

## Drug Repositioning: A Review

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### ABSTRACT

Drug repositioning (also referred to as drug repurposing) the process of finding new uses of existing drugs, has been gaining popularity in recent years. The availability of several established clinical drug libraries and rapid advances in disease biology, genomics and bioinformatics has accelerated the pace of both activity-based and in silico drug repositioning. Human diseases can be caused by complex mechanisms involving aberrations in numerous proteins and pathways. With recent advances in genomics, elucidating the molecular basis of disease on a personalized level has become an attainable goal. In many cases, relevant molecular targets will be identified for which approved drugs already exist, and the potential repositioning of these drugs to a new indication can be investigated. Repositioning is an accelerated route for drug discovery because existing drugs have established clinical and pharmacokinetic data. In the more conservative approach, termed "on-target repurposing," the drug's known pharmacological mechanism is applied to a new therapeutic indication, which in clinical terms might be quite far removed from the original one but is known to have the same pharmacological underpinning. About 80% of drug repurposing efforts that are currently ongoing (or have already resulted in a successful relaunch) have followed this route, which must not be confused with simple line extensions, e.g., a cancer drug obtaining additional approvals for other types of cancer.

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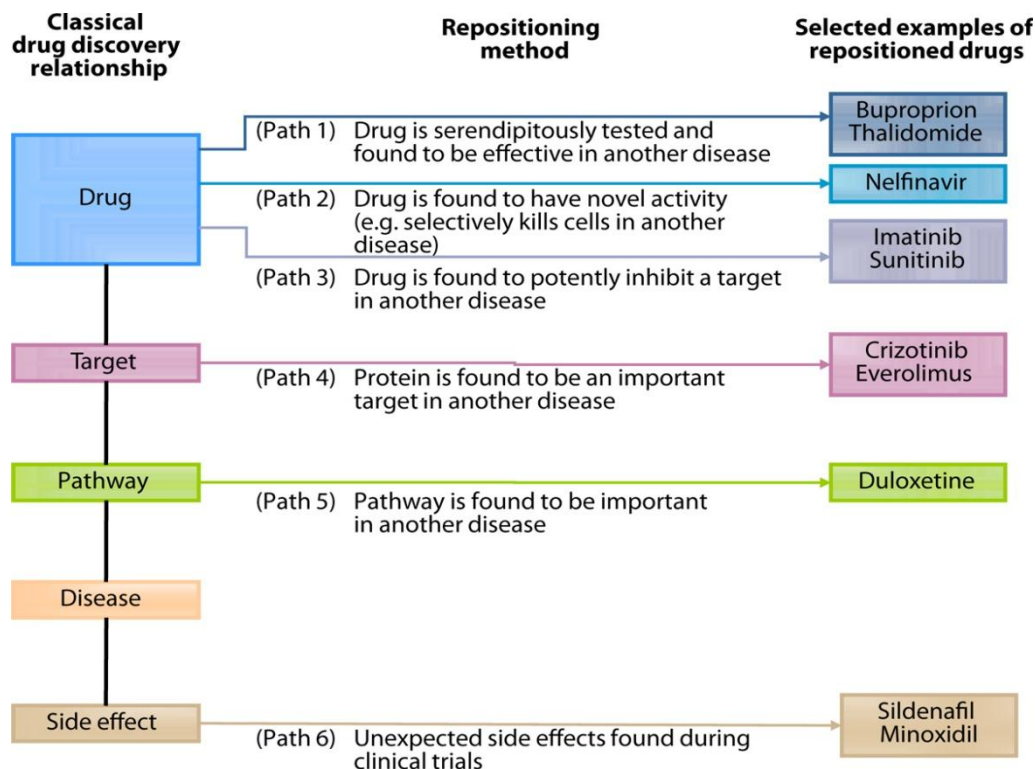
## INTRODUCTION

The biopharmaceutical industry has a problem: output has not kept pace with the enormous increases in pharma R&D spending[1]. This gap in productivity exists even though pharma companies have invested prodigious amounts in novel discovery technologies, such as structure-based drug design, combinatorial chemistry, high-throughput screening (HTS) and genomics[2], which were sold on the promise of improving productivity. For example, many in the industry invested heavily in the idea that HTS technology would bring 20-fold improvements in throughput. Well over US \$100 million has been invested to date in this technology[3]; so far, it has yielded few products[4]. This productivity problem — coupled with worldwide pressure on prices, challenges from generics and ever-increasing regulatory hurdles — has forced many drug

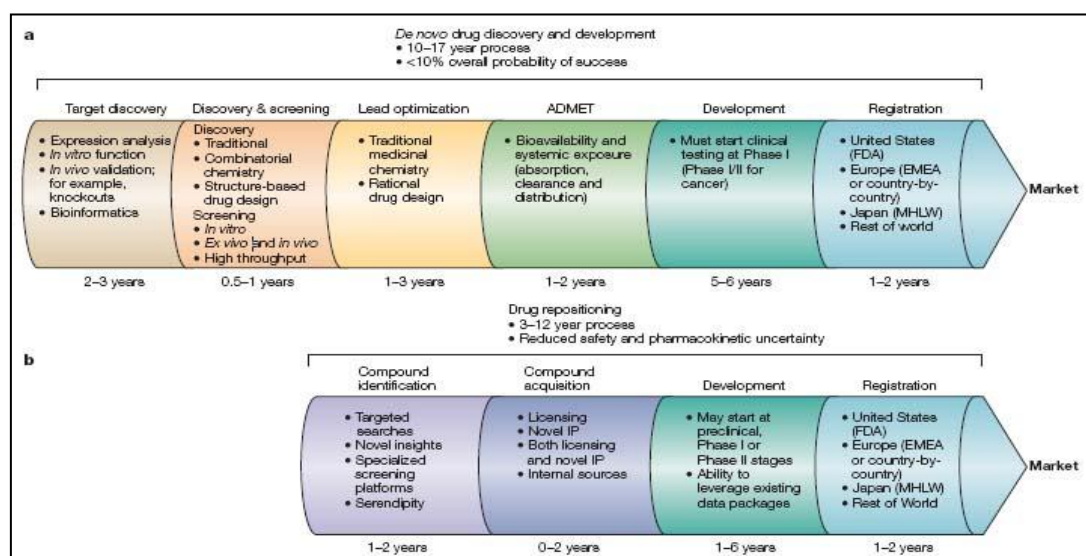
developers to become more creative in finding new uses for, and improved versions of, existing drugs[5,6]. For example, extended- or controlled-release formulations of marketed drugs have improved drug attributes, such as dosing frequency — for example, once-a-day methylphenidate (Concerta; ALZA) for attention-deficit and hyperactivity disorder — and side-effect profiles — for example, extended-release oxybutynin (Ditropan XL; Johnson & Johnson) and transdermal oxybutynin patch (Oxytrol; Watson), both for overactive bladder. Drug developers are also creating new product opportunities by combining therapeutically complementary drugs into one pill — for example, Advicor (Kos Pharmaceuticals) which contains lovastatin plus extended-release niacin for hyperlipidaemia; Glucovance (Bristol-Myers Squibb) which contains metformin plus

glyburide for diabetes; and Caduet (Pfizer) which contains amlodipine plus atorvastatin for hypertension and hyperlipidaemia [7,8]. The process of finding new uses outside the scope of the original medical indication for existing drugs is also known as redirecting, repurposing, repositioning and reprofiling [8–10]. Repositioning success stories and companies leveraging repositioning strategies are increasing in number. This review focuses on repositioning and will

describe its general advantages over *de novo* drug discovery and development; representative repositioning success stories; hurdles typically encountered during the repositioning process and approaches for overcoming them; the strategies applied by several biotech companies using this approach to drug development; and the relative merits of pursuing repositioning approaches inside pharmaceutical or biotech companies.



**Figure 1: Potential avenues of Drug repositioning**



**Figure 2: A comparison of traditional De-novo drug discovery and development Vs Drug Repositioning**

**Drug repositioning as an efficient approach to drug discovery**

Drug repositioning is the process of finding new therapeutic indications for existing drugs. It can be an efficient approach to discovery because many existing drugs have 1) established formulations and manufacturing methods, 2) extensive absorption distribution, metabolism, excretion and toxicity (ADMET) data, 3) previously passed clinical trial safety endpoints and are thus less likely to fail future clinical trials owing to adverse effects [11], and 4) phase IV (post-marketing surveillance) safety data, which are expensive and time consuming to obtain [12]. Reviews of the field indicate at least 46 approved drugs already repositioned for new therapeutic uses [11,13-15].

**The benefits of drug repositioning**

Drugs in development on the market or those that are shelved because of lack of efficacy, are excellent starting points for further development. Finding new indications for such drugs will benefit patients who will see a potential new therapy sooner, will maximize their value and will also protect the original IP owner against competitor adjacency moves. Typically repositioning is done by accident, or in a limited way. New technologies however enable the systematic evaluation of any drug or mechanism of action against any disease or adverse event.

**1. The safety advantage.** Existing drugs that are either approved or have been shown to be safe in late-stage trials, but have failed to meet end points of their originally-targeted indications, can leverage their inherently reduced development risk into potentially new indications. They can do so if they can be proven to be effective in the new indications and also sufficiently differentiated against standard of care. When such drugs enter clinical trials, they compete with non-repositioned drugs not in terms of safety, but in terms of efficacy. Since safety accounts for approximately 30% of drug failures in clinical trials, this is a significant development advantage that repositioned drugs enjoy.

**2. The money savings advantage.** According to a recent report based on a survey of 30 pharmaceutical and

biotechnology forms, the cost to relaunch a repositioned drug averages \$8.4 million, whereas to relaunch a new formulation of an existing drug in its original indication costs an average \$41.3 million[16]. In both cases, the drug has reached the market. The difference between the costs of market attainment for a repositioned drug versus a new drug, however, is simply staggering. Given that the latter averages more than \$1.3 billion, successfully bringing a repositioned drug to market seems to cost approximately 160 million times less than the current standard of NCE/NME development. Even if this differential is off by a hundred million or more, from the purely financial perspective, repositioning is in a completely different league of investment needed to create a new drug product in the market.

**3. The market potential advantage.** Not all drugs are blockbusters, but some that are achieved this status as repositioned drugs. Two excellent examples are Celgene's Thalomid®, which is repositioned thalidomide, and its derivative Revlimid® (lenalidomide). These two repositioned drugs represent a combined global revenue stream of more than \$2.8 billion for Celgene [17]. Although one should not assume that such success for a particular repositioned drug will automatically mean the same success for all repositioned drugs, it becomes very hard to argue against the financial potential of repositioning as a strategy. Potential for market success depends on numerous factors, including market need, competition, differentiation, an excellent product, IP barriers, payer acceptance, compliance and a successful market strategy. These factors apply for repositioned drugs in the same way as they do for NCE/NME drugs as well, and it is thus important to remember that there is no inherent property of repositioned drugs that would limit their market potential.

**4. The return on investment potential.** If it takes an average \$8.4 million to launch a successful repositioned drug, and there is no limit to market returns as the Celgene case shows, then all things being equal, the disparity in upfront investment means that repositioned drugs will always represent a better return on investment than NCE/NME drugs. However, exactly like with NCE/NME

drugs, it is very important to keep in mind that this should also be a portfolio strategy: it is prudent to have a reasonable stable of repositioned drugs under development as a portfolio, to allow for attrition due to potential lack of efficacy (but not safety), when any drug is tested in clinical trials.

### 5. The out-licensing potential

Pharmaceutical companies are said to be exploring new models to out-license some of their clinical drug candidates that may have been shelved for whatever reason, even though they have met their end points and have proven themselves to be safe. If such drugs were to be repositioned, then the

pharmaceutical company increases the attraction these drugs have, and gives itself more options to find interested buyers. For example, the pharmaceutical company may retain the original use rights to the drug, and out-license the rights to the new indication only. Or, the company may retain the rights to the new indication and out-license the original use if the latter has become a non-strategic one, whereas now the new use falls within the company's areas of interest. With either scenario, repositioning grants a pharmaceutical company specific and novel business development possibilities for out-licensing that it otherwise would not have.

**Table 1: Examples of repositioned drugs, their targets and indications\*[52]**

Drug name	Original target	Original indication	New target	New indication
<b>Successful repositionings from approved drugs</b>				
Duloxetine	Serotonin and nor epinephrine reuptake	depression	Serotonine and norepinephrine reuptake	Stress, urinary incontinence, fibromyalgia, chronic musculoskeletal pain
Everolimus	mTOR	Immunosuppressant	Unchanged	Pancreatic neuroendocrine tumors
Imatinib	BCR-ABL	CML	KIT, PDGFRA	GIST
Minoxidil	Unknown	Hypertension	Unknown	Hair loss
Nelfinavir	HIV-1 protease	AIDS	Inhibits AKT pathway	In clinical trials for multiple cancers
Sildenafil	PDE5	Angina	Unchanged	Erectile dysfunction, pulmonary arterial hypertension
Sunitinib	Multiple kinases	GIST, renal cell carcinoma	Unchanged	Pancreatic neuroendocrine tumors
Trastuzumab	HER2	HER2-positive breast cancer	Unchanged HER2-	HER2-positive metastatic gastric cancer
<b>Successful repositionings from investigational drugs</b>				
Crizotinib	MET kinase	Clinical trials for anaplastic large-cell lymphoma	<i>EML4-ALK</i> oncogene	NSCLC
Thalidomide	Unknown	Morning sickness (withdrawn)	Inhibits tumor necrosis factor $\alpha$ production	Leprosy
Thalidomide	Unknown	Morning sickness (withdrawn)	Inhibits angiogenesis	Multiple myeloma
Zidovudine	Reverse transcriptase	Failed clinical trials for cancer	Reverse transcriptase	AIDS
<b>Unsuccessful repositioning</b>				
Bevacizumab	VEGF	Multiple cancers	Unchanged	Failed clinical trial for gastric cancer
Bupropion	Unknown	Depression	Synergistic inhibition of appetite and energy expenditure	Obesity (rejected by FDA owing to adverse effects)
Naltrexone	Opioid receptors	Opioid addiction	Obesity (rejected by FDA owing to adverse effects)	Obesity (rejected by FDA owing to adverse effects)
Sunitinib	Multiple kinases	GIST, renal cell carcinoma	Multiple kinases	Failed clinical trials for multiple cancers

### **Current approaches to find new drug repositioning candidates**

Although the prospect of discovering specific multi-targeting drugs is attractive, the actual implementation is a complicated endeavor. Drugs must be screened against multiple targets at a time and attain specific combinations of target affinities. In the case of sunitinib, it is still not clear exactly which combinations of its target inhibitions are effective for which cancers [18]. A more rational approach at present would be to determine new targets for existing drugs.

### **Experimental approaches**

Experimental approaches to systematically elucidate new drug-target interactions fall into three categories. The first is to determine direct-binding partners of existing drugs. Examples of this approach include washing cell lysate extracts over a bead column fixed with an approved drug [19], high-throughput Biacore screening of an approved drug library against protein tyrosine phosphatase 1B [20], or high-throughput direct-binding assays to test drugs against 317 kinases [19]. In contrast, cell-based approaches screen for drugs that induce a desired change in cellular phenotype. They have been used to find approved drugs that can regulate autophagy [21], induce apoptosis in retinoblastoma cell lines [22], or inhibit proliferation of prostate cancer cell lines [23]. One recent study combined high-throughput cell proliferation, kinome binding assays and *in vivo* mouse studies to identify the chemotherapeutics 5-fluorouracil and bortezomib as inhibitors of ependymoma (a chemoresistant brain tumor) and as leads for immediate clinical translation [24]. The third approach uses gene expression analysis to identify drugs that show an opposite gene expression profile to that of a disease [25], or that have similar gene expression profiles in cell lines to other approved drugs [26].

For experimental repositioning screens, obtaining a physical collection of approved drugs has been the greatest obstacle. Several companies have marketed smaller libraries containing 500 to 1,000 approved or off-patent drugs, including Enzi Life Sciences (Plymouth Meeting, PA, USA), Prestwick (Washington DC, USA), and Spectrum (Microsource, Gaylordsville, CT, USA).

However, it was only in April 2011 that the National Institute of Health's Chemical Genomics Center (NCGC) pharmaceutical collection was initiated, containing 2,391 worldwide-approved drugs in a screenable format [27]. Their plan is to set up a screening service with collaborators and assess these drugs in a wide range of assays, and thus find new repositioning candidates for a wide range of diseases.

Aside from approved drugs, the multitude of compounds that have failed clinical trials because of lack of efficacy (not toxicity) also represent a rich resource for repositioning, as these drugs have known clinical and pharmacokinetic data. With results from personalized genomics studies underscoring the heterogeneity of diseases and patients, it is possible that many of these failed drugs were not tested on the correct subset of patients. Thus, failed drugs may still be useful for future personalized medicine approaches, particularly for those patients without other treatment options. For example, the ineffective cancer drug zidovudine later became a widely used anti-HIV drug [28]. A physical collection of failed compounds would be difficult to assemble because of the associated intellectual properties; however, we believe that this would be a valuable resource for both drug repositioning and personalized medicine.

### **Computational approaches**

Given the large number of druggable protein targets and existing drugs, it is infeasible to set up assays to test every interaction in the laboratory. In addition to the time and cost required, a tailored assay must be developed for each protein, and compound libraries of all existing drugs must be collated. Many computational approaches have been published in recent years, many of which mirror the types of repositioning summarized in Figure 1. Most methods are based on similarity, between drugs [29], proteins [30], or side effect phenotypes [31]. These methods hypothesize that drugs with similar chemical structures or side effects are likely to have similar targets. A higher resolution method is molecular docking, which simulates the binding of a drug inside a target three-dimensional structure at an atomic level. Docking is widely used to virtually screen large chemical libraries

against targets of interest. In 2001, 'inverse docking' was first proposed as an approach for investigating the docking of one drug against multiple protein binding sites [32], and subsequent methods have been scaled up to investigate hundreds of targets and thousands of drugs [33-36]. However, the lack of solved protein structures for many targets is a major limitation of structure-based approaches.

Computational methods have also been applied to analyze the wealth of existing experimental data in public databases such as PubChem Bioassays [37] and the Gene Expression Omnibus [38]. New target-disease associations can also be formed using systems biology approaches [39]; in one study, network analysis identified a new glioblastoma target protein that already had an approved drug [40]. Furthermore, literature-mining methods used by mode of action by network analysis (MANTRA) [71], IDMap [41] and CoPub [42] can search for associations that already exist but have yet to be linked.

The most useful resources for computational methods are datasets of known interactions, often used as training data, positive control data or benchmark data in analyses. A few drug-target databases focusing on approved drugs include DrugBank, Kyoto Encyclopedia of Genes and Genomes (KEGG) Drug, the Therapeutic Target Database, and Matador [43-46]. Overall, computational efforts are efficient complementary approaches to experimental studies and have been described in more detail elsewhere [47,48].

### **Failures in drug repositioning**

Not all cases of drug repositioning are successful. The kinase inhibitor bevacizumab failed to show efficacy in a phase III trial for gastric cancer despite having already been repositioned to many other cancers [49]. The multi-kinase inhibitor sunitinib has failed clinical trials for breast cancer, colorectal cancer, NSCLC and prostate cancer, but was approved for the treatment of GISTs, pancreatic neuroendocrine tumors and renal cell carcinomas among others [50]. The lack of efficacy of generic kinase-targeting drugs such as sunitinib suggests that, at least for some cancers, more targeted strategies need to be pursued.

The combination of bupropion and naltrexone, previously approved for the treatment of depression and opioid addiction, respectively, seemed to synergistically regulate appetite and energy expenditure in obesity; however, the FDA rejected this combination in February 2011 owing to potential cardiovascular adverse effects. Therefore, even repositioned drugs that have passed clinical safety standards might still be found to have adverse effects. In addition, it is important to consider the original drug indication during repositioning - for example, a cytotoxic chemotherapeutic may not be an ideal candidate for hypertension, as it may damage healthy cells at the required dosages [51].

### **CONCLUSION**

During the past several years, there has been a surge of interest in repositioning. Both pharmaceutical and biotech companies have recognized the advantages of repositioning, and activity in the area has increased dramatically. There are a number of examples in which serendipity or directed efforts have led to successful launches in new indications. The strategy is economically attractive when compared with the cost of drug development based on *de novo* drug discovery and development. Unique challenges are associated with repositioning strategies, which demand creative approaches and great dedication on the part of drug repositioners inside and outside pharmaceutical companies. Institutional bias often militates against developing a drug in a new indication in the same pharmaceutical company in which the drug was developed for the initial indication. But for those outside of big pharma, the challenge is equally great. Without a sense of trust based on a long-term relationship, pharmaceutical executives could be reluctant to make the deals with outside companies that are required to create out licensing opportunities. The current boom in repositioning raises an existential question about the approach: when the obvious candidates for repositioning have been exhausted, will anything be left to reposition? Fortunately, the number of potential indications for repositioned drugs exceeds the current screening capacity of

most companies. Although the boom will consume the most obvious candidates, it is likely that repositioning opportunities will continue to present themselves, albeit possibly at a lower rate. Those companies that have sufficient biological and technological expertise should be able to develop early-stage discovery compounds to fill their pipelines while still taking advantage of repositioning.

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