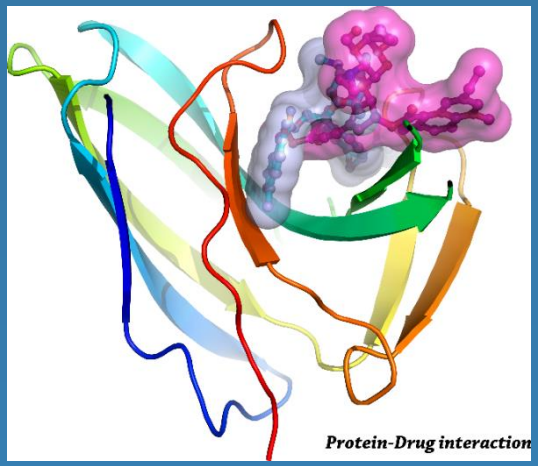
NYU-ECNU
Center for Computational Chemistry
at NYU Shanghai

Computer Aided Drug Design



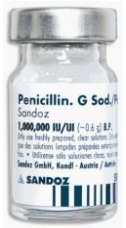
Tong Zhu
State key laboratory of precision spectroscopy
East China Normal University
2014.12.06

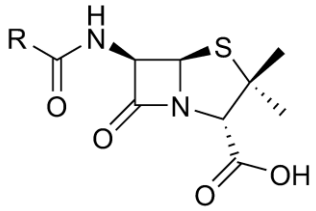
Overview

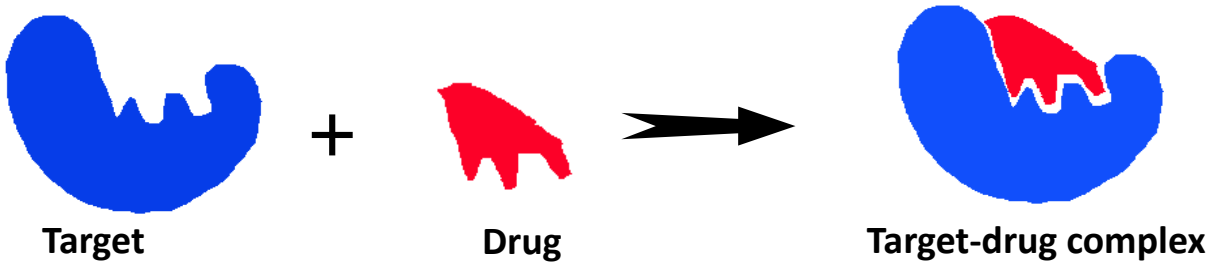
- Drug discovery process
- Overview of Computer-Aided Drug Design

How Drugs Work

Drug : A substance used in the diagnosis, treatment, or prevention of a disease or as a component of a medication.





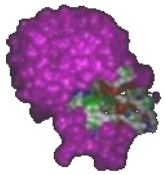


Lock-and-key model

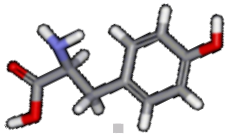
Drug Development Process

Disease

Isolate protein involved in disease
(2-5 years)



Find compounds effective against disease protein
Hit ID
Hit to Lead
(2-5 years)



Preclinical testing
Animal efficacy
Lead opt
(1-3 years)

File IND
Animal toxicity

Human clinical trials
Phase 1
Phase 2
Phase 3
(2-10 years)

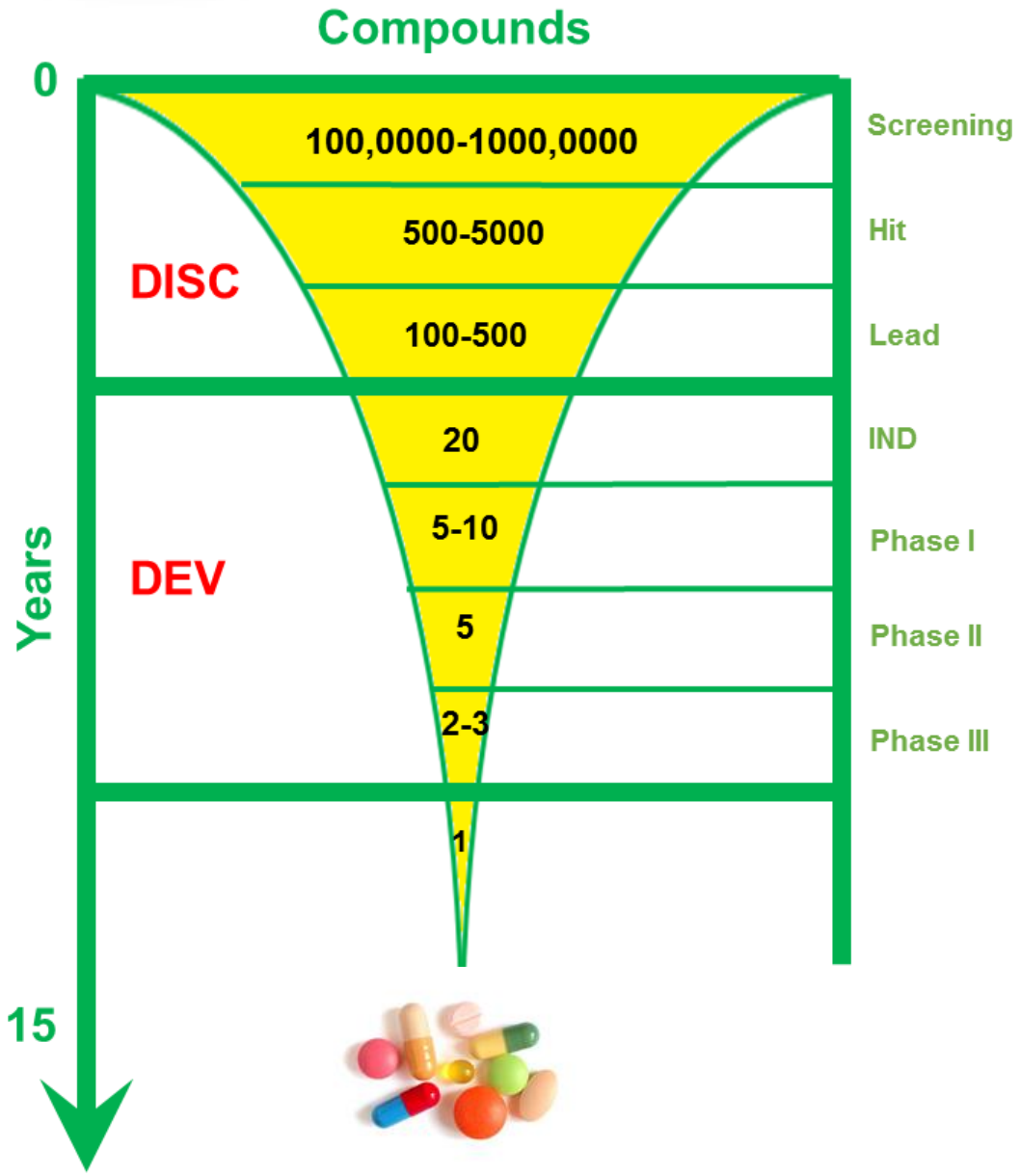
FDA approval
(2-3 years)

Drug Development Process

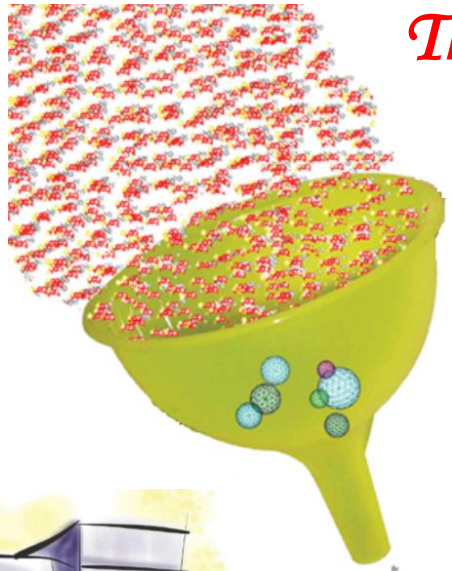
You have to test A LOT of compounds to find a drug

10 – 15 years,

500 - 1000 million US $



Why CADD ?



The future is bright, the future is virtual

- ✓ Virtual screening (Hit identification)
- ✓ Select leads
- ✓ Lead optimization

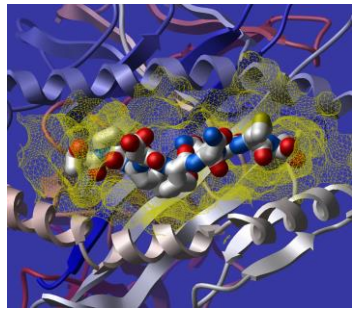
- ➢ Reduce costs / time
- ➢ Reduce animals used in experiment
- ➢ Improve success rate
- ➢ Improve understanding of drug-protein interactions

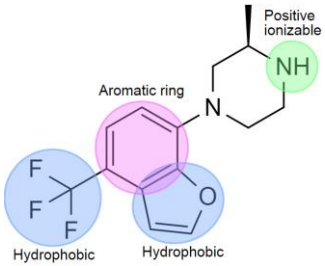
SAVING 2 – 5 years, 100 - 500 million US $

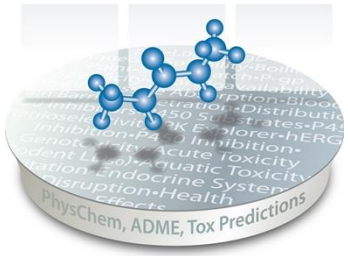
Methodologies and strategies of CADD

Computer aided drug design

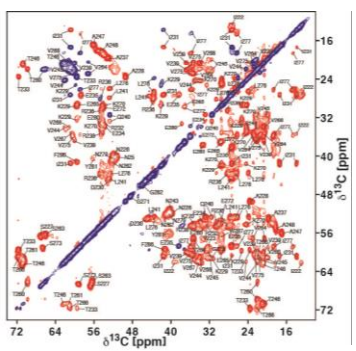
- Structure based drug design
  - Protein-ligand docking
  - Protein modeling
  - Molecular simulation
- Ligand based drug design
  - Similarity analysis
  - QSAR
  - Pharmacophore
- ADMET
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
  - Toxicity

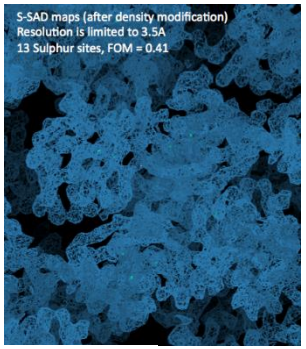


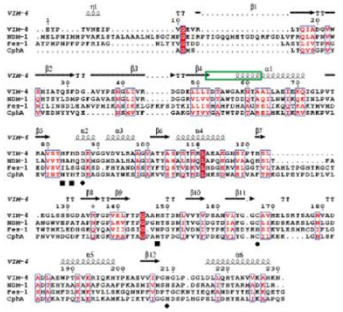




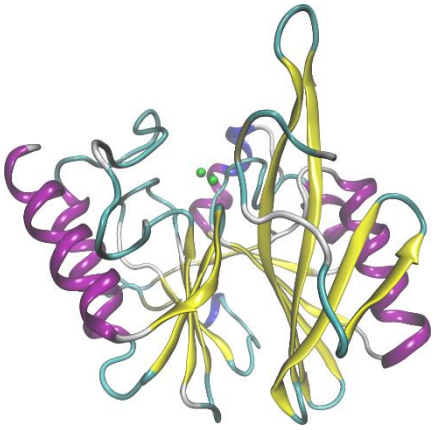
Structure based drug design



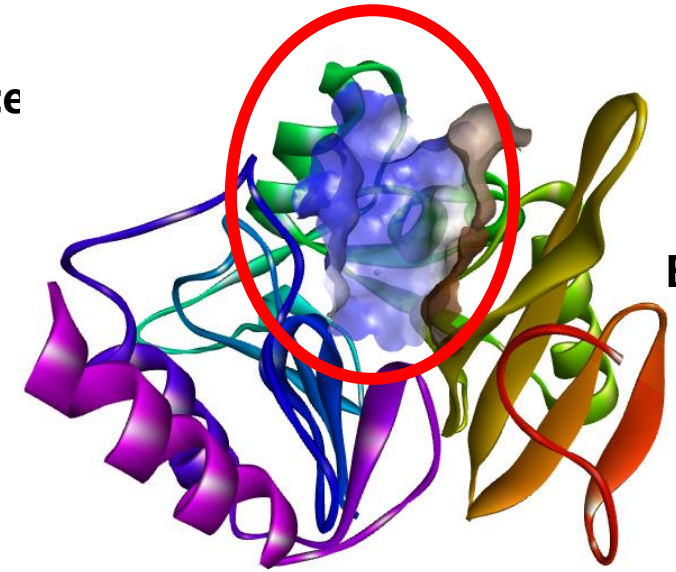




Experiment or sequence



Protein 3D structure

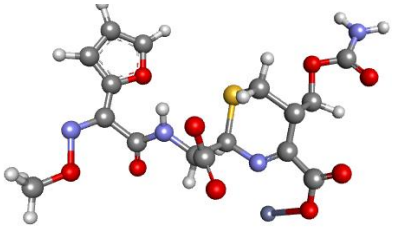


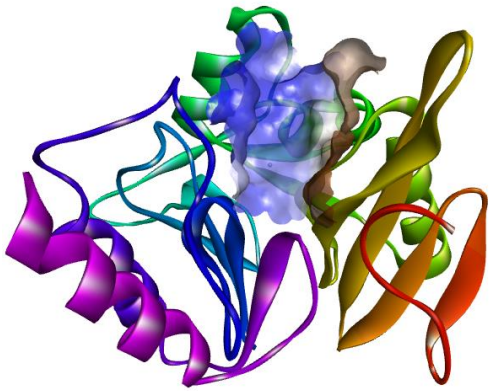
Binding pocket

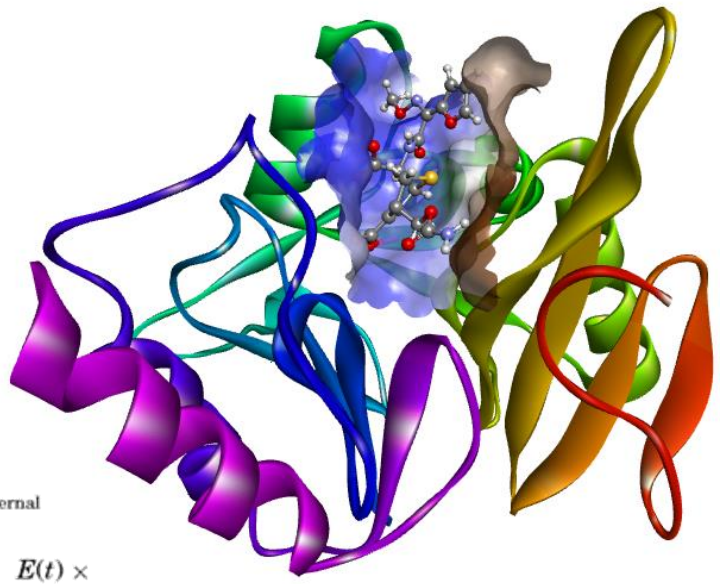
Modeller
Discovery studio
…

Structure based drug design

Docking : find the "best" matching between target protein and drug candidates.







$$E_{\text{dock}} = E_{\text{vdw}} + E_{\text{H-bond}} + E_{\text{electrostatic}} + E_{\text{internal}}$$

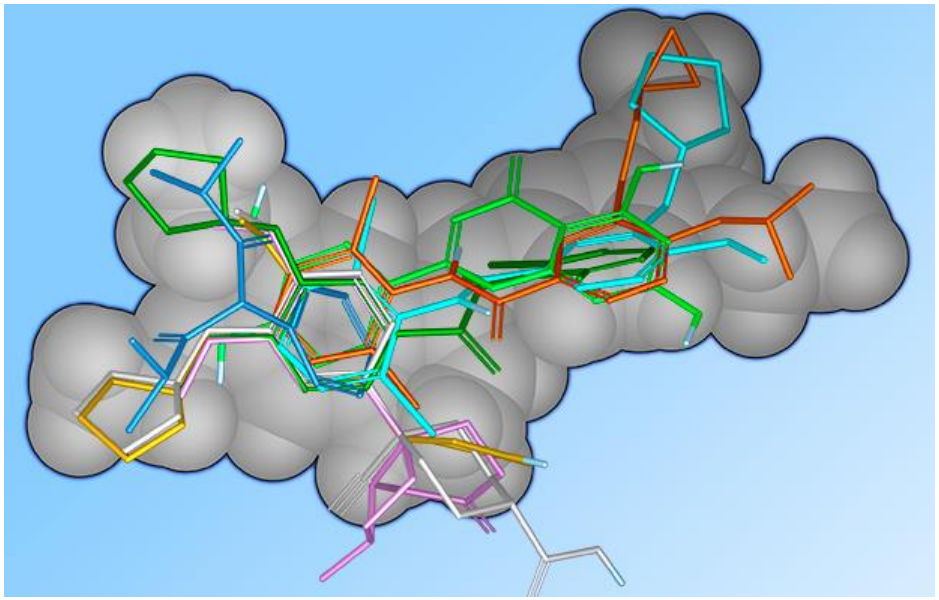
$$= \sum_{\text{protein}} \sum_{\text{ligand}} \left(\frac{A_{ij}}{d_{ij}^{12}} - \frac{B_{ij}}{d_{ij}^{6}} \right) + \sum_{\text{protein}} \sum_{\text{ligand}} E(t) \times \left(\frac{C_{ij}}{d_{ij}^{12}} - \frac{D_{ij}}{d_{ij}^{10}} \right) + \sum_{\text{protein}} \sum_{\text{ligand}} 332.0 \frac{q_i q_j}{\epsilon(d_{ij})\, d_{ij}} + \left\{ \sum_{\text{ligand}} \left(\frac{A_{ij}}{d_{ij}^{12}} - \frac{B_{ij}}{d_{ij}^{6}} \right) + \sum_{\text{ligand}} E(t) \left(\frac{C_{ij}}{d_{ij}^{12}} - \frac{D_{ij}}{d_{ij}^{10}} \right) + \sum_{\text{ligand}} 332.0 \frac{q_i q_j}{4 d_{ij} d_{ij}} \right\}$$

Autodock
Glide
Sybyl
MOE
.....

Ligand based drug design

Molecular shape matching

~millions of molecules / day



$$g_i(r) = pe^{-\left(\frac{3p\pi^{1/2}}{4\sigma_i^3}\right)^{2/3}(r-r_i)^2}$$

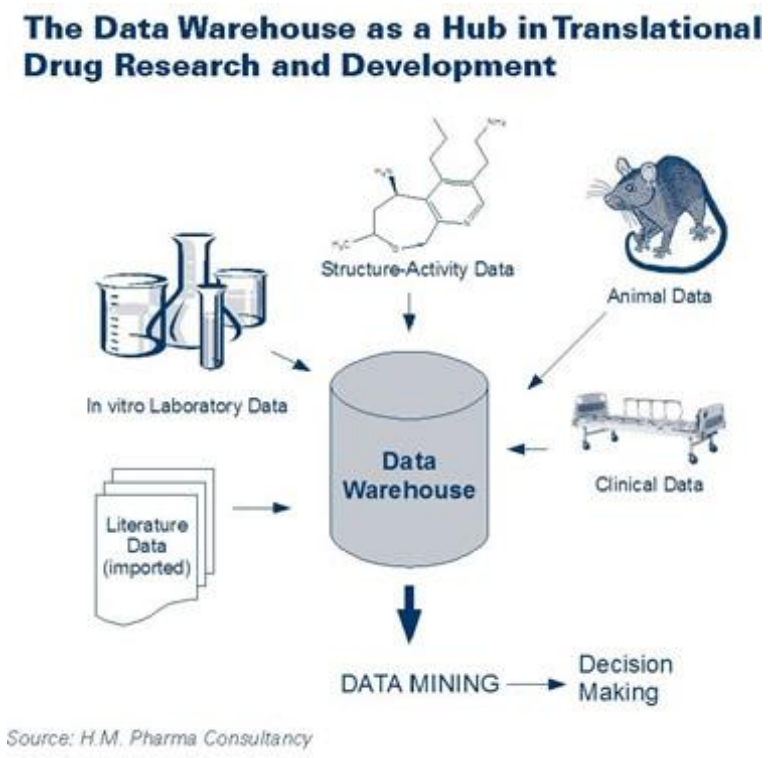
$$G(r) = \sum_i g_i(r) - \sum_{i<j} g_i(r)g_j(r) + \sum_{i<j<k} g_i(r)g_j(r)g_k(r) - \sum_{i<j<k<l} g_i(r)g_j(r)g_k(r)g_l(r) + \cdots$$

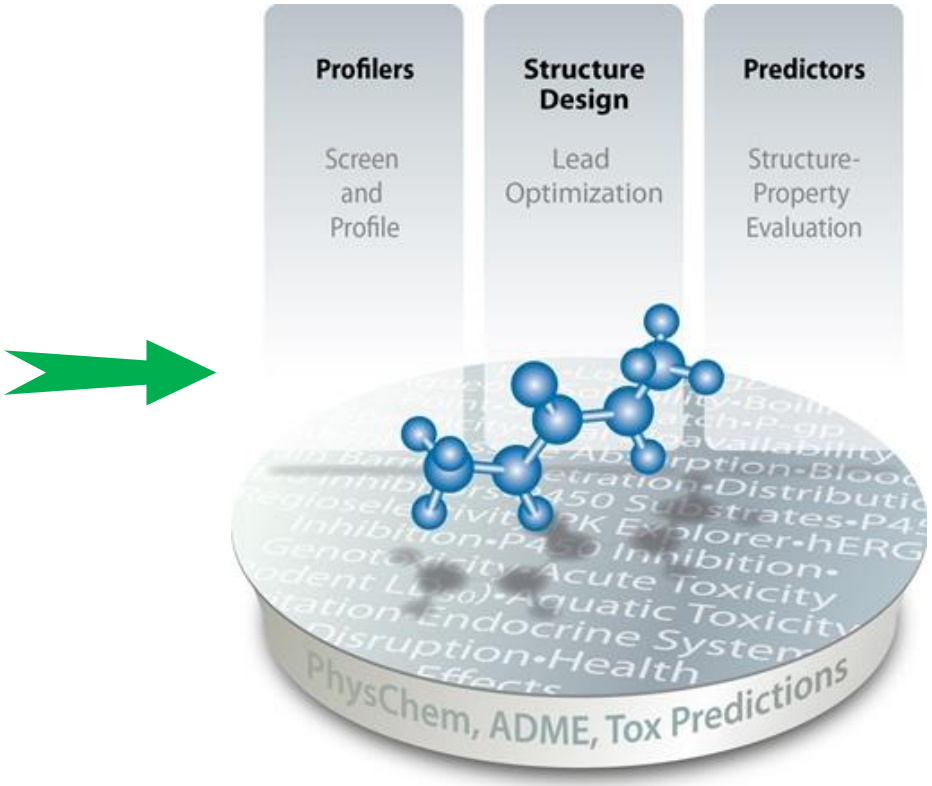
$$V_{AB}^g = \int G_A(r)G_B(r)dr = \sum_{i\in A, j\in B} v_{ij}^g - \sum_{i<j\in A, k\in B} v_{ijk}^g - \sum_{i\in A, j<k\in B} v_{ijk}^g + \sum_{i<j\in A, k<l\in B} v_{ijkl}^g - \cdots\cdots$$

ROCs
Omiga
gWEGA
.....

ADMET evaluation

Data mining….





Schrodinger
MOE
MedChem studio
…..

Available CADD software

www.click2drug.org

Thank you