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Conference on Structure and Dynamics in Soft Matter and Biomolecules: From Single Molecules to Ensembles

4 - 8 June 2007

The role of intrinsic structural disorder on protein-protein interactions

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The role of intrinsic structural disorder in protein-protein interactions

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1) disorder: general introduction

2) disorder: functional classification

3) disorder: its role in protein-protein interactions

1) **disorder: general introduction**

2) disorder: functional classification

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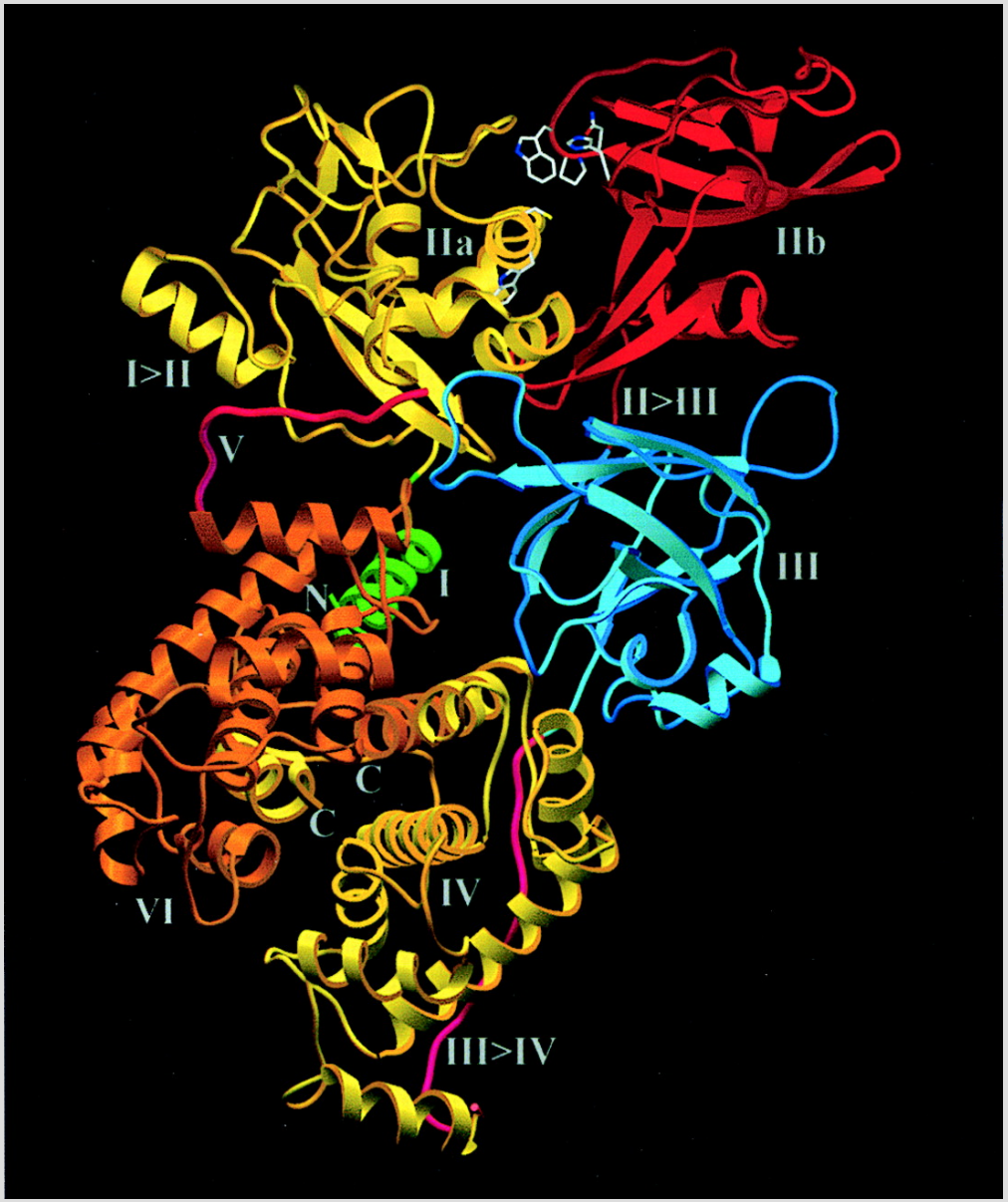
The X-ray structure of human m-calpain



Strobl et al. (2000) *PNAS USA* 97, 588

Early observations

Neurochemical Research, Vol. 17, No. 2, 1992, pp. 157–166

Is Myelin Basic Protein Crystallizable?

Jan Sedzik[1,2] and Daniel A. Kirschner[1]

(Accepted June 18, 1991)

Early observations

melting and other isobaric phase changes.

Jordan[2,8] instead attributes the high velocities below 200 km under shields to petrologically distinct material which accumulated during the early chemical fractionation of the continents. This compositional root must move with the underlying continental plate and it must resist the erosive effects of thermal convection in the surrounding system. It is also necessary to juggle possible chemical and temperature effects in the deep root to explain the absence of geoid (gravitational) anomalies associated with shields.

Additional evidence for the unusual properties of the deep continental environment have come from thermobarometry studies[9] of mantle xenoliths (emplaced rock fragments) and modelling studies of surface heat-flow measurements within and along the margins of continental shields[10]. These indicate that low temperatures underlying the upper 200 km of continental shields have persisted for up to 3,500 million years, despite dynamic processes which tend to destabilize thick thermal boundary layers. A thick, durable chemical and thermal boundary layer which formed very early in the continental evolution could explain this. But the interpretation is complicated by the intrinsic tendency of continents to override cool subducting oceanic plates, which provides an alternative mechanism for maintaining long-term lower temperatures beneath continents[7].

Although continental areas cover only one-third of the Earth's surface, and the stable shield regions are only a fraction of this area, it is still critical to resolve the thickness of the coherently translating surface plates. The maximum depth of the within continental regions. In fact, the most extreme lateral variations in shear velocity in the upper 300 km of the mantle that we know of are found between the Canadian shield and the tectonic belt of western North America. Temperature causes stronger variations in shear velocities than in compressional velocities, and thermally activated processes are also the cause of anelastic attenuation of seismic waves. Thus, modelling of regional variations in seismic attenuation, together with studies of the elastic velocities, could be the key to apportioning the chemical and thermal interpretations of the deep continental root controversy. □

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Transcriptional activation

Acid blobs and negative noodles

Paul B. Sigler

THE more that is known about the amino-acid sequences of proteins that participate in transcriptional activation, the clearer it becomes that many of the critical events cannot depend upon the precise geometrical complementarity that we associate with the interactions of globular proteins during molecular assembly, and the binding of substrates, cofactors and haptens. The latest entries in this chronicle of molecular imprecision are the activator domains of the proteins that stimulate for correct placement and orientation with respect to the start site of transcription[1]. The promoter sequences are a defined distance upstream of the transcriptional start site. Modulating the activity of the incipient transcriptional complexes is a wide variety of transcriptional activator proteins that bind to specific DNA targets called by various names, such as 'enhancers', upstream activating sequences (UASs) or hormone response elements (HREs). The position and polarity of

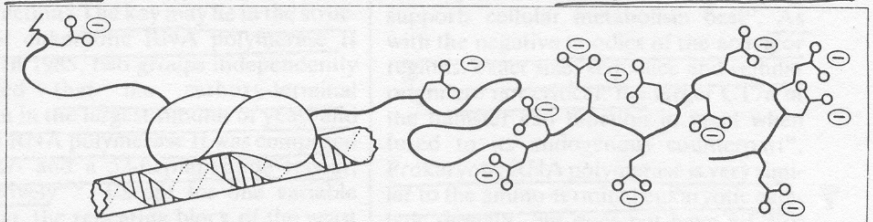
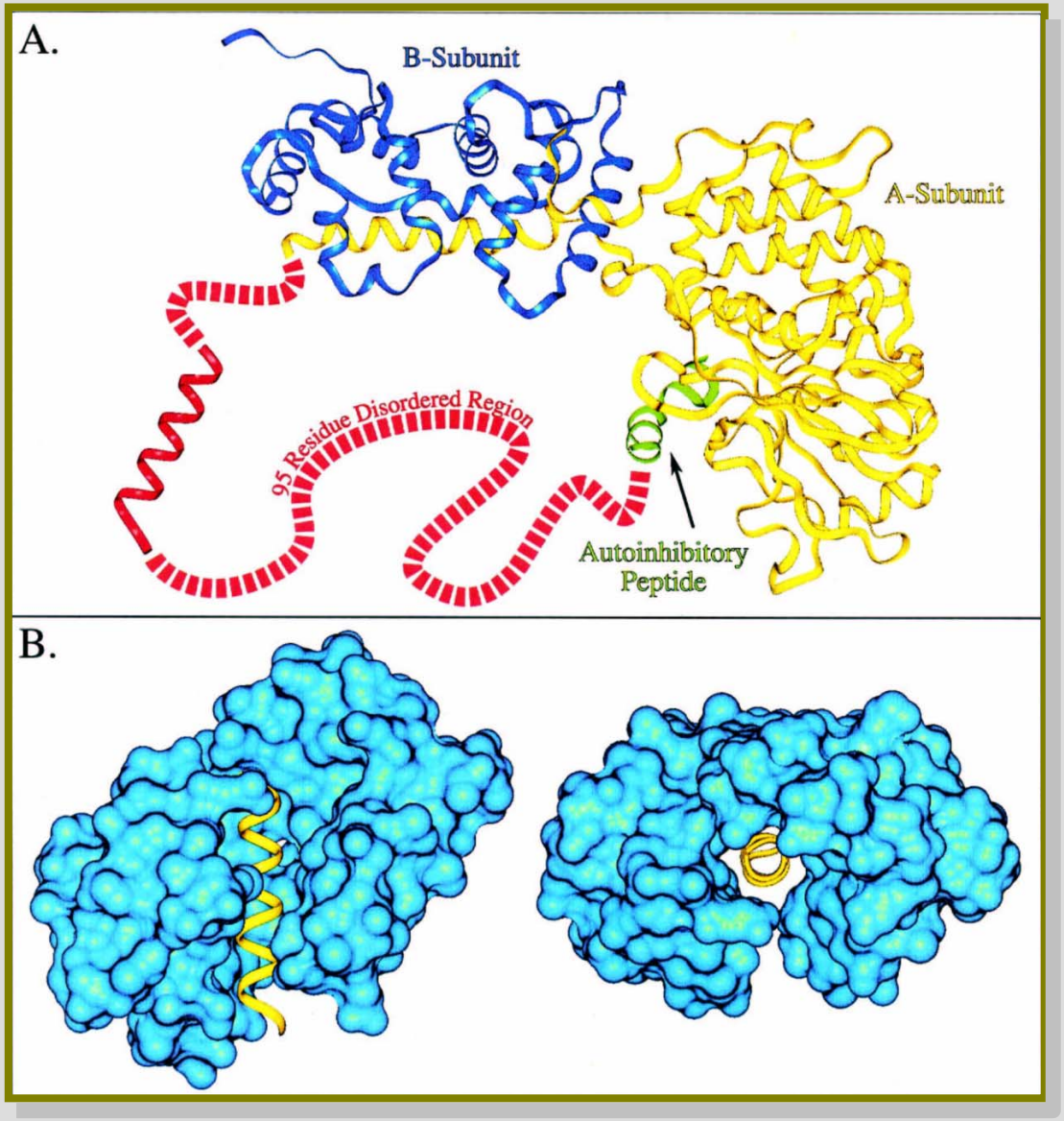


Fig. 1 A generic transcriptional-regulatory protein. A DNA-binding domain with a well-defined conformation (often dimeric) and a peptide with an excess of negatively charged side chains that has a poorly defined conformation (here, none at all).

An enzyme that made the difference: calcineurin



A change in paradigm: Dunker, 1998

Predicting Disordered Regions from Amino Acid Sequence: Common Themes Despite Differing Structural Characterization

Ethan Garner [1] Paul Cannon [2] Pedro Romero [2]

THOUSANDS OF PROTEINS LIKELY TO HAVE LONG DISORDERED REGIONS

PEDRO ROMERO, ZORAN OBRADOVIC
School of Electrical Engineering and Computer Science
Washington State University, Pullman, WA 99164

PROTEIN DISORDER AND THE EVOLUTION OF MOLECULAR RECOGNITION: THEORY, PREDICTIONS AND OBSERVATIONS

A. K. DUNKER, E. GARNER, S. GUILLIOT
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Department of Biochemistry & Biophysics,
Washington State University, Pullman, WA 99164-4660

A change in paradigm: Wright and Dyson, 1999

Article No. jmbi.1999.3110 available online at http://www.idealibrary.com on IDEAL® J. Mol. Biol. (1999) 293, 321–331

JMB

Intrinsically Unstructured Proteins: Re-assessing the Protein Structure-Function Paradigm

Peter E. Wright* and H. Jane Dyson*

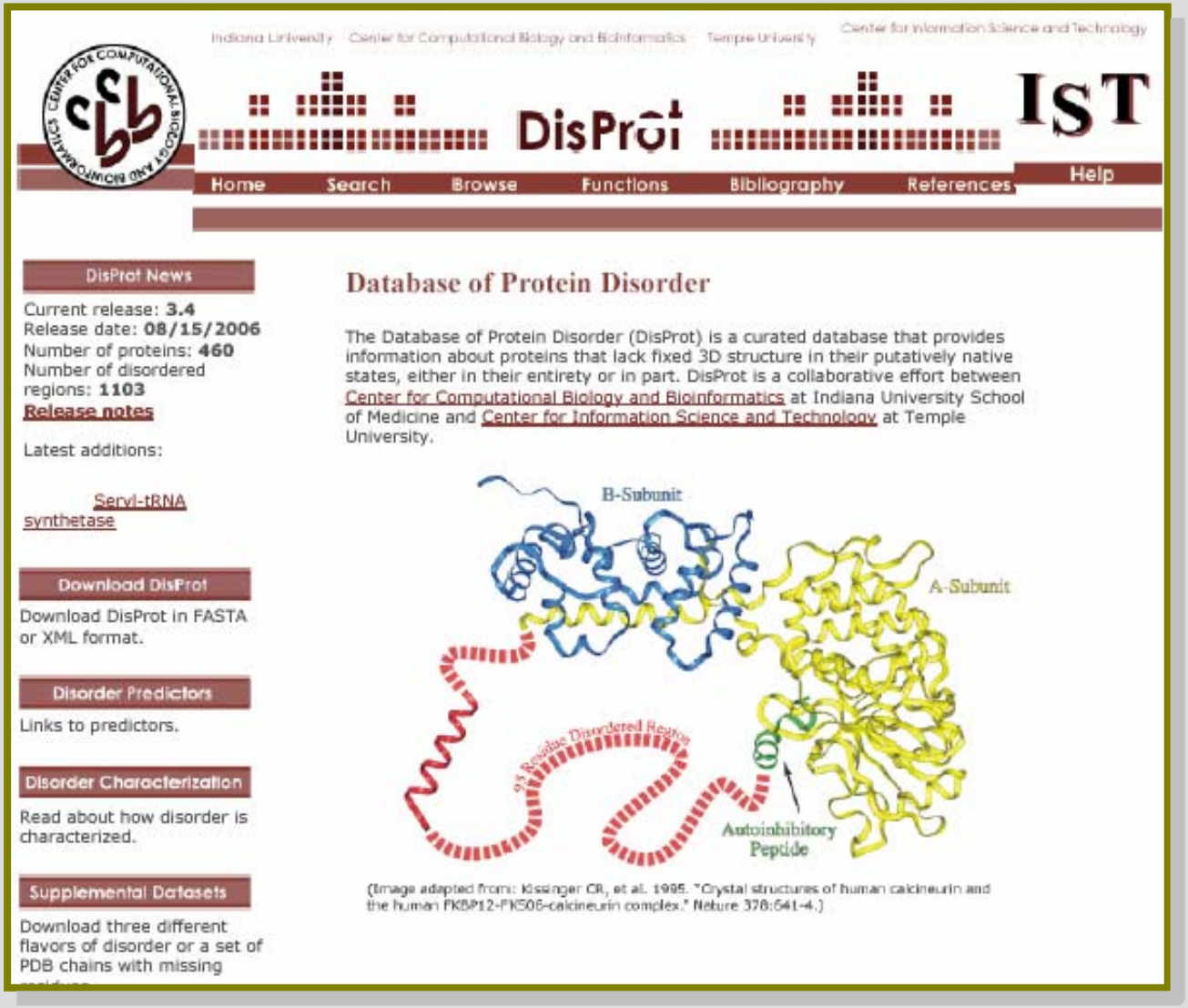
Department of Molecular Biology and Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla CA 92037, USA

A major challenge in the post-genome era will be determination of the functions of the encoded protein sequences. Since it is generally assumed that the function of a protein is closely linked to its three-dimensional structure, prediction or experimental determination of the library of protein structures is a matter of high priority. However, a large proportion of gene sequences appear to code not for folded, globular proteins, but for long stretches of amino acids that are likely to be either unfolded in solution or adopt non-globular structures of unknown conformation. Characterization of the conformational propensities and function of the non-globular protein sequences represents a major challenge. The high proportion of these sequences in the genomes of all organisms studied to date argues for important, as yet unknown functions, since there could be no other reason for their persistence throughout evolution. Clearly the assumption that a folded three-dimensional structure is necessary for function needs to be re-examined. Although the functions of many pro-

Intrinsically unstructured proteins (IUPs/IDPs)

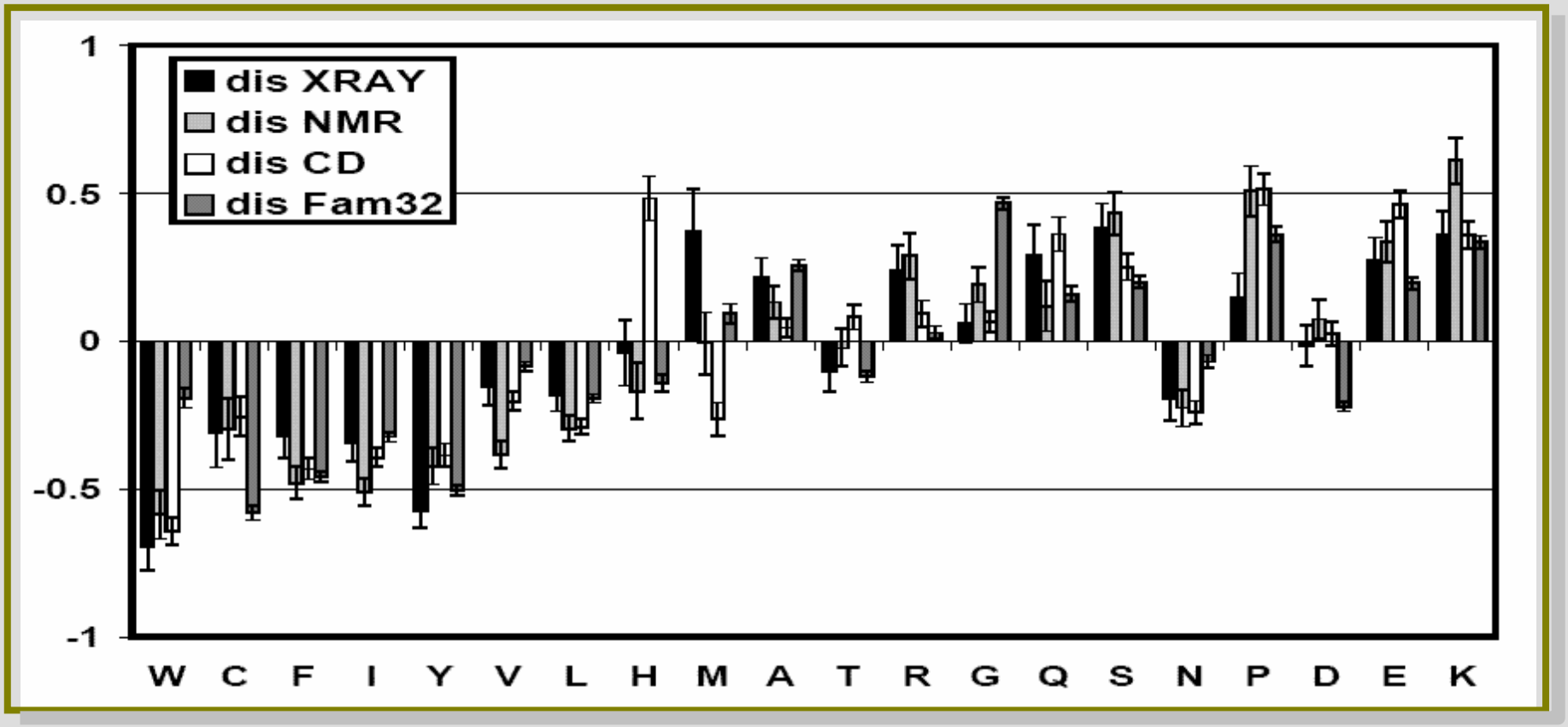
1) I*n vitro* evidence (X-ray, NMR, CD, SAXS, limited proteolysis…) shows that they lack a well-defined 3D structure (look like denatured globular proteins)
2) Evidence *in vivo* (rapid evolution, binding in an open conformation, predictability…)
3) Provides functional advantages (special functions, specificity without strong binding, binding promiscuity, increased speed of interaction…)
4) Frequent in proteomes

DisProt, http://www.disprot.org



Sickmeier et al. (2007) *NAR* 35, D786

The primary cause of disorder: AA composition



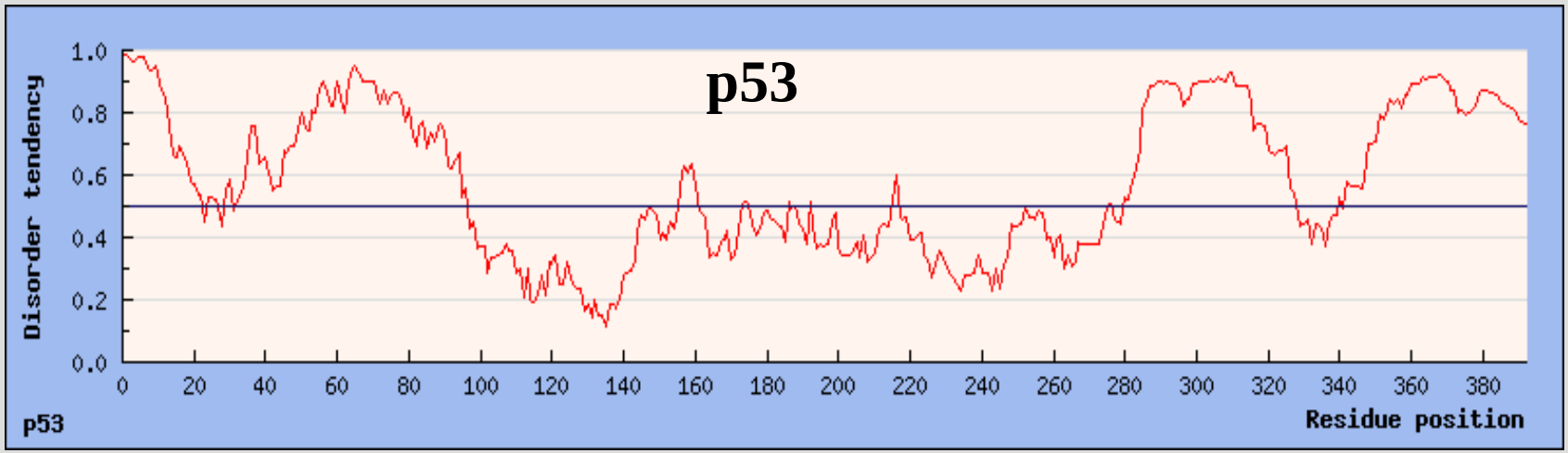
order-promoting

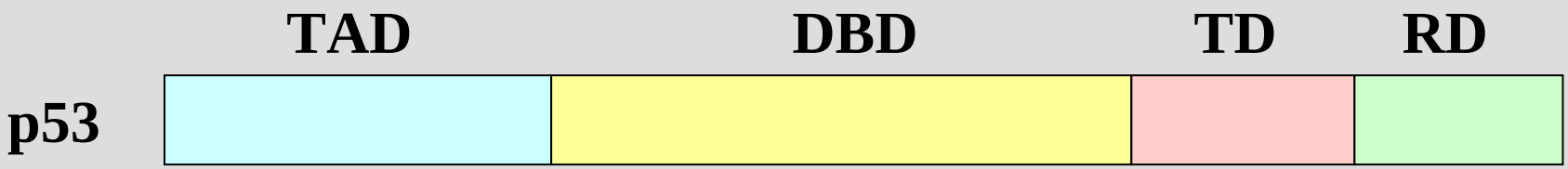
disorder-promoting

Dunker et al. (2001) *J. Mol. Graph. Model.* 19, 26

Prediction of disorder: IUPred

http://iupred.enzim.hu





Dosztányi (2005) *J. Mol. Biol. 347, 827*

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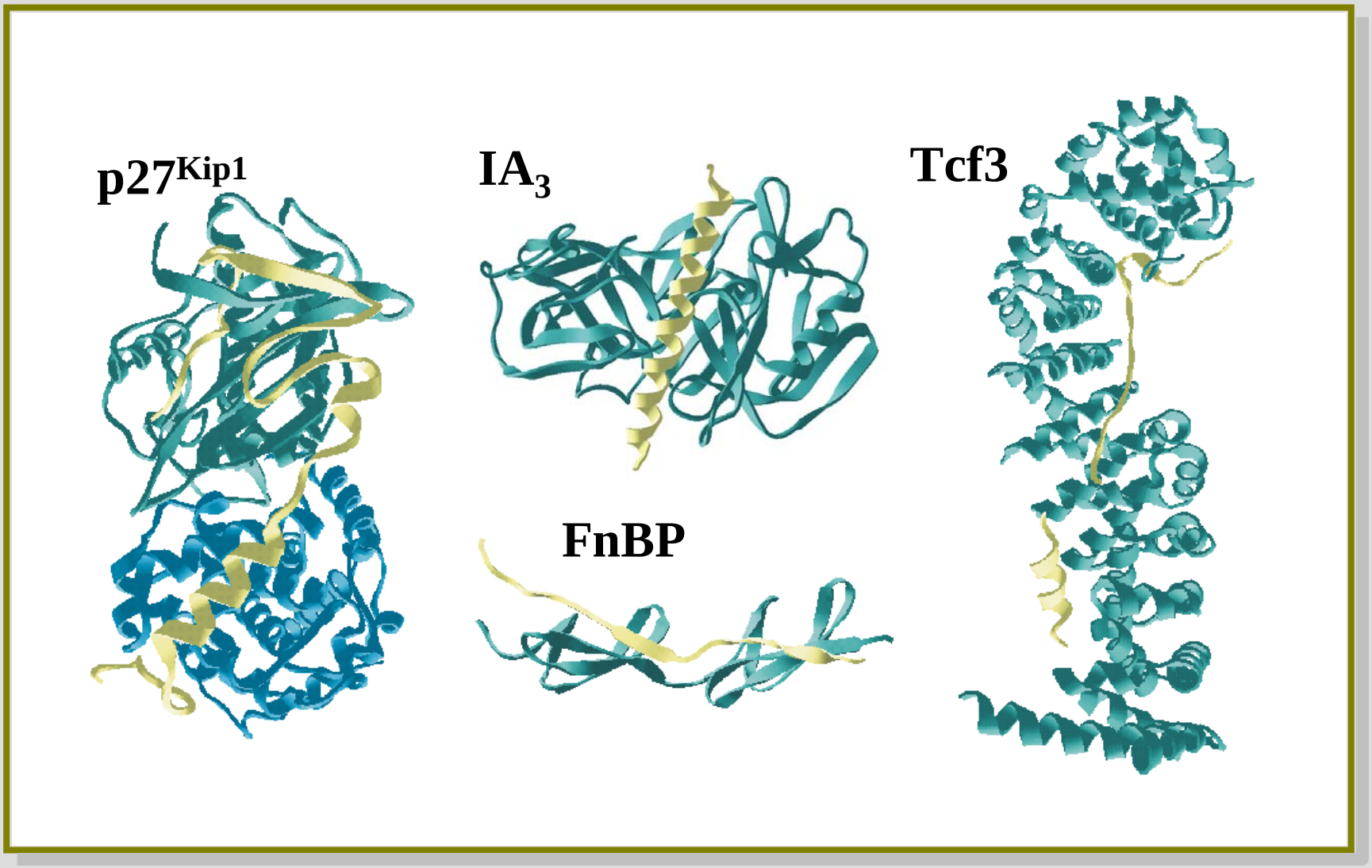
IUPs bind in an open conformation



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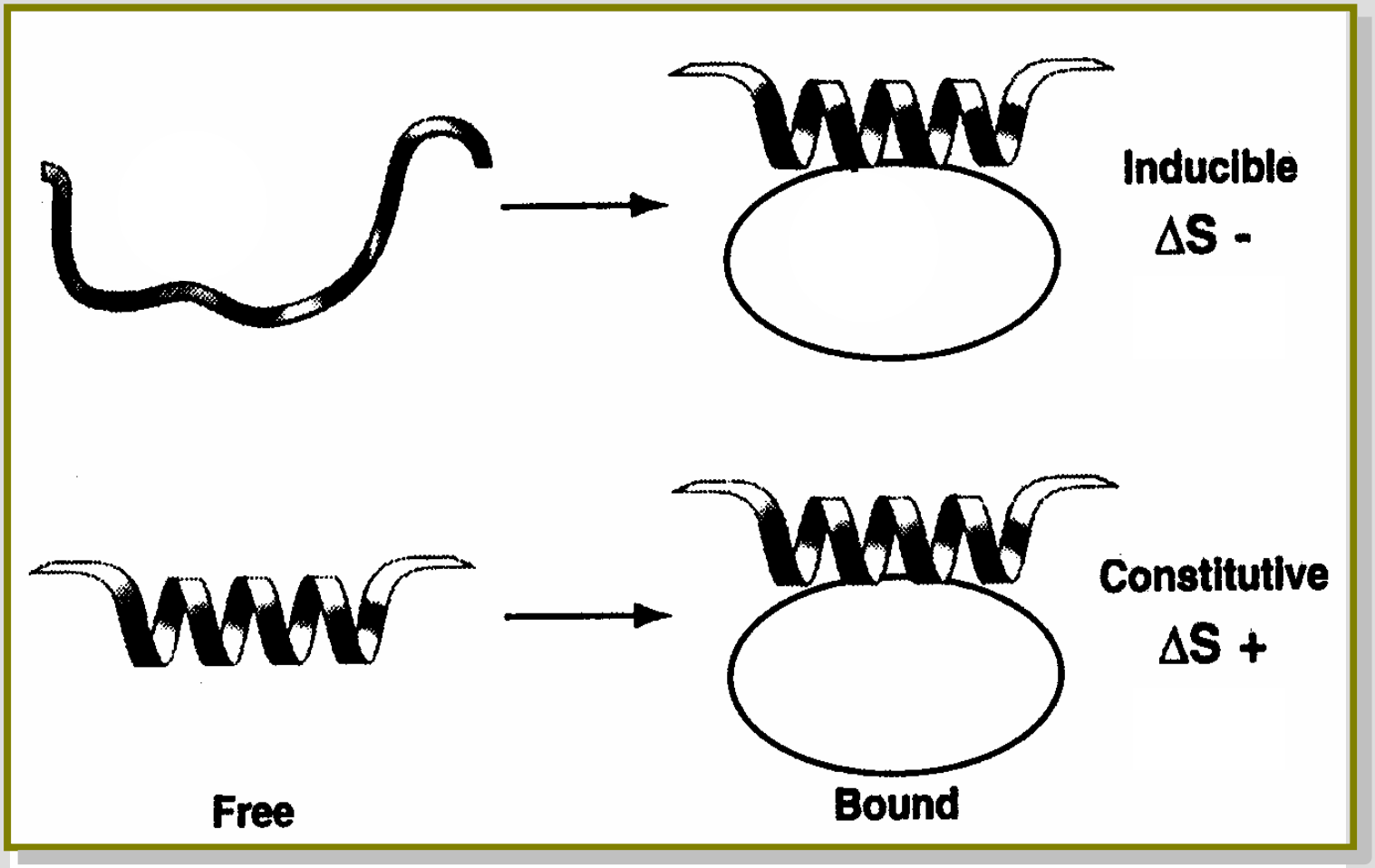
Specificity without excessive binding strength



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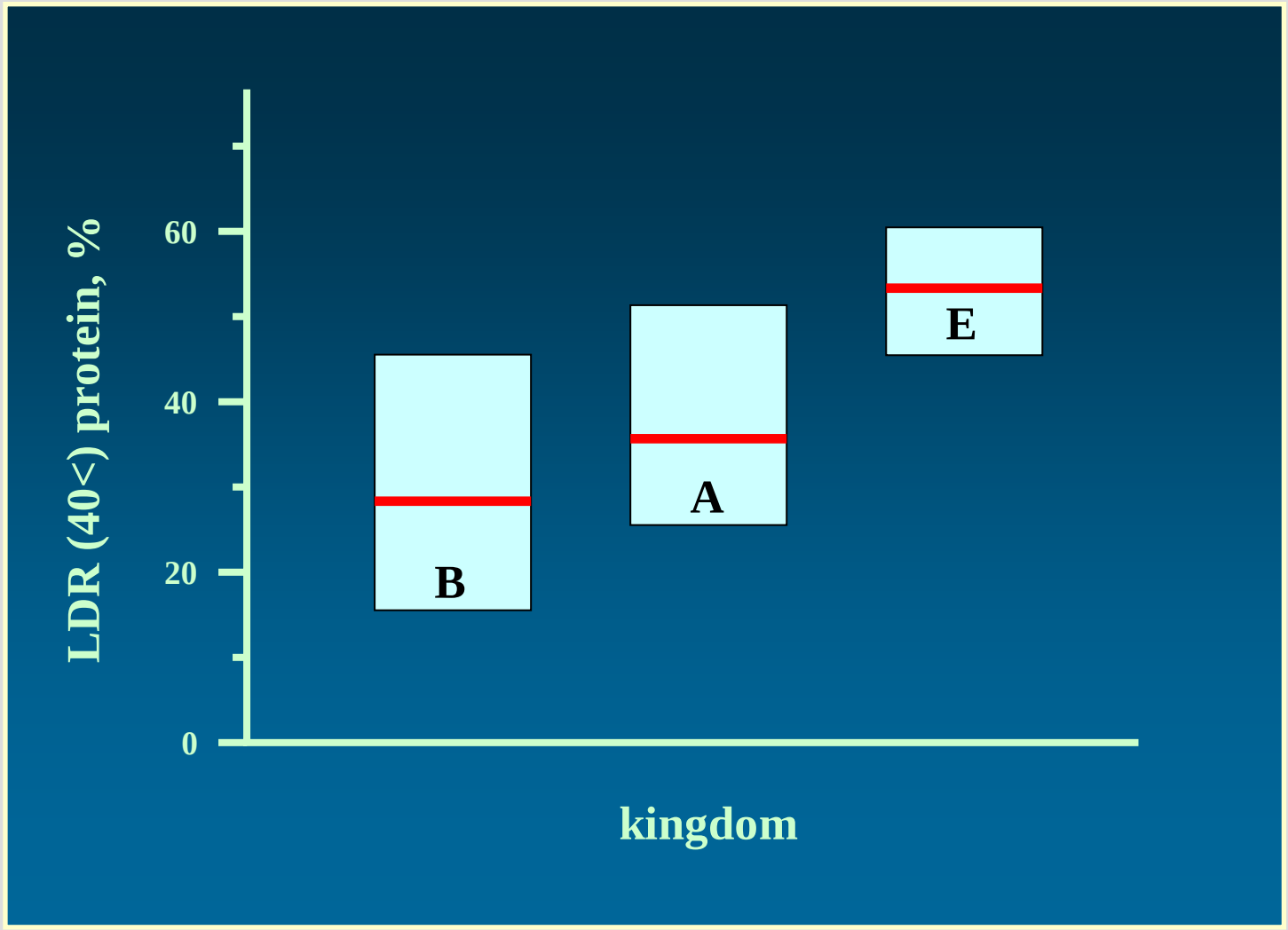
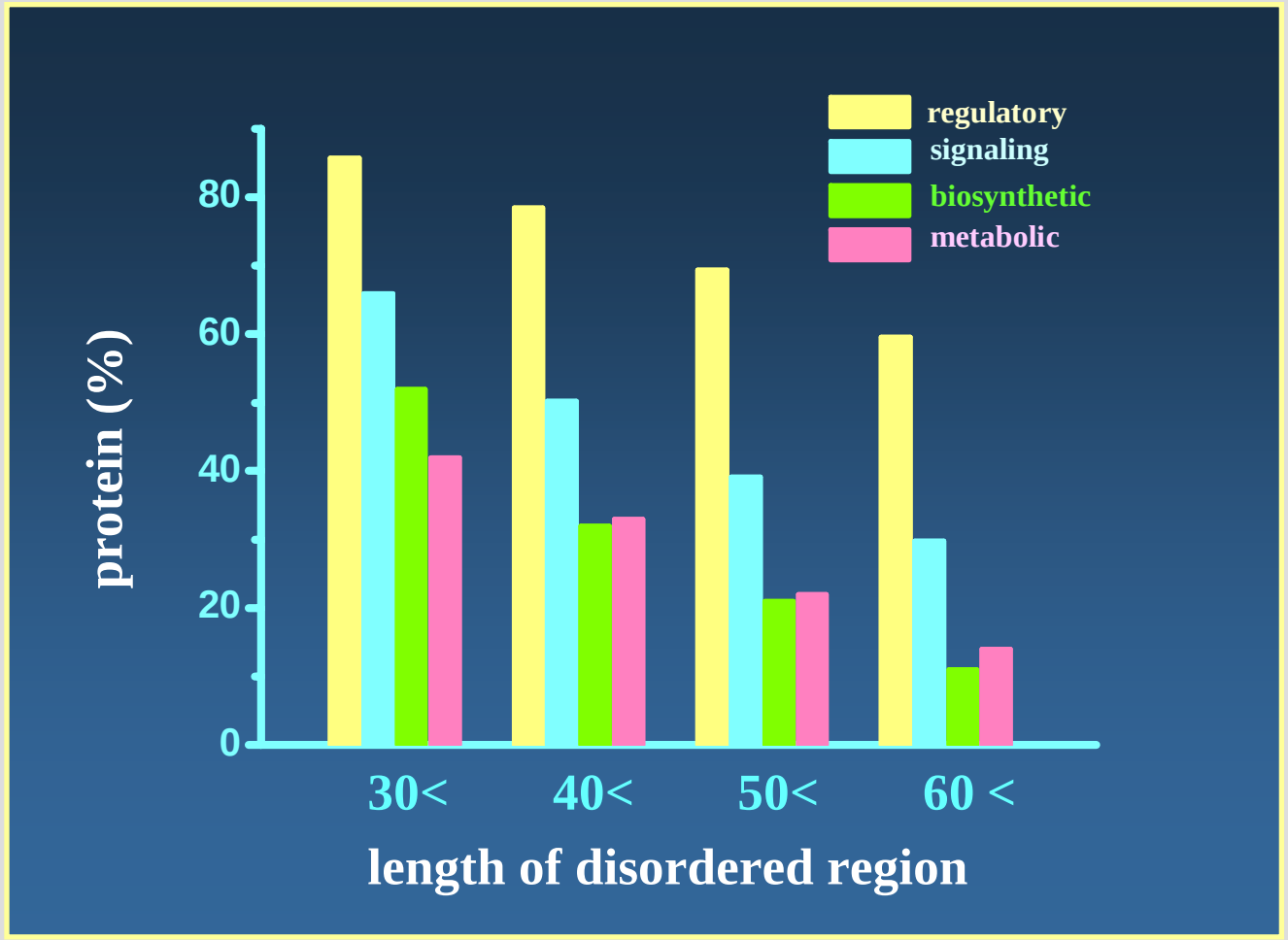
Protein disorder: an evolutionary success-story



Tompa et al. (2006) *J. Proteome Res. 5, 1996*

Prediction:

disorder prevails in regulatory proteins



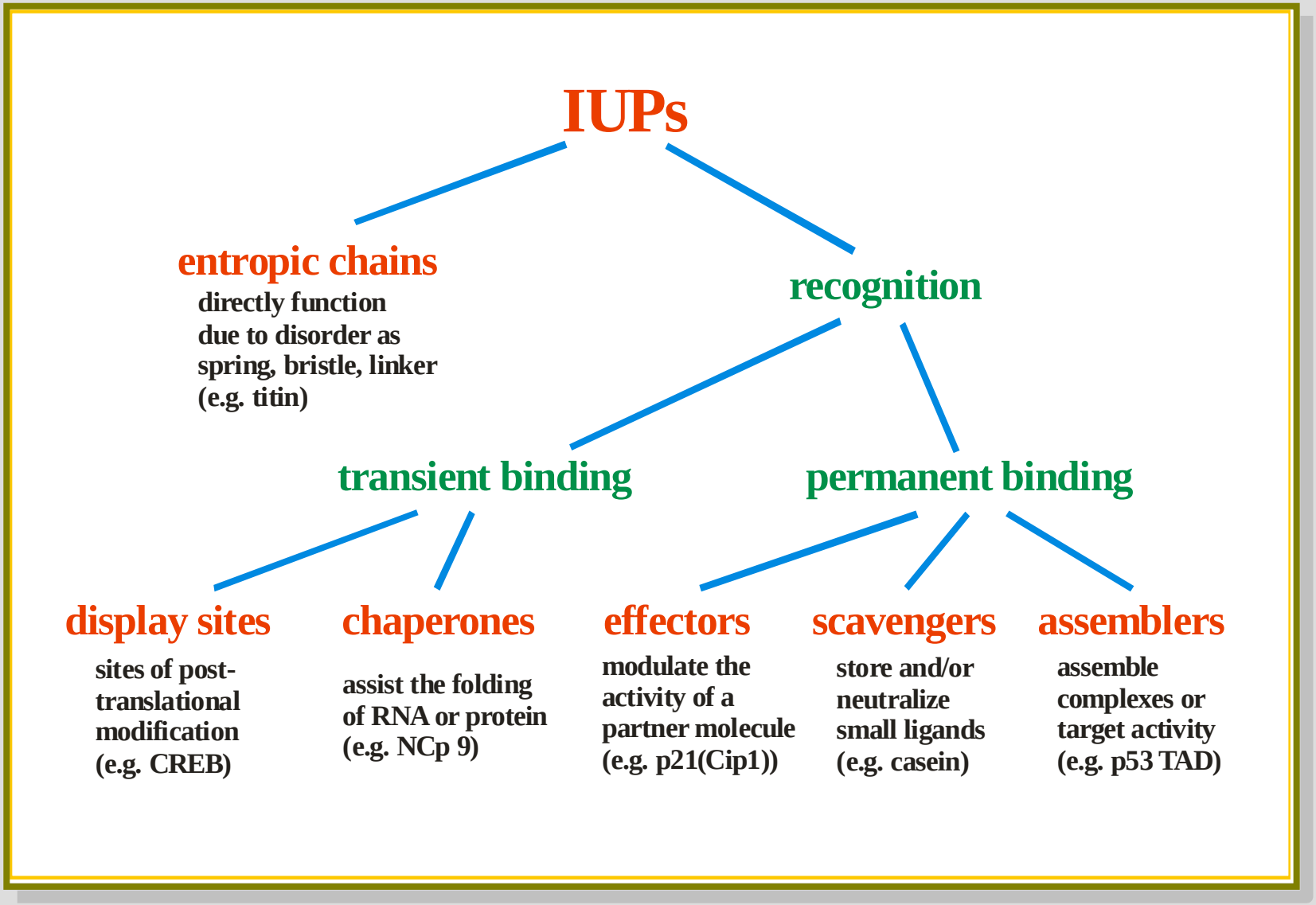
Iakoucheva et al. (2002) *J. Mol. Biol.* 323, 573

1) disorder: general introduction

2) disorder: functional classification

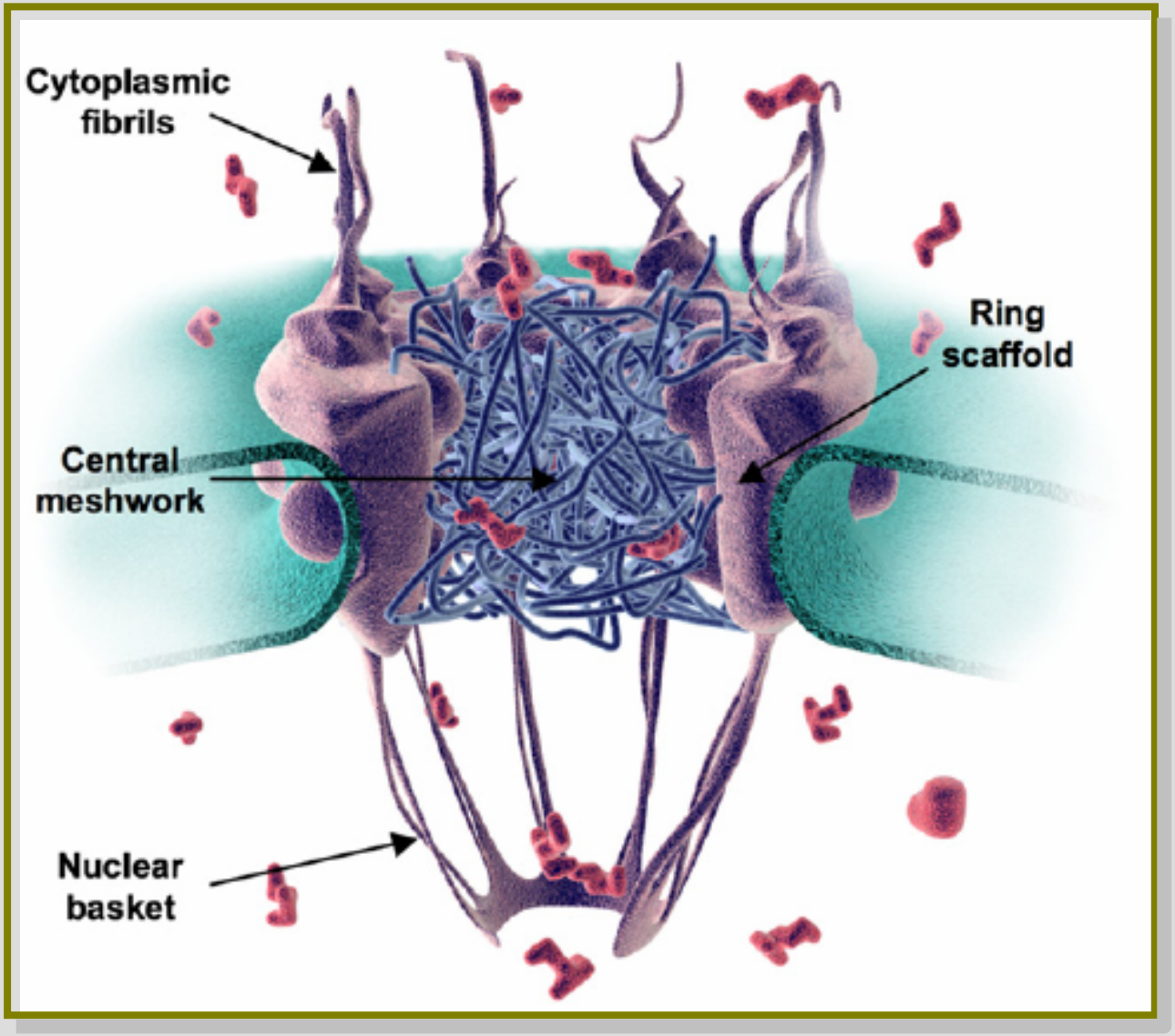
3) disorder: its role in protein-protein interactions

IUPs belong to 6 functional categories



Tompa (2005) *FEBS Lett.*, 579, 3346

Entropic gating in nuclear pore



Patel (2007) *Cell* 129, 83

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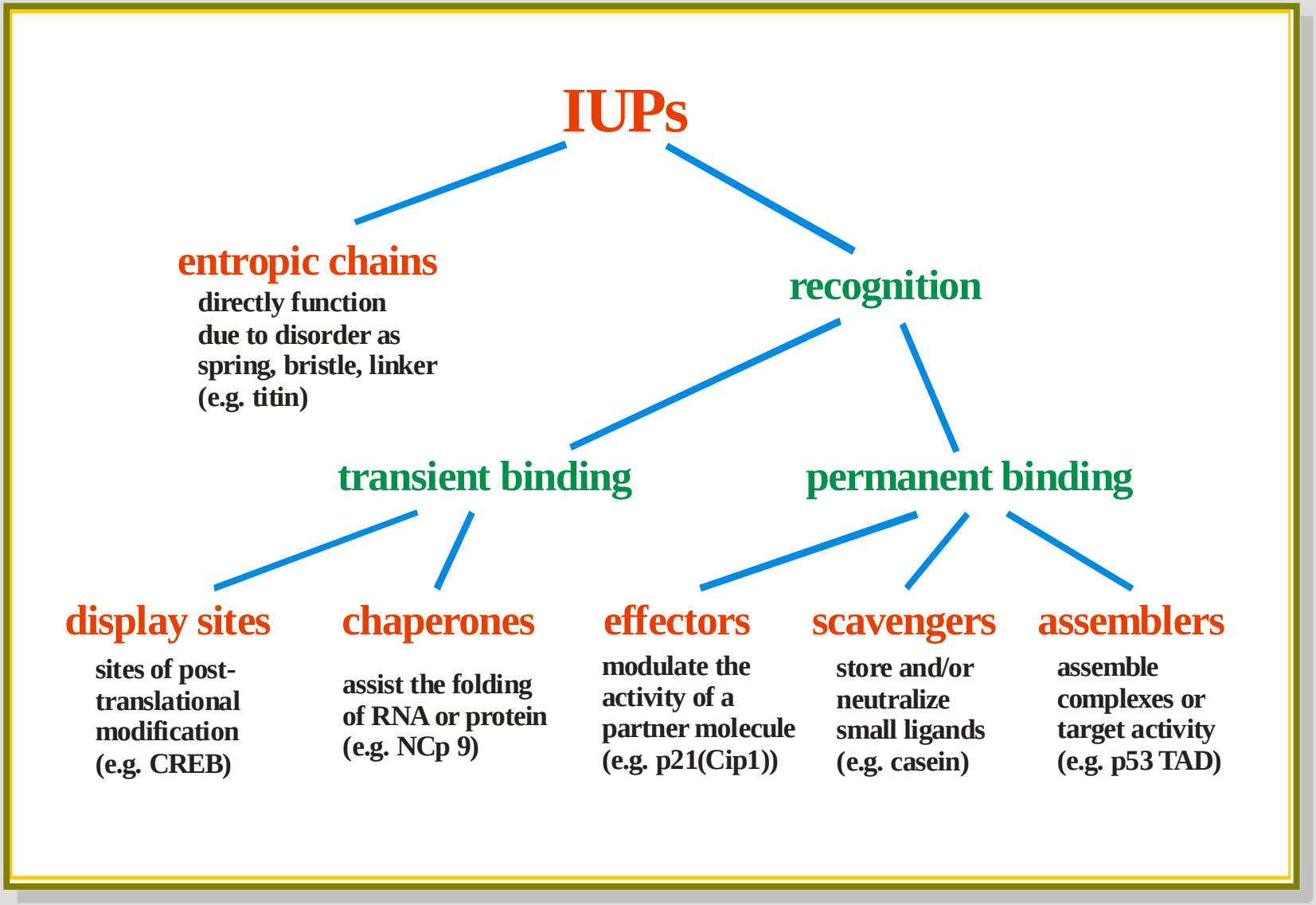
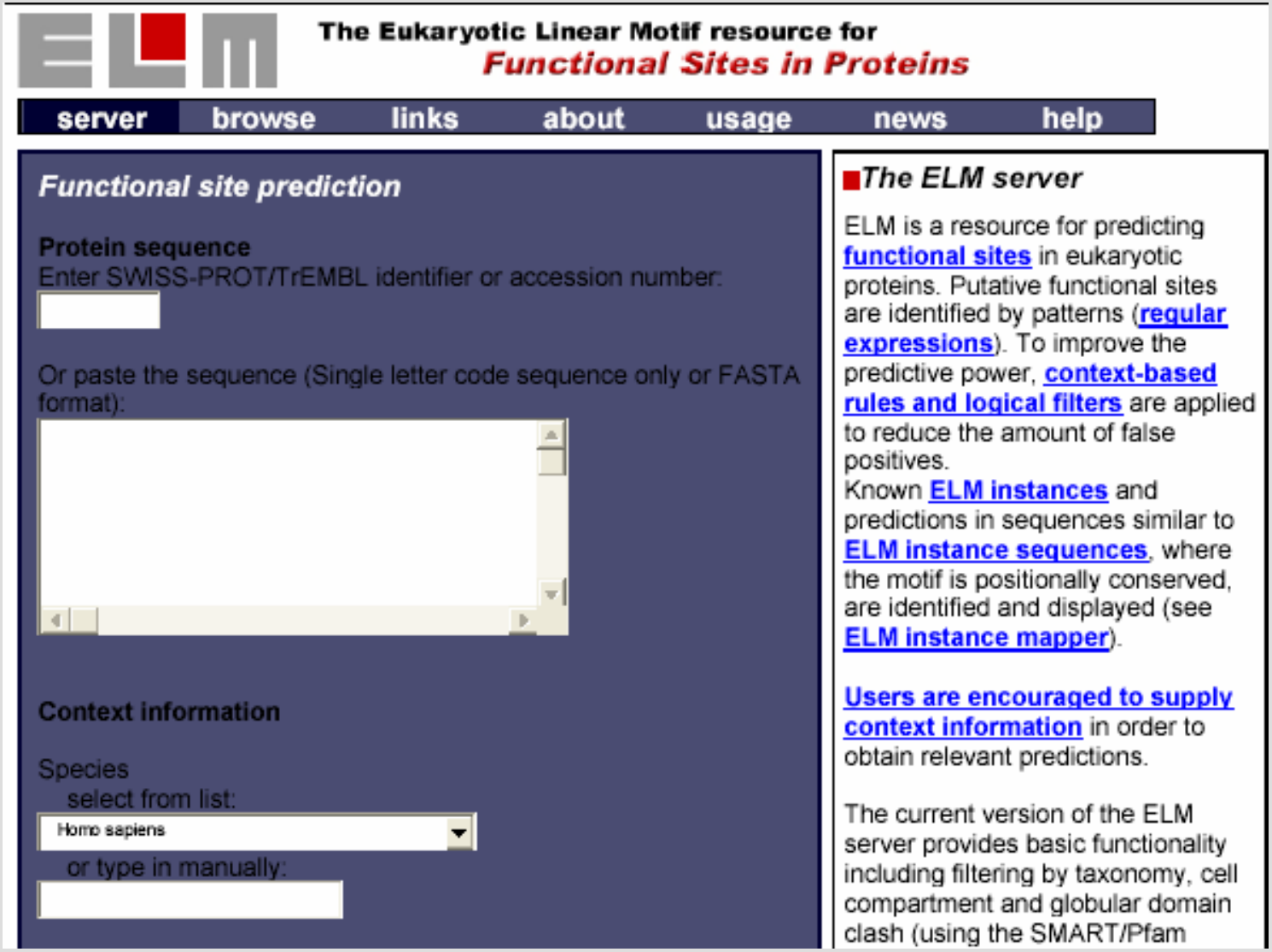


Tompa (2005) *FEBS Lett.*, 579, 3346

The ELM server http://elm.eu.org/



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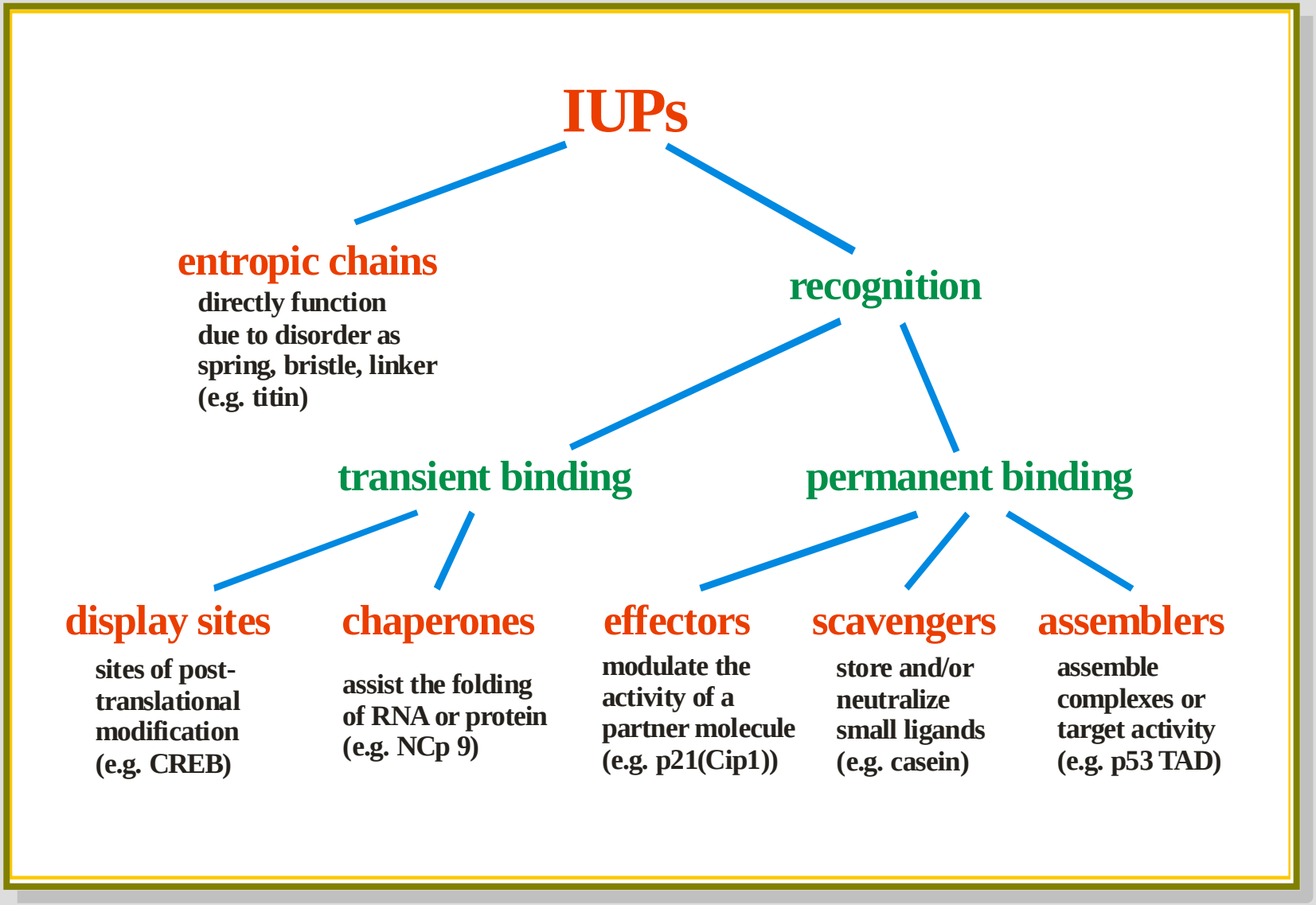
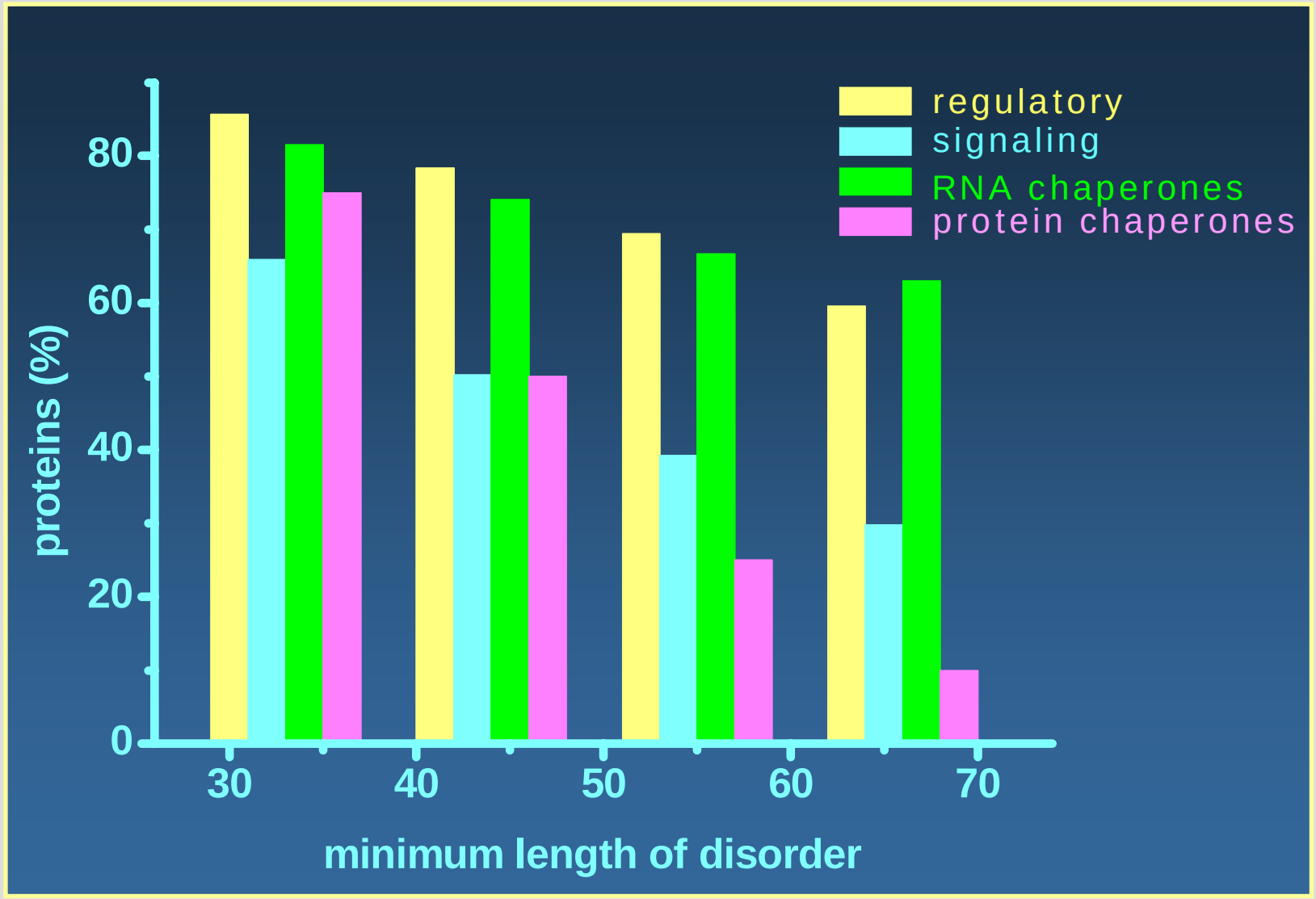


Tompa (2005) *FEBS Lett.*, 579, 3346

Prediction: disorder prevails in chaperones



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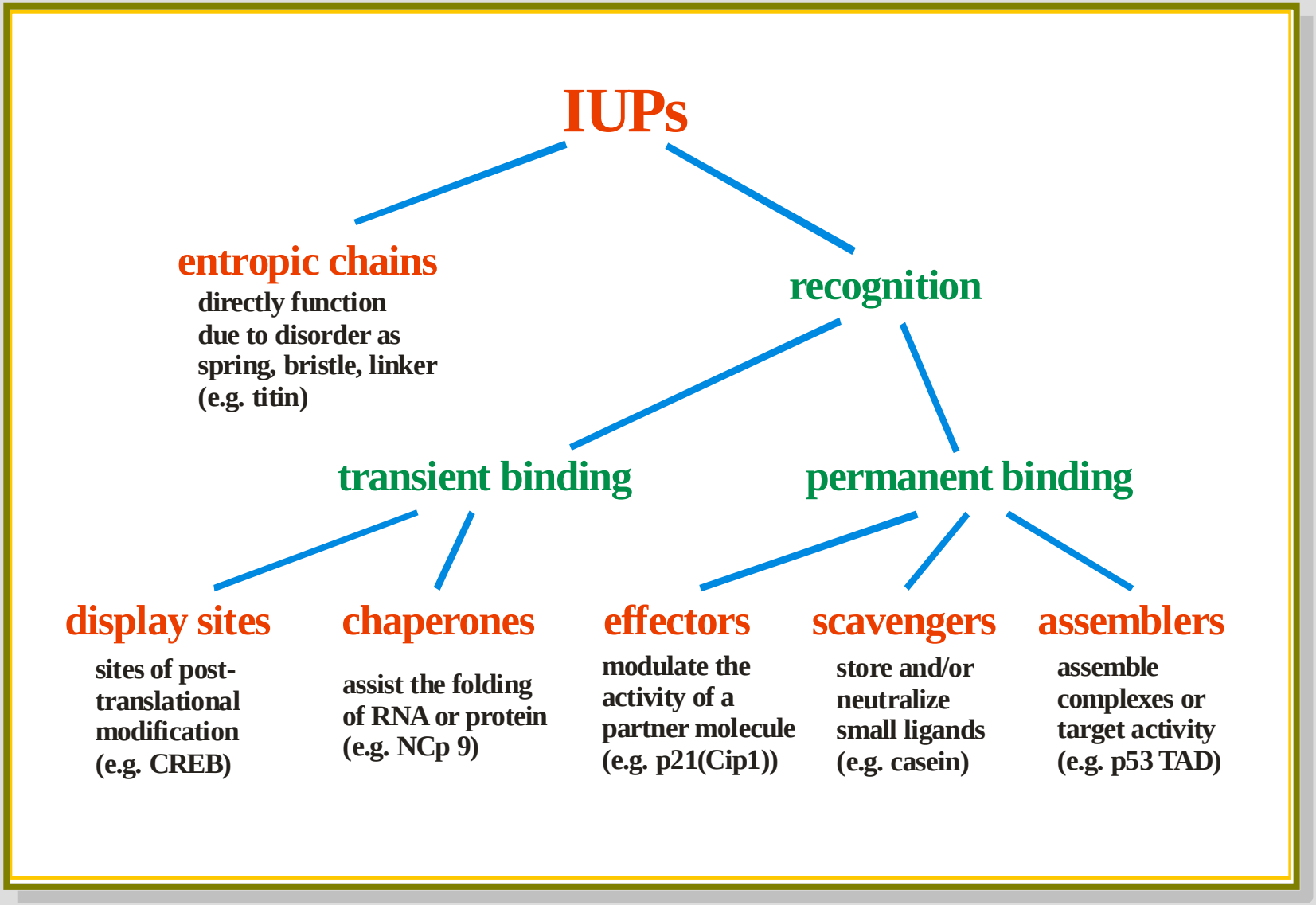
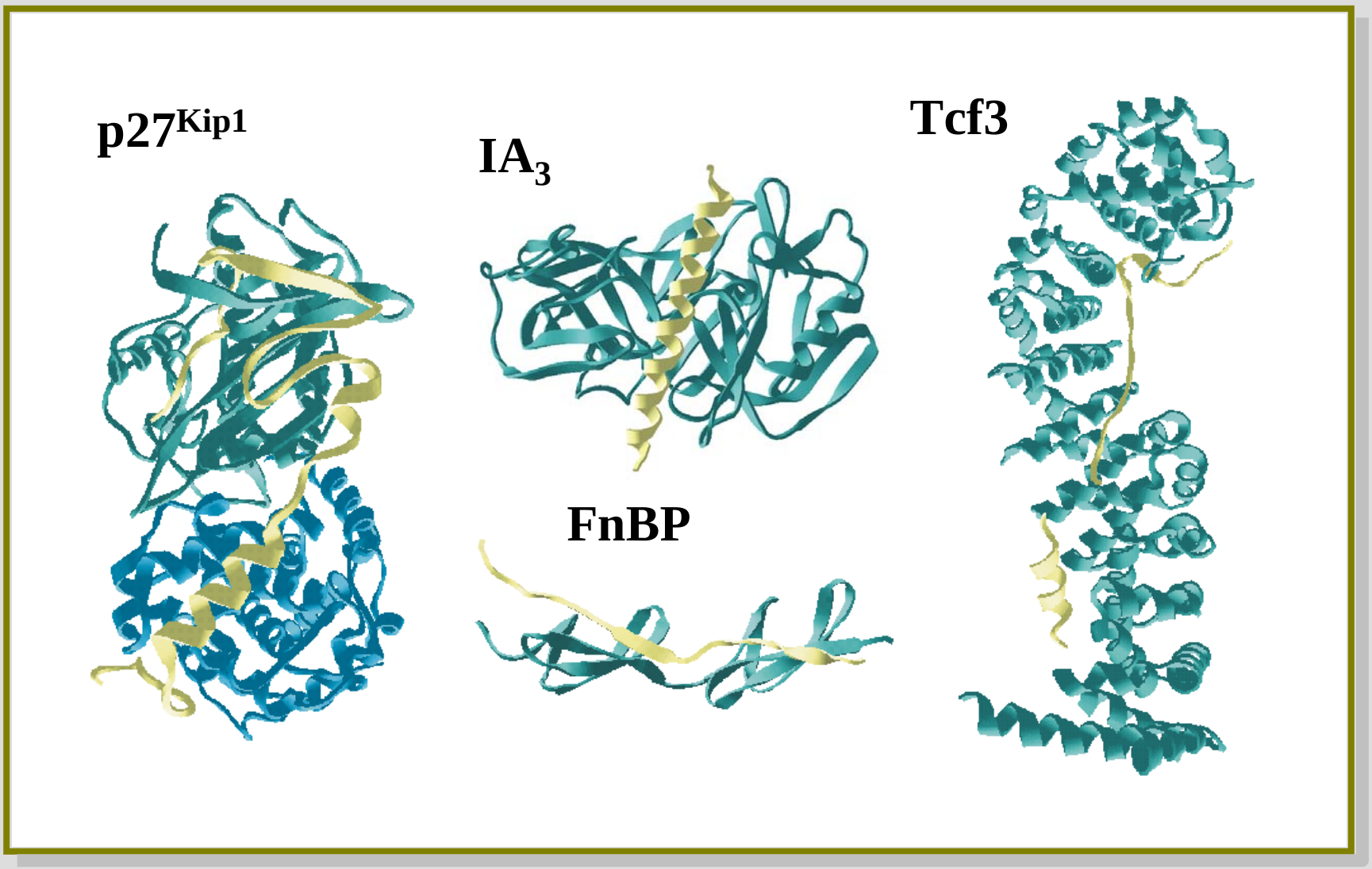


Tompa (2005) *FEBS Lett.*, 579, 3346

$p27^{Kip1}$: an effector (inhibitor) of Cdks



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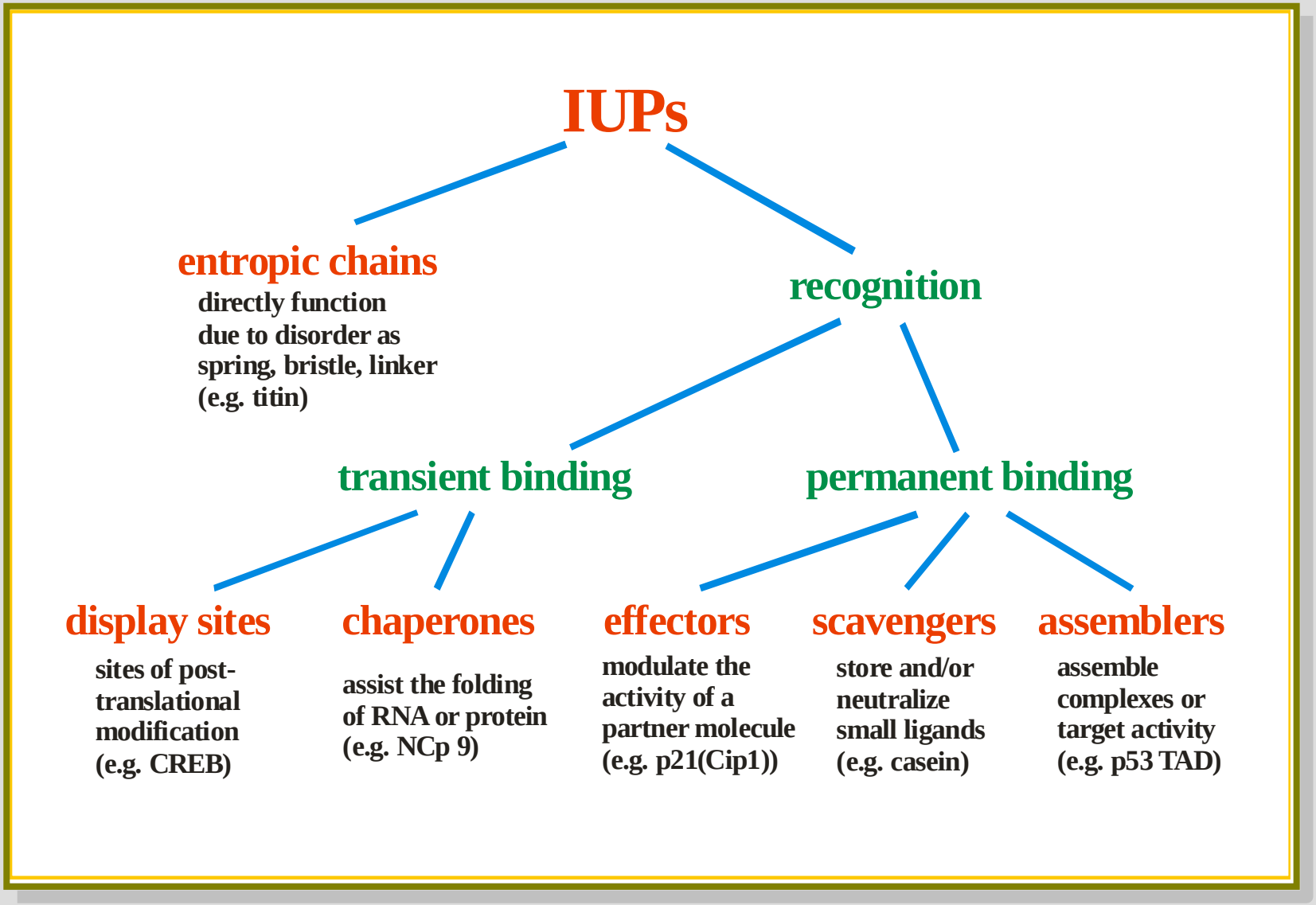
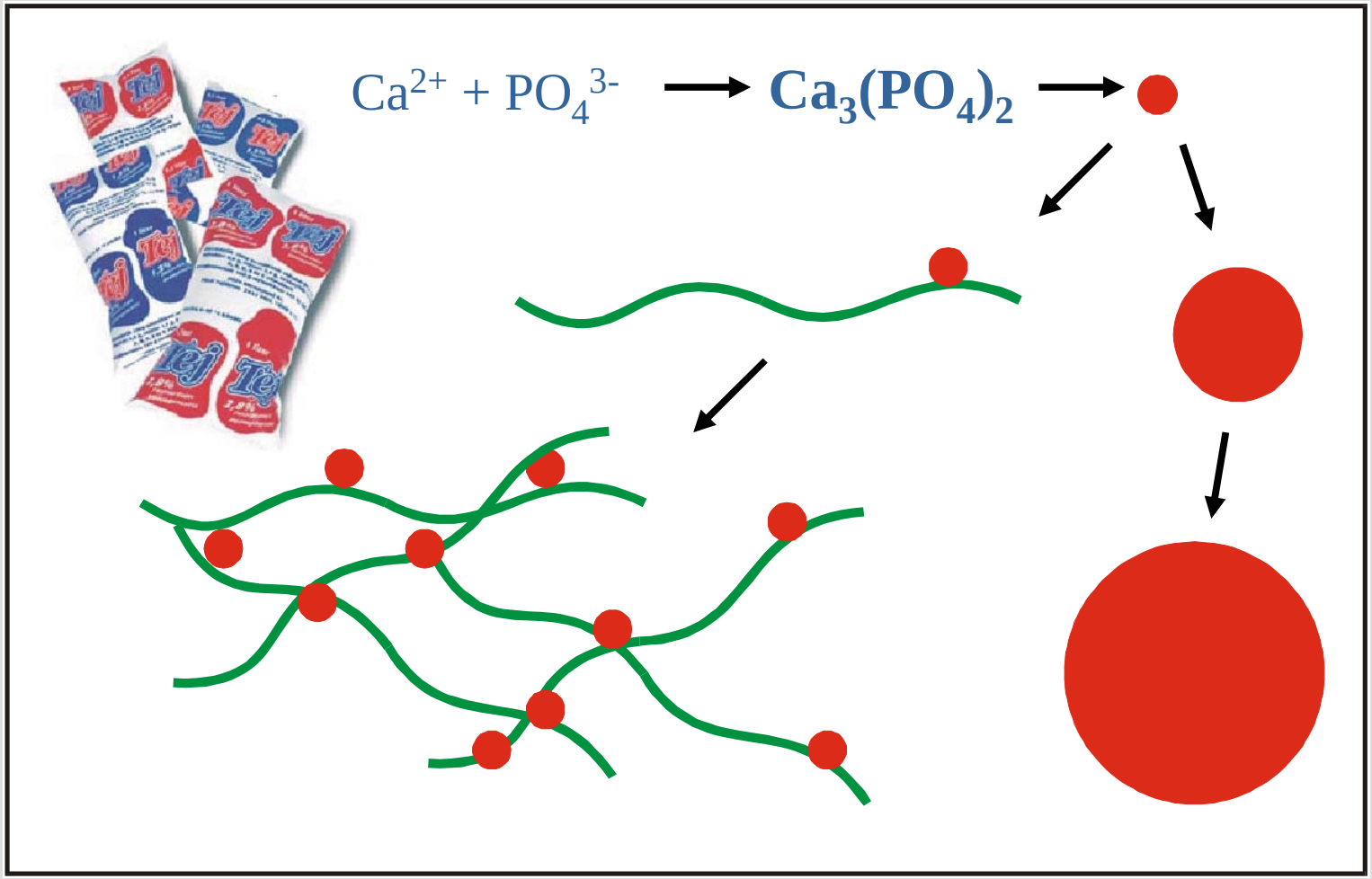


Tompa (2005) *FEBS Lett.*, 579, 3346

Casein: scavenger of calcium phosphate



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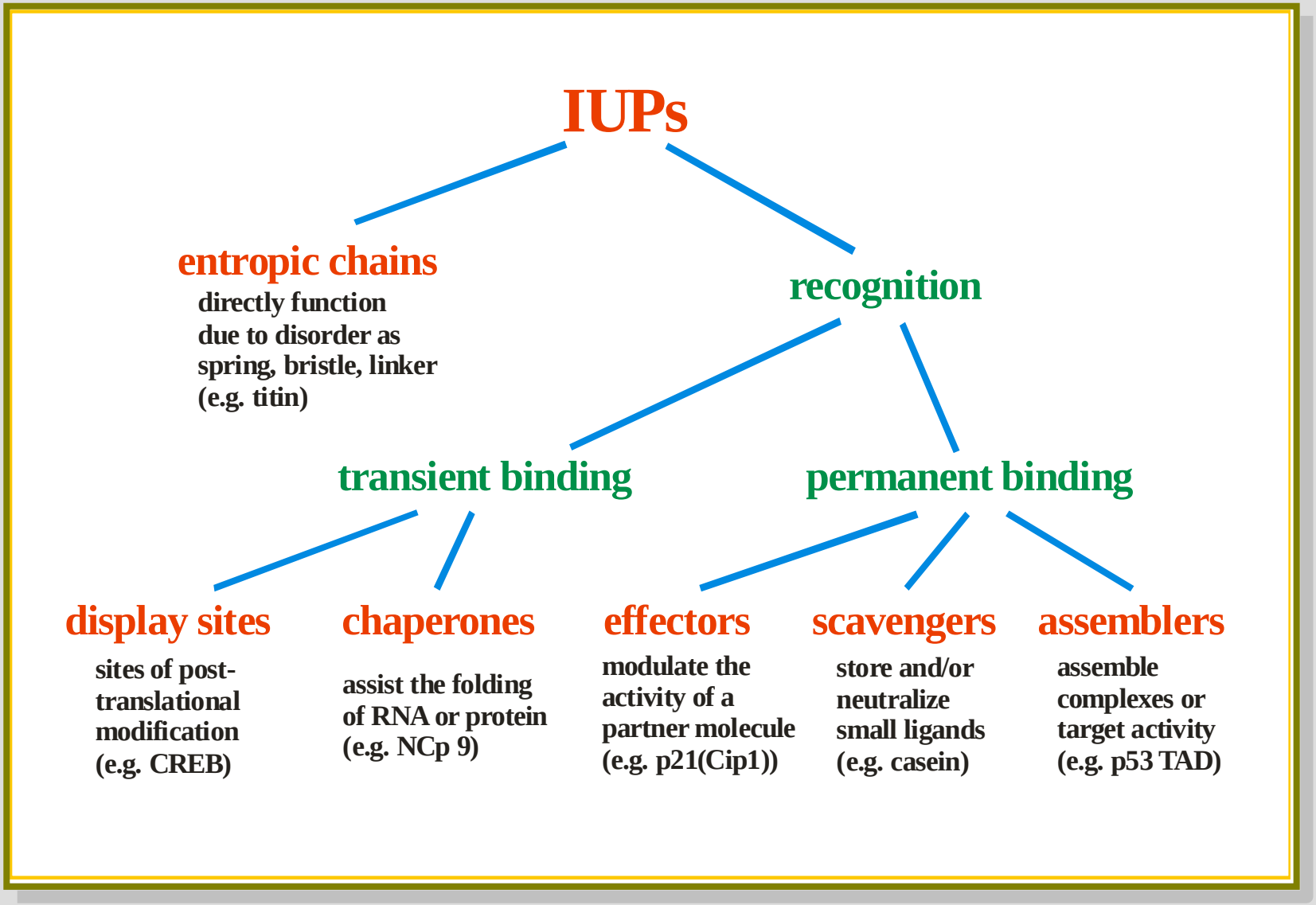
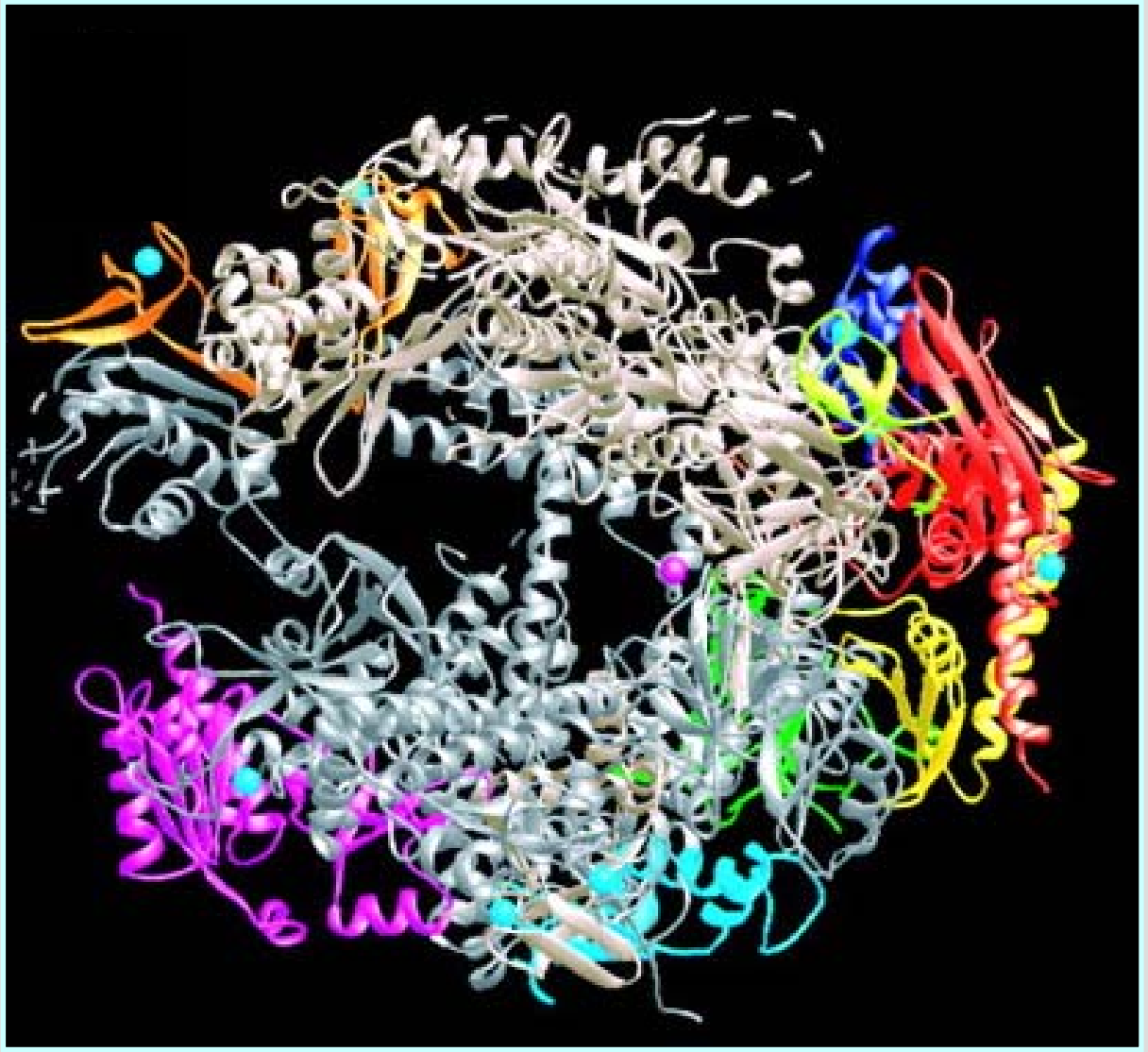
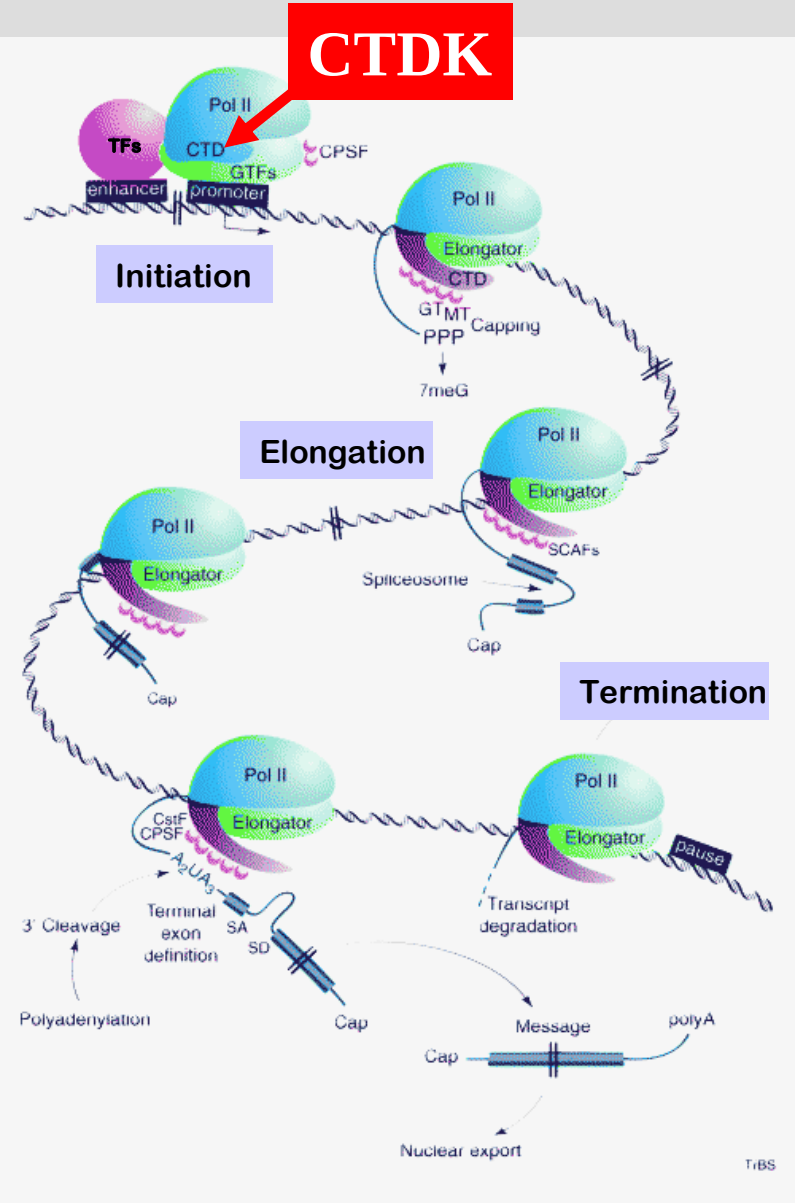


Tompa (2005) *FEBS Lett.*, 579, 3346

RNAP II



RNAP II CTD: coordination of 5’ capping, splicing, 3’ polyadenylation



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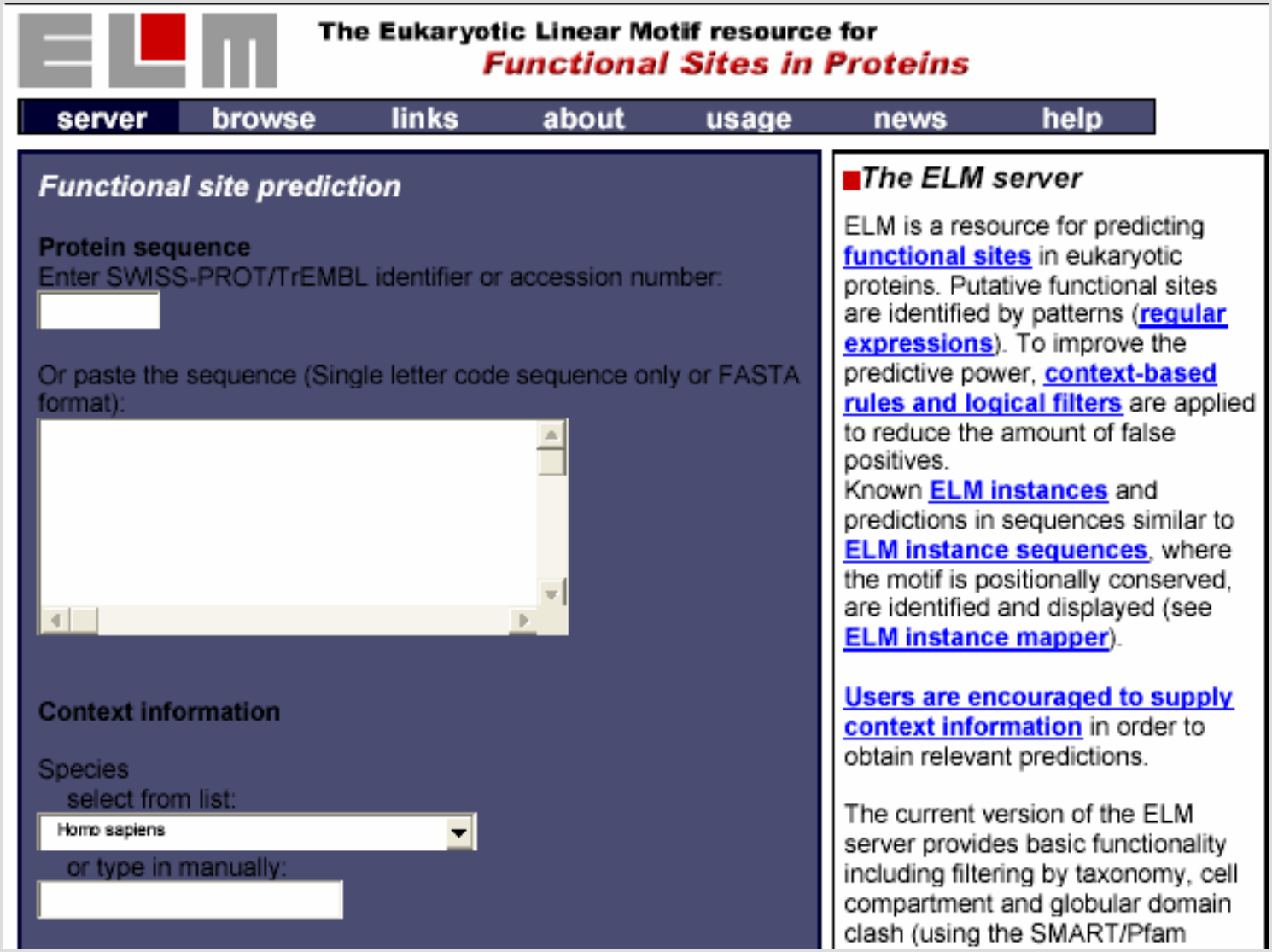
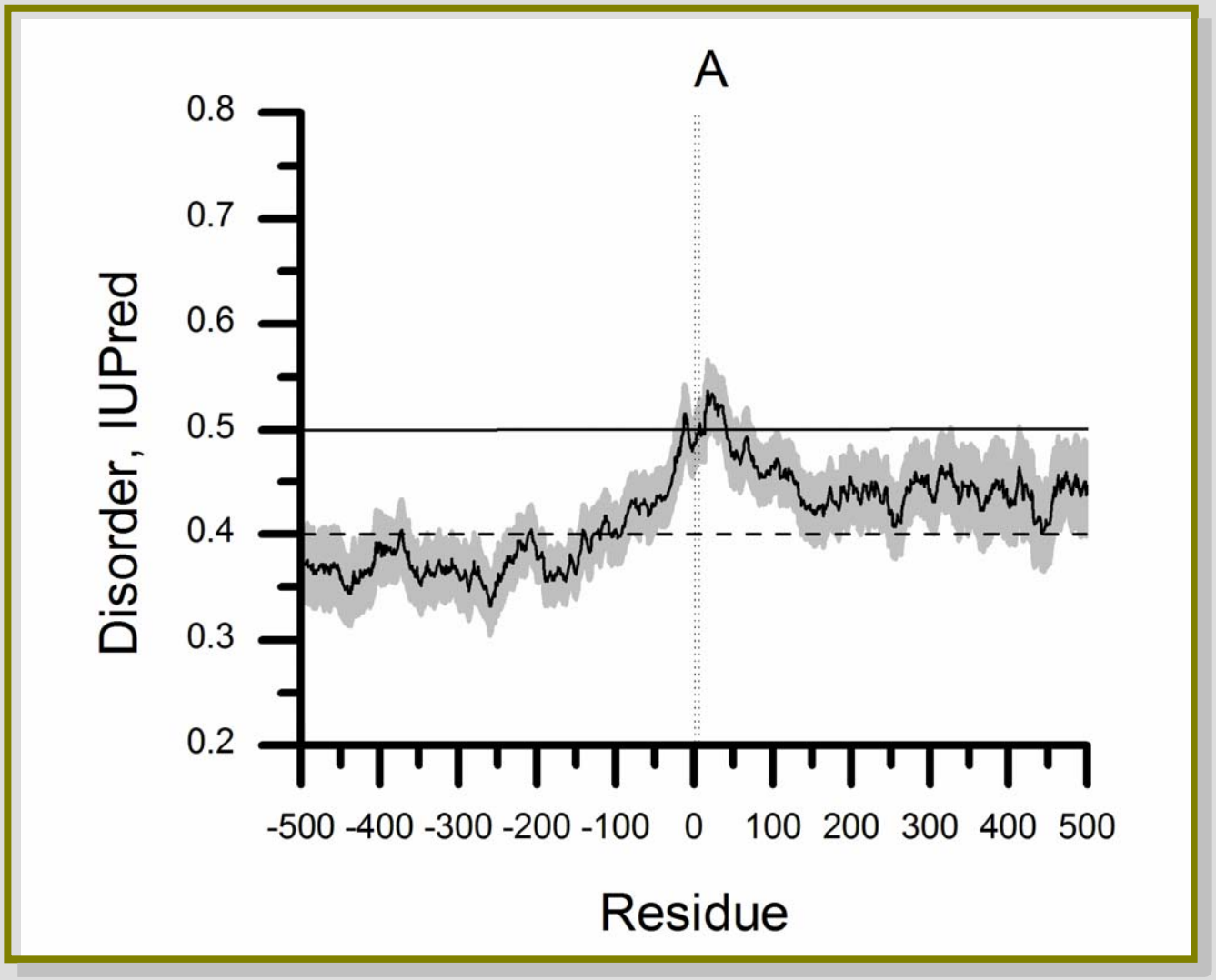
The ELM server http://elm.eu.org/

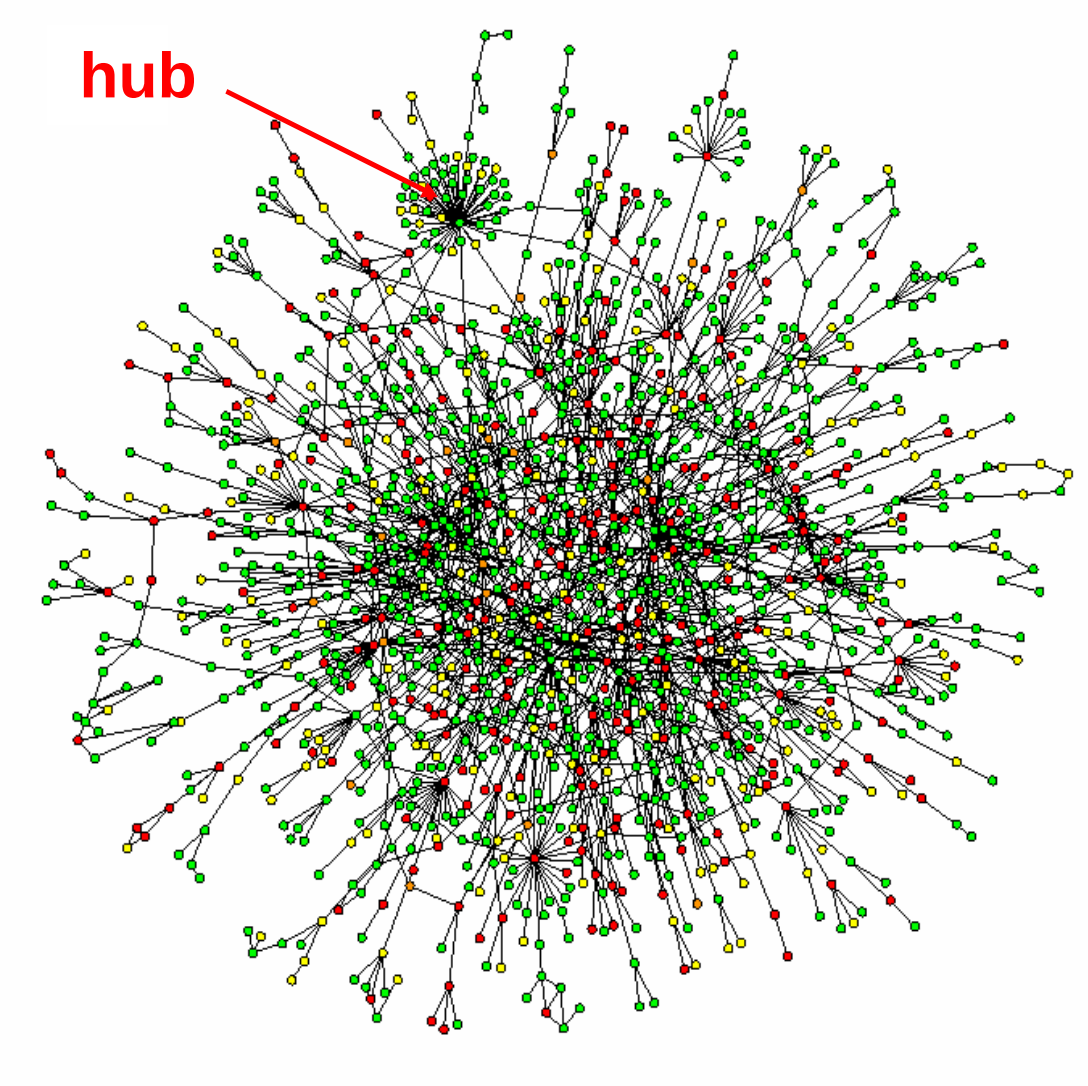


ELMs and local disorder



Fuxreiter et al (2006) *Bioinformatics*, 23, 950

The yeast interactome



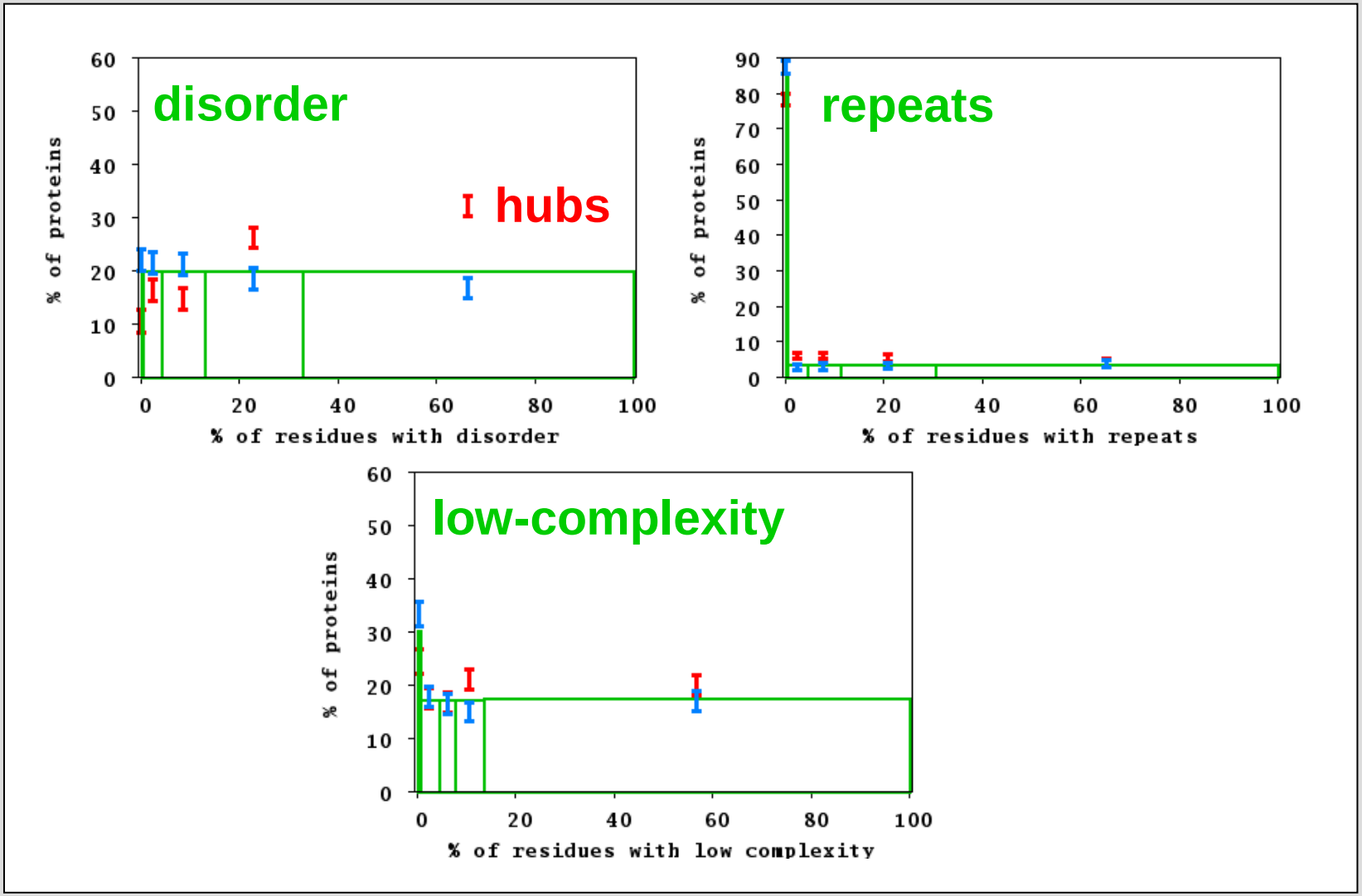
Uetz et al. (2000) *Nature* 403, 623

Disorder in hubs

Protein	PONDR %	STRING	Partners
α-synuclein	100	27	parkin, tau, CaM
caldesmon	100	27	ERK, S100, myosin, actin, CAM
HMGA	100	18	AP1, NF-κB, C/EBPβ, Oct-1, Sp1
synaptobrevin	100	8	syntaxin 1, BAP31, VAMP-ass. prot., SNAP-25
BRCA1	79	119	p53, ATM, BRCA2, c-Myc, Chk1
XPA	63	41	RPA70, RPA34, ERCC1, TFIIH, XAB1
estrogen receptor α	31	116	p53, BRCA1, CaM, c-Jun
p53	29	239	Mdm2, ATM, ERK, p38, BCL-Xl
Mdm2	26	72	p53, ARF, ATM, CK2, HIF-1α
calcineurin, subunit A	16	31	NFAT, calcipressin, cabin1, SOCS-3, calsarcin
14-3-3' ξ	12	97	p53, Wee1, tau, Raf-1, Cdc25c, Bad
Cdk2	7	125	PP2A, CycE1, DNA Pol α, BRCA1, cycA
actin	5	33	profilin, RNAse I, vit DBP, thymosin β4, cofilin
calmodulin	3	50	neurogranin, calcineurin, AC1, calponin, caldesmon

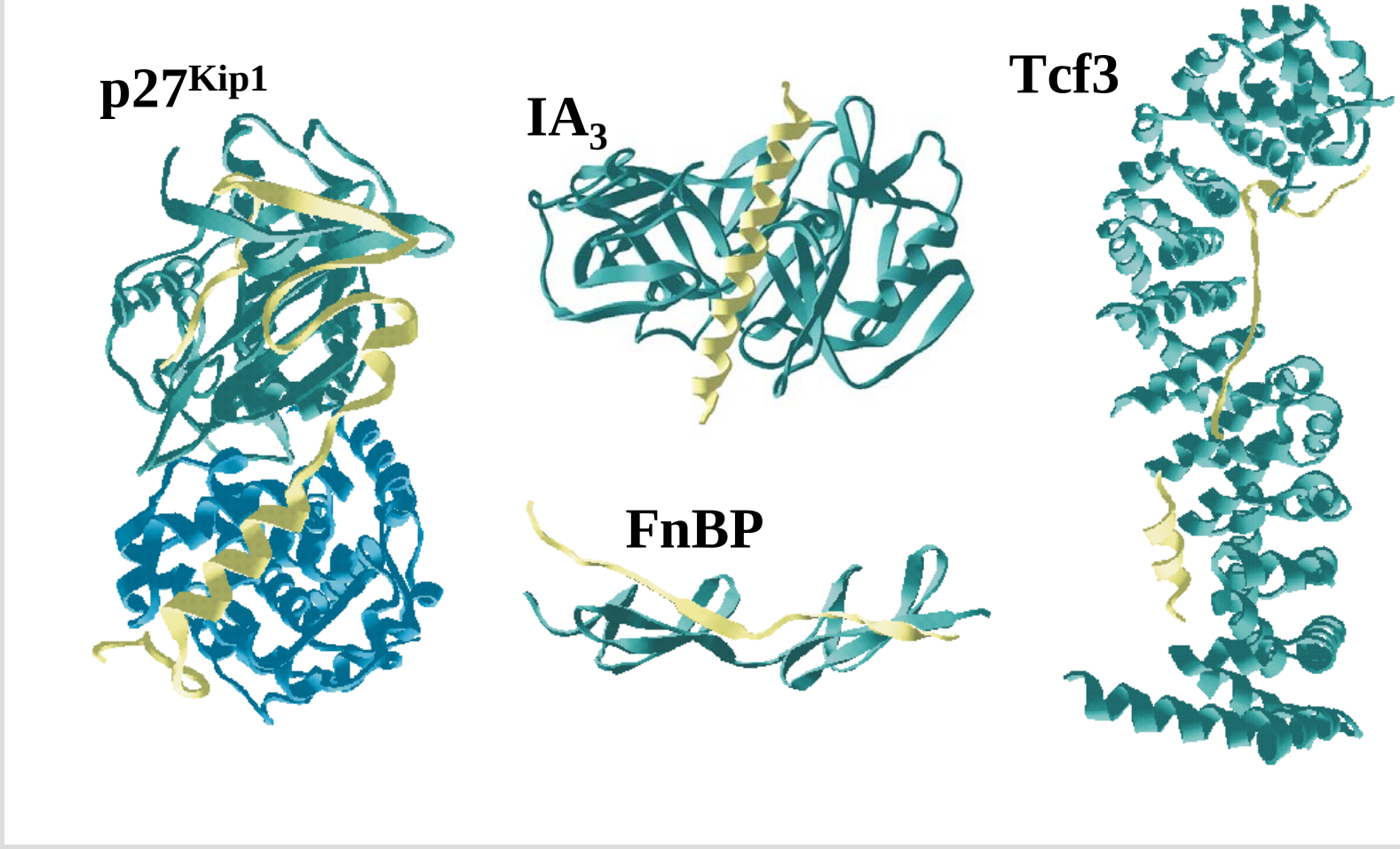
Dunker (2005) *FEBS J.* 272, 5129

(Yeast) hubs contain more of:

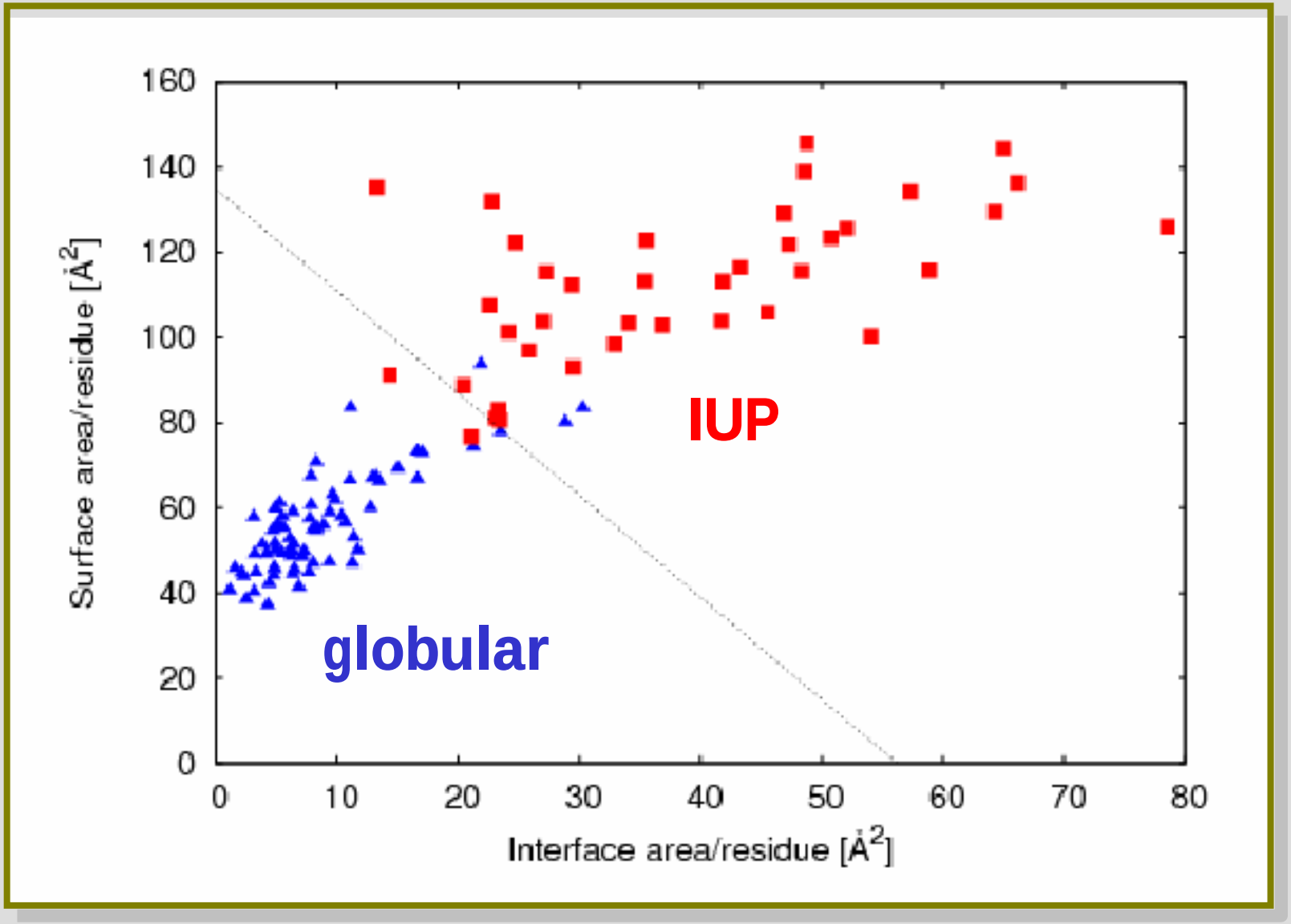


Dosztányi (2006) *J.Proteome. Res. 5, 2985*

IUP interfaces

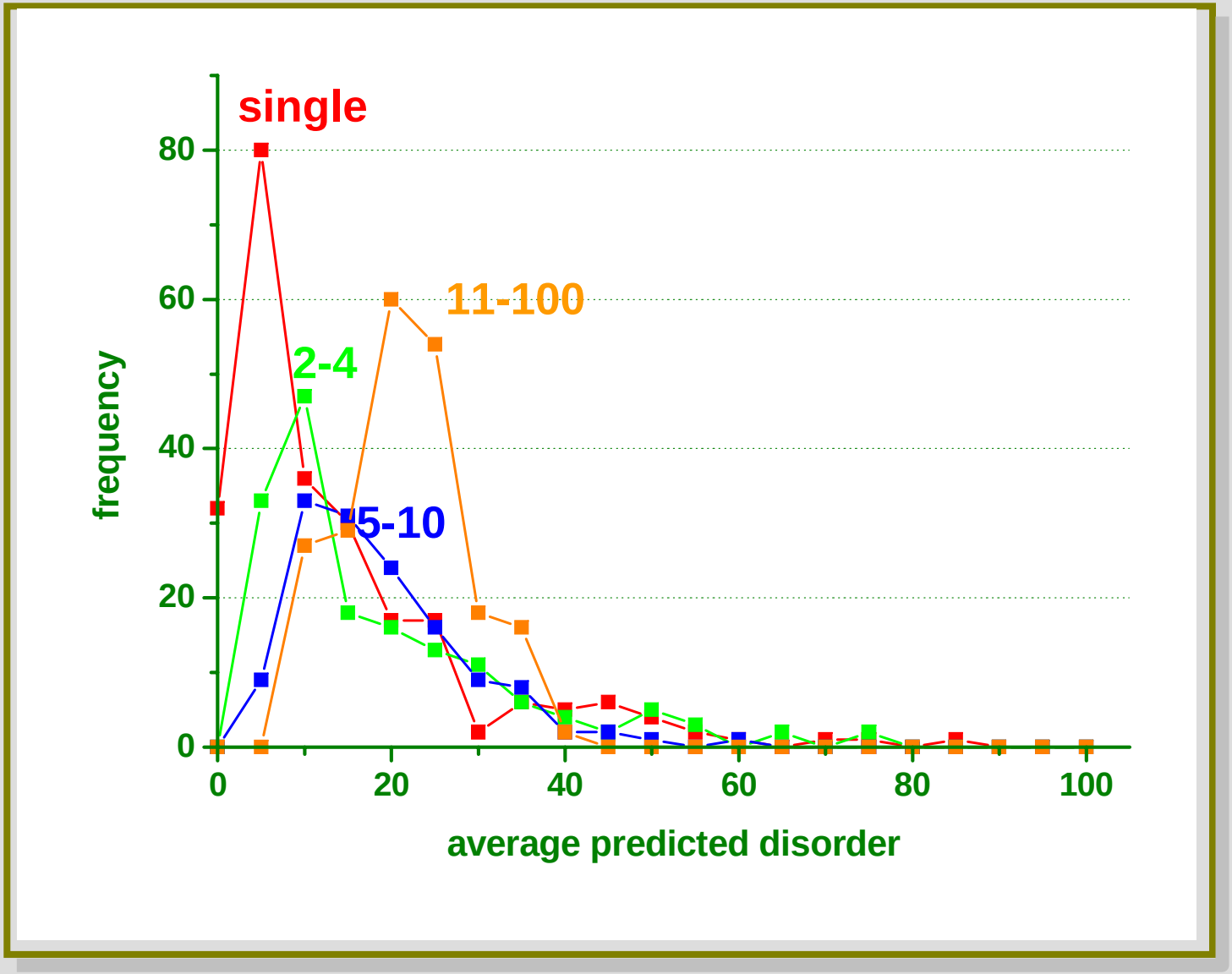


IUPs: extended interface for binding



Meszaros et al. (2007) *JMB* submitted

Disorder increases with complex size



Hegyi and Tompa. (2007) *BMC Stuct. Biol.* submitted

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