System and network biology-based computational approaches for drug repositioning

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13.1 Introduction

The current pandemic scenario has taught us the value of drug repurposing. Since late December 2019, the world is facing the surge of Coronavirus disease-2019 (COVID-19) pandemic caused by severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2). Initially, there were no specific drugs or vaccines against this virus (Khan et al., 2021; Parihar et al., 2020; Parihar et al., 2022). Researchers around the world have used multiple approaches to evaluate the antiviral efficacy of molecules from the existing Food and Drug Administration (FDA)-approved drug candidates. This strategy is known as drug repurposing. Mainly drug repurposing gave us suitable candidates which can be utilized for the treatment of disease for instance remedisvir was initially approved for the treatment of human immunodeficiency virus (HIV) and is now found to be efficacious for SARS-CoV-2.

These approaches have been used in the pharmaceutical industry to lower the cost and time for identifying a potential lead molecule as initially drug development strategies need multiple trial steps and, in this process, out of a million selected molecules only a quarter of drugs pass the clinical phase, which takes an average of 7 years or more which followed by clinical validation thereby only one or two potential candidates would get approval. The whole process is not only cumbersome but also needs billions of dollars of investment and it includes the cost of all drugs that do not gain FDA approval (Xue et al., 2018; Ashburn & Thor, 2004; Parihar et al., 2022). Given these daunting success rates or high failure rates, high costs, and a slow pace of drug discovery, by using drug repurposing approaches, one can save time and cost associated with the traditional drug development process and bring a successful drug to market faster and provide patients with more effective treatment in less time. This has compelled drug developers to be more inventive in their search for novel therapeutic applications for current medications. Drug repurposing, also known as drug redirecting, drug tasking, drug profiling, or drug recycling, is a promising strategy that offers many opportunities for drug candidates with well-established formulations, extensive pharmacokinetics, toxicity, clinical trial, and postmarketing surveillance safety data (Ashburn & Thor, 2004; Deotarse et al., 2015). Increased attrition rate due to toxicity, development of drug resistance, and uneven efficacy of medications in various individuals due to varying therapeutic responses are the most pressing issues in drug development (Hopkins, 2008; Pammolli et al., 2011). Recent advances in the process of computational-based system biology and bioinformatics have given a boost to the process of drug development. The systems biology approaches mainly utilize the information of drug-associated data for drug repositioning which will help to better understand the molecular basis of disease and mode of drug action. Several diseases including cancer and inflammatory disease have proven to be significantly more complex than previously assumed, as they are typically caused by a combination of many molecular abnormalities, providing a unique network of multiple linked pathways involved in disease complications (Barabási et al., 2011). The complexity of these diseases made researchers realize that the human body has an inbuilt integrated network with ongoing interactions both intracellular and between the organ systems. The understanding of these networks can help treat diseases by a combination of more holistic approaches which will decrease the chances of disease-associated morbidities. The interconnectedness of the body can be visualized by the fact that one drug can treat one symptom but causes side effects to other organs. For example, if a patient comes into the clinic with symptom **A** and is prescribed drug **A** to treat symptom **A**, but drug A causes side effects **B** to **F**, the patient will need to take additional medication to treat these additional side effects, which will often result in the patient taking a string of medications.

Identifying drug−target interactions is critical for better understanding the molecular mechanism of action of a chemical and optimizing the therapeutic effect (Bantscheff & Drewes, n.d.; Wu et al., 2013). As a result, systematic screening is a key stage in pharmaceutical research and development. However, due to the high number of pairwise interactions, experimentally screening all conceivable interactions between proteins and chemicals is extremely difficult. As a result, computational modeling and, in particular, network techniques appear to be a viable option. Such theoretical methods are not only speedier, but they can also reliably distinguish

potential drug—target interactions, which can help support experimental studies (Li et al., 2016).

The advances in biological sciences can be used to understand the body's connectivity and develop a viable treatment for the disease. Over the last several decades, advances in biological and computational sciences have resulted in the generation of a large number of omics based molecular databases at the genome, transcriptome, proteome, and metabolome levels such as DrugBank, ChemBank, OMIM, KEGG, and Pubmed (Oprea & Overington, 2015). Further, the rapid development of microarray techniques led to the establishment of enormous genomic databases, such as MIPS, PDB, GEO, and GenBank (Oprea & Overington, 2015). These offers a database of individual molecular components at the cellular and organellar level and this information can be put together as system/network biology-based approaches to further understand (1) how different components are placed together to form the structure of biological systems, (2) how these interacting components can produce complex system behaviors, and (3) how conditions can dynamically alter these behaviors (Breitling, 2010). Systems biology has arisen as a significant new science that entails computational modeling of biological systems to comprehend large amounts of genome-scale data at a systems level for a better understanding of disease conditions (Kitano, 2002). The pharmaceutical industry has taken systems biology into account and is attempting to understand the biological complexity of diverse diseases.

System pharmacology is a branch of systems biology that focuses on the investigation of putative mechanisms behind pharmacological activities in organisms (Hart et al., 1976). The main issue in system pharmacology is to combine the heterogeneous chemical, biological, and clinical data into interpretable and actionable mechanistic models for drug discovery and patient care decision-making (Audouze & Taboureau, 2015). In systems biology, rapid accumulation of experimental data and computational modeling approaches are critical for efficient in silico predictions. Compared to biological experimental procedures, computational approaches are less expensive and have fewer limitations (Hartmaier et al., 2017; Oprea & Mestres, 2012). The schematic diagram in Fig. 13.1 shows steps of drug repurposing using the systems biology approach. Systems biology is a broad term that refers to a variety of methodologies (methods) in drug development. It includes a variety of methodologies and models that aid in understanding disease mechanisms, generating novel medications, repurposing drugs, and forecasting beneficial medication combinations (Oprea & Mestres, 2012; Rai et al., 2018).

Network-based techniques provide the potential to investigate a drug candidate's effects in a global physiological context in a methodical manner (Panagiotou & Taboureau, 2012). Barabasi et al. describe the benefits of network-based approaches to human disease at the phenotype level, based on the assumption that the functions of molecular components in a human cell are closely connected and that disease is rarely the result of a single genetic variation, but rather of perturbations of complex intracellular and extracellular networks linking tissue (Barabási et al., 2011). There have been numerous network-centric approaches developed and implemented. At the molecular level, network-based techniques have lately been studied. Wawer et al. (2008) demonstrated that small molecule structure—activity relationships (SARs) are commonly structured in small communities that can be represented in networks, rather than being separated (Boezio et al., 2017). This chapter focuses on system and network biology-based approaches used for repurposing drugs for various diseases. Besides, various approaches and tools used in this process have been elucidated. Further, the COVID-19 based drug repurposing has also been discussed herewith.
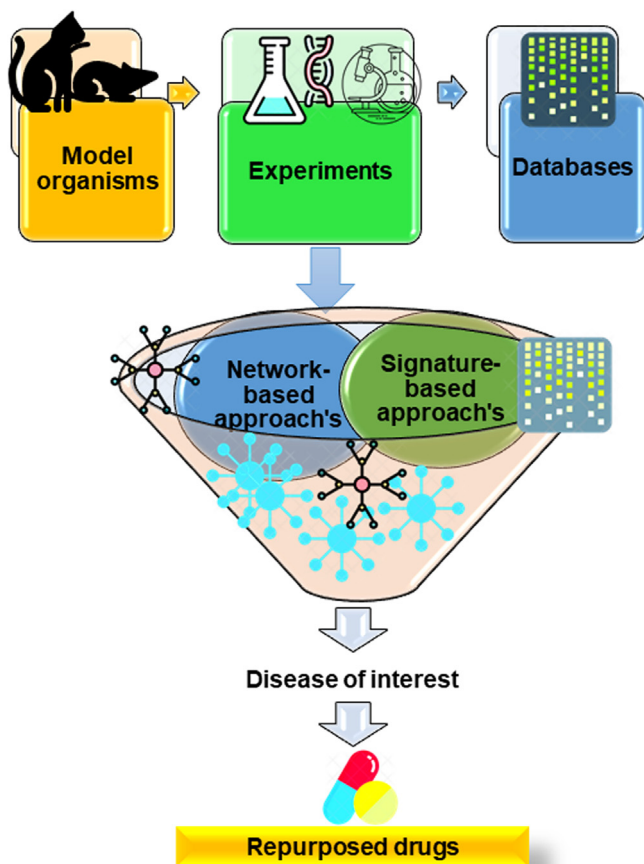
FIGURE 13.1 Drug repositioning via systems biology. Summary of components and methodologies used in drug repositioning studies from the perspective of systems biology.

13.2 Approaches of system biology towards drug repositioning

System biology is based on a combination of research that assesses a wide range of biological processes using computational methods which enable the interpretation of a wide range of data sets associated with disease (Rai et al., 2018; Kitano, 2002). Handling such biological data necessitates multidisciplinary expertise from various fields, such as biology, bioinformatics, mathematics, physics, chemical engineering, and computer science. Many techniques and approaches have been developed using multidisciplinary collaboration and system biology platforms that offer huge potential to influence biomedical science (Wang et al., 2015). Instead, of focusing on individual molecules, system biology attempts to understand more about a holistic view by investigating interactions among multiple components in a biological process. The system biology methodologies in pharmacology evaluate each biomolecular interaction between drugs and their respective targets in a human cellular setting (Turanli et al., 2021). System pharmacology when combined with wet-lab investigations can have the ability to quantify biological components with the help

of computational approaches and the outcome can be confirmed empirically (Zou et al., 2013). System pharmacology is becoming a more popular technique for identifying new drug targets and therapeutic molecules for designing effective therapeutics for patient treatment. Furthermore, drug−target networks, side effects, forecasts of drug−target interactions or drug combinations, and drug repositioning can be done by using systems pharmacology-based approaches.

Systems biology has been used in many studies to interpret disease mechanisms, diagnostic, prognostic, and theranostic properties of biomarkers (Turanli et al., 2021). In this context, Regan-Fendt et al. described an integrated drug combination prediction approach (SynGeNet, Synergy from Gene expression and Network mining) that included connectivity mapping and network centrality analysis. Their finding suggested that the combination of vemurafenib (BRAF inhibitor) and tretinoin (retinoic acid receptor agonist) could be useful in treating BRAF-mutant melanoma (Regan-Fendt et al., 2019). Other researchers such as Nagaraj et al. suggest that indomethacin could be utilized to treat epithelial ovarian cancer using a computational profile-based medication repurposing technique (drug predict) (Nagaraj et al., 2018). Experimental data for drug target relationships has amassed as a result of the advent of omics technologies (Systems Biomedicine Acts as a Driver for the Evolution of Pharmacology, 2017), and system pharmacology plays a key role in integrating and exploring all of this data using two basic strategies: signature-based and network-based techniques (Iorio et al., 2013)

13.2.1 Signature-based approaches

Signature-based techniques for drug repositioning involve the use of target-based and cell-based screening assays. Generally, it has been used to compare gene expression profiles in diseased conditions and drug-induced states to look for hallmark reversion and repurpose medications for a specific disease target (Iorio et al., 2013). This process helps generate a precise map of linkages between diseases and pharmacological activities of drugs which in turn is straightforward helpful to validate drug candidates in preclinical and clinical trials (Shim & Liu, 2014). The experimental assessment of computationally predicted drug candidates obtained from signature-based pharmacological studies can be exploited for drug repurposing. For instance, Chang et al. suggested a novel deep learning methodology (Cancer Drug Response profile scan) which includes genomic mutational fingerprints of human cancer cell lines as well as structural profiles of 244 medicinal drugs which can be explored to get lead drug molecules. The virtual molecular docking studies of 1487 authorized medications revealed 14 oncology and 23 non-oncology medications with the potential for cancer treatment as a repurposed drug (Chang et al., 2018). In another study, O'Donovan et al. used a signature-based connectivity analysis based on the extensive chemical perturbagen "omics" datasets deposited in the Library of Integrated Network-based Signatures (LINCS) database which helps uncover links between disease phenotypes in various disease conditions and has proven to be useful for drug repositioning. The LINCS database is a repository of "L1000" gene expression signatures created by treating different cell lines with over 20,000 small compounds (O'Donovan et al., 2021). Xu et al. used nontissue-specific core signatures from cancer transcriptomes in the TCGA

database and compared drug-to-gene profiles to the core signatures in a recent study. Psychiatric medicines anticipated to inhibit the TGF-b pathway, as well as seven other medications (including calcium channel blockers), may have repurposing potential by targeting the AMPK and AKT pathways, according to the findings (Xu et al., 2018). In the current COVID-19 pandemic, A two-pronged approach-based identified candidate drugs are (1) highly concordant with current medications used to treat diseases of the coronavirus family, and (2) highly conflicting with the SARS-CoV-2 transcriptome signature. Seven of the identified candidate medications have already been registered for clinical studies as COVID-19 treatments (clinicaltrials.gov).

13.2.2 Network-based approaches

Networks are important in systems biology because they provide a framework for integrating quantitative and qualitative links between biological elements, such as gene expressions, correlations, and the presence of interactions (Azuaje, 2013). To identify important biological pathways and functional modules behind complex diseases, network medicine techniques enable network-wise integrated investigation of diverse biological and clinical data sources. These approaches could be useful in identifying the lead molecule which could potentially be intervening with underlying risk factors and comorbidities at a community level (Azuaje, 2013). In many diseases, including metabolic disorders cancers, and infectious diseases such as COVID-19, networks-based models have been used to identify molecular mechanisms, prognostic and diagnostic disease biomarkers (Calimlioglu et al., 2015; Gov et al., 2017; Kori et al., 2016). The recent review emphasized the fact that network modeling can be used as a major approach for computational drug repositioning basically via creating a disease−gene−drug triangle. The nodes in the networks represent drug, disease, or gene products, while the edges reflect their interactions or linkages (Yella et al., 2018). The network-based approach, Netsig, a paradigm developed by Horn et al., combines protein interaction networks with cancer mutation data from 4742 tumor genomes. Netsig predicted 62 gene candidates, which were further supported by mechanistic in vitro studies. The outcome of this study suggested that TFDP2 and AKT2 could be tumor-inducing genes in oncogene-negative lung adenocarcinomas, and thus can be exploited as a target for searching lead drug candidates for complex diseases with varying degrees of clinical heterogeneity (Horn et al., 2018). Recent studies spread awareness of the network features of genes and proteins, and also in some cases the post-genome age and the links between diseases and the accompanying molecular pathways that fortify them (Zhang et al., 2018) (Fig. 13.2).

The basic steps involved in network modeling and analysis are (Rai et al., 2018; Vidal et al., 2011) as explained in the following:

1. Data mining, which involves extraction of interaction data of genes, proteins, metabolites, drugs, etc. from the database;
2. Construction of an interaction network using the extracted data;
3. Validation of interaction network by comparing it to random networks;
4. Analysis of interaction network for topological properties, overrepresented pathways, candidate disease genes, biomarkers, drug targets, etc.
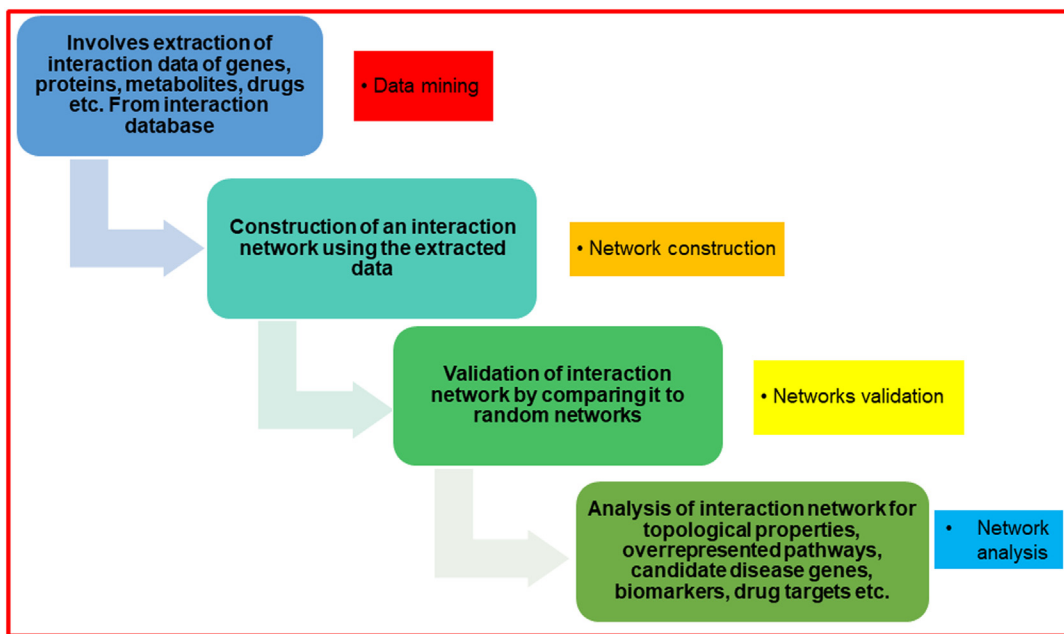
FIGURE 13.2 Basic steps involved in network modeling and analysis.

13.2.3 Examples of repositioned drugs using systems biology

There are several examples of repositioned drugs with computational systems pharmacology approaches for predictions of drug−target interactions in oncology. Here we focus on novel studies of well-known drugs from different drug families, namely metformin, aspirin, digoxin, itraconazole, and disulfiram. These drugs were initially repurposed based on clinical results or in vitro screening of approved drug collections. Table 13.1 enlisted a few of such drugs.

13.3 Computational approaches used in systems biology

Understanding the complex behavior of biological systems that emerges from separate cellular components and interactions between them is the goal of systems biology. Thus, systems biology relies on the perfect blend of experimental research that creates data about a system's biological components using computational tools that aid in the interpretation of multiple datasets (Sobie et al., n.d.). In systems biology, there are two main computational approaches involve data-driven (top-down method) and hypothesis-driven (bottom-up approach) (Sobie et al., n.d.; Faratian et al., 2009).

13.3.1 Top-down modeling approaches

These methods are basically utilized statistical models for handling large-scale datasets. The statistical approaches generally identify trends/patterns and analyzed data to make

TABLE 13.1 Original and new indications of repositioned drugs are presented together with their proposed molecular mechanisms.

Drug	Main indication	New indication	Proposed molecular mechanisms	References
Metformin	Antidiabetic	Breast, prostate, bladder, colorectal, endometrial, pancreatic, lung, thyroid, liver cancers	Inhibition of mTOR pathway Inhibition of insulin/IGF-1 pathway Inhibition of NF-κB pathway Activation of JNK/p38 MAPK pathway	Li et al. (2018), ClinicalTrials.gov. National Library of Medicine (U.S.) (2020)
Aspirin	Anti-inflammatory and analgesic	Colon, stomach, esophageal, breast, lung, prostate, and liver cancers	Inhibition of COX-1/COX-2 Modulation of NF-kB or STAT3 pathway Inhibition of Wnt/β-catenin pathway	Alfonso et al. (2014), ClinicalTrials.gov. National Library of Medicine (U.S.) (2021)
Digoxin	treatment of various heart failure diseases	Prostate, breast, renal, and lung cancers, melanoma, and leukemia	Inhibition of Na + /K + -ATPase pump and modulation of signaling cascades (MAPK, PLC, PI3K, and Src kinase) Acting as phytoestrogen and inhibiting androgen receptors signaling Inhibiting hif-1 synthesis	Lin et al. (2015), ClinicalTrials.gov. National Library of Medicine (U.S.) (2016)
Statins	Reduction of LDL-cholesterol levels	Breast, prostate, hepatocellular, head and neck cancers and lymphoma	Inhibition of Rho, Ras and Rab proteins MAPK and CDK2 regulation P2 × 7-mediated nuclear pAkt depletion Inactivation of NF-κB	Bird et al. (2018), Stenius (2011), Miraglia et al., (2012)
Itraconazole	Antifungal	Lung, prostate, esophageal hematologic, and brain cancers	Modulation of AMPK, mTOR, Hedgehog, and Wnt/β-catenin signaling pathways Inhibiting endothelial cell cholesterol trafficking and angiogenesis	Perfect (2017), Chong et al. (2007), Liang et al. (2017), ClinicalTrials.gov. National Library of Medicine (U.S.) (2013)
Disulfiram	Management of chronic alcoholism	Breast, colon, lung, thyroid, and uterine cancers	Inhibition of NF-κB, NPL4, and phosphoglycerate dehydrogenase Inhibiting DNA methyltransferases, inhibiting proteasome complexed with metals	Spillier et al. (2019), Fang et al. (2017), ClinicalTrials.gov. National Library of Medicine (U.S.) (2014)
Thalidomide	Morning sickness (withdrawn)	Erythemanodosum leprosum		Paravar and Lee (2008)
Everolimus	Immunosuppressant	Pancreatic neuroendocrine tumors (PNETs), renal cell carcinoma(RCC), and subependymal giant cell astrocytoma	mTOR	FDA Okays Everolimus for Rare Type of Pancreatic Cancer (n.d.)
Crizotinib	MET kinase	Clinical trials for anaplastic	EML4-ALK oncogene	Shaw et al. (2011)
Duloxetine hydrochloride	Major Depressive Disorder (MDD)	Neuropathic pain, generalized anxiety disorder (GAD), osteoarthritis, and stress incontinence	Serotonin and norepinephrine reuptake	Voelker (1998)

(*Continued*)

TABLE 13.1 (Continued)

Drug	Main indication	New indication	Proposed molecular mechanisms	References
Zidovudine	Failed clinical trials for cancer	Human immunodeficiency virus	Reverse transcriptase	Broder (2010)
Sildenafil	Angina	Erectile dysfunction (ED) and pulmonary arterial hypertension(PAH)	PDE5	Ghofrani et al. (2006)
Imatinib	Chronic myeloid leukemia	Gastrointestinal stromal tumors	BCR-ABL	Druker (2004)
Nelfinavir	Human immunodeficiency virus(HIV-1)	Colorectal cancer, lung cancer cervical cancer pancreatic cancer, ovarian cancer,	Inhibits AKT pathway	Chow et al. (2009)
Trastuzumab	Human epidermal growth factor receptor 2 (HER2)-positive	Metastatic breast cancer, gastric cancer, and early breast cancer	HER2	Rose and Bekaii-Saab (2011)
Sunitinib	Renal cell carcinoma (RCC) and Gastrointestinal stromal tumor breast cancer	Pancreatic neuroendocrine tumors	Multiple kinases	Delbaldo et al. (2012), FDA Expands Sutent Label to Include Pancreatic Neuroendocrine Tumors (2011)

predictions based on data analysis-derived system organization. Network modeling provides knowledge of interactions among diverse components of a biological system and commonly utilized data-driven techniques. The investigation of an interaction network for topological features is known as network analysis. In random networks, partial least squares regression is used, and the maximal nodes have nearly the same degree of distribution (Ma'ayan, 2011; Vidal et al., 2011a).

13.3.2 Bottom-up modeling approaches

It is used to investigate simpler systems with fewer interconnected components. Equations are used in mechanistic or dynamical models to describe how components interact. Herein, simulations are used to develop predictions and make comparisons between real-time and experimental time courses. For a mathematical description of paths, ordinary differential equations and partial differential equations are commonly utilized. A deterministic or stochastic dynamic system can be built to study the biological process (Przytycka & Yu, 2004; Aldridge et al., 2006). To build a dynamical model following steps are generally required (Costa et al., 2011; Neves, 2011a, 2011b):

1. Designing a connectivity diagram consisting of all the components of a biochemical pathway and connectivity between them.
2. Construction of mathematical equations from connectivity diagrams.

3. Calibration of the model to estimate unknown kinetic parameter values for a predefined set of parameters and initial concentration.
4. Model validation by subjecting simulation results to experimental test.

13.4 Drug repositioning strategies

Drug repositioning, also known as repurposing, is the process of discovering drug candidates from existing approved drugs or chemicals that are outside the scope of their original medical indications. It is a potential new avenue that provides financial incentives and intellectual property (patents) rights in the medical field (Li & Jones, 2012). Current drug repositioning successes have largely been the result of serendipity or clinical observation. The use of sildenafil for erectile dysfunction and pulmonary arterial hypertension, and the repurposed drug thalidomide for leprosy and multiple myeloma are the best examples of drug repositioning. Repurposing drugs offers several advantages which include finding new and more efficacious therapies for unmet medical conditions, replacing expensive drugs with cost-effective drugs, substituting safer drugs for drugs with undesirable side effects, and expanding the use of efficacious drugs to a larger population (Tobinick, 2009). Zhichao Liu et al. divide the in silico drug repositioning process into three interconnected steps (Liu et al., 2013): (1) repurposing with a purpose, (2) repurposing with a strategy, and (3) repurposing with confidence.

13.4.1 Drug repositioning with suitable purpose

Drug repositioning methods could be classified into two categories based on where the findings originate from. It is basically of two types first, drug-based strategies where discovery originates from knowledge related to drugs, and second the disease-based strategies where discovery originates from knowledge related to diseases. Drug-centric pharmaceutics concentrates on drug candidates that are safe in Phase I clinical trials but have failed in later clinical trials due to effectiveness concerns (Phases II and III). However, the effectiveness of this strategy is uncertain (Liu et al., 2013). In contrast to this, in the disease-centric sector, drug repositioning studies are mainly focused on specific diseases, particularly chronic conditions like inflammatory bowel disease that lack safe and effective therapeutic choices for long-term treatment and disease stability (Liu et al., 2013; Dudley et al., 2011).

13.4.2 Drug repositioning based on strategies

The knowledge of genotype and phenotype of disease can be exploited to plan strategies for drug repositioning. Rapid advancements in the field of human genomics have resulted in the development of massive amounts of genomic and transcriptome data for a wide range of illnesses. The genomic data collected from normal tissue samples, animal models, and cell lines can be useful in this regard. The most often used data is gene expression, but other genomic and genetic profiles have also been investigated for drug

repositioning (Li & Jones, 2012). These datasets offer the opportunity to learn more about disease mechanisms, unravel mechanisms of action of the drug, and discover novel applications for the old drug candidate. The Connectivity Map (CMap) project and its follow-up LINCS, which generated large-scale gene expression profiles from human cancer cell lines treated with various therapeutic molecules under various settings (Lamb et al., 2006; Vidović et al., 2014) have recently been used for drug repositioning purpose. Despite genomics data, phenome data can also be used for drug repurposing. The complete collection of phenotypic information of disease is the prime requirement for this purpose (Hebbring, 2014). The phenome-wide association study (PheWAS) has gained popularity as a method for identifying significant genetic connections with human disorders. In a study, Denny et al. demonstrated that PheWAS can be used to improve genomic analysis and they find new connections between genetic markers and human diseases utilizing electronic medical information (Denny et al., 2013). However, appropriate text mining is a crucial step during drug repurposing. The recent breakthroughs in text mining research, biomedical and pharmaceutical knowledge available in books and databases provides a better platform for gathering information about medications and diseases. The appropriate mined and retrieved information from the various database can be used for making proper strategies for drug repositioning (Dogan et al., 2009; Lu, 2011; Tari & Patel, 2014). Andronis et al. evaluated different literature mining methodologies and sources for pharmacological repurposing in a recent study (Andronis et al., 2011). This process can give the flow of information which can be understood by taking an example. For instance, if one study discovers that sickness A is caused by lack of nutrition B, and another study discovers that drug C, which was previously used to treat another condition, is an activator of nutrition B, drug C could be repurposed for disease A through literature mining. Another way of drug repurposing is the use of semantic technologies. These techniques make it easier to combine data from diverse sources and uncover new medicinal indications. Chen et al. created a statistical model to evaluate drug−target connections based on a semantic connected network of medications, chemical substances, protein targets, illnesses, side effects, and pathways, as well as their relationships (Dogan et al., 2009; Zhu et al., 2014).

13.4.3 Repurposing with confidence

Validation of a repurposing result is primarily based on wet-lab research, such as in vitro and in vivo assays, as well as controlled population studies, according to current methods. The many ways for exploring the repositioning space are numerous, making a full experimental validation strategy challenging to implement. Before experimental validation, this method can be used to help pick reasonable repositioning possibilities. For this reason, researchers created the Medications of New Indications (DNI) database (Knox et al., 2011), which presently contains 237 drugs with original and new indications, as well as extra information. Other sources will be evaluated for inclusion in DNI in the future, such as the conserved domain databases (Hohman et al., 2009), which comprises more than 100 repositioning candidates found using HTS techniques. The use of published reports from a variety of investigators and sites without overarching quality control raises concerns about such a strategy.

13.5 Validation of computational drug repositioning

Computational drug repositioning studies are carried out to find new uses for current medications and to speed up and reduce the cost of developing new medications in the preclinical stage. Researchers validate/evaluate their data before recommending a selection of drug repositioning candidates (Jarada et al., 2020). However, validation/evaluation models may differ from proposed computational models in some circumstances, or specific validation models may not be accurate or reliable. Due to a variety of variables, including high price, high toxicity, and poor bioavailability, as well as certain medications not favored by physicians or biologists, selecting the correct collection of drug repositioning candidates for validation is also crucial (Jarada et al., 2020; Li et al., 2016). Practically, validation/evaluation models vary from one study to another and can depend, up to a certain extent, on the nature of desired outcomes.

13.6 Recent systems biology and network-based approaches for drug repositioning for Coronavirus disease-2019

Although several clinical databases have been built, choosing the best strategy to make maximum use of the huge volumes of health information is still a concern. In this scenario, systems biology-driven applications can offer viable alternatives. Systems biology is the study of the entire biological system as it emerges through the interactions of distinct biomolecules. As a result, instead of looking at individual molecules, systems biology offers a comprehensive approach to analyzing interactions amongst multiple components. It combines wet-lab investigations that quantify cellular components with computational methodologies and concepts that permit the evaluation of relevant data sources or biological system recapitulation. It also uses a variety of computational methods to provide hypotheses that can be evaluated in the lab (Zou et al., 2013). Systems biology paradigms must continue to move toward quantifiable outputs to make significant predictions (Lee et al., 2017). To date, systems biology techniques have been used to interpret disease mechanisms, disease categorization, therapeutic alternatives, and prognostic, diagnostic, or theranostic properties of biomarkers (Lee et al., 2016; Mardinoglu et al., 2017; 2018; Benfeitas et al., 2019; Aydin and Arga, 2019; Kori and Yalcin Arga, 2018; Karagoz et al., 2016; Mardinoglu et al., 2018). In addition, using systems biology to make choices for drug development for varying illnesses could be more efficient (Bosley et al., 2017). The deadly COVID-19 viral infection is spreading rapidly over the globe, making conventional methods of disease management impractical at this time. Another, more persuasive technique is to identify already-approved medications that can be repurposed to treat the ailment. The creation of several networks to represent each level of the omics spectrum and their incorporation in a multilayer network that correlates data inside as well as between layers is the primary approach in systems biology-based methods (Oulas et al., 2017). The system-based molecular networks of accessible repurposed therapeutic options and their prospective targets give comprehensive information on the encoded proteins, genomic sequences and metabolites associated with stress

progression (Yadav et al., 2016). The information for the disease's genomics, proteomics, and metabolomics investigations was gathered from the research publications or via genome-wide association sequencing (GWAS) and next-generation sequencing studies (Yadav et al., 2017). In contrast to virtual screening, where target moieties are already known, systems biology possesses the ability to identify undiscovered target m in the pathogen's genome and metabolome (Yadav and Tripathi, 2018). Many computational approaches based on systems biology have been created and verified over the past decade (Guney et al., 2016; Cheng et al., 2018; Zitnik et al., 2018). These techniques improved the efficiency of therapeutic and diagnostic processes. A systems biology-based strategy adopted for the repurposing of drugs against SARS-Co-2 as proposed by Singh et al. (2020) is represented in Fig. 13.3.

In the latest investigation, Zhou et al. (2020) developed an integrated network-based strategy for repurposing antiviral medicines. The connection between the interactome
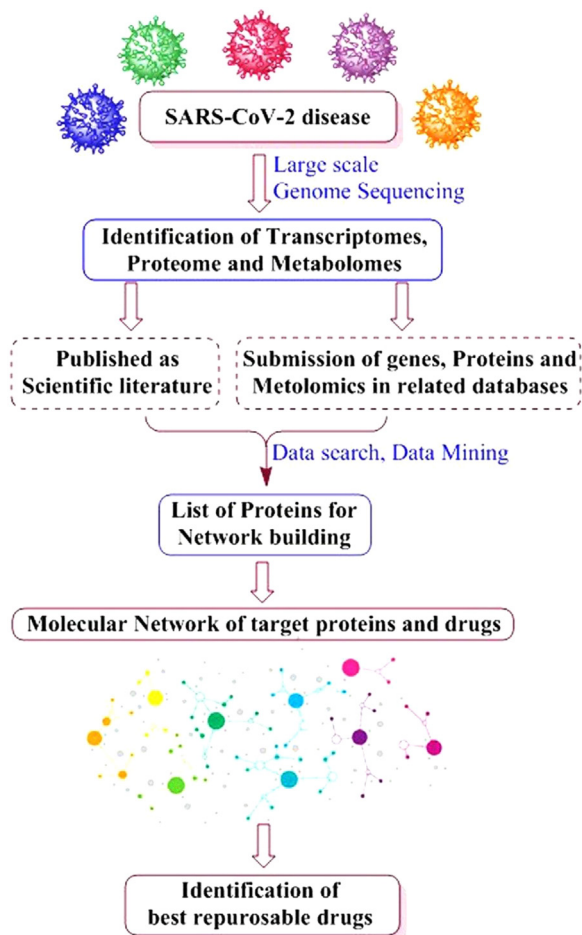

FIGURE   13.3 Systems   biology-based approaches for the repositioning of potential drugs against severe acute respiratory syndrome-Coronavirus-2. Source*: From Singh et al. (2020).*
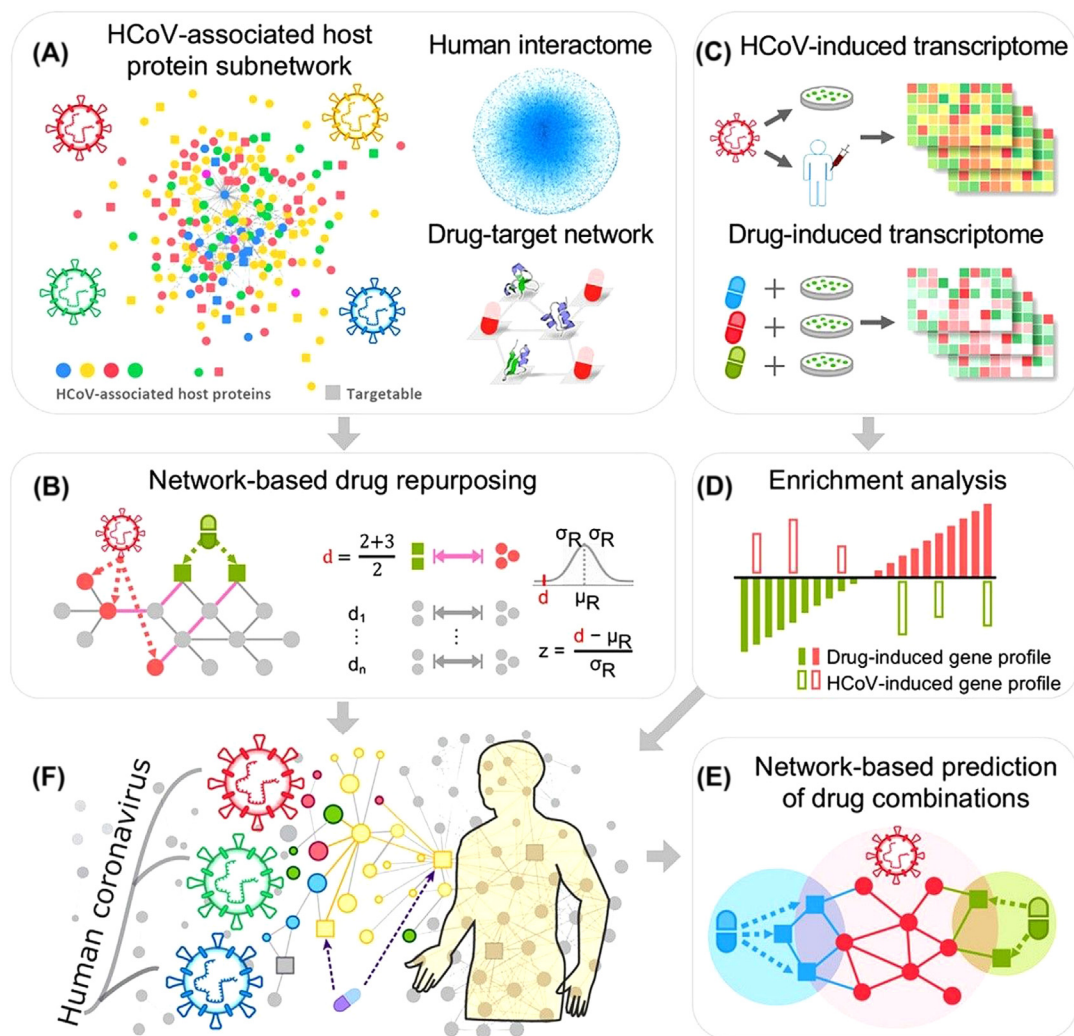
FIGURE 13.4 Network-based technique for the repositioning of drugs for severe acute respiratory syndrome-Coronavirus-2. Source: *From Zhou et al. (2020).*

virus−host and therapeutic target moieties in the human PPI network was assessed using a network therapeutics platform based on systems biology (as depicted in Fig. 13.4). Moreover, the concept is based on the idea that based on common protein−protein inter-actions, virus−host−protein, and functional mechanisms explicated by the human interac-tome, proteins that function as therapeutic target molecules for a disease-specific drug could also be efficient drug targets for other viral diseases. They prioritized 16 prospective repurposed anti-HCoV drugs (including sirolimus, mercaptopurine, melatonin, etc.) based

on similarity assessment of the HCoV−host interactions in the human interactome and drug−target network, which was further affirmed by enrichment assessment of HCoV and drug genetic signatures, generated by transcriptomic data in human cells. While most of the predictions were verified by diverse results published in the literature, all medications that can be repurposed and combination of drugs anticipated by the network must be evaluated in multiple SARS-CoV-2 clinical studies before being used in patient populations. They also used a complementary exposure pattern technique to evaluate two prospective therapeutic combinations (mercaptopurine plus melatonin, and sirolimus plus dactinomycin), in which drug targets access the host SARS-CoV-2 subnetwork, however targeting new areas in the human protein−protein interaction network. Nevertheless, the network data remains incomplete, and some of the drug−target interactions under consideration could only be linked functionally rather than physically. If broadly adopted, the network tactics used in this study might contribute to the development of new therapeutic strategies for various viral infections (Somolinos et al., 2021). Therefore, it could be concluded that systems biology and network-based approaches have become novel strategies and attractive tools for the discovery and development of newer repurposable drugs candidates and their combinations, as well as identification of their target molecules to combat SARS-COV-2 infection (Table 13.2).

TABLE 13.2 List of proposed therapeutic agents for the treatment of COVID-19.

S. no.	Proposed drugs	Action of mechanism	References
1.	Chloroquine	Increase endosomal pH for virus/cell fusion, and interfere with glycosylation of cellular receptors of SARS-CoV	Wang et al. (2020)
2.	Ritonavir	Inhibit HIV viral proteinase enzyme	Cheng et al. (2020)
3.	Methylprednisolone	Activation of specific nuclear receptors, alter gene expression and inhibit cytokine production	Yang et al. (2020)
4.	Hydrocortisone	Inhibitor of neutrophil apoptosis, phospholipase A2, NF-Kappa B	Russell et al. (2020)
5.	Remedisivir	Nucleic acid inhibition	Choy et al. (2020)
6.	Amodiaquinedihydrochloride	Heme polymerase activity inhibition	Lee et al. (2020)
7.	Lycorine	Cell division inhibition, antineoplastic and antiviral	Liu et al. (2020)
8.	Emetine	RNA, DNA, and protein synthesis inhibition, antiviral	Bleasel and Peterson (2020)
9.	Ribavirin	Inhibit RNA synthesis	Khalili et al. (2020)
10.	Pyrviniumpamoate	Mitochondrial respiration complex 1 inhibition and suppression of unfolded protein response	Jeon et al. (2020)
11.	Mycophenolate mofetil	Inosine monophosphate dehydrogenase inhibitor	Seminari et al. (2020)

13.7 Future aspects

In terms of both economic cost and time efficiency, medication repurposing can offer an alternate strategy to satisfy the demands of innovative, potent, and safe medicines. New paths for successful preanalytical screening have opened up due to network-based bioinformatics approaches that may combine the greatest knowledge about a specific condition with relevant pharmacological information.

Underlying complicated systems are responsible for human diseases. Each person has a unique set of inherited or acquired genetic defects that may cause them to respond to general therapies or medications less or not at all. Drug efficacy can change significantly in diverse gene profiles due to heterogeneity in human disease (Amir-Aslani & Mangematin, 2010), necessitating the use of personalized medicine to customize for each patient. Medication repositioning is crucial in reducing the lack of drug efficacy. In contrast to conventional treatment, which focuses on maximal tolerable doses, this can result in the finest medicine with great efficacy at the lowest toxicity levels conceivable for the unique individual (Sun et al., 2013; Fitzgerald et al., 2006). In accordance with the proper guidelines, repositioning the medicine based on stratification is critical.

Many proteins are already targeted by many medications, according to recent research, implying that multitarget candidates can be found automatically by examining relationships between proteins, drugs, and disorders. Prioritize the most effective drug–target combinations for in vivo or in vitro experimental validation (Turanli et al., 2018; Peyvandipour et al., 2018).

Because the number of possible drug combinations grows exponentially with the number of pharmaceuticals to be evaluated, testing all possible drug combinations is impossible. Huang et al. introduced an evaluation tool named DrugComboRanker (Huang et al., 2014) to facilitate the integration of knowledge sources about drug habits. Based on topological relatedness of drug targets in signaling networks, the semantic similarity of gene ontologies, and dissimilarity of gene expression profiles of different medications, the scientists established a synergistic score for drug combinations.

Despite all of these efforts, medication repositioning has some drawbacks. Drug patents can be quite useful in repositioning drugs. Patent protection for compound inventions Patenting can be difficult in drug repositioning, especially if the original indications have already been branded ahead of new competitors (Sternitzke, 2014; Roin, 2008). With medication repositioning, there are a variety of approaches to the existing COM patent. Prednisporin, for example, was created by Zalicus in partnership with Sanofi Aventis Paris to treat allergic conjunctivitis (Xu & Coté, 2011). It combines two ancient medications, glucocorticoid Prednisolone acetate, and immunosuppressant Cyclosporine A. Despite the fact that medication repositioning has significant advantages over the usual de novo strategy, it is not always successful. There have been a few drug repositioning projects that have failed. Bevacizumab, a kinase inhibitor originally developed to treat gastric cancer, failed to show efficacy in Phase III studies after extensive research and repositioning to multiple other tumors. (Kim & Oh, 2018). The disadvantages, which include the well-known impression of drug repositioning, financial needs, high demand for expertise, unforeseen side-effects, a scarcity of promising medication candidates, and a lack of

integrative platforms for data analysis, have made drug repositioning challenging. However, the disadvantages of medication repositioning can be positively alleviated by strong collaboration between pharmaceutical companies, governments, and academics, as well as the improvement of computational approaches today (Low et al., 2020).

13.8 Concluding remark

In conclusion, this chapter provides an overview of the system and network-based computational approaches that can be exploited for repurposing drugs quickly which in turn helps to tackle present and futuristic pandemic situations. These methods can reduce the amount of time spent in translating discrepancy between preclinical and clinical testing results which is a major issue in today's fast-paced world.

To enable drug design and automatically deliver or reuse personalized medicines for a certain disease or set of patients, the development of an efficient bioinformatics platform is critical. Due to the multifaceted character of cancer, it is difficult to thoroughly explore the molecular pathways underlying the disease. For pharmaceutical corporations and researchers, drug repositioning still holds a lot of promise in terms of fresh discoveries and giving established drugs a new lease on life. Old medications should be relooked at and evaluated with the goal of repositioning using new high throughput screening techniques along with modern computational tools like signature matching, molecular docking, GWAS, and route mapping. Drug repositioning enables the development of customized treatment, which benefits not only biotechnology and pharmaceutical corporations but also patients who are given a cheaper drug with improved efficacy against their disease. It is critical to emphasize the importance of medication repositioning efforts in the hunt for effective therapy in an urgent pandemic like COVID-19. Continued research and clinical evaluations are strongly encouraged to assess the repositioning potential of existing medications that provide significant symptom relief. Existing antiviral medications, among many others, are being given major consideration in the present search for a cure. A request for more government involvement in supporting research and development programs, whether through research grants, tax incentives, infrastructure, or clinical cooperation support, can help future drug repositories grow exponentially.

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