Expression corr. (Cytoscape)

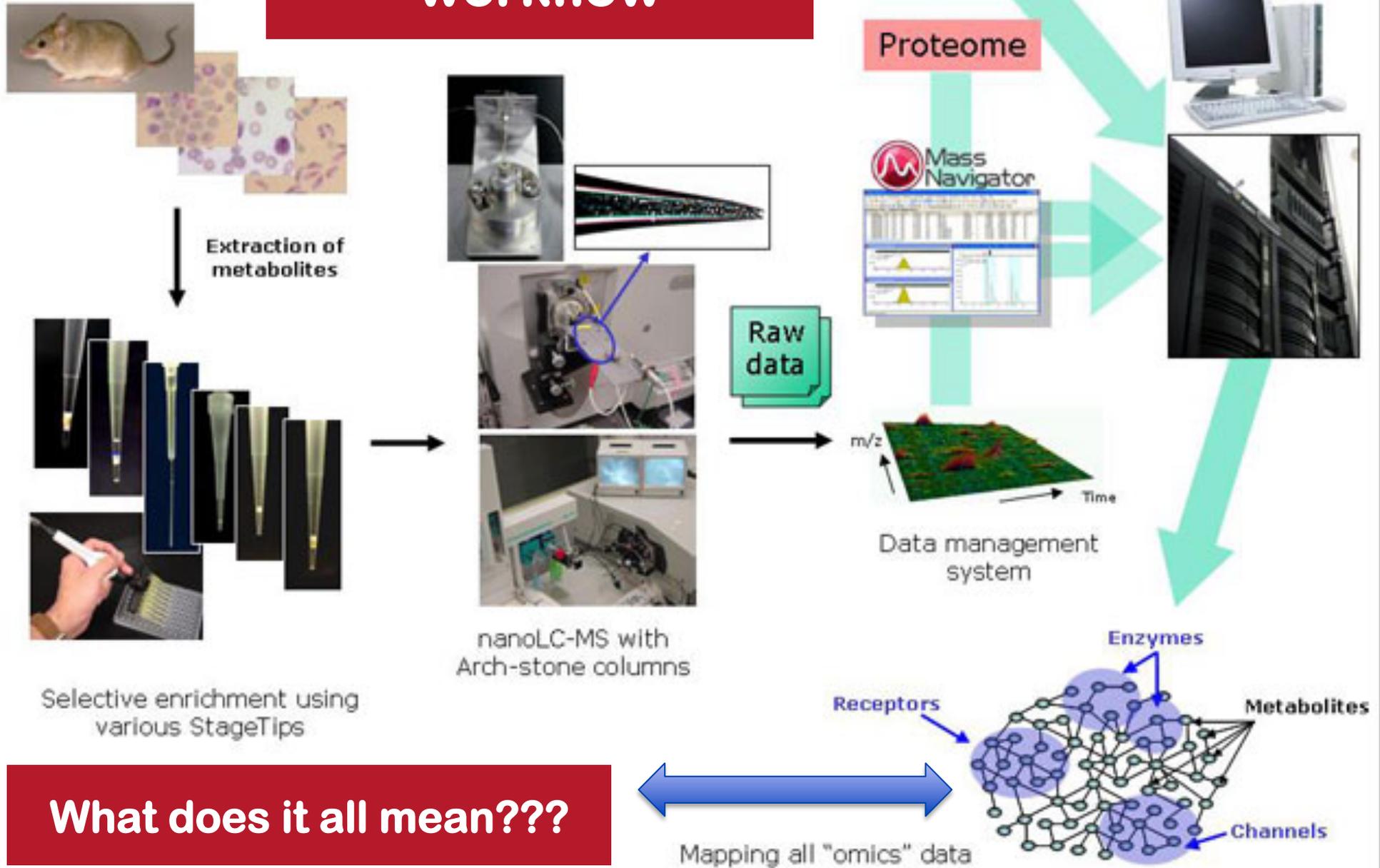


## Interactive Database (MySQL)

## Literature mining



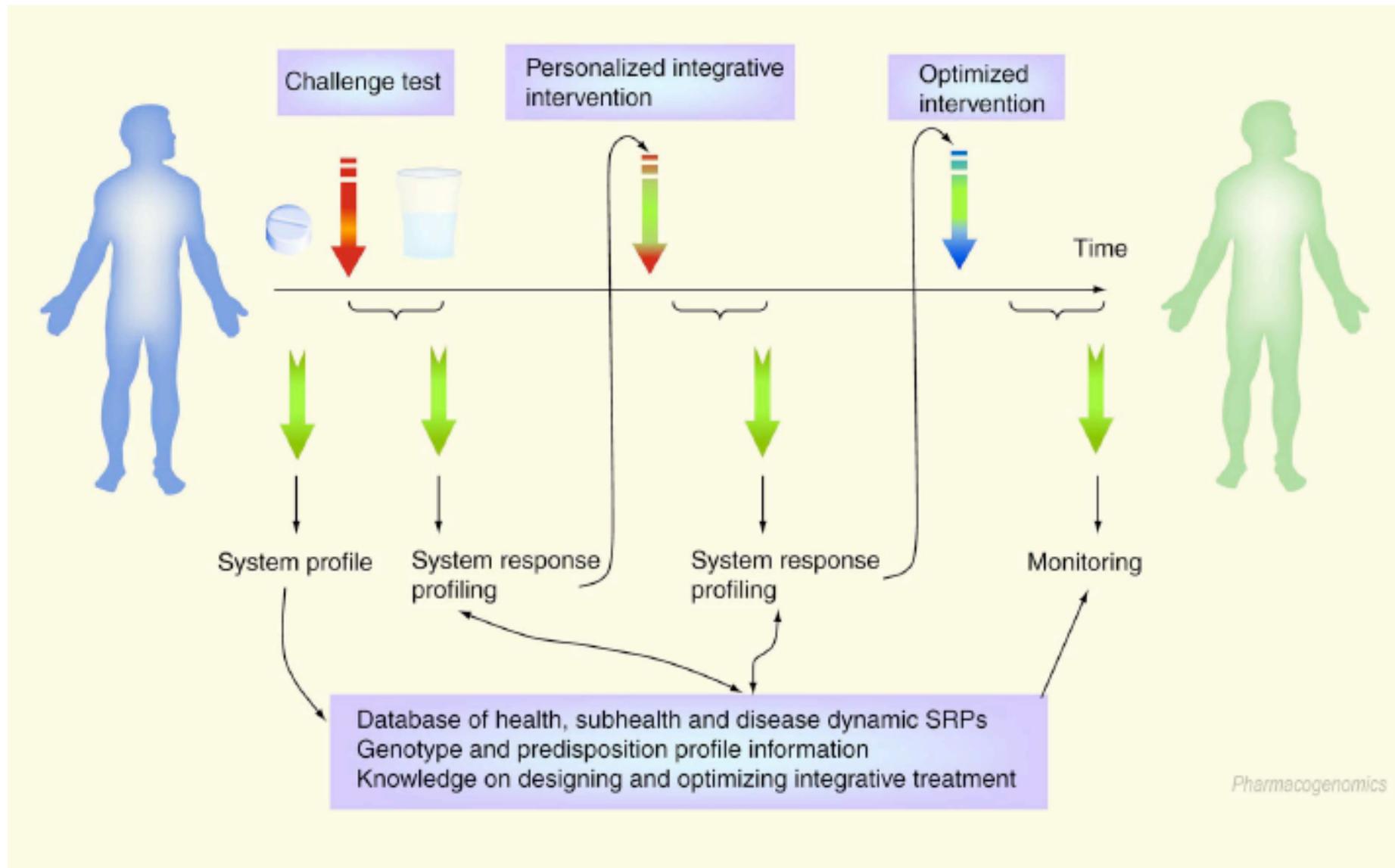
# Systems Biology workflow

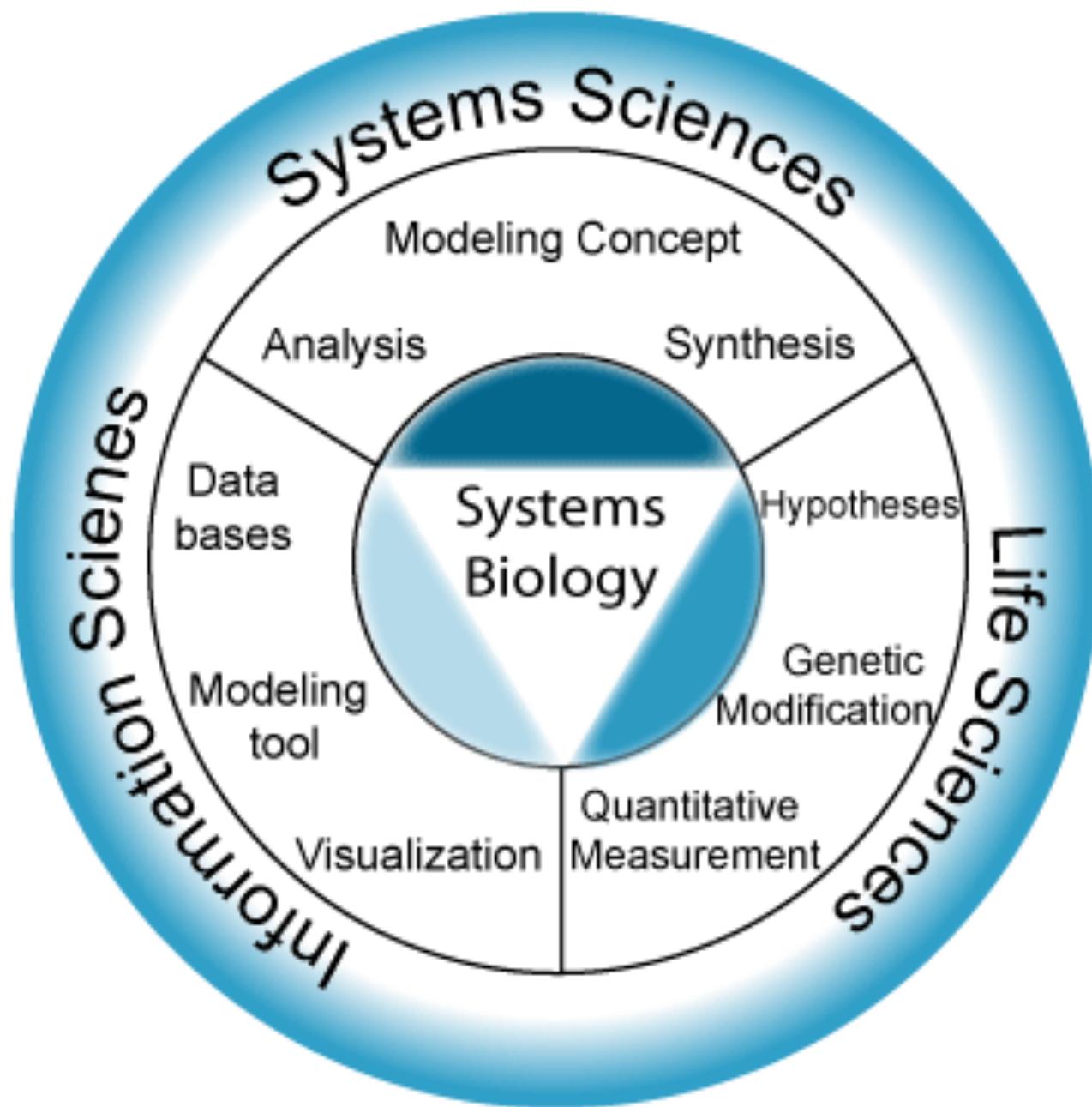


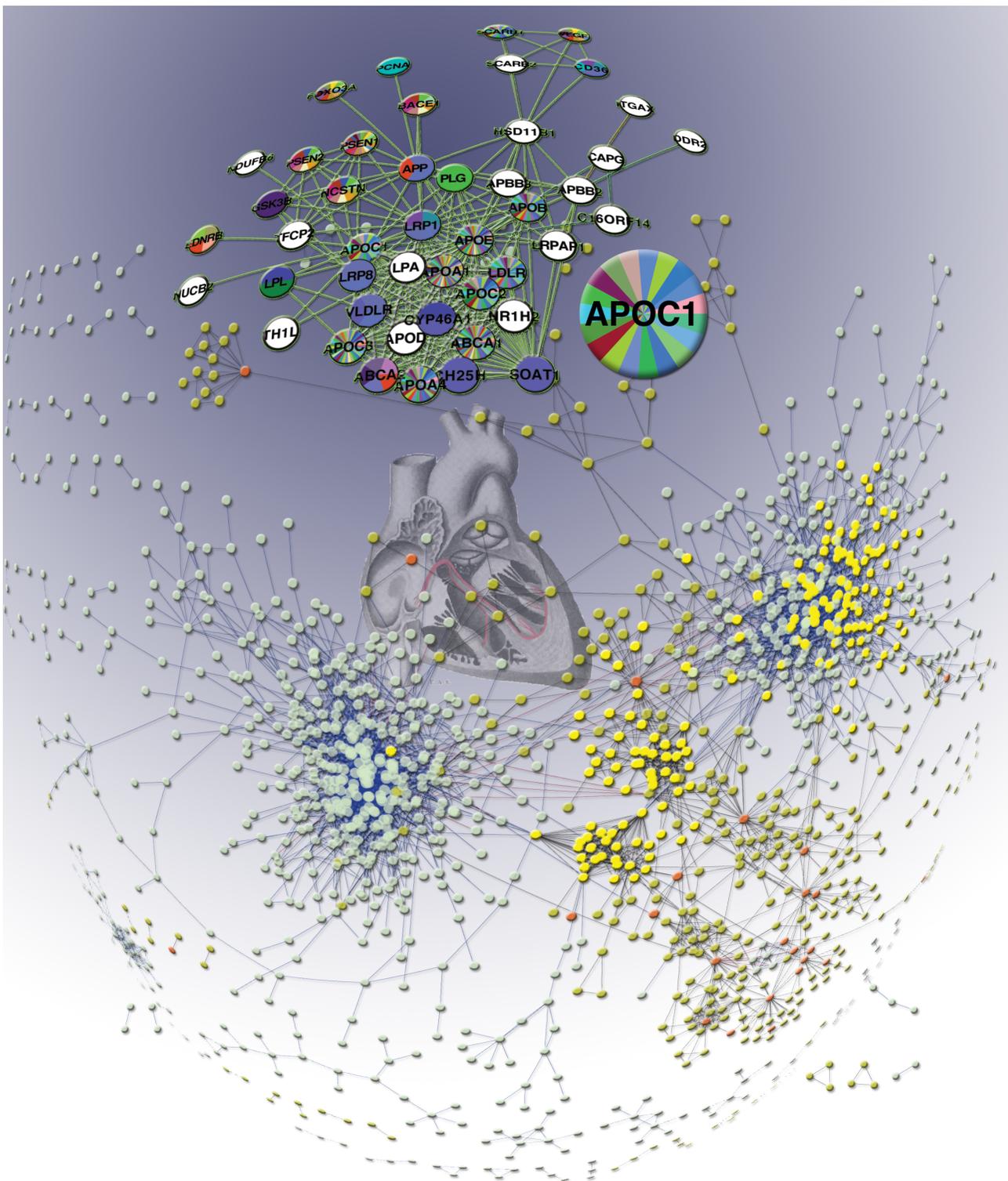
# The Holy Grail of Systems Biology



# n=1 clinical trials???







**Systems biology  
is an exciting  
approach to  
investigating  
diseases with  
complex  
etiologies**

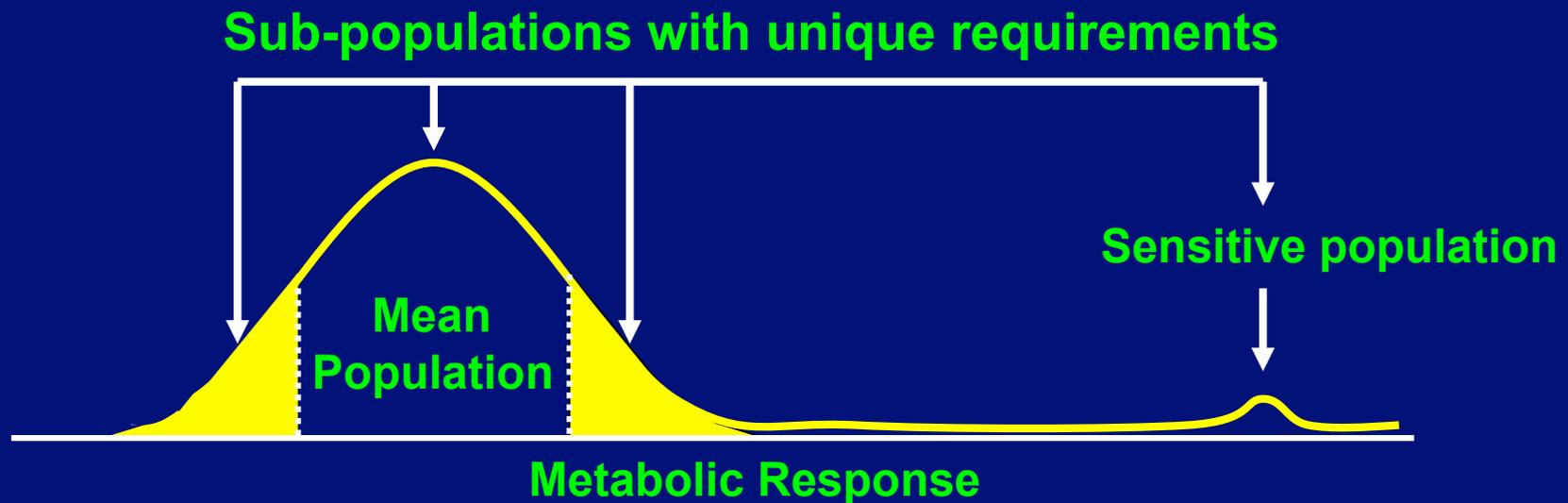


**but requires  
significant  
resources and  
a diverse  
research team**

# What is the pay off from metabolomics?

Mechanistic Insight into Biological Processes

A Step Towards Personalized Medicine



**We are not all the same!**



***And we do not want to be the same!!!!***



**Thank you for your attention**

