Metal-Protein Prediction Programs

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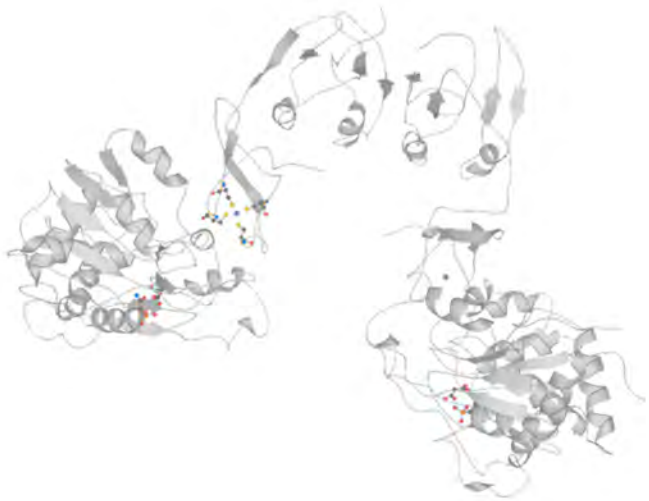
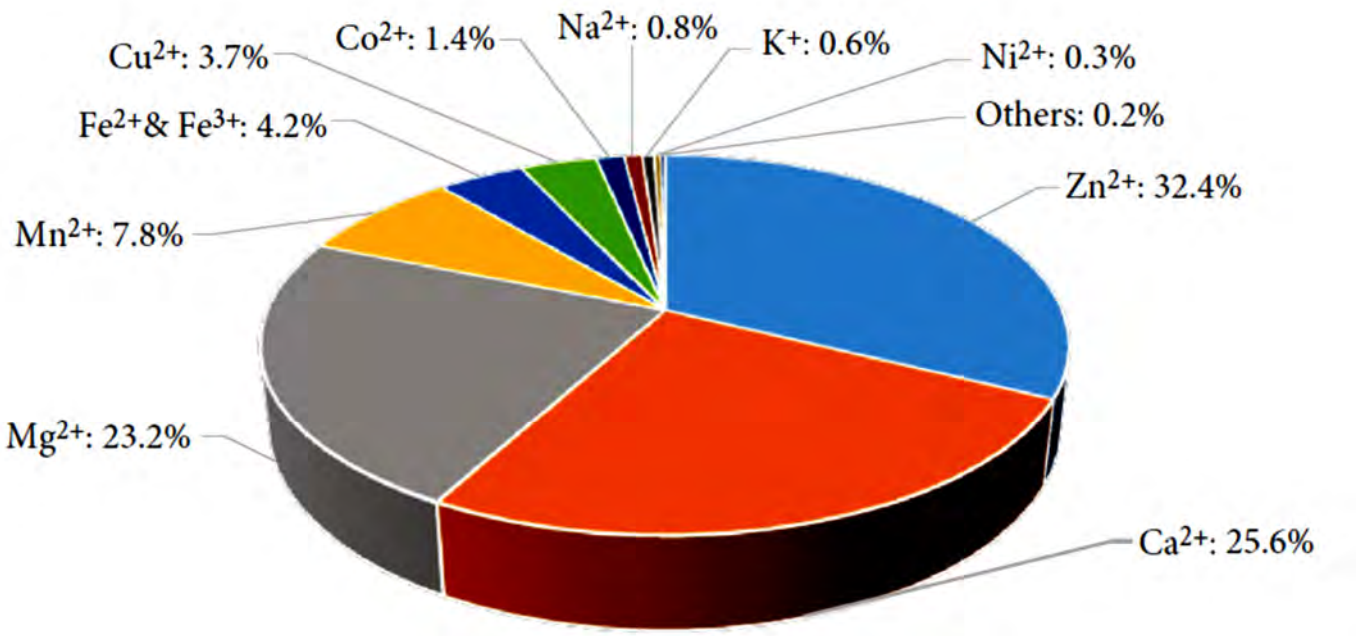
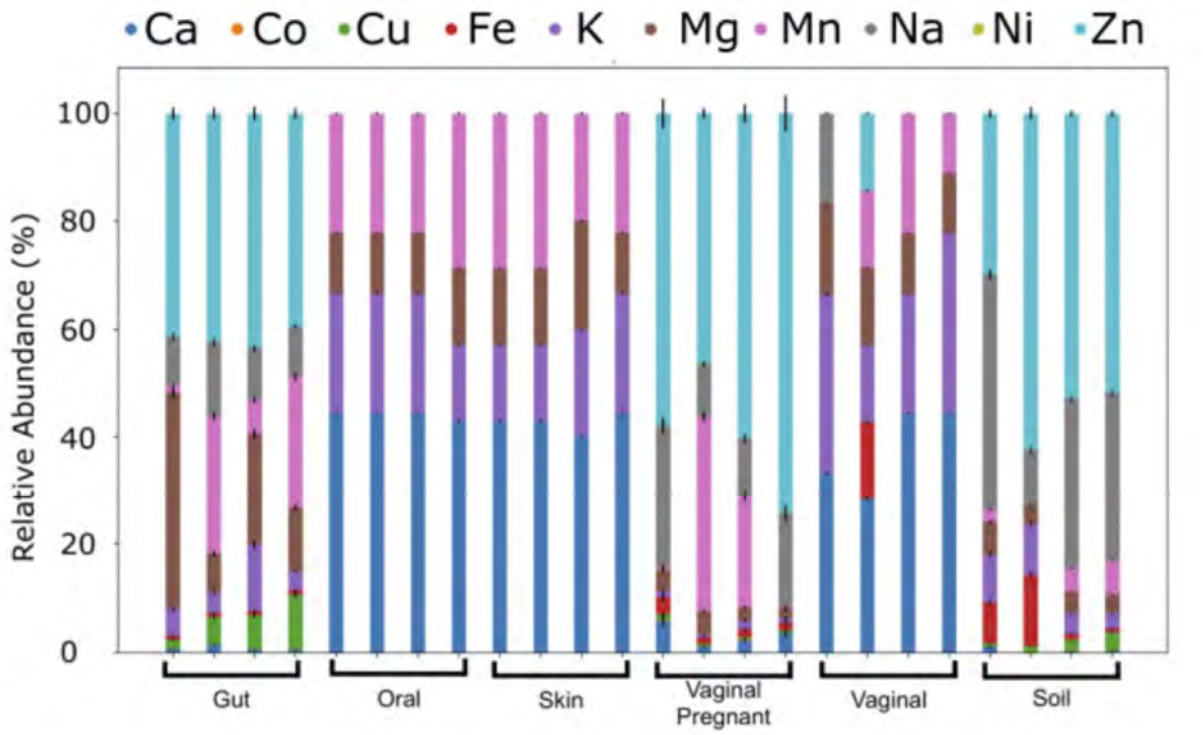


Top 10 metal-binding interactions stored in PDB



Abundance of predicted metal-binding proteins in human host and soil microbiomes by mebipred

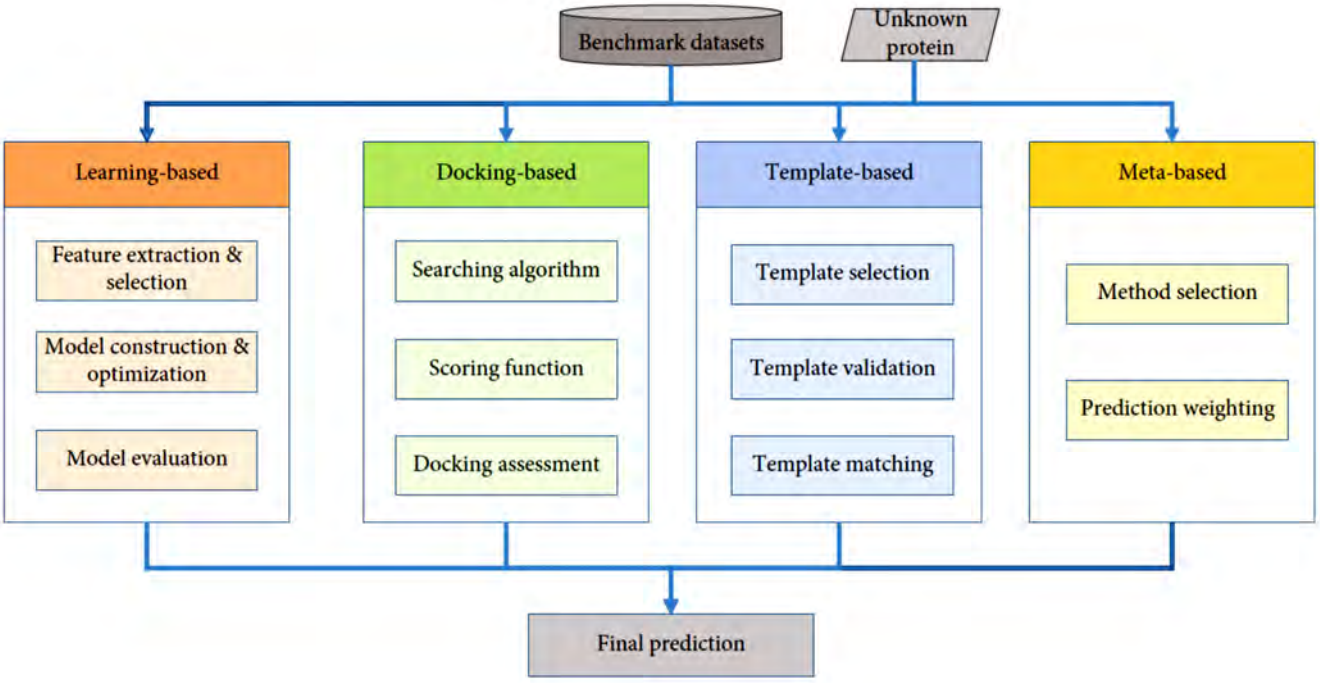


Database of Metal Ion Binding Interactions

Name	Year	Considered metal ions	Number of sites	Web link	Ref.	Citation	Availability
InterMetalDB	2021	All metal ion binding	6,423	https://intermetaldb.biotech.uni.wroc.pl/	[26]	N/A	Yes
MeLAD	2020	All metal ion binding	N/A	https://melad.ddtmlab.org/	[33]	9	Yes
ZincBindDB	2019	Zn	24,992	https://github.com/samirelanduk/ZincBindDB	[49]	23	Yes
MetalPDB (v2)	2018	All metal ion binding	N/A	http://metalweb.cerm.unifi.it	[34]	90	No
BioLiP	2013	All metal ion binding	146,969	https://zhanggroup.org/BioLiP/	[36]	446	Yes
ZiFDB (v2)	2013	Zn	N/A	http://bindr.gdcb.iastate.edu/ZiFDB	[37]	25	No
MetalPDB (v1)	2013	All metal ion binding	N/A	http://metalweb.cerm.unifi.it	[35]	108	No
BioMe	2012	All metal ion binding	20,307	http://metals.zesoi.fer.hr	[39]	30	No
MetLigDB	2011	Zn, Mn, Fe, Ni, mg, cu, co, Mo	732	http://silver.sejong.ac.kr/MetLigDB	[40]	13	Yes
MIPS	2010	All metal ion binding	N/A	http://dicsoft2.physics.iisc.ernet.in/mips/	[41]	28	Yes
MEDB	2010	All metal ion binding	N/A	http://www.uohyd.ernet.in/anambs/	[42]	14	No
ZiFDB (v1)	2009	Zn	N/A	http://bindr.gdcb.iastate.edu/ZiFDB	[38]	87	No
MetalMine	2009	All metal ion binding	412	http://metalmine.naist.jp	[43]	3	No
Metal-MACiE	2009	All metal ion binding	N/A	https://www.ebi.ac.uk/thornton-srv/databases/Metal_MACiE/home.html	[44]	60	Yes
ZifBASE	2009	Zn	N/A	https://web.iitd.ac.in/~sundar/zifbase/	[45]	35	Yes
MESPEUS	2008	Na, mg, K, ca, Mn, Fe, co, Ni, cu, Zn	34,896	http://eduliss.bch.ed.ac.uk/MESPEUS/	[46]	102	No
MSDsite	2005	All metal ion binding	N/A	http://www.ebi.ac.uk/msd-srv/msdsite	[47]	122	Yes
MDB	2002	All metal ion binding	N/A	http://metallo.scripps.edu/	[48]	276	No

[1]We estimate the availability on December 1st, 10th, and 20th of 2021, respectively.

Flowchart of computation-based methods for prediction of metal-binding residues



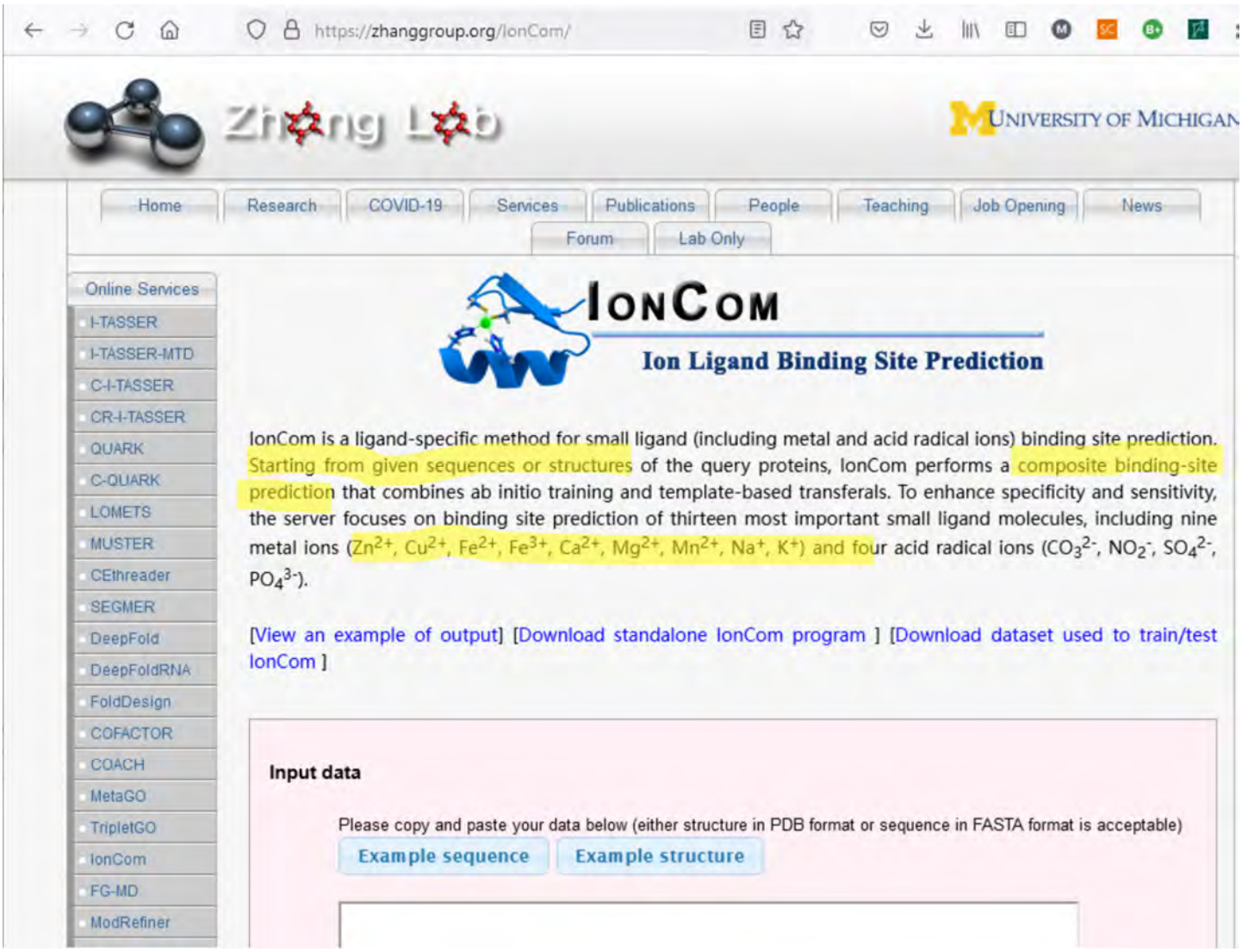
Summary of features and selection of learning/structure-based methods

Type	Method	Amino Acid Composition	Amino acid pairs[1]	Physiochemical properties	Position related	Evolution profile[2]	Conservation scores	Disorder	Secondary structure	Residue attributes	local structure	Contact graph[3]
Sequence-based	Liu et al.[56]	■		■		PWM			■			
	MIonSite [90]	■				PSSM	■		■			
	MPLs-Pred [91]			■		PSSM						
	SXGBsite[92]					PSSM						
	Wang et al. [50]	■		■		PMS	■		■			
	znMachine[51]		*k*-Spaced			PSSM	■		■			
	SSWPNN[93]				■	PSSM	■					
	ZinCaps[94]	■		■								
	Haberal et al.[65]	■		■		PAM						
	ZincBinder[87]	■				PSSM		■	■			
	EC-RUS [95]					PSSM						
	Cao et al.[52]	■		■			■		■			
	Kumar[96]	■	■	■								
	DeepMBS[97]					PAM						
	Qiao et al.[98]					PSSM	■		■			
	IonCom[99]					PSSM						
	Jiang et al.[77]	■		■	■	EMS						
	TargetCom[53]					PSSM	■		■			
	OSML[100]					PSSM			■			
	TargetS[101]	■		■		PSSM			■			
	ETMB-RBF [102]					PSSM						
	ZincExplorer[103]		*k*-Spaced			PSSM						
	Horst et al.[58]	■		■		PSSM	■					
Structure-based	Nguyen et al[104]											
	TMP-MIBS [54]			■		PSSM						TS
	Zincbindpredict[105]	■		■								
	Wang et al.[81]	■		■			■		■			
	DELIA[80]					PSSM	■		■			DM
	Hu et al.[57]			■		PWM			■			
	MetalExplorer[79]	■			■		■	■	■			GTN
	FINDSITE-metal[55]											
	Zincidentifier[78]				■		■	■	■			RRCG

Predictive Tools of Metal-Binding Residues

Method	Year	Platform[1]	Web link	Availability[2]
TMP-MIBS [54]	2021	SS	https://github.com/QuJing785464/TMP_MIBS	Yes
Wang et al. [50]	2021	WS	http://39.104.77.103:8081/lsb/HomePage/HomePage.html	No
Zincbindpredict [105]	2021	WS	https://zincbind.bioinf.org.uk/predict/	No
DELIA [80]	2020	WS	http://www.csbio.sjtu.edu.cn/bioinf/delia/	Yes
BioMetAll [151]	2020	SS	https://github.com/insilichem/biometall	Yes
MPLs-Pred [91]	2019	WS	http://icdtools.nenu.edu.cn/	Yes
SXGBsite [92]	2019	SS	https://github.com/Lightness7/SXGBsite	Yes
MIonSite [90]	2019	SS	https://github.com/LiangQiaoGu/MIonSite.git	Yes
znMachine [51]	2019	WS&SS	http://bioinformatics.fzu.edu.cn/znMachine.html	No
ZinCaps [94]	2019	SS	https://github.com/clemEssien/ActiveSitePrediction	Yes
EC-RUS [95]	2017	SS	https://github.com/6gbluewind/protein_ligand_binding_site	Yes
MetalExplorer [79]	2017	WS	http://metalexplorer.erc.monash.edu.au/	No
Cao et al. [52]	2017	WS	http://60.31.198.140:8081/metal/HomePage/HomePage.html	No
ZincBinder [103]	2017	WS&SS	http://proteininformatics.org/mkumar/znbinder/	Yes
SSWPNN [93]	2017	SS	http://net.jitsec.cn:88/UploadedImages/SSWPNN.rar	Yes
Jiang et al. [77]	2016	WS	http://202.207.29.245/	No
TargetCom [53]	2016	SS	http://dase.ecnu.edu.cn/qwdong/TargetCom/TargetCom_standalone.tar.gz	No
OSML [100]	2015	WS	http://www.csbio.sjtu.edu.cn/OSML/	Yes
mFASD [148]	2015	SS	http://staff.ustc.edu.cn/liangzhi/mfasd/	Yes
FunFOLD2 [157]	2013	WS	http://www.reading.ac.uk/bioinf/FunFOLD/FunFOLD_form_2_0.html	Yes
ZincExplorer [103]	2013	WS	http://protein.cau.edu.cn/ZincExplorer	No
TargetS [101]	2013	WS	http://www.csbio.sjtu.edu.cn/TargetS/	Yes
FunFOLDQA [156]	2012	SS	http://www.reading.ac.uk/bioinf/downloads/	Yes
Zincidentifier [78]	2012	WS	http://protein.cau.edu.cn/zincidentifier/	No
FINDSITE-metal [55]	2011	WS	http://cssb.biology.gatech.edu/findsite-metal/	No
FunFOLD [155]	2011	WS&SS	http://www.reading.ac.uk/bioinf/FunFOLD/	Yes
Goyal et al. [153]	2008	WS	http://sunserver.cdfd.org.in:8080/protease/PAR_3D/index.html	No
Deng et al. [152]	2006	SS	http://chemistry.gsu.edu/faculty/Yang/GG.htm	No

[1]WS: web server; SS: standalone software. [2]The availability was estimated on Dec 1st, 10th, and 20th of 2021, respectively.



results for ZN

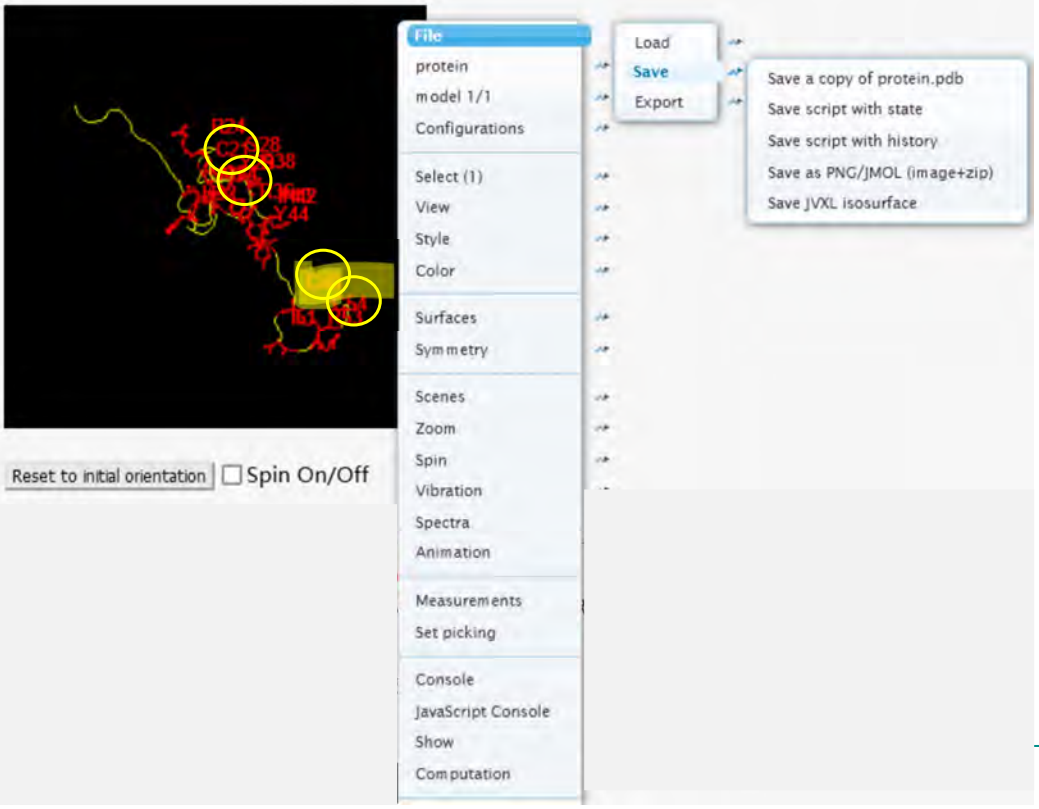
Squence (Binding Residues Highlighted in Red Color):

YWRRTKYYISYGALSAN RVPC PPR SGRS Y YTH N C FR AR GPVH P Y SRGC SSI TR C RR

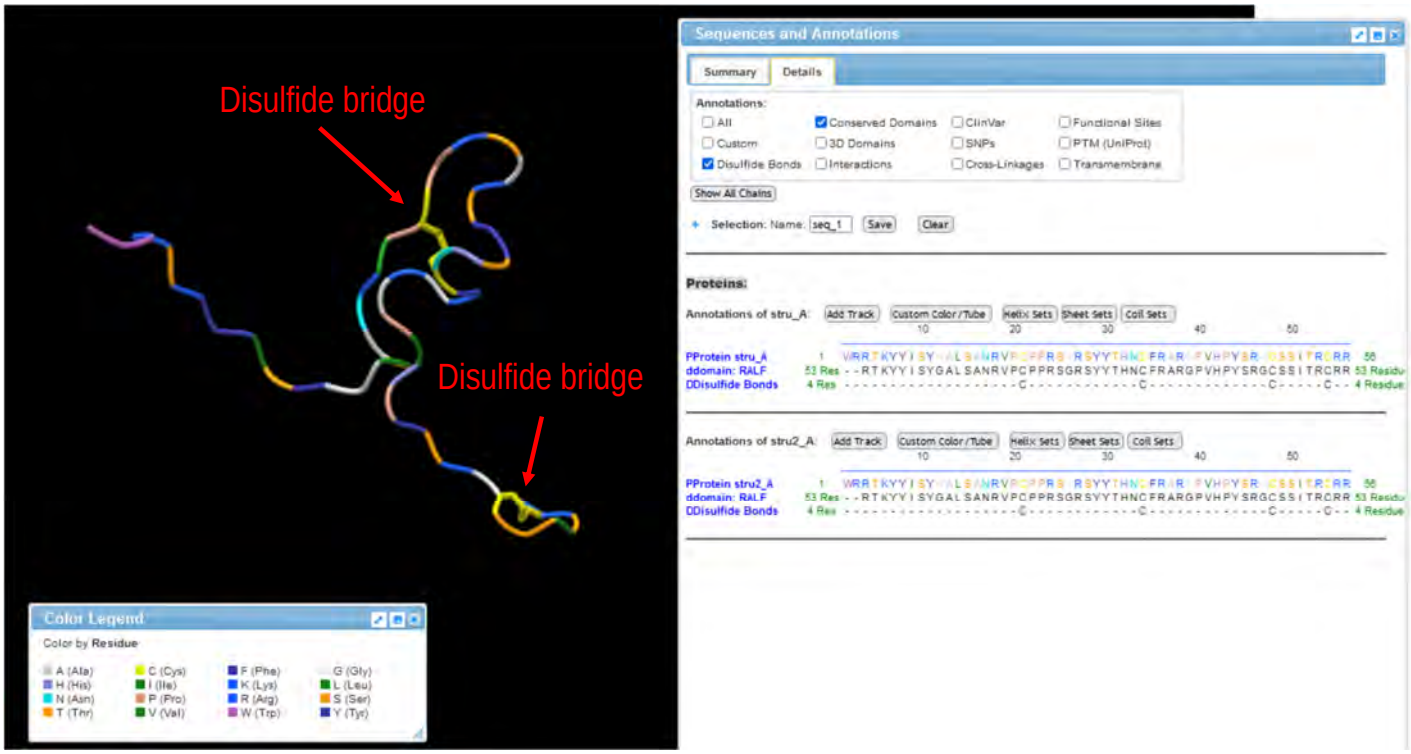
Predicted Binding Residue(s):

N17 C21 R24 S28 Y29 H32 N33 C34 R36 R38 H42 P43 Y44 C48 I51 R53 C54

3D View:



Visualized with iCn3D



https://www.ncbi.nlm.nih.gov/Structure/icn3d/full.html

I-TASSER

Protein Structure & Function Predictions

(The server completed predictions for 744289 proteins submitted by 183385 users from 160 countries)
(The template library was updated on 2023/05/01)

I-TASSER (Iterative Threading ASSEmbly Refinement) is a hierarchical approach to protein structure prediction and structure-based function annotation. It first identifies structural templates from the PDB by multiple threading approach LOMETS, with full-length atomic models constructed by iterative template-based fragment assembly simulations. Function insights of the target are then derived by re-threading the 3D models through protein function database BioLiP. I-TASSER (as 'Zhang-Server' or 'UM-TBM') was ranked as the No 1 server for protein structure prediction in recent community-wide CASP7, CASP8, CASP9, CASP10, CASP11, CASP12, CASP13, CASP14, and CASP15 experiments. It was also ranked the best for function prediction in CASP9. The server is in active development with the goal to provide the most accurate protein structure and function predictions using state-of-the-art algorithms. The server is only for non-commercial use. Please report problems and questions at I-TASSER message board and our developers will study and answer the questions accordingly. (>> More about the server ...)

D-I-TASSER: An updated I-TASSER pipeline built on deep neural network learning NEW

[Queue] [Forum] [Download] [Search] [Registration] [Statistics] [Remove] [Potential] [Decoys] [News] [Annotation] [About] [FAQ]

I-TASSER On-line Server (View an example of I-TASSER output):

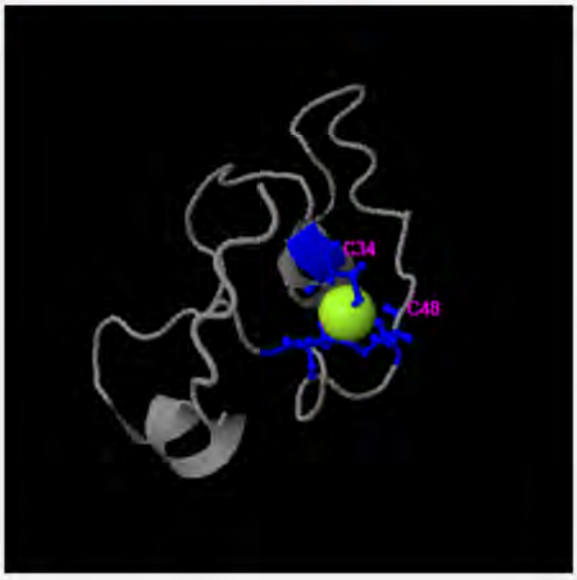
Copy and paste your sequence within [10, 1500] residues in FASTA format. Click here for a sample input:

Result of a Potential Metal-Binding Peptide

Predicted function using COFACTOR and COACH

(This section reports biological annotations of the target protein by COFACTOR and COACH based on the I-TASSER structure prediction. While COFACTOR deduces protein functions (ligand-binding sites, EC and GO) using structure comparison and protein-protein networks, COACH is a meta-server approach that combines multiple function annotation results (on ligand-binding sites) from the COFACTOR, TM-SITE and S-SITE programs.)

Ligand binding sites



Click to view	Rank	C-score	Cluster size	PDB Hit	Lig Name	Download Complex	Ligand Binding Site Residues
○	1	0.09	3	1e7iA	STE	Rep, Mult	7,12,28,30
○	2	0.09	3	4h03A	EDO	Rep, Mult	11,15
◉	3	0.06	2	2mziB	ZN	Rep, Mult	34,48,54
○	4	0.06	2	4woqD	2KT	Rep, Mult	8,9
○	5	0.06	2	5dwkB	78N	Rep, Mult	9,18

Download the residue-specific ligand binding probability, which is estimated by SVM
Download the all possible binding ligands and detailed prediction summary
Download the templates clustering results.

(a) **C-score** is the confidence score of the prediction. C-score ranges [0-1], where a higher score indicat
(b) **Cluster size** is the total number of templates in a cluster.
(c) **Lig Name** is name of possible binding ligand. Click the name to view its information in the BioLiP da
(d) **Rep** is a single complex structure with the most representative ligand in the cluster, i.e., the one list
Mult is the complex structures with all potential binding ligands in the cluster.

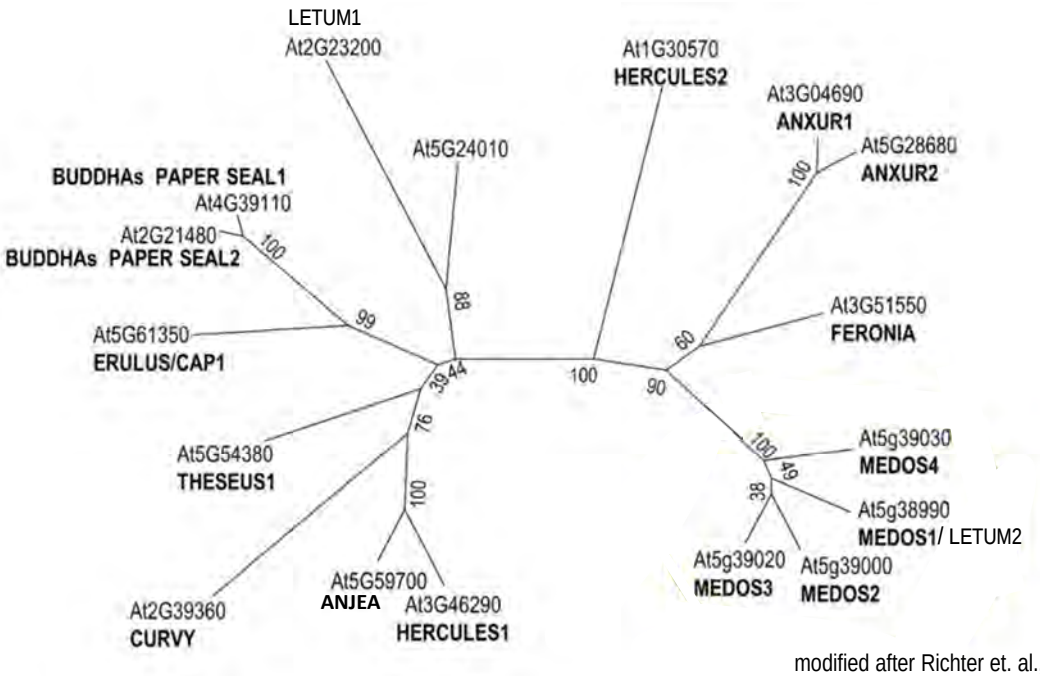
Contains in total 853.214 receptor-ligand interactions and 182784 with metal-ligands (Zhang et al., 2023)

Entries	Ions
59524	Zn^{2+}
46807	Mg^{2+}
41809	Ca^{2+}
12242	Mn^{2+}
2089	Co^{2+}
6867	Fe^{3+}
6184	Cu^{2+}
933	Na^{+}
629	K^{+}
404	Ni^{2+}
224	Cd^{2+}
16	Sr^{2+}
9	Sb^{3+}

https://seq2fun.dcmb.med.umich.edu//BioLiP/qsearch.cgi

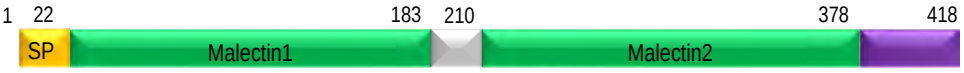
Catharanthus roseus Receptor Like Kinsase 1 Like Family (*Cr*RLK1L)

extracellular/ectodomain exJm cytoplasmic domain

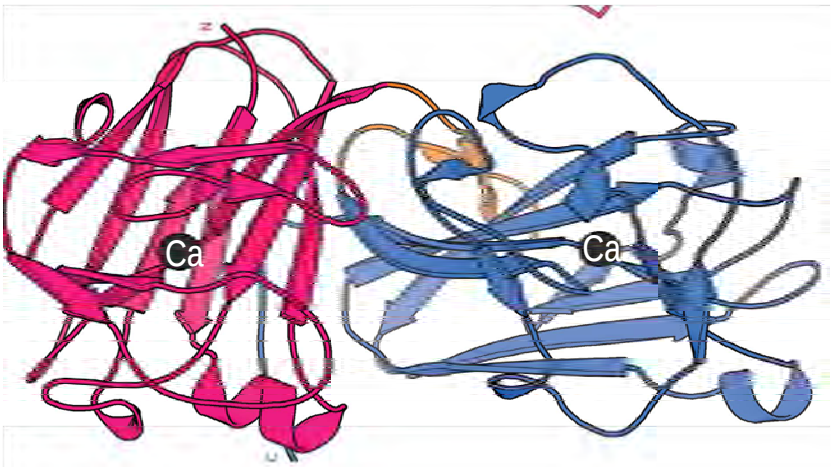


modified after Richter et. al., 2018

The ectodomain one member ANX*Cr*RLK1Ls



extracellular/ectodomain exJm



Malectin-like domains of ANX1 are structurally stabilized by Ca^{2+}

Moussu et al., 2018

Du et al., 2018

Ligands of the *Cr*RLK1L THESEUS1 predicted by IonCOM

results for CA

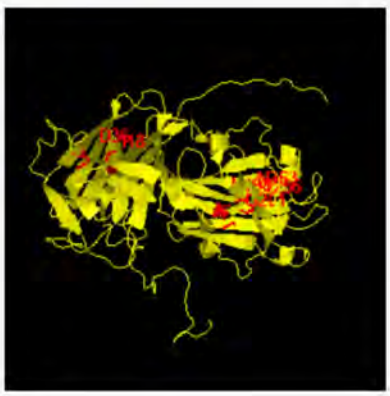
Squence (Binding Residues Highlighted in Red Colo

YTTTTSSALFNPPDNYLI SCGSSQNITFQNRIFVPD SLHSS
SLGRHWIRLHFSPINNSTNLTSASITVVTEDFVLLNNFSFNN
VPDNLIPDQALALNPSTPFSGLSLLAFETVYRLN MGG PLL
PSVTQETAPNMVYAT ADTMGDANVASPSFNVTWVLPVD
LSTLTNGLKVPYFKDFISNGSVESSGVLTVSVGPDSQADITN
KAV

Predicted Binding Residue(s):

I18 D36 N198 G201 T256 N363

3D View:



results for ZN

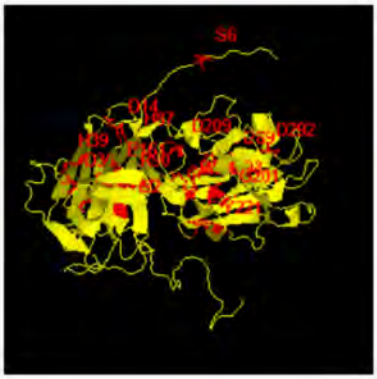
Squence (Binding Residues Highlighted in Red Color):

YTTTTS SALFNPPD NYLISC GSSQNITFQNRIFVPD SLH SSLVLKIGNSSVATSTTSNNSTNSIYQTARVFSSLASYRFK
ITSLGRH WIR LH FSPINNSTNLTSASITVVTEDFVLLNNFSFNNFNGSYIFKEYTVNVTSEFLTLSFIPSNNSVVFVNAIE
VVSVPDNLIPDQALALNPSTPFSGLSLLAFETVYR LN MGG PLLTSQND TLGRQW DNDAEY LHVNSSVLVVTANPS
SIKYSPSVTQETAPNMVYATADTMGDANVASPSFNVTWVLPVDPDFRYFVRVH FCD IVSQALNTLVFNLYVNDDLAL
GSLDLSTLTNGLKVPYFKDFISNGSVE SSGVLTVSVGPDSQADITNATMNGLEVLKISNEAKSLSGVSSVKSLLPGGSGS
KSKKKAV

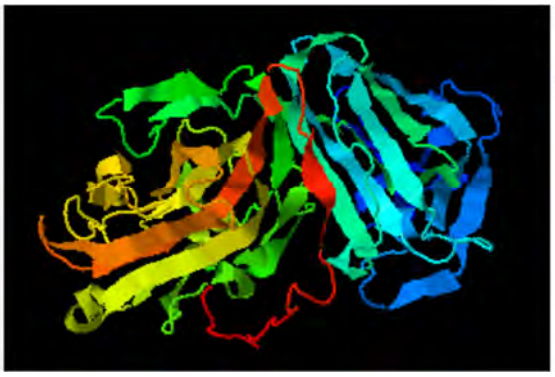
Predicted Binding Residue(s):

S6 D14 C20 D36 H39 H87 R90 H92 E161 R196 N198 G201 D209
W215 Y221 H289 D292 E340

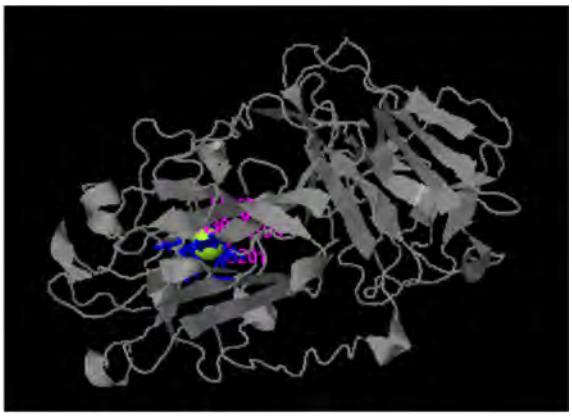
3D View:

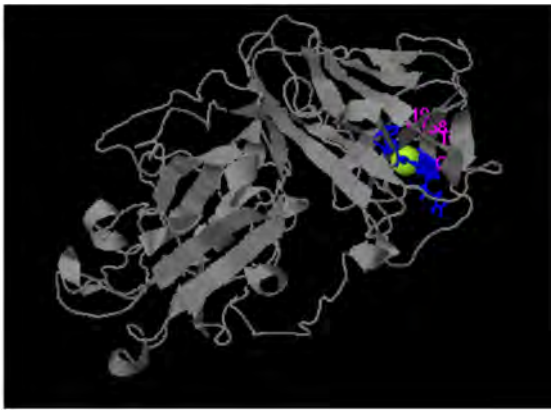


Ligands of the *Cr*RLK1L THESEUS1 predicted by i-TASSER



Click to view	Rank	C-score	Cluster size	PDB Hit	Lig Name	Download Complex	Ligand Binding Site Residues
◉	1	0.08	4	4itcA	CA	Rep, Mult	198,201,252,256,363,364
○	2	0.08	4	5a55A	CA	Rep, Mult	19,66,67,158
○	3	0.08	4	1cdgA	MAL	Rep, Mult	82,83,84,85,86,87,112,114,145
○	4	0.04	2	1cgvA	MAL	Rep, Mult	82,86,87,88,112,113,145
○	5	0.02	1	4k3xE	FUC	Rep, Mult	181,182





MIB2 : Metal Ion-Binding site prediction and modeling server

Computational Biology Labortory, National Yang Ming Chiao Tung University

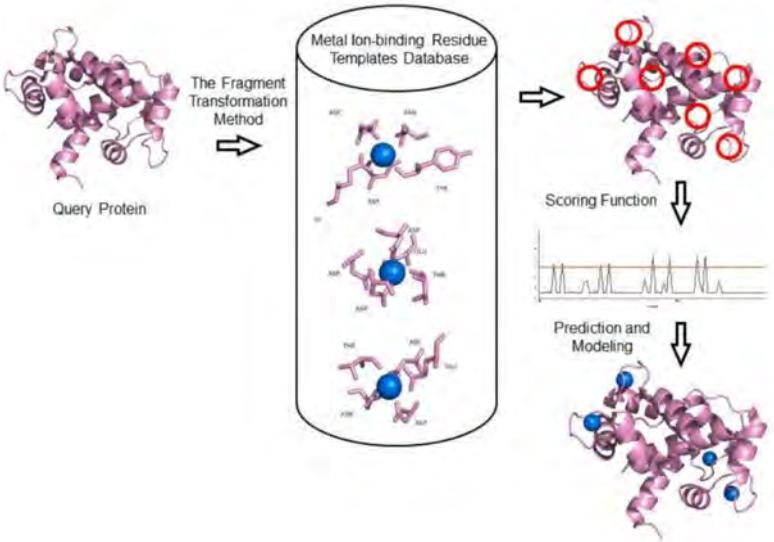
Computational Biology Labortory, China Medical University

http://combio.life.nctu.edu.tw/MIB2/

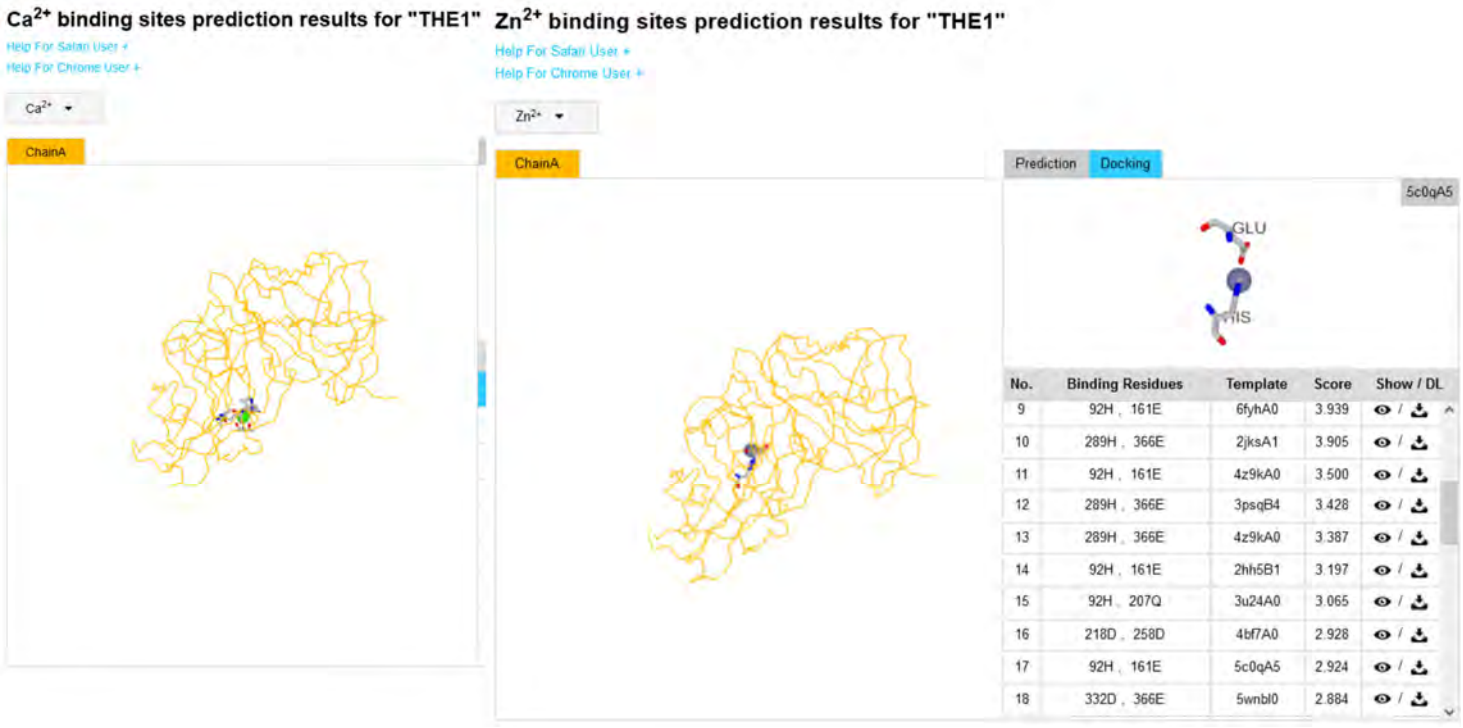
searches residues in metal ion-binding sites by using the fragment transformation method

utilizes both the $(PS)^2$ method and the AlphaFold protein structure database to acquire 3D information and performs metal ion docking and predict binding residues.

updated version of MIB, MIB2 offers a total of 18 types of metal ions (Ca^{2+}, Cu^{2+}, Fe^{3+}, Mg^{2+}, Mn^{2+}, Zn^{2+}, Cd^{2+}, Fe^{2+} ,Ni^{2+}, Hg^{2+}, Co^{2+}, Cu^{+}, Au^{+}, Ba^{2+}, Pb^{2+}, Pt^{2+}, Sm^{3+}, and Sr^{2+}).



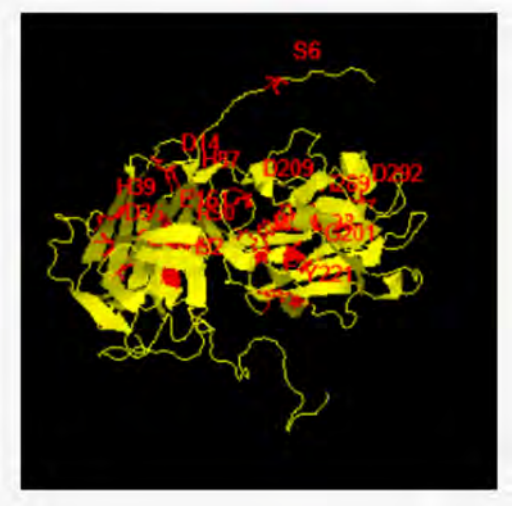
Ca^{2+} as ligand predicted by MIB2 of the *Cr*RLK1L THESEUS1



Comparison of THESEUS1 prediction for Ca^{2+} by IonCOM, i-TASSER, MIB2

IonCOM	i-TASSER	MIB2
I18	S19	S19
		C20
D36		
		I64
	66	
	T67	T67
	N158	N158
N198	N198	N198
		M199
G201	G201	(G201)
		V253
T256	T256	T256
N363	N363	N363
	364	

Comparison of THESEUS1 prediction for Zn^{2+} by IonCOM, ~~i-TASSER~~, MIB2



IonCOM	S6, D14, C20, D36, H39, H87, R90, H92, E161, R196, N198, G201, D209, W215, Y221, H289, D292, E340
MIB2	87H, 92H, 112E , 132K,141E, 161E, 207Q, 218D, 216D, 220E, 258D, 287R, 289H, 332D, 365L, 366E,

What do we learn from predictions?

1) Useful for structure function analyses

2) Crystal structures are essential for final proof

Thanks to

Julia Richter
Cornelia Konlechner
Mine Türktas
Marie Ploderer
Fariha Naz Apon
Sara Haghani
Stefanie Strobl
Shengqing Shi
Peter Stasnik
Julian Kelner
Ali Ünal
Serap Afsar
Eliza Polanyi

Herman Höfte (INRAE)
Jérôme Pelloux (Univ. Picardie)
Laurent Gutierrez (Univ. Picardie)
Markus Puschenreiter (BOKU)
Eva Oburger (BOKU)

FWF L433-B17, L561-B17, I1725-B16