



Stanford - South Africa

Biomedical Informatics Program



Pathways of drug metabolism and action

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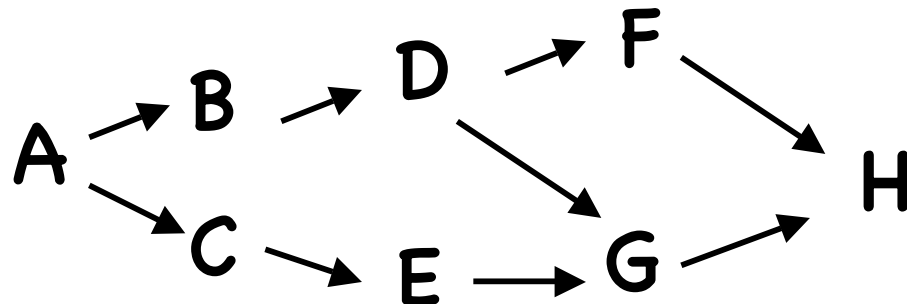
What is a pathway?

- A group of genes and small molecules that interact to create a phenotype
- The group may work in series:

A → B → C → D

Measure a phenotype

- Or in parallel:

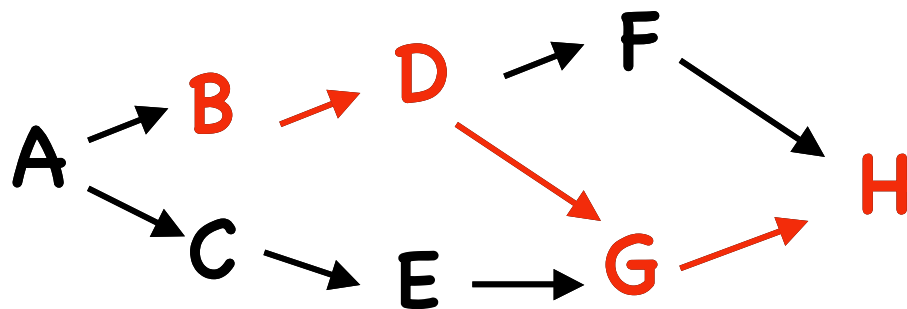


Measure a phenotype



Do pathways really exist?

- Linear pathways are useful to think about
- But there are many genes in the cell, and they can all potentially interact.
- There is really a NETWORK of interactions, and pathways just pick a commonly traversed subnetwork.



What kind of pathways in PGx?

- Pharmacokinetic pathways
 - Pathways of drug transport & metabolism
- Pharmacodynamic pathways
 - Pathways of drug and metabolite action



Where do pathways come from?

At PharmGKB...

1. Investigator announces interest in a pathway, calls for others to help
2. Conference calls to sketch out by hand the key players in pathway and evidence for them. Curator participates. Rarely achieve 100% agreement.
3. When consensus is reached, pathway is drawn graphically, and linked to PharmGKB contents.
4. Final conference call to approve the pathway and have it posted.



Why do we care about these?

Generating a list of “candidate genes” in which variation could affect drug response!

- If a gene is involved in PK, then it may affect drug or metabolite levels
- If a gene is involved in PD, then it may affect response to drug or side effects



Candidate gene lists are important

- If there are insufficient resources to genotype all possible genes, need to select a subset which may be important for determining a drug response phenotype.
- Candidate gene approaches group together genes that “make sense” and hope that they contain the answer.
- PROBLEM: May be biased by previous knowledge and will not produce entirely new “discoveries” (Cf VKORC1)

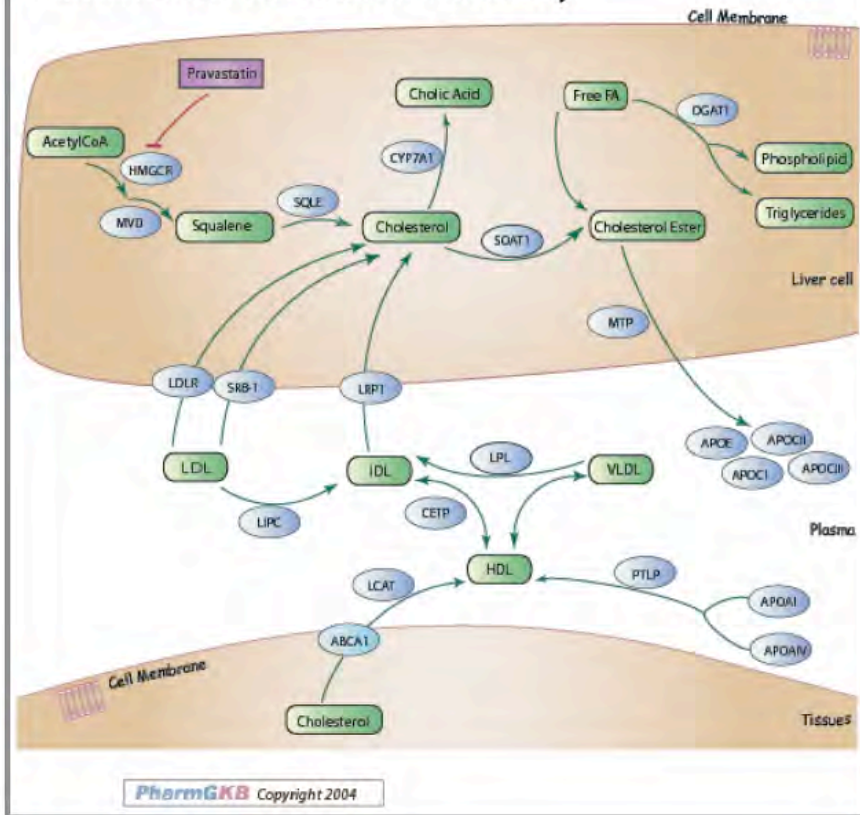


Why else do we care?

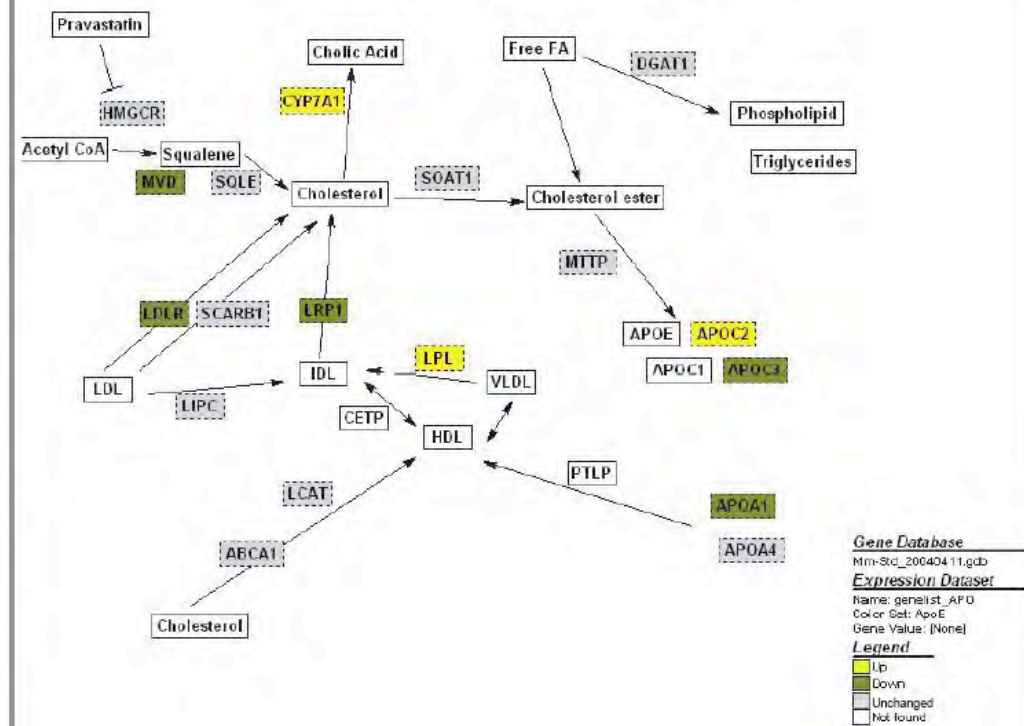
- Pathways are useful ways to look at high throughput data.
- Typically, the data is mapped onto the pathway with colors, so that the data can be viewed through the “lens” of the pathway.



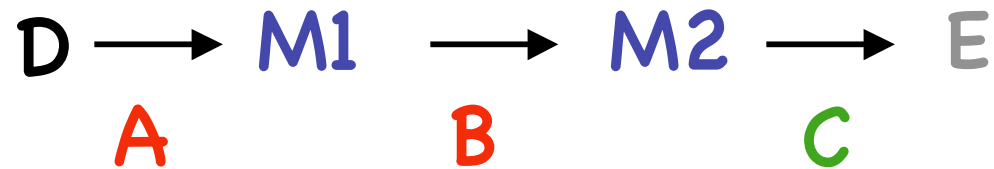
PharmGKB Pravastatin Pathway



Trends due to ApoE knockout



PK pathways are metabolic



D is drug, M1 & M2 metabolites, E = excreted metabolite

A, B are enzyme genes

C is a transporter gene that excretes into urine



“Typical” PK genes

- Phase I enzymes (cytochrome P450)
 - Reductases
 - Oxidases
- Phase II enzymes
 - Methylation
 - Sulfation
 - Acetylation
 - Glucuronidation



“Typical” PK genes

- Transporters (membrane-bound proteins)
 - Pumps (use ATP)
 - Symporters
 - Antiporters

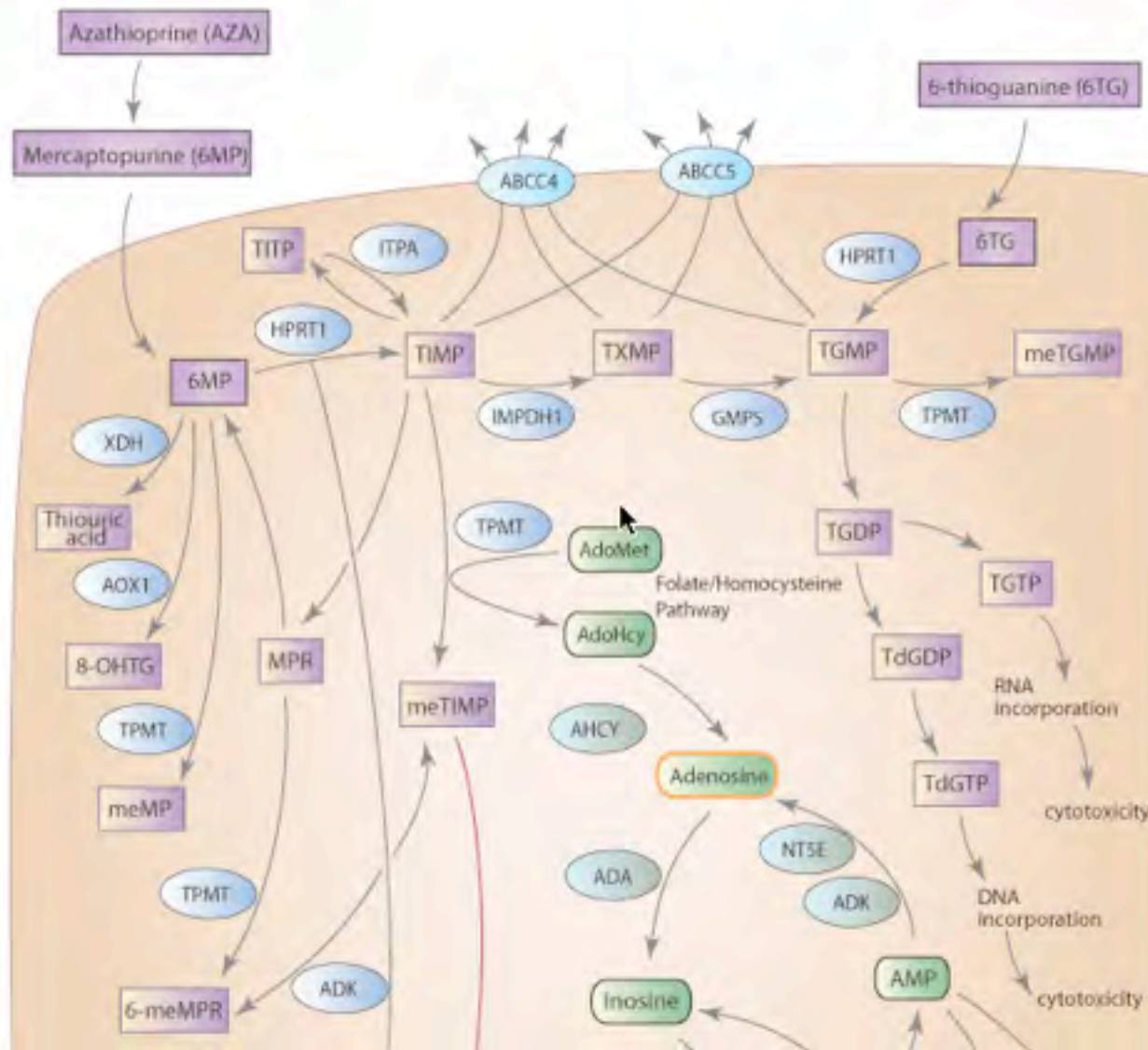


PK data

- Blood levels of drugs, metabolites (over time)
- Intracellular (Red blood cell) levels of drugs, metabolites
- Levels of enzymes
- Rate of transport of drugs



Thiopurine Pathway



Legend

All Pathways

RELATED PATHWAYS

- [Methotrexate](#)

DOWNLOADS

- [Illustrator file \(thiopurine.ai\)](#)
- [Supporting Evidence \(xls\)](#)



Nicotine Metabolism Pathway

Liver:

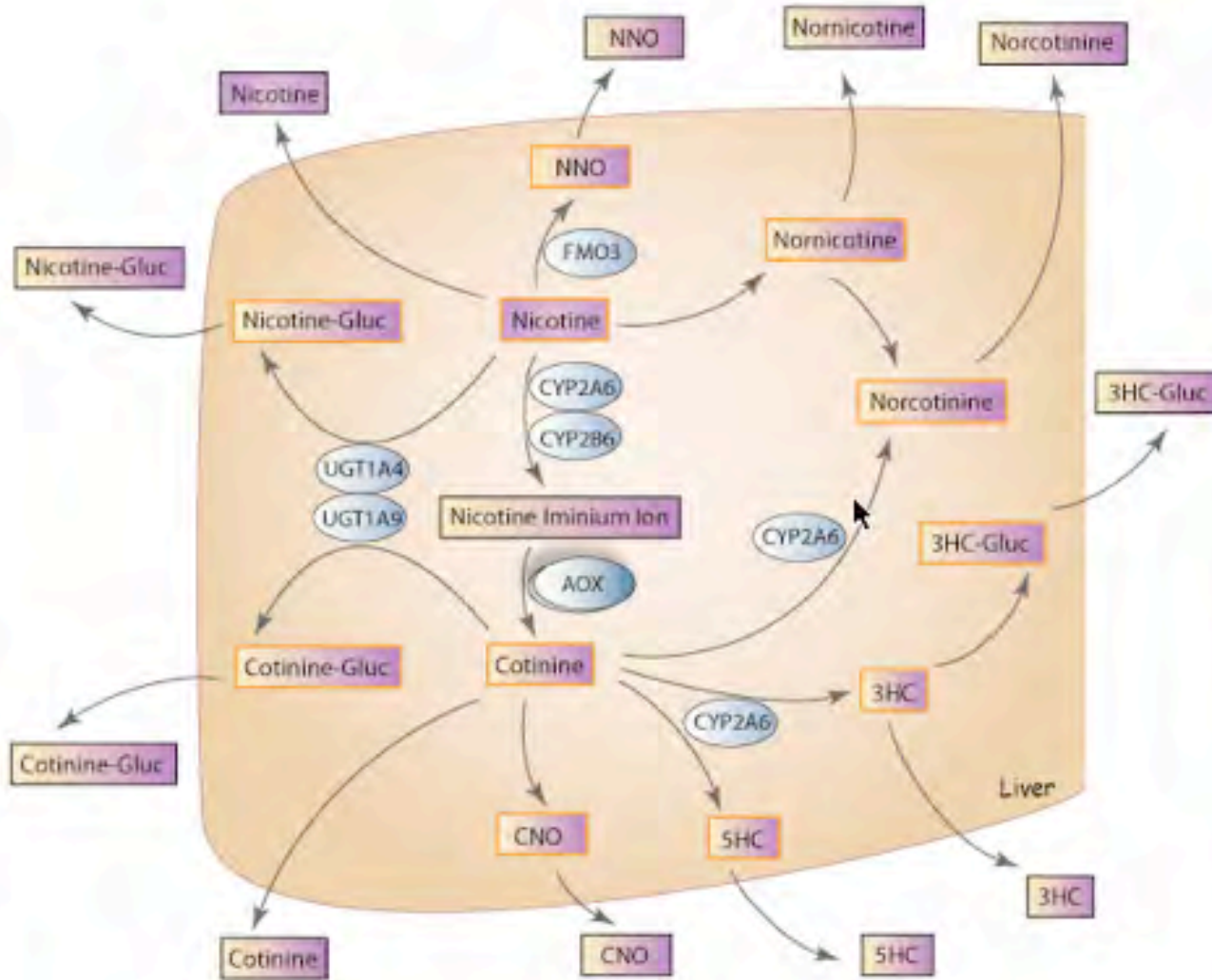
Summary of nicotine metabolism in human liver cell.

Legend

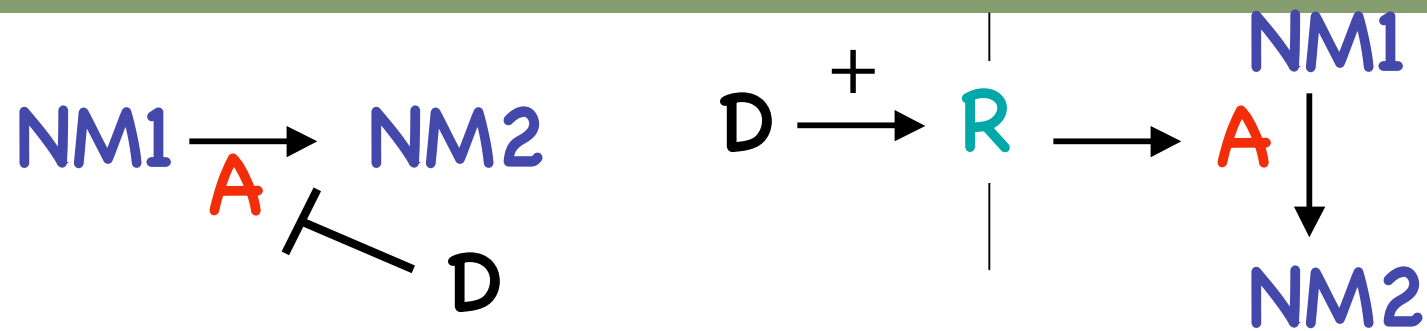
All Pathways

DOWNLOADS

- [Illustrator file \(nicotine.ai\)](#)



PD pathways are diverse



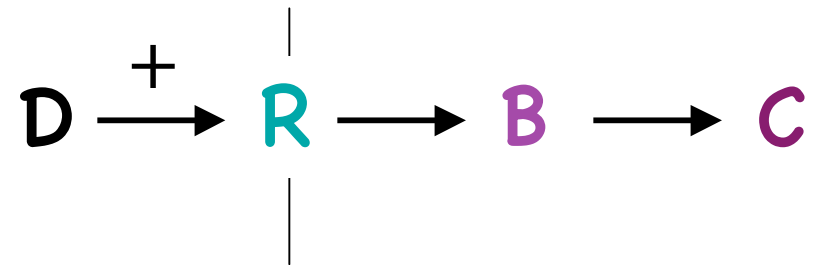
NM1, NM2 = natural metabolites

D = drug, R = receptor

A = Enzymes

B = kinase (phosphorylates)

C = kinase target protein



PD Genes

- The top drug targets (GPCRs, etc...) and how they work
 - Signaling within the cell
 - Control of gene expression
 - Control of metabolism



PD Data

- Any assay related to phenotype, including:
 - Molecular
 - Cellular
 - Organ
 - Organism
- Usually need all levels to make coherent story.

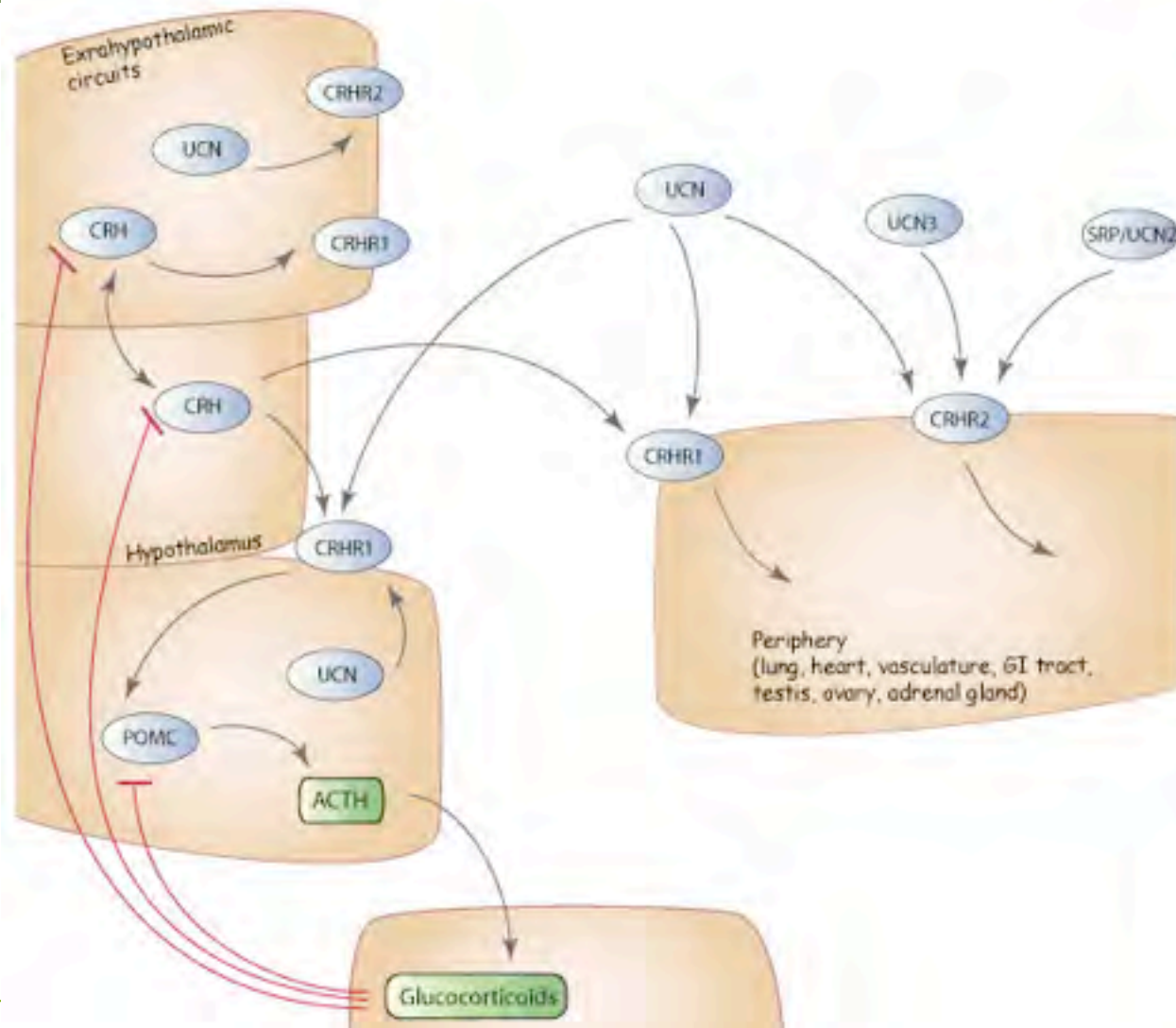


Glucocorticoid and Inflammatory genes pathway

HPA axis:

Simplified diagram of the actions of corticotropin releasing factor (CRH) and related hormones which regulate the release of glucocorticoids via the hypothalamic pituitary adrenal axis.

[Legend](#)



All Pathways

HPA axis

Go

RELATED PATHWAYS

- Steroid
- Genes Regulated by Steroid Activation
- Intracellular Inflammation
- Beta Adrenergic Receptor Signaling

DOWNLOADS

- [Illustrator file \(hpa-axis.ai\)](#)

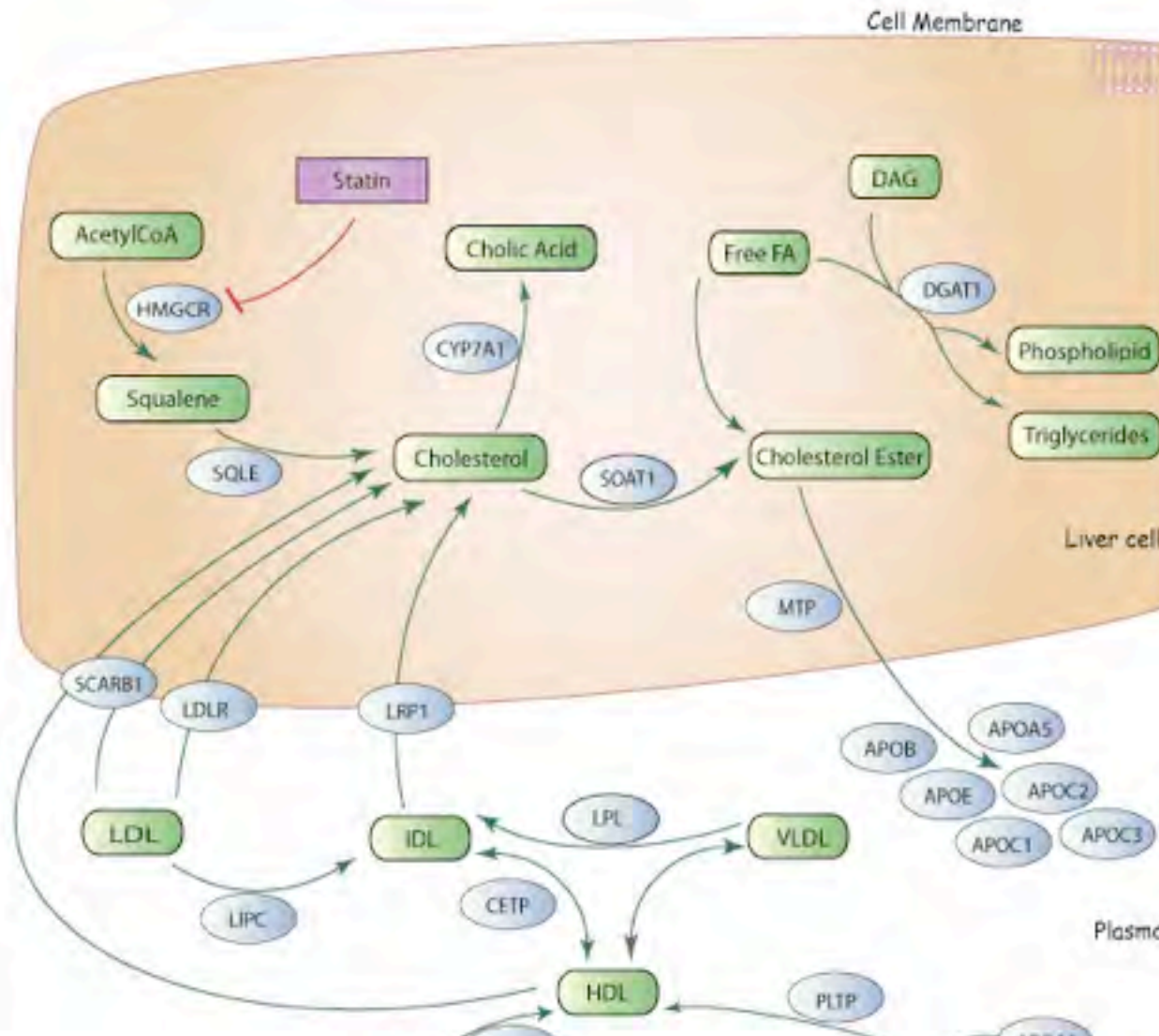


Statin Pathway

Cholesterol and Lipoprotein Transport:

Genes involved in mediating statin effects on hepatic cholesterol metabolism and consequent effects on plasma lipoprotein transport.

[Legend](#)



[All Pathways](#)

RELATED PATHWAYS

- Statin PK
- Ras Signaling
- Rho Signaling
- Ubiquinone

DOWNLOADS

- [Illustrator file \(statin.ai\)](#)
- [Supporting Evidence \(xls\)](#)



Standards for pathway exchange

- How to exchange pathway information?
 - Graphical pathways (e.g. PharmGKB, Biocarta)
 - Ad hoc network drawings (e.g. Cytoscape Inc, Ingenuity Inc)
 - Genmapp format (<http://>)
 - BioPAX = **B**iological **P**athway **X**ML format



Biocarta Pathway

BIOCARTA
FEATURES PATHWAYS CUSTOM SERVICES GENES PRODUCTS LOGIN
Interactive graphic models of molecular and cellular pathways

PATHWAYS ▶ Transcription Regulation by Methyltransferase of CARM1

Submitted by: Michael Shih, PhD ✉ Guru: ✉
[COMMENT ON THIS PATHWAY](#) | [DESCRIPTION](#) | [CONTRIBUTORS](#) | [SAVE THIS LINK](#) | [SUBMIT](#) | [LEGEND](#)

PRODUCT INDEX
PRODUCT SEARCH
SEARCH
Contains Exact Advanced Search
PRODUCT HIGHLIGHT
 ON OFF
PROTEIN LIST
REQUEST A CATALOG

Other Species: M H

August 2002



ACE Inhibitor Pathway (Homo Sapiens)

Author: Caroline F. Thorn
E-mail: feedback@pharmGKB.org
 Adapted from PharmGKB (right click for info)

Gene Database

Hs-Std_20031113.gdb

Expression Dataset

Name: Hs_ED_ProstateCancer_20040209

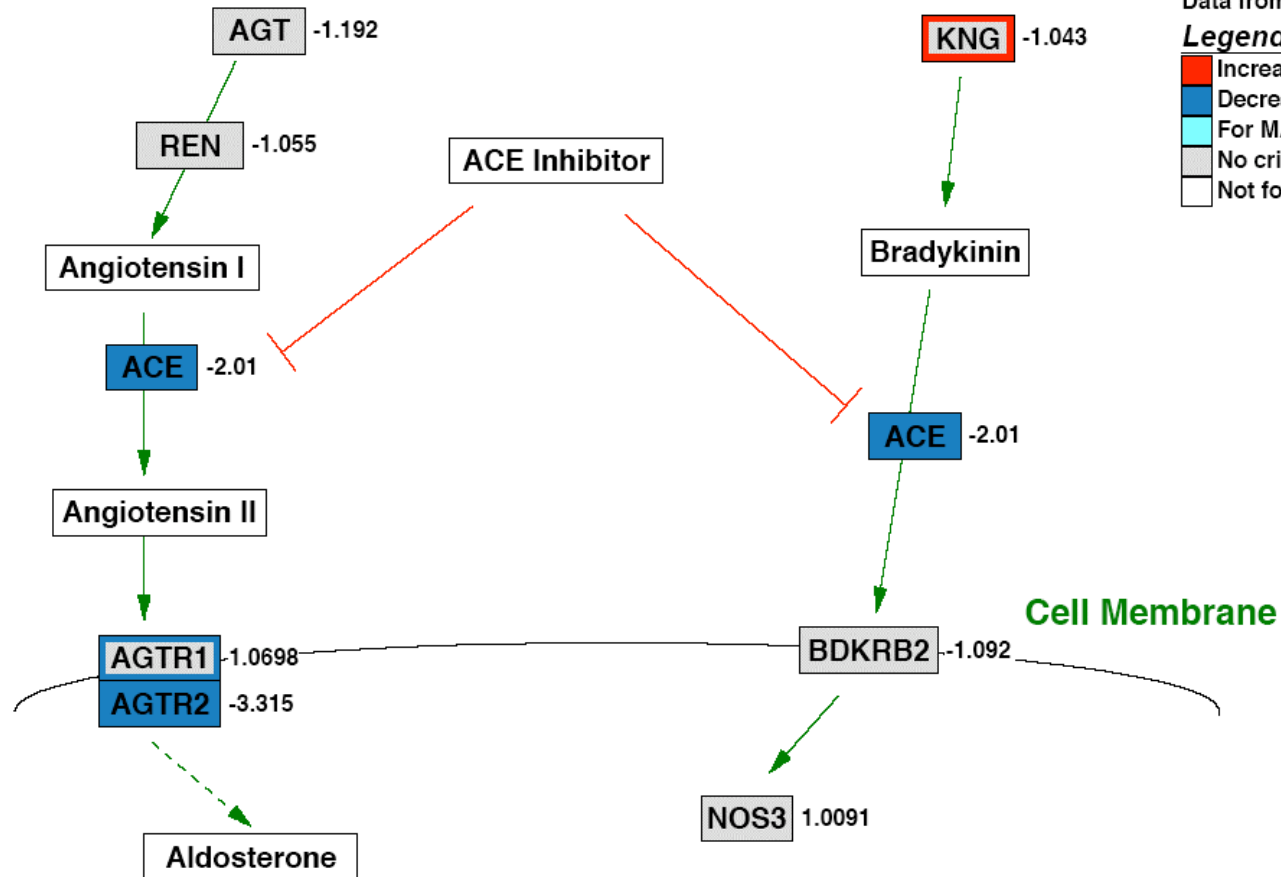
Color Set: Hormone vs. Primary

Gene Value: H vs PG Fold

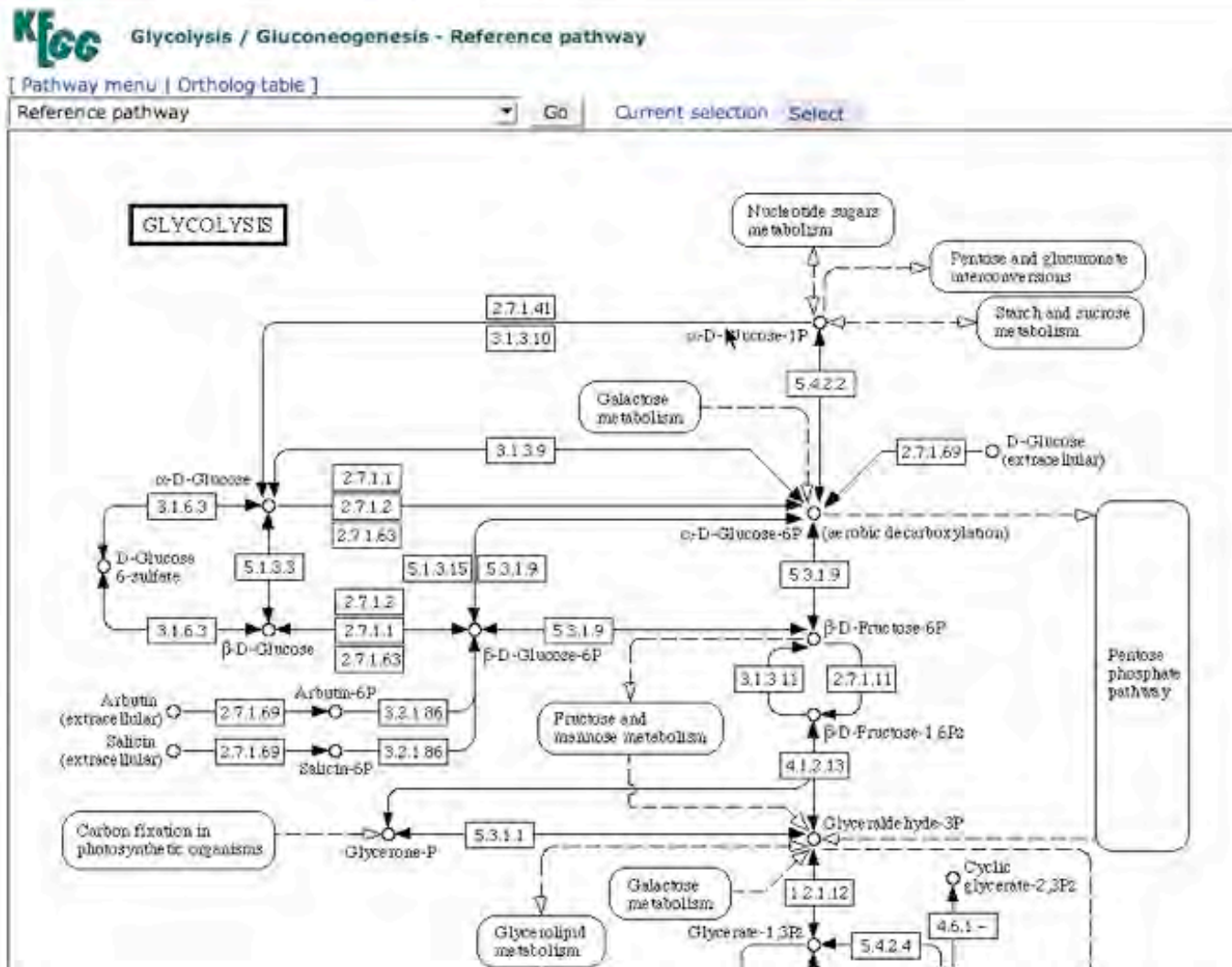
Data from Dr. William Gerald, Sloan-Kettering

Legend

- Increased due to Hormone Therapy
- Decreased due to Hormone Therapy
- For MAPPFinder
- No criteria met
- Not found



Kegg pathway/network



Reactome pathway

The screenshot displays the Reactome website interface. At the top, there is a navigation menu with links: Home, About, TOC, User Guide, Data Model, Schema, Extended Search, PathFinder, SkyPainter, Download, Linking, Citing, and Editorial C. Below the navigation menu is a search bar with the following elements: a 'Find' button, a dropdown menu set to 'everything', a dropdown menu set to 'with ALL of the words', an empty search input field, the word 'in', and another dropdown menu set to 'Homo sapiens'. Below the search bar is a 'Reactionmap' section. It features a dark blue header with the text 'Click on the map:' and three buttons: 'shifts focus', 'zooms in', and 'zooms out'. The main area of the reaction map shows a complex network of biochemical reactions represented by arrows and chemical structures. A legend at the bottom of the map identifies the reaction types: 'Reaction' (black arrow), 'Experimentally confirmed reaction' (blue arrow), 'Manually inferred reaction' (pink arrow), 'Electronically inferred reaction' (green arrow), and 'Linked reactions' (grey arrow). Below the reaction map is an 'Event hierarchy' section with a plus sign icon and the text 'open to selected event | open all | close all | show/hide hierarchy types'.



Useful pathway resources

<http://www.123genomics.com/files/pathway.html>



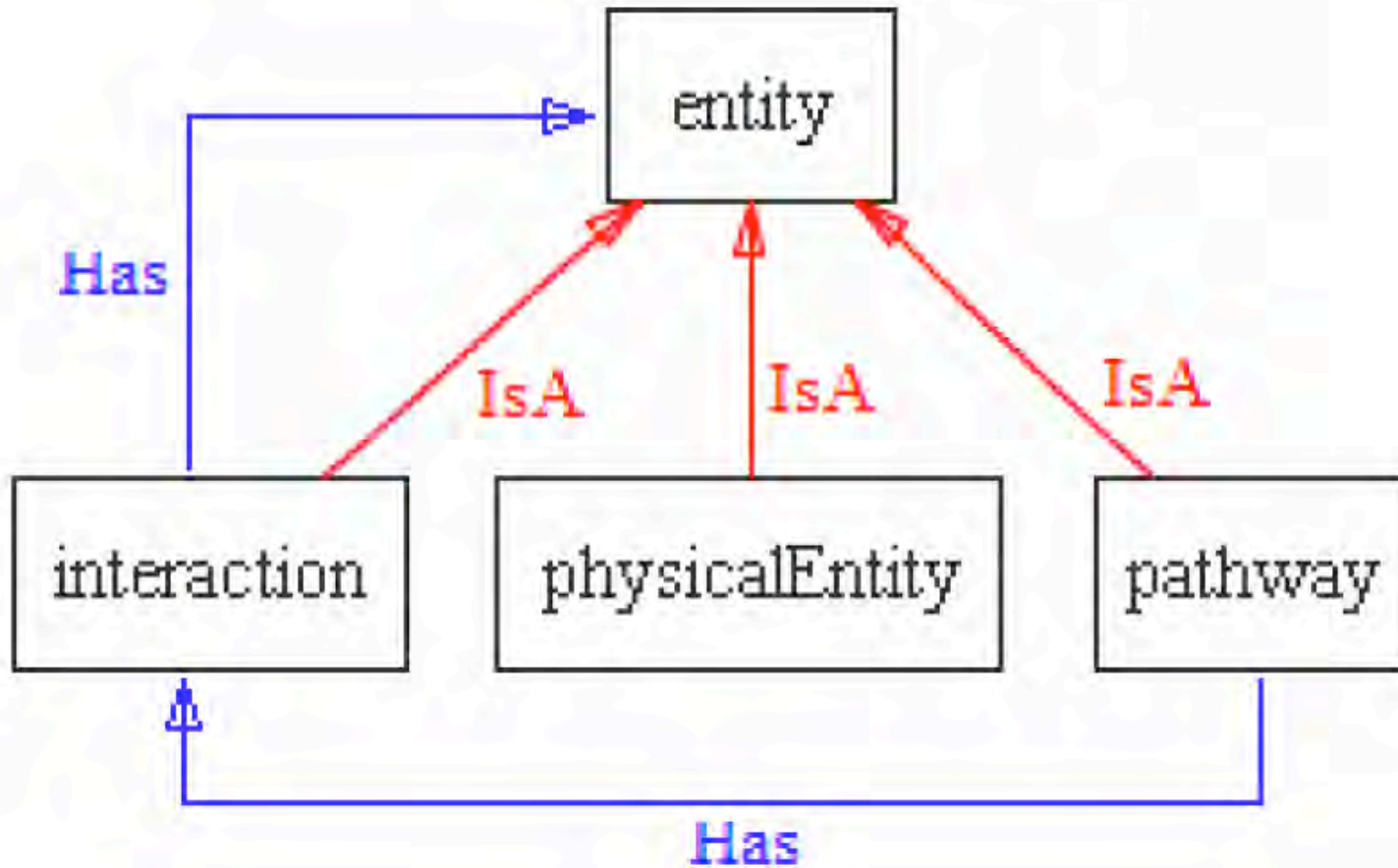
Goal of BioPAX

“The goal of the BioPAX project is to provide a data exchange format for pathway data that will represent the key elements of the data models from a wide range of popular pathway databases.”

<http://www.biopax.org/>



Top level classes



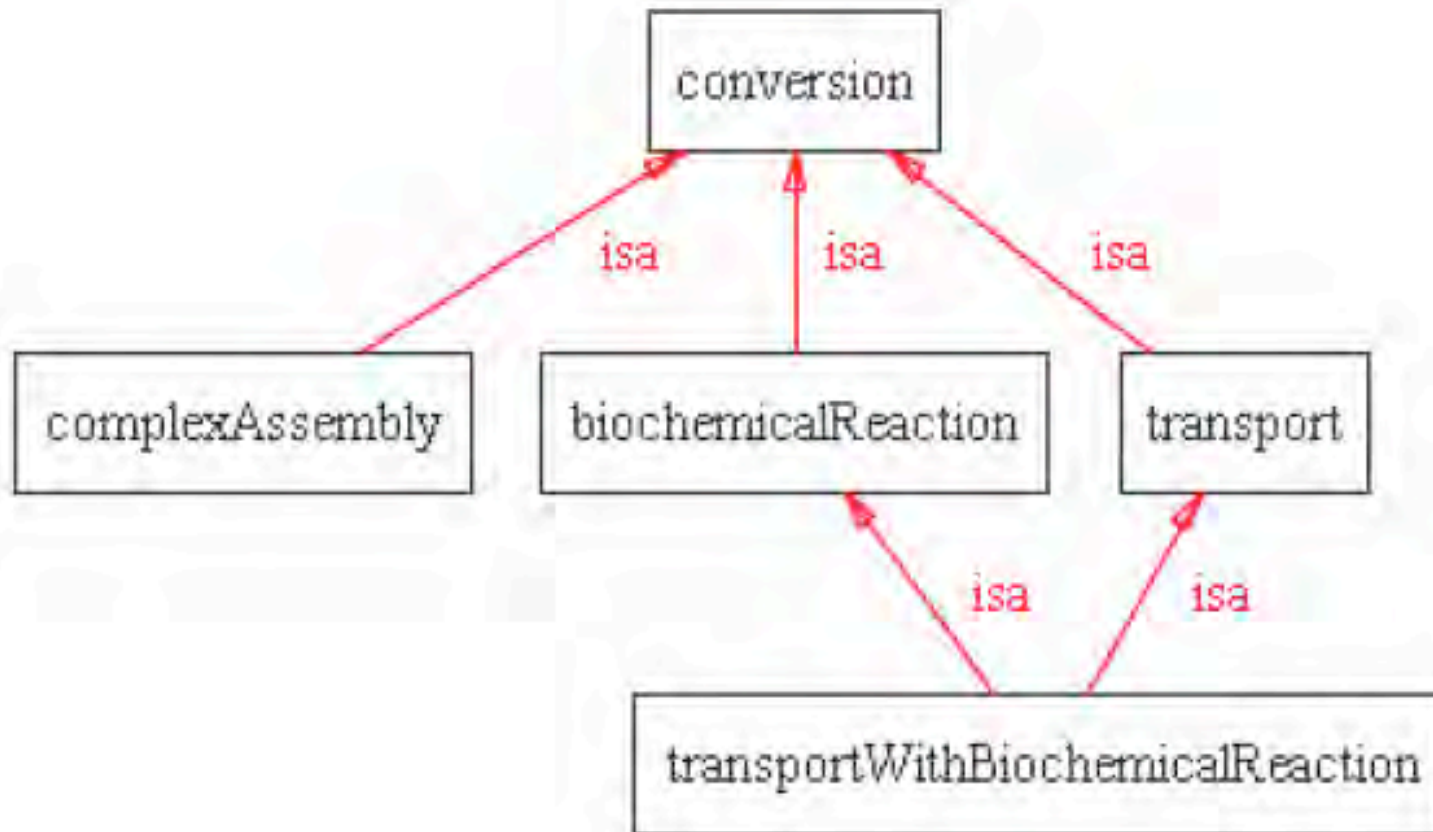
Properties of entities and pathways

entity	
0	SYNONYMS
0	COMMENT
0	DATA-SOURCE
0	SHORT-NAME
0	AVAILABILITY
0	NAME
0	XREF

pathway	
0	NAME
0	SHORT-NAME
0	SYNONYMS
0	DATA-SOURCE
0	XREF
0	AVAILABILITY
0	COMMENT
0	ORGANISM
0	EVIDENCE
0	PATHWAY-COMPONENTS



Conversion class



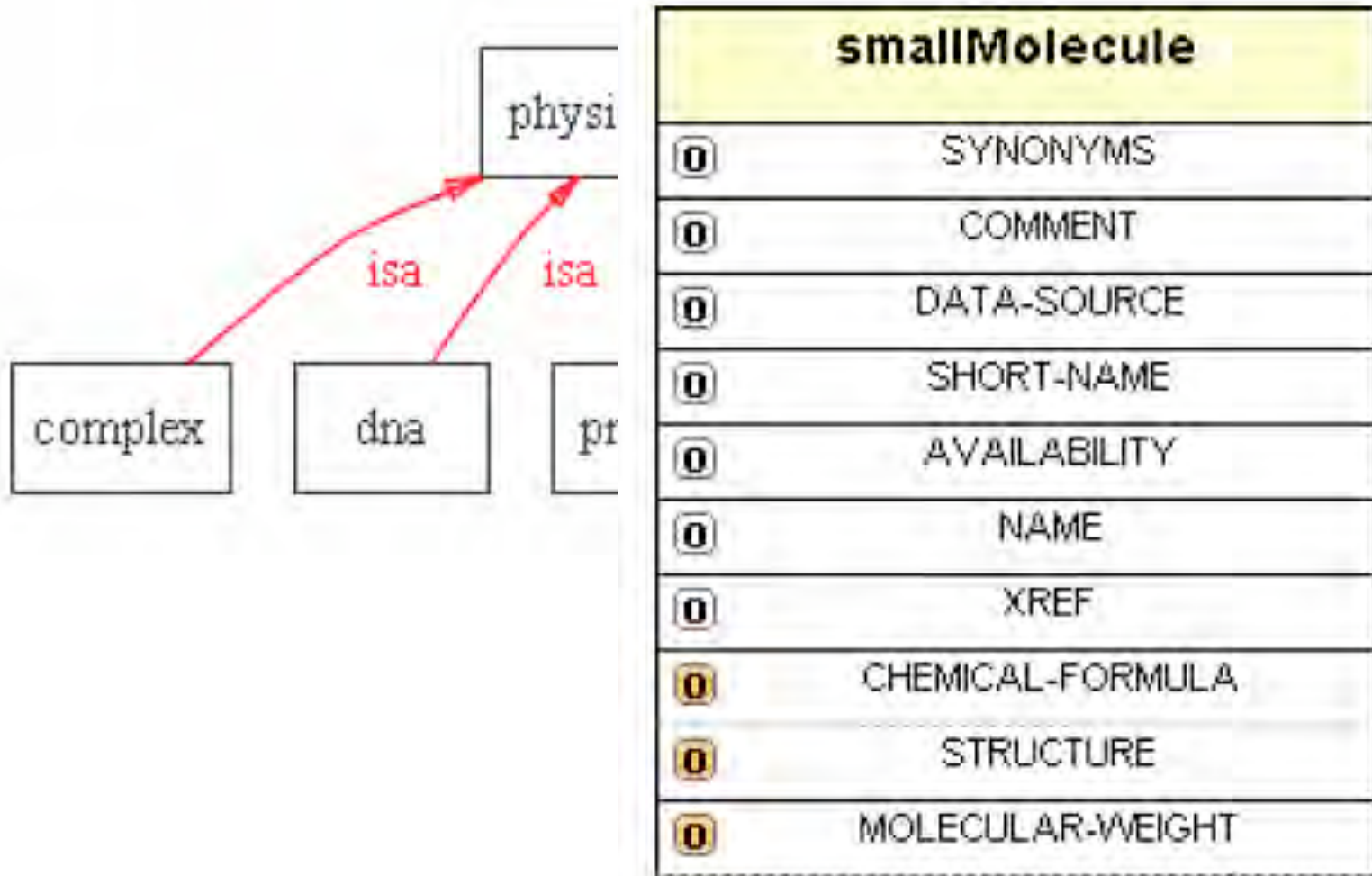
Biochemical reaction and transport

biochemicalReaction	
<input type="checkbox"/>	SPONTANEOUS
<input type="checkbox"/>	LEFT
<input type="checkbox"/>	RIGHT
<input type="checkbox"/>	INTERACTION-TYPE
<input type="checkbox"/>	PARTICIPANTS
<input type="checkbox"/>	EVIDENCE
<input type="checkbox"/>	NAME
<input type="checkbox"/>	SHORT-NAME
<input type="checkbox"/>	SYNONYMS
<input type="checkbox"/>	DATA-SOURCE
<input type="checkbox"/>	XREF
<input type="checkbox"/>	AVAILABILITY
<input type="checkbox"/>	COMMENT
<input checked="" type="checkbox"/>	DELTA-G
<input checked="" type="checkbox"/>	DELTA-H
<input checked="" type="checkbox"/>	EC-NUMBER
<input checked="" type="checkbox"/>	KEQ
<input checked="" type="checkbox"/>	DELTA-S

transport	
<input type="checkbox"/>	SPONTANEOUS
<input type="checkbox"/>	LEFT
<input type="checkbox"/>	RIGHT
<input type="checkbox"/>	INTERACTION-TYPE
<input type="checkbox"/>	PARTICIPANTS
<input type="checkbox"/>	EVIDENCE
<input type="checkbox"/>	NAME
<input type="checkbox"/>	SHORT-NAME
<input type="checkbox"/>	SYNONYMS
<input type="checkbox"/>	DATA-SOURCE
<input type="checkbox"/>	XREF
<input type="checkbox"/>	AVAILABILITY
<input type="checkbox"/>	COMMENT



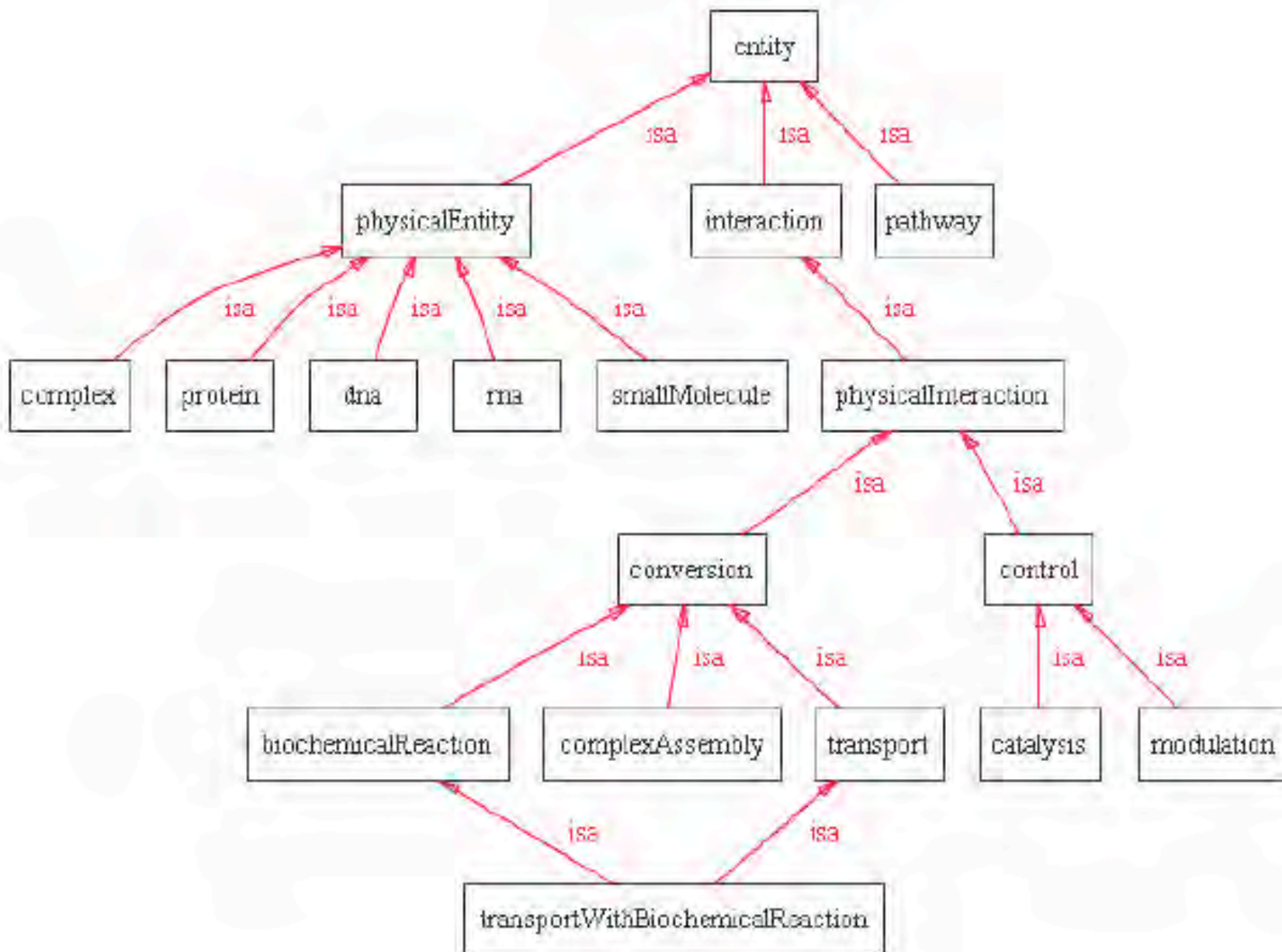
Physical entity classes

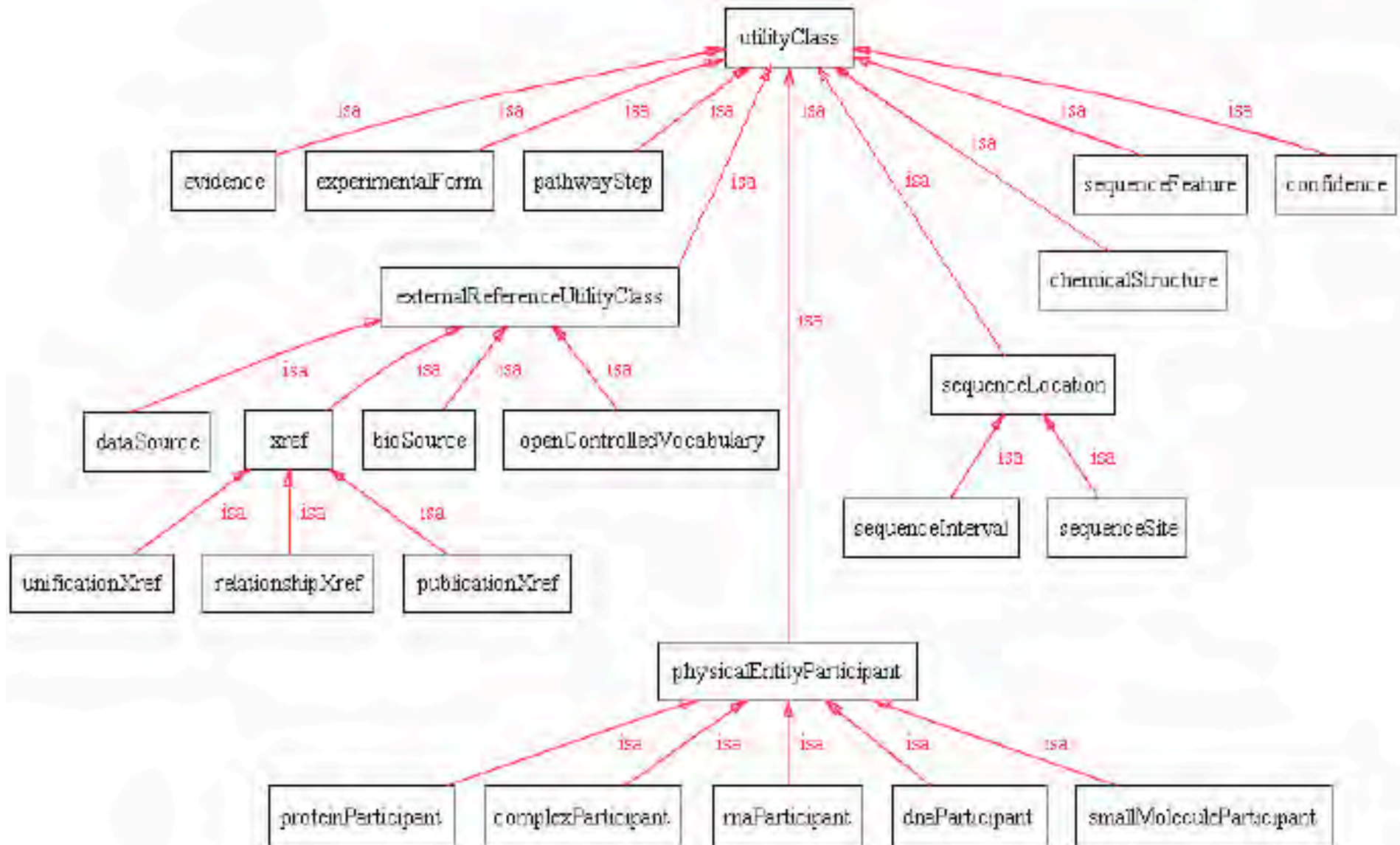


“utility” classes, e.g. `publicationXref`

publicationXref	
0	DB
0	DB-VERSION
0	ID
0	ID-VERSION
0	COMMENT
0	TITLE
0	YEAR
0	AUTHORS
0	URL
0	SOURCE







BioPAX Conclusions

- Emerging standard for representing pathway information
- Will allow transfer of pathway information between computational systems for 170+ pathway databases.
- Version 2.0 recently released, 3.0 under evaluation.



Pathway Conclusions

- Definition of PK/PD pathways is key to pharmacogenomics
- Representation of these pathways must include both metabolism, cell signalling, and control of expression.
- BioPAX is an emerging standard that is constantly improving.

