

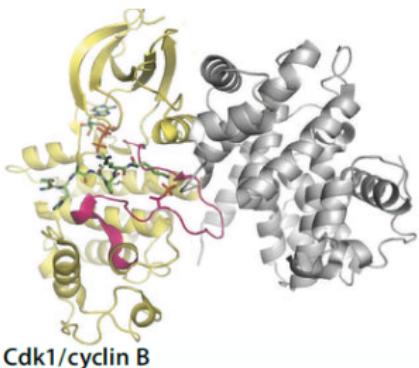
## Tools & Databases of Short Linear Motifs

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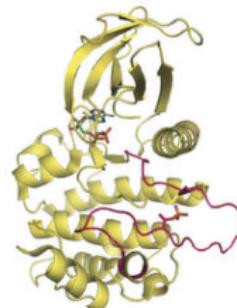
Holger Dinkel

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

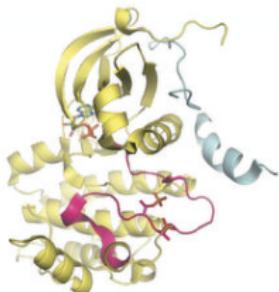
## Protein Phosphorylation Sites



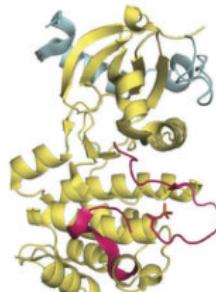
Cdk1/cyclin B



Plk1



Aurora A/TPX2

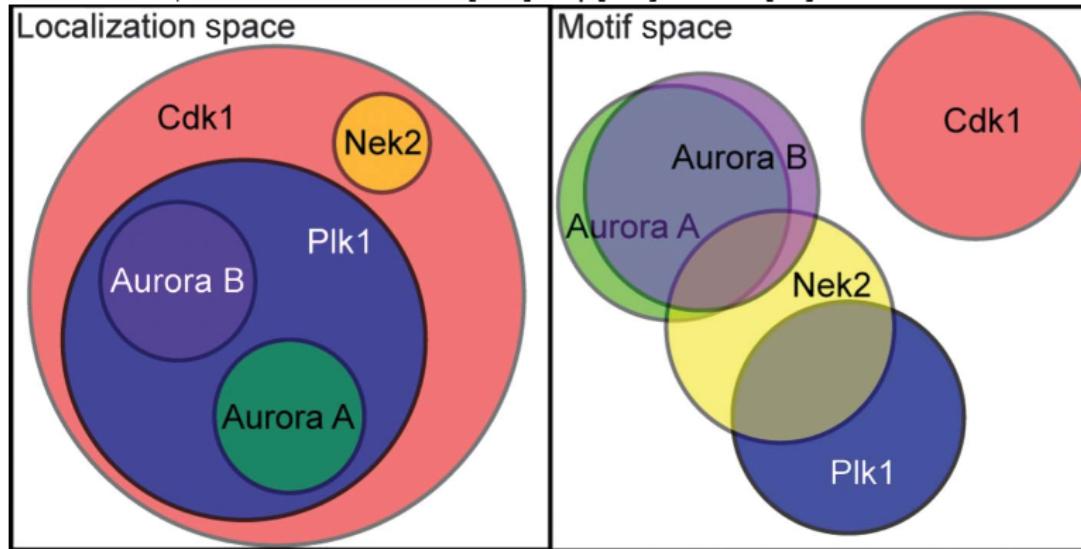


Aurora B/INCENP

"Spatial exclusivity combined with positive and negative selection of phosphorylation motifs is the basis for

## Protein Phosphorylation Sites

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



## 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

**Home** **PhosphoBlast** **Contribute** **Download** **Help** **Links** **About**

## SEARCH

- 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):

- by selected phospho-peptide binding domain (List):

- Choose which organisms to include  
 All  
 Caenorhabditis  
 Drosophila  
 Vertebrates

# Phospho.ELM

a database of S/T/Y phosphorylation sites

Substrate: Cyclin dependent kinase inhibitor 1B (Cyclin-dependent kinase inhibitor 1B (Cyclin-dependent kinase p46S27 [Homo sapiens])

Seq-ID: 14048527

Interaction Networks: STRING, NetworKIN

External Sources: MINT Interactions: [show]

[View Conservation](#)

```

PHESTIDEDEA_HUMAN-296
substrate,PHESTIDEDEA_HUMAN-296
substrate,PHESTIDEDEA_HUMAN-297
substrate,REVILIE_CD103-199
substrate,REVILIE_CD103-200
substrate,REVILIE_CD103-201
substrate,REVILIE_CD103-290
substrate,REVILIE_CD103-291
substrate,REVILIE_CD103-292
substrate,REVILIE_CD103-293
substrate,REVILIE_CD103-294
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substrate,REVILIE_CD103-321
substrate,REVILIE_CD103-322

```

Disorder tendency query sequence

MOD\_CK2\_1

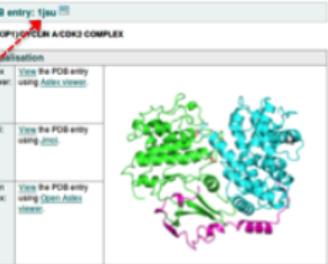
The ELM server [ELM details](#)

CK2 phosphorylation site  
Motif recognized by CK2 for Ser/Thr phosphorylation  
MOD\_CK2\_1  
The main determinant of CK2 phosphorylation specificity is a negative charge 3 positions after the modification residue  
Pattern: -S/T-P-  
Present in taxonomy: Not represented in taxonomy

[View Conservation](#)

Click on table headers for sorting

Res. #	Pos. #	Sequence	Kinase	PMID #	Src	Cons. #	ELM	Binding Domain	SMART/PIBM	IUPRED score	PDB #	PDB Acc.
S	10	R <b>S</b> EPTIDE <b>D</b> E <b>A</b>		12492075	LTP	0.08	-	-	-	0.74	-	-
S	10	R <b>S</b> EPTIDE <b>D</b> E <b>A</b>		145061280	LTP	0.08	-	-	-	0.74	-	-
S	10	R <b>S</b> EPTIDE <b>D</b> E <b>A</b>		187385781	LTP	0.08	-	-	-	0.74	-	-
S	10	R <b>S</b> EPTIDE <b>D</b> E <b>A</b>		188420114	LTP	0.08	-	-	-	0.74	-	-
S	10	R <b>S</b> EPTIDE <b>D</b> E <b>A</b>		188609386	HTP	0.08	-	-	-	0.74	-	-
S	10	R <b>S</b> EPTIDE <b>D</b> E <b>A</b>	PKB_group	167809393	LTP	0.08	-	-	-	0.74	-	-
S	10	R <b>S</b> EPTIDE <b>D</b> E <b>A</b>	KIS	12693740	LTP	0.08	-	-	-	0.74	-	-
T	74	P <b>R</b> EPTIDE <b>D</b> E <b>A</b>		18464177	LTP	1.00	-	-	-	0.64	-	-
Y	74	P <b>R</b> EPTIDE <b>D</b> E <b>A</b>	SRC	17254967	LTP	1.00	-	-	-	0.64	-	-
S	83	E <b>I</b> KEPTIDE <b>D</b> E <b>A</b>		15934903	HTP	0.18	MOD_CK2_1	-	-	0.57	1JBU	85.87%
Y	88	E <b>V</b> EPTIDE <b>D</b> E <b>A</b>		17254986	LTP	1.00	-	-	-	0.65	1JBU	70.31%
Y	88	E <b>V</b> EPTIDE <b>D</b> E <b>A</b>		18193327	LTP	1.00	-	-	-	0.65	1JBU	70.31%
Y	88	E <b>V</b> EPTIDE <b>D</b> E <b>A</b>	SRC	17254967	LTP	1.00	-	-	-	0.65	1JBU	70.31%
Y	88	E <b>V</b> EPTIDE <b>D</b> E <b>A</b>		18193327	LTP	0.22	-	-	-	0.63	1JBU	36.68%
Y	88	E <b>V</b> EPTIDE <b>D</b> E <b>A</b>	SRC	17254967	LTP	0.22	-	-	-	0.63	1JBU	36.68%
S	140	L <b>R</b> EPTIDE <b>D</b> E <b>A</b>		175205332	HTP	0.85	-	-	-	0.77	-	-
T	157	G <b>C</b> AKTIDE <b>D</b> E <b>A</b>	PKB_group	12344303	LTP	0.94	MOD_PKB_1	-	-	0.84	-	-
T	157	G <b>C</b> AKTIDE <b>D</b> E <b>A</b>	PKB_group	12244302	LTP	0.94	MOD_PKB_1	-	-	0.84	-	-
T	157	G <b>C</b> AKTIDE <b>D</b> E <b>A</b>	PKB_group	12344301	LTP	0.94	MOD_PKB_1	-	-	0.84	-	-
S	178	E <b>T</b> EPIDE <b>D</b> E <b>A</b>	MAPK1	10831586	LTP	0.15	MOD_ProtMAPK_1	-	-	0.94	-	-
T	187	G <b>R</b> EPIDE <b>D</b> E <b>A</b>		187385781	LTP	1.00	MOD_CDK_1	-	-	0.95	-	-
T	187	G <b>R</b> EPIDE <b>D</b> E <b>A</b>		188420114	LTP	1.00	MOD_CDK_1	-	-	0.95	-	-
T	187	G <b>R</b> EPIDE <b>D</b> E <b>A</b>		188609386	LTP	1.00	MOD_CDK_1	-	-	0.95	-	-
T	187	G <b>R</b> EPIDE <b>D</b> E <b>A</b>	CDK2	170980333	LTP	1.00	MOD_CDK_1	-	-	0.95	-	-
T	188	F <b>R</b> EPTIDE <b>D</b> E <b>A</b>		18042314	LTP	0.00	-	Y18NAQ	14-3-3	0.94	-	-
T	188	F <b>R</b> EPTIDE <b>D</b> E <b>A</b>	RSK	14094289	LTP	0.00	-	Y18NAQ	14-3-3	0.94	-	-
T	188	F <b>R</b> EPTIDE <b>D</b> E <b>A</b>	RSK-2	14094289	LTP	0.00	-	Y18NAQ	14-3-3	0.94	-	-



phospho3D

pT2TKP10/CDYLN A/CDKLX complex				
Line	Protein	Residues (aa)	Biochemical reactivities	bioRxiv doi
C-141	1jbu	18042314	modif18042314	bioRxiv doi
C-140	1jbu	18042314	modif18042314	bioRxiv doi
C-139	1jbu	18042314	modif18042314	bioRxiv doi

### Links to:

- STRING
- NetworKin
- Phosida
- Phospho3D

### Display:

- MINT interactions
- GO-Terms

Substrate:

Caspase 9 (Cysteine protease)

Seq-ID:

P55211 [*Homo sapiens*]

Interaction Network(s):

 STRING  NetworKin

External Source(s):

 PHOSIDA

[hide]

MINT-15372 APAF\_HUMAN

MINT-18815 CASP3\_HUMAN

MINT-25026 XIAP\_HUMAN

[hide]

**Molecular Function**

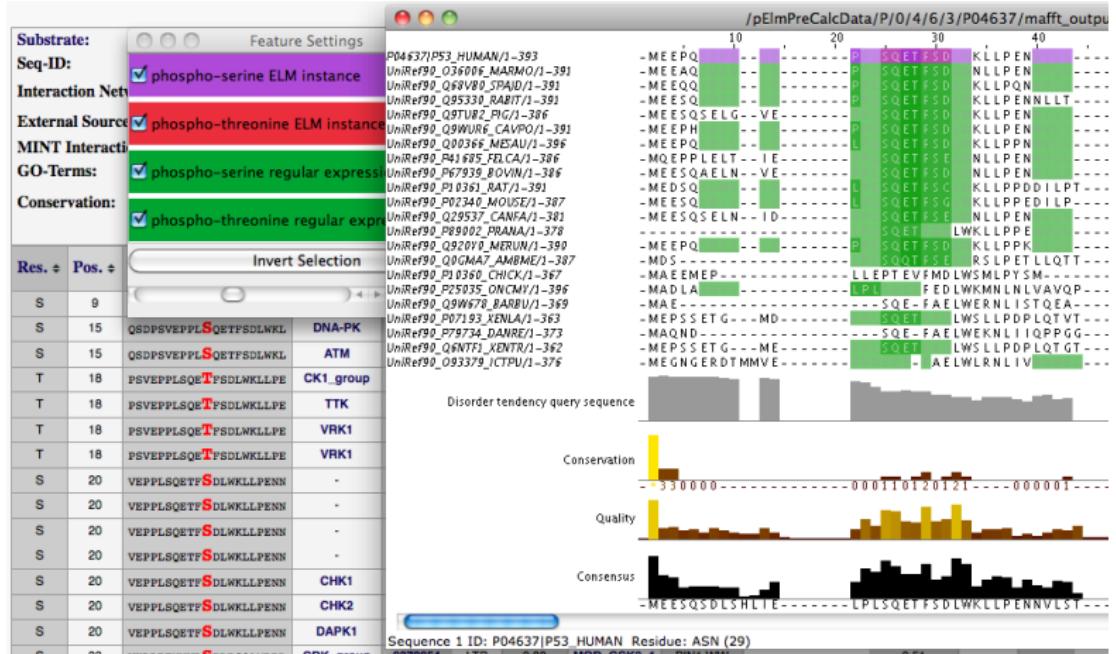
cysteine-type endopeptidase activity,  
protein binding,  
enzyme activator activity

GO-Terms:

# View Conservation in Jalview

# Phospho.ELM

Precalculated conservation scores for the phosphorylation sites

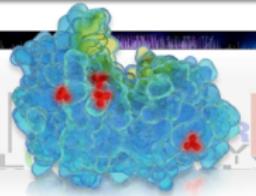




PhosphoSitePlus<sup>®</sup> (PSP) is an online systems biology resource providing comprehensive information and tools for the study of protein post-translational modifications (PTMs) including phosphorylation, ubiquitination, acetylation and methylation. See [About PhosphoSite](#) above for more information.

Please cite the following reference for this resource: Horbeck PV, et al. (2012) Nucleic Acids Res. 2012 40:D261-70. [epub]

## A PROTEIN MODIFICATION RESOURCE



### PROTEIN OR SUBSTRATE SEARCH

Protein Name: ▾ p53

**SEARCH**

### ADVANCED SEARCH AND BROWSE OPTIONS



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[Browse MS2 Data By Disease](#)



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[Browse MS2 Data by Tissue](#)

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### WHAT'S NEW

Aug 2014 [Download PTM-VarMut dataset](#): Overlap of disease missense mutations & genetic variants, with their corresponding PTMs and flanking sequences.

Jul 2012 [Download Datasets of Regulatory or Disease-Associated Sites](#).

Dec 2011 [Download "PhosphoSitePlus: a comprehensive resource..."](#) in January 2012 issue of *Nucleic Acids Research*.

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	Caspase cleavage:	481
Di-methylation:	2,555	Methylation:	163
Mono-methylation:	4,992	O-GalNAC:	2,118
O-GlcNAc:	1,390	Succinylation:	4,657
Sumoylation:	816	Tri-methylation:	321
Ubiquitination:	51,255		



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## The Eukaryotic Linear Motif resource for Functional Sites in Proteins

### The ELM resource

is a collection of nearly 200 thoroughly annotated motif classes with over 2400 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.

Functional Sites	ELM classes	ELM instances	PDB structures	GO terms
Total	127	197	2404	290
By category	LIG	103	Human	1391
	MOD	30	Mouse	211
	TRG	23	Rat	115
	DEG	15	Yeast	86
	DOC	15	Fly	77
	CLV	11	Other	524
				Biological Process
				Cell Compartment
				Molecular Function

# The ELM Database



## ELM Class

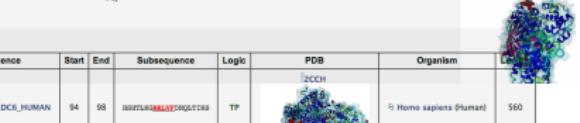
Condensed information about a motif. Regular Expressions used to annotate the motif (eg. "[KR]xLx{0,1}[FYLIVMP] for Cyclin motif)

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	KEV.	Organism	Notes
IRB_HUMAN	IRB1	873	877	RRRRRFL <b>KLQLP</b> EDDQEEKA	TP	3	Homo sapiens (Human)	1H2S 14
QUINW_H_CHICK	CDH1-A	394	398	R <b>LQDQEV</b> RLA <b>PLAMQPSR</b>	TP	1	Gallus gallus (Chicken)	
PWTT1_HUMAN	PWTT1	486	489	D <b>PPPFPE</b> PL <b>LLKCP</b> PSR	TP	1	Homo sapiens (Human)	
E2F1_HUMAN	E2F1	90	94	L <b>QDRFPV</b> PL <b>LLKCP</b> PSR	TP	3	Homo sapiens (Human)	1H24
CDN1C_HUMAN	CDKN1C	31	34	V <b>LVEPTEAK</b> PL <b>LLKCP</b> PSR	TP	1	Homo sapiens (Human)	
RUX_DROSOPHILA	rux	248	251	PTAKR <b>QV</b> PL <b>LLKCP</b> PSR	TP	1	Drosophila melanogaster (Fruit fly)	
E2F2_HUMAN	E2F2	87	91	A <b>GKLFAN</b> PL <b>LLKCP</b> PSR	TP	1	Homo sapiens (Human)	
E2F3_HUMAN	E2F3	134	138	D <b>GGPFAM</b> PL <b>LLKCP</b> PSR	TP	1	Homo sapiens (Human)	
AKAP12_MOUSE	AKap12	501	504	I <b>ERQEPK</b> PL <b>LLKCP</b> PSR	TP	1	Mus musculus (House mouse)	1A
CDCS_HUMAN	CDCS	94	98	H <b>BETTLPK</b> PL <b>LLKCP</b> PSR	TP	2	Homo sapiens (Human)	2CCH 14
CDN1A_HUMAN	CDKN1A	19	22	M <b>PQDKAC</b> PL <b>LLKCP</b> PSR	TP	4	Homo sapiens (Human)	1H26 14
CDN1A_HUMAN	CDKN1A	155	159	R <b>HEPESPKR</b> PL <b>LLKCP</b> PSR	TN	1	Homo sapiens (Human)	
ORC6_YEAST	ORC6	178	182	R <b>SPEPTEAK</b> PL <b>LLKCP</b> PSR	TP	1	Saccharomyces cerevisiae (Baker's yeast)	
PS2_HUMAN	TP53	381	385	Q <b>QPTTKE</b> PL <b>LLKCP</b> PSR	TP	5	Homo sapiens (Human)	1H26
IRBL1_HUMAN	IRBL1	658	661	E <b>PENPKAK</b> PL <b>LLKCP</b> PSR	TP	3	Homo sapiens (Human)	1H28
IRBL2_HUMAN	IRBL2	680	684	P <b>PAAPTKE</b> PL <b>LLKCP</b> PSR	TP	1	Homo sapiens (Human)	
IRRA_HUMAN	IRRA	629	633	K <b>AKSLAK</b> PL <b>LLKCP</b> PSR	TP	1	Homo sapiens (Human)	

## DOC\_CYCLIN\_1

**Functional site class:** Cyclin recognition site  
**Functional site description:** Functional site that interacts with cyclins, and thereby increases the specificity of phosphorylation by cyclin/CDK complexes.  
**ELM with this model:** DOC\_CYCLIN\_1  
**Description:** Substrate recognition site that interacts with cyclin and thereby increases phosphorylation by cyclin/cdk complexes. Selected proteins should have a CDK phosphorylation site (MOD\_CDk\_4). Also used by cyclin/cdk inhibitors.  
**Pattern:** [KR] . L . [D, E] {0, 1} [FYLIVMP]  
**Pattern Probability:** 0.0032329  
**Present in taxon:** Eukaryote  
**Interaction Domain:** Cyclin\_N (PF00134) Cyclin, N-terminal domain (Stoichiometry: 1 : 1)  
**PDB Structure:** 1H24



## ELM Instance

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

- Experimental Evidences
- Methods
- References
- Interactions

[TRG\\_AP2beta\\_CARGO\\_1](#)

&lt;&lt; MOD\_WntLipid &lt;&lt;

Menu

>> [TRG\\_Cilium\\_Arf4\\_1](#) >>**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.**ELMs:****Description:**[TRG\\_AP2beta\\_CARGO\\_1](#)

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

(Probability: 0.0000182)

**Present in taxons:**

Metazoa

PDB Structure: [2IV8](#)**Interaction Domain:**[B2-adapt-app\\_C \(PF09066\)](#)Beta2-adaptin appendage, C-terminal sub-domain  
(Stoichiometry: 1 : 1)■ See 4 Instances for [TRG\\_AP2beta\\_CARGO\\_1](#)■ **Abstract**

At least two different surfaces of the AP-2 beta2 appendage domain can bind linear motifs in other endocytic regulatory proteins. The platform subdomain or top surface binds a helical [ED]x(1,2)Fxx[FL]xxxR motif found in Epsin-1 and -2 which bind ubiquitinated growth factor receptors, the beta-arrestins which bind GPCRs and ARH which binds LDL receptor family members. All of these function as cargo-selective clathrin adaptors, targeting surface receptors for internalization by clathrin-mediated endocytosis.

In beta-arrestin, the cargo motif is regulated by a remarkable structural rearrangement. The motif maintains the endocytosis-incompetent state by

## 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, Weatheritt RJ, Dinkel H, Davey NE, Gibson TJ, (2014) Mol Biosyst.

### Noonan Syndrome

The developmental disorder "Noonan Syndrome" can be caused by mutations in [DRaf-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 [DRaf-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*" (FHHN), an autosomal recessive wasting disorder of renal Mg<sup>2+</sup> and Ca<sup>2+</sup> 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 [OZO-1](#) resulting in lysosomal mislocalization of the protein [[Müller et al., 2003](#), [Müller et al., 2006](#)].

## ELM database:Viruses



# The Eukaryotic Linear Motif resource for *Functional Sites in Proteins*

# ELM prediction tool

ELM



The Eukaryotic Linear Motif resource for  
*Functional Sites in Proteins*

Search ELMs Instances Candidates Links About News Help Diseases Viruses

## Functional site prediction

### Protein sequence

Enter Uniprot identifier or accession number: (auto-completion)

e.g. [EPN1\\_HUMAN](#), [P04637](#), [TAU\\_HUMAN](#)

EPN1

[EPN1\\_ARATH](#) [Q8VY07] Arabidopsis thaliana

[EPN1\\_HUMAN](#) [Q9Y6I3] Homo sapiens

[EPN1\\_MOUSE](#) [Q80VP1] Mus musculus

[EPN1\\_RAT](#) [O88339] Rattus norvegicus

RETGKEESSLMDLADVFATAPAPATTDPWGFPAPMAAVPTAAAPTSDPWGGPPVPPAADCWGGPAPTPASGDPWRPAAPAG  
PSVDPWGGTTPAPAAAGEGPTDWPWGSSDGGVPVSGPSPASDWPWTAPAPAFSDPWGGSPAKPSTNGTTAAGGFDTEPDEFSDFDRL  
RTALPTSGSAGELELLAGEVPARSPGAEDMSGVRSLEAEAVGSPPPAATPTPPTPKTPEFSLFLGPNAALVLDLSLVSPRG  
PTPPGAKASNPFLPGGGPATGSPVTFQAPPATLTNLNRLSPVPPVGAPPTYISPLGGPGLPPMPPGPPANPNFF  
LL.

### Cell compartment (one or several):

not specified  
extracellular  
nucleus  
cytosol  
peroxisome  
glycosome  
glyoxisome  
Golgi apparatus  
endoplasmic reticulum  
lysosome  
endosome  
plasma membrane  
mitochondrion

### Context information

Type in species name (auto-completion):

Homo sapiens

### Motif Probability Cutoff

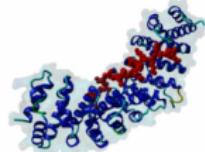
1

Submit

Reset Form

### Disclaimer

Short patterns applied to proteins are usually not statistically significant: Therefore we can't provide E-values as with BLAST searches. This means that most matches shown are more likely to be false positives than true matches. We hope that ELM server results will prove useful as guides to experimentation but they should not be treated as factual findings.



PDB-Structure [1PJM](#) showing a peptide from ELM class  
**TRG\_NLS\_Bipartite\_1**

- ELM database update  
One new ELM class has been annotated ([■ LIG\\_SPRY\\_1](#)) and existing ones have been updated:  
[■ LIG\\_Integrin\\_IsoDGR\\_1](#),  
[■ TRG\\_PEX](#),  
[■ LIG\\_Integrin\\_IsoDGR\\_1](#),  
[■ LIG\\_PCNA\\_PIPBox\\_1](#),  
[■ LIG\\_CRL4\\_Cdt2\\_1](#),  
[■ LIG\\_CtBP\\_PxDLS\\_1](#). Many new instances have been added to the database...
- ELM update paper published  
All the latest updates and improvements have been written up in the latest [ELM paper](#) (≈22110040)

### Featured paper:

"Caskin1, Mint1 and TIAM1 motif docking to the CASK hub kinase affecting brain, synapse, cell polarity."

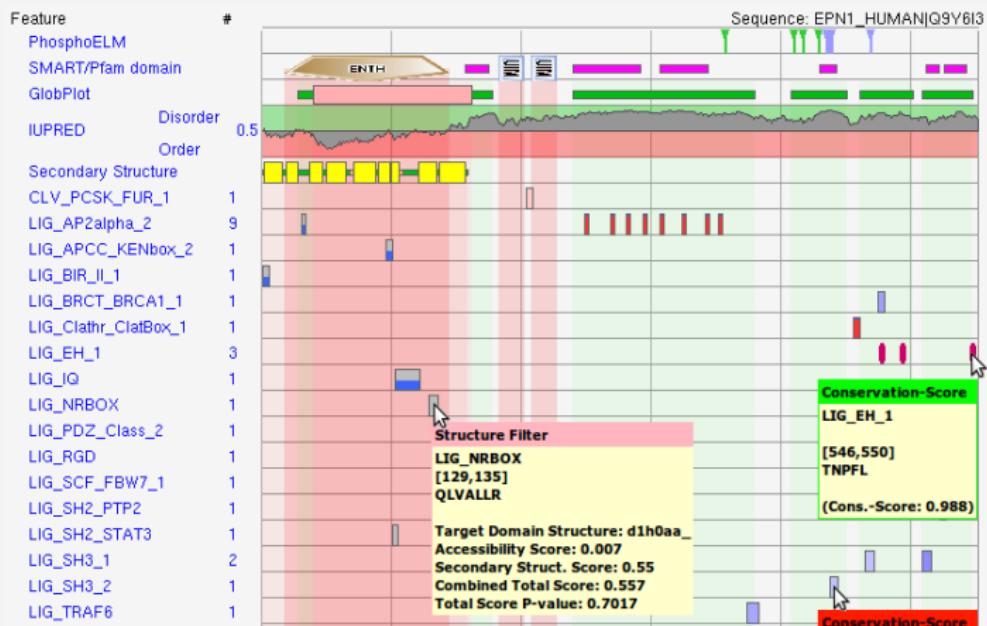
- Become an ELM sponsor?
- The ELM phosphorylation DB

## ■ Summary of features reported by the ELM resource.

### KEY

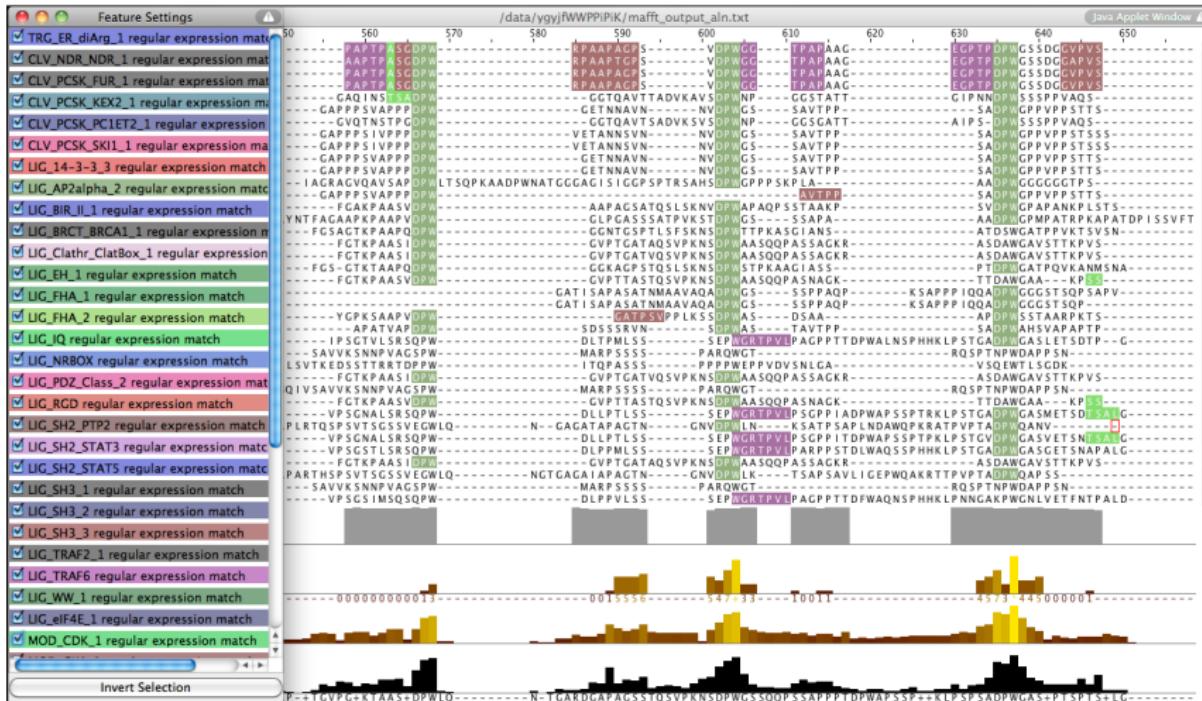
DOMAINS:	Smart/Pfam domain	Signal peptide (pred.)	Low-complexity region	Coiled-coil (pred.)	TM helix (pred.)
GLOBPLOT:	GlobDom		Disorder		
2D STRUCT:	Strand	Helix	Loop	3/10 Helix	
MOTIFS:	Favourable Context	Sparse/Smart filtered	Neutral	Annotated:	TP FP TN FN < Assigned by homology
CONSCORE:	low Conservation	medium Conservation	high Conservation		

(Mouseover the matches for more details )



# View Conservation in Jalview

ELM



# Linear Motifs as Molecular Switches

## 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

## Motif-mediated interactions

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

## 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.

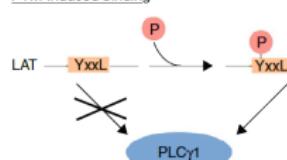
Motif Switching can be mediated by multiple mechanisms that often depend on posttranslational modifications and the cooperative or competitive use of multiple overlapping or adjacent SLiMs.

# Linear Motifs as Molecular Switches

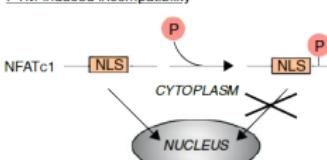
switches.ELM

## (a) Binary switch

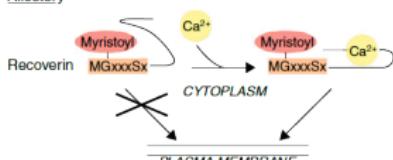
### PTM-induced binding



### PTM-induced incompatibility

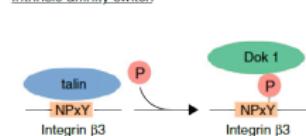


### Allotropy

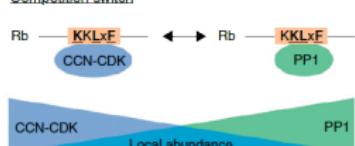


## (b) Specificity switch

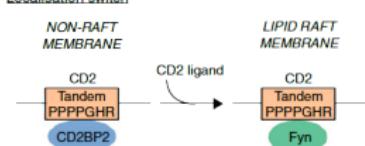
### Intrinsic affinity switch



### Competition switch

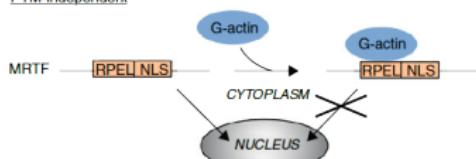


### Localisation switch



## (c) Motif hiding

### PTM-independent



### PTM-dependent

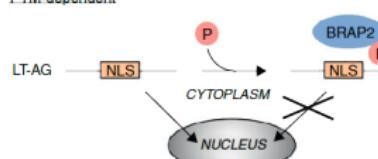


Figure legend

Protein

Protein

Small molecule

Post-translational modification

Motif (Regular expression)

Motif (Name / Abbreviation)

# Linear Motifs as Molecular Switches

switches.ELM

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.

Switch #: SWTI0000055 ◊

Switch type: Binary ◊

Switch subtype: 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<sub>206</sub>) in Steroidogenic factor 1 (Nr5a1)  
(2) WW domain 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  
Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) - 28 more (view)

Other switches involving interfaces  
LIG\_WW\_Pin1\_4 - 89 more (view)  
WW domain - 102 more (view)

**Steroidogenic factor 1 (Nr5a1)**

Alignment Mots Modification Switches Structure Mutation Isoforms SNPs Features Disorder

offset: 2182  
Motif of interest:

MOUSE ( toggle extra species )

MACM1  
BOVIN  
HUMAN  
MONDO  
PROTH  
CIOH  
DROME  
APIME  
CAEEL

**switches**

Modification switches:

ELM ( toggle predicted hits )

ELM regex:

modified residue

phosphoELM

phosphoSitePlus

secondary structure (+ details)

chain

cross-link

disorder

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hover over features for details