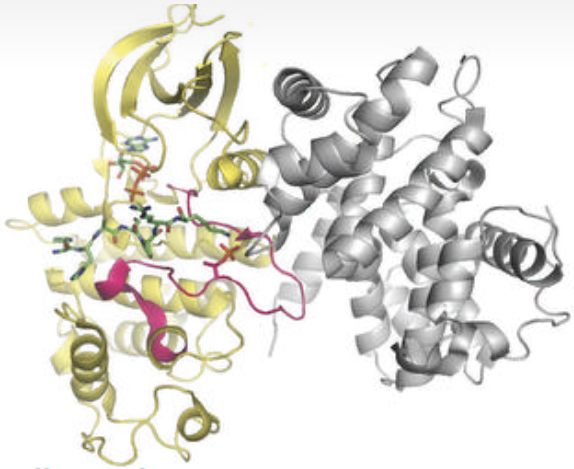
Tools & Databases of Short Linear Motifs

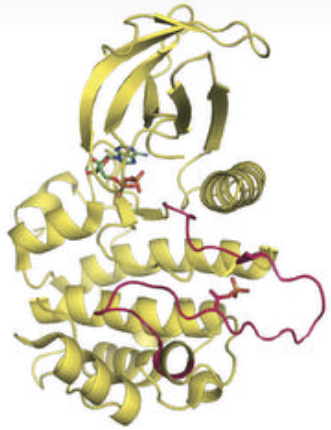
Holger Dinkel

EMBO Practical Course Computational analysis of protein-protein interactions: From sequences to networks

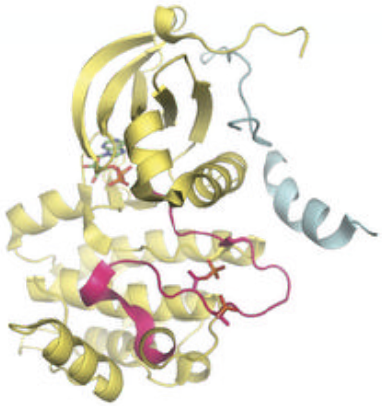
Protein Phosphorylation Sites



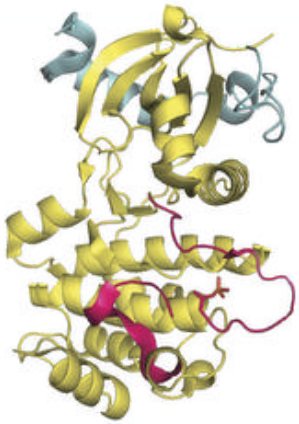
Cdk1/cyclin B



Plk1



Aurora A/TPX2



Aurora B/INCENP

"Spatial exclusivity combined with positive and negative selection of phosphorylation motifs is the basis for context-dependent mitotic signaling"; Alexander et al.; (Sci. Sig 2011)

Protein Phosphorylation Sites

Kinase	-3	-2	-1	0	1	2	3
Cdk1	.	.	.	p[ST]	P	.	[KR]
Plk1	.	[DEN]	.	p[ST]	[ILMVFWY]	.	.
Nek2	[FML]	[!P]	[!P]	p[ST]	[ILMV]	.	.
AuroraA	R	[KR]	.	p[ST]	[!P]	.	.
AuroraB	.	R	[KR]	p[ST]	[!P]	.	.

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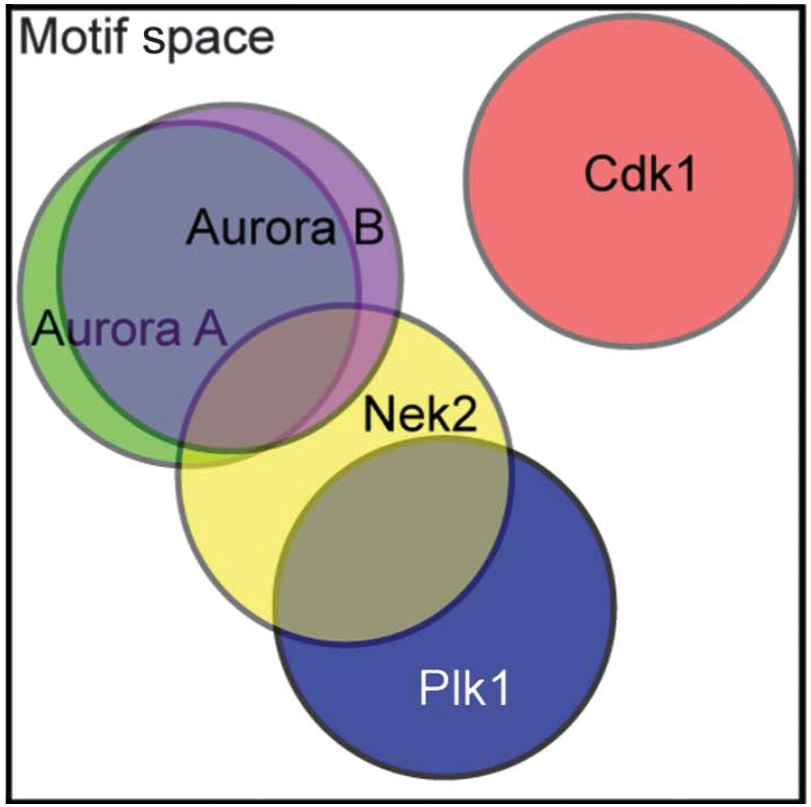
Cdk1	.	.	.	p[ST]	P	.	[KR]
Plk1	.	[DEN]	.	p[ST]	[ILMVFWY]	.	.
Nek2	[FML]	[!P]	[!P]	p[ST]	[ILMV]	.	.
AuroraA	R	[KR]	.	p[ST]	[!P]	.	.
AuroraB	.	R	[KR]	p[ST]	[!P]	.	.



"Spatial exclusivity combined with positive and negative selection of phosphorylation motifs is the basis for context-dependent mitotic signaling"; Alexander et al.; (Sci. Sig 2011)

Protein Phosphorylation Sites

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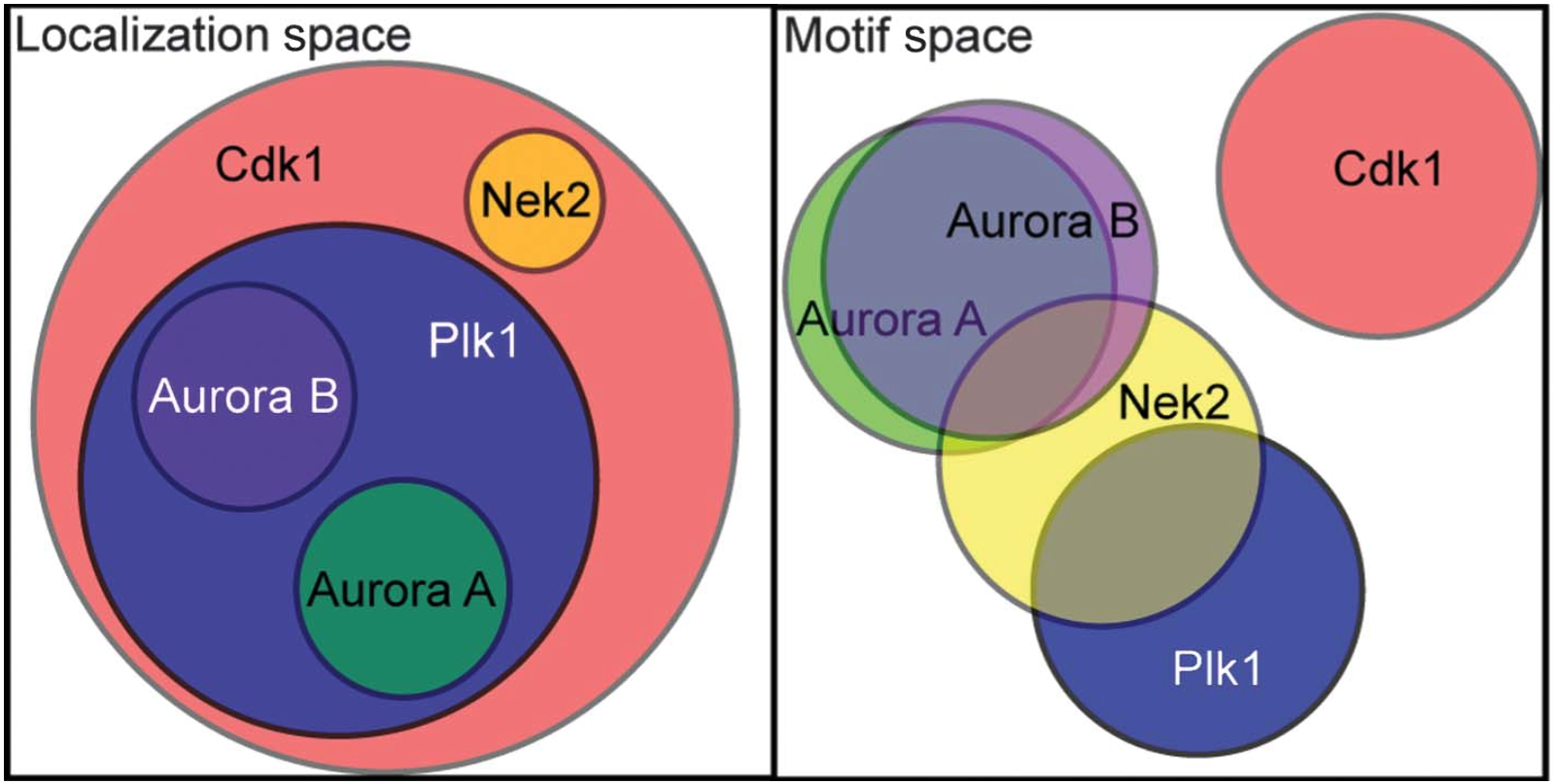
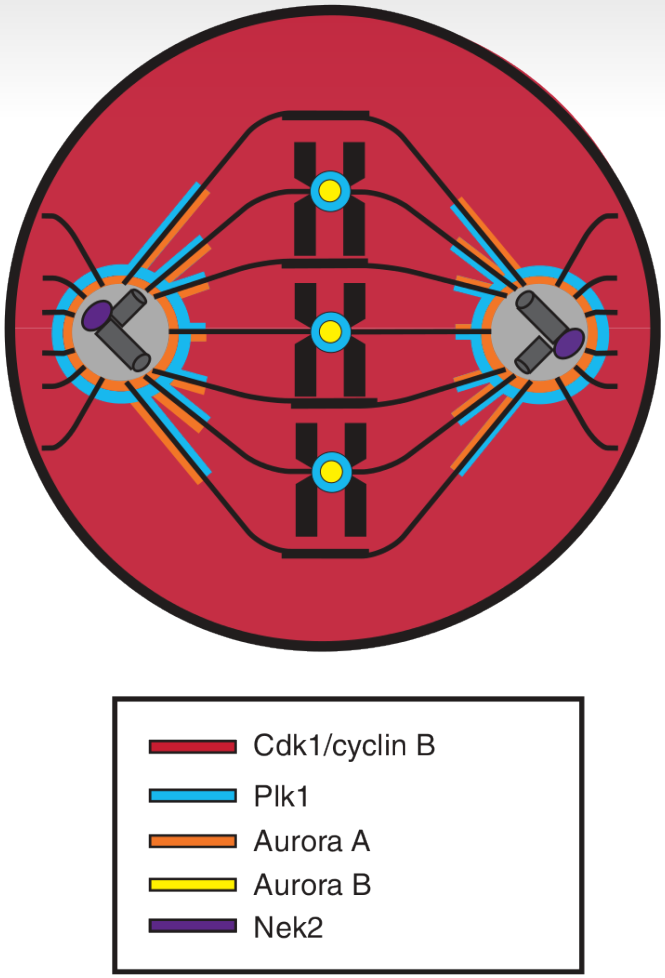
Cdk1	.	.	.	p[ST]	P	.	[KR]
Plk1	.	[DEN]	.	p[ST]	[ILMVFWY]	.	.
Nek2	[FML]	[!P]	[!P]	p[ST]	[ILMV]	.	.
AuroraA	R	[KR]	.	p[ST]	[!P]	.	.
AuroraB	.	R	[KR]	p[ST]	[!P]	.	.



"Spatial exclusivity combined with positive and negative selection of phosphorylation motifs is the basis for context-dependent mitotic signaling"; Alexander et al.; (Sci. Sig 2011)

Protein Phosphorylation Sites



Kinase localization in Metaphase:

Cdk1	whole cell
Plk1	kinetochores
Aurora A	centrosomes & microtubules
Aurora B	centromeres & spindle
Nek2	centrosomes

"Spatial exclusivity combined with positive and negative selection of phosphorylation motifs is the basis for context-dependent mitotic signaling"; Alexander et al.; (Sci. Sig 2011)

Phospho.ELM

Database of experimentally verified phosphorylation sites in eukaryotic proteins.
Current release contains 8,718 protein entries covering more than 42,500 instances. (Instances are fully linked to literature references.)


Phospho.ELM
a database of S/T/Y phosphorylation sites
Statistics:
Instances 42.575
Kinases 310
Reference 3.672
Sequences 11.223
Substrates 8.718
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for phosphorylation sites in proteins using protein name or gene name
(eg. Paxillin, Shc, MAPK)
by UniPROT accession or Ensembl identifier:
(eg. P12931 or P55211)
by selected kinase (List):
None
by selected phospho-peptide binding domain (List):
None
Choose which organisms to include
All
Caenorhabditis
Drosophila
Vertebrates
Do not show high throughput data
Output as Comma-Separated-Values (.csv)
Search
Reset

Phospho.ELM

Phospho.ELM
a database of S/T/Y phosphorylation sites

Statistics:

Instances	42.575
Kinases	310
Reference	3.672
Sequences	11.223
Substrates	8.718

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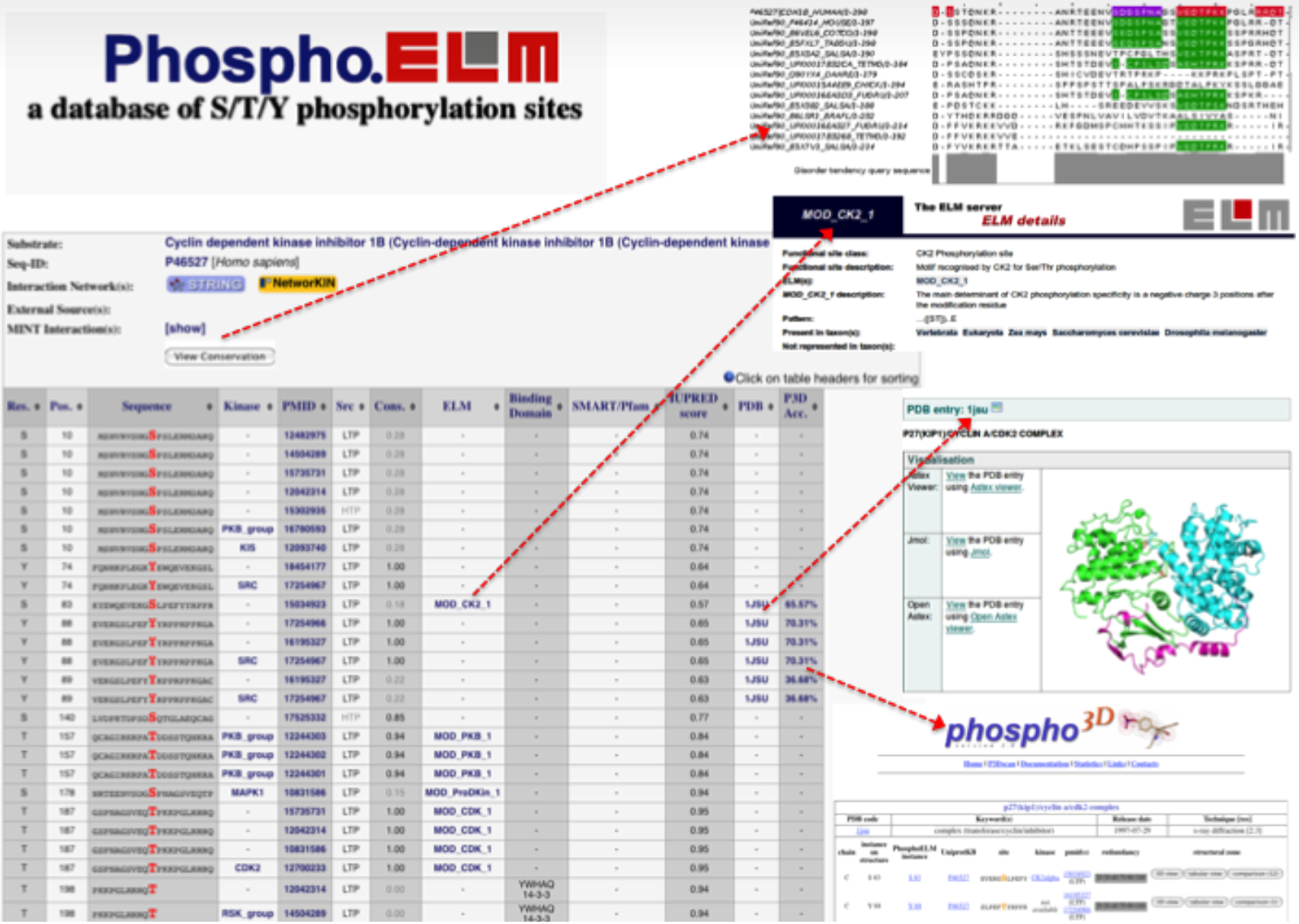
Substrate: **p53** (Cellular tumor antigen p53)
Seq-ID: **P04637** [*Homo sapiens*]
Interaction Network(s): STRING NetworKIN
External Source(s): PHOSIDA
MINT Interaction(s): [show]
GO-Terms: [show]
Conservation:

Click on table headers for sorting

Res.	Pos.	Sequence	Kinase	PMID	Src	Cons.	ELM	Binding Domain	SMART/Pfam	IUPRED score	PDB	P3D Acc.
S	9	MEEPQSDP**S**VEPPLSQETF	-	11875057	LTP	0.75		-	P53_TAD	0.94	-	-
S	15	QSDPSVEPPL**S**QETFSDLWKL	DNA-PK	10446957	LTP	1.00	MOD_PIKK_1	-	P53_TAD	0.66	-	-
S	15	QSDPSVEPPL**S**QETFSDLWKL	ATM	11875057	LTP	1.00	MOD_PIKK_1	-	P53_TAD	0.66	-	-
T	18	PSVEPPLSQE**T**FSDLWKLLPE	CK1_group	10606744	LTP	1.00	MOD_CK1_1	-	P53_TAD	0.66	-	-
T	18	PSVEPPLSQE**T**FSDLWKLLPE	TTK	19332559	LTP	1.00	MOD_CK1_1	-	P53_TAD	0.66	-	-
T	18	PSVEPPLSQE**T**FSDLWKLLPE	VRK1	10951572	LTP	1.00	MOD_CK1_1	-	P53_TAD	0.66	-	-
T	18	PSVEPPLSQE**T**FSDLWKLLPE	VRK1	15542844	LTP	1.00	MOD_CK1_1	-	P53_TAD	0.66	-	-
S	20	VEPPLSQETF**S**DLWKLLPENN	-	15254178	LTP	0.95		-	P53_TAD	0.58	-	-
S	20	VEPPLSQETF**S**DLWKLLPENN	-	15489221	LTP	0.95		-	P53_TAD	0.58	-	-
S	20	VEPPLSQETF**S**DLWKLLPENN	-	10801407	LTP	0.95		-	P53_TAD	0.58	-	-
S	20	VEPPLSQETF**S**DLWKLLPENN	-	12111733	LTP	0.95		-	P53_TAD	0.58	-	-


Phospho.ELM
a database of S/T/Y phosphorylation sites
Substrate:
Cyclin dependent kinase inhibitor 1B (Cyclin-dependent kinase inhibitor 1B (Cyclin-dependent kinase
Seq-ID:
P46527 [Homo sapiens]
Interaction Network(s):
STRING
NetworKIN
External Source(s):
MINT Interaction(s):
[show]
View Conservation
Click on table headers for sorting
MOD_CK2_1
The ELM server
ELM details
PDB entry: 1jsu
P27(KIP1)/CYCLIN A/CDK2 COMPLEX
Visualisation
phospho3D

Link Out To Other Databases

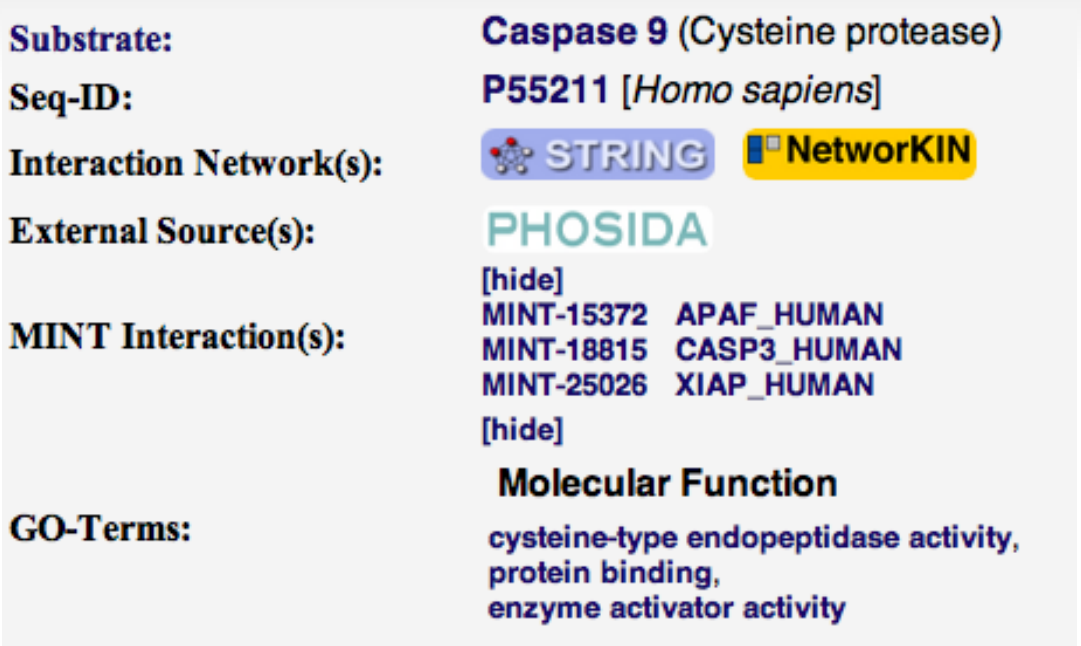
Phospho.ELM

Links to:

- STRING
- NetworKin
- Phosida
- Phospho3D

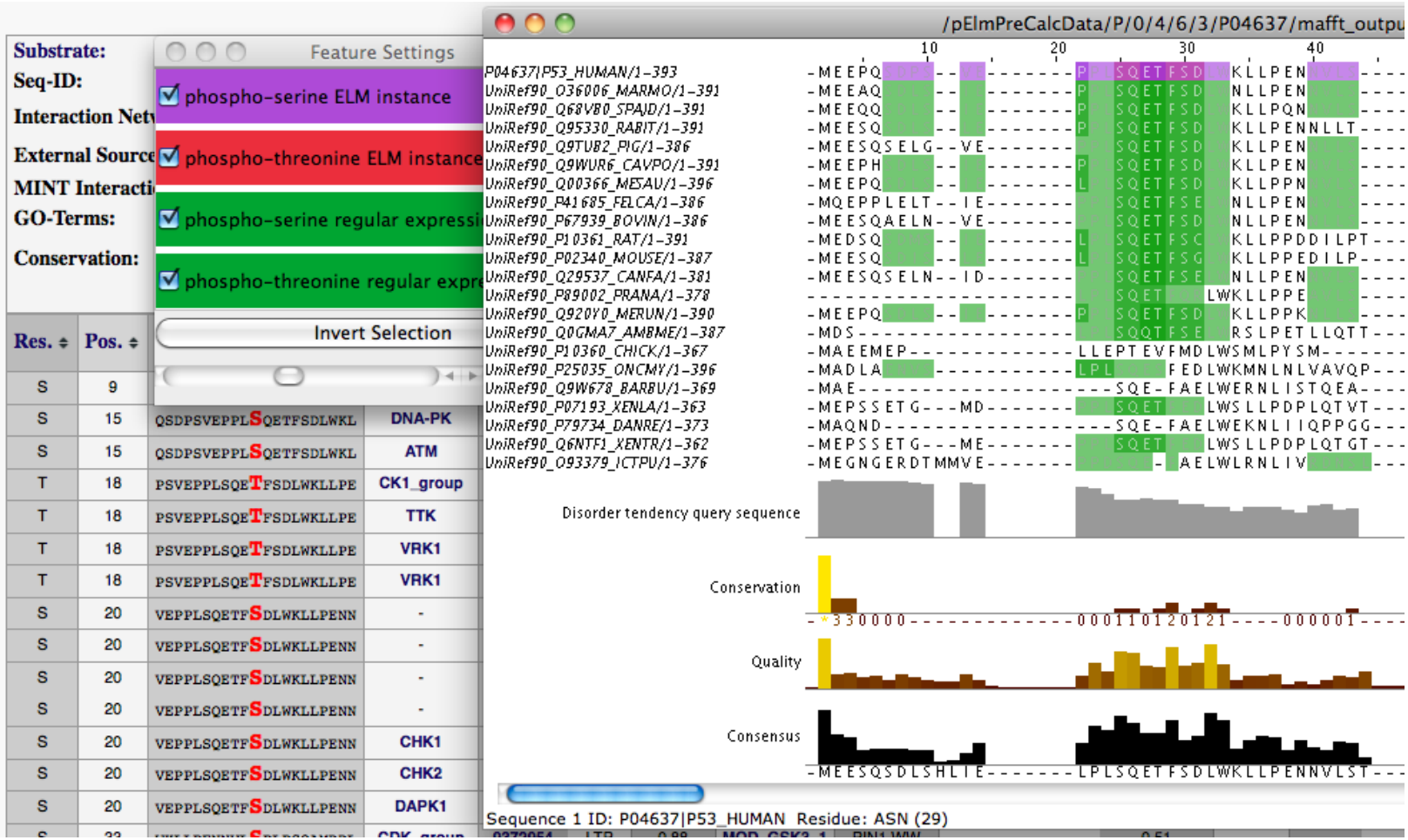
Display:

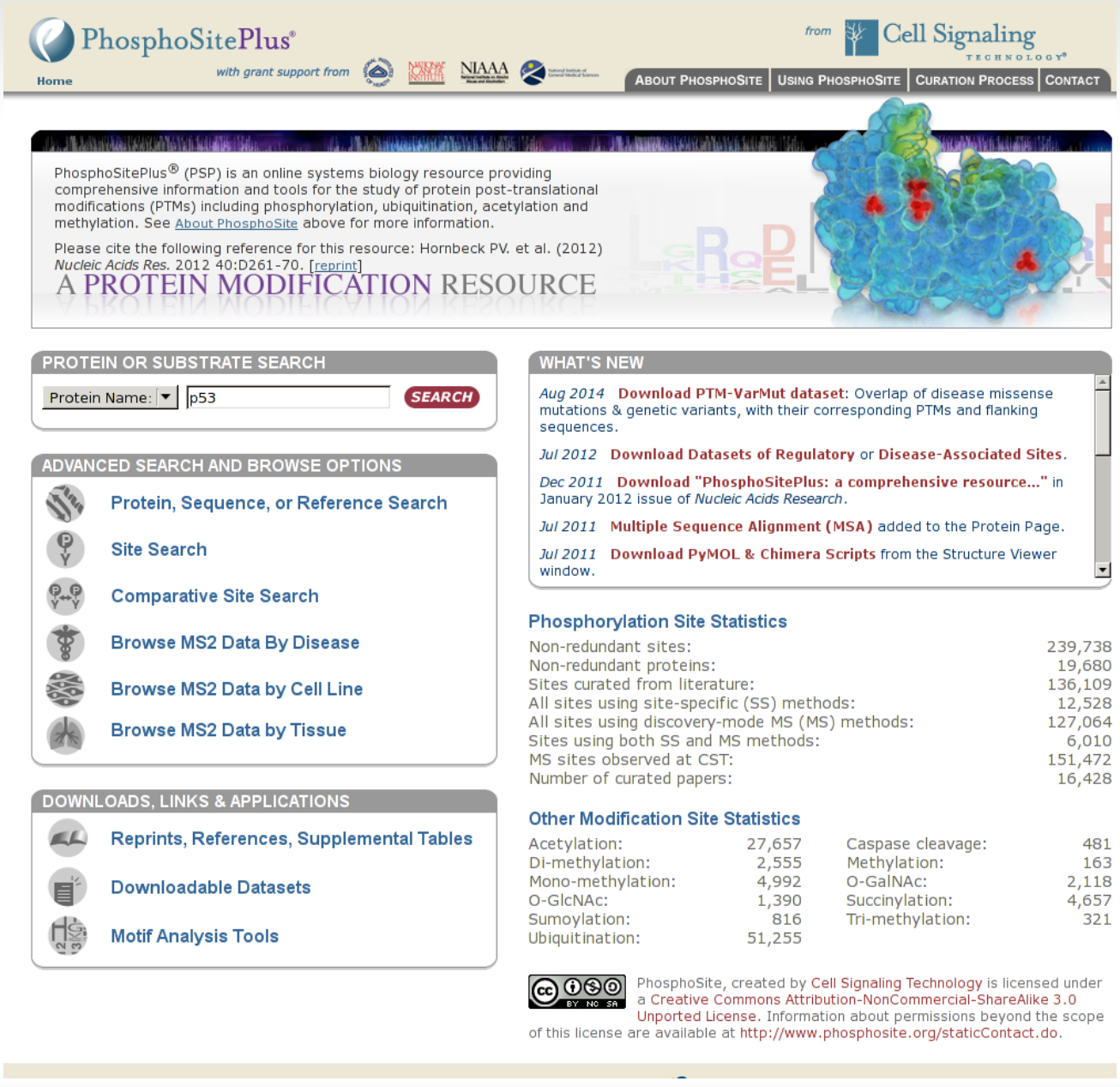
- MINT interactions
- GO-Terms



Phospho.ELM

Precalculated conservation scores for the phosphorylation sites are presented using **Jalview**

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A PROTEIN MODIFICATION RESOURCE
PROTEIN OR SUBSTRATE SEARCH
Protein Name:
p53
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ADVANCED SEARCH AND BROWSE OPTIONS
Protein, Sequence, or Reference Search
Site Search
Comparative Site Search
Browse MS2 Data By Disease
Browse MS2 Data by Cell Line
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Jul 2011 Multiple Sequence Alignment (MSA) added to the Protein Page.
Jul 2011 Download PyMOL & Chimera Scripts from the Structure Viewer window.
Phosphorylation Site Statistics
Non-redundant sites: 239,738
Non-redundant proteins: 19,680
Sites curated from literature: 136,109
All sites using site-specific (SS) methods: 12,528
All sites using discovery-mode MS (MS) methods: 127,064
Sites using both SS and MS methods: 6,010
MS sites observed at CST: 151,472
Number of curated papers: 16,428
Other Modification Site Statistics
Acetylation: 27,657
Di-methylation: 2,555
Mono-methylation: 4,992
O-GlcNAc: 1,390
Sumoylation: 816
Ubiquitination: 51,255
Caspase cleavage: 481
Methylation: 163
O-GalNAc: 2,118
Succinylation: 4,657
Tri-methylation: 321
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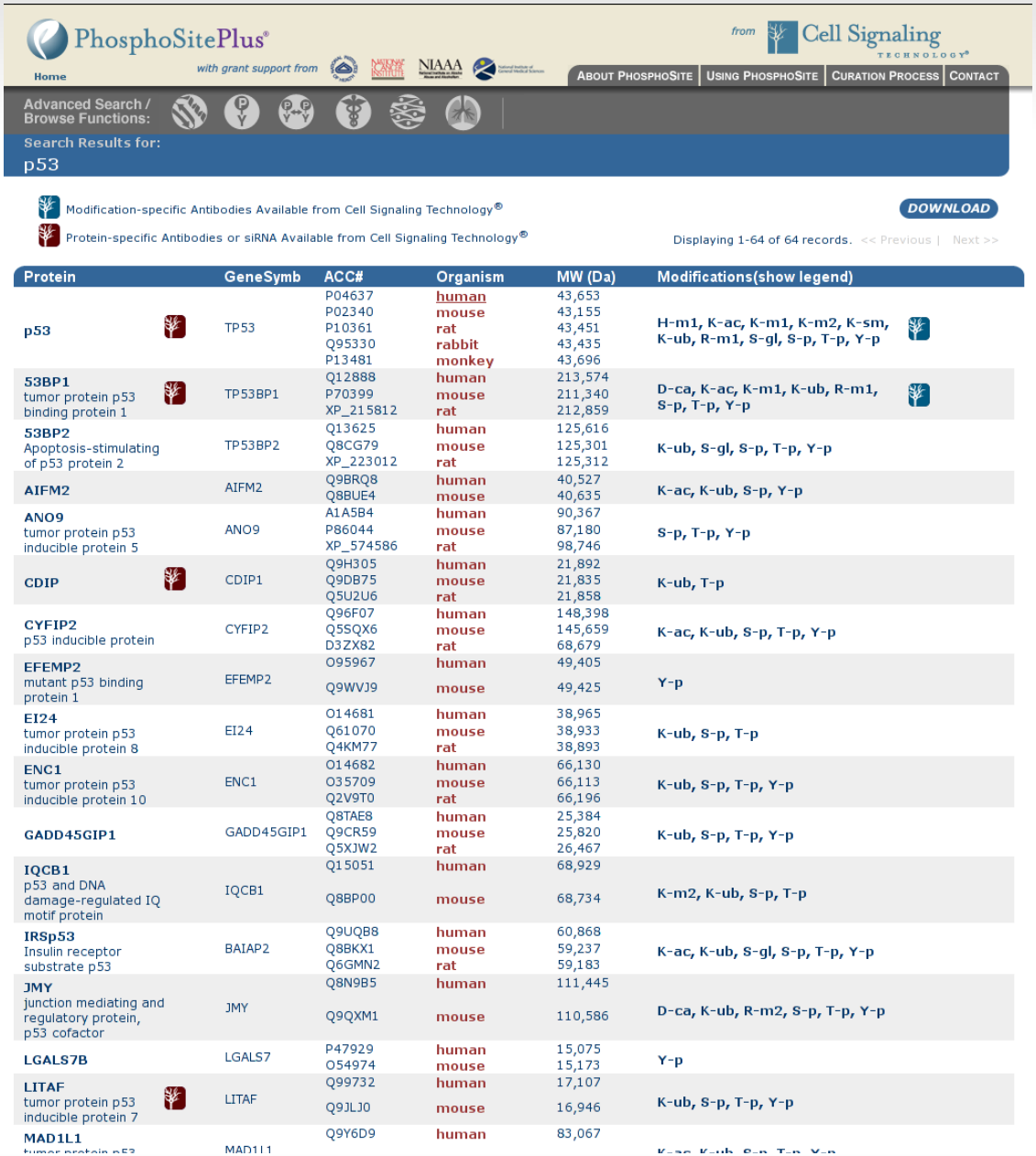

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p53

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Protein-specific Antibodies or siRNA Available from Cell Signaling Technology®

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Protein	GeneSymb	ACC#	Organism	MW (Da)	Modifications(show legend)
p53	TP53	P04637 P02340 P10361 Q95330 P13481	human mouse rat rabbit monkey	43,653 43,155 43,451 43,435 43,696	H-m1, K-ac, K-m1, K-m2, K-sm, K-ub, R-m1, S-gl, S-p, T-p, Y-p
53BP1 tumor protein p53 binding protein 1	TP53BP1	Q12888 P70399 XP_215812	human mouse rat	213,574 211,340 212,859	D-ca, K-ac, K-m1, K-ub, R-m1, S-p, T-p, Y-p
53BP2 Apoptosis-stimulating of p53 protein 2	TP53BP2	Q13625 Q8CG79 XP_223012	human mouse rat	125,616 125,301 125,312	K-ub, S-gl, S-p, T-p, Y-p
AIFM2	AIFM2	Q9BRQ8 Q8BUE4	human mouse	40,527 40,635	K-ac, K-ub, S-p, Y-p
ANO9 tumor protein p53 inducible protein 5	ANO9	A1A5B4 P86044 XP_574586	human mouse rat	90,367 87,180 98,746	S-p, T-p, Y-p
CDIP	CDIP1	Q9H305 Q9DB75 Q5U2U6	human mouse rat	21,892 21,835 21,858	K-ub, T-p
CYFIP2 p53 inducible protein	CYFIP2	Q96F07 Q5SQX6 D3ZX82	human mouse rat	148,398 145,659 68,679	K-ac, K-ub, S-p, T-p, Y-p
EFEMP2 mutant p53 binding protein 1	EFEMP2	O95967 Q9WVJ9	human mouse	49,405 49,425	Y-p
EI24 tumor protein p53 inducible protein 8	EI24	O14681 Q61070 Q4KM77	human mouse rat	38,965 38,933 38,893	K-ub, S-p, T-p
ENC1 tumor protein p53 inducible protein 10	ENC1	O14682 O35709 Q2V9T0	human mouse rat	66,130 66,113 66,196	K-ub, S-p, T-p, Y-p
GADD45GIP1	GADD45GIP1	Q8TAE8 Q9CR59 Q5XJW2	human mouse rat	25,384 25,820 26,467	K-ub, S-p, T-p, Y-p
IQCB1 p53 and DNA damage-regulated IQ motif protein	IQCB1	Q15051 Q8BP00	human mouse	68,929 68,734	K-m2, K-ub, S-p, T-p
IRSp53 Insulin receptor substrate p53	BAIAP2	Q9UQB8 Q8BKX1 Q6GMN2	human mouse rat	60,868 59,237 59,183	K-ac, K-ub, S-gl, S-p, T-p, Y-p
JMY junction mediating and regulatory protein, p53 cofactor	JMY	Q8N9B5 Q9QXM1	human mouse	111,445 110,586	D-ca, K-ub, R-m2, S-p, T-p, Y-p
LGALS7B	LGALS7	P47929 O54974	human mouse	15,075 15,173	Y-p
LITAF tumor protein p53 inducible protein 7	LITAF	Q99732 Q9JLJ0	human mouse	17,107 16,946	K-ub, S-p, T-p, Y-p
MAD1L1	MAD1L1	Q9Y6D9	human	83,067	

Modification Sites in Parent Protein, Orthologs, and Isoforms

Show Multiple Sequence Alignment

SS	MS	human		mouse ▼ Show Isoforms		rat		rabbit		monkey	
6	0	P4	____MEEPQsDPsVE	S4-p	____MEEsQsDIsLE	S4-p	____MEDsQsDMsIE	S4	____MEESQSDLSLE	P4	____MEEPQSDPSIE
31	4	S6-p	__MEEPQsDPsVEPP	S6-p	__MEEsQsDIsLELP	S6-p	__MEDsQsDMsIELP	S6	__MEESQSDLSLEPP	S6	__MEEPQSDPSIEPP
34	3	S9-p	EEPQsDPsVEPPLsQ	S9-p	EEsQsDIsLELPLsQ	S9-p	EDsQsDMsIELPLsQ	S9	EESQSDLSLEPPLSQ	S9	EEPQSDPSIEPPLsQ
358	2	S15-p	PsVEPPLsQEtFsDL	S15-p	IsLELPLsQEtFsGL	S15-p	MsIELPLsQEtFsCL	S15	LSLEPPLSQETFSDL	S15-p	PSIEPPLsQETFSDL
28	0	T18-p	EPPLsQEtFsDLWKL	T18-p	ELPLsQEtFsGLWKL	T18-p	ELPLsQEtFsCLWKL	T18	EPPLSQETFSDLWKL	T18	EPPLsQETFSDLWKL
110	1	S20-p	PLsQEtFsDLWKLLP	S20-p	PLsQEtFsGLWKLLP	S20-p	PLsQEtFsCLWKLLP	S20	PLSQETFSDLWKLLP	S20	PLsQETFSDLWKLLP
30	3	S33-p	LPENNVLsPLPsQAM	P33	LPPEDILPsPHCMDD	P33	LPPDDILPTTATGsP	T33	LPENNLLTTSLNPPV	S33-p	LPENNVLsPLPSQAV
65	3	S37-p	NVLsPLPsQAMDDLM	S34-p	PPEDILPsPHCMDDL	S39-p	LPTTATGsPNSMEDL	N37	NLLTTSLNPPVDDLL	S37	NVLsPLPSQAVDDLM
85	2	S46-p	AMDDLMLsPDDIEQW	L43	HCMDDLLLPQDVEEF	L48	NSMEDLFLPQDVAEL	S45	PPVDDLLSAEDVANW	S46	AVDDLMLSPDDLAQW
15	0	T55-p	DDIEQWFtEDPGPDE	-	gap	-	gap	N54	EDVANWLNEDPEEGL	T55	DDLAQWLTEDPGPDE
2	0	D61	FtEDPGPDEAPRMPE	S55-p	EEFFEGPsEALRVSG	E60	AELLEGPEEALQVSA	E58	NWLNEDPEEGLRVPA	D61	LTEDPGPDEAPRMSE
8	2	T81-p	APAPAAPtPAAPAPA	G75	DPVTETPGPVAPAPA	A79	EPGTEAPAPVAPASA	A78	APAPAAPALAAPAPA	T81	APTPAAPTPAAPAPA
0	2	S99-p	PLSSSVPsQkTYQGs	S93	PLSSFVPSQKTYQGN	S97	PLSSSVPSQKTYQGN	S96	PLSSSVPSQKTYHGN	S99	PLSSSVPSQKTYHGS
1	2	K101-ub	SSSVPsQkTYQGsYG	K95	SSFVPSQKTYQGNYG	K99	SSSVPSQKTYQGNYG	K98	SSSVPSQKTYHGNYG	K101	SSSVPSQKTYHGSYG
1	0	S106-p	sQkTYQGsYGFrLGF	N100	SQKTYQGNYGFHLGF	N104	SQKTYQGNYGFHLGF	N103	SQKTYHGNYGFRLGF	S106	SQKTYHGSYGFRLGF
0	1	R110-m1	YQGsYGFrLGFLhSG	H104	YQGNYGFHLGFLQSG	H108	YQGNYGFHLGFLQSG	R107	YHGNYGFRLGFLHSG	R110	YHGSYGFRLGFLHSG
0	1	H115-m1	GFrLGFLhSGTAkSV	Q109	GFHLGFLQSGTAkSV	Q113	GFHLGFLQSGTAkSV	H112	GFRLGFLHSGTAKSV	H115	GFRLGFLHSGTAKSV
23	1	K120-ac	FLhSGTAkSVTCTyS	K114-ac	FLQSGTAkSVMCTYS	K118-ac	FLQSGTAkSVMCTYS	K117	FLHSGTAKSVTCTYS	K120	FLHSGTAKSVTCTYS
1	19	K120-ub	FLhSGTAkSVTCTyS	K114	FLQSGTAKSVMCTYS	K118	FLQSGTAKSVMCTYS	K117	FLHSGTAKSVTCTYS	K120	FLHSGTAKSVTCTYS
1	0	Y126-p	AkSVTCTySPALNkM	Y120	AkSVMCTYSPPLNKL	Y124	AkSVMCTYSISLNKL	Y123	AKSVTCTYSPCLNKL	Y126	AKSVTCTYSPDLNKM
1	1	K132-ub	TySPALNkMFCQLAk	K126	TYSPPLNKLFCQLAK	K130	TYSISLNKLFCQLAK	K129	TYSPCLNKLFCQLAK	K132	TYSPDLNKMFCQLAK
1	0	K139-ub	kMFCQLAkTCPVQLW	K133	KLFCQLAKTCPVQLW	K137	KLFCQLAKTCPVQLW	K136	KLFCQLAKTCPVQLW	K139	KMFCQLAKTCPVQLW
3	1	S149-p	PVQLWVDstPPPGtR	A143	PVQLWVSATPPAGsR	S147	PVQLWVTSTPPPGTR	S146	PVQLWVDSTPPPGTR	S149	PVQLWVDSTPPPGSR
1	1	S149-gl	PVQLWVDstPPPGtR	A143	PVQLWVSATPPAGsR	S147	PVQLWVTSTPPPGTR	S146	PVQLWVDSTPPPGTR	S149	PVQLWVDSTPPPGSR
4	8	T150-p	VQLWVDstPPPGtRV	T144	VQLWVSATPPAGsRV	T148	VQLWVTSTPPPGTRV	T147	VQLWVDSTPPPGTRV	T150	VQLWVDSTPPPGSRV
4	1	T155-p	DstPPPGtRVRAMAI	S149-p	SATPPAGsRVRAMAI	T153	TSTPPPGTRVRAMAI	T152	DSTPPPGTRVRAMAI	S155	DSTPPPGSRVRAMAI
4	1	K164-ac	VRAMAIYkQSQHMTE	K158	VRAMAIYKKSQHMTE	K162	VRAMAIYKKSQHMTE	K161	VRAMAIYKKSQHMTE	K164	VRAMAIYKQSQHMTE
1	1	K164-ub	VRAMAIYkQSQHMTE	K158	VRAMAIYKKSQHMTE	K162	VRAMAIYKKSQHMTE	K161	VRAMAIYKKSQHMTE	K164	VRAMAIYKQSQHMTE
2	0	S183-p	CPHHERCsDSDGLAP	S177	CPHHERCSDGDGLAP	S181	CPHHERCSDGDGLAP	S180	CPHHERCSDSDGLAP	S183	CPHHERCSDSDGLAP
0	1	R209-m1	RVEYLDDrNtFrHsV	R203	YPEYLEDRQTFRHSV	R207	YAEYLDDRQTFRHSV	R206	RAEYLDDRNTFRHSV	R209	RVEYSDDRNTFRHSV
1	0	T211-p	EYLDDrNtFrHsVVV	T205	EYLEDRQTFRHSVVV	T209	EYLDDRQTFRHSVVV	T208	EYLDDRNTFRHSVVV	T211	EYSDDRNTFRHSVVV
0	1	R213-m1	LDDrNtFrHsVVVPy	R207	LEDRQTFRHSVVVPY	R211	LDDRQTFRHSVVVPY	R210	LDDRNTFRHSVVVPY	R213	SDDRNTFRHSVVVPY
4	0	S215-p	DrNtFrHsVVVPyEP	S209	DRQTFRHSVVVPYEP	S213	DRQTFRHSVVVPYEP	S212	DRNTFRHSVVVPYEP	S215	DRNTFRHSVVVPYEP

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p53 (human)

Overview

p53 a transcription factor and major tumor suppressor that plays a major role in regulating cellular responses to DNA damage and other genomic aberrations. Activation of p53 can lead to either cell cycle arrest and DNA repair or apoptosis. More than 50 percent of human tumors contain a mutation or deletion of the TP53 gene. p53 is modified post-translationally at multiple sites. DNA damage induces phosphorylation of p53 at S15, S20 and S37, reducing its interaction with the oncoprotein MDM2. MDM2 inhibits p53 accumulation by targeting it for ubiquitination and proteasomal degradation. Phosphorylated by many kinases including Chk2 and Chk1 at S20, enhancing its tetramerization, stability and activity. The phosphorylation by CAK at S392 is increased in human tumors and has been reported to influence the growth suppressor function, DNA binding and transcriptional activation of p53. Phosphorylation of p53 at S46 regulates the ability of p53 to induce apoptosis. The acetylation of p53 appears to play a positive role in the accumulation of p53 during the stress response. Following DNA damage, p53 becomes acetylated at K382, enhancing its binding to DNA. Deacetylation of p53 can occur through interaction with SIRT1, a deacetylase that may be involved in cellular aging and the DNA damage response. p53 regulates the transcription of a set of genes encoding endosomal proteins that regulate endosomal functions. These include STEAP3 and CHMP4C, which enhance exosome production, and CAV1 and CHMP4C, which produce a more rapid endosomal clearance of the EGFR from the plasma membrane. DNA damage regulates a p53-mediated secretory pathway, increasing the secretion of some proteins such as Hsp90, SERPINE1, SERPINB5, NKEF-A, and CyPA, and inhibiting the secretion of others including CTSL and IGFBP-2. Two alternatively spliced human isoforms have been reported. Isoform 2 is expressed in quiescent lymphocytes. Seems to be non-functional. May be produced at very low levels due to a premature stop codon in the mRNA, leading to nonsense-mediated mRNA decay. Note: This description may include information from UniProtKB.

Protein type: DNA binding protein; Nuclear receptor co-regulator; Motility/polarity/chemotaxis; Transcription factor; Activator protein; Tumor suppressor

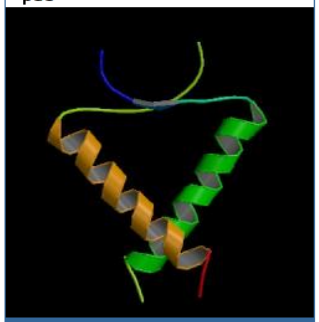
Cellular Component: PML body; transcription factor TFIID complex; protein complex; nuclear matrix; mitochondrion; endoplasmic reticulum; replication fork; cytosol; nucleoplasm; nuclear body; mitochondrial matrix; cytoplasm; nuclear chromatin; nucleolus; chromatin; nucleus

Molecular Function: identical protein binding; protease binding; zinc ion binding; protein phosphatase 2A binding; p53 binding; protein N-terminus binding; receptor tyrosine kinase binding; transcription factor binding; protein phosphatase binding; protein kinase binding; histone acetyltransferase binding; protein binding; copper ion binding; histone deacetylase regulator activity; enzyme binding; DNA binding; protein heterodimerization activity; chaperone binding; ubiquitin protein ligase binding; damaged DNA binding; chromatin binding; transcription factor activity; ATP binding

Biological Process: central nervous system development; viral reproduction; positive regulation of apoptosis; multicellular organismal development; positive regulation of transcription, DNA-dependent; T cell differentiation in the thymus; gastrulation; determination of adult life span; DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest; response to antibiotic; regulation of apoptosis; cellular response to glucose starvation; protein localization; negative regulation of neuroblast proliferation; base-excision repair; transforming growth factor beta receptor signaling pathway; protein complex assembly; cell cycle arrest; ER overload response; response to X-ray; somitogenesis; release of cytochrome c from mitochondria; chromatin assembly; cell aging; rRNA transcription; positive regulation of peptidyl-tyrosine phosphorylation; negative regulation of DNA replication; negative regulation of fibroblast proliferation; embryonic organ development; positive regulation of transcription from RNA polymerase II promoter; regulation of mitochondrial membrane permeability; negative regulation of transcription, DNA-dependent; regulation of tissue remodeling; negative regulation of apoptosis; G1 DNA damage checkpoint; DNA damage response, signal transduction by p53 class mediator; apoptosis; negative regulation of transcription from RNA polymerase II promoter; response to salt stress; negative regulation of cell proliferation; positive regulation of protein oligomerization; positive regulation of histone deacetylation; DNA damage response, signal transduction by p53 class mediator resulting in transcription of p21 class mediator; regulation of transcription, DNA-dependent; T cell proliferation during immune response; double-strand break repair; positive regulation of neuron apoptosis; response to gamma radiation; cell differentiation; DNA damage response, signal transduction by p53 class mediator resulting in induction of apoptosis; protein tetramerization; Notch signaling pathway; in utero embryonic development; multicellular organism growth; B cell lineage commitment; cell proliferation; neuron apoptosis; T cell lineage commitment; negative regulation of helicase activity; nucleotide-excision repair; protein import into nucleus, translocation; DNA strand renaturation; Ras protein signal transduction; negative regulation of cell growth; negative regulation of transforming growth factor beta receptor signaling

Select Structure to View Below

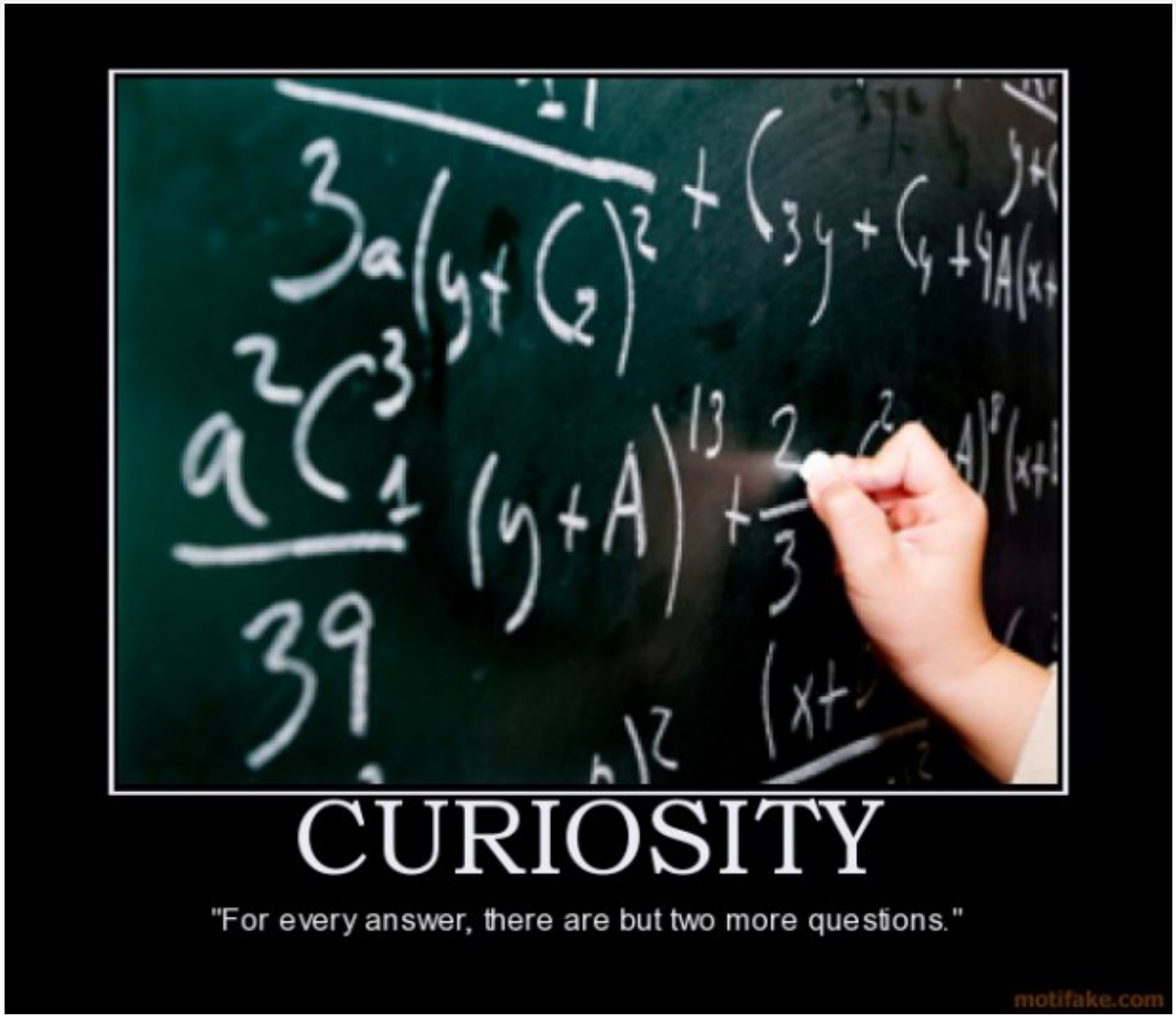
p53



1A1U - A/C=324-358 (human)

Open Viewer

QUESTIONS?


CURIOSITY
"For every answer, there are but two more questions."
motifake.com

The Eukaryotic Linear Motif resource for
Functional Sites in Proteins

The ELM resource

is a collection of more than 240 thoroughly annotated motif classes with over 2700 annotated instances.
It is also a prediction tool to detect these motifs in protein sequences employing different filters to distinguish between **functional** and **non-functional** motif instances.

"The eukaryotic linear motif resource ELM: 10 years and counting"; DINKEL, VAN ROEY, MICHAEL, DAVEY, WEATHERITT, BORN, SPECK, KRÜGER, GREBNEV, KUBAŃ, STRUMILLO, UYAR, BUDD, ALTENBERG, SEILER, CHEMES, GLAVINA, SÁNCHEZ, DIELLA & GIBSON; (NUCLEIC ACIDS RES. 2014)

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Functional Sites		ELM classes		ELM instances		PDB structures	GO terms		PubMed Links	
Total	155		242		2675	347	495			2392
By category		LIG	133	Human	1583					
		MOD	31	Mouse	252		Biological Process	256	From ELM class	1124
		DEG	25	Rat	129					
		DOC	22	Yeast	94		Cell Compartment	112	From instance	1734
		TRG	20	Fly	90					
		CLV	11	Other	547		Molecular Function	127		

"The eukaryotic linear motif resource ELM: 10 years and counting"; DINKEL, VAN ROEY, MICHAEL, DAVEY, WEATHERITT, BORN, SPECK, KRÜGER, GREBNEV, KUBAŃ, STRUMILLO, UYAR, BUDD, ALTENBERG, SEILER, CHEMES, GLAVINA, SÁNCHEZ, DIELLA & GIBSON; (NUCLEIC ACIDS RES. 2014)

ELM Class

Condensed information about a motif. Regular Expressions used to annotate the motif (eg. "[KR]xLx{0,1}[FYLIVMP] for Cyclin motif)

DOC_CYCLIN_1

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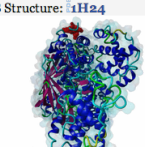
Pattern Probability:	0.0053239
Present in taxon:	Eukaryota
Interaction Domain:	Cyclin_N (PF00134) Cyclin, N-terminal domain (Stochiometry: 1 : 1)

PDB Structure: 1H24



ELM Class

Condensed information about a motif. Regular Expressions used to annotate the motif (eg. "[KR]xLx{0,1}[FYLIVMP] for Cyclin motif)

24 Instances for DOC_CYCLIN_1
(click table headers for sorting; Notes column: =Number of Switches, =Number of Interactions)

Protein Name	Gene Name	Start	End	Subsequence	Logic	#Ev.	Organism	Notes
RB_HUMAN	RB1	873	877	SNPPKPLKKLRFDIEGSDEA	TP	3	Homo sapiens (Human)	1H25 1
Q8UWJ8_CHICK	CDH1-A	394	398	KLTGHSYRVLYLAMSPDGEA	FP	1	Gallus gallus (Chicken)	
PMYT1_HUMAN	PKMYT1	486	489	GSFPSFEPRNLLSLFEDTLD	TP	1	Homo sapiens (Human)	
E2F1_HUMAN	E2F1	90	94	LGRPPVKRRLDLETDHQYLA	TP	3	Homo sapiens (Human)	1H24
CDN1C_HUMAN	CDKN1C	31	34	VLVRTSACRSLFGPVDHEEL	TP	1	Homo sapiens (Human)	
RUX_DROME	rux	248	251	PTARRCVRRTLFTEENTQKE	TP	1	Drosophila melanogaster (Fruit fly)	
E2F2_HUMAN	E2F2	87	91	AGRLPAKRKLDLEGIGRPVV	TP	1	Homo sapiens (Human)	
E2F3_HUMAN	E2F3	134	138	GGGPPAKRRLELGESGHQYL	TP	1	Homo sapiens (Human)	
AKA12_MOUSE	Akap12	501	504	IKVQGSPLKKLFSSSGLKKL	TP	1	Mus musculus (House mouse)	1
CDC6_HUMAN	CDC6	94	98	HSHTLKGRRLVFDNQLTIKS	TP	2	Homo sapiens (Human)	2CCH 1
CDN1A_HUMAN	CDKN1A	19	22	NPCGSKACRRLFGPVDSEQL	TP	4	Homo sapiens (Human)	1 1
CDN1A_HUMAN	CDKN1A	155	159	TSMTDFYHSKRRLIFSKRKP	TN	1	Homo sapiens (Human)	
ORC6_YEAST	ORC6	178	182	ESPSITRRKLAFEEDEDEDE	TP	1	Saccharomyces cerevisiae (Baker's yeast)	
P53_HUMAN	TP53	381	385	GQSTSRHKKLMFKTEGPDSD	TP	5	Homo sapiens (Human)	1H26
RBL1_HUMAN	RBL1	658	661	SPTAGSAKRRLFGEDPPKEM	TP	3	Homo sapiens (Human)	1H28
RBL2_HUMAN	RBL2	680	684	PPASTTRRRLFVENDSPSDG	TP	1	Homo sapiens (Human)	
HIRA_HUMAN	HIRA	629	633	KASSLSKRKLELEVETVEKK	TP	1	Homo sapiens (Human)	

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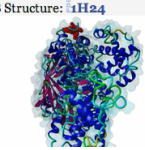

ELM Instance

An experimentally verified instance of an ELM class in a particular sequence.

ELM Class

Condensed information about a motif. Regular Expressions used to annotate the motif (eg. "[KR]xLx{0,1}[FYLIVMP] for Cyclin motif)

Instance

Sequence	Start	End	Subsequence	Logic	PDB	Organism	Length
(Q99741) CDC6_HUMAN	94	98	HSHTLKGRRLVFDNQLTIKS	TP	2CCH 	Homo sapiens (Human)	560

Instance evidence

Evidence class	PSMI	Method	BioSource	PubMed	Logic	Reliability	Notes
experimental	MI:0114	x-ray crystallography	in vitro	Cheng,2006	support	certain	InteractionDetection FeatureDetection
experimental	MI:0096	pull down	in vivo/in vitro	Petersen,1999	support	certain	InteractionDetection

This ELM instance is part of the following switching mechanism(s) annotated at the switches.ELM resource:

SWTI000330:

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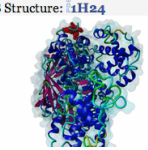
PDB Structure: 1H24 

ELM Instance

An experimentally verified instance of an ELM class in a particular sequence.

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- Methods
- References
- Interactions

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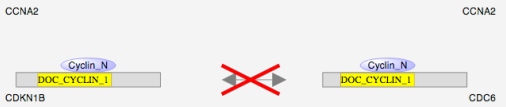

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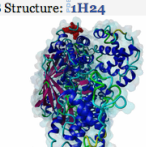

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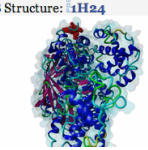
PDB Structure: 1H24 

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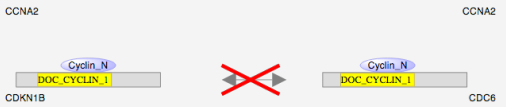

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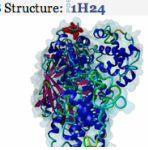
PDB Structure: 1H24 

ELM Instance

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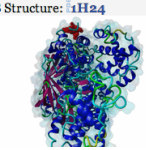

ELM Instance

An experimentally verified instance of an ELM class in a particular sequence.

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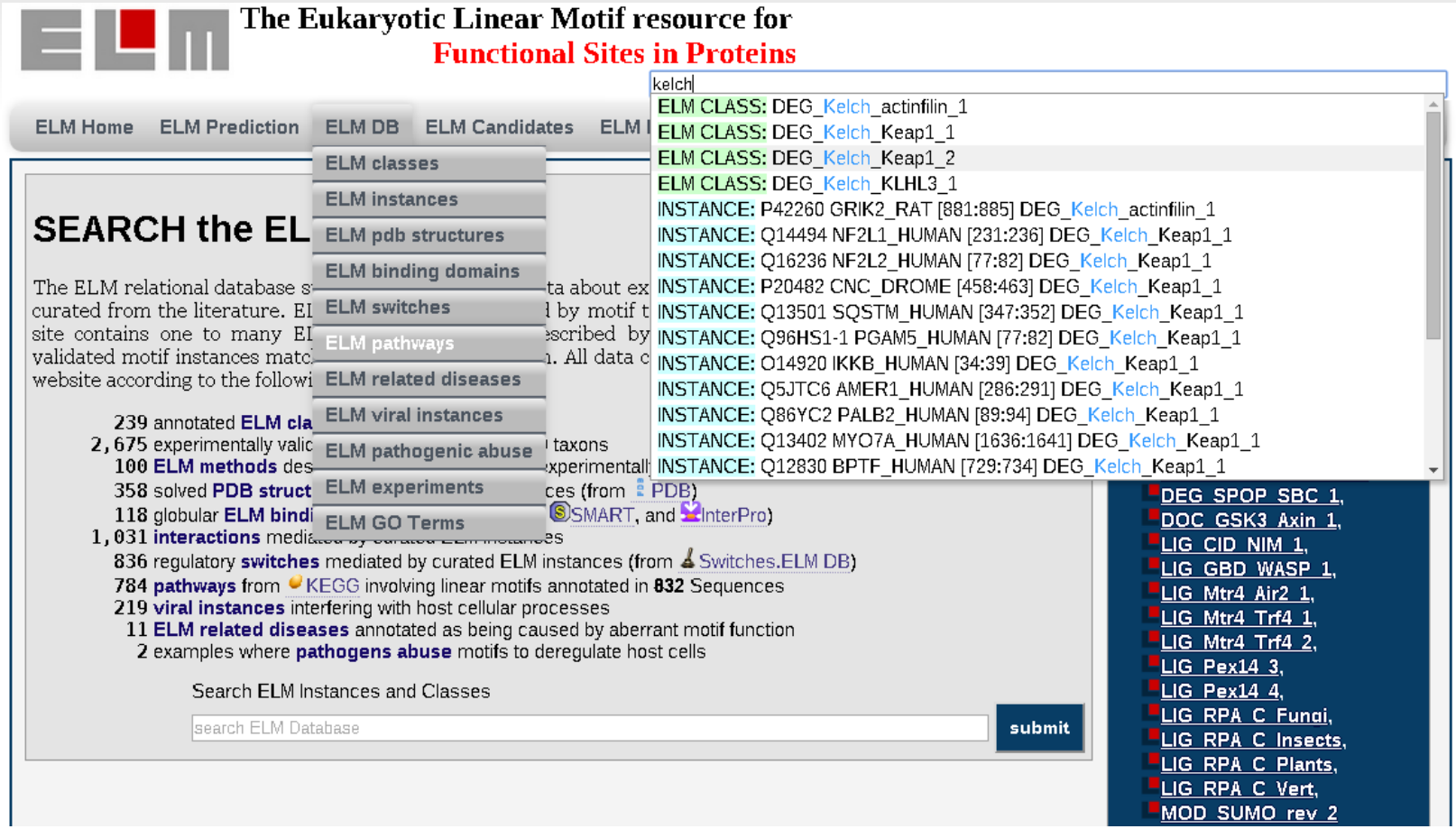
- Methods
- References
- Interactions

"iELM – a web server to explore short linear motif-mediated interactions."; WEATHERITT, JEHL, **DINKEL** & GIBSON ; (NUCLEIC ACIDS RES. 2012)


The Eukaryotic Linear Motif resource for
Functional Sites in Proteins
kelch
ELM CLASS: DEG_Kelch_actinfilin_1
ELM CLASS: DEG_Kelch_Keap1_1
ELM CLASS: DEG_Kelch_Keap1_2
ELM CLASS: DEG_Kelch_KLHL3_1
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INSTANCE: Q14494 NF2L1_HUMAN [231:236] DEG_Kelch_Keap1_1
INSTANCE: Q16236 NF2L2_HUMAN [77:82] DEG_Kelch_Keap1_1
INSTANCE: P20482 CNC_DROME [458:463] DEG_Kelch_Keap1_1
INSTANCE: Q13501 SQSTM_HUMAN [347:352] DEG_Kelch_Keap1_1
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INSTANCE: Q5JTC6 AMER1_HUMAN [286:291] DEG_Kelch_Keap1_1
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INSTANCE: Q13402 MYO7A_HUMAN [1636:1641] DEG_Kelch_Keap1_1
INSTANCE: Q12830 BPTF_HUMAN [729:734] DEG_Kelch_Keap1_1
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ELM pdb structures
ELM binding domains
ELM switches
ELM pathways
ELM related diseases
ELM viral instances
ELM pathogenic abuse
ELM experiments
ELM GO Terms
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239 annotated ELM cla
2,675 experimentally valic
100 ELM methods des
358 solved PDB struct
118 globular ELM bindi
1,031 interactions
836 regulatory switches mediated by curated ELM instances (from Switches.ELM DB)
784 pathways from KEGG involving linear motifs annotated in 832 Sequences
219 viral instances interfering with host cellular processes
11 ELM related diseases annotated as being caused by aberrant motif function
2 examples where pathogens abuse motifs to deregulate host cells
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DOC_GSK3_Axin_1,
LIG_CID_NIM_1,
LIG_GBD_WASP_1,
LIG_Mtr4_Air2_1,
LIG_Mtr4_Trf4_1,
LIG_Mtr4_Trf4_2,
LIG_Pex14_3,
LIG_Pex14_4,
LIG_RPA_C_Fungi,
LIG_RPA_C_Insects,
LIG_RPA_C_Plants,
LIG_RPA_C_Vert,
MOD_SUMO_rev_2

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«MOD_WntLipid« »TRG_Cilium_Arf4_1»

TRG_AP2beta_CARGO_1

Accession: ELME000247

Functional site class: AP-2 beta2 appendage CCV component motifs

Functional site description: Several motifs are responsible for the binding of accessory endocytic proteins to the beta2-subunit appendage of the adaptor protein complex AP-2 as part of their recruitment to the site of clathrin coated vesicle (CCV) formation. Proteins binding the platform subdomain have been found to be cargo family specific (for example can load all GPCRs, or all LDL receptor family members) clathrin adaptors. Accessory proteins which help in CCV formation bind the sandwich subdomain site or the alpha ear domain.

ELM Description: Motif binding as a helix in a depression on the top surface of the AP-2 beta appendage platform subdomain. The pattern [ED]x(1,2)Fxx[FL]xxxR is conserved in beta Arrestins, ARH and Epsin-1, -2 of vertebrates. It is also found in homologues of other metazoans, but the pattern is sometimes not matched exactly, meaning that the ELM regular expression will not provide a match. In other lineages, if there is an equivalent motif, the pattern is likely to have diverged.

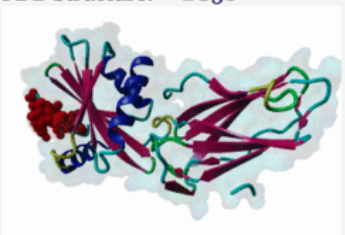
Pattern: `[DE].{1,2}F[^P][^P][FL][^P][^P][^P]R`

Pattern Probability: 0.0000182

Present in taxon: Metazoa

Interaction Domain: B2-adapt-app_C (PF09066) Beta2-adaptin appendage, C-terminal sub-domain (Stochiometry: 1 : 1)

PDB Structure: 2G30



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Search ELM Instances

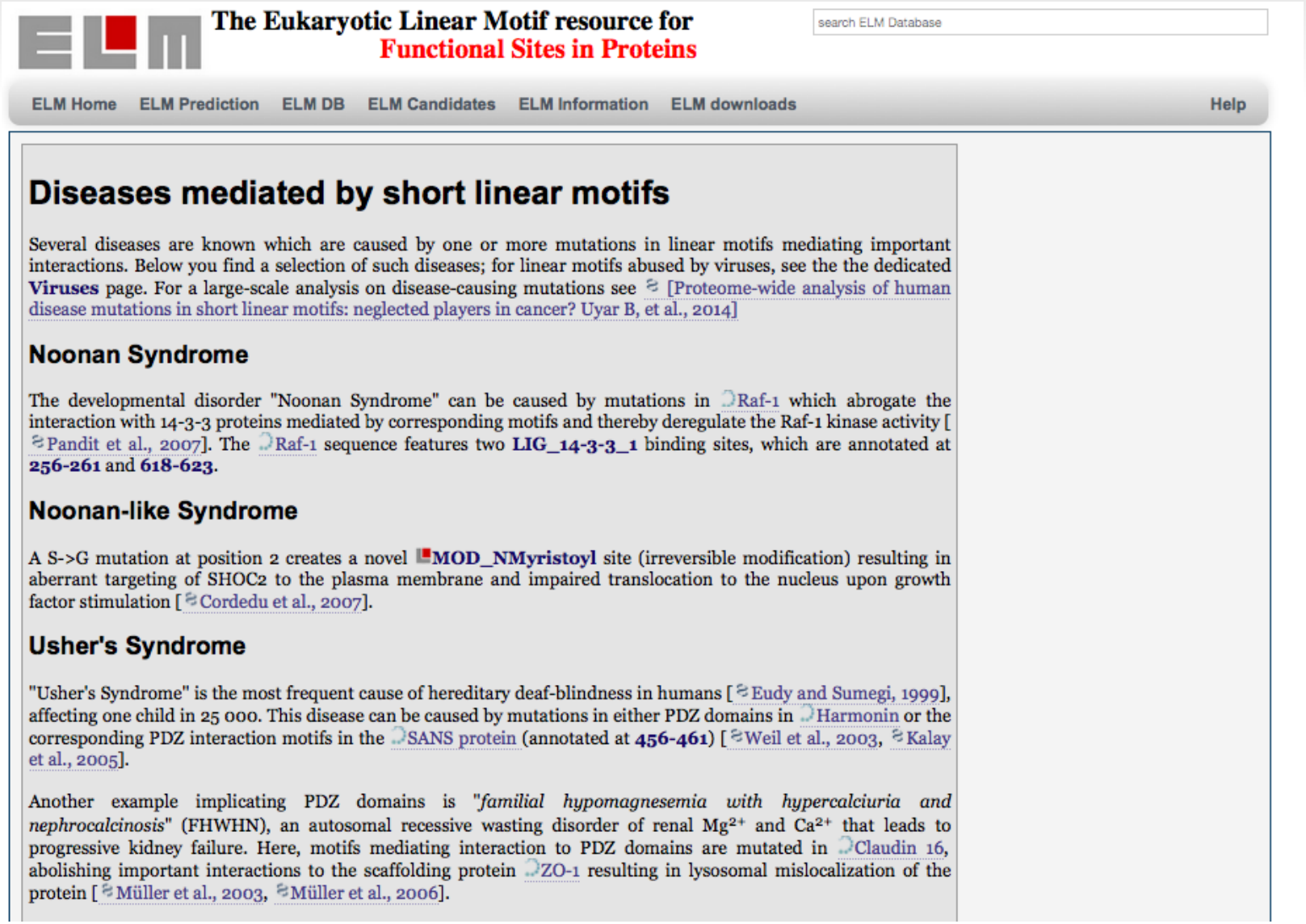
Full-Text Search (to show all instances, enter 'all' or '*') ap2
Filter by instance Logic true positive | Filter by organism Homo sapiens
submit | Reset

export 58 instances as: fasta tsv

58 Instances for search term 'ap2':
(click table headers for sorting)

CLV
LIG
MOD
TRG

ELM identifier	Sequence	Start	End	Subsequence	Instance Logic	#Evidence	PDB	Organism
TRG_LysEnd_APsAcLL_1	OPRD_HUMAN	241	246	GLMLLRLRSVRLLSGSKEKD	true positive	8	---	Homo sapiens (Human)
TRG_AP2beta_CARGO_1	ARRB1_HUMAN	385	395	TNDDDIVFEDFARQRLKGMK	true positive	5	2IV8	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	HG2A_HUMAN	19	24	DQKPVMDDQRDLISNNEQLP	true positive	5	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	672	674	DPFATSSTDPFSAANNSSIT	true positive	4	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	692	694	SVETLKHNDPFAPGGTVVAA	true positive	4	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	709	711	VAASDSATDPFASVFGNESF	true positive	4	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	737	739	TLSKVNNEDPFRSATSSSVS	true positive	4	---	Homo sapiens (Human)
TRG_AP2beta_CARGO_1	EPN1_HUMAN	377	386	FDTEPDEFSDFDRLRTALPT	true positive	4	---	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	ATP7A_HUMAN	1483	1488	SVVTSEPDKHSLLVGDFRED	true positive	4	---	Homo sapiens (Human)
LIG_SxIP_EBH_1	CLAP2_HUMAN	492	502	ASAQKRSKIPRSQGCSREAS	true positive	3	---	Homo sapiens (Human)
LIG_SxIP_EBH_1	CLAP2_HUMAN	515	525	LSVARSSRIPRPSVSQGCSR	true positive	3	---	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	BCAM_HUMAN	604	609	HSGSEQPEQTGLLMGGASGG	true positive	3	---	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	NPC1_HUMAN	1271	1276	KSCATEERYKGTERERLLNF	true positive	3	---	Homo sapiens (Human)
LIG_APCC_KENbox_2	CKAP2_HUMAN	80	84	KLKTKMADKENMKRPAESKN	true positive	2	---	Homo sapiens (Human)
LIG_MAPK_1	MP2K1_HUMAN	3	11	MPKKKPTPIQLNPAPDGSAV	true positive	2	---	Homo sapiens (Human)
LIG_MAPK_1	MP2K4_HUMAN	40	48	SSMQGKRKALKLNFANPPFK	true positive	2	---	Homo sapiens (Human)
TRG_AP2beta_CARGO_1	ARH_HUMAN	256	266	DDGLDEAFSRLAQSRTNPQV	true positive	2	2G30	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	CD44_HUMAN	708	713	GEASKSQEMVHLVNKESSET	true positive	2	---	Homo sapiens (Human)
LIG_AP2alpha_1	AMPH_HUMAN	324	328	QENIISFFEDNFVPEISVTT	true positive	1	1KY7	Homo sapiens (Human)



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Diseases mediated by short linear motifs

Several diseases are known which are caused by one or more mutations in linear motifs mediating important interactions. Below you find a selection of such diseases; for linear motifs abused by viruses, see the the dedicated **Viruses** page. For a large-scale analysis on disease-causing mutations see [Proteome-wide analysis of human disease mutations in short linear motifs: neglected players in cancer? Uyar B, et al., 2014]

Noonan Syndrome

The developmental disorder "Noonan Syndrome" can be caused by mutations in Raf-1 which abrogate the interaction with 14-3-3 proteins mediated by corresponding motifs and thereby deregulate the Raf-1 kinase activity [Pandit et al., 2007]. The Raf-1 sequence features two **LIG_14-3-3_1** binding sites, which are annotated at **256-261** and **618-623**.

Noonan-like Syndrome

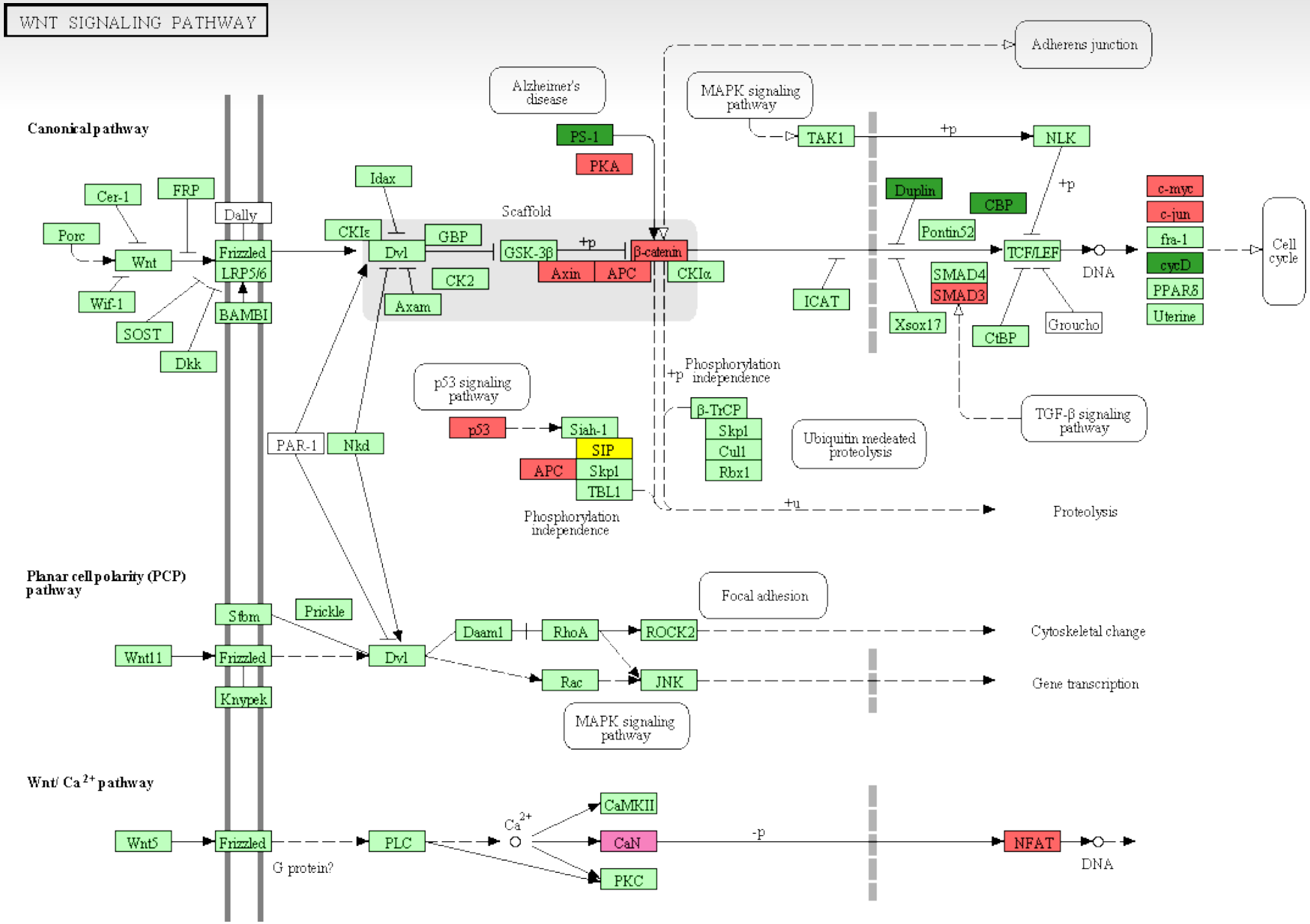
A S->G mutation at position 2 creates a novel **MOD_NMyristoyl** site (irreversible modification) resulting in aberrant targeting of SHOC2 to the plasma membrane and impaired translocation to the nucleus upon growth factor stimulation [Cordedu et al., 2007].

Usher's Syndrome

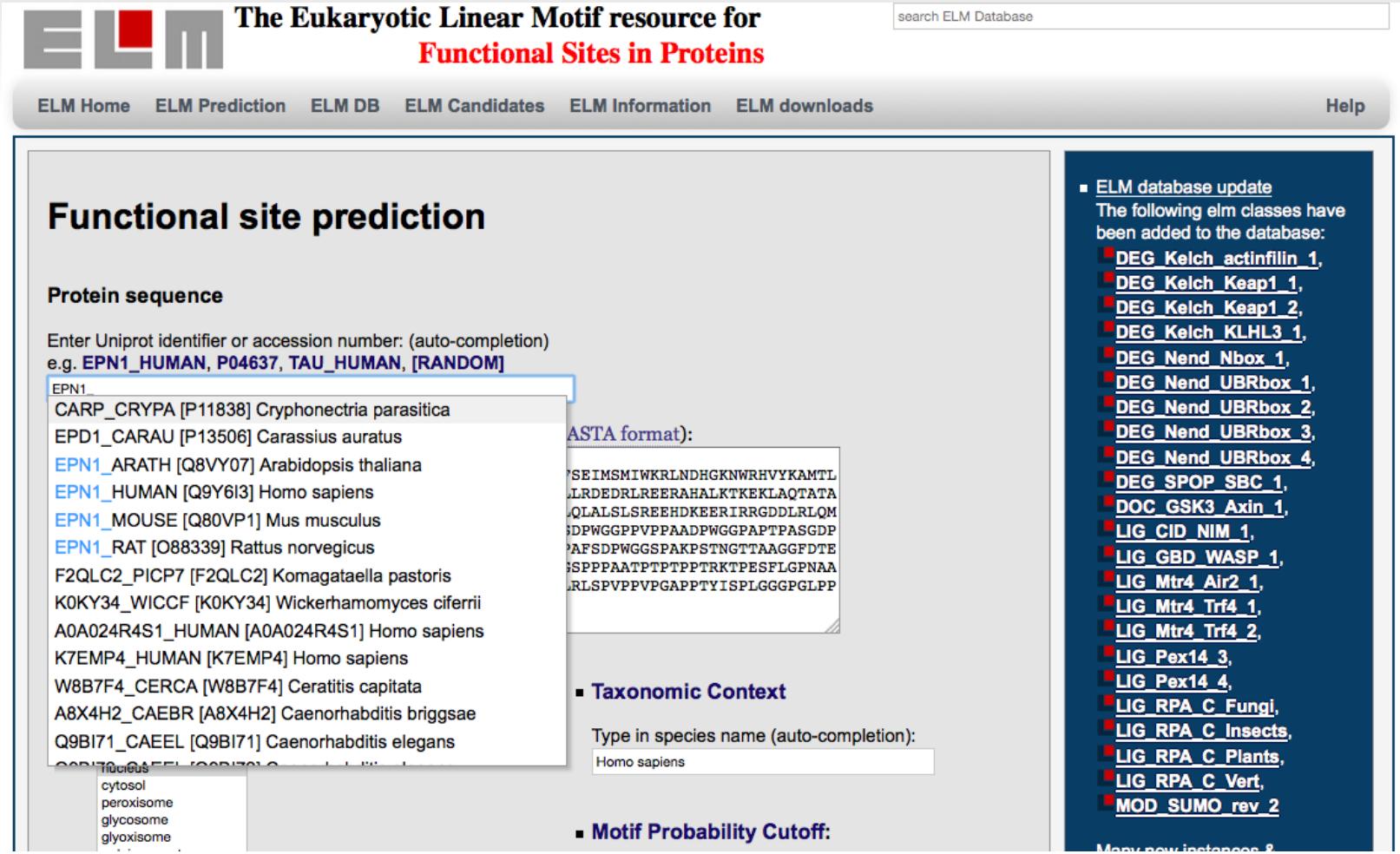
"Usher's Syndrome" is the most frequent cause of hereditary deaf-blindness in humans [Eudy and Sumegi, 1999], affecting one child in 25 000. This disease can be caused by mutations in either PDZ domains in Harmonin or the corresponding PDZ interaction motifs in the SANS protein (annotated at **456-461**) [Weil et al., 2003, Kalay et al., 2005].

Another example implicating PDZ domains is "*familial hypomagnesemia with hypercalciuria and nephrocalcinosis*" (FHWHN), an autosomal recessive wasting disorder of renal Mg^{2+} and Ca^{2+} that leads to progressive kidney failure. Here, motifs mediating interaction to PDZ domains are mutated in Claudin 16, abolishing important interactions to the scaffolding protein ZO-1 resulting in lysosomal mislocalization of the protein [Müller et al., 2003, Müller et al., 2006].

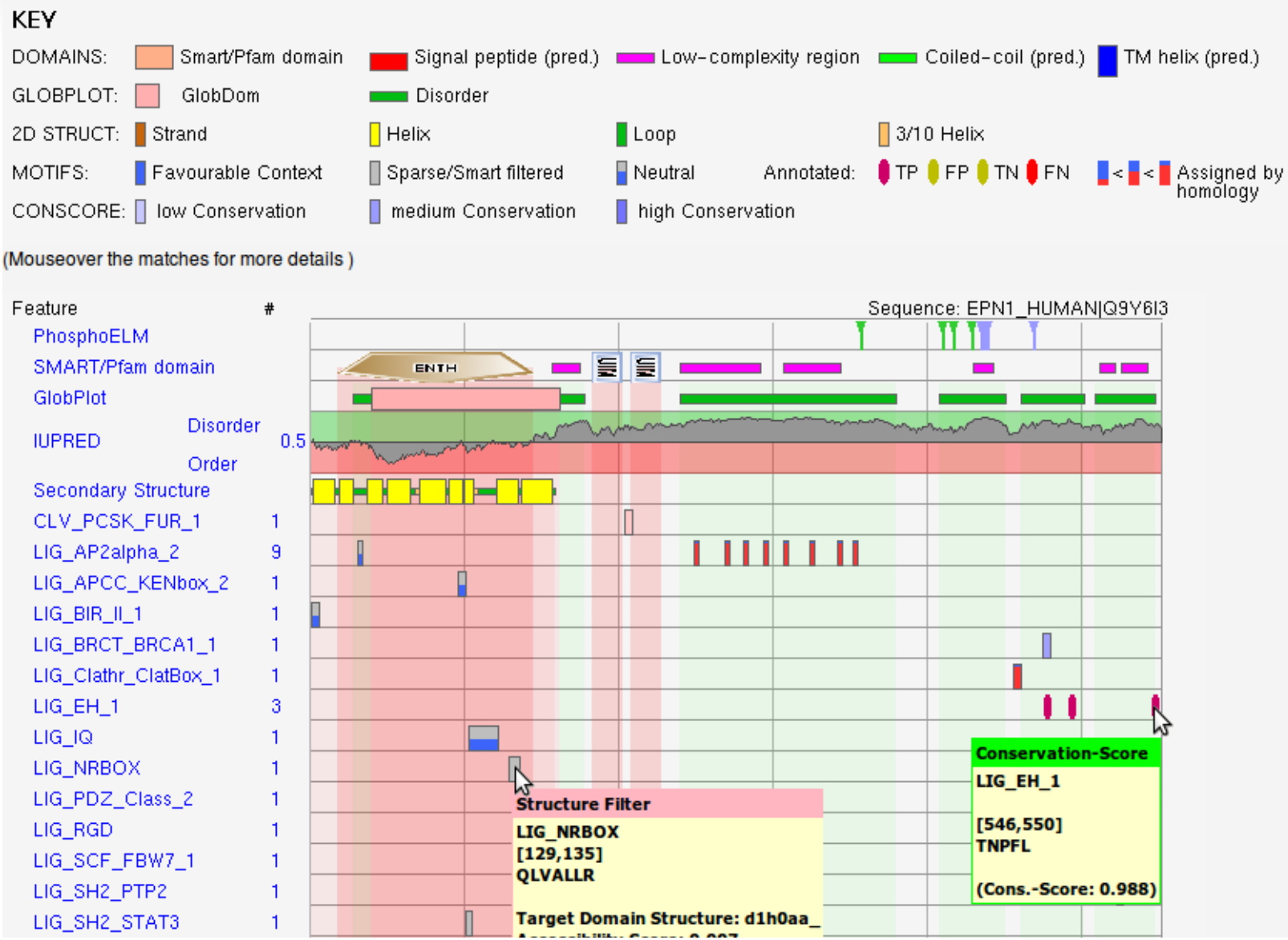
ELM DATABASE:PATHWAYS



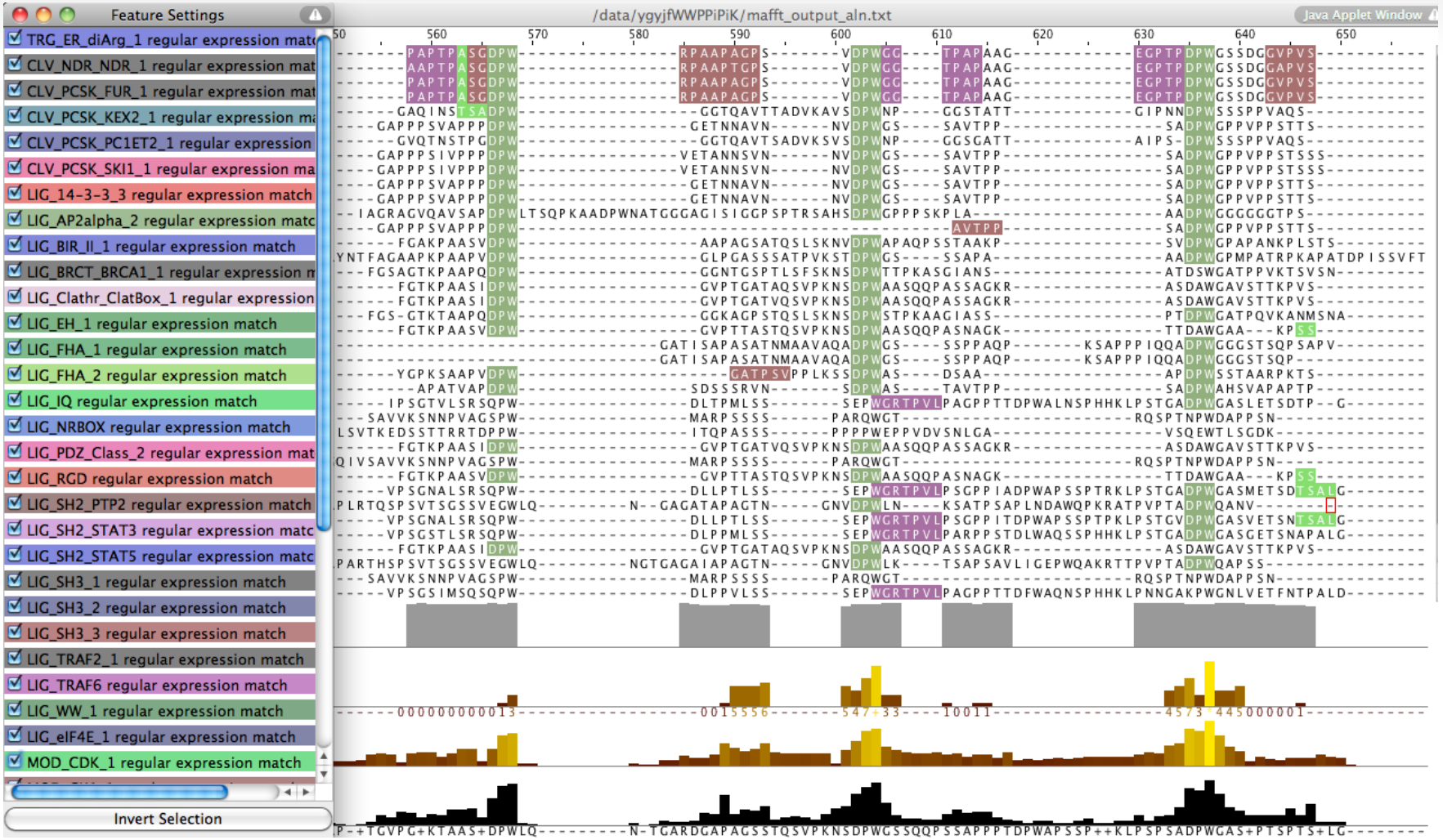
ELM PREDICTION TOOL



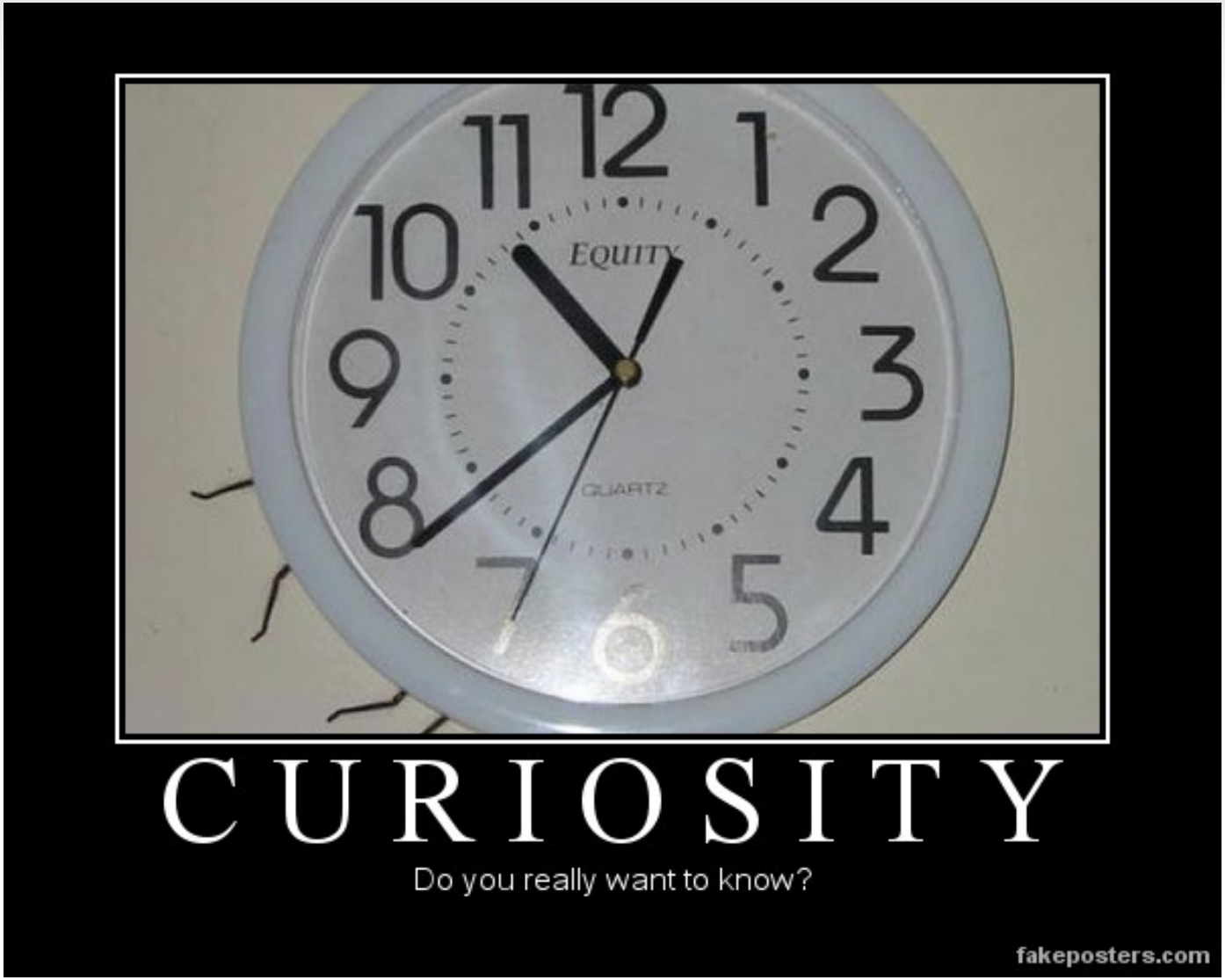
Summary of features reported by the ELM resource.



View Conservation in Jalview



Questions?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Short Linear Motifs

- are compact, degenerate protein interaction interfaces (in IDRs)
- are ubiquitous in eukaryotic proteomes and mediate many regulatory functions:
  - directing ligand binding
  - providing docking sites for modifying enzymes
  - controlling protein stability
  - acting as signals to target proteins to specific subcellular locations

"The switches.ELM Resource: A Compendium of Conditional Regulatory Interaction Interfaces"; VAN ROEY, DINKEL, WEATHERITT, GIBSON AND DAVEY; (SCIENCE SIGNALING. 2013)

Linear Motifs as Molecular Switches

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Motif-mediated interactions

- occur with low affinity,
- are transient & reversible
- can be easily modulated.

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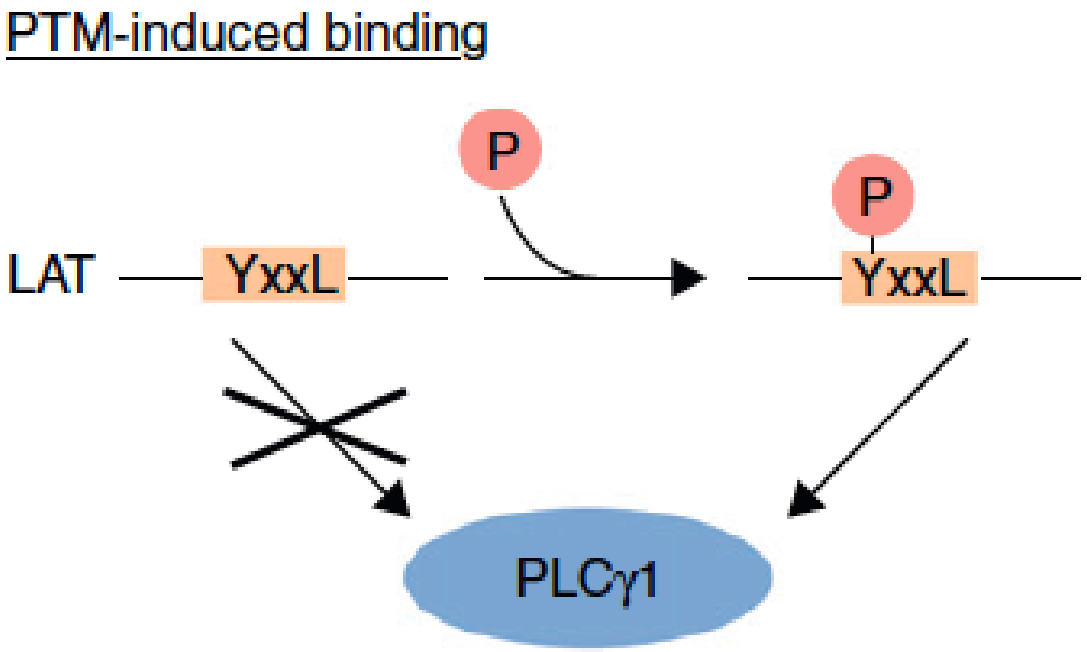
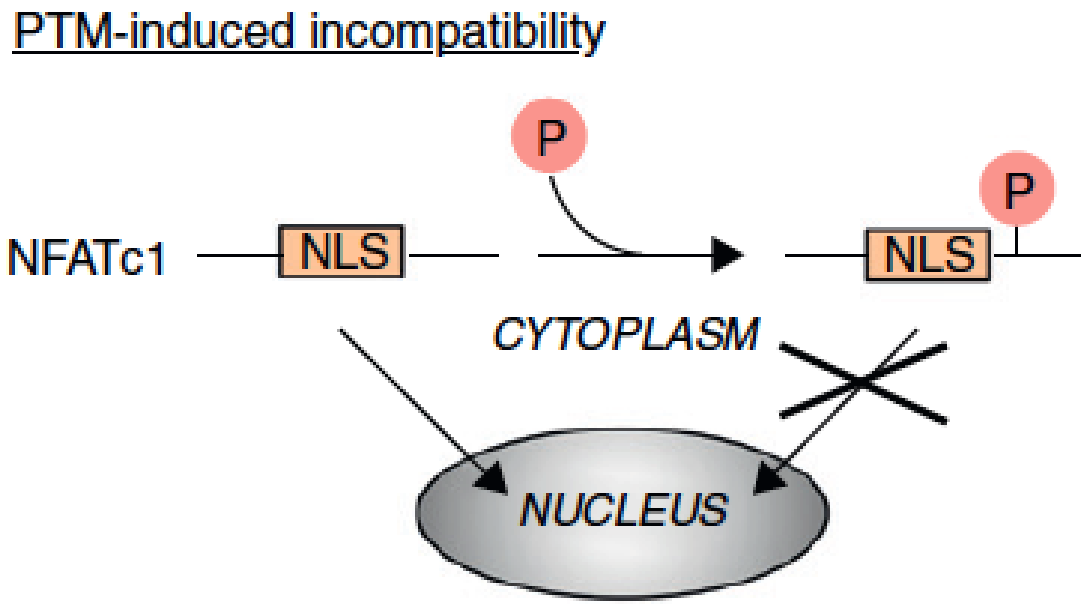
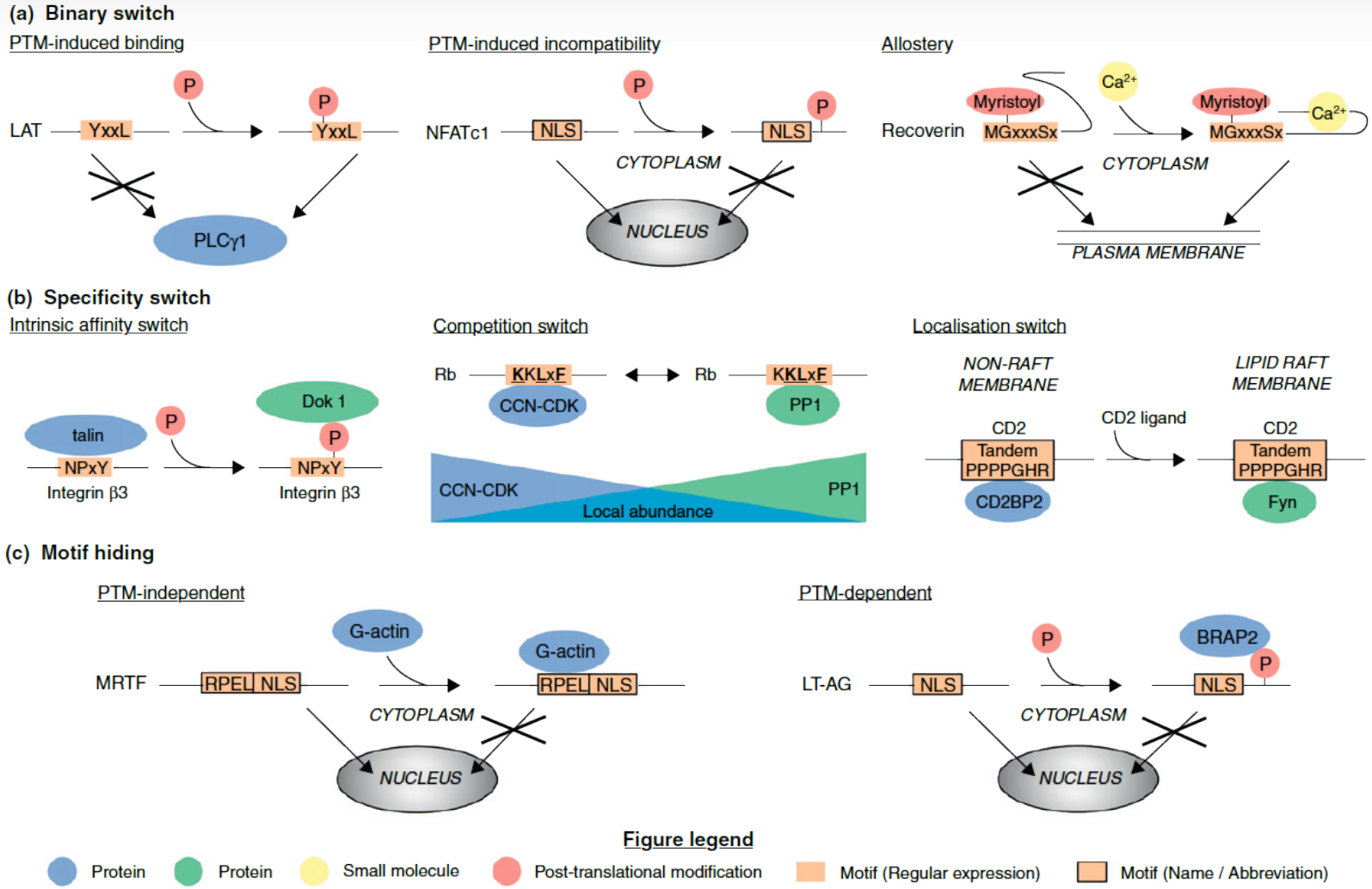
Motifs mediate switches

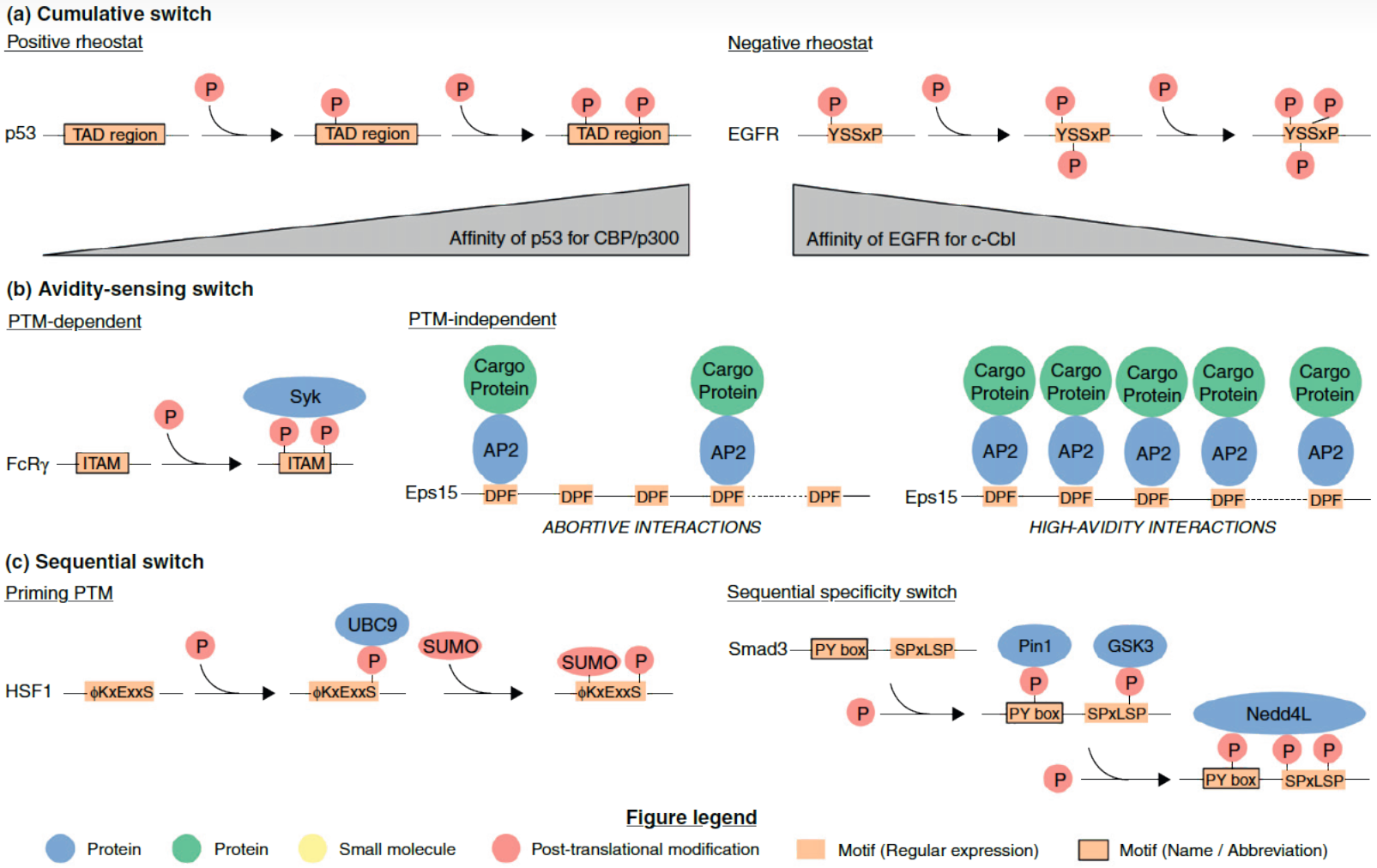
This makes SLiMs ideal regulatory modules and enable them to conditionally **switch** between “on” and “off” states or between multiple, functionally distinct on states.

”The switches.ELM Resource: A Compendium of Conditional Regulatory Interaction Interfaces“; van Roey, Dinkel, Weatheritt, Gibson and Davey; (Science Signaling. 2013)

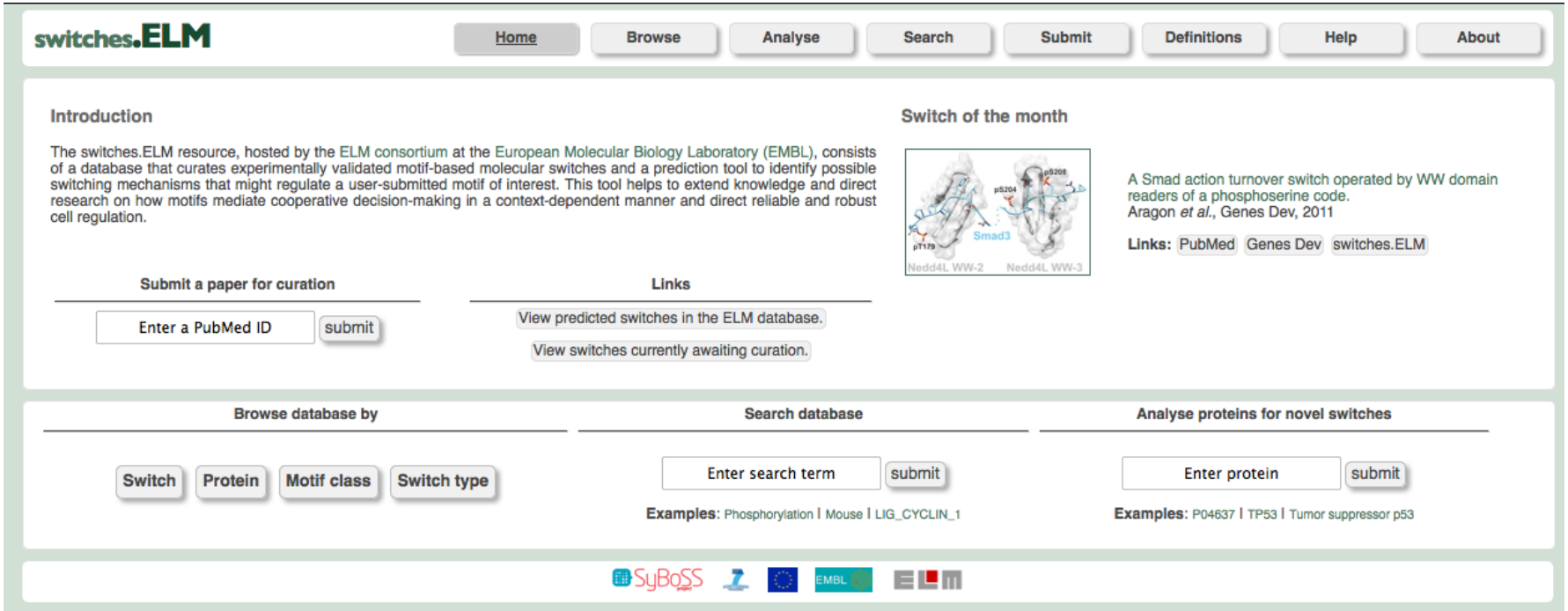

PTM-induced binding
P
P
LAT
YxxL
YxxL
PLCγ1


PTM-induced incompatibility
P
P
NFATc1
NLS
NLS
CYTOPLASM
NUCLEUS


(a) Binary switch
PTM-induced binding
LAT
YxxL
P
YxxL
PLCγ1
PTM-induced incompatibility
NFATc1
NLS
P
NLS
P
CYTOPLASM
NUCLEUS
Allostery
Recoverin
Myristoyl
MGxxxSx
Ca2+
Myristoyl
MGxxxSx
Ca2+
CYTOPLASM
PLASMA MEMBRANE
(b) Specificity switch
Intrinsic affinity switch
talin
P
NPxY
Integrin β3
Dok 1
P
NPxY
Integrin β3
Competition switch
Rb
KKLxF
CCN-CDK
Rb
KKLxF
PP1
CCN-CDK
PP1
Local abundance
Localisation switch
NON-RAFT MEMBRANE
LIPID RAFT MEMBRANE
CD2
Tandem PPPPGHR
CD2BP2
CD2 ligand
CD2
Tandem PPPPGHR
Fyn
(c) Motif hiding
PTM-independent
MRTF
RPEL
NLS
G-actin
G-actin
RPEL
NLS
CYTOPLASM
NUCLEUS
PTM-dependent
LT-AG
NLS
P
BRAP2
P
NLS
CYTOPLASM
NUCLEUS
Figure legend
Protein
Protein
Small molecule
Post-translational modification
Motif (Regular expression)
Motif (Name / Abbreviation)


(a) Cumulative switch
Positive rheostat
p53
TAD region
Affinity of p53 for CBP/p300
Negative rheostat
EGFR
YSSxP
Affinity of EGFR for c-Cbl
(b) Avidity-sensing switch
PTM-dependent
FcRγ
ITAM
Syk
PTM-independent
Cargo Protein
AP2
Eps15
DPF
ABORTIVE INTERACTIONS
HIGH-AVIDITY INTERACTIONS
(c) Sequential switch
Priming PTM
HSF1
ϕKxExxS
UBC9
SUMO
Sequential specificity switch
Smad3
PY box
SPxLSP
Pin1
GSK3
Nedd4L
Figure legend
Protein
Protein
Small molecule
Post-translational modification
Motif (Regular expression)
Motif (Name / Abbreviation)

The switches.ELM **database** curates experimentally validated motif-based molecular switches.
In addition, based on these validated instances, the switches.ELM **prediction** tool was developed to identify possible switching mechanisms that might regulate a motif-containing protein of interest.



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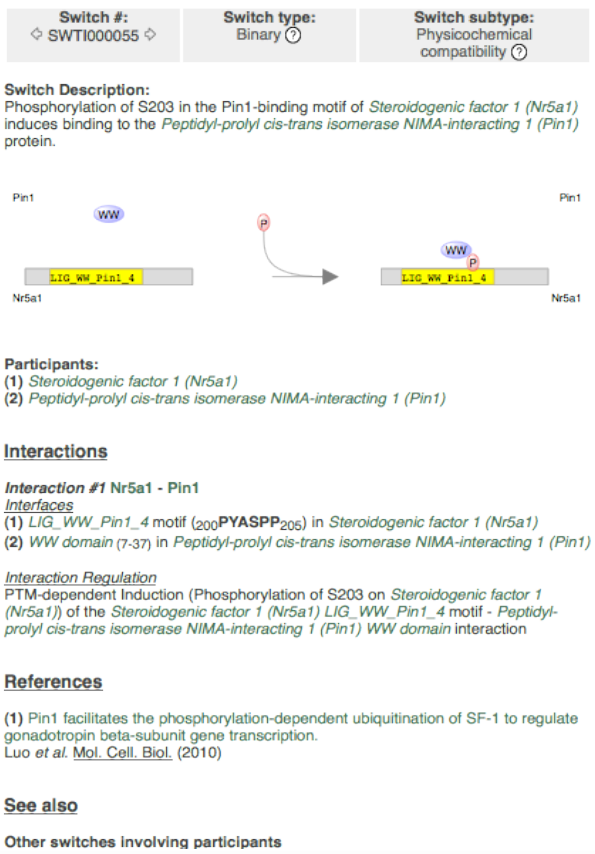

Switch #:	Switch type:	Switch subtype:
◇ SWTI000055 ◇	Binary ?	Physicochemical compatibility ?

Switch Description:
Phosphorylation of S203 in the Pin1-binding motif of *Steroidogenic factor 1 (Nr5a1)* induces binding to the *Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1)* protein.

Participants:
(1) *Steroidogenic factor 1 (Nr5a1)*
(2) *Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1)*

Interactions

Interaction #1 **Nr5a1 - Pin1**
Interfaces
(1) *LIG_WW_Pin1_4* motif ($_{200}$**PYASPP**$_{205}$) in *Steroidogenic factor 1 (Nr5a1)*
(2) *WW domain* $_{(7\text{-}37)}$ in *Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1)*

Interaction Regulation
PTM-dependent Induction (Phosphorylation of S203 on *Steroidogenic factor 1 (Nr5a1)*) of the *Steroidogenic factor 1 (Nr5a1) LIG_WW_Pin1_4* motif - *Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) WW domain* interaction

References

(1) Pin1 facilitates the phosphorylation-dependent ubiquitination of SF-1 to regulate gonadotropin beta-subunit gene transcription.
Luo *et al.* Mol. Cell. Biol. (2010)

See also

Other switches involving participants

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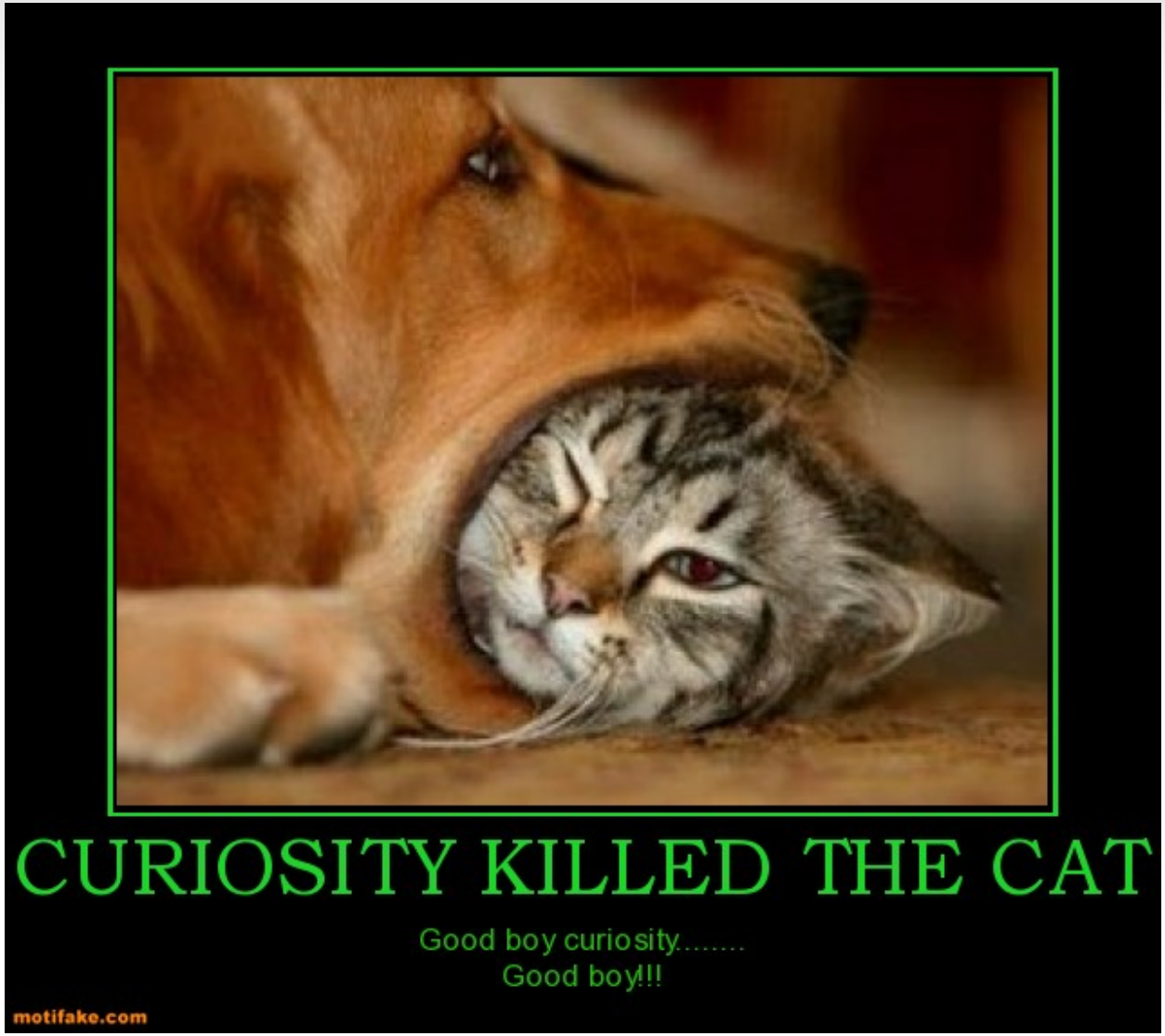
Questions?


CURIOSITY KILLED THE CAT
Good boy curiosity.....
Good boy!!!
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