

SHORT LINEAR MOTIFS

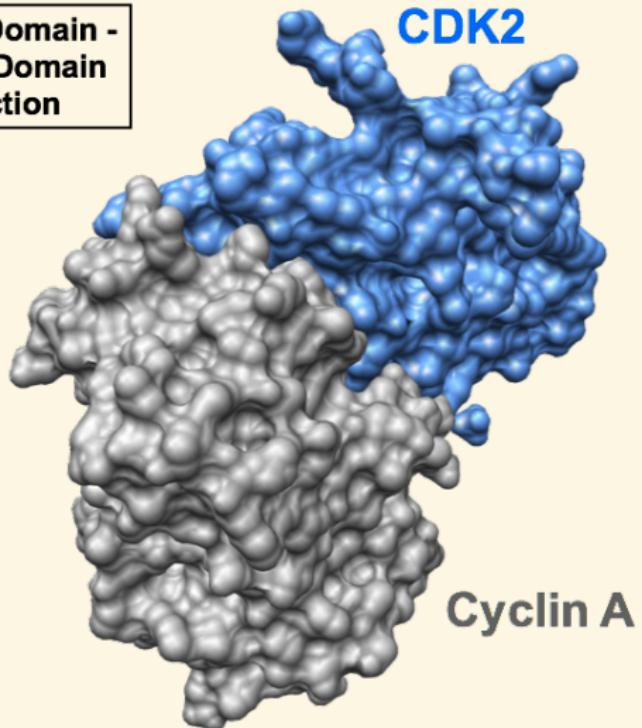
Holger Dinkel

EMBO Practical Course:
“Computational analysis of protein-protein interactions
in cell function and disease”

Bangalore, 04. 12. 2019

IMPORTANCE OF SHORT LINEAR MOTIFS

**Globular Domain -
Globular Domain
Interaction**

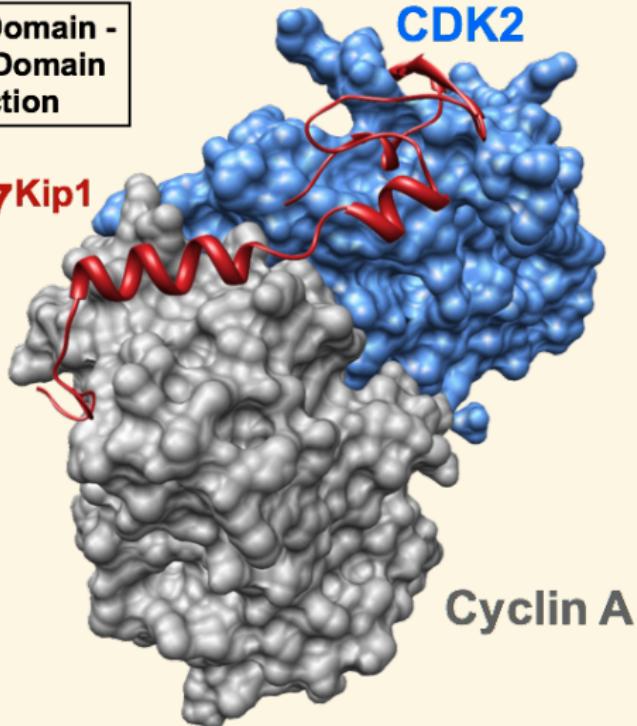


IMPORTANCE OF SHORT LINEAR MOTIFS

Globular Domain -
Disordered Domain
Interaction

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Globular Domain
Interaction

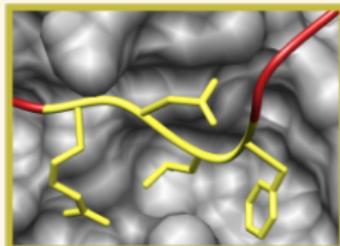
p27^{Kip1}



IMPORTANCE OF SHORT LINEAR MOTIFS

Globular Domain -
Disordered Domain
Interaction

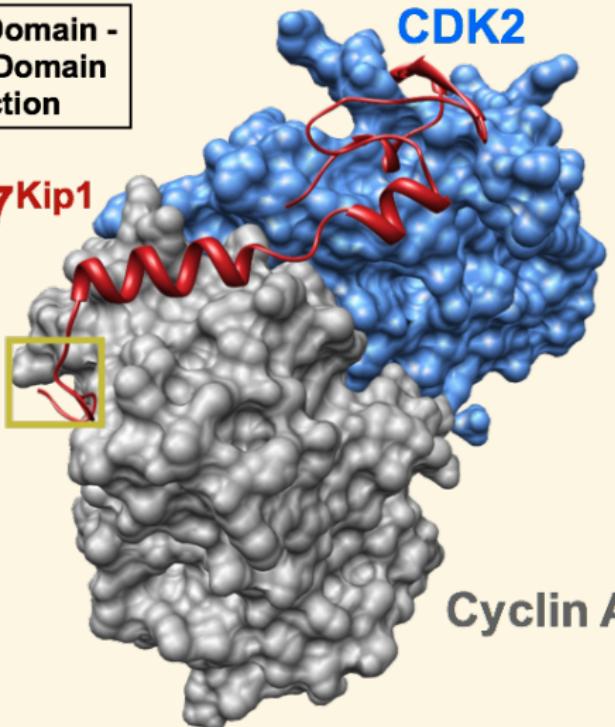
Globular Domain -
Short Linear Motif
Interaction



RNLF

Globular Domain -
Globular Domain
Interaction

p27Kip1



Cyclin A

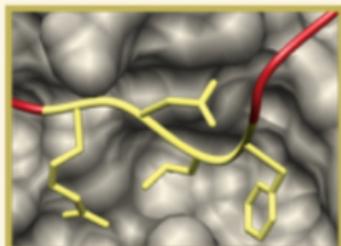
CDK2

IMPORTANCE OF SHORT LINEAR MOTIFS

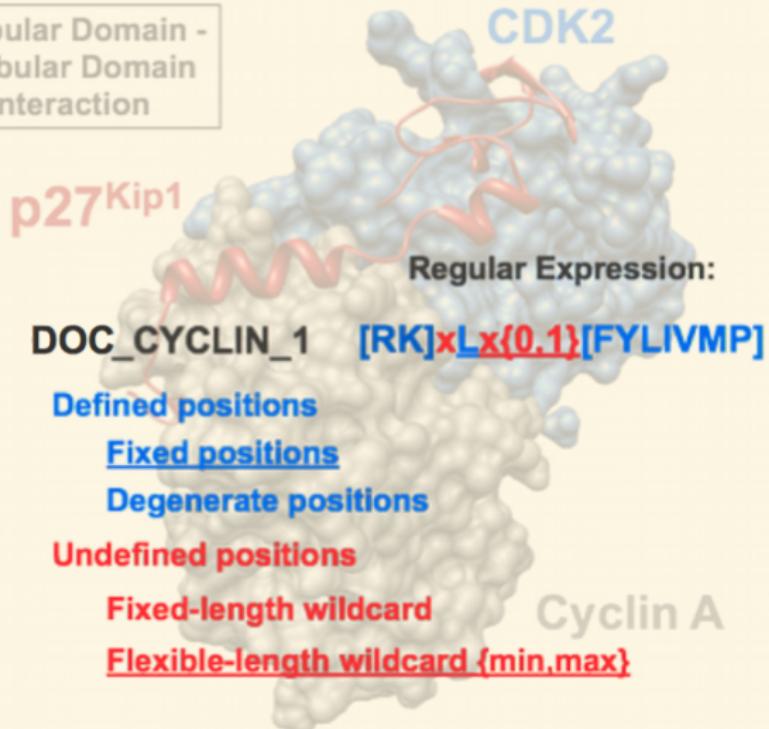
Globular Domain -
Disordered Domain
Interaction

Globular Domain -
Globular Domain
Interaction

PDB 1JSU
Russo *et al.*, Nature, 1996;
382: 325-331.



RNLF



REGULAR EXPRESSIONS ARE USED TO DESCRIBE SHORT LINEAR MOTIFS

Character Meaning

- . Any amino acid allowed
- [xy] Amino acids **listed** are allowed
- [^xy] Amino acids listed are **not** allowed
- {min,max} **Min** required, **max** allowed
 - ^ Matches the **amino** terminal
 - \$ Matches the **carboxy** terminal
- ab||cd Matches **either** expression it separates
- (xy) Used to mark positions of specific interest (amino acid being covalently modified) or to group parts of the expression

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DOC_CYCLIN_1

[RK].L.{0,1}[FYLIVMP]

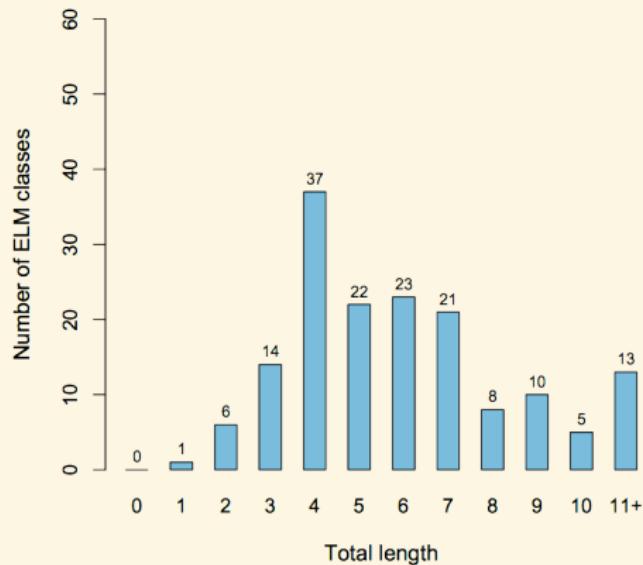
has been replaced by the more specific DOC_CYCLIN_RxL_1:

(.||([KRH].{0,3}))[^EDWNSG][^D] L.{0,1}[FLMP].{0,3}[EDST]

ATTRIBUTES OF SHORT LINEAR MOTIFS

LINEAR MOTIFS

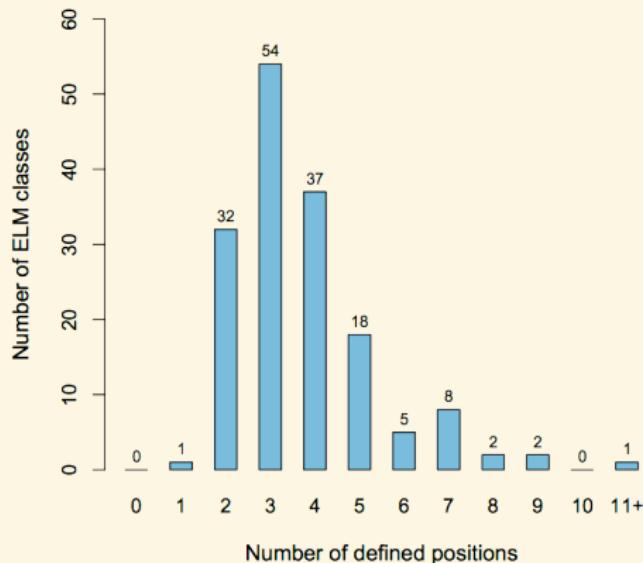
- are small.
- have few defined positions.
- mediate transient, low affinity interactions.



ATTRIBUTES OF SHORT LINEAR MOTIFS

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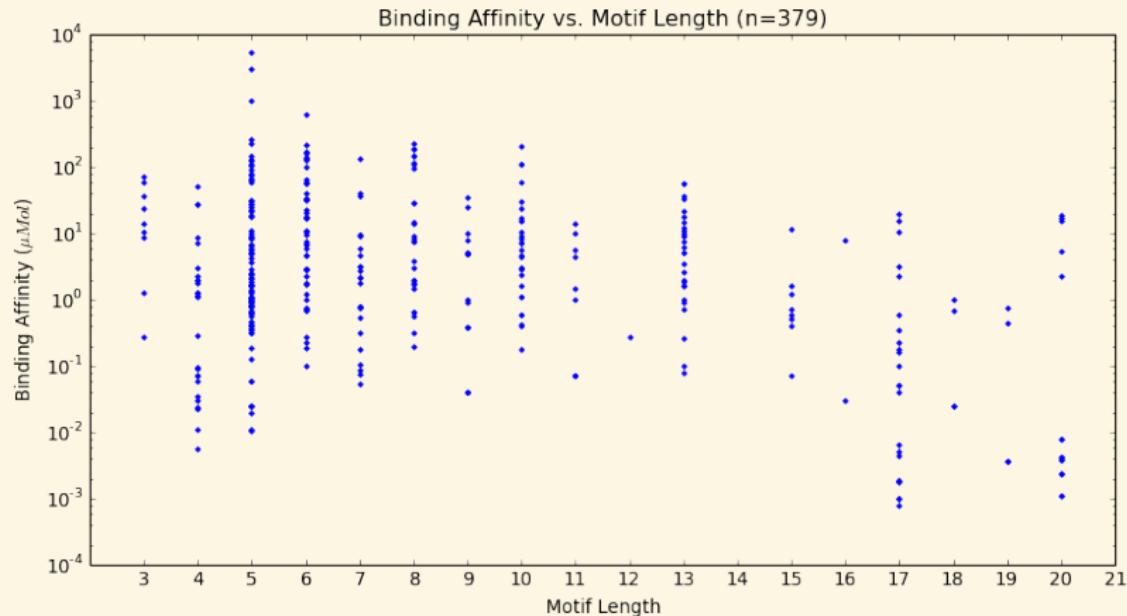
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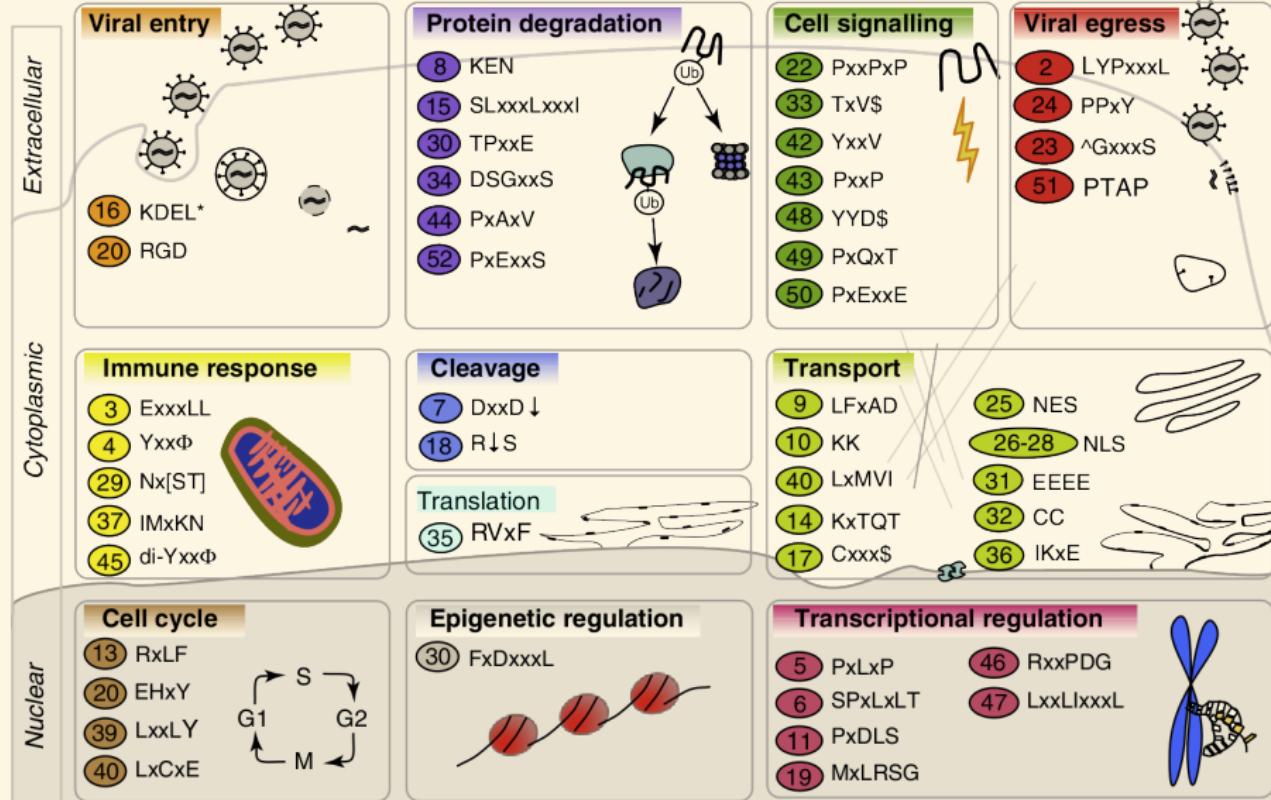
ATTRIBUTES OF SHORT LINEAR MOTIFS

LINEAR MOTIFS

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- have few defined positions.
- mediate transient, low affinity interactions.



IMPORTANCE OF SHORT LINEAR MOTIFS: VIRUSES



"How viruses hijack cell regulation"; DAVEY, TRAVÉ & GIBSON; (TIBS 2010)

IMPORTANCE OF SHORT LINEAR MOTIFS: DISEASES

LIDDLE'S-SYNDROME: WW-INTERACTION MOTIF

has been implicated with autosomal dominant activating mutations in the WW interaction motif in the β - and γ -subunits of the epithelial sodium channel ENAC. These mutations abrogate the binding to the ubiquitin ligase NEDD4-2, ultimately resulting in increased Na^+ reabsorption, plasma volume extension and hypertension.

IMPORTANCE OF SHORT LINEAR MOTIFS: DISEASES

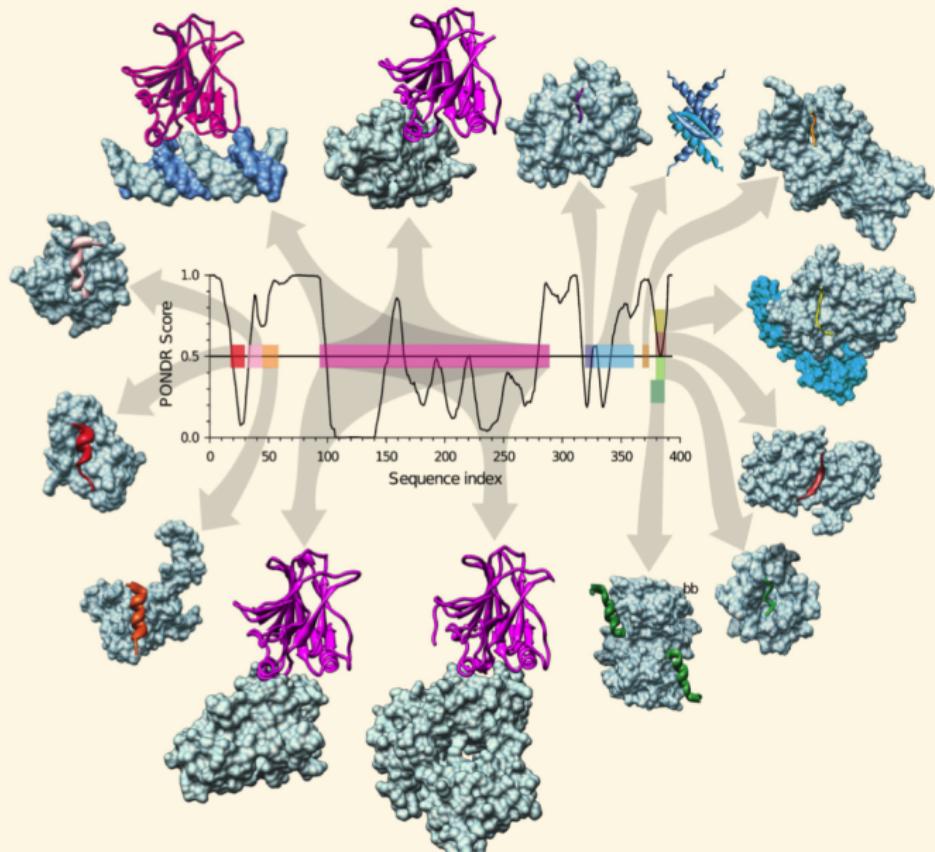
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BACILLUS ANTHRACIS “LETHAL FACTOR”

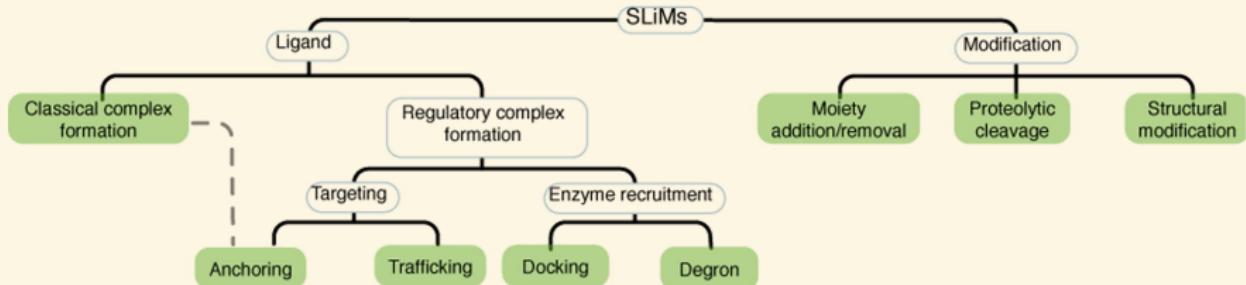
The protein LEF_BACAN is a metalloprotease (one of the three proteins composing the anthrax toxin) that specifically targets mitogen-activated protein kinase kinases (MKKs), which are important regulators of signal transduction as they phosphorylate and thus activate specific MAPKs (such as ERK1, ERK2, p38 or JNK). *Bacillus anthracis*’ “lethal factor” cleaves its MKK substrates within or close to the MAPK docking sites, thus effectively preventing the MKK to dock to its MAPK.

IMPORTANCE OF SHORT LINEAR MOTIFS: P53



"Understanding protein non-folding"; UVERSKY & DUNKER; (BIOCHIMICA ET BIOPHYSICA ACTA 2010)

CLASSIFICATION OF MOTIFS



MOTIF CLASSES: MODIFICATION SITES

DESCRIPTION:

Modification Motifs mediate specific binding to the active site of a modifying enzyme to allow subsequent catalytic post-translational modification of the target site.

EXAMPLE:

NAME MOD_CDK_1
REGEx ...([ST])P.[KR]

Kinase domain

CDK site

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Kinase domain

P
CDK site

MOTIF CLASSES: DOCKING MOTIFS

DESCRIPTION:

Docking motifs recruit enzymes via a surface that is distinct from the active site.

EXAMPLE:

NAME DOC_CYCLIN_1
REGEx [RK].L.{0,1}[LFY]



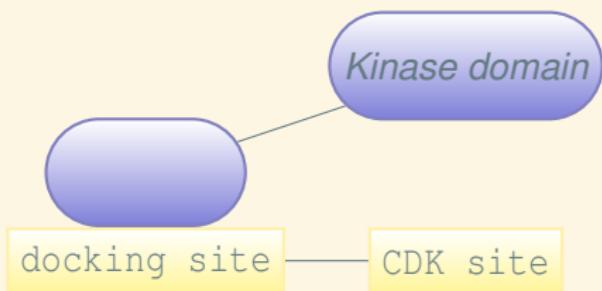
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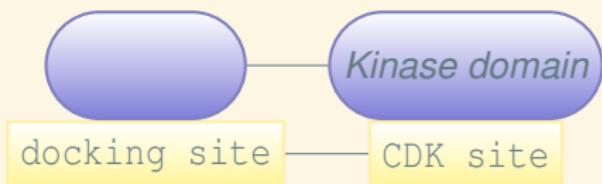
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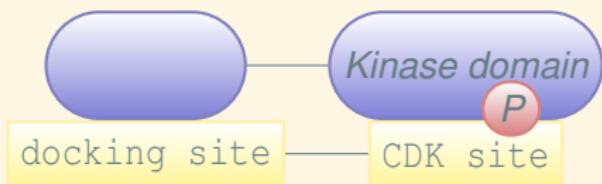
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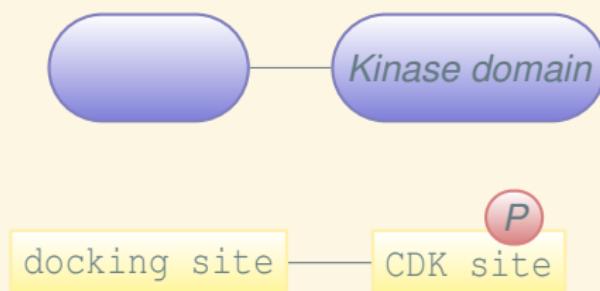
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MOTIF CLASSES: CLEAVAGE MOTIFS

DESCRIPTION:

Proteolytic processing of proteins into smaller polypeptides by protease-catalyzed hydrolysis of specific peptide bonds

EXAMPLE:

NAME CLV_Separin_Metazoa
REGEx $E[IMPVL][MLVP]R.$



— Cleavage site —

A yellow horizontal bar with the words "Cleavage site" centered in a white sans-serif font, flanked by two short black horizontal lines extending to the left and right.

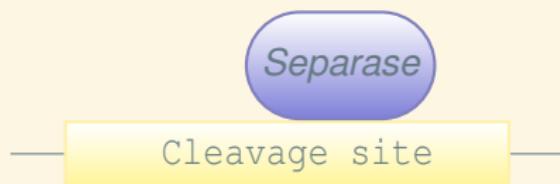
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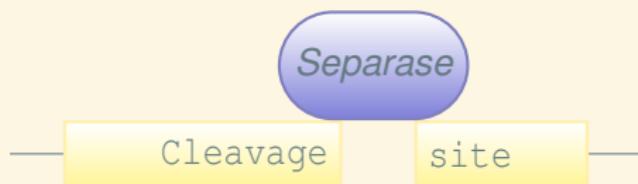
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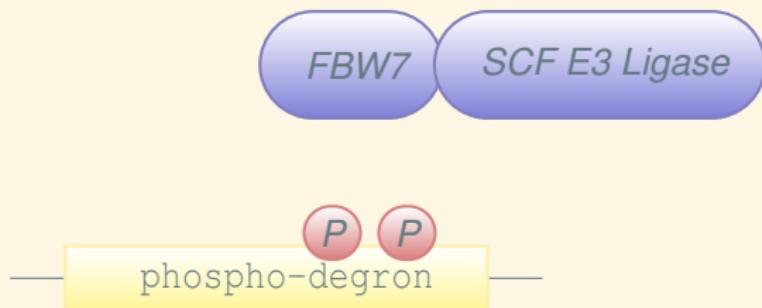
MOTIF CLASSES: DEGRADATION MOTIFS

DESCRIPTION:

Degradation motifs (Degrons)
recognized by E3 Ubiquitin Ligase
complexes priming proteins for
degradation, regulating protein half-life.

EXAMPLE:

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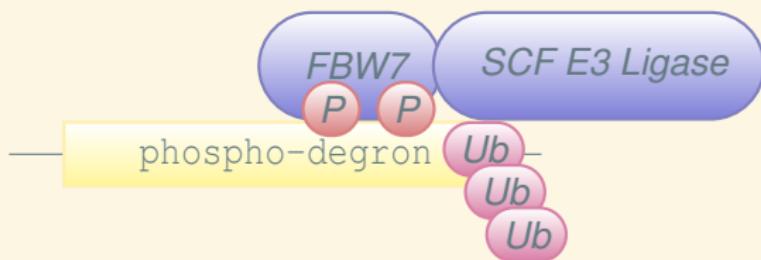
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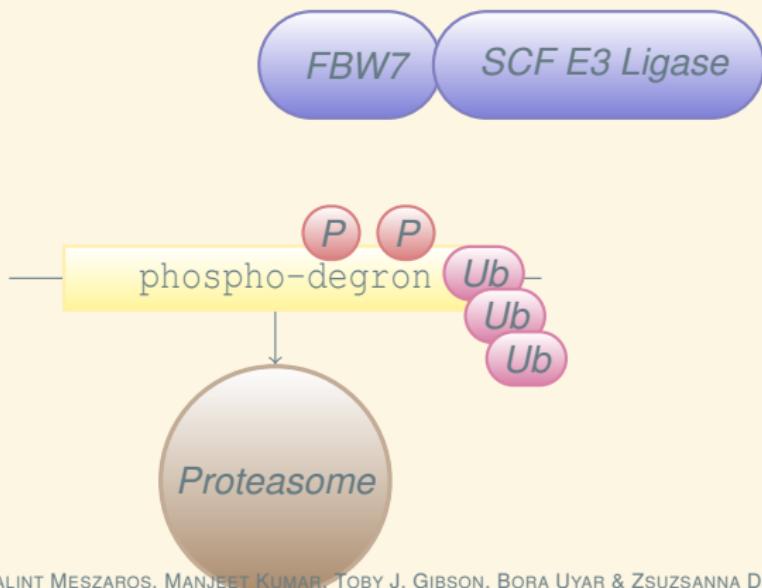
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EXAMPLE:

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REGEx $D(S)G..([ST])$



MOTIF CLASSES: TARGETING/ANCHORING MOTIFS

DESCRIPTION:

TARGETING motifs allow a protein to bind to the transport machinery that relocalizes it to a particular sub-cellular location.

ANCHORING motifs are recognized by biomolecules specific to a sub-cellular location and thereby retain the motif-containing protein at that location.

EXAMPLE:

NAME TRG_NLS_MonoCore_2

REGEx $[\wedge DE](K[RK]|RK)[KRP][KR][\wedge DE]$

Importin α

NLS

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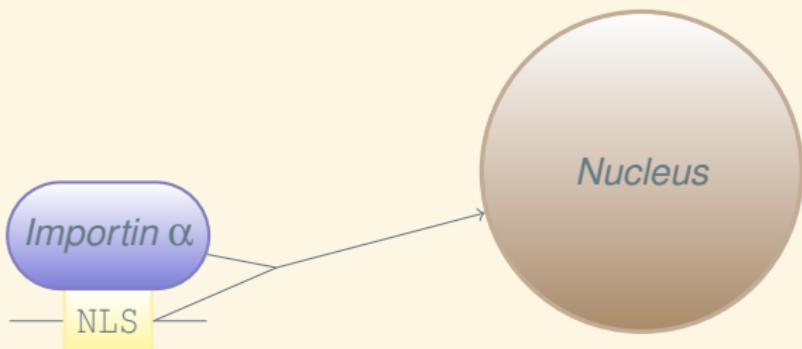
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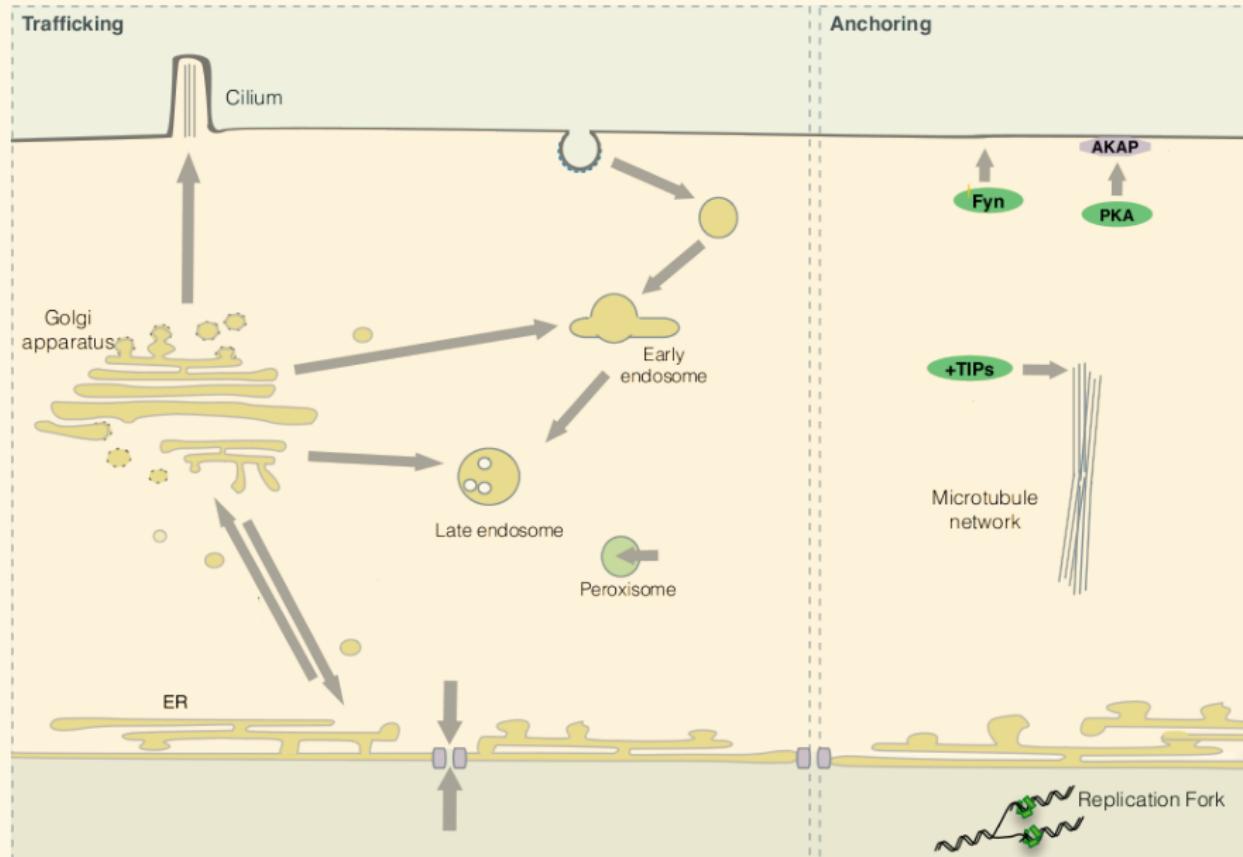
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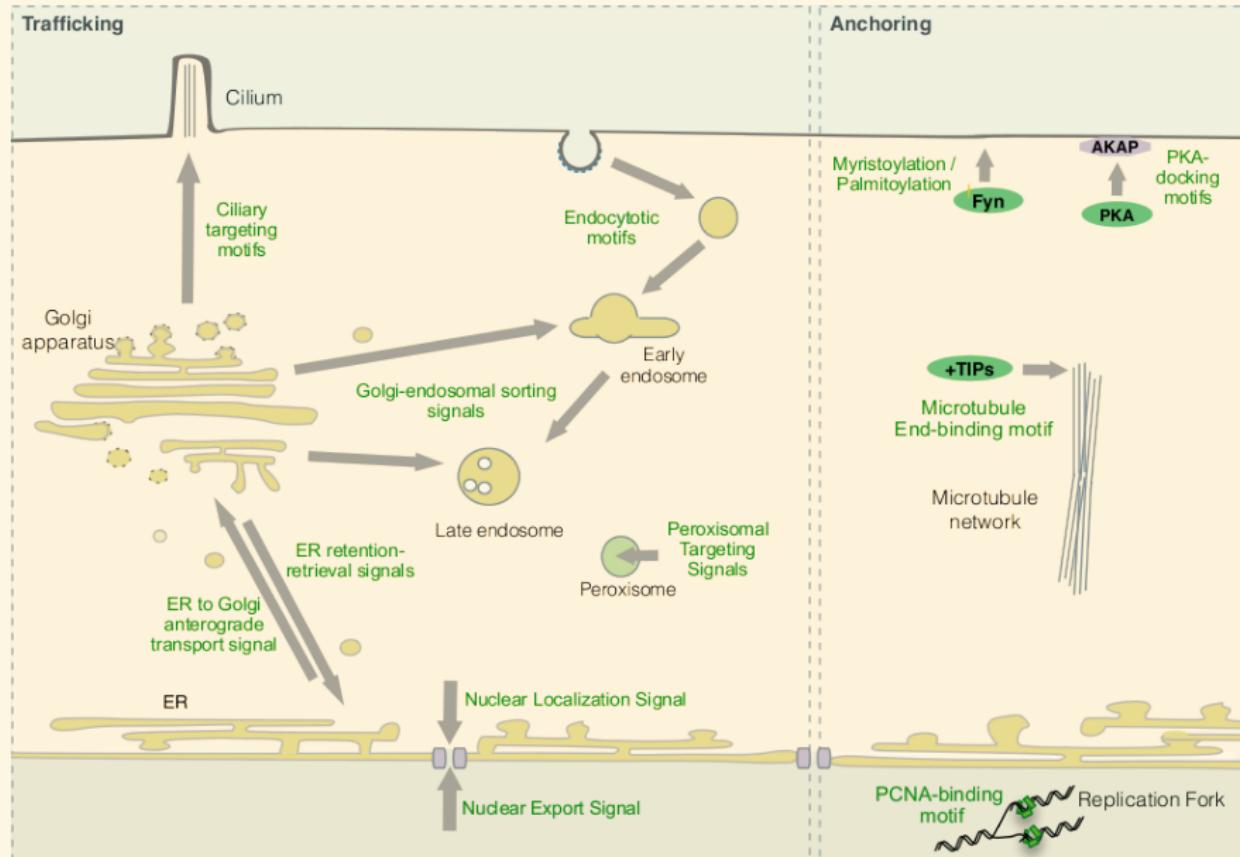


MOTIF CLASSES: TARGETING/ANCHORING MOTIFS



"Short linear motifs: Ubiquitous and functionally diverse protein interaction modules directing cell regulation"; VAN ROEY, UYAR, WEATHERITT, DINKEL, SEILER, BUDD, GIBSON & DAVEY; (CHEM. REVIEWS; 2014)

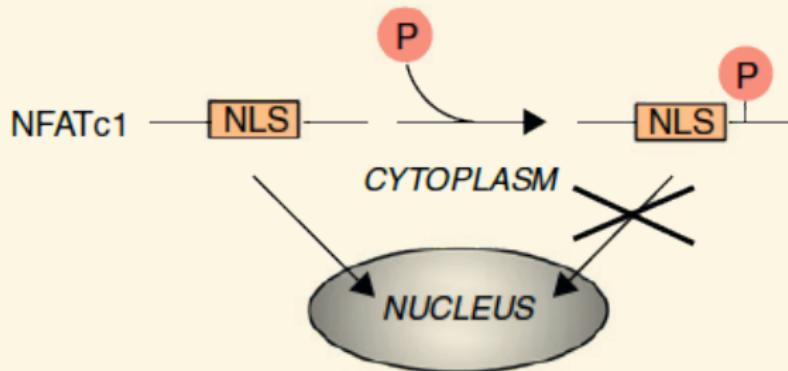
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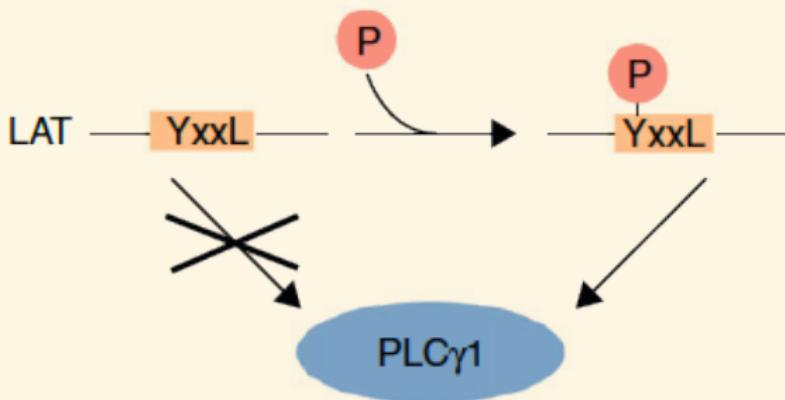
SHORT LINEAR MOTIFS

PTM-induced incompatibility



SHORT LINEAR MOTIFS

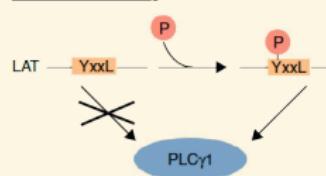
PTM-induced binding



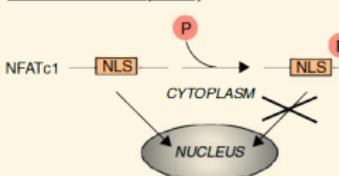
SHORT LINEAR MOTIFS

(a) Binary switch

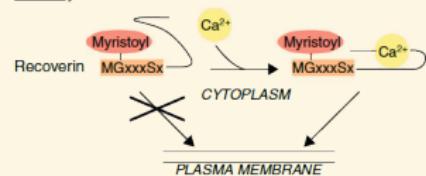
PTM-induced binding



PTM-induced incompatibility

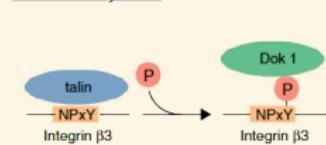


Allotropy

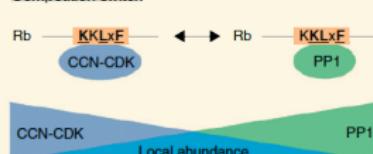


(b) Specificity switch

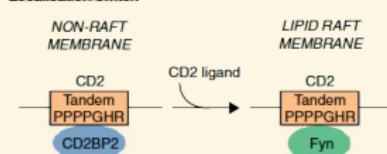
Intrinsic affinity switch



Competition switch

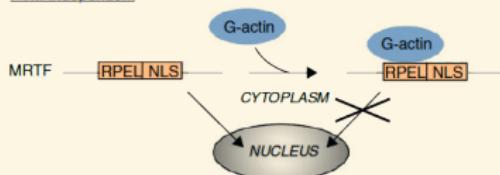


Localisation switch



(c) Motif hiding

PTM-independent



PTM-dependent

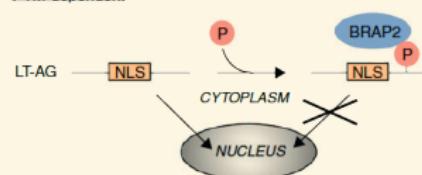


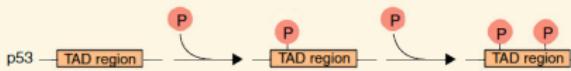
Figure legend

- Protein
- Protein
- Small molecule
- Post-translational modification
- Motif (Regular expression)
- Motif (Name / Abbreviation)

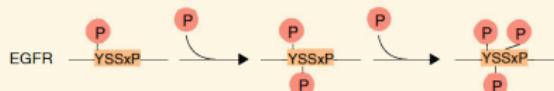
SHORT LINEAR MOTIFS

(a) Cumulative switch

Positive rheostat



Negative rheostat

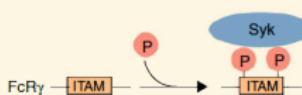


Affinity of p53 for CBP/p300

Affinity of EGFR for c-Cbl

(b) Avidity-sensing switch

PTM-dependent



PTM-independent

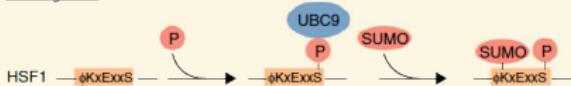


ABORTIVE INTERACTIONS

HIGH-AVIDITY INTERACTIONS

(c) Sequential switch

Priming PTM



Sequential specificity switch

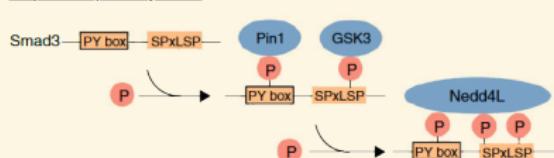


Figure legend

- Protein
- Protein
- Small molecule
- Post-translational modification
- Motif (Regular expression)
- Motif (Name / Abbreviation)

SHORT LINEAR MOTIFS

Switch #: ◊ SWT1000055 ◊	Switch type: Binary ②	Switch subtype: Physicochemical compatibility ②
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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 - Pln1

Interface:

- (1) LIG_WW_Pin1_4 motif (200PYASPP205) in Steroidogenic factor 1 (Nr5a1)
 (2) WW domain (7-37) 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

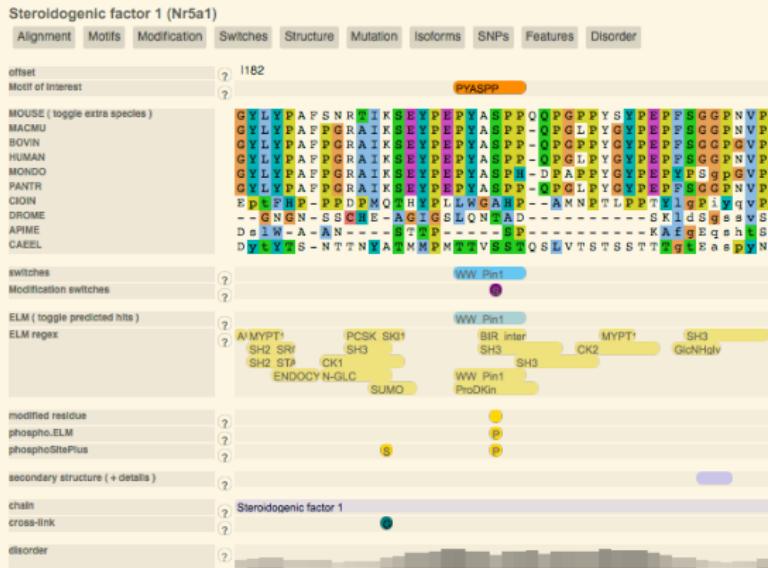
Other switches involving participants

[Bentiginol-prolyl cis-trans isomerase NIMA-interacting 1 \(Pin1\)](#) - 28 more (view)

Other switches involving interfaces

[HG_WW_Pin1_4-89 more \(view\)](#)

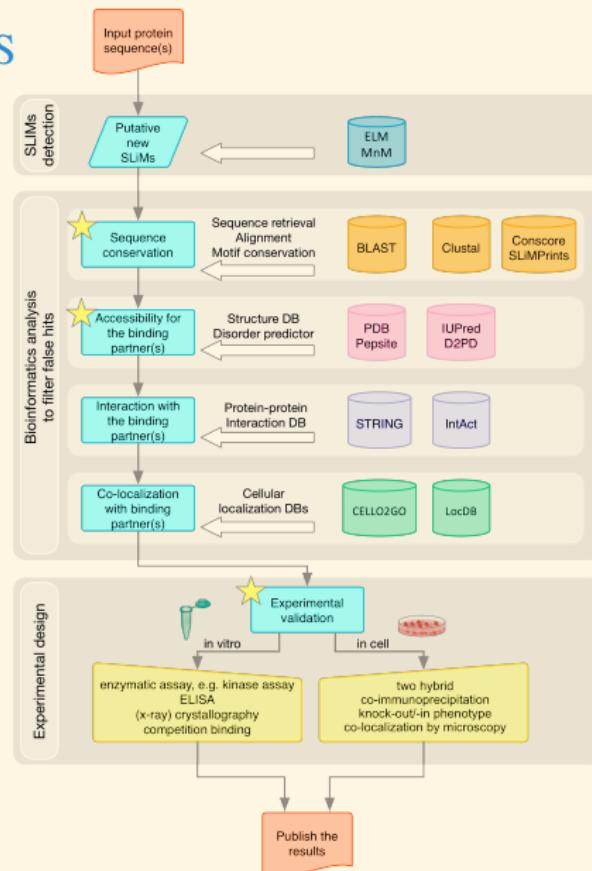
[WW domain - 102 more \(view\)](#)



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hover over features for details

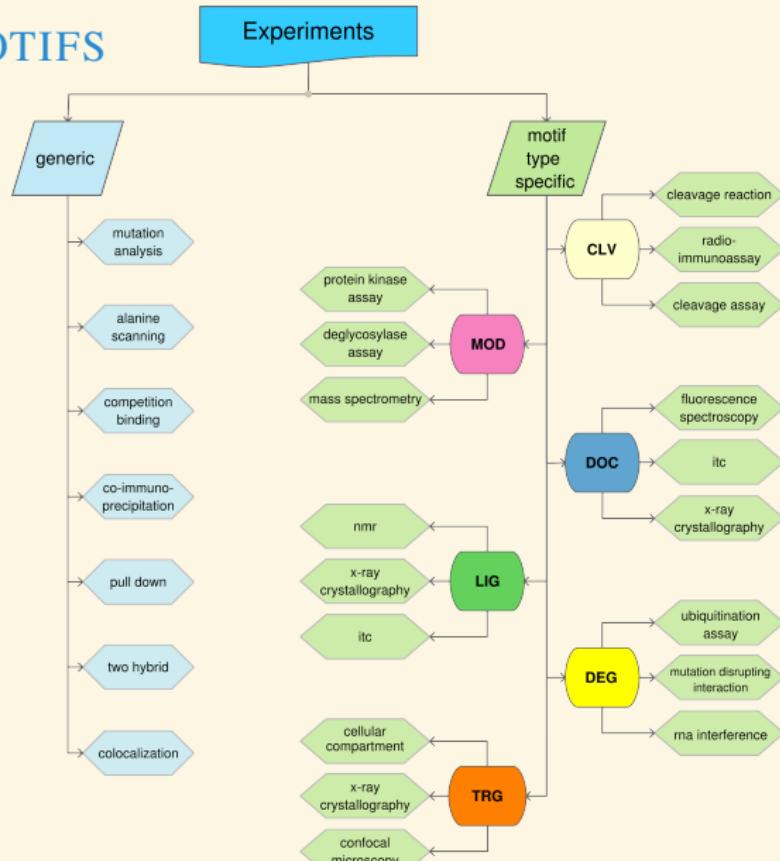
"The switches.ELM resource: a compendium of conditional regulatory interaction interfaces."; VAN ROEY, DINKEL, WEATHERITT, GIBSON & DAVEY; (SCI. SIGNAL. 2013)

GUIDELINES FOR EXPERIMENTAL DETECTION OF SHORT LINEAR MOTIFS



"Experimental detection of short regulatory motifs in eukaryotic proteins: tips for good practice as well as for bad."; GIBSON TJ, DINKEL H, VAN ROEY K, DIELLA F; (CELL COMMUN. SIGNAL 2015)

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SUMMARY

SHORT LINEAR MOTIFS

- small, versatile modules which mediate transient interactions
- important regulators of cellular processes.
- “kidnapped” by viruses
- play an important role in diseases
- collected in the Eukaryotic Linear Motif Resource (ELM)

QUESTIONS?



I mustache you a
Question

BUT I'M SHAVING IT
for later.