Bioinformatics: Computational Drug Discovery and Design

Module 1a: Bioinformatics: Role in Drug Design

Olatomide Oluwasegun Davis M.Sc
Ahmadu Bello University, Zaria, Nigeria.

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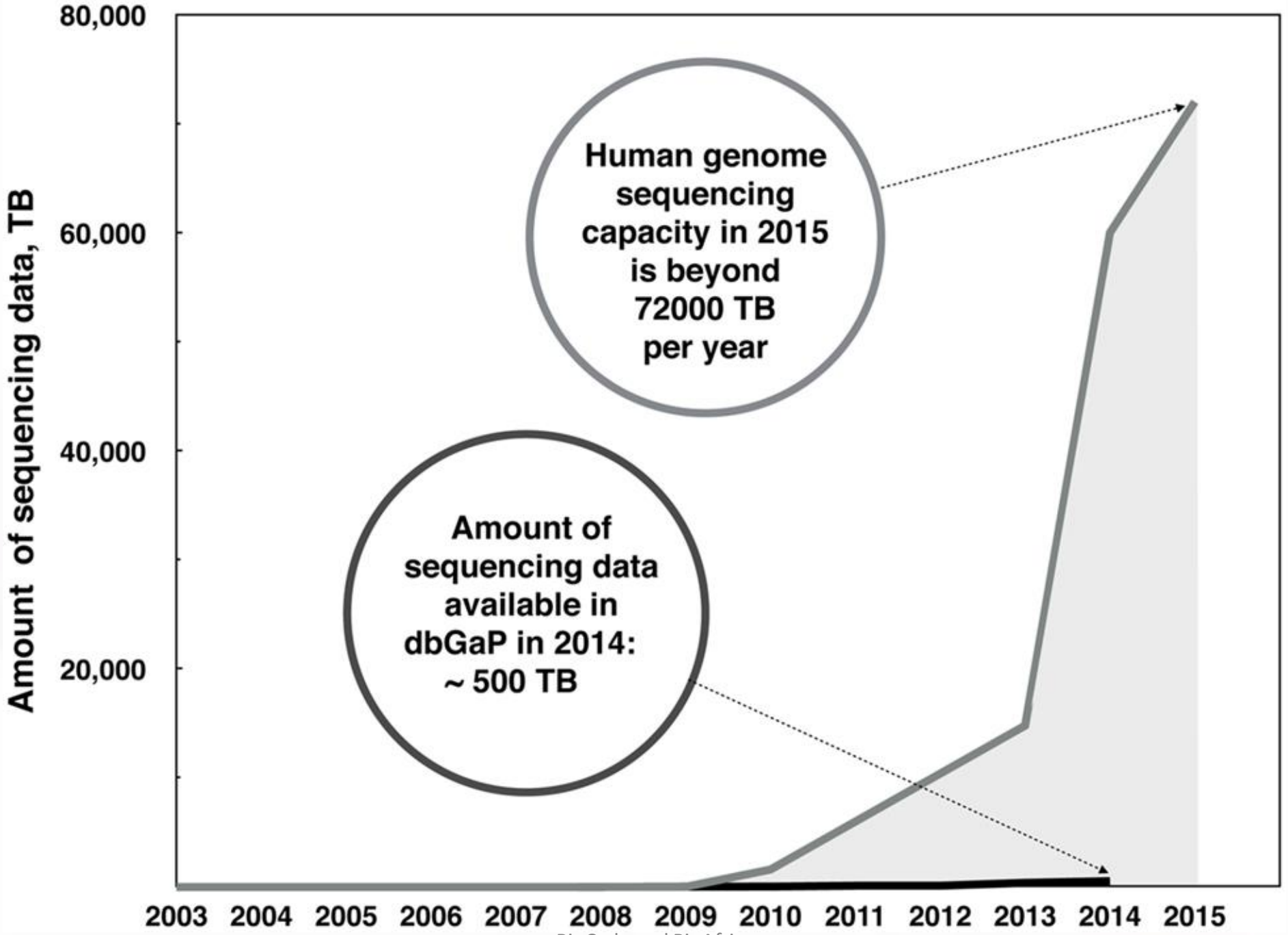
What is Bioinformatics

https://www.youtube.com/watch?v=8OH1Qrvf1G4


Amount of sequencing data, TB
80,000
60,000
40,000
20,000
Human genome sequencing capacity in 2015 is beyond 72000 TB per year
Amount of sequencing data available in dbGaP in 2014: ~ 500 TB
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

IMAGES
CLINICAL
OBSERVATION
LABORATORY

PHENOTYPIC

HIGH PERFORMANCE
COMPUTING

RAW OMICS

SEQUENCING
MASS-SPEC
STRUCTURAL
CHEMICAL

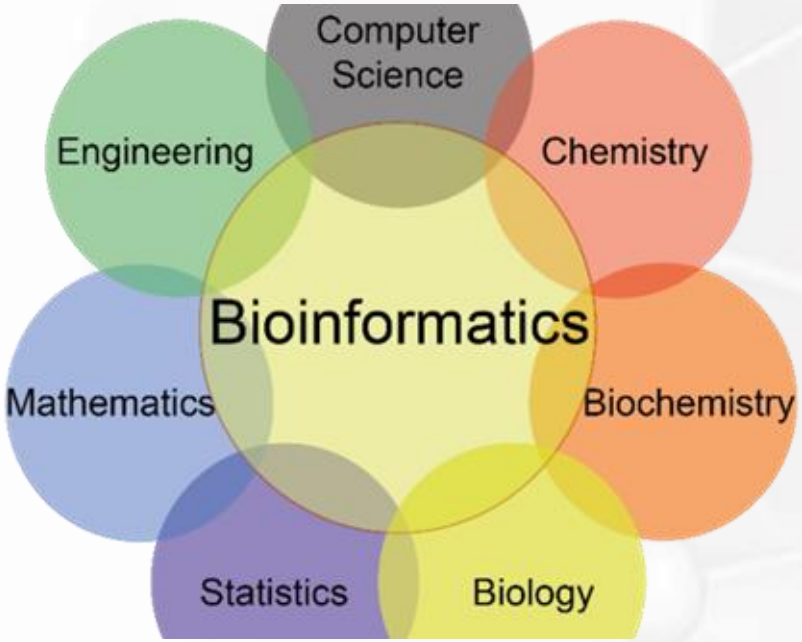
data management **data-driven methods** **scalable tools** **skilled interdisciplinary workforce**

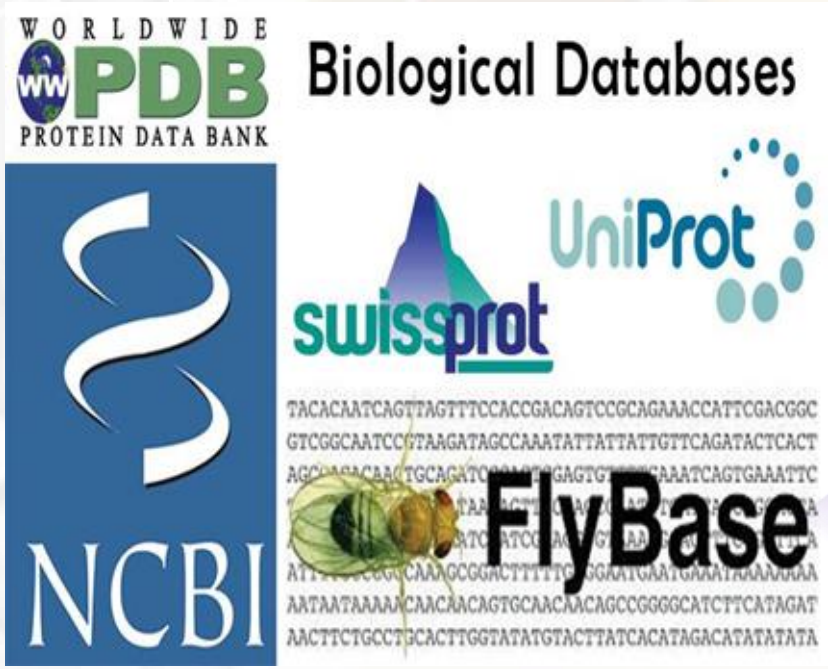
RESEARCH **AGRICULTURE** **PERSONALIZED MEDICINE** **PHARMA R&D**

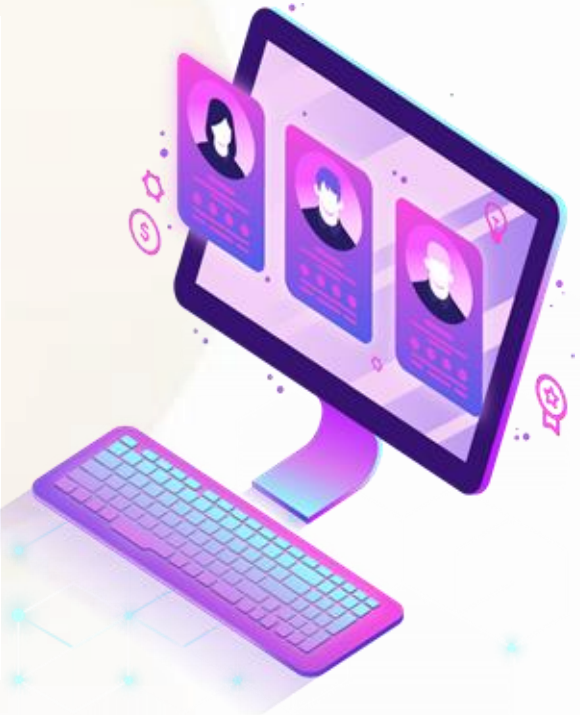
What is Bioinformatics

Bioinformatics is an interdisciplinary scientific field

Develops methods and software tools for storing, retrieving, organizing and analyzing biological data (Bartlett *et al.*, 2016).







History

1950s

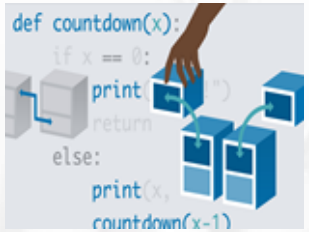
Insulin sequenced

1970s

Polymerase chain reaction developed

1980s

Dynamic programming algorithms



1990s

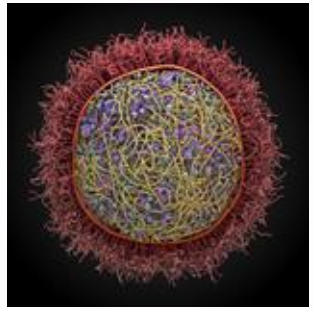
HGP launched

2000s

Human genome sequenced

2050s

Complete computational model of a cell or organism



DNA double helix model proposed

Protein data bank created

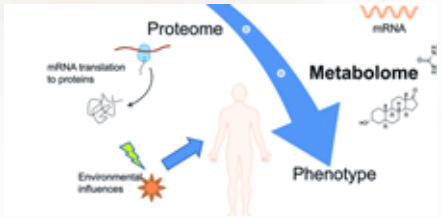
Bioinformatics coined

SWISS-PROT created

NCBI and EBI-EMBL founded

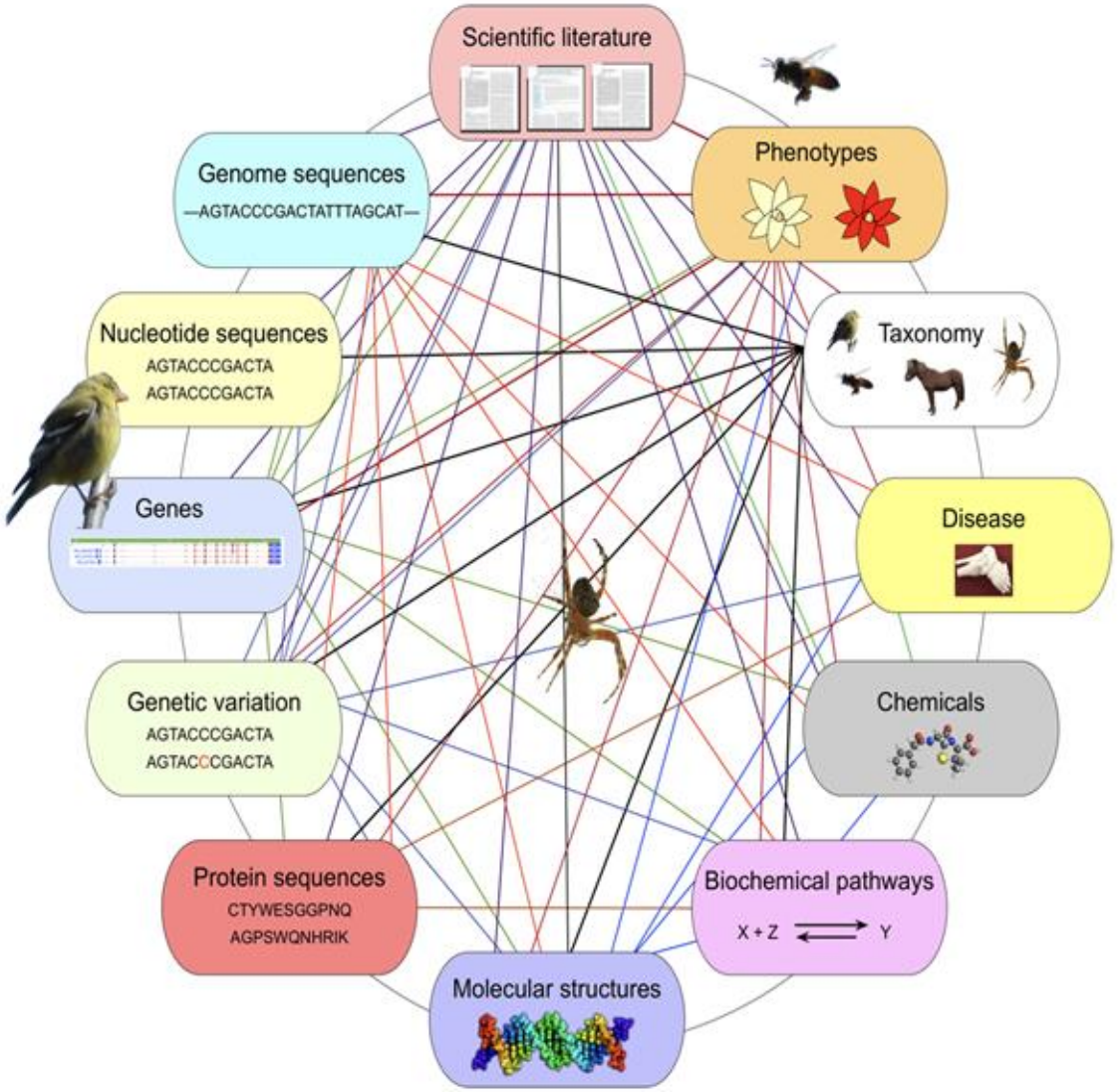
BLAST program made available

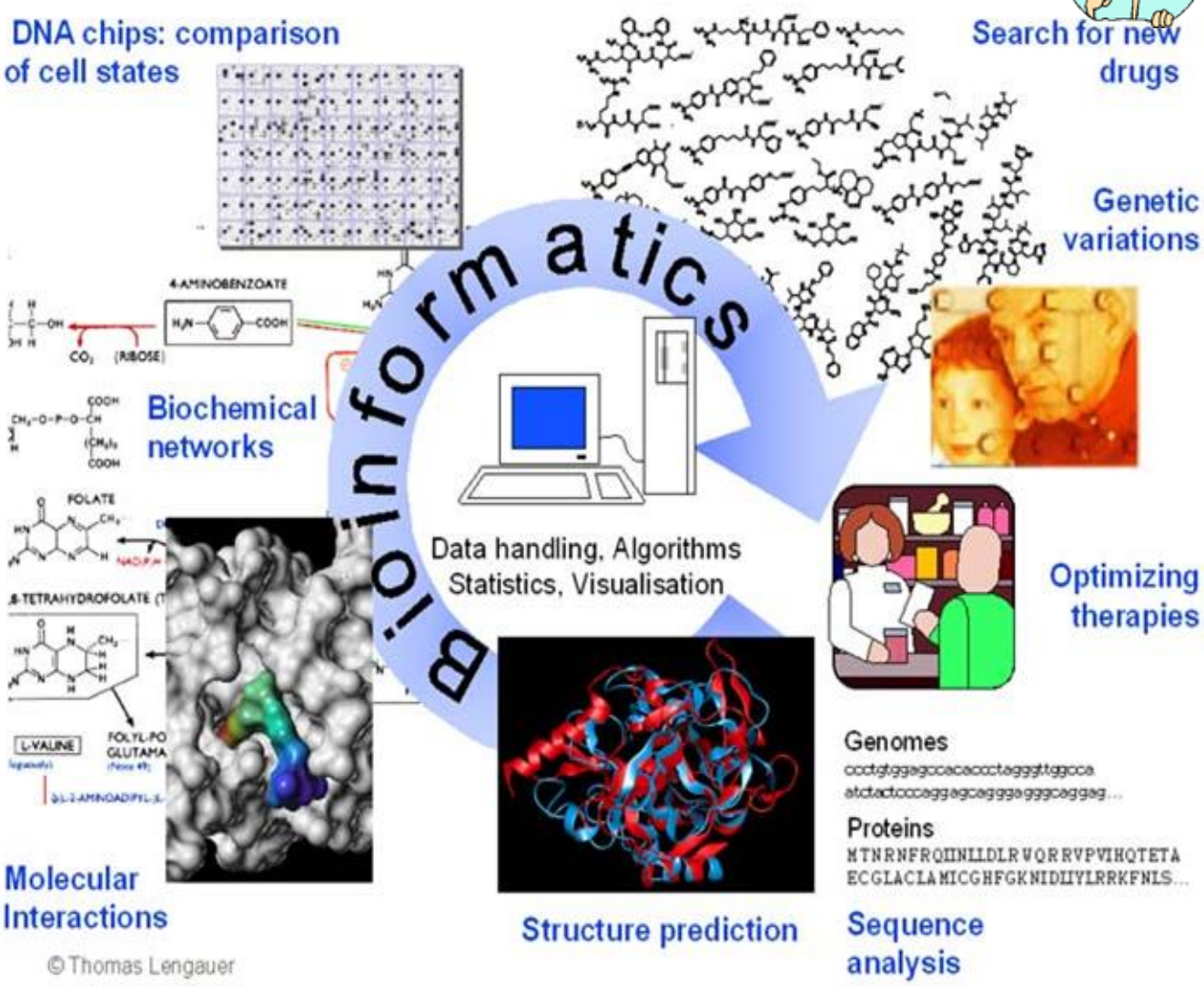
Proteomics and metabolomics unfolds



(Sahinidis *et al.*, 2005)

Applications of Bioinformatics





Application in Drug Design

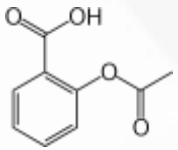
What is a Drug?

A substance that, when absorbed, alters normal bodily function

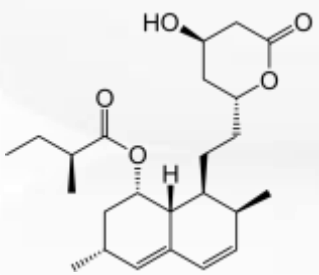
In pharmacology: FDA-approved for the diagnosis, treatment, or prevention of disease.

Classification

Small Molecule

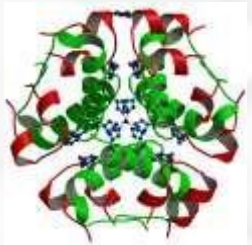


Aspirin

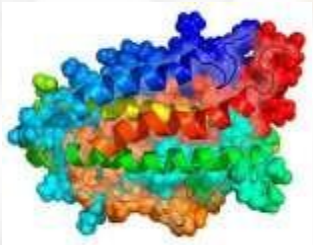


Lovastatin

Protein

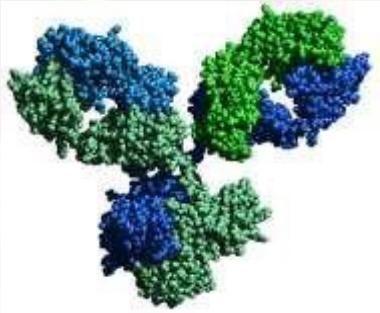


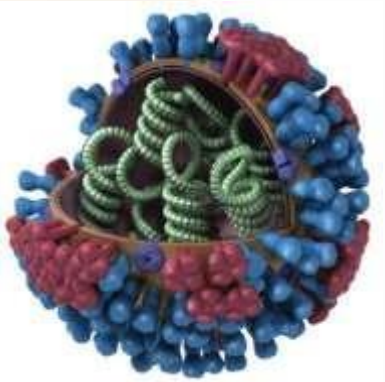
Insulin



Erythropoietin

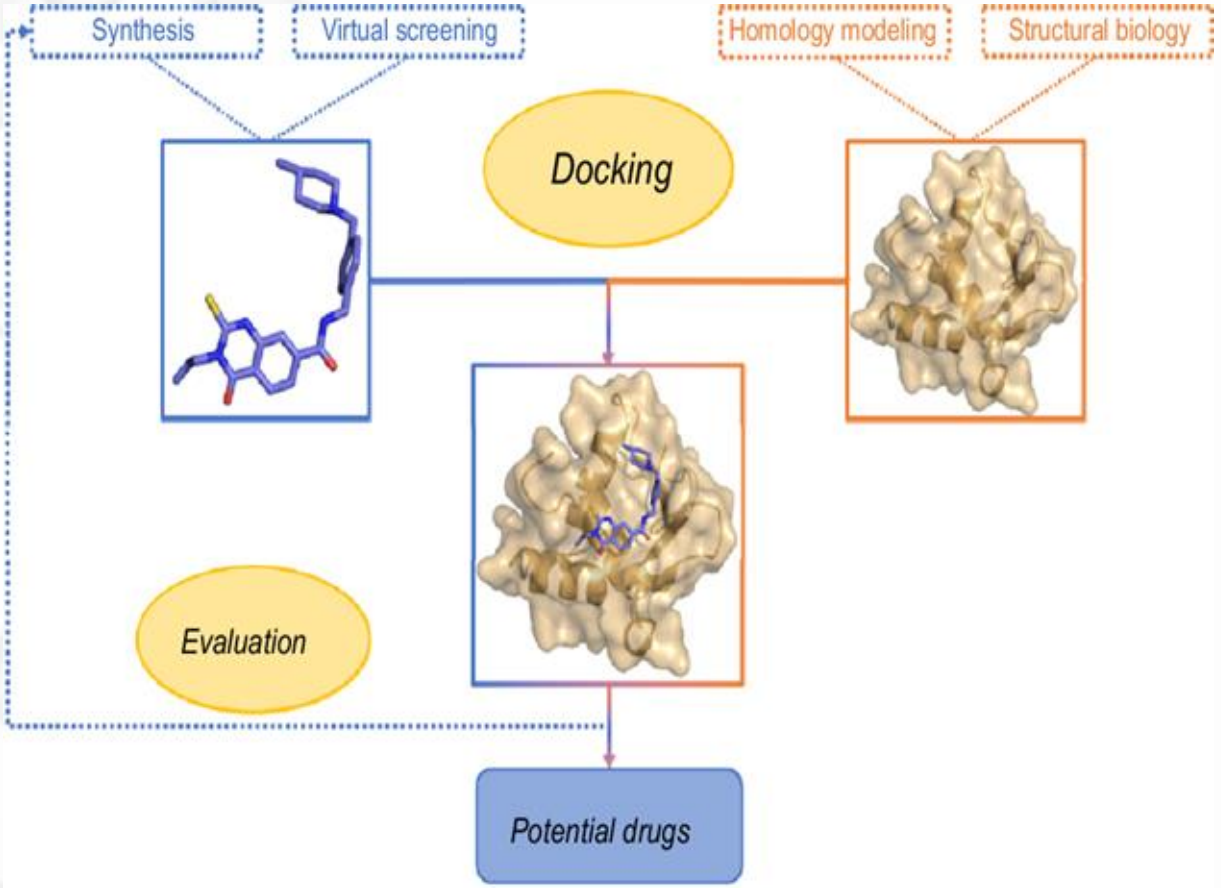
Vaccine





Different Terms Used in CADD

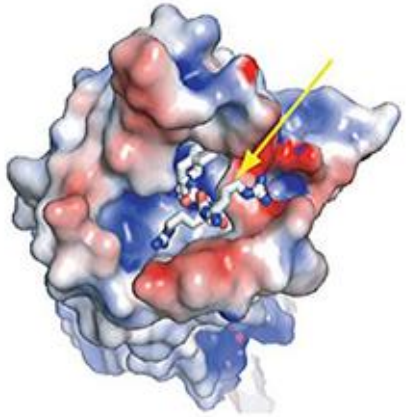
- **Receptor/Host** – large molecule (protein) receiving ligand.
- **Ligand/Key** – small molecule that binds to receptor
- **Docking** – Computational simulation of a candidate preferred orientation to a receptor.
- **Binding mode** – conformation of ligand-receptor bound to each other.
- **Pose** – a candidates binding mode.



Terms…

- **Scoring** – evaluating a particular pose by counting the number of favourable intermolecular interactions.
- **Ranking** – classify ligands most likely to interact favourably to a particular relation based on ΔG of binding.
- **Hit** – Ligand with high rank.
- **Lead** – hit with biological activity.

Drug Design



is the inventive process of finding new medications based on the knowledge of the biological target (Liljefors *et al.*, 2002).

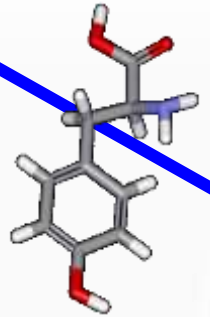
It involves design of small molecules complementary in shape and charge to the bio-molecular target (Ghasemi *et al.*, 2017).

Traditional Drug design

Random screening

Serendipity

Ethnopharmacology (2-5 years)



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

Preclinical testing (1-3 years)

Scale-up

Formulation

File IND

Human clinical trials (2-10 years)

File NDA

FDA approval (2-3 years)

(Naga, 2019)

- Drug discovery takes decades and it is costly (Mohs and Greig, 2017).
- To cut down the research timeline and cost, computational biology is imperative.

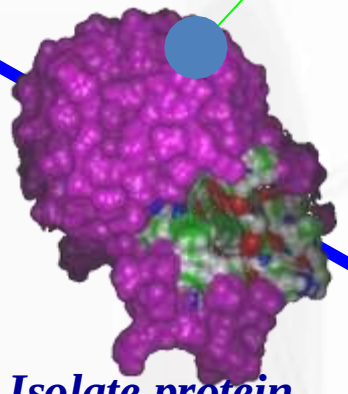
Computer Aided Drug Design (CADD)

- represents computational methods and resources that are used to facilitate the design and discovery of new therapeutic solutions (Yu and MacKerell, 2017).

Identify disease

GENOMICS, PROTEOMICS & BIOPHARM.

Potentially producing many more targets and "personalized" targets



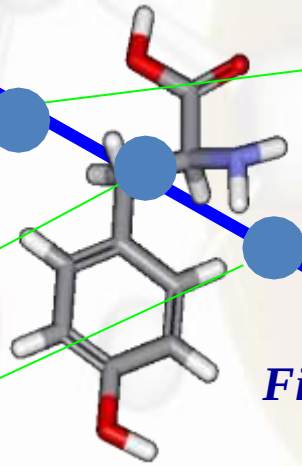
Isolate protein

VIRTUAL SCREENING

Using a computer to predict activity

COMBINATORIAL CHEMISTRY

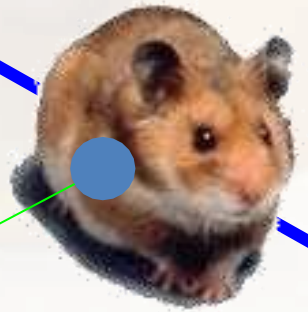
Rapidly producing vast numbers of compounds



Find drug

MOLECULAR DYNAMICS

Computer graphics & models help improve activity



Preclinical testing

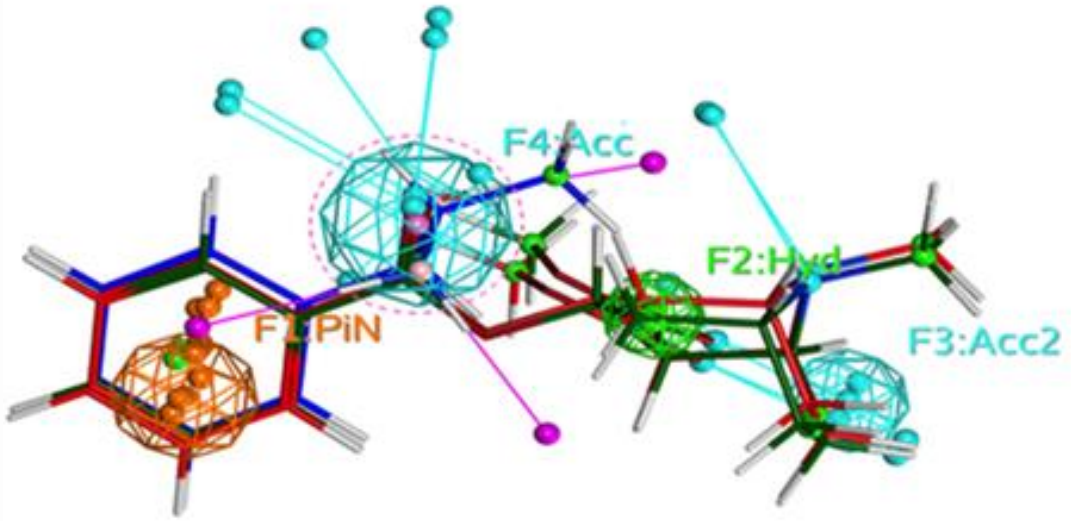
IN VITRO & IN SILICO ADME/T MODELS

Tissue and computer models begin to replace animal testing

(Naga, 2019)

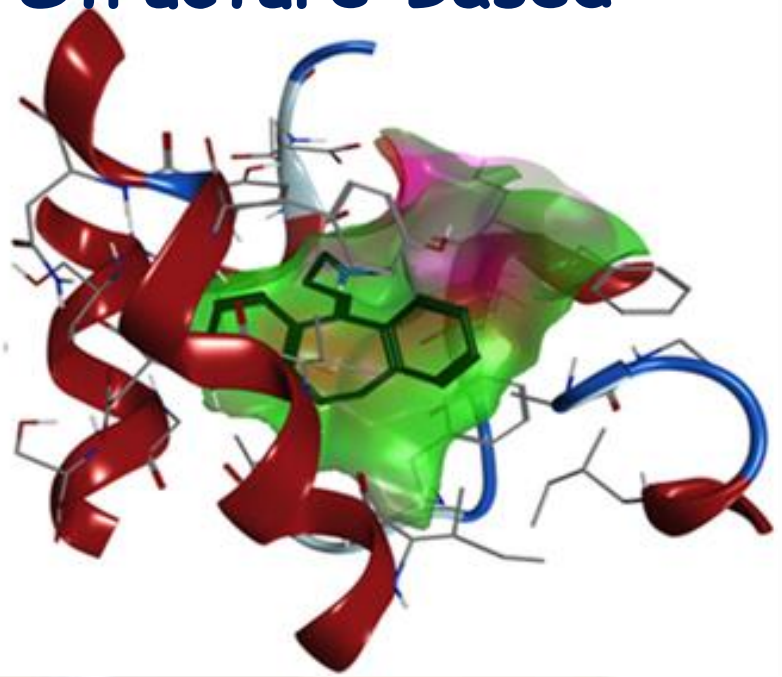
Approaches to CADD

Ligand Based



- Relies on knowledge of other molecules that bind to the biological target of interest.
- Used to derive a pharmacophore quantitative structure-activity

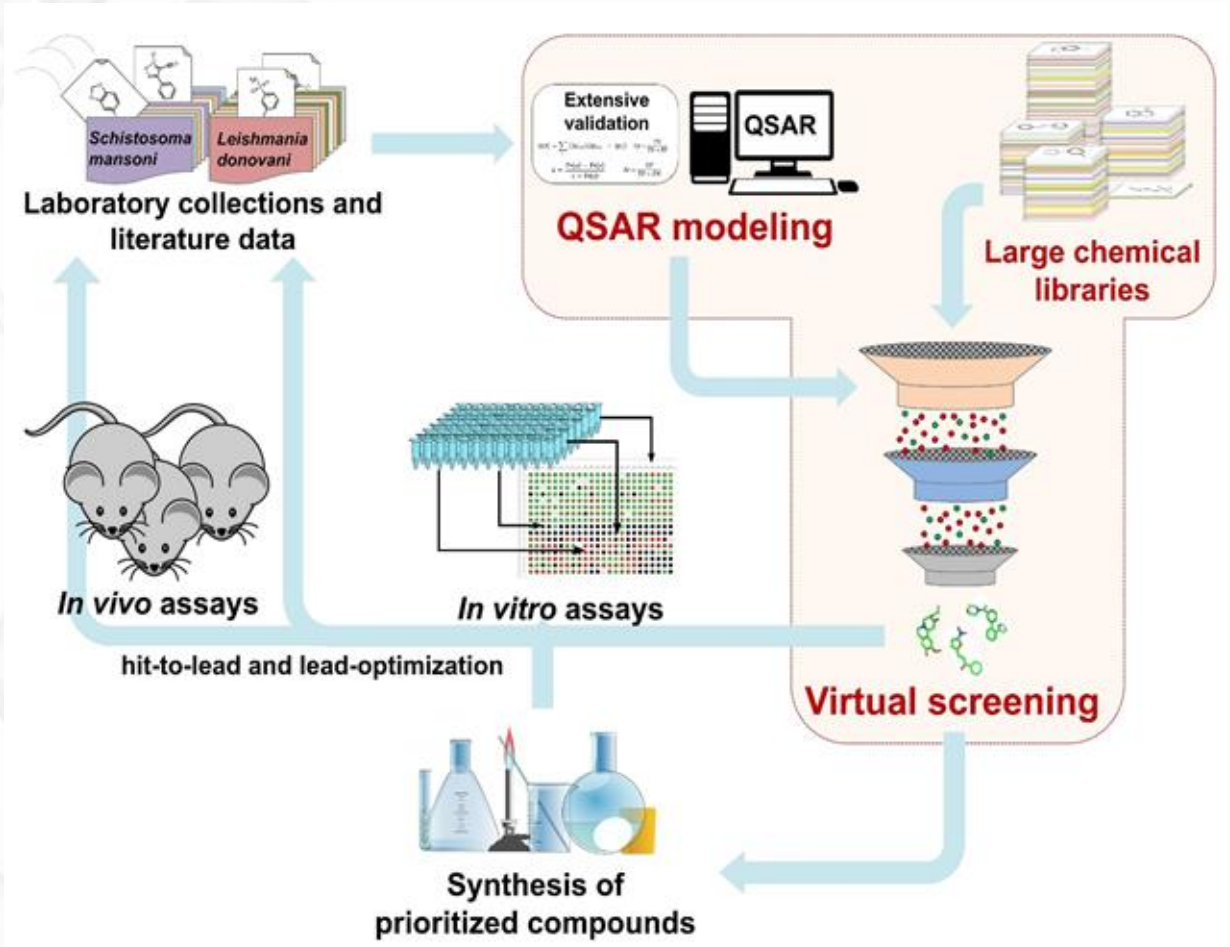
Structure Based



- Relies on 3D structure of the biological target :
- X-ray crystallography, NMR spectroscopy and homology modelling (Surabhi and Singh, 2018).

Steps in Ligand Based CADD

- Ligand CADD
  - 2DQSAR/3D QSAR
  - Pharmacophore modelling
- Virtual Screening
- Lead
- Lead Optimization
- Drug Candidate



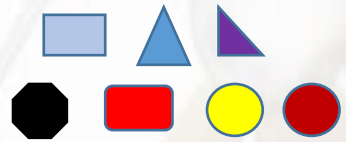
Steps in Ligand Based CADD…

Remdesivir

Ligand CADD

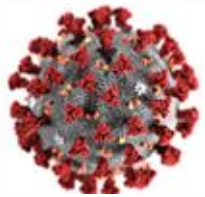
QSAR/3D QSAR

Pharmacophore modelling



Virtual Screening

Lead

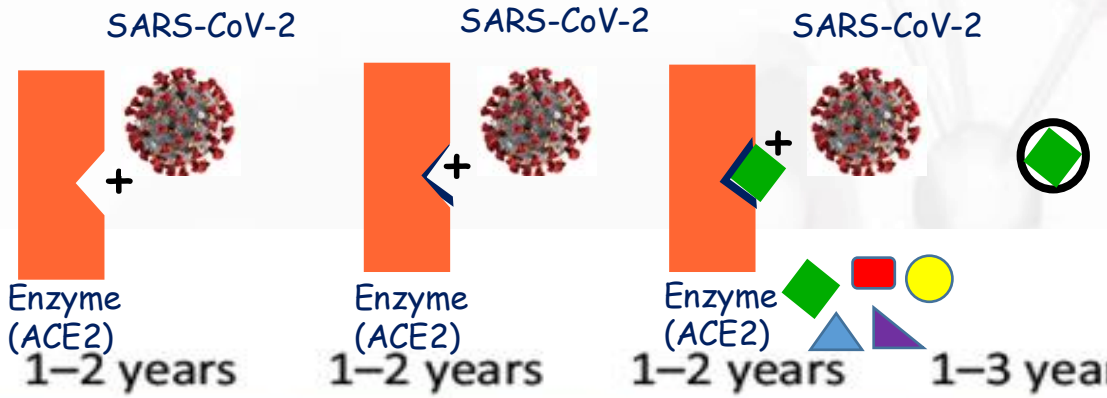


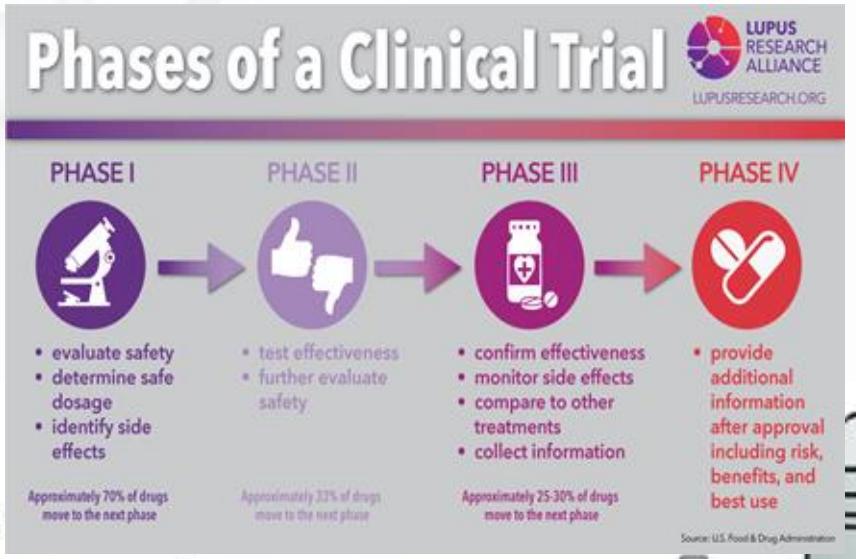
SARS-CoV-2
Target

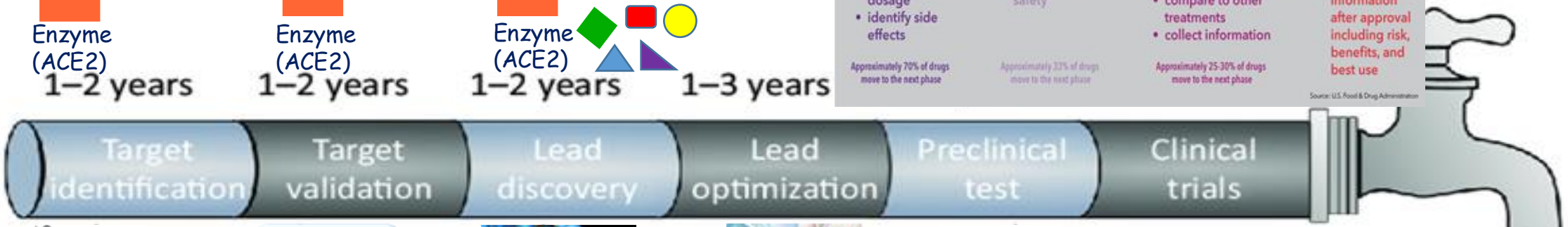
Lead Optimization

Drug Candidate

Steps in Structure Based CADD

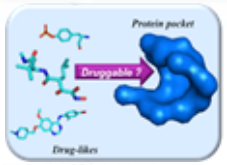




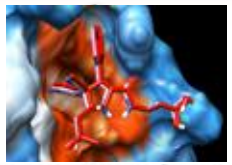


(Yuan *et al.*, 2017)

- Biointformatics
- Reverse docking
- Computational chemical biology
- **X-ray Crystallography**
- **NMR Spectroscopy**
- **Homology Modelling**
- **Binding site identification**



- Target druggability prediction
- Computational system biology



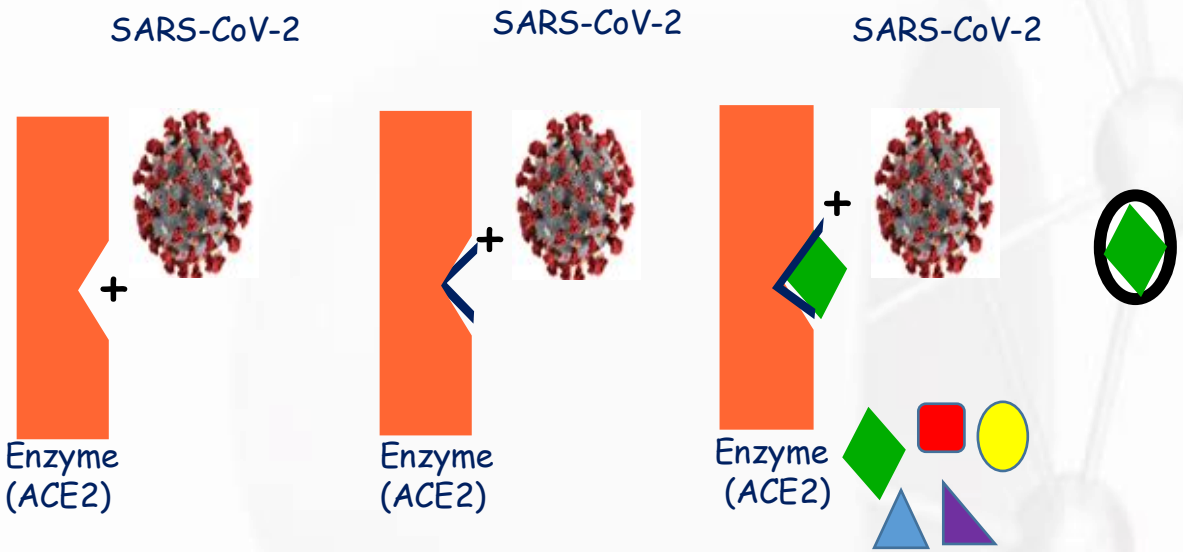
- Virtual screening
- *De novo* design
- Optimization

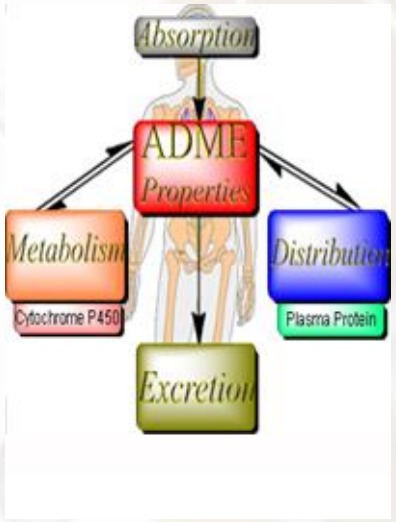
- Scaffold hopping
- SAR analysis
- *In situ* design

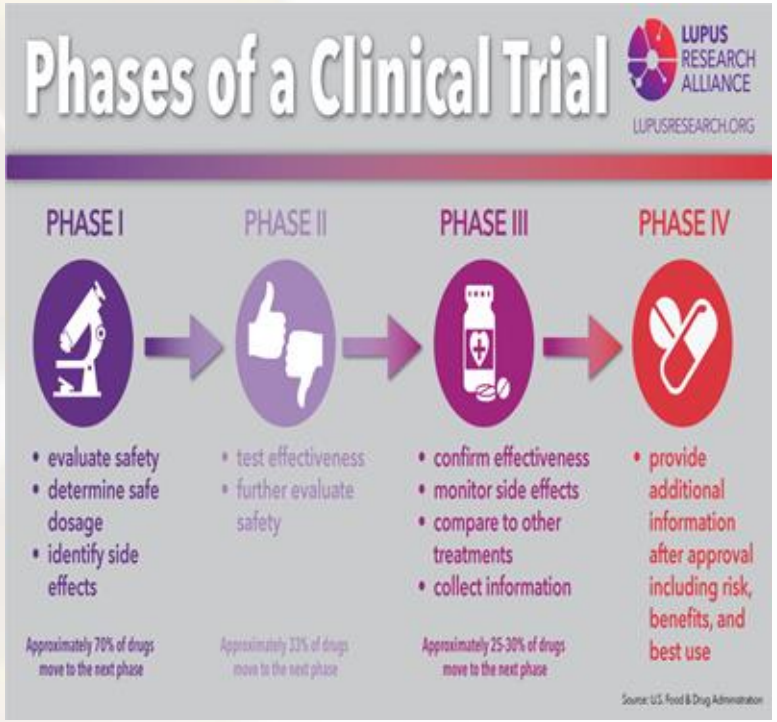
ADMET

- *In silico* ADMET prediction
- DMPK simulation
- Computational system biology

Steps in Structure Based CADD…



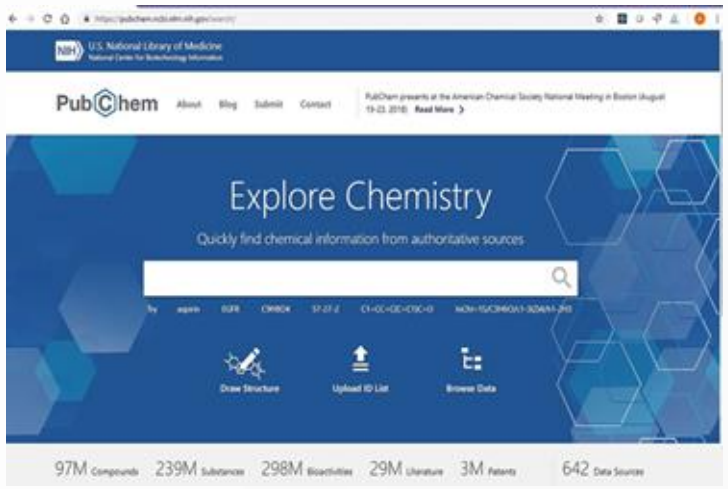




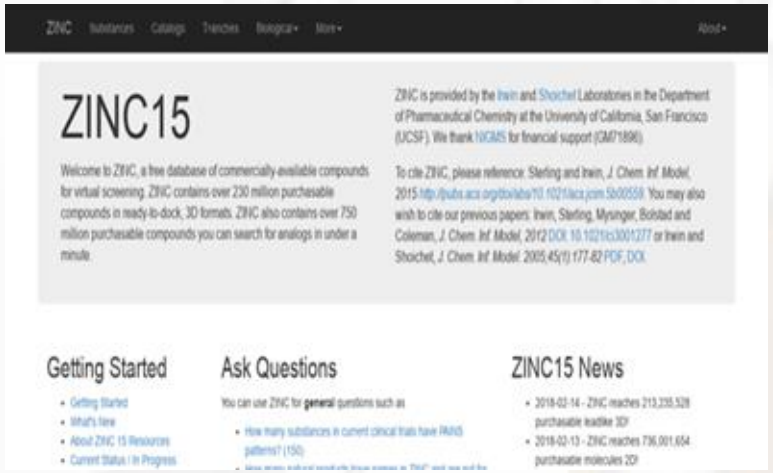
Computational Tools for Drug Designing

1. Databases and Draw Tools
2. Homology Modeling and Binding Site Prediction
3. Docking and Molecular Dynamics
4. Ligand Design Screening and Target prediction
5. ADME & Toxicity
6.

Databases

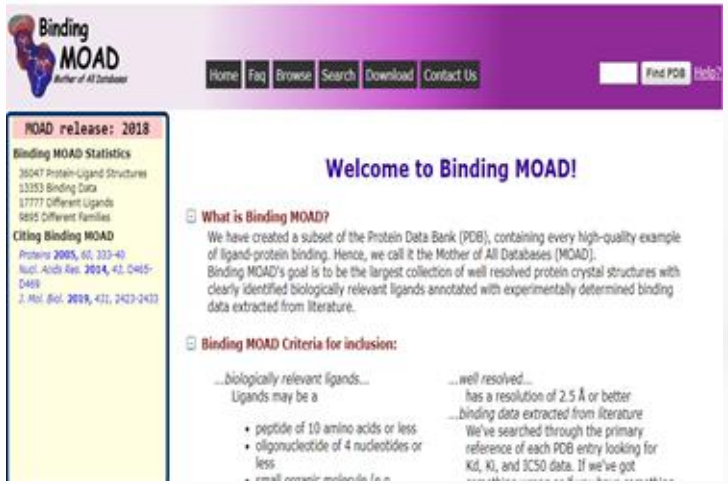


PubChem Database



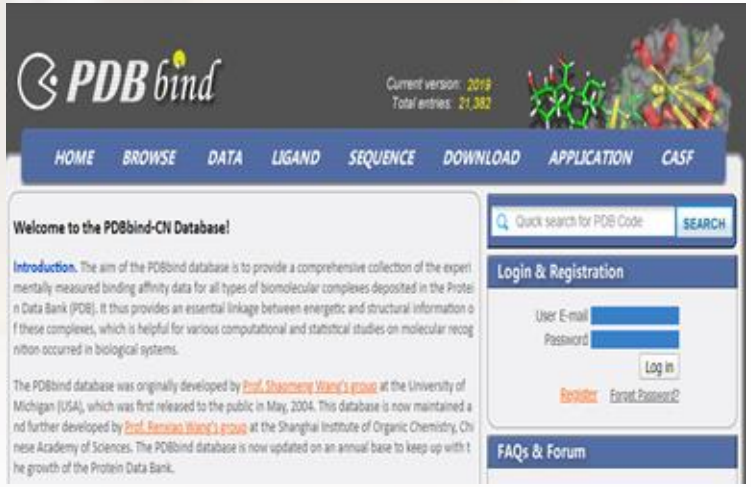
Zinc Database

Protein Data Bank(PDB)



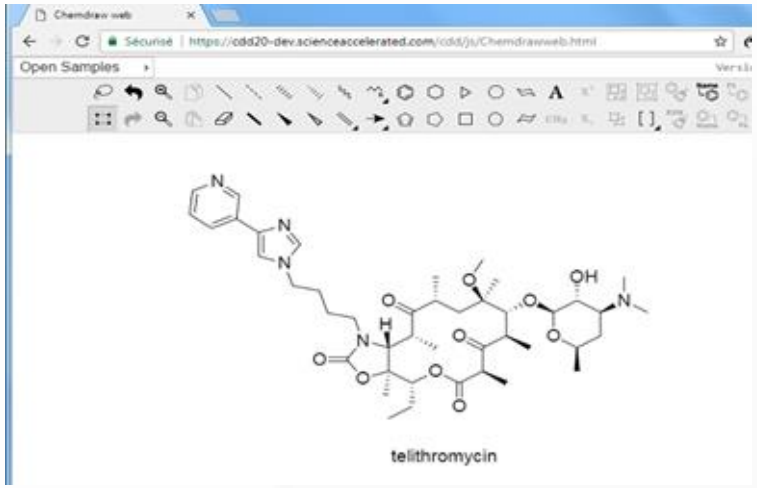
BindingMOAD

SMP Database

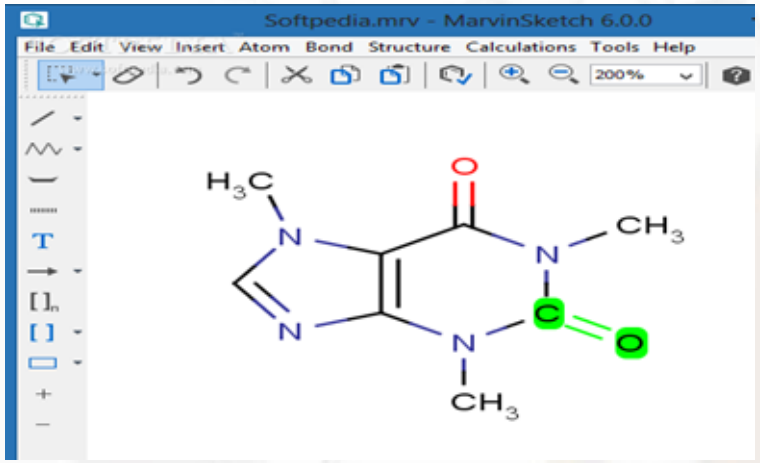


PDBbind Database

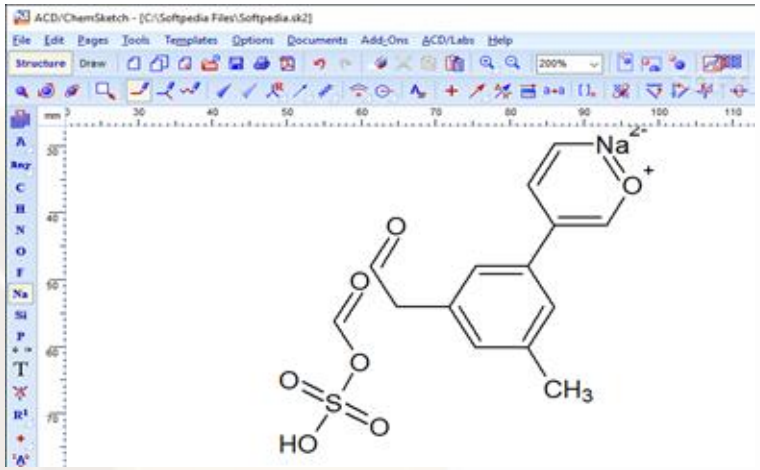
Draw Tools



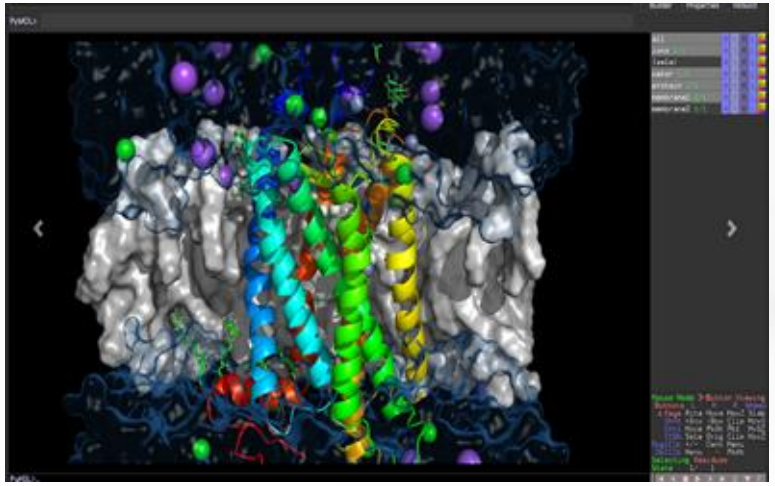
ChemDraw



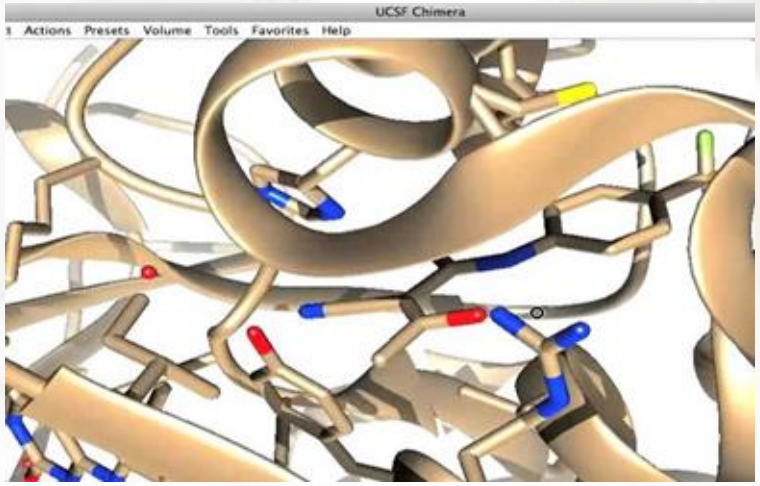
MarvinSketch



ACD/ChemSketch

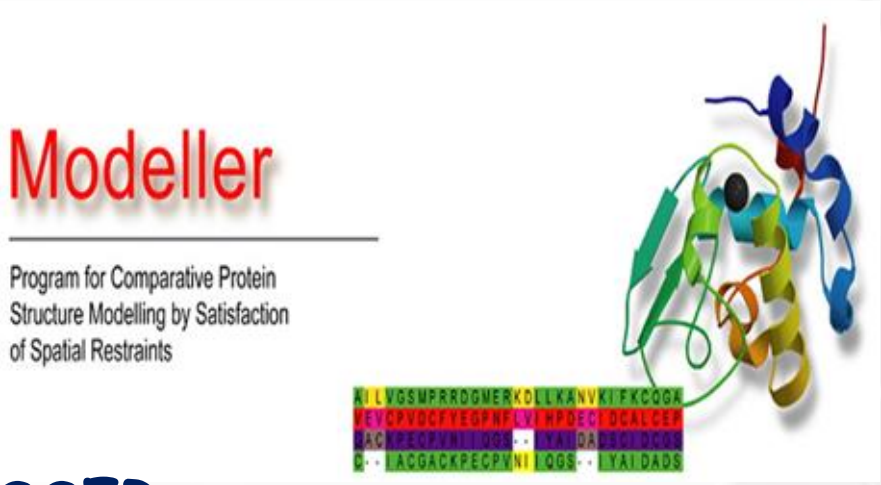


Pymol



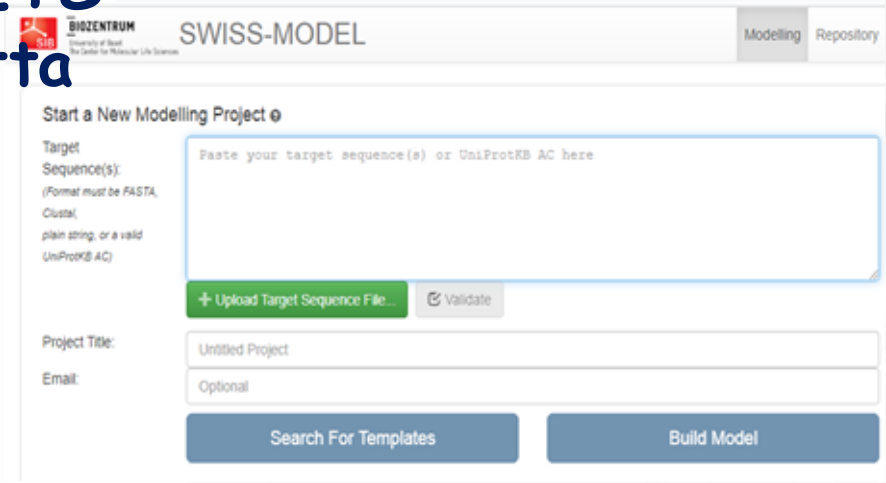
UCSFChimera

Homology Modeling



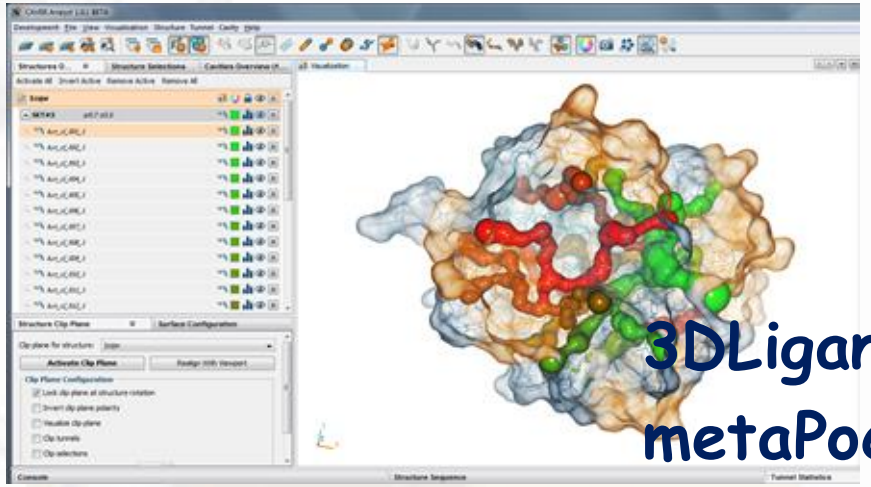
Modeller

I-TASSER
LOMETS
Robetta



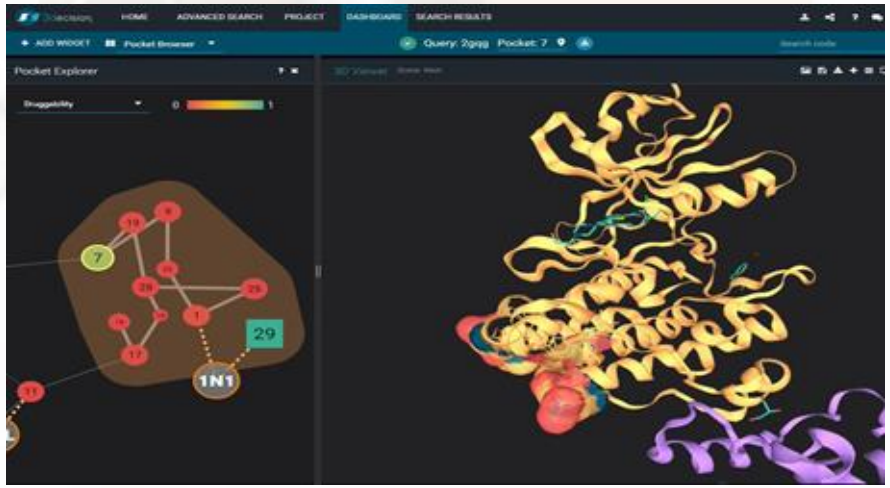
SWISS-MODEL

Binding Site Prediction



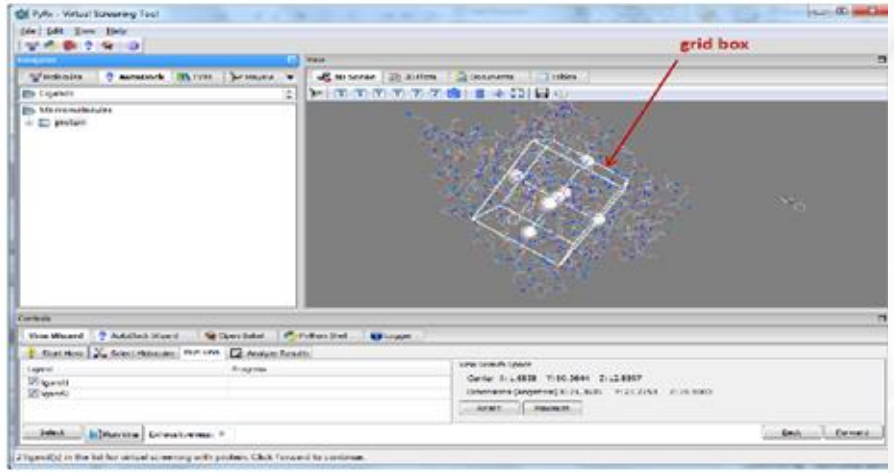
3DLigandSite
metaPocket
FINDSITE

CAVER



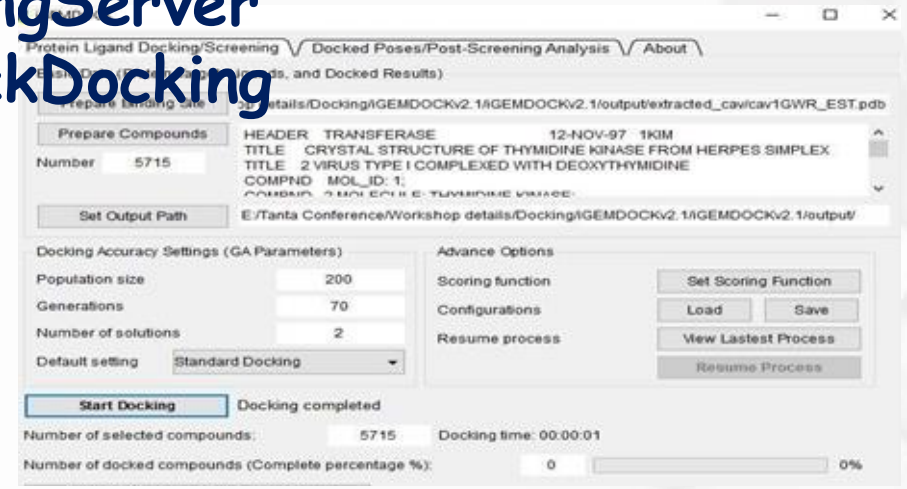
Pocketome

Molecular Docking



GOLD
SwissDock
DockingServer
1-ClickDocking

Autodock Vina



iGemdock

Molecular Dynamics

GROMACS

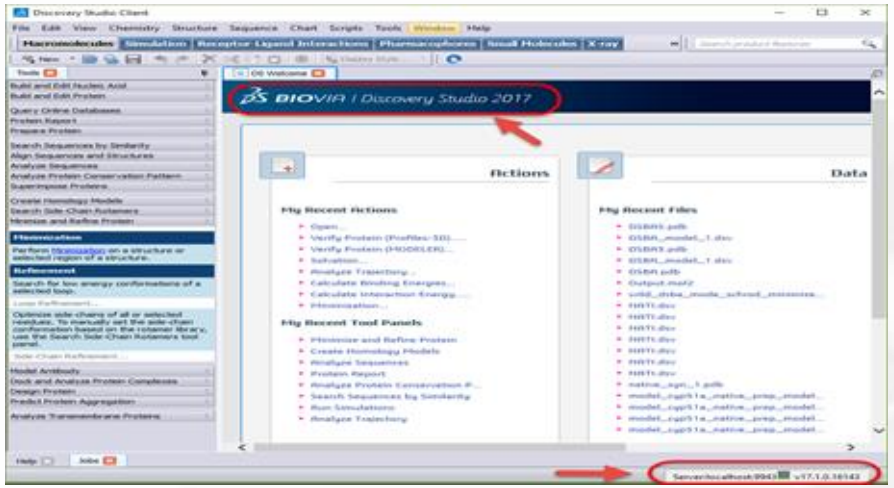
Amber

SwissParam

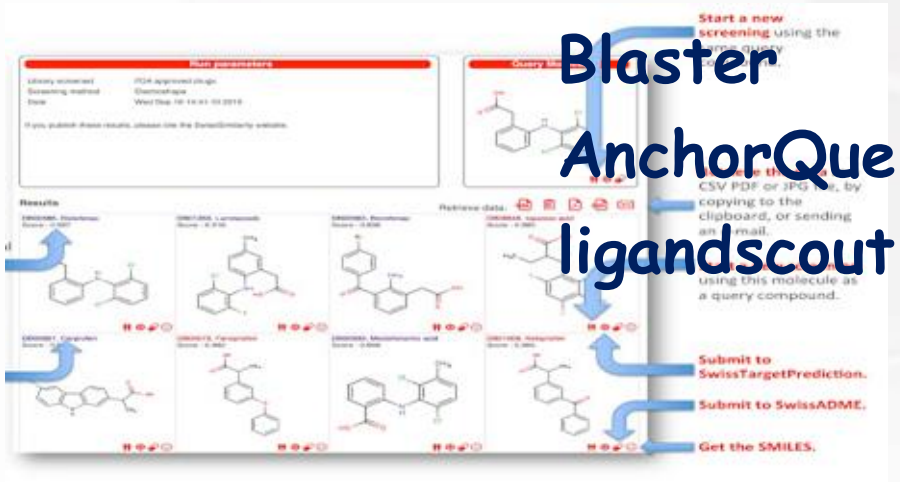
SwissSideChain

CHARMM-GUI

Ligand Screening



Discovery Studio



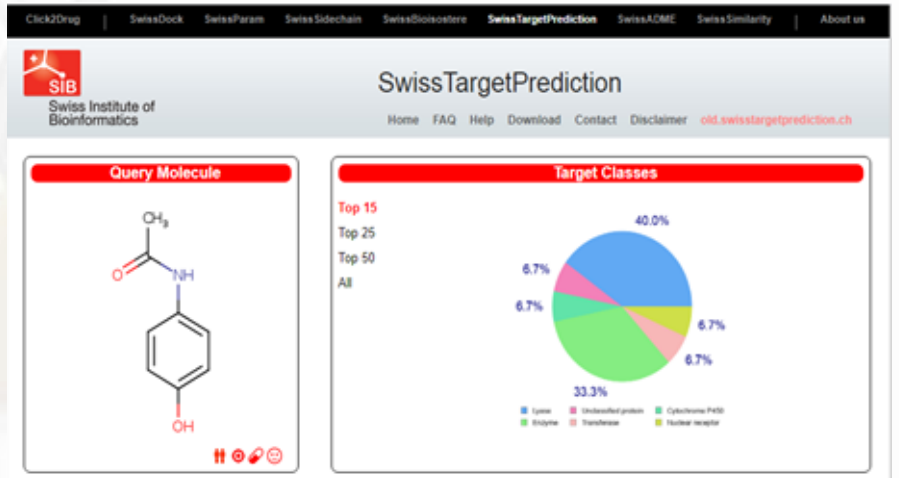
Blaster

AnchorQuery

ligandscout

SwissSimilarity

Target Prediction

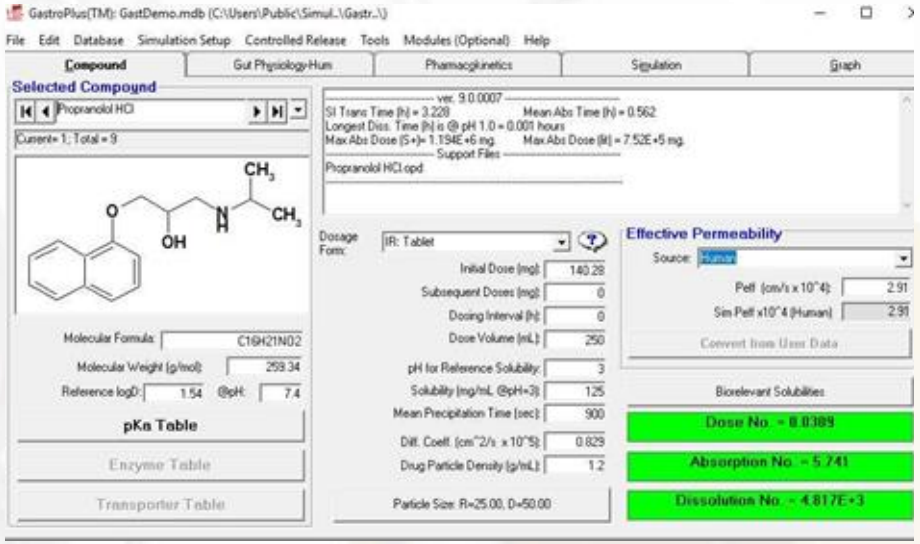


Swiss Target Prediction

MolScore-Antibiotics

ADME Toxicity

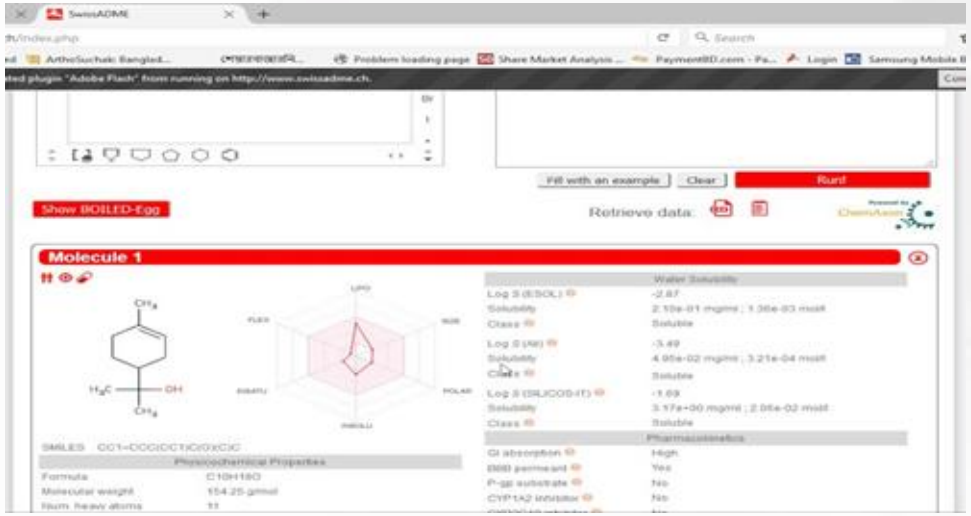
VolSurf



GastroPlus

Molinspiration

PACT-F



SwissADME

OSIRISPropertyExplorer

Some Uncomfortable Truths

- This course will not make you a Bioinformatician/Drug design expert
  - But practice will. . .
- The best way to learn is to do ("I don't know how to do this yet, but I will find out.")

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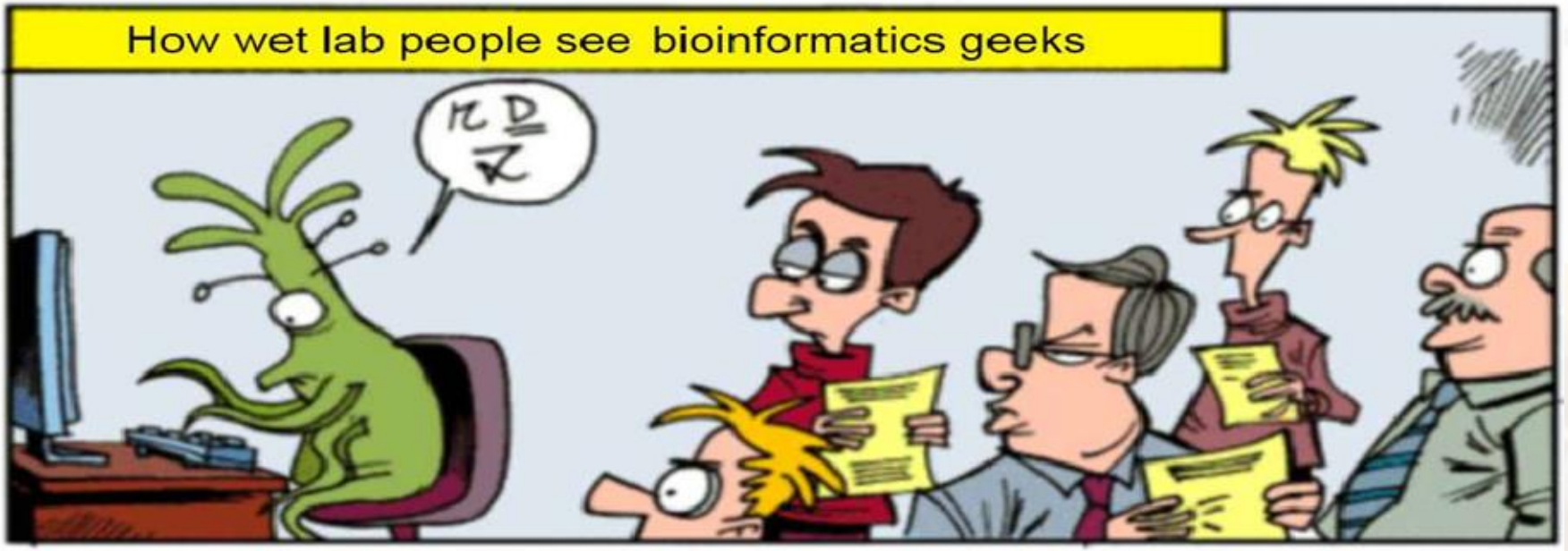
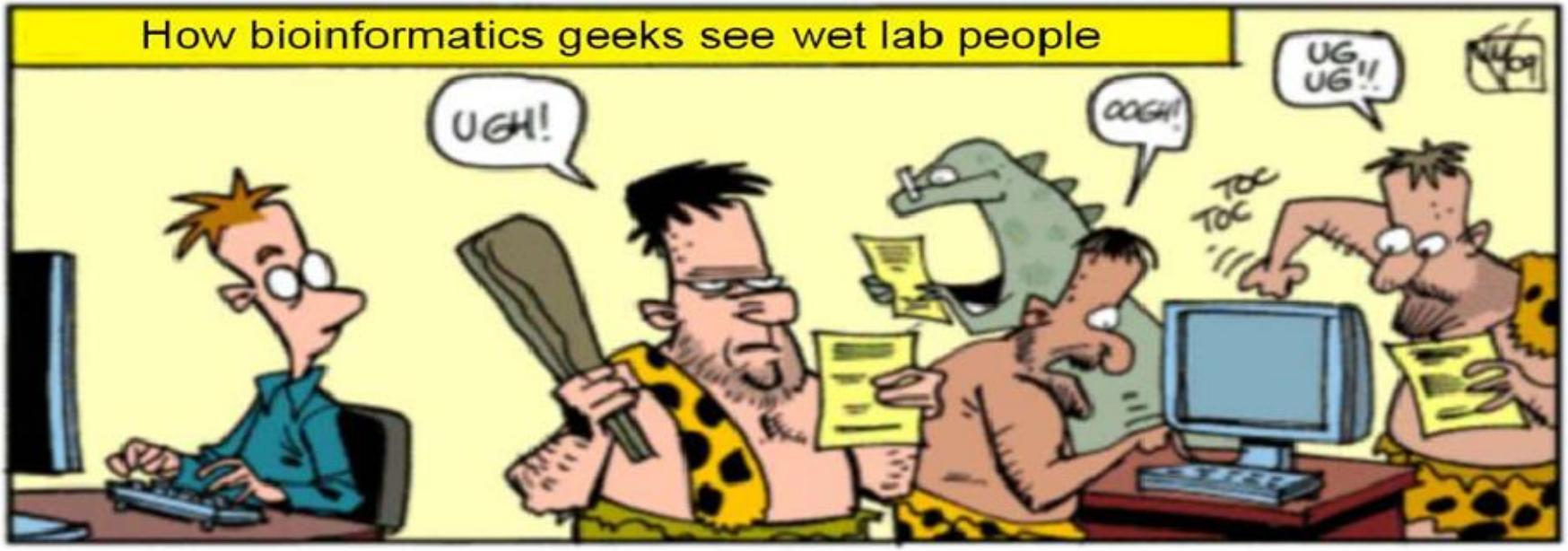




segundavis1995.olatomide@gmail.com
+2348064770402
www.biocode.ltd

THANK YOU

Bioinformatics: Computational Drug Discovery and Design

Module 1b:

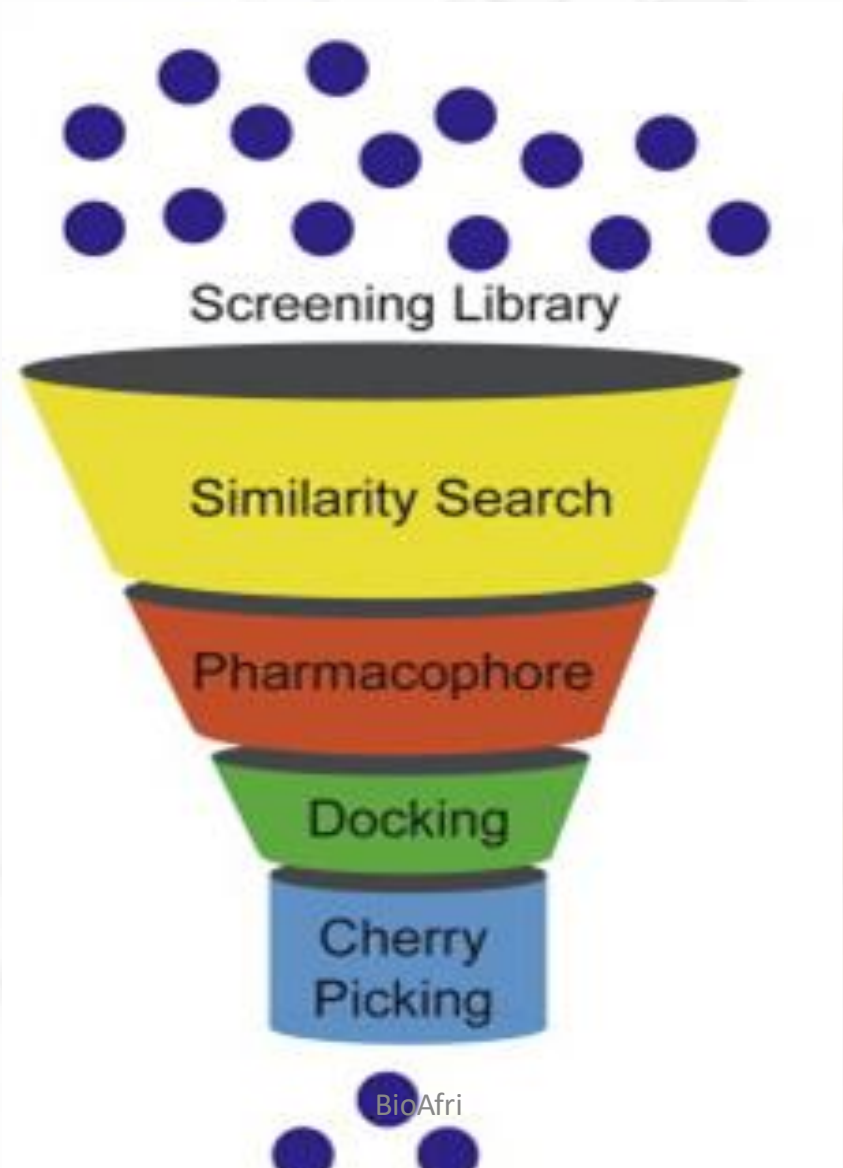
Bioinformatics: Role in Drug Design

Ms. Madhana Priya (M.Phil, P.G.D.S.P)
Research Scholar
Department of Biotechnology
SRIHER, Porur, Chennai, India

What is Virtual Screening

- Computational technique used in drug discovery to search libraries of small molecules
- To identify those structures which are most likely to bind to a drug target, typically a protein receptor or enzyme
- Mainly used when the ligand number is >10,000

Steps in Virtual Screening



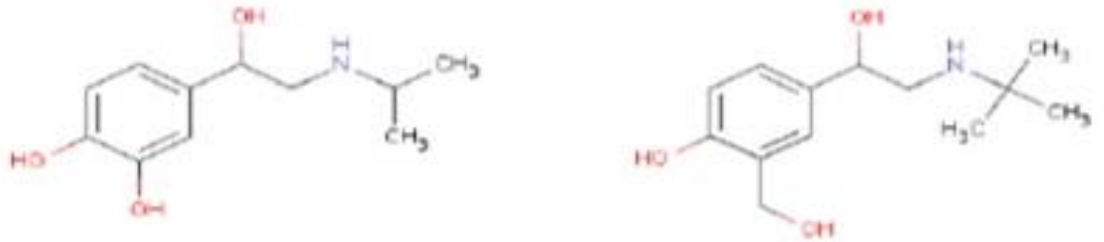
Step1: Libraries for Virtual Screening

- ZINC DataBase
- Maybridge
- Seleck Chem
- Asinex
- ChemBridge
- Drug Bank
- Natural Compounds. Etc.

Step 2: Similarity Search

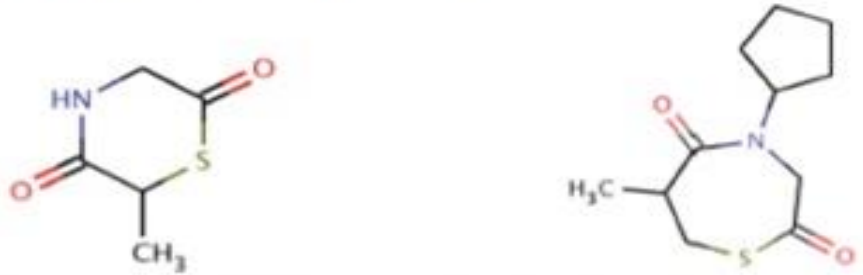
- Matching of Chemical, Biological and Pharmacological Features of two compounds

Chemical



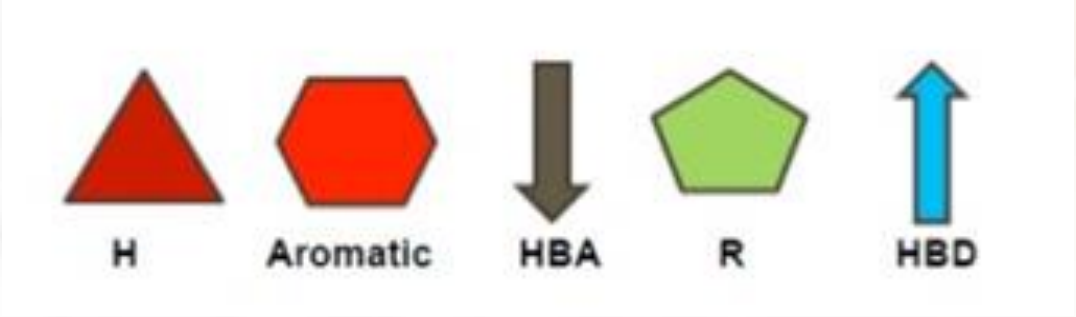
The two structures on top are chemically similar to each other. This is reflected in their common sub-graph, or scaffold: they share 14 atoms

Pharmacophore



E-Pharmacophore Screening

- Set of features common to series of active molecule
- Hydrogen-Bond donors and acceptors, Positively and Negatively charged groups and hydrophobic regions are the general feature,
- These features are known as pharmacophoric groups

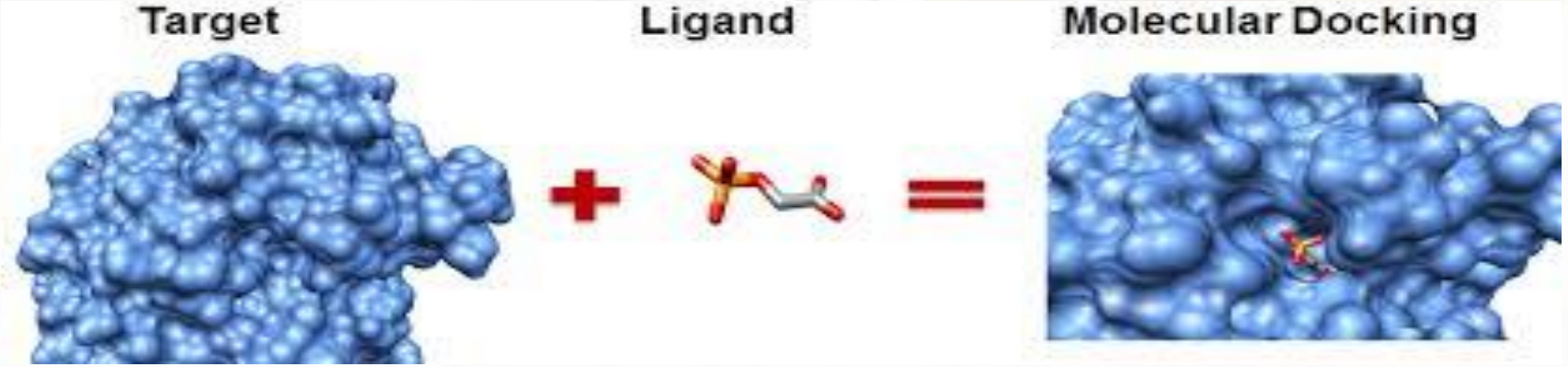


Tools for Pharmacophore Screening

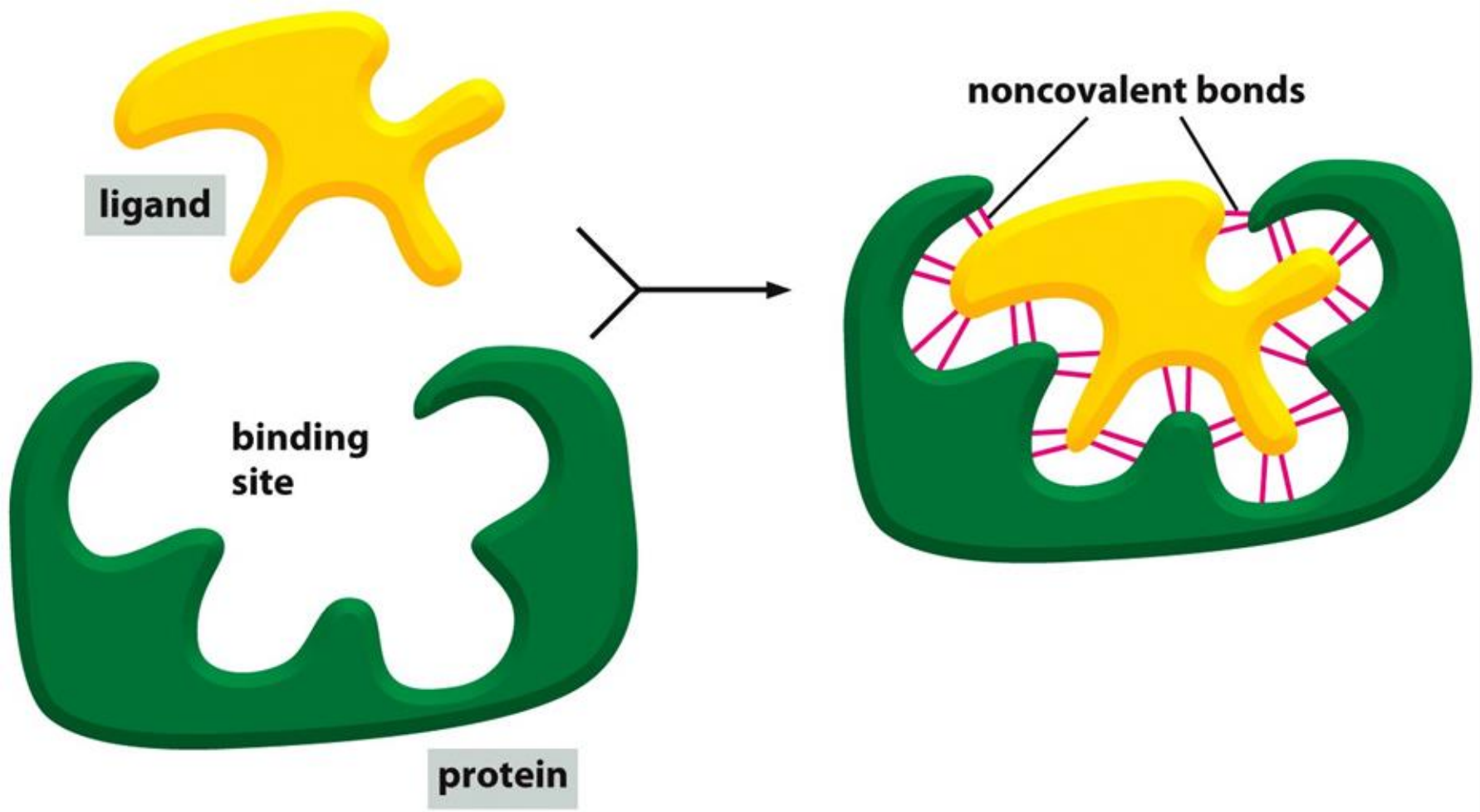
1. Catalyst
2. Ligand Scout
3. Pharner
4. SHAFTS
5. PharmaGist
6. Phase- Schrodinger

Step 3: Docking

- **Docking** is the study of how two or more molecular structures (e.g., drug and enzyme or protein) fit together. In a simple definition, **docking** is a molecular modeling technique that is used to predict how a protein (enzyme) interacts with small molecules (ligands).

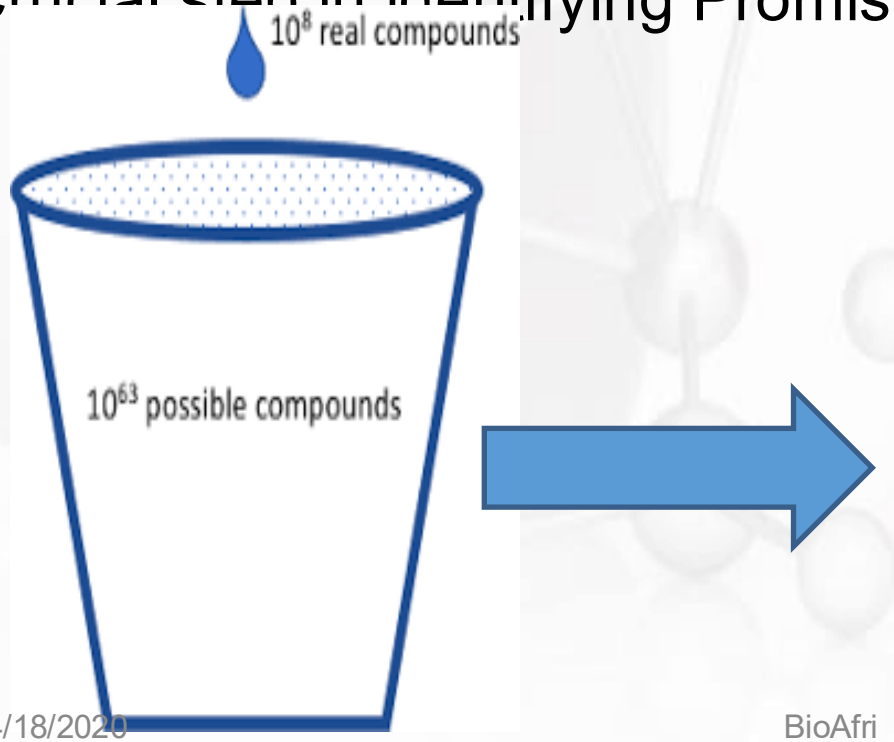


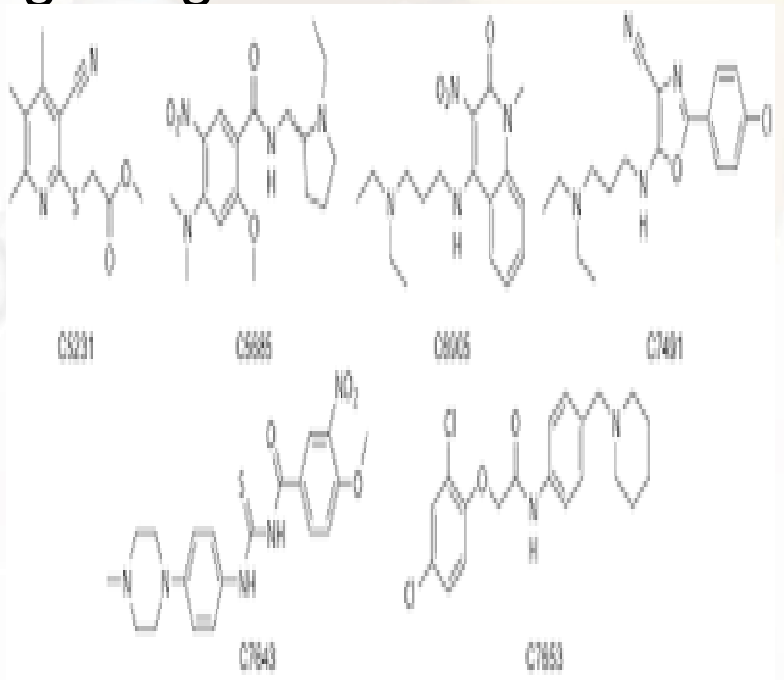
Concept of Docking: Lock and Key Model



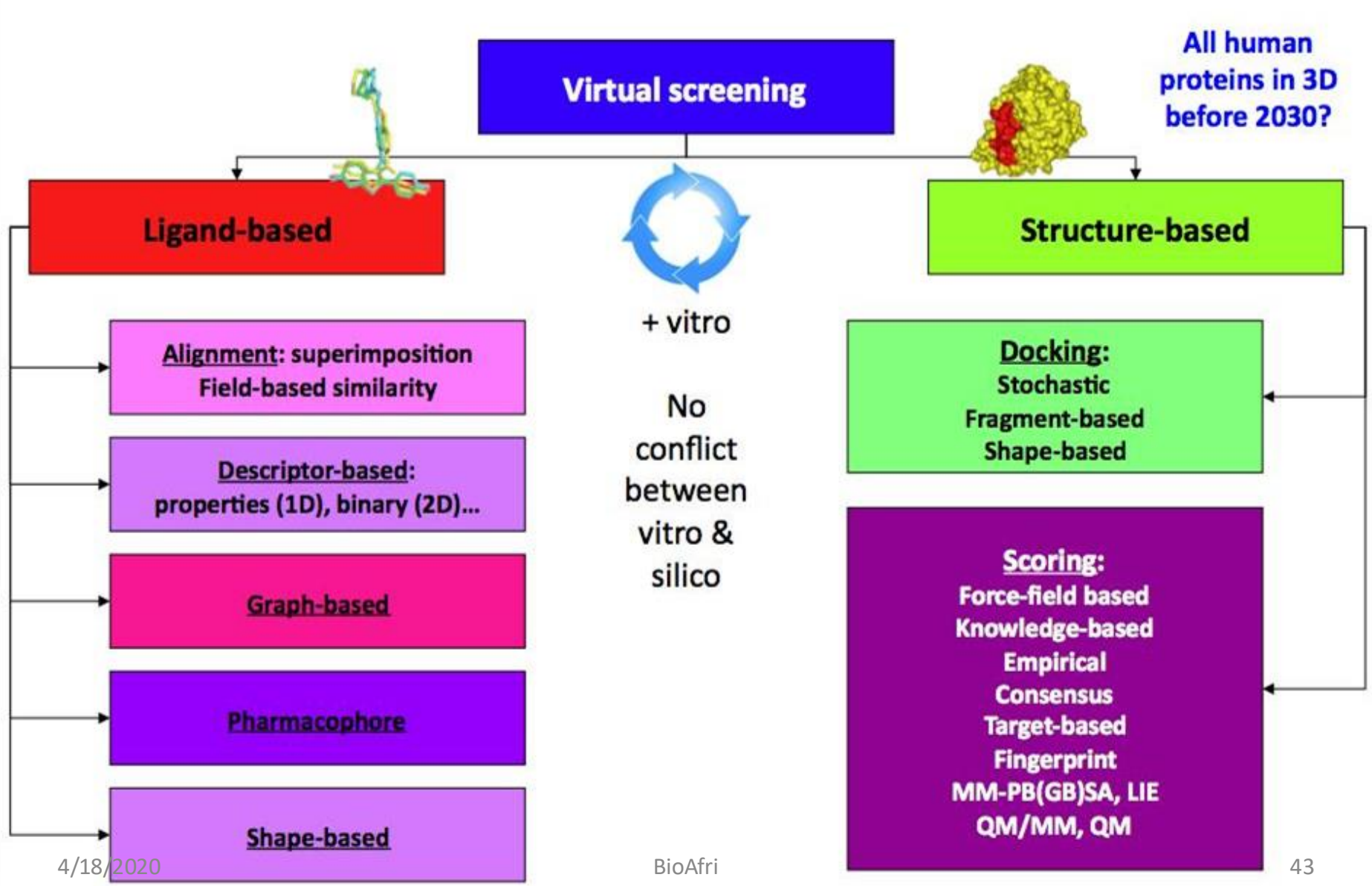
Step 4: Cherry Picking

- The identification of lead **molecules**
- Selection, based on own criteria, from filtered collection of small molecule structures, and also has a lower binding energy.
- Crucial step in identifying Promising Drug like molecules





Types of Virtual Screening



Importance of Molecular Docking in drug design

- **Molecular docking** is one of the most frequently used methods in structure-based **drug design**, due to its ability to predict the binding-conformation of small **molecule** ligands to the appropriate target binding site
- Drug Designing is a long Process. Docking reduces the time
- Cost Efficient

- Complementary approach to experimental HTS
- Identifying hit molecules as a beginning for medicinal chemistry
- Different approaches of VS have been created for lead discovery depending each time on the availability of experimental information (SBVS Ligand-Based VS, Fragment-Based VS,etc.)
- Several successful examples of identifying low nM leads that show the intended biological activity
- A large number of docking programs and scoring functions
- VS can use as input a desirable target structure complexed with a specific ligand even if there are no experimental data, through molecular modeling

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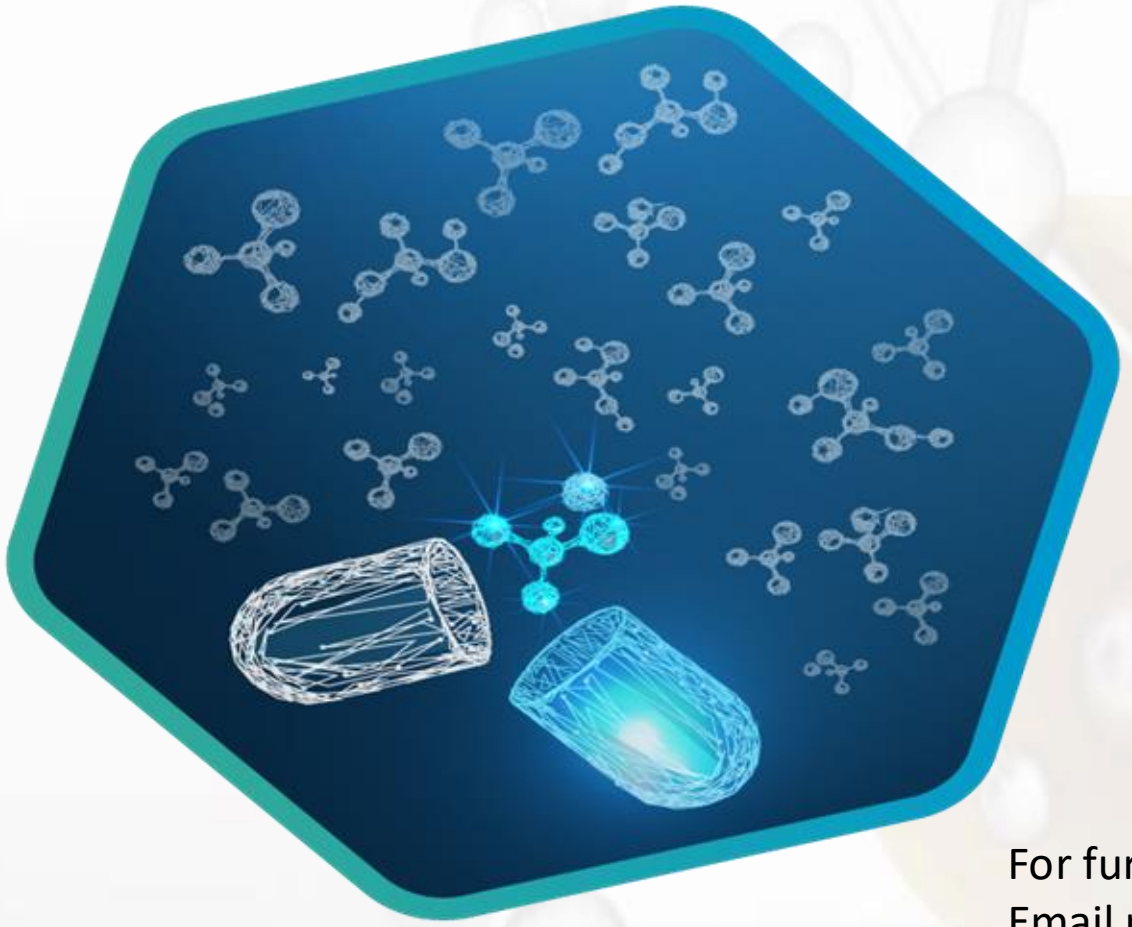

For further queries:
Email me at
madhanapriya7@gmail.com

THANK YOU