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Bridging technology and medicine: artificial intelligence in targeted anticancer drug delivery

Danial Khorsandi,[a] Amin Farahani,[b] Atefeh Zarepour,[cd] Arezoo Khosravi,[ef] Siavash Iravani *[g] and Ali Zarrabi *[h]

The integration of artificial intelligence (AI) in targeted anticancer drug delivery represents a significant advancement in oncology, offering innovative solutions to enhance the precision and effectiveness of cancer treatments. This review explores the various AI methodologies that are transforming the landscape of targeted drug delivery systems. By leveraging machine learning algorithms, researchers can analyze extensive datasets, including genomic, proteomic, and clinical data, to identify patient-specific factors that influence therapeutic responses. Supervised learning techniques, such as support vector machines and random forests, enable the classification of cancer types and the prediction of treatment outcomes based on historical data. Deep learning approaches, particularly convolutional neural networks, facilitate improved tumor detection and characterization through advanced imaging analysis. Moreover, reinforcement learning optimizes treatment protocols by dynamically adjusting drug dosages and administration schedules based on real-time patient responses. The convergence of AI and targeted anticancer drug delivery holds the promise of advancing cancer therapy by providing tailored treatment strategies that enhance efficacy while minimizing side effects. By improving the understanding of tumor biology and patient variability, AI-driven methods can facilitate the transition from traditional treatment paradigms to more personalized and effective cancer care. This review discusses the challenges and limitations of implementing AI in targeted anticancer drug delivery, including data quality, interpretability of AI models, and the need for robust validation in clinical settings.

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1. Introduction

Cancer progression is a complex and multifaceted process that involves a series of biological changes that enable normal cells to transform into malignant tumors. Understanding these mechanisms is crucial for developing effective cancer therapies and interventions. According to the World Health Organization (WHO), cancer remains one of the leading causes of death globally, accounting for approximately 10 million deaths in 2020, with the most common types including lung, breast, colorectal, prostate, skin (non-melanoma), and stomach cancers. WHO forecasts indicate a continued rise in cancer burden, particularly in low- and middle-income countries, due to aging populations, lifestyle factors, and limited access to early diagnostics and treatments. This underscores the critical need for more efficient, personalized, and scalable treatment strategies, an area where artificial intelligence (AI) has shown immense promise in transforming traditional cancer care paradigms, especially in the domain of targeted drug delivery.[1–3] The progression of cancer can generally be categorized into several key stages and mechanisms, including genetic mutations, dysregulation of cell signaling pathways, evasion of apoptosis, angiogenesis, metastasis, and the tumor microenvironment (Fig. 1).[4,5] At the core of cancer progression are genetic mutations that alter the normal functions of cells. These mutations can occur in proto-oncogenes, tumor suppressor genes, and DNA repair genes (Fig. 1).[6] Proto-oncogenes are responsible for promoting cell growth and division; when mutated, they can become oncogenes, leading to uncontrolled proliferation.[6] Conversely, tumor suppressor genes, which normally inhibit cell division or promote apoptosis, can be inactivated through mutations, further contributing to tumor

[a]*Terasaki Institute for Biomedical Innovation, Woodland Hills, California 91367, USA*
[b]*Cellular and Molecular Endocrine Research Center, Research Institute for Endocrine Molecular Biology, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[c]*Department of Biology, Faculty of Arts and Sciences, Kocaeli University, 41001, İzmit, Kocaeli, Türkiye*
[d]*Department of Research Analytics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-600 077, India*
[e]*Department of Genetics and Bioengineering, Faculty of Engineering and Natural Sciences, Istanbul Okan University, Istanbul 34959, Türkiye*
[f]*Graduate School of Biotechnology and Bioengineering, Yuan Ze University, Taoyuan 320315, Taiwan*
[g]*Independent Researcher, W Nazar ST, Boostan Ave, Isfahan, Iran. E-mail: siavashira@gmail.com*
[h]*Department of Biomedical Engineering, Faculty of Engineering and Natural Sciences, Istinye University, Istanbul 34396, Türkiye. E-mail: alizarrabi@gmail.com*

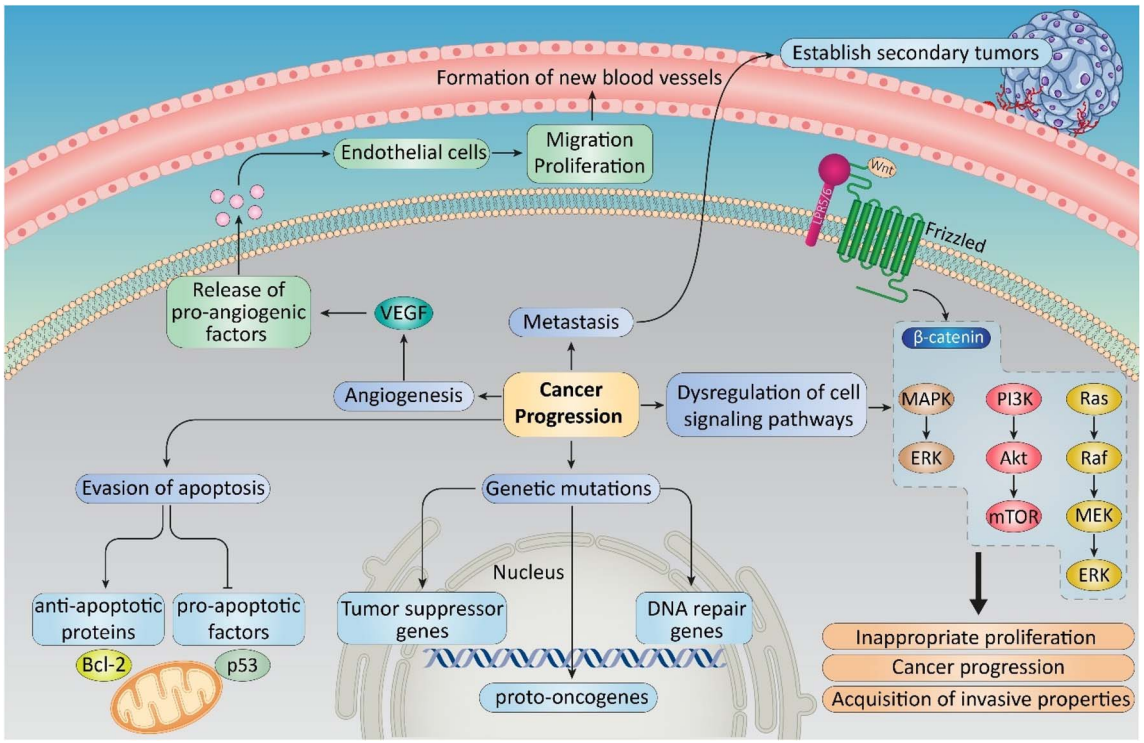

Fig. 1 Different mechanisms that could affect cancer progression.

development. Additionally, defects in DNA repair mechanisms can lead to the accumulation of further mutations, creating a vicious cycle that accelerates cancer progression. Dysregulation of cell signaling pathways is another critical mechanism in cancer progression. Cancer cells often exploit key signaling pathways, such as the phosphoinositide 3 kinase/protein kinase B/mammalian (or mechanistic) target of rapamycin (PI3K/Akt/mTOR) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathways, to promote survival, growth, and migration (Fig. 1). These pathways can become constitutively active due to mutations or aberrant expression of upstream signaling molecules. As a result, cancer cells can proliferate inappropriately, resist programmed cell death, and acquire invasive properties.[7,8] For instance, the activation of the wingless-related integration site (Wnt)/β-catenin pathway is often associated with colorectal cancer progression, while the activation of the Rat sarcoma (Ras)/Rapidly accelerated fibrosarcoma (Raf)/MEK/ERK pathway is common in various cancers. Evasion of apoptosis, or programmed cell death, is a hallmark of cancer. Cancer cells develop mechanisms to bypass apoptosis, allowing them to survive despite the presence of DNA damage or other cellular stressors.[9,10] Overexpression of anti-apoptotic proteins, such as B-cell lymphoma 2 (Bcl-2), or downregulation of pro-apoptotic factors, such as p53, enables cancer cells to evade cell death signals. This ability to survive and proliferate in unfavorable conditions not only facilitates tumor growth but also contributes to treatment resistance, making it challenging to eradicate cancer cells with conventional therapies.[11] Angiogenesis, the formation of new blood vessels, is crucial for tumor growth and progression. As tumors grow, their demand for oxygen and nutrients increases, prompting the release of pro-angiogenic factors such as vascular endothelial growth factor (VEGF). These factors stimulate the proliferation and migration of endothelial cells, leading to the formation of new blood vessels that supply the tumor with the necessary resources to support its continued growth. The ability to induce angiogenesis is a vital step for tumors transitioning from a small, localized mass to a larger, more aggressive form capable of metastasis.[12,13] Metastasis, the spread of cancer cells from the primary tumor to distant sites in the body, is the final and most lethal stage of cancer progression (Fig. 1). This complex process involves several steps, including local invasion, intravasation into the bloodstream or lymphatic system, survival in circulation, extravasation into new tissues, and colonization. Cancer cells undergo epithelial-to-mesenchymal transition (EMT), a process that enhances their migratory and invasive capabilities. Once metastasized, cancer cells can establish secondary tumors that often exhibit different characteristics than the primary tumor, complicating treatment efforts.[14,15]

Cancer treatment encompasses a variety of methods, each tailored to the specific type and stage of cancer, as well as the patient's overall health.[16] The primary treatment modalities include surgery, where tumors are physically removed from the body; radiation therapy, which uses high-energy radiation to damage or kill cancer cells; and chemotherapy, involving the administration of cytotoxic drugs that target rapidly dividing cells, albeit with effects on healthy cells as well. Immunotherapy leverages the body's immune system to recognize and attack cancer cells, while targeted therapy focuses on specific

molecular targets associated with cancer, minimizing damage to normal tissues. Additionally, hormone therapy is used for cancers that are hormone-sensitive, such as certain breast and prostate cancers, to block hormone production or action. Emerging approaches, including personalized medicine and gene therapy, aim to tailor treatments based on an individual's genetic makeup, further enhancing the effectiveness of cancer care.[16–18]

Targeted anticancer drug delivery is an innovative approach designed to improve the efficacy and safety of cancer treatments by directing therapeutic agents specifically to cancer cells while minimizing exposure to healthy tissues.[19] This method utilizes various technologies, including nanoparticles, liposomes, and monoclonal antibodies, to enhance the specificity of drug delivery. By exploiting the unique characteristics of tumor cells, such as overexpressed receptors or the tumor microenvironment, targeted delivery systems can increase drug concentration at the tumor site, thereby maximizing therapeutic effects and reducing systemic side effects. For instance, nanoparticles can be engineered to encapsulate chemotherapeutic agents and release them in response to specific stimuli, such as pH changes or enzymatic activity prevalent in the tumor environment. This precision not only enhances the effectiveness of conventional chemotherapies but also paves the way for the development of novel therapeutic agents that can act selectively on cancer cells.[19–21]

AI is rapidly transforming the field of targeted anticancer drug delivery, offering innovative solutions to some of the most pressing challenges in cancer treatment.[22,23] By leveraging advanced algorithms and machine learning (ML) techniques, researchers can analyze vast datasets, including genomic, proteomic, and clinical data, to identify patterns and correlations that may not be apparent through traditional analytical methods.[24] For instance, ML algorithms can be utilized to predict how specific types of cancer will respond to various targeted therapies based on the genetic profiles of tumors.[25] This predictive capability enables the development of personalized treatment plans tailored to individual patients, optimizing therapeutic efficacy while minimizing side effects. Additionally, AI-driven analyses can help identify novel drug candidates and optimize their formulations for better targeting and effectiveness, significantly accelerating the drug discovery process.[26] Moreover, AI technologies enhance the design and implementation of targeted drug delivery systems by improving precision in several ways.[25] For instance, algorithms can be employed to model the interactions between drug carriers and cancer cells, allowing for the optimization of nanoparticle designs that maximize uptake and minimize toxicity. ML can also aid in real-time monitoring of treatment responses, enabling clinicians to adapt therapies dynamically based on patient-specific data. By integrating imaging data and biological markers, AI can facilitate the identification of tumor heterogeneity, guiding the selection of the most effective targeted therapies. In the field of targeted anticancer drug delivery, several key algorithms and ML techniques play a vital role in enhancing treatment precision and efficacy. Supervised learning algorithms, such as Support Vector Machines (SVM) and Random Forests, are frequently employed to predict patient outcomes and classify cancer types based on historical data and gene expression profiles. Deep learning approaches, particularly Convolutional Neural Networks (CNNs), excel in analyzing complex datasets, including medical imaging, by automatically extracting features for improved tumor detection.[27] Reinforcement learning optimizes treatment protocols by learning from previous patient responses, allowing for personalized dosing and timing of drug administration. Additionally, clustering algorithms like *k*-means and hierarchical clustering group patients based on similarities in their genomic data, facilitating tailored treatment approaches. Bayesian networks provide a probabilistic framework to analyze relationships between biological factors and treatment outcomes, incorporating prior knowledge with new data.[22,24,28,29]

AI is advancing targeted anticancer drug delivery by optimizing nanoparticle design, predicting effective therapeutic targets, and enabling stimuli-responsive controlled drug release, all of which enhance treatment precision and reduce toxicity. By forecasting drug resistance and tailoring delivery systems to individual tumor profiles, AI supports personalized therapy approaches that improve treatment efficacy and minimize side effects. These advancements collectively contribute to improving overall survival in cancer patients, addressing a critical clinical challenge by maximizing therapeutic impact while reducing harm, as emphasized in recent oncology research. Overall, the incorporation of AI and ML into targeted anticancer drug delivery not only streamlines the research and development process but also holds the potential to enhance clinical outcomes, making cancer treatment more effective and personalized for patients. This review aims to illuminate the multifaceted purposes of employing AI in targeted anticancer drug delivery. It underscores the recent advancements, such as ML algorithms that predict drug responses and optimize delivery mechanisms. Furthermore, it highlights the challenges faced in the realm of data variability, regulatory hurdles, and the need for robust clinical validation. Additionally, the review delves into future perspectives, exploring the potential for AI to enhance personalized medicine approaches, thereby tailoring treatments to individual patient profiles. This exploration seeks to provide a comprehensive understanding of how AI can transform cancer therapeutics, paving the way for innovative solutions that tackle the complexities of cancer treatment.

2. The role of AI in cancer therapies

With increasing incidence rates and difficulties in early identification and efficient treatment, cancer continues to be a major cause of death. Therapeutic approaches are made more difficult by tumor heterogeneity, underscoring the necessity of patient-specific precision medicine.[30] With an emphasis on data analysis, biomarker discovery, and ML-driven approaches, this section examines AI's involvement in cancer therapy (Fig. 2).

2.1. AI algorithms and data analysis

Algorithms used in AI evaluate information, identify patterns, and generate well-informed predictions or decisions, especially when it comes to diagnosing and treating illnesses. By

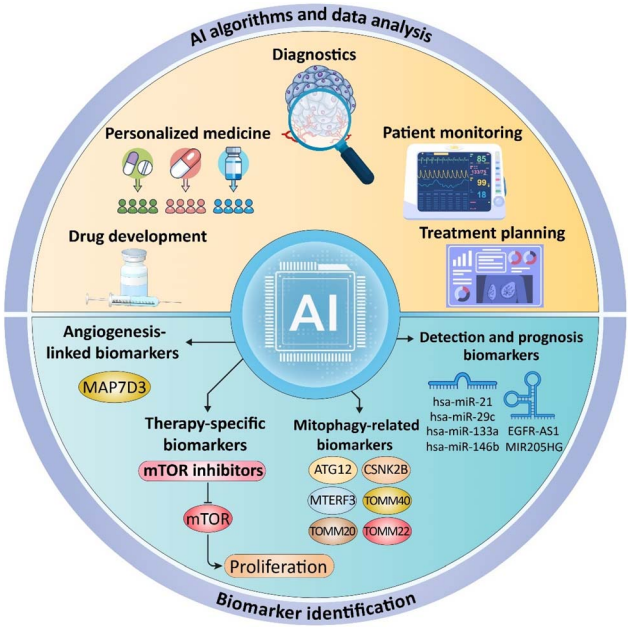

Fig. 2 Application of AI in cancer therapy could be categorized into two main groups; analyzing data with AI algorithms and utilizing AI for biomarkers identification.

identifying patterns in data and enhancing performance without explicit programming, ML, a subset of AI, enables systems to learn from experience. These models take data out of datasets and link patterns to specific categories. A subfield of ML called deep learning (DL) uses neural network-based architectures to process large volumes of complex data in a way that mimics human cognitive processes. In contrast to conventional techniques, AI can gather, process, and analyze data on its own to enhance patient outcomes. AI helps with drug development, personalized medicine, patient monitoring, treatment planning, and diagnostics through deep learning and ML.[31] Historically, clinicians in oncology relied on experience to predict cancer outcomes. However, the digital data era has highlighted the importance of AI-driven innovations such as ML and DL for better prognosis and treatment planning.[32,33] Oncology ML approaches are classified into three types: (I) supervised, (II) unsupervised, (III) and semi-supervised learning methods, each with its own set of advantages for evaluating cancer-related datasets. Supervised learning uses labeled inputs and maps known factors, such as omics data, to a specified output, such as the presence or absence of disease. This allows the algorithm to identify patterns that can be used to forecast cancer diagnosis and prognosis. Unsupervised learning, on the other hand, does not rely on labeled data; instead, it identifies spontaneously existing patterns within datasets, making it especially beneficial for uncovering previously unknown molecular characteristics associated with cancer. Furthermore, semi-supervised learning, which uses both labeled and unlabeled data, is gaining popularity in multi-omics research, allowing for higher predictive accuracy while lowering reliance on large-scale labeled datasets.[34] The architecture of neural networks is frequently used to describe them. An input and output layer forms the foundation of any neural network architecture, while the number of hidden layers and how they are connected determines the architecture's specificity. Computational units, neurons, and receiving inputs from upstream levels that are transformed into outputs sent to downstream layers make up each layer. Numerous hidden layers characterize deep neural networks. The deep architecture of convolutional neural networks is intended to identify patterns in spatially rich data, including whole-slide photographs, computed tomography (CT) scans, magnetic resonance imaging (MRI), ultrasound images, X-rays, and clinical imaging.[35]

ML has transformed virtual screening by improving the more accurate identification of possible drug candidates. Predictive accuracy was limited by traditional techniques like pharmacophore modeling and molecular docking, which depended on simplistic ligand–target interactions and rigid structures. On the other hand, in order to enhance prediction performance, ML algorithms integrate several data sources such as gene expression profiles, protein structures, and drug-induced phenotypic changes with complex chemical characteristics. Virtual screening is made more effective and dependable by models like support vector machines, random forests, and deep-learning networks that can precisely predict binding affinities and find novel compounds by learning patterns from enormous databases of known ligand–target interactions.[36,37]

By evaluating enormous biological datasets, such as genomic, proteomic, and clinical data, ML plays a critical role in therapeutic target selection by identifying disease-associated targets for additional research. By uncovering hidden patterns and relationships, ML algorithms overcome the complexity and scale of such data that traditional statistical methods frequently find difficult to handle. Methods such as t-distributed stochastic neighbor embedding (t-SNE) and principal component analysis (PCA) are used to identify connections between illness symptoms, protein–protein interactions, and gene expression profiles. Furthermore, databases like the Connectivity Map (CMap) and the Drug Gene Interaction Database (DGIdb) employ ML to curate drug–gene interactions and examine gene expression profiles from drug-treated cells, enabling target prioritization and revealing new therapeutic relationships.[38]

While AI applications in oncology have shown tremendous promise, it is essential to recognize that not all domains present equal methodological challenges. For instance, image-based cancer diagnosis (*e.g.*, radiology or histopathology) often benefits from the availability of large, well-annotated datasets and relatively lower feature dimensionality. These characteristics allow deep learning models, particularly CNNs, to perform with high accuracy and generalizability across diverse settings. In contrast, omics-based prediction of drug responses (*e.g.*, transcriptomics, genomics, proteomics) involves high-dimensional datasets with far fewer samples. This "large p, small n" scenario introduces risks of overfitting and model instability. As a result, traditional deep learning architectures often underperform when applied directly to omics data, and more tailored approaches are needed. These may include feature selection

Table 1 Comparison of AI challenges in imaging-based *vs.* omics-based cancer applications

Aspect	Imaging-based cancer diagnosis	Omics-based drug response prediction	Ref.
Data dimensionality	Low to moderate (2D/3D pixel arrays)	Extremely high (>20 000 genes)	39–41
Sample size availability	Often large (public image banks)	Often small (biopsy-based omics)	41
Model performance	CNNs perform well	Deep learning may underperform	42 and 43
Overfitting risk	Lower due to regularity and scale	High due to dimensionality/sample imbalance	39 and 40
Preferred techniques	Deep CNNs (ResNet, EfficientNet)	Feature selection, hybrid/ensemble ML models	44
Interpretability	Lower, but visual explanation possible	Higher with feature-selected models	45

algorithms, regularization techniques, hybrid models, or multimodal integration strategies that fuse biological domain knowledge with computational rigor. This contrast is summarized in Table 1, which compares the key technical attributes of image-based *vs.* omics-based AI applications in oncology.

2.2. Biomarker identification

With continuous improvements in biomarker identification and detection enhancing precision medicine, cancer biomarkers are essential to cancer care, supporting early diagnosis, prognosis prediction, and therapy monitoring.[46] This section explores how AI-driven approaches are advancing biomarker identification, covering AI-based gene panels for drug sensitivity, prognostic biomarker discovery, therapy response prediction, and the role of non-coding RNA biomarkers.

One important restriction in precision medicine is the lack of solid predictive biomarkers, which makes therapy response highly varied. To address this, Shin *et al.* created a Boolean-based ML framework for identifying multi-gene biomarker panels that can predict drug sensitivity. They used this technique to heat shock protein 90 (HSP90)-targeted therapy for prostate cancer by creating expression profiles that correlate with treatment response using proteomic data from patient-derived explants. This method maximizes predictive accuracy by improving biomarker selection through the use of Boolean algebra. The framework's adaptability to different medicines and tumor types beyond prostate cancer shows how AI can be used to improve therapy efficacy and patient selection.[47] Beyond biomarker panels, AI is being utilized to improve drug response predictions. One of the most difficult issues in oncology is that preclinical models do not always accurately represent how actual tumors behave, making treatment response difficult to predict. To address this, Hostallero *et al.* created Tissue-Informed Deep Learning (TINDL), a deep learning framework trained on cancer cell lines that incorporates tissue-informed normalization and addresses biological differences between lab models and patient tumors. By correctly identifying drug-sensitive *vs.* drug-resistant tumors for 10 out of 14 treatments, TINDL beat traditional ML models. Furthermore, it discovered gene biomarkers that predicted treatment response; which were confirmed to play a role in tamoxifen sensitivity through experimental validation using siRNA knockdown.[48] AI is also revolutionizing prognostic biomarker discovery, overcoming the limits of current markers, which frequently fail to deliver meaningful survival forecasts. Zhang *et al.* created a ML-based autophagy-related long non-coding RNA (lncRNA) signature for osteosarcoma, which has a dismal prognosis. They discovered 13 important autophagy-related lncRNAs that had a substantial correlation with overall survival using patient data from the therapeutically applicable research to generate effective treatments (TARGET) and gene expression omnibus (GEO) databases. The higher predictive value of this signature in comparison to conventional biomarkers was validated by Kaplan–Meier and receiver operating characteristic (ROC) curve studies. Interestingly, these lncRNAs were also connected to the infiltration of immune cells, indicating a potential role in the development of tumors.[49] Similarly, in hepatocellular carcinoma (HCC), the lack of accurate biomarkers hinders prognosis and treatment planning. To address this, Tu *et al.* used ML (Least Absolute Shrinkage and Selection Operator (LASSO) regression, Support Vector Machine – Recursive Feature Elimination (SVM-RFE)) to derive six mitophagy-related biomarkers (Autophagy Related Gene 12 (ATG12), Casein Kinase II Subunit Beta (CSNK2B), Mitochondrial Transcription Termination Factor 3 (MTERF3), Translocase of Outer Mitochondrial Membrane 20 (TOMM20), TOMM22, and TOMM40) from gene expression data. Using non-negative matrix factorization (NMF), HCC patients were divided into two molecular groups, indicating relationships with tumor immune microenvironment (TIME), clinicopathological characteristics, and survival rates. A prognostic model (riskScore) that included 10 mitophagy-related genes also showed predictive potential for somatic mutations, chemotherapy efficacy, Trans Arterial Chemo-Embolization (TACE), and immunotherapy response.[50]

Aside from autophagy and mitophagy-related indicators, AI is discovering novel angiogenesis-linked biomarkers in prostate adenocarcinoma (PRAD). Although angiogenesis plays an important role in tumor growth, its prognostic and therapeutic significance in PRAD is unknown. Wang *et al.* used ML approaches (Weighted Gene Co-expression Network Analysis (WGCNA), Least Absolute Shrinkage and Selection Operator (LASSO), and Cox regression) to discover Microtubule-Associated Protein 7 Domain-Containing 3 (MAP7D3) as an important angiogenesis biomarker. The strongest predictive marker among the ten important genes was MAP7D3, which was correlated with immunotherapy response and immune infiltration. The significant binding affinity of MAP7D3 to angiogenic medicines was established by molecular docking analysis, and its clinical relevance was confirmed by immunohistochemistry in 60 PRAD tissue samples.[51] AI is also helping to find therapy-specific biomarkers, allowing for more effective

usage of tailored medicines such as mTOR inhibitors. Everolimus is an effective treatment for metastatic ER+ breast cancer, but there are no good indicators to predict which patients would benefit. To address this, Nath *et al.* created a ML-based biomarker that predicts everolimus response by analyzing gene expression profiles from ER+ breast cancer cell lines and patient data. Their model successfully differentiated between responders and non-responders, suggesting its utility in optimizing patient selection for mTOR-targeted therapy (Fig. 3).[52]

In addition to predicting drug response, AI is transforming drug combination discovery by overcoming the constraints of expensive and time-consuming experimental screening. Liu and Xie developed TranSynergy, a deep learning model that improves model interpretability and predicts synergistic pharmaceutical interactions. In contrast to earlier methods, TranSynergy explicitly models gene dependencies, gene–gene interactions, and drug–target linkages in order to improve prediction accuracy by incorporating biological information. The model reveals novel pathways backed by experimental evidence by using Shapley Additive Gene Set Enrichment Analysis (SA-GSEA) to identify essential genes contributing to drug synergy. TranSynergy surpasses current models, as shown by benchmark tests, and its predictions helped find new synergistic drug combinations for ovarian cancer, which currently has few options for treatment.[53]

AI is also assisting with biomarker development in extremely diverse tumors such as triple-negative breast cancer (TNBC). TNBC's intricacy makes it difficult to identify clear predictive biomarkers, restricting precision medicine methods. To address this, Ghazal *et al.* used ML-guided gene selection to examine gene expression data from the Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) repositories in order to enhance biomarker identification. They discovered 27 important differentially expressed genes by combining Linear Models for Microarray Data (LIMMA) and ML-based feature selection; the models that performed the best were Multi-Layer Perceptron, Random Forest, XGBoost, and CatBoost. Among them, a densely interconnected hub gene cluster was created by Estrogen Receptor 1 (ESR1), Forkhead Box A1 (FOXA1), GATA3, X-box Binding Protein 1 (XBP1), Gene Regulated by Estrogen in Breast Cancer 1 (GREB1), Androgen Receptor (AR), and Anterior Gradient 2 (AGR2), indicating possible functions as pharmacological targets and diagnostic biomarkers.[54] Beyond protein-coding gene panels, AI is extending biomarker identification to non-coding RNAs, especially in immune-related malignancies such as colorectal cancer (CRC). While lncRNAs are rapidly being discovered in CRC, their clinical significance is uncertain. Liu *et al.*, created a ML-based immune-derived lncRNA signature (IRLS) to improve survival prediction and treatment stratification in CRC patients. IRLS outperformed standard clinical and molecular characteristics, serving as an independent risk factor for overall survival.

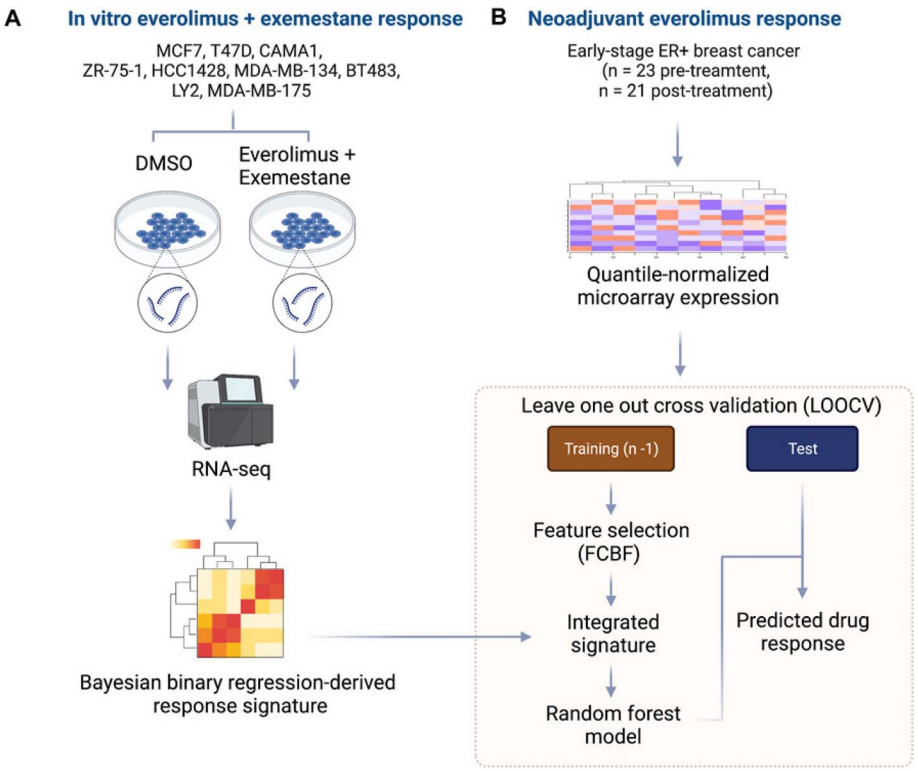

Fig. 3 Integrative workflow for mTOR inhibitor biomarker development. (A) Generation of an *in vitro* gene expression signature from ER+ breast cancer cell lines treated with everolimus and exemestane. (B) Integration of patient microarray data and *in vitro* signatures within a cross-validation framework to identify predictive biomarkers of response using a random forest model. Reproduced from ref. 52 under the terms of the Creative Commons Attribution License (CC BY). Copyright 2022, Nath, Cosgrove, Chang and Bild.

Additionally, high-risk patients responded better to fluorouracil-based chemotherapy, but low-risk patients benefited more from bevacizumab and pembrolizumab, indicating its significance in customized immunotherapy.[55] In addition to immune-related lncRNAs, AI discovered pharmacogenomic biomarkers other than protein-coding genes (PCGs), underlining the potential of lncRNAs in drug response prediction. Nath *et al.*, developed a ML-based approach for comprehensively evaluating lncRNAs as predictors of drug sensitivity. According to their data, the accuracy of lncRNA expression in predicting susceptibility to hundreds of anticancer medicines was comparable to that of PCGs. They discovered some lncRNA-specific biomarkers, such as Epidermal Growth Factor Receptor Antisense RNA 1 (EGFR-AS1) and MicroRNA 205 Host Gene (MIR205HG), which were experimentally confirmed to be predictors of anti-EGFR medication response after adjusting for proximal PCG effects.[56] Finally, AI is also addressing the urgent need for reliable biomarkers in gastric cancer (GC), a leading cause of cancer-related mortality. Despite its high prevalence, GC lacks effective markers for early detection and prognosis. To bridge this gap, Azari *et al.*, analyzed TCGA database using ML methods (SVM, Random Forest, and *k*-Nearest Neighbors (*k*-NN)), finding a panel of 29 miRNAs that may be biomarkers. Among them, there was a significant correlation between early detection and increased mortality and hsa-miR-21, hsa-miR-133a, hsa-miR-146b, and hsa-miR-29c. With an accuracy of 93% and an Area Under the Curve (AUC) of 88.5%, the SVM model showed excellent prediction performance. The biological significance of these miRNAs was confirmed by functional pathway analysis, which connected them to networks linked to cancer.[57]

3. AI for monitoring and adapting treatment

As cancer treatment becomes more personalized, AI is helping to bridge the gap between complex biological data and clinical decision-making. AI-powered approaches are changing how treatments are tailored to individual patients, from identifying new therapeutic targets to predicting drug response and tracking tumor evolution.[30] This section examines the AI applications for real-time data collection, targeted drug delivery, personalized treatment strategies, predictive modeling, and imaging-based tumor characterization.

3.1. Real-time data collection

The integration of AI in cancer treatment has revolutionized real-time data collection, enabling more precise monitoring and adaptation of therapeutic strategies. AI systems can process vast amounts of data from various sources, including electronic health records, imaging studies, and genomic data, facilitating a comprehensive understanding of patient responses to treatment. This capability is particularly crucial in oncology, where the heterogeneity of tumors necessitates personalized treatment approaches. For instance, AI algorithms can analyze real-time data to identify patterns that predict patient outcomes, thereby allowing oncologists to adjust treatment regimens dynamically based on individual responses.[30,58,59] Wearable biometric monitoring devices (BMDs), which enable continuous, non-invasive patient monitoring, are a significant development in AI-driven real-time data collection. Real-time biometric data analysis by these devices allows for early health issue detection and individualized treatment modifications. However, patient acceptance is crucial to their success. In a survey of more than 1100 chronic illness patients, Tran *et al.*, discovered that although 80% of respondents were positive about AI-assisted monitoring, 35% were worried about data privacy or the displacement of human decision-making.[60] Beyond general surveillance, AI improves preoperative decision-making in oncology, especially for ovarian cancer treatment. Traditional diagnostic approaches based on blood biomarkers frequently fail to provide an accurate prognosis prior to surgery. To address this, Kawakami *et al.*, created an ML approach that combines clinical data with numerous blood indicators, resulting in better forecasts of surgical outcomes, clinical stage, and tumor kind. Among the seven AI models examined, Random Forest (RF) had the highest accuracy (92.4%) and AUC (0.968) for differentiating epithelial ovarian cancer (EOC) from benign tumors. Furthermore, RF models identified high-risk early-stage EOC subgroups with worse survival rates and predicted histotypes and the likelihood of surgical resection, proving AI's ability to improve surgical planning.[61]

Additionally, AI's role in real-time intraoperative imagery improves surgical precision. In a study, the use of hyperspectral imaging (HSI) in conjunction with a SVM classifier was investigated to identify tumorous from healthy tissue during advanced-stage ovarian cancer surgery. Their *ex vivo* investigation on tissue samples from ten patients revealed an AUC of 0.83, a sensitivity of 81%, and a specificity of 70%, demonstrating the potential of HSI for quick, non-contact tumor detection during surgery.[62] Similar to this, Chalopin *et al.*, looked into AI-driven HSI for minimally invasive cancer procedures, where tissue classification in real time is still difficult. Their AI-assisted HSI system was able to differentiate 20 different organs with over 95% accuracy using experimental animal models. With a sensitivity of 90% and an F_1 score of 79%, it successfully distinguished the bile duct from surrounding tissue *in vivo* and achieved an AUC of over 0.91 in *ex vivo* tumor tissue identification.[63] Furthermore, AI is propelling advancements in real-time metabolic imaging, especially with Hyperpolarized Magnetic Resonance (HP-MR), which increases the sensitivity of MR signals by more than 10 000 times. The joint roles of AI and HP-MR in early tumor diagnosis, aggressiveness evaluation, and therapeutic response tracking were highlighted by Enriquez *et al.*, in their study of the applications of these technologies in pancreatic ductal adenocarcinoma (PDAC). Six preclinical studies and one clinical trial were included in their systematic review, which showed how AI improves image interpretation and metabolic biomarker discovery. Due to its accessibility, computed tomography (CT) has been the primary focus of AI research; however, the increasing usage of MR imaging is anticipated to broaden AI-HP-MR integration, allowing for more accurate, real-time

metabolic insights for the diagnosis and treatment of pancreatic cancer.[64]

3.2. Predictive modeling

Oncology predictive modeling uses ML and DL to predict patient survival, therapy response, and disease progression. Traditional ML techniques like logistic regression, decision trees, and support vector machines are frequently employed, but sophisticated deep learning models improve accuracy by identifying patterns in data. For the analysis of high-dimensional clinical data, such as omics, imaging, and electronic health records, these methods are especially useful.[65]

Predictive modeling based on radiomics is improving the assessment of treatment response by combining ML with routine imaging data. Dercle *et al.*, used serial CT scans to create radiomics signatures that predict how sensitive non-small cell lung cancer (NSCLC) is to systemic treatments including gefitinib, docetaxel, and nivolumab. Their ML model, which was trained using 1160 radiomics characteristics taken from lung lesions, showed promise for clinical decision-making by achieving AUC values of 0.77 for nivolumab, 0.67 for docetaxel, and 0.82 for gefitinib in validation cohorts. The model supported more individualized treatment approaches by examining tumor volume dynamics, invasion patterns, and spatial heterogeneity. This analysis gave insights into treatment response and overall survival prognosis.[66]

Extending radiomics to immunotherapy response, Sun *et al.*, created a ML biomarker based on radiomics to forecast tumor-infiltrating CD8 cells and how they could react to anti-Programmed Death-1 (PD-1)/PD-L1 treatment. They trained a model on 135 patients and verified it in three other datasets, including TCGA, using contrast-enhanced CT images and RNA-seq genomic data from four separate cohorts. The radiomic signature predicted immunotherapy response at 3 months ($p = 0.049$) and 6 months ($p = 0.025$), and it differentiated immune-inflamed tumors from immune-desert tumors (AUC = 0.76, $p < 0.0001$). Overall survival was significantly higher for patients with higher radiomic scores (HR = 0.52, $p = 0.0022$), indicating AI's promise for non-invasive immunotherapy outcome prediction.[67] Because standard CT sometimes misses complete responders, evaluating the response of bladder cancer to neoadjuvant chemotherapy is still challenging. Cha *et al.* improved this by using pre- and post-treatment CT scans to create three radiomics-based models: a hybrid model employing paired lesion radiomics features-regions of interest (RF-ROI), a radiomics feature model which was applied to the segmented lesions (RF-SL), and a deep-learning convolutional neural network (DL-CNN). These models, which were evaluated on 41 patients and trained on 82, were designed to forecast pathologic complete response (T0 stage). After being trained on 6700 ROI pairs, the DL-CNN and RF-SL demonstrated encouraging results, occasionally outperforming radiologists in identifying minute post-treatment alterations. The study shows how radiomics, particularly with deep learning, may help earlier, noninvasive treatment assessment and lead more individualized care in bladder cancer, even though none significantly surpassed specialists.[68]

AI-driven models that forecast treatment response and direct drug combination tactics are transforming targeted cancer therapy. DrugCell, a deep learning model developed by Kuenzi *et al.* using 684 medicines and 1235 tumor cell lines, combines drug structures and tumor genotypes to forecast therapeutic results. By simulating biological subsystems within cells, DrugCell provides mechanistic interpretability in contrast to conventional models. High predictive accuracy (Spearman $\rho = 0.80$) was attained, and actionable pathways associated with medication response were also found. CRISPR knockouts, drug synergy screens, and patient-derived xenografts are examples of experimental validations that supported the logical design of combination therapies and validated the model's predictions.[69] Drug sensitivity prediction is limited by model interpretability and inconsistent accuracy across datasets. Pang *et al.* introduced DrugGene, a type of deep learning model that combines data from gene expression, mutation, copy number variation, and drug chemical structure to predict anticancer response (Fig. 4A). Built on 8969 drug-cell line pairs from Cancer Therapeutics Response Portal (CTRP) and Genomics of Drug Sensitivity in Cancer (GDSC), the model combines a visual neural network structured around 2086 biological subsystems with a standard neural network for drug features. DrugGene achieved the lowest mean squared error (0.11) compared to DrugCell (0.14), expBox (0.17), and elastic net (0.27). It also revealed interpretable mechanisms of drug response, identifying key predictive subsystems such as phagocytosis.[70] Given the lack of clinical scalability of current biomarkers, accurately predicting response to immune checkpoint inhibitors (ICI) in advanced melanoma remains a challenge. In order to predict ICI response, Johannet *et al.* created a deep learning-based classifier that combines clinical data and histology slide analysis. The algorithm, which was trained using data from New York University and verified at Vanderbilt University, successfully classified patients into groups with high and low risk progression, achieving an AUC of 0.80. Significantly lower progression-free survival was observed in high-risk patients ($P = 0.02$, $P = 0.03$), highlighting AI's potential for clinical integration in immunotherapy decision-making. Precision oncology may be able to apply it with additional validation.[71]

In low-resource environments, where visual inspection is frequently employed but frequently unreliable, cervical cancer screening is still a significant gap. To get around this, Hu *et al.* trained a deep learning model to analyze digital cervical images from 9406 women in Costa Rica who were tracked for a maximum of 18 years. With an AUC of 0.91, the model produced image-based risk scores that correctly detected cervical cancer and precancer. This performance outperformed both traditional cervicography interpretation (AUC 0.69) and cytology (AUC 0.71). The model identified 55.7% of all precancers discovered in the entire adult cohort during a simulated screening round for women ages 25 to 49, but only 11.0% of them were referred for additional care. These findings highlight the potential of AI-based picture evaluation as a reliable, scalable screening method in situations without conventional infrastructure.[72] Moreover, teledermatology is essential for the early diagnosis of skin cancer, but it frequently leads to needless

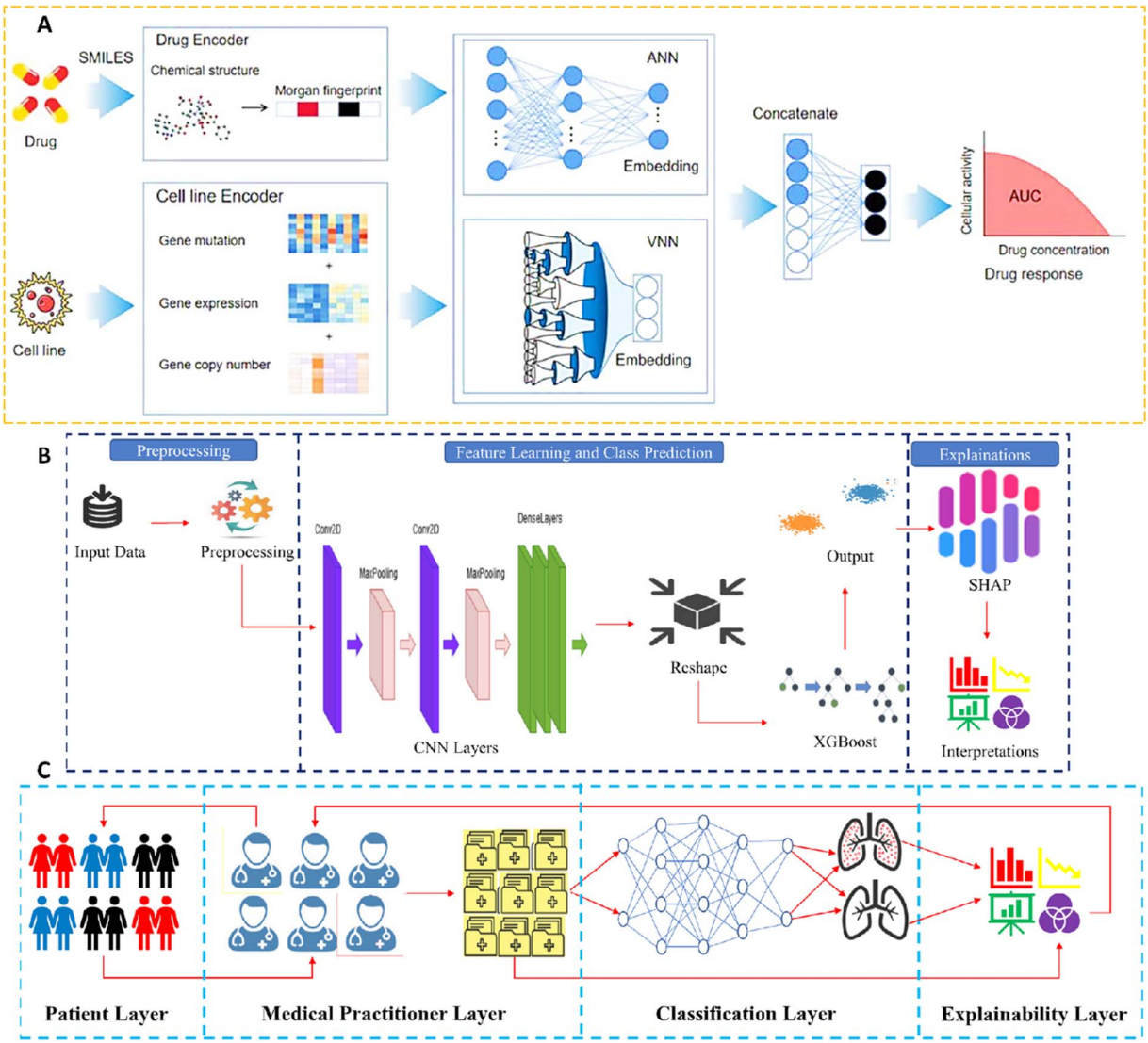

Fig. 4 Overview of the DrugGene model architecture and representation analysis. (A) Schematic image related to the flow chart steps of DrugGene. It works *via* integrating the outputs of visible neural networks (VNNs) and traditional artificial neural networks (ANNs) for drug response prediction. Reprinted from ref. 70 under the terms of the Creative Commons CC BY license. Copyright 2024, The Author(s). (B) Workflow of DeepXplainer model. (C) Utilizing hybrid model (combination of CNN and XGBoost) for predicting lung cancer. Reproduced with permission from ref. 74. Copyright 2023, Elsevier B.V.

biopsies and referrals, which raises the cost of healthcare. An AI as a Medical Device (AIaMD) based on CNNs was assessed by Marsden *et al.*, to classify skin lesions within a UK-based teledermatology cancer pathway in order to address this issue. AIaMD maintained good sensitivity (91–92.5%), equivalent to dermatologists, while accurately identifying more lesions that did not require a biopsy or urgent review than teledermatology's standard-of-care ($p = 0.001$) in a prospective trial of 789 lesions. AIaMD offered an effective and scalable solution for maximizing teledermatology services in skin cancer diagnosis by cutting down on pointless referrals without sacrificing accuracy.[73] AI-assisted lung cancer detection has made great strides, but a big obstacle still exists: deep learning models' lack of interpretability, which breeds mistrust among physicians. Wani *et al.*, created DeepXplainer, a hybrid deep learning model, to address this issue (Fig. 4B and C). It incorporates SHAP (Shapley Additive Explanations) for interpretability and CNNs with XGBoost for lung cancer classification. DeepXplainer outperformed conventional techniques with 97.43% accuracy, 98.71% sensitivity, and an F_1-score of 98.08% using the Survey Lung Cancer dataset. DeepXplainer offered a more transparent and dependable AI-powered lung cancer detection tool by bridging the gap between physician trust and AI decision-making by presenting both local and global explanations for its forecasts.[74]

Planning for radiation therapy by hand takes a lot of time and is frequently constrained by variations in dose complexity and quality. Babier *et al.* used data from 217 oropharyngeal cancer patients to create an automated planning pipeline that combines inverse optimization and ML-based Dose–Volume

Histogram (DVH) prediction to address this issue. The bagging query (BQ) and generalized PCA (gPCA) KBP models were evaluated. Even when plan complexity was limited, gPCA plans continued to outperform clinical plans by 21.2 percentage points, meeting 90.2% of target criteria. Despite surpassing clinical performance by 6.3 points and meeting 74.4% of organs at risk (OARs) criteria, BQ plans suffered under complexity controls. Radiation therapy planning that is fully automated and clinically feasible can be achieved with this method.[75] Furthermore, SigMA, a ML-based technique created by Gulhan *et al.*, eliminated the need for whole-genome or whole-exome sequencing by identifying homologous recombination deficiency (HRD) mutational signals from specific gene panels. Their algorithm predicts ovarian cancer patients' susceptibility to PARP inhibitors and platinum-based treatment by correctly identifying HR-deficient tumors. AI-driven predictive modeling in precision oncology was demonstrated by SigMA's capacity to identify HRD signatures even in samples with low mutation counts, increasing the number of patients eligible for targeted therapies.[76]

3.3. AI for imaging and tumor characterization

AI-powered imaging technologies are revolutionizing cancer diagnosis by improving tumor characterization *via* automated picture analysis. AI models help to differentiate tumor stages during endoscopic operations, hence improving clinical decision-making. Ebigbo *et al.*, created a deep learning model to categorize Barrett's cancer into T1a (localized) and T1b (submucosal invasive) using white-light endoscopic images. The AI system attained a 71% accuracy rate, equivalent to expert endoscopists, confirming its clinical utility. However, while promising, current AI models require additional improvement for real-time video analysis.[77]

In addition to endoscopic imaging, AI is essential for differentiating between benign and malignant tumors using various imaging modalities. Wang *et al.* used ultrasound images from 251 patients to assess the diagnostic performance of four deep learning models: ViT-B\16, EfficientNetB3, DenseNet121, and ResNet50. With an AUC of 0.82 and an accuracy of 80%, EfficientNetB3 outperformed the others. ResNet50, with an AUC of 0.80, and ViT-B\16 and DenseNet121, both with an AUC of 0.81, came in close succession. All models outperformed less experienced radiologists, whose AUCs ranged from 0.68 to 0.75, and performed comparably to experienced clinicians. These findings imply that AI can assist in making diagnoses, especially in situations where specialized knowledge might be scarce.[78] Additionally, it can be difficult to distinguish between benign and malignant parotid tumors on plain CT, especially when contrast enhancement is not present. To address this, Hu *et al.* used 917 cropped tumor images from 283 patients to train deep learning models (ResNet50, VGG16_bn, and DenseNet169). With an AUC of 0.96 and image-level accuracy, sensitivity, and specificity of 90.8%, 91.3%, and 90.4%, respectively, ResNet50 demonstrated the best performance. Accuracy increased to 92.3% when a voting model was used for patient-level classification. The model performed better than two radiologists, indicating that it could be used as a helpful tool for early diagnosis with routine CT scans.[79]

Treatment planning depends on accurate lymph node staging, but conventional imaging techniques frequently can't tell the difference between benign and metastatic nodes. The use of AI in CT and MRI for the diagnosis of lymph node metastases from colorectal cancer was the subject of a comprehensive review and meta-analysis by Bedrikovetski *et al.* Their results demonstrated that AI may improve preoperative staging accuracy, with deep learning models outperforming radiologists (Area Under the Receiver Operating Characteristic Curve (AUROC) 0.917 *vs.* 0.688).[80] Similarly, conflicting imaging interpretations make it difficult to diagnose lymph node metastases in oral squamous cell cancer (OSCC). With an AUC of 0.92, sensitivity of 0.79, and specificity of 0.90, Deng *et al.*'s analysis of AI applications in CT and MRI for LN metastatic prediction showed that AI models performed better than skilled radiologists.[81] Furthermore, in order to diagnose lymphoma, Bai *et al.* carried out a thorough investigation and meta-analysis of AI's diagnostic capabilities in 30 research. With 87% sensitivity, 94% specificity, and an AUC of 97%, AI models showed great promise for enhancing lymphoma detection. Overestimation issues and the requirement for uniformity, however, continue to be important research topics.[82]

Although accurate tumor segmentation is necessary for glioma diagnosis and treatment planning, manual delineation is still time-consuming and labor-intensive. To overcome this difficulty, Li *et al.* produced a transformer-based multi-task deep learning model that can identify invaded brain regions and segment tumors at the same time, a task that has seldom been handled by earlier models. The model, which was trained on 354 patients with grade II–IV gliomas, demonstrated consistently high AUCs across tumor grades and demonstrated outstanding performance on an independent test set (AUC: 94.95%; Dice score: 87.60%). The model provides a more thorough understanding of tumor spread by combining the two tasks, which may help surgeons make better judgments. The study was constrained by its retrospective methodology and absence of external validation, and it is yet unclear if transformer architectures can be used in clinical workflows in the real world (Fig. 5).[83]

Effective treatment of gliomas requires molecular characterization. A multi-task deep learning model was created by Van der Voort *et al.* that accurately predicts important molecular features from preoperative MRI, such as tumor grade, isocitrate dehydrogenase (IDH) mutation status, and 1p/19q co-deletion, while also concurrently segmenting gliomas. AUCs of 0.90 for IDH mutation, 0.85 for 1p/19q co-deletion, and 0.81 for tumor grading were attained by the model, which was trained on a sizable multi-institutional dataset of 1508 patients from 16 centers and assessed on an independent cohort of 240 patients from 13 centers. An average Dice score of 0.84 was attained for tumor delineation. This method has shown good generalizability across institutions and provides a non-invasive, integrated solution for glioma assessment, indicating potential for wider clinical application.[84] When it comes to pediatric brain tumors, especially those located in the posterior fossa, precise

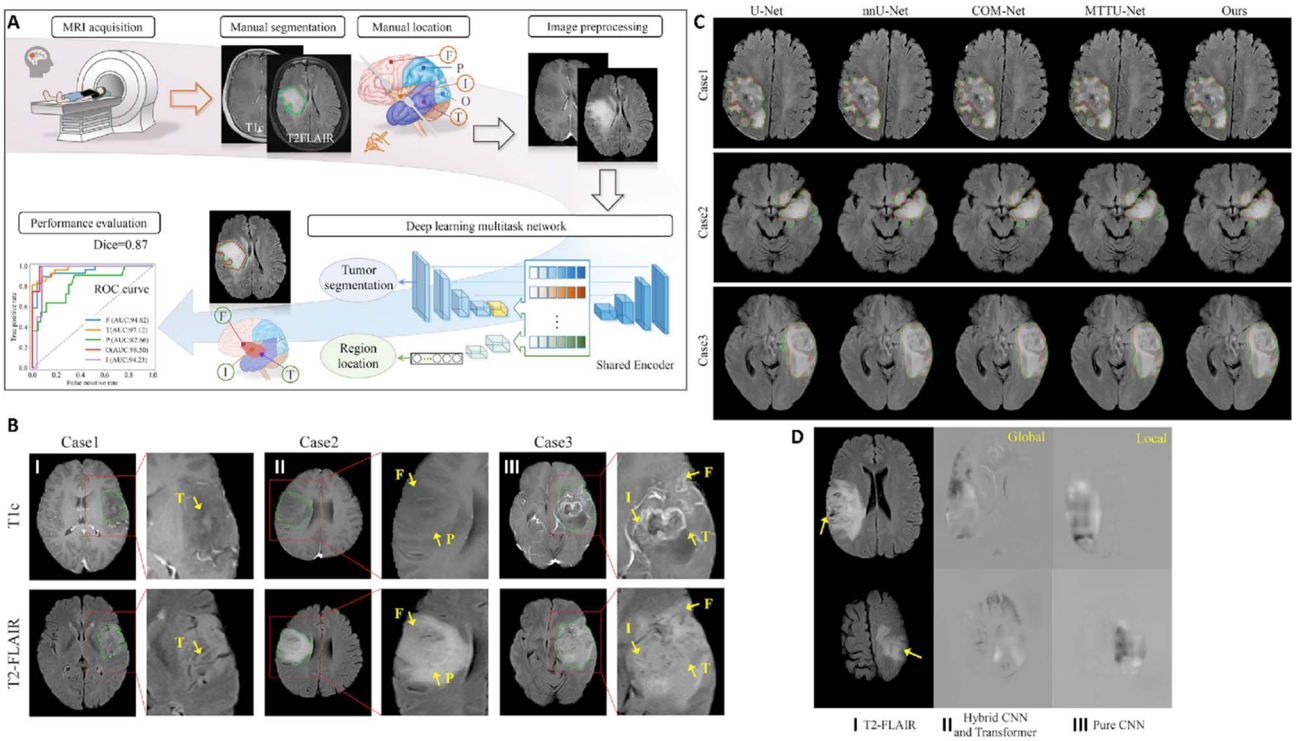

Fig. 5 Utilizing the transformer-based multi-task deep learning framework for glioma infiltration analysis and segmentation. (A) Schematic representation of the proposed architecture integrating a transformer-based multi-task network for identification of infiltrated brain areas and glioma segmentation, simultaneously. (B) Representative MR image of glioma patients showing different levels of brain infiltration: (I) single-region infiltration, (II) dual-region infiltration, and (III) tri-region infiltration. (C) Comparative segmentation outcomes got from different methodologies. The red contour indicates the ground truth delineation, while the green contour represents the algorithm-predicted segmentation. (D) Guided backpropagation maps illustrating the attention mechanisms: (II) hybrid CNN-transformer network emphasizing both global contextual and local spatial features, and (III) pure CNN model primarily capturing local feature representations. Reproduced from ref. 83 under the terms of the Creative Commons CC BY license. Copyright 2023, Springer Nature.

classification is essential but frequently arbitrary. To overcome this limitation, a deep learning model trained on MRI data from five pediatric facilities was created by Quon *et al.*, which used a modified ResNeXt-50-32x4d architecture, performed better than expert radiologists in differentiating between ependymomas, pilocytic astrocytomas, medulloblastomas, and diffuse midline gliomas, providing a more accurate diagnostic tool for treatment planning.[85]

The choice of treatment for nasopharyngeal carcinoma (NPC) is still difficult because concurrent chemoradiotherapy (CCRT) and induction chemotherapy (ICT) are both effective alternatives. Zhong *et al.* created a deep learning-based radiomic nomogram that uses pre-treatment MRI data to predict disease-free survival in order to improve individualized treatment plans. When AI-driven suggestions were implemented, the model's ability to classify patients into ICT-preferred and CCRT-preferred groups greatly improved survival results.[86]

3.4. AI in targeted anticancer drug delivery systems

Drug development has been transformed by the introduction of cutting-edge technologies, such as computer-aided and AI-based techniques. The timeframe for early-stage procedures like target screening has been drastically reduced to a few years because of these advancements. With these advancements, approximately one in fifty compounds from preclinical studies could progress to clinical trials in as little as two years, while up to one in twenty compounds entering preclinical trials could progress within three to five years. Artificial intelligence and computational methods aid in structure design by modifying bioactive molecules, predicting drug–protein interactions, assessing ADME (absorption, distribution, metabolism, and excretion) properties, and analyzing bioavailability. These methods save time and money by assisting in the early elimination of non-viable candidates, even though not all compounds are successful in subsequent stages.[87,88]

Computational models are required for better discovery because experimental methods for identifying novel anticancer peptides (ACPs) are expensive and ineffective. ACP-DL, a deep learning model built on long short-term memory (LSTM) neural networks, was created by Yi *et al.*, to address this. ACP-DL efficiently separates ACPs from non-ACPs by combining binary profile features with *k*-mer sparse matrices. Through cross-validation, their model outperformed current methods in terms of accuracy and specificity. To aid in future research, the authors also presented two benchmark datasets, ACP740 and ACP240. This study demonstrates how deep learning helps speed up the discovery of ACP, which will ultimately aid with the

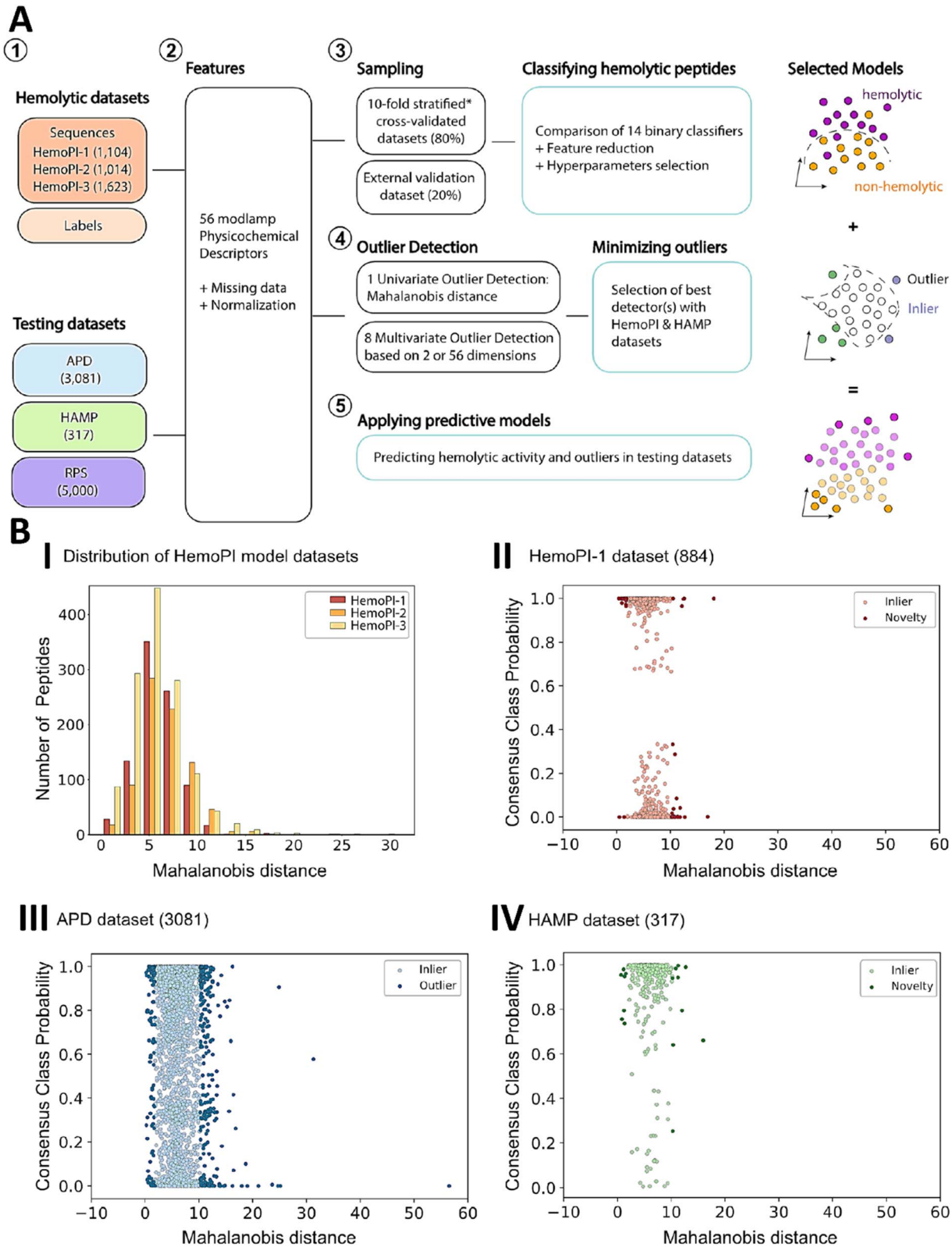

Fig. 6 Discovery workflow and outlier analysis for non-hemolytic antimicrobial peptides. (A) Different steps used for differentiating the non-hemolytic peptides from antimicrobial peptide database: (1) data collection about peptide sequences, (2) determining 56 physicochemical properties for each sequence, (3) utilizing HemoPI datasets to determine the hemolytic activity *via* producing the binary classifier, (4) estimating the applicability domain using univariate and multivariate outlier detection, and (5) implementation of optimized models on the antimicrobial peptide database (APD), hemolytic AMP subset (HAMP), and random peptide sequences (RPS) datasets. (B) Outlier analysis using Mahalanobis distance. (I) Distance distributions for HemoPI-1, -2, and -3 datasets. (II–IV) Projection of Mahalanobis distance against consensus class probabilities for the HemoPI-1 dataset, APD dataset, and HAMP, respectively. Inliers (light colors) and outliers (dark colors) were categorized according to the 99.7% confidence threshold of a normal distribution. Reproduced from ref. 90 under the terms of the Creative Commons Attribution License (CC BY). Copyright 2020, Springer Nature.

creation of tailored anticancer drugs.[89] Peptide-based therapeutics often suffer from toxicity concerns, such as hemolytic activity, limiting their systemic application. Addressing this, Plisson *et al.*, created ML algorithms to forecast hemolytic characteristics and direct the creation of safer antimicrobial peptides (AMPs). Their gradient boosting classifier model was able to categorize hemolytic peptides with 95–97% accuracy. By using outlier detection techniques to further hone the predictions, 34 high-confidence non-hemolytic natural AMPs were found, and 507 non-hemolytic peptides were designed from scratch. These results create a computational paradigm that optimizes therapeutic efficacy while reducing toxicity risks, which could be applied to the discovery of anticancer peptides (Fig. 6).[90]

Beyond peptides, AI also have the capability of transforming nanoparticle-based drug delivery, enabling precise control over particle size, drug release kinetics, and biodistribution. An AI-based computational model was created by Baghaei *et al.*, to maximize the release behavior of poly (lactic-*co*-glycolic acid) (PLGA) biodegradable nanoparticles for targeted medication administration. They used artificial neural networks (ANNs) to simulate the link between the output parameters (PLGA particle size and initial drug burst) and the important input factors (polymer molecular weight, stabilizer concentration, polymer concentration, and sonication rate). The most important factor affecting the size of nanoparticles and the drug release profile was found to be the molecular weight of PLGA by the AI-driven regression analysis. Additionally, multi-objective optimization using a genetic algorithm allowed for the precise modifying of PLGA nanoparticles to reduce size and initial burst.[91] Additionally, Mostafavi *et al.*, optimized the size of paclitaxel-loaded poly (D,L-lactide-*co*-glycolide-*N*-*p*-maleimido benzoic hydrazide) (PLGA-PMBH) nanoparticles made using a modified nanoprecipitation process using artificial neural networks (ANNs). Using 40 experimental samples to train the AI model, the study examined the effects of sonication power, drug content, polymer content, and the organic/aqueous phase ratio (acetone/water) on nanoparticle size. Particle size was directly correlated with polymer and drug concentration, according to 3D modeling, with the acetone/water ratio having the most effect. Furthermore, at lower values, sonication power had an indirect effect on nanoparticle size, but at higher values, it had a direct effect.[92] The drug release kinetics of pH- and temperature-responsive poly(*N*-isopropyl acrylamide-*co*-acrylic acid)/poly(ethylene glycol) (poly(NIPAAm-*co*-AAc)/PEG) interpenetrating polymer network (IPN) hydrogel loaded with doxorubicin (DOX) were modeled by Boztepe *et al.* using an AI-driven methodology. They successfully predicted drug release profiles under various physiological situations by using support vector regression (SVR), least squares SVM (LS-SVM), and artificial neural networks (ANNs). Their ANN-based model performed better than alternative approaches, indicating AI's potential to improve controlled release mechanisms and optimize medication delivery using nanoparticles.[93]

While AI has optimized nanoparticle formulation, ensuring effective drug transport and biodistribution remains a challenge. In order to anticipate NP biodistribution and tumor-targeted delivery efficiency, Chou *et al.* created an AI-assisted physiologically based pharmacokinetic (PBPK) model. This model demonstrated good correlations with experimental data ($R^2 \geq 0.70$ for 133 out of 288 datasets). Although long-term forecasts ($R^2 = 0.56$ at 168 hours) were less accurate, their model was notable for its excellent accuracy in projecting maximal delivery efficiency ($R^2 = 0.83$) and early tumor accumulation ($R^2 = 0.82$ at 24 h). This method improves computational screening for cancer nanomedicines by improving NP cellular absorption kinetics, providing a viable substitute for extensive animal testing (Fig. 7).[94] Additionally, a ML-based bioinformatics tool called CPPred-FL was created by Qiang *et al.*, to identify cell-penetrating peptides (CPPs) on a wide scale. CPPs are transporter vehicles that transfer anticancer medicines into living cells. To extract pertinent compositional, positional, and physicochemical aspects, their approach combined random forest classifiers with numerous feature descriptors that resulted in better prediction performance than current CPP predictors. By using this method, targeted peptide-based drug delivery systems for cancer treatment can be developed more quickly because to CPPred-FL's quick identification of CPPs.[95]

3.5. Personalized treatment adjustments

Early detection and individualized treatment planning are critical for increasing cancer survival rates while reducing the hazards of ineffective aggressive therapy. ML algorithms can evaluate medical photos, clinical data, and molecular profiles to detect tiny patterns that the human eye may miss, resulting in faster diagnosis and more effective drug choices.[30,96] For instance, reliability in predicting neoantigens, or tumor-specific peptides that elicit immune responses, is a major obstacle in cancer immunotherapy. Traditional techniques are either restricted to particular human leukocyte antigen (HLA) alleles or necessitate time-consuming peptide screening. To address this issue, Bulik-Sullivan and colleagues created EDGE (a type of mass spectroscopy-based model), a deep learning algorithm that was trained using data from HLA peptide mass spectrometry and genomic datasets. When compared to conventional binding affinity models, their method increased the positive predictive value of HLA antigen presentation predictions by up to nine times. This improvement was seen in tumor mass spectrometry test datasets, where EDGE significantly outperformed binding affinity models using gene expression thresholds, achieving an average Positive Predictive Value (PPV) of 0.54 at 40% recall. The benefit remained constant across different memory levels, proving the resilience of EDGE in neoantigen prediction. The foundation for AI-powered immunotherapies is laid by EDGE's precise identification of neoantigen-reactive T cells, which permits highly individualized, patient-specific immune responses (Fig. 8).[97]

Predicting chemoresistance is a crucial use of AI that helps oncologists choose the best drugs for each patient. To predict paclitaxel and gemcitabine resistance in breast cancer, different types of ML models were created by Dorman *et al.*, that incorporated copy number variations and gene expression data.

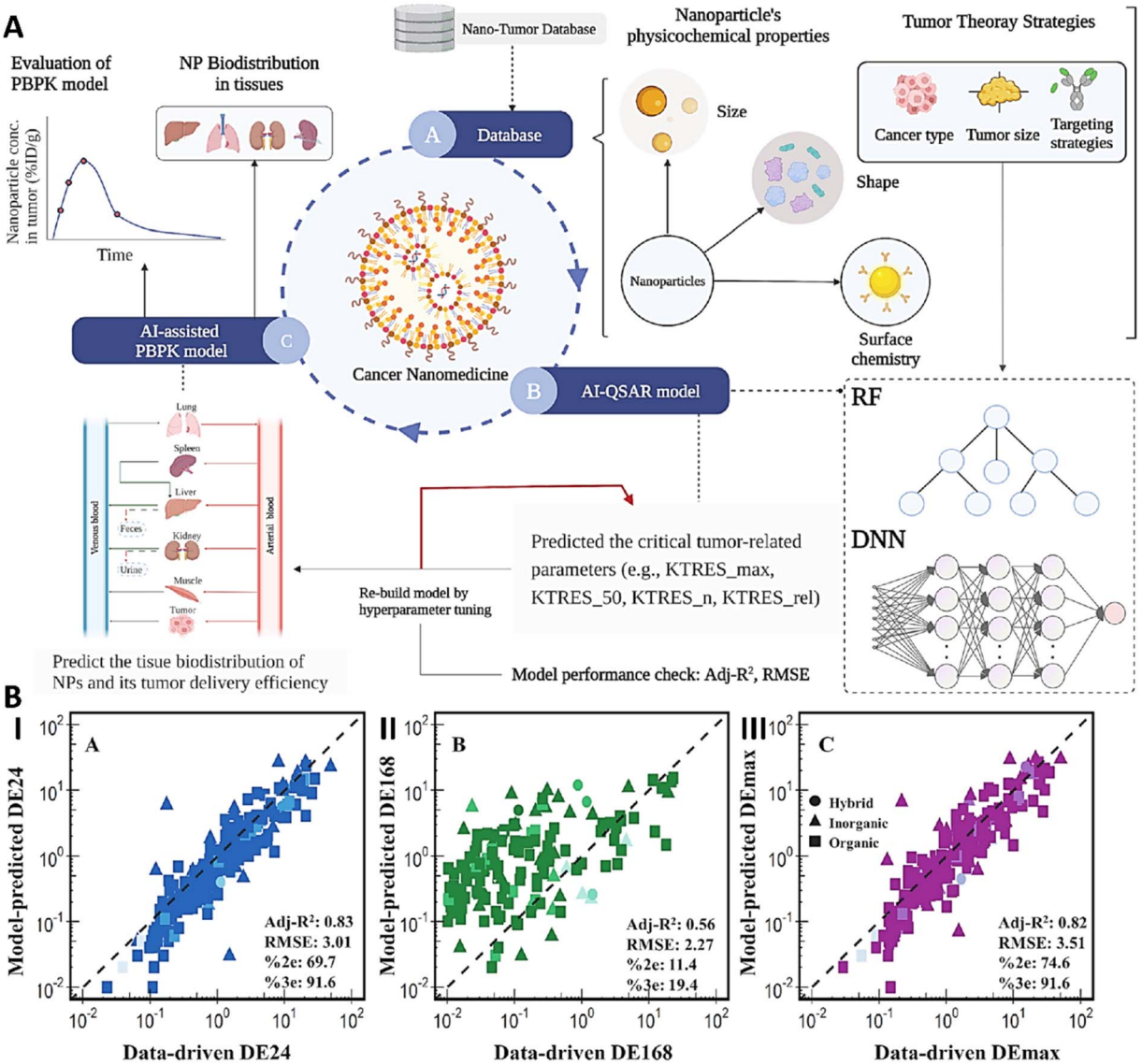

Fig. 7 Integration of AI models with PBPK modeling for predicting nanoparticle delivery efficiency. (A) Computational workflow combining physiologically based pharmacokinetic (PBPK) modeling with deep learning and ML to predict nanoparticle (NP) delivery to tumors in mice. Steps include: (1) nano-tumor database, (2) AI-QSAR model development, and (3) AI-assisted PBPK modeling. (B) Assessment of AI-PBPK model predictions for tumor delivery efficiency (DE) in comparison to data-driven values at (I) 24 h, (II) 168 h, and (III) maximum DE. % 2e and % 3e indicate the percentage of predictions within 2-fold and 3-fold error, respectively. Adj-R^2 and RMSE indicate model performance. Abbreviations: DNN (deep neural network), KTRES_n (Hill coefficient; KTRES_rel, release rate constant), KTRES_max (maximum uptake rate; KTRES_50, time to half-max uptake), RF (random forest; Adj-R^2, adjusted R-squared), RMSE (root mean square error). Reproduced with permission from ref. 94. Copyright 2023, Elsevier.

Their SVM-based approach produced cell lines with 85% gemcitabine resistance and 82% paclitaxel resistance accuracy. 84% of the time, the paclitaxel model accurately detected sensitivity in patient samples, demonstrating the potential of AI-powered predictive models to maximize chemotherapy selection and enhance patient outcomes.[98]

Additionally, AI is revolutionizing surgical decision-making by assisting physicians in avoiding needless procedures. A random forest ML model was created by Bahl *et al.*, to forecast which high-risk breast lesions (HRLs) have the highest chance of developing into cancer. Using patient age, pathology text traits, and histology, the model successfully prevented 30.6% of needless procedures while accurately identifying 97.4% of malignant cases. This AI-powered tool for decision-making could save expenses, surgical complications, and patient suffering.[99] Similar to this, a key surgical choice in gastric cancer is the extent of lymphadenectomy (D1 *vs.* D2). Liu and colleagues created a ML model that optimized lymphadenectomy planning by combining logistic regression (LR), SVM, and auto-encoder (AE) approaches. Overtreatment rates were lowered by their model from 15.1% (JPN 4th criteria) and 21.7% (treat-all) to as low as 0.7–0.9%, while validation tests showed an AUC of 0.946. This demonstrates how AI can enhance surgical techniques and patient results.[100]

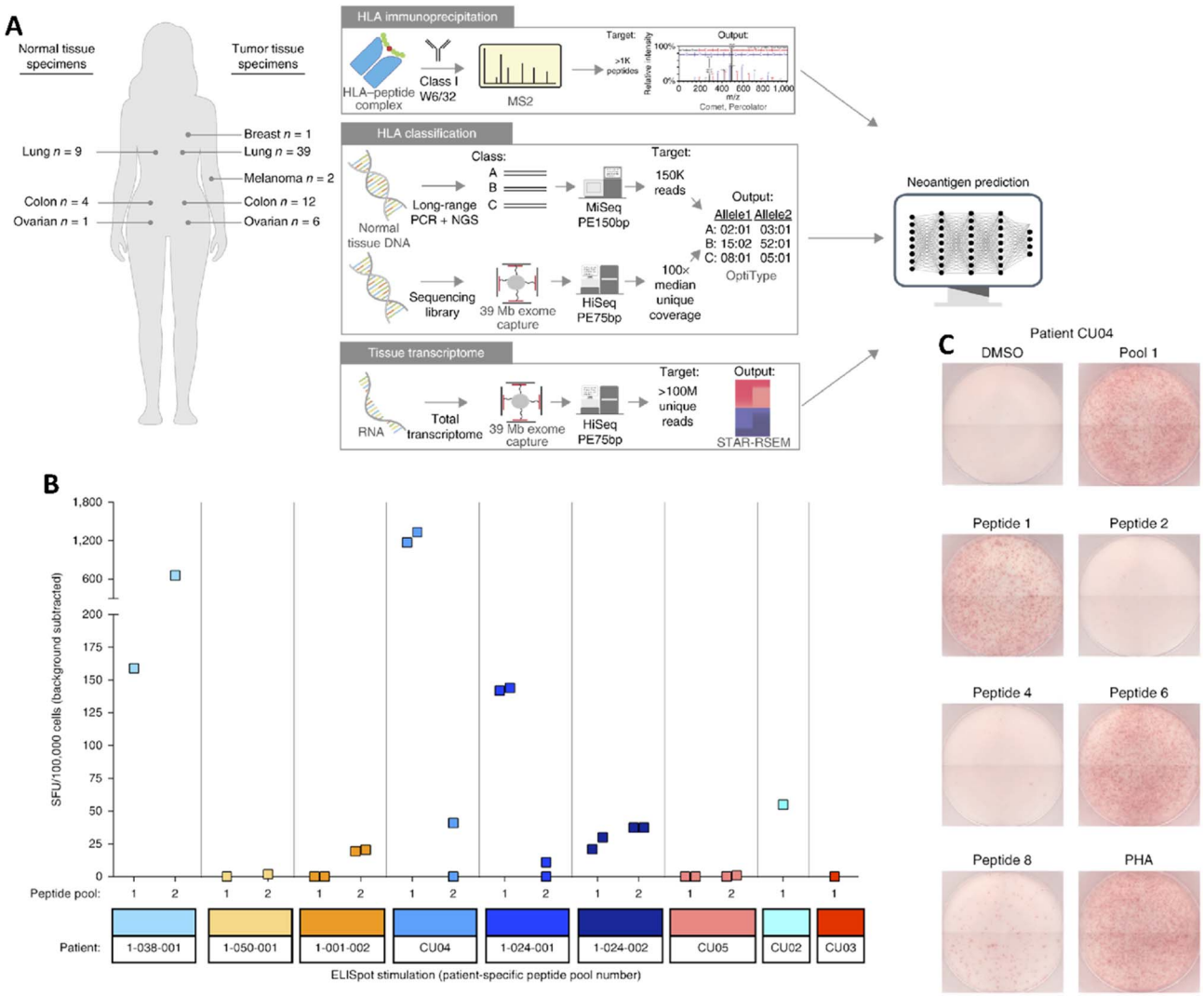

Fig. 8 Sample processing, model training, and T cell response evaluation. (A) Overview of tissue samples and data types used for training. Tumor and normal tissues were processed to generate HLA peptide sequences, HLA types, and transcriptome profiles. Samples underwent HLA immunoprecipitation, peptide sequencing (MS), and RNA-seq. HLA types were determined *via* gathering data from exome or sequencing the matched normal tissue. HLA epitope is then predicted using the integration of datasets. (B) Evaluation of responses of T cells to neoantigen peptide pools using Interferon-Gamma Enzyme-Linked ImmunoSpot Peripheral Blood Mononuclear Cells (IFN-γ ELISpot. PBMCs) from patients were stimulated with two peptide pools based on model-predicted neoantigens. Patients with positive responses are shown in blue; non-responders in orange/red. (C) Representative ELISpot wells from patient CU04, confirming responses in an independent culture repeat. Reproduced with permission from ref. 97. Copyright 2018, Springer Nature America, Inc.

4. Challenges

As promising as the future of AI in targeted anticancer drug delivery appears, several critical challenges must be addressed to fully realize its potential. These challenges span technical, ethical, regulatory, and practical dimensions that require careful consideration and strategic planning.

4.1. Data quality and standardization

The effectiveness of AI algorithms largely depends on the quality and quantity of data available for training. In the field of oncology, data can be fragmented across various institutions, lacking standardization in formats, definitions, and collection methods.[101,102] This inconsistency can lead to biases in AI models, resulting in inaccurate predictions and recommendations. Furthermore, many datasets are limited in scope, often reflecting specific patient demographics or treatment protocols that may not be generalizable. To overcome this challenge, there is a critical need for collaborative efforts to create centralized, standardized databases that encompass diverse patient populations and comprehensive clinical, genomic, and treatment data. Additionally, ensuring data integrity and accuracy is essential for training robust AI models capable of yielding reliable insights.

4.2. Interpretability and transparency

The "black box" nature of many AI algorithms, especially deep learning models, poses a significant challenge in clinical

settings.[103] Healthcare professionals must understand the rationale behind AI-driven recommendations to trust and adopt these technologies effectively. Lack of interpretability can lead to skepticism among clinicians, hindering the integration of AI into routine practice. To address this challenge, researchers must prioritize the development of explainable AI models that provide clear insights into their decision-making processes. Techniques such as feature importance analysis, visualization of model predictions, and the use of simpler models when appropriate can enhance transparency. Engaging clinicians in the development of AI tools can also ensure that the outputs are relevant and understandable.

4.3. Regulatory hurdles

The deployment of AI technologies in healthcare is subject to complex regulatory frameworks that vary by region. Regulatory agencies must establish guidelines that ensure the safety, efficacy, and ethical use of AI in clinical practice.[104] However, existing regulations may not adequately address the unique challenges posed by AI, such as algorithm validation, data privacy, and accountability for AI-driven decisions. Navigating this regulatory landscape can be daunting for developers and healthcare providers. To mitigate these challenges, there is a need for ongoing dialogue between AI developers, regulatory bodies, and healthcare stakeholders. Establishing clear guidelines and pathways for the approval of AI technologies will facilitate their integration into clinical practice while ensuring patient safety.

4.4. Bias and equity issues

AI algorithms are susceptible to biases that can arise from the data used to train them. If the training data lacks diversity or does not accurately represent the patient population, the resulting AI models may perpetuate existing disparities in healthcare outcomes.[105,106] For instance, algorithms trained predominantly on data from specific demographic groups may not perform well for underrepresented populations, leading to inequitable treatment recommendations. Addressing bias requires a concerted effort to ensure that training datasets are inclusive and representative of diverse populations. Additionally, ongoing monitoring and evaluation of AI models must be conducted to identify and mitigate bias in real-world applications. Engaging diverse stakeholders in the development process can also help ensure that the technology is designed with equity in mind.

4.5. Integration into clinical workflows

Successfully integrating AI technologies into existing clinical workflows poses practical challenges. Healthcare providers must navigate the complexities of integrating AI systems with electronic health records (EHRs) and other clinical tools. Moreover, clinicians may face resistance to adopting new technologies, especially if they perceive them as disruptive to established practices.[107,108] To facilitate successful integration, AI solutions must be designed with usability and workflow compatibility in mind. Providing adequate training and support for healthcare professionals is also essential to ensure they feel comfortable using AI tools in their practice. Collaborative efforts between AI developers and healthcare institutions can ensure that solutions are aligned with clinical needs and workflows.

4.6. Clinical validation and reproducibility

AI models must undergo rigorous clinical validation to demonstrate their effectiveness and safety in real-world settings. However, achieving reproducibility across diverse patient populations and clinical environments can be challenging.[109] Variability in treatment responses, tumor heterogeneity, and differences in healthcare systems complicate the validation process, making it difficult to generalize findings from one study to another. To address this challenge, researchers must prioritize robust validation studies that encompass diverse populations and clinical scenarios. Utilizing multi-institutional collaborations and large-scale datasets can enhance the generalizability of AI models, ensuring that they are applicable in various contexts.[110]

4.7. Cost and resource allocation

The development and implementation of AI technologies can be resource-intensive, requiring significant financial investment and skilled personnel. Many healthcare institutions, particularly those in low-resource settings, may struggle to allocate the necessary resources for AI adoption.[111] This disparity can exacerbate existing inequalities in healthcare access and outcomes. To address cost barriers, stakeholders must explore innovative funding models, partnerships, and collaborations that can support the development and implementation of AI technologies. Moreover, demonstrating the potential return on investment for AI solutions through improved patient outcomes and operational efficiencies can encourage healthcare organizations to invest in these technologies.[112]

4.8. Interoperability issues

The integration of AI systems within the healthcare ecosystem often faces interoperability challenges. Different healthcare institutions may utilize various EHR systems and data formats, making it difficult for AI algorithms to access and analyze comprehensive patient data.[112,113] The lack of standardized data formats and communication protocols can hinder the seamless integration of AI tools into clinical workflows. To address interoperability challenges, stakeholders must collaborate to establish universal standards for data sharing and integration. Developing AI solutions that can adapt to diverse data sources while maintaining data integrity and security will be essential to overcoming this barrier.

4.9. Scalability of AI solutions

While AI models may perform well in controlled research settings, scaling these solutions for widespread clinical use poses significant challenges. Factors such as computational demands, infrastructure requirements, and resource

availability can limit the scalability of AI technologies.[114] Additionally, models that are effective in one clinical environment may not translate well to another due to variations in patient populations, treatment protocols, and healthcare systems. To enhance scalability, AI developers must focus on creating lightweight models that require fewer computational resources while maintaining accuracy. Leveraging cloud computing and distributed systems can also facilitate the deployment of AI solutions across different healthcare settings.[115]

4.10. Patient privacy and data security

The use of AI in healthcare raises significant concerns regarding patient privacy and data security. AI algorithms often require access to sensitive patient information, and any breaches or misuse of this data can have serious consequences.[116] Ensuring compliance with data protection regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States, is crucial for maintaining patient trust. Additionally, the implementation of robust cybersecurity measures is essential to safeguard patient data from potential threats. Developing AI solutions that prioritize privacy by design—such as using federated learning techniques that allow model training without sharing raw data—can help mitigate these concerns.[116,117]

4.11. Clinical acceptance and change management

The successful implementation of AI technologies in oncology requires not only technological readiness but also cultural acceptance within healthcare organizations. Clinicians may be resistant to adopting new technologies, especially if they perceive them as a threat to their expertise or if they lack confidence in the reliability of AI-driven recommendations. Change management strategies that involve engaging stakeholders, providing adequate training, and demonstrating the value of AI in enhancing clinical decision-making are essential for fostering acceptance. Building a culture of collaboration between AI technologists and healthcare providers will also facilitate the integration of AI solutions into everyday practice.[118,119]

4.12. Long-term sustainability and maintenance

AI models require ongoing maintenance and monitoring to ensure their continued effectiveness and relevance. As treatment guidelines, clinical practices, and patient populations evolve, AI algorithms must be updated to reflect these changes.[120] However, the long-term sustainability of AI solutions can be challenging due to resource constraints and the need for continuous investment in technology and personnel. Healthcare organizations must develop strategies for the ongoing support and maintenance of AI systems, including regular performance evaluations and updates based on new data and clinical insights.[121]

4.13. Ethical decision-making and accountability

The use of AI in clinical decision-making raises ethical questions about accountability and responsibility. In cases where AI-driven recommendations lead to adverse outcomes, it may be unclear who is accountable—the AI developers, the healthcare providers, or the institutions using the technology. Establishing clear guidelines for ethical decision-making and accountability in AI applications is essential to address these concerns. Engaging ethicists, legal experts, and healthcare professionals in discussions about the ethical implications of AI can help create frameworks that guide responsible AI use in oncology.[104,122]

4.14. Public perception and trust

The acceptance of AI technologies in healthcare also hinges on public perception and trust. Patients may have concerns about the accuracy and reliability of AI-driven recommendations, fearing that their care may be compromised by technology. Building public trust in AI applications requires transparent communication about how AI works, its potential benefits, and the safeguards in place to protect patient welfare. Initiatives aimed at educating patients and the general public about the role of AI in cancer care can help demystify the technology and foster a more positive perception.[104,123]

4.15. Integration with existing treatment protocols

Integrating AI solutions with established treatment protocols can be complex, as healthcare providers often have ingrained practices based on years of experience. Introducing AI-driven recommendations may require significant adjustments to existing workflows and clinical guidelines. Ensuring that AI tools complement rather than disrupt established practices is vital for acceptance. Engaging clinicians in the development phase can ensure that AI solutions are designed to fit within current treatment protocols while enhancing them.[120,124]

5. Future perspectives

The future of AI in targeted anticancer drug delivery holds immense promise, with several innovative directions poised to reshape cancer treatment paradigms. As technology advances, the integration of AI into oncology will likely lead to more personalized, effective, and efficient therapies.

5.1. Personalized nanomedicine

One of the most significant future perspectives is the continued evolution of personalized medicine. AI has the potential to analyze an individual's genetic makeup, tumor biology, and treatment history to develop tailored therapeutic strategies. By leveraging multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, AI can identify specific biomarkers that predict treatment responses. This personalized approach not only enhances the efficacy of targeted therapies but also minimizes adverse effects, ultimately improving patient outcomes. Innovations in nanotechnology, coupled with AI, will drive advancements in personalized nanomedicine. AI algorithms will enable the design of smart nanoparticles that can deliver drugs directly to tumor sites while responding to specific tumor microenvironment stimuli,

such as pH or temperature changes. This targeted approach will improve drug bioavailability and therapeutic efficacy while minimizing systemic toxicity. Furthermore, AI-driven simulations will optimize nanoparticle formulations, ensuring that they are tailored to specific tumor characteristics, thus enhancing treatment precision.

5.2. Enhanced drug discovery

Innovations in AI-driven drug discovery are expected to expedite the identification of novel therapeutic agents and optimize existing drugs for enhanced efficacy. ML algorithms can analyze vast chemical libraries, predict compound interactions, and identify potential drug candidates more rapidly than traditional methods. Furthermore, AI can facilitate the design of combination therapies by predicting synergies between drugs, which could lead to more effective treatment regimens for complex cancers.

5.3. Real-time data analytics

The integration of AI with wearable technologies and mobile health applications will enable real-time monitoring of patient responses to treatment. Continuous data collection from devices measuring vital signs, symptoms, and treatment side effects will provide clinicians with valuable insights into patient health. AI algorithms can analyze this data to adjust treatment plans dynamically, ensuring that therapies remain effective and responsive to patients' needs throughout the treatment process.

5.4. Advanced predictive analytics for treatment planning

Predictive analytics powered by AI will revolutionize treatment planning in oncology. Future AI models will leverage vast datasets to predict not only how a patient will respond to a specific therapy but also the likelihood of adverse effects over time. By simulating various treatment scenarios and outcomes, AI can assist clinicians in selecting the most effective treatment regimens while minimizing risks. This predictive capability will extend to identifying optimal drug combinations, enabling oncologists to tailor therapies that significantly enhance treatment efficacy against complex tumor types.

5.5. Integration of AI with robotics

The combination of AI with robotic systems holds potential for enhancing precision in drug delivery. Robotic-assisted drug delivery systems can utilize AI algorithms to navigate complex tumor environments and accurately deliver therapies directly to cancer cells. This targeted approach minimizes damage to surrounding healthy tissues and increases the likelihood of treatment success.

5.6. Collaborative AI systems

Future advancements may also involve collaborative AI systems that integrate insights from multiple sources, including clinical data, research literature, and patient-reported outcomes. By synthesizing information from diverse datasets, these systems can provide comprehensive treatment recommendations, facilitating multidisciplinary collaboration among healthcare professionals and improving the overall quality of care.

5.7. Ethical AI and bias mitigation

As the use of AI in oncology expands, future perspectives will need to address the ethical implications of AI applications. Researchers and clinicians will focus on developing frameworks to ensure fairness and equity in AI algorithms, mitigating biases that may arise from uneven data representation. Efforts will include creating diverse datasets that accurately reflect patient demographics, ensuring that AI-driven recommendations are applicable to all populations. Ethical considerations will also encompass data privacy and security, reinforcing the need for transparent practices in AI utilization.

6. Conclusion

The integration of AI in targeted anticancer drug delivery has witnessed remarkable advancements in recent years, significantly enhancing the efficacy and precision of cancer treatments. Innovations such as ML algorithms, deep learning techniques, and advanced imaging analysis have empowered researchers to analyze complex biological datasets and identify patient-specific characteristics that influence treatment responses. These advancements have led to the development of personalized treatment strategies, allowing for more effective targeting of therapies to cancer cells while minimizing harm to healthy tissues. However, several challenges remain in the widespread implementation of AI-driven targeted drug delivery systems. Data quality and availability are critical hurdles, as the success of AI models heavily relies on large, well-curated datasets that accurately represent diverse patient populations and tumor biology. Additionally, issues related to the interpretability of AI algorithms pose significant concerns, as clinicians must understand and trust the decision-making processes behind AI-driven recommendations. Furthermore, the integration of AI technologies into existing clinical workflows requires careful consideration of regulatory frameworks and ethical implications to ensure patient safety and data privacy. Additional explorations should focus on enhancing data sharing and collaboration among institutions to create comprehensive databases that reflect diverse cancer types and treatment responses. Moreover, the development of explainable AI models will be crucial in fostering clinician trust and facilitating the adoption of AI-driven solutions in clinical practice. ML algorithms analyze complex genomic and clinical datasets to identify patterns that help predict patient responses to treatments. Deep learning techniques, particularly CNNs, improve the accuracy of tumor detection and characterization through advanced imaging analysis. Real-time monitoring and adaptive learning allow for dynamic adjustments in drug dosages and treatment schedules based on patient responses. Additionally, AI optimizes nanoparticle design for drug delivery, expedites drug discovery through predictive analytics, and integrates multi-omics data to provide a comprehensive understanding of tumor biology.

Author contributions

Danial Khorsandi: writing – review & editing; Amin Farahani: writing – review & editing; Atefeh Zarepour: writing – review & editing; Arezoo Khosravi: writing – review & editing; Siavash Iravani: supervision, conceptualization, writing – review & editing; Ali Zarrabi: supervision, writing – review & editing.

Conflicts of interest

Author(s) declare no conflict of interest.

Data availability

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

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