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단백질-단백질 상호작용 기반의 약물 리포지셔닝 맵

Drug-repositioning map based on protein-protein interactions

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Abstract

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Introduction: The development of new drugs is recognized as a time-consuming and risky process, which has increased interest in drug repositioning, i.e., the identification and development of new uses for FDA-approved drugs, as repurposed drugs can bypass much of the early cost- and

time-investment. I have developed the large-scale DreMap tool, featuring a web-based tool to discover new implementations for an existing drug's, based on known protein-protein interactions. According to data released by the Centers for Disease Control and Prevention, Ovarian cancer was ranked the fifth cause of cancer-associated death in women in the USA. To establish proper diagnosis and repositioning functions for ovarian cancer, I analyzed differentially expressed genes between 5-years survival group and 5-years death group of lymphatic invasion in serous ovarian epithelial cancer with DNA microarray. I suggested repositioning available drugs for ovarian cancer using Dremap database.

Methods: I connected the drug–target-protein information, protein-protein interaction information, protein–relevant disease information and protein–function relations to each other. Data from 63 ovarian cancer patients with lymphatic invasion and 35 ovarian cancer patients without lymphatic invasion from TCGA data were analyzed. DEGs identified with Bioconductor R package. Functional analyses of genes were analyzed with DAVID web tool.

Results: DReMap provides possible indications of 8849 drugs. I found 20 DEGs (*P*-value<0.001) from 35 ovarian cancer patients without lymphatic invasion. To gain insight into the 5-year survival related gene expression signatures, I demonstrated survival score values for 5 prognostic marker genes of patients without lymphatic invasion. I also suggested 13 repositioning available drugs for ovarian cancer using 5 prognostic marker genes and Dremap database.

Conclusions: Until now, most cases of drug repositioning have been the result of serendipitous observations. Through exploring the DreMap, researchers can obtain useful clues in regard to additional therapeutic effects of pre-existing drugs and explore their novel functions. I believe that my database will supply valuable information to users with regard to unknown pathways in drug mechanisms. I also suggested 5 prognostic marker genes and repositioning drug lists of ovarian cancer. These findings may have implications for future diagnosis and treatment of ovarian cancer.

Keywords: Drug repositioning, PPI, network analysis, database, OSE (ovarian serous epithelial cancer), biomarker

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Drug-repositioning map based on protein-protein interactions

Introduction

Until now, drug takers are unaware of the possible specific drug adverse effects, except for the noticed adverse effects which have been offered by the pharmaceutical companies. Pharmaceutical agents or drug users could know another actual adverse drug effects depends on the drug taker's reaction. However, in the several drug cases, it revealed that knowing the adverse effect after the patient took the drug was risky. Thalidomide was originally developed in Germany in 1954 as a cure for morning sickness. In the late 1950s and early 1960s, the woman received thalidomide has birth deformities **(Figure 1-12)**, the company stopped the sales of the drug. In 2010, it was indicated that birth deformities effect of the thalidomide is associated with suppressed expression of chick genes encoding Fgf8 and Fgf10 **(Figure 1-13)** (1). However, exactly how is unclear. In the lethal effect of the drug,

nevertheless, thalidomide had been studied to use in another reaction. In 1994, it was proposed that thalidomide can be a potent angiogenesis inhibitor (2). Numerous cancer clinical trials for thalidomide began based upon this finding (3, 4). In 2006, the FDA approved for thalidomide for the treatment of the multiple myeloma patients (5). Although the multiple myeloma treatment effects of the Thalidomide was presumed to be angiogenesis, lung cancer untreatable effect was not entirely understood. Thalidomide didn't improve survival in lung cancer (6). There are more cases without an accurate understanding of exactly how the drug worked, majority of drugs are being used. It has been demonstrated that leukemia treatment Novartis, Gleevec was designed to hit single protein (Bcr-Abl fusion protein). But it soon became apparent that Gleevec was not as specific. It revealed that Gleevec also inhibits a second protein PDGF receptor (7). Because the PDGF and Kit protein seemed like similar, the idea was proposed Gleevec could probably inhibit KIT (known to be linked to the GIST) as well (7). It has been suggested that Gleevec is effective to GIST (gastrointestinal stromal tumor).

Subsequently, several studies reported that Gleevec is an active agent for GIST. In spite of the secondary effect of the drug has been accepted effective, Gleevec's secondary target: PDGFR's action has not yet been elucidated. PDGFR is widely expressed in the majority of other STS (soft-tissue sarcoma) subtypes (8). however, results of the previous study confirmed that Gleevec does ineffective in other soft-tissue sarcomas (8). If the drug developers didn't understand the exact mechanism of action of the drug, then how does the pharmaceutical company do developed the drugs?

Drug developing concept and drug repositioning

In modern drug discovery, drugs have typically been developed for a specific gene product target, based on a “one target–one disease model”(7). It has long been recognized that an ideal drug was designed to hit single gene product completely **(Figure 1-1)**. For this reason, drug developers have firstly identified the three-dimensional structure of the target protein which causes the disease. X-ray crystallography has been used to elucidate the structure of the target protein complexes. If the novel synthesized ligand positioned within the binding pocket of the target protein and they didn’t have the toxicity in the animal test, this ligand can be a drug candidate.

However, due to the complexity of the many intricately interwoven cellular biological processes, numerous unexpected adverse drug reactions, like toxicity or drug resistance, occur. Therefore, many promising drug candidates

have failed to be approved by the FDA during clinical phases of drug development. For this reason, pharmaceutical companies have sought other approaches for drug development: drug repositioning or drug repurposing, i.e., to find new uses for existing drugs (9, 10). Since previously approved drugs have already passed a significant number of toxicity tests, this could result in faster drug development and reduced adverse risks. Drug repositioning can be a chance to new uses for existing drugs **(Table 1-1)**. Furthermore, it can find a rare disease treatment drugs. Nevertheless, previous drug studies have been limited by the lack of a technique that permitted prediction of secondary targets in vivo. In addition, previous pharmacological works have failed to show that trying to predict adverse effects and exactly how the drug worked. A proper understanding of mechanisms of the biological effects is needed because it guides prevention of the severe adverse effect.

In this regard, it is important to predict the secondary adverse effect of the drugs, using the human biological network resources and the adverse drug reactions, which has already been reported.

There have been several systematic approaches to understanding drug actions. There are two conceptual approaches for drug repositioning. One is 'On-target' drug repositioning, and another one is 'Off-target' drug repositioning (11). 'On-target' drug repositioning approach is using previous elucidated pharmacological mechanism to find novel repositioning indications. 'Off-target' drug repositioning approach is finding novel pharmacological mechanisms for known drugs **(Figure 1-2)**.

One of the most recent developments has been network studies in systems pharmacology, which incorporates relationships between drugs, their targets and disease components (12, 13). Many other computational drug repositioning methods have also been developed. Dudley et al. classified these computational repositioning strategies as "drug-based computational approaches" and "disease-based computational approaches." (14) The drug-based computational approaches infer similar binding sites for drugs, based on similarities in their chemical and molecular activities, or molecular docking. The disease-based computational approaches infer new indications for drugs,

using the associative transfer of indications, shared molecular pathology, or side effect similarities (15-18). Many network-based repositioning approaches have been applied in attempts to identify the novel repositioning functions for treating patients. However, in previous reports, drug-target relations, target-disease relations, and target compound (target interactive protein) relations have only been made available in separate databases or web texts, and compound-disease relations have not been clear or have been hidden in the databases (19).

Human biological network system

In our body, there exist many protein interactions and drug target proteins. If the target protein cannot function normally, target interactive proteins can take effect. Also, Target interactive proteins' original functions or related disease can take effect. If the target proteins interactive proteins function is directly related to adverse drug effect, we can explain or predict the unknown drug adverse effects. Large sets of protein–protein interaction (PPI) data hold the promise of providing many clues to the intricate web of intracellular systems. However, because of the limited reliability of lack of PPI data and the difficulties entailed in processing complex multidimensional data (20, 21), a large set of PPI proteins, that are not yet been considered to explain the adverse drug effect or drug repositioning mechanism of action of previously developed drugs. Typically, when unexpected adverse effects of a drug occur,

biologists attempt to explain the mechanisms underlying these adverse effects by turning to the relevant pathways. They surmise that the unexpected adverse effects of the drug involve particular pathways, and they attempt to reconcile pathways associated with the action of the drug to these novel pathways. Yet, explanation of drug mechanisms through known pathways does not provide sufficient information to lead to the understanding of an entire process.

PPI reliability

Experimental verification of PPI data has been problematic in the past (20, 21). Validation of high throughput screening methods tends to miss weak interactions, which can cause a decrease in reproducibility of PPI data. Decreasing the error rate and increasing reproducibility are important. However, the strength of the biological interactions cannot determine the clinical importance of these reactions, and weak interactions can still offer excellent insights into human cellular mechanisms.

Previous technical problems: PPI data

Previously, PPI data was not easily accessible to biologists because of its complexity and the paucity of analysis tools. PPI is not unidirectional, but multi-dimensional. When pharmacologists and biologists convert the available binary PPI data into multi-dimensional network data, they can easily miss the direction of the interactions. Furthermore, because of the complexity of the data integration problem, previous PPI visualization tools could not offer the disease-related functions of the proteins and their function of interest to pharmacologists. These instruments could only offer each protein's disease function by means of a web link. For this reason, pharmacologists have been burdened with manually accessing multiple disease and function links. Moreover, PPI networks did not consider an explanation of the drug mechanism or the drug repositioning method. In this respect, it is necessary to

develop more efficient systems as pharmacological tools; and tools currently being developed will help to solve these problems.

Previous works

I have developed the Cytoscape plugin tools and implemented the existing drug targets in the Cytoscape tools. **Figure 1-3** shows human protein interaction networks in the Cytoscape tools. Blue dots are proteins, and cyan lines are edges representing protein interactions. Yellow dots are drug targets. Because of its complexity and the absence of the drug names and protein functions, this couldn't explain the exact drug mechanisms or drug functions in these networks.

Technical purpose of this study

In relation to the systems pharmacology and drug-based approach, I have attempted to extend the possible indications of 8849 drugs by presenting the disease name in relation to the protein that interacts with the drug-target protein. Before I constructed the DReMAP database, I first mapped the drug-target proteins within the protein interaction network, and sought the functions of each protein and the associated disease names.

Interestingly, I found that many of these functions and disease names that were related to the primary interactive proteins were directly related to drug repositioning functions. Although more experimental proof is needed to support this mechanistic observation, I considered that this mechanism is potentially important, because researchers can obtain the names of potential therapeutic-target diseases through the protein-protein interaction network.

For this reason, I parsed web texts and constructed a secondary database, integrating the drug–target-protein interactions, target-protein–protein interactions, protein–disease relations, and protein–function relations. All of these drug relations are available in a single network, and thus, researchers can easily perform a search of the drugs' secondary functions through the integrative DReMap network.

Materials and Methods

To obtain the drug and target protein list, I initially downloaded and parsed DrugBank's DrugCard.txt file (22), and extracted the drug name and the target-protein names. Most drugs target only a few proteins, but some target many proteins. Likewise, many proteins are targeted by more than 1 drug. For this reason, I used a hash function to identify target proteins to their associated values. Next, I extracted protein-protein interaction information from the human protein interaction database in the BOND website (23).

I then required the disease names and functions linked to the target proteins. For that purpose, I parsed the OMIM (24) disease text file and Drugcard website text files. Moreover, I parsed the Genecards webpage and constructed the gene alias database. Then, I connected the drug target-protein information, protein-protein interaction information, protein–relevant disease information

and protein–function relations to each other. My web application model follows a model-view-controller (MVC) architectural pattern. The model is written in Java and MySQL while the visualization network and controller modules are based on Flex.

Results

The complex networks of cellular processes present two main challenges: to infer potential off- target effects from networks and to reposition pre-existing drugs for novel clinical uses. In response to the latter, I have developed the large-scale DReMap website, featuring a web-based tool to find new implementations of existing drugs based on known protein-protein interactions. I can find useful clues for drug repositioning through protein-protein interaction data representing molecular networks. DReMap provides 8849 drug-target networks. Dremap include Drug-target protein interactions, target protein-protein interactions, protein-disease relationships and protein-function relationships **(Figure 1-4) (Fig 1-16)**.

Difference between the previous works

In previous works, available in the databases or web texts, the relationship between (target protein) – (disease) relations and that between the (target protein) – (interactive protein or gene) relations are often available, but the relationship between (target interactive protein or gene) – (disease) relations are unavailable. Also, in previous works, each relationship is either individually available or partially available in the databases or web texts, in this work, on the other hand, all of the relationships are available in the network **(Figure 1-5)**.

First of all, Dremap provides 8849 drug-target network **(Figure 1-6)**. In Dremap website (Fig 1-17) users can see their (target proteins and their interacting proteins) functions, Genesymbol names and their related disease names.

In addition, I solved the gene alias problems. For example, one of the drug Reteplase target protein is F10. And eco is its interacting protein. As shown in bottom figure (genecard website) **Figure 1-8** ICK aliases are intestinal cell (MAK-like) kinase, EC 2.7.11.22, etc. Therefore, I considered standard names for the alias (ECO=ICK) and constructed the database. As in the bottom **Figure 1-9,** Dremap shows the eco function with ICK function.

Efficiency of Dremap

Here, I use the drug Finasteride as an example to show the efficiency of my database, in **Figure 1-10**. Originally, Finasteride was reported to be effective for treating male baldness and benign prostatic hyperplasia. However, recent clinical studies have reported Finasteride's new indication, for treating prostate cancer (25, 26). Still, the mechanism of drug action explaining this new indication remains unclear. In **Figure 1-10**, Finasteride's direct target proteins are clearly shown as SRD5A1 and AR. When a user double-clicks on the "Finasteride" cell in the table on the left side, the drug–target-protein network becomes visible. Users can then click on the next target protein (e.g., AR), as shown in Figure 1b. In a similar manner, users can see the name and function of the next interactive target-protein.

Interestingly, the previous study reported FGF10 (FGF10 is related to Ladd syndrome occurrence) **(Figure 1-11**) and Thalidomide primary target FGFR2 protein is related to protein interaction. Also, I found the relationship between Gleevec's target protein abl1 and robo1 protein (it is related to small cell lung cancer) is again based on protein interaction (**Table 1-3)**.

Previous explanation of the mechanism of drug adverse effects

There are insufficient explanations of the drug mechanisms using the previously identified mechanisms. Three typical, well-known examples of adverse drug effects are the anticancer effect of statins, and coronary artery disease prevention and reduction of colorectal cancer related to contraceptive drug use.

Statins were originally developed as cholesterol-lowering drugs. However, recent studies have suggested that statins reduce the risk of many malignancies (27-29). Statins are 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors that limit the mevalonate pathway in cholesterol synthesis (30). The mevalonate pathway results in isoprenoid synthesis; isoprenoids, in turn, activate Ras and Rho GTPases (30), which are involved in regulation of the cell cycle and apoptosis. Therefore, many oncologists

consider that this tumor-treatment effect is related to the Ras and Rho proteins (31). However, only 20% of human tumors have point mutations in the RAS gene (31), and the relation between specific oncogenes and Ras and Rho have not been defined. Therefore, the precise mechanisms of anti-oncogenic responses to statins remain to be elucidated.

Furthermore, recent clinical studies have demonstrated a relationship between contraceptive drug use and coronary artery disease (32-34). Many clinical studies have shown that estrogen prohibits the development of coronary artery disease (35). One mechanism by which estrogen can have protective effects appears to be through changes in carbohydrate and lipoprotein metabolism (36). However, the molecular mechanisms by which estrogens prevent coronary artery disease are not clear.

Lastly, the use of contraceptive drugs has been shown to be associated with a reduced risk of colorectal cancer (37-39). One explanation for this involves the effect of hormones on bile acid (40). This hypothesis states that hormonal

status affects bile acid metabolism, thereby influencing the proclivity for colon cancer. However, this hypothesis cannot explain a direct correlation between bile acid metabolism and colon cancer, and therefore, it does not explain the effect of contraceptives on colorectal cancer.

Disease-related function of the target protein interactor and possible therapeutic effects

PPI analyses clearly show that some drug repositioning functions coincide with the disease-related function of a protein that interacts with the original drug-target protein. As the table below shows, the primary target protein for atorvastatin is AHR, and one of the AHR-interacting proteins is ARNT. The disease-related functions of ARNT are associated with acute myeloblastic leukemia. Another interactor of the target protein AHR is RB1; the disease-related functions of RB1 are associated with retinoblastoma, osteosarcoma, and bladder cancer. Similarly, HDAC1 is the primary target protein of lovastatin. One of the HDAC1-interactive proteins is BRCA1; the disease functions of BRCA1 are associated with breast cancer and ovarian cancer.

Thus, analysis of PPI data has been able to demonstrate that the functions of the target protein interactors relate to the anticancer effects of the statin drugs seen in clinical studies.

How does this explain the relationship between the PPI and the therapeutic effect? PPI occurs when 2 or more proteins bind to each other. PPI is a two-way process, and it does not per se imply a direction in terms of activation or suppression. Let us consider 3 cases of protein interaction (**Figure 1-14)**:

1) Protein A activates the function of protein B

2) Protein A suppresses the function of protein B

3) Proteins A and B simply interact with each other

This can be explained by the concept of agonist.

1) Protein A is the full or partial agonist of protein B

2) Protein A is the reverse full or partial agonist of protein B

3) Protein A is the neutral agonist of protein B

For the first case, where protein A activates the full agonist of protein B, let us consider that protein A is the drug target protein (**Figure 1-15)**. When the drug inhibits the function of protein A, Protein A can be the partial agonist of protein B. Protein B cannot be activated due to the lack of protein A function. When the function of protein B relates to disease occurrence, protein B-related disease then cannot occur (**Figure 1-16)**. Using this mechanism, we can explain the repositioning mechanism (**Table 1-4)**. If the protein AHR is the full agonist of protein ARNT, Protein AHR can be the partial agonist of protein ARNT when atorvastatin inhibits the function of the target protein AHR. Consequently, ARNT, which is activated by AHR, cannot function either, and the disease-related function of ARNT is also inhibited. According to this mechanism, atorvastatin could be used to treat acute myeloblastic leukemia. Evidently, this method of deduction also has to consider the relation

between the interactor protein and its disease-related function. Here, as a tumor suppressor, RB1 inhibits tumor formation when functioning normally. Yet when it is inhibited, tumors may result. By this reasoning, in the context of a wild-type RB1, it is plausible that atorvastatin may promote these cancers in which RB1 is involved. In situations where RB1 is defective or absent, the drug may result in inhibition of the defective RB1, and thereby treat an existing condition.

As the table below shows, the primary target of contraceptive drugs is ESR1, and one of its interactors is ABC1 (**Table 1-5)**. The disease-related functions of ABC1 involve coronary artery disease. Another ESR1 interactor is EP300, which exerts disease-related functions associated with colorectal cancer.

According to this analysis, the relationship between ESR1 and ABC1 is that of PPI. When a contraceptive drug inhibits the function of the target protein ESR1, then ABC1 cannot function, given that ESR1 activates the function of

ABC1. Therefore, contraceptive drugs could be used to treat coronary artery disease.

Likewise, the secondary function of contraceptive drugs can be explained. Once again, the relationship between ESR1 and EP300 (**Table 1-6)** is that of PPI. When the contraceptive drug inhibits the function of the target protein ESR1, EP300 cannot function either, given that ESR1 activates the function of EP300. Thus, contraceptive drugs could be used to treat colorectal cancer (**Table 1-7)**.

Using this type of analysis, I suggest that the interactors of primary drugs and target proteins can become secondary targets of the same drug, possibly for a secondary use.

Explanation of the adverse effects

This approach works well for drug repositioning in the case of a target protein A that activates protein B. However, drugs also have negative side-effects. Thus, I have to consider a case where the drug target, protein A, suppresses the function of protein B. In this case, if protein A suppresses the function of protein B, the disease-related functions of protein B will be activated. Therefore, by this mechanism, the drug could have a worsening effect in disease treatment.

A previous study has shown that diethylstilbestrol increases the risk of thyroid cancer (41). However, the exact mechanisms remained unexplained. Through PPI analyses, this effect of diethylstilbestrol on thyroid carcinoma can be explained by examining the interactors of ESR1, the primary target of the drug. TIF1 protein is one of the interactors of ESR1 (**Table 1-8)**.

Equation in the Dremap

In the paragraphs to follow, Drug repositioning method for determining the direction of the disease equation is described.

Disease will be caused by protein,

$$\sum_i P_{ij} S_i \xrightarrow{k} \sum_i D_{ij} S_i$$

Energy value means a direction of the agonist.

$$E = \begin{cases} +1: & agonist \\ -1: & reverse\ agonist \\ 0: & neutral\ agonist \end{cases}$$

Protein interaction reaction and the formation of protein interaction complex will be represented by this equation

$$P_1 + P_2 \rightleftharpoons P_1 P_2$$

Chemical equilibrium of drug-protein binding will be represented that,

Drug+Protein ↔ Drug Protein

Keq=Kassoc (association constant)=Kb (binding constant)

Keq =[Drug Target]/[Drug][Target]

Velocity of reaction value will be determined by Michaelis–Menten kinetics,

$$V_0 = \frac{V_{\max}[S]}{K_m^{\text{app}} + [S]}$$

Thus, the direction of disease (direction of the Dremap's repositioning function) will be determined by the existence of inhibitor (I_c), the velocity of reaction and direction value of the agonist.

$$K = E * V_0 * I_c$$

Through exploring the DreMap, researchers could obtain useful clues in regard to additional therapeutic effects of pre-existing drugs and explore their novel function.

Validation of Dremap

To validate my system, I compared dremap repositioning result to the drug repositioning results, which is presented in the previous paper (11). Many of previous reported repositioning indications were due not to specific disease, but due to diverse symptoms of disease, and, therefore, comparing repositioning functions were rather ambiguous. In spite of such hardship, I manually validated and annotated common mesh terms with Dremap predictions and previous reported repositioning indications.

Among previous reported 83 repositioning drugs, 25 drugs have target interactive proteins. Among those 25 drugs, repositioning functions of 13 drugs (52%) could be fully inferred from my dremap system **(Table 1-3)**.

I also tested some variables that represent whether the availability of actual repositioning or not. I divided the variables into 2 groups: (Prediction (+): Dremap can predict previous repositioning result) and (Prediction (-): Dremap can't be predict) based on the previous reported repositioned cases. From this test, I found out that 2 variables (Length of P2 protein, Molecular weight of P2 protein) can be used to predict two groups (Prediction (+), Prediction (-)). *F*-test result shows a statistical difference between two groups using variable factor **(Table 1-2)**. Several studies reported that molecular binding affinity depends on molecular weight and binding site residue (42). Because of the pharmaceutical companies have been selected small molecules that bind with high affinity to ligand (43), the majority of previous drug repositioning results would have been based on high-affinity binding results rather than low affinity binding. Low-affinity binding can also plays an important role in the

drug mechanism. In this respect, the result which Dremap cannot predict is not only false positive results but also could be a novel possible repositioning list.

Table 1-1. Examples of drug repositioning [1]

Generic	Original indication	New indication
Buproion	Depression	Smoking cessation
Dapoxetine	Analgesia	Premature ejaculation
Duloxetine	Depression	Stress urinary incontinence
Fluoxetine	Depression	Premenstrual dysphoria
Milnacipran	Depression	Fibromyalgia syndrome
Sibutramine	Depression	Obesity

http://www.nature.com/nrd/journal/v3/n8/fig_tab/nrd1468_T1.html

[1] Drug repositioning: identifying and developing new uses for existing drugs, Ted T. Ashburn & Karl B. Thor, Nature Reviews Drug Discovery 3, 673-683 (August 2004), doi:10.1038/nrd1468

Table 1-2. Prediction rate of repositioning function

	Prediction (+)		**Prediction (-)**		***p*-value**
	Mean	SD	Mean	SD	
Length of P2	947.92	798.53	617.33	334.04	0.0075
Molecular weight of P2	104600.41	87452.67	68964.00	37270.60	0.0087

Table 1-3. Validation results of Dremap

Drug	Original indication	New indication	Target Interactive protein	p1	p2	p2-disease	Common Mesh term
Thalidomide	Morning sickness	**multiple myeloma** and erthema nodosum leprosum	exist	NFKB1	BCL3	**Leukemia/lymphoma**, B-cell, 3	Neoplasm
Raloxifene hydrochloride	Osteoporosis in postmenopausal women	Breast **cancer** in postmenopausal women	exist	ESR1	EP300	Colorectal **cancer**, 114500	Neoplasm
Amantadine	Influenza	**Parkinson's disease**	exist	GRIN3A	Tat	**Tyrosinemia, type II**, 277660	Brain Disease
Etanercept	Rheumatoid arthritis	Anti-TNF treatment for **neurological disorders.**	exist	TNF	Tat	**Tyrosinemia, type II**, 277660	Nervous System Diseases
Tamoxifen	Treats metastatic breast cancers,	**Bipolar disorder**	exist	ESR1	ABC1	**Tangier disease**, 205400	Nervous System Diseases
Memantine	Anti-influenza	**Parkinson disease**	exist	GRIN2A	Tat	**Tyrosinemia,** type II, 277660	Brain Disease
Bexarotene	Used to treat patients with T cell lymphoma	Pathological and behavioral improvements in transgenic mouse models of **AD**	exist	RXRA	PPARG	Obesity, severe, 601665 ; [Obesity, resistance to] ; **Glioblastoma**, susceptibility to, 137800 ; Lipodystrophy, familial partial, type 3, 604367 ; Diabetes, type 2,	Nervous

Canakinumab	RA in a Phase II trial	**Muckle–Wells syndrome**	exist	IL1B	Tat	**Tyrosinemia,** type II, 277660	Genetic Diseases, Inborn
Fulvestrant	Cancer	**Glioblastoma**	exist	ESR1	EP300	**Colorectal cancer**, 114500 ; Rubinstein-Taybi syndrome 2, 613684	Neoplasms
Imatinib	Certain types of leukaemia and soft tissue sarcoma	may provide a new option for treating advanced **Pulmonary Arterial Hypertension**.	exist	ABL1	NTRK1	Insensitivity to pain, congenital, with **anhidrosis**, 256800	Sweat
Galantamine	Glaucoma	**Alzheimer's disease**	exist	CHRNA4	CHRNB2	**Epilepsy**, nocturnal frontal lobe	Brain Diseases
Nilotinib	Leukemia	**Alzheimer's disease**, Parkinson's disease	exist	ABL1	NTRK1	**Insensitivity to pain**, congenital, with anhidrosis, 256800	Nervous System Diseases
Avastatin	Metastatic colon cancer and nonsmall cell lung cancer	**Metastatic breast cancer**	exist	HDAC2	BRCA1	**Breast-ovarian cancer, familial, 1,Pancreatic cancer**	Neoplasm

Drug	Drug's primary target	target protein interactor	Function of the interacting protein

Table 1-4. Drug repositioning effects of Thalidomide

Thalidomide	FGFR2	FGF10	Aplasia of lacrimal and salivary glands, 180920 ; LADD syndrome,149730
Thalidomide	TNF	Tat	Tyrosinemia, type II, 277660
Thalidomide	NFKB1	BCL3	Leukemia/lymphoma, B-cell, 3
Thalidomide	NFKB1	CTNNB1	Colorectal cancer ; Hepatoblastoma ; Pilomatricoma, 132600 ;Ovarian cancer, 167000 ; Hepatocellular carcinoma
Thalidomide	NFKB1	NFKBIA	Ectodermal dysplasia, anhidrotic, with T-cell immunodeficiency,612132
Thalidomide	NFKB1	Tat	Tyrosinemia, type II, 277660

Table 1-5. Anticancer repositioning effect in statin drugs

Generic name	Medical use	Novel effect	Novel effect direction	Drug's primary target	Function of the target protein	Primary target protein interactor	Function of the interacting protein
Atorvastatin	Cholesterol lowering	Acute myeloblastic leukemia (44)	Decrease	AHR	Regulates xenobiotic-metabolizing enzymes	ARNT (45)	Acute myeloblastic leukemia
Atorvastatin	Cholesterol lowering	Retinoblastoma (46)	Decrease	AHR	Regulates xenobiotic-metabolizing enzymes	RB1 (47)	Retinoblastoma
Atorvastatin	Cholesterol lowering	Osteosarcoma (48)	Decrease	AHR	Regulates xenobiotic-metabolizing enzymes	RB1 (47)	Osteosarcoma
Atorvastatin	Cholesterol lowering	Bladder cancer (49)	Decrease	AHR	Regulates xenobiotic-metabolizing enzymes	RB1 (47)	Bladder cancer
Lovastatin	Cholesterol lowering	Breast cancer (50)	Decrease	HDAC2	Deacetylation of lysine residues	BRCA1 (51)	Breast cancer
Lovastatin	Cholesterol lowering	Ovarian cancer (52)	Decrease	HDAC2	Deacetylation of lysine residues	BRCA1 (51)	Ovarian cancer

Table 1-6. Beneficial effect of contraceptive drugs on coronary artery disease

Generic Name	Medical Use	Novel effect	Novel effect direction	Drug's primary target	Function of the target protein	Primary target protein interactor	Function of the interacting protein
Medroxyprogesterone	Contraceptive	Coronary artery disease (53)	Decrease	ESR1	Nuclear hormone receptor	ABC1 (54)	Coronary artery disease related
Levonorgestrel	Contraceptive	Coronary artery disease (55)	Decrease	ESR1	Nuclear hormone receptor	ABC1 (56)	Coronary artery disease related
Norgestrel	Contraceptive	Coronary artery disease (57)	Decrease	ESR1	Nuclear hormone receptor	ABC1 (56)	Coronary artery disease related
Toremifene	Contraceptive	Coronary artery disease (58)	Decrease	ESR1	Nuclear hormone receptor	ABC1 (56)	Coronary artery disease related

Table 1-7. Beneficial effect of contraceptive drugs on colorectal cancer

Generic Name	Medical Use	Novel effect	Novel effect direction	Drug's primary target	Function of the target protein	Primary target interactor	Function of the interacting protein
Medroxyprogesterone	Contraceptive	Colorectal cancer treatment (37)	Decrease	ESR1	Nuclear hormone receptor	EP300 (59)	Colorectal cancer treatment
Levonorgestrel	Contraceptive	Colorectal cancer treatment (37)	Decrease	ESR1	Nuclear hormone receptor	EP300 (59)	Colorectal cancer treatment

Table 1-8. Effect of diethystilbestrol on thyroid carcinoma

Generic Name	Medical Use	Adverse effect	Novel effect direction	Drug's primary target	Function of the target protein	Primary target interactor	Function of the interacting protein
Diethylstilbestrol	Endocrine disruptor	Thyroid carcinoma (41, 60)	Increase	ESR1	Nuclear hormone receptor	TIF1	Thyroid carcinoma

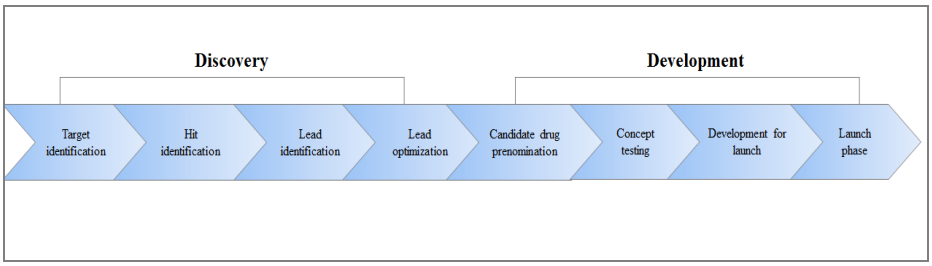
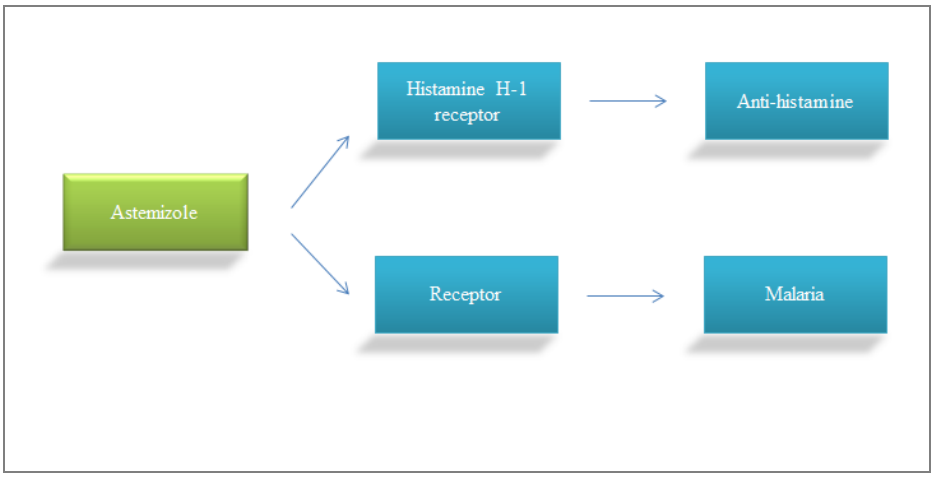


Figure 1-1. Drug development process[2]

On- target drug repositioning



Off-target drug repositioning

[2] Ashburn, Ted T., and Karl B. Thor. "Drug repositioning: identifying and developing new uses for existing drugs." Nature reviews Drug discovery 3.8 (2004): 673-683.

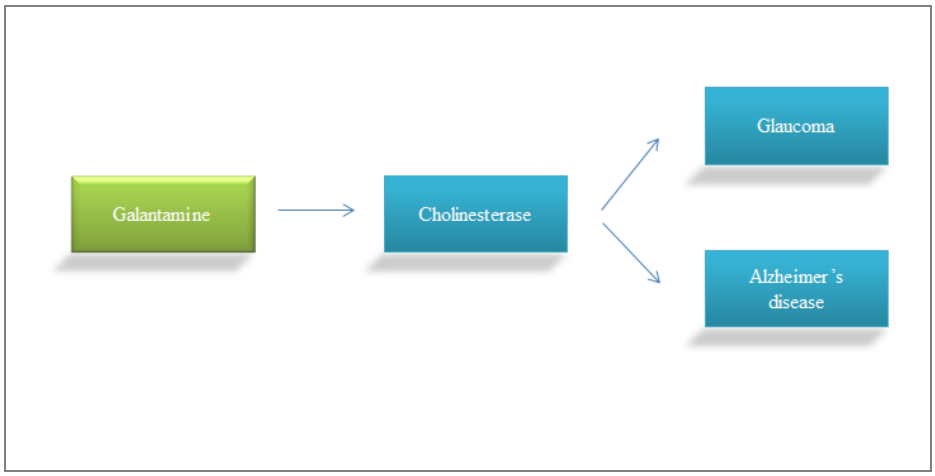


Figure 1-2. Two approaches for drug repositioning[3]

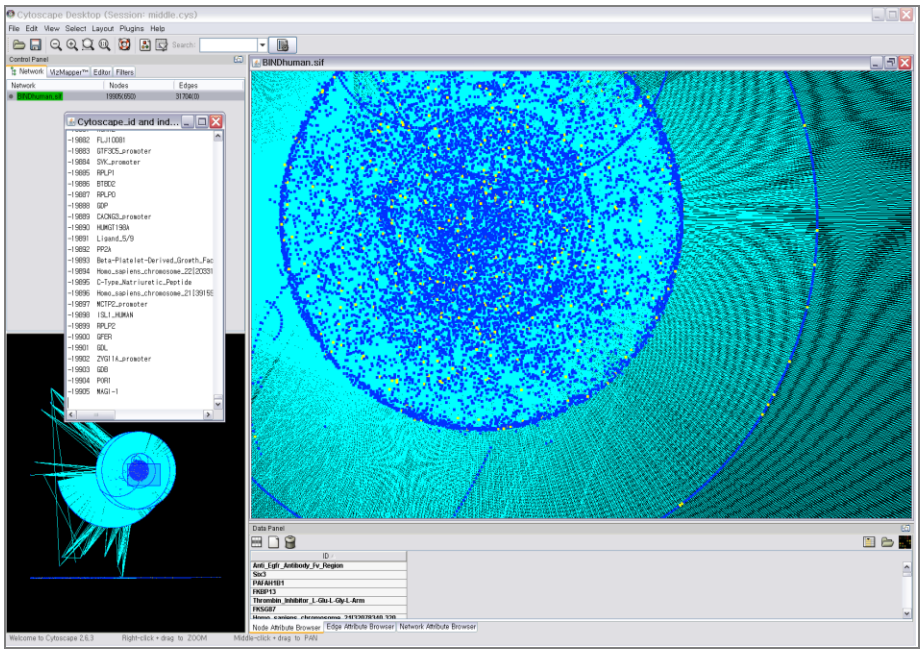


Figure 1-3. Previous network analysis works

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[3] Ekhon BS. Repositioning drugs and biologics: Retargeting old/existing drugs for potential new therapeutic applications. J Pharm Educ Res. 2013;4:1-15.

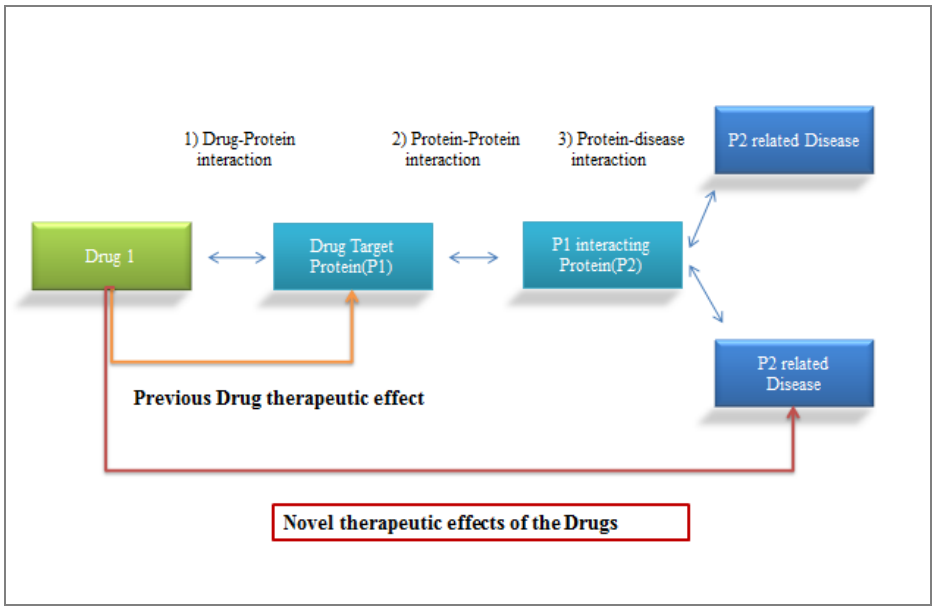
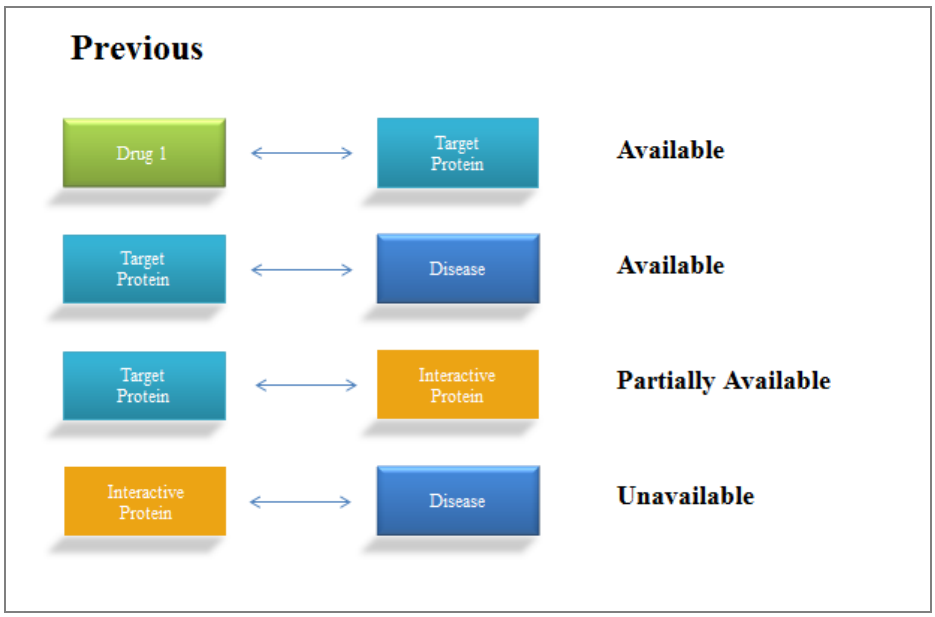


Figure 1-4. Dremap workflow



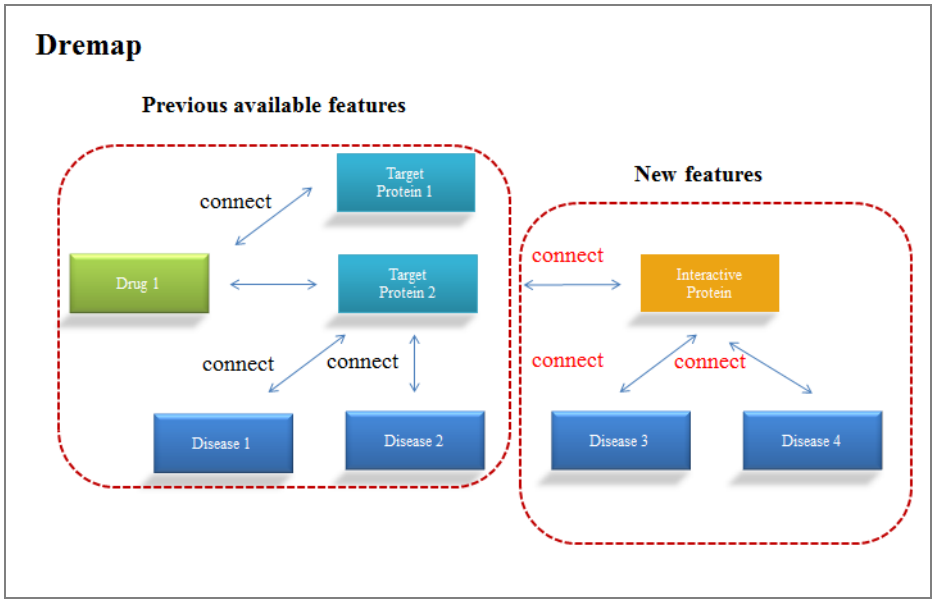


Figure 1-5. Difference between the Dremap and the previous works

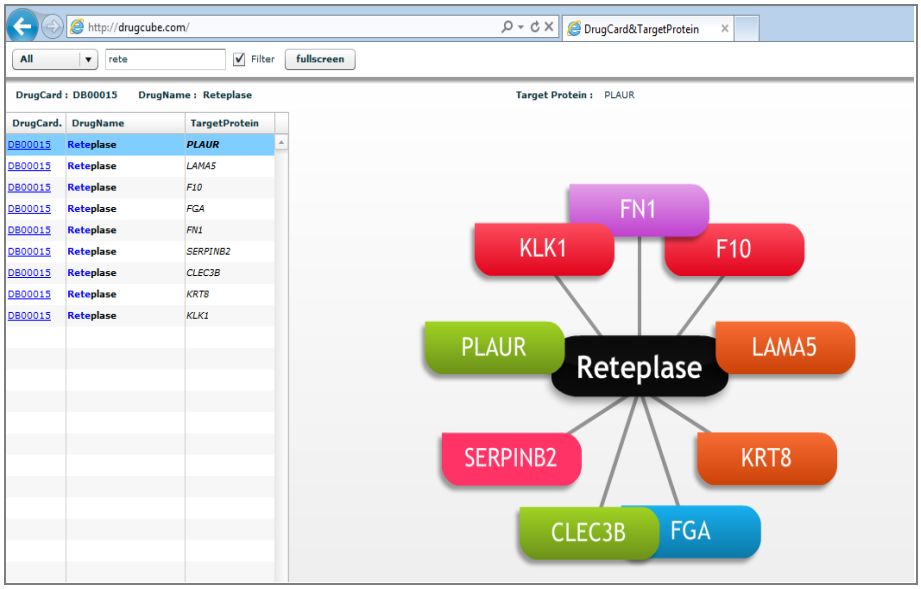


Figure 1-6. Dremap result

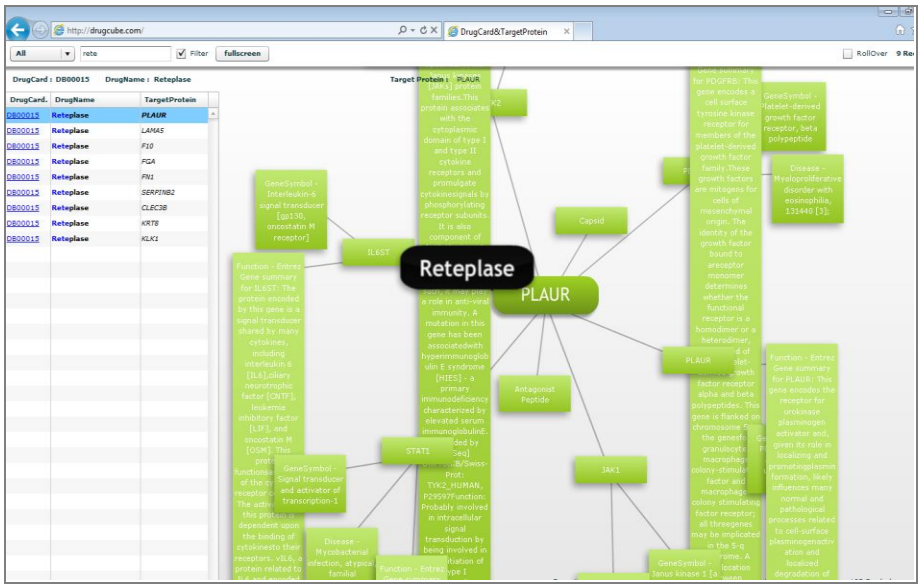


Figure 1-7. Dremap result

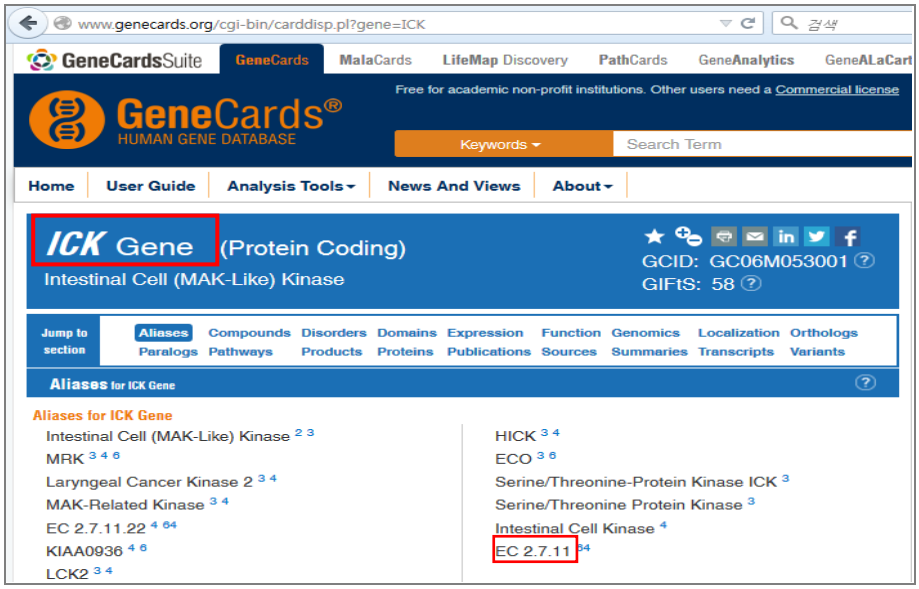


Figure 1-8. Gene alias example[4]

[4] Genecard, 2015, http://www.genecards.org/cgi-bin/carddisp.pl?gene=ICK

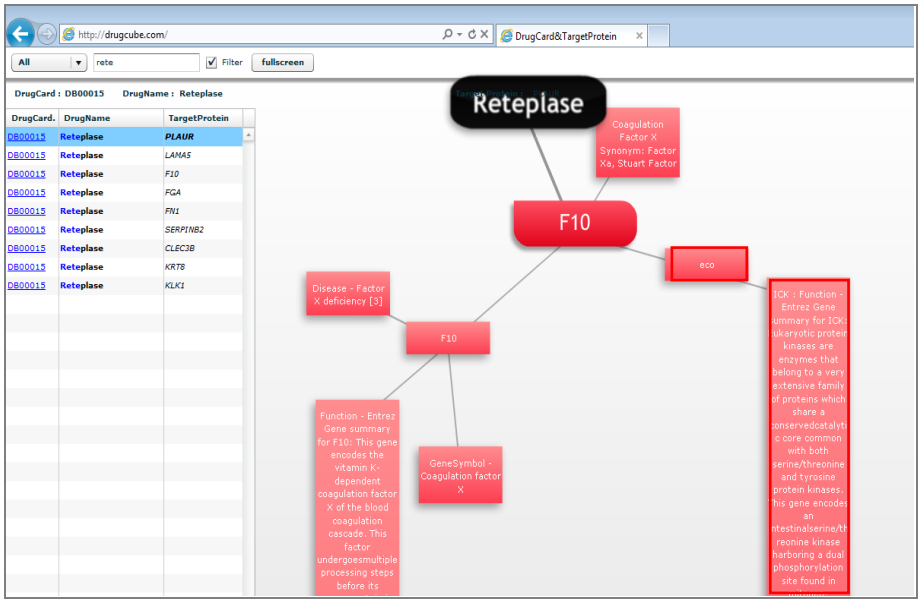
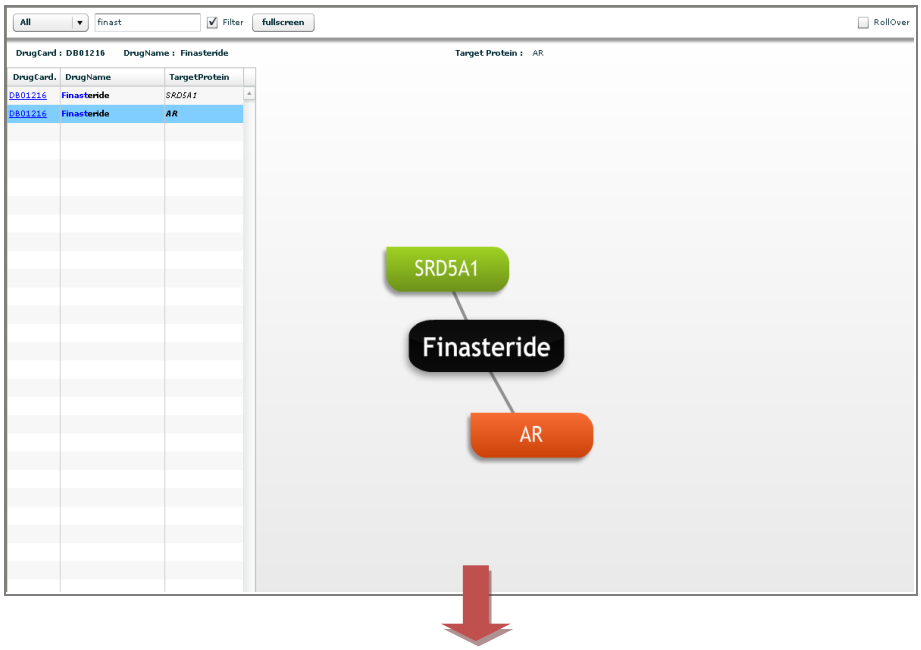


Figure 1-9. Dremap Gene alias example

(A)



(B)

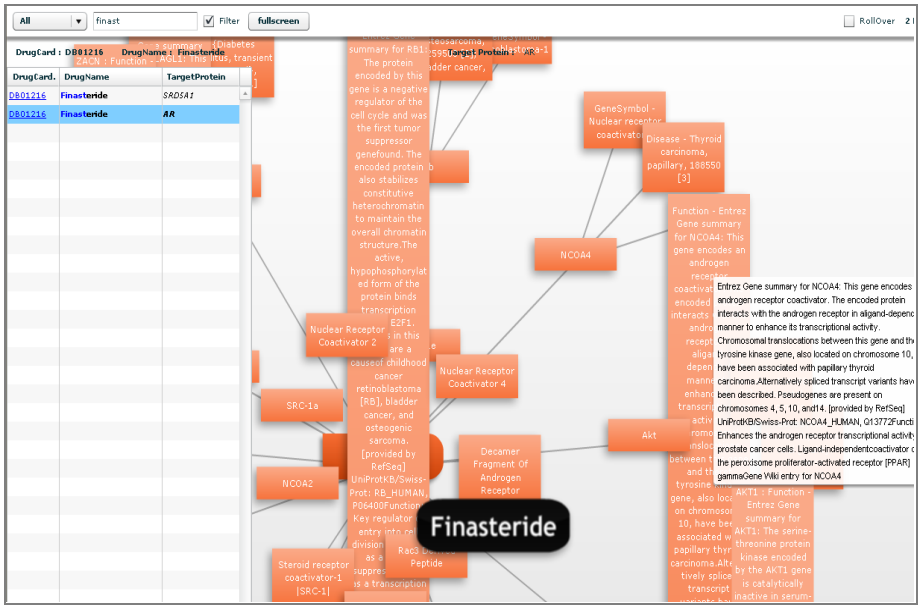


Figure 1-10 Finasteride example of Dremap The analysis view of DreMAP showing (a) the target network of the drug Finasteride and (b) the secondary functions of Finasteride (i.e., diseases and functions that are related to proteins interacting with Finasteride's target protein).

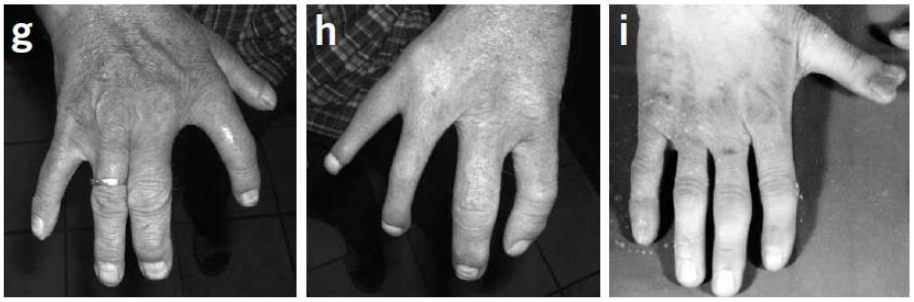


Figure 1-11. Ladd syndrome (Mutations in different components of FGF signaling in LADD syndrome)[5]

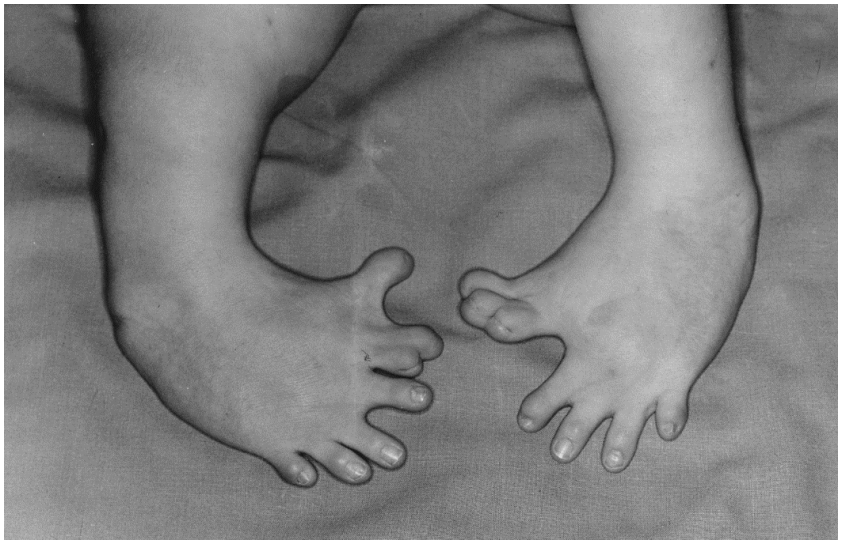


Figure 1-12. Adverse effect of Thalidomide[6]

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[5] Rohmann, Edyta, et al. "Mutations in different components of FGF signaling in LADD syndrome." *Nature genetics* 38.4 (2006): 414-417, http://www.nature.com/ng/journal/v38/n4/fig_tab/ng1757_F1.html

[6] Fig 1-12 , 2015, Wikipedia, https://ko.wikipedia.org/

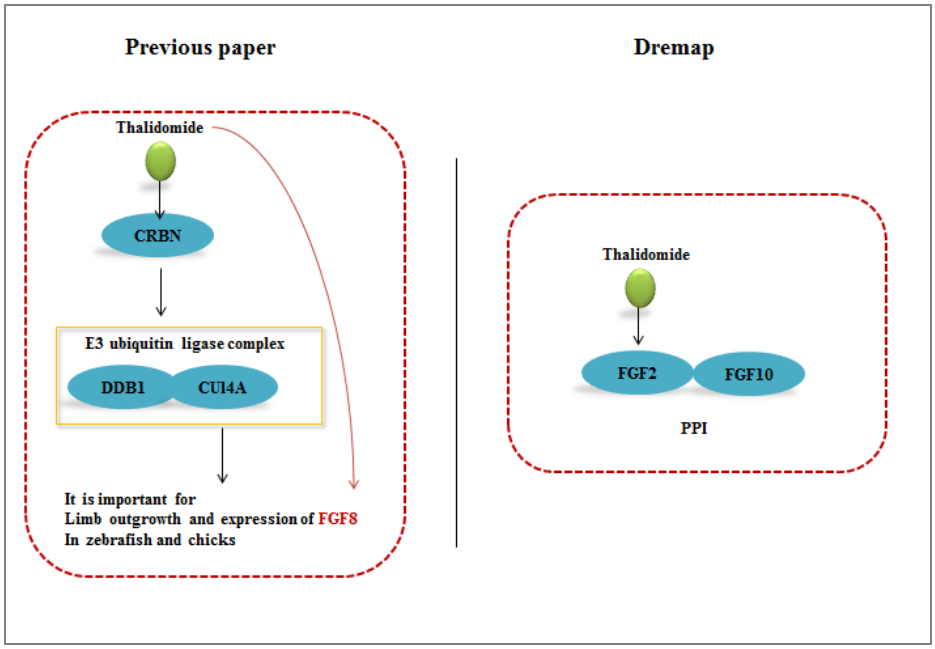


Figure 1-13. Mechanism explanation of Thalidomide

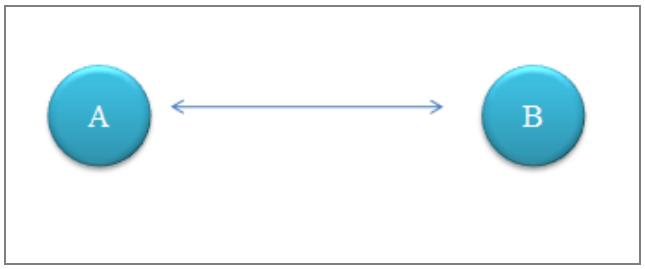


Figure 1-14. Relationship between the PPI

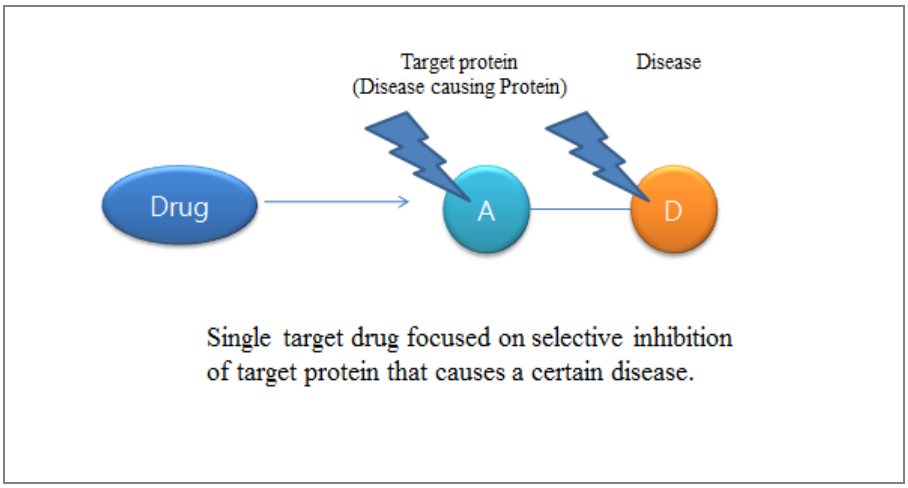


Figure 1-15. Therapeutic effects of drug

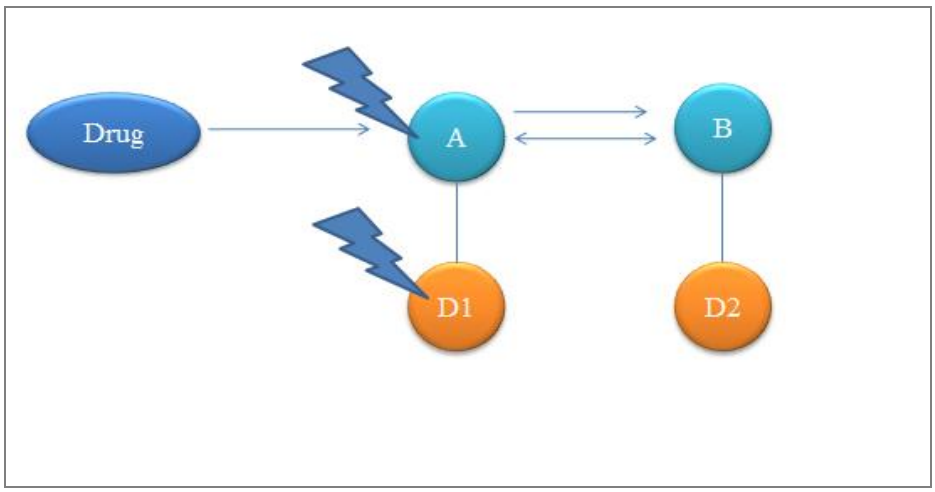


Figure 1-16. Relationship between the PPI and the therapeutic effect

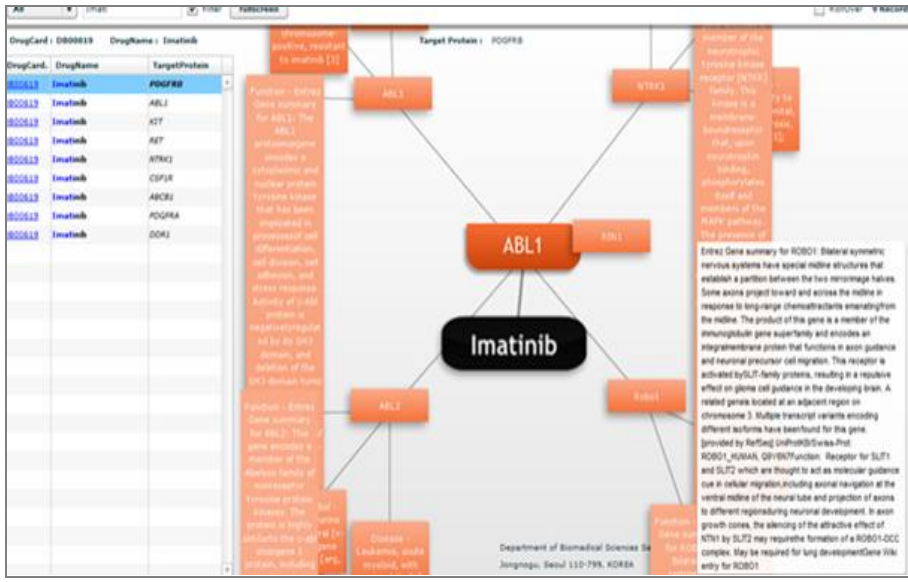


Figure 1-17. Result of Dremap

Discussion

Previously, large sets of PPI data did not provide data on the direction of interactions. However, these PPI directions can also be inferred through the patients' adverse effect phenotype data and accessible expression data. Since PPI data can offer keywords related to the treatable diseases, it can be useful to drug developers. I can explain the therapeutic effect and the adverse drug effect through drug target interactors. Traditionally, adverse effects of a drug occur have been explained by invoking a pathway. However, through this PPI network, we can explain more undefined drug mechanisms. Moreover, we can predict patients' symptoms even before the adverse effects of the drug occur. Therefore, I do not need to restrict the explanation of the range of a drug mechanism to a previously established pathway. PPI interaction can actually

be a part of the overlooked pathways. Target protein interactor proteins can be considered as a secondary target when considering the relational aspects of the network.

CHAPTER 2

Estimation of prognostic marker genes by public microarray data in patients with ovarian serous cystadenocarcinoma

Introduction

According to data released by the Centers for Disease Control and Prevention, ovarian cancer (OC) was ranked the fifth cause of cancer-associated death in women in the USA (61), and 14,270 cases of deaths from OC were reported in that country in 2014 (62). Many prognostic methods have been evaluated in attempts to identify the most reliable diagnostic strategies for treating women with OC (63, 64). Among these, tumor stage and the degree of lymphatic invasion have been considered to be determinants of overall survival (64-66). However, there is a need for better prognostic indicators, because the tumor stage merely indicates how the cancer cells have spread to the body but does not predict their response to chemotherapy.

The improvement of methods for analyzing a large set of gene expression data has provided useful insights for cancer treatment (67, 68). Although there have been several relevant studies for OC (69), there have been only a limited number of gene expression studies suggesting a clinical subclassification associated with survival or treatment strategies. A recent study using the Cancer Genome Atlas (TCGA) described prognostic gene expression profiles in patients with OC (70). Among 193 suggested prognostic marker genes, only four common genes were validated in three different sets ($p<0.05$), and none of them was validated with more strict statistical criteria ($p<0.01$) (70). This reflects the difficulty of finding representative marker genes for overall survival among patients with OC. Subgroup analysis may show either consistent or largely different results among different categories of patients (71). I hypothesized that prognostic indicators might vary between patients with and without LI because different sets of co-regulated genes were induced by the activation of different pathways related to invasion (72). In this study, I divided patients with OC into subgroups with or without lymphatic invasion

(LI) and analyzed those significantly differentially expressed genes (DEGs) that were linked with 5-year survival. Also, I suggested 13 repositioning available drugs for ovarian cancer using Dremap database and DEGs.

Materials and Methods

Patients

I analyzed data from 98 patients with serous OC using the TCGA datasets. Gene expression profiles were produced on an Affymetrix Human Genome U133 Array (Affymetrix, Inc. Santa Clara, CA, USA). Between 1995 and 2010, 489 clinically annotated patients with high-grade serous OC at tumor stages II–IV underwent surgery before systemic treatment. All patients received a platinum-based agent. Among 489 patients, the clinical annotation of 309 patients did not contain information on lymphatic invasion, and no information on 5-year survival was available for 82 patients. For patients with LI phenotypes described as 'lymphatic invasion' and 'lymphovascular invasion indicator' in the TCGA database, only 98 had LI, and for those I can trace

possible 5-year survival, only 63 had LI and 35 did not. All patients were classified as having grade II or IV tumors. The patients were followed until 25 August 2010.

Gene expression analysis

I performed microarray gene expression analysis of these patients using the TCGA database with Bioconductor R (73). Background adjustment was carried out employing the Robust Multi-Array Analysis algorithm from the 'affy' package for preprocessing, and the 'limma' package for differential expression analysis.

Statistical analysis

I identified significant DEGs between patients with and without 5-year survival and those with or without LI. The p-values were adjusted using the Benjamini–Hochberg method. Two-sided Student's t tests were applied, and statistical criteria of $p<0.01$ or $p<0.001$ were used as thresholds to determine the significance of any differences in gene expression.

Hierarchical clustering and heat maps

The Hierarchical clustering (HC) analysis was performed based on Pearson correlation coefficients in the expression pattern of genes. For gene clustering, I used ‘pvclust’ in the R package to assess any uncertainty of HC analysis (74). For each HC result, p-values were calculated using multiple bootstrap resampling.

Function analysis

I performed Gene Ontology annotations and Pathway Mapping of DEGs using the DAVID program (75). I used the Pathway category provided by DAVID for analysis of pathways that were overrepresented by three genes (EPAS1, WNT6, and PIK3R1) as 5-year survival-related DEGs for patients with OC without LI.

Regression analysis

Statistical analyses were performed using the R package (above). Multiple linear regression analyses were considered in modeling predictions of the 5-year survival score by the expression of five marker genes among patients with serous OC without LI. The five marker genes were selected by a combination of pathway-associated DEGs and rank correlation analysis. Pearson's correlation coefficients were also calculated to assess the associations between five marker genes (WNT6, EPAS1, SWAP70, PIK3R1, and IGFBP2) and 5-year survival outcomes. Receiver operating characteristics (ROC) curves were analyzed using IBM SPSS Statistics (version 23, IBM Corp., Armonk, NY, USA).

Results

In total, 180 patients (116 with, and 64 without LI) were enrolled in the study using the TCGA database. Among the enrolled patients, 82 (53 with and 29 without LI) were excluded from the analysis because their follow-up period was less than 5 years. Finally, 98 patients (63 with, and 35 without LI) were analyzed in this study (**Table 2-1**).

I divided these 98 patients into two groups: those who survived for 5 years and those who did not. I identified 133 differentially expressed genes (DEGs) (**Table 2-1**) between the survival and nonsurvival groups. As shown in the heat map in **Figure 2-1A,** clustering of these DEGs could not clearly distinguish the survival from the nonsurvival groups.

I tried to identify DEGs in subgroups of respective OCs with and without LI. As shown in the heat map **Figure 2-1B**, 55 DEGs (**Table 2-3**) identified from

the patients with LI could fairly well divide the survival from the nonsurvival groups. However, measurements of Manhattan distance and Pvclust dendrograms indicated that the patients with LI could *not* be clearly divided into survival and nonsurvival groups by the expression pattern of these 55 DEGs (data not shown).

I conducted the same analysis for 35 patients with OC without LI, and 20 DEGs were identified **(Table 2-2).** The heat map **(Figure 2-1C)** showed an obvious difference in the expression patterns of the survival and nonsurvival groups. Results from a Manhattan distance plot **(Fig. 2-2A)** and hierarchical clustering dendrogram (**Figure 2-2B)** confirmed that patients without LI could be clearly classified into 5-year survival and nonsurvival groups by these DEGs.

Pathway analysis showed that among the 20 DEGs, *EPAS1*, *WNT6*, and *PIK3R1* were associated with cancer and renal cell carcinoma pathways **(Table 2-3)**. To gain further insight, I selected five genes (*WNT6*, *EPAS1*, *SWAP70*, *PIK3R1*, and *IGFBP2*) among 20 DEGs whose expression showed

strong correlation with the 5-year survival pattern. After normalization to the expression of five housekeeping genes (*ACTB*, *GAPDH*, *RPLP0*, *GUSB*, and *TFRC*) found in both tumor and normal tissues in equivalent amounts, I formulated one equation to predict the 5-year survival scores for five marker genes using multiple linear regression analysis as follows.

$$Y = 0.946094\times(x1) - 1.42646\times(x2) - 0.73215\times(x3) - 1.14288\times(x4) + 1.378633\times(x5) - 2.19895$$

Using H as the mean expression value of the five housekeeping genes, the following factors were derived.

$x1 = \log_2$ (*WNT6* expression value/H)

$x2 = \log_2$ (*EPAS1* expression value/H)

$x3 = \log_2$ (*SWAP70* expression value/H)

$x4 = \log_2$ (*PIK3R1* expression value/H)

$x5 = \log_2$ (*IGFBP2* expression value/H)

As shown in **Fig. 2-3**, all six patients who survived for 5 years showed positive score values, while all 27 non-surviving patients showed negative values from this equation. When comparing the ROC curve estimates, I found high precision for my formula for estimating patient survival (**Fig. 2-4**) I also suggested 13 repositioning available drugs for ovarian cancer using Dremap database **(Table 2-4)**. Among 13 repositioning available drugs for ovarian cancer, 5 drugs were antidiabetics. The relation between antidiabetic drug and ovarian cancer has been addressed severally by investigators. Antidiabetic drug metformin has been reported that decreased risk of ovarian cancer (76) (77). It is considered that cancer treatment effect of metformin is related to AMP-activated protein kinase activation (78)(79). Despite of this consideration, other antidiabetic agents have not been considered in the experiment of treatment effect in ovarian cancer. My results suggest that not only metformin but also the other antidiabetic drugs might be useful for patients with OC.

Table 2-1. TCGA Data for Patients with Ovarian Cancer, with or without Lymphatic Invasion, in Terms of 5-year Survival Outcomes

	5 year death	5 year survival	Total
With Lymphatic invasion	55 patients	8 patients	63
Without Lymphatic invasion	27 patients	8 patients	35
Total	82 patients	16 patients	98

Table 2-2. DEG List for Patients with Ovarian Cancer, without Lymphatic Invasion

Gene Symbol	Gene Title	Log FC	*P*-value (<0.001)
INTS3	integrator complex subunit 3	0.786775	1.67E-05
EMID1	EMI domain containing 1	1.373029	2.56E-05
SMUG1	single-strand-selective monofunctional uracil-DNA glycosylase 1	0.828731	3.43E-05
PSMD4	proteasome (prosome, macropain) 26S subunit, non-ATPase, 4	0.590697	5.11E-05
ZNF643	zinc finger protein 643	0.89256	9.06E-05
WNT6	wingless-type MMTV integration site family, member 6	0.928701	0.000195
IGFBP2	insulin-like growth factor binding protein 2, 36kDa	1.653866	0.00022
PEX14	peroxisomal biogenesis factor 14	0.472971	0.000223
LOC728855	hypothetical LOC728855	0.827733	0.00025
ZBTB48	zinc finger and BTB domain containing 48	0.792063	0.000371
KCNMB2	potassium large conductance calcium-activated channel, subfamily M, beta member 2	1.287017	0.000421

FAM86A	family with sequence similarity 86, member A	0.625278	0.000488
PIWIL1	piwi-like 1 (Drosophila)	0.493027	0.000521
EPAS1	endothelial PAS domain protein 1	-0.90994	0.000545
SWAP70	SWAP switching B-cell complex 70kDa subunit	-0.68606	0.000657
MPPE1	metallophosphoesterase 1	0.731374	0.000681
FLAD1	FAD1 flavin adenine dinucleotide synthetase homolog (S. cerevisiae)	0.638619	0.000703
LIMA1	LIM domain and actin binding 1	-1.00453	0.000811
PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	-0.95753	0.000894
SCNM1	sodium channel modifier 1	0.716235	0.00093

Category	Term	Count	%	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment
KEGG_PATHWAY	hsa05200: Pathways in cancer	3	15	*EPAS1, WNT6, PIK3R1*	8	328	5085	5.813643
KEGG_PATHWAY	hsa05211: Renal cell carcinoma	2	10	*EPAS1, PIK3R1*	8	70	5085	18.16071

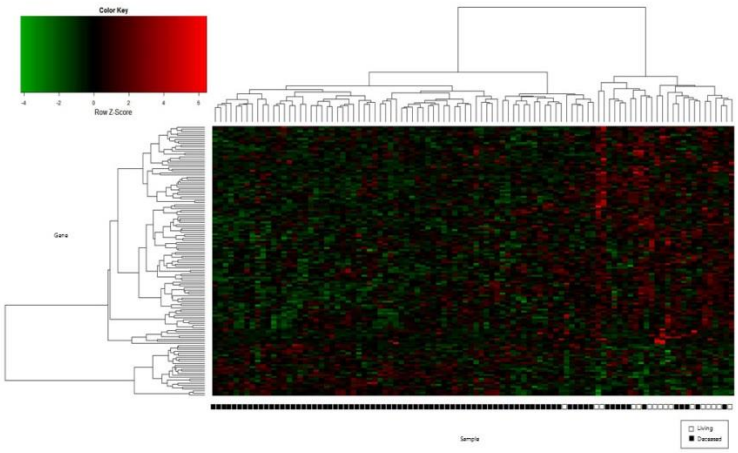
Table 2-3. Pathway Analysis of DEGs in Patients with Ovarian Cancer, without Lymphatic Invasion

Table 2-4. Possible repositioning drug list for ovarian cancer

Drug Name	Primary indication	Approval	P1	P2
Insulin recombinant	Hypoglycemic Agents	Approved	INSR	PIK3R1
Insulin Lispro	Antidiabetic	Approved	INSR	PIK3R1
Insulin Glargine	Antidiabetic	Approved	INSR	PIK3R1
Insulin, porcine	Hypoglycemic Agents	Approved	INSR	PIK3R1
L-Phenylalanine	Dietary supplement	Approved	TAT	PIK3R1
L-Tyrosine	Dietary supplement	Approved	TAT	PIK3R1
Imatinib	Antineoplastic Agents	Approved	CSF1R	PIK3R1
Mecasermin	Not Available	Approved	INSR	PIK3R1
Sunitinib	Angiogenesis Inhibitors	Approved	CSF1R	PIK3R1
Insulin Aspart	Antidiabetic	Approved	INSR	PIK3R1
Insulin Detemir	Antidiabetic	Approved	INSR	PIK3R1
Insulin Glulisine	Antidiabetic	Approved	INSR	PIK3R1
K-252a	Enzyme Inhibitors	Experimental	MET	PIK3R1

Figure 2-1.

(A)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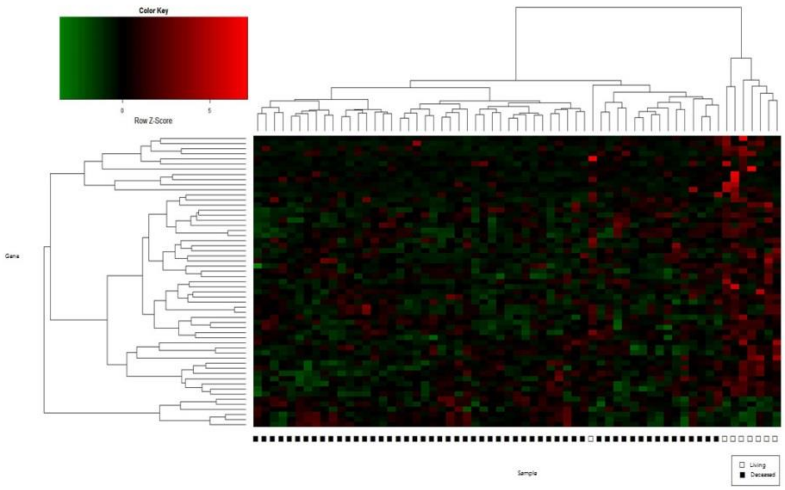
Row Z-Score
Genes
Samples
Living
Deceased

(B)


Color Key
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Samples
Living
Deceased

(C)

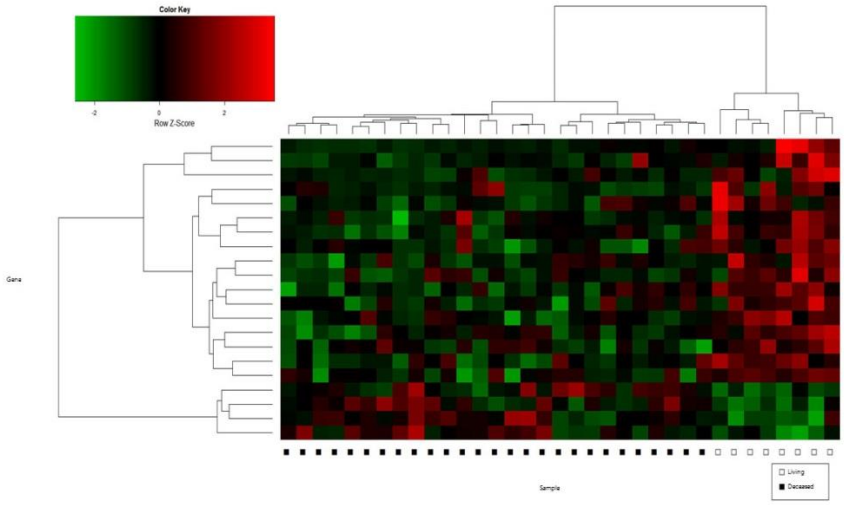
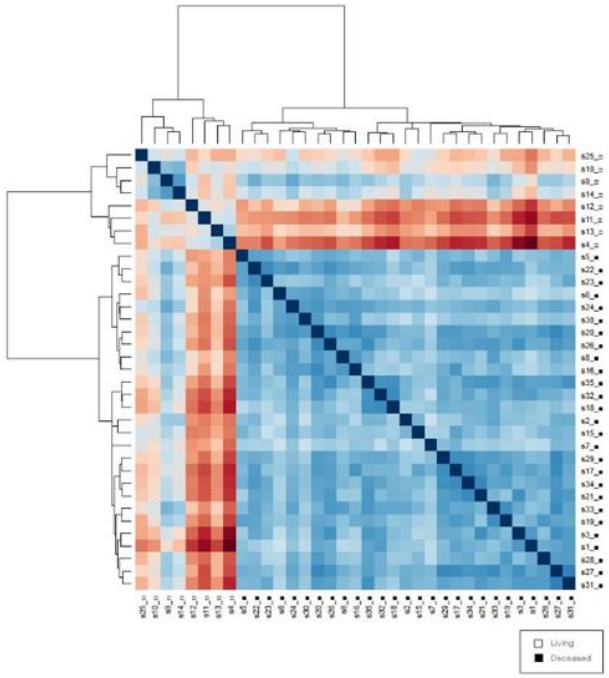


Figure. 2-1 Heat map of gene expression profiles from patients with OC.

The rows represent genes, and columns represent individual patients. Red indicates a high, and green indicates a low expression level. Differentially expressed genes between 5-year survival and nonsurvival groups were selected from all patients with ovarian cancer (A, $p<0.01$), patients with lymphatic invasion (B, $p<0.01$) and patients without lymphatic invasion (C, $p<0.001$)

Figure 2-2.

(A)



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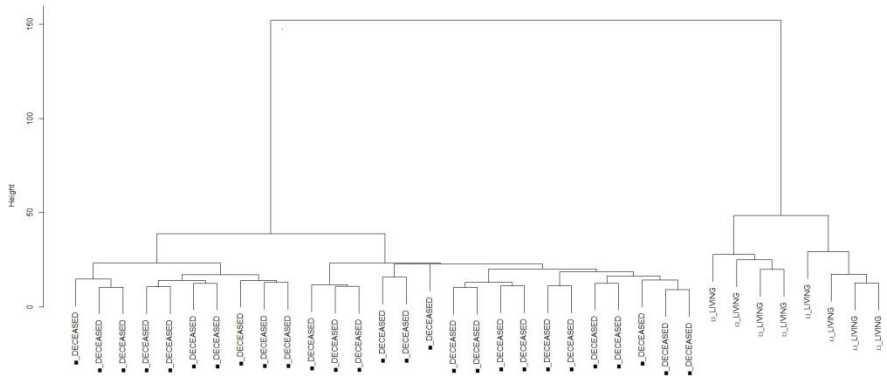

Figure 2-2. Clustering of 5-year survival and nonsurvival groups of patients with OC without lymphatic invasion.

(A) Manhattan distance plot of gene expression profiles in 20 survival-related genes and their association with patients without lymphatic invasion.

(B) Cluster dendrogram of gene expression profiles and their association with patients without lymphatic invasion.

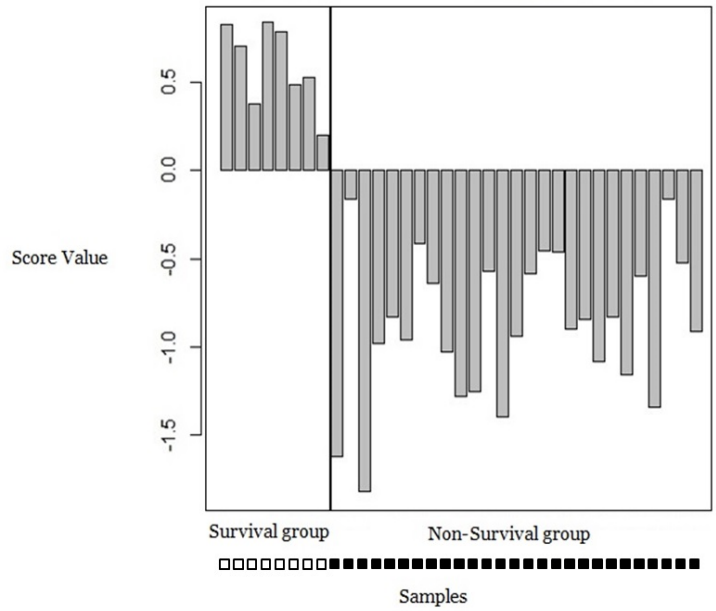

Figure 2-3. Survival score values calculated by multiple linear regression analysis with the five prognostic marker genes. The Y-axis indicates the score values; the 5-year survival group showed positive values, while the nonsurvival group showed negative values.

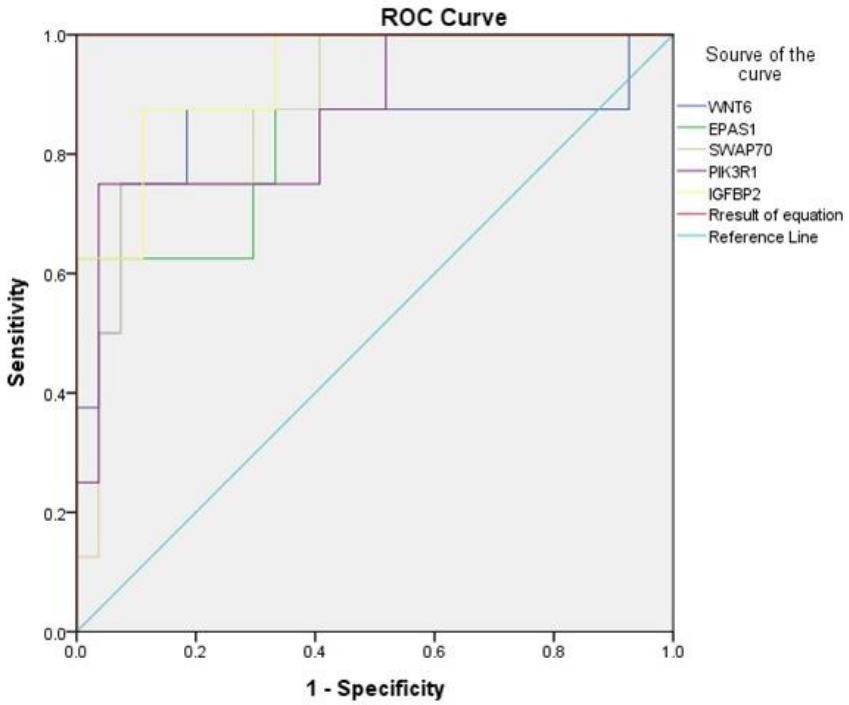

Figure 2-4. ROC curve of survival for patients with ovarian cancer predicted by five marker genes and the result of the equation used for calculating risk. All values were log-transformed and divided by the average expression level of five housekeeping genes.

Discussion

The Lymphatic invasion has been considered an important predictive component for many cancers. However, my TCGA-based analysis showed that LI alone could not predict the 5-year survival of these patients with OC efficiently. If I could find prognostic markers for the OCs, I could then select patients who would gain an advantage from adjuvant therapy. Therefore, I used expression profiles to detect prognostic markers that could predict the 5-year survival rates. I found that information about the presence of LI alone was not sufficient, but it still affected the efficiency of prediction using gene expression profiling. The clustering of survival and nonsurvival groups from all patients with OC using DEGs was not as clear as the subgroups with or without LI. This result suggests that the cancers from each subgroup might have had a different pathophysiology that influenced the survival of the

patients. Most previous research of OC has focused on LI. However, none of these studies have attempted to separately analyze the factors influencing survival between patients with or without LI. My study is the first to use OC samples to analyze survival by subgroup with or without LI.

The subgroup of patients without LI could be divided into 5-year survival and nonsurvival groups using the 20 DEGs more clearly and significantly than among all patients with OC or subgroups with LI. The survival score values using five prognostic marker genes (*WNT6*, *EPAS1*, *SWAP70*, *PIK3R1*, and *IGFBP2*) among 20 DEGs could efficiently predict the 5-year survival of patients with OC without LI. Patients with low expression levels of three genes (*PIK3R1*, *EPAS1*, and *SWAP70*) and high expression of two genes (*WNT6* and *IGFBP2*) showed longer survival.

PIK3R1 encodes the 85 kDa regulatory subunit of phosphatidylinositol 3-kinase, which is an important player in cancer development and progression. The PI3K/AKT/mTOR signaling pathway is frequently activated and has been considered as a possible therapeutic target for OC (80, 81). A recent meta-

analysis showed that high PI3K levels were associated with poor survival in patients with epithelial OC (82). Lower expression of *PIK3R1* might lead to downregulation of the PI3K/AKT/mTOR pathway and thereby contribute to the increased survival of patients with OC.

EPAS1, also known as *HIF2A*, encodes a transcription factor and is induced by hypoxic stress. There have been many publications about the link between hypoxia and cancers. Thus, the level of expression of *EPAS1* and genes of its downstream signaling pathways affect the aggressiveness of OC (83). In that report, higher expressions of those genes were significantly correlated with poor prognosis, similar to my findings. Better adaption to the hypoxic microenvironment common in solid tumors might explain those findings.

SWAP70 is expressed in various cell types including activated B-lymphocytes and mast cells (84). Although its role in cancer has not frequently been reported, one recent study showed increased expression of *SWAP70* in malignant gliomas and a strong correlation between high expression and poor patient survival (85). My data also showed that its expression was upregulated

in poorly surviving patients with OC but without LI, suggesting a similar mechanism.

WNT6 is a member of the WNT family of genes, which encode highly conserved glycoproteins secreted during embryonic development. The WNT signaling pathway is altered in many types of cancers and is regarded as a good candidate for cancer therapy (85). WNT family members have been generally regarded as poor prognostic factors for patients with cancer because of their effects on cell proliferation, migration, and survival (86). However, there is also a report that elevated levels of the Wnt-5a protein were associated with better outcomes for patients with prostate cancer, similar to my findings (87).

IGFBP2 encodes one of the members of the insulin-like growth factor binding (IGFBP) proteins, and its oncogene-like action by activation of Akt signaling has been reported (88). There have been contradictory reports about the prognostic value of circulating and intratumorous IGFBP2 levels (89). A recent report showed that expression of IGFBP2 was associated with better

survival in a specific group (body mass index, BMI $\leq$ 25 kg/m^2) of patients with breast cancer (90). That report and my findings here suggest that the prognostic efficacy of gene expression patterns can be useful in specific subclasses of patients, which requires further validation studies. My results suggest that the expression level of these five marker genes and 13 repositioning available drugs might be useful for deciding a prognosis and treatment for patients with OC and in making decisions on adjuvant hormonal therapy.

There were not enough data on patients that contained both LI and 5-year survival rates within the open serous OC dataset. Nonetheless, validation of the equation using an independent cohort can be done in the future. I believe that this topic is worthy of future studies and that my results will be helpful for researchers as well as clinicians in the OC field.

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초 록

서론: 신약 개발은 상당 시간이 소요되는 모험적인 프로세스로 여겨짐에 따라, 약물리포지셔닝에 대한 관심이 증가되었다. 미국식품안정청에서 기존에 승인된 약물의 새로운 적용점을 찾아내어 개발하는 약물 리포지셔닝은 약물개발 초기에 드는 막대한 비용과 시간을 절약할 수 있다. 본 논문에서는 기존에 알려진 단백질 상호작용 데이터에 기반하여 기존 약물의 새로운 적용점을 찾는 대량스케일의 웹 기반 툴을 개발했다. 미국 질병관리 예방본부에서 출간된 데이터에 의하면, 난소암은 미국에 있는 여성 암에 있어 5 번째로 사망률이 높은 암으로 보고된 바가 있다. 난소암 환자를 위한 적절한 진단과 리포지셔닝 방법을 확립하기 위해, 나는 마이크로어레이데이터를 사용하여 장액성 난소 암 환자들의 림프절 전이가 있는 5 년 이후에 살아있는 사람과 5 년 이전에 죽은

그룹간에 다르게 발현되는 유전자들을 찾아냈다. 또한, Dremap 데이터베이스를 이용하여 장액성 난소암에 리포지셔닝 가능한 약물 리스트를 제공하기도 했다.

방법: 약물-타겟 단백질, 단백질-단백질 상호작용정보, 단백질-연관질병 및 기능 정보를 연결시키는 작업을 수행했다. 난소 암 데이터는 TCGA 데이터를 사용했으며, 63 명의 림프절 전이가 있는 난소 암 환자와 림프절 전이가 없는 16 명의 난소 암 환자데이터가 분석되었다. 유의한 유전자는 바이오컨덕터 R 패키지를 이용하여 분석하였으며, 유전자들의 기능분석은 데이비드 웹 툴을 이용하여 분석하였다.

결과: Dremap 은 8849 개의 약물의 새로운 적용점에 관한 네트워크를 제공한다. 나는 림프절 전이가 없는 35 명의 난소 암 환자들에 대한 20 개의 유의한 유전자를 발견했다. 5 년 생존예후관련 유의 유전자들의 발현 특성에 대한 통찰력을 얻기 위해, 마커 유전자들에

대한 생존 값을 보여주었다. 또한 dremap 을 이용하여 난소 암 환자를 위한 13 개의 리포지셔닝 약물들을 제시했다.

결론: 현재까지, 대부분의 약물리포지셔닝의 케이스는 우연에 의한 관찰의 결과였다. Dremap 을 통하여, 연구자들은 기존 약물에 대한 추가적인 치료효과와 새로운 약물 기능들에 대한 유용한 증거들을 획득할 수 있다. 나는 Dremap 데이터베이스가 이제까지의 약물 메커니즘에 있어 기존에 알지 못했던 패스웨이에 해당하는 귀중한 정보를 사용자들에게 제공해줄 수 있을 것이라고 믿는다. 또한 난소암환자들을 위한 5 개의 예후 마커 유전자와 리포지셔닝 약물리스트들을 제안하기도 했다. 이 발견은 미래의 난소 암 환자들의 치료와 진단에 적용될 수 있을 것이다.

주요어: 약물 리포지셔닝, 단백질 상호작용, 네트워크 분석, 데이터베이스, 장액성 난소 암, 바이오마커

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