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Review

Reprogramming cancer therapeutics through artificial intelligence-guided drug repurposing: Computational innovation, experimental validation, and translational challenges

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ABSTRACT

Drug repurposing, which involves identifying the anticancer activity of drugs initially developed for non-oncologic diseases, has shown particular promise in oncology. Artificial intelligence (AI), with its capacity to rapidly combine chemical, biological, clinical, and real-world evidence and generate novel hypotheses and predictions beyond traditional discovery paradigms, has the potential to transform the drug repurposing process in oncology. Here, we provide an overview of the translational challenges in AI-based predictions for cancer drug repurposing. A PubMed and Google Scholar literature search was conducted using Medical Subject Headings and Boolean logic operators related to drug repurposing and artificial intelligence or machine learning. Peer-reviewed, English-language literature describing AI-enabled approaches to drug repurposing was primarily considered, with an emphasis on foundational work and, when possible, on the last five years. Particular focus was placed on literature that provided preclinical or clinical validation. The reviewed literature indicates that AI can facilitate a variety of overlapping repurposing strategies, including new drug–target pair identification, candidate prioritization, drug combination synergy prediction, and patient-level opportunity stratification. Areas of increasing focus include toxicity-aware repurposing modeling, enhanced interpretability, multi-omics molecular signature integration, and formulation/delivery optimization guided by AI. In summary, AI-based repurposing is an evolving, cost-effective, and promising approach for advancing precision oncology, and it will require greater emphasis on data quality, biological validation, and model interpretability to enable the translation of computational predictions into real-world impact.

Introduction

Cancer remains a major source of morbidity and mortality globally, and, although breakthroughs have occurred in cancer therapies, the emergence of new drugs for this indication remains hindered by a series of challenges [1–3]. The conventional drug development process takes 10–15 years and requires substantial financial investment, yet it is accompanied by a high attrition rate in late-stage clinical trials [4]. In cancer therapy, failures often arise from limited efficacy in genetically heterogeneous tumors, unacceptable toxicity profiles, or insufficient target validation. Such obstacles have driven a parallel approach: drug repurposing, the identification of a new indication for an existing drug

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with a known pharmacokinetics/pharmacodynamics/toxicology profile already partly or fully elucidated in preclinical studies [5,6]. Such an approach can therefore quickly bring a new candidate into clinical trials at reduced cost and enable rapid translation based on prior knowledge of existing drugs [7,8].

Recent advances in AI and machine learning (ML) have, in turn, accelerated the promise of drug repurposing, a strategy that targets the discovery of new therapeutic applications for already approved drugs, extending their use beyond their initial medical indications [9]. All biomedical data types, including transcriptomic profiles, chemical structures, protein–protein interaction networks, clinical phenotypes, and high-content imaging outputs, are analyzed by AI to identify non-obvious relationships among drugs, targets, and disease states. These computational approaches can systematically screen large therapeutic libraries, prioritize candidate mechanisms, and generate hypotheses that may not emerge through strategies. Specifically, deeper integration of biological context was achieved through network-based learning, generative models, and representation learning, enabling deeper integration and uncoveringepositioning candidates tailored to tumor molecular subtypes [10–13].

Biological validation, tumor heterogeneity, biomarker identification, dosing regimen, and approval barriers represent critical factors in translating success [14]. Moreover, repurposing small molecules that were not primarily developed for tumor-selective delivery and optimized intratumoral pharmacokinetics may pose formulation considerations for translation into an oncology setting [15,16]. A summary of formulation and delivery aspects is therefore necessary to situate computational discoveries within realistic translational pipelines [17].

Therefore, this review will analyze how AI is transforming repurposing in cancer therapy by identifying opportunities within existing drugs and accelerating their conversion into therapies. By integrating computational modeling, machine learning, and multi-omics analysis, AI technology has absolutely redefined the field of personalized cancer therapy, from accurate predictions of new relationships between drugs and targets to the identification of therapy combinations with greater accuracy. Moreover, this review highlights how AI-driven insights can affect formulation and delivery strategies to improve bioavailability, specificity, and efficacy, and how AI-guided drug repurposing can bridge the gap between computational prediction and clinical reality.

Here, “reprogramming cancer therapeutics” indicates a model shift enabled by artificial intelligence, in which the classical linear drug discovery process is translated into an always-evolving, data-rich, and systems-based form. Instead of finding new compounds, AI helps reinterpret existing drugs by integrating multi-omics, chemical, clinical, and real-world datasets to delineate unrecognized drug mechanisms. This reprogramming accordingly occurs across multiple hierarchies: transitioning drug-target relationships from single-target to network-based and polypharmacological models; evolving from population-level treatment paradigms to matching therapeutic regimens to patients; and catalyzing the progression of computationally driven predictions into clinical validation via predictive and evidence-based modeling. Together, these capabilities place AI at the forefront not only of optimization but also as a transformative engine, leveraging new approaches to how we conceive and discover cancer therapies for translation into clinical practice.

Foundations of drug repurposing in oncology

Drug repurposing, also known as drug repositioning or labeling extension, involves using known pharmacologic agents for new indications. In cancer drug development, drug repurposing is an attractive option because many known drugs have human safety data, enabling researchers to skip toxicology testing and progress more quickly toward clinical studies. There is a conceptual classification of drug repurposing based on the major aim and the source of supporting evidence.

In general, the drug repositioning/repurposing process can be broken down into three major stages: first, the identification of the basic molecules and/or pathological targets of the disease (hypothesis formation), second, screening of the therapeutic efficacy of the drug *in vitro* and *in vivo* studies, and third, advancing to phase II trials upon the availability of positive phase I findings regarding their toxicity and pharmacokinetics [15,18]. In fact, the hypothesis-generation step in this process is fundamental and pivotal in any repurposing effort [19]. Usually, oncology-related drug repurposing has been guided either by mechanistic insights into disease biology or unexpected clinical observations. Consequently, more sophisticated strategies could be used to align existing drugs with new therapeutic opportunities to increase the success rate of the programs [15].

Candidate identification could be done either manually or using computers. Manual methods employ techniques such as induced pluripotent stem cell disease models and function-first phenotypic screening platforms, commonly known as the reverse chemical biology approach [19]. Computerized methods rely on target-focused, knowledge-driven signature matching, pathway-focused concepts, and mechanism-driven models[20]. However, a combination of the two methods can help in efficient discovery. Notably, modern high-throughput analysis systems using a complex biological model can help discover molecules with the potential to alter disease phenotypes, with no prior knowledge or experience of the relationship between targets and drugs [21,22]. In addition, new computer models, including those that integrate drug-induced signatures with disease-specific clinical profiles or predict disease-modifying effects, can help in selecting potential candidates for cancer drug repurposing. The models have the potential to identify interactions between ligands and targets and to aid in interpreting drug binding properties. They help prioritize molecules using an extensive chemical library[23,24]. Thus, while drug repurposing is a well-known strategy in drug development, advances have enabled the development of more deliberate, evidence-driven strategies aligned with new, uncharacterized clinical applications, as described in Fig. 1.

Organoid models in cancer research

The term organoids refers to stem cell-based self-organizing three-dimensional entities, of which tumoroids are the cancer-derived subset [25]. These *in vitro* models are created using human stem cells, organ-specific progenitor cells, or dissociated tumor tissues grown in media enriched with extracellular matrices, typically generated with high efficiency. Tumoroids closely replicate primary tumor architecture and functionality, preserving histopathological characteristics, genomic profiles, mutational patterns, and therapeutic response behaviors. The application of tumoroids has vastly grown and become accepted as a reliable tool for basic research studies and early drug development [26, 27] For instance, cisplatin was found to have diminished efficacy in patient-derived organoids (PDOs) of non-small cell lung cancer relative to the commonly used two-dimensional cell line cultures, validating the application of PDOs to identify drug resistance mechanisms [28]. Such examples have also been shown in gastrointestinal cancers, in hepatocellular carcinoma HCC, and in esophageal carcinoma, where the role of PDOs has been crucial in assessing drugs and identifying possible therapeutic targets [29,30]. Accordingly, because they can reproduce organ-level architecture, gene expression programs, and essential functional attributes, tumoroids have been identified as a substantial benefit for drug assessment in oncology (Fig. 2).

Tumoroids closely resemble the biological properties and anatomy of human tumors, making them a valuable tool for basic and translational research. In this regard, tumoroids are employed in tumor modeling to explore cancer initiation and development, predict responses to therapies, provide optimal treatment schemes, and screen for new anticancer agents [31]. However, there are certain limitations related to the application of tumoroid models at a broader scale. First, the tissue fragments used to obtain organoids represent only a small fraction of the

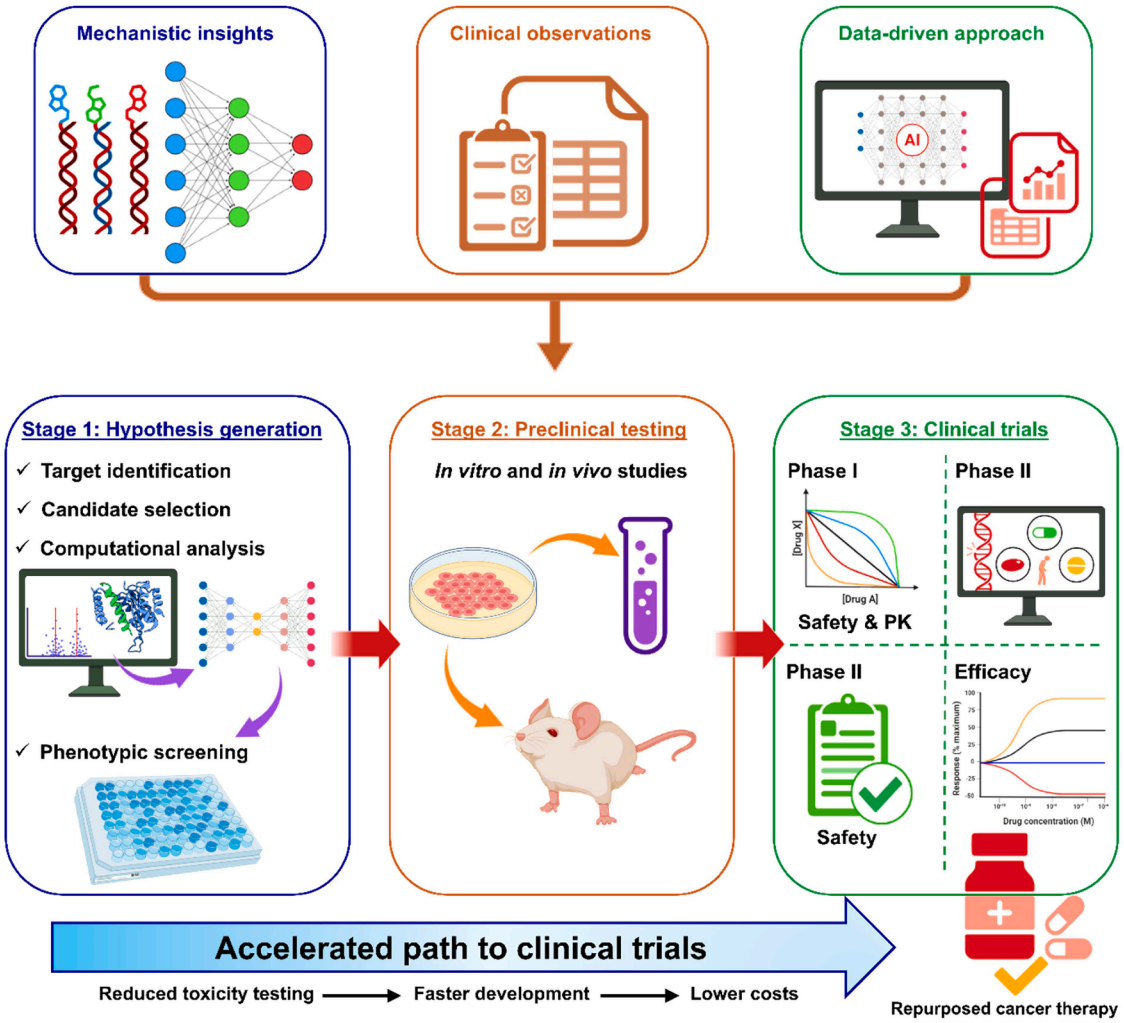

Fig. 1. Foundations of drug repurposing in oncology. Partially created based on (https://www.biorender.com/).

tumor originally obtained. Additionally, relying on such limited samples may affect the accuracy with which tumoroids reflect the tumor's overall landscape, given the profound intratumoral heterogeneity in most malignancies. Hence, great caution is required when interpreting results derived from these models [32,33].

Moreover, tumeroids might also fail to contain essential non-cancerous cell types, such as mesenchymal stromal cells, neural components, and immune cells, thereby limiting their ability to recapitulate the complex multicellular structure and functionality of the natural tissue microenvironment [34]. In fact, an incomplete representation of the cancer tissue immune environment poses a significant limitation when applying tumoroids in precision cancer therapy studies. Another major challenge is the insufficient vascularization of tumoroids [35]. Functional vasculature is essential for mimicking tumor physiology, and integrating a functional vascular system with tumoroid cell cultures remains an unresolved problem. In addition, there is a lack of standardized culture conditions, making it challenging to achieve reproducibility, scalability, and the effortless integration of tumoroid systems into a high-throughput drug-screening pipeline [36]. Also, prolonged, uncontrolled passaging may risk loss of innate tissue heterogeneity. In summary, whereas tumoroid systems offer numerous potential benefits for cancer research, these challenges must be addressed to fully leverage their capabilities 34).

Phenotypical analysis

Drugs known for their high off-target or unintended biological activities in cancer could also present attractive leads for repurposing, where such off-target activity could indicate recognized applications (phenotypic analysis) [37]. Phenotypic screening evaluates observable biological responses in experimental models ranging from cell cultures to whole organisms to identify candidate drugs and define their targets [38]. Various repurposing leads have already been identified through large-scale cell-based screens using cell cultures, focusing strictly on typical cancer phenotypes such as sustained proliferation, increased angiogenesis, or reduced apoptosis, as illustrated in Fig. 3. Thus, phenotypic screening is a cost- and time-efficient process, especially for discovering new lead drugs targeting unrecognized targets, thereby minimizing the risk of failure in early-stage clinical development [15].

Computational approaches

In modern drug repurposing, computational methodologies have become indispensable [39]. The rapid advance of omics technologies, together with advances in big-data analytics, machine learning, and algorithmic modeling, has dramatically expanded our ability to interrogate disease mechanisms and drug activity. These provide broad access to disease-centric and drug-centric datasets [40]. A wide array of *in silico* strategies, including molecular docking, network pharmacology, data mining, similarity-based analysis, machine–learning–driven

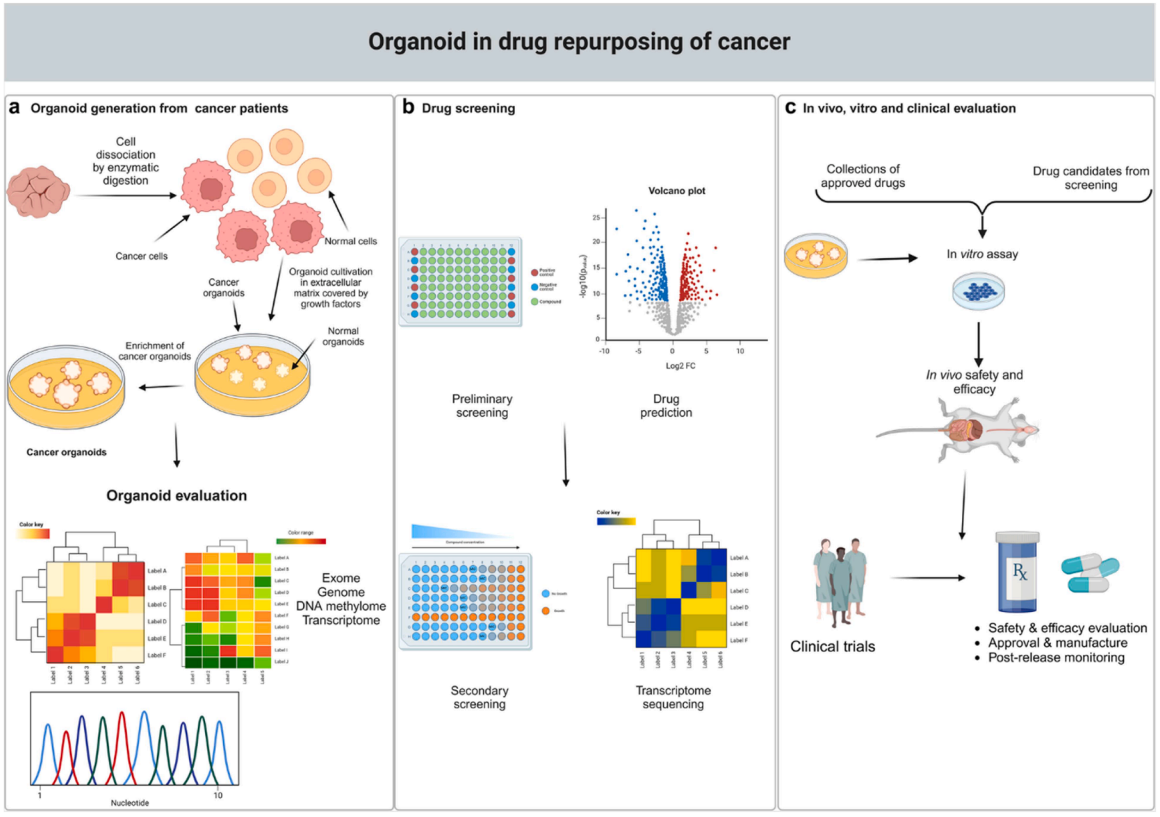

Fig. 2. A schematic representation describing the preparation of PDOs from tumor biopsy specimens, including tissue dissociation using an enzyme treatment, embedding of these dissociated tissues into an extracellular matrix, supplementation with appropriate growth media, and subsequent enrichment of cancer-specific tumoroids through selective withdrawal of medium components and/or incorporation of mutation-targeted inhibitors. These tumoroid systems serve as platforms for drug-discovery screening and for translating repurposed drug candidates into preclinical or even clinical trials. This figure is retrieved from [15]. Copyright Signal Transduction and Targeted Therapy, 2024, 9, 92.

prediction models, and transcriptional signature matching, are now available to researchers [41].

Using these computational models, the potential of approved anticancer drugs and the development of disease-specific knowledge for informed repurposing efforts could be investigated [42]. Besides, the discovery of inhibitors for oncogenic pathways using computational models for repurposing and employing network-based systems biology approaches has been found to be most effective, and several publicly available databases are available for conducting extensive bioinformatics analyses of drugs. All these have facilitated drug repurposing for different diseases [43] and have improved chemotherapy approaches and overcome the problem of drug resistance to serve patients better [43], as outlined in Table 1.

Target-centric approaches

Target-centered drug repurposing focuses on identifying disease-related protein targets or pathways involved in oncogenesis and assessing whether existing drugs can modulate these targets, even if originally developed for other therapeutic areas. This strategy is based on the fact that many approved or investigational agents have polypharmacological properties, meaning they interact with multiple proteins beyond their primary indications. This approach has enabled the identification of new drug candidates with potential use in cancer therapy [53,54].

AI enhances Target-centric research by quickly screening libraries against validated or predicted targets based on docking, molecular dynamics simulations, and structure-activity relationship-based neural networks. Improvements in protein structure modeling, especially AI-powered tools that can simulate challenging cancer targets, have widened the scope of targetable proteins, including kinases, transcription factors, and unconventional signaling modulators [55,56].

One essential aspect of the target-centric paradigm is the need for high-quality molecular data to identify the target's role, structure, or interaction network. Several tools have been developed and have become integral to this paradigm [57,58]. The Human Protein Reference Database (HPRD) is a database that encompasses proteins encoded by human genes, including expression data, post-translational modifications, and interactions [59]. The STRING database takes it a step further, covering structural, functional, and predicted protein-protein interactions, providing a systems-level view of how the targeted protein functions within a cellular environment [60]. These datasets are especially useful for oncology, where pathway disruption is critical within tumorigenesis [61].

Further, drug-target relationships can be explored through resources like the Therapeutic Target Database (TTD), which compiles therapeutic targets alongside associated diseases, pharmacologic agents, and supporting literature. By linking disease biology with drug mechanism, TTD facilitates the identification of existing compounds that may already modulate cancer-relevant proteins. These tools collectively support the systematic interrogation of whether a given cancer target is "druggable" using compounds approved for other indications. By linking disease biology with drug mechanism, TTD facilitates the identification of existing compounds that may already modulate cancer-relevant proteins. These tools collectively support the systematic interrogation of whether a given cancer target is "druggable" using compounds approved for other indications [61,62].

Target-centric repurposing has proven effective across various therapeutic areas. For example, similar strategies have been used to identify repurposable drugs against Candida albicans in multidrug-resistant

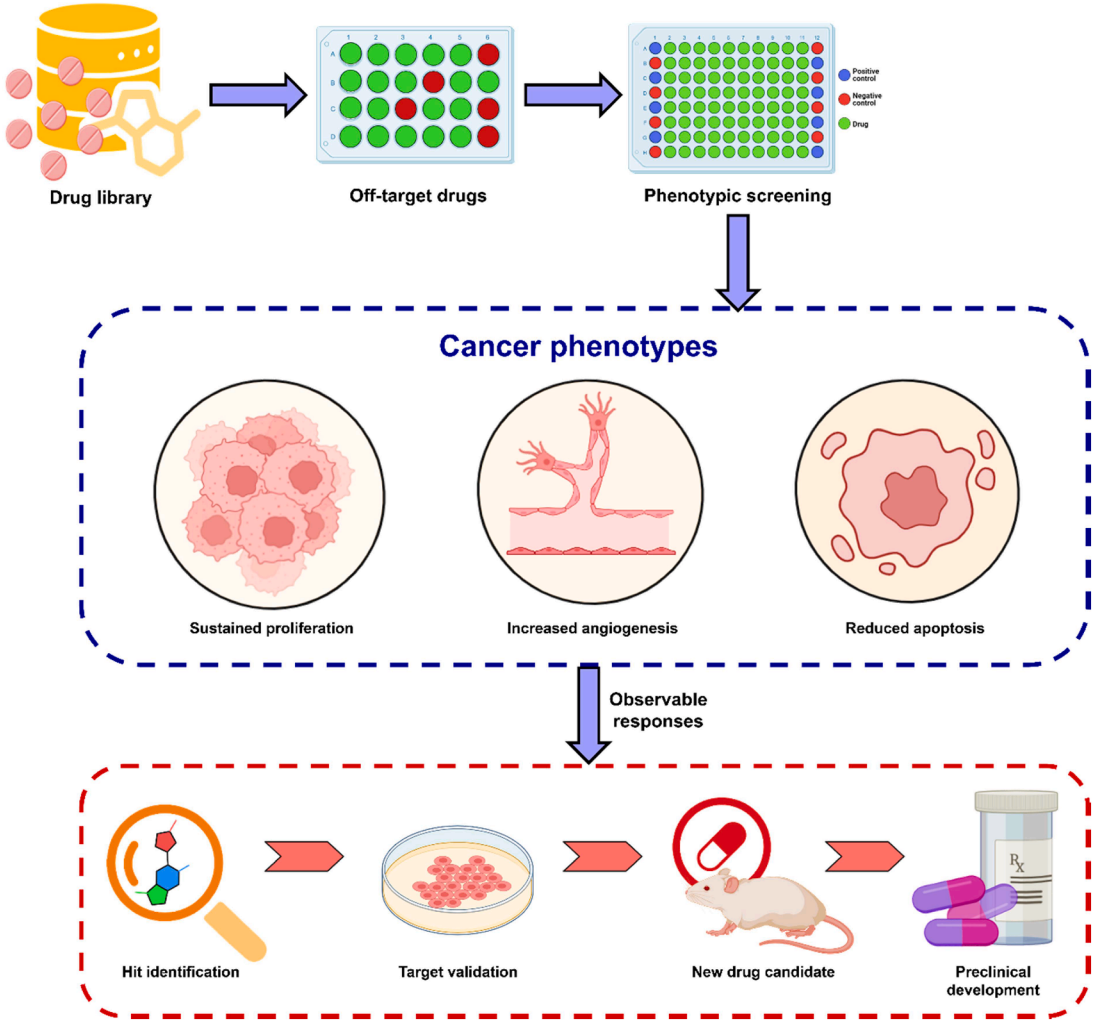

Fig. 3. Phenotypical analysis in drug repurposing. Partially created based on (https://www.biorender.com/).

settings by mapping molecular targets to existing drugs that modulate them. Translating this approach to oncology, such methods enable researchers to pinpoint non-cancer drugs that bind oncogenic kinases, transcriptional regulators, metabolic enzymes, or immune-modulating pathways, thereby contributing to the discovery of new anticancer drugs without performing target discovery and validation [63].

Drug-centric approaches

Drug-centric strategies begin with an existing drug and evaluate its biochemical, pharmacological, and molecular properties to identify new therapeutic uses [64]. AI models, especially graph neural networks and transformer-based architectures, have the potential to infer anticancer use-related effects by identifying the underlying chemical properties associated with treatment outcomes. In consideration of the large-scale compound screening data, the side effects, and the real-world pharmacovigilance signals, a drug-centric strategy may identify the unexpected anticancer property of compounds that were previously used for indications other than oncology through the vast experience that exists within approved compounds for safety and toxicity data that can be quickly applied to oncology drug development [65–67].

Several publicly available resources are replete with data for drug-centric analysis. The National Library of Medicine Drug Information Portal provides access to drug mechanisms, uses, and approval statuses through a single portal [68]. PubChem is essentially a chemical encyclopedia rich in data on molecular topology, physicochemical properties, bioactivities, toxicology, patent information, and links to relevant literature [69]. DrugBank is a repository that compiles pharmacologic, biochemical, and clinical data for several thousand drug candidates, both approved and under investigation, thereby serving as the backbone for drug repurposing strategies [70]. The FDA Online Drug Label Repository provides official regulatory information, including prescribing details and safety disclosures, to guide early feasibility assessments [71].

As the predictive ability of drug-centric methods largely depends on the quality and scope of available data, several private-sector platforms have emerged, providing proprietary drug databases with more sophisticated curation and advanced search algorithms. When coupled with AI methods, including molecular fingerprinting, similarity learning, and deep learning algorithms applied to high-dimensional chemical data, drug-centric drug repurposing can be accomplished much more efficiently through rapid hypothesis generation and candidate prioritization based on the highest translational potential [65,72].

The difference between target-based and drug-based approaches in drug repurposing is shown in Fig. 4. It illustrates how target-centric strategies begin with a disease-relevant molecular target, whereas drug-centric strategies start with the compound's pharmacological properties to identify novel therapeutic indications [73].

Toxicity-based approaches

The toxicity-based approach leverages the established safety profiles

Table 1
AI computational repurpose strategies in oncology.

Strategy	Starting point	Tools/Databases	Example drugs	Application in oncology	Cancer type	Key limitations	Ref.
AI phenotypic clustering	High-throughput phenotypes	Clustering and ML	NA	Phenotypic response repurposing	Cell panel studies	Not target/ mechanism specific	[44]
Bayesian factor models	Statistical integration of omics	Custom AI libraries	NA	Off-target mechanism predictions	Consult literature	Hard to interpret biologically	[45]
Cloud/GenAI drug mini ng	Real-world trials and literature	ChatGPT/LLM and clinical trials	Drug combos identified	Repurposing with evidence	Breast	Hallucination and irrelevant matches	[46]
Counterfactual ML for treatment	Multi-omics and clinical outcomes	Multi-omics ML frameworks	NA	Personalized repurposed recommendations	Ovarian	Bias in observational datasets	[47]
Deep learning virtual screening	Structural models and docking	AlphaFold, AutoDock, and DeepVS	NA	Predict novel drug-target binding	Multiple	Docking scoring inaccuracies	[44]
Drug-centric (Ligand-based)	Drug chemical structure similarity	PubChem, ChEMBL, and chemogenomics databases	Ruxolitinib is predicted for breast cancer	Drug repurposing based on chemical similarity	Breast cancer	False positives due to structural similarity without a mechanism	[48]
Evidence aggregation NLP	Text mining clinical/ biomedical literature	PubMed and NLP/LLMs	Resistant drug roles from review text	Evidence-based suggestions	Multiple	Misinterpretation of text and bias	[44]
Genomic signature reversal	Disease gene expression signatures	LINCS L1000 and GEO	Drugs inverse to cancer signatures	Signature reversal drugs predicted	Multiple	Requires high-quality expression data	[49]
Genomic signature reversion (LINCS)	Reverse gene signatures	LINCS and Connectivity Map	NA	Identify drugs reversing cancer signatures	Multiple	Signature artefacts, off-target effects	[50]
Graph neural network synergy prediction	Drug-protein interaction graphs	GNNs (e.g., MOOMIN)	Combination therapy pairs	Predict synergistic combos	Multiple	Data sparsity and synergy validation	[51]
Knowledge graph-transformer (HGTDR)	Heterogeneous graphs	Custom GNNs and NLP extraction	Top 10 candidate drugs (validated)	Data-driven candidate repurposing	Broad	Requires expert implementation	[52]
Machine-learning DTI models	Drug-target interaction data	BindingDB, PubChem and supervised ML	NA	Predict repurposed DTI for oncology	Multiple	Requires large and labeled training data	[44]
Multi-omics integration	Omics layers (genome and transcriptome)	TCGA, CCLE and multi-omics AI models	NA	Integrative predictions of drug response	Ovarian, Breast and Lung	Integration complexity and missing data	[47]
Network medicine	Disease/pathway networks	KEGG and Reactome	Combination therapy candidates	Pathway coverage repurposing	Breast	Pathway overfitting and complexity	[46]
Phenotype-based prediction	Phenotypic drug response data	CellProfiler and high-content imaging	NA	Predict drugs that alter cancer cell phenotypes	Cell line panels	Poor translation to clinical outcomes	[44]
QSAR-ML hybrid methods	Chemical structure and activity	QSAR and XGBoost/ SVM	NA	Predict new therapeutic indications	Multiple	Extrapolation beyond the training domain	[44]
Target-centric	Known cancer targets/proteins	AlphaFold, PDB, UniProt, and Deep learning DTI models	NA	Prediction of drugs for pan-oncogenic targets	Multiple	Limited by the accuracy of predicted target structures	[44]

of approved drugs to identify those that may be repurposed for oncology. Mechanistic hypotheses are generated when cytotoxicity or specific adverse effects suggest potential anticancer activity. Compounds that show off-target cellular stress, DNA damage, metabolic disruption, or apoptosis in non-oncologic indications may have similar effects in tumor settings, with therapeutically relevant consequences. High-content toxicogenomic databases and adverse event reporting systems, such as FAERS, have recently been mined using AI and machine learning to identify statistically enriched toxicities associated with anticancer mechanisms. The use of this approach diminishes several limitations in the early development stage by focusing on drugs with well-characterized pharmacokinetic and safety data, thereby accelerating the pace toward clinical testing [63,75].

Genomics-based approach

Genomics-based repurposing integrates mutational landscapes, gene-expression signatures, and systems-level molecular networks to match existing drugs to the genetic vulnerabilities of a given cancer type [76]. From transcriptomic perturbation signatures (LINCS/L1000) analysis, machine learning algorithms can predict whether a particular drug induces a gene expression pattern that reverses or negatively interacts with oncogenic signatures [77]. Similarly, computational models can identify associations between drugs and specific genetic mutations found in tumors, dysregulated pathways, or synthetically lethal interactions detected by CRISPR and RNAi screens. This approach has proven particularly powerful in precision oncology, where identifying drugs that selectively target molecular subtypes can dramatically refine treatment strategies. Genomic-driven repurposing can serve as the biological framework for repurposing drugs, using tumor dependencies rather than the drugs themselves (Fig. 5) [76,78].

Evidence-based/clinical data–driven approach

The evidence-based approach uses real-world evidence, observations, electronic health records (EHRs), and retrospective analyses to identify unsuspected beneficial effects of existing drugs in cancer patients. Using AI, natural language processing, and statistical modeling, researchers can identify patterns of lower cancer incidence, slower disease progression, or improved survival rates among patients treated with similar drugs for similar ailments. Such correlations can then be experimentally verified or simulatedo assess their physiological feasibility [79,80]. This approach has been crucial in the identification of repurposing drugs such as metformin, as well as the usage of statins against malignancy [81,82]. The evidence-based repurposing approach provides a practical, relevant discovery pipeline for drug development

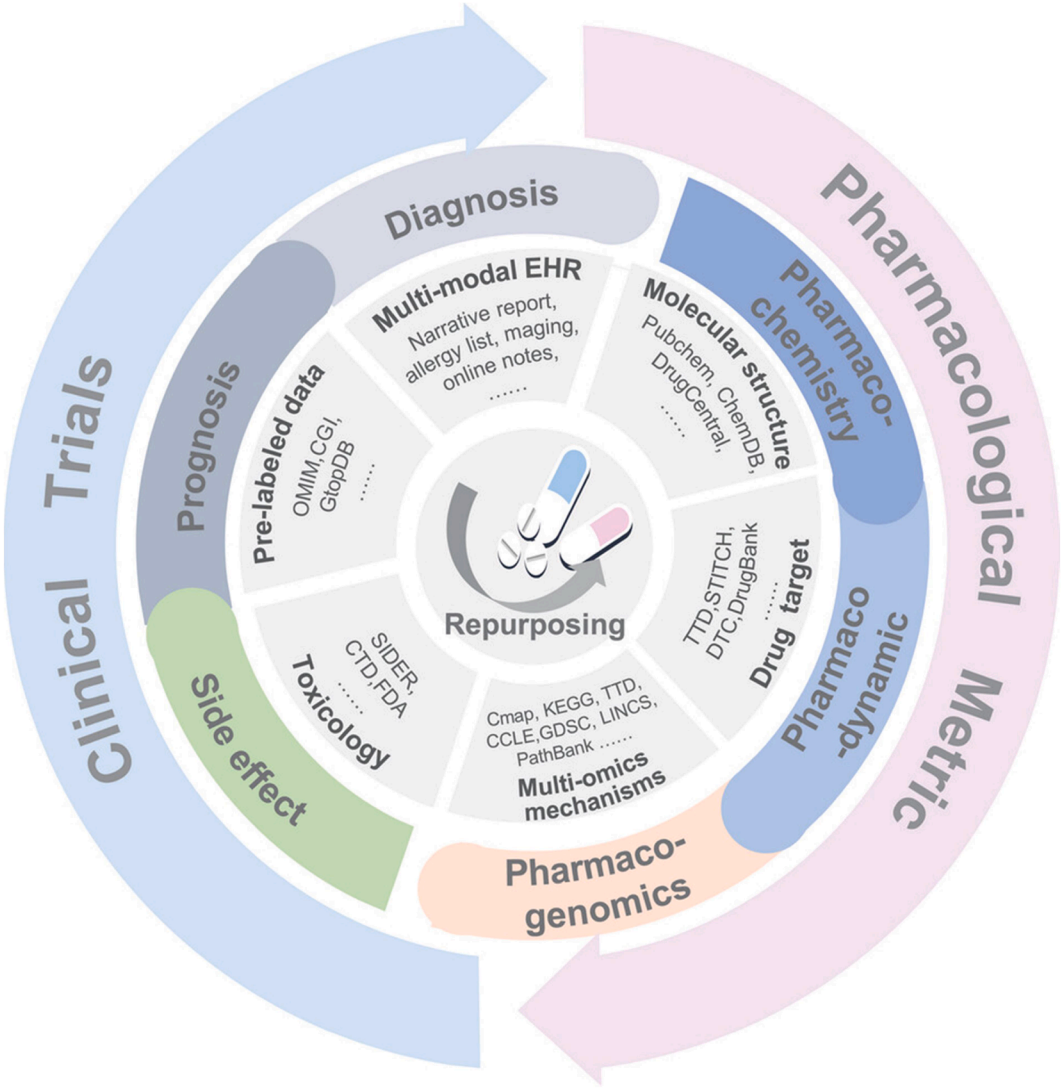

Fig. 4. The evolution of artificial intelligence learning approaches and the therapeutic benefits of repurposing medication [74]. Copyright Advanced Science, 2025, 12(14), 2411325.

that leverages real-world evidence and can thus supplement computational or molecular repurposing methods.

AI methodologies in drug repurposing

AI methodologies used in drug repurposing can be broadly categorized by their functional roles in the discovery and translational pipelines [83]. In this review, we classify these approaches into four major categories: predictive modeling approaches, which aim to infer drug–target interactions, therapeutic responses, or toxicity profiles from structured datasets; generative and representation learning approaches, which learn latent features from chemical, biological, or clinical data to enable similarity-based repurposing or de novo hypothesis generation; network- and systems-based approaches, which model biological interactions and disease modules to identify multi-target or pathway-level therapeutic opportunities; and evidence-mining and language-based approaches, which extract and synthesize knowledge from unstructured sources such as scientific literature, clinical records, and real-world data [84,85]. This classification framework is used to organize the following subsections and to distinguish conceptual roles rather than specific algorithmic implementations.

Advances in AI and computational biology have significantly improved current drug repurposing approaches, especially in oncology, as the complexity of biological information exceeds the processing capacity of conventional analysis models. AI approaches make it easier to derive relevant therapeutic information from datasets, including multi-omics data, compound libraries, clinical information, and published scientific literature [86,87]. Machine learning algorithms, for example, can predict drug efficacy and the dosage associated with toxicity using large datasets, such as random forests, to yield promising drug candidates [88].

These candidates could either be obtained from known chemical scaffolds or computationally designed to target specific biological pathways. Moreover, models based on neural networks could develop knowledge graphs to integrate the biological interactions of a compound, hence improving target selection and, in return, enabling better understanding of the underlying mechanism [89]. Recent applications of these computational tools include the prediction of SARS-CoV-2 protein structure, which helped accelerate the detection of pharmaceuticals and vaccine development during the COVID-19 crisis [90]. The following subsections discuss the main models used for AI-based cancer-targeted drug repurposing, as summarized in Table 2.

Machine learning approaches

Machine learning methods are based on predictive modeling

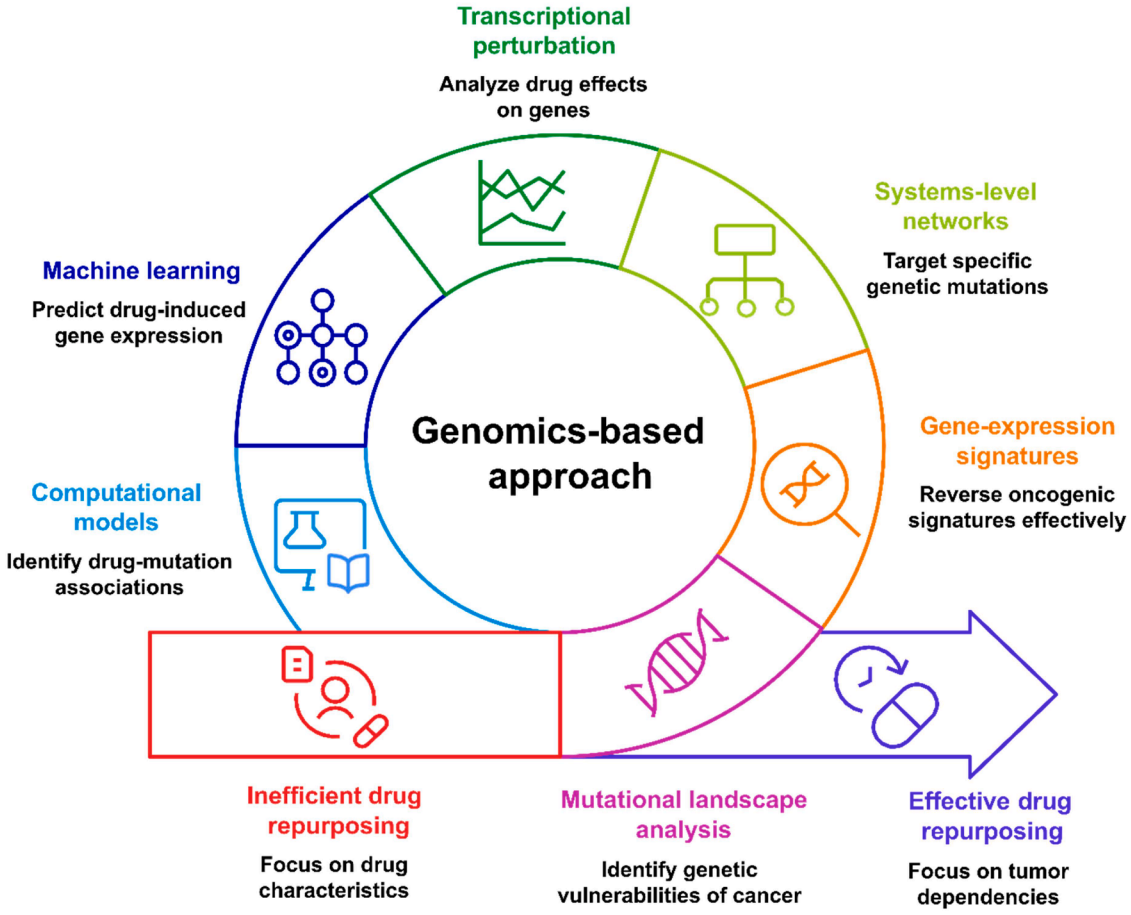

Fig. 5. Genomics-based approach to drug repurposing.

frameworks that use structured datasets (e.g., chemical descriptors, gene expression profiles, and pharmacological features) to predict drug–target interactions or therapeutic responses. In contrast to the previous approaches, however, these do not focus exclusively on specific algorithms but rather derive interpretable patterns from labeled data, facilitating hypothesis-driven repurposing. ML includes a wide variety of algorithms that enable computational systems to learn from data without explicit programming, allowing them to conduct independent analyses of large and complex datasets [111]. As illustrated in Fig. 6, ML methods are broadly categorized into supervised, unsupervised, and reinforcement learning. The choice of algorithm will depend on the nature of the research question and available data [112].

Traditional ML is a key part of computational drug repurposing in oncology applications, assisting in predicting drug-target interactions, predicting compound activity, and categorizing cancer subtypes. Supervised learning algorithms such as random forests, support vector machines, gradient boosting models, and logistic regression leverage labeled biochemical or pharmacological datasets to learn patterns that differentiate active from inactive compounds. This is most often carried out using chemical fingerprints, physicochemical properties, or high-content assay data to identify drugs with novel anticancer properties [113,114].

These unsupervised learning algorithms and techniques, such as clustering (k-means and hierarchical clustering) and dimensionality reduction (PCA, t-SNE, and UMAP), have contributed to the discovery of structure-activity relationships and the identification of hidden biological patterns across different tumor types [115,116]. Reinforcement learning is increasingly being integrated into repurposing workflows to optimize compound prioritization and guide iterative decision-making for experimental validation [117]. Together, these ML approaches provide robust, interpretable, and computationally efficient frameworks that enhance drug repurposing pipelines, particularly when working with structured and moderately sized datasets.

Deep learning approaches

Deep learning (DL) techniques generalize predictive modeling beyond traditional data to high-dimensional, unstructured input domains, enabling hierarchical extraction of large-scale feature representations in complex biological and chemical datasets. Among the inductive bias methods proposed in this framework, these methods also indirectly support representation learning by enabling models to discover latent relations not captured by traditional machine learning approaches. DL extends the capabilities of ML by leveraging neural network architectures that learn hierarchical, complex representations directly from raw data, making it an excellent tool for predicting clinical relevance from large, heterogeneous datasets, but often requires substantial computational power and large sample sizes to generalize effectively [118]. Convolutional neural networks (CNNs) are applied to chemical structure images, molecular graphs, and histopathology slides to predict anticancer activity or drug sensitivity [119]. Recurrent neural networks (RNNs) and transformers process sequential data, including SMILES strings, protein sequences, and gene expression time courses, to model drug behavior with high fidelity [120].

Graph neural networks (GNNs) have rapidly gained prominence due to their ability to encode molecular topology, protein–protein interactions, and multi-layered biological networks [121]. Autoencoders and variational autoencoders (VAEs) are employed for latent feature extraction and similarity-based repurposing [122], while generative adversarial networks (GANs) support de novo generation of structural

Table 2
Overview of AI approaches in oncology drug repurposing.

AI approach/ Model	Input data types	Application in oncology	Studying cancer type(s)	Advantages	Limitations	Key findings/ Output	Ref.
AI-guided nanocarrier optimization	Formulation and delivery models	Improving repurposed drug bioavailability	Multi-cancer	Optimizes delivery	Data scarcity	Enhances tumor targeting and EPR	[91]
Bayesian network inference	Clinical and genomic data	Probabilistic interaction mapping	Ovarian	Handles uncertainty	Prior bias	Defines mechanistic pathways	[92]
Convolutional neural network (CNN)	Chemical images and histopathology	Predicting anticancer potency	Colon and Gastric	Learn from structure	Needs large data	Identifies potent analogs	[93]
Deep neural network (DNN)	Multi-omics (RNA-seq and proteomics)	Drug-disease mapping	Breast and Ovarian	Captures nonlinear patterns	Black-box interpretability	Reveals new drug-cancer links	[94]
Generative adversarial network (GAN)	Molecular libraries	De novo analog generation	Lung and Pancreatic	Generates novel analogs	Training instability	Improves potency/ toxicity ratio	[95]
Gradient boosting (XGBoost)	Pharmacogenomic data	Predicting clinical response	Glioblastoma	High performance	Overfitting risk	Enhance clinical prioritization	[96]
Graph neural network (GNN)	Drug-target networks	Multi-target prediction	Glioblastoma and Melanoma	Model's topological features	Computationally heavy	Identifies synergistic combinations	[97]
Knowledge graph embedding	Drug-gene-disease triples	Inferring hidden relations	Leukemia and Breast	Multi-relational	Sparse graph issue	Reveals novel drug links	[98]
Multi-omics integration ML	Genomic and proteomic	Target discovery	Pan-cancer	Systems-level insight	Integration complexity	Identifies multi-pathway targets	[99]
Natural language processing (NLP)	PubMed, patents, and trials	Extracting repurposing clues	Multi-cancer	Text mining scalability	Context loss	Automates discovery from literature	[100]
Network diffusion/ Graph propagation	PPI and metabolomic data	Pathway-target repurposing	Gastric and Glioma	Maps disease modules	Data integration challenge	Identifies polypharmacology	[101]
Random forest (RF)	Chemical fingerprints, toxicity, and efficacy data	Predicting drug-target activity and toxicity	Breast and Lung	High interpretability, and robust	Limited with sparse data	Identifies promising drug candidates via feature ranking	[102]
Recurrent neural network (RNN)	SMILES strings and gene time-series	Predicting compound interactions	Pancreatic and Liver	Sequence modeling	Vanishing gradient	Identifies novel interactions	[103]
Reinforcement learning (RL)	Drug response simulations	Optimizing repurposing actions	Personalized oncology	Learns adaptively	Reward signal dependency	Prioritizes synergistic drug sets	[104]
Signature matching (CMap)	Gene expression	Reversing disease signatures	Breast and Colon	Hypothesis-free	Needs validated profiles	Identifies anti-cancer reversers	[105]
Support Vector Machine (SVM)	Protein descriptors and gene expression	Drug-target prediction, and subtype classification	Prostate, and Leukemia	Good with small datasets	Kernel selection critical	Effective in target-based repurposing	[106]
Toxicogenomic AI models	FAERS and CTD datasets	Detecting toxic-to-therapeutic links	Breast and Colon	Leverages safety data	Causal ambiguity	Finds cytotoxic repurposables	[107]
Toxicity prediction neural net	PK/PD and ADMET profiles	Safety-based repurposing	Glioblastoma	Reduces attrition	Generalizability limits	Predicts dose-response relationships	[108]
Transformer (BERT/GPT-like)	Literature and EHRs	Evidence mining for repurposing	Multi-cancer	Automated pattern recognition	Requires fine-tuning	Extracts drug-gene-disease relations	[109]
Variational autoencoder (VAE)	Molecular graphs	Latent space similarity search	Breast and Ovarian	Extracts deep features	Risk of mode collapse	Identifies structurally similar drugs	[110]

analogs to improve potency or reduce toxicity [123].

In contrast to conventional machine learning, where the interpretability of classifiers is not an issue, the added predictive power of deep learning models has often been undermined by a loss of interpretability and high computational cost, which are critical factors for clinical adoption and regulatory approval.

Signature-based approaches

Signature-based repurposing relies on the idea that drugs can be identified by their ability to reverse or mimic disease-associated molecular signatures. This approach utilizes transcriptomic, proteomic, or epigenomic profiles of tumors and compares them to drug-induced perturbation signatures [124]. Databases such as the Connectivity Map (CMap) [125] and LINCS L1000 provide millions of gene-expression signatures across cell types, treatments, and doses, making them powerful resources for AI-driven matching [126].

Network-based approaches

Network approaches, as a systems-level paradigm of AI-driven drug repurposing, focus on modeling cooperative biological interactions rather than non-interactive entities. These methods are consistent with system biology concepts for disease modules and multi-target intervention strategies. Network approaches conceptualize biological systems as interconnected graphs of genes, proteins, metabolites, and pathways. AI-enhanced network pharmacology integrates graph theory, GNNs, and systems biology to predict how drugs modulate disease-associated modules within the interactome. Protein–protein interaction networks, drug–disease associations, drug–target associations, regulatory networks, metabolic pathways, and multi-omics networks can be layered to model complex oncogenic processes such as metastasis, immune evasion, or therapy resistance. Network algorithms identify repositioning opportunities through proximity analysis, shortest-path scoring, community detection, and network diffusion metrics. These models stand out for elucidating polypharmacology by revealing multi-target drug effects and synergistic combinations that

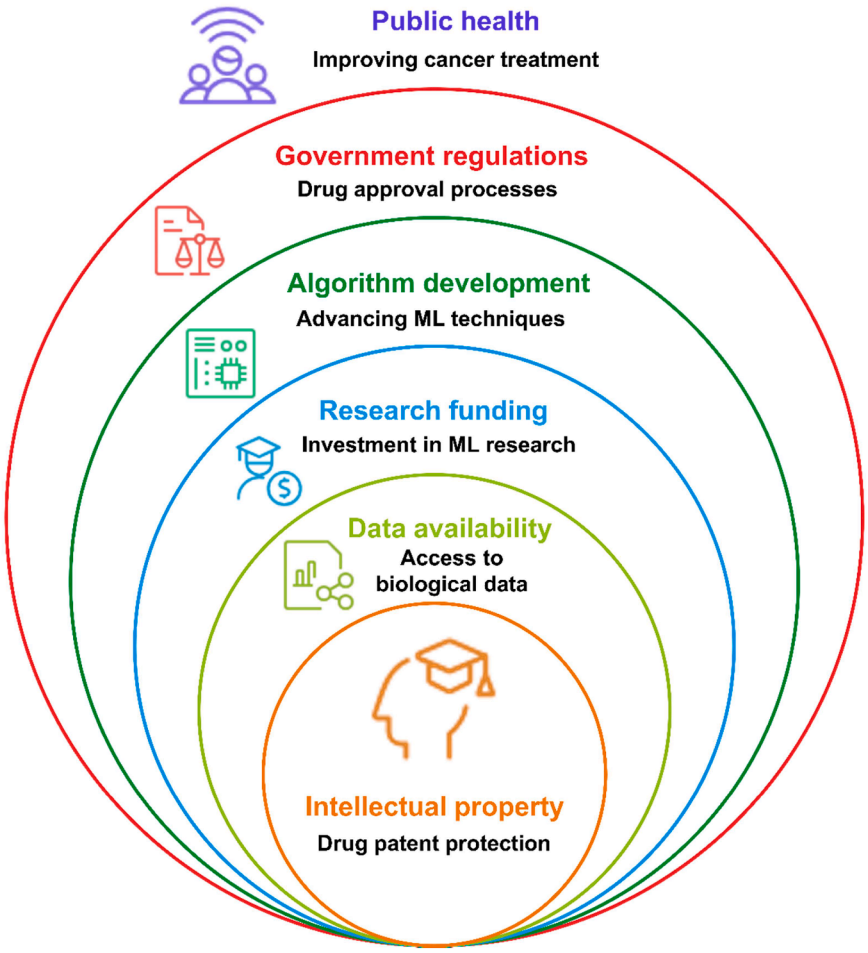

Fig. 6. Machine learning approaches in drug repurposing.

may outperform single-agent strategies [127–129].

Natural-language and evidence mining approaches

A separate category of AI-driven drug repurposing uses evidence-mining and language-based strategies to extract relevant, actionable knowledge from unstructured biomedical data sources, such as literature, clinical trial databases, and electronic health records. Large language models (LLMs) and natural language processing (NLP) techniques enable automated extraction of repurposing clues from scientific literature, clinical trial databases, patents, and electronic health records. NLP pipelines identify patterns in how drugs are discussed, infer mechanistic relationships, and detect emerging evidence linking compounds to cancer phenotypes. Techniques such as named-entity recognition, relation extraction, sentiment scoring, and transformer-based contextual modeling (e.g., BERT, GPT) help identify drug-gene interactions, adverse effects, and off-label usage trends. More advanced LLMs can synthesize diverse evidence, adjudicate mechanistic plausibility, and suggest repurposing ideas based on the available dataset. Such methods are very relevant to the field of oncology because of the rapidly increasing, highly fragmented nature of the literature on cancer research [130–132].

Case studies of AI-driven drug repurposing in oncology

There are quite a few drugs that were developed initially for conditions other than oncologic diseases and have demonstrated the potential for clinically significant anticancer activity. The following examples illustrate the successful repurposing of drugs and show that approaches that use data and simulations could improve the development process, reduce costs, and enhance translational aspects of oncologic drugs.

Successful applications of AI-driven drug repurposing in oncology

Metformin

Metformin is one of the most well-described instances of AI-guided drug repurposing in cancer. Systems-level deep learning models such as DSPathNet using multi-omics data, including gene expression profiles and pathway-level information, have supported its repositioning. Leveraging this framework, AI models recognized metformin as a modulator of oncogenic signaling pathways, notably the Wnt/β-catenin axis, based on its predicted capacity to revert tumor-associated transcriptional signatures. These predictions were based on network-based representations of disease pathways and drug-induced perturbation profiles. They uncovered metformin's ability to disrupt energy metabolism and signaling cascades important for tumor growth. Crucially, AI-guided prioritization recognized metformin not only as a putative antidiabetic agent but also as a systems-level metabolic modulator with anticancer activity acrossultiple tumor types [133].

Statins

Based on AI-based network pharmacology and systems biology approaches, the anticancer mechanisms of statins have been further elucidated. Machine-learning models identified statins as modulators of oncogenic pathways, including those involving histone deacetylases and tumor suppressor genes such as TP53 by integrating protein–protein interaction networks with transcriptomic datasets and drug-target databases. Inference methods based on the network indicated that statins

are strongly positioned within disease-associated modules, implying their multi-target effects. Such predictions were corroborated by machine learning models applied to clinical and pharmacovigilance data, which suggested possible associations between statin use and lower cancer incidence or progression. Thus, AI facilitated the redefinition of statins as drugs relevant for polypharmacology and oncology [134].

Disulfiram

Network-based AI models, including balanced substructure–drug–target network-based inference (b-SDTNBI), revealed disulfiram as a repurposable anticancer agent. Inferred from chemical substructure data, known drug-target interactions, and disease-associated protein networks, this approach predicts novel therapeutic associations. Using this framework to identify target interactions, disulfiram was predicted to bind cancer-relevant molecular targets in proteasome-inhibition and oxidative-stress pathways. The model used graph-based learning to predict indirect links between disulfiram and oncogenic pathways, which were subsequently experimentally confirmed in breast and other relevant cancers. This method is an example of AI identifying non-obvious drug–target relationships that were not already known to pharmacological science [96].

Propranolol

AI-assessed drug–target interaction analyses, integrating pharmacological databases and signaling pathway models, identified propranolol as a promising anticancer agent. These strategies predicted that β-adrenergic signaling is involved in tumor progression and angiogenesis. After mapping what we knew about the targets of propranolol to known cancer-related pathways, AI models indicated potential effects on VEGF signaling and interactions within the tumor microenvironment. Follow-up experimental studies validated these predictions, showing decreased proliferation, angiogenesis, and metastatic potential in melanoma models [135,136].

Conventional usage of metformin, an antidiabetic drug, has emerged as a promising therapeutic approach for breast, pancreatic, and prostate cancers by targeting and reducing Wnt pathway activation, as shown in Fig. 7, by various mechanisms. The idea of repurposing emerged using DSPathNet, a deep learning tool, for the combined analysis of different -omics data, such as gene expression and pathway-level data [137]. Similarly, the potential of statins in cancer prevention has emerged from network-level analysis [138]. Lovastatin, a Lipstatin derivative, has been shown to possess therapeutic potential in gastric cancer by inhibiting histone deacetylase 2 (HDAC2), which is often overexpressed in gastric cancer cells [139,140]. Simvastatin has also emerged as a promising candidate across multiple cancer types due to its ability to activate the tumor suppressor gene TP53 [141], with ongoing clinical trials exploring its utility in breast, gastrointestinal, and urinary tract malignancies [15].

Another example is b-SDTNBI (Balanced Substructure–Drug–Target Network-Based Inference). This network-driven algorithm identified disulfiram, which is initially approved for treating alcohol dependence, as a drug with significant antitumor activity in breast cancer [142]. Beyond its established pharmacological use, disulfiram has demonstrated therapeutic potential in several additional cancers, including colon, prostate [143], thyroid malignancies [144], and glioblastoma [145].

In addition, Mebendazole, an antiparasitic agent that disrupts helminth infections by inhibiting tubulin polymerization in microtubules, has also demonstrated activity relevant to cancer therapy, as this exact mechanism can impede cancer cell proliferation [146]. Propranolol, a β-adrenergic blocker traditionally used to treat hypertension, was identified as a potential melanoma therapy through AI-based analyses of drug–target interaction networks [145]. Further studies later showed that propranolol inhibits melanoma by reducing cell proliferation and migration, decreasing VEGF secretion, and inducing apoptosis and G1-phase cell arrest [147].

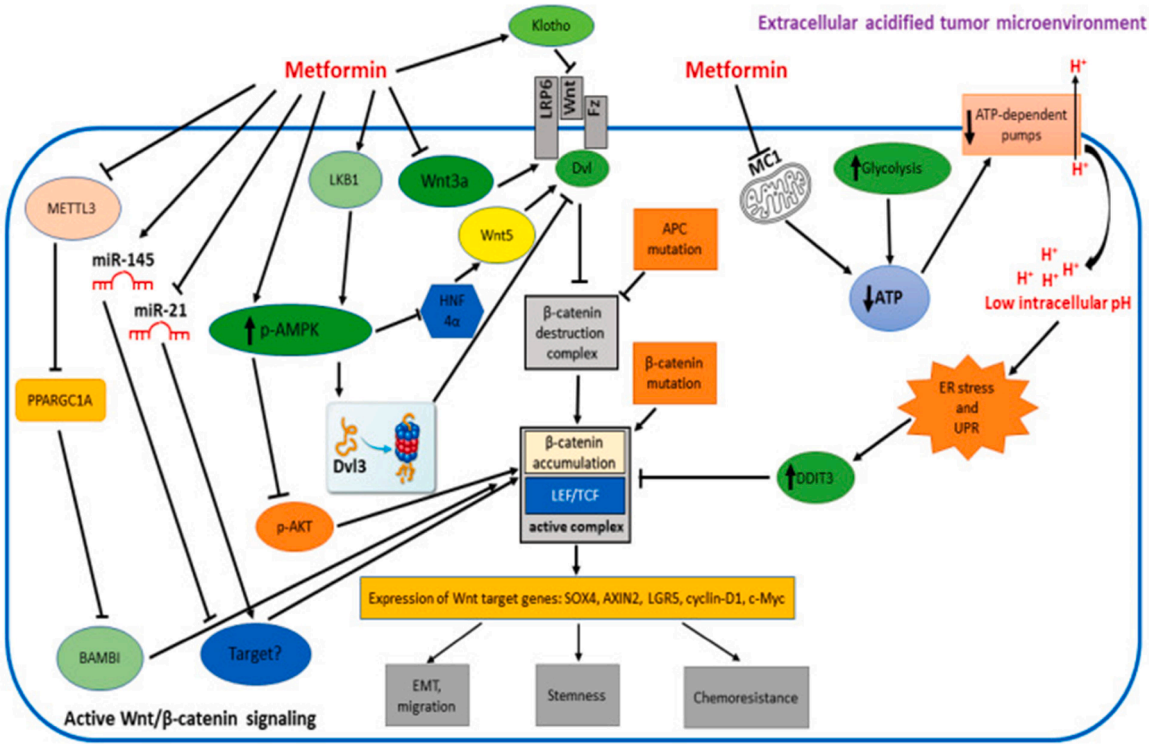

Fig. 7. Metformin inhibits Wnt/β-catenin signaling through several mechanisms. It reduces ATP production, impairs H^+ pump activity, and induces ER stress, thereby disrupting β-catenin–LEF/TCF transcriptional activity. Metformin also upregulates Klotho, blocks Wnt3a, and activates AMPK to suppress AKT-mediated β-catenin stabilization and promote Dvl3 degradation. Additionally, it reduces METTL3-dependent m^6A modification of PPARGC1A and modulates miR-145/miR-121 to inhibit β-catenin further. This figure was retrieved from [137]. Copyright Cells, 2023, 12(17), 2182.

Additionally, molecular docking analysis suggests potential for using proton pump inhibitors in cancer treatment. For example, pantoprazole and lansoprazole have been shown to inhibit the growth of colorectal cancer cells via a kinase-inhibitory mechanism [148,149]. Given the established connection between inflammation and cancer, anti-inflammatory drugs are also promising candidates. Celecoxib, which selectively inhibits cyclooxygenase-2 enzymes, decreases inflammation via prostaglandins and has demonstrated effectiveness in clinical trials for breast, colon, head and neck, and prostate cancers [150].

Clinical trials of repurposed anticancer agents

Clinical trials continue to constitute the gold standard for evaluating their efficacy and safety in oncology. Although preclinical models and computational-based predictions identify anticancer activity, the therapeutic benefit, optimal dosing, and safety of any regimen must be confirmed in human clinical investigations. In this context, Table 3 provides an overview of representative clinical trials utilizing repurposed agents, including details on study design, type of malignancy, and ongoing clinical status, which is cross-referenced with key examples outlined below. Clinical trials remain the cornerstone for assessing the efficacy and safety of repurposed drugs in oncology. While preclinical studies and computational predictions help highlight potential anticancer activity, clinical investigation is required to confirm therapeutic benefit, optimal dosing, and safety in patient populations. In the context of drug repurposing, clinical trials offer the opportunity to validate hypotheses generated through artificial intelligence–driven approaches, thereby translating *in vivo* and preclinical findings into evidence-based clinical practice [151]. Therefore, the following section summarizes recent clinical trials investigating repurposed drugs for oncology, presented in Table 3.

[152] is a Phase 0 clinical trial (CT) evaluating the feasibility of repurposing pitavastatin, a lipid-lowering agent, for glioblastoma therapy through AI-supported pharmacokinetic and pharmacodynamic modeling. The trial aims to determine whether preoperative oral pitavastatin administration can achieve therapeutically significant intratumoral concentrations in patients with newly diagnosed or recurrent glioblastoma. Specifically, it investigates whether pitavastatin reaches cytotoxic concentrations within gadolinium-enhanced tumor regions and whether it attains levels in the non-enhancing infiltrative margins that could act synergistically with temozolomide, the current standard-of-care chemotherapeutic agent. By combining drug-level measurements with computational predictions of statin–glioma interactions, this study exemplifies how AI-guided repurposing strategies are being translated into early clinical testing for aggressive brain

Table 3
Selected clinical trials of repurposed drugs in oncology. Data were obtained from ClinicalTrials.gov (terminated trials are excluded).

Trial code	Conditions	Repurposed drug(s)	Phase	Type	Status	Ref./ URL
NCT03628079	Gastrointestinal cancer or cancer of unknown origin. (RepoMeb)	Mebendazole	Phase I and Phase II	Interventional	Terminated	https://www.clinicaltrials.gov/study/NCT03628079?utm=
NCT03925662	Colorectal cancer (adjuvant)	Mebendazole	Phase III	Interventional	Recruiting	https://clinicaltrials.gov/study/NCT03925662?utm=
NCT00897884	Breast cancer (presurgical)	Metformin	Phase II	Interventional	Completed	[160]
NCT00930579	Breast cancer (presurgical)	Metformin	Phase II	Interventional	Completed	[160]
NCT01101438	Breast cancer	Metformin	Phase III	Interventional	Completed	https://clinicaltrials.gov/study/NCT01101438?utm
NCT01243385	Locally advanced or metastatic prostate cancer	Metformin	Phase II	Interventional	Completed	https://clinicaltrials.gov/study/NCT01243385?utm=
NCT01266486	Breast cancer metabolism	Metformin	Phase II	Interventional	Completed	https://clinicaltrials.gov/study/NCT01266486?utm=
NCT01981525	Li-Fraumeni syndrome	Metformin	Phase I	Interventional	Completed	https://www.clinicaltrials.gov/study/NCT01981525?utm=
NCT02028221	Obesity-associated breast cancer prevention	Metformin	Phase II	Interventional	Completed	https://www.clinicaltrials.gov/study/NCT02028221?utm=
NCT03359681	Colon cancer (MECORA)	Metformin	Phase II	Interventional	Completed	https://www.clinicaltrials.gov/study/NCT03359681?utm=
NCT01266486	Breast cancer	Metformin	Phase II	Interventional	Completed	[161]
NCT01911247	Endometrial cancer (Proliferation biomarkers)	Metformin	Phase 0	Interventional	Completed	[161]
NCT02042495	Endometrial cancer (K_i-67 and pS6 endpoint)	Metformin	Phase II	Interventional	Recruiting	[161]
NCT01877564	Endometrial cancer (Pathologic response rate)	Metformin	Phase II	Interventional	Recruiting	[161]
NCT01205672	Endometrial cancer (Presurgical effects)	Metformin	NA	NA	Active	[161]
NCT02083692	Head and neck/ squamous cell (Tissue marker changes)	Metformin	Phase 0	Interventional	Recruiting	[161]
NCT01997775	Lung cancer (IL-6 and PFS outcomes)	Metformin + Chemo/Targeted	Phase II	Interventional	Recruiting	[161]
NCT01433913	Prostate cancer (Neoadjuvant safety and markers)	Metformin	Phase II	Interventional	Active	[161]
NCT01849276	AML (MTD and response rate)	Metformin + Cytarabine	Phase I	Interventional	Recruiting	[161]
NCT01929811	Breast cancer (Clinical response)	Metformin + Docetaxel/ Epirubicin/ Cyclophosphamide	Phase II RCT	Interventional	Recruiting	[161]
NCT01589367	Breast cancer (Response rate)	Metformin + Letrozole	Phase II RCT	Interventional	Recruiting	[161]
NCT01042379	Breast cancer (Chemo + Biologic combination)	Metformin + Ganitumab	Phase II RCT	Interventional	Recruiting	[161]
NCT02949700	Head and neck/ squamous cell	Metformin + Chemo/Radiation	Phase I and Phase II	Interventional	Completed	https://www.clinicaltrials.gov/study/NCT02949700?utm=
NCT04682158	Esophageal adenocarcinoma	Propranolol with standard chemoradiation	Phase II	Interventional	Recruiting	https://www.clinicaltrials.gov/study/NCT04682158?utm=
NCT03108300	Metastatic STS	Propranolol hydrochloride + Doxorubicin	Phase II	Interventional	Unknown	https://clinicaltrials.gov/study/NCT03108300?utm=

tumors.

Based on the principle of the concurrent inhibition of multiple tumor-sustaining pathways, the study [153] focuses on the CUSP9v3 protocol, a novel multi-drug repurposing strategy for recurrent glioblastoma. This Phase I trial integrates these nine repurposed therapies (aprepitant, auranofin, captopril, celecoxib, disulfiram, itraconazole, minocycline, ritonavir, and sertraline) into a combination regimen based on metronomic temozolomide, informed by computational insights that identified complementary mechanisms of action sufficient to destabilize cancer cell survival mechanisms. This trial recruits subjects with glioblastoma who have relapsed following standard chemoradiation therapy. Notably, the trial seeks to evaluate the safety, tolerability, and feasibility of the combination therapy. This clinical trial seeks to evaluate the potential feasibility of multiple oncogenic pathway suppression without excessive toxicity treatment to produce an innovative treatment approach against one of the most treatment-refractory types of cancer.

The REPAIR-MDS trial [154] is another example of the power of repurposing in hematological malignancies, focusing on low-risk Myelodysplastic Syndromes (MDS), a condition that currently affects over 7000 individuals in the UK and often leads to acute myeloid leukemia (AML). This multicenter, open-label Phase II study compares the combination regimen VBaP (comprising sodium valproate, bezafibrate, and medroxyprogesterone) with danazol in patients who have failed or are unlikely to respond to erythropoiesis-stimulating agents (ESAs). The trial is designed to enhance the production of healthy, functional blood and immune cells, aiming not only to reduce infections but also to strengthen immune-mediated control of the MDS clone.

The IMPACT trial is a Phase 0, randomized, window-of-opportunity study exploring the repurposing of existing drugs in women with advanced high-grade serous ovarian cancer (HGSOC, stages IIIa–IV). Patients undergo short-term preoperative therapy with various investigational medications such as metformin, acetylsalicylic acid, olaparib, or letrozole prior to the surgery through diagnostic laparoscopy. Participants are recruited based on the standard care diagnostic evaluation and are assayed unblinded. The proposed study aims to determine how tumor tissue harvested during surgery responds to these repurposed and targeted medications across various molecular pathways that mediate tumor development and progression [155].

A Phase II clinical trial aimed to investigate the repurposing of Atorvastatin and Celecoxib for patients with early-stage, hormone-sensitive prostate cancer with rising prostate-specific antigen levels (PSA) after local therapy. It was based on preclinical data supporting the hypothesis that Atorvastatin and Celecoxib have antitumor activity, mediated by the inhibition of enzymes crucial for cell proliferation, and that their co-administration might synergistically augment antitumor activity. Across multiple centers, patients were treated with Oral Atorvastatin once daily and Celecoxib twice daily for up to six cycles, each cycle lasting 28 days, with correlative blood samples analyzed for NF-kB, ERK, PGE2, and IL-6 levels in peripheral blood mononuclear cells. The primary aim was to monitor biological activity, assessed by the PSA response, defined as a $\geq$ 25% reduction in the slope of log (PSA) over time. The whole trial aimed to determine the activity, reflected by the PSA response, and the toxicities and feasibility of co-administration with these drugs [156].

The trial NCT01101438 is a Phase III trial assessing the possible repurposing use of metformin, a commonly employed antidiabetic drug, in early-stage breast cancer. The trial is a multicenter, randomized trial assessing the ability of metformin to prevent the growth and recurrence of breast cancer either as monotherapy or in combination with other therapies. The trial will randomize patients according to hormone receptor status, HER2 status, body mass index, and chemotherapy status, with patients receiving either metformin or placebo by oral administration for a period not to exceed 5 years, andith repeated blood and tissue samples for correlative studies [157].

A pilot trial [158] explores repurposing metformin for patients with head and neck cancer, specifically its effects on cytokine and exosome levels related to disease progression and treatment-related toxicity. Patients take metformin hydrochloride alongside external beam radiation therapy, and the main goals include evaluating its impact on inflammatory cytokines and reducing common side effects of radiation therapy, such as mucositis, dysphagia, xerostomia, and fatigue. Secondary outcomes include evaluations of safety and tolerability, and patient-reported symptom changes, using validated questionnaires such as the Xerostomia Questionnaire, the WHO mucositis classification, the MD Anderson Dysphagia Inventory, and the Multidimensional Fatigue Inventory.

The second pilot clinical trial involves the repositioning of ascorbic acid as an adjunct to a combination chemotherapeutic regimen. This investigation assesses the safety and tolerability of ascorbic acid infusion concurrent with FOLFIRINOX, a combination of fluorouracil, irinotecan, leucovorin, and oxaliplatin, in patients at risk of metastatic, recurrent, or unresectable disease. This trial will also evaluate the potential to collect patient-reported outcomes [153].

The purpose of the current prospective Phase II clinical trial is to understand better the dose-response relationship as well as the safety profile of topical timolol for the treatment of infantile hemangiomas. Current evidence suggests that topical timolol is effective for small, thin hemangiomas, although its efficacy is limited in thicker or deeper lesions, for which oral beta-blockers remain the preferred therapy. Notably, topical timolol results in measurable systemic exposure similar to that seen with oral agents; however, retrospective and meta-analyses report very few adverse events among infants treated with 1–2 drops of 0.5% timolol solution daily, the dose range for which safety data are available. Because children may be particularly vulnerable to beta-blocker–related adverse effects when physiologic stress responses are required, clinicians should consider temporarily discontinuing both topical and oral beta-blockers in the setting of severe infection, bronchospasm, or reduced feeding. The results of [159] will help clarify the optimal and safest dosing strategies for topical timolol in clinical practice.

Prominent examples of the unique and combined use of AI-driven hypotheses moving toward clinical verification include metformin (NCT01101438) Phase III trials and propranolol-based combinations, indicating the translational potential of repurposing strategies.

Formulation and delivery considerations in translating repurposed agents

While AI has accelerated the identification of repurposed oncologic candidates, successful clinical translation depends equally on whether these molecules can be delivered safely, effectively, and at therapeutically relevant concentrations [10,162]. Many repurposed agents initially belonged to compound categories not related to oncology and thus were not optimized for cancer treatment in terms of their pharmacokinetic or biodistribution properties [163]. However, overcoming these challenges requires integrating formulation sciences and modeling capabilities to improve the therapeutic index and reduce systemic toxicities [164].

Specifically, nanotechnology-based delivery systems also pose a particular importance under these circumstances. Liposomes, polymer nanoparticles, dendrimers, micelles, and exosomes can be used to encapsulate the repurposed drug, thereby enhancing solubility, minimizing degradation risk, and ensuring controlled release [165,166]. Moreover, nanocarriers can exploit unique tumor characteristics, such as enhanced permeability and retention (EPR), acidic pH, and overexpressed receptors, to increase intratumoral retention [167]. For repurposed small molecules that face dose-limiting toxicities, nanoformulations can reduce off-target exposure and modulate pharmacokinetics to achieve more favorable safety profiles [168].

AI-driven formulation design is an emerging area that further strengthens this intersection [169,170]. Applications of machine

learning models have been reported for predicting excipient compatibility, interactions between polymers and drugs, nanoparticle stability, and release kinetics, enabling quick evaluation of various design parameters without a trial-and-error process [171]. Deep learning models will also help select carrier materials or surface ligands to achieve maximum cancer selectivity [172]. Once large data sets for various formulations are available, AI may also optimize drug, nano-carrier, and dose regimen within a single predictive pipeline[173].

For Biologics, repurposed therapeutic proteins, and RNA medicines, improved delivery methods, such as lipid nanoparticles, viral vectors, and engineered extracellular vesicles, can help circumvent issues of immunogenicity, degradation, and cell entry [174]. At the same time, AI-assisted characterization of tumor microenvironmental heterogeneity can inform the design of patient-specific routes for tumor cell-selective delivery based on receptor expression, vascular structure, or stromal density [175].

The science of formulation bridges the gap between computer-aided drug discovery and clinical effectiveness. There appears to be immense potential for a combination of prediction through AI technology and next-generation drug delivery systems that could bring promising "repurposed hits" into a more practical therapeutic modality, especially within malignancies that demand a targeted, sustained, or combination strategy [176].

Challenges and emerging directions

Although major breakthroughs have been made through AI-assisted drug repurposing, many scientific, technical, and translation hurdles still hinder the smooth incorporation of model predictions into practice [177]. One major problem is that biomedical data sources are fragmented and heterogeneous, especially for uncommon types and drugs. Owing to the lack of comprehensive biomedical data, models have been designed using disconnected multi-omics data sources, missing annotations, or proofs based on cell line data, which may not capture the complexity of biological tumors [178]. The presence of data noise, effects, and variability in the preprocessing methods hampers the accuracy of the models [179]. Additionally, the limited availability of negative data makes it difficult for algorithms to learn robust decision boundaries [180].

These challenges, however, are small compared to the very substantial limits of current fieldwork methods and to recent advances in artificial intelligence that enable us to meaningfully address many of them. Multimodal learning frameworks and foundation models are being developed to incorporate heterogeneous modalities of datasets, ranging from genomics, transcriptomics, and imaging to clinical records, into holistic predictive architectures. These models enable cross-modal representation learning, mitigating information fragmentation and boosting generalizability across heterogeneous patient populationand tumor types [136].

The major limitation of most current AI models is their black-box nature, which complicates biological interpretation that could win regulatory acceptance. Some partial ways out include approaches that rely on SHAP values, feature attribution, and attention mechanisms. These do not fill the gap between computational insight and accurate mechanistic understanding [181,182]. Moreover, there is little effort invested in the biological or clinical validation of models, resulting in a persistent gap between computational lead and translational potential. The absence of coordinated or normalized datasets and metrics for assessment also makes progress difficult [183].

Explainable AI (XAI) techniques and causal inference frameworks are increasingly used to address the fundamental limitations (black-box behavior) that many AI models encounter. Techniques such as SHAP-based attribution, attention mechanisms, and graph explainability tools enable associating predictions with features of biological relevance, thereby enabling interpretability to meet regulatory standards. Meanwhile, causal AI approaches go beyond prediction based on correlation, framing mechanistic relationships going beyond correlation, which is especially important in oncology, where treatment decisions need to be grounded mechanistically [184].

Even if promising candidates for repurposing are identified, the regulatory processes are not well-suited to AI use in repurposing, especially when involving off-target or combination therapies. The limitations of intellectual property, the lack of commercial gain, and the varying regulatory processes worldwide make repurposing difficult [185]. Additionally, multidisciplinary collaboration among computational scientists, oncologists, and pharmacologists, as well as with industry partners, is not consistent [186].

Solving data quality and accessibility issues will require mechanisms such as federated learning and privacy-preserving AI frameworks. These methods allow multiple institutions to collaboratively train models without sharing data centrally, thereby protecting patient privacy while expanding the diversity of the training set. These studies will further benefit from standardization efforts, such as harmonized data formats and ontology-driven integration, which provide greater interoperability and reproducibility [187].

Many repurposed candidates, especially those with non-oncology indications, exhibit optimal solubility, stability, and pharmacokinetic properties, hindering their application in cancer [15]. Despite the emerging development of AI-based formulations, a scalable approach to integrate pharmacology, address limitations in ADME, or ensure nano-carrier compatibility has yet to be established for repurposing solutions [10].

Bridging traditional computational predictions with clinical validation could partly be facilitated by AI-assisted experimental design and digital twin technologies. As such, this minimizes costs while maximizing success by using virtual patient models and trial simulation platforms to test repurposed drug candidates *in silico* across a multitude of clinical scenarios, optimizing for their respective trial designs. Moreover, reinforcement learning frameworks can inform adaptive trial approaches by leveraging feedback from patient responses and biomarker data to drive the experimentalrocess over time [188].

The vision for future AI models is expected to incorporate multi-omics profiles, spatial transcriptomics, electronic health records, imaging, and real-world evidence into holistic repurposing models. This could potentially enable dynamic and individualized predictions and help move repurposing towards precision oncology [189]. In addition, large-scale models of biological foundations trained on protein structures, omics, and chemical libraries are anticipated to revolutionize this field, enabling zero-shot prediction of drug-target interactions, rapid generation of molecular analogues, and repurposing recommendations [190].

Furthermore, integrating repurposing with nanomedicine design frameworks represents a promising direction. AI tools capable of predicting the compatibility, release rate, and accumulation rate in cancer cells will also make repurposing more viable [191]. Current movements pushing open datasets, transparent benchmarks, and a collaborative approach will be crucial to the accelerated development of AI repurposed for a larger population [192]. The challenges and solutions in AI-guided drug repurposing in oncology were summarized in Table 4.

However, the future will see an even more revolutionary and transformative era of drug repurposing in oncology, propelled by a nuanced integration of foundation AI models, systems biology paradigms, and real-world data. In this context, continuously learning algorithms that can incorporate ever-changing biomedical knowledge will open a new path to update experimental hypotheses in real time systematically. These adaptive frameworks may be launched to enable fully personalized, dynamically optimized cancer treatment strategies in combination with breakthroughs in nanomedicine and precision delivery systems [193].

Table 4
Challenges and solutions in AI-guided drug repurposing.

Challenge	Description	AI/Tech-based solution	Example tools/ Approaches	Emerging solutions/ Future directions	Ref.
Adverse effect predictions	Hard to foresee side effects in repurposed contexts	Adverse event risk models	EHR data models	Generative adversarial effect predictors	[194]
Bias and representation issues	Biases in training data affect generalizability	Bias detection and correction pipelines	Reweighting and adversarial training	Diversity-aware algorithms	[195]
Biological mechanism integration	AI predictions often miss underlying mechanistic biology	Integrative multi-omics modeling	Graph representation learning	Causal inference and mechanistic models	[194]
Clinical relevance gap	Computational hits often fail clinical validation	Clinical outcome prediction models	Real-world data integration	Hybrid AI and clinical trial simulators	[196]
Computational cost	Deep models require huge resources	Model compression and pruning	Knowledge distillation	Efficient neural architecture search	[196]
Data quality and standardization	Heterogeneous biomedical and clinical datasets vary in format, completeness, and noise	Preprocessing pipelines with normalization, robust missing-data imputation, and harmonization	Standardization frameworks and deep learning with uncertainty quantification	AI-assisted metadata alignment and federated learning to preserve privacy	[44]
Drug combination modeling	Predicting synergistic effects is complex	Multi-agent and combinatorial AI	Reinforcement learning	High-throughput combination prediction	[197]
EHR integration challenges	EHR data are heterogeneous and inconsistent	Standardized EHR embeddings	FHIR-compliant ML tools	NLP for unstructured clinical notes	[194]
Ethical and equity issues	AI may amplify health inequities	Fairness-aware AI	Equity constraints in training	Ethical AI governance	[195]
Integration of physics/ chemistry constraints	Pure data models ignore biophysics	Physics-informed AI	QSAR and mechanistic modeling	Hybrid physics/ML models	[74]
Integration of real-world data (RWD)	RWD sources are messy and incomplete	Robust RWD ingestion models	EHR and claims data integration	AI for propensity score matching	[198]
Interpretability (Black Box)	Deep models often lack transparency for biological insights and regulatory trust.	Explainable AI (XAI) and attention mechanisms	SHAP and LIME integrated with drug-target prediction	Causal AI and interpretable graph embeddings	[44]
Lack of interdisciplinary expertise	Teams lack both AI and biomedical expertise	Collaborative platforms	AI-bioinformatics workbenches	Cross-domain training curricula	[195]
Limited annotated clinical data	Sparse labeled outcomes hinder supervised learning models	Transfer learning, semi-supervised learning, and weak supervision	Pretrained biomedical LLMs and graph neural networks (GNNs)	Synthetic data generation (GANs) and simulated clinical trials	[44]
Multi-omics integration complexity	Integrating genomics, proteomics, and metabolomics is computationally intensive and noisy.	Multi-modal deep learning and knowledge graphs	GNNs with heterogeneous biomedical graphs	Cross-modal transformers for unified biological representation	[96]
Overfitting and generalization	Overfitting on small datasets	Regularization and cross-validation	Dropout and ensemble learning	Meta-learning approaches	[194]
Privacy concerns	Patient data is sensitive and protected	Federated learning	Privacy-preserving ML	Differential privacy in models	[195]
Public database bias	Popular drugs overrepresented	Debiasing and augmentation	Rebalancing training data	Synthetics underrepresented data	[194]
Regulatory uncertainty	Lack of AI-specific regulatory pathways for repurposing	Standards for AI validation and reporting	Regulatory sandboxes	AI-ready regulatory frameworks	[195]
Scalability issues	Large biomedical datasets slow training/inference	Distributed/cloud computing	GPU/TPU pipelines	AI-optimized accelerators	[196]
Semantic data linking	Linking biomedical ontologies is non-trivial	Semantic embeddings and ontologies	UMLS and MeSH integrated embeddings	Ontology-aware AI	[194]
Software/tool usability	Tools may be inaccessible to non-experts	User-friendly GUIs	Web portals: Drug Repurposing Hub	Low-code AI repurpose platforms	[199]
Sparse drug-target interactions	Incomplete known interactions limit the discovery scope	Knowledge graph completion and link prediction	Drug-disease GNNs	Transformer-based graph models	[200]
Time for clinical translation	Translational gap from *in silico* to clinic	Trial simulation models	Virtual patient cohorts	Digital twin models	[196]
Unknown disease subtypes	Disease heterogeneity confounds repurposing	Subtype stratification via clustering	Deep clustering ML	Single-cell and ML integration	[194]
Updating legacy models	Rapid AI advances make older models obsolete	Continuous learning frameworks	Online learning ML	Lifelong learning AI	[195]
Validation cost and time	Biological validation expensive	*In silico* prioritization	Predictive ranking of candidates	AI-driven wet lab guidance	[195]

Conclusion

Artificial intelligence represents an innovative and revolutionary modality for cancer drug repurposing, enabling the rapid translation of promising targets identified through *in silico* discovery into clinical practice. By integrating machine learning, deep learning, network analysis, signature matching, and natural language processing, AI can efficiently map complex biological relationships and identify a set of mechanistically relevant targets. However, significant challenges persist, including data quality limitations, model interpretability issues, regulatory uncertainty, and formulation barriers, that must be addressed to realize the promise of AI-guided repurposing fully. Emerging technologies set to reshape the next decade in this area include multimodal foundation models, real-world data integration, and AI-driven formulation design. In summary, the convergence of AI, systems Biology, and translational Oncology can provide one of the most potent avenues for advancing the therapeutic field or optimizing the distribution and application of these therapeutics.

CRediT authorship contribution statement

Marola Paula Fawzy: Writing – review & editing, Writing – original draft, Visualization. **Mohamed S. Nafie:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis. **Nadine Wafik Nabih:** Writing – review & editing, Writing – original draft. **Mohamed K. Diab:** Writing – review & editing, Visualization. **Asaad Babker:** Writing – review & editing. **Hatem Mohamed:** Writing – review & editing. **Hatem A.F.M. Hassan:** Writing – review & editing, Writing – original draft, Visualization. **Sherif Ashraf Fahmy:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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