

Molecular Networks

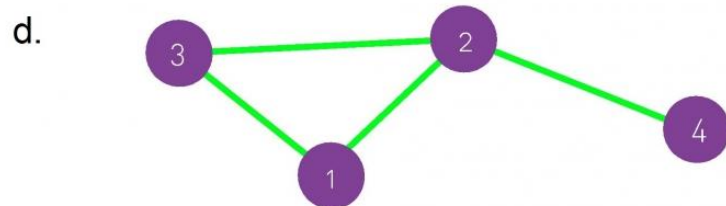
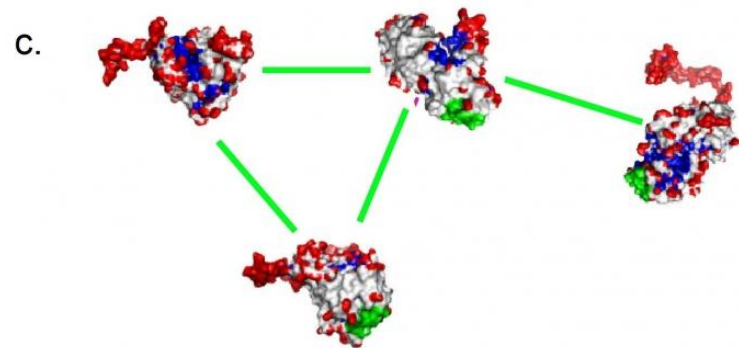
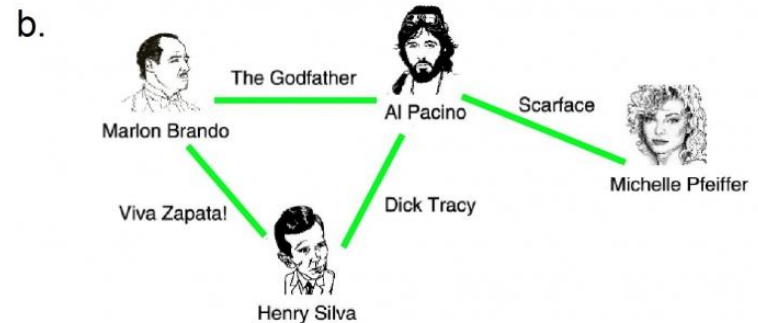
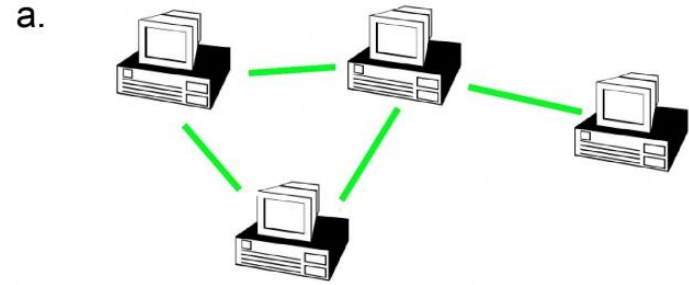
Networks

→ Graph:

- ◆ abstract mathematical representation, data structure

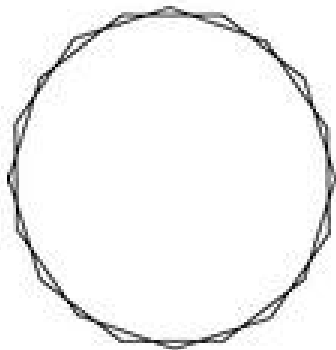
→ Network

- ◆ phenomenon modelled by graph



Network topology

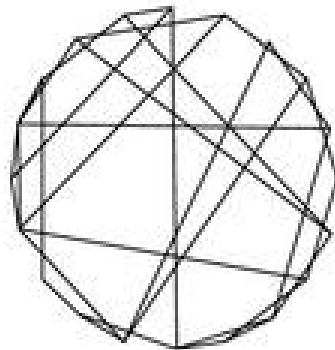
Regular



$$\rho = 0$$

(a)

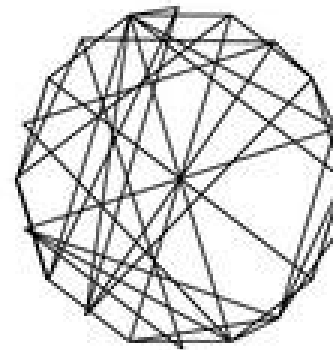
Small world



$$N = 20, k = 4$$

(b)

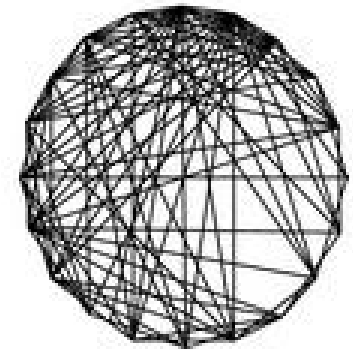
Random



$$\rho = 0$$

(c)

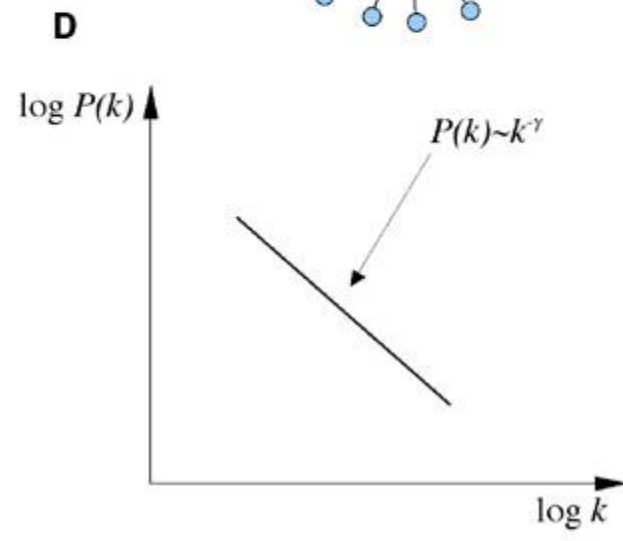
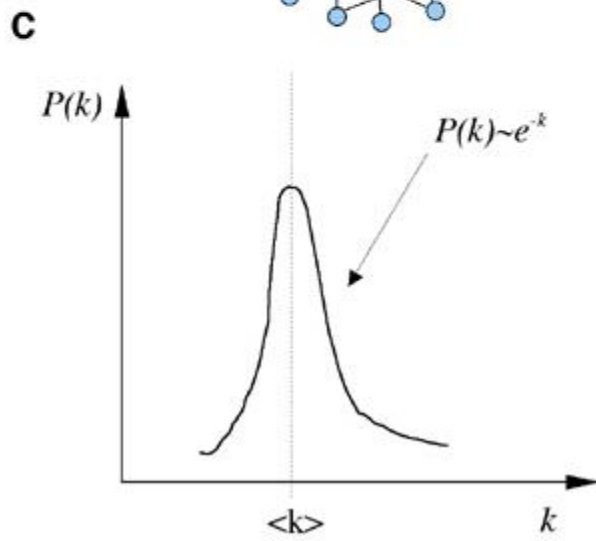
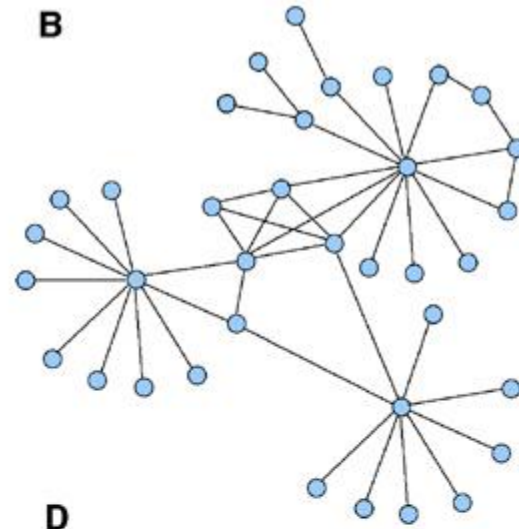
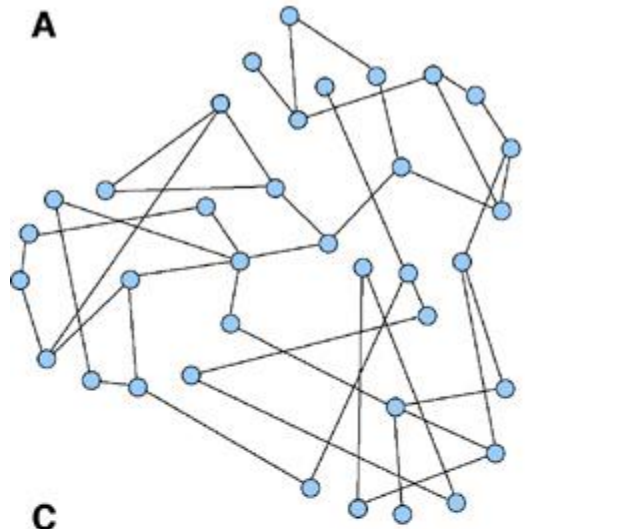
Free-scale



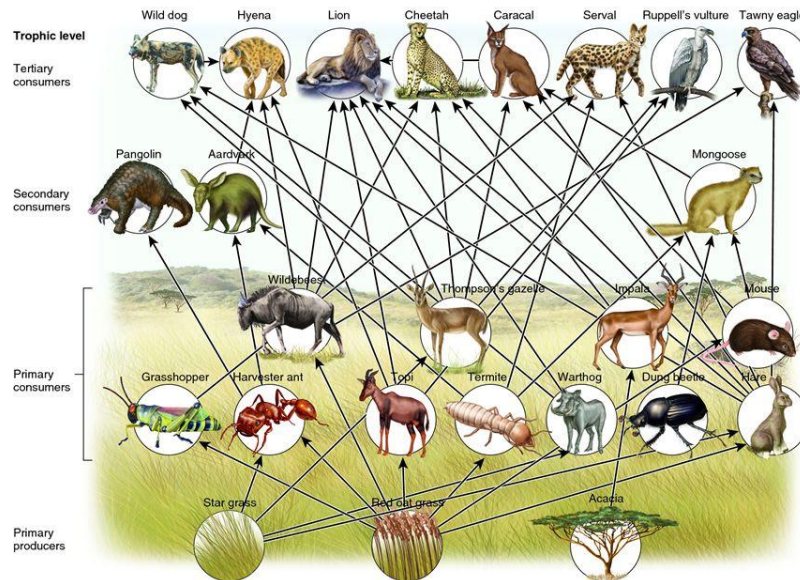
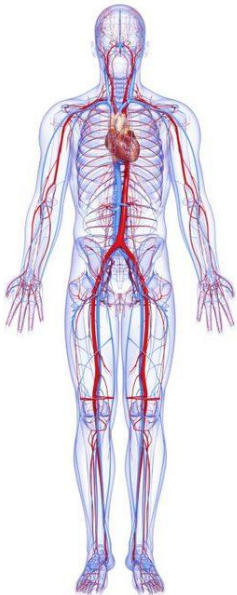
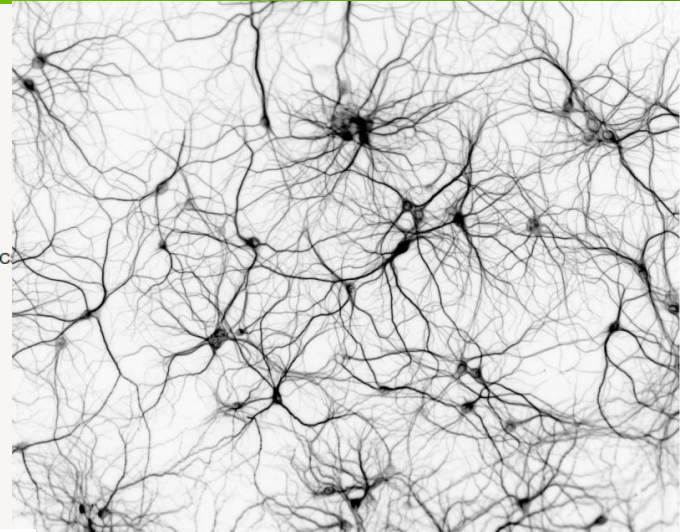
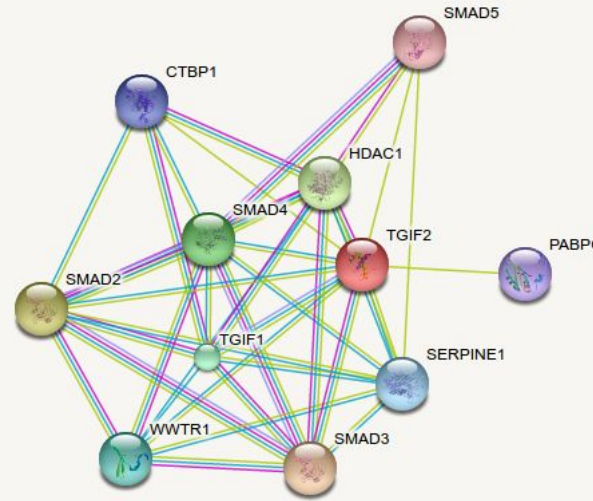
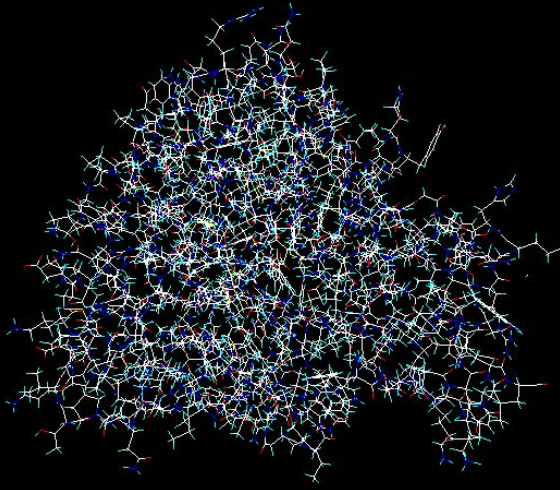
$$N = 30, m_0 = 6, k = 4$$

(d)

Network topology



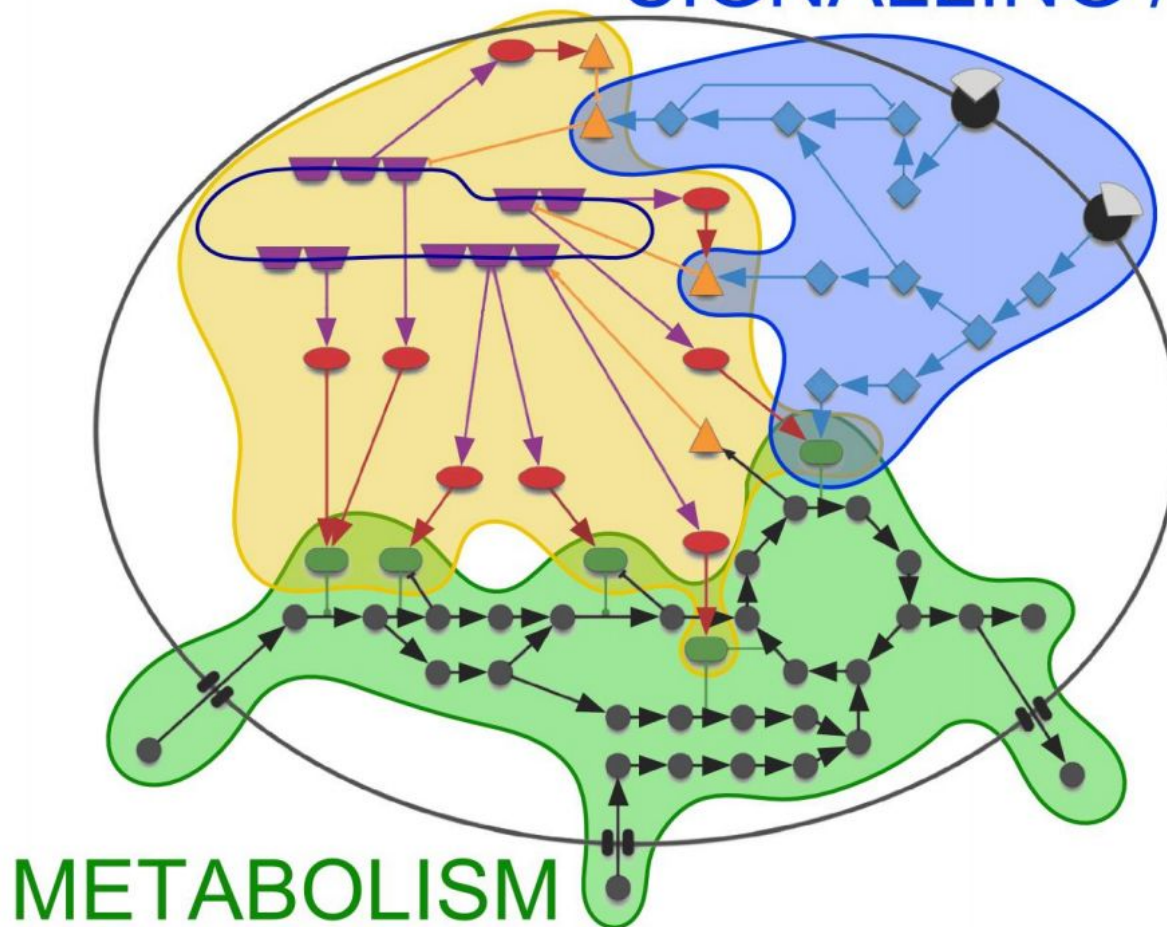
Networks in biology



Molecular networks

REGULATION

SIGNALLING / PPI



Nodes and edges in molecular networks

→ Nodes:

- ◆ DNA: DNA region, gene
- ◆ RNA: mRNA, non-coding RNA (miRNA, lncRNA)
- ◆ Protein
- ◆ Sub-protein: Domain, protein sequence region

→ Edges:

- ◆ DNA-DNA: sequence similarity
- ◆ Protein-DNA: DNA binding
- ◆ DNA-mRNA: transcription
- ◆ miRNA-mRNA: RNA interference
- ◆ mRNA-Protein: translation
- ◆ Protein-Protein: physical interaction

Sources of Protein-Protein Interactions

→ Small scale

- ◆ Few interaction / publication
- ◆ Could be directed
- ◆ Many information / interaction
- ◆ Individual errors
- ◆ Local data
- ◆ No central database (publications)
- ◆ Curation

→ Large scale

- ◆ Lot interaction / publication
- ◆ Mostly undirected
- ◆ Few information / interaction
- ◆ Systematic errors
- ◆ Global data
- ◆ Few database
- ◆ High-throughput – HTP methods

Collecting PPI data

- Manual curation / literature mining
 - ◆ +: Small scale high precision data
 - ◆ -: Huge work, biased

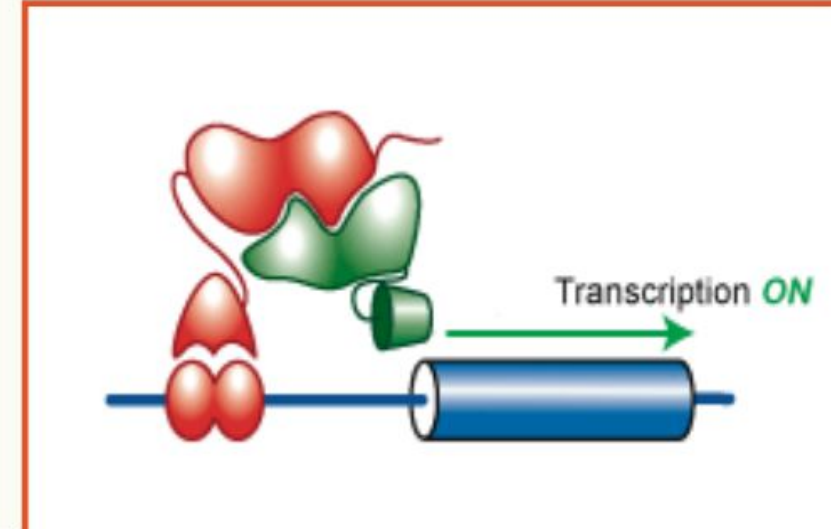
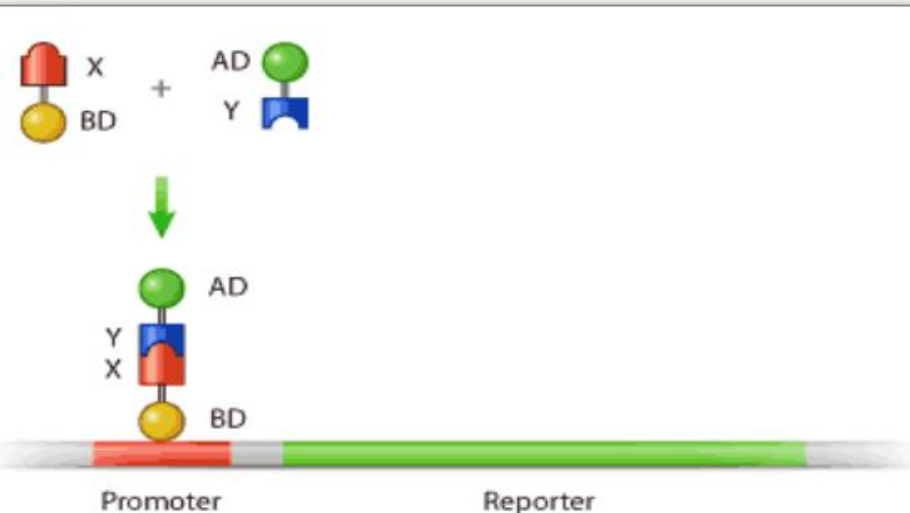
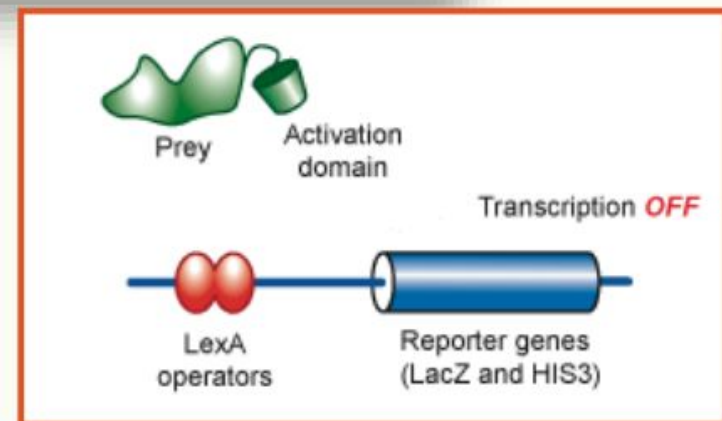
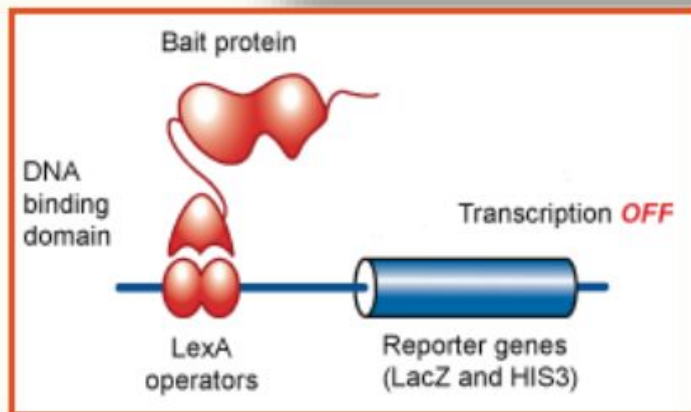
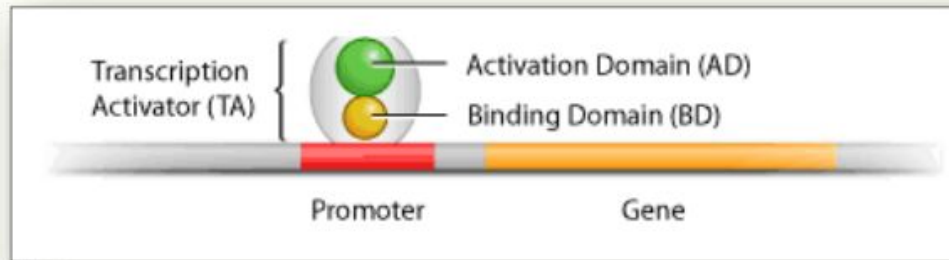
- Prediction (homologous transfer)
 - ◆ +: Lot of data, low human/computer time
 - ◆ -: Quality of predicted data based on the quality of the original data

- Data integration
 - ◆ +: Wide scale of data
 - ◆ -: Systematic error

High-throughput methodes

- Y2H: Two-hybrid screening
- AP-MS: Affinity purification-mass spectrometry
- Co-IP: Co-immunoprecipitation
- FRET (Fluorescence Resonance EnergyTransfer)
- biFC (Bimolecular Fluorescence Complementation):
- Protein-chip

Two-hybrid screening



Limitations of two-hybrid screening

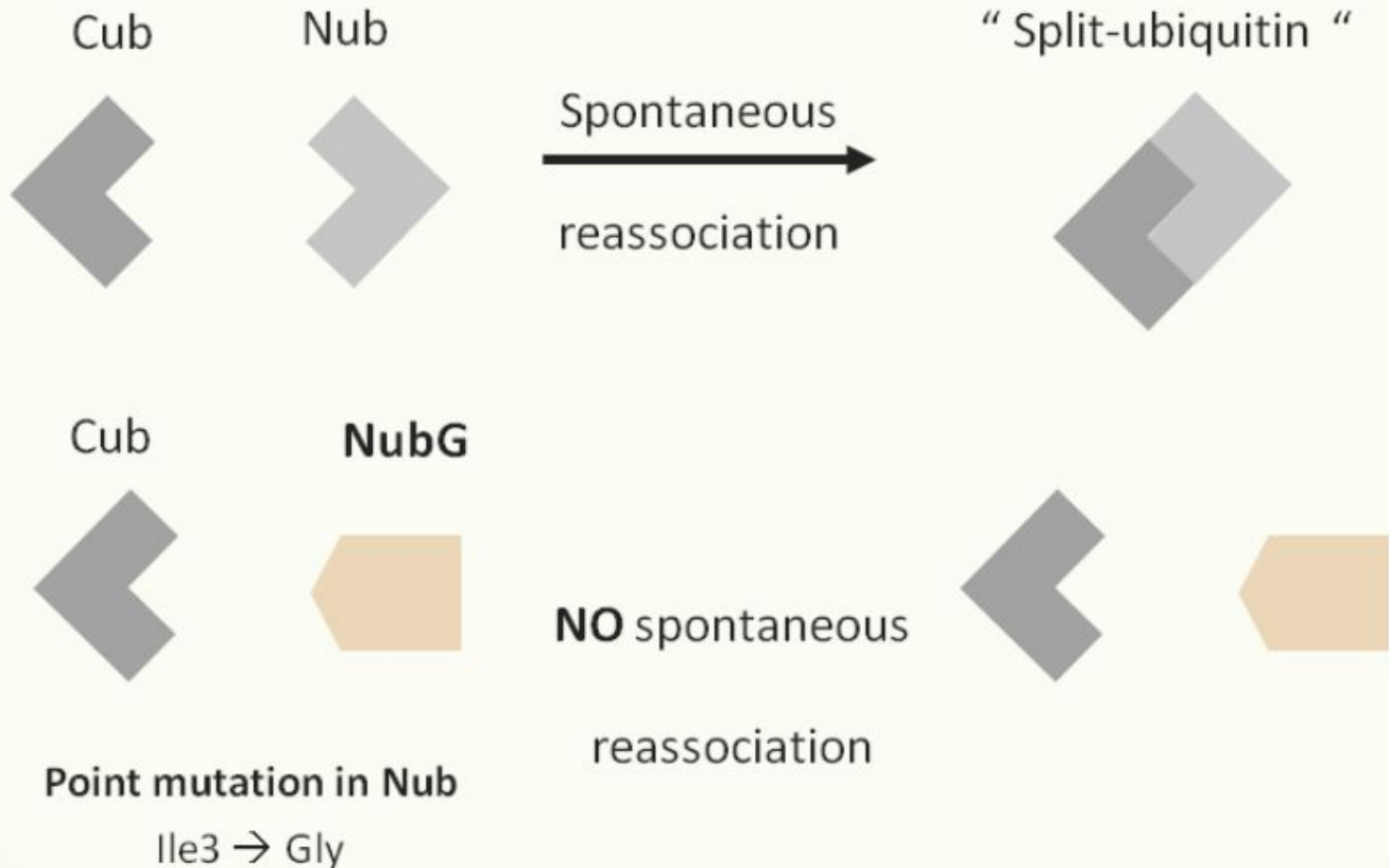
- Self activator bait
- Too big complex: can not enter to the nucleus

Excluded proteins:

- Membrane proteins
- Extra cellural proteins
- Transcription factors
- Proteins with acidic side chains

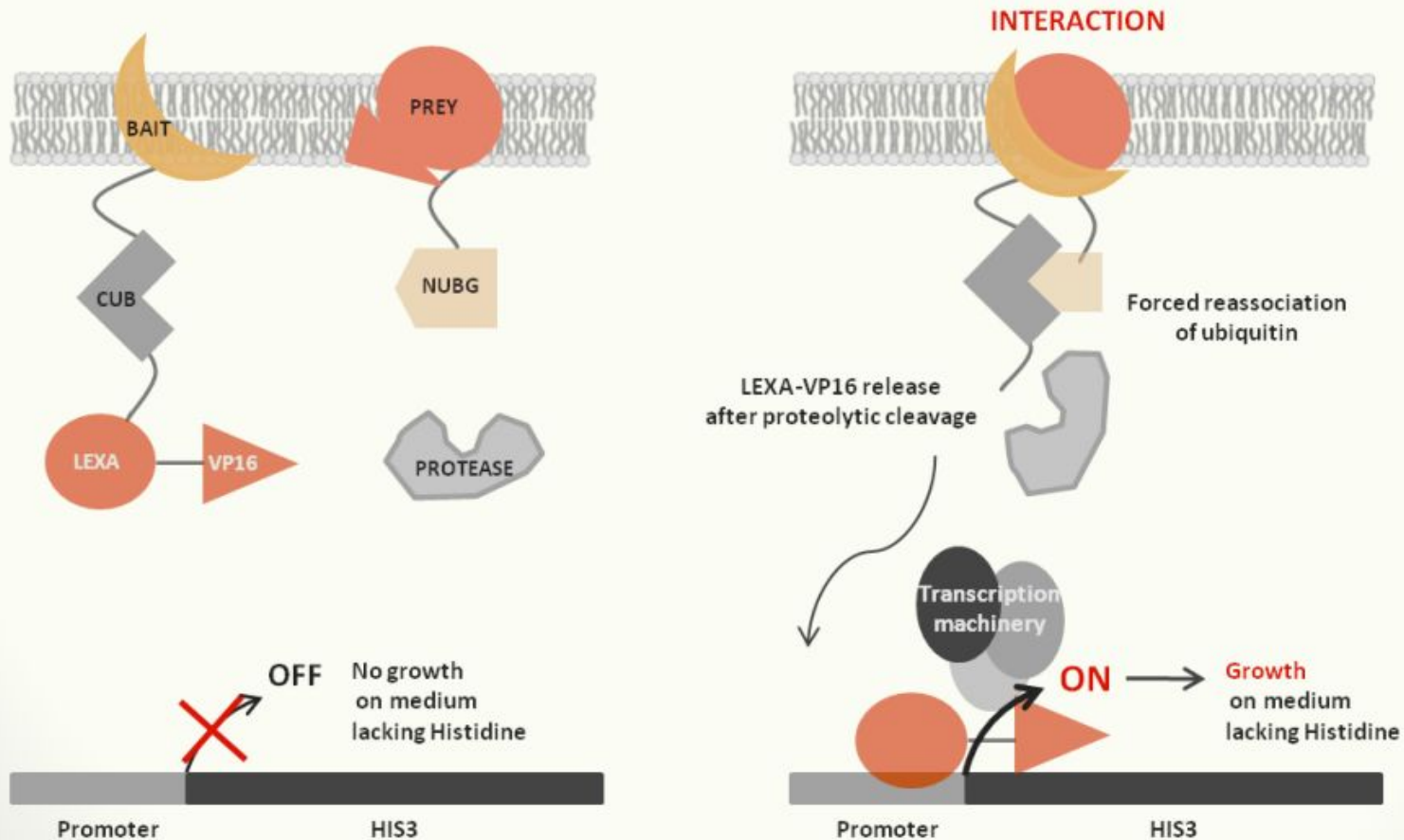
Modified Y2H system with split-ubiquitin system

SPLIT-UBIQUITIN

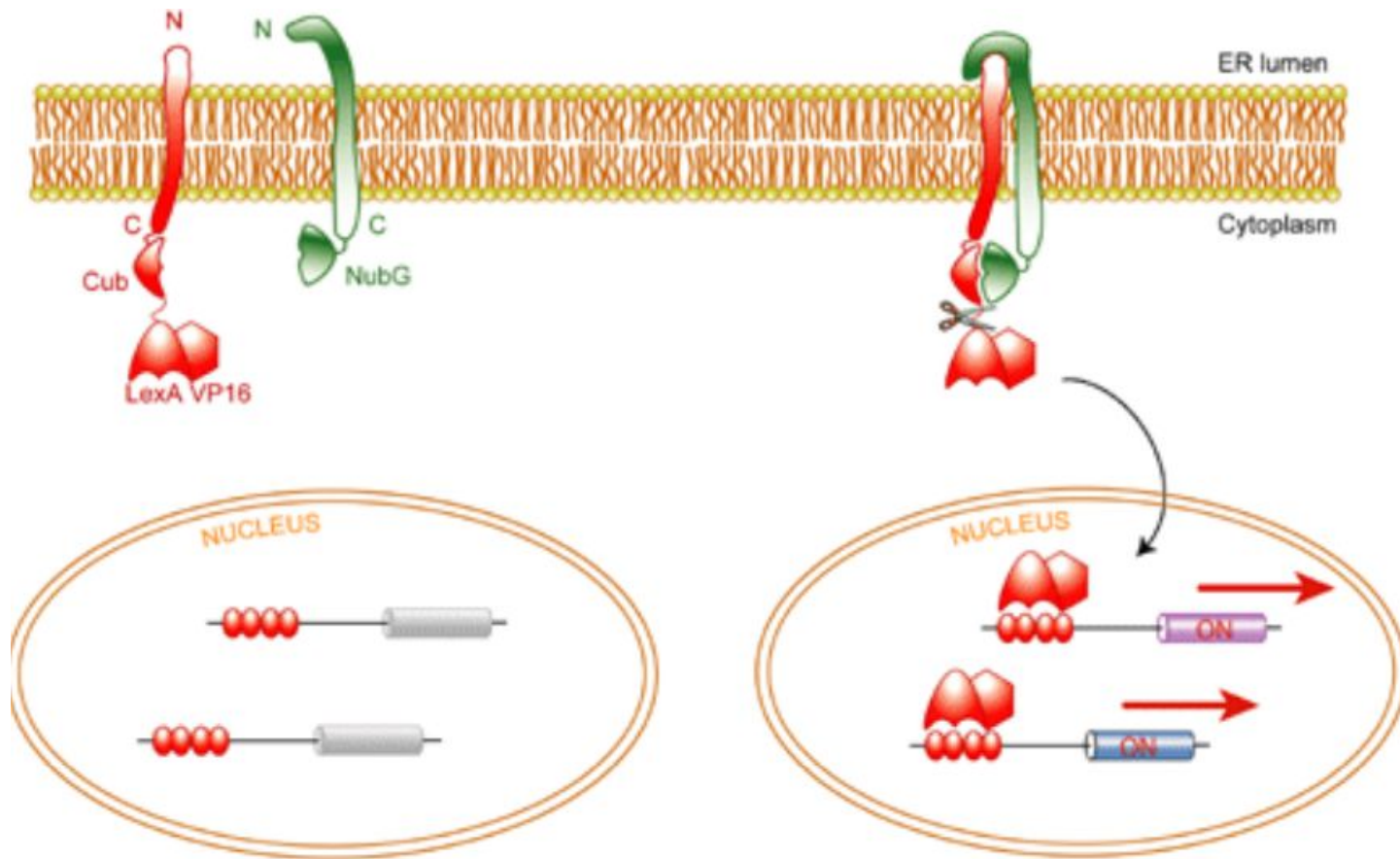


Modified Y2H system with split-ubiquitin system

MBMATE Y2H PRINCIPLE



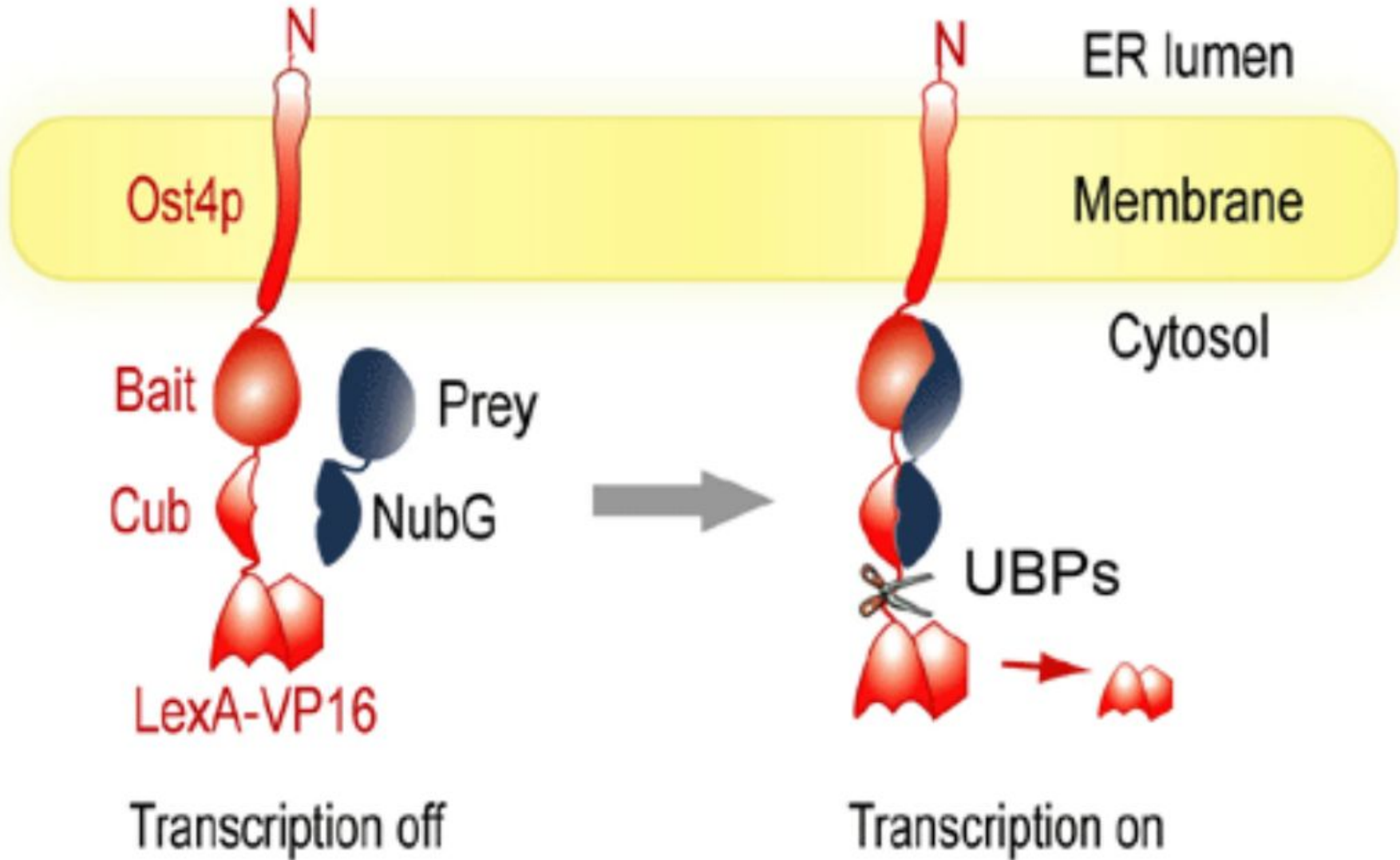
Study integral membrane proteins with split-ubiquitin-Y2H system



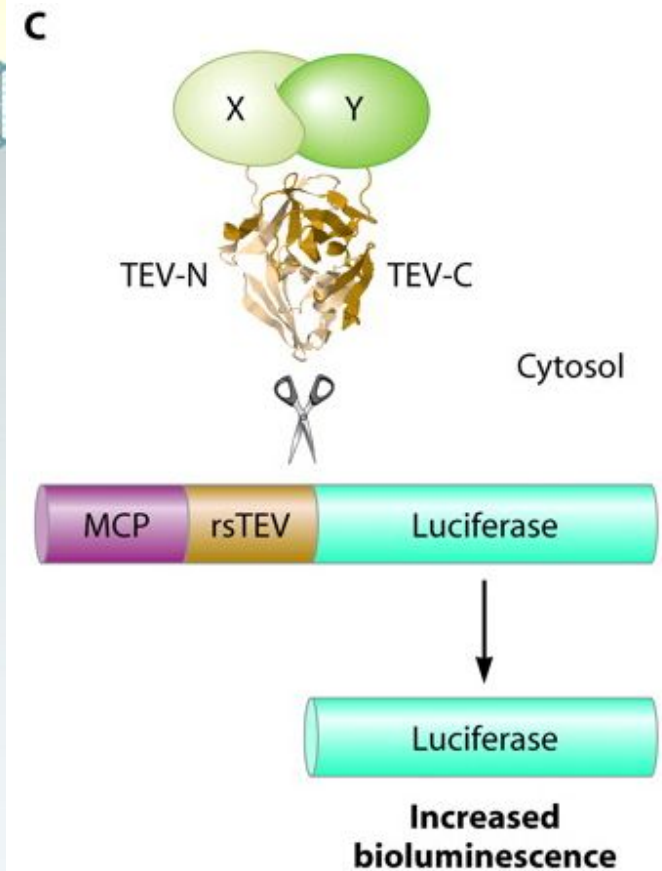
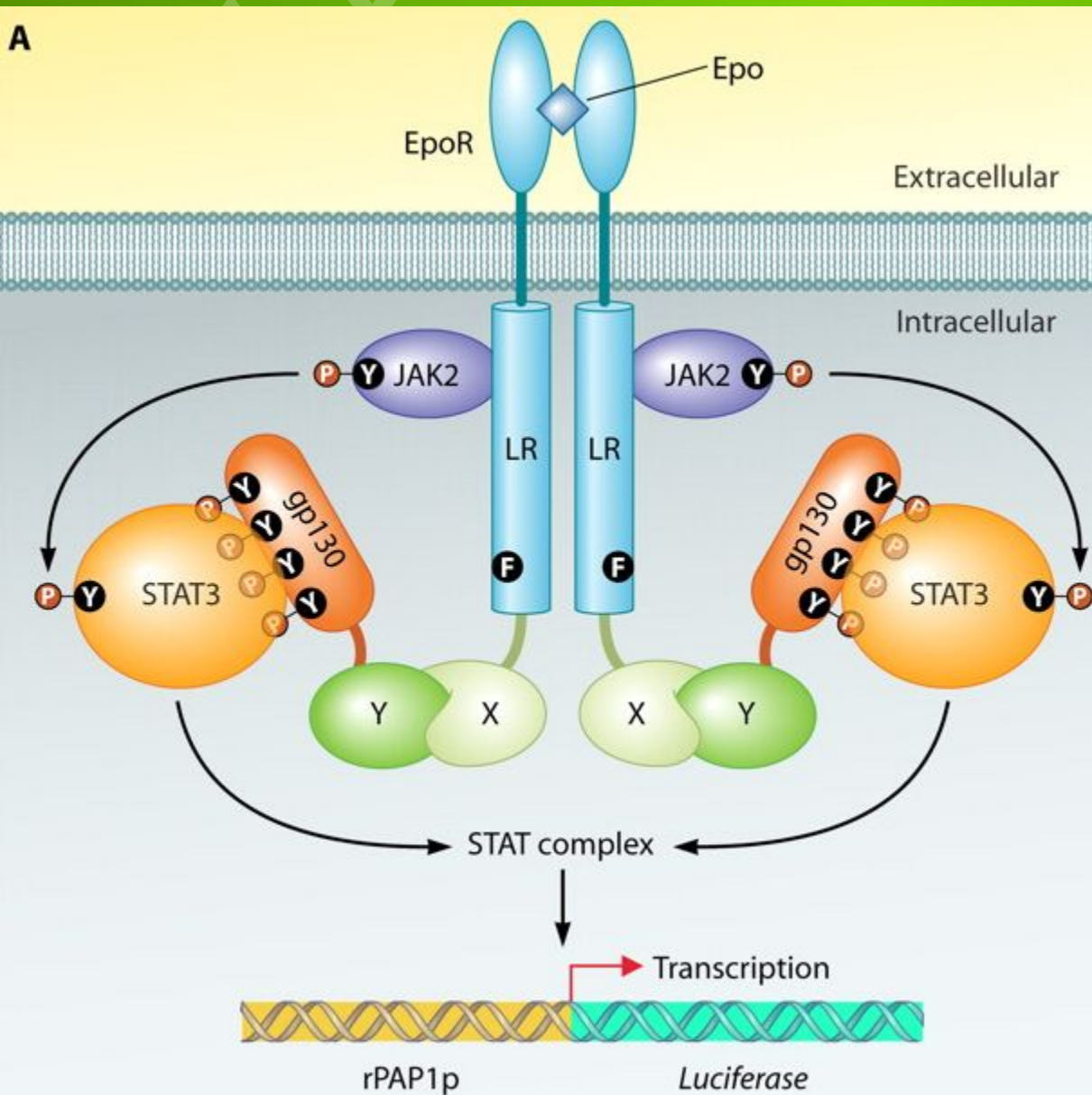
Growth on selective medium

Blue coloration

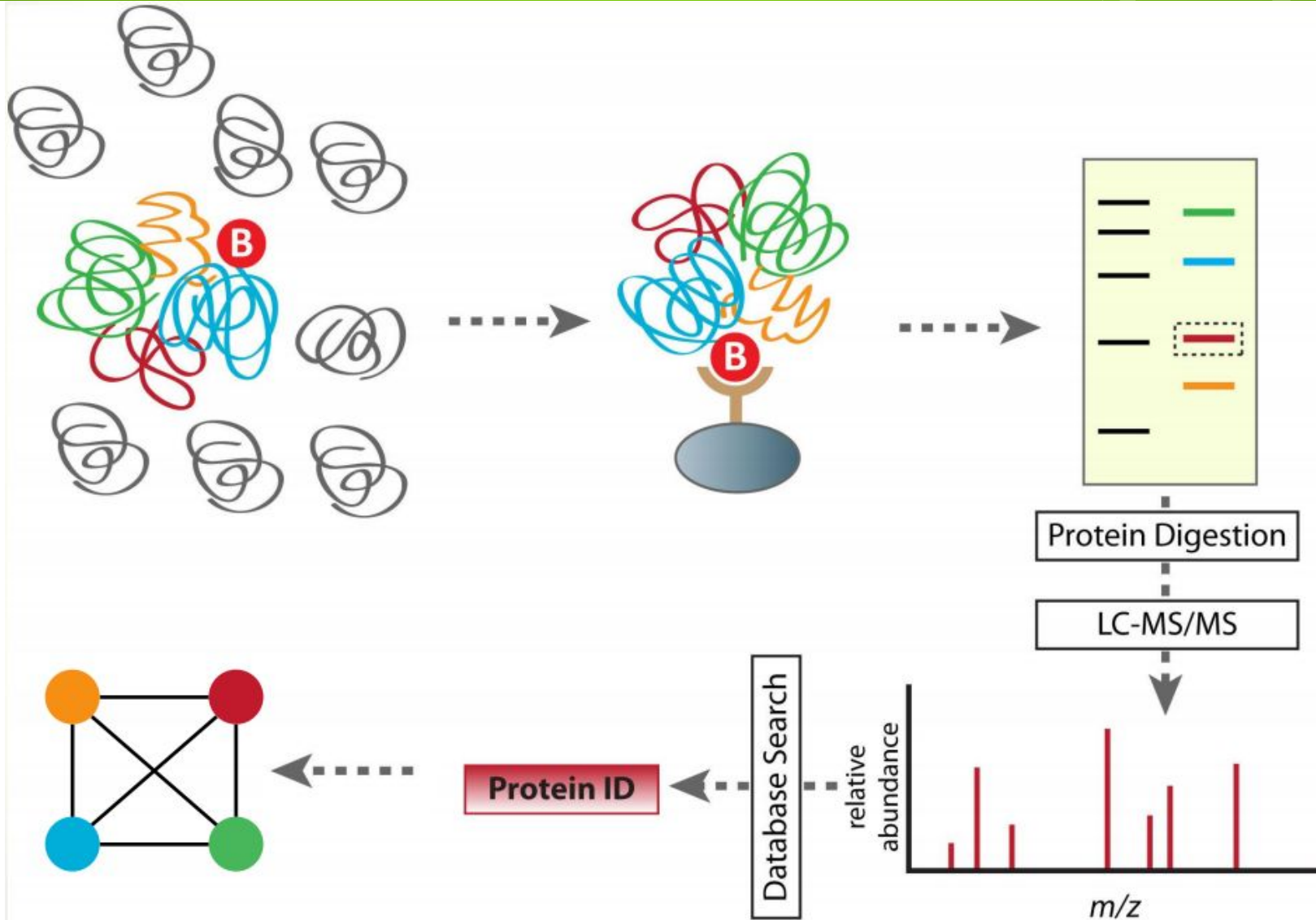
Study transcription factors with split-ubiquitin-Y2H system



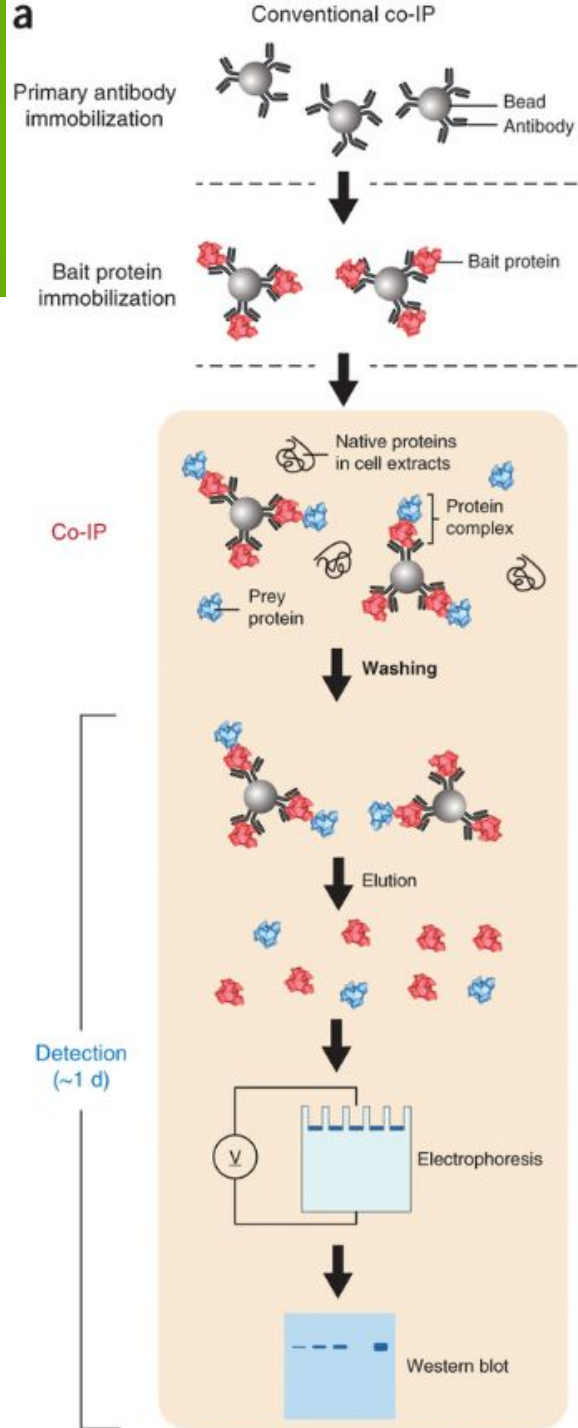
MAPPIT - mammalian protein protein interaction trap



Affinity Purification - Mass Spectrometry

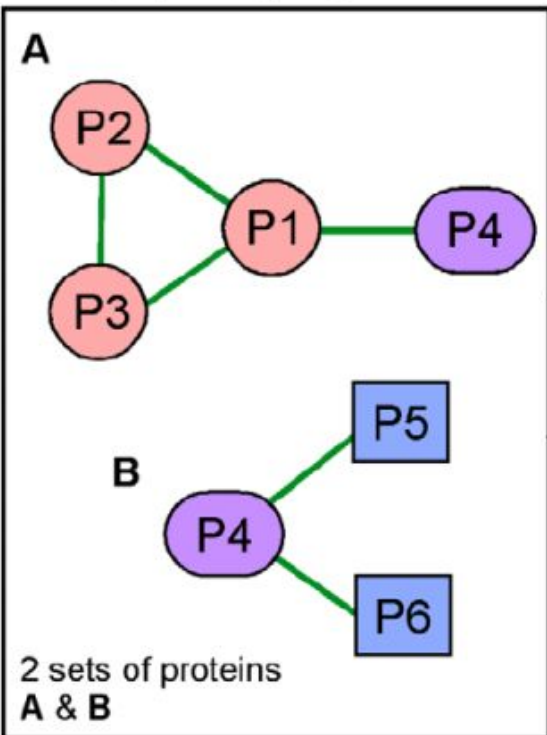


Co-immunoprecipitation



Y2H vs. TAP-MS / CoIP

True interactions (PPIs)
physical topology *in vivo*



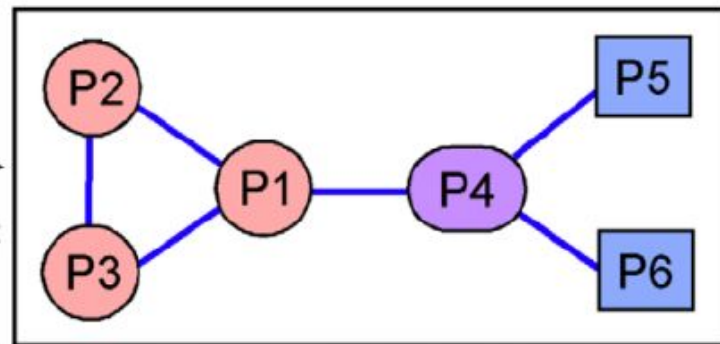
Binary methods
measure physical direct PPIs

e.g.
Y2H

P1-P2 P2-P3
P1-P3 P4-P5
P1-P4 P4-P6

direct
assignment

Experimental interactions (PPIs)
obtained from binary or co-complex methods



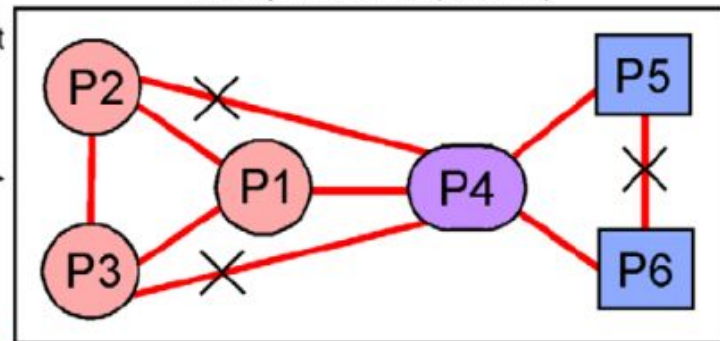
Two different PPI **networks** derived from two types of experimental data (the **X** below indicate interactions that do not occur, i.e. they will be false positives)

e.g.
TAP-MS
CoIP

P1=P2,P3,P4
P2=P1,P3,P4
P3=P1,P2,P4
P4=P1,P2,P3,P5,P6
P5=P4,P6
P6=P4,P5

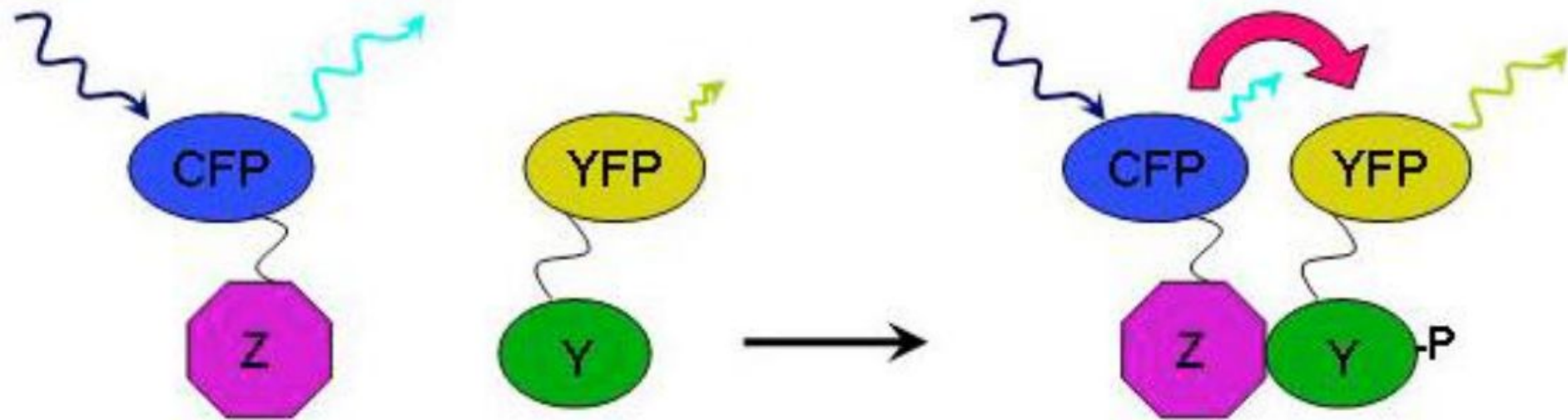
assignment
with
spoke
model

Co-complex methods
measure physical PPIs (direct & indirect)



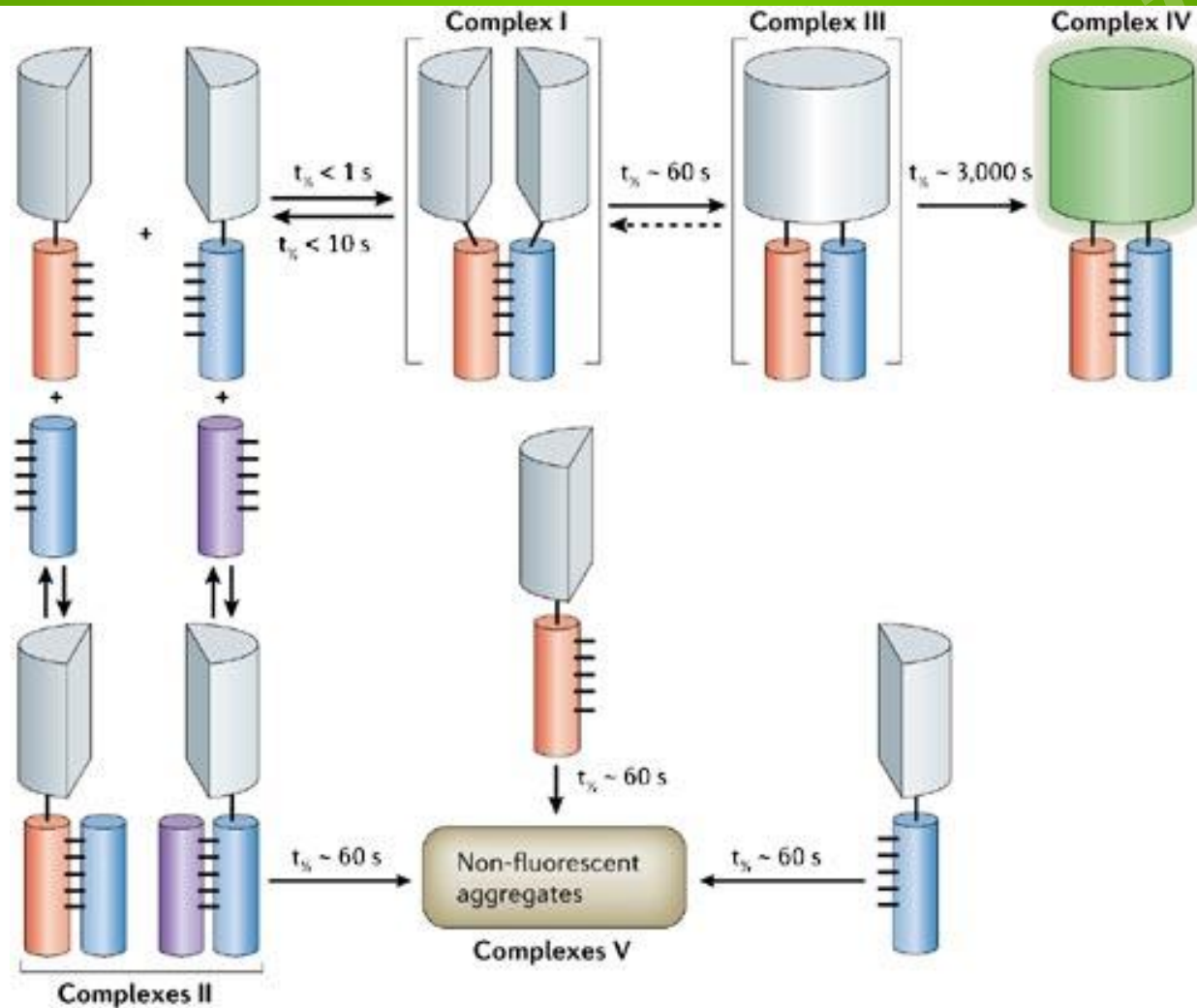
FRET

Fluorescence Resonance Energy Transfer

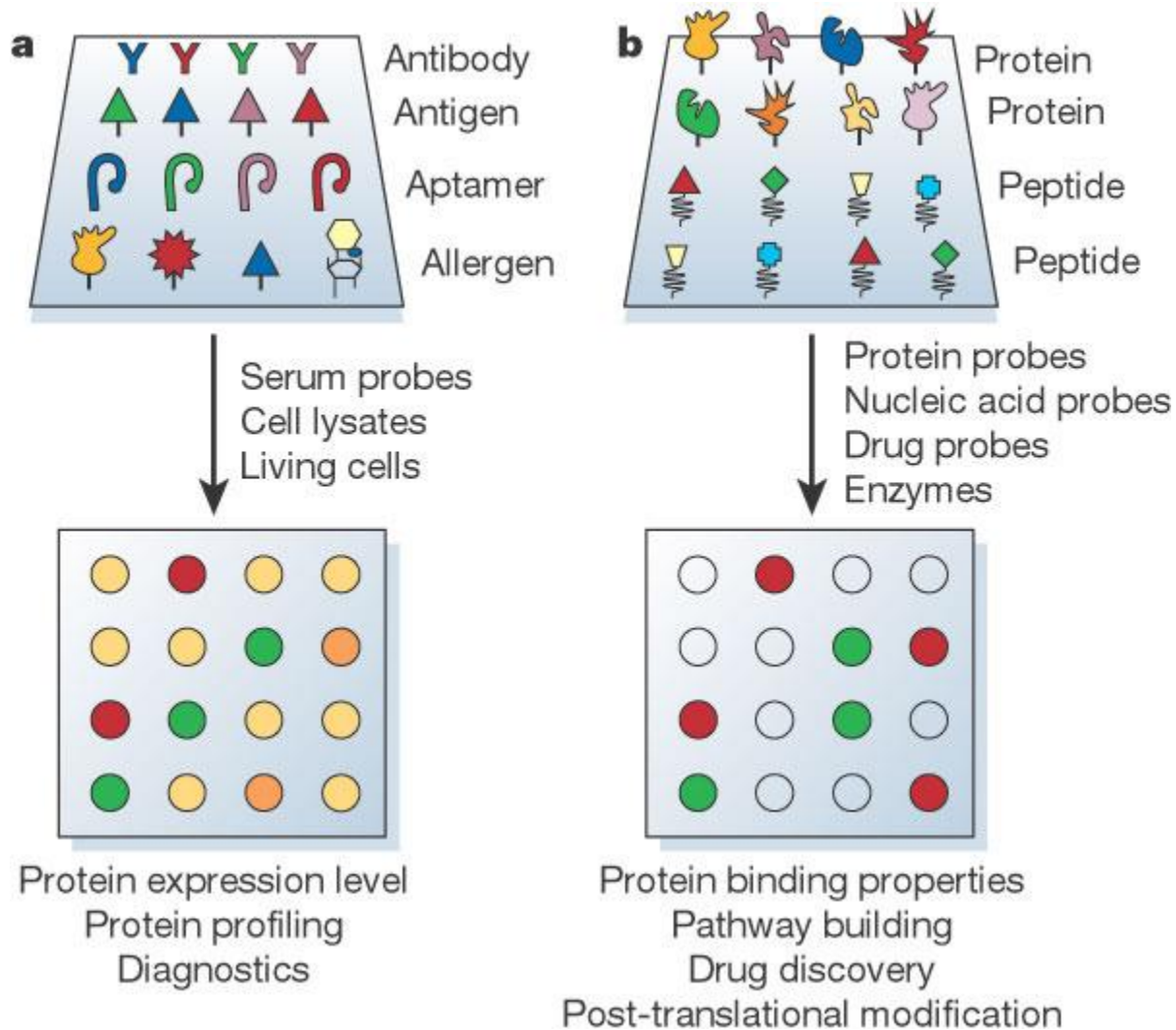


biFC

Bimolecular Fluorescence Complementation



Protein chip



PPI prediction

- Homologous transfer
 - Enzyme binding motif search
 - Based domain-domain interaction
 - 3D docking
-
- Literature mining
 - Co-expression