OMICS A Journal of Integrative Biology
Volume 21, Number 10, 2017

DOI: 10.1089/omi.2017.0127

Transcriptomic-Guided Drug Repositioning Supported by a New Bioinformatics Search Tool: geneXpharma

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Abstract

Drug repositioning is an innovative approach to identify new therapeutic indications for existing drugs. Drug repositioning offers the promise of reducing drug development timeframes and costs, and because it involves drugs that are already in the clinic, it might remedy some of the drug safety challenges traditionally associated with drug candidates that are not yet available in the clinic. The gene-by-drug interactions are an important dimension of optimal drug repositioning and development strategies. While gene-by-drug interactions have been curated and presented in various databases, novel bioinformatics tools and approaches are timely, and required with a specific focus to support drug positioning. We report, in this study, the design of a public web-accessible transcriptomic-/gene expression-guided pharmaceuticals search tool, geneXpharma (www.genexpharma.org). GeneXpharma is a public platform with user-centric interface that provides statistically evaluated gene expressions and their drug interactions for 48 diseases under seven different disease categories. GeneXpharma is designed and organized to generate hypotheses on druggable genome within the disease–gene–drug triad and thus, help repositioning of drugs against diseases. The search system accommodates various entry points using drugs, genes, or diseases, which then enable researchers to extract drug repurposing candidates and readily export for further evaluation. Future developments aim to improve the geneXpharma algorithm, enrich its content, and enhance the website interface through addition of network visualizations and graphical display items. Bioinformatics search tools can help enable the convergence of drug repositioning and gene-by-drug interactions so as to further optimize drug development efforts in the future.

Keywords: systems biomedicine, transcriptomics, drug repositioning, gene-by-drug interactions, pharmacogenomics

Introduction

Drug development is costly and resource and time intensive, often requiring a decade and more to bring a new drug into the clinic (Shim and Liu, 2014). Drug repositioning is an innovative approach to identify new therapeutic indications for existing drugs. Drug repositioning offers the promise of reducing drug development timeframes and costs. Because it involves drugs that are already in the clinic, it might remedy some of the drug safety challenges traditionally associated with drug candidates that are not yet available in the clinic.

Recent overviews note that numerous approved drugs have been of interest for drug repositioning for new therapeutic uses (Cha et al., 2017; Deotarse et al., 2015). Most repositioned drugs so far have been discovered through serendipitous treatment or side effects observed during clinical trials. More rational approaches to the identification of drug repositioning candidates would demand identifying drugs that can modulate specific disease phenotypes, or target specific interactions and pathways (Li and Jones, 2012).

Interestingly, the gene-by-drug interactions are an important dimension of optimal drug repositioning and development strategies. While gene-by-drug interactions have been curated and presented in various databases, novel bioinformatics tools and approaches are timely and required with a specific focus to support drug positioning. The disease–gene–drug (DGD) triad ought to be taken into consideration employing distinct analysis methods and information sources. In this realm, several methods and tools have been developed to interpret large sets of genes or proteins, using information

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available in biological databases. For example, the ConnectivityMap was the first comprehensive study applied on cell cultures to present drug effects on gene expressions (Lamb et al., 2006). Subsequently, the clinical transcriptome data were evaluated within a comprehensive, systematic, and integrative analysis framework applied on various disease conditions (Amar et al., 2015).

Despite valuable information presented, providing a user-friendly interface for multidisciplinary research is crucial as well. Publicly available web tools, such as PharmDB (Lee et al., 2012), PROMISCUOUS (Von Eichborn et al., 2011), and DRUGSURV (Amelio et al., 2014), offer practical interfaces for researchers from different disciplines. Recently, ''RE:fine Drugs'' was focused on DGD triad where the gene–disease associations were originating from phenome-wide association studies (PheWAS) and genome-wide association studies (GWAS) (Moosavinasab et al., 2016). These analysis tools differ in several respects, including statistical methodology, supported organisms and gene identifiers, coverage of functional categories, source databases, and user interface.

Multiple data sources are generally employed for both broad and in-depth depictions of enrichment. A major challenge is to develop a straightforward and easy-to-use application, resulting with intuitive outputs, and rendering the tool accessible to inexperienced users with little or no bioinformatics background.

In this study, we report on the design and use of the geneXpharma as a new bioinformatics search tool with a user-friendly interface to support transcriptomic-guided drug repositioning and attendant hypothesis generation supported by statistical analyses. GeneXpharma provides drug candidates for 48 diseases obtained through gene expression-based repositioning analyses, utilizing a comprehensive drug–gene association data from Drug Gene Interaction Database (DGIdb 2.0) comprising 15 different databases (Wagner et al., 2016), 118 disease-specific gene expression profiling datasets for 48 diseases, and statistical evaluations for gene–disease and drug–disease associations.

Materials and Methods

Gene expression data

To distinguish disease-associated gene expression datasets, Gene Expression Omnibus (NCBI-GEO) (Barrett et al., 2013) and ArrayExpress (Kolesnikov et al., 2015) databases were searched for potential datasets in accordance with the following criteria: (a) each dataset should include both diseased and healthy samples, (b) samples should not have undergone any manipulation or treatment (drug, mutation, siRNA, etc.), (c) number of samples should be at least three in each group. Transcriptome data from 118 microarray datasets (Supplementary Table S1 in Supplementary File B) comprising 48 different diseases (Supplementary Table S2 in Supplementary File B) were obtained. WHO International Statistical Classification of Diseases (ICD-10, Version 2016) was followed in the identification of diseases.

Library construction of disease–gene and gene–drug associations

To identify disease-associated differentially expressed genes (DEGs), each microarray dataset was statistically analyzed to determine DEGs according to the previously published pipeline (Calimlioglu et al., 2015; Karagoz et al., 2015; Kori et al., 2016), which includes data normalization by Robust MultiArray Average (Bolstad et al., 2003), hypothesis testing by linear models for microarray data method (Smyth, 2004), and controlling the False Discovery Rate through Benjamini-Hochberg's method. Results with adjusted p-value <0.05 were considered significant. Consequently, the library of disease-DEG associations comprised information on datasets, DEGs, and their p values and fold changes.

Gene–drug interactions were acquired from the recent version of DGIdb 2.0 (Last updated February 2, 2016) and PharmGKB with their special permission (on October 25, 2016). Currently, the library of gene–drug associations in geneXpharma contains 50,304 gene–drug interactions involving 4344 genes and 11,939 drugs. Supplementary Data elaborating on the determination of the gene and drug annotations with additional details are summarized in Supplementary Tables S3 and S4 of Supplementary File B.

Prediction of drug–dataset associations

The statistical linkage method (Amelio et al., 2014) was adopted to gene expression data and employed in the prediction of drug–dataset associations. The association of a drug with a disease dataset was expected through a statistical test employing the hypergeometric probability density function:

$$p_{\alpha,\beta} = \frac{\binom{m}{x}\binom{N-m}{n-x}}{\binom{N}{n}}$$

At this point, p describes the estimated probability of the association of drug α with dataset β. N is the number of probes in dataset β, whereas m is the total number of DEGs in dataset β. n is the number of genes interacting with drug α regarding the whole gene–drug interactions, whereas x is the number of genes interacting with drug α in dataset β. Concisely, m/N reflects the proportion of disease-associated genes among the human genome and x/n reflects the proportion of genes interacting with the drug α, but related to the dataset β. The same procedure was repeated for each possible drug–dataset pair, including at least one interaction between the drug and DEG in any dataset.

Performance analysis

Receiver operating characteristic (ROC) curve analysis (Irizarry et al., 2003) was used to criticize the performance of geneXpharma search tool. The information on approved and failed drugs for various diseases presented in repoDB database (Brown and Patel, 2017), which is presented as a standard database for drug repositioning, was employed to construct gold standard datasets for each disease. The gold standard-positive sets included drugs that were already approved for specific diseases according to repoDB, in addition to those obtained through comprehensive literature researches. The sizes of gold standard-positive sets were ranging between 10 and 20. The gold standard-negative sets included randomly selected 20 drugs for each simulation from total drug list

(Supplementary Table S2 in Supplementary File B), with the exception of gold positives. Simulations were repeated 100 times to sustain robustness, and the mean value of performance metrics (i.e., sensitivity and specificity) was determined and employed in performance evaluations. The area under the curve (AUC) metric was computed for each disease to obtain the predictive power of geneXpharma.

Results

Construction of the druggable genome network within DGD triad

Taking into consideration that the coverage of druggable genome is a key parameter for accurate prediction of new therapeutic targets, transcriptome data from 118 independent microarray datasets (Supplementary Table S1 in Supplementary File B) comprising 48 different diseases (Supplementary Table S2 in Supplementary File B) were evaluated to distinguish disease-associated DEGs. These datasets were categorized into seven major disease classes: cancers, gynecological diseases, neurodegenerative diseases, psychiatric diseases, rheumatological diseases, metabolic diseases, and others. Applying a standardized algorithm to the gene data would increase the comparability of the resulting DEG.

Therefore, each microarray dataset was statistically analyzed through our previously published pipeline (Calimlioglu et al., 2015; Karagoz et al., 2015; Kori et al., 2016), and consequently, a comprehensive library of disease-DEG associations was constructed. Despite the fact that there are numerous publicly available sources to represent drug–gene interactions, the recent version of DGIdb 2.0 has been announced to have the most comprehensive content for drug–gene interactions compiled from 15 publicly available sources, including DrugBank, CIVIC, ChEMBL, and My Cancer Genome (Wagner et al., 2016), and was employed in this study in combination with the data presented by PharmGKB. Based on these data, the statistical significance of drug–disease (dataset) associations was predicted for all possible drug–gene–disease combinations through the statistical linkage method (Amelio et al., 2014), which was adopted to gene expression data, and stored in the database.

Database

GeneXpharma was introduced as a search tool with a user-centric interface to encourage drug repositioning by gene expression-based hypothesis generation supported by statistical analyses. It provides drug candidates for 48 diseases, obtained through gene expression-based repositioning analyses, utilizing a comprehensive DGD association data and statistical evaluations for gene–disease and drug–disease associations.

geneXpharma is designed as a web-accessible platform with two primary tiers. The back tier is a MySQL-based database in which the results of statistical analyses for each dataset are stored in the system for user search and retrieval. Gene–drug interaction and disease-DEG association libraries labeled with dataset serial numbers are stored in the back tier. These lists are used to predict statistical parameters for drug–dataset associations. On the other hand, the front tier is a PHP-based user interface that runs on LiteSpeed web server. The database implemented with ID-based and standardized core data and relational data tables of gene–drug and DEG-dataset associations can be easily maintained or updated.

User interface

GeneXpharma is designed as an intuitive platform, which makes it functional for researchers from different disciplines, from natural sciences to clinics, who are not experts on the field. Web tool is designed to provide a search form for genes (through Entrez Gene ID or Entrez Gene symbols) and drugs (via drug names). Search can be achieved through gene or drug names with or without specifying certain disease(s). Search option by gene name allows users to identify diseases if the gene in query is among the DEGs associated with the disease and candidate drugs interacting with the gene. On the other hand, search option by drug name will implicitly connect the drug to diseases through DEGs (Fig. 1). The detailed information on search options is available in Supplementary File A. Searching a gene is actualized in all diseases, whereas filtering option is provided for a specific set of diseases.

Search results are represented in a tabulated form with the following content: Dataset ID, Disease, Gene Symbol, Entrez Gene ID, Gene P-value (representing the significance of the disease–gene association), Fold Change, Drug, and Drug P-value (representing the significance of the disease–drug association). The results can also be exported as a .csv file. Drug or disease of interest and list of drugs, genes, and diseases are also supplemented (Supplementary Tables S2–S4 in Supplementary File B). These lists are expanded with the alternative IDs of genes, drugs, and diseases to enhance the functionality of the searches.

A critical analysis on the performance of geneXpharma

To estimate the discriminatory capability through the cut-offs between sensitivity and specificity (Karagoz et al., 2015) and to reveal the predictive power of geneXpharma-proposed drugs for specific diseases, ROC curve analysis, which is a graphical representation of the accuracy of an algorithm presenting trade-off between the sensitivity and the specificity, was used. For this purpose, seven different diseases were randomly selected to represent each disease category considered in geneXpharma. The simulation results indicated excellent discrimination (AUC >0.8) for multiple myeloma and psoriasis, and acceptable discrimination (AUC >0.65)

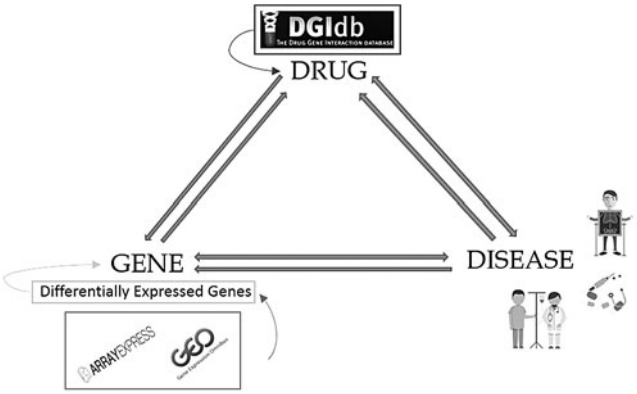


FIG. 1. The disease–gene–drug triad and data flow in geneXpharma search tool. *Green* route represents a search through drug name where significantly associated genes and diseases were acquired. *Orange* route represents a search through gene name to identify associated drugs and diseases.

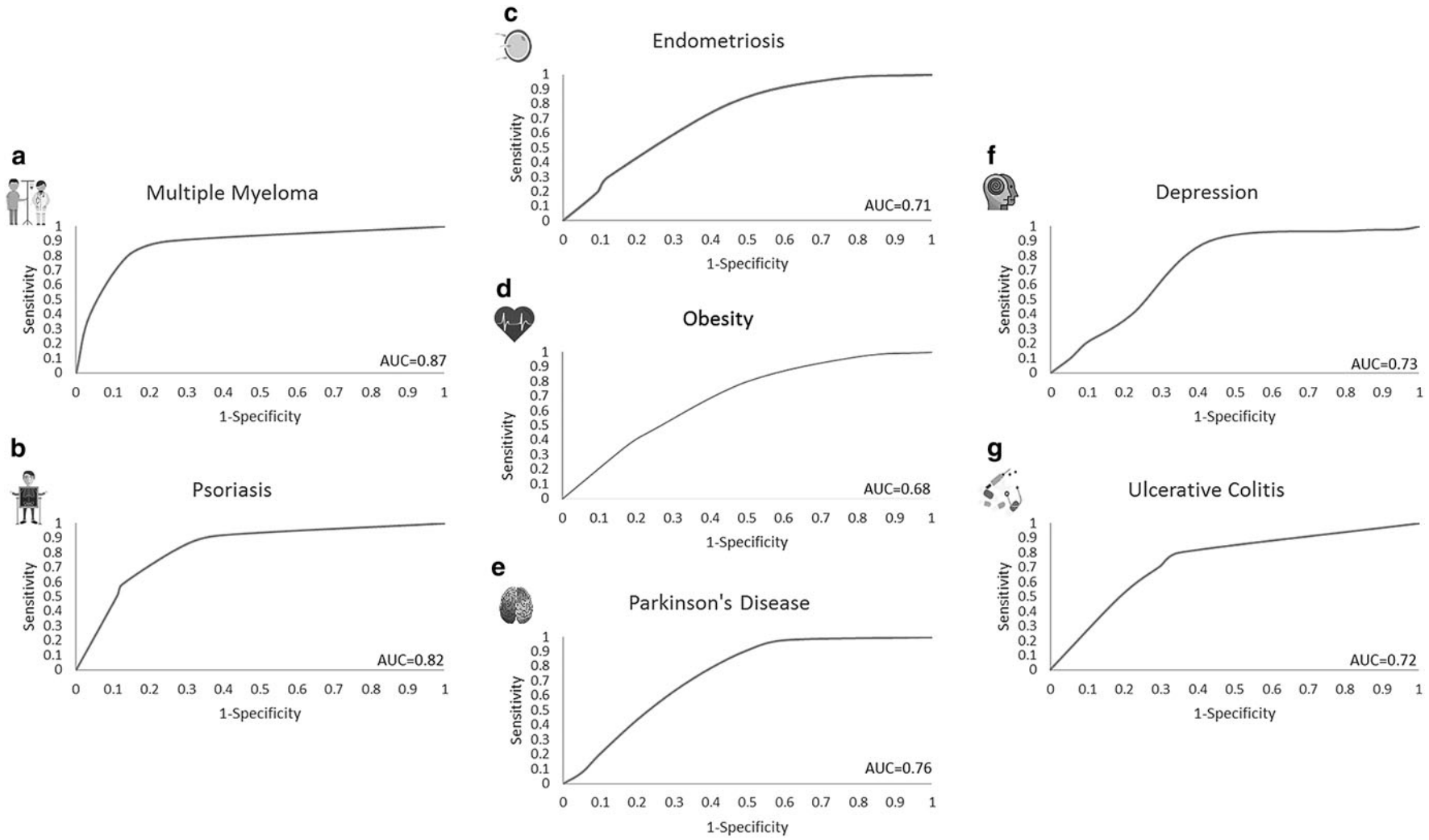


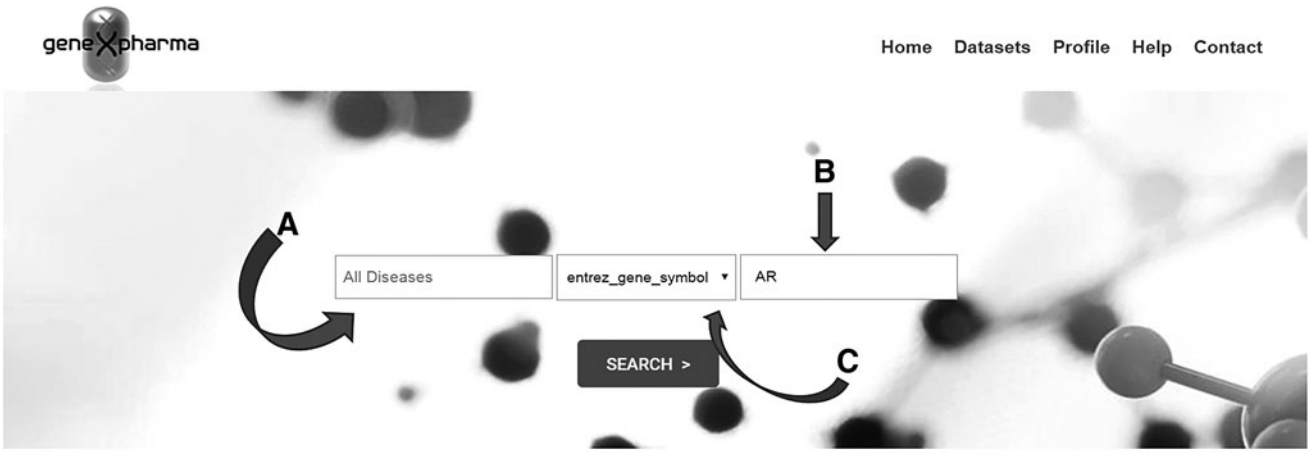
FIG. 2. Performance analysis of selected diseases belonging to different disease categories based on ROC curves and AUC metric. **(a)** Multiple myeloma (belonging to cancers), **(b)** psoriasis (belonging to rheumatological diseases), **(c)** endometriosis (belonging to gynecological diseases), **(d)** obesity (belonging to metabolic diseases), **(e)** Parkinson's Disease (belonging to neurodegenerative diseases), **(f)** depression (belonging to psychiatric diseases), and **(g)** ulcerative colitis (belonging to others category). AUC, area under the curve; ROC, receiver operating characteristic.

for other diseases (Fig. 2) according to the general rules used in interpretation of AUC values (Lin et al., 2004).

Case study

geneXpharma provides the opportunity to do a search based on drug or gene, while users have the chance to specify a certain disease or set of diseases. Search using a gene name provides results indicated with datasets and/or diseases, in which the query gene is differentially expressed, together with statistical parameters (p-value and fold change ratio) representing the significance of the gene–disease associations. In additon, drugs associated with the gene in query and the statistical significance of the gene–drug associations within a certain disease dataset are also presented. These drugs may be the molecules that are already used or repurposed for the disease, or novel candidates. The search results can be downloaded in the table format and are easy to manipulate for goal-directed filtering and sorting.

As a detailed example, androgen receptor (AR) gene is selected as a query and results are shown in Figure 3. The



Search Results

D

SERIAL_NO	DISEASE_NAME	ENTREZ_GENE_SYMBOL	ENTREZ_ID	P_VALUE	FC	DRUG_PRIMARY_NAME	HYPERGEOMETRIC
GSE6798	Insulin-resistant polycystic ovary syndrome	AR	367	1.52E-02	1.16	OSTARINE	5.20E-02
GSE6798	Insulin-resistant polycystic ovary syndrome	AR	367	1.52E-02	1.16	SORBINIL	2.70E-03
GSE6798	Insulin-resistant polycystic ovary syndrome	AR	367	1.52E-02	1.16	SULINDAC	4.27E-03
GSE6798	Insulin-resistant polycystic ovary syndrome	AR	367	1.52E-02	1.16	FIDARESTAT	2.70E-03
GSE6798	Insulin-resistant polycystic ovary syndrome	AR	367	1.52E-02	1.16	ZENARESTAT	2.70E-03
GSE6798	Insulin-resistant polycystic ovary syndrome	AR	367	1.52E-02	1.16	EPALRESTAT	5.20E-02
GSE6919	Prostate cancer	AR	367	1.27E-03	1.19	LEVONORGESTREL	3.57E-05
GSE6919	Prostate cancer	AR	367	1.27E-03	1.19	ENZALUTAMIDE	1.73E-01
GSE6919	Prostate cancer	AR	367	1.27E-03	1.19	DROSPIRENONE/ETHINYL ESTRADIOL	1.72E-02
GSE6919	Prostate cancer	AR	367	1.27E-03	1.19	TESTOSTERONE	1.42E-02

FIG. 3. A screenshot of search using a gene name. Androgen receptor is considered a case study. **(A)** Search form to specify disease(s). Searching a gene can be actualized in all diseases, whereas filtering option is provided for a specific set of diseases. **(B)** Search form to enter the gene or drug name. **(C)** The identifiers used in the search are as follows: genes (by Entrez Gene ID and Entrez Gene symbols) and drugs (by drug names). **(D)** Search results in tabulated form. **(E)** Button used to download the search results in .csv format.

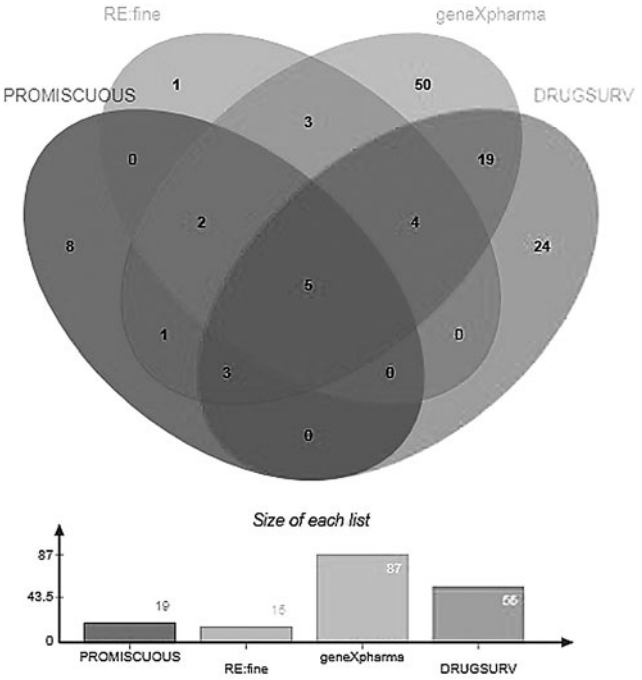


FIG. 4. The comparative analysis of drug candidates associated with androgen receptor gene acquired by geneXpharma, Re:fine, PROMISCOUS, and DRUGSURV tools.

role of the AR in the prostate cancer is largely dependent on dysregulation of its function. Abnormal profile of AR-regulated genes, including cell cycle regulators, transcription factors, and proteins important for cell survival, lipogenesis, and secretion was observed in prostate cancer. Thus, significance of the AR in the development and progression of prostate cancer is well known (Huang and Tindall, 2002).

Drugs that have been approved and are currently in use, such as flutamide (p-value = 0.01) and bicalutamide (p-value = 0.03), were reported in search results. In addition, repurposed drugs for prostate cancer were also obtained. For instance, mifepristone is a progestational and glucocorticoid hormone antagonist used as an abortifacient (Yu et al., 2015). Chen et al. (2014) comprehensively analyzed preclinical and clinical studies using mifepristone as an anticancer drug for several tumors, including prostate cancer. Moreover, it has been mentioned that the primary metabolite of mifepristone may have potential for cancer metastatic chemoprevention. In our case study, mifepristone was one of the repurposed drugs (p-value = 0.0002). On the other hand, results also provided a chance to create a drug repurposing hypothesis for zenarestat (p-value = 0.03), which is an aldose reductase inhibitor and previously purposed for treatment of diabetic neuropathy (Brown et al., 2004). Zenarestat is an example of a novel candidate drug based on this case study since it has never been associated with prostate cancer.

The similar web tools mentioned in this article were also utilized to search AR gene to reveal its drug interactions. Results have shown that the most comprehensive interaction list was provided by geneXpharma and zenarestat was presented only in its drug list. As a result of this comparative analysis, it has been observed that geneXpharma comprise the drug interactions %93.3 of Re:fine, %57.9 of PROMISCOUS, and %56.4 of DRUGSURV, respectively (Fig. 4). Five drugs (i.e., nilutamide, flutamide, oxandrolone, spironolactone, and testosterone) were common in all tools.

Discussion

While drug repositioning studies have gained popularity in the literature and drug development practices, the attendant computational methodologies and bioinformatics output representations are in need of innovation. The lack of firmly established gold standards for repositioning studies make performance evaluations for the studies or the bioinformatics tools difficult. In this context, geneXpharma is one of the first to critique its own data in regard to standards from repoDB (Brown and Patel, 2017) that collects the gold standards for drug repositioning (true positives and true negatives) and enables investigators to benchmark their repositioning methods. The methodology embedded into geneXpharma can pinpoint drugs based on associations between DEGs and small molecules with high precision and prioritize them for specific diseases to generate hypothesis. GeneXpharma is designed with the aim of offering the wide biomedical research community a new tool in support of drug repositioning, with potential advantages over several comparable tools such as Re:Fine, Promiscous, and DRUGSURV. These aspects are discussed below.

A simple-to-use interface

geneXpharma provides comprehensible representation of results covering all statistical parameters associated with genes, diseases, and drugs in a tabulated form. Search results can be downloaded as a .csv file and easily interpreted without the need for complex bioinformatics expertise or external tools. However, Re:fine tool does not have any option to download results, which makes the analysis within high number of interactions tougher. Moreover, DRUGSURV also has an easy interface, except the disadvantage of segmented result representation, which means every attempt causes to open a new tab. PROMISCOUS has a very robust user interface with many search options in addition to visualization; however, the representation of the results is not user friendly.

A rich integrated data resource of gene–drug interactions

DRUGSURV covers both FDA-approved drugs ($\sim$1700) and experimental drugs ($\sim$5000). Drug signature information is integrated from DrugBank and Pubchem Bioassays databases. PROMISCUOUS integrates drug–target relationships from DrugBank, SuperTarget, and SuperCyp, covering 21,500 relationships connecting 5000 drugs with 6500 target proteins. On the other hand, Re:fine tool covers only 916 drugs and 567 genes. The drug–gene relationships of Re:fine were extracted only from DrugBank 4.0. As curation of drug–gene interaction library, geneXpharma preferred taking advantage of using constantly updated DGIdb, which encompasses information from 15 data repositories such as PharmGkB, DrugBank, ChEMBL, and so on. The library of gene–drug associations in geneXpharma contains 50,304 interactions involving 4344 genes and 11,939 drugs. As a result, the coverage of drugs by geneXpharma considerably surpasses any previous efforts in the field.

Biological concepts and scoring

Some drug repositioning web tools sound similar since they are designed based on the outline of DGD associations. However, utilized biological concepts of genomic data are diverse. For instance, the gene–disease associations were extracted through GWAS and PheWAS data in the Re:fine tool. DRUGSURV established their system on the cancer survival data, solely. For each gene in the datasets of DRUGSURV, samples were grouped with respect to the expression rank of the gene and computed the set of genes whose upregulation /downregulation is associated (p-value <0.01) with patient survival, whereas hypergeometric distribution was used to link statistically drug targets with cancer survival gene signature. On the other hand, PROMISCOUS utilized proteins as drug targets and protein information was retrieved from UniProt. SuperPred (Dunkel et al., 2008) server was used for drug–target prediction by PROMISCUOUS to provide user the results with literature evidences of interactions instead of any statistical parameter. Beyond, there is no disease information or gene signatures of diseases from clinical studies.

Gene expression data in the geneXpharma tool are obtained through the use of a standardized algorithm to analyze raw data. Also, gene signatures of diseases are scored at the transcriptome level; their drug interactions in each disease dataset are also scored with the aid of the statistical linkage method employed. These scores provide quantitative information for both associations (i.e., gene–disease and drug–disease) and reflect the value added with the high-quality data, despite given extra weight into algorithms.

Number of disease and gene expression profiles

As previously mentioned, each web tool has its own unique result based on the biological concepts considered and its data coverage. DRUGSURV is based on 44 clinical cancer expression datasets covering 17 different cancers. Therefore, there is no chance to evaluate their statistical approach on other disease classes. PROMISCOUS does not provide opportunity to search for diseases. On the other hand, Re:fine currently contains 60,911 opportunities among 916 drugs, 567 genes, and 1770 diseases for generation of hypothesis for drug repositioning. Unfortunately, its website does not provide the list of 1770 diseases. In contrast to others, geneXpharma includes 118 clinical gene expression datasets covering 48 different diseases. Datasets and disease information are available on the website to ensure transparency.

Conclusions and Outlook

In this study, we present an easy and fast access to results of an integrative data analysis framework, taking into consideration comprehensive gene expression profiling and DGD association data, which will enable researchers from different disciplines to explore drug repositioning opportunities for future studies.

An advantageous aspect and aim of geneXpharma are to expand the data size (both in terms of the number of datasets and number of samples) to improve prediction accuracy, and to take gene expression profiles from the next-generation sequencing (RNAseq) studies into account. There are a couple of enhancements we are planning for already. In the next release, we intend to incorporate analysis results of data from The Cancer Genome Atlas.

Future developments aim to improve the geneXpharma algorithm, enrich its content, and enhance the website interface through addition of network visualizations and graphical display items. In addition, we are developing a freely available software (embedded into the website) for users to perform the analysis through their own dataset. In all, bioinformatics search tools can help enable the convergence of drug repositioning and gene-by-drug interactions so as to further optimize drug development efforts in the future.

Acknowledgments

This work was supported by Marmara University Scientific Research Projects Committee (BAPKO) in the context of the project FEN-C-DRP-250816-0417. We thank the TÜBİTAK BİDEB 2211-D National Doctoral Fellowship Program provided to Beste Turanli, and Korcan Gulfidan, Huseyin Yasar, and Erhan Poyraz (Aristod Digital) for logo design, technical support, and web designing, respectively.

Author Disclosure Statement

The authors declare that no conflicting financial interests exist.

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Abbreviations Used

AR = androgen receptor
AUC = area under the curve
DEG = differentially expressed gene
DGD = disease–gene–drug
GWAS = genome-wide association studies
PheWAS = phenome-wide association studies
ROC = receiver operating characteristic