北京大学定量生物学中心
CENTER FOR QUANTITATIVE BIOLOGY

Intrinsically disordered proteins and its drug design
天然无序蛋白及其药物设计

Reporter : Jun Cheng(程军) Beiming Cheng(程北溟)

June 16, 2019

Content

Part I: Intrinsically disordered proteins(IDPs)

- What is IDPs?
- Why don’t IDPs fold into 3D structures?
- How common are IDPs?
- What are the functions of IDPs?

Part II: Drug design in IDPs

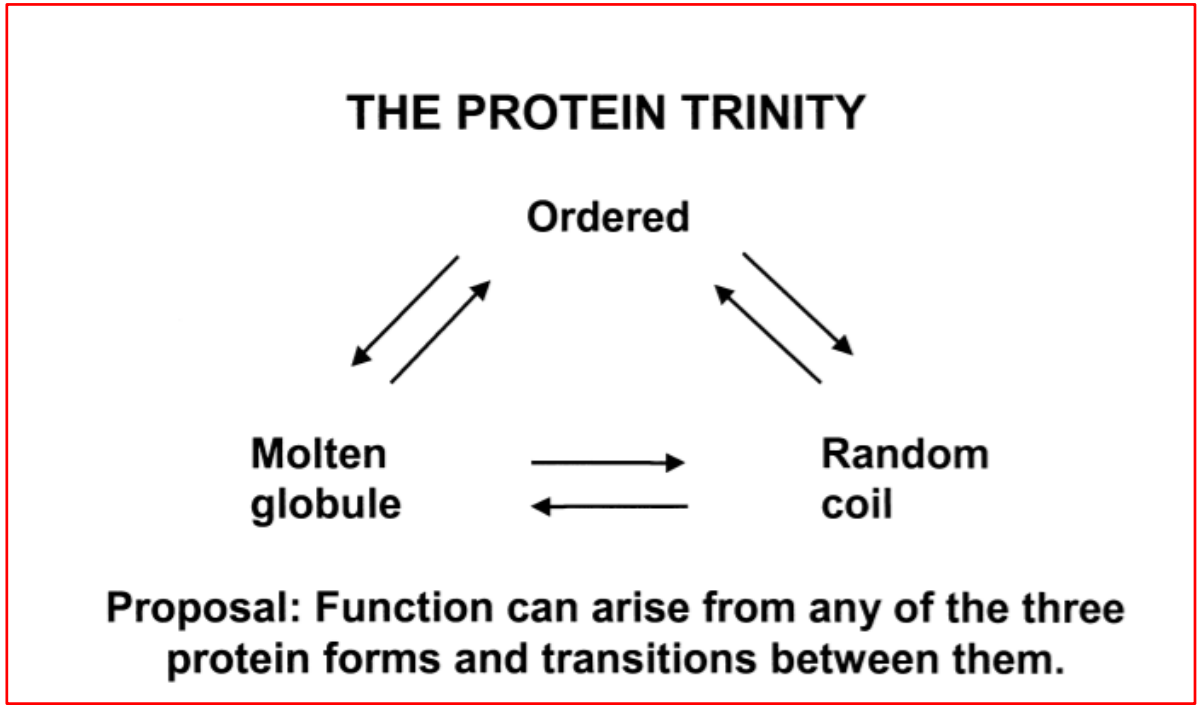
- Traditional drug design
- Drug design for IDPs —c-Myc

Current Protein Structure/Function Paradigm

Amino-Acid Sequence → 3Dimensional Structure → Function

"Folding Problem"

["Lock & Key";
"Induced Fit"]



Dunker A K, Lawson J D, Brown C J, et al, 2001.

Intrinsically disordered proteins(IDPs)

- **Some proteins & regions lack structure, yet carry out function. We call these intrinsically disordered proteins (IDPs) and IDP Regions.**
- **Whole proteins and regions of proteins are intrinsically disordered if:**
  - **they lack stable 3D structure under physiological conditions, and**
  - **they are flexible molecules that form dynamic ensembles with inter-converting configurations and without particular equilibrium values for their coordinates.**

From Workshop by A. Keith Dunker, April 16, 2019

IDPs & IDRs or not?

F1000Reports BIOLOGY

Protein flexibility, not di
to molecular recognitio

Joël Janin[1]* and Michael J.

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[2]Division of Molecular Biosciences, Faculty of Natural Sciences, Imperial College, London, SW7 2AZ, UK

With regard to replacing disorder with either flexibility or PWPs, our view on these suggestions can be summarized by a well-known phrase: "What's in a name? That which we call a rose by any other name would smell as sweet". [75].

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Published: 11 January 2013

The case for intrinsically disordered proteins playing contributory roles in molecular recognition without a stable 3D structure

Vladimir N. Uversky[1,2] and A. Keith Dunker[1]*

Addresses: [1]Department of Molecular Medicine, USF Health Byrd Alzheimer's Research Institute, University of South Florida, Tampa, FL 33612, USA; [2]Institute for Biological Instrumentation, Russian Academy of Sciences, 142290 Pushchino, Moscow Region, Russia; [3]Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, Indianapolis, IN 46202, USA

Some examples of IDPs & IDRs

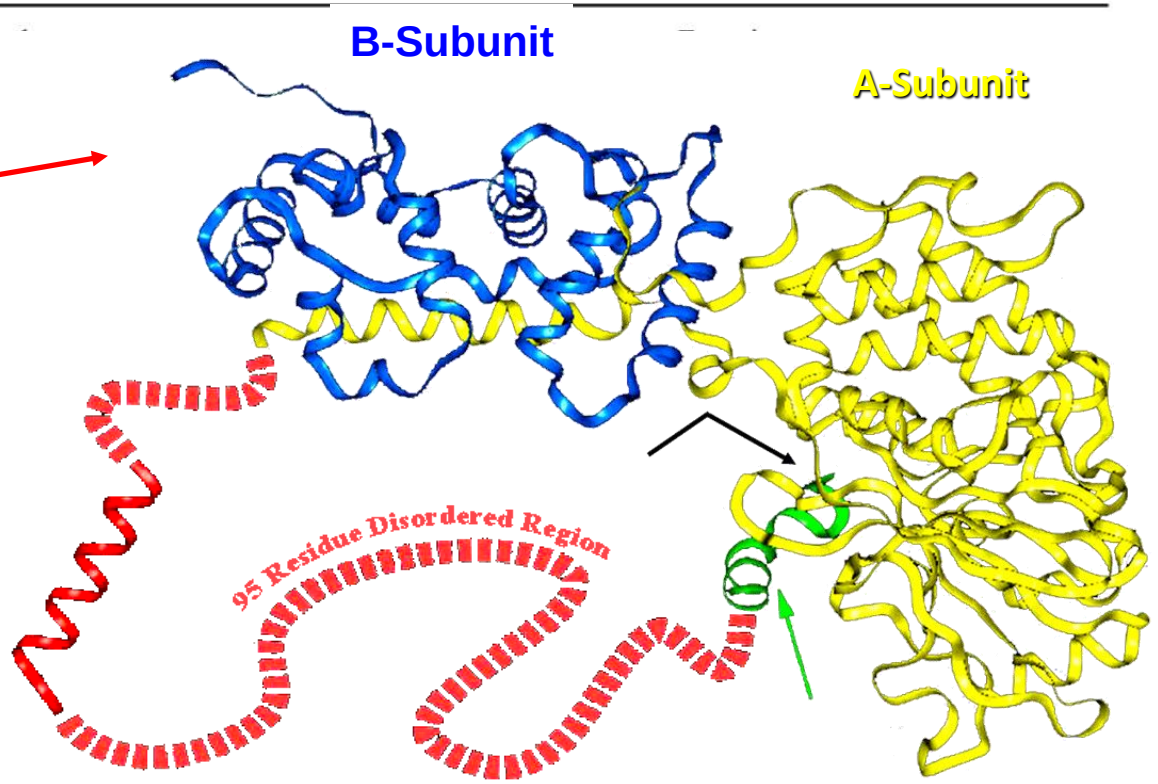
Table 1. Five Examples of Functional Disorder

Protein	Disc
fd Phage	ordered → m
Histone octamer	ordered → m
Clusterin	Native molte
Calcineurin	95 aa disorde
Calsequestrin	21 aa disorde

钙调磷酸酶

Table 2. Important Examples of Native Dis

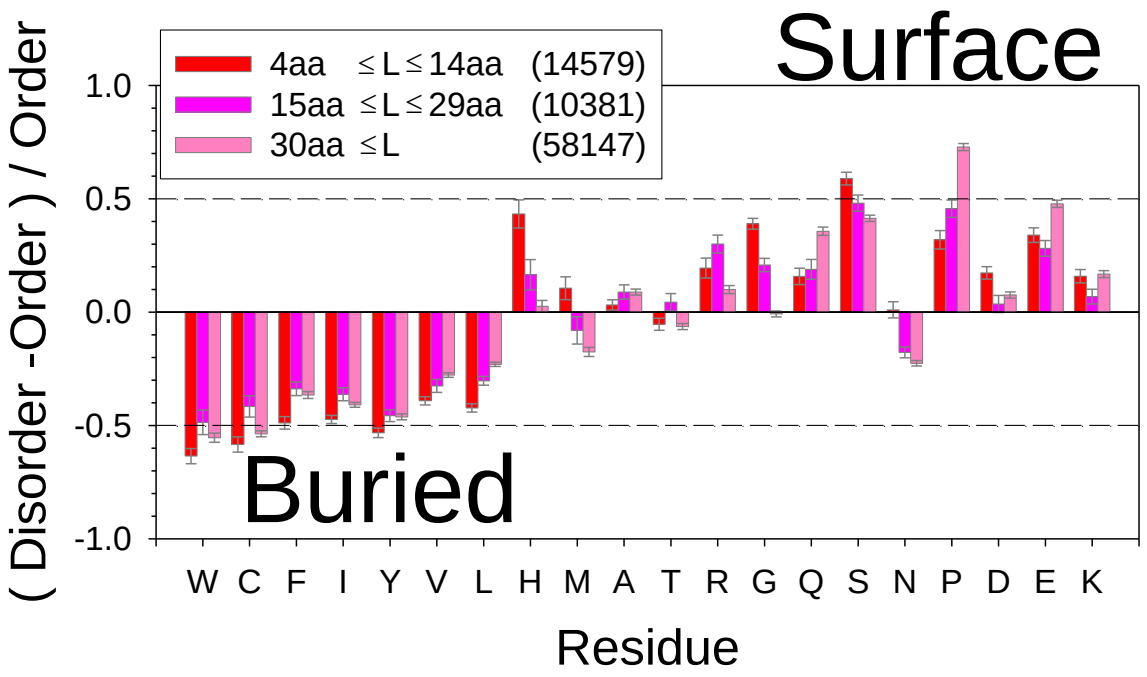
Protein	Disorder Length	Fu
Trypsinogen	~15	Folding i
TMV capsid	25	RNA bin
Lac repressor	61	DNA bin
Calmodulin	4	Flexible l binding
p21$^{Waf1/Cid1/Sdi1}$	164	Kinase in
HIV-1 gp120 V3 loop	24	Cell attac



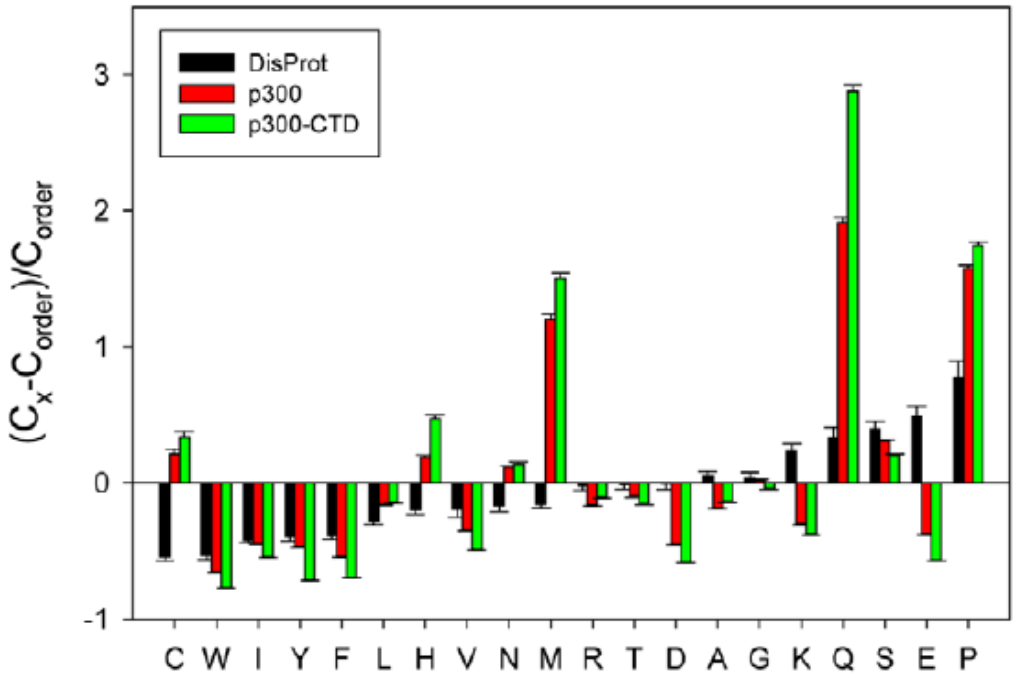
Dunker A K, Lawson J D, Brown C J, et al, 2001.

Why don’t IDPs fold into 3D structure?

Amino acid composition determines whether a protein will fold or remain unfolded



Dunker et al., *Adv.Prot.Chem.* 62: 25-37 (2002)



Kirilyuk, A. et al. PLoS ONE 7, e48243 (2012).

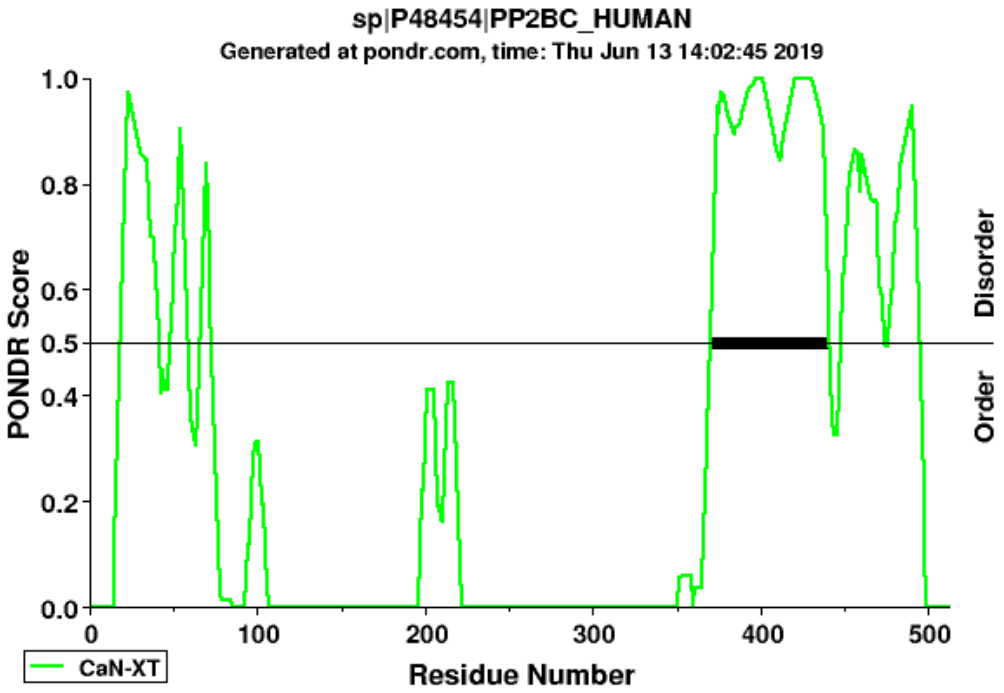
Why don’t IDPs fold into 3D structure?

- IDPs have too few aromatics – aromatics are important for the stability of hydrophobic cores;
- IDP ratio of hydrophilic amino acids to hydrophobic amino acids is too high for folding;
- IDPs have too low of a sequence complexity
- IDPs have too large of a net charge – charge repulsion inhibits folding;
- IDPs have too many prolines – prolines cannot form backbone H–bond, so helices and sheets are destabilized by prolines.

From Workshop by A. Keith Dunker, April 16, 2019

Methods to characterize intrinsic disorder in proteins

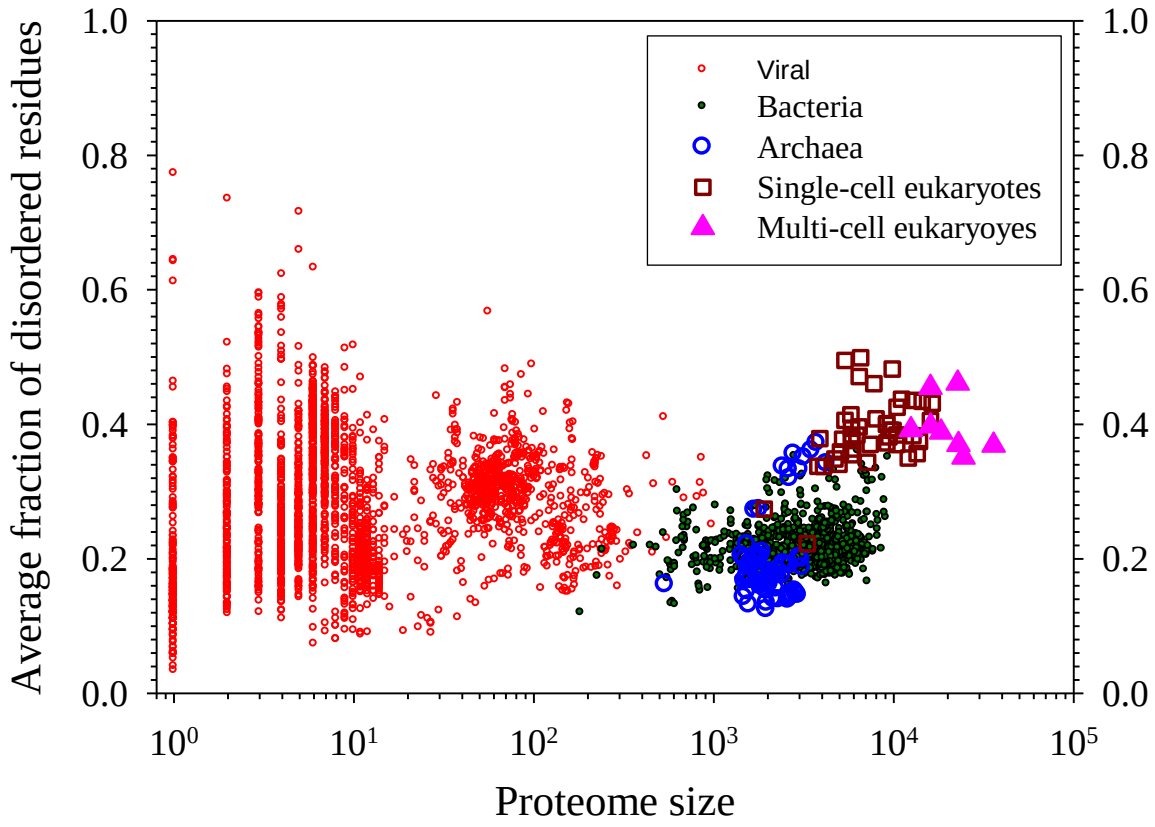
- *In vitro*
  - X-ray crystallography
  - NMR spectroscopy
  - Cryo-EM
  - Circular dichroism (CD) spectroscopy
  - Stoke's radius determination
- *In silico*
  - Pondr: http://www.pondr.com/
  - DisEMBL: http://dis.embl.de/
  - PredictProtein: https://www.predictprotein.org/
  - IUPred: https://iupred2a.elte.hu/
  - and many others…



Calcineurin(钙调磷酸酶)

Dunker A K, Lawson J D, Brown C J, et al, 2001.

How common are IDPs?



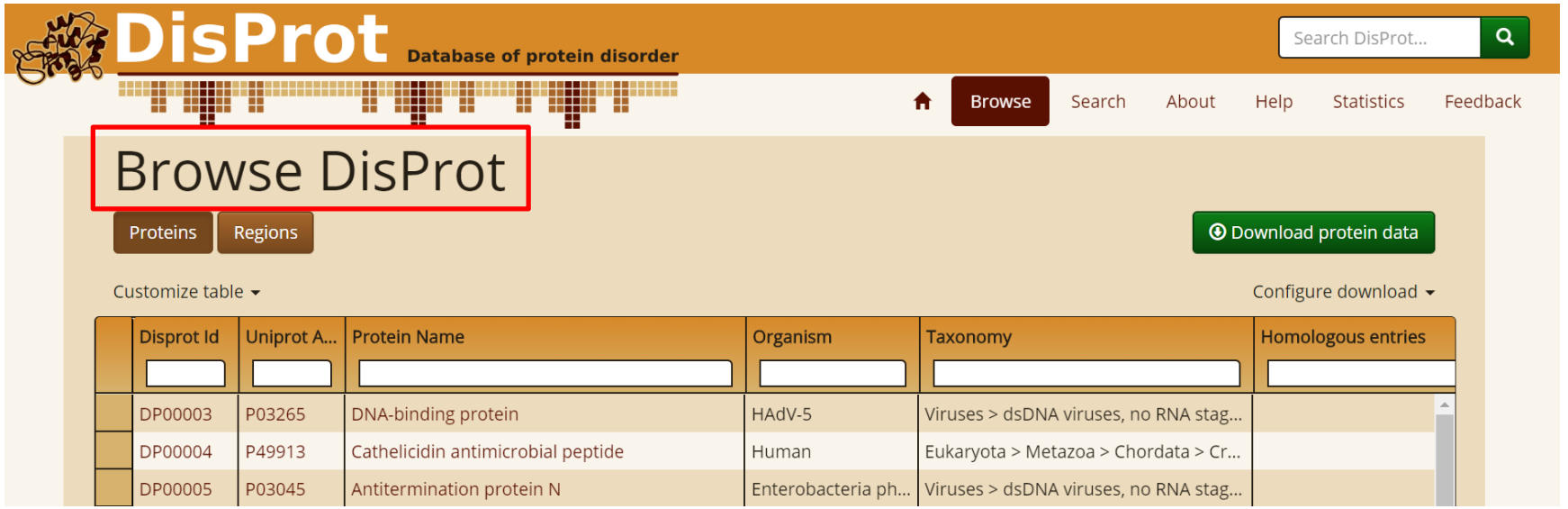
For the human proteome:

35% residues are in

IDPs or IDP regions

Xue et al., *J Biomol Struct Dyn* 30: 137-149 (2012)

Database of disorder proteins



- Contains 803 proteins and 2167 regions
- Manually curated and experimentally determined to be disordered

http://www.disprot.org/

Database of disorder proteins

MobiDB

a database of protein disorder and mobility annotations

Search MobiDB

search

help UniProt query, UniRef, UniParc, Proteome, UniProt accession, NCBI taxon id

Example entries RPO21 SNCA MAPT CITRX2

Citing MobiDB

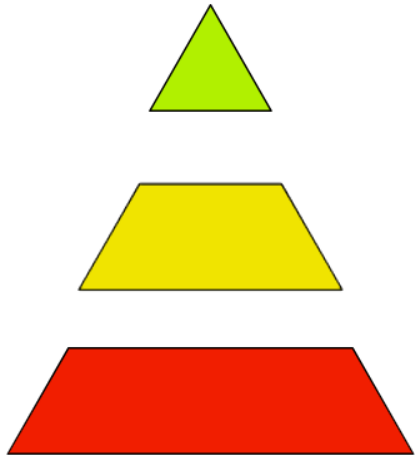
MobiDB3.0: More annotations for intrinsic disorder, conformational diversity and interactions in proteins

Piovesan D, Tabaro F, Paladin L, Necci M, Mičetić I, Camilloni C, Davey N, Dosztányi Z, Meszaros B, Monzon AM, Parisi G, Schad E, Sormanni P, Tompa P, Vendruscolo M, Vranken WF and Tosatto SCE

Nucleic Acid Research 2017 (Database issue) launch

Annotation quality

MobiDB features three quality **levels of annotation** from high to low quality (pyramid). Different sources present a clear tradeoff between quality and coverage.



Database

Manually curated annotations from external databases

Indirect

Derived/calculated information from **experimental data**, i.e. PDB structures and/or chemical shifts

Predictions

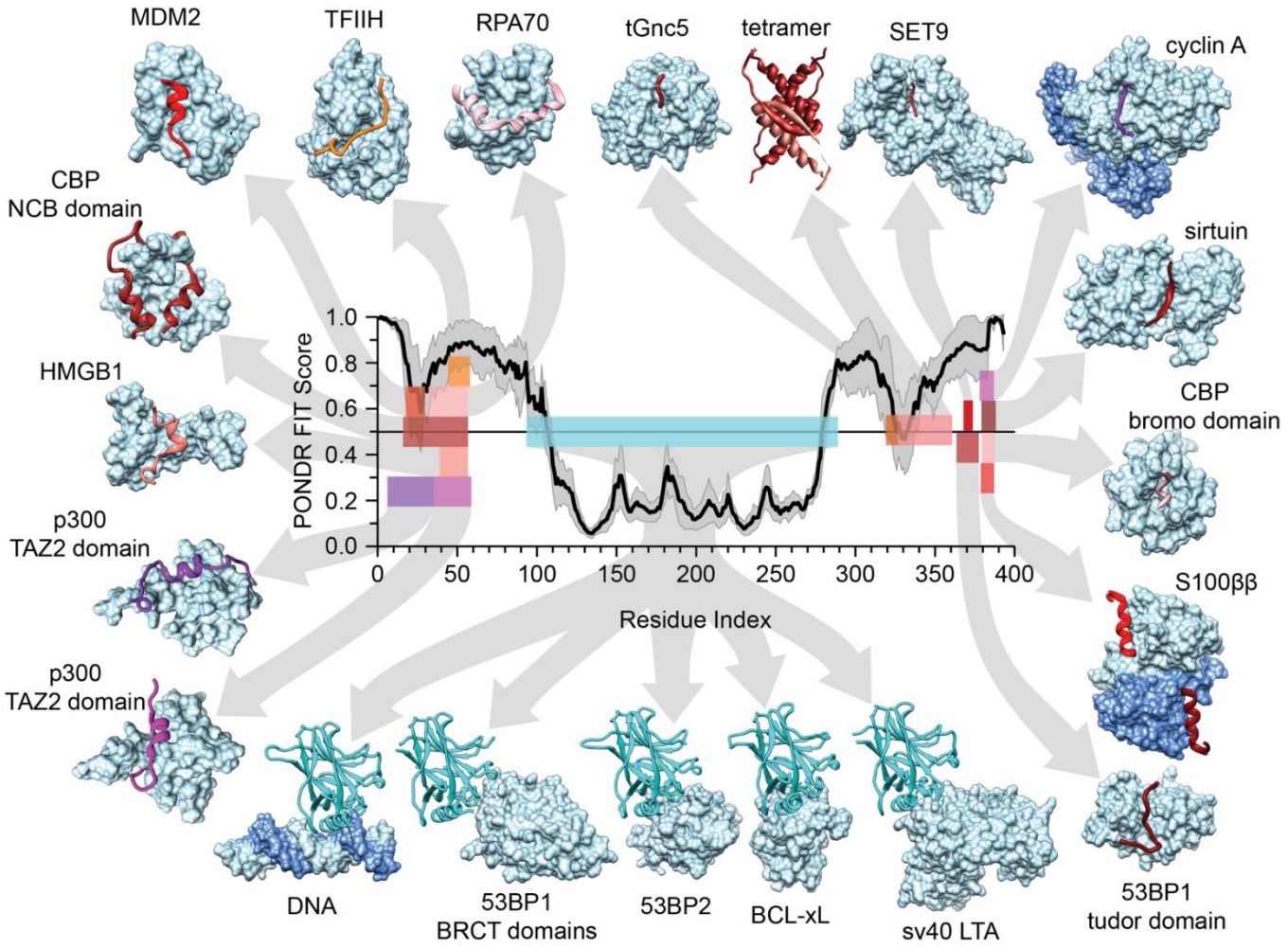
Predicted annotations

http://mobidb.bio.unipd.it/

What are the functions of IDPs?

P53: Tumor suppressor

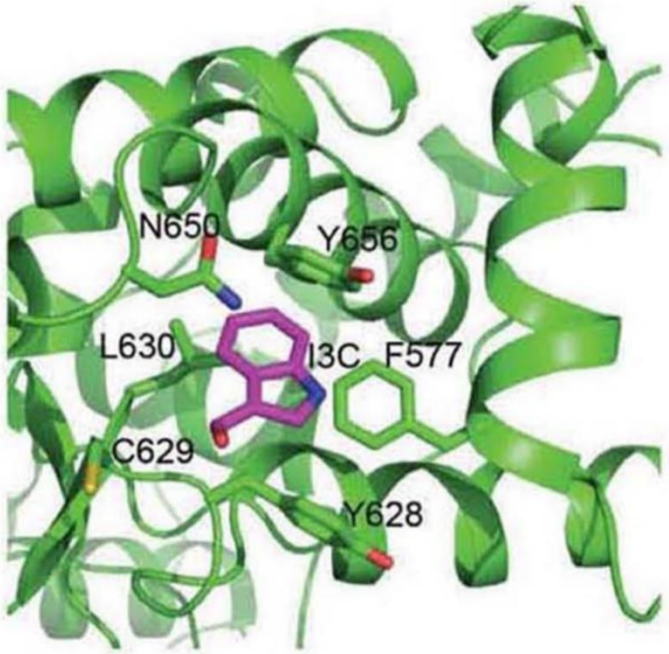
- Initiates apoptosis
- Arrests cell growth
- Increases genome stability
- Inhibits angiogenesis
- Activates the expression of hundreds of genes



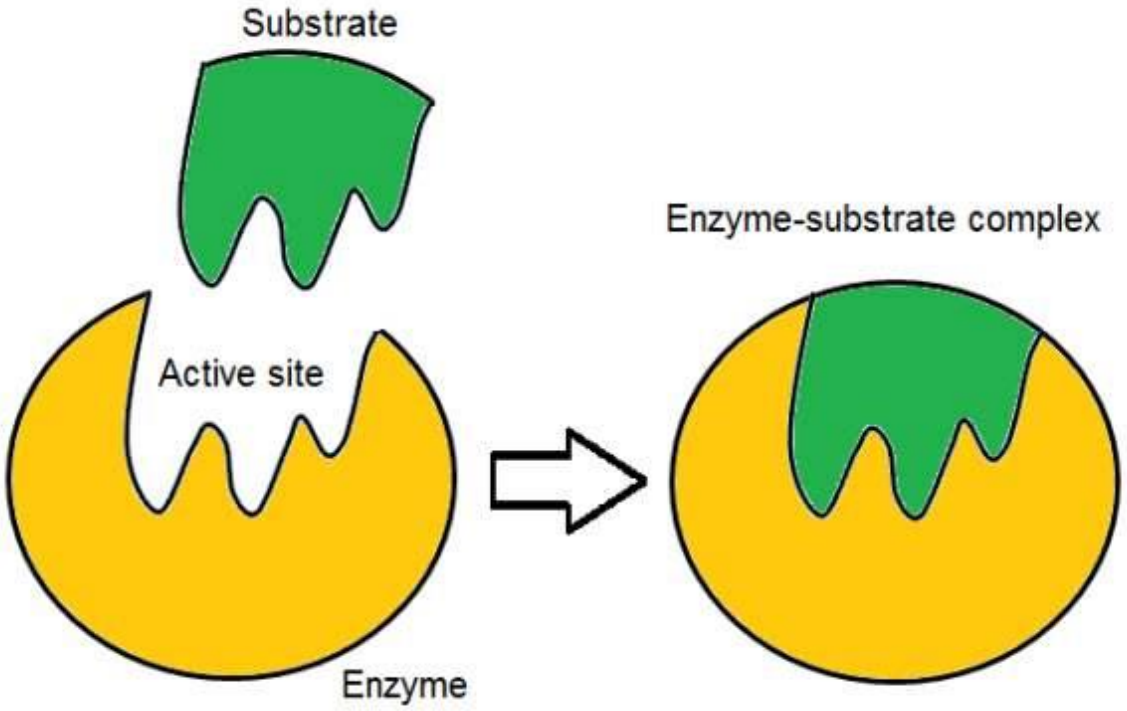
Modified from: Oldfield & Dunker, *Ann Rev Biochem* 83: 553 – 584 (2014)

Drug Design

Traditional Drug Design for ordered protein

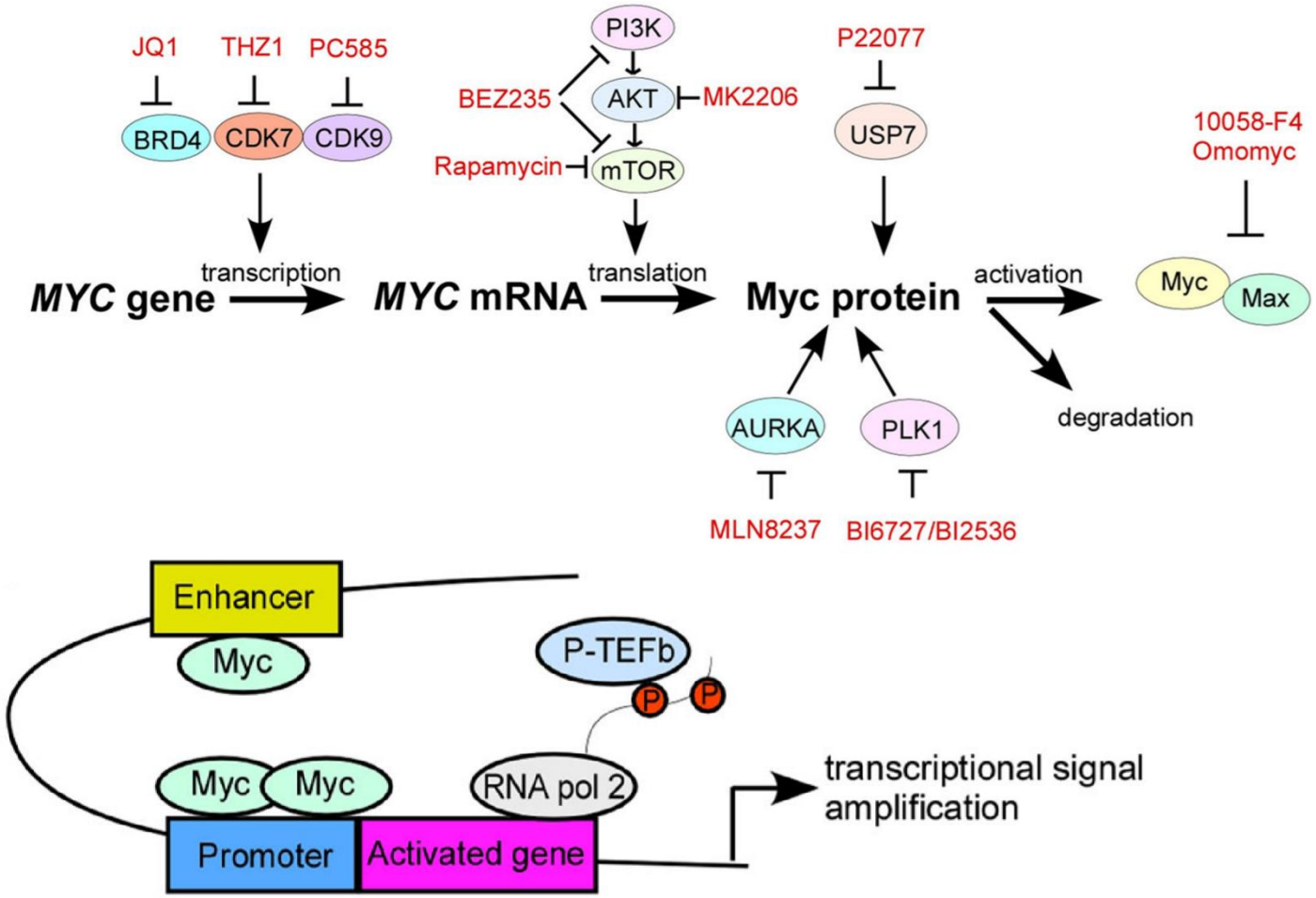


Lock and key



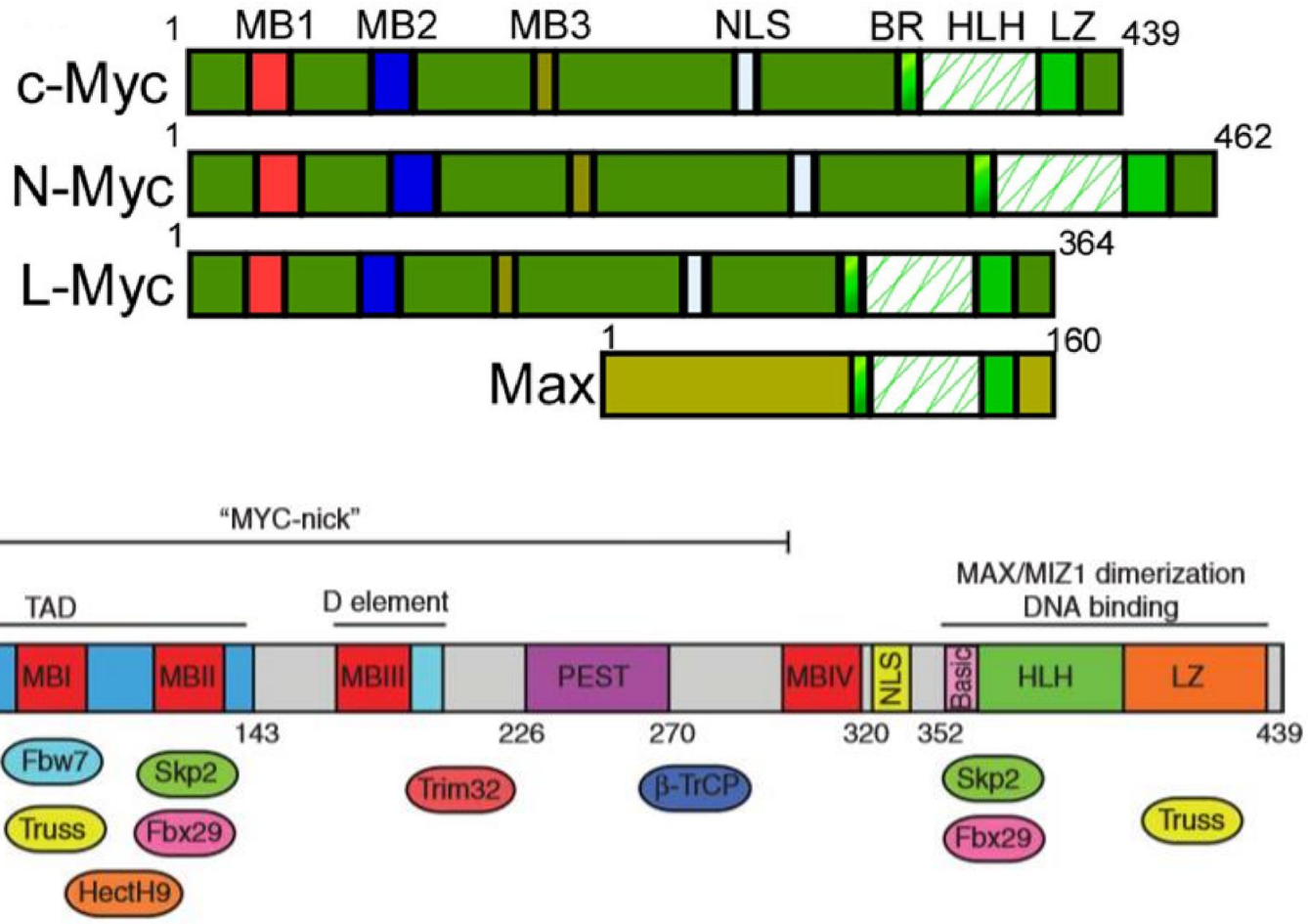
Lee, Y.-R. and P. P. Pandolfi (2019). "Reactivation of PTEN tumor suppressor for cancer treatment through inhibition of a MYC-WWP1 inhibitory pathway." Science 364(6441): eaau0159.

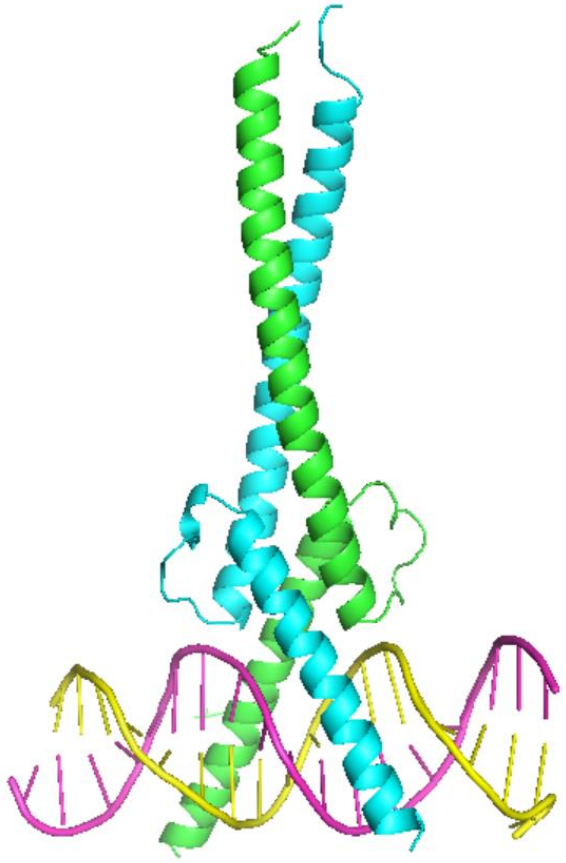
Background



Chen, H., H. Liu and G. Qing (2018). "Targeting oncogenic Myc as a strategy for cancer treatment." Signal Transduction & Targeted Therapy **3**(1): 5.

Structure of c-Myc





PDB: 1NKP
Green: Myc; Blue: Max

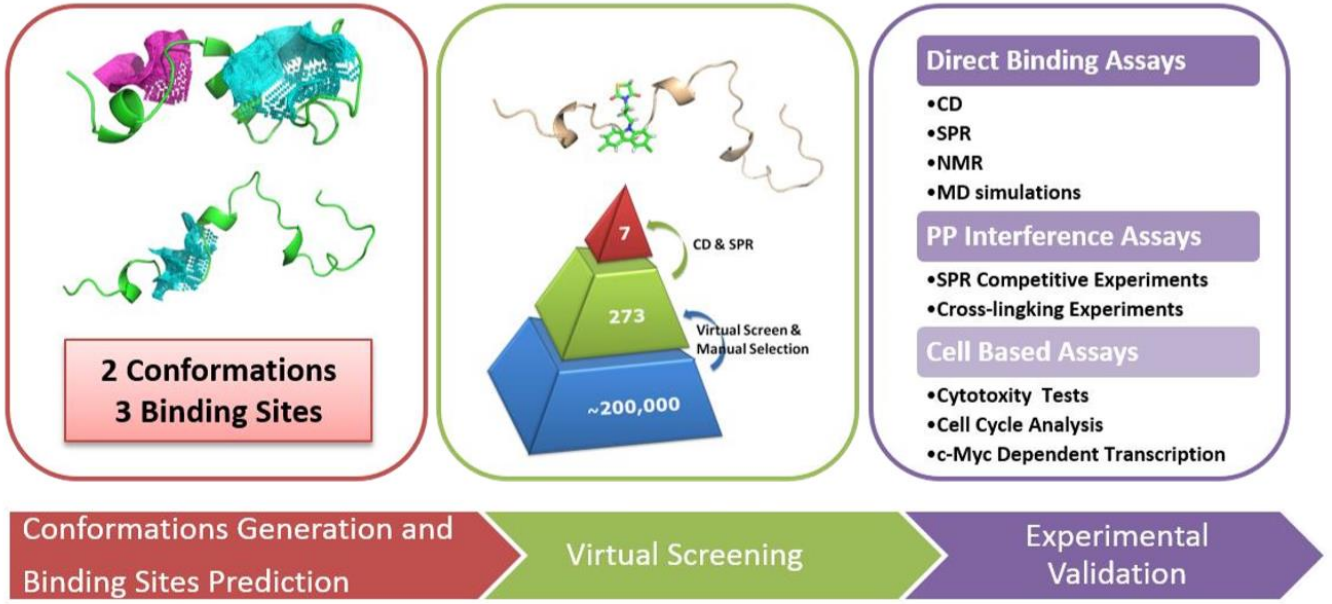
Chen, H., H. Liu and G. Qing (2018). "Targeting oncogenic Myc as a strategy for cancer treatment." Signal Transduction & Targeted Therapy **3**(1): 5.

Methods of Drug Design and Screening

High throughput screening

Beckman FX, ORCA Optimized Robot,
Microplate Carousel and Paradigm Detection Platform

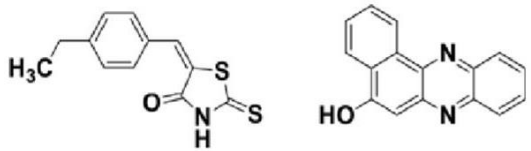
Virtue screening

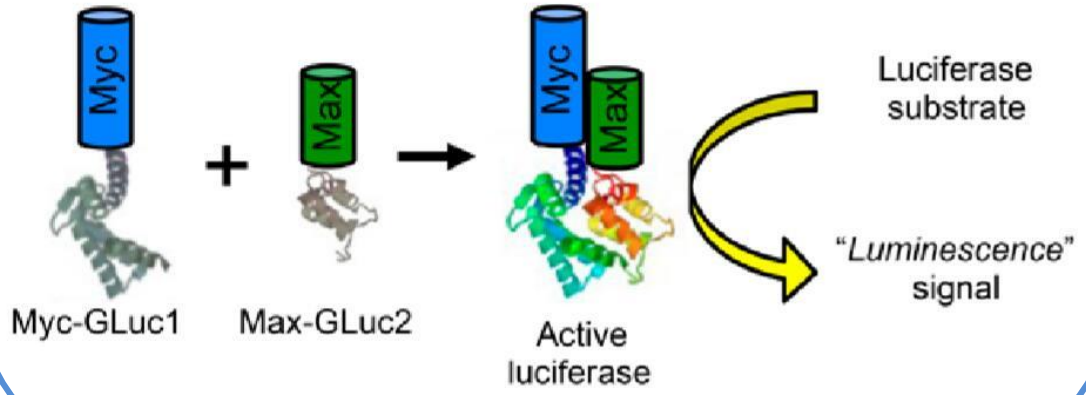


Screening on computer

Result Screening

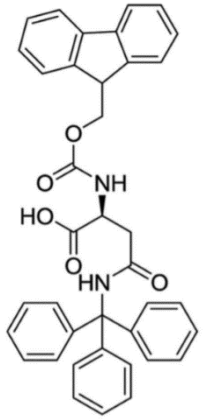
High throughput screening

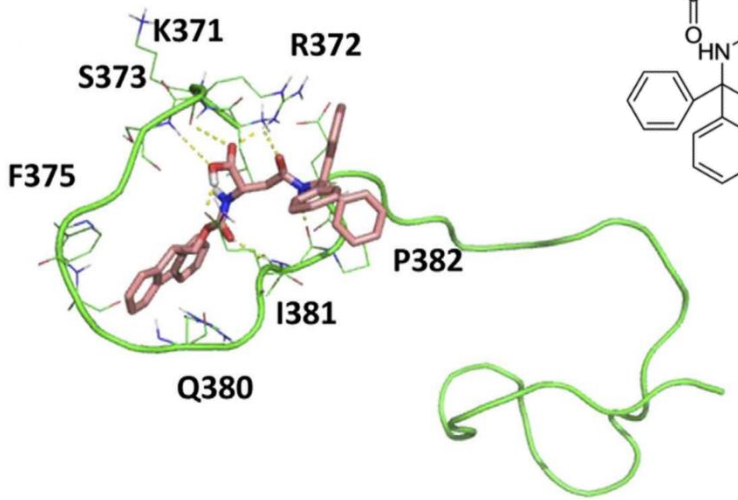




Choi, Seung H , et al. "Targeted disruption of Myc-Max oncoprotein complex by a small molecule." *ACS Chemical Biology* (2017):acschembio.7b00799.

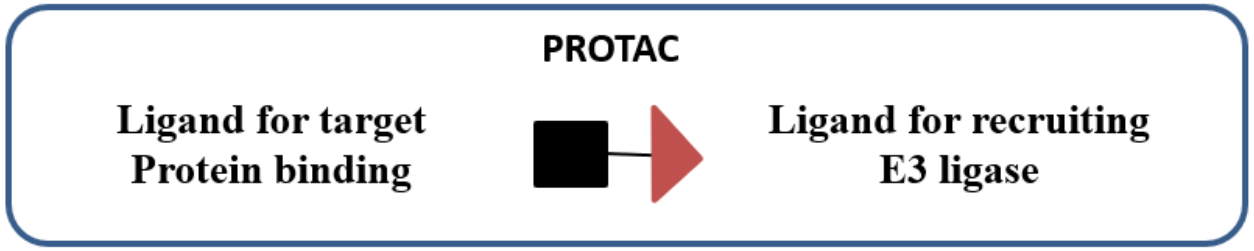
Virtue screening

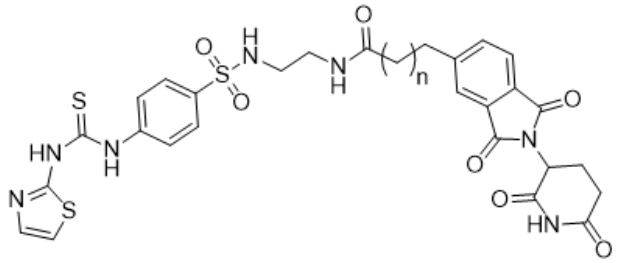




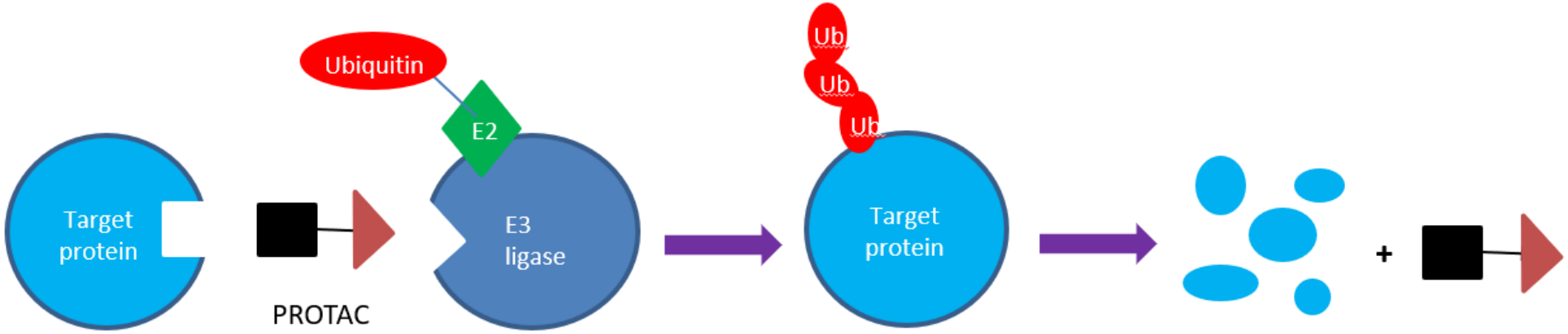
Yu, Chen , et al. "Structure-based Inhibitor Design for the Intrinsically Disordered Protein c-Myc." *Scientific Reports* 6(2016):22298.

PROTAC: PROteolysis TArgeting Chimeras





The structure of PROTAC



E3 ligase is recruited to
Target protein by PROTAC

Target protein is recognized and
Degraded by proteasome

Drug and Patent Discovery

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艾尔建（Allergan）近日宣布，美国食品和药物管理局（FDA）已批准复方抗生素Avycaz（ceftazidime-avibactam，CAZ-AVI，头孢他啶-阿维巴坦）的一...

赛诺菲新型降脂药Praluent新适应症获欧...

法国制药巨头赛诺菲（Sanofi）与合作伙伴再生元（Regeneron）近日宣布，欧盟委员会（EC）已批准PCSK9抑制剂类降脂药Praluent（alirocumab）一个新的适...

美国FDA批准抗生素Avycaz治疗儿科复杂腹腔 19-03-19

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