

REVIEW

CURRENT ADVANCES AND FUTURE VISION OF DRUG DELIVERY SYSTEMS FOR CANCER

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ABSTRACT: conventional cancer treatments often damage both tumour and healthy cells, leading to significant systemic toxicity. This has created an urgent need for the advancements of targeted drug delivery systems that can selectively reach cancer cells or tissues and release the drug precisely at the intended site. Recent advancements in anticancer therapy have highlighted the importance of innovative drug delivery strategies in enhancing treatment efficacy and improving patient outcomes. This review provides an analysis of advanced drug delivery systems, exploring their mechanisms of action, key developments, and therapeutic applications. Particular relevance is given to self-assembling nanosystems, with a focus on bioinspired nanomaterials, such as self-assembled peptide nanosystems, which constitute promising drug delivery tools due to their biocompatibility and potential lack of toxicity. The review also addresses the advantages, challenges, and future potentials of drug delivery systems in cancer treatment.

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Impact statement: advanced drug delivery systems, including self-assembling peptide nanosystems, offer targeted and bio-compatible solutions for cancer therapy, reducing the systemic toxicity of chemotherapy drugs and improving treatment efficacy.

Key words: *drug delivery systems; cancer; active targeting; supramolecular assembly; artificial intelligence.*

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INTRODUCTION

Drug discovery represents an important clinical challenge. Unfortunately, despite significant advancements, many approved drugs still face critical limitations, including poor absorption, distribution and metabolism, which often hinder their clinical effectiveness (1, 2). Furthermore, the complex pathophys-

iology of many diseases remains poorly understood, impairing the development of precise therapeutic intervention (3-5). This gap in knowledge continues to hamper the development of effective therapeutic interventions with the advancement of innovative drug delivery systems (DDS) becoming increasingly vital to deliver therapeutic agents effectively, safely, and precisely to their intended sites of action (6-8).

DDSs are also designed to control the rate, timing, and location of drug release, optimizing efficacy while minimizing side effects and enhancing patient compliance (9). A well-designed DDS should take into account multiple factors, including the properties of the drug, the characteristics of the disease, and the specific therapeutic target thus requiring a thorough understanding of critical molecular features, alongside their interrelations which can help researchers to develop more effective and safe therapies (10, 11). The integration of advanced technologies, such as nanotechnology, biomaterials, and molecular biology, is redefining the boundaries of drug delivery. Nanotechnology plays a crucial role, offering innovative solutions to overcome the limitations of traditional therapies through the control of building blocks at the nanoscale level (12). This strategy involves the development of nanosized entities, typically ranging from 1 to 100 nm, which possess unique physicochemical properties distinct from their bulk counterparts. These properties have made nanotechnology a vital tool in advancing personalized medicine and addressing the limitations of traditional therapies (13-15), as also seen in the recent Covid pandemic with the successful exploitation of lipid nanoparticles for the development of mRNA vaccines (16-20). In fact, biomaterials enable controlled release and reduced toxicity (21), and are essential to assist recent breakthroughs in molecular biology, such as RNA-based therapeutics and CRISPR gene editing, which demand sophisticated delivery systems to achieve intracellular precision (22). Moreover, understanding disease-specific characteristics, such as pH, enzyme activity, or the hypoxic microenvironment, allows researchers to develop stimuli-responsive DDS that release drugs on demand in targeted tissues (23-25). Also, exploitation of active targeting strategies using ligands, antibodies, or aptamers enable precision delivery to diseased cells, sparing healthy tissues and minimizing systemic toxicity (22).

The future of drug delivery lies in integrating these advanced approaches to meet the demands of precision medicine. The possibility of addressing these challenges, not only will improve the effectiveness and safety of treatments but also improve patient compliance, paving the way for more accessible and impactful therapies.

In cancer treatment, conventional therapies, including chemotherapy and radiation, are often limited by significant drawbacks, (26) including a lack of specificity and severe off-target toxicity (7, 27);

these problems stem from the heterogeneous and adaptive nature of cancer, where tumours evolve mechanisms to evade treatment, develop resistance to drugs, and continuously metastasize to different organs. Emerging approaches, such as nuclear medicine which employs the use of radiopharmaceuticals, like chemotherapy and radiation, aim to selectively target cancer cells while minimizing systemic toxicity (28). However, these newer strategies also struggle with issues such as poor tumour penetration, non-specific uptake, and variable patient response to treatment (29). Consequently, research in this area increasingly recognizes the need for advanced DDS to overcome these barriers, ensuring more precise targeting, sustained drug release, and improved therapeutic outcomes while minimizing unintended side effects.

DDSs IN THE CANCER ERA

DDSs have emerged as a ground-breaking solution, offering innovative ways to enhance the effectiveness of cancer therapies while reducing damage to healthy tissues (10). Traditional chemotherapy cannot differentiate between healthy and cancerous cells and often cancer cells develop resistance to chemotherapy following the long-term treatments (27, 30, 31). In addition, the tumour microenvironment, characterized by abnormal blood vessels, hypoxia, and high interstitial pressure, can create physical and biochemical barriers that hinder drug delivery and penetration (32). It should also be considered that many therapeutics, especially biological drugs, have short half-lives or poor stability, making it difficult for them to reach and act on tumours effectively (31, 33). DDSs offer a cutting-edge approach to overcoming these challenges, providing a more precise and controlled way to deliver therapeutics and opening new doors for personalized therapies. DDSs such as liposomes, micelles, lipid nanoparticles (LNPs) and nanoparticles from various origins improve drug solubility and protect drugs from degradation caused by enzymes, pH, and other factors during blood circulation (8, 34). Additionally, their tuneable size, shape, and structure allow for significant drug loading capacity and enable precise delivery (**Table 1**). Since their size is comparable to that of human cell organelles, they can efficiently interact with a range of hydrophilic and hydrophobic ligands, target specific cells, and access intracellular compartments (10).

Table 1. Examples of drug delivery strategies and clinical progress.

| DRUG DELIVERY SYSTEMS | ADVANTAGES | EXAMPLES |
|---------------------------------------|---|---|
| Nanoparticle-Based DDSs | Tumours' leaky vasculature allows nanoparticles to accumulate in cancerous tissues through the enhanced permeation and retention (EPR) effect | Doxil: A liposomal formulation of doxorubicin that reduces cardiac toxicity (39) |
| | Nanoparticles protect drugs from degradation in the bloodstream, prolonging their circulation time and improving stability | Abraxane: Nanoparticle-bound paclitaxel that improves solubility and efficacy (40) |
| | Surface modifications, such as PEGylation, prevent off-target effects, enhancing bioavailability | Onivyde: A nanoliposomal formulation of irinotecan, which protects the drug active lactone configuration, prolonging circulation time (41) |
| Stimuli-Responsive DDSs | Targeted activation ensures the drug is released only at the tumour site, minimizing side effects | ThermoDox: An experimental formulation of doxorubicin encapsulated in thermosensitive liposomes (42) |
| | Adaptability to the acidic, enzyme-rich, or hypoxic conditions of tumours | Jelmyto: an FDA-approved gel-based chemotherapy for treating low-grade upper tract urothelial carcinoma (43) |
| Targeted DDSs | High specificity reduces damage to surrounding healthy tissues | Trastuzumab emtansine (T-DM1): An ADC designed for HER2-positive breast cancer, combining targeted action with a cytotoxic payload (44) |
| | Improves the therapeutic index of potent drugs, such as antibody-drug conjugates (ADCs) | Brentuximab (Adcetris): An ADC that delivers the potent cytotoxic agent monomethyl auristatin E (MMAE) specifically to CD30-expressing cancer cells (45) |
| Immunotherapy | Protect sensitive biologics like proteins or RNA during transport | Moderna and BioNTech: COVID-19 vaccine (46) |
| | Enable targeted delivery to immune cells or tumour tissues for heightened efficacy | Immunoliposomes: currently being investigated in ongoing Phase II studies (47) |
| Gene Therapy and RNA-Based Treatments | Enable precise silencing of oncogenes or correction of genetic mutations driving cancer | Onpattro (patisiran): LNPs to deliver siRNA targeting transthyretin for hereditary amyloidosis treatment (48) |
| | Overcome delivery barriers using lipid nanoparticles or viral vectors | Luxturna: Adeno-associated virus AAV2 vector to deliver RPE65 cDNA into retinal cells, restoring enzyme function (50) |
| Combination therapy | Target multiple pathways simultaneously, reducing the likelihood of drug resistance | Vocimagene amiretrorepvec/fluycytosine: in phase-II clinical trials, is a retroviral vector to deliver the gene cytosine deaminase gene, converting the prodrug into 5-fluorouracil (5-FU) (49) |
| | Combine chemotherapy, immunotherapy, or RNA therapies in a single formulation | mRNA-4157/V940 and pembrolizumab: A personalized mRNA-based cancer vaccine encapsulated in lipid nanoparticles under Phase III clinical trial (50) |

DDSs can be designed to: i) extend the circulation time of drugs in the bloodstream, ensuring they remain active and available for longer periods; ii) facilitate penetration through biological barriers, such as cell membranes or the blood-brain barrier (BBB); iii) increase the accumulation of the drug in the target tissues; iv) enhance cellular uptake, ensuring the drug enters the appropriate cells more efficiently (6, 35).

To release drugs specifically to diseased tissues or cells, the surface of DDSs may be decorated with ligands, antibodies, or aptamers, that target specific receptors on cancer cells, inflamed tissues, or other pathological sites, reducing off-target effects and toxicity (36). The ability to provide a platform for controlled and sustained drug release reduces the frequency of dosing and maintains therapeutic drug levels in the body for extended periods, enhancing treatment adherence (21, 37, 38).

SUPRAMOLECULAR PLATFORMS: A PARADIGM FOR DDS IN CANCER

Supramolecular platforms, inspired by naturally occurring self-assembly processes, are widely employed in DDS. These systems exploit the spontaneous organization of constituent molecules into intricate organic and inorganic structures (51). This organization is governed by non-covalent forces, including electrostatic interactions, π - π stacking, hydrogen bonding, and van der Waals forces. While individually weak (2-250 kJ/mol) relative to covalent bonds (100-400 kJ/mol), these non-covalent interactions collectively generate robust and stable functional materials (52). Nature is rich in examples of self-assembled structures, including double-stranded DNA, the triple helix of collagen, viral structures, metal ions and membrane bilayers (53). The specific order and magnitude of these interactions dictate the shape, function, and size of the resulting assemblies. Researchers have designed and synthesized a diverse array of building blocks including but not limited to metal ion, amphiphiles, peptides, dendrimers, polymers, fullerenes, calixarenes, cyclodextrins, and lipids, to explore structure-assembly relationships and create novel architectures (53-55). Indeed, understanding, controlling, and predicting the complex interplay between individual components and the final thermodynamic state of the assembly is essential to develop the next generation of complex materials.

For instance, Liu *et al.* (56), introduced a facile and universal strategy to construct a DNA nanostructure-based co-delivery system containing a linear tumour therapeutic gene (*TP53*) and a chemotherapeutic drug (doxorubicin, DOX) for combined therapy of multidrug resistant tumour (MCF-7R). Furthermore, Lv *et al.* (57) developed a dual-targeting nanoplatforam for cancer therapy, combining a hyaluronic acid-paclitaxel (HA-PTX) prodrug with marimastat (MATT)-loaded, thermosensitive liposomes (MATT-LTSLs). The HA-PTX prodrug spontaneously assembles into both positively and negatively charged liposomes, creating hybrid nanoparticles (HNPs) approximately 100 nm in size. Upon application of mild hyperthermia, these HNPs (HA-PTX/MATT-LTSLs) rapidly release their drug payloads. The released HA-PTX then efficiently enters 4T1 cancer cells via CD44-mediated binding with hyaluronic acid. The collective behaviour of these self-assembled nanostructures can lead to functions and properties beyond those of the individual building blocks

and can be further tailored by incorporating additional functional molecules (51, 58). Supramolecular materials are typically constructed using a bottom-up approach, starting from various building blocks such as atoms, small molecules, or macromolecules (59). Additionally, novel building blocks can be engineered by altering the chemical composition, length, and directionality of interactions in existing units that already possess the inherent capacity for self-assembly (54). The spontaneous formation of self-assembled structures represents a system reaching a state of minimum free energy, often achievable by manipulating environmental variables (60). Given that non-covalent interactions are the driving forces, self-assembly is inherently a reversible process, sensitive to environmental conditions (61), enabling the design of materials with on-demand properties through controlled manipulation of the self-assembly process.

A variety of morphologies, including vesicles, micelles, ribbons, helices, spherical nanoparticles, nanorods, nanotubes, and nanofibers, can be obtained depending on the chosen building blocks. The complexity of these structures, and consequently their potential function, generally increases with size (**Table 2**).

TARGETED SUPRAMOLECULAR DDSs

DDSs can be targeted to tumours through two primary mechanisms: passive and active targeting. Passive targeting takes advantage of the enhanced permeability and retention (EPR) effect, while active targeting exploits the specific interaction between ligands on the DDS and receptors overexpressed on tumour cells (35, 70). In cancer treatment, nanoparticles with diameters ranging from 10-100 nm are particularly effective because they can exploit the EPR effect. Particles smaller than 1-2 nm may leak from normal vasculature and damage healthy cells, while particles larger than 100 nm are more likely to be cleared from circulation by the immune system's phagocytes (71-73).

Active targeting is essential for maximizing the specificity and effectiveness of cancer therapies. Tumour cells often exhibit altered gene and protein expression profiles compared to normal cells, which can be exploited as markers for targeted drug delivery (74). Many tumours overproduce certain molecular components that support their growth and metastasis, including G-protein-coupled receptors, growth factor

Table 2. Examples of self-assembled nanocarriers.

| CARRIER TYPE | SIZE RANGE | FEATURES | SHAPE | PAYLOAD | APPLICATIONS | REFERENCES |
|------------------------------------|--------------------------|--|--|---|---|--------------|
| Lipids | 10–1000 nm | Small unilamellar (20–100 nm), large unilamellar (100–500 nm), multilamellar (500–5000 nm). Surface-modified with peptides for targeting | Monolayers, bilayers, micelles, vesicles, giant vesicles | Hydrophilic & hydrophobic drugs | Liposomal Doxil, first FDA-approved liposomal formulation for tumours | (34) |
| Dendrimers | 1.5–10 nm | Monodispersed, multibranched core-shell structure, enabling controlled drug release & selective toxicity | Nanoparticles, nanofibers | Multitherapeutic cargo loading for targeted delivery | Cancer therapy, gene delivery | (55, 62, 63) |
| Hydrogels/ Nanogels | 100 nm–100 μ m | 3D polymeric network, physically/chemically crosslinked, high porosity | Hydrogels, microspheres, nanogels | Small molecules, polymers, nanoparticles | Tissue engineering, wound healing, drug delivery | (64, 65) |
| Peptides | Nano to micrometer scale | Biodegradable, modular, composed of natural amino acids | Nanoparticles, nanofibers | Insulin, glucagon, chemotherapeutics | Drug delivery, regenerative medicine | (66) |
| Virus-Like Particles (VLPs) | 20–200 nm | Self-assembled protein structures mimicking viruses, strong immune activation | Spherical | Encapsulates nucleic acids, chemotherapeutics, antigens | Cancer vaccines, targeted drug delivery | (67) |
| Polymersomes | 10 nm– μ m | Amphiphilic polymer vesicles with membranes (5–10 nm thick), tunable stability | Spherical, tubular, donut-shaped, cucurbit-shaped | Proteins, nucleic acids, anticancer drugs | Chemotherapy, immunotherapy, antigenic vaccine development | (68, 69) |
| Nucleic Acids | 1–100 nm | Self-assembled DNA/RNA nanostructures for precise targeting & stimuli-responsive release | DNA origami, tiles, modular assemblies | Proteins, small molecules, nano/nucleic acid drugs | Gene therapy, chemotherapy, immunotherapy | (53) |

receptors, interleukins, transferrin receptors, folate receptors, and polysaccharide moieties (75–77). While monoclonal antibodies have been the cornerstone of targeted cancer therapies, alternative targeting moieties such as small molecules and peptides are

increasingly being explored to improve tissue selectivity (78). Aptamers, which are single-stranded DNA or RNA molecules, can bind specific targets with high affinity and specificity, offering advantages such as biostability, versatile chemical modification, low

immunogenicity, and rapid tissue penetration (79). Nanobodies derived from camelid heavy-chain antibodies provide benefits like enhanced tumour penetration and the ability to reach cells in poorly perfused tumour areas (80). Antibody-drug conjugates (ADCs) have also proven a highly effective strategy, combining the specificity of monoclonal antibodies with the potency of cytotoxic agents. Recent innovations include optimized linkers, novel payloads, and bispecific ADCs targeting multiple tumor antigens (81, 82). In fact, Synan *et al.* (82) further validated this strategy by demonstrating that bispecific antibodies with enhanced cross-arm binding affinity effectively target dual-positive cells, improving specificity and therapeutic potential.

Targeting peptides are typically composed of 3-15 amino acids (aa) and are designed to specifically bind to tumour cells or tumour vasculature, allowing for targeted delivery to the tumour and its microenvironment (83, 84). These peptides can be used to decorate the surface of DDSs, enhancing their ability to target tumours (85). Common targeting peptide motifs include the RGD sequence (Arg-Gly-Asp), which binds to integrins on the tumour vasculature, and the NGR sequence (Asn-Gly-Arg), which binds to

aminopeptidase on endothelial cells (86). The epidermal growth factor receptor (EGFR), which is overexpressed in many types of cancer, is another important target (87). In addition, a variety of other peptides targeting different receptors overexpressed in tumours or blood vascular endothelium can be employed to improve the specificity and efficacy of cancer therapies (83).

Tumour targeting can greatly enhance the precision of cancer treatments, leading to improved drug accumulation at tumour sites while minimizing the impact on healthy tissues (**Figure 1**).

ENHANCEMENT OF PENETRATION OF SUPRAMOLECULAR DDSs

Poor tumour penetration is one of the biggest hurdles in cancer treatment. Typically, nanoparticles accumulate near tumour blood vessels but fail to penetrate deep into the tumour tissue, which often leads to drug resistance and reduced therapeutic efficacy (88). This limitation underscores the need for more effective DDSs. One promising solution to overcome this obstacle and reduce drug resis-

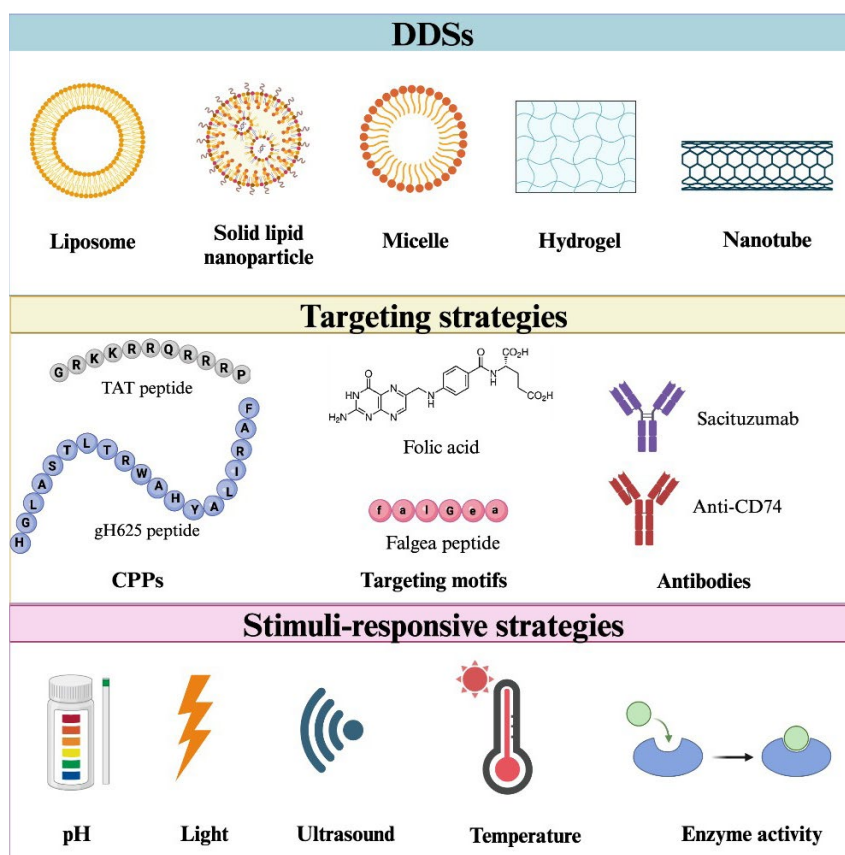


Figure 1. Examples of different drug delivery systems strategies.

tance is the exploitation of cell-penetrating peptides (CPPs) (89).

CPPs are short peptides, typically up to 40 aa, known for their ability to cross cellular membranes and are particularly attractive due to their low cytotoxicity, high efficiency, and the absence of limitations regarding the size or amount of the cargo (88). These peptides have been widely explored for delivering a variety of therapeutic molecules, especially in cancer treatment. The potential of CPPs to enhance drug delivery to tumours while sparing healthy tissues has been demonstrated across several tumour models. Currently, over 30 CPPs are undergoing clinical trials, though only a few have reached Phase III (90). The most well-known cationic CPP is TAT, derived from HIV-1 proteins (91, 92). Cationic CPPs bearing amino acids like arginine and lysine are positively charged, which gives them a strong affinity for the negatively charged cell membrane (92). This electrostatic interaction facilitates internalization through a receptor independent mechanism which involves endocytic pathways (93). Amphipathic CPPs, have both polar and non-polar domains. Their amphipathic nature allows them to interact with both hydrophilic and hydrophobic environments, facilitating their integration into cellular membranes. Examples include Penetratin and MAP, which have distinct structural characteristics in aqueous and membrane environments, changing from random coil to secondary structures such as α -helical or β -sheet conformations; the modification of the secondary structure is essential in cellular uptake (94-96). Hydrophobic/membranotropic CPPs contain a high number of hydrophobic residues that enhance their affinity for lipid membranes, though the content of hydrophobic residues is low enough to avoid haemolysis of healthy cells. These peptides are capable of penetrating deeper into the membrane hydrophobic core compared to cationic CPPs (97). Notably, viral fusion peptides are examples of membranotropic CPPs that effectively penetrate cellular membranes (98, 99).

Despite the potential of CPPs, factors such as the peptide concentration, structure, charge, and length, as well as the cell type and the properties of the associated cargo (size, type, and charge), influence the efficiency of cellular uptake (100, 101). The two main internalization pathways are energy-independent (direct translocation) and energy-dependent (endocytosis) mechanisms. In both cases, peptides initially interact electrostatically with cell surface glycosaminoglycans, which facilitates their entry

into cells (102). The subsequent transduction models, such as barrel-stave and toroidal pore models, or carpet models, explain how some peptides may destabilize the membrane or form pores, aiding their internalization (103).

However, one of the key challenges is overcoming endosomal entrapment, as the endocytosis process often leads to cargo being trapped in endosomes or lysosomes, hindering its release into the cytoplasm. As said, cationic peptide exploits essentially endocytosis mechanism of internalization, while membranotropic CPPs are thought to bypass this issue by directly penetrating the plasma membrane, allowing the cargo to be immediately bioavailable (104). Galdiero *et al.* developed a membranotropic peptide, namely gH625 (105) that interacts with the cell membranes and spontaneously inserts into the bilayer forming an amphiphilic α -helical structure. The N-terminal histidine residue is strongly involved in the fusogenic activity of the peptide, while the hydrophobic residues of tyrosine and tryptophan are fundamental for the structural stability during the interaction with the lipidic membrane. gH625 was proved to be able to carry different cargos inside several cell lines and to enhance internalization across the BBB (106, 107).

Studies have shown that combining CPPs with chemotherapeutic agents can improve drug delivery, even in drug-resistant cancer cells (108-110). Doxo, when coupled with Penetratin and Tat, showed increased cytotoxicity in both drug-sensitive and drug-resistant cancer cells. Liposomes conjugated to gH625 were able to overcome Doxo resistance in lung adenocarcinoma cell lines (111).

ON-DEMAND STRATEGIES FOR DRUG RELEASE

The development of stimuli-responsive DDSs has become a significant area of scientific research, offering new approaches for targeted drug delivery. These systems exploit the unique features of the tumour microenvironment to enhance the specificity and effectiveness of treatment (78, 111). For instance, cancer cells rely on anaerobic glycolysis for energy, leading to an accumulation of lactate and protons, which makes the surrounding tumour microenvironment more acidic (111). This acidic environment not only contributes to tumour growth and metastasis but also plays a key role in drug resistance. To exploit this, pH-responsive peptides can be conjugated to DDSs. pHLIPs

is a pH-low insertion peptide which can change its structure in response to acidic conditions. In particular, at lower pH, the acidic aa bind protons, lose their negative charge, and can more effectively penetrate cell membranes, promoting internalization and drug delivery into tumour cells (112). Chen *et al.* reported a new pH-responsive nano-drug delivery system using boronic acid-ester chemistry (23). They synthesized nanoparticles (PTXPBA NPs) from hydrophobic phenyl-boronic acid-modified polyesters and hydrophilic PEGs, loading them with the chemotherapy drug paclitaxel. The resulting nanoparticles were tested *in vitro* and *in vivo*, showing improved drug release, encapsulation efficiency, anticancer activity, pharmacokinetics, and reduced toxicity compared to traditional methods. Another hallmark of cancer cells is the redox-active environment, which can be exploited to design redox-sensitive DDS. The intracellular levels of glutathione (GSH) in cancer cells are much higher than in normal cells and this difference can be used to trigger drug release from DDSs that are conjugated through disulfide bonds or di-selenide bonds, which are cleaved by GSH (113).

Many enzymes that are upregulated in cancer cells can also be used to modify DDSs and trigger drug release. For instance, matrix metalloproteinases (MMPs), which are enzymes involved in tumour invasion and metastasis, are overexpressed on the surface of cancer cells (114). MMP-sensitive DDSs can be designed to release drugs when cleaved by these enzymes. Nagel *et al.* (115) developed MMP-sensitive, peptide-crosslinked nanogels (pNGs) for improved drug delivery to solid tumours using a dendritic polyglycerol scaffold and strain-promoted click chemistry. The pNGs were stable in physiological conditions but degraded by MMP-7, leading to size reduction and enhanced penetration in agarose matrices and multicellular tumour spheroids (MCTS) (115).

Guarnieri *et al.* (116) developed tumor-activated pro-drug-conjugated nanoparticles (TAP-NPs) that release Doxo in MMP2-rich tumor environments. In a similar study, Del Genio *et al.* (58) designed self-assembled peptide-based nanofibers for TNBC therapy, incorporating a CCP and an MMP-9-responsive sequence. Characterization confirmed efficient drug loading, release, and *in vitro* cytotoxicity. Also, Bellavita *et al.* (117) functionalized peptide-based nanofibers with a CPP and EGFR-targeting peptide to enhance Doxo specificity in TNBC. MTT assays showed superior efficacy compared to free Doxo, demonstrating the potential of peptide-decorated nanofibers in targeted cancer therapy.

Interestingly, Ramezani *et al.* (24) created a DDS by grafting poly(dimethylaminoethyl methacrylate) (PDMAEMA) onto silica nanoparticles with two different lengths using an *in-situ* atom transfer radical polymerization, obtaining a pH- and temperature-sensitive shell. The drug release followed the polymer shell protonation at pH 5 while a critical temperature of 41 °C aided rapid solvation of the shell polymers in the blood. Wang *et al.* (8) reported the creation of photocleavable hydrogels by directly gelling 4-arm thiol-terminated polyethylene glycol with 3,6-dichloro-1,2,4,5-tetrazine, forming S, S-tetrazine linkages. They stated that these hydrogels degraded efficiently when exposed to ultraviolet or green light, with a possibility of hydrogen peroxide significantly catalysing the degradation. Furthermore, they reported that loading the hydrogels with either calcium peroxide microparticles or glucose oxidase/catalase enzymes allowed for precise and efficient *in vivo* photocontrol of both gel breakdown and drug release for cancer treatment. Regarding drug delivery methods generated by ultrasound, lipid-supported mesoporous silica nanoparticles (MSNPs) were used by Amin *et al.* (118) to create a stimuli-responsive DDS that would activate drug release at the target location while preventing an early release into the systemic circulation. They used perfluoropentane (PFP), a US responsive material, as a model drug and created MSNPs with a release profile that complied with FDA-approved US-irradiation, which is characterised by a larger drug loading capacity and extremely gradual release. They reported these MSNPs to provide stable and non-toxic delivery of anticancer drugs, with ultrasound triggering the release of PFP gas to disrupt the lipid coating and release the drug.

The development of stimuli-responsive DDS offers great potential for improving the specificity and effectiveness of cancer therapies (119). The combination of multiple responsive triggers, such as pH, temperature, and enzymatic activity, enables more precise control over drug release, improving both the therapeutic outcome and reducing systemic toxicity.

EMERGING SUPRAMOLECULAR DDSs

Peptides offer functional diversity based on their sequence, making them excellent candidates for creating self-assembling systems with distinct properties (54). The nature of their amino acid side chains is responsible for key noncovalent interactions that make them ideal components for constructing com-

plex supramolecular assemblies (120). Peptides are relatively simple to synthesize using solid-phase techniques, allowing researchers to explore various designs and understand how molecular changes affect their characteristics (121). Additionally, peptides possess high biocompatibility, biodegradability, and low immunogenicity, which are advantageous when developing functional nanomaterials (120).

Peptides can spontaneously self-assemble into various nanostructures, such as vesicles, nanotubes, fibers, sheets, micelles and nanospheres according to their sequence length, amino acid side chains, and external conditions like pH and ionic strength (54, 122). Researchers can create diverse nanostructures with desired features by modifying these parameters and these nanostructures can be exploited as DDSs, opening the path to the modification of existing self-assembly sequences to optimize their functions. It is possible to easily incorporate cell-targeting sequences into these structures enhancing the specificity of drug delivery and reducing the impact on healthy tissues (58). Additionally, peptides can be modified to produce structures that respond to environmental changes, such as low pH or elevated temperature, making them ideal for on-demand drug release (123). In the context of cancer theranostics, self-assembling peptides offer dual benefits by delivering anticancer drugs while also providing a means for bioimaging and diagnosis (124). Peptide-based carriers are thus designed to bind specific tumour markers, allowing for targeted therapy and non-invasive monitoring of the treatment's effectiveness. Biological distribution of peptide self-assembled DDSs is influenced by their size and shape. While spherical nanoparticles have been commonly used in carrier designs, recent research has shifted toward anisotropic nanoparticles, which differ in shape depending on the direction (125). These anisotropic nanoparticles tend to exhibit greater resistance to non-specific elimination by cells, making them "stealthier" compared to spherical ones and have also been proved to have improved penetration efficiency. For example, Ben-Akiva *et al.* (126) synthesized spherical PLGA nanoparticles and then stretched them above the glass transition temperature of PLGA. These anisotropic nanoparticles-maintained fluidity and stability similar to spherical ones and could be coated with naturally derived cell membranes. When coated with red blood cell membranes, anisotropic nanoparticles were better able to evade macrophage clearance, leading to a longer half-life compared to spherical nanoparticles. In fact, around 50% of mice treated

with ellipsoidal nanoparticles remained healthy a week after being administered alpha toxin (126). Galdiero Group developed self-assembled peptide-based nanofibers from two amphiphilic peptides P1 and P2 bearing both an hydrophobic (C19 lipid tail and hexa-alanine sequence) and a hydrophilic (-GDDS- and -GKRS-) domain (58). The two peptides were the building blocks used to obtain the nanofiber structure, while the nanofiber surface was decorated with gH625 and Doxo, as delivery peptide and anticancer drug, respectively (**Figure 2**). Doxo was released due to the presence of a peptide sequence cleaved by the MMP-9 enzyme for on demand delivery into Triple-negative breast cancer lines (58). Similarly, this self-assembled peptide-based nanofibers can be used for gene therapy; in fact, the functionalization of nanofiber surfaces with R9 peptides allowed to electrostatically bind a siRNA, targeting and silencing epidermal growth factor receptor (EGFR) gene overexpressed in triple-negative breast cancer (127). This evolution would expand the system's application to combined approaches, including

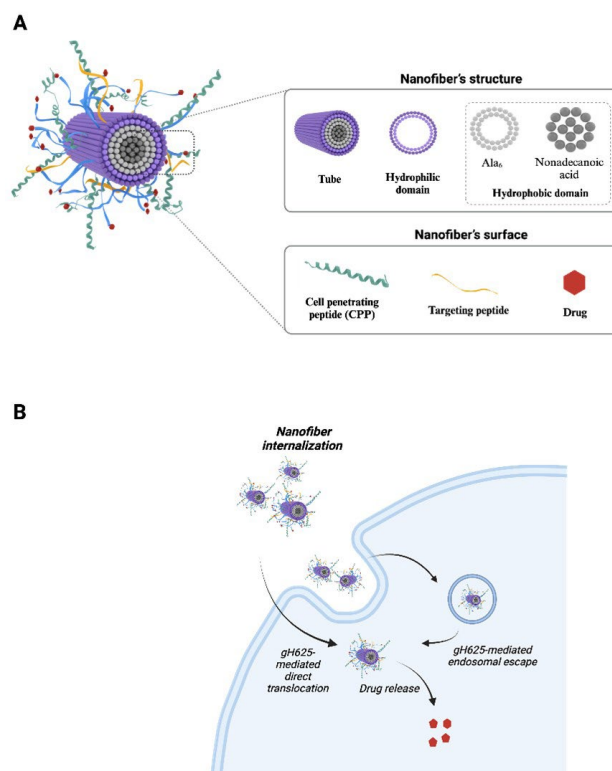


Figure 2. (A) Schematic representation of self-assembled nanofiber composed of amphiphilic peptides, which can be functionalized with specific ligands for targeted delivery and conjugated with chemotherapeutic drug; (B) Mechanism of nanofiber internalization: the system, decorated with the cell penetrating peptide, facilitates cellular uptake and drug release in cancer cells.

both pharmacological treatment and gene therapy, particularly relevant in resistance subtypes of cancer.

ARTIFICIAL INTELLIGENCE AND DDSs

The development of increasingly sophisticated and accurate artificial intelligence (AI) systems has in recent years enabled the integration of machine learning and bioinformatics algorithms for the design and development of DDSs. These algorithms allow the optimization of the property of delivery systems and predict both the behaviour in the microenvironment in which they will be inserted through external solvent simulations and the properties of interactions of lipid or polymeric components in the case of lipid- and polymer-based particles, with a predictive index of, for example, the critical aggregation. Dong *et al.* have designed a web platform namely FormulationAI that allows in silico pharmaceutical formulation design, with data collected regarding used and known six DDS and solubility of drugs in different solvents reported from public databases and literature data referring to a time range of 10 years prior to writing the project (128), while another strategy combines AI methods and target fishing that allows the rapid identification of biological targets, an important aspect for linking novel compounds (129). To fully unlock the potential of nanomedicine, the integration of artificial intelligence plays a crucial role. In particular, the use of artificial neural networks (ANNs) can aid in predicting how the characteristics of a designed nanosystem influence its interactions with target tissues and cells (130). In addition, machine learning methods of this kind would facilitate rapid assessments of both therapies and patients, strengthening the connection between scientific research and clinical practice while advancing the development of highly precise personalized treatments (131). These conceptual tools can provide theoretical and predictive support during the design phase of a delivery system, simulating both the interaction of the nanosystem constituents with the microenvironment and the interaction of the drug against the specific therapeutic target.

FUTURE PERSPECTIVE

In summary, with the promising advancements in DDS, the horizon of possible treatments is expand-

ing, enabling the development of novel therapies, the delivery of previously inaccessible treatments, and ultimately paving the way for precision medicine. At the clinical level, these advancements have led to improved patient compliance, reduced exposure to frequent dosing, and alternative administration routes. One of the most significant impact of DDSs in cancer is the site-specific delivery of cytotoxic payloads to tumoral cells, and patients with metastatic cancer now have access to therapies that can specifically target metastatic zones. For instance, Antibody-Drug Conjugates (ADCs) have been developed to deliver cytotoxic agents directly to cancer cells, minimizing systemic exposure and enhancing treatment efficacy (132). Moreover, DDS are particularly beneficial for diabetes patients, reducing the need for repeated insulin injections and improving overall disease management (133).

In addition, the rapid advancement of focuses on minimizing chemotherapeutic side effects by utilizing biocompatible and biodegradable materials that do not accumulate in the body but instead provide beneficial effects through their metabolism; for instance, substances like chitosan, gelatine, alginate, peptides are used for oral administration (54, 134). Solid lipid nanoparticles and liposomes have gained widespread acceptance, especially after the success of lipid-based COVID-19 vaccines, though concerns about immune responses to certain materials remain. Fully peptide-based delivery systems, like those developed in our lab, present a promising strategy for creating biodegradable and biocompatible nanoparticles (54). Ultimately, the development of innovative requires a multidisciplinary approach that integrates clinical needs with chemical and biological expertise. Interdisciplinary collaboration can help overcome challenges in traditional therapies and bridge the gap between research and medical application. Continued innovation in DDS design and manufacturing could improve automation, reduce costs, and enhance healthcare accessibility (10).

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COMPLIANCE WITH ETHICAL STANDARDS

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Conflicts of interests

The authors have declared no conflicts of interests.

Availability of data and materials

The data underlying this article are available in the public domain.

Authors' contributions

SB, OEA, SP, LEI, were responsible of the initial draft; RB, AF, LA, revised the manuscript; AG and SG conceived the content of the manuscript.

Ethical approval

Ethical approval was not necessary for this study.

Publications ethics

Plagiarism

The article provides a comprehensive review of the latest studies in the field, with accurate citations.

Data falsification and fabrication

The writing and contents of the article are entirely original and were developed entirely by the authors.

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