Drug repositioning: Achievements, advancements and barriers

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Abstract
The humongous cost and long-time duration of new drug development surpasses the rewards in form benefit to patients and cost recovered by the pharmaceutical firms. The problem which this situation gives rise to are productivity gap, pressure by sky soaring prices, incompetency with respect to beneficial generics and issues from regulatory authorities. One advanced approach of drug development which shows potential to tackle these issues is what we refer to as drug repositioning. Drug repurposing is an economical option, time duration to bring a new drug to the market is lesser. There are different approaches to drug repositioning including two broad categories – data driven (computational approaches) and experimental approach. Data driven approaches include - signature matching, molecular docking, genetic mapping, pathway mapping, retrospective clinical analysis, novel data sources while the experimental approach include assays defining target drug interactions, phenotypic screening. Drug repositioning is associated with challenges like chances of failure, regulatory barriers, patency issues and lack of financial incentives. For maximizing the drug repositioning process and to increase its productivity challenges posed to drug repositioning need to be addressed.

Keywords: Drug repositioning, Computational approach, Experimental approach.

Introduction
The cost incurred in developing a drug has doubled and the success rate of approval of a drug to the market has been decreasing.[1] The huge cost and long duration of a new drug development process outperforms the benefits obtained by the new drug in both the outcomes of clinical benefits and cost recouped by the pharmaceutical firms. Consequently the issues raised by this situation is efficiency hole, expensive drug costs, unbeatable competition with the generics and regulatory issues.[2,3] With time evolution of the technologies and research has brought in new dimension to the drug development process. One advanced approach of drug development which shows potential to tackle these issues is what we refer to as drug repositioning.

Drug repositioning has numerous synonyms – drug retasking/ drug reprofiling/ drug repurposing. Drug repositioning is the science of identifying and putting to use an approved drug for an indication other than what it was originally introduced for.[4] Drug repositioning has advantages over the traditional drug development process

1. Firstly, drug repositioning is an economical option when it comes to the expenditure in phase one and phase two trial (although the cost of phase three and regulatory remains the same.[5] The overall cost of developing the drug for the new indication is significantly lower as compared to the traditional approach.
2. Secondly, the time required for bringing a new drug to the market is lesser compared to the traditional approach where almost 12-17 years are taken to bring the drug to the market. The drug repositioning process is completed in 3- 12 years3
3. Thirdly, risk of failure in a drug being repositioned is lesser due to safety issues are very low as the candidate drug has already been tested in the preclinical phase and clinical phase one and phase two trials during the initial introduction in the market.

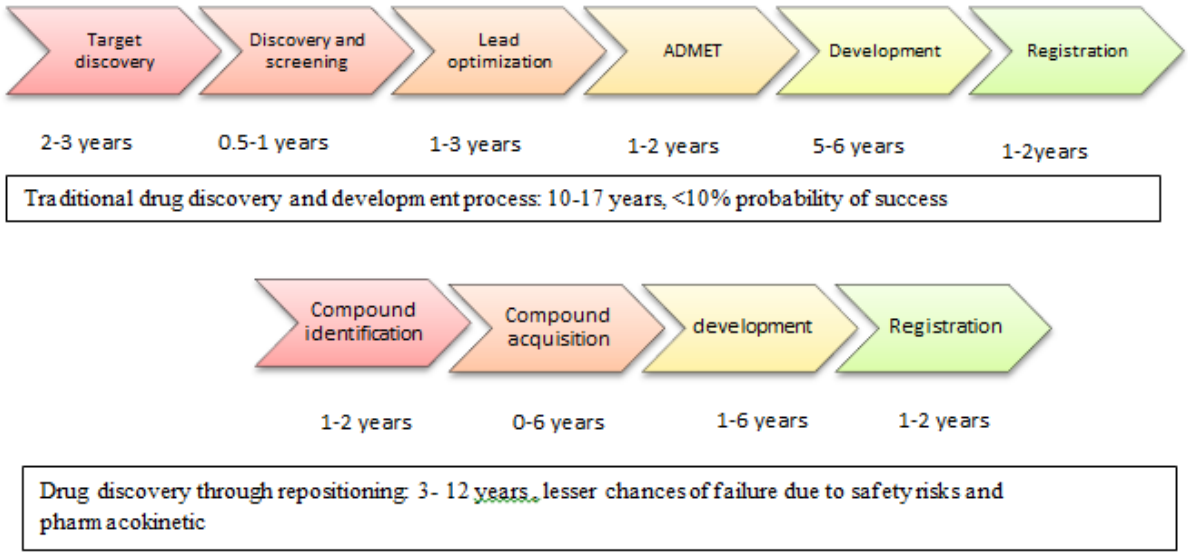

Fig. 1: Comparison of time taken for a traditional new drug development process versus repositioned drug development process (Adapted from *Ashburn*)

Table 1: Examples of successfully repositioned drugs in the past[6,7]:

Drug	Original Indication	Additional Indication
Acetyl salicylic acid	Analgesic	Antiplatelet
Allopurinol	Cancer	Gout
Amantadine	Antiviral	Parkinson's disease
Amphoterecin	Fungal infection	Leishmaniasis
Arsenic	Syphilis	Leukemia
Atomexitine	Antidepressant	Attention deficit hyperkinetic disorders
Beta Blocker	Arrhythmia/angina	Hypertension
Bromocriptine	Parkinson's disease	Diabetes mellitus
Bupropion	Depression	Smoking cessation
Colchicine	Gout	Recurrent pericarditis
Doxepin	Antidepressant	Topical antipruritic
Finasteride	Prostate cancer	Hair loss
Gabapentin	Epilepsy	Neuropathic pain
Gemcitabine	Antiviral Candidate	Cancer – Pancreatic cancer, bladder cancer
Hydroxychloroquine	Antiparasitic	Arthritis
Lidocaine	Local anaesthetic	Antiarrhythmic
Methotrexate	Cancer	Psoriasis, Rheumatoid arthritis
Miltefosine	Cancer	Visceral leishmaniasis
Minoxidil	Hypertension	Hair loss
Naltrexone	Opioid addiction therapy	Alcohol withdrawal therapy
Nitric oxide	Angina	Pulmonary Hypertension
Pametrexed	Mesothelioma	Lung Cancer
Pencillamine	Copper chelating agent	Antirheumatic
Raloxifine	Contraceptive	Osteoporosis
Retenoic acid	Acne	Acute Promyelocytic leukemia
Ropirinole	Parkinson's disease	Restless leg syndrome
Sildenafil	Angina	Erectile dysfunction
Thalidomide	Sedative/anti emetic	Cancer – Non Hodgkins lymphoma
Tretinoin	Severe acne	Leukemia
Zidovudine	Cancer	HIV/AIDS

Table 2: Examples of drugs which failed in repurposing

Drug Name	Original indication	New indication	Approach used for repurposing	Outcome of repurposing
Latrepirdine	Antihistamine	Huntington's disease	Pharmacological analysis	Phase III trial (known as HORIZON) by Pfizer and Medivation was unsuccessful[28]
Ceftriaxone	Antibiotic	Amyotrophic lateral sclerosis	High through put drug screening in animal models	Phase III trial failed to show efficacy[29]
Topiramate	Antiepileptic	Inflammatory Bowel Disease	Transcriptome based signature Matching	Successful in a rodent model of inflammatory bowel disease but failed in a retrospective cohort study; no randomized clinical trial conducted to date[30]

Drug repositioning in the past could be thought of either as serendipity or utilization of a side effect into desirable therapeutic effect. Advancement of technology has brought into picture various efficient and robust technologies have aided target identification and hypothesis generation. There are different approaches to drug repositioning including - Two broad categories – computational approaches and experimental approach

Data driven approaches

1. Signature matching
2. Molecular docking
3. Genetic mapping
4. Pathway mapping
5. Retrospective clinical analysis
6. Novel data sources

Experimental Approaches

1. Assays defining target drug interactions
2. Phenotypic screening

Data driven approaches: More commonly referred to as the computational approach. In a computational approach data obtained through the systematic analysis of various data available in the form of chemical structure of the drug, phenotype, genotype, metabolomic data from diseases is analysed and any hint to satisfying the potentials of a drug target or hit is used for generating a new research hypothesis.[8]

1. **Signature matching**: A signature is a single/multiple set of characteristics in a definite pattern unique to a gene which might be a physiological attribute or might have occurred after a pathological insult.[9] A signature remains fixed for a diseased condition. This property is exploited for discovering new targets by matching the signature of one drug over that of another drug, disease or genotypes. The technique which is used by signature matching is the Signature Reversion Principle (SRP). SRP is the property of a drug to revert the expression of a gene proved to be causal of a disease characteristic (proved by a negative correlation between the gene expression and the drug). Examples of drug repositioned through signature matching are topiramate, belongs to the class of antiepileptics which has been repositioned for use in Inflammatory bowel disease(IBD).[10] Another successfully repositioned drug by signature matching is Fasudil, a potent Rho kinase inhibitor and vasodilator, is up for trails for treatment of amyotrophic lateral sclerosis(ALS).[11]
2. **Molecular Docking:** The molecular docking approach in computational methods acts by virtual screening of the candidate compounds to be repositioned. In molecular docking the structure based compatibility between the drug and the receptor molecule (mostly a protein) is assessed. Post docking the stability and effect of the drug-complex generated as a result of the interaction is analysed.[12] A complex with a higher stability and desirable response post docking is considered as a favourable candidate for repositioning. This structure based approach can be done in two ways[13]
   a. **Conventional docking:** One target is interrogated for multiple ligands (one drug – multiple receptor approach)
   b. **Inverse docking:** One ligand is interrogated for multiple targets (one receptor- multiple drug approach)
3. The contribution of molecular docking in drug repositioning is the discovery of mebendazole, an antiparasitic drug in inhibiting the Vascular Endothelial Growth Factor(VEGF) in the process of angiogenesis.[14]
4. **Genetic mapping:** Genetic mapping is the method by which the exact location of the genes in entire chromosome is determined. The presence or absence of the culprit gene and its locus if defined a priori can help predict targets for new drug therapy. Large genetic studies, like Genome Wide Association Studies (GWAS) has helped to identify genetic variants for various diseases.[15] Drugs can be designed which act as activators or inhibitors of these genes and modify genetic response. Secukinumab an antibody which targets IL -17A originally indicated for the treatment of psoriasis, Rheumatoid arthritis and uveitis has been found to be in association to another IL 23A and has

been repositioned for the treatment of another inflammatory disorder ankylosing spondylitis.[16]

5. **Pathway mapping:** Drug targets identified by genetic mapping whose association with the disease has been established might always not be suitable drug targets. Under such condition the upstream or downstream pathway of gene might give additional information of targets which can be repositioned.[17] To get this information a new technology Network Wide Association Study(NetWAS) which uses GWAS for nominally significant genetic associations along with tissue specific network to identify genes that are associated with the study.[18]
6. **Retrospective clinical analysis:** Data obtained from the retrospection of clinical data already available in the form of electronic health records, data from the trials, registries, hospital information sources are huge sources of information which can be employed for creating new drug targets from past experiences.This knowledge based approach from a priori knowledge of adverse drug reaction, drug target interaction, FDA labels has been used in the past. Discovery of Sildenafil for erectile dysfunction,[19] aspirin for the prevention of cardiovascular disease or colorectal carcinoma,[20] raloxifine for breast cancer,[21] propranolol for osteoporosis.[22]
7. **Big Data:** Advances in scientific technologies and innovations are generating huge data sets and information about the genetic, phenotypic, transcriptomic, metabolomic data from scientific studies. Also data from clinical trials and studies is easily available which adds information that can update a drugs profile for its exploration. But the data which is being collected through these techniques is huge enough for traditional processing, integrating and analysing techniques to handle.[23] All this data is referred to as the BIG DATA. Drug repositories and databases for data driven therapeutic target identification and data driven drug identification, resources for computational prediction of drug toxicity are various yields of Big data.[24]

Experimental approaches

1. **Assays defining target drug interactions:** Drugs target interaction to investigate or prove a new therapeutic target by use of assays like Cellular Thermo Shift Assay[7] and chemical genetics are novel and efficient introductions to the evolving scientific technology.
2. **Phenotypic screening:** Phenotypic screening is concerned with the identification of molecules and targets which result in phenotypes of desired outcome associated with a disease. In drug repurposing the compound is already proved investigational product, assigning an in vitro cell based assay or any phenotypic screening test if the results are positive the candidate drug can be readily approved for repurposing.[25] Zebra fish is an excellent example of in vivo phenotypic screening which has been widely used for screening of various investigational drugs.[26] The antineoplastic property of disulfiram (originally a drug used for treatment of alcohol addiction) was discovered by a cell based high throughput screening approach.[27]

Challenges and Barriers to drug repositioning

The drug repositioning offers major advantages but certain challenges which remain associated with it and need consideration are:

1. Chances of failure: There are numerous advantages of drug repositioning, but like every other process failures are also reported along with drug repositioning. Examples of drug candidates that have failed are (Table 2)
2. Regulatory barriers: As mentioned, a drug repositioning drug development process is of shorter duration as compared to a new developed drug as we can bypass the Phase I and II on the basis of data already available for the original indication of the studies. In certain cases the regulatory bodies might not approve to go ahead with the existing data and may demand additional phase I and phase II trials which will increase the expense, duration of the study. Thus compromising with the major advantages of time, money and also increasing the risk of regulatory disapproval.
3. Patency Issues: Obtaining rights for patents for a repositioned drug might be a big hurdle. The market analysis, regulatory requirements are all worked upon since the beginning of the process. But since the drug already exists in the market for some other indication, the owner pharmaceutical firm might pose issues in obtaining patents.
4. Weak financial incentives: The return obtained by a repurposed drug is not rewarding enough so as to encourage further investments. This challenge is more often witnessed if the repurposed drug is indicated for a rare or neglected disease.[31]

Conclusion

Drug repositioning has advanced by leaps and bounds since the advent in the biotechnology. Serendipity and the hit and trial methods have been largely superseded by newer approaches that are data driven, experimental or computational – experimental collaborated. Despite the advantages that drug repurposing offers to the development process of a drug for new indications the involvement of the pharmaceutical firms has not been satisfying owing to numerous hurdles which come along the way of drug repositioning. There is a need of encouraging and promoting drug repurposing ideas, research and strengthening funding. The works done in the attempts taken to repurpose a drug should be incentivized.

Conflict of Interest: None.

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