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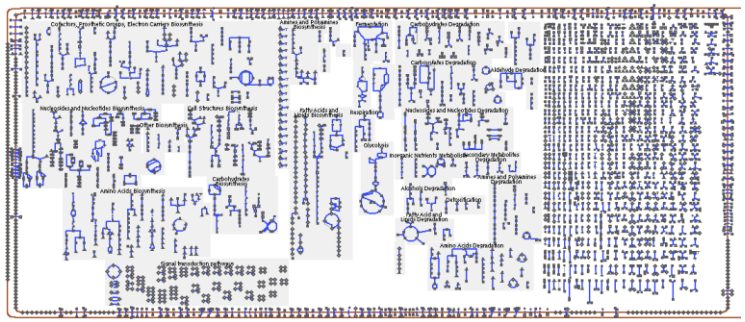
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OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

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Analyzing Metabolomics Data with SmartTables

Peter D. Karp
SRI International

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Overview

- Overview of MetaCyc family of Pathway/Genome Databases (PGDBs)
- Overview of Pathway Tools software
- SmartTables

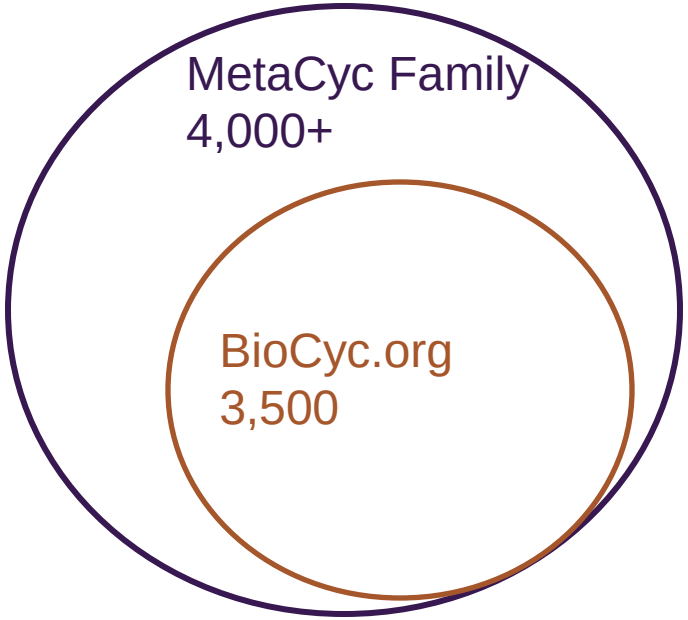
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MetaCyc Family of Pathway/Genome Databases

- 4,000+ databases from many institutions
- All domains of life with microbial emphasis
- Genomes plus predicted metabolic pathways

- DBs derived from MetaCyc via computational pathway prediction

- Common schema
- **Common controlled vocabularies**
- Managed using Pathway Tools software



Archives of Toxicology 85:1015 2011

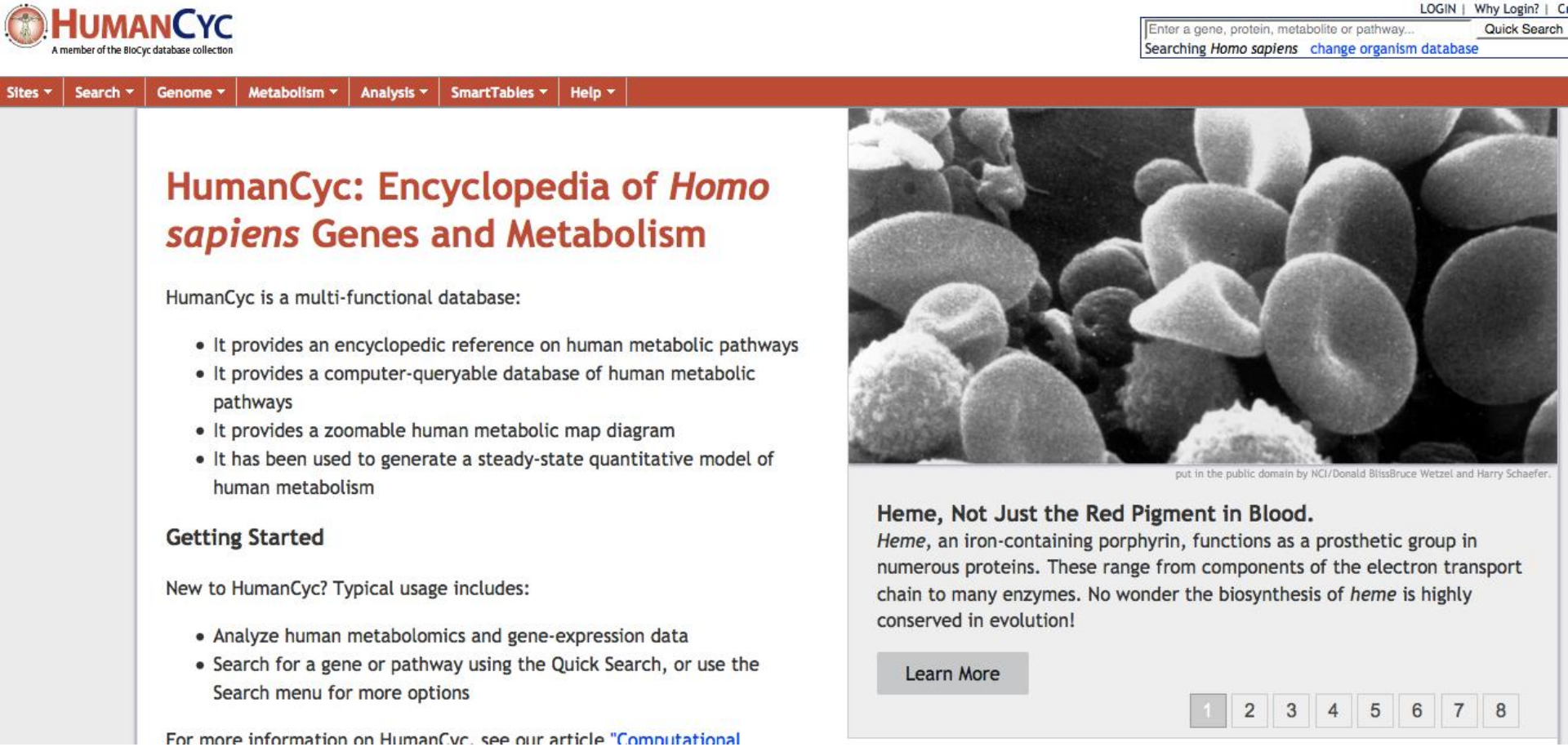
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Curated Databases Within the MetaCyc Family

Database	Organism	Organization	Publications Curated From
MetaCyc	Multiorganism	SRI	35,000
EcoCyc	*E. coli*	SRI	25,000
HumanCyc	*H. sapiens*	SRI	
AraCyc	*A. thaliana*	TAIR/Carnegie Institution	2,282
YeastCyc	*S. cerevisiae*	SGD/Stanford/SRI	565
MouseCyc	*M. musculus*	MGD/Jackson Laboratory	

http://biocyc.org/otherpgdbs.shtml

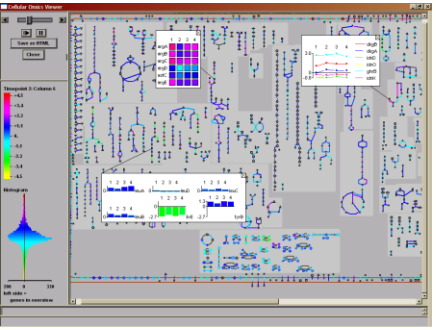
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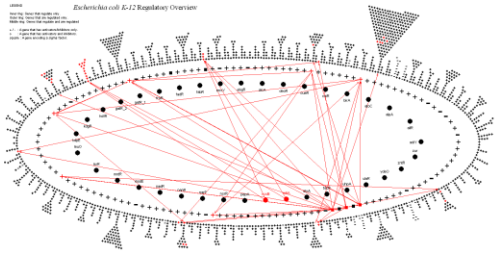
- Human pathways predicted from the human genome in 2004
  - Romero *et al*, *Genome Biology* 6(1):1-17 2004
- 295 pathways, 2600 reactions, 1700 metabolites
- Extensive query and visualization tools linking genome to metabolome
- HumanCyc.org

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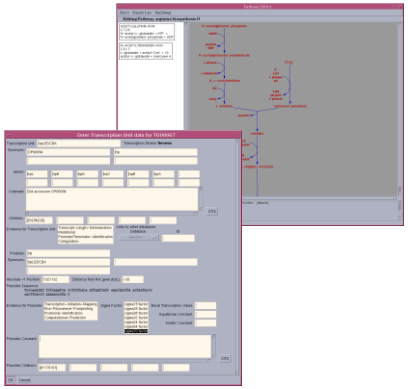
Pathway Tools Software



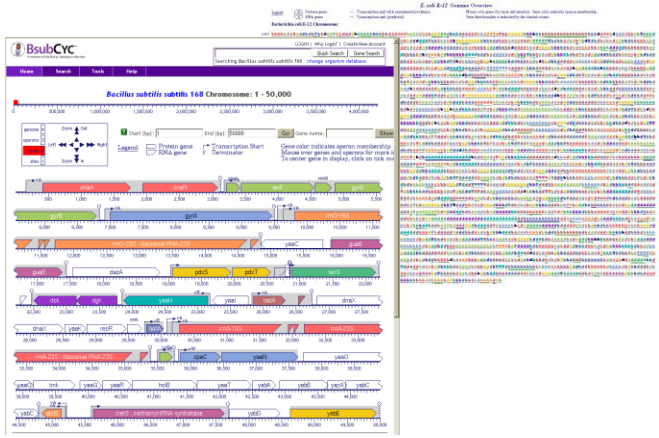
Annotated Genome + PathoLogic



MetaFlux ← Pathway/Genome Database → Pathway/Genome Navigator



Pathway/Genome Editors



Briefings in Bioinformatics 11:40-79 2010

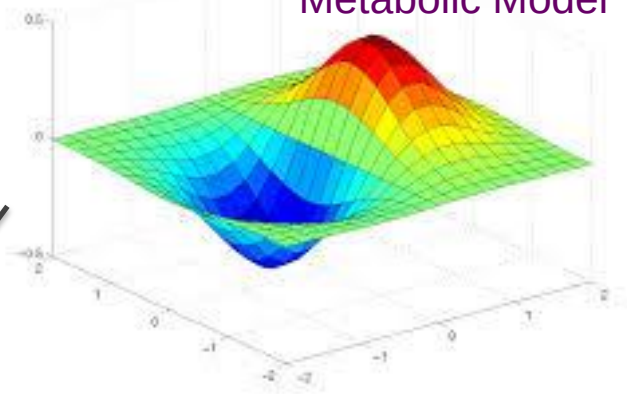
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Pathway Tools Enables Multi-Use Metabolic Databases

Encyclopedia



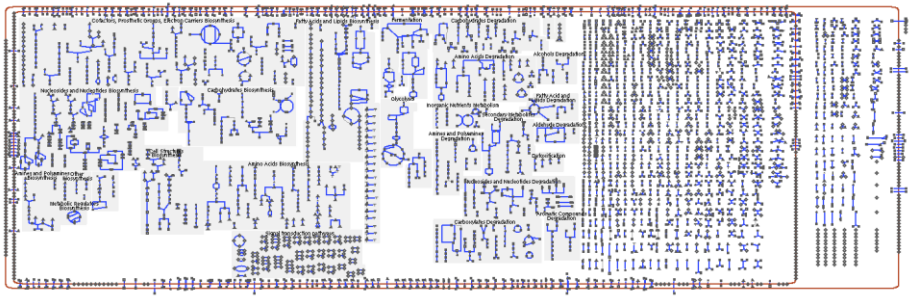
Metabolic Model



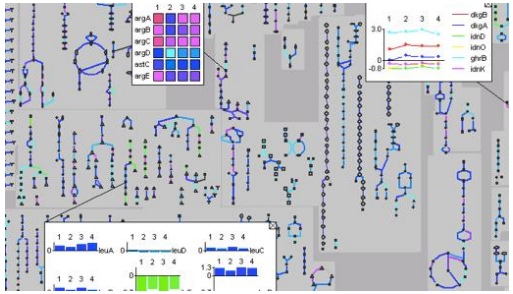
Queryable Database



Zoomable Metabolic Map



Omics Data Analysis

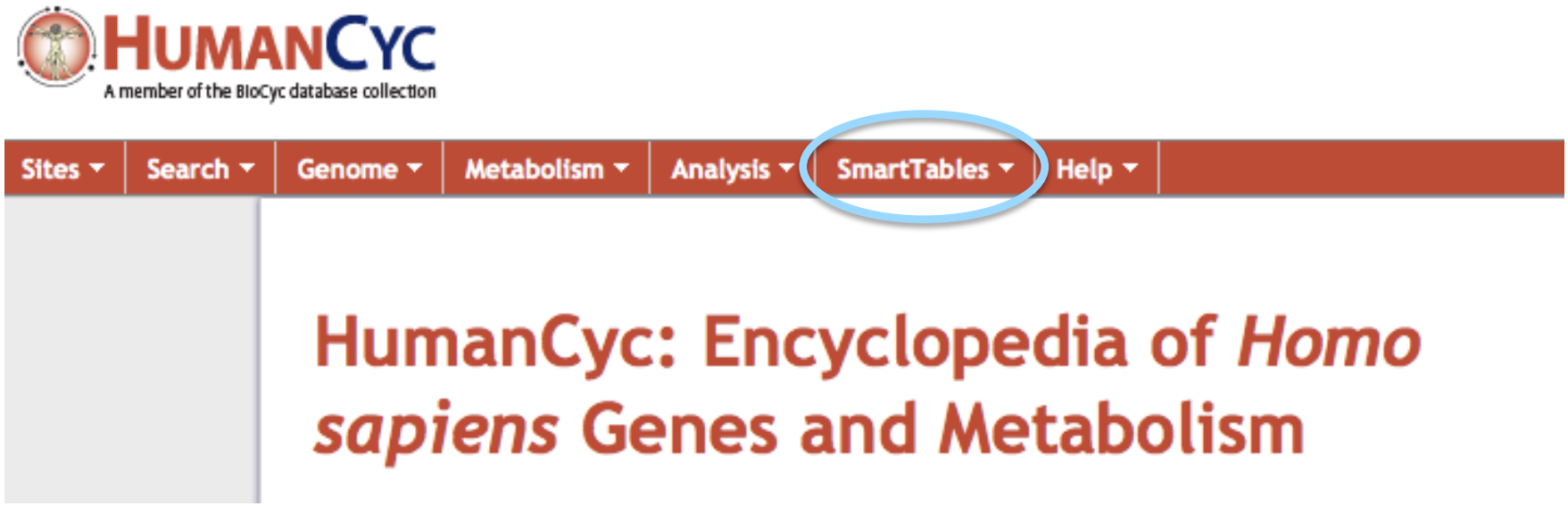


SmartTables (formerly Web Groups)

- Collect lists of database objects
  - Genes, metabolites, pathways, sequence regions, …
- Transform them into related objects
  (eg: transform list of genes → list of pathways)
- Filter and combine
- Share with public or specific collaborators
- Export to spreadsheet
- Omics analyses

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Accessing SmartTables



- BioCyc.org, HumanCyc.org, EcoCyc.org…
- To create saved SmartTables, create a (free) BioCyc account for yourself
- From the web menu:
- SmartTables->My SmartTables

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Creating SmartTables: User-Defined SmartTables

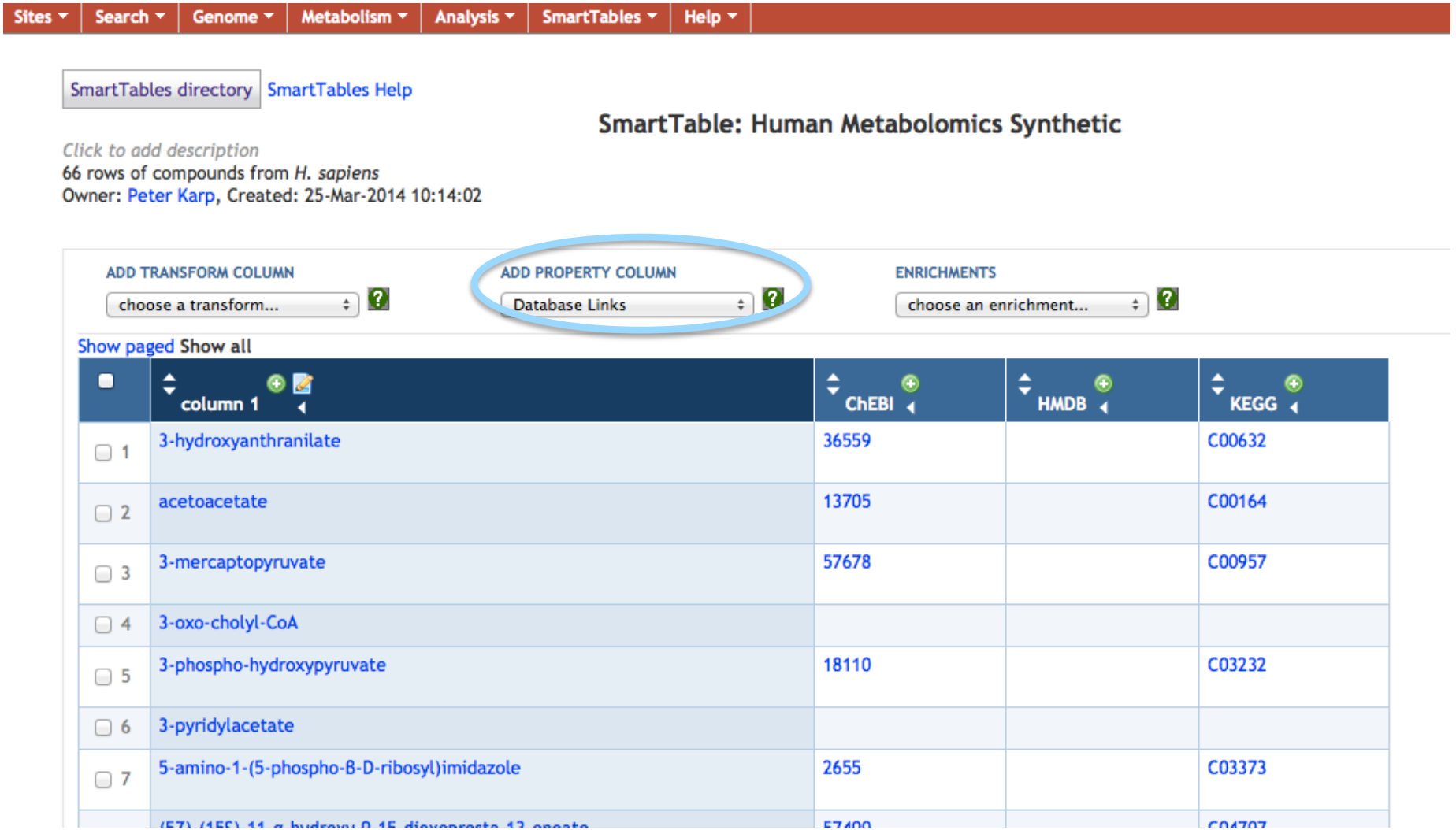
- Create a SmartTable
  - Type in metabolite names
  - From search results
  - Upload a tab-delimited text file



	column 1
1	a 2-(2-hydroxyacyl)sphingosine
2	3-hydroxyanthranilate
3	acetoacetate
4	3-mercaptopyruvate
5	3-oxo-cholyl-CoA
6	3-phospho-hydroxypyruvate
7	3-pyridylacetate
8	5-amino-1-(5-phospho-β-D-ribosyl)imidazole
9	(5Z)-(15S)-11-α-hydroxy-9,15-dioxoprosta-13-enoate
10	prostaglandin E_2
11	acetol
12	β-D-galactosyl-1,3-(*N*-acetyl-β-D-glucosaminyl-1,6)-*N*-acetyl-D-galactosaminyl-R
13	betaine aldehyde
14	citrate

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Using SmartTables: Browsing Attributes



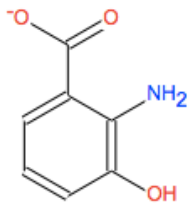
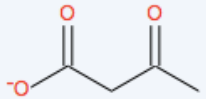
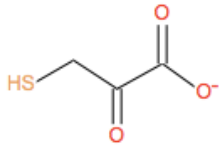
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Using SmartTables: Browsing Attributes

column 1	Molecular-Weight	Monoisotopic-Molecular-Weight
3-hydroxyanthranilate	152.129	153.04259
acetoacetate	101.082	102.03169
3-mercaptopyruvate	119.115	119.98811
3-oxo-cholyl-CoA	1152.048	1155.3766
3-phospho-hydroxypyruvate	181.018	183.9773
3-pyridylacetate	136.13	137.04768
5-amino-1-(5-phospho-β-D-ribosyl)imidazole	294.18	295.05695
(5Z)-(15S)-11-α-hydroxy-9,15-dioxoprosta-13-enoate	349.446	350.20932
prostaglandin E_2	351.462	352.22498
acetol	74.079	74.03678
betaine aldehyde	102.156	102.09189
citrate	189.101	192.02701
nicotine-1'-N-oxide	178.233	178.11061
glutarate semialdehyde	115.108	116.04734
trans-1,2-dihydrobenzene-1,2-diol	112.128	112.05243
D-gluconate 6-phosphate	273.113	276.02463

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Using SmartTables: Browsing Attributes

	column 1	SMILES	Structure of compound
1	3-hydroxyanthranilate	C1(C=C(C(N)=C(O)C=1)C([O-])=O)	
2	acetoacetate	CC(=O)CC([O-])=O	
3	3-mercaptopyruvate	C(C(C(=O)[O-])=O)S	

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Using SmartTables: Browsing Attributes

Show paged **Show all**

	column 1	Mechanism	Regulates
1	3-hydroxyanthranilate		
2	acetoacetate	COMPETITIVE	Regulation of acetyl-coA synthetase by acetoacetate
3	3-mercaptopyruvate		
4	3-oxo-cholyl-CoA		
5	3-phospho-hydroxypyruvate		
6	3-pyridylacetate		
7	5-amino-1-(5-phospho-β-D-ribosyl)imidazole		
8	(5Z)-(15S)-11-α-hydroxy-9,15-dioxoprosta-13-enoate		
9	prostaglandin E_2		
10	acetol		
11	betaine aldehyde		
12	citrate		
13	nicotine-1'-N-oxide		
14	glutarate semialdehyde	ALLOSTERIC	Regulation of succinate semialdehyde dehydrogenase by glutarate semialdehyde
15	*trans*-1,2-dihydrobenzene-1,2-diol		

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SmartTable Transformations

- Create new columns that are computed from existing columns

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Transformations: Reactions and Pathways of Metabolite

ADD TRANSFORM COLUMN: Pathways of compound

ADD PROPERTY COLUMN: choose a property

ENRICHMENTS: choose an enrichment...

Show paged | Show all

	column 1	Reactions of compounds	Pathways of compound
1	3-hydroxyanthranilate	3-hydroxyanthranilate + oxygen → aminocarboxymuconate semialdehyde + H^+ 3-hydroxy-L-kynurenine + H_2O → 3-hydroxyanthranilate + L-alanine + H^+	L-kynurenine degradation tryptophan degradation to 2-amino-3-carboxymuconate semialdehyde
2	acetoacetate	succinyl-CoA + acetoacetate → succinate + acetoacetyl-CoA acetoacetate + ATP + coenzyme A → acetoacetyl-CoA + AMP + diphosphate acetoacetate + H^+ → acetone + CO_2 acetoacetate$_{[extracellular\ space]}$ + $H^+_{[extracellular\ space]}$ → acetoacetate$_{[cytosol]}$ + $H^+_{[cytosol]}$ (*S*)-3-hydroxybutanoate + 2-oxoglutarate = (*R*)-2-hydroxyglutarate + acetoacetate 4-fumaryl-acetoacetate + H_2O → fumarate + acetoacetate + H^+ (*R*)-3-hydroxybutanoate + NAD^+ ↔ acetoacetate + NADH + H^+ (*S*)-3-hydroxy-3-methylglutaryl-CoA → acetoacetate + acetyl-CoA	leucine degradation I tyrosine degradation ketogenesis acetone degradation I (to methylglyoxal) ketolysis
3	3-mercaptopyruvate	hydrogen cyanide + 3-mercaptopyruvate → pyruvate + thiocyanate + H^+ 2-oxoglutarate + L-cysteine → L-glutamate + 3-mercaptopyruvate	L-cysteine degradation II
4	3-oxo-cholyl-CoA	$NAD(P)^+$ + choloyl-CoA = NAD(P)H + 3-oxo-cholyl-CoA + H^+	
5	3-phospho-hydroxypyruvate	3-phospho-D-glycerate + NAD^+ → 3-phospho-hydroxypyruvate + NADH + H^+ 3-phospho-L-serine + 2-oxoglutarate ← 3-phospho-hydroxypyruvate + L-glutamate	serine biosynthesis (phosphorylated route)
6	3-pyridylacetate	4-(3-pyridyl)-butanoate → 3-pyridylacetate	nicotine degradation IV nicotine degradation III
7	5-amino-1-(5-phospho-ß-D-ribosyl)imidazole	ATP + 2-(formamido)-N^1-(5-phospho-ß-D-ribosyl)acetamidine → ADP + 5-amino-1-(5-phospho-ß-D-ribosyl)imidazole + phosphate + H^+ 5-amino-1-(5-phospho-D-ribosyl)imidazole-4-carboxylate + 2 H^+ ← 5-amino-1-(5-phospho-ß-D-ribosyl)imidazole + CO_2	inosine-5'-phosphate biosynthesis 5-aminoimidazole ribonucleotide biosynthesis

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Transformations: Genes of Pathway

Show paged **Show all**

	column 1	Reactions of compounds	Pathways of compound	Genes of pathway
1	3-hydroxyanthranilate	3-hydroxyanthranilate + oxygen → aminocarboxymuconate semialdehyde + H^+ 3-hydroxy-L-kynurenine + H_2O → 3-hydroxyanthranilate + L-alanine + H^+	L-kynurenine degradation tryptophan degradation to 2-amino-3-carboxymuconate semialdehyde	ACMSD DHTKD1 CCBL1 GOT2 CCBL2 AADAT AFMID KMO KYNU HAAO IDO1 IDO2 TDO2
2	acetoacetate	succinyl-CoA + acetoacetate → succinate + acetoacetyl-CoA acetoacetate + ATP + coenzyme A → acetoacetyl-CoA + AMP + diphosphate acetoacetate + H^+ → acetone + CO_2 $acetoacetate_{[extracellular\ space]} + H^+_{[extracellular\ space]}$ → $acetoacetate_{[cytosol]} + H^+_{[cytosol]}$ (*S*)-3-hydroxybutanoate + 2-oxoglutarate = (*R*)-2-hydroxyglutarate + acetoacetate 4-fumaryl-acetoacetate + H_2O → fumarate + acetoacetate + H^+ (*R*)-3-hydroxybutanoate + NAD^+ ↔ acetoacetate + NADH + H^+ (*S*)-3-hydroxy-3-methylglutaryl-CoA → acetoacetate + acetyl-CoA	leucine degradation I tyrosine degradation ketogenesis acetone degradation I (to methylglyoxal) ketolysis	BCAT1 BCAT2 MCCC2 MCCC1 AUH HMGCL HMGCLL1 IVD TAT HPD HGD GSTZ1 FAH ACAT1 HMGCS2 BDH1 CYP2U1 CYP2S1 CYP4X1 CYP2A6 AKR1B1 AKR1B10 CYP2E1

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Transformations: New SmartTable from Column

1 2 3 4 Next Show all

	Pathways of compound from Human Metabolomics Synthetic	Genes of pathway	Compounds of pathway
1	4-hydroxybenzoate biosynthesis	TAT	L-tyrosine 2-oxoglutarate L-glutamate 4-hydroxyphenylpyruvate ATP AMP diphosphate 4-hydroxybenzoate NAD^+ coenzyme A 4-coumaryl-CoA H^+ 4-hydroxybenzoyl-CoA acetyl-CoA NADH 3-(4-hydroxyphenyl)lactate 4-coumarate H_2O
2	5-aminoimidazole ribonucleotide biosynthesis	PPAT PFAS GART	5-amino-1-(5-phospho-ß-D-ribosyl)imidazole 2-(formamido)-N^1-(5-phospho-ß-D-ribosyl)acetamidine 10-formyl-tetrahydrofolate tetrahydrofolate N^2-formyl-N^1-(5-phospho-ß-D-ribosyl)glycinamide glycine ATP H^+ ADP phosphate N^1-(5-phospho-ß-D-ribosyl)glycinamide L-glutamate diphosphate 5-phospho-ß-D-ribosylamine 5-phospho-α-D-ribose 1-diphosphate

Other Operations on SmartTables

- Set union, intersection, difference among two SmartTables
- Filter SmartTable rows to keep/reject all rows containing specified value or substring or regular expression
- Share SmartTable with public or specified users
- Freeze SmartTable for publication

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Enrichment Analysis

- Statistical method to find classes of objects that have more or less objects than would be expected by chance

* Based on the Hypergeometric Distribution

- Can perform enrichment, depletion, or both

- Multiple ontologies can be used in Pathway Tools

* Multiple testing correction optional

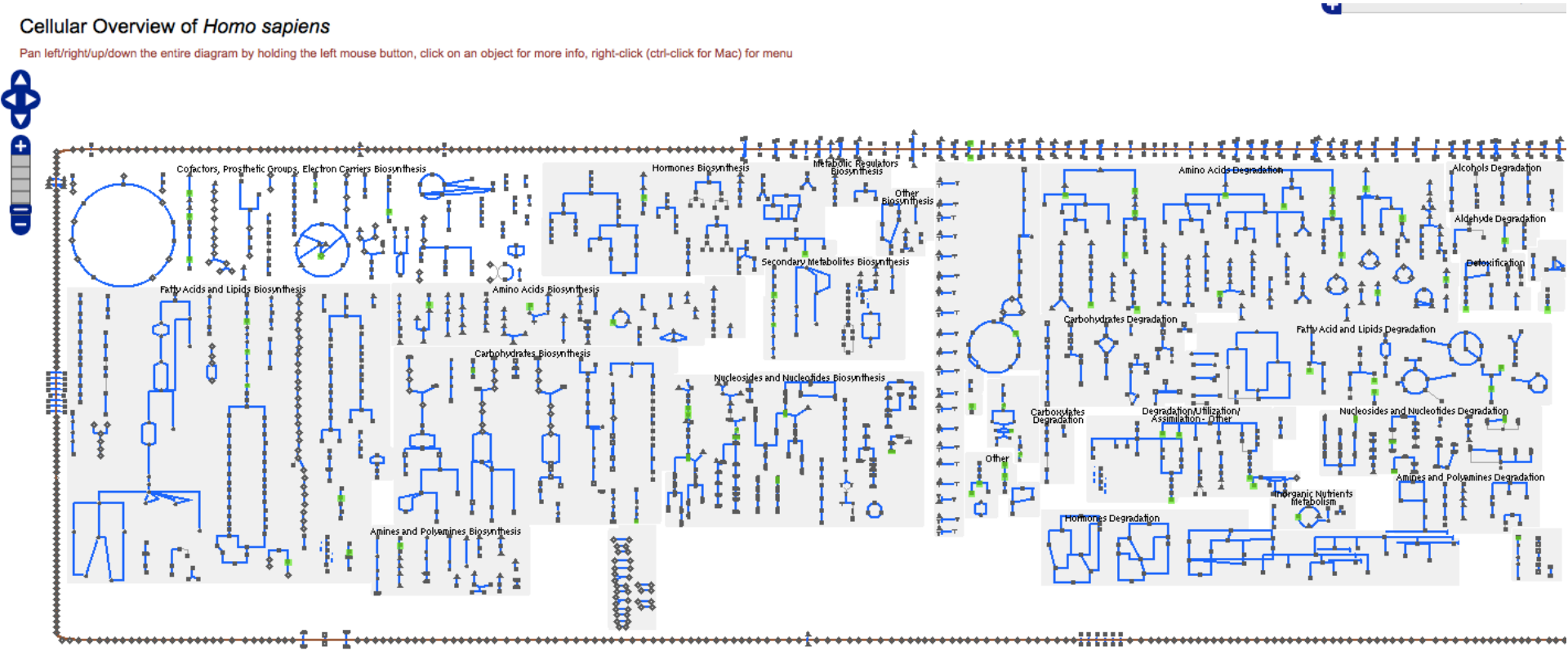
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Enrichment Analysis

1	NAD *de novo* biosynthesis	0.01065204	nicotinate adenine dinucleotide formate *N*-formylkynurenine 3-hydroxyanthranilate
2	tryptophan degradation to 2-amino-3-carboxymuconate semialdehyde	0.010885004	formate *N*-formylkynurenine 3-hydroxyanthranilate
3	NAD Biosynthesis	0.014184234	nicotinate adenine dinucleotide formate *N*-formylkynurenine 3-hydroxyanthranilate
4	NAD Metabolism	0.01838762	nicotinate adenine dinucleotide formate *N*-formylkynurenine 3-hydroxyanthranilate
5	tryptophan utilization II	0.030494805	formate *N*-formylkynurenine 3-hydroxyanthranilate serotonin nicotinate adenine dinucleotide
6	tryptophan degradation	0.04628297	formate *N*-formylkynurenine 3-hydroxyanthranilate
	tryptophan utilization I	0.050800793	formate *N*-formylkynurenine 3-hydroxyanthranilate

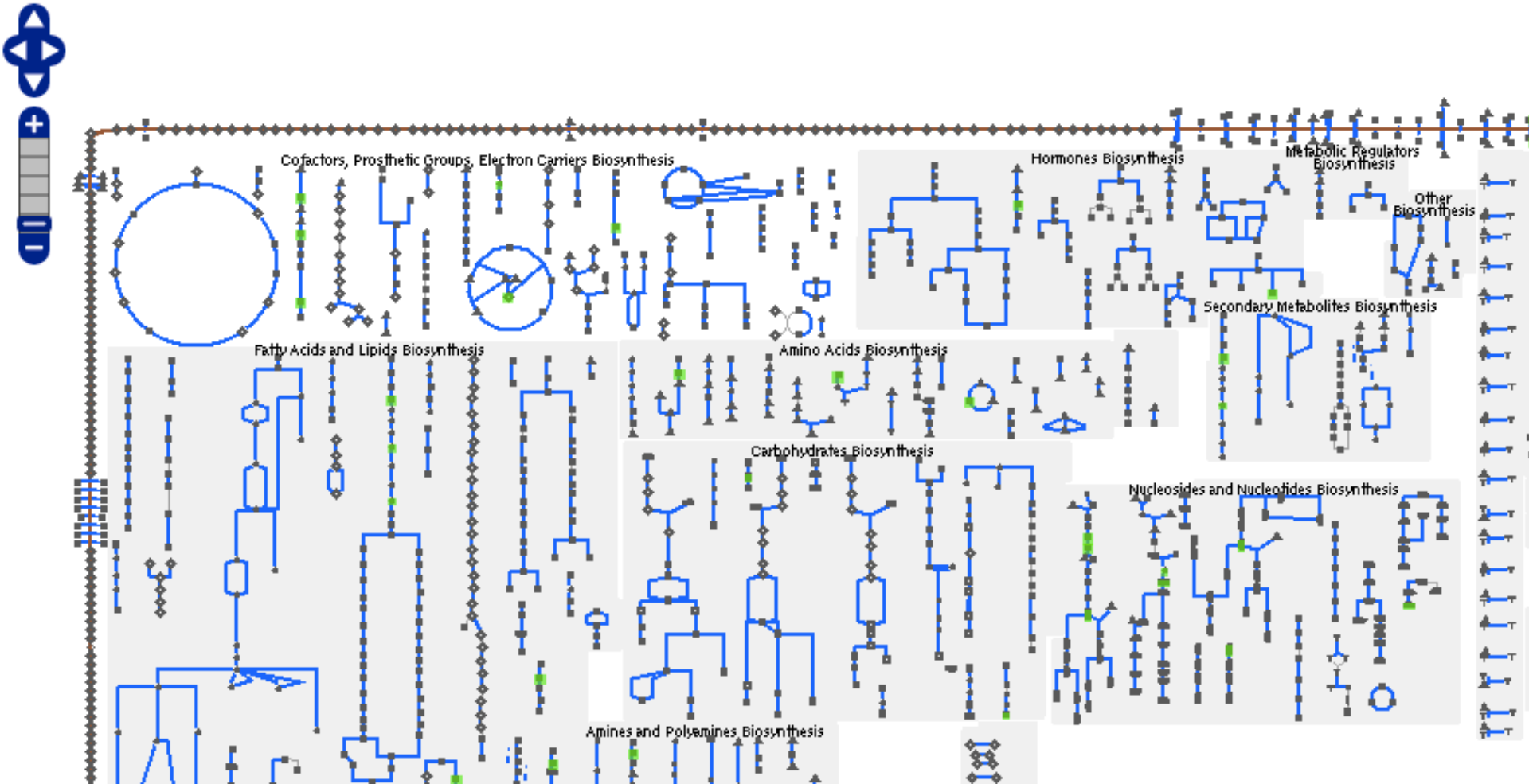
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Paint Metabolomics Data onto Cellular Overview – Boolean Data

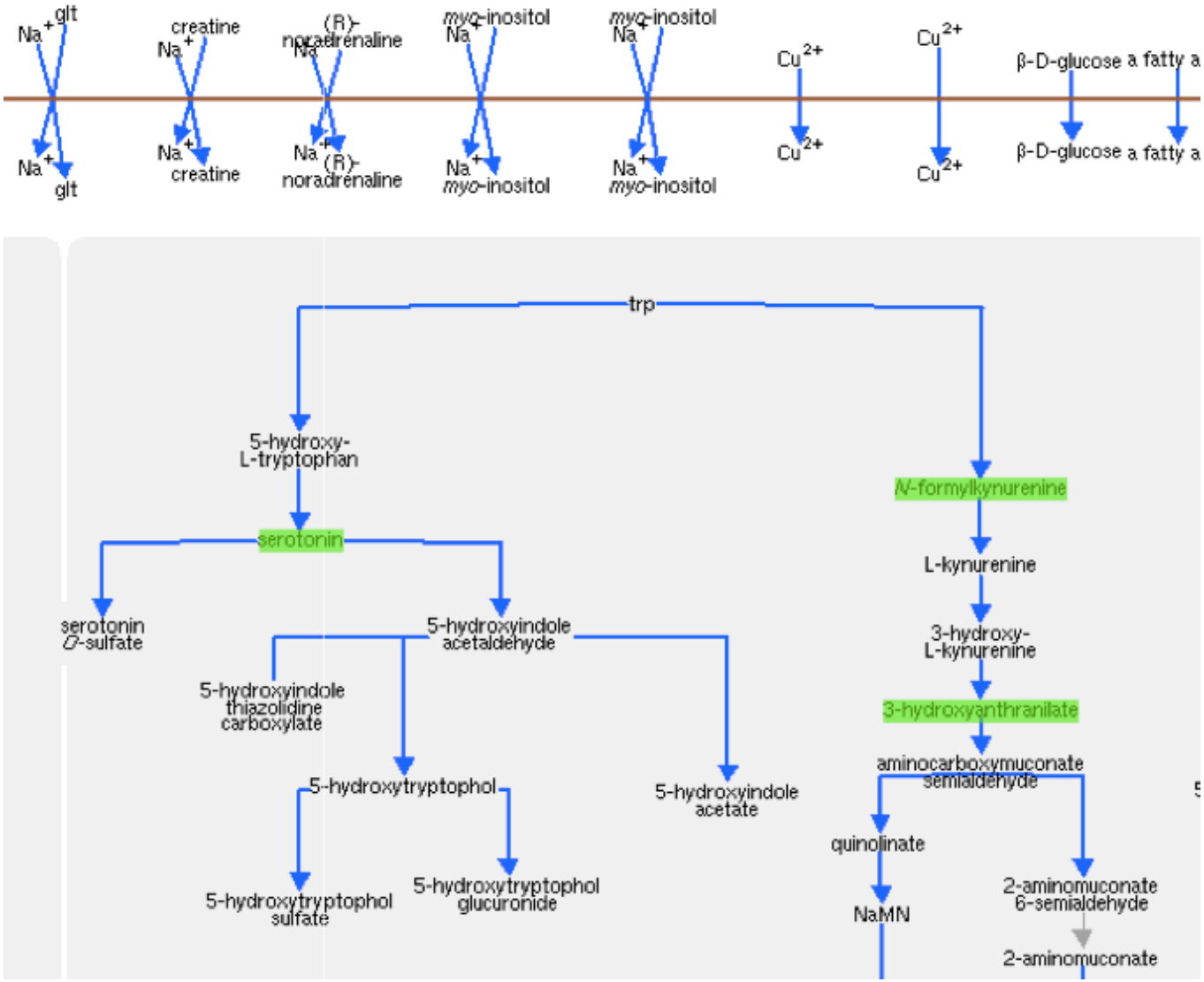


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Paint Metabolomics Data onto Cellular Overview

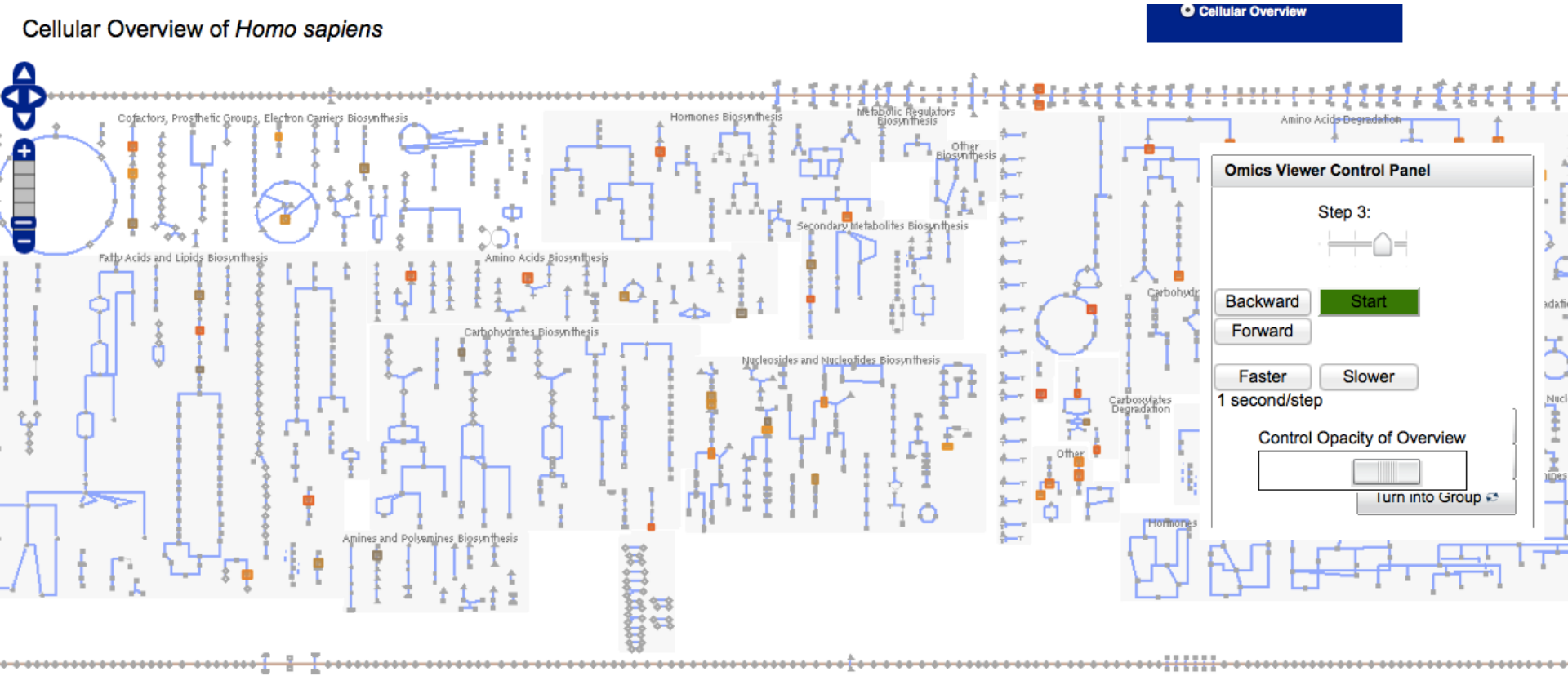


Paint Metabolomics Data onto Cellular Overview

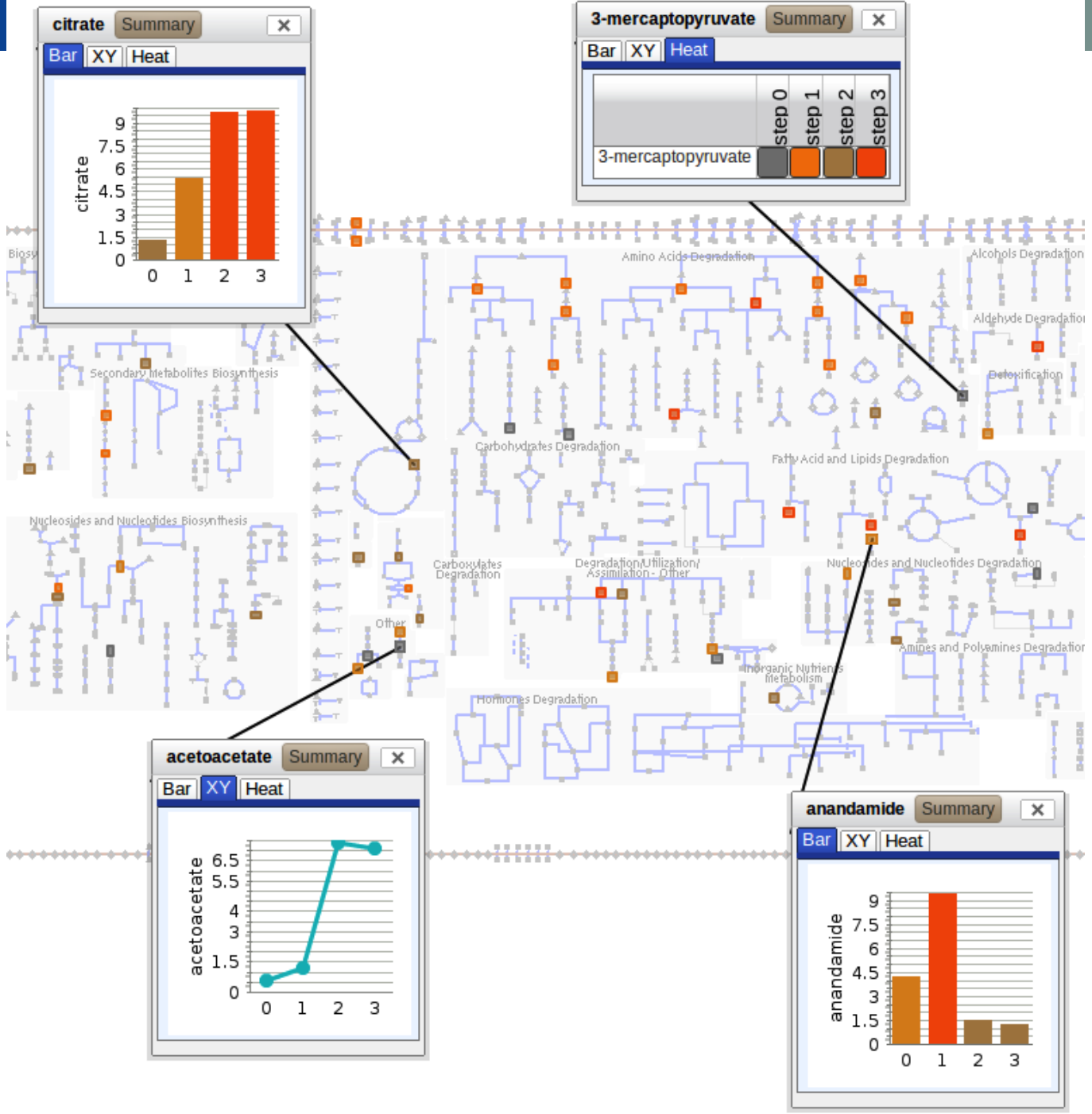


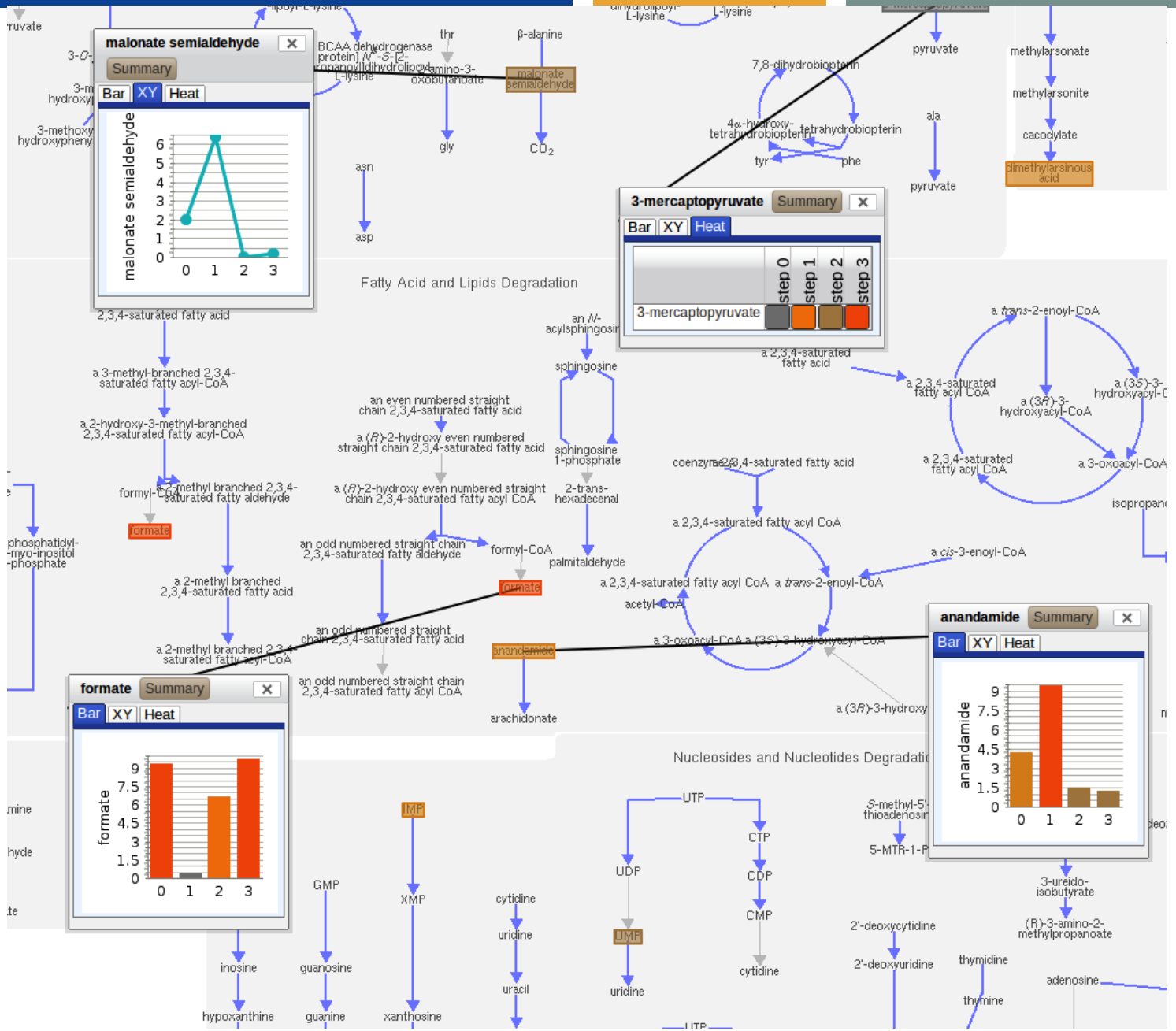
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Paint Metabolomics Data onto Cellular Overview – Animation of Numeric Data



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citrate
Summary
Bar
XY
Heat
citrate
9
7.5
6
4.5
3
1.5
0
0 1 2 3
3-mercaptopyruvate
Summary
Bar
XY
Heat
step 0
step 1
step 2
step 3
3-mercaptopyruvate
Amino Acids Degradation
Alcohols Degradation
Aldehyde Degradation
Detoxification
Secondary Metabolites Biosynthesis
Carbohydrates Degradation
Fatty Acid and Lipids Degradation
Nucleosides and Nucleotides Biosynthesis
Carboxylates Degradation
Degradation/Utilization/ Assimilation - Other
Nucleosides and Nucleotides Degradation
Other
Amines and Polyamines Degradation
Inorganic Nutrients Metabolism
Hormones Degradation
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Summary
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- MetaCyc Collaborators
  - **Sue Rhee, Peifen Zhang, Kate Dreher**
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