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Incorporating AI, *in silico*, and CRISPR technologies to uncover the potential of repurposed drugs in cancer therapy

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Patients with cancer have faced exhausting physical and mental obstacles as a result of traditional treatment methods including chemotherapy and radiation therapy. In cancer, drug repurposing—the use of already-approved medications for novel therapeutic indications—has become a game-changing tactic. This method greatly lowers development costs and durations by utilizing the wealth of safety and pharmacokinetic data available for licensed medications. Large-scale databases and advanced computer techniques enable it to logically find either combinations of traditional medications or selective "non-selective" target medications. Furthermore, repurposing cancer drugs can undergo a significant and profound change thanks to genome-editing technologies like CRISPR-dCas9. It is recognized that there is yet unrealized potential of these advanced methods in further applications. Understanding the pros and cons of these technologies can provide valuable insights for clinical practice and fundamental research projects. This research will explore various innovative methods, including artificial intelligence (AI) algorithms, supervised machine learning (ML), data resources for *in silico*, microbial clustered regularly interspaced short palindromic repeats-dCas9 (CRISPR-dCas9) based artificial transcription factors, and combination therapy. This comprehensive guide outlines various methods for repurposing drugs, addressing effects, trials, barriers, and potential solutions to aid clinicians and researchers in maximizing efficacy and efficiency.

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1. Introduction

Even with today's sophisticated technology, treating cancer remains one of the most difficult tasks in modern life since it is complex, heterogeneous, and hard to diagnose because of a number of biochemical, physiological, and genetic aspects. Reducing symptoms is especially difficult because cancer frequently becomes resistant to therapy. Drug repurposing techniques entail investigating novel therapeutic uses for previously licensed medications. The popularity of medications that were first approved for a single application but have later been researched and utilized to treat a variety of illnesses is growing. This strategy is demonstrated in the thorough review by Xia *et al.*, which highlights the creative approaches and potentially game-changing effects of drug repurposing, particularly in the cancer area.[1] When candidates that have demonstrated safety in preclinical models or clinical human usage also demonstrate efficacy for a rare condition and can be repositioned for the new indication, it presents a feasible substitute for new drug discovery. Understanding disease pathways and the relationships between target proteins in diseases which can be accomplished through computational and experimental methods has been its driving force.[2] The complicated and multifaceted nature of cancer serves as the justification for therapeutic repurposing in oncology. The fundamental processes of tumor growth and metastasis frequently coincide with those of other illnesses or cellular dysfunctions that are the focus of current medications.[3] Typically, drug repurposing begins with a computational screening of existing drugs using a variety of computational techniques, including machine learning, molecular docking, and ligand similarity analysis. AI-based deep learning technology is proposed as a next-gene-

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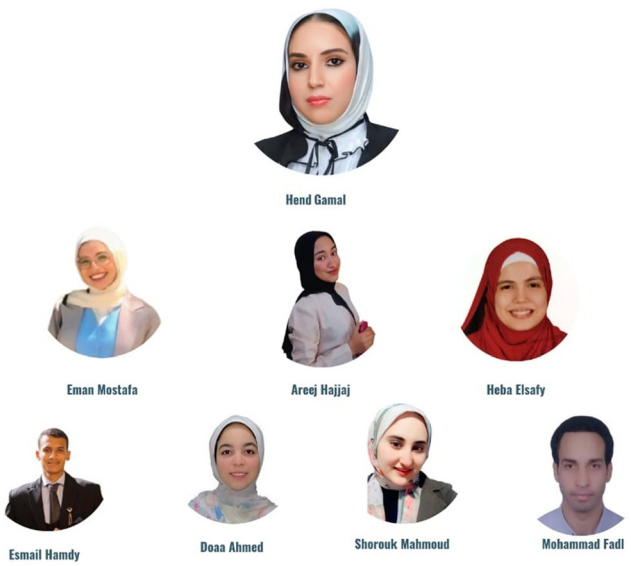
ration drug research method, capable of integrating extensive information to forecast therapeutic correlations. New drug development is classically expensive and takes more than ten years, from target identification to FDA approval. For both academic institutions and biotechnology businesses, this is a major obstacle. As a result, medication repurposing by AI techniques is perhaps a practical strategy for time- and money-efficient drug development.[4] A cross-disciplinary team's analytical skills, clinical development procedure, experimental setup for validation, and availability and access to molecular data are all necessary for an effective drug repurposing workflow for academic institutions and pharmaceutical businesses. In this sense, repurposing techniques can be discreetly separated into two categories: experimental screening-based techniques and *in silico* approaches, which use data analysis to find possible new drug–disease connections. Providing tailored and targeted cancer treatments in order to reduce medication toxicity and boost patient response rates is a major problem in contemporary oncology.[5] In addition to offering novel therapeutic indications, *in silico* drug repurposing could improve the effectiveness of precisely targeted cancer therapies. Besides computational approaches, the use of gene function science has increased thanks to gene editing, particularly with CRISPR-Cas9. The progress of genotype–phenotype correlations is being revolutionized by CRISPR technologies, which are also changing gene- and cell-based therapeutics. By generating cancer models, examining tumor evolution, and discovering target genes implicated in cancer growth and chemosensitivity, CRISPR/CRISPR-associated protein 9 (Cas9), Cas12, and Cas13 have significantly improved oncology. Additionally, preclinical treatment approaches using CRISPR/Cas have surfaced.[6,7] In this review, we explore various novel approaches merged to get new datasets from existing drugs, such as AI algorithms and supervised ML, *in silico* data resources, CRISPR-dCas9, and combination therapy. We also provide an in-depth analysis of each strategy, including its expected outcomes, preclinical and clinical trials, challenges to drug repurposing, and potential solutions. Also, we focus on helping researchers and clinicians better understand these various methods so that they can optimize the effectiveness of cancer-repurposed medications and more effectively navigate their path in research.

2. Drug repurposing strategies

Understanding disease pathways and the relationships between target proteins in disorders, which can be accomplished through computational and experimental methods, has motivated drug repurposing (Fig. 1). Each approach makes use of distinct scientific and technological developments. Researchers can uncover oncogenic pathway inhibitor activity and give disease-related data by using computer-assisted drug repurposing procedures, which are a strong tool in medication repurposing.[8] Network-centric systems biology approaches enhance the therapeutic potential of repurposed medications, preventing resistance development, and customizing treatments for individual patient outcomes. They provide comprehensive drug repurposing libraries for effective data assessment. Target-based and drug-based drug discovery techniques



A photograph and biography of me and my co-authors

Hend Gamal, Ph.D., is a highly accomplished Cancer Biology Scientist. She has highlighted the different novel methods for cancer treatment including modified chemotherapeutic drugs, natural products, gold nanoparticles, and finally photothermal techniques. This work has resulted in numerous publications, frequent appearances at prestigious conferences, and numerous scientific prize awards. Dr Hend is a recognized scientific reviewer for numerous prestigious journals, including the Royal Society of Chemistry *and the* American Journal of Applied Scientific Research *(AJASR). She also holds positions on the editorial boards of publications such as the* European Journal of Medical and Health Research *and is a guest editor for JoVE. Eman Mostafa is a molecular genetics-focused biotech researcher with a strong background in PCR and bioinformatics who is motivated to further science. Areej Hajjaj is an ambitious biochemistry researcher interested in cancer, antibiotics, and AI in biology. Heba Elsafy is a researcher in biochemistry who is attentive to antibiotics, cancer, and AI applications. Esmail H. Elramy is an aspiring biochemistry researcher driven by cancer innovation, AI integration, and scientific entrepreneurship. Doaa Ahmed is a thriving researcher passionate about cancer, drug discovery and academic growth. Shorouk Mahmoud is passionate about biotechnology, pharmacogenetics, genetic engineering, bioinformatics, and impactful scientific research. Mohammad Fadl is an effective researcher aspiring to contribute to solving contemporary research issues.*

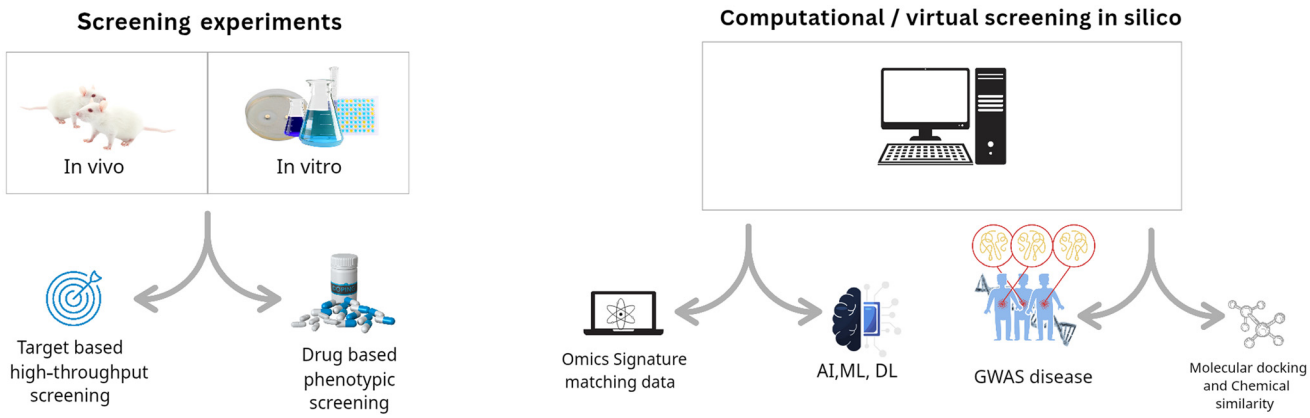


Fig. 1 Experiments can be conducted *in vitro* or *in vivo*, using target-based tests, drug-based screens, computational or virtual screening methods, genome-wide association studies, AI, and signature matching. Created with BioRender.com.

use genomes and recombinant technology to identify molecular targets and phenotypic effects, with reverse pharmacology prioritizing genomic studies over functional ones. Drug development based on targets is a method that uses molecular hypotheses developed from existing knowledge, sometimes discovered through phenotypic screening.[9] To find possible targets, target-based strategies are employed for novel medications to treat untreated illnesses. Common targets include proteins, regulatory factors, cell-signaling receptors, and enzymes. Target validation measures the drug's therapeutic functionality by correctly eliciting the biological response. Phenotypic screening drug discovery (PDD) is an alternative method for finding drugs based on targets and examining active biological molecules within relevant biological systems or pathways.[10] PDD helps identify target interactions and reveals the drug's potential impacts on the human body. Phenotypic tests improve drug discovery translation to clinics because of their capacity to test medications in complex human biological systems. The "chain of translatability" enables predictive validity, crucial for forecasting a drug's clinical therapeutic response in humans. To choose and confirm an experimental cellular system, the chain of translatability requires a thorough knowledge of the illness's molecular basis. The computational approach is one of the most useful instruments in the field of medicine repurposing.[11,12] Our understanding of the processes and modes of action in oncology has greatly increased because of the developments in big data analytics, machine learning, and computational algorithms as well as the development of omics technology. Both disease-centric and drug-centric data are widely accessible because of these computational methods.[13] Signature matching screens can predict drug effectiveness by comparing cancer cell proteomic, metabolomic, and genomic signatures with drug-treated cells, reversing dysregulation and restoring a healthy omics profile. Cimetidine, an anti-peptic ulcer medication, has been identified as a possible treatment for lung cancer using this *in silico* screening technique.[14] Detroja *et al.* confirmed the prediction *in vitro* and *in vivo*, demonstrating that the medication may inhibit lung cancerous cells in mouse xenograft models. Algorithms for artificial intelligence biology analysis are efficient ways to handle biological network data. To perform biological network classification, grouping, and prediction tasks, they develop tools or software that simulate human intelligence.[15] Systems with artificial intelligence can effectively understand carcinogenesis and explore new anticancer targets by addressing the complexity of cancer because of gene–product interactions in biological network architectures.[16] To find genetic variants connected to particular diseases and possible therapeutic targets, genome-wide association studies (GWASs) are employed. A repurposed drug may be investigated for the treatment of the disease if it is known to target the protein or pathway identified in the GWAS. A recent study by Najafi *et al.* indicated that imipramine, an anti-psychotic, was useful in treating glioblastoma (GB).[17] Researchers discovered that imipramine-targeted GB cells are more sensitive to temozolomide, the standard chemotherapeutic drug for this tumor, highlighting the potential of text mining in uncovering new drug-related connections.[18] In order to find repurposed medications that might target the genes linked to cancer metastasis, a recent text mining analysis leverages PubMed literature. Aspirin can be used to target two targets that are strongly associated with cancer metastasis: TP53 and curcumin for MMP9. Similar text mining approaches can be used to analyze clinical observations and find links between possible drug repositioning and diseases. Because of systematic reviews looking into its association with a lower incidence of cancer, metformin is being utilized to treat a variety of malignancies.[19,20] Apart from strengthening chemotherapeutic tactics by offering new ways to prevent resistance development and customize therapies to optimize patient-specific outcomes, these repositories also increase the therapeutic potential of repurposed pharmaceuticals across a range of disorders.[21,22] Molecular docking simulations are used to repurpose medications by analyzing interactions between ligands and targets. This involves positioning molecules within the target's active site using docking algorithms.

Glide is a popular molecular docking algorithm used in drug development to identify lead compounds with high selectivity and binding affinity for cancer targets.[23] Huang *et al.* developed the molecular docking program AutoDock in 2009. It is notable for its ability to precisely simulate protein–ligand interactions by controlling variable ligands and receptor locations. Computational software techniques speed up the development of drugs by identifying lead compounds with strong cancer target proteins, based on resource and research goals.[24]

3. Supervised ML and AI algorithms for cancer drug repurposing

The ability of supervised ML and AI to evaluate large, complicated datasets and forecast new therapeutic applications for already-approved medications has made them indispensable in the domain of repurposing drugs. These techniques make use of structured datasets in which known outputs (*e.g.*, efficacy, toxicity, or target pathways) correlate with input properties (*e.g.*, chemical structures or biological interactions). Finding appropriate medication candidates can be sped up by their accurate analysis of repurposing medication databases.[25] Algorithms for machine learning are essential in early drug development stages, assisting in compound screening, drug design, patient classification, biomarker discovery, clinical trial optimization, and therapeutic target identification. For example, ML models use orthogonal drug–target space deconvolution, wherein the *in silico* predictions are guided by the molecular structures of the medications and targets.[26] Another line of research has successfully predicted target activities for kinase inhibitors using crowdsourcing-based AI and ML systems.[27,28] As biotechnology companies immediately integrated ChatGPT to create new paths for target medicines, it demonstrated AI's ability to synthesize informative responses from pertinent published publications. Researchers discovered that ChatGPT can provide a promising list of medications for clinical study in addition to fresh concepts for repurposing drugs. The state-of-the-art methods are best shown by the following algorithms: decision trees (DTs) and random forests (RFs).[29,30] These ensemble methods are frequently used to prioritize feature importance and classify drug candidates. Random forests enhance generalizability in drug–target interaction prediction by reducing overfitting and combining the outputs of several decision trees. Their effectiveness in detecting off-target effects and novel possible therapeutic indications is evidenced in recent research.[31] Support vector machines, or SVMs, work especially well with high-dimensional data, which is common in proteomics and pharmacogenomics. They classify data points using hyperplanes, which allows for reliable drug–disease relationship prediction. Studies show that SVMs effectively identify molecular similarities, resulting in the discovery of repurposed medications with similar modes of action.[32] Processing complex biological data, such as gene expression patterns and molecular fingerprints, requires sophisticated neural network (NN) and deep learning (DL) structures, such as recurrent neural networks (RNNs) and convolutional neural networks (CNNs). CNNs have been shown to be useful in predicting protein–ligand binding affinities and learning spatial connections between molecular substructures. A recent study showed how deep neural networks can identify COVID-19 repurposing candidates by analysing transcriptome responses.[33] Because of their excellent accuracy and speed in training predictive models, gradient boosting algorithms (GBAs) like XGBoost and LightGBM are widely used. By gradually creating models that fix the mistakes of earlier ones, these algorithms significantly increase the ability to forecast large-scale, heterogeneous data. They are essential tools in repurposing pipelines due to their capacity to control non-linear interactions in pharmacological characteristics and therapeutic effects. The efficacy of supervised machine learning in drug repurposing is improved through the integration of many data types, such as empirical evidence, clinical trial findings, and omics data. Methods for feature selection and cross-validation ensure that the model works effectively and may be used in a range of drug–disease situations.[34] How far can you envision the prospects for using innovative methods to treat cancer using currently available medications? These methods speed up the repurposing and the search for new drug processes, which results in quicker therapeutic breakthroughs. In intricate biological networks, they may be exploited to find possible cancer targets and medications to cure cancer. AI biology analysis, which includes proteomics, metabolomics, genomes, and epigenetics, can find novel anticancer targets and create medications.[35] Pacini *et al.* developed an anticancer target priority map using multi-omics data to identify 370 targets for 27 cancer types.[36] Sakellaropoulos *et al.* demonstrated the effectiveness of an AI system in precise tumor therapy, training a deep neural network on 1001 cancer cell lines to predict medication responses.[37]

3.1. AI bias mitigation through external validation

Despite its potential, AI and ML rely significantly on the quality and diversity of the input data to predict results. Risks include bias, overfitting, and poor generalisability to real patient populations. Through testing on separate datasets, external validation of AI models in drug development guarantees dependability, generalisability, risk mitigation, regulatory compliance, and patient safety. One growing societal duty for AI-healthcare providers and developers is to offer standardized and reproducible methods for reducing these hazards. The task is dynamic and longitudinal, evolving over time due to evolving clinical practice, community needs, and societal influence.[38] Since trained AI models on certain datasets might not function well on other patient populations or therapeutic circumstances, external validation might help reduce the usage of AI in medications by guaranteeing generalizability. The model's ability to generalize to a range of groups and situations is evaluated with the aid of it. Overfitting occurs when a model learns the training data, including noise and irrelevant information, too well and then performs poorly on new data.

The model can identify and lessen overfitting by being tested on data that hasn't been seen before.[39] The FDA and other regulatory bodies frequently demand external validation to prove the precision, dependability, and security of AI-powered medical equipment as well as algorithms. AI technologies improve accuracy and safety, reduce errors, and save time, money, and resources while ensuring equitable and moral application, particularly in diverse patient populations.[40]

4. Data resources for *in silico* repurposing of drugs

The term "*in silico* repurposing of drugs" refers to a hypothesis-driven approach that leverages big data to identify therapies that target cancer. *In silico* drug repurposing analyses many data resources to identify potential new applications for authorised drugs. By turning cancer phenotypes and targets into druggable targets, this method can provide FDA-approved medicines with possible modulatory or inhibitory properties.[39] Data integration requires precise algorithms and a processing pipeline. The appropriate gathering and analysis of accessible omics data pertaining to health/disease processes, cancer biology (disease-related data), and medication method of operation (drugs-related data) is a vital stage in this pipeline. Computational techniques enable linking several levels of information produced by omics technologies, including transcriptomics, genomes, metabolomics, and proteomics, which unravel the biology of both novel and established cancer targets in addition to details regarding how medicines work.[41]

4.1. Computational tools and resources for *in silico* drug repurposing

We can efficiently sort through enormous amounts of data using computational techniques and algorithms to find potential drug candidates with undiscovered medical uses. The pharmaceutical repositioning pipeline has made use of computing techniques. *In silico* drug target identification, the initial stage of the pipeline for drug development, identifies genes and proteins linked to the disease using various algorithms. To find new potential links between a treatment and a condition, the approaches used advanced analytical tools to assess data that already exist.[42,43] Because it can accurately anticipate the shape of small-molecule ligands inside the proper target binding site, molecular docking is one of the most popular *in silico* methods. Furthermore, by carrying out quantitative predictions of binding energetics, molecular docking algorithms rank docked molecules based on the binding affinity of ligand–receptor complexes.[44] The two main categories of *in silico* methods are molecular procedures and real-world data approaches.

4.1.1. Molecular approaches. Understanding pharmacological activity and disease pathophysiology forms the basis of molecular techniques. They are often powered by large-scale molecular data, or omics data, including transcriptional, proteomic, or genomic data, as well as data based on chemical structure and therapeutic targets. The two data types most commonly used to facilitate medication repurposing are transcriptomics and genomes due to the availability of databases on medications and illnesses, as well as the reproducibility and robustness of the data.[45] In transcriptomics, which looks at the expression levels of hundreds of genes, RNA is commonly quantified using RNASeq or gene expression microarrays. Using transcriptomics for drug repurposing suggests that reversing gene expression profiles could be therapeutically beneficial.[46]

4.1.2. Real-world data approaches. Finding unidentified and perhaps surprising connections between medications and illnesses or their symptoms is the main goal of the real-world data strategy. These are statistics derived from people's health, routines, and actions that were recorded without having an impact on the environment or prejudice brought about by data gathering techniques. Real-world data techniques include network-based medication repurposing, ligand-based drug repurposing, and structure-based drug repurposing.[47]

4.1.2.1. Network-based drug repurposing. Network-based computational biology has become more and more popular in recent years. It integrates the interactions between biological molecules into networks to uncover freshly discovered features at the network level and investigate how cellular systems generate diverse biological phenotypes under different conditions. Each node in the network pharmacology framework can be represented as a biological target, target pathway, modifier molecule in a biological process, or individual molecular entity. Each edge in the network can be thought of as a direct or indirect interaction between two connected nodes.[48] In 2012, Jin *et al.* created a unique method of repurposing medications for cancer treatments that takes advantage of off-target effects that may affect crucial signalling pathways in cancer cells. A hybrid model comprising a Bayesian factor regression model and a network component called a cancer-signalling bridge was used to identify the off-target effects of medications on signalling proteins. Because biological factors interact to form complex systems, network-based approaches may not produce viable therapy choices, and there are still many biological components of the disease that need to be discovered. Therefore, the results of this class of procedures might be more beneficial.[43]

4.1.2.2. Repurposing drugs based on ligands. Techniques based on ligands are studied because related chemicals share comparable biological properties. These methods are widely used to evaluate and predict ligand activity for new targets in cancer drug repurposing. Currently, there are approximately 100 million publicly accessible compound records (only made available by PubChem) in the Protein Data Bank (PDB), where less than 150 000 protein crystal structures have been uploaded.[49,50] Ligand-based methods rely on the chemical space of known compounds being covered. Deep learning and multi-task learning have been successfully used in ligand chemogenomic benchmark investigations. When target and drug similarities were considered, the algorithm was able to identify novel drug–target associations with more accuracy.[51]

4.1.2.3. Structure-based drug repurposing. Structure-based related protein structures improve the likelihood of similar

functions and comparable ligands. Protein comparison is a technique used in cancer drug repurposing to find secondary targets for a licensed treatment. Proteins can be compared on a broad scale due to the similarity of their sequences. The kinome is the most popular example of a phylogenetic tree constructed from protein sequences.[52,53] Sequence alignments work best when proteins have a high degree of sequence identity. However, when proteins have minimal sequence identity, local protein comparison works better at discovering unknown targets of known ligands. When the structure of the protein–ligand complex is unknown, hot spots at the binding site can be predicted using computational techniques.[12,53] Protein–ligand complex crystallographic structures must be feasible for structure-based approaches to be effective. The specificity of a binding site's representation depends on its resolution and sensitivity to atomic coordinates. Even though a protein's crystallographic structure displays its static model, additional pockets may arise as a result of conformational changes.[54]

4.1.3. Applications of molecular resources. By finding novel therapeutic applications for already-approved medications, molecular resources are essential to drug repurposing. They have numerous important uses in the recycling of cancer medications. The recognition of repurposed medications is sped up by the use of AI-driven predictive modelling, network pharmacology, and a docking method for molecules to find possible drug–target interactions. Additionally, the amalgamation of omics data, such as transcriptomic, proteomic, and genomic studies, reveals molecular markers and disease pathways that can be modulated by already available medications.[55,56] Gene expression profiling, for instance, assists in finding anti-cancer qualities in medications that are not oncology-related. Recent studies discovered that molecular docking and high-throughput screening methods evaluate how current medications connect to novel targets, maximizing their capacity for therapy. Additional uses of molecular resources include computational forecasts that have been validated by *in vitro* and *in vivo* studies.[57]

4.2. Omics resources and drug–target bioactivity data

Omics studies provide disease-related information to understand oncogenic signalling activation or tumor suppressor genes, aiding in the formation of relevant molecular signatures for tumor cell growth and survival. These can then help with repurposing computations of medications against these molecular targets.[58] Gene mutations, neo-angiogenesis, positive regulator activation, metastatic phenotype, and metabolic rewiring are confirmed as legitimate therapeutic targets in both preclinical and clinical settings. Certain regulators of these characteristics have been proven to serve as reliable clinical molecular indicators for predicting the prognosis or outcome of disorders. Research at various levels is crucial to understanding the complex mechanics and molecular targets of cancer hallmarks. Multi-layered omics research on specific anticancer targets has been made accessible, allowing system biology techniques for *in silico* medication repurposing using disease-related data.[59,60] Patient-derived resources offer pharmacogenomic data on primary cells tested against drugs, while cell line omics resources provide drug response data and multi-omics profiles for tumor cell lines.[61] These resources lack a programmatic API and information sourced from a particular lab or study, but they are useful for AI systems that repurpose medications. Additionally, cell-based omics tools can forecast how patients will react to drug therapies.[51]

5. Artificial transcription factors based on CRISPR-dCas9 in cancer drug repurposing

CRISPR-dCas9-based artificial transcription factors (CRISPR-ATFs) offer precise gene regulation and manipulation, presenting new opportunities for therapeutic repurposing. The CRISPR-Cas9 system, which combines transcriptional activators or repressors with a catalytically inactive Cas9 (dCas9), is the origin of CRISPR-ATFs. Without causing DNA double-strand breaks, these designed structures enable the exact activation or suppression of target genes. The ATFs are molecular instruments that can affect different biological phases by altering gene expression. The kind of tumor determines whether CRISPR therapeutic targets are selected for cancer.[62] Target genes can be expressed or suppressed by ATFs. They are composed of molecular domains like DNA-binding domains (DBDs), which provide sequence specificity and can have different levels of affinity for similar locations in the genome. ATFs are designed using a diversity of DBDs, such as zinc fingers (ZFs) (Fig. 2A), transcription activator-like effectors (TALEs) (Fig. 2B), and the CRISPR-dCas9 system (Fig. 2C).[63] CRISPR-ATFs are also essential for comprehending gene regulatory networks and detecting side effects of currently available medications. By enabling high-throughput functional screening of numerous genes, they make it possible to identify new druggable targets linked to the etiology of the disease. The discovery and verification of novel calming targets is one of the key uses of CRISPR-ATFs in cancer drug repurposing.[64] Clinical trials for the treatment of cancer are presently underway for all drugs, and *in vitro* research has demonstrated antitumor effects as a result of regulating gene expression in cell death and proliferation. To produce cancer treatment with a higher success rate, it is suggested to combine the gene regulation effects of repurposed medications with CRISPR-dCas9-based ATFs.[65] This combination allows CRISPR-dCas9-based ATFs to synergistically regulate target genes, improving the efficacy of repurposed medications. Additionally, MDR genes can be silenced to increase treatment success rates, and genes implicated in the signalling cascade of processes linked to cancer development can be complementarily controlled,[66] as compiled in Table 1. Notwithstanding their promise, there remain issues with CRISPR-ATF delivery system optimization, specificity, and off-target effect reduction. To increase the technology's clinical application, developments in guide RNA design and viral and non-viral delivery techniques are essential.[84]

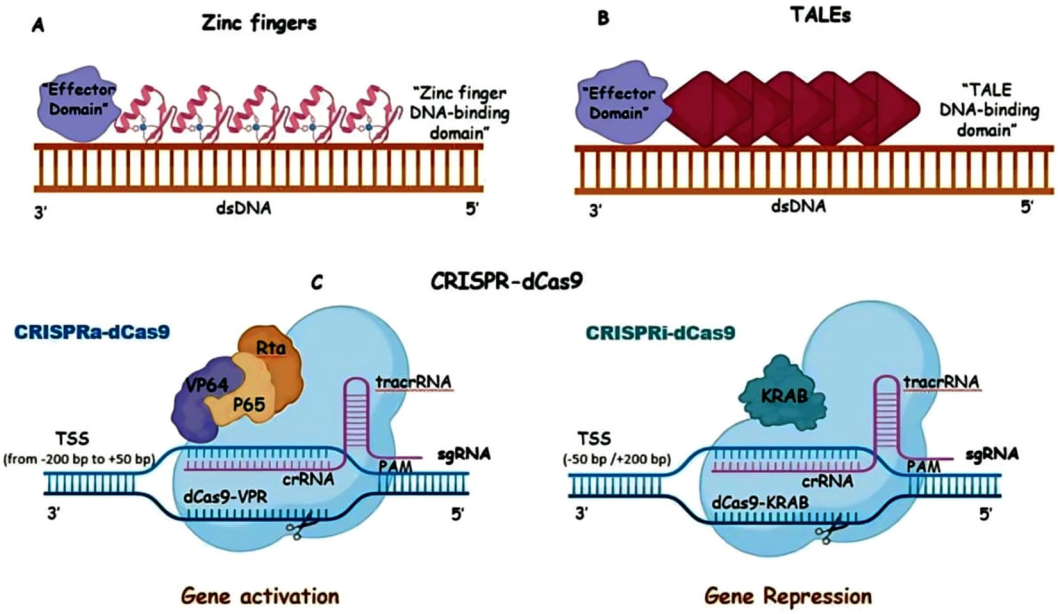


Fig. 2 Types of ATFs that are involved in transcription activation or repression. (A) Finger-based zinc ion ligands, like the Cys2-His2 domain, consist of an effector domain and a DNA-binding domain in ATF. (B) ATF, based on TALEs, has an effector domain and a diamond red DNA-binding domain consisting of 33–35 amino acid arrays, each representing a single DNA base. (C) A single guide RNA (sgRNA) and the dCas9 protein make up CRISPR-dCas9-based ATFs. CRISPRa involves TRNA activation *via* VP64, p65, and Rta domains, RNAP aggregation, and transcription interference *via* dCas9 linked to the KRAB domain. Created with BioRender.com.

5.1. Challenges in editing of genome technologies

Off-target effects provide several challenges for genome editing techniques, especially CRISPR-based systems. Unintentionally altering unwanted genomic locations with CRISPR-Cas9 can result in mutations that could interfere with vital genes or have negative consequences. High-fidelity Cas variants and optimized guide RNA designs are two behaviours to lessen this. Furthermore, a barrier still exists in the effective transport of genome-editing components into target cells. The scalability, toxicity, and intensity of viral vectors, nanoparticles, and electroporation techniques are all constrained.[85] Furthermore, immunogenicity—the bacterial source of CRISPR components—is known to cause immune responses. Humans have been exposed to have pre-existing immunity to Cas9, and repeated injection may cause inflammatory responses. To reduce immune activation, researchers are looking into temporary delivery systems and other Cas enzymes. A modified form of the Cas9 enzyme that is incapable of cleaving DNA is called dCas9 (dead Cas9), which is a safer option for genome editing.[86] By reducing off-target effects, it aids in reducing these hazards. dCas9 prevents unwanted mutations because it does not cleave DNA. Rather than changing the genome, it may be combined with transcriptional regulators to precisely control gene expression. dCas9-based schemes may be administered *via* nanoparticles or viral vectors, which reduces the toxicity of traditional methods of genome editing D The absence of double-strand breaks in Cas9 lowers immunogenicity, which makes it appropriate for therapeutic uses since it lowers the possibility of triggering an immune reaction.[87]

6. Applications of AI, *in silico*, and CRISPR technologies

We will discuss a few of the numerous uses of AI, *in silico* experiments, and CRISPR technology. AI has made cancer treatments much better, especially when it comes to repositioning drugs for breast cancer (BC). Researchers have identified possible drugs based on risk genes using data mining and machine learning. A neural network model called GraphRepur has found eleven BC medications with supporting research. Protease-targeting small compounds were designed using deep neural networks, transfer, and reinforcement learning. By properly predicting protein structures, the AI tool AF2 helps design new cancer drugs and find new targets for existing ones. Knowledge of cancer pathways is enhanced using the AlphaFold protein structure database, which offers precalculated predictions for more than 200 million protein structures.[88,89] Besides, drug repurposing in oncological research relies on molecular modelling to suggest pipelines and inhibitors with a strong emphasis on *in silico* approaches. Disulfiram and valproic acid have been repurposed for lung and BC treatment. A study on the valproic acid–simvastatin combination for pancreatic cancer revealed significant interactions influencing treatment outcomes, potentially benefiting patients whose pancreatic ductal adenocarcinoma has spread.[90] The drug interaction checker uses machine-learning-based scoring functions to evaluate pharmacokinetic interactions, enhancing medication development and clinical applications. It uses datasets from the protein data bank and drug

Table 1 Repurposed medications and CRISPR-dCas9-based ATFs are suggested for use in cancer treatment

Drug	Pharmacological Class	Original Use	Impact of the medication on cancer-related gene regulation	CRISPR-dCas9-assisted complementary gene regulation	Cancer types
Aspirin	Salicylate	Pain and fever	Downregulation of the Sp family of transcription factors	Inhibition of genes for COX-enzymes	Colorectal[64,65,67,70–72]
Metformin	Oral antidiabetic	Type 2 diabetes	Blocking mTORC1 activity and turning on AMPK	Expression of AMPK	Hepatocarcinoma, breast, colorectal, and prostate[66,73]
Doxycycline	Antibiotic	Bacterial infections	Inhibition of MMP-2 and MMP-9	Expression of TIMP-2	Hepatocarcinoma, lung, prostate, and colorectal[66,80,81]
Nelfinavir	Antiviral	HIV treatment	Increasing DR5 expression and inhibiting AKT	Expression of SREBP-1 and ATF6	Lung, ovary, and breast[66,74]
Lithium	Antidepressant	Major depression and bipolar disorder	Inhibition of glycogen synthase kinase 3	Inhibition of Smad3 and TGFBIp	Prostate and colorectal[66,82,83]
Ibuprofen	NSAIDs	Pain, fever, and inflammation	Levels of Akt, p53, Bcl-2, and Bax expression	Inhibition of genes encoding COX enzymes	Colorectal and melanoma[66,75,76]
Digitoxin	Cardiac glycosides	Cardiac complications	Expression of p21	Inhibition of HIF-1 and HIF-2	Prostate, lung, and breast[12,67,68]
Ritonavir	Antiviral	HIV treatment	Increase in p53 expression and suppression of pRb	Expression of p21	Ovary, breast, and pancreatic[66,73]
Mebendazole	Microbiological agent	Parasitic worm infection	Expression of pro-apoptotic Bcl-2	Inhibition of ABL and BRAF	Colorectal, melanoma, and glioblastoma[66,70–72]
Itraconazole	Microbiological agent	Fungal infections	Blocking the activity of 14-alpha-lanosterol demethylase	Reduced activity of AKT1	Lung and prostate[66,79]
Chlorpromazine	Antipsychotic drugs	Schizophrenia, and bipolar disorder	Expression of p21 suppression of the oncogene K-Ras	Expression of p53	Colorectal, glioma, and leukemia[66,69]
Artesunate	Microbiological agent	Malaria	Production of pro-apoptotic proteins like caspase-3	Inhibition of anti-apoptotic proteins and MYC oncogenes.	Lymphoma, myeloma, and hepatocarcinoma[66,77–79]

bank to gather structural data on proteins and ligands, expediting the discovery of effective cancer treatments and reducing costs. It is also known that CRISPR-Cas9 technology enables gene editing and medical applications, such as growing MHC class I and PD-L1 expression on tumor cells, improving tumor-intrinsic IFNg signalling and inhibiting immunosuppressive myeloid cells. It also targets ABC transporter-related cancer cells' resistance to many drugs, increasing doxorubicin sensitivity in resistant lines like A2780/ADR, MCF7/ADR, and KHOSR2/U-2OSR2. BEND3 knockdown increases the levels of the efflux transporter BCRP in AML cells, decreasing TAK-243 levels and causing drug resistance.[91] Inhibiting A20 modifies susceptibility to brentuximab vedotin in Hodgkin lymphoma, improving its combat ability. CRISPR-Cas9 library screens aid in identifying druggable targets and understanding drug resistance processes.[92]

7. Justification for combined treatment in the field of cancer

Combination therapy is a good cancer treatment because it requires multi-target pathways, as illustrated in Fig. 3. This is due to the complex interactions between cancer cells and their environment as well as tumour heterogeneity. Therefore, it is critical to comprehend the dynamic tumor microenvironment (TME), signalling pathways, immune cells, and interactions inside the tumor's surrounding microenvironment.[93] By preventing the tumors from becoming resistant, it seeks to overcome resistance and may improve patient outcomes. Additionally, by increasing the demise of cancer cells, it can improve the therapeutic response, producing more profound and long-lasting effects than monotherapy, showing potential in metastasis, treatment resistance, tumour recurrence, and cancer biology. One of the primary justifications for combination therapy is that most cancers have a polygenic mutational base.[2] Tumour heterogeneity provided a biological rationale for combination therapy by demonstrating varying responses to drugs. Combinatorial methods are more successful in treating cancer because they disrupt several targets rather than just one signalling channel.[94,95] The rational combinations create strong target inhibition and work against tumour heterogeneity. Targeting several signalling pathways, blocking immune system proteins, switching up treatments, focussing on distinct tumour subpopulations, and employing synthetic lethality connections are all strategies to create synergistic combinations.[4] This approach can overcome cancer resistance mechanisms and increase therapeutic efficacy.

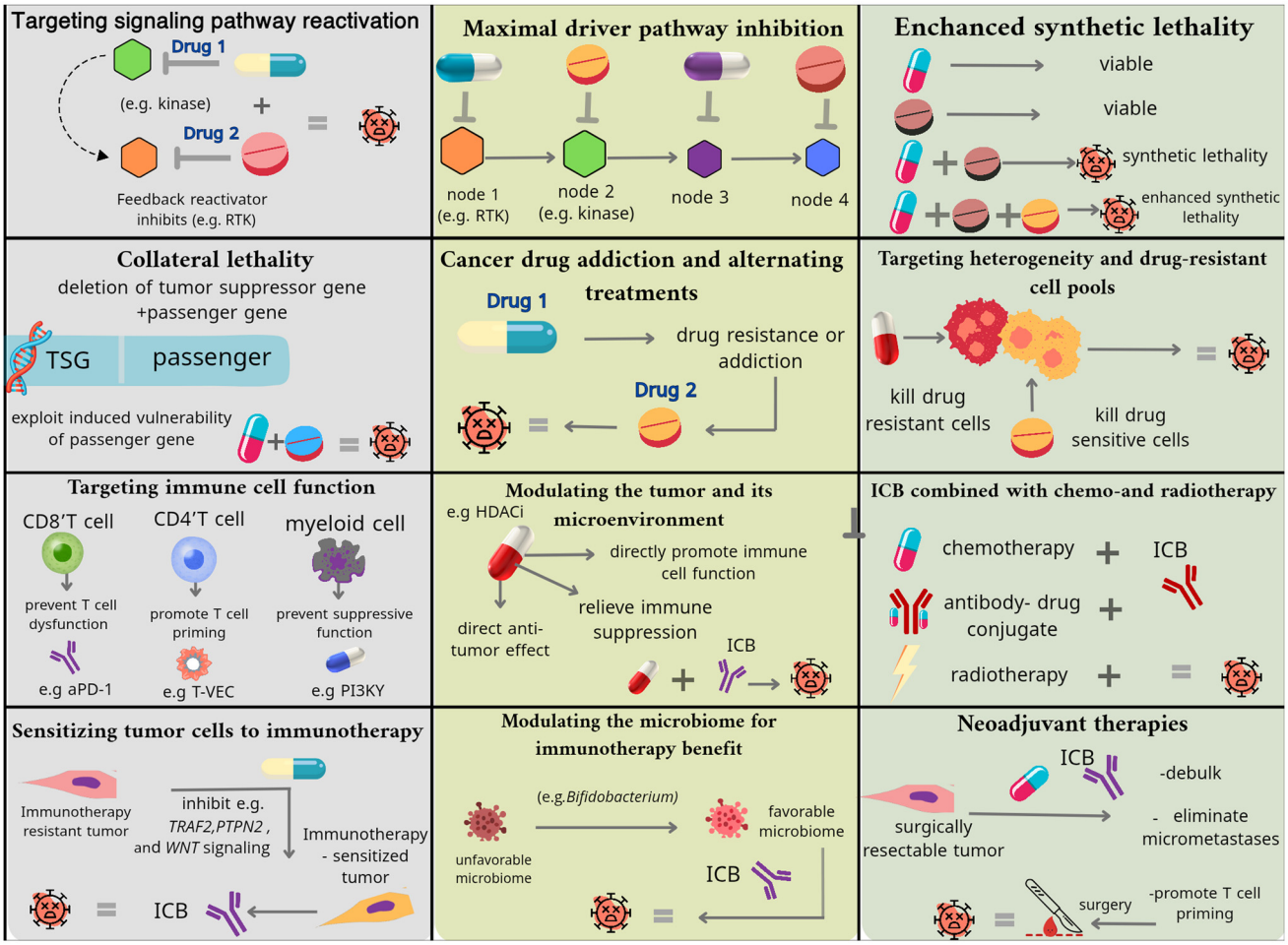


Fig. 3 Combination cancer therapies, based on biological and mechanistic discoveries, optimize treatment efficacy by addressing intricacies of cancer biology, signaling pathway connections, synthetic lethality interactions, genetic dependencies, and tumor heterogeneity. Created with BioRender.com.

Because biological regulatory circuits include built-in redundancies and feedback mechanisms that make them resistant to single perturbations, combination therapies are effective. They may result in more effective treatment for a disease than separate treatments since they target numerous parts of these circuits at once.[2] When the standard anti-cancer monotherapy has shown difficulties in the safety and tolerability of oncological patients, combining chemotherapeutic and repurposing medicines has also shown highly intriguing results. By focussing on several pathways, combining medications with different mechanisms seeks to increase the effectiveness of growth inhibition or cancer cell death.[96] As an example, chloroquine restores tamoxifen sensitivity by inhibiting autophagy, a survival mechanism that breast cancer cells use to resist anti-estrogenic therapy. Tamoxifen-resistant breast cancer cells often activate autophagy to evade treatment, but chloroquine blocks the later stages of autophagy, preventing cancer cells from using it as a survival strategy, as shown in Fig. 4. In preclinical studies, combining chloroquine with a significant amount of tamoxifen decreased the tumour size in tamoxifen-resistant breast cancer models. Clinical trials are being conducted to evaluate the efficacy of this combination in patients with oestrogen receptor-positive (ER+) breast cancer.[97,98] Despite significant benefits, oncological combo treatments still face numerous obstacles. Notably, the toxicity to healthy cells still places some limitations on this sort of treatment. For molecularly targeted medicines and various combinations of these therapies to be active, target inhibition must occur simultaneously. Consequently, we still deal with pharmacokinetic issues and possible injury to healthy tissue.[99]

8. Drug repurposing challenges

Despite the fact that repurposing drugs has opened up new possibilities, few repurposed medications in oncology or even cancer have made it into clinical use to date. Rushing into medical studies may hinder the quest for more precise medicines, despite the fact that the drug repurposing process is supposed to be much faster and less costly than traditional

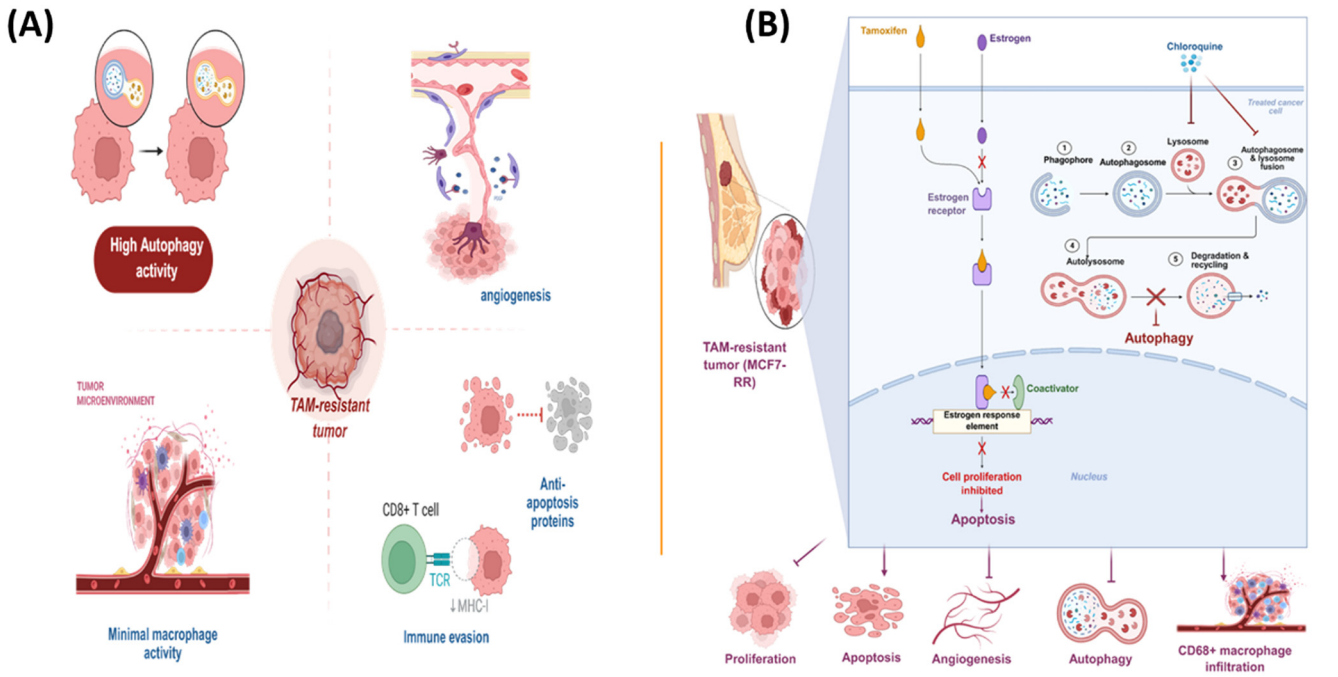


Fig. 4 Molecular and cellular mechanisms underlying the synergistic effect of tamoxifen (TAM) and chloroquine (CQ) in overcoming antiestrogen resistance in ER$^+$ breast cancer. (A) Demonstrates this resistant profile by exhibiting a weakly penetrated tumor microenvironment, increased autophagosome production, and reduced apoptosis. (B) Illustrates how the autophagy inhibitor chloroquine disrupts the survival advantage provided by autophagy by preventing autophagosome–lysosome fusion and restoring tamoxifen sensitivity. Created with BioRender.com.

drug research. Additionally, the final stages of clinical research still carry the chance of failure, just like in any medication development process. Other challenges include issues with payment and intellectual property, as well as legal and regulatory issues. We hope that these barriers may be eliminated so that drug repurposing can reach its full potential.[100]

8.1. Intellectual property, regulatory issues, and reimbursement

When equated to the traditional drug development pipeline, drug repurposing can result in the expedited approval of medicines, saving time and money. This method's potential for medication approval is especially intriguing in areas such as unmet medical needs and rare disorders. However, there are obstacles in the technique of drug repurposing. Reimbursement, intellectual property challenges, regulatory concerns, and the essential for creative clinical trial designs all are barriers to the reusing of drugs. The study will explore ethical issues in relation to patient safety and consent, emphasizing the rank of balancing speed and comprehensive assessment through precision diagnostics and novel disease classifications.[101] There are frequently no clear guidelines or regulatory incentives to encourage corporations to spend in the study and creation of novel applications of current pharmaceuticals, or should they be, they are insufficient. Hospital chemists can enhance therapeutic options for unmet clinical needs by rethinking medication uses and funding investigator-initiated research. Another important issue that requires attention is intellectual property (IP) rights.[102] Intellectual property can protect a newly repurposed medicinal usage of a known therapeutic molecule in major pharmaceutical markets as long as it is innovative and novel. However, the option of obtaining patent protection for the repurposed context is limited because many possible repurposing uses are already recognized in the scientific literature. In some situations, intellectual property rights conflicts may prevent a medicine from entering the market, even if it has shown encouraging results. Additionally, there is little chance of a return on investment when repurposing an off-patent medication, which deters corporations from supporting a trial. Drug repurposing has several legal and regulatory obstacles, and, patent concerns.[103] Due to the absence of commercial incentives, repurposing off-patent drugs creates a particularly difficult set of financial challenges. In order to commercialise a medication for a new medical indication, pharmaceutical corporations may repurpose their on-patent assets or new medicine developers may invest in clinical studies. By doing this, they might provide a return on investment, which would make the trial's expenditures justified. Off-patent and non-regulatory product producers face the risk of successful clinical studies favouring rivals due to low profit likelihoods, making trial expenditures unsustainable.[104] Clinical trials lacking commercial sponsorship and financial disincentives are often referred to as "financial orphans" for off-patent repurposing. These trials, often academic or investigator-led, may not receive per-patient payments, which can encourage patients to contribute to commer-

cially supported trials. Non-commercial repurposing trials in oncology can be difficult because of the competition from commercial organizations. Public funds, grants, subsidies, and patents can help defray costs. However, intellectual property concerns limit the rate at which repurposed drugs can reach the cancer market.[105]

8.2. Biases affecting drug repurposing

Medical and scientific studies often face biases, hindering therapeutic repurposing as a result of the scientific focus on creating innovative medications rather than exploring existing ones. Funding systems, which are more inclined to encourage innovative programs for the development of drugs than repurposing initiatives, frequently serve to further reinforce this prejudice. Consequently, cancer-proven drugs that have been licensed for other purposes have not received the attention they deserve. The usefulness of repurposed drugs is sometimes underestimated by the scientific community, despite evidence suggesting that they may be as effective as new treatments.[106] Furthermore, repurposed medications face major obstacles to clinical validation because clinical trial designs are frequently skewed towards evaluating the success of novel medications. Because standard clinical studies are sometimes not set up to examine the potential of repurposed drugs in cancer, promising treatments may be postponed or even abandoned. To overcome this bias, the scientific community must recognise repurposed drugs as legitimate and potentially effective cancer treatments.[107,108] Graph-based models and zero-shot learning are two examples of advanced computational techniques that are being used more and more to find potential cancer treatment repurposing opportunities.[109] Graph-based models predict drug–disease connections, incorporate intricate biological information, and outperform outdated approaches in accuracy and scalability, with various approaches and strategies available. Graph models like power graph analysis and knowledge graphs, which compactly represent therapeutic-target–disease interactions, make it easier to efficiently explore and identify new therapeutic candidates for cancers like lung and breast tumors.[110] Graph neural networks, like GraphRepur and GraphDTA, outperform traditional methods for machine learning by predicting drug–target affinities and repurposing chances using biological and drug structure data. Because graph-based approaches can manage large-scale datasets well, especially when they use power graphs and neural networks, they are suitable for modern, data-rich cancer research. Furthermore, massive language models like ChatGPT can do zero-shot information extraction from clinical trial articles and meta-analyses.[111] This proposes that people may identify and extract relevant information on the protection and effectiveness of medications for cancer therapies without prior task-specific training. These models enhance efforts to recycle medications for cancer by effectively aggregating and synthesizing information from randomized clinical trials. Although systematic errors can still occur, they can identify when information is absent and are regularly accurate in extracting appropriate information.

8.3. Combination therapy's challenges

A promising tactic for overcoming cancer's resistance to treatment and enhancing patient outcomes is combination therapy. Nevertheless, there are particular difficulties in creating combination treatments with repurposed medications. First, many repurposed medications have been researched as monotherapies, and it is unclear how they interrelate with other medications. Because a thorough grasp of the pharmacodynamics and pharmacokinetics of each agent is required, repurposing drugs in well-established treatments like immunotherapy, targeted therapy, or chemotherapy introduces complexity.[112] Determining the right dosages, the best order of management, and the therapy's start time are all critical when combining medications. Combination regimens with poor design can result in toxicities, decreased effectiveness, or even therapy failure. Moreover, not all medicine combinations work well together, and some may have adverse side effects that negate the desired therapeutic outcomes. Combination therapy clinical trials are challenging because of the necessity for larger patient populations, longer follow-up times, and advanced statistical techniques to assess drug combinations' effects on different tumor types. The regulatory approval of combination medicines is another major obstacle.[113] Before approving a combination treatment for clinical use, regulating agencies such as the FDA and EMA frequently want independent trials for each drug in the regimen. This adds time, expense, and complexity to the approval process. The procedure is made more difficult by the fact that some of the medications used in combination therapy are repurposed and may already have approval for other uses. To better support the testing and authorisation of combination medications, especially those containing repurposed medications, regulatory bodies may need to update existing frameworks.[114] Combination remedy is further hampered by patient heterogeneity. Due to variations in tumor biology, genetics, and the immunological milieu, no two patients will react similarly to the same combination treatment. Combination therapy may need specialised approaches, including biomarker-guided treatment, to maximise efficacy and minimise side effects. This necessitates further research into the molecular and genetic features of tumours and how they interact with different forms of treatment. Lastly, there is the issue of accessibility and expense.[115] Because combination therapies require several medicines, some of which may be pricey biologics or innovative treatments, they may be costly. The price of developing new formulations or combination regimens for repurposed medications may not be justified by the cost of individual medications, particularly if they are off-patent and inexpensive. This cost barrier might keep combo medicines from being widely used, even if they show a lot of promise in clinical trials.

9. Clinical and preclinical studies of repurposed medications for cancer

New studies on preclinical and clinical trials of repurposed drugs offer an exciting avenue for enhancing oncology treat-

ments. The basis for evaluating the viability of repurposed medications in oncology is preclinical trials. Prior to conducting human trials, the usage of animal models aids in determining suitable dosage schedules and possible adverse effects. Using animal models, preclinical research is carried out to assess the compound's safety and effectiveness under lab conditions. An investigational new drug application (NDA) is then submitted to obtain approval to test the medication on humans.[116,117] Several repurposed drugs have entered clinical trials for the treatment of cancer; these trials are usually carried out as monotherapy rather than in combination with other drugs. Combination therapy might be more effective than single-agent therapy. Therefore, it is more important to undertake clinical trials for repurposed drugs in combination with other cancer treatments.[3] Preclinical research has shown promise for a number of repurposed medications. For instance, it has been demonstrated that the common antidiabetic medication metformin inhibits the growth of cancer cells. Metformin, according to *in vitro* and animal studies, can slow down tumor growth and increase cancer cell sensitivity to chemotherapy or radiation treatments.[118] Clinical investigations have also demonstrated encouraging results. For instance, a number of trials have demonstrated that patients with ovarian, breast, and colorectal cancers who got metformin in addition to other treatments had greater survival rates.[119] Aspirin, a repurposed NSAID, has been revealed to slow cancer spread by inhibiting COX-2, a key enzyme in tumor inflammation and angiogenesis. Current clinical trials are investigating its potential for usage in treating a number of other malignancies, including breast, lung, and prostate cancers.[118] Furthermore, preclinical models have shown promise in stopping the growth, metastasis, and resistance mechanisms of cancer cells using drugs that have previously been used to treat conditions like epilepsy or parasitic infections, such as the anti-parasitic drug ivermectin.[33] Transitioning from preclinical research to clinical use of repurposed cancer medications remains challenging due to potential adverse effects and complex regulatory processes. By using available safety and efficacy data, researchers hope to lower drug development costs and accelerate therapy development.[120–122]

10. Conclusions and viewpoints

Drug development may be facilitated by using repurposed pharmaceuticals in the treatment of cancer, which could help solve the shortage of new therapies and resistance to existing treatments. Furthermore, researchers and the pharmaceutical industry throughout the world have shown a great deal of interest in it thus far. Clinical symptoms, transcriptome and genomic data, and a variety of databases have been used to promote the creation of repurposed medications for the treatment of tumours. The repurposing of cancer medications can be drastically changed by developments in genome-editing tools like CRISPR-dCas9, bioinformatics, and computational methods. It is acknowledged that there is still untapped potential for these creative approaches to advance. A comprehensive understanding of the benefits and drawbacks of these technologies may result in novel ideas for basic research and clinical practice. Using structured datasets, we discussed in this paper how supervised machine learning and AI algorithms are essential to the field of medicine repurposing. Additionally, they have the ability to expedite the process of identifying suitable drug candidates through accurate analysis of drug repurposing databases. The aptitude of the *in silico* medication repurposing technique to employ large data to find therapeutics against cancer targets makes its exploration vital. The system predicts druggable cancer targets using system biology data, ideally involving FDA-approved chemicals with potential modulatory or inhibitory functions. Also, we discussed the importance of CRISPR-ATFs in comprehending gene regulation networks and detecting side effects of currently prescribed medications. Additionally, they might trigger tumor-suppressor genes like p53, reorganize cancer cellular pathways, and possibly repurpose current cancer drugs based on novel targets. In summary, this work seeks to enhance treatment results, increase therapeutic options for cancer patients, and open the door for their application in research.

Abbreviations

DNA	Deoxyribonucleic acid
CSCs	Cancer stem cells
CRISPR-dCas9	Clustered regularly interspaced short palindromic repeats-dCas9
ML	Machine learning
AI	Artificial intelligence
PDD	Phenotypic screening drug discovery
GWASs	Genome-wide association studies
GB	Glioblastoma
TP53	Tumor suppressor gene 35
MMP9	Matrix metalloprotease 9
CRISPR-ATFs	CRISPR-dCas9-based artificial transcription factors
DBDs	DNA-binding domains
ZFs	Zinc fingers
TALEs	Transcription activator-like effectors
sgRNA	Single guide RNA
DTs	Decision trees
RFs	Random forests
SVMs	Support vector machines
NN	Neural network
DL	Deep learning
RNNs	Recurrent neural networks
CNNs	Convolutional neural networks
GBA	Gradient boosting algorithms
TME	Tumor microenvironment
BC	Breast cancer
FOLFIRI	FU/leucovorin/irinotecan
CAPOX	Capecitabine/oxaliplatin

NDA	New drug application
IP	Intellectual property

Author contributions

Conceptualization: Hend Gamal, Areej Hajjaj M. Mohammed, and Mohammad Fadl Khder; writing – original draft preparation: Esmail H. Elramy, Doaa Ahmed Abd Ellah, and Shorouk Mahmoud El-Sayed; writing – review and editing: Eman Mostafa Shoeib and Heba Elsafy Abdelaziz Abdullah; and supervision: Hend Gamal. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that there are no competing interests.

Data availability

All data generated or analyzed during this study are included in this manuscript.

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