

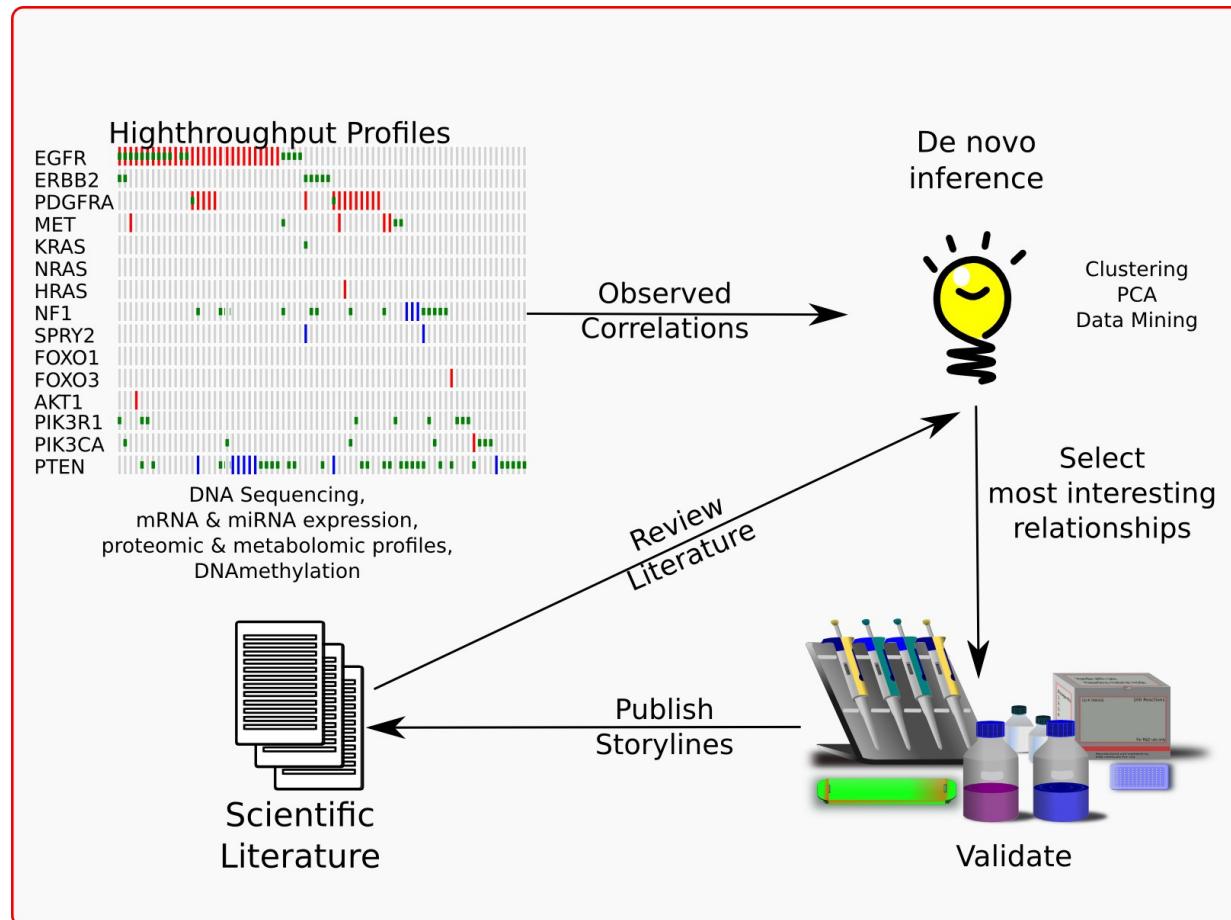
Building Cell Maps: Status and Challenges



Emek Demir, MSKCC



Data-driven Discovery Cycle



Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network

[Affiliations](#) | [Contributions](#) | [Corresponding authors](#)

Nature **497**, 67–73 (02 May 2013) | doi:10.1038/nature12113

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[Erratum \(August, 2013\)](#)

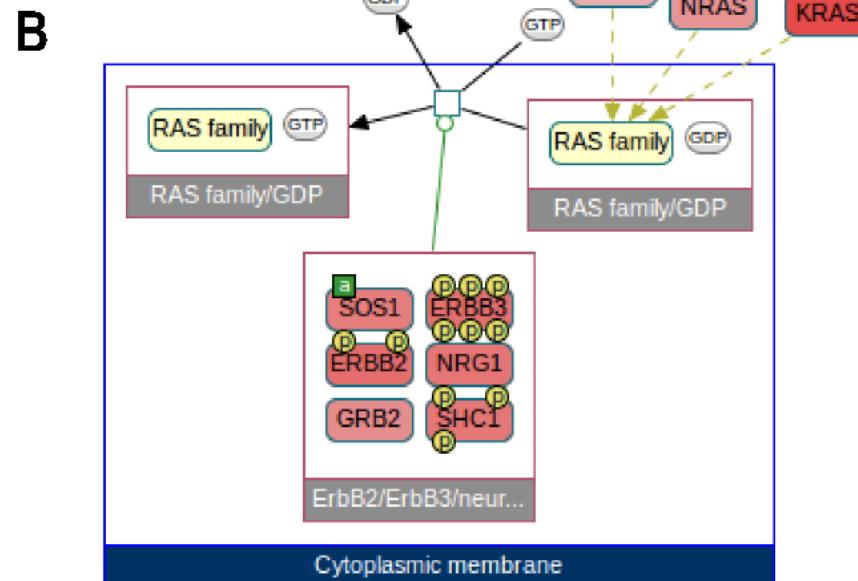
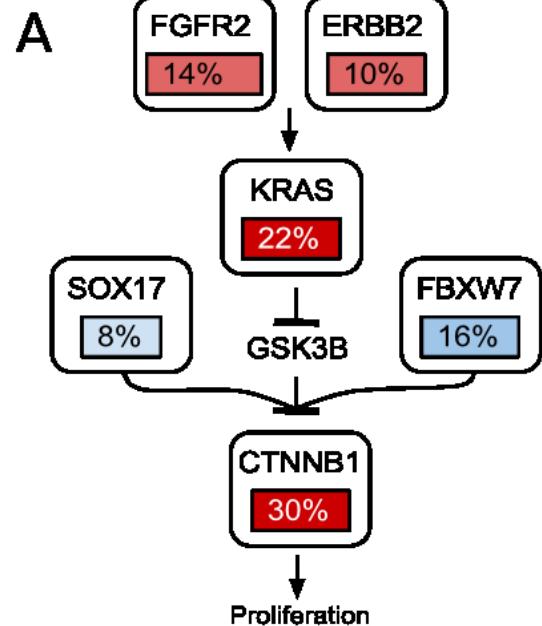


Abstract

[Abstract](#) · [Introduction](#) · [Results](#) · [Somatic copy number alterations](#) · [Exome sequence analysis](#) · [Multiplatform subtype classifications](#) · [Structural aberrations](#) · [Pathway alterations](#) · [Comparison to ovarian and breast cancers](#) · [Discussion](#) · [Methods](#) · [References](#) · [Acknowledgements](#) · [Author information](#) · [Supplementary information](#)

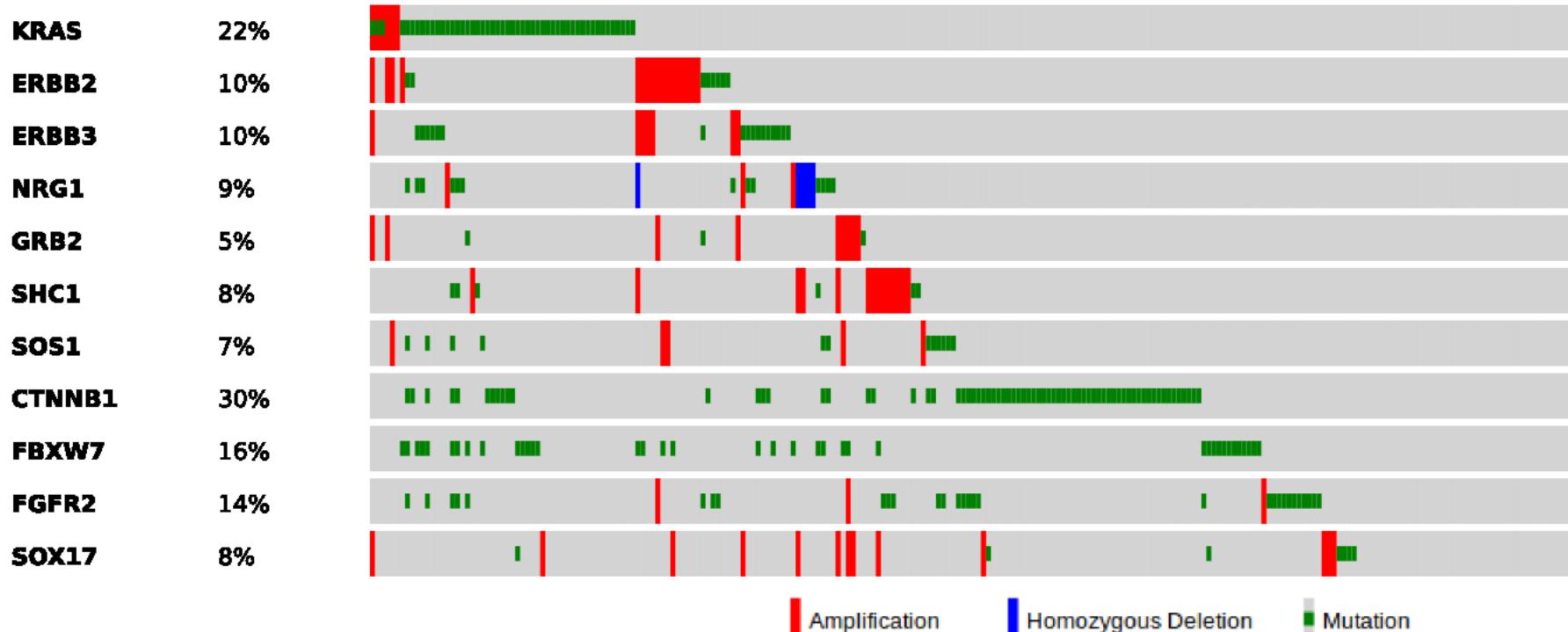
We performed an integrated genomic, transcriptomic and proteomic characterization of 373 endometrial carcinomas using array- and sequencing-based technologies. Uterine serous tumours and ~25% of high-grade endometrioid tumours had extensive copy number alterations, few DNA

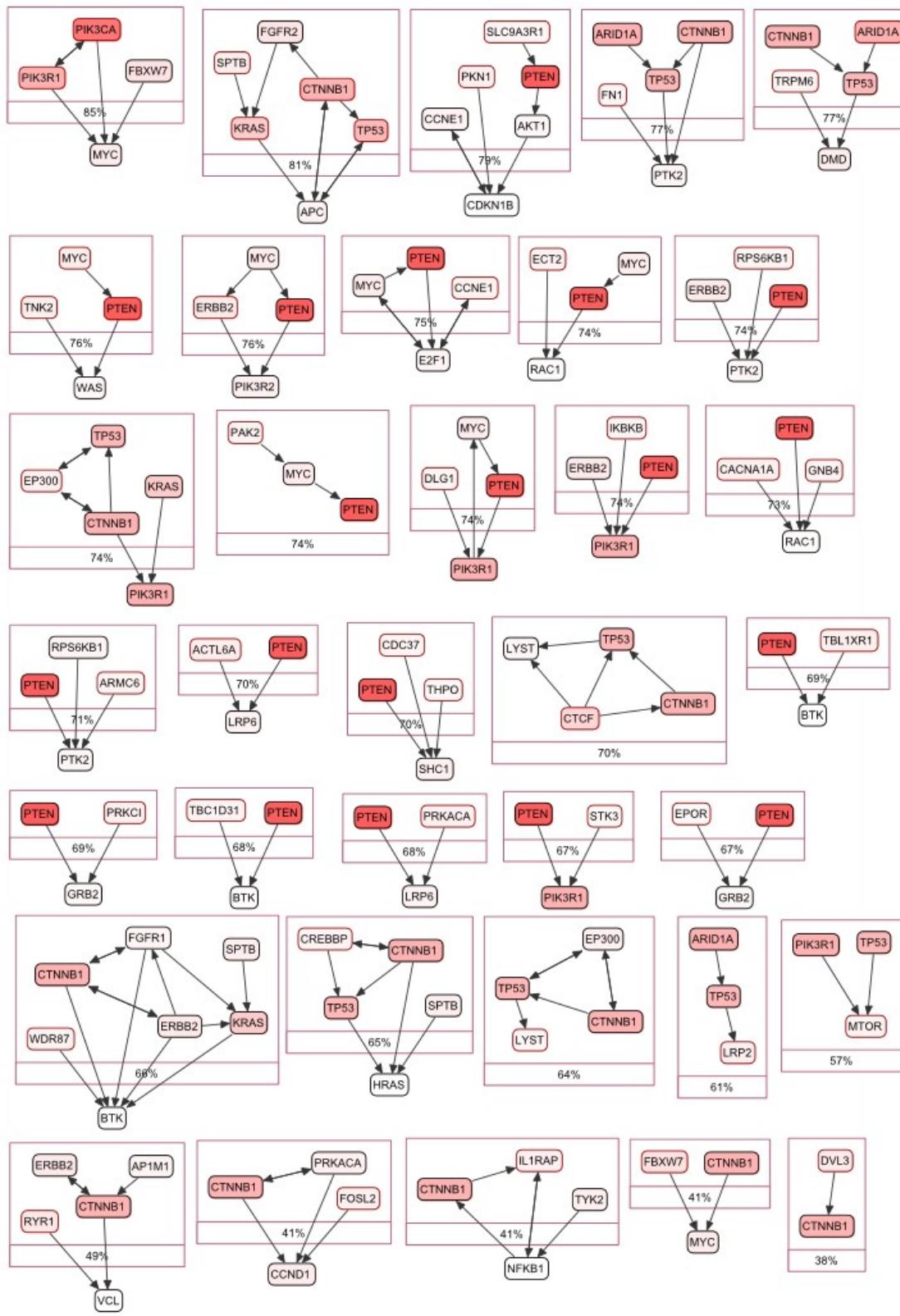
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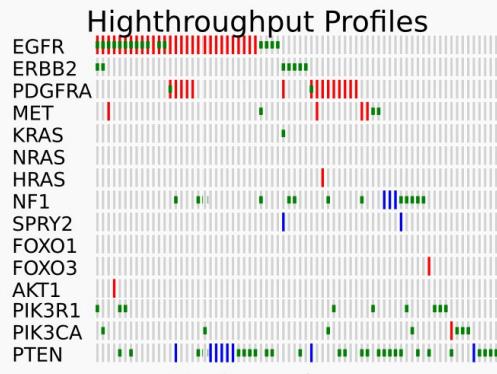
Altered in 197 (82%) of cases



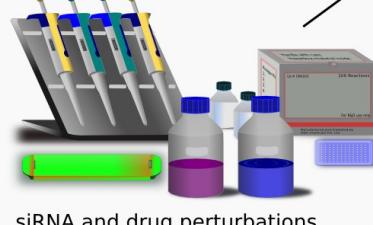


Model Driven Discovery Cycle

Discovery



DNA Sequencing,
mRNA & miRNA expression,
proteomic & metabolomic profiles,
DNAmethylation



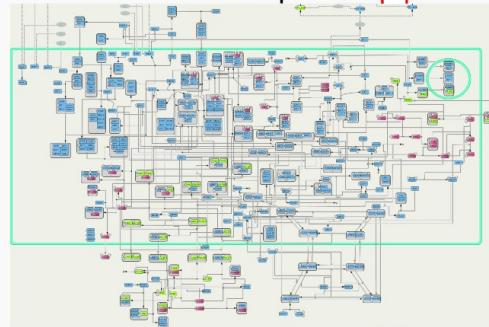
siRNA and drug perturbations

Observed Correlations

Incremental Model Improvement

Perturb Validate

Cell Map



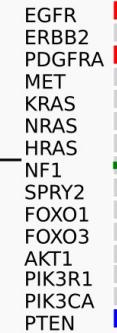
TF activity,
Belief Propagation,
Rule based modeling

Infer active pathways



Application

Profile from Patient



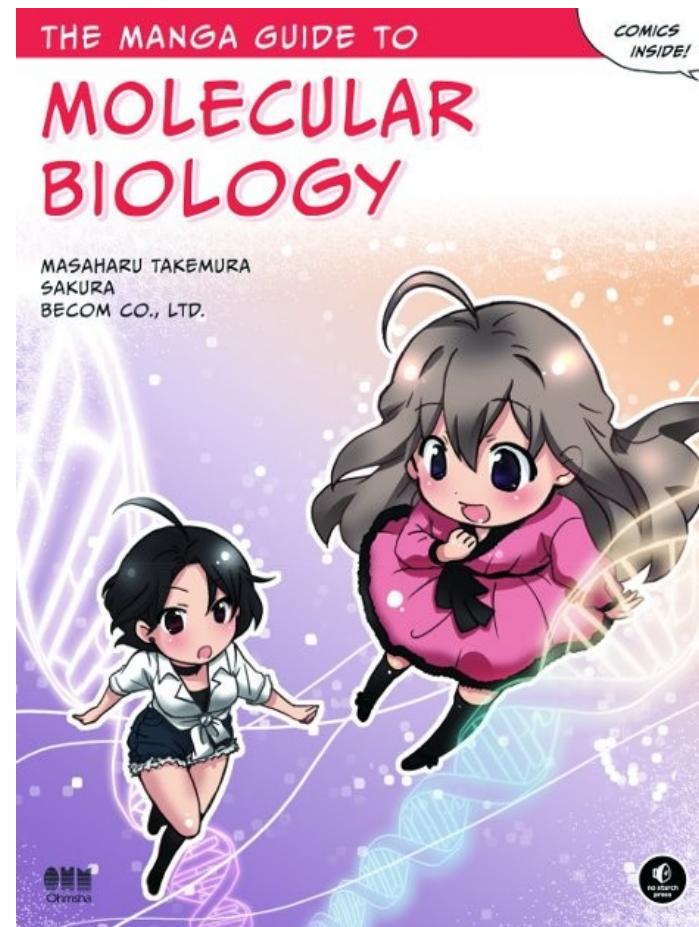
Determine active pathways

Personalized Medicine

Infer disease subtype,
drug response and drug combination



You may say I'm a dreamer..



Pathguide

the pathway resource list

But I'm not
the only one..

Navigation

Protein-Protein
Interactions

Metabolic Pathways

Signaling Pathways

Pathway Diagrams

Transcription Factors /
Gene Regulatory
Networks

Protein-Compound
Interactions

Genetic Interaction
Networks

Protein Sequence
Focused

Other

Search

Organisms

All

Availability

All

Standards

All

Analysis

Statistics

Database Interactions

Contact

Comments, Questions,
Suggestions are
Always Welcome!

Statistical Summary of Pathguide Resources

Note that some enumerations, such as the resources under Availability, are exclusive while others, such as those under Tools, may count the same resource for every criteria it satisfies.

Unless otherwise noted, the values represent the number of resources that contain/satisfy the specified data/criteria.

The "Contents" section also includes values denoted as "Totals". This is a simple summation and does not account for any overlaps in data between the resources.

General

Total Resources	328
Resources with Primary Data Sources	160
Resources with Secondary Data Sources	155

Availability

Free to all users	238
Free to academic users	37
Not currently available	28
License purchase required	18
Unknown	7

Data Access Methods

Browsing / Canned queries	232
Keyword searches	219
Download in other format	127
Download in BioPAX format	22
Download in SBML format	20
Download in PSI format	19
SQL queries	3
Download in CellML format	2

Tools

Pathway diagram tools	47
Interaction or functional association prediction	41
Pathway discovery tools	21
Text mining	12
Expression analysis	7

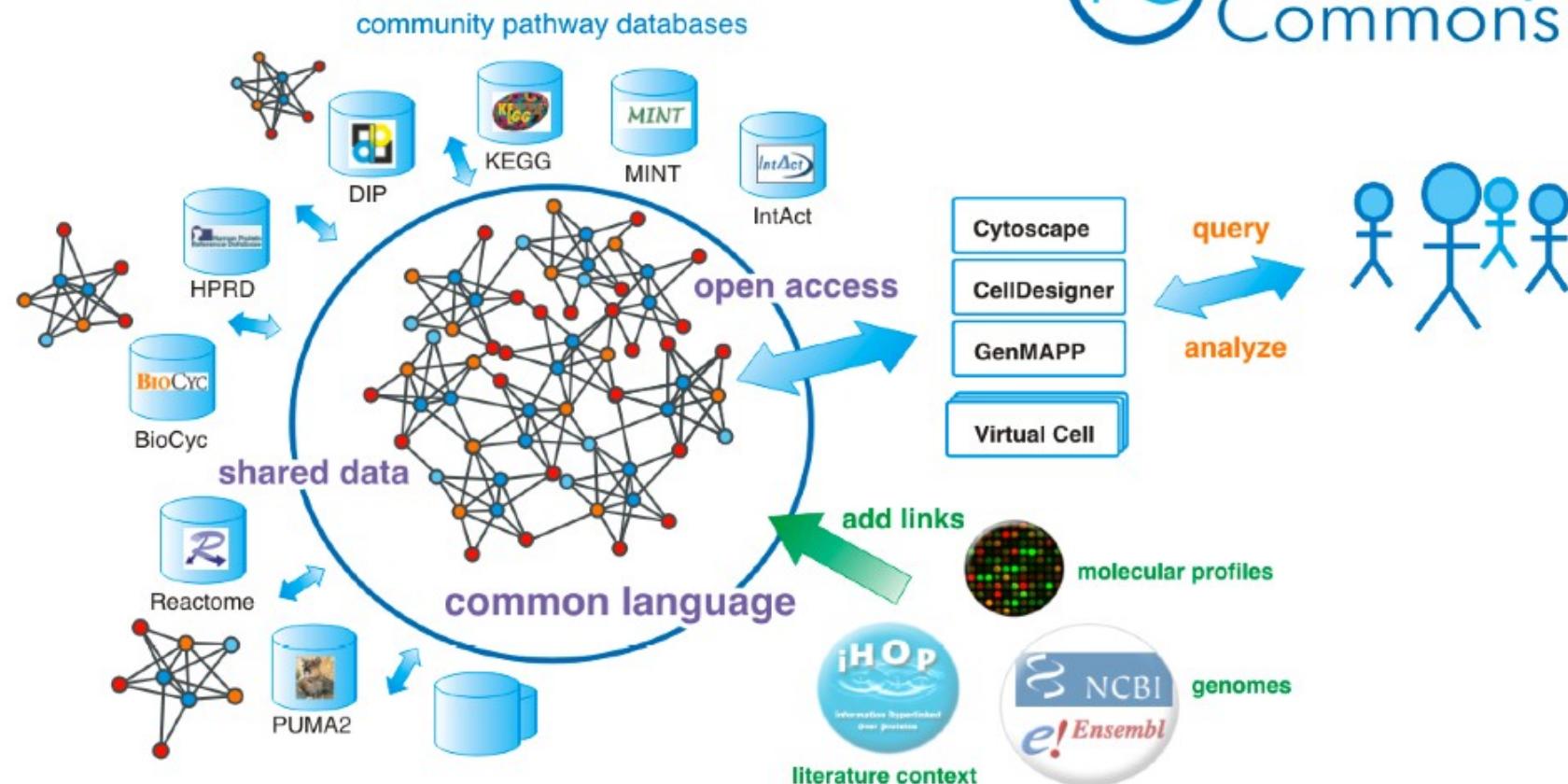
Organisms

Homo sapiens	91
Mus musculus	53
Saccharomyces cerevisiae	38
Rattus norvegicus	34
Drosophila melanogaster	31
Caenorhabditis elegans	27
Arabidopsis thaliana	26
Escherichia coli	25
Helicobacter pylori	12
Bos taurus	11
Plasmodium falciparum	10
Danio rerio	9
Oryza sativa	9
Bacillus subtilis	9
Schizosaccharomyces pombe	7
Human immunodeficiency virus	7
Xenopus laevis	6
Hepatitis C virus	5
Zea mays	5
Chlamydomonas reinhardtii	3
Dictyostelium discoideum	3
Mycoplasma pneumoniae	2
Pneumocystis carinii	1
Takifugu rubripes	1

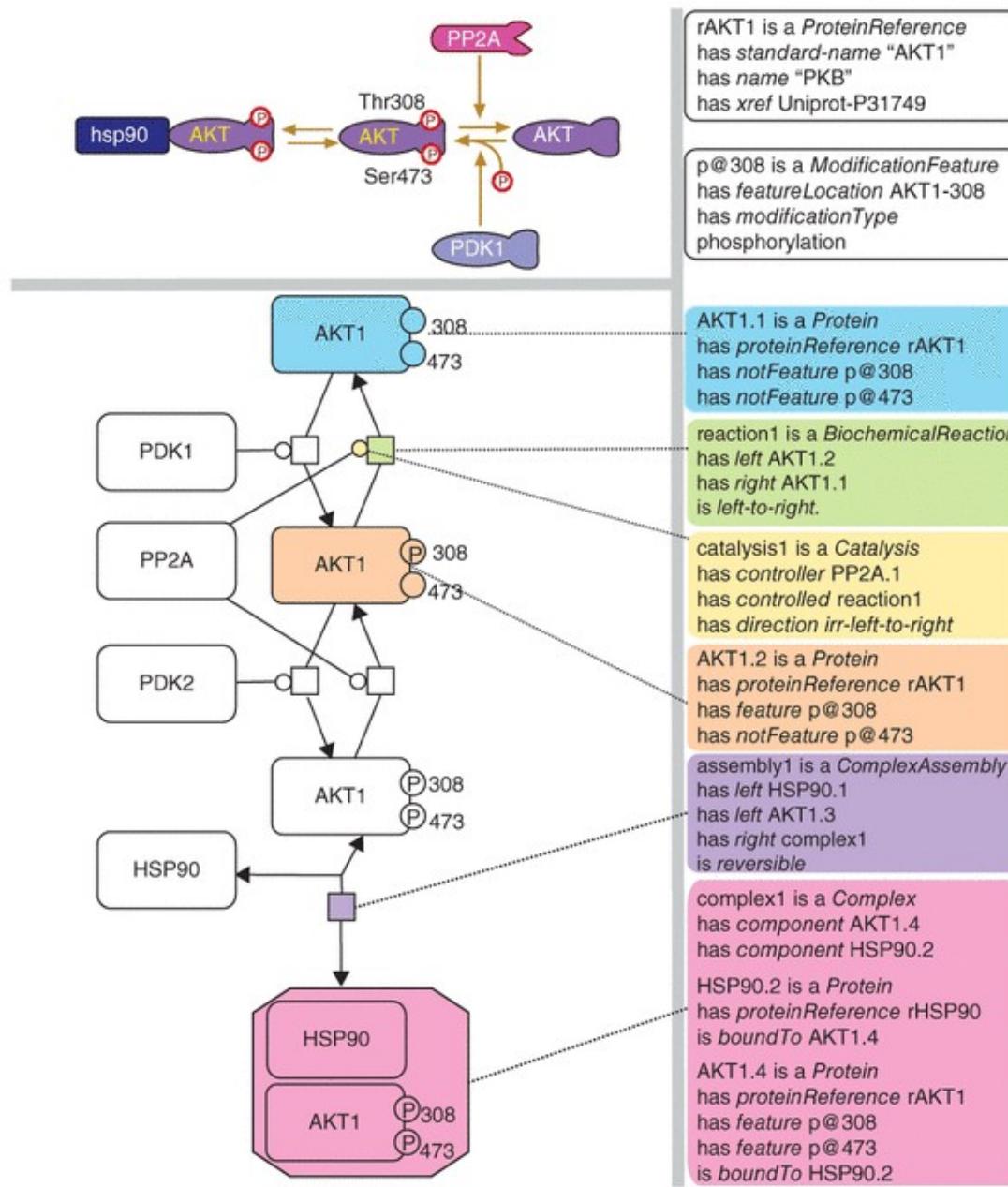
Categories

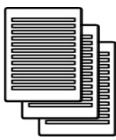
Protein-Protein Interactions	132
Metabolic Pathways	73
Signaling Pathways	62
Transcription Factors / Gene Regulatory Networks	51
Protein-Compound Interactions	43
Pathway Diagrams	38
Protein Sequence Focused	20
Genetic Interaction Networks	9
Other	14

Why standardize? Interoperability

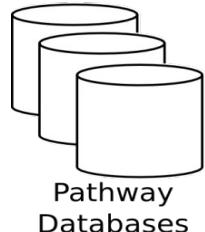


BioPAX at a Glance





Scientific
Literature



Automated
Semantic
Parsing

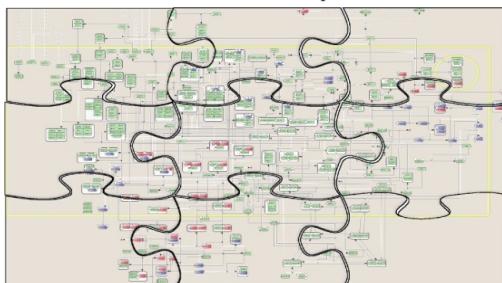
Fragments in
Common Representation
(AF & PD)



Align and merge through
redundant reactions

Detect inconsistencies

Cell Map



fragmented,
incompatible,
human readable

fragmented,
incompatible,
computable

fragmented,
compatible
computable

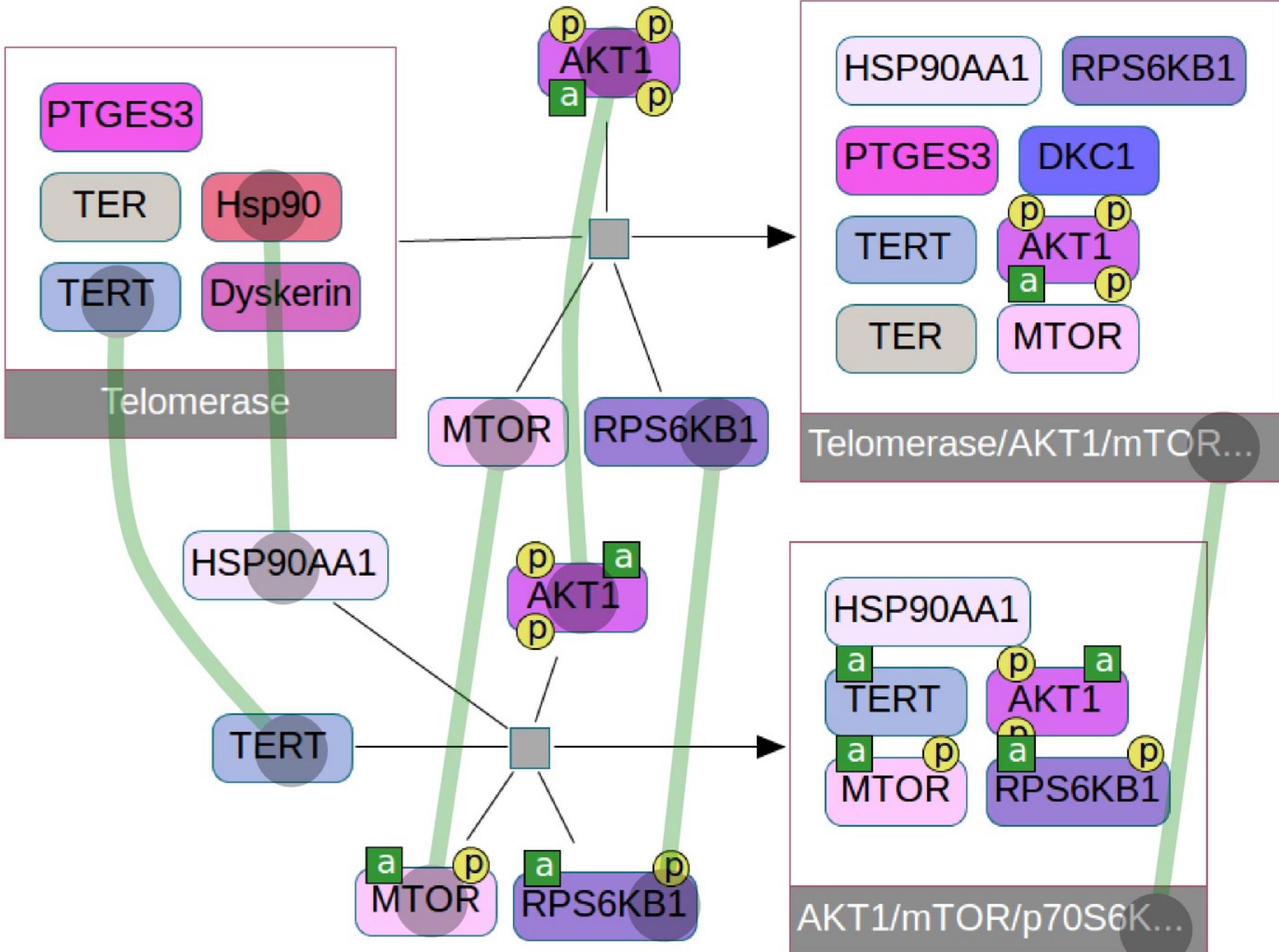
integrated
compatible
computable

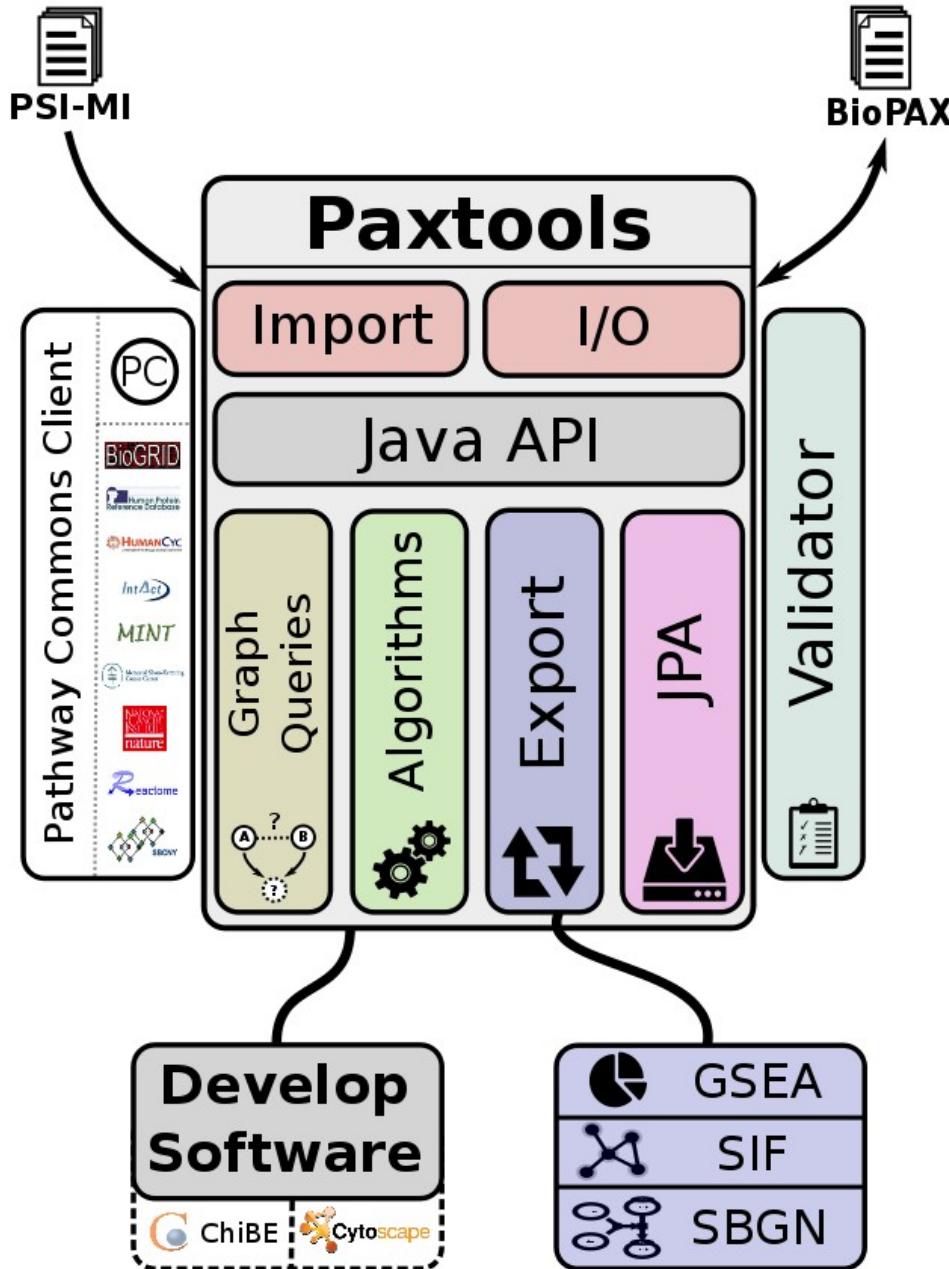
Building Cell Maps

Develop Standard representation
Construct cell maps from literature
Aggregate, Validate, Normalize
Align and Match fragments

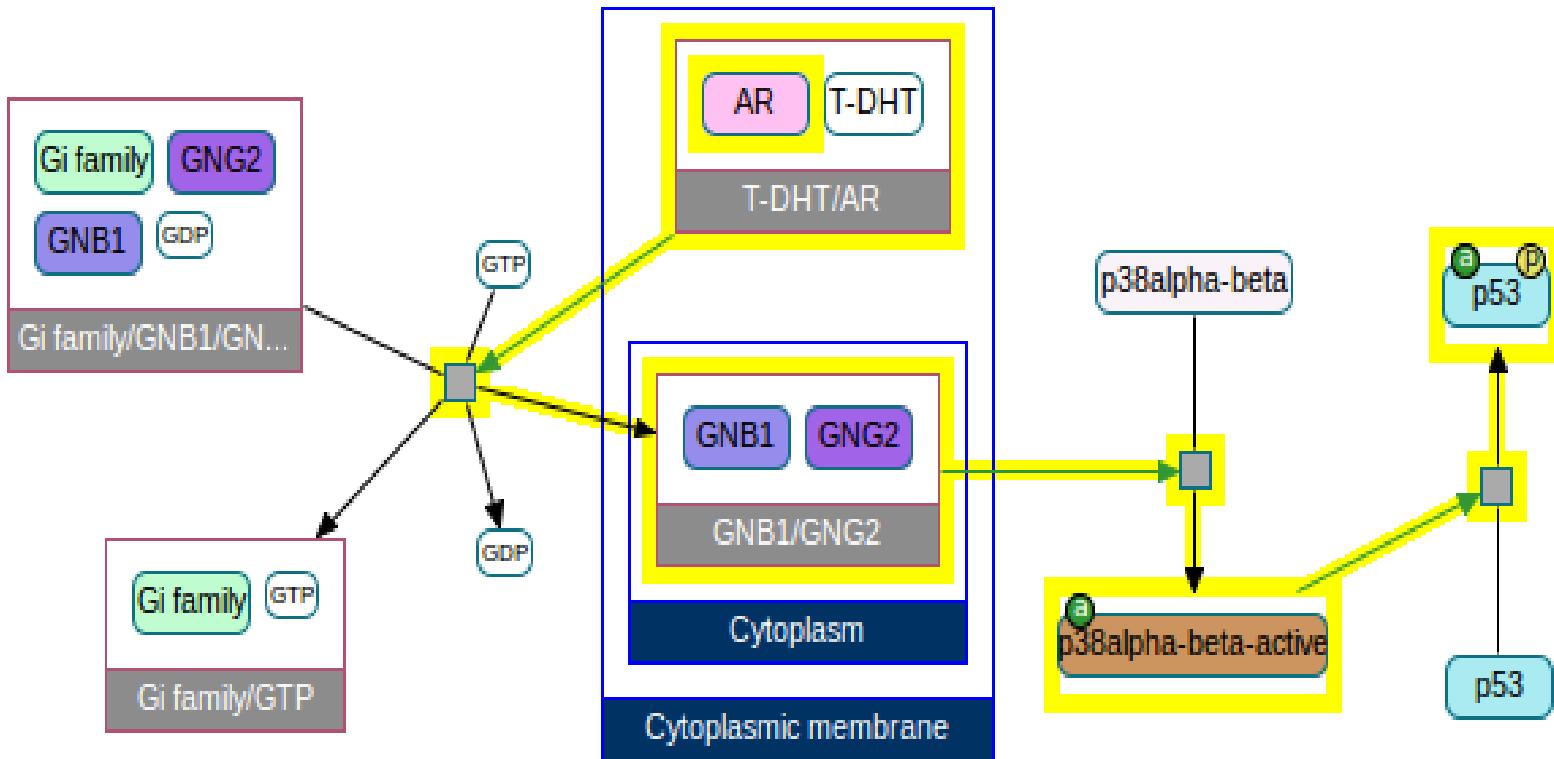
Using Cell Maps

Map correlations to models
Infer missing parts of the network
Predict response to a perturbation





Accessing PC



Web Services: Graph queries, Field searches, Path Traversal,

SPARQL endpoint

Batch Downloads

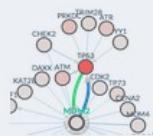
Different Formats: BioPAX, SIF, GSEA, SBGN

Clients:

Cytoscape, Cytoscape Web, Chibe 2, Virtual Cell, PC Java Client, PaxtoolsR

For biologists

Search, visualize and download Pathway Commons pathways ([more](#))



PCViz: Visualize pathways

Visualize pathways and networks in your web browser

[PCViz](#)

CyPath2

Download pathways and networks from Pathway Commons in [Cytoscape](#) for analysis

[CyPath2](#)

ChiBE

Pathway viewer and editor linked to Pathway Commons

[ChiBE](#)

For computational biologists and software developers

Download all pathways in BioPAX, SIF and other formats for global analysis. Build software on top of Pathway Commons using our web service API ([more](#))



PC2: Web service

BioPAX Level 3. Advanced graph queries. Normalized and up-to-date data. Programmatic access. Batch downloads.

[Pathway Commons 2](#)

BioPAX & Paxtools

Standard language for Biological Pathway Exchange and a software library for handling data in BioPAX.

[BioPAX & Paxtools](#)

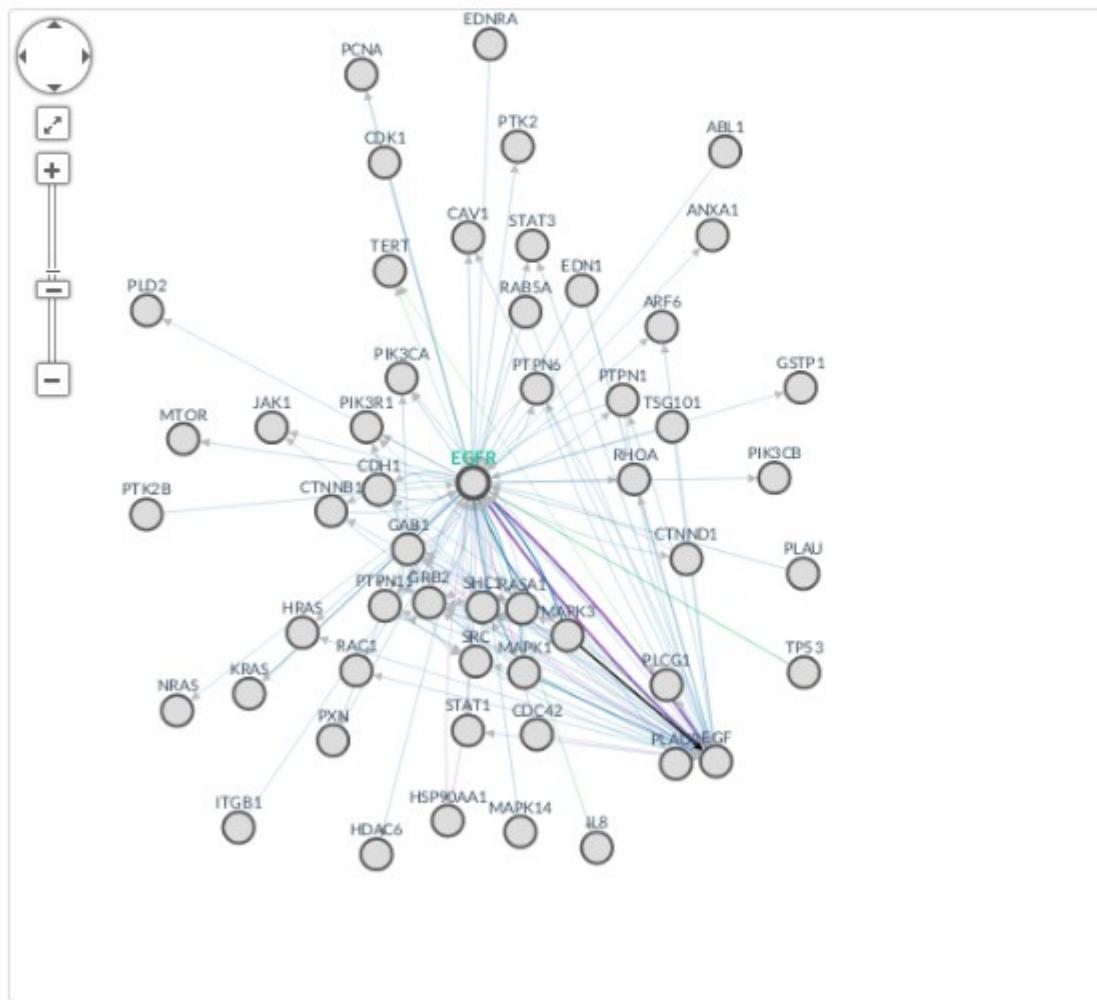
PC: Previous web service

Obsolete, last updated 2011

[Pathway Commons](#)

Genes of interest

EGFR



≡ Details

⚙️ Settings

💡 Context

MAPK3 - EGF

MAPK3 changes the state of EGF.

Co-citations

736

Interaction Type

controls state change ?

References

6 publication(s)

- [Pubmed: 9346957](#)
- [Pubmed: 7478553](#)
- [Pubmed: 7478566](#)
- [Pubmed: 7592690](#)
- [Pubmed: 8621459](#)
- [Pubmed: 8626525](#)

⬇️ Download detailed process
(BioPAX)

⬇️ Download

</> Embed

↻ Reset

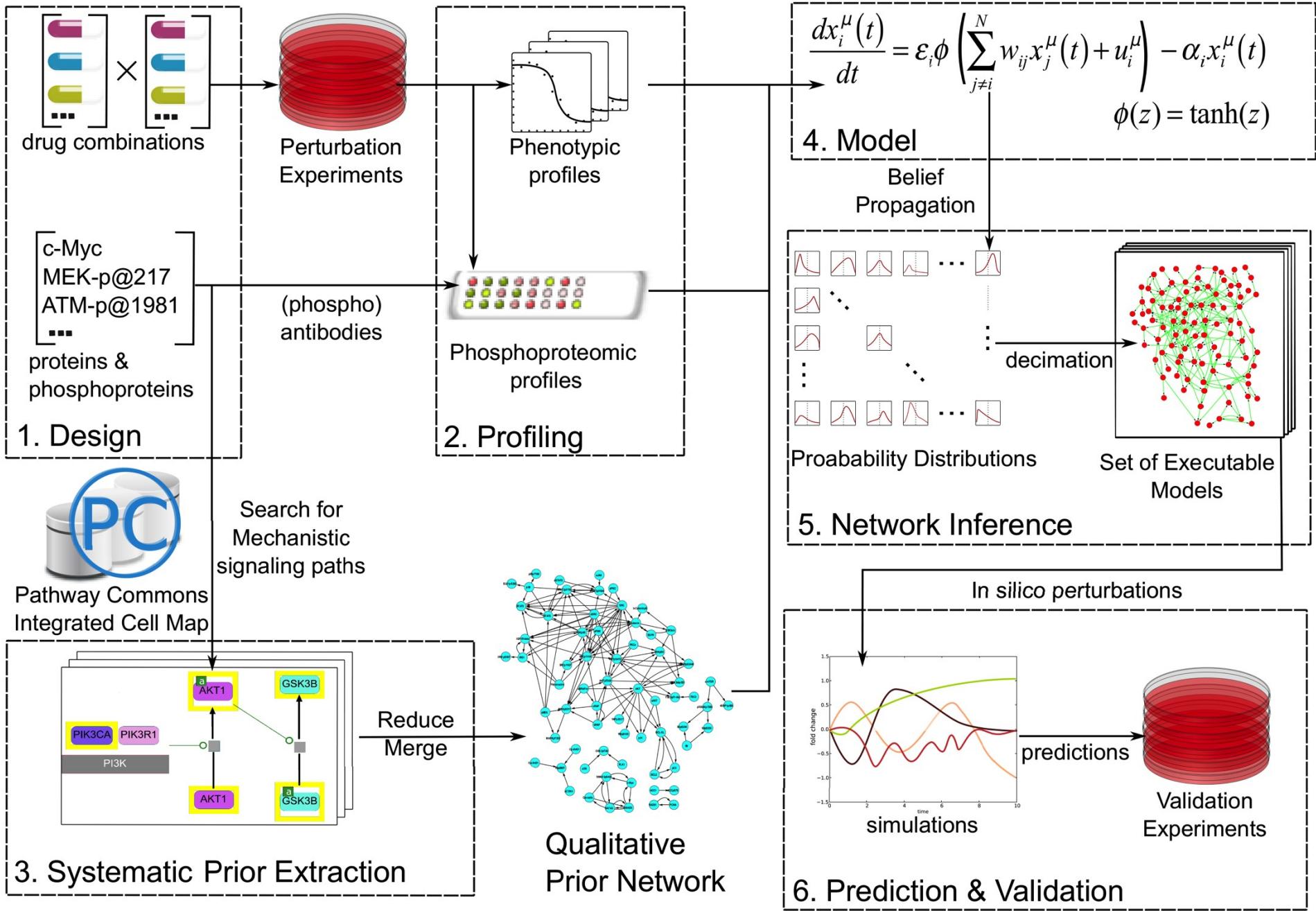
↗ Full screen

35
32
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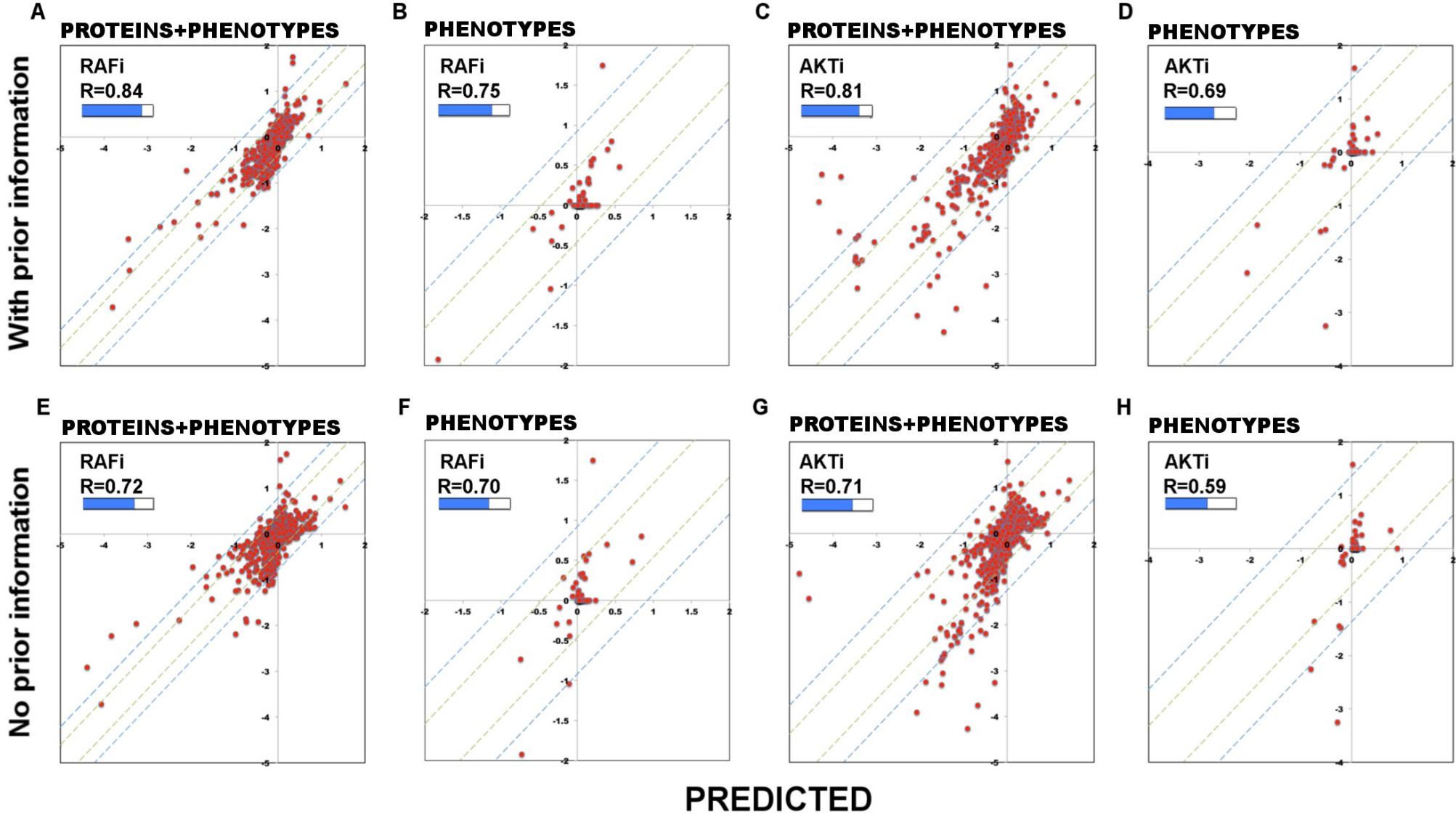
3 95 97 99 101 103 105 107 109 111 113 115

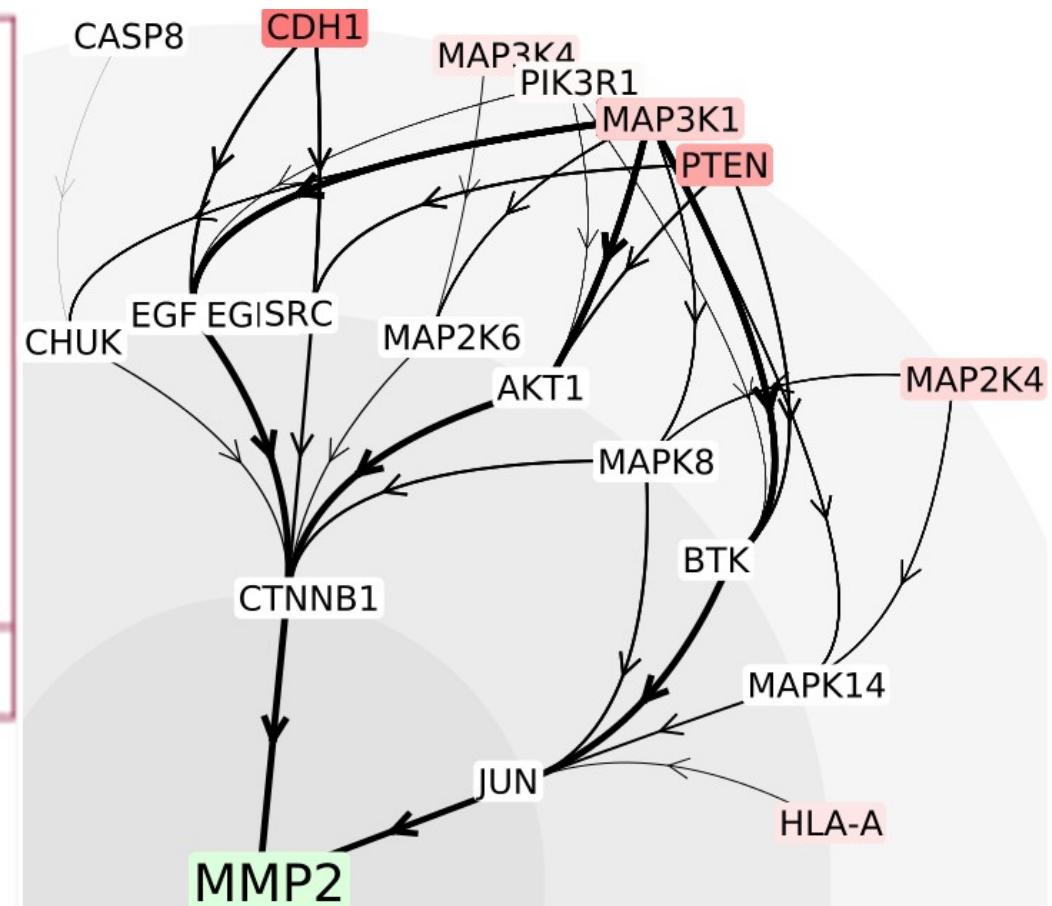
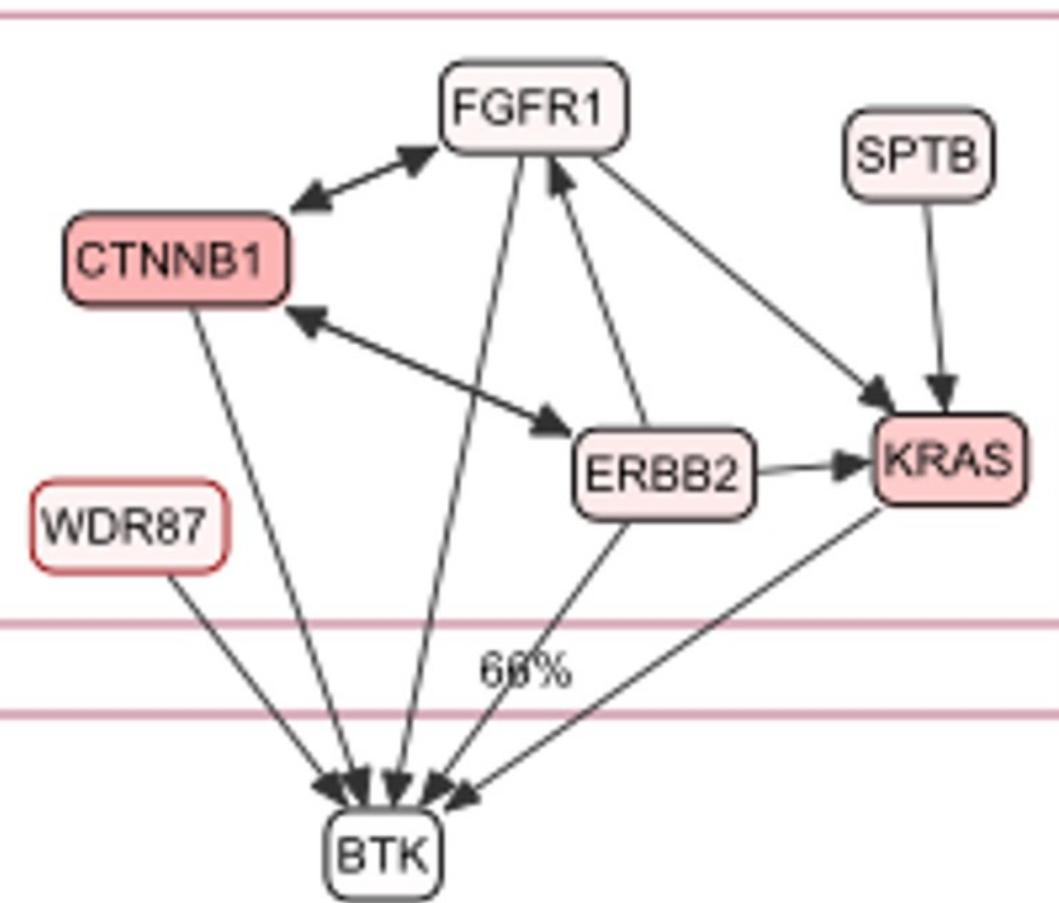






EXPERIMENTAL

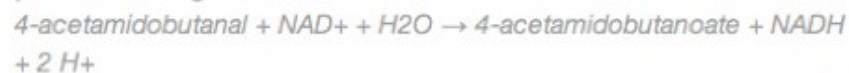




Sample	Context	Genes & Alterations	
		Gene	Annotation
TCGA-59-2372	superoxide dismutase $2 O_2 \cdot - + 2 H^+ = O_2 + H_2O_2$	SOD1	E/G Drugs: 1
	Hit Score: 0/4 (★ ★ ★ ★)	SOD3	TS/E
		SOD2	E/G HomDel
TCGA-09-0369	formate---tetrahydrofolate ligase $ATP + \text{formate} + \text{tetrahydrofolate} = ADP + \text{phosphate} + 10\text{-formyltetrahydrofolate}$	MTHFD1	Drugs: 2
	Hit Score: 2/4 (★ ★ ★ ★)	MTHFD1L	N/E HomDel
TCGA-24-2281	putrescine degradation III $4\text{-acetamidobutanal} + NAD^+ + H_2O \rightarrow 4\text{-acetamidobutanoate} + NADH + 2 H^+$	ALDH2	Drugs: 5
	Hit Score: 3/4 (★ ★ ★ ★)	ALDH3A2	N/E HomDel
TCGA-29-1698	carnitine O-palmitoyltransferase $\text{palmitoyl-CoA} + L\text{-carnitine} = \text{CoA} + L\text{-palmitoylcarnitine}$	CPT1C	TS/E Drugs: 2
	Hit Score: 2/4 (★ ★ ★ ★)	CPT1B	N/E HomDel
		CPT2	Drugs: 2
		CPT1A	E/G TS/E Drugs: 3

TCGA-24-2281

putrescine degradation III

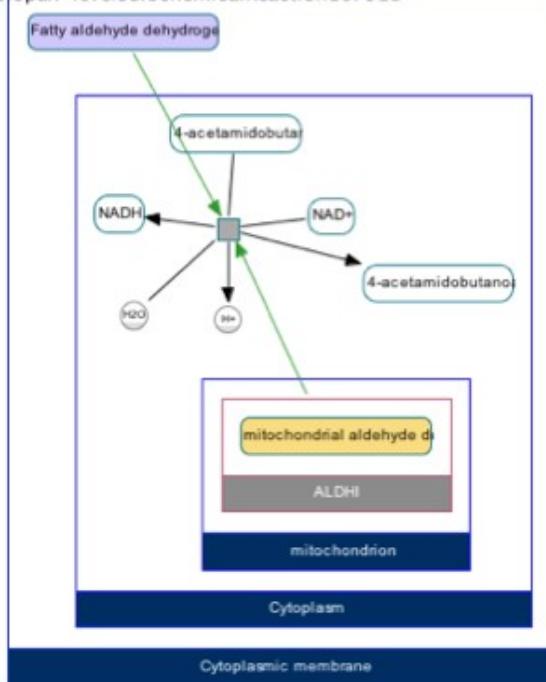


Gene	Annotation
ALDH2	Drugs: 5
ALDH3A2	N/E HomDel

[Details](#)
[PIHelper](#)

Hit Score: 3/4 (★ ★ A ★)

biopax_level3BiochemicalReaction167918

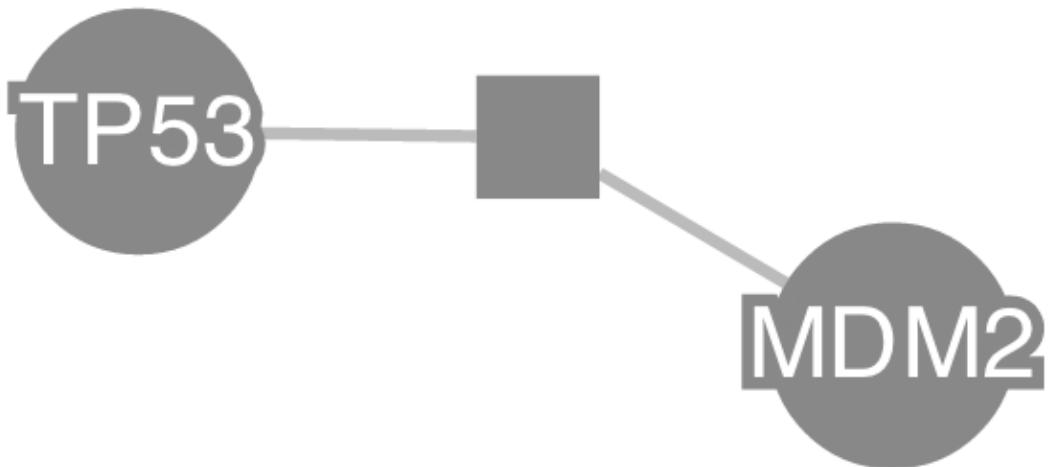


Targeted-drugs for ALDH2

Drug	Annotation
Disulfiram	Targets: 4 FDA-approved
Cyanamide	Targets: 4
Daidzin	Targets: 1
Crotonaldehyde	Targets: 1
Guanidine	Targets: 4 FDA-approved

DARPA Big Mechanism Program

- Reading
 - NLP, Tables, Figures, Distance Learning
- Assembly
 - Pathway Alignment, Conflict detection, Confidence Inference
- Explanation
 - Genomic and other high throughput data

[+ Entity](#)[+ Interaction](#)[+ Text](#) interaction[+](#) [X](#)

MDM2

[X](#)

TP53

[X](#) TP53[X](#) MDM2[X](#)

MDM2

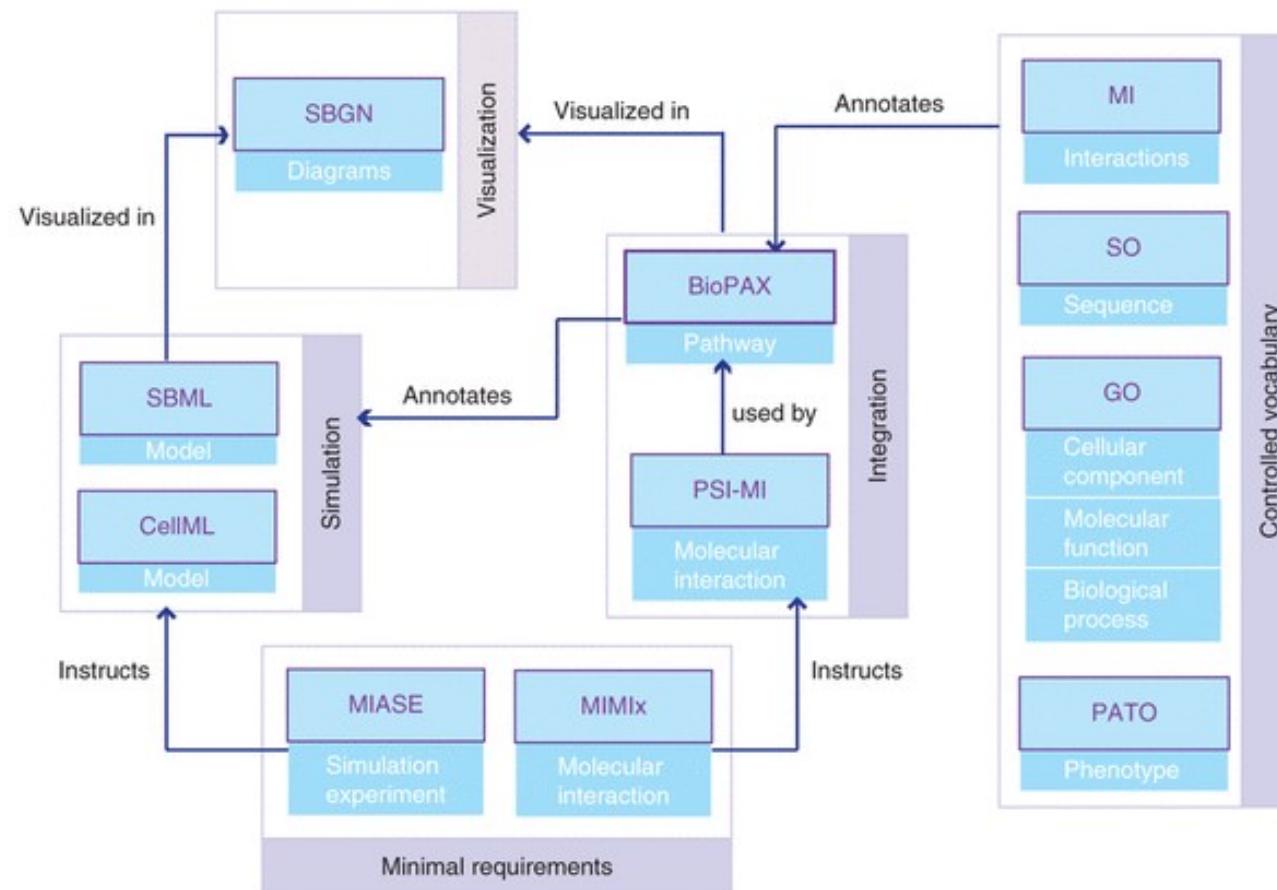
aka MDM2_HUMAN (MDM2_HUMAN)

Homo sapiens
protein

[Full details at UniProt](#)

E3 ubiquitin-protein ligase that mediates ubiquitination of p53/TP53, leading to its degradation by the proteasome. Inhibits p53/TP53- and p73/TP73-mediated cell cycle arrest and apoptosis by binding its transcriptional activation domain. Also acts as an ubiquitin ligase E3 toward itself and ARRB1. Permits the nuclear export of p53/TP53. Promotes proteasome-dependent ubiquitin-independent degradation of retinoblastoma RB1 protein. Inhibits DAXX-mediated apoptosis by inducing its ubiquitination and degradation. Component of the TRIM28/KAP1-MDM2-p53/TP53 complex involved in stabilizing p53/TP53. Also component of the TRIM28/KAP1-ERBB4-MDM2 complex which links growth factor and DNA damage response.

Systems Biology Standards





Memorial Sloan Kettering
Cancer Center™



UNIVERSITY OF
TORONTO

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- Arman Aksoy
- Onur Sumer
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- Chris Sander

- Igor Rodchenkov
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- Bilkent University
- Istemci Bahceci
- Macit Sari
- Ugur Dogrusoz

combine community!



National Human
Genome Research
Institute