


# Research Progress Evaluating the Function and Mechanism of Anti-Tumor Peptides

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**Abstract:** Malignant tumors cause a high mortality rate worldwide, and they severely threaten human health and negatively affect the economy. Despite the advancements in tumor-related molecular genetics and effective new processes in anti-tumor drug development, the anti-tumor drugs currently used in clinical practice are inadequate due to their poor efficacy or severe side effects. Therefore, developing new safe and efficient drugs is a top priority for curing cancer. The peptide has become a suitable agent due to its exact molecular weight between whole protein and small molecule, and it has high targeting ability, high penetrability, low immunogenicity, and is convenient to synthesize and easy to modify. Because of these advantages, peptides have excellent prospect for application as anti-tumor agents. This article reviews the recent research progress evaluating anti-tumor peptides and their anti-tumor mechanisms, and may act as a reference for the future development and clinical application of anti-tumor peptides.

**Keywords:** anti-cancer, small biomolecule, medicine, drug development

## Introduction

According to the latest cancer statistics of the International Agency for Research on Cancer, in 2018, there were an estimated 18.1 million new cancer cases and 9.6 million cancer deaths worldwide.<sup>1</sup> Cancer severely threatens human health and decreases life expectancy, and it has become one of the most important public health problems in every country of the world in the 21st century.

Although the conventional anti-tumor drugs currently in use are multitudinous, their therapeutic effect remains unsatisfactory and could not meet clinical requirements. In addition, drug resistance, biological distribution change, biological transformation and drug clearance are currently common problems in cancer treatment. It has become clear that there is still an impending need for more effective anti-tumor candidate molecules with less side effects.

With an increasing number of protein receptors, peptide receptors, and protein-related signaling pathways that have been discovered, tumor-related peptides may lead to a surge of newly developed anti-tumor drugs. In addition, peptide-based anti-tumor drugs possess many exclusive advantages. Due to their small molecular weight, anti-cancer peptides can effectively spread through tissues or easily cross biological barriers that macromolecule-like mono-antibodies cannot cross. Because peptide therapeutics are not dependent on flow pumps, it is less likely that drug resistance will be encountered with their use compared with DNA alkylating agents. Peptides possess excellent clinical safety because their biocompatibility

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profile is superior to chemical compounds. Their degradation products are amino acids, which are natural entities that are used as nutrients or cellular building blocks. Peptides naturally participate in immune regulation and are more synergistic with the body's immune system compared with common hormone agonists/antagonists. Theoretically, peptides can act precisely on any specified interaction site, and thus, are stronger targets than anti-metabolites. Additionally, there are rich sources of anti-tumor peptides, and they have the superiority of ease of acquisition, low preparation cost, and simple modification, which enables large-scale clinical applications.

## Definition of Anti-Tumor Peptides

A peptide is a compound consisting of two or more  $\alpha$ -amino acids joined together by a peptide bond. When 2 to 100 amino acids are joined, it is commonly called a polypeptide. Peptides participate in almost all cellular activities and are closely related to immune regulation,<sup>2,3</sup> neurohormone transmitter regulation,<sup>4,5</sup> and tumor lesions.<sup>6,7</sup> From the point of view of clinical indications, different types of peptides are associated with different diseases, such as endocrine diseases, diabetes and tumors, among which peptides with specific anti-tumor activity are what we call "anti-tumor peptides".<sup>8</sup>

Anti-tumor peptides are specifically applied in the field of cancer therapy. They are usually positively charged, with high hydrophobicity and strong penetrability. Compared with ordinary chemotherapy drugs, they are more specific to tumor cells and can affect host immunity through a variety of mechanisms to destroy various cancers.

## Sources of Anti-Tumor Peptides

Peptides from various sources have been found to have anti-tumor effects (Table 1).

### Naturally Existing Peptides

Peptides with anti-tumor activity are widely found in animals, plants, and microorganisms in nature. An example is the main composition of bee venom. The bee venom peptide (GIGAVLKVLTGTPALISWIKRKRQQ) has a therapeutic effect on a variety of cancers, including breast cancer, ovarian cancer, prostate cancer, and melanoma.<sup>38</sup> Two tripeptides extracted from pig spleen, Tyr-Ser-Leu (YSL) and Tyr-Ser-Val (YSV), play an important role in human liver cancer cells.<sup>39,40</sup> The natural cyclic peptide RA-V extracted from the medicinal plant *Ormosia yunnanensis* Prain can induce mitochondrially

mediated apoptosis by blocking pdk1-akt interaction, thus killing human breast cancer cells.<sup>41</sup> A fungal metabolite, apicidin(cyclo(N-O-methyl-L-tryptophanyl-L-isoleucinyl-D-pipecolinyl-L-2-amino-8-oxodecanoyl)), can inhibit the proliferation of eight tumor cell lines, including the human cervical cancer cell line HeLa, human breast cancer cell line MCF-7, and human gastric adenocarcinoma cell line HBL-100.<sup>42</sup>

## Peptides Obtained from a Combined Library

The combinatorial peptide libraries used to screen anti-tumor peptides can be divided into two categories: biological libraries and chemical libraries. The biological library contains DNA sequences encoding peptides, whose composition determines the abundance of the peptide sequences in the library. A typical example of this genotypic-phenotypic peptide library is the phage display library, which is also the most commonly used. Other types of biological libraries include bacteria, ribosomes, mRNAs, yeast, cDNA, retrovirus, baculovirus, and mammalian cell display libraries, but are not commonly used. Among the various types of chemical libraries, the one-bead-one-compound (OBOC) library and the positional scanning-synthetic peptide combinatorial library (PS-SPCL) are commonly used to screen anti-tumor peptides. The phage display library, OBOC library, and PS-SPCL are briefly described below.

(A) Phage display technology was first proposed by George Smith in 1985.<sup>43</sup> He found that after cloning the DNA sequence encoding the unique peptide into the phage genome, the phage's shell protein would display the peptide encoded by foreign DNA. According to the principle of molecular interaction, target ligand peptides can be screened from a phage library. This technology has been successfully used in ligand receptor interaction detection, affinity characterization, high affinity protein/peptide separation, epitope mapping, drug discovery, and other fields.

A variety of phage display peptide libraries have since been established, and many anti-tumor peptides have been separately identified. For example, a specific gastric cancer multi-drug resistant (MDR) cell-specific binding peptide, ETAPLSTMLSPY, was screened by a phage display. It can combine with MDR gastric cancer cells and reverse their MDR phenotype.<sup>44</sup> As another example, Li isolated a synthetic peptide (CTPSPFSHC) with the ability to bind to colorectal cancer tissue that is 11–94 times higher than that of other tissues by using an in vivo phage library, and

**Table 1** Diverse Sources of Anti-Tumor Peptides

Name	Amino Acid Sequence	Source	Mechanism of Action	References
LfcinB	FKCRRWQWRMKKLGAPSITCVRRAF	Cow milk	Halts cells in the S phase	[9]
–	KPEGMDPPLSEPEDRRDGAAGPK	Tuna cookingjuice	Induces cell cycle arrest in S phase	[10]
–	HVLSRAPR	Spirulina platensis	Anti-proliferation	[11]
–	FIMGPY	Raja porosa	Induces apoptosis	[12]
–	GLTSK	Common bean	Inhibits cell growth, modifies the expression of cell cycle regulatory proteins	[13]
MPI	IDWKLLDAAKQIL	Polybiapadista	Destroys membrane	[14]
KahalalideF	A cyclic depsipeptide	Marine mollusks	Interferes with lysosomal function	[15]
Alloferon 1	HGVSGHGQHGVBHG	Calliphora vicina	Stimulates cytotoxic activity of natural killer cells	[16]
Alloferon 2	GVSFGHGQHGVBHG	Calliphora vicina	Stimulates cytotoxic activity of natural killer cells	[16]
TsAP-1	FLSLIPSLVGGISAFK	Brazilian yellow scorpion	Destroys cell membrane	[17]
TsAP-2	FLGMIPGLIGGLISAFK	Brazilian yellow scorpion	Destroys cell membrane	[17]
MiniCTX3	A monocyclic lactam-bridge peptide	Scorpion venom	Destroys cell membrane	[18]
Melittin	GIGAVLKVLTGLPALISWIKRKRQQ	European honeybee	Destroys cell membrane	[19]
Aurein 1.2	GLFDIIKKIAESF	Australian bell frog	Destroys cell membrane	[20]
SALF	ECKFTVKPYLKRFRQVYYKGRMWCP	Black tiger shrimp	Destroys cell membrane	[21]
Polybia-MPI	IDWKLLDAAKQIL	Wasp	Destroys cell membrane	[22]
LL-37	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLPRTES	Human	Activates P53-mediated cascade of caspase-free apoptosis	[23]
CPI 5	VHLGYAT	Phage display peptides library	Possesses strong affinity for intestinal cancer cells	[24]
VP2	GFRFGALHEYNS	Phage display peptides library	Binds to VPAC1 receptor	[25]
F56	WHSDMEWYLLG	Phage display peptides library	Competitively inhibits the binding of VEGFA to Flk-1, thereby inhibiting lung cancer angiogenesis	[26]
–	HTMYHHYYQHHL	Phage display peptides library	Competes with KDR to interfere with the binding of VEGF to KDR, thereby inhibiting lung cancer angiogenesis	[27]
HTP	GPTAKYI	Phage display peptides library	Hepatic stellate cells-penetrating peptide	[28]

(Continued)

**Table 1** (Continued).

Name	Amino Acid Sequence	Source	Mechanism of Action	References
Peptide I-N $\Delta$	TCTWLKYHS	mRNA display random peptide library.	Targets glioblastoma multiforme	[29]
BPI6	KKLFKKILKKL-NH <sub>2</sub>	Library of cecropin-melittin hybrids (CECMELI I)	Clathrin dependent endocytosis	[30]
–	VPEYINQ	Artificial synthesis	Inhibits site auto phosphorylation caused by EGFR dimerization	[31]
–	DYQQD	Artificial synthesis	Inhibits site auto phosphorylation caused by EGFR dimerization	[31]
Elisidepsin	A cyclic depsipeptide	Artificial synthesis	Interferes with lysosomal function	[32]
CB1a	KWKVFKKIEK- KWKVFKKIEK-AGP KWKVFKKIEK-NH <sub>2</sub>	Artificial synthesis	Arrests cell cycle	[33]
CREKA	CREKA	Artificial synthesis	Binds to fibrin-fibronectin complexes	[34]
Mca <sub>UF1-9</sub>	GDCLPHLKL	Artificial synthesis	Penetrates cell membrane	[35]
TP-LYT	LTVSPWY-GG-KLAKLAKLAKLAK	Artificial synthesis	Destroys membrane	[36]
MTD	KLLNLISKLF	Artificial synthesis	Induces necrosis	[37]

demonstrated the tumor homing ability of this peptide.<sup>45</sup> Li identified an epidermal growth factor receptor (EGFR)-specific binding peptide GE11 (YHWYGYTPQNVI) from a phage display peptide library.<sup>46</sup> In the H1299 xenograft mouse model, GE11 liposomes showed good tumor targeting and drug delivery ability.<sup>47</sup>

(B) The OBOC library is a compound peptide library constructed by solid phase synthesis on beads 80–100  $\mu$ m, and its split-mix strategy was first described by Lam.<sup>48</sup> Construction of easy linear  $\alpha$ -amino acid libraries can be accomplished using standard solid-phase peptide chemical synthesis. Construction of complex peptide libraries such as cyclic peptides, branched-chain peptides, or peptides containing  $\beta$  or  $\gamma$ -amino acids requires adding specific tags to the bead structure.

APN is a cell membrane protein that plays a key role in tumor angiogenesis. Wang reported that AP-1 (YVEYHLC), a peptide with high affinity and specificity for APN, was screened by an OBOC combination peptide library.<sup>49</sup> In vitro and in vivo optical imaging showed AP-1 accumulation in the tumor tissues of a xenograft mouse model of HepG2 liver cancer. Similarly, using OBOC library screening, Zhang

identified a cyclic peptide of PLZ4 that specifically recognized and combined with human bladder cancer cells, and this specificity was demonstrated in mouse bladder cancer xenograft models.<sup>50</sup> Xiao screened a cyclic peptide composed of nine amino acids named LXY30 and confirmed its tumor targeting by combining it with SKOV3 cells and clinical ovarian tumor tissues in vitro.<sup>51</sup>

(C) Positional scanning combinatorial synthesis of peptides (PS-SPCLs) has become a useful tool in recent years for cancer drug research, vaccine development, and protease research. In this research, many subset libraries are built, and each offshoot peptide set in the library maintains a designated site of amino acids that are changeless. The rest of the amino acids change, and then, the performance of the members of each subset is tested to identify the amino acid in designed sites with the highest activity. Bae identified a peptide anti-Flt1 (GNQWFI) from PS-SPCLs that blocks vascular endothelial growth factor (VEGF)-induced endothelial cell migration and angiogenesis in vitro and inhibits VEGF-secreted cancer cell growth and metastasis in vivo.<sup>52</sup> Denholt identified a peptide H-FALGEA-NH with high EGFRvIII specificity, and it is expected to be used in the

diagnosis and treatment of ovarian cancer, glioblastoma, and breast cancer with high EGFRvIII expression.<sup>53</sup>

## Artificial Synthesis

Merrifield has made an outstanding contribution to the field of peptide synthesis by creating and developing a feasible method for the solid-phase synthesis of peptides.<sup>54</sup> The principle of solid-phase synthesis is that the N-terminal of the first amino acid is linked to the resin, and then, amino acids are added to the peptide chain in a known sequence. In order to prevent side reactions, the amino acid side chains are protected throughout the reaction.

Anginex is an artificially designed peptide based on the sequence of several types of anti-angiogenesis proteins (including platelet factor 4 and interleukin-8). It is proven to block the growth of endothelial cells by combining with galactose clotting protein-1, thereby exerting strong anti-angiogenesis activity to inhibit tumor development.<sup>55</sup> The expression of YAP is significantly upregulated in gastric cancer, and VGLL4 is a natural antagonistic protein of YAP by competitively binding TEAD4. Jiao found that VGLL4's Tandu (TDU) domains are not only essential but also sufficient for its antagonism toward YAP. Thus they synthesized artificially a peptide called "Super-TDU" that can effectively hinder the progress of gastric cancer.<sup>56</sup> Li determined that the gN spiral domains played an important role in FGF8b uniting its receptors by analyzing the FGF8b-FGFR structure.<sup>57</sup> Therefore, a short gN spiral peptide 8b-13 (PNFTQHVREQLV) was fabricated, and in vitro experiments confirmed that the peptide inhibited prostate cancer cell (such as PC-3, DU-145) proliferation by interfering with the function of FGF8b.

## Mechanisms of Anti-Tumor Peptides

Peptides participate in all processes of life activities, and thus, they can assume anti-tumor roles in various aspects through a variety of ways, such as preventing the translation of genetic information, affecting energy metabolism, regulating immunity, and inhibiting tumor angiogenesis. The most important molecular mechanisms by which peptides exert their anti-tumor function are reviewed below (Figure 1).

## Competitively Bind to the Targets of Precursor Proteins and Prevent Protein-Protein Interactions

The cell-penetrating peptide RT53 derived from AAC-11 can partially mimic the leucine repeat region of AAC-11,

and then it reduces the generation of the endogenous AAC-11-Acinus complex and blocks the anti-apoptotic properties of AAC-11.<sup>58</sup> Su found a new peptide, S7, that selectively binds to the interleukin (IL)-6 receptor gp80 and thus negatively regulates the IL-6 signaling pathway and reduces the IL-6 mediated occurrence and development of cervical cancer.<sup>59</sup>

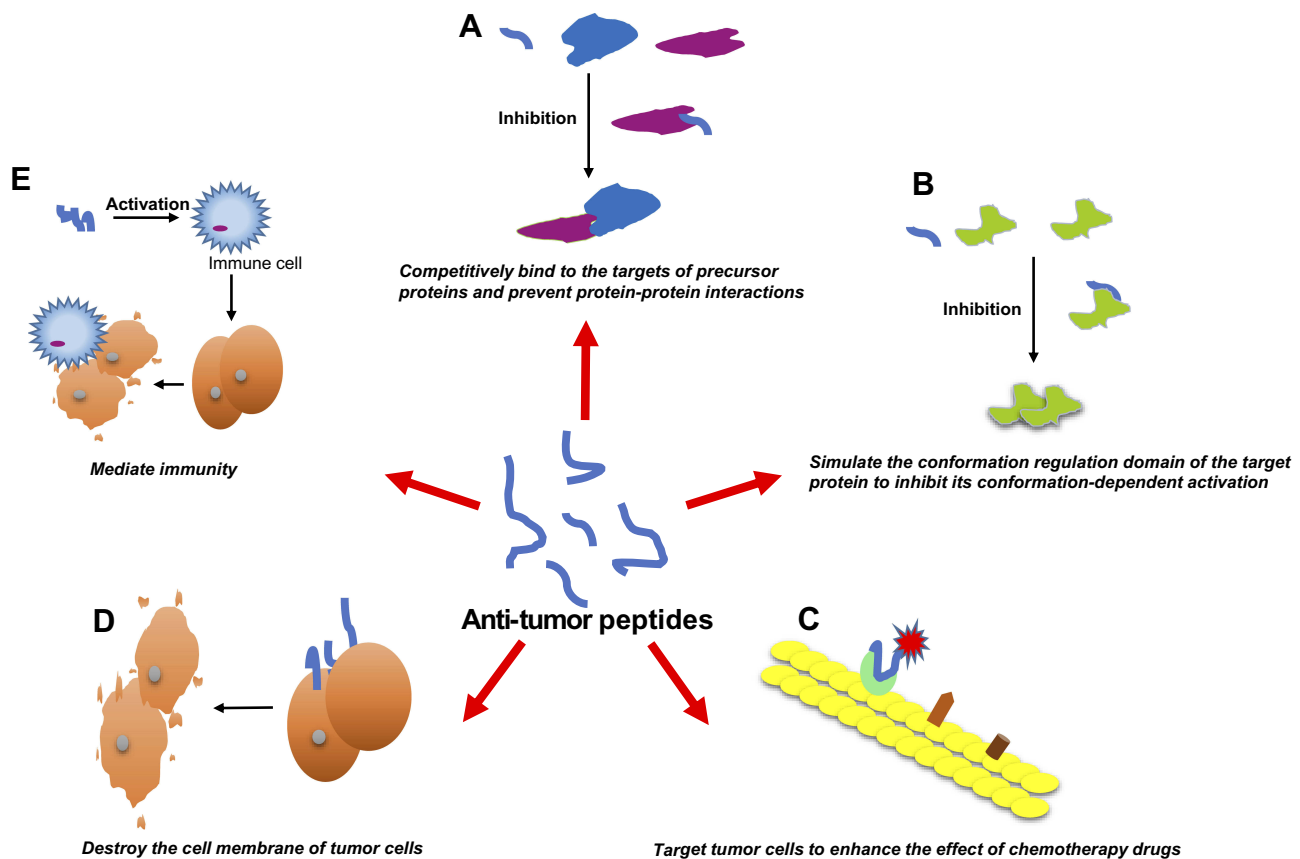
The signaling pathway of  $\beta$ -catenin/LEF-1 plays an important role in tumor formation and evolution. The peptide BLBD synthesized by Hsieh can competitively bind to  $\beta$ -catenin with LEF-1 to interfere with the  $\beta$ -catenin/LEF-1 pathway, inhibiting growth, invasion, migration, and colony formation of breast cancer cells.<sup>60</sup> The WASF3-CYFIP1 activated complex can promote actin cytoskeleton recombination, leading to the invasion and metastasis of cancer cells. The peptide WAHM synthesized by Yong has a high affinity for CYFIP1, which can prevent the formation of the WASF3-CYFIP1 complex.<sup>61</sup>

## Simulate the Conformation Regulation Domain of the Target Protein to Inhibit Its Conformation-Dependent Activation

The activation of many proteins depends on conformational changes such as dimerization and isomerization. Therefore, peptides homologous to the conformational regulatory domain sequences of target proteins can be used as analogues to bind and aggregate with the target proteins and inactivate them. For example, previous studies have shown that the dimerization status of ErbB2, one of the ErbB family members, can trigger the MAPK and PI3K/Akt pathways, which are closely related to breast cancer progression, and this dimerization process is dependent on the transmembrane domain of normal ErbB2. Arpel subsequently designed a peptide that imitates the natural transmembrane domain of ErbB2 to block the dimerization reaction of ErbB2, and demonstrated the anti-cancer properties of this peptide when it was used in micromolar doses in a mouse tumor transplantation model.<sup>62</sup>

Soragni found that high-grade serous ovarian carcinoma (HGSOC) development was associated with p53 protein forming itself into an amyloid structure. Thus, he designed and synthesized a peptide named ReACp53, which can mask the 252–258 loci in the p53 protein's adhesion region to restrain amyloid accumulation and preserve the function of p53.<sup>63</sup> Moreover, intraperitoneal administration of ReACp53 was proved to shrink the





**Figure 1** Anti-tumor peptides can function through a variety of mechanisms. Anti-tumor peptides may function through several mechanisms: **(A)** Competitively bind to the targets of precursor proteins and prevent protein-protein interactions; **(B)** Simulate the conformation regulation domain of the target protein to inhibit its conformation-dependent activation; **(C)** Target tumor cells to enhance the effect of chemotherapy drugs; **(D)** Destroy the cell membrane of tumor cells; **(E)** Mediate immunity.

peritoneal metastases in a mouse HGSOc xenotransplantation model.

NRP1 is a VEGF165 receptor, an important regulatory element of angiogenesis and tumor metastasis. Nasarre found that NRP1 has a GxxxG dimer motif that is necessary to trigger effective signal transmission in its transmembrane domain. On this basis, they designed a peptide to target the transmembrane sequence and inhibit NRP1 oligomerization. The experimental results showed that the synthetic peptide can prevent the subsequent biological function of NRP1 and act antagonistically in VEGF-dependent cell migration and cell proliferation.<sup>64</sup>

## Target Tumor Cells to Enhance the Effect of Chemotherapy Drugs

The target polypeptide is a brand-new type of target carrier, like those such as nanoparticles and liposomes. The polypeptide carrier can directly position the loaded drug on the surface of the cell membrane receptor to exert pharmacological effect.

There is increased expression of membrane heat shock protein 70 (memHSP70) in breast cancer cells, which is significantly different from normal breast cells. Meng designed a memHSP70-targeted peptide called TKD according to the structural domain of memHSP70. The uptake of doxorubicin (DOX) modified with TKD was significantly increased in memHSP70-positive breast cancer cell lines in vitro.<sup>65</sup> Similarly, the erbB2-targeted peptide LTVSPWY can enhance the proapoptotic effect of the vitamin E analogue  $\alpha$ -TOS on erbB2-positive breast cancer cells.<sup>66</sup> The  $\alpha$ -enolase ligand peptide pHCT74 can target human colorectal cancer cells with high expression of  $\alpha$ -enolase, and it can enhance the efficacy of anti-tumor drugs such as DOX and vinorelbine.<sup>67</sup>

Another exciting example is BT1718, which is a drug-binding peptide that has been initiated in Phase I/II clinical trials for advanced solid tumors. It specifically binds to overexpressed MMP14 in tumors, thereby enhancing drug targeting and penetration into tumors.<sup>68</sup>

## Destroy the Cell Membrane of Tumor Cells

Some peptides are positively charged and can be folded or bent to form a special membrane structure, so as to dissolve the cancer cell membrane or form holes on the surface of the cell membrane, and then kill the tumor by lysing cells. A typical example is cell-penetrating peptide SVS-1, which is a small anti-cancer peptide. Due to the different lipid composition and electronegativity characteristics between tumor cells and normal cells on the cell membrane surface, SVS-1 only drives its own  $\beta$ -folding on the tumor cell surface, where it subsequently forms pores to destroy the cell membrane. Through this process, SVS-1 can kill A549 lung cancer, MCF-7 breast cancer, and other cell lines.<sup>69</sup>

## Mediate Immunity

Polypeptides play an important role in the immune regulation of our body. Many polypeptides can kill tumor cells by activating the body's own immune system and achieve the goal of curing cancer.

Alloferons, a group of peptides with anti-virus and anti-tumor activity, were primarily isolated from the hemolymph of insects after bacterial infection. Both alloferon-1 and alloferon-2 can stimulate cytotoxic activity of natural killer cells in mammals, including mice and humans. Alloferon-1 monotherapy showed moderate tumor suppressor and tumoricidal activity comparable to low dose chemotherapy in a mouse tumor transplantation model.<sup>70</sup>

In addition to naturally occurring immunoregulatory peptides, scientists are also trying to identify potential immunogenic peptides, for example, peptides containing MHC1 mutations could be immunogenic, as they should be recognized as "non-self" neo-antigens by the adaptive immune system. On this basis, Yadav conducted an approach that combines whole-exome and transcriptome sequencing analysis with mass spectrometry, and two mutant peptides that can induce a T cell immune response in vivo were identified: AQL[P/A]NDVVL and ASMTN[R/M]ELM.<sup>71</sup>

In recent years, due to the development of biotechnology, a variety of tumor peptide vaccines also show a strong momentum of development. Thoman constructed a series of lipid ErbB2/HER2 epitope peptide vaccines against ErbB2 protein-expressing tumor cells.<sup>72</sup> Granadillo designed a novel fusion protein vaccine by combining an immune-stimulating peptide LALF (32–51) with HPV 16 E7 antigen, which significantly improved

the presentation of E7-derived peptides to T-cells in a preclinical model.<sup>73</sup>

## Research Progress in the Processing and Modification of Anti-Tumor Peptides

Natural peptides are usually not suitable for direct application as drugs because they have inherent weaknesses, including poor chemical or physical stability, easy hydrolysis, and low concentration in tumors. Therefore, artificial modification of peptides is usually necessary to improve the physicochemical properties of peptide compounds. Chemical modification optimizes the original peptides with higher biological activity and lower immunogenicity and toxicity, and confers new desirable properties such as high targeting and excellent stability. The traditional modification methods are mainly based on the structure-activity relationship to change the main chain structure or side chain groups of the peptide to optimize the structural stability and physicochemical properties. Some common peptide modification methods are described below.

### Polyethylene Glycol (PEG) Modification

PEG modification refers to covalent coupling of biomolecules with PEG, which is a non-toxic, non-immunogenic, non-ionic polymer that possesses excellent properties of biocompatibility, biodegradability, and hydrophilicity. It is often applied in biopharmaceutical transformation to increase the size and molecular weight, improve the solubility, and reduce the immunogenicity. Moreover, PEG can increase the stability of the drug, reduce protein hydrolysis and renal excretion, and lengthen the retention time of the conjugate in the blood, thereby reducing the dose frequency.

### Amino Acid Substitution Modification

Lycosin-I is an anti-cancer peptide extracted from spiders that can activate the mitochondrial death pathway to induce tumor cell apoptosis, but the peptide's application was limited due to its low permeability in solid tumors. Zhang thus designed and synthesized arginine-modified lycosin-I (R-lycosin-I) by substituting arginine for lysine. Fluorescence analysis showed that the modified peptide significantly increased the uptake rate.<sup>74</sup>

The response of T cells to antigenic epitopes is influenced not only by their own affinity for the presented

major histocompatibility complex (MHC) molecule but also by the affinity of the MHC-epitope complex for the T cell receptor (TCR). AH1 (SPSYVYHQF) is a specific tumor antigen peptide extracted from gp70, which is the main target of CD8 T cells in response to CT26 colorectal cancer, but its affinity for the TCR is weak. Slansky replaced the proline with alanine at position 5 of the AH1 peptide, which increased the affinity of the MHC peptide for TCR. Thus the modified peptide can more automatically activate the recognition by T cells, and thereby enhance systemic anti-tumor immunity.<sup>75</sup>

Kohno combined an EGFR-binding peptide with a newly designed cellular lytic peptide rich in cationic amino acids that can break down cell membranes and kill cancer cells, resulting in an EGFR-targeted hybrid peptide.<sup>76</sup> In order to enhance the cytotoxic effect of this EGFR-lytic peptide on EGFR-positive tumor cells, based on analysis of biomolecular interaction and biophysical circular dichroism spectroscopy, they replaced histidine at the second site with arginine, and the cytotoxic activity of the modified hybrid peptide was 1.2–1.9 times that of the original.<sup>77</sup>

## Cyclization Modification

Peptide drugs usually are degraded by enzymes in the digestive tract and have low bioavailability when taken orally. By cyclization, the cleavable N- and C-termini can be removed, the enzyme recognition site can be changed, and the degradation of peptides in the intestine, blood, and tissues can be reduced, thereby increasing the oral bioavailability degree.

The  $\alpha_v\beta_3$  integrin receptor plays an important role in human tumor metastasis and tumor-induced angiogenesis, and the Arg-Gly-Asp (RGD) peptide can antagonize the function of the receptor. The FITC-conjugated cyclic RGD peptides are as effective as the fluorescence-labeled anti-integrin  $\beta_3$  antibody, and they can be used as fluorescent probes for staining integrin  $\alpha_v\beta_3/\alpha_v\beta_5$  in Tumor Tissues.<sup>78</sup> Moreover, Cyclic RGD peptide-modified liposomes may provide a targeted delivery system for apatinib in the treatment of colonic cancer.<sup>79</sup>

Gomesin is a dithiol-rich anti-microbial peptide derived from the Brazilian tarantula *Acanthoscurria gomesiana* and has been shown to have selective anti-cancer effects on melanoma cells. Henriques increased the anti-bacterial activity of gomesin 10 fold by designing circular gomesin analogues, which meanwhile increased the sensitivity and membrane binding affinity of the peptide to cancer cells.<sup>80</sup>

## Fluorescence (FAM, FITC, TAMRA, CY) or Isotopic Labeling

The EPPT1 peptide can target the cell transmembrane underglycosylated MUC-1, which is overexpressed in colorectal cancer cells. After EPPT1 is fluorescently tagged, it can be used as a detection marker for malignant tissues in colorectal cancer after luminal instillation.<sup>81</sup> CN-peptide and its analog-derived peptides (NS3)(CN-AVP) have strong specific recognition and ability to bind to the small cell lung cancer cell line H69. It is expected that labeling these peptides with <sup>99m</sup>Tc may be an ideal diagnostic radiopharmaceutical.<sup>82</sup> Samit developed a peptide WL12 that specifically binds to PD-L1, and found that <sup>64</sup>Cu-labeled WL12 can trace the expression of tumor PD-L1 to estimate tumor response to PD-1 or PD-L1 targeted therapy.<sup>83</sup>

## Clinical Application of Anti-Tumor Peptides

Due to the many superior qualities of peptides mentioned above, there has been great activity in the development of peptides as anti-tumor drugs. In the past decade, an increasing number of peptide anti-tumor drugs have entered the market or have been tested in clinical trials. For example, gonadotropin-releasing hormone (GnRH) analog Lupron<sup>®</sup> (Abbott Laboratories, Chicago, Illinois, the USA), which is used to treat diseases such as prostate cancer, had global sales of more than \$2 billion in 2011.<sup>84</sup> A search of the US National Institutes of Health database ClinicalTrials.gov (<https://clinicaltrials.gov/>) using the phrase “anticancer peptides” performed in November 2019 found 1002 peptide-based clinical trials that target different types of cancer. As of Nov 2019, more than 20 anti-tumor peptides have been approved by the FDA and the EMA (Table 2).

Peptide drugs have become an emerging weapon for the treatment of tumors, showing not only good clinical efficacy, but also considerable economic benefits. However, the clinical application and marketization of peptide drugs still face many challenges. One of the main technical challenges is the large and complex procedures in preclinical and clinical trials, such as the need for continuous functional verification and modification of candidate peptides. These procedures also ensure higher therapeutic performance and safety for peptides in clinical trials than similar drugs in existing markets.

Anti-tumor peptides, as a new class of anti-cancer drugs, are expected to be a prominent target for designing



**Table 2** Currently Marketed Anti-Tumor Peptides

Trade Name	Indication	Route of Administration	Mechanism of Action	FDA Approval	EMA Approval
Coly-mycin S	Solid tumor	Intramuscular, intravenous, eye	Penetrates into and disrupts the cell membrane.	1962	–
Cosmegen	Wilms' tumor; childhood rhabdomyosarcoma, Ewing's sarcoma	Intravenous injection	Binds to DNA and inhibits transcription	1964	–
Blenoxane	Malignant neoplasm (trachea, bronchus, lung), squamous cell carcinoma, lymphomas	Intramuscular and intravenous injection	Inhibits DNA synthesis	1973	1970
Chirhostim	Gastrinoma detection	Subcutaneous injection	Stimulates gastrin secretion	1974	–
Peptavlon	Gastrinoma detection	Subcutaneous injection	Stimulates gastric acid, pepsin, and intrinsic factor secretion	1974	–
Factrel	Pituitary tumor	Subcutaneous and intravenous injection	Simulates the physiologic release of GnRH from the hypothalamus	1982	–
Lupron	Prostate cancer	Subcutaneous injection	Binds to the gonadotropin-releasing hormone receptor and acts as a potent inhibitor of gonadotropin secretion	1985	–
Buserelin	Prostate cancer, breast cancer	Nasal spray	Desensitizes the GnRH receptor to reduce the amount of gonadotropin	–	1985
Octerotide Acetate	Reduce side effects from cancer chemotherapy	Subcutaneous and intravenous injection	Binds to somatostatin receptors and inhibits growth hormone, glucagon, and insulin	1988	
Zoladex	Prostate cancer	Subcutaneous transplantation	Competes with natural GnRH and controls the release of LH and FSH	1989	1987
Octreoscan	Neuroendocrine tumour and lymphoma detection	Intravenous injection	Imaging agent; indium-111-labelled octreotide	1994	1994
Cetrotide	Ovulation, uterine tumor	Subcutaneous injection	Binds to the gonadotropin-releasing hormone receptor and acts as a potent inhibitor of gonadotropin secretion	2000	1999
Tractocile/ Antocin	Uterine tumor	Intravenous injection and infusion	Binds to oxytocin receptors and prevents oxytocin-stimulated increases in inositol triphosphate production	–	2000
Plenaxis	Prostate cancer	Intramuscular injection	Binds to the gonadotropin releasing hormone receptor and acts as a potent inhibitor of gonadotropin secretion	2003	2007
Velcade	Multiple myeloma	Static artery subcutaneous injection	Induces apoptosis	2003	2004
Plenaxis	Prostate cancer	Intramuscular injection	Binds to the gonadotropin-releasing hormone receptor and acts as a potent inhibitor of gonadotropin secretion	2003	2011

(Continued)

Table 2 (Continued).

Trade Name	Indication	Route of Administration	Mechanism of Action	FDA Approval	EMA Approval
Vantas	Prostate cancer	Subcutaneous injection	A GnRH agonist that acts as a potent inhibitor of gonadotropin	2004	2010
Supprelin LA	Prostate cancer	Subcutaneous injection, implant	A GnRH agonist that acts as a potent inhibitor of gonadotropin	2007	–
Firmagon	Prostate cancer	Subcutaneous administration	Competitively inhibits GnRH receptors in the pituitary gland; prevents the release of luteinizing hormone (LH) and follicle stimulating hormone	2008	2009
Istodax	T-cell lymphoma	Intravenous drip	Inhibits enzymatic activity of HDAC to restore normal gene expression in cancer cells	2009	–
Mepact	Osteosarcoma	Subcutaneous injection	Stimulates innate immunity by activating monocytes and macrophages	–	2009
Trelstar	Prostate cancer	Intramuscular injection	A synthetic agonist analog of gonadotropin releasing hormone (GnRH)	2010	1997
Egrifta	Prostate cancer	Intramuscular injection	Stimulates production and release of endogenous hormone (hGRF)	2010	1997
Kyprolis	Multiple myeloma	Intravenous injection, infusion	Acts as a proteasome inhibitor to decrease cellular proliferation, ultimately resulting in cell cycle arrest and apoptosis of cancerous cells	2012	2008
SomaKit TOC	Neuroendocrine tumor	Intravenous injection	A ligand analog that is radiolabeled; binds to the somatostatin subtype 2 receptor, which is overexpressed in malignant cells	–	2016
Lutathera	Gastroenteropancreatic neuroendocrine tumors	Intravenous injection	A <sup>177</sup> Lu-labeled somatostatin analog peptide, binds to the SSRT2 receptor in malignant somatostatin receptor-positive tumors and damages tumor cells by formation of free radicals	2018	2017
Gallium Dotatoc Ga68	Neuroendocrine tumor	Intravenous injection	A ligand analog that is radiolabeled; binds to the somatostatin subtype 2 receptor, which is overexpressed in malignant cells	2019	–

innovative drugs. It is expected that they will have a huge development space and broad prospects in future clinical applications.

## Conclusion and Perspectives

The development of anti-tumor drugs has been focused on DNA alkylating agents, hormone agonists/antagonists, and anti-metabolites. Anti-tumor polypeptides currently show a strong development momentum in the field of cancer drug therapy due to their small molecular weight, weak antigenicity, good targeting, convenient synthesis, and many other natural advantages. Anti-tumor peptides inhibit

tumorigenesis and development by preventing protein interaction, regulating the conformation of biomolecules, competing for binding receptors, and destroying cell membranes.

It is highly likely that the future development of anti-tumor peptides will continue to build on the advantages of natural peptides, and use new polypeptide modification methods to create peptides with longer half-life, increased resistance to enzymatic hydrolysis, and compensation for other deficiencies, so as to obtain relatively perfect pharmacokinetic properties. Perhaps, in the near future, a gratifying breakthrough in the area of tumor therapy will emerge, and the efficacious agent will be an anti-tumor peptide.

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## Disclosure

The authors report no conflicts of interest in this work.

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