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A New Therapeutic Applications for Drug Repositioning on the Cloud Computing

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Abstract- *Market pressures and reassess their current drug development model drugs by pharmaceutical companies to tap into new and innovative business models that have driven. Converter is used in medicine as a variety of techniques lend themselves to distributed computing model. Cloud optimizes resource usage and various pilot projects into pharmaceutical companies that reflect the current trend of a computer model. Widespread adoption of cloud security and data provenance drug Converter is the biggest challenge. Drug discovery and development are a time-consuming, expensive and risky venture. As an alternative approach, the pharmaceutical companies, the relatively low cost of failure risks in order to accelerate the drug discovery and development process of repositioning the drug (the drug Repurposing, drug re-profiling, drug review process, treatment modification) approach reduced. Drug repositioning existing drugs / pro-drugs / biologics process of developing a new symptom is a superb strategy to maximize the value of the optimal potential as a therapeutic drug. In other words, rather than an alternative to the drugs or other disease-diseases by targeting the sale of new drugs that are useful in explaining a part of a balanced biological Converter can be bypassed when compared to traditional drug discovery, drug discovery and development, common in many phases of de novo cost, risk and time -reduced has many advantages. Data mining, bioinformatics, and a variety of techniques including the use of novel screening platforms have been used for screening for the identification of potential candidates to replace. According to experts, Efficacy end points have the opportunity to meet with the same success as the original drug. Also, they are not without risks of original drugs. FDA's 505 (b) (2) approval to change the route and marketing allows companies to offer improved safety and efficacy of drugs will be able to reposition. Drugs can also be repositioned to provide the tools and understanding needed to create second-generation drugs. In the end, a large number of patients with a wide range of conditions and regulatory approval process to go through at least once and have an abundance of human experience that can benefit from such drugs. In various ways, such as disease or cancer drugs targeting other complex diseases (eg, obesity, rare diseases), drug converter can provide a good opportunity to have a goal. Drug repositioning technology experts have the opinion that better coordination of research in the next decade Pharma.*

Keywords: Drug Repositioning, in silico, Rare Disease, Drug Repurposing, High-Throughput Screening, Off-Target Drug Repositioning, On-target Drug Repositioning

I INTRODUCTION

Various drug discovery technologies, such as structure-based drug design, combinatorial chemistry, or high-throughput screening have not been successful as expected compared to conventionally developed drugs. However, it takes too long and costs too much to bring new drugs to market. Drug companies have turned to drug repositioning (also known as drug repurposing, drug re-profiling, drug re-tasking, drug rescuing, therapeutic switching, etc.) as a means of drug rediscovery. Drug repositioning concept evolved in the early 1990s and has become a matter of intense interest during the past few years. Repositioning failed or already marketed drug candidates for alternative disease indications (i.e., new diseases) offers a valuable opportunity to alleviate pipeline gaps and increases success rates 1. Increasing interest in drug repositioning has occurred due to sustained high failure rates and costs involved in attempts to bring new drugs to market. Reasons for epositioning clinical effect of drug compound are shown in Fig. 4. Failed drugs include; some for safety reasons, some for lack of efficacy in the target indication, some because the patient population has not been appropriately stratified to

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eliminate non-responders and some because they no longer fit into a portfolio. Little research has been done to address the huge opportunities that may exist to reposition existing approved or generic drugs for alternate uses in therapy of many diseases. Schematic diagram for drug positioning is given in Fig. 1.

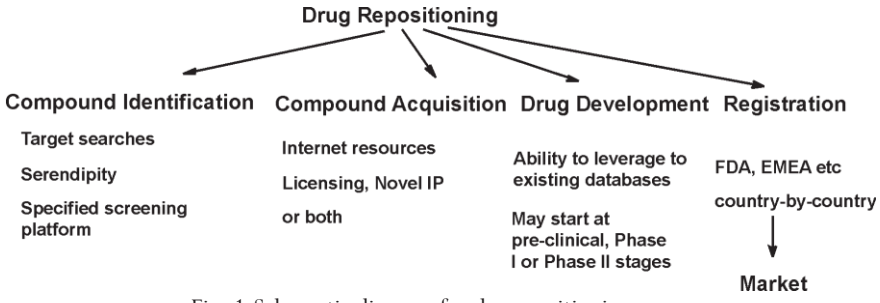

Fig. 1.Schematic diagram for drug positioning

In 'on-target" drug repositioning approach (Fig. 2), the drug's (e.g., galantamine) known pharmacological mechanism is applied to a new therapeutic indication. 'Off-target" drug repositioning approach (e.g. astemizole, Fig. 3) is looking for pharmacological mechanisms that have not yet been described for a known molecule. The discovery of novel drug targets is a significant challenge in drug development. Less than 400 proteins are used as drug targets in the treatment of diseases. On the other hand, many of the currently known drug targets are functionally pleiotropic and involved in multiple pathologies. Several of them are exploited for treating multiple diseases, which highlights the need for methods to reliably reposition drug targets to new indications. There are two approaches for drug repurposing (Fig. 5)

i) Known compound → new target ii) Known target → new indication

Examples of repurposed drugs invariably fit within one or both of these models. Some drugs such as Chlorpromazine fulfill both approaches for drug repositioning.

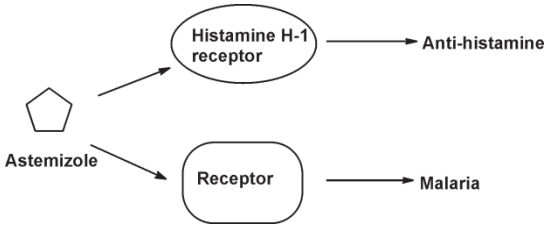

Fig. 2.On-target drug repositioning

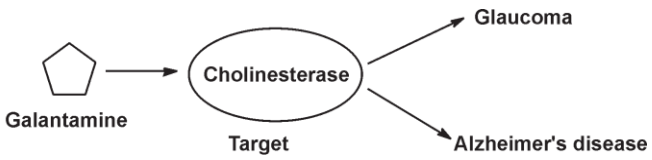

Fig. 3.Off-target drug repositioning

Many effective drugs act via modulation of multiple targets and many adverse drug reactions are due to activity towards multiple targets. Many drugs may have yet unknown therapeutic applications (drug repurposing).

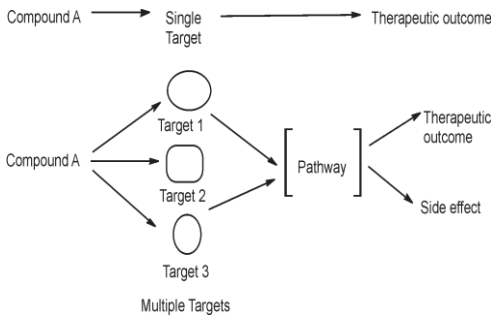

Fig.4. Clinical effect of drug compound

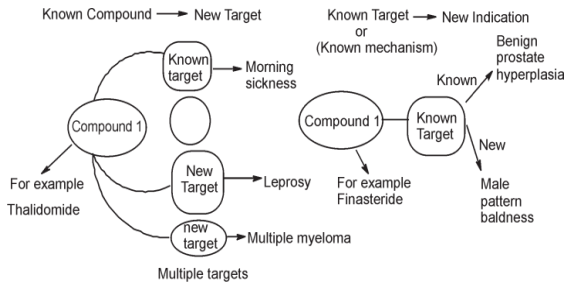

Fig. 5.Two approaching for drug repositioning

The Drug repositioning as a business opportunity was analyzed for pharmaceutical companies, weighing both challenges and

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opportunities of repositioning. Historically, drug repositioning has come from serendipitous discoveries in late stage clinical trials or post approval. The classic example is sildenafil (under brand name Viagra) which was unsuccessful in its development as a new drug for common hypertension but became immensely successful as a drug for male erectile impotence; it then established itself as a drug to treat pulmonary arterial hypertension. Sildenafil is a potent inhibitor of cGMP-specific phosphodiesterase type5) (PDE5), an enzyme that regulates blood flow. PDE5 degrades cGMP in penile corpus cavern sum tissue. When PDE5 actions is prevented, increased cGMP level result in smooth vascular muscle relaxation and increased blood flow to the penile sponge tissue resulting in erection. Recently discovered uses of this drug include alleviation of altitude sickness and jetlag [9].Examples of drug repositioning are numerous [10-24](Table1).Many older drugs and drug candidates in development have never been fully explored. These can be exploited as resources, as they already have stores of valuable preclinical and clinical data on toxicity, safety, and dosing. Patent cliff, generics pressures, competitor adjacency threats, productivity and innovation are among the key trends that are paving the path in drug repositioning [25].

II ADVANTAGES OF DRUG REPOSITIONING OVER CLASSIC DRUG DISCOVERY PROCESS

A cost effective approach to reduce the burden of disease and increasing the productivity of the pharmaceutical industry may be new uses for existing drugs as repositioning candidates have frequently been through several phases of development (ADMET, absorption, distribution, metabolism, excretion and toxicity; EMEA, European Medicines Agency; FDA, Food and Drug Administration; IP, intellectual property; MHLW, Ministry of Health, Labor and Welfare) for their original indication. Drug repositioning offers real, valuable advantages of adopting or integrating a drug repositioning strategy. These include: i) the easy availability of active ingredients , ii) repositioned drugs have the potential to show increased success rates, decreased time to launch [26] and reduced development costs compared with conventionally developed drugs, iii) large numbers of "druggable" compounds sit in libraries with the potential to be repurposed, iv) repurposing technology will see increasing integration as a standard process of resource utilization, de-risking, and acceleration of drug development, v) repositioned drug will have passed a significant number of toxicology and safety assessments so the chances of failure are greatly reduced. Pharmaceutical companies can reduce risk and costs by finding new uses for existing products [27]. Acloser attention should be paid to the side-effects observed in trials not just to evaluate the harmful effects, but also to rationally explore the repositioning potential based on this "clinical phenotypic assay" [28]. Side-effects, the unintended consequence of therapeutic treatments, can also be seen as valuable read-outs of drug effects in humans. Some studies suggested that drugs with similar side-effect profiles may also share therapeutic properties through related mechanisms of action [28-29].

Two main selection criteria for drug repurposing candidates have been followed: i) known compounds with new targets in the first place, and ii) known mechanisms with new indications in the second place [26] Therapeutic Target Database has been developed to provide comprehensive information about efficacy targets and the corresponding approved, clinical trial and investigative drugs. Updates for facilitating target discovery and validation, drug lead discovery and optimization, and the development of multi-target drugs and drug combinations have been recently reported [30].

Screening technology platforms and drug repositioning process

Drug-target interaction is the basis of drug discovery and design. Computational methods find new uses for drugs and are important and necessary steps toward reducing the burden of disease. Two types of computational methods i) drug/target based (based on chemical or pharmaceutical perspective), ii) disease based (based on clinical perspective of a disease or its pathology and symptoatology) are used. In drug/target based methods, chemical similarity, molecular activity similarity and molecular docking are considered. In disease-based methods, side-effect similarity, shared molecular pathology and associative indicative transfer is considered [31].

In silico methods have been applied to drug repositioning projects. These include data mining, bioinformatics, and usage of novel screening platforms have been used for identification and screening of Potential repositioning candidates. Researchers reported computational methods to represent and align binding sites (Fig. 6). Ais a targeted by C to treat disease 1 and B is a therapeutic target for disease 2. Due to similarity of A to B, C could be re-positioned for disease [2].

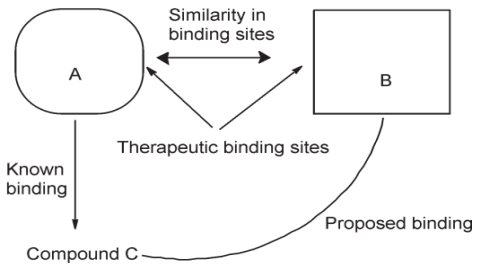

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Fig. 6. Exploiting binding sites similarities between A and B for binding of compound C.

An approach that analyzes protein structures and their binding sites to predict new proteins and off-target interactions for known compounds was reported [32]. In this context, a computational method based on full 3D comparisons of 3D structures was proposed. Using this approach, scientists described how MED-SuMo reproduces the repurposing of tadalafil from PDE5A to PDE4A and a structure of PDE4A with tadalafil. Searching for local protein similarities generated more hits than for whole binding site similarities and therefore fragment repurposing occurred more than for drug-sized compounds. This was illustrated by mining the PDB for proteins sharing similarities with the hinge region of protein kinases. The experimentally validated examples, biotin carboxylase and synapsin, were retrieved. Further to fragment repurposing, this approach was applied to the detection of druggable sites from 3D structures and was illustrated with detection of the protein kinase hinge motif in the HIV-RT non-nucleosidic allosteric site [32].

Unimodal approaches are likely to be limited by their respective shortcomings, e.g. inverse docking by scoring limitations [33]. Multimodal approaches may offer better solutions by offsetting the weakness of individual methods. In this direction, integrative analysis of chemical-genomic features and molecular networks of drug-targeted interactions, combined with structure-based high-throughput docking could be successfully applied to drug repurposing for potent inhibitor discovery. This approach was applied to identification of existing drugs as ACK1 inhibitors for prostate cancer treatment, and multiple potent inhibitors have been discovered. Repositioned marketed drugs can receive approval from the FDA in the United States through a type of NDA (new drug application) known as the 505[b][2] application. This can use the FDA's existing data to reduce the number of trials required and does not require a "right of reference" from the original applicant (repositioned pipeline drugs will use the standard 505[b][1] route). The EMEAArticle 10 of Directive 2001/83/EC are a similar approach in Europe. Researchers developed an in silico approach based on topic modelling to calculate a probabilistic topic distribution of adverse event terms appearing in the sections related to safety issues for each drug . Drugs considered to be similar by topic modeling may often be effective for the same disease and this modeling framework suggests drugs that can be repurposed, and also provides insight into the safety of repositioned drugs [34].

By combining PharmDB, an integrated tripartite database (which integrates data associated with disease indications, drug development, and associated proteins, and known interactions extracted from various established databases), with Shared Neighborhood Scoring (SNS) algorithm, researchers developed a knowledge platform to rationally identify new indications for known FDA approved drugs, which can be customized to specific projects using manual curation. PharmDB reported data is open access and can be easily explored with phExplorer and accessed via BioMart web service [35] [36]. Approaches used to identify drug repurposing opportunities with a focus on hematologic malignancies and regulatory issues were reported [37]. Drug repositioning to identify new drug candidates for Alzheimer's disease was reported [38]. The basic principles and recent advances in structure-based virtual screening have been reported. The powerful synergy of in silico techniques in drug repositioning has been demonstrated [39].

Table 1: Repositioned drugs.

Drug	original indication	New indication
Sildenafil	Angina	Erectile dysfunction, pulmonary hypertension
Thalidomide	Morning sickness	Leprosy, multiple myeloma and erthema nodosum leprosum
Raloxifene hydrochloride	Osteoporosis in postmenopausal women	Breast cancer in postmenopausal women
Amphotericin B	Fungal infections	Leishmaniasis
Lipitor	Statin class of cholesterol reducing drugs	Strokes
Aspirin	Inflammation, pain	Antiplatelet agent helping to prevent blood clotting, hint at a role for aspirin in the prevention of certain cancers
Amantadine	Influenza	Parkinson's disease
Zyban	Antidepressant	Smoking cessation
Celecoxib	Anti-inflammatory	STAT3 inhibitors for osteosarcoma therapy
Etanercept	Rheumatoid arthritis	Anti-TNF treatment for neurological disorders.
Bromocriptine	Parkinson's disease	Diabetes mellitus
Buprenorphine	Anti-analgesic	Treatment of drug addiction (for detoxification and long term replacement therapy)

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Buproprion	Depression	Smoking cessation
Finasteride	Benign prostate hyperplasia	Male pattern baldness(Hair loss)
Gemcitabine	Viral infections	Cancer
Methotrexate	Cancer	Psoriasis, rheumatoid arthritis
Amitriptyline	Antidepressant	Effective in the relief of neuropathic pain
Minoxidil	Hypertension	Hair loss
Tamoxifen	Treats metastatic breast cancers.	Bipolar disorder
Pentostatin	Leukemia	Hairy Cell Leukemia.
Lomitapide	Lower cholesterol and triglycerides,	To treat a rare genetic disorder that causes severe cholesterol problems called homozygous familial hypercholesterolemia.
Rapamycin	Prevent organ transplant rejection.	Autoimmune Lympho-proliferative Syndrome and lymphangioleiomyomatosis, a rare lung disease.
Colesevelam	Low-density lipoprotein cholesterol lowering agent	Improve glycemic control in adults with type 2 diabetes mellitus
Rogaine	High blood pressure	Hair loss
carmustine	Oncology	Anti- amyloid beta drug (AD)
Memantine	Anti-influenza	Parkinson disease
Donepezil	Alzheimer's	Other neurological disorders
Depoxetine	Analgesia	Premature ejaculation (PE) in men
Cymbalta	Antidepressant	Fibromyalgia, a long-term condition which causes pain all over the body
Gemzar	antiviral	Cancer
Bexarotene	Used to treat patients with T cell lymphoma	Pathological and behavioral improvements in transgenic mouse models of AD, Bexarotene's effect in human AD patients is unknown

Ibuprofen	Anti-inflammatory	Parkinson's disease
Nelfinavir	AIDS	Cancer
Gabapentin	An epilepsy drug	Anxiety disorders and neuropathic pain
Pregabalin	An epilepsy drug	Anxiety disorders and neuropathic pain
Ritonavir	AIDS	Tuberculosis(TB)

Orlistat	Obesity	Alzheimer's disease
Ropinirole	Parkinson,'s	Angina
Targretin	Anti-cancer	Work synergistically with 5-Fluorouracil in treating colorectal cancer.
Carvedilol	Treat heart failure and hypertension	At specific regime dosages, RDC5 also functions to delay ageing related phenotypes in cultured mammalian tissues.
levo-Leucovorin	The rescuing of patients from high-dose methotrexate treatment.	Tuberculosis
RDC5	Anti-ageing factor	Muckle –Wells syndrome
Iproniazid	Antidepressant	Pertuzumab and trastuzumab have a synergistic effect.
Canakinumab	RA in a Phase II trial	Fibromyalgia
Pertuzumab	HER2-positive metastatic breast cancer	Major depression and anxiety disorders
Milnacipran	Antidepressant	Restless leg syndrome
Paroxetine hydrochloride	An immediate-release formulation	Immuno-stimulant used to multiply hematopoietic stem cells in cancer patients
Pamipexole	Parkinson's disease	Multiple myeloma
Plerixafor	HIV	Chronic musculoskeletal pain.

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Plerixafor	HIV infection	Prevention of chronic migraine.
Duloxeti	Major depressive disorder, neuropathic pain	Glioblastoma
Onabotulinumtocin	Cervical dystonia, severe primary axillary hyperhidrosis and upper limb spasticity	Premenstrual dysphoria
Fulvestrant	Cancer	Antiarthritic
Fluoxetine	Depression	Eyelash growth
Hydroxychloroquine	Antiparasitic	Antipruritic
Bimatoprost	Glucoma	Certain types of tremor associated with multiple sclerosis
Doxepin	Antidepressant	may provide a new option for treating advanced Pulmonary Arterial Hypertension.
Isoniazid	Tuberculosis	Pleural effusion
Imatinib	Certain types of leukaemia and soft tissue sarcoma	Renal transport
Bleomycin	Various cancers	Tuberculosis
Azathioprine	Immunosuppressant Rheumatoid arthritis	Attention deficit hyperactivity disorder
Cycloserine	Urinary tract infection	Migraine prophylaxis
Atomoxetine	Antidepressant	Acute promylelocitic leukemia
Propranolol	Hypertension	Various cancers
Retinoic acid	Acne	Various cancers
Rituximab	Rheumatoid arthritis	Mediterranean fever, recurrent paricarditis
Interferon alfa	Hepatitis B and C	Sleeping sickness
Colchicine	Gout	HIV/AIDS
Eflornithine	Unwanted facial hair	Metastatic breast cancer
Zidovudine	Cancer	Sedative and antinausea effects when given at higher dosages, anti-emetic, chlorpromazine's role in inhibition of an important mitotic kinesin (Combination, CRx-026, inhibits the growth of tumor cell lines *in vivo* more effectively than either pentamidine or chlorpromazine alone)
Avastin	Metastatic colon cancer and nonsmall cell lung cancer	
Chlorpromazine	Antipsychotic action, Treat schizophrenia, Cancer, Restless Leg Syndrome and SSRI-induced sexual disfunction	
Xalkori	Adult lung cancer	Two rare childhood cancers, childhood form of lymphoma, neuroblastoma
Clofazimine	Leprosy	Drug-resistant tuberculosis
Mirapex	Parkinson's disease	Restless Leg Syndrome
Duloxetine	Antidepressant	Fibromyalgia
Azidothymidine	Cancer	HIV
Galantamine	Glaucoma	Alzheimer's disease
Cicletanine	Antihypertensive	Pulmonary Hypertension
Benzbromarone	Gout	MRSA Infections
Clioquinol	Antiprotozoal	Neuroprotection
Astemizole	Anti-histamine	Malaria
Nilotinib	Leukemia	Alzheimer's disease, Parkinson's disease

III DRUG REPOSITIONING FOR RARE/ORPHAN AND NEGLECTED DISEASES

An orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease. There is enormous need and opportunity to discover therapeutics for rare or orphan diseases. However, pharmaceutical companies are not likely to engage in drug repositioning efforts for rare childhood diseases. Drug repositioning has the potential to identify medications for rare and neglected diseases. Combining current in silico technologies with chemical information, biological activities data, and in vitro screening data could improve and enhance repositioning efforts specifically

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for rare and neglected diseases. Researchers introduced and recommended the Collaborative Drug Discovery database which is particularly useful for neglected diseases [40]. In addition, Blatt et al. [41] found that approximately 10% of drugs with primary uses in pediatrics have been repositioned in pediatric hematological oncology or other pediatrics uses. Breast cancer drug Fulvestrant was found as a potential treatment against glioblastoma. Researchers described a novel computational workflow for designing therapy using Ariadne Genomics Pathway Studio software. They used publically available microarray experiments for glioblastoma and automatically constructed ResNet and ChemEffect databases.

Computational techniques for systematic analysis of transcriptomics (Connectivity Map, CMap), side effects, and genetics (genome-wide association study, GWAS) data to generate new hypotheses for additional indications were explored. In addition, data domains such as electronic health records and phenotypic screening are promising for novel computational repositioning methods [42]. Personalized drug repositioning could be particularly rewarding for diseases that are rare or have specific mutations. An increasing number of drugs were approved for rare cancer subtypes, thus it is expected that personalized medicine and repositioning approaches are poised to significantly modify the diagnosis of diseases, deduce treatments and develop new drugs [43].

Drug repositioning through pharmacological spaces integration based on networks projections approach can be successfully applied to discover potential drug candidates for novel therapeutic indications [44]. Widely accepted in medical practice, off-label prescribing is not regulated by the FDA. In some cases, doctors in clinical practice prescribe medications off-label—that is, for uses other than those approved by the FDA. Examples include albuterol which is approved for treating asthma but is sometimes prescribed for patients with chronic obstructive pulmonary disease. The anticonvulsant gabapentin is often prescribed for pain. The biological processes associated with diseases along with their known drugs and drug targets predicted Biological Process-Drug relationships. Network analysis was used to further refine these associations to eventually predict new Disease-Drug relationships [45].

Bioinformatics-based approaches offer systematic insights into the complex relationships among drugs, targets and diseases which are necessary for successful repositioning. The key bioinformatics steps essential for discovering valuable repositioning methods include: repurposing with a purpose, repurposing with a strategy and repurposing with confidence which can be used alongside currently available resources to improve *in silico* drug repositioning [46].

A two-step method for drug repositioning based on the protein -protein interaction network of genes shared by two diseases and the similarity of drugs prescribed for one of the two was proposed. At the first step, scientists applied the proposed two-step method to four different types of diseases: hypertension, diabetes mellitus, Crohn disease, and autism. Some repositioning candidates were found both at the first and second steps. However, experimental investigations are required to verify whether the candidates can actually be repositioned. Scientists are planning to fully automatize the repositioning processes [47].

IV SYSTEMS PHARMACOLOGY AND DRUG REPOSITIONING

PROMISCUOUS is a database for network based drugs repositioning and provides a public resource to predict off-target effects by integrating relationship between drugs, targets, and side effects [48]. Researchers reported strengths and weaknesses of academic-based drug repositioning research. Translational, target and disease foci were found strategic advantages fostered by close proximity and frequent interactions between basic and clinical scientists, which often result in discovering new modes of action for approved drugs. The development of a more streamlined regulatory process worldwide, and the development of precompetitive knowledge transfer systems such as a global healthcare database focused on regulatory and scientific information for drugs worldwide, is among the ideas proposed to improve the process of academic drug discovery and repositioning [49]. Personalized medicine and drug repositioning both aim to improve the productivity of current drug discovery pipelines and can alter the way we diagnose diseases, infer treatments and develop new drugs [50].

V GENOME-BASED DRUG REPOSITIONING APPROACHES

Every biological state can be described by a given gene expression signature [51]. Genome-based drug repositioning approaches include: disease signature, drug response signature. It is considered that drugs "reverting" a phenotype signature "revert the phanotype". Drugs eliciting similar transcriptional responses could share therapeutic effect [52]. Alibrary of 2,687 existing drugs was created and screened for inhibitors of the human malaria parasite *Plasmodium falciparum*. The antihistamine astemizole and its principal human metabolite were found promising new inhibitors of chloroquine-sensitive and multidrug-resistant parasites, and they showed efficacy in two mouse models of malaria [53]. Network-based methods have been successfully applied to prioritize novel disease-associated genes. Common to all methods is the understanding that novel disease-associated candidates are in close overall proximity to known disease genes. However, the relevance of these methods to the prediction of novel drug targets has not yet been assessed.

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VI DRUG REPOSITIONING IN THE TREATMENT OF MALARIA AND TUBERCULOSIS (TB)

Some examples of repurposing of drugs in the treatment of TB, newer candidates for repurposing for which there is already preliminary evidence of activity and possible new options need further study. Researchers reported how drug repositioning has been used in the past to discover antimalarial and anti-TB drugs, and summarized strategies that can lead to the discovery and development of new drugs. For example, sulfa-based drugs for malaria, and fluoroquinoline for TB were initially developed for the treatment of non-malaria or TB diseases [54]. Current anti-tuberculosis therapeutics is not sufficiently effective against drug-resistant tuberculosis. Clofazimine could be considered as an additional therapeutic option in the treatment of drug-resistant tuberculosis. However, the optimal dose of clofazimine and duration of use require further investigation. In the field of TB, there have been several examples in recent years of drug repositioning approach leading to the use of drugs for which there is undeniable evidence of efficacy in the treatment of the disease, the best example being the fluoroquinolones, which were not developed originally to treat TB [55].

VII DRUG REPOSITIONING FOR TREATMENT OF ALZHEIMER'S DISEASE

Due to the recent failures of various novel disease-modifying therapies in clinical trials for Alzheimer's disease, a complementary strategy based on repositioning drugs that are approved for other indications could be attractive. Indeed, a substantial body of preclinical work indicated that several classes of such drugs have potentially beneficial effects on Alzheimer's-like brain pathology, and for some drugs the evidence is also supported by epidemiological data or preliminary clinical trials. Researchers highlight several compounds for which sufficient evidence is available to encourage further investigation to clarify an optimal dose and consider progression to clinical trials in patients with Alzheimer's disease [56]. The clinical relevance of an attractive candidate compound carmustinee reported in a recent paper [57] as well as perspectives regarding the possible repositioning of oncology drugs for the treatment of AD were reported [58]. Researchers from Georgetown University successfully used small doses of the drug nilotinib, used to treat chronic myelogenous leukemia in order to eliminate abnormal protein build-up in the brains of mice [59].

VIII REGULATORY ISSUES RELATED TO DRUG REPURPOSING

In the United States, there are three common paths available to obtain approval for drug products: 505(b)(1), 505(j), and 505(b)(2). The 505(b)(2) pathway focuses on a new formulation or new use of an already approved drug product. In this pathway, the previous findings of safety and efficacy of known drugs can be leveraged so that only studies necessary to support the safety and/or efficacy of the new indication need to be conducted. In other regions, including Canada, Australia, and Europe, regulatory paths similar to the 505(b)(2) mechanism exist. Like the United States, the regulatory agencies will accept data from the published literature and drug product monographs to support trials of drug repositioning. Three dedicated extensions to the risk-adjusted net present value calculation for drug discovery projects were reported. The process of setting parameters for the models and their overall utility has been discussed [60] Researchers reported systems biology-based methods for repositioning known pharmaceutical compounds to new indications (anti-breasttumor initiating cell, orphan diseases), through the identification of network-based signatures. Methods for identifying anti-breast tumor initiating cell-based therapeutics were reported [61].

The drug-target bipartite network-based inference method could be a useful tool for fishing novel drug-target interactions in molecular poly-pharmacological space [62]. In selecting a drug for successful repositioning, careful consideration must be given to sources of potential competition in view of patent and regulatory exclusivity available to protect the repositioned drug product in the marketplace. The strongest and longest lived exclusivity should attach to resurrected APIs that have never been on the market, or have been recalled from the market (so no generic substitutes are available), and are being applied to new indications.

Drug repositioning is a major approach to identify novel treatments for Duchenne muscular dystrophy. DART Therapeutis Inc. and Biovista have entered into a research collaboration to identify and develop novel drug repositioning candidates for using Biovista's Clinical Outcome Search Space (COSS) ™ technology. Identification of novel repositioning candidates will be carried out by Biovista and DART Therapeutics will have the option to select a certain number for further development.

Recently, signatures have been used as proxies of clinicopathological phenotypes. Drug–drug/drug–disease 'connections'have been inferred by signature matching. Researchers described related methods, case studies and resources while discussing challenges and benefits of exploiting existing repositories of microarray data that could serve as a search space for systematic drug repositioning [63].

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IX DRUG REPOSITIONING AND INTELLECTUAL PROPERTY CHALLENGES

Successful repositioning of a drug product depends on integration of both intellectual property and regulatory exclusivities. Patent strategies directed to protecting new formulations, indications and methods of use, when combined with strategically repositioned products, can provide effective and long lasting product exclusivity even where the underlying API, and the original formulations, indications and methods of use are off-patent. Strategies that include IPand legal input can transform an apparently nonviable drug repurposing project into a success [64-65].

X CONCLUSION AND PERSPECTIVE

Although medical science and technology is advancing by leaps and bounds, there remain many illnesses with no effective cure. Market pressures have driven pharmaceutical companies to reassess their current drug development model. The most fruitful basis for the discovery of a new drug is to start with an old drug. There are likely many undiscovered uses of known (safe and approved) drugs to new therapeutic indications. In this context, drug repositioning is promising and valuable as developing a drug de novo is a lengthy and costly venture. This approach has opened up a new source of revenue to large, medium and small Pharma companies as well as attracting venture capital funding. Many drug targets were found involved in multiple biological pathways, and, as such, can be repurposed against that same target acting in a different disease or biological process. The safety advantage, the money savings advantage, the market potential advantage, return on investment potential, the out-licensing potential and motivations are among significant advantage of drug repositioning over traditional drug development. One limitation is the dependence on public domain data that can have an impact on drug repositioning as there is a risk that their discovery may be found simultaneously by others, and thus repositioned drug should have at least some patent protection. In addition, it may be difficult for drug repositioning companies to get funding and many may be more familiar with traditional drug development.

Anew drug Xalkori, originally targeted as a treatment for adult lung cancer, showed great promise against two rare childhood cancers. This drug eradicated the cancer in seven of eight children with a childhood form of lymphoma and in two other children with a lethal form of anervous-systemcancer called neuroblastoma. Sodium nitrite (antidote to cyanide poisoning) is under testing as a treatment for the chronic leg ulcers associated with sickle cell and other blood disorders. Physicians Group Calls on the FDA to repurpose existing drug Enbrel (already approved for the treatment of rheumatoid arthritis and psoriasis) for thetreatment of TBI, stroke and Alzheimer's disease. Public available gene expression massive data potential has not been fully exploited. Genome-wide signature-matching methods have been used to identify drug repositioning opportunities. Academia, industry, and non-profit charitable organizations should work together to enhance drug repurposing. In addition to providing new treatments, repurposing can assist in dissecting complex disorders, discovering molecular targets, and unraveling disease processes. Drug repositioning may be fruitful for economic and public health for Pharmacy companies, regulatory agencies, patients and taxpayers. The scope of repurposing should be extended to the repurposing of excipients as therapeutic agents as NIH reports on repurposing cyclodextrin as a potential therapy for Niemann-Pick type C1 are there. Thus, drug repurposing holds much appeal and has the potential to accelerate the drug discovery.

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