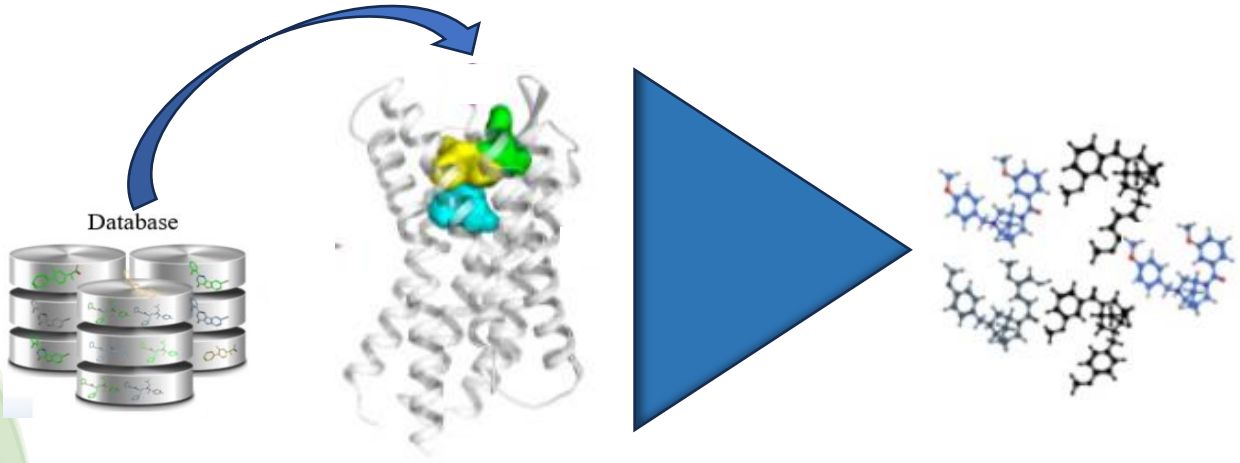
7th Advanced in silico Drug Design workshop/challenge 2024

Molecular Drug Design Lecture

Dr. Federica Moraca
Department of Pharmacy, University "Federico II" of Naples, Italy



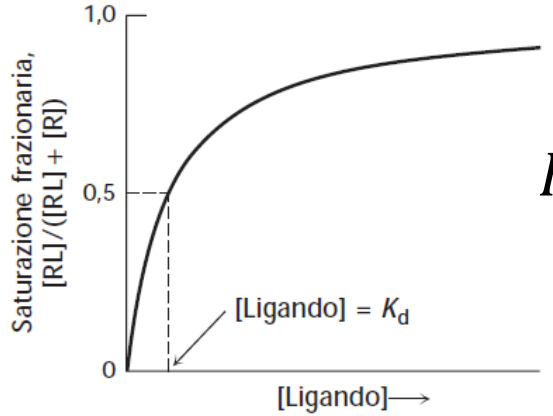
UP Olomouc 29.01. -01.02.2024

A Drug Discovery process

The choice of biological target is crucial to the success of a drug design process

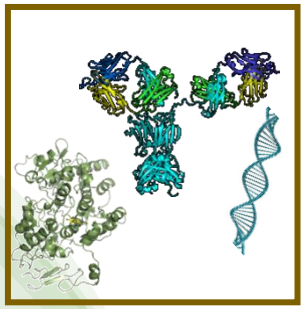
An important factor, which determines the effectiveness of the drug, is also **the binding strength**

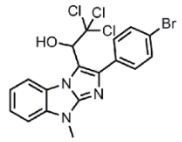
Most drugs produce their effects by binding to specific biological targets (proteins/enzymes, receptors, DNA) **(binding curve)**

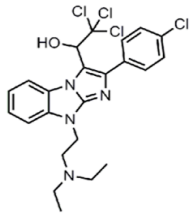


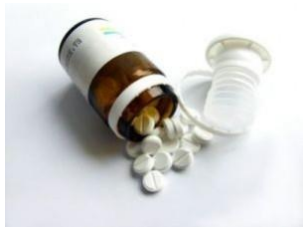
$$K_d = \frac{[R][L]}{[RL]}$$

The completion of a typical drug discovery cycle from target identification to an FDA-approved drug takes **up to 14 years** with the approximate cost of **800 million dollars**









12/15 years!

FDA

Disease

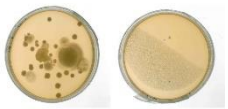
Cancer, AIDS, Alzheimer, Parkinson...

Biological Target

Hit identification

Lead optimization

Preclinical assays



Clinical studies

Phase I, II, III

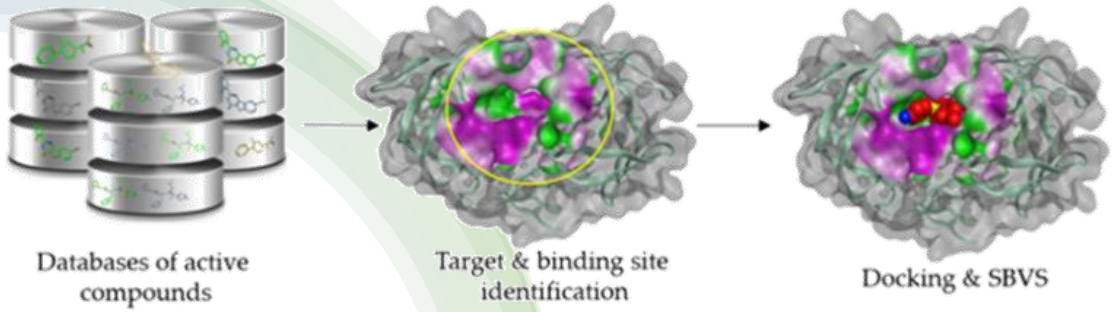
A Drug Discovery process

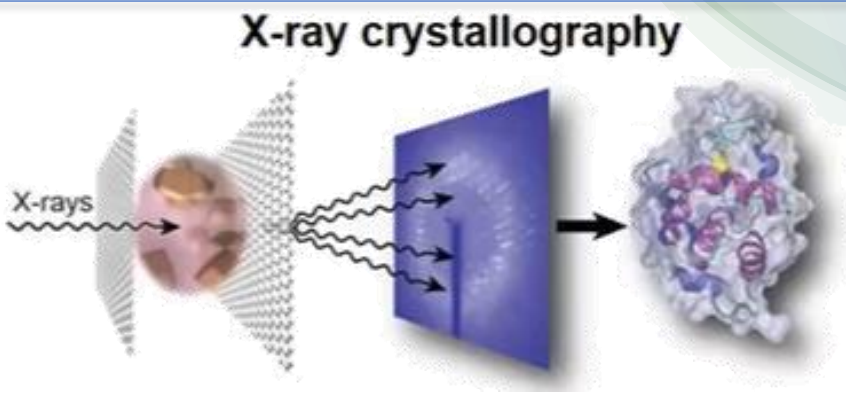
Decrease rate of approved drugs

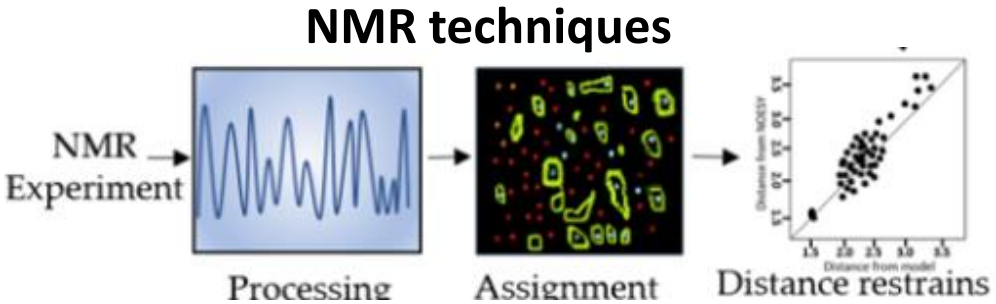
A decrease in the number of new drugs on the market was noted due **to failure in different phases of clinical trials**

In November 2018, a study was conducted to estimate the total cost of pivotal trials for the development of novel FDA-approved drugs. The median cost of efficacy trials for 59 new drugs approved by the FDA in the 2015–2016 period was $19 million.

Thus, it is important to overcome limitations of the conventional drug discovery methods with efficient, low-cost, and broad-spectrum computational alternatives.



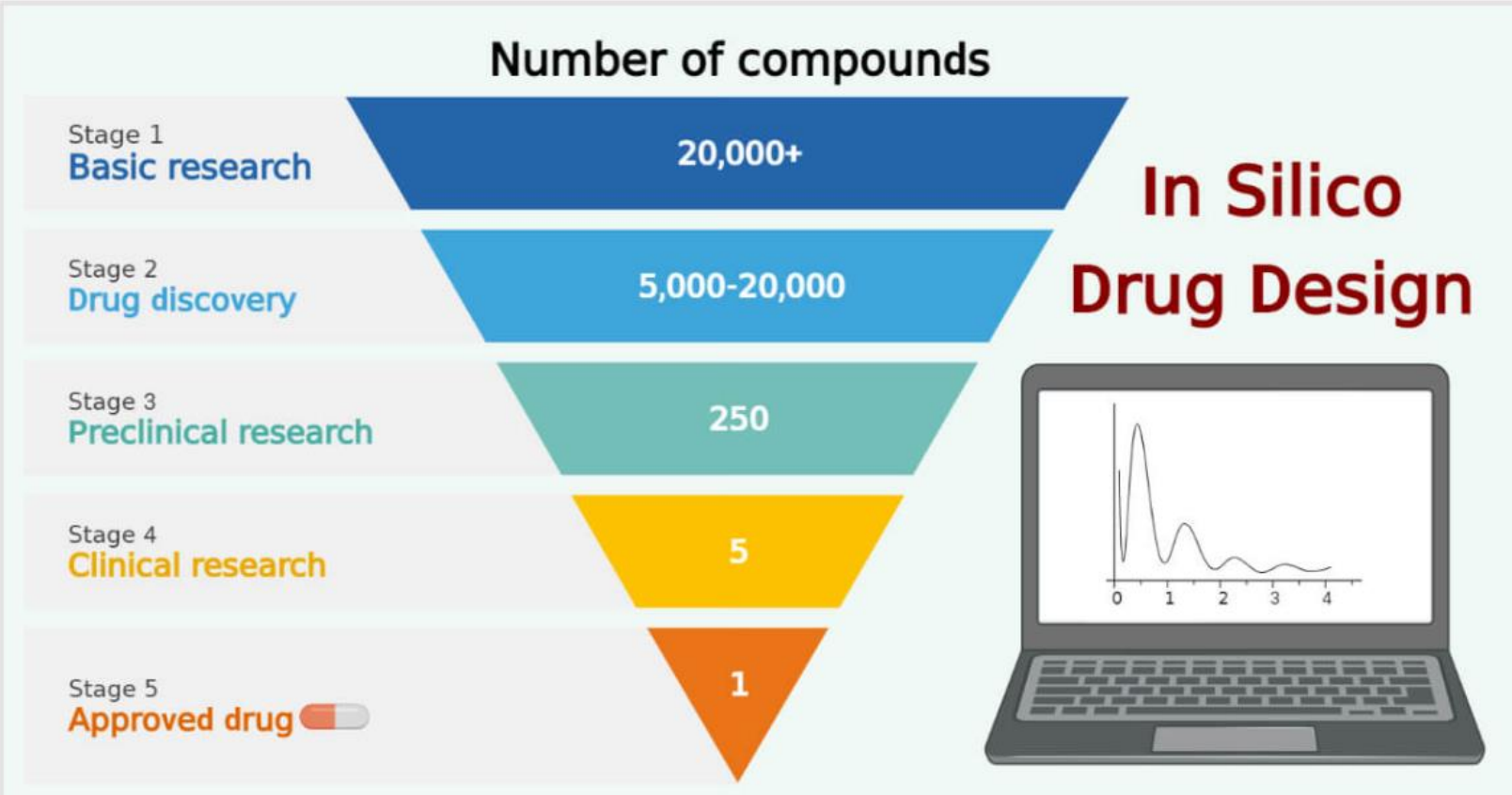




Traditional drug discovery → **Rational drug design**

Lavecchia, A.; Cerchia, C. *Drug Discov. Today* **2016**, *21*, 288–298
Moore T.J. JAMA Int. Med. 2018, 178. 1451-1457

The pipeline of a Drug Discovery process



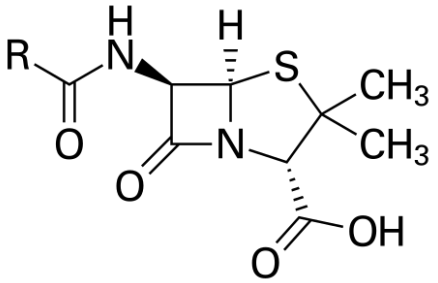
How can we find a drug candidate?

Some history

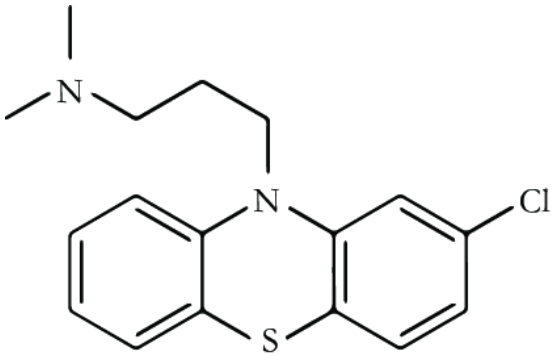
Serendipity

For a long time, many drugs were discovered by chance observation or serendipity

Fleming noticed that the growth of certain bacterial colonies that had accidentally come into contact with *Penicillium notatum* spores was inhibited.



The anti-neuroleptic drug chlorpromazine was discovered during research into the treatment of septic shock from surgery



How can we find a drug candidate?

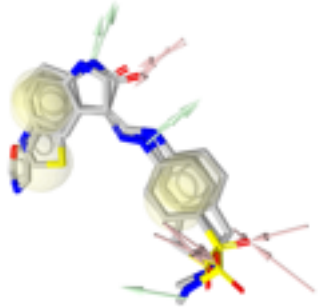
Today…

Computer Aided Drug Design

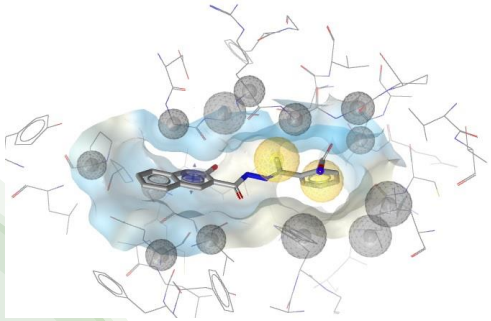
Computer-aided drug discovery and design involve the use of information technologies to identify and develop, chemical compounds that align a set of desired physicochemical and biological properties.

Molecular determinants of the drug/target interactions

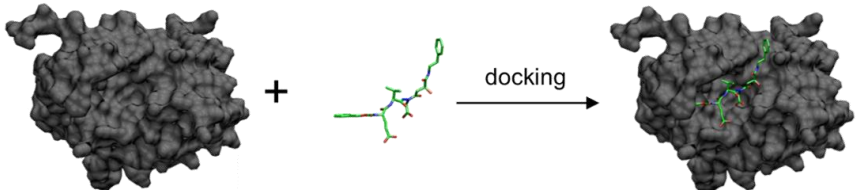
In silico CADD techniques



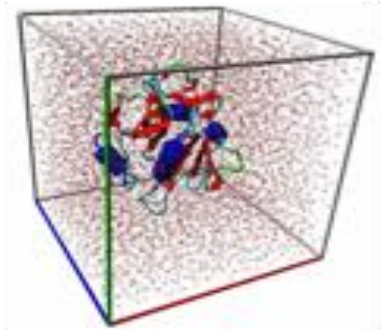
Ligand-based



Structure-based



Docking



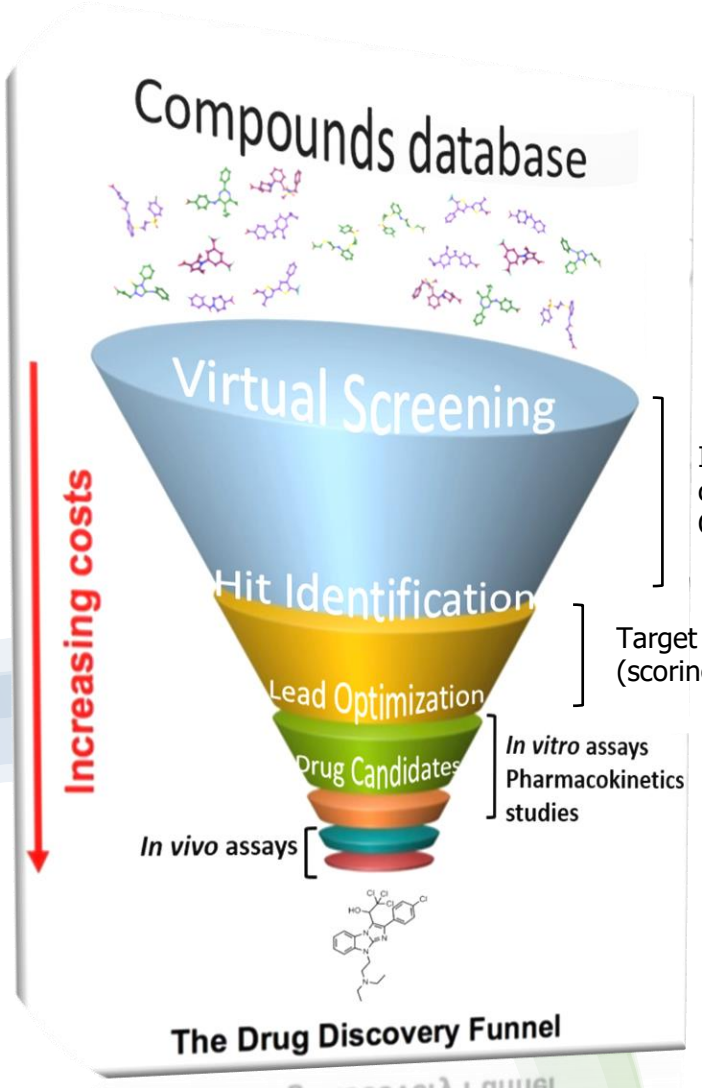
Molecular Dynamics

Moraca, F.; et al. *Physical Sciences Reviews.* **2019**; 20180114.

Talevi A, Computational Drug Discovery and Design, 2024

How can we find a drug candidate?

Today...



In silico filters for characteristics Chemical-physical

Target affinity evaluation (scoring function)

In vitro assays
Pharmacokinetics studies

Virtual Screening (VS)

VS consists of processing a database of hundreds of thousands of compounds, available online, to arrive at a reasonable number of potentially active molecules for our target (drug candidates).

Lipinski's Rule of Five

- HBD < 5
- HBA < 10
- PM < 500 Dalton
- logP <5

ADMET profile

- Absorption
- Distribution
- Metabolism
- Excretion

Other...

- PAINS
- Deduplication
- Eterogeneity
- Reactive functional groups

Two main approaches

Structure-based | Ligand-based

Moraca, F.; et al. *Physical Sciences Reviews.* **2019**; 20180114.

How can we find a drug candidate?

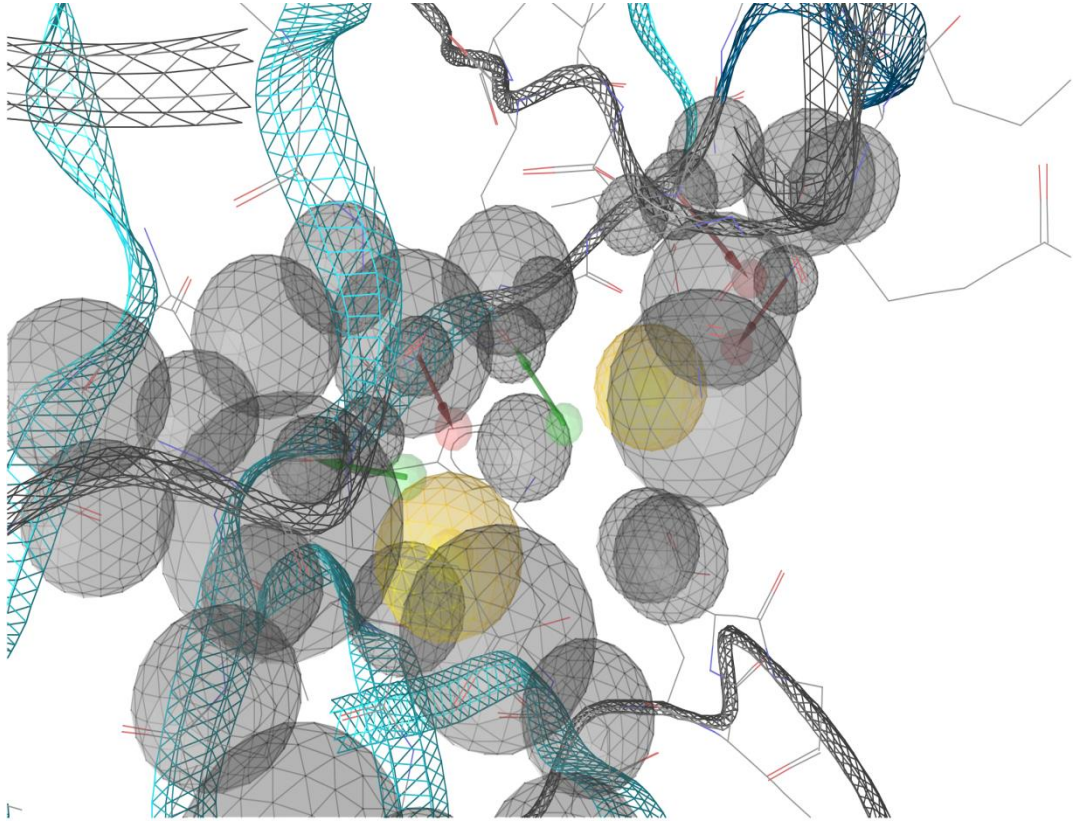
Structure-based Design

Which features of drug molecules are needed for their biological activity?

Paul Ehrlich (1909)

"Pharmacophore model"

A pharmacophore is a set of structural features needed to ensure optimal interaction with a specific biological target to activate (or inactivate) its biological response.

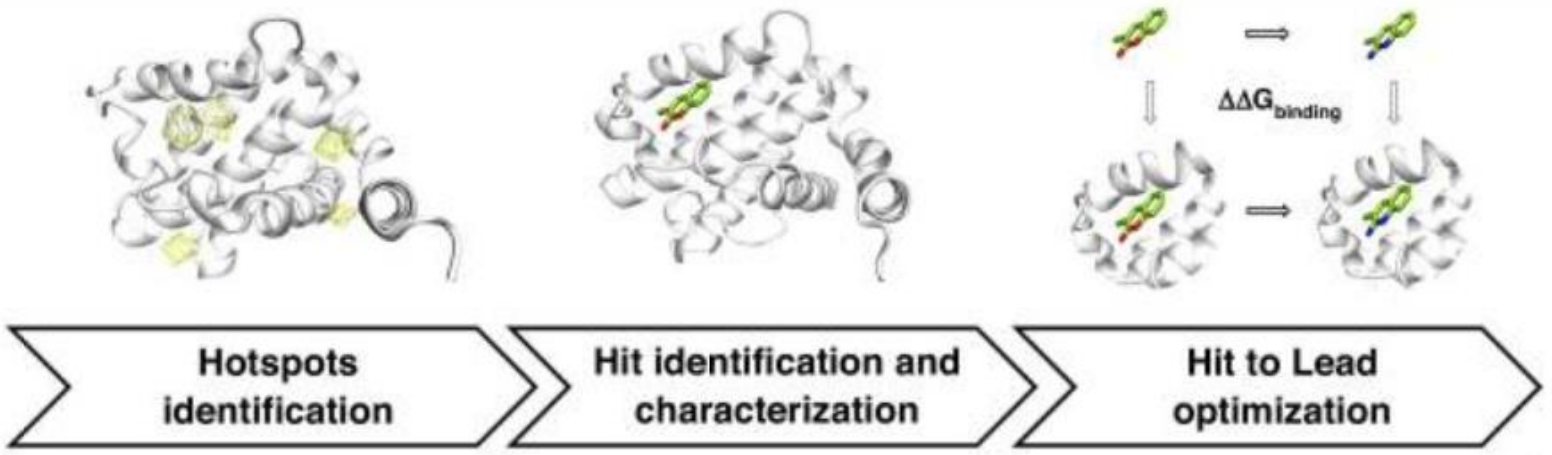


(Wolber, G.; Langer, T.; *J. Chem. Inf. Model.* **2005**, *45*, 160-169)

Fragment Based Drug Design (FBDD)

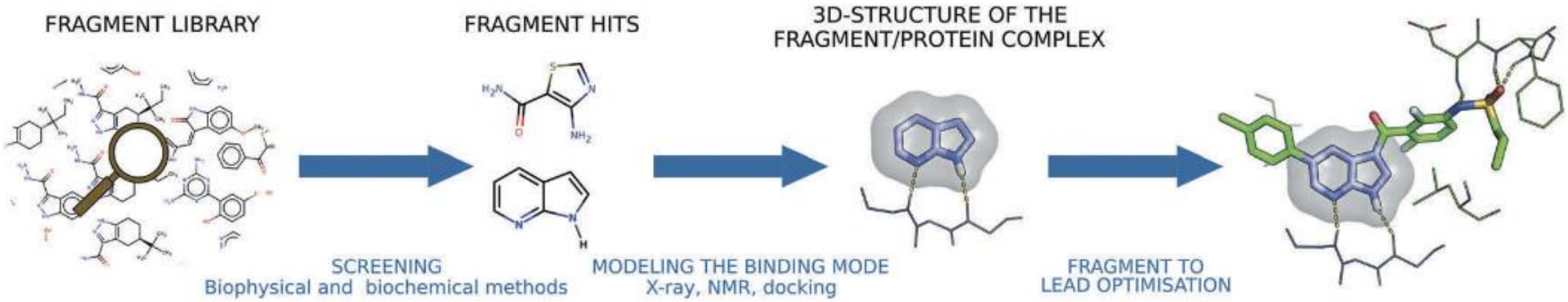
In the last 20 years, Fragment-Based Drug Discovery(FBDD) has established itself as a key approach for finding high-quality lead candidates.

- Fragments (MW: 150–250 Da) tend to bind to **protein hot spots**;
- Fragment binding is generally enthalpy-driven;
- Fragment forms on average two high-quality hydrogen bonds;
- Interactions patterns defined by the fragments are similar to those defined by the drug-like ligands



Jacquemard C. et al. EXPERT OPINION ON DRUG DISCOVERY, 2019, VOL. 14, NO. 5, 413–416

Fragment Based Drug Design (FBDD)



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Fragment Based Drug Design (FBDD)

Close relationship between FBDD and hot-spots

Hot-spots: protein sites that are capable of binding fragment-sized or even smaller probe molecules

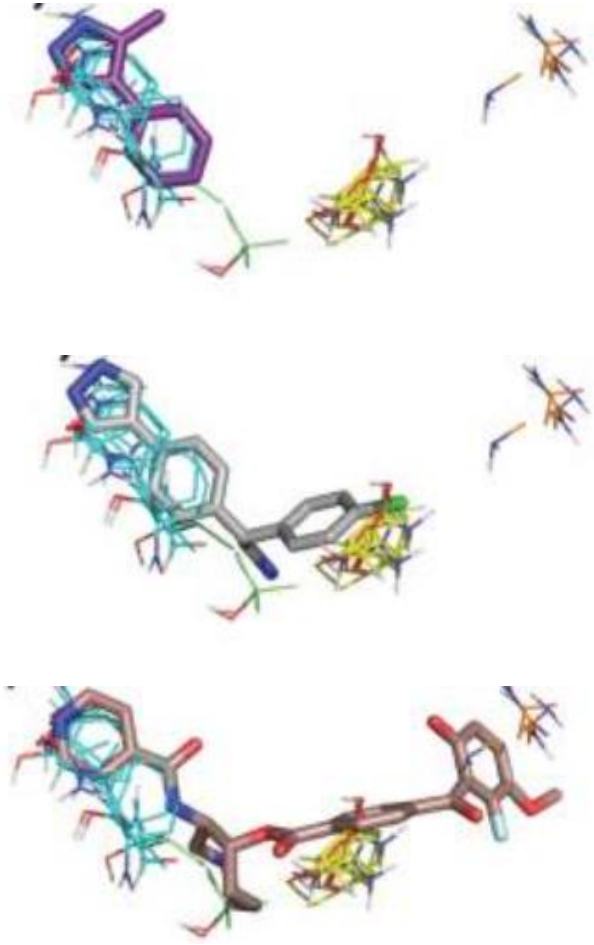
Two fairly straightforward consequences

no strong hot spot
=
no rate of fragment screen

primary hot spots
=
highest binding potency

relationship between hot spots and druggability

Fragment hits bind at primary hot spots



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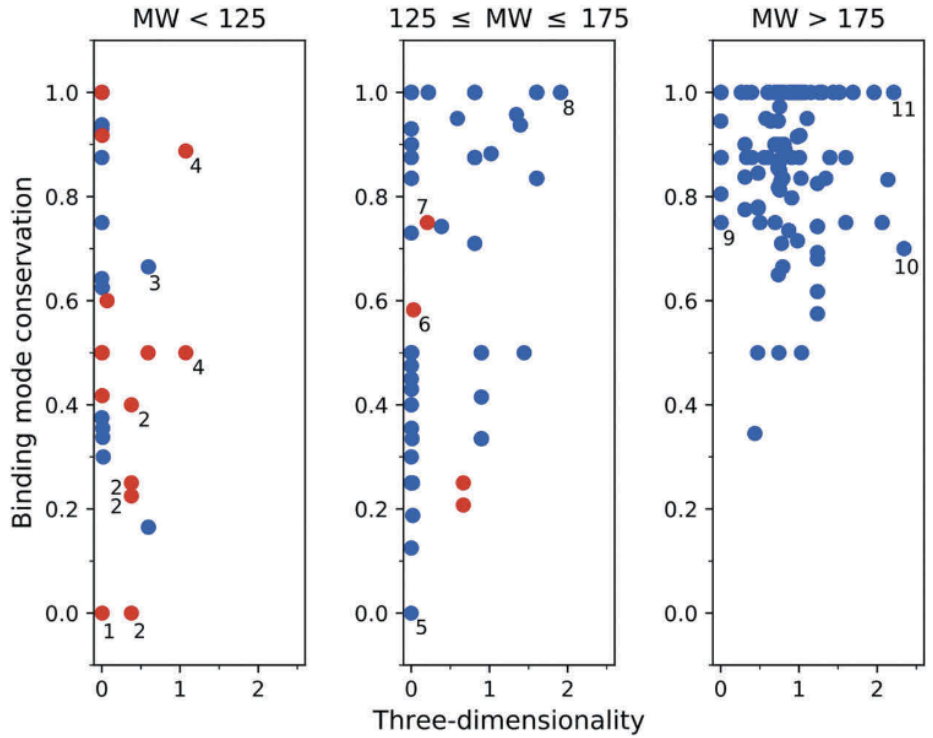
Fragment Based Drug Design (FBDD)

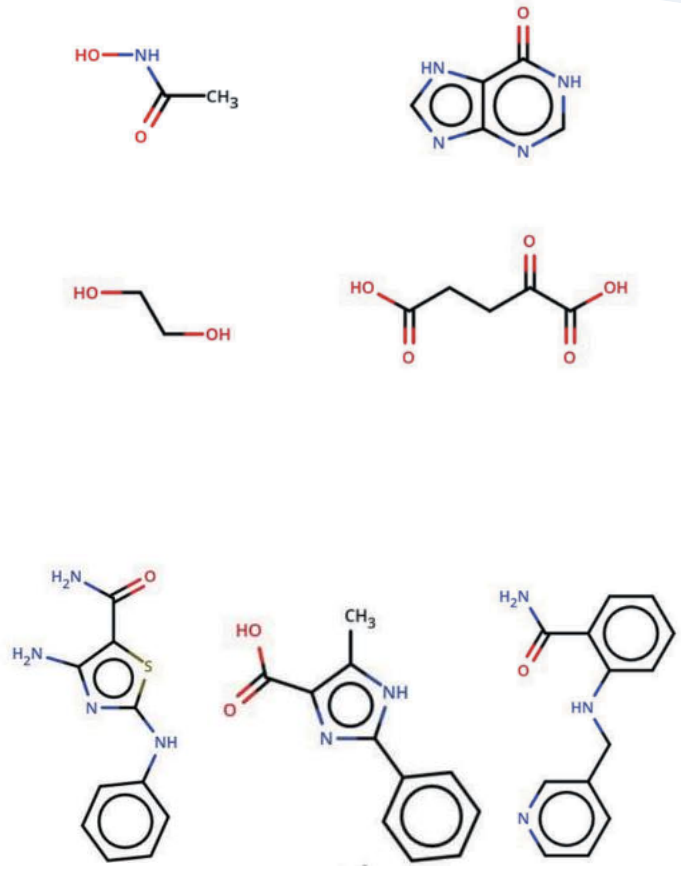
Fragment binding mode conservation

As shown previously, a common assumption in FBDD is that the binding mode does not vary during the fragment-to-lead optimization

Are there exceptions?

‘flipping’fragments





Drwal M.N et al. J. Med. Chem. 2018, 61, 14, 5963−5973
Jacquemard C. et al. EXPERT OPINION ON DRUG DISCOVERY, 2019, VOL. 14, NO. 5, 413–416

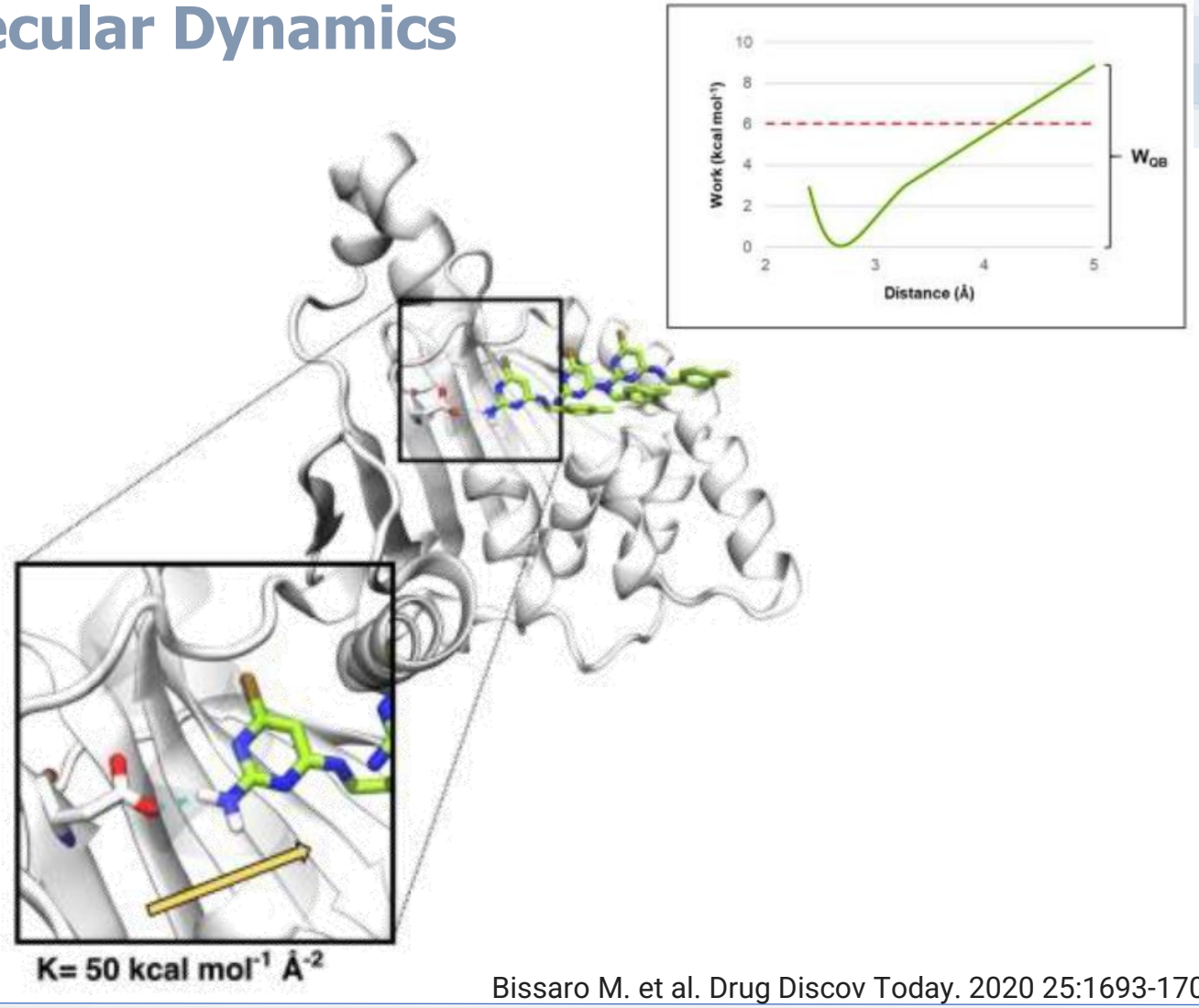
Benefits to FBDD from Molecular Dynamics

Steered-Molecular Dynamics

In a structure-based drug discovery (SBDD) pipeline, the identification and characterization of druggable binding sites represent a key element in determining screening success

However, many of these grid-based methodologies **lack an adequate description of target conformational flexibility**, an aspect that could limit the discovery of cryptic binding pockets

implementation of molecular simulation-based approaches (Molecular Dynamics)



Bissaro M. et al. Drug Discov Today. 2020 25:1693-1701

The Retro Drug Design (RDD)

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

pubs.acs.org/jcim Article

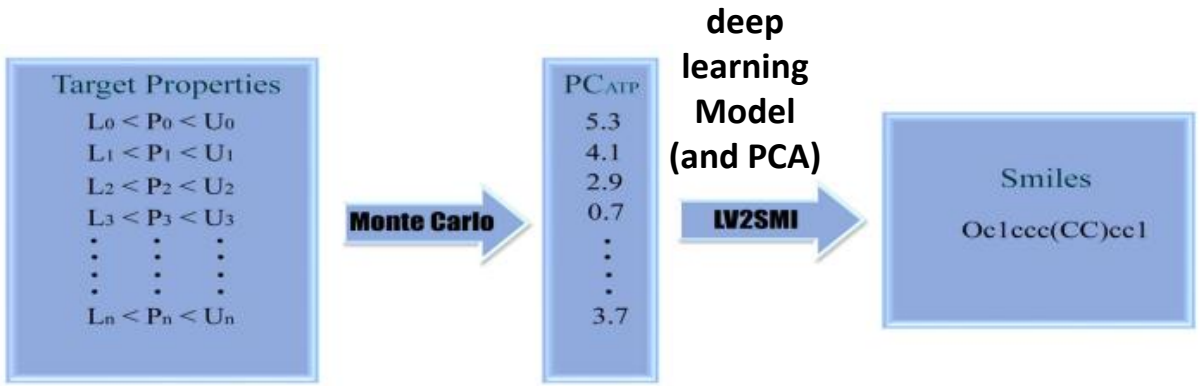
Retro Drug Design: From Target Properties to Molecular Structures

Yuhong Wang,* Sam Michael, Shyh-Ming Yang, Ruili Huang, Kennie Cruz-Gutierrez, Yaqing Zhang, Jinghua Zhao, Menghang Xia, Paul Shinn, and Hongmao Sun*

Cite This: *J. Chem. Inf. Model.* 2022, 62, 2659−2669 Read Online

	Predicted						Measured				
ID	Kinase	logP	Solubility	Cytotoxicity	HERG	PAMPA	Kinase	Solubility	Cytotoxicity	HERG	PAMPA
NCGC00689655	0.99	3.43	0.56	0.38	0.05	0.98	w	s	n	n	w
NCGC00689656	0.99	3.78	0.38	0.45	0.02	0.69	w	s	n	n	s
NCGC00689657	0.98	3.10	0.72	0.69	0.06	0.95	s	n	n	n	w
NCGC00689658	0.97	3.46	0.38	0.46	0.17	0.97	w	s	n	n	s
NCGC00689659	0.97	3.46	0.38	0.46	0.17	0.97	w	s	n	n	s
NCGC00689660	0.95	3.51	0.98	0.50	0.10	0.81	s	s	n	n	s
NCGC00689661	0.98	1.56	0.87	0.25	0.01	0.53	s	s	n	n	s
NCGC00689662	0.98	3.27	0.83	0.29	0.16	0.70	w	s	n	n	n
NCGC00689663	0.97	3.62	0.08	0.27	0.03	0.85	n	n	n	n	s
NCGC00689664	0.99	2.49	0.96	0.17	0.01	0.53	w	s	n	n	s
NCGC00689665	0.99	4.67	0.20	0.78	0.10	0.50	n	w	n	n	s
NCGC00689666	1.00	3.30	0.77	0.41	0.01	0.76	n	s	n	n	s
NCGC00689667	0.97	3.05	0.84	0.28	0.04	0.32	n	w	n	n	s
NCGC00689668	0.93	2.17	0.72	0.38	0.02	0.68	n	w	n	n	s
NCGC00689669	0.99	2.68	0.57	0.71	0.03	0.64	s	s	n	w	s
NCGC00689670	1.00	2.91	0.83	0.48	0.01	0.78	s	s	w	n	s
NCGC00689671	0.99	3.11	0.64	0.47	0.02	0.87	w	s	n	n	s
NCGC00689672	0.95	2.71	0.81	0.34	0.02	0.30	w	s	n	n	s
NCGC00689673	1.00	3.69	0.37	0.42	0.03	0.88	w	n	n	n	s
NCGC00689674	0.98	3.17	0.61	0.78	0.09	0.86	s	s	n	n	s

Starts with multiple preselected target properties and their optimal ranges, working backward to generate "qualified" compound structures



Target identification: This starts by identifying a specific biological target, such as a protein or enzyme, involved in a specific disease.

Conclusions

- Drug discovery still faces a lot of challenges and problems

  - upgrading the efficacy of virtual screening methods;
  - improving computational chemogenomic studies
  - enhancing the algorithms for toxicity prediction

- Computer-aided drug discovery can be used in combination with combinatorial chemistry or HTS

  - VS is known to shorten the time and cost of HTS methods, but it ignores the protonation and tautomerism effect as well as ionization states of compounds

- Integrating Molecular Modeling with ML/DL techniques to avoid high false positive rate