SIGNIFICANCE OF COMPUTATIONAL TOOLS IN DRUG DISCOVERY

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INTRODUCTION

- Developing a new drug from original idea to the launch of a finished product is a complex process which can take 12–15 years and cost in excess of $1 billion.
- Simply put, approval of a new drug is a massive undertaking and fast turnaround, goes a long way in avoiding missteps and moving your drug program closer to success.
- A drug discovery programme initiates because there is a disease or clinical condition without suitable medical products available and it is this unmet clinical need which is the underlying driving motivation for the project.

ROAD TO NEW DRUGS

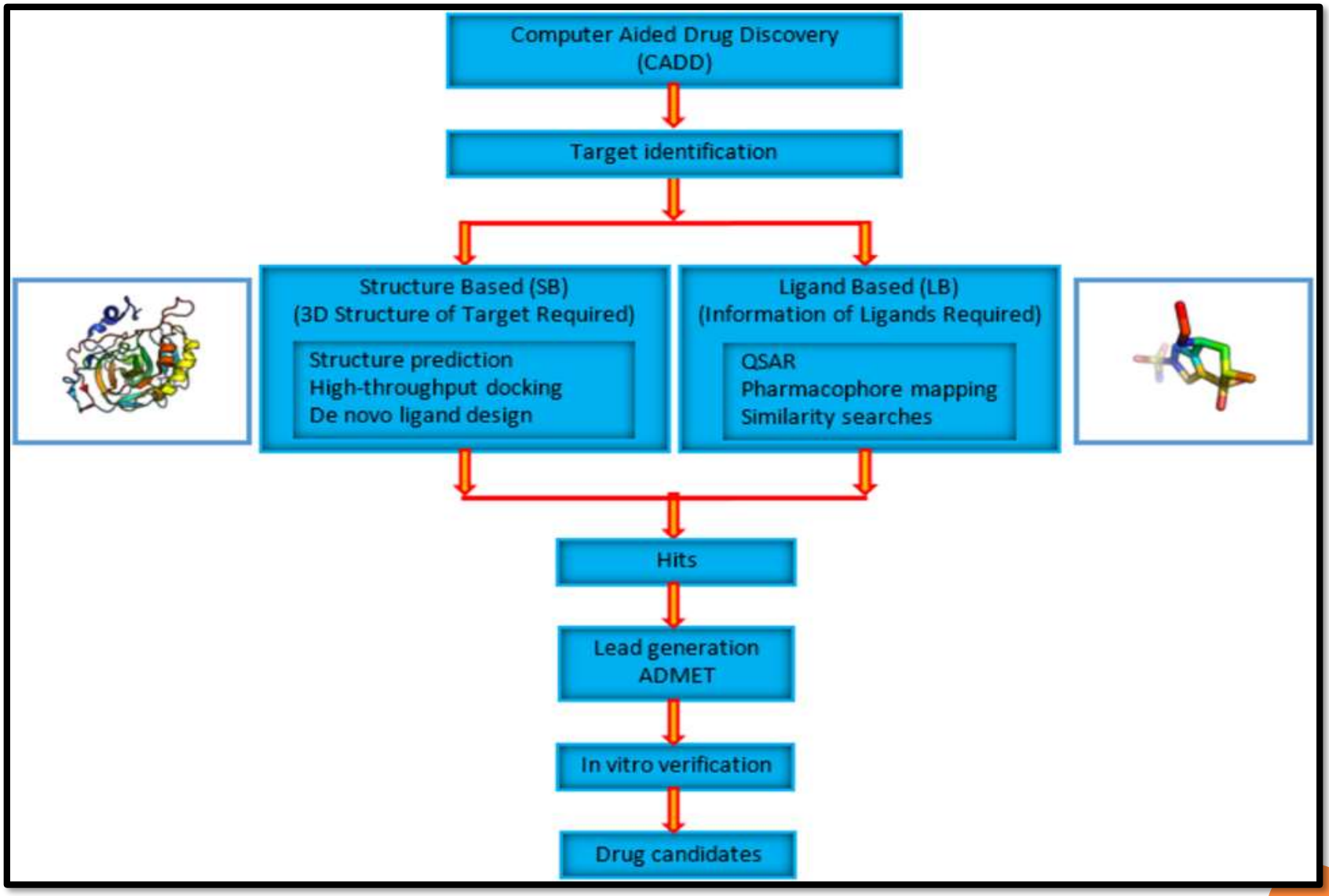
BASIC STUDIES	PRE CLINICAL TRIAL	CLINICAL TRAIL	REGISTRATION
1-4 YEARS	5-6 YEARS	6-12.5 YEARS	12.5-14 YEARS

RESEARCH DEVELOPMENT

COMPUTER AIDED DRUG DESIGN

- Once a target has been identified, there are several *in silico* tools to initiate a drug design process.
- The use of these methods depends on the nature of the target and the available information on the system.
- CADD methods can be broadly classified into two groups, namely structure-based (SB) and ligand-based (LB) drug discovery
- When neither is available, computational methods such as homology modeling may be used to predict the three-dimensional structures of targets.

- CADD is generally helpful in three major aspects:
- 1. Filtering large libraries of compounds into smaller more active sets of compounds.
- 2. Oversee lead optimization of compounds by checking ADMET - Absorption, distribution, metabolism, excretion, potential for toxicity
- 3. Designing new compounds.



Schematic representation of a computer-aided drug discovery (CADD) pipeline

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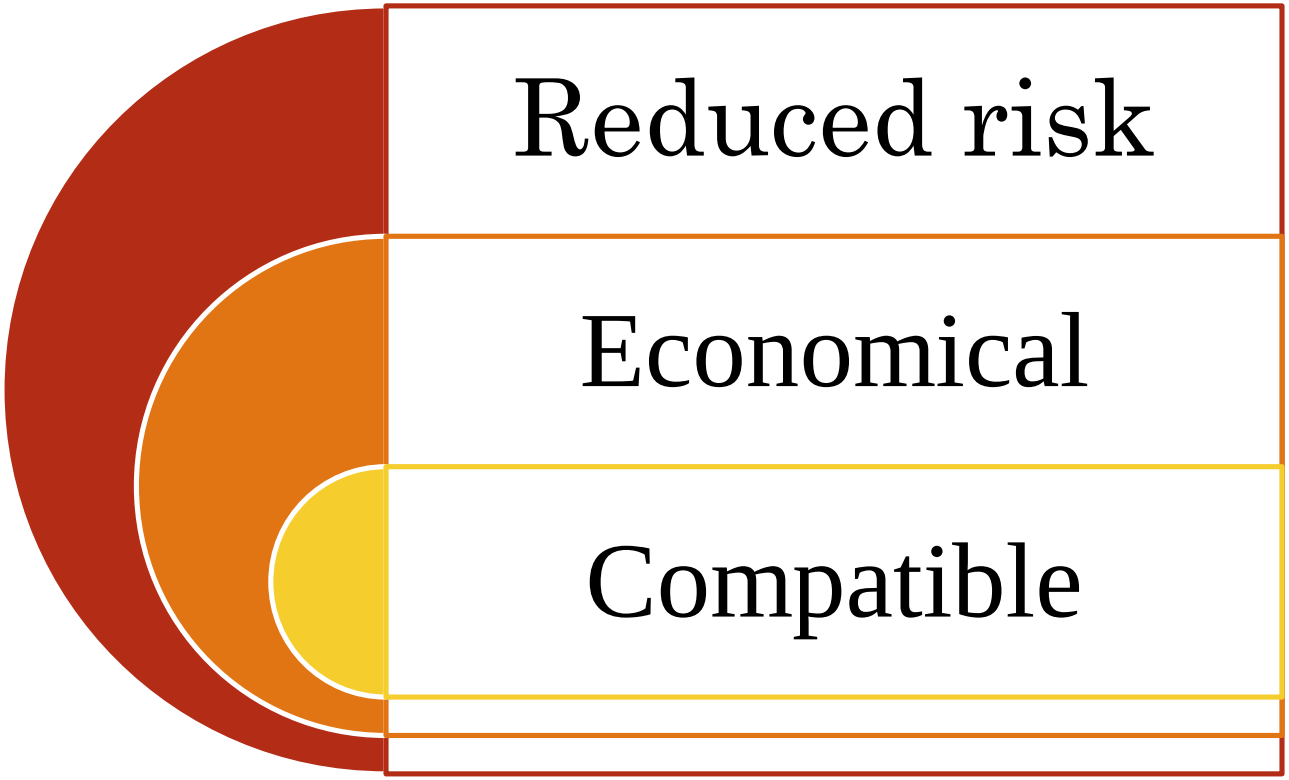
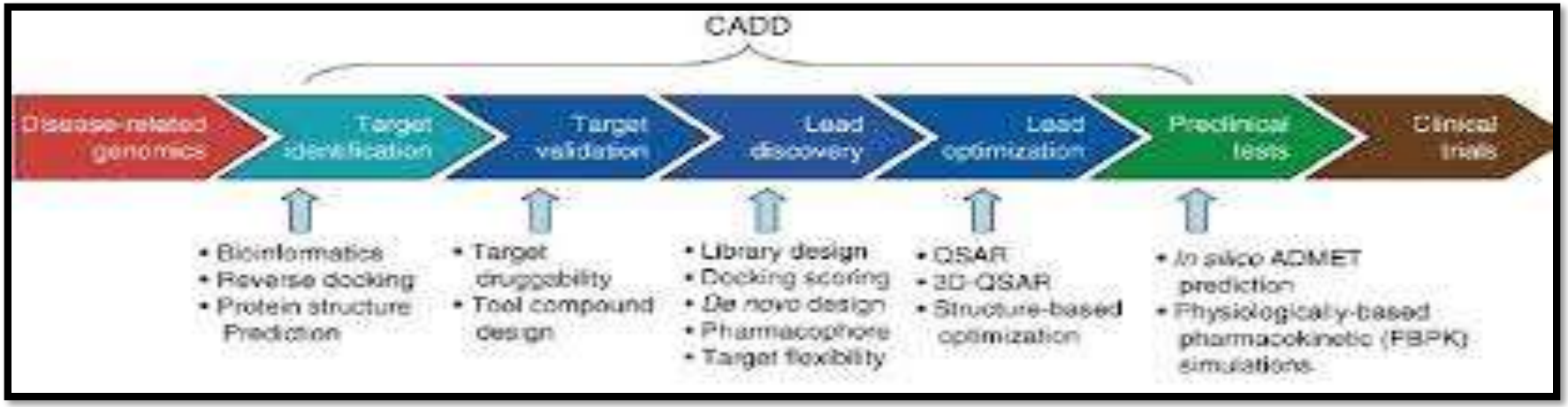


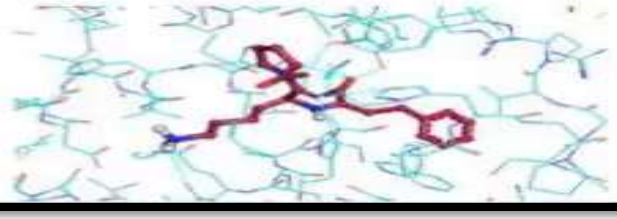


STRUCTURE BASED AND LIGAND BASED DRUG DESIGNING

STRUCTURE BASED

- Don't know ligands
- Know receptor structures

3D structure of receptor



LIGAND BASED

- Don't know receptors
- Know ligands

no 3D structure of receptor

WHY TARGET IDENTIFICATION ????

Drugs fail in the clinic for two main reasons;

- the first is that they do not work and
- the second is that they are not safe.

❖As such, one of the most important steps in developing a new drug is target identification and validation.

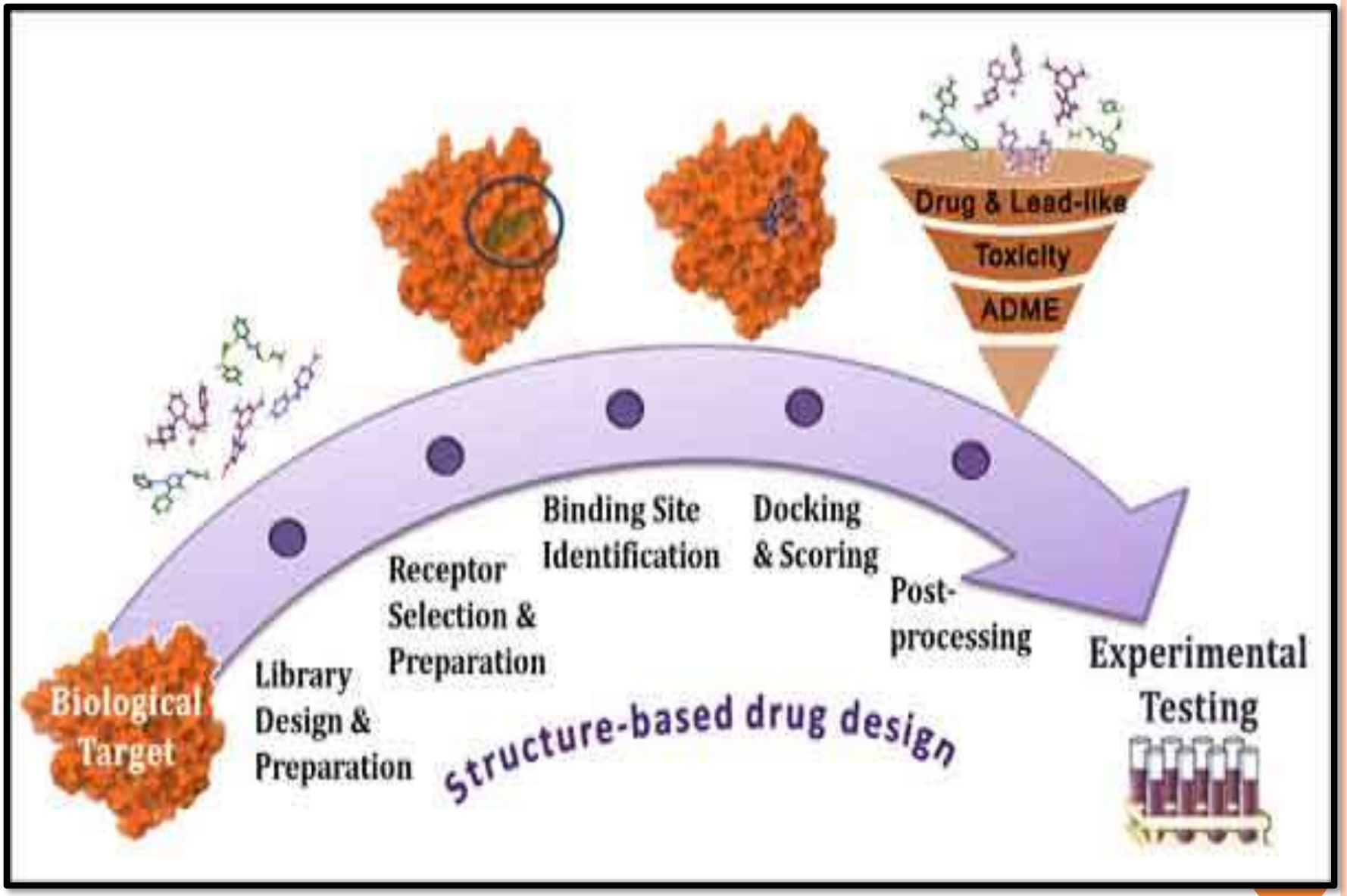
❖Target identification of the known bioactive compounds and novel synthetic analogs is a very important research field in medicinal chemistry, biochemistry, and pharmacology. It is also a challenging and costly step.

❖*In silico* identification of potential biological targets for chemical compounds offers an alternative avenue for the exploration of ligand–target interactions and biochemical mechanisms, as well as for investigation of drug repurposing.

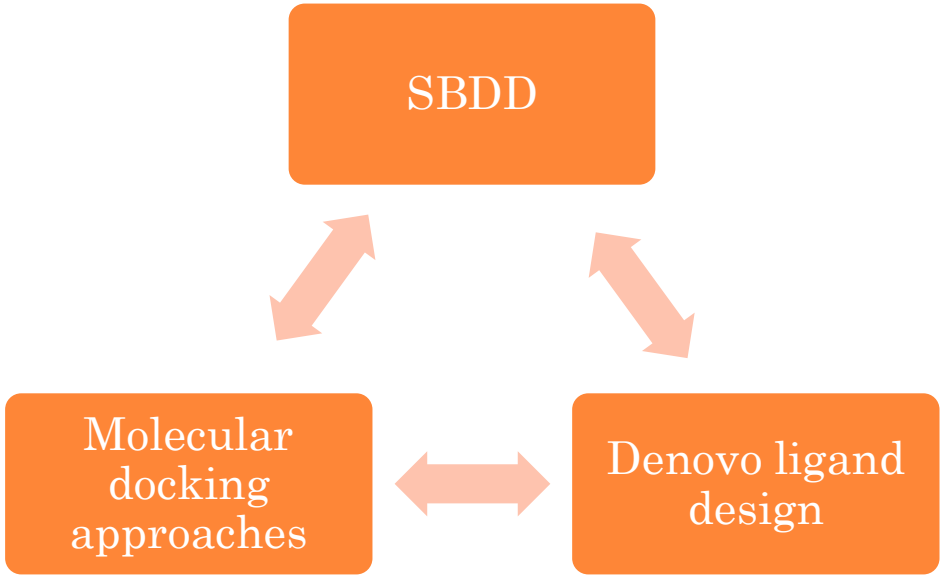
Web-accessible databases for drug target identification.

Utility	Url
Human metabolome data	http://www.hmdb.ca
In silico target identification	http://www.dddc.ac.cn/pdtd/
Pathway analysis	http://www.genome.jp/kegg/
	http://www.geneontology.org
	http://www.reactome.org
	http://www.pantherdb.org
	http://www.biocarta.com
	http://www.ingenuity.com/
Chemogenomic data	http://www.ebi.ac.uk/chembldb
	http://pubchem.ncbi.nlm.nih.gov
Drug target database	http://www.drugbank.ca
Protein data bank	http://www.pdb.org
Disease specific target database	http://thomsonreuters.com/metacore
Pharmacogenomic data	http://www.pharmgkb.org
Multi-level drug data	http://r2d2drug.org/DMC.aspx
Comparative toxicogenomic database	http://ctdbase.org

STRUCTURE BASED DRUG DESIGN

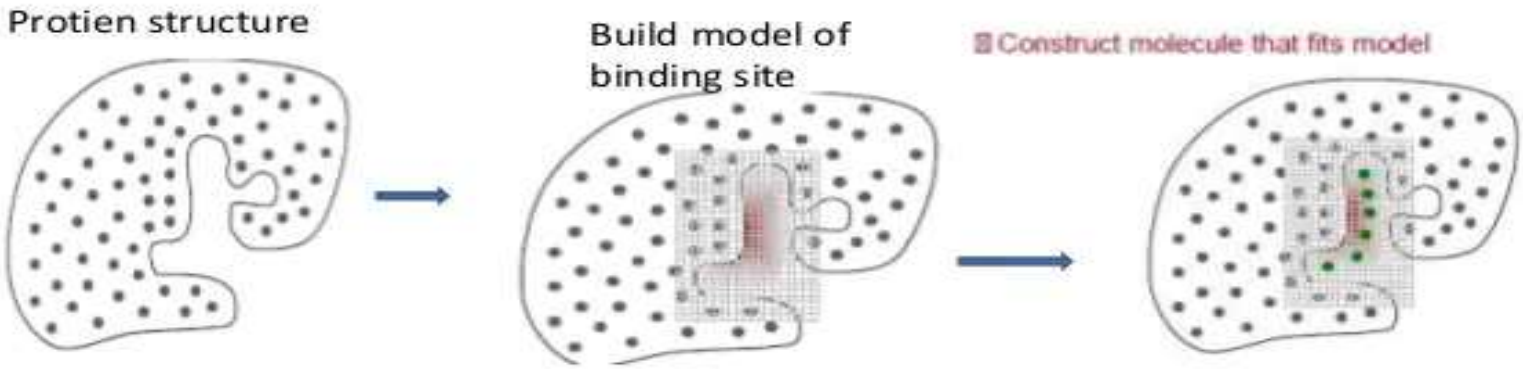

Drug & Lead-like
Toxicity
ADME
Biological Target
Library Design & Preparation
Receptor Selection & Preparation
Binding Site Identification
Docking & Scoring
Post-processing
Experimental Testing
Structure-based drug design

- If the three-dimensional structure of a disease-related drug target is known, the most commonly used CADD techniques are structure-based.



PRINCIPLES OF DENOVO DRUG DESIGN

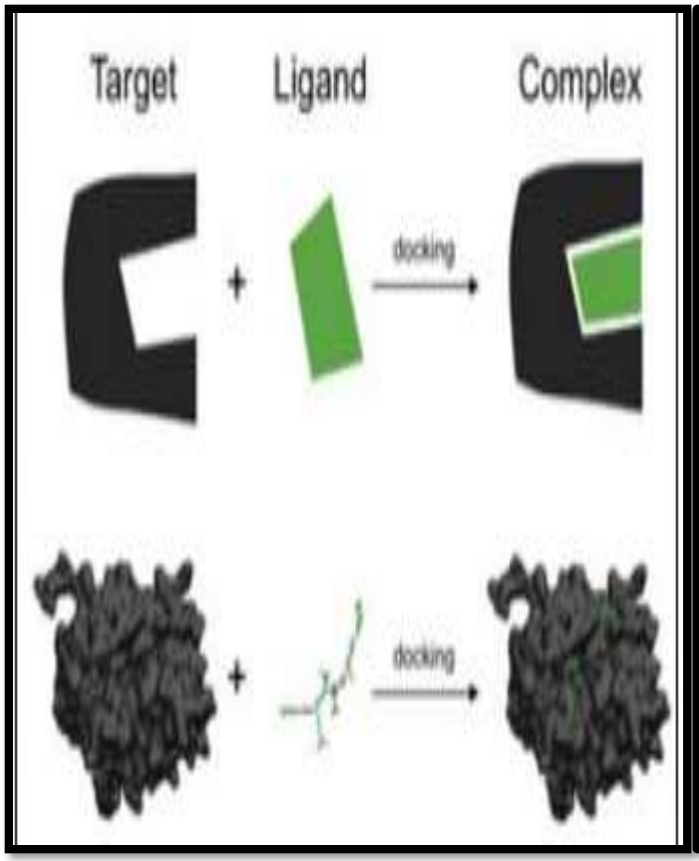
- Assembling possible compounds and evaluating their quality.
- Searching the sample space for novel structures with drug like properties.

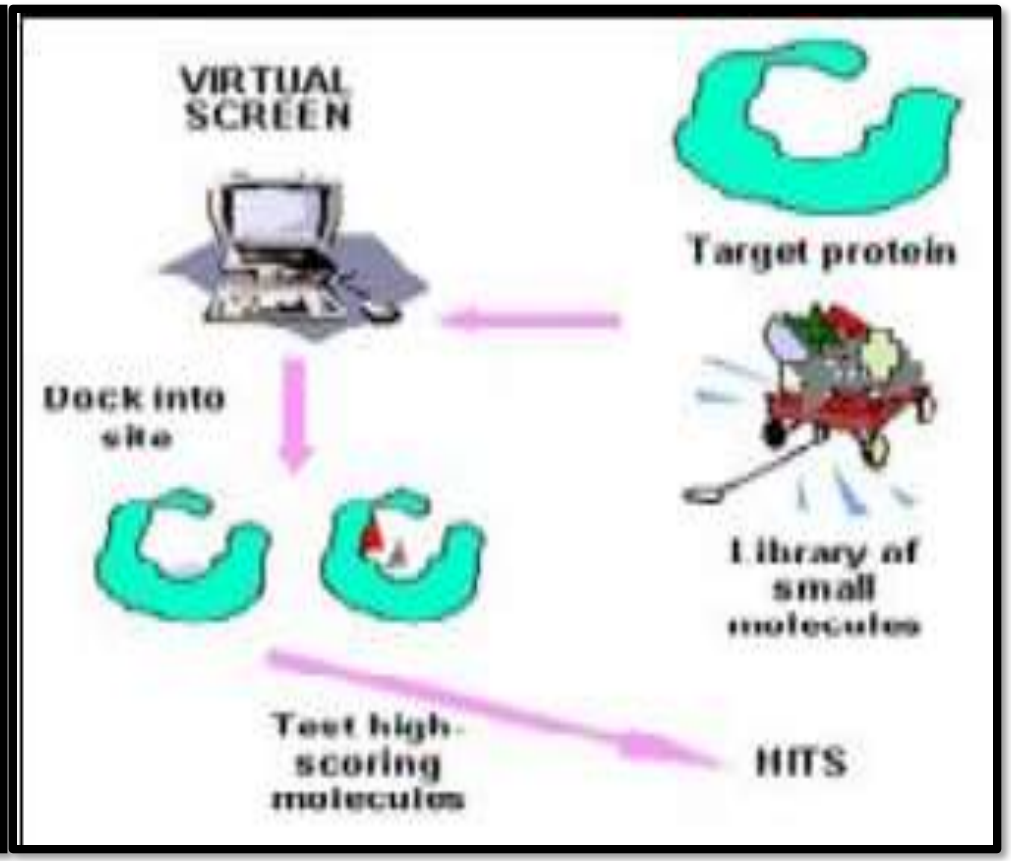


- Molecular dynamics (MD) simulations are frequently used in SBDD to give insights into not only how ligands bind with target proteins but also the pathways of interaction and to account for target flexibility.
- This is especially important when drug targets are membrane proteins where membrane permeability is considered to be important for drugs to be useful
- Successes have been reported for SBDD and it has contributed to many compounds reaching clinical trials and get FDA approvals to go into the market

- In the early 1990s many approved HIV protease inhibitors were developed to target HIV infections using structure-based molecular docking. It was a ground breaking success at that time and made it possible for HIV infected individuals to live longer than they could have without the treatment
- Saquinavir, Amprenavir
- FDA approved Dorzolamide is a carbonic anhydrase II inhibitor which is used in the treatment of glaucoma and was developed using structure-based tools

Illustrations of docking and virtual screening





PROTEIN AND SMALL MOLECULE DATABASES

- PubChem, a small molecule repository is available through NIH which contains millions of biologically relevant small molecules
- ZINC is a virtual high-throughput screening compound library which is a free public resource contains over 35 million molecules that are purchasable and are available in 3D formats. These molecules have all been pre-processed and are ready for docking.
- DrugBank has about 5000 small molecules and more than 3000 of these are experimental drugs . There are over 800 compounds in DrugBank that are FDA approved.
- The Protein Databank (PDB), a global resource that contains a wealth of 3D information about experimentally determined biological macromolecules
- The structures in the PDB are individual macromolecules, protein–DNA/RNA or protein–ligand complexes. Experimental methods used in structure determination are mostly X-ray crystallography and NMR spectros

Protein structure determination

All structure-based methods rely on the three-dimensional target structure and in the cases where the target structure is not possible to be determined by experimental methods, computational methods become useful. Several methods have been used for protein structure prediction including homology modeling

Homology (comparative) Modeling

- In homology modeling, the first task is to find a homologous structure to the sequence of interest. To do that, the sequence is compared against a database of protien. Homology modeling is commonly applied in structure-based drug discovery to predict target structures that are important in diseases.
- Once a homologous protein structure for the sequence has been identified, building the models for the target structure is done using comparative modeling algorithm

PREPROCESSING OF TARGET AND LIGAND

- Target and ligand preparation steps are crucial and are often done before docking is performed to ensure good screening results .
- In experimental methods such as X-ray crystallography the hydrogen atoms of structures are not generally present. However, the presence of these atoms and the locations of these bonds are important for molecule docking algorithms.
- SPORES is one program that is used for the prepossessing of proteins for protein–ligand docking. It can generate different protonated states, tautomeric states and stereoisomers for protein structures .
- LigPrep from the Schrodinger Suite allows to obtain all-atom 3D structures of ligands.

BINDING POCKET IDENTIFICATION AND VOLUME CALCULATION

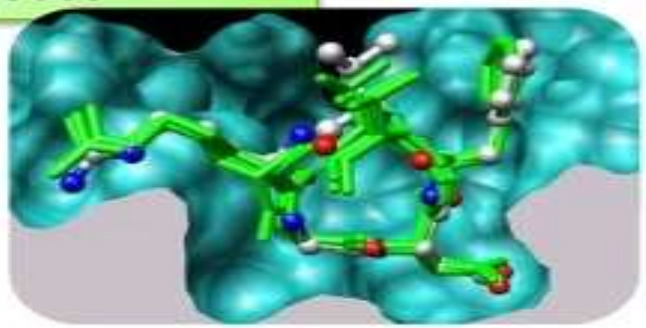
- Once a protein's three-dimensional structure is known, finding binding pockets on that protein is an important next step in structure-based drug discovery.
- It can give indications of where small molecules can bind to target structures, which are associated with diseases, contributing to increase or decrease of target activity.
- Binding sites in target proteins can be experimentally determined; for example using site-directed mutagenesis or X-ray crystallography.
- Binding pocket predicting algorithms can be grouped into two broad categories; geometry-based and energy-based methods.

VIRTUAL HIGH THROUGH PUT SCREENING

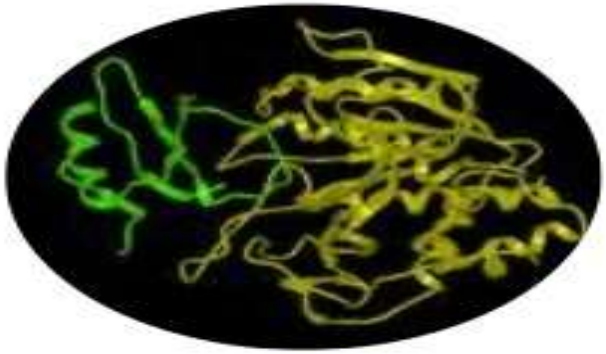
- Virtual high-throughput screening or vHTS is a technique done with the help of computations, in which the *in-silico* compound libraries are screened so that the binding affinity of the target receptors with the library compounds is checked and analyzed.
- A small molecule is virtually screened against a library of protein structures. Predicting receptors to which a synthesized compound may bind would give insights to drug repurposing, metabolism, toxicity, and lead optimization

DOCKING CAN BE BETWEEN....

- Protein - Ligand

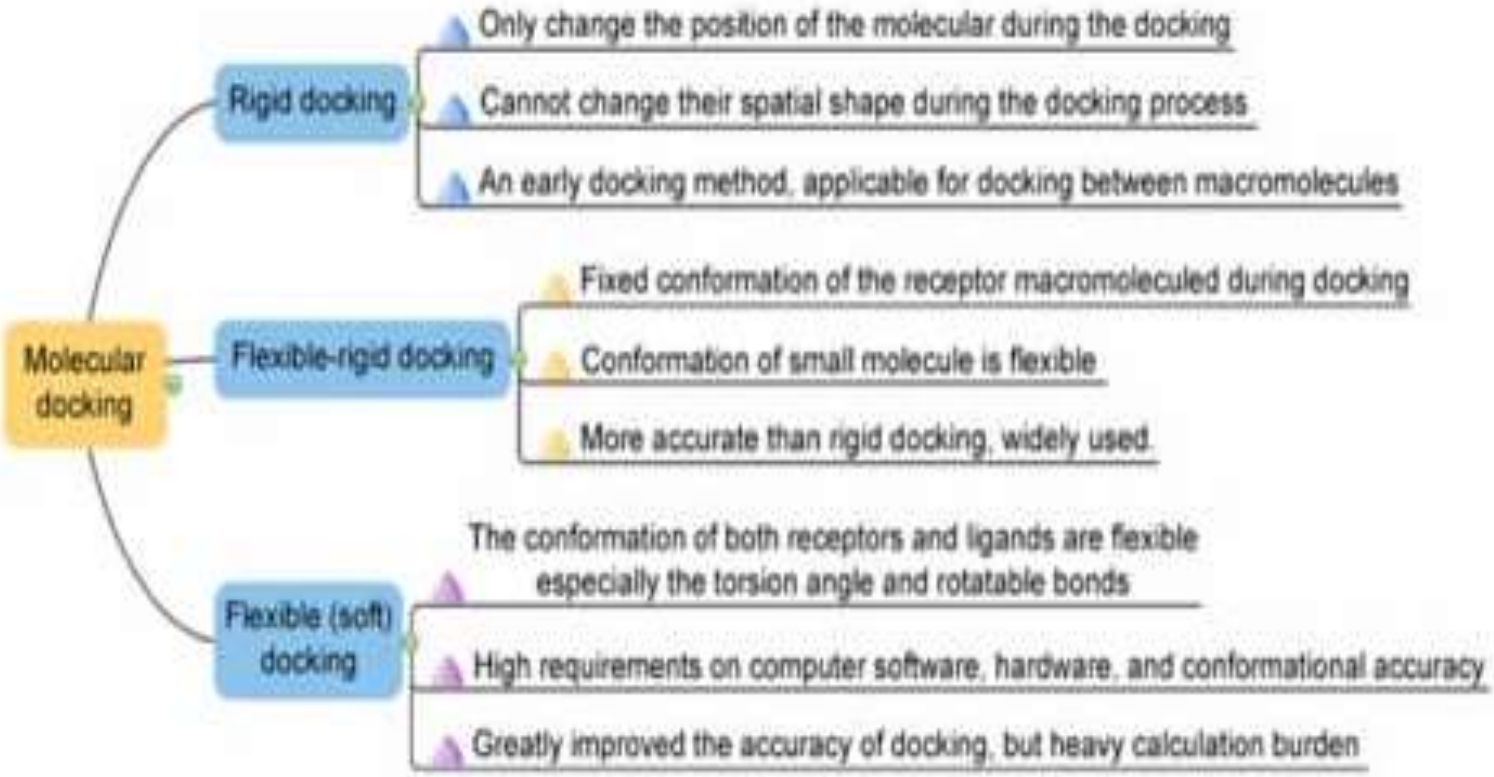


- Protein – Protein



- Protein – Nucleotide

Molecular docking software classification



TARGET FLEXIBILITY IN MOLECULAR DOCKING

- In conventional docking algorithms the target is held rigid while the ligand molecule is generally assumed to be flexible.
- This rigid body docking of ligands to the target is not realistic and can give misleading results because targets are actually able to freely undergo side chain and backbone movements as a result of ligand binding by an induced fit mechanism.
- Two approaches that can be taken to account target flexibility are induced fit docking methods and ensemble-based screening methods.

SCORING FUNCTIONS USED IN DOCKING

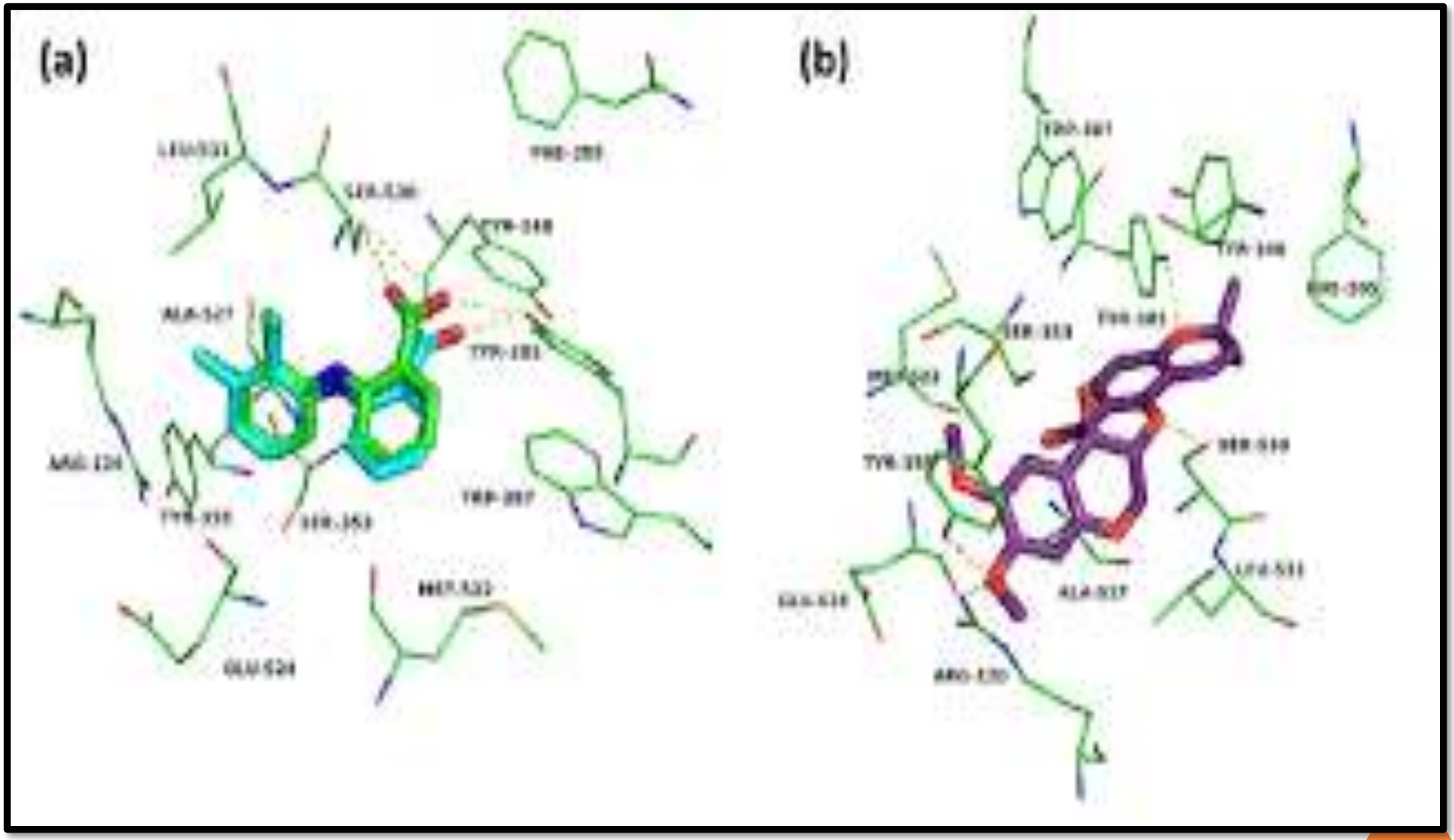
- In molecular docking, how well a drug binds to its target is determined by the binding affinity prediction of the pose. This is done by scoring.
- Scoring is used to evaluate and rank the target–ligand complexes predicted by docking algorithms. Scoring functions are used in SBDD for scoring and evaluating protein–ligand interactions.
- Docking method scoring functions use evaluation criteria such as binding pose, binding affinity
- Empirical scoring functions are obtained by using data from experimentally determined structures and fitting this information to parameters.

PROTEIN–LIGAND DOCKING ALGORITHMS

❖In docking, predictions are made on how intermolecular complexes are formed between a target and a ligand.

❖These algorithms search for the best target–ligand poses with the right conformational state and relative orientation. The algorithms also crudely estimate the binding affinities of the target–ligand complexes in terms of scoring.

❖Docking algorithms require a target protein structure and a library of small molecules. Popular molecular docking programs include Glide, Fred , AutoDock3, Auto Dock Vina , GOLD and FlexX.


(a)
(b)

LEAD OPTIMISATION AND ASSESSMENT OF ADME AND DRUG SAFETY

When hits are obtained for a target structure by screening small molecule databases, the next step usually is lead optimization.

During lead optimization, the effectiveness of promising hits obtained is generally enhanced while at the same time obtaining the desired pharmacological profiles to reach the required affinity, pharmacokinetic properties, drug safety, and ADME (absorption, distribution, metabolism, and excretion/elimination) properties.

By increasing the affinity of a drug to the target its potency (efficacy) can be increased.

QikProp is an ADME program

- VolSurfFAF-Drugs2 is an ADME and toxicity filtering tool that can calculate physicochemical properties, toxic and unstable groups, and key functional components
- Computational ADME methods have advanced greatly in the last few decades and pharmaceutical companies are showing great interest in this area

LIGAND-BASED DRUG DESIGN (LBDD)

- The main alternative to SBDD is LBDD.
- In the case where the potential drug target structure is unknown and predicting this structure using methods such as homology modeling or ab initio structure prediction is challenging or undesirable, the alternative protocol to use is Ligand-based drug design
- Importantly, however, this method relies on the knowledge of small molecules that bind to the target of interest. Pharmacophore modeling, molecular similarity approaches and QSAR (quantitative structure–activity relationship) modeling are some popular LBDD approaches .

PHARMACOPHORE MODELLING

- A pharmacophore is a molecular framework that defines the essential features responsible for the biological activity of a compound. When structural information about the drug target is limited or not known, pharmacophore models may be built using the structural characteristics of active ligands that bind to the target
- When 3D information of the target structure is known this binding site information can also be used in generating pharmacophore models .
- Pharmacophore modelling is a useful technique which classifies a group of ligands or molecules into active or inactive compounds. It is extensively used to identify new compounds when compared to drug targets
- There are programs developed to identify and generate pharmacophore models such as DISCO, GASP and Catalyst.

- There are two main methods for the identification of pharmacophores.
- On one hand, if the target structure is available, the possible pharmacophore structure can be inferred by analyzing the action mode of receptor and drug molecule.
- On the other hand, when the structure of the target is unknown or the action mechanism is still unclear, a series of compounds will be studied for pharmacophores, and information on some groups that play a key role in the activity of compound is considered.

❖In spite of extensive effort by industry and academia to develop new drugs, there are still several diseases that are in need of therapeutic agents and have yet to be developed.

❖10 years the identification rate of disease-associated targets has been higher than the therapeutics identification rate.

❖ Nevertheless, it is apparent that computational tools provide high hopes that many of the diseases under investigation can be brought under control.


Thank You!