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Global Health Commentary

Pharmacodynamics and Systems Pharmacology Approaches to Repurposing Drugs in the Wake of Global Health Burden

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ABSTRACT

There are emergent needs for cost-effective treatment worldwide, for which repurposing to develop a drug with existing marketing approval of disease(s) for new disease(s) is a valid option. Although strategic mining of electronic health records has produced real-world evidences to inform drug repurposing, using omics data (drug and disease), knowledge base of protein interactions, and database of transcription factors have been explored. Structured integration of all the existing data under the framework of drug repurposing will facilitate decision making. The ability to foresee the need to integrate new data types produced by emergent technologies and to enable data connectivity in the context of human biology and targeted diseases, as well as to use the existing crucial quality data of all approved drugs will catapult the number of drugs being successfully repurposed. However, translational pharmacodynamics databases for modeling information across human biology in the context of host factors are lacking and are critically needed for drug repurposing to improve global public health, especially for the efforts to combat neglected tropic diseases as well as emergent infectious diseases such as Zika or Ebola virus.

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Introduction

Drug repurposing (repositioning) is defined as developing a drug with existing marketing approval of disease(s) for new disease(s). Observations of treatment-related adverse reactions during drug development have led to repositioning for different indications; such cases include antihypertensive drugs, minoxidil repurposed for alopecia[1] and sildenafil for erectile dysfunction.[2] There are successes achieved in drug repurposing (Drugs@FDA) and ongoing efforts are being made (ClinicalTrials.Gov). Using key words of drug repurposing or drug repositioning, only a handful of studies were found at various stages of clinical trial (https://clinicaltrials.gov/). However, there are still unmet medical needs for communicable diseases (CDs) and noncommunicable diseases (NCDs) worldwide, and creative new measures are needed for the efforts of drug repurposing. Many neglected tropical diseases are prevalent in poor countries, affecting millions of people, and they occasionally cause deadly outbreaks invoking global panic and inflicting harms to global economy and well-being. Recent outbreaks of deadly Ebola virus disease (EVD) and current spreading of Zika virus infection that has caused birth of babies with microcephaly have caused global distress. In addition, there are millions of people and their families struggling with NCDs including mental illnesses in developed and underdeveloped countries.[3,4] There is tremendous need for costeffective medications to treat emergent diseases to reduce global health burden.

Because of advances in molecular biology, big data of transcriptomic, proteomic, phosphoproteomic, and functional profiles of thousands of drugs and chemicals across many cell types (immortal cell lines, primary cells, stem cells, stem cells—derived cells) and from 2-D and 3-D tissue constructs enable us to more realistically capture the mode of action of drugs and the disease biology. Furthermore, electronic health records (EHRs) in claims databases can be aggregated across institutes for observational studies of discovering novel new therapeutic effects of drugs for drug repurposing to treat diseases with unmet medical needs.

To efficiently navigate through the abundance of biomedical data and accumulated life science knowledge, one should address the following key questions to cost-effectively repurpose a drug for a new indication.

1. What data sources are available for real-world medical evidences or biomedical clues?

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Table 1
List of Drug-Repurposing Clinical Trials (https://clinicaltrials.gov/)

Drug/Approved Indication(s)	ClinicalTrials.gov Identifier/Status	Repurposed Indication
Nelfinavir/HIV	NCT01445106/completed	Solid tumors
Ivermectin/head lice, nematode parasite, inflammatory lesion of rosacea	NCT02046200/completed	Alcohol use disorders
Probenecid/hyperuricemia associated with gout and gouty arthritis	NCT01814319/completed	Systolic heart failure
Propofol/general anesthesia and monitored anesthesia care	NCT02492295/ongoing	Severe refractory migraine headache (low dose)
Dexmedetomidine/sedation	NCT02630290/ongoing	Perineural adjuvant (low dose added to ropivacaine)
Galantamine/mild to moderate Alzheimer's type	NCT01845961/ongoing	Smoking abstinence
Guanabenz/hypertension	NCT02443103/ongoing	Bone cancer metastasis
Verapamil/hypertension and angina	NCT02372253/ongoing	Beta cell survival therapy in type 1 diabetes
Ramelteon/insomnia	NCT02560324/not yet open for recruitment	Smoking abstinence
Omeprazole/GERD, upper GI ulcer	NCT02595372/ongoing	Breast cancer
Ibuprofen	NCT01606540/ongoing	Colles fracture

GERD, gastroesophageal reflux disease; GI, gastrointestinal.

2. What molecular level and translational data can be leveraged to establish the biological linkage from molecular level to organ phenotypes?
3. What systems pharmacology models can be constructed for assessing the dose and response relationship to facilitate the design and conduct of clinical trials?

In brief, we are at the forefront of a tremendous opportunity to use omic, imaging and phenotypic data and knowledge of diverse nature to discover the new mode(s) of action of drugs for repurposing, thereby aiding the global efforts on combating diseases. Considering the volume and types of data and accumulated knowledge and the technologies of systems pharmacology analysis and modeling in pharmaceutical research and development, a quality translational database of pharmacodynamics of approved drugs is needed. Such a database will support a cross-hierarchy translation from the molecular-level information of drug actions and disease biology to the macro-level phenotypic and functional measures including natural history of disease, markers for disease progression, and responses to drugs, and thereby accelerate successes in drug repurposing.

Successes Achieved

Progress has been made on repurposing drugs for new indications, as evidenced by the number of drugs approved for rare diseases.[5,6] There are close to 100 drug products with each one of them approved for an orphan disease as well as at least 1 marketing approval for a common disease indication. There are more than 40 drug products each with marketing approvals for both common and rare disease indications.

Ongoing Efforts Range From Preclinical to Clinical Trials

The efforts on drug repurposing are continuously being made, as demonstrated by the list of ongoing drug-repurposing clinical trials (https://clinicaltrials.gov/) that are summarized in Table 1. In addition, National Center for Advancing Translational Sciences provides funding to support early-stage and late-stage drug-repurposing efforts along with its institutional research efforts on drug repurposing (https://ncats.nih.gov/news/releases/2015/preclinical-repurposing/). The ongoing clinical trials (ClinicalTrials.Gov) are either focused on cancers or smoking abstinence or alcohol abuse. In light of global economy and health burden, more efforts on repurposing drugs with known safety profiles are needed. In the following, urgent medical needs to reduce global health burden are highlighted.

Unmet Medical Needs to Reduce Global Health Burden

According to the World Health Organization (WHO) report published in 2015, among the 3 major infectious diseases affecting global health, HIV/AIDS caused 1.2 million deaths, tuberculosis 1.1 million deaths, and Malaria 0.438 million deaths.[3] The number of tuberculosis cases was 9.6 million in 2014, with 5.4 million men, 3.2 million women, and 1 million children.[4] Most notably infectious disease outbreaks in recent years have caused global panic and disrupted global travel and trade, including deadly EVD, Middle East respiratory syndrome, and severe acute respiratory syndrome; particularly concerning, Zika virus disease that has been associated with birth defects.[3,7] These infectious diseases cause high mortality and serious side effects such as irreversible birth defects due to lack of effective treatment. Other emerging infectious diseases with local outbreaks include measles (since 2010), pandemic influenza caused by H1N1 (Swine flu) in 2009 and by H1N1 or H3N2 in 1996, cholera (2008-2010), and Chikyngunya (since 2013).[7,8] According to WHO (http://www.who.int/neglected_diseases/diseases/en/), 1 billion people across 149 countries are affected by neglected tropical diseases. NCDs caused 68% deaths worldwide and have led to 34% deaths in those aged less than 70 years compared to 52% by CDs according to a 2012 WHO statistics[4]; cardiovascular diseases caused 6 million deaths, chronic respiratory diseases 1.3 million deaths, cancers 4.3 million deaths, diabetes 0.6 million deaths, and other NCDs the rest.[4]

With economic and social globalization, infectious diseases and adverse impacts of NCDs are global issues. There is a tremendous need for cost-effective medicines to reduce the global health burden. Repurposing of drugs with known characteristics and safety profiles constitutes part of the solution.

Informatics-Based Efforts From Aggregated Patient-Level Data to Knowledge of Protein Interactions

Advances in biomedical and computer technologies have led to production of a tremendous volume of quality data and made available big data and accumulated knowledge in diverse organized platforms. Pharmacokinetic (PK) characteristics of more than 1200 drugs with marketing approval are available in multiple data sources (Drugs@FDA, DailyMed, PubMed); pharmacogenomics of drugs and human genetics (HapMap) are available on PubMed (curated information on PharmGKB, https://www.pharmgkb.org/), respectively, for exploring personalized drug repurposing. On the other side of the horizon, EHRs have emerged as a resource to evaluate the effectiveness and safety of therapeutics and most importantly any new therapeutic uses.

Medical Informatics and Electronic Health Records

Medical records in digital era offer an opportunity for using real-world evidences to discover new, novel therapeutic effects of approved drugs. For example, metformin, a drug for treating type II diabetes, was reportedly associated with a lower risk of colon or pancreatic cancer in the United Kingdom[9] and a reduced prevalence of malignancies in Germany,[10] as well as increased survival benefits in cancer patients.[11-13] Mechanistic *in vitro* inhibition of mitochondrial respiratory complex I was reportedly a plausible mechanism for its antineoplastic effects.[14] Another example is statins. Statin use has been associated with a reduced incidence of uveitis[15]; statins reportedly possessed anti-inflammatory effect[16] and reduced the use of oral steroids in inflammatory bowel disease patients study.[17] Most recently, patients prescribed with artesunate-amodiaquine for malaria reportedly had a lower mortality rate by EVD than those not prescribed with this regimen, suggesting that artesunate and amodiaquine warrant further investigation for their therapeutic benefit for treating EVD.[18] A mining of EHRs identified terbutaline (approved for treating asthma) as a candidate for amyotrophic lateral sclerosis,[19] which was supported by *in vivo* effects in zebrafish. All the aforementioned examples illustrate that mining real-world evidences are worthwhile for drug repurposing.

Finding Druggable Targets Needs Systems Biology Approach Across Biological Hierarchy

Computational methods have been applied to gene expression data for drug repurposing.[20] The failure of topiramate repurposed for inflammatory bowel disease[21] and a subsequent disappointment of no therapeutic benefit of topiramate in reducing irritable bowel syndrome flares[22] pointed out that transcriptomics alone cannot, and will not, unveil drug and human biology interactions. We computationally showed that the pharmacological targets of more than 200 drugs associated with treatment-related neuropathy were linked, via protein-protein interactions, to a very small list of statistically significant transcription factors,[23] which laid the foundation for our latter work on computing signaling pathways of drugs from drug targets to differentially perturbed genes. We were able to link drug-induced, differentially expressed genes to drug targets by using integer linear programming across prior knowledge of protein interaction networks and transcription factors.[24] Drug targets are proteins; there is a critical need for using transcription factors as linkers to establish computational connectivity between mRNAs and intracellular, biological protein networks in the context of understanding the effects of drugs.

Summary

Big data, such as *in vitro* omics data, real-world EHRs, knowledge base of biological protein interactions, and signaling propagation provide rich information for drug repurposing. Integrative utilization of various data types would help us understand biological connectivity in the context of human biology on perturbation by drugs would be a crucial step in repurposing the drugs.

Big Data Needed to Accelerate Success

Polypharmacy

Polypharmacy has long been a medical practice and is used for strategic uses of combination products to combat diseases, such as HIV disease. Repurposing approved drugs in combination to combat viral diseases by blocking key points in the life cycle of a virus using host cells' apparatus is a reasonable approach. Looking forward, there are 2 potential strategies for drug repurposing: (1) identifying a new novel target for an approved drug and (2) identifying combination products useful for a target disease, as shown in Figure 1. Identifying potent combinations of 2 approved drugs for treating diseases is a viable option; for example, combination of statins and topoisomerase inhibitors reportedly enhanced the proapoptotic activity of the latter for glioblastoma.[25]

Once the matching of a few drugs or drug pairs with a disease is completed, one could use historical biopharmaceutics and clinical pharmacology data to conduct systems pharmacology modeling to optimize dosing regimens for studies in clinical trials for the new indication (Fig. 2). Adding relevant biomarkers to the matching models could make modeling more powerful and useful. Discussions in the following highlight the types of data useful for drug repurposing, as shown in Figure 2.

Biopharmaceutics and Clinical Pharmacology Database

For each potential candidate, accumulated data of their biopharmaceutics and clinical pharmacology characteristics, physicochemical properties, formulations, dosing regimens, clinical pharmacology characteristics including pharmacokinetics (PK), PK in specific populations of renal impairment and hepatic impairment, in the elderly and in children, food effect, and population, PK and most importantly data on human physiology[26] are extremely valuable to construct systems pharmacology model. To access such data, Drugs@FDA, PubMed, books or commercial products with a large compilation of all approved drugs, their dosing regimen, and associated pharmacokinetics and absorption, distribution, metabolism, and excretion are available. However, physicochemical properties such as aqueous solubility and pH profiles are not readily available in commercial sources, concerted efforts on compilation; curation and generation of data will be a productive way to achieve the common goal of drug repurposing.

Pharmacodynamics Database for Translational Systems Analysis and Modeling

Searching PubMed using key words of “FDA-approved drugs” and “drug repurposing” identified hundreds of publications on drug repurposing; examples include doxapram, amoxapine, and trifluoperazine for their potency against respiratory and gastrointestinal tract bacterial pathogens[27]; amodiaquine and chloroquine for Parkinson disease by activating nuclear receptor−related protein 1[28] that is important for maintaining dopamine neurons; lansoprazole for killing *Mycobacterium tuberculosis* by inhibiting cytochrome bc1 and depleted ATP needed for *M. tuberculosis*' survival.[29] Findings such as these are useful for inclusion when constructing a pharmacodynamics and disease biology database for drug repurposing.

Another worthwhile pharmacodynamics database is a community-consensus database specifically for tackling infectious diseases including neglected tropic diseases. Infectious diseases share a common feature that virus use to gain entry into a host cell via a specific protein; host cell proteins or function are then used by virus for replication and subsequent infection. Therefore, there are 2 paths to tackle viral diseases, one is targeting viral enzymes and the other is targeting human functions required for viral entry and replication.[30] These host cells' proteins are the primary targets for control and treatment of infection. To illustrate the usefulness of such a database, Zika virus disease is discussed herein. Zika virus disease is an emerging public health issue because it has been associated with microcephaly of newborns, premature births, blindness of newborns, neurological disorders in the elderly or vulnerable populations, and it can be transmitted via mosquitoes bite or sexually. Entry of Zika virus into human cells is mainly mediated by dendritic cell-specific intracellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN), AXL receptor

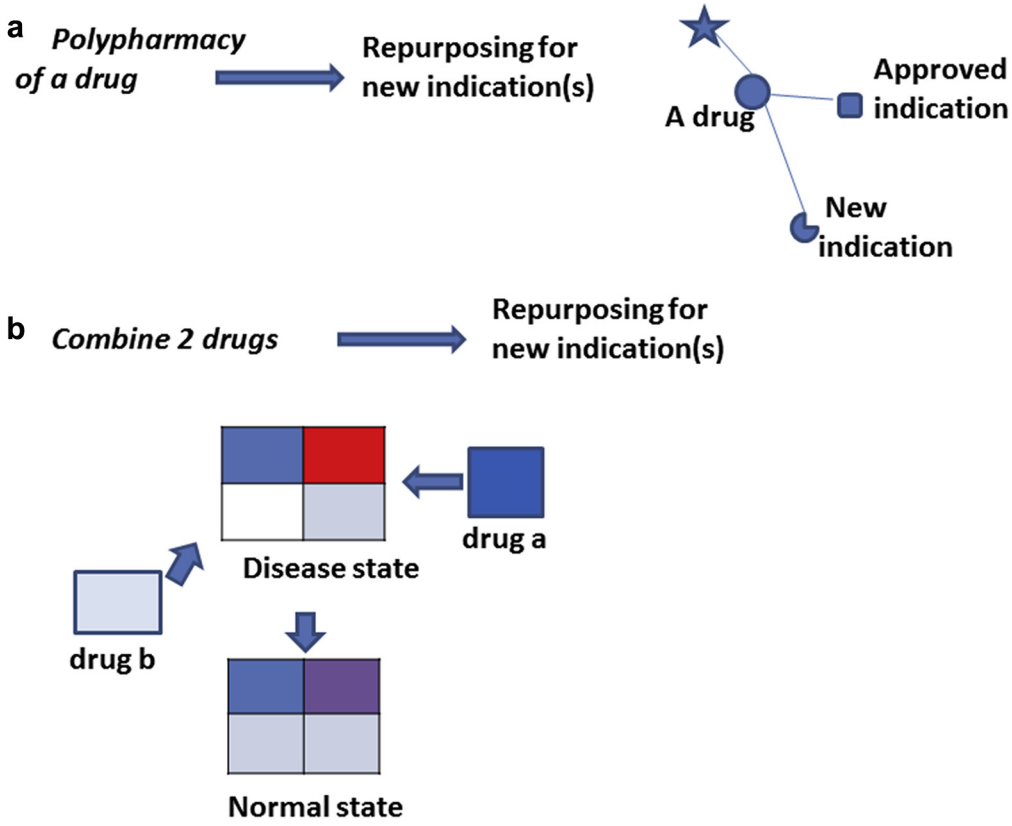

Figure 1. (a) Polypharmacy of a drug constitutes the underlying molecular basis for repurposing to treat a new indication. In the scheme, a drug is shown as a circle and its multiple pharmacological targets are shown as (1) a square (a target for an approved indication), (2) a star (an unexplored target), and (3) a 3-quarter of a circle (a target for repurposing the drug to treat a new indication). (b) Repurposing a drug pair is an option with drug 1 targeting part of a disease pathogenesis and drug 2 targeting the rest. When used together, synergistic or additive effects of both drugs can effectively treat a target disease.

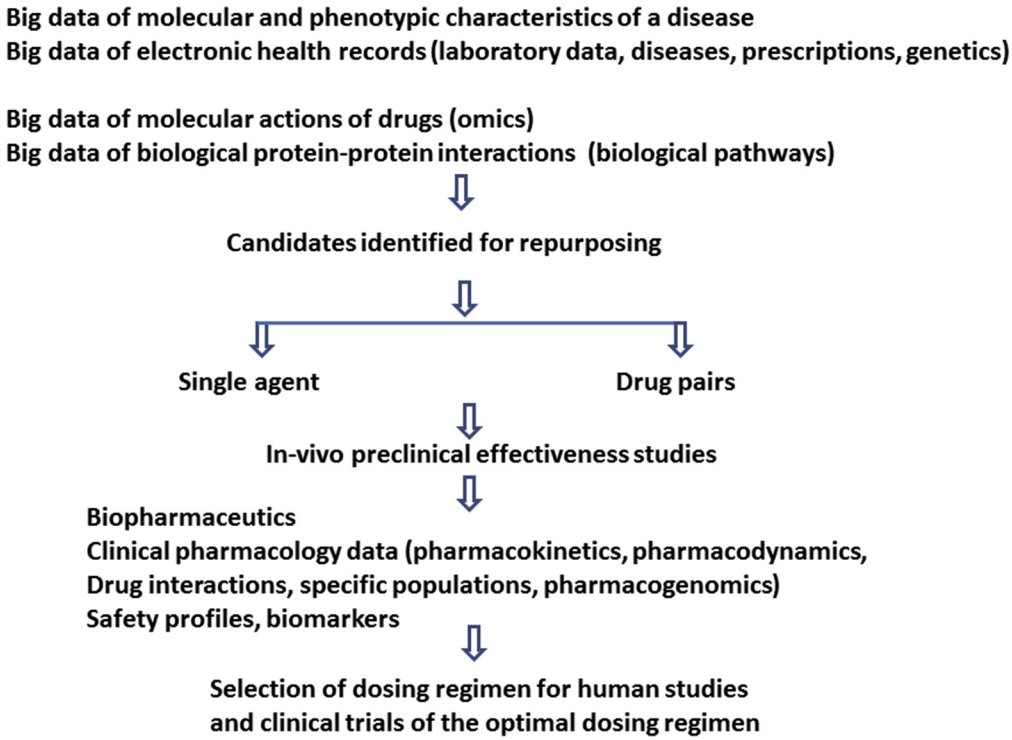

Figure 2. Workflow of big data-driven and knowledge-based drug repurposing. Existing data and knowledge accumulated for drugs and for human diseases with ever-advancing technologies in the past several decades are useful for drug repurposing.

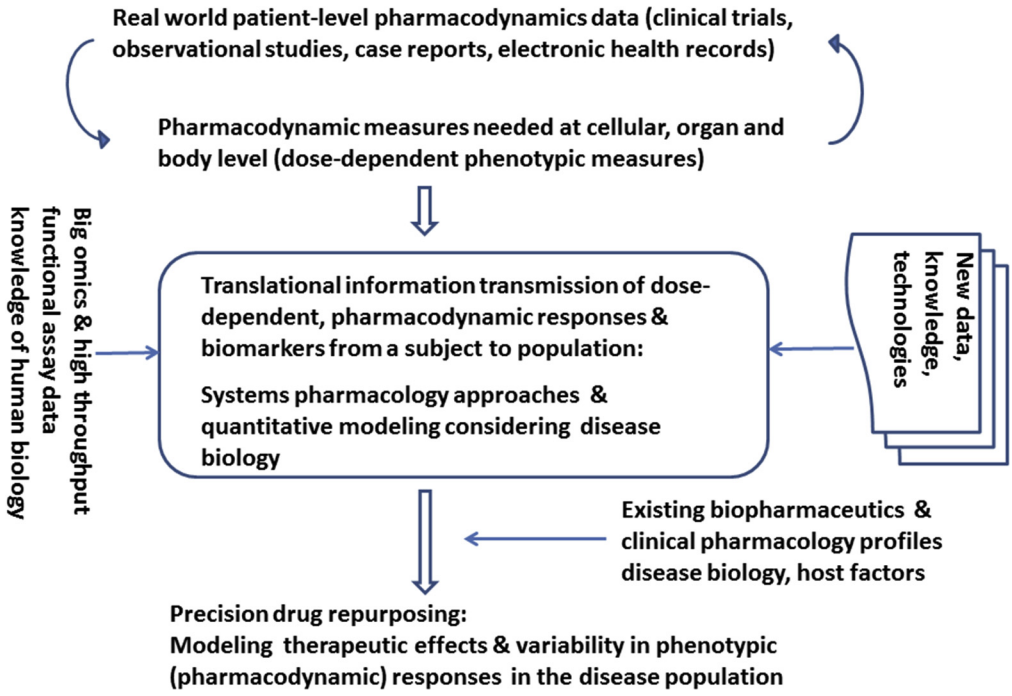

Figure 3. A systems pharmacology framework for drug repurposing in which pharmacodynamics is needed to translate across the hierarchy of human biology. Initiation of evidence-based drug repurposing originates from real-world pharmacodynamic evidences or from dose-dependent pharmacodynamic measures in cells and organs (organs-on-the-chip or preclinical organs). *In vitro*/preclinical pharmacodynamic/phenotypic measures transmit the information of molecular-level and cell community-level interactions and reveal interactions between a drug and a human body at the subject level. In the target disease population, pharmacodynamics reflects the repurposed therapeutic effects of a drug and associated population variability. Ultimately, with existing biopharmaceutics and clinical pharmacology characteristics, successes in drug repurposing are facilitated by systems pharmacology modeling of pharmacodynamic responses.

tyrosine kinase, Tyro3 protein tyrosine kinase.[31] These proteins are also the receptors of other flavivirus for entry into human cells.[32] TYRO3, protein tyrosine kinase, is also a human protein for entry of Ebola and Marburg viruses; (http://www.ncbi.nlm.nih.gov/gene). TYRO3 is abundant in the brain. In rat brains, TYRO3 is widely expressed throughout the development stages after birth compared to AXL; and these receptor tyrosine kinases play a key role in the maturation and development of the central nervous system,[33] thereby constituting potential targets to battle Zika virus. A database and knowledge base of pharmacodynamics across all approved drugs with individual antiviral potency will be the foundation for conducting systems pharmacology analysis, as well as for constructing systems pharmacology framework and models to battle infectious diseases such as Zika virus disease.

Systems pharmacology analysis integrating gene expression, protein networks, and drug targets can facilitate drug repurposing.[24] Once a handful of candidates are identified, next step would be to use existing data and knowledge about these drugs along with knowledge of human biology to conduct quantitative systems pharmacology modeling to further select best candidate(s) or candidate pairs for further development. As illustrated in Figure 3, systems pharmacology modeling is a translational tool that is constructed by design to capture information transmission across select levels of human body hierarchy; *in vitro* and *in vivo* pharmacodynamics data are critically needed to enable translational information transmission via systems pharmacology modeling for drug repurposing. Clinical markers measured during treatment either from published clinical trials or from EHRs can be incorporated into the pharmacodynamics database so that systems pharmacology approaches can meaningfully infer drug and disease interactions and model reversal of disease biology.

Conclusion

There is a tremendous medical need to treat and control CDs and NCDs worldwide. Emerging infectious diseases and neglected tropic diseases are no longer local health issues and should be preemptively controlled before they spread globally. The availability of big data ranging from omics to readouts of imaging and biochemical phenotypes, clinical laboratory and phenotypic profiles of individual natural diseases, and medical records of population responses to prescribed treatment regimens across ethic groups presents a new opportunity at the frontier of drug repurposing. Human-induced pluripotent stem cells, specific organ cell types derived from human-induced pluripotent stem cells, and cancer stem cells are being actively investigated and used in life science research. High-throughput screening technologies are being applied to facilitate the use of these cells for screening of new chemical entities and for fingerprinting individual marketed drugs to decipher the pharmacological network of a drug in the context of human biology. Our ability to discover the mode of action of an approved drug from the systems pharmacology perspective is increasing at a fast pace with advances in informatics and omics technologies (transcriptomics, proteomics, metabolomics, and genomics). So is our ability to use big data with informatics technologies. What is needed is a database that translates the action of drugs at the molecular level to the response phenotypes observed either in 2-D or 3-D cell culture constructs or animals or humans. A database of pharmacodynamics in connection to clinical markers and end points in the context of human biology will aid the use of systems pharmacology methods to facilitate drug repurposing in the wake of global health burden and to improve global well-being. A pharmacodynamics database dedicated to neglected tropic diseases will benefit as well as improve global economy and well-being.

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