

What is so special with Systems Biology?

What it delivers?

Examples from cancer studies

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Karolinska Institutet

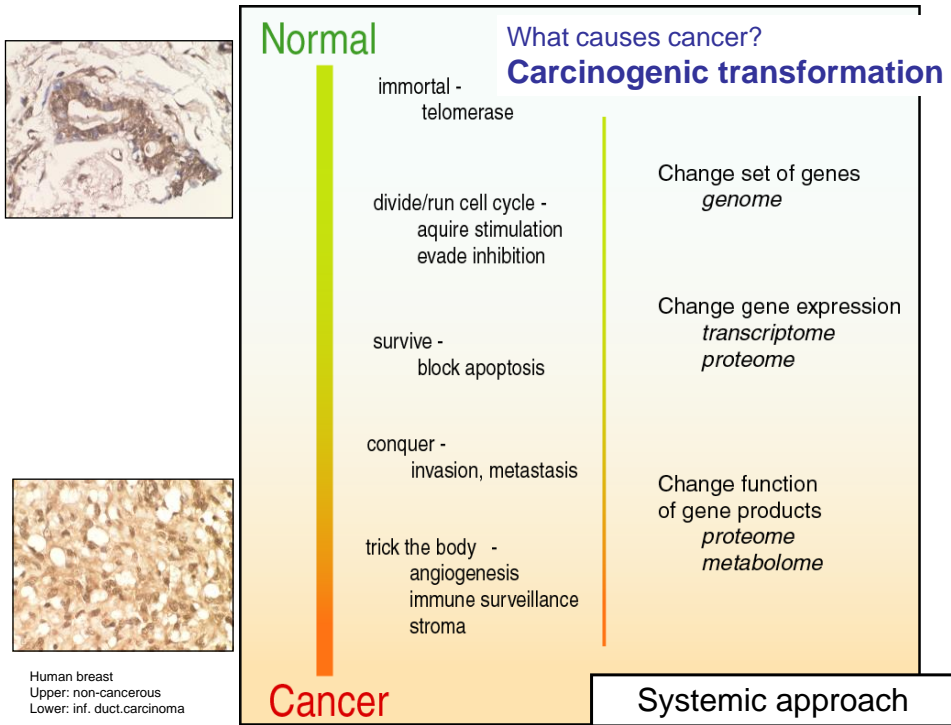
Systems Biology course, KI
13.06.2008

Overview

- Cancer is a systemic disease

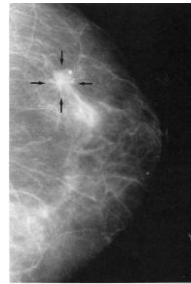
- Systemic analysis tools
 - Data presentation
 - Clustering
 - Analysis of dependencies
 - Modeling
 - Interrogation

- Examples of systemic analysis
 - Carcinogenesis studies
 - Clinical applications



Breast cancer

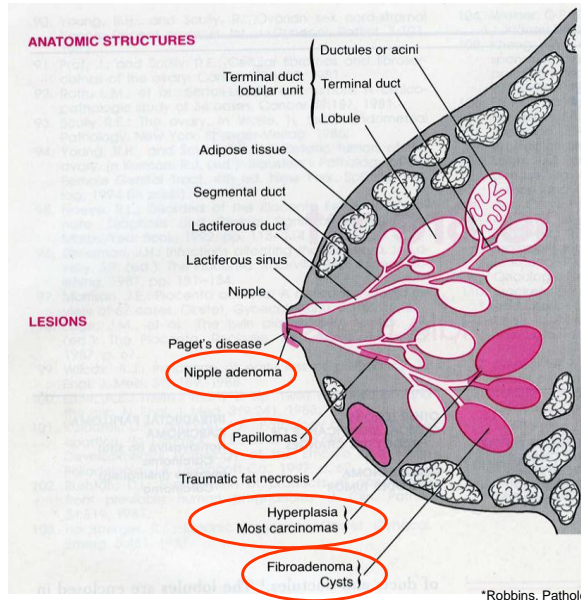
Europe
detected cases - 350.000/year*
deaths - 130.000/year*



- * Find novel mechanisms of tumorigenesis
- * Find novel anti-cancer drug targets
- * Development of "smart" drugs
- * Find markers of breast cancer

*estimates for 2000; Tyczynski et al., ENCR CFS, 2, 2002

Human breast and lesions

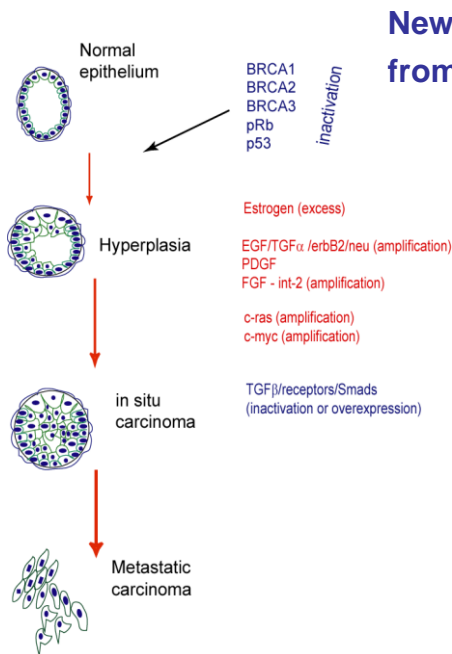
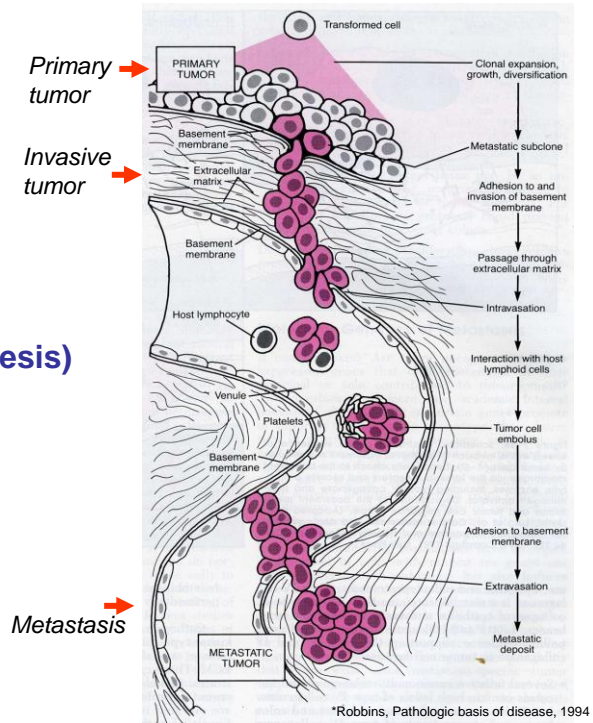


*Robbins, Pathologic basis of disease, 1994

Histopathological type of invasive breast carcinoma	Frequency
Invasive ductal carcinoma, not otherwise specified	50–80%
Invasive lobular carcinoma	5–15%
Mixed type, lobular and ductal features	4–5%
Tubular/invasive cribriform carcinoma	1–6%
Mucinous carcinoma	<5%
Medullary carcinoma	1–7%
Invasive papillary carcinoma	<1–2%
Invasive micropapillary carcinoma	<3%
Metaplastic carcinoma	<5%
Adenoid cystic carcinoma	0.1%
Invasive apocrine carcinoma	0.3–4%
Neuroendocrine carcinoma	2–5%
Secretory carcinoma	0.01–0.15%
Lipid-rich carcinoma	<1–6%
Acinic-cell carcinoma	7 cases
Glycogen-rich, clear-cell carcinoma	1–3%
Sebaceous carcinoma	4 cases

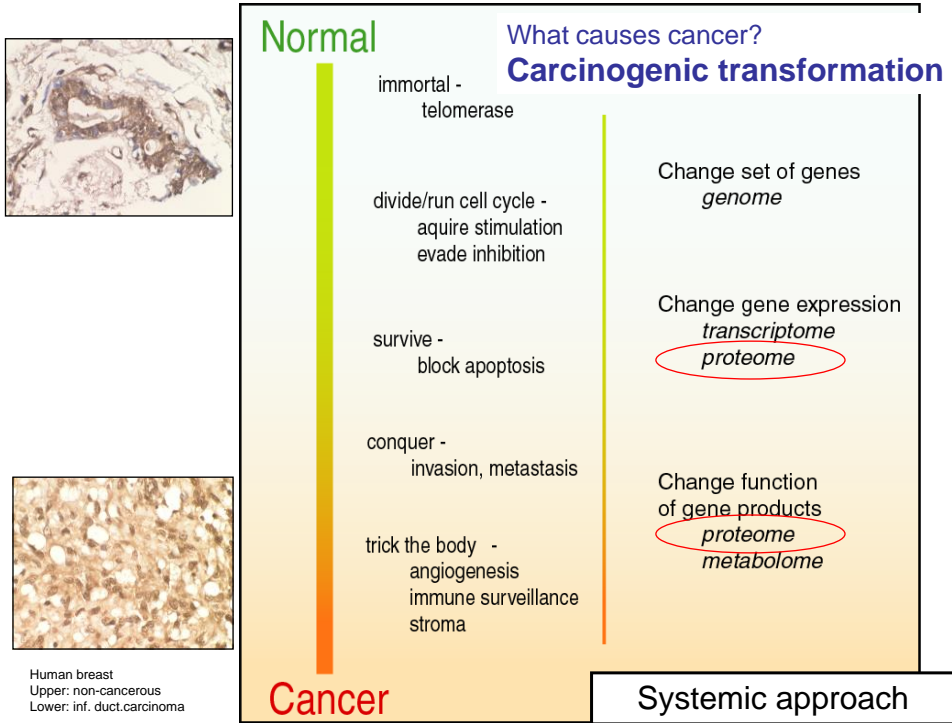
*Weigelt et al., Nature Rev. Cancer, 2005

Breast cancer treatments (stages of tumorigenesis)

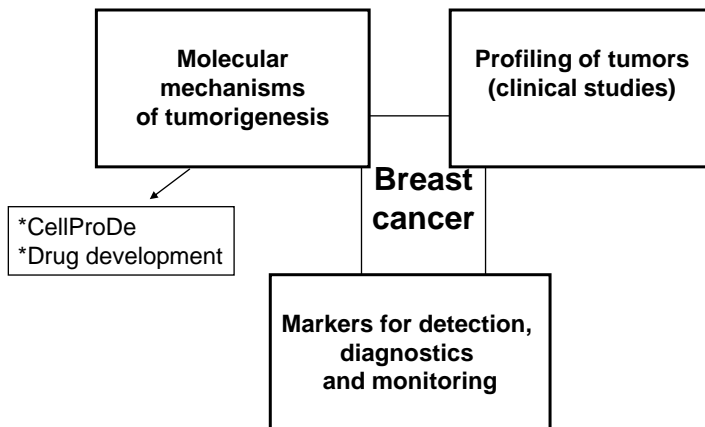


New drugs and markers come from in-depth and omics studies

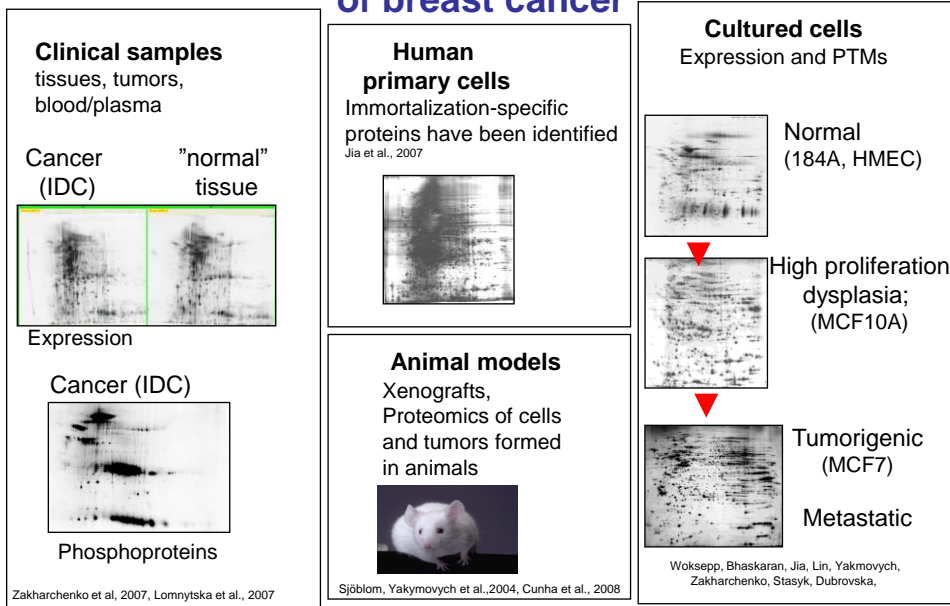
<u>Markers</u>		<u>Drugs</u>
BRCA1	CA125	Tamoxifen
BRCA2	CA12-3	Raloxifen
ER/PgR	BR 27.29	Fulverstrant
p53	cSHMT	Herceptin
uPA	Tbx3	Trastuzumab
PAI-1	utrophin	ZD1839
ErbB2/neu		<small>*examples</small>
CEA		
<u>Detection</u>		<u>+ Treatments</u>
Mammography		Surgery
		Radiotherapy
		Chemotherapy



Deliverables of Proteomics



Ways to study molecular mechanisms of breast cancer



What proteomics generates? *type of data and informational value* **LIST OF PROTEINS**

Comprehensive vs selected

All proteins

(e.g. total extraction)

Enrichment/purification

- by PTMs
- by PTMs chemistry
- by chemical modifications (peptide backbone, e.g. ICAT)
- by activity (ABPP)
- by purification (PTMs and complexes)

Deposition of information

PRIDE - Microsoft Internet Explorer

Address: <http://www.ebi.ac.uk/pride/>

PRIDE Proteomics IDentifications database

Searching PRIDE

You can use the simple search box on the main PRIDE website page to perform simple keyword queries.

- PRIDE Experiment accession number (plain integers).
- PRIDE CV term (e.g. PRIDE:0000018)
- GO term (GO:0000116)
- Protein accession (e.g. IP100295313) This will search the database and return the experiments where this protein was identified. You can use IPI, UniProt or Swiss-Prot accessions.

Introduction

- The **PRIDE Proteomics IDentifications database** is a **centralized, standards compliant, public data repository for proteomics data**. It has been developed to provide the proteomics community with a public repository for protein and peptide identifications together with the evidence supporting these identifications.
- PRIDE has been developed through a collaboration of the EMBL/EBI and Ghent University in Belgium. The original motivation behind its development was to provide a common data exchange format and repository to support proteomics literature publications. This remit has grown with PRIDE, with the hope that PRIDE will provide a reference set of tissue-based identifications for use by the community. The future development of PRIDE has become closely linked to HUPO-PS.
- In addition to identifications, PRIDE is able to capture details of post-translational modifications coordinated relative to the peptides in which they have been found.
- View the [PRIDE publicity flyer](#)
- Read [PRIDE conference abstracts](#)

Members of the PRIDE development collaboration:

- EBI - European Bioinformatics Institute, Cambridge, United Kingdom
- Universiteit Ghent - Ghent University, Ghent, Belgium
- Faculty of Life Sciences, The University of Manchester - Manchester, UK
- The Yonsei Proteomics Research Center (YPRC), Yonsei University, Seoul, Korea.

The YPRC has recently joined the PRIDE development effort, contributing requirements specifications, design and coding time under the coordination of Sang Y'oon Cho.

Software:

PRIDE Basic Statistics

The PRIDE database currently contains:

- 3,217 Experiments
- 371,300 Identified Proteins
- 2,150,091 Identified Peptides
- 300,145 Unique Peptides
- 2,699,562 Spectra

Clustering:

Functional /alphabet/



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

the Gene Ontology - Microsoft Internet Explorer

Address: <http://www.geneontology.org/>

the Gene Ontology

Gene Ontology Home

The Gene Ontology project provides a controlled vocabulary to describe gene and gene product attributes in any organism. [Read more about the Gene Ontology.](#)

Search the Gene Ontology Database

Search for genes, proteins or GO terms using AmiGO:

is gene or protein name GO

is GO term or ID GO

AmiGO is the official GO browser and search engine. [Browse the Gene Ontology with AmiGO.](#)

GO website

- GO downloads, including ontology files, annotations and the GO database
- Tools for using GO, including OBO-Edit, downloads, AmiGO, and the GO Online SQL Environment.
- Request new terms or ontology changes via the [GO curator requests tracker](#) - help with new term submission is available.
- Documentation on all aspects of the GO project and the [GO FAQ](#).
- Gene Ontology mailing lists and contact details
- The [GO newsletter](#) has all the latest news and views from the GO project.

News

GO Consortium meeting minutes available

The minutes from the GO Consortium meeting held at Jesus College, Cambridge, UK from Jan 8-10, 2007 are now available. (posted June 22, 2007)

AmiGO: Gene Product Search Results - Microsoft Internet Explorer

Address: http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?action=query&view=query&query=ss&search_constraint=mgp

Gene Product Search Results

9201 results for **ss** in field(s) name(s), symbol, synonyms

Filter search results

Filter Gene Products: Species, Data source, Evidence Code, Ontology

Name	Details
10CB.340 Fatty acid desaturase, putative	protein from <i>Trypanosoma brucei</i>
134P10.12 Putative 3-phosphoshikimate 1-carboxyvinyltransferase	protein from <i>Oryza sativa (japonica cultivar-group)</i>
14-3-3epsilon Query matches synonym Suppressor of RNAiSD 3-9	gene from <i>Drosophila melanogaster</i>
1F7.245 Tyrosyl-DNA Phosphodiesterase (Tdp1), putative	protein from <i>Trypanosoma brucei</i>
29N14.40 Methyltransferase, putative	protein from <i>Trypanosoma brucei</i>
27H14.40 DNA polymerase delta catalytic subunit, putative	protein from <i>Trypanosoma brucei</i>
2BH13.415 Enoyl-CoA hydratase/Enoyl-CoA isomerase/3-hydroxyacyl-CoA dehydrogenase, putative	protein from <i>Trypanosoma brucei</i>
30M24.115 Esterase, putative	protein from <i>Trypanosoma brucei</i>
30M24.275 Branched-chain amino acid aminotransferase, putative	protein from <i>Trypanosoma brucei</i>
30M24.285 Branched-chain amino acid aminotransferase, putative	protein from <i>Trypanosoma brucei</i>

AmiGO: Gene Product Search Results - Microsoft Internet Explorer

Address: http://amigo.geneontology.org/cgi-bin/amigo/go.cgi?query=hras&search_constraint=gol&action=query&view=query&session=92011194343763

the Gene Ontology AmiGO

Advanced Search BLAST search Browse Help

Search GO **hras** Terms Genes or proteins Exact Match Submit Query

Gene Product Search Results

1 result for **hras** in field(s) name(s), symbol, synonyms

Filter search results

Filter Gene Products: Species, Data source, Evidence Code, Ontology

Name	Details
hras1 Harvey rat sarcoma virus oncogene 1 Query matches synonyms c- src and 1 more	gene from <i>Mus musculus</i>

Last updated 2007-11-01
How can we improve AmiGO? Send us your suggestions.
Copyright © 1999-2007 The Gene Ontology. • Contact Us.

17-beta-hsd 1
 hsd17b1
 edh17b2
 MGC2803
 cpn10
 hspe1
 hsp10
 krt10
 hmg-14
 hmg-17
 hmgn1
 anxa1
 lpc1
 lmna
 lmn1
 emd2
 fpld
 cmd1a
 hgps
 lgmd1b
 krt10
 krt10
 tacstd1
 trop1
 m4s1
 mic18
 ly74
 mnda

Proteins
 Presented in the "right" GO alphabet

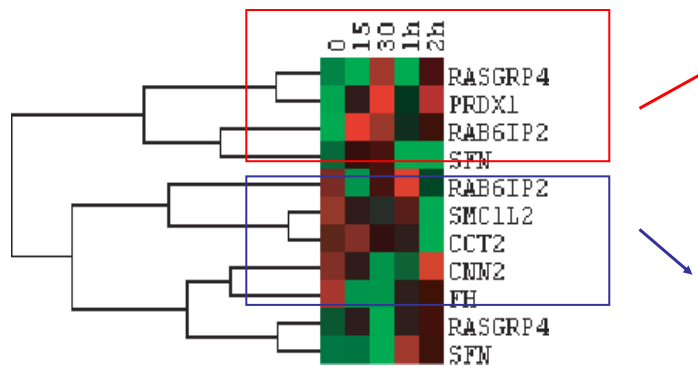
.... But it is based on genes.

Protein Ontology is under construction

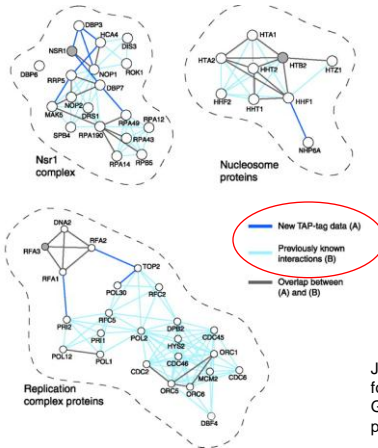
<http://www.ebi.ac.uk/>

Clustering:

Time points



Clustering:
Structural Groups
organelles



Jansen et al. (2003) A Bayesian Networks Approach for Predicting Protein-Protein Interactions from Genomic Data. Science, Vol. 302. no. 5644, pp. 449 - 453

Clustering:
Functional

/sentences/

Example:

GoMiner

<http://discover.nci.nih.gov/gominer/>

GoMiner Home Page - Microsoft Internet Explorer

Address: http://discover.nci.nih.gov/gominer/

Genomics and Bioinformatics Group
 NCI, FCR, National Cancer Institute

Home | High-Throughput | Getting Started | Requirements | Installation | Command Line | Database | FAQ | News | Citing | GoMiner in Papers | Credits

GoMiner™ is a tool for biological interpretation of 'omic' data – including data from gene expression microarrays. Omic experiments often generate lists of dozens or hundreds of genes that differ in expression between samples, raising the question

What does it all mean biologically?

To answer this question, GoMiner leverages the Gene Ontology (GO) to identify the biological processes, functions and components represented in these lists. Instead of analyzing microarray results with a gene-by-gene approach, GoMiner classifies the genes into biologically coherent categories and assesses these categories. The insights gained through GoMiner can generate hypotheses to guide additional research.

We have updated our [Getting Started](#) section with guidance on choosing between GoMiner and High-Throughput GoMiner

New Features

- Latest! [Get faster performance more easily - Get a local GO database and GoMiner in a single download package](#)
- Latest! We have updated our documentation to provide a guides on which [GoMiner version](#) and [database configuration](#) to use
- [New Startup Wizard](#)
- [False Discovery Rate in the GUI](#)
- [SVG Support for Firefox](#)
- [Other Recent GoMiner Highlights...](#)

To get started using GoMiner

- Choose the right [GoMiner version](#) for your situation
- Choose the right [database configuration](#) for your situation
- Read the [instructions](#), and verify that your environment satisfies the system requirements
- For Classic or GUI GoMiner, download the program file, [gominer.jar](#) or go to the [High-Throughput GoMiner](#) web page.
- Read the [Quick Start](#) and try out the [sample files](#)
- You can also take a [Powerpoint tour](#) of the major features of GoMiner. (~1.5Mb)

GoMiner displays the genes within the framework of the Gene Ontology hierarchy in two ways

In the form of a tree, similar to that in AmiGO

In the form of a Directed Acyclic Graph (DAG)

Size of the box is proportional log n

The program also provides:

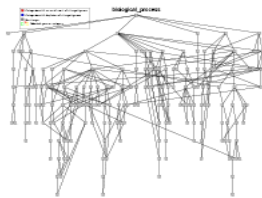
Quantitative and statistical analysis

Under	Over	Change	P-Value
2	5	7	0.01
2	5	7	0.01
2	5	7	0.01
5	6	11	0.01

Seamless integration with important public databases

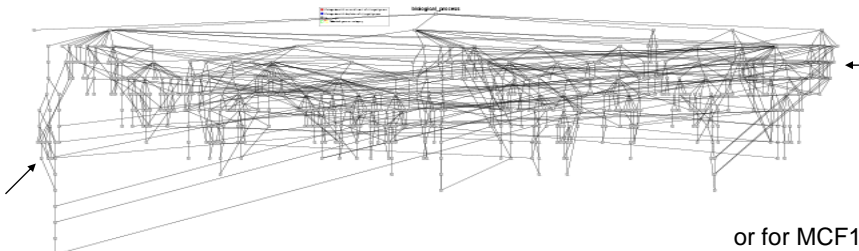
Receive Updates

Clustering:

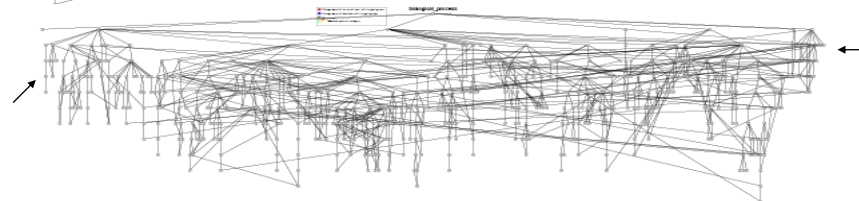


Overview of TGFβ targets common for both cell lines,

or specific for 184A1



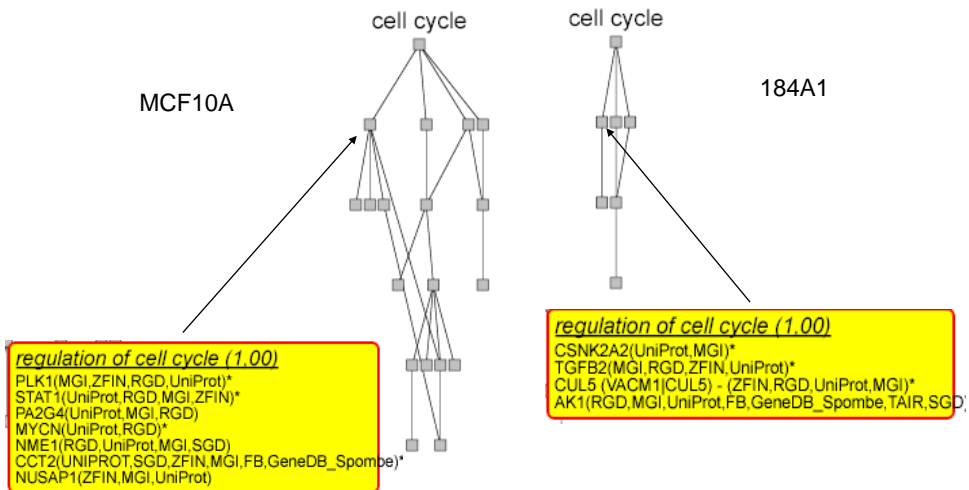
or for MCF10A



*DAGs represent functional clusters of common and specific proteins

Clustering:

Different pattern of TGF β -dependent regulation of the cell cycle



**Primary data were generated by Hanna Woksepp (184A1 cells) and Nimesh Bhaskaran (MCF10A cells)

- "traditional" analysis
- large-scale analysis without analysis of dependencies
- **systemic analysis**

Systemic analysis is a study of properties which appear as a result of interaction of components

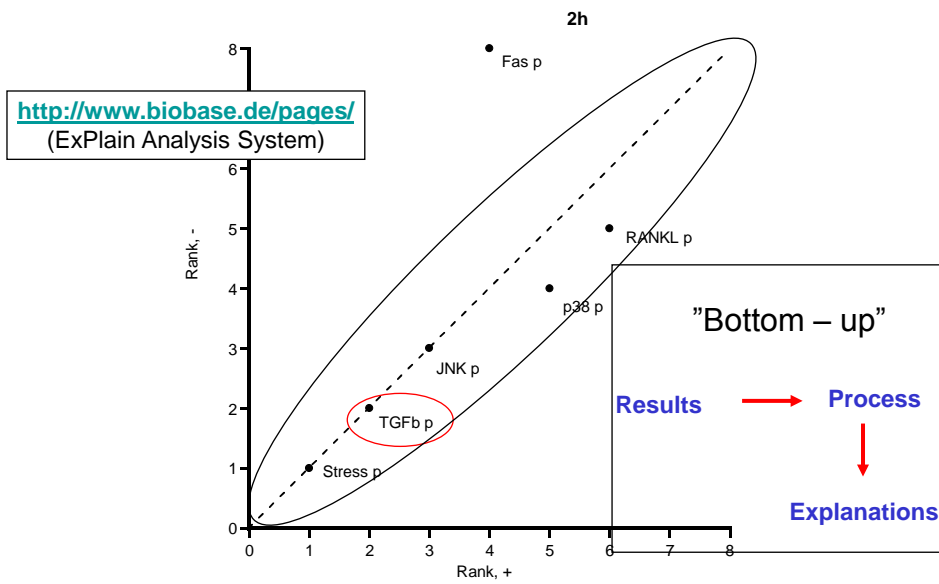
("it takes two to tango", or "cancer is not a gene disease")

Systemic Analysis

Functional analysis

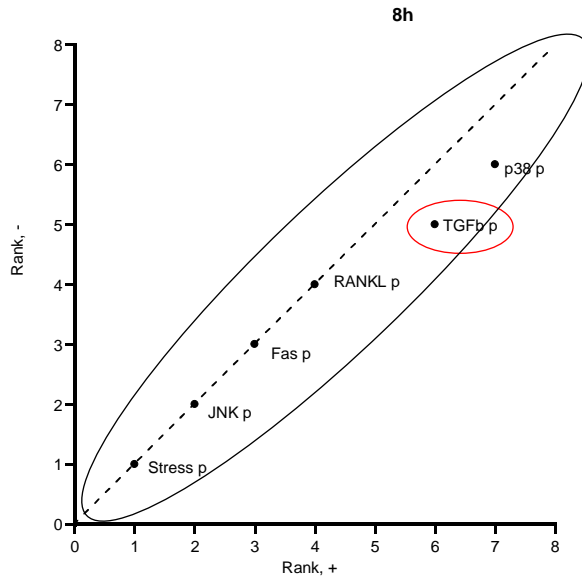


How much of TGFβ signalling is induced by TGFβ?



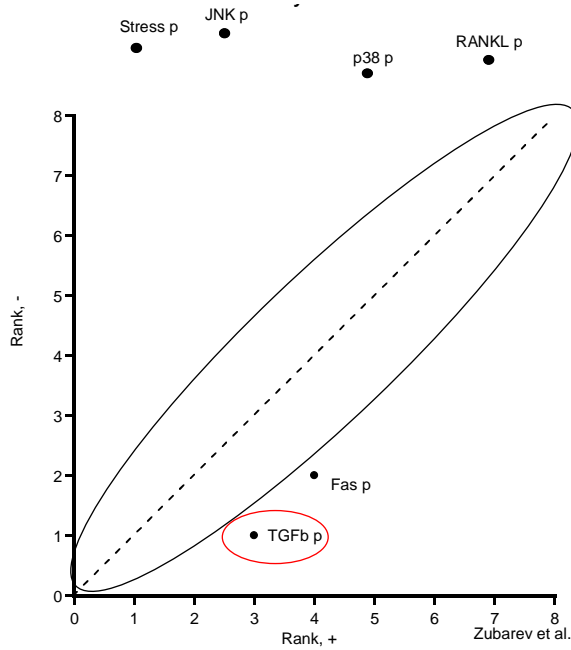
Zubarev et al., unpublished observation

How much of TGF β signalling is induced by TGF β ?



Zubarev et al., unpublished observation

How much of TGF β signalling is induced by TGF β ?



Zubarev et al., unpublished observation

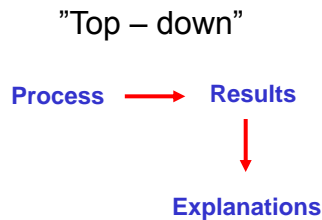
Conclusion:

TGF β regulates targets which are not considered to be TGF β targets by majority of TGF β scientists.

Shall TGF β signalling change its shape?

systemic analysis

Functional analysis



Example:
Ingenuity Pathway Analysis (<http://www.ingenuity.com>)

In application to TGFbeta-regulated proteins in human breast epithelial cells

Workflow

Cells,
Treated or not with TGFbeta

2D gels

Image analysis
(statistics)

Identification
(mass spectrometry)

17-beta-hsd 1
hsd17b1
edh17b2
MGC2803
cpn10
hspe1
hsp10
krt10
hmg-14
hmg-17
hmg1
anxa1
lpc1
lmna
lmn1
emd2
fpld
cmd1a
hgps
lgmd1b
krt10
krt10
tacstd1
trop1
m4s1
mic18
ly74

The screenshot shows the Ingenuity Systems website interface. At the top, there is a navigation bar with 'FREE TRIAL' highlighted. Below the navigation bar, there are several promotional banners and news sections. The 'NEWS' section features an article about the identification of an Alzheimer's-specific plasma biomarker signature. The 'SCIENCE SPOTLIGHT' section highlights the classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. The 'EVENTS' section lists Thursday Trainings, including IPA Data Analysis using Functions and Pathways, IPA Data Analysis using Network Analysis, Biomarker Filter and Comparison Analysis, and Molecular Toxicology Analysis. The website also includes a 'Discover The Biology' banner and an 'IPA-Metabolomics™ is Here' banner.

Mr. Souchehnytskyi CLOSE SESSION

Enter gene names/symbols/IDs or chemical/drug names here SEARCH ADVANCED

184A, all, HW data - 2007-11-07 09:35 AM

REFRESH Summary Networks Functions Canonical Pathways Lists Pathways Molecules Network Explorer Overlapping Networks

Top Networks

ID	Associated Network Functions	Score
1	View Cancer, Cellular Growth and Proliferation, Cell-To-Cell Signaling and Interaction	40

Top Bio Functions

Diseases and Disorders

Name	p-value	# Molecules
Cancer	6.15E-07 - 2.00E-02	6
Cardiovascular Disease	8.47E-06 - 2.05E-02	5
Organismal Injury and Abnormalities	8.47E-06 - 1.15E-02	4
Gastrointestinal Disease	8.43E-05 - 1.94E-02	4
Dermatological Diseases and Conditions	2.76E-04 - 1.04E-02	2

Molecular and Cellular Functions

Name	p-value	# Molecules
Cell-To-Cell Signaling and Interaction	6.48E-06 - 1.97E-02	4
Cellular Growth and Proliferation	8.51E-06 - 1.94E-02	7
Cell Signaling	1.64E-04 - 2.00E-02	6
Molecular Transport	1.64E-04 - 2.00E-02	4
Small Molecule Biochemistry	1.64E-04 - 1.91E-02	8

Physiological System Development and Function

Name	p-value	# Molecules
Tissue Development	6.48E-06 - 1.86E-02	4
Tissue Morphology	8.47E-06 - 1.62E-02	3
Hematological System Development and Function	1.71E-05 - 2.02E-02	4
Immune and Lymphatic System Development and Function	1.71E-05 - 1.97E-02	4
Connective Tissue Development and Function	2.76E-04 - 1.94E-02	4

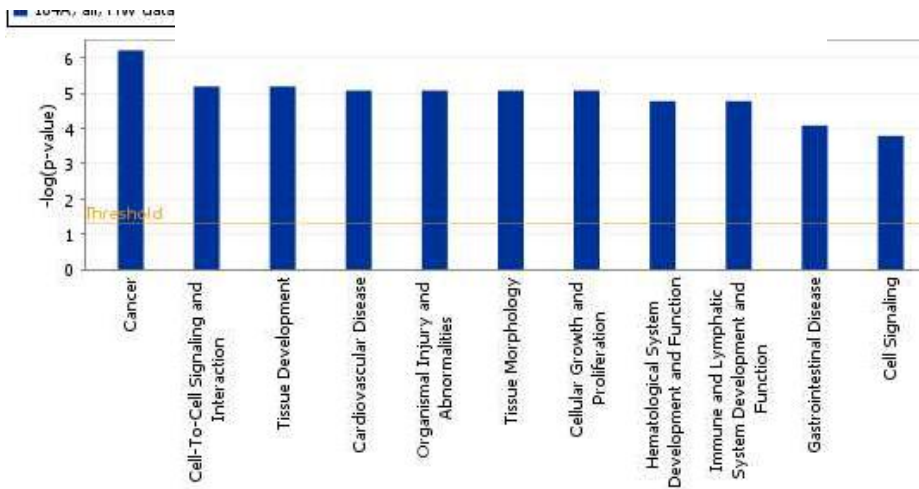
Top Canonical Pathways

Name	p-value	Ratio
Coagulation System	9.62E-03	1/35 (0.029)
Fructose and Mannose Metabolism	1.43E-02	1/140 (0.007)
Androgen and Estrogen Metabolism	2.27E-02	1/137 (0.007)
p38 MAPK Signaling	2.59E-02	1/95 (0.011)
Apoptosis Signaling	2.86E-02	1/110 (0.009)

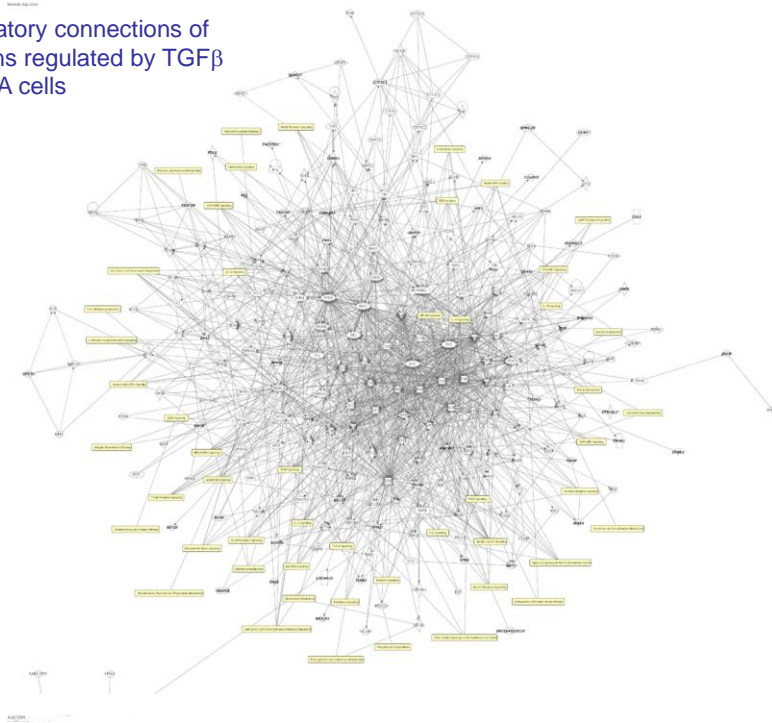
Top Molecules

This analysis has no expression values.

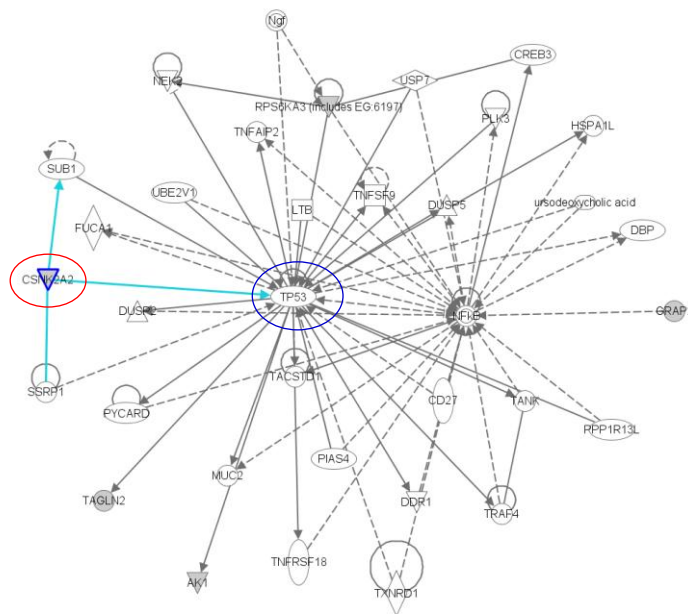
Functions affected by TGFbeta-regulated proteins

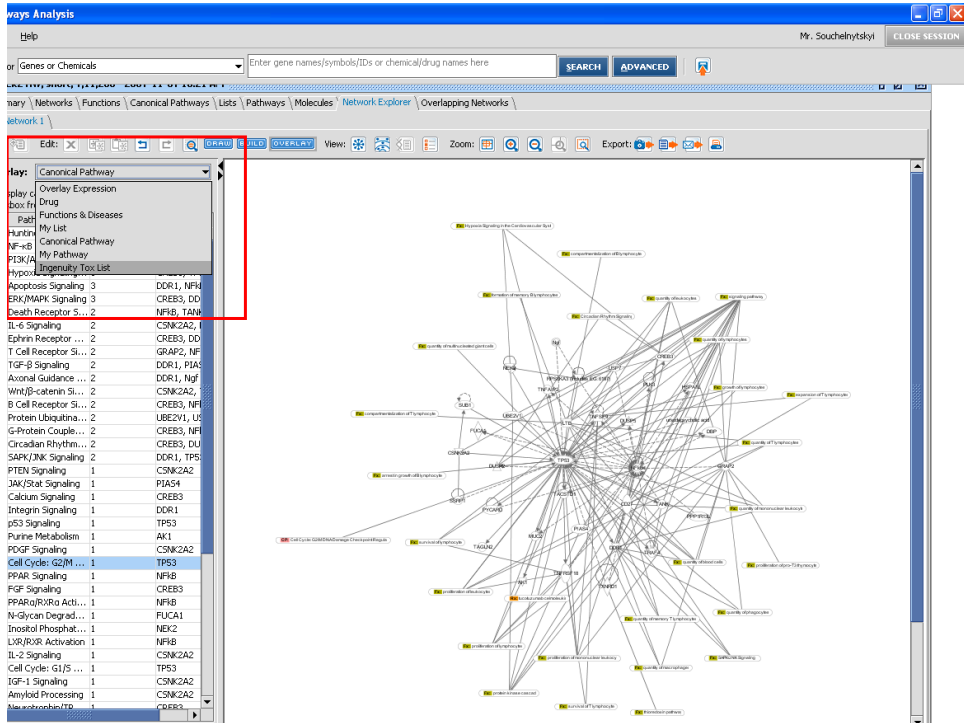


Regulatory connections of proteins regulated by TGFβ in 184A cells



CK2-dependent sub-network





FunCoup - Microsoft Internet Explorer

Other tools are available as well...

http://funcoup.sbc.su.se

FunCoup online

Query: physical interactions

in: human

Which gene/protein IDs to use?

See some example queries

Run <<< Less options

Add gene groups to the query

KEGG pathway map(s): ALL: Carbohydrate Metabolism, KEGG01110

disease-related genes as OMIM ID(s)

Network(s) in: human, M. musculus, R. norvegicus, D. rerio

Use evidence from: all available species, the same kingdom, the same class, only this species

Show evidence of category: human, mouse, rat, zebrafish, fly, worm, yeast, Arabidopsis, Protein interactions, Co-expression, Phylogenetic profiles, Cell co-localization

Minimal amount of evidence to show a category line: 1.00

Simulation

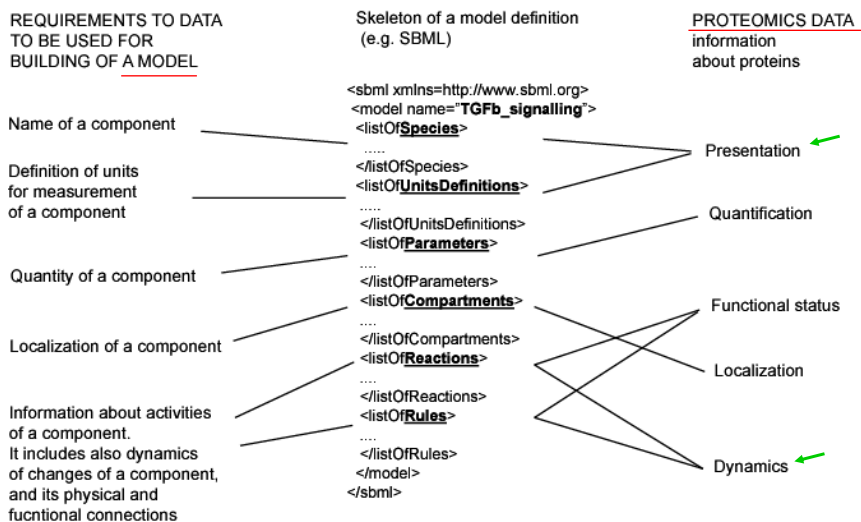
- Acquisition of data
- Presentation of data
- Architecture of dependencies
- Description of dependencies
- Evaluation of results

Systems Biology or large-scale modeling

Study of systemic properties of biological systems, i.e. properties which appear as a result of interactions

(Souchelnytskyi, 2005)

Large-scale analysis of proteomics data



Souchelnytskyi, Proteomics, 2005

SBML.org - The home site for the Systems Biology Markup Language - Microsoft Internet Explorer

Address: http://sbml.org/index.jsp

SBML Systems Biology Markup Language

home • contacts • documents • downloads • FAQs • forums • Level 3 • models • news • online tools • vsls • workshops

The Systems Biology Markup Language (SBML) is a computer-readable format for representing **models of biochemical reaction networks**. SBML is applicable to metabolic networks, cell-signaling pathways, regulatory networks, and many others.

Internationally Supported and Widely Used

SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is supported by **over 110 software systems**, including the following (where "*" indicates SBML support in development):

acsDreame	Dizzy	Molecuizer	SBMLSim
BALSA	E-CELL	Monod	SBMLToolbox
BALSA	ecell	Namator	SBO
BIOCHAM	ESS	NetBuilder	SBToolbox
BioCharon	FluxAnalyzer	Oscill	SBW
BioDyn	Fluxor	PANTHER Pathway	SCpath
BioCyc	Genetides	PathArt	semanticSBML
BioGrid	GePasi	PathwayAnalyzer	Sigmoid*
BioModels	Gillespie2	PathwayLab	SigPath
BioNetGen	HMSB	PathwayTools	SigTran
BioPathwise	HybridSBML	PathwayBuilder	SIMBA
Bio Sketch Pad	INSULCO discovery	PathWeb	Simbiology
BioSens	JACOBIAN	FAVESy	Simpathica
BioSPICE Dashboard	Jamrac	PET	SimPheny*
BioSpreadsheet	JDesigner	PKK	Simviz
BioTapestry	JigCell	PotersWheel	SloppyCell
BiOUMIL	JSim	ProcessDB	SmartCell
BSTLab	JWS Online	PROTON	SRS Pathway Editor
CADLIVE	Kayote*	psbmi	StochSim
CellDesigner	KEGG2SBML	PyCes	StochKit
Cellerator	Kinelon	RAVOC	STOCKS
Cell Illustrator	Kinsolver*	Reactome	TERANODE Suite
CellML2SBML	libSBML	RMNTToolbox	Trellis
Cellware	MathSBML	RSMB	WANTED
CL-SBML	MesoRD	ruSBML	Virtual Cell
CLEMIL	Meta-All	SABIO-PK	WebCell
COPASI	MetaFluxNet	SBML-ODE Soher	WiredCAMP
Cyto-Sim	MIRIAM	SBML-PET	Xholon
Cytoscape	MMT2	SBMLeditor	XPPAUT
DBsolve	Modesto	SBMLR	

A Free and Open Language

Advances in biotechnology are leading to larger, more complex quantitative models. The systems biology community needs information standards if models are to be shared, evaluated and developed cooperatively. SBML's widespread adoption offers many benefits, including (1) enabling the use of multiple tools without rewriting models for each tool, (2) enabling models to be shared and published in a form other researchers can use even in a different software environment, and (3) increasing the amount of models for the biological and other research community.

Done

NEMO compiler supports SBML
(Oct. 31, 2007) NEMO is generator of random transcription networks and NEMO is a network motif language. The NEMO compiler can read SBML.
[read more](#)

New version of SBW
(Oct. 25, 2007) The SBW Development Team has released SBW version 2.1.8. SBW is a software communications framework allowing different tools to be networked.
[read more](#)

New version of VCell
(Oct. 5, 2007) The VCell project has released both a stable and a new beta release of VCell. Among the new features are improved SBML compatibility.
[read more](#)

New version of COPASI
(Oct. 5, 2007) The COPASI project has released development version Build 23, featuring several new capabilities and improvements to SBML compatibility.
[read more](#)

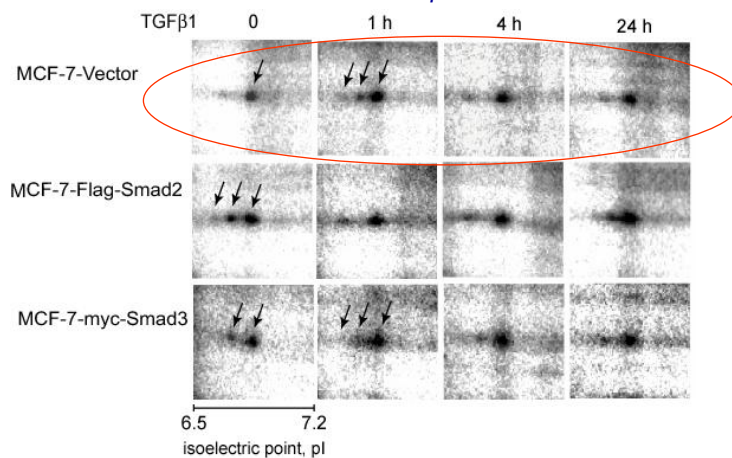
SBML Level 2 Version 3 Release 2
(Sep. 27, 2007) Release 2 of the SBML Level 2 Version 3 specification is now available. It corrects typos and small errors in Release 1.
[read more](#)

See older news items.

Example 1

Simulation

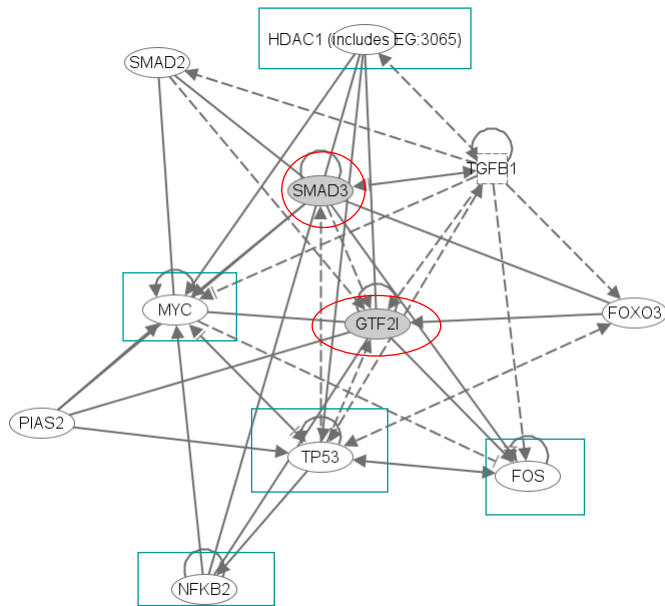
Primary proteomics data: transcription factor TFII-I is phosphorylated upon treatment of MCF7 cells with TGFβ1



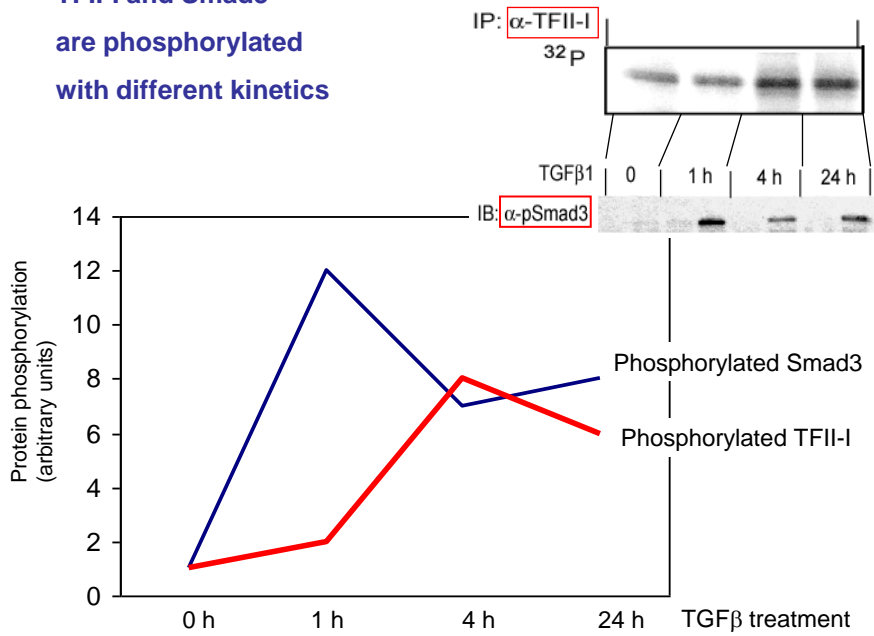
*Areas of images of 2D gels showing TFII-I-containing spot
TFII-I interacts with c-myc, NfκB, ATF6, STAT1, HDAC3

Stasyk, Dubrovskaya, et al, 2005

TFII-I (gtf2i) and Smad3-centered network

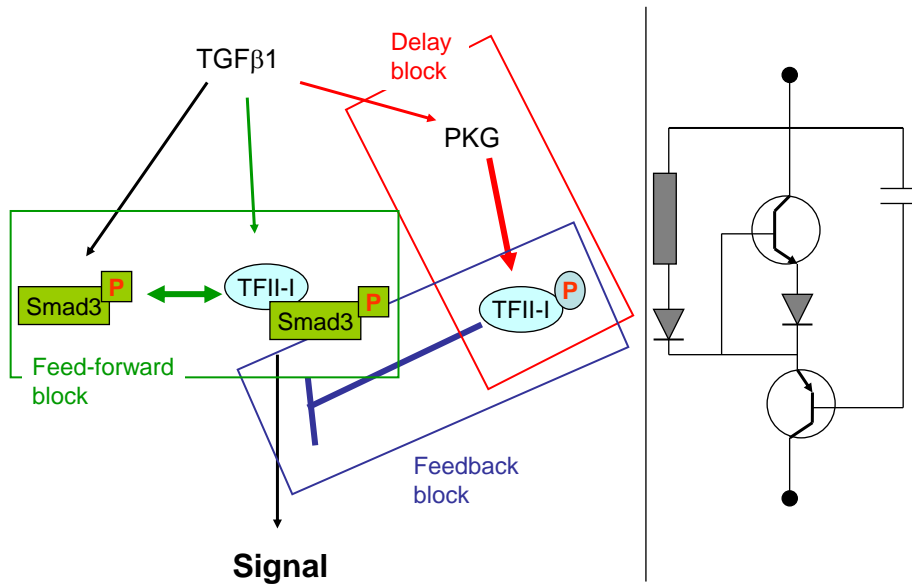


TFII-I and Smad3 are phosphorylated with different kinetics



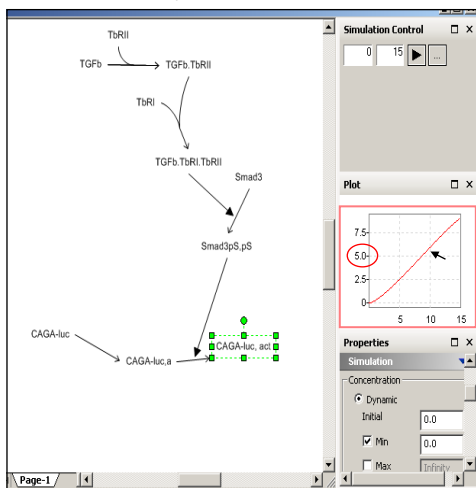
TGFβ-dependent phosphorylation of TFII-I as a negative feed-back mechanism

Feedback, feed-forward and time delay blocks

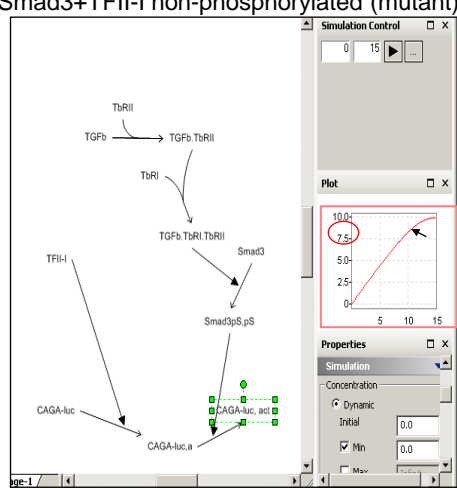


Modeling of signalling to transcriptional regulation by Smad3 and TFII-I

Smad3 only

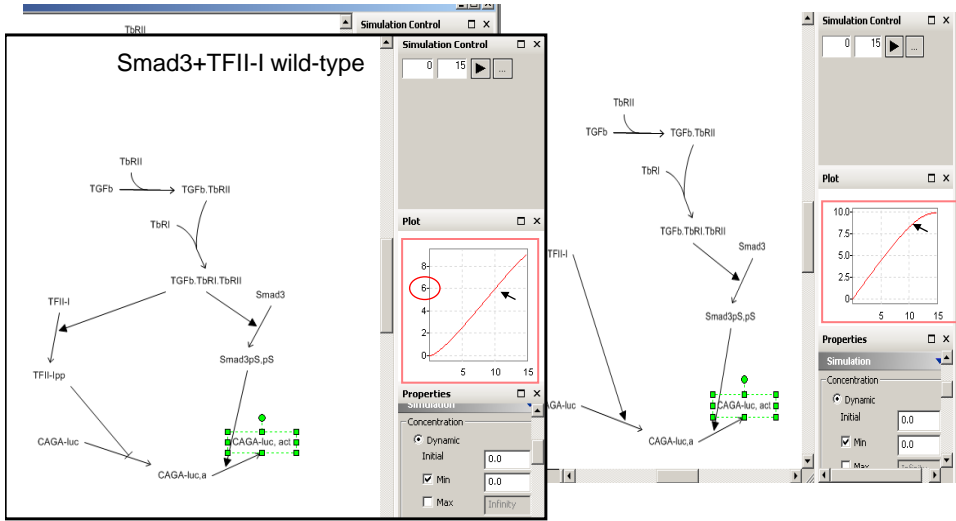


Smad3+TFII-I non-phosphorylated (mutant)



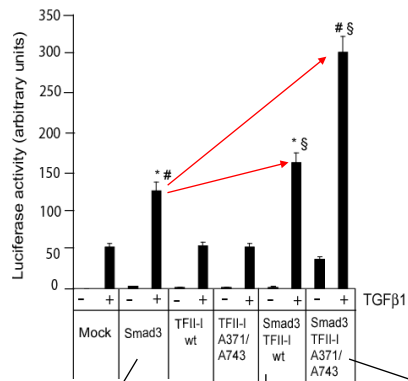
*PathwayLab

Modeling of signalling to transcriptional regulation by Smad3 and TFII-I

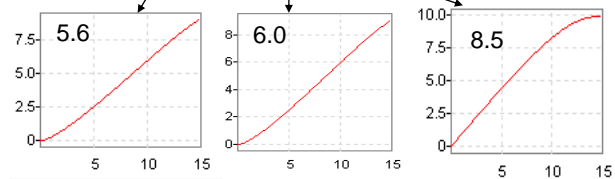


Modeling of signalling to transcriptional regulation by Smad3 and TFII-I

Experimental



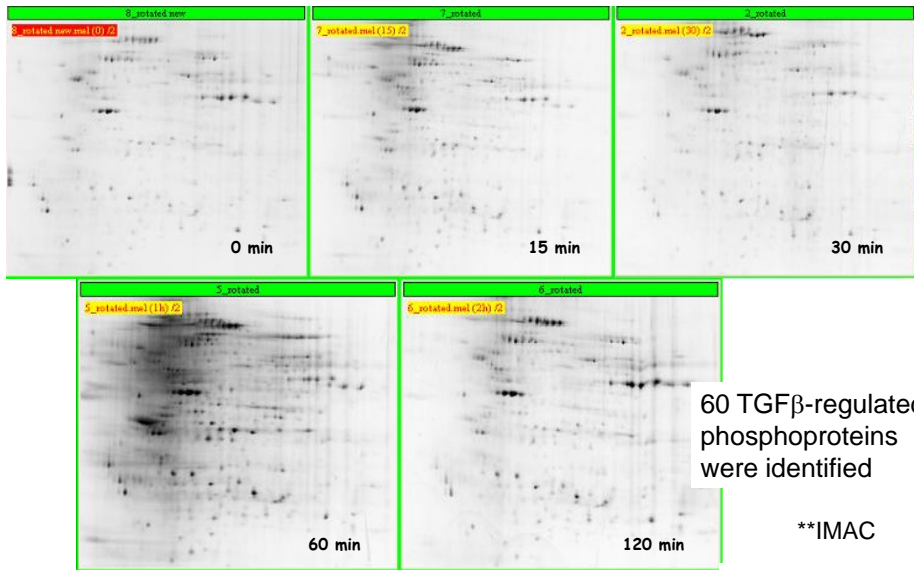
Predicted



Example 2

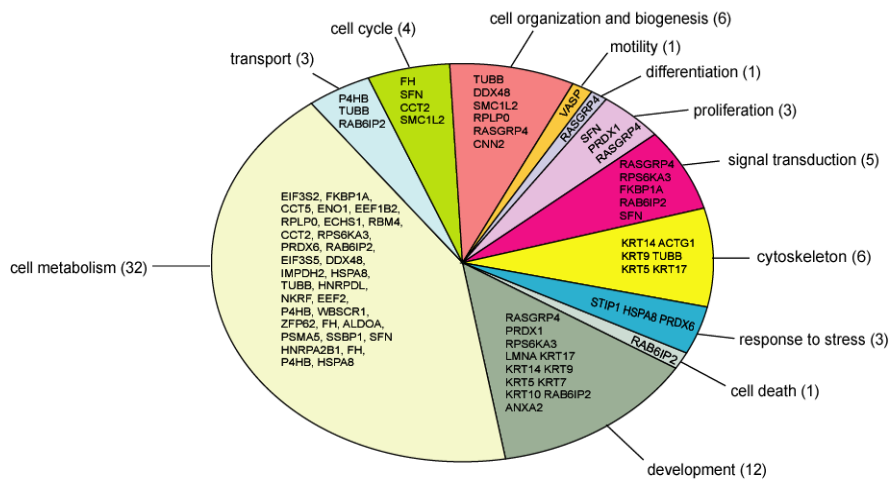
TGFβ1-dependent effect on phosphoproteome

MCF10A human breast epithelial cells



*Dubrovskaja et al., 2008

Functional clusters affected by TGFβ (phosphoproteins)

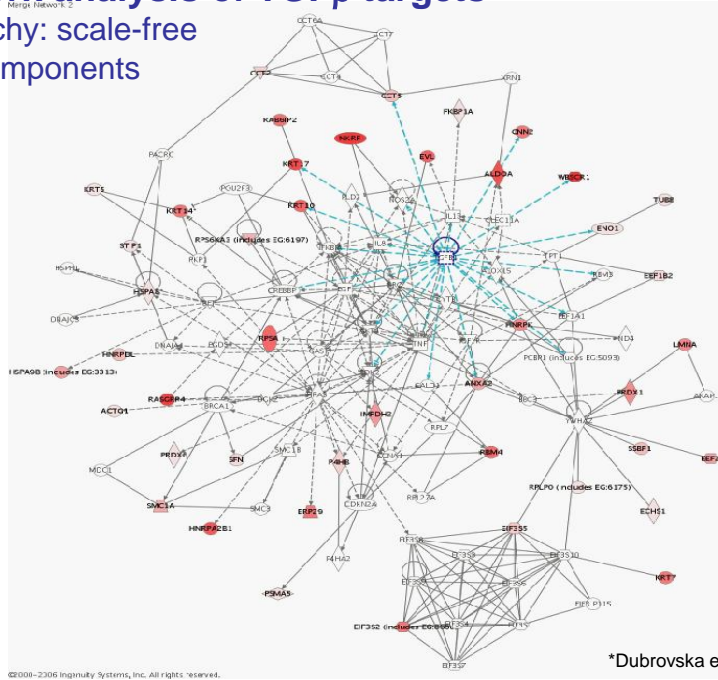


*Dubrovskaja et al., 2008

Network analysis of TGFβ targets

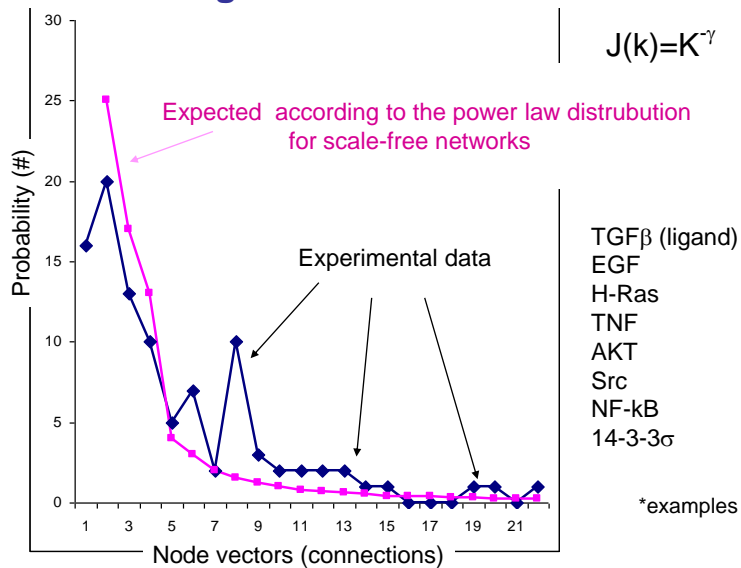
*hierarchy: scale-free

*key components

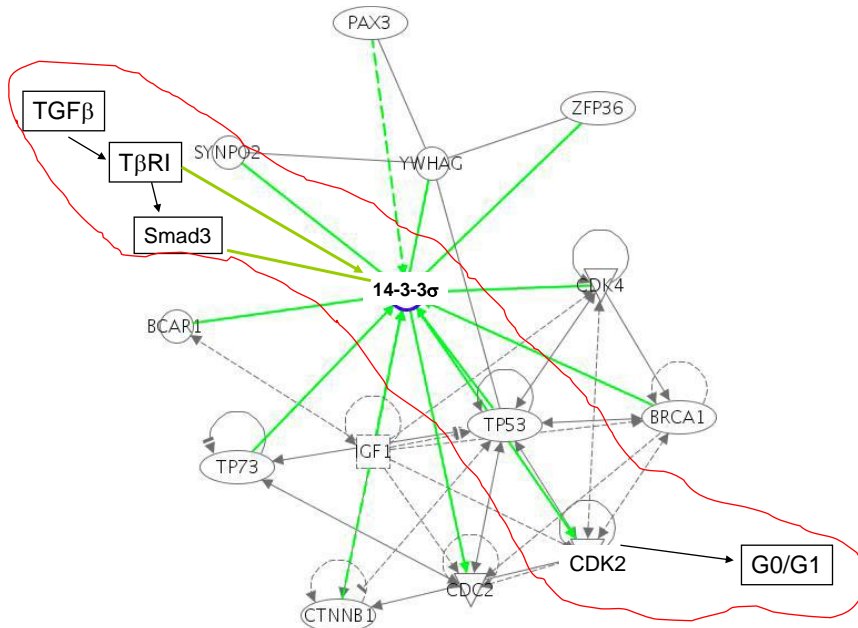


*Dubrovka et al., 2008

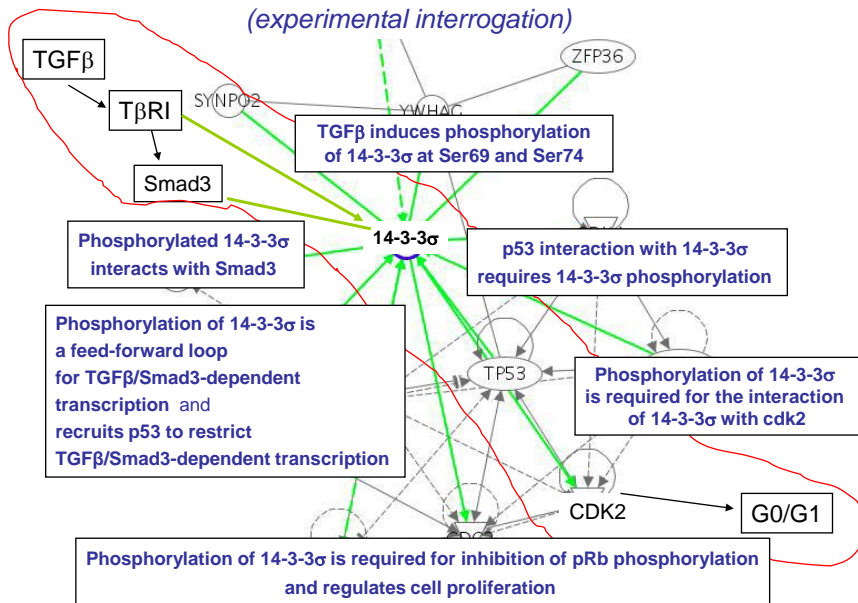
Deviating high-density nodes indicate points of fragile robustness



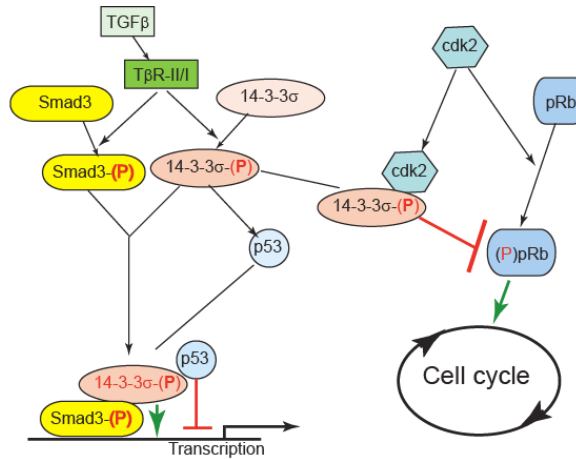
14-3-3 σ –centered sub-network



14-3-3 σ –centered sub-network (experimental interrogation)

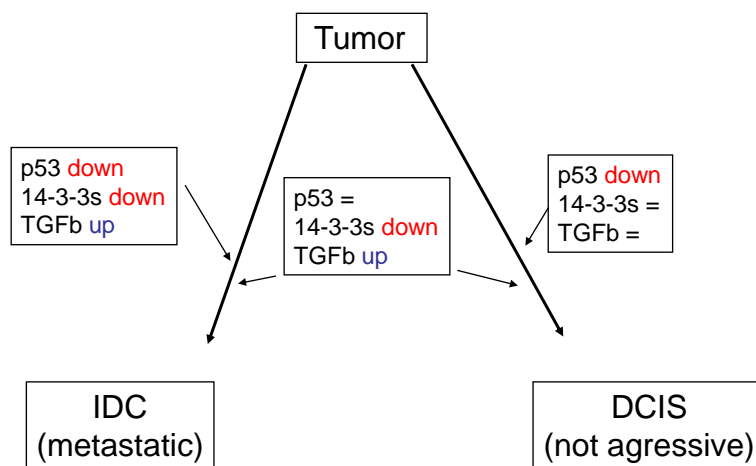


Cooperation between two tumor suppressors



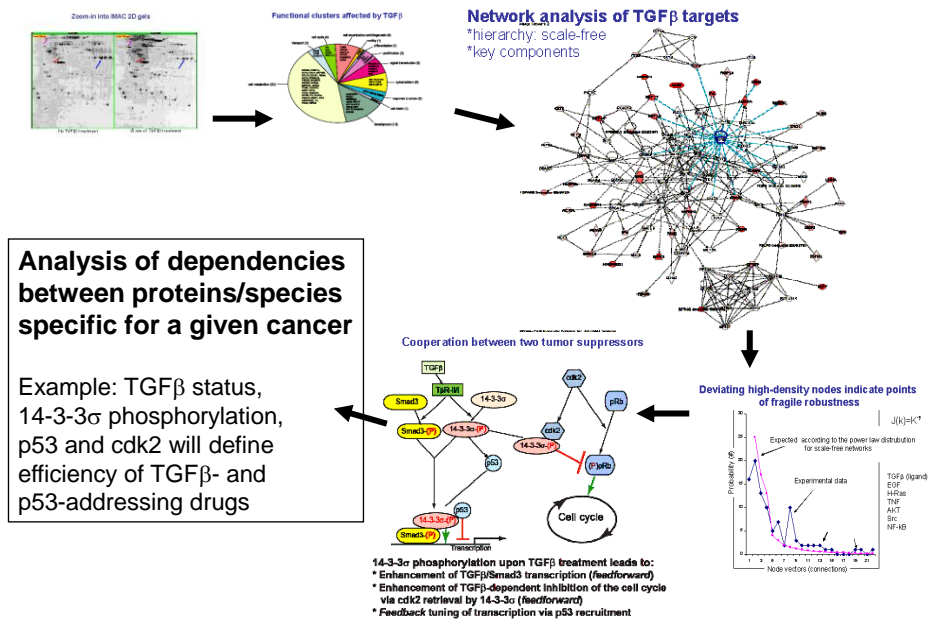
- 14-3-3σ phosphorylation upon TGFβ treatment leads to:**
- * Enhancement of TGFβ/Smad3 transcription (*feedforward*)
 - * Enhancement of TGFβ-dependent inhibition of the cell cycle via cdk2 retrieval by 14-3-3σ (*feedforward*)
 - * *Feedback* tuning of transcription via p53 recruitment

Status of network components may define probability of aggressive tumor development



*examples; other components to be considered are Smad3, Smad2, Smad4, cdk2, pRb, CAGA- and E2F-read-outs.

From 2D gels, via systemic analysis to clinics



Does systemic approach is important for treatment of cancer?

It is in use now: combinations of various schemes of chemotherapy, radiotherapy, hormone-therapy, surgery.

But most often, use of combinatorial treatment is **empiric**

Example: FOAM scheme

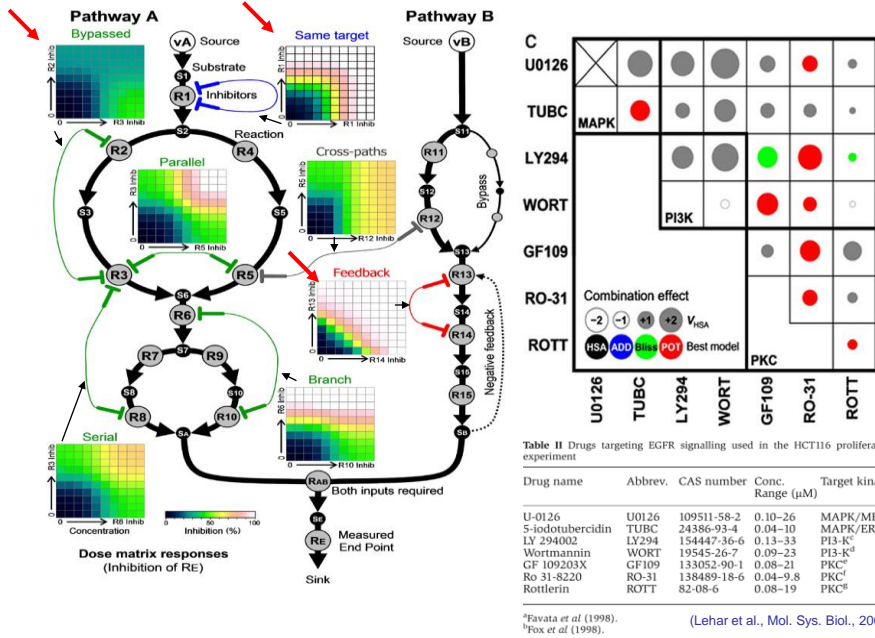
MMC – day 1

Adriamycin – days 1 and 29

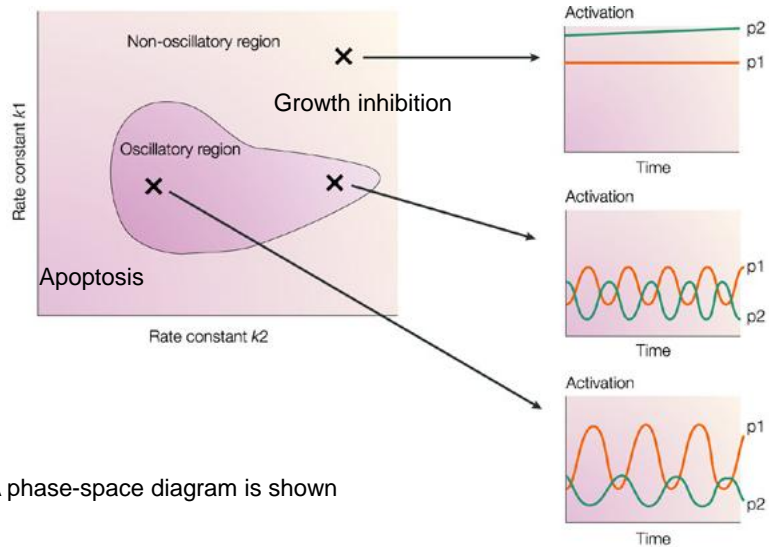
5FU – days 1, 8, 29, 36

Vincristine – days 1, 8, 29, 36

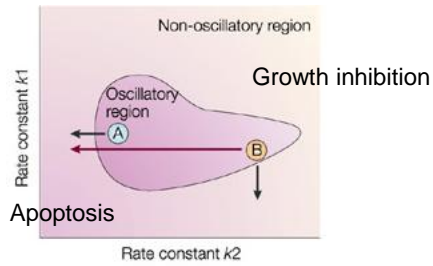
Combinatorial treatment as the tool to improve clinical benefit



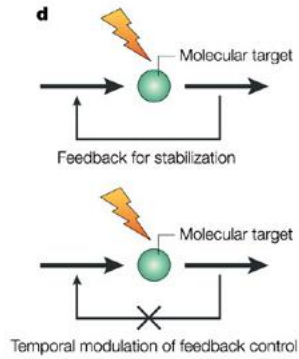
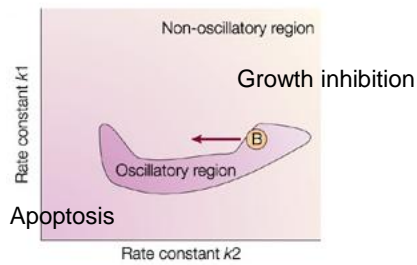
Search for efficient drugs and their combinations



Search for efficient drugs and their combinations



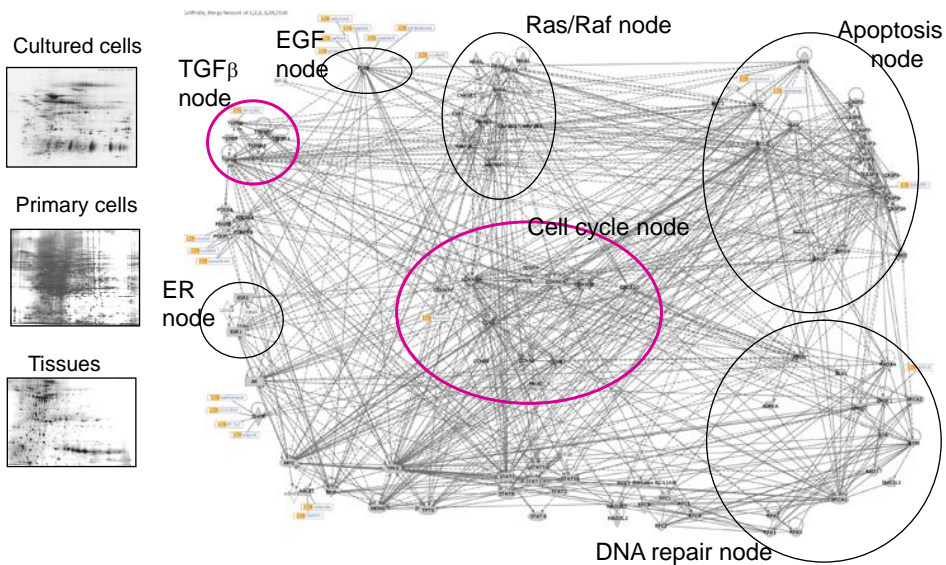
Shifting cell responsiveness to cell death or to growth inhibition



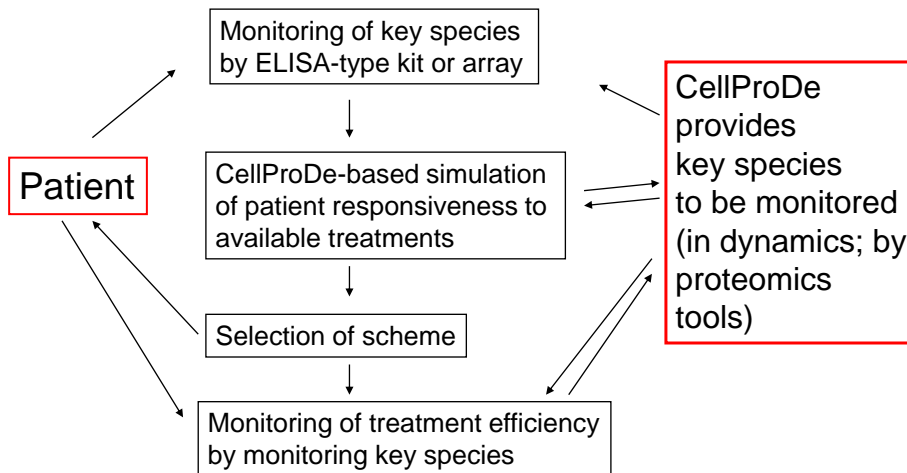
Kitano, Nature Rev. 2004

Cell Proliferation or Death (CellProDe) for individualized treatment and drug discovery

"Big" network with indication of some drugs which affect species of the network



CellProDe for individualized treatment



Summary

- Cancer is a systemic disease, and it requires a systemic approach
- Systemic analysis tools are under development, with significant progress reported for data presentation, clustering, analysis of dependencies, modeling and interrogation
- Examples of systemic analysis have shown that we can analyze systemic properties of relatively simple systems. The challenge is to model complex multi-component systems, e.g. tumor growth, and to find ways to destabilize them, e.g. eliminate cancer.