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Using What We Already Have: Uncovering New Drug Repurposing Strategies in Existing Omics Data

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Abstract

The promise of drug repurposing is to accelerate the translation of knowledge to treatment of human disease, bypassing common challenges associated with drug development to be more time- and cost-efficient. Repurposing has an increased chance of success due to the previous validation of drug safety and allows for the incorporation of omics. Hypothesis-generating omics processes inform drug repurposing decision-making methods on drug efficacy and toxicity. This review summarizes drug repurposing strategies and methodologies in the context of the following omics fields: genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, phenomics, pregomics, and personomics. While each omics field has specific strengths and limitations, incorporating omics into the drug repurposing landscape is integral to its success.

INTRODUCTION

Bringing a novel therapy from bench to bedside is an extremely lengthy and costly endeavor (taking anywhere from 10 to 20 years and $1.2–2.7 billion) (1); an increase in regulatory hurdles suggests that this process will become costlier and take more time unless substantial changes are made (1, 2). Even for therapies that make it to human testing in clinical trials, 90% ultimately fail (3). There is a significant need for new strategies aimed at safely bringing drugs to market more rapidly and cost-effectively in order to close the gap between our knowledge of human disease and the treatment of human disease. Indeed, while there are approximately 5,700 known human diseases, treatments exist for only about 500 (4).

Drug repurposing is a strategy in which new indications are identified for existing therapies. These therapies can have been US Food and Drug Administration (FDA)-approved or shown to be safe in phase 1–2 trials but never reached the market for reasons unrelated to safety (5). This approach to drug development arguably has a greater likelihood of success given that the repurposed therapeutic has an established safety profile. In addition, the drug repurposing method should require significantly less time and monetary investment. A recent repurposing effort of the approved antiprotozoal fexinidazole (Sanofi) for sleeping sickness by the Drugs for Neglected Diseases initiative was executed for just $55 million, or around 2% of traditional drug development costs (6).

Some of the earliest drug repurposing efforts were serendipitous. Among the most widely known are the well-established cardiovascular benefits of aspirin. Observations in clinical trials changed the development of sildenafil from coronary artery disease toward erectile dysfunction. Bupropion was developed as an antidepressant and then showed promise in smoking cessation. Botox (onabotulinumtoxinA) was being used for eye muscle disorders when cosmetic effects became apparent. Minoxidil was used to treat hypertension before hair growth effects were established. Thalidomide and its derivatives have been repurposed for erythema nodosum laprosum (leprosy), multiple myeloma, myelodysplastic syndrome, mantle cell lymphoma, and metastatic prostate cancer (7–9). Since initial drug repurposing success, many novel methods have been developed and proposed for identifying and validating repurposing targets and ideas. These approaches are often categorized as computational approaches, such as signature matching, genetic association, and pathway-mapping, or experimental approaches, including binding assays for target identification and phenotypic screening (2). While these methodologies differ in many ways, one commonality among them is the incorporation of omics.

The field of omics aims to present a holistic view of the entities that make up a cell, tissue, or organism in a nontargeted, nonbiased manner (10). Omics can be directed at anything from genes (genomics) or proteins (proteomics) all the way up to the composite human being (personomics) (**Figure 1**). These strategies can be useful in understanding not only normal physiological processes but also disease processes. The advent of omics technologies has led to significant advancements in the medical field in terms of biomarker identification, as well as enabled the more accurate diagnosis and prognosis of diseases (11). More recently, these approaches have been applied to the fields of drug discovery and development to help inform decisions on efficacy and toxicity (11). In this review, we discuss the current landscape of drug repurposing within the framework of the most developed and well-known omics fields.

GENOMICS

Genomics is the most mature of the omics fields. The advent of large-scale genetic studies has significantly improved our knowledge of the genetic basis of many complex diseases. Thus, repurposing drugs that target proteins encoded by known genetic drivers has become an attractive

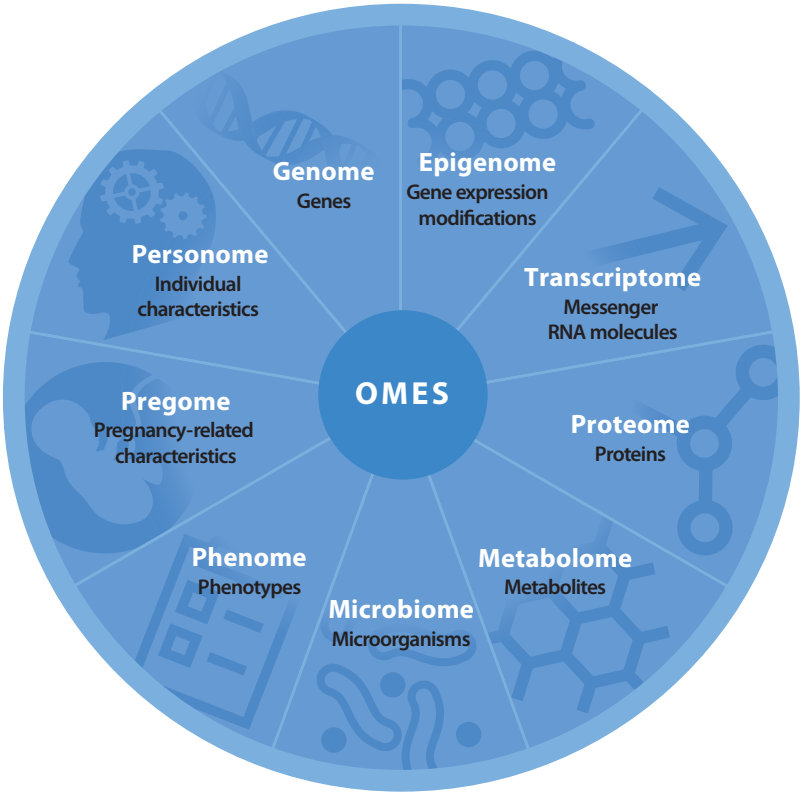

Figure 1

An ome is the entire complement of a given field of biological study, such as all of the genes in the genome or the entirety of the proteins in the proteome. Omics-based research aims to understand how all of these omes contribute to the overall dynamics of an organism. Depicted is an overview of the omes discussed in this review. The epigenome, metabolome, and microbiome silhouettes were adapted from Freepik; the proteome silhouette was adapted from Site Hurrera; and the phenome silhouette was adapted from Vectors Market (**https://www.flaticon.com**).

approach in drug development (12). Novel drug–disease relationships can be inferred by using tools that identify genetic variants in humans and mining drug target and gene–disease data.

In the context of drug discovery, development, and repurposing, the genome-wide association study (GWAS) identifies genomic loci tagged by single-nucleotide polymorphisms (SNPs) from affected and unaffected individuals and matches these data to known drug–disease or drug target data. Furthermore, databases like ClinVar, a publicly available archive that reports relationships between human genetic variation and phenotype maintained by the National Institutes of Health, have been developed to aid in the analysis and interpretation of GWAS data. GWAS results have identified risk loci for many common diseases (13–16), including various cancer types (17–21). And while the power of GWAS is clear, determining causal genes from SNPs has been challenging. The ENCODE (Encyclopedia of DNA Elements) project has made important contributions to our understanding of the various regulatory elements in the human genome (22). Furthermore, tools like PreSTIGE (Predicting Specific Tissue Interactions of Genes and Enhancers) (23) and IM-PET (Integrated Methods for Predicting Enhancer Targets) (24), which integrate functional

genomic data to predict interactions between genes and regulatory regions, have aided in these efforts.

Using human genetic data for drug repurposing requires mapping disease-associated SNPs to gene-encoding, druggable proteins and their cognate compounds. Resources like the Drug Gene Interaction database (25), which integrates published drug–gene interaction data with potential drug candidates currently in clinical development, are helping to streamline this process. New analytical methods for drug repurposing are also being developed, including an approach combining GWAS meta-analysis with a novel in silico pipeline that helped identify 42 new risk loci for rheumatoid arthritis (RA). Importantly, proteins encoded within the RA risk loci include targets of currently approved therapies (15, 26), highlighting the utility of this approach in drug repurposing.

While relatively few disease risk loci identified by GWAS have been comprehensively studied for drug repurposing, these efforts are ongoing. Using human genetic data, Grover et al. (27) recently identified over 900 therapeutics for repurposing in coronary artery disease. Kinnersley et al. (28) used GWAS data to map risk variants across 37 cancers to protein-encoded target genes, further utilizing the Pharmaprojects database (29) to prioritize 15 drugs for repurposing in oncology. Furthermore, and built upon GWAS findings, efforts to repurpose denosumab (a RANKL antibody currently approved for the treatment of osteoporosis) for Crohn's disease have gained ground (30, 31), and results are awaited from a recently completed phase 1–2 trial of denosumab in patients with Crohn's disease (32).

The phenome-wide association study (PheWAS) is a complementary approach to GWAS and uses deidentified electronic health records (EHRs) linked to genetic data (33, 34). This platform allows for a reverse genetic approach of uncovering potentially novel phenotypes associated with a specific genotype. PheWAS was recently used in a drug discovery effort by Diogo et al. (35) to identify candidate drug targets for common disease indications. One example validating the use of PheWAS for drug repurposing utilized this methodology to identify phenotypes associated with a loss-of-function SNP in the gene *PCSK9*. Results indicated that this SNP was associated with a significantly reduced risk of hypercholesterolemia (36). This finding is supported by the current use of effective, FDA-approved *PCSK9* inhibitors for lowering cholesterol. Currently, our group utilizes PheWAS for repurposing efforts by first identifying SNPs in genes with known drug targets and mapping those to phenotypes in order to identify novel indications for drugs with known mechanisms of action (37).

The genetic basis of many common diseases is quite complex. Given the polygenic nature of many diseases (13, 15, 16), the need for a multipronged approach in drug development is clear, and methods to identify polygenic risk factors for disease are currently being generated (38). Regardless, harnessing the power of novel analytical methods that combine genetic variation, molecular phenotype, and disease phenotype data holds potential for discovering the biological bases of disease and exploiting these discoveries to identify new therapeutics for translation into the clinic.

EPIGENOMICS

Although a genetic contribution to human disease is clear, the importance of epigenetics, another heritable layer of the regulation of gene expression, is also now being recognized. Epigenetics encompasses all heritable changes that alter gene activity without affecting DNA sequence; many types of epigenetic modifications have been identified, including methylation and acetylation (39). Importantly, epigenetic changes can be reversible, and thus drugs that target epigenetic processes are gaining traction in drug discovery. Indeed, compounds targeting epigenetic enzymes are now approved to treat diseases such as myelodysplastic syndromes (40). Additionally, many tumors are associated with widespread changes in chromatin acetylation (41), and epigenetic drugs such as

histone deacetylase (HDAC) inhibitors are currently approved for treatment in multiple cancer types (42, 43). Other epigenetic drugs, including bromodomain inhibitors and DNA methyltransferases (DNMTs), are being investigated in both preclinical and clinical studies for cancer treatment (44, 45).

Epigenetics has also emerged as an important field in drug repurposing, and research is underway to identify FDA-approved drugs that exert off-target effects on epigenetic pathways. For example, researchers have long known that lithium, which is used to treat mental illnesses like bipolar syndrome, exerts powerful neuroprotective effects in preclinical models of Huntington's disease (46) and Alzheimer's disease (AD) (47), but the mechanisms underlying this effect were unclear. Harnessing the knowledge that lithium and the HDAC inhibitor valproic acid both have similar clinical efficacy (48), Wu et al. (49) assessed lithium's ability to alter protein acetylation. These studies identified HDAC1 as a novel target of lithium, uncovering a previously unreported mechanism for lithium's neuroprotective function that could be exploited for repurposing.

The discovery that hydralazine, an approved vasodilator with an established safety profile, also functions as a non-nucleoside DNMT inhibitor has led to the repurposing of hydralazine for cancer treatment where studies show that hydralazine decreases promoter methylation of cancer-related genes and reduces oncogenic properties in prostate cancer cells (50). Moreover, hydralazine in combination with valproate was shown to be safe and effective in a phase 2 study of patients with cutaneous T-cell lymphoma (51). Results are also awaited from a phase 3 clinical trial evaluating hydralazine/valproate combined with standard-of-care chemotherapy in recurrent metastatic cervical cancer (52).

Resources like the Human Epigenetics Drug Database (53), which integrates epigenetic drug data sets from laboratory experiments with manually curated information, are also aiding researchers in epigenetic drug repurposing efforts. The Database of Epigenetic Modifiers (dbEM) is another resource available to support epigenetic drug repurposing. dbEM includes the genomic information of over 150 epigenetic modifiers/proteins as well as information on drug molecules targeting various epigenetic proteins. Novel approaches combining analytical and experimental methods to assess epigenetic mechanisms for drug repurposing are also being generated. For example, Méndez-Lucio et al. (54) used a similar approach to query the DrugBank database (55–58) where they identified olsalazine, an anti-inflammatory drug approved for the treatment of Crohn's disease, as a potential DNMT inhibitor. The authors further confirmed olsalazine's hypomethylating activity in live cells using a novel cell-based screen, highlighting the utility of this approach for drug repurposing strategies in epigenetics.

Although epigenetic processes are complex, with multiple enzymes often interacting to contribute to disease, strategies to repurpose epigenetic drugs for new indications will likely gain momentum as novel experimental models and new technologies advance our understanding of the epigenetic mechanisms contributing to human disease.

TRANSCRIPTOMICS

Comparing the expression profile before and after drug exposure can elucidate the changes brought about by drugs on the transcriptional program (59). Several computational approaches have been proposed for drug repurposing based on transcriptional data (60–66). The signature of differential gene expression reflects the impact of a drug on gene expression. Drug-induced transcriptional changes can then be compared with disease-associated gene expression. If there is a negative correlation between the disease-induced transcriptional changes and the drug-induced transcriptional changes, then the drug may have efficacy in treating the disease. The drug may be able to reverse the disease-induced gene expression and mitigate the disease phenotype.

One notable example of this oppositional approach to the transcriptional signatures of drugs and disease comes from Dudley et al. (67). Using publicly available molecular data reporting gene expression in inflammatory bowel disease (IBD) samples, the authors searched a database of small-molecule drug compounds. Gene expression signatures were compared across a range of known drug compounds to a gene expression signature of IBD from the National Center for Biotechnology Information's Gene Expression Omnibus (GEO) (67). GEO is an international public database that archives microarray, next-generation sequencing, and other forms of high-throughput functional genomics data (68).

Dudley et al. (67) generated predictions for drug–disease relationships based on the hypothesis that if a drug has a gene expression profile that is opposite of the disease expression profile, then that drug represents a potential treatment for that disease. The authors validated their method by showing, for example, that their model predicts the corticosteroid drug prednisolone to show the opposite gene expression profile of Crohn's disease; prednisolone is indeed a well-known treatment approach for managing the symptoms of Crohn's disease. When applied to the expression profile for ulcerative colitis, the drug topiramate was demonstrated to have an opposite gene expression profile and therefore represents a potential therapeutic agent. Dudley et al. went on to validate their computational repurposing finding by demonstrating that topiramate is effective in a rodent model of IBD (67). Topiramate is a safe, FDA-approved drug for the treatment of epilepsy and migraine headaches and, therefore, was identified as a promising candidate for repurposing to treat IBD. As a retrospective administrative claims study did not provide evidence to support this indication of topiramate (69), additional research is needed.

As an alternative strategy, if two drugs have a similar gene expression impact, then the two drugs could share a therapeutic application, regardless of chemical structure or direct drug target. The rationale is that finding another drug with a similar genetic mechanism of action could result in a new therapy with improved efficacy or safety. Iorio et al. (70) developed an automated approach that exploits similarity in transcriptional response in human cell lines following drug treatment (across multiple cell lines and dosages) to predict similarities in drug effect and mechanism of action. The result is a publicly available Mode of Action by Network Analysis (MANTRA; **http://mantra.tigem.it/**) tool for the analysis of the mode of action of novel drugs and the identification of candidates for drug repositioning (71).

Expression quantitative trait loci analysis (72), which melds genomics approaches with transcriptomic approaches, has proven useful for mapping genetic variants with tissue-specific gene expression (73). Another tool, PrediXcan, tests the molecular mechanisms through which genetic variation affects phenotype (74). Together, these tools, in combination with in vitro reporter assays and functional in vivo assays, can help identify genes associated with disease for further exploration. Combining various omics to generate more holistic hypotheses and approaches represents an important advancement in the use of existing data and is a strategy that should continue to be employed and improved.

PROTEOMICS

Most drugs exert their therapeutic effects by binding to one or more protein targets. Furthermore, adverse effects of drugs are typically also mediated through their interactions with proteins. Therefore, understanding drug interactions with the proteome is critical to drug development and safety predictions. Several methods have been proposed to apply the proteome to target identification of small-molecule drugs, including empirical and computational approaches (75–82).

Chemical proteomics provides an opportunity to gain insight into the mode of action of small-molecule drugs (77). For example, chemical proteomics have been applied to protein kinases, an

important class of drug targets, because these signaling molecules often contribute to pathophysiology (83, 84). Klaeger et al. (84) evaluated 243 kinase inhibitors that were either approved for use or in clinical trials in a chemical proteomics screen, providing a large data set for potential use in drug repurposing. While some compounds showed strong selectivity, others targeted multiple kinases. This study reports a substantial number of novel molecular interactions not previously reported in the scientific literature (84). Some novel findings were identified that are particularly relevant for drug repurposing. For example, the mesenchymal–epithelial transition/vascular endothelial growth factor receptor inhibitor cabozantinib (approved for the treatment of medullary thyroid cancer and advanced renal cell carcinoma) is a potent inhibitor of the mutated tyrosine kinase FLT3-ITD, which is associated with an aggressive form of acute myeloid leukemia (84).

As a complement to the targeted biological assay approaches described above, there are also computational methods to probe drug–protein interactions. For example, the Computational Analysis of Novel Drug Opportunities platform (**http://protinfo.org/cando**) uses the similarity of drug–proteome interaction signatures to determine the homology of small-molecule drug behavior (85–87). The approach utilizes several types of information, including molecular docking. This platform was applied to identify potential repurposing candidates for Ebola virus disease. Chopra et al. (88) were able to identify and rank FDA-approved drug candidates that bind to and inhibit proteins from five different Ebola virus strains. Importantly, these computational results were compared to two published biological data sets, validating the computational approach (89, 90). In addition to predicting candidates for drug repositioning, proteomics approaches can also be used to inform potential drug toxicity implications. Wilson et al. (91) took a comprehensive approach in generating the algorithm PathFX. This program contains drug pathways in the context of protein–protein interactions annotated with the diseases and off-target effects associated with the pathway genes. PathFX was tested for its ability to predict adverse events using the FDA Adverse Event Reporting System and was indeed able to generate these phenotypes.

While some repurposing approaches study large data sets to define disease signatures, one area of current research is the application of personalized proteomic analysis to guide drug repurposing. One example is the approach taken by Velez et al. (92–94), who used personalized proteomics of liquid biopsies for drug repositioning. Proteomic analysis of the vitreous humor of the retina may serve as way to indirectly biopsy the diseased retina and identify changes in its proteome (95). Using proteomics in real time, Velez et al. (92) detected changes in inflammatory signals and identified cytokine targets, allowing repositioning of interleukin-6 inhibition therapies. Thus, cytokine profiles of retinal biopsies from neovascular inflammatory vitreoretinopathy patients guided personalized drug repositioning strategies for a previously untreatable population.

METABOLOMICS

Metabolomics is broadly defined as the study of the small-molecule intermediates and products of cellular metabolism. The metabolome is highly dynamic and time-sensitive due to the varying properties of metabolites. Large-scale mapping of the human metabolome via the Human Metabolome Database has provided an important foundation for application of this field to clinical chemistry, biomarker identification, and drug discovery and repositioning (96). Containing over 114,100 metabolite entries, this repository links to several other databases, including the Kyoto Encyclopedia of Genes and Genomes for comparison with genetic data; UniProt for protein mapping; and DrugBank, which provides drug target information (58, 97, 98).

Most metabolomic drug repurposing initiatives to date have focused on computational approaches to identify potentially druggable targets in various diseases. A study by Zhang et al. (99) identified 86 metabolites that were altered in AD patients. By mapping this information to

DrugBank, along with epigenomic and proteomic data, investigators identified approximately 75 existing drugs that may have efficacy in AD (99). This group applied a similar technique to uncover 58 potentially novel therapies for type 2 diabetes (100).

Metabolomics is also being applied to drug repositioning efforts in the field of oncology. A recent study by Kobayashi et al. (101) looked at the antitumor effects of the statin drug lovastatin from a metabolic perspective by measuring metabolites in the mevalonate pathway in SKOV3 ovarian cancer cells before and after treatment. Results showed several metabolic changes in these cells following lovastatin treatment, suggesting efficacy in tumor clearance and that drugs targeting the mevalonate pathway should continue to be considered for clinical application (101). A study attempting to validate metformin as a cancer therapeutic analyzed the metabolic signatures of tumors resected from patients who were also taking metformin. Liu et al. (102) found that metformin accumulated in the tumors and affected many metabolic pathways, which were all involved in mitochondrial function. Interestingly, metabolite profiles in tumors resected from patients taking metformin closely mirrored the profiles in a responsive animal tumor (102). Taken together, these studies indicate that metabolomics provides important insights into cancer biology and potential therapeutics.

The field of metabolomics, both singularly and as a complementary approach, has been instrumental in both hypothesis generation and target validation for drug repurposing. To date, metabolomics-based drug repurposing efforts have not translated directly to a human clinical trial; however, as this field quickly continues to become more established and sophisticated, it is likely that this will not be the case for long. As the metabolome is much more dynamic and fluid than some of the other omes, it will be important to consider the effects of these fluctuations when using any metabolomics tool or approach for drug repurposing.

MICROBIOMICS

The human microbiome is also inspiring several research avenues with applications to the field of drug repurposing. With the advent of high-throughput metabolomics, there is a heightened focus on redefining pharmacokinetics from a systems perspective. Fully intertwined in this effort is the microbiome, a metabolic organ defined as the total microbial population existing within the human body; one recent review aptly referred to this mechanism as "the microbial pharmacists within us" (103). Cohabitant microbiota may act in the degradation of administered drugs or sustain damage from exposure to toxic molecules, resulting in adverse effects from the death of mutualistic bacteria essential in processes like digestion, and also may alter pharmacokinetics in ways that further affect in vivo efficacy and safety (103). Therefore, considering the interactions of the microbiome with drug repurposing candidates may be a key complementary approach to traditional evaluation strategies, as the safety and efficacy of a drug may be altered by underlying microbial interactions at sites of absorption, distribution, metabolism, and excretion.

The microbiome can also reduce intended drug effects, as resident bacteria alter a xenobiotic substance and reduce its bioavailability (103). This occurs through numerous mechanisms; however, common interfering interactions include hydrolysis, deacylation, decarboxylation, dehydroxylation, demethylation, and dehalogenation, reducing effective target binding. The microbiome also provides competitive inhibition for many hepatic enzymes implicated in xenobiotic metabolism: Since most drugs are lipophilic—though their excretive mechanisms prefer hydrophilicity—agents require functional modification to increase their polarity for elimination. Bacteria directly interfere with this process, as microbial metabolites may compete for active sites with drug molecules. This suggests that the microbiome can significantly alter drug elimination, increasing the potential for cytotoxicity. A recent large, high-throughput screen of 1,000

nonantibiotic approved drugs revealed that one in four led to significant effects on the gut microbiota, suggesting both opportunities for further elucidation of the involved biologic pathways as well as the potential for unintended effects of those agents (104).

Beyond these effects of the microbiome on pharmacokinetics, safety, and efficacy of medications, manipulation of the microbiome as a therapeutic strategy is experiencing a period of diverse and intensifying research. Given the early relative success of fecal transplantation for addressing persistent disease in individuals with *Clostridium difficile* colitis, this approach for significantly altering the microbiome is now being repurposed for a range of other conditions, including obesity, metabolic syndrome, and graft-versus-host disease, as well as for the amelioration of multidrug-resistant organisms (105, 106). Early data also suggest potential for precision editing of the gut microbiota by repurposing tungstate to ameliorate IBD (107), liraglutide to reduce fatty liver disease in obesity (108), and probiotics to manage osteoporosis (109).

The range of applications suggests that the field of microbiomics may one day be a powerful tool for drug repurposing investigations. Repurposing candidates with direct effects on the microbiome may offer new strategies for treating the underlying cause of various diseases. Given the nascency of systematic, high-throughput microbiomic screening—and the lack of standardized protocols for this task—microbiomics may be challenging to incorporate systematically into drug repurposing studies (110). However, the further development of promising new tools for profiling microbial interactions with xenobiotic substances and for interrogating the microbiome itself presents the prospect of tremendous future research enabled by these new approaches (111).

PHENOMICS

Decades ago, drug development was based on phenotypic observations. Specifically, preclinical drug discovery and development were both driven by phenotypic observations. The era of target-based drug discovery did not emerge until the late twentieth century (112). Ideally, the modern approach links a deep understanding of disease biology to a deep understanding of target biology, often making use of human genetic evidence early in the preclinical drug development process, as described above (see the section titled Genomics). Unfortunately, this is not always possible, and the lack of a deep understanding of the causal biology behind a disease is one of the main reasons new drugs fail to show efficacy in clinical development, even if they appeared promising in preclinical development (113).

Much like drug discovery, drug repurposing has followed a similar path. Historically, the only possible approach for drug repurposing was to use phenotypic readouts to guide the development of a drug for a new use. What has remained constant over time is that a drug can only be repurposed after it has already been used in humans. While modern drug discovery has shifted to become target based, modern drug repurposing can be either (*a*) target based or (*b*) phenome based. In one approach, which has been referred to as genome-based drug repurposing, large data sets of clinical observations (phenotypic readouts) linked to patient genetic data can be used to identify new uses for drugs based on their targets and the underlying target and disease biology (37).

In another distinct approach, which we term phenome-based drug repurposing, patient experiential knowledge and/or healthcare provider observations can be aggregated to identify previously unknown effects of drugs in routine clinical use, which may suggest a given drug could be useful for treating a new disease (114, 115; **https://www.patientslikeme.com/**). Historically, drug repurposing based on phenotypic effects occurred as one-offs, or serendipitously in the clinical development process. As mentioned above, perhaps the best example is the repurposing of sildenafil citrate to treat erectile dysfunction (116). Much like genome-based drug repurposing, advances

in technology, computing, data storage, and sharing, among others, have also made it possible for phenome-based (i.e., PheWAS) drug repurposing to be approached in a more systematic fashion.

Much like the *PCSK9* example outlined above, there have been several other efforts both to validate PheWAS associations and to apply this technology to identify potential drug repositioning strategies. Rastegar-Mojarad et al. (117) linked currently identified drug-targeted genes in DrugBank to PheWAS associations and not only validated 127 drug indications but also identified 2,583 potentially novel drug–disease associations. A study by Millwood et al. (118) used the China Kadoorie Biobank ICD-10 codes to determine the potential efficacy of lipoprotein-associated phospholipase A2 (Lp-PLA_2) inhibitors in the treatment of atherosclerosis. This group found no association of loss-of-function mutations in the Lp-PLA_2 target gene *PLA2G7* with improved vascular disease outcomes. This finding paired nicely with clinical trial results that reported a lack of efficacy of the Lp-PLA_2 inhibitor darapladib in preventing ischemic events in coronary heart disease (119). In addition to target validation and hypothesis generation, phenomics-based drug repositioning has translated all the way to human clinical trials. Efforts from our group have led to three actively enrolling phase 2 trials across the fields of cancer, autoimmunity, and infectious disease.

Both genetic and phenomic approaches make use of data/information resources that were not available until relatively recently, but they come at the problem from different ends. Drug repurposing based on a drug target requires an understanding of the biology of both a disease and a drug's mechanism of action. Drug repurposing based on a phenotypic readout technically does not require an understanding of the biology of the disease; however, an understanding of the disease biology almost certainly would improve the odds of success.

Ideally, future drug repurposing projects will make use of both approaches and will arrive at a consilience of evidence from both real-world phenotypic observations of patients taking drugs (for other uses) and disease/target biology based on human genetic evidence and preclinical models of disease.

PREGOMICS

At the point of care, pregnant women are considered a vulnerable population, given therapeutic risks for both a mother and her developing fetus. However, this designation extends beyond risk aversion, as diseases of female health during pregnancy remain understudied, resulting in limited therapeutic options for obstetrical and gynecological morbidity. This gap is largely attributable to our limited understanding of the alteration of the physiological state in a pregnant woman, along with barriers to investigation established for the protection of expectant patients (120).

Herein lie the promise and peril of drug repurposing in pregnancy. Repurposing may address the so-called orphaned state of many obstetrical and gynecological diseases by providing new avenues for treatment. Additionally, the application of repurposed drugs with established safety profiles mitigates the risk of adverse outcomes in expectant populations. Nevertheless, these benefits also present challenges to further investigation given the sparse data on drug teratogenicity and fetal toxicity and the need to validate findings in systems truly representative of the pregnant state. Indeed, a drug that is safe for an adult might have negative effects on a developing fetus; knowledge about this is captured in the FDA's categorization system (121). With large gaps in the understanding of physiological alterations in pregnancy, selection of appropriate testbeds for screening presents a significant challenge to all drug development efforts, including repurposing.

Among the limited number of studies with this intention, targeted methods of drug screening have provided meaningful leads. In 2018, Goldstein et al. (122) identified the repurposability of calcium channel blockers (CCBs)—originally indicated for hypertension—in treating gestational diabetes mellitus (GDM). The authors employed large-scale EHR analysis to identify drug classes associated with an increase in oral glucose tolerance test results, integrating this list with a pool of

drugs with SNPs on their target genes implicated in the development of GDM. The authors thus identified the therapeutic potential of CCBs for treating GDM. Through medium-throughput screening derived from a systematic literature review of therapeutic options for Zika virus, Mesci et al. (123) successfully demonstrated the repurposability of the small-molecule drug sofosbuvir—originally indicated for Hepatitis C infection—in blocking transmission of Zika pathogens from mother to child.

Drug failure is also instructive in stimulating the development of tools essential for drug repurposing in pregnancy. Given the infamous thalidomide disaster of the 1960s, in which pregnant mothers prescribed thalidomide for nausea and vomiting during pregnancy delivered babies with severe upper and lower limb malformations, there has been a continued focus on appropriately scoring the teratogenic potential of drugs commonly prescribed in pregnancy (8). To our knowledge, only three studies have attempted to add quantitative rigor to definitions of drug teratogenicity, including Modeling Adverse Drug Reactions in Embryos (MADRE), an ongoing collaboration among Vanderbilt University, Northwestern University, and the Harvard T.H. Chan School of Public Health, which seeks to derive quantitative structure–activity definitions and retrospective data-driven predictions of small-molecule teratogenicity with new methods of in silico drug profiling.

Hence, systematic evaluation of fetal toxicity and generalized improvements in the understanding of pregnant physiology are essential for the successful development of new repurposing programs for pregnancy.

PERSONOMICS

Roy Ziegelstein (124) developed the concept of personomics, defining it as "an individual's personality, preferences, values, goals, health beliefs, social support network, financial resources, and unique life circumstances that affect how and when a given health condition will manifest in that person and how that condition will respond to treatment." Extending upon his proposal that personomics is the missing link in the evolution from precision to personalized medicine (124), we reason that personomics can be a valuable information source in repurposing drugs for precision indications. Personomic data sources that can aid the development of drug repurposing priorities, hypotheses, and approaches are growing and include social media sites (e.g., Twitter and Facebook), wearable devices (e.g., Fitbit and Apple Watch), and patient forums (e.g., PatientsLikeMe and WebMD), to which a variety of analytical tools and techniques can be applied such as natural language processing (NLP), artificial intelligence, and machine learning.

Strategies that have been proposed for deriving drug repurposing signals include systematic analyses of known drug side effects (125), outcomes recorded in EHRs (126), and adverse events reported by ClinicalTrials.gov (127). Leveraging the personome for drug repurposing can employ similar strategies but utilize data originating directly from patients. In their recent review on advances in NLP of health-related text, Gonzalez-Hernandez et al. (128) described the rapid growth of research on social media mining to capture patient perspectives on numerous health topics. For example, some have applied recurrent neural network models to social media posts to detect adverse drug reactions (129) and map language to medical concepts (130), and both methods can be scaled to larger data sets and potentially be applied to drug repurposing. Other examples specific to repurposing include feasibility studies using machine learning methods to analyze patient drug reviews on WebMD (131, 132), one of which found 447 novel drug uses and successfully predicted several known repurposing indications such as tramadol for depression (131). In addition to generating repurposing hypotheses, these approaches can provide secondary support to repurposing efforts through the identification of unrecognized and unmet medical needs and the refinement of precision phenotypes.

Several challenges and limitations exist, however, when working with personomic data sources, including poor data quality, difficulties mapping lay language/social media posts to medical diagnoses and concepts, demographic biases related to technology access, and overall data noisiness. Continued development and improvement of analytical tools holds the promise to overcome some of these challenges and generate better findings, even while personomic data sources continue to grow in size and complexity. Drug repurposing efforts may be able to capitalize on emerging big data repositories that arise as tech giants such as Google and Amazon continue their moves into the healthcare space. For example, Amazon is in the early stages of efforts to expand Alexa's capabilities to include a series of health-related tasks, including detecting when individuals may be sick, suggesting medications, and scheduling doctor's appointments (133). While this type of health-related data collection presents significant ethical questions and privacy concerns, the potential utility of such a data source for drug repurposing applications is compelling.

A final consideration for personomics and drug repurposing is enhancing patient engagement throughout the entire development process, as described by Allarakhia (134), which includes not only the hypothesis generation and priority-setting touched on above but also the codesign of clinical trials. One platform that has enabled this type of work is Transparency Life Sciences (TLS), "the first all-digital drug development services company, [harnessing] crowdsourcing and mobile health technology to advance biopharma candidates through clinical trials with unprecedented patient relevance and efficiency" (**https://www.transparencyls.com/about-us/**). The TLS protocol builder tool crowdsources input from physicians and patients to develop clinical trial protocols. This tool was used to develop a protocol to repurpose lisinopril as an adjunctive therapy for multiple sclerosis, the first-ever protocol developed via crowdsourcing methods to clear FDA approval and proceed to phase 2 testing (135). This platform was subsequently used to develop a protocol to repurpose metformin for prostate cancer, crowdsourcing input from 60 physicians/researchers and 42 patients/advocates, which resulted in nine total changes to an initial draft protocol (136). Future opportunities and challenges in this area include more and better inclusion of patient-reported outcomes in clinical trial protocols [as advocated in the recent expansion of SPIRIT-PRO recommendations (137)] and continued innovation in clinical trial end points, particularly those that incorporate patient perspectives.

CONCLUSIONS AND FUTURE DIRECTIONS

Omics-based methodologies and technologies are integral to the success of drug repurposing in terms of both hypothesis generation and efficacy and toxicology prediction (**Figure 2**). In the construct presented here, even the earliest drug repurposing successes incorporated aspects of omics-based research. In the case of sildenafil, personal experience and self-reporting (personomics) coupled with phenotypic observations (phenomics) led to the repositioning of an intended antihypertensive as an effective therapy for erectile dysfunction. Likewise, knowledge of the protein changes (proteomics) that occur in multiple myeloma and metastatic prostate cancer helped to identify thalidomide as a novel and potentially efficacious therapy.

Currently, many drug repositioning initiatives utilize a singular omics approach for their research strategy. While these tools and technologies have greatly enhanced both our depth and breadth of knowledge of many biological systems, each one has its own specific limitations. Despite initial hopes, GWAS has identified only a handful of causal variants to date (138). Mapping genetic variants to conditions through PheWAS analyses is often limited to ICD-9/ICD-10 codes; however, it is well known that every phenotype does not have a unique ICD-9 or ICD-10 code (139). Fields such as microbiomics and pregomics are just emerging and, while informative, at this point provide little insight to drug repurposing on their own. Personal beliefs, values, and

Ome	Data sources	Repurposing opportunities	Future directions
Genome	• DGIdb • PrediXcan • ClinVar	• Deriving hypotheses • Using in combination with phenomic data	• Incorporating polygenic expression • Combining genetic variation, omics data, and phenotype
Epigenome	• HEDD • dbEM	• Deriving hypotheses • Uncovering new disease mechanisms	• Advancing understanding of disease mechanisms • Integrating with genomics
Transcriptome	• GEO • MANTRA	• Deriving hypotheses • Predicting potential drug efficacy	• Advancing understanding of disease mechanisms • Integrating with other omics
Proteome	• CANDO • PathFX	• Deriving hypotheses • Predicting potential drug efficacy and toxicity	• Developing cost effective methods for personalized care • Integrating with other omics
Metabolome	• HMBD • KEGG • SMPD	• Deriving hypotheses • Combining with other omic datasets for holistic approaches	• Accounting for dynamic nature • Collating larger human datasets • Informing trial design
Microbiome	• Human Microbe Project Database • Virtual Metabolic Human • HPMC database	• Modulating to increase drug efficacy • Utilizing as a therapeutic strategy	• Improving understanding of microbe/drug interactions • Building on existing studies
Phenome	• EMRs • Patient-reported outcomes	• Deriving hypotheses • Using in combination with genomic data	• Aggregating of larger datasets • Developing more systematic approaches (not serendipitous)
Pregome	• safefetus.com • FDA resources	• Identifying unmet medical needs • Improving understanding of pregnant physiology	• Aggregating of larger datasets • Developing systematic evaluation of fetal toxicity
Personome	• Social media • Online patient forums • Patient-reported outcomes	• Identifying unmet medical needs • Deriving hypotheses • Defining precision phenotypes	• Improving analytical tools • Mining larger patient data sources • Increasing clinical trial engagement

Figure 2

A chart containing specific omic data sources, repurposing opportunities, and future directions. Abbreviations: CANDO, Computational Analysis of Novel Drug Opportunities; dbEM, Database of Epigenetic Modifiers; DGIdb, Drug Gene Interaction database; EMR, electronic medical record; FDA, Food and Drug Administration; GEO, Gene Expression Omnibus; HEDD, Human Epigenetics Drug Database; HMBD, Human Metabolome Database; HPMC, Human Pan-Microbe Communities; KEGG, Kyoto Encyclopedia of Genes and Genomes; MANTRA, Mode of Action by Network Analysis; SMPD, Small Molecular Pathway Database. The epigenome, metabolome, and microbiome silhouettes were adapted from Freepik; the proteome silhouette was adapted from Site Hurrera; and the phenome silhouette was adapted from Vectors Market (**https://www.flaticon.com**).

experience are paramount in effective medical care, but personomics data are highly subjective and difficult to standardize.

The limitations of singular omics approaches to drug repurposing could be one explanation for why only 30% of repositioned drugs gain market approval (140). While this is a vast improvement over 10% of new drug applications, there is clearly still room for refinement (140). Moving forward, it will be important to place more emphasis on the integration of multiple omics into a holistic systems biology approach to drug repurposing. Omics technologies have generated massive amounts of informative data that provide snapshots of the biological changes associated with various conditions; future tools that integrate all omics data sets will further the understanding of human health and disease. For example, the field of pathogen resistance has worldwide implications for human health and would likely benefit tremendously from novel approaches to complement current repurposing strategies. While screens suggest that antineoplastic agents and other

compounds may be attractive candidates for treating challenging bacterial infections (141, 142), explanatory pathways can be murky and hamper planning for follow-on research. New ways of integrating various omics data could provide powerful new strategies for elucidating compound effects on target pathogens and selecting the most promising candidates for further repurposing work.

As yet, the methods and approaches described in this review are relatively new. In the context of clinical development and marketing approval for a new indication and real-world use, most methods have not yet been demonstrated successful. Over time, as methods produce varying degrees of success, more emphasis will be placed on those methods that provide the strongest clues and directional insights into pathophysiology, as it relates to the application of pharmacotherapeutics. We expect that repurposing methods will eventually be quantitatively proven to provide novel solutions for millions of people still in need of a therapeutic option.

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