Chapter

Drug Repurposing in Oncotherapeutics

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Abstract

Repurposing or repositioning means validating and application of previously approved drugs in the treatment of another disease that might be relevant or irrelevant to existing use in disease based on the principle of polypharmacology. Repurposed drugs are already well documented for pharmacokinetic, pharmacodynamic, drug interaction, and toxicity parameters. In 1962, thalidomide treatment in pregnant women led to phocomelia in their newborn but while repurposed based on anti-angiogenesis property, it showed efficacy in hematologic malignancies like multiple myeloma. The repurposing is becoming an essential tool in the anti-cancer drug development due to existing drugs are not effective, high cost of treatment, therapy may degrade the quality of life, improvement of survival after treatment is not guaranteed, relapse may occur, and drug resistance may develop due to tumor heterogeneity. Repurposing can be addressed well with the help of literature-based discovery, high throughput technology, bioinformatics multi-omics approaches, side effects, and phenotypes. Many regulatory bodies like EML, NIH, and FDA promote repurposing programs that support the identification of alternative uses of existing medicines. Cancer becomes the major health issue, and the need to discover promising anti-cancer drugs through repurposing remains very high due to decline in FDA approval since 1990, huge expenses incurred in the drug development and prediction of dangerous future burden.

Keywords: repurposing, cancer, bioinformatics, multi-omics, thalidomide tragedy, metformin

1. Introduction

1.1 What are the problems?

Cancer is the second deadliest disease after cardiovascular diseases, causing loss of billions of lives across the world. Although human kind has developed so many anti-cancer medicines, none of them are able to cure the disease. After spending of around $650 million for the development in research and development of New Chemical Entity (NCE) during time periods of 12–17 years, successful outcome compared to standard drugs is less [1]. The success ratio for this NCE in clinical trial is less than 10%. Many times, the effects on outcomes like disease free survival, quality of life treatment related side effects and complications are discouraging. According to ESMO 2019 press release, there was no link between drug cost and clinical benefit measured by ESMO-MCBS and the American Society of Clinical Oncology Value Framework (ASCO-VF) for various drugs approved for adult solid tumor in four European countries and the USA from 2009 to 2017. So, it would

add extra treatment cost to patient therapy. According to Prof. Kerstin Vokinger, University of Zurich, Switzerland, and affiliated with the Program on Regulation, Therapeutics, and Law (Harvard Medical School, USA), drug pricing should be aligned with clinical value [2]. There was drastic decline in average number of FDA approved drug since the 1990, but the number of cancer cases rising every year for each cancer. So, this imbalance of demand and supply of effective anti-cancer drugs can be balanced by implication of drug repurposing [3]. In the oncology medicine, the US FDA approved 4 new drugs in 2016 while it was 14 drugs in 2015 and 9 drugs in 2014 and 2013 that indicate decrease in anti-cancer drug discovery [4].

1.2 How repurposing can help?

To overcome the problems linked to high expenditures, lengthy and tedious research for every NCE with low success in clinical trial, repurposing can help where scientists are trying to investigate new therapeutic indication for existing approved drugs. Drug repurposing has many advantages in terms of efficient utilization of time and money for drug discovery and development processes. The proposed medicines for repurposing already have approved pharmaceutical data related to its formulation, Pharmacokinetic (absorption, distribution, metabolism and excretion) and pharmacodynamic profile that collected during preclinical and clinical trial. The proposed medicine also passed through much toxicity, side effects testing and passed the phase 4 of post marketing surveillance so the safety is already established and that reduce the chances of drug failure at the end screening process of drug discovery [5]. The repurposing can drastically reduce drug discovery time line from 12–17 years to 3–12 years due to availability of drug's pharmacology and pharmaceuticals data [6]. The concept of Drug Repurposing is based on validating and application of previously approved drug by FDA in the treatment of another disease that might be relevant or irrelevant to existing use in disease. The principle of polypharmacology and pleiotropy was working behind drug repurposing. The anti-cancer drugs receive FDA approval are very costliest in recent years that significantly affect pharmacoeconomics of patients. For consideration, the cost for a combination-targeted therapy of monoclonal antibodies ipilimumab and nivolumab in treatment of metastatic melanoma has been estimated to per responder is around $400,000 US [7, 8]. So, all these problems can be targeted by drug repurposing where it improves the chances of success, shortens the testing time, and reduces the huge investment in cancer drug design and development.

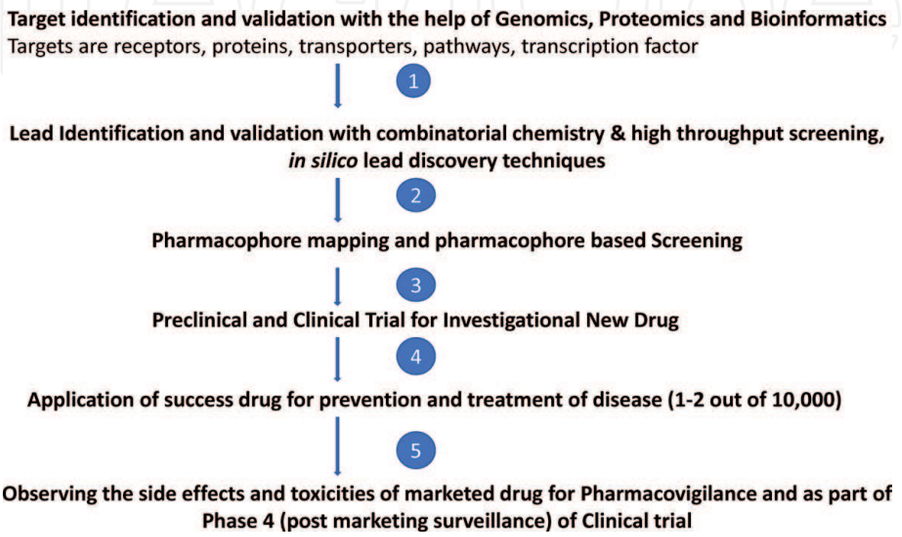

Figure 1.
Drug discovery and development with potential windows for drug repurposing.

1.3 Opportunities for drug repositioning comes from path of drug discovery and development

The process of new drug designing and development involve many steps as mentioned in **Figure 1**. It may happen that Drug is serendipitously screened and found positive result for another disease. Gills et al. tested few anti-HIV drugs against many cancer cell lines using cytotoxicity assays. He found that nelfinavir has potent broad-spectrum antitumor activity [9]. Repurposing can also possible if new role discovered for an existing target. In case of metformin, the similar pathway of is found to be important in two different diseases like diabetes and cancer. It has been observed that unexpected side effects found during and after clinical trials show lead for drug repurposing like thalidomide for certain cancer.

2. Drug repositioning strategy

During preliminary screening on Drug, many possibilities of drug repurposing may arise by chance and later based on proper justification few of them have been tested for alternate application in another disease that called as shifting from bench to bedside. Oppositely, it may happen that unpredicted results of clinical trials suggest ideas for drug repurposing and later same things justified by scientific experiments that called as bedside to bench. According to FDA approved drug database, around 80–90% of drug gets failed in clinical trials due to various reasons and one of the majors is that the lack of efficacy during phase- III of clinical trial. That failure rate figures out around 30–50% and all these drugs might be good candidate for repurposing. The **Figure 2** indicate different approaches that begin with constructing hypothesis based on existing fund of knowledge to expanding its *in silico* frame work for preliminary testing and later on validating facts based on more vigorous and stringent analysis like preclinical and clinical studies [10].

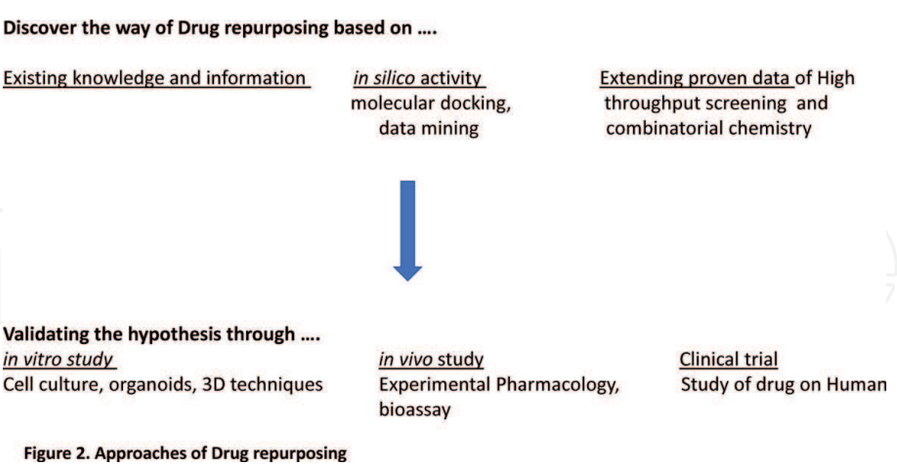

Figure 2.
Various approaches of drug repurposing.

3. Necessity for drug repurposing in cancer treatment and availability of attractive candidates

Comparing cancer with other disease that takes much time to develop and working insidiously. Every cancer begins with few mutations that suppress tumor suppression gene and promoting oncogene that leads to abnormal cell proliferation, escape of apoptosis, immune evasion, inflammation, defects in DNA damage repair mechanism,

Warburg effects, angiogenesis and lack of differentiation of cell with most of the cells remain immature. As there is progress happen the picture of tumor microenvironment become more and more complicated. At this time tumor is no more homogenous but packed with heterogeneous cells and changing itself to more resistance form. The cancer might be supported by systemic condition of the body or in the other words internal anti-cancer mechanism become compromised to eradicate the tumor. The tumor microenvironment begins to secret many immunosuppressive cytokines and inflammatory mediators that sustain the tumor growth and save this corrupted cellular structure against honest immune system that work in the form of vigilance. After dominate at local region, tumor intrude to the other favorable region. Later on, metastasis start based on seed and soil theory of Stephan Paget, where cancer cells work as "seeds" and the specific organ microenvironments work as "soil." The success interaction between these two entities determines the development of a secondary tumor [11].

After get metastasis, the most of the patients give response to first line treatment not more than 50% for various cancers. At advance stages of cancer, majority of patients will develop anti-cancer resistance due to drastic abnormal genetic, epigenetic changes and surviving of cancer stem cells that not killed even after the death of tumor cells [12, 13]. So, it becomes important to repurpose drugs that able to act at multiple targets in tumors in patient that display genetic heterogeneity.

The following table (**Table 1**) consists of brief reviews of available good drug candidates for drug repurposing and some of that already approved.

Drug	First approved target	Approved in disease	Repurposed in cancer (preclinical/clinical)
Thalidomide [14]	Might affect the medullary control centers (the vomiting center and the chemoreceptive trigger zone) or affect the peripheral receptors	Nausea, vomiting of pregnant woman (banned now)	Multiple myeloma by targeting TNF-α
Metformin [15]	Activate the adenosine monophosphate activated protein kinase (AMPK) signaling pathway	Type-II diabetes mellitus	Mitochondrial respiration, reducing insulin and insulin-like growth factor levels, inhibits mTOR and activate p53, AMPK pathway
Everolimus [16]	mTOR	Immuno-suppressant	In Pancreatic neuroendocrine by targeting mTOR signaling pathway
Trastuzumab [17]	HER2	HER2-positive breast cancer	For HER2-positive metastatic gastric cancer
Aspirin (low dose; 50–100 mg daily)	COX-1	Prevent Platelets aggregation in cardiovascular disease	Prostaglandin E2 (PGE2) decreased in colon cancer [18], inhibition of platelets to suppress NK cell-mediated lysis of cancer cells [19]
Propranolol [20]	β-receptor blocker	Cardiovascular diseases	Reduced 57% risk of metastasis in Breast cancer by blocking cyclic AMP (cAMP), focal adhesion kinase (FAK)
Digoxin [21, 22]	Na + -K + -ATPase	Heart failure, to reduce heart rate	Rise in intracellular Na + and Ca2+ in human prostate adenocarcinoma cells, lead to activation of calcineurin and transcriptional upregulation of Fas ligand cause apoptosis. Also, suppression nuclear factor-kappa B and inhibition of DNA topoisomerase II are well documented.

Drug	First approved target	Approved in disease	Repurposed in cancer (preclinical/clinical)
Chlorpromazine [19]	Dopamine receptor antagonist	In psychosis, bipolar disorder, schizophrenia	Increase in p21 [23], p51 expression [24]
Artemisinins	Induce formation of reactive oxygen species (ROS) within the infected red blood cells (RBC)	Anti-malarial [25]	Anti-proliferative, pro-apoptotic effects [26]
Doxycycline	Protein synthesis in bacteria	Antibiotics	Down regulation of MMP-2 and MMP-9 expression in leukemia [27] and colorectal cancer cells [28]

Table 1.
Repurposed drug for the cancer treatment.

3.1 Various anti-cancer targets that can be used for repurposing of drug

Based on global statistics, more than 20 million individuals will be detected with cancer in 2025. Certain cancer like breast cancer, colorectal, prostate is mostly remaining incurable in advanced stages with existing treatment and that leads to increase in number of cases. Thus, addressing these present and future challenges requires more effective cancer drugs [29]. Traditional anti-cancer therapy like Chemotherapy and radiation have dangerous side effects that range from bone marrow suppression, oral mucositis, arising of secondary cancer to vomiting, diarrhea and organ specific toxicity that drastically decrease the quality life and overall survival of cancer patients [30]. From this point of view, drug repositioning option is promising strategy to identify non-cancer drugs like aspirin and chlorpromazine which have anti-tumor activity with less side effects comparable to traditional anti-cancer drugs. Traditionally limited targets were identified for anti-cancer drugs that involve cell cycle inhibitors, anti-metabolites, anti-angiogenesis, growth factor inhibitors, pro-apoptotic. But today many new targets identified that work in more specific way and reduce dangerous side effects of anti-cancers. Some novel drug target mentioned in following diagram that might be work well for future drug repurposing in oncotherapeutics (**Figure 3**).

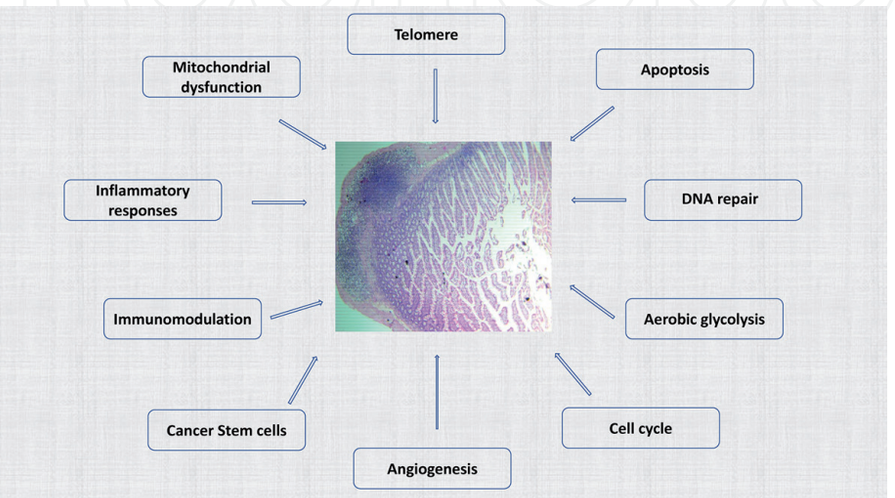

Figure 3.
Hall marks of cancer.

4. Methods for drug repurposing

It might be apparent that identifying specific drugs with pleiotropic effects is easy task but the execution is a complex. Following methods work well to repositioning of drug with the help of existing data, reducing the time of investigation, helping to reduce unnecessary animal experiments and regulatory obligations.

4.1 Computational methods

Although high through put screening (HTS) and many assay techniques available, it is difficult to predict drug and target interaction and its subsequence consequences [31]. Every drug bind with variety of targets but most of them attach with proteins that present in the form of receptors, ion channels, enzymes, antigen and transcriptional factors [32]. To screen the drugs interaction with every of this target is not possible and also it consumes lots of time and money. Certain computational approaches are available that able to screen thousands of test drug molecule with many targets within short time period. The selection of drug and its possible targets are based on similarities based on structure, its protein binding and typical side effects that drugs produce [33–35]. Many molecular docking software are available that predict binding of drug molecule within active site of the target and able to predict the three-dimensional interaction at atomic level. In this approach it is necessary to discover protein structures of both normal and disease condition to target it in proper way else binding of drug with normal protein structure may lead to side effects. Computational approach needs lots of information that can be derived from various databases and webservers like DrugBank [36], E medstore [37], KEGG: Kyoto Encyclopedia of Genes and Genomes [38], SuperTarget and Manually Annotated Targets and Drugs Online Resource (MATADOR) [39], Potential Drug Target Database (PDTD) [40], ZINC [41], CancerDR [42] and many others. Computational models broadly categorized in to network based model that working based on the principles of multiple target optimal intervention (MTOI) [43], Drug side-effect similarity-based method [35] and machine learning-based model that further categorized into supervised learning method and semi-supervised learning method [32].

4.2 Biological experimental approaches

In this method the interaction in between drug and its target is determined. To accomplish this, we may fix the drugs on certain bead and allowing reaction of washing cell lysate extracts with drugs [44]. It is also possible to carry out high-throughput screening based direct-binding assays to test drugs against certain kinases [45]. Cell based screening examine the evidence of autophagy, apoptosis or inhibition of proliferation in proper cell culture environment of different cancer cells [46–48]. Also, genetic expression study of drugs based on cell line can help in drug repurposing.

5. Drug repurposing database

Physical collection of approved drugs to carry out experimental repositioning screens is challenging task. Smaller digital libraries containing information of approved drugs or drugs with expired patents are available to serve drug repurposing like Enzi Life Sciences, Prestwick, Spectrum and many other like National Institute of Health's Chemical Genomics Center (NCGC) [49]. It may happen that drug get failed in clinical trials because of lack of effectiveness (efficacy) but not due to toxicity represent good candidate for drug repositioning. There is some web

portal available that store large drug screening database based on clinical trials and can be used for repurposing.

- http://drugrepurposingportal.com
- CLUE: The Drug Repurposing Hub

Current status of drug repurposing based on drug and disease search option is available at repoDB site. This drug repositioning database contains information of about 2051 diseases, all mapped to UMLS terms for easier integration [50].

- http://apps.chiragjpgroup.org/repoDB/

6. Conclusion

The process of drug repurposing or repositioning help the Pharmaceutical companies in terms saving capital expenditure and decrease efforts of scientific community from long drug discovery and development process that pass through much experimental and regulatory task. Drug repositioning works well for those drug molecules for which disease targets are not get altered over a period of time. All the drug repositioning hypothesis will not transferred to successful outcome. It was happened with bevacizumab (Avastin), a kinase inhibitor drug that failed to prove its efficacy during phase- III of clinical trial in gastric cancer therapy although it has good efficacy against colon, rectal, brain, lung and kidney cancer by targeting vascular endothelial growth factor (VEGF) and decreasing the blood supply to the tumor that required for tumor growth and metastasis [51, 52]. Similar thing happened for sunitinib, a kinase inhibitor where it has proven its efficacy in certain cancers while unable to show same in other cancers [53]. It is significant to consider the unique drug indication during repositioning with proper justification for risk and benefits ratio. Any cytotoxic anti-cancer drug may not be an ideal drug for cardiovascular disorder in same dose, as it may kill many normal cells with high proliferation index. But it can be utilized at low doses for drug repurposing with less side effects as in the case of methotrexate at 10–20 mg per week for rheumatoid arthritis due to its anti-inflammatory property. Although, there are many obstacles present on the path of drug repurposing now, but future will bring more advancement in the technologies with the help of combinatorial chemistry, virtual screening, data mining and artificial intelligence that raise the success rates. At the last, we hope that all these scientific advancements translated into clinical setting to improve oncotherapy and reduce the burden of cancer related mortality in the world.

7. Future perspective

Tumor is heterogeneous mutated cell mass with genomic instability that acquired new forms over period of time. As time goes on, tumor heterogeneity environment become less vulnerable to chemotherapeutic and radiation agent with development of tumor resistance in multiple ways. So, every tumor shows different pathological picture in every cancer patient and even different pattern of intratumoural mutation in same patient at different time interval. Based of therapeutic modality, specific subpopulation of drug tolerant cancer cells come out as resistant cells within tumor. So, it seems personalized medicine will be future of Cancer medicines. In these regards, single cell analysis, multiple omics, research autopsy,

and sampling from multiple regions can help. Based on tumor heterogeneity and evolution of drug resistance point of view, the drug repurposing might be not evolved as unjustifiable tool with time consuming approach, if not utilized for early stages of Cancer patients.

Drug repurposing involves many challenges like proper utilization of database, demand of expected repurposing drug, issues associated with intellectual property rights and patents. Although to accomplish efficient drug repurposing, there is a need to work from multiple paradigms. Many drugs get failed in third phase of clinical trials and Drug repurposing trials due to lack of efficacy, so it should be realized in well advance by combining multiple techniques. Literature belongs to applied sciences and medical fields containing important information for complementary relationship in between repositioning of drugs and its proposed targets. The vital information can be extracted with "text mining" tools like Biovista, BioWisdom, TextFlow, DrugQuest, Polysearch, etc. Based on semantic integration network approach, diverse information can be interrelated. Later, many algorithms in machine learning techniques can be developed to promote the efficacy and speed of drug repurposing. At present, multiple-omics discipline emerge out like genomics, proteomics, transcriptomics, bioinformatics, metabolomics and interactomics that consist of vast data related to biological sciences. Analyzing these multiple-omics disciplines with computational methods by integrative approach can be utilized to identify the best drug molecule that work at more than single target in different diseases. This approach may suit well with personalized medicine concept that will become inadvertent reality and demand in the case of oncotherapeutics. With these diverse but harmonizing computational with multi-omics incorporation, scientist and researcher achieve meaningful understanding of cellular physiology, Drug -receptor interaction, pathogenesis and prognosis of diseases, stages and types of same disease with acquired changes at molecular level, possible drug reactions, on-target and off-target interactions, diagnostic and prognostic biomarkers.

According to WHO, Cancer is a leading cause of death worldwide, accounting for an estimated 9.6 million deaths in 2018. The most common causes of cancer death are cancers of lung (1.76 million deaths), colorectal (862,000 deaths), stomach (783,000 deaths), liver (782,000 deaths), and breast (627,000 deaths). Definitely at present scenario priority should be given for these cancers. There are many diseases are coming under the category of orphan disease. According to U. S. FDA, an orphan disease defined as a condition that affects fewer than 200,000 people nationwide. There is good opportunity for repurposing to orphan drugs. According to Genetic and rare diseases (GARD) information center, many cancers comes under orphan diseases category like CDK4 linked melanoma (orphan drug Aldesleukin), carcinoid tumor (orphan drug Everolimus, Lutetium Lu 177 dotatate), chronic myeloid leukemia (orphan drug Bosutinib, Omacetaxine mepesuccinate), clear cell renal cell carcinoma (orphan drug Sorafenib, Temsirolimus). These all orphan drugs that utilized for rare cancers are good candidates for Drug repurposing in other common types of cancer. Also, the drugs like thalidomide which was once withdraw from the market due to its dangerous teratogenic effects in one class of human population but later approved by FDA for myeloma and other disease treatment. The negative and positive sides of this drug are contributed by anti-angiogenesis property. But this one off-target property was proved to defame its efficacy in one situation while with Drug repurposing in other condition it has proved its anti-cancer effects. Future will become where more robust and sound techniques will be utilized to create successful Drug repurposing candidate and making drug discovery and development process beneficial to Human kind.

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Conflict of interest

The authors declare that they have no competing interests.

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