

Short Linear Motifs

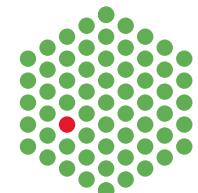
Computational and experimental high throughput approaches

Jelena (Lena) Čalyševa

Toby Gibson's group

Predoc course 2019
November 11th / 13th

EMBL



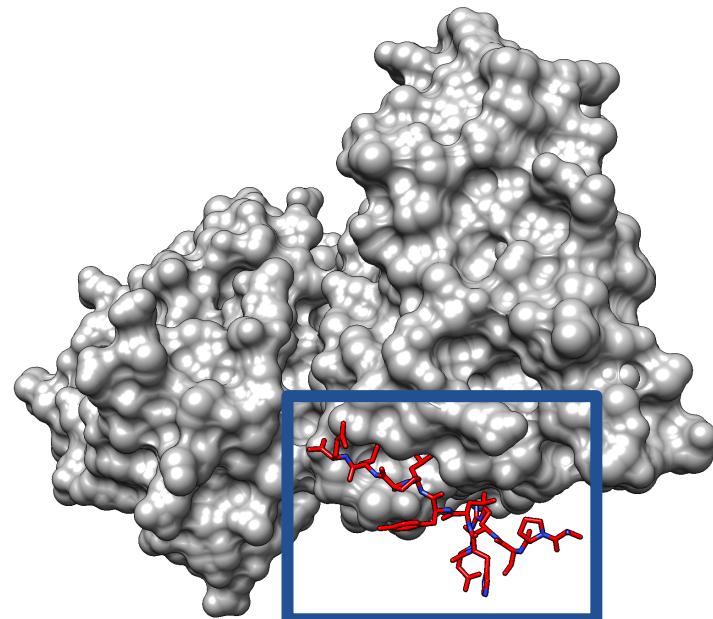
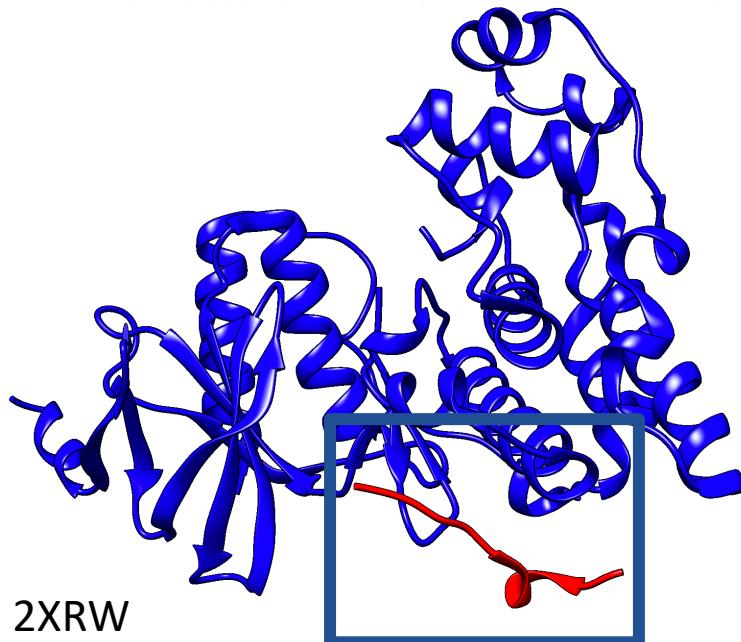
Short Linear Motifs (SLiMs)

Pattern:

[RK] [^P] [^P] [LIM] . L. [LIVMF] .

R D H L Y L P L E

> M...or of activated T-cells, cytoplasmic 3
CLPHHGLPSHSSVLSPSFQLQSHKNYEGTCEIPESKYSPLGGPKPFECPSIQITSISPNC
HQELDAHEDDLQINDPEREFLERPS RDHLYLPLE PSYRESSLSPSPASSISSRSWFSDAS
SCESLSHIYDDVDSELNEAAARFTLGSPLTSPGGSPGGCPGEETWHQQYGLGHSLSPRQS
PCHSPRSSVTDENWLSPRPASGPSSRPTSPCGKRRHSSAEVCYAGSLSPHHSPVPSPGHS



Short Linear Motifs (SLiMs)

Pattern:

[RK] [^P] [^P] [LIM] .L. [LIVMF] .

RDHLYLPLE.

[RK] R or K

[^P] not P

[LIM] L, I or M

.
(for readability, sometimes "X")

Which of these follow this regular expression?

a) KLPLPLPLL

b) RLLLPLPLL

c) RRRLLLLLL

d) RRRIILLWL



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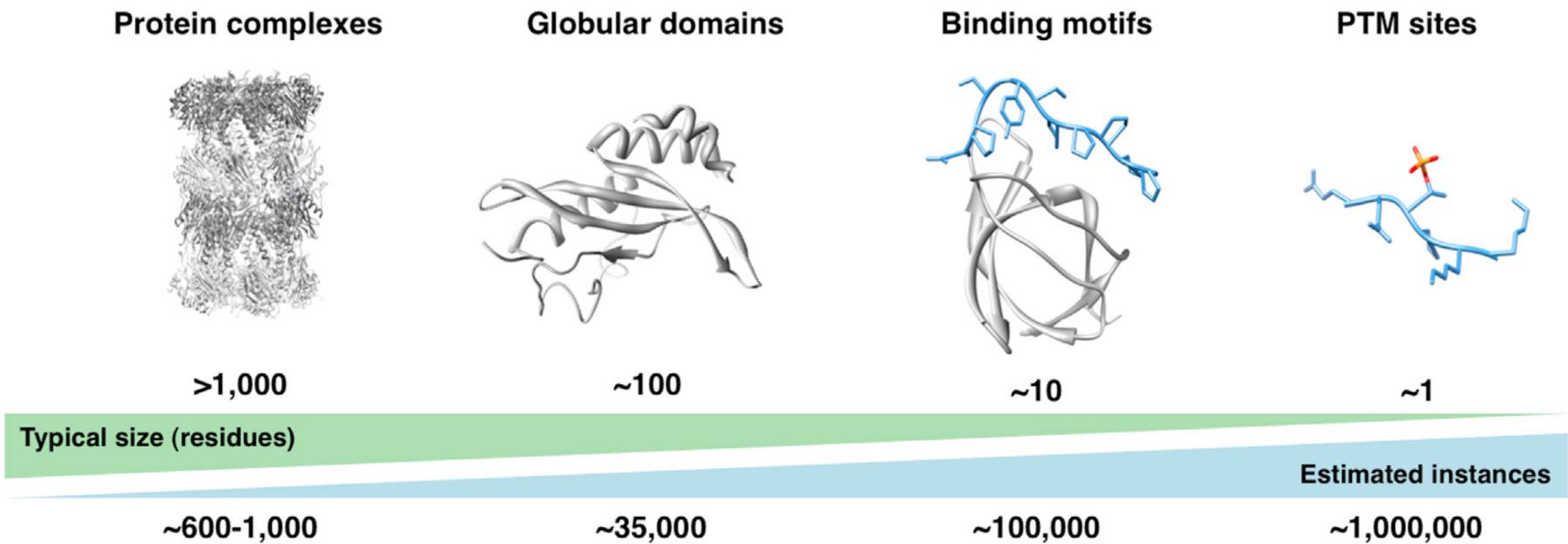
.
(for readability, sometimes "X")

Which of these follow this regular expression?

- a) KLPPLPLPLL
- b) RLLLPLPLL
- c) RRRLLLLLL
- d) RRRIILLWL



Short Linear Motifs (SLiMs)



A Million Peptide Motifs for the Molecular Biologist
Tompa et al, *Molecular Cell*, 2014

Short Linear Motifs (SLiMs)



The Eukaryotic Linear Motif resource for Functional Sites in Proteins

search ELM Database

ELM Home ELM Prediction ELM DB ELM Candidates ELM Information ELM downloads Help

Welcome to the Eukaryotic Linear Motif (ELM) resource

This computational biology resource mainly focuses on annotation and detection of eukaryotic linear motifs (ELMs) by providing both a repository of annotated motif data and an exploratory tool for motif prediction. ELMs, or short linear motifs (SLiMs), are compact protein interaction sites composed of short stretches of adjacent amino acids. They are enriched in intrinsically disordered regions of the proteome and provide a wide range of functionality to proteins ([Davey, 2011](#), [Van Roey, 2014](#)) They play crucial roles in cell regulation and are also of clinical importance, as aberrant SLiM function has been associated with several diseases and SLiM mimics are often used by pathogens to manipulate their hosts' cellular machinery ([Davey, 2011](#), [Uyar, 2014](#))

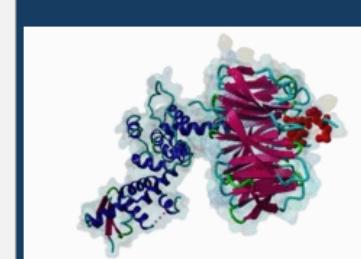
ELM Prediction

The **ELM prediction** tool scans user-submitted protein sequences for matches to the regular expressions defined in ELM. Distinction is made between matches that correspond to experimentally validated motif instances already curated in the ELM database and matches that correspond to putative motifs based on the sequence. Since SLiMs are short and degenerate, overprediction is likely and many putative SLiMs will be false positives. However, predictive power is improved by using additional filters based on contextual information, including taxonomy, cellular compartment, evolutionary conservation and structural features.

Protein sequence

Enter Uniprot identifier or accession number: (auto-completion)
e.g. [EPN1_HUMAN](#), [P04637](#), [TAU_HUMAN](#), [\[RANDOM\]](#)

Or paste the sequence (Single letter code sequence only or [FASTA](#) format):



PDB-Structure [2OVQ](#) showing a peptide from ELM class **DEG_SCF_FBW7_1**

- ELM database update
Three new classes added
 - [LIG_PCNA_yPIPBox_3](#)
 - [DOC_PP4_MxPP_1](#)
 - [DOC_PP4_FxxP_1](#)
- ELM database update
Four new classes inserted
 - [LIG_SH2_STAP1](#)
 - [LIG_SH2_NCK_1](#)
 - [LIG_PCNA_APIM_2](#)
 - [LIG_ARL_BART_1](#)

Additionally, we have revised four other ELM classes

<http://elm.eu.org>

- ELM database updates
In a major update, more than 60 bacterial effector instances belonging to 20 different ELM

EMBL



Computational and experimental approaches for SLiMs

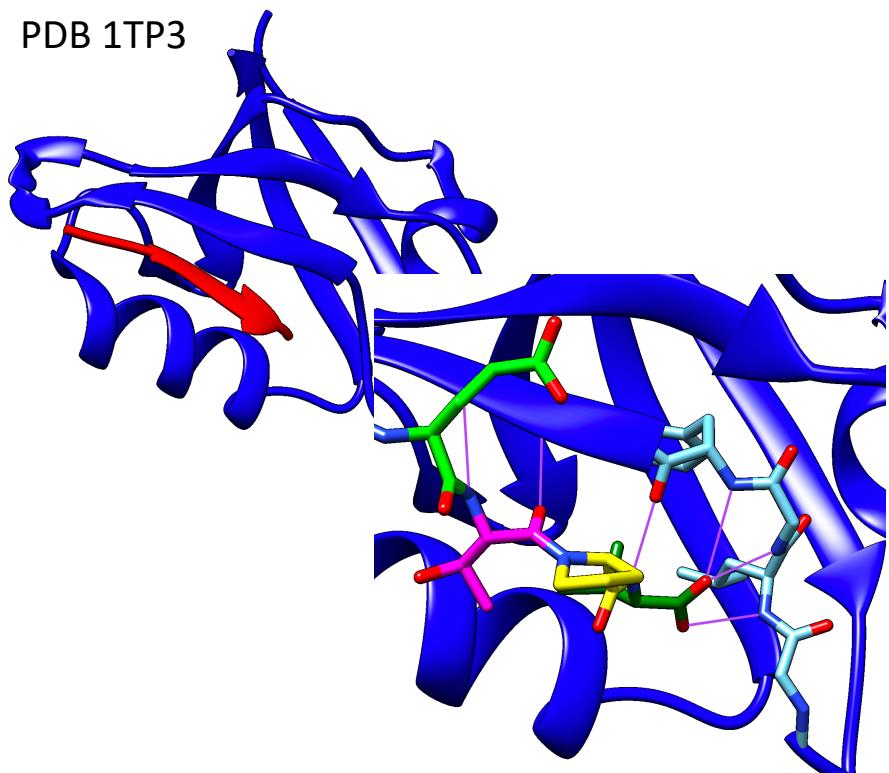
PDZ binding internal motifs

C-terminal motifs:

x[ED]xΦ, x[ST]xΦ and xΦxΦ

β -strand augmentation

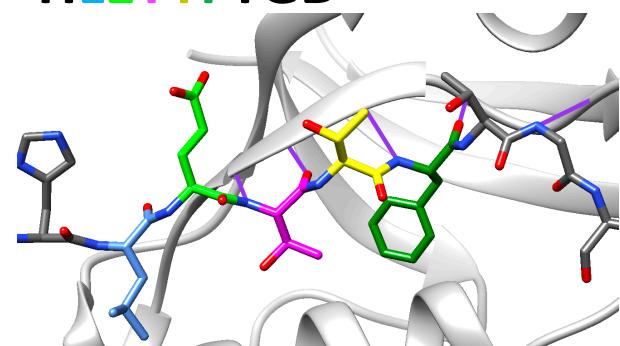
PDB 1TP3



Internal binding:

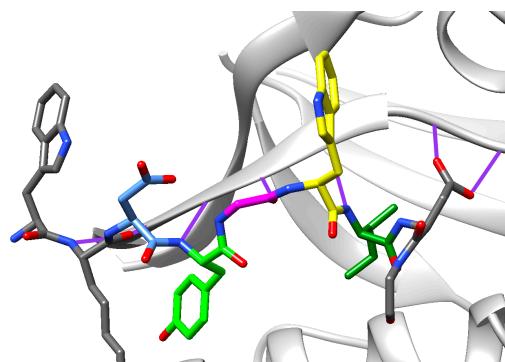
PDB 1QAV

HLETTFTGD



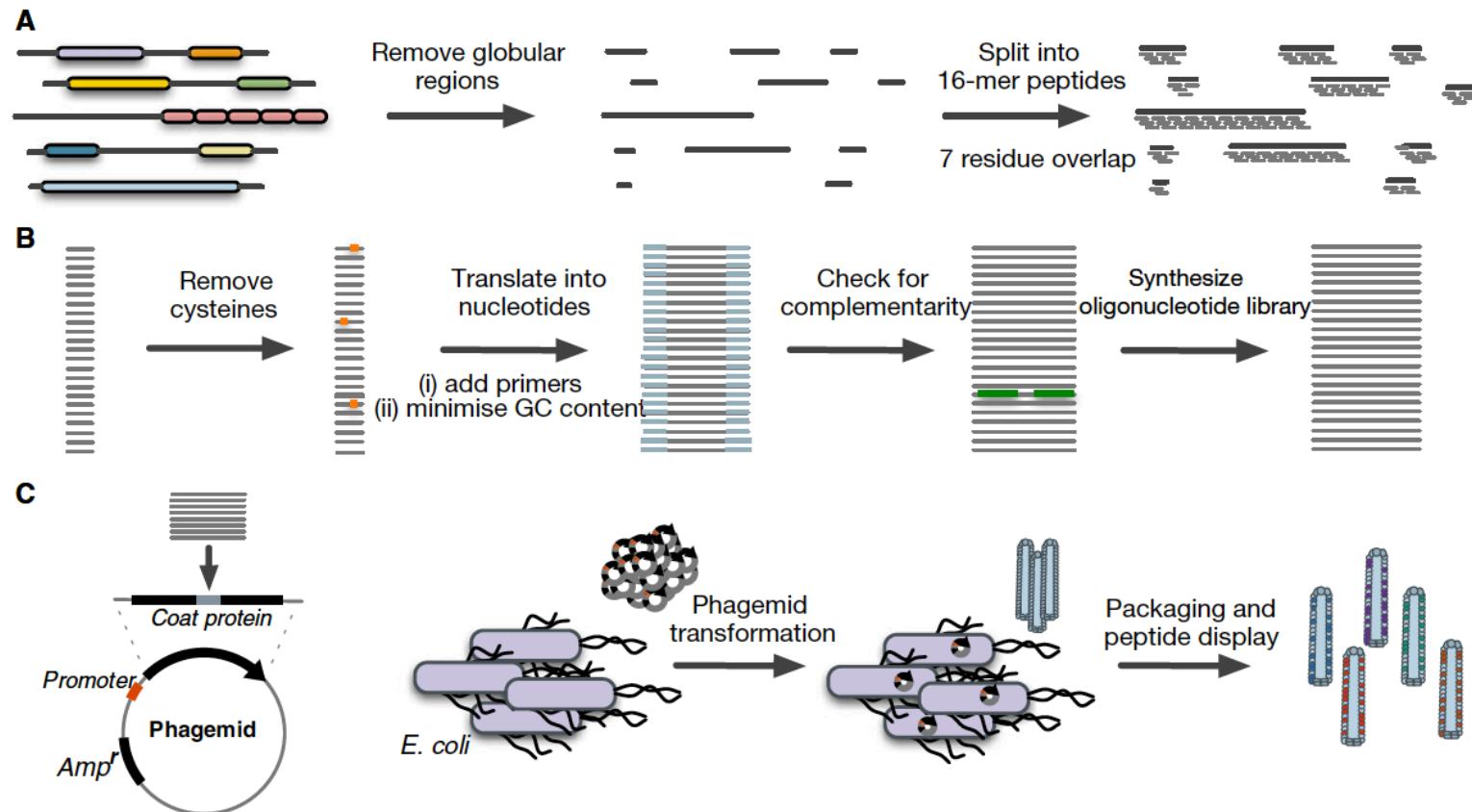
PDB 3CBY

WKDYGYWIDG



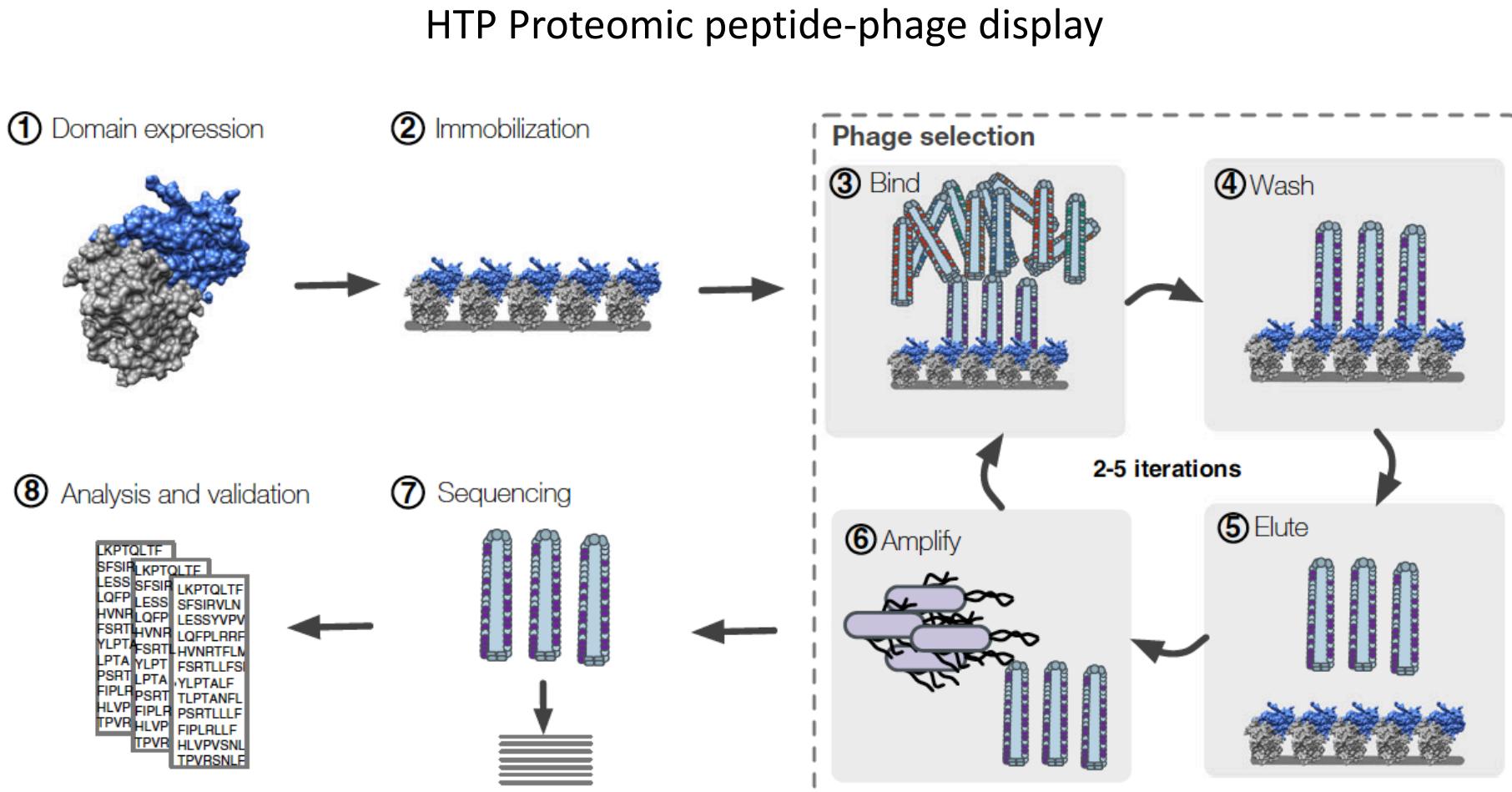
Computational and experimental approaches for SLiMs

HTP Proteomic peptide-phage display

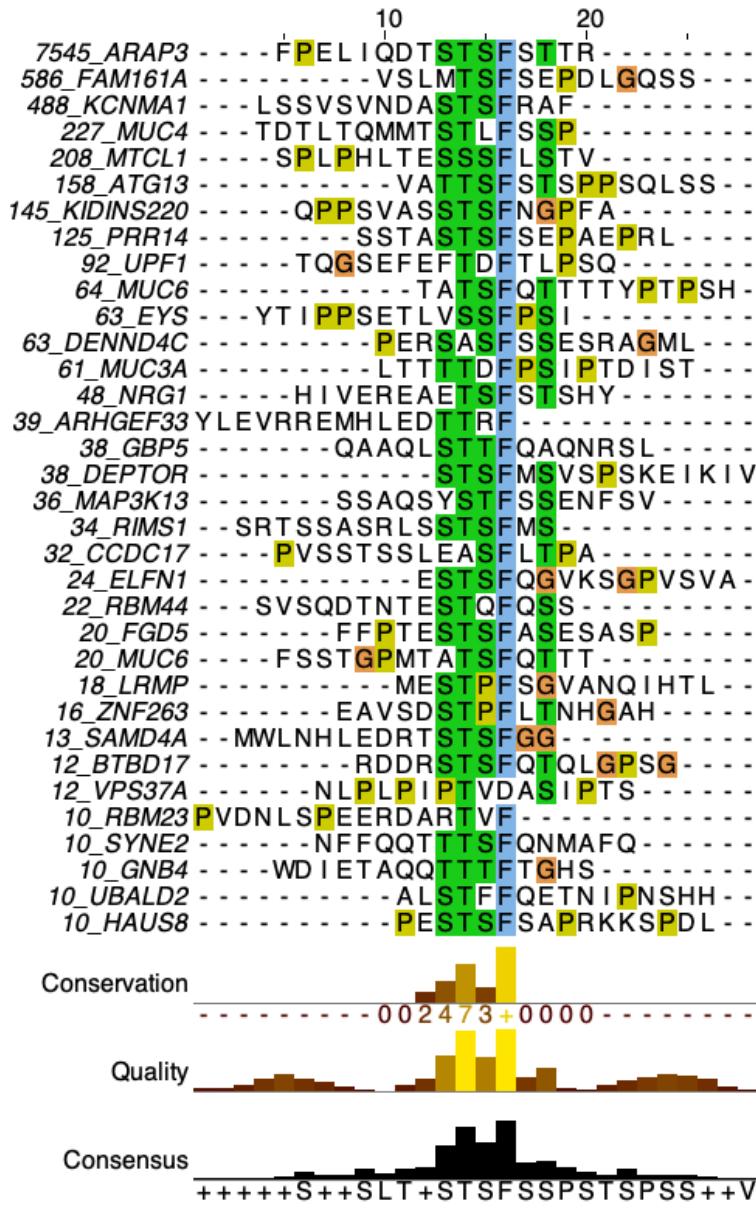


N.E. Davey, M.-H. Seo, V.K. Yadav, J. Jeon, S. Nim, I. Krystkowiak, C. Blikstad, D. Dong, N. Markova, P.M. Kim, Y. Ivarsson, Discovery of short linear motif-mediated interactions through phage display of intrinsically disordered regions of the human proteome, FEBS J., 284 (2017) 485–498.

Computational and experimental approaches for SLiMs



Computational and experimental approaches for SLiMs



Open shank1.fasta in Jalview

Open shank1_aligned.fasta in Jalview

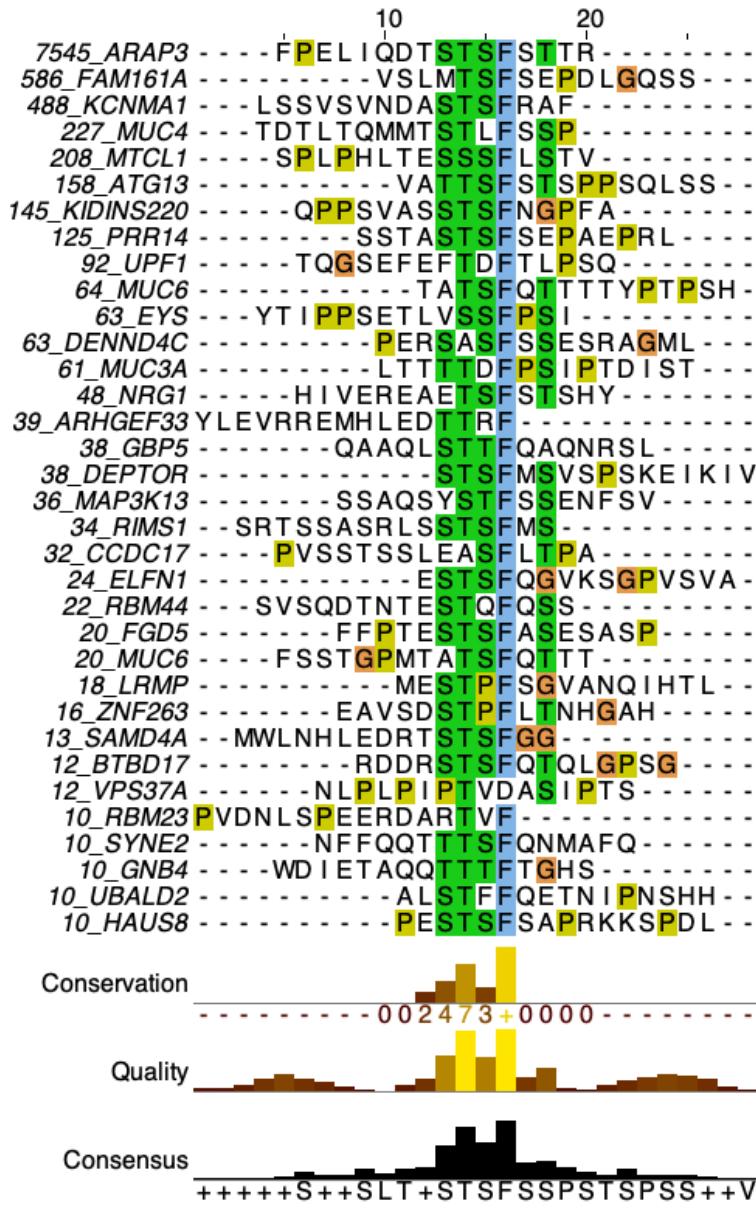
[ST] TSF ?

TSF ?

T . F ?

<http://slim.ucd.ie/slimsearch/>

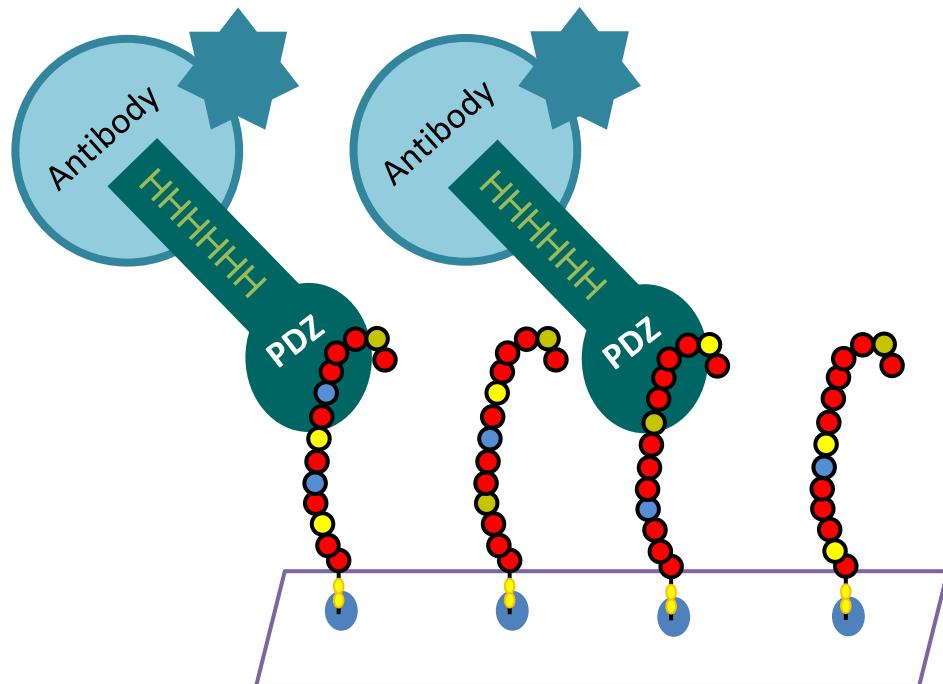
Computational and experimental approaches for SLiMs



If you could validate binding of 50 different sequences, what sequences would you use?

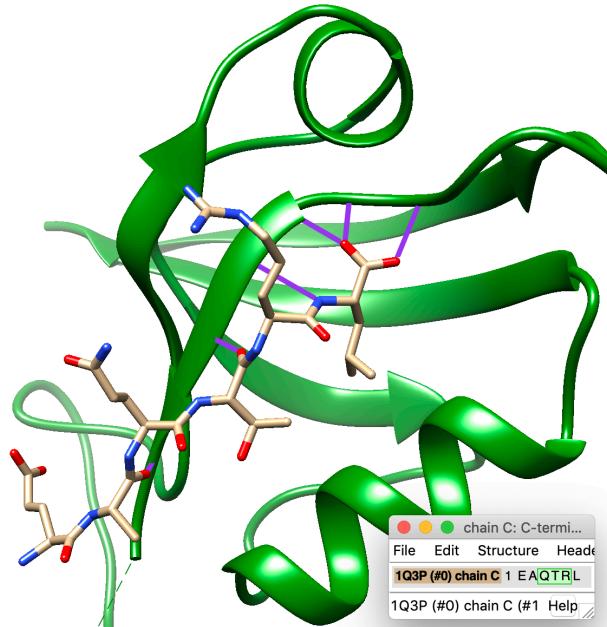
Computational and experimental approaches for SLiMs

SPOT arrays

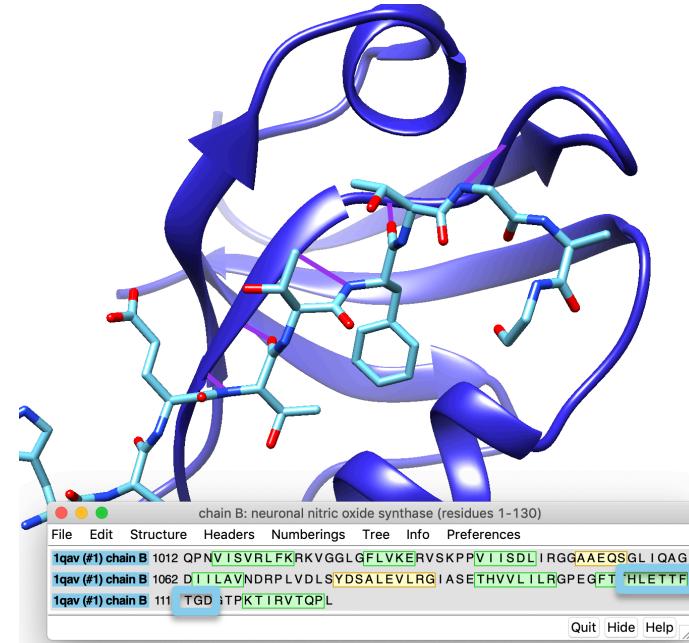


Computational and experimental approaches for SLiMs

How does SHANK1 bind to its internal ligand?



PDB: 1Q3P
SHANK1 and C-terminal ligand



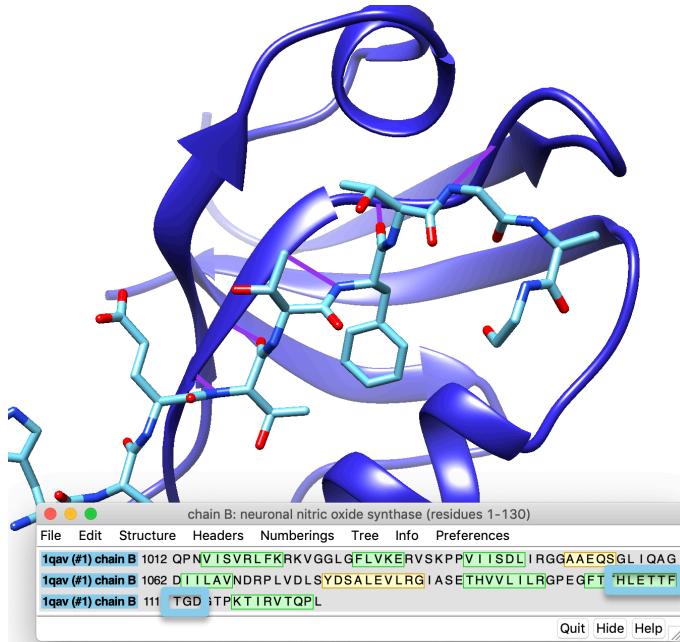
PDB: 1QAV
 α -1 syntrophin and internal ligand

in Chimera:

Tools → Structure Comparison → MatchMaker
Tools → Structure Comparison → Match -> Align

Computational and experimental approaches for SLIMs

Does beta-1 syntrophin bind internal ligands too?



PDB: 1QAV
 α -1 syntrophin and internal ligand

https://www.uniprot.org/uniprot/Q13884#family_and_domains

disks large 4-like pr... iTOL: Interactive Tr... Dacina PHAST: Home MView < Multiple S...

Family & Domainsⁱ

Domains and Repeats

Feature key	Position(s)	Description
Domain ⁱ	19 – 298	PH 1 PROSITE-ProRule annotation
Domain ⁱ	112 – 195	PDZ PROSITE-ProRule annotation
Domain ⁱ	322 – 433	PH 2 PROSITE-ProRule annotation
Domain ⁱ	482 – 538	SU

SWISS-MODEL

Start a New Modelling Project

Target Sequence(s):
(Format must be FASTA, Clustal, plain string, or a valid UniProtKB AC)

Paste your target sequence(s) or UniProtKB AC here

+ Upload Target Sequence File... Validate

Project Title: Untitled Project

Email: Optional

Search For Templates Build Model

Supported Inputs

- Sequence(s)
- Target-Template Alignment
- User Template
- DeepView Project

By using the SWISS-MODEL server, you agree to comply with the following [terms of use](#) and to cite the corresponding [articles](#).

Acknowledgements

Gibson team

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Thesis Advisory Committee

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Evangelia Petsalaki

Rebecca Wade

PDZnet consortium

Ylva Ivarsson

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Søren Østergaard

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