State-of-the-art computational drug design, discovery, and development: Challenges and opportunities

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UK CCS Seminar, March 19, 2024

Contents

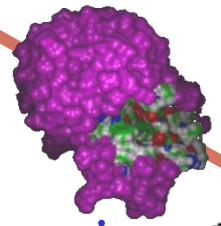
- Challenges and opportunities for a computational drug designer in discovery and development
- Overview of our projects in drug discovery and development
- An example of virtual screening for drug repurposing
- Concluding remarks

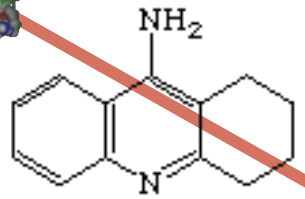
Overview

Traditional Drug Discovery & Development

Identify disease

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

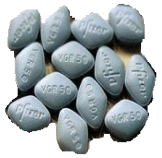




Isolate protein involved in disease (2-5 years)

Preclinical testing (1-3 years)

Scale-up



Formulation

File IND

Human clinical trials (2-10 years)

File NDA

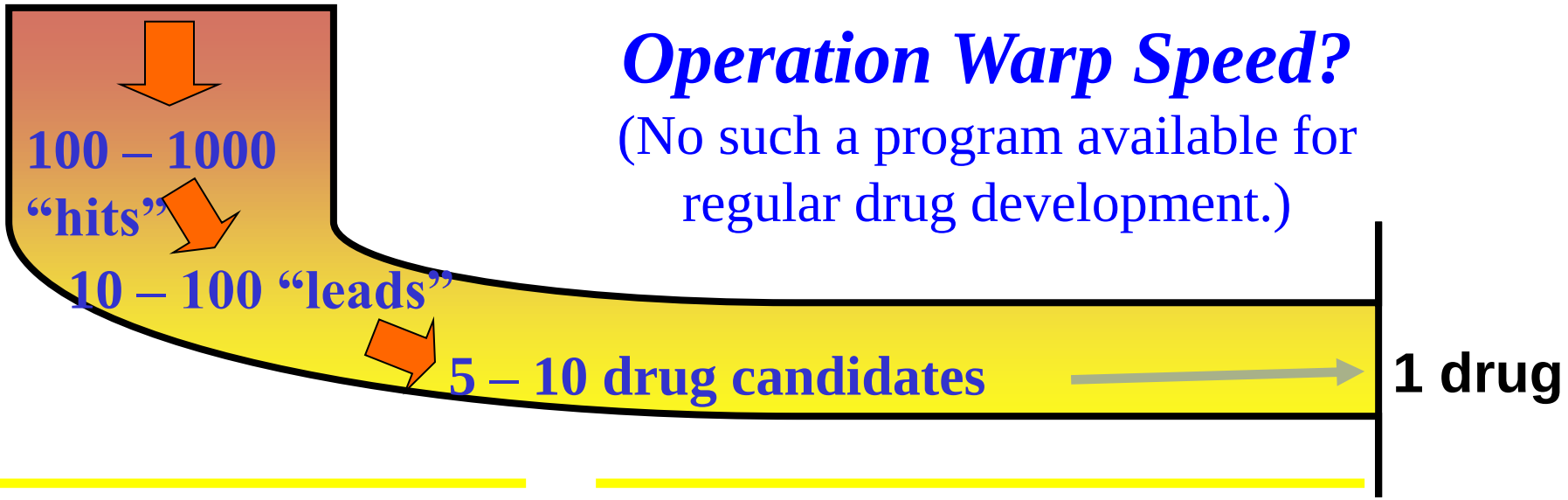
FDA approval (2-3 years)

Investigational New Drug (IND)
New Drug Application (NDA)

Drug discovery and development process

Time and money

10,000 - 10,000,000 compounds are often screened to find a single drug



Operation Warp Speed?

(No such a program available for regular drug development.)

Discovery & Preclinical trials | Clinical trials: Phase I, Phase II, Phase III

12 to 25 years

Usually >$1 billion

The average cost for a drug approved recently: ~$1.3–2.8 billion

Average success rate of clinical trials: <10%

Drug discovery and development process

Pharmaceutical company	Number of drugs approved	Average R&D spending per drug (in $ Millions)	Total R&D spending from 1997-2011 (in $ Millions)
AstraZeneca	5	$11,790.93	$58,955
GlaxoSmithKline	10	$8,170.81	$81,708
Sanofi	8	$7,909.26	$63,274
Roche Holding	11	$7,803.77	$85,841
Pfizer	14	$7,727.03	$108,178
Johnson & Johnson	15	$5,885.65	$88,285
Eli Lilly & Co.	11	$4,577.04	$50,347
Abbott Laboratories	8	$4,496.21	$35,970
Merck & Co Inc.	16	$4,209.99	$67,360
Bristol-Meyers Squibb Co.	11	$4,152.26	$45,675
Novartis	21	$3,983.13	$83,646
Amgen Inc.	9	$3,692.14	$33,229

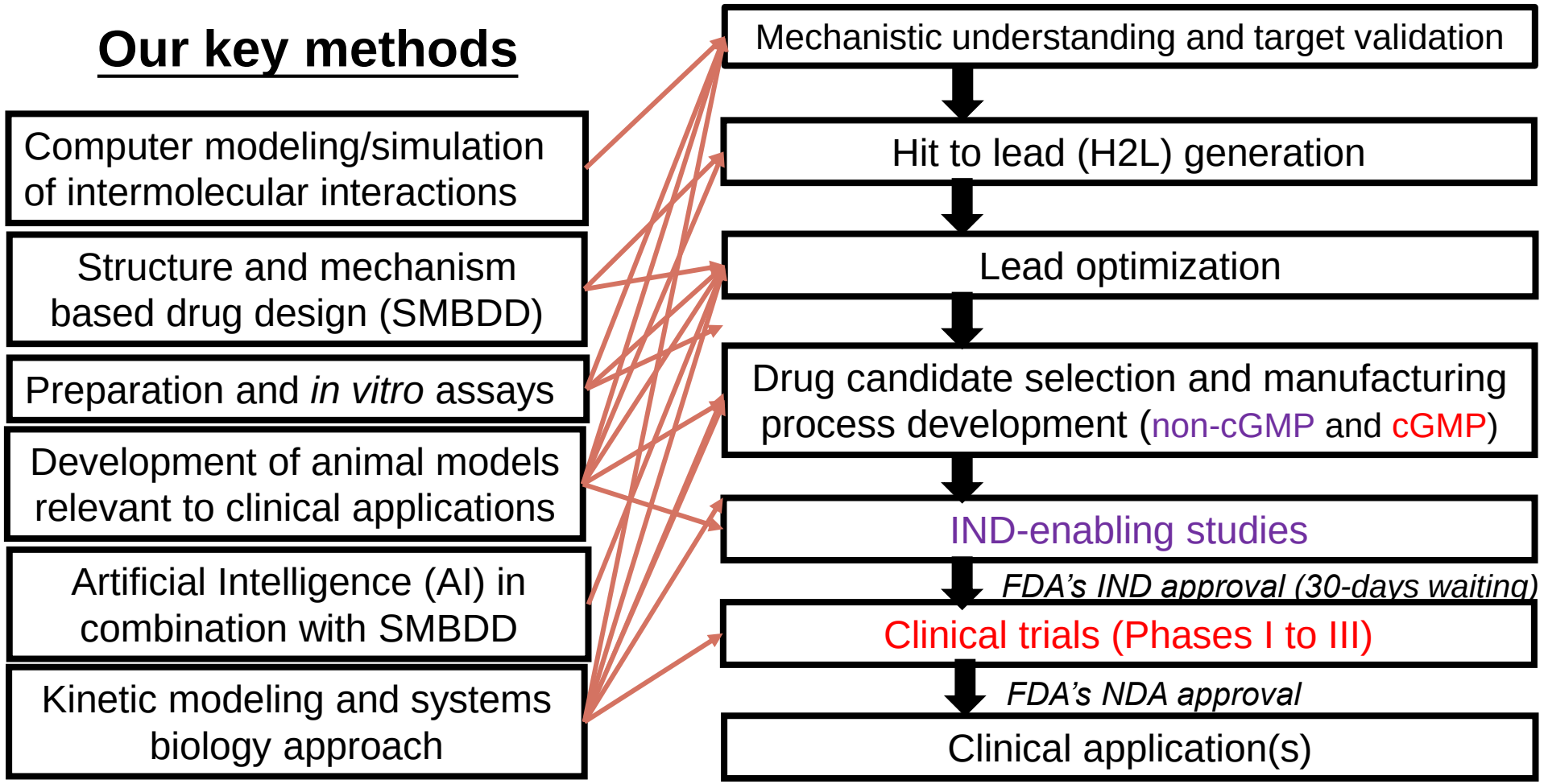
Severin Schwan, the CEO of the Swiss company Roche, reported that Roche's research and development costs amounted to $12.3 billion in 2018[7], a quarter of the entire National Institutes of Health budget.

Challenges and opportunities for a computational drug designer in discovery and development

- Perception of “drug design”: Design of drug candidates
- Definition of a drug candidate? Not just merely an active and selective compound (“hit” → ”lead” → ”drug candidate” → ”drug”).
- Necessity of extensive *in vitro* and *in vivo* tests and formulation development – very time-consuming.
- What is your expectation? Publication or drug product?
- Who still want to do the real “drug design”? Think about how history will remember you.

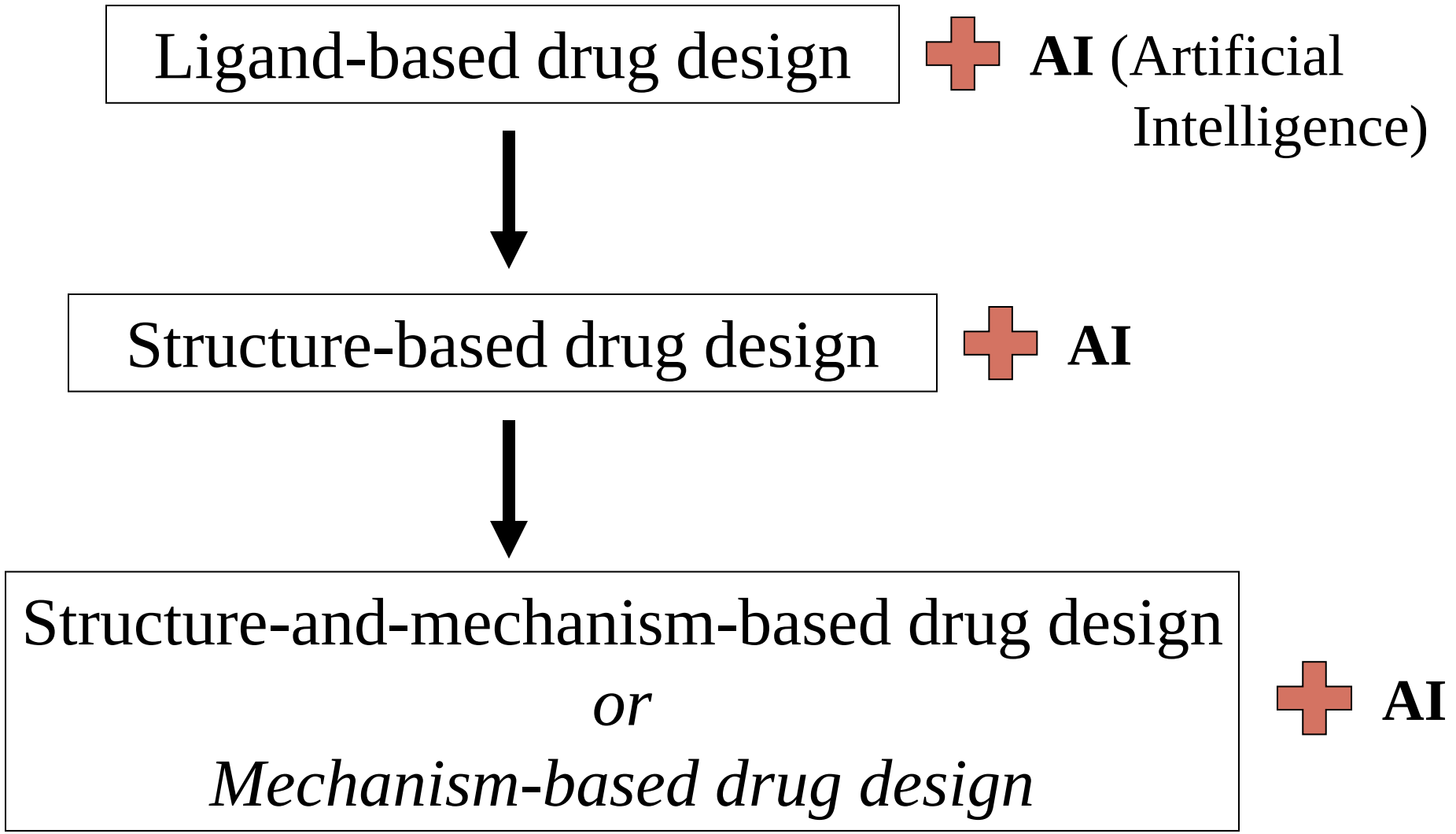
Take-home message: Drug discovery is much more than identification of an active compound.

Integrated computational & experimental Approach



Take-home message: Computational modeling can be valuable in all stages of modern drug discovery and development process.

Evolution of Rational Drug Design



Ongoing Research Efforts in My Lab

Ultimate goal of our current research:

To discover and develop effective first-in-class therapeutic agents.

- **Type I Projects: Development of novel computational methodologies**

Summary of computational methods for a large biological/material system

- **Scaling – multi-scale approach**:
  - Quantum Mechanics (QM)

Quantum Mechanics

P. A. M. Dirac

'... all the mathematics to solve the whole of chemistry is known, but the equations are too difficult to solve ...'

The two shared *Nobel Prize in Physics* in 1933.

Erwin Schrödinger

Dirac Equation

$$i\hbar\gamma^\mu \partial_\mu \psi(x) - mc\psi(x) = 0$$

To obtain relativistic wavefunction (accounting for relativistic effects)

Time-dependent Schrödinger Equation

$$\hat{H}|\psi_n(t)\rangle = i\hbar\frac{\partial}{\partial t}|\psi_n(t)\rangle$$

Neglect relativistic effects

Practical QM Computations for Molecules

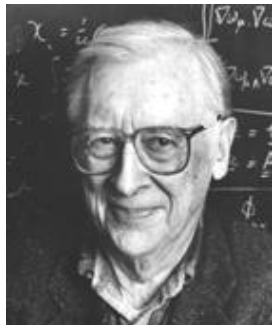
Schrödinger's equation for electronic systems

$$H^{el}\psi^{el} = E^{el}\psi^{el}$$

Wavefunction Methods

Density Functional Methods (DFT)

John Pople
(*Gaussian* program)



Walter Kohn
(DFT)

1998 Nobel Prize in Chemistry (for development of computational methods to solve the **Schrödinger** equation for electronic system)

Martin
Karplus

Arieh
Warshel

Michael
Levitt

2013 Nobel Prize in Chemistry (for development of computational methods in studying biological systems)

Ongoing Research Efforts in My Lab

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- **Type I Projects: Development of novel computational methodologies**

Summary of computational methods for a large biological/material system

- **Scaling – multi-scale approach**:
  - Quantum Mechanics (QM)
  - all-atom force field (MM)
  - coarse-grained (CG)
  - …. (further larger scale)?
- **Computational level for each scale, *e.g*. QM results are affected by**
  - Electron correlation level
  - basis set
  - relativistic effects
  - solvent/environmental effects
- **Dynamics of biological systems**
  - Time step and total simulation time
- **AI as a plus to expand the computational approach**
  - AI relies on large data set available.

Ongoing Research Efforts in My Lab

***Ultimate goal of our current research*:**

To discover and develop effective first-in-class therapeutic agents.

- **Type I Projects: Development of novel computational methodologies**
  e.g. Development of first-principles electronic structure approach (NSF CHE-1111761); Development of novel AI approach to molecular design (NSF CNSF DMS-2245903 with Dr. Duc Nguyen)
- **Type II Projects**: **Understanding molecular mechanisms of diseases to identify/validate novel drug targets** (*e.g*. NIH R01 DA057866, NIH 2R01 DA035714, NIH P01 NS097197, and NIH P20 GM130456)
- **Type III Projects**: **Design, discovery and development of small-molecule drugs** (sponsored by NIH, DoD, and/or pharmaceutical companies)
  e.g. Topic for presentation today: DoD W81XWH2211000, NIH U01 HL152392 and KYNETIC Grant.
- **Type IV Projects**: **Design, discovery and development of protein/peptide drugs** (*e.g*. NIH U01 DA051079, NIH UG3/UH3 NS134920, NIH R01 DA056646, NIH R01CA279455, VA 1I01BX004639-01 & DoD contract)

Why Biologics? Top Selling Drugs in 2018

	DRUG	INDICATION	COMPANY	REVENUE (in Millions)	MONTHLY PRICE
1	HUMIRA ® (Adalimumab)	Immunology (RA)	Antibody targeting TNF-α	$ 420	$ 6,600
2	ELIQUIS ® (Apixaban)	Blood Clot	Bristol-Myers Scuibb	$ 9,879	$ 472
3	REVLIMID ® (Lenalidomide)	Blood-related Disorders	Celgene	$ 9,690	$ 21,000
4	OPDIVO ® (Nivolumab)	Oncology	Antibody blocking PD-1	$ 630	$ 12,500
5	ENBREL ® (Etanercept)	Immunology (RA)	Antibody targeting TNF-α	$ 60	$ 5,560
6	KEYTRUDA ® (Pembrolizumab)	Oncology	Antibody targeting PD-1 receptor	$ 70	$ 13,500
7	HERCEPTIN ® (Trastuzumab)	Oncology	Antibody targeting HER2	$ 0	$ 6,391
8	EYLEA ® (Aflibercept)	Retinal Disease (AMD)	Fc fusion protein inhibiting VEGFs	$ 70	$ 2,000
9	AVASTIN ® (Bevacizumab)	Oncology	Antibody inhibiting VEGF-A	$ 0	$ 840
10	RITUXAN ® (Rituximab)	Oncology/Immunology	Antibody against CD20	$)	$ 989

Eight out of 10 top selling drug = Biologics

Top Selling Drugs in 2020 and 2021

2020			2021		
Rank	Drug	Sale(10x$B)	Rank	Drug	Sale(10x$B)
1	Humira	203.9	1	Comirnaty	368
2	Keytruda	143.8	2	Humira	207
3	Revlimid	121.5	3	Spikevax	177
4	Eliquis	91.7	4	Keytruda	172
5	Imbruvica	84.3	5	Eliquis	167.3
6	Eylea	83.6	6	Revlimid	128
7	Stelara	79.4	7	Imbruvica	98
8	Opdivo	79.2	8	Stelara	91
9	Biktarvy	72.6	9	Eylea	89
10	Xarelto	69.3	10	Biktarvy	86
11	Enbrel	63.7	11	Opdivo	85
12	Prevnar 13	59.5	12	Xarelto	75
13	Ibrance	53.9	13	Ronapreve	75
14	Avastin	53.2	14	Trulicity	65
15	Trulicity	50.7	15	Darzalex	60
16	Ocrevus	46.1	16	Trikafta/Kaftrio	57
17	Rituxan	45.2	17	Gardasil 9	57
18	Xtandi	43.9	18	Dupixent	56
19	Tagrisso	43.3	19	Veklury	56
20	Remicade	41.95	20	Ibrance	54

→ Pfizer vaccine

→ Moderna vaccine

Our designed first generation of therapeutic enzymes studied in Phase II clinical trials in humans

Enzyme ID	k_{cat} (min^{-1})	K_M (μM)	k_{cat}/K_M ($min^{-1}M^{-1}$)	$t_{1/2}$ (hours)	
				Rat	Human
CocE-DM or RBP-8000	1,080	13	8.3×10^7	0.2	
Albu-CocH1 or TV-1380	3,060	3.1	9.9×10^8	8	43-77

PNAS

Computational redesign of human butyrylcholinesterase for anticocaine medication

Yongmei Pan, Daquan Gao, Wenchao Yang, Hoon Cho, Guangfu Yang, Hsin-Hsiung Tai, and Chang-Guo Zhan†

Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, 725 Rose Street, Lexington, KY 40536

Edited by Stephen L. Mayo, California Institute of Technology, Pasadena, CA, and approved October 3, 2005 (received for review August 23, 2005)

Molecular dynamics was used to simulate the transition state for the first chemical reaction step (TS1) of cocaine hydrolysis catalyzed by human butyrylcholinesterase (BChE) and its mutants. The

down by the mutation. Reported computational modeling and experimental data indicated that the formation of the prereactive BChE–(−)-cocaine complex (the prereactive enzyme–substrate

Daquan Gao, Diwahar T. Narasimhan, Joanne Macdonald, Remy Brim, Mei-Chuan Ko,

Dor 16656–16661 | PNAS | November 15, 2005 | vol. 102 | no. 46 han

Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, Kentucky (D.G., C.-G.Z.); Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan (D.L.N., R.B., M.-C.K., J.H.W., R.K.S.); and Division of Clinical Pharmacology and Experimental Therapeutics, College of Physicians & Surgeons, Columbia University, New York, New York (J.M., D.W.L.)

Received June 5, 2008; accepted November 4, 2008

Our second generation of therapeutic enzyme: *e.g.* CocH5-Fc(M6)

- In preparation with NIH funding support (NIH U01 DA051079)

Received FDA's ***Breakthrough Therapy*** designation.

Presentation (11/17/2021) as one of the six Finalists for

Gordon Bell Special Prize in COVID-19

ACM (Association of Computing Machinery)

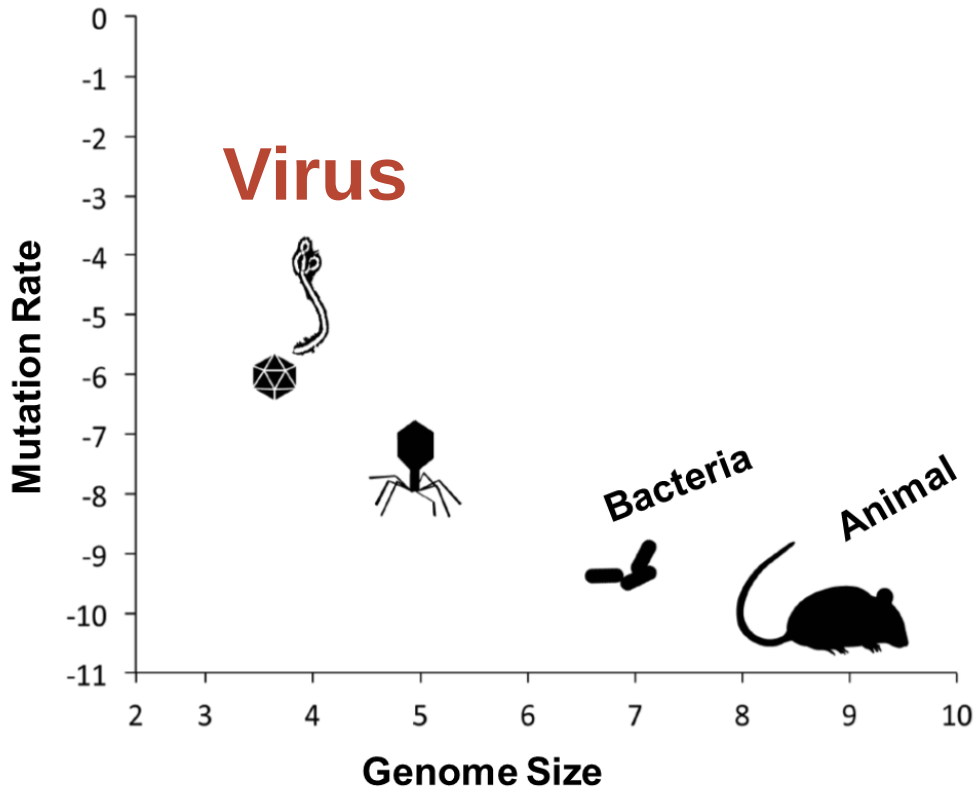
(Highlighted in *Nature Computational Science* in 2021)

FEP-based large-scale virtual screening for effective drug discovery against COVID-19 and clinical trials

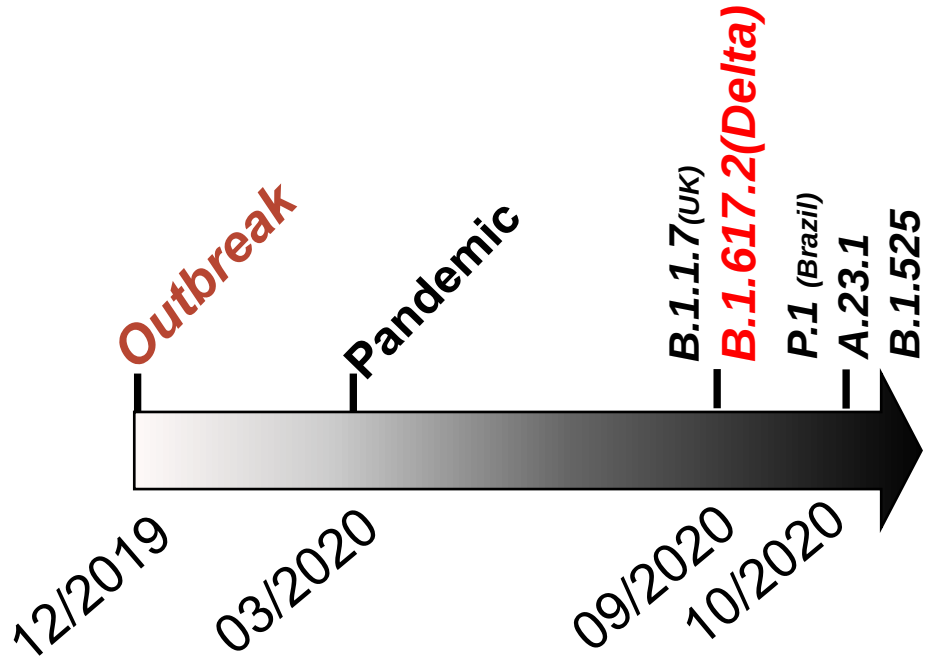
Zhe Li, Chengkun Wu, Yishui Li, Runduo Liu, Kai Lu, Ruibo Wang, Jie Liu, Chunye Gong, Canqun Yang, Xin Wang, Chang-Guo Zhan, and Hai-Bin Luo

Contents

Virus SARS-CoV-2 has generated hundreds of variants within 0.5 year



Siobain Duffy, PLoS Biology, 2018. with modifications



0.5 year
hundreds of variants

https://covid.cdc.gov/covid-data-tracker

High Mutation Rate of Viruses

Emerging New Variants/Viruses

Drug discovery: Not fast enough against viruses with a high mutation rate

Veklury
(Remdesivir)

11 years

Compound screening → lead compound (GS 441524) → Preclinical study → Clinical study → FDA Emergency Use

2006 SARS | 2012 | 2017- Ebola | 2020- | 10/22/2020 Redirection to COVID-19

Tamiflu
(Oseltamivir)

3 years

Target → lead compound (GS 4071) → Preclinical study → Clinical study → FDA approval

1992 | 1995 | 1998 | 1999

CADD

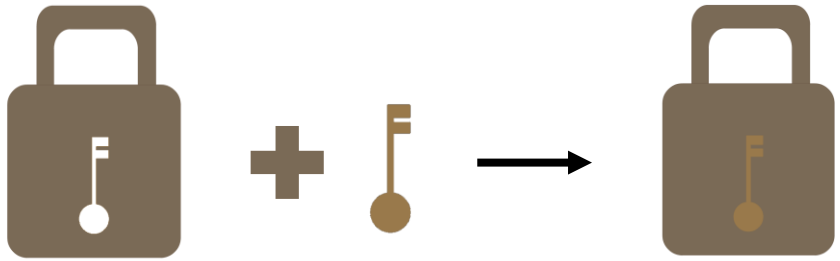
CADD (Computer-Aided Drug Design) has accelerated the drug discovery
BUT not fast enough!

Influenza

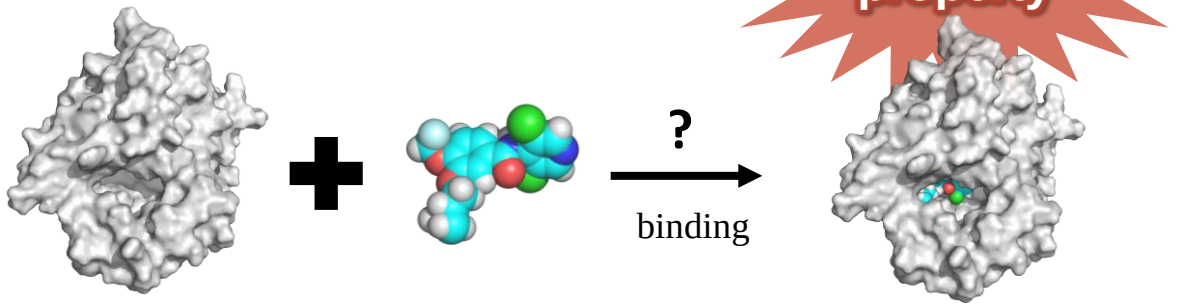
- Chu CK, Antimicrob Agents Chemother, 2006;
- Sheahan TP, Sci Transl Med. 2017;
- Eisenberg EJ, Antimicrob Agents Chemother. 1997;
- https://www.fda.gov/;
- https://clinicaltrials.gov/

CADD: Predicting binding affinity of each potential drug candidate with a given target

Lock and key model for drug-target interaction



A drug bind to its target like lock and key

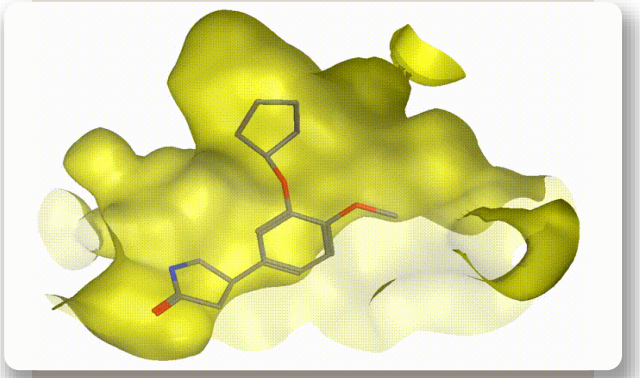


Key point in CADD:

To reliably predict binding free energy of each potential drug candidate with a given drug target

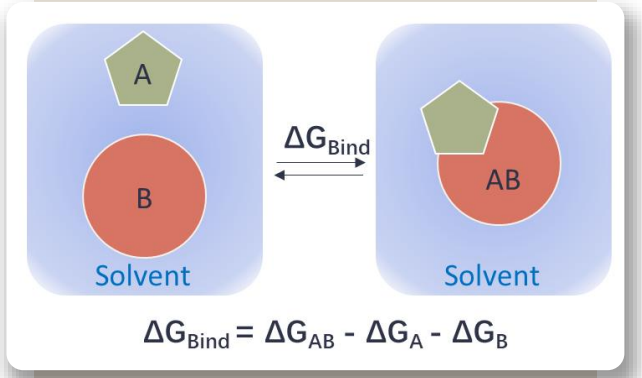
Limitation of traditional computational methods for binding free energy prediction

Scoring function
(Molecular docking)



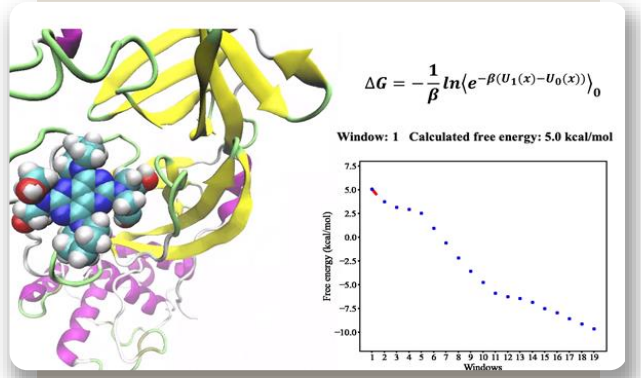
- **Fast** (billions of compounds)
- **Inaccurate**, low hit rate (~2%)[a]

End point methods
(MM-PBSA)



- **Moderate speed**
- **Moderate**, hit rate (<10%)[b]

Statistical mechanical methods
(FEP – Free Energy Perturbation)



- **Theoretically rigorous for relative binding free energy calculation**
- **Not designed for virtual screening**
- **Time consuming**

Unmet need: A truly accurate and efficient computational approach to absolute binding free energy calculations suitable for virtual screening

a. Gorgulla C, et al, Nature, 2020; b. Kuhn B, et al, J. Med. Chem. 2019

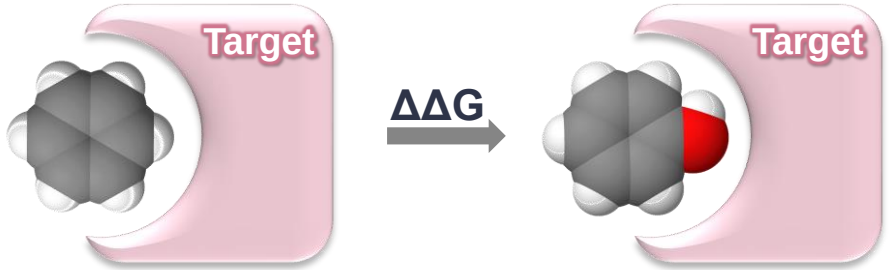
Contents

Why was FEP difficult for absolute binding free energy (ABFE) calculation?

FEP was designed to simulate a “perturbation” – a minor change of molecular structure;
Computational simulation of the *perturbation* is reliable only for a truly *minor* structural change.

$$\Delta A = -\frac{1}{\beta}\ln\langle\exp[-\beta\Delta\mathcal{H}(\mathbf{x},\mathbf{p}_x)]\rangle_0 = -\frac{1}{\beta}\ln\iint \exp[-\beta\Delta\mathcal{H}(\mathbf{x},\mathbf{p}_x)]\,P_0(\mathbf{x},\mathbf{p}_x)\,d\mathbf{x}\,d\mathbf{p}_x$$

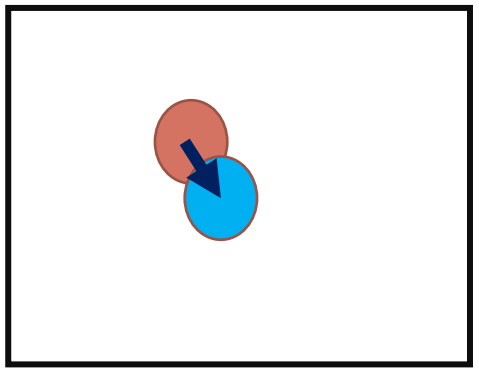
Current FEP: simulate a minor structural change



Relative binding free energy

- Changing < 10 atoms

Easy to calculate



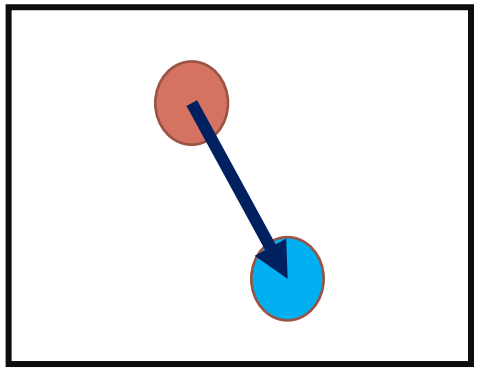
Needed FEP: simulate disappearance of an entire molecule

Absolute binding free energy

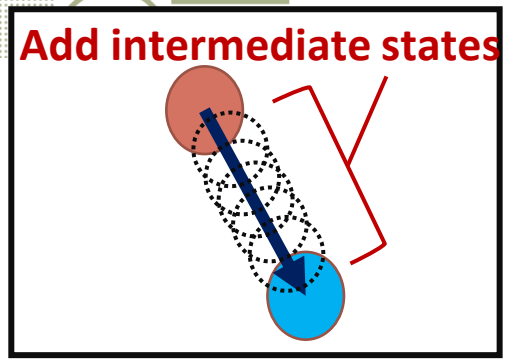
- Changing 50 ~ 100 atoms

Difficult to calculate

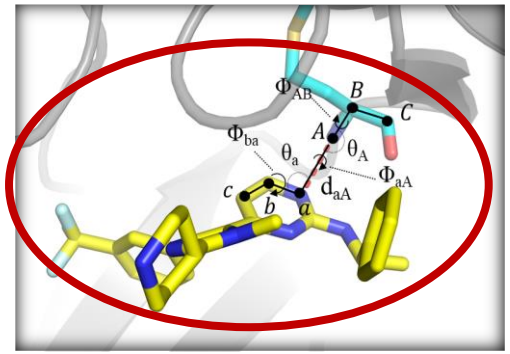
Phase space



Major problems preventing FEP-ABFE calculations-based virtual screening



- To deal with the large change, one must add many intermediate states, which means that one has to perform many FEP simulations for each FEP ABFE prediction--***Computationally time-consuming***



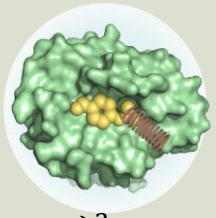
- Technically, to reliably evaluate conformational entropy contribution to ABFE, certain restraints are required. The choice of restraints required is case by case -- ***Difficult for automated virtual screening***

Our solution to the problems:

- A restraint energy distribution (RED) function derived and used to minimize the # of intermediate states required for a converged ABFE calculation.
- A unique algorithm enabling to automatically identify restraints (with three ligand atoms and three target atoms, restrained to their equilibrium).

Performance of our novel approach to the conformational entropy estimation

Physical model derivation



$$U_{ini} = k_{ini}\,(r - r_0)^2 \qquad \text{(S1)}$$

$$\Delta U_{i+1,i} = \Delta\lambda_{i+1,i} k_{res} (r - r_0)^2 \qquad \text{(S2)}$$

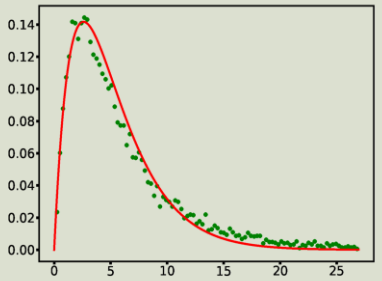
$$P(U_i) = \frac{ex\,p(-\beta U_i)\Omega(U_i)}{Z} \qquad \text{(S3)}$$

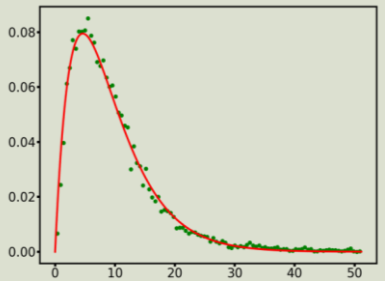
$$P(U_i) = \frac{exp(-\beta(k_{ini}+\lambda_i k_{res})(r-r_0)^2)4\pi(r-r_0)^2}{Z} \qquad \text{(S6)}$$

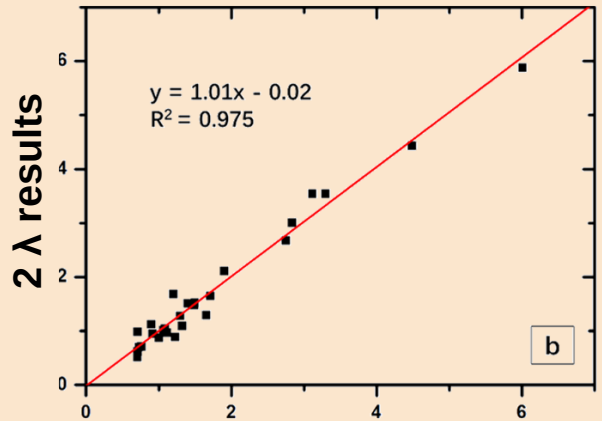
★ **RED function:**

$$\boldsymbol{P(\Delta U) = b^2 \cdot \exp(-\mathrm{b}\Delta U) \cdot \Delta U}$$

Finding the best match







- Fast
- Accurate
- Automatic

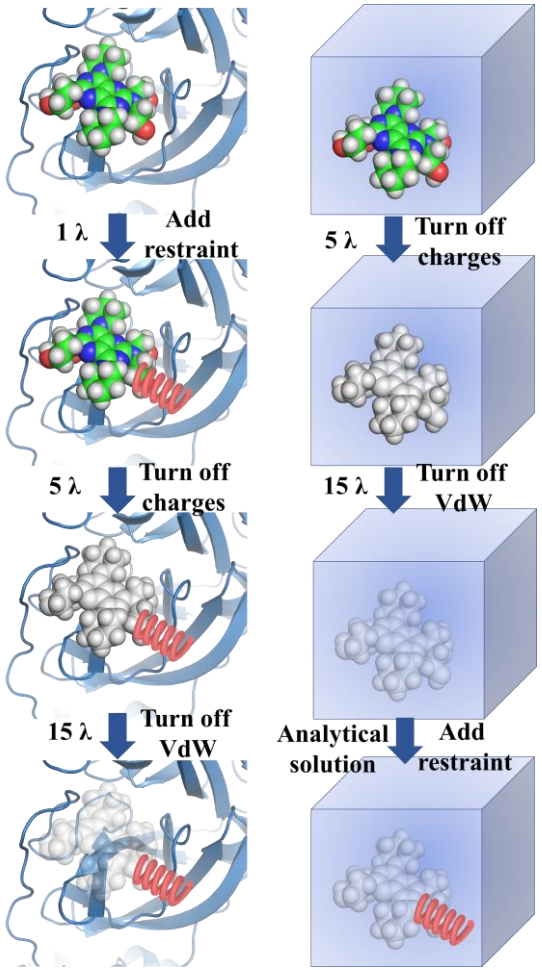
Z. Li, et al. Proc. Natl. Acad. Sci. USA 2020

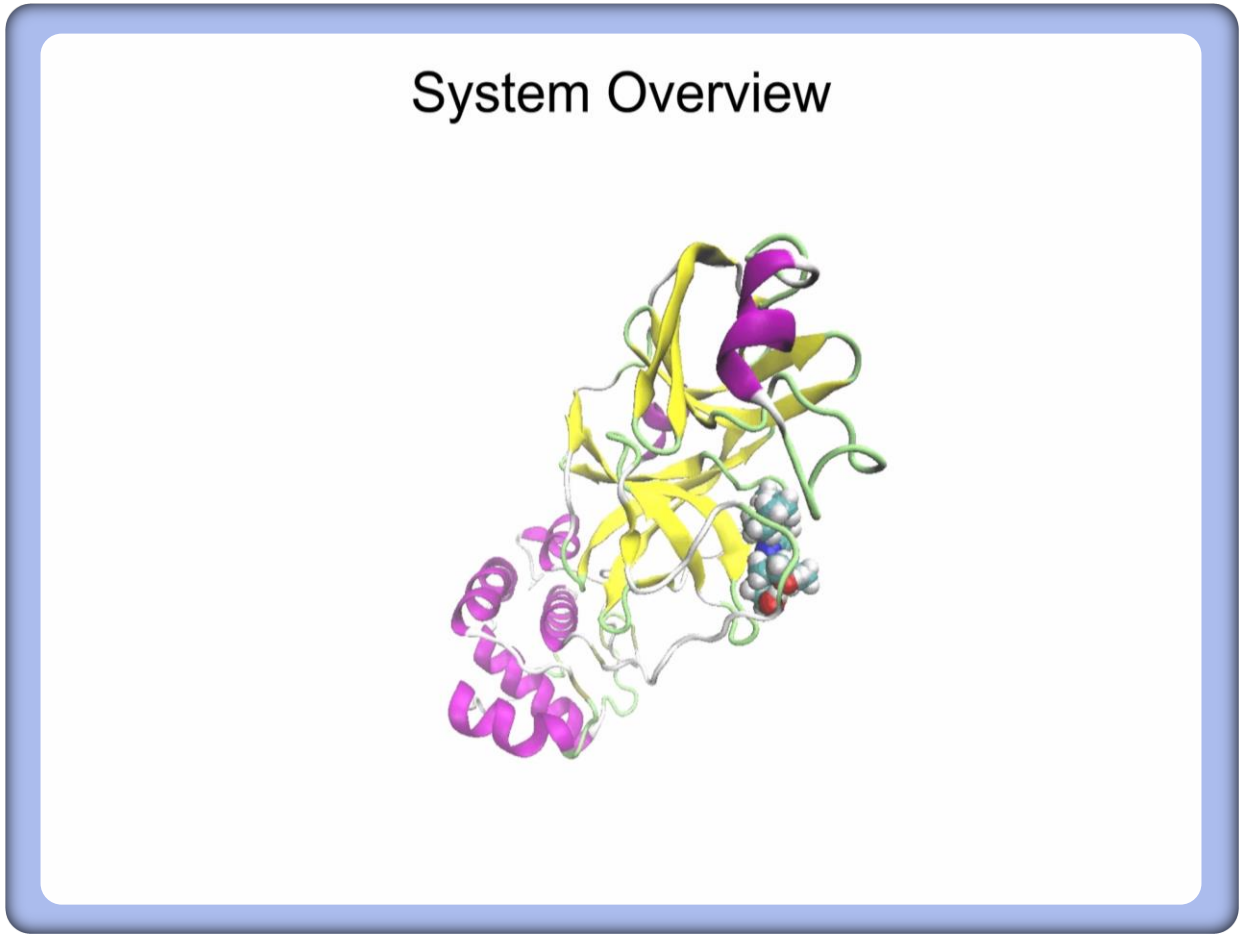
Designed algorithm

Conformational entropy estimation accelerated > 6 times

FEP-ABFE protocol used in this work

1. Pre-equilibrate MD
2. Automatic restraint addition
3. Turn off charges (5 λ)
4. Turn off vdW (15 λ)





42 MD simulations for each FEP-ABFE calculation

Acceleration of FEP-ABFE calculation using the new protocol on Tianhe HPC

A single 8-cores server
Traditional protocol

Intel Xeon E5
~30 days/compound

~60,000 times faster

Tianhe supercomputer
New protocol

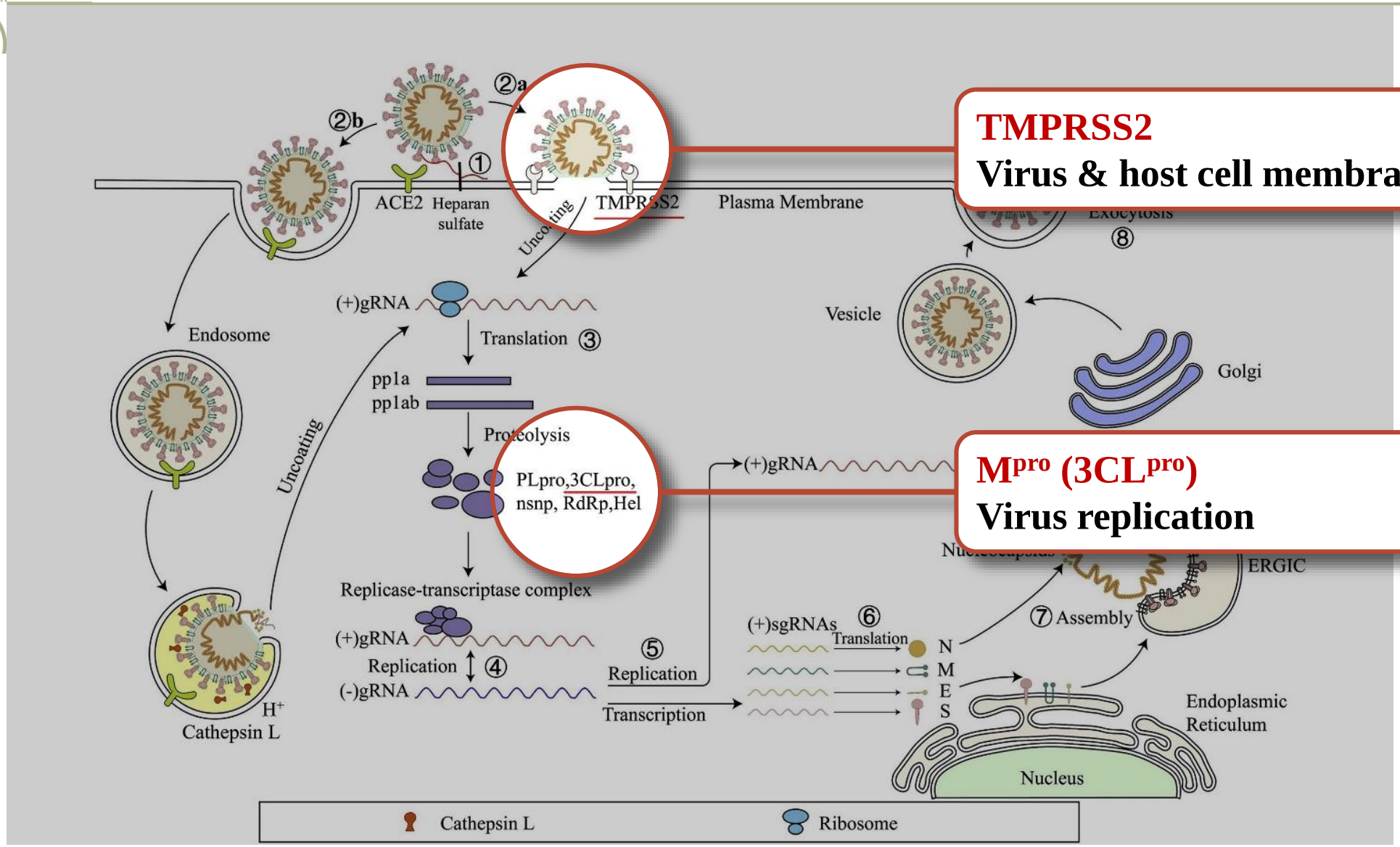
6 days / **12,000** compounds

(or **2,000** compounds per day)

Emergency drug discovery

Contents

Choose key targets for large-scale FEP-ABFE based virtual screening

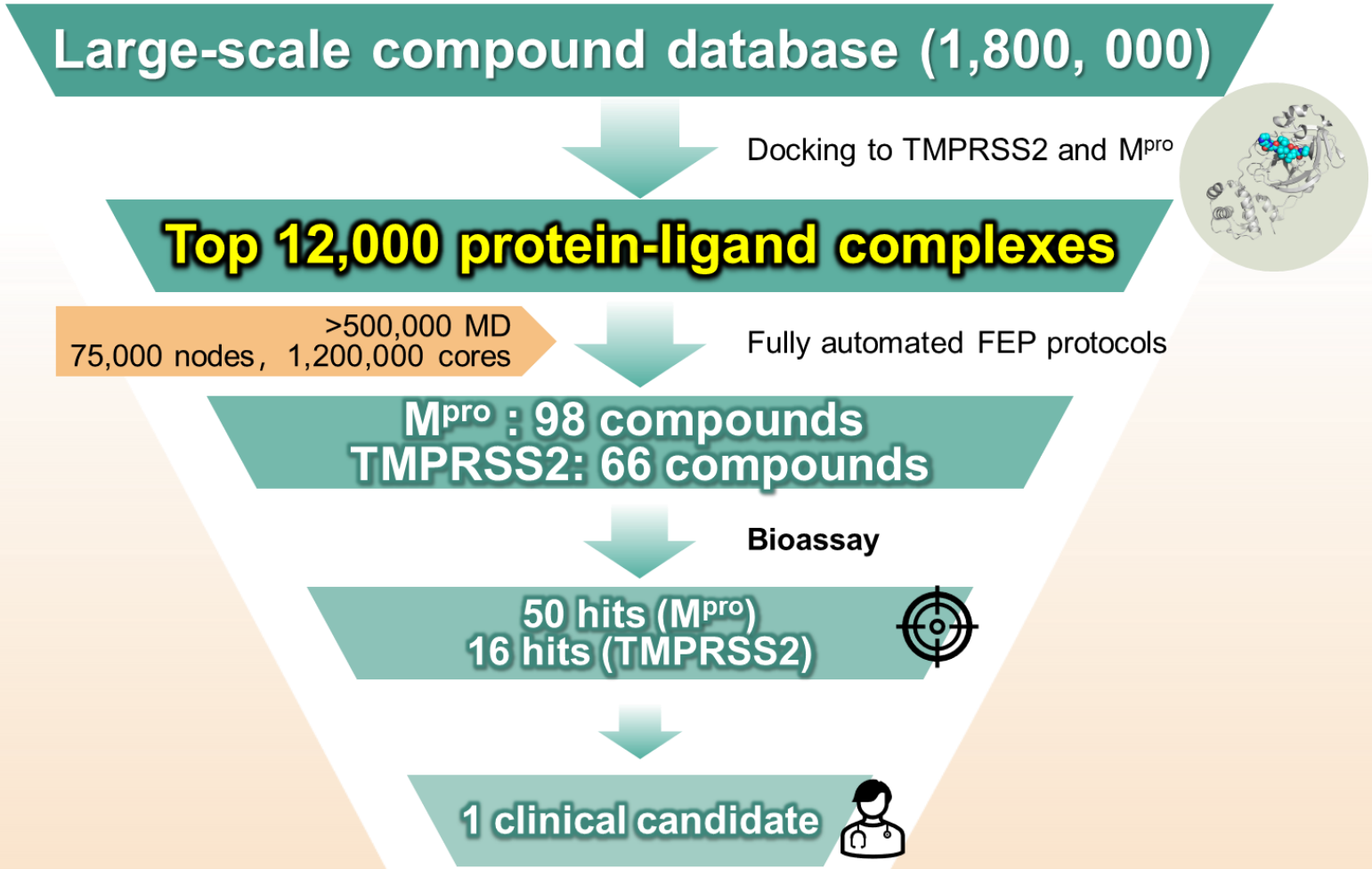


TMPRSS2
Virus & host cell membrane fusion

M^{pro} ($3CL^{pro}$)
Virus replication

Xiang R, et al, Acta Pharm. Sin. B. 2020.

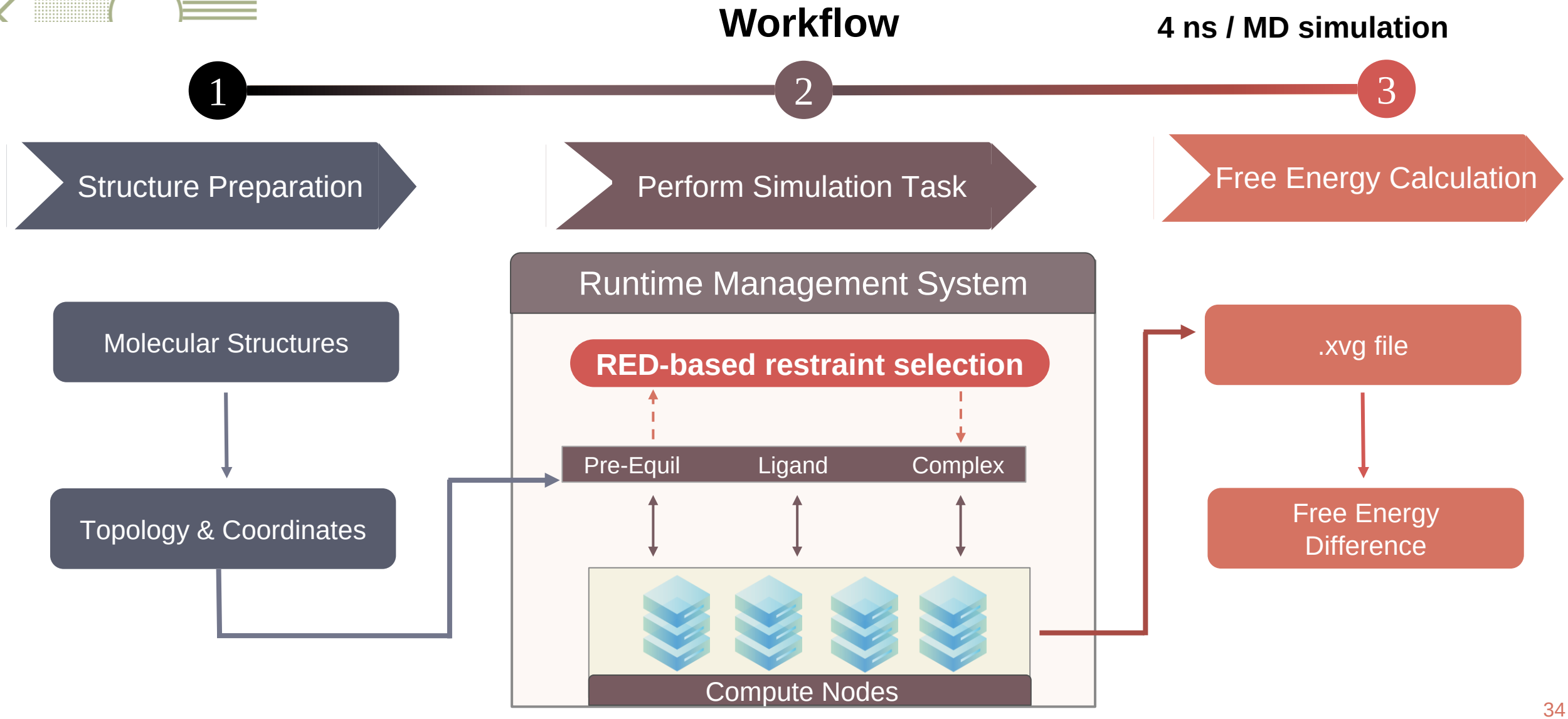
Large-scale virtual screening on Tianhe supercomputer



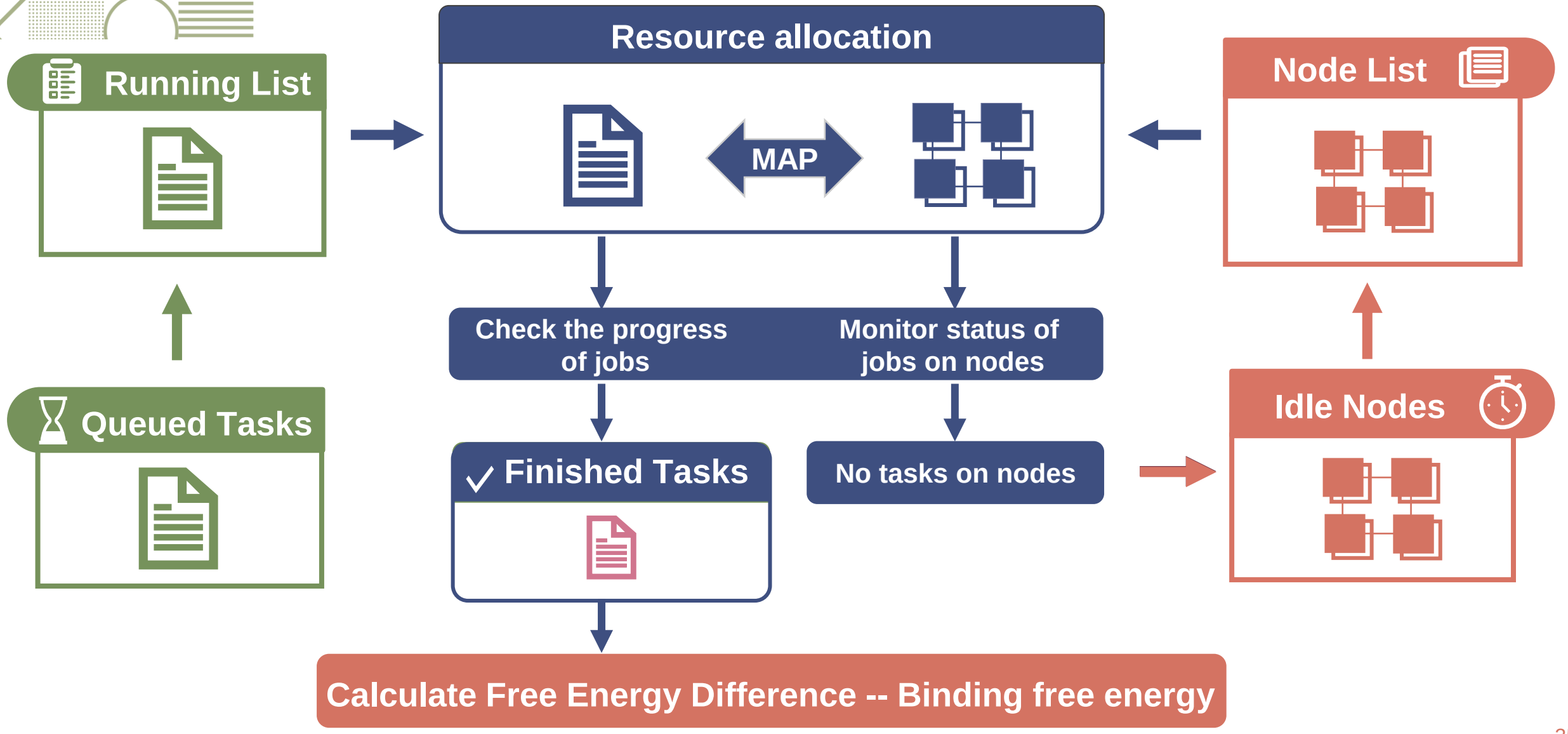
Total number of MD simulation jobs (4 ns / MD simulation)

Target	Ligand DB	Pre-Equilibrate	Ligand	Complex
M^{pro}	FDA	100	2000	2100
	Chemdiv	3143	62860	66003
	SPECS	3027	60540	63567
TMPRSS2	Chemdiv	3004	60060	63084
	SPECS	2825	56500	59325
Total		12099	241960	254079
		508,138		

Intelligent job management system (>500,000 MD simulation tasks)



Intelligent job management system (>500,000 MD simulation tasks)



Computational resource and time used for the large-scale virtual screening

Time for the virtual screening with single precision

Job Type	System used	Time (including IO)
Pre-Equilibrate	12,000 nodes	27.4 h
Ligand	63,000 nodes	23.7 h
Complex	75,000 nodes	114.5 h
Total	**1,200,000 CPU cores 75,000 nodes**	**141.9 h**

Contents

Experimental validation of the computational predictions

Hits against M^{pro}

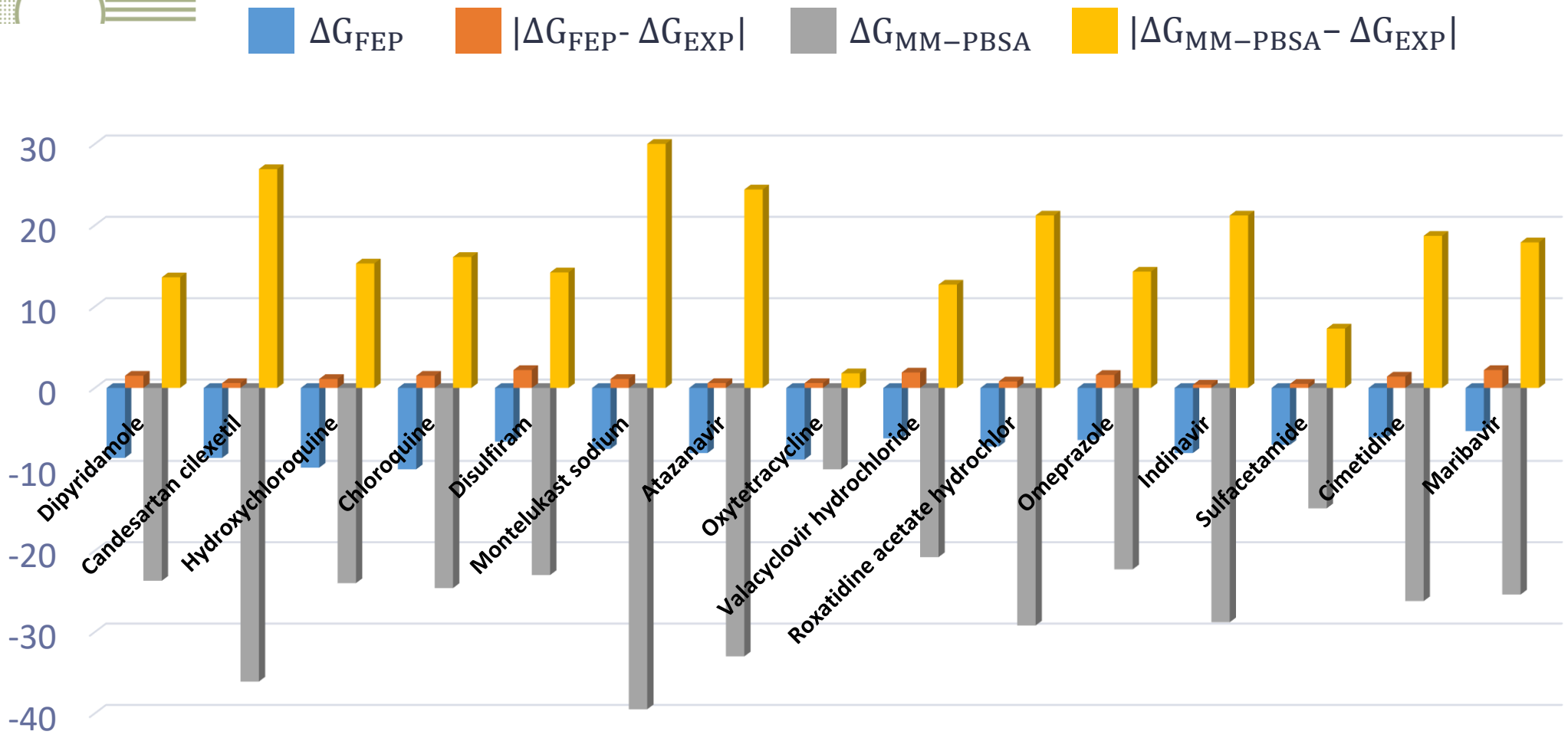
Database	Number of tested compounds	>50% Inhibition at 100 µM	>33% Inhibition at 100 µM
SPECS	38	18	24
ChemDiv	35	16	19
FDA	25	16	20
Total	**98**	**50 (51%)**	**63 (64%)**

Experimental validation of the computational predictions

Hits against TMPRSS2

Database	Number of tested compounds	>50% Inhibition at 100 µM	>33% Inhibition at 100 µM
SPECS	35	9	24
ChemDiv	31	7	20
Total	**66**	**16 (24%)**	**44 (67%)**

Superior performance of the FEP-ABFE predictions compared to the MM-PBSA

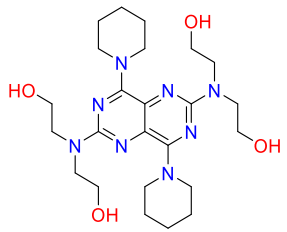


Li Z, et al. Proc. Natl. Acad. Sci. USA. 2020

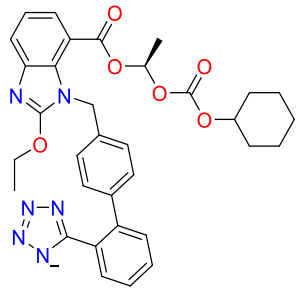
Representative Hits

Further consideration in repurposing a drug for treatment of COVID-19 patients: Known functions of the drug

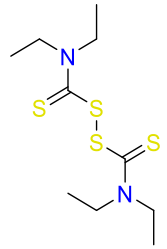
1) Active M^{pro} inhibitors from known FDA-approved drugs



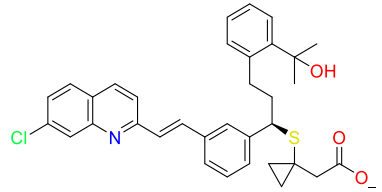
Dipyridamole



Candesartan Cilextil

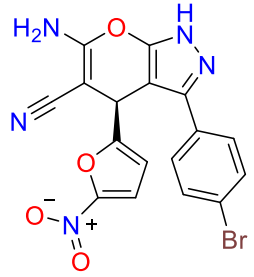


Disulfiram



Montelukast Sodium

2) Active M^{pro} inhibitors from commercial compound libraries



Analogue 1

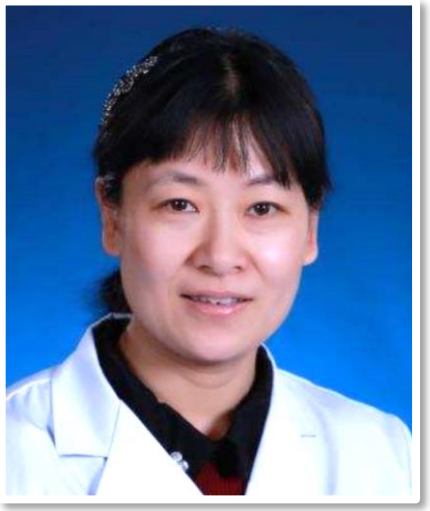
Analogue 2

Analogue 3

……

Structural optimizations are being performed…

Inspiration: Identify a drug with both anti-viral and anti-thrombosis activities



Prof. Fuling Zhou

Head of hematology

Zhongnan Hospital of Wuhan University

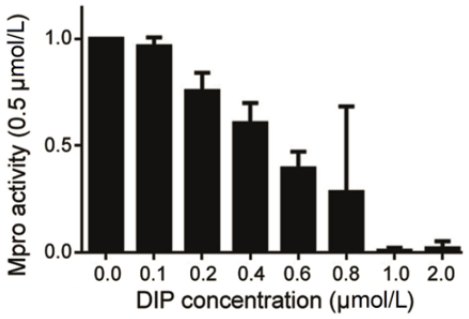
Clinical variables in 124 patients with COVID-19

Variable	Range for normal subjects	Range for COVID-19 patients (Total number = 124)
PLT (109/L)	125-350	191.7 ± 80.0 (54-525)
Lymphocyte (109/L)	1.1-3.2	0.9 ± 0.6 (0.1-5.0)
MPV (fL)	6-12	9.1 ± 1.3 (6.6-12.3)
PT (S)	9.4-12.5	13.0 ± 1.4 (8.6-17.8)
APTT (S)	25.1-36.5	30.3 ± 3.2 (22.4-38.1)
FIB (mg/dL)	238-498	429.8 ± 88.7 (203-750)
D-dimer (μg/L)	**0-500**	**1168.6 ± 3652.7 (35-26315)**

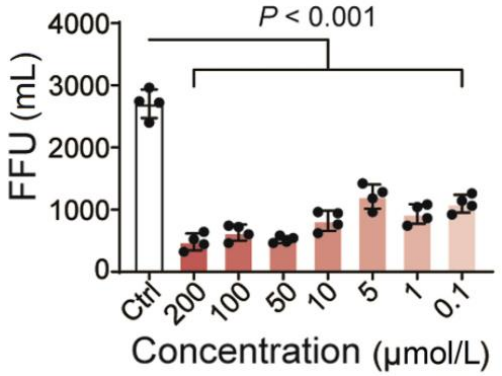
Liu XY, et al, Acta Pharm. Sin. B. 2020.

Hypercoagulability was associated with COVID-19 disease severity.

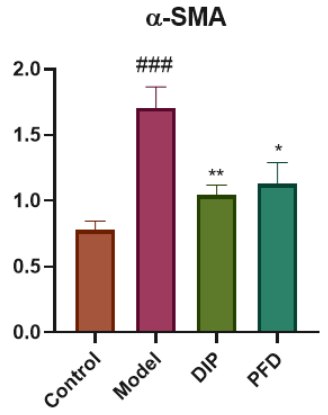
Identified clinical candidate against COVID-19: Persantine (Dipyridamole or DIP)



A) M^{pro} inhibition



B) Anti-viral replication



C) Anti-pulmonary fibrosis

D) Anti-thrombosis

New discovery in this work

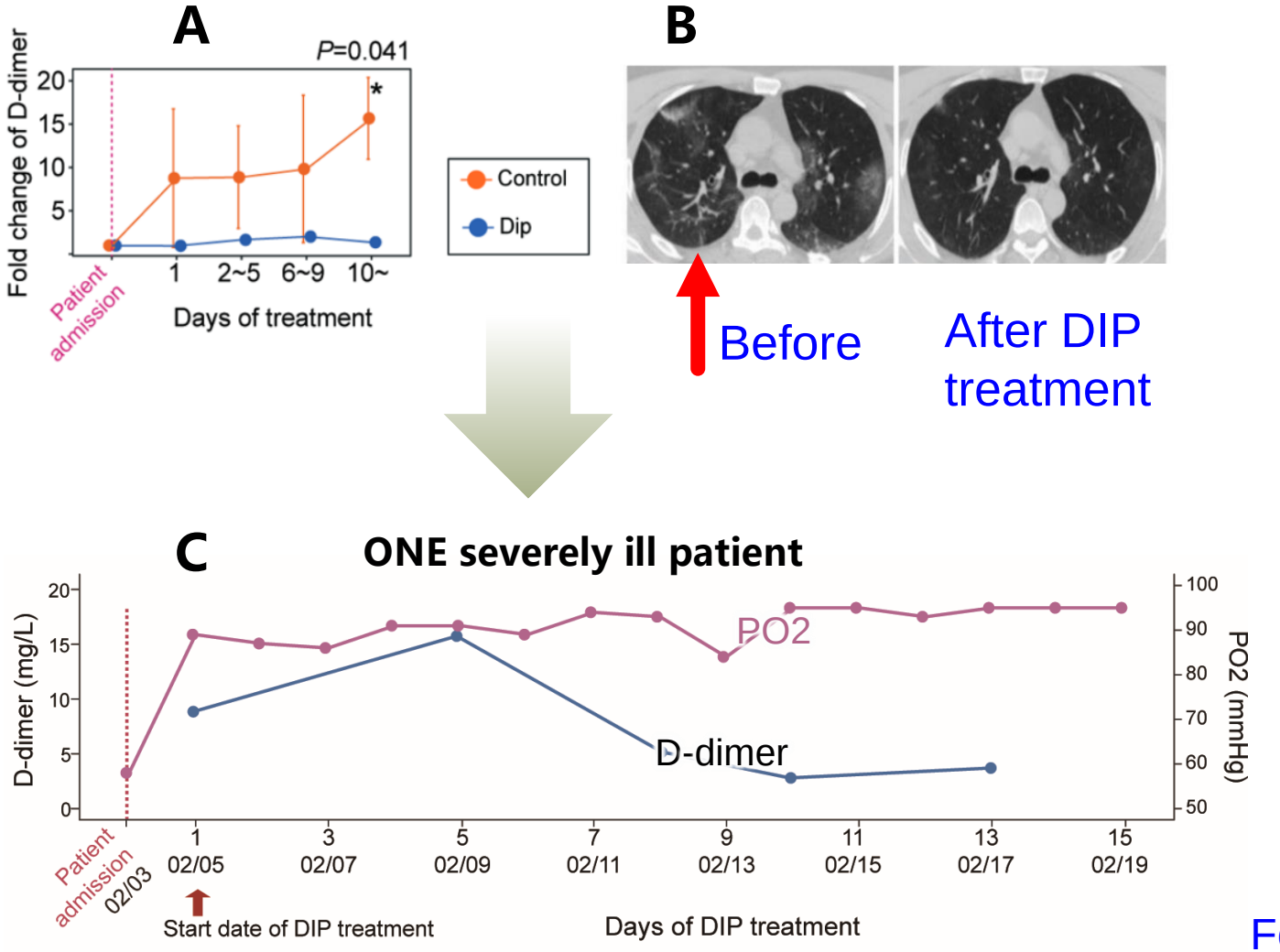
Known function

In vitro and in vivo validation: Emergency drug discovery

Liu XY, et al, Acta Pharm. Sin. B. 2020.

Contents

DIP adjunctive therapy improved the coagulation profiles and shortened the time for discharging the patients

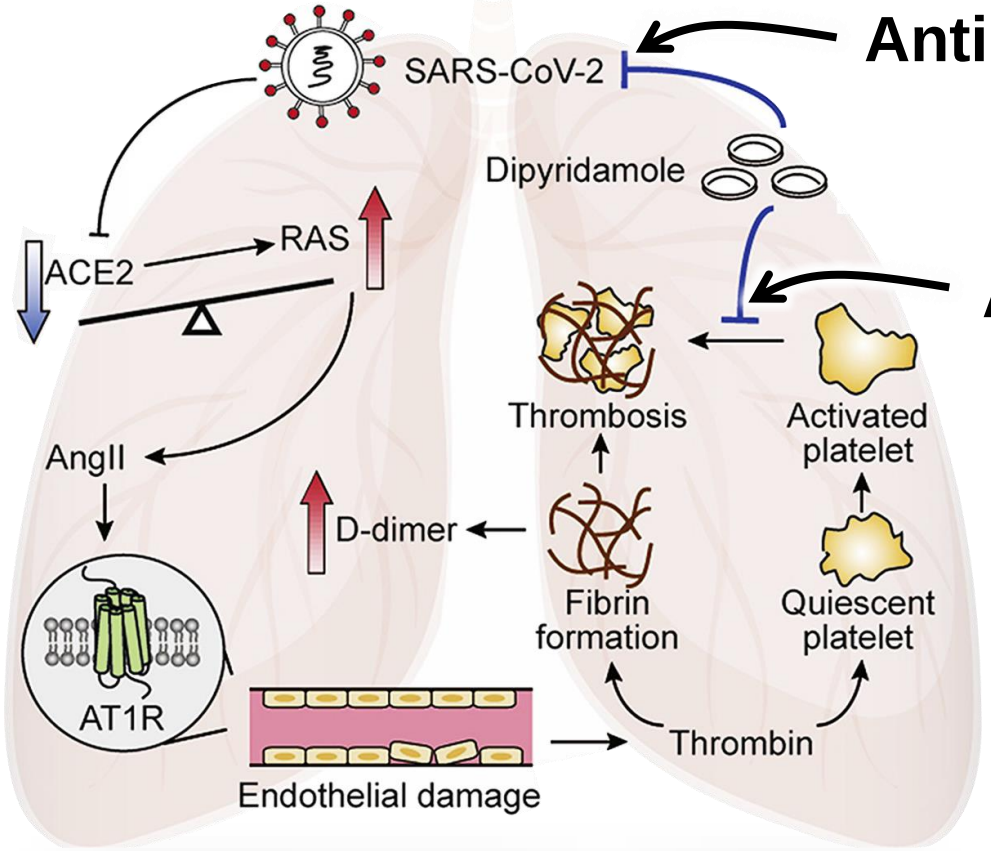


Discharge time for the patients

Group	Patients	Median time from treatment to discharge (days)
Control	86	11
DIP	37	7

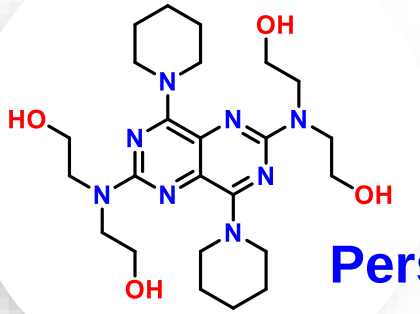
Feb.-Apr., 2020 Jiang M, et al, J. Cell. Mol. Med. 2021.

The mechanism of dipyridamole: Anti-viral and anti-thrombosis



Xiaoyan Liu, et al, 2020.

Clinical Studies



Persantine

(Dipyridamole, DIP)

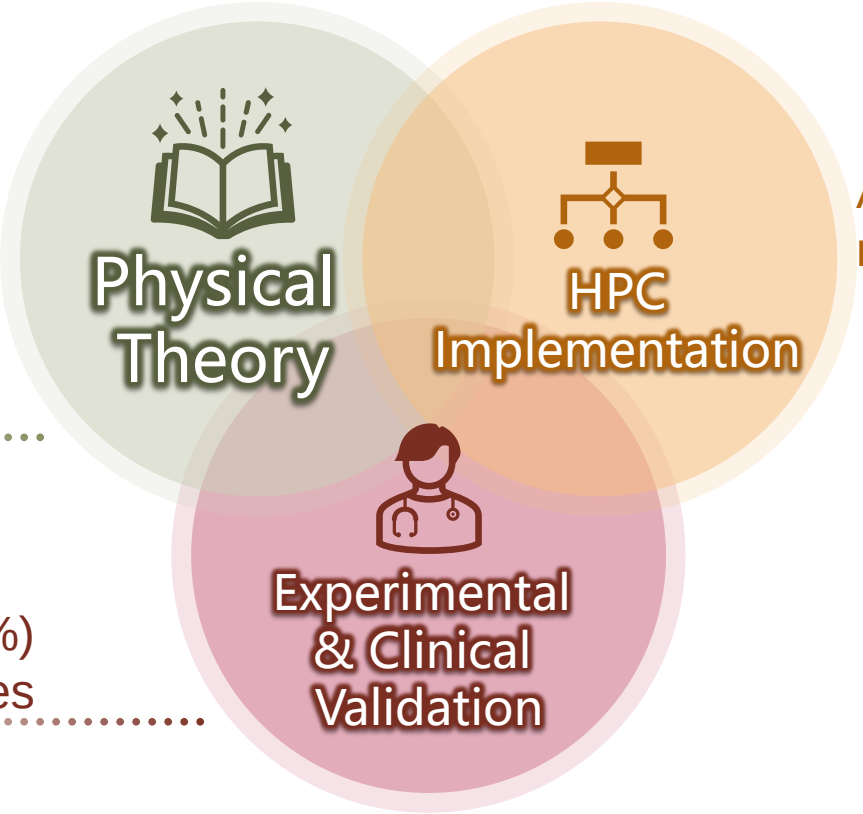
Ongoing clinical trials of dipyridamole against COVID-19 (by other independent groups)

Trial and Title	**NCT04424901:** Open Label Dipyridamole- In Hospitalized Patients With COVID-19	**NCT04410328**: Aggrenox To Treat Acute COVID-19	**NCT04391179**: Dipyridamole to Prevent Coronavirus Exacerbation of Respiratory Status (DICER) in COVID-19
Trial Type	**Randomized Phase II Open Label clinical trial**	**Randomized Phase III clinical trial**	**Randomized Phase II clinical trial**
Status	Recruiting	Recruiting	Completed; results not yet disclosed
Conditions	➢ COVID-19 Pneumonia ➢ Vascular Complications	➢ COVID-19	➢ COVID ➢ Corona Virus Infection ➢ COVID-19 ➢ SARS-CoV-2 Infection
Interventions	➢ Drug: Dipyridamole (Standard Care *vs* Standard Care with Dipyridamole)	➢ Drug: Dipyridamole ER 200mg/ Aspirin 25mg orally/enterally and Standard of care ➢ Other: Standard of care	➢ Drug: Dipyridamole 100 Milligram(mg) ➢ Drug: Placebo oral tablet
Locations	UConn Health, Farmington, Connecticut, United States	Rutgers New Jersey Medical School University Hospital, Newark, New Jersey, United States	University of Michigan, Ann Arbor, Michigan, United States

Contents

Summary of the major innovation and an unprecedentedly high hit rate

A new restraint energy distribution (RED) function for accelerated ABFE prediction & a novel algorithm allowing FEP-ABFE-based automated virtual screening



A large-scale virtual screening runtime management system

High hit-rate (51%)
Promising clinical outcomes

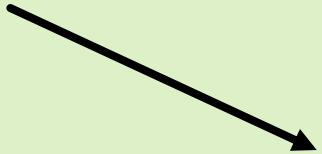
- Automated high-throughput FEP-ABFE calculation protocol
- **Milestone**: The first time FEP-ABFE was used in large-scale virtual screening
- Efficiency of FEP was greatly increased – applied in emergency drug discovery

Outlook

Serve as a general approach for emergency drug discovery using a supercomputer like Tianhe to make us ready against next breakout

FEP algorithm optimization

More reliable and more efficient

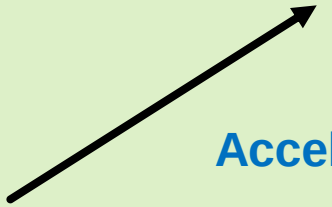


Ultra-large scale FEP-ABFE-based virtual screening

Wet lab validation

(FEP-ABFE predictions for millions of compounds)

Accelerate



HPC on a larger scale

Pushing CADD to the next generation

SC21

Concluding Remarks

- Discovery and development of a novel class of drug are usually a very long, complex process.
- Computational modeling and simulation can be valuable in accelerating the complex process.
- It is always important to develop more accurate and efficient computational approaches even with increasingly more powerful HPC resources.
- State-of-the-art computational methods can make truly valuable predictions.
- Integrated computational-experimental approaches are promising.

Acknowledgements

$$$ from NIH (PIs):

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R01 CA187273 (Rangnekar); U01 HL152392 (Dwoskin) – KYNETIC project (Zheng);
P01 NS097197 (Gentry); UL1 TR000117 (Kern, CTSA); R01 CA172379 (Liu);
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Supercomputing Time

University of Kentucky Computer Center