

# SHORT LINEAR MOTIFS

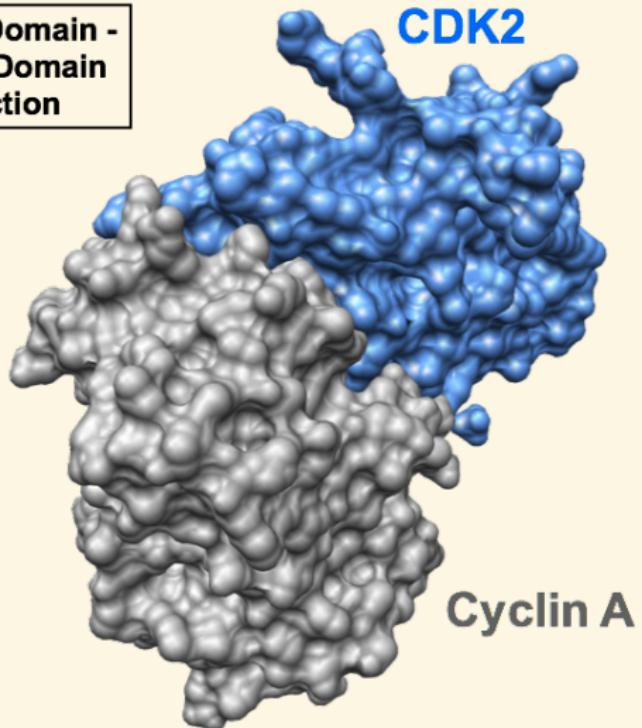
Holger Dinkel, Manjeet Kumar, Toby Gibson

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**

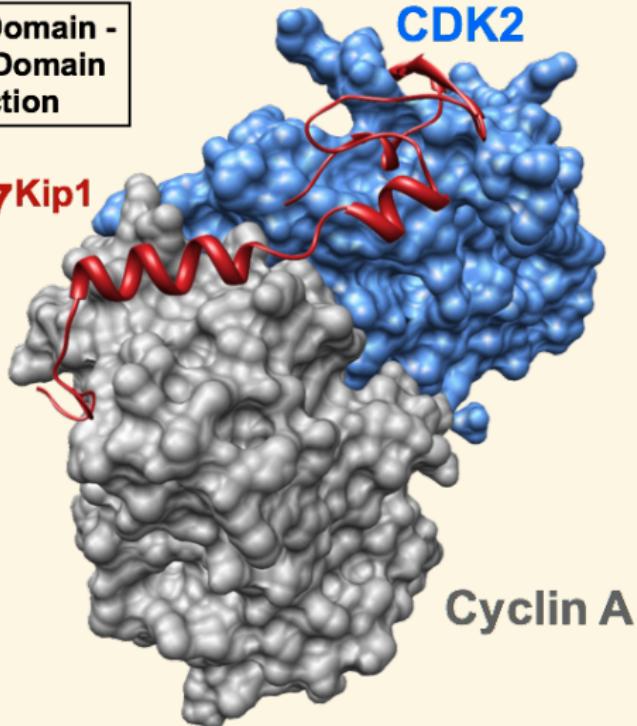


# IMPORTANCE OF SHORT LINEAR MOTIFS

Globular Domain -  
Disordered Domain  
Interaction

Globular Domain -  
Globular Domain  
Interaction

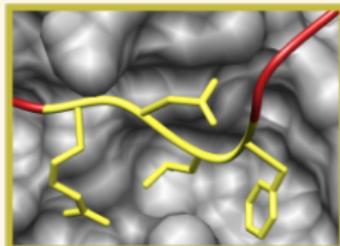
p27<sup>Kip1</sup>



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Disordered Domain  
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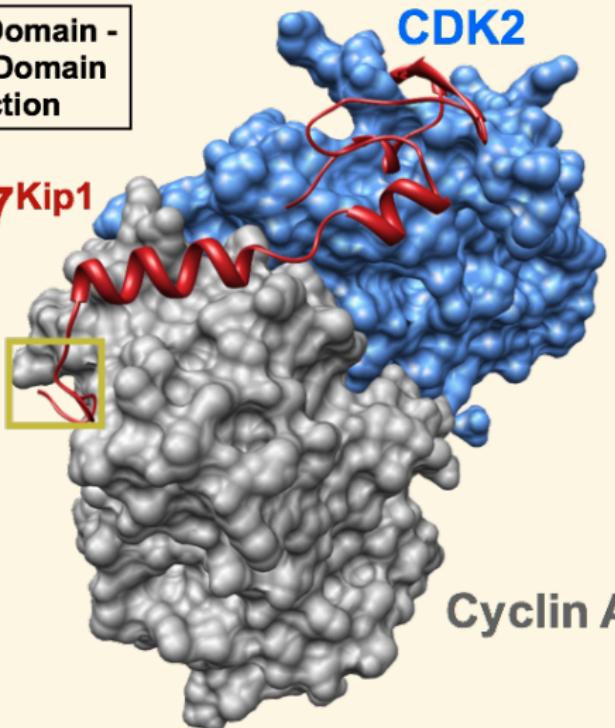
Globular Domain -  
Short Linear Motif  
Interaction



RNLF

Globular Domain -  
Globular Domain  
Interaction

p27<sup>Kip1</sup>



Cyclin A

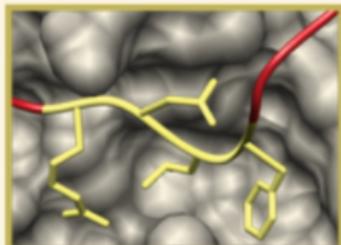
CDK2

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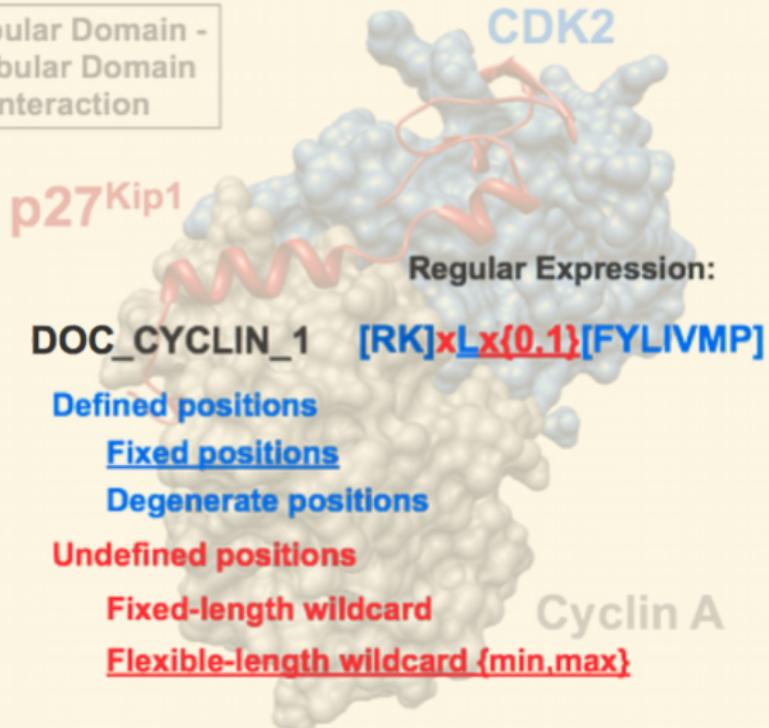
Globular Domain -  
Disordered Domain  
Interaction

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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]

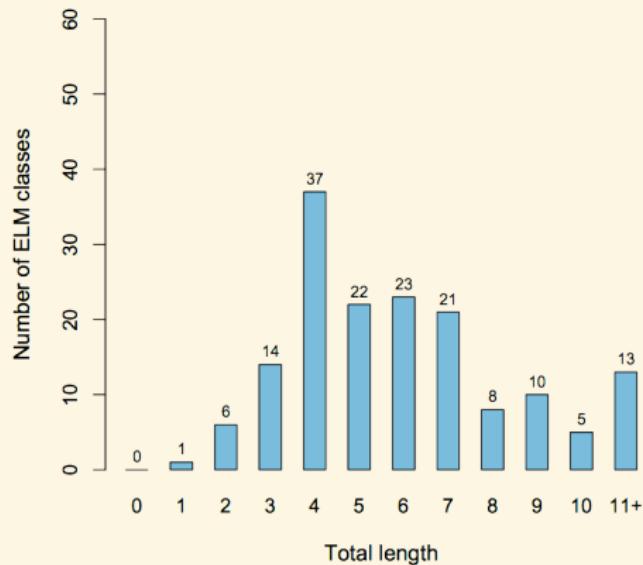
has been replaced by the more specific DOC\_CYCLIN\_RxL\_1:

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

# ATTRIBUTES OF SHORT LINEAR MOTIFS

## LINEAR MOTIFS

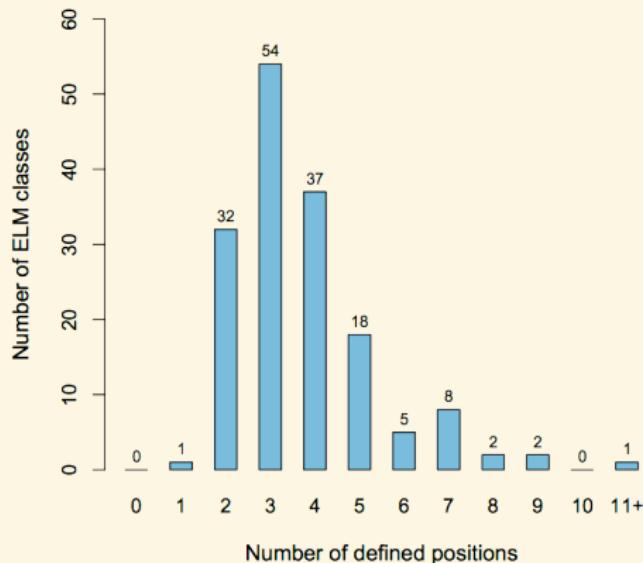
- are small.
- have few defined positions.
- mediate transient, low affinity interactions.



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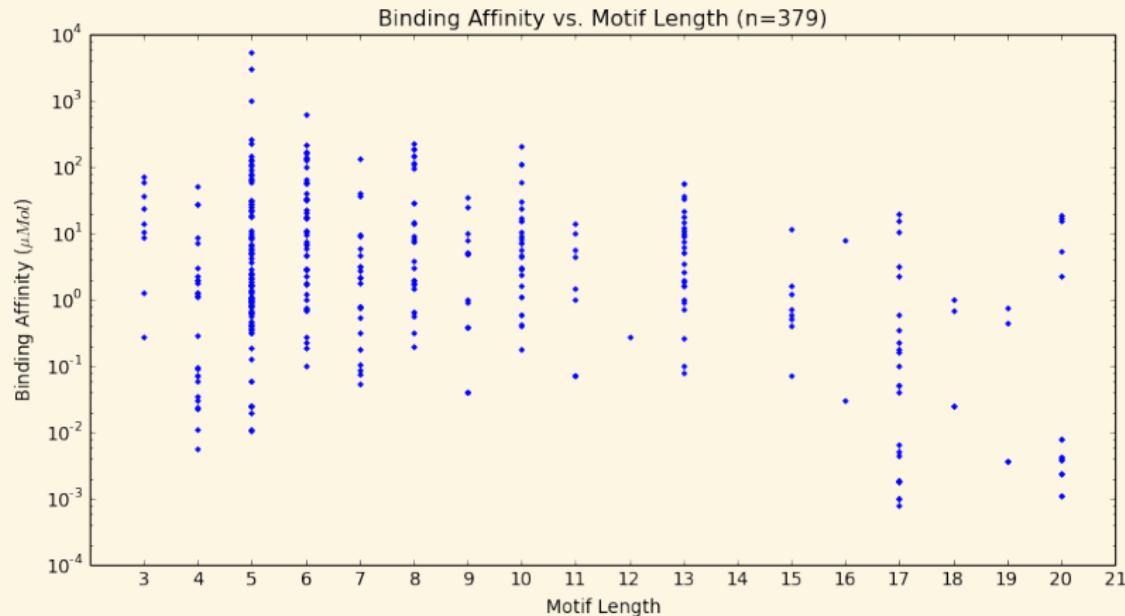
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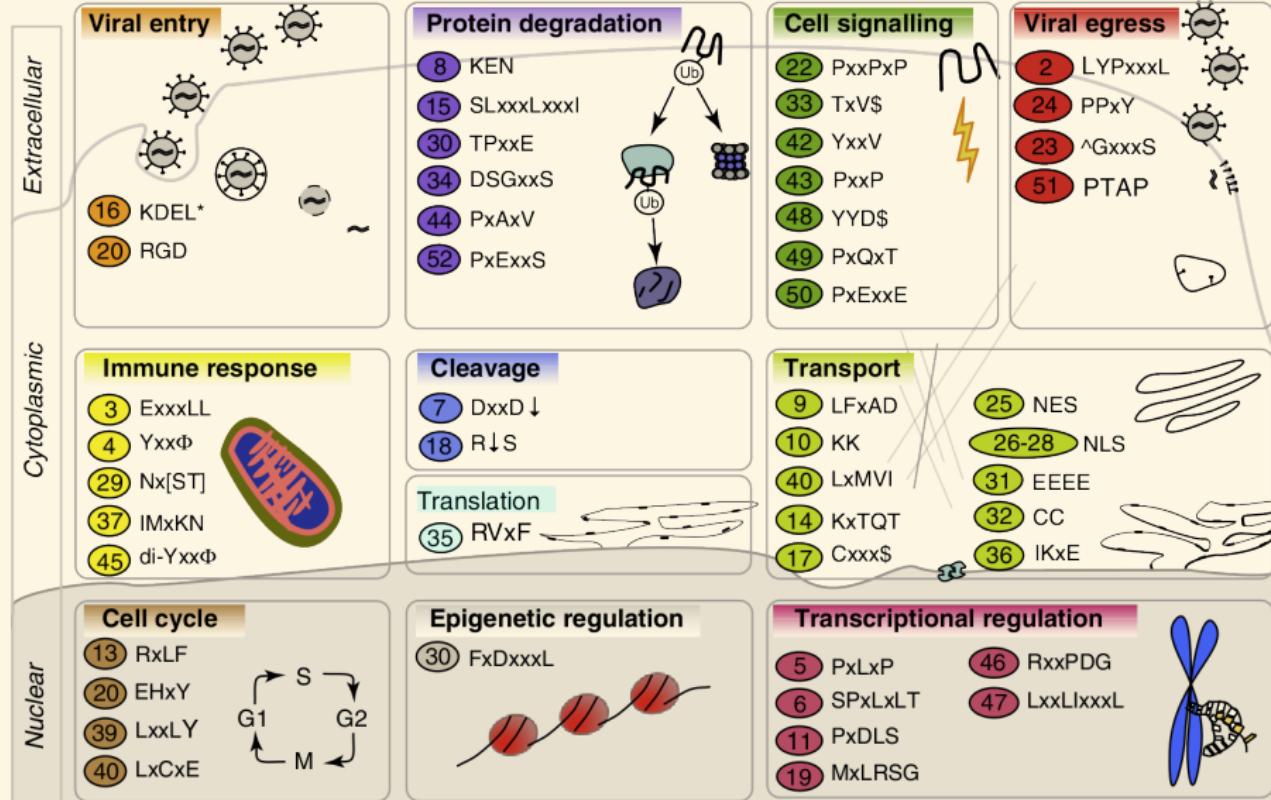
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## LINEAR MOTIFS

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- 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  $\beta$ - and  $\gamma$ -subunits of the epithelial sodium channel ENAC. These mutations abrogate the binding to the ubiquitin ligase NEDD4-2, ultimately resulting in increased  $\text{Na}^+$  reabsorption, plasma volume extension and hypertension.

# IMPORTANCE OF SHORT LINEAR MOTIFS: DISEASES

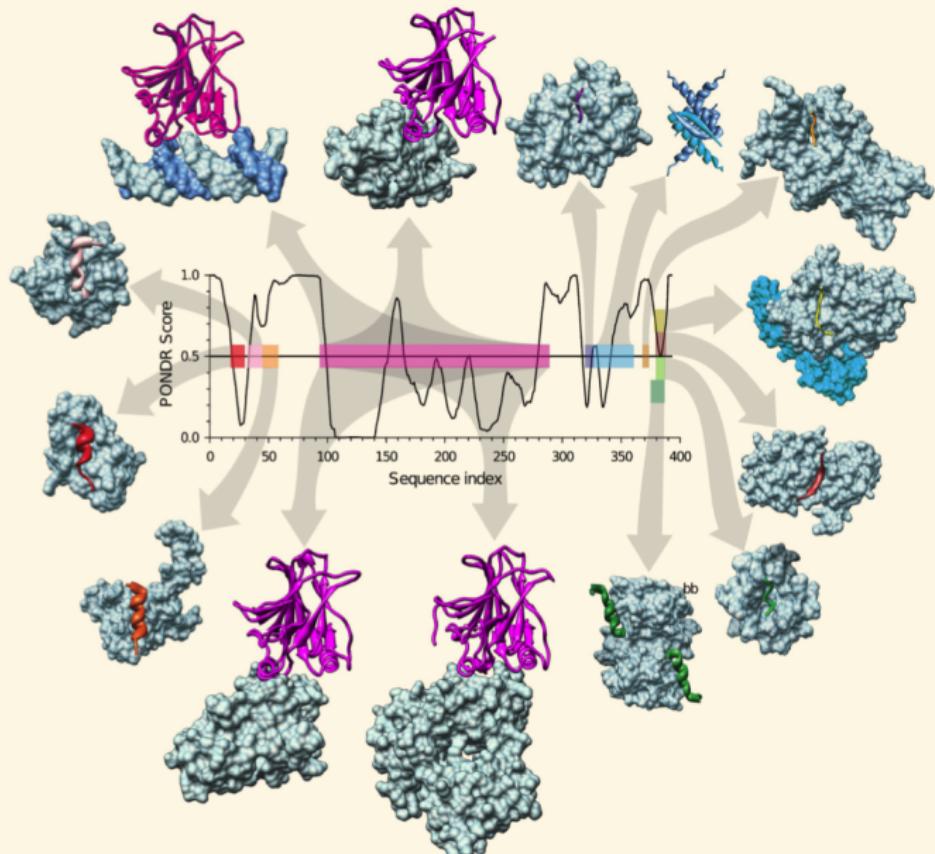
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## BACILLUS ANTHRACIS “LETHAL FACTOR”

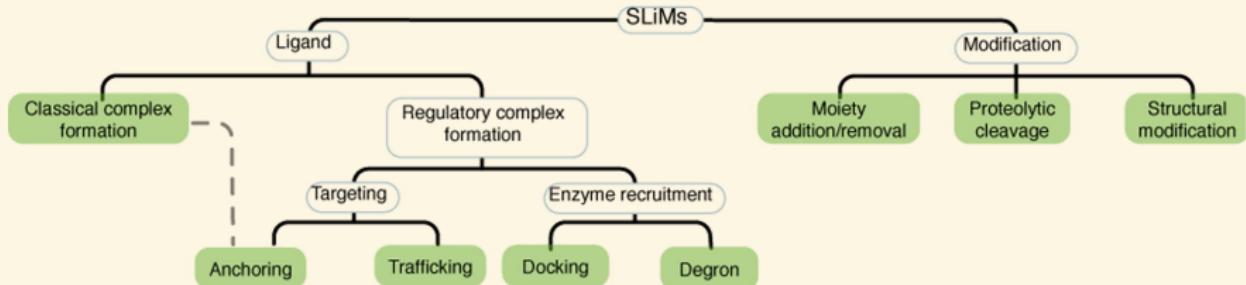
The protein LEF\_BACAN is a metalloprotease (one of the three proteins composing the anthrax toxin) that specifically targets mitogen-activated protein kinase kinases (MKKs), which are important regulators of signal transduction as they phosphorylate and thus activate specific MAPKs (such as ERK1, ERK2, 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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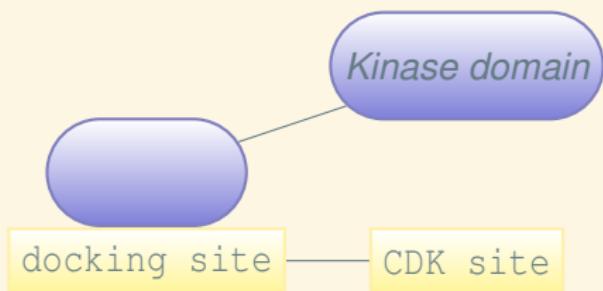
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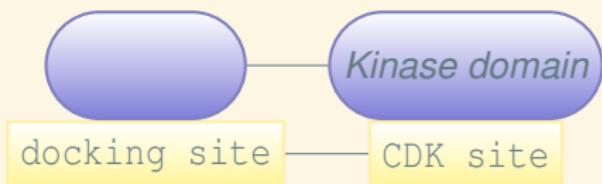
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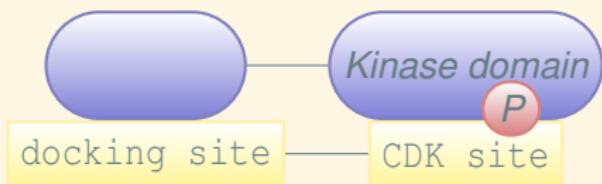
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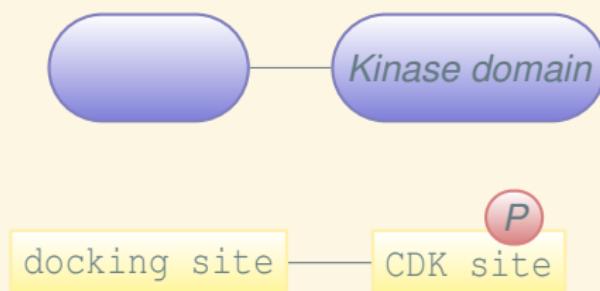
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## MOTIF CLASSES: CLEAVAGE MOTIFS

### 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. On either side of the bar are two short black horizontal lines, creating a bracket-like effect.

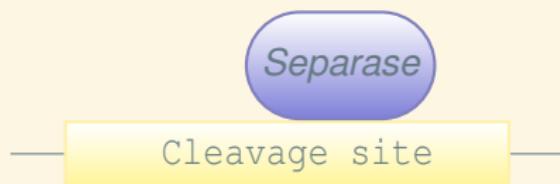
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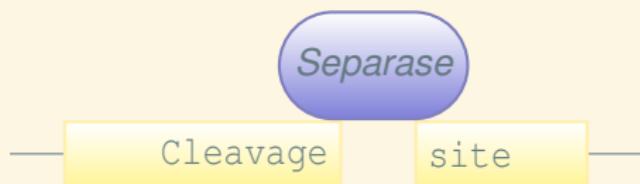
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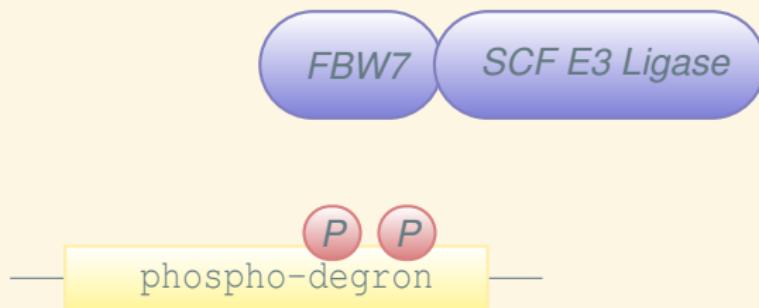
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## DESCRIPTION:

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

## EXAMPLE:

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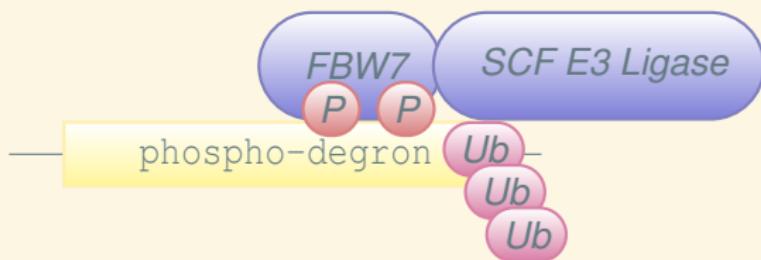
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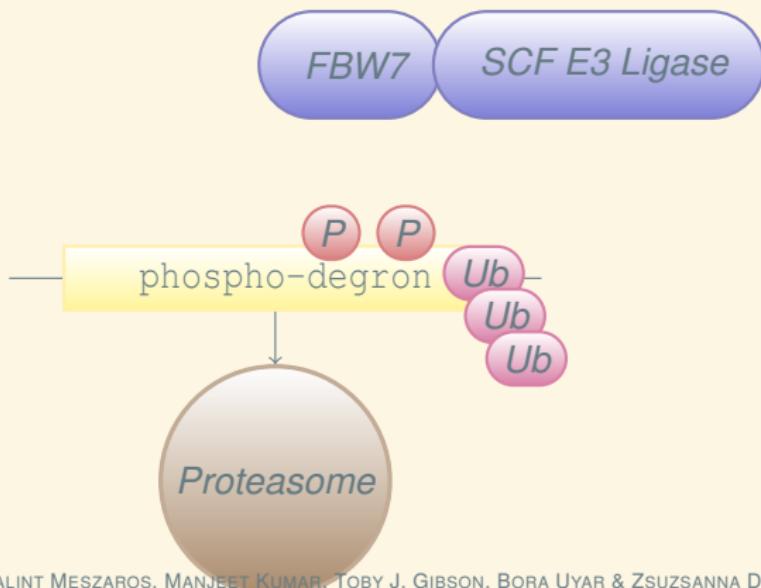
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# MOTIF CLASSES: TARGETING/ANCHORING MOTIFS

## 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  $\alpha$*

NLS

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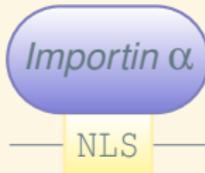
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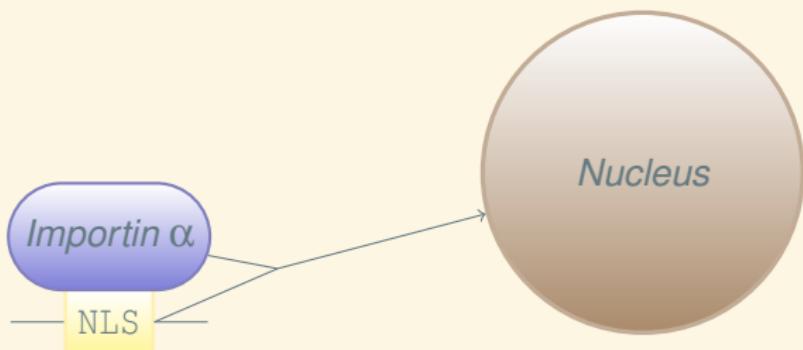
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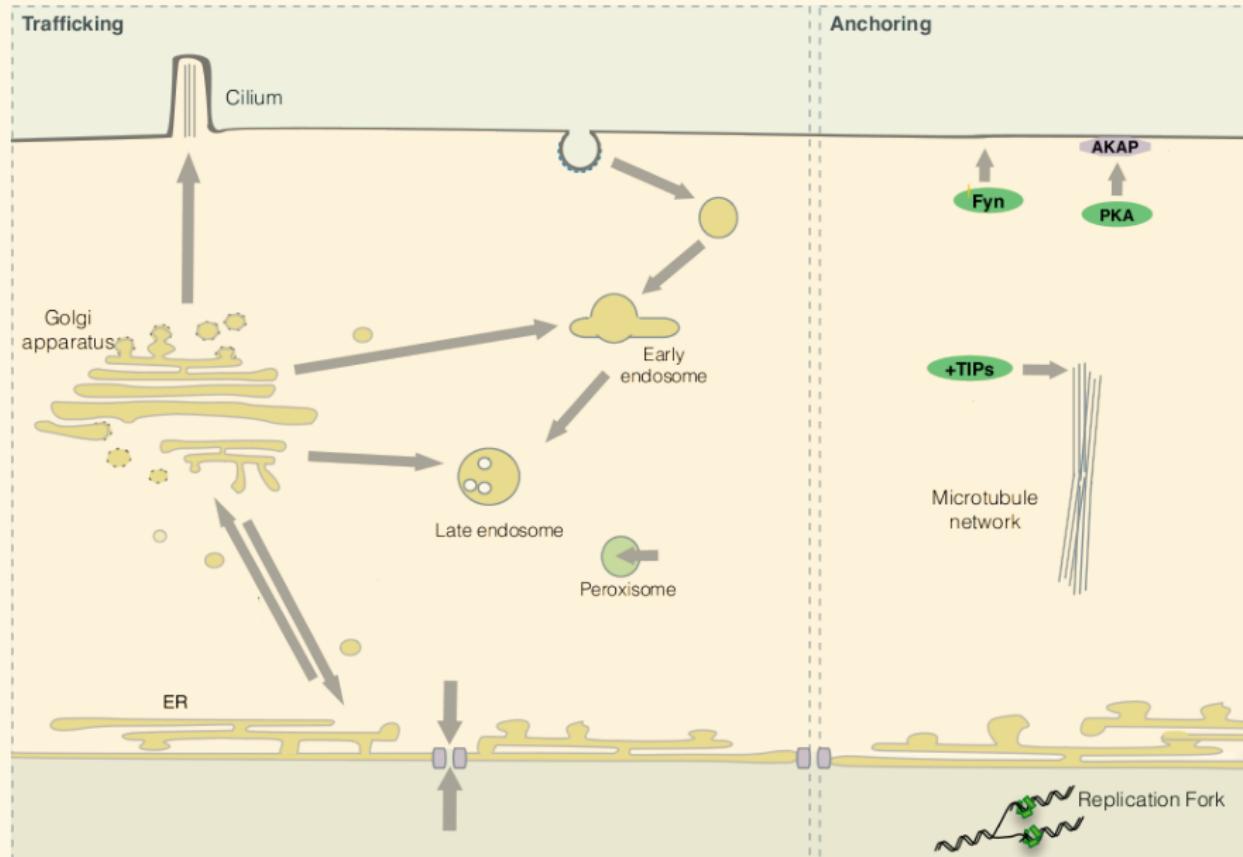
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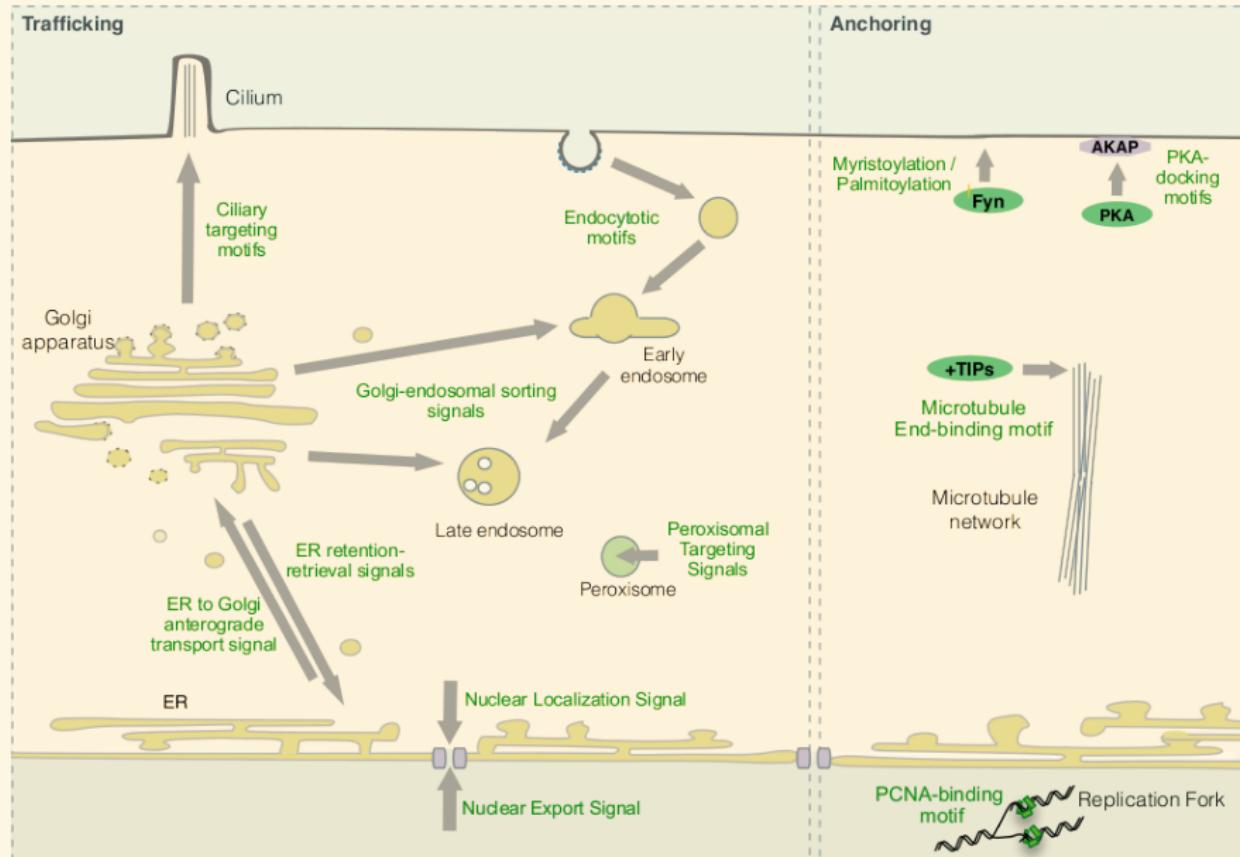


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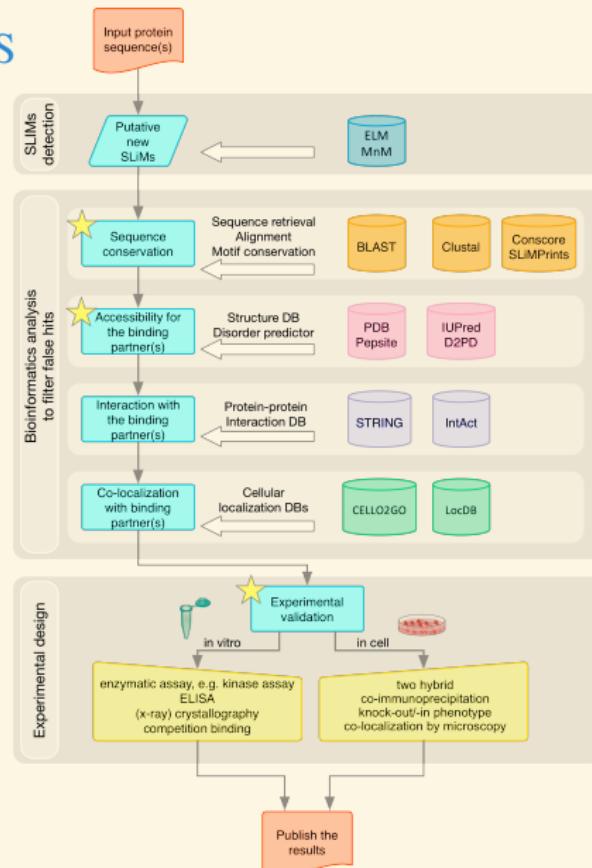
"Short linear motifs: Ubiquitous and functionally diverse protein interaction modules directing cell regulation"; VAN ROEY, UYAR, WEATHERITT, DINKEL, SEILER, BUDD, GIBSON & DAVEY; (CHEM. REVIEWS; 2014)

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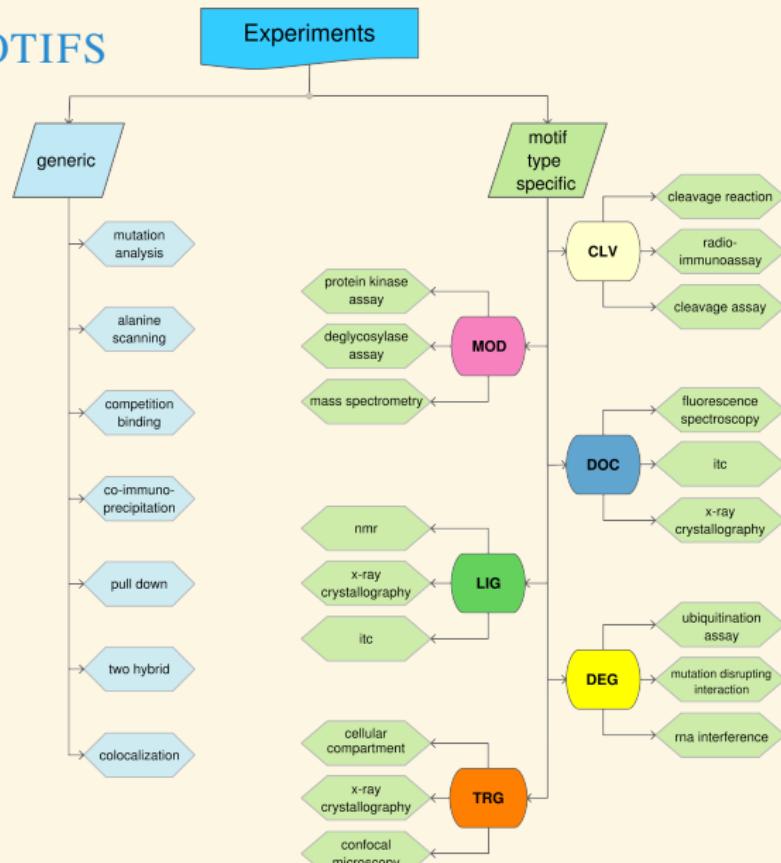
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# GUIDELINES FOR EXPERIMENTAL DETECTION OF SHORT LINEAR MOTIFS



*"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.