



## Review Article

## Advancements in therapeutic peptides: Shaping the future of cancer treatment

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## ARTICLE INFO

## ABSTRACT

**Keywords:**  
 Anti-cancer peptides  
 Mechanism  
 Immunotherapy  
 Drug delivery systems  
 Clinical therapeutics

In the evolving landscape of cancer treatment, therapeutic peptides are assuming to play an increasingly vital role. Although the number of peptide drugs available for clinical cancer treatment is currently limited, extensive preclinical research is underway, presenting a promising trajectory for the future. The collaborative efforts of natural anti-cancer peptides (ACPs) and synthetic ACPs, propelled by advancements in molecular biology and peptide chemistry, are steering remarkable progress in this domain. We explore the intricate mechanisms underlying the anti-cancer effects of these peptides. The exploration of innovative strategies, including cancer immunotherapy and advanced drug delivery systems, is likely to contribute to the increasing presence of peptide drugs in clinical cancer care. Furthermore, we delve into the potential implications and challenges associated with this anticipated shift, emphasizing the need for continued research and development to unlock the full therapeutic potential of peptide drugs in cancer treatment.

## 1. Introduction

Cancer treatment is a significant challenge given the increased incidence of tumorigenesis due to aging populations and lifestyle changes. Based on the most recent global cancer statistics, in 2019, there were 23.6 million new cancer cases and 10.0 million deaths globally, reflecting a 26.3 % increase in cases and a 20.9 % increase in deaths since 2010. Cancer ranks second only to cardiovascular diseases in terms of global deaths. The cancer burden varies across sociodemographic index quintiles, with higher quintiles contributing more significantly to years lived with disability [1]. The clinical treatment of malignant

cancers primarily encompasses surgery combined with radiotherapy and chemotherapy. Surgical treatment is susceptible to recurrence, but radiotherapy and chemotherapy have limitations such as poor specificity, severe side effects, and harm to the nervous system and the gastrointestinal tract [2]. Clinical practitioners are presently focused on enhancing the precision, safety, and efficacy of cancer treatments. Targeted cancer therapies with high selectivity and few side effects are urgently needed. In recent years, researchers have investigated peptides with anti-cancer properties as promising alternatives for cancer therapy.

The US Food and Drug Administration (FDA) considers any polymer composed of 40 or fewer amino acids to be a peptide. Anti-

**Abbreviations:** AAs, Amino Acids; ACPs, Anti-Cancer Peptides; AHX, 6-aminohexanoic acid; CD, Circular Dichroism; CD13, Mammalian Aminopeptidase N; CD4+ T cells, Cluster of Differentiation 4 Positive T cells; CD8+ T cells, Cluster of Differentiation 8 Positive T cells; CL, Leucine-zipper-like motif; CPPs, Cell Penetrating Peptides; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; DBAASP, Database of Antimicrobial Activity and Structure of Peptides; DDS, Drug Delivery System; EBRT, External Beam Radiotherapy; GA, Genetic Algorithms; GH, Growth Hormone; GLP-1, Glucagon-Like Peptide-1; GnRH, Gonadotropin-Releasing Hormone; HTVS, High-Throughput Virtual Screening; ICD, Immunogenic Cell Death; IL-1, Interleukin-1; IL-2, Interleukin-2; IL-6, Interleukin-6; IL-10, Interleukin-10; LJP, Laminaria japonica Peptides; MHC I, Major Histocompatibility Complex Class I; MHC II, Major Histocompatibility Complex Class II; MMP9, Matrix Metalloproteinase 9; NDVs, Numerical Descriptive Vectors; PD-1, Programmed Cell Death Protein 1; PD-L1, Programmed Cell Death Ligand 1; PDGF, Platelet-Derived Growth Factor; PEG, Polyethylene Glycol; PPIs, Protein-Protein Interactions; QSAR, Quantitative Structure-Activity Relationship; SPR, Surface Plasmon Resonance; TAMs, Tumor-Associated Macrophages; TANs, Tumor-Associated Neutrophils; Treg cells, T Regulatory cells; TNF- $\alpha$ , Tumor Necrosis Factor Alpha; VEGF, Vascular Endothelial Growth Factor; VEGFR2, Vascular Endothelial Growth Factor Receptor 2; VHL, Von Hippel-Lindau; WT1, Wilms' Tumor 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IFA, Incomplete Freund's Adjuvant.

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<https://doi.org/10.1016/j.bbcan.2024.189197>

Received 10 May 2024; Received in revised form 3 October 2024; Accepted 7 October 2024

Available online 14 October 2024

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cancer peptides (ACPs) are short peptides that are typically composed of 5–40 amino acids and are primarily derived from natural sources [3]. It is worth noting that the FDA guidelines mentioned earlier are shaped by considerations of synthetic feasibility, a factor that has evolved over time and is expected to continue changing in the future. In recent years, peptide-based drugs have emerged as remarkable and promising tools in cancer therapeutics, offering a multitude of exceptional capabilities, including precise targeting of specific cells, control over cellular fate, deep penetration into tumor tissues, and the ability to generate immune responses that enhance the effectiveness of conventional anti-cancer treatments [4]. The anti-cancer peptide leuprolide, developed and produced by AbbVie, was first approved by the FDA in 1985. Within two years, leuprolide also received approval in Canada and European countries for treating different types of cancer, such as prostate [5] and breast cancer [6]. With further research and clinical trials, the use of leuprolide in cancer treatment has been continuously evolving and expanding. In 2019, the global sales volume reached 2022 million dollars [2]. Currently, approximately 80 peptide drugs have been approved for clinical use by governmental agencies in several countries, and research on peptide therapeutics is ongoing. With over 150 peptides in clinical development and another 400–600 peptides undergoing pre-clinical studies [2], we expect the market for peptide therapeutics to maintain growth and expand.

The mechanisms of action of anti-cancer peptides include the direct killing of cancer cells, destruction of extracellular conditions favorable for tumor growth, inhibition of tumor cell metastasis and invasion, and activation of cancer patient immune systems. Immunotherapy represents a highly potent approach for combating cancer. By leveraging the immune system, immunotherapy targets and eliminates cancer cells, resulting in enduring anti-cancer responses and facilitating significant disease regression. Immunotherapy also safeguards against metastasis and recurrence, enhancing its effectiveness as a therapeutic strategy. Based on their distinct mechanisms of action, ACPs offer potential solutions to the challenges encountered in cancer immunotherapies, including tumor immune evasion, immune tolerance, limited presence of tumor-specific antigens, immune-related adverse events such as autoimmune diseases or immune-related inflammation, and the emergence of treatment resistance [7]. For instance, anti-cancer peptide vaccines have emerged as novel therapies in the field of oncology. In comparison to conventional chemotherapy, peptide vaccines offer advantages such as enhanced stability, robust targeting ability, minimal toxic side effects, and facile preparation. Peptide vaccines substantially augment the patient's immune system, leading to prolonged overall survival and favorable tolerability [8].

Peptides can also play a role in enhancing the delivery of other drugs to specific tissues or cells as part of a drug delivery system (DDS). Peptides have good biocompatibility and can be coupled with drug carriers to generate cancer-targeted carriers. The development of peptide DDSs encompasses carrier systems, targeting strategies, controlled release systems, codelivery systems, and personalized therapies. These advancements aim to enhance drug delivery efficiency, improve targeting specificity, and minimize adverse effects<sup>9</sup>. Carrier systems such as nanoparticles, liposomes, and polymer microspheres are employed to encapsulate and deliver peptide drugs. Controlled release systems respond to specific proteins/components within tumor microenvironments, as well as signals or stimuli, for regulated drug release. Codelivery systems enhance drug treatment efficacy by delivering multiple drugs together, leading to synergistic effects, optimized dosages, reduced drug resistance, and minimized side effects. Personalized therapy involves the design and optimization of DDSs based on patient genotype, tumor characteristics, and treatment needs.

The utilization of peptides or protein-based biomolecules in anti-cancer therapeutics is becoming increasingly important. Within the Drug Bank Database, approximately 460 compounds target cancer, 29 of which fall under the category of peptide or polypeptide-based anti-cancer drugs. These peptides are further classified into three groups:

approved, under investigation, and in trial phases [3]. In cancer treatment, ACPs are often used in combination with traditional chemotherapy drugs to enhance their targeting efficacy and reduce toxic side effects. For instance, goserelin and leuprolide are utilized in androgen deprivation therapy for pre- or postsurgical interventions in prostate or breast cancer. Octreotide, on the other hand, is primarily employed to alleviate symptoms and control the growth of neuroendocrine tumors [9]. These developments offer new directions for drug research and bring new hope for cancer treatment and other disease therapies. This paper provides a comprehensive review of the classification, mechanism of action, and clinical applications of ACPs. The aim of this review is to offer valuable insights for the discovery and development of peptide-based anti-cancer drugs.

## 2. Classification of anti-cancer peptides

Anti-cancer peptides can be classified based on their spatial structure (Fig. 1) and origin. These classification methods aid in understanding the structure and function of ACPs and provide a foundation for further drug development. It is important to note that peptides may possess multiple structural characteristics and sources, and these classifications are not absolute but serve as convenient tools for research and discussion.

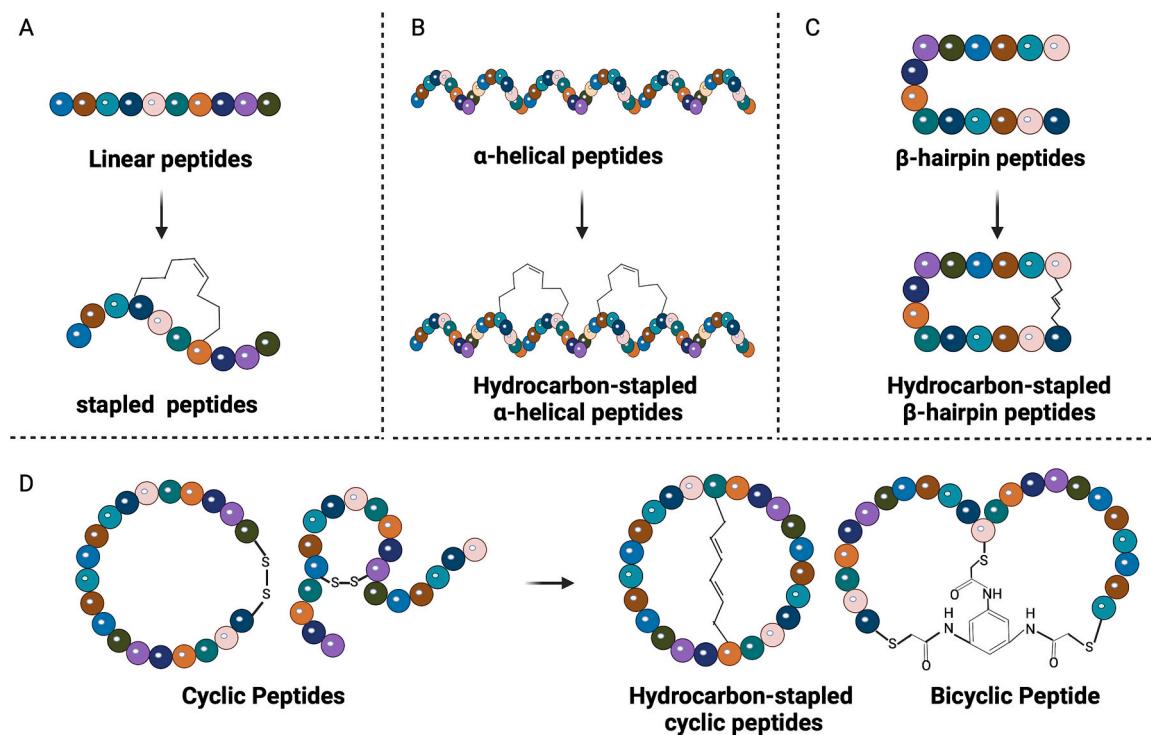
### 2.1. Spatial configuration-based classification

Anti-cancer peptides can be classified into four categories based on their spatial configuration. Linear peptides are composed of amino acids that are sequentially linked without folding or bending. They have fewer binding sites on the surface antigens of cancer cells, resulting in weaker recognition. Therefore, modifying the structure or delivery method of linear peptides can increase their anti-cancer efficacy [10].

$\alpha$ -Helical peptides adopt a stable coiled  $\alpha$ -helical structure and display diverse biological activities, including protein–protein interactions, membrane fusion, antimicrobial properties, and anti-cancer effects. Examples of alpha-helical peptides include silk fibroin, magainin, and melittin. They exhibit random conformations in water and organize into  $\alpha$ -helical structures upon interacting with cell membranes [11]. Hydrocarbon-stapled  $\alpha$ -helical peptides are a new class of artificially crafted peptides. They are locked in their bioactive  $\alpha$ -helical structure through the targeted use of an all-hydrocarbon staple, which significantly enhances their pharmacological performance. The stapled peptide N1S, designed based on AlphaFold predictions by Ramya Modi, inhibits Nrf2/MafG heterodimerization, reducing the transcription of Nrf2-dependent genes and enhancing cisplatin sensitivity in Nrf2-dependent cancer cells, suggesting that this peptide is a promising lead for sensitizing Nrf2-dependent cancers [12]. This stapling technique increases the target affinity, proteolytic resistance, and serum half-life of peptides [12]. Additionally, it facilitates effective cell penetration by leveraging endocytic vesicle trafficking pathways.

$\beta$ -folded peptides are peptides with a specific structure featuring  $\beta$ -folding, a common secondary structure in proteins. This structure consists of  $\beta$ -folded chains arranged in a stable three-dimensional form, providing these peptides with unique biological activity. They have potential applications in biomedical research and drug development.  $\beta$ -folded peptides included gramicidin, lactoferrin, and horseshoe crab peptide. These peptides are rich in proline, glycine, tryptophan, and arginine residues; moreover, the presence of multiple cysteine residues facilitates the maintenance of their folded state through disulfide bond formation [13]. Recently, synthesized hydrocarbon-stapled  $\beta$ -hairpin peptides have also undergone validation in the field of antimicrobial research [14].

Cyclic peptides are peptides with a stable circular structure formed by connecting the two ends of the peptide chain. This cyclic structure can be achieved through various connection methods, including but not limited to chemical bonds between nonnatural amino acid residues,



**Fig. 1.** Anti-cancer peptides can be classified based on their spatial structure. A. Linear peptides and stapled peptides, B.  $\alpha$ -helical peptides and hydrocarbon-stapled  $\alpha$ -helical peptides, C.  $\beta$ -hairpin peptides and hydrocarbon-stapled  $\beta$ -hairpin peptides, D. Cyclic 12 peptides, stapled cyclic peptides and bicyclic peptides. The figure was created with BioRender.com.

disulfide bonds between cysteine residues, or the introduction of special linking bridges such as alkyl chains. This cyclic arrangement enhances their stability and makes them valuable in drug development, biological research, and bioengineering. SFTI-G5, designed by Sitanshu S. Singh and employing a sunflower trypsin inhibitor (SFTI-1) template, was engineered to inhibit protein–protein interactions involving EGFR:HER2 and HER2:HER3. It demonstrated significant antiproliferative activity in HER2-positive NSCLC cell lines and effectively inhibited tumor growth *in vivo* [15]. Disulfide-bonded peptides are subtypes of cyclic peptides and form a cyclic structure through the linkage of cysteine residues via disulfide bonds. The developed peptide targeting the RbAp48/MTA1 interaction demonstrated a low nanomolar KD value of 8.56 nM, demonstrating the efficacy of a structure-based design strategy for protein–protein interaction inhibitors [16]. Cyclic stapled peptides, such as CP21, enhance the stability of cyclic peptides. CP21, a bicyclic peptide ligand targeting DCP2, exhibits high affinity and selectivity, inhibiting DCP2 decapping activity on specific RNA substrates in human cells. CP21 promotes the formation of P-bodies, which are liquid condensates enriched in RNA decay intermediates, resembling the effects observed with DCP2 deletion or mutation. Bicyclic peptides, which exhibit enhanced rigidity and stability, exhibit antibody-like affinity for challenging drug targets.

In addition, there are also intrinsically disordered peptides and hybrid peptides. Intrinsically disordered peptides typically contain high levels of proline and glycine and lack typical secondary structures. They exhibit weaker cytotoxic effects against tumor cells than other structural types of anti-cancer peptides [17]. The term “hybrid peptides” can be broad and covers a variety of peptide structures and compositions. These peptides can be designed for specific purposes, such as improved stability, enhanced bioavailability, or targeting specific biological activities. Although the structure of hybrid peptides is complex, they can be obtained through rational design and synthesis [18]. Hybrid peptides can be used in cancer therapy, immunoregulation, drug delivery, and other fields. For example, some hybrid peptides can be used as tumor vaccines to induce an immune response in the body, enhancing tumor

cell clearance [19]. In addition, some hybrid peptides can also be used as tools for the early detection and diagnosis of tumors [20]. Hybrid peptides can also be used in drug delivery systems to achieve targeted delivery of drugs through specific structural domains, thereby improving the therapeutic effect of drugs and reducing side effects [21]. Dual-functionalized peptides, currently a research hotspot in the development of peptide-based anti-cancer drugs, are peptides that couple two or more peptide sequences and exhibit multiple pharmacological activities. These peptides target multiple pathways simultaneously, demonstrating synergistic effects through different mechanisms and ensuring enhanced safety [22]. For complex diseases such as cardiovascular, metabolic, central nervous system, cancer, and immune-related disorders, intricate pathogenic mechanisms often pose challenges for achieving desired effects through the conventional model of single-target drugs. In the context of cancer research, dual-function peptides have emerged as a focal point, harnessing their potential to address diverse targets and enhance therapeutic outcomes. This innovative approach capitalizes on simultaneous action on different signaling pathways, significantly improving drug efficacy, presenting a more balanced pharmacokinetic profile, and reducing side effects [23]. Many peptide molecules with dual functionalities have undergone clinical validation, providing a foundation for creatively discovering better combinations to seek improved drugs [22,24]. Regarding risks and costs, dual-function peptides are generally on par with other single-entity molecules in clinical development. Compared to cocktails or multicomponent drugs, dual-function peptides avoid complex drug–drug interactions, resulting in lower risks and better patient and physician compliance due to simplified pharmacokinetic/pharmacodynamic behaviors [25]. In terms of structure, dual-functionalized peptides can be categorized into linear peptides, stapled peptides, and cyclic peptides. The increasing complexity of peptide molecular structures is an important developmental trend, manifested not only in the introduction of nonnatural amino acids or additional functional groups (proteins, small molecules) but also in diverse structural motifs such as cyclic peptides, disulfide-bonded peptides, stapled peptides,  $\beta$ -turns, and more. The

hybridization of peptide sequences or structures allows researchers to harness the beneficial properties of different peptide components, creating molecules with tailored characteristics. The design and synthesis of hybrid peptides are areas of ongoing scientific exploration and innovation.

## 2.2. Source-based classification

According to their sources, anti-cancer peptides can be classified into two categories: natural peptides and artificially synthesized peptides [26]. Natural peptides are derived from natural proteins within organisms, including venom, serum, immune cells, and tissues. Representative endogenous natural peptides are summarized in Table 1. Cecropins, derived from houseflies, exhibit growth inhibition and membrane permeabilization effects in vitro against various cancers, including

hepatocellular, esophageal, cervical, lung, breast, colon, and ovarian cancers, with derivatives such as Cecropin B, Cecropin A, Cecropin D, Moricin, Melittin-Cecropin, and hybrid peptides [27]. These natural peptides can be scarce and typically have high efficacy, but their structure and properties are often complex, thus restricting their research and application [28].

Typically, artificially designed and synthesized anti-cancer peptides are generated using two methods. The first method involves simulating the structure and function of natural peptide molecules by synthesizing peptide chains [29,30]. The second method involves the synthesis of new molecules by analyzing and modifying known peptide molecules, such as artificial toxins with enhanced anti-cancer activity [31]. Artificially designed peptides are synthesized by chemical or biological methods. Compared with those of natural peptides, the structure and properties of artificially synthesized peptides are easier to control. As

**Table 1**  
Examples of intrinsic anti-cancer peptides.

Name	Species	Exp	Mechanism and action	Cancers	Derivatives	Refs
Cecropin	Housefly	In vitro	Growth inhibition, membrane permeabilization	Hepatocellular, esophageal, cervical, lung, breast, colon, and ovarian cancers	Cecropin B, Cecropin A, Cecropin D, Moricin, Melittin-Cecropin, Hybrid Peptides	[27]
Epinicidin-1	<i>Epinephelus</i> spp	In vitro	Membrane permeabilization, growth inhibition, apoptosis	Synovial Sarcoma Leukemia		[135]
TH2-3	<i>Oreochromis mossambicus</i>	In vitro	Membrane permeabilization, growth inhibition	Fibrosarcoma, oral cancer		[136]
Temporin-1CEa	<i>Rana chensinensis</i>	In vitro and in vivo	Membrane permeabilization intracellular pathway modification	Breast cancer		[137,138]
HBD-3	<i>Homo sapiens</i>	In vitro	PIP2-mediated membrane permeabilization, growth inhibition	Oral carcinoma, Cervical and skin cancers	C-terminal of HBD-3, N-terminal of HBD-3	[139,140]
Gomesin	<i>Grammostola</i> spp	In vitro	Membrane permeabilization/necrotic cell death	Melanoma, breast cancer, colon and cervical cancers, neuroblastoma	CLS001, CGP3466B	[141]
Tachyplesin	<i>Limulus polyphemus</i>	In vitro	Activation of complement pathway, Membrane permeabilization	Bladder cancer, melanoma	Polyphemusin, Polyphemusin II-III	[142]
NaD1	<i>Nicotiana</i> spp	In vitro	PIP2-mediated membrane permeabilization, growth inhibition	Leukemia, Cervical cancers, Prostate cancer	D1-7, D1-23, D1-51	[143]
TPP3	<i>Solanum lycopersicum</i>	In vitro	IP2-mediated membrane permeabilization	Cervical cancers, Leukemia, Prostate cancer	TPP3-YrFK	[144,145]
Sesquelin	<i>sesquipedalis</i>	In vitro	Growth inhibition	Leukemia, Breast cancer		[146]
Magainin II	<i>Xenopus laevis</i>	In vitro	Growth inhibition	NSCLC, Breast cancer	MSI-136, MSI-238, MSI-78, MG2B, MG2A	[147]
Melittin	<i>Apis mellifera</i>	In vitro and in vivo	Membrane permeabilization Growth inhibition	Leukemia, breast cancer, ovarian cancers, hepatocellular and cervical cancers, osteosarcoma	D-K6L9, D-K4L7, D-L5, D-L5L8, Mel12, Melimine, Melacon	[148]
BF-30	<i>Serpentes</i>	In vitro	Membrane permeabilization	Melanoma, NSCLC	Cbf-K16	[149]
Spotted bean defensin	<i>Phaseolus vulgaris</i>	In vitro	Growth inhibition	Leukemia		[150]
Lunatusin	<i>Phaseolus lunatus</i>	In vitro	Growth inhibition	Breast cancer		[151]
LL-37	<i>Homo sapiens</i>	In vitro	Membrane permeabilization	Leukemia	FK-16, RL-37	[152]
	<i>Macaca mulatta</i>		Apoptosis	Colon cancers		
BMAP-27/ BMAP-28	<i>Bos taurus</i>	In vitro	lasma/mitochondrial membrane permeabilization	Leukemia Leukemia, Activated human lymphocytes	IB-367, IDR-1018	[153]
Lfcin B	<i>Bos taurus</i>	In vitro	Apoptosis, mitochondrial membrane damage	A range of leukemia, Breast, colon and ovarian cancers	LTX-315, LF11-322,6-MOLF11-322, R-DIMP-LF11-322, LfcinB(20-25)4	[154]
Protegrin-1	<i>Sus scrofa</i>	In vitro	Membrane permeabilization, growth inhibition	Leukemia	PG-1, Analog, Protegrin-1 P1V, Protegrin-1 P3	[155,156]
HNP	<i>Homo sapiens</i>	In vitro and in vivo	Membrane permeabilization Growth inhibition Activation of immature dendritic cells	Colon cancer, breast cancer	HNP-1, HNP-2, HNP-3 R-NH2, p-113, C16G2	[51]
Azurin	<i>Pseudomonas aeruginosa</i>	In vitro	Nuclear membrane permeabilization ubiquitination inhibition	Breast cancer Colon cancer fibrosarcoma	AzP-17, PNC-28, P28, CT-p19LC	[157,158]
FK-16	<i>Homo sapiens</i>		Apoptosis, autophagy	Colon cancer		[159]
KT2	<i>Crocodylinae</i>	In vivo	apoptosis	Colon cancer		[160]
TAT-derived anticancer peptide	Human immunodeficiency virus	In vitro and in vivo	Growth inhibition	Breast cancer, NSCLC	TAT-PTD, TAT-GRKKRRQRRRPPQ, TAT-Cre, BTapep-TAT	[161,162]

such, synthetic peptides can be designed and modified to target specific tumor cell targets with increased specificity and affinity. Additionally, the stability and efficacy of artificially synthesized peptides can also be improved through structural modification. Currently, artificially synthesized peptides are the most clinically used peptide drugs.

### 3. Key features of a good ACP drug and how to obtain one

For peptides, the majority of peptide drugs are utilized in the treatment of endocrine, metabolic, cardiovascular disorders, as well as cancer, with metabolic disorders, particularly diabetes, and cancer constituting the largest sources of revenue. The focus of peptide research in the early 20th century predominantly revolved around peptide engineering. Peptide engineering refers to the modification of existing natural peptides or their variants to improve their properties, stability, or functionality. Its applications include optimizing existing peptide drugs to enhance pharmacokinetic properties, increase bioactivity, or reduce side effects. Additionally, it can be used to modify the stability or specificity of peptides, making them more suitable for drug development. One of the key advantages of peptide engineering is that it allows the use of existing natural peptides as a foundation for enhancement, thus improving drug performance without starting from scratch.

As researchers have delved deeper into peptide studies, they have revealed the distinct advantage of peptides over small molecules due to their larger surface area, greater chiral complexity, and structural intricacy [32]. These characteristics can be leveraged for drug targets that require interactions at multiple and distant sites to activate the target. However, ensuring the effectiveness, stability, and safety of a peptide drug is crucial. By examining leuprolides as a case in point, several critical characteristics have emerged, revealing nuanced considerations in designing effective peptide drugs [33,34].

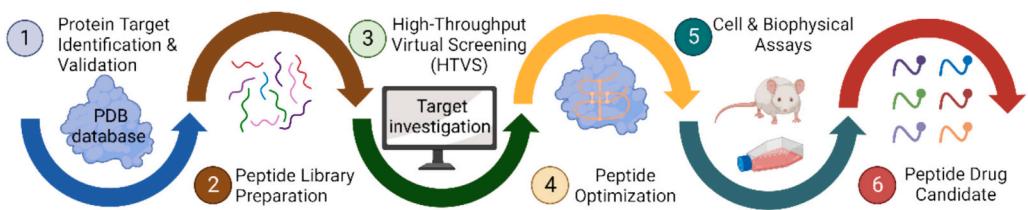
Leuprolide can effectively inhibit the function of the pituitary-gonadal system. The ability to promote luteinizing hormone (LH) release is approximately 20 times greater than that of GnRH. It also has a stronger inhibitory effect on hypothalamus-pituitary-gonadal function than does GnRH. The precision of target specificity exhibited by leuprolide, particularly in modulating LHRH receptors, underscores the importance of tailored interactions for therapeutic success [35]. Its high affinity and potency not only emphasize the necessity for strong molecular binding but also highlight the potential for robust pharmacological effects. Therefore, good anti-cancer peptides drugs should possess high potency and specificity. To achieve this goal, we first need to identify specific molecular targets associated with cancer cells for a focused therapeutic strategy. We can utilize bioinformatic methods and structural biology approaches to identify cancer-related or newly identified targets through genomic and proteomic analyses [36]. Subsequently, peptide sequences are designed based on structural and functional information to achieve effective binding to target proteins. We can also employ high-throughput virtual screening (HTVS) to swiftly and efficiently screen peptide drugs with specific biological activities, offering robust support for the development and optimization of peptide drugs. Next, we need to conduct structural modifications and optimizations to enhance the stability, bioavailability, and target binding [37]. Effective utilization of peptide drugs by the body is a key prerequisite for their efficacy; therefore, optimizing their administration is crucial. For instance, leuprolide is not effective when administered orally but is well absorbed through subcutaneous or intramuscular injection. The choice of administration route considers the challenges peptides face in the gastrointestinal environment, highlighting the importance of strategic drug delivery methods.

Stability, a cornerstone of any successful drug, is exemplified by the stability of leuprolide under physiological conditions, emphasizing the need for structural integrity to ensure prolonged efficacy [30]. Currently, the clinically applied formulations are often extended-release preparations, with a single subcutaneous injection of 3.75 mg reaching peak plasma drug concentrations at 4 h. The peak concentration ranged

from 4.6 to 10.2 ng/ml. Subsequently, within 2 days, the plasma drug concentration stabilized at 0.30 ng/ml, and this steady-state concentration was relatively stable for 4 to 5 weeks. In the body, leuprolide undergoes hydrolysis, resulting in four degradation products, which are then excreted through the kidneys. After a single subcutaneous injection, the urinary excretion rates of the parent drug and its metabolites are 2.9 % and 1.5 %, respectively, after 28 days [38]. Therefore, a successful anti-cancer peptide drug should possess stability in vivo and undergo thorough pharmacological research, including investigations into its absorption, distribution, metabolism, and excretion properties, to understand the peptide's behavior in the body. We can use the methods mentioned earlier to conduct structural modifications and optimizations, enhancing the stability, bioavailability, and target binding.

The strategic design of leuprolides with limited immunogenicity has led to advancements in minimizing adverse immune reactions and enhancing the drug's safety profile [39]. Although leuprolide has been used for many hormone-dependent diseases and is considered a relatively safe drug, its application may lead to certain side effects. For instance, diabetic patients may experience elevated blood sugar levels during leuprolide use, and some individuals may experience decreased liver function and jaundice symptoms [33]. In the initial phase of leuprolide treatment, testosterone secretion is transiently promoted, potentially causing the exacerbation of bone pain, urinary retention, and symptoms of spinal cord compression. Adverse reactions in the treatment of prostate cancer include erectile dysfunction, hot flashes, cardiovascular complications, and symptoms of breast feminization. Prolonged use in female patients may result in a range of postmenopausal androgen-like side effects, including fever and night sweats, headache, mood depression, gastrointestinal disturbances, acne, reduced libido, weight gain, and breast changes [34]. Due to the inhibitory effect of leuprolide on estrogen, long-term use can lead to decreased bone density in female patients [40]. Therefore, while ensuring efficacy and stability, rigorous toxicity studies must be conducted to ensure minimal adverse effects on normal tissues. In general, higher specificity is associated with reduced side effects and increased efficacy. Therefore, by enhancing specificity, we can improve efficacy and minimize toxic side effects. Before entering clinical trials, *in vivo* and *in vitro* experiments, along with pharmacological studies, are indispensable. Additionally, determining the appropriate dosage is essential to balance therapeutic efficacy and minimize potential side effects. The consideration of cell permeability, metabolic stability, and optimal size and structure in the design of leuprolides further underlines the multifaceted nature of peptide drugs [34].

Finally, the ease of synthesis demonstrated by leuprolide highlights the practicality and scalability necessary for pharmaceutical production, contributing to the feasibility of translating peptides into clinically viable therapies [29]. The discovery of solid-phase peptide synthesis revolutionized the process of developing synthetic peptides. The integration of microwave irradiation and automation in solution and solid-phase synthesis, along with advances in metal catalysis and C–H functionalization, has led to a reduction in the coupling cycle time to minutes and an increase in the substrate scope for peptide synthesis beyond esters/acids and amines [41]. Given the complexity of bioactive peptides, developing cell factories offers a promising strategy for bypassing intricate chemical synthesis. Hence, genetic engineering and synthetic biology play crucial roles in modern peptide synthesis. Fig. 2 offers a comprehensive overview of the de novo peptide design process, incorporating the application of several new technologies. In essence, leuprolide serves as a paradigm for the intricate interplay of characteristics necessary for a successful peptide drug. The ongoing advancements in peptide-based therapies underscore the potential of this class of molecules in addressing complex biological targets and advancing precision medicine. As research progresses, a deeper understanding of peptide characteristics will likely unveil new possibilities and refine the landscape of drug development.



**Fig. 2.** A comprehensive overview of the de novo peptide design process. Figure was created with-BioRender.com. A comprehensive overview of the de novo peptide design process. Figure was created with-BioRender.com.

#### 4. Mechanisms of anti-cancer peptides

ACPs have a multifaceted impact on cancer hallmarks, including immune system regulation, induction of cancer cell apoptosis, cell cycle regulation, inhibition of migration and invasion, and modulation of the tumor microenvironment (Fig. 3). The diverse mechanisms exhibited by anti-cancer peptides underscore their potential to effectively target specific facets of cancer cell biology.

##### 4.1. Immune regulation

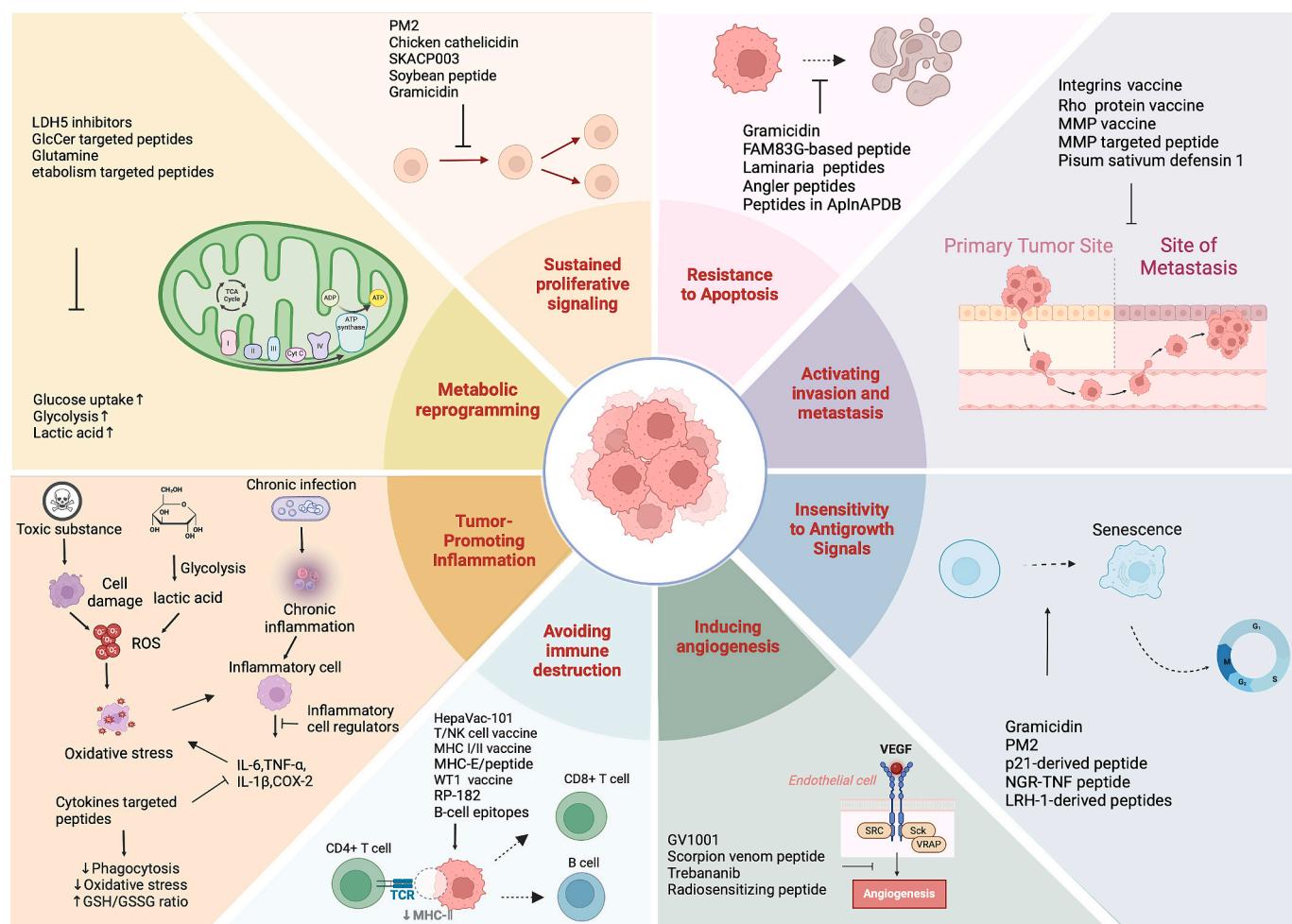
In recent years, ACP drugs have played a crucial role in cancer immunotherapy because they are precisely engineered to selectively interact with specific cells of the innate or adaptive immune system (Fig. 4a) [42,43]. The primary objective of ACP therapy is to modulate

the immune microenvironment in a targeted manner, ultimately leading to the suppression of tumor growth (Fig. 4b).

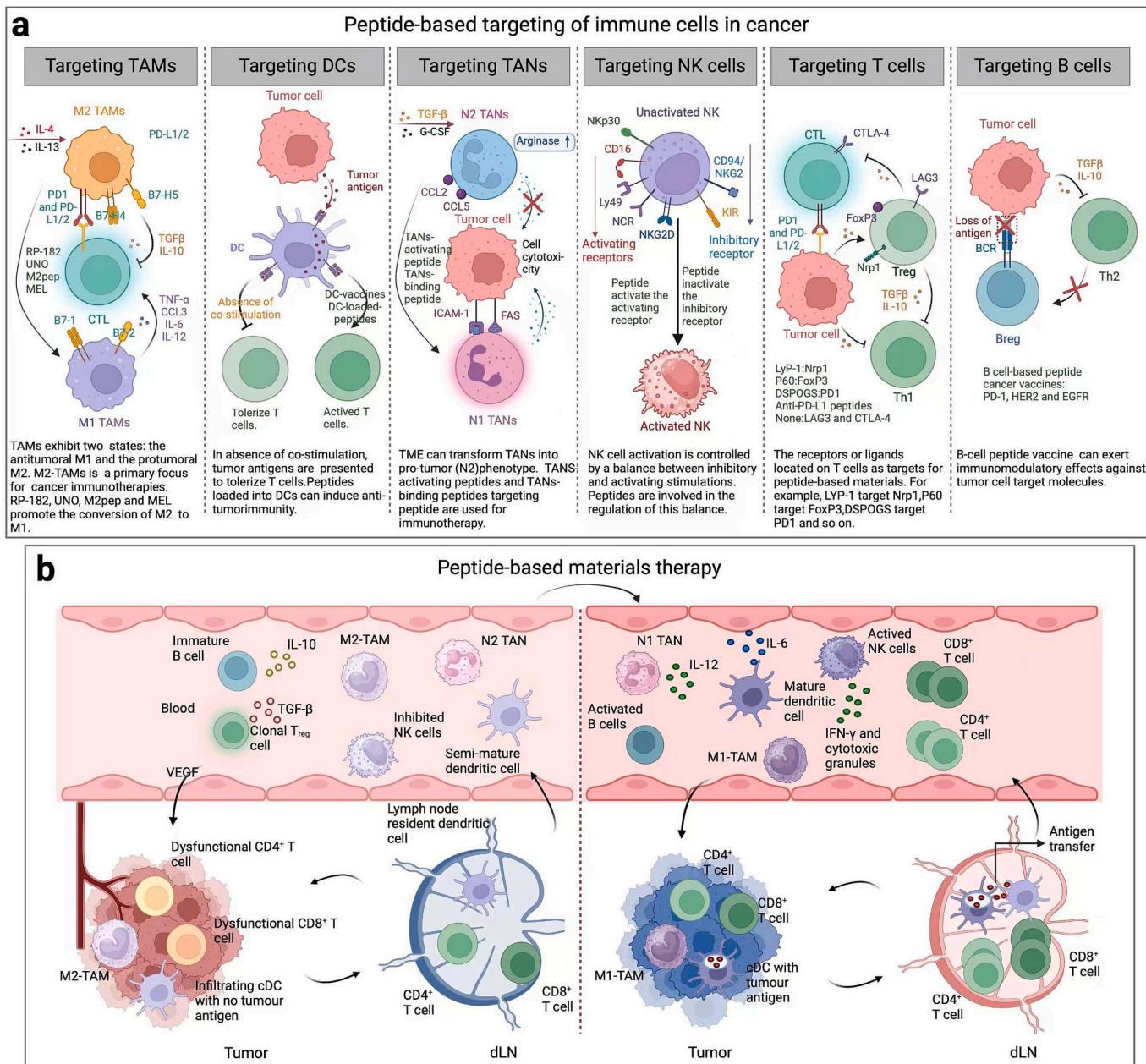
##### 4.1.1. Activation of the innate immune system

The innate immune system consists of a broad spectrum of cellular components, including macrophages, dendritic cells, neutrophils, natural killer cells, and various other cell types. These cells play a crucial role in mounting an effective immune response against tumors.

Tumor-associated macrophages (TAMs) are a specialized and unique subset of phagocytic cells known for their remarkable capacity to efficiently locate and target cancer cells that are present in tissues outside the circulatory system. TAMs are a diverse population that can be classified into two distinct activation states: the anti-cancer M1 phenotype and the protumor M2 phenotype. M1-TAMs display anti-cancer properties and can induce proinflammatory responses, facilitate



**Fig. 3.** Effect of ACP drugs on cancer hallmarks. Anticancer peptides target various hallmarks of tumors, including combating sustained proliferative signaling, resistance to apoptosis, metabolic reprogramming, activating invasion and metastasis, tumor-promoting inflammation, insensitivity to antigrowth signals, avoiding immune destruction, and inducing angiogenesis. The figure was created with BioRender.com.



**Fig. 4.** Effects of ACPs on immune cells and microenvironment. **a.** Peptide-based targeting of immunosuppressive cells in cancer. For example, peptides can target tumor-associated macrophages (TAMs), dendritic cells (DCs), tumor-associated neutrophils (TANs), natural killer (NK) cells, T cells, and B cells. **b.** Therapeutic 20 peptides for modulating the immune microenvironment. The figure was created with BioRender.com.

antigen presentation, and enhance cytotoxicity against cancer cells. Conversely, M2-TAMs exhibit immunosuppressive characteristics and contribute to tumor progression by promoting angiogenesis, remodeling the tumor microenvironment, and suppressing immune responses. The balance between the M1 and M2 activation states within the tumor microenvironment plays a critical role in shaping the immune response against cancer [44]. RP-182, a synthetic peptide, activates CD206 in M2-like TAMs, driving their transformation into anti-cancer M1-like macrophages. This reprogramming effect of RP-182 induces endocytosis, phagosome-lysosome formation, and autophagy. In murine cancer models, RP-182 has demonstrated notable effects, including tumor growth inhibition, improved survival rates, and synergistic effects with other therapies. Moreover, RP-182 has exhibited remarkable anti-cancer effects in patient-derived xenotransplantation models by reducing the immunosuppressive TAM population and enhancing immune responses

against cancer cells [45]. The peptide antagonist PCP has been used to codeliver DOX and R848 via the prodrug PCP@R848/DOX, which is subsequently cleaved by FAP- $\alpha$  in the tumor stroma [46]. Cargo-localized release of DOX and R848 triggers immunogenic cell death (ICD) and TAM reprogramming, thereby promoting anti-cancer immunity. The sustained release of PD-1/PD-L1 antagonists blocks the PD-L1 pathway, resulting in the subsequent activation of cytotoxic T cells. Triple-modality therapy activates ICDs, TAMs, and T cells, eliciting a strong systemic anti-cancer response [46]. In the context of peptide-mediated therapeutic modulation of the tumor immune microenvironment, the reprogramming of TAMs can function as an independent intervention and as an integral component of comprehensive immunotherapeutic strategies.

Dendritic cells (DCs), which are found throughout peripheral tissues, can detect antigens and initiate immune responses. DCs are crucial for

activating CD4<sup>+</sup> and CD8<sup>+</sup> T cells, leading to targeted cytotoxic effects on cancer cells. DC-mediated peptide delivery has consistently shown significant immunomodulatory effects in various studies [8]. Dual-modified iron oxide nanoparticles incorporating hyaluronic acid and mannose effectively target and repolarize tumor-associated macrophages (TAMs), leading to a modified tumor microenvironment. When combined with antigenic peptides, this nanovaccine promoted CD8<sup>+</sup> T-cell infiltration and activated dendritic cells. This approach results in significant lymphoma growth inhibition, achieving a remarkable 40 % cure rate in a mouse model [47].

Tumor-associated neutrophils (TANs) have various effects on the tumor microenvironment and can exhibit either protumor (N2) or antitumor (N1) phenotypes [48]. Targeting TANs has demonstrated promise in enhancing cancer immunotherapy [49]. Given the rapid uptake of NE (neutrophil elastase) by NE-negative tumor cells, NE-derived peptides are currently utilized as immunotherapies for solid tumors. The uptake of NE by tumors is regulated by neuropilin-1, a protein that is abundantly expressed by breast cancer cells. Targeting neuropilin-1 presents a promising avenue for immunotherapeutic strategies focused on cross-presented antigens [50]. In a study conducted by Shirin Ferdowsi et al.,  $\alpha$ -defensins were isolated from neutrophils that were trapped in leukofilters, and their anti-cancer activity was evaluated. Compared with the untreated group and commercially available HNPs 1–3, purified HNPs 1–3 reduced Jurkat T-cell line viability and increased apoptosis [51].

NK cells play a critical role in the early recognition and elimination of tumor cells due to their unique ability to detect stressed cells independently of antibodies and MHC molecules. The activation of NK cells is finely regulated by a delicate balance between inhibitory and activating signals [52]. The tumor microenvironment can suppress the activation of NK cells, but ACPs offer a promising approach for restoring the activation of NK cells within the tumor microenvironment [53]. Huang et al. developed a novel peptide ligand called Natein using T7 phage display technology that can bind specifically to CD56, a protein expressed in immune cells and cancer cells. Natein demonstrated functional cytotoxicity against CD56+ cancer cells and exhibited potential as an alternative to CD56 antibodies for use in peptide-based lymphoma cell isolation and diagnosis [54].

#### 4.1.2. Activation of the adaptive immune system

The adaptive immune system, which primarily consists of T cells and B cells, provides a sophisticated defense against foreign pathogens and possesses strong anti-cancer properties.

T cells include cytotoxic CD8<sup>+</sup> T cells, helper CD4<sup>+</sup> T cells, and regulatory T (Treg) cells. CD8<sup>+</sup> cytotoxic T cells play a crucial role in eliminating cancer cells by recognizing and attacking cells presenting tumor-specific antigens. However, the function of these cells can be hindered by inhibitory receptor ligands such as PD-L1 or PD-L2, which may be expressed by cancer cells. Moreover, the activation of CD8<sup>+</sup> cytotoxic T cells can lead to the generation of T regulatory cells, which suppress effector T-cell activity [55]. Checkpoint blockade immunotherapy is an innovative and promising treatment that aims to restore the ability of the immune system to detect and eliminate hidden cancer cells. By targeting inhibitory checkpoints, such as PD-1/PD-L1 or CTLA-4, this therapeutic approach unleashes the full potential of the immune response against cancer, resulting in better patient outcomes and long-term survival [56]. DSPOGS, a chimeric peptide able to target PD-L1 and VEGFR2, exhibits high-affinity binding and effectively inhibits tumor growth, migration, and angiogenesis. DSPOGS stimulates an anti-cancer immune response by increasing the infiltration of CD8<sup>+</sup> T cells and IFN- $\gamma$  secretion. Combining radiotherapy with DSPOGS further enhances treatment outcomes, offering a potential paradigm for multimodal cancer therapy [57]. Macrocyclization scanning can identify cyclic anti-PD-L1 peptides with improved activity and stability. These peptides exhibit enhanced PD-1/PD-L1 blocking and in vivo anti-cancer effects. This approach can optimize bioactive peptides for the

modulation of protein–protein interactions in cancer immunotherapy and other therapeutic applications [58]. By screening peptide libraries and conducting a thorough investigation of the Foxp3:NFAT structure, researchers have discovered a series of peptides capable of binding to Foxp3 and effectively inhibiting the activity of T regulatory cells (Tregs). These peptides exhibit anti-cancer activity in vivo [59]. This significant discovery provides exciting prospects for the development of targeted therapies that can modulate Treg function, ultimately leading to enhanced immune responses against tumors.

B cells, a subtype of lymphocytes, play a vital role in the adaptive immune system by producing antibodies. In the realm of cancer vaccines, B-cell peptide-based approaches typically involve the formulation of an adjuvant and an immunogenic protein containing a B-cell epitope peptide. This combination aims to trigger B cells to generate targeted antibodies, fostering an immune response against cancer cells. However, improvements in cost, adverse effects, and resistance are needed. The anti-cancer immune response of patients can be stimulated through active immunization using mimotopes, which are B-cell peptides that mimic the binding epitopes of monoclonal antibodies (mAbs). The patient immune system can be activated upon administration of mimotopes, eliciting a robust immune response against cancer. Tobias et al. identified and evaluated mimotopes of the immune checkpoint PD1. The mimotopes effectively blocked PD1/PD-L1 interactions and reduced leukemia cell growth in a mouse model. Moreover, synergistic anti-cancer activity was observed when mimotopes were used in combination with a tumor-specific vaccine. Active immunization with mimotopes has shown promise as a new strategy for cancer treatment [60]. Guo et al. developed a novel B-cell vaccine called PD1-Vaxx [MVF-PD-1 (92–110)] and conducted extensive preclinical pharmacology studies, including primary and secondary pharmacodynamics, biodistribution, and safety evaluations. The findings from these studies strongly support the advancement of PD1-Vaxx into a first-in-human clinical trial for patients with non-small cell lung cancer (NSCLC). Currently, a phase I trial in NSCLC patients is already underway, marking an important milestone in the development of this vaccine [61].

#### 4.1.3. Peptide-based anti-cancer vaccines

A peptide-based cancer vaccine aims to achieve the crucial objective of activating a patient's immune system and priming it to recognize and mount a targeted response against cancer cells. Peptide vaccines typically consist of peptides and adjuvants [62]. Peptide-based cancer vaccines are carefully designed to selectively activate specific effector cell types within the immune system. MHC I peptides, consisting of 8–10 amino acids, are designed to interact with CD8<sup>+</sup> T cells, facilitating their recognition and immune response [63]. On the other hand, MHC II peptides, comprising 13 to 18 amino acids, are predominantly recognized by CD4<sup>+</sup> T cells [64]. Brett J Hos et al. successfully induced the expression of MHC class II molecules on tumor cells that were originally lacking MHC class II molecules by introducing the MHC class II transactivator (CIITA). This enabled the identification of oncoviral and neo-epitopes, as well as shared epitopes, on the cell surface. These epitopes have immunological relevance and are naturally presented by dendritic cells, demonstrating their immunogenicity. Moreover, synthetic peptide vaccination elicits functional CD4<sup>+</sup> T-cell responses. These responses have been demonstrated to aid in the in vivo control of tumor growth, expansion, metastasis, and related phenomena. The CIITA transfection approach offers a valuable method for identifying T helper epitopes presented by various MHC class II alleles. This approach also revealed significant targets for cancer immunotherapy, which can be achieved through the utilization of peptide-based anti-cancer vaccines [65].

Yusuke Oji et al. reported the results of a clinical trial investigating the efficacy of a biweekly Wilms' tumor 1 (WT1) tri-peptide-based vaccine for the treatment of recurrent or advanced rare cancers. In their study, they compared the biweekly WT1 Trio vaccine, which incorporates the WT1-332 helper T lymphocyte peptide, with the weekly WT1-235 CTL peptide vaccine. Their findings revealed that the

biweekly administration of the WT1 Trio vaccine resulted in more potent immune responses, specifically targeting WT1 [66]. Jinho Kang et al. successfully identified MHC class II epitopes derived from HSP90 that exhibit high binding affinities across various human HLA class II genotypes. These selected MHC class II HSP90 peptides have been demonstrated to induce robust antigen-specific T-cell responses. Specifically, in the context of breast cancer, these peptides have been shown to trigger cross-priming of CD8<sup>+</sup> T cells, resulting in potent immune responses against cancer cells [67].

Regarding antigen-based immunotherapy, there are challenges related to the limited accuracy of algorithms in efficiently predicting immunogenic neoantigens derived from peptides. Additionally, there is a lack of comprehensive research and predictions for CD4<sup>+</sup> T cells, which requires further investigation. However, in the case of low-mutation burden tumors with low-frequency neoantigen expression, a recent study demonstrated the potential use of radiotherapy to induce mutations and generate neoantigens [68]. These neoantigens contribute to intratumor heterogeneity, highlighting the importance of identifying all neoantigens present in tumors to ensure effective treatment. These issues require in-depth exploration and investigation in future research.

#### 4.2. Apoptosis induction

Apoptosis-inducing peptides exert anti-cancer effects by regulating the apoptosis pathway in tumor cells [69]. The ApInAPDB (Apoptosis-Inducing Anti-cancer Peptides Database, <http://bioinf.modares.ac.ir/software/ApInAPDB/>) is a comprehensive library of 818 anti-cancer peptides known for their ability to induce apoptosis. These peptides were manually curated from various research articles, ensuring a reliable and curated collection. The database serves as a valuable resource for scholars, providing detailed information on peptide functions, target binding affinities, IC<sub>50</sub> values, and other pertinent data [70]. Philippe et al. developed angler peptides by conjugating KD3 with cyclic cell-penetrating peptides. These peptides activate p53-mediated apoptosis in cancer cells via endocytic pathways or direct membrane translocation entry mechanisms. The angler strategy has proven effective for targeted anti-cancer therapeutics [71]. Laminaria japonica peptides (LJPs) exhibit strong effects against hepatocellular carcinoma both in vitro and in vivo. The administration of LJP-1 induced apoptosis, inhibited cell cycle progression, and blocked tumor growth through multiple pathways. LJPs, especially LJP-1, show promise as potential therapeutic options for liver cancer [72].

#### 4.3. Cell cycle regulation

Certain peptides can interfere with tumor cell cycle progression, thus inhibiting tumor cell growth and proliferation [73,74]. Protein hydrolysates from various sources were screened for their anti-proliferative effects on oral squamous carcinoma cells. The hydrolytic peptides of soybean protein strongly induced cell cycle arrest, thereby inhibiting tumor growth. As such, soybean protein can serve as a functional food to prevent oral squamous cell carcinoma [75]. Gramicidin, a natural antibiotic derived from *Bacillus brevis* bacteria, comprises two complementary peptide chains (gramicidin A and gramicidin B). Gramicidin exhibits anti-cancer effects on gastric cancer cells by inhibiting proliferation and inducing cell cycle arrest [76]. Mechanistically, gramicidin downregulates cyclin D1 and phosphorylates FoxOZO1; however, further research is needed to investigate its potential as a therapeutic agent for gastric cancer [76]. The tumor suppressor p53 is a key mediator of the cell cycle. The peptide PM2 has shown promise as a therapeutic agent when used in combination with external beam radiotherapy (EBRT) for treating cancer cells with wild-type p53. PM2 prevents MDM2 from suppressing p53, leading to increased p53 expression and decreased cell viability [77].

#### 4.4. Modulation of the tumor cell microenvironment

Modulating the tumor cell microenvironment can be accomplished through various strategies, such as inhibiting angiogenesis, regulating the immune system, regulating inflammatory factors, and inducing metabolic reprogramming. Targeting these mechanisms can effectively hinder tumor growth and progression. Regulation of the immune system has been discussed earlier and will not be reiterated here. Inhibiting tumor angiogenesis through targeting proteins such as vascular endothelial growth factor (VEGF) [113] and platelet-derived growth factor (PDGF) [114] reduces the dilation and permeability of blood vessels and thus inhibits tumor growth and metastatic potential. Anti-angiogenic peptides can inhibit the secretion of angiogenic factors by tumor cells, disrupting the binding of VEGF to VEGFR [113] and of PDGF to PDGFR [114]. This interference prevents the formation of blood vessels around cancer cells, ultimately restricting tumor growth and metastasis. Trebananib, also known as AMG 386, is an antiangiogenic peptide. Trebananib works by inhibiting the interaction between vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptors (VEGFRs) [78]. A phase II study evaluated the efficacy and safety of bevacizumab plus trebananib as a first-line treatment for metastatic colorectal cancer (mCRC) [78] and revealed that this combination had manageable toxicity and the potential to enhance the Anti-cancer immune response [79].

Cellular inflammatory cytokines play a crucial role in tumor progression. Tumors themselves can stimulate immune responses in the body, leading to the generation of inflammatory reactions and the release of cellular inflammatory cytokines. These cytokines can directly or indirectly impact tumor cell proliferation, survival, invasion, and metastasis. The key cellular inflammatory cytokines closely associated with tumor progression include TNF- $\alpha$ , interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), and interleukin-10 (IL-10). Excessive secretion of TNF- $\alpha$  from immune cells promotes tumor cell proliferation, survival, and metastasis, while normal secretion induces apoptosis, inhibits proliferation, and enhances immune recognition of tumor cells [80]. Combining peptide vaccination with F8-TNF, a tumor-homing TNF fusion protein, was shown to significantly induce leukemia cell necrosis and expand antigen-specific CD8<sup>+</sup> T cells, highlighting the potential of this combination therapy for cancer treatment [81]. IL-1 $\alpha$  and IL-1 $\beta$ , which are produced by immune cells, tumor cells, and other tissues, play a role in tumor progression by promoting inflammation, enhancing tumor cell growth, invasion, and metastasis, and suppressing immune responses [82]. Gong et al. discovered that by blocking the IL-1 $\alpha$ /VEGF signaling pathway, interleukin-1 receptor antagonist (IL-1RA) effectively inhibits gastric cancer metastasis [83]. IL-2, produced by activated immune cells, promotes the proliferation and function of immune cells, leading to anti-cancer effects, but can also increase regulatory T cells and suppress other immune cells, hindering the anti-cancer immune response [84]. Utilizing high-dose IL-2/CD25 fusion proteins, Hernandez et al. amplified neoantigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T-cell responses, enhancing antitumor immunity and enabling effective melanoma and mammary carcinoma cell clearance [85]. IL-6, produced by immune cells, tumor cells, and stromal cells, promotes tumor cell growth, invasion, and metastasis through JAK/STAT signaling while inhibiting anti-cancer immune responses and promoting inflammation and angiogenesis [86]. IL-10 produced by immune cells can suppress inflammation and immune cell activation, potentially reducing tumor development; however, IL-10 may also inhibit anti-cancer immune responses, promoting tumor growth and immune evasion [87]. Chen et al. discovered that blocking IL-10 signaling during HPV long E7 peptide/LPS immunization enhances T-cell responses, facilitates immune cell infiltration, and results in improved regression of HPV-16 immortalized TC-1 tumor cells, suggesting a potential strategy for more effective treatment of HPV infection-related tumors [88].

Certain tumor cells rely on specific metabolic pathways, such as glycolysis, fatty acid synthesis, and glutamine metabolism, to produce

energy and promote survival. Targeting these pathways can effectively inhibit tumor growth. LDH5, an isoform of lactate dehydrogenase, is highly expressed in a wide range of cancer types, making it a compelling target for anti-cancer treatments. The critical role of LDH5 in aerobic glycolysis, a metabolic pathway utilized by cancer cells, further highlights its potential as a therapeutic target. Both the cGmC9 peptide and its analog inhibit cancer cell proliferation. While the cGmC9 peptide acts as a noncompetitive inhibitor, disrupting LDH5 activity, its analog, a closely related compound, effectively impedes glycolysis in cancer cells and triggers metabolic alterations. The cGmC9 peptide and its analog demonstrate significant potential as therapeutic agents that are specifically designed to enhance cellular permeation and target LDH5, as well as to modulate intracellular pathway interactions within cancer cells [89]. Psd1 is a plant defensin with broad antifungal activity. In certain cancer cells, an imbalance in lipid metabolism results in the excessive accumulation of glucosylceramide (GlcCer) in the plasma membrane. Psd1 targets GlcCer in cancer cells, causing nuclear fragmentation and cell cycle arrest. In a murine melanoma model, Psd1 was shown to reduce metastatic nodules and lung inflammation without any significant side effects, thus illustrating its promise as a therapy for lung metastatic melanoma [90]. In summary, ACPs exert their inhibitory effects on tumor growth by modulating the tumor microenvironment through various mechanisms, including suppressing angiogenesis, regulating immune responses, suppressing inflammatory factors, disrupting tumor cell metabolism, and interfering with signaling pathways.

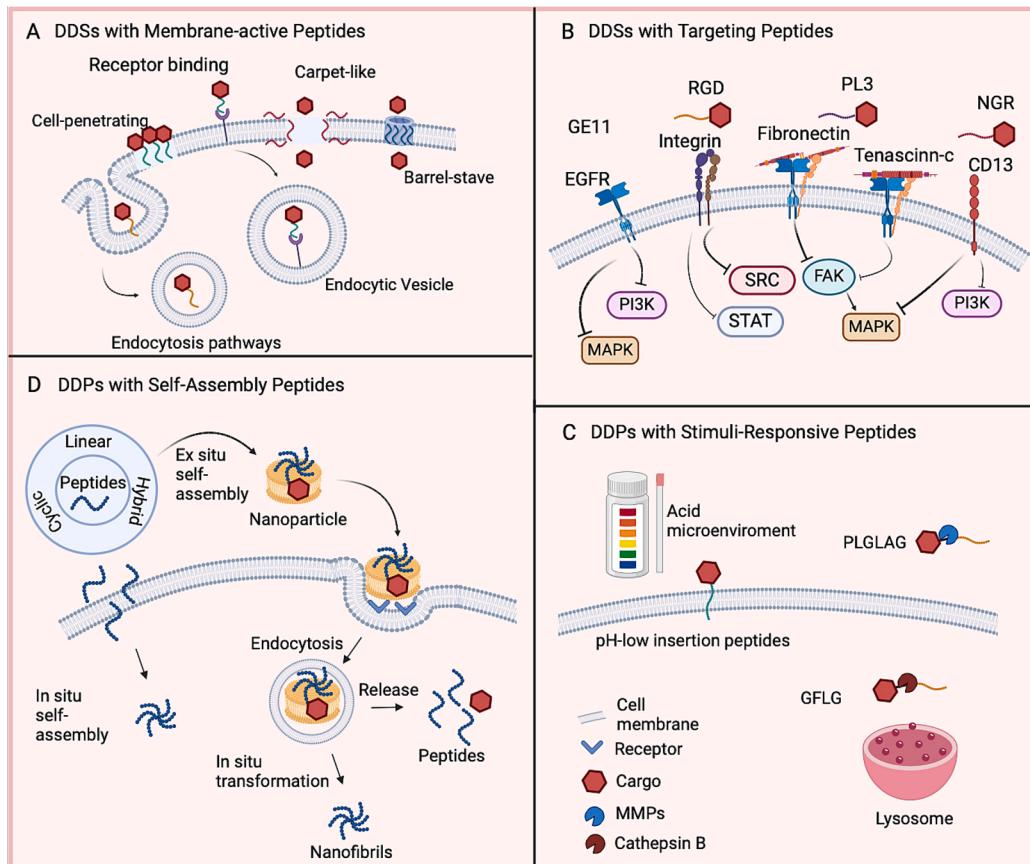
## 5. Drug delivery systems (DDSs)

Peptides, with their favorable biocompatibility, can enhance drug delivery by serving as components in a drug delivery system (DDS), facilitating the development of cancer-targeted carriers when coupled

with drug carriers. The peptides utilized in DDSs possess five essential characteristics [91]. First, they can selectively bind to receptors or molecules present on target cells, thereby enhancing drug specificity and minimizing toxicity toward normal cells. Second, peptides are rapidly cleared through metabolic pathways, reducing the likelihood of potential side effects. Third, they are highly customizable and can be easily synthesized with various modifiable functional groups. Fourth, peptides exhibit excellent combinability, forming peptide complexes with other compounds to improve their stability and solubility. Finally, peptides are less prone to induce drug resistance because they target cell surface receptors, thus mitigating resistance in tumor cells. Drug delivery peptides commonly draw inspiration from natural peptides and are widely applied in cancer treatments. Compared to small molecules, peptides offer greater selectivity as targeted ligands for drug delivery and imaging. Methods employed include DDSs with cell-penetrating peptides, DDSs with targeting peptides, stimuli-responsive peptides, and peptide supramolecular self-assembly (Fig. 5).

### 5.1. DDSs with membrane-active peptides

Peptides with cell-penetrating capabilities, alternatively referred to as protein transduction domains or cell-penetrating sequences, are short peptide sequences that can traverse cell membranes and facilitate the delivery of various molecules into the cellular interior (Fig. 4A) [4]. R8-conjugated DDSs have been reported to penetrate cancer cells (Table 2). Wu et al. made a significant breakthrough by developing a charge-reversible DDS demonstrating the remarkable ability to penetrate mucus and epithelial barriers when administered orally [92]. This pioneering system is based on poly(lactic-co-glycolic acid) (PLGA) nanoparticles conjugated with octa-arginine peptides (R8) and phosphoserines (Pho) through polyethylene glycol (PEG) linkages,



**Fig. 5.** The mode and mechanism of action of polypeptide drugs in cancer drug delivery systems. A DDSs with cell-penetrating peptides, B DDSs with targeting peptides, C Stimuli-responsive peptides, D Peptide supramolecular self-assembly. Figure was created with BioRender.com.

**Table 2**  
Peptide drug delivery systems.

Peptide Name	Mechanism	Delivery Vehicle	Therapeutic Agent	Cancer	Exp	Refs
HIV1-TAT	Plasma membrane permeable	Heparin/protamine-regulated delivery system, Liposomes, Carcinoembryonic antigen monoclonal antibodies	Asparaginase, camptothecin, curcumin, gelonin fusion chimera	Leukemia, cervical cancer, breast cancer, colon cancer	in vitro, in vivo	[163,164,165]
arginine (R8) peptide	Penetrates the mucus membrane and epithelial barriers	Cationic liposomes, upconversion nano-onions	CRISPR/Cas9, small interference RNA	Pancreatic cancer, hepatocellular cancers	in vitro, in vivo	[166,167]
DP7	Plasma membrane permeable	Cholesterol-modified DP7 (DP7-C)	microRNA	Breast cancer	in vitro, in vivo	[93]
RGD (Arginine-glycine-aspartic)	RGDs are ligands for integrin receptors	lipid nanoparticles	Curcumin	Breast cancers	in vitro	[168]
PL3	Specificity against tenascin-C	Iron oxide nanofilaments, metallic silver nanoparticles	pro-apoptotic p(KLAKLAK) <sub>2</sub> peptide	Glioblastoma (GBM), prostate carcinoma,	in vitro, in vivo	[169]
GE11 (3Glu-5Gly Lys)	Specificity against EGFR	Micellar	Doxorubicin	Breast cancer	in vitro, in vivo	[101]
NGR (Asn-Gly-Arg)	NGRs are ligands for aminopeptidase N (CD13) receptors	Anthanide nanoparticles	PMI and BIM	Colon cancer	in vitro, in vivo	[170]
GFLG (Gly-Phe-Leu-Gly)	GFLG can be cleaved by cathepsin B	PEGylated lysine dendrimer nanoparticles CREKA (Cys-Arg-Glu-Lys-Ala) peptide mPEGylated dendron SKAAKN (Cys-Lys-Ala-Ala-Lys-Asn) peptide	Gemcitabine, squaraine photosensitizer, doxorubicin, daunomycin	Breast cancer Pancreatic adenocarcinoma	in vitro, in vivo	[171,172,173]
PLLAG	PLLAG can be cleaved by MMPs	PEGylated nanoparticles	Paclitaxel	Fibrosarcoma	in vitro, in vivo	[175]
pHLIP (pH-low insertion peptides)	pH-responsive delivery	thermoresponsive gold nanocages (pPGNCs), PEGylated Fe3O4 nanoparticles PEGylated nanoparticles	Doxorubicin HA peptide epitope	Breast cancer, pancreatic ductal adenocarcinoma, melanoma, breast cancer Glioblastoma	in vitro, in vivo	[176,177,178]
Fmoc-Trp(Boc)-OH	Peptide-based nanosystems increase the transmembrane efficiency of doxorubicin	Nanoparticles	Doxorubicin	Glioblastoma	in vitro	[179]
5-Fluorouracil dilysine	5-Fu is slowly released by the nanotubes to maintain the effective concentration.	Hydrogels	5-Fluorouracil	Lung cancer	in vitro	[180]
Cyclo histidine-histidine-Zn(II)	self-encapsulation nanoparticles	Nanoparticles	Epirubicin	Cervical cancer	in vitro	[102]
Arginine- $\alpha,\beta$ -dehydrophenylalanine	pH-responsive delivery	Nanoparticles	Doxorubicin	Gastric adenocarcinoma, Glioblastoma, Colon cancer	in vitro	[181]
Tryptophan-phenylalanine-Zn(II)	Fluorescent peptide nanoparticles	Nanoparticles	Doxorubicin	Lung cancer	in vitro	[182]
Lysine-phenylalanine-glycine	pH-sensitive drug delivery	Nanospheres and nanotubes	Doxorubicin	Glioblastoma, Lung cancer	in vitro	[183]
Boc-triphenylalanine-COOH	Hydrogel drug delivery	Hydrogel nanoparticles	Doxorubicin	Breast cancer	in vitro	[184]
iRGD-lipid-polymer hybrid	Supramolecular drug delivery	Lipid-polymer hybrid nanoparticles	Doxorubicin with sorafenib	Hepatocellular carcinoma	in vitro, in vivo	[185]
Cyclic arginine-glycine-aspartic acid-liposome conjugate	Targeted liposomal delivery	Liposomes	Doxorubicin	Glioblastoma	in vitro, in vivo	[186]
Arginine-glycine-aspartic acid peptide conjugated liposome	Peptide liposomal drug delivery system	Liposomes	Cisplatin	Prostate cancer	in vitro, in vivo	[187]
Azabicycloalkane- and aminoproline-based cyclic arginine-glycine-aspartic acid semipeptide ligand	Peptide-targeted liposomes	Liposomes	Doxorubicin	Breast cancer	in vitro	[188]
Octreotide	Octreotide-targeted delivery	Nanoparticles	Doxorubicin	Hepatocellular carcinoma Lung cancer	in vitro, in vivo	[189]

resulting in the formation of P-R8-Pho nanoparticles. DHSHKKK (DP7), a cationic antimicrobial peptide, serves as a dual-function carrier and immune adjuvant for microRNA delivery. DP7 efficiently transduces and escapes endosomes, activates dendritic cells, and transforms the immunosuppressive tumor microenvironment into an immune-activated microenvironment, offering a promising approach for anti-cancer therapy [93]. Cholesterol-modified DP7 (DP7-C) serves as a versatile agent with dual capabilities as a carrier and an immune adjuvant. The most notable efficacy of DP7-C lies in its ability to effectively transfect cells and evade endosomes. Furthermore, DP7-C exhibits a remarkable capacity to activate dendritic cells, thereby triggering an immune response. Additionally, DP7-C plays a pivotal role in reshaping the tumor microenvironment, transforming it from an immunosuppressive state to an immune-activated milieu [93]. These remarkable features make DP7-C a promising candidate for anti-cancer therapy, with the potential to significantly impact cancer treatment by enhancing immune responses against tumors.

### 5.2. DDSs with targeting peptides

Targeted peptide drug delivery systems pertain to a category of therapeutic strategies that employ peptides for the precise delivery of drugs or therapeutic agents to specific target sites within the human body (Table 2). The Arg-Gly-Asp (RGD) peptide exhibits affinity for a class of integrin receptors known as RGD-binding receptors. The RGD-integrin interaction serves as a crucial link to activate SRC and STAT signaling pathways, promoting various cellular responses relevant to cancer progression, tissue repair, and immune modulation [94]. Yi Yang and colleagues successfully synthesized [<sup>68</sup>Ge]-DOTA-c(NGR)<sub>2</sub> and demonstrated its ability to effectively target CD13 through in vitro experiments and microPET imaging using ovarian cancer xenografts. These findings suggest that [<sup>68</sup>Ge]-DOTA-c(NGR)<sub>2</sub> is a promising potential PET imaging probe for noninvasive assessment of CD13 receptor expression in tumors. When CD13 interacts with its ligands or is activated, it can stimulate downstream signaling pathways, including the PI3K pathway. This leads to the phosphorylation of PIP2 to PIP3, activating AKT and promoting cell survival and growth [95]. Additionally, EGFR, a protein overexpressed in various cancer cells, can serve as a reliable target for peptide-mediated delivery of different therapeutics. In particular, GE11 (YHWYGYTPQNVI) has been reported to exhibit high uptake levels in triple-negative breast cancer cell lines characterized by elevated expression of EGFR (Fig. 4B) [96]. Upon binding to EGFR, G11 triggers the PI3K pathway, which enhances cell survival, growth, and metabolism. This pathway is initiated when PI3K is activated, resulting in the conversion of PIP2 to PIP3, subsequently recruiting and activating AKT, which promotes cell survival and growth by inhibiting apoptosis and stimulating mTOR. Additionally, G11 activates the MAPK pathway via the Ras protein. This cascade regulates gene expression and cellular processes such as proliferation and differentiation. It is important to select appropriate targeting ligands for peptide-based drug delivery, considering their biological stability and drug release rate.

### 5.3. Stimuli-responsive peptides

Stimuli responsiveness refers to the capacity of these systems to undergo configuration changes in response to specific triggers. Triggers can include external factors such as photothermal, magnetic, electric, or ultrasonic impacts, as well as local environmental conditions, including pH, temperature, redox state, and concentration of specific molecules (e.g., O<sub>2</sub>, urea, enzymes) [97,98]. Stimulus-responsive DDSs possess the ability to modulate their structure, properties, or drug release behavior upon activation by triggers (Table 2). This responsiveness allows for targeted and controlled drug delivery, where the therapeutic agents are released at the desired site or under specific conditions. By harnessing external or internal stimuli, these systems can achieve enhanced drug efficacy, reduced side effects, and improved patient outcomes (Fig. 4C).

Wan et al. developed TPGS3350-GPLGVRGDG-DOX&DOX micelles by incorporating the MMP-responsive peptide GPLGVRGDG into a block copolymer, enhancing the efficacy of doxorubicin delivery. The micelles demonstrated improved cytotoxicity against 4T1 cells, long circulation, and efficient tumor accumulation *in vivo* [99]. This approach holds promise for advancing drug delivery strategies in clinical applications, with enhanced anti-cancer activity and reduced toxicity. The choice of stimuli and the design of responsive components in DDSs are crucial considerations.

### 5.4. Peptide supramolecular self-assembly

Self-assembling peptide drug delivery systems utilize the unique properties of peptides, such as structural diversity, biocompatibility, and functionalization potential, to design delivery platforms that enable controlled and efficient encapsulation, protection, and release of drugs (Table 2). Loading drugs or therapeutic agents into self-assembled peptide nanostructures can enhance their stability, solubility, bioavailability, and targeted delivery. The nanostructures can protect drugs from degradation and provide sustained release, enabling long-term therapy and reduced dosing frequency. Furthermore, functionalizing these systems with targeting ligands or responsive moieties allows site-specific targeting at disease sites or triggered release in response to physiological stimuli (Fig. 4D) [100]. Guo, Z. et al. developed an epidermal growth factor receptor-targeted multifunctional micellar nanoplateform (GE11-DOX + CEL-M) [101]. The study highlights that the GE11 peptide plays a crucial role in enhancing the targeted delivery of the drug combination within the multifunctional micellar nanoplateform, significantly improving tumor cell uptake and resulting in superior tumor growth suppression and reduced metastasis compared to non-targeted systems. Chen et al. demonstrated that the engineered self-assembled peptides, employing a “self-encapsulation” strategy, function as advanced nanocarriers with integrated *in situ* monitoring capabilities, highlighting their potential for improved delivery in eco-friendly optoelectronic and biomedical applications [102]. Self-assembling peptide drug delivery systems possess biocompatibility, tunability, multifunctionality, and potential for multiple applications. They demonstrate promising prospects in various biomedical applications, including cancer therapy, regenerative medicine, tissue engineering, and diagnostics.

## 6. Applications of anti-cancer peptides

The utilization of peptides or protein-based biomolecules in anti-cancer therapeutics is becoming increasingly important. Currently, regulatory agencies such as the Food and Drug Administration (FDA) in the USA and the European Medicines Agency (EMA) have approved only five peptides for therapeutic use. Tebentafusp, an FDA-approved agent for HLA-A\*02:01-positive uveal melanoma, binds bispecifically to gp100 and CD3 T cells to trigger an anti-cancer immune response [103]. Buserelin, which is approved in the EU, is utilized in hormone-responsive cancer treatment by desensitizing the GnRHR receptor to reduce testosterone and estrogen release [104]. Plitidepsin, which is also approved by the EU, induces apoptosis and inhibits cell growth by targeting eEF1A2 and VEGF. Triptorelin, an FDA-approved palliative treatment for advanced prostate cancer, acts as a synthetic agonist analog of GnRH [105]. Dactinomycin, an FDA-approved agent for a variety of cancers, binds to DNA, inhibiting RNA synthesis [106]. These peptide drugs have diverse mechanisms and applications in the clinical landscape, we categorized ACPs based on their diverse clinical purposes.

### 6.1. Cancer diagnosis

The function of peptides as molecular probes and diagnostic tools in pharmacological and neurological investigations has resulted in

numerous diagnostic agents and devices successfully entering the commercial market [107]. The primary field of therapeutic application for these peptides is oncology, where they are extensively employed for tumor detection and targeted radiotherapy [108,109]. There is ample evidence supporting the significant impact of receptor overexpression on breast cancer initiation and progression. Targeting these specific receptors using radiolabeled biomolecules has emerged as a promising approach for early breast cancer diagnosis. Using diverse characterization techniques, a wide range of peptides can be prepared, facilitating efficient labeling with clinically relevant SPECT radionuclides such as  $^{99m}\text{Tc}$ ,  $^{123}\text{I}$ , and  $^{111}\text{In}$  [110]. The  $^{68}\text{Ga}$ -DOTA-LS7 peptide showed rapid and selective detection of CD133-positive tumors using PET [111]. The favorable characteristics of  $^{68}\text{Ga}$ -DOTA-LS7, such as its straightforward synthesis and specific uptake, make it a promising candidate for CD133 expression imaging. However, further investigations are needed to explore its full potential. With the continuous development of anti-cancer peptide technology, its prospects in tumor treatment and diagnosis are rapidly expanding.

## 6.2. Adjuvant surgery and radiochemotherapy

Traditional approaches such as surgery and radiochemotherapy have limited efficacy for advanced-stage tumors [112]. Emerging methods, including hormone therapy, immunotherapy, targeted therapy, and stem cell transplantation, are increasingly being applied in clinical settings to enhance the survival outcomes of patients with advanced-stage tumors [113]. In these novel adjunctive approaches, the role of anti-cancer peptides is indispensable. In one pioneering phase I/II study, a synthetic long peptide vaccine targeting was administered to 22 post-radical prostatectomy patients, resulting in a robust and enduring CD4 T cell response in the majority of participants. The vaccination regimen, involving subcutaneous injections of RhoC-derived peptides, exhibited excellent safety and tolerability, with no grade  $\geq 3$  treatment-related adverse events reported. Notably, immune responses included poly-functional and persistent CD4 T cells expressing PD-1 and OX-40, alongside the identification of three HLA-class II epitopes [114]. The study's impact extended beyond the treatment period, as serum PSA levels were measured up to 26 months post-vaccination, underscoring a sustained influence on the immune system.

Ipilimumab, an immune checkpoint inhibitor, is employed in the management of malignant melanoma. It is an anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) antibody that targets specific molecules in the immune system to enhance the immune system's ability to attack cancer cells. It has received approval for the treatment of advanced malignant melanoma and, under certain circumstances, for other cancer types [115]. In a completed Phase III clinical trial, patients were divided into three groups receiving either ipilimumab 3 mg/kg + gp100 vaccine, ipilimumab 3 mg/kg + placebo, or gp100 vaccine alone. Among patients with at least 2 years of potential follow-up, the survival rates at 2 and 3 years were 19 % and 15 %, respectively, in the ipilimumab + gp100 group, compared to 25 % at both time points in the ipilimumab alone group [116]. The results suggest that the addition of the gp100 vaccine to ipilimumab did not yield the anticipated improvements in survival outcomes in pretreated patients with metastatic melanoma. Subsequent research, utilizing a mouse model of melanoma, revealed that gp100/IFA vaccination induced gp100-specific effector T cells (Teffs). Dominantly, these cells redirected non-gp100-specific Teffs induced by anti-CTLA-4 away from the tumor, diminishing tumor control. Inflammation at the vaccination site also sequestered and destroyed anti-CTLA-4-induced Teffs with specificities for tumor antigens other than gp100, reducing the anti-tumor efficacy of anti-CTLA-4 therapy. In contrast, nonpersistent vaccine formulations based on water-based gp100 peptide strongly synergized with CTLA-4 and PD-L1 checkpoint blockade therapy, inducing complete tumor regression, even in cases of primary resistance to dual checkpoint blockade [103]. The two study concludes that the formulation of cancer vaccines can dominantly

determine their synergistic effects with CTLA-4 and PD-L1 checkpoint blockade therapies or the lack thereof.

The increasing number of preclinical trials involving anticancer peptides is propelling the advancement of clinical trials for peptide-based therapeutics. To improve the tumor specificity of radiosensitizers, Dina V et al. explored active tumor targeting using peptide-based drug conjugates. The research group developed matrix metalloproteinase-cleavable cell-penetrating peptides that accumulate in tumor tissues. These protease-triggered peptides enabled the targeted delivery of radiosensitizers [117]. This finding highlights the advantages of protease-triggered cell-penetrating peptides over antibody-drug conjugates for delivering small molecule radiosensitizers. Jie Gao et al. created a peptide-based "nanobat" that targets mitochondria for combined chemo-radiotherapy. This innovative system efficiently induces cancer cell apoptosis by inhibiting energy metabolism through multiple pathways [118]. This finding have implications for designing effective mitochondrion-targeted drug delivery systems for cancer therapy.

## 6.3. Prevention of tumor recurrence and metastasis

Anti-cancer peptides can also be used to prevent tumor recurrence. After tumor treatment, residual tumor cells may enter a dormant state. Anti-cancer peptides can activate immune cells to eliminate dormant tumor cells, thus preventing tumor recurrence. L-BLP25 is a peptide vaccine composed of a segment of the cell surface glycoprotein MUC1. The L-BLP25 vaccine stimulates the patient's immune system to attack tumor cells expressing MUC1, thereby achieving therapeutic effects and preventing lung cancer recurrence [119]. G17DT is a peptide vaccine derived from the N-terminal region of gastrin-17 (G17-NTP). Chemical modification enhances the immunogenicity of G17-NTP, stimulating an immune response against gastric cancer cells [120]. E75 is a synthetically generated segment of MUC1 that is used to activate the patient's immune system to combat tumor cells. Upon treatment with E75, immune cells are primed to recognize and attack breast cancer cells expressing the MUC1 peptide segment [121]. The use of peptide-based drugs for preventing tumor recurrence is still in the research stage and has not been widely applied in clinical practice.

ACPs can inhibit the invasion and metastasis of cancer cells by targeting cancer cell surface proteins and proteins/constituents of the tumor microenvironment. Several ACP drugs have shown clinical efficacy in preventing cancer metastasis. Cancer metastasis-related peptide vaccines, such as those targeting MUC1 [122], HER2 [123] and GP100 [124,125], stimulate the immune response to prevent tumor metastasis. Peptides that inhibit tumor cell adhesion and invasion, such as the Arg-Gly-Asp (RGD) peptide, bind to integrins on the surface of tumor cells, preventing their adhesion and invasion [126].

## 7. Adverse reactions and side effects of anti-cancer peptide drugs

Anti-cancer peptides are known for their favorable biocompatibility and targeting properties, making them a promising option for cancer treatment with relatively few side effects. However, as clinical trials of peptide-based drugs continue to expand, researchers have discovered that adverse reactions and side effects can still occur in certain cases (Table 3). Reactions can manifest in different ways depending on the specific peptide drug being used [127]. Peptide drugs can elicit favorable immune responses but may also trigger adverse immune reactions. These reactions can range from immune suppression to infections and allergies. One common type of adverse reaction is an allergic reaction, which can include symptoms such as rash, urticaria, shortness of breath, and decreased blood pressure. Gastrointestinal reactions, including nausea, vomiting, and diarrhea, are also possible, as certain peptide drugs can affect the digestive system [128,129]. Additionally, peptide drugs may trigger neurological reactions such as headaches, dizziness, and insomnia [130]. It is worth emphasizing that different peptide drugs

**Table 3**  
Recently, completed clinical trials.

#	Study Title	Disease	Treatment (Intervention)	Current Status and Phase	Enrollment Estimated (Treated)	Number Trial	Serious Adverse Events (peptide group)	Other Adverse Events (peptide group)
1	RV001V, a RhoC Anti-cancer Vaccine, Against solid tumor metastasis [114]	Prostate Cancer	0.1 mg RV001V, s.c. every 2 weeks for the first six times, then five times every 4 weeks, 30 weeks	CompletedPhase I/ II	22	NCT03199872	4/22 (18.18 %)	22/22 (100 %)
2	Study of NY-ESO-1 ISCOMATRIX® in Patients With Measurable Stage III or IV Melanoma [128,129]	Melanoma	100 µg NY-ESO-1, i.m. every 4 weeks for 3 doses.	CompletedPhase II	46	NCT00518206	5/27(18.52 %)	27/27 (100 %)
3	MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDX-010/ MDX-1379 Combination Treatment for Patients With Unresectable or Metastatic Melanoma [116,190]	Melanoma	2 ml gp100, s.c. every 3 weeks for 4 doses.	CompletedPhase III	1783	NCT00094653	2/132 (39.39 %)	124/132 (93.94 %)
4	A Study of Melphalan Flufenamide (Melflufen)in Combination With Dexamethasone in Relapsed Refractory Multiple Myeloma Patients (HORIZON) [191]	Multiple Myeloma	40 mg melflufen, i.v. on day 1 of each 28-day cycle	Not yet recruiting, Phase II	157	NCT02963493	88/157 (56.05 %)	157/157 (100.00 %)
5	A Study of Melphalan Flufenamide (Melflufen)-Dex or Pomalidomide-dex for RRMM Patients Refractory to Lenalidomide [130]	Multiple Myeloma	40 mg melflufen i.v. on Day 1, 28-day cycle.	Active, not recruiting, Phase III	495	NCT03151811	95/228 (41.67 %)	226/228 (99.12 %)
6	ANG1005 in Breast Cancer Patients With Recurrent Brain Metastases [192]	Breast cancer, brain metastases	600 mg/m <sup>2</sup> ANG1005, i.v. on day 1 of each 21-day cycle.	Completed, Phase II	72	NCT02048059	5/72 (7 %) [192]	69/72(96 %) [192]

**Serious adverse events:** An adverse event that results in death, is life-threatening, requires inpatient hospitalization or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect. Medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered serious adverse events if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above.

**Other adverse events:** An adverse event that is not a serious adverse event.

may have varying adverse reactions and side effects. Furthermore, individual responses to medications can differ, highlighting the importance of monitoring patients for any adverse reactions or side effects. Continuous monitoring during treatment is crucial for ensuring patient safety and optimizing therapeutic outcomes. This includes monitoring for potential adverse effects, assessing treatment response, and adjusting the therapeutic regimen as needed.

## 8. Future development of anti-cancer peptide drugs

The current development status of peptide-based drugs has shaped the landscape of therapeutics for cancer treatment, shedding light on viable approaches and prospects. It is evident that significant progress has been made in overcoming major obstacles within the field. However, there is still ample space for further advancement.

First, the biosynthesis and purification processes of peptide drugs are complex and pose challenges to production. While the cost of manufacturing synthetic peptide drugs exceeds that of their small-molecule counterparts, the overall research and development costs are likely to be lower. This is attributed to their intrinsic synthetic feasibility, which offers advantages in enabling rapid and extensive structure-activity relationship studies for lead optimization. Moreover, their reduced risk of off-target effects potentially leads to higher clinical trial success rates. These factors position peptide drugs as a promising avenue for cost-effective therapeutic development. These factors make peptide drugs a promising avenue for cost-effective therapeutic development. For example, gene editing techniques and plasmid transfection enable the introduction of peptide sequences into tumor cells, thereby enhancing their immunogenicity and antigen-presenting capacity [131].

Second, researchers are conducting more precise screening and design of peptide drugs to enhance their targeting and specificity. Further understanding of the molecular characteristics and

immunological mechanisms of tumor cells is needed, along with the development of more precise diagnostic techniques and predictive models.

Third, peptide drugs are prone to recognition and clearance by the human immune system, necessitating chemical modifications or structural alterations to enhance drug stability and bioavailability. Researchers are developing new delivery systems for peptide drugs to improve their bioavailability and therapeutic efficacy. Examples include the use of carriers such as nanoparticles or liposomes to enhance the targeting and stability of peptide drugs.

Fourth, technologies such as artificial intelligence and machine learning are being utilized to rapidly screen and optimize the design of peptide drugs, accelerating the research and development process and reducing costs. With the aid of technologies such as 3D printing, personalized preparation and precise delivery systems for peptide drugs, including scaffolds and delivery systems, can be achieved [132]. Overall, these advancements in technology and methodology are revolutionizing the field of peptide drug research and development, offering new opportunities for improved therapeutic outcomes and personalized medicine.

Finally, due to the heterogeneity of tumor cells among different patients, there is a need to develop individually tailored peptide drugs. The most suitable treatment regimen can be selected based on individual patient characteristics, thereby improving treatment efficacy and safety through genetic testing and molecular diagnostic techniques.

## 9. Conclusion

Peptide drugs are ideally suited for cancer treatment since an estimated one out of every five peptides that undergo clinical trials exhibits anti-cancer activity [2]. Several factors contribute to this trend, including the significant unmet needs in oncology, advances in peptide

synthesis and delivery, a growing understanding of tumor biology, and the availability of regulatory frameworks that facilitate the development of new drugs. There are four compelling reasons why peptide drugs hold great promise in the field of cancer treatment. First, many peptide hormone receptors exhibit increased expression in tumor cells, making them excellent targets for distinguishing cancer cells from healthy cells. Peptides, whether equipped with imaging tags or drug cargo, can enter tumor cells through receptor-mediated internalization. Second, peptides can display remarkable selectivity for specific receptor subtypes, akin to monoclonal antibodies, but with superior penetration into tumor tissues and reduced immunogenicity. Moreover, peptides are rapidly cleared from the body, minimizing the risk of off-target effects and toxicity. Third, certain peptide hormone analogs can inhibit tumor growth and impede cancer progression in hormone-dependent diseases, where tumor cell proliferation and survival rely on specific hormone levels. The presence of these peptide hormone analogs can block the binding of hormones to tumor cells, thereby suppressing tumor proliferation and advancement. Finally, the administration of peptides via injection is widely accepted by cancer patients. Therefore, we expect this field to continue expanding, with a particular focus on peptide-based cancer immunotherapy and drug delivery, which are currently receiving significant attention [133,134]. ACPs offer vast prospects but also require overcoming multiple technological and scientific challenges. With continuous advancements in technology and in-depth basic research, it is believed that anti-cancer peptide drugs will play an increasingly important role in future clinical regimens.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data and materials

Not applicable.

### Funding

This work was supported by Natural Science Foundation of Henan province (242300421308) and the National Natural Science Fund (82073075, 81872335).

### Authors' contributions

D-ZG and L-KD conceived and drafted the outline. C-XJ and Z-ZW drafted the manuscript and drew the figures. KVL, L-FF and L-H conducted language modification and coloring.

### Declaration of competing interest

The authors declare no conflict of interest.

### Data availability

No data was used for the research described in the article.

### Acknowledgements

The figures are created with [Biorender.com](#).

### References

- [1] J.M. Kocarnik, et al., Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: a systematic analysis for the global burden of disease study 2019, *JAMA Oncol.* 8 (2022) 420–444, <https://doi.org/10.1001/jamaoncol.2021.6987>.
- [2] M. Muttenthaler, G.F. King, D.J. Adams, P.F. Alewood, Trends in peptide drug discovery, *Nat. Rev. Drug Discov.* 20 (2021) 309–325, <https://doi.org/10.1038/s41573-020-00135-8>.
- [3] R.K. Chinnadurai, et al., Current research status of anti-cancer peptides: mechanism of action, production, and clinical applications, *Biomed. Pharmacother.* 164 (2023) 114996, <https://doi.org/10.1016/j.biopha.2023.114996>.
- [4] M. Zhou, et al., The role of cell-penetrating peptides in potential anti-cancer therapy, *Clin. Transl. Med.* 12 (2022) e822, <https://doi.org/10.1002/ctm2.822>.
- [5] S.J. Freedland, et al., A phase 3 randomised study of enzalutamide plus leuproreotide and enzalutamide monotherapy in high-risk non-metastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design, *BMJ Open* 11 (2021) e046588, <https://doi.org/10.1136/bmjopen-2020-046588>.
- [6] D.C. Kendzierski, B.P. Schneider, P.J. Kiel, Efficacy of different leuproreotide administration schedules in premenopausal breast cancer: a retrospective review, *Clin. Breast Cancer* 18 (2018) e939–e942, <https://doi.org/10.1016/j.cldbc.2018.04.005>.
- [7] L. Zhang, et al., Peptide-based materials for cancer immunotherapy, *Theranostics* 9 (2019) 7807–7825, <https://doi.org/10.7105/thno.37194>.
- [8] W. Liu, et al., Peptide-based therapeutic cancer vaccine: current trends in clinical application, *Cell Prolif.* 54 (2021) e13025, <https://doi.org/10.1111/cpr.13025>.
- [9] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury, National Institute of Diabetes and Digestive and Kidney Diseases, 2012.
- [10] X. Yu, et al., Melittin-lipid nanoparticles target to lymph nodes and elicit a systemic anti-tumor immune response, *Nat. Commun.* 11 (2020) 1110, <https://doi.org/10.1038/s41467-020-14906-9>.
- [11] D. Juretić, J. Simunić, Design of  $\alpha$ -helical antimicrobial peptides with a high selectivity index, *Expert Opin. Drug Discov.* 14 (2019) 1053–1063, <https://doi.org/10.1080/17460441.2019.1642322>.
- [12] R. Modi, et al., Stapled peptides as direct inhibitors of Nrf2-sMAF transcription factors, *J. Med. Chem.* 66 (2023) 6184–6192, <https://doi.org/10.1021/acs.jmedchem.2c02037>.
- [13] K.M. Saravanan, H. Zhang, H. Zhang, W. Xi, Y. Wei, On the conformational dynamics of  $\beta$ -amyloid forming peptides: a computational perspective, *Front. Bioeng. Biotechnol.* 8 (2020) 532, <https://doi.org/10.3389/fbioe.2020.00532>.
- [14] V. Selvarajan, et al., Stapled  $\beta$ -hairpin antimicrobial peptides with improved stability and activity against drug-resistant gram-negative bacteria, *J. Med. Chem.* 66 (2023) 8498–8509, <https://doi.org/10.1021/acs.jmedchem.3c00140>.
- [15] S.S. Singh, et al., A grafted peptidomimetic for EGFR heterodimerization inhibition: implications in NSCLC models, *Eur. J. Med. Chem.* 216 (2021) 113312, <https://doi.org/10.1016/j.ejmech.2021.113312>.
- [16] P. Hart, et al., Structure based design of bicyclic peptide inhibitors of RbAp48, *Angew. Chem. Int. Ed. Eng.* 60 (2021) 1813–1820, <https://doi.org/10.1002/anie.202009749>.
- [17] A. Baruch Leshem, et al., Biomolecular condensates formed by designer minimalistic peptides, *Nat. Commun.* 14 (2023) 421, <https://doi.org/10.1038/s41467-023-36060-8>.
- [18] I.W. Hamley, V. Castelletto, Small-angle scattering techniques for peptide and peptide hybrid nanostructures and peptide-based biomaterials, *Adv. Colloid Interf. Sci.* 318 (2023) 102959, <https://doi.org/10.1016/j.cis.2023.102959>.
- [19] P.M. McCarthy, et al., AE37: a HER2-targeted vaccine for the prevention of breast cancer recurrence, *Expert Opin. Investig. Drugs* 30 (2021) 5–11, <https://doi.org/10.1080/13543784.2021.1849140>.
- [20] B. Sharma, S.S. Kanwar, Phosphatidylserine: a cancer cell targeting biomarker, *Semin. Cancer Biol.* 52 (2018) 17–25, <https://doi.org/10.1016/j.semcancer.2017.08.012>.
- [21] A. Boruah, A. Roy, Advances in hybrid peptide-based self-assembly systems and their applications, *Biomater. Sci.* 10 (2022) 4694–4723, <https://doi.org/10.1039/d2bm00775d>.
- [22] X. Meng, et al., Dual functionalized brain-targeting nanoinhibitors restrain temozolamide-resistant glioma via attenuating EGFR and MET signaling pathways, *Nat. Commun.* 11 (2020) 594, <https://doi.org/10.1038/s41467-019-14036-x>.
- [23] F. Posa, et al., Surface co-presentation of BMP-2 and integrin selective ligands at the nanoscale favors  $\alpha(5)\beta(1)$  integrin-mediated adhesion, *Biomaterials* 267 (2021) 120484, <https://doi.org/10.1016/j.biomaterials.2020.120484>.
- [24] S. Lakkadwala, B. Dos Santos Rodrigues, C. Sun, J. Singh, Dual functionalized liposomes for efficient co-delivery of anti-cancer chemotherapeutics for the treatment of glioblastoma, *J. Control. Release* 307 (2019) 247–260, <https://doi.org/10.1016/j.jconrel.2019.06.033>.
- [25] M. Leo, L. Sabatino, Targeting CXCR4 and CD47 receptors: An overview of new and old molecules for a biological personalized anticancer therapy, *Int. J. Mol. Sci.* 23 (2022), <https://doi.org/10.3390/ijms232012499>.
- [26] C.A. Roque-Borda, M.W.L. Gualque, F.H. da Fonseca, F.R. Pavan, N.A. Santos-Filho, Nanobiotechnology with therapeutically relevant macromolecules from animal venoms: venoms, toxins, and antimicrobial peptides, *Pharmaceutics* 14 (2022), <https://doi.org/10.3390/pharmaceutics14050891>.
- [27] F. Ramos-Martín, C. Herrera-León, N. D'Amelio, Molecular basis of the anticancer, apoptotic and antibacterial activities of Bombyx mori Cecropin a, a

- Arch. Biochem. Biophys. 715 (2022) 109095, <https://doi.org/10.1016/j.abb.2021.109095>.
- [28] D. Yu, et al., Marine-derived bioactive peptides self-assembled multifunctional materials: antioxidant and wound healing, *Antioxidants* (Basel, Switzerland) 12 (2023), <https://doi.org/10.3390/antiox12061190>.
- [29] S.A. Rosenberg, J.C. Yang, N.P. Restifo, Cancer immunotherapy: moving beyond current vaccines, *Nat. Med.* 10 (2004) 909–915, <https://doi.org/10.1038/nm1100>.
- [30] A. Legat, et al., Vaccination with LAG-3Ig (IMP321) and peptides induces specific CD4 and CD8 T-cell responses in metastatic melanoma patients—report of a phase I/IIa clinical trial, *Clin. Cancer Res.* 22 (2016) 1330–1340, <https://doi.org/10.1158/1078-0432.Ccr-15-1212>.
- [31] I. Castillo-Juárez, B.E. Blancas-Luciano, R. García-Contreras, A.M. Fernández-Presas, Antimicrobial peptides properties beyond growth inhibition and bacterial killing, *PeerJ* 10 (2022) e12667, <https://doi.org/10.7717/peerj.12667>.
- [32] C. Zhou, D. Peng, B. Liao, R. Jia, F. Wu, ACP\_MS: prediction of anticancer peptides based on feature extraction, *Brief. Bioinform.* 23 (2022), <https://doi.org/10.1093/bib/bbac462>.
- [33] LiverTox Clinical and Research Information on Drug-Induced Liver Injury, National Institute of Diabetes and Digestive and Kidney Diseases, 2012.
- [34] D.V. Swasyer, V. Gerriets, StatPearls (StatPearls Publishing Copyright © 2023), StatPearls Publishing LLC, 2023.
- [35] K. Desai, J.M. McManus, N. Sharifi, Hormonal therapy for prostate cancer, *Endocr. Rev.* 42 (2021) 354–373, <https://doi.org/10.1210/endrev/bnab002>.
- [36] Y. Gomez Rodriguez, et al., Synergic effect of anticancer peptide CIGB-552 and cisplatin in lung cancer models, *Mol. Biol. Rep.* 49 (2022) 3197–3212, <https://doi.org/10.1007/s11033-022-07152-3>.
- [37] K. Sharma, K.K. Sharma, A. Sharma, R. Jain, Peptide-based drug discovery: current status and recent advances, *Drug Discov. Today* 28 (2023) 103464, <https://doi.org/10.1016/j.drudis.2022.103464>.
- [38] R.R. McKay, et al., Evaluation of intense androgen deprivation before prostatectomy: a randomized phase II trial of enzalutamide and leuproreotide with or without Abiraterone, *J. Clin. Oncol.* 37 (2019) 923–931, <https://doi.org/10.1200/jco.18.01777>.
- [39] N.D. Shore, et al., Impact of concomitant cardiovascular therapies on efficacy and safety of Relugolix vs leuproreotide: subgroup analysis from HERO study in advanced prostate Cancer, *Adv. Ther.* 40 (2023) 4919–4927, <https://doi.org/10.1007/s12325-023-02634-7>.
- [40] J. Kurebayashi, et al., A follow-up study of a randomized controlled study evaluating safety and efficacy of leuproreolin acetate every-3-month depot for 2 versus 3 or more years with tamoxifen for 5 years as adjuvant treatment in premenopausal patients with endocrine-responsive breast cancer, *Breast Cancer* (Tokyo, Japan) 28 (2021) 684–697, <https://doi.org/10.1007/s12282-020-01205-w>.
- [41] M. Raj, H. Wu, S.L. Blosser, M.A. Vittoria, P.S. Arora, Aldehyde capture ligation for synthesis of native peptide bonds, *J. Am. Chem. Soc.* 137 (2015) 6932–6940, <https://doi.org/10.1021/jacs.5b03538>.
- [42] L. Scheetz, et al., Synthetic high-density lipoprotein Nanodiscs for personalized immunotherapy against gliomas, *Clin. Cancer Res.* 26 (2020) 4369–4380, <https://doi.org/10.1158/1078-0432.Ccr-20-0341>.
- [43] R. Kuai, L.J. Ochyl, K.S. Bahjat, A. Schwendeman, J.J. Moon, Designer vaccine nanodiscs for personalized cancer immunotherapy, *Nat. Mater.* 16 (2017) 489–496, <https://doi.org/10.1038/nmat4822>.
- [44] Y. Pan, Y. Yu, X. Wang, T. Zhang, Tumor-associated macrophages in tumor immunity, *Front. Immunol.* 11 (2020) 583084, <https://doi.org/10.3389/fimmu.2020.583084>.
- [45] J.M. Jaynes, et al., Mannose receptor (CD206) activation in tumor-associated macrophages enhances adaptive and innate antitumor immune responses, *Sci. Transl. Med.* 12 (2020), <https://doi.org/10.1126/scitranslmed.aax6337>.
- [46] M. Sun, et al., Fibroblast activation protein- $\alpha$  responsive peptide assembling prodrug nanoparticles for remodeling the immunosuppressive microenvironment and boosting cancer immunotherapy, *Small* (Weinheim an der Bergstrasse, Germany) 18 (2022) e2106296, <https://doi.org/10.1002/smll.202106296>.
- [47] Y. Nie, L. Shi, Y. Zhang, Y. Guo, H. Gu, Mannose and hyaluronic acid dual-modified Iron oxide enhances neoantigen-based peptide vaccine therapy by polarizing tumor-associated macrophages, *Cancers* 14 (2022), <https://doi.org/10.3390/cancers14205107>.
- [48] S. Patel, et al., Unique pattern of neutrophil migration and function during tumor progression, *Nat. Immunol.* 19 (2018) 1236–1247, <https://doi.org/10.1038/s41590-018-0229-5>.
- [49] I.L. Linde, et al., Neutrophil-activating therapy for the treatment of cancer, *Cancer Cell* 41 (2023) 356–372.e310, <https://doi.org/10.1016/j.ccr.2023.01.002>.
- [50] C. Kerros, et al., Neuropilin-1 mediates neutrophil elastase uptake and cross-presentation in breast cancer cells, *J. Biol. Chem.* 292 (2017) 10295–10305, <https://doi.org/10.1074/jbc.M116.773051>.
- [51] S. Ferdowsi, A.A. Pourfathollah, F. Amiri, M.H. Rafiee, A. Aghaei, Evaluation of anticancer activity of  $\alpha$ -defensins purified from neutrophils trapped in leukoreduction filters, *Life Sci.* 224 (2019) 249–254, <https://doi.org/10.1016/j.lfs.2019.03.072>.
- [52] J. Das, S.I. Khakoo, NK cells: tuned by peptide? *Immunol. Rev.* 267 (2015) 214–227, <https://doi.org/10.1111/imr.12315>.
- [53] C. Guillerey, N.D. Huntington, M.J. Smyth, Targeting natural killer cells in cancer immunotherapy, *Nat. Immunol.* 17 (2016) 1025–1036, <https://doi.org/10.1038/ni.3518>.
- [54] Q. Hammer, et al., Peptide-specific recognition of human cytomegalovirus strains controls adaptive natural killer cells, *Nat. Immunol.* 19 (2018) 453–463, <https://doi.org/10.1038/s41590-018-0082-6>.
- [55] C. Tay, A. Tanaka, S. Sakaguchi, Tumor-infiltrating regulatory T cells as targets of cancer immunotherapy, *Cancer Cell* 41 (2023) 450–465, <https://doi.org/10.1016/j.ccr.2023.02.014>.
- [56] T. Chen, et al., Peptide-based and small synthetic molecule inhibitors on PD-1/PD-L1 pathway: a new choice for immunotherapy? *Eur. J. Med. Chem.* 161 (2019) 378–398, <https://doi.org/10.1016/j.ejmchem.2018.10.044>.
- [57] L. Jiao, et al., A PD-L1 and VEGFR2 dual targeted peptide and its combination with irradiation for cancer immunotherapy, *Pharmacol. Res.* 182 (2022) 106343, <https://doi.org/10.1016/j.phrs.2022.106343>.
- [58] J. Fetse, et al., Discovery of cyclic peptide inhibitors targeting PD-L1 for Cancer immunotherapy, *J. Med. Chem.* 65 (2022) 12002–12013, <https://doi.org/10.1021/acs.jmedchem.2c00539>.
- [59] T. Lozano, et al., Searching for peptide inhibitors of T regulatory cell activity by targeting specific domains of FOXP3 transcription factor, *Biomedicines* 9 (2021), <https://doi.org/10.3390/biomedicines9020197>.
- [60] J. Tobias, et al., A new strategy toward B cell-based cancer vaccines by active immunization with Mimotopes of immune checkpoint inhibitors, *Front. Immunol.* 11 (2020) 895, <https://doi.org/10.3389/fimmu.2020.00895>.
- [61] L. Guo, J. Overholser, A.J. Good, N.J. Ede, P.T.P. Kaumaya, Preclinical studies of a novel human PD-1 B-cell peptide cancer vaccine PD1-Vaxx from BALB/c mice to beagle dogs and to non-human primates (Cynomolgus monkeys), *Front. Oncol.* 12 (2022) 826566, <https://doi.org/10.3389/fonc.2022.826566>.
- [62] M.W. Löffler, et al., Phase I/II multicenter trial of a novel therapeutic cancer vaccine, HepaVac-101, for hepatocellular carcinoma, *Clin. Cancer Res.* 28 (2022) 2555–2566, <https://doi.org/10.1158/1078-0432.Ccr-21-4424>.
- [63] S. Badrinath, et al., A vaccine targeting resistant tumours by dual T cell plus NK cell attack, *Nature* 606 (2022) 992–998, <https://doi.org/10.1038/s41586-022-04772-4>.
- [64] I. Esposito, et al., MHC class II invariant chain-adjuvanted viral vectored vaccines enhances T cell responses in humans, *Sci. Transl. Med.* 12 (2020), <https://doi.org/10.1126/scitranslmed.aaz7715>.
- [65] B.J. Hos, et al., Cancer-specific T helper shared and neo-epitopes uncovered by expression of the MHC class II master regulator CIITA, *Cell Rep.* 41 (2022) 111485, <https://doi.org/10.1016/j.celrep.2022.111485>.
- [66] Y. Oji, et al., WT1 tripe peptide-based cancer vaccine for rare cancers expressing shared target WT1, *Cancers* 15 (2023), <https://doi.org/10.3390/cancers15020393>.
- [67] J. Kang, et al., Novel peptide-based vaccine targeting heat shock protein 90 induces effective antitumor immunity in a HER2+ breast cancer murine model, *J. Immunother. Cancer* 10 (2022), <https://doi.org/10.1136/jitc-2022-004702>.
- [68] D.M. Lüssier, et al., Radiation-induced neoantigens broaden the immunotherapeutic window of cancers with low mutational loads, *Proc. Natl. Acad. Sci. USA* 118 (2021), <https://doi.org/10.1073/pnas.2102611118>.
- [69] J. Okada, et al., FAM83G-based peptide induces apoptosis on cultured liver cancer cell, *Protein Pept. Lett.* 29 (2022) 1082–1087, <https://doi.org/10.2174/092986652966220928155400>.
- [70] N. Faraji, S.S. Arab, A. Doustmohammadi, N.L. Daly, A.Y. Khosrourshahi, ApInAPDB: a database of apoptosis-inducing anticancer peptides, *Sci. Rep.* 12 (2022) 21341, <https://doi.org/10.1038/s41598-022-25530-6>.
- [71] G.J. Philippe, et al., Angler peptides: macrocyclic conjugates inhibit p53:MDM2/X interactions and activate apoptosis in cancer cells, *ACS Chem. Biol.* 16 (2021) 414–428, <https://doi.org/10.1021/acscchembio.0c00988>.
- [72] Y. Wu, et al., Laminaria japonica peptides suppress liver cancer by inducing apoptosis: possible signaling pathways and mechanism, *Mar. Drugs* 20 (2022), <https://doi.org/10.3390/md20210704>.
- [73] M.M. Mahmoud, et al., Anticancer activity of chicken cathelicidin peptides against different types of cancer, *Mol. Biol. Rep.* 49 (2022) 4321–4339, <https://doi.org/10.1007/s11033-022-07267-7>.
- [74] K. Selvarathinam, et al., Wnt signaling pathway collapse upon  $\beta$ -catenin destruction by a novel antimicrobial peptide SKACP003: unveiling the molecular mechanism and genetic activities using breast cancer cell lines, *Molecules* (Basel, Switzerland) 28 (2023), <https://doi.org/10.3390/molecules28030930>.
- [75] C.H. Hsieh, et al., The hydrolytic peptides of soybean protein induce cell cycle arrest and apoptosis on human oral cancer cell line HSC-3, *Molecules* (Basel, Switzerland) 27 (2022), <https://doi.org/10.3390/molecules27092839>.
- [76] T. Chen, et al., Gramicidin inhibits human gastric cancer cell proliferation, cell cycle and induced apoptosis, *Biol. Res.* 52 (2019) 57, <https://doi.org/10.1186/s40659-019-0264-1>.
- [77] A.C.L. Mortensen, D. Spiegelberg, C.J. Brown, D.P. Lane, M. Nestor, The stapled peptide PM2 stabilizes p53 levels and radiosensitizes wild-type p53 cancer cells, *Front. Oncol.* 9 (2019) 923, <https://doi.org/10.3389/fonc.2019.00923>.
- [78] B.J. Monk, et al., Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial, *Lancet Oncol.* 15 (2014) 799–808, [https://doi.org/10.1016/s1470-2045\(14\)70244-x](https://doi.org/10.1016/s1470-2045(14)70244-x).
- [79] J. Mooi, et al., Dual Antiangiogenesis agents bevacizumab plus trebananib, without chemotherapy, in first-line treatment of metastatic colorectal cancer: results of a phase II study, *Clin. Cancer Res.* 27 (2021) 2159–2167, <https://doi.org/10.1158/1078-0432.Ccr-20-2714>.
- [80] D. Müller, Targeting co-stimulatory receptors of the TNF superfamily for cancer immunotherapy, *BioDrugs Clin. Immunother. Biopharmaceut. Gene Ther.* 37 (2023) 21–33, <https://doi.org/10.1007/s40259-022-00573-3>.

- [81] P. Probst, M. Stringhini, D. Ritz, T. Fugmann, D. Neri, Antibody-based delivery of TNF to the tumor neovasculature potentiates the therapeutic activity of a peptide anticancer vaccine, *Clin. Cancer Res.* 25 (2019) 698–709, <https://doi.org/10.1158/1078-0432.Ccr-18-1728>.
- [82] V. Pretre, D. Papadopoulos, J. Regard, M. Pelletier, J. Woo, Interleukin-1 (IL-1) and the inflammasome in cancer, *Cytokine* 153 (2022) 155850, <https://doi.org/10.1016/j.cyto.2022.155850>.
- [83] Z. Gong, et al., Interleukin-1 receptor antagonist inhibits angiogenesis in gastric cancer, *Int. J. Clin. Oncol.* 23 (2018) 659–670, <https://doi.org/10.1007/s10147-018-1242-2>.
- [84] M.E. Raebet, D. Sahin, U. Karakus, O. Boyman, A systematic review of interleukin-2-based immunotherapies in clinical trials for cancer and autoimmune diseases, *EBioMedicine* 90 (2023) 104539, <https://doi.org/10.1016/j.ebiom.2023.104539>.
- [85] R. Hernandez, K.M. LaPorte, S. Hsiung, A. Santos Savio, T.R. Malek, High-dose IL-2/CD25 fusion protein amplifies vaccine-induced CD4(+) and CD8(+) neoantigen-specific T cells to promote antitumor immunity, *J. Immunother. Cancer* 9 (2021), <https://doi.org/10.1136/jitc-2021-002865>.
- [86] T. Hirano, IL-6 in inflammation, autoimmunity and cancer, *Int. Immunopharmacol.* 33 (2021) 127–148, <https://doi.org/10.1093/intimm/dxa078>.
- [87] N. Sharifnejad, et al., The clinical, molecular, and therapeutic features of patients with IL10/IL10R deficiency: a systematic review, *Clin. Exp. Immunol.* 208 (2022) 281–291, <https://doi.org/10.1093/cei/uxac040>.
- [88] S. Chen, et al., Blocking IL-10 signalling at the time of immunization renders the tumour more accessible to T cell infiltration in mice, *Cell. Immunol.* 300 (2016) 9–17, <https://doi.org/10.1016/j.cellimm.2015.11.002>.
- [89] F. Nadal-Bufi, et al., Peptide-based LDH5 inhibitors enter cancer cells and impair proliferation, *Cell. Mol. Life Sci.* 79 (2022) 606, <https://doi.org/10.1007/s00018-022-04633-3>.
- [90] V. Amaral, et al., *Pisum sativum* Defensin 1 eradicates mouse metastatic lung nodules from B16F10 melanoma cells, *Int. J. Mol. Sci.* 21 (2020), <https://doi.org/10.3390/ijms21082662>.
- [91] L. Yin, C. Yuvienco, J.K. Montclare, Protein based therapeutic delivery agents: contemporary developments and challenges, *Biomaterials* 134 (2017) 91–116, <https://doi.org/10.1016/j.biomaterials.2017.04.036>.
- [92] J. Wu, et al., Biomimetic viruslike and charge reversible nanoparticles to sequentially overcome mucus and epithelial barriers for oral insulin delivery, *ACS Appl. Mater. Interfaces* 10 (2018) 9916–9928, <https://doi.org/10.1021/acsami.7b16524>.
- [93] R. Zhang, et al., A peptide-based small RNA delivery system to suppress tumor growth by remodeling the tumor microenvironment, *Mol. Pharm.* 18 (2021) 1431–1443, <https://doi.org/10.1021/acs.molpharmaceut.0c01253>.
- [94] J. Zhao, F. Santino, D. Giacomini, L. Gentilucci, Integrin-targeting peptides for the design of functional cell-responsive biomaterials, *Biomedicines* 8 (2020), <https://doi.org/10.3390/biomedicines8090307>.
- [95] Y. Yang, et al., Synthesis and evaluation of (68)Ga-labeled dimeric cNGR peptide for PET imaging of CD13 expression with ovarian cancer xenograft, *J. Cancer* 12 (2021) 244–252, <https://doi.org/10.7150/jca.49628>.
- [96] H. Gu, et al., EGFR-targeted liposomes combined with ginsenoside Rh2 inhibit triple-negative breast cancer growth and metastasis, *Bioconjug. Chem.* (2023), <https://doi.org/10.1021/acs.bioconjchem.3c00207>.
- [97] X. Chen, S. Lei, J. Lin, P. Huang, Stimuli-responsive image-guided nanocarriers as smart drug delivery platforms, *Expert Opin. Drug Deliv.* 19 (2022) 1487–1504, <https://doi.org/10.1080/17425247.2022.2134853>.
- [98] F. Li, et al., Stimuli-responsive nano-assemblies for remotely controlled drug delivery, *J. Control. Release* 322 (2020) 566–592, <https://doi.org/10.1016/j.jconrel.2020.03.051>.
- [99] D. Wan, Y. Liu, X. Guo, J. Zhang, J. Pan, Intelligent drug delivery by peptide-based dual-function micelles, *Int. J. Mol. Sci.* 23 (2022), <https://doi.org/10.3390/ijms23179698>.
- [100] V.B. Kumar, et al., Peptide self-assembled nanocarriers for cancer drug delivery, *J. Phys. Chem. B* 127 (2023) 1857–1871, <https://doi.org/10.1021/acs.jpcb.2c06751>.
- [101] Z. Guo, et al., GE11 peptide-decorated acidity-responsive micelles for improved drug delivery and enhanced combination therapy of metastatic breast cancer, *J. Mater. Chem. B* 10 (2022) 9266–9279, <https://doi.org/10.1039/d2tb01816k>.
- [102] Y. Chen, et al., High-efficiency fluorescence through bioinspired supramolecular self-assembly, *ACS Nano* 14 (2020) 2798–2807, <https://doi.org/10.1021/acsnano.9b10024>.
- [103] P. Nathan, et al., Overall survival benefit with tebentafusp in metastatic uveal melanoma, *N. Engl. J. Med.* 385 (2021) 1196–1206, <https://doi.org/10.1056/NEJMoa2103485>.
- [104] A. Cicione, et al., Cardiovascular adverse events-related to GnRH agonists and GnRH antagonists: analysis of real-life data from Eudra-vigilance and Food and Drug Administration databases entries, *Prostate Cancer Prostatic Dis.* 26 (2023) 765–771, <https://doi.org/10.1038/s41391-022-00640-4>.
- [105] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury, National Institute of Diabetes and Digestive and Kidney Diseases, 2012.
- [106] D.S. Hawkins, et al., Addition of vincristine and irinotecan to vincristine, Dactinomycin, and cyclophosphamide does not improve outcome for intermediate-risk rhabdomyosarcoma: a report from the Children's oncology group, *J. Clin. Oncol.* 36 (2018) 2770–2777, <https://doi.org/10.1200/jco.2018.77.9694>.
- [107] S.F. Askari Rizvi, H. Zhang, Emerging trends of receptor-mediated tumor targeting peptides: a review with perspective from molecular imaging modalities, *Eur. J. Med. Chem.* 221 (2021) 113538, <https://doi.org/10.1016/j.ejmech.2021.113538>.
- [108] K. Chakraborty, J. Mondal, J.M. An, J. Park, Y.K. Lee, Advances in radionuclides and Radiolabelled peptides for Cancer therapeutics, *Pharmaceutics* 15 (2023), <https://doi.org/10.3390/pharmaceutics15030971>.
- [109] J. Hofland, T. Brabander, F.A. Verburg, R.A. Feeders, W.W. de Herder, Peptide receptor radionuclide therapy, *J. Clin. Endocrinol. Metab.* 107 (2022) 3199–3208, <https://doi.org/10.1210/clinend/dgac574>.
- [110] S. Ahmadpour, S.J. Hosseiniemehr, Recent developments in peptide-based SPECT radiopharmaceuticals for breast tumor targeting, *Life Sci.* 239 (2019) 116870, <https://doi.org/10.1016/j.lfs.2019.116870>.
- [111] Y. Liu, et al., Peptide-based 68Ga-PET radiotracer for imaging CD133 expression in colorectal cancer, *Nucl. Med. Commun.* 42 (2021) 1144–1150, <https://doi.org/10.1097/mnm.00000000000001435>.
- [112] R.L. Siegel, A.N. Giaquinto, A. Jemal, Cancer statistics, 2024, *CA Cancer J. Clin.* 74 (2024) 12–49, <https://doi.org/10.3322/caac.21820>.
- [113] J.E. Chaft, et al., Evolution of systemic therapy for stages I–III non-metastatic non-small-cell lung cancer, *Nat. Rev. Clin. Oncol.* 18 (2021) 547–557, <https://doi.org/10.1038/s41571-021-00501-4>.
- [114] J. Schuhmacher, et al., Vaccination against RhoC induces long-lasting immune responses in patients with prostate cancer: results from a phase I/II clinical trial, *J. Immunother. Cancer* 8 (2020), <https://doi.org/10.1136/jitc-2020-001157>.
- [115] T.K. Choueiri, et al., Cabozantinib plus Nivolumab and Ipilimumab in Renal-Cell Carcinoma, *N. Engl. J. Med.* 388 (2023) 1767–1778, <https://doi.org/10.1056/NEJMoa2212851>.
- [116] D. McDermott, J. Haanen, T.T. Chen, P. Lorigan, S. O'Day, Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20), *Ann. Oncol.* 24 (2013) 2694–2698, <https://doi.org/10.1093/annonc/mdt291>.
- [117] D.V. Hingorani, et al., Redirecting extracellular proteases to molecularly guide radiosensitizing drugs to tumors, *Biomaterials* 248 (2020) 120032, <https://doi.org/10.1016/j.biomaterials.2020.120032>.
- [118] J. Gao, et al., Mitochondrion-targeted supramolecular "nano-boat" simultaneously inhibiting dual energy metabolism for tumor selective and synergistic chemo-radiotherapy, *Theranostics* 12 (2022) 1286–1302, <https://doi.org/10.7150/thno.67543>.
- [119] J.D. Patel, et al., Phase II study of immunotherapy with tecemotide and bevacizumab after chemoradiation in patients with unresectable stage III non-squamous non-small-cell lung cancer (NS-NSCLC): a trial of the ECOG-ACRIN Cancer research group (E6508), *Clin. Lung Cancer* 21 (2020) 520–526, <https://doi.org/10.1016/j.cllc.2020.06.007>.
- [120] J.P. Smith, et al., Gastrin vaccine alone and in combination with an immune checkpoint antibody inhibits growth and metastases of gastric cancer, *Front. Oncol.* 11 (2021) 788875, <https://doi.org/10.3389/fonc.2021.788875>.
- [121] P. Zamani, et al., Nanoliposomal vaccine containing long multi-epitope peptide E75-AE36 pulsed PADRE-induced effective immune response in mice TUBO model of breast cancer, *Eur. J. Cancer (Oxford, England : 1990)* 129 (2020) 80–96, <https://doi.org/10.1016/j.ejca.2020.01.010>.
- [122] R.E. Schoen, et al., Randomized, double-blind, placebo-controlled trial of MUC1 peptide vaccine for prevention of recurrent colorectal adenoma, *Clin. Cancer Res.* 29 (2023) 1678–1688, <https://doi.org/10.1158/1078-0432.Ccr-22-3168>.
- [123] A.E. O'Shea, et al., Phase II trial of nelipepimut-s peptide vaccine in women with ductal carcinoma in situ, *Cancer Prev. Res. (Phila.)* (2023), <https://doi.org/10.1158/1940-6207.Capr-22-0388>.
- [124] M. Yazdani, et al., Liposomal gp100 vaccine combined with CpG ODN sensitizes established B16F10 melanoma tumors to anti PD-1 therapy, *Iran. J. Basic Med. Sci.* 23 (2020) 1065–1077, <https://doi.org/10.22038/ijbms.2020.46654.10762>.
- [125] F. Xu, Y. Yuan, Y. Wang, Q. Yin, Emerging peptide-based nanovaccines: from design synthesis to defense against cancer and infection, *Biomed. Pharmacother.* 158 (2023) 114117, <https://doi.org/10.1016/j.biopha.2022.114117>.
- [126] E.A. Egorova, M.P. Nikitin, Delivery of Theranostic nanoparticles to various cancers by means of integrin-binding peptides, *Int. J. Mol. Sci.* 23 (2022), <https://doi.org/10.3390/ijms232213735>.
- [127] Y. Fang, et al., A Pan-cancer clinical study of personalized Neoantigen vaccine monotherapy in treating patients with various types of advanced solid tumors, *Clin. Cancer Res.* 26 (2020) 4511–4520, <https://doi.org/10.1158/1078-0432.Ccr-19-2881>.
- [128] O. Klein, et al., Low-dose cyclophosphamide enhances antigen-specific CD4(+) T cell responses to NY-ESO-1/ISCOMATRIX™ vaccine in patients with advanced melanoma, *Cancer Immunol. Immunother.* 64 (2015) 507–518, <https://doi.org/10.1007/s00262-015-1656-x>.
- [129] T. Nicholaou, et al., Regulatory T-cell-mediated attenuation of T-cell responses to the NY-ESO-1 ISCOMATRIX vaccine in patients with advanced malignant melanoma, *Clin. Cancer Res.* 15 (2009) 2166–2173, <https://doi.org/10.1158/1078-0432.Ccr-08-2484>.
- [130] F.H. Schjesvold, et al., Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEAN): a randomised, head-to-head, open-label, phase 3 study, *Lancet Haematol.* 9 (2022) e98–e110, [https://doi.org/10.1016/s2352-3026\(21\)00381-1](https://doi.org/10.1016/s2352-3026(21)00381-1).
- [131] G.E. Holt, P. Daftarian, Non-small-cell lung cancer homing peptide-labeled dendrimers selectively transfect lung cancer cells, *Immunotherapy* 10 (2018) 1349–1360, <https://doi.org/10.2217/imt-2018-0078>.
- [132] A.C. Farshaei, A.J. Thomas, B.H. Pogostin, J.D. Hartgerink, 3D printing of self-assembling nanofibrous multidomain peptide hydrogels, *Adv. Materials (Deerfield Beach, Fla.)* 35 (2023) e2210378, <https://doi.org/10.1002/adma.202210378>.

- [133] J. Jou, K.J. Harrington, M.B. Zocca, E. Ehrnrooth, E.E.W. Cohen, The changing landscape of therapeutic Cancer vaccines-novel platforms and Neoantigen identification, *Clin. Cancer Res.* 27 (2021) 689–703, <https://doi.org/10.1158/1078-0432.Ccr.20-0245>.
- [134] C. Diaferia, E. Rosa, A. Accardo, G. Morelli, Peptide-based hydrogels as delivery systems for doxorubicin, *J. Pept. Sci.* 28 (2022) e3301, <https://doi.org/10.1002/psc.3301>.
- [135] B.C. Su, C.C. Li, J.L. Horng, J.Y. Chen, Calcium-dependent Calpain activation-mediated mitochondrial dysfunction and oxidative stress are required for cytotoxicity of Epinecidin-1 in human synovial sarcoma SW982 cells, *Int. J. Mol. Sci.* 21 (2020), <https://doi.org/10.3390/ijms21062109>.
- [136] G.S. Sarode, et al., Use of Tilapia Hepcidin in Oral Cancer therapeutics: a proposal, *J. Contemp. Dent. Pract.* 20 (2019) 403–404.
- [137] C. Wang, et al., Melanoma cell surface-expressed phosphatidylserine as a therapeutic target for cationic anticancer peptide, temporin-1CEa, *J. Drug Target.* 24 (2016) 548–556, <https://doi.org/10.3109/1061186x.2015.1113539>.
- [138] Q.Z. Yang, et al., Design of potent, non-toxic anticancer peptides based on the structure of the antimicrobial peptide, temporin-1CEa, *Arch. Pharm. Res.* 36 (2013) 1302–1310, <https://doi.org/10.1007/s12272-013-0112-8>.
- [139] Y. Du, Y. Yang, W. Zhang, C. Yang, P. Xu, Human  $\beta$ -defensin-3 and nuclear factor-kappa B p65 synergistically promote the cell proliferation and invasion of oral squamous cell carcinoma, *Transl. Oncol.* 27 (2023) 101582, <https://doi.org/10.1016/j.tranon.2022.101582>.
- [140] S.K. Ghosh, T.S. McCormick, A. Weinberg, Human Beta Defensins and Cancer: contradictions and common ground, *Front. Oncol.* 9 (2019) 341, <https://doi.org/10.3389/fonc.2019.00341>.
- [141] X. Liu, S.T. Henriques, D.J. Craik, L.Y. Chan, Unlocking the potential of the antimicrobial peptide Gomesin: from discovery and structure-activity relationships to therapeutic applications, *Int. J. Mol. Sci.* 24 (2023), <https://doi.org/10.3390/ijms24065893>.
- [142] S. Lu, et al., Tachyplesin I and its derivatives: a pharmaco-chemical perspective on their antimicrobial and antitumor potential, *Expert Opin. Drug Discov.* 17 (2022) 1407–1423, <https://doi.org/10.1080/17460441.2023.2157402>.
- [143] A.A. Baxter, I.K. Poon, M.D. Hulett, The plant defensin NaDT induces tumor cell death via a non-apoptotic, membranolytic process, *Cell Death Dis.* 3 (2017) 16102, <https://doi.org/10.1038/cddiscovery.2016.102>.
- [144] R.A. Ishkaeva, et al., A new triphenylphosphonium-conjugated amphiphatic cationic peptide with improved cell-penetrating and ROS-targeting properties, *Curr. Rese. Pharmacol. Drug Discov.* 4 (2023) 100148, <https://doi.org/10.1016/j.craphar.2022.100148>.
- [145] A.A. Baxter, et al., The tomato Defensin TPP3 binds phosphatidylinositol (4,5)-bisphosphate via a conserved dimeric cationic grip conformation to mediate cell lysis, *Mol. Cell. Biol.* 35 (2015) 1964–1978, <https://doi.org/10.1128/mcb.00282-15>.
- [146] J.H. Wong, T.B. Ng, Sesquin, a potent defensin-like antimicrobial peptide from ground beans with inhibitory activities toward tumor cells and HIV-1 reverse transcriptase, *Peptides* 26 (2005) 1120–1126, <https://doi.org/10.1016/j.peptides.2005.01.003>.
- [147] K.A.M. McMillan, M.R.P. Coombs, Review: examining the natural role of amphibian antimicrobial peptide magainin, *Molecules* (Basel, Switzerland) 25 (2020), <https://doi.org/10.3390/molecules25225436>.
- [148] A. Wang, et al., Melittin-based Nano-delivery systems for Cancer therapy, *Biomolecules* 12 (2022), <https://doi.org/10.3390/biom12010118>.
- [149] J. Qi, et al., Design and biological evaluation of novel BF-30 analogs for the treatment of malignant melanoma, *J. Cancer* 11 (2020) 7184–7195, <https://doi.org/10.7150/jca.47549>.
- [150] H.X. Wang, T.B. Ng, Isolation and characterization of an antifungal peptide with antiprofilar activity from seeds of Phaseolus vulgaris cv. ‘Spotted Bean’, *Appl. Microbiol. Biotechnol.* 74 (2007) 125–130, <https://doi.org/10.1007/s00253-006-0650-9>.
- [151] J.H. Wong, T.B. Ng, Lunatusin, a trypsin-stable antimicrobial peptide from lima beans (*Phaseolus lunatus* L.), *Peptides* 26 (2005) 2086–2092, <https://doi.org/10.1016/j.peptides.2005.03.004>.
- [152] H. Memariani, M. Memariani, Antibiofilm properties of cathelicidin LL-37: an in-depth review, *World J. Microbiol. Biotechnol.* 39 (2023) 99, <https://doi.org/10.1007/s11274-023-03545-z>.
- [153] A. Risso, et al., BMAP-28, an antibiotic peptide of innate immunity, induces cell death through opening of the mitochondrial permeability transition pore, *Mol. Cell. Biol.* 22 (2002) 1926–1935, <https://doi.org/10.1128/mcb.22.6.1926-1935.2002>.
- [154] Y. Hao, et al., A review of the design and modification of lactoferricins and their derivatives, *Biometal Int. J. Role Metal Ions Biol. Biochem. Med.* 31 (2018) 331–341, <https://doi.org/10.1007/s10534-018-0086-6>.
- [155] P. Koszalka, E. Kamysz, M. Wejda, W. Kamysz, J. Bigda, Antitumor activity of antimicrobial peptides against U937 histiocytic cell line, *Acta Biochim. Pol.* 58 (2011) 111–117.
- [156] A.N. Chernov, et al., Anticancer effect of cathelicidin LL-37, protegrin PG-1, nerve growth factor NGF, and temozolomide: impact on the mitochondrial metabolism, clonogenic potential, and migration of human U251 glioma cells, *Molecules* (Basel, Switzerland) 27 (2022), <https://doi.org/10.3390/molecules27154988>.
- [157] F. Huang, et al., Anticancer actions of Azurin and its derived peptide p28, *Protein J.* 39 (2020) 182–189, <https://doi.org/10.1007/s10930-020-09891-3>.
- [158] A.R. Garizo, et al., The Azurin-derived peptide CT-p19LC exhibits membrane-active properties and induces Cancer cell death, *Biomedicines* 9 (2021), <https://doi.org/10.3390/biomedicines9091194>.
- [159] N. Zhang, et al., Polypeptide-engineered DNA tetrahedrons for targeting treatment of colorectal cancer via apoptosis and autophagy, *J. Control. Release* 309 (2019) 48–58, <https://doi.org/10.1016/j.jconrel.2019.07.012>.
- [160] P. Maraming, et al., The cationic cell-penetrating KT2 peptide promotes cell membrane defects and apoptosis with autophagy inhibition in human HCT 116 colon cancer cells, *J. Cell. Physiol.* 234 (2019) 22116–22129, <https://doi.org/10.1002/jcp.28774>.
- [161] Y. Zhang, et al., BTapep-TAT peptide inhibits ADP-ribosylation of BORIS to induce DNA damage in cancer, *Mol. Cancer* 21 (2022) 158, <https://doi.org/10.1186/s12943-022-01621-w>.
- [162] M. Lichtenstein, et al., TAT for enzyme/protein delivery to restore or destroy cell activity in human diseases, *Life (Basel, Switzerland)* 11 (2021), <https://doi.org/10.3390/life11090924>.
- [163] Y.M. Kwon, et al., PTD-modified ATTEMPTS system for enhanced asparaginase therapy: a proof-of-concept investigation, *J. Control. Release* 130 (2008) 252–258, <https://doi.org/10.1016/j.jconrel.2008.06.017>.
- [164] C. Gao, et al., Pulmonary delivery of liposomes co-loaded with SN38 prodrug and curcumin for the treatment of lung cancer, *Eur. J. Pharm. Biopharm.* 179 (2022) 156–165, <https://doi.org/10.1016/j.ejpb.2022.08.021>.
- [165] M.C. Shin, et al., PTD-modified ATTEMPTS for enhanced toxin-based Cancer therapy: An in vivo proof-of-concept study, *Pharm. Res.* 32 (2015) 2690–2703, <https://doi.org/10.1007/s11095-015-1653-y>.
- [166] M. Li, et al., Knockdown of hypoxia-inducible factor-1 alpha by tumor targeted delivery of CRISPR/Cas9 system suppressed the metastasis of pancreatic cancer, *J. Control. Release* 304 (2019) 204–215, <https://doi.org/10.1016/j.jconrel.2019.05.019>.
- [167] Y. He, et al., Near-infrared boosted ROS responsive siRNA delivery and cancer therapy with sequentially peeled upconversion nano-onions, *Biomaterials* 225 (2019) 119501, <https://doi.org/10.1016/j.biomaterials.2019.119501>.
- [168] R. Mahmoudi, et al., RGD peptide-mediated liposomal curcumin targeted delivery to breast cancer cells, *J. Biomater. Appl.* 35 (2021) 743–753, <https://doi.org/10.1177/0885328220949367>.
- [169] P. Lingasamy, et al., Tumor-penetrating peptide for systemic targeting of tenascin-C, *Sci. Rep.* 10 (2020) 5809, <https://doi.org/10.1038/s41598-020-62760-y>.
- [170] A.A.P. Tripodi, et al., In vivo tumor growth inhibition and antiangiogenic effect of cyclic NGR peptide-Daunorubicin conjugates developed for targeted drug delivery, *Pathol. Oncol. Res.* 26 (2020) 1879–1892, <https://doi.org/10.1007/s12253-019-00773-3>.
- [171] C. Zhang, et al., Enzyme-responsive peptide dendrimer-gemcitabine conjugate as a controlled-release drug delivery vehicle with enhanced antitumor efficacy, *Acta Biomater.* 55 (2017) 153–162, <https://doi.org/10.1016/j.actbio.2017.02.047>.
- [172] Y. Wang, et al., Fibronectin-targeting and Cathepsin B-Activatable Theranostic Nanoprobe for MR/fluorescence imaging and enhanced photodynamic therapy for triple negative breast Cancer, *ACS Appl. Mater. Interfaces* 12 (2020) 33564–33574, <https://doi.org/10.1021/acsami.0c10397>.
- [173] J. Wang, et al., DOX-loaded peptide dendritic copolymer nanoparticles for combating multidrug resistance by regulating the lysosomal pathway of apoptosis in breast cancer cells, *J. Mater. Chem. B* 8 (2020) 1157–1170, <https://doi.org/10.1039/c9tb02130b>.
- [174] L.E. Dókusz, et al., Phage display-based homing peptide-Daunomycin conjugates for selective drug targeting to PANC-1 pancreatic Cancer, *Pharmaceutics* 12 (2020), <https://doi.org/10.3390/pharmaceutics12060576>.
- [175] J. Huang, et al., Core-Shell distinct Nanodrug showing on-demand sequential drug release to act on multiple cell types for synergistic anticancer therapy, *ACS Nano* 13 (2019) 7036–7049, <https://doi.org/10.1021/acsnano.9b02149>.
- [176] W. Huang, et al., pH- and photothermal-driven multistage delivery nanoplateform for overcoming cancer drug resistance, *Theranostics* 9 (2019) 3825–3839, <https://doi.org/10.7150/thno.33958>.
- [177] H. Han, et al., Metformin-induced stromal depletion to enhance the penetration of gemcitabine-loaded magnetic nanoparticles for pancreatic Cancer targeted therapy, *J. Am. Chem. Soc.* 142 (2020) 4944–4954, <https://doi.org/10.1021/jacs.0c00650>.
- [178] M. DuPont, et al., Tumor treatment by pHLIP-targeted antigen delivery, *Front. Bioeng. Biotechnol.* 10 (2022) 1082290, <https://doi.org/10.3389/fbioe.2022.1082290>.
- [179] T. Dube, S. Mandal, J.J. Panda, Nanoparticles generated from a tryptophan derivative: physical characterization and anti-cancer drug delivery, *Amino Acids* 49 (2017) 975–993, <https://doi.org/10.1007/s00226-017-2403-8>.
- [180] Y. Sun, et al., Self-assembly of a 5-fluorouracil-dipeptide hydrogel, *Chem. Commun. (Camb.)* 52 (2016) 5254–5257, <https://doi.org/10.1039/c6cc01195k>.
- [181] P.K. Singh, S. Chibh, T. Dube, V.S. Chauhan, J.J. Panda, Arginine- $\alpha$ ,  $\beta$ -dehydrophenylalanine dipeptide nanoparticles for pH-responsive drug delivery, *Pharm. Res.* 35 (2018) 35, <https://doi.org/10.1007/s11095-017-2299-8>.
- [182] Z. Fan, L. Sun, Y. Huang, Y. Wang, M. Zhang, Bioinspired fluorescent dipeptide nanoparticles for targeted cancer cell imaging and real-time monitoring of drug release, *Nat. Nanotechnol.* 11 (2016) 388–394, <https://doi.org/10.1038/nnano.2015.312>.
- [183] P. Moitra, K. Kumar, P. Kondaiah, S. Bhattacharya, Efficacious anticancer drug delivery mediated by a pH-sensitive self-assembly of a conserved tripeptide derived from tyrosine kinase NGF receptor, *Angew. Chem. Int. Ed. Eng.* 53 (2014) 1113–1117, <https://doi.org/10.1002/anie.201307247>.
- [184] K. Basu, et al., Peptide based hydrogels for cancer drug release: modulation of stiffness, drug release and proteolytic stability of hydrogels by incorporating d-amino acid residue(s), *Chem. Commun. (Camb.)* 52 (2016) 5045–5048, <https://doi.org/10.1039/c6cc01744d>.

- [185] E. Parisi, A.M. Garcia, D. Marson, P. Posocco, S. Marchesan, Supramolecular tripeptide hydrogel assembly with 5-fluorouracil, *Gels* (Basel, Switzerland) 5 (2019), <https://doi.org/10.3390/gels5010005>.
- [186] Z. Chen, J. Deng, Y. Zhao, T. Tao, Cyclic RGD peptide-modified liposomal drug delivery system: enhanced cellular uptake in vitro and improved pharmacokinetics in rats, *Int. J. Nanomedicine* 7 (2012) 3803–3811, <https://doi.org/10.2147/ijn.S33541>.
- [187] F. Wang, L. Chen, R. Zhang, Z. Chen, L. Zhu, RGD peptide conjugated liposomal drug delivery system for enhance therapeutic efficacy in treating bone metastasis from prostate cancer, *J. Control. Release* 196 (2014) 222–233, <https://doi.org/10.1016/j.jconrel.2014.10.012>.
- [188] L. Battistini, et al., Enhancement of the uptake and cytotoxic activity of doxorubicin in cancer cells by novel cRGD-semipeptide-anchoring liposomes, *Mol. Pharm.* 11 (2014) 2280–2293, <https://doi.org/10.1021/mp400718j>.
- [189] H. Li, D. Yuan, M. Sun, Q. Ping, Effect of ligand density and PEG modification on octreotide-targeted liposome via somatostatin receptor in vitro and in vivo, *Drug Deliv.* 23 (2016) 3562–3572, <https://doi.org/10.1080/10717544.2016.1209797>.
- [190] Y. Koguchi, et al., Serum Immunoregulatory proteins as predictors of overall survival of metastatic melanoma patients treated with Ipilimumab, *Cancer Res.* 75 (2015) 5084–5092, <https://doi.org/10.1158/0008-5472.Can-15-2303>.
- [191] A. Larocca, et al., Patient-reported outcomes in relapsed/refractory multiple myeloma treated with melphalan plus dexamethasone: analyses from the phase II HORIZON study, *Br. J. Haematol.* 196 (2022) 639–648, <https://doi.org/10.1111/bjh.17887>.
- [192] P. Kumthekar, et al., ANG1005, a brain-penetrating peptide-drug conjugate, shows activity in patients with breast cancer with leptomeningeal carcinomatosis and recurrent brain metastases, *Clin. Cancer Res.* 26 (2020) 2789–2799, <https://doi.org/10.1158/1078-0432.Ccr-19-3258>.