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Original Article

Reinventing Medicines: Drug Repurposing as A New Frontier in Cancer Therapy

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ABSTRACT

Cancer is still the fourth major cause of morbidity and mortality despite the great progress made in the past few years in the understanding of the molecular mechanisms and the development of targeted therapeutic approaches. The very long and expensive timelines and the remarkably high failure rates that characterize the conventional drug development processes have lately brought attention to the concept of drug repositioning. Drug repositioning entails the search for new therapeutic applications for compounds that have long been approved and/or investigated for other diseases. This very appealing and innovative strategy has the capability to considerably reduce the costs and timelines associated with the drug development processes and also to overcome the safety concerns that are often caused by the conventional processes. This review aims to give a brief overview on the idea of the repositioning strategy for the treatment of cancer and its biological bases. The mechanisms that have the capability to behave in the role of antitumor compounds for those repositioned compounds include the interference of metabolic pathways, the prevention of angiogenesis, the induction of apoptosis and autophagy, the regulation of the immune system, the interference of the repair mechanisms for the DNAs, and the epigenetic mechanisms. The efficient repositioning compounds that have already demonstrated their therapeutic efficacy in the clinics are briefly discussed. Moreover, the promising techniques that have the ability to outline the new prospects for the repositioning strategy for the treatment of oncologic diseases in the near future are also briefly mentioned and discussed. This concerns the integration of the Artificial intelligence and big data for the repositioning strategy for the treatment of oncologic diseases. Additionally, the new concept for the repositioning strategy for the treatment of oncologic diseases also entails the concerns on intellectual property rights.

Keywords: Drug Repurposing, Cancer Therapeutics, Polypharmacology, Personalized Oncology

INTRODUCTION

Cancer is a group of several diseases that arise in a progressive manner due to uncontrolled cellular proliferation [1,2]. Although each has distinct properties, all contribute to the disease through basic mechanisms [3,4]. The cells in cancer can be malignant or normal. They proliferate when no signals are given, ignoring signals for its end or apoptosis. They induce vascular proliferation towards malignancies; supply oxygen and nutrition; remove toxic material. They also evade the immune system's attention so it does not hinder their proliferation and survival. Cancerous cells often have a large assortment of alterations in chromosomes. The cells become so dependent on them that they cannot function normally without those changes [5]. Tumor progression is usually depicted as stages of mutation and growth. A normal cell is converted into a malignant cell with less than 10 mutations [2,6]. Stages include initial mutation, hyperplasia, dysplasia, in situ cancer, and invasive/malignant tumors. In situ cancer is characterized by abnormal development and appearance of the cell and its progeny, while invasive/malignant tumors allow the tumor to disseminate to other tissues and discharge cells into the lymph or bloodstream, potentially generating new malignancies. Malignant tumors can metastasize across the body, contributing to targeted therapy resistance [3]. Cancer-critical genes usually fall into two main classes: proto-oncogenes and tumor suppressor genes [7]. Proto-oncogenes promote cell growth, while tumor suppressor genes halt the process. Changes in the genes may lead to the hyperactivity of proteins that support growth-promoting pathways, causing cells to proliferate at a

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faster rate than they would without mutation [2]. Most malignancies fall into three major categories, which are carcinomas, sarcomas, and leukemias or lymphomas. Human cancers are dominated by carcinomas, accounting for 90%; whereas sarcomas form solid tumors that invade connective tissues. The immune system and blood-forming cells are responsible for lymphomas and leukemias, respectively, and account for 8% of all human malignancies. Tumors are also classified based on their cell type and tissue of origin [8]. Radiation and chemical carcinogens induce mutations and DNA damage, and can be regarded as "initiating agents" since mutations in critical target genes represent the earliest event in the process leading to malignancy. [9]

2. Drug repurposing strategies

In summary, drug repurposing can be divided into three stages: identifying the core targets of the disease (hypothesis generation), determining the efficacy of the drug through in vitro and in vivo models and proceeding to phase II clinical trials in cases where phase I trials have yielded adequate data. [10-12] The inception stage is critical since hypothesis generation is the key to any drug repurposing endeavor. [13] Historically, drug repurposing in oncology has largely been driven by either an understanding of the disease pathways or through serendipitous findings. Thus, designing innovative strategies to match existing drugs with newfound applications could increase the success of drug repurposing. Identification of a potential repurposed drug can be made using computational and experimental methods. The experimental approach considers tools such as induced pluripotent stem cell models and function-first phenotypic screenings (or reverse chemical biology), [14,15] while computational methods use target-centric, knowledge-driven, signature-aligned, pathway-focused, and mechanism-specific strategies. [16,17] More often, these techniques are synergistically utilized. Notably, high-throughput screening using sophisticated models can identify compounds that mitigate disease symptoms without necessitating pre-existing knowledge about the drug-target interactions. [18,19] Current computational methodologies, such as merging drug effects with clinical disease signatures and model systems that predict disease-modifying effects, are available for the selection of drug candidates suitable for drug repurposing in cancer. These tools can identify ligands, decode drug ingredient binding schemas, and highlight promising candidates from an expansive list of potential compounds. [18,20,21] In summary, although the idea of drug repurposing is long-established, it is only recently that technological advances, such as the ones outlined in this article, have led to the development of cutting-edge strategies that can be consciously paired with novel indications.

Experimental Approaches

Organoid Models of Cancer

Organoids are described as "stem cell-containing self-organizing structures" and tumoroids represent a special form of cancer organoids. [22] Organoids represent in vitro tissues that are derived from human stem cells, organ-specific progenitor cells, or even disassociated tumor tissues, that are cultured in special ECM-based media with relatively high success rates. Tumoroids reflect the primary tissue both architecturally as well as functionally and maintain the histopathological features, genetic profile, mutational landscape, and even responses to therapy. [23] The utilization of tumoroids is growing, and their value for basic research and the initial phases of drug development has been realized. [24] The antitumor efficacy of cisplatin was discovered to be significantly lower in PDOs prepared from NSCLC tissues compared to cell lines, which exemplified how patient-derived material can provide valuable information about possible resistance mechanisms.[25] Regarding gastrointestinal malignancies, several studies have utilized PDOs as tools to assess drugs and probe into likely therapeutic pathways.[26,27] Such models have successfully reflected the utility of tumoroids in the correct reproduction of KRAS-mutant metastatic rectal cancer with microsatellite stability following hepatic resection and treatment with neoadjuvant combination chemotherapies in colorectal cancer,[28] as well as assessed drug responses in HCC [29,30] and also model treatment resistance patterns observed in esophageal squamous cell carcinoma. [31]

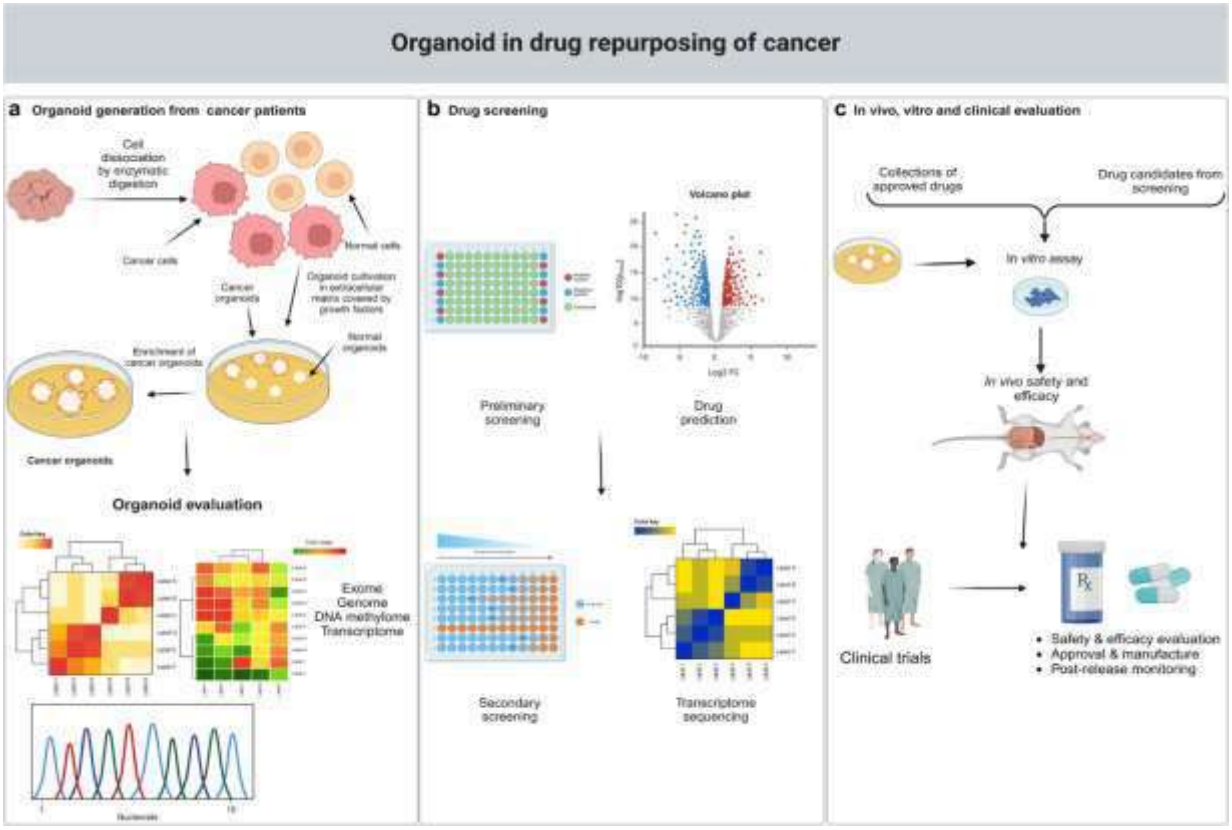

Figure 1: Tumoroids model in drug repurposing. a Schematic showing the generation of patient-derived organoids (PDOs) from a cancer biopsy: enzymatic digestion, embedding in extracellular matrix, addition of growth medium and cancer tumoroids enrichment by media compound withdrawal and/or addition of mutation related inhibitors. b, c the tumoroid model is used to screen drug repurposing candidates, resulting in the identification of drugs for preclinical and clinical testing.

Computational approaches

Computational methodology has emerged as a powerful tool in drug repurposing. [32,33] With increased omics technologies along with breakthroughs in big data analytics, machine learning, and computational algorithms, our understanding of the mechanisms and modes of action within oncology has deepened considerably. These computational techniques give wide access to disease-centric as well as drug-centric data. [34,35] Multiple computer-assisted drug repurposing strategies such as molecular docking, network analysis, data mining, similarity analysis, machine learning, and transcriptional signature techniques, are at the doorstep of the researchers. [36,37] By these computational approaches, we can investigate the anticancer prospect of drug repurposing further and provide disease-related data for the repurposing of drugs. [38,39] The identification of oncogenic pathway inhibitor activity through computer-aided drug repurposing approaches also represents a robust method. [40,41] These repositories not only amplify the therapeutic potential of repurposed drugs across various diseases, [42,43] but also strengthen chemotherapeutic strategies providing novel strategies to reduce the development of resistance and tailor treatments for maximizing patient-specific outcomes. [44,45]

3. Classes of Repurposed Drugs in Cancer

Table1: Repurposed drugs for cancer treatment with their new indication, old and new targets and development status

Pharmacological Class and Drug name	New Therapeutic Indication	New Target	Original Target	Development Status	References
Anti-Platelet Aspirin	Gastric, esophageal, colorectal, pancreatic, ovarian, endometrial, breast, and prostate cancers	P1K3CA, Mtorc1 and AMPK	COXs	Phase II (NCT00468910) and III (NCT02301236) clinical trails, meta-analysis	[46-54]
Anti-Diabetic Metformin (Biguanides)	Colorectal, breast, pancreatic, prostate, lung and cervical malignancies	Cell cycle/Pstat3, S6 kinase, and Mtor/AMPK/	Mitochondrial respiration	Phase II (NCT05929495) and III (NCT03685409)	[55-63, 64-66, 67-76]
Pioglitazone (TZDs)	Breast, prostate, and colon cancer	PPARy	PPARy	Phase II trails (NCT00099021)	[77-83]
Desmopressin	Colon cancer	COX-2 and CD1	AVPR2	Preclinical	[84,85-87]
Anti-Helminthic Flubendazole (benzimidazole)	Neuroblastoma, multiple myeloma, leukemia, lung, liver, colorectal, and breast cancer	Apoptosis (caspase 3 and 7)	Tubulin polymerization	Preclinical	[88-92]
Parbendazole	Pancreatic cancer	Apoptosis, cell cycle, and DNA damage	Tubulin polymerization	Preclinical	[93]
Mebendazole (MZ)	Glioblastoma, melanoma, prostate, breast, brain, ovarian, colon, lung, colorectal and endocrine cancers	Cell cycle, apoptosis (caspase-3 pathway), ABL and BRAF	Tubulin polymerization	preclinical	[94-96, 97-100,101,102]
Niclosamide	Colon, prostate, liver, ovarian and breast cancers	Wnt/ beta-catenim, NF-KB, Mtor and JAK/STAT3 pathways	Uncoupling of oxidative phosphorylation	Preclinical	[103,104 105,106-108]
Clioquinol	Leukemia and maliganant myeloma	HDAC	DNA replication	Preclinical	[109,110]
Ritonavir	Ovarian, pancreatic, and breast cancer, lymohocytic leukemia	Apoptosis	Protease inhibitors target HIV	Preclinical	[111-113]
Anti-viral Ribavirin	Acute myeloid leukemia (AML)	Induces VEGF mRNA translation	RNA replicating	Phase II clinical trial (NCT00559091)	[114]
Cidofovir	Glioblastomas	Apoptosis	Viral DNA polymerase	Preclinical	[114]
Angiotensin Receptor Blocker Losartan	Pancreatic cancer	Depleting the matrix and reducing collagen I levels	Angiotensin receptor	Phase II clinical trails (NCT01821729)	[115,116, 117,118]
Candesartan	Colon cancer, prostate cancer, liver and kidney cancer	VEGF expression	Angiotensin receptor	Preclinical	[117,119, 120,121,122,123]

Irbesartan	Colon cancer, liver and kidney cancer	AP-DNA binding, pErbB3, and p38/ MAPK	Angiotensin receptor	Preclinical	[115,116, 117,119,120,123]
Telmisartan	Colon cancer, liver and kidney cancer	pErbB3, p38/MAPK caspase-3, Bcl-2, PI3/AKT pathway	Angiotensin receptor	Preclinical	[115,116, 117,123,124]
ACE Inhibitor Captopril	Colorectal liver metastases, prostate cancer, liver and kidney cancer	P53 expression	ACE	Preclinical	[115,116, 117, 119,120,121,122,123,124]
Enalapril	Colorectal cancer (CRC)	IGF-IR 1	ACE	Preclinical	[117, 119,120]
Beta-Blockers Propanolol	Ovarian, colorectal, lung, prostate, breast cancer, multiple myeloma, pancreatic, neuroblastoma, angiosarcoma, and leukemia	p-AKT/p-ERK/p-MEK and CD8+ T cells JNK signaling pathway and ROS.	Beta receptors	Phase I trails (NCT03633747) Phase II trails (NCT02596867)	[125,126-132,133,134]
Direct Vasodilator Minoxidil	Ovarian cancer	Caspase-3	ATP- sensitive potassium channels	Phase II trials (NCT05272462)	[135-137]
Hydralazine	Prostate cancer	Induces demethylation, re-expressing suppressed genes	Direct vasodilator	Preclinical	[121,122]
Tezosentan	Various cancer types, especially with high expression of endothelin receptor type A	Endothelin receptor A	Endothelin receptor A/B	Preclinical	[138,139]
Cardiovascular Antihyperlipidemic Fenofibrate	Breast cancer, lung cancer	AMPK, NF-KB, and ERK signaling	PPARa	Preclinical	[140,141]
Potassium K+ Channel Inhibitors Glipalamide	Melanoma, lung, stomach, and breast cancers	Kv10.1, Kv10.2 (EAG2), and Kv11.1 channels	K channel (SUR)	Preclinical	[142,143]
Verapamil	Neuroblastoma and prostate cancer	K and Ca channels	T- and L- type Ca2+ channel antagonist	Preclinical	[142,143]
Astemizole	Various cancer cell lines	Kv10.1	H1- antagonist	Preclinical	[142,143]
Calcium (Cav) Channel Blockers Mebefradil	High-grade glioma tumors	T- type Ca2+ channel	T and L-type Ca2+ channel	Phase I trails (NCT01480050)	[144,145]
Nifedipine	Colon cancer	PDL-1	Calcium channel	Preclinical	[117, 119,120]

Antibiotic Bedaquiline	Breast	Mitochondrial ATP-synthase	ATP synthase	Preclinical	[146-148]
Doxycycine (tetracycline)	Various cancer cell lines	AMPK-mediated Mtor, WNT/b-catenin, and PI3K/AKT	30S ribosomal subunit	Preclinical	[111,149, 150,151-154,155-157]
Clofoctol	Various cancer cell lines	UPR pathway	Bacterial protein synthesis	Preclinical	[158,159]
Doxorubicin (Anthracyclines)	Breast cancer	DNA intercalator	DNA intercalator	Approved	[160-162]
Minocycline (Tetracycline)	Ovarian, breast, cancer, glioblastoma	Cell cycle arrest, cyclins A, B and E	Inhibit the 30S ribosomal subunit	Phase II trails (NCT01580969)	[163]
Tigecycline (tetracycline)	Gliomas, myeloid leukemia, non-small cell lung cancer	Cell cycle arrest	Inhibit the 30s ribosomal subunit	Phase I trails (NCT01332786)	[149,150, 164,165,166,167]
Ciprofloxacin (Fluoroquinolones)	Leukemia, osteoblastoma, osteosarcoma, colon, bladder and prostate cancers	mRNA production	Inhibit bacterial gyrase	Preclinical	[168,169]
Anti-Malarial Chloroquine	Glioblastoma	Autophhagy	Inhibits heme polymerase	Preclinical	[94,95,170-172]
Artesunate	Leukemia, Kaposi's sarcoma	ROS production and apoptosis	Free radicals' generation	Preclinical	[170]
Mefloquine	Breast, leukemia, gastric, cervical, and colon cancers	P-gp expression, production of ROS	Inhibits 80S ribosome	Preclinical	[170-172]
Antipsychotic Haloperidol	Pancreatic cancer	DRD2	DRD2	Preclinical	[173-175]
Penfluridol	Pancreatic cancer	DRD2, autophagy, JAK2-STAT3 and ERK/AKT signaling pathways	DRD2	Preclinical	[173-175]
Nonsteroidal Anti-Inflammatory Drug (NSAID) Diclofenac	Pancreatic cancer	Wnt/Beta-catenin signaling pathway	COX5	Preclinical	[176,177, 178]
Celecoxib (selective COX-2 inhibitor)	Breast cancer	Wnt/Beta-catenin signaling pathway	COX-2	Phase II trials (NCT01695226)	[164,165]
Disease-Modifying Antirheumatic drug (DMARD) Auranofin	Various cancer types	TrxR, UPS system	Redox enzymes	Phase I (NCT01737502) and Phase II (NCT01419691) trails	[179-181]
Anti-Epileptic Oxcarbazepine	Various cancer types	Cell cycle arrest, HDAC, P13K-Akt-mTOR pathway	Na channel inhibitor	Preclinical	[182,183]
Lacosamide	Glioblastoma	CRMP2	Na channel	Preclinical	[184-189]

Lamotrigine	Brain tumors	N-, L-, and P-type Ca channels, 5-HT3 receptors	Na+ channels	Preclinical	[188,189]
Anesthetic Medications Ketamine	Lung cancer, ovarian cancer, breast cancer, hepatocellular carcinomas	CD69, P57, glutathione peroxidase 4	NMDA receptor	Preclinical	[85]
Propofol	Squamous cell carcinoma	Caspase and MAPK pathways	GABA receptors	Preclinical	[190,191]

4. Rationale for Drug Repurposing in Oncology

Cancer is a biologically complex and heterogeneous disorder that comprises several genetic, epigenetic, and metabolic changes, and it is often challenging to treat using single-target anticancer therapies. Also, despite recent advances in the field of oncology, a significant proportion of cancer patients have a poor prognosis because of the late stage of cancer diagnosis, development of resistance to cancer therapies, toxicological effects of available anticancer medicines, and higher costs associated with cancer therapies. The above-stated challenges associated with cancer therapies have established the need for alternative and complementary therapies. Repurposing of medicines provides a reasonable approach by which novel anticancer therapies can be identified using already approved or investigational medicines. One of the main drivers facilitating the repurposing of drugs for cancer therapy would be polypharmacology, which pertains to the interference of a single compound in several target molecules involved in the pathogenesis of cancer. Many drugs used in non-cancer therapy tend to be pleiotropic; these drugs affect biological processes such as cell proliferation, apoptosis, angiogenesis, inflammation, immunomodulation, and metabolism. The pleiotropy associated with these non-cancer drugs can be beneficial in cancer therapy because it would be possible to target several pathological pathways simultaneously. There are a number of examples that have proven that drug repurposing is a feasible area to target for effective treatment of cancer. For instance, thalidomide, which acts as a sedative, has been repurposed as a treatment for multiple myeloma owing to its antiangiogenic and immunomodulatory action. Another example is metformin, an antidiabetic drug, which has been proven to act as an anticancer drug owing to its ability to target cancer cell metabolism and impede growth. [192] Repurposing of drugs is equally important within the context of the treatment of rare cancers and drug-resistant cancers, in which the development of drugs faces the constraint of the smaller number of patients as well as the associated high research costs. Repurposing of drugs acts as an affordable and accessible treatment approach having an established safety profile. Repurposing drugs in the case of drug-resistant cancers can either function alone or along with standard treatment approaches in eliminating the drug-resistance mechanism. Hence, repurposing of drugs is an innovative approach in the treatment of cancers. [193,194]

5. Mechanisms of Action Underlying Repurposed Drugs

Repurposed drugs demonstrate anticancer properties by modulating various hallmark pathways of cancer biology. Another mechanism of repurposed drugs is the use of aberrant metabolism in cancer cells. Tumors exhibit a high reliance on aerobic glycolysis, glutamine metabolism, and lipogenesis for supporting high cell division rates. Repurposed drugs like metformin and statins work by interfering with these high dependencies of tumors. Another mechanism used by repurposed drugs is the inhibition of angiogenesis. Angiogenesis is a highly essential mechanism for the development of tumors. Repurposed drugs like thalidomide and propranolol work by interfering with the signaling of vascular endothelial growth factor (VEGF) and the proliferation of endothelial cells. This results in the reduction of tumor vasculature and the deprivation of nutrients. [195] In addition to metabolic and vascular properties, repurposed drugs also demonstrate properties in cell survival, immunity, as well as genomic stability. Most of these drugs cause

apoptosis or autophagy via the activation of intrinsic cell death pathways, induction of oxidative stress, or inhibition of pro-survival signaling pathways PI3K/Akt/mTOR. For instance, antipsychotic and antimalarial drugs can cause mitochondrial dysfunction-mediated autophagic cell death. Moreover, some repurposed drugs demonstrate immunomodulatory properties by upregulating antitumor immunity through the attenuation of immunosuppression or activation of immune effector cells. Some repurposed drugs also affect DNA repair pathways by making cancer cells hypersensitive to DNA damage or chemotherapeutic drugs. This occurs in antiparasitic/antibiotic drugs. Lastly, epigenetic modulation stands as an important principle. This takes place when drugs cause changes in DNA methylation status as well as histone acetylation status, resulting in the reactivation of tumor suppressor genes and downregulation of oncogene expression. [196,197]

6. Challenges of Drug Repurposing

Whereas systematic drug repurposing has opened new avenues, few of the repurposed drugs in cancer or indeed in oncology have ultimately entered clinical practice so far. Although the drug repurposing process is considered to be much faster and cheaper compared with classical drug development, prematurely entering clinical trials may actually delay the detection of more specific therapies. In addition, as is true for all drug development, late-stage clinical trial failure can still occur. Other challenges include legal and regulatory barriers and pharmacological/dosing issues. [198,199] We would hope that these might be surmounted to realize fully the potential of drug repurposing. Pharmacological challenges with high effective concentrations may not be clinically achievable. While the idea of drug repurposing is certainly in its promising stages, there are a variety of pharmacological concerns. Drugs targeted against specific receptors, cells, or organs may not prove as effective when utilized for different disease indications. As such, higher doses or increased drug interactions may be required to achieve therapeutic levels, which may then introduce new mechanisms of action unrelated to their indicated use. [200]

FUTURE DIRECTIONS

The future trends in repurposing drugs for cancer treatment are being increasingly determined by the incorporation of artificial intelligence (AI) technology into big-data platforms, which allow for quick screening of drugs based on large genome, transcriptome, and clinical data. Such technology will be able to provide new target relationships for drugs, predict the efficacy of drugs, and reveal new patterns in real-world data in an efficient manner without increasing the cost associated with discovering new drugs. Use of AI modeling with electronic health records will improve the efficacy of repurposing in cancer treatment. A further significant area of research encompasses the combination of repurposed drugs with conventional therapies such as chemotherapy, targeted therapies, immunotherapy, and radiation. A combination of various therapies can improve therapeutic efficacy and sensitivity to cancers caused by resistance to existing therapies and decrease toxicity levels of existing drugs by taking them in lower concentrations. Meanwhile, personalized medicine and biomarker-assisted repurposing have been increasingly emphasized, wherein the molecular profiles of patients are taken into consideration for deciding the repurposing of appropriate drugs for the patient based on their molecular profiles. It is also expected that collaborative efforts in the form of consortia of drug repurposing and public/private collaborations would increase. This would help in collaborative work in the area of data sharing, resource integration, and expertise. Also, the development of better and adaptive regulatory infrastructure specific to the area of repurposed drugs would be essential. This would help in quicker approvals, clarity in terms of intellectual properties, and incentivation of clinical trials. Thus, the area of drug repurposing would emerge as a sustainable, innovative, and patient-focused area in the future of cancer therapy. [201-204]

CONCLUSION

In conclusion, repurposing of drugs appears to be a very useful approach for tackling the ever-ongoing issues connected with cancer therapy by providing a means for efficiently lowering cancer treatment costs, overcoming the problem of resistance, cytotoxicity, and helping in the treatment of aggressive or rare types of cancers with very limited therapeutic alternatives. This present review describes the

effectiveness of repurposed drugs with the ability to combat several "hallmarks of cancer" including their aberrant metabolism, angiogenic potential, evasive immunity, instability in the genome, and mutated cell survival pathways by using the pleiotropic effects of repurposed drugs with the advantage of well-recognized safety profiles. Advances in patient-derived in vitro organoids and computer-aided methodologies using artificial intelligence tools greatly improved the chances of rediscovering repurposed antitumor drugs for future therapy. Despite the presence of pharmacological barriers, dealing with the problem using joint collaborative research and improved biotechnological strategies for a better understanding would greatly improve the speedy translation of repurposed antitumor drugs at the clinical trial phase for better future outcomes in cancer treatment.

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