RESEARCH PAPER | Medical Science | Volume : 4 | Issue : 8 | August 2014 | ISSN - 2249-555X

Drug Repositioning : Old Drugs For New Indications

KEYWORDS: repositioning, drug development, repurposing

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ABSTRACT *The process of finding new uses of existing drugs outside the scope of the original indication is known as drug repositioning. Drug repositioning is a low risk, high reward strategy as compared to the de novo drug discovery. New drug discovery is a very costly and time consuming process. It is associated with high failure rates, high cost, poor safety and bioavailability, limited efficacy, lengthy design and testing process. Now many pharmaceutical companies are trying to reposition the existing drugs for various indications. It is less costly, less time consuming and relatively safe method. Though there are intellectual property(IP) related issues, which can hinder the repositioning process. There are many examples of drugs, which are successfully repositioned.*

Introduction

De novo drug discovery is very costly and time consuming process. The discovery of one drug takes 10-17 years, with 1.3 billion USD as overall estimate. But still there are less than 10% chances of success. The process is mainly divided into 3 stages, discovery, preclinical stage and clinical stage. The discovery stage involves identification and screening of new compounds, and includes target discovery and validation, lead identification and lead optimization. In preclinical stage, the compounds are screened in vitro and in vivo (toxicology, efficacy and interactions study). In clinical studies, the effects of drugs are observed on human beings in clinical trials. There are high chances of failure and adverse effects associated with this process. Only one of every 5000–10,000 prospective anticancer agents receives FDA approval and only 5% of oncology drugs entering Phase I clinical trials are ultimately approved.[1]Progressively increasing failure rates, high cost, poor safety, poor bioavailability, limited efficacy, lengthy design and testing process associated with drug development have necessitated alternative approaches to drug discovery.

Another strategy for drug discovery is drug repositioning (also called as repurposing, redirecting, reprofiling, retasking, therapeutic switching, indication switching or new uses for old drugs). The process of finding new uses of existing drugs outside the scope of the original indication is known as drug repositioning.The concept of repositioning evolved in the early 1990s. This stems from the fact that different diseases share common molecular pathways and targets in the cell. Common molecular origins of different diseases have been discovered through advances in genomics, proteomics, and informatics technologies and through the development of analytical tools that allow researchers to screen large numbers of existing drugs simultaneously against a particular disease target. The existing drugs include marketed drugs as well as failed compounds. It gives a new life for shelved or abandoned drugs that have never been on the market and extended life for marketed drugs via new indications or formulations. The duration of the process is less compared to *de novo* drug discovery (3-12 years). The pharmacokinetic and safety uncertainty is reduced and there is 25% overall probability of success.[2-4]

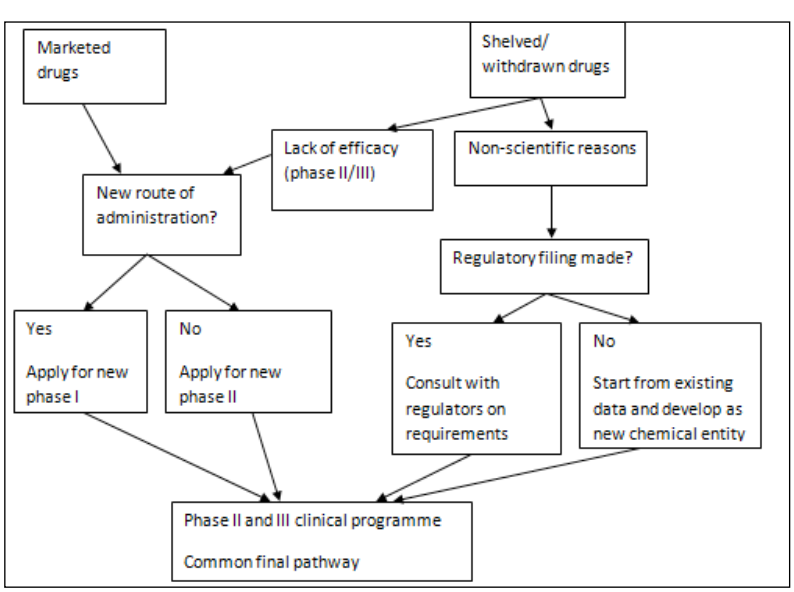

Figure 1 : Drug repositioning Regulatory Pathways For tha marketed versus shelved / withdrawn drugs

Volume : 4 | Issue : 8 | August 2014 | ISSN - 2249-555X

Reduced risk strategy for developing new drug products:[3-4]

Drug repositioning is a low risk, high reward strategy as compared to *de novo* drug discovery, which is high risk, high reward strategy. Major pharmaceutical companies need to reduce development costs and development risks. They need to speed the drug development and cope up the market competition.

In addition to repositioning actively developed or marketed drugs, there are 2000 failed drugs sitting in drug libraries that have the potential to develop into successful repositioned drugs. The list of failed drugs is increasing at the rate of 150-200 compounds per year. Regulatory pathways for the marketed versus shelved/ withdrawn drugs are described in Fig1.

Advantages of drug repositioning:[2,4]

Drug repositioning helps to recover the existing investment. It saves time and money and there is better utilization of sources. The cost to relaunch repositioned drug is around 8.4 million USD, while to relaunch the new formulation of existing drug in its original indication is 41.3 million USD. The development of new drug costs more than 1.3 billion USD. So to bring the repositioned drug successfully to the market is much less costly than that of new drug. As mentioned previously, it reduces developmental risks as the repositioned drug has already passed a significant number of toxicity and other tests. When such repositioned drugs enter clinical trials, they compete with non-repositioned drugs in terms of efficacy, not in terms of safety. As safety accounts for approximately 30% of clinical trials drug failures, this is a significant development advantage that repositioned drugs enjoy.

Potential for market success of any drug depends on many factors, including market need, competition, differentiation, excellence, IP barriers, payer acceptance, compliance and a successful market strategy. These factors apply for repositioned drugs in the same way as that of the new drugs. So the repositioned drugs have the same market potential as that of new drugs in the market. The repositioned drugs can also get the good market returns on the investment; the examples are sildenafil and thalidomide.

Examples of successful drug repositioning:[2,4]

Thalidomide was used in pregnant women to prevent morning sickness. But it was withdrawn after reporting the cases of phocomelia in newborn babies. It was again repositioned for the treatment of erythema nodosum leprosum and multiple myeloma.

Minoxidil is potassium channel opener, which was approved for the treatment of hypertension. It was again repositioned in 1998 by USFDA for the treatment of male pattern baldness, based on the finding that it promotes the facial hair growth.

Sildenafil is phosphodiesterase 5 inhibitor; it was initially used for treatment of angina. But phase I trial findings showed that it produced penile erection in subjects. So it was switched for the treatment of erectile dysfunction.

Raloxifene is a selective estrogen receptor modulator. It was approved by USFDA for the treatment of osteoporosis after initial trials for breast cancer.

The more examples of drug repositioning are given in the table 1 & 2.

Table 1.List of successfully repositioned drugs[2-5]

Drug	Original indication	New indication
Amantadine	Influenza	Parkinson's disease
Amphotericin	Antifungal	Leishmaniasis
Aspirin	Inflammation, pain	Antiplatelet
Bromocriptine	Parkinson's disease	Diabetes mellitus
Bupropion	Depression	Smoking cessation
Colchicine	Gout	Recurrent pericarditis
Finasteride	Benign prostatic hyperplasia	Male pattern baldness
Gabapentin	Epilepsy	Neuropathic pain
Methotrexate	Cancer	Psoriasis, rheumatoid arthritis
Miltefosine	Cancer	Visceral leishmaniasis
Minoxidil	Hypertension	Male pattern baldness
Propranolol	Hypertension	Migraine prophylaxis
Sildenafil	Angina	Erectile dysfunction, pulmonary hypertension
Thalidomide	Morning sickness	Erythema nodosum leprosum
Zidovudine	Cancer	HIV/AIDS

Table 2.Potential drug candidates for repositioning[2-5]

Drug	Original indication	Potential use
Bimatoprost	Glaucoma	Promoting eyelash growth
Ceftriaxone	Antibacterial	Amyotrophic lateral sclerosis
Clofazimine	Leprosy	Tuberculosis
Colesevelam	Hyperlipidemia	Type 2 dm
Dapsone	Leprosy	Malaria
Disulfiram	Alcoholism	Melanoma
Minocycline	Antibacterial	Amyotrophic lateral sclerosis
Naproxen	Inflammation, pain	Alzheimer's disease
Nortriptyline	Depression	Neuropathic pain
Statins	Hyperlipidemia	Inflammatory and autoimmune diseases
Zileuton	Asthma	Acne

Approaches of drug repositioning:[6]

1. Drug focus:

Structural features of molecules already approved for particular indications can help to identify active compounds that were originally developed for different indications. It is based on the concept that single drug often interacts with

Volume : 4 | Issue : 8 | August 2014 | ISSN - 2249-555X

multiple targets. e.g. Repositioning of sildenafil, previously used to treat angina, in erectile dysfunction.

2. Target focus:
To find new indications when primary and/or secondary targets of compounds are known, implies that targets relevant to one disease or biological process are often involved in several biological processes. e.g. repositioning of aspirin as an antithrombotic therapy following identification of its action against prothrombic thromboxane A2 activity in platelets

3. Disease focus:
Experimental data related to disease (e.g. omics data collected from patients) or knowledge on how drugs modulate phenotypes related to disease (e.g. known from their side effects) is utilized in disease focused approaches.e.g. Sunitinib and dasatinib for breast cancer brain metastases.

Sources for repositioning:[2]

- **Drugs in clinical development**

For drugs whose mechanism of action is relevant to more than one disease entity, clinical development for the new indication and the original indication can be carried out simultaneously. e.g. Duloxetine, a nonselective serotonin reuptake inhibitor, was under trials simultaneously for depression and stress urinary incontinence.

- **Drugs that failed to demonstrate efficacy for a particular indication** during phase II or III clinical trials but which have no major safety concerns, can be the candidates for repositioning. Pharmaceutical companies shelve 150-200 compounds every year, 50% of which after phase II due to efficacy issues.
- **Drugs that have been discontinued for commercial reasons**
  e.g. budgetary issues, duplicate projects, or change in portfolio strategy.
- Marketed drugs for which patents are close to expiry or when generic versions are already available
- Drugs that have been discovered, developed, and marketed in emerging markets but not launched in large markets of the developed world, especially in US and Europe, also known as geographical or transnational drug repositioning.
- **Half-baked drugs** from academic institutions and public sector laboratories are the candidates for repositioning. In this case, the drug development research may not proceed further due to reasons like lack of resources, expertise and collaboration, institutional policy change or change in scientist's focus.

Fig 2. Repositioning of shelved/ abandoned drugs

Challenges during clinical trials of repositioning:[2]
If initial clinical trials do not meet current regulatory requirements, new phase I trials may be required to complete or supplement the data package for the candidate, which add further cost, time and risk of regulatory disapproval. There is possibility of failure of proof-of-concept studies in the new indication, if the new target is clinically unprecedented, or if serious safety concerns emerge during clinical trials.

Intellectual property related issues and strategies:[2,7]

- The successful repositioning of the drug, which was never approved, creates substantial value for repositioning company. But if it belongs to any scientific community, prior art can render a repositioning idea unpatentable.
- The same issue is with pre-existing patents, which could hinder commercialization of the repositioned drug.
- Composition-of-matter (COM) IP on the compound of interest is held by another party. In that case, repositioning companies can exploit a number of strategies to add value such as obtaining COM and use patents. Companies developing drugs in combination can also obtain new COM patent.
- The compound is off-patent and therefore generic

Strategies:

- Strike a deal with the holder of the composition-of-matter patent (COM).'Buy back' options in the licensing deal and applying accounting methods thatinvolve placing discontinued compounds to a non-basisasset pool and capitalizing the associated expenses.[8]
- If the patent is set to run out within a few years, a company can use the waiting time to complete clinical development and launch a repurposed product to coincide with the patent expiration.
- For off-patent candidate, rely on novel memorandum of understanding (MOU) patents.
- Invent new formulations, dosage forms, drug combinations or geographic strategies.
- Obtaining exclusive marketing approval in new geographic markets.

Prioritizing available drug-repositioning methods: [6,9]
There are several options for drug repositioning.

Option 1:phenotypic screening or FDA off-label use, when little information is available for the disease

Option 2:target-based or knowledge-based methods, if there exists one protein biomarker for the disease

Option 3:knowledge-based or signature-based methods, if there is more disease information available (to integrate available disease pathways or disease omics data into the drug-repositioning process)

Option 4:signature- based or targeted-mechanism-based methods, if omics data generated from drug treatment are available (to elucidate unknown targeted mechanisms, such as off-targets and targeted signaling pathways)

Computational drug repositioning methods:[6,9,11]
It is hard to satisfy unmet medical needs by successfully repositioning a large number of existing or shelved drugs due to low knowledge content of elucidated mechanisms for traditional drug-repositioning methods. Computational methods alleviate this problem by high-level integration of available knowledge and elucidation of unknown mechanisms. Computational methods significantly improve the discovery process to identify new indications for a drug or new drugs for a disease. These computational methods enable researchers to examine nearly all drug candidates and test on a relatively large number of diseases in relatively short period of time. The computational drug repositioning methods are classified into following types:

Volume : 4 | Issue : 8 | August 2014 | ISSN - 2249-555X

1. **Blinded search or screening methods**
These methods do not include pharmaceutical or biological information and are less likely to help clarify any mechanisms of action of drugs. Most of these methods depend on serendipitous identification from tests aimed at specific diseases and drugs. The advantage of these methods is that they have high flexibility for application to a large number of drugs or diseases. These methods include FDA off-label use and phenotypic screening.

2. Target-based methods
These methods comprise in vitro and in vivo high-throughput (HTS) and/or high-content screening (HCS) of drugs for a protein or a biomarker of interest. These methods also involve in silico screening of drugs or compounds from drug libraries, such as ligand-based screening or docking. These methods significantly improve the likelihood of drug discovery compared with blinded methods, because most targets link directly with the disease mechanisms. Due to integration of target information into the drug repositioning process, there is a higher possibility of finding useful drugs compared with traditional blinded methods. The advantage of targeted-based methods (such as docking) is that these methods enable researchers to screen nearly all drugs or compounds with known chemical structure information within a few days (e.g. Simplified Molecular- Input Line-Entry System SMILES).

3. Knowledge-based methods
These methods are those applying cheminformatics or bioinformatics approaches to include the available information of drugs, drug–target networks, chemical structures of targets and drugs, clinical trial information (adverse effects), FDA approval labels, signaling or metabolic pathways into drug-repositioning studies. Knowledge-based methods incorporate known information into predicting unknown mechanisms, such as unknown targets for drugs, unknown drug–drug similarities, and new biomarkers for diseases, while the information content of blinded and target-based methods are poor and they cannot be used to identify new mechanisms beyond the known targets. The advantage of knowledge-based methods is that they include a large amount of known information into the drug-repositioning process to improve its prediction accuracy. These methods have been applied to reposition known drugs to paediatrichaematology oncology. THOMSON REUTERS has used this strategy to do drug repositioning based on its rich volumes of accumulated prior knowledge.

4. Signature-based methods
These methods use gene signatures derived from disease omics data with or without treatments to discover unknown off-targets or unknown disease mechanisms. Gene signatures can be used to discover unknown mechanisms, as the advancement of microarray and next generation sequencing techniques speed up the generation of vast volumes of genomics data pertinent for drug-repositioning studies. Publicly available databases to assess genomic data are SRA Sequence Read Archive (http://www.ncbi.nlm.nih.gov/ Traces/sra/), NCBI-GEO (http://www.ncbi.nlm.nih.gov/ geo/), CMAP Connectivity Map and CCLE Cancer Cell Line Encyclopedia. The advantage of signature-based methods is that they are useful to identify unknown mechanisms of action of molecules and drugs. Signature- based methods involve more molecular level mechanisms, such as the use of computational approaches to significantly changethe genes as compared to knowledge-based methods.

5. Pathway- or network-based methods
These methods utilize disease omics data, protein interaction networks and available signaling or metabolic pathways, to reconstruct disease specific pathways that provide the key targets for repositioned drugs. The advantage of these methods is that they are helpful in narrowing general signaling networks from a large number of proteins down to a specific network with a few proteins (or targets). Knowledge-based and signature-based methods can not address these repositioning results because the subtype signaling mechanisms are hard to clarify from existing breast cancer pathways or the gene signatures.

6. Targeted mechanism-based methods
These methods integrate treatment omics data, protein interaction networks and available signaling pathway information to delineate the unknown mechanisms of action of drugs. The era of precision medicine motivates such drug-repositioning studies. For example, in case of drug resistance in cancer therapy,although patients respond well to a drug initially, they often acquire resistance to that drug after a few months of treatment. So, deriving successful drug treatment needs additional information about the mechanisms of action of drugs to find better drug targets. The use of systems biology approaches is promising in addressing this challenge. The advantage of these methods is that their goals are to discover the mechanisms related to diseases or drugs as well as to identify those directly related to treatments of drugs to specific diseases. There are only a few studies on these methods that developed elegant computational models to predict the drug effects and related targeted pathways,owing to the difficulties in deriving effective computational models.

Drug repositioning in India:[2]
India is very prone to diseases like HIV, TB and diabetes, which contribute significantly to mortality and morbidity. Also there are certain diseases like malaria, kala-azar, lymphatic filariasis, responsible for significant mortality and morbidity. But these diseases get little attention due to inadequate research, limited resources, lack of priorities within healthcare strategies and limited interventions. The pharmaceutical companies are disinclined to develop drugs against these non-transmissible diseases as compared to chronic lifestyle diseases like diabetes, hypertension and heart diseases, as profit is less for the prior. Now several global initiatives based on public-private partnership models like WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR), Global Alliance for TB Drug Development, Medicines for Malaria Venture, Drugs for Neglected Diseases Initiative are proposed to carry out pioneering research on these diseases. Drug repositioning is the most cost effective method to provide faster access to drugs to large number of patients of developing world. Paromomycin and miltefosine are the examples of drugs that were successfully repositioned for the treatment of kala-azar after clinical trials in India.

Drug repositioning for orphan diseases:[10]
Orphan or rare disease is any disease that affects a small percentage of the population. Most of the known rare diseases are genetic, and therefore, are present throughout the entire life of an affected individual. Many appear early in life and about 30% of children with rare diseases die before the age of 5 years. There are more than 6000 orphan (rare) diseases and less than 325 of them are amenable to treatment. Due to low prevalence and/or commercial potential, only small fraction (5%) is of interest to biopharmaceutical industries. Drug repositioning provides

Volume : 4 | Issue : 8 | August 2014 | ISSN - 2249-555X

an excellent alternative for the treatment of such diseases. List of the orphan diseases and their drugs is provided by various resources like NIH rare diseases (GARD) (Genetic and Rare Diseases;http://rarediseases.info.nih.gov/GARD/), List of the American ODs (http://rarediseases.info.nih.gov/RareDiseaseList.aspx), Oprhan drugs at FDA (Orphan drug designations and approvals; http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm), RDRD from FDA (Rare Disease Repurposing Database; http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/) etc. Pharmaceutical companies can use the strategies like knowledge-based drug repositioning, rescreening the pharmacopoeia against new targets and endpoint screening. Examples of successful drug repositioning for the treatment of orphan diseases are dimethyl sulfoxide (DMSO) for severe closed traumatic brain injury and scleroderma, mifepristone for Cushing syndrome, eflornithine for anaplastic glioma, thalidomide and lenalidomide for multiple myeloma and myelodysplastic syndrome etc.

Future opportunities:

Now high and medium- throughput laboratory approaches are utilized to identify large number of potential drug candidates through combinations of transcriptomics and microarray techniques together with established in vitro and in vivo models. High content quantitative methodology is offered by global gene expression to compare biological states. This serves as the basis of the Broad institute's connectivity map (CMAP) project, through which a database of the transcriptional profiles associated with a spectrum of drugs and drug-like compounds is established. Through an anti-correlation of the respective transcriptional profiles, CMAP is responsible for the marrying of disease state to drug. Recently, the CMAP methodology is extended by a searchable platform-independent expression database (SPIED) to cover transcriptional data in the public domain. [3]

Conclusion

De novo drug discovery is lengthy, costly drug development method with high failure rates. Drug repositioning is less time consuming and less costly method. With increasing market competition and pressure, pharmaceutical companies are trying to adopt less costly and speedy methods to develop new drugs. There are issues related to intellectual property, which are the major limitations to repurpose the drug. With the advancement in the technology, more and more drug candidates are in the process of drug repositioning. In future, drug repositioning may provide affordable and new treatment options for both common and rare diseases.

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