データ統合と計算の融合による創薬研究

水口　賢司

http://mizuguchilab.org
kenji@nibiohn.go.jp

NIBIOHN
国立研究開発法人
医薬基盤・健康・栄養研究所
National Institutes of
Biomedical Innovation, Health and Nutrition

MIZUGUCHI
GROUP

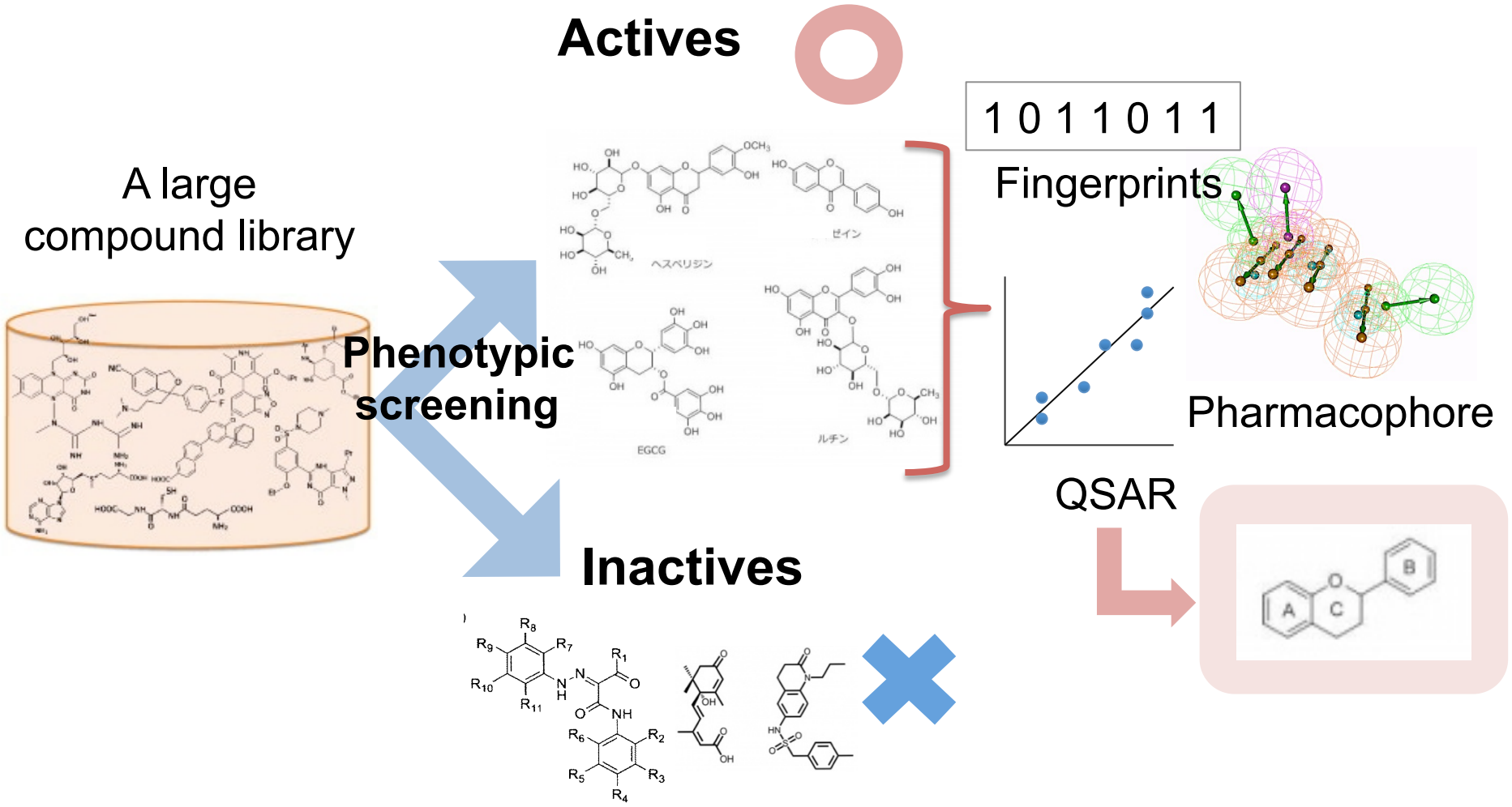
Outline

- Phenotypic and target-based screening with ligand-based and structure-based drug design
- Systems biology based approach
- Data integration
- Application to cancer drug discovery

Phenotypic screening and target-based screening

http://www.sulsa.ac.uk/research-facilities/uk-npsc/phenotypic-screening

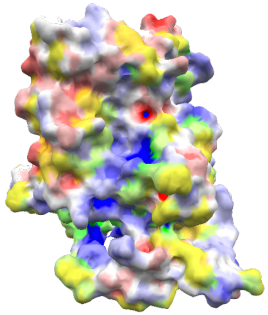
Ligand based drug design (LBDD)



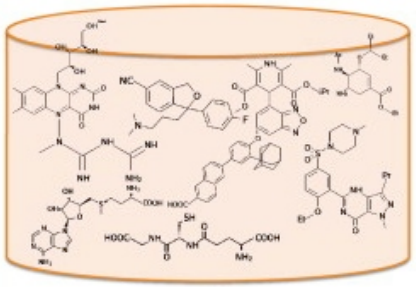
http://www.shirokawa.jp/column/amakura_yoshiaki/366/

Structure based drug design (SBDD)

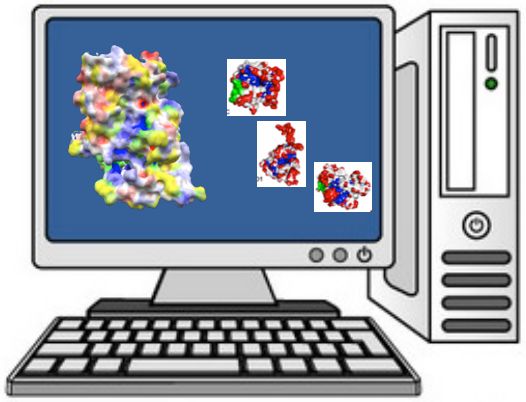
Target



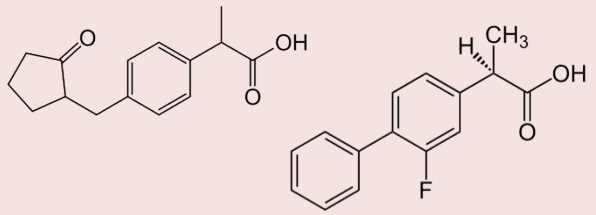
A large compound library/database



Docking
Scoring

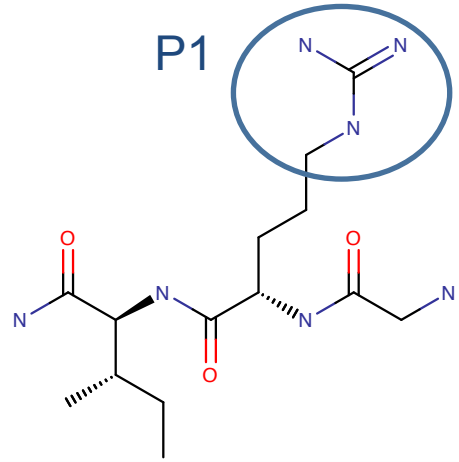


List of compounds for assays



How SBDD can assist target-based screening

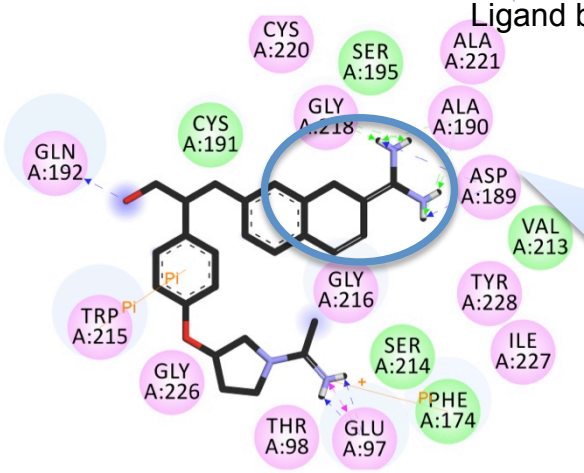
e.g., FXa inhibitors

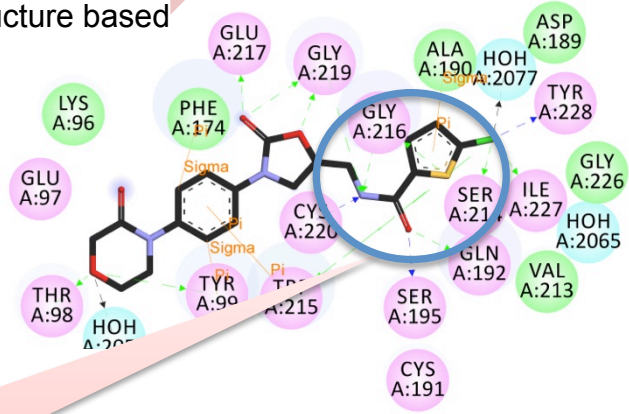


A basic fragment at P1 site was shown to be essential for mimicking the natural substrate by ligand based approaches

Dabigatran ← Ligand based

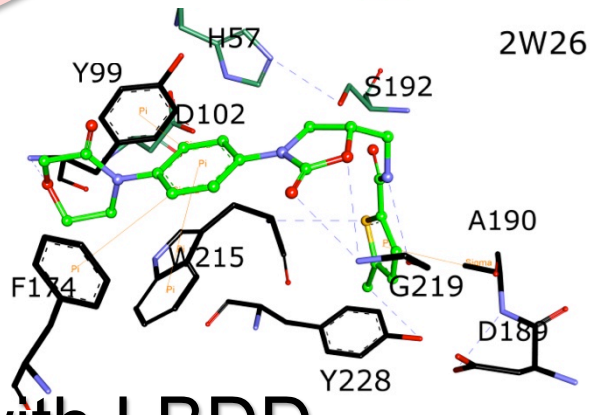
Structure based → Rivaroxaban





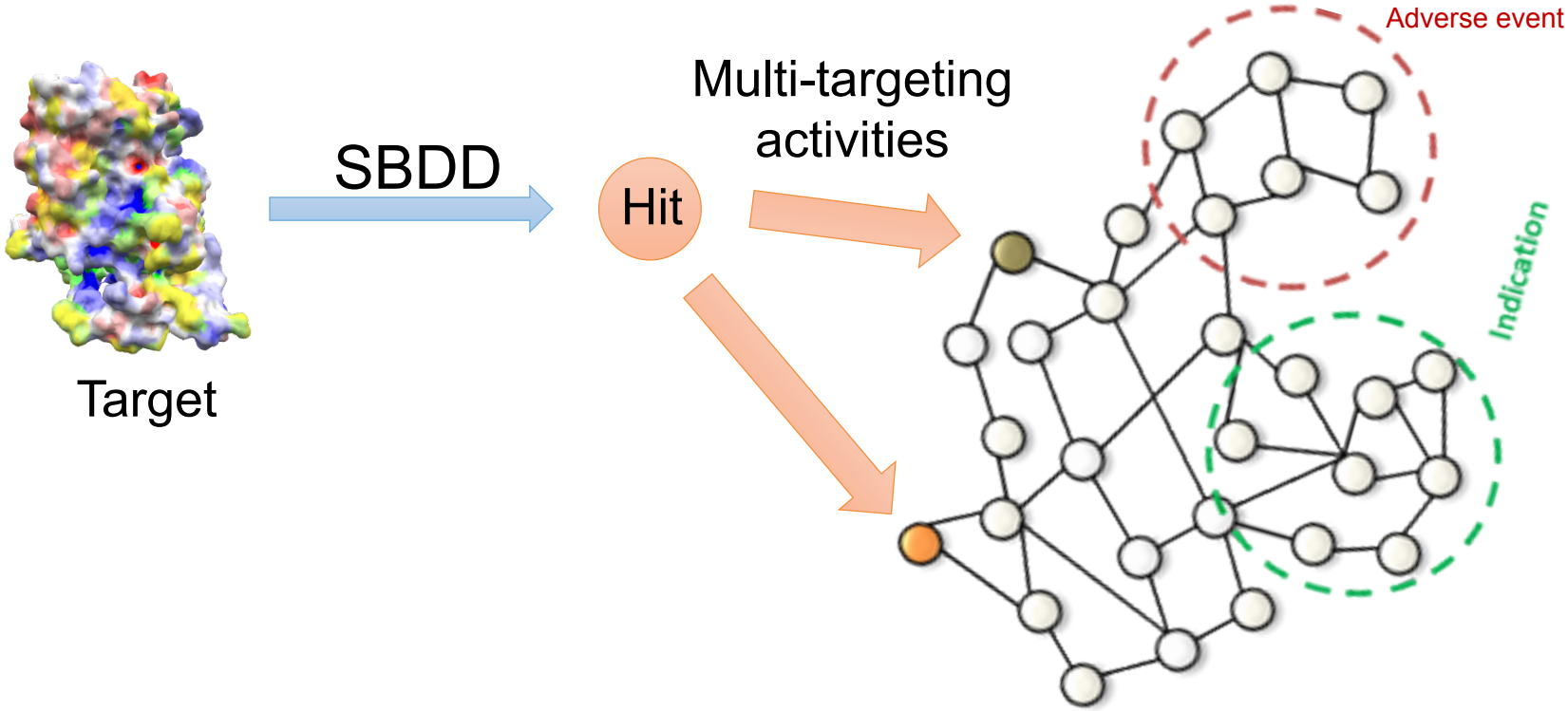
<u>Unfavorable</u> ADMET profiles
(Poor oral bioavailability)

A neutral fragment
→ **<u>Favorable</u> ADMET profiles**



SBDD solved the problem with LBDD

Fundamental limitations of structure-based approaches



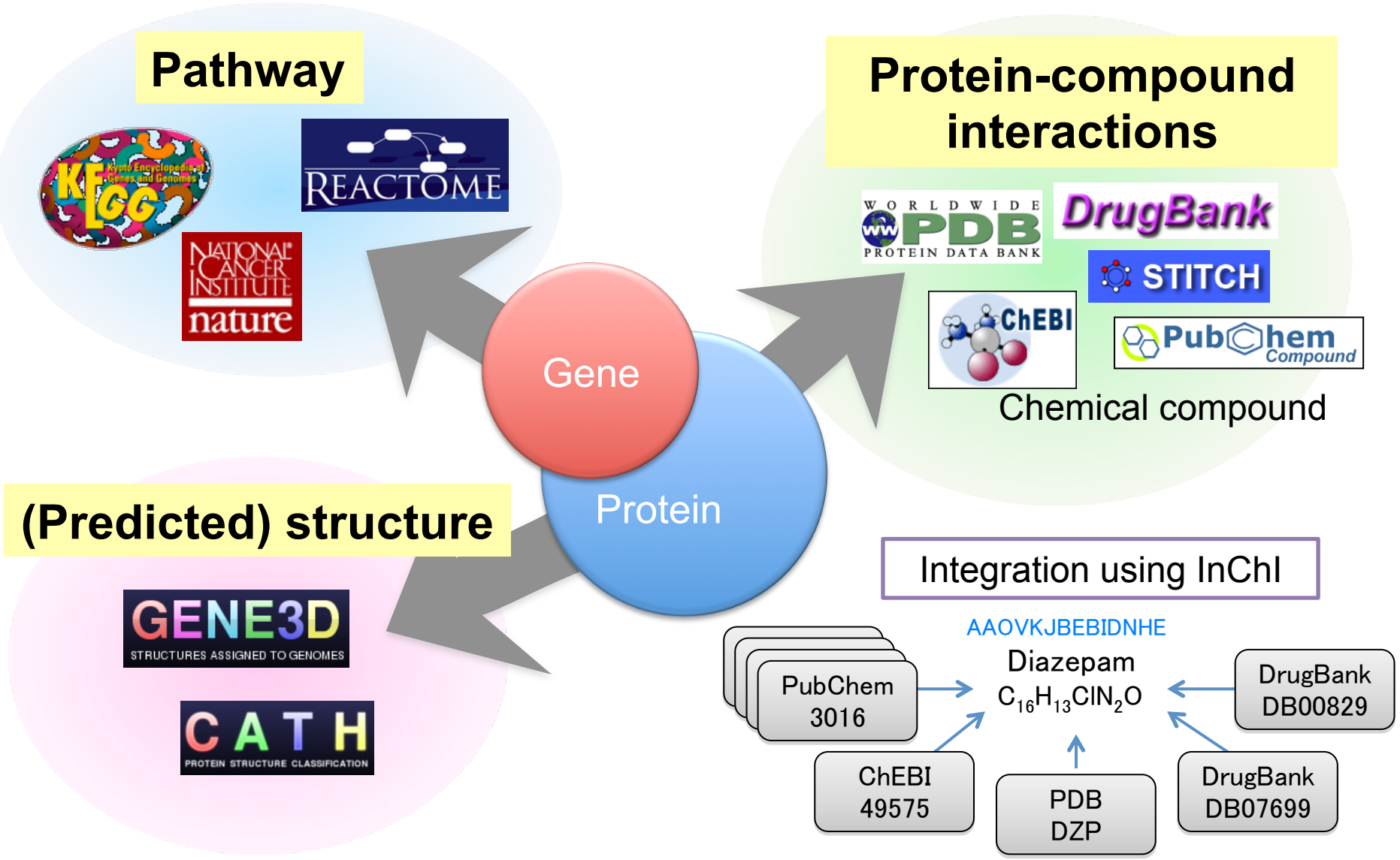
The systems biology approach to drug discovery

Healthy Individual **Disease State** **Treatment Prediction**

Source: Ingenuity Pathway Analysis, Causal Network Analysis suite

Prathipati and Mizuguchi, Current Topics in Medicinal Chemistry (in press)

Data integration

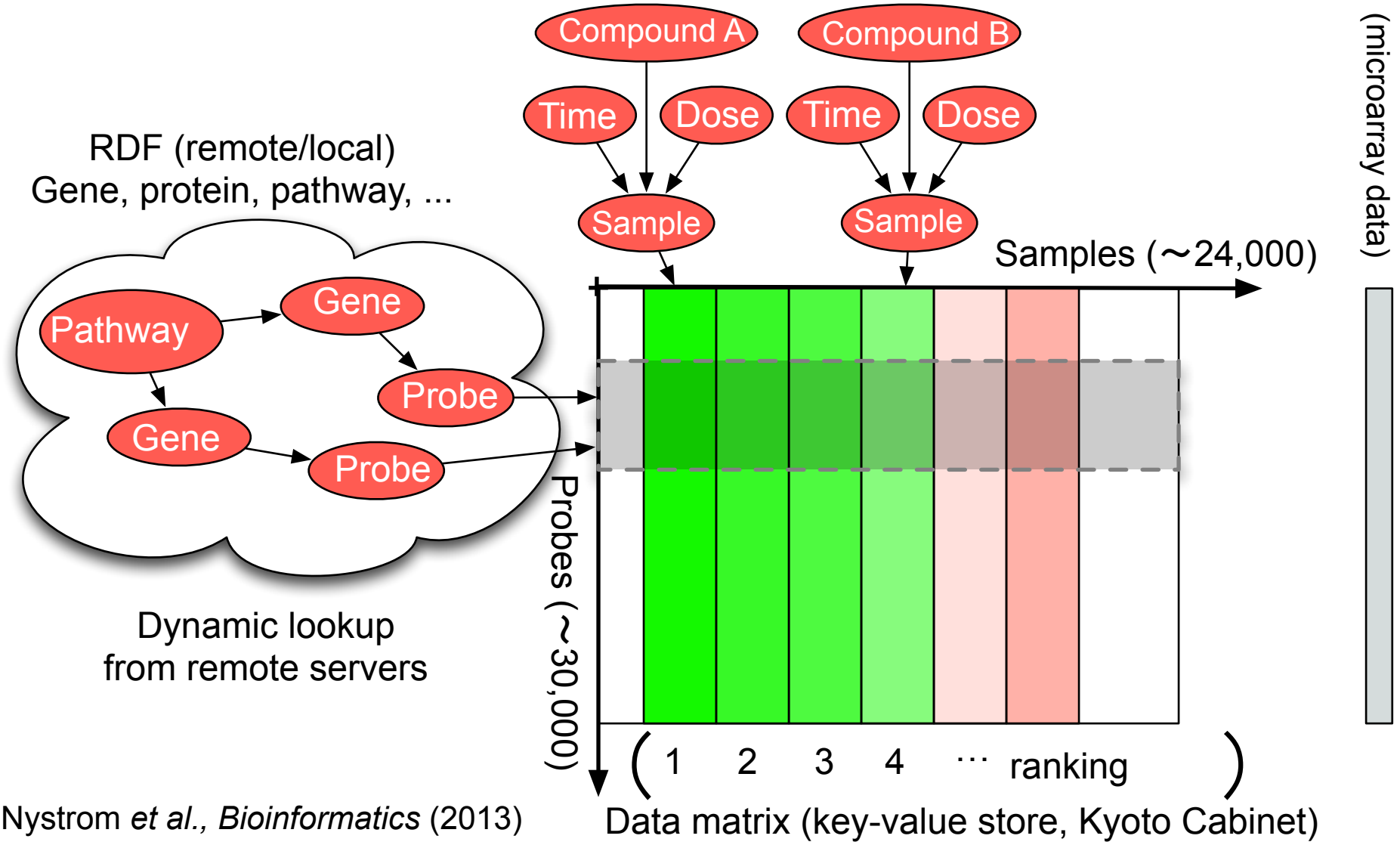


Data warehouse system

A Data warehouse compiles the contents of multiple databases to fit a common data model (Stein 2003, *Nat Rev Genetics* 4, 337-345)

Toxygates: an integrated platform for toxicogenomics data analysis

http://toxygates.nibio.go.jp/

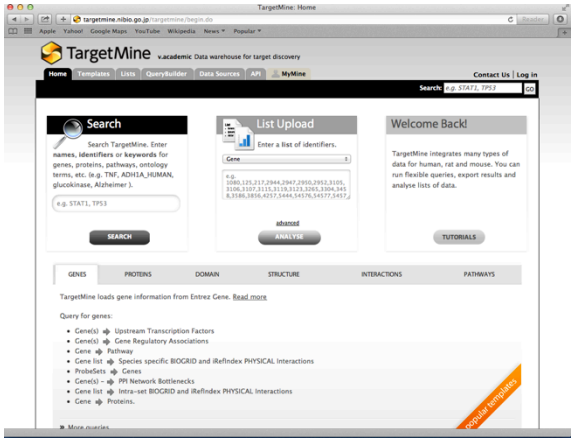


Nystrom *et al., Bioinformatics* (2013)

TargetMine

Data warehouse for drug target prioritization

http://targetmine.mizuguchilab.org

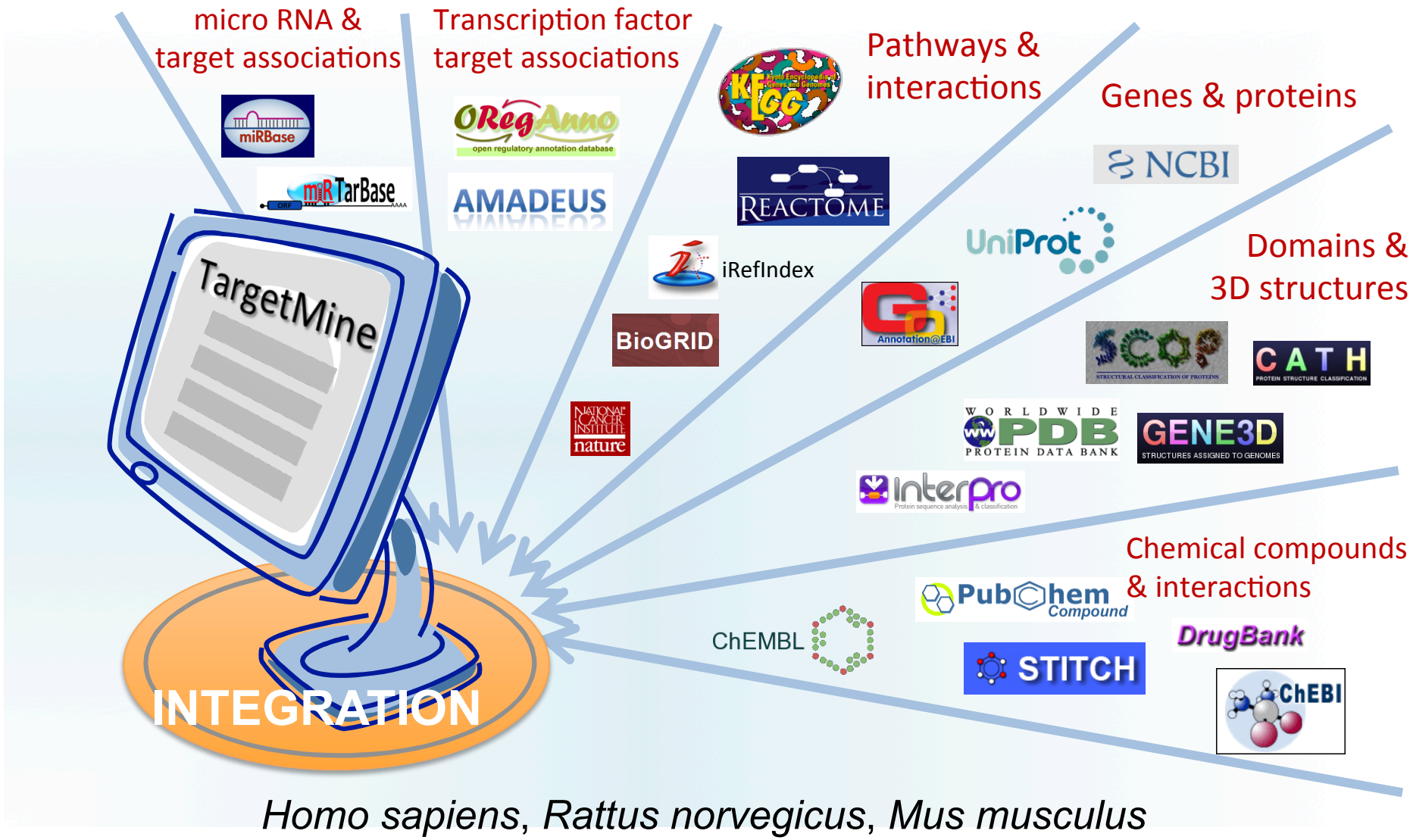


- Integrate a wide range of data sources.
- Enable complicated searches that are difficult to achieve with existing tools.
- Custom annotations and in-house data.

Powered by InterMine at the Cambridge Systems Biology Centre

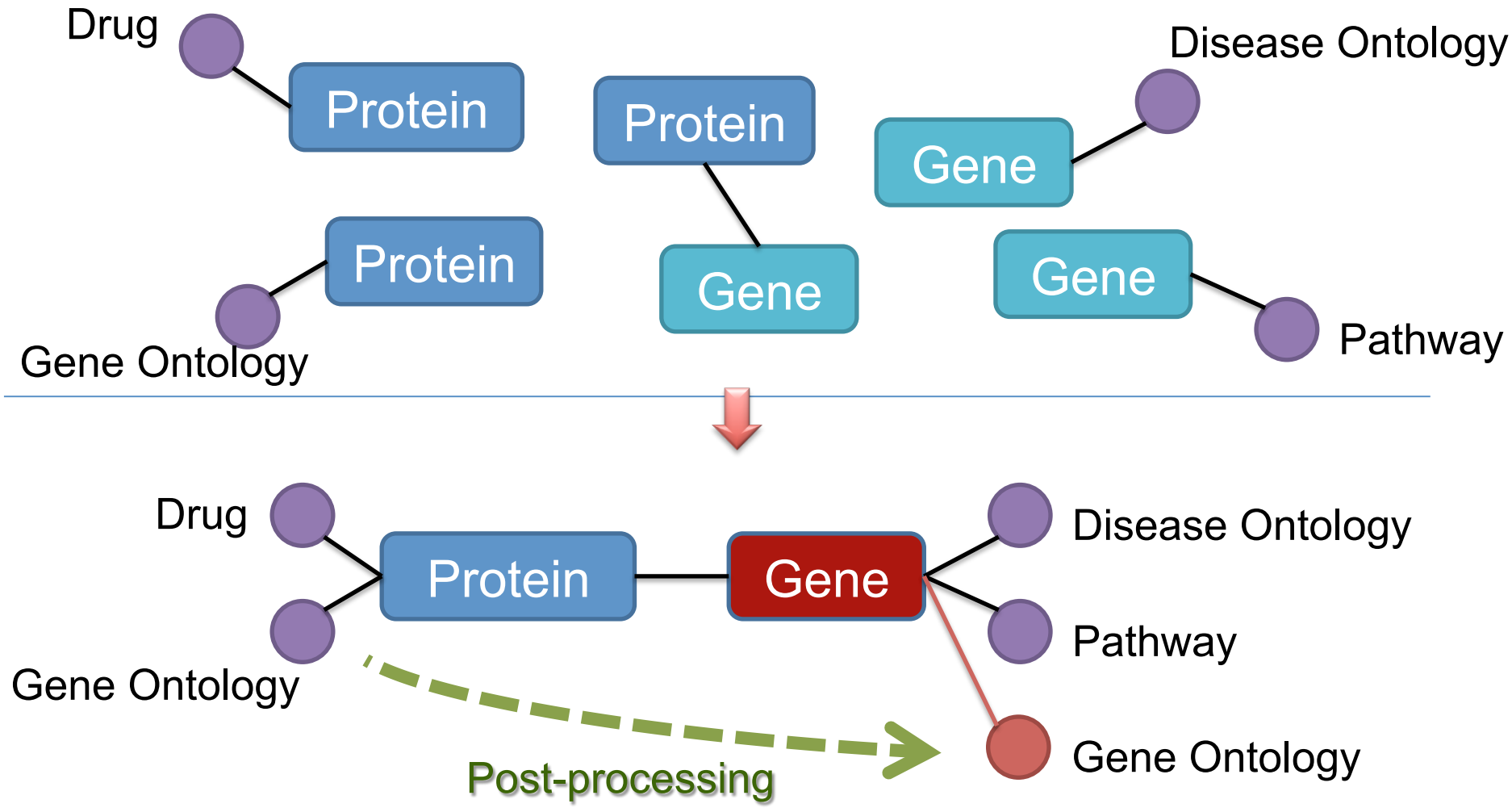
Chen *et al.*, ***PLoS ONE*** 6(3): e17844 (2011)

Data sources in TargetMine



Homo sapiens, *Rattus norvegicus*, *Mus musculus*

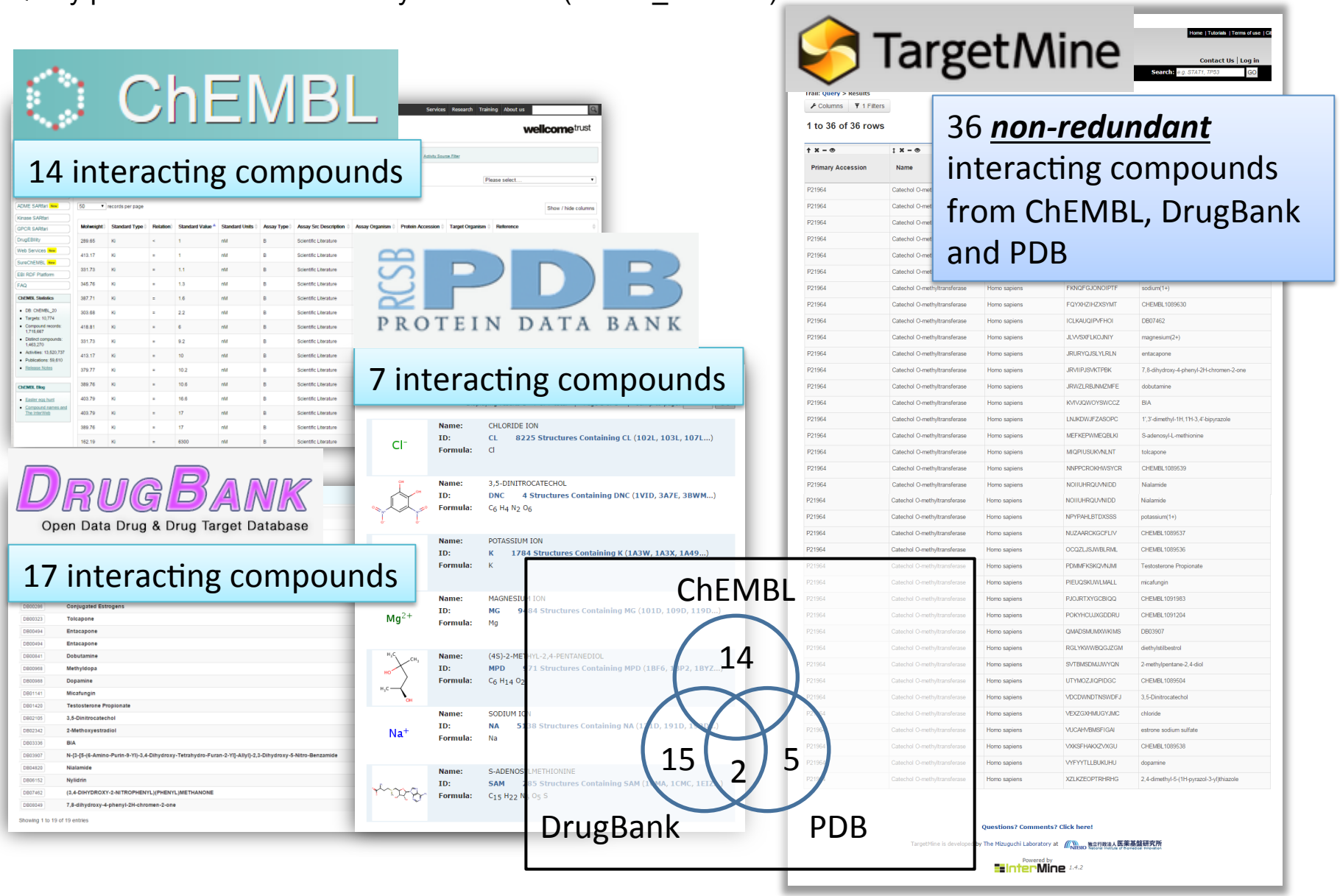
How InterMine integrates data



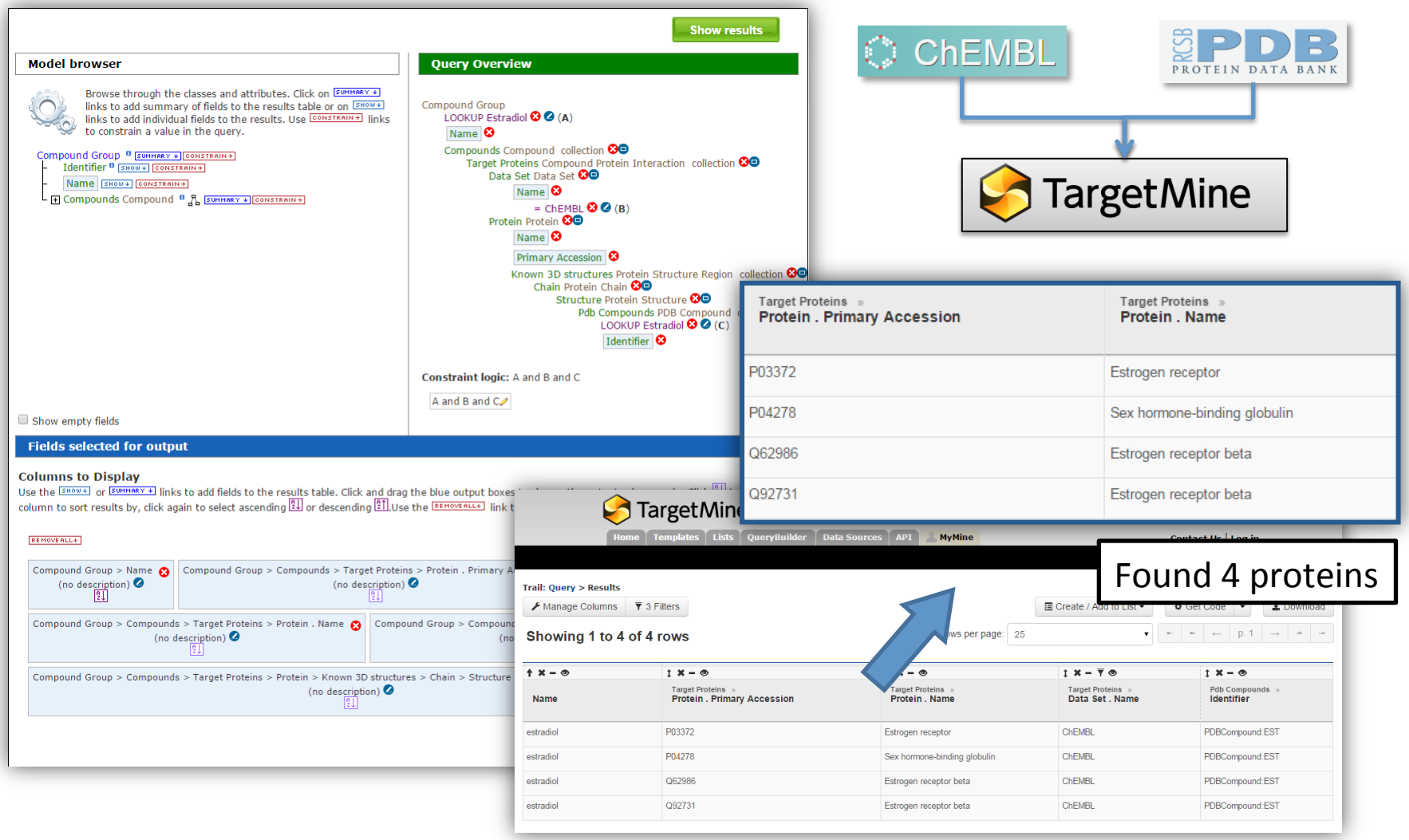
(Java, PostgreSQL)

Given a protein, find all the compounds that target this protein

Query protein: Catechol O-methyltransferase (COMT_HUMAN)



Given a drug, find all the ChEMBL targets that have been co-crystalized with that drug



Targeting cancer stem cells using a systems biology approach

Philip Prathipati

In silico スクリーニングコンテスト

Wetなキナーゼアッセイで活性が認められる化合物を同定

2014年7月18日

日経バイオテク ONLINE

Chiba et al., Scientific Reports (in press)