

Battery of the Computational Drug Design: The Avenue of Drug Repositioning

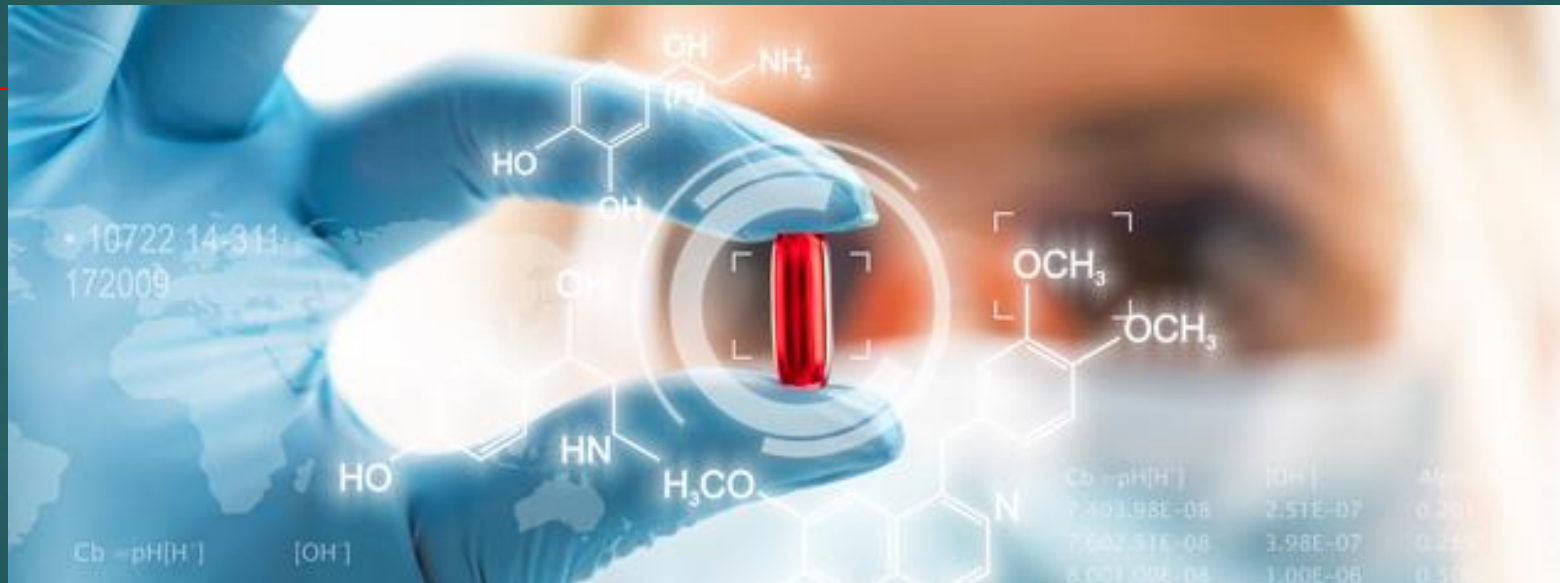
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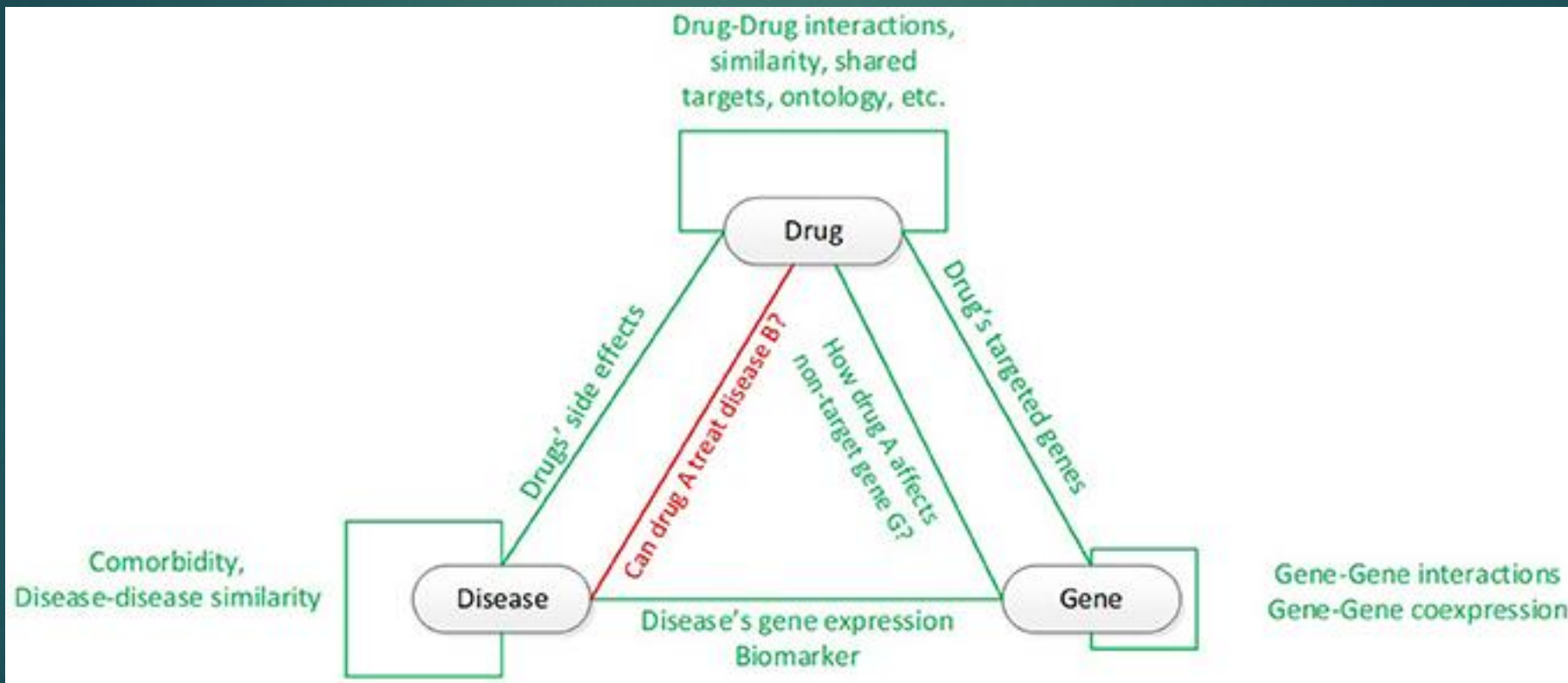
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Drug Repositioning

The process of **finding** new uses or indications for existing drugs



Connectivity among drugs, genes, and diseases



Successful repurposed drugs have been found in recent years ...

Drug name	Intended use	New use	Current development status	References
Thalidomide	Introduced as hypnotic drug, later withdrawn due to adverse teratogenic effects	Multiple myeloma, leprosy	Approved	Antitumor activity [43], leprosy [44]
Itraconazole	Fungal infections	Anticancer properties	Clinical trials	[45–47]
Celecoxib	Osteoarthritis	Colorectal polyps	Approved	[48]
All-trans retinoic acid (ATRA)	Severe acne	Acute promyelocytic leukemia	Approved	[49]
Metformin	Diabetes	Breast cancer	Clinical trials	[50]
Chloroquine	Malaria	Lung cancer (as part of combinatorial drug therapy)	Clinical trials	[51–53]
Raloxifene	Osteoporosis	Invasive breast cancer in postmenopausal women	Approved	[54]
Tamoxifen	Metastatic breast cancers	Bipolar disorder	Approved	[55]

N Engl J Med 1999, 341:1565–1571
Microbes Infect 2002, 4:1193–1202

Oncol Lett 2017,14:1240–1246
Ecancer medical science 2015, 9:521
Med Chem 2016, 59:3635–3649

Oncology (Williston Park) 2002, 16:17–21

Semin Hematol 2001, 38:13–25

Breast Cancer Res 2015, 17:88

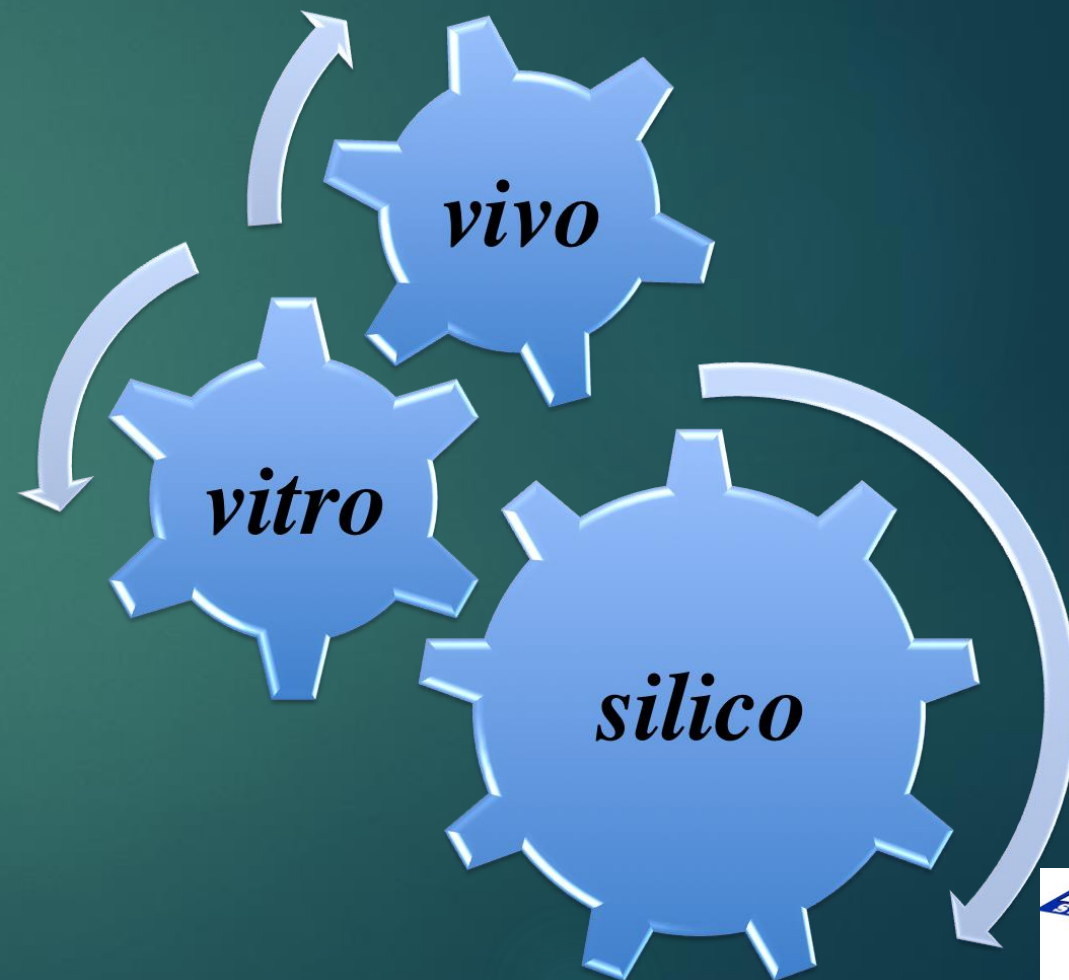
Acta Pharmacol Sin 2014, 35:645–652
Mol Cancer 2013, 12:16
Mol Cell Oncol 2014, e29911

Expert Opin Drug Saf 2008, 7:259–270
Iran J Child Neurol 2016,10:16–25

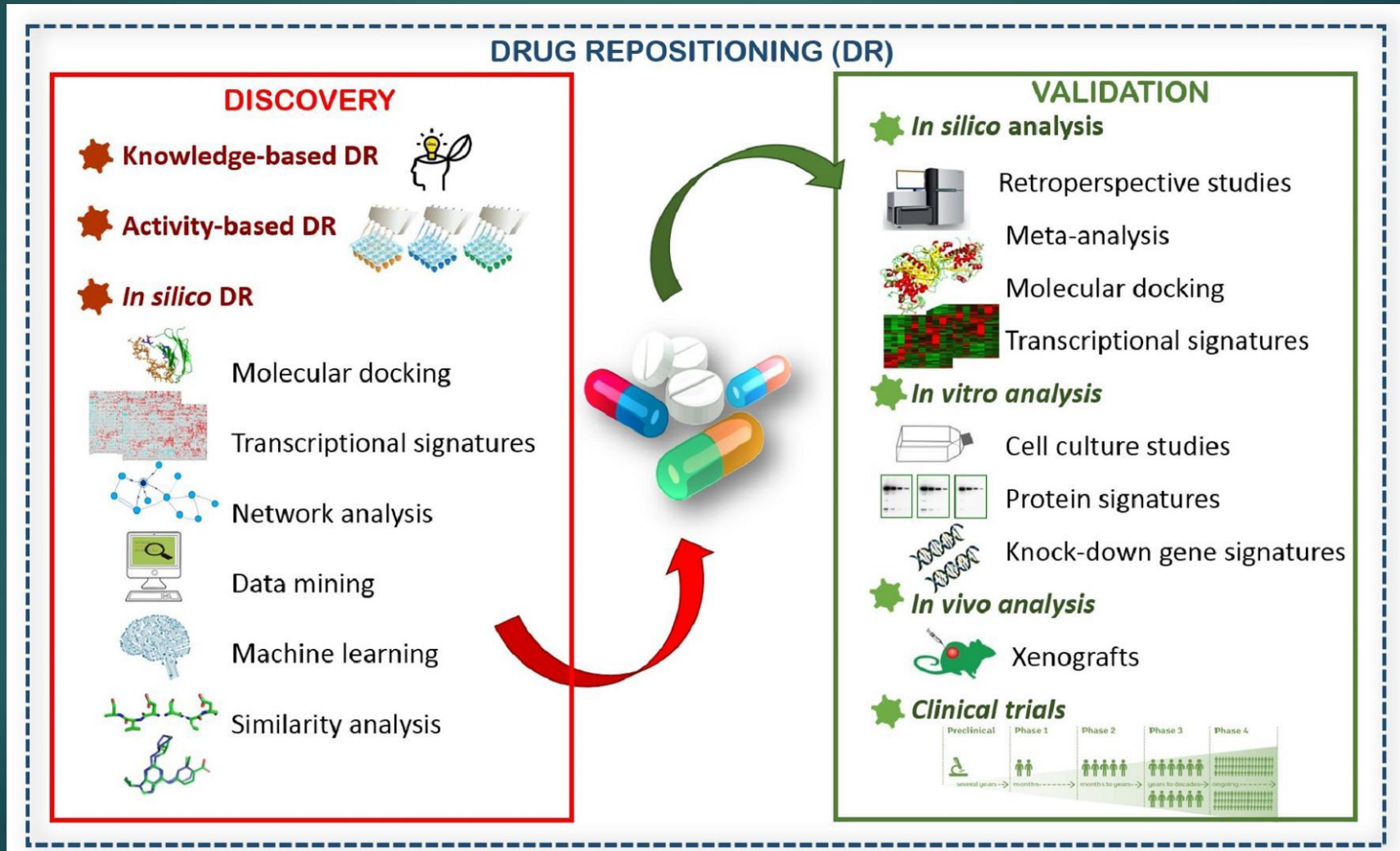


The main challenge in drug repurposing Finding the new indication ...

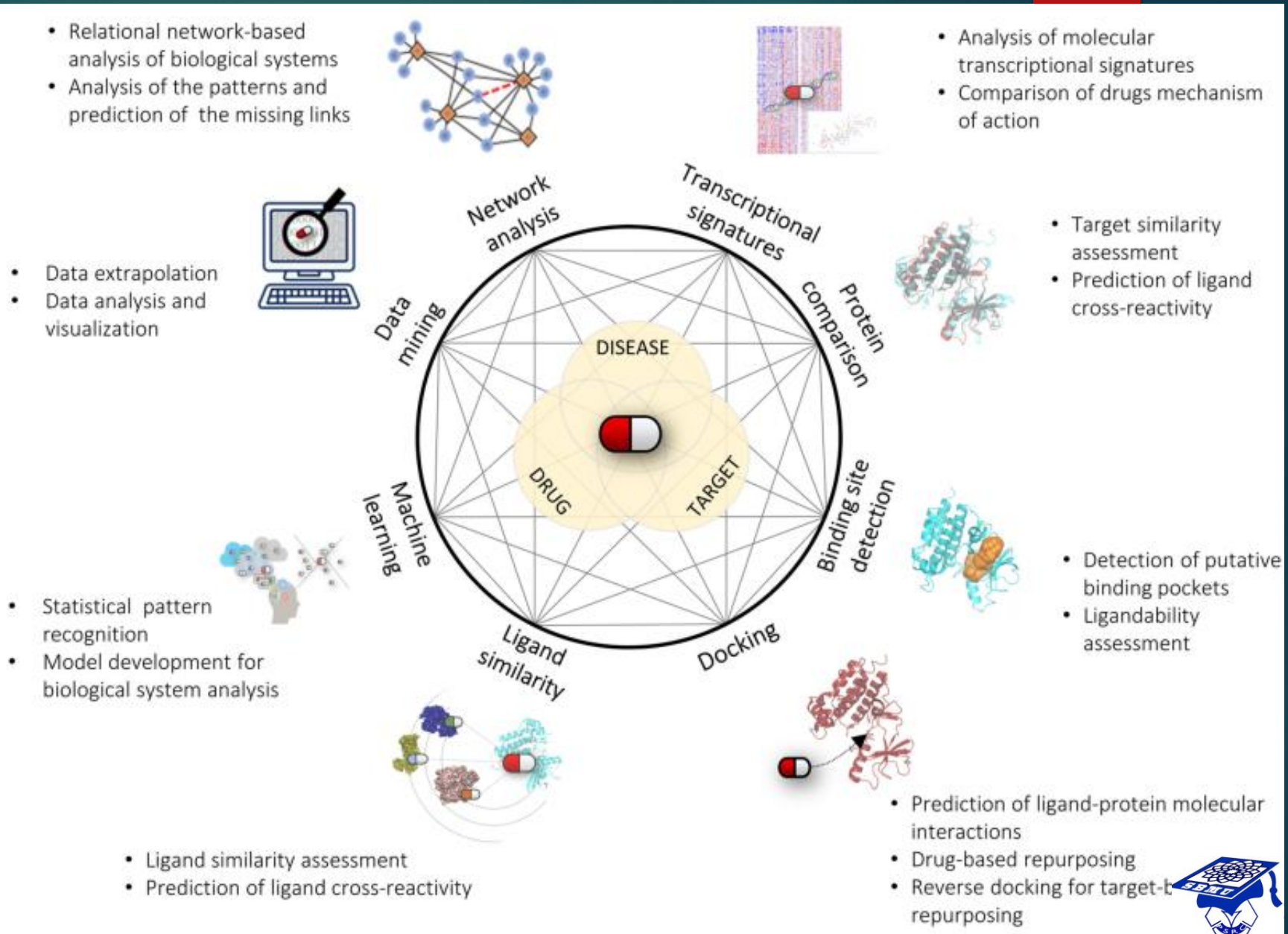
Bioinformatics tools



Different drug repositioning approaches for drug discovery and validation

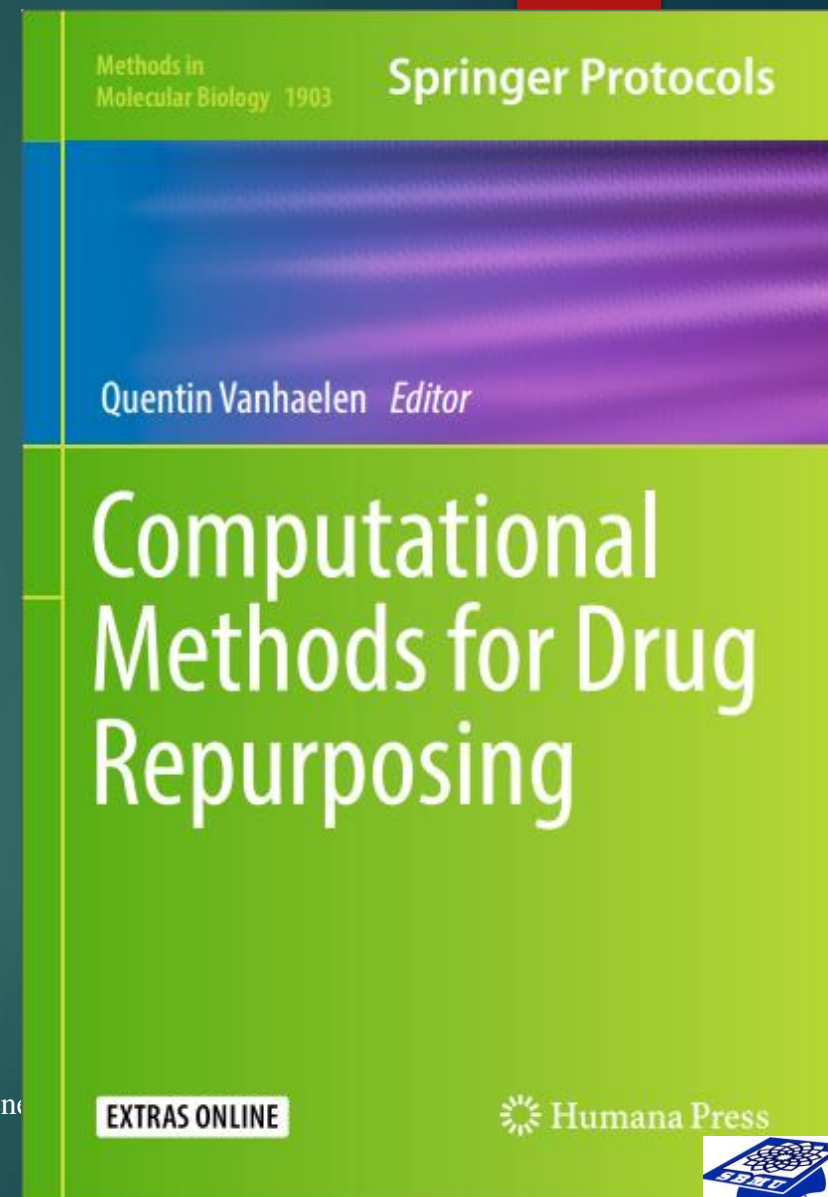


Connecting Drugs, Targets, Diseases by *in silico* methods

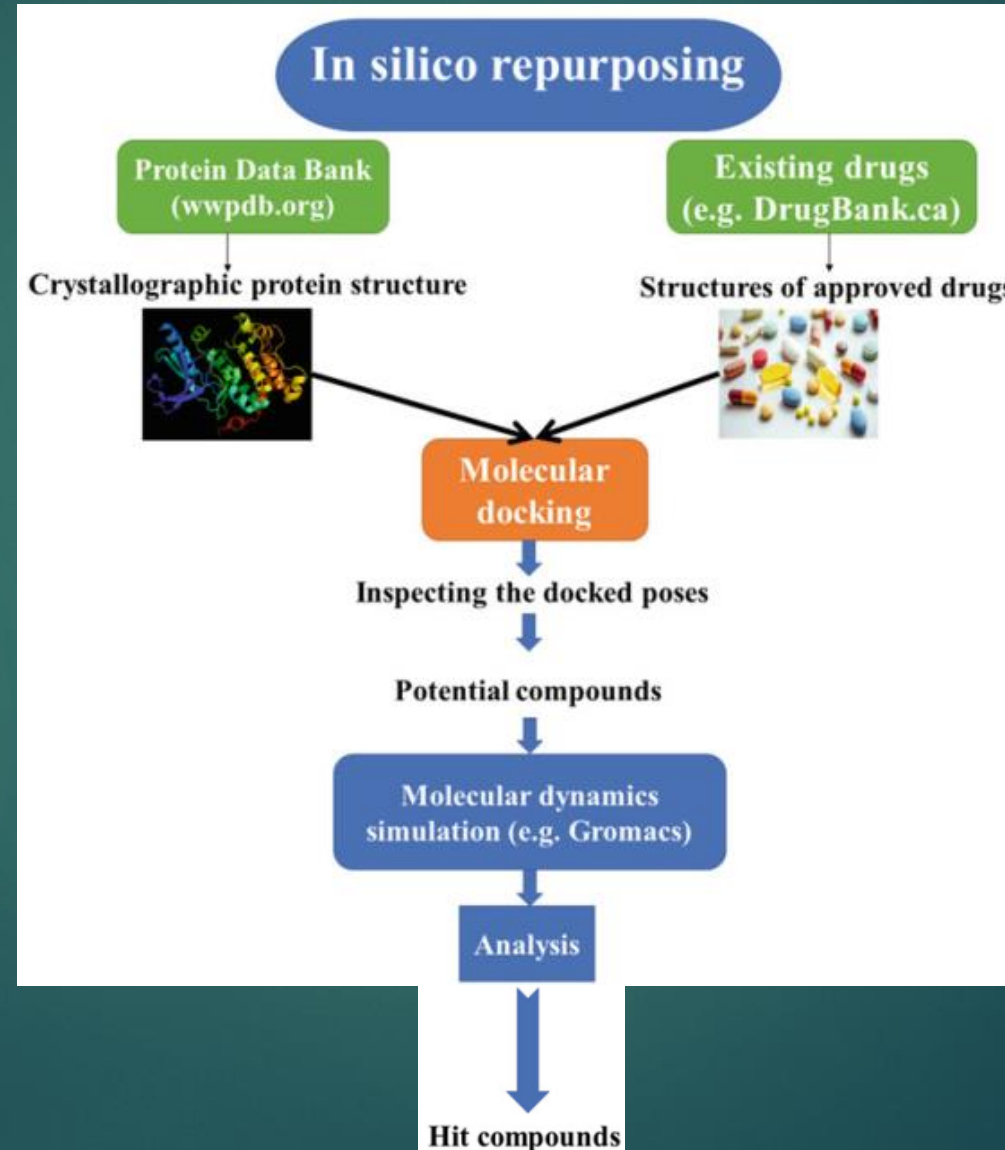


In silico Repositioning methods

- ▶ Integrated ligand-based and structure-based study
- ▶ Combining Virtual Screening and Molecular Dynamics Simulation
- ▶ Evolutionary Relationships Between Targets of Approved Drugs and Proteins of Interest
- ▶ Mining Adverse Event Data in ClinicalTrials.gov
- ▶ Transcriptomic Data Mining for Computational Drug Discovery
- ▶ Network-Based Drug Repositioning: Approaches, Resources, and Research Directions
- ▶ A Computational Bipartite Graph-Based Drug Repurposing Method
- ▶ Implementation of a Pipeline Using Disease-Disease Associations for Computational Drug Repurposing
- ▶ An Application of Computational Drug Repurposing Based on Transcriptomic Signatures
- ▶ Drug-Induced Expression-Based Computational Repurposing of Small Molecules Affecting Transcription Factor Activity
- ▶ A Drug Repurposing Method Based on Drug-Drug Interaction Networks and Using Energy Model Layouts
- ▶ Integrating Biological Networks for Drug Target Prediction and Prioritization
- ▶ Using Drug Expression Profiles and Machine Learning Approach for Drug Repurposing
- ▶ Computational Prediction of Drug-Target Interactions via Ensemble Learning
- ▶ A Machine-Learning-Based Drug Repurposing Approach Using Baseline Regularization
- ▶ Machine Learning Approach for Predicting New Uses of Existing Drugs and Evaluation of Their Reliabilities
- ▶ A Drug-Target Network-Based Supervised Machine Learning Repurposing Method Allowing the Use of Multiple Heterogeneous
- ▶ Heter-LP: A Heterogeneous Label Propagation Method for Drug Repositioning
- ▶ Tripartite Network-Based Repurposing Method Using Deep Learning to Compute Similarities for Drug-Target Prediction



In Silico Repurposing by Combining Virtual Screening and Molecular Dynamics Simulation

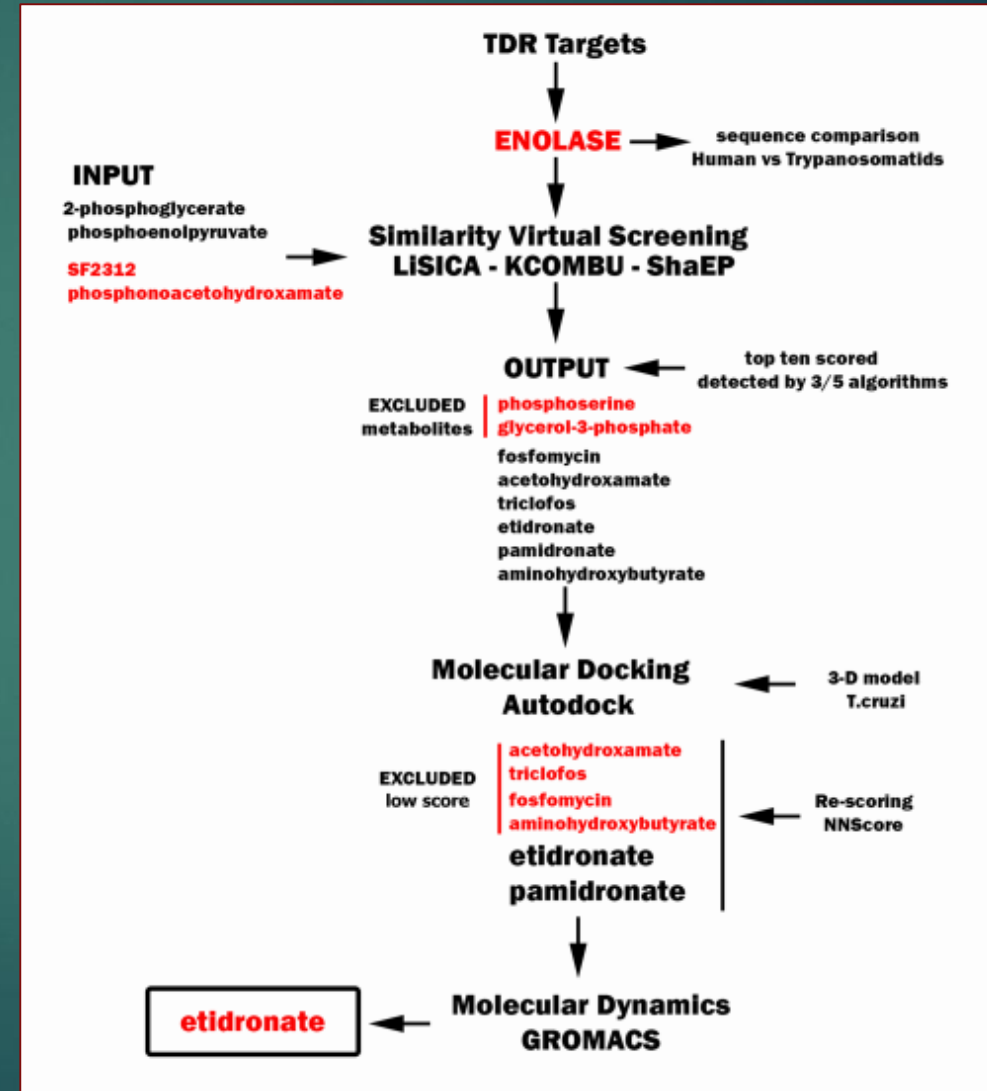
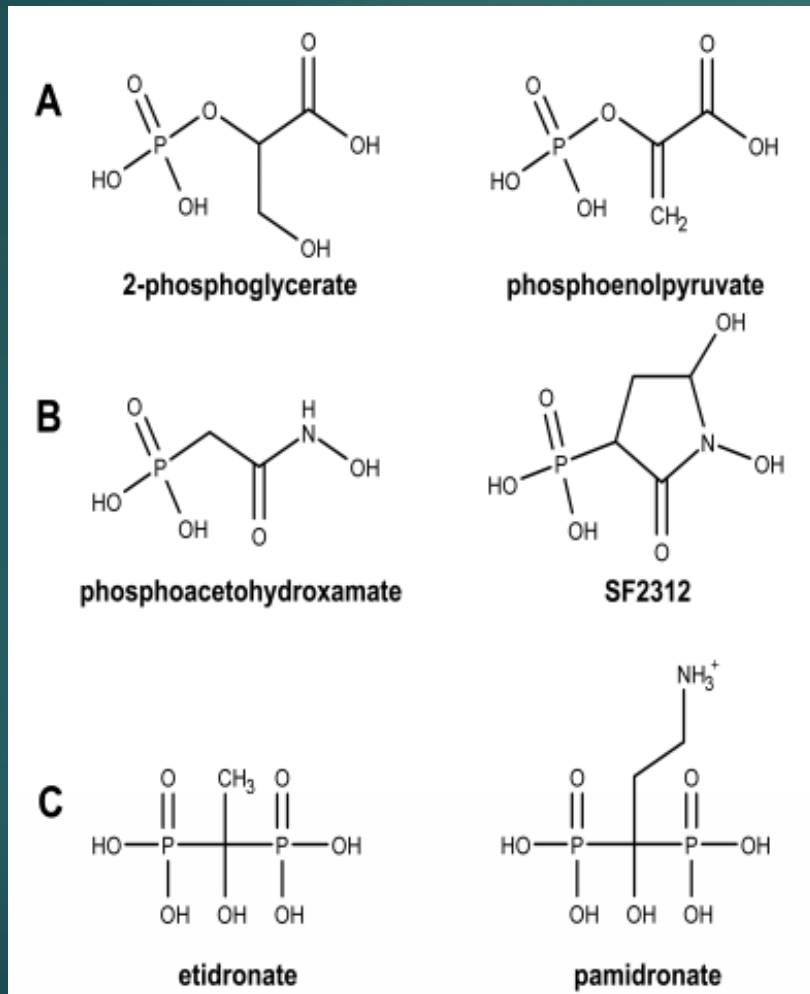


Sweetlead database

Similarity-based search

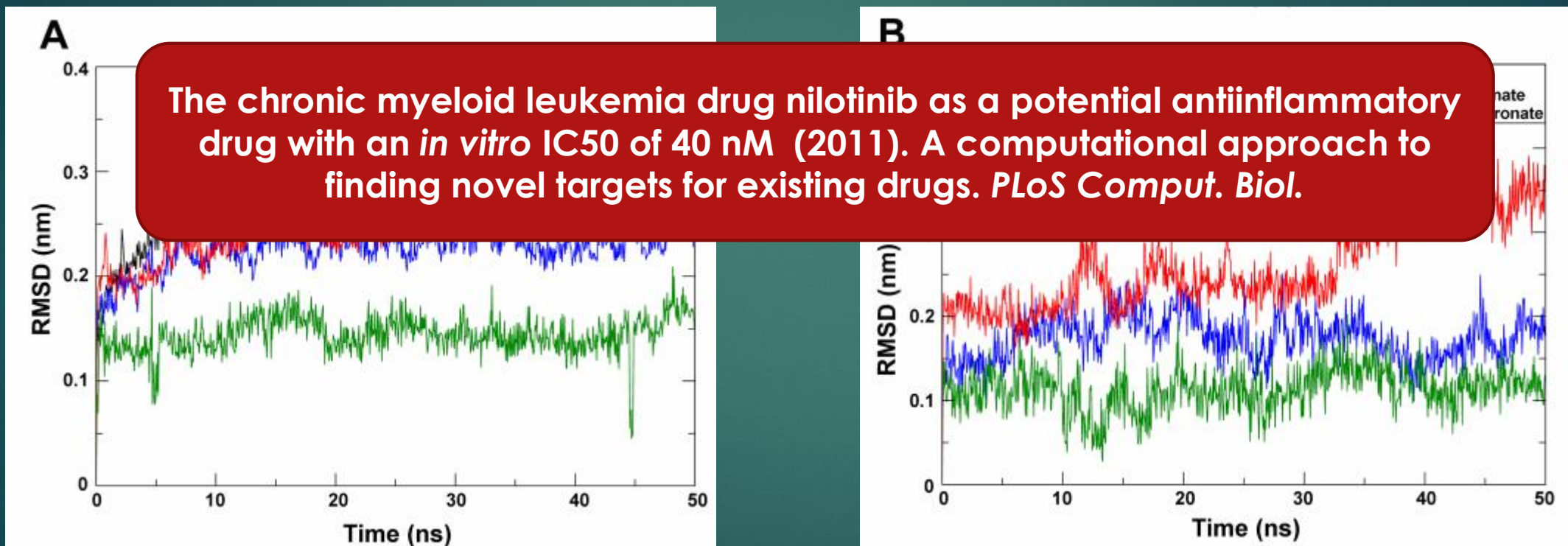
In silico repositioning of etidronate as a potential inhibitor of the Trypanosoma cruzi enolase: T. cruzi enolase inhibitors

Journal of Molecular Graphics and Modelling, 2020

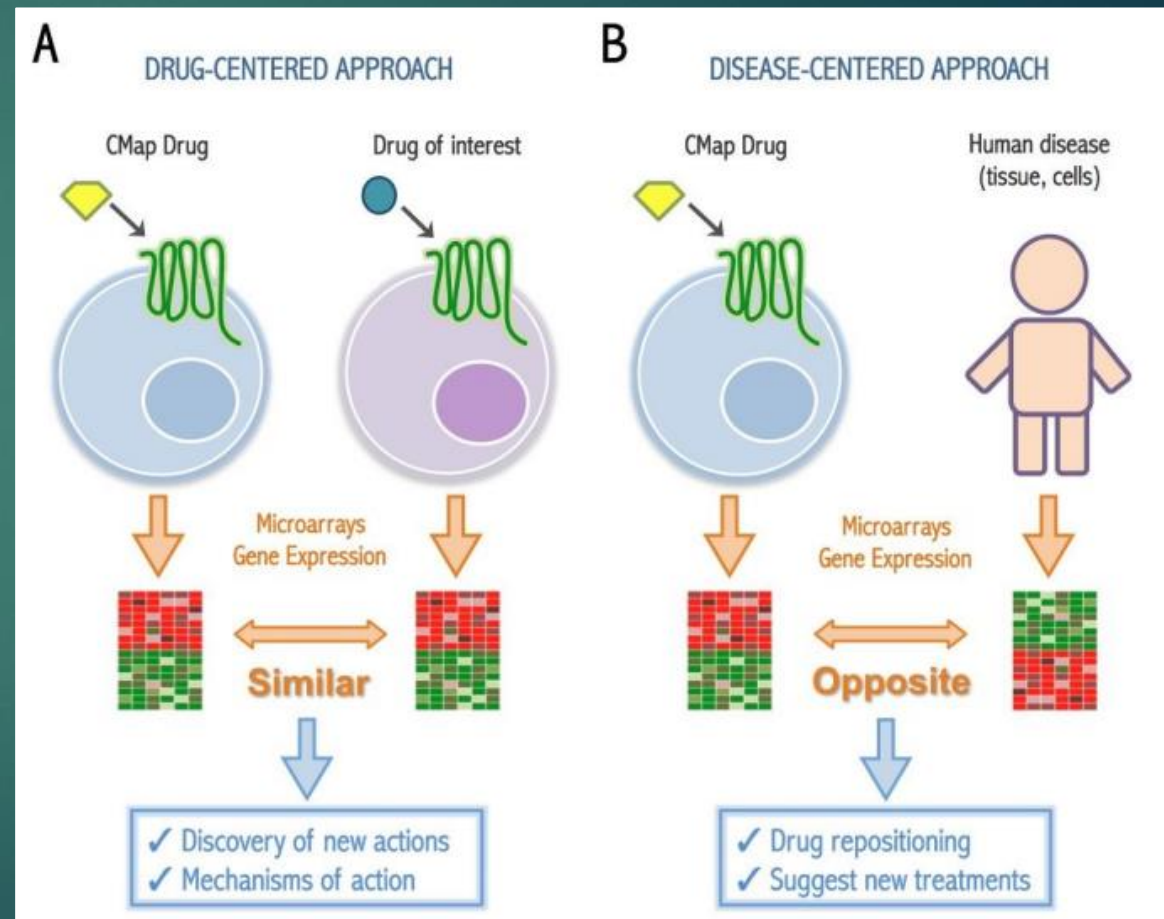
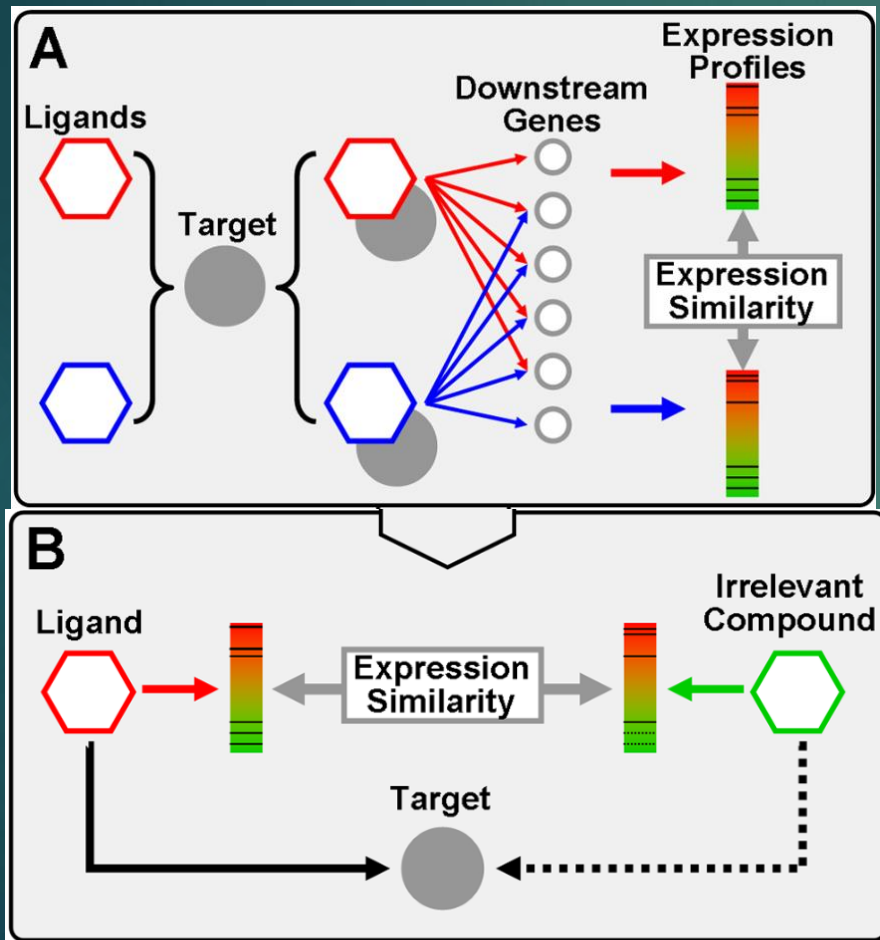


RMSD plot of TcENO backbone (a) and the probed ligands (b) during the MD simulation

Journal of Molecular Graphics Modelling, 2020and



Computational Drug Repositioning strategy Based On Transcriptional Signature



CMap database

The screenshot displays the CLUE CONNECTIONS web interface. The browser address bar shows the URL: `clue.io/connection?url=macchiato.clue.io/builds/touchstone/v1.1/arfs/BRD-A81772229`. The page title is "Connections of reference perturbagens to Index". The index is set to "simvastatin" (HMGCR inhibitor). The "Perturbagen Type" section shows: Compound x 0, Gene Knock-Down x 0, Gene Over-Expression x 2160, and CMap Class x 0. The "Data Lens" section is set to "None". The main content area shows four histograms for OE, KD, and CP. Below the histograms is a search bar and an "Export" button. A table of results is shown below, with columns for Rank, Score, Type, ID, Name, and Description. The table shows results for CDKN1B, MEIS2, AGPAT1, and HMOX2.

CLUE CONNECTIONS

Tools

INDEX: simvastatin

simvastatin
HMGCR inhibitor

Perturbagen Type

- Compound x 0
- Gene Knock-Down x 0
- Gene Over-Expression x 2160
- CMap Class x 0

Data Lens

- Genes with both OE and KD constructs
- None

Perturbagens in which both OE and KD constructs exist for the same gene.

Connections summary

Subset by Perturbagen type

SUMMARY OE KD CP

Version: 1.1.1.2

Search

Export

Viewing: 2,160 / 2,160

Rank	Score	Type	ID	Name	Description
82	84.83	+	5980	CDKN1B	-
83	84.63	+	0998	MEIS2	Homeoboxes / TALE class
84	84.57	+	2467	AGPAT1	1-acylglycerol-3-phosphate O-acyltransferases
85	84.46	+	0759	HMOX2	Haem oxygenase

Chang, *et al.* (2010). Evaluation of phenoxybenzamine in the CFA model of pain following gene expression studies and connectivity mapping. *Mol. Pain* 6:56

Iskar, M., et al. (2013). *Mol. Syst. Biol.* vinburnine, a vasodilator, and sulconazole, a topical antifungal, as interesting cell cycle blockers for cancer therapy

Categories for assessment of drug repositioning

Table 1. Classification of Drug Repurposing Claims According to Scientific Evidence

Drug repositioning evidence level	Quality of scientific evidence
0	No evidence; includes <i>in silico</i> predictions without confirmation
1	<i>In vitro</i> studies with limited value for predicting <i>in vivo</i> /human situation
2	Animal studies with hypothetical relevance in man
3	Incomplete studies in man at the appropriate dose, e.g., proof of concept; very few cases or inference from medical records; some clinical effects observed
4	Well-documented clinical end points observed for the repurposed drug at doses within safety limits

Drug repositioning evidence level	Active pharmaceutical ingredient	Comments
0	Many examples	Quite often, such articles are published in informatics/computational journals without experimental evidence
1	Benzbromarone	Showed <i>in vitro</i> activity as quorum sensing inhibitor; could not be confirmed in animal models ⁹
2	Astemizole	Showed effective activity as radiosensitizer when co-administered to mice with xenograft tumors ⁹
3	Ketorolac	Confirmed <i>in vitro</i> and <i>in vivo</i> activity as Rac1 and Cdc42 GTP-ase inhibitor*; undergoing clinical trial for ovarian cancer ¹⁰
4	Sildenafil	Revatio™ for pulmonary hypertension following i launch as Viagra™ for erectile dysfunction

The END

THANK YOU FOR YOUR ATTENTION

