Video Article Drug Repurposing Hypothesis Generation Using the "RE:fine Drugs" System

Kelly Regan¹, Soheil Moosavinasab², Philip Payne¹, Simon Lin²

¹Department of Biomedical Informatics, The Ohio State University

²Research Information Solutions and Innovation, The Research Institute at Nationwide Children's Hospital

Correspondence to: Kelly Regan at Kelly.Regan@osumc.edu

URL: http://www.jove.com/video/54948 DOI: doi:10.3791/54948

Keywords: Medicine, Issue 118, Drug repurposing, Drug discovery, Database, Hypothesis generation, Genome-wide association study (GWAS), Phenome-wide association study (PheWAS)

Date Published: 12/11/2016

Citation: Regan, K., Moosavinasab, S., Payne, P., Lin, S. Drug Repurposing Hypothesis Generation Using the "RE:fine Drugs" System. J. Vis. Exp. (118), e54948, doi:10.3791/54948 (2016).

Abstract

The promise of drug repurposing is that existing drugs may be used for new disease indications in order to curb the high costs and time for approval. The goal of computational methods for drug repurposing is to enable solutions for safer, cheaper and faster drug discovery. Towards this end, we developed a novel method that integrates genetic and clinical phenotype data from large-scale GWAS and PheWAS studies with detailed drug information on the concept of transitive Drug-Gene-Disease triads. We created "RE:fine Drugs," a freely available, interactive dashboard that automates gene, disease and drug-based searches to identify drug repurposing candidates. This web-based tool supports a user-friendly interface that includes an array of advanced search and export options. Results can be prioritized in a variety of ways, including but not limited to, biomedical literature support, strength and statistical significance of GWAS and/or PheWAS associations, disease indications and molecular drug targets. Here we provide a protocol that illustrates the functionalities available in the "RE:fine Drugs" system and explores the different advanced options through a case study.

Video Link

The video component of this article can be found at http://www.jove.com/video/54948/

Introduction

The costly and inefficient processes associated with traditional drug discovery approaches, including high-throughput drug and lead compound screening, are contributing to delays in translating research discoveries into therapies for patients ^{1,2}. An average of 1 billion U.S. dollars and 15-20 years is required to bring a new drug from the bench to the bedside ³. Further, 52% of drugs fail during development in phase 1 clinical trials, and only 25% of compounds that enter phase 2 proceed into full phase 3 clinical studies ⁴. The goal of drug repurposing or drug repositioning is to renew failed drugs and/or find novel indications for approved drugs in order to deliver new therapies to patients faster and with a higher success rate. Drug repurposing may decrease the timeline to make drugs available for use in patients to 3-12 years ⁵. Important medical applications for drug repurposing include: diseases with poor prognosis and low survival rates, drug-resistant diseases, underfunded disease research areas and impoverished and underserved patient populations.

Computational drug repurposing is defined as the process of designing and validating automated workflows that can generate hypotheses for new indications for a drug candidate⁶. Existing computational drug repurposing methods have been categorized target-based, knowledge-based, signature-based, network-based, and targeted-mechanism-based, and can be oriented from gene, disease or drug perspectives. Furthermore, computational approaches may further accelerate proof-of-concept validation experiments and small-scale clinical studies for repurposed drug candidates⁷. We have previously reported on "RE:fine Drugs", a freely available, interactive web-based tool for drug repurposing hypothesis generation based on the transitive theory of Drug-Gene-Disease relationships⁸. The overall goal of this method is to systematically integrate diverse types of drug, genetic and clinical data to enable drug repurposing for users from diverse communities, including clinical, industry and regulatory communities. The foundational methods for this system have been previously reported for the use of genome-wide association study (GWAS) and phenome-wide association study (PheWAS) data in drug repurposing research^{9,10}. The novel combination of these types of data distinguishes our webtool from other target-based methods^{6,11}.

The RE:fine Drugs system currently contains 60,911 drug repurposing hypotheses covering 916 drugs, 567 genes and 1,770 diseases. The webtool provides a user-friendly interface for researchers to interactively search drug repurposing hypotheses and prioritize them using diverse criteria. For instance, users can filter drug repurposing hypotheses with support in the biomedical literature and clinical trials database, significant p-values, association odds ratios or by specific indications. The only requirement for this system is Internet access.

Protocol

1. Initiation of Queries from Gene, Drug or Disease Terms

- 1. Access the homepage for "RE:fine Drugs" at the following link: http://drug-repurposing.nationwidechildrens.org. Begin by entering a query term in the search bar from any of the following three categories: drug (generic drug name), disease (new disease indication) or gene (official HGNC gene symbol).
- 2. Filter the search bar function to include only "Drug Name", "New Disease Indication", "Gene Symbol" or "All" categories. The search bar includes an auto-fill function for query entries.
- Put in a keyword, and click on the "Search" button. Sort the table of results by any of the following columns: "Drug", "Registered Indication", "P-Value", "P-Value Adjusted", "Odds Ratio", "Study", "New Indication", "Drug Bank Indication", "# of Medline Abstracts", "# of Clinical Trial Registry", "Potential", "SNP", "Gene" or "action".
- 4. Navigate to the advanced search option in order to enable the drug information feature. Click on the icon in the "Info" column for a particular drug. Observe a page that lists the all the corresponding information including p-Value for the association, Disease name, Drug name, Gene details (NCBI Gene link) and Drug details (DrugBank link).

2. Exploration of Advanced Options

- 1. Click on the "advanced" button located on the right side of the page, and several options to further refine the results are provided. The advanced search options include modifications to the following: drug, association, disease, potential, gene and action.
- 2. Export results tables by clicking on the "Export" button on the right side of the page. Click on the "Simple" button in order to fold down the advanced search window.
- 3. Under the advanced option "drug" tab, specify a particular drug indication or an additional drug name to filter results.
- 4. Under the "association" tab, filter results by the significance level P-Value, Adjusted P-Value with FDR, effect size (Odds Ratio), and/or Study type (GWAS, PheWAS or Both).
- 5. Under the "disease" tab, specify a certain disease description for the predicted new use.
- 6. Under the "potential" tab, filter results according to any of the following criteria: (i) whether the drug indication is contained in the DrugBank database, (ii) number of Medline abstracts with co-occurrence of the drug and the disease, (iii) number of ClinicalTrials.gov database entries with co-occurrence of the drug and the disease and (iv) Repurposing Potential. NOTE: The Repurposing Potential option describes the novelty of the discovery: (i) Known: relationship already exists in the DrugBank database, (ii) Strongly supported: some support in both clinical trial registry and the Medline abstracts, (iii) Likely: some support in either clinical trial registry or the Medline abstracts.
- 7. Under the "gene" tab, enter a SNP identifier or Gene Symbol to filter results by specific drug target genes.
- 8. Under the "action" tab, specify the drug action type against the drug target(s), including agonist, antagonist, other, unknown or all (source: DrugBank database).

Representative Results

In this example, the gene "IL2RB" was entered as a gene-based query, and was automatically recognized as such by the auto-fill function (Figure 1). The twelve drug repurposing hypotheses for the IL2RB gene are returned, as shown in Figure 2. Detailed information page for a particular drug repurposing hypothesis, "daclizumab" in this case, is provided from the "Info" column (Figure 3). The results were filtered on the drug tab was by all results corresponding to the "daclizumab" drug, as shown in Figure 4. Figure 5 shows only those drugs with a known indication for the "transplant" disease term (source: DrugBank database). The association tab allows the user to filter SNP-Phenotype relationships by statistical significance (P-value) and genetic effect size (odds ratio), defined as the ratio of the odds of presence of disease in individuals with a specific genotype (SNP allele) over the odds of presence of disease in individuals without the SNP allele. Figure 6 shows the results filtered under the association tab within the P-Value range of 0.000001 to 0.05. Figure 7 shows drug repurposing hypotheses specific for "asthma" based on the new indications we found in the study. Figure 8 shows results under the potential tab to filter by a minimum number of 5 Medline abstracts containing a co-occurrence of drug and disease terms. In this example, all drugs results under the gene tab are targeted for the "IL2RB" gene, corresponding to the original query term (Figure 9). Finally, Figure 10 shows results filtered under the "action" tab to return all drugs that act as agonists on the IL2RB gene.



Figure 1: The RE:fine Drugs interactive dashboard homepage. Users may begin a query by entering a drug name, new disease indication or gene symbol. Links are also provided for the GWAS and PheWAS reference papers describing methodologies for generating drug repurposing hypotheses. Please click here to view a larger version of this figure.

rug Rep	ourposing Opportunities	5			When your child week a huspital, every	ibing matters."	TRANSLATION	AL SCENCE	
E:fine Drugs urrently conta	is an interactive dashboard of drug repositio ins 60,911 opportunities covering 916 drugs	ning opportunit 1, 567 genes an	ies by "drug-gene d 1770 diseases.	-disease" triads,	using the methods described in Nature Biote	ch 2012 (GWAS)	and Nature Biot	lech 2015 (P	heWAS). It
'lease start yo	ur search by entering a drug name (e.g. Zid:	wudine), a dise	ase name (e.g. Al	theimer's Disease), or a gene symbol (e.g. IL2RB).				
setting Starter	J Guidelines								
IL2HB		Gene Symbol +	Search						advanced
how 100 ‡ e	Total # of Records: 12								1.2
Drug	Registered Indication	P-Value	11 Odds Ratio	Study	New Indication	# of Medline 11 Abstracts	# of Clinical 11 Trial Registry	Potential	Gene
basilximab	for prophylactic treatment of kidney transplant rejection	10-8	1.12	GWAS	Asthma	0	0	Novel	12/b
denileukin diftitox	for treatment of cutaneous t-cell lymphoma	10-8	1.12	GWAS	Asthma	0	0	Novel	il2rb
declizumab	zenapax is a humanized monoclonal antibody used for prevention of renal transplant rejection	1e-8	1.12	GWAS	Asthma	6	0	Likely	il2rb
aidesieukin	for treatment of adults with metastatic renal or carcinoma.	N 1e-8	1.12	GWAS	Asthma	0	0	Novel	il2rb
basiliximab	for prophylactic treatment of kidney transplant rejection	20-6	1.1	GWAS	Type 1 diabetes autoant/bodies	20	0	Likely	il2rb
denileukin dihitox	for treatment of cutaneous t-cell lymphoma	29-6	1.19	GWAS	Rheumatoid arthritis	4	0	Likely	il2rb
aidesleukin	for treatment of adults with metastatic renal or carcinoma.	20-6	1.1	GWAS	Type 1 diabetes autoantibodies	0	1	Likely	il2rb
basiliximab	for prophylactic treatment of kidney transplant rejection	20-6	1.19	GWAS	Rheumatoid arthritis	3	0	Likely	il2rb
aldesleukin	for treatment of adults with metastatic renal or carcinoma.	d 2e-6	1.19	GWAS	Rheumatoid arthritis	0	0	Novel	il2rb
declizumab	zenapex is a humanized monoclonal antibody used for prevention of renal transplant rejection	20-6	1.1	GWAS	Type 1 diabetes autoantibodies	34	2	Strongly supported	il2/b
denileukin dihitox	for treatment of cutaneous t-cell lymphoma	20-6	1.1	GWAS	Type 1 diabetes autoant/bodies	3	0	Likely	il2rb
daolizumab	zenapex is a humanized monoclonal antibody used for prevention of renal transplant rejection	20-6	1.19	GWAS	Rheumatoid arthritis	5	0	Likely	ii2rb

Figure 2: Auto-fill function for query entries. As an example, the gene query term "IL2RB" was automatically recognized as a gene term. Please click here to view a larger version of this figure.

J	pve	Journal of Visualized Experiments

RE:fine Drugs – An Interactive Dashboard of Drug Repurposing Opportunities	NATIONWIDE CHILDRENS Filos par child unde a hopstal, encycling maters."	CENTRE FOR CLINICAL AND CENTRE FOR CLINICAL AND TRANSLATIONAL SOFICE
Drug: bosikirrab		
Registered Indication: for prophylactic treatment of kidney transplant rejection		
P-Malue: 1e-8		
P-Value Adjusted: 1.09+-8		
Shudy: GWAS		
New Indication: Asthma		
# of Medine Abstracts: 0		
# of Clinical Trial Registry: 0		
Potential: Novel		
SNP: m2284033		
Gene: II2rb		
Action: antibody		
Gene Details: Details of gene at nobliniminih gov		
Drug Details: Details of drug at drugbank.ca		
Leave Feedback;		FAQ

Figure 3: Drug repurposing results table produced from a gene-based query (e.g., IL2RB). Twelve drug repurposing hypotheses for the IL2RB gene are produced. Please click here to view a larger version of this figure.

RE:fine Drug Rep	Drugs – An Interactive ourposing Opportunities	Dashbo	ard of			VATIONWIDE CHI Vice yuar child work a hospital, corr	LDREN'S oling matter."	C THE OHIC CENTER FOR TRANSLATION	STATE UN DUNICAL AND IAL SOENCE	VERSITY
RE:fine Drugs is currently contain	an interactive dashboard of drug repositioni ns 60,911 opportunities covering 916 drugs,	ng opportunitie 567 genes and	s by "drug-gene- 1770 diseases.	disease" tris	ada, usi	ng the methods described in Nature Biote	ch 2012 (GWAS)	and Nature Biot	ech 2015 (P	heWAS). It
Getting Started	Guidelinea	uumej, a uisea	se name (e.g. 2021	Internet's Dis	wase), c	a a gene symoon (e.g. ilizhib).				
IL2RB	0	ene Symbol +	Search							advanced
drug as	ocistion disease potential gene	action						† 6	xport Sir	npie 🔻
Info	Show Drug			🕑 Show	Regis	stered Indication	2 Show	·		
	dad	izumab			alpt	hanumeric keyword				
O daolizumab										
Show 100 \$ en	tries Total # of Records: 3									1.1
Drug	Registered Indication	P-Value	b Odds Ratio	Study	11° N	lew Indication	# of Medline Abstracts	# of Clinical	Potential	Gene
daolizumab	zenapax is a humanized monoclonal antibody used for prevention of renal transplant rejection	1 e-8	1.12	GWAS	1	listhma	6	0	Likely	il2rb
daolizumab	zenapax is a humanized monoclonal antibody used for prevention of renal transplant rejection	20-6	1.1	GWAS	Т	ype 1 diabetes autoantibodies	34	2	Strongly supported	il2rb
daolizumab	zenapax is a humanized monoclonal antibody used for prevention of renal transplant rejection	20-6	1.19	GWAS	F	Reumatoid arthritis	6	0	Likely	il2rb
Leave Feedbar	*									FAQ

Figure 4: Information page for individual drugs from results page. Clicking on the icon from the "Info" column shows detailed information for the drug daclizumab. Please click here to view a larger version of this figure.

ug Rep	ourposing Opportuniti	es	ourd of		When your child week a bu	piul coysking nation."	CENTER FOR C TRANSLATION	OLINICAL AND AL SCIENCE	
Efine Drugs is mently contai	s an interactive dashboard of drug reposi ins 80,911 opportunities covering 916 dru	tioning opportuni ugs, 567 genes ar	ties by "drug-gene- nd 1770 diseases.	disease" triad	s, using the methods described in Natu	re Biotech 2012 (GWAS)	and Nature Biot	ech 2015 (P	heWAS).
ease start you	ur search by entering a drug name (e.g. Z	lidovudine), a dise	sase name (e.g. Alz	heimer's Disea	ise), or a gene symbol (e.g. IL2RB).				
tting Started	Guidelines								
L2RB		Gene Symbol -	Search						advance
cirug as	sociation disease potential gen	e action					t e	xport Sir	mpie 🔻
Info	Show	Drug		Show	Registered Indication	× Show			
		alphanumeric			transplant				
transplant	nties Total # of Records: 6								1
) transplant w 100 ¢ en ug II	nnes Total # of Records: 6 Registered Indication	17 P-Value	11 Odds Ratio	Study	17 New Indication	i of Medine ()	# of Clinical	Potential	1 Gene
) transplant . w 100 ¢ en ug II zaliximab	ntins Total # of Records: 6 Registered Indication for prophytactic treatment of kidney transpi rejection	II P-Value	Odds Ratio II 1.12	Study GWAS	New Indication	i e of Medine II Abstracts 0	ë of Clinical ∏ Trial Registry 0	◄ Potential [™] Novel	1 Gene II2rb
transplant w 100 ¢ en ug II ssiliximab solizumab	trites Total II of Records: 0 Registered Indication for proshytocic treatment of kidney transpi evotion zenapse is a humanaed monocional artibu	II P-Value lant 1e-8 stop 1e-8	^{1k} Odds Ratio ¹⁷ 1.12 1.12	Study GWAS GWAS	¹⁷ New Indication Asthma Asthma	i of Medline II Abstracts 0 6	∉ of Clinical ∏ Trial Registry 0 0	Potential Noval Likely	1 Gene ii2rb
) transplant w 100 \$ en ug II saliximab saliximab	ntes Total # of Records: 6 Registered Indication for penghalacis treatment of kidney transpir rejection zenapsis is a humanaed monodional antibio used for prevention of renal transpiratin rejec- for penghalacis treatment of kidney transpir metholon	IT P-Value lant 1e-8 idy 1e-8 iant 2e-6	 Odds Ratio 1.12 1.12 1.12 1.13 	Study GWAS GWAS GWAS	 New Indication Asthma Asthma Type 1 diabetes autoentibodies 	II # of Medline II Abstracts 0 6 20	# of Clinical Trial Registry 0 0 0 0	4 Potential Novel Likely	1 Gene 12/b 12/b 12/b
) transplant w 100 ; en ug II salkimab salkimab salkimab	Total # of Records: 6 Registered Indication for prophyticatic breatment of Midray transpie records anapter is a howaread menocoord antibio used for provement on if multi-transpieler transpie records for prophyticatic breatment of Midray transpie rection	II P-Value lart 1e-8 ddy 1e-8 dant 2e-6 lart 2e-6	Ib Odds Ratio IT 1.12 1.12 1.12 1.12 1.1 1.1 1.12 1.1 1.1	Study GWAS GWAS GWAS GWAS	II New Indication Asthma Asthma Type 1 diabetes autoantibodies Rheumatoid anthritis	II # of Medius II Abstracts 0 6 20 3	# of Clinical Trial Registry 0 0 0 0	Potential Iliosiy Likely	1 Gene ii2rb ii2rb ii2rb
y transplant w (100) en ug II usikidmab esikidmab esikidmab esikidmab	Total if of Records: 0 Registered Indication for prophylacits brainert of kidney transpi mystorion zenapse is a humanized monocional ambit orce of the senament of kidney transpi mystorion for prophylacits brainert of kidney transpi mystorion der prophylacits brainert of kidney transpi mystorion aenapse is humanized monocional ambit aenapse is humanized monocional ambit mystorion	I P-Value art 19-8 do 19-8 art 2e-6 art 2e-6 do 2e-6	Ib Odds Ratio IT 1.12 1.12 1.1 1.1 1.1 1.1 1.1 1.1 1.1	Study GYWAS GYWAS GYWAS GYWAS GYWAS	New Indication Asthma Asthma Type 1 diabetes autoartibodies Rheumanical arthretis Type 1 diabetes autoartibodies	i f or Medine J Abstracts 0 6 20 3 3 34	# of CEinical Trial Registry 0 0 0 0 0 2	Potential Novel Likely Likely Strongly supported	1 Gene ii2rb ii2rb ii2rb ii2rb
transplant w 100 t en w 100 t en	Total II of Records: 0 Registered Indication Be pachylactic treatment of kidney transpi Application antipase is humaneed monoplonal antibu antipase is humaneed monoplonal antibu antipase is humaneed monoplonal antibu audit for prevention for prophylactic treatment of kidney transpi myction antipase is humaneed monoplonal antibu audit for prevention of real-prevention of antibular transpiler antipase is humaneed monoplonal antibu audit for prevention of antibular transpiler antipase antipase	P-Value arr.t 10-8 rdy 20-6 rdy 20-6	Ib Odde Retio III 1.12 1.12 1.12 1.12 1.12 1.11 1.11 1.11 1.11 1.12 1.11 1.11 1.13 1.11 1.11	Study GWAS GWAS GWAS GWAS GWAS	New Indication Asthma Asthma Type 1 diabetes autoantibudies Pleaumatoid anthmites Type 1 diabetes autoantibudies Pleaumatoid anthmites Pleaumatoid anthmites	i é of Medfine (Abstracts 0 6 20 20 3 4 34 8	# of Clinical Triat Registry 0 0 0 0 0 0 2 0 0	Potential Noval Likely Likely Strongly supported Likely	1 * Gene 12b 12b 12b 12b 12b

Figure 5: Advanced search option under drug tab to filter by a specific drug. In this example, three results are shown for the drug daclizumab. Please click here to view a larger version of this figure.

. .

RE:fi Drug	ne Dru Repurpo	gs – An Interactive Das osing Opportunities	hboard o	of		NATIONWIDE CH	ILDREN'S	CENTER FOR CLINC CENTER FOR CLINC TRANSLATIONAL SC	ATE UNIVERS	ятч
RE:fine (currently Please s	Drugs is an inter v contains 60,91 tart your search	active dashboard of drug repositioning oppo 1 opportunities covering 916 drugs, 567 ger by entering a drug name (e.g. Zidovudine), r	ortunities by "dru les and 1770 dis a disease name	ig-gene-disease esses. (e.g. Alzheimer':	" triads, using t s Disease), or a p	e methods described in Nature Bio gene symbol (e.g. IL2RB).	ech 2012 (GW/	NS) and Nature Biotech	2015 (PheWA	.S). II
Getting :	Started Guidelin	Gene Svm	bol - Search						adva	Inces
dinua	association	disease potential gene action						† Export	Simple T	
P-Va	lue Range	Show P-Value Adjus	ited Range	O Shi	w Odds Rati	o ⊻ Sho	w Study		🖉 Show	
	0.000001	to 0.05	1E-600 to 3	5E-2	0	0 - 117.5	Gwas	⊖ PheWAS ⊛ Both		
0 0.00	00001 to 0.05	Total # of Records: 8							• •	
Info 11	Drug	Registered Indication	P-Value	Odds Ratio	Study	New Indication	Abstro	edline # of Clinical acts Trial Registry	Potential	Ge
0	basilximab	for prophylaotic treatment of kidney transplant rejection	20-6	1.1	GWAS	Type 1 diabetes autoantibodies	20	0	Likely	#2
0	denileukin diftitox	for treatment of cutaneous t-cell lymphoma	2e-6	1.19	GWAS	Rheumatoid arthritis	4	0	Likely	82
0	aidesleukin	for treatment of adults with metastatic renal cell carcinoma.	2e-6	1.1	GWAS	Type 1 diabetes autoantibodies	0	1	Likely	82
0	basiliximab	for prophylactic treatment of kidney transplant rejection	20-6	1.19	GWAS	Rheumatoid arthritis	3	0	Likely	12
0	aldesleukin	for treatment of adults with metastatic renal cell carcinoma.	20-6	1.19	GWAS	Rheumatoid arthritis	0	0	Novel	12
0	daolizumab	zenapax is a humanized monoclonal antibody used for prevention of renail transplant rejection	20-6	1.1	GWAS	Type 1 diabetes autoantibodies	34	2	Strongly supported	12
0	denileukin diftitox	for treatment of cutaneous t-cell lymphoma	20-6	1.1	GWAS	Type 1 diabetes autoantibocies	з	0	Likely	12
0	dacizumab	zenapax is a humanized monoclonal antibody used for prevention of renal transplant rejection	2e-6	1.19	GWAS	Rheumatoid arthritis	5	0	Likely	13

Figure 6: Advanced search option under drug tab to filter by a specific disease indication from the DrugBank database. All drugs with a known indication for the disease term "transplant" are shown. Please click here to view a larger version of this figure.

RE:fi Irug	ne Dru Repurpo	gs – An Intera osing Opportu	active Das Inities	hboa	rd c	of		NATION WIDI When your child made a lo	E CHILDRE apital, conjuting mat	N'S 🚺	THE OHIO STAC CENTER FOR CLINICA TRANSLATIONAL SCI	LAND NCE	SITY
RE:fine (currently	Drugs is an inter contains 60,91	active dashboard of drug 1 opportunities covering f	repositioning opp 916 drugs, 567 ger	ortunities b nes and 17	ny "dru 70 dise	g-gene-disease eases.	* triads, using t	he methods described in Natu	re Biotech 201	2 (GWAS) and 1	Nature Biotech 2	015 (PheWA	45). It
Please s	tart your search	by entering a drug name	(e.g. Zidovudine),	a disease	name (e.g. Alzheimer's	s Disease), or a	gene symbol (e.g. IL2RB).					
Betting 1	Started Guidelin	85											
IL2RB			Gene Syn	ibol - Se	arch							adva	anced
drug	association	disease potential	gene action								1 Export	Simple *	-
New	Indication	¥ Sho	w										
	ing of the second		-										
ast	hmaj												
0 880	ima												
thow 1	00 ¢ entries	Total # of Records: 4										x 1	*
Info 11	Drug	Registered Indication		P-Value	17	Odds Ratio	Study	New Indication		# of Medline Abstracts	# of Clinical II Trial Registry	Potential	Gene
0	basiliximab	for prophylactic treatment rejection	of kidney transplant	1e-8		1.12	GWAS	Asthma		0	0	Novel	ii2rb
0	denileukin diftitox	for treatment of outaneous	t-cell lymphoma	1e-8		1.12	GWAS	Asthma		0	0	Novel	12rb
0	daclizumab	zenapax is a humanized m used for prevention of rena rejection	onocional antibody al transplant	10-8		1.12	GWAS	Asthma		6	0	Likely	i@rb
0	aldesleukin	for treatment of adults with cell carcinoma.	n metastatio renal	10-8		1.12	GWAS	Asthma		0	0	Novel	il2rb
Leave	Feedback											,	FAQ

Figure 7: Advanced search option under association tab to filter by significance level. In this case, eight results are provided whose association significance level falls within the P-Value range of 0.000001 to 0.05. Please click here to view a larger version of this figure.

RE:fine Drug Rep	Drugs – An Interactiv ourposing Opportunitie	e Dashboa s	ard of			DE CHIL	DREN'S	CENTER FOR TRANSLATION	STATE UNI CLINICAL AND VAL SCIENCE	VERSITY
RE:fine Drugs is currently contain Please start you	a an interactive dashboard of drug repositi ins 60,911 opportunities covering 916 drug ur search by entering a drug name (e.g. Zic	oning opportunities (s, 567 genes and 1 lovudine), a disease	by *drug-gene-i 770 diseases. e name (e.g. Alzh	disease* tria veimer's Dise	ds, using the methods described in 8 sase), or a gene symbol (e.g. IL2RB).	lature Biotec	h 2012 (GWAS)	and Nature Biol	tech 2015 (Pr	neWAS). It
Getting Started										
IL2RB		Gene Symbol •	Bearch							advanced
drug as	sociation disease potential gene	action						† E	aport Sin	volo 🕶
Found India DrugBank	ation in O Show Nu Ab	mber of Medline stracts		Show	Number in Clinical Trial Registry	2 Show	Repurposing	Potential		Show
O Yes O I	No * All	ø	- 1000	1000	0 - 1000X	tacee	O Novel O O Known B	Likely O Stron	gly Supported	
O Medine Ab Show 100 ¢ en	stracts: 5 - 1000 trics Total # of Records: 4									1 1
Drug	Registered Indication	P-Value	Odds Ratio	Study	IT New Indication		# of Medline 1 Abstracts	# of Clinical	Potential	Gene 🗍
dacizumab	zenapax is a humanized monocional antibod used for prevention of renal transplant rejecti	y 1e-8 on	1.12	GWAS	Asthma		6	0	Likely	12/b
basiliximab	for prophylactic treatment of kidney transplar rejection	nt 2e-6	1.1	GWAS	Type 1 diabetes autoantibodies		20	0	Likely	il2rb
dacizumab	zenapax is a humanized monoclonal antibod used for prevention of renal transplant rejecti	y 2e-6 on	1.1	GWAS	Type 1 diabetes autoantibodies		34	2	Strongly supported	it2rb
daolizumab	zenapax is a humanized monoclonal antibod used for prevention of renal transplant rejecti	y 20-6 on	1.19	GWAS	Pheumatoid arthritis		5	0	Likely	12rb
Leave Feedba	0k									FAQ

Figure 8: Advanced search option under disease tab to filter by a specific disease indication we extracted in this study. In this example, four results are shown for asthma as a new use disease indication. Please click here to view a larger version of this figure.

RE:fi Drug	ne Dru Repurpo	gs – Ar osing O	n Intera pportu	ctiv nitie	e Das es	hbo	ard	of		NATIONWI IShen yaur ohdid nood	IDE CHILDRE	NS 🚺	THE OHIO STAT	TE UNIVER:	SITY
RE:fine (currently	Drugs is an inter y contains 60,91	active dashb 1 opportunitie	card of drug r as covering 9	epositi 16 dru;	ioning oppo gs, 567 gen	rtunitie es and	s by "dn 1770 dis	ug-gene-diseas leases.	ie" triads, using	the methods described in M	lature Biotech 201	2 (GWAS) and 1	Nature Biotech 2	015 (PheWA	.S). It
Nease s	tart your search	by entering a	a drug name (e.g. Zic	dovudine), a	1 disea	se name	(e.g. Alzheimer	's Disease), or i	i gene symbol (e.g. IL2RB).					
Betting :	Started Guidelin	85			C C		Count								
LEND					Gene Sym	001 *	Search							advi	nced
drug	association	disease	potential	gene	action								t Export	Simple *	r .
SNP			Show	Ge	ene Symbol			⊻ S	how						
alp	hanumeric				alphanumerk	c keywa	rd								
how 1	00 ¢ entries	Total # of	Records: 12											$ \mathbf{x}_{i} _{1}$	٠
nfo ¹¹	Drug	Registered li	ndication			P-Val	, IL	Odds Ratio	Study	New Indication		# of Medine Abstracts	# of Clinical Trial Registry	Potential	Gen
0	basiliximab	for prophylac rejection	tic treatment o	rl kidney	y transplant	1e-8		1.12	GWAS	Asthma		0	0	Novel	i@rb
Ð	denileukin diftitox	for treatment	of cutaneous	t-cell lyr	mphoma	1e-8		1.12	GWAS	Asthma		0	0	Novel	112rb
0	daclizumab	zenapax is a used for prev rejection	humanized mo rention of renal	noclon transpi	al antibody lant	10-8		1.12	GWAS	Asthma		6	0	Likely	igrt
0	aldesleukin	for treatment cell carcinom	of adults with a.	metasta	atic renal	10-8		1.12	GWAS	Asthma		0	0	Novel	il2rb
0	basiliximab	for prophylac rejection	tic treatment o	rl kidney	y transplant	20-6		1.1	GWAS	Type 1 diabetes autoantibo	dies	20	0	Likely	ii2rb
Ð	denileukin diftitox	for treatment	of outaneous	-cell lyr	mphoma	2e-6		1.19	GWAS	Rheumatoid arthritis		4	0	Likely	il2rb
0	aldesleukin	for treatment	of adults with a.	metasta	atic renal	2e-6		1.1	GWAS	Type 1 diabetes autoantibo	dies	0	1	Likely	il2rb
0	basiliximab	for prophylad	tic treatment o	f kidney	y transplant	2e-6		1.19	GWAS	Rheumatoid arthritis		3	0	Likely	ii2rb
0	aldesleukin	for treatment	of adults with	metasti	atic renal	2e-6		1.19	GWAS	Rheumatoid arthritis		0	0	Novel	il2rb
0	daclizumab	zenapax is a used for prev rejection	humanized mo ention of renal	transpi	al antibody iant	20-6		1.1	GWAS	Type 1 diabetes autoantibo	dies	34	2	Strongly supported	12rb
0	denileukin diftitox	for treatment	of outaneous t	cell lyr	mphoma	20-6		1.1	GWAS	Type 1 diabetes autoantibo	dies	3	0	Likely	1210
0	daciizumab	zenapax is a used for prev rejection	humanized mo rention of renal	transpi	al antibody iant	28-6		1.19	GWAS	Rheumatoid arthritis		6	0	Likely	il2rb
		rejection													

. .

Figure 9: Advanced search option under potential tab to filter by a co-occurrence of drug and disease terms in Medline abstracts. In this example, four results are shown that are supported by a minimum number of 5 Medline abstracts containing a co-occurrence of drug and disease terms. Please click here to view a larger version of this figure.

e methoda described in Nature Biotech 2012 (XWAS) and Nature pane symbol (a.g. IL2PRS). New Indication II of eff description (a.g. IL2PRS). New Indication (a.g. IL2PRS). New I	
New Indication I # of Medine) # of Addine) Asthma 0 0 Asthma 0 0 Pieumatod arthrifis 4 0 Type 1 dabories autoartibodies 0 1	liotech 2015 (PheWAS). It
New Indication II # of Medine) # of C Adhma 0 Abstraction 0 Adhma 0 0 0 Pleaunatoid arthritis 4 0 0 Type 1 debates autoarthbodies 0 1 1	
New Indication II # of Medines # of Advination Advination 0 0 0 Anthreat 0 0 0 Presumationi antivities 4 0 0 Type 1 debanese autoentibucties 0 1 1	
New Indication I If of Medines If of Medines Advination II If of Medines If of Medines Advination 0 0 Anthreat 0 0 Pre-unstood arthritis 0 0 Type 1 debanes externitioodes 0 1	advanced
New Indication I of of Medinesi 8 of C Abbinacion Adhma 0 0 Anthma 0 0 Presumation antivitias 4 0 Type 1 diabanes autoentibodes 0 1 Presumation antivitias 0 0	Export Simple 🔻
New Indication If of Medines 8 edf Abstraction 8 edf Triver I Adhma 0 0 0 Anthma 0 0 0 Presunatiod artivitias 4 0 1 Pre-unstood artivitias 0 1 1	
New Indication If of Mudiani, if of Mudia	
New Indication If of Mudilion () Abstraction If of Mudilion () Their II Abstraction If of Mudilion () Their II Abstraction If of Mudilion () Abstraction If of Mudilion () Abstraction <th< td=""><td></td></th<>	
New Indication If of Mediane): If of Media	
New Indication # of Medianistic # of Medianistic <th# medianistic<="" of="" th=""> <th# medianistic<="" of="" th=""></th#></th#>	_
New Indication If of Medianic II of Characteristic Tell Astrona 0 0 Pre-unstoci arthritis 0 0 Pre-unstoci arthritis 0 0	1 1 F
Asthma 0 0 Authma 0 0 Preumutoid arthritis 4 0 Type 1 diabries autoantibodies 0 1 Preumutoid arthritis 0 0	egistry Potential Ger
Anthma D D Rhaumatold arthritis 4 0 Type 1 discerse autoantibodies 0 1 Preumstoid arthritis 0 0	Novel ii2r
Phaumatoid arthritis 4 0 Type 1 diabates autoentibodies 0 1 Rheumatoid arthritis 0 0	Novel it2r
Type 1 disbetes autoentibodies 0 1 . Pheumatoid arthritis 0 0 0	Likely it2r
Pheumstoid arthritis 0 0	Likely it2r
	Novel it21
Type 1 diabetes autoantibodies 3 0	
	0 0 4 0 0 1 0 0

Figure 10: Advanced search option under gene tab to filter by a specific gene symbol, where all results correspond to the IL2RB gene used for the original query. In this example, all drugs results under the gene tab are targeted for the "IL2RB" gene, corresponding to the original query term. Advanced search option under action tab to filter by agonist drugs only. In this example, six results are returned for all drugs that act as agonists on the IL2RB gene. Please click here to view a larger version of this figure.

Discussion

The protocol described here for the RE:fine Drugs interactive dashboard can be modified in different ways according to the user's preferences. This method uniquely integrates GWAS and PheWAS data as a novel paradigm underlying drug repurposing hypothesis generation. Specifically, this system provides access to both 52,966 PheWAS associations and 7,945 GWAS associations with advanced options to filter the results by the study type, effect size and/or significance level. Another advantage of this method over existing computational drug repurposing tools is that queries may be made from drug, gene or disease perspectives.

There are several limitations to this method. Currently, the PheWAS data is limited to primarily adult patient population from five institutions contained in the Electronic Medical Records and Genomics (eMERGE) network with a mean age of 69.5 years ¹². Additionally, the "repurposing potential" feature uses co-occurrence of search terms in Medline abstracts as one of its criteria. It is well known that text mining methods using co-occurrence have limitations with respect to syntactical structure and literature bias. Thus, we recommend this feature be used as a starting point to explore the potential novelty and/or evidence supporting specific drug repurposing hypotheses and recommend additional investigation into the biomedical literature and clinical trial databases.

Future directions for this work not described here would be to extend this database to additional sources of GWAS and PheWAS data as they become available. Similar efforts to systematically translate results from large-scale GWAS studies into drug repurposing hypotheses have been previously published ^{9,13-14}. It may be useful to compare these different workflows to predict drug candidates from GWAS data in future studies. Additionally, several other methods exist to computationally generate drug repurposing hypotheses from different data sources, including: genomics, transcriptomics, chemical structures, drug side effect profiles, as previously summarized ^{6,11}. Future methodological advancements could also include automating drug combination predictions and providing information on drug toxicity to guide follow up studies for drug candidates.

Furthermore, the hypotheses generated from RE: fine Drugs may be further validated using electronic health records, before initiating clinical trials ¹⁵. Finally, future studies will be needed to compare this system to other target-based drug repurposing methods.

Disclosures

The authors declare that they have no competing financial interests.

Acknowledgements

This work was partially supported by the National Institutes of Health (NIH) Clinical and Translational Science Awards (CTSA) Grant (UL1TR001070) to the Ohio State University's Center for Clinical and Translational Science (CCTS) and the National Library Of Medicine under Award Number T15LM011270.

References

- 1. Borisy, A. A. et al. Systematic discovery of multicomponent therapeutics. Proc Natl Acad Sci U S A. 100 (13), 7977-7982 (2003).
- 2. Zhang, L. et al. High-throughput synergy screening identifies microbial metabolites as combination agents for the treatment of fungal infections. *Proc Natl Acad Sci U S A*. **104** (11), 4606-4611 (2007).
- 3. Adams, C. P., & Brantner, V. V. Estimating the cost of new drug development: is it really 802 million dollars? *Health Aff (Millwood).* 25 (2), 420-428 (2006).
- 4. Bunnage, M. E. Getting pharmaceutical R&D back on target. Nat Chem Biol. 7 (6), 335-339 (2011).
- 5. Ashburn, T. T., & Thor, K. B. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov. 3 (8), 673-683 (2004).
- 6. Hurle, M. R. et al. Computational drug repositioning: from data to therapeutics. Clin Pharmacol Ther. 93 (4), 335-341 (2013).
- 7. Jin, G., & Wong, S. T. Toward better drug repositioning: prioritizing and integrating existing methods into efficient pipelines. *Drug Discov Today.* **19** (5), 637-644 (2014).
- 8. Moosavinasab, S. et al. "RE:fine Drugs": An Interactive Dashboard to Access Drug Repurposing Opportunities. Database (Oxford). (2016).
- 9. Zhang, J. et al. Use of genome-wide association studies for cancer research and drug repositioning. PLoS One. 10 (3), e0116477 (2015).
- Rastegar-Mojarad, M., Ye, Z., Kolesar, J. M., Hebbring, S. J., & Lin, S. M. Opportunities for drug repositioning from phenome-wide association studies. *Nat Biotechnol.* 33 (4), 342-345 (2015).
- 11. Li, J. et al. A survey of current trends in computational drug repositioning. Brief Bioinform. 17 (1), 2-12 (2016).
- 12. Denny, J. C. *et al.* Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nat Biotechnol.* **31** (12), 1102-1110 (2013).
- 13. Wang, H., *et al.* Mining drug-disease relationships as a complement to medical genetics-based drug repositioning: Where a recommendation system meets genome-wide association studies. *Clin Pharmacol Ther.* **97** (5), 451-454 (2015).
- 14. Sanseau, P., et al. Use of genome-wide association studies for drug repositioning. Nat Biotechnol. 30 (4), 317-320 (2012).
- 15. Xu, H. *et al.* Validating drug repurposing signals using electronic health records: a case study of metformin associated with reduced cancer mortality. *J Am Med Inform Assoc.* **22** (1), 179-191 (2015).