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Editorial

Streamlining the Drug Discovery Process through Repurposing of Clinically Approved Drugs

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Editorial

Drug repurposing (also known as Drug repositioning) is an approach to drug design and development where known compounds are assigned to new indications. In this process one starts from already existing clinical drugs and assigns a new therapeutic target to the molecule. This approach is quickly gaining popularity both in industry as well as in academia as it banks upon the initial knowledge and investment which brought the drug to the market at the first instance. The major bottleneck of de novo drug development is that almost 90% of the identified novel molecules fail the clinical trials, resulting in the rise of the overall pharmaceutical R&D cost. The repurposing strategy helps to overcome such barriers. There are notable advantages of this approach over the traditional drug discovery process (Figure 1). Firstly, the repurposed drugs have already undergone clinical trials in the past and as a result their safety is ensured. Secondly, the repurposing strategy is cheap and takes much lesser time to develop a drug. Several pharmaceutical companies therefore endorse this low-risk repositioning strategy to improve their profits.

The Drug Repurposing Work Flow

The starting materials for a repurposing process are drug molecules which (a) have been approved for clinical use (b) have passed safety trial (Phase I) but failed to demonstrate efficacy (Phase II) for a disease (c) have been replaced by better therapeutics and (d) have become generic due to patent expiry [1]. The drug repurposing process can be broadly classified into the following two strategies: (i) Existing compound-novel target approach: It is based on the observation that many drugs bind to multiple targets. These secondary targets could be related to a different disease or physiological condition and (ii) Known mechanism-new disease: It is based on the observation that several biological processes and signaling pathways are relevant for more than one disease and hence the same drug which inhibits a biological process can exert effect on two different disease states [1]. Once a secondary target has been assigned to a drug, proof-of-concept experimentation has to be performed to study the effect of the drug on the newly identified target. Computational biology, chemical biology, in vitro/cell-based assays and in vivo analysis are frequently used to validate the repositioning. Upon validation of the hypothesis, the drug can leap directly into the phase II and III clinical trials. Moreover the availability of previous clinical and pharmacokinetic data along with the knowledge of the range of viable dose for that particular drug substantially reduces the risks associated with the further development of the molecule.

Case Studies

One of the most promising instances of a repurposed drug is Zidovudine, which was originally designed for cancer in 1964 [2]. The drug was later found to be potent against HIV in 1985. Released in 1987 by Glaxo Smithkline as AZT, it became the first drug to be approved for HIV treatment. Mifepristone, a glucocorticoid receptor antagonist, is another example of a repurposed drug which was initially synthesized in 1980 in France by Danco laboratories as an oral abortifacient and was licensed for use in France in 1988 and in the USA in 2000 [3]. The Drug has been repositioned for psychotic major depression and bipolar disorder under the trade name of Corlux by Corcept therapeutics [4]. Aspirin is the most frequently used analgesic and antipyretic drug in the world. It was licensed by the German company Bayer pharmaceuticals in 1897. The drug was later found to possess anti-cancer properties (Table 1). Clinical trials held in 2011 studied the risk of cancer death among patients who regularly took aspirin for 4 years and patients who did not take the drug. It was found out that, aspirin use lowered the overall risk of cancer by 20%. Another example of repositioning is that of the acetyl cholinesterase inhibitor Galantamine which was licensed as Nivalin by Sopharma in 1960 as a treatment for paralysis due to Polio. With the licensing of the polio vaccine in 1962 and the gradual eradication of polio, Galantamine remained abandoned for years until 2000 when it was repurposed for Alzheimer's disease by Johnson & Johnson under the trade name Reminyl.

Conclusion and Future Directions

The Drug repositioning strategy is widely used as an alternative

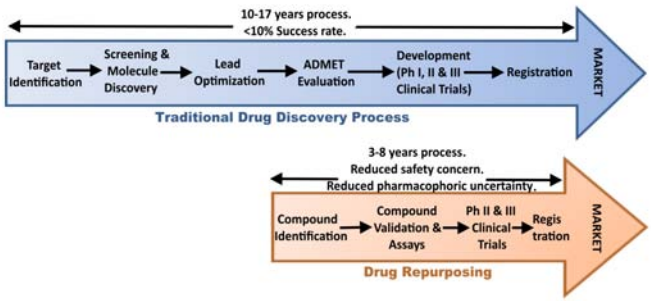

Figure 1: Schematic representation of the steps involved in Traditional drug discovery process *vs.* Drug repurposing with the salient features of both the processes.

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Table 1: List of repurposed clinical drugs for the treatment of various diseases.

	Original Indication		Repurposed Indication	
Drug	**Disease**	**Target/s**	**Disease**	**Target/s**
(a) Drugs repurposed for Infectious diseases				
Zidovudine	Cancer	Telomerase [2]	HIV/AIDS	HIV reverse transcriptase [4]
Amphotericin	Fungal infections	Cell membrane sterols [5]	Leishmaniasis	Signaling pathways for IFN-γ, IL-12 and TNF- α activation in host [6]
Cycloserine	Urinary tract infections	Peptidoglycan synthesis in *E.Coli* [7]	Tuberculosis	Peptidoglycan synthesis in *M. tuberculosis* [8]
Clindamycin	Skin infections/acne	Ribosomal peptidyl transferase [9]	Malaria	*Plasmodium* apicoplast [10]
Paromomycin	Amoebiasis	16S Ribosomal rRNA [11]	Leishmaniasis	Mitochondrion function [12]
(b) Drugs repurposed for Neurological diseases				
Milnacipran	Depression	Serotonin–Norepinephrine re-uptake [13]	Fibromyalgia	Serotonin–Norepinephrine re-uptake [14]
Atomoxetine	Parkinson's disease	Noradrenaline re-uptake [15]	Attention deficit hyperactivity disorder	Noradrenaline re-uptake [16]
Galantamine	Polio, paralysis	Acetylcholinesterase [17]	Alzheimer's disease	Acetylcholinesterase [18]
Ropinirole	Hypertension	Dopamine D2 receptor [19]	Parkinson's disease/ restless leg syndrome	Dopamine D2 receptor [20]
Mifepristone	Pregnancy termination	Progesterone receptor [3]	Psychotic major depression	Glucocorticoid receptors [3]
(c) Drugs repurposed for Cancer				
Aspirin	Analgesic and antipyretic	COX-1 and COX-2 [21]	Colorectal cancer	COX-2 inhibition and down-regulation of NF-κB and AP-1 signaling [22]
Rapamycin	Immunosuppressant	mTOR signaling [23]	Lymphoma and leukemia	mTOR pathway/VEGF signaling [24]
Methotrexate	Acute leukemia	Dihydrofolate reductase [25]	Osteosarcoma, breast cancer and Hodgkin lymphoma	NF-κBandTNF-α signaling [26]
Nitroxoline	Urinary tract infections *(P. aeruginosa)*	Bacterial biofilm formation [27]	Bladder and breast cancer	Cathepsin B [28]
Minocycline	Acne vulgaris	Bacterial protein synthesis [29]	Ovarian cancer	NF-κB and TGF-β1 signaling [30]

approach to drug development since it lowers the risk of safety and toxicity and at the same time saves millions of dollars worth of pharmaceutical R&D. Over the decades many drugs have been repositioned and licensed for use in alternate indications and many more repurposed drugs are currently at the phase II and III clinical trials. The Drug repositioning approach is thus a simple yet powerful strategy to fuel pharmaceutical research and streamline the drug discovery process.

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