# Application of Deep Learning to Drug Discovery

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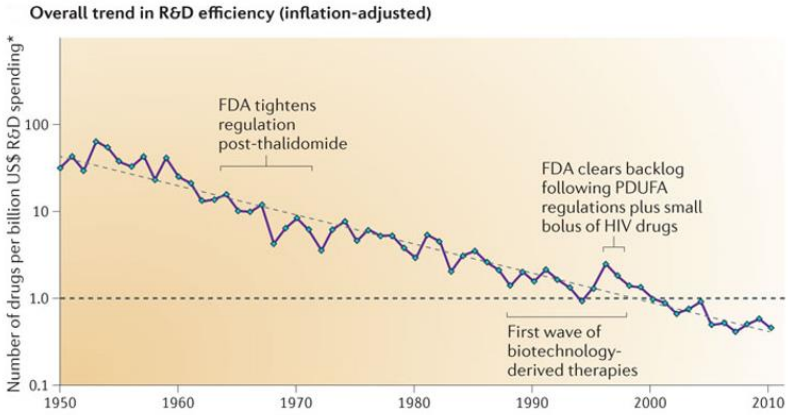
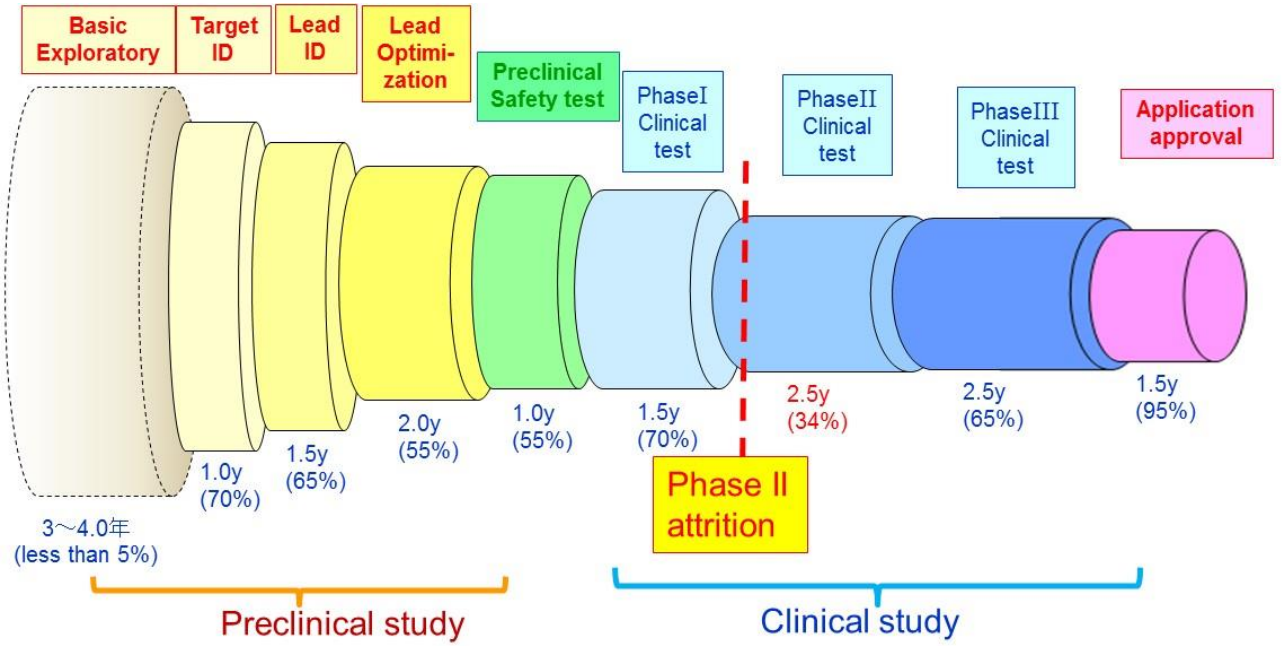
# Current Situation of Drug Discovery

- Rapid increase of R&D expenditure
  - More than 1B $ for one marketed drug
- Decrease of success rate
  now about 1/20,000～1/30,000
  - Remarkable Drop Between non-clinical and clinical test **(phase II attrition)**
- **Clinical Predictability**
  - At as early as possible stage,
    **Estimation of clinical efficacy and toxicity**
- **Efficient measures**
  - **Use Disease-specific iPS cell**
  - **Use of Human Bio Big Data in early stage**




*Nature Reviews Drug Discovery* (2012)



# Relation among Drug, Disease and Target

Main causes of Disease

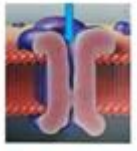
**Disease-related molecules**

**Drug**: acting through Drug **Target** to exert influences on **Disease-related genes**

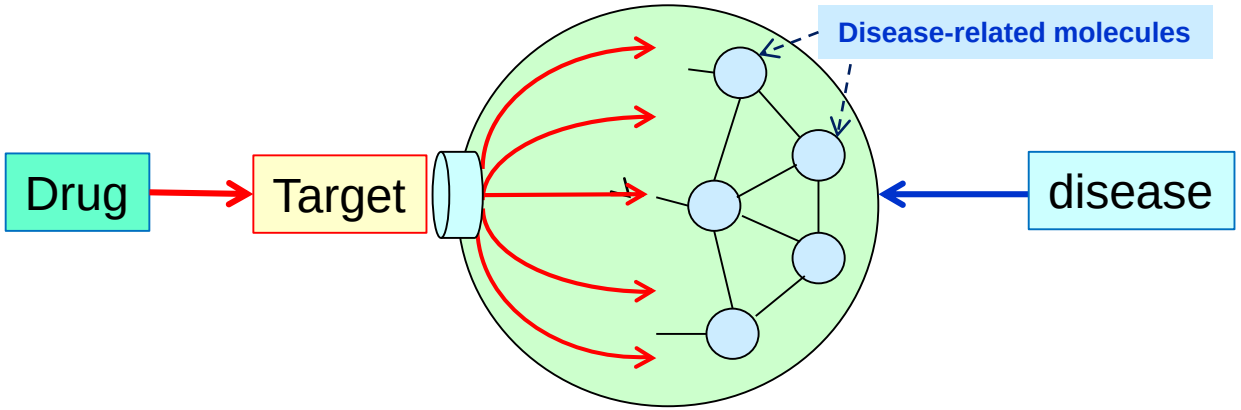
Target Molecule of Drug
Receptor, Enzyme, Channel

receptor

enzyme



channel




Human biological system(network)

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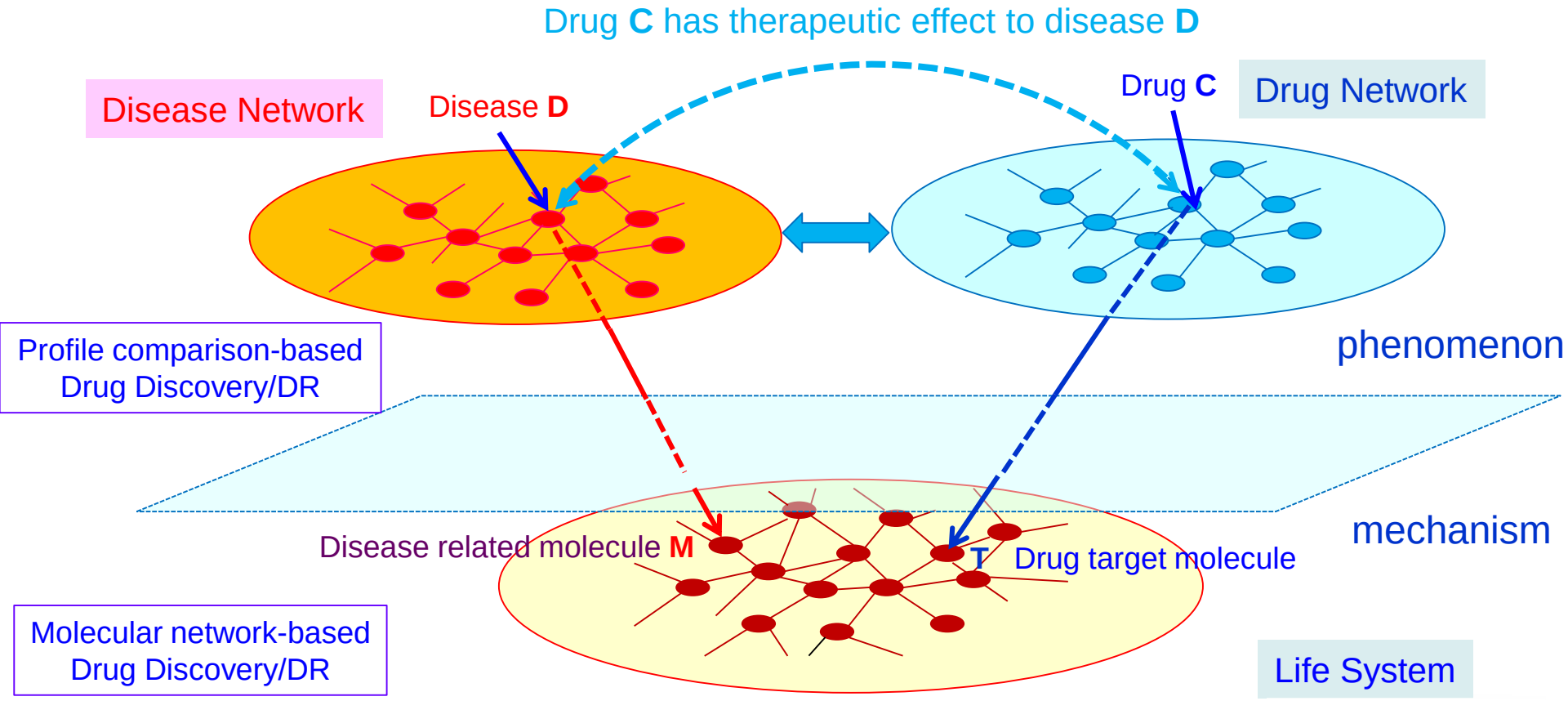
# Basic structure of profile-based computational drug discovery

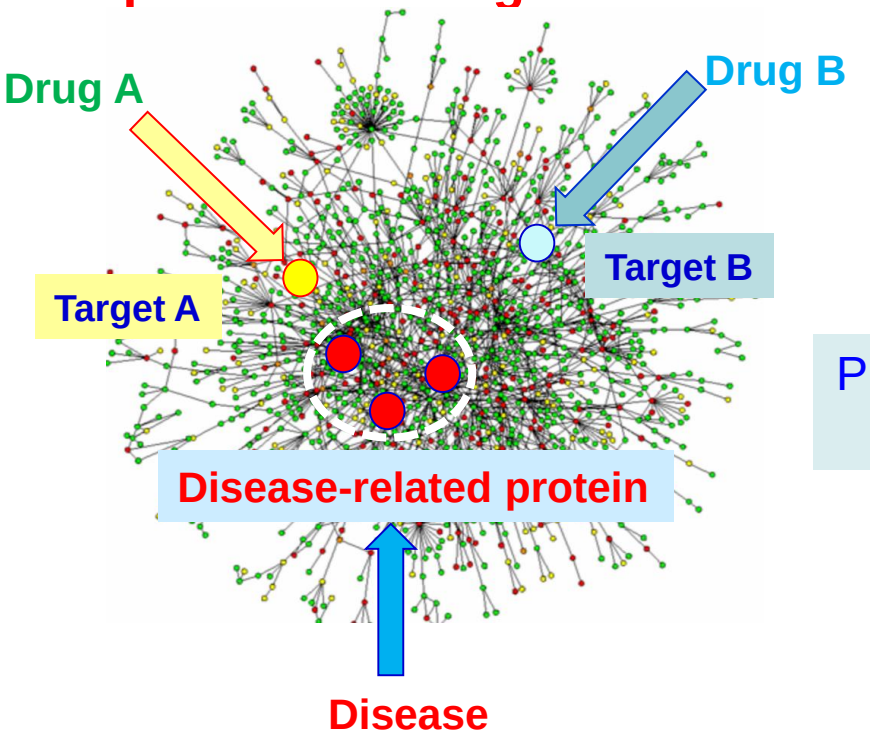
## Framework of Triple-layer disease and drug network




**DR**: Drug Repositioning: is the application of known drugs (compounds) to treat new indications (i.e., new diseases)

# Common Platform of DrugDiscovery/DR
## Protein-Protein interaction network（PPIN）

- Common Platform bionetwork: mediating disease and drug action
- **Protein-protein interaction network（PPIN）** as common platform
- **Disease:** Scaffolding in PPIN: **Disease-related protein** (gene)
- **Drug** : Scaffolding in PPIN**: Drug Target protein**
- Based on **the distance (proximity)** between **Disease-related protein** and **target protein**,
  **the impact of the drug** is measured




Protein-protein Interaction Network（PPIN）

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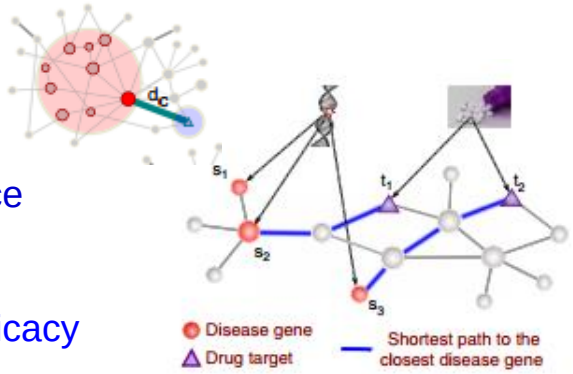
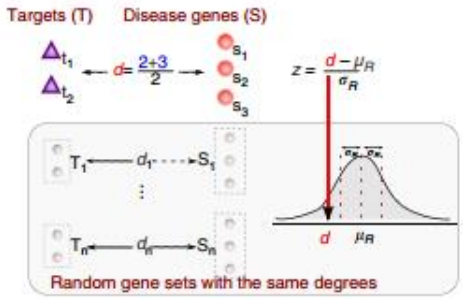
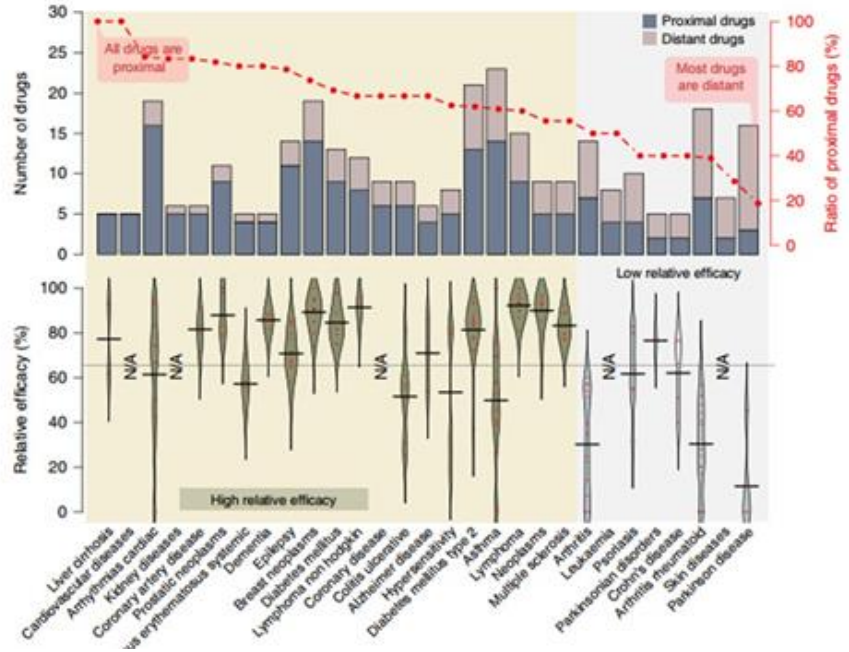
# Proximity between Drug and Disease at PPIN

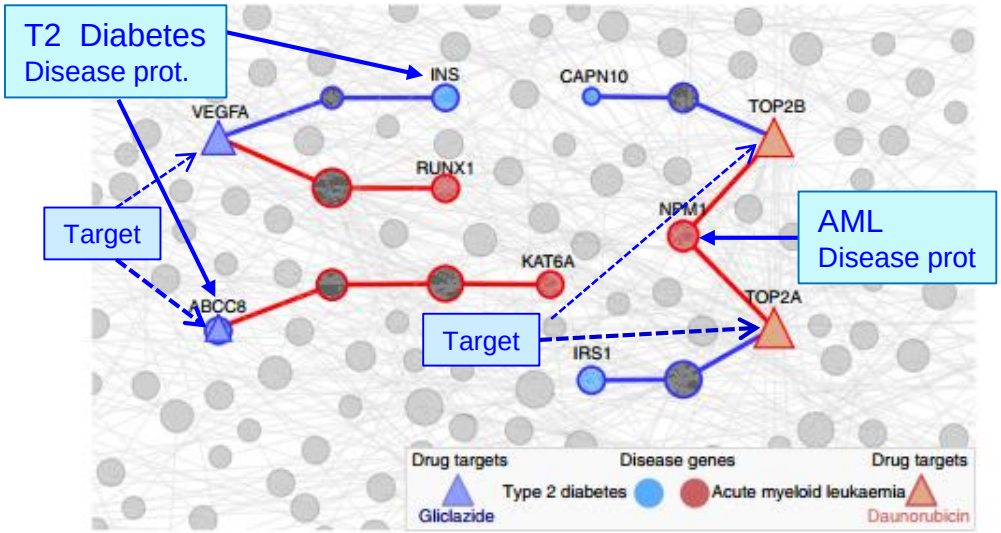
**Relaltive Proximity Index $d_c$** :
①Distance between Target and the nearest protein among disease-related protein module
②The distance is normalized among the distance of the molecules in same context
$z < -0.15 \Rightarrow$ proximate
③closest measure $d_c$ : best index to measure efficacy

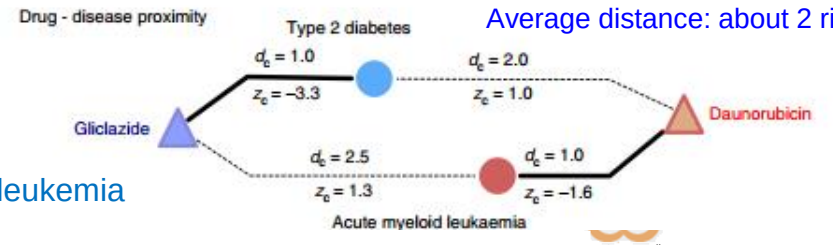



(Guney, Barabasi,2016, Nat. Com)




Average distance: about 2 rinks

AML: acute myeloid leukemia

# Need for Learning

- We are **still missing in understanding** of the necessary conditions for molecule to be effective
- We should find these conditions by **learning from the succeeded <disease-drug-target molecule> combinations**
- **Artificial Intelligence** (AI), specially **Deep Learning** is now the most powerful method

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# Artificial Intelligence based DrugDiscovery/DR

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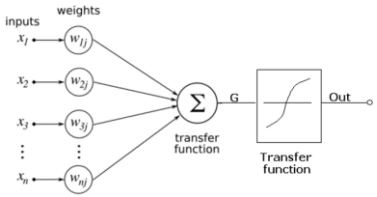
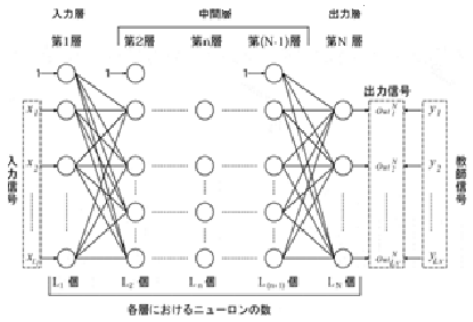
# Artificial Intelligence revolution by Deep Learning

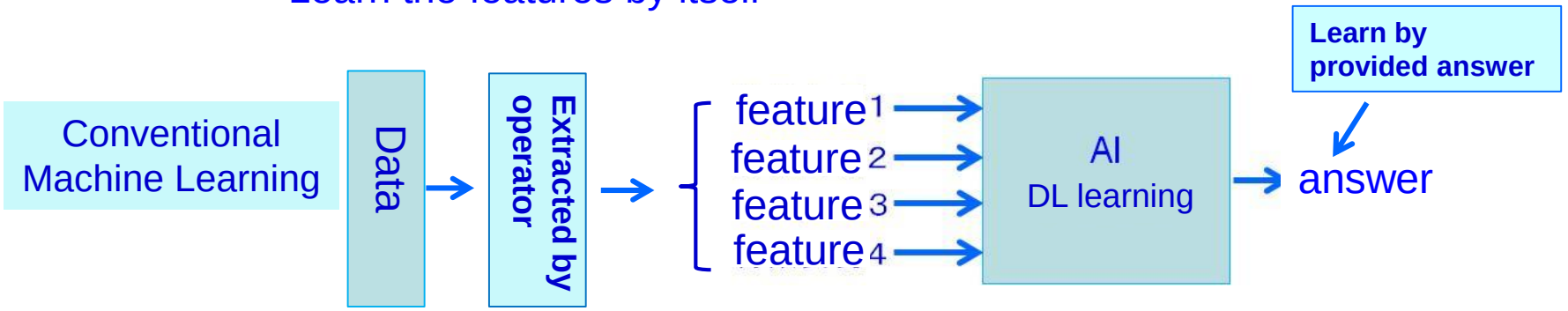
- Limitation of Machine Learning
  - "Supervised learning"
    - Construct AI by providing the feature and answer
- Deep Learning revolution
  - "Unsupervised learning"
    - Learn the features by itself

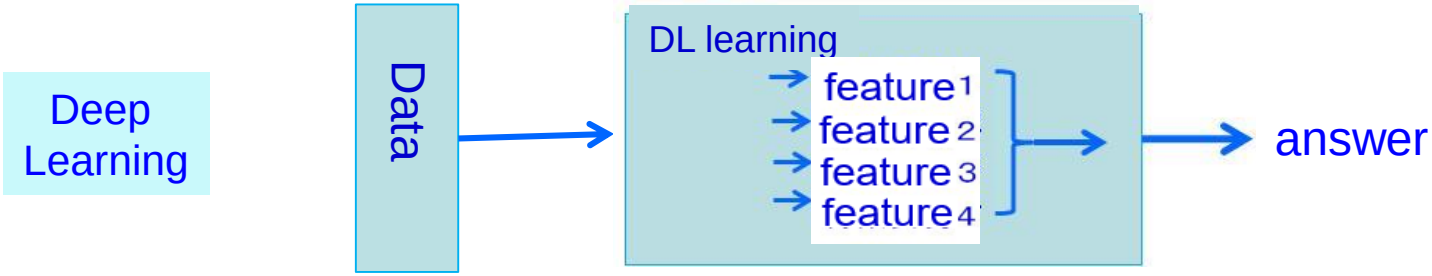



Neural information element



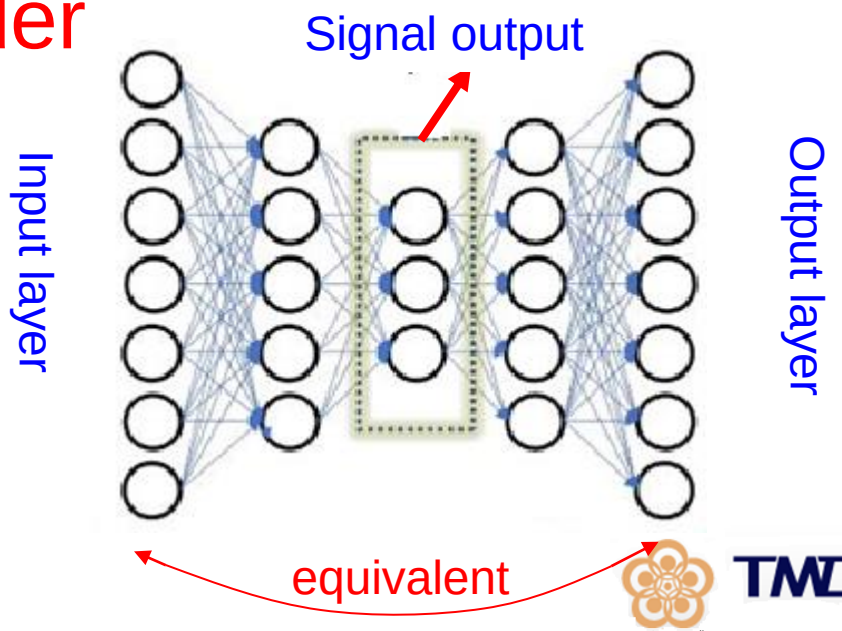
Multiple Layer neuro-network



# Revolutionary point of DL Autoencoder 2

- Consisting of multiple layers of autoencoders
  - stacked autoencoder
- Consisting of input layers(encoder) and output layers(decorder) which are contrasted
  - deep autoencoder

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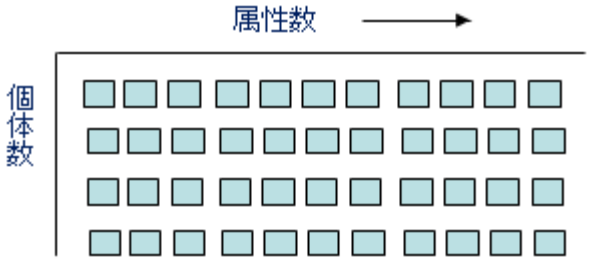
# Date principle of “Big Data”

Problem : number of attribute value (p)≫ number of sample (n)

p: may be several hundred million　n: At most tens of thousands, normally thousands




If all these huge nuber of attribute variables are independent, structural analysis of big data is impossible.

Big Data・Sparse theory

Big data is composed of a large number of independent components but less than the number of attribute values as its basis.

**Principle of compositionality**

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# Contracting method for multidimensional network by Deep Learning

- Application to big data of medicine and drug discovery
- Increase of “multidimensional network information structure”
  - Genome medicine : <comprehensive molecular information – clinical phenotype information>
  - Genome cohort : <gene – environment information> (lifestyle)
- Deep Learning-based Network Contraction

Multidimensional network information structure
⇒ Contact to be composed of a few network bases

- Not linear decomposition.
- Project to be composed of intrinsic bases by nonlinear decomposition.

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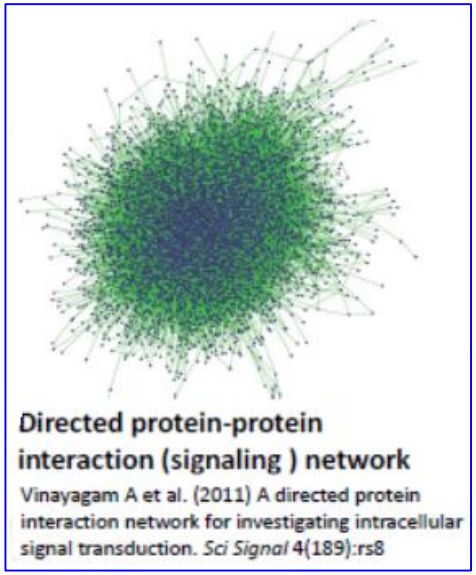
# Decomposition to intrinsic network basis

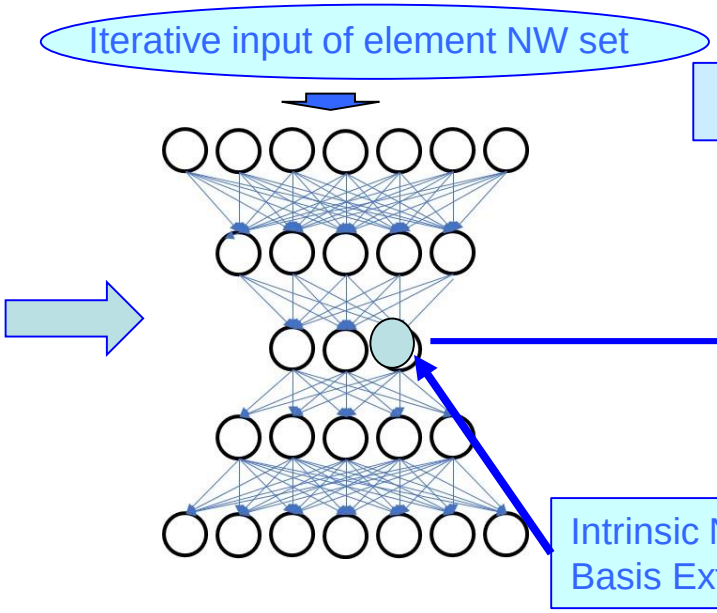
## Contracting to sum of intrinsic network bases

DL is applied to iterative presentation of element NW, where all network links are viewed as a sum of element NW (partial NW)

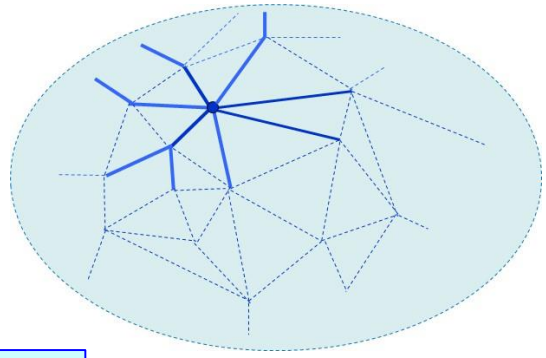
Sum of intrinsic network basis that reproduces all networks




PPI Network



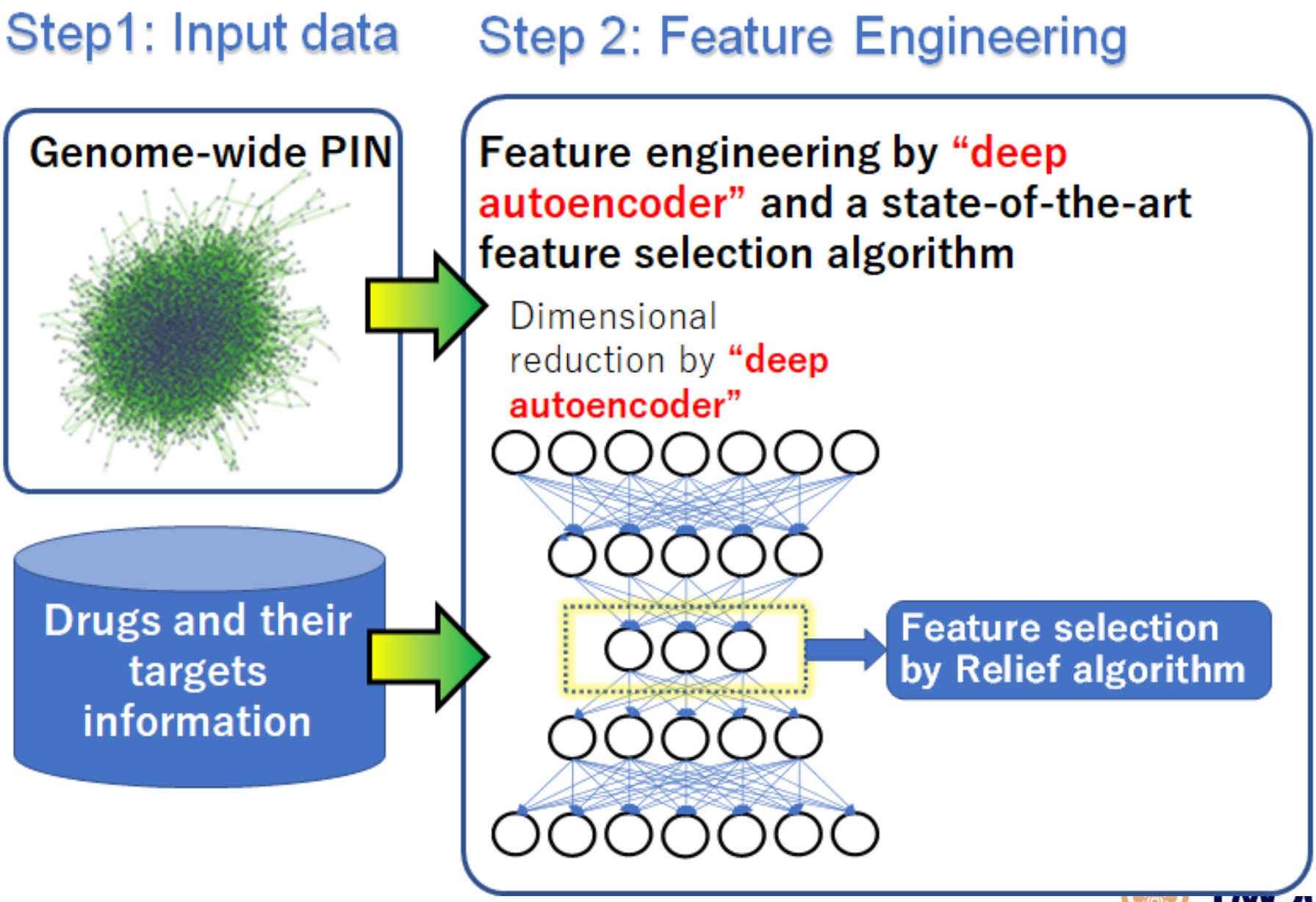

Intrinsic feature network basis



# Our Approach

- By using deep learning and genome-wide protein interaction network,
- We build a computational framework to predict potential Drug Target genes and
- Repositionable drugs for Alzheimer's disease.

## Our computational workflow

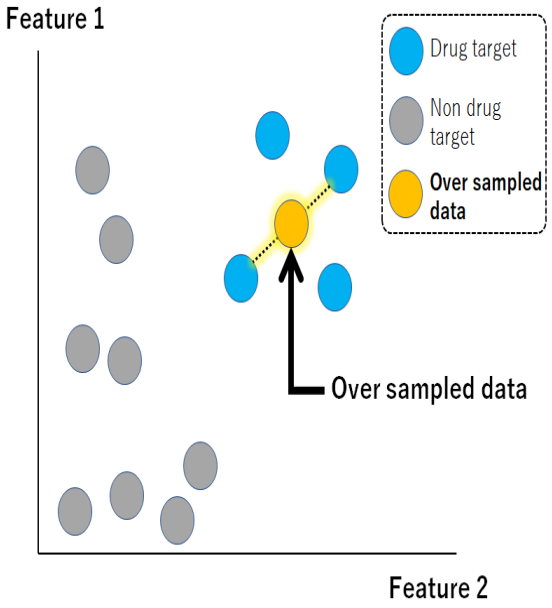


## Step 3: Classifier model

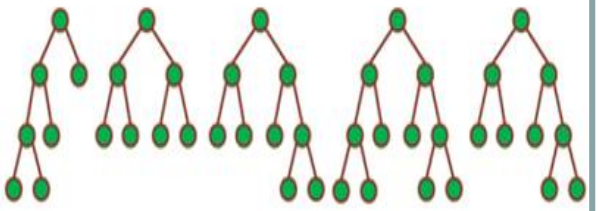
## Step 4: Target prioritization

**A binary classifier model to target prioritization by state-of-the-art machine learning algorithms**

SMOTE algorithm to build a training data




Xgboost algorithm to build a binary classfier



**Scores for potential targets**

| Gene | Score (mean probability) |
|---|---|
| GRASP | 0.982971499 |
| PGRMC1 | 0.98234516 |
| GPM6A | 0.98234516 |
| NRP2 | 0.975193546 |
| PFKM | 0.972127568 |
| DLGAP2 | 0.953659343 |
| CD81 | 0.941095327 |
| IQGAP1 | 0.926867425 |
| TROVE2 | 0.916886333 |
| TOP3B | 0.915745595 |
| TJP1 | 0.914564961 |
| PDGFB | 0.914082375 |
| SETD2 | 0.905462331 |
| CFLAR | 0.900456515 |
| PROS1 | 0.883435477 |
| SIT1 | 0.879989294 |
| SIGLEC7 | 0.879989294 |
| SHC2 | 0.879989294 |

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| | | |
|---|---|---|
| GRASP | PIK3C2B | PKIA |
| PGRMC1 | NEU3 | PFKP |
| GPM6A | SLC25A38 | PAN2 |
| NRP2 | TNFSF12 | GLUD1 |
| PFKM | ADRA1B | DNM3 |
| DLGAP2 | DPM2 | ITGA5 |
| CD81 | NLRP12 | RILPL2 |
| IQGAP1 | NLRC4 | MAEA |
| TROVE2 | UIMC1 | NCDN |
| TOP3B | IL8 | DGCR14 |
| TJP1 | VAV1 | PACSIN3 |
| PDGFB | ARHGEF1 | CD46 |
| SETD2 | WISP2 | NIT1 |
| CFLAR | PRKCE | ICAM4 |
| PROS1 | TBXA2R | GNA13 |
| SIT1 | TSPAN4 | STK40 |
| SIGLEC7 | EPHB4 | ROGDI |
| SHC2 | LOC63920 | CDH10 |
| SH2D1A | PSEN1 | WSB2 |
| | SPOCK3 | PHPT1 |
| | TSPO | |
| | SLC4A1 | |

By using the AI-based method, we successfully predict potential drug targets (more than 100 genes) for Alzheimer's disease.

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# Example,

# SLC25A38 (APPOPTOSIN)

SLC25A3 increases in the brain from Alzheimer's disease patients as well as from infarct patients. Further, SLC25A38 downregulation is likely to inhibit apoptosis induced by Bax/BH3I and neuronal death induced by Aβ/glutamate.

Previous Next

Featured Article | Articles, Cellular/Molecular

## Appoptosin is a Novel Pro-Apoptotic Protein and Mediates Cell Death in Neurodegeneration

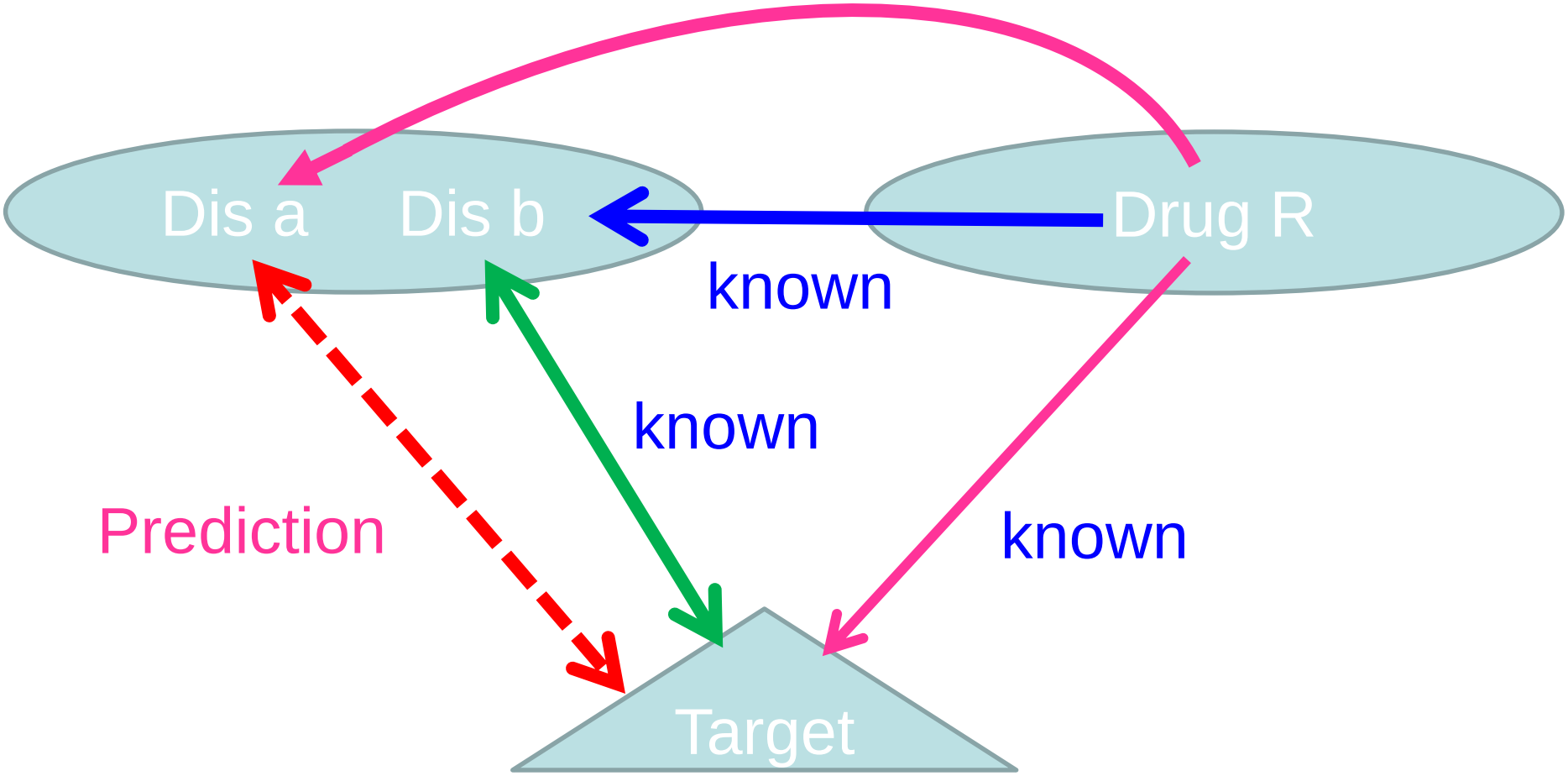
Han Zhang, Yun-wu Zhang, Yaomin Chen, Xiumei Huang, Fangfang Zhou, Weiwei Wang, Bo Xian, Xian Zhang, Eliezer Masliah, Quan Chen, Jing-Dong J. Han, Guojun Bu, John C. Reed, Francesca-Fang Liao, Ye-Guang Chen, and Huaxi Xu

Journal of Neuroscience 31 October 2012, 32 (44) 15565-15576; DOI: https://doi.org/10.1523/JNEUROSCI.3668-12.2012

# Possible DR for Alzheimer's Disease

- Computational network based methods may be among the most promising approaches for **computational drug repositioning.**
- Especially, drug-disease-target network would be useful resources to investigate novel indications for existing drugs.
- We mapped **predicted targets** on the drug-disease-target network and analysed the network to investigate **novel indications for existing drugs**

If predicted target for disease A is known drug-target of drug R for disease B, the drug R may be repositionable drug for disease A.



# Potential (predicted) repositionable drugs for Alzheimer's disease

| repositonable drug | taregt | # of target | category |
|---|---|---|---|
| Tamoxifen | PRKCB PRKCE PRKCG ESRRG | 4 | Anti-Estrogens; Antineoplastic Agents; Antineoplasti |
| Mianserin | SLC6A4 DRD3 OPRK1 ADRA1B | 4 | Adrenergic Agents; Adrenergic alpha-Antagonists; A |
| Amitriptyline | SLC6A4 OPRK1 ADRA1B OPRM1 | 4 | |
| Dextromethorphan | SLC6A4 PGRMC1 OPRM1 OPRK1 | 4 | Alkaloids; Antitussive Agents; Central Nervous Syste |
| Mirtazapine | OPRK1 ADRA1B DRD3 SLC6A4 | 4 | Adrenergic Agents; Adrenergic alpha-Antagonists; A |
| Tramadol | OPRM1 OPRK1 SLC6A4 | 3 | Alcohols; Amines; Analgesics; Analgesics, Opioid; C |
| Zinc | MPG SERPINA1 SERPIND1 | 3 | Acetates; Acetic Acid; Acids; Acids, Acyclic; Acids, N |
| Amoxapine | SLC6A4 DRD3 ADRA1B | 3 | Adrenergic Agents; Adrenergic Uptake Inhibitors; Al |
| Etorphine | OPRM1 OPRK1 OPRL1 | 3 | Alkaloids; Analgesics; Analgesics, Opioid; Central N |
| Tapentadol | OPRM1 OPRK1 SLC6A4 | 3 | Analgesics; Analgesics, Opioid; Benzene Derivatives |
| Loxapine | ADRA1B DRD3 SLC6A4 | 3 | Antipsychotic Agents; Antipsychotic Agents (First Ge |
| Pethidine | OPRK1 OPRM1 SLC6A4 | 3 | Acids, Heterocyclic; Adjuvants; Adjuvants, Anesthesi |
| Talampanel | GRIA1 | 1 | Benzazepines; Heterocyclic Compounds; Heterocycli |
| Etanercept | FCGR3B | 1 | Amino Acids, Peptides, and Proteins; Analgesics; A |
| Vitamin E | PRKCB | 1 | Antioxidants; Benzopyrans; Chemical Actions and Us |
| N-[(2R)-2-benzyl-4-(hydroxyamino)-4- | LTA4H | 1 | |
| Adalimumab | FCGR3B | 1 | Amino Acids, Peptides, and Proteins; Anti-Inflamm |
| ALPHA-HYDROXYFARNESYLPHOSPH | FNTB | 1 | Alcohols; Fatty Alcohols; Hydrocarbons; Lipids; Orga |

# Example,

The two FDA-approved drugs, **adalimumab and etanercept**, may be most promising candidates, because they are inhibitors of TNF-alpha (a key cytokine to regulate immune response) and overexpression of TNF-alpha cause inflammation in various organs, especially in central nerve system.

MedGenMed
Medscape General Medicine

MedGenMed. 2006; 8(2): 25.
Published online 2006 Apr 26.
PMCID: PMC1785182

**TNF-alpha Modulation for Treatment of Alzheimer's Disease: A 6-Month Pilot Study**

Edward Tobinick, MD, Assistant Clinical Professor of Medicine, Hyman Gross, MD, Clinical Professor of Neurology, Alan Weinberger, MD, Associate Clinical Professor of Medicine/Rheumatology, and Hart Cohen, MD, FRCPC, Associate Clinical Professor of Medicine/Neurology


CNS Drugs
November 2016, Volume 30, Issue 11, pp 1111–1120

Treatment for Rheumatoid Arthritis and Risk of Alzheimer's Disease: A Nested Case-Control Analysis

Authors Authors and affiliations

Richard C. Chou, Michael Kane, Sanjay Ghimire, Shiva Gautam, Jiang Gui

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**Our computational method would be promising approach to investigate novel drug targets and new indications for FDA-approved drugs.**

**We are now applying the method to investigate novel targets and repositionable drugs for various diseases including various types of cancers, rheumatoid, diabetes and etc.**

# Future strategies and trends

- Second stage of **genomic medicine and drug discovery**
- Contracting method for multidimensional network by Deep Learning
  - Apply to big data medicine
  - Correlative network structure of comprehensive molecular information – clinical phenotype in genome medicine
  - Disease onset and genetic – environment factor in biobank
- Framework of AI drug discovery has possibility to achieve
- Undertake the implementation of AI drug discovery at the end of this year. Otherwise all will be taken to the United States.
  - Establish the "Big data medicine/AI drug discovery consortium" to promote the project, coordinated by pharmaceutical company, IT company and medical institution

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