Drug Discovery Grid (DDGrid)

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Agenda

1. DDGrid Overview
2. DDGrid Architecture
3. Result Analysis
4. Future Work

Background

Large-scale High-throughput Virtual Screening

- **in Silico**

  The computational analysis of chemical databases to identify compounds appropriate for a given biological receptor

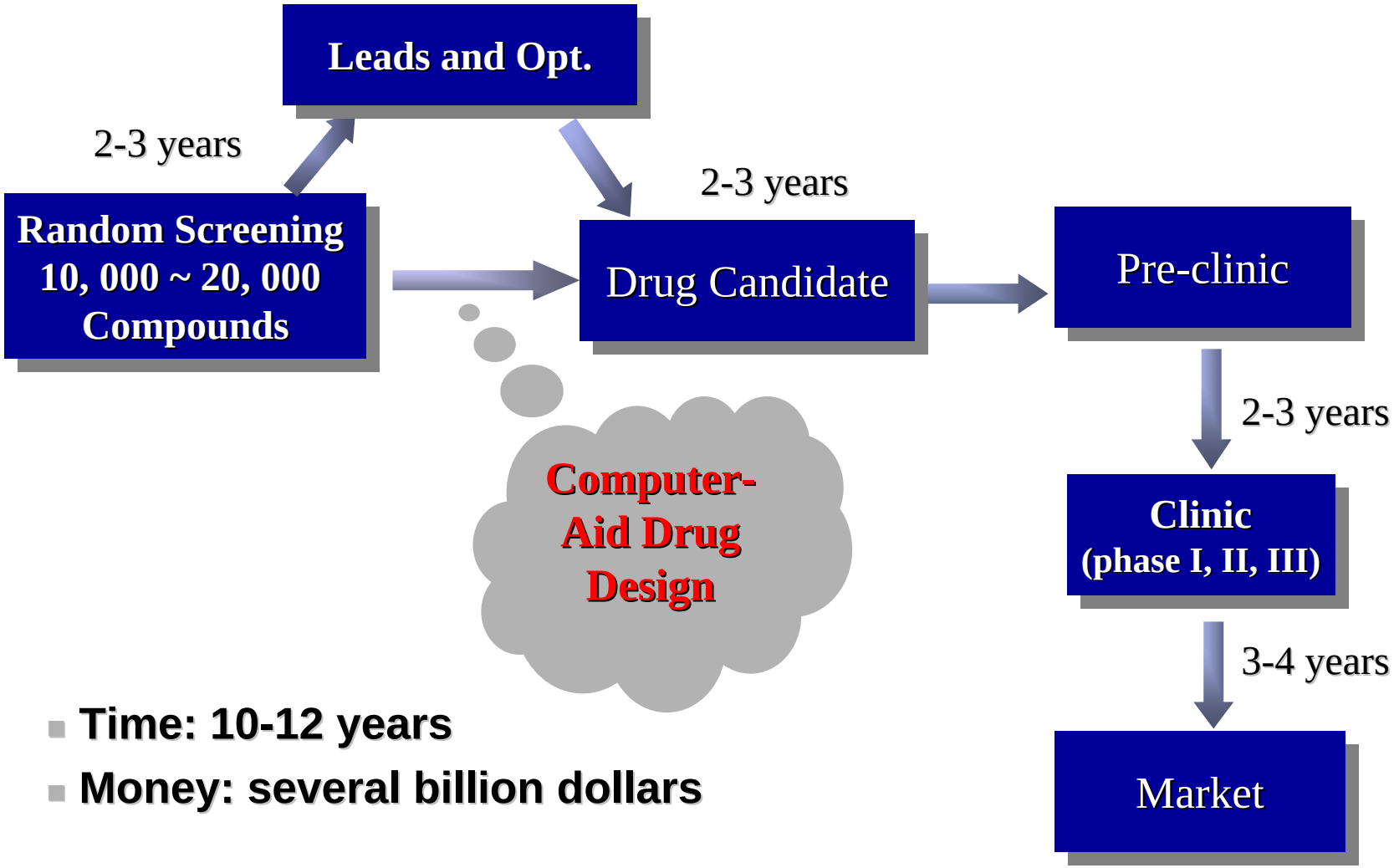
- **in Vitro**

  the progressive optimization of these leads to yield a compound with improved potency and physicochemical properties *in vitro*

- **in Vivo**

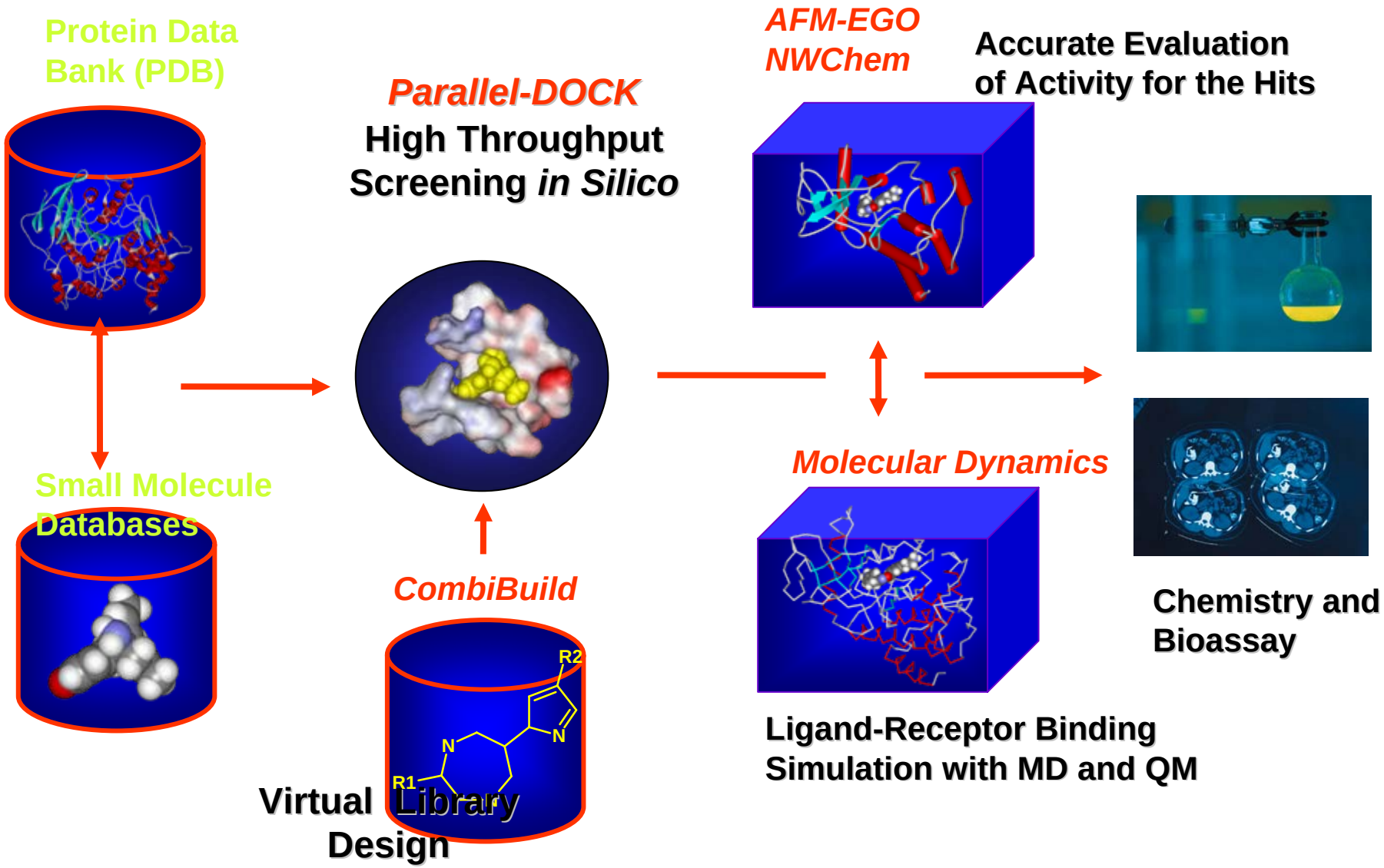
  eventually, improved efficacy, pharmacokinetics, and toxicological profiles *in vivo*.

General Process of Drug Discovery and Design

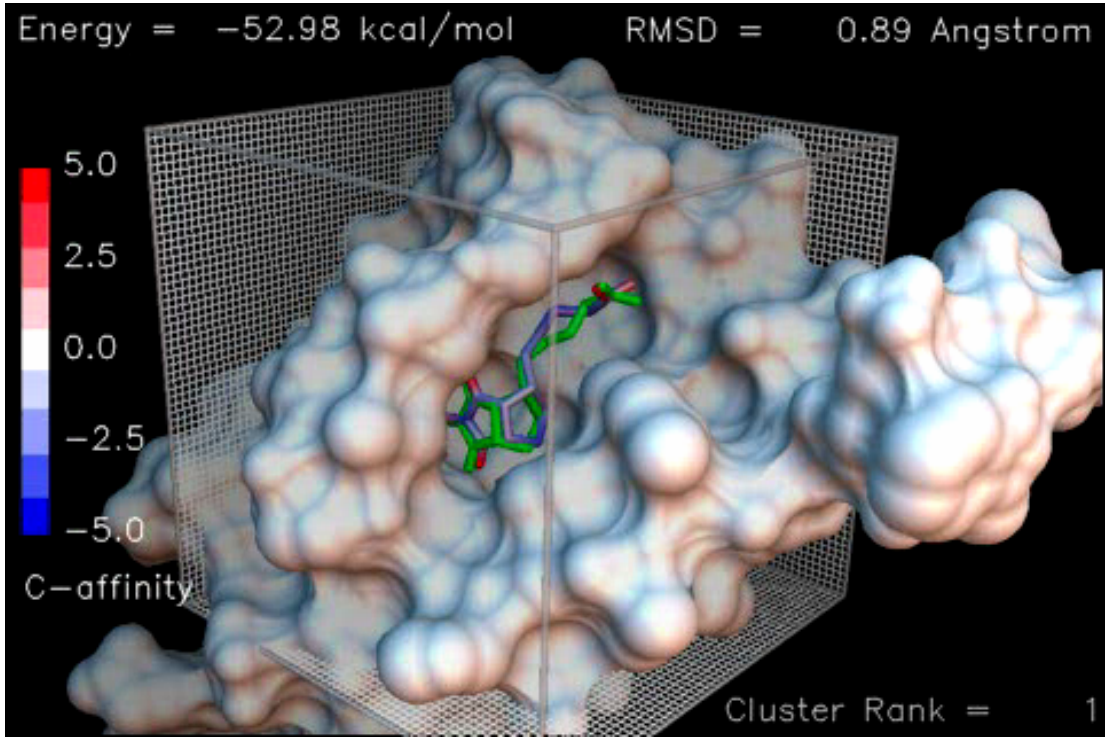


- **Time: 10-12 years**
- **Money: several billion dollars**

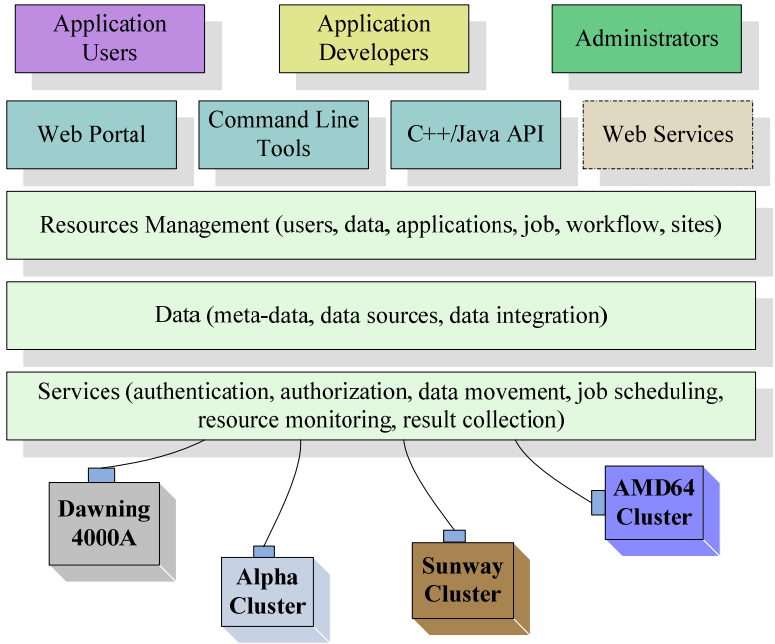
Drug discovery in SIMM

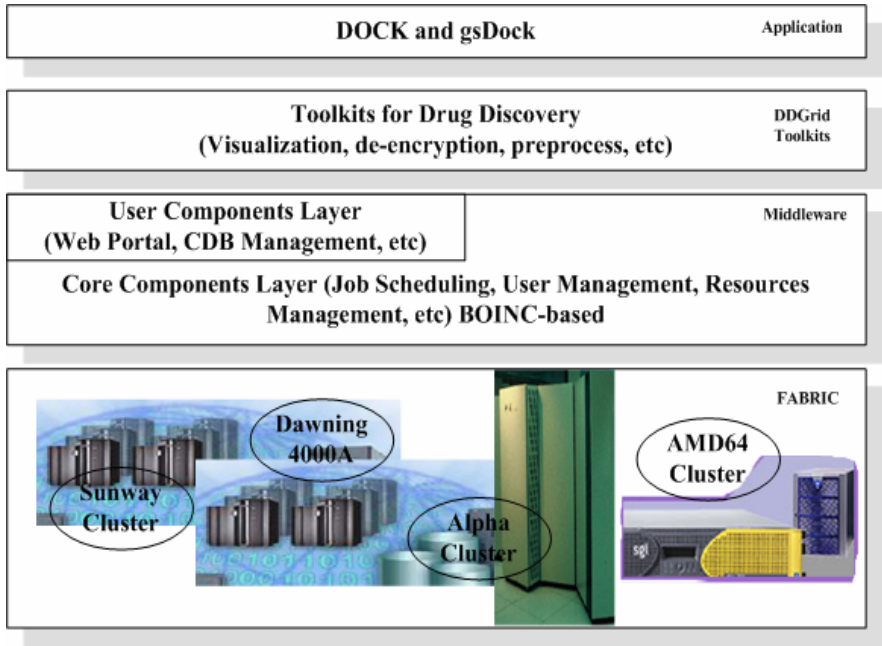


Virtual screening

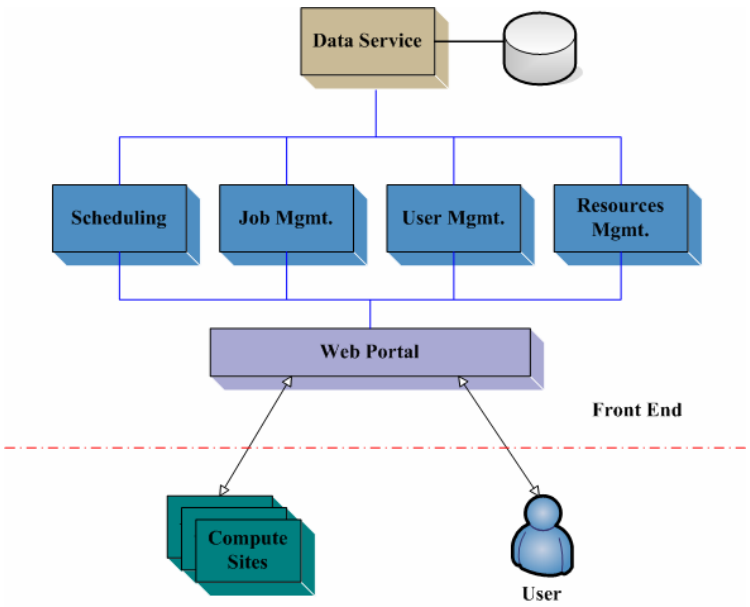


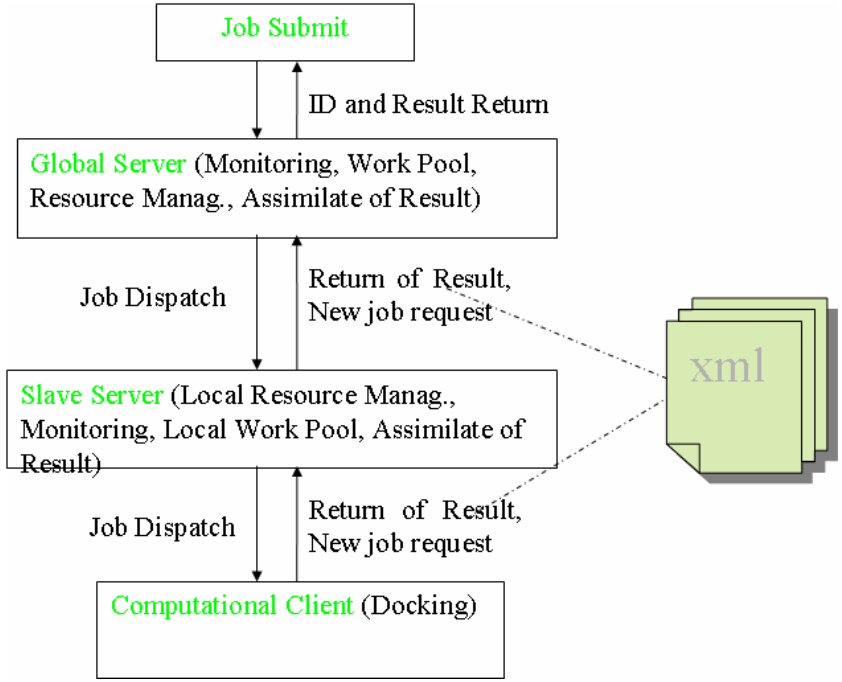
DDGrid Architecture





DDGrid Architecture





Comp. resources aggregated

Computing Resource

No.	Location	Unit	Slave Server	Server Type	Total CPU Number	Avail. CPU Number	Avail. :Busy :Idle	
A	Shanghai	Shanghai Supercomputing Center	SSC	Dawning 4000A	128	0		0% Avail.
B	Shanghai	Shanghai Institute of Materia Medica	SIMM_ALPHA	Sunway 32A				N/A
C	Beijing	Beijing Molecule Company	Molecule	Sunway 256P				N/A
D	Hong Kong	Hong Kong Univ.	HKU	Gideon Cluster	16	16		100% Avail.
E	Shanghai	Shanghai Institute of Materia Medica	SIMM_PC	Sunway 32A	16	0		0% Avail.
F	Dalian	Dalian University of Technology	DLUT	Lenovo Shenteng1800				N/A
G	Shanghai	Shanghai Jiaotong Univ.	sjgcc					N/A
H	Singapore	Singapore Polytechnic Univ.	SP	Sun	32	0		0% Avail.
I	London	London e-Science Centre	LeSC					N/A

Data resources on DDGrid

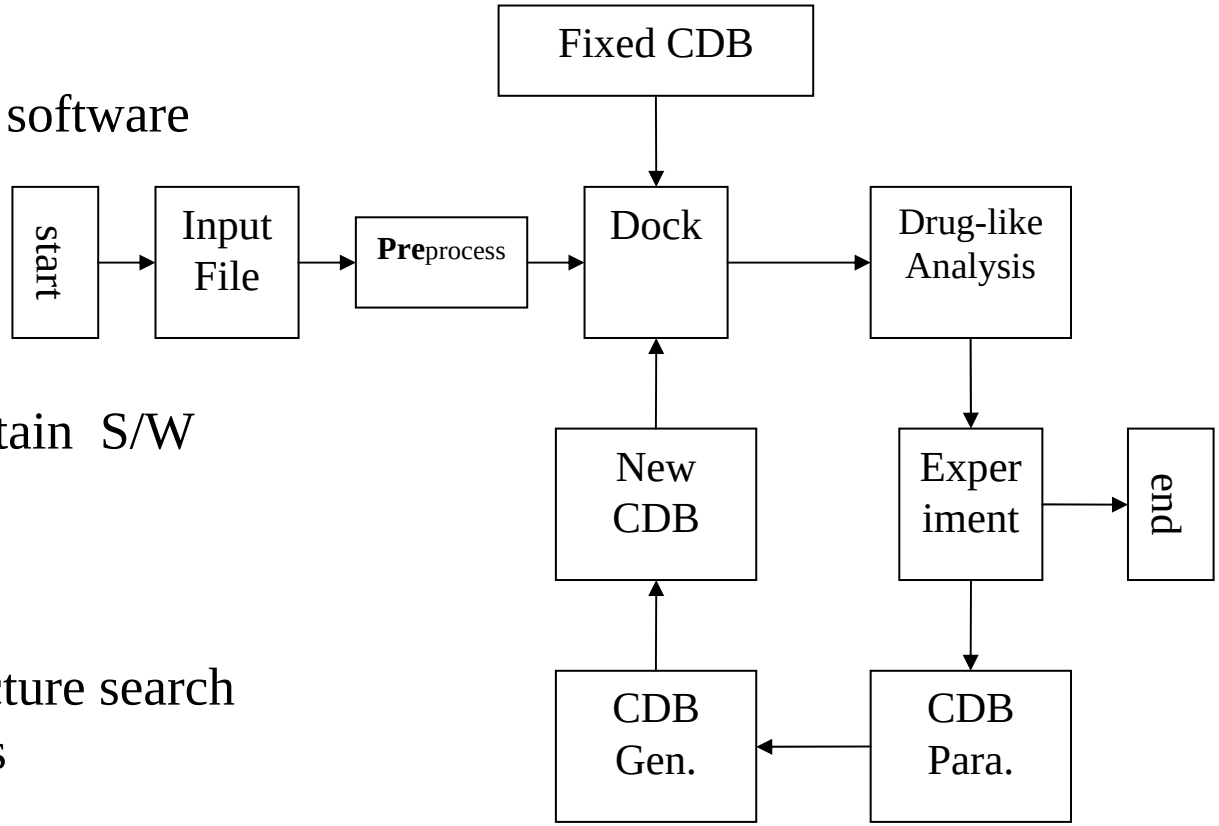
Commerical CDB

Data Resource			
Database Name	Status	Numbers	Description
Specs	Available	230,000+	Chemical available compounds' structure database
MDL Comprehensive Medicinal Chemistry 3D	Available	8,400+	Pharmaceutical compounds (1900- present)
MDL Available Chemicals Directory 3D	Available	200,000+	Commercially available chemical's 3D structure database
National Cancer Institute Databases NCI-3D	Available	213,000+	Structures with corresponding 3D models
China Natural Products Database	Available	12,000+	Chemical, structural and bibliographic data are provided for natural products first isolated in China.
Traditiona Chinese Medicinal Database TCMD	Available		9127 chemical structures, 3922 medicinal herbs or plants
ZINC - ChemBridge	Available	562,624	Chemical structures, web site: www.chembridge.com
ZINC - MayBridge	Available	53,042	Chemical structures, web site: www.maybridge.com

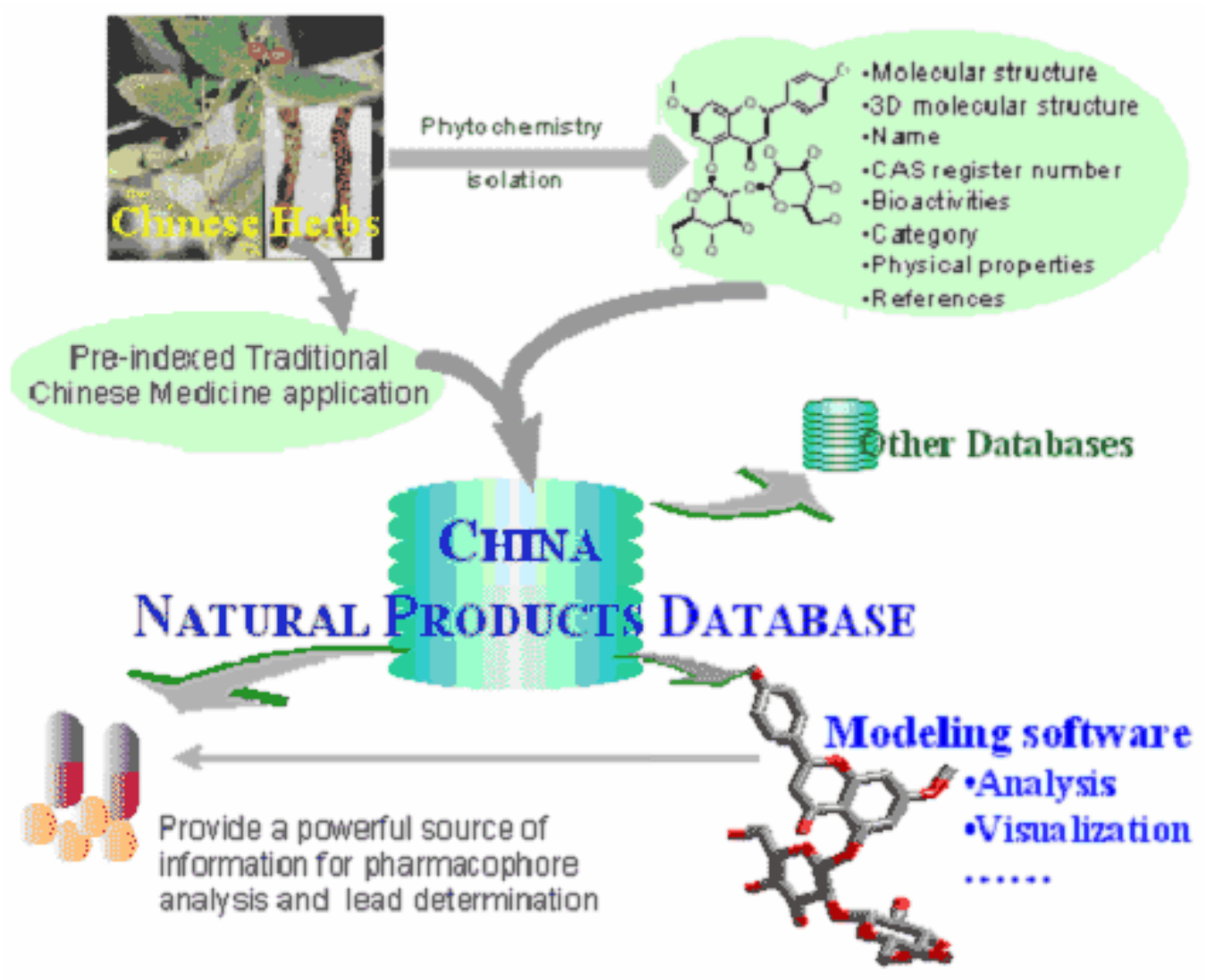
Application softwares

DDGrid Apps.

1. Docking pre-process software
   Combimark
2. Docking software
   1) Dock UCSF
   2) gsDock SIMM
3. CDB build and maintain S/W
   Combilib
4. AutoDock
5. AutoGrid
6. Visualisation & structure search
7. Security-related tools



CDB example：CNPD-China Natural Products Database

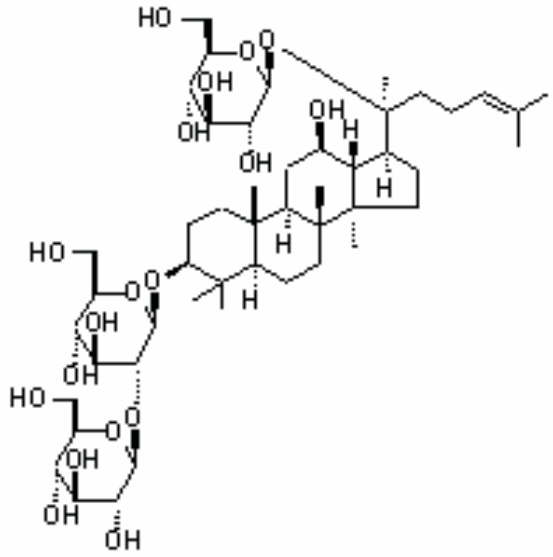


CDB example：TCMD-Traditional Chinese Medicine Database

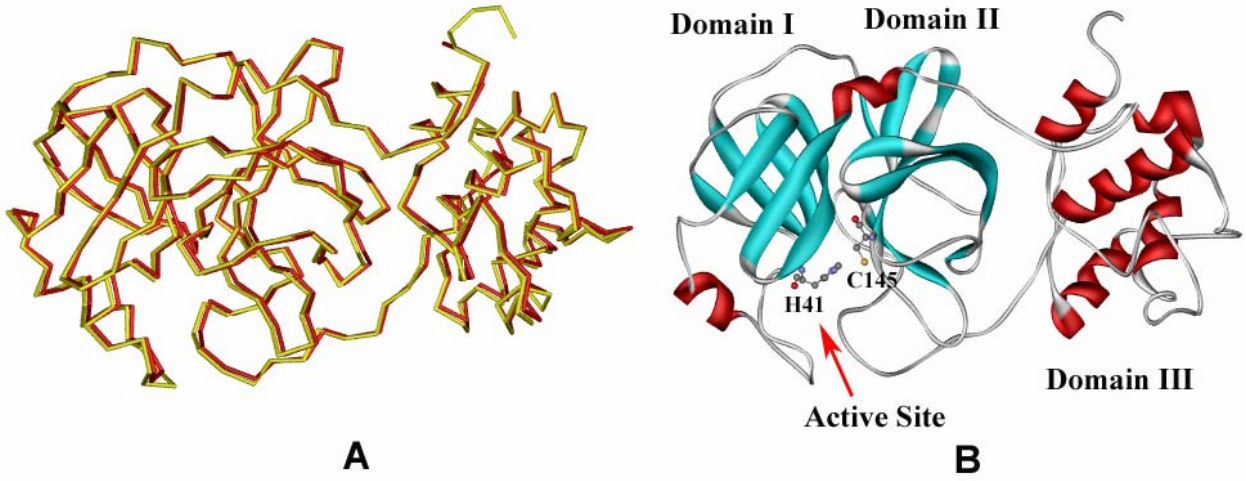
3368 Ginsenoside Rd 人参皂甙Rd

Gypenoside VIII 52705-93-8 C48H82O18 947.18 物化性质： 白色粉末（乙醇-正丁醇 1:1），mp 206-209° C，[α]D22 = +19.38° （c = 1.03，甲醇）。 药理活性：抗心律失常（BaCl2引起的大白鼠心律不齐）；抗病毒；抑制HSV-1的复制；大白鼠肝脏匀浆的抗氧化剂（H2O2所致，IC50 = 12.0±0.8μg/ml，by FeSO4，IC50 = 457.5±15.4μg/ml）；11-β-羟甾脱氢酶抑制剂；cAMP磷酸二酯酶抑制剂（in vitro，IC50 = 84μM）；促进软毛霉素和长春花碱的细胞毒作用；促进皮质酮血浆分泌（ED50 = 112 mumol/kg）；调节肾功能和抑制肾小球再生；血管扩张剂。原植物： 绞股蓝，秦岭珠子参，人参，西洋参。参考文献：

4,87,451,900



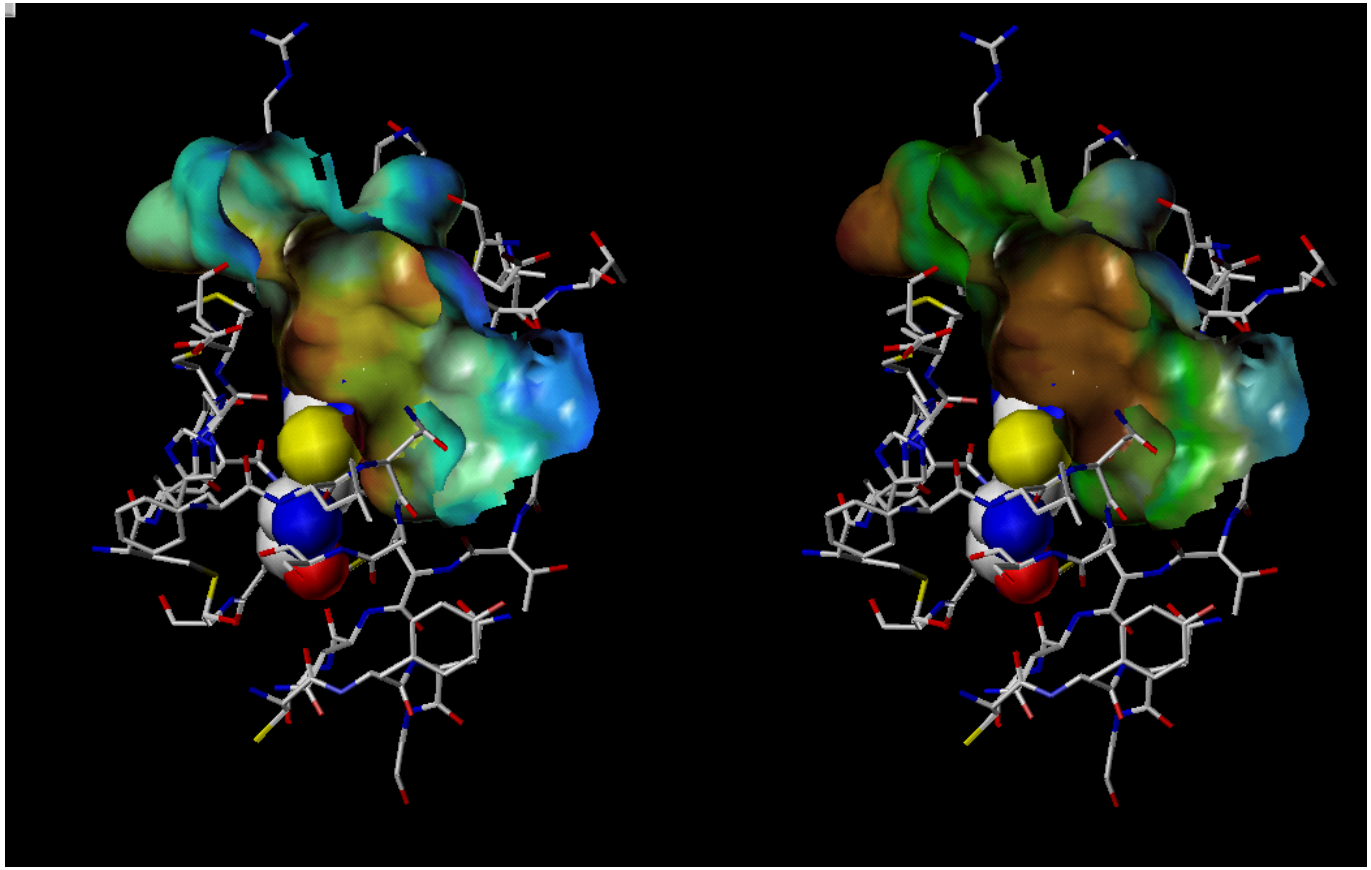
3D Model of SARS-CoV 3CL Proteinase



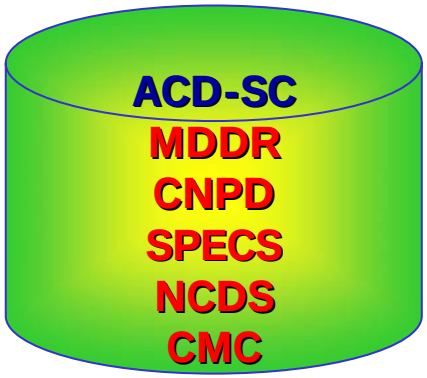
identity: 43%, similirity: 60%, gap: 1%.

(A) Structure superposition of the modeled structure of SARS 3CL proteinase (yellow) with the X-ray crystal structure of the M^{pro} of TGEV (transmissible gastroenteritis virus)(red). Only backbones are shown in this picture. (B) The solid ribbon representation of the structure model of SARS 3CL proteinase. The substrate-binding site is located at the deep cleft between domains I and II, and the active site is situated at the center of the cleft, the catalytic residues H41 and C145 are represented by ball-and-stick.

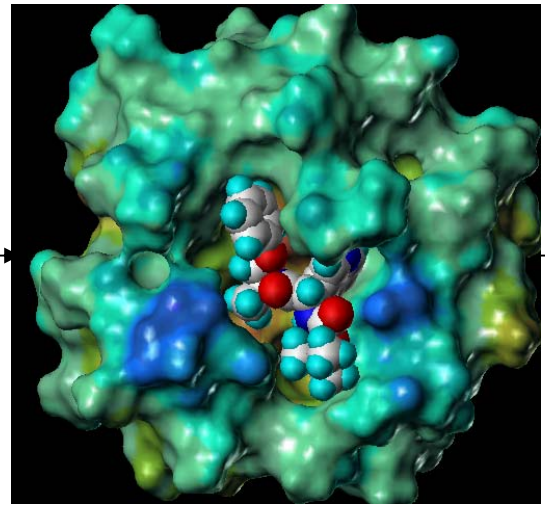
Active site of the SARS 3cl proteinase



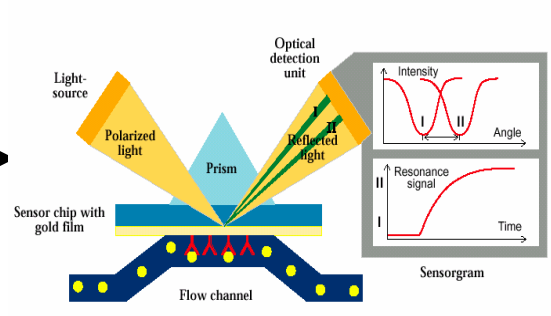
Virtual screening for SARS 3cl proteinase



Databases



Docking



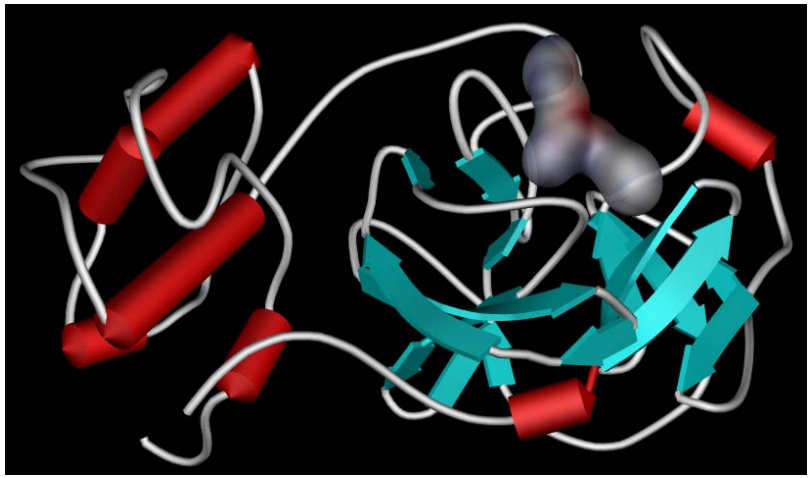
Biacore 3000

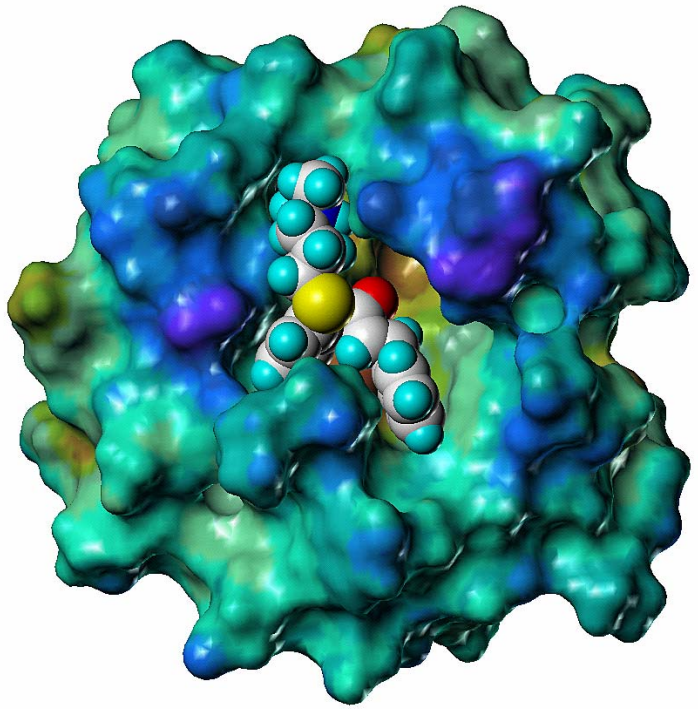
Binding Assay

CMC Virtual Screening Result

	MDLNUMBER	Dock (kcal/mol)	Autodock (kcal/mol)	Cscore
1	DDDCS001	-30.99	-9.68	**5**
2	DDDC001	-37.06	-8.79	**4**
3	DDDCS002	-35.09	-8.60	**5**
4	DDDCS003	-35.52	-8.76	**5**
5	DDDCS004	-32.52	-9.55	**5**
6	DDDCS005	-34.60	-7.57	**5**
7	DDDCS006	-31.98	-9.27	**5**
8	DDDCS007	-33.72	-8.69	**4**
9	DDDCS008	-37.45	-8.07	**4**
10	DDDCS009	-36.06	-7.08	**4**

Result visualization





Selected users of DDGrid

Future work

- **New application and upgrade**
  - Screening considering Protein flexibility,
  - Target Fishing Dock (TarFishDock)
- **Architecture refactoring**
  - adopt to recent common standards,
  - publishing services to remote consumer,
  - swappable screening methods and software,
  - workflow-oriented resource composition
- **Chemical database increment**
  - more self-made CDB
  - more commercial CDB

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Drug Discovery Grid

Q & A

Drug Discovery Grid

Thank you very much!