STRING and STITCH: known and predicted interactions between proteins and chemicals

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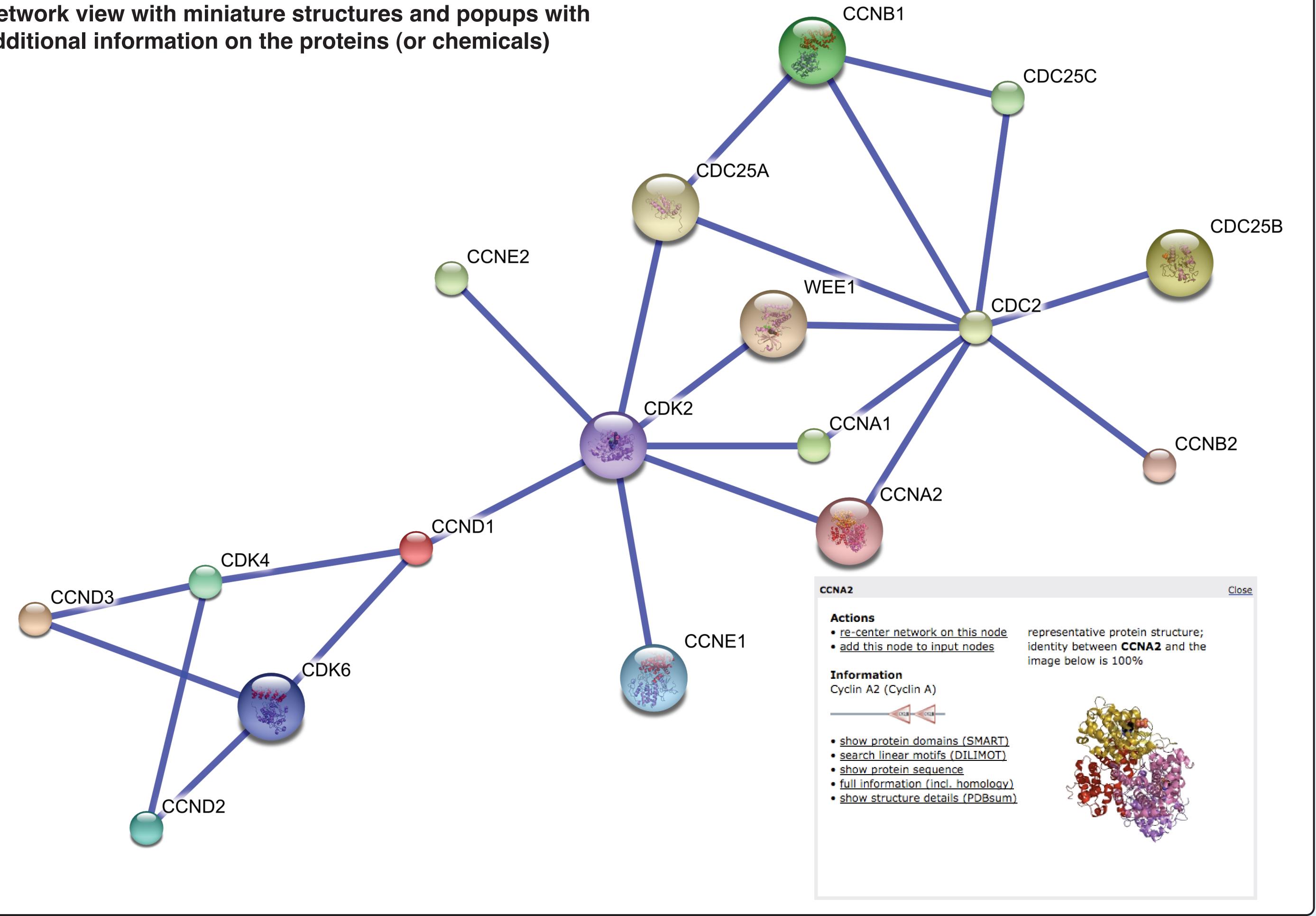
Motivation

A full description of a protein's function requires knowledge of all molecules with which it specifically associates. From a functional perspective, 'association' can mean direct physical binding, but can also mean indirect interaction such as participation in the same metabolic pathway or cellular process.

STRING: protein-protein interactions

Currently, information about protein association is scattered over a wide variety of resources and model organisms. The STRING web resource (von Mering et al., 2007) aims to simplify access to this information by providing a comprehensive, quality-controlled collection of protein-protein associations for a large number of organisms. We achieve this by combining curated knowledge on protein complexes and pathways, information extracted through automatic literature mining (Saric et al., 2006), gene coexpression and interaction data from high-throughput experiments, and associations predicted by genomic context methods (Korbel et al., 2004). To integrate and rank the associations from such heterogeneous sources, we benchmark all associations against a gold standard, use orthology assignments to extend the interactions beyond the organisms in which they were originally described, and finally combine the resulting confidence scores using a probabilistic framework. The resulting functional association network covers over 1.5 million genes from 373 genomes and can be accessed via an intuitive web interface at http://string.embl.de/

Network view with miniature structures and popups with additional information on the proteins (or chemicals)



STITCH: protein-chemical interactions

Knowledge about interactions between proteins and small molecules is also essential for the understanding of molecular and cellular functions. For example, enzymes interact with their substrates, products and allosteric inhibitors, and drugs interact with their target proteins. However, information on such interactions is as widely dispersed as information on protein-protein interactions. To facilitate access to this data, the STITCH resource (Kuhn et al., 2008) integrates information about interactions from metabolic pathways, crystal structures, binding experiments and drug-target relationships. Inferred information from phenotypic effects, text mining and chemical structure similarity is used to predict relations between chemicals. The resource further allows exploring the network of chemical relations, also in the context of associated binding proteins. Our database contains interactions for over 68,000 different chemicals, including 2200 drugs, and connects them to the same gene set used in STRING. The STITCH web resource is available at http://stitch.embl.de/

Prediction of interactions from genomic context

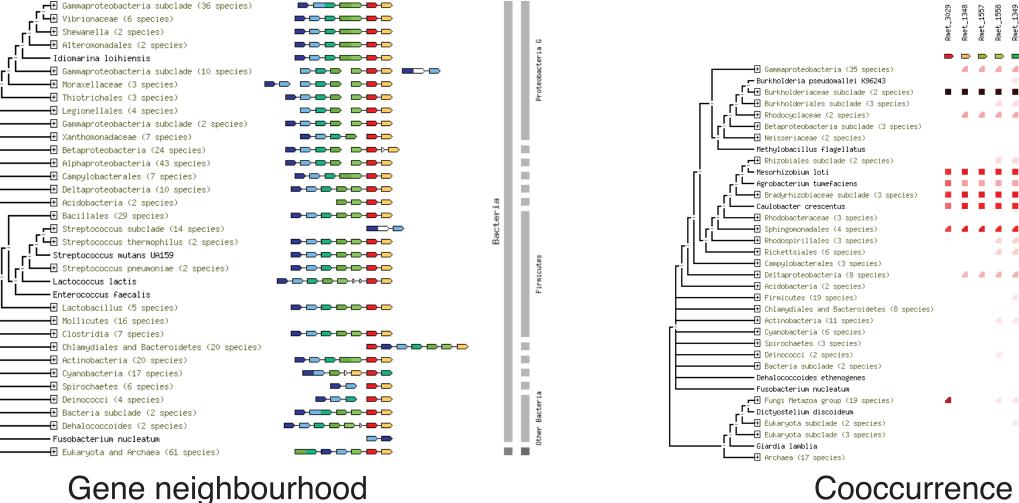
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	Rmet_3029	Rmet_1348	Rmet_1557	Rmet_1558	Rmet_1349	Rmet_1254	Rmet_1485	Rmet_3024	Rmet_1345			
🛨 Gammaproteobacteria (35 species)										1.1	1.1	
Burkholderia pseudomallei K96243											11	
➡ Burkholderiaceae subclade (2 species)												8
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+ Acidobacteria (2 species)												1
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 Chlamydiales and Bacteroidetes (8 species) 												1
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► Cyanobacteria (6 species)												1
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Eukaryota subclade (3 species)										uke	L p	2
Giardia lamblia										ũ		
+ Archaea (17 species)												

Integration of interaction and pathway databases

protein-protein interaction (grid)	info	protein-protein interaction (grid)	info	annotated pathway (KEGG)	info	curated pathway	info		
● ABL1 ● RB1		● ABL1 ● TP53		ABL1	proteins]	● ABL1 ● TP53 ● TP73 [and 14 othe	er proteins]		
protein-protein interaction (grid)	info	protein-protein interaction (hprd)	info	curated pathway	<u>info</u>	curated pathway	info		
● ABL1 ● TP53		🖶 ABL1 🛛 CRK		● ABL1 ● TP53 ● RB1 [and 19 other p	roteins]	● ABL1 ● TP53 ● RB1 [and 23 other	r proteins]		
protein-protein interaction (mint)	info	protein-protein interaction (mint)	info	curated pathway	<u>info</u>	curated pathway	<u>info</u>		
● ABL1 ● TP53		● ABL1 ● TP73		TP53 RB1 [and 8 other proteins]		TP53 RB1 [and 10 other proteins]		
protein-protein interaction (mint)	info	protein-protein interaction (mint)	info	curated pathway	<u>info</u>	curated pathway	<u>info</u>		
● TP53 ● TP73		🖶 ABL1 🛛 RB1		TP53 RB1 [and 11 other proteins]		● TP53 ● RB1 [and 12 other proteins]		
protein-protein interaction (mint)	info	protein complex (pdb)	info	curated pathway	<u>info</u>	Drug-Target Database	<u>info</u>		
🖶 ABL1 🛛 TP73		e Abli e CRK		TP53 RB1 [and 12 other proteins]		🖶 ABL1 🛛 🚍 imatinib			
protein-chemical binding (kidb)	info	protein-chemical binding (kidb)	info	curated complex	<u>info</u>	annotated pathway (KEGG)	info		
🖶 ABL1 🛛 🚍 imatinib		🖶 ABL1 🛛 🚍 imatinib		● TP53 ● RB1		CRK	is]		
protein-protein interaction (hprd)	<u>info</u>	protein-protein interaction (bind)	info	Drug-Target Database	<u>info</u>	curated complex	<u>info</u>		
● TP53 ● RB1 [and 1 other protein]		🖶 ABL1 🛛 CRK		ABL1 = imatinib [and 3 other protein	s]	ABL1 RB1 [and 3 other proteins]			
protein-protein interaction (mint)	info	protein-protein interaction (mint)	info	curated pathway	info				
● TP53 ● TP73		🖶 ABL1 🛛 CRK		TP53 RB1 [and 7 other proteins]					
							•		
Primary experimental data			Pathway and drug-target databases						

Literature mining based on cooccurrence and NLP

Inhibition of <u>c-Abl</u> () with <u>STI571</u> () attenuates stress-activated protein kinase activation and apoptosis in the cellular Pub Med response to 1-beta-D-arabinofuranosylcytosine. Mol Pharmacol (2002)

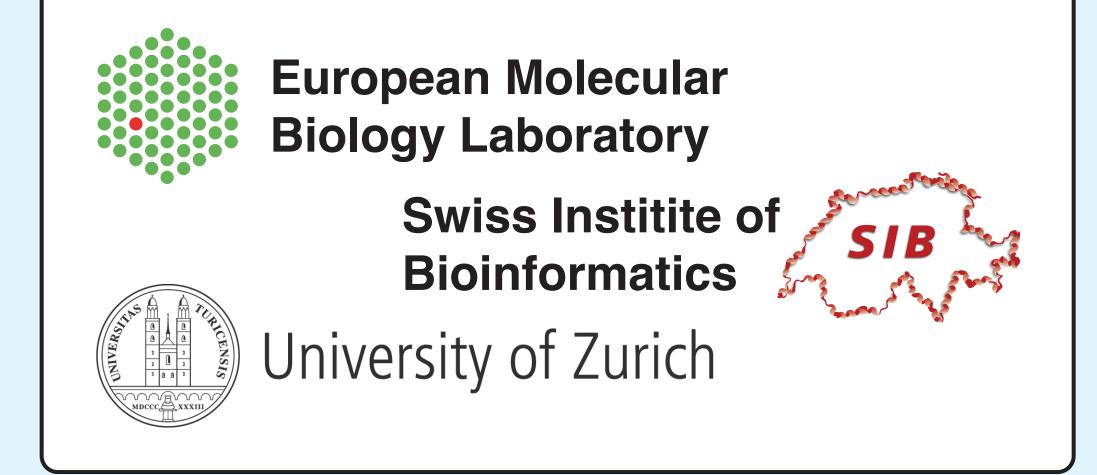
The web resources string.embl.de and stitch.embl.de

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The response of myeloid leukemia cells to treatment with 1-beta-D-arabinofuranosylcytosine (ara-C) includes activation of the c-Abl () protein tyrosine kinase and the stress-activated protein kinase (SAPK). The present studies demonstrate that treatment of human U-937 leukemia cells with ara-C is associated with translocation of SAPK to mitochondria. STI571 (=) (imatinib mesylate (=)), an inhibitor of c-Abl (), blocked both activation and mitochondrial targeting of SAPK in the ara-C response. In concert with these effects of STI571 (=), similar findings were obtained in c-Abl (=) - deficient cells. The results further show that STI571 (=) inhibits ara-C induced loss of mitochondrial transmembrane potential, caspase-3 activation, and apoptosis. These findings demonstrate that STI571 () down-regulates c-Abl () - mediated signals that target the mitochondria in the apoptotic response to ara-C.

Imatinib (=) - induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. Pub Med Eur J Haematol (2002).

Imatinib mesylate () blocks bcr / abl () kinase activity effectively, and thus is a promising drug in Philadelphia chromosome positive leukemias. While under imatinib () treatment high hematological and cytogenetic response rates could be observed, usually only mild non-hematological side-effects like skin rash, edema, and muscular cramps occur. Here we report two severe cases of acute generalized exanthematous pustulosis due to imatinib (). In both patients the generalized pustular eruptions could be observed 12 wk after initiation of imatinib () treatment. Numerous microbiological investigations excluded an infectious etiology, and histopathology of cutaneous lesions was consistent with acute generalized exanthematous pustulosis. Accordingly, withdrawal of imatinib () led to a restitutio at integrum of the integument. Our report confirms another single observation of acute generalized exanthematous pustulosis in chronic myeloid leukemia under imatinib () therapy, and confirms that this is a rare but proven adverse effect of imatinib ().

