Drug Repositioning Strategies for the Identification of Novel Therapies for Rheumatic Autoimmune Inflammatory Diseases

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KEYWORDS

• SLE • Lupus • Rheumatic autoimmune inflammatory disease (RAID)
• Drug repositioning • Drug repurposing • Bioinformatics

KEY POINTS

- RAID such as systemic sclerosis, myositis, Sjögren's syndrome and systemic lupus erythematosus (SLE) have had few new treatments developed over the past half century.
- Of the 82 drugs approved by the FDA from 2014 to mid-2016, only three had a RAID indication (http://www.centerwatch.com/drug-information/fda-approved-drugs/year/).
- There are four major approaches to drug repositioning: computational modeling, disease mechanism-of-action based approaches, genetic profiling and translational bioinformatics.
- Artificial intelligence cognitive computer systems (AICCS) or human bioinformaticians narrow down drug repositioning candidates using similar tools but the background and experience of human biologists inform the bioinformatic analysis in a way that a machine cannot replicate.

INTRODUCTION

There are many and varied approaches to drug repositioning that have been used in the search for effective treatments for patients with a variety of different diseases[1,2] (**Box 1**). Methodologies typically use information from one of the following: structural similarity, adverse events, literature mining, clinical trials, gene expression, genome-wide association studies (GWAS), pathways, and/or the interactome.[3,4] Drug

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Box 1
Strategies to identify novel therapies for rheumatic autoimmune inflammatory diseases

Predicting drugs that bind protein products of genes abnormally expressed in disease	
Molecular docking	
PharmMAPPER	http://59.78.96.61/pharmmapper/help.php
Computational modeling	
CANDO	http://ram.org/compbio/protinfo/cando/
SDTNBI	http://lmmd.ecust.edu.cn/methods/bsdtnbi/
Using molecular activity similarity to predict drugs from differentially expressed gene profiles	
cMAP/LINCS	http://www.lincscloud.org/l1000/
D-GEX	https://github.com/uci-cbcl/D-GEX
Cogena	https://bioconductor.org/packages/release/bioc/html/cogena.html
QUADrATiC	https://omictools.com/qub-accelerated-drug-and-transcriptomic-connectivity-tool
DTome	https://bioinfo.uth.edu/DTome/
Translational bioinformatics	
HumanDiseaseNetwork	https://exploringdata.github.io/info/human-disease-network/
eMERGE	https://emerge.mc.vanderbilt.edu/
RE:fineDrugs	http://drug-repurposing.nationwidechildrens.org/search
Identifying disease-drug and gene-drug relationships	
Protein-protein interactions	
BioGRID	http://thebiogrid.org/
Domain-domain interactions	
PFam	http://pfam.xfam.org/
Integrates interaction networks	
Consensus DB	http://consensuspathdb.org/
Machine learning drug prediction	
GOPredict	http://csblcanges.fimm.fi/GOPredict/

Abbreviations: cMAP, Connectivity Map; CANDO, computational analysis of novel drug opportunities; D-GEX, Deep machine learning-Gene EXpression; DTome, Drug-Target Interactome; LINCS, Library of Integrated Network-Based Cellular Signatures; QUADrATiC; QUB Accelerated Drug And Transcriptome Connectivity; SDTNBI, Substructure-Drug-Target Network-Based Inference.

repositioning is an important approach, as it can decrease the time/cost of drug approval because it takes into account issues of toxicity and specificity from early testing and, thereby, paves the way for future discoveries by categorization of drugs by physiologic proxy.[5] Purposeful drug repositioning is often called retooling, reprofiling, retasking, and even drug rescue.[6]

The field of drug repositioning has emerged over the past decade, driven by collaborations among structural scientists, physicians, medicinal chemists, animal model experts, geneticists, computational modelers, immunologists, artificial intelligence/machine learning experts, and bioinformaticians. There are 4 major approaches to drug repositioning that have been used over the years: computational modeling, disease mechanism of action–based approaches, genetic profiling, and translational bioinformatics. Some approaches, such as computational modeling, are most appropriate for small molecules, whereas other approaches can be used to reposition either biologics or small molecules. The focus here is on techniques that stem from genomic information gathered from patients with rheumatic autoimmune inflammatory disease (RAID) and compared with healthy individuals. Small molecules that bind protein products of differentially expressed genes (DEGs) identified following microarray or RNA-Seq can be predicted by computational modeling. Patterns of DEGs in a particular disease can be compared with those in a variety of databases composed of cells cultured