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MINI-REVIEW

Peptide cargo administration: current state and applications

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Abstract

Effective delivery of drug molecules to the target site is a challenging task. In the last decade, several innovations in the drug delivery system (DDS) have tremendously improved the therapeutic efficacy of drug molecules. Among various DDS, cell-penetrating peptides (CPPs) based DDS have gathered notable attention owing to their safety, efficacy, selectivity, specificity, and ease of synthesis. CPPs are emerging as an efficient and effective pharmaceutical nanocarriers-based platforms for successful management of various important human health disorders. Failure of several current chemotherapeutic strategies is attributed to low solubility, reduced bioavailability, and off-target delivery of several anti-cancer drugs. Similarly, development of therapeutics for vision-threatening disorders is challenged by the anatomical as well as physiological complexity of the eye. Such therapeutic challenges in cancer and ocular disease management can be overcome by developing cell-penetrating peptide (CPP) based peptide drug conjugates (PDCs). CPPs can be used to deliver various types of cargo molecules including nucleic acids, small molecules, and peptides/proteinaceous agents. In this review, we have briefly introduced CPPs and the linker strategies employed for the development of PDCs. Furthermore, recent studies employing CPP-based PDCs for cancer and ocular disease management have been discussed in detail highlighting their significance over conventional DDS. Later sections of the review are focused on the current status of clinical trials and future implications of CPP-based PDCs in vaccine development.

Key points

- *Cell-penetrating peptides (CPPs) can deliver a variety of cargo macromolecules via covalent and non-covalent conjugation.*
- *CPP-based peptide drug conjugates (PDCs) can overcome drawbacks of conventional drug delivery methods such as biocompatibility, solubility, stability, and specificity.*
- *Various PDCs are in clinical trial phase for cancer and ocular therapeutics.*

Keywords Cancer therapeutics · Cell-penetrating peptides · Clinical trials · Ocular therapeutics · Peptide drug conjugates

Introduction

A successful and stable drug delivery system (DDS) is designed in such a way that it primarily delivers therapeutic agent in sufficient amount at the target site while minimizing undesirable side effects in the off-target cells. Use of nanotechnology-driven delivery vehicles such as nanocarriers aid in targeted delivery with an additional advantage of increased biodistribution or bioavailability of the encapsulated cargo molecule (Patra et al. 2018). Many a times, drug molecules exhibit issues related to stability and off-target effects for which researchers are trying to employ strategies to present a safe and effective approach by either modifying the active drug molecule chemically or linking a carrier moiety to formulate prodrug that will act as a bioprecursor (Jornada et al. 2016). Peptide-drug conjugates (PDCs) are now emerging as a promising class of prodrugs that consists of a specific peptide coupled to a drug/small molecule via cleavable or non-cleavable linker. Use of peptides over other molecules as carrier moieties in drug conjugates offer numerous advantages such as safety, efficacy, high selectivity and specificity, and ease of synthesis (Chavda et al. 2022). To achieve target specificity or enhanced bioavailability, these carrier peptides can be modified into cell-penetrating peptides (CPPs) by incorporating selective amino

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acids during designing and synthesis. PDCs that are formed from CPPs enter the cells via non-specific mechanisms and results in increased drug delivery (Lindberg et al. 2021; Fu et al. 2022).

Several studies have highlighted the role of peptide drug conjugates in both therapeutic as well as diagnostic field (Ma et al. 2017; Hoppenz et al. 2020; Battistini et al. 2021; Lindberg et al. 2021; Fu et al. 2022; Chavda et al. 2022). Multiple linker strategies especially involving covalent conjugation have been reported to effectively conjugate cargo molecules to CPPs to enhance their cellular internalization (Feni and Neundorf 2017). This adeptness of CPPs to efficiently carry covalently linked cargos along with themselves makes them promising peptidic carrier for theragnostic. Various PDCs have emerged in the past years to treat different diseases and disorders, including cancer, cardiovascular diseases, neurodegenerative disorders, ocular, and respiratory disorders (Kurrikoff et al. 2021). This review focuses on the therapeutic aspects of cell-penetrating peptide conjugated drugs in cancer and ocular diseases. Present review is broadly divided into four sections that discusses an overview of PDC components, in vitro/preclinical status of PDCs in cancer and ocular therapeutics, and clinical status of PDCs in cancer and ocular therapeutics.

Overview of PDC components

In the area of therapeutics, peptide research is gaining popularity as peptides are less toxic, more specific, and immunologically acceptable molecules (Loffet 2002). Due to the wide range of applications of peptides in the management of diseases such as cancer, metabolic disorders, cardiovascular diseases, and hematological disorders, peptide therapeutics is emerging as a promising area for the pharmaceutical R&D sector. The discovery of self-translocating short chain peptides (5–30 amino acids long), also known as cell-penetrating peptides (CPPs), has marked the promising advancement in the area of nanocarrier-mediated drug delivery. A major shift from conventional therapy can be seen after the year 1988, when two independent research groups made a breakthrough by uncovering the role of trans-activator of transcription (TAT) peptide from human immune deficiency virus (HIV) as a cell-penetrating peptide (Frankel and Pabo 1988; Green and Loewenstein 1988). Soon after the discovery of TAT peptide, penetratin that was derived from the homeodomain of Antennapedia peptide gathered attention in the year 1994 as another promising CPP (Joliot et al. 1991; Derossi et al. 1994) followed by plethora of CPPs that have been discovered, synthesized and investigated since then for the management of several diseases (Pescina et al. 2018). Although their mechanism of entry inside the cells remains intriguing, they have been shown to successfully deliver numerous molecules of pharmaceutical interest such as nucleic acids, proteins, and small drug molecules inside various types of cells**.** CPPs can employ different endocytic pathways depending on the type of CPP and cargo molecule (Gupta et al. 2005; Lindberg et al. 2011; Tripathi et al. 2018). CPPs indeed exhibit several advantages such as low oncogenicity, safe and efficient translocation of drug/cargo, absence of cytotoxicity and stability at physiological conditions as compared to other conventional drug delivery systems (Borrelli et al. 2018; Aroui and Kenani 2020).

In a review by Ruseska and Zimmer 2020, various internalization pathways exploited by CPPs are described along with their regulatory mechanisms as well as factors influencing the nature of cellular uptake (Ruseska and Zimmer 2020). Cellular uptake of CPPs can be categorized into energy-dependent (endocytosis) and energy-independent (direct translocation) pathways. Figure 1 illustrates a summary of cellular entry mechanisms exhibited by various cell-penetrating peptides.

Energy dependent pathways (endocytosis)

Endocytosis is an active process facilitated by ATP consumption and involves translocation of peptides or peptide cargo molecules through vesicle formation. Most of the studies have described at least four types of endocytic pathways viz. macropinocytosis, clathrin dependent, caveolin dependent, and clathrin/caveolin independent mechanisms and choice of pathway depends on the cell type as well as the

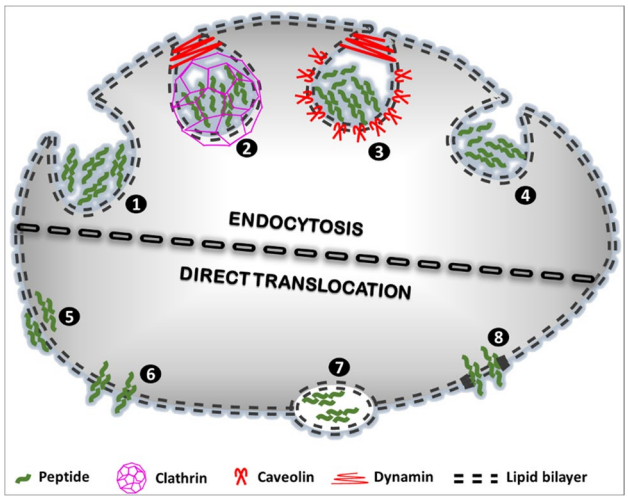

Fig. 1 Schematic representation of various pathways of cellular uptake exhibited by cell-penetrating peptides. A. Mechanisms involving energy dependent endocytosis: 1. Macropinocytosis, 2. Clathrin dependent endocytosis, 3. Caveolin dependent endocytosis, and 4. Clathrin/caveolin-independent endocytosis. B. Mechanisms/models involving energy independent direct uptake: 5. Carpet model, 6. Toroidal pore formation, 7. Inverted micelle, and 8. Barrel stave pore formation

physicochemical properties of peptides (Jones 2007; Patel et al. 2007; Madani et al. 2011; Guidotti et al. 2017; Ruseska and Zimmer 2020).

Energy independent pathways (direct translocation)

Direct translocation is a single-step process that includes various proposed methods such as carpet like, toroidal pore formation, inverted micelle model, and barrel stave pore formation model. Energy-independent mechanism involves interaction of peptide with the lipid bilayer of plasma membrane that further changes the membrane dynamics at the site of contact facilitating peptides to enter cells by forming transient pores or inverted micelles (Alves et al. 2010; Allolio et al. 2018).

Although, more than 3 decades have passed since the discovery of the first CPP; however, realization of their full potential has yet to be done. Initial years of the discovery were invested in studying the characteristics and cellular uptake mechanisms of these cell-penetrating peptides, the focus now has shifted to the applications of CPPs in areas such as therapeutic drug delivery, in vivo imaging/diagnostics, radiotherapy, and chemotherapy or anti-cancer therapy (Gallo et al. 2019). Only a limited number of CPPs are therapeutic in nature and to drive their biomedical applications, they are loaded with different cargos via various non-covalent and covalent interactions such as hydrophobic interaction, electrostatic interaction, amide bond, maleimide bond, disulfide bond, or triazole bond (Kim et al. 2021). Generally, CPPs with signal sequences are very efficient in the targeted delivery of intracellular cargos but sometimes due to lack of specific amino acids for targeting, they suffer from drawbacks such as unintended drug accumulation at a non-target site resulting in poor efficacy and increased side effects. To address this issue, various strategies are being employed to make a CPP target specific. Strategies such as pH responsive change, specific enzyme-triggered cleavage, and multiple targeting ligands are discussed in details for selective delivery of CPP drug conjugates (Nam et al. 2023). While attempting covalent conjugation of a cargo to peptide moiety or imparting selectivity to the carrier peptide, it is very important not to disrupt cell-penetrating activity of the peptide molecule in order to formulate a successful and fully functional PDC. To achieve this, flexible linkers with cleavable or non-cleavable properties can be introduced between carrier peptide and payload to maintain the functionality as well as integrity of a PDC.

Linker strategies for PDCs

An effective delivery system should release the payload once it reaches the target. Different strategies have been adapted to link a bioactive moiety to the peptide to ensure its effective release. PDCs for targeting specific cells usually consist of a peptide carrier, a chemical linker and a payload. Stable and low-molecular weight linkers are a critical part of the conjugate that, in concert with peptide and drug, maintain the structural integrity of the conjugate during circulation and play a significant role in delivering the drug to its targeted site (Ma et al. 2017). Different types of linkers and their encompassing release strategies are shown in Fig. 2.

Linkers can be classified as cleavable and non-cleavable based on the nature of their cleavage site. Cleavable linkers can be enzyme-sensitive, pH-sensitive, and glutathione

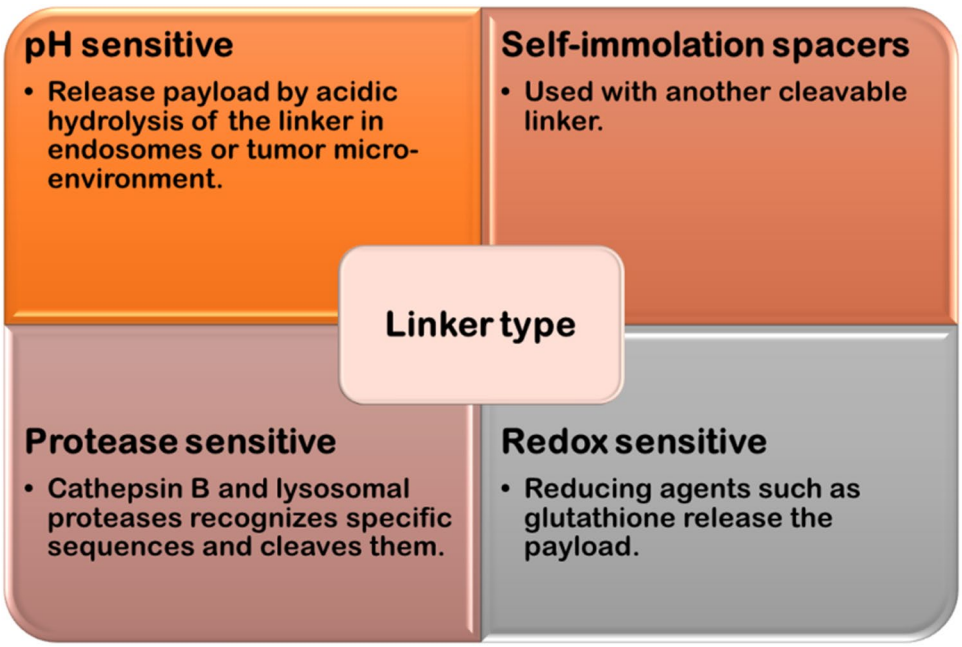

Fig. 2 Different type of linkers along with their mode of release

sensitive whereas non-cleavable linkers include very stable amide, carbon or ether chain, that works best with the drugs not affected by post-chemical modifications with the linker molecule. Although, cleavable linkers are preferred for targeted therapeutics; however, non-cleavable linkers are more stable in terms of in vivo metabolic cycling (Fu et al. 2022).

In a PDC, payload can be conjugated to a carrier molecule via hydrolyzable linker such as carboxylate ester or stimuli-responsive linker (Poreba 2020; Hoppenz et al. 2020; Alas et al. 2021). In order to exploit the selectivity as well as potential efficacy of the payload, linker molecules are designed in such a way that the payload is selectively cleaved and released from the PDC once it reaches the target cell to avoid the off-target hydrolysis. One such example of selective linker is Ala–Ala–Asn tripeptide linker which is cleaved by Legumain, a cysteine protease having high substrate specificity overexpressed in solid tumors. Another protease that is often overexpressed in cancer lesions is Cathepsin B. Among Cathepsin B (lysosomal protease) sensitive peptide linkers, initially Gly-Phe-Leu-Gly and Ala-Leu-Ala-Leu were widely used linkers but due to their undesirable properties such as slow drug release and hydrophobicity leading to prodrug aggregation and reduced therapeutic efficacy, they are now substituted by dipeptide linkers such as Val-Cit and Phe-Lys. However, in some cases, the linker cleavage is hindered by the proximity of the drug and carrier. To overcome such problems, a self-immolation linker is placed between the drug and payload in addition to the existing linker. In a study by Zang and co-workers, a biocompatible self-immolative linker for controlled drug release has been described for targeted delivery of anticancer drugs (Zang et al. 2019). PC4AP is a light-responsive and self-immolative linker that can be conjugated to any amine- or hydroxyl-bearing drug via a carbamate or carbonate bond on one side and a carrier peptide or protein via an alkyl chain on the other side.

Applications of peptide drug conjugates in cancer and ocular therapeutics

According to a recent report on the peptide drug conjugates market, global PDC market size was given a valuation of USD 596.27 million in 2021 which is anticipated to expand at a compound annual growth rate (CAGR) of 18.58% from 2022 to 2030 to generate a revenue of USD 2.67 billion in 2030 (Grand View Research 2022). The report also highlights the dominance of therapeutic segment of PDC market with the revenue share of 82.3% in 2021. ConjuPepBD, a freely available database of peptide drug conjugates lists out more than 1600 conjugates for various biomedical applications (Balogh et al. 2021). Unlike most of the pre-clinical or clinical studies utilizing PDCs in anti-cancer therapy, very few pre-clinical studies have mentioned the use of ocular targeting conjugates probably due to the limited therapeutic research in the area of ocular disease management owing to the physiological as well as anatomical complexity of the eye. One of the components of peptide drug conjugates is a carrier peptide. Due to the unique properties of CPPs, they have been employed as pharmaceutical agents for the delivery of small molecules in the management of various diseases and disorders related to oncology, ophthalmology, neurology, and diabetes (Fig. 3) (Johnson et al. 2011; Derakhshankhah and Jafari 2018; Langel 2019; Xie et al. 2020). This review focuses on the role of CPPs as carrier peptides for nucleic acids, proteins/peptides and small drug molecules in the field of cancer and ocular therapeutics in the forthcoming sections.

Peptide-drug conjugates in cancer therapeutics

Despite significant development in the delivery of potential chemotherapeutics over the last decade, cancer remains one of the major causes of death (WHO 2022). Although many potential chemotherapeutics against cancer are in the market, many are associated with inadequate pharmacological profiling. Major challenges faced by DDS in delivering cancer therapeutics are low solubility, reduced bioavailability, and off-target delivery (Lorscheider et al. 2021). To achieve the tumor-targeted delivery of conjugated drugs, tumor microenvironment is often exploited to release the cargo from peptide drug conjugate at the specific site. Acidic pH, overexpression of certain enzymes and receptors, and high glutathione (GSH) levels are hallmarks of tumor cells (Li et al. 2020b). Moreover, addition of a cell/tumor-targeting peptide (CTP/TTP) also enhances the specificity of a PDC towards specific tumor cells. In modern medicine, peptides with diverse functions are being explored. Tumor penetrating peptides (TPPs) are CPPs with tumor-targeting properties that can interact with receptors overexpressed on the cancer cell surface, thereby delivering anti-cancer drugs specifically to the tumor cells with enhanced cellular bioavailability. Peptide therapeutics using TPP/CPP as a carrier molecule is a promising strategy to deliver bioactive molecules such as nucleic acids, proteins/peptides, or small drug molecules inside the cells efficiently. In addition to well-characterized examples of CPPs, for instance Penetratin, Tat, oligoarginine, and Transportan (TP), TPPs such as SP5-52, RVG peptide, and RVG-9R can also be used as therapeutic molecules for drug delivery (Tripathi et al. 2018; Nam et al. 2023).

Peptide nucleic acid complex for cancer management

For the past few years, PDCs have been widely studied, especially in cancer therapy, to enhance the efficacy of the

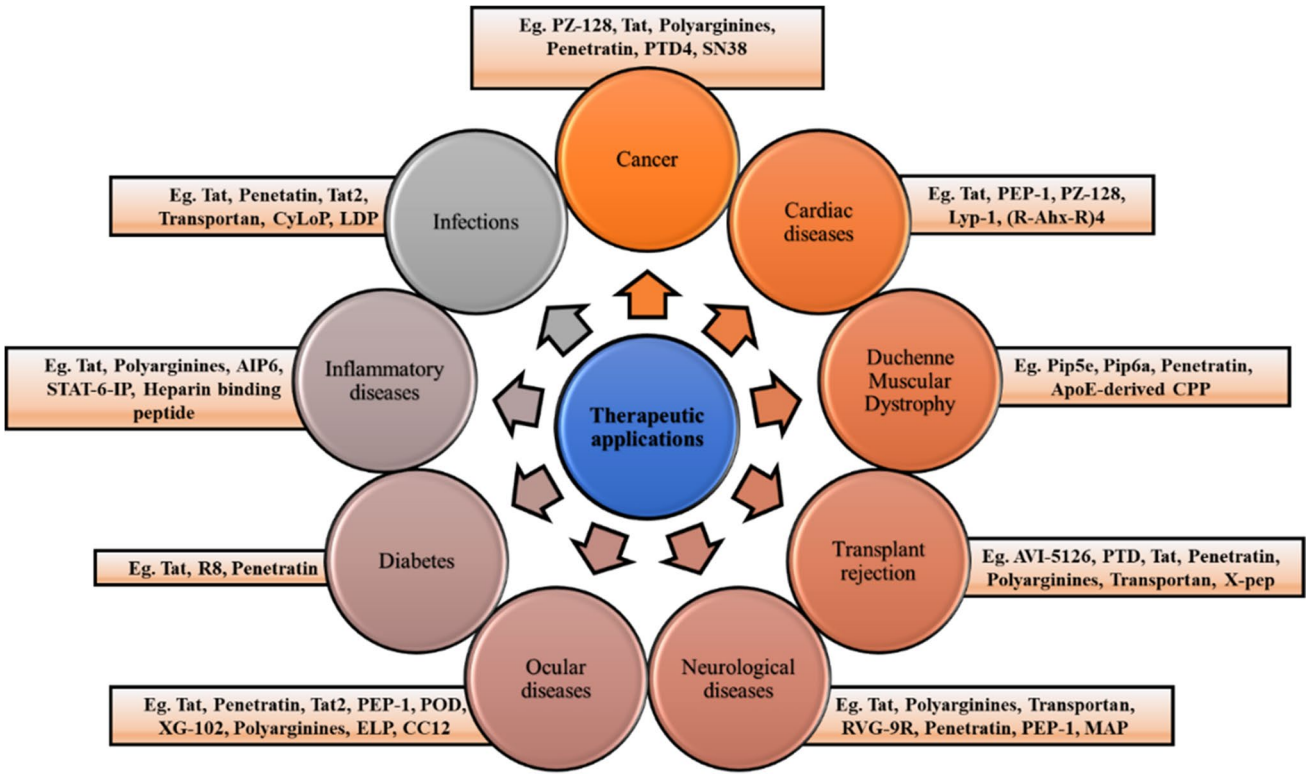

Fig. 3 CPP mediated drug delivery in various therapeutic regimes

therapeutic agent. Figure 4a and b depicts two promising strategies to enhance the cellular penetration as well as specificity of the drug conjugate towards cancer cells. In most of the cancers, genetic factors play a major role in its progression and severity. As a potential anticancer therapeutic, pharma companies are investing a lot more in the area of gene therapy to reverse or slow down the growth of cancerous cells. One of the strategies is small interfering RNAs (siRNA) that are being exploited for silencing tumor initiation and progression-associated genes. However, poor biodistribution, nuclease sensitivity, instability, off-target effects, and nonspecific activation of the innate immune system by siRNAs are the major factors contributing to the delays in their clinical translation (Seth et al. 2012; Shoari et al. 2021). To overcome the challenge associated with poor permeability of siRNA-based therapeutics, CPPs have emerged as a promising strategy to be used as vehicles for gene delivery as shown in Fig. 4c. The positive charge on CPPs imparted primarily by amino acid residues arginine and lysine, facilitates the non-covalent interaction between peptide and negatively charged nucleic acid molecules to form CPP-nucleic acid complex, nonetheless complex formation can also take place via covalent bonding between peptide and cargo (Huang et al. 2015). One of the major advantages of charge-based interaction is that the complex formation following non-covalent bonding overcomes the stearic hindrance while loading siRNA into an RNA-induced silencing complex (RISC) (Cummings et al. 2019). A few examples of CPPs that are being employed for the delivery of nucleic acids, proteins, peptides, nanoparticles and small drug molecules include TAT, Octahistidine-octaarginine (H8R8), MPG, Pep-1, Pep-2, Pep-3, EN1-iPeps and RGD, SP90, and GALA (Tripathi et al. 2018; Gautam et al. 2022). A detailed review of various CPP-based oligonucleotide delivery systems has been carried out elsewhere (Shoari et al. 2021).

CPP-based cargo delivery enhances the cellular uptake of nucleic acids inside the cells; however, shielding nucleic acids from various endo- and exo-nucleases following in vivo delivery remains a major concern. These nucleic acids are often encapsulated in viral or non-viral delivery vectors such as lentivirus, adeno-associated virus, retrovirus, liposomes, and polymeric nanoparticles to escape the action of nucleases (Mendes et al. 2022). Therapeutic efficacy of any drug delivery system can be enhanced by combining different strategies to exploit their valuable properties. As for example, conjugating CPPs to polymeric nanoparticles reduces toxicity and provides potential application in gene therapy. Recently, Zhou et al. reviewed the role of CPPs in delivering anti-cancer cargoes such as chemotherapeutic agents, siRNA, peptides and nanoparticles in various in vitro and in vivo models (Zhou et al. 2022). Table 1 lists out some

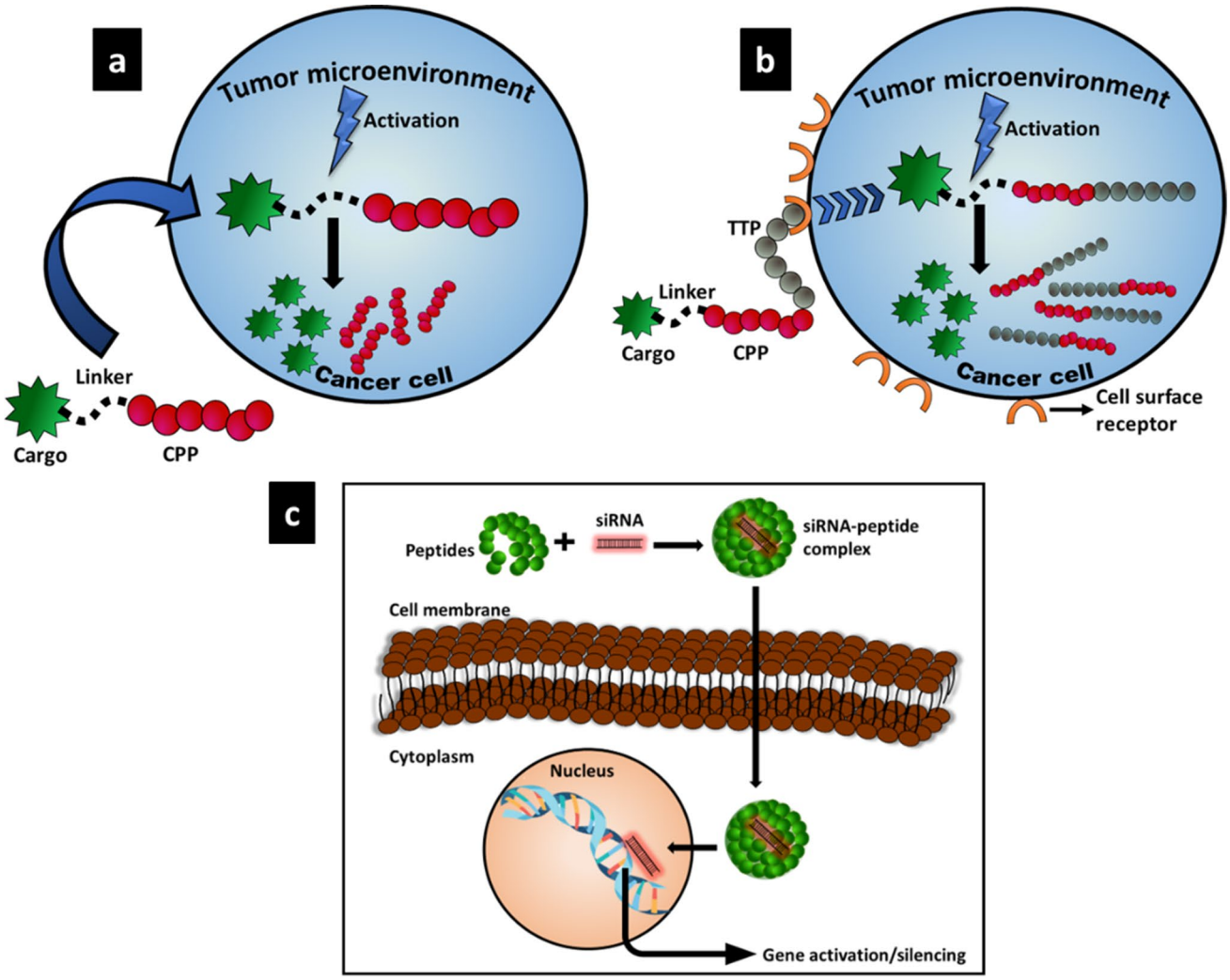

Fig. 4 Delivery strategies of peptide drug conjugates to improve intracellular uptake of drug. **a** Tumor microenvironment-specific linkers are introduced in the CPP-drug conjugate to release the drug only in the tumor cells. **b** Tumor-targeting peptide (TTP) is conjugated to the CPP-cargo complex employed in strategy A to drive the peptide drug conjugate to specific tumor cells. **c** Cell-penetrating peptide mediated delivery of nucleic acid inside the cells

preclinical studies based on CPP cargo conjugates for cancer therapeutics that have been carried out during last 5 years.

The role of micro RNAs (miRNAs or miR) has been very well established in the pathogenesis of various type of cancers, making them a promising targets for anti-cancer therapeutics (Syeda et al. 2020). Glioblastoma (GBM) is one of the aggressive cancers which is characterized by overexpression of miR210 resulting in poor prognosis of the patients (Gee et al. 2010). Efficient delivery of RNA therapeutic into glioblastoma cells by complexing anti-cancer cell-penetrating peptide, Tachyplesin (Tpl) electrostatically with anti-miR210 has been shown in a recent study (Jana et al. 2019). A significant reduction in miR210 levels as well as induction of apoptosis were evident after treating GBM cell lines with Tpl-anti-miR210 complex. Furthermore, pre-treatment of cells with the peptide cargo complex resulted in enhanced sensitivity towards temozolomide (TMZ), a current chemotherapeutic treatment.

In another interesting study, a PIP (pre/intra/post operative) therapeutic was designed using a modular peptide probe T_{CD}TMP that includes TMTP1 (targeting peptide), TAT (CPP), PLGLAG (cleavable linker) and PyTPA (triphenyl derivative for tumor imaging) (Dai et al. 2020). T_{CD}TMP is a self-assembly peptide that can form nanoparticles when loaded with miR-145-5p (promoting tumor cell apoptosis) or vascular endothelial growth factor (VEGF) siRNA (inhibiting angiogenesis). This PIP therapeutic system was tested in various models of ovarian tumor and was shown to result in reduced reoccurrence of the ovarian cancer. At the pre-operative stage, this system was specifically targeted to tumor cells ensuring the delivery of miR-145-5p, thereby stimulating the apoptosis of cancerous cells. Another role

Table 1 In vitro/in vivo studies involving cell/tumor penetrating peptide cargo conjugates for cancer therapeutics

Peptide moiety (sequence)	Cargo	In vitro/in vivo model system	Reference
Activatable cell-penetrating peptide (ACCP) consisting of a cell-penetrating domain octa-arginine (RRRRRRRR)	siRNA-loaded liposomes	**In vitro**- human breast adenocarcinoma cell line (MCF-7 cells) and human pulmonary adenocarcinoma cell line (A549 cells)	(Xiang et al. 2017)
BR2 peptide (RAGLQFPVGRLLRRLLR)	siRNA	**In vitro**- human cervical cancer cells (HeLa), human colon cancer cells (HCT116), mouse fibroblast cells (NIH3T3), and human keratinocyte cells (HaCaT)	(Lee et al. 2018)
Tat-(His)n peptide coupled to γ-cholesterol glutamate (Glu-Chol) [(His)nGRKKRRQRRR]	siULK1/Narc co-delivery or single delivery	**In vitro**- normal human liver cell line (L02) and human hepatocellular carcinoma (HCC) cell lines **In vivo**- BALB/c nude mice carrying HCC xenografts	(Wang et al. 2018b)
Palmitoyl-transportan-iRGD (pTP-iRGD) peptide (CH3(CH)15- GWTLNSAGYLLGKINLKALAALAKKIL- GGK(TAMRA)GGCRGDKGPDC, Cys-Cys bridge])	siRNA	**In vitro**- human and murine pancreatic ductal adenocarcinoma (PDAC) cell lines **Ex vivo**- pancreatic organoids from primary mouse and human tumors **In vivo**- KPC mice model of pancreatic cancer	(Lo et al. 2018)
PepFect 14 (PF14) peptides (Stearyl-AGYLLGKLLOOLAAAALOOLL)	siRNA	**In vitro**- luciferase stably expressing cell lines, human glioblastoma cell line (U87 MG-luc2), and cervical cancer cell line (HeLa-luc)	(Srimanee et al. 2018)
gH625 peptide (HGLASTLTRWAHYNALIRAF)	siRNA encapsulated superparamagnetic iron oxide nanoparticles (SPION)	**In vitro**- triple negative breast cancer cell line (MDA-MB-231)	(Ben Djemaa et al. 2018)
RGDfC peptide	Doxorubicin and siRNA	**In vitro**- HCC cell line (HepG2) and human normal liver cell line (Lo2) **In vivo**- xenograft mouse model	(Xia et al. 2018)
GALA peptide	siRNA encapsulated MEND (multifunctional envelope type nanodevice)	**In vivo**- metastatic lung cancer murine model	(Abd Elwakil et al. 2019)
Lin TT1 peptide conjugated with cholesterol and histidine 7 (AKRGARSTA)	siRNA and an indoleamine 2,3-dioxygenase inhibitor	**In vitro**- breast cancer cell line (4T1) **In vivo**- 4T1 mouse breast cancer allograft tumor model	(Li et al. 2019)
TAT (in prodrug formation) and cRGD (conjugated to lipid) peptides (TAT: KTGRKKRRQRRRG and cRGD: KFDGR)	Cisplatin and siRNA	**In vitro**- human lung carcinoma cell line (A549) **In vivo**- A549 tumor model in nude mice	(Lin et al. 2019)
LAH4-L1 peptide (KKALLAHALHLLALLALHLAHALKKA)	Self-assembled polypeptide nanoparticles encapsulating siRNA	**In vitro**- multi-drug resistant human breast cancer cell line (MCF-7/ADR) **In vivo**- MCF-7/ADR tumor model in BALB/c nude mice	(Liu et al. 2019a)
cRGD peptide with a polyhistidine sequence	siRNA encapsulated peptide nanoparticles (PNPs)	**In vitro**- triple-negative breast cancer cell line (MDA-MB-231) and 4T1 cell line **In vivo**- breast tumor bearing mouse model	(Liu et al. 2019b)
iRGD peptide (CRGDKGPDC)	siRNA encapsulated iRGD-exosomes	**In vitro**- adenocarcinomic human alveolar basal epithelial cell line (A549) **In vivo**- tumor xenograft mouse model	(Zhou et al. 2019)

Table 1 (continued)

Peptide moiety (sequence)	Cargo	In vitro/in vivo model system	Reference
RGDfC peptide	siRNA encapsulated selenium nanoparticles (SeNPs)	**In vitro**- human colorectal cancer cells (HT-29) **In vivo**- tumor xenograft mouse model developed with HT-29 cells	(Xia et al. 2020)
RGDfC peptide	siRNA encapsulated selenium nanoparticles (SeNPs)	**In vitro**- HCC cell line (HepG2) **In vivo**- HepG2 tumor xenograft model	(Xia et al. 2021)

of miR-145-5p came into effect during the intra-operative stage where residual tumor cells were eliminated through T_{CD}TMP- miR-145-5p-mediated photodynamic therapy. To delay the reoccurrence of ovarian cancer, T_{CD}TMP- VEGF-siRNA was given post-operatively as an anti-angiogenic molecule to inhibit the angiogenesis. Another example of self-assembly peptide system is the plectin-1 targeting peptide with arginine-rich motif to deliver RNA therapeutics against pancreatic ductal adenocarcinoma (PDAC) (Chen et al. 2019; Wu et al. 2020). The arginine-rich motif of the chimeric peptide system aids in miRNA binding and increased cellular permeability of the self-assembled peptide nanoparticles. These nanoparticles showed successful delivery of miRNA in PDAC cells and enhanced doxorubicin induced apoptosis, thereby indicating the potential of PL-1/miRNA nanoparticles in treating PDAC.

The progression of cancer depends on the expression level of several cancer-promoting factors, one of which is CD73 that is generally induced by some transcription factors such as signal transducer and activator of transcription 3 (STAT3) and other factors such as cytokines, signaling factors, and hypoxia-inducible factor (HIF)-1 (Ghalamfarsa et al. 2019). To suppress CD73 and HIF-1α genes, a delivery system using siRNA-loaded superparamagnetic iron oxide nanocarriers (SPION) has been reported (Hajizadeh et al. 2020). Furthermore, the complex was coated with chitosan derivatives and TAT peptide in order to enhance the complex stability and cellular penetration ability respectively. Similar system was designed for concurrent inhibition of HIF-1α and STAT3, and tested in two different tumor types, 4T1 breast cancer and CT26 colon cancer (Budi et al. 2021). SPIONs were coated with chitosan derivatives to increase the loading efficiency of siRNA followed by functionalization with hyaluronate and TAT peptide to increase the cellular uptake of nanoparticles (NPs) in cancer cells. The results of the study were suggestive of an effective CPP-based DDS to treat cancer by inhibiting HIF-1α/STAT3 molecules simultaneously. Selenium nanoparticles (seNPs) are another well-known system that is being widely used in cancer therapeutics. seNPs are known for their anticancer activity as well as low toxicity in non-cancerous cells (Martínez-Esquivias et al. 2022). In two different studies, RGDfC peptide-coated seNPs loaded with siRNA were investigated for their anti-tumor activity in vitro as well as in vivo (Xia et al. 2020, 2021). RGDfC-seNP-siRNA successfully induced apoptosis in the treated cells and inhibited the tumor growth without causing any obvious side effects.

Besides selenium NPs, other metallic NPs are also used to study cancer therapeutics. iRGD-functionalized mesoporous silica nanoparticles (MSN) have been employed for the co-delivery of siRNA (siPlk1) and miRNA (miR-200c) in 3-D tumor spheroids in vitro and breast tumor in vivo (Wang et al. 2020b). To facilitate endosomal escape, a

photosensitizer indocyanine green (ICG) was also encapsulated in the NPs. This dual delivery of RNA therapeutics along with photodynamic therapy offers a potential strategy for the management of metastatic cancers. Recently, a cell-penetrating peptide (polyarginine; R10) conjugated targeting ligand (chlorotoxin; CTX) was utilized to formulate a nanoparticle system by functionalizing iron oxide nanoparticles with R10-CTX peptide (Chung et al. 2023). These NPs were able to deliver electrostatically complexed siRNA successfully to various tumor cells, hence, making these cells sensitive to an alkylating drug Temozolomide (TMZ). The study demonstrates shielding of siRNA from degradation followed by its efficient delivery into cancer cells.

Delivery of protein/peptides for cancer therapeutics

Intracellular signaling circuit controls major pathways that are involved in the regulation of cancers (Hanahan and Weinberg 2011). Protein–protein interactions (PPIs) are a significant part of signaling reactions that are often dysregulated in cancers. Targeting these deregulated PPIs by therapeutic proteins could be an efficient anti-cancer strategy; however, adequate delivery of these therapeutics across the tumor cell membranes is equally challenging (Au et al. 2016; Habault and Poyet 2019). More than 2 decades ago, delivery of a 120 kDa beta-galactosidase protein in mice tissues by a cell-penetrating peptide TAT was demonstrated by Dowdy and his co-workers in the year 1999 that encouraged many research groups to investigate CPPs for the cellular delivery of macromolecules including large proteins for therapeutic uses (Schwarze et al. 1999).

In the year 2017, chimeric peptides having CPP as a shuttle linked to binding sites of Ras or Raf were designed to disturb the Ras-Raf interaction of the RAS-RAF-MEK-ERK pathway that has been shown to be a promising target for cancer therapeutics (Marin et al. 2017). Chimeric peptides having Mut3DPT CPP shuttle were tested in BALB/c mice model of spontaneous leukemia for demonstrating their anti-tumor activity and have been patented as WO2015001045 A2 (PCT/EP2014/064243) (Rebollo et al. 2015). Same group studied different sets of chimeric peptides targeting another PPI, SET-PP2A interaction, in which SET is an oncoprotein that interacts with PP2A (tumor suppressor) leading to the inhibition of tumor suppression (Tian et al. 2018). The CPP moiety in these chimeric peptides was again Mut3DPT but conjugated to binding sites of PP2A or SET instead of Ras or Raf. These chimeric peptides modulated SET-PP2A interaction hence, demonstrating in vitro apoptotic effects as well as in vivo anti-tumoral activities.

Few CPPs are also being designed as tumor-homing peptides that can direct the cargos specifically to the cancerous cells. Such examples include RT53 and MT23 where RT53 is a chimeric peptide consisting of Penetratin (a CPP) conjugated to leucine zipper domain of AAC-11 (anti-apoptotic protein) that specifically target tumor cells and MT23 is a CPP specific for B16 melanoma cancer cells (Jagot-Lacoussiere et al. 2016; Zhou et al. 2017). In mouse tumor model as well as prophylactic mouse model, RT53 demonstrated anti-cancer effects through tumor regression and prevention of tumor growth respectively in addition to causing immunogenic cell death (ICD) (Pasquereau-Kotula et al. 2018). In the case of novel MT23, cargo delivery and specificity towards mouse melanoma cells were shown in vitro as well as in vivo (Zhou et al. 2017). To ascertain cargo carrying ability in vivo, functional Apoptin was conjugated to MT23 and delivered to B16 tumor bearing mice that resulted in inhibition of tumor growth and induction the cell apoptosis. This strategy of using peptides with dual function of CPP as well as CTP might advance the development of peptide-based cancer therapeutics.

CPP-conjugated cytotoxic drugs as an anti-cancer strategy

Chemotherapy is the commonly used conventional strategy to manage most of the cancers. However, chemotherapeutic drugs lack tumor cell specificity that causes an array of side effects leading to poor disease management and reduced patient compliance. Conjugating chemotherapeutic drugs with cell-penetrating peptides can enhance the drug delivery, tumor specificity as well as pharmacokinetic properties of the drug molecule (Rusiecka et al. 2022). In further sections, recent studies on CPP conjugated chemotherapeutic drugs have been discussed.

Epigallocatechin gallate

Epigallocatechin gallate (EGCG) is a versatile bioactive polyphenolic constituent present in green tea extracts; however, poor stability as well as bioavailability of EGCG limits its utilization in various biomedical applications including cancer and diabetes (Yang et al. 2019). To exploit the anti-cancer activities of EGCG with increased bioavailability, various researchers are investigating nano-vehicle drug delivery systems of EGCG for cancer therapy (Li et al. 2020a). To increase the tumor targeting of EGCG-encapsulated mesoporous silica nanoparticles in breast-tumor bearing mice, Ding et al. coated these nanoparticles with tumor-homing cell-penetrating peptide PEGA-pVEC (Ding et al. 2015). Targeted delivery and release of EGCG with the help of peptide-coated nanoparticles demonstrated highest tumor inhibition rate of approximately 90% in mice model of breast tumor. The same research group also showed co-delivery of siRNA and EGCG through hyaluronic acid and tumor-homing CPP-coated nanogels for the treatment of drug-resistant breast-tumor bearing mice (Ding et al. 2018).

In vivo results were corroborated with in vitro results where authors showed 15-fold increased cytotoxic effect of the formulated nanogels as compared to free EGCG in the drug-resistant MDA-MB-231 cell line.

Camptothecin

Camptothecin (CPT) is a natural alkaloid and a DNA topoisomerase 1 inhibitor with potent antitumor activity; however, its use is limited by low solubility and stability (Martino et al. 2017). A cyclic cell-penetrating peptide [$W(WR)_4$ K] has been conjugated to modified camptothecin to enhance its solubility and compare anti-proliferative activities of parent CPT with peptide-conjugated CPT conjugates (CPT1 and CPT2) in the breast cancer cell line MCF-7 (El-Sayed et al. 2019). After conjugation, both the conjugates demonstrated enhanced water solubility; however, only one conjugate (CPT2) had comparative anticancer activity with the parent molecule. Based on these results, authors concluded their study by hypothesizing the formation of prodrug in the case of CPT1 upon peptide conjugation and suggested that further studies are required to explore the potency of these peptide conjugated drugs on various cancer cell lines. In the same year, Zhang et al. designed pH-activable cell-penetrating peptide, LH, by modifying few amino acids of an existing CPP, LK to further increase the tumor specificity of CPP (Zhang et al. 2019). Selectivity and anti-tumor activity of camptothecin (CPT) upon conjugation with LH or LK peptide were investigated in HeLa as well as MDA-MB-231 cell lines. LH-CPT showed significantly increased selectivity as well as anti-tumor activity of CPT at low pH as compared to LK-CPT or CPT alone, suggesting a potential to deliver anticancer drugs with lower cytotoxicity of the carrier peptide molecule.

Wang et al. formulated CPT containing supramolecular hydrogel system to deliver stimulator of interferon genes protein (STING) agonists against malignant tumors (Wang et al. 2020a). A self-assembled diCPT–iRGD conjugate was first formed by conjugating tumor penetrating iRGD peptide with CPT followed by spontaneous assembly into supramolecular nanotubes in aqueous system. Electrostatic complexation of cyclic di-AMP (CDA), a STING agonist, was carried out in the presence of positively charged diCPT–iRGD nanotubes forming CDA-NT solution that can immediately form hydrogels when injected into tumors. This hydrogel system allows targeted and enhanced delivery of both CPT and CDA to evoke immune system and achieve chemoimmunotherapy.

Paclitaxel

Paclitaxel (PTX) is a microtubule inhibitor used to treat breast cancer and solid tumors. However, its effectiveness is limited due to poor solubility, lack of specificity, dose-limited toxicity, and emergence of drug resistance (Ma et al. 2021). Several peptide-paclitaxel conjugates have been reported to overcome multidrug resistance and improve solubility. The conjugation between highly soluble collagen-CPP hybrid carrier (COL-CPP) and PTX to formulate a soluble PTX prodrug has been reported (Ayalew et al. 2017). Conjugation of PTX to COL-CPP resulted in a highly soluble PDC (400-fold increase in solubility) with similar potency as compared to free PTX in Jurkat (human T lymphocyte of acute T cell leukemia) cell line. Surprisingly, the same conjugate exhibited significantly increased IC_{50} value as compared to PTX alone in A549 (human epithelial of lung carcinoma) cell line probably due to endosomal entrapment that warrants further research on PTX-COL-CPP conjugates in various cancer cell lines. When different CPPs were conjugated to PTX (PTX-TAT and PTX-LMWP) and the conjugates were investigated in A549 and A549T cell lines, significantly enhanced cellular uptake as well as anti-cancer activity was demonstrated (Duan et al. 2017). In addition to in vitro activity, PTX-CPPs exhibited potent anti-tumor activity than free PTX in tumor-bearing mice establishing the efficiency of PTX-TAT and PTX-LMWP in inhibiting tumor growth significantly.

Furthermore, smart PDC (LTP-1) by conjugating PTX with multifunctional peptides composed of tumor-targeting peptide (TTP) and CPP has been reported (Deng et al. 2021). The peptide component of LTP-1 consisted of antineoplastic peptide B1-derived cell-penetrating peptide and luteinizing hormone-releasing hormone (LHRH; also named as gonadotropin-releasing hormone) as TTP along with a peptide spacer. LTP-1 showed two-fold higher cellular uptake in LHRH receptor overexpressed MCF-7 cells along with enhanced cytotoxicity as compared to PTX alone. LTP-1 also demonstrated higher anti-tumor efficacy in vivo than PTX in MCF-7 xenograft mice model. In another study, PTX was conjugated covalently/non-covalently to a pH-activatable cell-penetrating peptide dimer LH_2 and the anti-tumor activity of the conjugate was assessed in vitro as well as in vivo in triple-negative breast cancer cells, MDA-MB-231 (Nam et al. 2021). LH_2 conjugation resulted in enhanced bioavailability and prolonged circulation in addition to increased anti-tumor activity at significantly lower dosage.

To address the issues such as solubility and bioavailability, various researchers have used nano-scaled systems such as nanoparticles, micelles, or nanofibers as carrier vehicles for the delivery of PTX. In a study by Wang and co-workers, dual drug-loaded lipid polymeric nanoparticles were synthesized by encapsulating RGD-modified paclitaxel (PTX) and cisplatin (CDDP) to increase the tumor targeting and tumor penetrating properties of dual drug system (Wang et al. 2018a). These redox- sensitive nanoparticles were evaluated for anti-tumor efficiency in lung cancer cell lines as well as

tumor xenograft mice model and were found to exhibit better anti-cancer activity than the drugs alone. This study suggests that a synergistic nanosystem with lowered systemic toxicity could be developed with the help of tumor-penetrating peptides for the management of lung cancer. Shi and co-workers also reported use of RGD peptide for enhanced therapeutic efficacy of nanomicelles. Self-assembled micelles consisting of RGD-polyethylene glycol (PEG) molecules conjugated with PTX via disulfide linkages were employed to deliver PTX inside tumor cells. Release of PTX was investigated through in vitro cell-based assays that suggested gastric cancer cell specificity of PTX containing RGD nano-micelles where this peptide-based nanosystem inhibited cell proliferation via apoptosis. Results of in vivo study also validated the specificity as well as anti-cancer efficacy of RGD-micelles by targeting and inhibiting gastric tumor efficiently in tumor model (Shi et al. 2019).

Doxorubicin

Doxorubicin (DOX) is a part of the anthracycline group of chemotherapeutic agents that causes double-strand DNA breakage and inhibition of nucleic acid synthesis. It has been used as a therapeutic agent since the 1960s; however, due to its high cardiotoxicity, alternative strategies are being explored for DOX delivery into tumor cells (Mobaraki et al. 2017). Octa-arginine (R8) is one of the cell-penetrating peptides that has been employed in CPP-Dox conjugates to overcome the issue of drug resistance in cancer cell lines (Lelle et al. 2017, 2018). Another recent study aimed at targeting drug-resistant cancer cell line with (WR)8WKβA conjugated DOX demonstrated significant reduction in the cell proliferation when Dox-resistant cells (MES-SA/MX2) were treated with [(WR)8WKβA]-DOX conjugate as compared to free DOX alone (Zoghebi et al. 2022). Apart from drug-resistant cell line, [(WR)8WKβA]-DOX conjugate also inhibited cell growth significantly in other cancer cell lines when compared with the treatment of DOX alone. Furthermore, a novel lysine-rich CPP (KRP) was conjugated to DOX in order to enhance tumor penetration as well as drug accumulation of doxorubicin in tumor tissues (Yu et al. 2019). Darwish and co-workers (2019) attempted cell-penetrating cyclic peptide, $C(WR)_4K$ conjugation to DOX via thiol linkage in order to improve cytotoxicity profile and cellular accumulation of DOX (Darwish et al. 2019). After 72 h of incubation with the cells, cytotoxic effects of CPP-conjugated DOX were found to be significantly higher than DOX alone in HEK-293, HT-1080, and SKOV-3 cell lines suggesting $C(WR)_4K$ conjugated DOX as a potential candidate for further anticancer studies.

Malignant brain tumors, consisting of primary as well as secondary tumors, are one of the highly aggressive and difficult to treat tumors that are the most common type of brain tumor found in adults (Schouten et al. 2002; Barnholtz-Sloan et al. 2004). One of the major impediments in the management of primary brain tumor by systemic chemotherapy is the presence of the blood–brain barrier (BBB) that consists of endothelial cells and numerous tight junctions forming a dense meshwork (Rick et al. 2019). Because of the small size, nanoparticles offer an advantage to improve the delivery of chemotherapeutic drugs across BBB for the treatment of malignant brain tumors (Zottel et al. 2019). However, conjugating cell-penetrating peptides to various nanoparticles may further enhance the translocation potential of NPs across BBB. The delivery potential of CPP-conjugated liposomes to deliver DOX across BBB has been also investigated (Yuan et al. 2019). U87-MG cells were treated with DOX-encapsulated octa-arginine (R8) coated liposomes to assess the cellular penetration as well as cytotoxicity of the nano-system. CPP-coated liposomes were found to exhibit 8.6-fold higher cellular uptake and 18.11% more cytotoxicity than DOX alone. This study suggests the potential of CPPs in the development of therapeutic systems against malignant brain tumors that can cross BBB.

Cisplatin

Metal complexes such as cisplatin are one of the most versatile chemotherapeutic agents because of the properties like redox potential or charge variation; however, they also suffer from drawbacks such as poor water solubility and cellular penetration (Ndagi et al. 2017; Neundorf 2017). To address the issue of poor cellular uptake, CPPs offer a suitable strategy for developing effective cisplatin-based cancer therapies. Effects of cisplatin complexation with the malonate derivative of buforin IIb, a potent antimicrobial, anticancer as well as cell-penetrating peptide, on cell targeting and anti-proliferative activities of the conjugate have been investigated (Parker et al. 2016). In vitro data showed enhanced cytotoxicity of the conjugate towards cisplatin-resistant ovarian cancer cell line A2780 cisR with an IC_{50} value of 7.8 ± 0.2 μM as compared to cisplatin alone having an IC_{50} value of 9.7 ± 1.0 μM. Surprisingly, this conjugate demonstrated lower cytotoxicity towards cisplatin-sensitive A2780 cell line as compared to cisplatin alone. Another study in ovarian cancer line established the role tumor-targeting peptide RGD in enhancing the tumor penetration of cisplatin to achieve better therapeutic efficacy (Lai et al. 2017). In an interesting study by Izabela and co-workers, Transportan 10 (TP10) being a well-established CPP could only enhance anticancer activity of cisplatin in vitro. Moreover, TP10-cisplatin conjugate was shown to be relatively safe in non-cancerous cell line (Izabela et al. 2016).

Peptide drug conjugates in ocular therapeutics

According to the last reported data by the World Health Organization (WHO), vision impairment (VI) and blindness have affected at least 2.2 billion people out of which 1 billion people have a preventable or yet to be addressed vision impairment (Mario 2010). Leading causes of blindness among population aged 50 years or more includes cataract followed by glaucoma, under-corrected refractive errors, age-related macular degeneration (AMD) and diabetic retinopathy (DR) (Adelson et al. 2021). Extensive research is being carried out in order to develop novel therapeutics for such vision-threatening disorders. However, therapeutic research in the area of ocular diseases is limited by the physiology and anatomy of the human eye which is considered to be one of the most complex organs of the body. Anatomically, it is divided into anterior and posterior segments. The presence of various physiological and anatomical barriers such as pre-corneal barrier, corneal barrier, conjunctival barrier, and blood retinal barrier (BRB) render ophthalmic drug delivery a challenging task to overcome the drawback of reduced bioavailability molecule (Agrahari et al. 2016; Bachu et al. 2018). Consequently, various routes of administration have been employed to overcome these barriers, as shown in Fig. 5 (Rohira 2021).

Topical instillation, being a conventional mode of drug delivery, is still considered as the best strategy for the effective treatment of ocular diseases because of its association with high patient compliance and non-invasiveness. However, drug absorption is hindered by static epithelial and dynamic tear-film barriers. It has been reported that only 5% of the drug is absorbed via corneal tissue after topical application whereas remaining 95% of the drug gets drained through nasolacrimal flow or other channels resulting in reduced bioavailability of the drug inside ocular tissues (Chrai et al. 1973, 1974). Unlike anterior segment of the eye, posterior segment is not easily accessible to ocular drug administration. Intraocular drug delivery to posterior segment is challenged by blood-aqueous barrier (BAB) as well as blood-retinal barrier along with posterior compartment barriers such as neural retina, vitreous humor, choroid or sclera (Cabrera et al. 2019; Varela-Fernández et al. 2020). Figure 6 summarizes various routes of ocular drug delivery with their benefits and limitations (Gaudana et al. 2010).

To overcome these drawbacks, numerous novel drug delivery systems have been developed over the past few years that are based on nanoparticles, liposomes, CPPs, and hydrogels (Agarwal et al. 2016; Omerović and Vranić 2020; Meza-Rios et al. 2020; Torres-Luna et al. 2020; Hu et al. 2022). CPP-based drug delivery approaches have been widely employed for the successful administration of therapeutic agents across ocular tissues in a non-invasive or minimally invasive manner because of their high biocompatibility, low cytotoxicity, and efficient cargo delivery (Pescina et al. 2018). In a review by Parsons et al. and

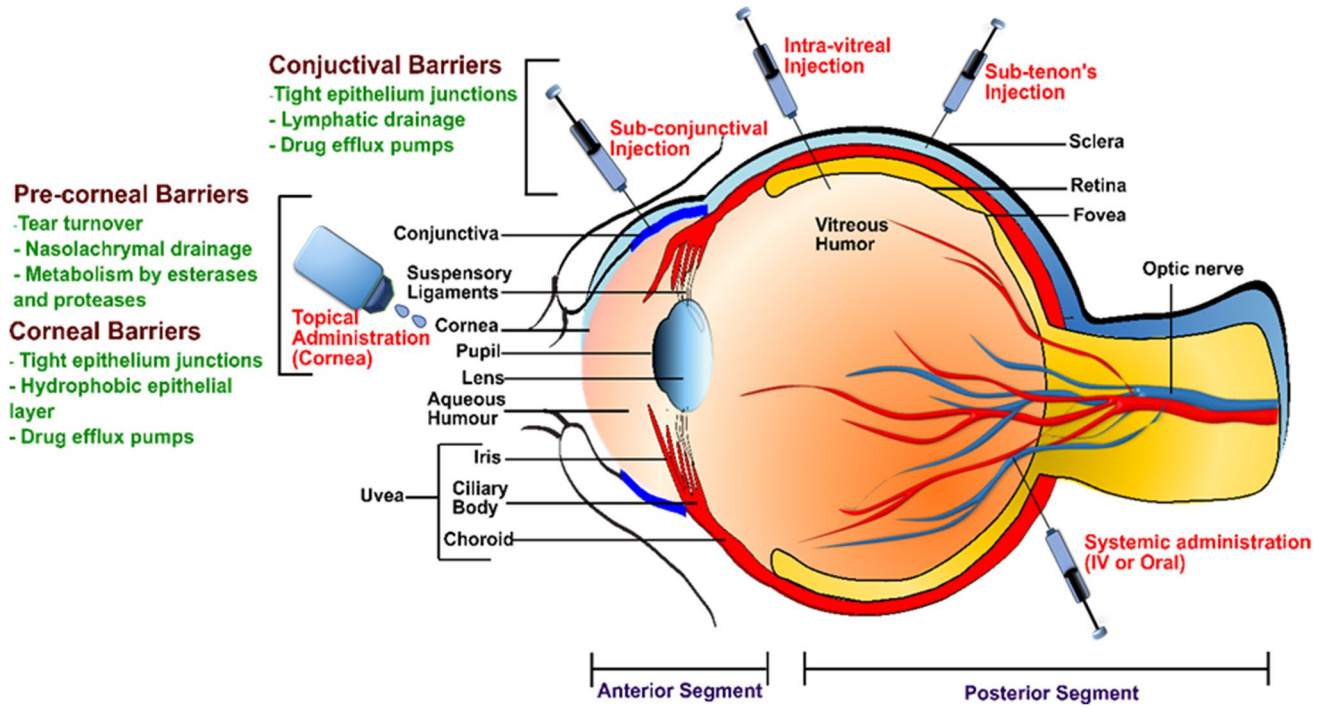

Fig. 5 Anatomical barriers of a human eye and current routes of drug administration

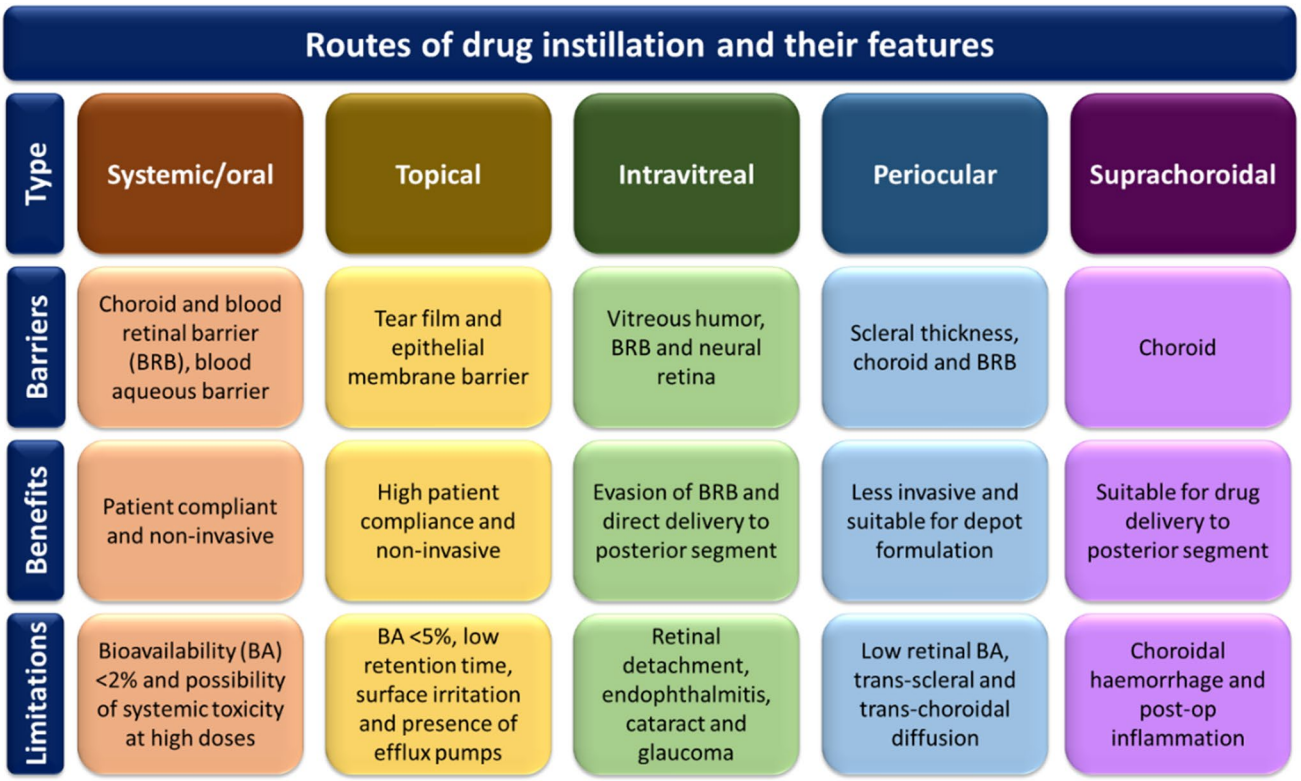

Fig. 6 Benefits and limitations of various routes of ocular drug administration

Pescina et al., various CPPs based PDCs are discussed for the management of retinal disorders (Pescina et al. 2018; Parsons et al. 2021).

CPP mediated delivery of nucleic acids in ocular tissues

The development of peptide for ocular delivery (POD) for delivering nucleic acid and other small drugs to posterior segment of the eye opened up avenues for CPP-mediated delivery of nucleic acids in ocular tissues (Johnson et al. 2008). Successful in vitro delivery and regulation of green fluorescent protein (GFP) expression by the POD-plasmid/siRNA complex in human embryonic retinal (HER) 911 cells have been reported. In subsequent studies, it was shown that POD/DNA nanoparticles failed to deliver cargo to post-mitotic cells in the murine retina; however, the PEGylated POD/plasmid polyplex successfully delivered the glial cell line-derived neurotrophic factor (GDNF) plasmid and effectively attenuated retinal degeneration in a retinitis pigmentosa murine model (but not in vitro in ARPE-19 cells) (Read et al. 2010). Another study using PEGylated POD reported the development of reducible PEGylated POD (PEG-SS-POD) to deliver a human fms related receptor tyrosine kinase 1 (FLT1)-carrying plasmid to murine retina (Dasari et al. 2017). Functionalization of CPP with PEG using a reducible orthopyridyl disulfide bond resulted in a complex capable of in vitro as well as in vivo delivery of gene-carrying plasmid. When the efficiency of POD-conjugated FLT1 was tested in CNV mice model, significant reduction in neovascular retinal lesions was observed in mice treated with PEG-POD-FLT1 nanoparticles suggesting the potential of POD peptide to deliver bioactive DNA into the retina. Later in 2019, Davide Schiroli led research group reported a successful reduction in the reporter gene levels when it was topically delivered in the cornea using a mutated POD-siRNA complex (Schiroli et al. 2019). They developed a covalently modified variant of POD (QN-Palm-POD) to investigate the role of lysogenic compounds such as chloroquine (Chlq) in the release and consequent inhibition of siRNA-targeted genes. The efficiency of QN-Palm-POD to deliver siRNA was investigated in animal model for knockdown of luciferase expression. Treatment with QN-Palm-POD/siRNA was terminated after 4 days followed by quantitative estimation of luciferase activity till day 10. Significant reduction in the luciferase activity was seen 3 days post-termination that went upto a maximum of 30% reduction at day 9 following which the luciferase levels returned back to pre-treatment levels.

Penetratin (PNT) is another cell-penetrating peptide that has been explored for cargo delivery, particularly in the posterior segment of eye. Penetratin (and dendrimers) mediated

delivery of luciferase-specific antisense oligonucleotides (ASO) to the retina was reported when applied topically (Tai et al. 2017b). Inclusion of polyamidoamine (PG5) to condense ASO via noncovalent interactions was included in the study when PNT failed to efficiently compact nucleic acids. Treatment of U87-Luc cells with PNT-conjugated ASO complex (PG5/ASO/PNT) resulted in enhanced cellular uptake as well as luciferase knockdown in comparison to the cells treated with naked ASO or PG5/ASO complex. When the efficiency of PG5/ASO/PNT was investigated in tumor bearing mice model, immunohistochemical staining of tumor tissue sections revealed significant reduction in the expression levels of luciferase in mice treated with PG5/ASO/PNT as compared to treatment with saline, ASO alone or PG5/ASO complex. Moreover, significant weakening of bioluminescence was observed in orthotopic tumor-bearing animals treated with PG5/ASO/PNT, suggesting an effective RNA interference (RNAi) effect at the in vivo level. To increase the nucleic acid condensation capacity of penetratin, Multivariant Penetratin (MVP) has been developed through fusion of the peptide with multi-armed PEG molecules such that PEG forms the core moiety with PNT molecules being terminally present on each arm (Jiang et al. 2019). Conjugation of DNA with eight-valent PNT (8VP) resulted in the formation of stable positively charged peptide/DNA polyplexes (> 100 nm). In vitro studies revealed 50-fold higher fluorescence intensities of the human corneal epithelial cells (HCEC) treated with 8VP/ASO as compared to ASO alone whereas it was 150-fold in human conjunctival epithelial cells (NHC) suggesting higher selectivity of 8VP/ASO towards NHC cells. In addition to enhanced cellular uptake in anterior segment cell lines (HCEC and NHC), 8VP/siRNA also demonstrated successful permeation across in vitro blood-retinal barrier model (HUVEC and ARPE-19 cells). Furthermore, intraocular distribution analysis suggested that 8VP-delivered nucleic acids could be detected 10 min after the application to mouse conjunctival sac, with traces found in the retina even after 6 h. To test the potential of 8VP/siRNA in the management of posterior segment disorders, retinoblastoma-carrying mice were treated with 8VP/siRNA where significantly weakened bioluminescence signal was observed 13 days post-treatment initiation. In order to further stabilize compacted DNA in a CPP/DNA complex, explored the effect of chondroitin sulfate (CS) coating on these arginine-rich cationic or amphipathic peptide-pDNA complexes (Subia et al. 2019). Preclinical studies on dividing, differentiated, and primary retinal pigment epithelial (RPE) cells have demonstrated a positive correlation between CS coating and transfection efficiency. In addition, particle tracking assessment in the vitreous humor suggested that CS coating enhanced the stability and mobility of the polyplex. Most importantly, coated and uncoated peptide/DNA polyplexes successfully transfected differentiated and human primary RPE cells, which are generally recalcitrant to transfection. A list of few recent studies involving CPP-mediated delivery of nucleic acids in ocular tissues is summarized in Table 2 below.

CPP-mediated delivery of therapeutic protein/peptide for the management of ocular disorders

Several therapeutic proteins have been approved by the Food and Drug Administration (FDA) for treating ocular disorders; however, their ocular delivery especially to posterior segment is very challenging owing to the presence of physiological as well as anatomical barriers in the eye (Shastri et al. 2023). Initial studies on CPP-mediated protein delivery in ocular tissues primarily focused on TAT. One of the early studies by Wang and co-workers, reported the successful application of $TAT_{49–57}$ CPP for the delivery of human acidic fibroblast growth factor (aFGF) in a rat model of retinal ischemia–reperfusion (IR) injury (Wang et al. 2010). Both TAT-conjugated aFGF-His (TAT-FGF-His) and aFGF-His alone were topically administered; however, only TAT-linked protein was detected in the retina with a highest level being detected between 30 and 60 min post topical application. Moreover, animals treated with TAT-FGF-His exhibited reduced apoptosis in ganglion cells and better maintenance of retinal function. This study showed that conjugation with TAT enhanced the permeation of FGF across ocular tissues without affecting its biological activity. The role of TAT and RGD peptide to deliver anti-angiogenic molecule Endostatin (Es) topically to inhibit angiogenesis in the retina has been assessed (Li et al. 2016). In vitro study demonstrated successful penetration in corneal barrier as well as BRB models in addition to anti-angiogenic effect of TAT-Es-RGD on chick embryo using chorio-allantoic membrane (CAM) assay. Inhibition of neovascularization was also assessed in oxygen-induced retinopathy (OIR) mice model by TAT-Es-RGD eye drops where significant reduction in the avascular area as well as vessel tufts were seen as compared to negative control group of animals. Being a versatile and a potent peptide, TAT has been used in numerous studies involving ocular disorders. PDCs involving TAT conjugated vasoactive intestinal peptide (VIP) or pituitary adenylate cyclase activating polypeptide (PACAP) were investigated for their retinoprotective roles (Atlasz et al. 2019). Both VIP and PACAP are protective peptides exerting anti-inflammatory and anti-apoptotic effects, respectively (Olson et al. 2015; Reglodi et al. 2018). Efficiency of TAT-VIP/PACAP to reach retina was evaluated on rats after 2 h of FITC-conjugates instillations via fluorescence imaging of the retina. After calculating Efficiency for Traversing Eye (EtE) to retina, it was found that TAT-conjugates reached retina with an efficiency of approximately 3.35% as compared to approximately 1.1% of efficiency exhibited by VIP/PACAP alone.

Table 2 In vitro/in vivo studies involving CPP-nucleic acid or CPP-peptide/protein conjugates for ocular therapeutics

Peptide moiety	Cargo	In vitro/in vivo model system	Reference
Nucleolin binding peptide (NBP) (CAKVKDEPQRRSARLSAK-PAPP-KPEPKPKKAPAKK)	Luciferase and LacZ DNA	**In vivo-** BALB/c mice	(Binder et al. 2011)
Penetratin (RQIKIWFQNRRMKWKKK)	Red fluorescent protein plasmid (pRFP) and/or (G3 PAMAM)	**In vitro-** Human conjunctival epithelial cells (NHC), spontaneously derived human corneal epithelial cells (SDHCEC) **In vivo-** Sprague–Dawley rats	(Liu et al. 2016)
Penetratin (alone or with PAMAM and HA (5G)) (RQIKIWFQNRRMKWKKK)	Antisense oligonucleotide (ASO)	**In vitro-** Human conjunctival epithelial cells (NHC), murine fibroblast cell line (L929) **In vivo-** ICR mice	(Tai et al. 2017a)
PEP-1 (KETWWETWWTEWSQPKK-KRKV)	FK506 binding proteins (FK506BPs)	**In vitro-** Human corneal epithelial cells **In vivo-** Male Sprague–Dawley (SD) rats (dry eye model) and Male C57BL/6 (dry eye model)	(Kim et al. 2013, 2015)
HSV-1 gC peptide or TAT peptide (gC: GSRVQIRCRFRNSTR and TAT: GRKKRRQRRRPQ)	αB-Crystallin protein	**In vitro-** HLE B3 cells	(Mueller et al. 2013)
TAT (GRKKRRQRRRPPQ)	μ- CL (calpain inhibitory peptide)	**In vivo-** Sprague–Dawley rats	(Ozaki et al. 2015)
TAT PTD (YGRKKRRQRRR)	Endostatin (Es)/Es-RGD protein fragment	**In vivo-** C57BL/6 mice (Oxygen-induced retinopathy model) and C57BL/6 mice (Choroidal neovascularization model)	(Li et al. 2016; Zhang et al. 2015)

However, TAT conjugation inhibited the activity of PACAP whereas significantly enhanced retinoprotective activity of VIP was observed when bound to TAT peptide. In bilateral carotid artery occlusion (BCCAO) rat model, significant reduction in the retinal thickness was observed in case of control group as compared to PACAP derivates (TAT-VIP/PACAP) treated groups where the retinal thickness was significantly ameliorated (Atlasz et al. 2019).

In the mid-2010s, a shift from TAT-based delivery strategies was observed. Chen and co-workers identified CC12, a novel CPP, using evolution-directed phage-display technology. This dodecapeptide (EMFTPPSMIERLK) successfully permeated ocular tissue in minimally invasive and non-invasive manner. CC12 was then used to topically deliver KV11, an anti-angiogenic therapeutic peptide, to the retinal tissue. The authors reported a significant enhancement in the permeation of KV11 after its covalent conjugation to CC12 across the trans-corneal and trans scleral pathways in rabbit ex vivo studies. Successful permeation of the CC12-KV11 complex (but not KV11 alone) to the neural retina 30 min after topical administration was reported in mice studies. Furthermore, mouse oxygen-induced retinopathy assay revealed inhibition of pathological neovascularization in the retina of the CC12-KV11 treated groups only and not in animals treated with cargo alone (KV11). Additionally, based on intraocular distribution and cellular uptake studies in ARPE-19 cells, it has been suggested that CC12-KV11 traverses mainly via trans-scleral pathway (Chen et al. 2017). Exploiting the simple electrostatic interaction between synthetic CPP- oligoarginine and clinically relevant antibodies, successful delivery of CPP/bevacizumab and CPP/ranibizumab complex to the posterior eye after topical instillation has been shown (Cogan et al. 2017). Antibody and CPP were mixed to form a charge-based complex prior to administration. In vivo studies in mice showed a significant increase in the tissue-permeating potential of the CPP-antibody complex. When CPP-Bevacizumab was applied topically, 0.2% of the initial payload was detected in tissue homogenates through ELISA just after 30 min that was significantly higher than the individual controls. The maximum retinal concentration was obtained just after 45 min with the traces of the fluorescent complex detected in the aqueous humor only 6 min after instillation. CPP-antibody conjugates were also tested in porcine cornea to assess their permeation capability after 45 min of topical instillation. As compared to controls, significantly higher levels of CPP-ranibizumab and CPP-bevacizumab were observed in total vitreous as 17.09 ± 4.68 μg/mL and 10.68 ± 3.57 μg/mL, respectively. Similarly, significantly higher levels of CPP-bevacizumab (0.10 ± 0.03 μg per retina) was found in the retina than that

of controls alone. Furthermore, preclinical data also demonstrated an equally comparable therapeutic effect of the CPP complex applied twice a day for 10 days to that of systemically delivered dexamethasone or intravitreal injection of cargo alone once every 10 days. Since only OCT-based qualitative assessment of fluorescently labeled drugs in the aqueous humor with no quantification in the cornea, choroid, or conjunctiva was performed, an accurate penetration pathway could not be discerned (Cogan et al. 2017). Few examples of CPP mediated delivery of proteinaceous cargo are summarized in Table 2. Although cargo delivery ability of cell-penetrating peptides has been well established, there have been very few reports on the ocular delivery of therapeutic peptide/protein. Extensive research in this area is needed as CPPs offer a promising peptide mediated non-viral drug delivery systems.

CPP mediated delivery of small drug molecules for the management of ocular disorders

Early studies on CPP-mediated delivery of small molecules showed the successful entry of fluorophore labels such as lissamine and streptavidin-coated quantum dots into ocular cells upon conjugation with cell-penetrating peptides (Johnson et al. 2008). Enhanced penetration ability of natamycin in human corneal epithelial cells in vitro after conjugating it with TAT dimer (Tat_2) peptide has been reported (Jain et al. 2015). Endocytic inhibitors-based study suggested that the complex was principally internalized via endocytosis. Moreover, an increase in antifungal efficacy of the CPP-natamycin complex as compared to natamycin alone was also observed. It is speculated that an intrinsic antifungal effect of Tat_2 as well as enhanced internalization of CPP-natamycin complex in fungal spores and hyphae could be the reason behind such observations. Furthermore, in vitro results of CPP-natamycin complex have been validated in vivo in New Zealand white rabbits and murine model of infectious keratitis (Rohira et al. 2021). A five-fold increase in the ocular penetration of Tat_2 conjugated Natamycin was noted when applied topically as compared to natamycin alone. When antifungal efficacy of CPP-natamycin conjugate was assessed in murine model of fungal keratitis, 44% of the animals treated with Tat_2-natamycin exhibited complete resolution of keratitis whereas only 13% of the natamycin treated animals showed complete resolution of the infection. Interestingly, the authors also observed significant reduction in the levels of inflammatory cytokines IL-1β and IL-6 when the animals were treated with CPP-natamycin conjugate or CPP alone, suggesting a potential anti-inflammatory effect of Tat_2.

Recently, a CPP-based delivery system with controlled intracellular release of dexamethasone (Dex) in the retina upon intravitreal administration has been reported (Bhattacharya et al. 2020). Various CPP-Dex conjugates were synthesized that differed only in their CPP sequences containing varying number of Lys and Arg amino acid residues. In vitro studies with CPP-Dex conjugates demonstrated significantly higher cellular uptake and cathepsin D-mediated enzymatic release of dexamethasone from the PDCs. Furthermore, docking studies revealed binding of released Dex-Arg fragments with glucocorticoid receptor that was also corroborated with thermophoresis assessment. Ex vivo stability analysis in porcine vitreous demonstrated a chemical stability for over 6 weeks suggesting retinal delivery of intact CPP-Dex conjugates. Retinoblastoma (RB) is one of the most frequent childhood intraocular malignancy that could be life-threatening because of its nature of extraocular extension into brain and bone marrow (Dimaras et al. 2012, 2015). In an attempt to develop a topical anti-retinoblastoma therapy, a covalent conjugate of 89WP (a mutant penetratin peptide) and Melphalan (antitumor drug) has been reported (Jiang et al. 2017, 2022). In vitro cytotoxicity studies established the safety of 89WP-Melphalan upto 100 µM in both HCE and ARPE-19 (normal) cells; however, viability of cancer cell line WERI-Rb-1 was found to be less than 50% suggesting a tumor-specific activity of the conjugate. Animal studies in an intraocular tumor-bearing murine model demonstrated significant tumor inhibitory effect of the topically applied conjugate at higher concentration (3 mg/ml) that was comparable to intravitreally injected melphalan. Moreover, such a high dose of conjugate restricted the vitreous seed proliferation more efficiently than the drug alone. Interestingly, positive metastasis of the tumor in brain tissue of topical melphalan-treated mice was reported but no such observations were made in the mice treated with the conjugate, further highlighting better anti-tumor effect of the 89WP-Melphalan. Table 3 lists out few recent examples of CPP-conjugated drug molecules or cargo-carrying NPs employed in various in vitro and in vivo ocular studies.

Cancer and ocular peptide drug conjugates in clinical development—current status

For more than 3 decades, octreotide (a stable somatostatin analog) has been implicated in the clinical investigations of neuro-endocrine tumors because of its ability to bind over-expressed somatostatin receptors on tumor cells (Lamberts et al. 2019). In the history of octreotide, ^{111}In-diethylenetriaminopentaacetic acid (DTPA)-octreotide is the first ever PDC to be launched in the US market in 1994. Since then, only a handful of PDCs have been approved to be used in imaging or therapeutics (Zhu et al. 2021).

Since this review focuses on therapeutic PDCs in cancer and ocular diseases, PDCs developed in these fields will be discussed that are either FDA-approved or undergoing/

Table 3 In vitro/in vivo studies involving CPP-small drug conjugates for ocular therapeutics

Peptide moiety	Cargo	In vitro/in vivo model system	Reference
TAT and Penetratin	Pazopanib loaded HDL mutant	**In vivo-** C57BL/6 J mice (Choroidal neovascularization model)	(Suda et al. 2017)
TAT, Penetratin, G2 (TAT: CGGGRKKRRQRRR; Penetratin: CGGGRQIKIWFQNRRMKWKK; and G2: CGGGMPRRRRIRRRQK)	Fluorometholone-loaded PEG-PLGA nanoparticles	**In vitro-** HCE-2 cell line **In vivo-** C57BL/6 J	(Gonzalez-Pizarro et al. 2019)
CPP1, CPP2, CPP3 (CPP1: GRKKRRQRRPPQ; CPP2: FNLPLPSRPLLR; and CPP3: AAVLLPVLLAAP)	Dexamethasone	**In vitro-** ARPE-19 cells **In vivo-** Dutch belted rabbits (Linkoping, Sweden)	(Bhattacharya et al. 2020)
TAT dimer (Tat_2) (RKKRRQRRRRKKRRQRRR)	Natamycin	**In vitro-** human corneal epithelial cells **In vivo-** New Zealand white rabbits (tissue penetration), BALB/c mice (antifungal efficacy)	(Jain et al. 2015; Rohira et al. 2021)
TAT (Cys-AYGRKKRRQRRR)	Flurbiprofen loaded liposomes	**In vitro-** HCE-T cell line **In vivo-** New Zealand rabbits (conjunctivitis model)	(Wu et al. 2021)
89WP (RQIKIWFWWRRMKWKK)	Melphalan	**In vitro-** HCEC and ARPE-19 cells **Ex vivo-** excised rabbit cornea and sclera **In vivo-** intraocular tumor-bearing BALB/c mice	(Jiang et al. 2022)

completed phase III clinical trials. Out of all marketed PDCs, only three of them (Lutathera, PEPAXTO, and Pluvicto) have been approved for the therapeutic use in various cancers. In the year 2018, first therapeutic PDC for the treatment of somatostatin receptor-positive gastro-entero pancreatic neuroendocrine tumors (GEP-NETs) was approved by FDA on the basis of Phase III clinical trial results (FDA 2018). A randomized, controlled phase III clinical trial (NETTER-1) to assess the efficacy and safety of Lutathera (lutetium-177 (^{177}Lu)–Dotatate) in 229 patients with somatostatin receptor-positive midgut neuro-endocrine tumors was carried out under national clinical trial registry number NCT01578239 (Strosberg et al. 2017). Lutathera is an octreotide-based therapeutic PDC that contains ^{177}Lu, a radio therapeutic agent. Patients were randomly divided (1:1) into 2 groups; one group received ^{177}Lu–Dotatate at a dose of 7.4 GBq every 8 weeks upto 4 administrations along with 30 mg long-acting octreotide intramuscularly every 4 weeks (Group 1) and the second group received a dose of 60 mg long- acting octreotide only intramuscularly every 4 weeks (Group 2). When the primary endpoint (progression-free survival) was measured at month 20, group receiving ^{177}Lu–Dotatate along with octreotide outperformed octreotide-only treated group with an estimated rate of progression-free survival of 65.2% (10.8% in octreotide-treated group). Moreover, 18% response rate was observed in Group 1 as compared to 3% in the control group. However, Group 1 patients were also found to exhibit Grades 3–4 neutropenia, thrombocytopenia or lymphopenia unlike control group in 1%, 2%, and 9% of the patients, respectively. Additionally, efficacy of Lutathera was also assessed in 360 out of 1214 patients with gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) enrolled in the ERASMUS Medical Center (MC) study. Based on these results, approval of Lutathera was granted by the USFDA to treat patients with advanced and progressive midgut neuroendocrine tumors.

After Lutathera, another approval by the USFDA was granted to PEPAXTO (Melflufen) in February 2021 based on the results of Phase II HORIZON study (NCT02963493) for the treatment in patients with relapsed/refractory multiple myeloma (RRMM) after at least two prior lines of therapy via fast track mode (Richardson et al. 2021; Larocca et al. 2022). HORIZON study assessed efficacy of Melflufen along with Dexamethasone and was carried out in 157 patients with a primary end point being overall response rate that was reported to be 29% in all-treated patient group. The study reported a median progression-free survival of 4.2 months and median overall survival of 11.6 months when a median follow-up of 14 months was carried out. However, treatment-related adverse events such as neutropenia, thrombocytopenia and anemia were also reported in 96% of the patient population. After Phase II HORIZON trial, an open-label and randomized Phase III trial study (OCEAN) was carried out to investigate the efficacy of melflufen over pomalidomide

both in conjunction with dexamethasone (Schjesvold et al. 2022). Out of 495 patients randomly assigned to melflufen group ($n=246$) or pomalidomide group ($n=249$), safety population comprised of 474 patients receiving atleast one dose of study drug ($n=228$ in melflufen group and $n=246$ in pomalidomide group). When primary analysis was carried out at a median follow-up of 15.5 months, melflufen group reported a median progression-free survival of 6.8 months as compared to 4.9 months in pomalidomide group. However, melflufen group underperformed when compared to pomalidomide group in terms of median overall survival that was found to be 19.8 months for melflufen group (median follow-up of 19.8 months) and 25 months for pomalidomide group (median follow-up of 18.6 months). Moreover, most common Grades 3–4 treatment-related adverse events occurred more in melflufen group (thrombocytopenia, neutropenia and anemia) than in pomalidomide group. Unfortunately, frequency of adverse events and more specifically overall survival results led to the withdrawal of fast-tracked approved melflufen (PEPAXTO) in the same year, October 2021 (Olivier and Prasad 2022).

Recently, in March 2022, USFDA approved Novartis' Pluvicto (^{177}Lu-PSMA-617) for the treatment of malignant form of prostate-specific membrane antigen–positive metastatic castration-resistant prostate cancer (PSMA-positive mCRPC) (Novartis 2022; Sternberg 2022). Approval was based on the results of an open-label, Phase III clinical trial (VISION study; NCT03511664) that was conducted on 831 patients randomly divided to receive either ^{177}Lu-PSMA-617 plus protocol-permitted standard care ($n=551$) or standard care alone ($n=280$) (Sartor et al. 2021). Out of 831 patients, 531 formed the analysis set for imaging-based progression-free survival (385 in ^{177}Lu-PSMA-617 plus standard care and 196 in standard care alone). Results of primary end point 1 analysis demonstrated better median imaging-based progression-free survival in ^{177}Lu-PSMA-617 plus standard care group (8.7 months) as compared to the control group (3.4 months). Moreover, similar pattern in an ad hoc analysis was found when complete set of randomized population ($n=831$) was analyzed for primary end point. When median overall survival (Primary end point 2) was compared between 2 study arms of randomized population ($n=831$), ^{177}Lu-PSMA-617 group showed 15.3 months whereas it was 11.3 months for the control group. Treatment-emergent grades 3–4 adverse effects were more frequent in ^{177}Lu-PSMA-617 group (52.7%) than control group (38%). However, significant reduction in the risk of death and radiographic disease progression or death from ^{177}Lu-PSMA-617 treatment resulted in the successful approval from FDA.

Apart from approved anti-cancer PDCs, few have also completed their Phase III clinical trials or are in active Phase III of their clinical development stage. One such example of PDC that has completed Phase III trial is Zoptarelin (AEZS-108, AN-152, ZEN-008), investigated for the treatment of advanced, recurrent or metastatic endometrial cancer (NCT01767155). A randomized, Phase III control study (ZoptEC) was conducted on patients who were unresponsive to prior platinum and taxane therapy for endometrial cancer to compare the efficacy of zoptarelin vs doxorubicin (Miller et al. 2018). One group of patients ($n=256$) received zoptarelin (267 mg/m^2) and another group of patients ($n=256$) received doxorubicin (60 mg/m^2) intravenously for a median of 5 vs 4 cycles respectively. The median overall survival for zoptarelin-treated patients was 10.9 months as compared to 10.8 months for patients treated with doxorubicin. Interestingly, both the groups reported similar progression-free survival of 4.7 months. Moreover, objective response rate (ORR) and clinical benefit rate (CBR) were also not significant between zoptarelin and doxorubicin groups. The study concluded non-superiority of zoptarelin over doxorubicin as second line of treatment for advanced, recurrent or metastatic endometrial cancer. Another such example of PDC is NGR-hTNF that has completed Phase III clinical trial (NCT01098266) with unmet primary endpoints of the study (Gregorc et al. 2018). The study was conducted on 400 malignant pleural mesothelioma patients with 1:1 randomization in NGF-hTNF plus best investigator choice or placebo plus best investigator choice groups. No significant differences were observed in overall survival of study group (8.5 months) and placebo-treated group (8 months) with a median follow-up of 18.7 months. Surprisingly, number of deaths and frequency of study-emergent adverse events were also similar in both the groups. Like ZoptEC study, this study also requires a confirmatory randomized trial because of unmet hypothesis-driven primary endpoints and poor prognosis of patients who rapidly progressed after first line of treatment. ANG1005 (also known as GRN1005), a brain-penetrating peptide-drug conjugate consisting of 3 paclitaxel molecules conjugated to Angiopep-2 peptide is in Phase III clinical trial of drug development (ANGLeD study) for the treatment of HER2-negative breast cancer patients with newly diagnosed leptomeningeal disease and previously treated brain metastases (NCT03613181). Phase II clinical trial of ANG1005 was conducted on a single cohort of 72 female patients having breast cancer with brain metastasis with or without leptomeningeal carcinomatosis (Kumthekar et al. 2020). After the treatment with ANG1005, similar safety profile as that of paclitaxel was demonstrated in patients along with benefits such as stable disease or better disease control in 77% (intracranial) and 86% (extracranial) of the evaluable patients. Out of 72 patients, 28 were found to be positive for leptomeningeal carcinomatosis where ANG1005 treatment led to an intracranial disease control in 79% of the patients with an estimated median overall survival of 8 months.

Till date, numerous CPPs have demonstrated cargo-carrying potential to various ocular tissues including posterior segment of the eye; however, only one anti-inflammatory CPP-based drug XG-102 (brimapitide) has been reported to complete Phase III clinical trials for post-operative ocular inflammation (NCT02235272, NCT02508337; results not published) (Chiquet et al. 2017). XG-102 (formerly D-JNKI-1) contains a JNK-binding domain (20-aa) combined to a 10-aa long TAT sequence of the HIV TAT protein that is responsible for cellular penetration activity. In preclinical studies, XG-102 demonstrated anti-inflammatory potential to treat experimental uveitis in murine model after being administered through different routes (intravenous, intravitreal and subconjunctival) (Touchard et al. 2010; Zaoui et al. 2015). Among various routes, subconjunctival route appeared to be the safest route with limiting side effects and sufficient therapeutic effect. On the basis of these results, a Phase II non-inferiority, multicentre randomized clinical study was conducted on 145 patients who underwent anterior and posterior segments combined surgery or glaucoma surgery or complex posterior segment surgery. Patients were administered a single subconjunctival injection of XG-102 (90 µg or 900 µg), or topical dexamethasone 4 times a day for 21 days (Chiquet et al. 2017). The efficacy of XG-102 or dexamethasone was analyzed on the basis of mean anterior chamber cell grade (primary outcome) at day 28 and clearing of ocular inflammation. Results of the primary endpoint demonstrated non-inferiority of XG-102 (90 µg or 900 µg) to dexamethasone. Moreover, proportion of patients with cleared ocular inflammation was also similar in both the groups (XG-102 and dexamethasone) indicating the potential to treat post-operative ocular inflammations in preference to topical steroids.

In addition to above-listed studies, numerous other PDCs that are under different phases of clinical trials for the management of cancer have been reviewed elsewhere (Vhora et al. 2015; He et al. 2019; Kurrikoff et al. 2021; Zhu et al. 2021; Lindberg et al. 2021; Zhou et al. 2022; Fu et al. 2022). Table 4 lists few PDCs that have completed Phase III and Phase II clinical trials or are still undergoing Phase II.

Future perspective of peptide drug conjugates as vaccines

Apart from providing a treatment option for various types of diseases/disorders, PDCs have a potential to grow as candidate vaccines to strengthen the immune system or prevent the occurrence of a particular disease. Versatility of peptides, that are employed in the construction of PDCs, has a major role in influencing the function of peptide drug conjugates from being preventive to therapeutic candidates. Sections in the study focused primarily on the therapeutic aspect of CPP-drug conjugates in the field of cancer and ocular; however, this section will provide a glimpse of another blooming application of PDCs, i.e., vaccine development. There are accelerated efforts to develop peptide-based vaccines; however, peptide alone is a weaker immunogenic agent due to which conjugation of a stronger adjuvant(s) or immune system stimulator(s) to these peptides is highly recommended to develop a successful peptide-conjugate vaccine (Stephens et al. 2021). Few studies have reported the use of PDCs as vaccine candidates mostly targeting various form of cancers (Licari et al. 2017; Belnoue et al. 2019; Lynn et al. 2020; Matsoukas et al. 2021). A strategy to conjugate several antigenic stimulators to a peptide so as to activate multiple levels of immune system synergistically has been proposed (Belnoue et al. 2019). Upon injecting, highly potent T-cell immune responses were observed in several murine tumor models. The study also demonstrated safety and efficacy of a designed human colorectal cancer vaccine in non-human primate. On the similar lines, Lynn et al. developed a peptide-TLR-7/8a conjugate platform (SNP-7/8a) to address the targeting of patient-specific neoantigens as a potential anti-cancer modality (Lynn et al. 2020). This self-assembled nanoparticle system was capable of loading TLR-7/8a-linked diverse neo-antigenic peptides in such a way that upon their cellular uptake, antigen-presenting cells (APCs) are activated followed by the stimulation of T-cell immunity. When mice tumor models were vaccinated with SNP-7/8a containing predicted neo-antigens, significant induction in T-cell immunity was observed against approximately 50% of the neoantigens that subsequently resulted in enhanced tumor clearance from the mice model. Another recent study reported a PDC-based vaccine system for the immunotherapy of multiple sclerosis (Matsoukas et al. 2021). Antigenic nature of the Myelin peptide in mannan-based conjugate resulted in antigen presentation by dendritic cells along with MHC class cells consequently leading to T-cell stimulation. The role of these immunomodulatory Myelin peptides as a potential candidate for vaccine-based clinical trials has been proposed. Vaccines have a great potential to combat highly aggressive diseases; however, PDC-based vaccine strategy being in their nascent stage is a very promising approach yet very challenging.

Conclusion

Peptide drug conjugates consists of a peptide moiety that can impart multiple functions such as selectivity, specificity, increased cellular/tissue penetration, solubility, and stability on conjugation with different types of cargo molecules. With the growing advancements and newer modalities in the field of biotechnology, scope of PDCs continue to expand covering numerous disease conditions.

Table 4 List of PDCs undergoing different clinical trial phases

PDCs	Peptide sequence/ molecular formula	Clinical trial phase	Indication (s)	NCT number
^{177}Lu-PSMA-617 [Human prostate-specific membrane antigen (PSMA)-targeting peptidomimetic ligand, conjugated to the beta-emitting radioisotope lutetium-177]	**Peptidomimetic ligand-** C49H71N9O16	Approved for marketing	Prostate Cancer	NCT03511664
XG-102 (TAT- coupled dextrogyre peptide)	DQSRPVQPF-LNLTTPRKPR-PPRRRQRRKKRG	Phase III completed	Cataract, pain, inflammation	NCT02508337, NCT02235272
AEZS-108 (Zoptarelin doxorubicin; Doxorubicin conjugated peptide agonist of the LHRH receptor)	**Zoptarelin-** [D-Lys^{6}]-LHRH	Phase III Completed	Endometrial Cancer	NCT01767155
CT2103 (Paclitaxel conjugated polypeptide)	**Polypeptide-** α-poly-(lE)	Phase III (Withdrawn)	Non-small Cell Lung Cancer (NSCLC)	NCT00576225
Lutathera [^{177}Lu-labeled tetra-azacyclododecanetetra-acetic acid (DOTA) conjugated somatostatin analog peptide, Tyr^{3}-octreotate]	**Somatostatin analog peptide-** FCYWK-TCT (cyclic disulfide)	Approved for marketing	GEP-NETs	NCT01578239
NGR-hTNF [Recombinant protein- peptide fused with human tumor necrosis factor alpha (TNF-α)]	**Peptide-** CNGRCG	Phase III completed	Malignant Pleural Mesothelioma	NCT01098266
tTF-NGR [Truncated tissue factor (tTF) with a C-terminal NGR-peptide]	**NGR peptide-** GNGRAHA	Phase III (recruiting)	Soft Tissue Sarcoma	NCT05597917
Melflufen (Dipeptide containing Melphalan and a fluorinated amino acid)	**Fluorinated amino acid-** para-(fluoro)-F	Phase III (active)	Multiple Myeloma	NCT04649060, NCT03151811
		Approved for marketing	Relapsed and/or Refractory Multiple Myeloma	NCT04534322
		Phase II (active)	Renal Impairment, RRMM	NCT03639610
		Phase II (active)	Multiple Myeloma	NCT02963493
ANG1005 or GRN1005 (3 molecules of Paclitaxel conjugated with Angiopep-2 peptide)	**Angiopep-2 peptide-** TFFYGGSRGKRN-NFKTEEY	Phase III (active)	Leptomeningeal Carcinomatosis	NCT03613181
		Phase II (active)	NSCLC with Brain Metastases	NCT01497665
		Phase II (active)	Breast Cancer, Brain Metastases	NCT01480583
		Phase II (active)	Breast Cancer, Lung Neoplasms, Breast Neoplasms, Lung Cancer	NCT01679743
		Phase II completed	Glioblastoma Multiforme	NCT02067156
		Phase II (withdrawn)	Glioblastoma	NCT02876003
		Phase II (active)	Clear Cell Renal Cell Carcinoma	NCT02607553
BT1718 (Maytansinoid toxin conjugated membrane type 1 matrix metalloproteinase targeting bicyclic peptide)	**Bicyclic peptide-** proprietary sequence	Phase I/II (active)	Advanced Solid Tumors, non-small cell lung cancer, non-small cell lung sarcoma and esophageal cancer	NCT03486730
BIM-23A760 [Chimeric dopamine (DA)-somatostatin (SST) compound]	**Chimeric peptide-** XaCYWKXbCT; where Xa is Unk-D-Lys(Unk) and Xb is aminobutyric acid (Abu)	Phase II (active)	Carcinoid Syndrome	NCT01018953

Table 4 (continued)

PDCs	Peptide sequence/ molecular formula	Clinical trial phase	Indication (s)	NCT number
G-202 or Mipsagargin (Targeting peptide conjugated cytotoxic thapsigargin analog)	**Targeting peptide-** βDEγEγEγE	Phase II (active)	Prostatic Neoplasms	NCT02381236
		Phase II completed	Advanced Adult Hepatocellular Carcinoma	NCT01777594
		Phase II completed	Glioblastoma Multiforme	NCT02067156
		Phase II (active)	Clear Cell Renal Cell Carcinoma	NCT02607553
ALRN-6924 (cell-penetrating α-helical stapled peptide)	LTFAEYWAQL(dA)-AAAAA(dA) (stapled between Ala4 and d-Ala11)	Phase IIa completed	Solid tumor, lymphoma and peripheral T-cell lymphoma	NCT02264613

As mentioned before, PDC market is expected to grow at a fascinating compound annual growth rate of 18.58% from 2021 to 2030 contributing significantly in the theragnostic sector. This review highlighted the therapeutic contribution of cell-penetrating peptide-containing PDCs in the management of various cancers and ocular disorders. Cell-penetrating peptides, not only are self-sufficient to traverse cellular membranes but are also capable of carrying diverse cargo molecules along with them. In addition to therapeutic potential, CPPs based PDCs are also excelling in diagnostic area because of the versatility of conjugated peptides. Regardless of numerous in vitro and in vivo studies, very few peptide drug conjugates have reached clinical developmental phases. Due to scarcity of approved PDCs for the treatment of various diseases, we have still not been able to harness the true potential of peptide drug conjugates over synthetic drugs. To bridge the gap between number of pre-clinical studies and FDA approvals of peptide drug conjugates, stringent studies are required to conclusively demonstrate the potential of PDC under study and to validate the number of off-target and on-target effects in case of cancer therapeutics. To address the drawback of untimely activation of peptide-drug conjugate, various researchers are now focusing on prodrug approach so as to enhance the selectivity as well as specificity of the cargo molecule when it reaches the desired site of action. Till date, only a handful of PDCs have been approved by the FDA for the use in therapeutics or diagnostics with DAXXIFY™ (Revance Therapeutics, Inc.) being the first CPP-based neuromodulator that has been recently approved for the treatment of cervical dystonia in adults. As several potential CPP-based therapeutic candidates are in pre-clinical/clinical studies, it is highly likely that near future may soon experience a boom in PDC approvals by FDA for the management of difficult to treat or multi-drug resistant diseases.

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Data availability The data analyzed and reported in the review have been indexed in the reference section.

Declarations

Ethics approval The authors were not part of any studies involving human participants that have been reported in this article.

Competing interests The authors declare no competing interests.

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