

データ統合と計算の融合による創薬研究

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*National Institutes of
Biomedical Innovation, Health and Nutrition*

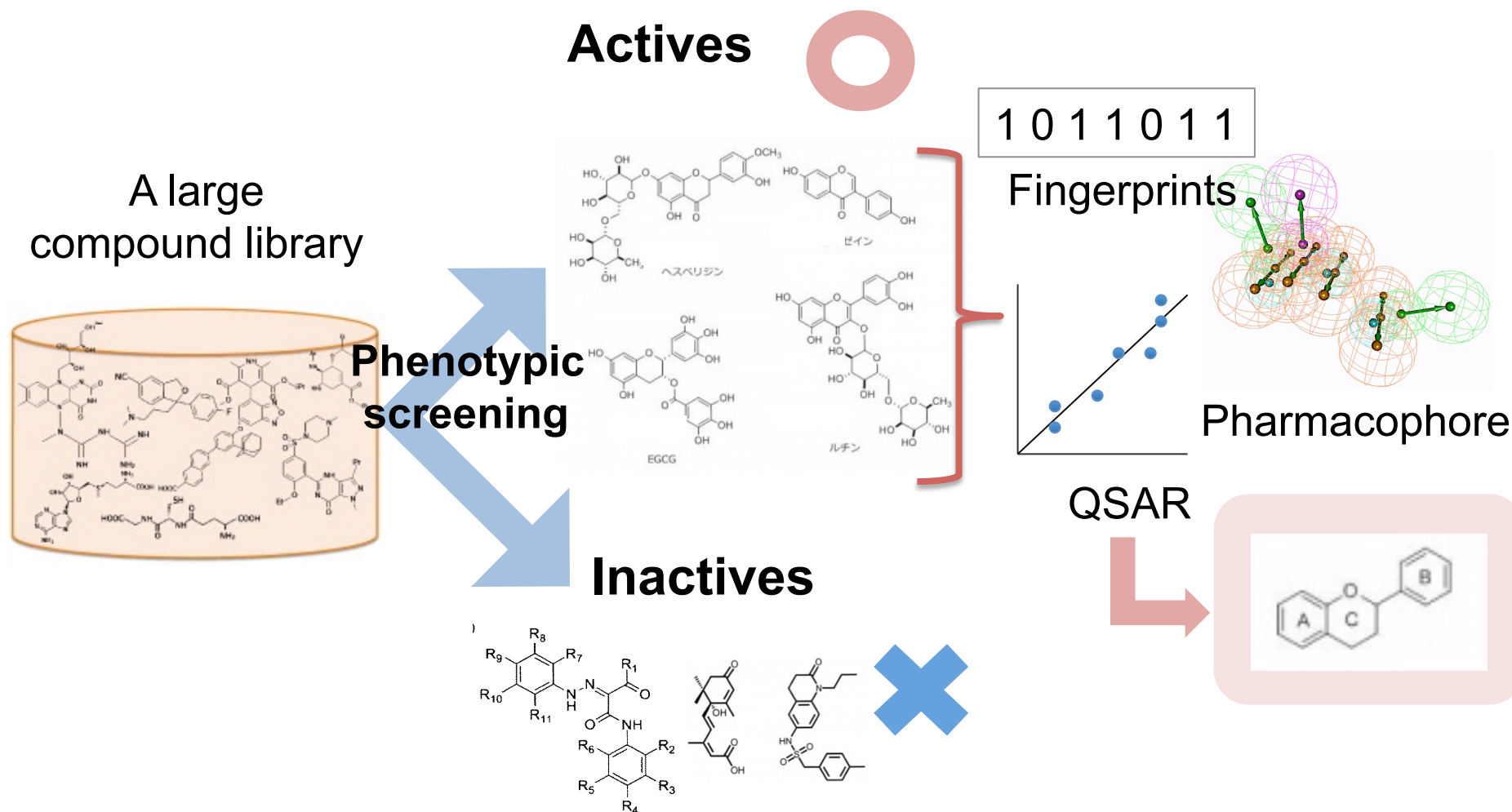


Outline

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

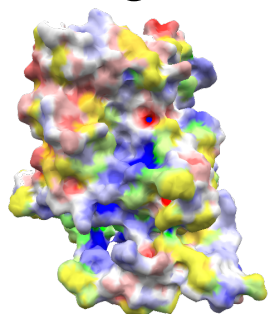
Phenotypic screening and target-based screening

Ligand based drug design (LBDD)

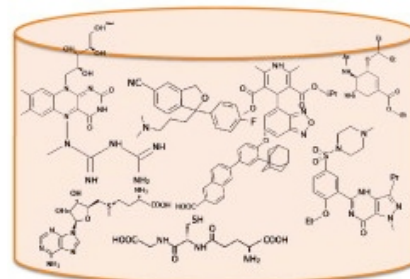


Structure based drug design (SBDD)

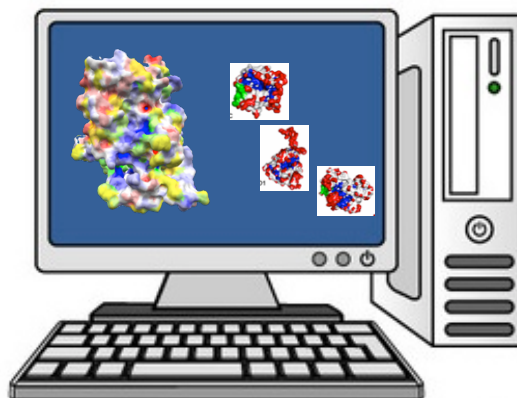
Target



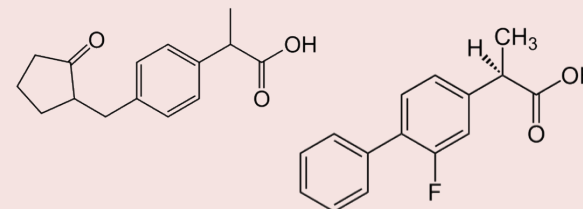
A large compound library/database



Docking
Scoring

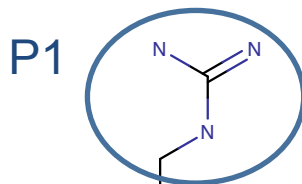


List of compounds for
assays



How SBDD can assist target-based screening

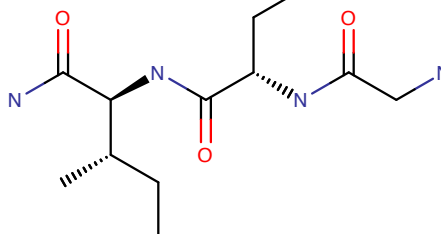
e.g., FXa inhibitors



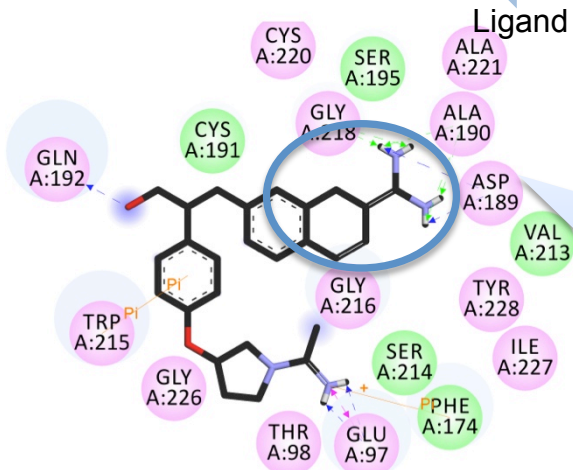
A basic fragment at P1 site was shown to be essential for mimicking the natural substrate by ligand based approaches



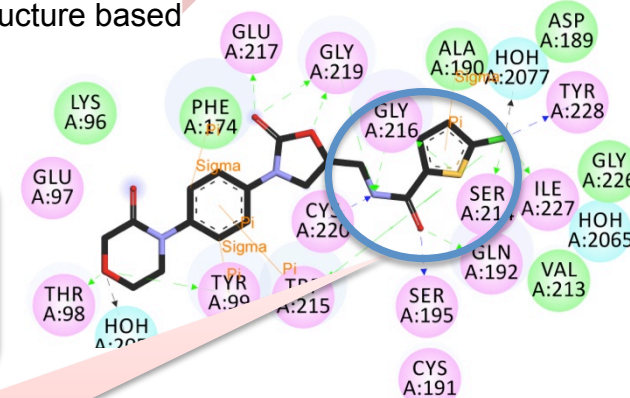
Ligand based



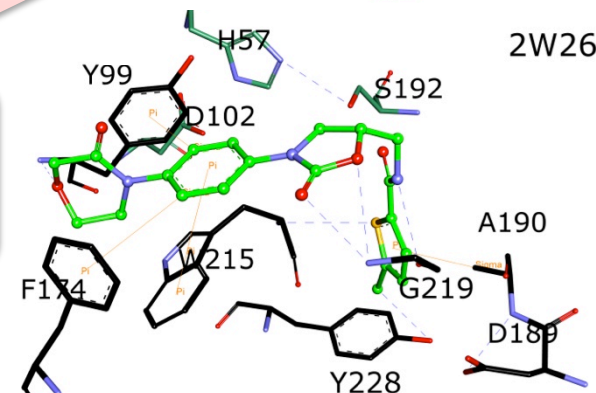
Structure based



**Unfavorable ADMET
profiles**
(Poor oral bioavailability)

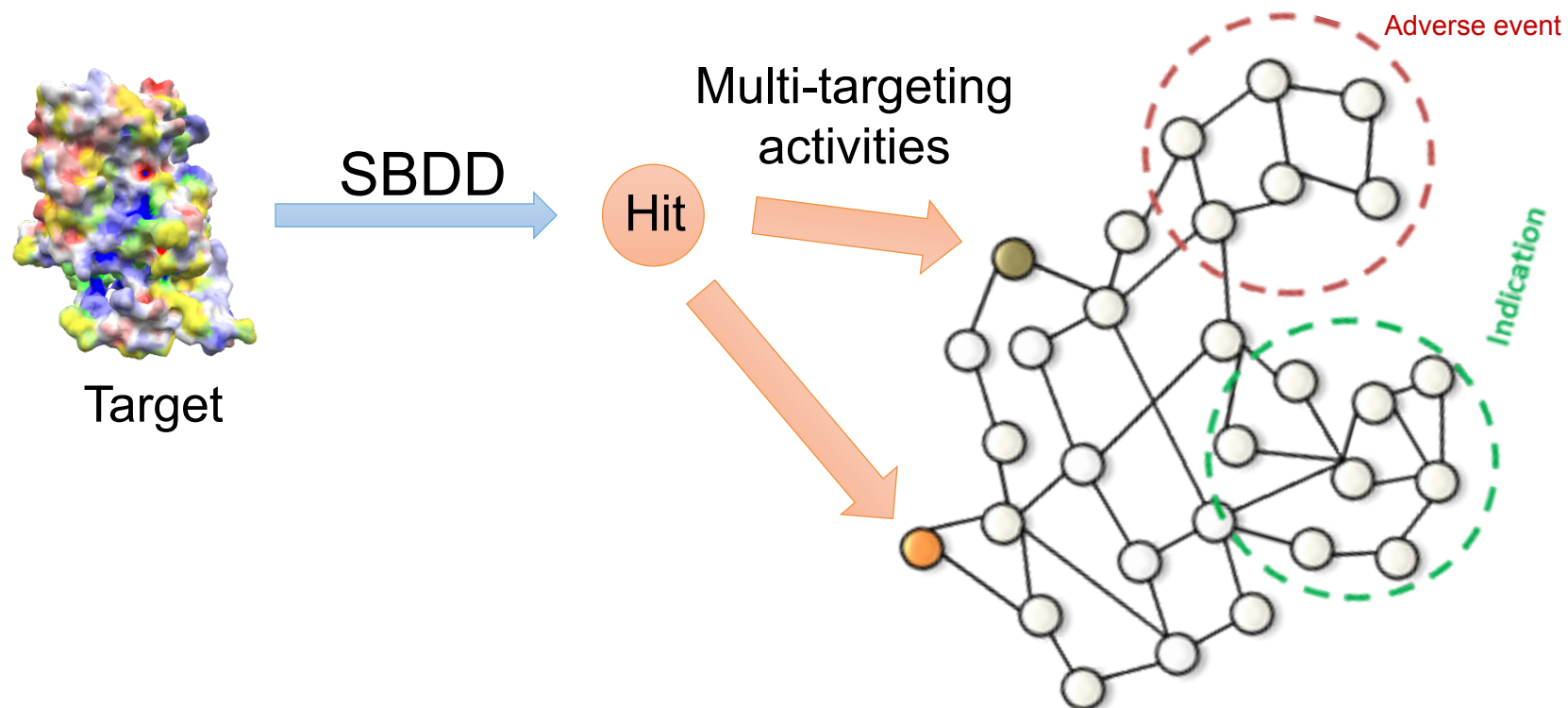


A neutral fragment
→ **Favorable ADMET profiles**



SBDD solved the problem with LBDD

Fundamental limitations of structure-based approaches



The systems biology approach to drug discovery

Healthy Individual

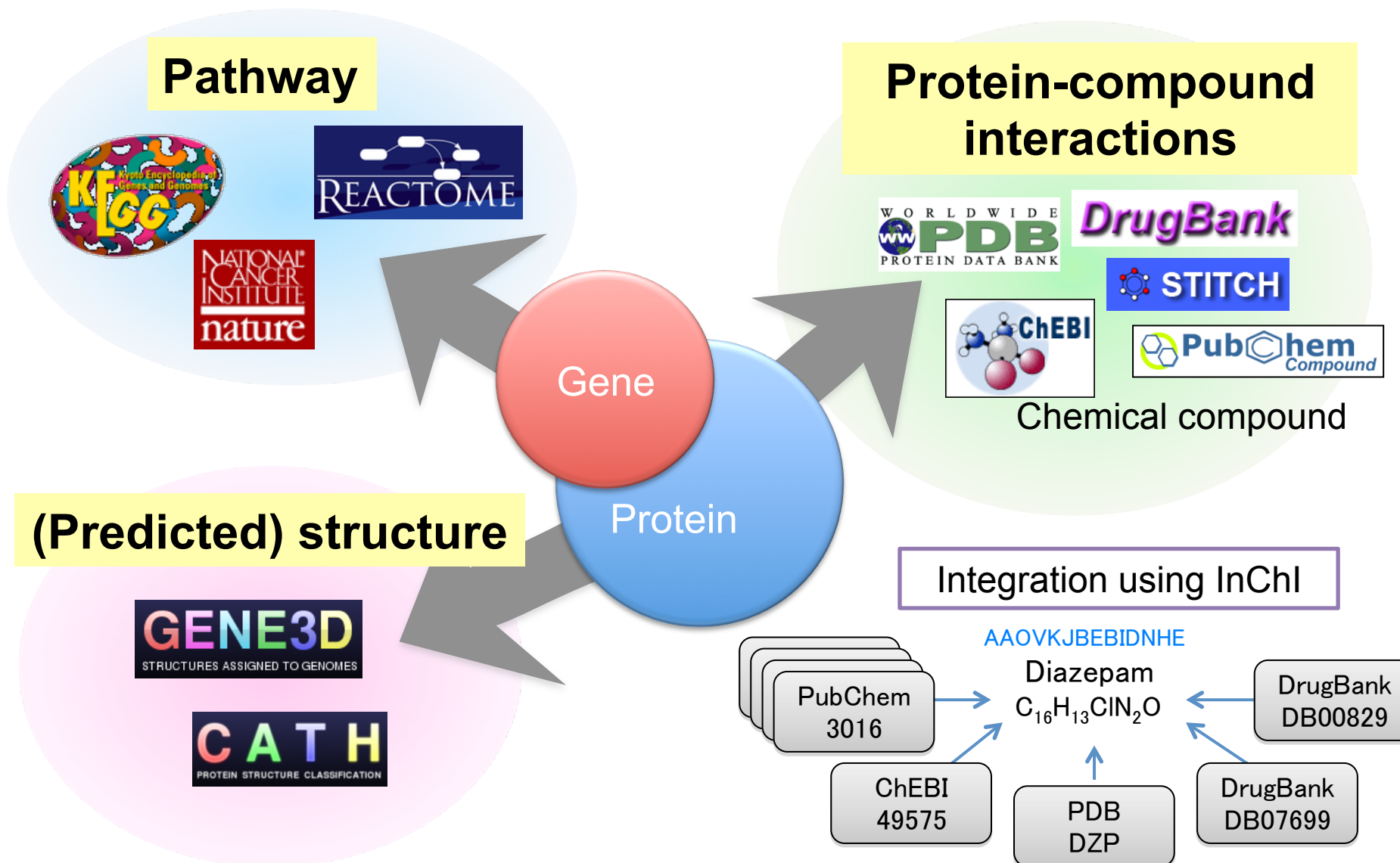
Disease State

Treatment Prediction

Source: Ingenuity Pathway Analysis, Causal Network Analysis suite

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

Data integration

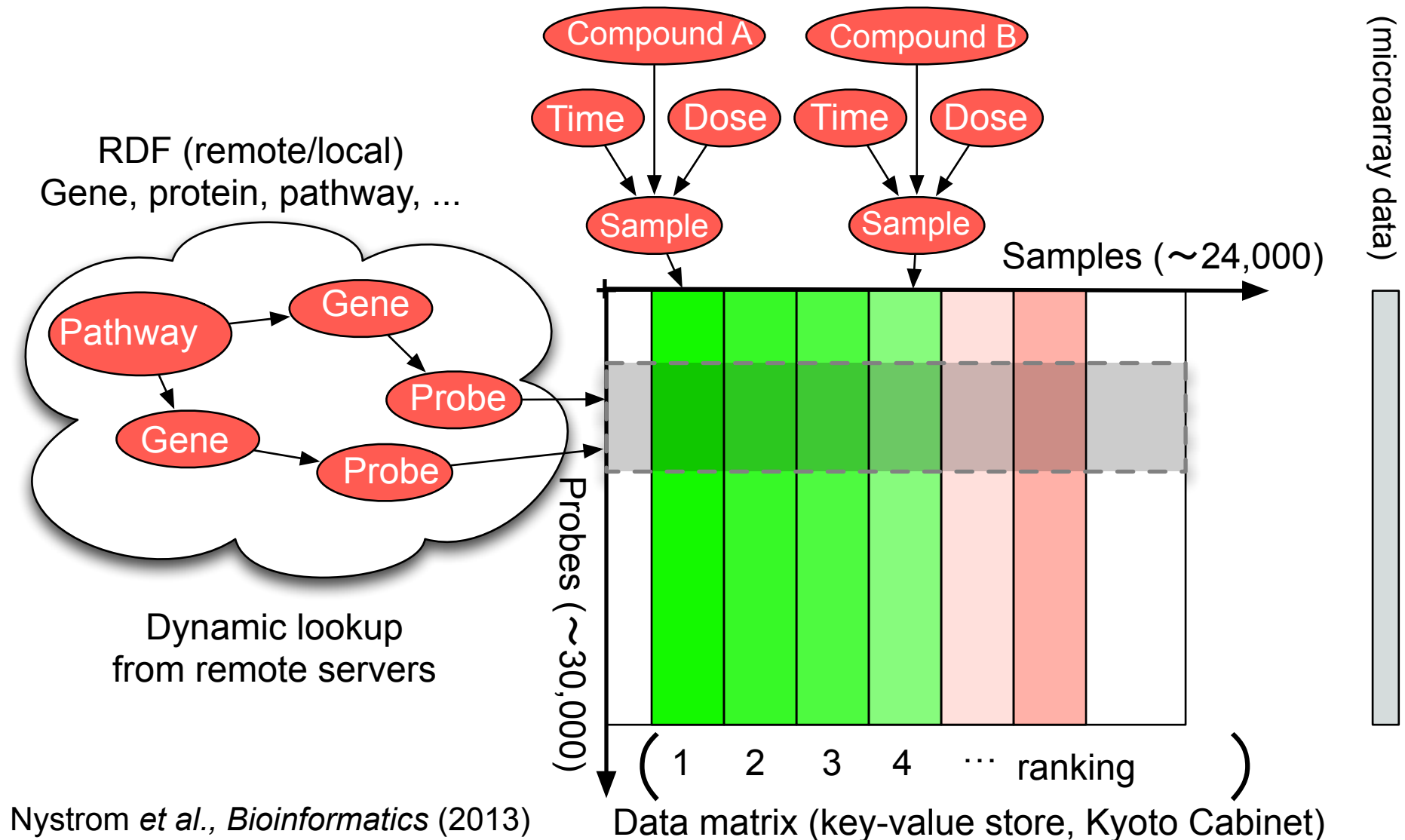


Data warehouse system

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/>

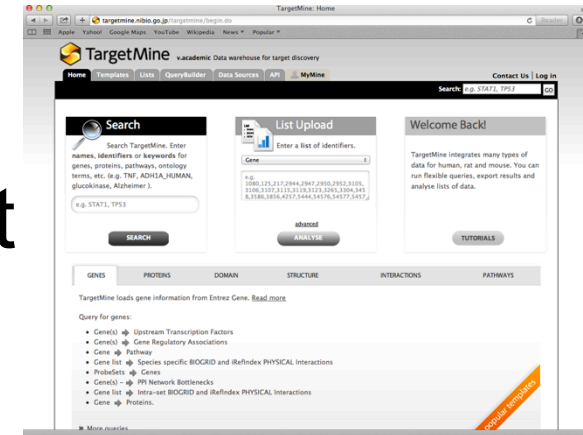




TargetMine

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.

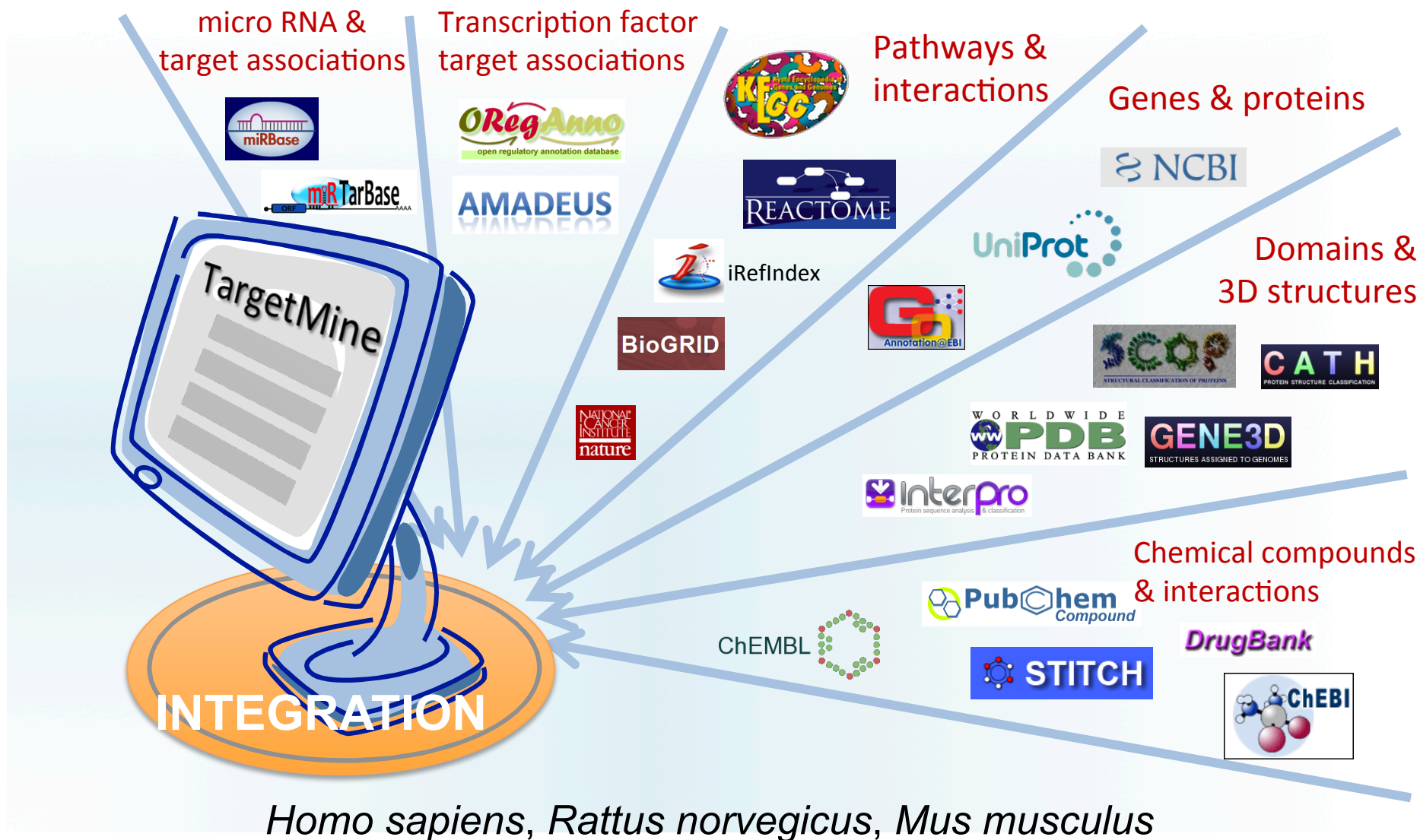
Powered by



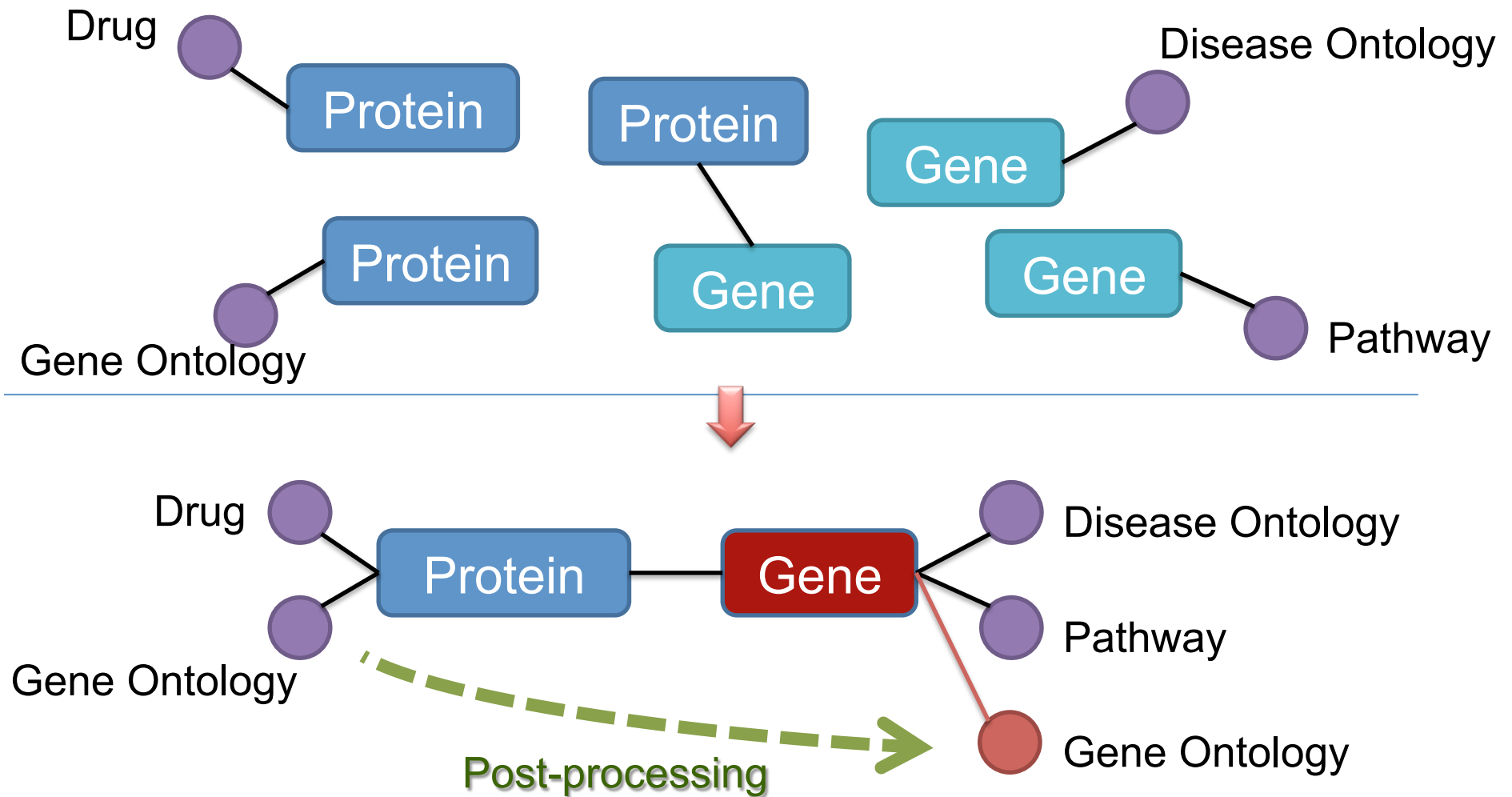
at the Cambridge Systems Biology Centre

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

Data sources in TargetMine



How InterMine integrates data



(Java, PostgreSQL)

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

Query protein: Catechol O-methyltransferase (COMT_HUMAN)

ChEMBL
14 interacting compounds

The screenshot displays the RCSB Protein Data Bank (PDB) search results page. The top navigation bar includes links for Home, Search, About, and Help. The search criteria are set to 'Chloride Ion' with 150 results per page. The results table lists various PDB entries, including 2B8.65, 4Y3.17, 3J1.73, 345.76, 387.71, 303.68, 418.81, 331.73, 413.17, 379.77, 389.76, 403.79, 403.79, 389.76, and 162.19. The table columns include Molweight, Standard Type, Relation, Standard Value, Standard Units, Assay Type, Assay Src Description, Assay Organism, Protein Accession, Target Organism, and Reference. A sidebar on the left offers filters for Chemical, Statistics, and Chemical, along with a 'Chloride Ion' link. A large text overlay '7 interacting co' is visible in the bottom right corner.

Molweight	Standard Type	Relation	Standard Value	Standard Units	Assay Type	Assay Src Description	Assay Organism	Protein Accession	Target Organism	Reference
289.65	KI	<	1	mM	B	Scientific Literature				
413.17	KI	=	1	mM	B	Scientific Literature				
331.73	KI	=	1.1	mM	B	Scientific Literature				
345.76	KI	=	1.3	mM	B	Scientific Literature				
387.71	KI	=	1.6	mM	B	Scientific Literature				
303.68	KI	=	2.2	mM	B	Scientific Literature				
418.81	KI	=	6	mM	B	Scientific Literature				
331.73	KI	=	9.2	mM	B	Scientific Literature				
413.17	KI	=	10	mM	B	Scientific Literature				
379.77	KI	=	10.2	mM	B	Scientific Literature				
389.76	KI	=	10.6	mM	B	Scientific Literature				
403.79	KI	=	16.6	mM	B	Scientific Literature				
403.79	KI	=	17	mM	B	Scientific Literature				
389.76	KI	=	17	mM	B	Scientific Literature				
162.19	KI	=	6300	mM	B	Scientific Literature				

7 interacting co


DRUGBANK
Open Data Drug & Drug Target Database

17 interacting compounds

RCSB PDB
PROTEIN DATA BANK

7 interacting compounds

Cl ⁻	Name:	CHLORIDE ION
	ID:	CL 8225 Structures Containing CL (102L, 103L, 107L...)
	Formula:	Cl


Name: 3,5-DINITROPHENOL
ID: DNC 4 Structures Containing DNC (1VID, 3A7E, 3BWM...)
Formula: C₆ H₄ N₂ O₆

Name:	POTASSIUM ION
ID:	K 1784 Structures Containing K (1A3W, 1A3X, 1A49...)
Formula:	K

Mg²⁺

Name:	MAGNESIUM ION
ID:	MG 9484 Structures Containing MG (101D, 109D, 119D)
Formula:	Mg

Name: (4S)-2-METHYL-2,4-PENTANEDIOL
ID: MPD 471 Structures Containing MPD (18F6, 18P2, 18YZ)
Formula: C₆ H₁₄ O₂

Na ⁺	Name:	SODIUM ION
	ID:	NA 5138 Structures Containing NA (191D, 191D, 191D)
	Formula:	Na

Name: S-ADENOSINOMETHIONINE
ID: **SAM** 285 Structures Containing SAM (1CMA, 1CMC, 1ETZ)
Formula: C₁₅H₂₂N₆O₅S


[Home](#) | [Tutorials](#) | [Terms of use](#) | [Contact Us](#) | [Log in](#)
 Search:

36 **non-redundant**
interacting compounds
from ChEMBL, DrugBank
and PDB

Iran Query > Results

Columns1 Filters

1 to 36 of 36 rows

Primary Accession	Name
P21964	Catechol O-methyltransferase
P21964	Catechol O-methyltransferase
P21964	Catechol O-methyltransferase
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P21964	Catechol O-methyltransferase
P21964	Catechol O

[Questions? Comments? Click here!](#)

TargetMine is developed by The Mizuguchi Laboratory at 独立行政法人 医薬基盤研究所

Powered by
InterMine 1.4.2

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

Model browser

Browse through the classes and attributes. Click on [SUMMARY](#) links to add summary of fields to the results table or on [SHOW](#) links to add individual fields to the results. Use [CONSTRAIN](#) links to constrain a value in the query.

Compound Group [SUMMARY](#) [CONSTRAIN](#)

- Identifier [SHOW](#) [CONSTRAIN](#)
- Name [SHOW](#) [CONSTRAIN](#)
- Compounds Compound [SUMMARY](#) [CONSTRAIN](#)

Query Overview

Compound Group
LOOKUP Estradiol (A)

Compounds Compound collection

Target Proteins Compound Protein Interaction collection

Data Set Data Set

Name

= ChEMBL (B)

Protein Protein

Name

Primary Accession

Known 3D structures Protein Structure Region collection

Chain Protein Chain

Structure Protein Structure

Pdb Compounds PDB Compound

LOOKUP Estradiol (C)

Identifier

Constraint logic: A and B and C

A and B and C

☐ Show empty fields

Fields selected for output

Columns to Display

Use the [SHOW](#) or [SUMMARY](#) links to add fields to the results table. Click and drag the blue output boxes to the column to sort results by, click again to select ascending or descending. Use the [REMOVE ALL](#) link to remove all fields.

[REMOVE ALL](#)

Compound Group > Name (no description) [SUMMARY](#) [CONSTRAIN](#)

Compound Group > Compounds > Target Proteins > Protein . Primary Accession (no description) [SUMMARY](#) [CONSTRAIN](#)

Compound Group > Compounds > Target Proteins > Protein . Name (no description) [SUMMARY](#) [CONSTRAIN](#)

Compound Group > Compounds > Target Proteins > Protein > Known 3D structures > Chain > Structure (no description) [SUMMARY](#) [CONSTRAIN](#)

ChEMBL

RCSB PDB
PROTEIN DATA BANK

TargetMine

Target Proteins > Protein . Primary Accession	Target Proteins > Protein . Name
P03372	Estrogen receptor
P04278	Sex hormone-binding globulin
Q62986	Estrogen receptor beta
Q92731	Estrogen receptor beta

TargetMine

Home Templates Lists QueryBuilder Data Sources API MyMine

Trail: Query > Results

Manage Columns 3 Filters

Showing 1 to 4 of 4 rows

Rows per page: 25

Name	Target Proteins > Protein . Primary Accession	Target Proteins > Protein . Name	Target Proteins > Data Set . Name	Pdb Compounds > Identifier
estradiol	P03372	Estrogen receptor	ChEMBL	PDBCompound:EST
estradiol	P04278	Sex hormone-binding globulin	ChEMBL	PDBCompound:EST
estradiol	Q62986	Estrogen receptor beta	ChEMBL	PDBCompound:EST
estradiol	Q92731	Estrogen receptor beta	ChEMBL	PDBCompound:EST

Found 4 proteins

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)

