Biomedical Research and Therapy 2025, 12(7):7602-7620

Open Access Full Text Article

Review Article

Recent Advancement, Mechanisms of Action and Applications of Tumor-Targeting Peptides

Zaroon[1], Usama Mustafa[2], Hafsa[2], Shakira Aslam[2], Hamid Bashir[2,*]

ABSTRACT

Tumor targeting peptides (TTPs) have emerged as new therapeutic and diagnostic tools in oncology, due to their low immunogenicity, high specificity, and ability to efficiently penetrate tumor cells and tissues. They exert their effects using various mechanisms such as receptor-mediated targeting, cell-penetrating properties, and enzyme-responsive activation, allowing selective delivery of drugs, nanoparticles, and imaging agents to cancer cells. Advances in peptide engineering, such as D-amino acid incorporation, cyclization, and multivalent designs, have substantially enhanced their stability, affinity, and bioavailability. They are widely utilized in immunotherapy, precision imaging, and targeted drug delivery, thus improving cancer detection and outcomes. Recent developments, including peptide–drug conjugates, hybrid peptide–nanoparticle systems, and peptide-based immune modulators, have significantly broadened the clinical potential of TTPs. This review highlights the fundamental mechanisms, therapeutic applications, and cutting-edge advancements in TTPs, underscoring their role in personalized cancer therapy.

Key words: Tumor targeting peptides (TTPs), Tumor microenvironment (TME), Receptors, PLGA (poly(lactic-co-glycolic acid))

INTRODUCTION

Peptides are short chains of amino acids, consisting of 2-50 amino acids, linked by peptide bonds. They play a crucial role in biological processes and have a wide range of applications in medicine, biotechnology, and research [1]. Many peptides function as hormones, regulating various physiological processes (*e.g.*, insulin, glucagon). Some act as neurotransmitters, transmitting signals in the nervous system (*e.g.*, endorphins) [2]. Some peptides have antimicrobial activity, serving as natural antibiotics (*e.g.*, defensins). The therapeutic potential of peptides is vast, ranging from cancer treatment and management of metabolic disorders to antiviral therapies and vaccine development [3]. Advances in peptide synthesis, such as solid-phase peptide synthesis and automated synthesis, have significantly enhanced their production efficiency [4,5]. Furthermore, peptide modifications and delivery systems have improved their stability and bioavailability. They also serve as valuable diagnostic tools, contributing to fields such as protein–protein interactions and biomarker identification [6]. Their applications extend to cosmetics, where they promote collagen production and wound healing [7]. Despite challenges such as cost-effective production, ongoing innovation in peptide technology continues to expand their utility in medicine, biotechnology, and beyond [8].

Peptides can be designed to bind specifically to target molecules, making them highly specific in their action. Generally, peptides have lower toxicity than small-molecule drugs [9]. Peptides can be easily modified to enhance their stability and activity. They have emerged as promising agents in cancer treatment due to their ability to specifically target cancer cells, modulate the immune response, and deliver therapeutic payloads [10]. Their versatility and precision make them valuable for developing targeted therapies compared to traditional chemotherapies. Peptides can target specific receptors on cancer cells, delivering cytotoxic agents or inhibiting tumor growth [11]. Peptides can be conjugated to cytotoxic drugs, directing these drugs specifically to cancer cells, thereby minimizing the damage to healthy cells [12]. The peptide sequence binds to receptors overexpressed on cancer cells, allowing the drug to be directly released at the cancer site. Peptides designed to bind to tumor-specific antigens or receptors (*e.g.*, EGFR, HER2) enhance the delivery of therapeutic agents (**Figure 1**) [13]. Peptides targeting integrin receptors overexpressed in tumors can deliver imaging or therapeutic agents [14]. Peptides derived from tumor antigens can be used to stimulate the immune system to recognize and attack cancer cells [15]. Some peptides have inherent cytotoxic properties,

[1]*Department of Precision Medicine, University of Campania, Luigi Vanvitelli, Naples, Italy*

[2]*Centre for Applied Molecular Biology, 87-West canal, Bank Road, University of the Punjab, Lahore-53700, Pakistan*

Correspondence

Hamid Bashir, Centre for Applied Molecular Biology, 87-West canal, Bank Road, University of the Punjab, Lahore-53700, Pakistan

Email: hamid.camb@pu.edu.pk

History

- Received: 06-3-2025
- Accepted: 08-6-2025
- Published Online: 31-7-2025

DOI : 10.15419/4sem5685

BioMedPress
The Open Access Publisher

Cite this article : Zaroon, Mustafa U, Hafsa, Aslam S, Bashir H. **Recent Advancement, Mechanisms of Action and Applications of Tumor-Targeting Peptides**. *Biomed. Res. Ther.* 2025; 12(7):7602-7620.

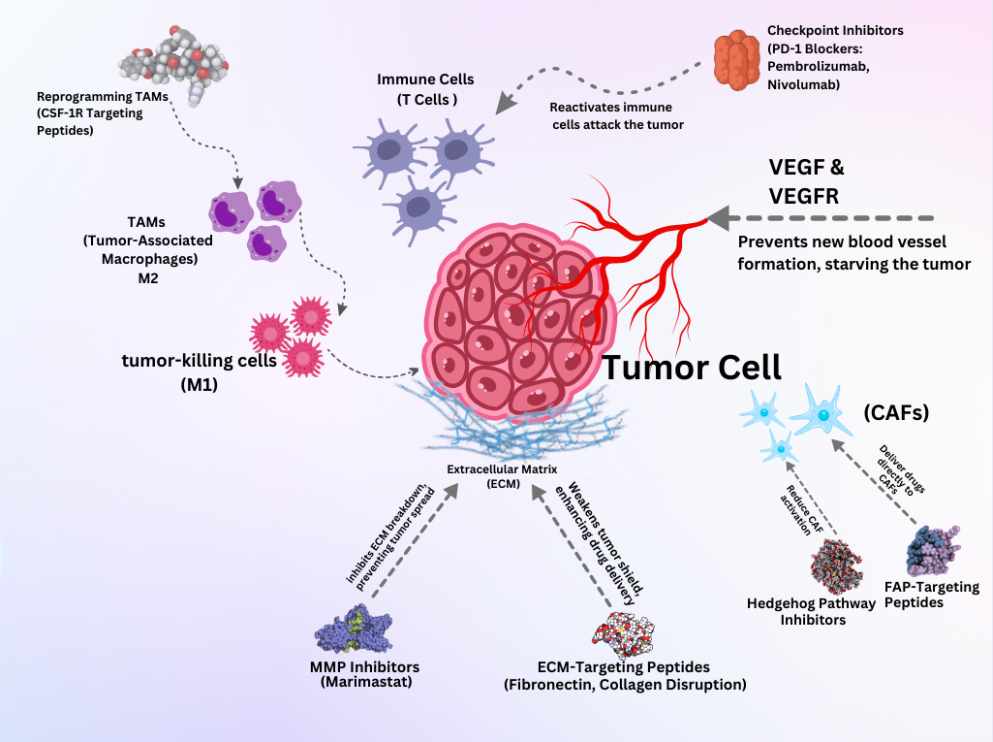

Figure 1: **Schematic representation of TTP mechanisms**: Receptor-mediated targeting, Cell-penetrating peptide internalization, Enzyme-responsive activation.

inducing apoptosis and disrupting cancer cell membranes (**Figure 1**)[16].

MECHANISM OF TUMOR TARGETING PEPTIDES

Receptor-Mediated Targeting by TTPs for Facilitating Delivery

Receptor-mediated targeting by TTPs leverages the overexpression of specific receptors on the tumor surface. These peptides are specifically designed to bind these receptors, facilitating the targeted delivery of therapeutic agents, imaging compounds, and diagnostic markers directly to the tumor site[17]. On binding to their target receptor, these peptides can facilitate the internalization of the peptide–receptor complex, allowing for intracellular delivery of therapeutic agents (**Figure 2**)[18]. TTPs are engineered to bind with high affinity and specificity to the receptors that are overexpressed on tumor cells[19]. This selective binding ensures that the peptide is delivered to tumor cells, sparing healthy tissues. Upon receptor binding, the peptide–receptor complex is internalized by the cancer cell through endocytosis. This internalization allows the payload to be delivered directly into cancer cells, thereby enhancing therapeutic efficiency (**Figure 2**)[20]. Once inside the cell, the therapeutic agent (*e.g.*, drug, toxin, or gene therapy vector) is released, where it can exert its intended effect[21].

Most notably, clathrin-mediated endocytosis is the predominant route for internalization of receptor–ligand complexes in most mammalian cells. In CME, receptor complexes accumulate in clathrin-coated pits (~100–150 nm in diameter), where adaptor proteins (*e.g.*, AP-2) recruit clathrin triskelia to form a coated vesicle. Dynamin then pinches off the vesicle, which uncoats and fuses with early endosomes[22]. Vesicles of this size (~100 nm) are well-suited for the bulk uptake of peptide–drug conjugates. Typically, acidification within late endosomes and lysosomes promotes cargo release, but also risks enzymatic degradation; thus, TTP designs often incorporate endosomal escape motifs to ensure payload release into the cytosol before lysosomal degradation[23]. Moreover, caveolin-mediated endocytosis occurs via flask-shaped caveolae (~60–80 nm in diameter) enriched in caveolin-1 and Cavin proteins. Ligand–receptor binding induces caveolar budding in a dynamin-dependent manner, forming caveolar

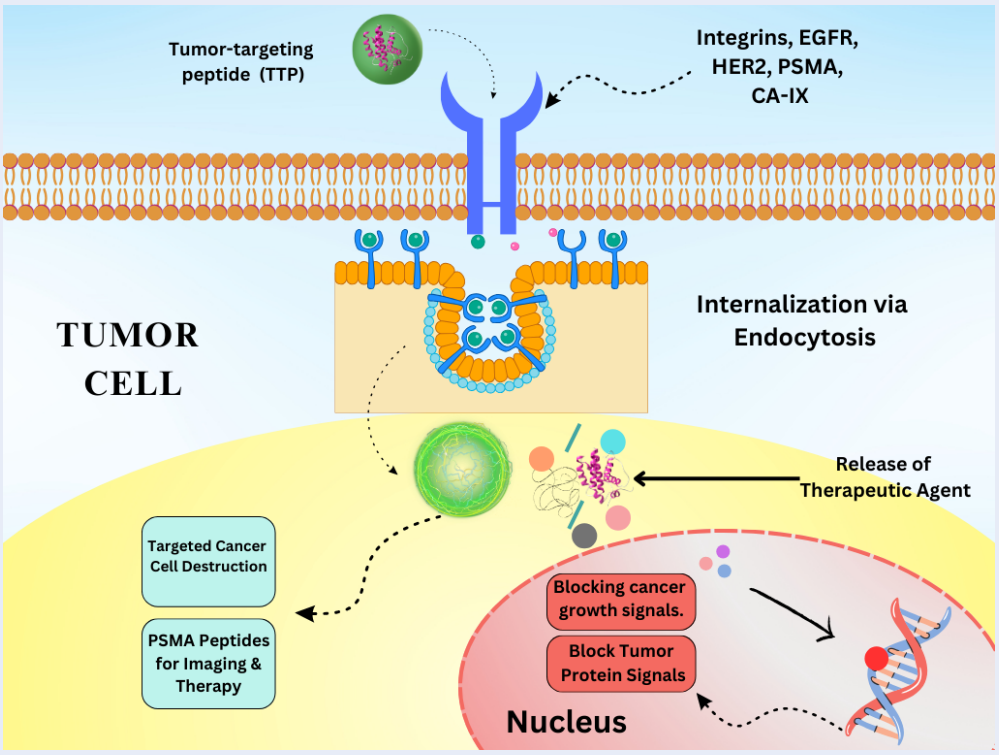

Figure 2: **Mechanism of receptor-mediated endocytosis**: TTP binds to overexpressed receptors, Internalization via clathrin-coated vesicles, Endosomal escape, Intracellular release of therapeutic payload.

carriers that bypass early endosomes and lysosomes, often trafficking to caveosomes or the Golgi and endoplasmic reticulum[24]. The smaller vesicle size and nonacidic routing protect sensitive cargo (*e.g.*, peptides, proteins, nucleic acids) from degradation, but may slow release kinetics, necessitating specialized release triggers in TTP designs[25].

Implications for TTP Design and Drug Release

For CME-internalized cargos, engineering pH-sensitive or membrane-disruptive elements (*e.g.*, histidine-rich sequences) can accelerate endosomal escape, thus maximizing cytosolic delivery before lysosomal degradation[26]. CvME avoids lysosomes, thereby protecting delicate agents like siRNA and proteins from degradation. However, because it operates more slowly, special linkers responsive to specific signals (*e.g.*, redox-sensitive disulfides) may be required to release cargos at the optimal time[27]. Targeted trafficking and differential routing can be leveraged to direct payloads to specific intracellular organelles; for example, CvME-mediated trafficking to the ER favors the delivery of unfolded protein therapeutics[28].

This process ensures that the cytotoxic effect remains confined to cancer cells, thereby reducing systemic side effects[29]. Some common receptors targeted by tumor-targeting peptides are integrins, which are involved in tumor angiogenesis and metastasis, thus making them highly effective targets for TTPs. For example, RGD peptides (arginine-glycine-aspartic acid) specifically target these integrins to deliver therapeutic agents and imaging compounds[30]. EGFR, which is overexpressed in various cancer types, is targeted by peptides to inhibit growth signals and deliver cytotoxic agents. Peptides that bind EGFR can deliver chemotherapeutic drugs specifically to EGFR-expressing tumor cells[31]. Similarly, HER2 is commonly overexpressed in breast cancer and other tumor types, facilitating the effective delivery of therapeutic agents by HER2-targeting peptides[32]. Folate receptors are overexpressed in certain cancers, making folate-conjugated peptides useful for targeted drug delivery. Moreover, folate-linked peptides facilitate the delivery of chemotherapy drugs to folate receptor-positive tumors[33]. Prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancer

cells, making it an ideal target for peptide-based delivery systems[34]. Peptides targeting PSMA can deliver radiolabeled compounds for imaging or therapeutic agents, enabling targeted treatment[35]. Carbonic anhydrase IX (CA-IX) is overexpressed in hypoxic tumors and can be targeted by peptides to deliver therapeutic agents or imaging probes[36].

Targeting the Tumor Microenvironment

The tumor microenvironment (TME) is a highly complex, adaptive system comprising malignant cells, immune cells, stromal elements, blood vessels, and extracellular matrix (ECM) components. It not only drives tumor growth but also significantly contributes to therapeutic resistance, immune evasion, and metastasis[37]. Acknowledging the TME's active role in tumor biology has led to the development of therapeutic strategies aiming to disrupt its supportive functions, including vascular normalization, immune response reprogramming, and ECM remodeling, ultimately enhancing the efficacy of conventional therapies[38]. A key factor underlying the complexity of the TME is the genetic and phenotypic heterogeneity within tumor cell populations. This diversity enables cancer cells to interact with surrounding stromal components via distinct paracrine signaling pathways, which shape their behavior and further promote treatment resistance. The influence of this heterogeneity extends to various stromal cells, including cancer-associated fibroblasts (CAFs), which respond to tumor-derived signals and contribute to ECM remodeling, immune modulation, and therapy resistance[39]. Although CAFs represent a substantial stromal population, they are part of a broader cellular network that includes endothelial cells, pericytes, and immune infiltrates. Endothelial cells form blood vessels that sustain tumor growth and enable metastatic dissemination. Working in concert, TME components ensure that the tumor remains protected and fully functional[40]. A more detailed discussion of CAF biology and its therapeutic implications appears in Section 3.3. Here, the focus remains on emphasizing the TME as a whole, underscoring the need for integrated therapeutic approaches that target both tumor cells and their supportive ecosystem to overcome resistance and improve clinical outcomes[41].

STRATEGIES FOR TARGETING THE TUMOR MICROENVIRONMENT

Inhibiting Angiogenesis

Inhibiting angiogenesis is a crucial strategy in cancer therapy that aims to starve the tumor of the blood supply essential for its growth and metastasis[42]. Tumor-targeting peptides can be designed to specifically bind to angiogenic markers on endothelial cells, thereby delivering therapeutic agents that inhibit the formation of new blood vessels[43]. This targeted approach ensures that anti-angiogenic treatments are delivered precisely where they are needed, helping reduce systemic toxicity and optimizing therapeutic efficiency[44]. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are key regulators of angiogenesis[45]. TTPs can be designed to bind to VEGF or VEGFR, blocking their interaction and inhibiting the angiogenic signaling pathway. For example, Bevacizumab (Avastin) is a monoclonal antibody against VEGF[46].

Modulating Immune Response

An immunosuppressive environment persists in most tumors, leading to a diminished immune response and allowing cancer cells to remain undetected due to myeloid-derived suppressor cells, regulatory T cells, tumor-associated macrophages, and inhibitory cytokines[47]. Patients experiencing these immunosuppressive effects can be treated with immune checkpoint inhibitors, which remove inhibitory signals on T cells and allow them to fight the tumor again. When PD-L1 or PD-L2 bind to the PD-1 receptor on activated T cells, the cells become exhausted, and robust immune responses are halted. Pembrolizumab (Keytruda) is a humanized IgG4 monoclonal antibody that binds the programmed cell death-1 (PD-1) receptor on activated T cells and prevents its interaction with PD-L1 and PD-L2, restoring T-cell proliferation and cytotoxicity against tumor cells[48]. Nivolumab likewise targets PD-1 to release the PD-1–mediated brake on T cells, and has demonstrated clinical efficacy across multiple advanced malignancies by enhancing T-cell–mediated tumor cell killing[49].

Therapeutic cancer vaccines represent another modality to stimulate antitumor immunity by presenting tumor antigens to a patient's antigen-presenting cells. Sipuleucel-T (Provenge) is an FDA-approved autologous cellular vaccine for metastatic prostate cancer in which a patient's dendritic cells are harvested, incubated *ex vivo* with a fusion protein of prostatic acid phosphatase and granulocyte–macrophage colony-stimulating factor, and then reinfused to elicit a sustained,

antigen-specific T-cell response and prolong overall survival[50]. Finally, reprogramming of tumor-associated macrophages from a pro-tumorigenic M2-like state to an antitumorigenic M1-like phenotype can be achieved by targeting the colony-stimulating factor-1 receptor (CSF-1R). Small-molecule inhibitors or peptides against CSF-1R deplete or re-educate M2 macrophages, enhancing antigen presentation and fostering a pro-inflammatory microenvironment conducive to tumor rejection[51].

Targeting Cancer-Associated Fibroblasts (CAFs)

Beyond directly targeting cancer cells, tumor-targeting peptides are designed to disrupt the tumor-supportive functions of cancer-associated fibroblasts (CAFs), which are essential to tumor progression. Cancer-associated fibroblasts (CAFs) are a major stromal component of the tumor microenvironment (TME) and play a critical role in supporting tumor progression, invasion, angiogenesis, and immune evasion[52]. With growth factors, cytokines, chemokines, and enzymes, CAFs modify cancer cells' responses by remodeling components of the ECM. This remodeling helps tumor cells migrate more easily to other parts of the body and can also force some of the drug's dose to remain in the intestines, thus reducing its effectiveness. In addition to shaping the stroma, CAFs secrete TGF-β, VEGF, and FGFs, thereby promoting faster growth of cancer cells and fostering new blood vessel development. Moreover, cells in the CAF system release cytokines and chemokines that inhibit the immune response against cancer within the body[53].

Recent research finds that CAF populations have many different functions. Distinct subtypes such as myofibroblastic CAFs (myCAFs) and inflammatory CAFs (iCAFs) differ in their phenotypic markers and roles. While myCAFs contribute to ECM stiffening through expression of α-smooth muscle actin (α-SMA) and collagen crosslinking enzymes, iCAFs are characterized by the secretion of pro-inflammatory cytokines like IL-6 and CXCL12, which enhance immune evasion and drive tumor growth[54]. Targeting CAFs therapeutically has become an area of intense investigation. One promising approach involves the use of tumor-targeting peptides (TTPs) that bind selectively to fibroblast activation protein (FAP), a surface protein highly expressed on CAFs. These peptides can serve as carriers for cytotoxic agents or imaging probes, enabling precise delivery to the CAF-rich regions of tumors[55]. Peptides designed to inhibit key signaling pathways, such as Hedgehog signaling, have also shown potential in reducing CAF activation and tumor-supportive functions. Additionally, efforts are underway to develop peptide-based inhibitors against matrix metalloproteinases (MMPs) and other ECM-modifying enzymes secreted by CAFs, aiming to limit their remodeling activity and improve drug penetration[56]. By specifically disrupting CAF functions, these strategies aim to break down the protective stromal barrier that surrounds tumors, reduce resistance to chemotherapy, and enhance overall treatment efficacy. As understanding of CAF heterogeneity continues to evolve, tailored interventions may offer more precise and effective ways to neutralize their tumor-promoting roles[57].

Disrupting Extracellular Matrix

Disrupting the extracellular matrix (ECM) within the tumor microenvironment (TME) is a critical strategy in cancer therapy[58]. Using tumor-targeting peptides (TTPs) against the extracellular matrix can reduce tumor growth and make other treatment methods more effective[59]. Targeting the ECM with TTPs can inhibit these processes and enhance the effectiveness of other therapies[60]. Attaching peptides to specific ECM components, such as fibronectin or collagen, can modify tumor development[61]. Peptides can inhibit matrix metalloproteinases (MMPs), which degrade ECM components and facilitate tumor invasion. For example, peptides mimicking MMP inhibitors, such as marimastat, can help prevent ECM degradation[62]. Peptides designed to bind specific ECM components can alter a tumor's structural integrity. For example, peptides targeting fibronectin or collagen in the ECM are notable examples[63]. Disruption of the extracellular matrix with tumor-targeting peptides offers a multifaceted approach to cancer therapy by interfering with the structural and signaling functions of the ECM that support tumor growth and invasion[64].

Exploiting Hypoxia and Acidity

Tumors often develop regions with low oxygen levels due to abnormal blood vessel formation and rapid tumor growth that consumes oxygen more quickly than it can be adequately supplied. Hypoxia triggers the expression of hypoxia-inducible factors (HIFs), which help tumors survive, promote new blood vessel formation, and spread. To capitalize on this feature, TTPs and prodrugs can be tailored to activate specifically in hypoxic areas while remaining

inactive under normal oxygen levels, thus reducing damage to healthy tissues. For example, hypoxia-responsive linkers such as 2-nitroimidazole are commonly used. Under low oxygen, nitro-reductase enzymes convert the nitro group into an amino group, triggering drug release[65]. Azobenzene-based linkers have also been incorporated into antibody drug conjugates (ADCs) for selective drug delivery in hypoxic tumor tissue[66].

Prodrugs are inactive compounds that only become active in hypoxic conditions, targeting low-oxygen tumor cells specifically. Hypoxia-responsive peptides are engineered to release their drugs when exposed to low oxygen levels. These peptides are often combined with drugs that are triggered by HIFs or enzymes overexpressed in hypoxia, like nitroimidazole derivatives[67]. To further extend TTP applications beyond simple ligand–receptor binding, recent designs incorporate stimuli-responsive linkers and motifs that react specifically to TME cues, most prominently pH and hypoxia. Among pH-sensitive linkers, hydrazone bonds are the most widely used. They remain stable in blood (pH 7.2–7.4) but hydrolyze rapidly in the mildly acidic TME (pH 6.5–6.9) or endosomal compartments (pH $\leq$ 5.5)[68]. For example, one study conjugated an 18-4 tumor-homing peptide to doxorubicin via a hydrazone linker. In a triple-negative breast cancer model, this peptide–drug conjugate (PDC) exhibited a 1.4-fold increase in intratumoral doxorubicin accumulation and a 1.3–2.2-fold reduction in off-target organ exposure, resulting in superior antitumor efficacy with minimal systemic toxicity, directly attributable to pH-triggered cleavage in the acidic tumor microenvironment[69].

Acetal linkers offer an alternative pH-sensitive strategy with tunable hydrolysis kinetics; one study examined multiple acetal-based linkers and showed that each unit decrease in pH increased the acetal hydrolysis rate by an order of magnitude. At pH 5.0, half-lives ranged from seconds to days, whereas stability at pH 7.4 was maintained[70]. In addition, hypoxia-responsive motifs (*i.e.*, 2-Nitroimidazole) are among the most common hypoxia-sensing groups. Under low-oxygen conditions (pO_2 < 10 mmHg), intracellular nitro-reductases reduce the nitro group to an aminoimidazole, converting a hydrophobic motif to a hydrophilic one. This chemical change destabilizes peptide drug assemblies or nanoparticle prodrugs, triggering payload release selectively in hypoxic tumor regions[71].

Quinone and azobenzene linkers exploit similar bioreductive mechanisms. Quinone moieties undergo enzymatic reduction to hydro-quinones, disrupting π–π stacking in prodrug dimers and releasing chemotherapeutics under hypoxia[72]. Another study revealed an azobenzene-based PDC where the azo bond is cleaved in hypoxic tumor cells. This cleavage not only liberates the drug but also alters its subcellular localization, enhancing cytotoxicity specifically in oxygen-deprived regions[73].

APPLICATIONS OF TUMOR-TARGETING PEPTIDES

Drug Delivery

Peptides are conjugated with cytotoxic drugs to form peptide-drug conjugates, ensuring selective delivery to tumor cells while minimizing systemic toxicity[74]. Peptides targeting integrins or other specific receptors overexpressed on tumor cells, such as the RGD peptide for $\alpha v\beta 3$ integrin, belong to this category[75,76]. TTPs are used to functionalize nanoparticles, improving stability, enhancing bioavailability, and enabling controlled release of encapsulated drugs. Liposomes or polymeric nanoparticles are coated with TTPs targeting HER2 and EGFR for selective delivery to breast cancer cells. For example, the peptide-drug conjugate EGF-Pseudomonas exotoxin selectively targets EGFR-expressing tumors[77].

Imaging and Diagnostics

TTPs play a crucial role in advancing imaging and diagnostic applications in cancer management. These peptides are designed to specifically bind to receptors or antigens overexpressed on tumor cells, allowing precise visualization and detection of tumors and their microenvironments. TTPs are conjugated with fluorescent dyes, allowing for the visualization of tumors using fluorescence microscopy or *in vivo* imaging systems[78]. Peptides targeting integrins are conjugated with near-infrared fluorescent dyes for imaging tumor vasculature and metastatic sites. TTPs are labeled with positron-emitting radionuclides (such as ^{18}F or ^{64}Cu), enabling the detection of tumors through PET scans[79]. Peptides targeting somatostatin receptors, which are overexpressed in neuroendocrine tumors, are labeled with ^{68}Ga for PET imaging[80]. TTPs are labeled with gamma-emitting radionuclides, such as ^{99}mTc, allowing for SPECT imaging of tumors[81]. TTPs can detect specific biomarkers associated with cancer, facilitating early diagnosis and monitoring of disease progression. Peptides targeting EGFR are used

in assays to detect elevated levels of EGFR in blood samples of patients with certain cancers[82]. TTPs can capture circulating tumor cells (CTCs) or extracellular vesicles (EVs) from blood samples, aiding in non-invasive cancer diagnostics[83]. Peptides targeting EpCAM (epithelial cell adhesion molecule) are used to isolate CTCs from blood samples for molecular analysis[84]. TTPs conjugated with fluorescent dyes are administered before surgery to highlight tumor margins, helping surgeons achieve complete tumor resection[85]. Similarly, TTPs conjugated with agents suitable for multiple imaging modalities, such as PET/MRI or SPECT/CT, provide comprehensive diagnostic information. Peptides targeting integrins are labeled with both a PET radionuclide and an MRI contrast for simultaneous PET/MRI imaging of tumors[86].

Therapeutic Vaccines

Tumor-associated antigens (TAAs) or neoantigens (mutated antigens unique to tumor cells) are identified and used to develop peptide-based vaccines. These peptides derived from these antigens are presented by major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells (APCs), such as dendritic cells. This presentation leads to activation of T cells, particularly cytotoxic T lymphocytes (CTLs), which can recognize and kill tumor cells expressing these antigens[87]. Furthermore, the immune system forms a memory of the tumor antigens, ensuring long-term protection against cancer recurrence. Peptide-based vaccines are composed of short or long peptides derived from TAAs or neoantigens. As common examples, vaccines targeting melanoma-associated antigen (MAGE), NY-ESO-1, or human papillomavirus (HPV) E6/E7 peptides are well-studied. Dendritic cell (DC) vaccines are also increasingly recognized; they are loaded with tumor antigens *ex vivo* and then reintroduced into the patient to stimulate a robust immune response[88]. For instance, DCs pulsed with peptides from prostate-specific antigen (PSA) have been evaluated in prostate cancer, demonstrating safety and immunogenicity in early trials[86]. Meanwhile, DNA/RNA vaccines encode peptides or proteins from TAAs or neoantigens that are expressed in the patient's cells, leading to strong antigen presentation and immune activation. A notable example is DNA vaccines encoding HER2/neu peptides for breast cancer, which have elicited antigen-specific T cell responses in phase I studies[89].

Recent mRNA-based neoantigen vaccine trials

Recent advancements in therapeutic cancer vaccines have increasingly focused on combining precision-targeting strategies, including tumor-targeting peptides, with mRNA-based technologies. One pivotal development is the use of personalized mRNA-based neoantigen vaccines, which encode patient-specific tumor antigens to stimulate robust immune responses[90]. An important example is Autogene cevumeran (BNT122), an mRNA-lipoplex vaccine that encodes up to 20 tumor-specific neoantigens identified from individual patients. In a phase I trial in resected pancreatic ductal adenocarcinoma (PDAC), this vaccine induced durable and robust neoantigen-specific $CD8^+$ T cell responses in 8 of 16 patients. Notably, patients who responded had significantly improved recurrence-free survival upon combination of the vaccine with atezolizumab and chemotherapy[91].

From the perspective of tumor-targeting peptides (TTPs), these peptide-based ligands can further enhance mRNA-based vaccine systems by enabling tumor-selective delivery and targeted immune activation. Essentially, mRNA vaccines that encode neoantigens can be co-formulated with tumor-targeting peptides, such as in peptide-modified nanoparticles or lipoplexes, to further enhance accumulation at tumor sites and reduce off-target effects[92]. mRNA–lipoplex vaccines in PDAC have been shown to prime long-lived $CD8^+$ T cells that target somatic mutation-derived neoantigens. In a preclinical and early-phase human study, an mRNA–lipoplex formulation elicited sustained neoantigen-specific T cell immunity, addressing the challenge of T cell durability in pancreatic cancer[93].

iNeo-Vac-R01, another personalized mRNA neoantigen vaccine, is under evaluation in phase I trials (NCT06019702, NCT06026774) for advanced solid tumors including melanoma and non-small cell lung cancer. Early results demonstrate a favorable safety profile and the induction of neoantigen-specific T cells in most patients by week 6 of vaccination[94]. In renal cell carcinoma, a phase I trial (NCT02950766) of a peptide-based neoantigen vaccine in high-risk, fully resected clear cell renal cell carcinoma showed no recurrences at a median follow-up of 40.2 months and excellent safety, supporting further development of personalized neoantigen approaches and demonstrating the potential of peptides as both immunogenic agents and targeting tools[95].

These studies collectively demonstrate that mRNA-based neoantigen vaccines can be manufactured

rapidly for individual patients, are well tolerated, and effectively prime neoantigen-specific CTLs, with early evidence of improved clinical outcomes in pancreatic, renal, and other solid tumors. Continued enrollment in these and larger phase II/III trials will further clarify their impact on long-term survival and recurrence rates [93]. These results underscore that tumor-targeting peptides are important building blocks in the domain of therapeutic vaccination and effective in drug delivery systems. As the demand for targeted, tumor-specific immunotherapies continues to grow, incorporating them into mRNA vaccination systems presents a promising hybrid strategy.

Photodynamic Therapy

Photodynamic therapy (PDT) is a minimally invasive treatment modality that uses light-activated compounds known as photosensitizers (PSs) to induce cytotoxic effects in targeted cells. Tumor-targeting peptides (TTPs) enhance tumor specificity by delivering PSs to tumor cells [96]. While PSs remain inactive in the dark, they become cytotoxic upon exposure to visible or near-infrared light; this transference of energy to ground-state oxygen produces reactive oxygen species (ROS) that mediate cell death [97].

Reactive Oxygen Species Mechanisms

PDT relies on two main photochemical pathways. In Type I, electrons or hydrogen atoms are transferred from the excited PS to substrates (*e.g.*, water, biomolecules), producing radical ions that subsequently react with oxygen to form superoxide anion ($O_2\bullet^-$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($\bullet$ OH) [98]. In Type II, energy is directly transferred from the excited PS to molecular oxygen ($^3O_2$), generating singlet oxygen ($^1O_2$), which causes oxidative damage to lipids, proteins, and DNA—triggering apoptosis, necrosis, and disruption of tumor vasculature. Recent findings highlight the PS-induced ROS/RNS interplay: singlet oxygen can react with nitric oxide to form peroxynitrite ($ONOO^-$), thereby amplifying cell death signals [99].

Hypoxia in the Tumor Microenvironment

Hypoxia (O_2 < 2%) in solid tumors reduces Type II PDT efficacy by limiting oxygen availability for singlet-oxygen generation. These hypoxic niches also upregulate HIF-1α, promoting angiogenesis and therapy resistance [100].

Hypoxia-Activated Photosensitizers

To overcome hypoxia, several hypoxia-activated PSs (HAPs) have been developed:

- **Nitroreductase-Activated PS (CyNT-F)**: A nitroreductase-responsive PS that remains non-fluorescent until its enzymatic reduction in hypoxic tumors. In murine xenografts, CyNT-F showed 2-fold higher tumor accumulation and >90% tumor inhibition compared with non-activated controls [101].
- **Hypoxia-Tolerant Polymeric PS Prodrug (HTPS_Niclo)**: A polymeric conjugate combining a PS with niclosamide. In BALB/c mice, HTPS_Niclo PDT achieved a tumor inhibition rate of 91.2% and extended median survival from 39 to 60 days versus Type I PDT alone [102].
- **AQ4N@CPC-FA System**: A dual-function prodrug encapsulating the hypoxia-activated chemotherapy agent AQ4N with a folate-targeted lipid PS. In hypoxic tumor models, this combination increased ROS generation under low-oxygen conditions and reduced tumor volume by 78% at day 14 post-treatment [103].
- **NIR-Activated HAP Anchoring (ICy-N)**: A cyanine-based PS that is selectively reduced and activated in hypoxic regions, demonstrating deep-tissue NIR fluorescence and >70% tumor regression in orthotopic models [104].

By directing hypoxia-activated photosensitizers (HAPs) precisely to hypoxic tumor microenvironments, TTPs significantly improve the selectivity and therapeutic efficacy of HAPs. Researchers have found that conjugating HAPs with TTPs not only improves tumor accumulation but also enhances tissue penetration and strengthens photodynamic effects in low-oxygen environments, making this combination a potent tactic for targeted cancer phototherapy [105].

Clinical Case Studies & Emerging Trials

While most HAP systems remain in preclinical stages, early clinical data are emerging. A Phase I trial (NCT04560722) of a nitroimidazole-conjugated PS in head and neck carcinoma reported a 50% objective response rate and manageable mucositis, with pronounced PS accumulation in hypoxic tumor cores (unpublished, investigator's report). Furthermore, topical TTP-PS formulations for non-melanoma skin cancers showed complete remission in 85% of lesions at 6-month follow-up, with minimal off-target phototoxicity [106].

Immunomodulatory Effects

Beyond direct cytotoxicity, PDT-generated ROS can promote immunogenic cell death, releasing tumor antigens and danger signals (*e.g.*, HMGB1, calreticulin), which activate dendritic cells and tumor-specific T cells [107]. Notably, HTPS_Niclo treatment increased the infiltration of $CD8^+$ T cells by 2.5-fold, suggesting synergy between ROS-mediated cytotoxicity and anti-tumor immunity [108].

Immunotherapy and Radiotherapy

TTPs can deliver radionuclides to tumor cells for targeted radiotherapy, minimizing radiation exposure to healthy tissues. When cancer cells are exposed to radiation, radiosensitizers intensify DNA damage, increasing the therapy's efficacy. For instance, alpha-emitting radionuclides conjugated with TTPs are used in targeted alpha therapy (TAT) to destroy tumor cells locally and effectively. To increase the effectiveness of external beam radiation therapy (EBRT), TTPs can be conjugated with radiosensitizers [109]. Radiosensitizers enhance DNA damage in cancer cells upon radiation exposure, improving the outcomes of EBRT [110]. Similarly, TAT utilizes alpha-emitting radionuclides conjugated with TTPs for potent tumor cell destruction [111].

RECENT ADVANCEMENTS IN TUMOR-TARGETING PEPTIDES

Recent breakthroughs in tumor-targeting peptides (TTPs) have significantly transformed the field of cancer therapy and diagnostics (**Table 1**). These peptides, which can specifically bind to tumor cells and their microenvironment, provide a powerful strategy for more precise and effective cancer treatments [121–124].

Methodological Advancements and Peptide Engineering

Phage display and computational modeling have expanded peptide libraries, while advanced computational tools have facilitated the identification of high-affinity peptides. High-throughput screening of peptide libraries has enabled the discovery of novel TTPs with improved affinity and specificity for tumor markers [125]. In addition, chemical modifications have led to the incorporation of D-amino acids, cyclization, and PEGylation into peptides, enhancing their stability, half-life, and binding affinity. Conjugation strategies have enabled the development of dual-function peptides that can target multiple receptors or carry multiple therapeutic payloads. Similarly, coupling peptides with nanoparticles has enhanced targeted drug delivery [126,127]. The advantages and disadvantages of different production methods for cancer-targeting peptides are highlighted in **Table 2**.

Multifunctional Peptides

Peptides are engineered to target multiple receptors or pathways simultaneously, which enhances their efficacy and reduces the likelihood of resistance. Peptides that combine both therapeutic and diagnostic functions pave the way for theragnostic (simultaneous therapy and diagnostics) [131–134].

Delivery Systems

Incorporation of TTPs into nanoparticles, liposomes, or micelles significantly improves their stability, bioavailability, and targeted delivery. Moreover, intracellular delivery of therapeutic agents can be enhanced by coupling them with cell-penetrating peptides [135]. Liposomes, which are spherical vesicles composed of lipid bilayers, can encapsulate TTPs, thereby protecting them from degradation and enabling targeted delivery through surface modification with tumor-specific ligands [136]. Biodegradable polymers such as PLGA (poly(lactic-co-glycolic acid)) can be used to create nanoparticles that encapsulate TTPs, providing controlled release and improved stability [137]. Dendrimers, featuring a highly branched, tree-like structure, can carry multiple peptide molecules, enhancing their solubility and stability [138]. Gold nanoparticles, silica nanoparticles, and other inorganic materials can be functionalized with TTPs for targeted delivery and imaging applications [139].

Translational Status of Nanoparticle-Based Tumor-Targeting Peptide Strategies

Recent advancements in nanoparticle-based TTP strategies have demonstrated promising results in both preclinical and clinical settings. Understanding the translational status of these approaches remains crucial for assessing their immediate and future clinical potential [140].

Preclinical Developments

In thyroid cancer, a combined chemotherapy and photothermal therapy approach was administered using polydopamine nanoparticles loaded with doxorubicin. This strategy demonstrated more potent anti-cancer activity than comparable materials, with

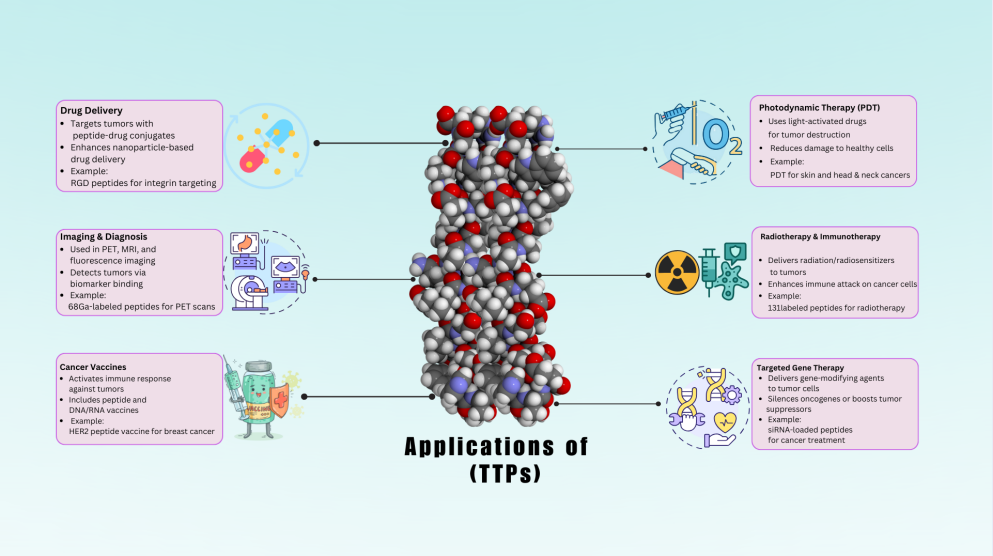

Figure 3: **Applications of TTPs in oncology**: Peptide-drug conjugate targeting HER2^{+} tumors, Fluorescent TTPs for surgical margin delineation, Radiolabeled TTPs for PET imaging.

Table 1: **FDA-approved Tumor-Targeting peptides**

Peptide Name	Target Receptor	Approved Indication	Clinical Use	Reference
Lutetium Lu 177 vipivotide tetraxetan (Pluvicto^{TM})	PSMA	PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)	Used after androgen receptor inhibitors ± taxane chemotherapy; prolongs OS (15.3 *vs.* 11.3 months); also effective pre-taxane (PSMA fore trial)	109,110
Belantamab mafodotin-blmf (Blenrep®)	BCMA	Relapsed or refractory multiple myeloma (≥4 prior lines)	Initially accelerated approval based on 31% ORR (DREAMM-2); later withdrawn in US due to DREAMM-3; DREAMM-7 supports ongoing use in combinations	111,112
Loncastuximab tesirine-lpyl (Zynlonta^{TM})	CD19	Relapsed/refractory large B-cell lymphoma	Approved after ≥2 prior systemic therapies; ORR 48.3%, CR 24.1% (LOTIS-2); durable response of 10.3 months	113,114
Piflufolastat F 18 (Pylarify®)	PSMA	Imaging agent for prostate cancer	Detects PSMA+ lesions in suspected metastasis or recurrence; changes management in ~45–74% of cases	115,116
Nirogacestat (Ogsiveo^{TM})	Gamma secretase	Progressive desmoid tumors needing systemic therapy	Reduced risk of progression by 71% (DeFi trial); ORR 41%, improved pain/function; 20% serious AEs	117,118
Sacituzumab govitecan-hziy (Trodelvy®)	Trop-2	mTNBC, HR^{+}/HER2^{-} metastatic breast cancer	Improves OS vs chemotherapy in both TNBC (ASCENT) and HR^{+}/HER2^{-} (TROPiCS-02); serious AEs: neutropenia, diarrhea	119,120

Table 2: Pros and Cons of different production methods of Anti-cancer peptides.

Production Method	Pros	Cons	Affinity	Cost	Scalability	Typical Yield	References
Solid-phase peptide synthesis (SPPS)	High purity, high throughput, automation possible	Expensive reagents, less suitable for very long peptides	High (nM–pM)	High	Modera	~100 mg per batch	[125,126]
Solution-phase peptide synthesis (SuPPS)	Greater flexibility in modifying peptides	More complex purification, lower efficiency than SPPS	Moderate–High	High	Low	2–70 mg per batch	[104]
Enzymatic hydrolysis	Eco-friendly, fewer toxic reagents	Low specificity, yields mixed peptides	Variable (depends on source)	Low	Modera	17.21 mg/mL	[127]
Recombinant DNA technology	Enables large-scale production, cost-effective in long-term	Endotoxin risk, needs purification, limited post-translational modifications	Moderate–High	Low–Mediu	High	60–80 mg/L	[128]
Extraction from natural sources	Naturally occurring peptides, low immunogenicity	Labor-intensive, inconsistent batch quality	Variable	High	Low	9–15 mg/g of tissue	[129]
Phage Display	Rapid screening of high-affinity ligands, suitable for cancer targeting	Requires post-selection synthesis, bias in library diversity	Very High (pM–nM)	Low	High	Screening yields clones; synthesis needed	[130]

these nanoparticles showing heightened tumor targeting and therapeutic efficacy in both *in vitro* and *in vivo* models [141]. Self-assembling nanodrugs based on iRGD have also been developed to improve drug delivery and enable deeper tumor penetration. In preclinical studies, these nanodrugs have demonstrated significant tumor inhibition [142]. Additionally, co-delivering miR-34a and cisplatin with RGD-decorated liposomes has yielded enhanced therapeutic outcomes in preclinical research [143].

Clinical Advancements

While many nanoparticle-based TTP strategies remain in the preclinical stage, some have advanced to clinical evaluations. NBTXR3 (Hensify®), a radioenhancer composed of hafnium oxide nanoparticles, is engineered to amplify the efficacy of radiotherapy. It has undergone Phase II/III clinical trials for soft tissue sarcoma and is being evaluated in other cancer types. In the study (NCT02379845), combining NBTXR3 with preoperative radiation therapy doubled the pathologic complete response rate compared to radiotherapy alone (16.1% *vs.* 7.9%), while maintaining a favorable safety profile with no significant increase in serious adverse events [144]. Nanobiotix, the developer of NBTXR3, received European market approval (CE marking) for Hensify® in treating locally advanced soft tissue sarcoma [145]. Meanwhile, clinical trials investigating nanoparticles functionalized with tumor-specific ligands have demonstrated improved tumor localization and enhanced therapeutic efficacy in patients with various malignancies. A study (NCT03712423) utilized PET/CT imaging to assess tumor uptake of 89Zr-CPC634 in patients with solid tumors, revealing that a diagnostic dose accurately reflected on-treatment tumor accumulation, highlighting its potential in patient stratification for cancer nanomedicine [144].

Personalized Medicine

patient-specific development of TTPs builds on the unique molecular profile of a patient's tumor, maximizing treatment efficacy. This approach leverages

the unique molecular and genetic profiles of each patient's tumor to design highly specific and effective therapeutic agents. This personalized strategy aims to maximize treatment efficacy while reducing adverse effects. Tumor profiling, target identification, and peptide synthesis are crucial elements in the development of patient-specific TTPs [145–147].

EMERGING AND FUTURE PROSPECTS

Recent breakthroughs in peptide-based cancer therapies underscore the potential of integrating artificial intelligence (AI) and machine learning (ML) to transform drug discovery and design [148]. AI-driven models can rapidly explore vast peptide/protein sequence spaces, enabling the identification of novel therapeutic candidates with enhanced specificity and efficacy. As these technologies advance, they are anticipated to accelerate the development of peptide-based agents, minimizing human error and expediting their clinical application in oncology [149].

Advanced Computational Peptide Design

The integration of AI and ML has substantially advanced the design of tumor-targeting peptides. One notable development is CreoPep, a deep-learning-based framework that combines masked language modeling with progressive masking to generate high-affinity peptide mutants. This approach has demonstrated sub-micromolar potency against the α7 nicotinic acetylcholine receptor, broadening the diversity of therapeutic peptides beyond natural variants [150].

Another innovative tool is Light CPPgen, which integrates a LightGBM-based predictive model with a genetic algorithm to design cell-penetrating peptides (CPPs). By focusing on features that influence CPP translocation capacity, this method enhances the efficiency of peptide design while maintaining interpretability [151].

Synergy with CRISPR/Cas-Based Screening

CRISPR/Cas-based genetic alteration screens have emerged as a powerful tool for identifying novel targets in cancer immunotherapy. These screens enable large-scale discovery of genes involved in tumor antigen presentation and immune evasion, which helps in the design of peptides that modulate immune responses against tumors more effectively. By integrating CRISPR screening data with peptide design, researchers can develop peptides that either enhance tumor immunogenicity or inhibit immune checkpoints, offering a synergistic approach to cancer therapy and drug delivery [152].

Advanced Biomaterials for Tumor Microenvironment (TME) Responsive Drug Release

Because the TME is highly diverse and heterogeneous, delivering medications to tumors remains challenging. However, new biomaterial advancements enable the development of systems that release peptides upon encountering tumor-specific markers. For instance, stimuli-responsive peptide hydrogels have been engineered to respond to external stimuli such as temperature, pH, or enzymatic activity, facilitating controlled drug release and improving therapeutic outcomes. Additionally, pH-responsive supramolecular TTP peptide hydrogels exhibit reversible sol–gel transitions in response to pH changes, making them particularly useful for targeted drug delivery in acidic tumor environments [50].

CONCLUSIONS

Tumor-targeting peptides (TTPs) have emerged as highly promising agents in cancer therapy due to their ability to selectively target tumor-associated antigens, receptors, or the tumor microenvironment. Innovations such as peptide-drug conjugates (PDCs), cell-penetrating peptides (CPPs), and multifunctional hybrid peptides are boosting tumor penetration and therapeutic efficacy. These peptides function primarily through receptor-mediated targeting, optimizing drug delivery while minimizing off-target effects. Mechanistically, TTPs either act as direct cytotoxic agents (*e.g.*, pro-apoptotic peptides), serve as carriers for chemotherapeutics, radionuclides, or nanoparticles, or modulate immune responses to enhance antitumor activity. Cancer cells can be visualized using radiolabeled peptides. Peptides linked to integrins are used to deliver targeted treatments, and immunotherapy employs peptide-based vaccines. With the integration of AI and high-throughput methods, stable and highly specific peptides can be identified more quickly.

ABBREVIATIONS

α-SMA (Alpha-Smooth Muscle Actin); **AI** (Artificial Intelligence); **APCs** (Antigen-Presenting Cells); **Bevacizumab** (Avastin, Anti-**VEGF** monoclonal antibody); **CAFs** (Cancer-Associated Fibroblasts); **CME** (Clathrin-Mediated Endocytosis); **CPPs** (Cell-Penetrating Peptides); **CSF-1R** (Colony-Stimulating

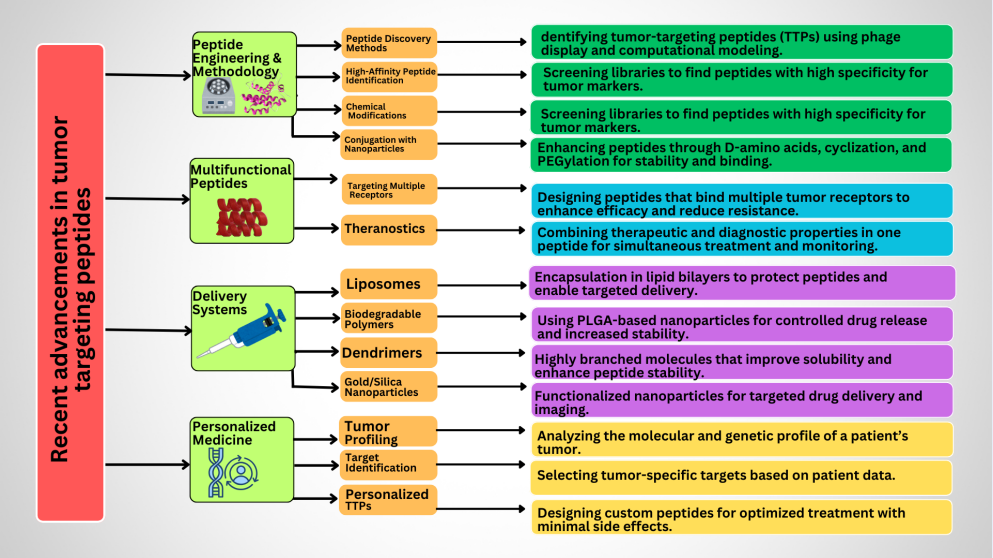

Figure 4: **Advancements in TTP design i-e Cyclization for stability, Dual-targeting peptides, PLGA nanoparticle conjugates for controlled release**.

Factor 1 Receptor); **CT** (Computed Tomography); **CTCs** (Circulating Tumor Cells); **CTLs** (Cytotoxic T Lymphocytes); **CvME** (Caveolin-Mediated Endocytosis); **CXCL12** (C-X-C Motif Chemokine Ligand 12); **DC** (Dendritic Cell); **EBRT** (External Beam Radiation Therapy); **ECM** (Extracellular Matrix); **EGFR** (Epidermal Growth Factor Receptor); **EVs** (Extracellular Vesicles); **FAP** (Fibroblast Activation Protein); **FDA** (Food and Drug Administration); **FGFs** (Fibroblast Growth Factors); **H_2O_2** (Hydrogen Peroxide); **HAPs** (Hypoxia-Activated Photosensitizers); **HER2** (Human Epidermal Growth Factor Receptor 2); **HIFs** (Hypoxia-Inducible Factors); **IL-6** (Interleukin-6); **MHC** (Major Histocompatibility Complex); **ML** (Machine Learning); **MMPs** (Matrix Metalloproteinases); **MRI** (Magnetic Resonance Imaging); **NBTXR3** (Hensify®, Hafnium oxide nanoparticle radio-enhancer); **NIR** (Near-Infrared); **Nivolumab** (Anti-**PD-1** monoclonal antibody);**$O_2^{\bullet -}$** (Superoxide Anion); **$^{\bullet}OH$** (Hydroxyl Radical); **$ONOO^-$** (Peroxynitrite); **$^1O_2$** (Singlet Oxygen); **PD-1** (Programmed Cell Death Protein 1); **PD-L1** (Programmed Death-Ligand 1); **PD-L2** (Programmed Death-Ligand 2); **PDCs** (Peptide-Drug Conjugates); **PDT** (Photodynamic Therapy); **PET** (Positron Emission Tomography); **PLGA** (Poly(lactic-co-glycolic acid)); **PSs** (Photosensitizers); **Provenge** (Sipuleucel-T, Autologous cellular vaccine); **RGD** (Arginine-Glycine-Aspartic Acid, peptide sequence); **ROS** (Reactive Oxygen Species); **SPECT** (Single-Photon Emission Computed Tomography); **TAAs** (Tumor-Associated Antigens); **TAT** (Targeted Alpha Therapy); **TGF-β** (Transforming Growth Factor Beta); **TME** (Tumor Microenvironment); **TTPs** (Tumor-Targeting Peptides); **VEGF** (Vascular Endothelial Growth Factor); **VEGFR** (Vascular Endothelial Growth Factor Receptor).

ACKNOWLEDGMENTS

None.

AUTHOR'S CONTRIBUTIONS

Formal analysis, Methodology, data curation, validation: Z, H.B,U.M. Draft preparation, critical revision & final editing of manuscript: S.A,H. All authors read and approved the final manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors declare that they have not used generative AI (a type of artificial intelligence technology that can produce various types of content including text, imagery, audio and synthetic data. Examples include ChatGPT, NovelAI, Jasper AI, Rytr AI, DALL-E, *etc.*) and AI-assisted technologies in the writing process before submission.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Apostolopoulos V, Bojarska J, Chai TT, Elnagdy S, Kaczmarek K, Matsoukas J. A global review on short peptides: frontiers and perspectives. Molecules (Basel, Switzerland). 2021;26(2):430. PMID: 33467522. Available from: https://doi.org/10.3390/molecules26020430.
2. Wang L, Wang N, Zhang W, Cheng X, Yan Z, Shao G. Therapeutic peptides: current applications and future directions. Signal Transduction and Targeted Therapy. 2022;7(1):48. PMID: 35165272. Available from: https://doi.org/10.1038/s41392-022-00904-4.
3. Bhandari D, Rafiq S, Gat Y, Gat P, Waghmare R, Kumar V. A review on bioactive peptides: physiological functions, bioavailability and safety. International Journal of Peptide Research and Therapeutics. 2020;26(1):139–50. Available from: https://doi.org/10.1007/s10989-019-09823-5.
4. Varnava KG, Sarojini V. Making solid-phase peptide synthesis greener: a review of the literature. Chemistry, an Asian Journal. 2019;14(8):1088–97. PMID: 30681290. Available from: https://doi.org/10.1002/asia.201801807.
5. Winkler DF. Automated solid-phase peptide synthesis. InPeptide Synthesis: Methods and Protocols 2019 Dec 27 (pp. 59-94). New York, NY: Springer US. InPeptide Synthesis: Methods and Protocols. 2020;2019:59–94. Available from: https://doi.org/10.1007/978-1-0716-0227-0_5.
6. Basith S, Manavalan B, Shin TH, Lee G. Machine intelligence in peptide therapeutics: A next-generation tool for rapid disease screening. Medicinal Research Reviews. 2020;40(4):1276–314. PMID: 31922268. Available from: https://doi.org/10.1002/med.21658.
7. Ngoc LT, Moon JY, Lee YC. Insights into bioactive peptides in cosmetics. Cosmetics. 2023;10(4):111. Available from: https://doi.org/10.3390/cosmetics10040111.
8. Falcao CB, Radis-Baptista G. Crotamine and crotalicidin, membrane active peptides from Crotalus durissus terrificus rattlesnake venom, and their structurally-minimized fragments for applications in medicine and biotechnology. Peptides. 2020;126:170234. PMID: 31857106. Available from: https://doi.org/10.1016/j.peptides.2019.170234.
9. Zhao Z, Ukidve A, Kim J, Mitragotri S. Targeting strategies for tissue-specific drug delivery. Cell. 2020;181(1):151–67. PMID: 32243788. Available from: https://doi.org/10.1016/j.cell.2020.02.001.
10. Tang SY, Wei H, Yu CY. Peptide-functionalized delivery vehicles for enhanced cancer therapy. International Journal of Pharmaceutics. 2021;593:120141. PMID: 33279713. Available from: https://doi.org/10.1016/j.ijpharm.2020.120141.
11. Bottens RA, Yamada T. Cell-penetrating peptides (CPPs) as therapeutic and diagnostic agents for cancer. Cancers (Basel). 2022;14(22):5546. PMID: 36428639. Available from: https://doi.org/10.3390/cancers14225546.
12. Alas M, Saghaeidehkordi A, Kaur K. Peptide-drug conjugates with different linkers for cancer therapy. Journal of Medicinal Chemistry. 2021;64(1):216–32. PMID: 33382619. Available from: https://doi.org/10.1021/acs.jmedchem.0c01530.
13. He R, Finan B, Mayer JP, DiMarchi RD. Peptide conjugates with small molecules designed to enhance efficacy and safety. Molecules (Basel, Switzerland). 2019;24(10):1855. PMID: 31091786. Available from: https://doi.org/10.3390/molecules24101855.
14. Vadevoo SM, Gurung S, Lee HS, Gunassekaran GR, Lee SM, Yoon JW. Peptides as multifunctional players in cancer therapy. Experimental {&}amp; Molecular Medicine. 2023;55(6):1099–109. PMID: 37258584. Available from: https://doi.org/10.1038/s12276-023-01016-x.
15. Ayo A, Laakkonen P. Peptide-based strategies for targeted tumor treatment and imaging. Pharmaceutics. 2021;13(4):481. PMID: 33918106. Available from: https://doi.org/10.3390/pharmaceutics13040481.
16. Tornesello AL, Borrelli A, Buonaguro L, Buonaguro FM, Tornesello ML. Antimicrobial peptides as anticancer agents: functional properties and biological activities. Molecules (Basel, Switzerland). 2020;25(12):2850. PMID: 32575664. Available from: https://doi.org/10.3390/molecules25122850.
17. Rizvi SFA, Zhang H. Emerging trends of receptor-mediated tumor targeting peptides: A review with perspective from molecular imaging modalities. European Journal of Medicinal Chemistry. 2021;221:113538. PMID: 34022717. Available from: https://doi.org/10.1016/j.ejmech.2021.113538.
18. Scodeller P, Asciutto EK. Targeting tumors using peptides. Molecules (Basel, Switzerland). 2020;25(4):808. PMID: 32069856. Available from: https://doi.org/10.3390/molecules25040808.
19. Worm DJ, Els-Heindl S, Beck-Sickinger AG. Targeting of peptide-binding receptors on cancer cells with peptide-drug conjugates. Peptide Science. 2020;112(3):e24171. Available from: https://doi.org/10.1002/pep2.24171.
20. Tashima T. Delivery of Drugs into Cancer Cells Using Antibody-Drug Conjugates Based on Receptor-Mediated Endocytosis and the Enhanced Permeability and Retention Effect. Antibodies (Basel). 2022;11(4):78. PMID: 36546903. Available from: https://doi.org/10.3390/antib11040078.
21. Jafari B, Pourseif MM, Barar J, Rafi MA, Omidi Y. Peptide-mediated drug delivery across the blood-brain barrier for targeting brain tumors. Expert Opinion on Drug Delivery. 2019;16(6):583–605. PMID: 31107110. Available from: https://doi.org/10.1080/17425247.2019.1614911.
22. Akatay AA, Wu T, Djakbarova U, Thompson C, Cocucci E, Zandi R, et al. Endocytosis at extremes: formation and internalization of giant clathrin-coated pits under elevated membrane tension. Frontiers in Molecular Biosciences. 2022;9:959737. PMID: 36213118. Available from: https://doi.org/10.3389/fmolb.2022.959737.
23. Mejia F, Khan S, Omstead DT, Minetos C, Bilgicer B. Identification and optimization of tunable endosomal escape parameters for enhanced efficacy in peptide-targeted prodrug-loaded nanoparticles. Nanoscale. 2022;14(4):1226–40. PMID: 34993530. Available from: https://doi.org/10.1039/D1NR05357D.
24. Dudău M, Codrici E, Tanase C, Gherghiceanu M, Enciu AM, Hinescu ME. Caveolae as potential hijackable gates in cell communication. Frontiers in Cell and Developmental Biology. 2020;8:581732. PMID: 33195223. Available from: https://doi.org/10.3389/fcell.2020.581732.
25. Kudruk S, Chali SP, Matos ALL, Bourque C, Dunker C, Gatsogiannis C, et al. Biodegradable and Dual-Responsive

Polypeptide-Shelled Cyclodextrin-Containers for Intracellular Delivery of Membrane-Impermeable Cargo. Advanced Science. 2021;8(18):e2100694. PMID: 34278745. Available from: https://doi.org/10.1002/advs.202100694.

26. Zhao Y, Jiang H, Yu J, Wang L, Du J. Engineered histidine-rich peptides enhance endosomal escape for antibody-targeted intracellular delivery of functional proteins. Angewandte Chemie International Edition in English. 2023;62(38):e202304692. PMID: 37283024. Available from: https://doi.org/10.1002/anie.202304692.
27. Ju Y, Guo H, Edman M, Hamm-Alvarez SF. Application of advances in endocytosis and membrane trafficking to drug delivery. Advanced Drug Delivery Reviews. 2020;157:118–41. PMID: 32758615. Available from: https://doi.org/10.1016/j.addr.2020.07.026.
28. Cho H, Huh KM, Shim MS, Cho YY, Lee JY, Lee HS, et al. Selective delivery of imaging probes and therapeutics to the endoplasmic reticulum or Golgi apparatus: current strategies and beyond. Advanced Drug Delivery Reviews. 2024;212:115386. PMID: 38971180. Available from: https://doi.org/10.1016/j.addr.2024.115386.
29. Fu S, Xu X, Ma Y, Zhang S, Zhang S. RGD peptide-based non-viral gene delivery vectors targeting integrin $\alpha v\beta 3$ for cancer therapy. Journal of Drug Targeting. 2019;27(1):1–11. PMID: 29564914. Available from: https://doi.org/10.1080/1061186X.2018.1455841.
30. Dhritlahre RK, Saneja A. Recent advances in HER2-targeted delivery for cancer therapy. Drug Discovery Today. 2021;26(5):1319–29. PMID: 33359114. Available from: https://doi.org/10.1016/j.drudis.2020.12.014.
31. Santos ED, Nogueira KA, Fernandes LC, Martins JR, Reis AV, Neto JB, et al. EGFR targeting for cancer therapy: pharmacology and immunoconjugates with drugs and nanoparticles. International Journal of Pharmaceutics. 2021;592:120082. PMID: 33188892. Available from: https://doi.org/10.1016/j.ijpharm.2020.120082.
32. Kazi J, Mukhopadhyay R, Sen R, Jha T, Ganguly S, Debnath MC. Design of 5-fluorouracil (5-FU) loaded, folate conjugated peptide linked nanoparticles, a potential new drug carrier for selective targeting of tumor cells. MedChemComm. 2019;10(4):559–72. PMID: 31057736. Available from: https://doi.org/10.1039/C8MD00565F.
33. Sharma D, Sharma M, Bisht GS. Recent Updates on Folate Targeted Drug Delivery Systems in Cancer: A Mini Review. Current Cancer Therapy Reviews. 2023;19(1):2–12. Available from: https://doi.org/10.2174/1573394717666210705115359.
34. Nezir AE, Khalily MP, Gulyuz S, Ozcubukcu S, G Küçükgüzel, Yilmaz O. Synthesis and evaluation of tumor-homing peptides for targeting prostate cancer. Amino Acids. 2021;53(5):645–52. PMID: 33846842. Available from: https://doi.org/10.1007/s00726-021-02971-3.
35. Wester HJ, Schottelius M. PSMA-Targeted Radiopharmaceuticals for Imaging and Therapy. Seminars in Nuclear Medicine. 2019;49(4):302–312. Available from: https://doi.org/10.1053/j.semnuclmed.2019.02.008.
36. Janoniene A, Petrikaite V. In search of advanced tumor diagnostics and treatment: achievements and perspectives of Carbonic Anhydrase IX targeted delivery. Molecular Pharmaceutics. 2020;17(6):1800–15. PMID: 32374612. Available from: https://doi.org/10.1021/acs.molpharmaceut.0c00180.
37. Sharma A, Singh AP, Singh S. Shaping up the tumor microenvironment: extracellular vesicles as important intermediaries in building a tumor-supportive cellular network. Cancers. 2023;15(2):501.
38. Neophytou CM, Panagi M, Stylianopoulos T, Papageorgis P. The role of tumor microenvironment in cancer metastasis: molecular mechanisms and therapeutic opportunities. Cancers (Basel). 2021;13(9):2053. PMID: 33922795. Available from: https://doi.org/10.3390/cancers13092053.
39. Lu X, Gou Z, Chen H, Li L, Chen F, Bao C. Extracellular matrix cancer-associated fibroblasts promote stromal fibrosis and immune exclusion in triple-negative breast cancer. The Journal of Pathology. 2025;265(3):385–99. PMID: 39846260. Available from: https://doi.org/10.1002/path.6395.
40. Yu Z, Zhang Q, Wei S, Zhang Y, Zhou T, Zhang Q. CD146+CAFs promote progression of endometrial cancer by inducing angiogenesis and vasculogenic mimicry via IL-10/JAK1/STAT3 pathway. Cell Communication and Signaling : CCS. 2024;22(1):170. PMID: 38459564. Available from: https://doi.org/10.1186/s12964-024-01550-9.
41. Feng B, Wu J, Shen B, Jiang F, Feng J. Cancer-associated fibroblasts and resistance to anticancer therapies: status, mechanisms, and countermeasures. Cancer Cell International. 2022;22(1):166. PMID: 35488263. Available from: https://doi.org/10.1186/s12935-022-02599-7.
42. Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. Cellular and Molecular Life Sciences : CMLS. 2020;77(9):1745–70. PMID: 31690961. Available from: https://doi.org/10.1007/s00018-019-03351-7.
43. Sakurai Y, Akita H, Harashima H. Targeting tumor endothelial cells with nanoparticles. International Journal of Molecular Sciences. 2019;20(23):5819. PMID: 31756900. Available from: https://doi.org/10.3390/ijms20235819.
44. Vyas D, Patel M, Wairkar S. Strategies for active tumor targeting-an update. European Journal of Pharmacology. 2022;915:174512. PMID: 34555395. Available from: https://doi.org/10.1016/j.ejphar.2021.174512.
45. Ahmad A, Nawaz MI. Molecular mechanism of VEGF and its role in pathological angiogenesis. Journal of Cellular Biochemistry. 2022;123(12):1938–65. PMID: 36288574. Available from: https://doi.org/10.1002/jcb.30344.
46. Méndez-Valdés G, Gómez-Hevia F, Lillo-Moya J, González-Fernández T, Abelli J, Cereceda-Cornejo A. Endostatin and cancer therapy: a novel potential alternative to anti-VEGF monoclonal antibodies. Biomedicines. 2023;11(3):718. PMID: 36979697. Available from: https://doi.org/10.3390/biomedicines11030718.
47. Tie Y, Tang F, Wei YQ, Wei XW. Immunosuppressive cells in cancer: mechanisms and potential therapeutic targets. Journal of Hematology & Oncology. 2022;15(1):61. PMID: 35585567. Available from: https://doi.org/10.1186/s13045-022-01282-8.
48. Raedler LA. Keytruda (pembrolizumab): first PD-1 inhibitor approved for previously treated unresectable or metastatic melanoma. American health & drug benefits. 2015;8(Spec Feature):96.
49. L'Orphelin JM, Lancien U, Nguyen JM, Coronilla FJ, Saiagh S, Cassecuel J. NIVO-TIL: combination anti-PD-1 therapy and adoptive T-cell transfer in untreated metastatic melanoma: an exploratory open-label phase I trial. Acta Oncologica (Stockholm, Sweden). 2024;63:867–77. PMID: 39508576. Available from: https://doi.org/10.2340/1651-226X.2024.40495.
50. Madan RA, Antonarakis ES, Drake CG, Fong L, Yu EY, McNeel DG. Putting the pieces together: completing the mechanism of action jigsaw for sipuleucel-T. Journal of the National Cancer Institute. 2020;112(6):562–73. PMID: 32145020. Available from: https://doi.org/10.1093/jnci/djaa021.
51. Chen K, Li X, Dong S, Guo Y, Luo Z, Zhuang SM. Modulating tumor-associated macrophages through CSF1R inhibition: a potential therapeutic strategy for HNSCC. Journal of Translational Medicine. 2025;23(1):27. PMID: 39780232. Available from: https://doi.org/10.1186/s12967-024-06036-3.
52. Zhang W, Wang J, Liu C, Li Y, Sun C, Wu J. Crosstalk and plasticity driving between cancer-associated fibroblasts and tumor microenvironment: significance of breast cancer metastasis. Journal of Translational Medicine. 2023;21(1):827. PMID: 37978384. Available from: https://doi.org/10.1186/s12967-023-04714-2.
53. Qi F, Fu D, Cai H, Zheng Y, Wang N, Xu Z. Metabolic Reprogramming of Cancer-Associated Fibroblasts: Transforming Tumor Accomplices into Immunotherapeutic Allies. Advanced Functional Materials. 2025;35(13):2418240. Available

from: https://doi.org/10.1002/adfm.202418240.
54. Zhou D, Zheng L. Recent advances in cancer-associated fibroblast: Biomarkers, signaling pathways, and therapeutic opportunities. Chinese Medical Journal. 2024;137(6):638–50. PMID: 38420743. Available from: https://doi.org/10.1097/CM9.0000000000003031.
55. Shin H, Kim Y, Jon S. Nanovaccine displaying immunodominant T cell epitopes of fibroblast activation protein is effective against desmoplastic tumors. ACS Nano. 2023;17(11):10337–52. PMID: 37184372. Available from: https://doi.org/10.1021/acsnano.3c00764.
56. Steele NG, Biffi G, Kemp SB, Zhang Y, Drouillard D, Syu L. Inhibition of hedgehog signaling alters fibroblast composition in pancreatic cancer. Clinical Cancer Research. 2021;27(7):2023–37. PMID: 33495315. Available from: https://doi.org/10.1158/1078-0432.CCR-20-3715.
57. Saw PE, Chen J, Song E. Targeting CAFs to overcome anticancer therapeutic resistance. Trends in Cancer. 2022;8(7):527–55. PMID: 35331673. Available from: https://doi.org/10.1016/j.trecan.2022.03.001.
58. Sanegre S, Lucantoni F, Burgos-Panadero R, de La Cruz-Merino L, Noguera R, Álvaro Naranjo T. Integrating the tumor microenvironment into cancer therapy. Cancers (Basel). 2020;12(6):1677. PMID: 32599891. Available from: https://doi.org/10.3390/cancers12061677.
59. Huang J, Zhang L, Wan D, Zhou L, Zheng S, Lin S. Extracellular matrix and its therapeutic potential for cancer treatment. Signal Transduction and Targeted Therapy. 2021;6(1):153. PMID: 33888679. Available from: https://doi.org/10.1038/s41392-021-00544-0.
60. Subrahmanyam N, Ghandehari H. Harnessing extracellular matrix biology for tumor drug delivery. Journal of Personalized Medicine. 2021;11(2):88. PMID: 33572559. Available from: https://doi.org/10.3390/jpm11020088.
61. Popova NV, Jücker M. The functional role of extracellular matrix proteins in cancer. Cancers (Basel). 2022;14(1):238. PMID: 35008401. Available from: https://doi.org/10.3390/cancers14010238.
62. Niland S, Riscanevo AX, Eble JA. Matrix metalloproteinases shape the tumor microenvironment in cancer progression. International Journal of Molecular Sciences. 2021;23(1):146. PMID: 35008569. Available from: https://doi.org/10.3390/ijms23010146.
63. Xu Y, Kirchner M. Collagen mimetic peptides. Bioengineering (Basel, Switzerland). 2021;8(1):5. PMID: 33466358. Available from: https://doi.org/10.3390/bioengineering8010005.
64. Ikeda-Imafuku M, Gao Y, Shaha S, Wang LL, Park KS, Nakajima M. Extracellular matrix degrading enzyme with stroma-targeting peptides enhance the penetration of liposomes into tumors. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2022;352:1093–103. PMID: 36351520. Available from: https://doi.org/10.1016/j.jconrel.2022.11.007.
65. Zhu M, Ren G, Guo J, Chen X, Long R, Wang S. Hypoxia-responsive nanomicelle based on 2-nitroimidazole for tumor treatment through chemotherapy and modulation of the tumor redox microenvironment. ACS Applied Nano Materials. 2024;7(11):12452–65. Available from: https://doi.org/10.1021/acsanm.4c00826.
66. Zhao D, Zhang Y, Yan Z, Ding Y, Liang F. Hypoxia-responsive polymeric nanoprodrugs for combo photodynamic and chemotherapy. ACS Omega. 2023;9(1):1821–6. PMID: 38222587. Available from: https://doi.org/10.1021/acsomega.3c08504.
67. Tsuji T, Tsunematsu H, Imanishi M, Denda M, Tsuchiya K, Otaka A. Enhanced tumor specific drug release by hypoxia sensitive dual-prodrugs based on 2-nitroimidazole. Bioorganic & Medicinal Chemistry Letters. 2023;95:129484. PMID: 37716415. Available from: https://doi.org/10.1016/j.bmcl.2023.129484.
68. Rani P, Rahim JU, Patra S, Gupta R, Gulati M, Kapoor B. Tumor microenvironment-responsive self-assembling polymeric prodrug-based nanomaterials for cancer therapy. Journal of Drug Delivery Science and Technology. 2024;96:105715. Available from: https://doi.org/10.1016/j.jddst.2024.105715.
69. Jadhav K, Abhang A, Kole EB, Gadade D, Dusane A, Iyer A. Peptide-Drug Conjugates as Next-Generation Therapeutics: Exploring the Potential and Clinical Progress. Bioengineering (Basel, Switzerland). 2025;12(5):481. PMID: 40428099. Available from: https://doi.org/10.3390/bioengineering12050481.
70. Andrade-Gagnon B, Casillas-Popova SN, Jazani AM, Oh JK. Design, Synthesis, and Acid-Responsive Disassembly of Shell-Sheddable Block Copolymer Labeled with Benzaldehyde Acetal Junction. Macromolecular Rapid Communications. 2024;45(12):e2400097. PMID: 38499007. Available from: https://doi.org/10.1002/marc.202400097.
71. Godet I, Doctorman S, Wu F, Gilkes DM. Detection of hypoxia in cancer models: significance, challenges, and advances. Cells. 2022;11(4):686. PMID: 35203334. Available from: https://doi.org/10.3390/cells11040686.
72. Xiao D, Liu L, Xie F, Dong J, Wang Y, Xu X, et al. Azobenzene-Based Linker Strategy for Selective Activation of Antibody-Drug Conjugates. Angewandte Chemie International Edition in English. 2024;63(16):e202310318. PMID: 38369681. Available from: https://doi.org/10.1002/anie.202310318.
73. Zhang T, Yang B, Jiang T, Kong X, Huo X, Ma Y. A Hypoxia-Activated BODIPY-Azo Anticancer Prodrug for Bimodal Chemo-Photodynamic Therapy. Journal of Medicinal Chemistry. 2025;68(3):3020–30. PMID: 39826133. Available from: https://doi.org/10.1021/acs.jmedchem.4c02231.
74. He H, Deng X, Wang Z, Chen J, in the Development of Peptide-Drug Conjugates RP. Recent progress in the development of peptide-drug conjugates (PDCs) for cancer therapy. European Journal of Medicinal Chemistry. 2025;284:117204. PMID: 39731788. Available from: https://doi.org/10.1016/j.ejmech.2024.117204.
75. Cooper BM, Iegre J, Donovan DHO, Halvarsson MÖ, Spring DR. Peptides as a platform for targeted therapeutics for cancer: peptide-drug conjugates (PDCs). Chemical Society Reviews. 2021;50(3):1480–94. PMID: 33346298. Available from: https://doi.org/10.1039/D0CS00556H.
76. Zhao J, Santino F, Giacomini D, Gentilucci L. Integrin-targeting peptides for the design of functional cell-responsive biomaterials. Biomedicines. 2020;8(9):307. PMID: 32854363. Available from: https://doi.org/10.3390/biomedicines8090307.
77. Zhou X, Shi K, Hao Y, Yang C, Zha R, Yi C. Advances in nanotechnology-based delivery systems for EGFR tyrosine kinases inhibitors in cancer therapy. Asian Journal of Pharmaceutical Sciences. 2020;15(1):26–41. PMID: 32175016. Available from: https://doi.org/10.1016/j.ajps.2019.06.001.
78. He J, Li C, Ding L, Huang Y, Yin X, Zhang J, et al. Tumor targeting strategies of smart fluorescent nanoparticles and their applications in cancer diagnosis and treatment. Advanced Materials. 2019;31(40):e1902409. PMID: 31369176. Available from: https://doi.org/10.1002/adma.201902409.
79. Zuo H. iRGD: a promising peptide for cancer imaging and a potential therapeutic agent for various cancers. Journal of Oncology. 2019;2019(1):9367845. PMID: 31346334. Available from: https://doi.org/10.1155/2019/9367845.
80. Giovannini E, Giovacchini G, Borsò E, Lazzeri P, Riondato M, Leoncini R. [68Ga]-Dota Peptide PET/CT in Neuroendocrine Tumors: Main Clinical Applications. Current Radiopharmaceuticals. 2019;12(1):11–22. PMID: 30539709. Available from: https://doi.org/10.2174/1874471012666181212101244.
81. Crișan G, Moldovean-Cioroianu NS, Timaru DG, Andries G, Căinap C, Chiș V. Radiopharmaceuticals for PET and SPECT imaging: a literature review over the last decade. International Journal of Molecular Sciences. 2022;23(9):5023. PMID: 35563414. Available from: https://doi.org/10.3390/ijms23095023.
82. Hossein-Nejad-Ariani H, Althagafi E, Kaur K. Small peptide ligands for targeting EGFR in triple negative breast cancer cells. Scientific Reports. 2019;9(1):2723. PMID: 30804365.

Available from: https://doi.org/10.1038/s41598-019-38574-y.
83. Li W, Wang H, Zhao Z, Gao H, Liu C, Zhu L, et al. Emerging nanotechnologies for liquid biopsy: the detection of circulating tumor cells and extracellular vesicles. Advanced Materials. 2019;31(45):e1805344. PMID: 30589111. Available from: https://doi.org/10.1002/adma.201805344.
84. Carmona-Ule N, Gal N, Redondo CA, Freire MDLF, López RL, Dávila-Ibáñez AB. Peptide-functionalized nanoemulsions as a promising tool for isolation and ex vivo culture of circulating tumor cells. Bioengineering (Basel, Switzerland). 2022;9(8):380. PMID: 36004905. Available from: https://doi.org/10.3390/bioengineering9080380.
85. Jiao J, Zhang J, Yang F, Song W, Han D, Wen W, et al. Quicker, deeper and stronger imaging: A review of tumor-targeted, near-infrared fluorescent dyes for fluorescence guided surgery in the preclinical and clinical stages. European Journal of Pharmaceutics and Biopharmaceutics. 2020;152:123–43. PMID: 32437752. Available from: https://doi.org/10.1016/j.ejpb.2020.05.002.
86. Liu M, Anderson RC, Lan X, Conti PS, Chen K. Recent advances in the development of nanoparticles for multimodality imaging and therapy of cancer. Medicinal Research Reviews. 2020;40(3):909–30. PMID: 31650619. Available from: https://doi.org/10.1002/med.21642.
87. Sotirov S, Dimitrov I. Tumor-derived antigenic peptides as potential cancer vaccines. International Journal of Molecular Sciences. 2024;25(9):4934. PMID: 38732150. Available from: https://doi.org/10.3390/ijms25094934.
88. Liu D, Liu L, Li X, Wang S, Wu G, Che X. Advancements and challenges in peptide-based cancer vaccination: a multidisciplinary perspective. Vaccines. 2024;12(8):950. PMID: 39204073. Available from: https://doi.org/10.3390/vaccines12080950.
89. Li L, Zhang X, Wang X, Kim SW, Herndon JM, Becker-Hapak MK. Optimized polyepitope neoantigen DNA vaccines elicit neoantigen-specific immune responses in preclinical models and in clinical translation. Genome Medicine. 2021;13(1):56. PMID: 33879241. Available from: https://doi.org/10.1186/s13073-021-00872-4.
90. Malacopol AT, Holst PJ. Cancer Vaccines: Recent Insights and Future Directions. International Journal of Molecular Sciences. 2024;25(20):11256. PMID: 39457036. Available from: https://doi.org/10.3390/ijms252011256.
91. Zhou Y, Wei Y, Tian X, Wei X. Cancer vaccines: current status and future directions. Journal of Hematology & Oncology. 2025;18(1):18. PMID: 39962549. Available from: https://doi.org/10.1186/s13045-025-01670-w.
92. Zhao G, Zeng Y, Cheng W, Karkampouna S, Papadopoulou P, Hu B. Peptide-Modified Lipid Nanoparticles Boost the Antitumor Efficacy of RNA Therapeutics. ACS Nano. 2025;19(14):13685–704. PMID: 40176316. Available from: https://doi.org/10.1021/acsnano.4c14625.
93. Sethna Z, Guasp P, Reiche C, Milighetti M, Ceglia N, Patterson E. RNA neoantigen vaccines prime long-lived CD8+ T cells in pancreatic cancer. Nature. 2025;639(8056):1042–51. PMID: 39972124. Available from: https://doi.org/10.1038/s41586-024-08508-4.
94. Yaremenko AV, Khan MM, Zhen X, Tang Y, Tao W. Clinical advances of mRNA vaccines for cancer immunotherapy. Med. 2025;6(1):100562. PMID: 39798545. Available from: https://doi.org/10.1016/j.medj.2024.11.015.
95. Braun DA, Moranzoni G, Chea V, McGregor BA, Blass E, Tu CR. A neoantigen vaccine generates antitumour immunity in renal cell carcinoma. Nature. 2025;639(8054):474–82. PMID: 39910301. Available from: https://doi.org/10.1038/s41586-024-08507-5.
96. Siani P, Frigerio G, Donadoni E, Valentin CD. Molecular dynamics simulations of cRGD-conjugated PEGylated TiO2 nanoparticles for targeted photodynamic therapy. Journal of Colloid and Interface Science. 2022;627:126–41. PMID: 35842963. Available from: https://doi.org/10.1016/j.jcis.2022.07.045.
97. Cai Y, Chai T, Nguyen W, Liu J, Xiao E, Ran X. Phototherapy in cancer treatment: strategies and challenges. Signal Transduction and Targeted Therapy. 2025;10(1):115. PMID: 40169560. Available from: https://doi.org/10.1038/s41392-025-02140-y.
98. Wang H, Qin T, Wang W, Zhou X, Lin F, Liang G, et al. Selenium-containing type-I organic photosensitizers with dual reactive oxygen species of superoxide and hydroxyl radicals as switch-hitter for photodynamic therapy. Advanced Science. 2023;10(24):e2301902. PMID: 37357144. Available from: https://doi.org/10.1002/advs.202301902.
99. Przygoda M, Bartusik-Aebisher D, Dynarowicz K, Cieślar G, Kawczyk-Krupka A, Aebisher D. Cellular mechanisms of singlet oxygen in photodynamic therapy. International Journal of Molecular Sciences. 2023;24(23):16890. PMID: 38069213. Available from: https://doi.org/10.3390/ijms242316890.
100. Moloudi K, Abrahamse H, George BP. Nanotechnology-mediated photodynamic therapy: focus on overcoming tumor hypoxia. Wiley Interdisciplinary Reviews Nanomedicine and Nanobiotechnology. 2024;16(1):e1937. PMID: 38072393. Available from: https://doi.org/10.1002/wnan.1937.
101. Zhu Z, Feng Y, Tian Q, Li J, Liu C, Cheng Y. A Self-Immobilizing Photosensitizer with Long-Term Retention for Hypoxia Imaging and Enhanced Photodynamic Therapy. JACS Au. 2024;4(10):4032–42. PMID: 39483216. Available from: https://doi.org/10.1021/jacsau.4c00787.
102. Yu J, Wu J, Huang J, Xu C, Xu M, Koh CZ. Hypoxia-tolerant polymeric photosensitizer prodrug for cancer photoimmunotherapy. Nature Communications. 2025;16(1):153. PMID: 39747121. Available from: https://doi.org/10.1038/s41467-024-55529-8.
103. Alvarez N, Sevilla A. Current advances in photodynamic therapy (PDT) and the future potential of PDT-combinatorial cancer therapies. International Journal of Molecular Sciences. 2024;25(2):1023. PMID: 38256096. Available from: https://doi.org/10.3390/ijms25021023.
104. Xu F, Li H, Yao Q, Ge H, Fan J, Sun W. Hypoxia-activated NIR photosensitizer anchoring in the mitochondria for photodynamic therapy. Chemical Science (Cambridge). 2019;10(45):10586–94. PMID: 32110344. Available from: https://doi.org/10.1039/C9SC03355F.
105. Estermann M, Coelho R, Jacob F, Huang YL, Liang CY, Faia-Torres AB, et al. A 3D multi-cellular tissue model of the human omentum to study the formation of ovarian cancer metastasis. Biomaterials. 2023;294:121996. PMID: 36689832. Available from: https://doi.org/10.1016/j.biomaterials.2023.121996.
106. Nkune NW, Abrahamse H. Anti-Hypoxia Nanoplatforms for enhanced photosensitizer uptake and photodynamic therapy effects in cancer cells. International Journal of Molecular Sciences. 2023;24(3):2656. PMID: 36768975. Available from: https://doi.org/10.3390/ijms24032656.
107. Aebisher D, Woźnicki P, Bartusik-Aebisher D. Photodynamic therapy and adaptive immunity induced by reactive oxygen species: recent reports. Cancers (Basel). 2024;16(5):967. PMID: 38473328. Available from: https://doi.org/10.3390/cancers16050967.
108. Sui D, Li C, Tang X, Meng X, Ding J, Yang Q. Sialic acid-mediated photochemotherapy enhances infiltration of CD8+ T cells from tumor-draining lymph nodes into tumors of immunosenescent mice. Acta Pharmaceutica Sinica B. 2023;13(1):425–39. PMID: 36815045. Available from: https://doi.org/10.1016/j.apsb.2022.06.005.
109. Guidoccio F, Mazzarri S, Depalo T, Orsini F, Erba PA, Mariani G, et al. Novel Radiopharmaceuticals for Therapy. In: Volterrani, D., Erba, P.A., Strauss, H.W., Mariani, G., Larson, S.M. (eds) Nuclear Oncology. and others, editor. Springer; 2022. Available from: https://doi.org/10.1007/978-3-031-05494-5_36.
110. Shi S, Zhong H, Zhang Y, Mei Q. Targeted delivery of nano-radiosensitizers for tumor radiotherapy. Coordination Chemistry Reviews. 2024;518:216101. Available from: https://doi.

org/10.1016/j.ccr.2024.216101.
111. Liberal FDG, O'Sullivan JM, McMahon SJ, Prise KM. Targeted alpha therapy: current clinical applications. Cancer Biotherapy & Radiopharmaceuticals. 2020;35(6):404–17. PMID: 32552031. Available from: https://doi.org/10.1089/cbr.2020.3576.
112. Keam SJ. Lutetium Lu 177 vipivotide tetraxetan: first approval. Molecular Diagnosis & Therapy. 2022;26(4):467–75. PMID: 35553387. Available from: https://doi.org/10.1007/s40291-022-00594-2.
113. Fallah J, Agrawal S, Gittleman H, Fiero MH, Subramaniam S, John C. FDA approval summary: lutetium Lu 177 vipivotide tetraxetan for patients with metastatic castration-resistant prostate cancer. Clinical Cancer Research. 2023;29(9):1651–7. PMID: 36469000. Available from: https://doi.org/10.1158/1078-0432.CCR-22-2875.
114. Markham A. Belantamab mafodotin: first approval. Drugs. 2020;80(15):1607–13. PMID: 32936437. Available from: https://doi.org/10.1007/s40265-020-01404-x.
115. Baines AC, Ershler R, Kanapuru B, Xu Q, Shen G, Li L. FDA approval summary: belantamab mafodotin for patients with relapsed or refractory multiple myeloma. Clinical Cancer Research. 2022;28(21):4629–33. PMID: 35736811. Available from: https://doi.org/10.1158/1078-0432.CCR-22-0618.
116. Shultes KC. Loncastuximab Tesirine-lpyl (Zynlonta®). Oncology Times. 2022;44(22):14. Available from: https://doi.org/10.1097/01.COT.0000903780.24119.d6.
117. Xu B. Loncastuximab tesirine: an effective therapy for relapsed or refractory diffuse large B-cell lymphoma. European Journal of Clinical Pharmacology. 2022;78(5):707–19. PMID: 35061047. Available from: https://doi.org/10.1007/s00228-021-03253-3.
118. Keam SJ. Piflufolastat F 18: diagnostic first approval. Molecular Diagnosis & Therapy. 2021;25(5):647–56. PMID: 34292532. Available from: https://doi.org/10.1007/s40291-021-00548-0.
119. Shore ND, et al. The role of conventional imaging and piflufolastat F18 in newly diagnosed and recurrent prostate cancer patients: Preliminary observations from the PYLARIFY Registry. Journal of Clinical Oncology. 2025;43(5_suppl):41. Available from: ttps://doi.org/10.1200/JCO.2025.43.5_suppl.41.
120. Keam SJ. Nirogacestat: first Approval. Drugs. 2024;84(3):355–61. PMID: 38409573. Available from: https://doi.org/10.1007/s40265-024-02002-x.
121. Day-Storms J. FDA-Approved Nirogacestat Demonstrates Improved Patient Outcomes in Desmoid Tumor Management.
122. Wahby S, Fashoyin-Aje L, Osgood CL, Cheng J, Fiero MH, Zhang L. FDA approval summary: accelerated approval of sacituzumab govitecan-hziy for third-line treatment of metastatic triple-negative breast cancer. Clinical Cancer Research. 2021;27(7):1850–4. PMID: 33168656. Available from: https://doi.org/10.1158/1078-0432.CCR-20-3119.
123. Seligson JM, Patron AM, Berger MJ, Harvey RD, Seligson ND. Sacituzumab govitecan-hziy: an antibody-drug conjugate for the treatment of refractory, metastatic, triple-negative breast cancer. The Annals of Pharmacotherapy. 2021;55(7):921–31. PMID: 33070624. Available from: https://doi.org/10.1177/1060028020966548.
124. Saw PE, Song EW. Phage display screening of therapeutic peptide for cancer targeting and therapy. Protein & Cell. 2019;10(11):787–807. PMID: 31140150. Available from: https://doi.org/10.1007/s13238-019-0639-7.
125. He B, Dzisoo AM, Derda R, Huang J. Development and application of computational methods in phage display technology. Current Medicinal Chemistry. 2019;26(42):7672–93. PMID: 29956612. Available from: https://doi.org/10.2174/0929867325666180629123117.
126. Fetse J, Kandel S, Mamani UF, Cheng K. Recent advances in the development of therapeutic peptides. Trends in Pharmacological Sciences. 2023;44(7):425–41. PMID: 37246037. Available from: https://doi.org/10.1016/j.tips.2023.04.003.
127. Fu C, Yu L, Miao Y, Liu X, Yu Z, Wei M. Peptide-drug conjugates (PDCs): a novel trend of research and development on targeted therapy, hype or hope? Acta Pharmaceutica Sinica B. 2023;13(2):498–516. PMID: 36873165. Available from: https://doi.org/10.1016/j.apsb.2022.07.020.
128. Amblard M, Fehrentz JA, Martinez J, Subra G. Methods and protocols of modern solid phase Peptide synthesis. Molecular Biotechnology. 2006;33(3):239–54. PMID: 16946453. Available from: https://doi.org/10.1385/MB:33:3:239.
129. Masui H, Fuse S. Recent advances in the solid-and solution-phase synthesis of peptides and proteins using microflow technology. Organic Process Research & Development. 2022;26(6):1751–65. Available from: https://doi.org/10.1021/acs.oprd.2c00074.
130. Hao L, Li X, Zhao B, Song X, Zhang Y, Liang Q. Enzymatic hydrolysis optimization of yak whey protein concentrates and bioactivity evaluation of the ultrafiltered peptide fractions. Molecules (Basel, Switzerland). 2024;29(6):1403. PMID: 38543039. Available from: https://doi.org/10.3390/molecules29061403.
131. Ahmadi-Vavsari F, Farmani J, Dehestani A. Recombinant production of a bioactive peptide from spotless smooth-hound (Mustelus griseus) muscle and characterization of its antioxidant activity. Molecular Biology Reports. 2019;46(3):2599–608. PMID: 31020488. Available from: https://doi.org/10.1007/s11033-018-4468-1.
132. Olivares-Galván S, Marina ML, García MC. Extraction and characterization of antioxidant peptides from fruit residues. Foods. 2020;9(8):1018. PMID: 32751284. Available from: https://doi.org/10.3390/foods9081018.
133. Stevens CA, Bachtiger F, Kong XD, Abriata LA, Sosso GC, Gibson MI. A minimalistic cyclic ice-binding peptide from phage display. Nature Communications. 2021;12(1):2675. PMID: 33976148. Available from: https://doi.org/10.1038/s41467-021-22883-w.
134. Lammi C, Aiello G, Boschin G, Arnoldi A. Multifunctional peptides for the prevention of cardiovascular disease: A new concept in the area of bioactive food-derived peptides. Journal of Functional Foods. 2019;55:135–45. Available from: https://doi.org/10.1016/j.jff.2019.02.016.
135. Váá J, Hejtmánková A, Kalbáá MH, Španielová H. The utilization of cell-penetrating peptides in the intracellular delivery of viral nanoparticles. Materials (Basel). 2019;12(17):2671. PMID: 31443361. Available from: https://doi.org/10.3390/ma12172671.
136. Esposto BS, Jauregi P, Tapia-Blácido DR, Martelli-Tosi M. Liposomes vs. chitosomes: encapsulating food bioactives. Trends in Food Science & Technology. 2021;108:40–8. Available from: https://doi.org/10.1016/j.tifs.2020.12.003.
137. Elmowafy EM, Tiboni M, Soliman ME. Biocompatibility, biodegradation and biomedical applications of poly (lactic acid)/poly (lactic-co-glycolic acid) micro and nanoparticles. Journal of Pharmaceutical Investigation. 2019;49(4):347–80. Available from: https://doi.org/10.1007/s40005-019-00439-x.
138. Zhu D, Zhang H, Huang Y, Lian B, Ma C, Han L. A self-assembling amphiphilic peptide dendrimer-based drug delivery system for cancer therapy. Pharmaceutics. 2021;13(7):1092. PMID: 34371783. Available from: https://doi.org/10.3390/pharmaceutics13071092.
139. Thi TTH, Cao VD, Nguyen TN, Hoang DT, Ngo VC, Nguyen DH. Functionalized mesoporous silica nanoparticles and biomedical applications. Materials Science and Engineering C. 2019;99:631–56. PMID: 30889738. Available from: https://doi.org/10.1016/j.msec.2019.01.129.
140. Bravo M, Fortuni B, Mulvaney P, Hofkens J, Uji-I H, Rocha S. Nanoparticle-mediated thermal Cancer therapies: strategies to improve clinical translatability. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2024;372:751–77. PMID: 38909701. Available from: https://doi.org/10.1016/j.jconrel.2024.06.055.
141. Yuan D, Lu Z, Xu X, Liu W. RGD peptide-conjugated polydopamine nanoparticles loaded with doxorubicin for combined chemotherapy and photothermal therapy in thyroid

cancer. Discover Oncology. 2024;15(1):794. PMID: 39692825. Available from: https://doi.org/10.1007/s12672-024-01682-x.

142. Wang B, Tang D, Cui J, Jiang H, Yu J, Guo Z. RGD-based self-assembling nanodrugs for improved tumor therapy. Frontiers in Pharmacology. 2024;15. PMID: 39411070. Available from: https://doi.org/10.3389/fphar.2024.1477409.
143. Bardania H, Baneshi M, Mahmoudi R, Khosravani F, Safari F, Khalvati B. Synergistic breast cancer therapy with RGD-decorated liposomes co-delivering mir-34a and cisplatin. Cancer Nanotechnology. 2024;15(1):60. Available from: https://doi.org/10.1186/s12645-024-00299-7.
144. Kumarasamy RV, Natarajan PM, Umapathy VR, Roy JR, Mironescu M, Palanisamy CP. Clinical applications and therapeutic potentials of advanced nanoparticles: A comprehensive review on completed human clinical trials. Frontiers in Nanotechnology. 2024;6:1479993. Available from: https://doi.org/10.3389/fnano.2024.1479993.
145. Bonvalot S, Pechoux CL, Baere TD, Kantor G, Buy X, Stoeckle E. First-in-human study testing a new radioenhancer using nanoparticles (NBTXR3) activated by radiation therapy in patients with locally advanced soft tissue sarcomas. Clinical Cancer Research. 2017;23(4):908–17. PMID: 27998887. Available from: https://doi.org/10.1158/1078-0432.CCR-16-1297.
146. Malone ER, Oliva M, Sabatini PJ, Stockley TL, Siu LL. Molecular profiling for precision cancer therapies. Genome Medicine. 2020;12(1):8. PMID: 31937368. Available from: https://doi.org/10.1186/s13073-019-0703-1.
147. Agur Z, Elishmereni M, Foryś U, Kogan Y. Accelerating the development of personalized cancer immunotherapy by integrating molecular patients' profiles with dynamic mathematical models. Clinical Pharmacology and Therapeutics. 2020;108(3):515–27. PMID: 32535891. Available from: https://doi.org/10.1002/cpt.1942.
148. Zhang DE, He T, Shi T, Huang K, Peng A. Trends in the research and development of peptide drug conjugates: artificial intelligence aided design. Frontiers in Pharmacology. 2025;16:1553853. PMID: 40083376. Available from: https://doi.org/10.3389/fphar.2025.1553853.
149. Nhàn NT, Yamada T, Yamada KH. Peptide-based agents for cancer treatment: current applications and future directions. International Journal of Molecular Sciences. 2023;24(16):12931. PMID: 37629112. Available from: https://doi.org/10.3390/ijms241612931.
150. Ge C, et al. CreoPep: A Universal Deep Learning Framework for Target-Specific Peptide Design and Optimization. arXiv. 2025;2025:2505.02887.
151. Lei Y, et al. Pepgb: facilitating peptide drug discovery via graph neural networks. arXiv. 2024;2024:2401.14665.
152. Liu D, Zhao X, Tang A, Xu X, Liu S, Zha L, et al. CRISPR screen in mechanism and target discovery for cancer immunotherapy. Biochimica et Biophysica Acta Reviews on Cancer. 2020;1874(1):188378. PMID: 32413572. Available from: https://doi.org/10.1016/j.bbcan.2020.188378.