

Advances in Tracking Anticancer Drugs to Their Targeted Site: A Review

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Abstract:

The targeted delivery of chemotherapy drugs to their specific locations in a tumor is a cornerstone of current oncology for high therapeutic efficacy and reduced systemic toxicity. Recent breakthroughs in nanotechnology, molecular and imaging modalities have revolutionized the field of targeted delivery and tracking technology. With these new advances, the real-time tracking of drug routes and increased accuracy in tumor localization have become a reality.

This review has discussed advanced targeting approaches, such as passive and active targeting, multifunctional theranostics and stimuli-responsive platforms to describe their mechanism, clinical utility and challenges. In addition, tracking modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET) have played a key role in noninvasive tracking and have been discussed in detail. Challenges such as immune clearance, tumor heterogeneity and translational barriers have been discussed, and new avenues through artificial intelligence, biomarker-guided approaches and therapeutic platforms have been explored in detail. Emerging studies have also shed new light on targeted oncology, combining biomarker discovery and new therapeutic platforms with individualized patient requirements. A thorough analysis reveals an interdisciplinary obstacle in developing targeted delivery technology and shaping future cancer therapy.

Key words: theranostic, magnetic resonance imaging (MRI), positron emission tomography (PET), fluorescence imaging, artificial intelligence and machine learning in oncology

التطورات في تتبع الأدوية المضادة للسرطان إلى مواقعها المستهدفة

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الخلاصة:

يُعدّ التوصيل المستهدف لأدوية العلاج الكيميائي إلى مواقعها المحددة داخل الورم الأساس في علم الأورام الحديث، حيث يسهم في تحقيق فعالية علاجية عالية وتقليل السمية الجهازية. وقد أحدثت التطورات الحديثة في مجالات تقنية النانو، والوسائل الجزيئية، وتقنيات التصوير، ثورة في مجال تقنيات التوصيل المستهدف وتتبع الأدوية. وبفضل هذه الابتكارات، أصبح تتبع مسارات الأدوية في الوقت الفعلي وتحديد مواقع الأورام بدقة متزايدة واقعا ملموسا. حيث تناولت هذه المراجعة الأساليب المتقدمة في الاستهداف، مثل الاستهداف البسيط والنشط، والتشخيص العلاجي المتعدد الوظائف، والمنصات المستجيبة للمؤثرات، وذلك من خلال شرح آلياتها، واستخداماتها السريرية، والتحديات التي تواجهها. كما تم تسليط الضوء على وسائل التتبع بدون جراحة، مثل التصوير بالرنين المغناطيسي (MRI) والتصوير المقطعي بالإصدار البوزيتروني (PET)، لما لها من دور رئيسي في تتبع العقاقير داخل الجسم. علاوة على ذلك، تم تناول التحديات التي تواجه تقنيات التوصيل المستهدف، مثل التخلص المناعي، وتغايرية الأورام، والعوائق التحولية، مع استكشاف آفاق جديدة من خلال الذكاء الاصطناعي، والنهج القائمة على المؤشرات الحيوية، والمنصات العلاجية المتطورة. كما سلطت الدراسات الناشئة الضوء على مستقبل علم الأورام المستهدف، حيث يتم الجمع بين اكتشاف المؤشرات الحيوية والمنصات العلاجية الحديثة وفقاً للاحتياجات الفردية للمرضى. يكشف التحليل العميق لهذا المجال عن تحدّيات متعددة التخصصات في تطوير تقنيات التوصيل المستهدف، مما يساهم في تشكيل مستقبل علاج السرطان.

الكلمات المفتاحية: التشخيص العلاجي، التصوير بالرنين المغناطيسي (MRI)، التصوير المقطعي بالإصدار البوزيتروني (PET)، التصوير المشع، الذكاء الاصطناعي وتعلم الآلة في علم الأورام

Introduction

Cancer remains a leading cause of death worldwide, necessitating ongoing innovation and refinement in therapeutic strategies. (1). However, one of the most significant challenges in treating cancer is delivering drugs to their specific target sites in tumors with less impact on surrounding healthy tissue. Conventional chemotherapeutic drugs have no such specificity, leading to systemic toxicity and low therapeutic efficacy. With the development of targeted drug delivery systems, oncological therapy has optimized efficacy and accuracy (2, 3). Over the past several decades, significant efforts have been made to develop methodologies for enhancing the tracking of anticancer drugs to their target sites in tumors. Biological, chemical, and physical methods have been designed to enhance specificity, minimize systemic exposure and improve therapeutic efficacy. Real-time monitoring of drug biodistribution and accumulation in living organisms is essential for evaluating *in vivo*

pharmacokinetics and for the development of optimized therapeutic strategies. (4, 5).

Nanotechnology has emerged as a key technology, enabling the development of drug carriers designed to match the unique characteristics of tumor biology. Advances in imaging techniques, such as magnetic resonance imaging (MRI), positron emission tomography (PET), and fluorescence imaging, have further enhanced the ability to track drug delivery systems non-invasively. Together, these innovations form the foundation of recent targeted oncology (6, 7). This review discusses the most important targeted drug delivery and tracking platforms, focusing on advanced targeted technologies. It also explores key challenges, including biological, technical, and translational barriers, while highlighting future directions in this rapidly evolving field, particularly the integration of artificial intelligence and personalized medicine.



Strategies for Drug Targeting

The development of drug delivery systems is driven by an understanding of tumor biology and the pharmacokinetics of anticancer drugs. These strategies fall into four main

categories: stimuli-responsive systems, multifunctional targeting systems, active targeting, and passive targeting, each with strengths and challenges (as shown in Table 1).

Table (1): Summary of targeting strategies, drug carriers and tracking modalities in anticancer therapy

Category	Subtypes/Examples	Description / Notes
Targeting techniques	Passive, active, ligand-mediated, pH-sensitive	Mechanisms that guide drugs to tumor sites
Carriers	Liposomes, polymeric nanoparticles, dendrimers	Vehicles used for drug encapsulation/delivery
Tracking tools	PET, SPECT, MRI, Optical imaging	Methods to monitor drug distribution in vivo

Passive Targeting

Passive targeting takes advantage of the enhanced permeability and retention (EPR) effect, a characteristic of tumor vasculature where leaky blood vessels and inadequate lymphatic drainage allow nanocarriers and macromolecular drugs to accumulate selectively within the tumor microenvironment⁽⁸⁾. This strategy has been widely applied in developing liposomal drug formulations such as Doxil®, where doxorubicin is encapsulated to reduce systemic toxicity while enhancing therapeutic efficacy. However, passive targeting is challenged by the variability of the EPR effect across different tumor types and individual patients. Current research is focused on optimizing nanocarrier design to improve EPR-dependent drug accumulation and address tumor-specific barriers⁽⁹⁾.

Active Targeting

Active targeting involves modifying drug carriers with ligands that specifically bind to receptors overexpressed on cancer cells. Common ligands used in this approach include antibodies, peptides and small molecules that recognize targets such as

folate receptors, HER2, and integrins. For example, trastuzumab-conjugated nanoparticles have been shown to selectively deliver chemotherapeutic drugs to HER2-positive breast cancer cells, improving both specificity and treatment efficacy⁽¹⁰⁾. While active targeting provides a clear advantage over passive targeting, the variability in receptor expression among patients underscores the importance of biomarker-driven personalized therapies⁽¹¹⁾.

Multifunctional Targeting Systems

Multifunctional targeting platforms integrate both passive and active targeting mechanisms with therapeutic and diagnostic capabilities. These "theranostic" systems facilitate real-time drug delivery while simultaneously monitoring therapeutic responses. For instance, nanoparticles that incorporate both imaging agents and anticancer drugs have been designed to track biodistribution and deliver therapy simultaneously. Optimizing these systems is crucial to maintaining a balance between multifunctionality and biocompatibility^(12, 13).



One example is a SPION–pyoverdine (PVD)–doxorubicin (DOX) conjugate, in which superparamagnetic iron oxide nanoparticles (SPIONs) are functionalized with the siderophore pyoverdine (PVD) and the chemotherapeutic agent doxorubicin (DOX). This conjugate was targeted to MUC1-expressing cancer cells through the incorporation of an anti-MUC1 aptamer. The multifunctional platform enabled both magnetic resonance imaging (MRI)-based diagnosis and targeted drug delivery. *In vitro* studies revealed enhanced cytotoxicity against MUC1-positive cancer cells, giving the potential of this SPION-based theranostic system for targeted cancer therapy ⁽¹⁴⁾.

Stimuli-Responsive Systems

Stimuli-responsive systems deliver therapeutic payload in response to specific external or internal stimuli, including temperature, pH, enzymes and light. Tumor tissue possesses particular characteristics, including an acid environment and high activity of enzymes, and can, therefore, be exploited for selective drug delivery. For instance, acid-sensitive polymer micelles and acid-sensitive liposomes destabilized at acid environments can enable the delivery of drugs in tumor environments. Nanoparticle stimuli, such as nanoparticles stimulated with light, offer additional options for controlling delivery but can introduce penetration depth and safety complications ⁽¹⁵⁾.

In a recent publication, Tiryaki et al. developed a new mechanism for the delivery of drugs in a controlled manner with a miniature capsule robot powered by magnetism-related technology, MRI (magnetic resonance imaging). With such a capsule, one can magnetically drive it to a target location in a living organism. Once at its target location, high-intensity focused ultrasound (HIFU) is utilized for the delivery

of a stored drug in a capsule. With MRI-guided drive and HIFU-delivered delivery, one can have a high level of accuracy for controlling both delivery timing and location, and therefore, therapeutic accuracy and systemic toxicity can both be enhanced ⁽¹⁶⁾.

Challenges in Targeting Strategies

Targeted drug delivery systems represent a promising advancement in cancer therapy, aiming to enhance therapeutic efficacy while minimizing off-target toxicity. However, numerous barriers impede their optimal performance. The inherited heterogeneity of tumor masses, characterized by diverse cellular populations and complex microenvironments, complicates the identification of a universal drug delivery target. This non-uniformity contributes to variability in therapeutic outcomes and presents a significant obstacle to effective treatment strategies ⁽¹⁷⁾.

Moreover, variability in receptor expression across different malignancies, and even within subpopulations of a single tumor, further reduces the efficacy of receptor-targeted therapies. Biological barriers, such as the blood-brain barrier (BBB), giving additional challenges to drug delivery, particularly in the treatment of central nervous system malignancies. The selective permeability of the BBB significantly restricts the transport of therapeutic agents, thereby necessitating the development of novel strategies to overcome this limitation ^(18, 19).

The successful formulation of targeted delivery systems requires evaluation in both preclinical and clinical settings to ensure efficacy and safety. Overcoming these obstacles will require continuous innovation and collaboration between multidisciplinary teams. Future therapeutic approaches should



focus on the development of adaptable targeting platforms capable of dynamically responding to the evolving tumor microenvironment ⁽²⁰⁾.

Tracking Techniques

The recent technological advances in analysis and imaging tools have facilitated clinicians and researchers in tracking the delivery and effectiveness of anticancer drugs in real-time. These techniques are essential for optimizing drug delivery systems and assessing therapeutic outcomes ⁽²¹⁾.

Imaging-Based Techniques

Magnetic Resonance Imaging (MRI)

MRI is a noninvasive imaging technique that provides detailed anatomical and functional insights. High-performance contrast agents, such as superparamagnetic iron oxide nanoparticles (SPIONs), are specifically designed for MRI applications. These nanoparticles possess unique magnetic properties that enhance signal contrast, enabling high-resolution imaging of drug biodistribution within the body. One of the key advantages of SPIONs is their ability to be engineered for targeted drug delivery by functionalizing their surfaces with specific ligands or coatings, which allows them to selectively bind to specific tissues or cells, such as tumors or inflamed areas. This targeted approach not only enhances drug visualization but also minimizes off-target effects and improves therapeutic precision ⁽²²⁾.

A recent study demonstrated the potential of SPIONs functionalized with a tumor-penetrating peptide and loaded with the chemotherapeutic agent paclitaxel. These SPION-based carriers efficiently delivered paclitaxel directly to tumor cells and significantly inhibited tumor growth in mouse models. Additionally, the magnetic

properties of SPIONs enabled real-time monitoring of drug distribution and accumulation within tumors by using MRI, allowing for simultaneous therapy and imaging. This dual functionality highlights the potential of SPION-based systems in improving the accuracy and effectiveness of cancer treatment ⁽²³⁾.

Recent innovations, such as hyperpolarized MRI, offer even greater sensitivity, making it possible to track smaller-scale drug carriers with increased precision ⁽²⁴⁾.

Positron Emission Tomography (PET)

PET imaging employs radiolabeled compounds to assess the pharmacokinetics and biodistribution of anticancer drugs. One of the commonly used radiotracers is ¹⁸F-fluorodeoxyglucose (FDG), which plays a crucial role in positron emission tomography (PET) by precisely visualizing tumor metabolic activity. FDG's ability to highlight glucose consumption makes it an effective tool for identifying tumor regions and actively engaging in drug processing, as well as offering valuable insights into drug uptake and efficacy. Beyond FDG, ⁸⁹Zr-labeled nanoparticles have gained significant attention in both clinical and preclinical research. These nanoparticles are designed to target specific sites within tumors, enabling researchers to track drug retention and distribution over time by using PET imaging. The long half-life of ⁸⁹Zr allowed for extended monitoring, making it particularly useful for studying slow-release drug formulations and long-term therapeutic effects ⁽²⁵⁾.

A recent study explored the use of ⁸⁹Zr-labeled high-density lipoprotein (HDL) nanoparticles in PET imaging for patients with esophageal cancer. The study demonstrated that these nanoparticles



accumulated in tumors, enabling visualization and quantification of tumor-associated macrophages. This approach provides valuable insights into the tumor microenvironment and helps in monitoring therapeutic responses ⁽²⁶⁾.

By the integration of imaging and therapeutic functions, radiotracers like FDG and ⁸⁹Zr-labeled nanoparticles enhance our understanding of drug delivery mechanisms and treatment efficacy, paving the way for more precise and personalized cancer therapies ⁽²⁷⁾.

Fluorescence Imaging

Fluorescence imaging utilizes fluorescent dyes or proteins conjugated with drugs or carriers for visualization. Near-infrared fluorescence (NIRF) imaging is particularly advantageous due to its deep tissue penetration and reduced background signal. This technique has been widely used to track nanoparticle-based drug delivery systems in vivo, so providing real-time insights into drug biodistribution ⁽²⁸⁾.

A recent study by Park et al. introduced luminescent porous silicon nanoparticles (LPSiNPs) to enhance drug delivery and improve the tracking of doxorubicin. These nanoparticles, composed of a silicon core and a dextran coating, were specifically designed to extend the circulation time of loaded drugs within the body. When exposed to near-infrared (NIR) light, LPSiNPs emit fluorescence, allowing researchers to monitor the drug's metabolism in real-time within living organisms. The study revealed that these nanoparticles not only prolonged drug circulation but also enabled real-time tracking of drug distribution, demonstrating their potential to enhance targeted cancer therapies. Advances in fluorophore design continued to expand the applicability of this

method for increasingly complex biological systems ⁽²⁹⁾.

Hybrid Imaging Techniques

Hybrid imaging modalities, such as positron emission tomography/magnetic resonance imaging (PET/MRI) and single-photon emission computed tomography/computed tomography (SPECT/CT), integrate the complementary strengths of individual imaging techniques to provide comprehensive diagnostic information. PET/MRI combines the superior soft tissue contrast and functional imaging capabilities of MRI with the metabolic and molecular insights offered by PET. This fusion facilitates the precise anatomical localization of metabolic activity, thereby enhancing disease detection and characterization, particularly in the fields of oncology and neurology ⁽³⁰⁾.

In a recent study, Xiuyan et al. developed dual-modality PET/MRI probes designed to target acidic tumor microenvironments. These probes employed ultra-small superparamagnetic iron oxide nanoparticles (USPIOs) conjugated with a pH-responsive peptide, enabling selective binding to acidic tumor regions. This innovative design allowed for the simultaneous acquisition of metabolic and anatomical data, providing a more comprehensive understanding of the tumor microenvironment. Their findings demonstrated that these probes effectively delineated areas of tumor acidity, facilitating the assessment of drug delivery efficiency and offering valuable insights into tumor heterogeneity. Moreover, the study underscored the potential of PET/MRI hybrid imaging to advance multidimensional analyses of drug delivery systems in oncology ⁽³¹⁾.



Similarly, SPECT/CT merges the functional information obtained from SPECT with the high-resolution anatomical imaging of CT, significantly enhancing diagnostic accuracy, particularly in cardiology and bone imaging applications ⁽³²⁾. Meng et al. recently investigated the prognostic utility of SPECT/CT in patients with bone metastases, evaluating its role in predicting therapeutic responses to strontium-89 (⁸⁹Sr) chloride, a radiopharmaceutical used for palliative treatment of metastatic bone disease. Their analysis revealed that specific SPECT/CT-derived parameters, including the number of metastatic lesions and radiotracer uptake characteristics, served as reliable and independent predictors of poor therapeutic outcomes. These findings highlight the value of SPECT/CT in assessing tumor burden, evaluating radiopharmaceutical distribution, and informing personalized treatment strategies ⁽³³⁾.

Together, hybrid imaging systems such as PET/MRI and SPECT/CT provide critical multidimensional insights into the tumor microenvironment, thereby offering powerful tools for evaluating complex disease processes and optimizing drug delivery assessments.

Challenges and Limitations in Tracking Techniques

The advancements in drug delivery and tracking technologies face several challenges that hinder their widespread adoption and clinical success. These challenges can be broadly classified into biological, technical, and translational barriers, each requiring a tailored approach to overcome.

Biological Barriers

Tumor Microenvironment Heterogeneity

The tumor microenvironment (TME) is a heterogeneous and complex environment

comprising stromal cells, immune cells, extracellular matrix and cancer cells. Heterogeneity in the density of blood vessels, pH, and oxygen availability in TME generate enormous obstacles to the uniform distribution of drugs. For example, hypoxia generates challenges for nanoparticles to penetrate and subsequently compromise the therapeutic efficacy. To counteract such obstacles, drug delivery platforms must be designed to dynamically address the changes in TME ⁽³⁰⁾.

A recent study performed by Yang et al. discussed the effect of hypoxia in tumor regions, that limit nanoparticles infiltration as well as reducing their therapeutic effectiveness. In a new nanosystem, an oxaliplatin prodrug was first conjugated with HSA to form HO complexes and then cross-linked with Ce6-conjugated HSA (HC) through a hypoxia-responsive azobenzene linker. Such nanosystems will be disassembled in hypoxia microenvironments in tumor regions, thus improving drug delivery and therapeutic effectiveness. The new nanosystem exhibited deep infiltration in tumors and significantly increased therapeutic efficacy as well as overcoming hypoxia-related barriers in cancer therapy ⁽³⁴⁾.

Immune System Clearance

The immune system naturally detects and eliminates foreign particles, including drug carriers, which leads to rapid clearance by the mononuclear phagocyte system (MPS). This process reduces drug bioavailability and diminishes targeting efficiency. Strategies like PEGylation and stealth nanoparticles have been developed to have shown promise in evading immune recognition, but they are not always fully effective ⁽³⁵⁾.



A study by Verhoef and Anchordoquy examined the role of PEGylation in drug delivery systems. While PEGylation is widely used to improve the pharmacokinetics of therapeutic agents by enhancing solubility and extending circulation time. The study highlighted several drawbacks. For instance, PEGylation has been associated with reduced cellular uptake and lower therapeutic efficacy. Additionally, some patients develop anti-PEG antibodies, which can accelerate the clearance of PEGylated compounds and diminish their intended benefits. These findings suggest that while PEGylation offers certain advantages, it may not be universally effective and, in some cases, could even hinder drug delivery⁽³⁶⁾.

To overcome immune clearance, biomimetic approaches are being explored, such as coating nanoparticles with membranes derived from red blood cells or platelets. These strategies aimed to enhance drug carrier stability and prolong circulation time in the bloodstream⁽³⁷⁾.

Technical Challenges

Imaging Resolution and Sensitivity

Despite significant advancements, imaging techniques still face limitations in resolution, sensitivity and depth penetration. For instance, fluorescence imaging struggles with deep tissue penetration, making it less effective for tracking drug distribution in large or deeply embedded tumors. To overcome this challenge, novel molecular fluorophores have been developed for deep-tissue bioimaging. These fluorophores operate in the near-infrared (NIR) spectrum, allowing for improved tissue penetration and reduced scattering. However, ongoing innovation in fluorophore design remains essential for further enhancement in imaging

depth and resolution as well as improving drug monitoring in deep-seated tumors⁽³⁸⁾.

Advancements in imaging probe development and the integration of multimodal imaging techniques are crucial for addressing these limitations and expanding the capabilities of imaging technologies in cancer research.

Scalability and Cost

The development of advanced drug delivery systems and imaging agents often requires complex manufacturing processes, resulting in high costs and scalability challenges. These factors can limit the widespread adoption and clinical implementation. Therefore, creating cost-effective and scalable solutions is crucial for ensuring broader accessibility and integration into medical practice⁽³⁹⁾.

Translational Barriers

Regulatory challenges

The development of novel drug delivery systems and imaging technologies is regulated by frameworks designed to ensure safety, efficacy and biocompatibility. These regulations require extensive preclinical and clinical evaluations, often causing significant delays in bringing innovative solutions to clinical practice. For example, in the U.S., the Food and Drug Administration (FDA) mandates rigorous testing to evaluate new nanomedicine pharmacokinetics, toxicity and therapeutic potential, which can result in prolonged development timelines. Additionally, the complexity of these advanced systems makes it difficult to standardize assessment methods, balance safety with innovation, and account for the unique characteristics of novel molecular designs^(40,41).



Variability in Patient Responses

Interpatient physiological variability, including differences in immune responses, tumor receptor expression and metabolic processes poses a significant challenge to the widespread adoption of targeted drug delivery systems. These biological variations contribute to differences in therapeutic efficacy, meaning a treatment that works well for one patient may be less effective for another. To address this issue, personalized medicine is emerging as a transformative approach that tailor's treatments to individual patient profiles. This strategy leverages an advanced diagnostic tool, such as genomic sequencing and biomarker analysis, to identify patient-specific factors that influence drug response ⁽⁴²⁾.

However, the successful implementation of personalized medicine requires substantial clinical infrastructure, including specialized equipment, trained professionals and sophisticated data integration systems. Despite these technical and logistical challenges, personalized therapeutic approaches hold great promise for enhancing treatment effectiveness and minimizing adverse effects by aligning interventions with each patient unique molecular and physiological characteristics ⁽⁴³⁾.

Future Perspectives

The continuous advancement of drug delivery systems and tracking methodologies is shaping the future of cancer therapy. Innovations in technology and interdisciplinary approaches are opening new pathways to overcome challenges in targeted oncology ⁽⁴⁴⁾.

Artificial Intelligence and Machine Learning in Oncology

Artificial intelligence (AI) and machine learning (ML) are revolutionizing cancer

research by enabling predictive models for drug delivery and therapeutic efficacy. These advanced tools analyze vast datasets to uncover patterns in tumor biology and patient responses, thus helping to optimize drug delivery strategies. A recent study by the National Institutes of Health (NIH) introduced an AI-based tool designed to predict patient responses to immunotherapy drugs, particularly immune inhibitors, by using routine clinical data. Analyzing extensive datasets revealed that this model identifies key patterns in tumor biology and patient reactions, thus allowing for the development of more personalized treatment plans. The integration of AI and ML in oncology not only facilitates the creation of predictive models but also accelerates the discovery of novel therapeutic targets, ultimately leading to more effective and individualized cancer treatments ⁽⁴⁵⁾.

AI-driven algorithms are also being used to enhance imaging technologies, improving both the accuracy and efficiency of drug tracking. This advancement enables more precise monitoring of drug distribution and facilitates personalized treatment adjustments based on real-time insights. As a result, incorporating AI into imaging modalities holds significant promise for developing targeted therapies and optimizing clinical outcomes ⁽⁴⁶⁾.

Advancements in Theranostic Systems

Theranostic systems integrate both therapeutic and diagnostic functions within a single platform. These systems enable real-time monitoring of drug distribution, tumor response and potential toxicity. For instance, nanoparticles that combine therapeutic drugs with imaging agents allow clinicians to visualize treatment progress and make dynamic adjustments, thus paving the way for personalized medicine ⁽⁴⁷⁾.



This dual functionality allows for continuous adaptation of treatment regimens based on individual patient responses, thus ultimately improving the precision and effectiveness of cancer therapies. The integration of therapeutic and diagnostic capabilities within a single nanoparticle platform marks a significant advancement in personalized medicine, offering tailored treatment strategies that can be modified in real-time according to the unique characteristics of each patient disease ⁽⁴⁸⁾.

Gene-Editing Technologies

The emergence of gene-editing technologies like CRISPR-Cas9 has created new possibilities for targeted cancer therapies. This innovative approach enhances the effectiveness of anticancer drugs while minimizing off-target effects. Recent advancements have demonstrated the potential of combining CRISPR-Cas9 with nanoparticle-based delivery systems to achieve precise and efficient gene editing within tumors ⁽⁴⁹⁾.

For example, lipid nanoparticles have been successfully used to deliver CRISPR-Cas9 components directly to cancer cells, leading to significant gene-editing efficiency and inhibiting tumor growth. This strategy not only improves the accuracy of gene editing but also enables the modulation of the tumor microenvironment, thus ultimately enhancing therapeutic outcomes. Integrating CRISPR-Cas9 with advanced drug delivery platforms presents a promising avenue for developing personalized cancer treatments ⁽⁵⁰⁾.

Bioprinting and Tumor-on-a-Chip Models

Bioprinting and tumor-on-a-chip technologies are emerging as valuable tools in the preclinical testing of drug delivery

systems. These advanced models closely replicate the complexity of human tumors, thus allowing researchers to assess the efficacy and safety of targeted therapies in controlled environments. For instance, a study by Steinberg et al. introduced a fully 3D-printed tumor-on-a-chip device capable of sustaining patient-derived multicellular structures for extended periods, thus enabling multiple drug screening tests. This platform provides an environment that closely mimics *in vivo* tumor conditions and offers more predictive insights into therapeutic outcomes ⁽⁵¹⁾.

Similarly, advancements in bioprinting have led to the development of three-dimensional cancer-on-a-chip platforms that enhance biomimicry and improve the predictability of therapeutic performance. These hybrid platforms represent a new generation of sophisticated 3D tumor models, thus significantly improving the evaluation of drug delivery systems. By integrating bioprinting with microfluidic technologies, these models allow for precise spatial and temporal control over cell and nutrient distribution as well as effectively replicating the physiological conditions of human tissues. Such advancements have the potential to greatly reduce the time and cost associated with developing new cancer treatments by providing more accurate and reliable preclinical testing platforms ⁽⁵²⁾.

Innovations in Imaging Modalities

Emerging imaging technologies, including multimodal and hybrid techniques, are improving the resolution and sensitivity of drug-tracking systems. Advances in PET/MRI and fluorescence/photoacoustic imaging provide deeper insights into drug behavior *in vivo*. These innovations hold significant promise for studying deep-seated tumors and metastases ⁽⁵³⁾.



Sustainability and Cost-Effectiveness

As the field advances, ensuring the sustainability and affordability of innovative drug delivery and tracking systems is crucial. Collaborative efforts among researchers, policymakers, and industry stakeholders are necessary to develop cost-effective technologies that can be widely adopted in clinical practice, particularly in resource-limited settings ⁽⁵⁴⁾.

Precision Medicine and Biomarker Discovery

The integration of biomarkers into targeted drug delivery systems is expected to enhance their specificity and efficacy. Advances in proteomics, genomics and metabolomics enable the identification of novel biomarkers that can guide treatment decisions. Such personalized approaches hold promise for improving patient outcomes and reducing treatment-related toxicity ⁽⁵⁵⁾.

Conclusion

This review has highlighted the diverse strategies, advanced technologies, challenges and obstacles in passive and active targeting systems that contributed to the targeted drug therapy. Translational barriers, including regulatory complexities and patient variability, further complicate these systems development and clinical adoption. However, emerging technologies like artificial intelligence hold immense potential to address these challenges and transform the field of cancer therapy. Integrating biomarker-driven approaches and personalized medicine frameworks is paving the way for highly specific and effective cancer treatments. Accordingly, as research progresses, interdisciplinary collaboration among scientists, clinicians, and industry stakeholders will be vital to achieving sustainable, scalable, and accessible solutions in targeted drug delivery and

tracking. Through these collective efforts, the promise of precision oncology can be fully realized, significantly improving patient outcomes and revolutionizing cancer care.

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