MOLECULAR MODELLING AND DRUG DESIGNING

Outline of the Seminar

- Drug
- Drug Discovery and Development
- What is CADD
- Computer-Aided Drug Design Approaches
- What is Molecular Docking
- Applications of Molecular Docking in Drug designing
- Success stories in Molecular Docking
- Conclusion

What is drug ??

- The term "**drug**" means [any] particles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals
- A **drug** is any chemical or biological substance, synthetic or non-synthetic

Sources of drugs

Animal	insulin (pig, cow)
	growth hormone (man) (Creutzfeldt-Jakob)
Plant	digitalis (digitalis purpurea - foxglove)
	morphine (papaver somniferum)
Inorganic	arsenic mercury
	lithium
Synthetic	chemical (propranolol)
	biological (penicillin)
	biotechnology (human insulin)

Drug Discovery and Development

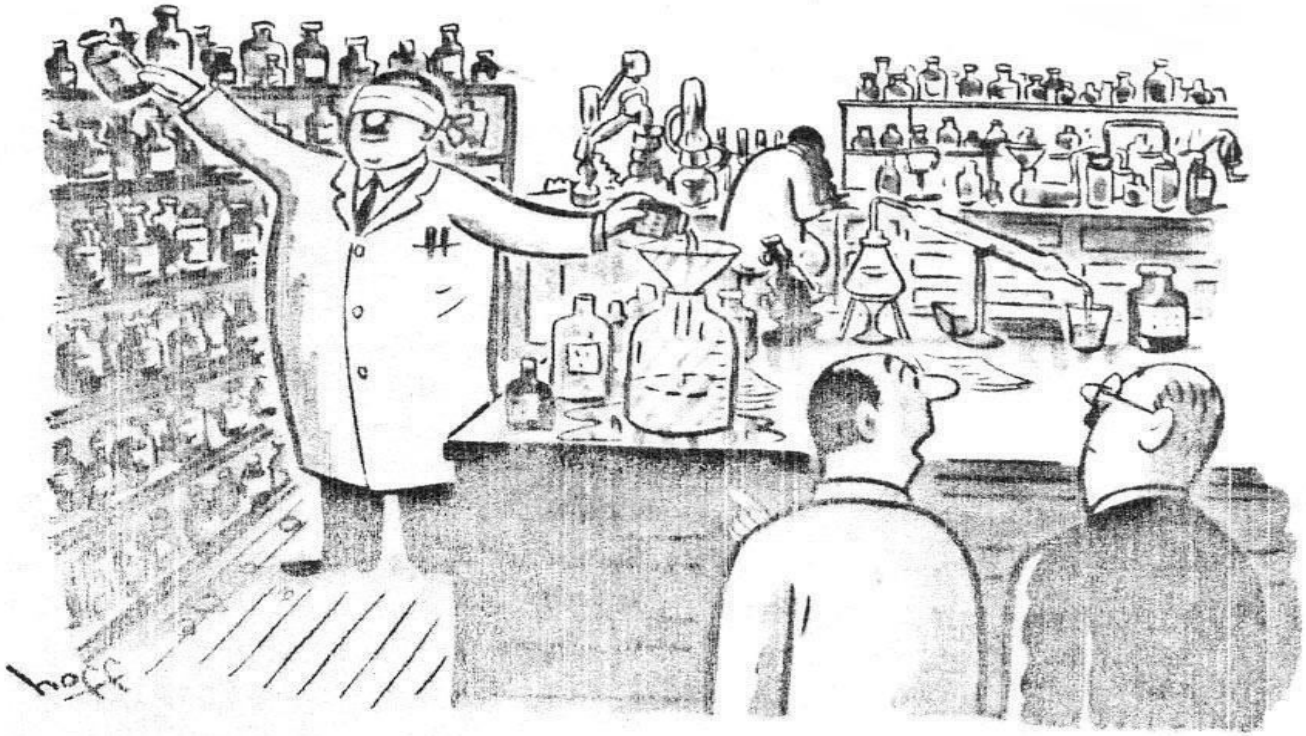
How are drugs discovered and developed?

New drugs

- Occasional new drugs found by accident (Serendipity).
- More frequently they are developed as part of an organized effort to discover new ways to treat specific disease.

Drug Discovery

One way to “discover” drugs



‘That’s Dr Arnold Moore. He’s conducting an experiment to test the theory that most great scientific discoveries were hit on by accident.’

Drawing by Hoff ; © 1957
The New Yorker Magazine, Inc.

Richard.B.Silverman

Drug discovery by serendipity

- 1928 Fleming studied Staph, but contamination of plates with airborne mold. Noticed bacteria were lysed in the area of mold. A mold product inhibited the growth of bacteria: the antibiotic penicillin.
- Development of propanolol (β-blocking) have unexpected give a benefit of discover Practolol.
  Propanolol is a β-blocker but it is a lipophilic drug and can enter CNS and cause side effect, by introducing hydrophilic amide group inhibit passage the blood-brain barrier and Practolol produced more selective cardioselective β1 inhibitor with fewer side effects on CNS.
- Sulfonamides and tolbutamide

Drug discovery by serendipity

- Workers in TNT factories always complained from headache due to dilatation of brain blood vessels. TNT was the basis to prepare nitro derivatives which were used in angina to dilate coronary blood vessels and alleviate pain.

- Mustard gas tanks used in second world war exploded in italian harbor. They discovered that persons who survived and inhaled this gas lost their defense against microorganisms due to destruction of white blood cells.

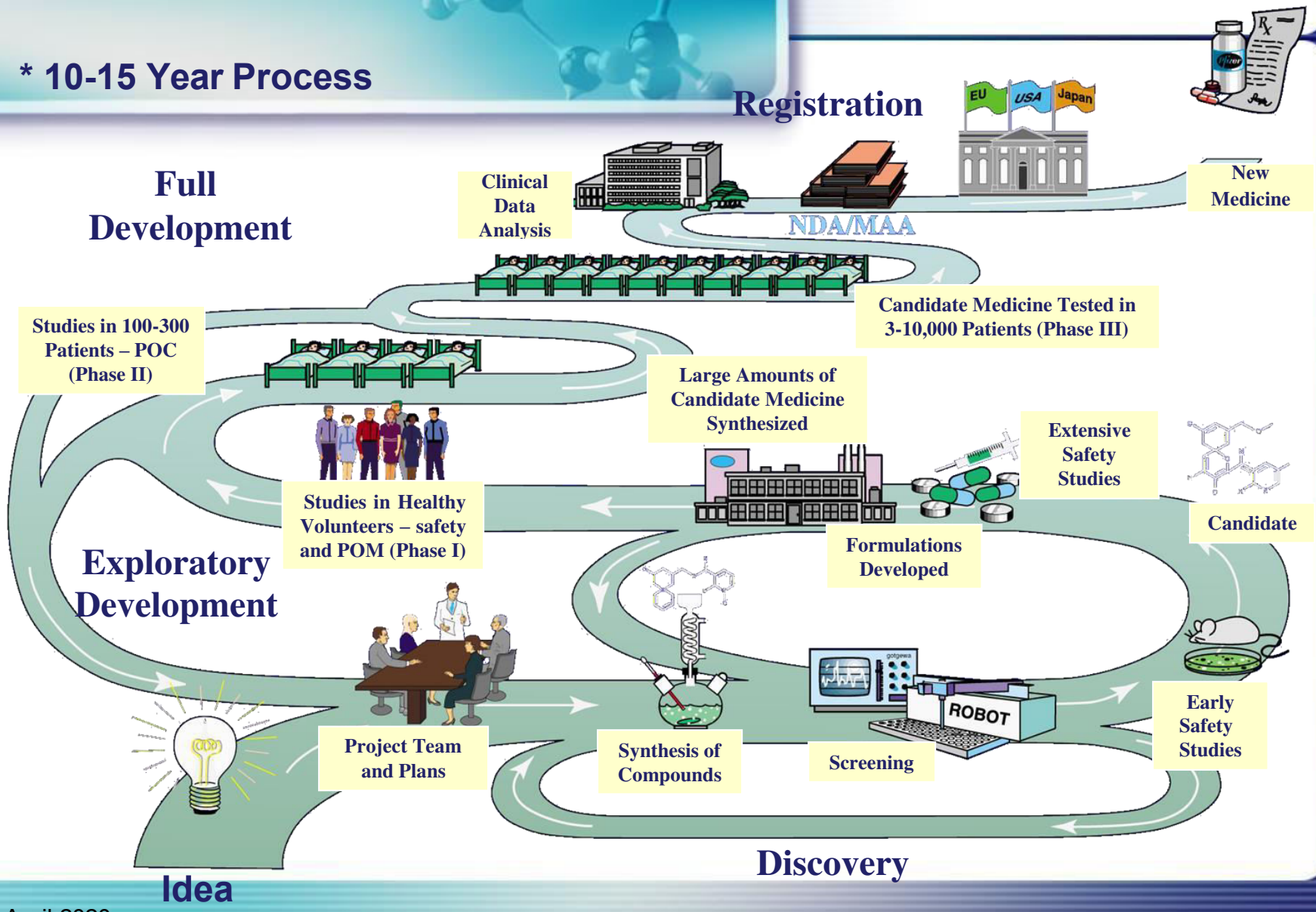
  This led to the discovery of mustard like drugs which were used in leukemia to inhibit excessive proliferation of white blood cells.

Drug discovery by serendipity

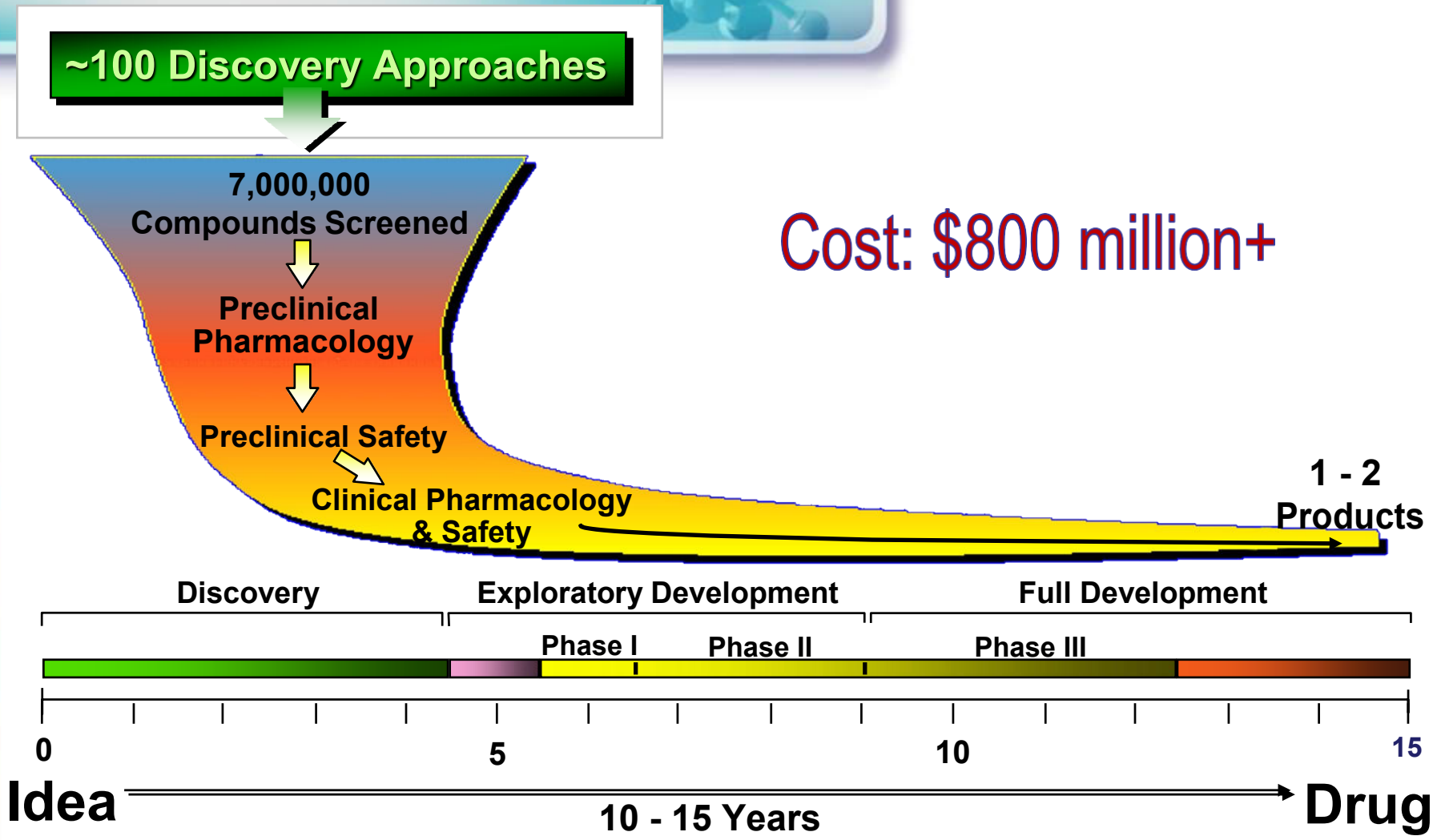
- Acetylsalicylic acid was thought to be just a better tolerable prodrug of salicylic acid, but turned out to have a unique mechanism.
- Phenolphthalein was considered as a useful dye for cheap wines; after a heroic self-experiment, a pharmacologist experienced its drastic diarrhoic activity.
- Warfarin was used a rat poison.

The Long Road to a New Medicine

* 10-15 Year Process



Involves high cost and time



Drug Discovery approaches

- Serendipity (luck)
- Screening
- Chemical Modification
- Rational drug design

Random Screening

Screen a large number of synthetic chemical compounds or natural products for desired effect.

Although this approach for the development of new drugs has been successful in the past, it is not ideal for a number of reasons.

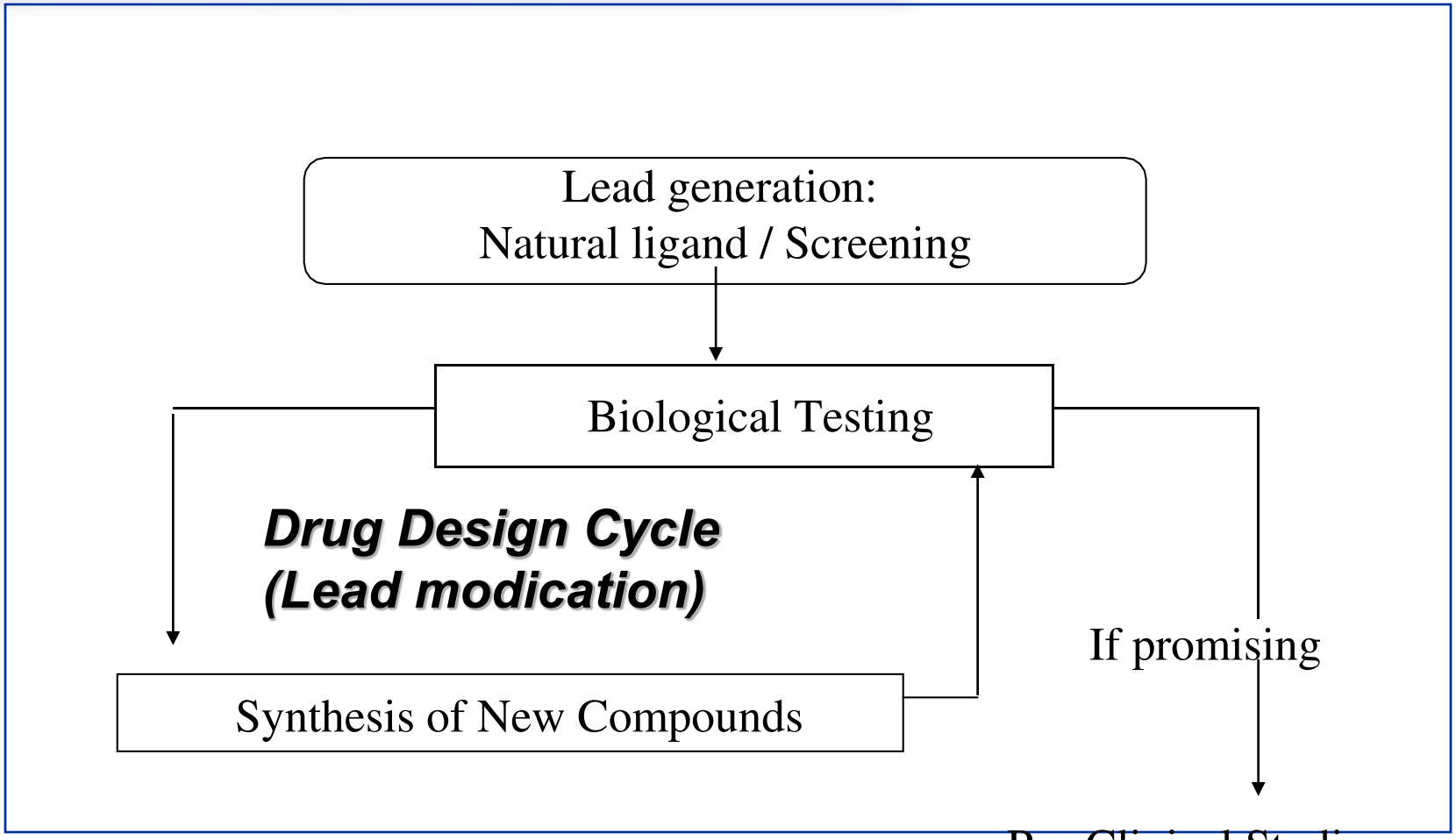
It is inherently repetitious and time consuming.

It is Trial & error approach

One does not need to know the structure of the drug nor the structure of the target upon which the drug will act.

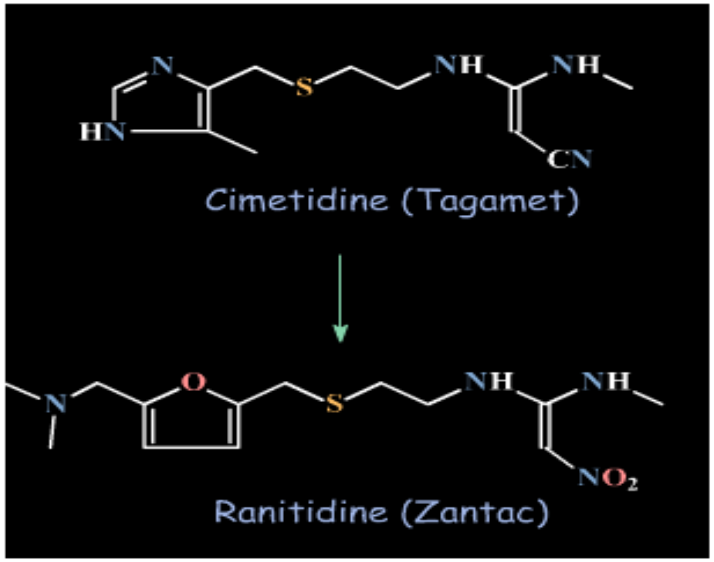
One does not need to know about the underlying mechanism of the disease process itself.

Chemical modification



Chemical Modification

Traditional method. An analog of a known, active compound is synthesized with a minor modification, that will lead to improved biological activity.



Advantage and Limitation: you end up with something very similar to what you start with.

MECHANISM BASED DRUG-DESIGN

Most rational approach employed today.

Disease process is understood at molecular level & targets are well defined.

Drug can then be designed to effectively bind these targets & disrupt the disease process

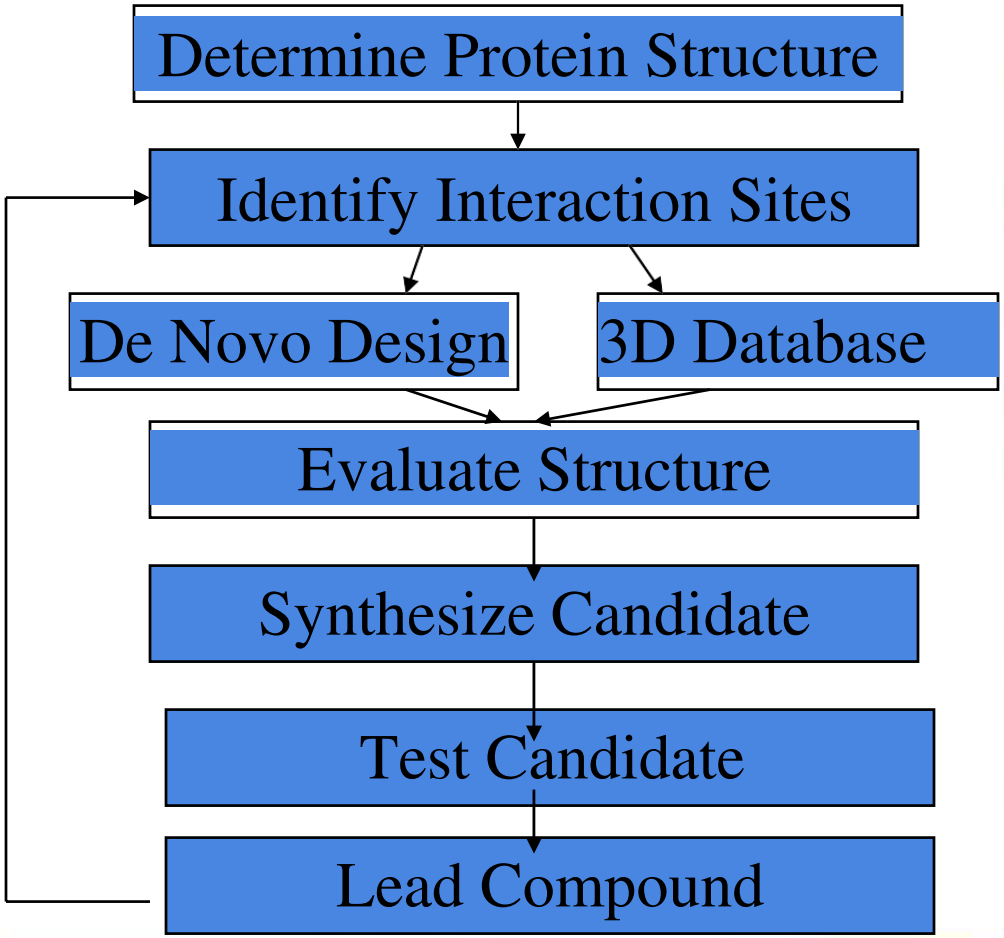
Very complex & intellectual approach & therefore requires detailed knowledge & information retrieval. (CADD Holds Great Future)

Methodologies and strategies of CADD:

- **Structure based drug design (SBDD) "DIRECT DESIGN"**
  - **Followed when the spatial structure of the target is known.**
- **Ligand based drug design (LBDD) "INDIRECT DESIGN"**
  - **Followed when the structure of the target is unknown.**

Structure Based Drug Design

Discovery or design of molecules that interact with biochemical targets of known 3D structure



Molecular modeling

The term “Molecular modeling” expanded over the last decades from a tool **to visualize three-dimensional** structures and **to simulate , predict and analyze the** properties and the behavior of the molecules on an atomic level to data mining and platform **to organize** many compounds and their properties into database and to perform virtual drug screening via 3D database screening for novel drug compounds .

Molecular mechanics

Molecular mechanics refers to the use of classical mechanics to model the geometry and motions of molecules.

 Molecular mechanics methods are based on the following principles:

1) Nuclei and electrons are lumped into atom-like particles.

2) Atom-like particles are spherical and have a net charge.

3) Interactions are based on springs and classical potentials.

4) Interactions must be preassigned to specific sets of atoms.

5) Interactions determine the spatial distribution of atom-like particles and their energies.

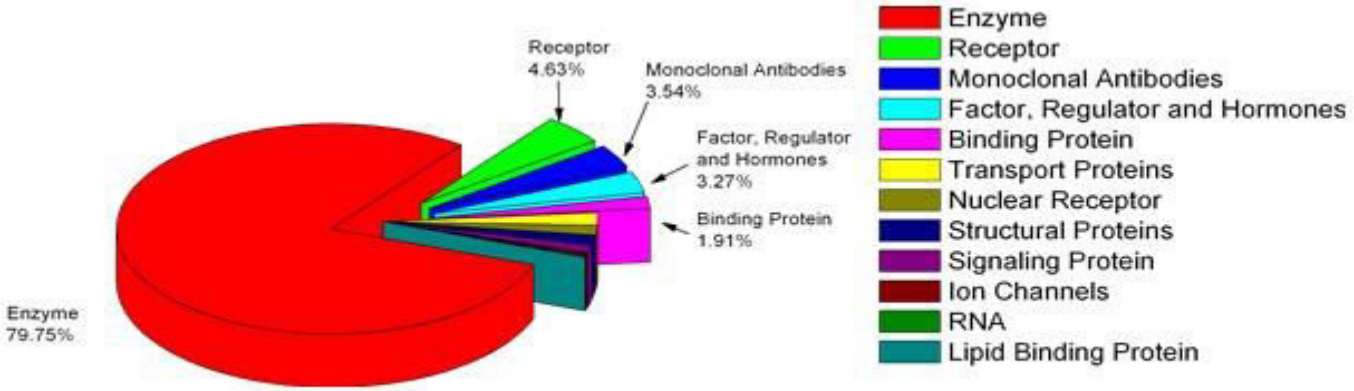
Structure-based library screening

What do we need:

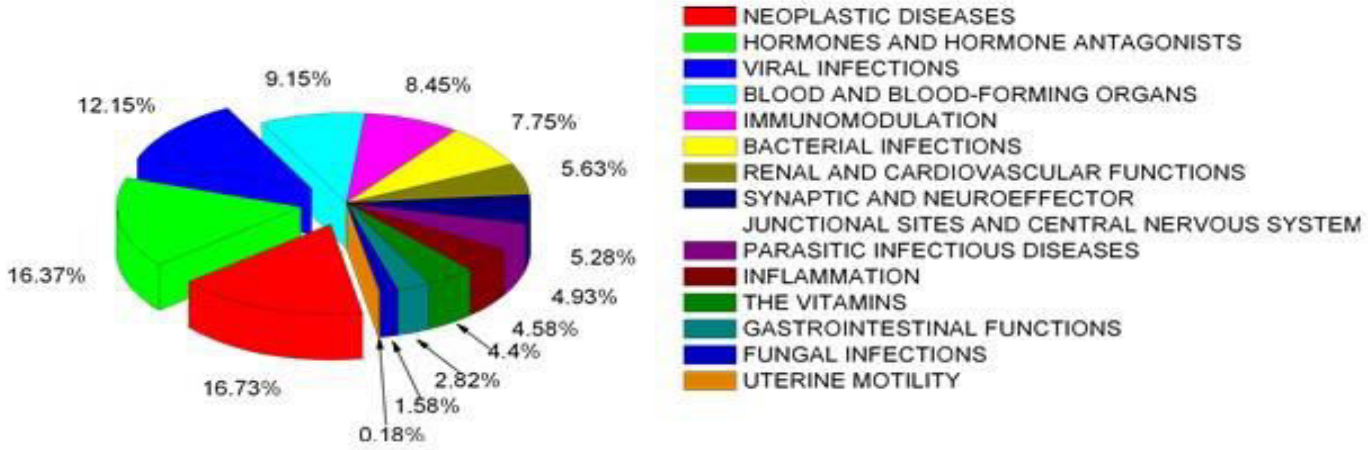
1) Compounds libraries
2) Protein target
3) Binding site in the protein
4) Docking: generate different (many) possible conformations of the compounds in the binding site
5) Scoring: evaluate the strength of the protein/ligand interactions (score).
6) Select preferred ligands to propose a list of prioritized compounds for experimental screening.

Drug Targets

Molecule or structure within the organism linked to a particular disease, whose activity can be modified by a drug.

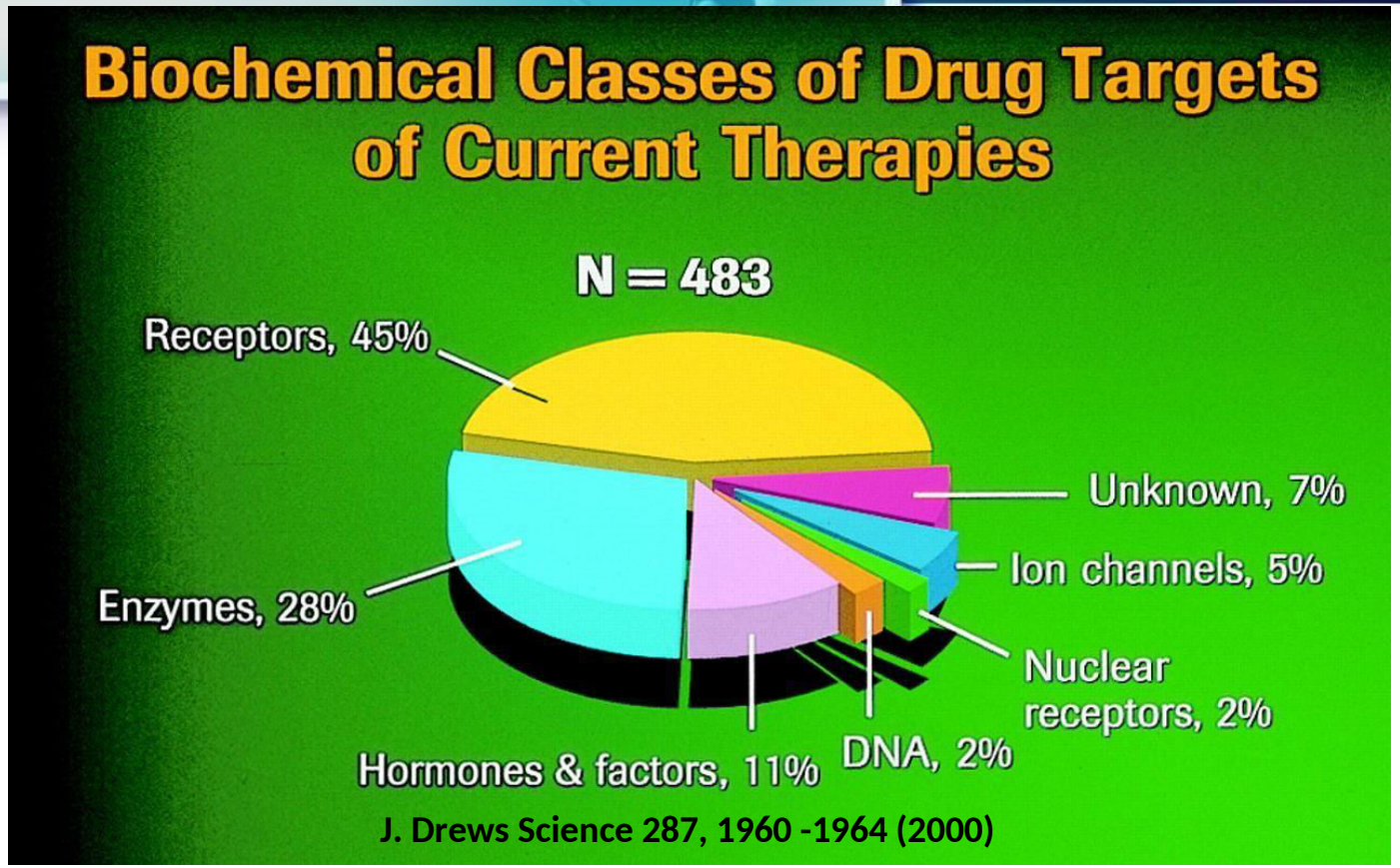


Distribution of targets by biochemical criteria



Distribution of targets in therapeutic areas

Currently used drug targets

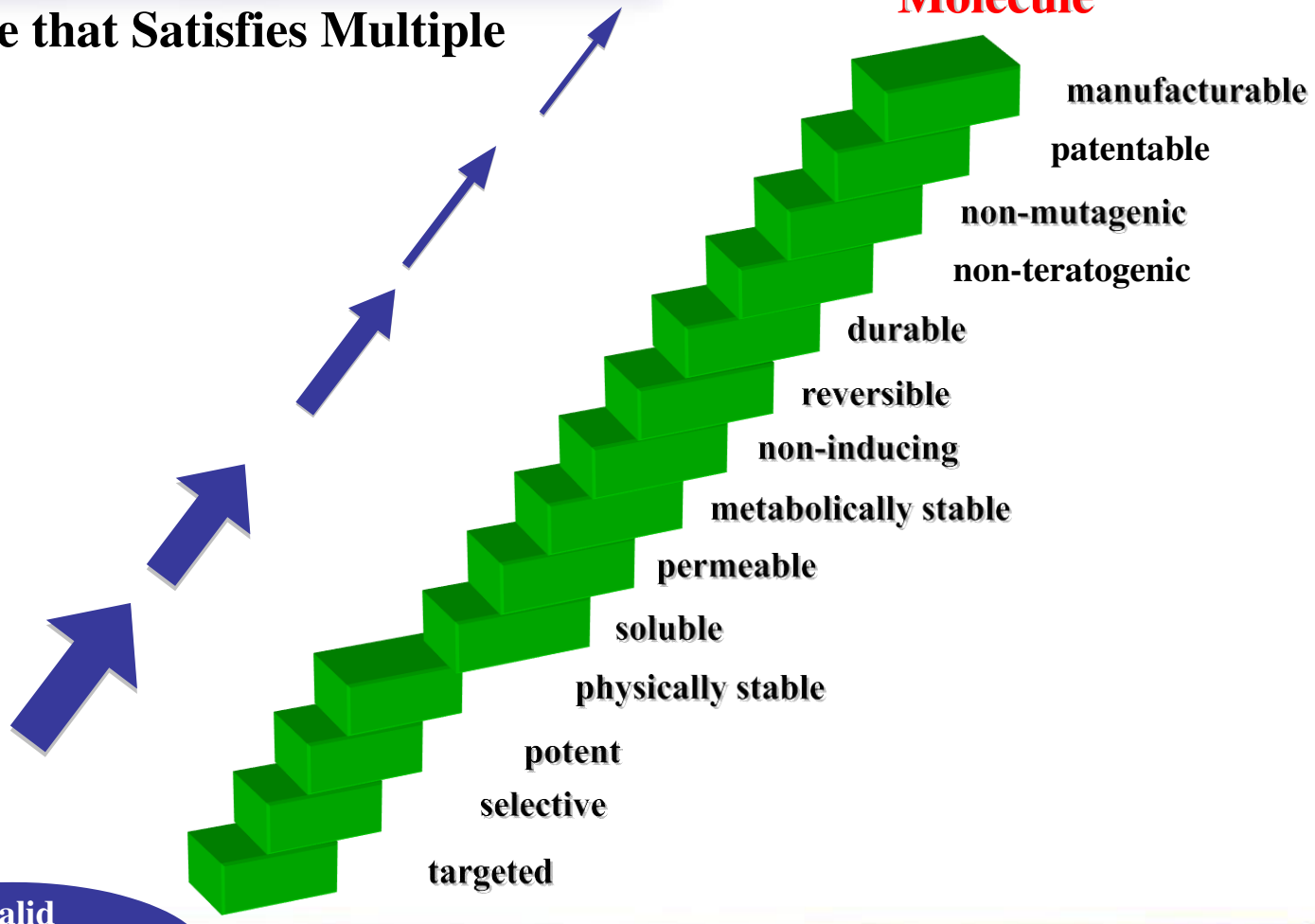


Why are new drugs needed?

- **unmet medical need**; new diseases (Corona Virus, Swine flu; AIDS, Alzheimer's; obesity); low efficacy (dementia, cancer); side effects (antidepressants, antipsychotics)
- **downstream health costs**; (Alzheimer's; spinal injury)
- **cost of therapy**; (Interleukins)
- **sustain industrial activity**; pharmaceutical industry employs thousands and makes a massive contribution to overseas earnings); *patent expiry*
- **Drug resistance**:

Complexity of Drug Discovery

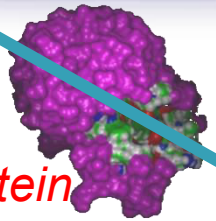
Finding a Molecule that Satisfies Multiple Criteria



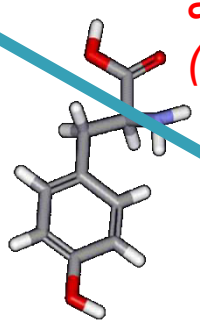
Valid Biomedical Hypothesis?

Drug Discovery & Development

Identify disease



Isolate protein involved in disease (2-5 years)



Find a drug effective against disease protein (2-5 years)

Preclinical testing (1-3 years)

Scale-up

File IND

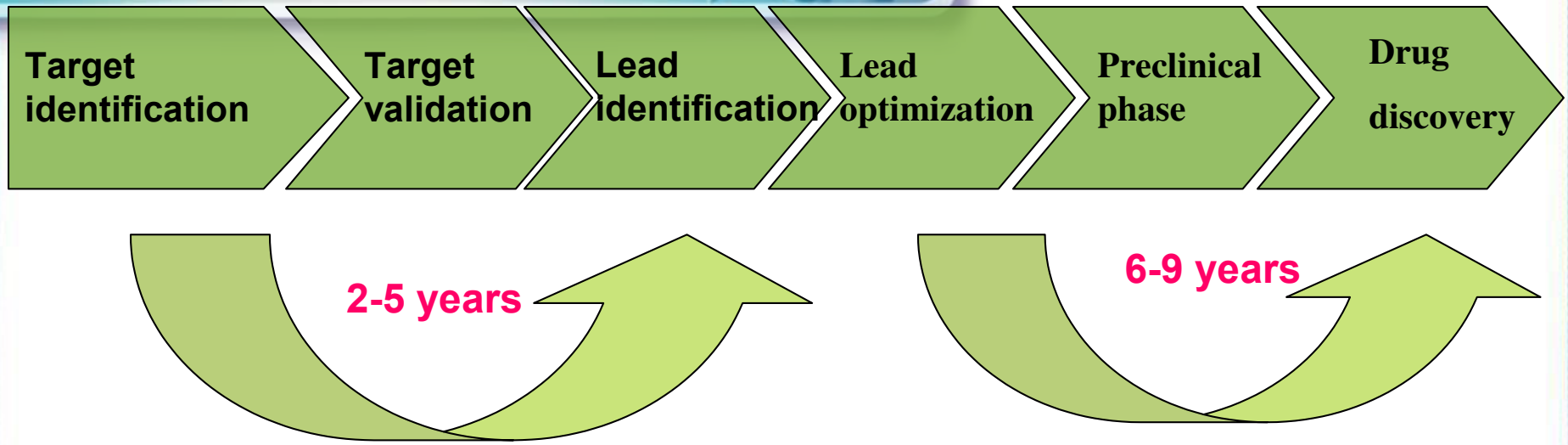
Human clinical trials (2-10 years)

File NDA

Formulation

FDA approval (2-3 years)

Modern drug discovery process



- Drug discovery is an expensive process involving high R & D cost and extensive clinical testing
- A typical development time is estimated to be 10-25 years.
- Costs an average of 1000 to 1500 million U.S. dollars per drug

Technology is impacting this process

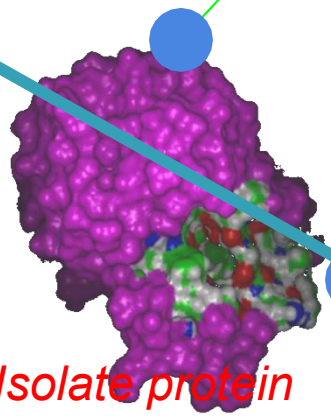
Identify disease

GENOMICS, PROTEOMICS & BIOPHARM.

Potentially producing many more targets and "personalized" targets

HIGH THROUGHPUT SCREENING

Screening up to 100,000 compounds a day for activity against a target protein



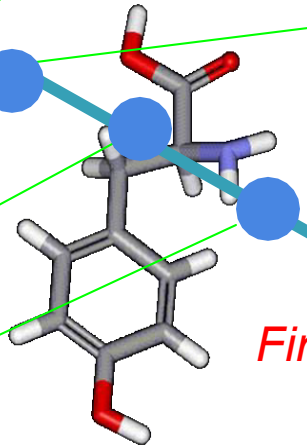
Isolate protein

VIRTUAL SCREENING

Using a computer to predict activity

COMBINATORIAL CHEMISTRY

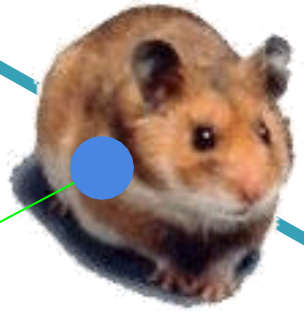
Rapidly producing vast numbers of compounds



Find drug

MOLECULAR MODELING

Computer graphics & models help improve activity



Preclinical testing

IN VITRO & IN SILICO ADME MODELS

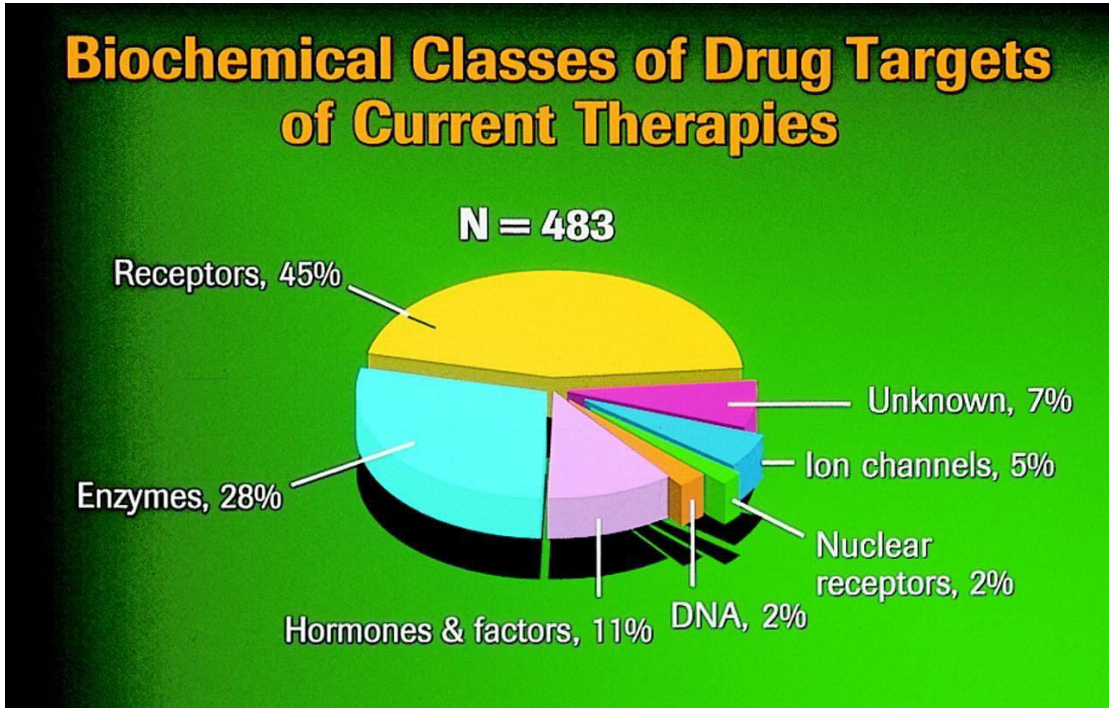
Tissue and computer models begin to replace animal testing

Drug discovery technologies

- Target identification
  - Genomics, gene expression profiling and proteomics
- Target Validation
  - Gene knock-out, inhibition assay
- Lead Identification
  - High throughput screening, fragment based screening, combinatorial libraries
- Lead Optimization
  - Medicinal chemistry driven optimization, X-ray crystallography, QSAR, ADME profiling (bioavailability)
- Pre Clinical Phase
  - Pharmacodynamics (PD), Pharmacokinetics (PK), ADME, and toxicity testing through animals
- Clinical Phase
  - Human trials

Drug Targets

- Enzyme – inhibitors
- Receptors - agonists or antagonists
- Ion channel – blockers
- Transporter –inhibitors
- DNA - blocker



This information is used by bio-informaticians to narrow the search in the groups

Table 1a | **Enzymes**

Type	Activity of drug	Drug examples
Oxidoreductases		
Aldehyde dehydrogenase	Inhibitor	Disulfiram[39]
Monoamine oxidases (MAOs)	MAO-A inhibitor	Tranylcypromine[40], moclobemide[41]
	MAO-B inhibitor	Tranylcypromine[40]
Cyclooxygenases (COXs)	COX1 inhibitor	Acetylsalicylic acid, profens, acetaminophen and dipyrone (as arachidonylamides)[42,43]
	COX2 inhibitor	Acetylsalicylic acid, profens, acetaminophen and dipyrone (as arachidonylamides)[44]
Vitamin K epoxide reductase	Inhibitor	Warfarin, phenprocoumon[45]
Aromatase	Inhibitor	Exemestane[46]
Lanosterol demethylase (fungal)	Inhibitor	Azole antifungals[47]
Lipoxygenases	Inhibitor	Mesalazine[48]
	5-lipoxygenase inhibitor	Zileuton[49]
Thyroidal peroxidase	Inhibitor	Thiouracils[50]
Iodothyronine-5′ deiodinase	Inhibitor	Propylthiouracil[50]
Inosine monophosphate dehydrogenase	Inhibitor	Mycophenolate mofetil[51]
HMG-CoA reductase	Inhibitor	Statins[52]
5α-Testosterone reductase	Inhibitor	Finasteride, dutasteride[53]
Dihydrofolate reductase (bacterial)	Inhibitor	Trimethoprim[54]
Dihydrofolate reductase (human)	Inhibitor	Methotrexate, pemetrexed[55]
Dihydrofolate reductase (parasitic)	Inhibitor	Proguanil[56]
Dihydroorotate reductase	Inhibitor	Leflunomide[57]
Enoyl reductase (mycobacterial)	Inhibitor	Isoniazid[58]
Squalene epoxidase (fungal)	Inhibitor	Terbinafin[59]

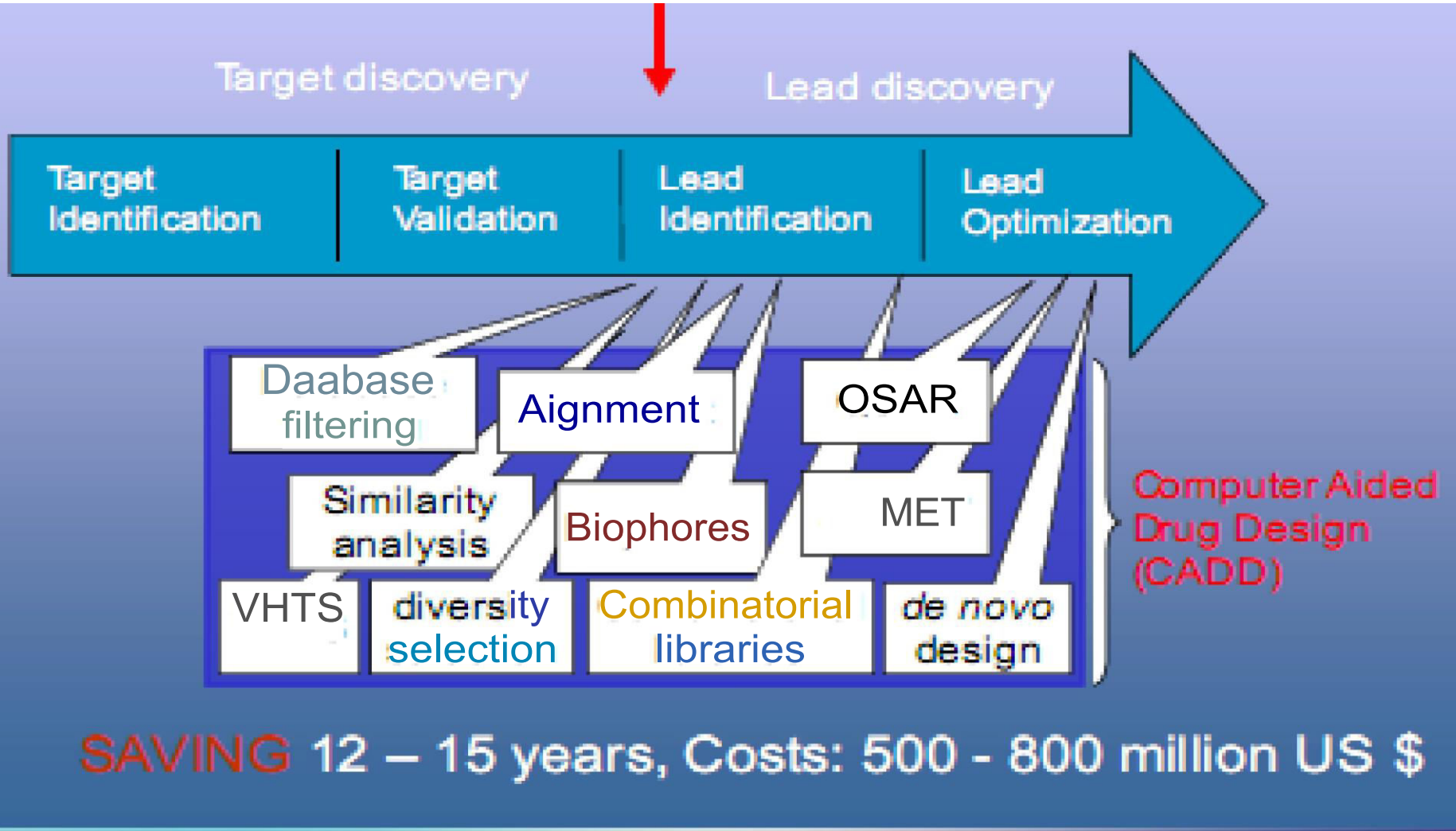
What is CADD?????

Computational Chemistry/CADD is the chemistry whose major goals are to create efficient mathematical approximations and computer programs that calculate the properties of future drug molecules and thus helping in the process of drug design and discovery.

Why CADD…?

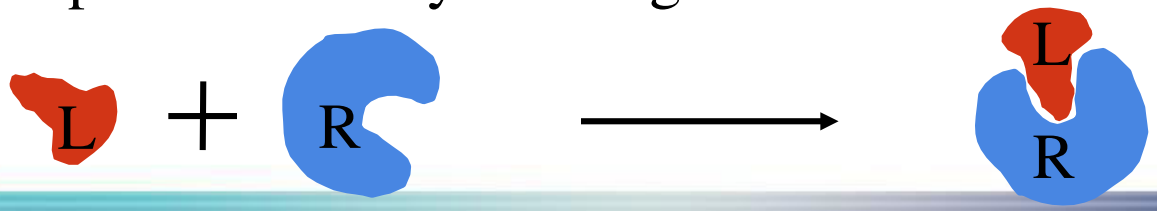
Drug Discovery today are facing a serious challenge because of the increased cost and enormous amount of time taken to discover a new drug, and also because of rigorous competition amongst different pharmaceutical companies

Phases of CADD



Molecular Docking

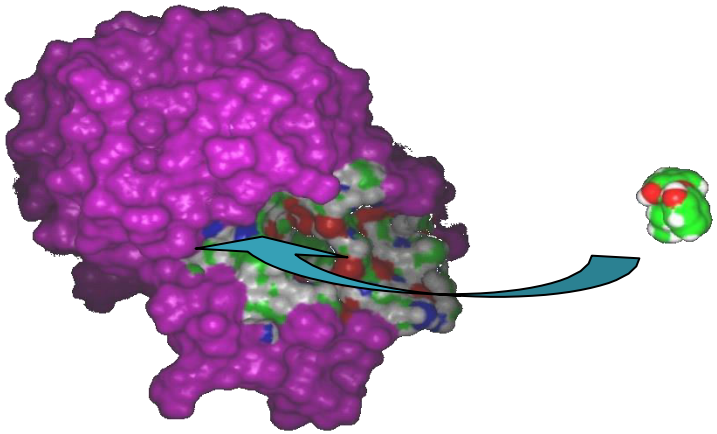
- Docking is the identification of the low-energy binding modes of a small molecule or ligand within the active site of a macromolecule, or receptor, whose structure is known.
- Docking is the computational determination of binding affinity between molecules (protein structure and ligand).
- Given a protein and a ligand find out the binding free energy of the complex formed by docking them.

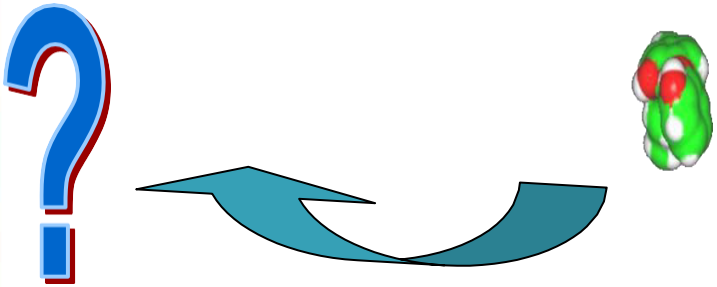


Why Modeling?

- Experimental determination of structure is still a time consuming and expensive process.
- Number of known sequences are more than number of known structures.
- Structure information is essential in understanding function.

Molecular Docking: classification





Docking or Computer aided drug designing can be broadly classified

- Receptor based methods- make use of the structure of the target protein.
- Ligand based methods- based on the known inhibitors

Receptor based methods

- Uses the 3D structure of the target receptor to search for the potential candidate compounds that can modulate the target function.
- These involve molecular docking of each compound in the chemical database into the binding site of the target and predicting the electrostatic fit between them.
- The compounds are ranked using an appropriate scoring function such that the scores correlate with the binding affinity.
- Receptor based method has been successfully applied in many targets

Ligand based strategy

- In the absence of the structural information of the target, ligand based method make use of the information provided by known inhibitors for the target receptor.
- Structures similar to the known inhibitors are identified from chemical databases by variety of methods,
- Some of the methods widely used are similarity and substructure searching, pharmacophore matching or 3D shape matching.
- Numerous successful applications of ligand based methods have been reported

Basic binding mechanism

Complementarities between the ligand and the binding site:

- Steric complementarities, i.e. the shape of the ligand is mirrored in the shape of the binding site.
- Physicochemical complementarities

Categories of docking

- Protein-Protein Docking:

  Both molecules are rigid

  Interaction produces no change in conformation

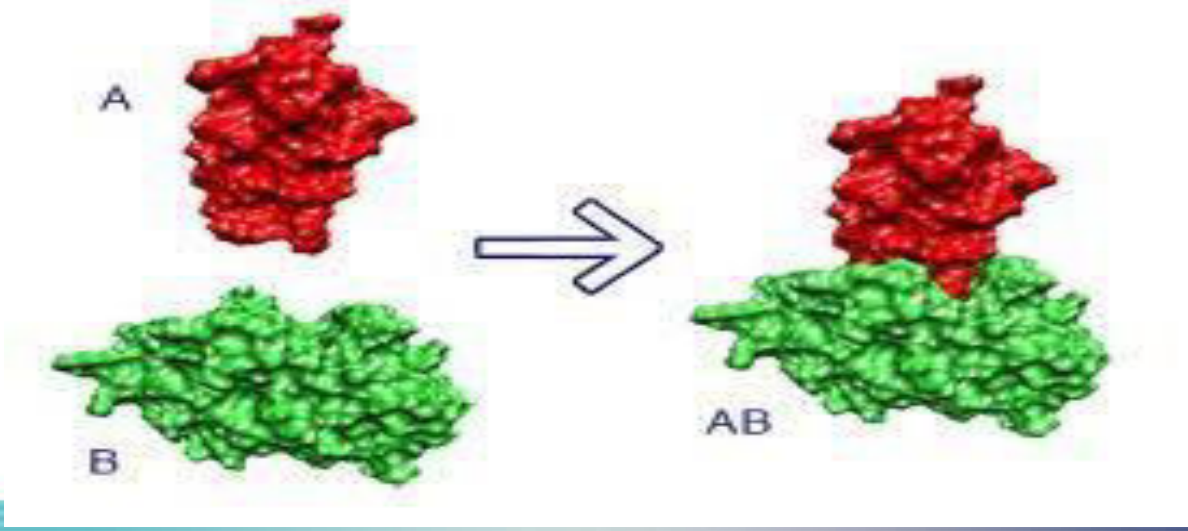
- Protein-Ligand Docking:

  Ligand is flexible but the receptor protein is rigid

  Interaction produces conformational changes in ligand

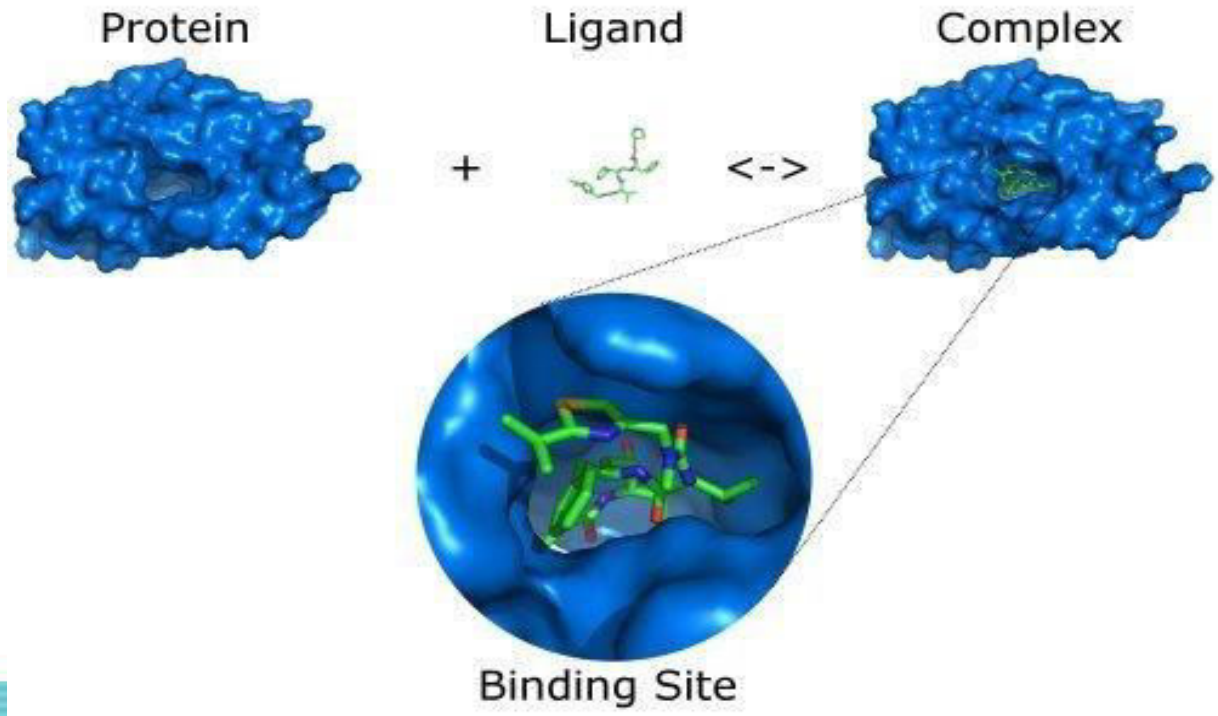
Protein – Protein Docking

- Computational modelling of the quaternary structure of complexes formed by two or more interacting biological macromolecules.
- Protein–protein complexes are the most commonly attempted targets of such modelling, followed by protein–nucleic acid complexes.



Protein - Ligand Docking

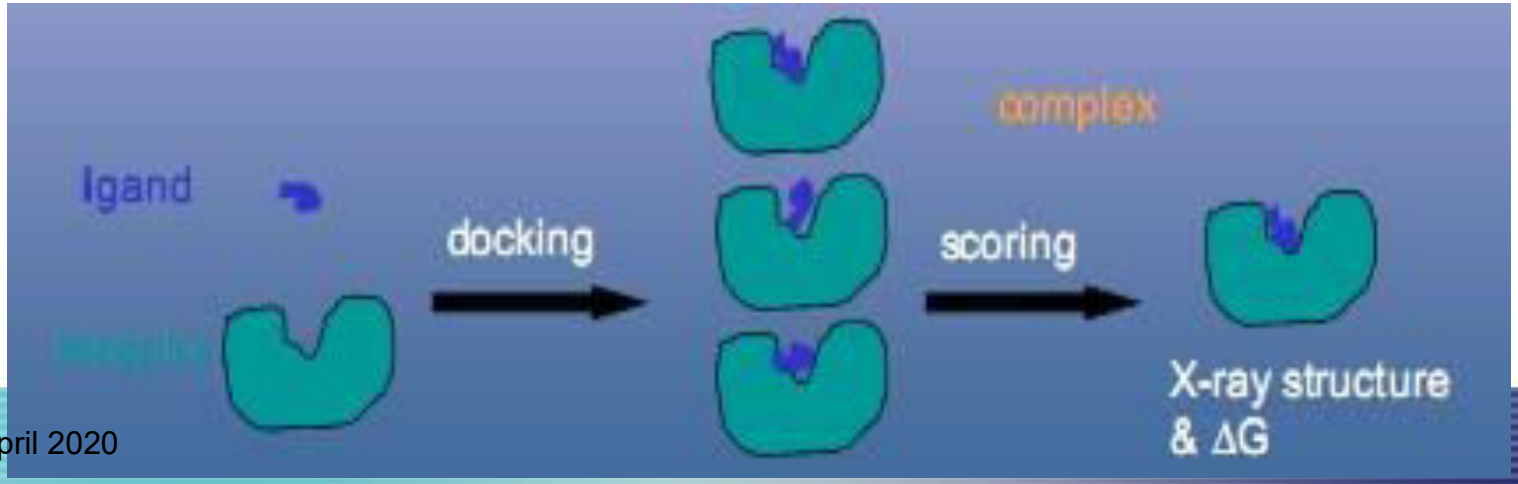
Protein-ligand docking is to predict the position and orientation of a ligand (a small molecule) when it is bound to a protein receptor or enzyme



What are Docking & Scoring?

To place a ligand (small molecule) into the binding site of a receptor in the manners appropriate for optimal interactions with a receptor.

To evaluate the ligand-receptor interactions in a way that may discriminate the experimentally observed mode from others and estimate the binding affinity



Available Docking Programs

- Schrodinger
- Acelerys Pro
- GOLD
- DOCK
- MOE-Dock
- FlexX
- AutoDOCK
- FRED
- Hammerhead
- Argus Lab

Components of docking software

Typically, protein-ligand docking software consist of two main components which work together:

Search algorithm

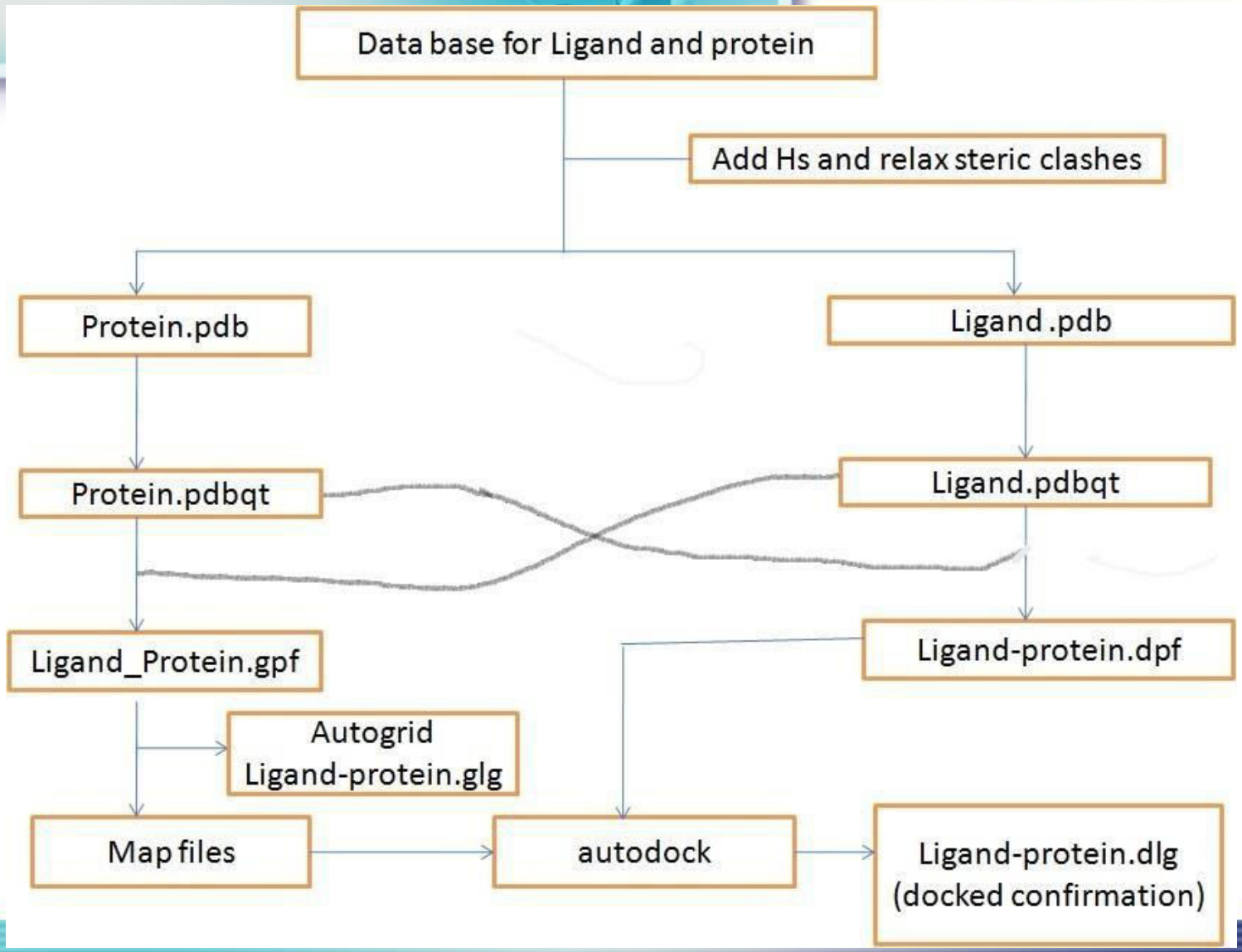
Generates a large number of poses of a molecule in the binding site

Scoring function

Calculates a score or binding affinity for a particular pose

The binding affinity or a score representing the strength of binding

Docking Flow Chart using Autodock

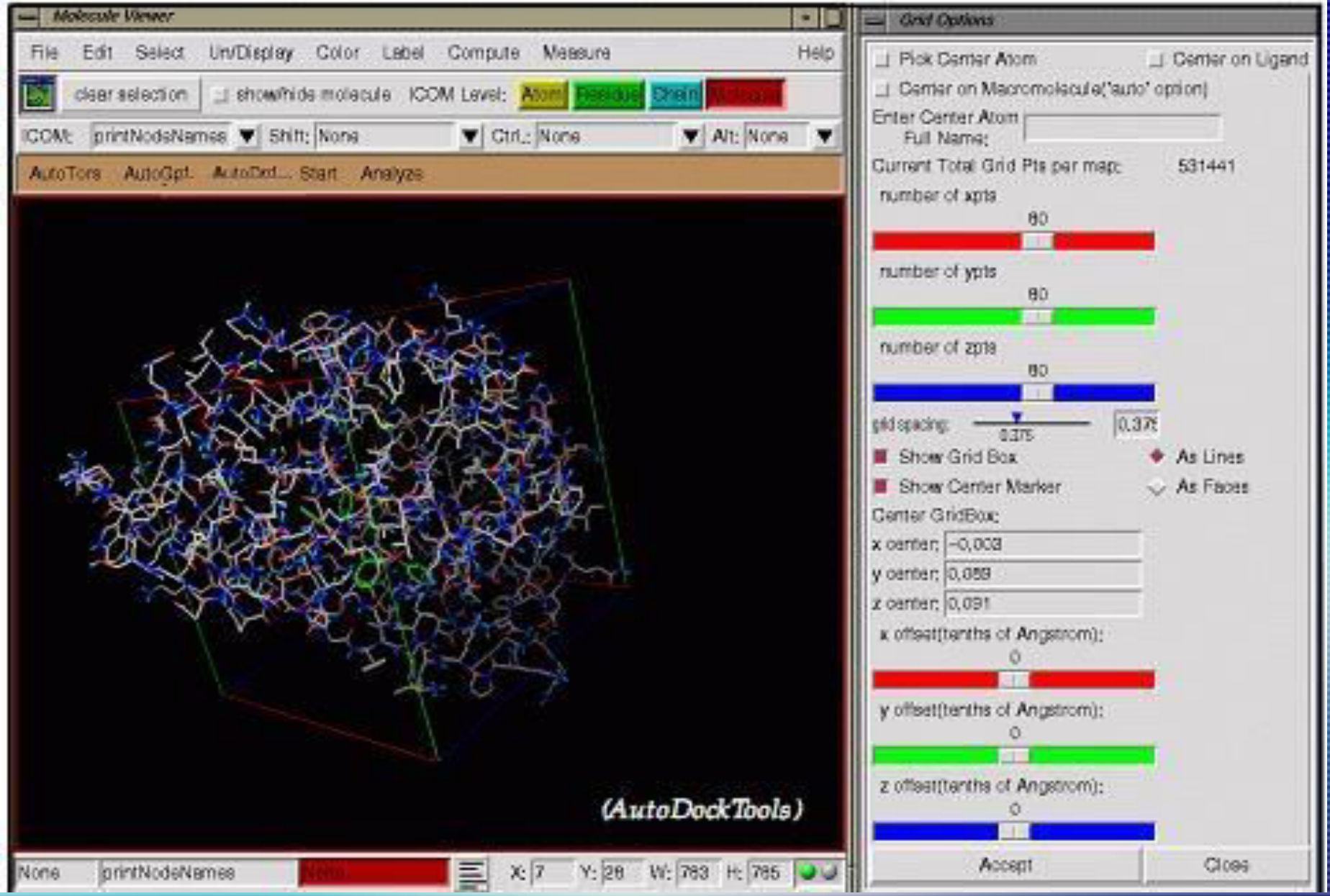


Ligand Preparation for Docking using Autodock

- Assign charges
- Define rotatable bonds
- Rename aromatic carbons
- Write .pdbqt ligand file

Preparation of Protein using Autodock

- Add essential hydrogen's
- Load charges
- Remove Water Molecules
- Write .pdbqt protein file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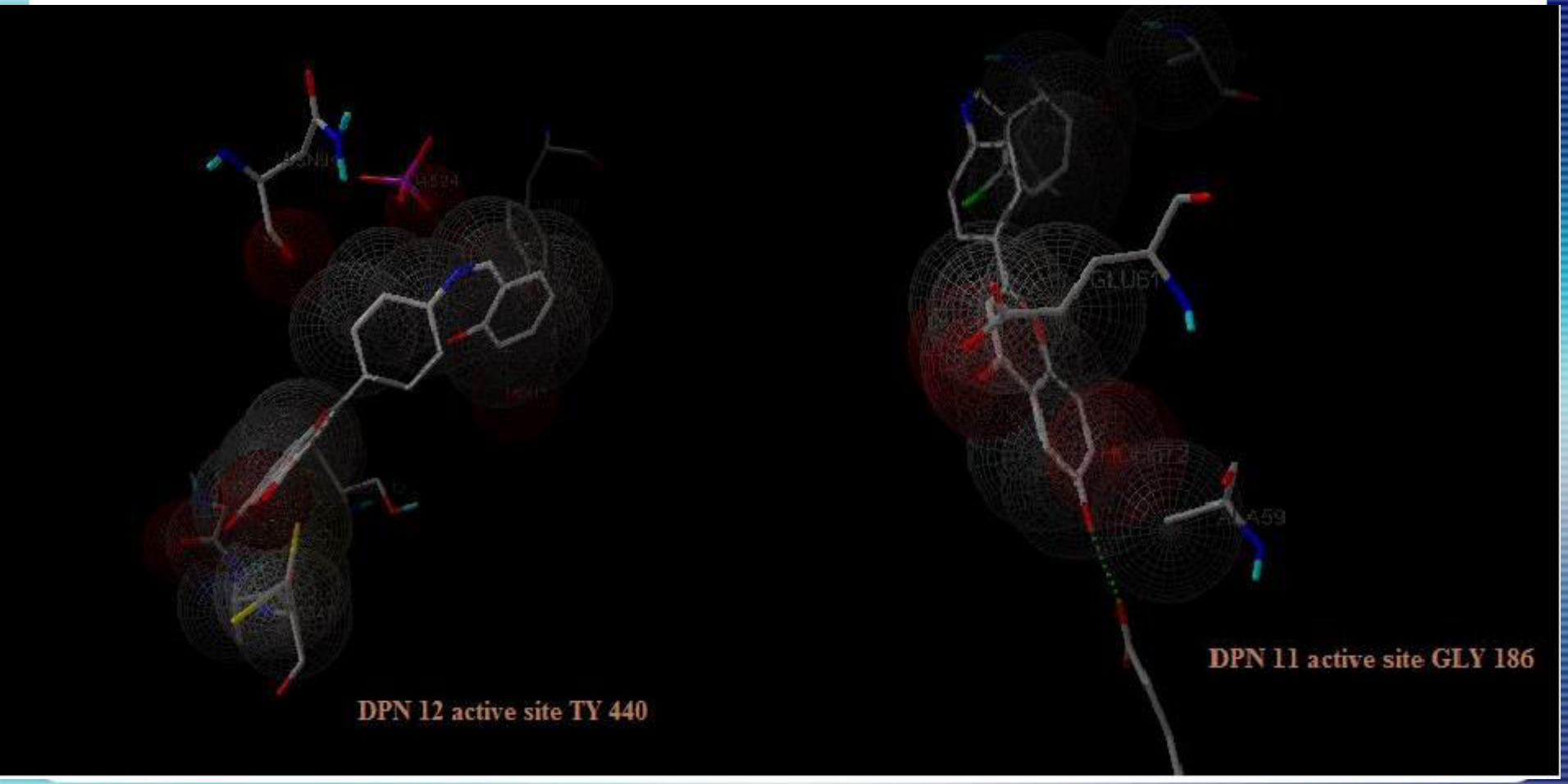
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Application of Molecular Docking in Modern Drug Discovery

- Determine the lowest free energy structures for the receptor - ligand complex
- Search database and rank hits for lead generation
- Calculate the differential binding of a ligand to two different macromolecular receptors
- Study the geometry of a particular complex
- Propose modification of a lead molecules to optimize potency or other properties de novo design for lead generation
- Library design
- Screening for the side effects that can be caused by the interactions with other proteins, like proteases, Cytochrome P450 and others can be done.

- It is also possible to check the specificity of the potential drug against homologous proteins through docking.
- Docking is also a widely used tool in predicting protein-protein interactions.
- Knowledge of the molecular associations aids in understanding a variety of pathways taking place in the living and in revealing of the possible pharmacological targets.
- Docking-Based Virtual High Throughput Screening

- Less expensive than High Throughput Screening
- Faster than conventional screening
- Scanning a large number of potential drug like molecules in very less time.
- HTS itself is a trial and error approach but can be better complemented by virtual screening.

Growing Evidence of Success…. !!

Drug	Target	Disease
Dorzolamide	Carbonic anhydrase	Diuretics
Saquinavir	HIV protease	AIDS
Relenza	Neuraminidase	AIDS
AG85, ag337, ag331	Thymidylate synthase	Cancer

- ✓ Discovery of Indinavir, the HIV protease inhibitor.
- ✓ Identification of Haloperidol as a lead compound in a structure-based design for non-peptide inhibitor of HIV.
- ✓ Carbonic Anhydrase (treatment of glaucoma)
- ✓ Renin (treatment of hypertension)
- ✓ Dyhrofolate reductase (antibacterial)
- ✓ Neuraminidase (antiviral)
- ✓ HIV-1 aspartic proteinase (anti-acquired immunodeficiency syndrome)

- ✓ Trypanosomal glyceraldehyde-3-phosphate dehydrogenase parasitic)
- ✓ Thymidylate synthase and purine nucleoside phosphorylase
- ✓ Collagenase (Rheumatoid and Osteoarthritis)
- ✓ Phospholipase A_2 (anti inflammatory)
- ✓ Glycogen phosphorylase (treatment of diabetes mellitus)

Conclusion

- Molecular docking give the promising effect on identification and optimization in modern drug discovery
- The combination of the chemical information of natural products with docking-based virtual screening will play an important role in drug discovery in the post-genomic era as more and more new potential targets are emerging from the functional genomic studies.
- Docking-based virtual screening lead to much higher hit rate than traditional screening methods (e.g., HTS)

- Docking method provides an opportunity for the designing of active compounds.
- However, it has to be emphasized that docking-based virtual screening is not the replacement of the actual experimental screening.
- As a matter of fact, these two methods are highly complementary.

Future Directions

- Pharmaceutical history indicated that natural products provided a large number of drugs to the market. But, even for the currently used drug targets, available natural products have not been tested completely.
- Computational medicinal methods, can contribute its unique role in achieving the task of examining the interaction of all existing natural products with all possible targets.

QUESTIONS

Target?

Drug?

Docking?

CADD?

HTS?

Thank you!

A man who never made a mistake
had never tried anything new – Albert Einstein

- Molecular Modelling Methods by William A. Wylie (springer)

- An introduction to molecular modeling and computer aided drug design by FJ Corcho Sanchez.
- Molecular Modeling and Drug Designing by Dr. R. Suresh (Associate Professor) Annamalai University Chidambaram, Tamil Nadu, India.13 April 2020