5th/June/2018@British Embassy in Tokyo

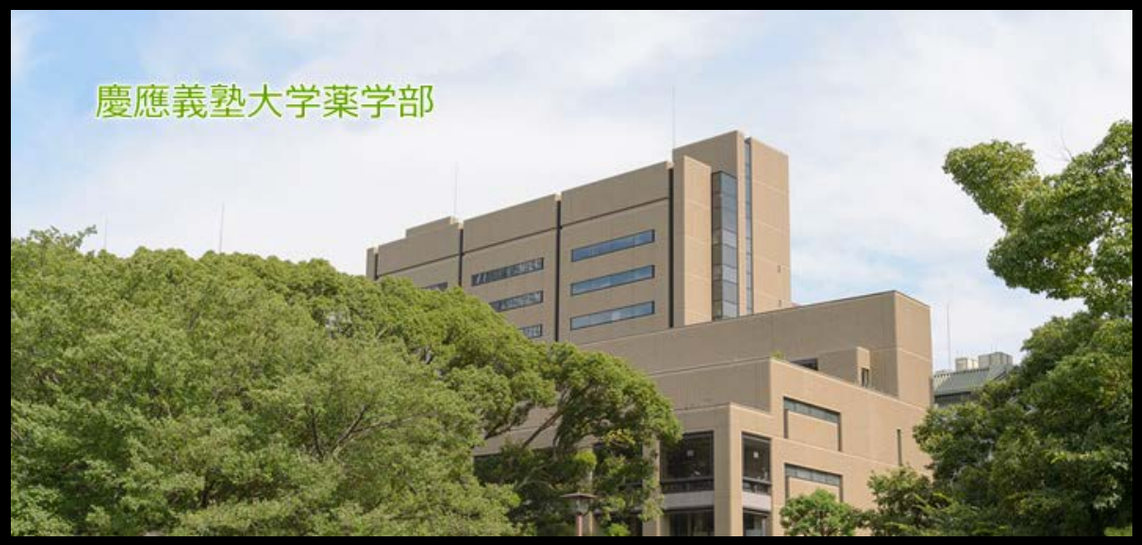
LIBRARY DESIGN FOR COLLABORATIVE DRUG DISCOVERY: EXPANDING DRUGGABLE CHEMOGENOMIC SPACE

Kazuyoshi Ikeda, Ph.D.
Keio University

SELF-INTRODUCTION

- Keio University, Faculty of Pharmacy
  (慶應義塾大学薬学部生命機能物理学研究室)
    - Bio/Chemo-informatics
    - in-silico drug discovery
    - Library design (a part of AMED project)

- Structural Biology (NMR, Prof.Osawa)



Onarimon (御成門), Tokyo

Near Zouzyougi Temple (増上寺)

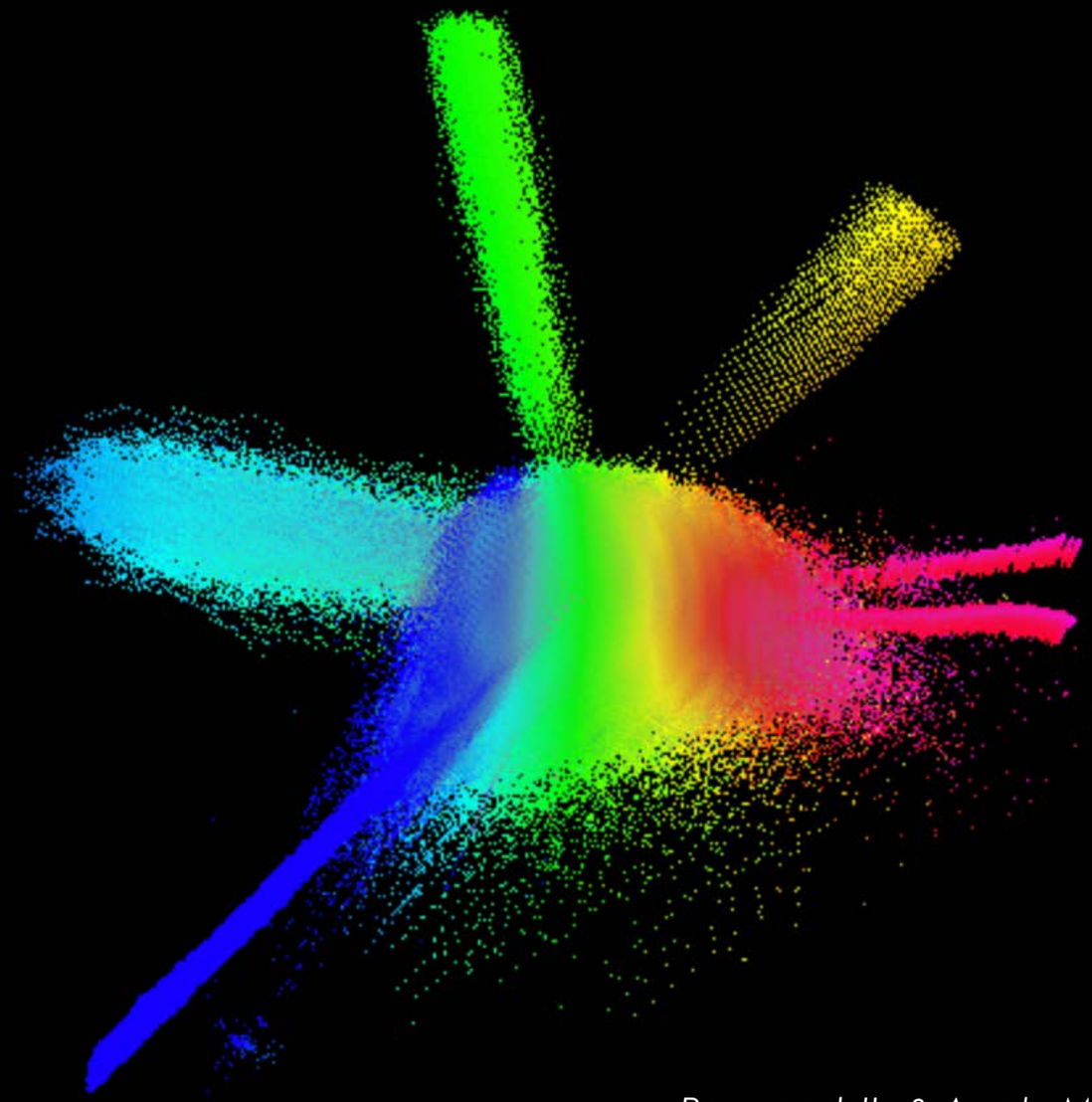
TODAY'S TOPICS

- Background: Comparison of Compound Libraries

- Library Design Informatics Using Drug Discovery Data and Virtual Compounds

- Collaborative Drug Discovery May Expand Druggable Chemical Space

CHEMICAL SPACE IS VAST

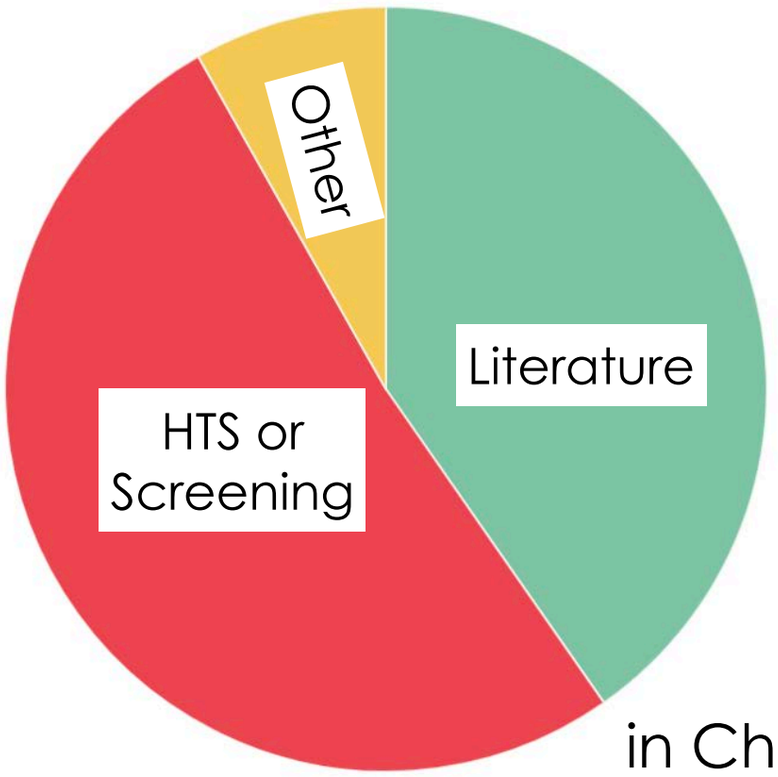


Reymond JL. & Awale M., ACS Chem Neurosci. (2012) 19;3:649-657.

- Number of stars in our galaxy: $\sim 10^{12}$
- Estimated size of small molecule chemical space: $> 10^{12}$

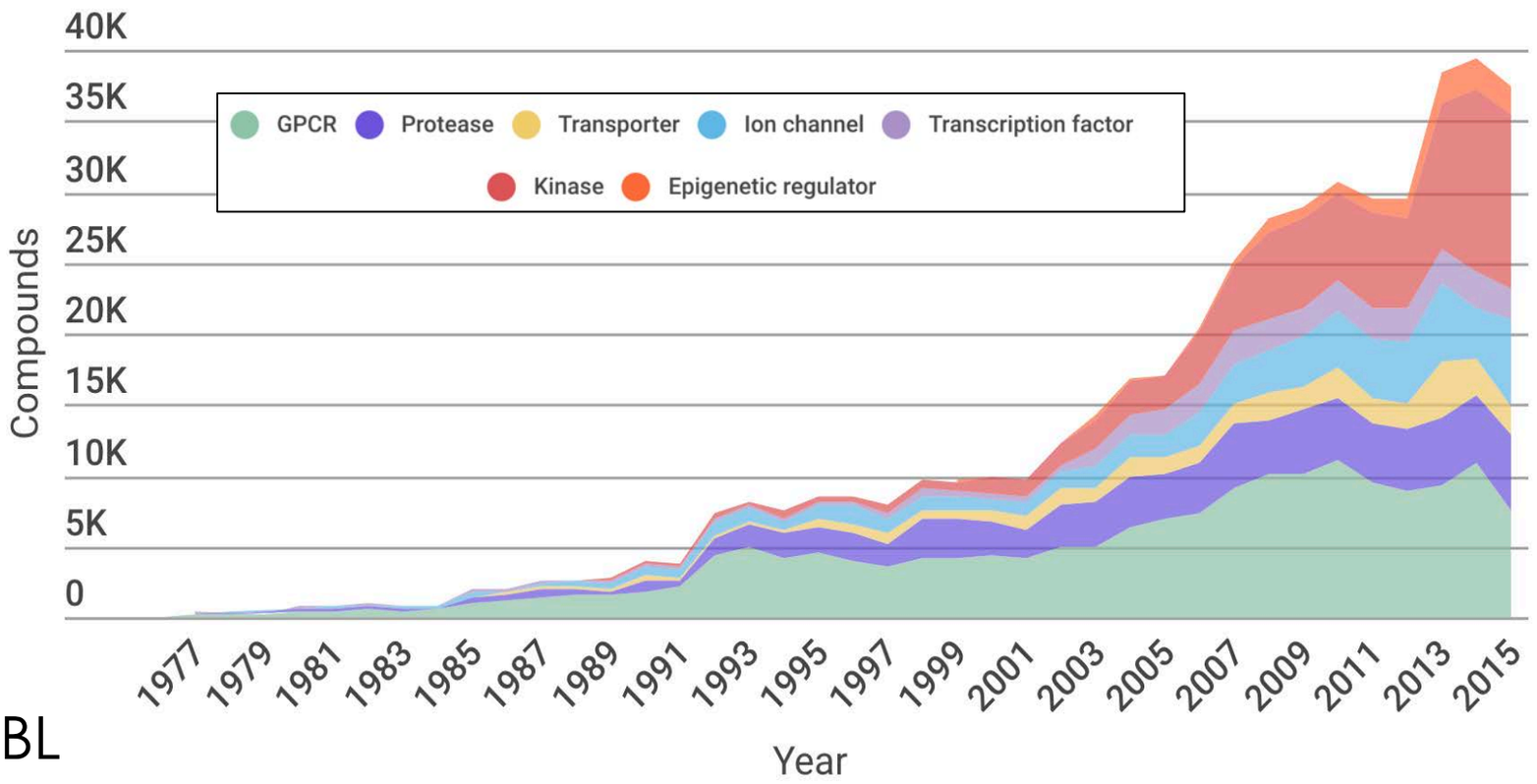
IMPACT OF OPEN SCREENING DATA

Drug Discovery Data Resources



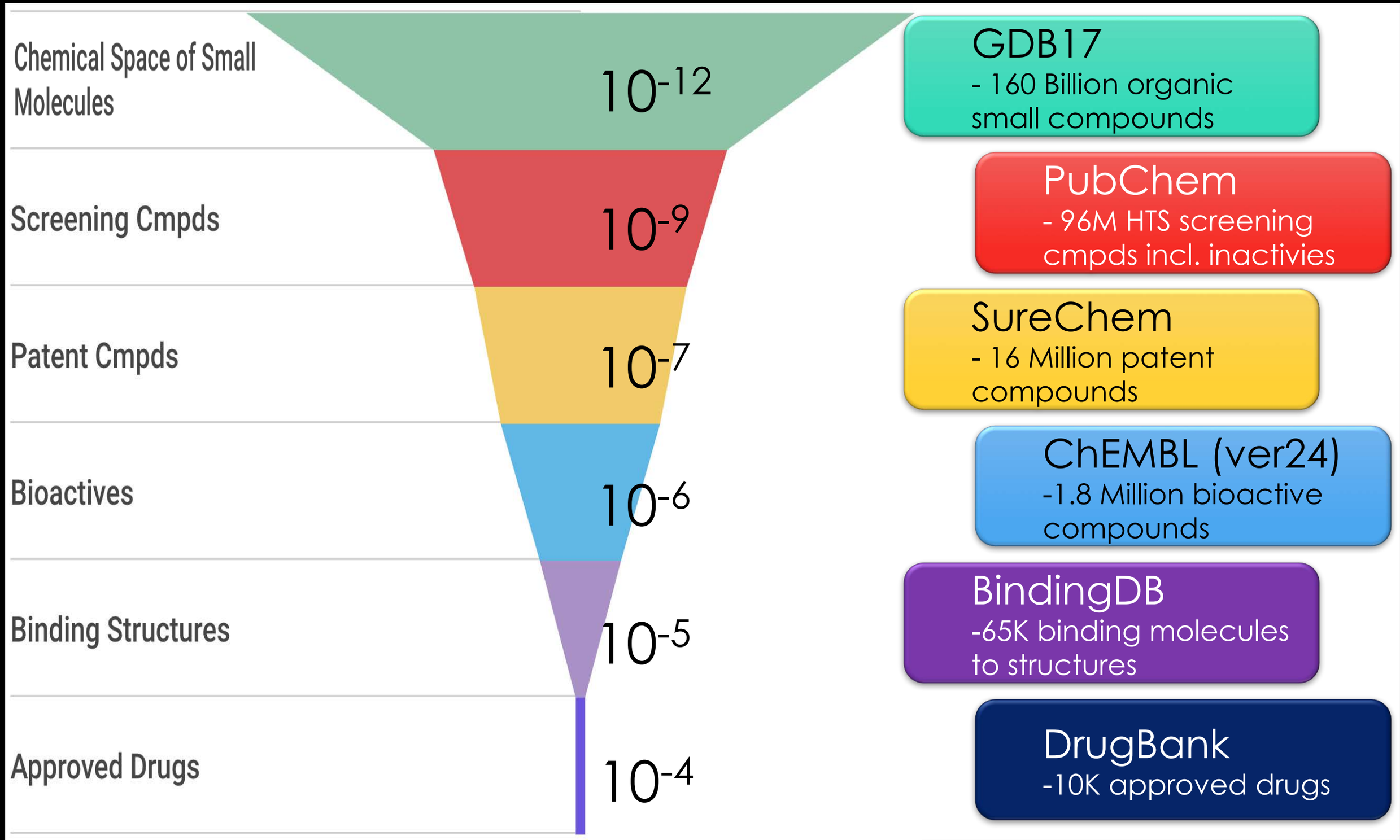
in ChEMBL

#Activities and Compounds by Year



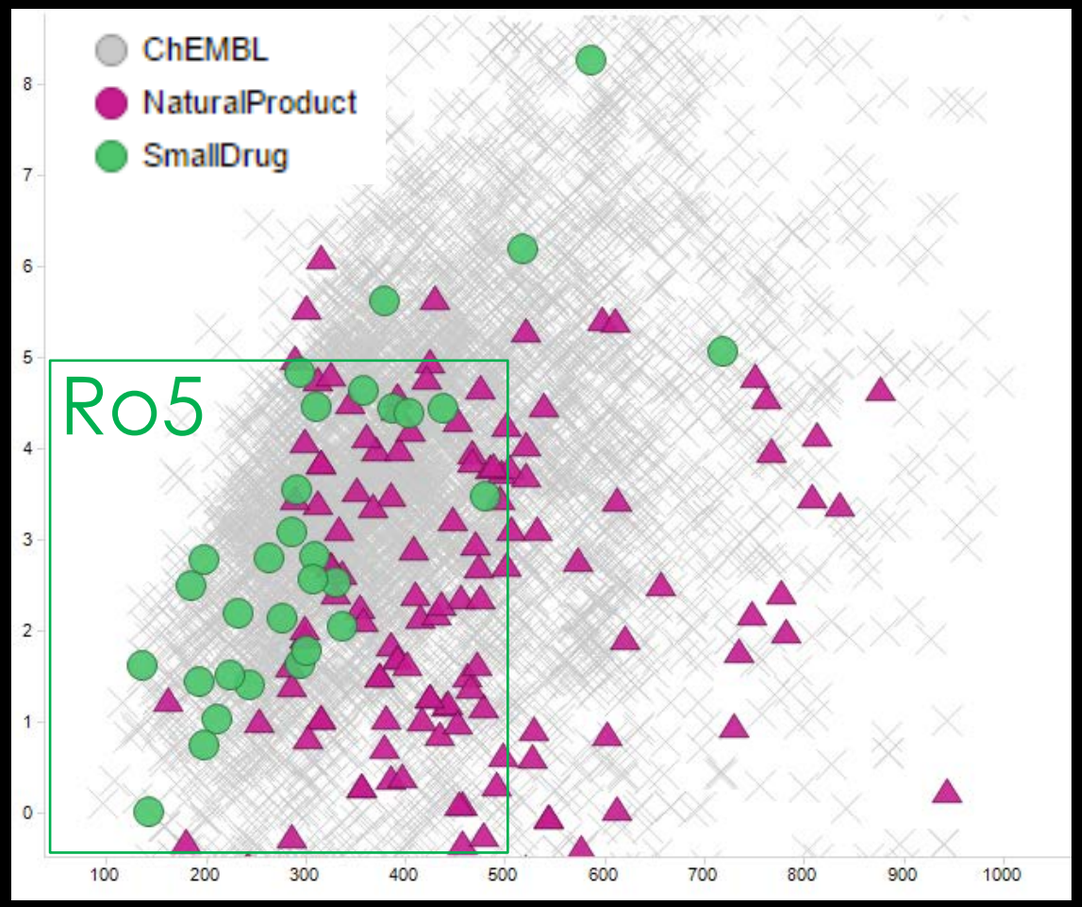
- ✓ >50% from non-Literature data
- ✓ HTS data is rapidly increasing by open drug discovery projects

SIZE OF PUBLIC CHEMICAL DATABASES



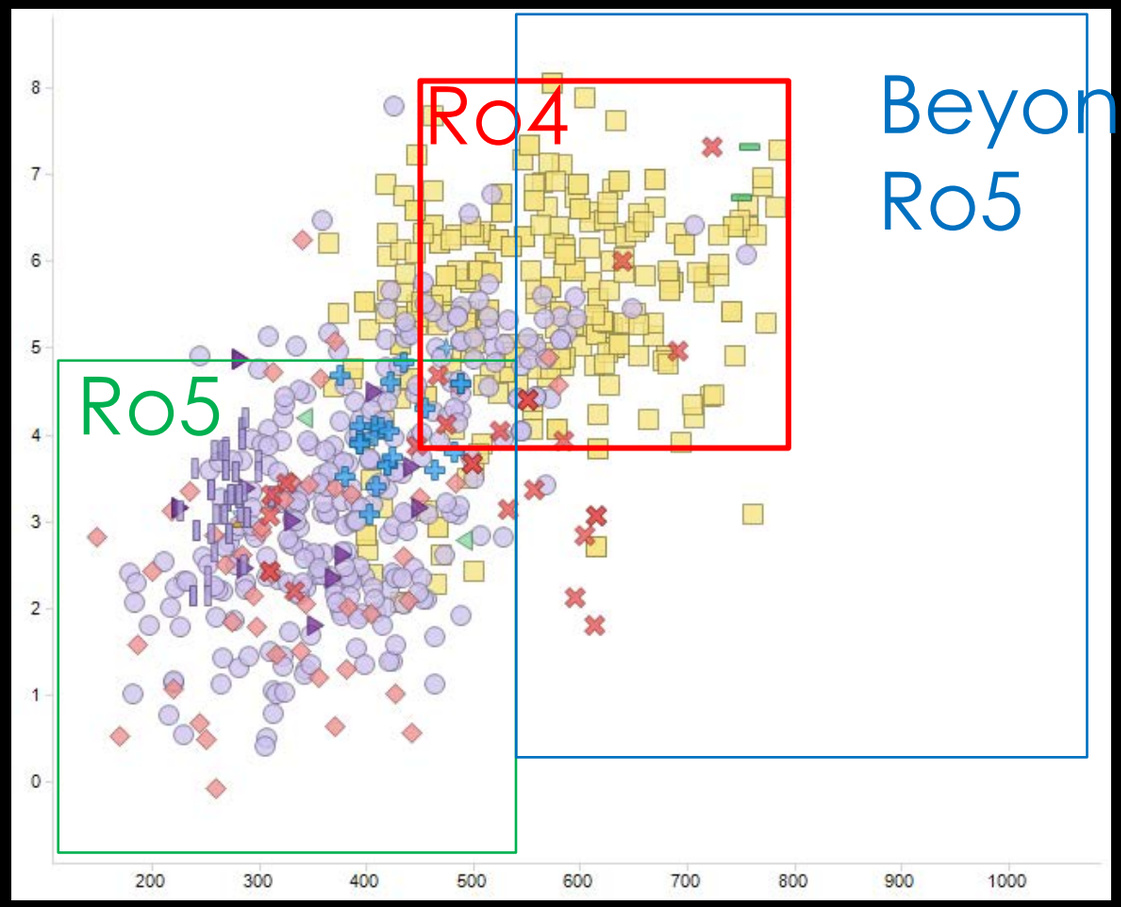
LIMITED BIOACTIVE SPACE

Small Drugs vs Natural Products



- ✓ 85% of approved small molecule drugs within Lipinski's Ro5 space

PPI Inhibitors



- ✓ Only half of PPI Inhibitors are within Ro5.
- ✓ Rule of 4 covers over 90% of those.

Mapping Virtual Rings on Patent Compounds

NIH-MLSMR Library

489

ChEMBL

931

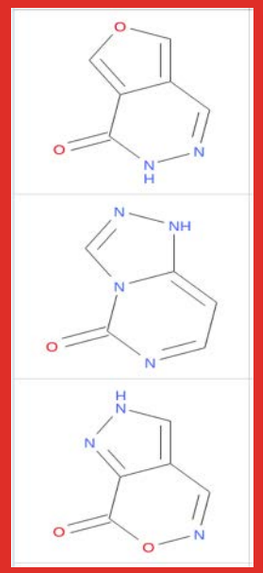
VEHICLe (virtual exploratory heterocyclic library)

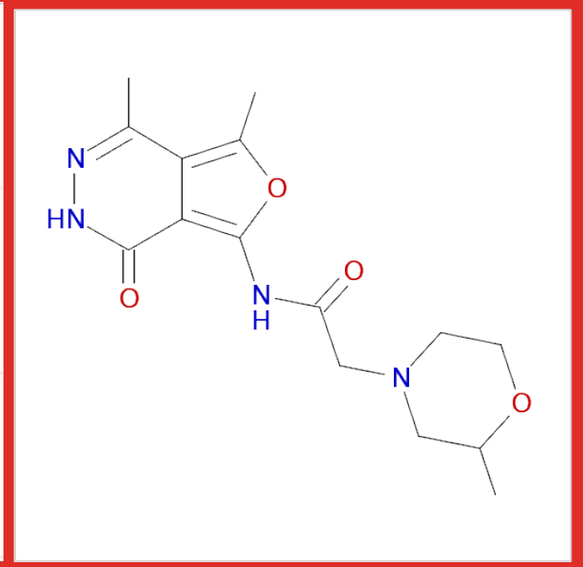
24,807 Rings

SureChem (Patent)

2,072

Unpatented Bioactive Compounds (45 Rings)

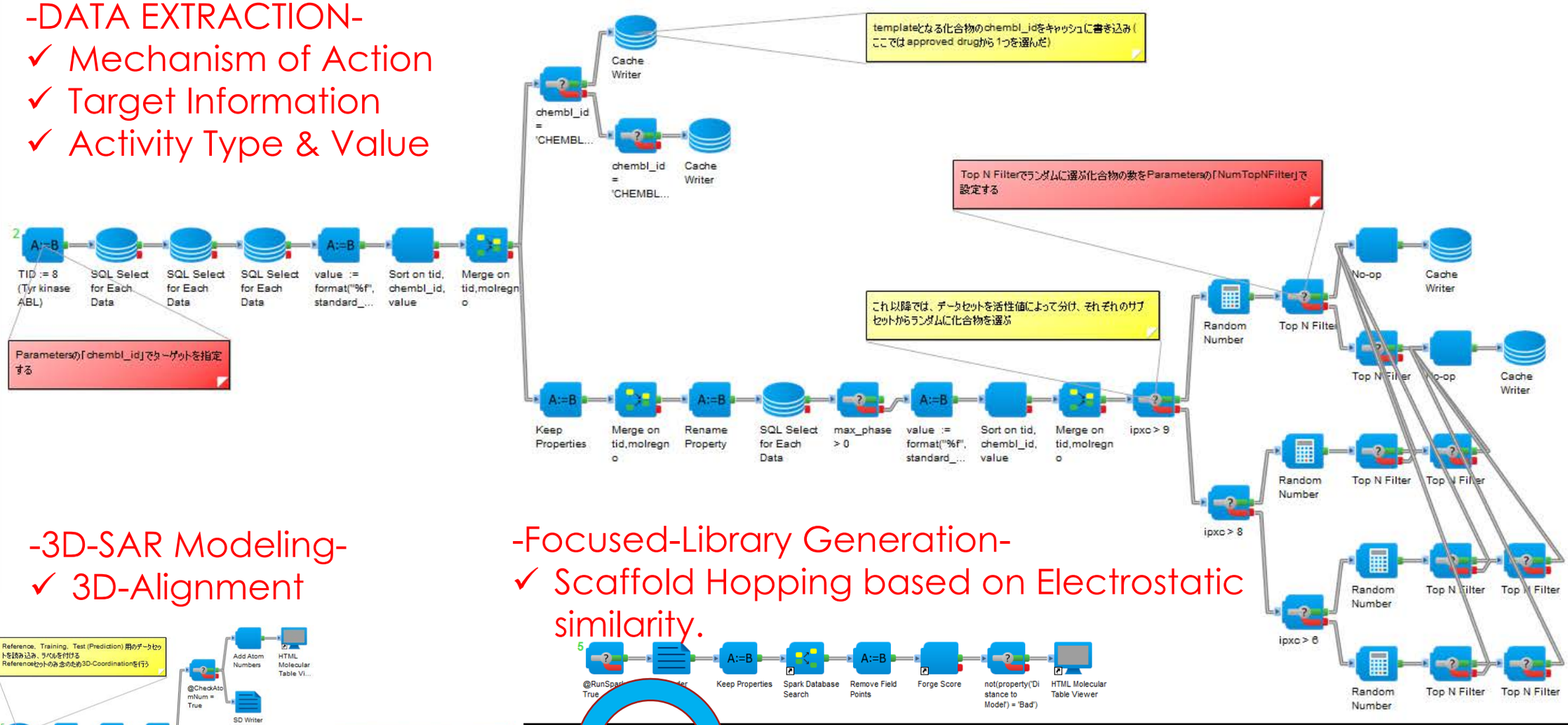




Library Design Protocol Using Patent & Virtual Cmpds

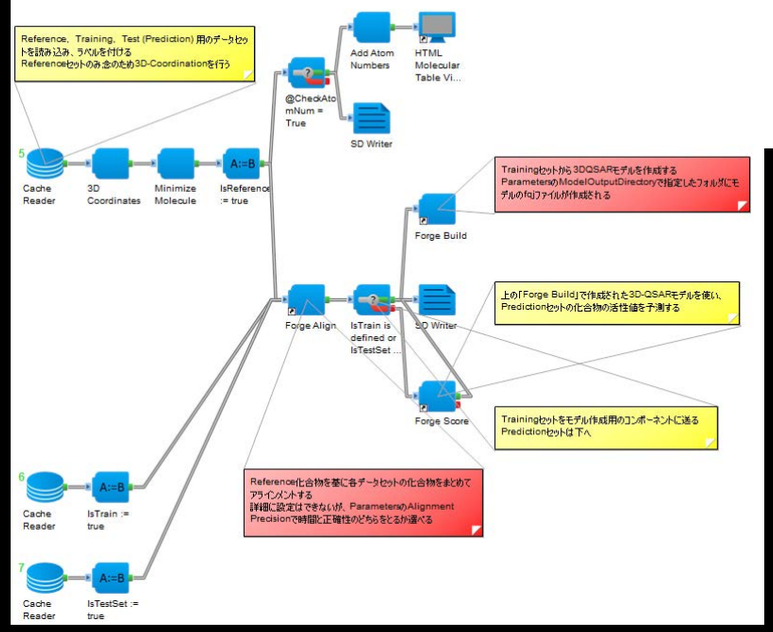
-DATA EXTRACTION-

- ✓ Mechanism of Action
- ✓ Target Information
- ✓ Activity Type & Value



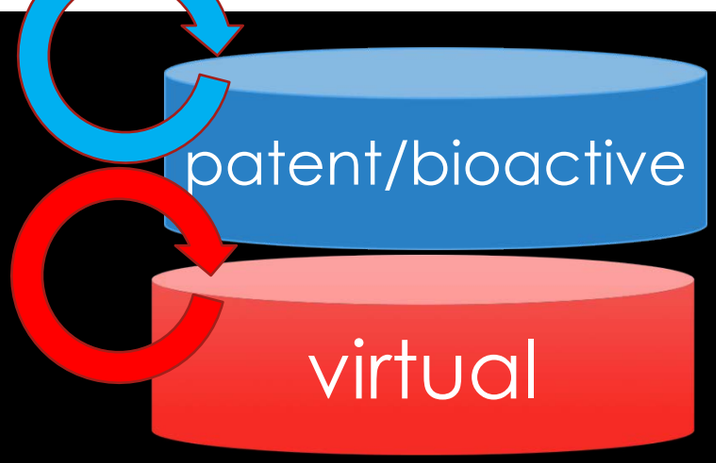
-3D-SAR Modeling-

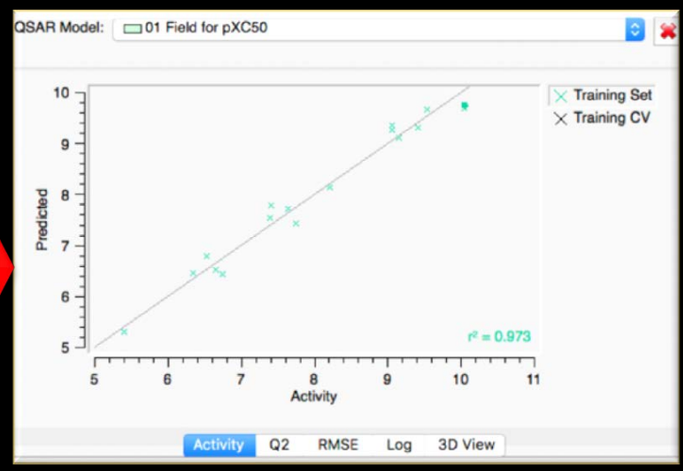
- ✓ 3D-Alignment



-Focused-Library Generation-

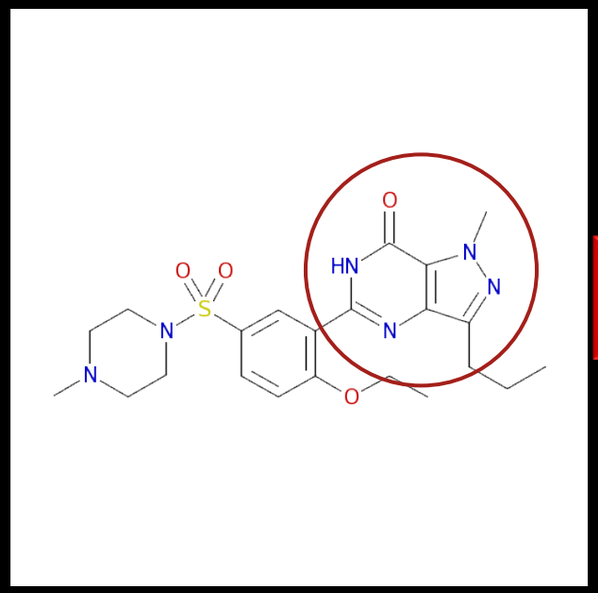
- ✓ Scaffold Hopping based on Electrostatic similarity.



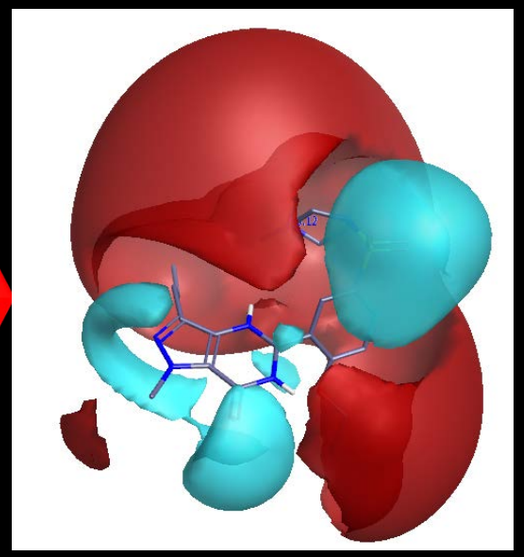


- ✓ 3D-QSAR Model Predicition

Phosphodiesterase 5A inhibitor (VIAGRA)

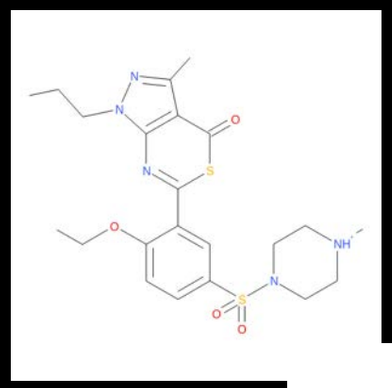


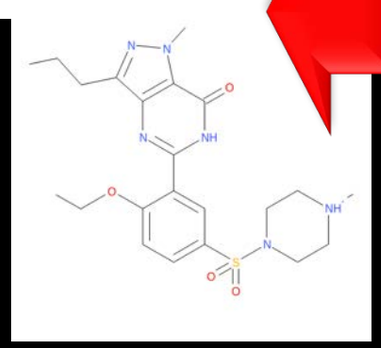
Sildenafil



Electrostatic Surface

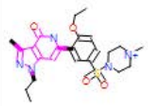
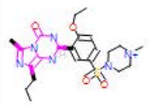
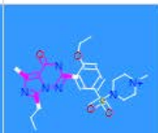
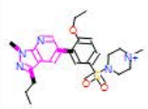
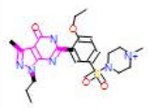
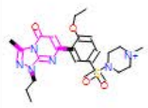
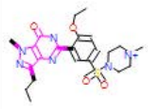
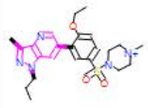
- ✓ Starting from Sildenafil, various scaffolds are generated by the similarity of electrostatic interaction surfaces.
- ✓ a library of compounds with the similar bioactivity is designed.





New Structures

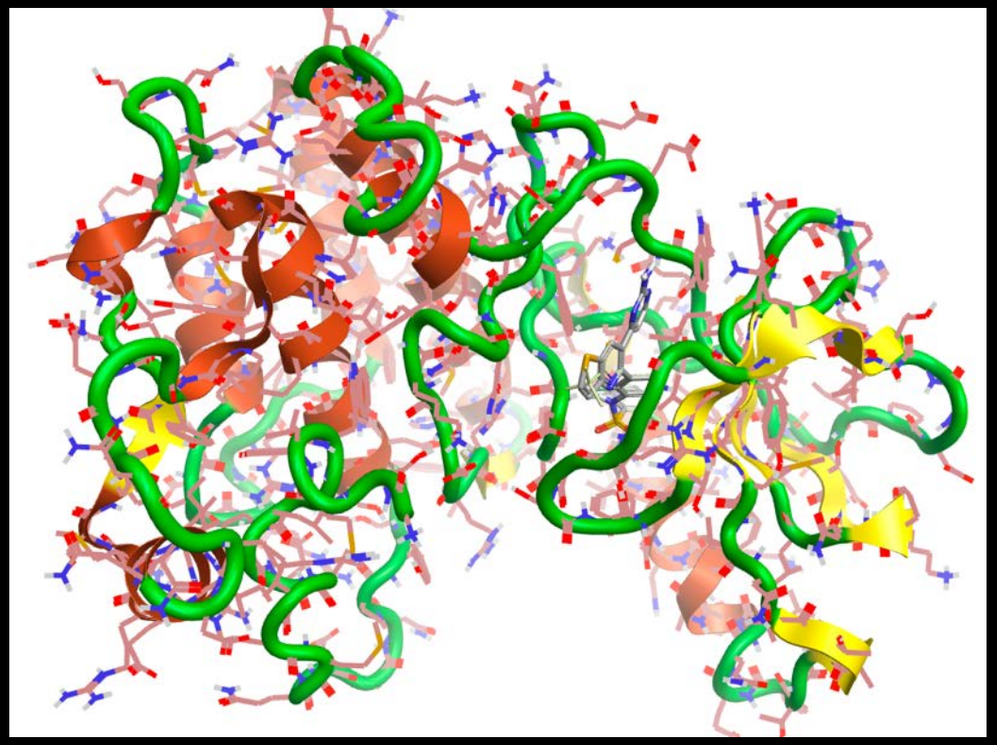
with Patent & Bioactive

Rank	Fav	Structure	BIF%	Score	2D Sim	Field Score	Shape Score	MW	Database	Radial Plot
1	☆		**1. SILDENAFIL**							
2	☆		69	0.957	0.775	0.926	0.989	478	ChEMBL_rare	
3	★		**3. VERDENAFIL**							
4	☆		66	0.954	0.665	0.919	0.988	459	ChEMBL_common	
5	☆		66	0.953	0.763	0.911	0.996	476	ChEMBL_common	
6	☆		64	0.951	0.62	0.906	0.996	476	ChEMBL_rare	
7	☆		64	0.95	0.886	0.904	0.996	476	ChEMBL_common	
8	☆		61	0.946	0.585	0.903	0.988	459	ChEMBL_veryrare	

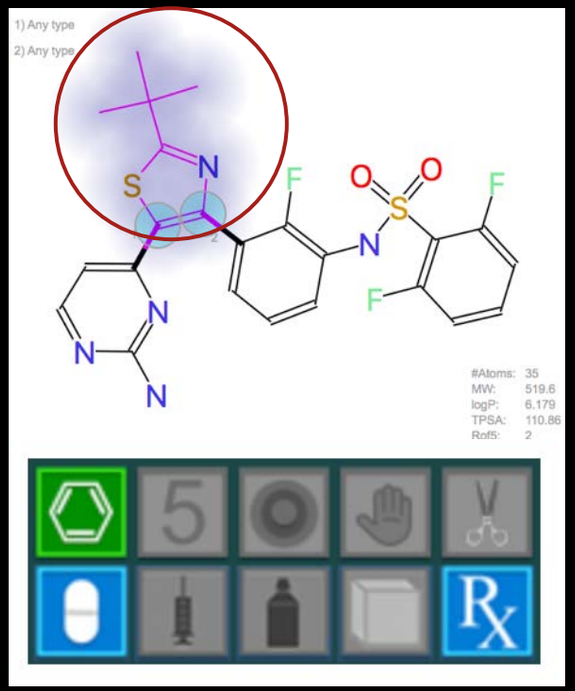
0.996

Possible Promising Structures

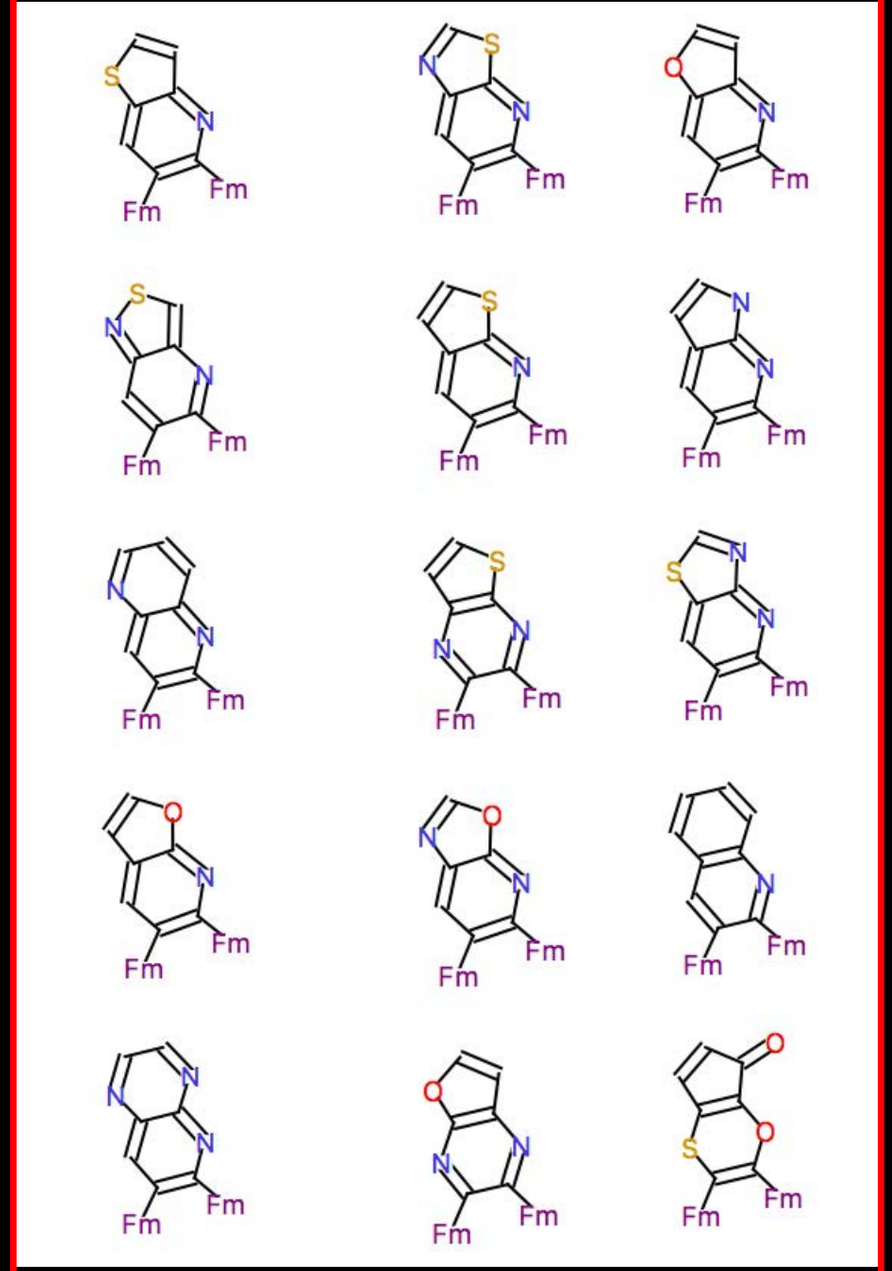
A Protein Try-Kinase (B-RAF)



B-RAF in complex with Dabrafenib (5csw)



with Virtual



Structural Alert Filter

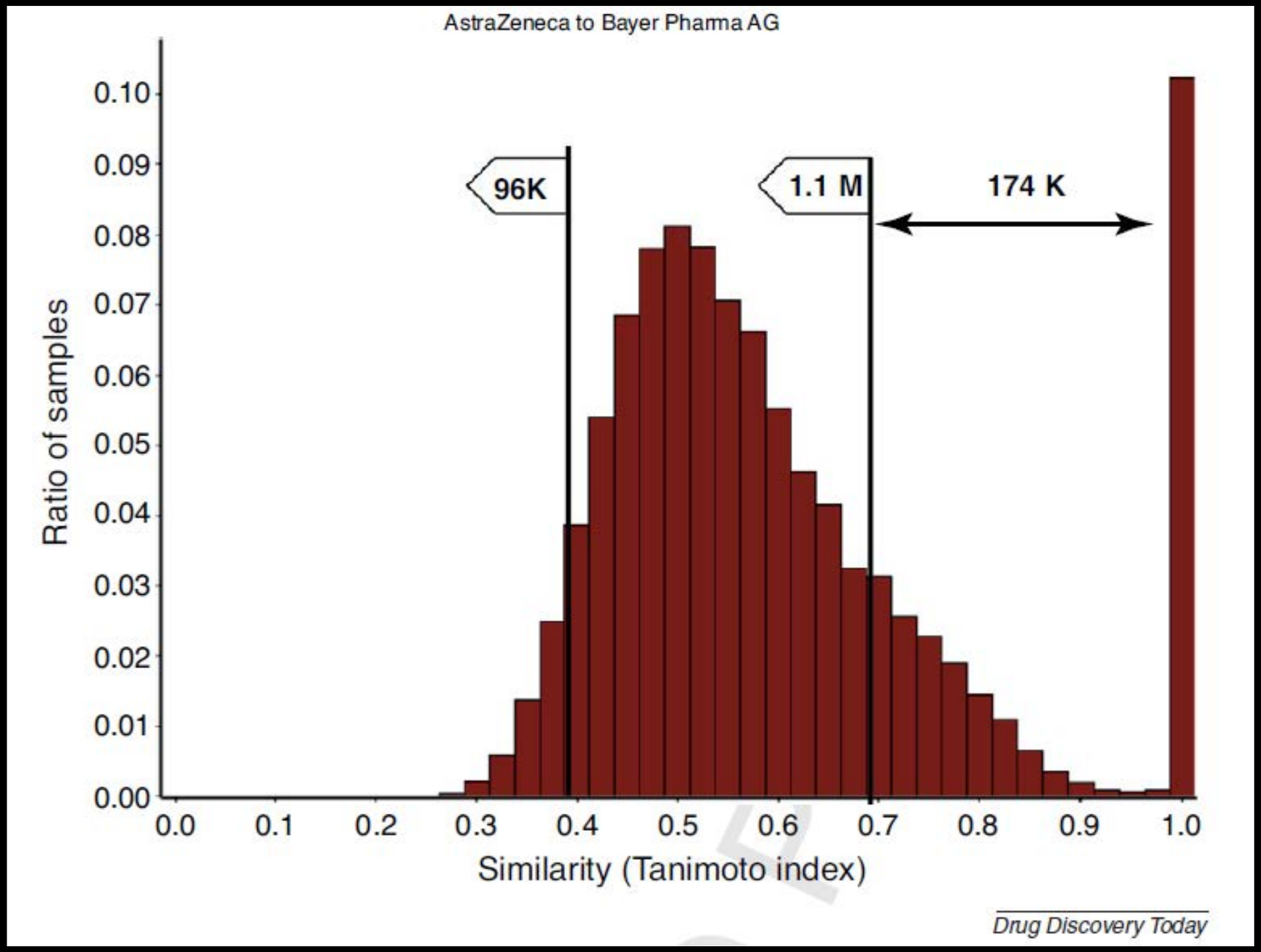
3D SAR Prediction

Drug-likeness

Novel Structure Library

COLLABORATIVE DRUG DISCOVERY

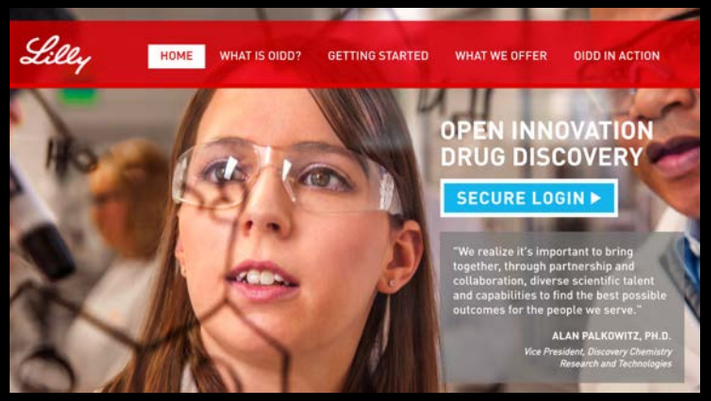
LIBRARY SHARING B/W ASTRAZENECA-BAYER

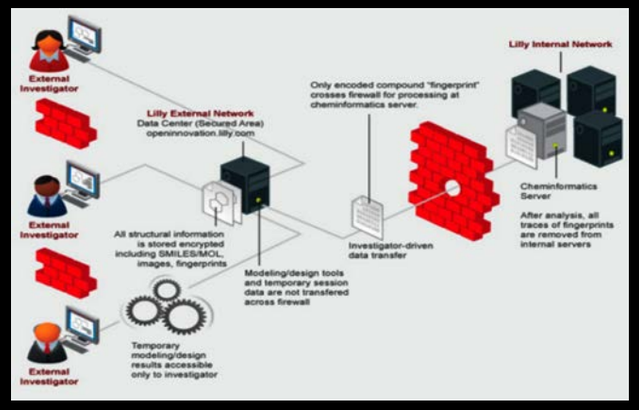


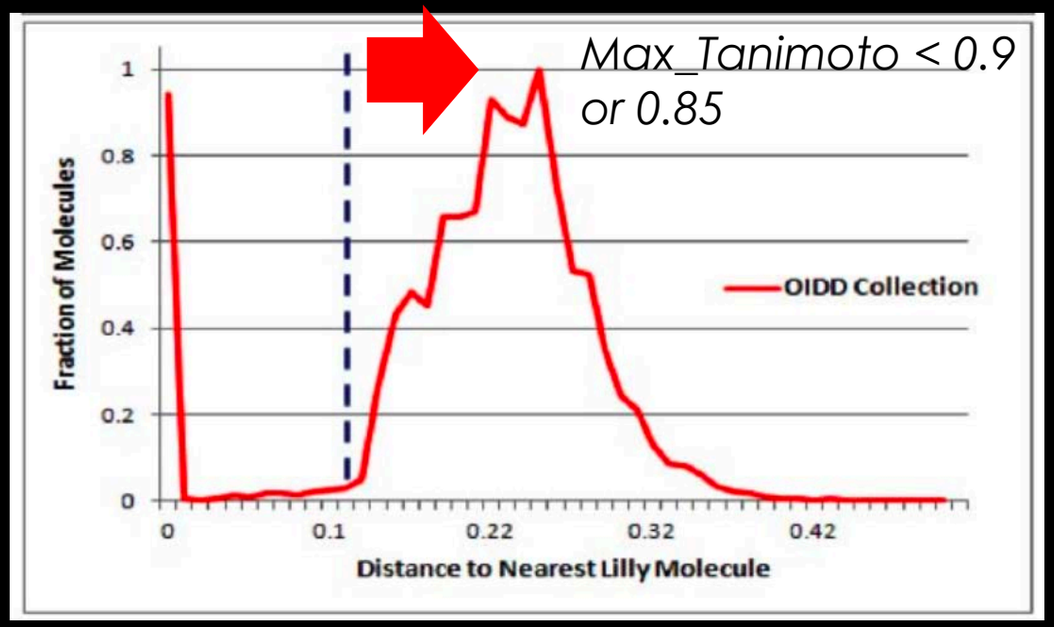
Big pharma screening collections: More of the same or unique libraries? the AstraZeneca-Bayer Pharma AG case (2013)

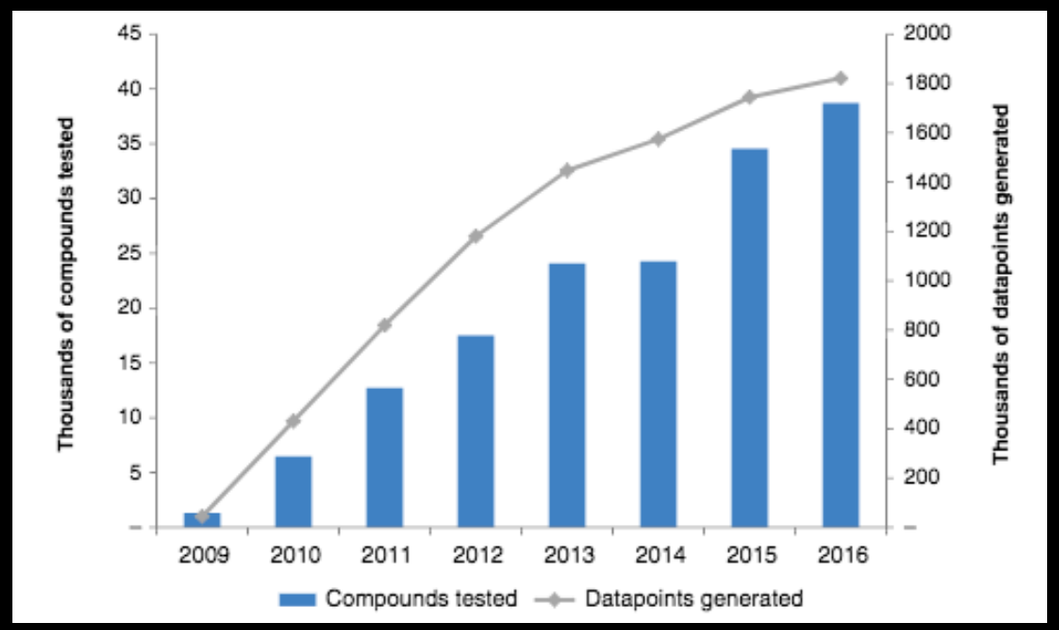
- ✓ Most compounds between AZ and BYR with <u>similarity of less than 0.7.</u>

LILLY'S OPEN INNOVATION PROGRAM





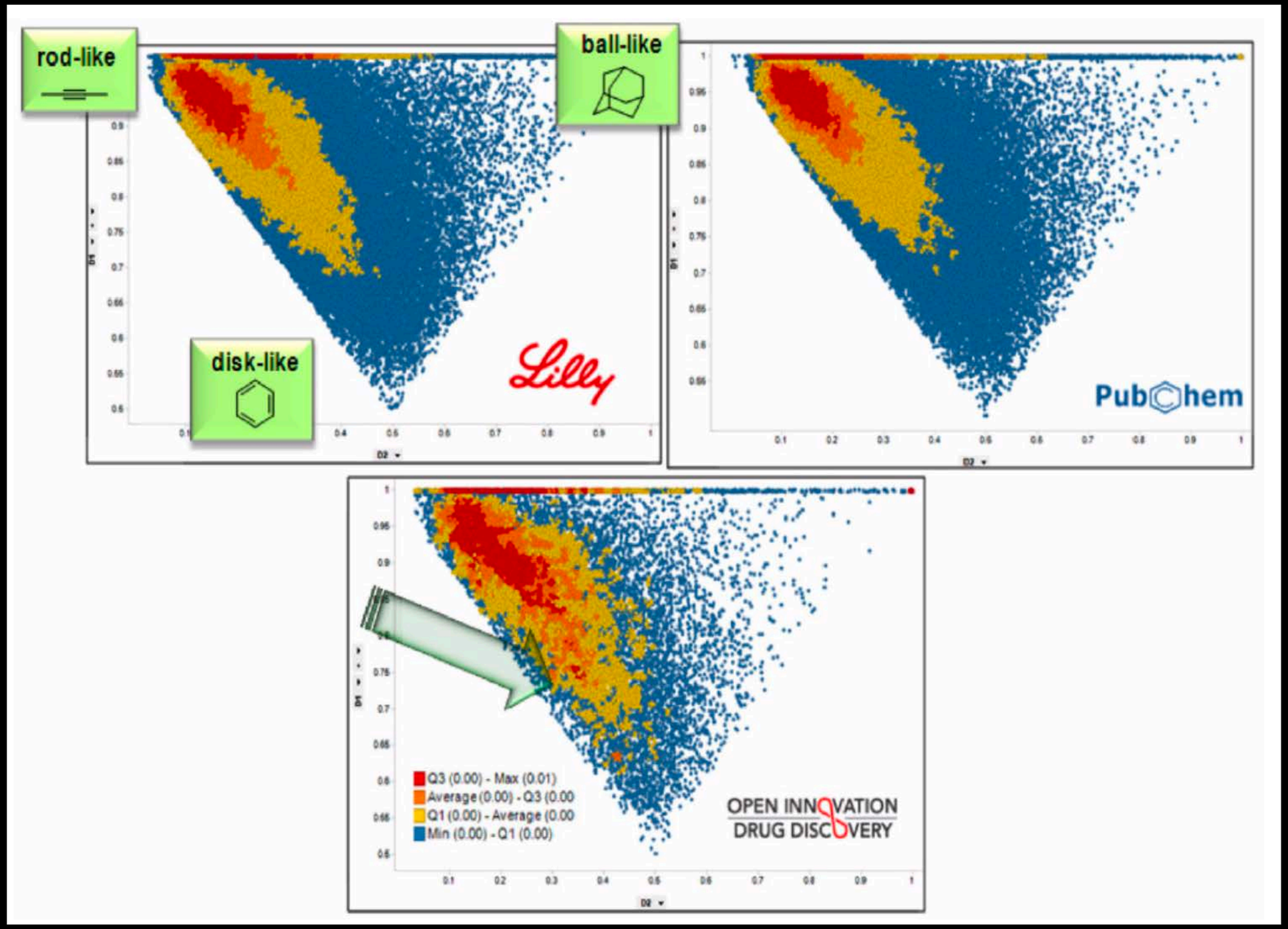




- Lilly collects compounds which didn't exist in their library from >300 external collaborators via secure informatics system.
- Total over 50K compounds tested including hits/leads for different targets.

Open Innovation Drug Discovery (OIDD): A Potential Path to Novel Therapeutic Chemical Space., Alvim-Gaston M, et al. **Current Topics in Medicinal Chemistry** 2014 vol: 14 pp: 294-303

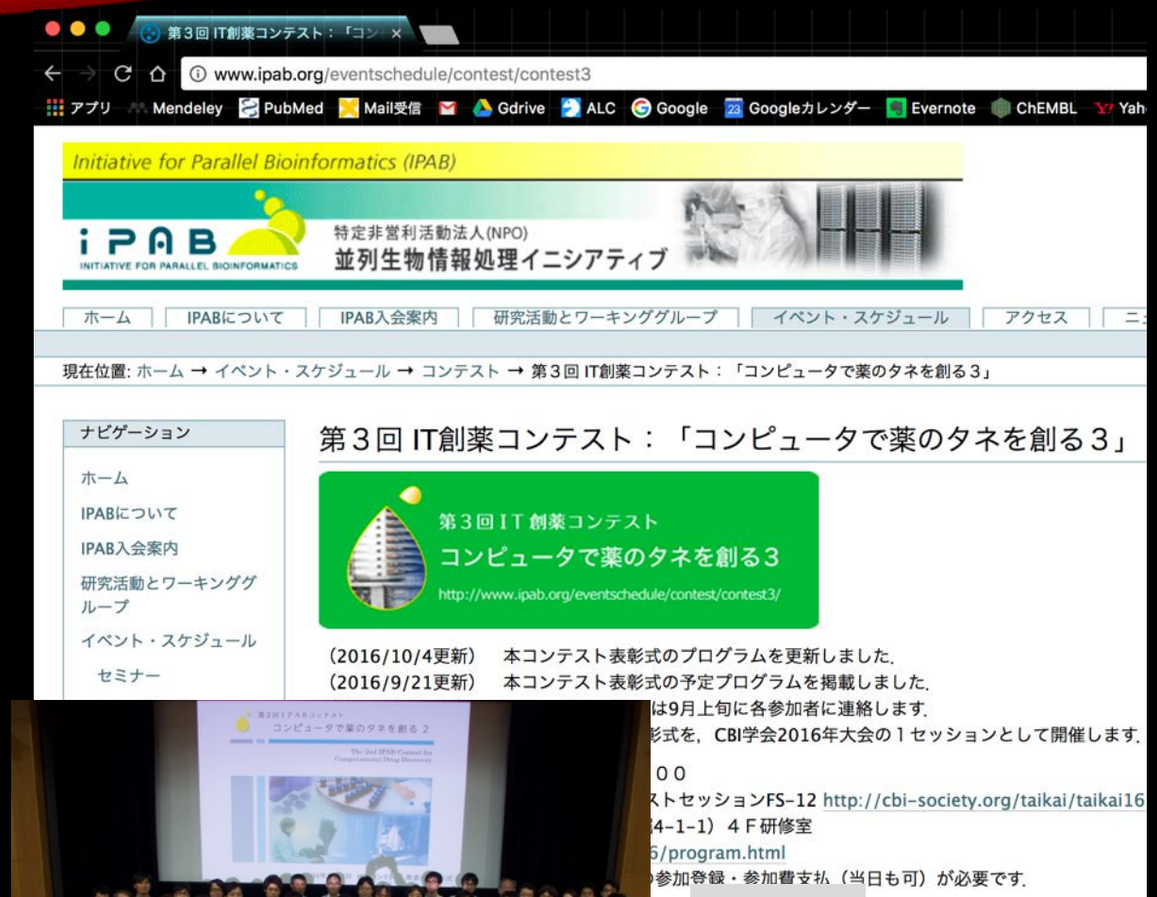
CHEMICAL SPACE COMPLEMENT

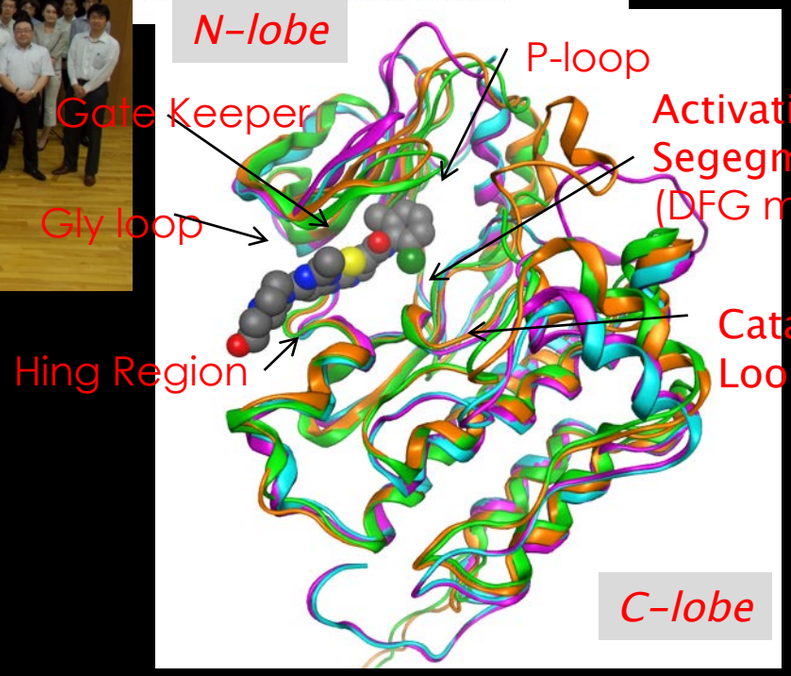


- ✓ Their original library was complemented with unique compounds that fill the gaps (disk-like).

CONTEST-BASED IN SILICO SCREENING

CONCEPT OF IPAB-CONTEST

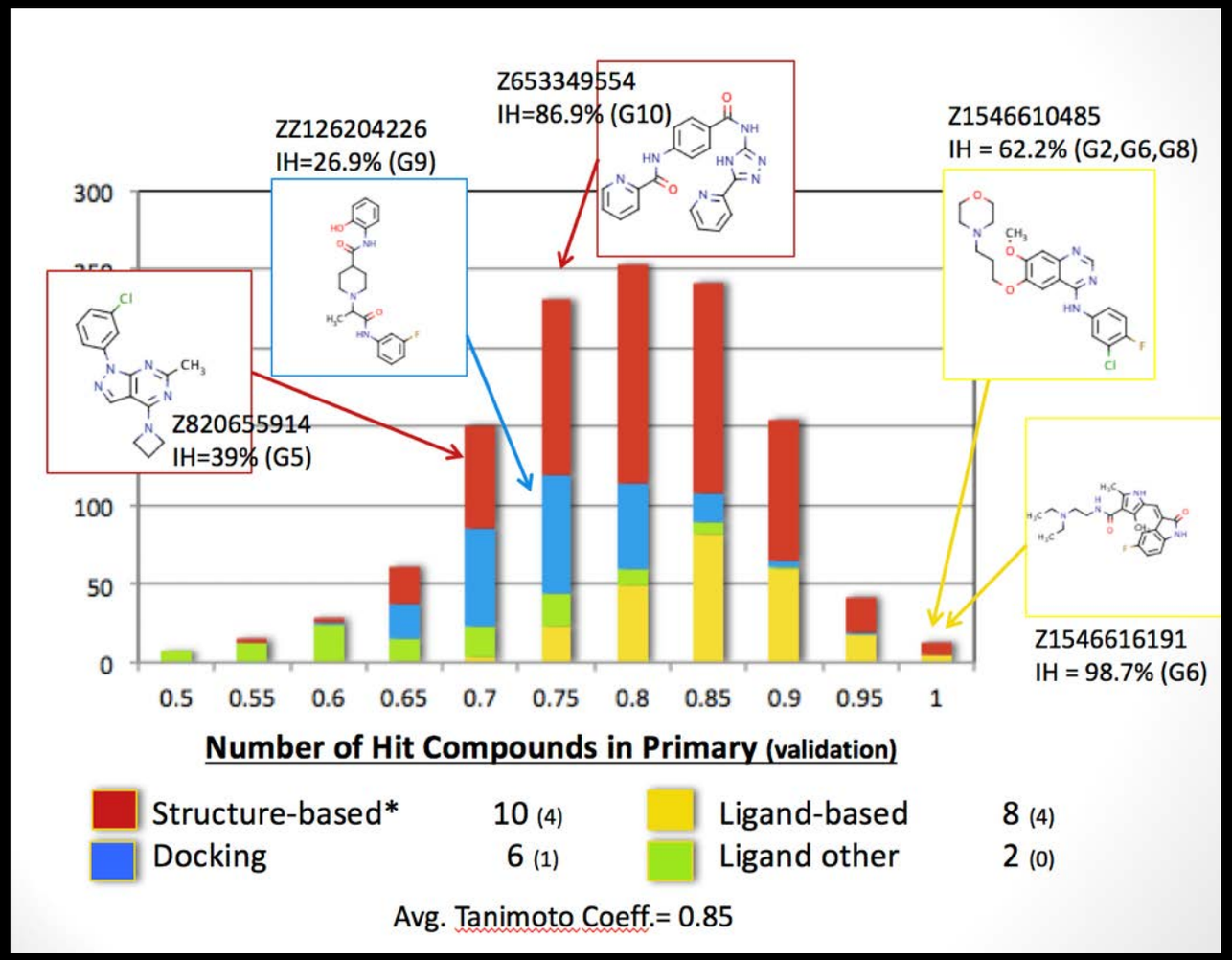




- A non-profit organization, IPAB (Initiative for PArallel Bioinformatics) and Tokyo Institute of Technology (東工大) organizes an open CADD contest.
- 10 teams joined to predict inhibitors for a Tyr Kinase (c-yes) using different computational methods applied.
- Assays were performed to confirm the submitted compound's activities later.

www.ipab.org/eventschedule/contest/contest3

IPAB CONTEST RESULT



Group ID	Modeling of Yes structure		
	3D structure prediction methods/tools	Template(s) PDB ID	Filter class
1	FAMS	1Y57	LB → SB[b]
2	Prime	2SRC	LB[a] LB&SB
3	Modeller	1Y57	LB[a] → SB LB[a] LB[a]&SB
4	—	—	LB[c]
5	Modeller	Close homologs	LB&SB
6	—	—	LB[a]
7	Prime	3G5D	SB
8	—	—	LB[a]
9	Prime	2SRC	SB
10	Modeller	1FMK	SB → LB[a]

chiba et al. scientific reports (2016, 2017)

SUMMARIES

- The understanding of the chemical space is important for designing efficient compound libraries.
- A library design informatics approach using drug discovery data and virtual compounds generates a drug-like focused library with novel structures.
- Collaborative drug discovery and informatics method may contribute to expand druggable chemical space.

ACKNOWLEDGEMENT

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