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REVIEW

Precision Nanomedicine for Cancer: Innovations, Strategies, and Translational Challenges

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Abstract: As nanotechnology advances rapidly, it has propelled nanomedicine into a revolutionary frontier for anticancer therapy. This review comprehensively analyzes the core principles, key innovations, and strategic approaches driving the development of targeted nanotherapeutics against tumors. We elucidate the distinctive properties of nanoscale drug delivery systems (eg, liposomes, polymeric nanoparticles, inorganic nanoparticles, and hybrid systems) and their capacity to be designed to surmount the constraints of traditional cancer treatments by potentially augmenting drug specificity, bioavailability, and minimizing systemic toxicity, with some nanocarriers (eg, liposomal doxorubicin) already approved for clinical use. With a focus on both the enhanced permeability and retention (EPR) effect-mediated passive targeting and ligand-based active targeting mechanisms employing peptides, aptamers, and antibodies, we investigate how these nanocarriers are engineered for efficient tumor-targeted drug delivery. The review further delves into the understanding of nano-bio interactions (eg, size-dependent cellular uptake) and their interplay with cancer biology. We discuss how this knowledge, alongside the rational design of stimuli-responsive and multifunctional "smart" nanoplatforms, informs the development of more precise and effective therapeutic strategies. Finally, we address the ongoing challenges in clinical translation, such as patient heterogeneity and physiological barriers, and emphasize that comprehending these aspects is pivotal for guiding future translational research towards the realization of truly patient-centric nanomedicines.

Keywords: targeted nanomedicine, cancer therapy, nanocarriers, drug delivery systems, active and passive targeting

Introduction

Cancer presents a profound and escalating menace to global health, underscoring an imperative demand for innovative and robust therapeutic strategies.[1,2] Traditional modalities of cancer treatment, including radiation and chemotherapy, are often characterized by a lack of precision. This deficiency leads to the onset of severe side effects and considerable damage to non-malignant tissues. The non-specific nature of these conventional therapies underscores the pressing requirement for targeted drug delivery systems. Such systems are designed to discriminate between cancerous and healthy cells, thereby minimizing collateral damage to the latter while effectively neutralizing the former. This targeted approach is essential to enhance the therapeutic index and improve patient outcomes in the ongoing struggle against cancer.[3–5]

Advancements in nanocarrier design have been significantly propelled by our growing understanding of cancer biology and the intricate dynamics at play between nanoparticles and biological systems, as illustrated in Figure 1. In nanomedicine, targeting strategies are divided into passive and active. Passive targeting uses the EPR effect to concentrate nanoparticles in cancer tissues due to their increased permeability. Active targeting involves decorating nanocarriers with specific ligands like proteins, peptides, antibodies, or aptamers that bind selectively to antigens or receptors overexpressed on cancer cells.[4–8] This selective binding enhances internalization and retention within the

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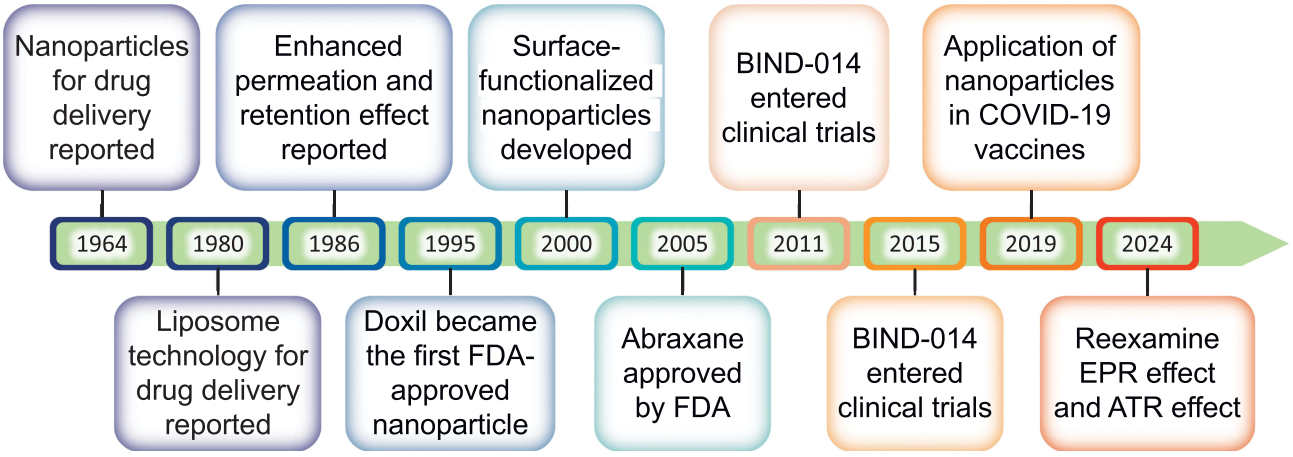

Figure 1 Milestones in Cancer Nanomedicine. The field has evolved through pivotal innovations, with key developments marking transformative phases in its progression.

tumor, optimizing treatment efficacy and minimizing side effects. This dual targeting strategy allows for more precise drug delivery to cancer cells, improving therapeutic outcomes in cancer treatment.[9–13]

This review covers the basics, innovations, and advancements in targeted nanomedicine for cancer. It examines different nanocarriers like polymeric, inorganic, liposomal, and hybrid systems for delivering therapeutic agents to cancer tissues. It also discusses ligand-based targeting with peptides, aptamers, and antibodies to improve drug delivery effectiveness. The review aims to inform and inspire dialogue among professionals in the cancer field, emphasizing nanomedicine's role in precision medicine, personalization, and its role in advancing minimally invasive interventions for enhanced tumor control and reduced systemic toxicity.

Nanocarriers in Cancer Therapy

In 1955, H. Jatzkewitz made a seminal contribution to the nascent field of nanoparticle therapeutics by developing the inaugural polymeric drug binder.[14] In a pioneering study published in Zeitschrift für Naturforschung (1955), Peptamin (glycyl-L-leucyl-mescaline) was conjugated with the plasma volume expander polyvinylpyrrolidone, establishing an innovative depot formulation for the bioactive primary amine mescaline.[15] As the field progressed into the 1960s, the nascent explorations into nanotechnology were marked by the discovery of liposomes, spherical lipid bilayer structures colloquially referred to as lipid vesicles.[16] Couvreur and associates pioneered the investigation into the lysosomal processing of poly(alkyl cyanoacrylate) nanoparticles, demonstrating their rapid biodegradation via lysosomal enzymes in 1977. In this year, Couvreur and associates unraveled the lysosomal impact of nanoparticles. This discovery initiated the first generation of rapidly biodegradable acrylic nanoparticles, leveraging the hydrolytic environment of the endo-lysosomal compartment for controlled drug release.[17] Cumulatively, these transformative advances in polymeric drug conjugates and liposomal systems established the foundation of nanocarrier technology,[18] enabling subsequent innovations in targeted drug delivery.

Liposomes, as a category of lipid-based nanoparticles, are renowned for their exceptional biocompatibility but are not without their drawbacks, such as susceptibility to drug leakage and challenges with storage stability. In stark contrast, polymer nanoparticles, or polymeric nanoparticles, offer a compelling solution to these issues, demonstrating superior encapsulation capacities and enhanced stability. As illustrated in Figure 2, the basic architecture of a liposome serves as a versatile platform for extensive functionalization, leading to several advanced types with distinct structural and functional properties. Conventional liposomes provide passive targeting but are rapidly cleared by the mononuclear phagocyte system (MPS). PEGylated liposomes feature a surface coating of polyethylene glycol (PEG) that confers steric stabilization, reduces opsonization, and prolongs systemic circulation—exemplified by the clinical success of Doxil®. Ligand-functionalized liposomes (Immunoliposomes) are engineered by conjugating antibodies, peptides, or other ligands to the surface, enabling active targeting to specific cell surface receptors. Finally, stimuli-responsive liposomes are designed with lipids or linkers that undergo structural changes in response to specific triggers, resulting in controlled,

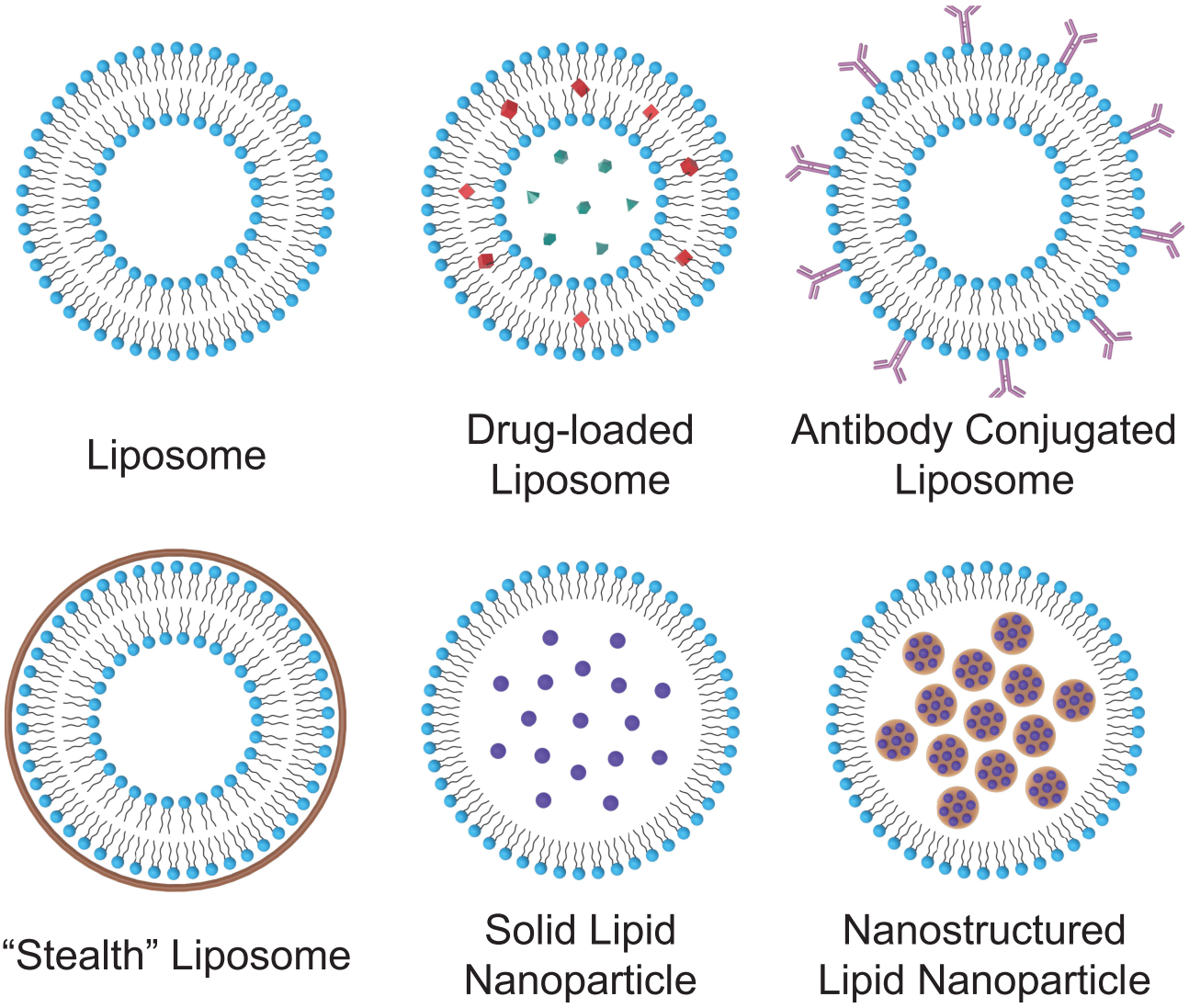

Figure 2 Liposomes serve as the evolutionary foundation for lipid nanoparticles (LNPs), offering a versatile nanomedicine delivery platform. Their advanced variants—such as solid-lipid nanoparticles, nanostructured carriers, and cationic lipid complexes—exemplify sophisticated engineering with enhanced structural robustness.

on-demand drug release. However, polymer nanoparticles may present their own set of challenges, notably a decrease in biocompatibility. To address these limitations and to capitalize on the strengths of both types of nanoparticles, the scientific community has innovated a cutting-edge hybrid system. This system, known as polymer-lipid hybrid nanoparticles (PLHNPs),[19,20] integrates the beneficial attributes of both, leading to a nanocarrier that is biocompatible, stable during storage, capable of sustained drug release, minimal drug leakage, and features a small particle size along with advanced packaging capabilities. The efficacy of PLHNPs has not only met but often exceeded clinical expectations, leading to their adoption in a myriad of therapeutic applications and diagnostic endeavors. The structure of PLHNPs is composed of three key components: 1. A polymer core engineered for effective encapsulation of therapeutics with divergent solubility properties. 2. A lipid shell that endows the nanoparticles with biocompatibility and augmented stability. 3. An exterior lipid bilayer modified with polyethylene glycol (PEG) encapsulates the nanoparticle core. This configuration enhances structural integrity, prevents immune recognition, and prolongs systemic circulation duration.[21]

The versatility of PLHNPs extends to delivering diverse oncologic payloads and nucleic acid therapeutics, including siRNA and DNA. They also play a significant role in advanced therapeutic modalities like photothermal and photodynamic therapy, as well as in ultrasound applications. Studies are beginning to reveal the potential of PLHNPs in

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vaccine delivery, immunostimulation, imaging, and therapies involving alternative magnetic fields (AMF). As such, their utility is expanding within the dynamic and swiftly progressing medical field.[22]

In the recent past, the domain of drug delivery systems has witnessed remarkable progress, particularly with the advent of organic, inorganic, and hybrid nanoparticles serving as actively targeted carriers.[23] These innovations in drug delivery systems enhance chemotherapeutic efficacy by reducing particle size, improving permeability, solubility, and potency. Targeted delivery maximizes therapeutic impact and minimizes side effects. Advanced nanoparticles improve drug stability, toxicity management, and enable sustained release for controlled drug administration, potentially improving patient compliance and outcomes. Compared to traditional chemotherapy, these systems significantly boost the performance of therapeutic agents.[24] By offering a more nuanced and sophisticated approach to drug administration, these advancements are set to redefine the standards of cancer therapy, offering new hope to patients and healthcare providers alike.

Natural nanomedicines stand out due to their superior biocompatibility and biodegradability, which are particularly advantageous over their inorganic counterparts, thereby providing an elevated level of safety and physiological stability.[25] The realm of organic nanocarriers has expanded significantly, especially in the context of anti-tumor therapies, where their diverse responses to stimuli have garnered profound interest and extensive research. Organic nanocarriers encompass a range of substances, with polysaccharides, liposomes, and synthetic polymer nanocarriers being at the forefront.[26,27] Polysaccharides, as natural biopolymers, fulfill a multitude of functions across microorganisms, plants, and animals.[28] Homopolysaccharides like starch, cellulose, and glycogen, composed of at least ten different monosaccharides, are valued for their uniform structure, availability, biocompatibility, and biodegradability, making them effective nanocarriers. They are widely used in nanocarrier design for delivering and protecting bioactive compounds and drugs, and in targeted therapies using mechanisms like enzyme-mediated hydrolysis and pH-responsive triggering for precise drug delivery. Moreover, polysaccharide-based nanocarriers facilitate targeted therapeutic approaches through mechanisms such as enzyme-mediated hydrolysis and pH-responsive drug release, enabling precise delivery to diseased tissues. This functionality underscores the potential of natural nanomedicines in modern therapeutics, especially in combating cancer cells with heightened specificity and reduced off-target effects. The following sections provide a refined and organized overview of these advances, emphasizing the efficacy and applicability of natural nanomedicines in cancer treatment. This approach highlights the potential of natural nanomedicines in modern therapeutics, with the text providing an overview of their effectiveness against cancer cells. Here is a refined and organized summary:

Hyaluronic Acid (HA) Nanoplatforms: These CD44 receptor-targeted carriers exemplify significant progress in precision oncology therapeutics. These systems are meticulously engineered to integrate with potent anticancer agents, such as doxorubicin (DOX) and cisplatin (CDDP), facilitating their precise delivery to $CD44^{-}$ expressing breast cancer cells.[29] In 4T1 breast tumor models, HA micelles co-encapsulating DOX and CDDP exhibit enhanced therapeutic efficacy through acid-triggered payload release within the tumor microenvironment. This targeted strategy substantially potentiates drug internalization and tumor-suppressive effects relative to single-agent regimens. The system's pH-responsive release ensures drug liberation in low pH tumor areas. The HA-DOX-CDDP system also uses CD44-targeted delivery to increase treatment specificity and minimize damage to healthy cells. The biocompatibility and biodegradability of HA nanocarriers enhance their safety. Their negative surface charge helps evade the reticuloendothelial system for prolonged circulation. This dual mechanism of action bolsters the precision and potency of the therapeutic intervention, establishing a novel paradigm for CD44-overexpressing breast malignancies.

Boron Nitride (BN) Nanosheets: Crystalline boron nitride, including cubic (c-BN) and hexagonal (h-BN) polytypes, delivers diverse applications due to its unique structural and chemical properties. Hexagonal boron nitride, often referred to as white lithomalene, possesses a two-dimensional layered structure akin to graphite. However, its uniqueness stems from exceptionally strong covalent bonding within the B-N atomic network.[30] This material has garnered attention for its utility as a drug carrier in the medical field. Research has demonstrated that the introduction of gold particles into h-BN can lead to a decrease in proliferation rates in MCF-7 breast tumor cell cultures. This method exploits the capacity of hexagonal boron nitride (h-BN) to absorb photons and produce reactive oxygen species, key elements that contribute to the potency of photodynamic therapy. The multifunctional nature of h-BN, therefore, positions it as a promising agent for

Table 1 Different Types of Targeted Therapeutic Vectors

Drug Delivery System	Advantages	Disadvantages	Ref
Red Blood Cell Membrane-Camouflaged Nanoparticles Drug Delivery System	Prevents immune activation while enabling prolonged systemic circulation. Inherent biocompatibility and controlled biodegradation minimize accumulation-related toxicity.	Despite biomimetic camouflage capabilities, regulatory complexities persist. Critical processes including protein identification, purification, and conjugation could potentially be circumvented.	[32–34]
Hyaluronic Acid-Based Drug Nano Carriers Drug Delivery Systems	Suboptimal drug encapsulation efficacy and inflammation-induced serum lipid destabilization may compromise nanocarrier performance.	These agents can stimulate proliferative signaling via specific receptor binding, posing oncological risks in cancer patients.	[35,36]
Hexagonal Boron Nitride Nano sheet Drug Delivery System	Biocompatible nanocarrier platform with minimal toxicity and superior payload capacity.	Lipophilic properties impede functionality in aqueous physiological environments.	[37]
Polymer-Lipid Hybrid Nanoparticles Drug Delivery System	Core nanocarrier performance metrics: encapsulation stability, biocompatibility, and validated cell delivery efficacy.	Suboptimal drug encapsulation efficacy and inflammation-induced serum lipid destabilization may compromise nanocarrier performance.	[38,39]

advanced cancer therapies, offering not only targeted drug delivery but also potential for synergistic treatment modalities that combine photothermal and photodynamic effects.

LDH Nanoparticles: Zhang et al demonstrate the immunomodulatory capacity of alkaline-layered hydroxide nanostructures in neoadjuvant cancer immunotherapy. These nanoparticles effectively counteract intratumoral acidosis and disrupt cancer cell autophagy. Notably, LDH NPs capture tumor-derived antigens in vivo, suppressing malignant progression in melanoma and colon carcinoma models. The research underscores the role of LDH NPs as an immunomodulator and adjuvant, adept at "awakening" and bolstering the host's innate and adaptive immune responses, thereby presenting a promising avenue for solid tumor immunotherapy.[31]

Folate-Functionalized Nano-Formulations: In another pivotal study, Stella and team have harnessed the targeting prowess of folate in nano-formulations. They utilized a soy phosphatidylcholine tin nano-formulation, functionalized with folate, to co-deliver serine C and 10-hydroxyconamycin specifically to HeLa cells. This precision-targeted strategy has resulted in improved cellular absorption in both laboratory settings and within living organisms, along with a notable decrease in tumor load compared to the direct application of unbound medications. Folate-functionalized nanovectors expand precision tumor targeting modalities, delivering innovative interventions in oncology clinicians' armamentarium.

These studies collectively accentuate the burgeoning potential of targeted drug delivery systems in revolutionizing cancer treatment (Table 1). They underscore an imperative need for persistent research and development in this domain, as we stand on the cusp of transforming cancer therapeutics through precision medicine.

Fundamental Strategies for Targeting

Active Targeting

Active targeting represents a sophisticated therapeutic strategy wherein nanocarriers are functionalized with specific ligands (eg, peptides, aptamers, antibodies) designed to recognize and bind molecular signatures overexpressed on target cells. While passive targeting via the Enhanced Permeability and Retention (EPR) effect relies on physicochemical properties and pathological vessel permeability, active targeting introduces an additional layer of precision by leveraging ligand-receptor interactions.[32] Active targeting strategies introduce a layer of complexity that surpasses that of passive targeting. They offer a distinct advantage by enabling nanomaterials to reach distant sites within the body, which is particularly beneficial for treating hematologic malignancies, such as leukemias and lymphomas, and metastatic lesions where the EPR effect falls short.[33] This method holds the promise to transform oncology by offering a more precise and potent delivery system for therapeutic substances to malignant cells, including scenarios where conventional strategies leveraging the EPR effect might be ineffective.

Peptide Targeting

As a versatile implementation of active targeting, peptides—ranging from linear, branched, or cyclic structures (<50 amino acids)—offer unique advantages. Their compact size facilitates straightforward synthesis, enhances stability, and enables high-density nanoparticle functionalization, thereby amplifying targeting precision. Peptides, in their various forms—linear, branched, or cyclic and typically consisting of fewer than 50 amino acid residues—present a host of advantages due to their compact size.[34] The smaller stature facilitates straightforward synthesis and conjugation processes, endows them with superior stability and biocompatibility, and allows for heightened surface loading on nanoparticles, thereby boosting the precision of targeting. The convergence of these attributes with sophisticated phage display technologies has propelled peptides to the forefront of targeted nanoparticle delivery over the past decade.

A quintessential case in point is the RGD (Arg-Gly-Asp) peptide motif, which has been extensively studied for its tumor-targeting prowess.[35] RGD peptides demonstrate selective high-affinity binding to integrin αvβ3 — a receptor overexpressed on malignant cells and associated vasculature but limited in normal tissues.[36] A plethora of studies has attested to the efficacy of RGD-modified nanoparticles in delivering a medley of therapeutic agents, including siRNAs aimed at genes like Luc, LacZ, and VEGFR2, chemotherapeutic drugs such as DOX and paclitaxel, gadolinium oxide for radio sensitization, and agents for photothermal and photodynamic therapies, as well as proteins like TRAIL and viral vectors like AAV. These targeted delivery systems have curtailed metastasis, angiogenesis, and tumor growth while minimizing the toxicity to off-target tissues.[37–45]

The 3D structure of RGD peptides is crucial for their targeting effectiveness and how they move in the body. Cyclic RGD (cRGD) peptides, which are more stable and bind better to integrin αvβ3, have shown better performance than linear RGD peptides. Examples include cRGDfV, RGD-4C, and RGD10. Notably, "Cilengitide", a cyclic RGD penta-peptide, has reached Phase II and III trials, highlighting the importance of peptide shape in cancer treatment (Figure 3).

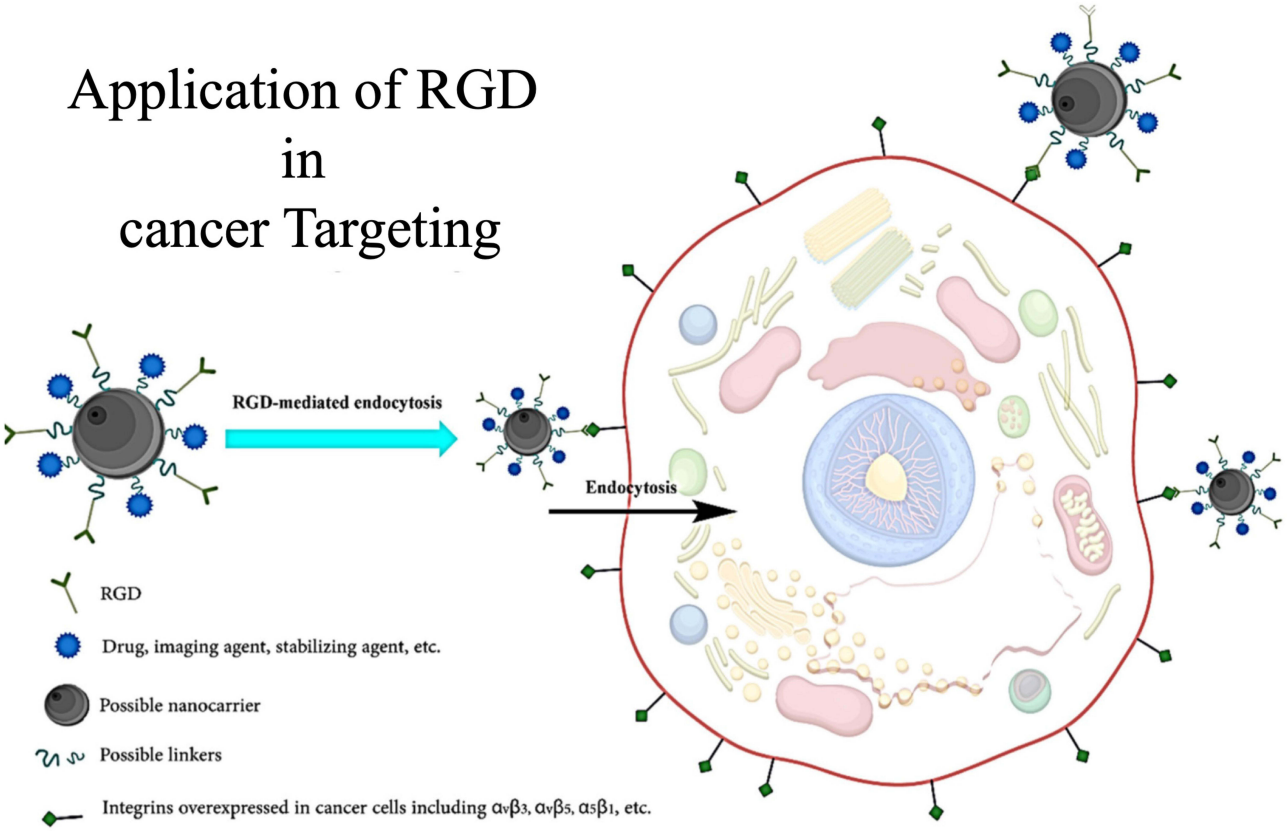

Figure 3 Receptor-mediated endocytosis using RGD-peptide drug, or carrier, etc. conjugates. Replicated with permission from Ref.[46] Copyright © 2023, Springer Nature Publishing Group.

Beyond established RGD peptides, diverse peptide modalities now enable precise tumor-targeted nanodelivery across malignancies, demonstrating promising preclinical efficacy. This encompasses peptides including D-AE (targeting EGFR), octreotide (binding somatostatin receptors), tLyp-1 (neuropilin-directed), AP (interleukin-4 receptors), U11 (uPAR-targeted), and apamin (p32-selective).[47] 2B3-101 represents a novel nanomedicine leveraging the tripeptide GSH for BBB-penetrating delivery to cerebral metastases from solid tumors. Currently in Phase I/IIa trials (NCT01386580), it is being evaluated for safety and efficacy in breast cancer patients with central nervous system involvement.[48,49] The trial of 2B3-101 in 25 breast cancer patients with brain metastases (BCBM) is administered alone or with trastuzumab. Early results show anti-tumor effects in the brain and beyond. In HER2-positive BCBM, a 56% progression-free survival rate at 12 weeks indicates the nanomedicine's potential to change BCBM treatment.[50]

Aptamer Targeting

Aptamers are advanced molecules with target-binding affinity comparable to monoclonal antibodies but offer benefits like easy storage at room temperature and reversible denaturation, making them more stable and easier to handle.[51] Aptamers can be readily produced at scale via solid-phase synthesis, enabling simplified purification and specific chemical modifications. They are quickly cleared from the bloodstream with a short half-life of about 10 minutes and have a low molecular weight of 10–20 kDa, leading to a small volume of distribution when given intravenously. Subcutaneous administration can prolong their presence in the body, making them adaptable for various uses where antibodies may not be suitable.[52]

The growing interest in aptamer development for cell surface receptor targeting stems from their ability to deliver diverse therapeutic payloads, including cytotoxic agents and therapeutic oligonucleotides. The exceptional selectivity and specificity these molecules exhibit towards their targets make them highly attractive for the design of precise drug delivery platforms.[53] The utility of aptamers reaches beyond mere targeting, as they also hold promise in the development of intelligent drug positioning systems. They are proficient in recognizing a variety of cancer indicators, including radioactive isotopes, mucin proteins, and the EGFR. The molecular aptitude to precisely identify unique cancer cell surface glycoproteins has established aptamer-based drug delivery systems at the forefront of oncology research.[54] This versatility and specificity underscore the burgeoning potential of aptamers as a cornerstone in the therapeutic arsenal against cancer (Table 2).

Aptamers are high-affinity single-stranded oligonucleotides that selectively bind diverse molecular and cellular targets. Called "chemical antibodies", they match the function of antibodies but excel in compact size and enhanced stability,[61] and the ease with which they can be synthesized and modified. The lack of batch-to-batch variability and minimal immunogenicity further augment their utility.

Aptamer creation typically involves a complex process known as SELEX, beginning with a vast pool of around 10^{15} unique oligonucleotide sequences. For DNA SELEX, this includes producing single-stranded DNA sequences of 20 to 100 bases, flanked by regions suitable for enzymatic processing.[62] RNA SELEX involves in vitro transcription of dsDNA templates generated by RT-PCR.[63] These libraries are then subjected to a series of iterative selection cycles that

Table 2 Aptamers for Targeting Drug Delivery Systems in Cancer Therapy Research

Aptamers	Nanoparticles	Payload	Tumor	Ref
AS1411	PEGylated CLPs	Anti-BRAF siRNA (siBraf)	melanoma	[55]
AS1411	PEGylated SLN	Docetaxel (DTX)	CRC	[56]
A15	PEGylated SLN	OXA	Hepatocellular carcinoma (HCC)	[57]
AS1411	Acetylated liposomes	taxol (PTX)	Renal cancer	[58]
A15	CLP	PTX and Survivin siRNA	Brain glioma	[59]
Anti-CD44 and EGFR aptamers	SLNs	DOX	Breast cancer	[60]

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encompass binding, partitioning, and amplification steps. The end goal is to isolate sequences with the most robust binding affinity—the aptamers—under conditions defined by temperature, pH, and buffer composition.

In summary, aptamers are highly engineerable precision ligands for diverse molecular targets. Their special features and advancements in SELEX technology have opened new ways for use in diagnostics, therapeutics, and especially targeted drug delivery, showing potential to revolutionize medicine. EpCAM, an oncoprotein overexpressed in malignancies and correlated with cancer stemness, critically regulates cellular adhesion, proliferation, epithelial-mesenchymal transition (EMT), tumor invasion, and stemness maintenance.[64–66] These characteristics have positioned EpCAM as a highly desirable target for therapeutic intervention. Consequently, the formulation of anti-EpCAM aptamers has risen as an advanced tactic for the precise conveyance of therapeutics to malignant tissues, demonstrating significant potential in both preliminary research and clinical trials.[67] A case in point is the use of mesoporous silica nanoparticles, laden with the chemotherapy agent DOX and equipped with EpCAM aptamers. These nanoparticles have been demonstrated to selectively home in on and bind to human colon cancer SW620 cells that express EpCAM, while leaving EpCAM-negative Ramos cells unscathed.[68,69] Aptamer-targeting improves cancer cell uptake of nanoparticles and their cytotoxicity. Research is using EpCAM aptamer-functionalized nanocomplexes for precise EpCAM siRNA delivery to cancer cells, effectively suppressing EpCAM and inhibiting proliferation. Dual-functionalized nanoparticles with a peptide and EpCAM aptamer have shown potential in damaging tumors and neutralizing circulating tumor cells with high EpCAM levels, demonstrated in a mouse lung metastasis model.[70]

Over the past decade, a non-SELEX derived aptamer named AS1411 has attracted considerable interest due to its remarkable ability to target tumors.[71–73] Subsequent studies identified its targeting of nucleolin—a multifunctional protein ubiquitously overexpressed across malignancies (Figure 4). AS1411's tumor-targeting capability has been leveraged in multiple studies to enhance precision oncology delivery systems. A prominent application involves its conjugation with PEGylated cationic liposomes (CLP) to construct ASLP (AS1411-PEG-CLP), a targeted probe that amplifies tumor-specific drug transport.[73] AS1411 is used in an innovative siRNA delivery system for nuclear protein targeting, showing promise for melanoma and other cancers. Its broad cancer targeting, enhanced therapeutic delivery,

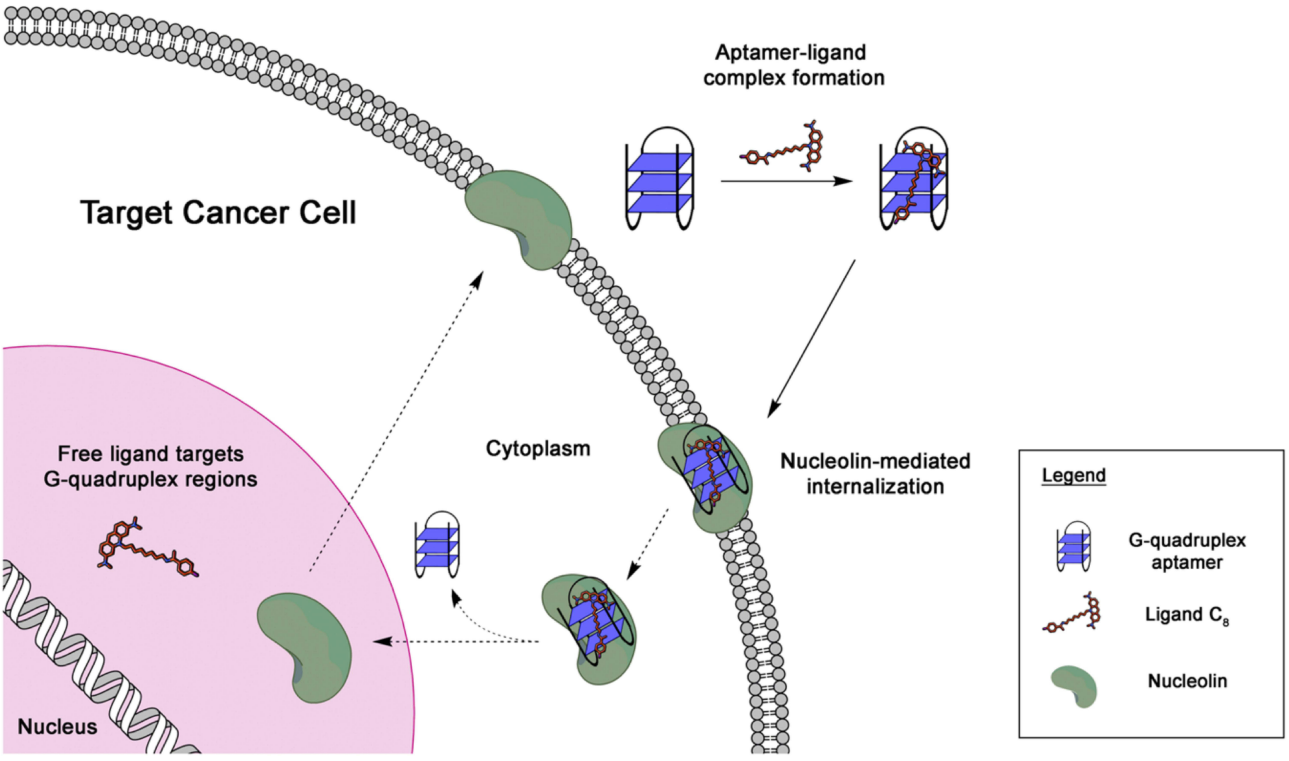

Figure 4 AS1411-mediated delivery of ligand C8 to nucleolin-overexpressing tumors. Replicated with permission from Ref.[72] Copyright © 2023, Van den Avont and Sharma-Walia.

and role in siRNA systems underscore its importance in targeted cancer therapy. The development of these systems reflects the increasing sophistication in nanomedicine and efforts to boost the efficacy and precision of cancer treatments.

The innovative application of AS1411, a non-SELEX derived aptamer, has opened new avenues for targeted cancer therapy. This 26-base G-quadruplex DNA sequence enhances anti-tumor efficacy of agents like paclitaxel via nucleolin-specific cellular internalization. In orthotopic GBM models, AS1411-enabled targeting of paclitaxel-loaded PEG-PLGA nanoparticles to glioma C6 cells markedly optimized pharmacologic outcomes.[74] Similarly, AS1411-modified PEGylated cationic liposomes enable melanoma-specific anti-BRAF siRNA delivery, effectively suppressing BRAF expression and inhibiting tumor progression.[75]

CD44, a transmembrane molecule often elevated in tumors, significantly contributes to tumor formation and progression through interactions with the microenvironment.[76] CD44's role in cell movement, tumor growth, and angiogenesis highlights its significance as a target for therapy. The findings underscore the improved sensitivity and selectivity of Apt1-Lip, illustrating its promise as a sophisticated drug delivery platform. Kim et al further engineered medication-loaded liposomes conjugated with dual DNA aptamers targeting MUC1 transmembrane glycoprotein and CD44 antigen on breast cancer cells and their stem cell derivatives.[76,77] Double aptamer-conjugated liposomes, known as Aptamerite bodies, with DOX, were more cytotoxic to cancer stem cells and cancer cells than non-targeted ones. Darabi's team developed a DOX-loaded solid lipid nanoparticle (SLN) with dual-RNA aptamers targeting EGFR/CD44, indicating potential for better drug delivery and needing clinical trials. EpCAM, a biomarker overexpressed in many cancers, was targeted by Zhao's team using an aptamer in cationic liposomes for colorectal cancer therapy.[78] The ER-lip platform, comprising PEGylated liposomal doxorubicin functionalized with EpCAM RNA aptamer, demonstrated enhanced survival rates and tumor suppression in animal models. This validates its ligand-directed delivery potential for EpCAM-positive malignancies. Variability in cancer-specific markers among individuals further complicates the development of a universal aptamer strategy, necessitating personalized therapeutic approaches. However, biotechnology and nanomedicine advances are expected to overcome these limitations, paving the way for enhanced precision oncology therapeutics. Despite current obstacles, the future of aptamer-based therapeutics remains optimistic, offering the prospect of precise and potent treatments.

Antibody Targeting

Antibodies, also known as immunoglobulins (Ig), are Y-shaped protein complexes synthesized by B cells to mediate humoral immunity. They are essential in the immune response, capable of recognizing and neutralizing alien substances, including bacterial and viral entities.[78] Among these, IgG stands out as the most prevalent isotype in the bloodstream.[79–82] The versatility and specificity of antibodies, particularly IgG, make them invaluable tools in therapeutic applications, diagnostics, and research. High-affinity antigen binding enables targeted therapeutics and precise immune modulation, critical for combating malignancies and autoimmune pathologies.

Antibodies leverage high specificity and affinity for tumor-associated antigens to enable precision cancer therapeutics, notably enhancing targeted nanoparticle delivery while sparing healthy tissue. These targeting agents comprise monoclonal antibodies (mAbs), fragments, and multi-specific formats, each with distinct applications in oncology. Conjugating therapeutic payloads to tumor-marker-specific mAbs achieves precise drug delivery, improving efficacy and minimizing adverse effects. Targets like EGFR, HER2, and PSMA are key for mAb-functionalized nanoparticles in cancer therapy, aiding in more accurate and potent treatments.[83–85]

In a significant research endeavor, Nagamitsu et al formulated polymeric nanoparticles adorned with Trastuzumab and infused with DOX, named aHER2-DOX-NPs. These nanoparticles demonstrated enhanced cellular uptake, nuclear accumulation, and cytotoxicity in HER2-overexpressing SK-BR-3 breast cancer cells.[86] Liu et al developed Her-DTX-NPs by attaching Herceptin to PLGA-PEG/PLGA nanoparticles carrying docetaxel. This nanoplatform enabled sustained docetaxel delivery to breast malignancies, enhancing stealth properties, cellular internalization, and cytotoxicity in $HER2^+$ tumors. Efficacy correlated directly with anti-HER2 mAb surface density, modifiable through trastuzumab-to-nanoparticle amino group molar ratio adjustments.[87,88]

Ngamcherdtrakul's team created trastuzumab-functionalized PEI-PEG-MSNPs delivering HER2-siRNA, constituting a targeted nanotherapeutic platform against $HER2^+$ malignancies.[89–92] The formulation improves siRNA stability and

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cellular delivery, achieving targeted apoptosis in HER2-overexpressing breast cancer with minimized collateral damage to healthy cells.[93,94] Furthermore, this formulation has exhibited remarkable effectiveness in reducing HER2 levels and curbing tumor progression in a mouse xenograft model of Trastuzumab-resistant, HER2-positive breast cancer (as depicted in Figure 5). Collectively, these results underscore the substantial promise of nanomedicines that target HER2, especially for malignancies characterized by high HER2 levels, presenting a hopeful path for advancing more accurate and potent oncology therapies.[94,95]

In a pivotal study, Mukherjee et al conjugated the humanized anti-PSMA mAb Hu-J591 to magnetic iron oxide nanoparticles (MIONs). They demonstrated that the resulting J591-MION complex exhibited a fivefold higher targeting affinity for PSMA+ cells than for $PSMA^-$ controls.[97] Their research showed that simply increasing antibody density on nanoparticles does not necessarily enhance targeting specificity. Optimal targeting requires balanced surface chemistry, PEGylation, and antibody density. In prostate cancer xenograft models, the J591-SPION-DTX formulation showed superior targeting and therapeutic efficacy, suggesting its clinical potential.[98,99]

In a recent breakthrough for metastatic castration-resistant prostate cancer therapy, Lankoff et al engineered the radioimmunoconjugate 223RaA-silane-PEG-D2B by conjugating anti-PSMA mAbs (D2B) to Ra-223-loaded NaA zeolite nanocarriers.[100] The radioimmunoconjugate exhibited high specificity for PSMA+ C4-2 prostate cancer cells via competitive bidding assays, with rapid internalization observed exclusively in PSMA+ lines, contrasting absent uptake in $PSMA^-$ DU-145 controls.[101] MTT cytotoxicity assays confirmed the selective potency of ^{223}RaA-silane-PEG-D2B, demonstrating approximately fourfold greater cytotoxicity toward PSMA+ C4-2 cells versus $PSMA^-$ DU-145 controls.[100,102]

New cancer biomarkers like the transferrin receptor, DR5, PSCA, and MUC1 are being studied for guiding mAb-linked nanoparticles in cancer therapy. These mAb-functionalized nanoparticles enable precision theragnostic delivery to malignancies, poised to revolutionize cancer therapy. Their increased effectiveness and minimized off-target effects

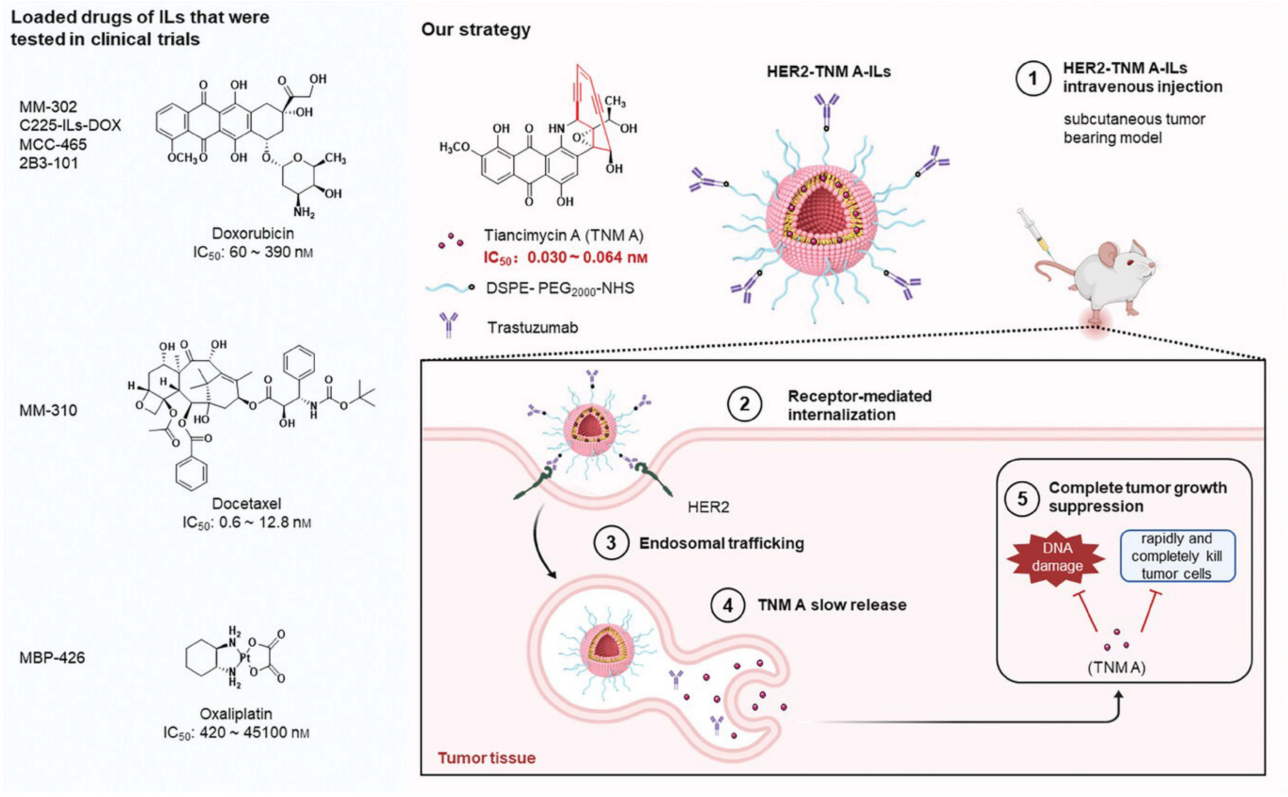

Figure 5 HER2-Targeted Immunoliposomes: Potent Antitumor Activity Mediated by Anthraquinone-Enediyne Payload Delivery. Replicated with permission from Ref.[96] Copyright © 2020, PubMed Central.

demonstrate significant potential in the field.[103] Several candidates are undergoing clinical evaluation, potentially enabling enhanced precision oncology.

Bispecific antibodies (BsAbs) have emerged as a groundbreaking class of biomolecules, unlocking a realm of therapeutic mechanisms and applications that extend beyond the reach of traditional IgG-based antibodies.[103–105] The progression of BsAbs has captured considerable interest in the scientific and medical communities, culminating in the approval of 14 such molecules by the end of 2023, with 11 specifically for oncological treatments and three for other medical conditions. Available in a variety of formats and engaging multiple targets through unique molecular mechanisms, BsAbs are revolutionizing cancer therapy. This review synthesizes the latest advancements in the application of BsAbs in oncology, reflecting the swift development and regulatory approval of nine BsAbs for cancer treatment between 2021 and 2023 in Figure 6.[106] The dual-targeting ability of BsAbs allows them to outperform standard antibodies, for instance, by directing immune cells to tumors or hitting multiple pathways at once. Their potency comes from binding two targets, which can enhance effects over conventional antibody combinations, as seen with drugs like blinatumomab that activates T cells. About half are in late-stage trials or approved, and around 10% target dual-signal suppression in solid tumors. BsAbs are becoming a versatile and powerful class in oncology, with ongoing innovation in antibody-drug conjugates and other therapies.

Beyond their large size, a fundamental limitation of using full-length antibodies is the inherent "Fc functionality". The Fc domain mediates binding to Fcγ receptors (FcγRs) on myeloid cells, leading to opsonization and accelerated

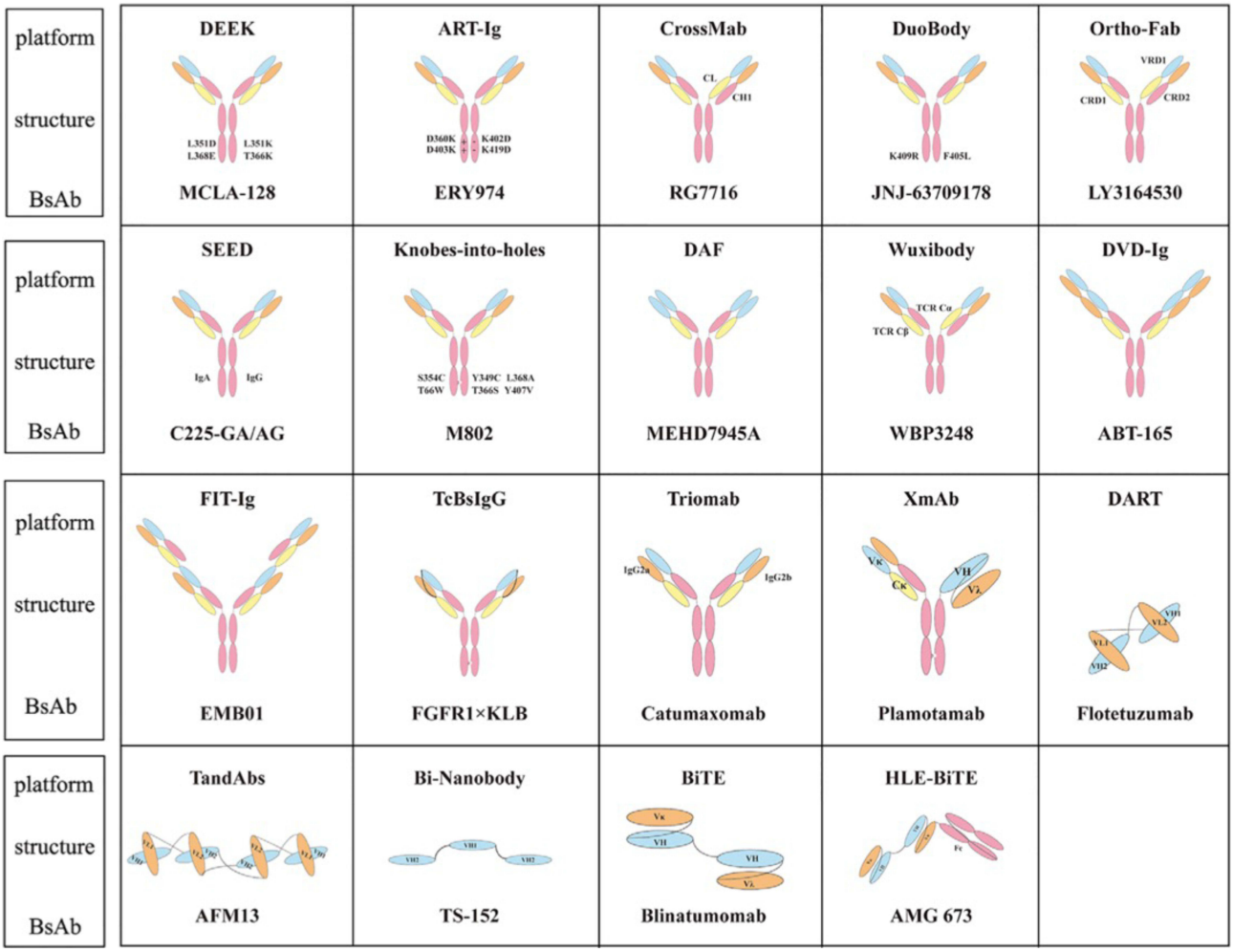

Figure 6 BsAb Structural Archetypes: Classic Formats & Representative Cases. Replicated with permission from Ref.[107] Copyright © 2020, by American Society of Hematology.

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clearance by the mononuclear phagocyte system (MPS). This not only shortens plasma half-life but also promotes off-target accumulation in the liver and spleen, potentially increasing toxicity and reducing the dose available at the intended site of action. This underscores a key advantage of using smaller antibody fragments (eg, Fab, scFv) or non-antibody ligands (eg, peptides, aptamers), which lack the Fc region and thus evade this predominant clearance pathway. Grasp of BsAb biology is crucial for their therapeutic impact. Optimal BsAb design aligns biological mechanisms with antibody features like format, affinity, and epitope targeting. Considerations span target selection, epitope location, binding properties, valency, site arrangement, size, flexibility, and Fc functions. Late-phase BsAbs indicate field maturity, with immunomodulators for solid tumors and TCEs for hematologic malignancies. This variety reflects innovative therapies enhancing immune cancer cell elimination and drug targeting (Table 3).

The development of BsAbs has moved from early trials to established clinical use, confirming their therapeutic value. Despite this, BsAbs still need more exploration and expansion in technology and clinical uses. Many early-stage strategies from various sectors are full of potential and could address unsolved therapeutic issues for BsAbs in development. Given the rapid pace of this field, it's hard to cover everything. We end our discussion by pointing out some emerging topics that we believe have the potential to greatly improve BsAb-based cancer treatments.

Epcoritamab (GEN3013) represents a novel therapeutic agent, a subcutaneous injection of a CD20/CD3 bispecific antibody, designed to target specific immune cells for the treatment of non-Hodgkin lymphoma (NHL).[107] In the NCT03625037 Phase I/II trial, 67 relapsed/refractory NHL patients received subcutaneous epcoritamab on an escalating schedule: twice-weekly during 28-day cycles, transitioning to biweekly or monthly maintenance. The patient breakdown was 67% diffused DLBCL, 18% FL, 6% MCL, and 9% with prior CAR T cell therapy. BsAbs' strong T cell activation, while good for fighting cancer, carries risks like CRS, neurotoxicity, and neoplastic growth. Identifying high-risk patients

Table 3 BsAbs for Solid Tumors

BsAb	Name	Targets	Year of First Approval/Region	Company
Removab	Catumaxomab	EpCAM × CD3ε	2009 Withdrawn EU 2013	Trion Pharma/Fresenius
Blincyto	Blinatumomab	CD19 × CD3ε	2014 United States/EU, Japan	Amgen
Rybrevant	Amivantamab	EGFR × MET	2021 United States/EU	J&J
KIMMTRAK	Tebentafusp	gp100-HLA-A*02 × CD3ε	2022 United States/EU	Immunocore
Lunsumio	Mosunetuzumab	CD20 × CD3ε	2022 United States/EU	Roche group
Kaitanni	Cadonilimab	PD1 × CTLA4	2022 China	Akeso Bio
Tecvayli	Teclistamab	BCMA × CD3ε	2022 United States/EU	J&J
Columvi	Glofitamab	CD20 × CD3ε	2023 United States/EU	Roche group
(T)Epkinly	Epcoritamab	CD20 × CD3ε	2023 United States/EU, Japan	Genmab, Abbvie
Talvey	Talquetamab	GPRC5D × CD3ε	2023 United States/EU	J&J
Elrexfio	Elranatamab	BCMA × CD3ε	2023 United States/EU	Pfizer

is key for managing these risks and maximizing BsAbs' therapeutic benefits. In other BsAb trials, adverse event rates leading to treatment discontinuation varied from 5% to over 20%, with severe neurotoxicity a major concern.[108]

Prodrug is Transformed Into Functional BsAbs

An innovative strategy in BsAb development is the creation of "safety-critical" prodrugs that are inactive in the bloodstream and activated at tumor sites. This is achieved through environmental triggers like tumor-associated proteases, which can activate prodrugs by revealing concealed binding sites or through prodrug activation chain exchange (PACE). A challenge is ensuring prodrugs remain monomeric and inactive until they reach the tumor. A new advancement is the ATP-dependent switch, which introduces binding sites in response to tumor ATP levels, enhancing tumor specificity and reducing off-target effects. These strategies highlight the ongoing innovation in the field of BsAb development, with a strong emphasis on creating therapies that are not only effective but also safer and more precise in targeting cancer cells while sparing healthy tissues.

Tri-Specific Antibody

Integrating costimulatory signals with T cell engagers (TCEs) boosts T cell activation potency. This can be done by combining TCEs with costimulatory bispecific antibodies or by adding a costimulatory receptor binding site to the TCE, creating tri-specific antibodies. Two such tri-specific TCEs are in trials, targeting tumor-associated antigens (TAAs), CD3, and CD28 to enhance T cell stimulation. SAR443216 is an Fc-silenced IgG4-based trispecific antibody targeting HER2, CD3, and CD28, engineered to prevent off-target immune activation.[109] In Phase I trials, SAR443216 induces T cell activation (CD4+/CD8+), driving proliferation, cytokine release, and lysis of low-HER2 tumor cells. SAR442257, also in Phase I, is a tri-specific antibody targeting CD38 for multiple myeloma, along with CD3 and CD28, to maximize T cell co-stimulation in immunotherapy. These developments demonstrate tri-specific antibodies' capacity to potentiate T cell-mediated antitumor immunity, enabling enhanced efficacy across diverse malignancies.

ADC

Even amidst a landscape rich with diverse new anti-cancer pharmaceuticals, the most recent global cancer burden statistics for the year 2020, a component of the World Health Organization—paint a sobering picture, with an estimated 19.3 million new cancer cases emerging globally that year. The quest for a "magic bullet", a term first introduced by Nobel laureate Paul Ehrlich in 1913, has found its modern embodiment in ADCs.[110] ADCs harness monoclonal antibody precision and cytotoxic potency for targeted oncotherapy. The antibody part of an ADC is designed to bind to a specific antigen on cancer cells, allowing the cytotoxic payload to be delivered and released inside the cell, neutralizing it. This approach seeks to enhance chemotherapeutic efficacy while minimizing off-target toxicity. ADC development represents a transformative breakthrough in oncology, achieving precision-targeted drug delivery.

This review comprehensively analyzes ADC biochemistry and structure-function relationships, critical for optimizing therapeutic design. We also offer an updated look at the clinical landscape, including 14 approved ADC drugs that target various antigens and treat a range of cancers (Table 4), showing the potential of ADCs in cancer therapy.[111]

(1) Trastuzumab emtansine (Kadcyla, T-DM1): FDA approved HER2-targeting ADC Kadcyla® in 2013 for HER2+ metastatic breast cancer and early-stage residual disease. China's NMPA subsequently authorized T-DM1 in 2020 for early breast cancer patients with post-neoadjuvant residual lesions. T-DM1 uses trastuzumab to target HER2 and carries the cytotoxic DM1, which inhibits microtubule assembly and induces cell death. A non-cleavable MCC linker provides stability and limits DM1 toxicity by avoiding systemic release. T-DM1 demonstrates extended circulation ($t_{1/2}\approx$4d, CL=0.68 L/day), enabling enhanced efficacy-toxicity balance in HER2-positive mammary carcinoma compared to standard chemoagents.[112]

(2) Brentuximab vedotin (Adcetris): Following Mylotarg's withdrawal, Adcetris emerged as a pivotal second-generation ADC, securing 2011 FDA approval for Hodgkin lymphoma and relapsed anaplastic large-cell lymphoma (ALCL).[113] Adcetris, the first approved ADC, gained NMPA approval in May 2020 for treating adult CD30-positive sALCL and cHL that is relapsed or refractory. This approval highlights the advancement in ADC technology and offers hope for patients with limited treatment options. Adcetris exemplifies oncology's precision medicine paradigm through

https://doi.org/10.2147/OTT.S550104

Table 4 14 ADC Drugs Have Received Worldwide Approval

	Drug names	Company	Approved Indications	Public Area	Target Point	Antibodies	Linker	Payload
1	Mylotarg	Pfizer, American pharmaceutical company	Acute myeloid leukemia	US/EU	CD33	IgG4	Hydrazones	Kachinomycin
2	Lumoxiti	AstraZeneca	Hairy cell leukaemia	US/EU	CD22	IgG1	Mc-VC-PABC	PD38
3	Polatuzumab Vedotin	F. Hoffmann-La Roche Ltd	Diffuse large B-cell lymphoma	US/EU /Japan	CD79-beta	IgG1	Dipeptide	MMAE
4	Enfortumab vedotin	Astellas & Seattle Genetics	Urothelial carcinoma	Japan/ US	Nectin-4	IgG1	Peptide	MMAE
5	Belantamab mafodotin	GlaxoSmithKline,	Multiple myeloma	US/EU	BCMA	IgG1	Sulfur ether	MMAF
6	Cetuximab saratolacan	Rakuten Medical	Squamous cell carcinoma of head and neck	Japan	EGFR	IgG1	Water-soluble silicon phthalocyanine derivatives	
7	Loncastuximab tesirine	Mitsubishi Tanabe Pharma &ADC Therapeutics& AstraZeneca & Tiling Road Pharmaceuticals	Diffuse large B-cell lymphoma	US	CD19	IgG1	Cleavable	PBD
8	Tisotumab vedotin	Genmab& Seattle Genetics	Cervical cancer	US	Tissue factor	IgG1	Cleavable	MMAE
9	Brentuximab vedotin	Takeda Pharmaceuticals & Seattle Genetics	Hodgkin's lymphoma, peripheral T-cell lymphoma	US/EU/China/Japan	CD30	IgG1	Cleavable, dipeptide	MMAE
10	Kadcyla/T-DM1	F. Hoffmann-La Roche Ltd	HER2-positive breast cancer	China/EU/ US	HER2	IgG1	Non-crackable, sulfur ether	DMI
11	Trastuzumab deruxtecan (Enhertu, DS-8201)	Daiichi Sankyo & AstraZeneca	Gastric cancer, HER2-positive breast cancer, gastroesophageal junction cancer	US/Japan/ EU/China	HER2	IgG1	Cleavable, peptide	Camptothecin
12	Disitamab vedotin	Rongchang Bio	Gastric cancer, gastroesophageal junction cancer, uroepithelial cancer	China	HER2	IgG1	Cleavable, dipeptide	MMAE
13	Besponsa	Pfizer	Acute lymphoblastic leukemia	China/ EU/ US/Japan	CD22	IgG4	Cleavable, peptide bonds	Kachinomycin
14	Sacituzumab govitecan	Genting Sinyo & Gullied Science & Seattle Genetics	Triple-negative breast cancer, urothelial carcinoma	EU/US	Trop-2	IgG1	Cleavable, peptide	Camptothecin

tumor-selective cytotoxicity with minimal off-target effects. Ongoing development and approval of such therapies show a dedication to enhancing patient outcomes and broadening cancer treatment options.[114]

(3) Trastuzumab deruxtecan (Enhertu, T-DXd): Enhertu—an innovative HER2+-targeting ADC—combines trastuzumab with the topoisomerase I inhibitor DXd via tetrapeptide linker. With a high DAR≈8, it potently disrupts DNA replication to induce apoptosis. DXd exhibits superior topoisomerase I inhibition versus SN38 and DX-8951f. Pivotal trial data: HR+/HER2-low metastatic breast cancer patients achieved 49% reduced progression/death risk and median PFS 10.1 months (vs 5.4 months for chemotherapy). This marks a therapeutic paradigm shift towards low HER2-targeted precision oncology.[115]

(4) Enfortumab vedotin (Padcev): Padcev, an innovative antibody-drug conjugate, utilizes a cleavable MC-Val-Cit linker to conjugate the potent cytotoxic payload MMAE to antibody cysteine residues. This targeted approach allows Padcev to specifically hone in on the cell surface protein Nectin-4, a marker that is often overexpressed in urothelial carcinoma cells. With a mean DAR of 3.8, Padcev enables precise cytotoxic delivery to malignancies while sparing healthy tissues. Padcev's clinical development and regulatory milestones are noteworthy.[116]

(5) Tisotumab vedotin (Tivdak): Tivdak, an ADC developed by Genmab and Seagen, links a TF-targeting human monoclonal antibody with Seagen's ADC technology and a microtubule-disrupting agent, MMAE. This agent selectively binds TF+ cancer cells, undergoes internalization, and releases MMAE via proteolytic cleavage to trigger cytotoxic cell cycle arrest and apoptosis. On September 20, 2021, FDA approved Tivdak for chemotherapy-refractory recurrent/metastatic cervical cancer in adults, providing a targeted therapeutic strategy with minimized off-target toxicity.[117]

Antibody Fragments

While the use of whole mAbs offers high specificity and affinity for tumor-associated antigens, their application in nanoparticle (NP) delivery systems faces certain challenges. The large size of mAbs can impede the efficient diffusion of nanoparticles into the tumor interstitium, limiting their penetration and distribution within the tumor microenvironment.[118] The effectiveness of mAb-functionalized nanoparticles in cancer therapy can be limited by size. Researchers are using smaller antibody fragments that retain antigen-binding sites for specific targeting but have a smaller size, which can increase therapeutic potency and the therapeutic index. These fragments are easier and cheaper to produce than whole mAbs, as they lack complex glycosylation and can be made using prokaryotic expression systems. Examples include Fab, Fab', and F(ab')2 fragments, which can be engineered to target tumor-associated antigens. The shift toward antibody fragment-based nanomedicine reflects advancing cancer therapeutic modalities—enhancing efficacy, targeting precision, and invasiveness reduction—with such constructs poised to become increasingly integral to future treatment paradigms.

Genetic engineering and phage display advances enable antibody fragment development, including scFv, sdAb, and diabody formats. These have been explored as targeting ligands for nanoparticle functionalization, showing great potential in preclinical studies. Several candidates, including C225-ILs-DOX (https://clinicaltrials.gov/study/NCT03603379), MM-302,[119] SGT-53,[120] and SGT-94 (https://classic.clinicaltrials.gov/ct2/show/NCT01517464), have entered clinical trials. Further validation of C225-ILs-DOX's antitumor efficacy came from studies in two additional EGFR-overexpressing tumor xenograft models. Immunoliposomes demonstrated superior antitumor efficacy versus free DOX or non-targeted formulations in preclinical models, confirming targeted delivery's therapeutic index enhancement.[121,122] In a Phase I trial (University Hospital Basel), 26 EGFR-overexpressing refractory solid tumor patients received C225-ILs-DOX dose escalation. Objective responses occurred in 2 patients, with 10 achieving stable disease (2–12 months duration).C225-ILs-DOX was well-tolerated, and anti-tumor effects were observed at a dose of 50 mg DOX per m^2, leading to its recommendation for phase II trials (https://classic.clinicaltrials.gov/ct2/show/NCT03603379).

Figure 7 illustrates MM-302: a pioneering HER2-targeted liposomal system for optimized doxorubicin delivery. This pioneering therapeutic approach is meticulously designed to augment the conveyance of doxorubicin to malignant cells exhibiting elevated levels of the HER2 receptor, a prevalent trait across a spectrum of cancer types.[123] The design of MM-302 is underpinned by a strategic approach that seeks to elevate the therapeutic index. By concentrating chemotherapeutics in tumors while sparing healthy tissues, this targeted system reduces systemic toxicity. Preclinical data confirm MM-302's efficacy: selective binding and internalization by HER2+ tumor cells enhance safety and antitumor activity.

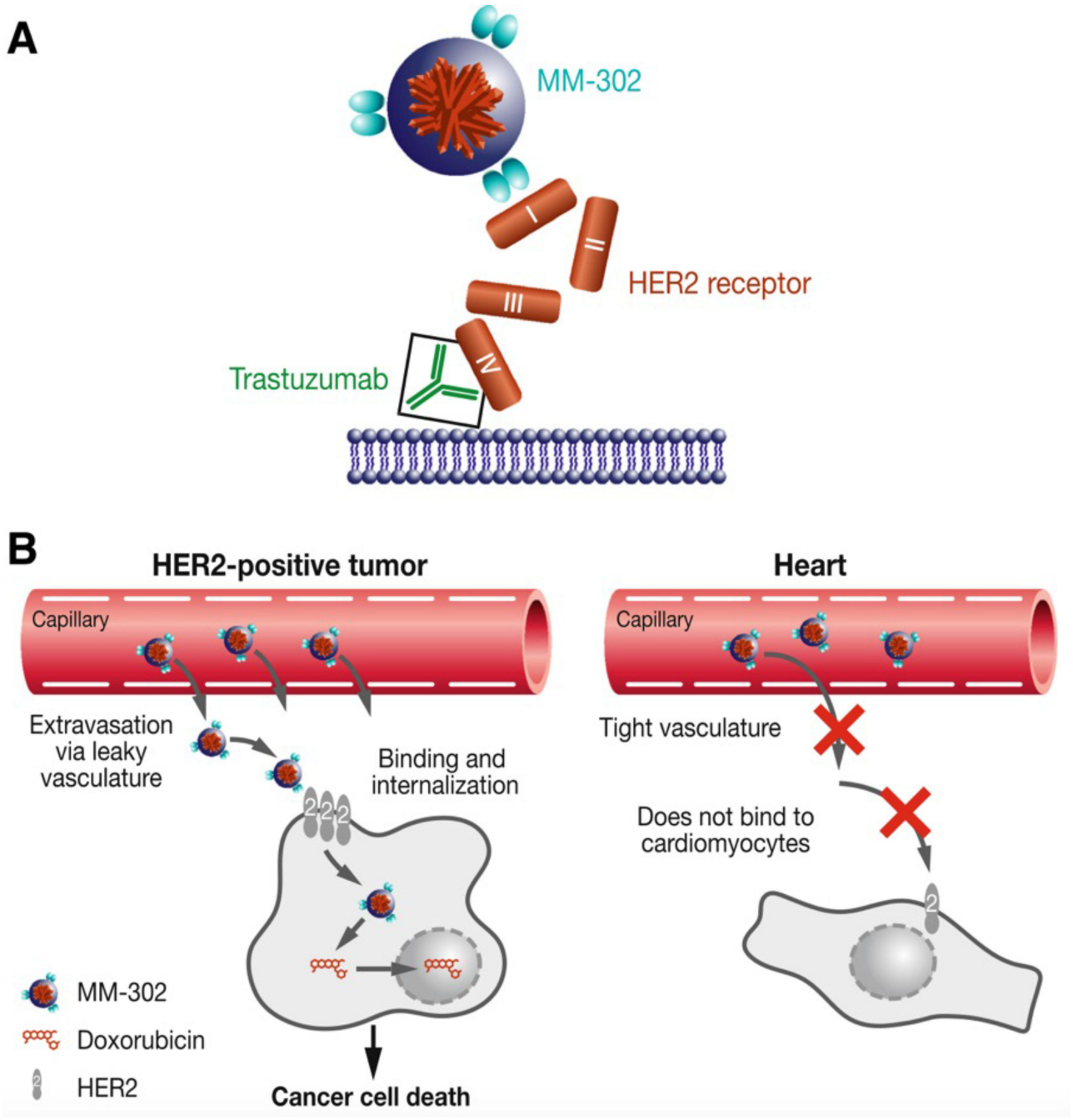

Figure 7 Mechanism of action of MM-302. (**A**) MM-302 specifically targets HER2 subdomain I, distinct from trastuzumab's subdomain IV binding. (**B**) Prolonged circulation enables tumor accumulation via enhanced permeability and retention (EPR) effect. Subsequent HER2-mediated endocytosis (>200,000 receptors/cell) releases doxorubicin intracellularly. Furthermore, cardiomyocytes express HER2 below the threshold required for uptake; therefore, MM-302 does not inhibit HER2-mediated signaling in cardiomyocytes. Replicated with permission from Ref.[125] Copyright © 2022 by nature outline.

Versus non-targeted liposomal or free doxorubicin, MM-302 shows superior therapeutic outcomes, supporting its clinical translation potential.[123–125]

In a pioneering Phase I trial by Munster et al, MM-302 was administered to patients with advanced HER2+ breast cancer. This first-in-human study explored the use of MM-302 both as a monotherapy and in conjunction with trastuzumab (Herceptin), an established HER2-targeting treatment, as well as with the addition of cyclophosphamide, a conventional chemotherapy agent.[125] The trial results for MM-302 were positive, showing good safety and potential efficacy against HER2-overexpressing breast cancer. Biopsies taken 72 hours post-treatment confirmed MM-302's ability

to target HER2. The established RP2D is 30 mg/m² MM-302 plus 6 mg/kg trastuzumab q3w, balancing efficacy and safety. Progression to Phase II trials signifies MM-302's potential as a HER2-targeted breast cancer therapy, leveraging synergistic delivery to improve advanced disease outcomes.[126]

A Phase I trial of SGT-53 in advanced solid tumor patients demonstrated favorable safety. Systemic IV infusion (3.6 mg DNA/dose) yielded dose-dependent p53 transgene accumulation in primary/metastatic tumors, indicating efficient tumor-selective gene delivery with minimal healthy tissue uptake.[127] After six weeks, most patients achieved stable disease; one adenoid cystic carcinoma case became operable post-first cycle, suggesting therapeutic efficacy. An ongoing phase II trial assesses SGT-53 combined with gemcitabine/nab-paclitaxel for metastatic pancreatic cancer, investigating synergy in refractory cases.

The development of SGT-53 and its progression indicate advances in gene therapy and targeted drug delivery in oncology, addressing gaps in cancer treatment. Building on the SGT-53 platform, SGT-94 delivers RB94 tumor suppressor via tumor-targeted liposomal nanocomplexes. A Phase I trial in 13 metastatic genitourinary cancer patients demonstrated tolerability up to 2.4 mg DNA per infusion and clinical activity including complete and partial remission responses. The expression of RB94 in metastatic nodules confirmed SGT-94's tumor-specific targeting (https://classic.clinicaltrials.gov/ct2/show/NCT01517464).

Beyond current clinical candidates, extensive preclinical research investigates antibody fragment-functionalized nanocarriers for oncology applications. Noteworthy is the ASSET platform engineered by Peer's team, enabling targeted delivery via anchored secondary scFv technology.[128,129] ASSET utilizes lipidated scFvs that self-assemble into nanoparticles, binding diverse mAbs to create multiplex targeted nanocarriers. This versatile system enables flexible construction, advancing personalized oncology therapeutics.

ASSET has shown promise in preclinical models for conditions like colitis and mantle cell lymphoma, highlighting the innovative role of nanomedicine in oncology. Therapies like SGT-94 and platforms like ASSET offer new hope for more effective, personalized cancer treatments. However, challenges remain in translating antibody fragment-functionalized nanocarriers into clinical use. These include rapid clearance from the bloodstream due to the lack of Fc regions, which extend the dwell time of antibodies, and susceptibility to degradation and instability. Addressing these issues to enhance stability and circulation time is a focus of ongoing research, with the aim of developing the next generation of cancer therapies that utilize the benefits of these targeted nanocarriers.

Challenges and Future Opportunities

Targeted drug delivery advances enable precise therapeutic transport, yet significant challenges persist. Large particle carriers can cause issues like limited absorption, instability, reduced bioavailability, and difficulties in targeted delivery. Using smaller particles could be a solution to these issues. Precision targeting is essential to enhance therapeutic efficacy while minimizing systemic toxicity. This is especially challenging for systemic siRNA administration, which faces hurdles like enzymatic degradation and reduced cellular uptake at high doses due to their negative charge.[130] These challenges necessitate innovations to advance targeted delivery systems for potent agents like siRNA, enhancing efficacy-toxicity profiles. Micelles and liposomes, as lipid-based nanoparticles, are under intense evaluation for their potential in targeted drug delivery.[131,132] They present a hopeful pathway for the direct conveyance of medicinal substances to afflicted areas, consequently amplifying therapeutic effectiveness and reducing adverse effects. However, their clinical use faces challenges. Interactions with the body, such as phagocytic uptake and hepatic filtration, can reduce the efficiency of these delivery systems, potentially undermining their targeted delivery capabilities. Moreover, there exists the risk of nanoparticle-induced toxicity, which necessitates thorough safety assessments.

A paramount challenge in the clinical translation of nanomedicines is their comprehensive toxicological profiling. The toxicological risks of nanomaterials are not merely a function of their bulk composition but are profoundly influenced by their physicochemical properties, including size, shape, surface charge, surface chemistry, and aggregation state. These properties collectively define their interactions with biological systems and their potential toxicity. To systematically evaluate these risks, a suite of toxicological assessment methods is employed. In vitroassays are crucial for high-throughput screening and mechanistic studies. These include colorimetric assays (eg, MTT, LDH for cell viability and membrane integrity), fluorescence-based assays (eg, Alamar Blue for metabolic activity, Annexin V-FITC/PI for

apoptosis), and luminometric assays (eg, ATP assays for cell viability). A central focus is on measuring oxidative stress through indicators like reactive oxygen species (ROS) generation, glutathione depletion, and lipid peroxidation, which is a primary mechanism of nanomaterial cytotoxicity. In vivostudies provide critical data on biodistribution, accumulation, and systemic toxicity. Techniques such as whole-body scanning, liquid scintillation counting, and electron microscopy are used to track the fate of nanoparticles and their accumulation in organs with high phagocytic activity, primarily the liver, spleen, and kidneys. Genotoxicity is another critical endpoint, assessed through methods like the comet assay and TUNEL assay.

Research results have revealed substance-specific concerns. Silver nanoparticles (AgNPs) are extensively studied for their antimicrobial properties but have been shown to cause cytotoxicity and organ accumulation. Titanium dioxide nanoparticles (TiO_2 NPs), widely used in sunscreens and paints, were once considered biologically inert but are now linked to potential inflammatory responses and pulmonary effects in rodents. Zinc oxide nanoparticles (ZnO NPs) exhibit toxicity linked to Zn^{2+} ion release and ROS generation, causing physical malformations in aquatic models like Artemia salinaand zebrafish, and accumulating in fish tissues. Carbon Nanotubes (CNTs) raise particular concern due to their high aspect ratio and biopersistence. Their lipophilic nature and long lifespan can adversely impact health. Inhalation exposure in mice has been associated with pleural fibrosis, and their toxicological profile has been compared to asbestos, leading to concerns about mesothelioma and granuloma formation. Furthermore, their ability to cross biological barriers means they can distribute into cellular and subcellular organs. A significant ecological study also found that CNTs can affect ingestion and digestion in ciliated protozoa, reducing iron bioavailability in marine environments.

Furthermore, the complexity of nanotoxicity extends beyond the material itself. The concept of a "nano-bio interface" highlights that upon entering biological fluids, nanoparticles are immediately coated with proteins, forming a "protein corona" that alters their identity, behavior, biodistribution, and cellular uptake compared to the pristine material. Environmental aging and transformation (eg, of ZnO NPs into zinc carbonate or hydroxide) can alter their toxicity profile, sometimes reducing acute cytotoxicity but potentially enhancing genotoxicity. Nanomaterials can also act as carriers for other contaminants (eg, adsorbing heavy metals like arsenic), leading to compounded toxic effects.

One of the significant hurdles in targeted drug delivery is the administration of medications to patients who are unable to ingest them, such as comatose individuals. Additional challenges include the low solubility and permeability of target sites, possible interactions with food, and the susceptibility of drug carriers to degradation by gastrointestinal flora. These factors highlight the intricate nature of developing an effective targeted drug delivery system and the critical considerations that must be addressed.

The foregoing discussion underscores that the toxicological profile of particles used in drug delivery is not merely a supplementary check but a substantial barrier to clinical adoption. The lack of standardized, precise methods for determining the cytotoxicity of different nanomaterials remains a significant hurdle for the field. Therefore, future research must prioritize the development of reliable testing protocols that address the special properties of nanomaterials, adopt a precautionary approach for individual evaluation of new nanomaterials, and invest in understanding the long-term fate and effects of these materials to ensure their sustainable and safe implementation.

The toxicological profile of particles used in drug delivery is another substantial barrier. Common biomedical nanomaterials like silver, gold, silica, and titanium—employed in drug conjugation and delivery—may pose significant biosafety risks. Research conducted both within living organisms (in vivo) and outside of them (in vitro) has demonstrated that these nanoparticles are capable of causing adverse effects, underscoring the necessity for prudence in their utilization.

Carbon nanotubes (CNTs) show promise for delivering biologics across cellular barriers in gene therapy and imaging applications. However, safety concerns due to potential harm to various organs and systems require thorough toxicity assessments before clinical use, especially in cancer treatment. The development of drugs that double as carriers and therapeutic agents faces challenges of biocompatibility and bioacceptability, with the body's immune response a critical factor. Biological versus synthetic materials elicit different responses, adding complexity. Physiological barriers like the blood-brain barrier inherently restrict therapeutic delivery, especially for neurological disorders requiring precise drug concentrations in target tissues.

mAb-derived immunoliposomes enable targeted drug delivery yet face limitations from immune responses and systemic ADME processes. Organs like the kidneys and liver can filter out nanoparticles. Despite challenges, extensive research is exploring drug delivery and nanomedicine, with cell-based therapies potentially improving bioacceptability. Innovations like inorganic nanoparticles, microfluidics, and imprinted polymers may enhance delivery, and initiators could adjust the biological environment for better efficacy and safety. Future opportunities lie in designing safer-by-design nanomaterials. This includes surface functionalization (eg, with PEGylation to improve stealth properties), designing nanocomposites to minimize cytotoxicity, and developing biodegradable or clearable nanoparticles to prevent long-term accumulation. The use of advanced in silicomodels and high-throughput screening platforms will be crucial for predicting toxicological outcomes early in the development process Theoretical strategies that combine cell-based systems with biomaterials need more research and clinical trials to enhance drug delivery effectiveness. Anti-tumor targeting nanotechnologies, while promising, face high clinical development failure rates, necessitating a deeper understanding and new targeting technologies for improved tumor accumulation and subcellular delivery.

Conclusion

Anti-tumor nanomaterials represent a rapidly advancing frontier in cancer therapeutics, holding immense promise for the treatment of hematologic malignancies through sophisticated active targeting strategies. However, their translation into effective solid tumor therapies remains constrained by a continued reliance on passive targeting mechanisms, which are fraught with significant limitations. The inherent drawbacks of passively targeted nanomaterials include inadequate penetration into the tumor microenvironment (TME) and insufficient accumulation at the tumor site, largely due to physiological barriers such as abnormal vasculature and high interstitial fluid pressure.

While actively targeted nanomaterials offer the potential for precision therapy by homing in on specific molecular markers, they face their own set of formidable challenges. These include cellular barriers that hinder therapeutic encapsulation and complicate the intracellular delivery of agents. Moreover, the complex interplay between nanoparticles and biological systems often leads to non-specific interactions, immune clearance, and limited trafficking to intended subcellular compartments, which collectively can compromise clinical efficacy.

To address these impediments, it is essential to integrate cutting-edge research insights and prioritize key parameters in the development pipeline for next-generation targeted nanomedicines. One promising approach involves surface modification of nanoparticles with biocompatible polymers such as polyethylene glycol (PEG) or chitosan, which enhances colloidal stability and reduces immune recognition. Furthermore, the emergence of biomimetic strategies, particularly cancer cell membrane-coated nanoparticles (CCM-NPs), has demonstrated improved immune evasion and homologous targeting capabilities by leveraging inherent biological communication mechanisms.

Concurrently, there is a pressing need for advanced preclinical models that better recapitulate human tumor complexity and predictive clinical response. Adherence to Good Laboratory Practice (GLP) and the implementation of standardized guidelines in academic research are crucial for bridging the gap between bench-side innovation and clinical application. Standardization efforts should focus on rigorous characterization of nanomaterials—including size, surface properties, and toxicological profiles—and a deeper understanding of tumor biology to identify robust biomarkers that can distinguish between treatment responders and non-responders.

The utilization of regulatory science programs and health authority initiatives focused on nanotechnology is vital for thorough assessment of the efficacy and safety profiles of nanomedicines. Meanwhile, the burgeoning application of artificial intelligence (AI) in this domain offers transformative potential: AI-driven approaches can refine predictive modeling of biological interactions, enhance understanding of targeting efficiency, and facilitate the design of safer, more effective nanomedicines. Although these technologies are still in nascent stages, they are poised to revolutionize anti-tumor targeted therapies and reshape cancer treatment paradigms. Through the integration of these innovations with ongoing research, nanomedicine continues to offer novel therapeutic avenues and enhanced strategies for cancer treatment.

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Disclosure

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