**DRUG
DELIVERY**

Nucleic acid delivery by cell-penetrating peptides

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Abstract. Establishment of multiple novel mechanisms and applications of cell-penetrating peptides (CPP) has been demonstrated, leading to novel drug delivery systems. Here, I present a brief introduction to the CPP area together with the selected recent achievements in the delivery of nucleic acids.

Keywords: cell-penetrating peptides, transfection, transportan, PepFect, NickFect.

1. INTRODUCTION

Nucleic acids are biopolymers with a strong potential as novel therapeutics for a number of acquired and inherited diseases. Polynucleotides, based on many different chemical structures, show high affinity and specificity for their intracellular targets. Plasmids (pDNA), antisense oligonucleotides (ASO), small interfering RNA (siRNA), micro RNA (miRNA), messenger RNA (mRNA), and CRISPR-Cas9 gene editing systems are the examples of therapeutic payloads being currently intensively studied in order to achieve their functional intracellular or trans-barrier delivery (Kulkarni et al. 2021).

Nucleic acids as therapeutics have received much attention in recent years; several oligonucleotides (ON) have been approved by the U.S. Food and Drug Administration (FDA), such as ds siRNA onpattro (Hoy 2018) and givosiran (Syed 2021) as well as the mRNA technology-based vaccines against COVID-19 by Pfizer/BioNTech and Moderna (Boisguérin et al. 2021). All these ON-based therapeutic strategies can be improved by developing efficient and safe delivery methods.

1.1. Major chemical approaches to improve nucleic acid therapies

Nucleic acid delivery issues are many since most therapies require the transmembrane delivery of relatively large amounts of ONs as the RNA or mRNA are supposed to cause cellular immune response. To name the main hurdles where novel chemical approaches are inevitable: packaging/conjugation of nanostructures between the nucleic acid payloads and the carrier system, protection of nucleic acids from enzymatic degradation, promoting cellular entry or trans-barrier delivery, and targeting the delivery to specific tissue types and sites within the cell in order to be used for gene therapy and gene editing purposes. To overcome these issues, it has been necessary to obtain a fundamental understanding of the nucleic acid interactions with the delivery systems as well as with the biological environment in order to understand the mechanisms of toxicity and minimize it.

Another area of chemical modification of nucleic acid therapies, especially in the case of vaccination, is the reduction of undesired immunogenicity to avoid the

cytokine storm. For example, the severe COVID-19 is characterized by dysregulated cytokine release profile, dysfunctional immune responses, and hypercoagulation with a high risk of progression to multi-organ failure and death (Premeaux et al. 2022). This issue was improved considerably by applications of ONs with incorporation of pseudouridine into mRNA, enhancing translation by diminishing RNA-dependent protein kinase (PKR) activation (Anderson et al. 2010). Hence, the delivery issues of modified ONs, often with considerable changes in backbones or nucleobases, are the subject of multiple reports concerning their possible therapeutic outcome.

Numerous scientific studies and applications of nucleic acid delivery systems, based on viral and non-viral methods, are available today. Non-viral delivery systems offer improved biosafety and flexibility and have been tremendously advanced during the recent year's development. One can find a plethora of non-viral nucleic acid delivery systems, including, e.g., protamines, PEI, GalNAc, carbohydrate-based cationic glycopolymers, cholesterol, folic acid, antibodies, exosomes, lipid nanoparticles, cell-penetrating peptides, etc. (Oyama et al. 2021), all devel-

oped in search of non-toxic and highly efficient therapeutic delivery systems (Fig.1).

Among the multiple non-viral delivery systems for ONs, cell-penetrating peptides (CPP) seem to be outstanding for their originality, chemical flexibility, low toxicity and high therapeutic potential. This review focuses on the possibilities to use CPPs in the delivery of nucleic acids.

2. CELL-PENETRATING PEPTIDES

The recent definition of CPPs (Langel 2022), previously also known as protein/peptide transduction domains, PTD, Trojan peptides or shuttling peptides, summarizes the diffuse diversity of a huge class of peptides with multiple bioactive properties and drug delivery abilities:

"Cell-penetrating peptides (CPPs) are relatively short peptides, 4–40 aa, with the ability to gain access to the cell interior by means of different mechanisms, mainly including endocytosis, and/or with the capacity to promote the intracellular effects by these peptides themselves, or
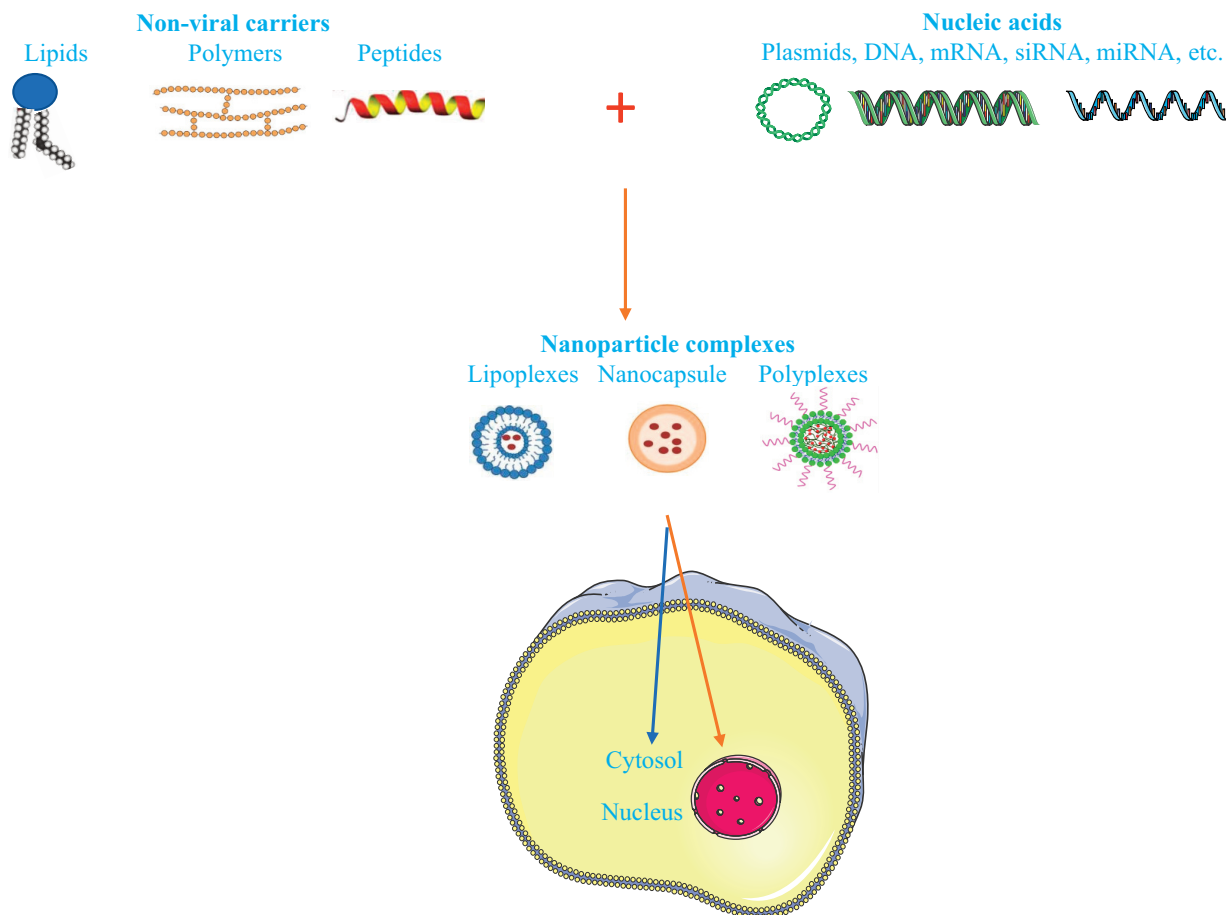

Fig. 1. Cellular delivery carrier strategies for nucleic acid drugs. The tools from smart.servier.com were used to create the image.

by the delivered covalently or non-covalently conjugated bioactive cargoes".

To date, the CPPsite 2.0 (http://crdd.osdd.net/raghava/cppsite/) database contains around 1700 unique, experimentally validated CPPs, together with their secondary and tertiary structures. In silico CPP predictions (Hällbrink and Karelson 2015) show thousands (if not millions by the predictions) of such peptides awaiting confirmation and application.

Recently (September 2022), Revance Therapeutics, Inc. (Nashville, TN, USA; revance.com) announced the FDA apporoval of DAXXIFY (daxibotulinumtoxinA-lanm), containing the complexed RTP004 (a 35 aa CPP), highly purified daxibotulinumtoxinA (RTT150, a 150-kDa botulinum toxin type A) and other excipients, for injection and temporay treatment of glabellar lines in adults. This denotes the first FDA-approved, CPP-based drug ever (Carruthers et al. 2020).

CPPs have been extensively employed to transport cargo molecules *in vitro* and *in vivo*; however, the delivery uptake mechanism of the particles formed by CPPs and their cargo is poorly understood. Two main types of CPP uptake mechanisms have been suggested: energy-independent ("direct penetration") and endocytotic pathways (Langel 2019), the latter mainly for large, CPP-conjugated cargos. Usually, the cellular uptake is the consequence of the parallel action of the above pathways, depending on the conditions. Also, the research today aims to specifically target certain cells or diseased tissues for highly efficient CPP-based targeted therapeutics.

2.1. Strategies for CPP conjugation to nucleic acid drugs

It is important to point out that two main strategies have been applied to attach the nucleic acid cargo to the CPPs: covalent conjugation and complex formation (Fig. 2). Both strategies are applicable for lipid nanoparticles (NP) and cell penetrating peptides, which have both demonstrated extraordinary delivery properties for nucleic acid drugs. **Covalent conjugation**, including the environment sensitive disulphide bridges, has been shown to be an efficient way to conjugate nucleic acids to the delivery systems; however, it is usually more difficult to achieve in case of altering ON cargo. **Complexing** of ONs to the delivery vehicle seems to be a more rational way since only a simple co-incubation of the cargo with the delivery vehicle is required. This should be considered in the design of therapeutic nucleic acid drugs. **Targeting** of nucleic acids is of high importance in the future therapeutic strategies (Fig. 2), which are currently carefully considered in the CPP technologies.

CPP-assisted functional and efficient delivery of all types of nucleic acid based therapeutic molecules to cells and *in vivo* has been demonstrated. Both the covalent and non-covalent strategies for conjugation have been suc-
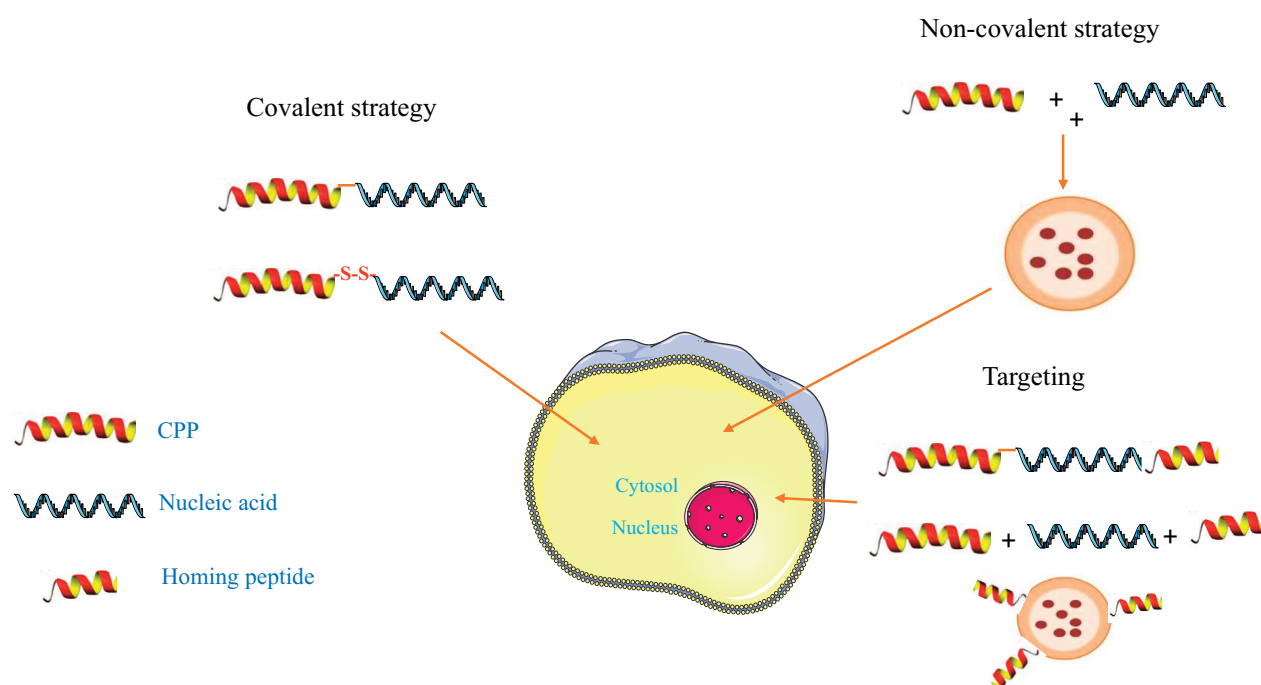

Fig. 2. Covalent and non-covalent strategies for attachment of nucleic acid cargos to the cell penetrating peptides.

cessfully applied (see Fig. 2.), making this chemical approach especially valuable. The innovation has been introduced at several levels: design and choice of the chemical design of the CPPs and nucleic acids, their attachment to each other, introduction of the chemical methods to decrease the toxicity of the system, targeting of the system to specific cells and barriers, endosomal escape, resistance to nucleases, the *in vitro* and *in vivo* modification of the efficacy of the transfection, etc.

The methods for gene silencing (or inhibiting specific genes) using **antisense ONs (ASO) and RNA interference (RNAi)** with CPP conjugates have often been reported. Classified by the antisense mechanisms and the character of the ONs, the antisense technologies include the use of classical single-strand antisense ON, antigene ON, splice-correcting antisense ON (SCO), double-strand small interfering RNA (siRNA), microRNA (miRNA) and anti-miRNA (antimiR), including promoting the degradation of the targeted RNA or modulating RNA function without degradation. Two major backbones for ASO platforms today are the phosphorodiamidate morpholino oligomers (PMO) and the phosphorothioates (PS) (Shadid et al. 2021). CPPs have been attached for such ON delivery in both covalent and non-covalent (usually forming nanoparticles) manner. Below, I briefly summarize the applications of CPPs as carriers for nucleic acids as possible future drugs.

Covalent strategy. Soon after the discovery of penetratin, the group of **A. Prochiantz** (Allinquant et al. 1995) in 1995 blocked APP (amyloid precursor protein) expression by antisense 25-mer ON, which was linked to pAntp (probably a 60-mer peptide was used) covalently, via disulfide bond. Internalization of the pAntp-S-S-ON was observed and it was noted that the APP knock-down initiated a distinct decrease in axon and dendrite outgrowth by embryonic cortical neurons developing *in vitro* (Allinquant et al. 1995). I believe this was the first demonstration of the CPP-aided ON cellular delivery with the required bio-response to the knock-down of a gene expression. Remarkably, the labile in cytosol disulfide conjugate was used, showing high efficacy in the following development of ON delivery.

In 1990s, the uptake of **PNA** (peptide nucleic acid) was a challenge in research, and several attempts were made to use different peptides to achieve the cellular uptake of PNAs. This interest was fuelled by the extraordinary properties of PNA, such as its high affinity to complementary sequences and high resistance to proteases and nucleases. In 1997, our group introduced (patent in 1997, USA Patent No. US6025140, and (Pooga et al. 1998a)) transportan and its conjugate via a disulfide bridge with PNA, using the penetratin-S-S-PNA for control. Both constructs successfully internalized into Bowes cells and knocked down the targeted galanin

receptors type 1 *in vitro* and *in vivo* (Pooga et al. 1998b). ON-functionalized transportan and its analogues have been widely used for ON delivery, reviewed in (Langel 2021).

Non-covalent strategy. ON complexing to CPPs often yields stable NPs, likely by the combination of electrostatic interactions (between the positively charged CPPs and negatively charged ONs) and the available hydrophobic interactions (from hydrophobic amino acids or inserted fatty acid chains), sometimes associated with an amphipathic feature of CPPs or specific structures of the complexes (Morris et al. 1997; Wyman et al. 1997; Futaki et al. 2001; Simeoni et al. 2003; Eguchi et al. 2009; Michiue et al. 2009). Multiple highly efficient transportan-based ON delivery vectors PepFects and NickFects were introduced by us, which are suitable for non-covalent simple formulation nanocomplex technology of almost any type of ONs (Langel 2021).

3. TRANSPORTAN AND ITS MODIFIED ANALOGUES IN NUCLEIC ACID DELIVERY

We have introduced several highly efficient transportan-based ON delivery vectors (multiple PepFects and NickFects), enabling non-covalent simple formulation nanocomplex technology of antisense, siRNA, miRNA, plasmid and mRNA delivery (Langel 2021). We have shown that these NPs are taken up by cells largely through scavenger receptor type A mediated endocytosis.

Transportan showed cystol translocation to the cell (Pooga et al. 1998a) and was able to translocate the covalently attached ON cargo (Pooga et al. 1998b). This fueled the systematic structure-activity studies of its structure, first enabling the development of the shorter transportan 10 (Soomets et al. 2000) and, later, the efficient transfection vector series of PepFects and (branched) NickFects (Langel 2021):

Transportan (TP):
GWTLNSAGYLLG-K*-INLKALAALAKKIL
Transportan 10 (TP10):
AGYLLG-K*-INLKALAALAKKIL
PepFect 14 (PF14):
stearoyl-AGYLLG-K*-LLOOLAAAALOOLL
NickFect 51 (NF51):
O(Nδ-stearoyl-AGYLLG)-INLKALAALAKKIL

In general, ***cellular translocation routes*** for CPPs are mainly divided into two general types: direct translocation and endocytosis, possibly occurring in parallel. The direct cellular translocation pathway has been explained by several experimental models, e.g., the inverted micelle model and the pore-formation carpet model (Langel 2019). The involvement of several endocytic pathways, especially in the case of CPP/cargo conjugates, e.g., macro-

pinocytosis and clathrin-mediated and caveolae/lipid-raft-mediated endocytosis (Pae and Pooga, 2014), are of high impact. It is likely that these conclusions hold even for the translocation mechanisms of transportan and its analogues.

Metabolomics studies by comparing the alterations in the cytosolic metabolome of CHO cells, caused by the exposure to transportan and other CPPs, showed that transportan mostly affected the cellular redox potential and depleted energy and the pools of purines and pyrimidines (Kilk et al. 2009). Transcriptional profiling of several CPPs, PF14 and TP10 in HeLa cells showed the response "the genes related to ribosome biogenesis, microtubule dynamics and long-noncoding RNAs being differentially expressed compared to untreated controls" (Venit et al. 2020).

Targeting. The lack of cell/organ specificity of drug delivery suggests non-desired off-target side-effects and, therefore, the development of the targeted delivery of CPPs and, especially, their conjugated cargos is of a high impact. In case of transportan, nuclear targeting by itself has been demonstrated (Pooga et al. 1998a). The transportan analogues PepFects and NickFects showed powerful DNA nuclear delivery properties (El-Andaloussi et al. 2011), and the nuclear uptake of a dsDNA NF-kappaB decoy ON in rat primary glial cells was shown (Fisher et al. 2007). The *in vivo* blood-brain-barrier (BBB) transport of TP10 and TP10-2 showed a low brain influx for transportan, TP10–dopamine conjugate showed the penetration of the BBB with anti-parkinsonian activity (Stalmans et al. 2015). A TP10–vancomycin conjugate showed antibacterial activity and crossed the BBB in a mouse brain after i.v. administration (Ruczynski et al. 2019). Few examples are available for tissue/organ-specific ON delivery.

Several attempts have been made to improve the **BBB-passing** ON delivery of transportan delivery of cargo. Myristoyl–transportan–transferrin (targeting) with encapsulated siRNA showed targeted delivery through BBB with functional gene silencing *in vitro* (Youn et al. 2014). The PepFect delivery strategy (see below) of ONs for drug delivery across the BBB has been attempted. PF32 with the targeting ligand angiopep-2 showed the complexed pDNA delivery in an *in vitro* Transwell model of the BBB through receptor-mediated endocytosis via scavenger receptors class A and B (SCARA3, SCARA5 and SR-BI) (Srimanee et al. 2016). PF14 and PF28, modified covalently with BBB targeting peptides and complexed with siRNA$_{Luc}$, showed specific gene-silencing efficiency in human glioblastoma cells U87 MG-luc2 (Srimanee et al. 2018).

Using the i.v. administration route *in vivo*, PEG- and MMP substrate-functionalized PF14 (a CPP approach) complexed with pDNA showed the efficient induction of gene expression specifically in **tumors** (Veiman et al.

2015). NF55/pDNA nanoparticles showed *in vivo* specific tumor transfection in various mouse tumor models, including an intracranial glioblastoma model (Freimann et al. 2016). MMP-2/-9 activatable PF144/pDNA nanocomplexes for anti-angiogenic gene delivery showed the inhibition of tumor growth by silencing the vascular endothelial growth factor (VEGF) expression in orthotopic 4T1 breast tumor bearing mice (Künnapuu et al. 2019).

PF14 and NF55 preferentially transfect **lung** tissue upon their systemic administration with the complexed siRNA and pDNA encoding shRNA against cytokine TNFα in models of acute lung inflammation and asthma in mice (Kurrikoff et al. 2019). PF14, covalently conjugated to **mitochondrial**-penetrating peptide, mtCPP1, complexed with ONs, affected biological functions both in the cytoplasm and on the mitochondria (Cerrato et al. 2020).

3.1. Nucleic acid delivery by covalent coupling

Multiple covalently CPP-conjugated **antisense ONs** have been reported, e.g., penetratin (Allinquant et al. 1995), Tat, Pip, (KFFK)$_3$R, (RXR)$_4$, Pep-3, MPG, R15, TP10, and Chol-R$_9$, *in vivo* and *in vitro*, as summarized in Langel (2019).

We introduced the CPP-S-S-PNA (peptide nucleic acid oligomers with high affinity to complementary DNA or RNA and high resistance to the protease or nuclease degradation) antisense conjugates with transportan (and penetratin) in 1998 (patented in 1997) (Pooga et al. 1998b). The antisense PNA oligomer knocked down galanin receptor 1 expression *in vitro* and *in vivo*, yielding functional physiological effects. This was followed by transportan-S-S-PNA (antisense to PTP sigma), increasing the glucose-induced insulin secretion from GK rat islet (Ostenson et al. 2002). The uptake into human fibroblasts was shown for CPPs and transportan-S-S-OMe/LNA ON conjugates targeted to the TAR RNA (Turner et al. 2005). Penetratin-, Tat-, TP-, TP-21- and TP-22-PNA, targeting the TAR region of the HIV-1 genome, showed cellular uptake and anti-HIV virucidal activity (Tripathi et al. 2005). TP10-S-S-PNA-Bpa (*p*-benzoylphenylalanine), targeting the regions of the 3′ and 5′ UTRs of ankylosis mRNA, showed intracellular crosslinking to RNA-binding proteins (RBP) that complex with a target RNA *in vivo* (Zielinski et al. 2006). TP10-S-S-PNA-based antisense conjugate was used to study "the role of subtypes of the L-type voltage-gated calcium channels (LTC), Ca(V)1.2 and Ca(V)1.3 in long-term pain sensitization in a rat model of neuropathy" (Fossat et al. 2010). TP-PNA$_{TAR}$ internalized into the cells with the functional inhibition of HIV-1 production in chronically HIV-1-infected H9 cells (Kaushik et al. 2002).

A novel antisense ON-based platform, introduced by R. Kole and co-workers (Dominski and Kole 1993),

splice correction by ASO became an important tool for CPP testing. We applied the luciferase aberrant splice site setup in HeLa cells with known splice-correcting PNAs (PNA705), tethered to a variety of CPPs (El-Andaloussi et al. 2006), Tat, penetratin and transportan, via a disulfide bridge. Seven different CPPs, among them transportan, as PNA-S-S-CPP conjugates, targeting luciferase expression correction were studied (Bendifallah et al. 2006). Disulfide-linked CPP conjugates with ON analogues, siRNA and PNA, in the HeLa cell assay with integrated plasmid reporters showed that TP-PNA and R6-penetratin-S-S-PNA caused the Tat-dependent trans-activation inhibition, suggesting them as potential anti-HIV agents (Turner et al. 2007).

TP-PNA was designed to interact with an overlap of the NFkappaB **decoy ON** consisting "of a double-stranded consensus sequence corresponding to the kappaB site localized in the IL-6 gene promoter", showing the inhibition of IL-1beta-induced NFkappaB activation (Fisher et al. 2004).

Using of CPP-**siRNA** covalent conjugates for the knock-down of gene expression has not been very successful; only a few reports are available. Covalent penetratin and transportan coupling of siRNA via disulfide showed an improvement of the cellular uptake as well as the expression reduction of reporter GFP transgenes (Muratovska and Eccles 2004). Conjugates of TP10-S-S-siRNA showed intracellular localization and silencing by siRNA-targeted firefly luciferase GL3 in FRSK cells (Ishihara et al. 2009).

The improvement of intracellular **plasmid delivery** by conjugation of TP has been achieved in few cases. It is likely that the covalent conjugation of CPPs to the functional plasmids is the main hurdle here. TP10 "crosslinked to a plasmid via a PNA oligomer, TP10 conjugation with polyethyleneimine (PEI), and addition of unconjugated TP10 to standard PEI transfection assay" increased the transfection efficiency several fold in Neuro-2a cells (Kilk et al. 2005). Fl-TP showed the maximum fluorescence among all of the tested CPPs in permeabilized wheat immature embryos (Chugh and Eudes 2008).

3.2. Nucleic acid delivery by complexation, PepFects and NickFects

Covalent conjugation of a CPP would require additional steps of chemistry and purification/characterization. Hence, the non-covalent complexation strategy would turn the transfection procedure simpler and more efficient. Our attempts to attach unmodified transportan non-covalently to several cargos were mainly unsuccessful.

Our first choice in the case of transportan was to test stearoyl–transportan (El-Andaloussi et al. 2011) for ON transfection, based on the idea of Prof. Shiroh Futaki's

group on stearoyl-R9 (Futaki et al. 2001). Testing of multiple fatty-acid-modified transportan analogues yielded the series of PFs and NFs, being the excellent ON delivery vectors, as exemplified below. For their structures see above.

PF analogues with introduced His residues for the PF/SCO **antisense** nanocomplexes revealed PF132 with high bioactivity (Regberg et al. 2016). An antisense nanoprobe, ^{99m}Tc-anti-miRNA ONs/PF6, was used for imaging the lung adenocarcinoma xenografts and *in vivo* (Yang et al. 2021). PF14/ASO in a muscle cell model of myotonic dystrophy yielded a dose-dependent correction of disease-typical abnormal splicing (van der Bent et al. 2019).

Few examples of myristoyl–transportan transfection are available. NPs incorporating myristoyl–transportan and tumor-homing peptides carrying **siRNA**, a CpG DNA ligand of TLR9, suppressed tumor growth i.v. in several animal models of various cancers (Buss and Bhatia 2020). Myristoyl–transportan conjugated to a transferrin receptor-targeting peptide (myr-TP-Tf), encapsulating siRNA, targeted it to the brain with a functional gene silencing effect in a human glioma (Youn et al. 2014).

A tandem peptide of myristoyl–transportan and Lyp-1 showed the internalization of **sgRNA**/Cas9 ribonucleoprotein complexes and genome editing in cell lines (Jain et al. 2019). The master regulator proteins in critical tumor regulation were confirmed using their lentivirus-mediated **shRNA** silencing with PF14 transfection (Alvarez et al. 2018). PF14/**mRNA** nanoparticles showed the expression of reporter protein eGFP "in two-dimensional tissue cultures and in three-dimensional cancer cell spheroids" (van den Brand et al. 2019). PF14/**mRNA** (eGFP) complexes in the glomerular endothelial cell line mGEnC, HeLa cells and SKOV-3 ovarian carcinoma cells showed uptake and protein expression *in vitro* and *in vivo* (van Asbeck et al. 2021). PepFects and NickFects supported the delivery of nanocomplexes of Fl-**miRNA mimics** (NF-miR-146a) into keratinocytes and dendritic cells with the downregulation of miR-146a-influenced genes by endocytosis as well as suppressed inflammatory responses in a mouse model of irritant contact dermatitis (Carreras-Badosa et al. 2020).

Stearoyl-TP10 was shown to form stable NPs with **plasmids**, transfecting *in vitro* and *in vivo* in mice (Lehto et al. 2011). Novel PFs and NFs were introduced using a QSAR prediction model, showing peptide-**plasmid** complexes and the transfection of cells with pDNA (Regberg et al. 2014). PepFect14, double-functionalized with PEG and an MMP substrate site, complexed with pDNA, showed efficient induction of gene expression specifically in tumors after i.v. injections (Veiman et al. 2015). The PepFects in complex with graphene oxide and plasmids, splice correction ONs and siRNA showed NPs

and a >10–25 fold increase of their cell transfection (Dowaidar et al. 2017a). Similar effects were achieved with magnetic NPs (Dowaidar et al. 2017b), zeolitic imidazolate frameworks (Abdelhamid et al. 2020a) and carbonized-chitosan-encapsulated hierarchical porous zeolitic imidazolate frameworks (Abdelhamid et al. 2020b). By modifying the net charge and the helicity of the NFs, a novel NF55 was introduced, showing *in vivo* **DNA** nanoparticle delivery with efficient gene induction in healthy mice, and showing tumor transfection in various mouse tumor models, e.g., an intracranial glioblastoma model (Freimann et al. 2016; Park 2016).

Two reports are available on the PF transfection of **peptides and proteins**. Calcium signal activity was tested following the application of a hemichannel blocking peptide, Gap19 (nine aa from connexin 43 cytoplasmic loop), complexed with PF6, showing the reduction of astrocyte response amplitudes and the proportion of [SE]astrocytes to the EtOH treatment in enriched astrocyte cultures (Kim et al. 2021). Nanoparticles of PF14, complexed with Heat Shock Protein (HSP70), suggested first by docking (Dowaidar et al. 2017c), showed delivery into Bomirsky Hamster Melanoma cells (Falato et al. 2022).

4. CONCLUSIONS

Transportan and its modified versions – e.g., TP10, PepFects and NickFects – are widely used as efficient delivery vectors of a wide range of cargos, such as small molecules, peptides and proteins, as well as oligonucleotides, such as short ONs, siRNA, miRNA, decoy ON, plasmids and mRNA. These various examples of applications have been used in studies of CPP mechanisms as well as for the development of therapies and the diagnosis of diseases.

Remarkably, PepFects and NickFects have demonstrated the ability to form stable nanoparticles with the very efficient transfection of ONs *in vitro* and *in vivo*, paving the way for future gene therapy. The addition of these CPPs to the available nanoparticle platforms may, in the future, contribute to novel, improved drug delivery systems.

Transportan and its versions have been modified in order to achieve the controlled targeted delivery of bioactive cargos, especially for future cancer gene therapy. For that, the detailed knowledge of CPP mechanisms, toxicity, immunogenicity, efficiency and kinetics should be achieved, and this work is ongoing.

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Photo: Estonian Academy of Sciences/Reti Kokk

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Nukleiinhapete tarne süstikpeptiidide abil

Ülo Langel

Süstikpeptiidide (CPP) mehhanismide uurimine koos nende kasutusalade laienemisega on meid toonud uute võimalusteni ravimitarnesüsteemide arendamisel. Artikkel on lühisissejuhatus süstikpeptiididele ning nende kasutusele nukleiinhapete tarnel.