

Bioinformatics: Computational Drug Discovery and Design

Module 1a: Bioinformatics: Role in Drug Design

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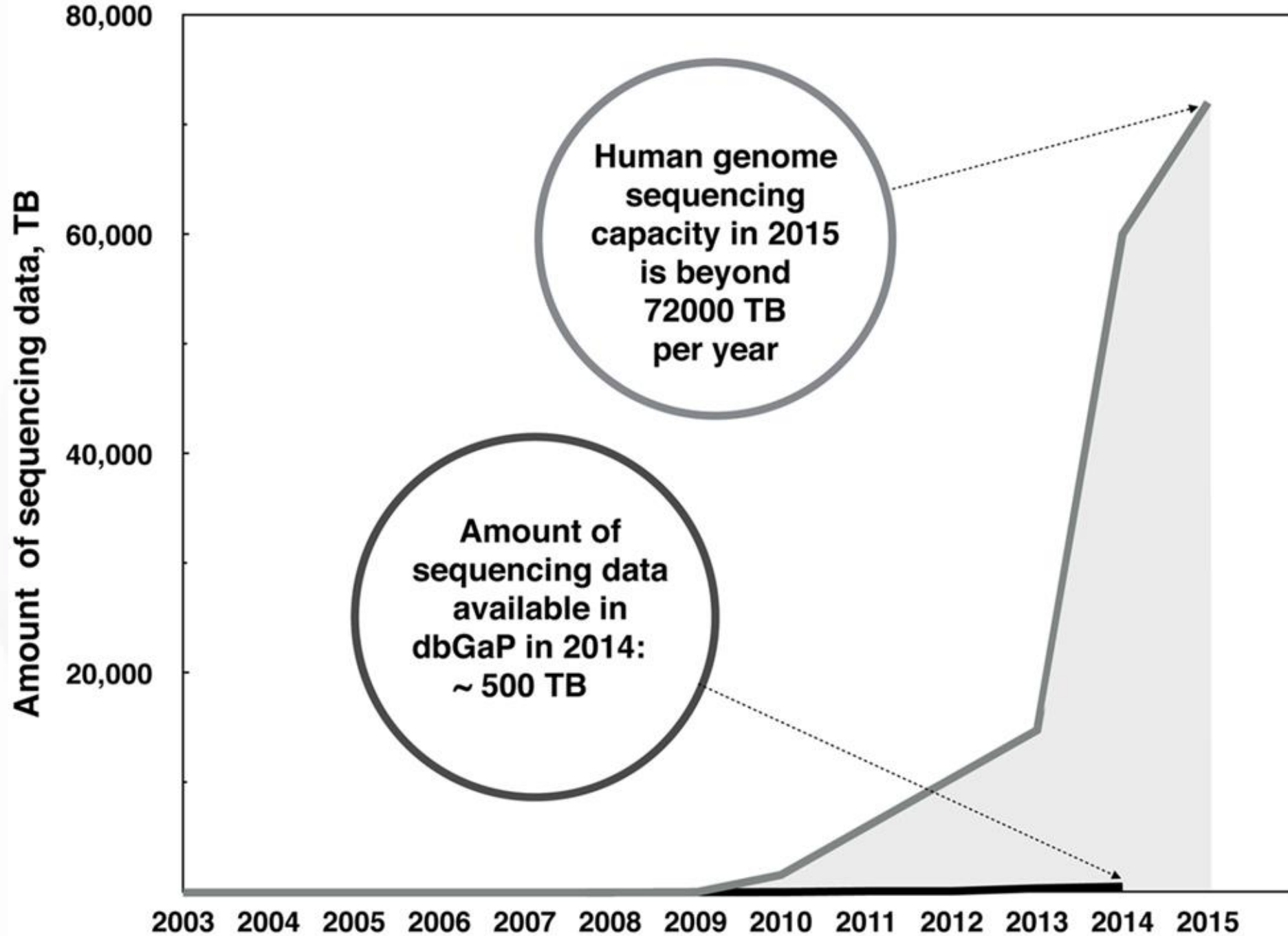
Computational Tools for Drug Designing

What is Bioinformatics



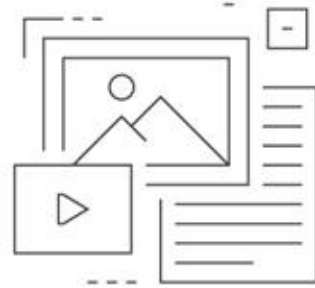
April 20

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



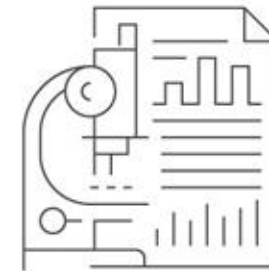
BIG DATA

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

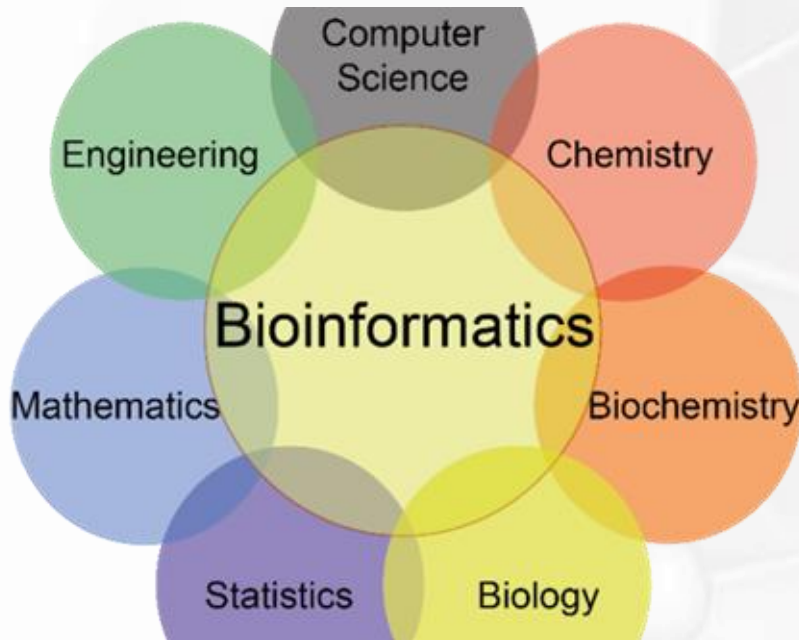
RESEARCH AGRICULTURE PERSONALIZED MEDICINE PHARMA R&D

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).



WORLDWIDE PDB PROTEIN DATA BANK

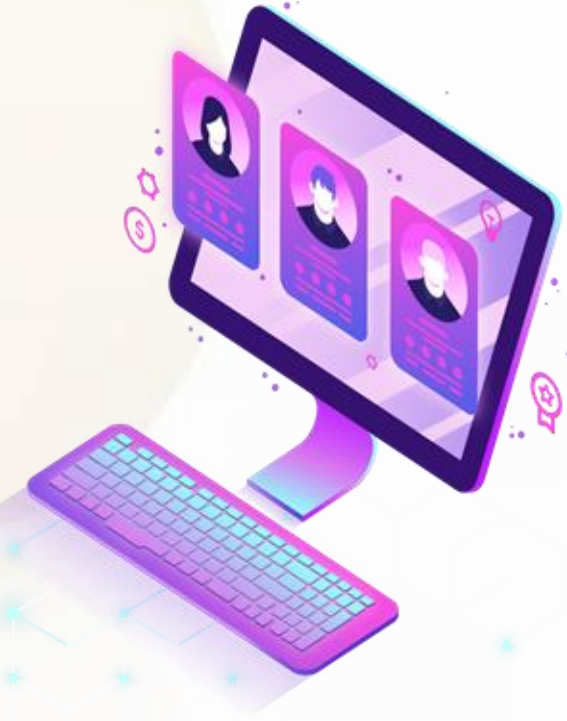
Biological Databases

swissprot UniProt

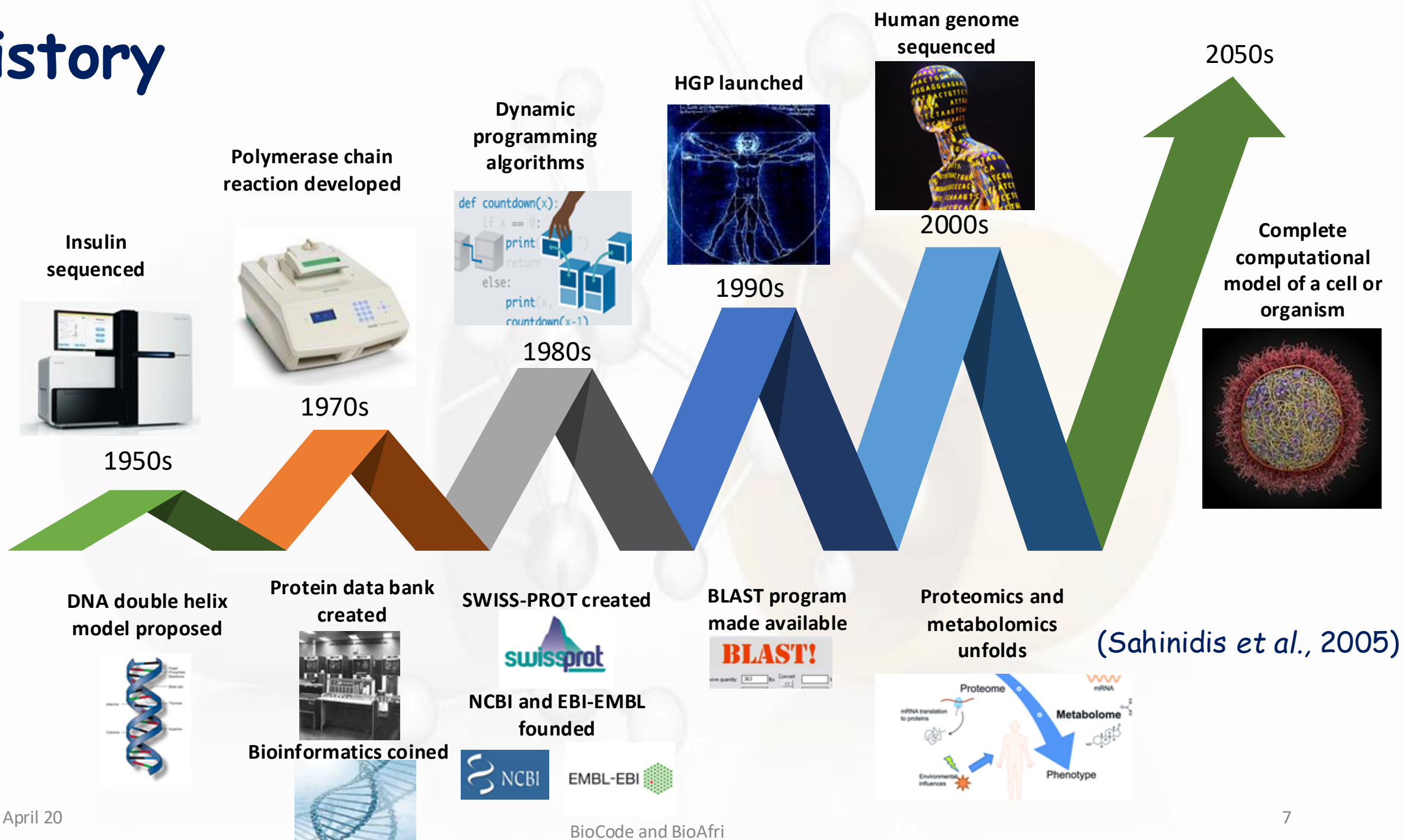
NCBI

FlyBase

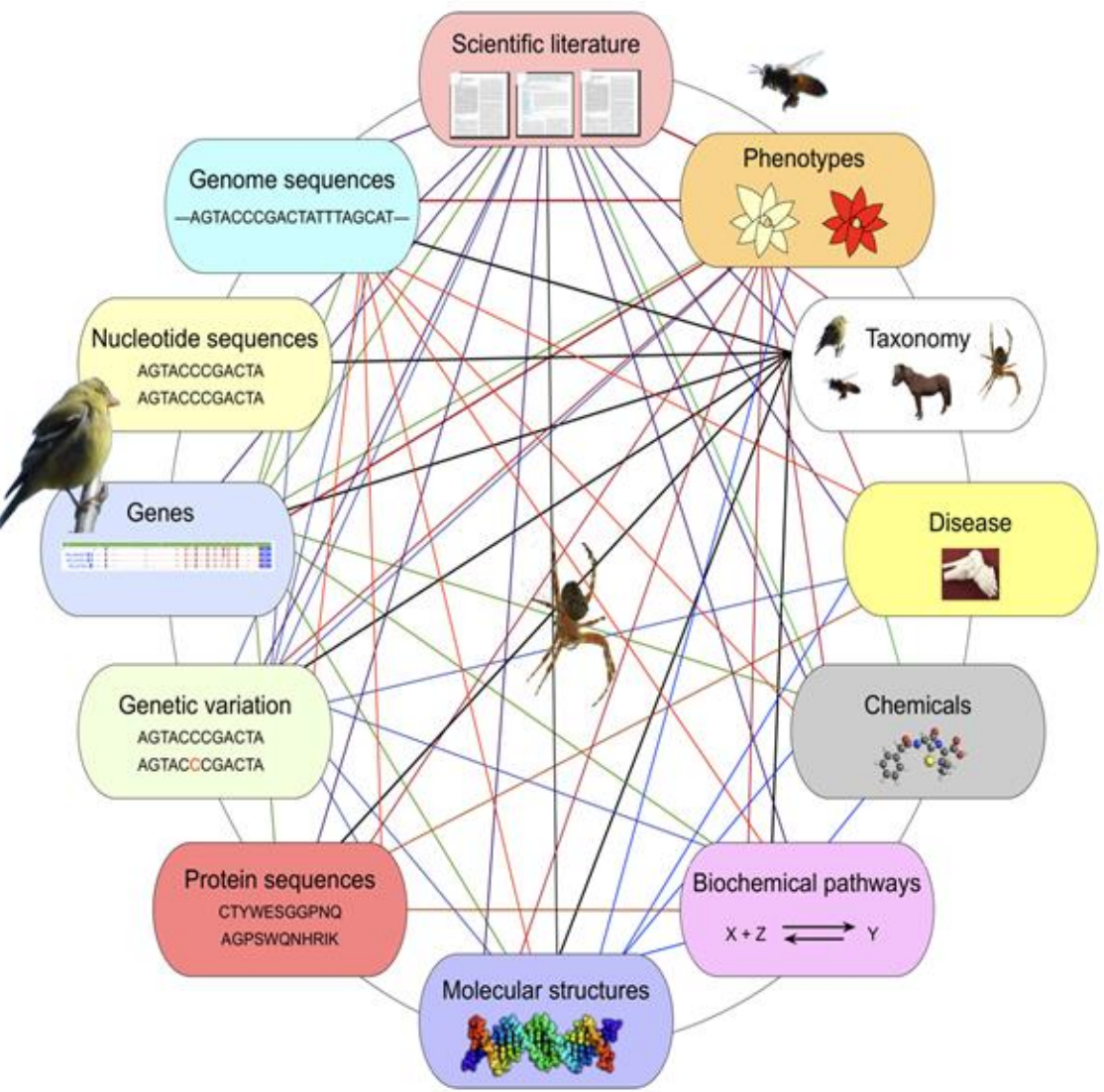
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ATTTCCTGGCAAGCCGGACTTTTTCGGATGAATGAAATGAAAAA
AATAAATAAACAACAAGTGCACAACAGCCGGGCATCTTCATAGAT
AACTTCTGCCTCACTTGGTATATGTACTTATCACATAGACATATATATA



History



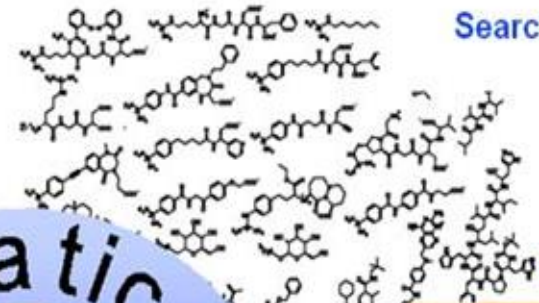
Applications of Bioinformatics



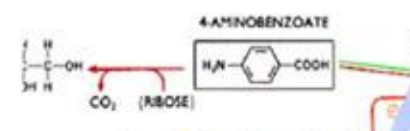
DNA chips: comparison of cell states



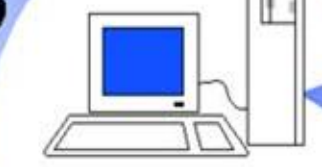
Search for new drugs



Genetic variations

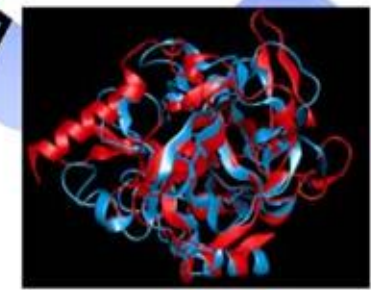
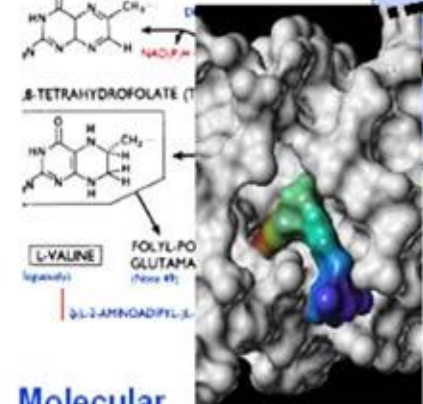


Bioinformatics



Data handling, Algorithms
Statistics, Visualisation

Optimizing therapies



Genomes
ccctgtggagcccccacteggggtggcc
ctctactcccaggagccagggagggagggag ...

Proteins
MTNRNFRQIINLLDLR VQR RVPVIHQ TETA
ECGLACLA MCGHF GK NIDIIYLRKFNLS ...

Sequence analysis

© Thomas Lengauer



Application in Drug Design

What is a Drug?

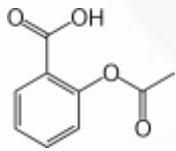


A substance that, when absorbed, alters normal bodily function

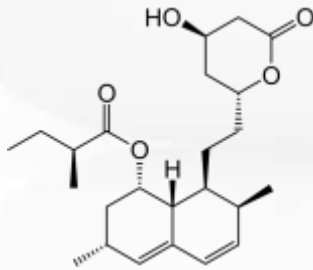
In pharmacology: FDA-approved for the diagnosis, treatment, or prevention of disease.

Classification

Small Molecule

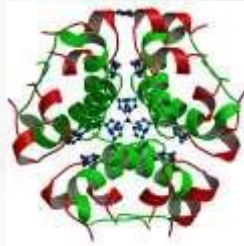


Aspirin

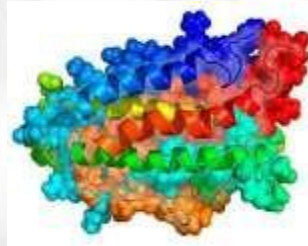


Lovastatin

Protein

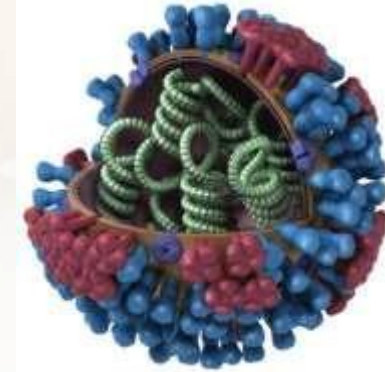
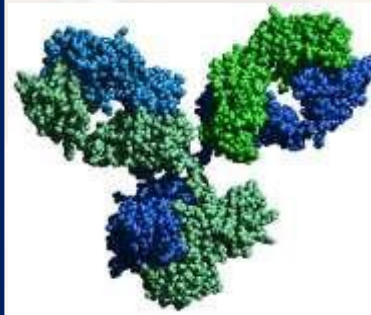


Insulin



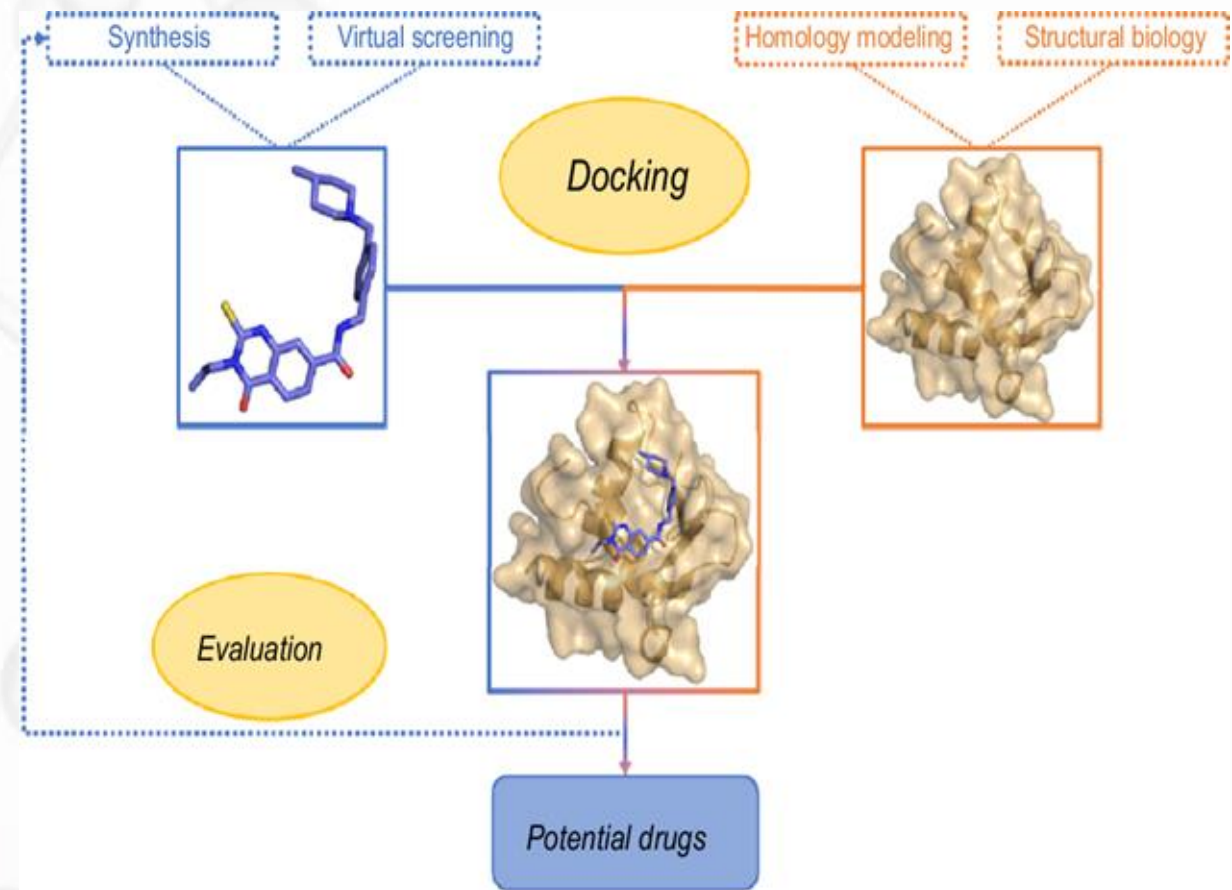
Erythropoietin

Vaccine



Different Terms Used in CADD

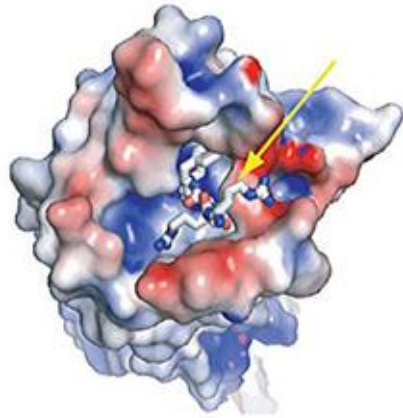
- **Receptor/Host** - large molecule (protein) receiving ligand.
- **Ligand/Key** - small molecule that binds to receptor
- **Docking** - Computational simulation of a candidate preferred orientation to a receptor.
- **Binding mode** - conformation of ligand-receptor bound to each other.
- **Pose** -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

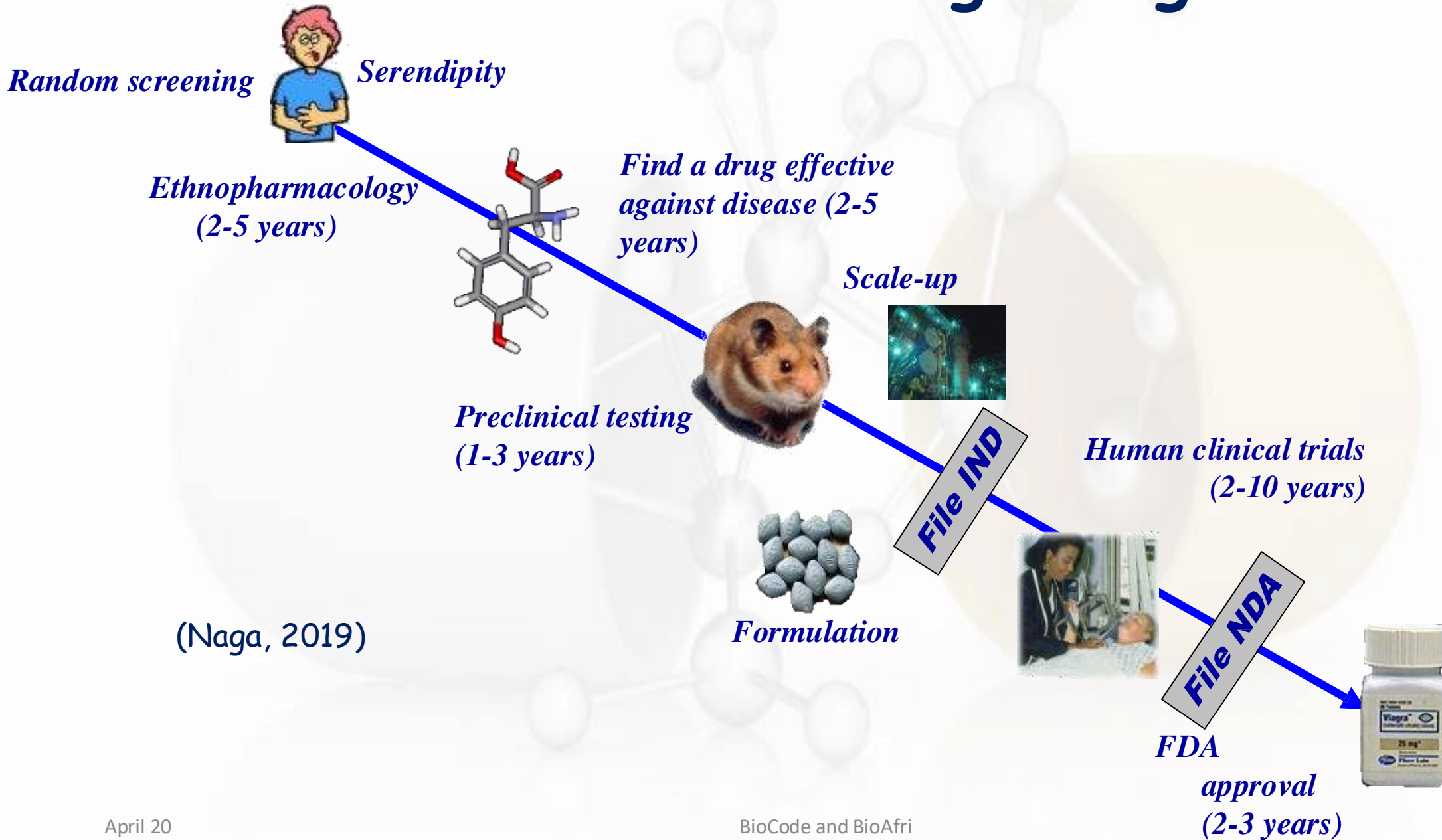


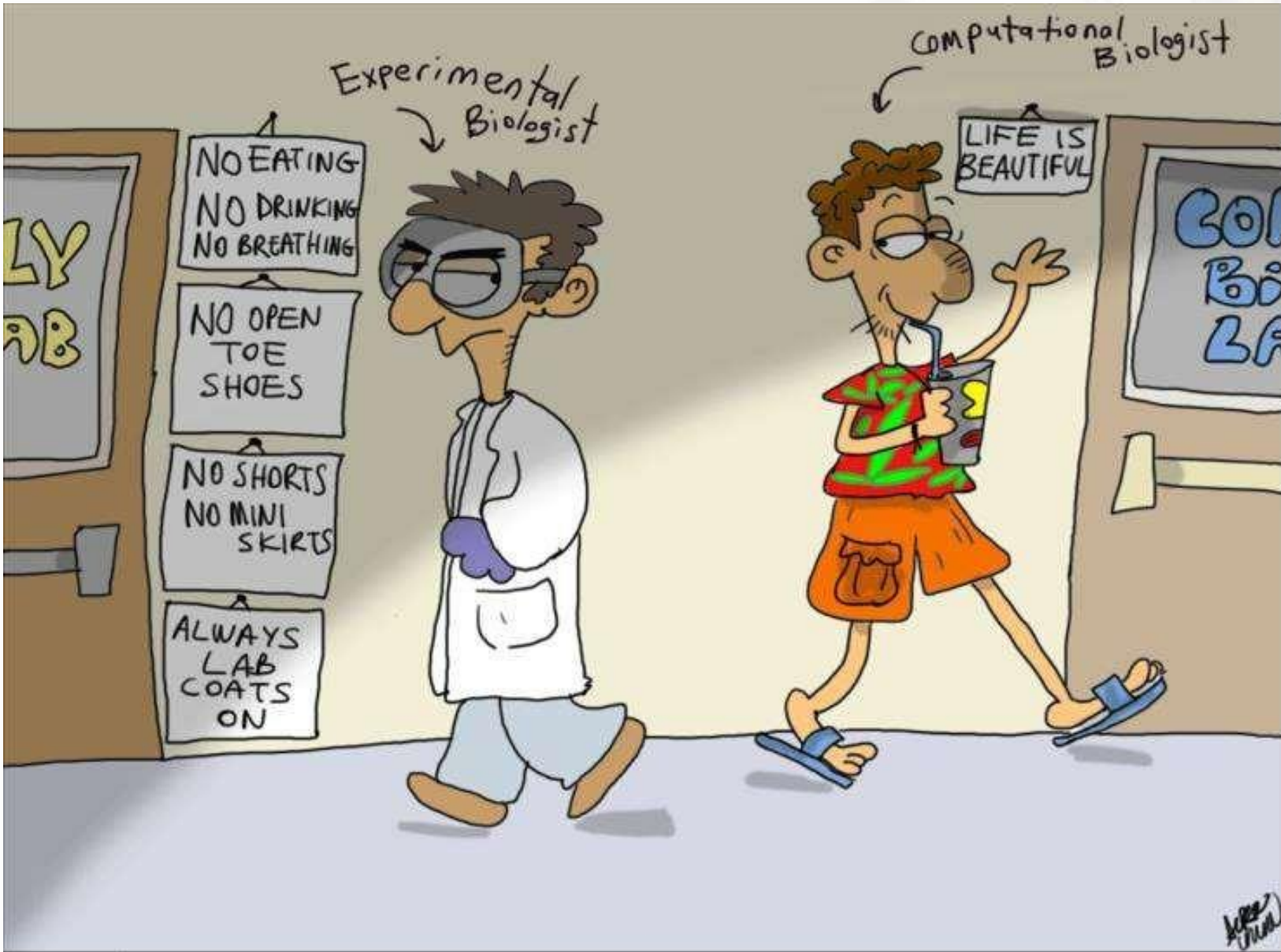
is the inventive process of finding new medications based on the knowledge of the biological target (Liljefors *et al.*, 2002).



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

Traditional Drug design

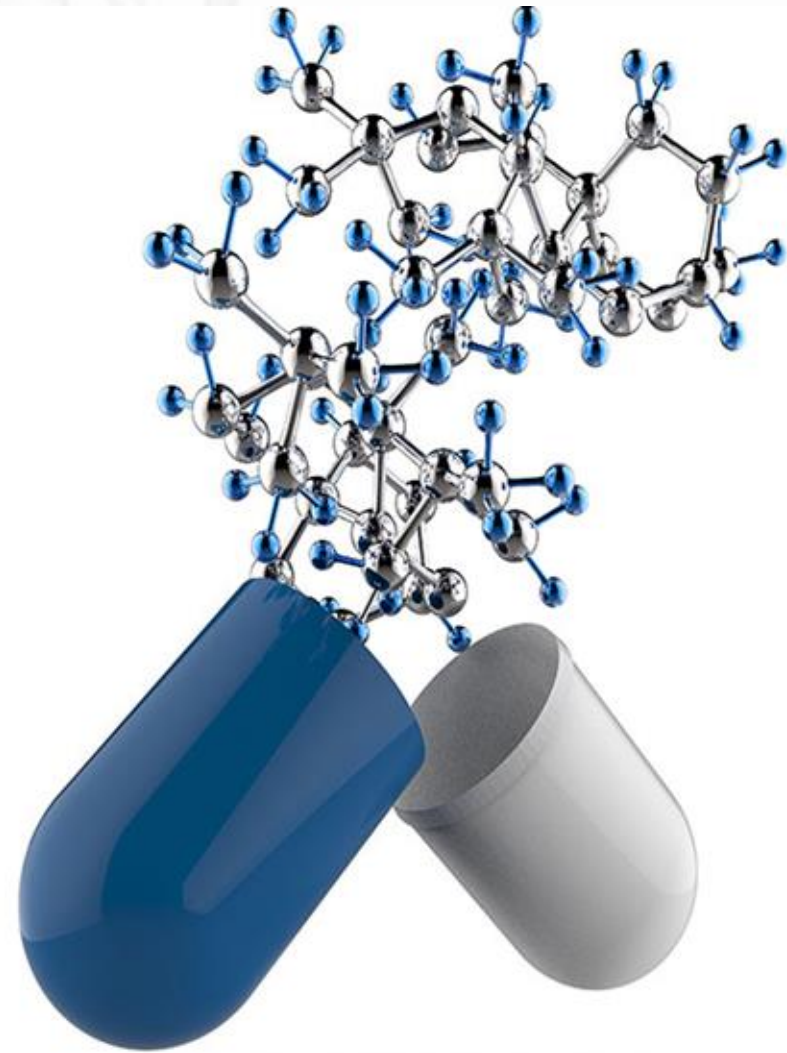


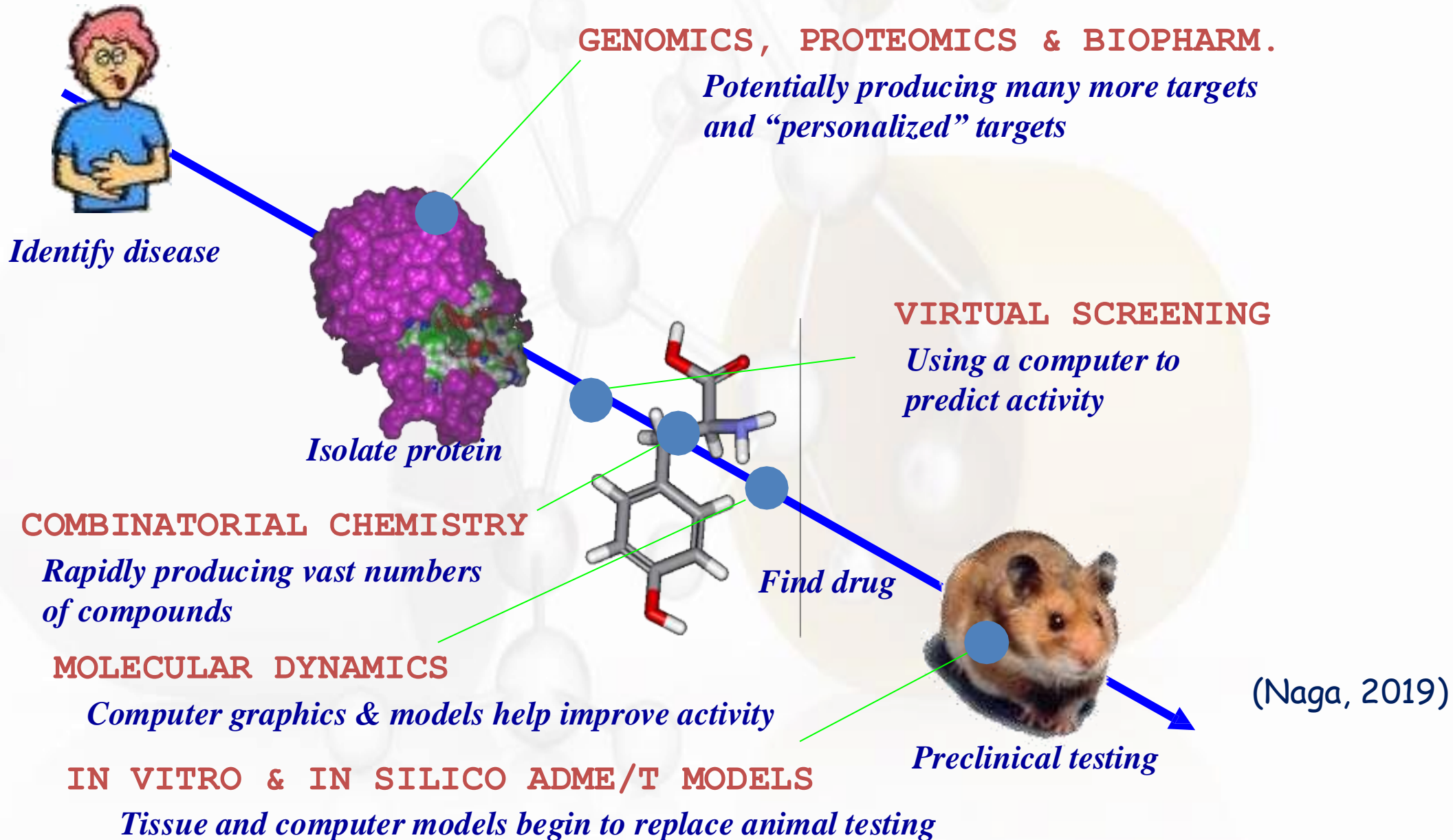


- Drug discovery takes decades and it is costly (Mohs and Greig, 2017).
- To cut down the research timeline and cost, computational biology is imperative.

Computer Aided Drug Design (CADD)

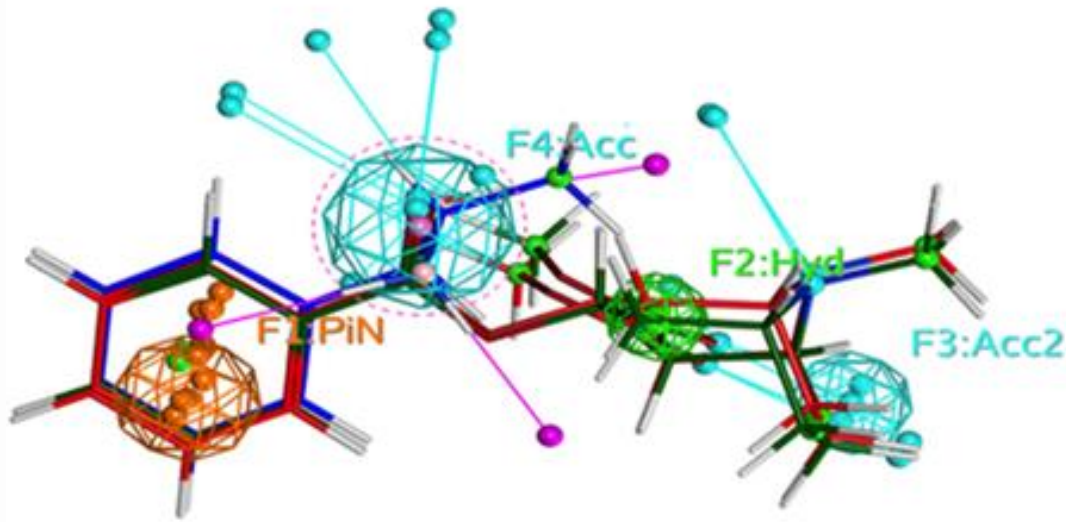
- represents **computational** methods and resources that are used to **facilitate** the design and discovery of new therapeutic solutions (Yu and Mackerell, 2017).





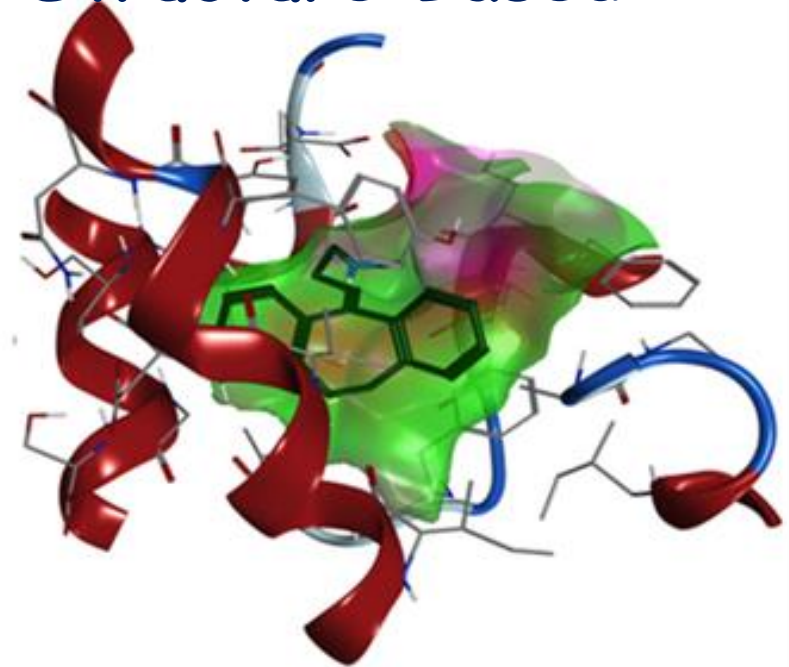
Approaches to CADD

Ligand Based



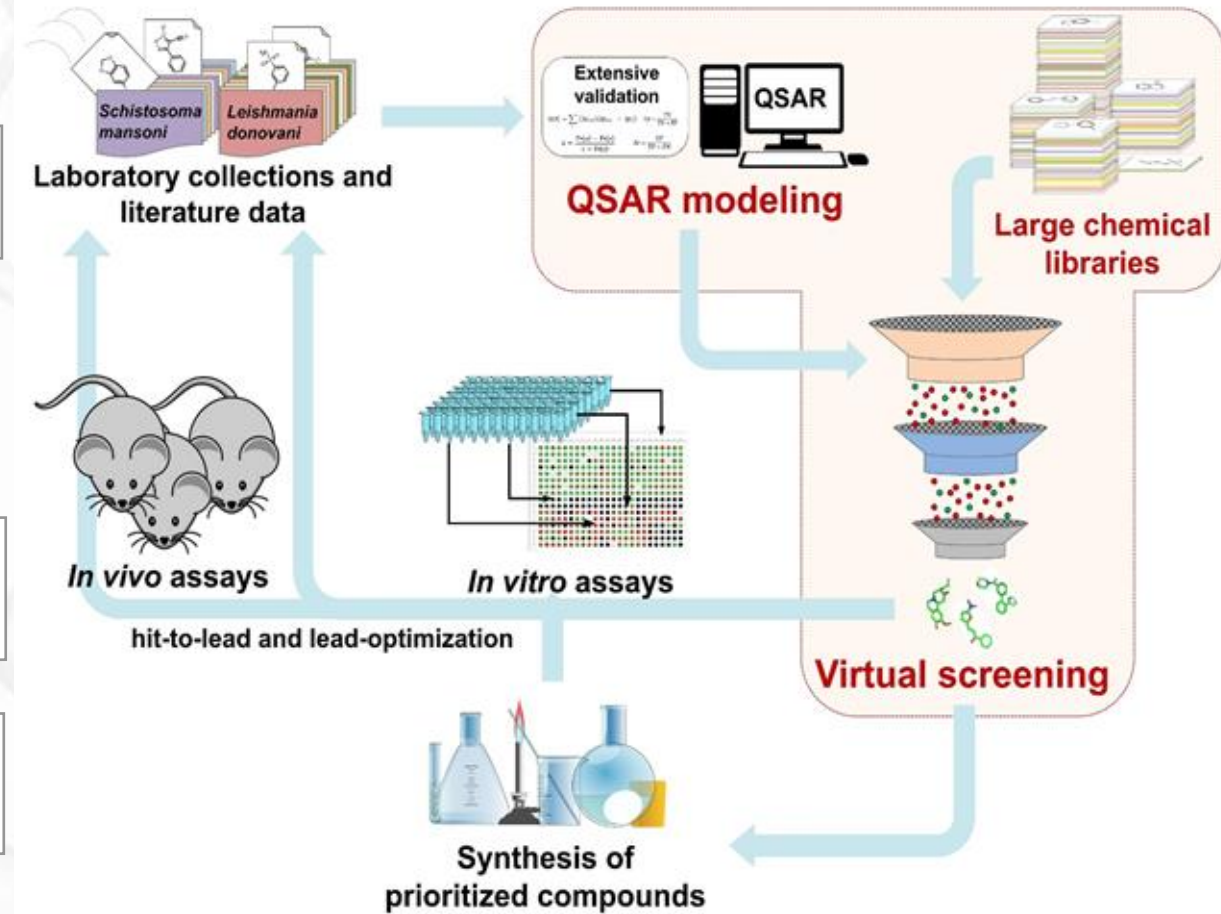
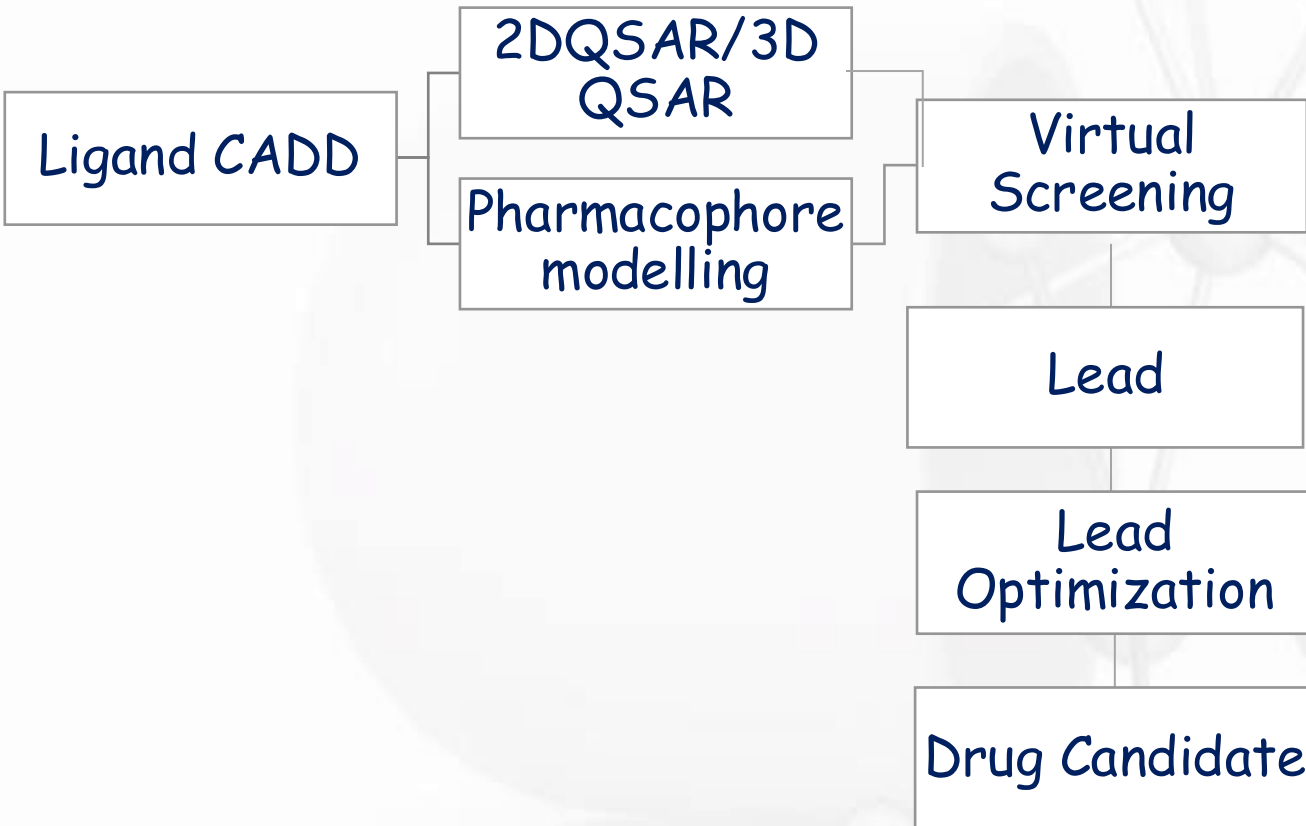
- Relies on knowledge of other molecules that bind to the biological target of interest.
- Used to derive a pharmacophore quantitative structure-activity relationship (QSAR) (Surabhi and Singh, 2018).

Structure Based

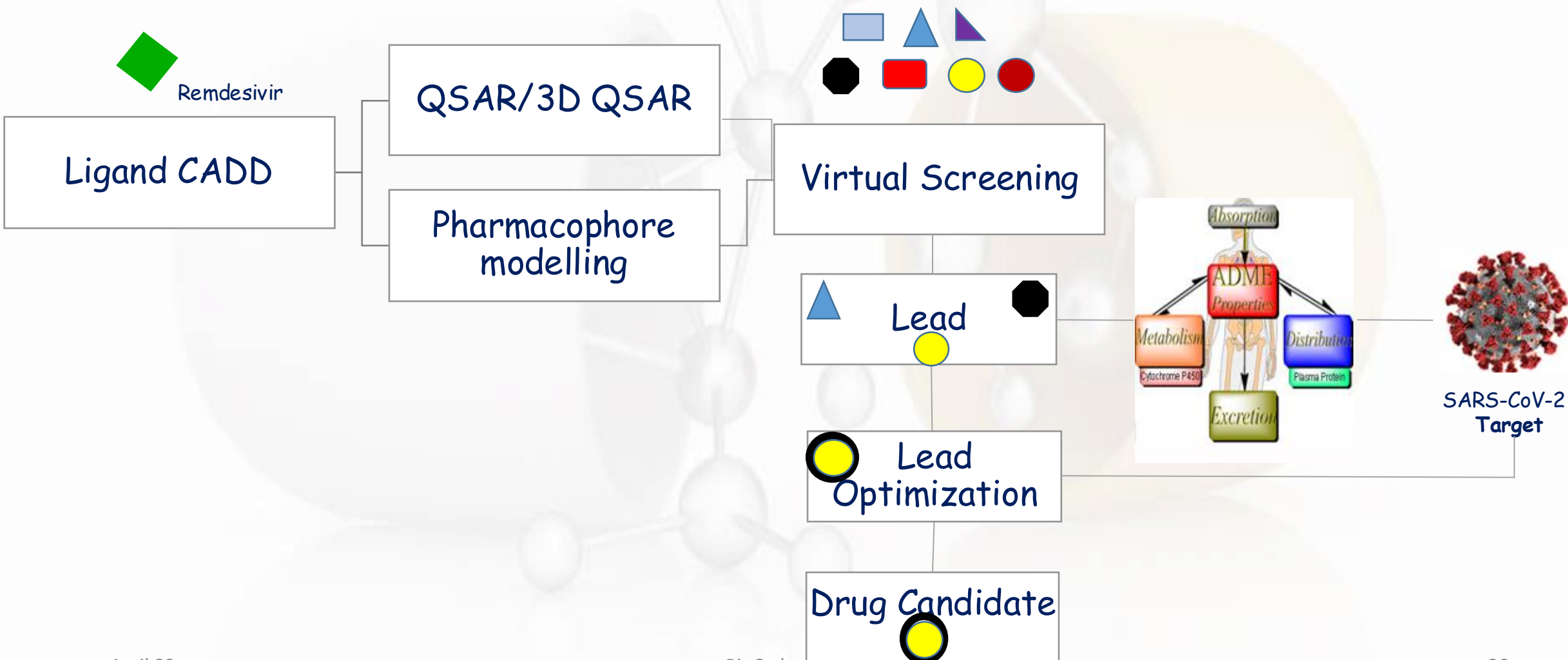


- Relies on 3D structure of the biological target :
- X-ray crystallography, NMR spectroscopy and homology modelling (Surabhi and Singh, 2018).

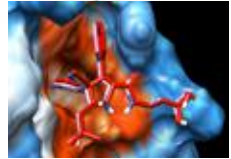
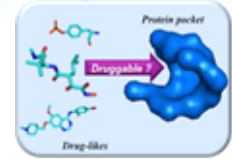
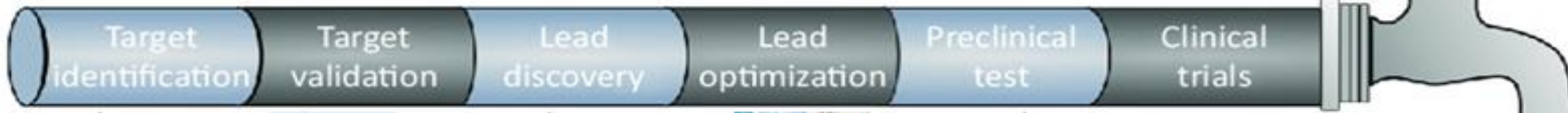
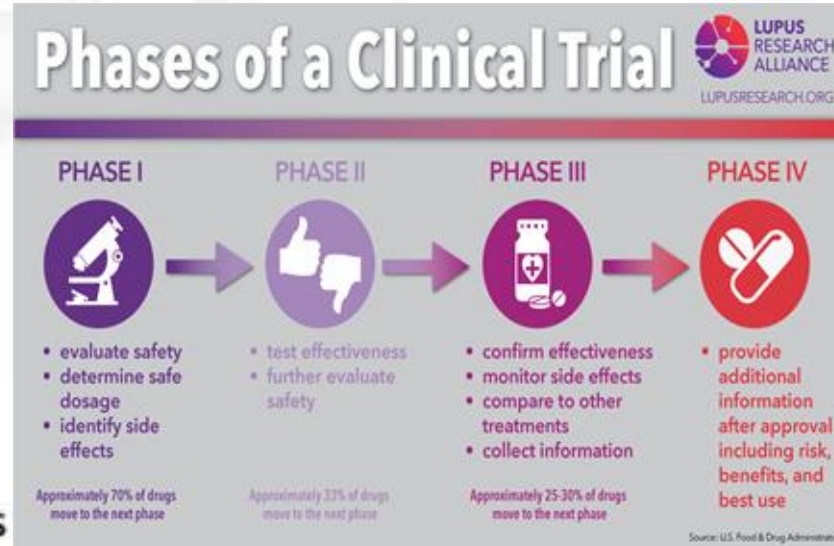
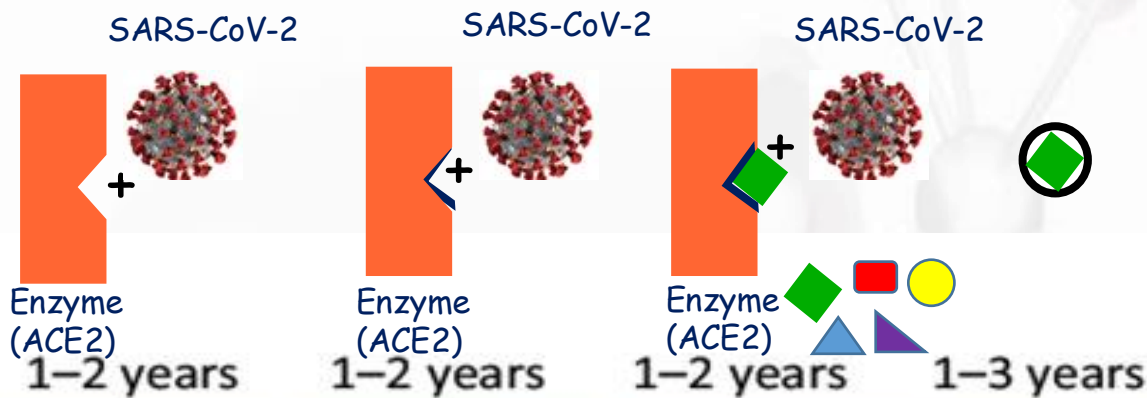
Steps in Ligand Based CADD



Steps in Ligand Based CADD...



Steps in Structure Based CADD



(Yuan et al., 2017)

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

- Target druggability prediction
- Computational system biology

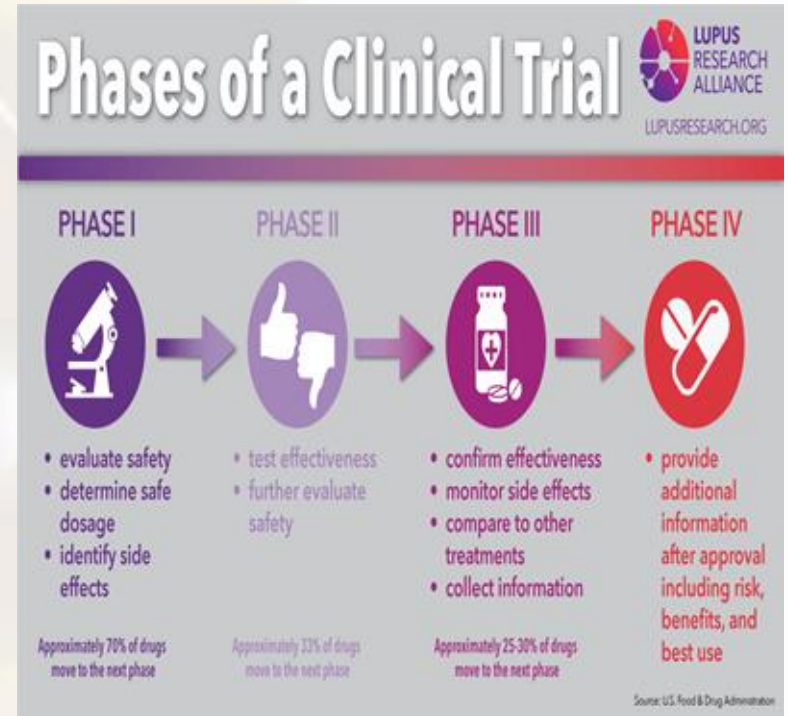
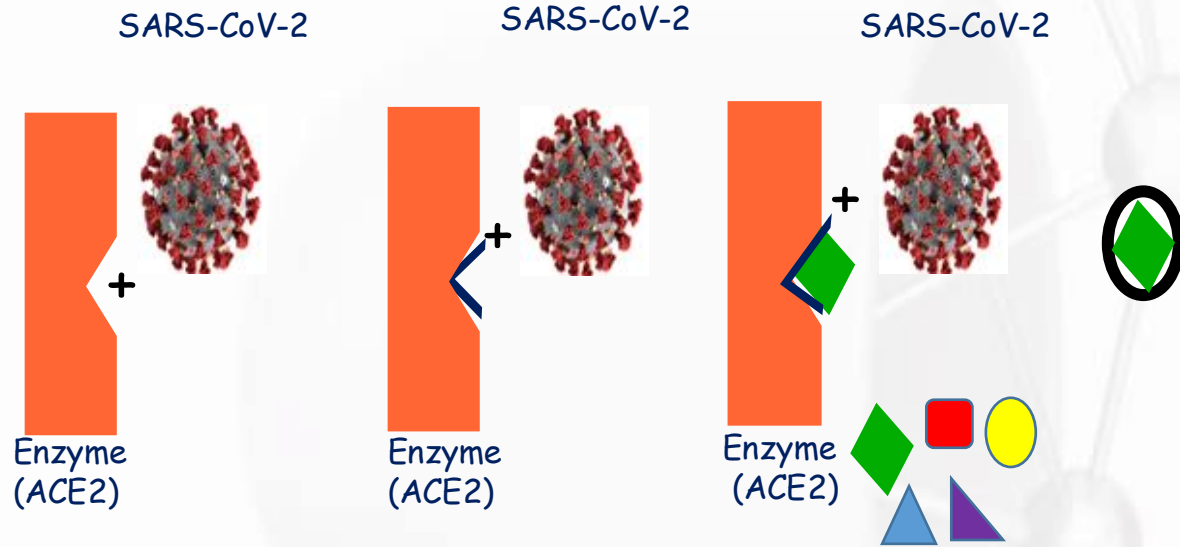
- Virtual screening
- De novo design
- Optimization

- Scaffold hopping
- SAR analysis
- In situ design

- *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 homepage showing search bar and statistics: 97M Compounds, 239M Substances, 298M Bioactivities, 29M Literature, 3M Patents, 642 Data Sources.

PubChem Database

ZINC Database homepage showing search bar and 'Getting Started' section.

Zinc Database

Protein Data Bank (PDB) homepage showing search bar and 'March Molecule of the Month' section.

Protein Data Bank(PDB)

Binding MOAD homepage showing search bar and 'Welcome to Binding MOAD!' section.

April 20 BindingMOAD

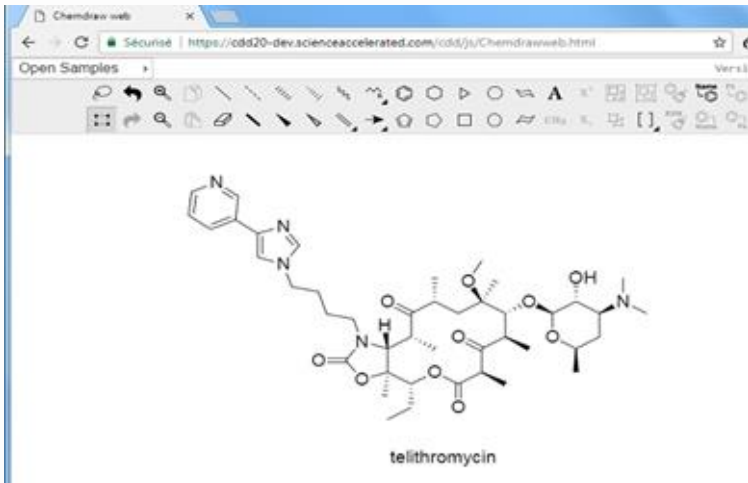
SMP Database homepage showing search bar and 'Welcome to the Small Molecule Pathway Database' section.

SMP Database

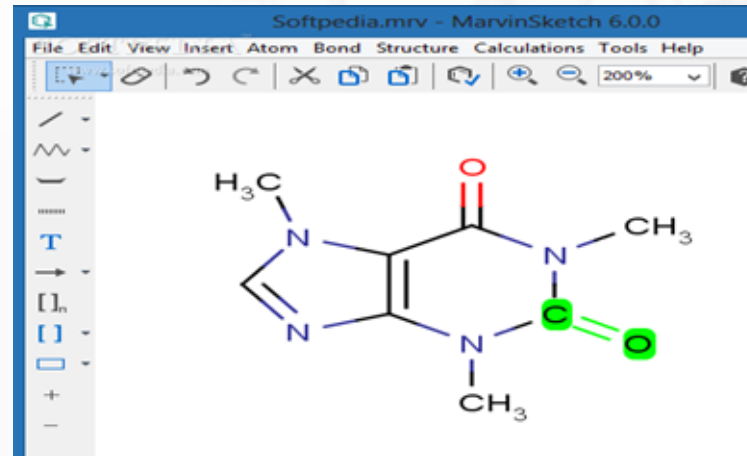
PDBbind Database homepage showing search bar and 'Welcome to the PDBbind-CN Database!' section.

PDBbind Database

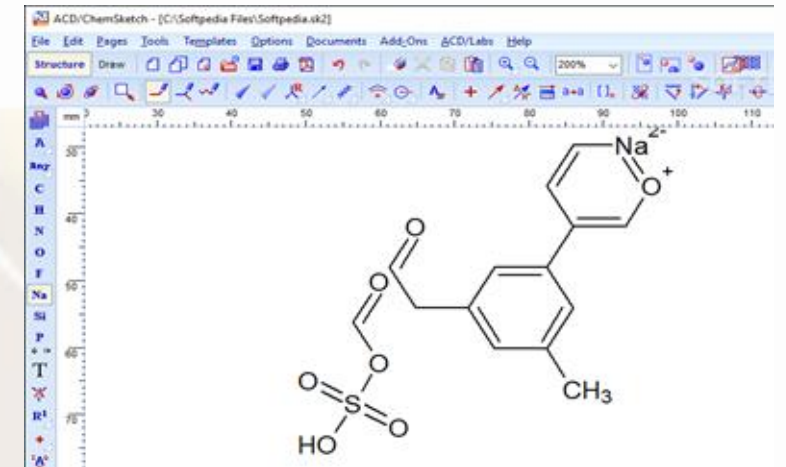
Draw Tools



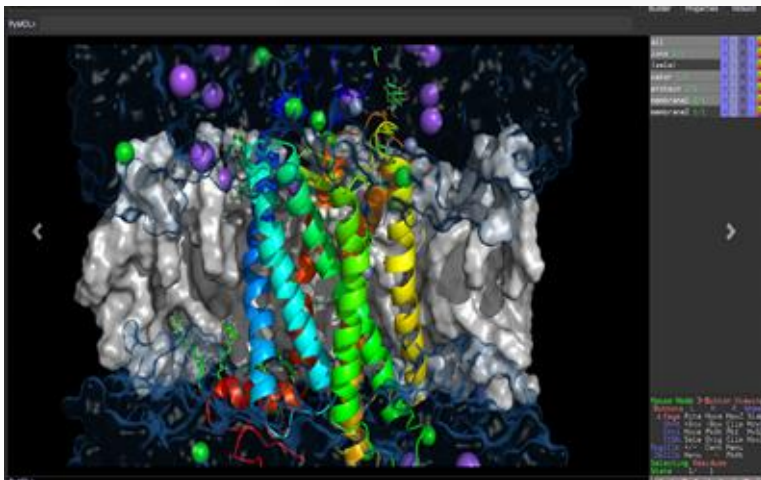
ChemDraw



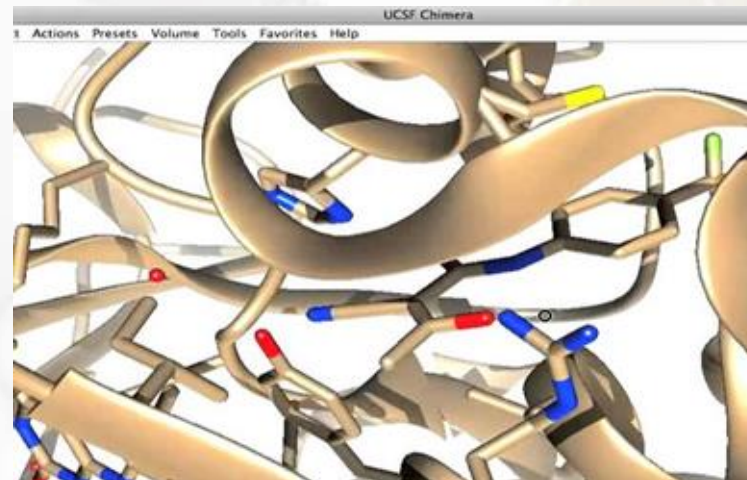
MarvinSketch



ACD/ChemSketch



April 20 Pymol



UCSF Chimera

Homology Modeling

Modeller

Program for Comparative Protein Structure Modelling by Satisfaction of Spatial Restraints

```
NI LVGSMFRRDGMERKOLLKAVKIFKCOGA  
EYVQRYOCFTYEGPFLHPDECIDCALCE  
IACPAQYVNIWV...LYAIQASVQVQ  
C...ACGACKPECPVNI LQGS...LYAIDADS
```



Modeller

I-TASSER
LOMETS
Robetta

BIOZENTRUM
University of Basel
The Center for Molecular Life Sciences

SWISS-MODEL Modelling Repository

Start a New Modelling Project

Target Sequence(s):
(Format must be FASTA, Clusta, plain string, or a valid UniProtKB AC)

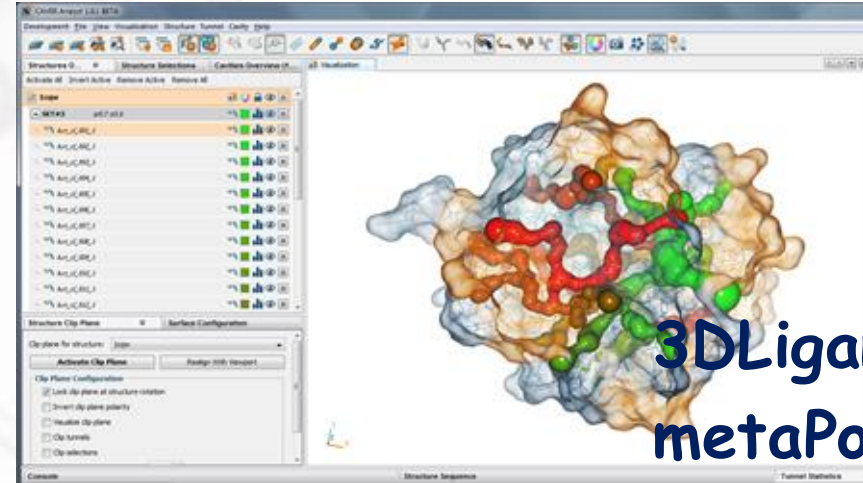
Project Title: Untitled Project

Email: Optional

Buttons: Search For Templates, Build Model

SWISS-MODEL

Binding Site Prediction

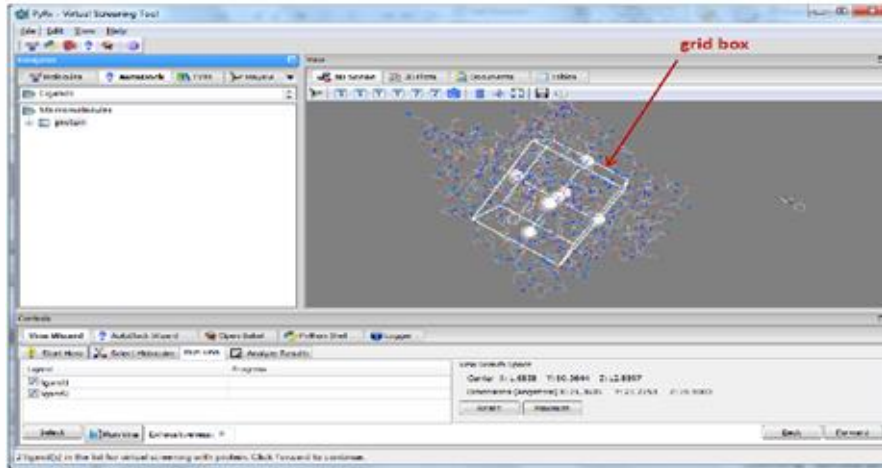


CAVER

3DLigandSite
metaPocket
FINDSITE

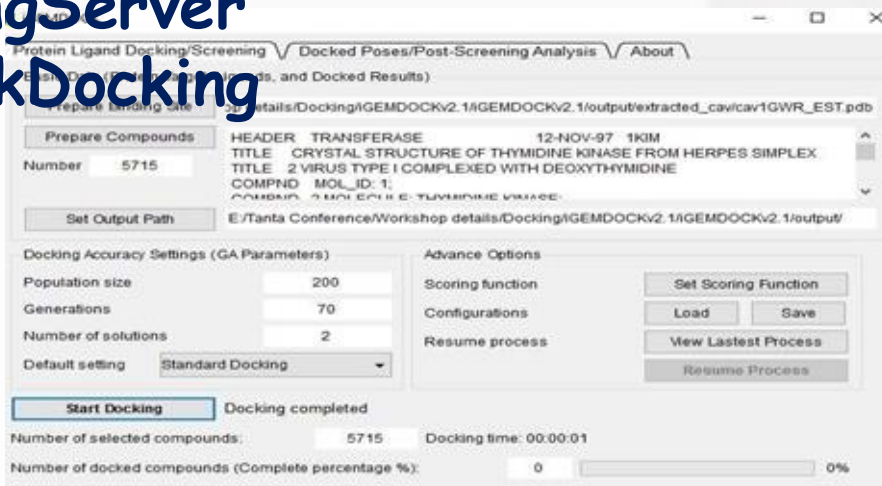


Molecular Docking



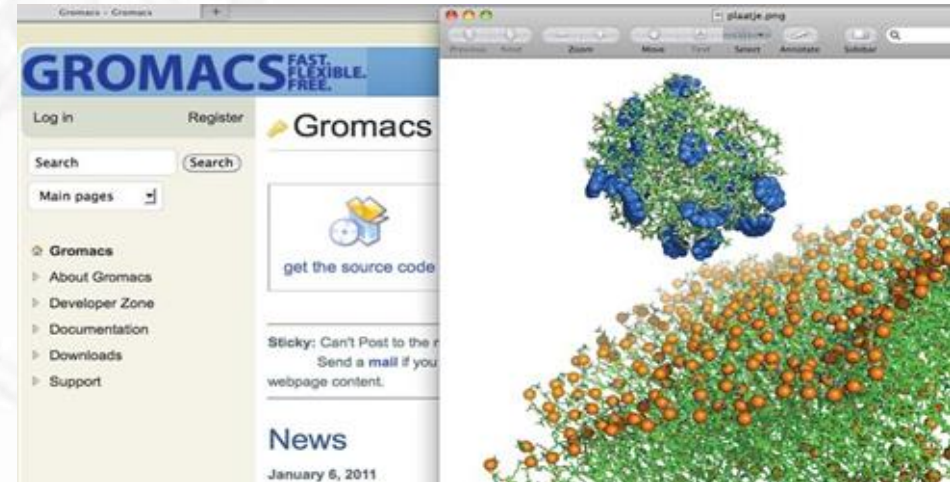
GOLD
SwissDock
DockingServer
1-ClickDocking

Autodock Vina



iGemdock

Molecular Dynamics



GROMACS

Amber

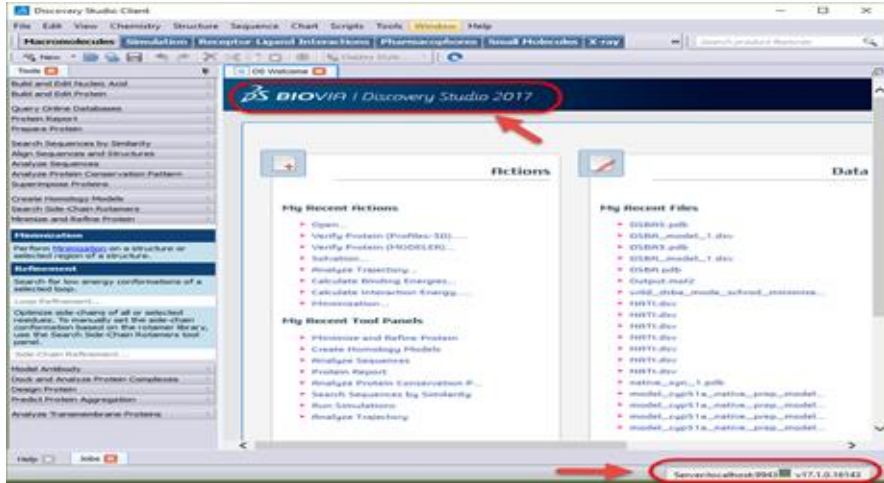
SwissParam

SwissSideChain

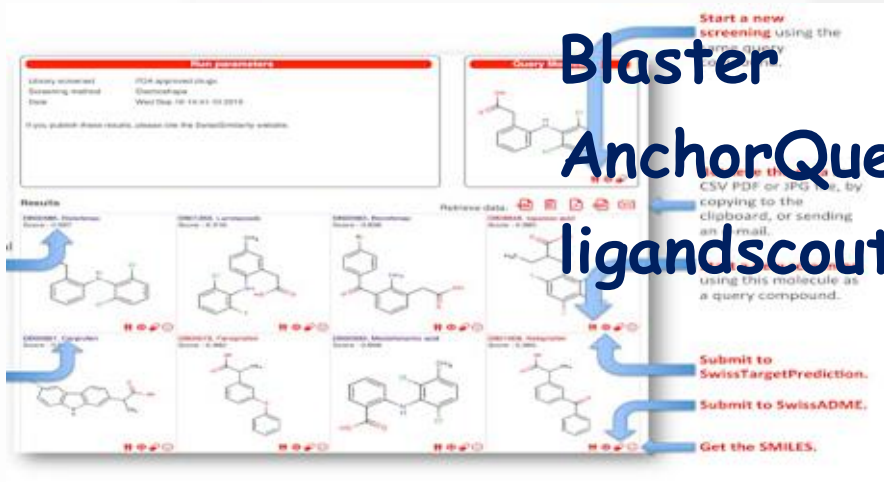


CHARMM-GUI

Ligand Screening

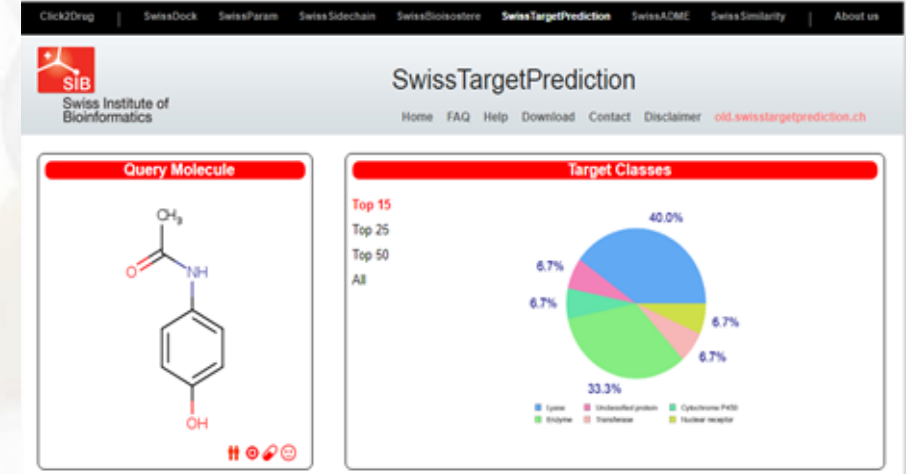


Discovery Studio



SwissSimilarity

Target Prediction



Swiss Target Prediction



MolScore-Antibiotics

ADME Toxicity

MD MOLECULAR DISCOVERY

... DEFINING THE FIELD

HOME

SOFTWARE

- MetaSite
- MassMetaSite
- WebMetabase
- Onco
- MoKa
- FLAP
- Lipostar
- LipStarMS
- VolSurf+
- GRD
- Pentacle

PLEASE LOGIN TO DOWNLOAD VOLSURF+

The pharmacokinetic behaviour of compounds is linked to their efficacy and thus is critical for drug discovery. Understanding how to optimise compounds according to multiple simultaneous criteria is a great advantage in focusing design efforts.

VolSurf+ creates 128 molecular descriptors from 3D Molecular Interaction Fields (MIFs) produced by our software GRD, which are particularly relevant to ADME prediction and are also simple to interpret. One example would be the interaction energy moment descriptor between hydrophobic and hydrophilic regions, which is important for membrane permeability prediction. These can then be used with provided chemometric tools to build statistical models.

VolSurf+ also comes with a number of models that we have developed using both public and pharmaceutical data, including passive intestinal rain barrier permeation, solubility, protein binding, volume of distribution, and metabolic stability.

VolSurf

GastroPlus(TM): GastDemo.mdb (C:\Users\Public\Simul...\Gastr...)

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Selected Compound: Propranolol HCl

Current: 1, Total: 9

Molecular Formula: C18H21NO2

Molecular Weight (g/mol): 259.34

Reference logD: 1.54 @pH: 7.4

pKa Table

Enzyme Table

Transporter Table

SI Trans Time (h) = 3.220 Mean Abs Time (h) = 0.562

Longest Diss. Time (h) @ pH 1.0 = 0.001 hours

Max Abs Dose (S+) = 1.194E+6 mg Max Abs Dose (R) = 7.52E+5 mg

Support Files

Propranolol HCl.opd

Dosage Form: [R]: Tablet

Initial Dose (mg): 140.28

Subsequent Doses (mg): 0

Dosing Interval (h): 0

Dose Volume (mL): 250

pH for Reference Solubility: 3

Solubility (mg/mL @pH=3): 1.25

Mean Precipitation Time (sec): 900

Diff. Coeff. (cm²/s x 10⁻⁵): 0.829

Drug Particle Density (g/mL): 1.2

Particle Size: R=25.00, D=50.00

Effective Permeability

Source: Human

Peff (cm/s x 10⁻⁴): 2.91

Sim Peff x10⁴ (Human): 2.91

Convert from User Data

Biorelevant Solubilities

Dose No. = 0.0389

Absorption No. = 5.741

Dissolution No. = 4.817E+3

GastroPlus

Molinspiration
PACT-F

SwissADME

20/Indice.php

ArtheoSearch: Eingabe...

Problem loading page: Share Market Analysis... PaymentID.com - Pa... Login Samsung Mobile B

Head plugin "Adobe Flash" from running on http://www.swissadme.ch

Fill with an example Clear Run

Show BOILED-Egg

Retrieve data: ChemAxon

Molecule 1

SMILES: CC1=CC(OC1C)C(C)C

Physicochemical Properties

Formula	C10H14O
Molecular weight	154.25 g/mol
Heavy atoms	11

Water solubility	-2.87
Solubility	2.10e-01 mg/mL ; 1.36e-03 mg/mL
Class	Soluble
Log P (ALIP)	-3.49
Solubility	4.05e-02 mg/mL ; 3.21e-04 mg/mL
Class	Soluble
Log P (SILICOS-IT)	-1.09
Solubility	3.17e+00 mg/mL ; 2.05e-02 mg/mL
Class	Soluble

GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No

Organic Chemistry Portal

Share: [Facebook] [LinkedIn] [Twitter]

Follow us: [Facebook] [LinkedIn] [Twitter]

Site Search: any all words

Main Categories

- Organic Reactions
- Org. Chem. Highlights
- Abstracts
- Chemicals
- Chemistry Tools
- Chemistry Books
- Job Market
- Product of the Month
- Archive
- Resources & Suppliers
- Advertisement
- Imprint

OSIRIS Property Explorer

The OSIRIS Property Explorer lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green color indicates drug-conform behaviour.

Download

Tutorial: Toxicity Risk cLogP Prediction Solubility Prediction Molecular Weights Drug-Likeness Overall Prediction Drug-Likeness Score

System Requirements

A working Java Runtime Environment (JRE) installed on your computer. Latest JRE can be downloaded from <https://java.com/en/download>

Privacy Information

If you draw chemical structures in Property Explorer, information is kept locally on your computer. The prediction databases is part of the app. However,

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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How wet lab people see bioinformatics geeks



How bioinformatics geeks see wet lab people



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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

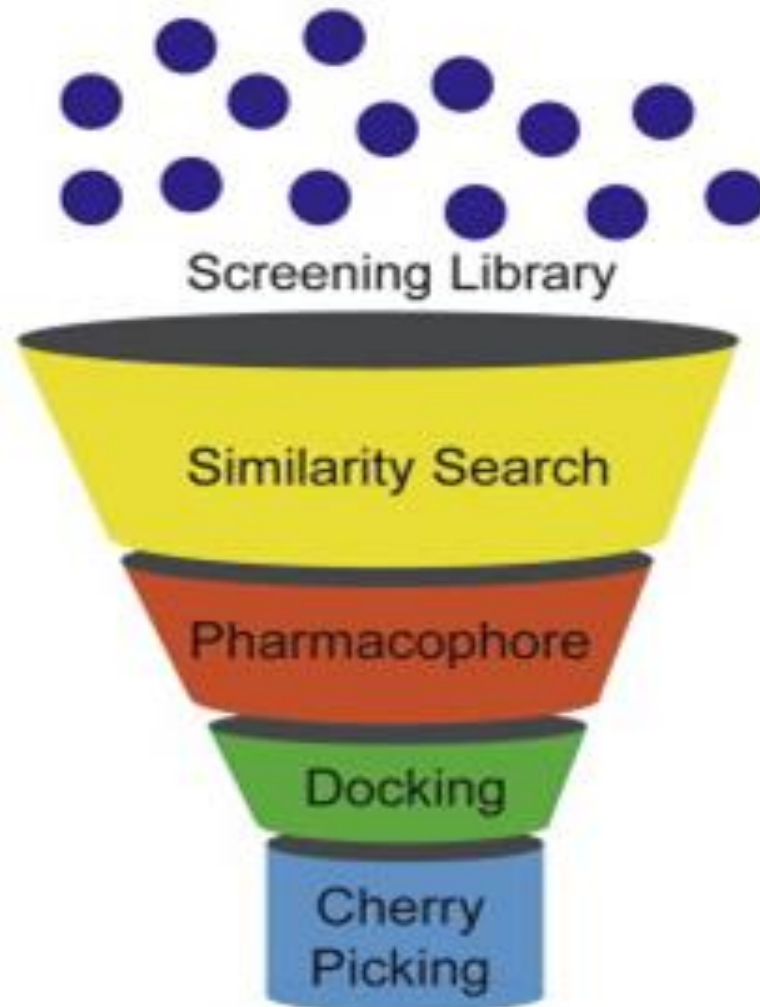
Department of Biotechnology
SRIHER, Porur, Chennai, India



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



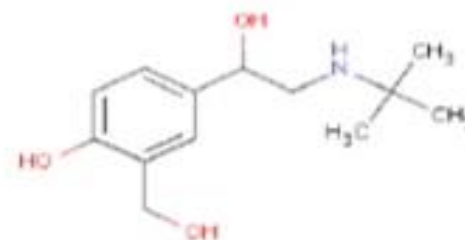
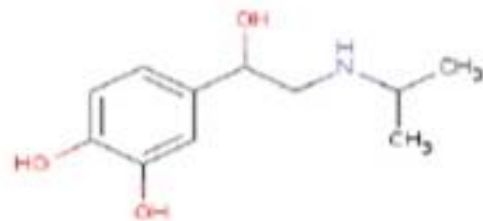
Step1: Libraries for Virtual Screening

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

Step 2: Similarity Search

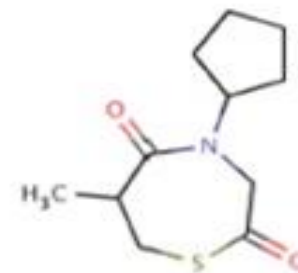
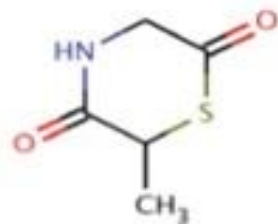
- Matching of Chemical, Biological and Pharmacological Features of two compounds

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

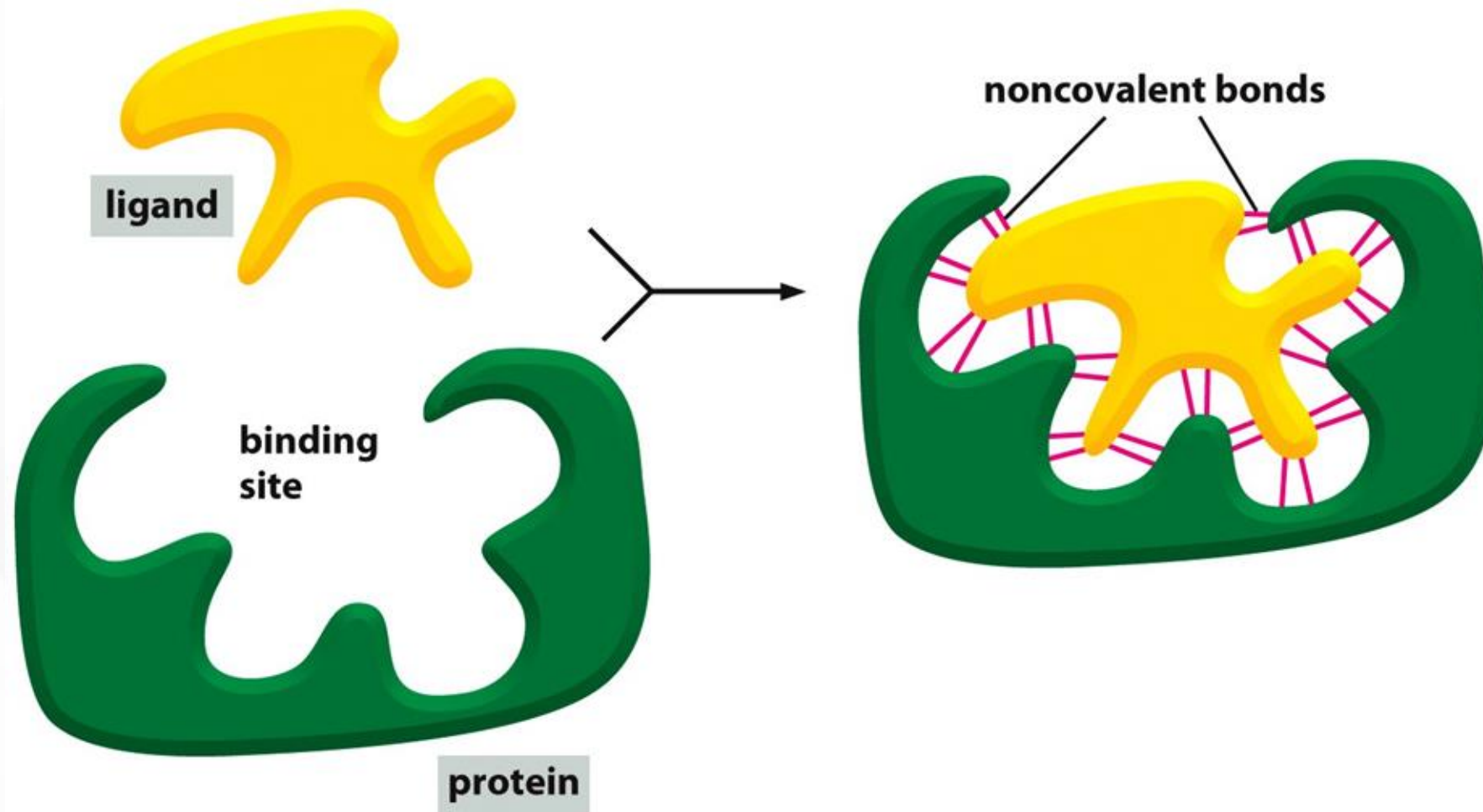
1. Catalyst
2. Ligand Scout
3. Pharner
4. SHAFTS
5. PharmaGist
6. Phase- Schrodinger

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).

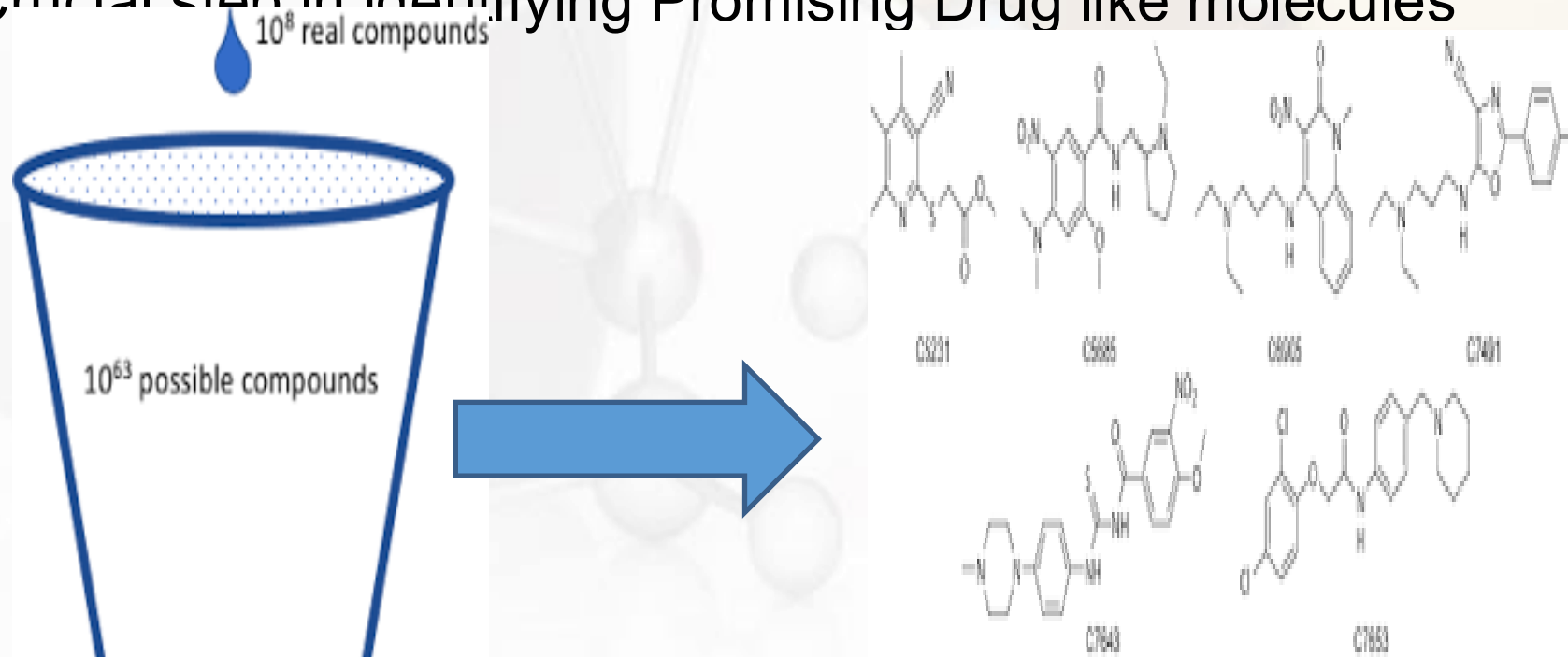


Concept of Docking: Lock and Key Model

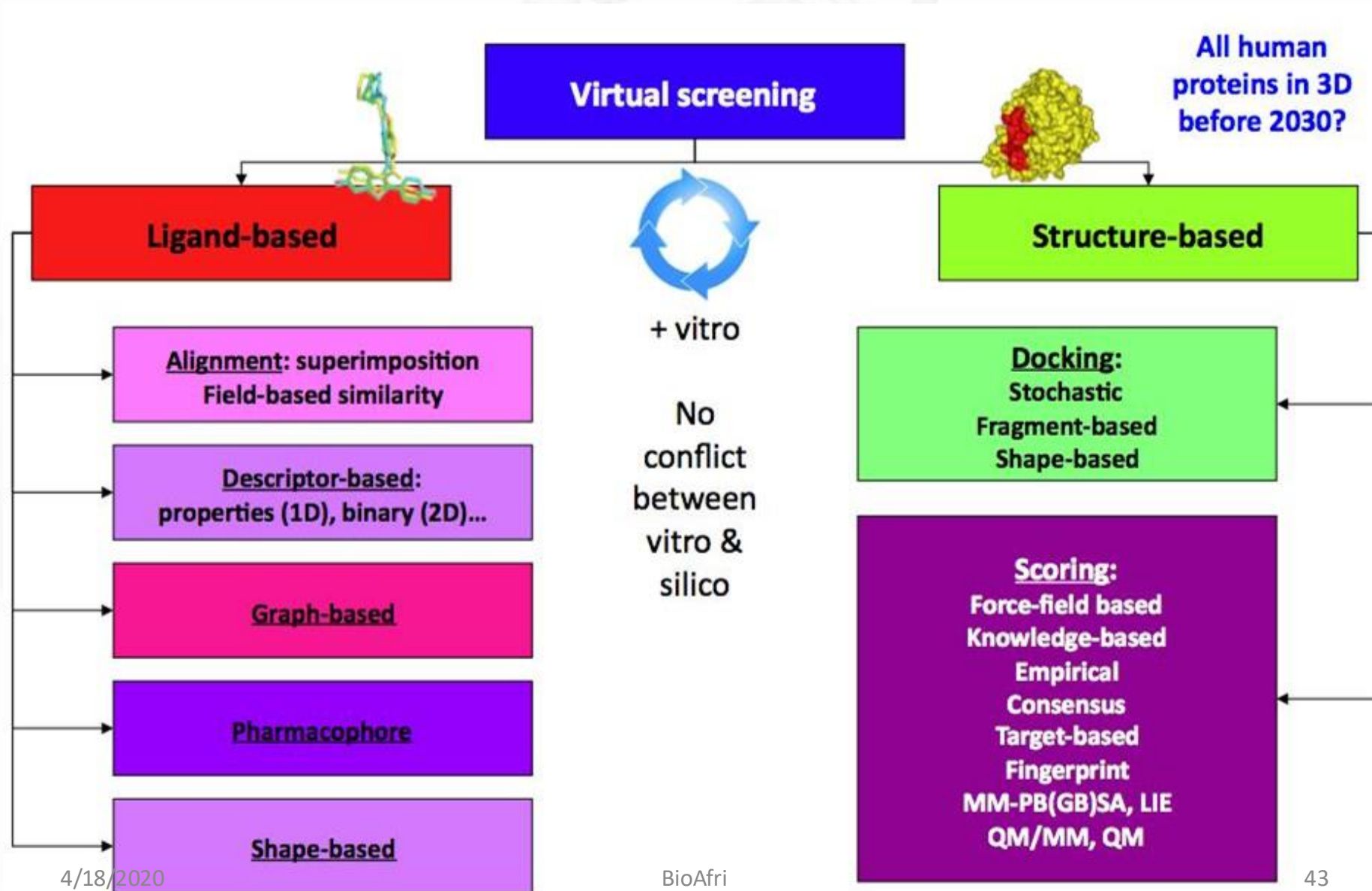


Step 4: Cherry Picking

- 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

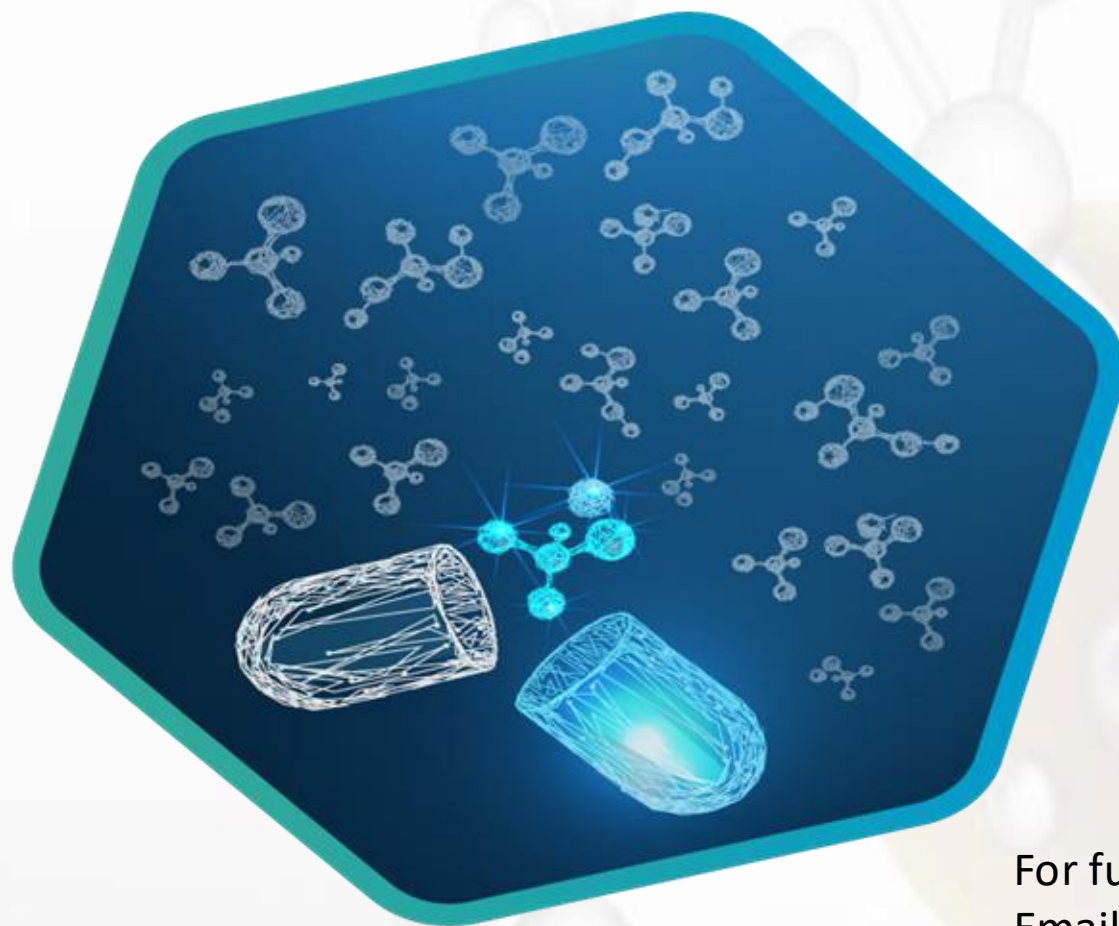
- **Molecular docking** is one of the most frequently used methods in structure-based **drug design**, due to its ability to predict the binding-conformation of small **molecule** ligands to the appropriate target binding site
- Drug Designing is a long Process. Docking reduces the time
- Cost Efficient

- 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:

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THANK YOU