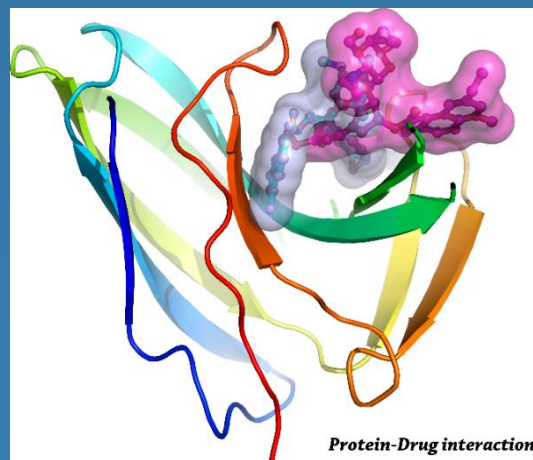


# Computer Aided Drug Design



**Tong Zhu**

State key laboratory of precision spectroscopy  
East China Normal University

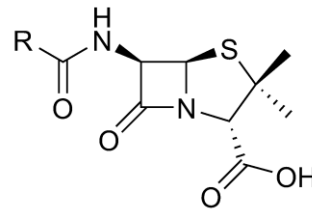
2014.12.06

# Overview

- Drug discovery process
- Overview of **C**omputer-**A**ided **D**rug **D**esign

# How Drugs Work

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



Target

+



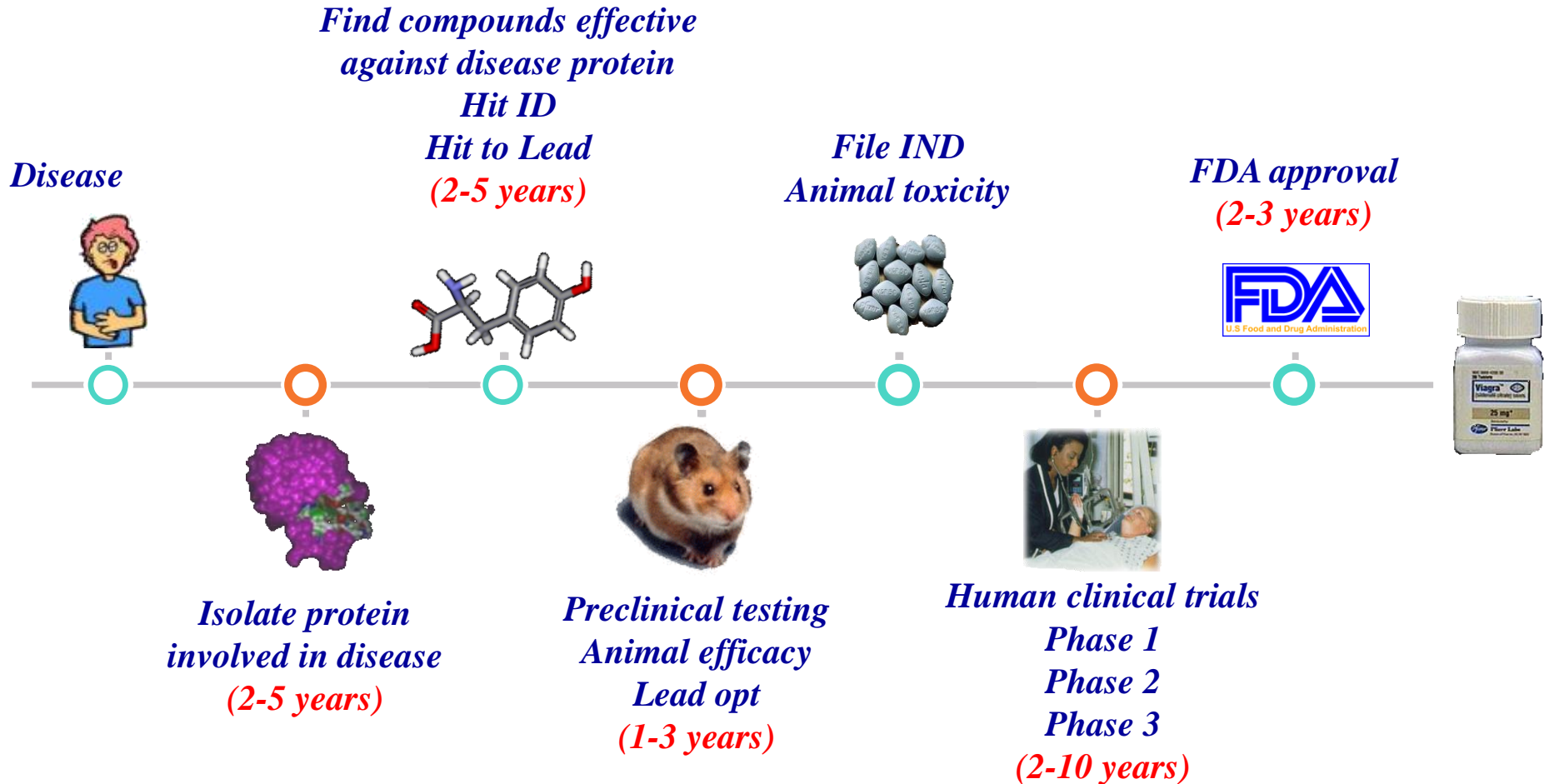
Drug



Target-drug complex

**Lock-and-key model**

# Drug Development Process

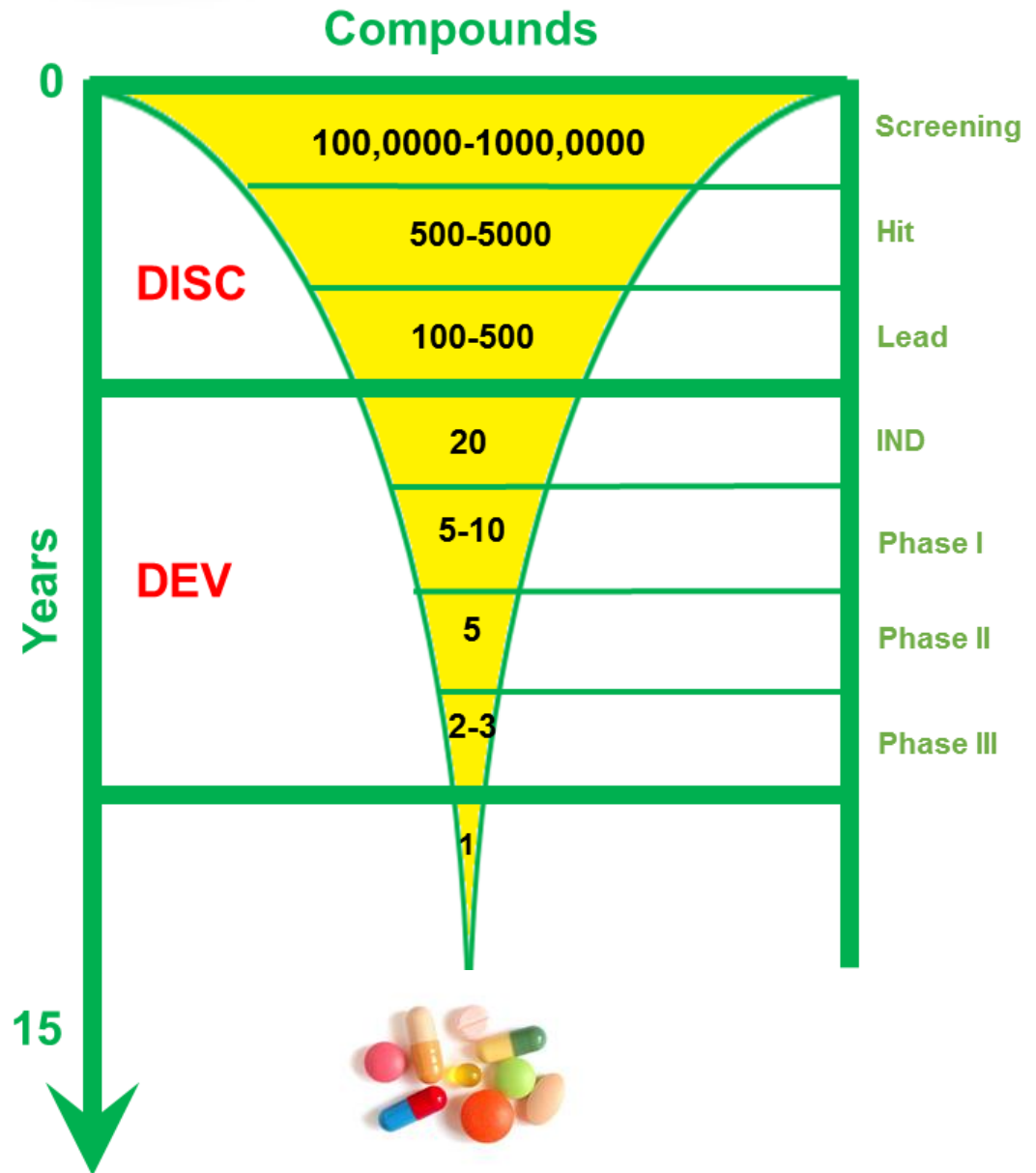


# Drug Development Process

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

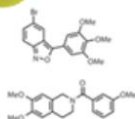
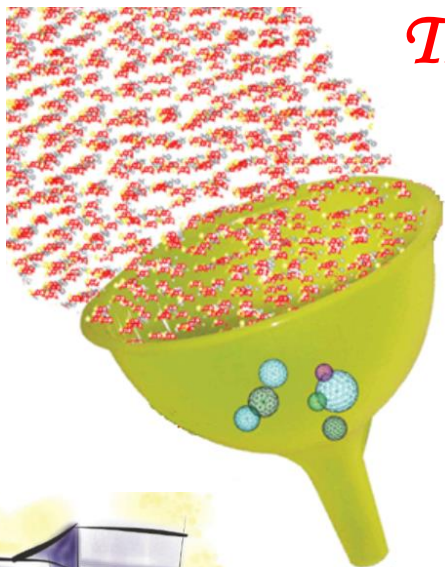
**10 – 15 years,**

**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

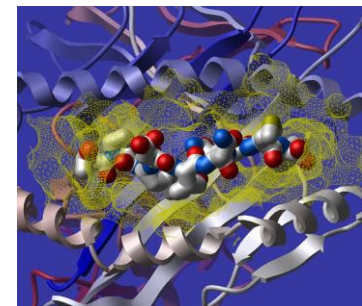
**SAVING 2 – 5 years, 100 - 500 million US \$**

# Methodologies and strategies of CADD

## Computer aided drug design

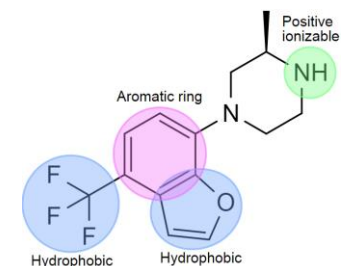
### Structure based drug design

- Protein-ligand docking
- Protein modeling
- Molecular simulation



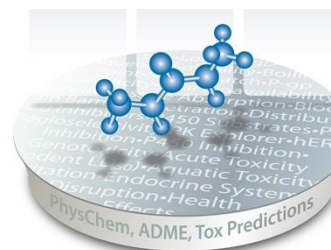
### Ligand based drug design

- Similarity analysis
- QSAR
- Pharmacophore

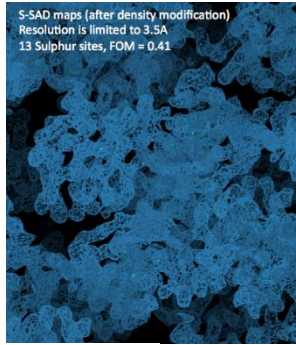
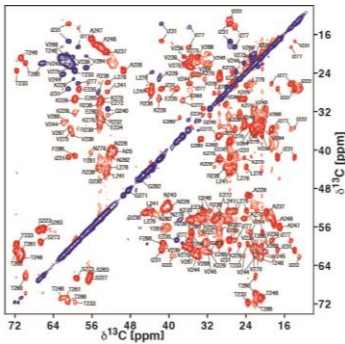


### ADMET

- Absorption
- Distribution
- Metabolism
- Elimination
- Toxicity

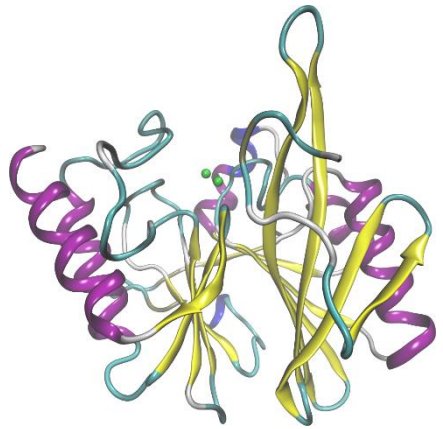
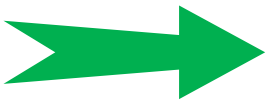


# Structure based drug design

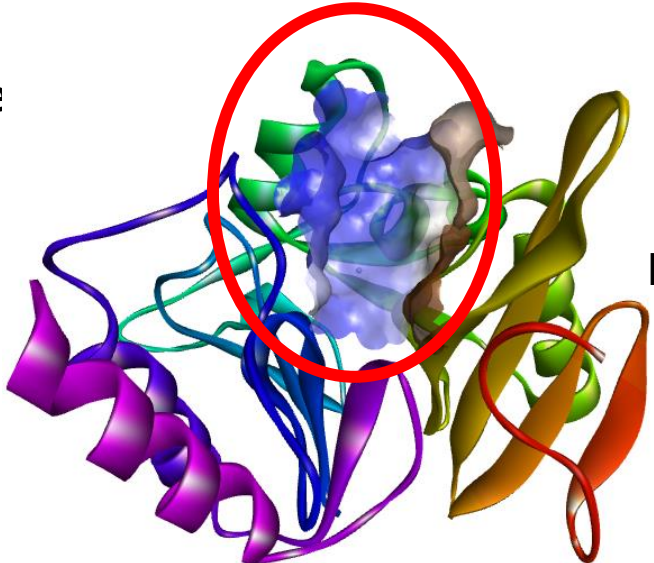
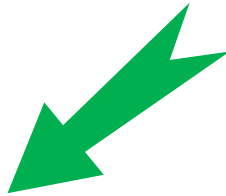


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V2M-4 1 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
V2M-4 1 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
V2M-4 1 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
V2M-4 1 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
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V2M-4 1 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
V2M-4 1 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
```

Experiment or sequence



Protein 3D structure



Binding pocket

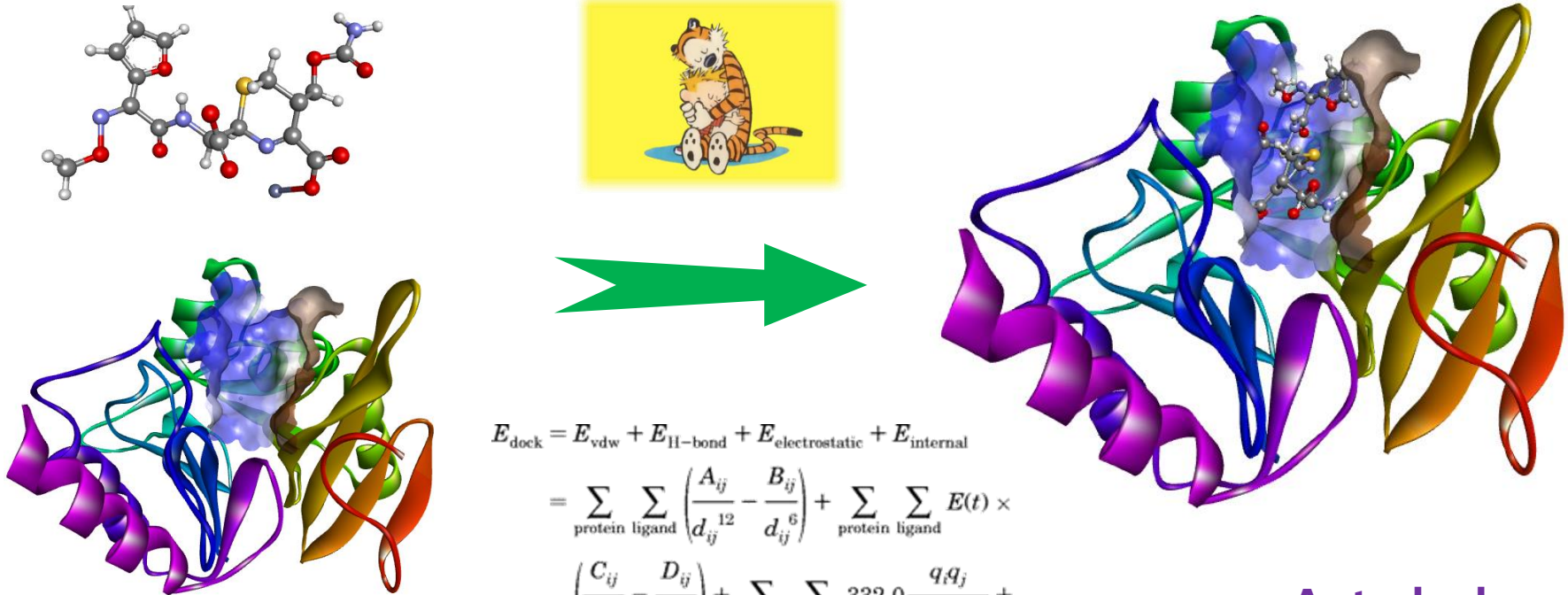
Modeller  
Discovery studio

...



# Structure based drug design

**Docking** : find the “best” matching between target protein and drug candidates.



$$\begin{aligned} E_{\text{dock}} &= E_{\text{vdw}} + E_{\text{H-bond}} + E_{\text{electrostatic}} + E_{\text{internal}} \\ &= \sum_{\text{protein}} \sum_{\text{ligand}} \left( \frac{A_{ij}}{d_{ij}^{12}} - \frac{B_{ij}}{d_{ij}^6} \right) + \sum_{\text{protein}} \sum_{\text{ligand}} E(t) \times \\ &\quad \left( \frac{C_{ij}}{d_{ij}^{12}} - \frac{D_{ij}}{d_{ij}^{10}} \right) + \sum_{\text{protein}} \sum_{\text{ligand}} 332.0 \frac{q_i q_j}{\epsilon(d_{ij}) d_{ij}} + \\ &\quad \left\{ \sum_{\text{ligand}} \left( \frac{A_{ij}}{d_{ij}^{12}} - \frac{B_{ij}}{d_{ij}^6} \right) + \sum_{\text{ligand}} E(t) \left( \frac{C_{ij}}{d_{ij}^{12}} - \frac{D_{ij}}{d_{ij}^{10}} \right) + \right. \\ &\quad \left. \sum_{\text{ligand}} 332.0 \frac{q_i q_j}{4d_{ij} d_{ij}} \right\} \end{aligned}$$

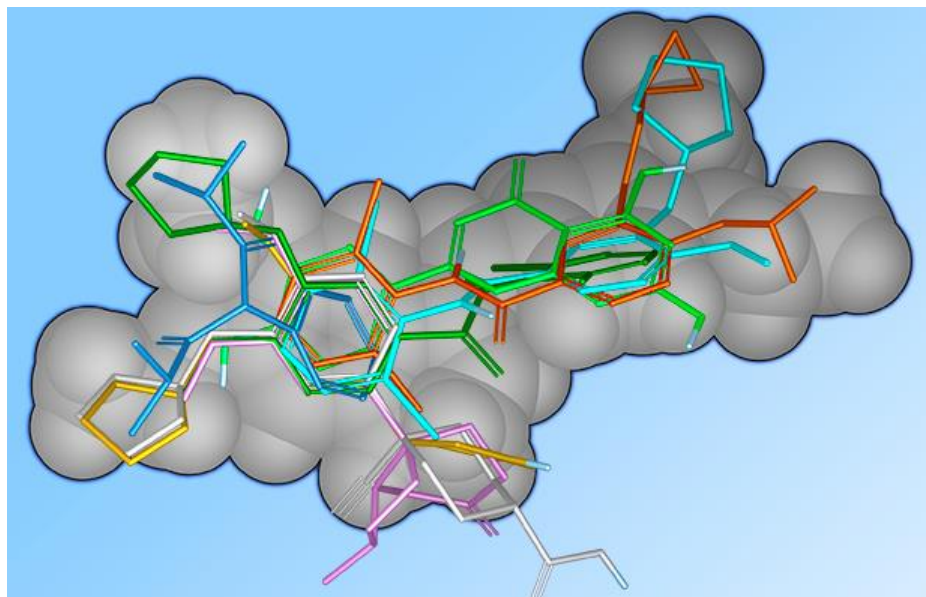
Autodock  
Glide  
Sybyl  
MOE

.....

# Ligand based drug design

Molecular shape matching

~millions of molecules / day



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

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

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

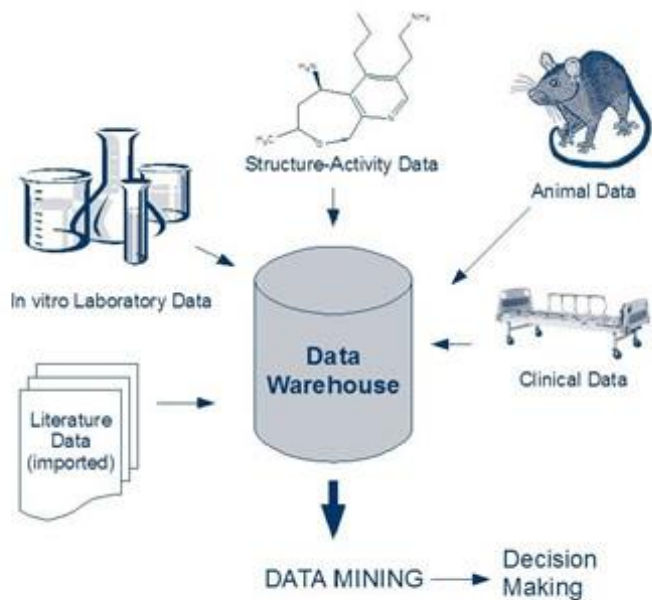
ROCs  
Omega  
gWEGA

.....

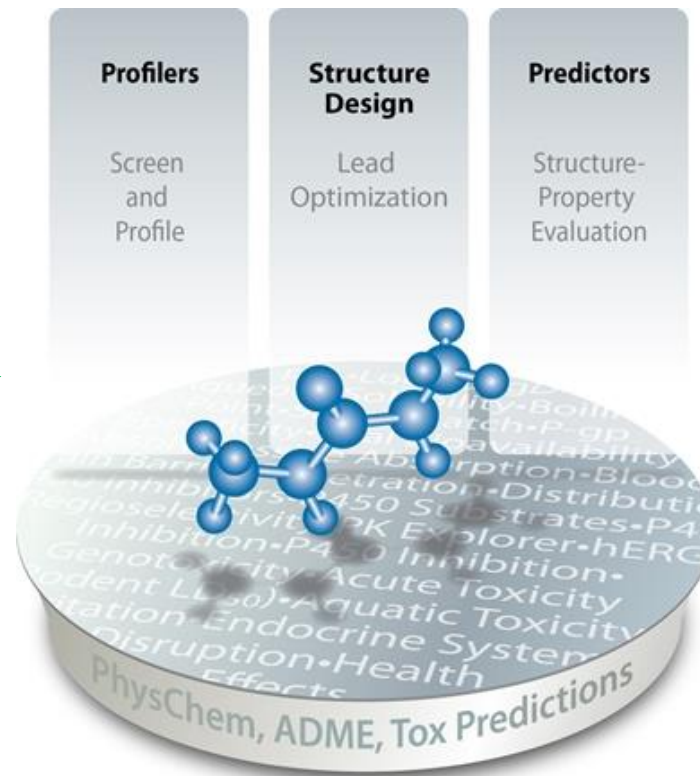
# ADMET evaluation

## Data mining....

### The Data Warehouse as a Hub in Translational Drug Research and Development



Source: H.M. Pharma Consultancy



Schrodinger  
MOE  
MedChem studio

.....

# Available CADD software

[www.click2drug.org](http://www.click2drug.org)

format **Blaster** MolScore-Drugs **e-LEA3D** Molprime+ ChemDiff ChemSpotlight SMARTCyp PROMISCUOUS Bingo **GROMACS** eHITS MEGA  
SMARTSviewer **CoLibri** SiteEngine **E-Dragon** MOLFEAT ADMEWORKS Predictor MolEngine ChemT Chemicalize Tuples TOPAS (now DOGS) Partial Least  
Squares Regression (PLSR) **MetaDock** TouchMol for Office SEA PocketDepth PDBSiteScan **ASEDock** Codessa NNScore **ChEMBL** RACHEL OCHEM Database  
VLifeDock **COPICAT** DockVision Pardock IntFOLD HHpred ACD/ChemSketch Imago OCR Visual Tool Marvin molecule editor and viewer VADAR Molcode  
Toolbox MultiBind Align-it WinDock Geno3D TCM PatchDock OLN Chem4SharePoint Chii<sup>2</sup> Viewer Biogenerator PLT The SDF Toolkit in Perl 5 CHARMM-GUI Fconv  
Desmond Absolute Solvation Free Energies Set SAR Table HomDock ZincPharmer **QikProp** ADMEWORKS ModelBuilder CATS PDB View 3D iHyperChem  
Free Version KKB ESyPred3D Cn3D RDKit Active Site Prediction CombiGlide fpocket SuMo **BAPPL-Z server** Chrawler Superpose wwLig-CSRre New Human GPCR  
modeling and virtual screening database REACTOR FLAP Chem3D for iPad **SwissDock** CLIDE Kuntz Protein Test Set ChemWriter FLOG eDesign CAESA  
eFindSite ChemDB/ChemicalSearch **OSIRIS Property Explorer** SwissParam COMPACT ICM Molinspiration WebME Molecule Editor LIGSITE<sup>CSC</sup>  
SMARTCyp Web Service **Zinc Database** SVILP\_ligand LCT LigPrep BioDrugScreen VSDMIP **cQSAR** Binding Database SiteComp Epik PDBBinder  
ProCESS CSAR PDBbind MetaPrint2D-React. **cQSAR** SIDER SCIGRESS JChemPaint TexMol DoGSiteScorer PoseView q-TOX **Hyde** UM-BBD Pathway  
Prediction System **CHARMMing.org** ChemDB/Datasets KeyRecep Balloon Elemental **GLL** Autodock Vina Corina online demo Protein Ligand Database (PLD)  
Screen2 ICM-Browser Fleksy **SPROUT-HitOpt** Aggregator Advisor **Binding MOAD (Mother Of All Database)** SCORPIO Bioclipse Indigo-depict I-TASSER  
CABS **BOMB** TIP database HazardExpert Pro SMART ElectroShape Polypharmacology server **FINDSITE** COSMOS Viewer **Ascalaph** SMPDB Atom 3D ChEBI  
HitPick metaPocket LAMMPS BSP-SLIM Chem4D **QSARpro** TOXNET PROPKA Structural Database (CSD) CheVi RasTop NOC UCSF Chimera ModWeb  
Cavimator ChemMobi Hologram **QSAR (HQSAR)** PEP-FOLD Ball&Stick rDock Abalone LPCCSU MORE **ORAC** Prime ePMV **Corina** SMARTSeditor ChemProt  
KnowItAll - ADME | Tox Edition **HYBRID** DS Visualizer **FINDSITE<sup>COMB</sup>** **OSIRIS Property Explorer** PACT-F DNP **LigBuilder** SURFNET GLmol Ki Database  
GLIDA DAIM-SEED-FFLD SimiCon idock ACD/DMSO Solubility DataWarrior Natural product likeness calculator TorsionAnalyzer **ACD/Structure Design Suite** **GlamDock**  
Topomer CoMFA GastroPlus RaptorX web server IBIS DecoyFinder HMDB **Autodock** TTD Discovery Studio TOPKAT Software **CODESSA Pro**  
iProtein POCASA ProBis eFindSite Open3DALIGN LigandScout **PRO\_LIGAND** Virtual library Repository **PharmaGist** Autogrow MetaPred MCASE aMD  
**PASS** **OSIRIS Property Explorer** **Pharmer** MOE **GANDI** MMsINC Accelrys Draw Fuzzee MolScore-Antivirals **Datasets from the Milano**  
**Chemometrics and QSAR Research Group** LIGSITE<sup>CSC</sup> web server Discovery Studio ADMET Software XDrawChem FunFOLD GPCRautomodel NRLiST Friend  
LeadGrow ilib diverse CNS (Crystallography & NMR System) **MedChem Studio** ToxiPred Chemtool ModBase JKluster Computer-Aided Drug-Design Platform  
using PyMOL GFscore E-Babel **e-LEA3D** smi23D web service **iScreen** Smi2Depict Comparative Toxicogenomics Database (CTD) CPHmodels **ReCore** RasMol  
**AnchorQuery** **MOLARIS-XG** JChem for Excel CASETOX **DOCK** kinDOCK CueMol for iOS PEPstr FunFOLDQA Pfinder McVol **MedChem Studio** PK-Sim

**Thank you**