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# A novel computational approach for drug repurposing using systems biology

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## Abstract

**Motivation:** Identification of novel therapeutic effects for existing US Food and Drug Administration (FDA)-approved drugs, drug repurposing, is an approach aimed to dramatically shorten the drug discovery process, which is costly, slow and risky. Several computational approaches use transcriptional data to find potential repurposing candidates. The main hypothesis of such approaches is that if gene expression signature of a particular drug is opposite to the gene expression signature of a disease, that drug may have a potential therapeutic effect on the disease. However, this may not be optimal since it fails to consider the different roles of genes and their dependencies at the system level.

**Results:** We propose a systems biology approach to discover novel therapeutic roles for established drugs that addresses some of the issues in the current approaches. To do so, we use publicly available drug and disease data to build a drug-disease network by considering all interactions between drug targets and disease-related genes in the context of all known signaling pathways. This network is integrated with gene-expression measurements to identify drugs with new desired therapeutic effects based on a system-level analysis method. We compare the proposed approach with the drug repurposing approach proposed by *Sirota et al.* on four human diseases: idiopathic pulmonary fibrosis, non-small cell lung cancer, prostate cancer and breast cancer. We evaluate the proposed approach based on its ability to re-discover drugs that are already FDA-approved for a given disease.

**Availability and implementation:** The R package DrugDiseaseNet is under review for publication in Bioconductor and is available at https://github.com/azampvd/DrugDiseaseNet.

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**Supplementary information:** Supplementary data are available at *Bioinformatics* online.

## 1 Introduction

Despite enormous investments in research and developments (R&D), it still takes approximately $800 million to $1 billion and 10–17 years to approve a new drug for clinical use (Adams and Brantner, 2006; Dickson and Gagnon, 2009; DiMasi *et al.*, 2003). More than 90% of drugs fail to pass beyond the early stage of development and toxicity tests, and many of the drugs that go through early phases of the clinical trials fail because of adverse reactions, side effects, or lack of efficiency. Indeed, the rate of failure is still significantly higher than the rate of approval (Booth and Zemmel, 2004; Dickson and Gagnon, 2009; DiMasi *et al.*, 2003). In order to overcome these challenges, drug repurposing, an approach aiming to find new indications for existing drugs (Chong and Sullivan, 2007), has emerged as an important strategy for drug discovery (Ashburn and Thor, 2004). This approach can also rescue drugs that are safe but fail to get to market due to the lack of efficacy against their initial clinical indication (Collins, 2011).

Repurposing approaches can be categorized as drug-based or disease-based. Disease-based approaches are developed to overcome the lack of knowledge about the pharmacology of a drug (Dudley *et al.*, 2011). Drug-based approaches are preferred when drug data

(e.g. transcriptomic data) are available. While each one of these approaches faces several challenges, successful repurposing approaches often take advantage of both drug and disease data. In this area, a number of approaches have been developed based on the analysis of transcriptomic data, such as gene expression signatures, defined as the changes in the expression of genes under a certain condition (e.g. administration of a drug, or a disease). Some of these approaches are based on the idea that if there is an anti-correlation between a drug-exposure gene expression signature and a disease gene expression signature, that drug may have a potential therapeutic effect on the disease (Lamb *et al.*, 2006; Sirota *et al.*, 2011). Drugs that are strongly anti-correlated with a disease are likely to be candidates for repurposing. Resources such as LINCS [new version of Connectivity Map (Lamb *et al.*, 2006)] allow for systematic search of candidates for drug repurposing.

The Connectivity Map (CMap) project (Lamb *et al.*, 2006) was the first systematic approach aimed at exploring functional connections between drugs, as well as between drugs and diseases. This project led to the first repository of genome-wide expression data from five human cancer cell lines exposed with 1309 compounds at different dosages, and integrated with other sources such as NCBI Gene Expression Omnibus (GEO). (Lamb *et al.*, 2006) evaluate the similarity of a query signature, that can be a drug-exposure gene expression signature or a disease gene expression signature, to each drug signature in Connectivity Map database (reference data). In (Sirota *et al.*, 2011) the authors developed a systematic approach based on the same idea originally proposed by (Lamb *et al.*, 2006). In this work, they use drug-exposure gene expression signature from Connectivity Map as the reference data and query this reference data with every single disease gene expression signature by applying a pattern-matching method.

Systems biology can be used as an effective platform in drug discovery and development by leveraging the understanding of interactions between the different system components (Butcher *et al.*, 2004; Kitano, 2002). In this paper, we propose a systems biology approach that takes advantage of prior knowledge of drug targets, disease-related genes and signaling pathways to construct a drug-disease network (DDN) composed of the genes that are most likely perturbed by a drug. By performing a system-level analysis on this network using disease gene expression signatures and drug-exposure gene expression signatures, our approach estimates the amount of perturbation caused by a drug on the genes that are associated to a disease of interest. Drugs are ranked based on the amount of perturbation they exercise on specific disease-related genes, and highest ranking drugs are proposed as candidates for repurposing.

We compare the results of our approach with the computational drug-repurposing approach proposed by (Sirota *et al.*, 2011) using 19 datasets involving 4 diseases: idiopathic pulmonary fibrosis (IPF), non-small cell lung cancer (NSCLC), prostate cancer and breast cancer. We show that our approach provides a more accurate prediction based on its ability to identify drugs that are already approved for the disease of interest.

## 2 Materials and methods

### 2.1 Data sources

**Disease and drug gene expression data.** Large scale drug-exposure gene expression data are obtained from two databases: Connectivity Map and the Library of Integrated Network-Based Cellular Signatures (LINCS; Lamb *et al.*, 2006; http://www.lincsproject.org/). Disease expression data are obtained from NCBI Gene Expression Omnibus (GEO; Edgar *et al.*, 2002) and Lung Genomics Research Consortium (http://www.lung-genomics.org).

In Connectivity Map, drug expression data are measured from the exposure of five human cell lines to bioactive small molecules. Differentially expressed genes (DEGs) are identified using a moderated *t*-test (Smyth, 2005) by comparing treated samples and the corresponding control (untreated) samples. The resulting *P*-values are FDR adjusted (Benjamini and Yekutieli, 2001) to correct for multiple comparisons.

The LINCS program, the successor of Connectivity Map (Lamb *et al.*, 2006), generated transcriptional gene expression data from cultured human cells exposed to small molecules and knock-down/overexpression of a single gene. The data is also available in GEO (GSE70138). This program provides DEGs in terms of z-score signatures by comparing two groups of samples (treatment versus control). In both Connectivity Map and LINCS, there are often more than one replicate for each drug. Replicates with at least (1%) DEGs (FDR-adjusted $P$-value $< 0.025$) are selected. Since measurements are carried out on different platforms, we standardize gene identifiers from chip specific probe identifiers to NCBI GeneID identifiers using the affy package (Gautier *et al.*, 2004). We average across distinct probe expression values when multiple probes mapped to the same NCBI GeneID.

**Drug-targets and disease-related genes.** The proposed approach needs to construct a network that includes all the shortest paths between the drug targets and genes known to be associated to the disease of interest. Drug targets and disease-related genes (genes associated with the disease of interest) are retrieved from the Comparative Toxicogenomics Database (CTD; Mattingly *et al.*, 2006) and Drugbank (Wishart *et al.*, 2006). CTD is a database that provides curated data describing cross-species chemical-gene/protein interactions and gene-disease associations. Drugs with no known targets are removed from the study. Such drugs are mostly not FDA-approved.

**Signaling pathways.** We obtain signaling pathways from Kyoto Encyclopedia of Genes Genomics (KEGG; http://www.genome.ad.jp/kegg/). A signaling pathway in KEGG is modeled by a graph in which nodes represent genes or proteins, and directed edges between them represent signals between genes or proteins. The edges are weighted based on the various types of signals, such as activation, inhibition, etc.

### 2.2 Framework overview

The first part of the framework consists in building the drug-disease network (DDN) by integrating knowledge about the disease-related genes, drug targets and gene-gene interaction knowledge. Then, a repurposing score is computed for each drug-disease pair by integrating expression data into this network. Figure 1 represents the proposed framework.

**Drug-disease network (DDN) construction.** As shown in Figure 1A, first, we construct a global network (GN) by performing the union of all nodes and edges of KEGG human signaling pathways. In a number of KEGG pathways, a gene 'a' interacts with gene 'b', through an intermediate pathway 'A'. This is represented by a link that starts from gene 'a' to gene 'b' through pathway 'A'. For example, in the Adherence Junction pathway, TGF$\beta$R activates Smad3 through the TGF-beta signaling pathway. Interactions between genes belonging to the pathway 'A' and genes 'a' and 'b' are not included in our model. There are some interactions between genes/pathways through DNA or small molecules in KEGG. For instance, there is a link between MAPK signaling pathway and

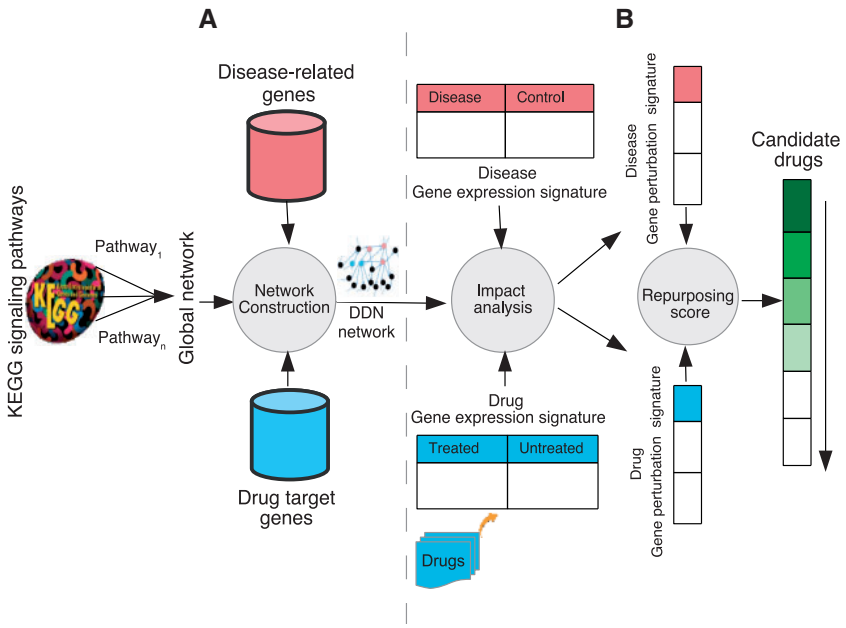


**Fig. 1.** Framework overview. (**A**) We construct a global network (GN) that is the union of all KEGG human signaling pathways. For each drug-disease pair, we extract a subgraph of *GN*, namely DDN, consisting of all shortest paths between two sets of disease-related genes and drug targets. (**B**) We then generate gene perturbation signatures of drug-disease pairs by applying a system-level analysis on their gene expression signatures in the drug-disease network (DDN). A comparative analysis is applied on drug and disease gene perturbation signatures. A repurposing score is assigned to each drug-disease pair. Finally, a ranked list of drugs with potential therapeutic effects for the given disease is generated based on repurposing scores

Phosphatidylinositol signaling system through a small molecule (compound) IP3 in KEGG. Such interactions are not part of the scope of this analysis and we do not include them in constructing the global network. We used ROntoTools package (Voichiţa and Drăghici, 2013; version 1.2.0) to calculate the union all KEGG signaling pathways that are represented by the adjacency matrices and obtain a unified adjacency matrix. In this step, we included some implicit interactions between the genes by performing the union of adjacency matrices representing KEGG signaling pathways. For example, suppose gene 'a' activate gene 'b' in pathway 'A' and gene 'b' activates gene 'c' in pathway 'B'. A path between gene 'a' and gene 'c' may be constructed by our analysis, while there was no path between them before this analysis.

Next, given the two sets of disease-related genes as $Disease_t = \{x_1, x_2, \ldots, x_n\}$, and drug targets as $Drug_t = \{y_1, y_2, \ldots, y_n\}$, we extract a subgraph of *GN* that consists of all the shortest paths connecting genes belonging to these sets. It means that a gene from either $Disease_t$ or $Drug_t$ can be a source or destination of the shortest path extracted from GN. This subgraph called Drug-disease network (DDN) represents all the interactions between drug targets and genes related to the given disease, through all the interactions described in KEGG signaling pathways.

**Drug-disease repurposing score computation.** In this stage, we capture the impact caused by a drug exposure or a disease on the genes that are specific to the condition of interest. In order to integrate the drug and disease gene expressions signatures, we generate gene perturbation signatures by computing the amount of perturbation upon the genes belonging to the drug-disease network (DDN) for all drug-disease pairs, as shown in Figure 1B. The gene perturbation signatures are calculated using the impact analysis method Drăghici *et al.* (2007) on the subgraph of global network we constructed in previous step. The impact analysis (IA) takes into account the structure and dynamics of a signaling pathway by considering a number of important aspects, including the measured gene expression changes, the direction and type of every gene signal and the position and role of every gene in a pathway. A perturbation factor for each gene, $PF(g_i)$, is calculated using the impact analysis method Drăghici *et al.* (2007), as follows:

A perturbation factor for each gene, $PF(g_i)$, is calculated using the impact analysis method (Drăghici *et al.*, 2007), as follows:

$$PF(g_i) = \Delta E(g_i) + \sum_{j=1}^{n} \beta_{ij} \frac{PF(g_j)}{N_{ds}(g_j)}, \quad (1)$$

where the term $\Delta E(g_i)$ denotes the signed normalized measured expression change of a gene $g_i$, added to the sum of all perturbation factors of the genes $g_j$ that are direct upstream of the gene $g_i$, normalized by the number of downstream genes of $g_j$, $N_{ds}(g_j)$. The coefficient $\beta_{ij}$ represents the type of the interaction, $\beta_{ij} = 1$ for activation and induction and $\beta_{ij} = -1$ for inhibition and repression. The second term in Equation (1) involves the PF values of those genes that are upstream of the gene for which the perturbation factor is calculated. For a gene with no upstream genes, the PF will be the measured expression gene $\Delta E(g)$.

Next, we calculate the repurposing scores for drug-disease pairs by computing the Pearson correlation coefficient between their gene perturbation signatures. The result score is from –1 to 1, where a high positive score shows that the drug and the disease both cause similar perturbations in the system, and therefore, that drug may cause the same effect as the disease. Conversely, a high negative score shows that the drug and disease have opposite gene perturbation signatures. Our hypothesis is that if the perturbation caused by a particular drug in the system is the reverse of the perturbation caused by a disease, that drug may have the potential to treat the given disease. Thus, we rank drugs from the strongly anti-correlated to the strongly correlated, according to their repurposing pathway perturbation scores.

In order to estimate the statistical significance of drug candidate repurposing scores, we generate 1000 random drug gene expression

signatures (by permuting gene labels) and then calculate random repurposing scores for all drug-disease pairs. We compute *P*-values as the percentage of the random scores higher than the observed score.

**A systematic method to select repurposing candidates.** We used a systematic method in order to rank repurposing candidates. To do this, given a ranked-list of drugs (drug instances) obtained by applying our approach on a disease dataset, we first compute a score for each drug that indicates how better or worse that drug is ranked in comparison to already FDA-approved drugs as follows:

$$\text{score}(\text{Drug}_x) = a - b, \quad (2)$$

where $a$ denotes the number of already FDA-approved drugs (gold standards) that are ranked worse than $\text{Drug}_x$, and $b$ denotes the number of FDA-approved drugs that are ranked better than $\text{Drug}_x$ (Supplementary Fig. S3). For instance, if there were $N$ FDA-approved drugs for a condition and an instance of a repurposing candidate were ranked higher than all $N$ FDA approved drugs, the score of this candidate would be $N$. Conversely, if the candidate were ranked lower than all $N$ FDA approved drugs, its score would be-$N$.

Using this objective measure, we then calculate an average score for each drug across different disease datasets (Supplementary Fig. S4B). Finally, we compute an average score for each distinct drug across different instances, if there are multiple instances for that drug (Supplementary Fig. S4C). We select the top 5% drug candidates from the ranked lists obtained by applying our approach on disease datasets and rank such drugs based on the scores computed by the this method, from highest to the lowest.

## 3 Results

To validate our approach, we analyzed 19 datasets from four different conditions: idiopathic pulmonary fibrosis (IPF; 6 datasets), non-small cell lung cancer (NSCLC; 4 datasets), prostate cancer (3 datasets) and breast cancer (6 datasets). The results of NSCLC, prostate cancer, and breast cancer are included in Supplementary Material. We compare the results of three computational drug repurposing approaches: our system-level approach, the most popular approach proposed by (Sirota *et al.*, 2011; henceforth drug-disease) and a classical method based on disease and drug signature anti-correlation (henceforth anti-correlation).

Both the drug-disease and the anti-correlation approaches are based on the hypothesis that if gene expression signature is perturbed in one direction in a disease state, and in the opposite (reverse) direction upon a drug exposure, then that drug may have the potential therapeutic effect for the disease. The difference between the two approaches is related on the approach used to calculated the match between a disease and a drug. Given a disease gene expression signature (query signature) and a drug gene expression signatures (reference signature), the Sirota *et al.*'s drug-disease similarity approach calculate an enrichment score for the up-regulated and down-regulated disease genes [by applying a Kolmogorov–Smirnov (KS) test]. We use the R implementation of this approach available in the package DrugVsDisease (Pacini, 2013).

In contrast, the classical anti-correlation method calculates a similarity score for drug-disease pairs by computing the Pearson correlation coefficient between the drug gene expression signature and the given disease gene expression signature. Drugs are ranked from the highly anti-correlated to the highly correlated, according to their score.

In this study, we compare the various approaches based on their ability to identify drugs that have already been FDA-approved for that condition (gold standard), based exclusively on the molecular data. In essence, a good repurposing approach should place already approved drugs at the very top of the list of drugs proposed for that particular disease. We used the Wilcoxon rank sum test (Wilcoxon, 1945) to determine whether the proposed approach is significantly better than the existing approaches.

Supplementary Table S2 shows the proposed candidates and the preliminary evidence that support the usefulness of those candidates in treatment of four human diseases: IPF, NSCLC, prostate cancer and breast cancer.

### 3.1 Drug repurposing using IPF data

The list of IPF datasets we used in our analysis is summarized in Supplementary Table S3. We compare the results of our approach with the existing approach proposed by (Sirota *et al.*, 2011; drug-disease), as well as the classical method (anti-correlation). The lists of the top 10 drugs are summarized in Table 1.

**Gold standard:** The gold standard for this disease is Nintedanib. This drug was approved for the treatment of IPF by FDA on October 2014. It is a small molecule inhibiting multiple tyrosine kinases (*RTKs*) and non-receptor tyrosine kinases (*nRTKs*). It is highlighted in Table 1.

As shown in Supplementary Table S4, We select the top 5% of drugs ranked lists obtained by applying our approach on 6 IPF datasets. We rank these drugs based on the scores computed by the systematic method from the highest to the lowest.

**Proposed candidates:** We propose Sunitinib ($P = 0.0009$), Dabrafenib ($P = 0.0009$) and Nilotinib ($P = 0.0009$) as repurposing candidates for treatment of IPF. Saracatinib, Linifanib, Buparlisib, GDC-0941 and Alvocidib are also highly ranked by our approach for treatment of IPF. Although these drugs are not approved by FDA yet, they can be considered for further experimental tests.

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), including vascular endothelial growth factor receptors (VEGFR) and platelet-derived growth factor receptors (PDGFR). It is approved by FDA for the treatment of Gastrointestinal stromal tumor, advanced renal cell carcinoma and progressive well-differentiated pancreatic neuroendocrine tumors (Demetri *et al.*, 2006; Motzer *et al.*, 2007). It was investigated for its anti-fibrotic and anti-angiogenic properties. Its efficiency was experimentally proved in a bleomycin-induced mouse model and it has been proposed for the treatment of IPF (Knoerzer *et al.*, 2013). Results of *in vitro* studies and animal models show that receptor tyrosine kinases, such as *PDGFR*, *VEGFR* and *FGFR*, and non-receptor tyrosine kinases, such as the *Src* family, play crucial roles in the pathogenesis of IPF (Grimminger *et al.*, 2010; Richeldi *et al.*, 2011).

Dabrafenib is approved by FDA for the treatment of patients with unresectable or metastatic melanoma. Recent clinical studies demonstrate that the extracellular signal regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) are up-regulated in lung tissues of patients with IPF (Madala *et al.*, 2012; Yoshida *et al.*, 2002). In particular, results of studies on MAPK signaling pathways show that the level of serine/threonine-protein kinase B-Raf (BRAF) is increased in patients samples compared to the normal ones, suggesting the potential therapeutic effects of MEK/ERK inhibitors for pulmonary fibrosis (Madala *et al.*, 2012; Olsen *et al.*, 2014). This supports the idea that the BRAF inhibitor Dabrafenib may have atherapeutic effect on IPF.

**Table 1.** A comparison between the results of three approaches: proposed, drug-disease, anti-correlation using IPF datasets (the top 10 drugs)

| Proposed | Drug-disease | Anti-correlation | Proposed | Drug-disease | Anti-correlation |
|---|---|---|---|---|---|
| GSE24206-early | | | GSE24206-advanced | | |
| GSM1740570_saracatinib | GSM1746916_radicicol | GSM1746916_radicicol | GSM1740570_saracatinib | GSM1746916_radicicol | GSM1746916_radicicol |
| GSM1743214_nintedanib | GSM1746864_radicicol | GSM1746864_radicicol | GSM1743214_nintedanib | GSM1746864_radicicol | GSM1746864_radicicol |
| GSM1742836_celastrol | GSM1738326_mocetinostat[a] | GSM1746893_radicicol | GSM1745714_buparlisib | GSM1738291_azacitidine[a] | GSM1746893_radicicol |
| GSM1745714_buparlisib | GSM1738291_azacitidine[a] | GSM1742836_celastrol | GSM1742836_celastrol | GSM1746893_radicicol | GSM1738290_azacitidine[a] |
| GSM1742552_linifanib | GSM1738794_garcinol[a] | GSM1738290_azacitidine[a] | GSM1742552_linifanib | GSM1738772_ischemin | GSM1742836_celastrol |
| GSM1742850_nintedanib | GSM1745213_nilotinib[a] | GSM1738291_azacitidine[a] | GSM1740917_saracatinib | GSM1742836_celastrol | GSM1738291_azacitidine[a] |
| GSM1740917_saracatinib | GSM1737397_quizartinib[a] | GSM1745530_nilotinib[a] | GSM1739549_saracatinib | GSM1737397_quizartinib[a] | GSM1742552_linifanib |
| GSM1740731_CH5424802 | GSM1743996_sirolimus[a] | GSM1745213_nilotinib[a] | GSM1742850_nintedanib | GSM1738326_mocetinostat[a] | GSM1743996_sirolimus[a] |
| GSM1743268_linifanib | GSM1742836_celastrol | GSM1742552_linifanib | GSM1740731_CH5424802 | GSM1742718_sorafenib[a] | GSM1742716_sorafenib[a] |
| GSM1739549_saracatinib | GSM1746893_radicicol | GSM1742716_sorafenib[a] | GSM1745213_nilotinib[a] | GSM1746811_ruxolitinib[a] | GSM1745530_nilotinib[a] |
| GSE44723 | | | GSE21369 | | |
| GSM1741104_sunitinib[a] | GSM1737411_NVP-BGT226 | GSM1737409_NVP-BGT226 | GSM1737700_rucaparib[a] | GSM1737352_everolimus[a] | GSM1737700_rucaparib[a] |
| GSM1740080_sunitinib[a] | GSM1743823_fostamatinib[a] | GSM1737411_NVP-BGT226 | GSM1740570_saracatinib | GSM1737699_rucaparib[a] | GSM1737699_rucaparib[a] |
| GSM1742552_linifanib | GSM1745509_NVP-BEZ235 | GSM1740923_BI-2536[a] | GSM1745714_buparlisib | GSM1737700_rucaparib[a] | GSM1738767_decitabine[a] |
| GSM1744393_gefitinib[a] | GSM1737409_NVP-BGT226 | GSM1740576_BI-2536[a] | GSM1740731_CH5424802 | GSM1738767_decitabine[a] | GSM1740731_CH5424802 |
| GSM1737353_everolimus[a] | GSM1738100_tranylcypromine[a] | GSM1745509_NVP-BEZ235 | GSM1745213_nilotinib[a] | GSM1746916_radicicol | GSM1737385_motesanib[a] |
| GSM1742436_GDC-0941 | GSM1741779_vorinostat[a] | GSM1740570_saracatinib | GSM1742504_nintedanib | GSM1737385_motesanib[a] | GSM1737624_entinostat |
| GSM1743268_linifanib | GSM1742856_canertinib[a] | GSM1737412_NVP-BGT226 | GSM1737448_idelalisib[a] | GSM1742800_palbociclib[a] | GSM1744048_imatinib[a] |
| GSM1743214_nintedanib | GSM1742795_palbociclib[a] | GSM1737353_everolimus[a] | GSM1745530_nilotinib[a] | GSM1737990_mocetinostat[a] | GSM1737698_rucaparib[a] |
| GSM1741743_sirolimus[a] | GSM1739241_olaparib[a] | GSM1745194_NVP-BEZ235 | GSM1742836_celastrol | GSM1737443_idelalisib[a] | GSM1738290_azacitidine[a] |
| GSM1740570_saracatinib | GSM1740387_CH5424802 | GSM1738308_entinostat | GSM1739679_dabrafenib[a] | GSM1742836_celastrol | GSM1741754_sirolimus[a] |
| LGRC-ILD | | | GSE1724 | | |
| GSM1740570_saracatinib | GSM1738326_mocetinostat[a] | GSM1738326_mocetinostat[a] | GSM1741104_sunitinib[a] | GSM1746800_nilotinib[a] | GSM1746916_radicicol |
| GSM1739549_saracatinib | GSM1742795_palbociclib[a] | GSM1737624_entinostat | GSM1740570_saracatinib | GSM1746916_radicicol | GSM1742552_linifanib |
| GSM1740917_saracatinib | GSM1737410_NVP-BGT226 | GSM1739358_mocetinostat[a] | GSM1739549_saracatinib | GSM1743953_linifanib | GSM1742836_celastrol |
| GSM1743214_nintedanib | GSM1741779_vorinostat[a] | GSM1739435_belinostat[a] | GSM1742552_linifanib | GSM1742836_celastrol | GSM1745213_nilotinib[a] |
| GSM1743268_linifanib | GSM1737624_entinostat | GSM1741779_vorinostat[a] | GSM1745714_buparlisib | GSM1745958_dasatinib[a] | GSM1743268_linifanib |
| GSM1742552_linifanib | GSM1737411_NVP-BGT226 | GSM1737410_NVP-BGT226 | GSM1743268_linifanib | GSM1743268_linifanib | GSM1746864_radicicol |
| GSM1742504_nintedanib | GSM1739435_belinostat[a] | GSM1746864_radicicol | GSM1740917_saracatinib | GSM1741215_veliparib[a] | GSM1745626_vemurafenib |
| GSM1744170_GDC-0941 | GSM1737409_NVP-BGT226 | GSM1741767_vorinostat[a] | GSM1740080_sunitinib[a] | GSM1741184_regorafenib[a] | GSM1743197_celastrol |
| GSM1745714_buparlisib | GSM1737455_vandetanib[a] | GSM1737409_NVP-BGT226 | GSM1742706_alvocidib | GSM1747067_mitoxantrone[a] | GSM1744371_selumetinib |
| GSM1741265_saracatinib | GSM1738350_pracinostat | GSM1737642_mocetinostat[a] | GSM1742850_nintedanib | GSM1741566_veliparib[a] | GSM1746881_mitoxantrone[a] |

*Note*: The *P*-values for Wilcoxon rank sum test comparing the results of the proposed approach and drug-disease approach using datasets GSE24206-early, GSE24206-advanced, GSE44723, GSE21369, LGRC- ILD and GSE1724 are 0.02, 0.02, 0.01, 0.02, 0.01 and 0.01, respectively. Highlighted drugs are FDA-approved for the treatment of IPF. The proposed approach was the only one that was able to rank the FDA-approved Nintedanib in the top 10. In contrast, none of the existing approaches was able to retrieve the FDA-approved drug in any of these six datasets.

[a]Drugs that are currently FDA-approved but for other indications.

Nilotinib is another FDA-approved drug we propose to be repurposed for the treatment of IPF. Nilotinib is a transduction inhibitor targeting *BCR-ABL*, *c-kit* and *PDGF*, that is approved by FDA for treatment of patients who are newly diagnosed with Philadelphia chromosome positive chronic myeloid leukemia (Ph + CML). It is also used for treatment of patients with Ph + CML in chronic phase and accelerated phase if they were resistant (or intolerant) to previous treatments. The potential roles of *PDGFs* in IPF have been shown by many studies (Antoniades *et al.*, 1990; Allen and Spiteri, 2001; Cao *et al.*, 2000; Homma *et al.*, 1995; Wollin *et al.*, 2015). The advantage of *PDGF* inhibition in IPF is well studied and supported by several studies (Abdollahi *et al.*, 2005; Chaudhary *et al.*, 2007; Wollin *et al.*, 2015). Authors of (Grimminger *et al.*, 2015; Rhee *et al.*, 2011) confirmed the potential effect of Nilotinib in decreasing the extent of pulmonary fibrosis in a mouse model.

The phosphatidylinositol 3 kinase (PI3K) inhibitors Buparlisib and GDC-0941 are undergoing clinical trials for a number of diseases. Buparlisib is in Phase III of clinical trials for treatment of breast cancer and in and Phase II for several other solid tumors. GDC-0941(Pictilisib) has been used in clinical trials for the treatment of several cancers, including breast cancer. Preclinical studies proved that PI3K inhibitors have potential roles in treatment of IPF by interfering with the fibrogenic effects of $TGF-\beta 1$ signaling (Beyer and Distler, 2013; Conte *et al.*, 2013; Hsu *et al.*, 2017; Mercer *et al.*, 2016). Based on this evidence, Buparlisib and GDC-0941 may have potential therapeutic effects on IPF.

The tyrosine kinase inhibitors Saracatinib and Linifanib are also highly ranked by our approach for treatment of IPF. Saracatinib (AZD0530) is an oral, tyrosine kinase inhibitor selective for *Src*. It underwent clinical tests at AstraZeneca for the treatment of cancer (Gucalp *et al.*, 2011; Lara *et al.*, 2009; Messersmith *et al.*, 2010; Poole *et al.*, 2010). However, it failed to show a sufficient efficacy in these studies. Subsequently, it was proposed for other usages such as Alzheimer's disease (in Phase II; Nygaard *et al.*, 2015). Linifanib (ABT-869) is also a multi-targeted receptor tyrosine kinase inhibitor that is intended to suppress tumor growth. It is investigated for treatment of leukemia (myeloid), myelodysplastic syndrome and solid tumors (Chen *et al.*, 2016; Chiu *et al.*, 2013; Wang *et al.*, 2012). The efficiency and tolerability of Linifanib versus Sorafenib has been assessed in patients with advanced hepatocellular carcinoma (Cainap *et al.*, 2013). The tyrosine kinase inhibitors are proven to be effective in treatment of IPF (Adamali and Maher, 2012; Beyer and Distler, 2013; Grimminger *et al.*, 2015; Richeldi *et al.*, 2011; Wollin *et al.*, 2014). In particular, the Src kinase inhibitor Saracatinib is reported to be useful in treatment of IPF through targeting the $TGF-\beta$ signaling pathway (Hu *et al.*, 2014). These represent additional and independent evidence supporting out findings that Linifanib and Saracatinib are expected to be useful in the treatment of IPF.

Alvocidib is a cyclin-dependent kinase (CDK) inhibitor that is undergoing clinical trials for a number of cancers: esophageal cancer, leukemia, lung cancer, liver cancer and lymphoma. Studies of murine models show that the CDK inhibitors block the epithelial apoptosis and decrease the tissue fibrosis in pulmonary fibrosis (Inoshima *et al.*, 2004; Leitch *et al.*, 2009). As a result, CDK inhibitors have been suggested as a novel therapeutic strategy against IPF (Zhou *et al.*, 2014).

## 4 Conclusion

In this paper, we presented a systems biology approach to discover new uses of existing FDA-approved drugs. We take advantage of known knowledge of disease-related genes, drug targets information and signaling pathways to discover drugs with the potential desired effects on the given disease. We estimate a network of genes potentially perturbed by drugs and integrate this network with drug and disease gene expression signatures to conduct a more powerful analysis at system level. To evaluate the proposed approach for drug repurposing, we analyzed four different diseases (IPF, NSCLC, prostate cancer and breast cancer) using three approaches: proposed, drug-disease and anti-correlation. For each disease, there is at least one FDA-approved drug that is used to treat that disease in our input drug data. The already FDA-approved drugs for a given disease are considered as the gold standard because such drugs successfully passed all the pre-clinical and clinical trials for that disease and were demonstrated to be efficacious in each disease. The approach is validated by its ability to identify drugs that are already approved by FDA for these conditions. The proposed approach was able to find such drugs based on the molecular profile alone, while existing repurposing approaches failed to do so. Specific drugs have been identified as repurposing candidates for the four diseases studied here. Although the proposed approach is studied in the context of drug repurposing, it also can be used to identify novel targets for FDA-approved drugs and understanding their mechanism of action.

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