AIによるデータ駆動型研究が拓く創薬と医療
Data-driven drug discovery and healthcare by AI

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Outline

- ドラッグリポジショニング
  Drug repositioning
- AI創薬・医療
  AI-based drug discovery and medicine
- 漢方薬リポジショニング
  Natural medicines repositioning
- 再生医療応用
  Regenerative medicine

創薬の問題
Problem of drug discovery

- 開発コストは高い
  数千億円、10年以上
- ほとんどが失敗に終わる
  - 有効性が不十分
  - 想定外の深刻な毒性

- Time consuming (10-15 years) and high cost: about 1 billion $ per drug
- High risk: result in failure
  - Insufficient efficacy
  - Unexpected serious toxicity

ドラッグリポジショニング
Drug repositioning

- 既存薬の新しい効能を発見し、別の疾患の治療薬として開発
- 高速・低コスト・低リスク（安全性が確認されている）

例　シルデナフィル（バイアグラ）:
狭心症治療薬　→　男性機能障害薬　→　肺高血圧症薬

- Identification of new therapeutic effects (i.e., new applicable diseases) of existing drugs.
- Fast development and low risk (safety is confirmed).

Example: Sildenafil (Viagra)
Angina → Erectile dysfunction → Pulmonary hypertension

新薬の多くが既存薬の新効果発見でもたらされてきた
Many drugs have been provided by finding new effects

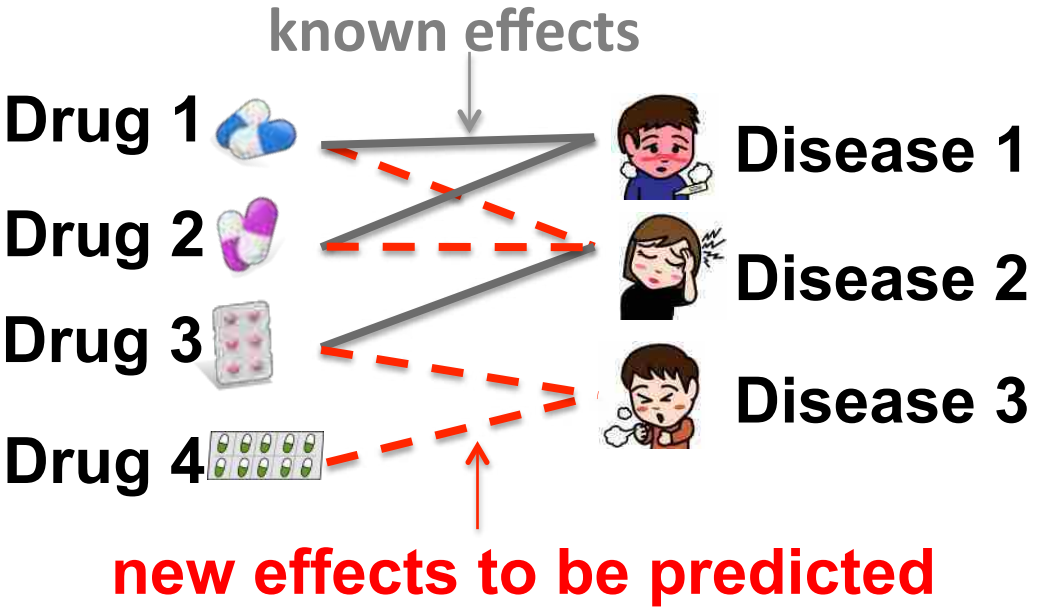
- ミノキシジル　Minoxidil
  - 高血圧薬　Hypertension medicine → 発毛薬　Hair growing agent
- ビマトプロスト　Bimatoprost
  - 緑内障薬　Glaucoma medicine → まつげを伸ばす薬　Eyelash stretch cosmetic
- ブプロピオン　Bupropion
  - 抗うつ剤　Antidepressant → 禁煙補助剤　Adjuvant for smoking cessation
- レバミピド　Rebamipide
  - 胃薬　Stomach medicine → ドライアイの目薬　Eye drops of dry eye

問題：これまでは偶然の発見に大きく依存していた
The previous approach has been dependent on serendipity.

ドラッグリポジショニングのAI創薬
AI-based drug repositioning

薬と疾患の関連を自動的に予測する機械学習の手法を開発

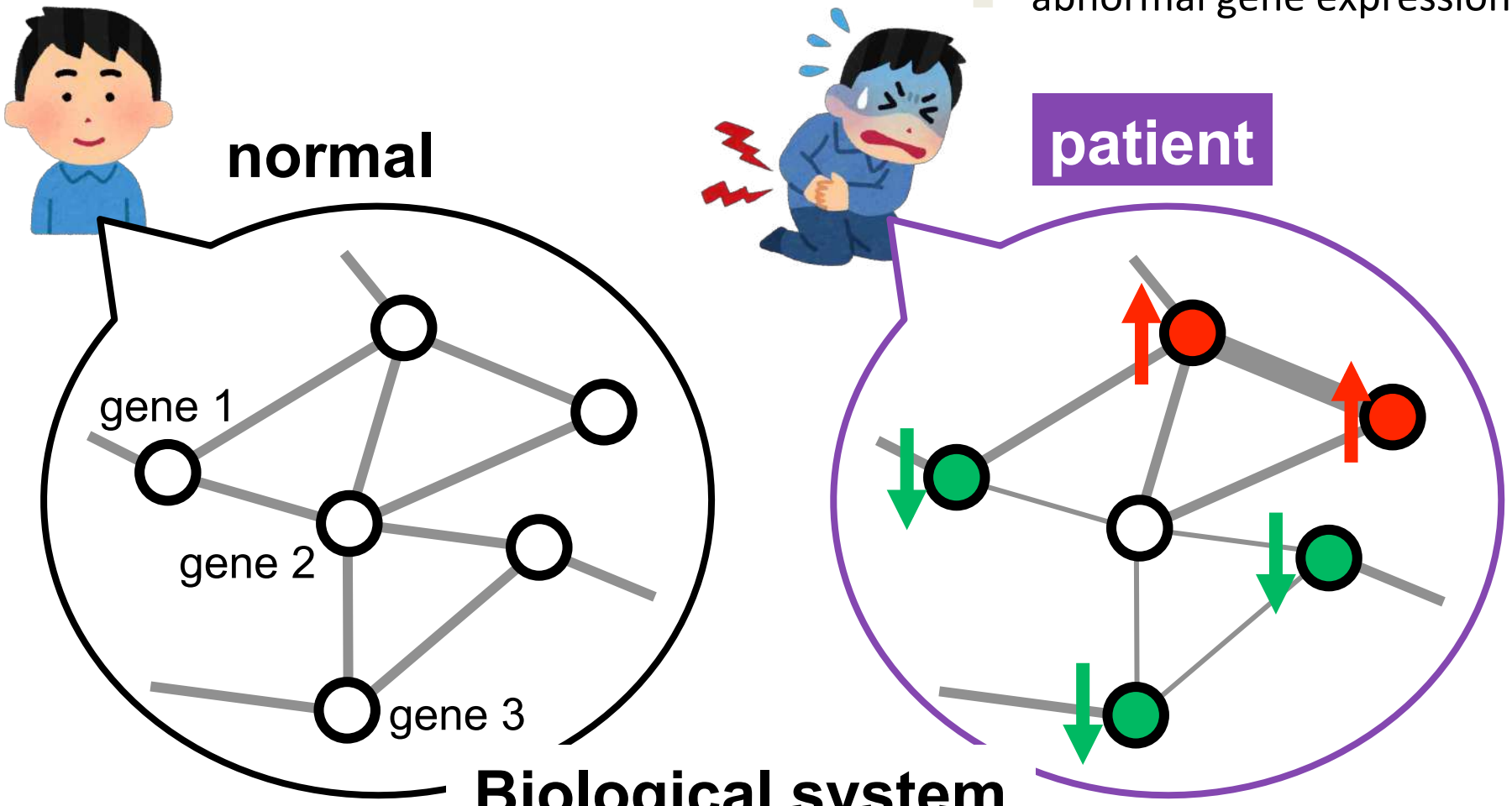
Machine learning methods to predict new associations between drugs and diseases



多様な疾患の分子レベルでの理解が進んできた

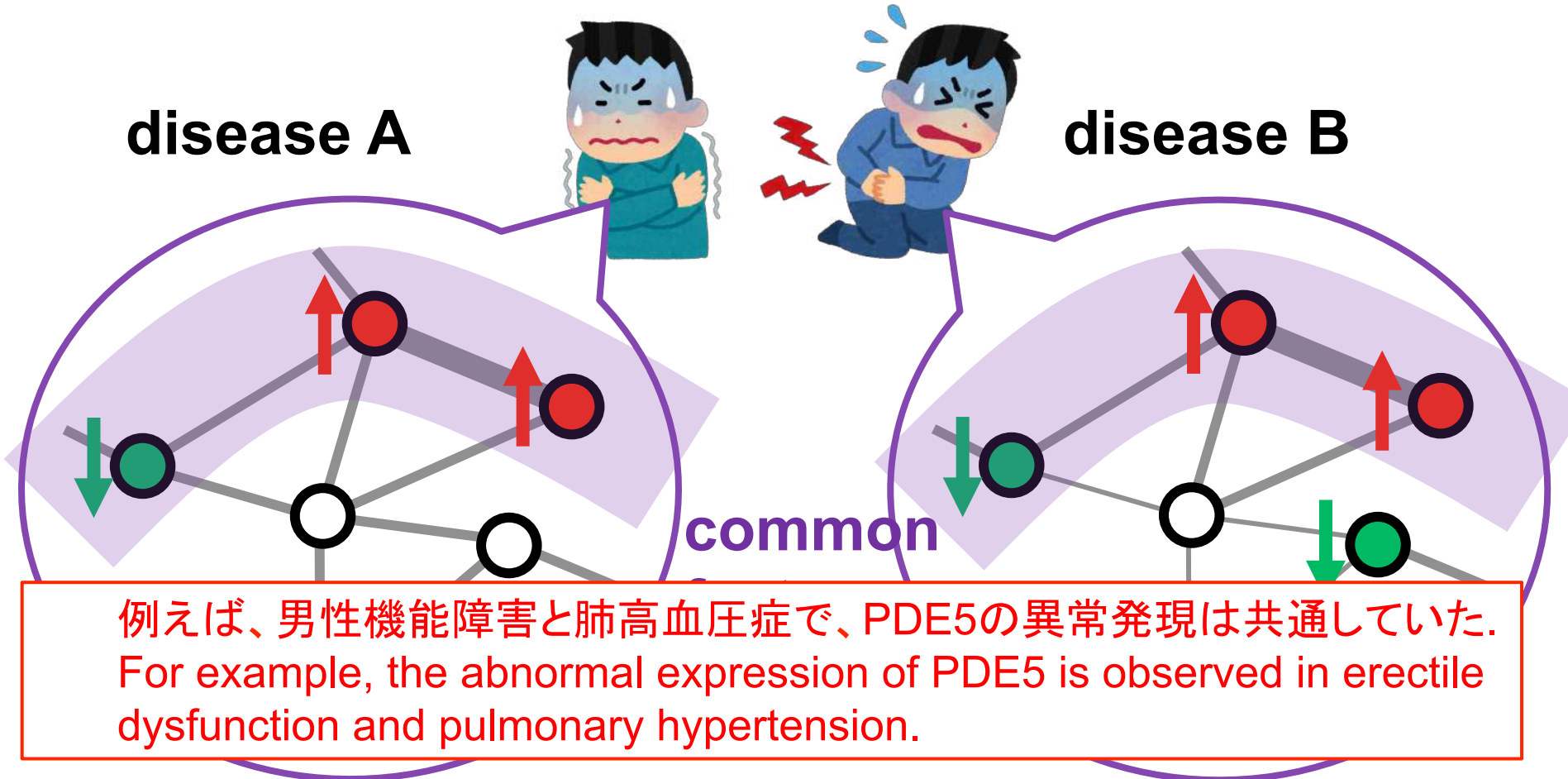
Molecular understanding of a variety of diseases

- 病因遺伝子
- 環境因子
- 発現異常遺伝子・蛋白
- disease-causing genes
- environmental factors
- abnormal gene expression



疾患の病態を表す分子的な特徴は、異なる疾患間でも共通する場合がある

Characteristic molecular features are often shared among different diseases

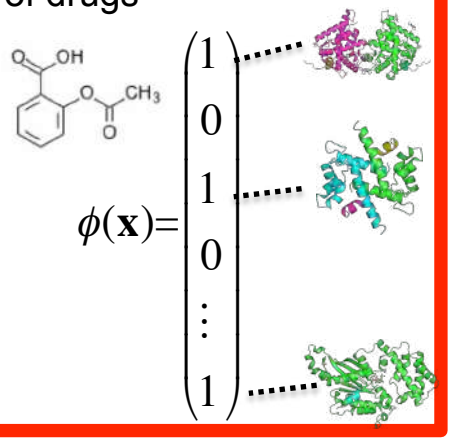


例えば、男性機能障害と肺高血圧症で、PDE5の異常発現は共通していた.
For example, the abnormal expression of PDE5 is observed in erectile dysfunction and pulmonary hypertension.

機械学習による治療薬の予測
Drug prediction by machine learning

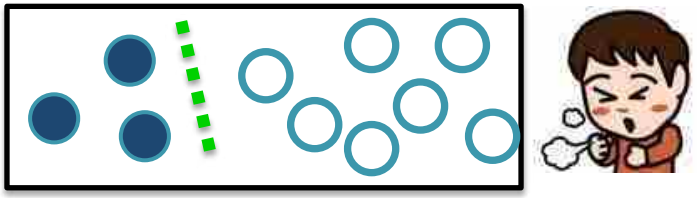
Input

Chemical structures and target protein profiles of drugs

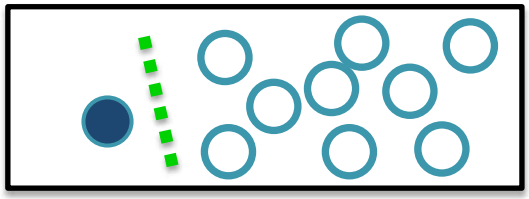


Predictive models

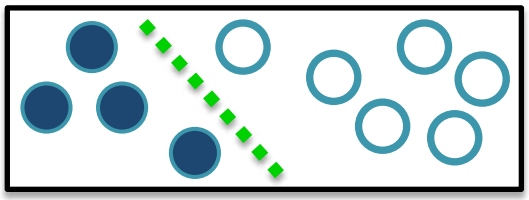
Model $f_A(x)$： disease A



Model $f_B(x)$：disease B



Model $f_C(x)$：disease C



output

Drug candidates for each disease

Drug class label

- applicable
- non-applicable

(Swada et al, *J Chem Inf Model*, 55(12), 2717–2730, 2015; Sawada et al, *Sci Rep*, 8:156, 2018)

安価で安全な抗がん剤を開発
Development of anti-cancer drugs with low prices and low toxic side-effects

Collaboration with Prof. Tani (University of Tokyo)
(Iwata et al, *J Med Chem*, 61, 9583−9595, 2018)

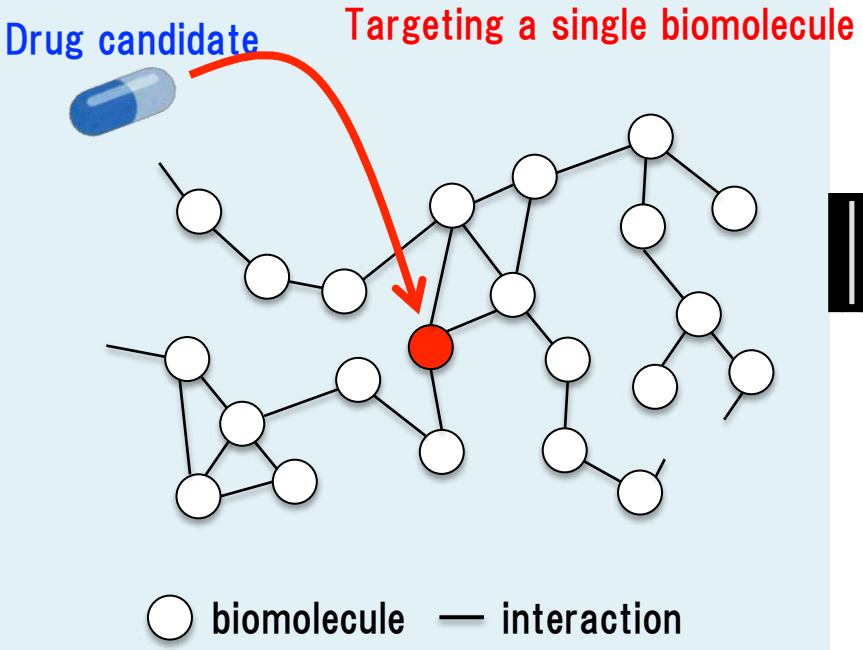
- 問題　Problem
  - がんは死亡原因の第1位
  - 化学療法は重篤な副作用を伴い、薬価は高騰
  - Cancer is a leading cause of death worldwide
  - Cancer treatment is painful and expensive
- 狙い　Aim
  - ヒトでの安全性が確認されている薬物から抗がん作用薬を新しく同定する。
  - Identification of new anticancer effects from existing drugs that have been confirmed to be safe for humans.

Pathway-based drug discovery

(Iwata et al, *J Med Chem*, 61, 9583-9595, 2018)

Traditional approach

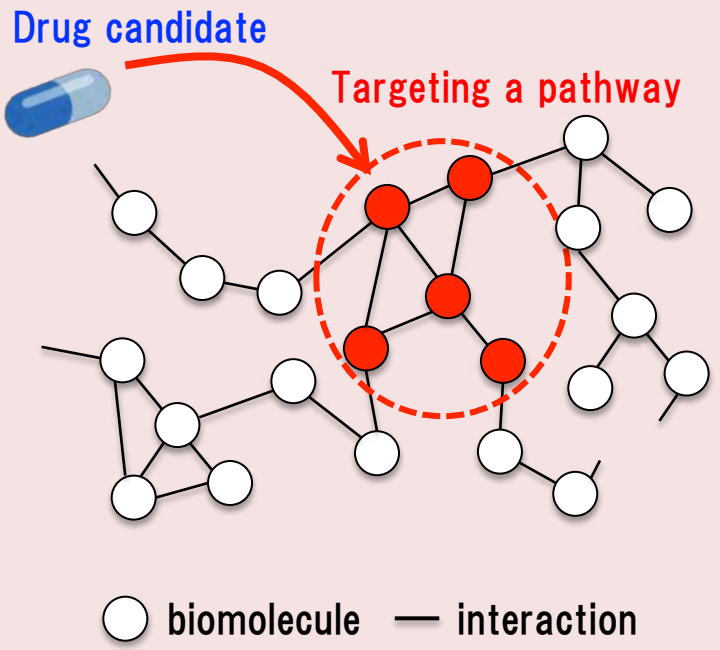
Search for drugs that regulate a single biomolecule



Problem:
Molecular interactions are not taken into account

Proposed approach

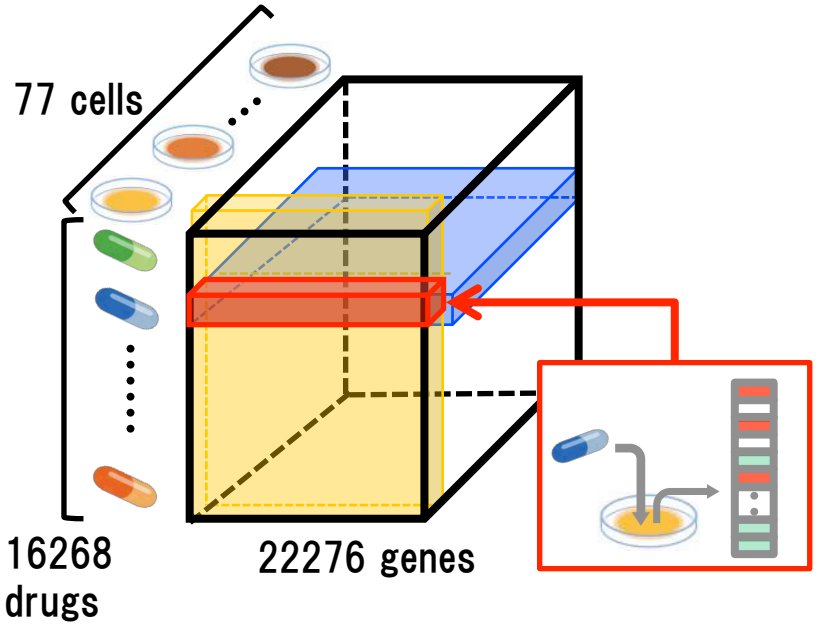
Search for drugs that regulate a pathway



Solution:
Molecular interactions are considered by using pathway information

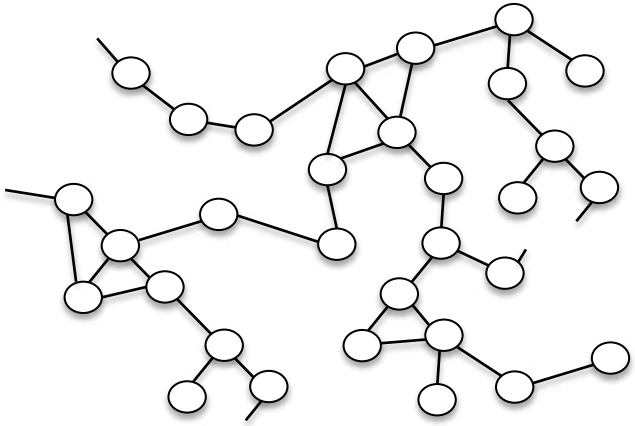
Integration of omics data analysis and molecular network analysis

Drug-induced gene expression data



Molecular interaction network

(signaling pathways, metabolic pathways, gene regulations, PPIs)



prediction

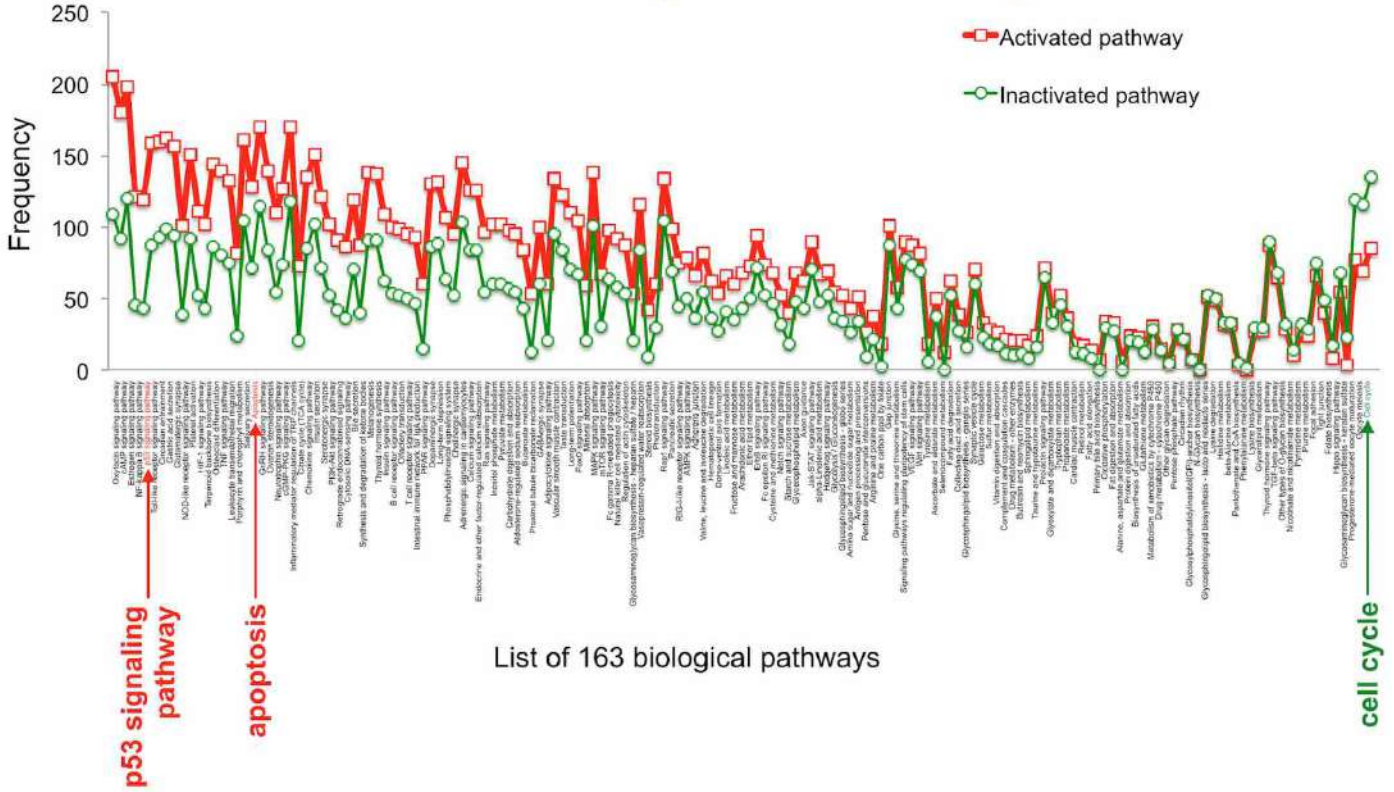
Drug candidates with expected effects

Pathway-based drug discovery for cancers

Exploring drugs that regulate the following pathways:

- Inactivate cell cycle pathways
- Activate p53 signaling pathways
- Activate apoptosis pathways

$$f_{\mathbf{path}} = (f_1^{\mathrm{inh}}, f_2^{\mathrm{inh}}, \ldots, f_{d_{\mathrm{path}}}^{\mathrm{inh}}, f_1^{\mathrm{act}}, f_2^{\mathrm{act}}, \ldots, f_{d_{\mathrm{path}}}^{\mathrm{act}})^{\mathrm{T}}$$



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  Regenerative medicine

漢方薬医療
Natural medicine
(e.g., Herbal medicines, Kampo drugs in Japan)

- 身近で有用だが、メカニズムは大半が不明。
- It is popular and useful, but the mechanism is unclear.

Ordinary drug

＋

Kampo drug

漢方は多くの化合物で構成され、メカニズムは複雑

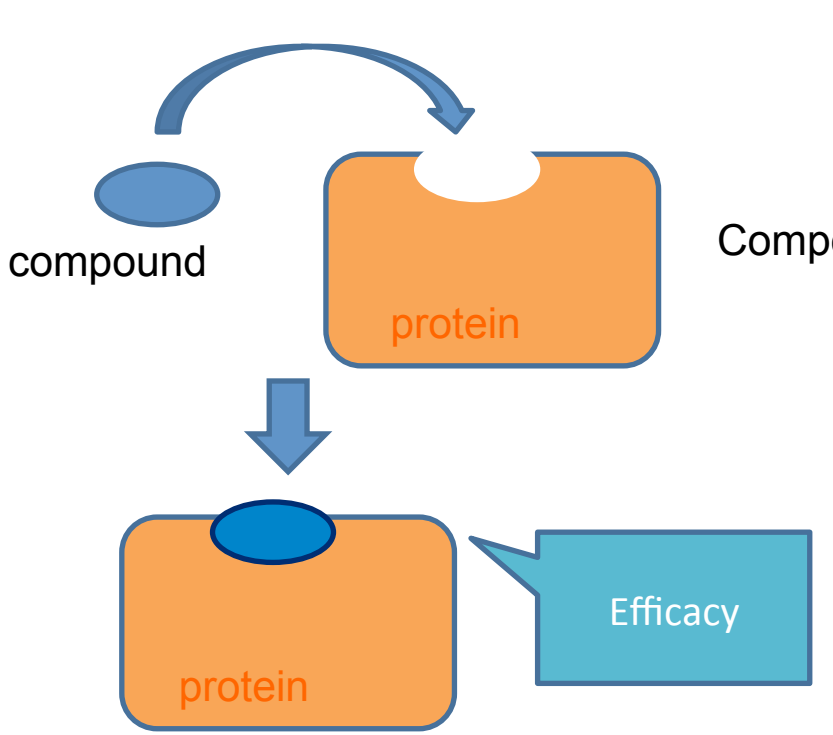
Each Kampo drug contains many compounds and the mode-of-action is complicated

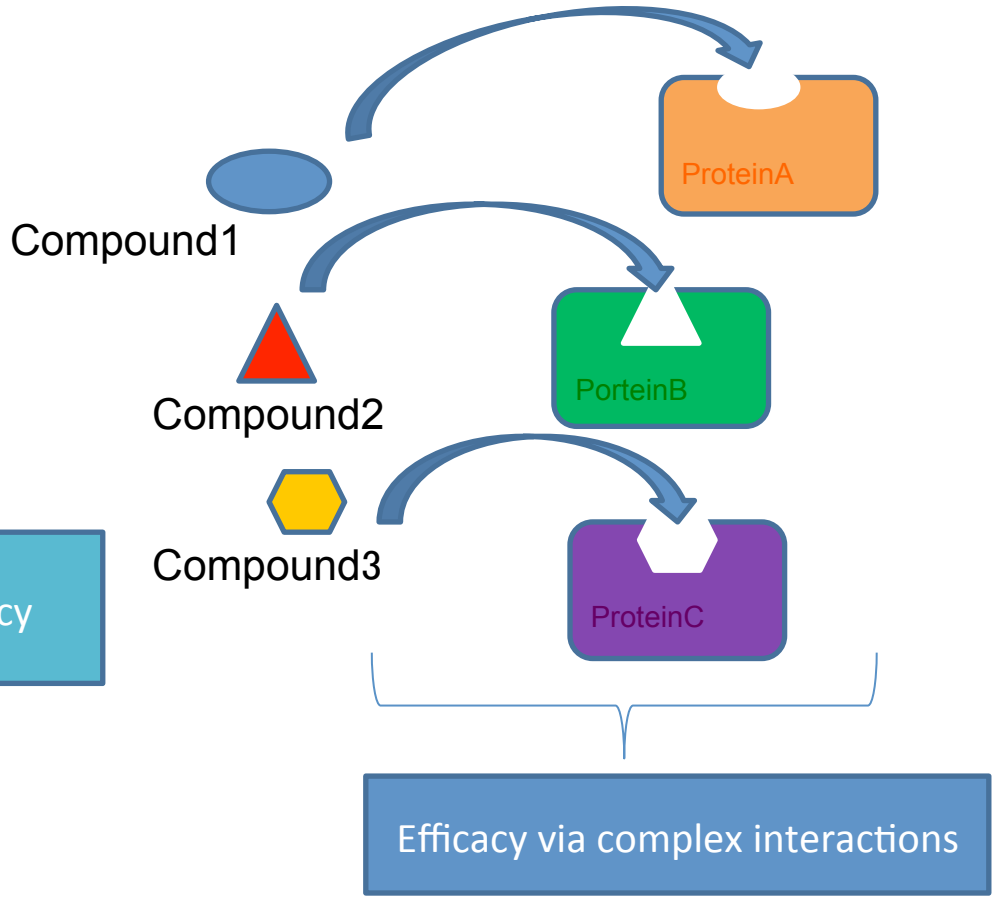
Ordinary drug

The mode-of-action: one compound-one target interactions

Kampo drug

The mode-of-action: multiple compound-multiple target interactions





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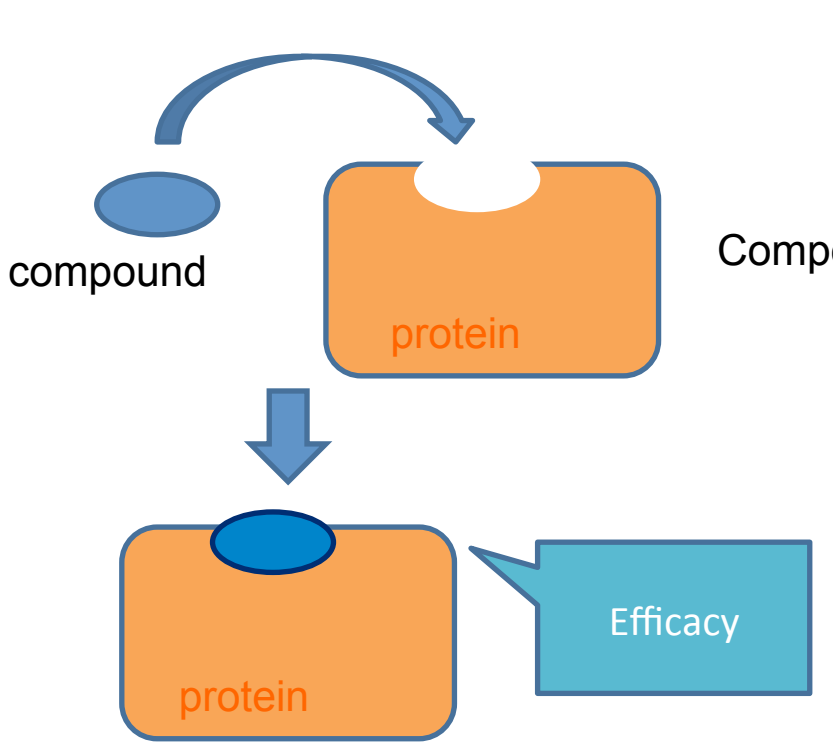
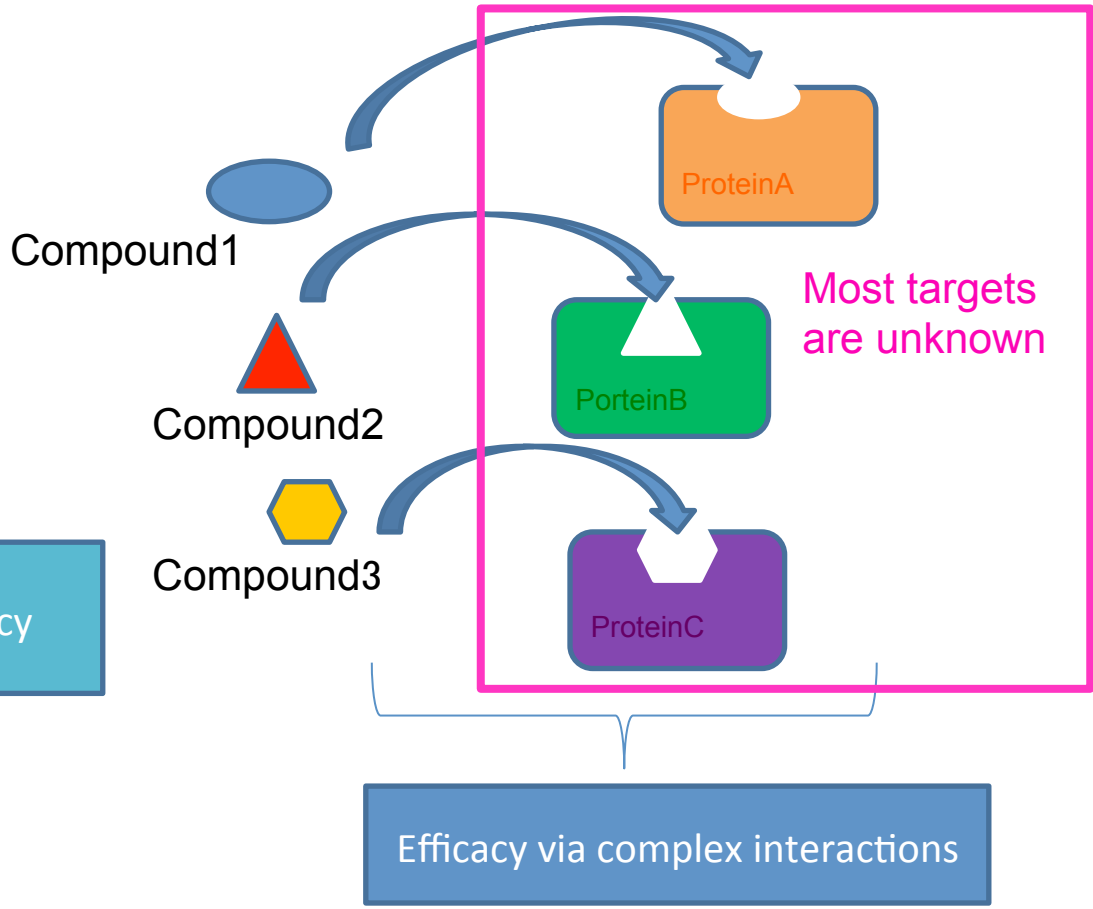
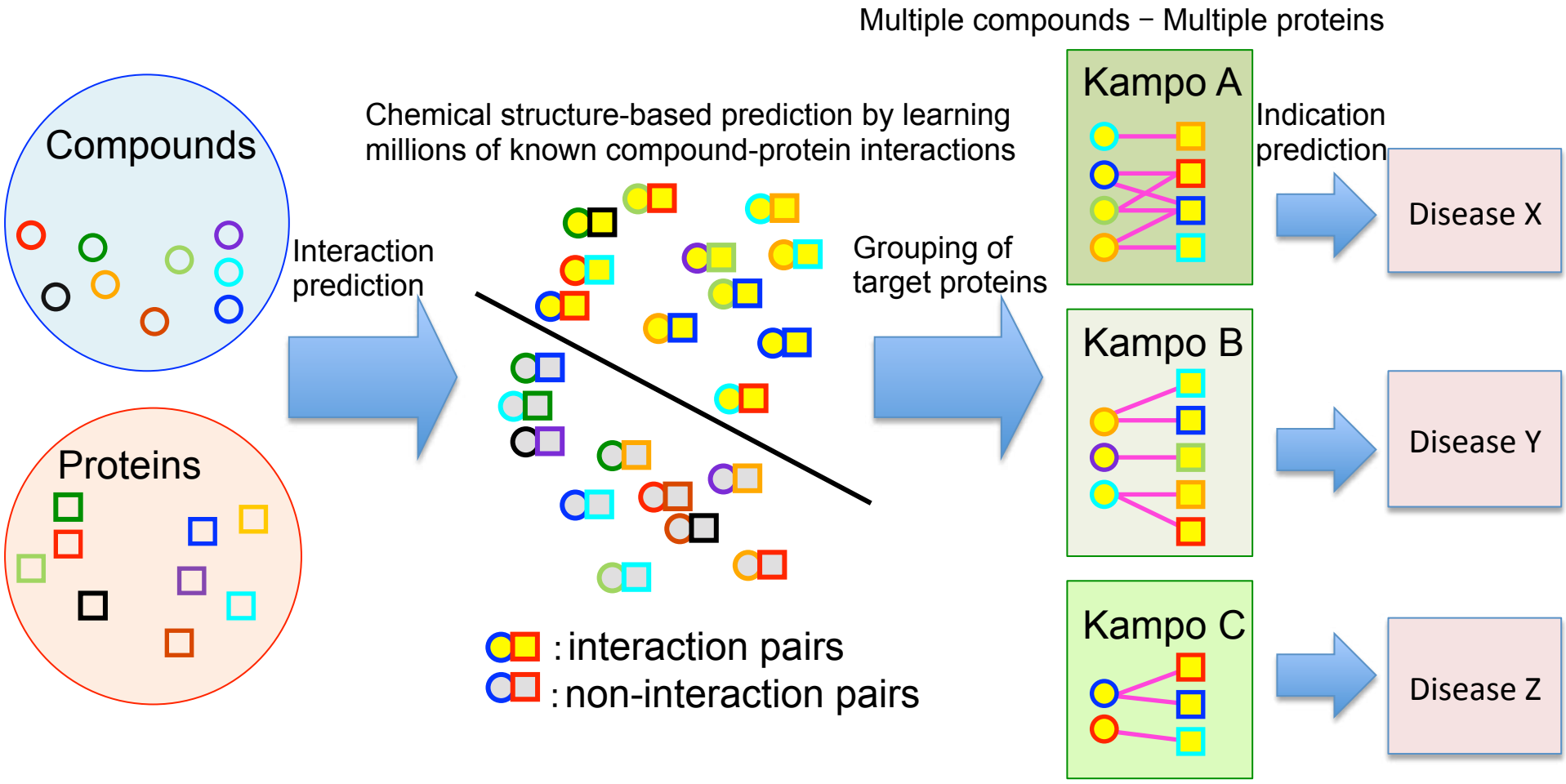




漢方薬ごとに、標的タンパク質群を予測＆グループ化し、効能予測

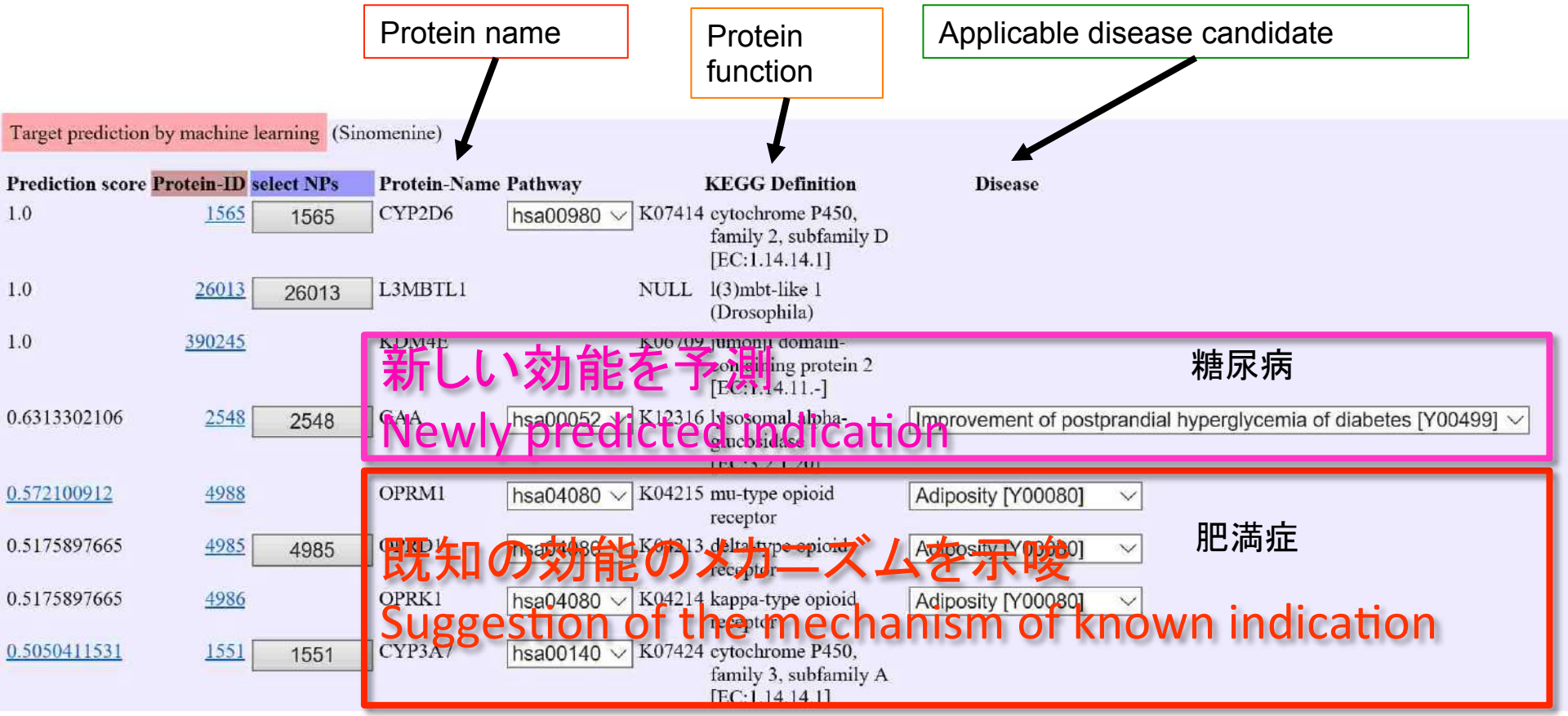
Target proteins and indications for each Kampo were predicted



(Sawada et al, *Sci Rep*, 8:11216, 2018;
Douke et al, submitted)

漢方薬の標的タンパク質や適応可能疾患を予測
Prediction of potential target proteins and new applicable diseases of Kampo drugs

防已黄耆湯（ぼういおうぎとう）の例　　Example: “Boiogito”



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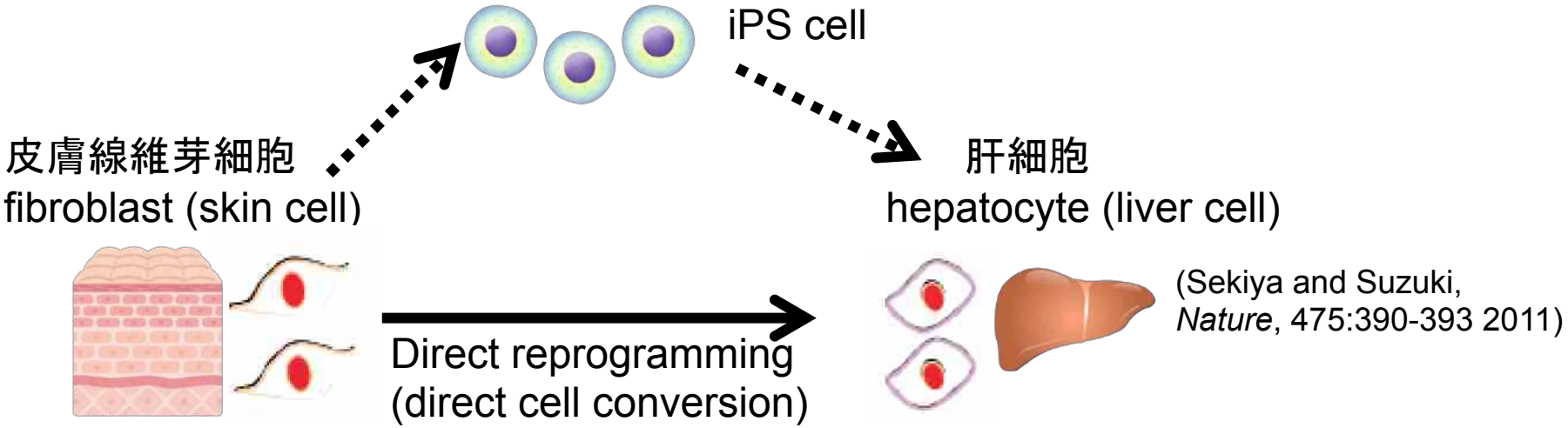
再生医療への応用　Regenerative medicine

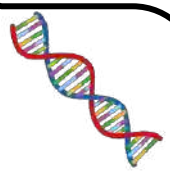
低分子化合物（薬など）によるダイレクトリプログラミング（細胞直接変換）のための情報技術を開発

Computational direct reprogramming (direct cell conversion) by small compounds (e.g., drugs)



これまでの方法：
遺伝子導入による誘導

Previous approach:
gene induction



本研究の方法：
低分子化合物による誘導

Proposed approach:
compound treatment

狙い：
ウィルスに起因する発がんリスクの問題を回避する

Aims:
Avoid cancer risk problem caused by viruses

まとめ　Summary

- 機械学習によるビッグデータ解析で、薬や化合物セットの新しい効能の予測が可能。
  - 治療効果、健康効果
  - 細胞分化誘導能

- Machine learning enables to predict new therapeutic effects of drug candidate compounds.
  - Applicable diseases and health effects
  - Cell differentiation abilities