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Review Article

Precision Targeting of Toxins for Enhanced Therapeutic Efficacy and Safety

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ABSTRACT

Considering the multiple problems related to many of today's drugs, such as inefficiencies and side effects, there is an increasing interest in targeted drug delivery methods in pharmaceutics. There is a significant potential of natural compounds in active targeting of drugs, as many of them display specific affinity towards molecules in the human body. This is exemplified by peptides found in animal venoms that have been adapted to attack certain targets in living organisms. In this review, we discuss the current research on the use of venom peptides for specific tissue targeting, in order to deliver therapeutic or diagnostic agents. Various delivery systems, predominantly nanoparticles and bioconjugates, have been developed using either natural, or modified venom peptides. Among these, chlorotoxin, a scorpion-derived toxin, and exendin-4, from lizard venom, have shown particular promise in targeted delivery. While many of these delivery systems have been designed for cancer or nervous system targeting, other con-ditions have also been approached. Besides therapeutic drug delivery, numerous targeted imaging agents have been developed and investigated for precise visualization of specific conditions

INTRODUCTION

1.1. Venom peptides in biomedical research

Natural products have been used in medicine since ancient times and they are still holding relevance today, as many pharmaceutical compounds originate from plants [3]. Some examples include: digoxin, isolated from foxgloves (Digitalis sp.), morphine and its analogues derived from poppies (Papaver somniferum), vincristine and vinblastine from Madagascar periwinkle (Catharanthus roseus) and paclitaxel from yewspecies (Taxus

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sp). In addition, many of the well-known antimicrobials, as well as immuno-modulators and other drugs have been developed from microorganisms and fungi [1, 2, 3] . Moreover, some products obtained from animals have also found their use in the medical field, even though many of them may be outdated in the present times. Even though the beginnings of studies into venoms from animals can be dated back to 17th-18th centuries, it is only from the 20th century onward that these studies gained any significance owing to technological developments [4]. The venom produced by an animal is a complicated blend of Peptides and proteins are significantly larger molecules than small organic compounds and require delivery directly to the victim via a sting or bite. In most cases, they can only be used for their effect if given parenterally, but there are exceptions. Considering that peptide toxins are quite fragile, chemical and biological approaches were not applicable to the investigation of their properties as they were for plant-made stable molecules [5, 6,]. As science moved forward, it was possible to develop highly accurate methods for analysis such as liquid chromatography, mass spectrometry, and nuclear magnetic resonance spectroscopy, which enabled a much deeper examination of proteins and peptides. This included the isolation, purification, identification of structure and bioactivity of those. Nowadays, the fields of proteomics, genomics, and transcriptomics are instrumental in the research of toxins made in venom. Venomous toxins are normally very effective biologically and have a great affinity toward particular protein molecules (receptors, ion channels, enzymes) in other organisms, being quite specific down to particular receptor subtypes. The composition of venoms is sometimes extremely complicated and incredibly diverse [8, 9]. There are some kinds of organisms that produce an enormous variety of peptide toxins. In many cases, toxins of venom itself appear to be mutant forms of native proteins carrying out biological activity. Because of the decline in the discovery rate of small molecule drugs over recent years, the attention paid to peptides and biological drugs has significantly increased. Due to great structural diversity and bioactivity of animal venoms, one may consider this type of natural substances rather unexploited pharmaceutical "mine," full of drug candidates for further investigation [10]. To date, five FDA-approved drugs have already been developed on the basis of animal venom. Another promising agent based on animal venom components is Cenderitide, a recombinant naturopathic peptide produced from human Carburettor peptide and Dendroaspis natriuretic peptide (DNP), the latter isolated from green mamba. It has already been tested in clinical trials as a prospective heart failure treatment agent. Moreover, due to great selectivity of certain toxins, such as connotations, they have been extensively studied to understand the mechanisms underlying action of certain receptors and ion channels. Consequently, apart from being directly applied for drug discovery and development, certain venom toxins or their derivatives due to extremely high affinity to certain biomolecules can be used as target agents in novel drug. [11]

1.2. Targeted drug delivery

Non-specific adverse effects/toxicity as well as non-desirable therapeutic efficiency because of poor pharmacokinetics are some of the major drawbacks that pharmaceuticals have in their current form. Many of these concerns can be addressed using approaches to achieve targeted drug delivery. In general, targeted drug delivery is categorized as either passive or active targeting. Passive targeting involves the selectivity of drug accumulation being dependent on Properties related to physiology or anatomy of the target

tissue are some examples include utilization of the compromised nature of blood vessels in tumors, such as use of cyclophosphamide based on the metabolic features of cancer. The compound is active under the condition of low aldehyde dehydrogenase concentration, which is typical for cancer cells.Active targeting, on the other hand, involves the functionalization ofdelivery systems using ligands that bind specifically to cell receptors,i.e., those with a high affinity towards ion channels or enzymes. Thus, targeted drug delivery technologies are still only achieving limited success, with passive targeting resulting in more achievements: this encompasses many nanomaterial drug products that exploit physiological tropism (such as liposomes, albumin particles, lipid nanoparticles/LNP vaccines), reviewed in total with more than 60 FDA-approved nanoparticles and 15 FDA-approved liposomal drug products. [12,13].

1.3. Peptides as targeting ligands

The comparison between different types of active targeting ligands is shown in Fig.1. Among those molecules which were studied in the course of searching for the targeting ligands, all of them possess some pros and cons.Small molecules, for instance, are considered to be very stable and membrane permeable. Nevertheless, the selectivity for target tissues remains low for them. As far as antibodies are concerned, which seem to be the most effective at present, they demonstrate very specific binding to the target molecule. In contrast to small molecules, antibodies show high affinity to the target molecule, yet a lot of problems can still be defined concerning the antibodies. Peptides have the same structure as proteins; yet, they are smaller molecules with molecular weights from 500 to 5000 Da, placing them between large proteins and small molecules. In this sense, peptides represent an intermediate level combining the best features of both types of molecules. For example, peptides have high specificity and high binding affinity toward the targets [14, 15].

Table 1: FDA approved drugs that originate from animal venom toxins

Compound	Species	Year of approval	Type of drug and clinical use	Comments
Captopril	Bothrops jararaca	1981	Angiotensin-converting enzyme (ACE) inhibitor for the treatment of hypertension.	Derived from teprotide, a peptide found in the venom of B. jararaca. First ACE inhibitor
Tirofiban	Echis carinatus	1999	Antiagreggant (gp IIb/IIIa inhibitor) for the prevention of thrombotic cardiovascular events	Derivative of echistatin, a disintegrin from E.carinatus venom
Eptifibatide	Sistrurus miliarius barbouri	1998	Antiagreggant (gp IIb/IIIa inhibitor) for the prevention of thrombotic cardiovascular events.	Derivative of barbourin, a disintegrin of S. b. barbouri venom
Ziconotide	Conus magus	2004	Non-opioid analgesic (inhibitor of Ntype calcium channels in spinal cord)	For intrathecal delivery only.

ACE – angiotensin-converting enzyme, GLP-1R – glucagon-like peptide-1 receptor, gp IIb/IIIa – platelet glycoprotein IIb/IIIa receptor.

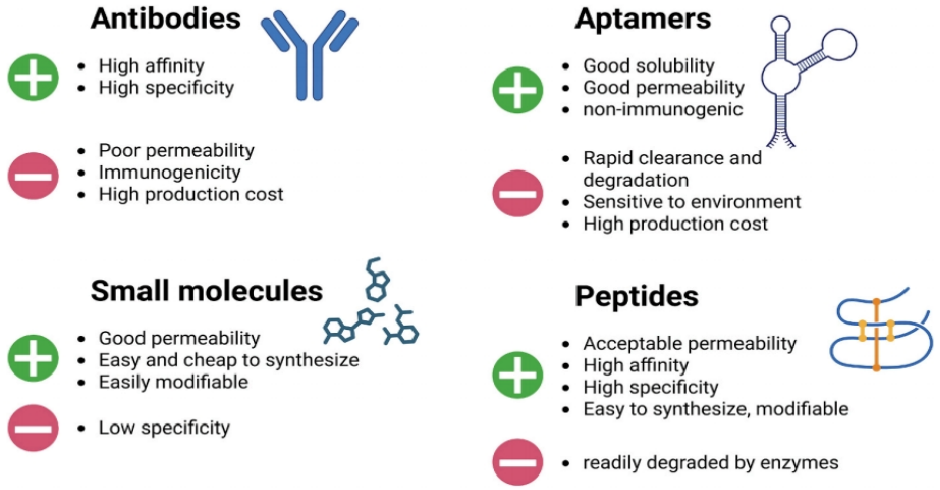


Fig. 1: summary of advantages and disadvantages of commonly used active-targeting ligands. Scheme based on the information in review articles Produced in BioRender

.1.3.1. Venom Peptides vs. Antibodies as Targeting Ligands

Unlike the large mAbs (~150 kDa), the size of venom peptides is usually < 5 kDa. In general, the smaller size makes penetrated into interstitial spaces more likely in comparison to mAbs that tend to remain perivascular. Numerous venom peptides have been shown to be highly specific and selective modulators of subtypes of various receptors/ ion channels that can serve as a means for tissue or disease specific homing where the target receptors/channels are overexpressed (i.e., integrins or ion channels). On the other hand, mAbs have the capacity to target a wide variety of molecules located in the extracellular matrix and on the surface of cells. However, they are unable to penetrate into channel pores and serve as modulators [15]. Thus, in this case, both types of targeting molecules represent complementary approaches rather than competitors. They do not compete in terms of binding similar targets since there is no duplication of efforts and both expand the pool of potential targets within the druggable space. With respect to stability, sulfiderich venoms (knottins, cyclized peptides) are highly stable against heat and enzymatic degradation, thus enabling them to withstand the conditions within biological fluids even when they are large molecules. On the other hand, unmodified venom peptides could be susceptible to proteases unless they are designed for resistance (cyclization, PEGylation) [15, 16].

1.4. Venom peptide sources and diversity

Peptides that can be used as targeting agents in drug delivery systems may be obtained in many different ways. Some methods include isolating appropriate peptides through high-throughput screening of large peptide libraries, which can be done using phage display screening technique or chemical libraries such as the OBOC library. On the other hand, peptides that exhibit biological activity in nature, where they have been designed to perform certain functions in organisms for

reasons such as food gathering, protection, competition, or physiological functions, can also be identified. [17] Evolutionarily, venom is a convergent phenomenon found in multiple groups of animals that are not closely related to each other, and many different toxins have been discovered in the animal kingdom. Typically, specific toxins, which are structurally and functionally alike, can be found among a group of organisms that are closely related to each other. Venom peptides' evolutionary adaptations are primarily determined based on their functionality and purpose. For instance, venom used for defensive purposes has been modified to be the most painful to ward off potential attackers. In contrast, venom used for predatory purposes tends to be lethal to the prey animals. Therefore, their actions and physiological functions are significantly different between the two classes of animals. Fig 2 shows some of the molecular targets of venom peptides for

TD [21]

Table 2: Comparison of venom peptides vs. antibodies as targeting ligands.

Criterion	Venom peptides	Antibodies
Size (molecular weight)	Small (<5 kDa)- better diffusion.	Large (~150 kDa) – limited tumor penetration.
Binding/ targets	Often subtype-selective for channels/ receptors; some penetrate tissues.	Broad extracellular targetability; very high affinity.
Stability	Disulfide-rich/ cyclized scaffolds can be highly protease-resistant; linear forms less so.	Intrinsically stable with long serum half-life.
Pharmacokinetics	Typically, short half-life (hours); needs extension (PEGylation/ albumin / NPs).	Long half-life (weeks) via neonatal Fc receptor.
Internalization/ transport	Several promote transvascular/ cellular entry; good for NPs/ drug delivery.	Mostly perivascular; internalization targetdependent.
Immunogenicity	Generally low for short sequences; scaffold dependent.	Higher immunogenicity; humanized mAbs still can elicit anti-drug antibodies.
Manufacturing	Chemical synthesis; easier chemical modification; potentially lower costs.	Bioprocessing; cell cultures and animals; higher costs
Maturity	Growing pre-clinical/ early clinical.	Extensive clinical/ regulatory precedence (mAbs, ADCs).

ADCs – antibody-drug conjugates, mAbs – monoclonal antibodies, NPs – nanoparticles, PEG – polyethylene glycol.

It was previously thought that only the lizard species belonging to genusHeloderma are venomous; however, it is now known that other Anguimorphyllizards such as the varanids have venom glands, are capable of producingvenom and belong to the recently introduced group of reptiles called Toxicofera. Though less studied than their snake counterparts, lizard toxins have a broad spectrum of biologic activities, among which are antihypertensive, neurotoxic (helofensins), as well asplatelet aggregation inhibitory activities, and many more [21, 22]. Also, the venom of wasps, ants

and bees includes several types of toxic peptides (for instance aculeotoxins, myrimecins and others) that have allergenic and cell-disrupting properties as well as disulfde-rich neurotoxins that affect voltage-gated ion channels and have, for the reason that numerous hymenopterans use their encountering venom as a defensive mechanism, been modified to prepare pain and inflammation. In addition to those examples ofinsect venoms, there are caterpillars of the lepidopteran species Lononia obliqua whose venom includes serine proteases,factor X and prothrombin activators. Contact with these caterpillars' bristles will result in coagulopathy, which is often fatal. Venoms of centipedes have not yet been studied well, but they contain many unique peptides that do not resemble any other peptides, for example, helical arthropod-neuropeptide-derived (HAND) toxins. [22, 25]

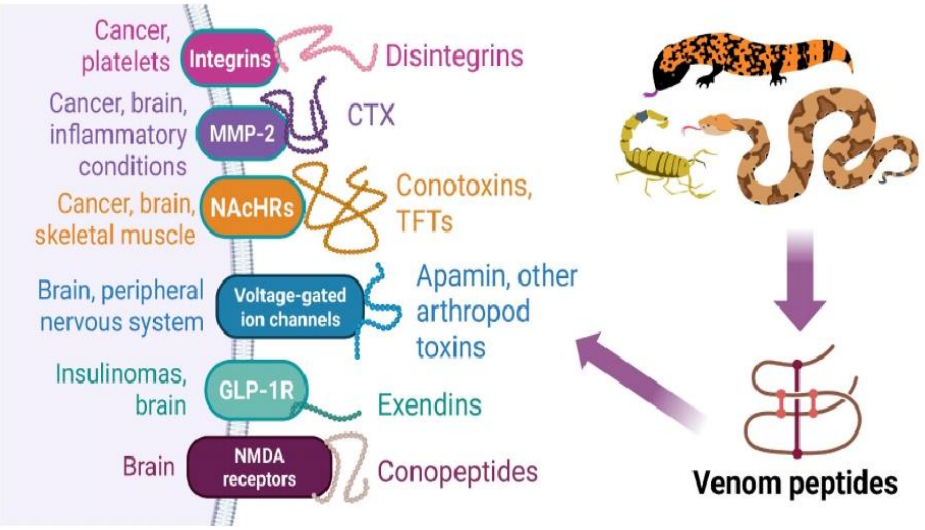


Fig. 2: A schematic representation of the main molecular targets for venom peptides in various conditions.

MMP-2 – matrix metalloprotease-2, GLP-1R – glucagonlike peptide-1 receptor, NMDA – N-methyl-D-aspartate, NAcHR – nicotinic acetylcholine receptor, CTX – chlorotoxin, TFTs – three-finger toxins. Image created in BioRender.

2. OVERVIEW OF THE CURRENT RESEARCH ON VENOM PEPTIDE-BASED TARGETED DELIVERY SYSTEMS

2.1. Cancer targeting

2.1.1. Chlorotoxin

Chlorotoxin (CTX) is a 36-amino acid peptide extracted from the venom of the deathstalker scorpion (Leiurus quinquestriatus) (Fig. 3). The name of the toxin came from its initial observation, in which it was found to inhibit small-conductance chloride channels in colonic epithelial cells. However, the most intriguing feature of this toxin has been revealed by its capacity for selective binding to glioma cells with extraordinary affinity while sparing normal brain tissue. In addition to gliomas, CTX also binds preferentially to other malignant tumours, expanding the range of possible applications for this toxin. A variety of molecules can be used as targets for CTX, such as matrix metalloprotease-2 (MMP-2), annexin A2, neuropilin-1 (NRP1) and CLC chloride channels. The existence of the "true" receptor for CTX remains a matter of debate, but there is sufficient evidence for all of the above-mentioned

candidates. MMP-2 appears to be the most probable choice.It is known that glioma is a particularly lethal brain tumor, where all the existing treatment strategies are rather inefficient [29,33].

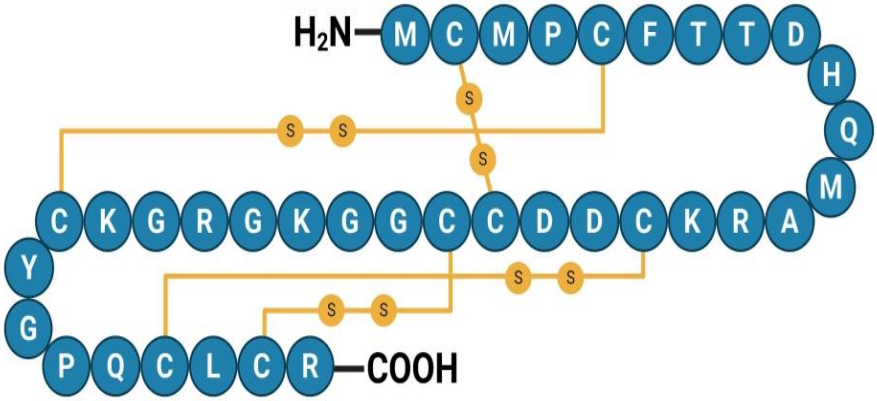


Fig. 3: Sequence and disulfide bond arrangement of chlorotoxin, redrawn from Sharma et al. Image created in BioRender.

The variety of delivery systems examined for modification by CTX is indeed quite remarkable in many studies. Table 3, 4, and 5 show some of the examined delivery systems. Without question, it seems like CTX is the most investigated peptide in the realm of venom peptides. Nonetheless, it does seem that even though there are many successful studies on CTX so far, success rate has not yet reached perfection. So far, only evidence from preclinical stages on active targeting through CTX has been gathered [1, 20, 30].

Table 3: Examples of CTX-functionalized nanoparticle systems for targeted therapy and imaging of cancer

Type of NP	Description	Purpose
Inorganic/ polymer NP	Hexagonal phase NaYF4: Yb, Er/Ce nanoparticles coated with PEI, conjugated to CTX	Up-conversion imaging of glioma.
Iron oxide/ polymer NP	Iron oxide-PEG-CTX nanoparticles	MR imaging of glioma.
Iron oxide/ polymer NP	Superparamagnetic iron oxide NPs conjugated to CTX via PEG.	MR imaging of cancer (hepatocellular carcinoma)
Iron oxide/ polymer NP	pH-sensitive iron oxide NPs coated in citraconic anhydride-modified PEI, bound to CTX and therapeutic siRNA	MR imaging and therapy of glioma.
Iron oxide/ polymer NP	PEG-coated, CTX and cyclodextrin-conjugated iron oxide NPs loaded with paclitaxel and fluorescein	Glioma therapy.
Iron oxide/ polymer NP	Iron oxide Nps coated in PEG, conjugated to cyclodextrin, CTX, paclitaxel and 1-adamanten methyl amide fluorescein.	Glioma therapy.

Iron oxide/ polymer NP	Iron oxide NPs coated with amine-functionalized PEGsilane, conjugated with CTX and a NIR-fluorescent dye AF680.	MRI and optical imaging of glioma; glioma therapy
Polymer NP	biotinylated chitosan NPs, labeled with neutravidinbound AF647 dye and PEGCTX, loaded with temozolomide.	Glioma therapy.

CTX – chlorotoxin, DODAP – 1,2-dioleoyl-3-dimethylammonium-propane, DSPC – 1,2-distearoyl-sn-glycero-3-phosphocholine, DSPE – 1,2-Distearoyl-sn-glycero3-phosphorylethanolamine, DTPA – diethylenetriaminepentaacetic acid, GFP – green fluorescent protein, HPAO – 3-(4 hydroxyphenyl)propionic acid-Nhydroxysuccinimide ester, HSPC – hydrogenated soybean phosphatidylcholine,mal – maleimide, mPEG – methoxypolyethylene glycol, MR – magnetic resonance, NIR – near infra-red, NP – nanoparticles, PEG – polyethylene glycol, PEI – polyethylene imine.

Nanoscopic imaging systems that use other types of inorganic components have also been developed. Research has also been conducted on polymeric NPs with imaging agents attached to them. In one instance, Huang et al. synthesized an MRI contrast agent composed of dendrigraft poly-L-lysine labeled with CTX and containing a DTPA-Gd complex. The CTX-labeled nanoscopic agent demonstrated signal intensity for imaging of liver cancers and gliomas.

Table 4: Other ctx-functionalized delivery systems for cancer therapy and diagnostics.

Type of delivery system	Description	Purpose
Bioconjugates	Pt (IV)-succinic acid complex conjugated to CTX	Cancer therapy
Bioconjugates	CTX conjugate with the Fc domain of human IgG.	Cancer chemotherapy
Bioconjugates	CTX conjugate with gelonin.	Cancer therapy.
Bioconjugates Bioconjugates	Conjugate of polymalic acid, CTX, indocyanine green dye and tri-leucine peptide.	NIR fluorescent visualization of cancerous tumors during surgery
	Conjugate with cytotoxic necrotizing factor-1	Cancer therapy
Bioconjugates	Conjugate of CTX with the NIR fluorescent dye indocyanine green (tozuleristide, BLZ-100)..	NIR fluorescent visualization of cancerous tumors during surgery
Immunotherapeutic agents	T cells expressing genetically engineered chimeric antigen receptors, which contain CTX as the targeting domain.	Glioma immunotherapy.
Radiolabeled analogues	131I-labeled CTX	Glioma therapy; potentially glioma imaging SPECT/MR.

CTX – chlorotoxin, IgG – immunoglobulin, MR – magnetic resonance, NIR – near infra-red, SPECT – single-photon emission computed tomography. Various types of polymeric and metal-oxide (mostly iron oxide) nanoparticles, alone and in combination with each other, have been utilized for the preparation of drug delivery systems targeting delivery of CTX. For example, the authors Mu et al. have developed iron oxide nanoparticles carrying CTX and gemcitabine via hyaluronic acid, as well as nanoparticles attached with CTX and a cyclodextrin molecule loaded with paclitaxel and 1 adamantenemethylamide-fluorescein. On the other hand, Stephen et al. used PEGylated, CTX and O6-benzylguanine-conjugated iron oxide nanoparticles for sensitizing glioma cells toward temozolomide, thereby overcoming their resistance toward the latter. [33]

This particular delivery system indeed showed improved effectiveness of temozolomide, 3 times enhanced median survival rate of mice and reduced toxicity of benzylguanine within the system. Yoo et al. also developed such a delivery system but with O6-methylguanine methyltransferase-silencing siRNA. There has also been research conducted on development of polymers for glioma gene therapy. Thus, for instance, Huang et al. synthesized nanoparticles of poly(amidoamine) (PAMAM) carrying genes on their surface and CTX via PEG. The DNA plasmid integrated into the nanoparticle carried the gene of tumor necrosis factor-related in any case, while the prospects might seem promising indeed, up until now there was only preclinical data demonstrating the effectiveness of such systems. Many times, the research was limited to only in vitro testing. It has been going on for more than two decades already since the beginning of the development of CTX. Still, at this time in 2025 none of the CTX-modified nanoparticle systems has even gotten to the clinical trials stage. Nanoparticles could provide for such property, but it still needs to be investigated thoroughly. Most of the tests done in vivo were conducted in rodents with a tumor xenograft model created. That does not really prove anything concerning their capability of crossing the BBB. [34, 35].

2.1.2. Radiolabeled CTX analogues

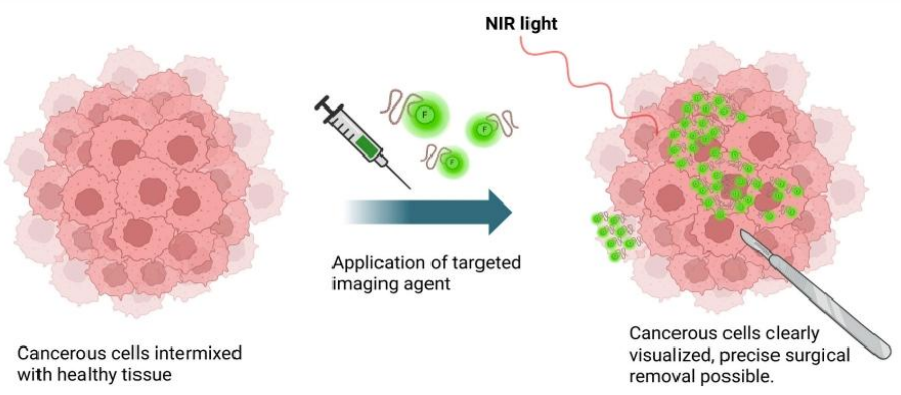
The most interesting compound used in this approach is 131ITM-601, i.e. an analog of CTX radiolabeled with iodine-131 radioisotope. 131ITM-601 has been proposed as a substance for intracavitary application post glioma resection, i.e. as radiotherapeutic or radiographic agent. An in vivo experiment using glioma-bearing mouse model revealed pronounced selectivity in accumulating the agent in tumor cells. Specifically, radiation exposure measured in the tumors was 18-45-fold higher compared to most of the other body tissues (except brain, kidneys, and stomach), while still much lower compared to the latter three. 131ITM-601 has moved to the clinical trials stage. In Phase I trial the safety, pharmacokinetics and dosimetry of a single injection of 131ITM-601 intracavitation 2 weeks after cytoreductive craniotomy were evaluated in 18 adult glioma patients. The results showed no toxicity up to dose-limiting concentration and accumulation at target site and quick elimination of unbound peptide from circulation. [35]

Table 5: Delivery systems using ctx derivatives or structural analogues for cancer therapy and diagnostics.

Description	Purpose
131I-labeled gold NPs entrapped in PEI which was conjugated to BmK CT toxin.	SPECT imaging of glioma; glioma radiotherapy
131I-labeled BmK CT toxin.	Cancer therapy.
Structurally modified and cyclized CTX conjugate with a NIRfluorescent dye.	Biophotonic imaging of cancer.
131I-labeled PAMAM dendrimers conjugated to BmK CT toxin.	SPECT imaging of cancer; cancer therapy
A truncated and modified derivative of CTX conjugated to gold NPs.	Enhancement of BBB permeability.
A conjugate of doxorubicin and biotinylated LqH-8/6b peptide.	Cancer therapy.

BBB – the blood–brain barrier, BmK CT – Buthus martensii Karsch. chlorotoxinlike toxin, CTX – chlorotoxin, NIR – near infra-red, NPs – nanoparticles, PAMAM – poly-amidoamine, PEI – polyethylene imine, SPECT – single-photon emission computed tomography Moreover, some of the patients experienced the amelioration of the disease, and so, it might prove the possible therapeutic effect of the drug and the need for further phase II trials. A phase I/II trial was designed to evaluate the appropriateness of using this drug for the determination of glioma extent using MR/SPECT imaging in cases of high-grade recurrent glioma. According to the findings, the drug was not considered optimal for imaging because of its poor resolution. Additionally, the necessity of the intracranial administration of the drug made the researchers believe that the use of 131I-TM-601 was inappropriate since it could not get through the blood-brain barrier. Several more phase I and phase I/II studies seem to have been performed; however, their status was listed as "unknown" while one study was terminated without the publication of any results. There were no publications regarding 131I-TM-601 within the last 15 years. So, there were no definite reasons for failure but it might be doubted that this drug would be used again in the future. [36,44]

Fig. 4: A schematic representation of the intraoperative application of NIR-fluorescent chlorotoxin conjugates – so called "Tumour paint".



3. SNAKE VENOM TOXINS

3.1. Snake venom disintegrins. Snake venom disintegrins are peptides that interfere with integrins – cell membrane receptors involved in numerous physiological processes such as cell adhesion, haemostasis and immune responses, among others. The majority of snake disintegrins contain a common element in their structure – the Arg-Gly-Asp or RGD motif, which is considered to be the binding site for integrins. This motif also occurs in naturally-occurring integrin binding proteins. The contribution of other peptide residues located around the RGD motif, as well as the importance of peptide structure, is demonstrated by various potencies and integrin-binding properties of the peptides, and by the fact that some of the disintegrins function only when dimerized, whereas others can act as monomers. With regards to medical research, the most important target for drug development based on snake venom disintegrins is integrin αIIbβ3, or glycoprotein IIb/IIIa receptor (gp IIb/IIIa). This protein takes part in platelet aggregation, and therefore drugs blocking this receptor would be able to prevent blood clotting. Two FDA approved antiplatelet drugs have been obtained through disintegrins – tirofiban and eptifibatide [37]. Because many integrins play key roles in metastatic spread of cancer, tumor invasion and angiogenesis, the use of disintegrins as anti-cancer drugs has also received attention. It is indeed true that integrin receptors are often cited as one of the major targets for cancer-specific delivery, with the RGD tripeptide or its analogs having already been utilized for such purposes. However, in this article, we shall confine ourselves only to those disintegrins found in snake venom. Cancer-specific delivery systems using snake venom disintegrins are tabulated in Table 6 [37, 38].

Table 6: Other venom peptide-functionalized delivery systems for cancer therapy and imaging

Target	Toxin	Description	Purpose
α7-nicotinic acetylcholine receptors	α-Conotoxin LsIA	Conjugates of α-Conotoxin LsIA with coumarin or camptothecin, created by stapling a linker between the cysteine disulfide bond.	cancer (studied for lung cancer) therap
	α-Conotoxin ImI	PEG/DSPE micelles conjugated to α-Conotoxin ImI, loaded with paclitaxel.	Cancer (studied for breast and lung cancer) therapy.
	α-bungarotoxin	Carboxylated nano-diamonds bound to α-BTX noncovalently (electrostatically).	Imaging of NAcHR-expressing cells, including cancers (lung cancer).
TrkA receptor	Russell's viper venom nerve growth factor	An isoform of nerve growth factor from Daboia russellii venom, conjugated to fluorescein isothiocyanate.	Cancer (studied for breast cancer) imaging.
1Kv1.1 voltage-gated potassium channels.	Dendrotoxin-1	QDs conjugated to DTX-1	Visualization of cellular structures (Kv1.1); potentially a diagnostic tool for cancer (glioma)
Calcium-activated potassium channels.	Apamin	ellagic acid-loaded phospholipid/cholesterol emulsosomes functionalized with apamin	Cancer (studied for breast cancer) therapy.

Integrin α1β1	Lebestatin	Fusion protein with annexin V.	Cancer (studied for melanoma) therapy.
Integrin αvβ3	A disintegrin from Gloydius ussuriensis.	Fusion protein with melittin, conjugated via a cleavable linker peptide.	Cancer (studied for lung carcinoma) therapy
	Bitistatin	Bitistatin labeled with 125I. Conjugate with 64Cu-labeled DOTA	Cancer (studied for mammary carcinoma) imaging
	ω-agatoxin IVB	Conjugate of a modified ω-agatoxin IVB with NIR fluorophore AF680	Cancer imaging

DMPC – 1,2-dimyristoyl-sn-glycero-3-phosphocholine, DOTA – 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid, DSPE – 1,2-Distearoyl-sn-glycero-3-phosphorylethanolamine, DTX-1 – dendrotoxin-1, NAcHR – nicotinic acetylcholine receptor, NIR – near infra-red, PEG – polyethylene glycol, PET – positron emission tomography.

3.2. Neurotoxins: Several nicotinic acetylcholine receptors blocking neurotoxins from snake venom have been considered for use against the brain, nervous system or muscles, and also cancer cells overexpressing the receptors. They belong to 3 finger toxins (3FT) because of the specific loops observed in the molecule structure. Being involved in nerve impulse transduction and contraction of skeletal muscles, these molecules generally cause neuromuscular paralysis. Moreover, they are very potent neurotoxins. Liu et al. constructed an imaging reagent consisting of carboxylated nanodiamonds (cND) and α-bungarotoxin (α-BTX) – an α7-NAcHR blocking three-finger neurotoxin from venom of the multi-banded krait Surprisingly, no covalent linkages were used. The binding was realized through electrostatic interaction between negatively charged cND and positively charged BTX. The complexes were capable of binding α7-NAcHRs present in Xenopus laevis oocytes and human lung cancer cells and allowed visualizing them using confocal fluorescence microscopy. Nevertheless, the ability of the construct to be used in vivo seems doubtful considering the extremely high toxicity of α-BTX.

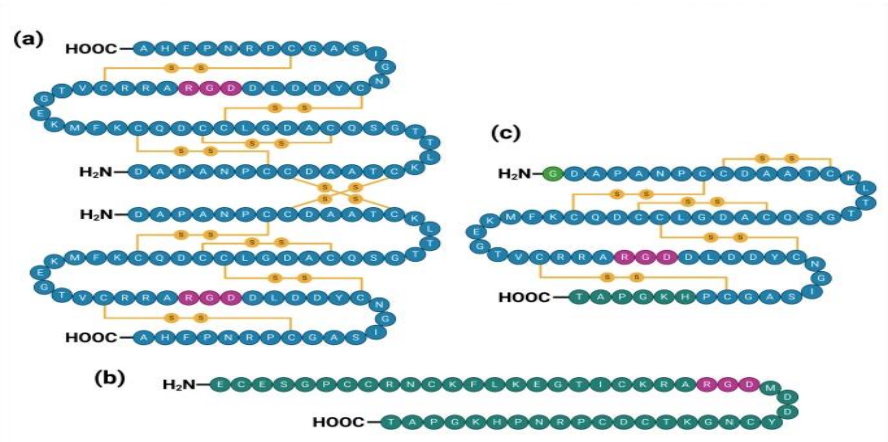


Fig. 5: Sequences and disulfide bond arrangement of contortrostatin (a), echistatin (b) and their recombinant fusion product vicrostatin (c)

4. OTHER TOXINS

4.1. Conotoxins

Conotoxins are highly diverse small and disulfide-rich pharmacologically active peptides isolated from the venom of cone snails (Conus sp.). At the current stage, only a tiny portion of these peptides and their pharmacological activities has been fully identified. Their high potency and highly selective affinity to biological targets make conotoxins interesting as potential candidates for targeted drug delivery systems development. So far it appears that α−conotoxins, known to target nicotinic acetylcholine receptors (NAcHRs), have been researched in this context. On the basis of the knowledge of α7 NAcHR overexpression in certain tumors, Mei et al. developed polymeric PEG-DSPE (1,2-distearoyl-sn-glycero3-phosphorylethanolamine) micelles conjugated with α-conotoxin ImI, isolated from the venom of Conus imperialis, as targeted carriers for cancer therapy. In vitro, those nanoparticles were able to selectively recognize A549 lung cancer and MCF-7 breast cancer cells through interaction with α7-NAcHRs.

4.2. Bee venom peptides: Venom derived from honeybees (Apis mellifera) has been widely employed in various types of medicine, both alternative and conventional. As regards modern medicine, compounds isolated from bee venom continue to remain relevant in this respect, due to the amount of research on their possible therapeutic application. For instance, melittin – a cytotoxic peptide – might have some limited application as a targeting agent: Yu et al. suggested application of melittin in immunomodulatory nanoparticles, aimed at targeting and activating liver sinusoidal endothelial cells (LSECs) in order to achieve suppression of tumour metastasis formation in liver. [38, 45].

5. INSULINOMA TARGETING

5.1. Exendins

Exendins are peptide toxins, discovered in the venom of the North American genus of lizards, Heloderma. The best examples of such compounds are exendin-3 from the venom of Mexican beaded lizard (H. horridum), and exendin-4 from the venom of Gila monster (H. suspectum). Exendins are unique compounds, because of the high degree of structural homology with the human glucagon-like peptide-1 (GLP-1) – incretin hormone known to participate in digestion and insulin secretion (see Fig. 6). Initial in vivo experiments showed significant and long-lasting hypoglycemic effect of exendins. Moreover, exendin-4, especially, is significantly more resistant to cleavage by dipeptidyl peptidase-4, compared to natural GLP-1, as well as exhibiting a longer half-life time.

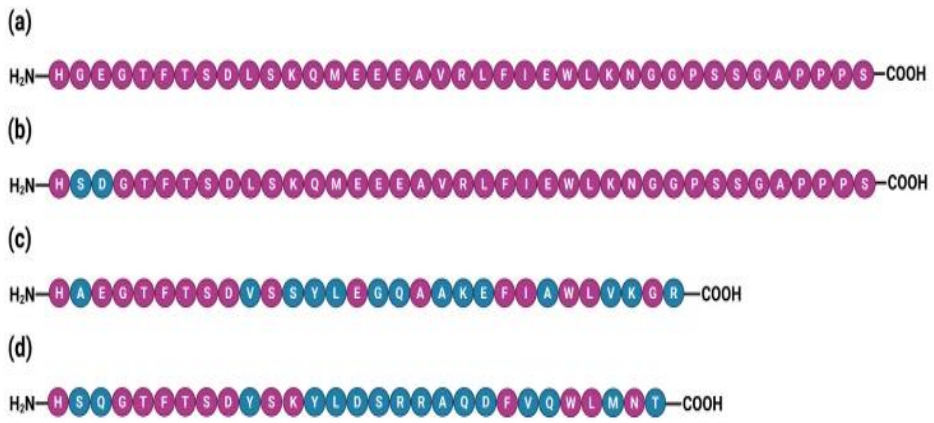


Fig. 6: Amino acid sequence comparison of exendins and related physiological peptides: a) exendin-4, b) exendin-3, c) glucagon-like peptide-1, d) glucagon. Sequence of exendin-4 and homologous parts in other peptides are highlighted in magenta.

It should come as no surprise that interest was piqued in the possibility of developing exendin-4 as a pharmaceutical drug. Indeed, in 2005, exenatide (exendin-4) received FDA approval for use as an insulin-releasing agent to help control type II diabetes in individuals who do not respond to metformin and sulfonylurea treatment options. The mode of action of exenatide can be described as potent stimulation of GLP-1 receptors (GLP-1R), located primarily in the pancreas, among other effects, which leads to insulin secretion. In spite of the approval of exenatide, studies continued to be conducted on the exendins, revealing that exendins could serve as therapeutic agents in some other conditions.

5.2. Radiolabeled exendin conjugates for PET/SPECT imaging. Many pre-clinical in vivo studies were done using various types of exendin conjugates for imaging purposes, mainly based on exendin-4, occasionally on exendin-3, and even exendin(9-39), the latter one beingm an analogue with antagonistic activity to GLP-1R. The list of these compounds is shown in Table 7. Chemically, these molecules are formed by chelator molecule holding radioisotope of metal, coupled to the peptide through linker. Often extended termini (additional amino acid residues at the end of the peptide) serve as the binding sites. One of the first studies in this field and concerned the design, synthesis, and testing of in vivo 111In-[DTPA]labeled exendin-4 conjugate as an insulinoma detector [45].

Table 7 Summary of radiolabeled exendin conjugates for GLP-1R-targeted SPECT and PET imaging

Radioisotope	Mode of imaging/ purpose
^{111}In	SPECT/CT, SPECT/MR and PET imaging of insulinomas.
^{68}Ga	PET and PET/CT imaging of insulinomas and pancreatic β-cells.
^{64}Cu	PET imaging of pancreatic tumours and β-cells
^{18}F	PET, PET/CT imaging of insulinomas and β-cells

CT – computed tomography, MR – magnetic resonance, PET – positron-emission tomography, SPECT – single-positron computed tomography

6. TARGETING THE BRAIN AND THE NERVOUS SYSTEM

6.1. CTX

In addition to targeting cancer cells, chlorotoxin (CTX) was also investigated for other purposes - including targeting the brain. The systems utilizing CTX for that purpose are presented in Table 10. described use of CTX modified liposomes for therapy of Parkinson's disease. This system was designed based on the reported capability of CTX to bind to microvascular endothelial cells which could potentially result in increased permeability of BBB and b metter delivery of drugs. In a mouse Parkinson's disease model, it was shown that the CTX modified and levodopa carrying liposomes resulted in an increase in Substantia nigra dopamine concentrations and amelioration of some neurological symptoms compared to the control group. Wang et al. investigated the autocatalytic polymeric nanoparticles carrying various substances aimed at increasing the permeability of BBB, such as lexiscan [1, 25, 32]. They discovered that attachment of CTX to the nanoparticle increased its delivery by a factor of 1.9. MiniCTX3 is the shortened and modified version of CTX designed by DiazPerlas et al. which proved to be stable in human serum, retained the ability to target certain sites and showed higher efficacy in crossing BBB in vitro as well as in transporting cargo through it. In another research, Han et al. used CTX and lexiscan in combination to design nanoparticles transporting Nogo-66 receptor antagonist NEP1-40 for the treatment of brain ischemic stroke. This design was used since it was discovered that in ischemic environment in brain there is upregulation of MMP-2.

6.3. Three-Finger Toxins

Another approach for enhancing the ability of BBB to permit passage is the targeting of particular receptors that are abundantly expressed in the brain, thus enabling receptor-mediated transport. Some neurotoxins that target NAcHRs have been studied for optimizing the BBB-permeation of CDX, a peptide that consists of 16 amino acid residues derived from the second loop of candoxin, which is a 3FT in the venom of the Malayan krait (refer to Figure 7). In this study, the researchers conjugated CDX to paclitaxel-loaded polymer micelles (polyethylene glycol-polylactic acid PEGPLA). It was shown that CDX micelles enabled drug delivery to the brain and suppressed the proliferation of glioblastoma cells in mice, thereby significantly increasing their lifespan compared to controls. conjugated CDX to red blood cell membrane-coated, doxorubicin-loaded poly-lactic co-glycolic acid (PLGA) nanoparticles. Such an approach showed an increased tumor accumulation of this system in the glioma mouse model, along with an increased lifespan of mice bearing glioma tumors, compared to the control group. [41, 45]

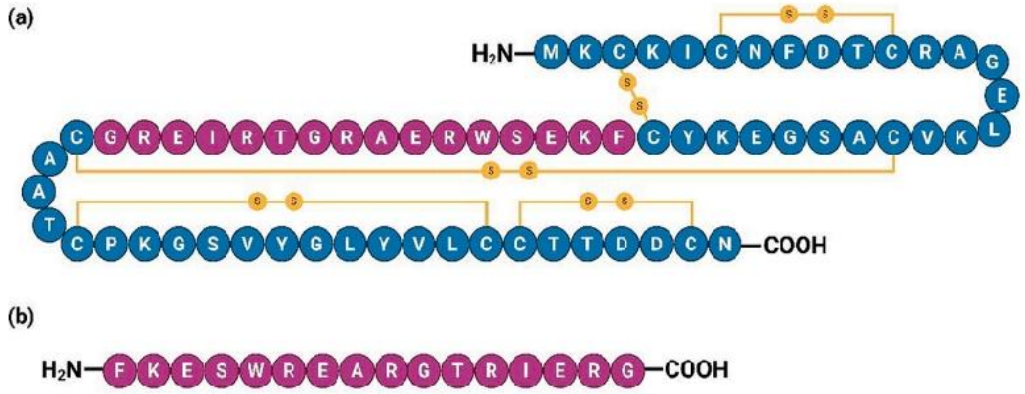


Fig. 7: Sequence and disulfide bond arrangement of a) candoxin, b) CDX

6.3.1. Bee venom peptides

Bee venom peptide apamin and its derivations are substantially used for CNS targeting due to their capability to increase blood – brain hedge (BBB) permeability. Apamin- grounded nanoparticles have shown picky accumulation in the spinal cord and bettered recovery in injury models. A crucial outgrowth, MiniAp- 4, is a more stable, less poisonous interpretation that retains apamin's parcels while enhancing BBB penetration. MiniAp- 4 effectively delivers loadings (e.g., fluorescent labels) across the BBB and shows strong brain and excrescence targeting, especially in glioblastoma models. Structural variations, like replacing proline with 5,5- dimethylproline, may further ameliorate BBB crossing effectiveness. [46].

6.3.2. Peptides from Tarantula Venom

Spiders' venom peptides are known to act as potent agonists against diverse types of ion channels. They might therefore be considered promising agents for targeted drug delivery. reported the case of μ-TRTX-Pn3a, which is a tarantula (Pamphobeteus nigricolor) Nav1.7 blocker. (Sharma et al., 2020) Modification (addition of one glycine residue) at the N-terminal part of the peptide allowed for simple chemical conjugation with another molecule with the help of sortase A. Such modifications might find applications in targeted therapy or development of imaging agents. As an example, they have developed a conjugate with FLAG peptide, which might serve as a tool to visualize tissues with peptide accumulation via immunofluorescence. Another example is a Nav1.7-blocking toxin Hs1a, isolated from the Chinese bird spider Haplopelma schmidti [46].

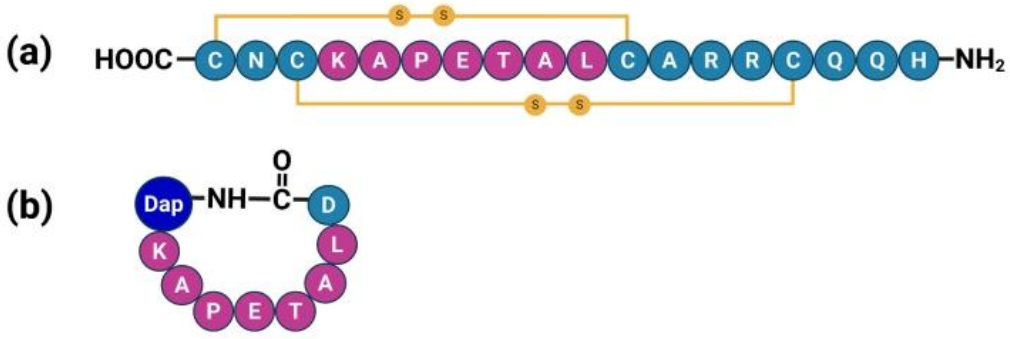


Fig. 8: Sequences and disulfide bond arrangement of a) apamin, b) MiniAp-4

6.3.3. Peptides from scorpion venom

Other than CTX that attracted lots of attention due to numerous studies conducted in the field of pharmaceutical and delivery systems creation, there are other peptides from scorpion venom, which also attracted the attention of scientists and researchers. Indeed, it should be noted that venoms of scorpions are considered to contain many different toxins targeting various ion channels. Hence, the peptides of interest are important in terms of designing systems targeted to those particular proteins. It is vital to mention that neurotoxicity should always be taken into consideration when working with such toxins, especially when they preserve the ability to inhibit particular channel. However, sometimes, it can be managed through certain structure modifications. For instance, one of Ts1 toxin analogs, named [S14R, W50Pra]Ts1, isolated from scorpion South American scorpion Tityus serrulatus, was suggested by Kubota et al. to bind to voltage-gated sodium channels. [46,47]

6.4. Targeted delivery in other conditions

6.4.1. Chlorotoxin in rheumatoid arthritis

Vyawahare et al. explored the potential use of CTX both for targeting and for achieving therapeutic effect in the treatment of rheumatoid arthritis due to overexpression of MMP-2, which is involved in the process of inflammation. Researchers created a polymeric nanomicelles delivery system conjugated with CTX and loaded with sivelestat. The possibility of reducing swelling and bone/cartilage damage due to raumatoid arthritis in vivo was demonstrated using the system. [47]

6.4.2. Bitistatin for the in vivo imaging of thrombi

Disintegrins from viper venom interact with integrin receptors on platelets, thus enabling platelet-targeting. Specifically, various systems based on bitistatin have reportedly been investigated as platelet-targeting agents; e.g., they were tested for their ability to perform in vivo imaging of thrombi. A conjugate of radiolabeled with 99mTc glucoheptonate and bitistatin was synthesized by Knight et al. and used for in vivo imaging of DVT and PE. In an in vivo canine model, it exhibited a high affinity for blood clots, and provided a clear visualization of DVT already within 30 min and of PE already within 1 hour following the injection. Moreover, Gerstenhaber et al. were able to visualize in vivo vascular thrombus in the rat carotid artery bifurcation model using fluorescent nanodiamonds conjugated with bitistatin for extracorporeal NIR imaging. In addition, it has a favorable safety profile since the system did not produce any adverse long-term effects after exposure to it (rats examined up to 12 weeks after infusion). [48,49.50]

CONCLUSION

This work provides a summary of actively targeted delivery systems for therapeutic or diagnostic purposes, employing venom peptides as targeting agents. It is clear that a number of peptide toxins from different animal species have been used to target different molecular entities in human cells. Researchers have looked into a wide range of drug delivery systems, mostly different kinds of nanoparticles and bioconjugates, for targeted therapy and diagnosis of different diseases. These mainly consist of malignant and benign tumors, along with disorders affecting the brain and other components of the nervous system, in addition to

various other conditions. An important, even if it seems obvious, idea to think about is that for the (active) targeted delivery of drugs to work well, a disease or condition should be linked to high levels of a certain target molecule. This molecule should not be present in healthy tissues, especially near the target area. Malignant tumors often overexpress certain types of proteins. This is not unusual. Aberrant gene expression is a hallmark of cancer resulting from the accumulation of genetic mutations. So, active targeting works best for certain types of cancer. Venoms have a lot of different parts and are very complicated. It is reasonable to anticipate that toxins derived from vertebrates exhibit a greater affinity for human receptors than those derived from invertebrates, considering their evolutionary purpose and origin. This review's research shows that this isn't always true, though. Chlorotoxin, which is probably the most successful of the peptides we talked about, was first found in the venom of a scorpion, which is an arthropod. Other toxins from invertebrates have also shown promise in preclinical studies for targeted delivery. These toxins are not usually made to kill warm-blooded animals; at best, they are meant to hurt them. The only reason a small insect or spider would want to envenomate a large mammal like a human is to protect itself. Because of this, many of these peptides may be much less harmful to us, but they still have the ability to target receptors and ion channels. That could make them a very useful source of ligands for active targeting. There are still problems that need to be fixed with venom peptide-functionalized delivery systems. Nanomedicines, in general, come with a number of problems when it comes to putting them into practice in the clinic. Peptide toxins can also cause serious problems, such as poor stability and harmful side effects. Most of the current research has not gone beyond the pre-clinical stage, probably because of those factors. In numerous instances, the examined delivery systems demonstrate highly promising outcomes in vivo, with some advancing to clinical trials, thereby maintaining the potential for future evolution into targeted therapeutic agents. Also, some of the relevant problems can be solved. Chemical changes to natural peptides, for instance, can make most of their properties better. That includes making it less toxic, more stable, more specific, and more powerful.

In short, the future looks good for using venom peptides in targeted drug delivery. Several systems are already in clinical trials, and a few have made a lot of progress. As stated before, the scorpion-derived chlorotoxin, which probably targets MMP-2, seems to be one of the most promising peptides for treating and diagnosing gliomas and some other cancers. Its high selectivity, ability to reach target tissue, and lack of toxicity make it a great choice for making targeted delivery systems. This is backed up by a lot of preclinical research and the fact that some of these systems have already been tested in clinical trials.

The CTX-modified CAR T cells are presently in a human trial, and early reports are quite encouraging. Tozuleristide, an imaging agent based on CTX, is also showing good results in clinical trials and has moved on to phase II/III. The lizard-derived peptide exendin-4, also known as exenatide, is another peptide that stands out. It targets GLP-1R and has been an approved drug for type II diabetes for almost 20 years. Exendin-4 has recently been studied for the development of imaging systems for insulinomas. Recent and current research seems to be very promising for radiolabeled exendins, especially 68Ga-labeled ones, which may soon be approved for use in hospitals. Furthermore, toxins such as viper venom disintegrins may ultimately be beneficial for the advancement of cancer therapies, given that

integrin/RGD binding has previously been utilized for cancer targeting.

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