Drug Repurposing In Oncology: Progress, Challenges, and Collaborative Pathways Toward Novel Cancer Therapies

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Drug repurposing is the process of trying to identify new therapeutic uses for approved existing drugs, which opens opportunities for development timescale shortening as well as early-stage safety de-risking. This review narrates the recent developments and challenges to drug repurposing in oncology, including translation strategies. We emphasize clinical examples, such as metformin (based on several randomised trials), propranolol (premature epidemiological and phase II proof) and thalidomide (FDA-approved for multiple myeloma). Repurposing has clear benefits but the reuse courses are difficult to realize because of lack of biomarkers, intellectual property barriers, regulatory issues and complicated trials designs. We also describe computational strategies, such as signature-reversal strategies interrogating from the TCGA integrative genomic resources. We conclude by delineating regulatory, economic and collaborative mechanisms that must be in place to achieve translation. This review offers current perspectives for biotechnological and clinical oncology researchers, and suggests actionable recommendations to sustain future repurposing pipelines.

Keywords: Drug repurposing; leukaemia; Novel cancer therapies oncology; Tumors.

In oncology, drug repurposing has become a promising translational strategy that provides a workable answer to the problems associated with conventional drug development, including exorbitant expenses, protracted timelines, and frequent failures.[1] This method increases patient access to novel treatments and lessens the burden of side effects by utilizing already-approved medications with proven safety profiles to speed the transition from lab research to clinical application.[2] In environments with limited resources, where access to innovative cancer treatments is still a constant obstacle, the importance of drug repurposing is especially evident.[3] Drug repurposing in oncology has a number of drawbacks despite its potential. In order to using single-agent approaches, combination therapies are frequently required due to the complexity of cancer biology, which is characterized by heterogeneity and multidrug resistance.[4] However, the requirement to manage drug interactions, coordinate dosing, and address various mechanisms of action complicates the design and implementation of clinical trials for combination regimens.[3] The incorporation of

repurposed medications into clinical practice is further impeded by regulatory and commercial obstacles, such as restricted patent protection and diminished financial incentives.[5] Recent developments in computational biology, organoid technology, and high-throughput screening have started to address some of these issues by making it possible to more precisely identify and validate repurposed medications.[6] Personalized therapy and the development of new anticancer agents from existing drug libraries are now supported by patient-derived tumor organoids and biomarker-driven approaches.[7] Precision oncology's reach has been expanded by the use of computational prediction tools and curated databases, which have improved the capacity to match patient tumor profiles with possible repurposed therapies.[8] Converting encouraging preclinical results into solid clinical outcomes is a recurring problem in the field, especially in light of the requirement for carefully planned prospective studies and the incorporation of multi-omics data for patient stratification.[9] The broad use of repurposed medications in oncology is still hampered by a lack of predictive biomarkers, regulatory barriers, and inadequate financial incentives.[10]

By showcasing noteworthy success stories and analyzing the field's potential future directions, this review seeks to present a thorough overview of the state of drug repurposing in oncology today. In order to influence future research and clinical practice, we will examine the approaches and technologies that have recently fueled advancements, assess the obstacles that still exist, and suggest solutions.[11]

Scope of the article

The following review provides an overview of the piece looks into drug repurposing by using current biotechnological tools. It covers approaches such as genomic profiling, transcriptomic signature analysis, molecular pathway mapping, computational prediction platforms, and high-throughput screening technologies. These techniques play a key role in modern bioscience studies. They help spot new ways to use existing drugs for treating cancer. The review pulls in details on mechanisms of action, biomarker creation, and strategies for moving research to real-world use. The article aims to present scientific advances, existing challenges, and future directions with the purpose of improving therapeutic development and patient outcomes in oncology.

What is Drug Repurposing in the Oncology context?

Beginning with the early days of cancer chemotherapy, drug repurposing in oncology has a long and dynamic history. One of the pioneering discoveries in the field was the discovery that mustard gas, a chemical warfare agent, could cause tumor regression in skin cancers.[12] This coincidental finding paved the way for later attempts to find novel therapeutic applications for already-existing substances. The approach grew over time to encompass not only off-patent, generic medications but also agents that were still under patent and even medications that had not worked for their initial purposes. A notable example of pharmaceutical innovation through repositioning is the conversion of tamoxifen, which was first created as a contraceptive, into a ground-breaking treatment for breast cancer.[13] Drug repurposing gained popularity as a practical substitute for traditional drug development as its cost, complexity, and duration increased. Due to established safety and pharmacokinetic profiles, which eliminate the need for early-phase clinical trials, the procedure is typically quicker and less costly. Repurposing can cut timelines to about six years and costs to a fraction of traditional approaches, whereas developing new drugs can take over ten years and cost billions of dollar.[14]

Collaborative efforts between academia, industry, and non-profit groups have advanced the field; organizations like the Repurposing Drugs in Oncology Project and the National Center for Advancing Translational Sciences have made significant contributions. Despite these developments, issues with profit and intellectual property have remained obstacles, especially for off-patent medications, which is why independent and academic research is crucial to producing clinical evidence.[15-16] Developments in artificial intelligence, computational biology, and genomics have influenced the evolution of drug repurposing strategies in oncology.[17-18] These days, personalized oncogenomics programs use tumor genetic data to inform logical clinical judgments, allowing for the choice of unconventional therapeutic approaches. For example, the discovery of particular genetic

changes in tumors has made it possible to repurpose medications like imatinib, which was first created to treat chronic myeloid leukemia, to treat gastrointestinal stromal tumors that have comparable mutations.[19-20]

The use of multidrug personalized approaches, which frequently combine repurposed agents with novel therapeutics to overcome resistance mechanisms, has been further spurred by the realization that tumor heterogeneity and clonal evolution are the main causes of therapy resistance and relapse.[21-24]

Drug repurposing has been transformed by computational and artificial intelligence (AI)-driven approaches that combine knowledge graphs, machine learning models, and automated literature searches to forecast drug-target interactions and suggest promising candidates.[25-27] As demonstrated by the use of tools such as the Connectivity Map and The Cancer Genome Atlas, signature-based and sequence-based approaches, which use gene or protein expression patterns from omics data, have also made it easier to identify medications that can reverse disease-associated signatures. Even with these technological advancements, there are still difficulties in managing large genetic datasets, detecting and validating cancer driver mutations, and dealing with resistance brought on by continuous tumor evolution.[28-29]

Traditional drug development is fundamentally different from drug repurposing. High attrition rates, a significant financial investment that frequently exceeds $2 billion and spans more than ten years, as well as extensive preclinical and clinical studies are characteristics of the conventional pathway for oncology drugs.[30-33] Repurposing, on the other hand, makes use of medications with proven pharmacokinetic, toxicity, and safety profiles, enabling quick clinical translation and a lower failure rate.[34-37] Cost and accessibility are important factors in low-income environments, where this strategy can be especially helpful.[38-39] Additionally, repurposed medications can be quickly used in combination therapies, providing patients with limited effective treatments or drug resistance with new options. The broad clinical use of repurposed medications in oncology is still limited, though, by financial and regulatory barriers as well as a lack of patent incentives.[40-41] Drug repurposing in cancer treatment has a number

of justifications. It is motivated by the pressing need for faster, less harmful, and more effective treatments, particularly given the limitations of existing therapies and the rising incidence of cancer.[42-43] By utilizing off-target effects pertinent to cancer pathways, like kinase inhibition, repurposing can reveal novel mechanisms of action for already-approved medications, facilitate combination strategies to overcome resistance, and broaden the clinical pipeline.[44] The possibility of cross-indication repurposing is further supported by the biological similarities between cancer and other illnesses, such as cardiovascular disorders.[45]

To find promising candidates for repurposing, systematic methods like gene expression profiling and connectivity mapping are being utilized more and more.[46-47]

In oncology, drug repurposing offers significant advantages. In settings with limited resources and for rare or neglected cancers, repurposed medications provide faster development timelines, lower costs, and better access to therapies.[48-50] The strategy boosts patient reach, permits individualized care, and raises the possibility of regulatory approval. Additionally, it makes it easier to implement combination treatments that can improve effectiveness, stop metastases, alter the metabolism of cancer cells, and get past resistance mechanisms. The discovery of novel therapeutic targets and drug interactions has been further improved by the application of computational and experimental approaches, as well as AI and bioinformatics tools.[51-52] Notwithstanding these benefits, there are still many obstacles to overcome in oncology drug repurposing. The development of universally effective treatments is complicated by the biological complexity and heterogeneity of cancer, and regulatory requirements that might not allow for combination strategies frequently hinder the design of clinical trials.[53] Financial and regulatory obstacles further impede clinical adoption, and intellectual property restrictions and a lack of patent incentives diminish industry interest, especially for generic medications.[54-55] Biases in retrospective research, restricted access to information on compounds that have been shelved, and the absence of centralized repositories for discontinued medications are further challenges. Technical constraints and data quality concerns also make it difficult to integrate

big datasets with sophisticated computational tools.[56-57] All things considered, drug repurposing in oncology has advanced from accidental discoveries to a complex, interdisciplinary strategy that capitalizes on developments in artificial intelligence, computational biology, and genomics. This approach has a lot of potential to increase the number of cancer treatment options available, speed up therapeutic development, and lower costs, but achieving its full potential will necessitate concerted efforts to remove financial, scientific, and regulatory obstacles.

Methods and Strategies for Drug Repurposing in the Treatment of Cancer

The integration of computational, experimental, and molecular approaches has changed the landscape of drug repurposing in oncology. Each of these approaches brings special strengths to the identification and validation of novel therapeutic opportunities for cancer patients. The field now uses a wide range of advanced in silico, high-throughput, and pathway-based techniques to speed up the conversion of current medications into new cancer indications, building on a history of fortuitous discoveries and practical clinical observations. In the current era of drug repurposing, computational and in silico screening techniques have become essential tools. These methods use artificial intelligence, systems biology, and bioinformatics to analyze large datasets, forecast drug-target interactions, and rank candidates for experimental validation. The methodical examination of molecular networks made possible by the application of knowledge graphs and machine learning algorithms reveals hitherto unknown links between medications and carcinogenic pathways. For instance, signature-based techniques look for substances that can reverse disease-associated transcriptional signatures by comparing the gene expression profiles of cancer cells with those produced by different medications. This has been made possible by resources like the Cancer Genome Atlas and the Connectivity Map, which offer extensive omics datasets that make it easier to find repurposing candidates based on pathway perturbation and molecular similarity. Prioritizing medications with good safety profiles and well-established pharmacokinetics is made possible by the combination of clinical and pharmacological data with these computational techniques.

Notwithstanding the potential of computational methods, strong experimental validation is necessary to convert in silico predictions into clinically useful outcomes. In this regard, high-throughput screening platforms have become essential because they allow for the quick evaluation of sizable drug libraries against a variety of cancer cell lines and patient-derived models. The impact of thousands of compounds on cell viability, proliferation, and apoptosis is assessed by these platforms using automated technologies, producing rich datasets that guide the selection of candidates for additional research. The resolution of these screens has been further improved by developments in transcriptomics and proteomics, which make it possible to identify medications that molecularly alter important oncogenic pathways. To guide the logical design of combination therapies, transcriptomic profiling, for example, can show how candidate drugs affect the expression of genes linked to tumor growth, metastasis, and resistance. By combining computational predictions with high-throughput screening data, a potent feedback loop is produced that improves the selection of repurposing candidates and speeds up their advancement through the preclinical pipeline.

Drug repurposing relies heavily on pathway analysis and molecular targets. The rational selection of medications that can modulate these pathways, either alone or in conjunction with other agents, has been made possible by the discovery of actionable genetic alterations and dysregulated signaling cascades. In order to guide the repurposing of medications that may have been developed for other indications but possess pertinent mechanisms of action, pathway-based approaches use knowledge of cancer biology to identify points of vulnerability within the tumor. For instance, imatinib, a medication initially created for chronic myeloid leukemia, was successfully repurposed for the treatment of this uncommon cancer after activating mutations in the KIT gene were found in gastrointestinal stromal tumors. Similarly, mTOR inhibitors, which were first approved for organ transplantation, are now being evaluated in oncology settings due to the discovery of aberrant PI3K/AKT/mTOR signaling

in a variety of malignancies. These examples underscore the importance of integrating molecular profiling with pharmacological knowledge to expand the repertoire of available cancer therapies. DNA methylation and other epigenetic changes are important for both the pathophysiology of cancer and the effectiveness of treatment. Understanding the mechanisms behind drug sensitivity and resistance can be gained by analyzing the methylation patterns in important oncogenes and tumor suppressor genes. For example, promoters of tumor suppressor genes may become silenced due to hypermethylation, which promotes unchecked cell division and tumor growth. DNA methyltransferase inhibitors and other medications that reverse abnormal methylation have demonstrated promise in the treatment of hematologic malignancies and are being investigated for potential repurposing in solid tumors. A thorough grasp of the molecular landscape of cancer is made possible by the combination of methylomics data with transcriptomic and proteomic analyses. This knowledge informs the choice of medications that can improve therapeutic efficacy and restore normal epigenetic regulation.

Numerous noteworthy success stories in oncology drug repurposing have resulted from the convergence of computational, experimental, and molecular approaches. The potential of this approach to provide patients with few options with transformative therapies is demonstrated by the repositioning of thalidomide, which was first created as a sedative, for the treatment of multiple myeloma. In a similar vein, a number of clinical trials are examining the potential of metformin, a commonly prescribed antidiabetic medication, to suppress the metabolism of cancer cells and make tumors more susceptible to traditional treatments. These illustrations show how important it is to use current pharmacological understanding and practical clinical experience to accelerate the creation of novel cancer therapies. Notwithstanding these developments, there are still a number of obstacles to overcome in the application of medication repurposing techniques in oncology. Finding universally effective treatments is made more difficult by the biological complexity and heterogeneity of cancer as well as the dynamic nature of tumor evolution. The durability of response to repurposed drugs is frequently limited by resistance mechanisms that are fueled by genetic diversification and clonal selection. Clinical decision-making involving large-scale omics datasets necessitates interdisciplinary cooperation and advanced analytical tools. The broad use of repurposed medications in oncology practice is further limited by regulatory and financial obstacles, such as complicated approval procedures and limited patent incentives.

Ongoing efforts are concentrated on improving computational models, increasing high-throughput screening capabilities, and integrating multi-omics data to fully capture tumor biology in order to overcome these obstacles. Collaborative initiatives involving academia, industry, and regulatory agencies are essential to facilitate data sharing, standardize methodologies, and streamline the translation of promising candidates into clinical trials. The effectiveness and impact of drug repurposing initiatives will be further increased by the creation of centralized repositories for shelved and abandoned compounds as well as methodical approaches to data integration and analysis.

Future developments in artificial intelligence, systems biology, and precision medicine will propel the ongoing development of drug repurposing in oncology. Deep learning algorithms have the potential to predict patient-specific therapy responses and reveal new drug-disease associations when applied to multi-dimensional datasets. Real-world data from patient registries, pharmacovigilance databases, and electronic health records will be integrated to offer important insights into the effectiveness and safety of repurposed medications in various clinical contexts. In order to ensure that cutting-edge treatments reach the patients who need them the most, a concerted effort to overcome scientific, regulatory, and financial obstacles will ultimately be necessary to realize the full potential of drug repurposing in oncology. All things considered, oncology drug repurposing is a vibrant and quickly developing field supported by developments in molecular pathway analysis, high-throughput testing, and computational biology. By combining these methods, new therapeutic opportunities have been found and validated, giving cancer patients hope for better results. Even though there are still many obstacles to overcome, maximizing the effectiveness of this strategy in the fight against

cancer will require ongoing improvement of repurposing tactics and the growth of cooperative networks.

Oncology Drug Repurposing Success Stories

The integration of computational, experimental, and molecular strategies has allowed for the identification and validation of non-oncology drugs with demonstrated efficacy in cancer, leading to notable advancements in the field of drug repurposing in oncology. The ability of thousands of currently available medications, many of which were first created for non-cancer indications, to specifically target cancer cell lines has been systematically assessed through extensive screening efforts. For instance, a thorough investigation that screened more than 4,500 compounds found that almost 50 non-cancer medications could kill particular cancer cell types, frequently by means of hitherto unknown mechanisms. Notably, tepoxalin, an anti-inflammatory drug licensed for veterinary osteoarthritis, showed cytotoxicity against cancer cells that overexpressed MDR1, a protein linked to chemotherapy resistance. Similarly, vanadium-based compounds, originally created for diabetes, were effective against cancer cells expressing the sulfate transporter SLC26A2, and disulfiram, a medication for alcohol dependence, demonstrated efficacy in cell lines with mutations resulting in metallothionein depletion. These results lay the foundation for future clinical development and validation by highlighting the possibility of using the genomic characteristics of cancer cells as biomarkers to direct the selection of repurposed medications[57]. In certain cancer subtypes,

like mucoepidermoid carcinoma (MEC), the repurposing of non-oncology medications has also shown promise. While antiviral drugs like acyclovir and ganciclovir may stop tumor growth, preclinical models have shown that tocilizumab, an anti-IL-6R antibody used for arthritis, can improve the effectiveness of chemotherapy in MEC. Additional examples include valproate, an antiepileptic medication that functions as a histone deacetylase inhibitor, which reduces the survival of cancer stem cells, and curcumin, which targets important oncogenic pathways. By altering the STAT3 and NF-êB pathways, the antidiabetic medication metformin has demonstrated antiproliferative and anti-metastatic effects in MEC models. These results call for more clinical research because they demonstrate the potential of combining repurposed medications with conventional therapies to improve outcomes in cancers that are challenging to treat.[58] Thalidomide, a medication with a complicated past, is one of the most noteworthy success stories in oncology drug repurposing. Thalidomide was first created as a sedative but subsequently discovered to have anti-inflammatory, immunomodulatory, and anti-angiogenic qualities. Though studies are frequently constrained by diverse patient populations and recruitment difficulties, thalidomide and similar drugs that target multiple cytokines and pathways have demonstrated clinical benefit in cancer-related cachexia. In multiple myeloma (MM), where it was the first immunomodulatory drug (IMiD) to increase survival, thalidomide had the most revolutionary effect. The median overall survival for younger MM patients has increased to more
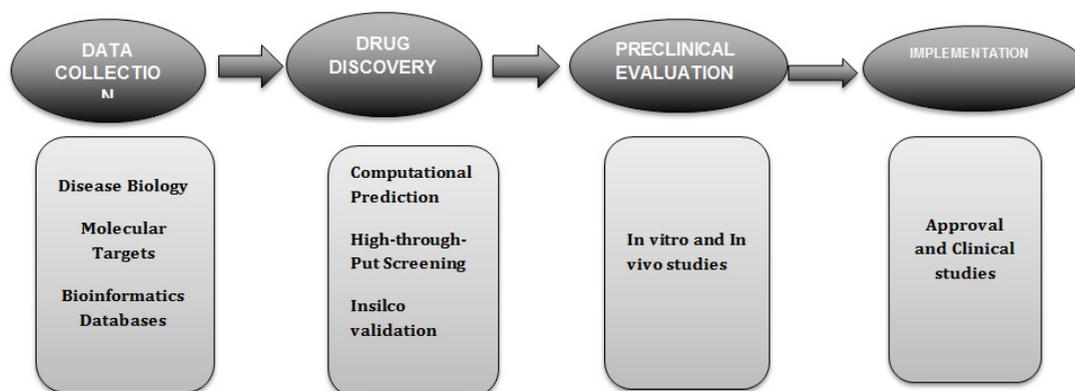

Fig. 1. Conceptual framework of the drug repurposing pipeline

Table 1. Summary of Computational Tools and Databases Used in Drug Repurposing

Tool / Database	Type	Primary Function / Features	Applications in Drug Repurposing
Connectivity Map (CMap) – Broad Institute	Transcriptomic signature database	Compares drug-induced gene expression signatures with disease signatures	Identifies drugs that can reverse cancer-specific gene signatures; signature-based repurposing
TCGA (The Cancer Genome Atlas)	Genomic & transcriptomic database	Multi-omics cancer datasets (mutations, expression, methylation)	Mutation mapping, biomarker identification, molecular pathway–based drug matching
Drug Repurposing Hub (Broad Institute)	Curated compound database	Contains >6,000 compounds with mechanisms and clinical status	Source for screening repurposable compounds, mechanistic insights
PRISM Repurposing Resource	High-throughput drug screening database	Screens drugs across hundreds of barcoded cancer cell lines	Identifies compounds killing specific cancer genotypes
ReDO Database (Repurposing Drugs in Oncology Project)	Literature-based evidence database	Catalogs non-cancer drugs with anticancer potential	Supports evidence-based identification of repurposable drugs
PAD – Predictive Database for Drug Repurposing	Computational prediction platform	Integrates drug–gene and disease–gene networks	Ranks drug repurposing candidates using network-based prediction
CADDIE Platform	Drug–gene and gene–gene interaction modeling	Maps molecular networks and recommends repositionable drugs	Prioritizes drugs targeting cancer-specific pathways
Every Cure Platform	AI-integrated multi-dataset platform	Uses machine learning to merge EHR, PubMed, clinical trials data	Predicts new drug–disease associations efficiently
RepoDB	Approved vs. failed drug–indication dataset	Contains clinical outcomes of prior repurposing attempts	Helps validate computational predictions, improves trial selection
CURE ID	FDA & NCATS real-world reporting tool	Collects global clinical case reports on off-label drug use	Useful for identifying real-world success signals
DrugCentral	Comprehensive drug information system	Offers drug properties, targets, regulatory status	Supports early-stage computational filtering
DrugRepoBank	Repurposing-suitable compounds repository	Includes drugs with IP/market exclusivity information	Helps navigate commercial feasibility of repurposing
TCM Drug Repurposing Hub	Traditional medicine-focused compound database	Contains bioactive natural compounds and targets	Supports discovery of natural product-based repurposing
DESSCD – Dragon Exploration System	Literature mining system	Uses NLP to explore biomedical connections	Extracts mechanistic links for new repurposing hypotheses
Cancer Pharmacogenomics Network (CPN)	Clinical-genomic interaction database	Links genomic variants to drug responses	Identifies mutation-specific repurposing opportunities

Table 2. Key Repurposed Oncology Drugs, Their Mechanisms, and Evidence Level

Drug	Original Indication	Repurposed Oncology Use	Proposed Mechanism(s) in Cancer	Evidence Level*
Metformin	Type 2 Diabetes	Breast, colorectal, prostate, ovarian, head & neck cancers	AMPK activation; mTOR inhibition; reduction in insulin/IGF-1 signaling; anti-proliferative and anti-metastatic effects	Moderate to Strong (multiple Phase II; mixed Phase III)
Thalidomide	Sedative (withdrawn)	Multiple myeloma, prostate cancer, cachexia	Anti-angiogenic effects; TNF-á suppression; immunomodulation; molecular glue degrader	Strong (FDA-approved for MM)
Propranolol	Hypertension, arrhythmias, anxiety	Angiosarcoma, breast cancer, neuroblastoma, HCC, gastric cancer	â-blockade; anti-angiogenesis; reduced VEGF; apoptosis induction; EMT inhibition	Moderate (preclinical + Phase II signals)
Aspirin	Analgesic, anti-inflammatory	Colorectal cancer prevention; adjuvant therapy	COX-2 inhibition; reduced PGE2; antiplatelet effects reducing metastasis	Strong for prevention, Moderate for adjuvant
Disulfiram	Alcohol dependence	Breast, lung, prostate cancers	ALDH inhibition; copper-dependent proteasome inhibition; cell death in resistant tumors	Moderate (Phase II trials ongoing)
Itraconazole	Antifungal	Lung cancer, prostate cancer, basal cell carcinoma	Hedgehog pathway inhibition; anti-angiogenesis; reversal of drug resistance	Moderate
Doxycycline	Antibiotic (tetracycline)	Breast cancer stem cell targeting, melanoma	Mitochondrial inhibition; suppression of CSC metabolism; anti-inflammatory effects	Early-Moderate
NSAIDs (e.g., Celecoxib)	Pain, inflammation	Colorectal, breast, lung cancers	COX-2 blockade; apoptosis induction; angiogenesis suppression	Moderate
Statins (e.g., Atorvastatin)	Hyperlipidemia	Breast, prostate, hepatocellular cancers	HMG-CoA reductase inhibition; impaired prenylation of oncogenic proteins	Moderate (preclinical + epidemiology)
All-trans Retinoic Acid (ATRA)	Dermatologic uses	Acute Promyelocytic Leukemia, NPM1-mutated AML	Differentiation induction; transcriptional reprogramming	Strong (FDA-approved for APL)
Chloroquine / Hydroxychloroquine	Antimalarial	Glioblastoma, pancreatic cancer	Autophagy inhibition; lysosomal disruption; sensitization to chemo/radiation	Moderate (ongoing Phase I/II)
Famotidine / Cimetidine	GERD & ulcers	Colorectal, gastric cancers	Histamine H2 receptor blockade; immune modulation; anti-adhesion	Early-Moderate

Table 3. Regulatory and Commercial Barriers to Drug Repurposing in Oncology

Barrier Category	Specific Barrier	Description / Impact
Regulatory Barriers	Requirement for monotherapy clinical trial evidence	Regulatory agencies (FDA, EMA) often require strong monotherapy data, even when repurposed drugs work best in combination regimens, complicating approval.
	High standard of proof for new indications	Despite existing safety data, regulators require robust Phase II/III trials, which are costly and time-consuming.
	Need for new clinical trials even for known drugs	Modified formulations, new dosing schedules, or combination therapy requires additional regulatory submissions and sometimes new Phase I trials.
	Slow approval pathways	Current frameworks were designed for *new* drugs, making the process inefficient for repurposed agents without dedicated pathways.
Commercial / IP Barriers	Lack of intellectual property protection	Most repurposed drugs are generic/off-patent, reducing commercial incentive to invest in costly clinical trials.
	Limited market exclusivity	Even if new indications are approved, generic substitution undermines profits, discouraging pharmaceutical industry participation.
	Weak financial incentives	Little ability to recoup investment; companies avoid repurposing unless new formulations or new delivery mechanisms can be patented.
	Patent challenges & legal ambiguity	Novel use patents are weak, hard to enforce, and often invalidated due to prior public knowledge or off-label use.
Clinical & Operational Barriers	Poor trial enrollment	Patients may choose off-label use instead of clinical trial participation, making recruitment difficult.
	Heterogeneity of cancer populations	Requires biomarker-based selection; smaller eligible populations increase cost and trial complexity.
	Limited access to abandoned or shelved compounds	Lack of centralized repositories limits repurposing of discontinued drugs that could still be effective.
Economic & Policy Barriers	Lack of government incentives	Few policies support repurposing; funding is mainly academic or philanthropic.
	High cost of evidence generation	Even for known drugs, conducting high-quality clinical trials is expensive, limiting academic-led repurposing.
	Misaligned reimbursement systems	Insurance systems may not reimburse repurposed drugs without formal approval, reducing clinical uptake.

than ten years since the introduction of thalidomide, lenalidomide, and bortezomib. Though results are still worse than those in MM, thalidomide-based regimens have shown some improvement in survival in plasma cell leukemia, an uncommon and aggressive cancer.[59-61]

The combination regimens of thalidomide and prednisone have demonstrated promising activity and favorable safety profiles in advanced castrate-resistant prostate cancer, where a significant percentage of patients have achieved notable reductions in prostate-specific antigen and a median overall survival of nearly 20 months. Thalidomide has also been evaluated in other malignancies. Thalidomide-based treatment, however, was linked to increased toxicity and failed to improve tumor response or survival in non-small cell lung cancer. Results for pancreatic and esophageal cancers have been conflicting; some studies have found poor tolerability and no benefit, while others have reported improvements in appetite and lean body mass at lower dosages. The significance of patient selection and disease context in repurposing strategies is underscored by these variable outcomes.[62-64] Thalidomide is now understood to function as a molecular glue degrader, a class of medication that attracts target proteins to the cellular degradation machinery in order to cause their degradation. Additional targeted protein degraders have been developed as a result of this mode of action, broadening the therapeutic options for immune disorders and cancer.[65]

The potential anticancer effects of metformin, a medication that is frequently prescribed to treat diabetes, have also drawn a lot of attention. Metformin has been shown in preclinical and early-phase clinical trials to inhibit the proliferation of cancer cells, lower the risk of cancer, and improve prognoses for a variety of cancers. However, due to a lack of late-phase trials, especially in cancer patients who do not have diabetes, it is still unclear whether these findings will translate into clinical benefit. The effectiveness of metformin in cancer chemoprevention and treatment is presently being studied in many ongoing RCTs and clinical trials; however, the results have been conflicting thus far, with some studies indicating improved tumor response but no discernible benefit in survival.

Metformin's safety profile in diabetic populations is well-established; however, more research is needed to determine how it affects cancer patients who are not diabetic. Although meta-analyses and observational studies show that metformin use lowers the risk of developing cancer and improves survival rates, there is currently insufficient strong evidence to support its use as an adjuvant therapy for particular cancer types. It is anticipated that ongoing randomized controlled trials will elucidate its function and pinpoint the patient populations most likely to benefit.[66-79]

Another repurposed medication with antitumor activity against over a dozen cancer types is propranolol, a non-selective beta-adrenergic receptor antagonist that was first prescribed for cardiovascular disorders. Its mechanisms include apoptosis induction, cell cycle disruption, tumor microenvironment modulation, and inhibition of cell proliferation. Propranolol has been demonstrated to improve apoptosis and decrease pro-proliferative markers in breast cancer, while it decreases proliferation indices like Ki-67 in gastric cancer. The use of propranolol has been associated in epidemiological studies with a decreased risk of a number of cancers, including esophageal, gastric, colon, prostate, and head and neck cancers. There is especially compelling evidence for hepatocellular carcinoma. Additionally, by downregulating prometastatic factors and the epithelial-mesenchymal transition, propranolol inhibits angiogenesis, lowers VEGF production, and compromises metastatic potential. In preclinical and clinical studies, combination therapies involving propranolol and chemotherapy, or targeted agents have shown improved efficacy and increased survival, particularly in gastric and breast cancers. Propranolol's benefits, however, seem to differ depending on the type of cancer, dosage, and length of treatment, and some large cohort studies have not discovered any appreciable reductions in either overall or cancer-specific mortality. These results emphasize the need for additional research to determine the best way to use propranolol in oncology.[80] In rare and difficult-to-treat cancers, where conventional drug development is frequently impeded by small patient populations and poor prognoses, the impact of drug repurposing is particularly noteworthy. Repurposing well-known medications lowers

expenses, speeds up access to novel treatments, and capitalizes on proven safety profiles—all of which are especially advantageous in environments with limited resources. Experimental screens have found synthetic lethal interactions in aggressive subtypes like PP2A-deficient uterine serous carcinoma, and computational analyses using large-scale cancer genomics datasets have shown that most rare cancer samples contain potential repurposing opportunities. Patients with rare cancers treated with repurposed agents, such as ribonucleotide reductase inhibitors in uterine serous carcinoma and the photosensitizer TLD1433 in conjunctival melanoma, appear to have better results, according to retrospective clinical data. Web-based tools and data-driven methodologies support these efforts by making it easier to identify repurposing candidates based on drug-target interactions, chemical structure, and disease-gene associations.[81]

Utilizing benefits like shortened time and cost to market, pre-existing supply chains, and the possibility of combination therapies, drug repurposing also provides a universal approach for neglected and challenging-to-treat cancers. Drugs with genetically supported targets have a higher chance of succeeding in clinical development, and advances in genomics and network biology have made it possible to identify repurposing candidates by connecting disease-associated genes with drug targets. Drug repurposing is still a viable and effective strategy for increasing therapeutic options in oncology, despite obstacles relating to data quality, patient heterogeneity, cost, intellectual property, and regulatory requirements. The use of antifungal medications like clotrimazole and ketoconazole for their anticancer effects and the combination of metformin and thymoquinone to treat leukemia's drug resistance are noteworthy examples. The ability of repurposed medications to address resistance mechanisms that restrict the effectiveness of conventional therapies is demonstrated by the antifungal itraconazole's ability to reverse docetaxel resistance in prostate cancer.[82]

In the end, drug repurposing in oncology has produced a number of noteworthy success stories and has a lot of potential going forward, especially for uncommon and challenging-to-treat cancers. The combination of experimental, computational, and molecular methods has increased the range of treatments that are now available, providing hope for better results in a variety of patient groups. Continued refinement of repurposing strategies, coupled with collaborative efforts across academia, industry, and regulatory agencies, will be essential to realize the full potential of this approach and translate scientific advances into tangible clinical benefits.

Implementing Drug Repurposing in Oncology: Obstacles and Restrictions

The regulatory, intellectual property, clinical, biological, and pharmacological aspects of drug repurposing in oncology interact in a complex way to determine the viability and success of converting non-oncology medications into potent cancer treatments. Regulatory considerations are one of the biggest obstacles because before approving new indications for already-approved medications, organizations like the FDA and EMEA need strong proof of efficacy, usually from monotherapy clinical trials. In oncology, where the therapeutic benefit of repurposed agents may only become evident in combination regimens and where the mechanistic justification for synergy is frequently compelling but challenging to prove in isolation, this requirement can be especially onerous. Incentives for formal clinical development may be undermined by the regulatory environment's requirement for high-quality clinical data, which can be difficult to produce for medications that are already widely accessible and used off-label.[83]

Issues with intellectual property (IP) make the repurposing process even more difficult. The conventional IP protections that encourage investment in clinical trials and regulatory approval for new indications are frequently absent from repurposed agents, particularly those that are generic or off-patent, in contrast to novel drugs. When there are few chances for market exclusivity and when generic substitution or off-label prescribing can reduce the commercial return on investment, pharmaceutical companies might be hesitant to invest in repurposing initiatives. The time and cost benefits usually associated with repurposing are further diminished when new formulations or dosing regimens are required to maximize efficacy in oncology. This can lead to additional regulatory requirements, such as new phase I trials. Legal ambiguities

brought about by the complexity of patent rights, such as those pertaining to novelty and public disclosure, may also discourage industry and academic stakeholders from exploring repurposing opportunities.[84] Another significant obstacle in the repurposing paradigm is the design of clinical trials. Phase II trials can be entered more quickly due to the established safety profiles of repurposed medications; however, the success of these trials depends on careful consideration of scheduling, dosing, and patient selection, which may differ significantly from the drug's original indication. Suboptimal trial designs and inconclusive results have resulted from the failure of many early repurposing trials to take into account mechanistic insights obtained from preclinical studies. Clinical trials should be guided by strong preclinical data, use biomarker-driven patient selection, and modify dosage schedules to attain the best antitumor activity while reducing toxicity in order to increase the chances of success. In order to navigate the changing landscape of evidence standards for repurposed drugs and to align trial design with approval requirements, early and continuous engagement with regulatory authorities is crucial. Additional challenges arise when recruiting patients, especially for rare cancers or trials that need biomarker stratification. Trial accrual may be slowed by the heterogeneity of cancer populations and the requirement for accurate molecular characterization, which may restrict the pool of eligible participants. Off-label use outside of clinical trials may result from the broad availability of repurposed medications for other indications, which could complicate recruitment and possibly skew trial results. Innovative trial designs, like basket or umbrella trials, and adaptable protocols that enable real-time modification based on new data are being used more and more to address these issues.[10] One important element of responsible clinical research that improves trial relevance and feasibility is the public's and patients' participation in research planning and execution .

One of the main obstacles to the success of drug repurposing in oncology is biological barriers. For instance, the majority of systemically administered medications, including many repurposed agents, are unable to reach therapeutic concentrations in the central nervous system, making the blood-brain barrier (BBB) a significant barrier to treating primary and metastatic brain tumors. To improve drug exposure at the tumor site while reducing systemic toxicity, strategies to improve BBB penetration are being investigated, such as the creation of innovative delivery systems or the application of focused ultrasound. The development of targeted delivery systems, such as nanoparticles or antibody-drug conjugates, is necessary for other cancer types because the tumor microenvironment, which includes elements like hypoxia, stromal barriers, and immune suppression, can restrict drug delivery and efficacy. Using developments in preclinical modeling and drug formulation, efforts are also being made to reevaluate medications that previously failed in clinical trials because of delivery issues.[86] Drug resistance, toxicity, and adverse pharmacokinetics are examples of pharmacological barriers, which are intimately related to biological barriers. Drug resistance, whether acquired or intrinsic, is still a major cause of treatment failure in oncology and can reduce the effectiveness of repurposed agents, especially when used as monotherapies. Even FDA-approved medications with favorable pharmacokinetic profiles cannot pass through the blood-spinal cord barrier (BSCB) and blood-brain barrier (BBB) in the context of brain tumors, so alternative delivery methods must be developed.[87] Liposomal or nanoparticle formulations are used to increase bioavailability for medications like amino-bisphosphonates because of their quick renal clearance and bone sequestration, which limit systemic exposure and antitumor efficacy.[79] Innovative pharmacological solutions are necessary because some cancers, like glioblastoma multiforme, have distinct anatomical and microenvironmental characteristics that make drug delivery even more difficult and increase resistance.

By connecting disease-associated genes with potential drug targets, advances in genomics, network biology, and chemoproteomics continue to propel the search for repurposing candidates in spite of these significant obstacles. Clinical development is more likely to be successful for drugs with genetically supported mechanisms, and the combination of computational and experimental methods is increasing the range of treatments that are currently available. However, it will take consistent work to address regulatory, intellectual

property, clinical, biological, and pharmacological challenges through cooperative, multidisciplinary strategies if these discoveries are to be translated into clinical benefit. The development of novel trial designs and delivery systems, the ongoing improvement of these strategies, and the balancing of commercial and regulatory incentives will be necessary for the future of drug repurposing in oncology in order to guarantee that promising treatments reach the patients who need them the most.

Resources and Cooperation to Support Drug Repurposing Projects

Drug repurposing in oncology has changed as a result of the combined efforts of public-private partnerships, cooperative consortia, and the inclusion of various stakeholders, each of whom has contributed special resources and knowledge to help the field get past its many obstacles. In oncology, where there are significant financial and regulatory barriers, public-private partnerships have become essential to the advancement of drug repurposing. One well-known example is the partnership between the non-profit group Cures Within Reach and the for-profit company Notable Labs. Notable Labs gave Cures Within Reach the commercial rights for pediatric leukemia as part of this collaboration, which resulted in the creation of ND-1000, a repurposed treatment for blood cancers in children and adults. With the help of philanthropic funding and leveraging incentives like the FDA's Pediatric Priority Review Voucher Program, this arrangement serves as an example of how common interests and resources can lower costs for vulnerable patient populations while facilitating access to innovative therapies. Highlighting the importance of academic participation in translational research, the University of Kansas Cancer Center further enhanced this partnership by contributing clinical trial expertise.[88] Additionally, collaborative research consortia have been essential in promoting drug repurposing innovation. For example, the Stowers Institute for Medical Research, Children's Mercy, and The University of Kansas Cancer Center collaborated to successfully repurpose doxorubicin in order to overcome leukemia resistance. By means of high-throughput screening and validation in animal models and patient-derived samples, the consortium showed that

low-dose doxorubicin could improve anticancer immunity and inhibit important molecular pathways, providing a new treatment option for refractory leukemia. These partnerships emphasize how crucial it is to combine clinical knowledge and mechanistic insights in order to maximize the use of current medications in novel oncologic settings. Large-scale consortia like PCM4EU and PRIME-ROSE, which bring together partners from all over Europe to create networks of clinical trials akin to the Drug Rediscovery Protocol (DRUP), have been funded by the European Union at the continental level. By standardizing molecular diagnostics, treatment plans, and reimbursement policies, these programs seek to expedite the adoption of precision cancer medicine an hasten the clinical application of repurposed therapies. The availability and integration of extensive databases and repositories that support drug repurposing research are essential to the success of these collaborative models. For instance, a literature-based resource cataloguing non-cancer medications with evidence of anticancer activity, was created by the Repurposing Drugs in Oncology (ReDO) project. It facilitates systematic literature mining as well as hypothesis generation; Additional noteworthy resources are the Drug Repurposing Hub and the PRISM drug repurposing resource, which together offer curated data on thousands of compounds, their activities, and clinical indications. These resources serve as fundamental tools for computational and experimental repurposing initiatives.[89] Additional examples of the expanding ecosystem of informatics tools intended to methodically identify and rank repurposing candidates in oncology include the Predictive Database for Drug Repurposing (PAD) and CADDIE, a web application that integrates gene-gene and drug-gene interaction data; Additional platforms are provided by DrugCentral and DrugRepoBank for ranking applicants according to market exclusivity and intellectual property factors, which are crucial for negotiating the commercial environment of repurposed medications.[90]

It is still difficult to integrate structured data from preclinical, clinical, and chemical sources because there may not be enough database overlap to allow for thorough analysis. Machine learning and natural language processing to combine data from various sources, such as electronic health

records, clinicaltrials.gov, and PubMed, improving the identification of promising repurposing opportunities. The potential for customized repurposing strategies is further increased by the use of biobanks that connect genomic data to clinical outcomes[91.] Additional resources like RepoDB, CURE ID, the Traditional Chinese Medicine Drug Repurposing Hub, and Broad Drug Repurposing Hub offer open-access platforms for discussing real-world clinical experiences with repurposed therapies, annotating compound activities, and investigating mechanisms of action.[92] The scope of resources available to support hypothesis generation and data-driven repurposing is further demonstrated by the Dragon Exploration System for Sickle Cell Disease (DESSCD) and the Cancer-based Pharmacogenomics Network (CPN).[93] The development of drug repurposing in oncology is largely dependent on the contributions of stakeholders in academia, government, and business. The majority of the evidence in favor of using off-patent medications for cancer has traditionally come from academia and independent researchers, frequently concentrating on generic medications with well-established safety profiles. However, academic groups may find it more difficult to obtain marketing exclusivity and handle the intricate approval process if they lack regulatory knowledge and intellectual property protections. As a result, collaborations with businesses and nonprofits have grown more alluring since they bring together academic creativity with the business and legal knowledge required for successful translation.[94]

Oncology drug repurposing's future hinges on these cooperative models' ongoing development, the incorporation of extensive data sources, and the balancing of business and regulatory incentives. To fully realize the potential of repurposed therapies, more funding for academically driven research, improved regulatory support, and the creation of creative trial designs are necessary. The combined efforts of academia, industry, government, and non-profit organizations will be essential in enhancing the therapeutic arsenal and improving outcomes for cancer patients as the disease's incidence and financial burden continue to rise globally.[95-99]

CONCLUSION

Drug repurposing has become a promising strategy in oncology, offering faster, safer, and more cost-effective therapeutic development by leveraging existing drugs with established safety profiles. Advances in computational biology, multi-omics technologies, and AI-driven prediction platforms have significantly improved the identification of repurposing candidates with strong mechanistic relevance. These approaches have already produced a number of clinical successes, particularly in rare and treatment-resistant cancers.

Despite these achievements, major barriers persist, including regulatory constraints, limited intellectual property protection, and inconsistent clinical validation across diverse patient populations. Tumor heterogeneity, lack of robust biomarkers, and challenges in translating preclinical findings into durable clinical responses further complicate progress.

To fully realize the potential of drug repurposing, stronger collaborative frameworks, improved patient stratification, and more rigorous prospective trials are urgently needed. Enhancing data integration, supporting academic-industry partnerships, and creating regulatory and economic incentives will accelerate the translation of repurposed agents into routine oncology practice. Ultimately, a coordinated, multidisciplinary effort will be essential for delivering more accessible and effective cancer therapies through repurposing.

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