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"ADVANCES IN PEPTIDE- AND ANTIBODY-TARGETED NANOCARRIERS FOR CANCER THERAPY AND IMAGING"

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Abstract
Using nanocarriers to deliver drugs directly to cancer cells is a new and effective approach that helps make treatments work better and causes less harm to healthy tissues. Specific peptides and special types of antibodies, called scFvs, are chosen through methods like in vivo and in vitro phage display. This help target only the receptors found on cancer cells. Nanocarriers, such as liposomes, polymeric nanoparticles, and mesoporous silica nanoparticles (MSNPs), are simple platforms that help carry the drugs to the right place as well as complex constructs like protocells, enable precise delivery of chemotherapeutics, imaging agents, and theranostic cargos. Surface functionalization of nanocarriers with targeting moieties through direct or multi-step conjugation strategies further enhances tumor accumulation, cellular uptake, and therapeutic outcomes while preserving ligand functionality. Advances in biocompatible, biodegradable, and high-capacity nanocarriers combined with optimized conjugation techniques hold significant potential for personalized cancer therapy and image-guided treatment.

Keywords: Tumor-targeted therapy; Nanocarriers; Mesoporous silica nanoparticles; Antibody phage display; Peptide targeting; Protocells; Chemotherapeutics; Imaging agents; Conjugation strategies; Theranostics

1. Introduction:

Limitations and Advances in Nanocarrier-Based Cancer Drug Delivery
Traditional cancer treatments with chemotherapy drugs often have problems like not dissolving well in water, harming healthy body parts, and creating resistance over time. These issues are made worse by serious side effects such as vomiting, tiredness, nerve damage, and organ failure. One good way to deal with these problems is to wrap the cancer drugs inside special tiny carriers made from safe materials. This helps the drugs dissolve better, stay in the body longer, and deliver the medicine more precisely to the cancer cells. (2).

Simple nanocarriers are fabricated from diverse materials, some types of nanocarriers used in drug delivery include magnetic or colloidal metals, carbon-based nanostructures, mesoporous silica, liposomes, and polymeric formulations.(3)These nanocarriers have different physical and chemical properties, such as size, shape, how much drug they can carry, how they release the drug, how stable

they are, how well they stay at a tumor site, and how the body gets rid of them. These differences can affect how well the treatment works. (4) The size of the nanocarriers is especially important. (5) Particles smaller than 5 nm are usually cleared from the body by the kidneys, though some up to 50 nm have been found in urine. Nanoparticles larger than 100 nm are mostly taken up by the mononuclear phagocyte system. (6).

The best-designed nanocarrier should stay stable while moving through the body, protect the medicine it carries, reach only the target area, move deep into the tumor, release the drug at the right time, and leave the body safely to prevent long-term harm (7). Scientists have combined features from various types of nanocarriers to create more effective ones that distribute better in the body and work better against cancer. (8).

Even though there have been some big improvements, one major problem still exists: the lack of natural ability to target specific places in the body. In solid tumors, though, the blood vessels are not properly formed. They have big holes in the endothelial cells and the pericytes aren't tightly attached. This allows nanoparticles to pass through the blood vessel walls and accumulate in the tumor area because of something called the enhanced permeability and retention (EPR) effect. (9,10) While the EPR effect helps nanoparticles reach the tumor without needing a direct target, it doesn't always lead to a strong enough drug buildup. Also, if the nanoparticles stay in the bloodstream for too long, they might not concentrate enough in the tumor, which can reduce their effectiveness. (11)

To solve this problem, researchers have looked into active targeting methods. Since 1996, both in vivo and in vitro phage display techniques have been commonly used to find pairs of ligand-receptor or single-chain variable fragment (scFv)-epitope that can target specific tumors (12,13,14). Peptides found through in vivo phage display only attach to receptors that are accessible in the body, and this process can be adjusted to focus on ligands that are taken up by receptors (15). This way of selecting works around problems like EPR effect reliance and non-specific absorption, and it skips the need for extra checks to see if the ligands get taken inside cells (16).

Depending on where the receptor is located—either on the tumor cell membrane or on the blood vessels around the tumor—the ability to bring the drug inside can be limited or increased.
This helps use the bystander effect to spread the drug more effectively (17). For instance, liposomes loaded with doxorubicin that are targeted have helped reduce unwanted effects in neuroblastoma models (18). Similar improvements have been seen in targeting breast and pancreatic cancer cells by adding peptides from bacteriophage pVIII fusion proteins to the surface of liposomes (19).
A promising idea is using functionalized protocells, which are special nanocarriers made up of a mesoporous silica nanoparticle (MSN) core covered with a supported lipid bilayer (SLB) (20,21).
The core can hold a lot of different drugs or diagnostic tools, while the SLB shields the contents, makes the system more compatible with the body, and provides a way to add coatings or attach proteins or antibodies for better targeting (22).

These protocells can be customized by swapping out targeting parts based on the type of tumor.
For example, peptides or scFvs can be made to target specific receptors in different cancers, like interleukin-11 receptor alpha (IL-11RÎ±) in prostate or breast cancer (23,24), glucose-regulated protein 78 kDa (GRP78) in breast cancer (13), or EphA5 in non-small cell lung cancer (26). These scFvs can also be made to change how the receptor works, help the drug work better, or get the drug inside the cell for release (27).
Table 1 lists examples of targeting peptides identified through phage display that have demonstrated receptor-mediated internalization, highlighting their potential in precise cancer nanomedicine

Table 1. Tumor-targeting peptide motifs, corresponding receptors, and internalization potential identified through phage display.

Peptide Motif	Target Receptor	Tumor Type(s)	Internalization	Reference(s)
CGRRAGGSC	Interleukin-11 receptor α (IL-11Rα)	Prostate, breast cancer	Yes	(28,29)
LTVSPWY	Unknown cell-surface receptor (tumor-specific)	Breast cancer	Yes	(30)
YHWYGYTPQNVI	Glucose-regulated protein 78 kDa (GRP78)	Breast, prostate cancer	Yes	(31)
VNTANST	Annexin A1	Breast cancer, angiogenic vasculature	Yes	(32)
NGR (CNGRC, GNGRAHA)	Aminopeptidase N (CD13)	Solid tumors, tumor vasculature	Yes	(33)
RGD (CRGDKGPDC, ACDCRGDCFCG)	αvβ3/αvβ5 integrins	Melanoma, glioblastoma, breast cancer	Yes	(34,35)
SWQIGGN	EphA5 receptor	Non-small cell lung cancer	Yes	(36)
CPRECESIC	Prohibitin	Breast cancer	Yes	(37)
CKGGRAKDC	p32/gC1qR protein	Glioma, breast cancer	Yes	(38)
FQHPSFI	Tenascin-C	Glioblastoma	Yes	(39)
CTTSPNLC	Neuropilin-1	Pancreatic adenocarcinoma	Yes	(35)
SP5-52 (GDSILPG)	HER2	Breast cancer	Yes	(40)

Other notable examples of targeting peptides come from luteinizing hormone/chorionic gonadotropin. When these peptides are linked to lytic peptides that break down cell membranes, they have shown strong ability to stop the growth and spread of human breast and prostate tumors in early research studies (42,48,49). Besides peptides and antibodies, aptamers are also being used as useful tools for treating cancer. Aptamers are short strands of RNA or DNA that have been tested in clinical trials for carrying chemotherapy drugs or attaching to nano-sized carriers that hold medicines (45,46). For example, combining aptamers with drugs like doxorubicin or a substance that blocks NF-κB has been effective in stopping the growth of pancreatic cancer cells in lab tests by stopping the movement of NF-κB into the cell nucleus (51).

Like conventional chemotherapeutics, targeted therapies operate via a dynamic and progressive process, ensuring that toxic cellular byproducts remain within physiological clearance limits (50). The enhanced permeability and retention (EPR) effect, resulting from the intrinsic leakiness of tumor vasculature, facilitates passive accumulation of nanocarriers within tumors. However, once such passive accumulation occurs, additional advantages can be achieved through active targeting. Specific binding to tumor-associated receptors, subsequent cellular internalization, and retention in the tumor microenvironment allow for localized therapeutic release, improving therapeutic indices while reducing systemic toxicity (44).

Functionalized protocells represent a particularly versatile platform in this context. By integrating targeting ligands with a high-capacity cargo system, these nanocarriers may overcome "binding site

barriers” that limit the performance of other targeted delivery systems, as receptor variability and turnover rates at tumor sites are not fully accounted for in classical models (41). Moreover, unlike passive nanocarriers, targeted protocells can be administered at lower doses while achieving higher effective concentrations at the target site, as confirmed by both experimental data and computational simulations (33,47). The high loading capacity of protocells prevents receptor saturation, and the targeting ligand density can be precisely modulated by altering the functional group composition in the lipid bilayer (43).

Considering these properties, selective targeting using functionalized protocells offers a promising strategy to bypass binding site inhibition. Furthermore, their modular design allows for customization based on tumor type or subtype, enabling the integration of single or multiple therapeutic payloads, including non-invasive imaging agents or combination therapies. This adaptability aligns well with the principles of personalized medicine, where payload selection and delivery parameters can be optimized for individual clinical treatment plans.
The main goals of this review are three: first, to explain how targeting peptides and single-chain variable fragments (scFvs) are chosen using methods like in vivo and in vitro phage or antibody display, and how they are used in clinical settings; second, to compare different types of nanocarriers and the drugs they carry; and third, to look at ways to attach these drugs to nanocarriers to make treatments more effective. In the end, making targeted nanomedicine work well and tailored for each patient will need thorough testing in various types of cancer models.

2. Targeting Strategies

2.1 Peptide Phage Display

Phage display was first introduced as an innovative molecular technique to clone genes by exploiting the binding specificity of antibodies to probe bacteriophage clones displaying peptide epitopes fused to the minor coat protein pIII of filamentous phages (53). In early experiments, the correct epitope could be enriched by several orders of magnitude—up to a thousand-fold—within a single selection round (54). Following this initial breakthrough, the display of random peptide libraries on pIII evolved into an unbiased and versatile in vivo screening platform for mapping ligand–receptor interactions (54,55).
Using this approach, numerous peptide ligands have been identified that selectively recognize vascular or cellular receptors in diverse normal tissues—such as brain, kidney, adipose tissue, lung, skin, pancreas, retina, intestine, uterus, prostate, and adrenal glands (58,59)—as well as in pathological contexts in both human patients and animal models (56,61). Importantly, in vivo phage display combined with laser capture microdissection has revealed that endothelial receptors can be differentially expressed at sub-organ or even sub-cellular levels—for example, within pancreatic islets—and that such receptors may be overexpressed in islet tumors (59). These findings emphasize the molecular heterogeneity of endothelial cell surface receptors and highlight a major advantage of in vivo phage display over conventional protein profiling methods, which often neglect anatomical context and fail to detect receptors that are spatially restricted or conditionally accessible (65).

2.1.1 Selecting Peptides by In Vivo Phage Display

In a standard in vivo phage display workflow, a diverse peptide library—linear or cyclic—with up to 10^9 unique sequences displayed on the bacteriophage pIII protein is administered intravenously (55). Circulating peptide ligands then interact with physiologically accessible receptors on target tissues. After a defined circulation period, the organ or tissue of interest is harvested, and the bound phage are recovered by infecting Escherichia coli host bacteria. The DNA sequences encoding the peptide inserts are subsequently determined via Sanger or high-throughput sequencing (61, 62).
An alternative strategy involves simultaneous recovery of phage from multiple organs, each uniquely barcoded using PCR amplification prior to next-generation sequencing, enabling parallel mapping of peptide–receptor interactions across tissue types (63,64). This barcoded approach

greatly increases throughput and provides a comparative tissue tropism profile of candidate ligands within a single experiment.

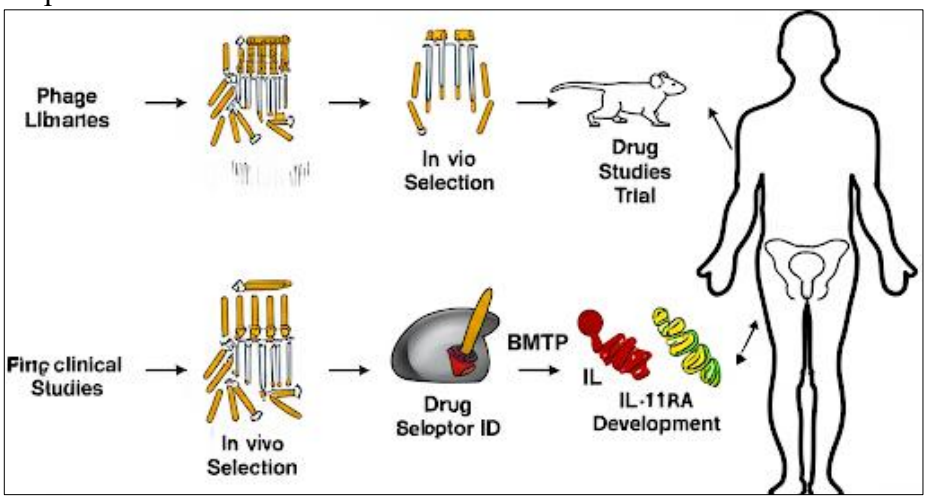

Figure 1: Phage Display and Drug Development Process

This title accurately reflects the key elements shown in the diagram, which illustrates the use of phage libraries for in vivo selection, receptor identification, and the subsequent development of drug candidates like BMTp and IL-11RA, culminating in preclinical and clinical studies.

After multiple iterative rounds of in vivo phage display selection, peptide ligands become progressively enriched in the target tissue. In each round, phage particles that display peptides binding to internalized or surface-exposed receptors are recovered, amplifying their representation in the subsequent selection cycle (23,24). Bioinformatic analysis of the recovered peptide sequences in both forward and reverse orientations has been employed to identify enriched tripeptide motifs, which are often associated with specific protein–protein interactions (30,31). These consensus motifs are cross-referenced against the NCBI protein database using the Basic Local Alignment Search Tool (BLAST) to predict potential protein ligands, which can subsequently suggest their corresponding receptors (32).

Candidate ligand–receptor pairs are further validated using in vitro phage binding assays and enzyme-linked immunosorbent assay (ELISA) when antibodies against the putative receptor are commercially available (33). In vivo validation involves testing the binding of individual phage clones displaying a single peptide ligand, followed by isolation of novel receptors via affinity chromatography using the synthetic peptide ligand (34,35).

This approach has successfully identified peptides that specifically recognize normal or diseased organs in diverse experimental systems, including mice, rats, swine, non-human primates, and even brain-dead human patients (26). Unlike untargeted nanocarriers, whose biodistribution is often influenced by serum protein interactions, synthetic peptides preserve their binding specificity to the same receptors observed in the phage-displayed format (37,38). Furthermore, phage display enables targeting of post-translationally modified receptors uniquely expressed in the pathological microenvironment (35, 39, and 40).

Successive selection cycles enhance the enrichment of phage in the target tissue by approximately 3- to 35-fold compared to non-targeted controls 33). Since its introduction in 1998, in vivo phage display combined with advanced bioinformatic analysis has greatly facilitated the discovery of tissue-specific and angiogenesis-related vascular ligand–receptor pairs (31,34,64). These have been effectively exploited for the targeted delivery of cytotoxic agents, pro-apoptotic peptides, fluorescent dyes, and cytokines to tumors, thereby improving selectivity and expanding the therapeutic window in preclinical models (28,35,40).

2.1.2. Applications of peptide targeting in cancer

In vivo phage display technology is particularly well suited for identifying and exploiting unique vascular receptors in human diseases such as cancer, where tumor progression depends heavily on the formation of aberrant, highly permeable blood vessels with distinct molecular profiles (37,42,56). Due to the leakiness of tumor vasculature, in vivo phage display has uncovered receptors expressed not only on tumor endothelial cells but also on stromal cells, extracellular matrix components, pericytes, lymphatic endothelial cells, and tumor cells themselves (68). Furthermore, angiogenic blood vessels acquire specific molecular signatures that can be leveraged for targeted delivery of therapeutic agents (74).

In addition to traditional in vivo approaches, a modified in vitro phage display technique called BRASIL (biopanning and rapid analysis of selective interactive ligands) enables separation of receptor-bound phage from unbound particles via centrifugation through a biphasic organic/aqueous interface (72) Using BRASIL, EphA5 was identified as a receptor on human non-small cell lung carcinoma cells (80). EphA5 overexpression was later confirmed in human lung tumors, where its presence correlated with radioresistance. Treatment with an EphA5-specific monoclonal antibody enhanced radiosensitivity and extended survival in lung tumor-bearing mice (80).
Phage display studies in a brain-dead cancer patient revealed non-random localization of peptide motifs to specific organs (57,61). One such motif, GRRAGGS, recovered from a prostate biopsy, showed homology to interleukin-11 (IL-11). IL-11 was confirmed to bind its cognate receptor IL-11Rα, which is overexpressed in advanced prostate cancer and metastases (74). IL-11/IL-11Rα overexpression has also been observed in breast cancer, with transcript levels significantly elevated in node-positive tumors (73), indicating a correlation with disease progression.

Building on these findings, a ligand-directed therapeutic, BMTP-11 (Bone Metastasis Targeting Peptidomimetic-11), was developed. BMTP-11 consists of the IL-11Rα-targeting peptide CGRRAGGSC conjugated to the mitochondria-disrupting pro-apoptotic peptide $D(KLAKLAK)_2$ (71). In murine and human xenograft models of prostate cancer and osteosarcoma, BMTP-11 treatment significantly reduced tumor size compared to controls (Arap et al., 2010). Preclinical toxicology studies in non-human primates demonstrated favorable stability, predictable pharmacokinetics, and tolerability. A phase 0 clinical trial in castration-resistant prostate cancer patients showed BMTP-11 could induce apoptosis in bone metastases (66).

In contrast to IL-11Rα, identification of GRP78 as a tumor target was more complex due to its role in the unfolded protein response (76). Using in vitro phage display of circulating antibodies from prostate cancer patients, the peptide CNVSDKSC was mapped to GRP78 (78). Additional ligands, including WDLAWMFRLPVG, WIFPWIQL, and SNTRVAP, were shown to bind cell-surface GRP78 (77,79). GRP78 expression is induced under hypoxia, acidosis, and glucose deprivation (70), and its presence on the cell surface predicts recurrence in prostate cancer (69) and poor survival in advanced breast cancer (81). Knockdown of GRP78 restores chemosensitivity, and monoclonal antibodies against GRP78 have shown therapeutic promise in preclinical studies (77). Like IL-11Rα, GRP78 is an attractive therapeutic target due to its selective overexpression on tumor cells and accessibility from the vasculature.

2.2. Antibody Display

The first therapeutic antibody approved by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) was the CD3-specific OKT3 monoclonal antibody (mAb) in 1986, which was indicated for the prevention of organ rejection in kidney transplant recipients (Orthoclone OKT3) (87, 93). Since then, the use of antibody-based biotherapeutics has increased substantially, with 38 such products in clinical use as of May 2015 and more anticipated by the end of that year (83). The clinical success of antibody therapeutics is attributed to their high specificity,

structural similarity to endogenous antibodies, and the utilization of natural catabolic pathways, which together reduce potential safety concerns during drug development (91).

2.2.1. Current Applications of Tumor-Targeting Antibodies

Antibody-based therapies exert anti-tumor activity through multiple mechanisms. One such mechanism is antibody-dependent cell-mediated cytotoxicity (ADCC), wherein antibody binding to a tumor cell surface receptor recruits immune effector cells to induce cell death. This is the primary mechanism of rituximab, an anti-CD20 mAb approved for the treatment of non-Hodgkin's lymphoma (88).

Another major therapeutic strategy involves inhibition of angiogenesis. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) mAb, prevents tumor vascularization by sequestering soluble VEGF and blocking its interaction with VEGFR-2, thereby starving the tumor of blood supply. This approach has been applied in breast cancer, metastatic colorectal cancer, and rectal carcinoma (84).

Antibodies targeting distinct epitopes of the same receptor can display synergistic effects. For example, trastuzumab and pertuzumab both target the human epidermal growth factor receptor 2 (HER2), but bind to different domains, thereby preventing receptor dimerization and enhancing antitumor activity (82,92). The advent of antibody–drug conjugates (ADCs), such as trastuzumab-DM1 (T-DM1), has further advanced personalized cancer therapy. T-DM1 utilizes the tumor-specific binding capacity of trastuzumab to deliver the cytotoxic microtubule-depolymerizing agent DM1, providing improved efficacy, favorable pharmacokinetics, and reduced systemic toxicity (95). Recent developments in immune checkpoint blockade have revolutionized cancer immunotherapy. Monoclonal antibodies targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4, e.g., ipilimumab) or programmed cell death protein 1 (PD-1, e.g., nivolumab) block negative regulatory signals, thereby reactivating T cells against tumor cells (86,94). Combination therapy with CTLA-4 and PD-1 inhibitors in advanced-stage melanoma patients has demonstrated improved tumor regression rates, although not all patients respond (90).

Additionally, antibodies have been developed as carriers for cytokines (85) or bacterial toxins (89) to selectively deliver therapeutic payloads to tumors. These approaches have shown variable efficacy in clinical trials and continue to evolve.
The subsequent sections discuss the selection of antibodies specific to cancer-associated antigens via naïve antibody library screening, followed by strategies to design antibody-based therapeutics capable of delivering nanocarrier-bound drugs. The integration of antibodies with nanomedicine and the exploitation of synergistic combinations between antibodies and their payloads represent promising avenues for clinical translation.

2.2.2. Selecting Targeting Antibodies

Antibodies can be generated through cultured cell systems (96) and can be engineered or selected against virtually any target protein to regulate downstream signaling pathways (99,107,109). Historically, the hybridoma technique developed by Köhler and Milstein (1975) remained the only reliable approach for producing monoclonal antibodies (mAbs) from splenocytes of mice immunized with specific antigens. However, murine-derived mAbs triggered human anti-mouse antibody (HAMA) responses, limiting their clinical utility due to immunogenicity (114). Recombinant antibody engineering subsequently reduced immunogenicity by creating chimeric antibodies, where murine complementarity-determining regions (CDRs) were grafted onto human antibody frameworks (96,110).

Further advances, such as the genetically engineered Xenomouse model, enabled the in vivo production of fully human antibodies upon antigen immunization (Green et al., 1994). Parallel

developments combined recombinant antibody methods with in vitro display technologies, enabling high-throughput selection of human recombinant mAbs (rhAbs) from large antibody diversity libraries (108). In these approaches, the complexity of the full immunoglobulin molecule (comprising two heavy and two light chains) is simplified to minimal antigen-binding formats such as single-chain variable fragments (scFvs) (Huston et al., 1988), antigen-binding fragments (Fabs) (97), or nanobodies derived from camelid heavy-chain antibodies (104). These formats, collectively termed “antibody-like binders,” retain full antigen-binding capacity and can later be re-engineered into full-length IgG molecules (107,109).

A major challenge in antibody displays technology lies in constructing highly diverse, functional libraries capable of yielding binders against virtually any antigen. Unlike peptide libraries, which can be generated using degenerate oligonucleotides, antibody libraries are constrained by structural requirements including correct chain pairing, disulfide bond formation, proper folding, and surface hydrophobicity (116). Despite these challenges, diverse libraries have been generated from naïve human repertoires (101,115), restricted scaffolds with natural diversity (97,111), and synthetic repertoires (118).

Library generation is typically achieved via cloning, though site-specific recombination strategies such as Gateway cloning have streamlined construction of large-scale libraries (Hartley et al., 2000). Among display platforms, phage display remains the most widely used (113,117), though alternative systems such as ribosome display (105) and yeast surface display (98,100,102) have also yielded high-affinity antibody binders.

2.2.3. Validation of Antibody-like Binders In Vivo

Unlike in vivo peptide phage display—which has been successfully employed to screen diverse peptide libraries in terminally ill patients and animal models (121,122,123,124,125,125,126)—in vivo antibody display has proven to be considerably more challenging. To date, notable progress has been achieved primarily by Shukla, Krag, and co-workers, who demonstrated the feasibility of injecting naïve antibody phage libraries directly into cancer patients, although the resulting antibody repertoires tended to be patient-specific (127).

One promising strategy involves isolating antibody-like binders to receptor targets that were first identified by in vivo peptide phage display, followed by screening a naïve human single-chain variable fragment (scFv) library against the purified receptor protein (128). Unpublished data from our group indicate that combining in vitro pre-selection with in vivo antibody display can yield tumor-specific antibodies when recombinant tumor receptors—identified via peptide phage display—are used as selection targets. In these experiments, an in vitro-enriched antibody phage sub-library containing clones specific to a known, overexpressed tumor-associated cell surface protein was injected into tumor-bearing mice. Several tumor-localizing recombinant human antibodies (rhAbs) were subsequently recovered from excised tumors. Their biodistribution was evaluated using next-generation sequencing (129,130) and immunohistological analysis of tumor sections compared to control organs.

3. Nanocarriers

The experimental strategy of selecting tumor-specific peptides and recombinant human single-chain variable fragments (scFvs) directly within the physiological setting represents a major advancement in targeted drug delivery, provided an in-depth overview of the design and application of magnetic and superparamagnetic nanoparticles for targeted drug delivery and cancer therapy. The review emphasized their unique physicochemical properties, such as magnetic responsiveness, biocompatibility, and potential for surface functionalization, which enable site-specific drug transport and controlled release. Furthermore, the study highlighted their dual role in both therapeutic applications and diagnostic imaging, positioning magnetic nanoparticles as promising

multifunctional platforms for cancer theranostics. (119,120). By leveraging tumor-targeting peptides, several studies, including our own, have demonstrated in vivo tumor growth inhibition through the delivery of diverse therapeutic cargos. For instance, tumor-targeting peptides have been conjugated with the pro-apoptotic peptide D(KLAKLAK) to selectively induce cancer cell death (120), loaded with doxorubicin to treat tumor-bearing mice (Garg et al., 2013), linked to tumor necrosis factor-alpha (TNF-α) for enhanced anti-tumor efficacy (121,122,123,124,125), and used to deliver reporter or suicide genes for cancer gene therapy (126,127).

3.1. Simple Nanocarriers

A diverse range of nanoparticles has been engineered for the delivery of therapeutic agents, each offering unique physicochemical properties that influence biodistribution, cellular uptake, and therapeutic index (142). These include:

Magnetic and metallic nanoparticles (e.g., iron oxide, gold), which not only act as efficient drug carriers but also serve as intrinsic contrast agents for magnetic resonance or computed tomography imaging (156).

- Carbon-based nanostructures such as graphene sheets and carbon nanotubes, notable for their high surface area and capacity for multifunctional drug loading (142).
- Polymeric nanoparticles and dendrimers, offering tunable surface chemistry and controlled release kinetics (157).
- Quantum dots for combined imaging and drug delivery due to their photoluminescent properties (158).
- Hydrogel-based delivery systems, which provide sustained release and biocompatibility (159).
- Liposomes, one of the most clinically established platforms, enabling both hydrophilic and hydrophobic drug encapsulation (160).
- Silica-based nanoparticles, known for high drug-loading capacity and surface functionalization flexibility (161).

Each nanocarrier type presents specific advantages and limitations. For example, metallic nanoparticles inherently function as imaging agents, reducing the need for additional diagnostic components, whereas polymeric or lipid-based carriers may require co-loading of contrast agents to achieve similar functionality (162). A comparative overview of these features, including their suitability for repetitive dosing and therapeutic delivery, is summarized in Table 2.

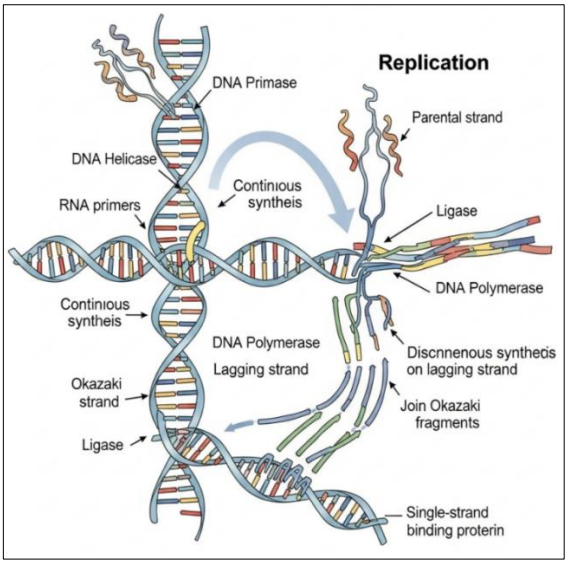

Figure 2: illustrated, which shows the unwinding of the DNA double helix and the synthesis of new strands by various enzymes.

"Table 2. Pros and Cons of Different Nanocarrier Platforms for Therapeutic Delivery"

Nanocarrier Type	Advantages	Disadvantages	References
Magnetic nanoparticles (e.g., iron oxide)	Dual functionality for therapy and MRI imaging; magnetic field-guided targeting; potential for hyperthermia treatment	Possible long-term toxicity; aggregation in vivo; limited biodegradability	(163,169)
Gold nanoparticles	Easy surface functionalization; photothermal conversion for cancer ablation; stable in physiological conditions	Non-biodegradable; potential cytotoxicity at high doses	(164,169)
Carbon nanotubes & graphene	High surface area for drug loading; ability to cross cell membranes; photothermal and photodynamic capabilities	Potential cytotoxicity and immunogenicity; low biodegradability; accumulation risk	(163)
Polymeric nanoparticles	Controlled and sustained release; versatile surface modification; biocompatibility; protection of cargo from degradation	Possible polymer degradation products causing toxicity; batch-to-batch variability	(165)
Dendrimers	Well-defined structure; multivalent surface for high drug loading and targeting; precise size control	Complex synthesis; possible cytotoxicity from cationic surface groups	(166)
Quantum dots	Strong fluorescence for imaging; tunable emission spectra	Heavy metal toxicity; concerns over long-term stability and clearance	(172)
Hydrogel-based systems	High water content mimicking biological tissues; controlled release via stimuli responsiveness	Mechanical weakness; possible burst release	(165)
Liposomes	Biocompatible; approved for clinical use; encapsulation of hydrophilic and hydrophobic drugs; modifiable with targeting ligands	Limited stability; short circulation time without PEGylation; possible rapid clearance by RES	(167,169)
Silica-based nanoparticles	High surface area; tunable pore size; ease of functionalization for targeting and controlled release	Long-term toxicity; slow biodegradation rate	(168)

Magnetic and Metallic Nanoparticles

Magnetic-based nanoparticles, most commonly iron oxide nanoparticles, offer the theoretical advantage of precise therapeutic delivery to a targeted region using external magnetic fields (172,173,174). In addition, metallic nanoparticles—including magnetic iron oxide—show potential for multimodal theranostic applications (175,176,177,178). The theranostic utility of magnetic iron oxide particles is supported by U.S. Food and Drug Administration (FDA) approval of several iron oxide nanoparticle-based imaging agents (179,180). However, their non-biodegradable nature limits repeated therapeutic applications because of gradual systemic accumulation (181,182). For example, even a single dose of iron oxide nanoparticles can result in measurable accumulation in the liver, spleen, and lungs 90 days post-injection (183), with slow elimination via urine and feces (184,185). The solid structure of these particles also inherently limits their therapeutic cargo-loading capacity.

Gold nanoparticles (AuNPs) represent another widely studied metallic nanocarrier, valued for their biocompatibility, imaging potential, and suitability for photothermal therapy (186,187,188,189,190). Despite these advantages, AuNPs also accumulate in the liver and spleen for months after administration, and while this has not been associated with overt toxicity, their lack of

biodegradation remains a concern (191,192,193,194). Similar to iron oxide nanoparticles, their solid structure restricts therapeutic payload per particle.

Carbon- and Silica-Based Nanocarriers

Carbon-based nanocarriers such as graphene sheets and carbon nanotubes offer extremely high surface areas, enabling dense functionalization and high therapeutic loading (195). However, their limited biodegradability leads to systemic buildup with repeated use, along with risks of pulmonary and immune toxicity (196,197,198,199,200,201,202,203).

Mesoporous silica nanoparticles (MSNPs) are distinguished by exceptionally high internal surface areas (500–1200 m^2/g) and uniformly sized mesopores (2–>20 nm) within an amorphous silica framework (204). These can be synthesized in diverse sizes (25–250 nm) and morphologies—prismatic, spherical, toroidal, or rod-shaped (205,206,207,208,209,210)—with pore chemistries modifiable via silane coupling for diverse cargo compatibility (211,212,213,214). Amorphous silica is classified as “Generally Recognized As Safe” (GRAS) by the FDA, and a silica-based nanoparticle formulation has advanced into Phase I clinical trials (215). While biocompatibility testing of MSNPs has shown variable results, toxicity is generally linked to incomplete removal of residual surfactants used during synthesis (216). Surfactant-free MSNPs have shown low toxicity even at high doses in mice (217), and amorphous silica dissolves into soluble silicic acid species that are readily cleared (218,219,220,221). Disadvantages include instability in physiological buffers and rapid clearance by the mononuclear phagocyte system (MPS) (222,223,224,225,226), which can be mitigated by polymer or lipid coating.

Polymer- and Lipid-Based Nanocarriers

To avoid bioaccumulation and MPS clearance, polymeric and lipid-based nanostructures have been extensively explored. Liposomes are among the most clinically successful nanocarriers, with several FDA-approved formulations (227,228,229).

3.2. Complex Nanocarriers

Complex nanocarriers integrate multiple functional features of simple nanocarriers to enhance therapeutic performance while reducing inherent limitations (239,240). For instance, liposomes and polymer-based nanoparticles offer good circulation half-lives and biocompatibility but often suffer from poor stability and drug retention (241,242). These drawbacks can be mitigated by incorporating a stable nanoparticle core—such as magnetic nanoparticles, gold nanoparticles, carbon-based carriers, or mesoporous silica nanoparticles (MSNPs)—within polymeric or liposomal systems (243,244).

MSNPs, in particular, possess high surface area, tunable porosity, biocompatibility, and biodegradability, enabling high drug-loading capacity and compatibility with diverse cargo molecules (245,246). Surface modification with polymers like polyethylene glycol (PEG) or PEG-polyethylenimine (PEI) can significantly extend blood circulation and enhance tumor accumulation via the enhanced permeability and retention (EPR) effect (247,248). Additionally, attaching targeting ligands such as transferrin or folic acid improves selective delivery and therapeutic efficacy (249,250,251,254,253,254,255,256).

3.3. Therapeutic payloads

3.3.1. Imaging Agents

The large surface area and tunable chemistry of mesoporous silica nanoparticles (MSNPs) allow simultaneous incorporation of imaging agents and therapeutics. Near-infrared (NIR) dyes or fluorescent labels such as fluorescein isothiocyanate (FITC) can be loaded into MSNPs for real-time in vivo biodistribution studies following intravenous administration (257,258). Surface modifications, including PEG or PEG-PEI coatings, further influence nanoparticle circulation and clearance (259). Multiple imaging modalities can be integrated into a single MSNP, including

radioactive isotopes for positron emission tomography (PET) or superparamagnetic iron oxide for magnetic resonance imaging (MRI), enabling simultaneous confirmation of biodistribution in vivo (260,261).

MSNPs also have clinical potential as image-guided diagnostic tools. For instance, “C dots,” ultrasmall silica nanoparticles (~6–7 nm) containing Cy5 fluorescent molecules, PEG coating, radiolabeling for PET, and the integrin-targeting cRGDY peptide, demonstrated dual optical and PET imaging in a first-in-human melanoma trial (262,263). By combining targeting ligands, imaging agents, and therapeutic cargos, MSNPs and functionalized protocells can serve as versatile theranostic platforms for both preclinical and clinical applications (264,265).

3.3.2. Chemotoxins

The primary application of therapeutic MSNPs is the delivery of chemotherapeutic agents. While most studies have focused on systemic delivery, localized administration can be advantageous depending on tumor location. For example, inhalation of luteinizing hormone-releasing hormone (LHRH) peptide-targeted MSNPs in a lung cancer model showed enhanced tumor localization compared to intravenous delivery (249).

Systemically delivered MSNPs exploit the enhanced permeability and retention (EPR) effect, which allows preferential accumulation in tumor tissue. Even uncoated MSNPs demonstrate improved therapeutic efficacy compared to free drugs in tumor xenografts (250). Surface engineering of mesoporous silica nanoparticles using polymers such as polyethylene glycol (PEG) or PEG–polyethylenimine (PEG–PEI) plays a crucial role in improving their pharmacokinetic and biodistribution profiles. These modifications enhance tumor accumulation through the enhanced permeability and retention (EPR) effect, resulting in higher drug payload delivery to malignant tissues while simultaneously reducing systemic side effects and improving overall therapeutic performance.

Protocell constructs, which combine a mesoporous silica core with a supported lipid bilayer, also improve chemotherapeutic delivery via the EPR effect. The lipid bilayer allows simultaneous delivery of hydrophilic drugs in the MSNP core and hydrophobic drugs within the lipid layer (168). Additionally, polymer additives can exert therapeutic effects; for instance, Pluronic 123 inhibits the breast cancer resistance protein (BCRP) pump, enhancing the efficacy of chemotherapeutic cargo in a xenograft breast cancer model (169).

4. Conjugation Strategies to Functionalize Nanocarriers

The therapeutic efficacy of advanced nanocarriers can be significantly enhanced through targeted delivery. Functionalization is achieved by conjugating targeting moieties, such as peptides, single-chain variable fragments (scFvs), or fluorescent molecules, to the surface of nanocarriers (170,171). Selecting an appropriate conjugation strategy is critical because the biological activity of the targeting moiety must be preserved, and its secondary structure should remain intact during the conjugation process. Other key considerations include the proper orientation of the targeting ligand and its surface density on each nanoparticle (172,173).

Conjugation strategies can be broadly categorized into direct and multi-step approaches. Direct conjugation uses pre-existing functional groups on the nanocarrier surface in a single-step reaction to attach the targeting ligand, whereas multi-step strategies involve introducing new chemical groups to the nanocarrier to enable ligand attachment in subsequent reactions (174,175). Both approaches require careful optimization to maximize targeting efficiency without compromising nanocarrier stability or ligand functionality.

Conclusion

Functionalization of nanocarriers through conjugation of targeting moieties such as peptides, scFvs, or imaging agents significantly enhances the specificity and efficacy of tumor-targeted therapies. Proper selection of conjugation strategies—whether direct single-step attachment or multi-step chemical modification—is critical to preserve ligand functionality, maintain nanocarrier stability, and achieve optimal orientation and surface density of the targeting molecules. By carefully optimizing these parameters, nanocarriers can achieve improved tumor accumulation, reduced off-target effects, and enhanced therapeutic outcomes. The integration of such functionalization strategies represents a key step toward the development of highly efficient, targeted nanomedicine platforms for cancer therapy.

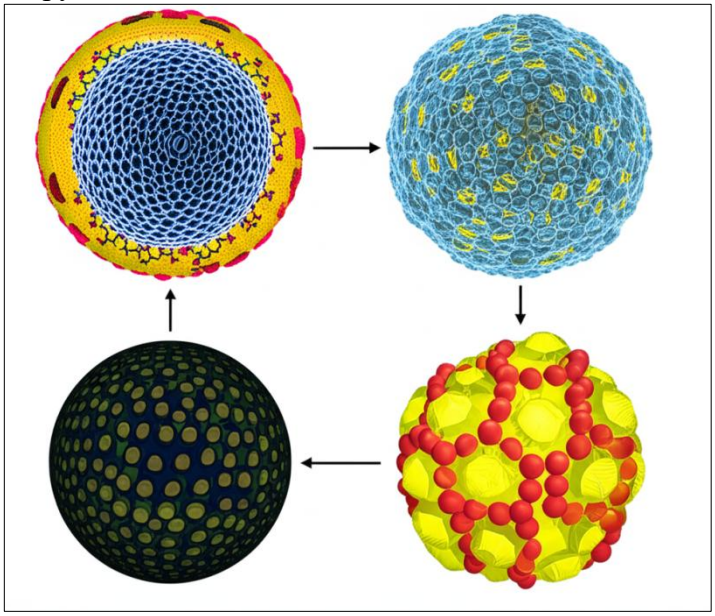

Figure 3: illustrates different chemical methods used to attach molecules (like targeting moieties, drugs, or fluorophores) to nanoparticles.

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