

Network pharmacology:

The next paradigm in drug discovery



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Web lab: ramirezlab.github.io

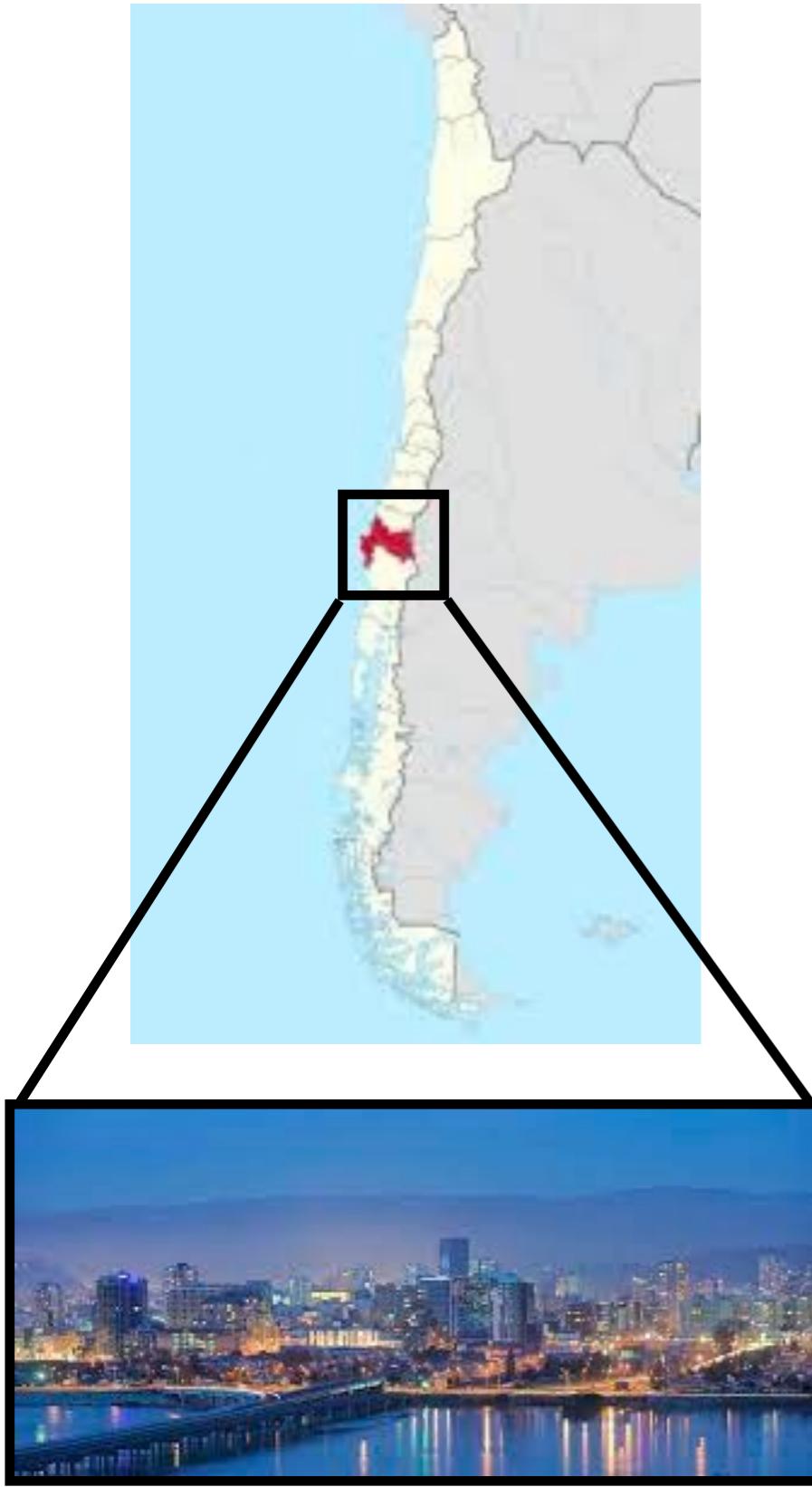


Pharmacoinformatics & Drug Design Lab
Departamento de Farmacología
Facultad de Ciencias Biológicas
Universidad de Concepción



Ramírez Lab

Departamento de Farmacología - Universidad de Concepción



Undergraduate student

2009 -> B.Sc. Chemistry -> Universidad Distrital Francisco Jose de Caldas

2012 -> B.Sc. Pharmaceutical Chemistry -> Universidad Nacional de Colombia

Graduate student

2016 -> Ph.D in Applied Sciences (*Biophysics*) -> Universidad de Talca

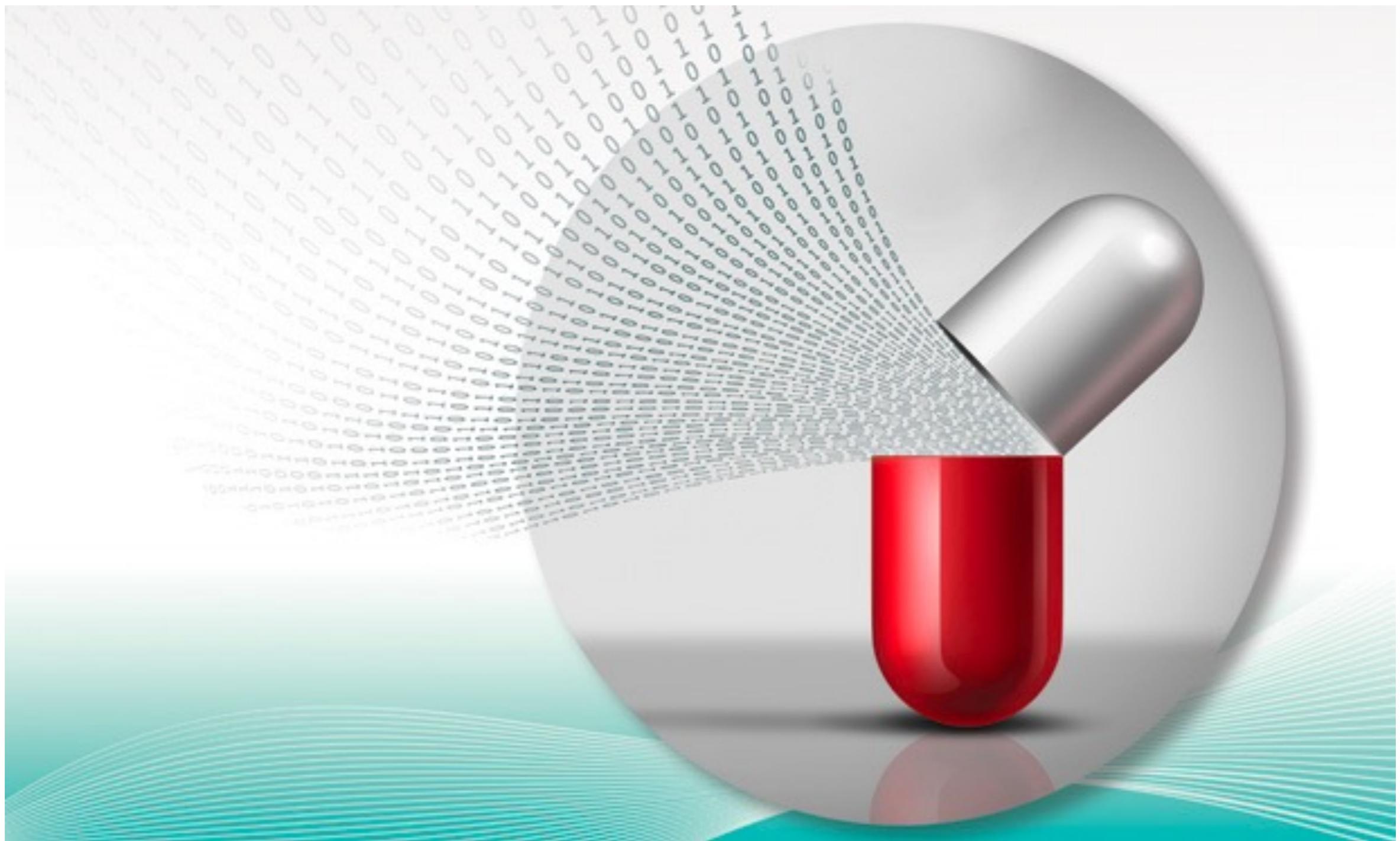
Postdoctoral fellow

2017 -> Drug Design -> Universidad de Talca

2018 -> Cu Homeostasis in Bacteria -> Worcester Polytechnic Institute (MA - USA)

Research lines -> Ramirez Lab

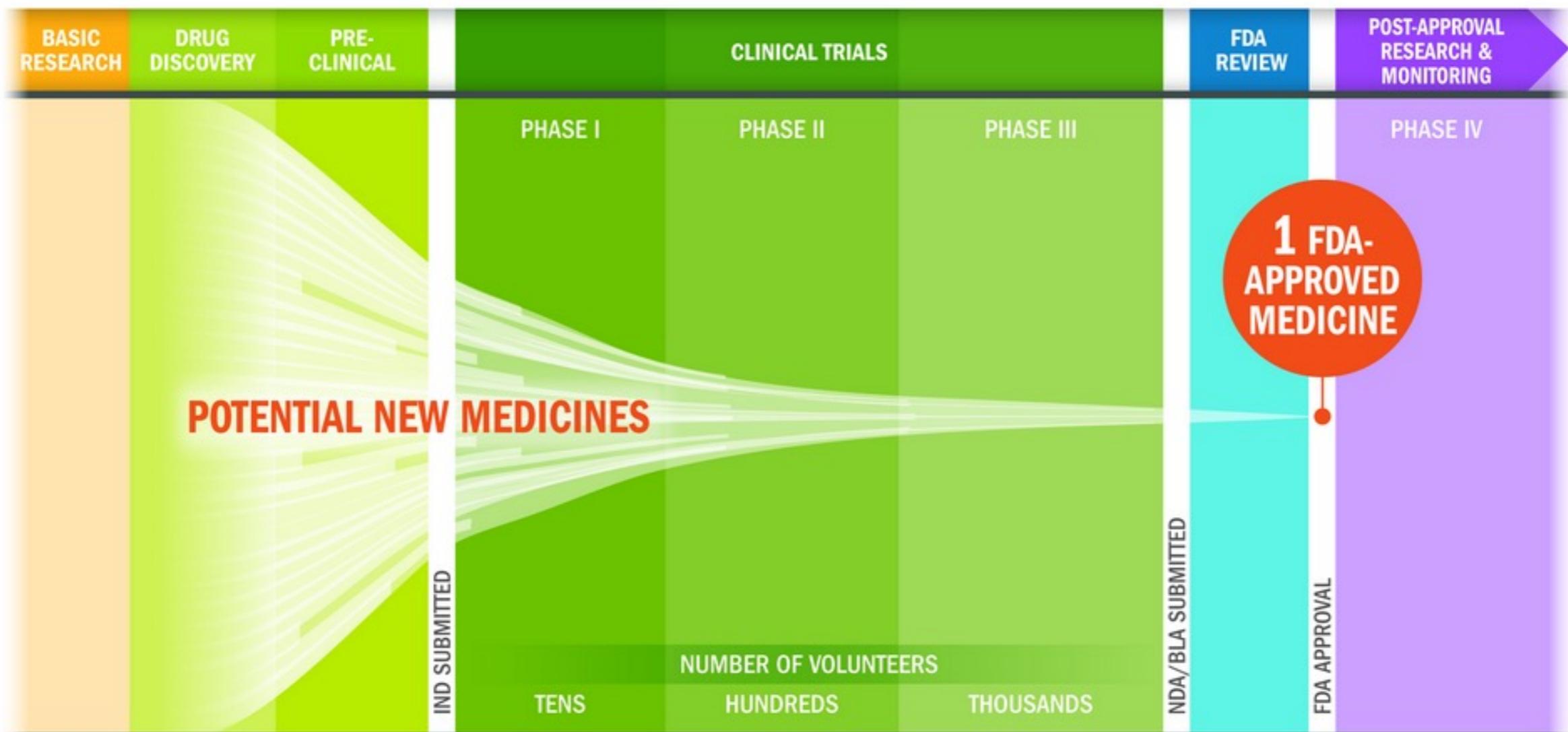
Pharmacology - Pharmacoinformatics - Drug Design



Keshava, Nirmal. "Opportunities for Data Science in the Pharmaceutical Industry" *IEEE pulse* 8.3 (2017): 10-14.

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

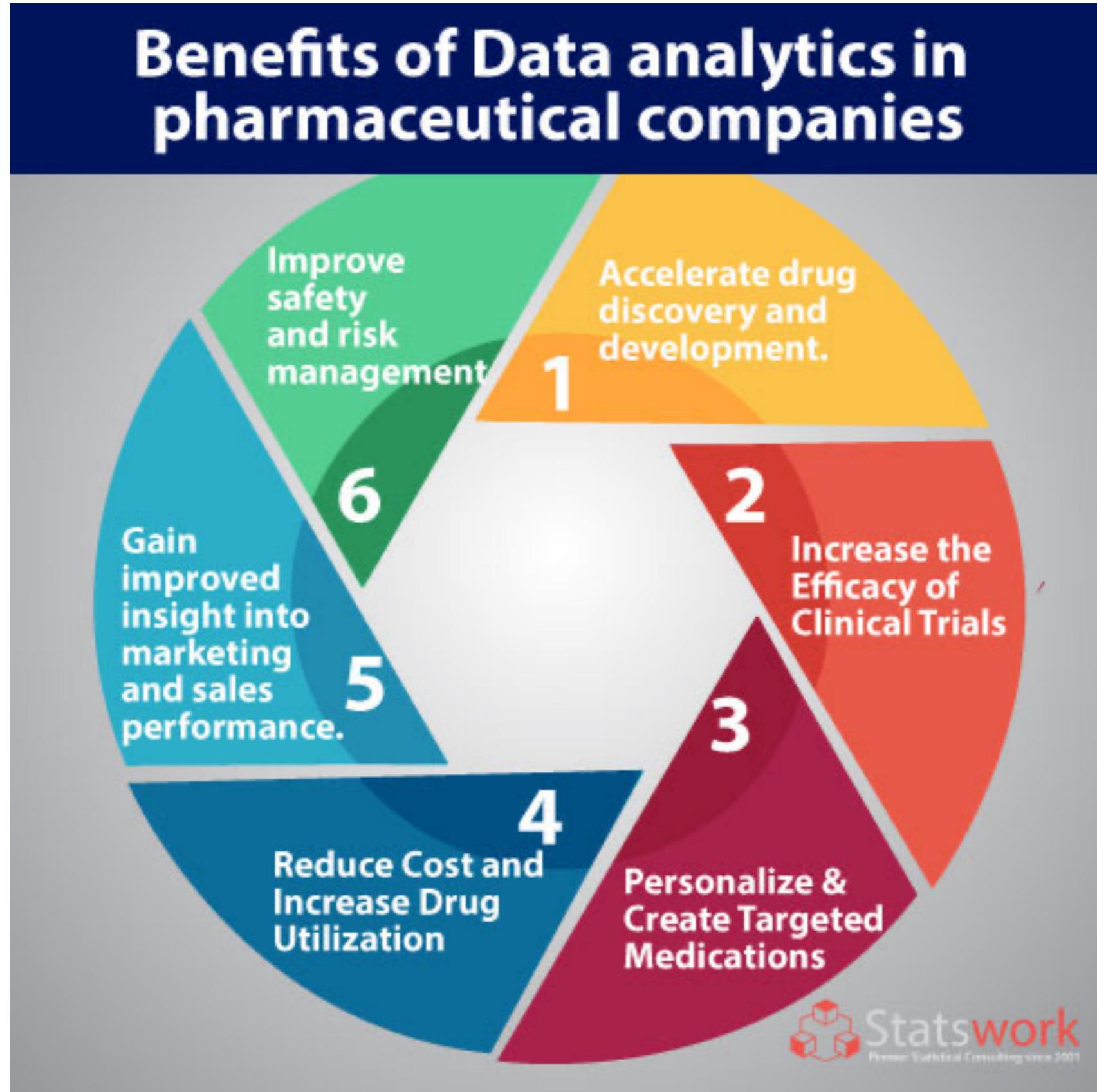
From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of \$2.6 billion.* Less than 12% of the candidate medicines that make it into Phase I clinical trials will be approved by the FDA.

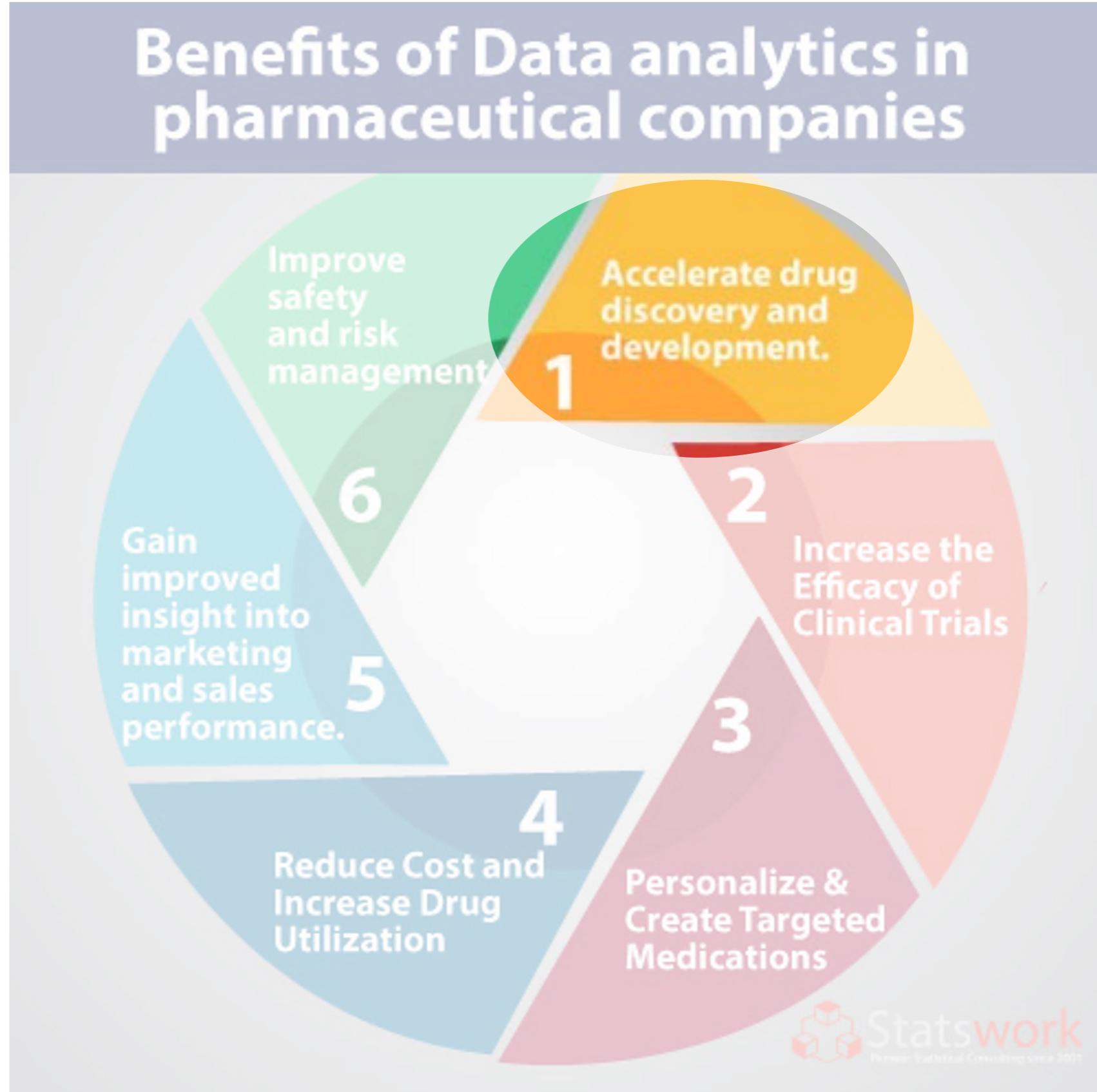


Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

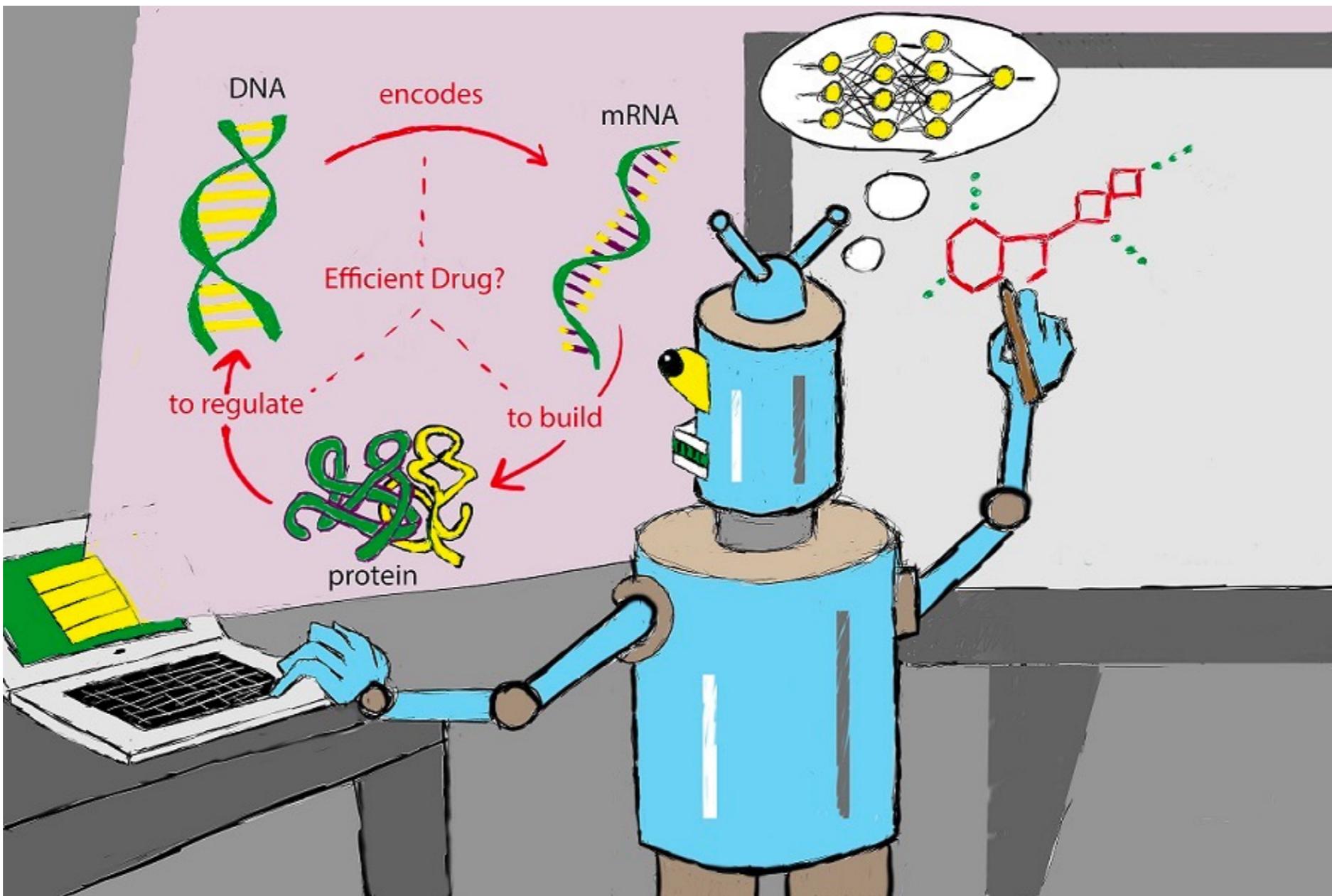
* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be \$2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," <http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf> (accessed Jan. 20, 2015).



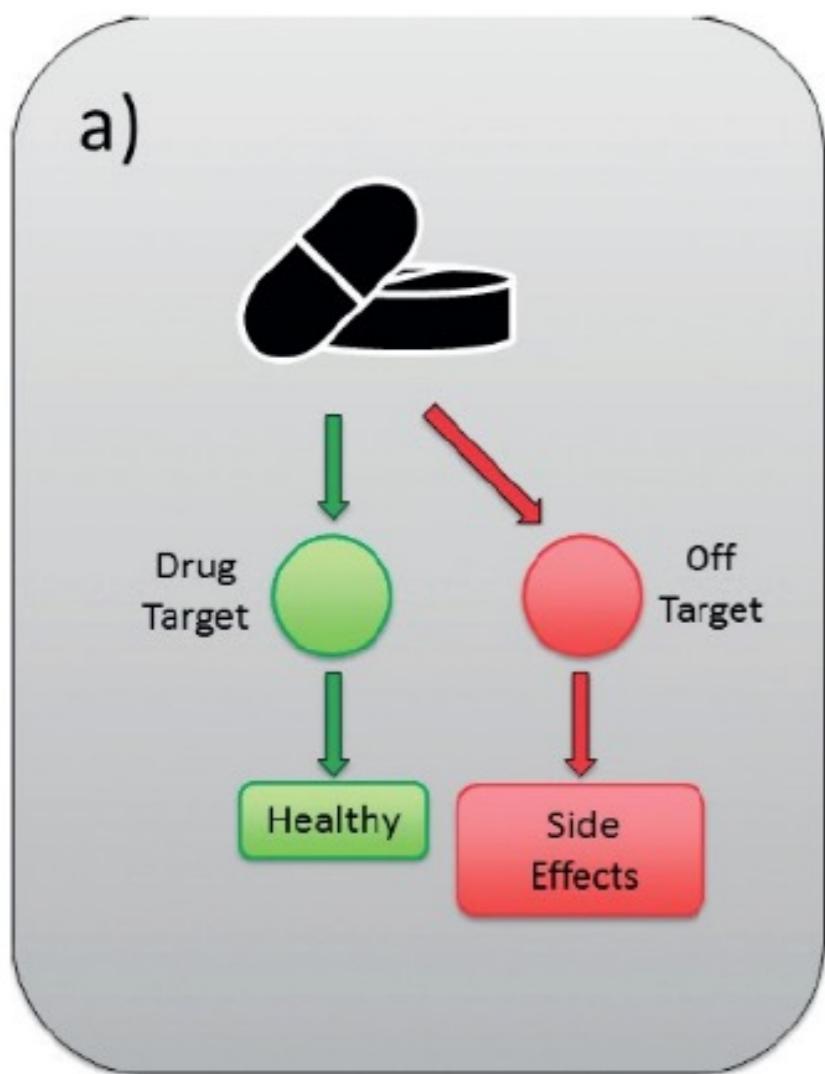


Data science & drug design

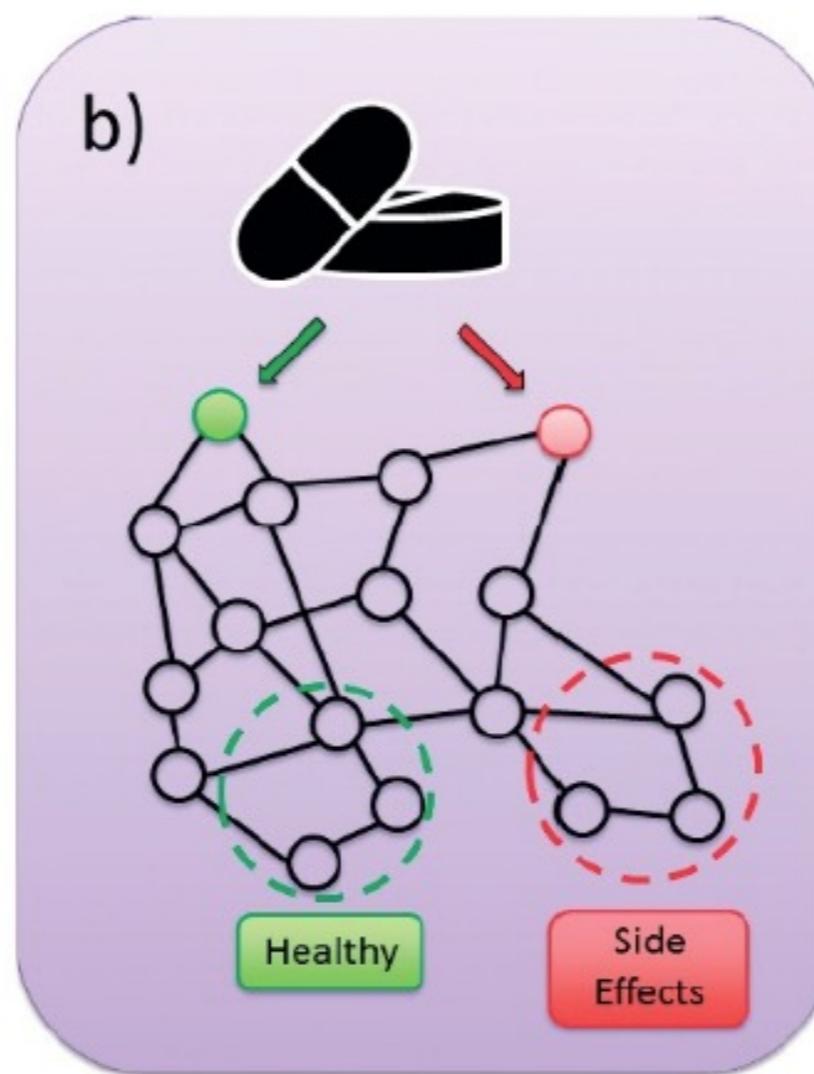


System Pharmacology

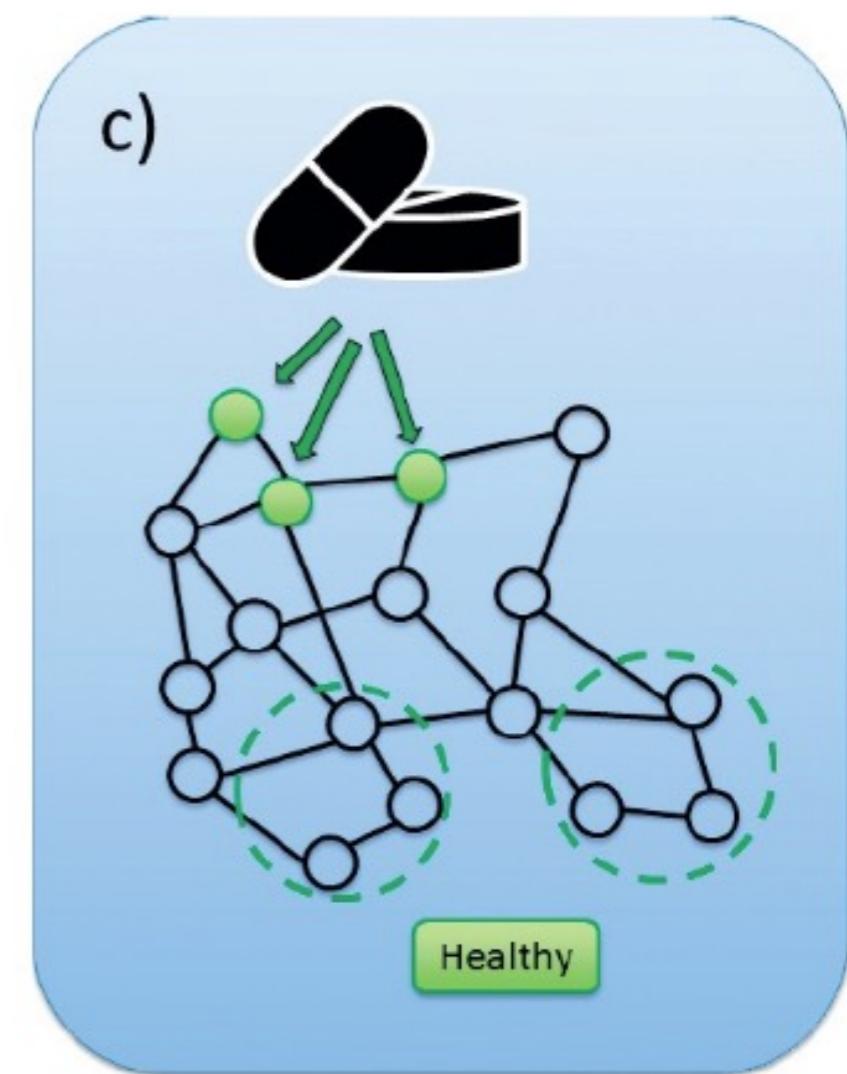
Classic
one drug - one target



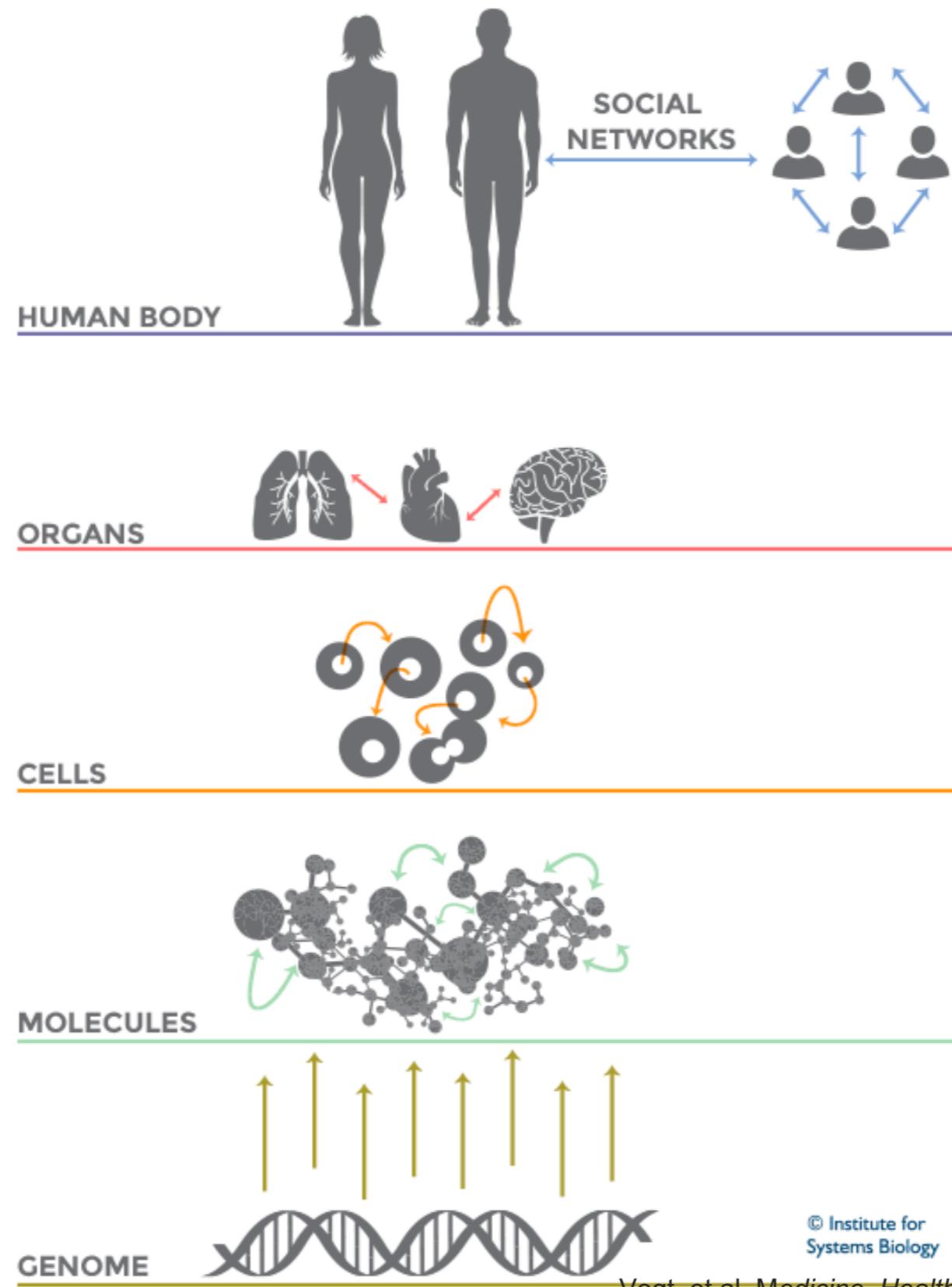
System
Biology



System
Pharmacology

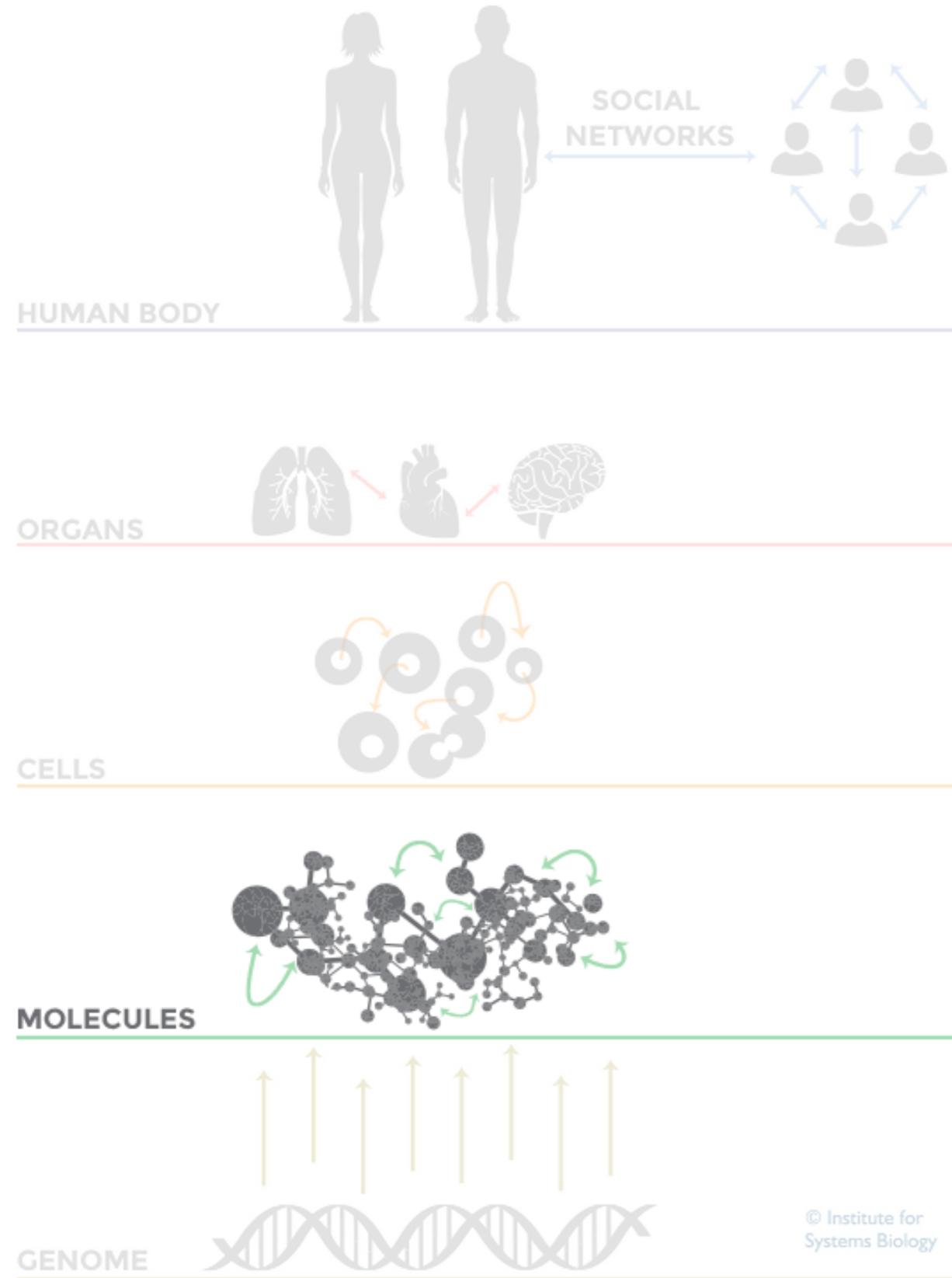


System Pharmacology

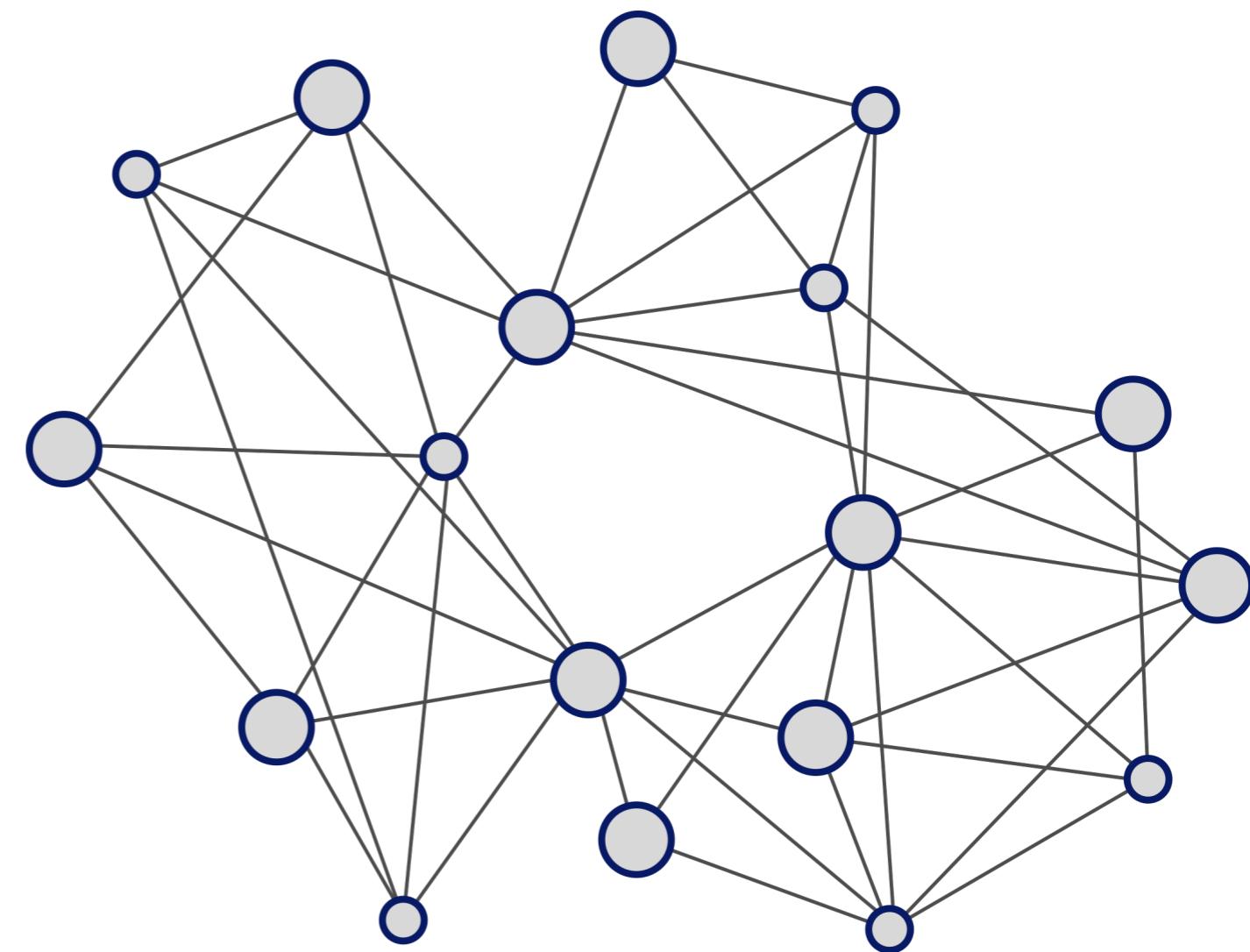


© Institute for
Systems Biology

System Pharmacology - graph theory

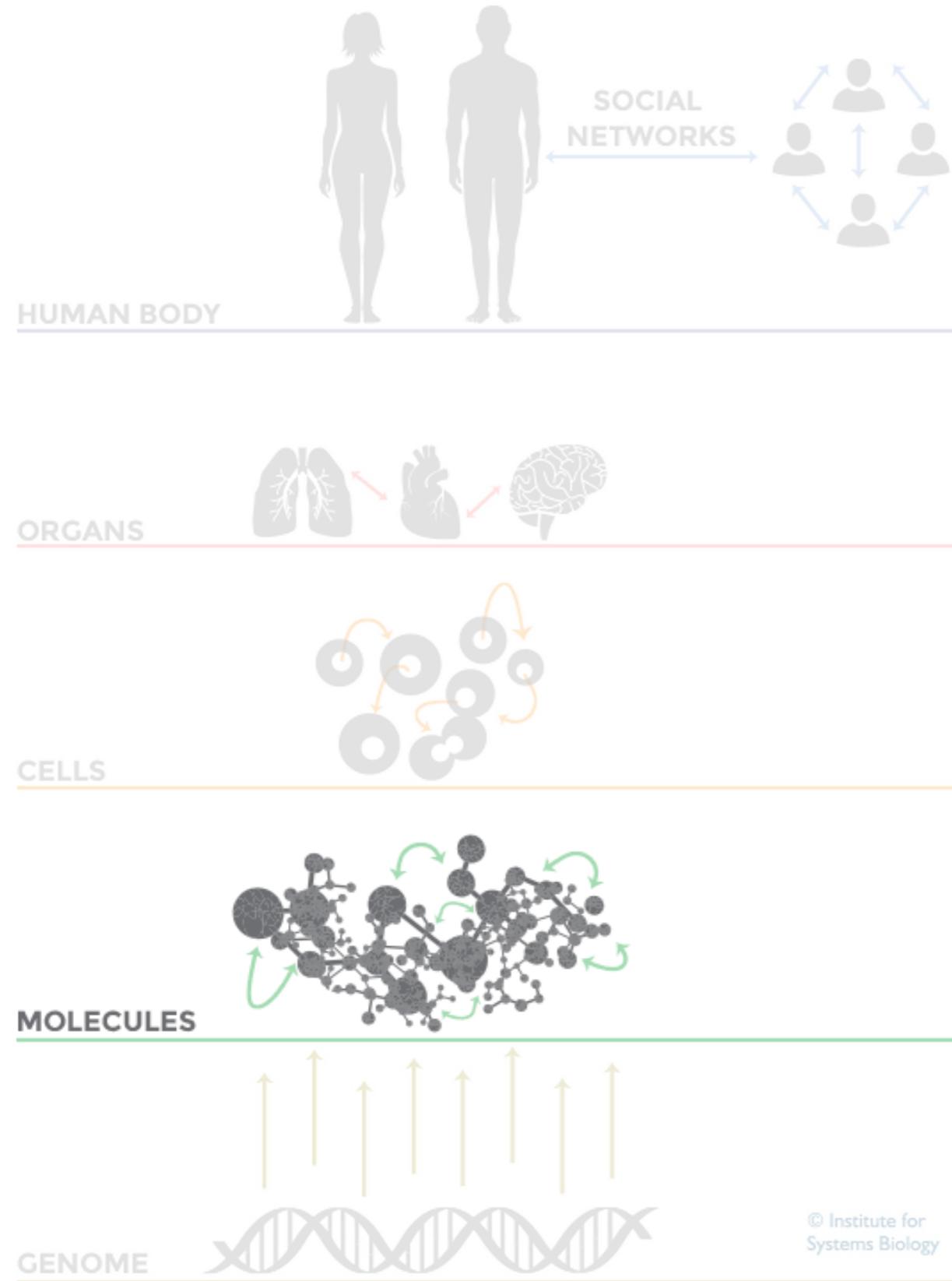


○ Functional nodes

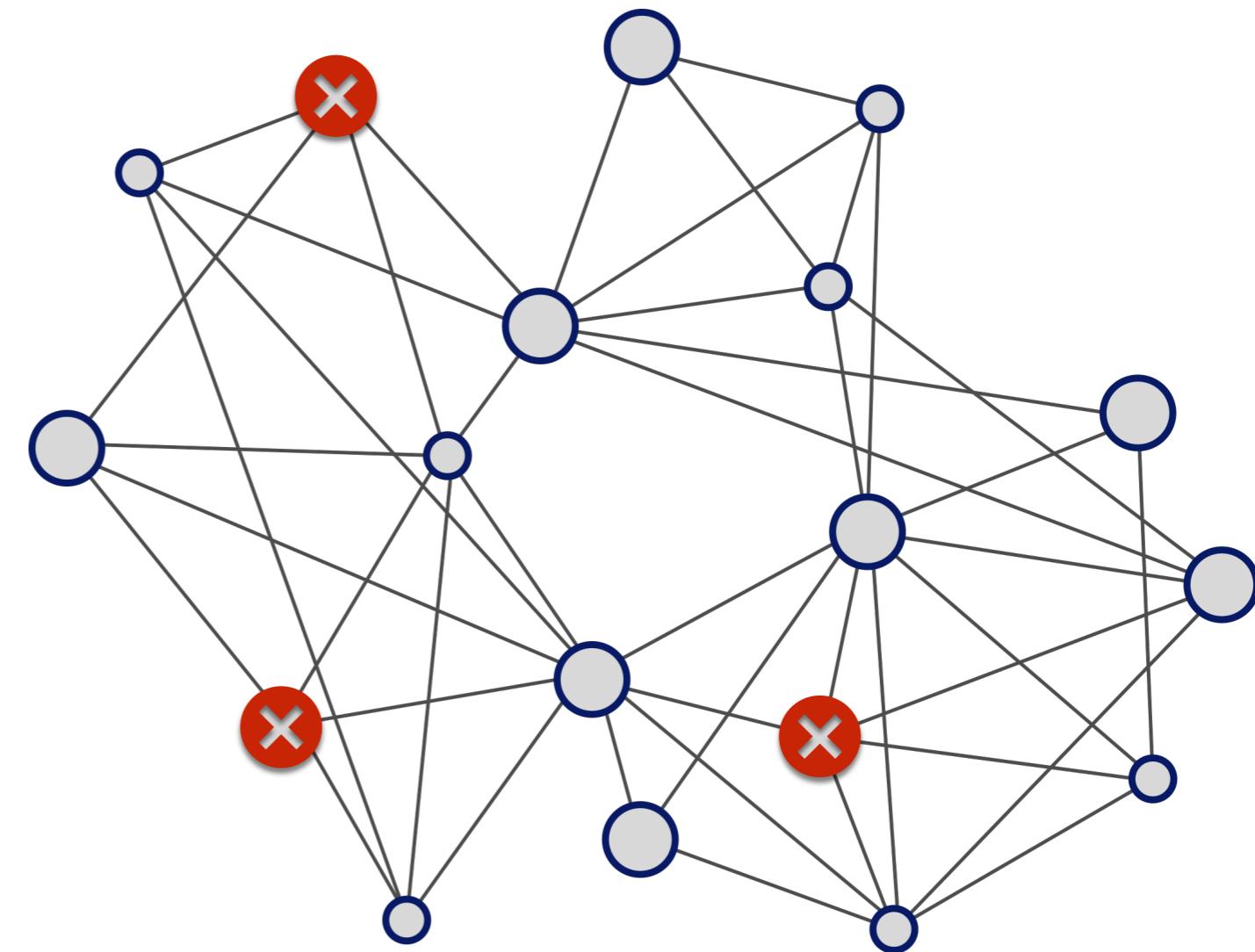


Healthy person

System Pharmacology - graph theory

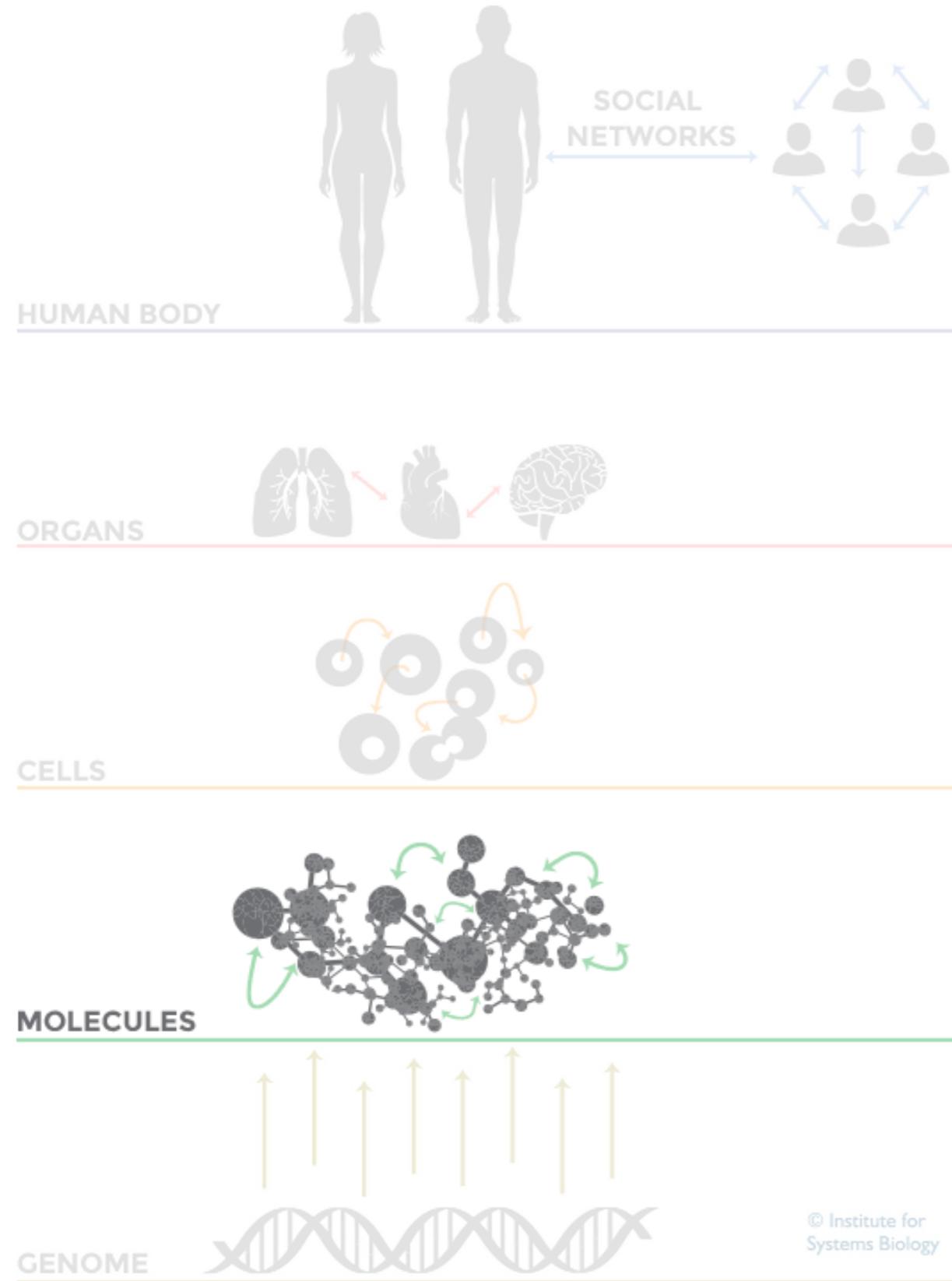


○ Functional nodes

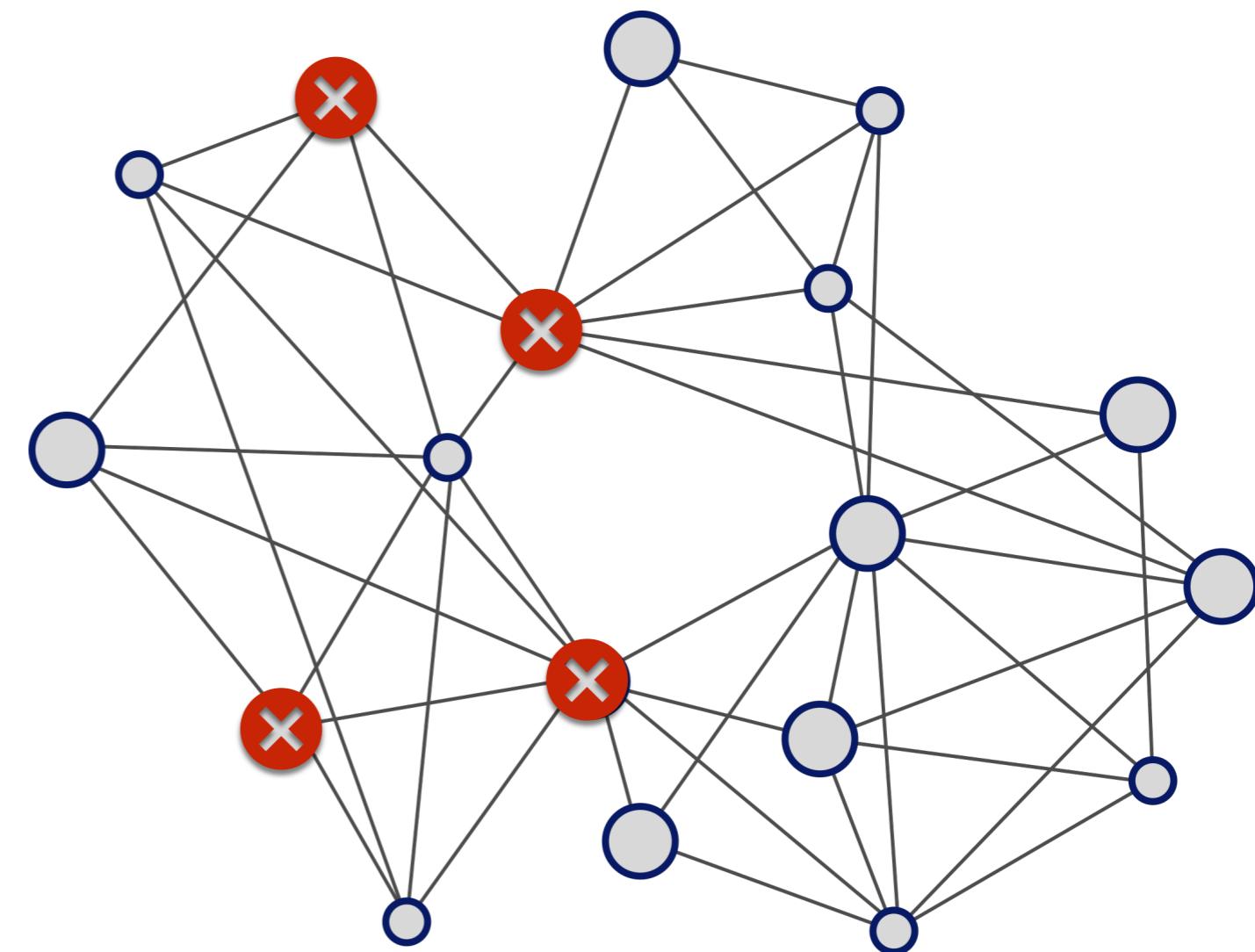


Person with symptoms

System Pharmacology - graph theory

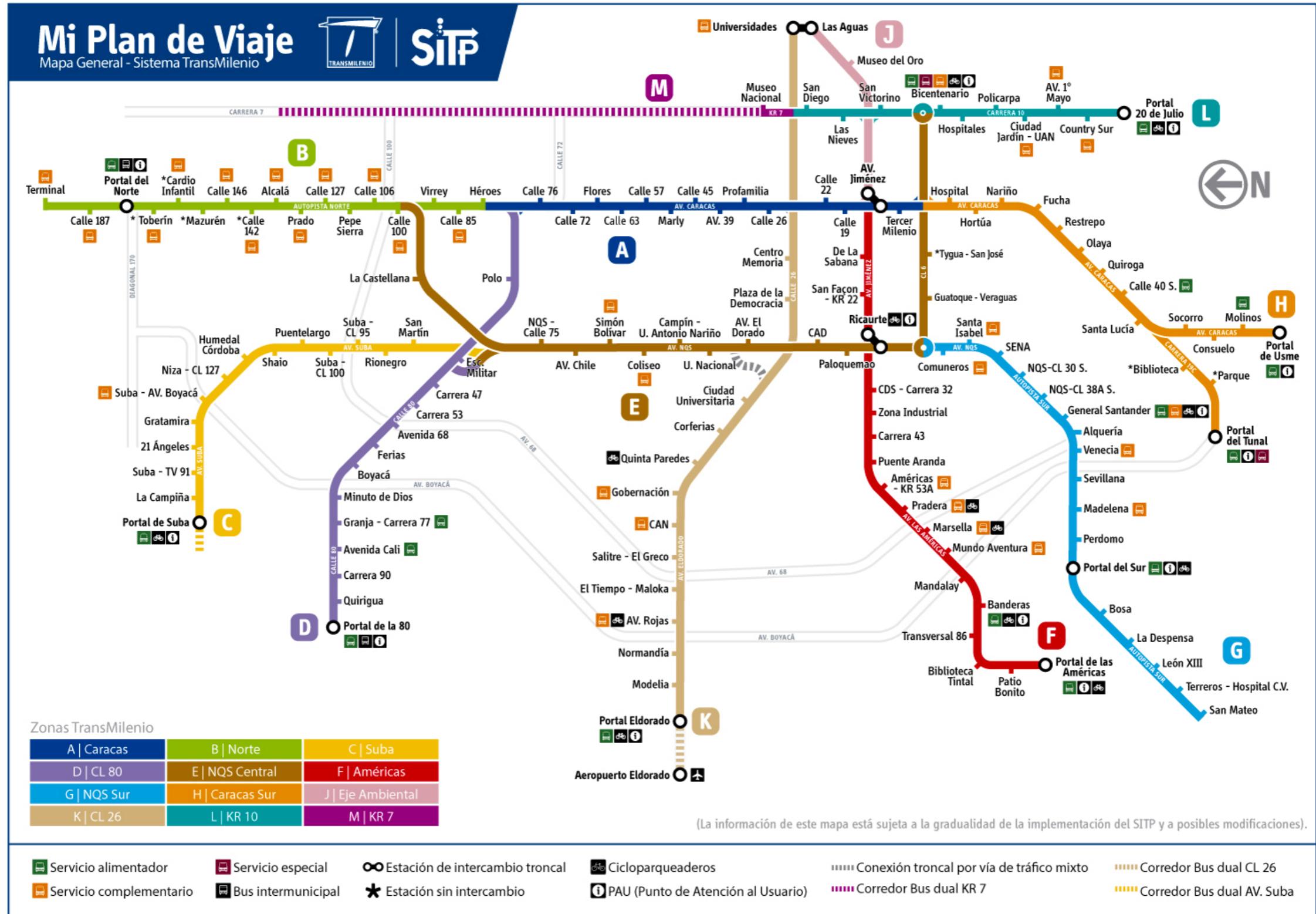


○ Functional nodes



Person sick

System Pharmacology - graph theory



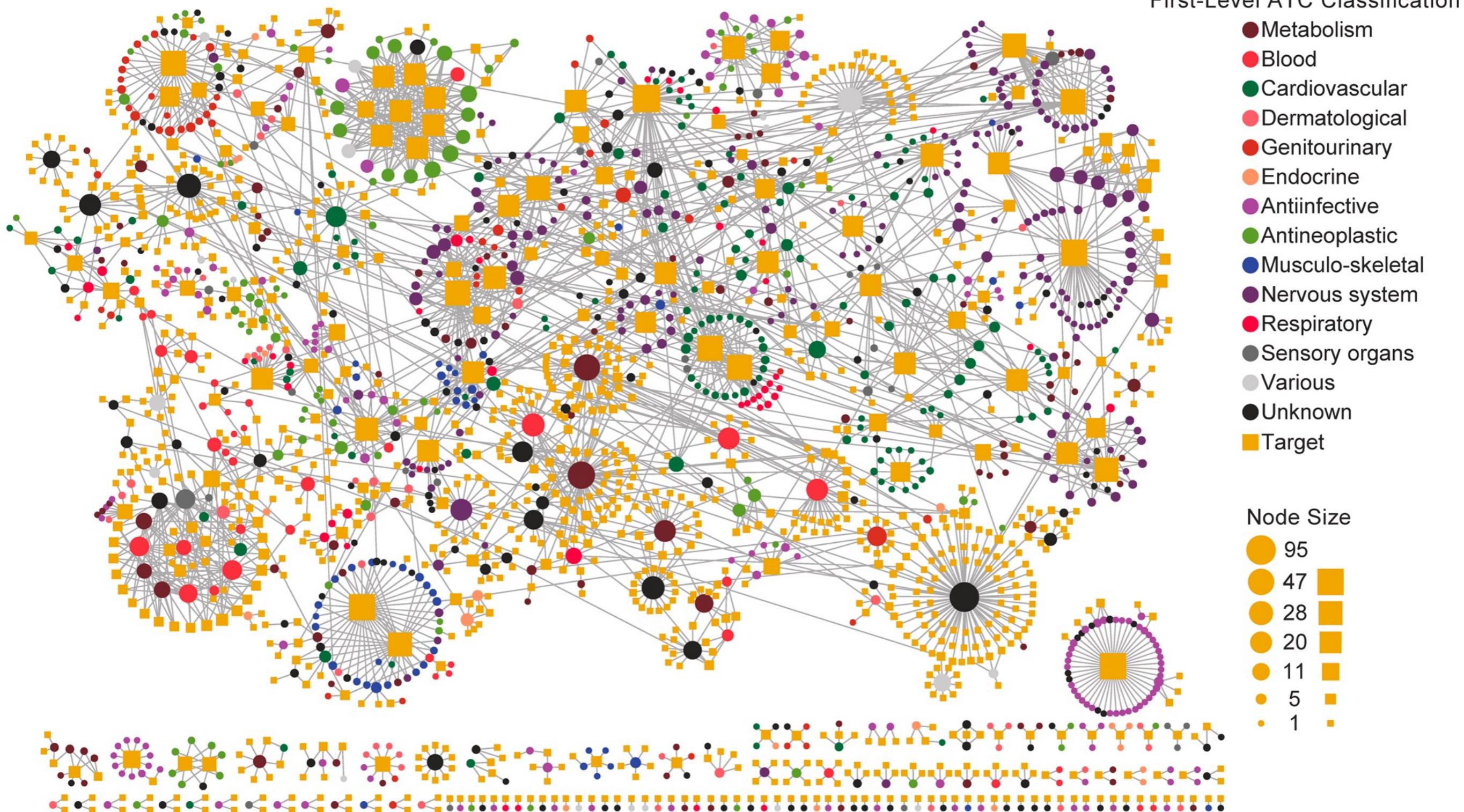
System Pharmacology - graph theory



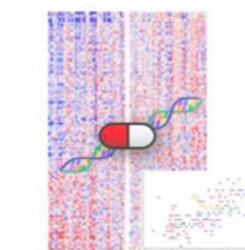
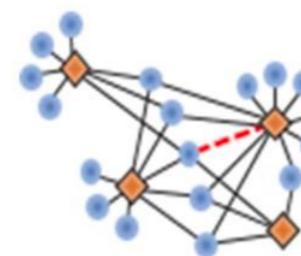




KNIME TV on **YouTube** https://www.youtube.com/watch?v=mGv0Nle_NrQ

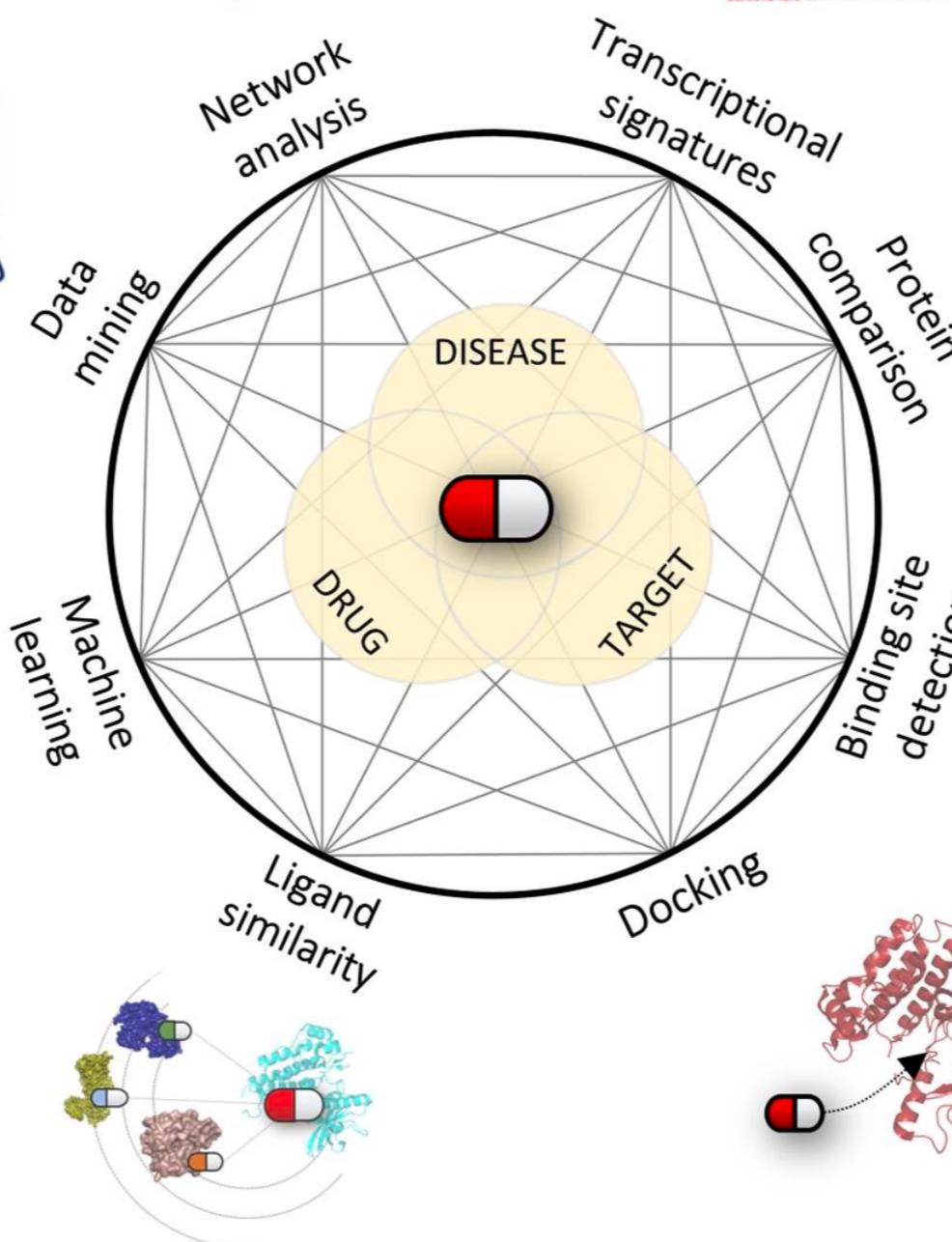


- Relational network-based analysis of biological systems
- Analysis of the patterns and prediction of the missing links



- Analysis of molecular transcriptional signatures
- Comparison of drugs mechanism of action

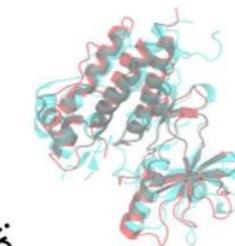
- Data extrapolation
- Data analysis and visualization



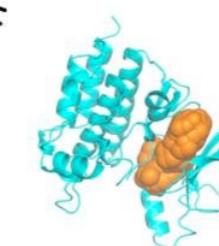
- Statistical pattern recognition
- Model development for biological system analysis



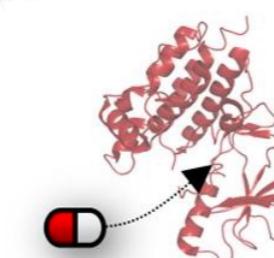
- Ligand similarity assessment
- Prediction of ligand cross-reactivity



- Target similarity assessment
- Prediction of ligand cross-reactivity



- Detection of putative binding pockets
- Ligandability assessment



- Prediction of ligand-protein molecular interactions
- Drug-based repurposing
- Reverse docking for target-based repurposing

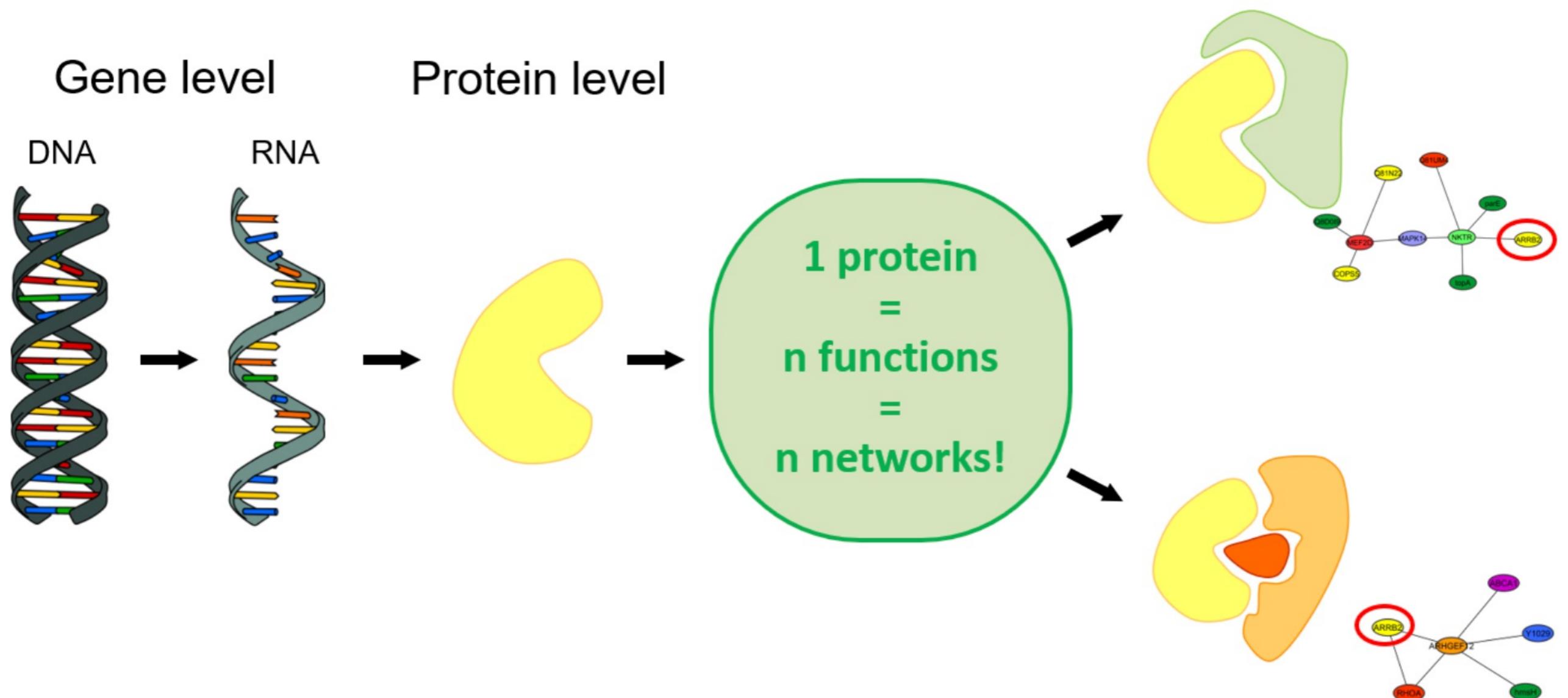
Protein-Protein interactions (PPI) and their importance

Molecular interaction data can be generated using many different techniques, all of which have their strengths and weaknesses. However, it is important to stress that **all molecular interaction data is to some degree artificial**. No single method can accurately reproduce a true binary interaction observed under physiological conditions.

Molecular interactions are important to molecular biologists because:

1. They help us to understand a protein's function and behaviour.
2. They can help us to predict the biological processes that a protein of unknown function is involved in:
 - We may assume “Guilt by association” if a protein of unknown function associates with one of known function
 - Proteins involved in the same process should cluster together in network maps
3. They can help us to characterise protein complexes and pathways; interaction networks can be used as a draft ‘map’ to add detail to biological processes and pathways and can help discover new pathways, complexes and functional modules within the cell.

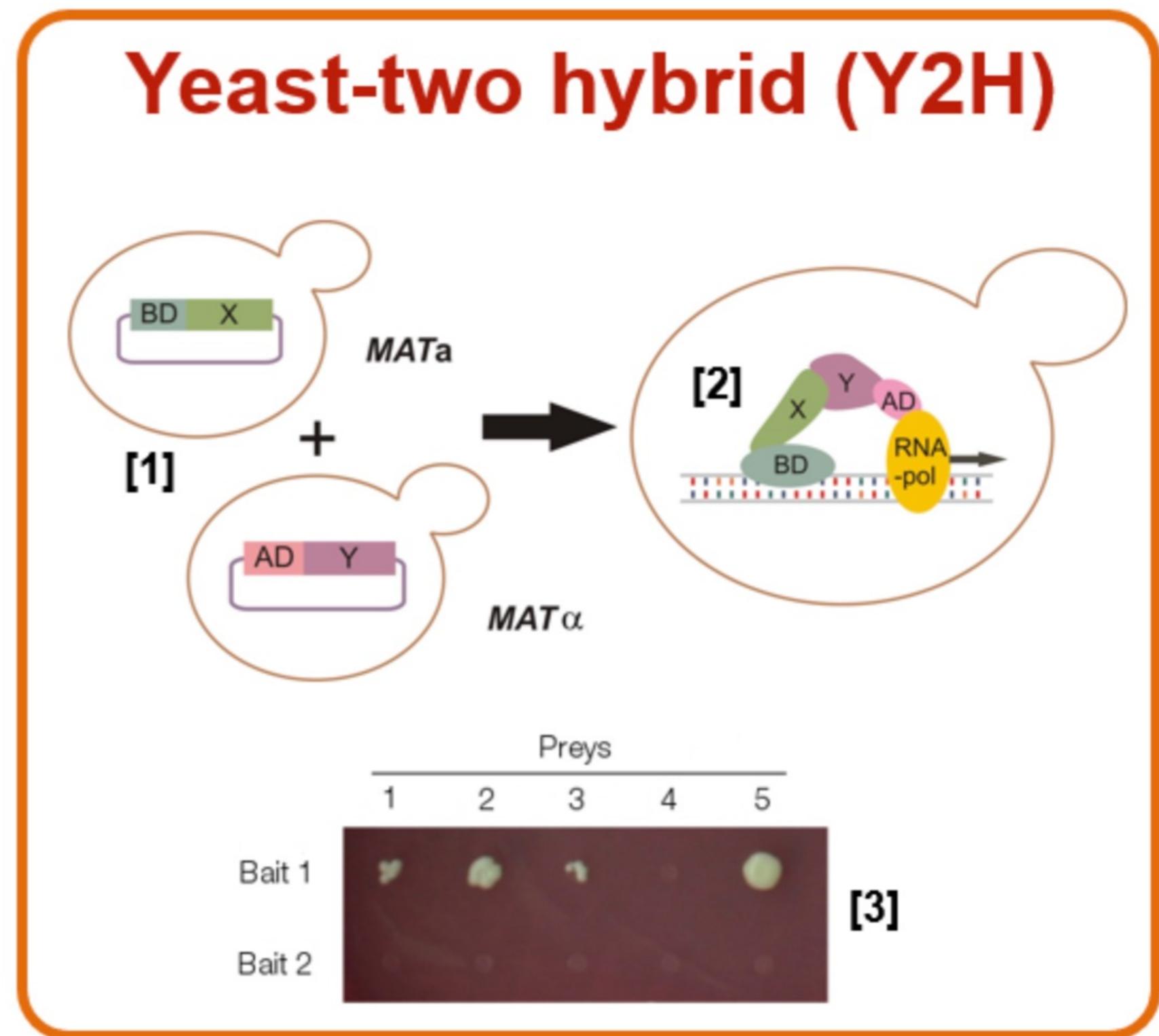
PPI - and their importance



PPI - Where the data come from?

High-throughput: yeast two-hybrid

[1] The Binding (BD) domain fused to the bait protein (X) and the Active (AD) domain fused to prey protein (Y) are expressed in yeast cells. [2] If proteins X and Y interact, BD binds DNA and AD activates RNA polymerase. An example readout [3] of a Y2H assay with two bait proteins (Bait 1 and Bait 2) and five prey proteins (1 to 5)



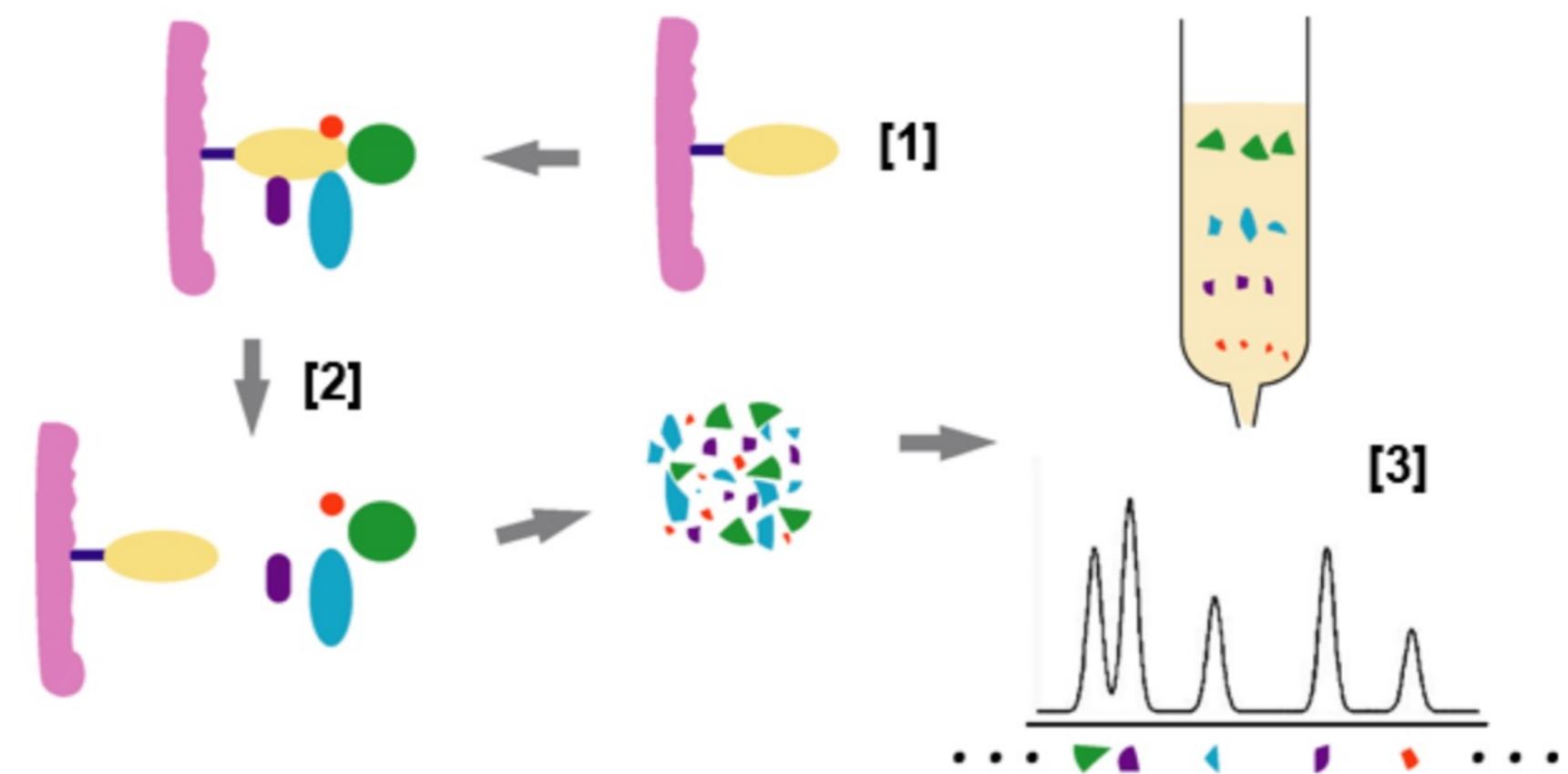
PPI - Where the data come from?

High-throughput:

Affinity purification mass spectrometry

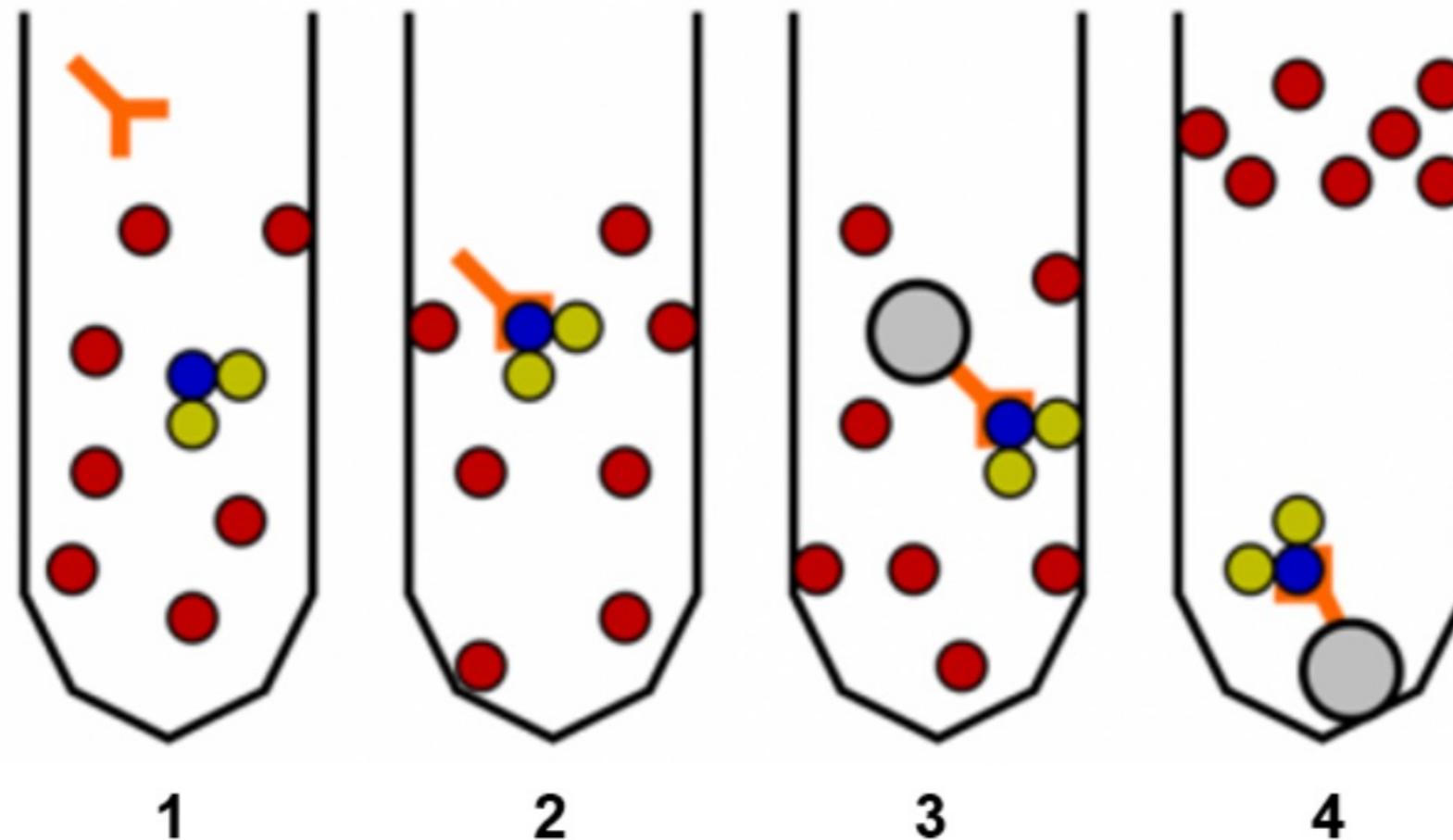
The bait protein (yellow) is immobilised on a matrix [1]. A protein mixture is passed through and only the interacting partners (prey) are retained [2]. In the following step the prey proteins are removed, digested with a protease and the resulting peptides are analysed by MS [3].

Affinity purification+ mass spectrometry (AP-MS)



PPI - Where the data come from?

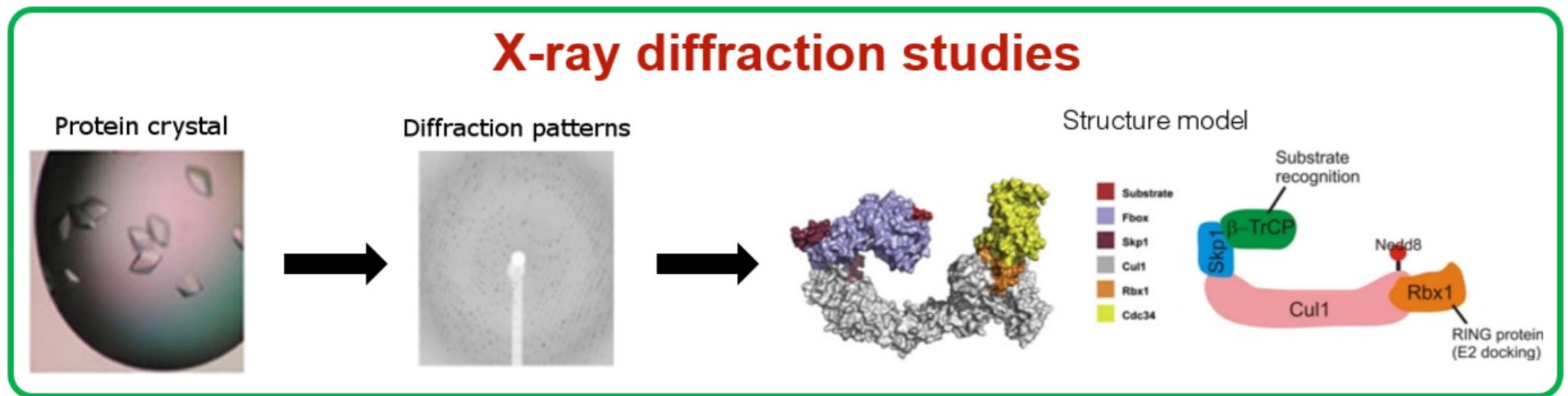
Co-immunoprecipitation



Protein complex immunoprecipitation (Co-IP) method. [1] Addition of antibody to protein extract. [2] Target proteins are immunoprecipitated with the antibody. [3] Coupling of antibody to beads. [4] Isolation of protein complexes.

PPI - Where the data come from?

X-ray crystallography

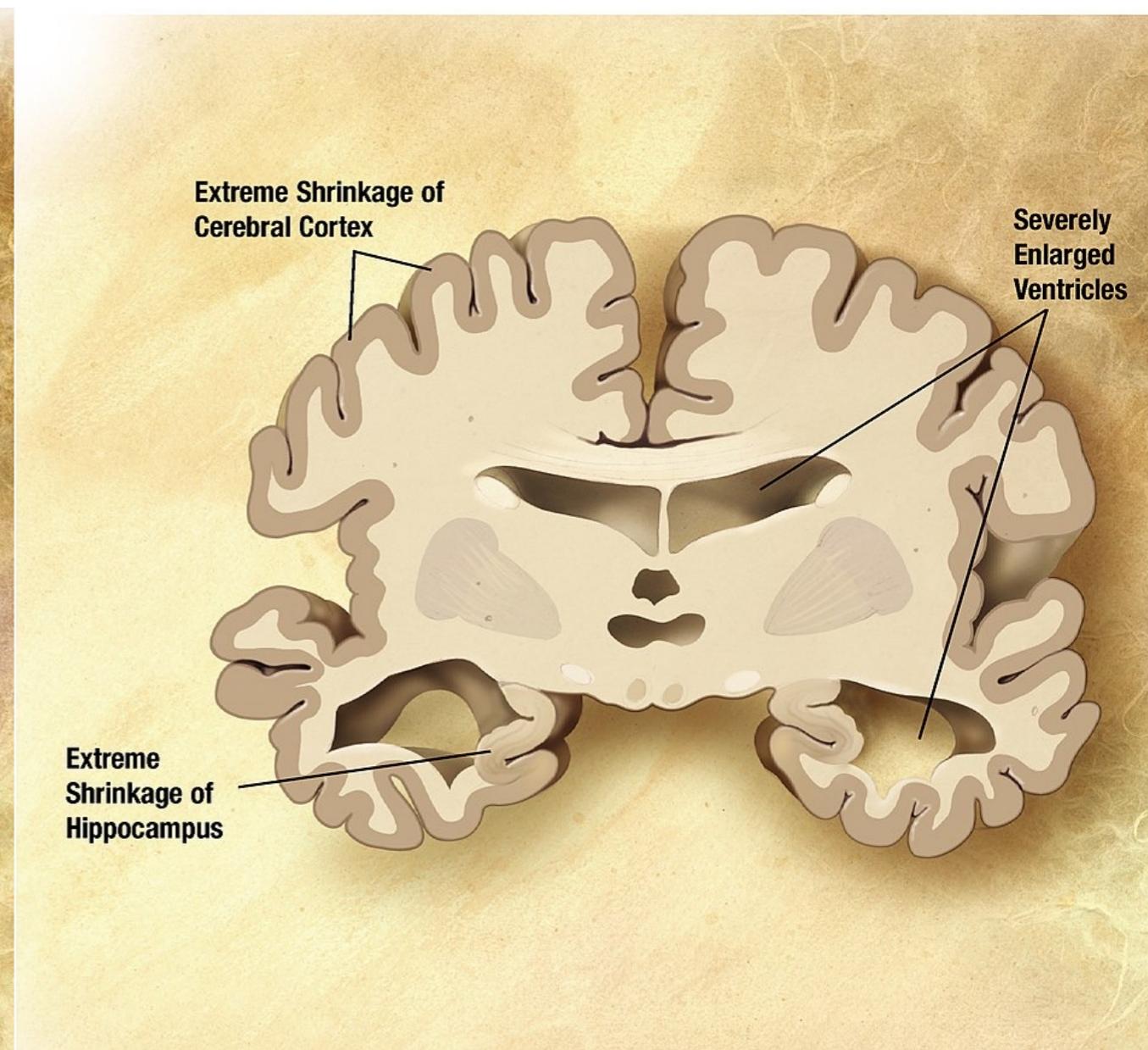
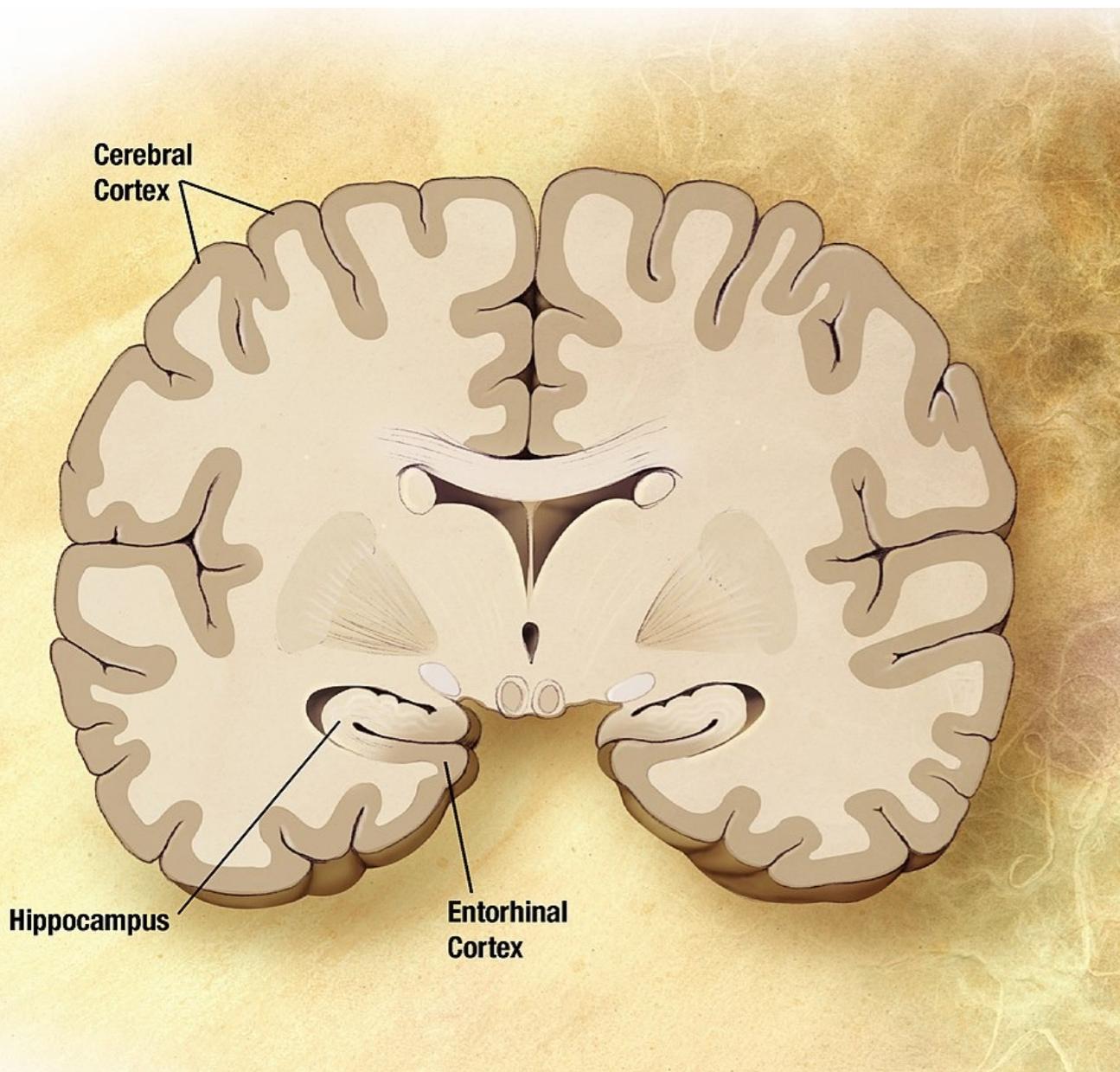


X-ray crystallography is used to obtain detailed structural and chemical insights for selected interactions. The figure shows a model of the cullin complex

Multi-target drug design against neurodegenerative diseases

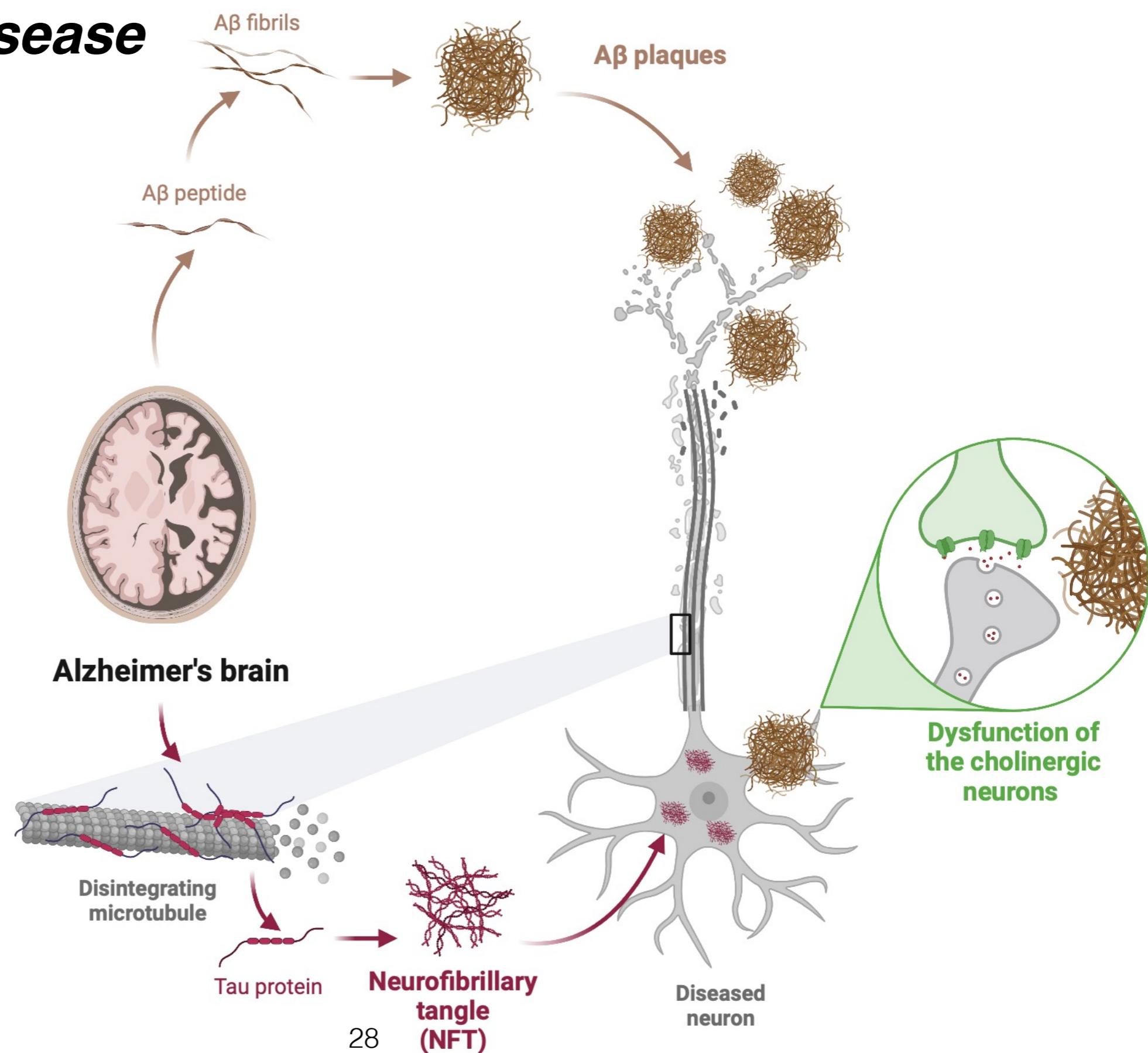
Alzheimer's disease

Multi-target drug design against neurodegenerative diseases



Alzheimer's disease

Alzheimer's disease



Hunting Alzheimer's disease targets



Literature

NIH National Library of Medicine
National Center for Biotechnology Information

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PubMed.gov

alzheimer + targets X **Search**

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Save Email Send to Sorted by: Best match Display options

MY NCBI FILTERS 25,637 results 25,637 results << < Page 1 of 2,564 > >>

RESULTS BY YEAR 1981 2022

Current and emerging avenues for Alzheimer's disease drug targets.
1 Loera-Valencia R, Cedazo-Minguez A, Kenigsberg PA, Page G, Duarte AI, Giusti P, Zusso M, Robert P, Frisoni GB, Cattaneo A, Zille M, Boltze J, Cartier N, Buee L, Johansson G, Winblad B.
Cite J Intern Med. 2019 Oct;286(4):398-437. doi: 10.1111/joim.12959. Epub 2019 Aug 29.
Share PMID: 31286586 **Free article.** Review.
Alzheimer's disease (AD), the most frequent cause of dementia, is escalating as a global epidemic, and so far, there is neither cure nor treatment to alter its progression. ...Our hope is to promote the continuing research of diverse **targets** affecting ...

TEXT AVAILABILITY

Hunting Alzheimer's disease targets



<https://www.ncbi.nlm.nih.gov/>



<https://www.rcsb.org/>



Open Targets

<https://www.targetvalidation.org/>



<https://www.ebi.ac.uk/>



<https://www.ebi.ac.uk/chembl/>



<https://go.drugbank.com/>



<https://pubchem.ncbi.nlm.nih.gov/>

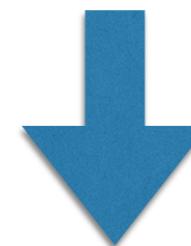


<http://db.idrblab.net/ttd/>



<https://www.uniprot.org/>

Hunting Alzheimer's disease targets



Alzheimer's disease

EFO: [EFO_0000249](#) | ICD10: [G30.9, G30](#) | OMIM: [608907, 502500, 615590](#) | UMLS: [C0002395](#) | MeSH: [D000544](#) | NCIt: [C2866, C34524, C38778](#) | MedDRA: [10001896](#) | MONDO: [0004975](#)

Associated targets Profile

7103 targets associated with Alzheimer's disease

Filter by

Evidence-specific filters

Data Types

Target-specific filters

Pathway Types

Target Classes

Tractability Antibody

Tractability Other Modalities

Tractability PROTAC

Tractability Small Molecule

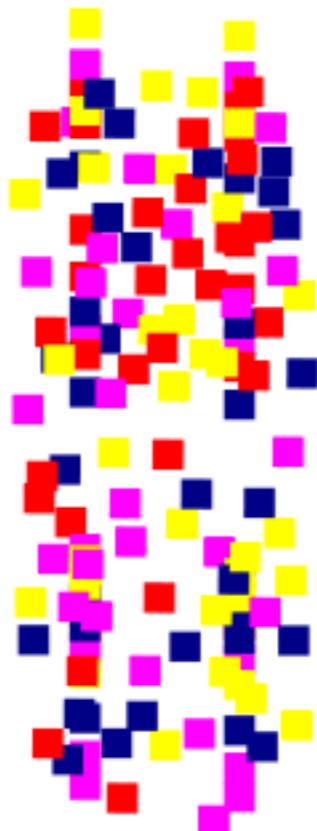
Search

Download table as [JSON](#) [TSV](#)

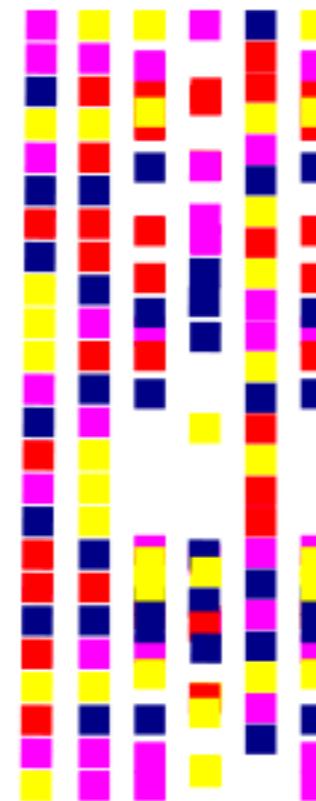


Hunting Alzheimer's disease targets

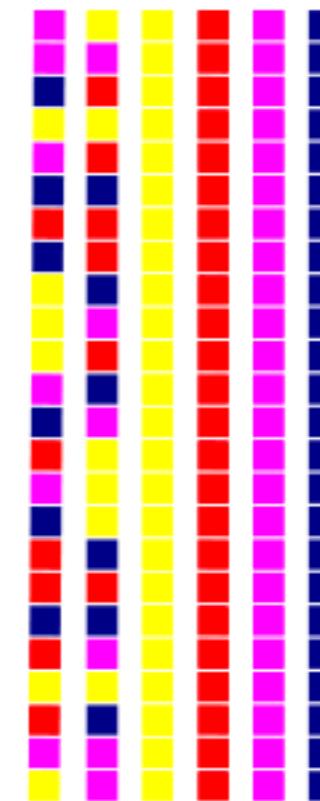
BIG DATA



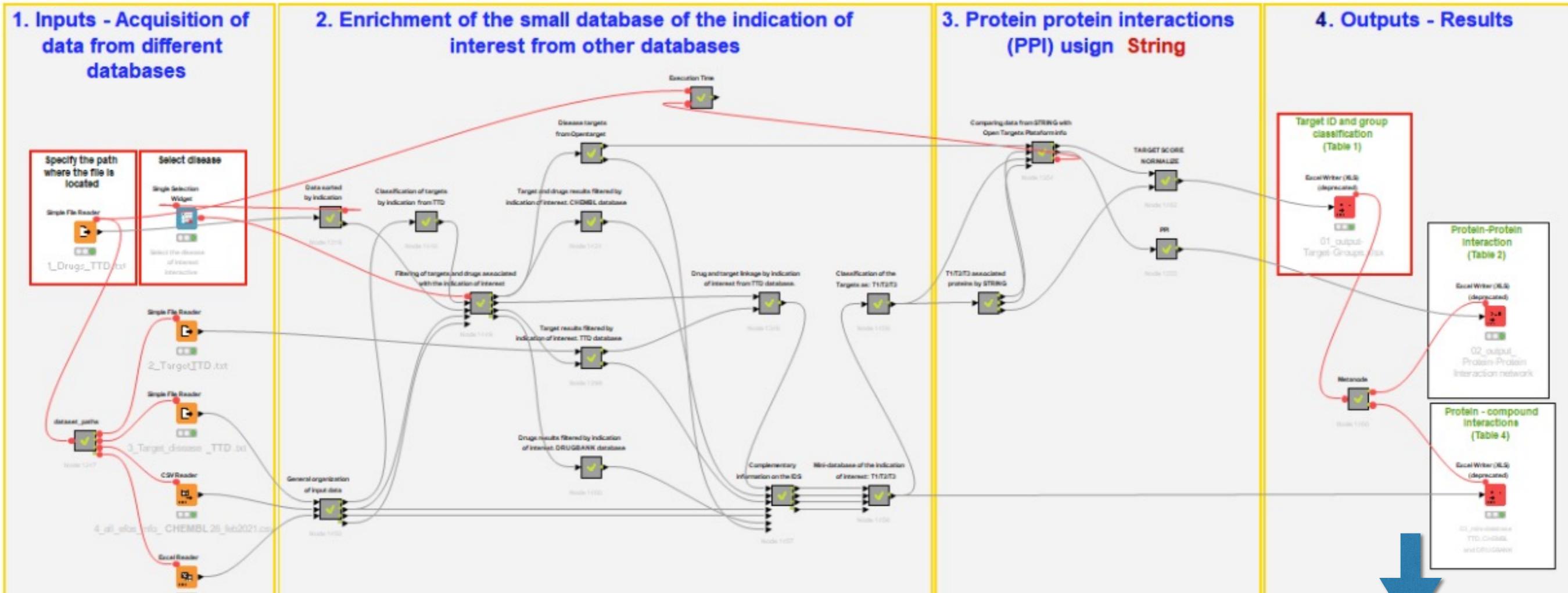
ANALYTICS



DECISIONS



Hunting Alzheimer's disease targets



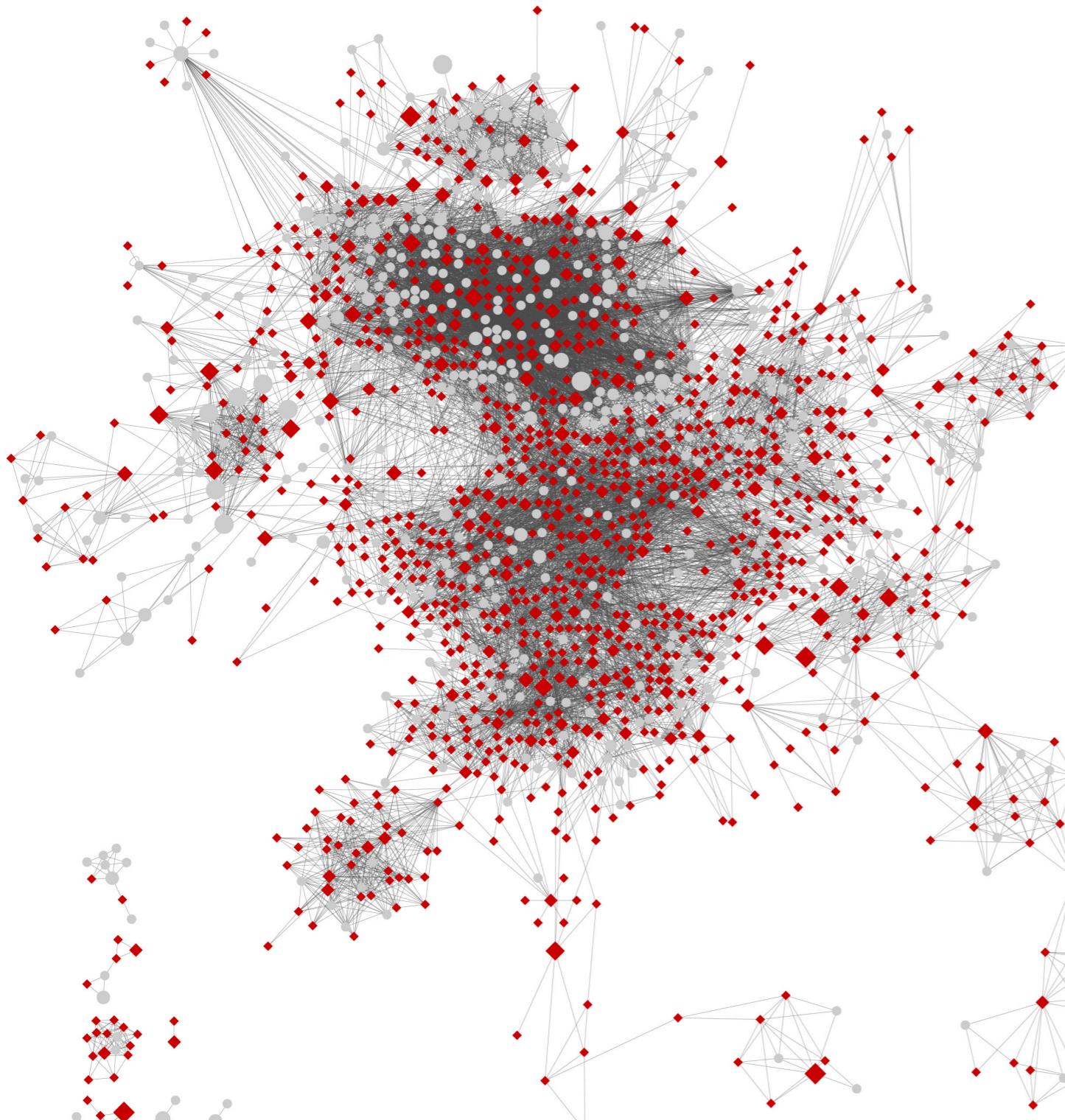
~1681 targets

- T1:** Associated with FDA approved (Phase IV) and marketed drugs
- T2:** Associated with drugs in Phase I-III
- T3:** Associated with drugs in preclinical phase
- T4:** Targets that interact with T1, T2 and/or T3

-> (score 1.0)	247 targets
-> (score 0.7)	
-> (score 0.4)	
-> (score 0.1)	1434 targets



Alzheimer's disease – PPI



PPI: Protein-Protein interaction network

34

Which targets should be modulated simultaneously to have a therapeutic impact on AD?

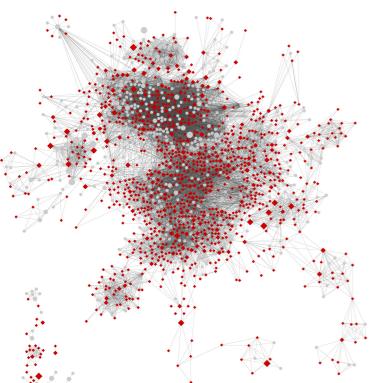
PPI network analysis via
topological and **functional module**

identification

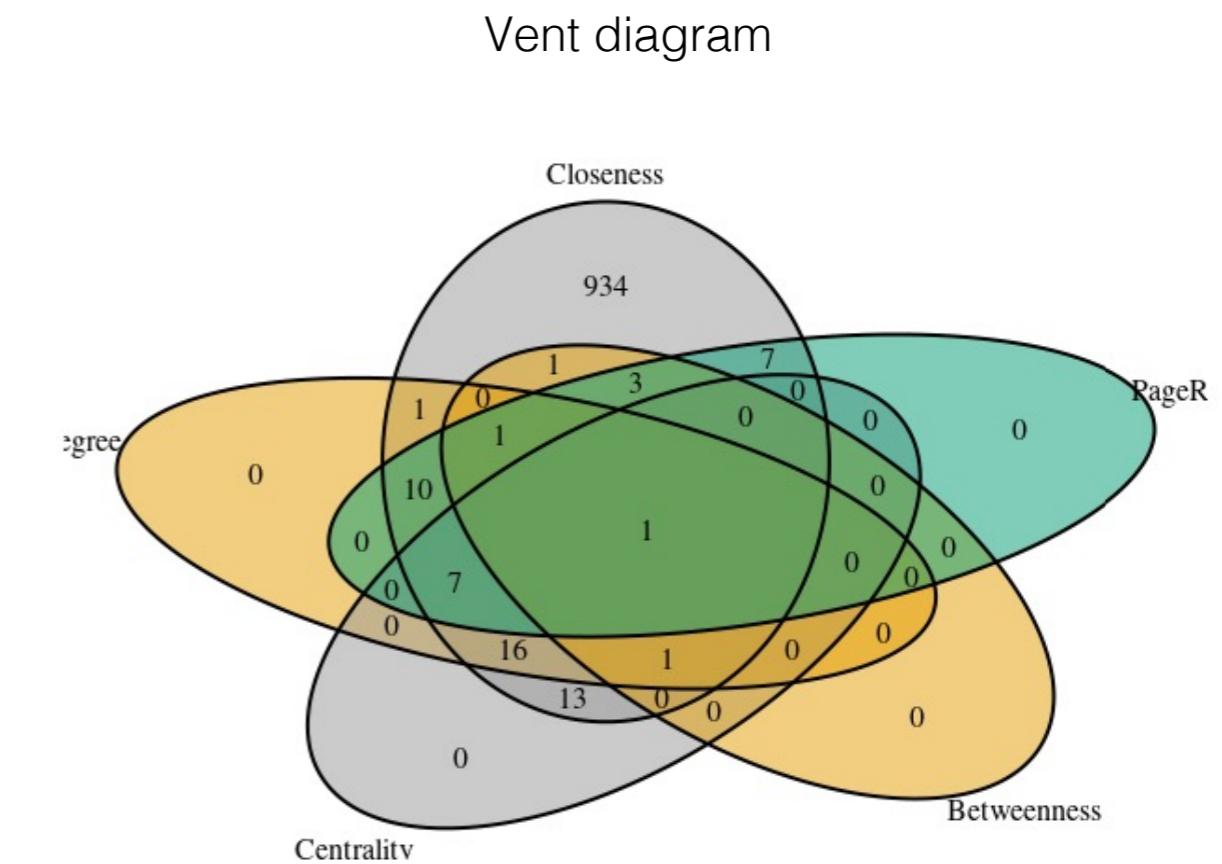
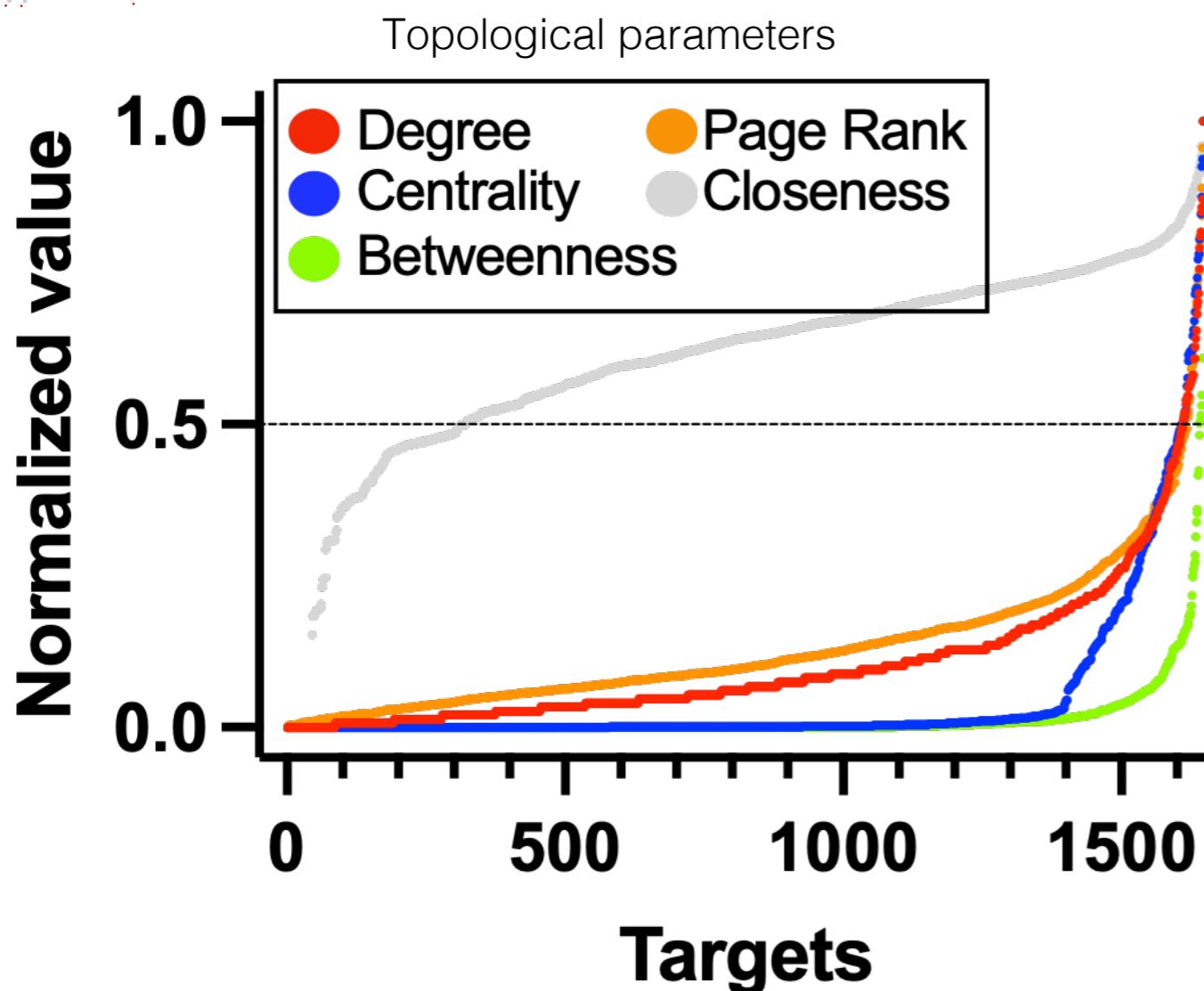
Cytoscape network analyzer

- R studio
- Python

MTGO



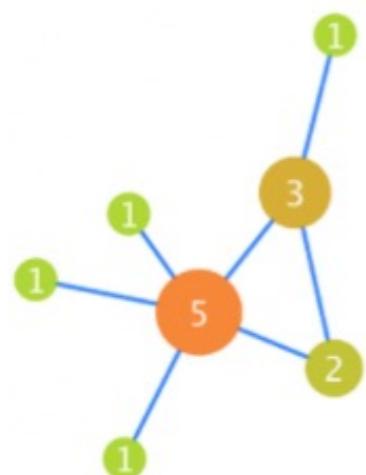
PPI network topological analysis



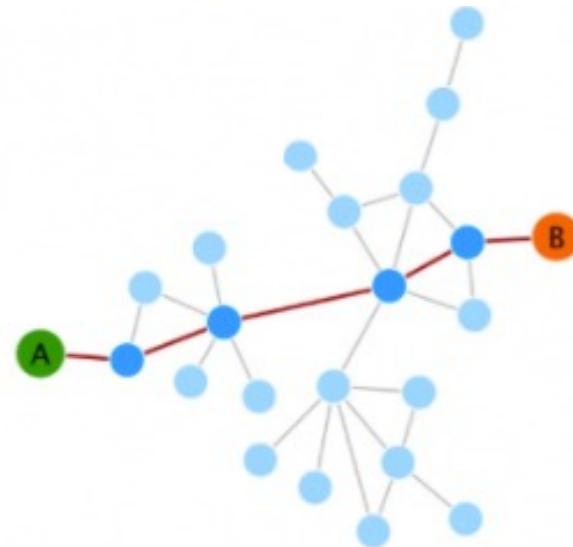
Proteins in the Top-50% for each topological parameter

Key proteins = **61** targets

PPI network topological analysis



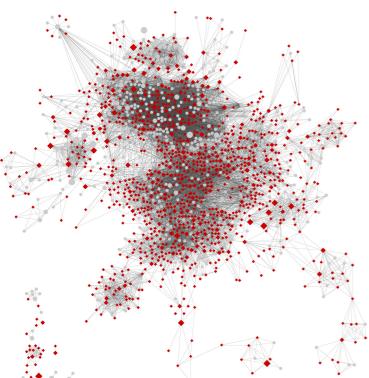
The degree of a network – The degree is the number of edges that connect to a node. It is a fundamental parameter that influences other characteristics, such as the centrality of a node.



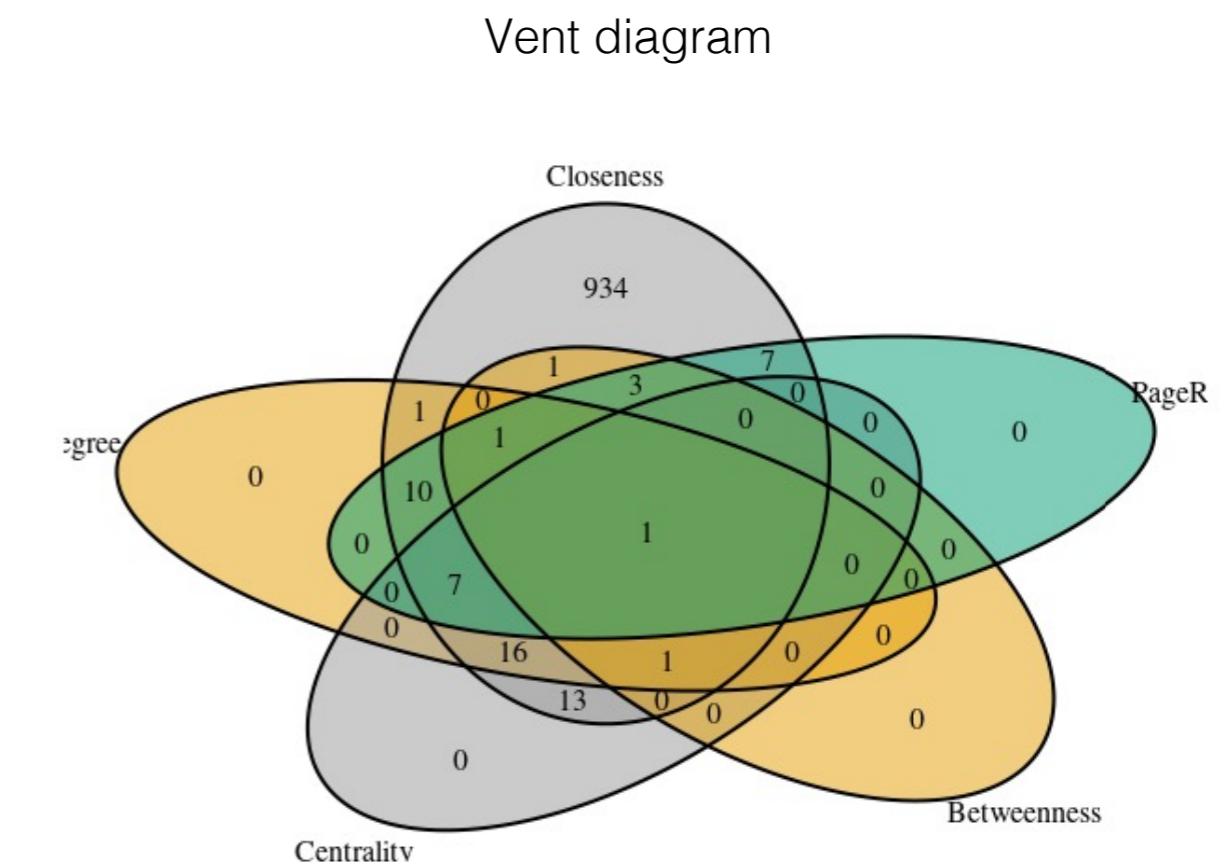
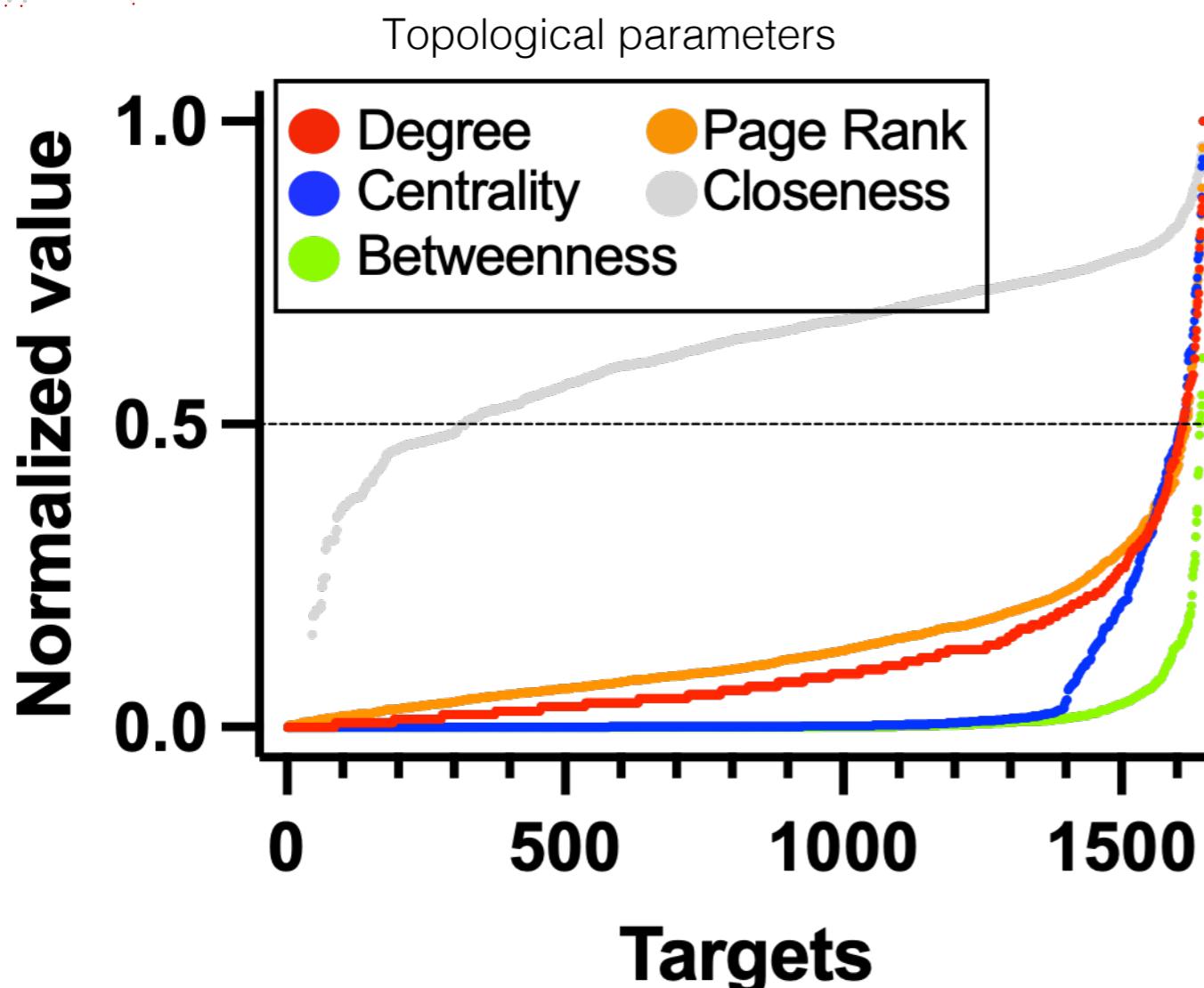
Betweenness – is used to model how information flows. This is especially relevant in many biological networks. In the figure, the shortest path between nodes *A* and *B* is highlighted and takes five steps.



Centralities – Centrality can be measured for nodes and for edges and gives an estimation on how important that node/edge is for the connectivity or the information flow of the network. The degree of a node has a direct influence on many centrality measures, most prominently on the ‘degree centrality’. Its significance is reduced in more sophisticated types of centrality measures, for example, betweenness centrality. In the figure, the most central nodes (according to their betweenness centrality) are highlighted in warm colours and the node size reflects its degree.



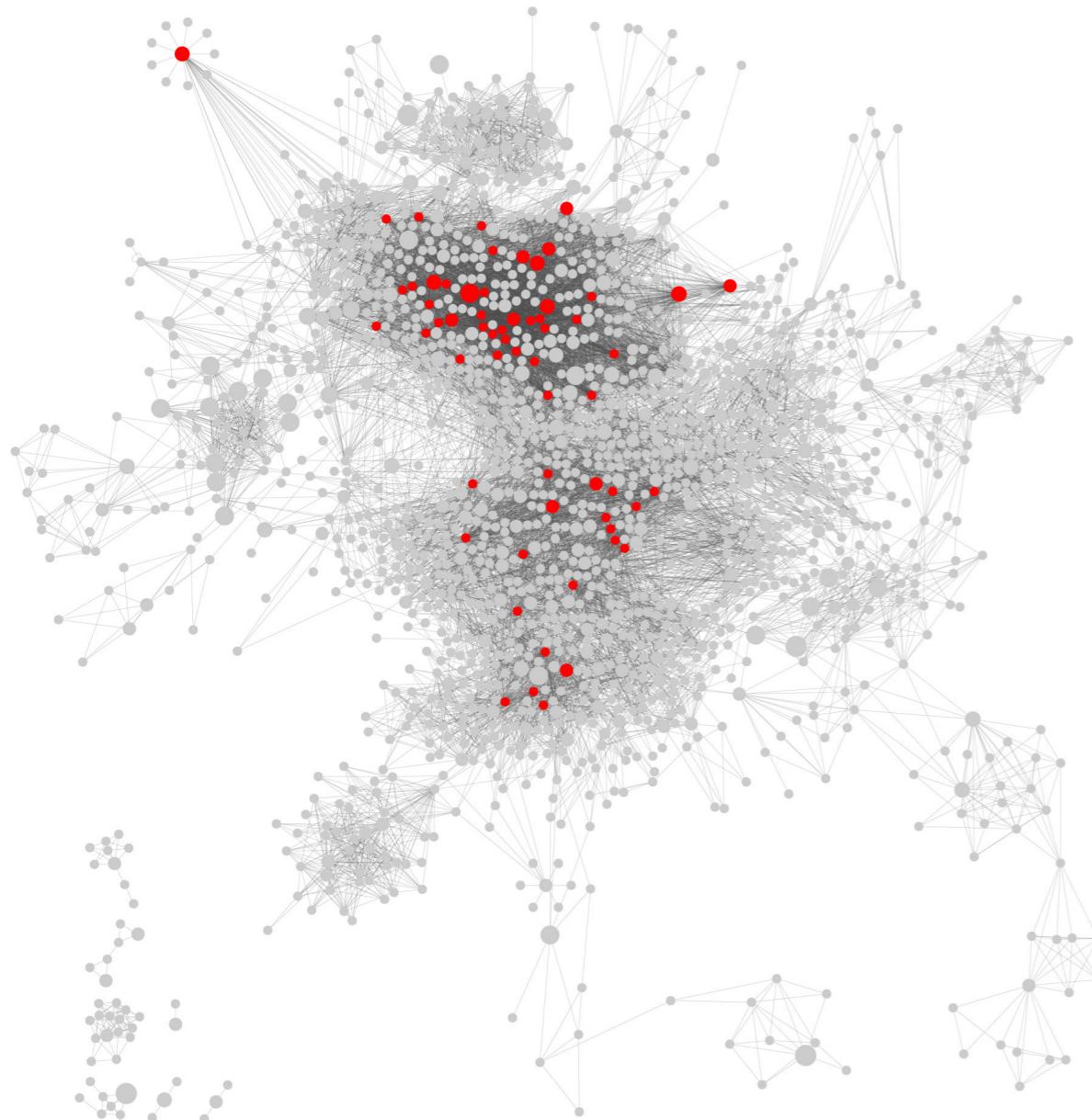
PPI network topological analysis



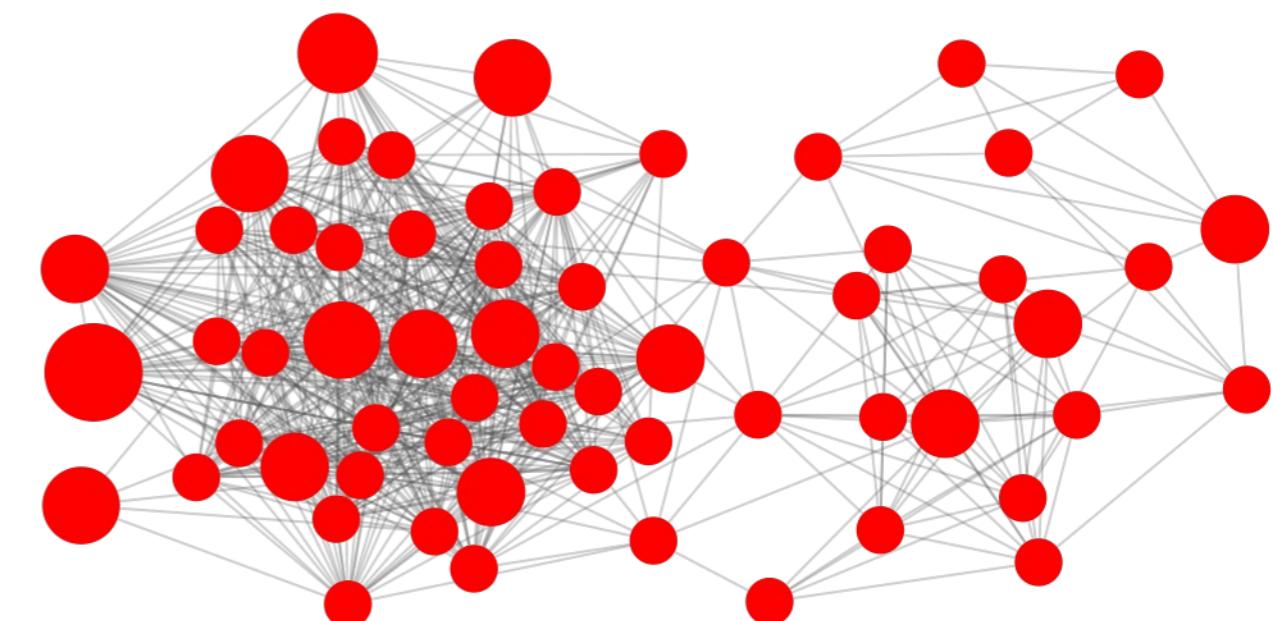
Proteins in the Top-50% for each topological parameter

Key proteins = **61 targets**

PPI network topological analysis

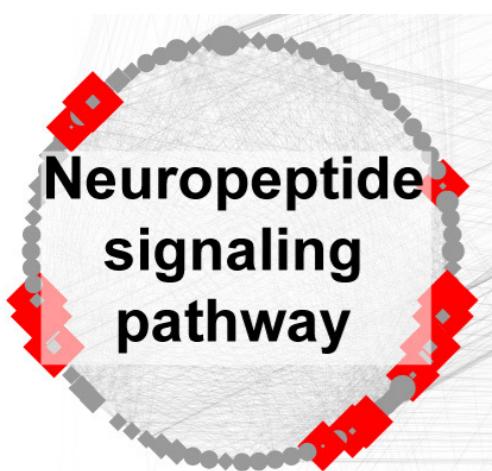
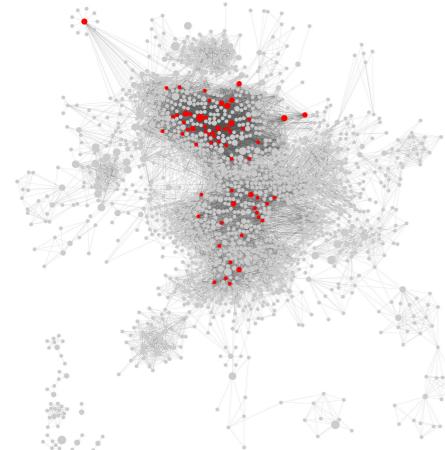


1681 targets



Key proteins = **61 targets**

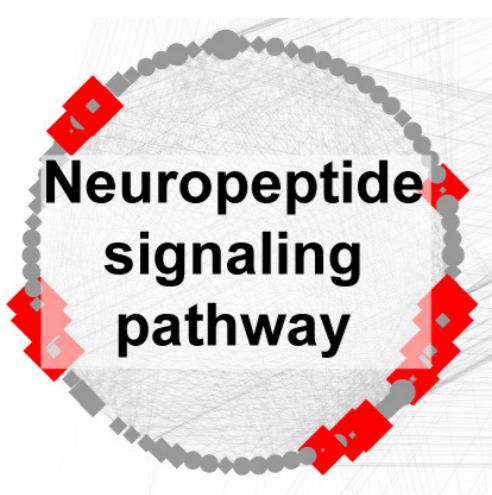
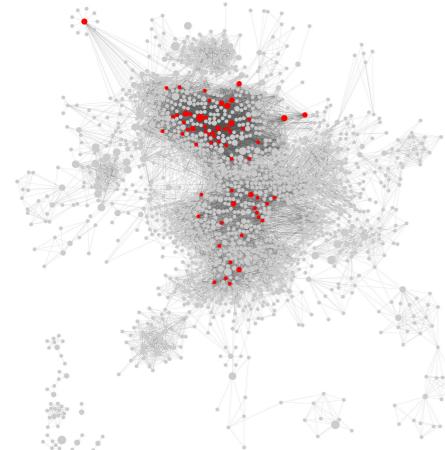
PPI network functional module analysis



15 key targets

Uniprot ID	Group	Gene	Protein
Q14416	T2T4	GRM2	Metabotropic glutamate receptor 2 (mGluR2)
P21554	T2T4	CNR1	Cannabinoid receptor 1 (CB-R) (CB1) (CANN6)
Q14832	T2T4	GRM3	Metabotropic glutamate receptor 3 (mGluR3)
P34972	T4	CNR2	Cannabinoid receptor 2 (CB-2)
P41145	T4	OPRK1	Kappa-type opioid receptor (K-OR-1) (KOR-1)
P01189	T4	POMC	Pro-opiomelanocortin (POMC) (Corticotropin-lipotropin)
P01213	T4	PDYN	Proenkephalin-B (Beta-neoendorphin-dynorphin) (Preprodynorphin)
P41146	T4	OPRL1	Nociceptin receptor (Kappa-type 3 opioid receptor) (KOR-3)
P41143	T4	OPRD1	Delta-type opioid receptor (D-OR-1) (DOR-1)
P01303	T4	NPY	Pro-neuropeptide Y
P21917	T2T4	DRD4	D(4) dopamine receptor
O75899	T1T4	GABBR2	GABA-B receptor 2
Q9UBS5	T1T4	GABBR1	GABA-B receptor 1
P08908	T2T4	HTR1A	5-hydroxytryptamine receptor 1A (5-HT-1A)
P30872	T4	SST	Somatostatin receptor type 1 (SS-1-R) (SS1-R) (SS1R) (SRIF-2)

PPI network functional module analysis

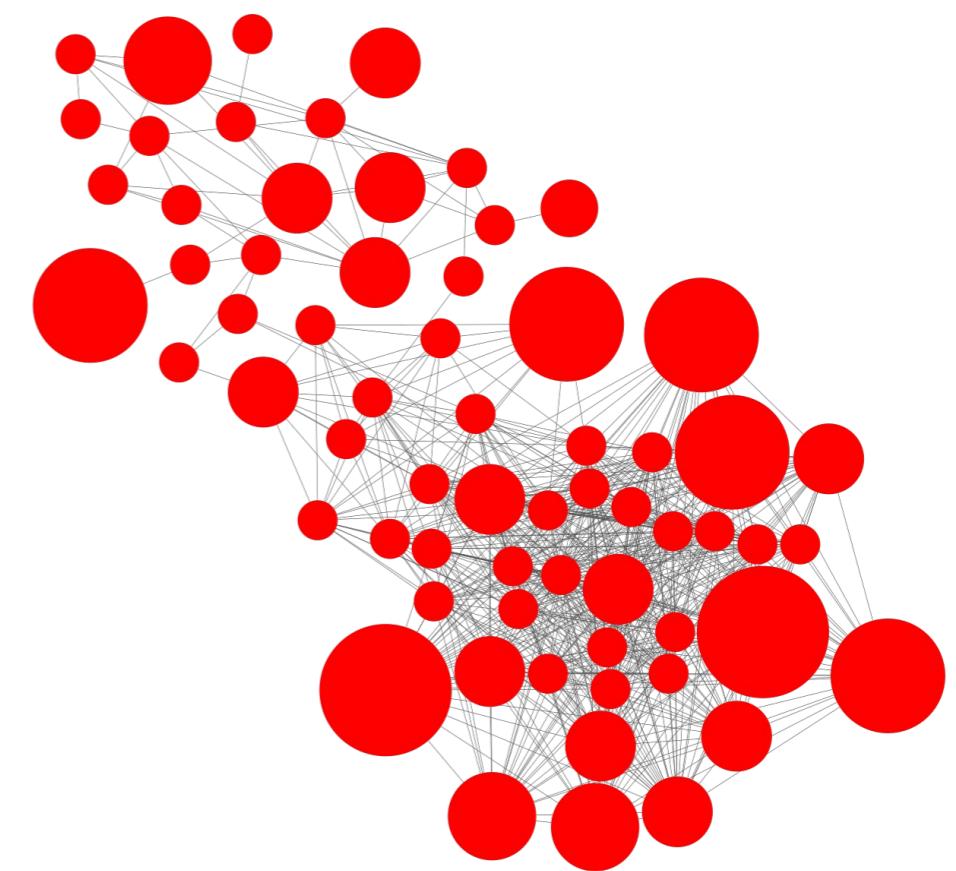
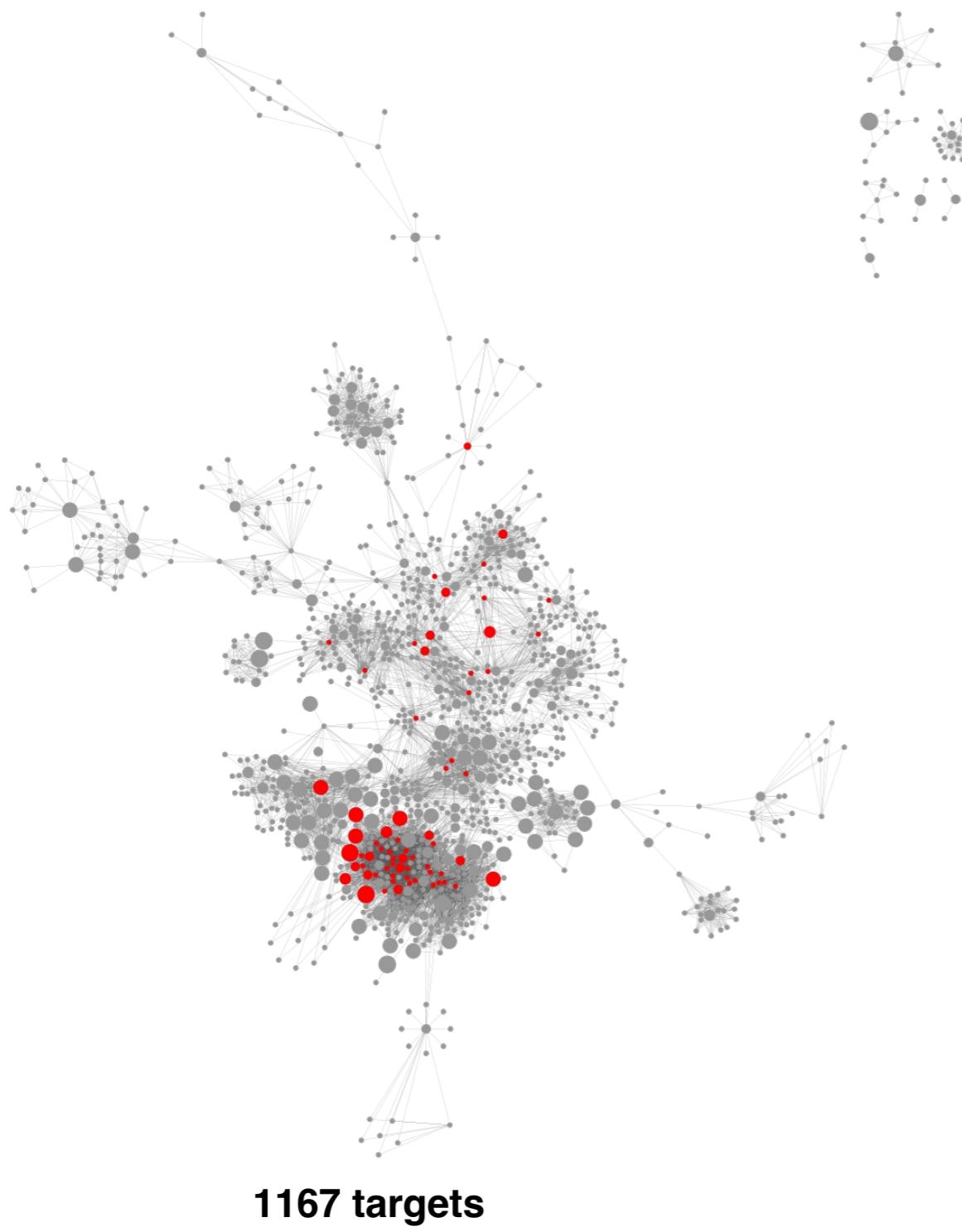


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P01189	T4	POMC	Pro-opiomelanocortin (POMC) (Corticotropin-lipotropin)
P01213	T4	PDYN	Proenkephalin-B (Beta-neoendorphin-dynorphin) (Preprodynorphin)
P41146	T4	OPRL1	Nociceptin receptor (Kappa-type 3 opioid receptor) (KOR-3)
P41143	T4	OPRD1	Delta-type opioid receptor (D-OR-1) (DOR-1)
P01303	T4	NPY	Pro-neuropeptide Y
P21917	T2T4	DRD4	D(4) dopamine receptor
O75899	T1T4	GABBR2	GABA-B receptor 2
Q9UBS5	T1T4	GABBR1	GABA-B receptor 1
P08908	T2T4	HTR1A	5-hydroxytryptamine receptor 1A (5-HT-1A)
P30872	T4	SST	Somatostatin receptor type 1 (SS-1-R) (SS1-R) (SS1R) (SRIF-2)

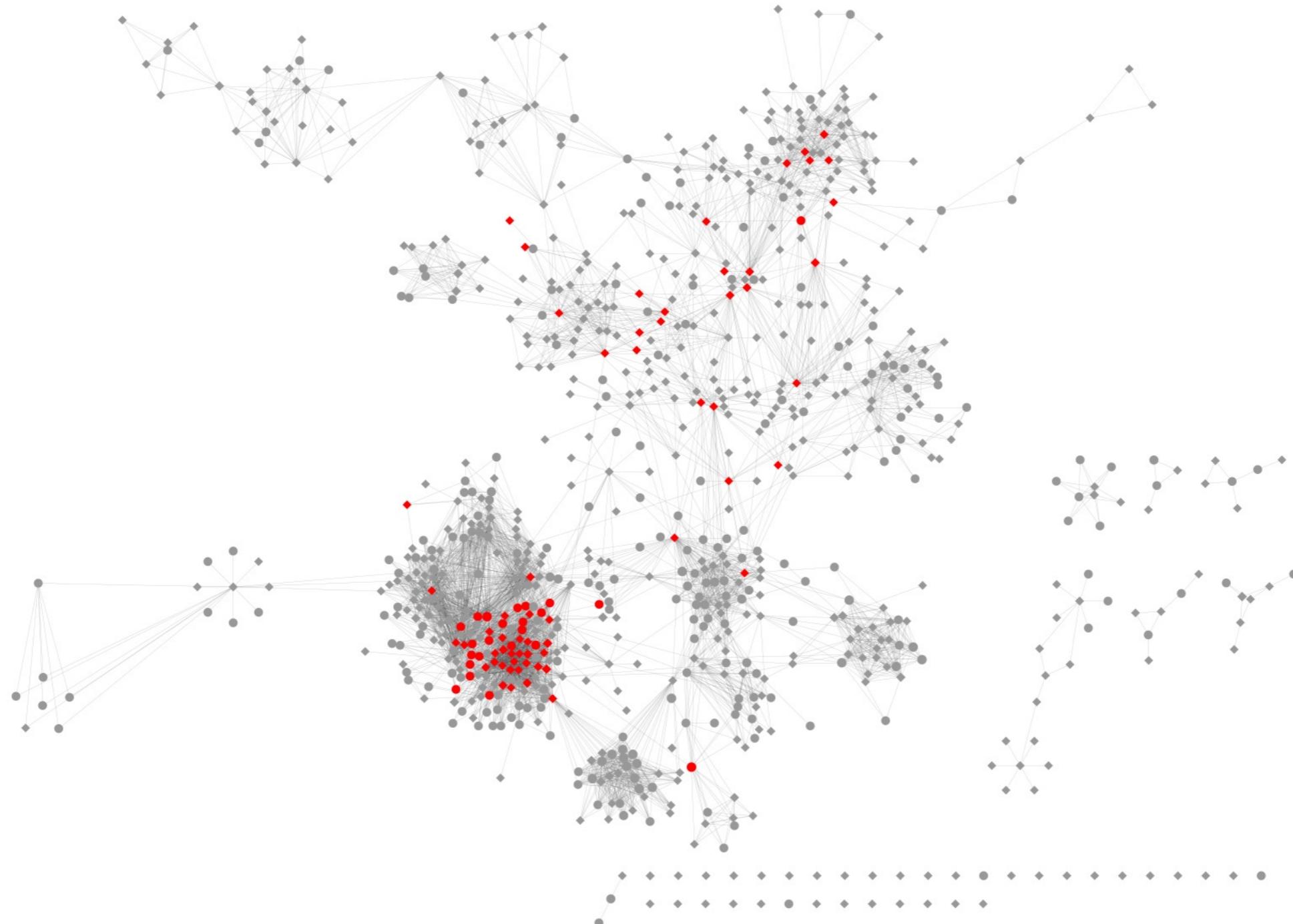
How to modulate multiple targets with the same compound?

PPI - Parkinson's disease



Key proteins = **65 targets**

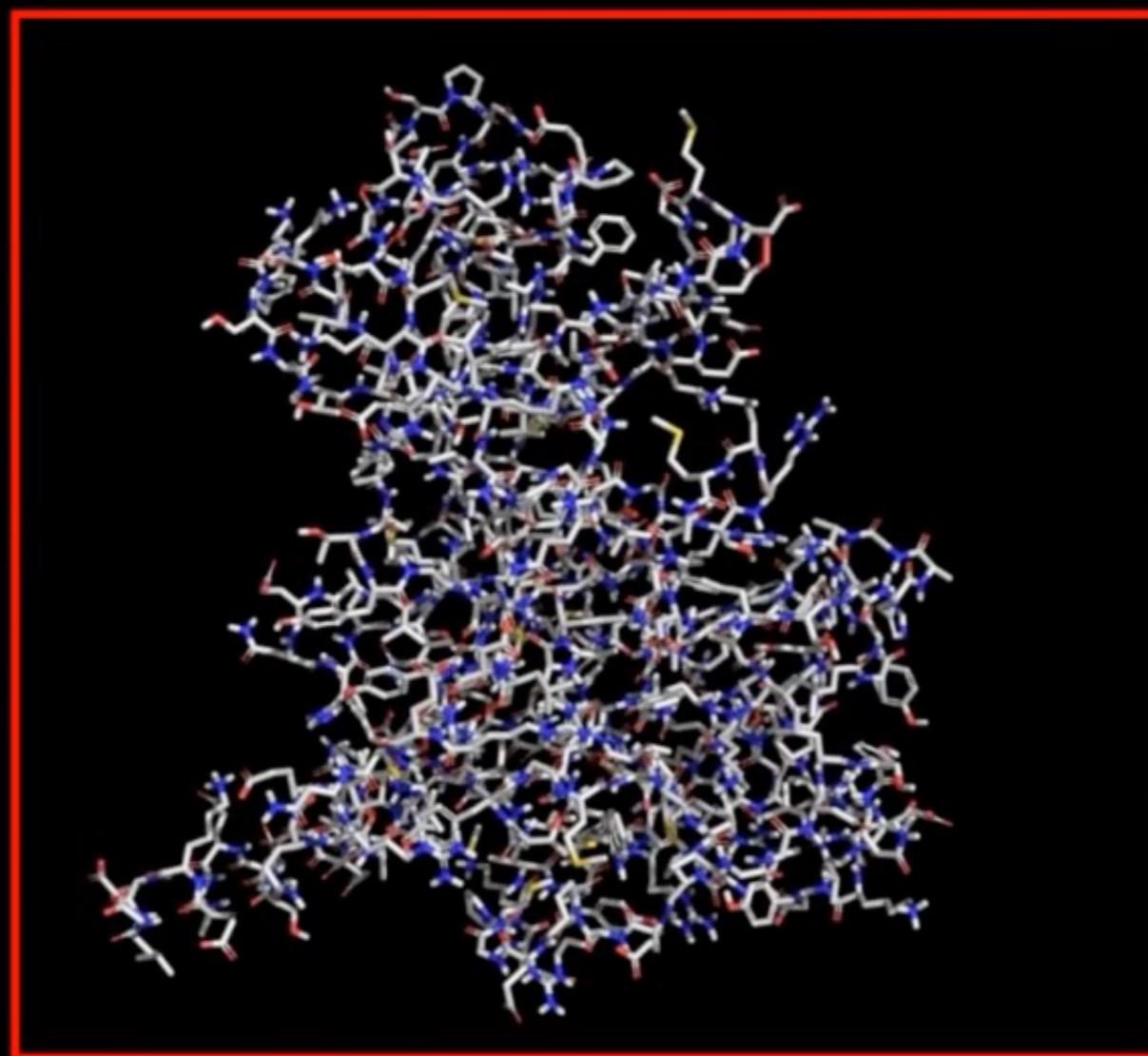
Merge PPI-AD + PPI-PD



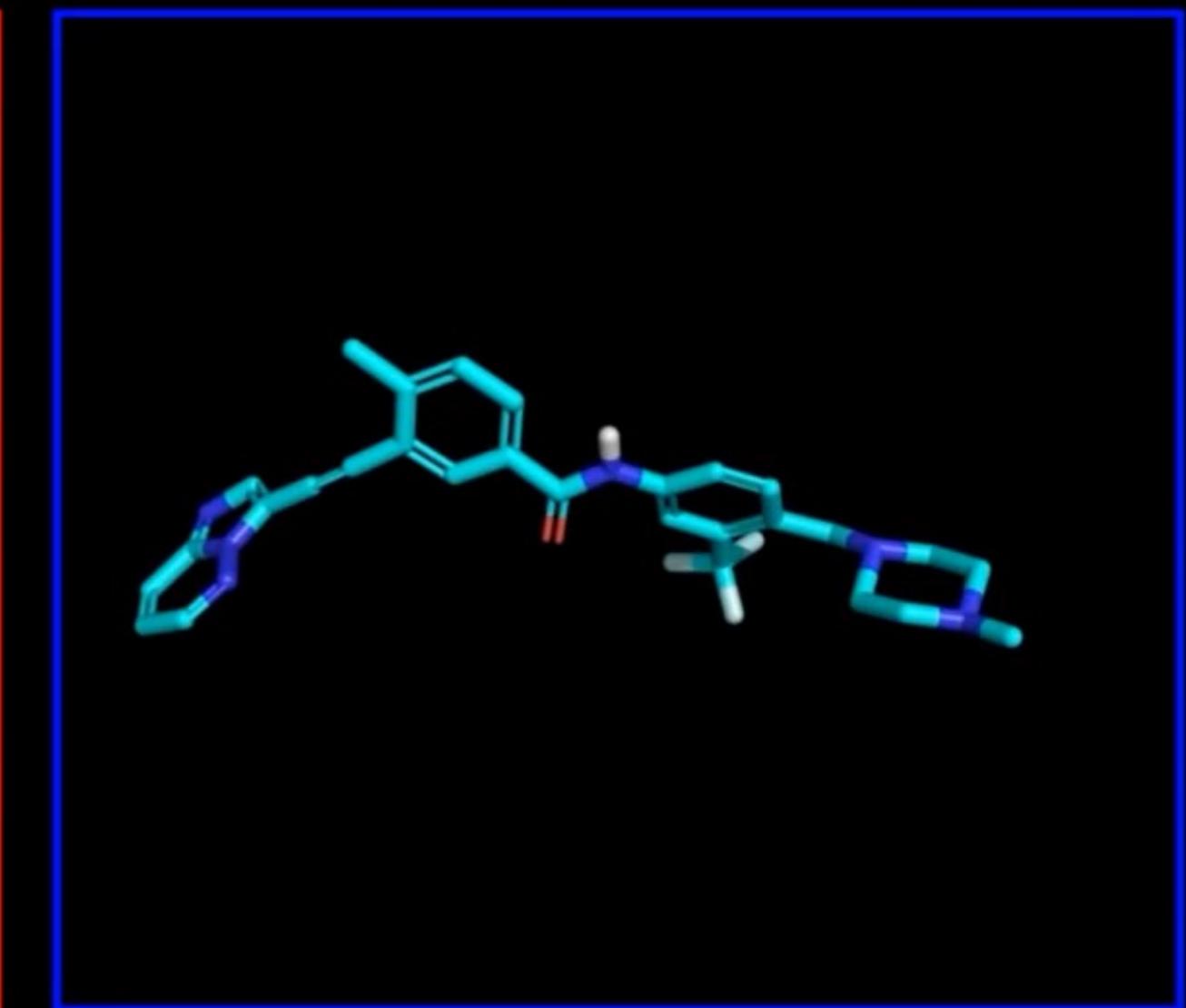
854 common nodes (proteins) - 5619 edges

Molecular modeling in drug design

Protein



Drug



Molecular Docking

Target

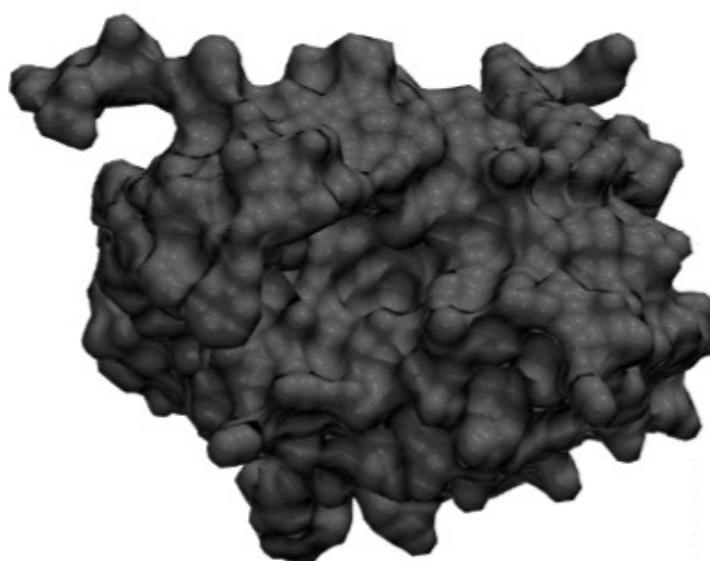
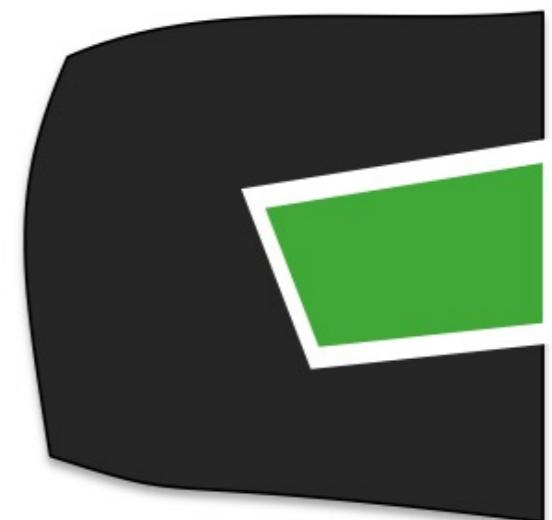


Ligand

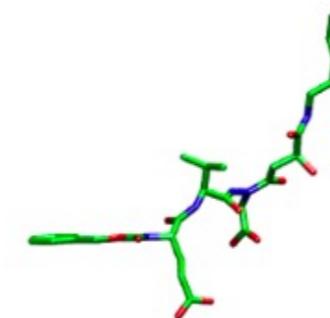


docking

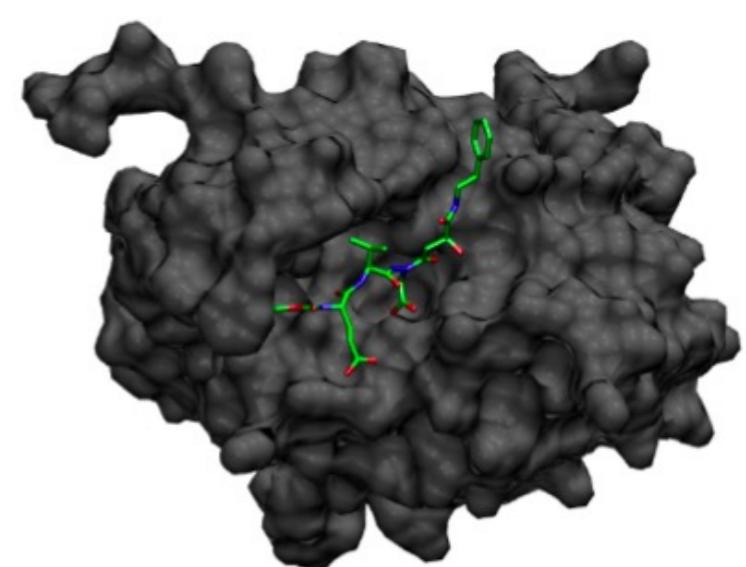
Complex



+



docking



Molecular Docking

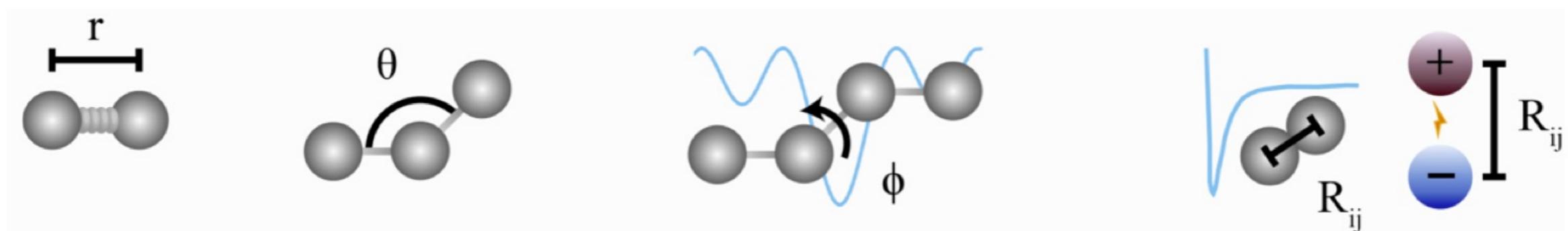


Molecular Dynamics simulations (MDs) as computational microscope!!

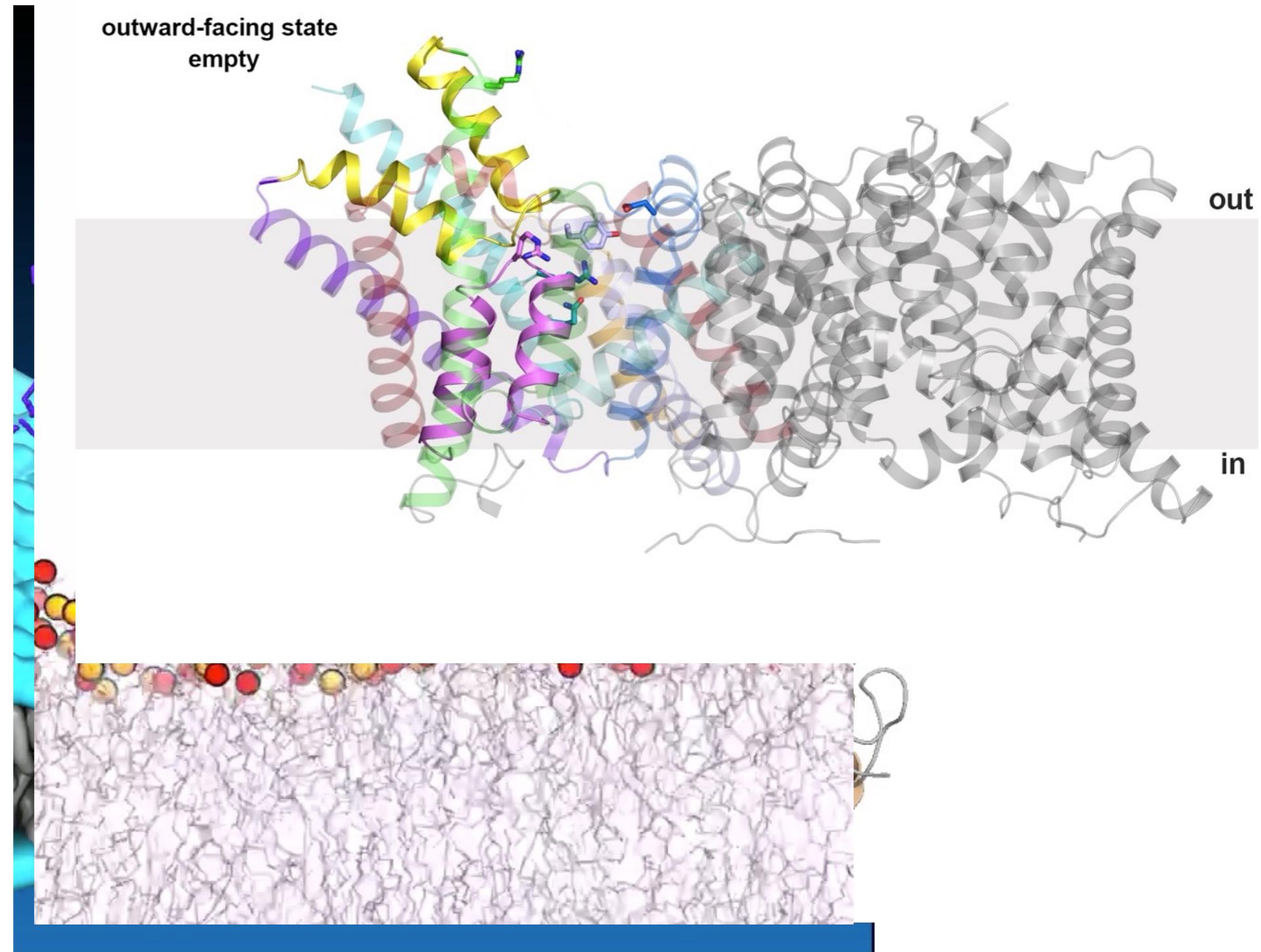
Se pretende integrar las ecuaciones de movimiento de Newton en cada paso de simulación para cada una de las partículas/átomos que integran el sistema. Dadas las posiciones y velocidades iniciales, es posible determinar los valores de dichas variables en un instante de tiempo t dependiendo de las fuerzas con que actúan los átomos.

Se debe calcular la energía total sobre cada partícula mediante **Mecánica Molecular**, estas contribuciones son integradas en un campo de fuerza así:

$$E_{total} = \overbrace{\sum_{enlaces} K_r(r - r_{eq})^2 + \sum_{ángulos} K_\theta(\theta - \theta_{eq})^2 + \sum_{dihedros} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)]}^{Enlazantes} + \overbrace{\sum_{i < j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]}^{No-enlazantes}$$



Molecular Dynamics simulations



Antimicrobial peptides acting
penetrating membranes



Ramírez Lab

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Welcome to the Ramírez Lab

We are a multidisciplinary group focused on the study of biomolecular systems by using theoretical and experimental approaches. We aim to use computational polypharmacology with wet lab analyses to strengthen the drug design and development processes. Our work involves collaboration with medicinal chemists, biochemists, and biologists, and we are part of the [Pharmacology Department](#) - [Faculty of Biological Sciences](#) at [University of Concepción](#).



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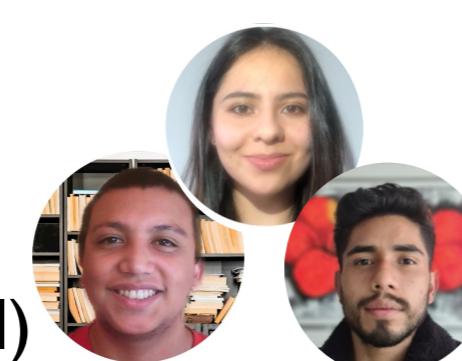
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Oportunidades



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Beca de Doctorado Nacional, Año Académico 2023

PRESENTACIÓN PÚBLICO OBJETIVO BITÁCORA RESULTADOS POSTULACIÓN

La Beca de Doctorado Nacional tiene por objetivo apoyar financieramente los estudios de doctorado en todas las áreas del conocimiento, en programas acreditados en conformidad con la Ley N° 20.129 e impartidos por universidades chilenas, por un plazo máximo de cuatro años, contados desde la fecha de inicio del programa de estudios. Además, en caso de que corresponda, una extensión de los beneficios de mantenimiento, hasta por un máximo de seis meses, para la redacción de la tesis doctoral.

En este concurso podrán postular personas chilenas o extranjeras, con o sin permanencia definitiva en Chile.

Con el objetivo de evaluar tus posibilidades de obtener esta beca, a modo de referencia, puedes consultar el Panel Interactivo, donde encontrarás información sobre personas seleccionadas en convocatorias anteriores, agrupadas por nota de licenciatura, título profesional o equivalente y ranking de egreso de pregrado. Asimismo, podrás simular tu puntaje parametrizado, asociado a tus antecedentes académicos de pregrado, en el Simulador de Puntajes Antecedentes Académicos de Pregrado.

INICIO: 09-11-2022
CIERRE: 14-12-2022 13:00h

POSTULAR

DOCUMENTOS DESCARGABLES

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Becas internas UdeC

Network pharmacology:

The next paradigm in drug discovery



DAVID RAMÍREZ



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Pharmacoinformatics & Drug Design Lab
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