

AI-Guided Therapeutic Discovery

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ICES Biennial Workshop VIII

Geneva, Switzerland

September 30, 2026



**Mount
Sinai**

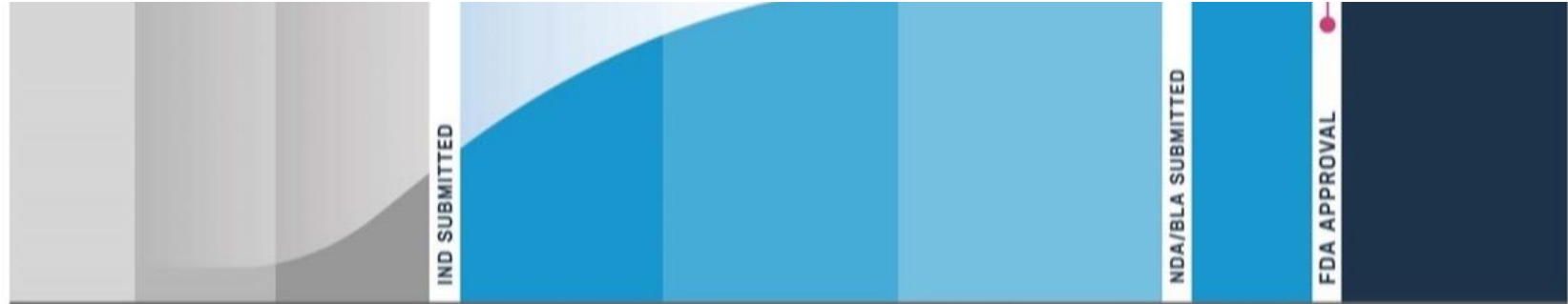
*Small Molecule AI
Drug Discovery Center*



Drug development is very expensive and lengthy



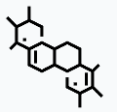
It takes 10-15 years and costs 3-5 billion dollars to develop a medicine!



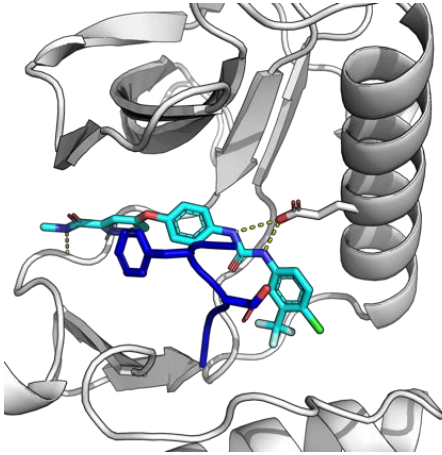
Source: Phrma foundation

What is a drug?

Drug action begins with a molecular interaction and propagates across biological scales



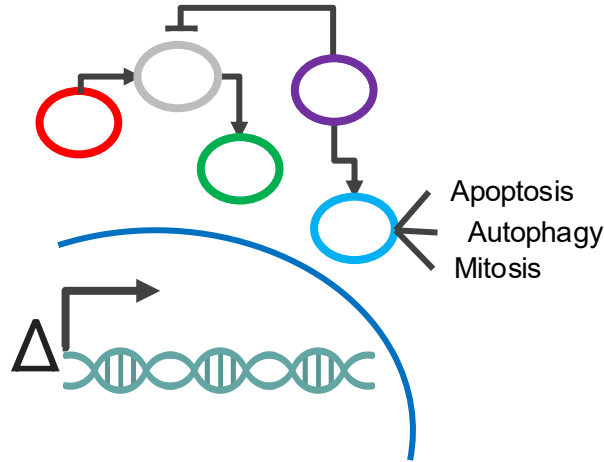
Molecular level



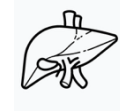
A drug engages a molecular target and alters its function.



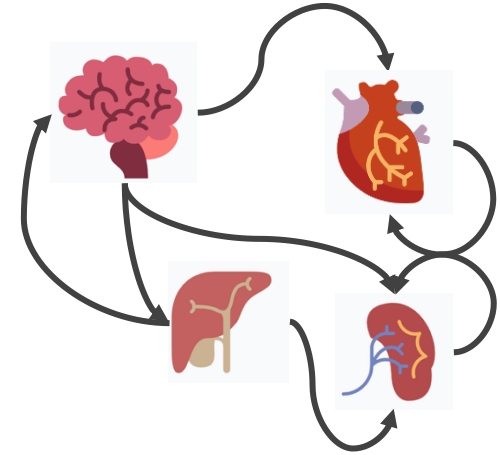
Cellular level



Target modulation changes cellular pathways, networks, and gene expression.



Organ & tissue level



Cellular changes alter physiology and produce therapeutic effects or toxicity.

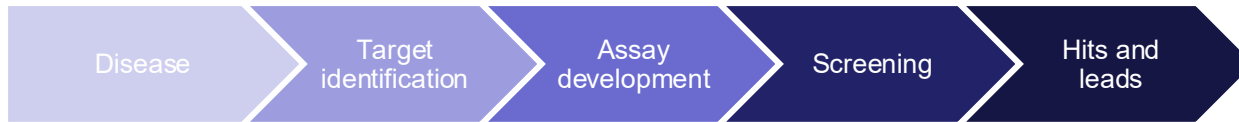
In this lecture, we focus on small molecules that alter the function of protein targets

How have drugs been discovered preclinically?

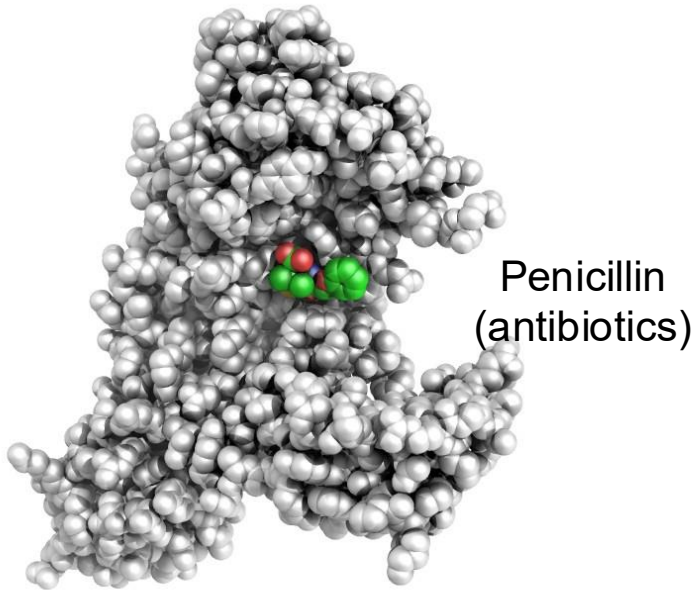
- **Natural product screening (e.g., aspirin)**
- **Serendipity (luck; e.g., penicillin, viagra)**
- **Repurposing (remdesivir)**
- **Biochemistry/Pathway Based**
 - Literature
 - Patent busting
 - Substrate/ligand analogs, mechanism based
- **High-throughput screening (since the 90's)**
- **Rational drug design**
 - Virtual screens
 - Structure-based design
- **Almost all feed into chemical optimization (Affinity, ADME/Tox)**
- **The rise of artificial intelligence and machine learning**

Target based drug discovery

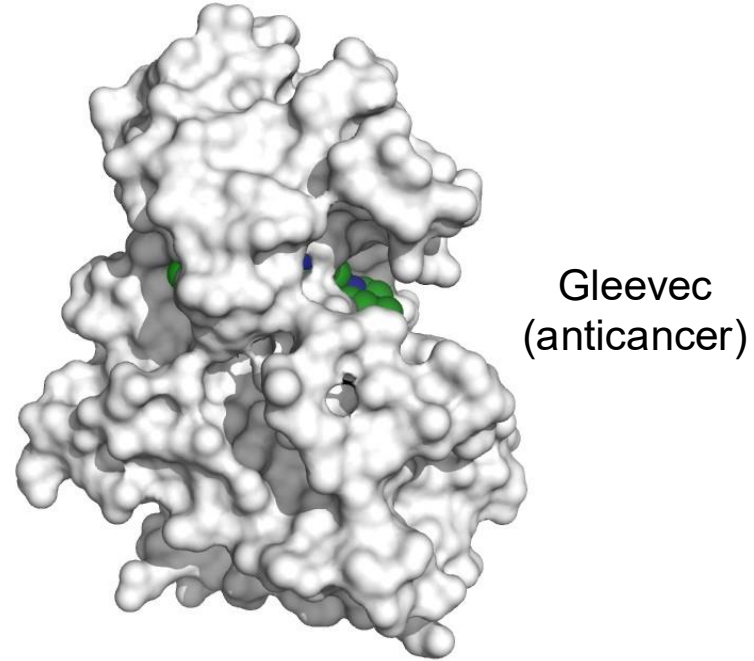
- **Drug target:** Specific macromolecule, or biological system that when modulated pharmacologically (e.g., by interaction with a drug), provides meaningful efficacy and acceptable safety for a specific human disease
- The process of identifying a **molecular target** for treatment of a disease is called **target identification**
- Drug candidates are often discovered by a process called **screening**, which uses knowledge about the target molecule (e.g. activity, structure) to identify small-molecules that can modulate its function



Understanding protein-drug interactions can help us design better and safer drug



D-alanyl-carboxypeptidase-transpeptidase



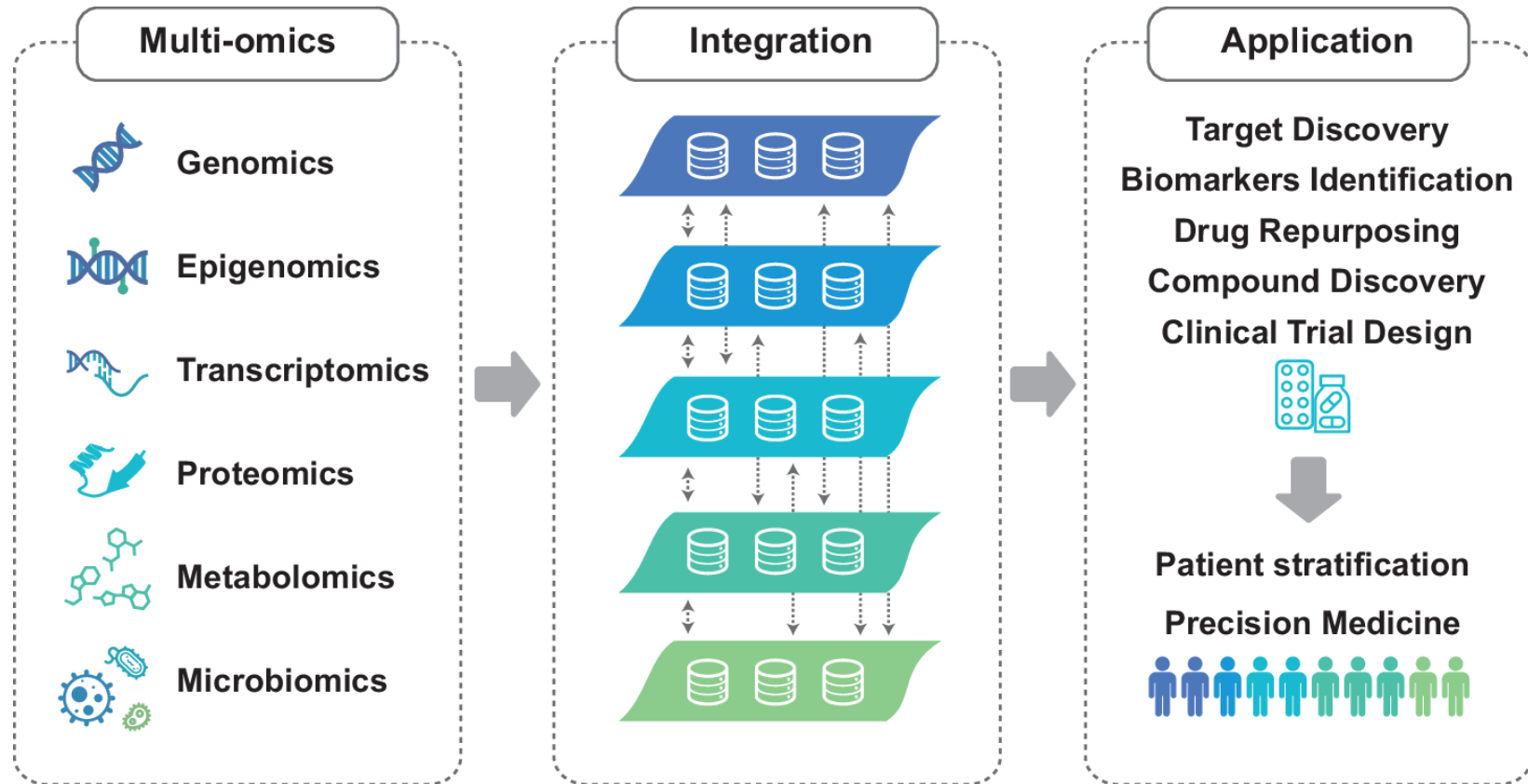
BCR-ABL Tyrosine kinase

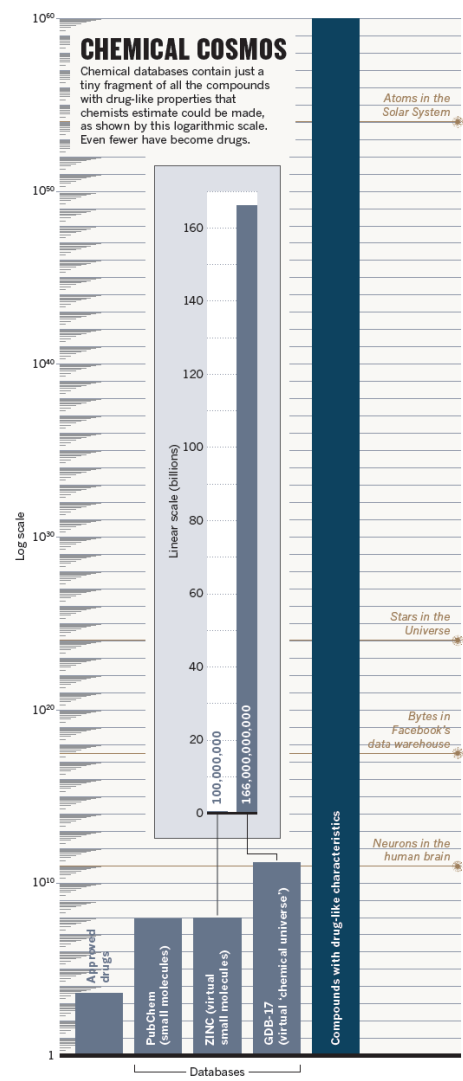
Drug act by binding to their protein targets

Three key challenges in modern drug discovery

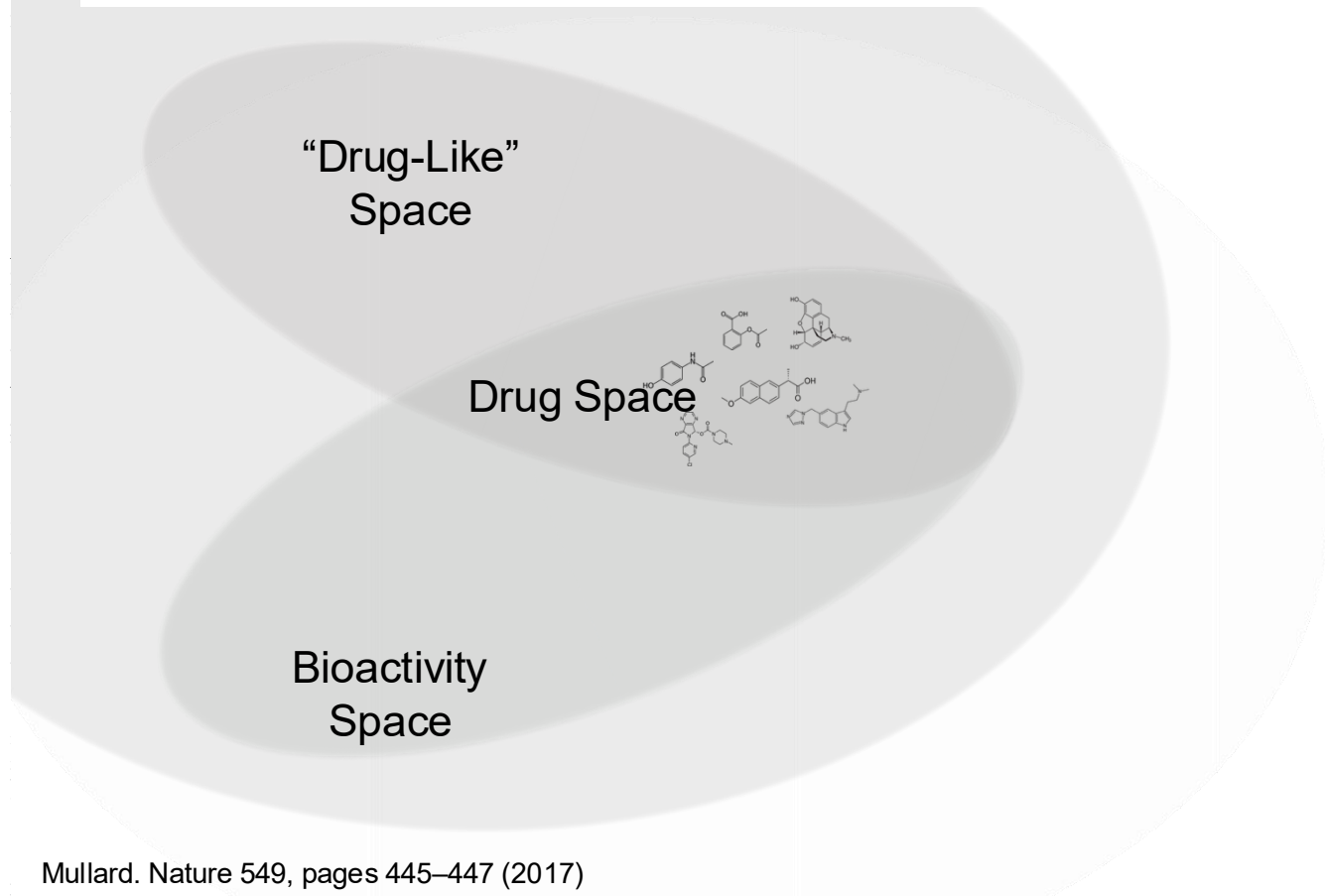
- **Identifying drug targets** whose modulation can reverse disease phenotype
- **Determining protein (target) structures** to guide drug development
- **Searching the vast chemical space** for novel, safe, and efficacious drugs

How can we find new drug targets?





The chemical space is estimated to be $\sim 10^{25}$ - 10^{60} drug-like molecules



Challenges in small molecule drug prediction

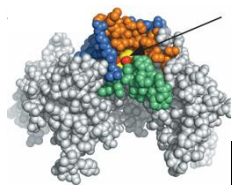
- **Chemical space:** $\sim 10^{25}$ - 10^{60} drug-like molecules
 - Stars in the universe: 10^{24}
 - Sand grains on earth: 10^{20}
 - TikTok data ever generated: 10^{18} bytes
- Off-target binding can occur unexpectedly
- Hard to find novel scaffolds

Current known experimental data of molecules covers around 10^{11} molecules

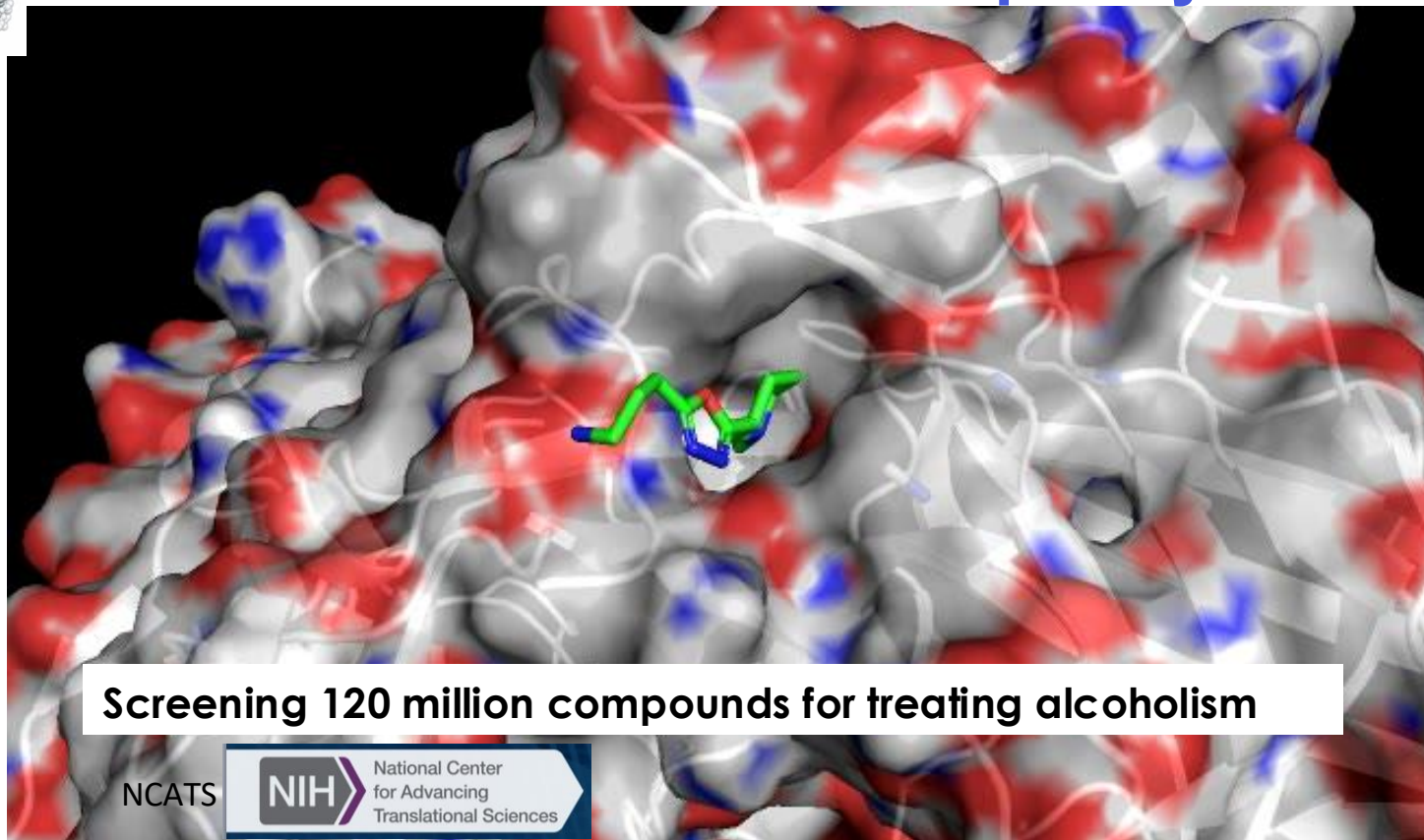
Schlessinger A *et al Cell Chem Biol.* 2017 Dec 21;24(12):1434-1435.

Vatansever *et al Med Res Rev.* 2021 May;41(3):1427-1473.





Virtual screening evaluates binding of millions of molecules quickly



New AI approaches allow us screen billions of potential compounds within weeks

- AI algorithms learns physics and can virtually screen faster
- The larger the library the hit-rate improves, more novel compounds, everything is faster

nature communications



Article

<https://doi.org/10.1038/s41467-024-52061-7>

An artificial intelligence accelerated virtual screening platform for drug discovery

Received: 5 March 2024

Accepted: 23 August 2024

Published online: 05 September 2024

Check for updates

Guangfeng Zhou^{1,2,10}, Domnita-Valeria Rusnac^{3,10}, Hahnbeom Park^{4,5}, Daniele Canzani⁶, Hai Minh Nguyen⁷, Lance Stewart², Matthew F. Bush⁶, Phuong Tran Nguyen⁸, Heike Wulff⁷, Vladimir Yarov-Yarovoy^{8,9}, Ning Zheng³ & Frank DiMaio^{1,2}✉

Structure-based virtual screening is a key tool in early drug discovery, with growing interest in the screening of multi-billion chemical compound libraries. However, the success of virtual screening crucially depends on the accuracy of the binding pose and binding affinity predicted by computational docking. Here we develop a highly accurate structure-based virtual screen method.

nature computational science



Article

<https://doi.org/10.1038/s43588-025-00777-x>

Rapid traversal of vast chemical space using machine learning-guided docking screens

Received: 5 June 2024

Accepted: 4 February 2025

Published online: 13 March 2025

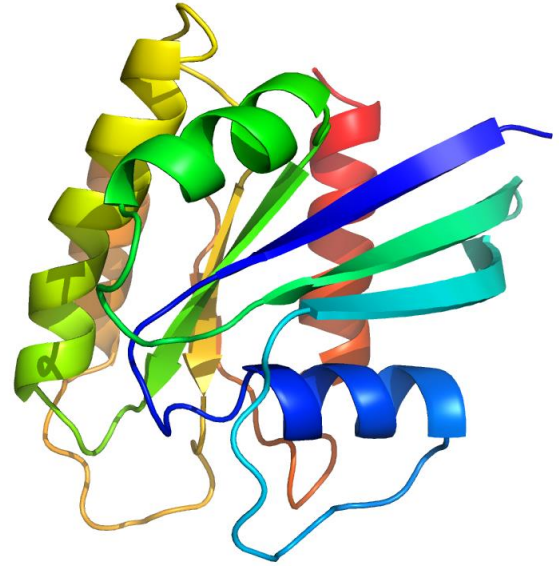
Check for updates

Andreas Lutten^{1,2,3}✉, Israel Cabeza de Vaca¹, Leonard Sparring¹, José Brea^{4,5}, Antón Leandro Martínez^{4,5}, Nour Aldin Kahlous¹, Dmytro S. Radchenko⁶, Yurii S. Moroz^{6,7,8}, María Isabel Loza^{4,5}✉, Ulf Norinder³✉ & Jens Carlsson¹✉

The accelerating growth of make-on-demand chemical libraries provides unprecedented opportunities to identify starting points for drug discovery with virtual screening. However, these multi-billion-scale libraries are challenging to screen, even for the fastest structure-based docking methods. Here we explore a strategy that combines machine learning and molecular docking to enable rapid virtual screening of databases containing billions of

Protein structure determines function and its structure determination can be challenging

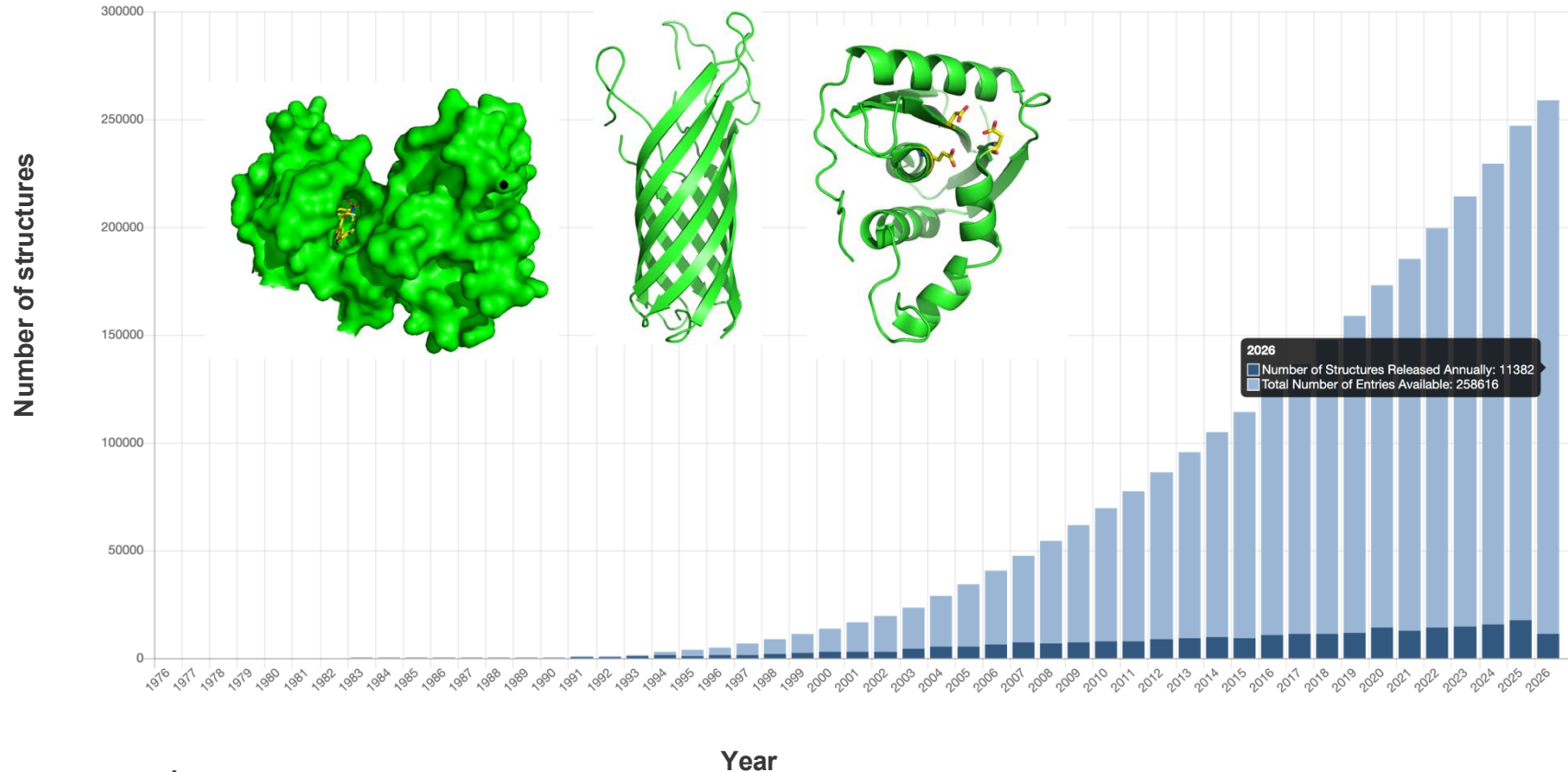
GFCHIKAYTRLIMVG...



Amino acid sequence

Protein structure

Experimentally determined structures are deposited to the Protein Data Bank (PDB)

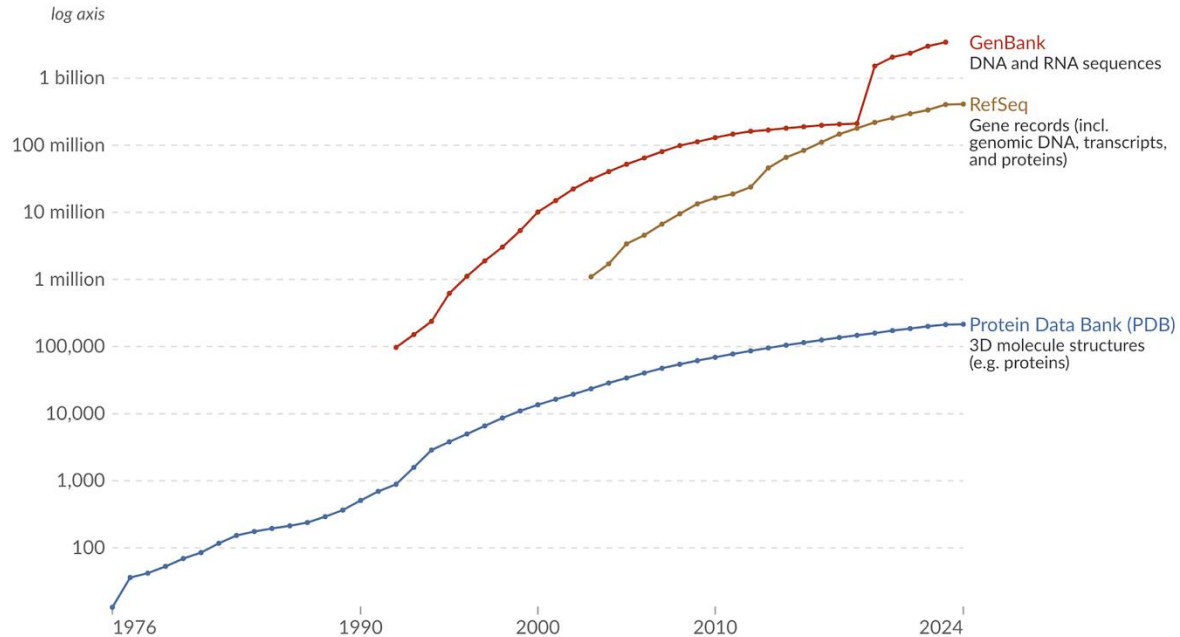


...but sequences outnumber protein structures

Number of entries in biological sequence databases

Our World
in Data

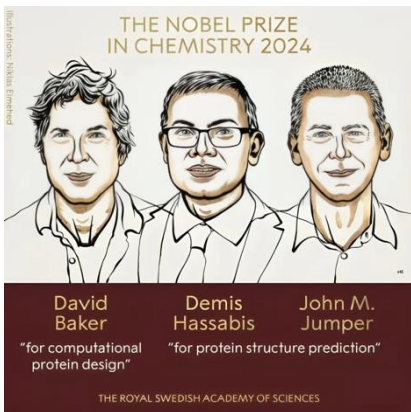
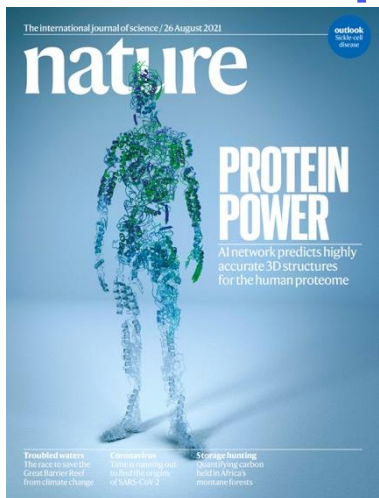
Biological sequence databases store data such as DNA, RNA, and amino acid sequences and 3D protein structures. This data includes entries from GenBank¹, RefSeq², PDB³, UniProtKB/SwissProt⁴, as well as predicted protein structures in AlphaFoldDB⁵ and ESMAtlas⁶.



Data source: Epoch AI (2024)

OurWorldinData.org/medicine-biotech | CC BY

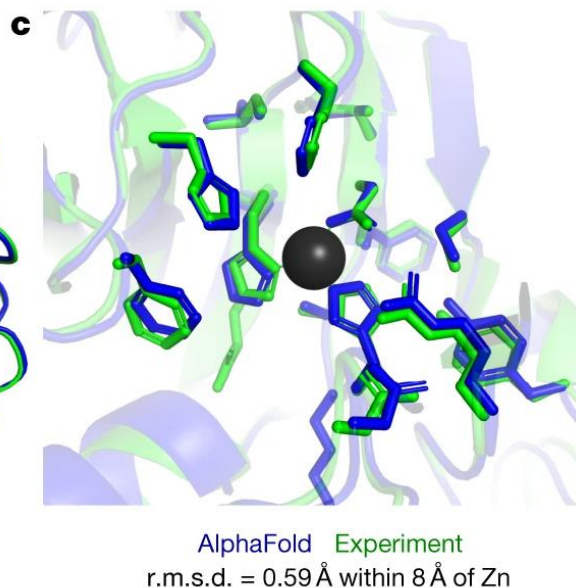
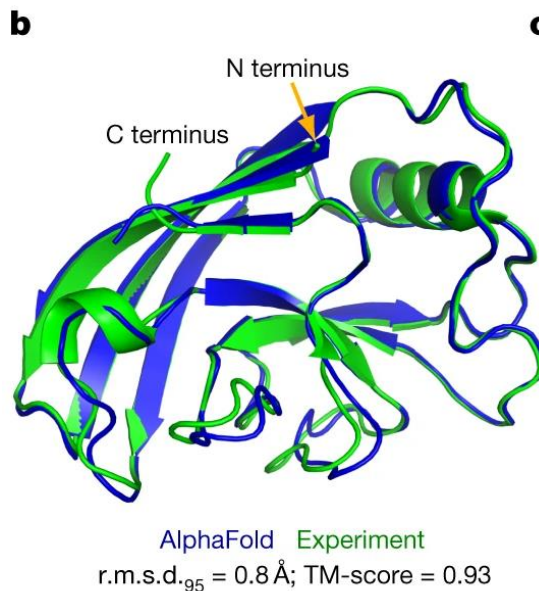
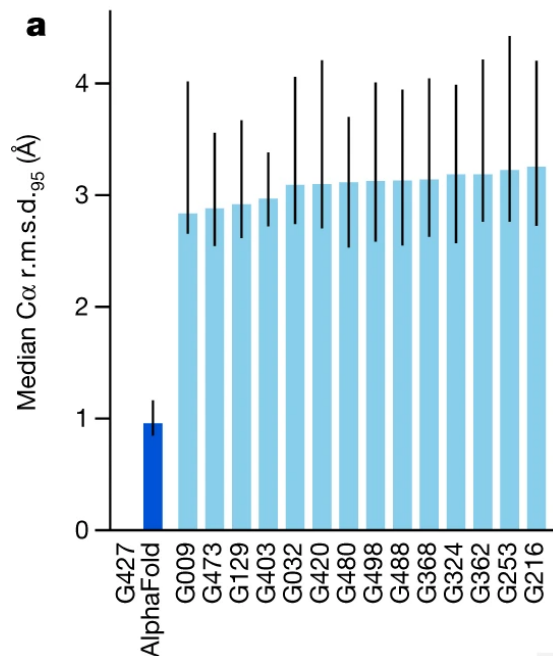
Has the protein folding problem been solved with AI?



London A.I. Lab Claims Breakthrough That Could Accelerate Drug Discovery

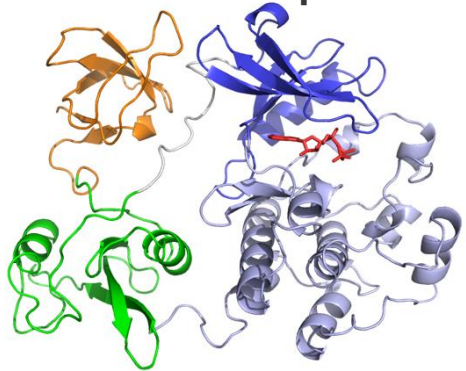
Researchers at DeepMind say they have solved “the protein folding problem,” a task that has bedeviled scientists for more than 50 years.

Google's AlphaFold outperforms all other modeling methods

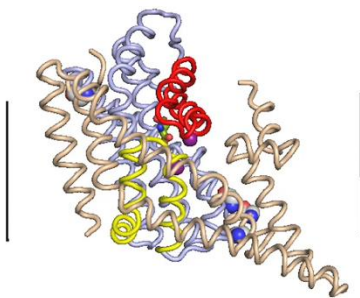


Is the protein folding problem solved?

Multi-domain proteins



Protein dynamics

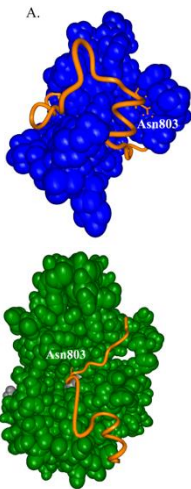
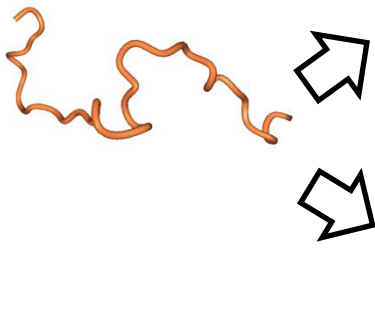
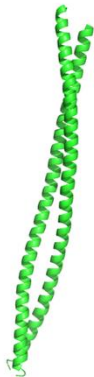


Akyuz *et al.* Nature. 2013 Oct 3;502(7469):114-8.

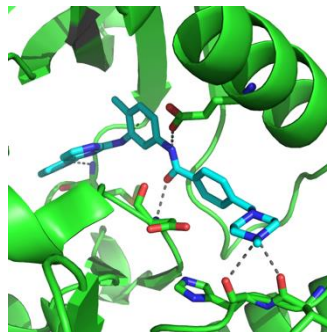
Binding



Non-globular proteins

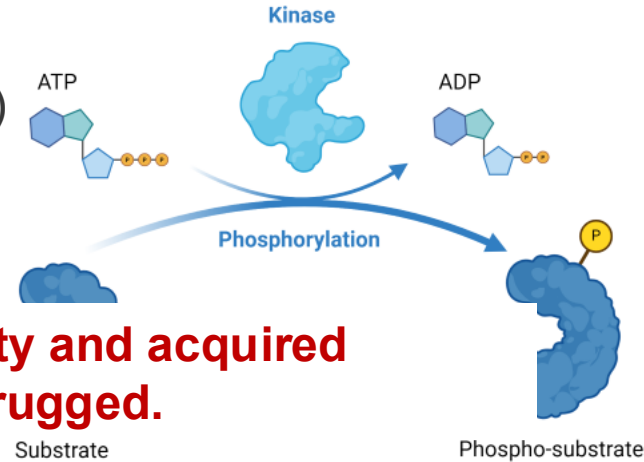


Protein-ligand interactions



Kinases are among the most important drug targets

- A kinase is an enzyme that catalyzes the **transfer of phosphoryl groups** from high-energy molecule (ATP) to specific substrates
- Protein kinases are a family of 500 proteins that **regulate many biological processes, including cell**



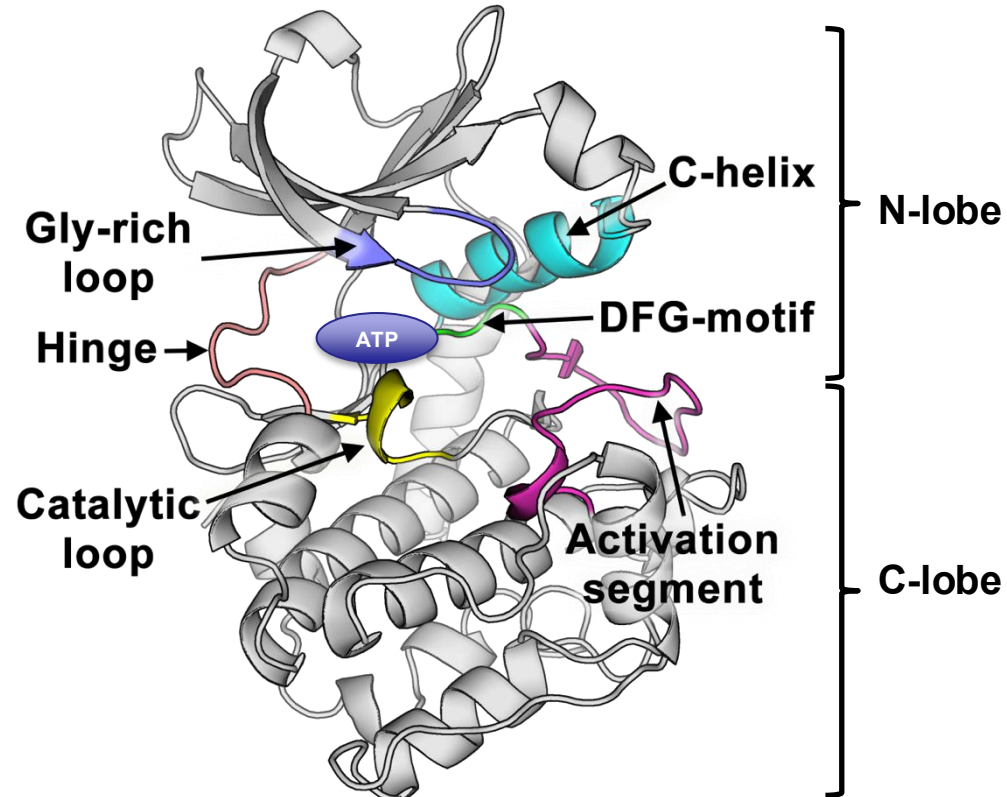
- **Problem: current drugs suffer from off-target toxicity and acquired resistance. Many high potential targets remain undrugged.**
- **distinct diseases**, including cancer, diabetes, and neurodegenerative disorders
- Protein kinases are **validated targets with >100 FDA-approved drugs**

Lemmon & Schlessinger. *Cell* 2010

Rudolph J, Hoeflich KP, Dar AC. *Nat Rev Drug Discov.* 2026

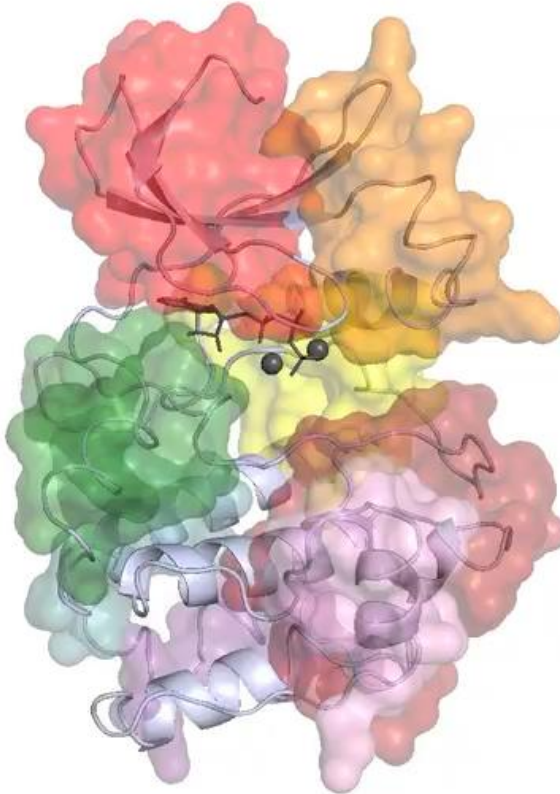
Manning et al. *Science.* 2002

Structure of protein kinases



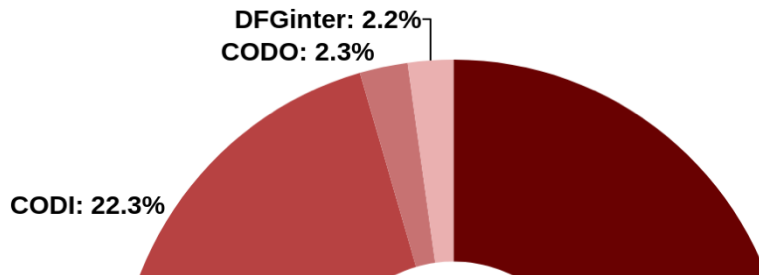
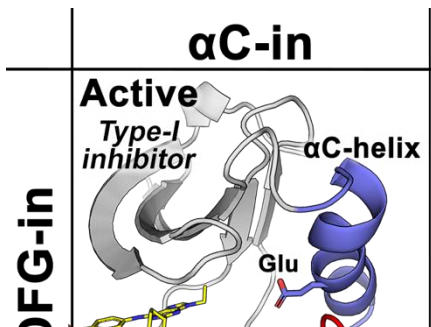
Kinases are dynamic

Most kinases adopt several **druggable** conformational states

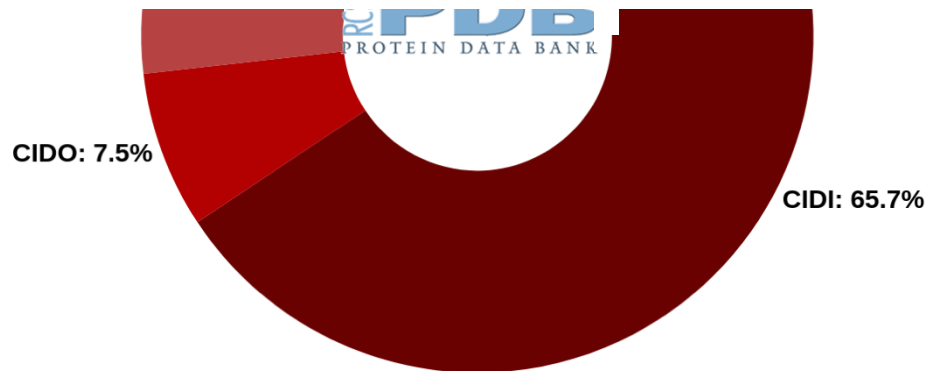
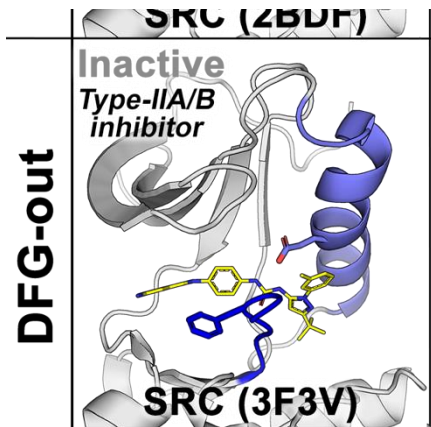


Kinase conformations can be defined by structural motifs

Only 10% (PDB) in the DFG-out state

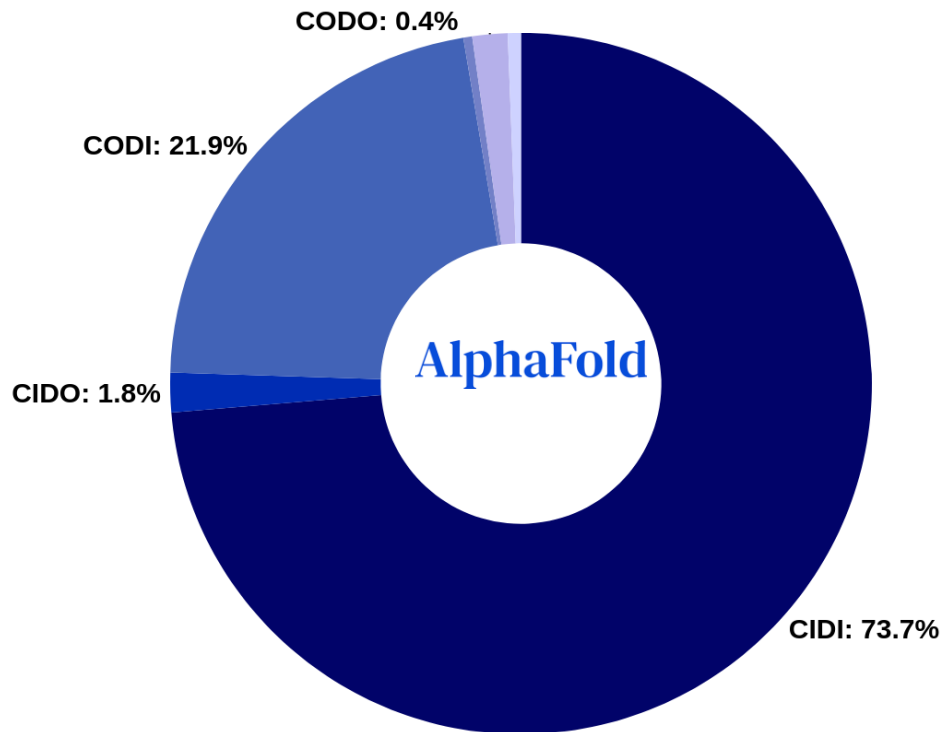


The Protein Data Bank is highly biased for specific conformations

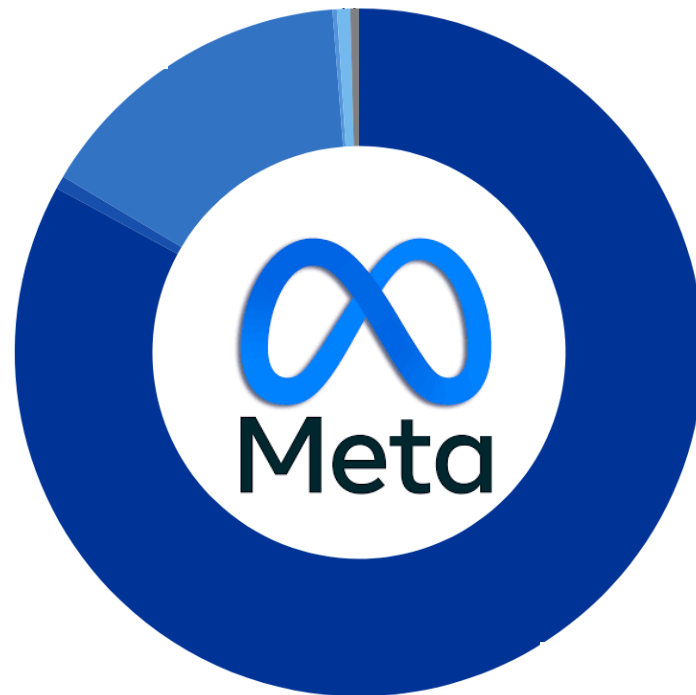


Default AF2-generated models exhibit similar bias

2% (AF2) and 1% (Meta ESMFold) are in the DFG-out state



AF2 models obtained from Varadi et al, *NAR*, 2022
Herrington et al. *PLoS Comput Biol.* 2024



Lin et al, *Science*, 2023

Allosteric Inhibition of PKMYT1 Induces a Unique, Inactive ATP Binding Site Conformation

Noah B. Herrington,[#] Susmita Khamrui,[#] Yihan Zhao, Carisse Lansiquot, Ruoxi Wu, Gaurav Pandey, Michael B. Lazarus,^{*} and Avner Schlessinger^{*}



Cite This: *J. Am. Chem. Soc.* 2026, 148, 24274–24286



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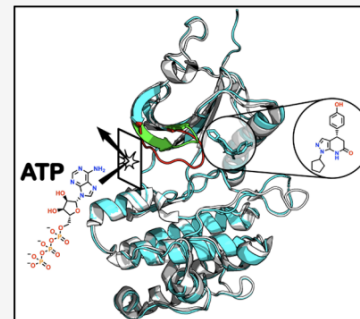


Article Recommendations

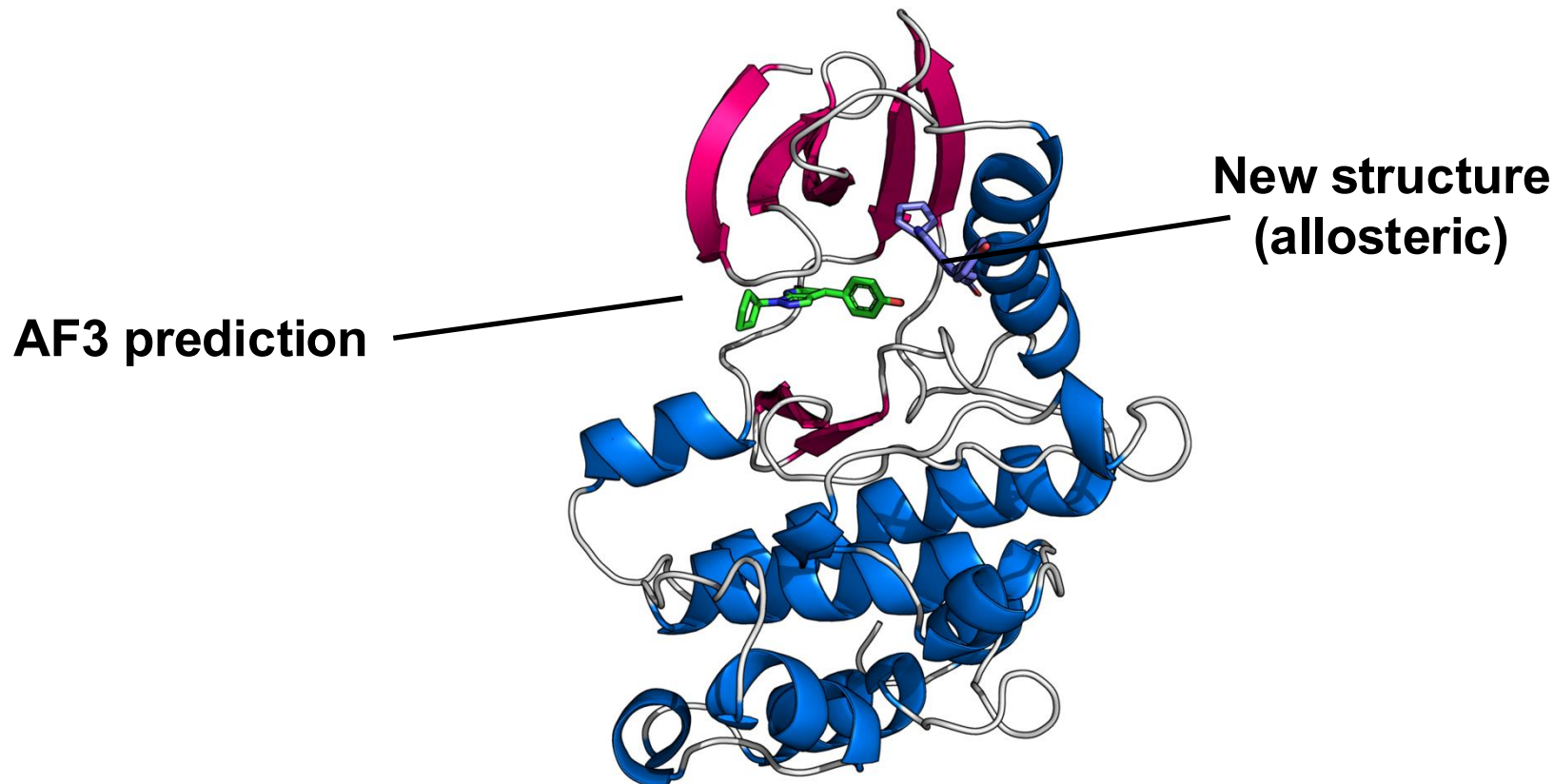


Supporting Information

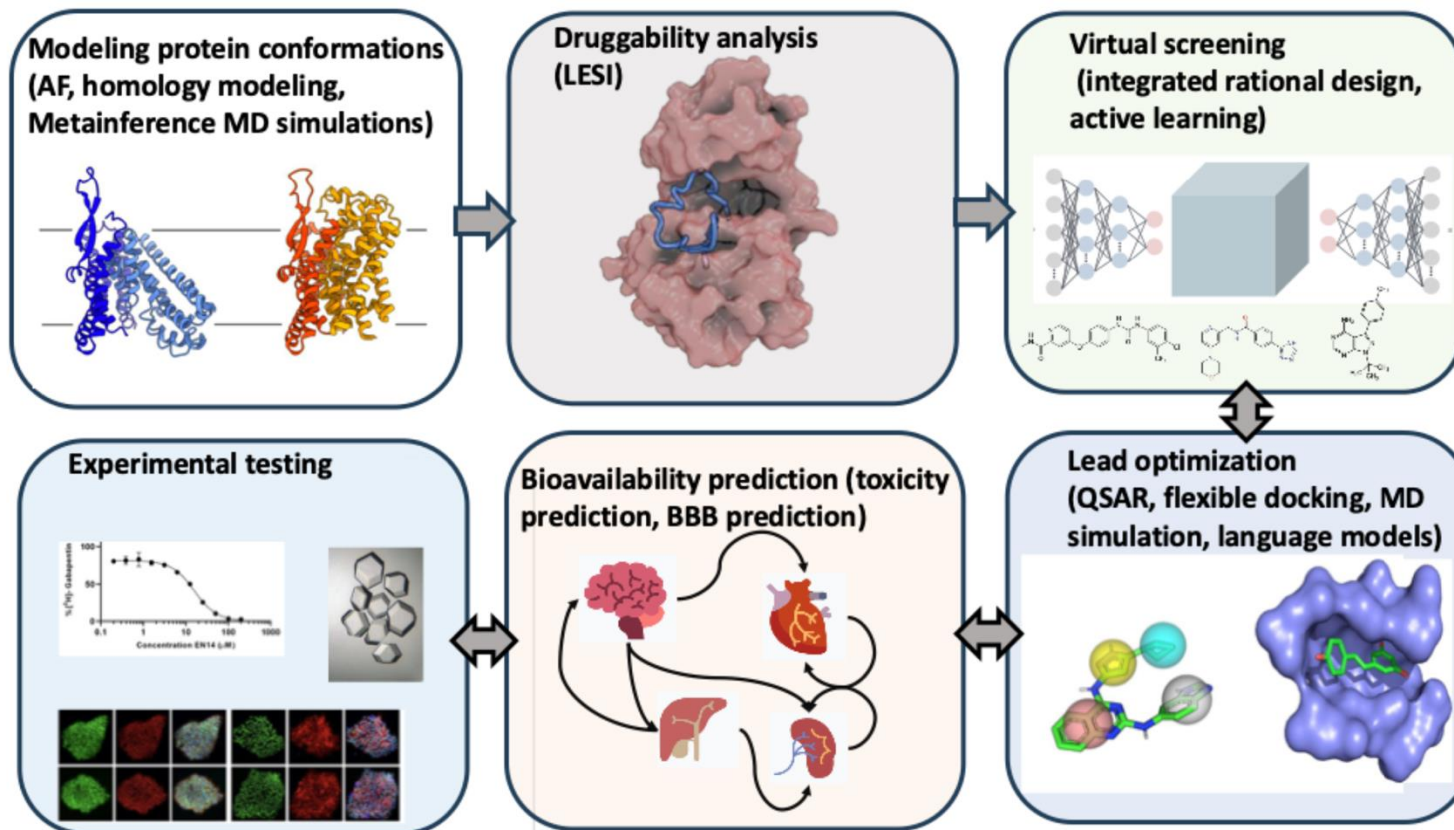
ABSTRACT: The protein kinase PKMYT1 regulates a key cell cycle checkpoint as part of the cell's DNA-damage repair response, but in cancer, this function can promote tumor cell survival through avoiding mitotic catastrophe. PKMYT1 has been linked to a variety of cancer types, including breast, gastric, and nonsmall cell lung cancers, as well as kidney renal clear cell carcinoma, making it an important therapeutic target. However, potent and selective small-molecule inhibitors of PKMYT1 are scarce, and its specific biological role in tumor proliferation remains understudied. Here, we report the discovery and characterization of a novel PKMYT1 inhibitor, **P29**, bound to a previously unknown allosteric site. Structural and kinetic data reveal that **P29** induces a conformational rearrangement of the P-loop and inhibits PKMYT1 through a mixed ATP competitive and noncompetitive mechanism. A closely related analogue, **P32**, exhibits selectivity and enhanced potency and engages PKMYT1 in cells. Surprisingly, however, it binds in the ATP binding pocket, demonstrating that subtle chemical modifications can shift binding mode and mechanism of inhibition. Furthermore, computational analysis using structural modeling methods, including AlphaFold2, AlphaFold3, Boltz-2, as well as unbiased MD simulations, indicates that these approaches are limited in their ability to capture this inhibitor-induced cryptic binding site and conformational change. Our study identifies an underexplored allosteric site in PKMYT1 and establishes a new avenue for the rational design of selective kinase inhibitors targeting a cryptic binding site in this emerging drug target. These findings also reveal intrinsic challenges in the computational discovery of noncanonical kinase binding sites and underscore the necessity of integrating computational modeling with experimental testing using structural and functional approaches.



AlphaFold3 places the compound in the ATP binding site (Type-I inhibitor)



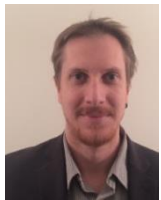
AI-enabled drug discovery loop



Targeting the bicarbonate transporter NBCn2 (SLC4A10) to modulate neuronal excitability



Bin Zhang (multi-omics)



Daniel Wacker
(structural biology)

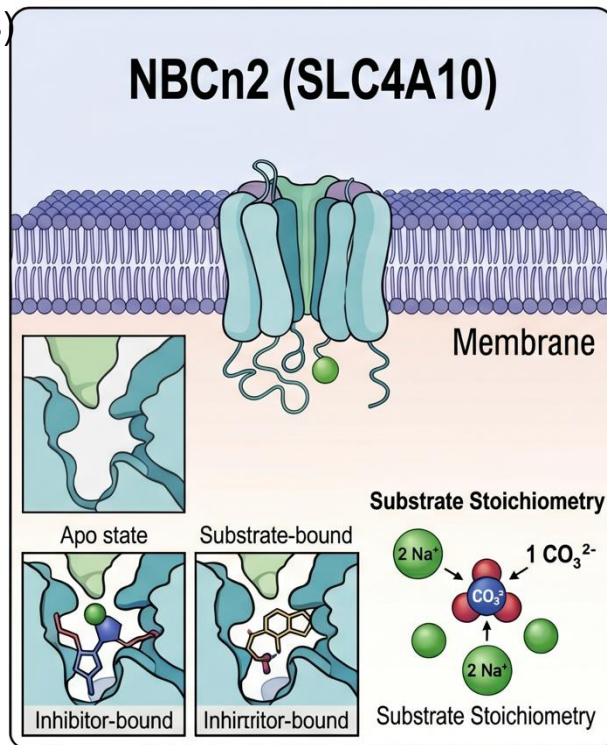


Jian Jin (chemistry)

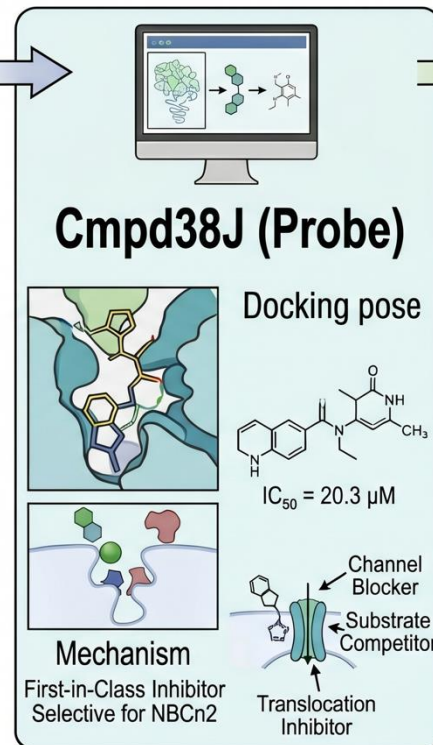


Jinye Dai (Epilepsy models)

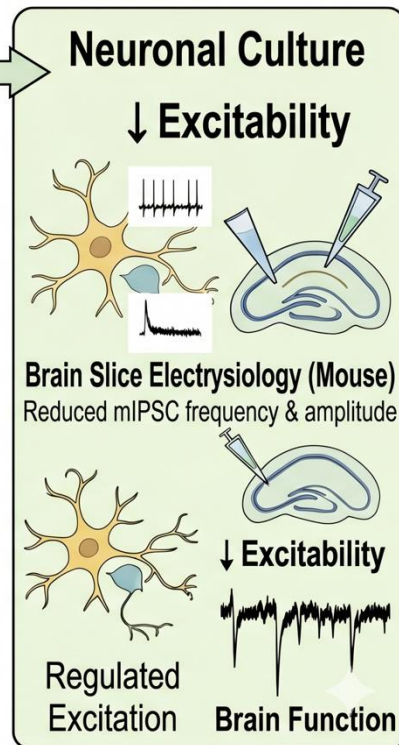
TARGET



PROBE



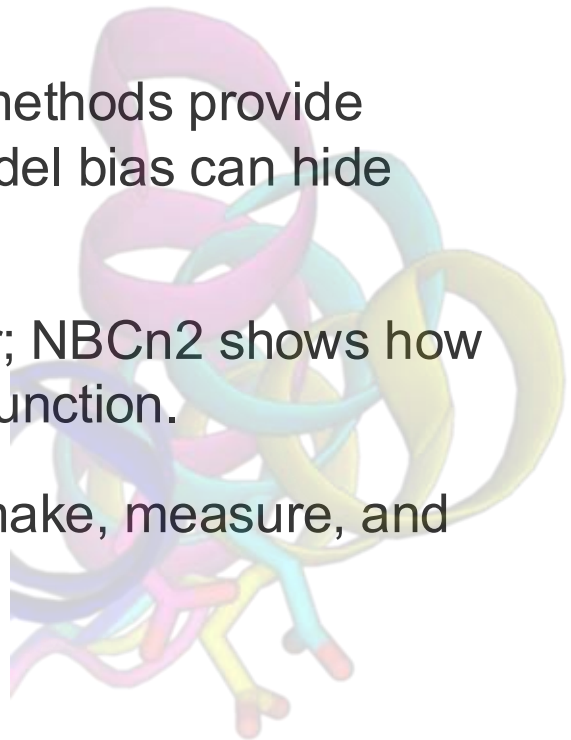
IMPACT



Yang and Zhao et al. Nat Commun. 2026 Jul 22;17(1):8923.

Conclusions

- AI helps prioritize disease targets and promising molecules across vast chemical space.
- AlphaFold and other AI protein structure modeling methods provide structural starting points, but protein motion and model bias can hide important binding sites.
- PKMYT1 shows why experimental structures matter; NBCn2 shows how a chemical probe can connect a target to neuronal function.
- Progress comes from repeating the cycle: predict, make, measure, and refine.

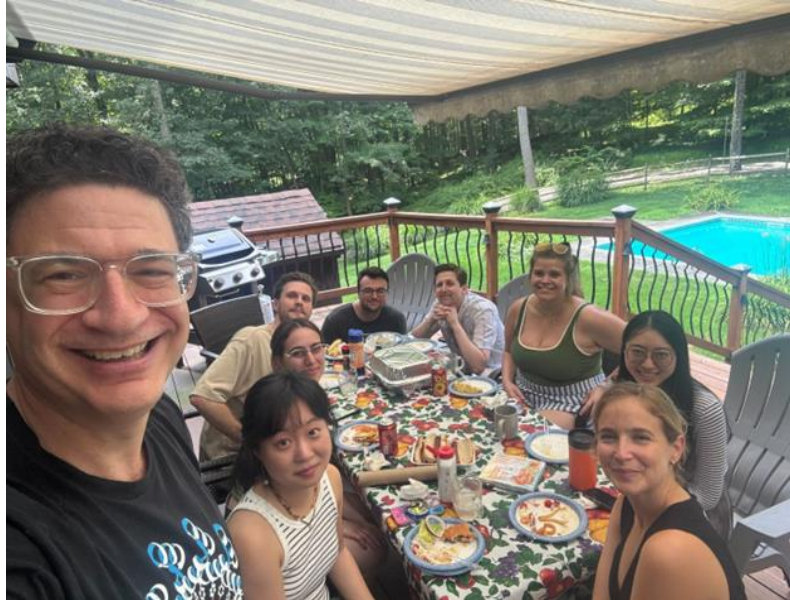


Research team and collaborators

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Funding:

- 1R01HD107528
- T32GM154814
- U01CA271318
- R01CA277794
- R01NS145483



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