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Drug repurposing

Orphan/rare drug discovery through drug repositioning

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There are many, often life-threatening, rare/orphan diseases for which there are few or no therapeutic options. They individually affect few people, but collectively impose very high social and economic burdens. New approaches are bringing big pharma resources to solving the problem through drug repositioning of approved drugs. Advances are being spurred by public and private partnerships, government incentives and awareness brought by patient support groups. Scientific discoveries and new technologies are creating many opportunities for drug repositioning.

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Introduction

Orphan/rare diseases are those diseases which affect small numbers of people compared to general population; the specific definition varies from country to country. Tropical or neglected diseases are recognized as orphan diseases in developed countries. Around the world, 15–20% of the population has some sort of rare disease. It is estimated that there are 7000–8000 known rare diseases. Drug companies do not often conduct research on drugs for rare diseases due to the limited market for each indication [1]. Traditional drug discovery for common diseases is long and expensive process. Orphan drug discovery is not different from discovering medicines for common diseases. Therefore, to encourage the drug companies to develop orphan products the US Orphan Drug Act provides several incentives, for example, financial assistance of various types, market exclusivity, among others. Combining these benefits with finding new uses for existing drugs (repositioning or repurposing) has motivated several drug companies to develop orphan products. In the past five years, there have been several journal review articles [2] and at least five conferences highlighting the potential value of repurposing.

There are several advantages to repurposing old drugs over *de novo* drug development. The traditional methods for drug discovery require a large infrastructure while repurposing FDA-approved drugs is relatively inexpensive; repositioning is especially valuable for smaller companies. With repurposed drugs, developers can bypass almost half of the overall cost by eliminating preclinical assessment. Venture capitalists prefer the repositioning over investing in technology platforms. Many reviews on orphan drug development trends utilizing repurposed drugs have appeared in recent years [1–8].

Technologies and strategies for orphan drug discovery

In the past, drug repositioning has mostly been accidental. Since then, several companies have included drug repurposing in their business models. More recently, instead of having to find repurposing opportunities serendipitously, novel technologies have been developed to identify useful hidden properties of approved drugs, as well as for compounds failed at phase II/III. Discovering and validating the repositioned drug for a disease is just the beginning of the drug development process. The remaining development steps are identical to *de novo* drug R&D. The same is true for orphan drugs, although many challenges associated with orphan drug development are unique. Just to name a few: underutilization

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of research resources (unused R&D programs of pharma companies), limitation in sharing existing knowledge from universities and other research labs, unavailability of animal models of disease, lack of easy accessibility of natural history data of diseases, and lack of validated drug targets for rare disease. A variety of strategies which are known in the industry have been used for orphan drug discovery. For example, serendipitous observation (still a popular strategy); informed insights of human biology and molecular pathways of the disease targets, and end point screening [9–11]; reformulation to change the route of administration [12]; off-label use for identifying the relevance of known targets in diseases, or identifying new targets of known drugs in new diseases [13] and monitoring: literature for case reports, statistical data mining of hospital records, internet resources obtained from patient advocacy groups, disease oriented social networks and post marketing surveillance to detect beneficial drug side effects for new indications during their development or use [14]. All the approaches mentioned above for drug repositioning are partly motivated by a need to reduce, but not eliminate, developmental risk.

Drug leads

For the purpose of repurposing approved drugs, several strategies are practiced to identify potential drug leads. For example, lead discovery technologies such as HTS, rational drug design, animal models, *in vitro* and cell-based screening, phenotype screening, mapping gene activity profiles of diseases, comparative studies from normal and diseased patients of intracellular pathways that regulate biological responses, exploiting the structural similarities of binding sites of known and new targets via computational methods, study of publicly available gene expression data of genes involved in diseases and selecting FDA-approved drugs that correct abnormal gene expression in these diseases [15–17], among others. Some specific examples show how repurposed drugs have been used to accelerate drug discovery. A library of 2687 existing drugs has been screened for inhibition of the human malaria parasite in two mouse models and found astemizole as an inhibitor for chlorquinine-sensitive and multidrug-resistant parasites [18]. With the hunch that glutamate transporter (GLT1) has been implicated in multiple neurological disorders, 1040 FDA-approved compounds and many nutriceuticals have been screened to identify ceftriaxone as a GLT1 inhibitor [19]. Screening the National Institute of Mental Health psychoactive drug program database has identified generic drugs, namely mirtazapine and cyproheptadine, as 5-HT2A affinity inhibitors for possible treatment for progressive multifocal leukoencephalopathy [20]. Another need is in the area of new antibiotics for treating drug-resistant infections. Screening a library of 1040 approved drugs from Microsource Inc. has identified nonantibiotics possible leads for antibiotic development [21]. A collection of 1057 previously approved drugs has been screened to find synergistic effects to augment the activity of the antibiotic minocycline. One such drug combination exhibited *in vitro* and *in vivo* activity against bacterial pathogens [21,22]. IDMap computer software which uses text mining and structural information, predicts novel relationships between drug targets and repositioning-capable chemicals to identify potential lead compounds [23]. A large number of neurological diseases and many assays for these are found in the NIH PubMed drug database [24]. Although neurodegenerative mechanisms affect different cells in different diseases, full understanding of the most relevant properties to neurodegeneration is achievable using the PubMed assay database.

The chemical space of potential repurposable compounds is limited and currently estimated to approach 9000 compounds. Probably this number will increase substantially as more and more companies and research institutions contribute to this chemical space. For many rare diseases, drug targets are not known. Several studies have been conducted to identify drug targets in those situations [11,21,24–26]. Many leads generated from studies conducted by academic and research institutions appear to have fallen in the 'Valley of Death' due to lack of translational research opportunities. To cross that valley (leads to products) NIH, Private Public Partnerships and industry are making serious efforts.

Private and public partnerships

Drug repositioning collaborations between big pharma and biotech/specialty pharma are becoming more common in this decade because they have something to offer the other. Governments and academic institutions are recognizing the importance of rescuing old drugs and are making serious efforts to make use of them for developing orphan drugs. Disease-specific support groups and foundations have initiated lead discovery programs. Academic investigators and disease foundations usually do not have the required infrastructure and expertise to develop drugs; when such capabilities exists the success rate for drug approval is low due to lack of required information in one place. Therefore, the National Institutes of Health (NIH) Chemical Genomics Center (NCGC) is acting as a national resource for the translation of information found in the genome into biological insights and to new therapeutics, particularly for Rare and Neglected Diseases. NCGC Pharmaceutical Collection (NPC) has a collection of drugs registered and approved for use in humans or animals. This database is a rich resource for bioinformatics, screening assays and profiling a broad array of human genetics pathways and diseases. The drug rescue and repurposing project is part of the National Center for Advancing Translational Sciences (NCATS) [27]. This is the result of a sincere commitment from the NIH to accelerate orphan drug development. They are making comprehensive and conscious efforts to identify appropriate abandoned

compounds and potential partners, and making data and resources available to the pharma industry [27]. The NPC program has been created in the context of the collaborative mission of the NCGC and the NIH's Therapeutics for Rare and Neglected Diseases RNDs (TRND). This is an ongoing project for NIH and is expected to benefit drug development communities via the NPC Informatics Resource browser [28]. NPC has the collection of more than 9000 drugs and drug-like compounds, which represent the repurposing compounds space, along with more than 200 assays for drug targets. They provide not only the possibility of rapid therapeutic advances but also provide new lead or probe development. The NPC community collaborates with industry, academia and nonprofit organizations [27]. To facilitate repurposing and speed the delivery of new therapies, the FDA created a comprehensive database, the Rare Diseases Repurposing Database (RDRD) along with known molecular targets. This database is created by matching the FDA orphan designation database to FDA drug and biological product approval lists. The Office of the Rare Diseases Research (ORDR) and other NIH partners initiated the therapeutics for The Rare and Neglected Diseases (TRND) program to help researchers traverse the pharmaceutical valley of death between drug discovery and clinical trials. The NIH is also cosponsoring the new International Rare Disease Research Consortium, a coalition of 170 research sites around the globe with a goal of producing treatments for rare diseases by 2020.

Through a partnership between Pfizer and Washington University, St. Louis, the Center for World Health & Medicine (http://www.cwhm.org/) pursues small molecule drug discovery and development for diseases in the developing world, and orphan diseases. With the assumption that the compounds which are no longer under IP protection are no longer of strategic interest to the industry, it focuses to reposition advanced clinical compounds and serve as a repository and distributor for off-patent discontinued drug library and shelved compound portfolios. The Pharmaceutical Assets Portal Project, a not-for-profit organization, has the aim of depositing compounds discontinued at various clinical stages to a central repository. They will facilitate the match between NIH's Center for Translational Science Awards (CTSA) institutions' affiliated investigators and the pharmaceutical industry for the purpose of developing research partnerships based on compounds shelved at the clinical stage (http://www.ctsapharmaportal.org/). The Consortium will make these compounds available to academic scientists for repurposing or screening for new indications.

There has been a tremendous increase in Private-Public-Partnership (PPP) [29] interactions in the past 10 years, mostly due to serious efforts by the NIH, along with changes in the discovery philosophy of drug companies. Partnership for Cures raises funds for rediscovery research that reuses recombines and reapplies existing science and medicine to quickly, safely and affordability create new treatments for patients with rare diseases [30].

More than 78 academic drug discovery centers in the US, representing universities and nonprofit research organizations [31], are investigating a broad range of therapeutic areas including diseases prevalent in less developed countries and orphan diseases (http://www.rarediseasefoundation.org/). The expected long-term outcome of PPP is the integration of academic investigators into collaborative repositioning efforts. This contributes substantially to the knowledge base for the rare diseases and aids the pool of methodologies available for proof-of-concept studies. This is expected to result in an increased number of approved drugs for new indications with considerable public benefit.

Patent pool

It is an undeniable fact that patents are crucial for innovation. Patent pools are a common practice in the electronic industry, whereas the concept of a medicines patent pool is a new initiative between pharma companies, governments and academic institutions for producing generic versions of patented drugs to supply patients who cannot afford them. However, to date no such patent pools have been assembled for the discovery and development of drugs to treat either common or rare/neglected diseases. Some critics believe this concept is not suitable for pharmaceutical discovery. However, under the right conditions, due to the changing landscape of the pharma industry, the idea of a patent pool for drug discovery is achievable. Particularly important for the pharma sector is the identification of specific patents which make the discovery process faster and much less expensive. The new chemical entities shelved due to lack of efficacy are ideal candidates for a patent pool. Research validating clinical observations or modifying treatment protocols with shelved compounds can quickly demonstrate proof of concept. Many disease foundations are now playing evolutionary roles for patent pools across the pharma industry, government and not-for-profit sectors to collaboratively enable translational drug discovery efforts. The patient organizations (examples of Foundations – Myelin Repair Foundation, M.J. Fox Foundation, Cure Alzheimer's Foundation, Cystic Fibrosis Foundation, Prostrate Cancer Foundation, among others) should be able to take a lead in assembling drug discovery patents. The use of patent pools (http://www.ntdpool.org/, http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf) could serve the interests of the public and private industry, a win-win situation and they can provide greater innovation due to parallel research and development, removal of bottlenecks for clinical studies and faster product development.

The latest and possibly most responsive action has come from GlaxoSmithKline (GSK). Early in 2009, GSK announced a major reform in their corporate policy on drug affordability and accessibility. GSK intends to foster interest in the

establishment of medicines for serious diseases that have a large social impact but for which there is no commercial interest despite the medical need. GSK contributed more than 500 granted patents in 80 different patent families to initiate the patent pool. Alnylam joined the patent pool in June 2009 by contributing 1500 issued and pending patents on RNAi technology. Gilead announced to share patents to basic research and to make their medicines more accessible through voluntary licensing of crucial intellectual property for public health, while giving pharmaceutical companies fair compensation for their work.

Priority voucher

Although the Orphan Drug Act provides several incentives for the development of orphan products, additional incentives are needed to speed up the process and bring more orphan products to market quickly. Priority vouchers have been created for neglected diseases; some orphan diseases should qualify for the credit. Developers of treatments for neglected diseases receive a priority review voucher which could save an average of one year of USFDA review which translates into substantial financial incentives. This program is expected to accelerate approval of any drugs in any disease indication that would not normally qualify for priority review. Thus the voucher could benefit consumers in both developing and developed countries with relatively low cost to the American taxpayer (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf). To date, only Novartis has received a priority review voucher for the development of the malaria treatment (*Coartem*) but they are unable to cash in due to some technical reasons. In addition, big pharma has less likelihood of getting blockbuster drugs in the near future due to lack of innovation. Therefore, in the future priority vouchers may not be attractive incentives for orphan drug development. New mechanisms for stimulating R&D for orphan drug development are needed. Through the use of repurposing drugs, the additional incentives may comprise product development partnerships, advance market commitments, prizes (e.g. award system by disease-specific foundations) and patent pools. None of these mechanisms is a standalone solution. They should be viewed as complementary mechanisms to existing intellectual property systems for stimulating further R&D for rare diseases.

Efforts of pharma

For a long time, the drug industry focused on developing billion-dollar drugs. It was thought that development of orphan drugs was unlikely to be pursued by big pharma due to limited commercial value. In recent years, orphan drugs have become attractive as companies are losing patent exclusivity and unable to increase the supply of new drugs causing them to look into ways to diversify their business. Therefore, the pharma business model is changing. Many biopharmaceutical companies attempting to increase productivity are pursuing drug repositioning. Companies are searching the existing pharmacopoeia for repositioning candidates, and the number of repositioning-success' stories is increasing. In the past rare disease R&D has most often been a background activity, and never been part of the central research or financial goals of pharma. Now big pharma is accelerating its efforts concentrating on rare disease programs. Business partnerships are designed to create value in compounds obtained from preclinical and clinical development programs. Biotechnology companies have built business models around this strategy. Major pharma companies have seen this as a profitable commercial opportunity. Novartis, GSK, J&J, Merck, Shire, Abbott Laboratories, Boeringer-Ingelheim, Bristol-Meyers Squibb and other major companies have taken the lead in developing drugs for rare and neglected diseases. New programs are incentivizing other research-based organizations to invest in rare or neglected diseases. Some companies are combining once scattered departments into R&D units dedicated to rare diseases drug development using a variety of business approaches and strategies. With its new Indication Discovery Unit (IDU), Pfizer is looking for ways to take underutilized assets, such as compounds, which failed due to lack of efficacy, and evaluate them against new targets or new indications. Many more such research units are expected from other major pharma companies. At the same time, the benefits of pursuing rare diseases at a small company have been numerous – priority review, FDA incentives, among others.

Drug reposition success

Since the inception of Orphan Drug Act, the RDRD lists 236 repurposed products that have received orphan designation status (indicating they are promising for the treatment of rare diseases) but which are not yet approved for marketing [32]. An additional 127 compounds have been approved for marketing. Some of the designations are for more than one indication. The data included in the database are a reconfiguration/cross-indexing of information already released by the FDA. This database offers sponsors a new tool for finding special opportunities to develop niche therapies for patients with rare diseases. In 2010 alone the USFDA Office of Orphan Products Development (OOPD) received 323 applications, 14 orphan drugs were approved. In 2009, there were 250 applications and 17 market approvals. From the new molecular entities approved between 2000 and 2010, 37 orphan products or drugs have been approved (http://ec.europa.eu/health/documents/community-register/html/orphreg.htm) [33] without comparative drug efficacy studies. Pfizer currently has 17 approved orphan products on the market. Novartis has 6, and GSK has 14. Some examples of drugs

Table 1. Some examples of orphan drugs developed from repurposed drugs

Drug	Condition	Orphan disease
Dulxetine	Antidepressant	Urinary continence
Difluoromethylornithine	Cancer	Sleeping sickness
Minocycline	Antibiotic	Ischemic stroke
Gentamycin	Antibiotic	Duchene muscular dystrophy
Thalidomide	Morning sickness	Multiple myeloma, leprosy
Amphothericin B	Anti fungal	Leishmaniasis
Tamoxifen	Breast cancer	Bipolar disorder
Closantel	Veterinary anthelminitic	Onchocerciasis
HIV protease inhibitors	HIV-AIDS	Cancer
Sulindac	Cyclooxygenase inhibitor	Cancer
Arsenic trioxide	Syphilis	Acute promyelocytic leukemia
Cozaar	Bloodpressure medication	Marfan syndrome
Viagra	Erectile dysfunction	Pulmonary hypertension
Memantine	Alzheimer's	Down syndrome
Arbaclafen	Cerebral palsy	Fragile X
Ivermectin	Antiparasitic (river blindness)	Malaria
Rituxan	Lymphoma	Rheumatoid arthritis
Miltefosine	Brest cancer	Leishmania
Tretinoin	Acne	Promyelocytic leukemia
Hydroxy urea	Cancer	Sickle cell disease

developed for rare diseases from repurposed chemical entities are shown in Table 1.

Conclusions

The rare disease field sets the stage for individualized medicines due to the small patient population for each indication. Therefore therapeutic development solutions involve new technology platforms consisting of policy makers, patient groups, researchers, industries and funding agencies. The objectives of these platforms should be lowering costs of drug availability. While drug companies feel the pressure of the recently near empty drug pipelines, incentivized orphan drug development could help pharma companies to improve their bottom line. One of the creative solutions appears to be the utilization of existing drugs for new indications. Repurposing typically achieves one of three objectives: (1) identifying as a drug for a new condition, (2) reformulation as a drug using a novel delivery systems or (3) identification of a lead for another indication. Repositioning has significant commercial value as it extends the markets for a repurposed chemical at lower financial risk. The benefits of repositioning including the easy availability of small molecules, and their published data (such as on long-term toxicology studies) that contributes significantly to time- and cost-effective research. The growth of innovative public–private partnerships bridges the gulf between basic research and translational research. Recent trends indicate that the value of orphan drug development is a niche business strategy for many pharma companies. Profit margins for orphan drugs are higher than blockbuster drugs due to a small patient pool resulting in smaller clinical trials and a higher price point support for orphan drugs. Often patient advocacy groups participate in clinical trials at their own expense and argue in support of the Accelerated Drug Approval process. The recent enhanced emphasis for translating discoveries into products such as the creation of NCATS highlights the importance of orphan drug development. In addition, NIH makes efforts to persuade drug companies to release abandoned drugs to academic researchers.

The current rate of drug repurposing activity raises the expectation that a substantial percentage of rare diseases if not all 8000 rare diseases might be treatable with drugs in the current pharmacopeia. Some believe that the more obvious winners have already been found. While these facts remain, repurposing should not be viewed as a substitute for drug discovery and development, but it means that, repurposing drugs requires fewer resources. Nevertheless, as new targets are discovered due to human genetics program, the repurposed chemical entities could serve as sources for screening new indications. Major companies are well positioned to benefit from the successful repurposing of drugs, especially

when they utilize both internal and external resources. The effective applications of repurposing technologies should enable major companies significantly enhance their development pipelines, especially for rare diseases caused by single gene mutations. Therefore, the repurposing of drugs and drug-like molecules should be anticipated to have a promising future.

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