Progress of Compound Library Design Using In-silico Approach for Collaborative Drug Discovery

Kaz Ikeda, Ph.D.

Keio University
Self Introduction

Keio University, Tokyo, Japan (Established in 1858)
- Bio/Chemo-informatics
- in-silico drug discovery
- Structural biology, NMR (Prof. Osawa)
Today’s Topics

- Collaborative drug discovery project and compound library design
- An in-silico collaborative screening project in Japan
- Refinement of docking simulation using Flare & WaterSwap
Open Innovation & Collaborative Drug Discovery

Lilly’s Open Innovation Program

European Lead Factory’s Joint Library (JECL)

- Open innovation and collaborative drug discovery is expanding due to increasing the cost of drug development.
- Lilly expands their library's chemical space by compounds from external collaborators.
- The ELF project collected over 300K druglike compounds from 7 big pharmaceutical companies for finding lead compounds.
Japan’s AMED Collaborative Screening Library (DISC: Drug Discovery Initiative Compound library)

In Japan, 22 pharmaceutical companies participated and submitted their compounds (total 200K) to the collaborative compound library (DISC library).

Keio University is involved with analyzing and designing the DISC library using informatics approach.

HTS campaign is carried out by the Japan’s medical agency (AMED) using the seeds from academia.

(Budget Amount)
2.3 million$/year [Total: ~10 M]
Keio Univ is now developing an in-silico platform to analyze the consortium-based compound-library without exact structure data.
Library Design Protocol Using Drug Discovery Data and Cresset Tools

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

- Focused-Library Generation-
  ✓ Scaffold Hopping based on Electrostatic similarity.

-3D-SAR Modeling-
  ✓ 3D-Alignment

-3D-QSAR Model Prediction

✓ Focused Library & Core Library
An in-silico collaborative screening project in Japan (IPAB-Contest)
In-silico Blind Prediction Contest (IPAB)

- The non-profit organization IPAB (Initiative of PArallel Bioinformatics in Japan) organizes an open Computer Aided Drug Design contest.

- 10 teams participated to predict inhibitors of 2 targets (c-yes Tyr kinase and Sirtuin-1) from 2.5 million compounds in a commercial library using various calculation methods.

- Assay was performed to confirm the activity of over 3,000 submitted compounds.

www.ipab.org/eventschedule/contest/contest3
Methods and Submitted Compounds in the IPAB Contest

<table>
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- Different groups use different methods (LBDD, SBDD, etc).
- Participants submitted unique and diverse compounds.

Tanimoto Similarity Histogram to Known Ligands

Refinement of Docking Simulation using Flare & WaterSwap
Docking study: Sirtuin-1 inhibitor

Prepare & Generate a Grid for Docking

PDB: 4ZZI (HET CODE: 1NS)

Electrostatic Surface Mapping by Forge
Result of Docking study

Re-docking *an inhibitor of the EX-527 analog* by Flare

X-ray structure (Red)
Docked conformation (Cyan)

RMSD = 1.48 Å
(Normal Mode)

✓ We succeeded in regenerating the conformation of the ligand-protein complex of inhibitor within 1.5 Å.
Focused Library Generation by Flare VS

Flare Top 500: 37/500 (7.4%)

Extracted a focused library in which the hit rate of the compounds was enriched to x4 times than that of the screening compounds.
Identification of Binding Site Residues by WaterSwap

Preparation of WaterSwap

- Charge Method: Gasteiger
- Minimize Energy Tolerance: 0.25 kcal/mol
- Solvate Box Buffer: 10Å
- Iterations: 400ns
- Water Monitor Distance: 7Å

WaterSwap is a thermodynamic simulation approach for analyzing ligand-protein energetics.

Energy Distribution of WS

(30 hours, 32xCPU cores)
The docking pose of the inhibitor in ChEMBL has been refined.

When water molecules exist, a hydrogen-bond network (green) via water was made, and its ΔG significantly has been improved.

A new grid will be used for further hit expansion and lead optimization.
Summaries

- We are developing a library design protocol for filling in the gap in the chemical space for a collaborative screening project in Japan using the Cresset software.

- The in-silico collaborative screening project succeeded in finding diverse hit compounds.

- Flare Docking and WaterSwap may help improving docking poses and generating a structure-based focus library for a specific target.
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