

[0006] The compositions and methods disclosed herein address these and other needs.

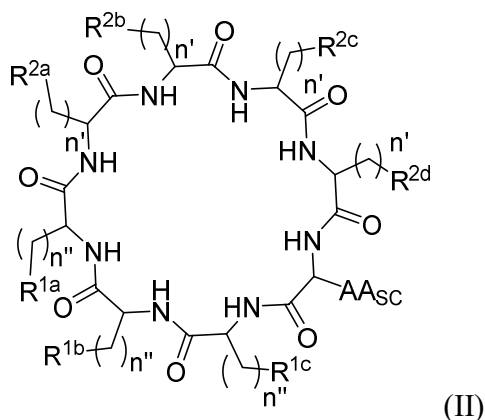
SUMMARY

[0007] One potential strategy to subvert the membrane barrier and deliver drugs into cells is to attach them to “cell-penetrating peptides” (also referred to herein as CPPs or EEVs (endosomal escape vehicles)). Certain residues, such as arginine, that facilitate cytoplasmic delivery have been implicated as significant contributors to systemic organ toxicity.

[0008] New cell penetrating peptides and compositions comprising peptides with a suitable toxicity profile are provided.

[0009] The compositions and methods disclosed herein address these and other needs.

10 [0009a] In one aspect, provided herein is a cyclic peptide of Formula (II):



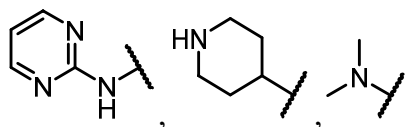
wherein:

AA_{SC} is an amino acid side chain;

R^{1a}, R^{1b}, and R^{1c} are each independently a 6- to 14-membered aryl or a 6- to 14-membered heteroaryl;

R^{2a}, R^{2b}, R^{2c} and R^{2d} are independently an amino acid side chain;

at least one of R^{2a}, R^{2b}, R^{2c} and R^{2d} is



at least one of R^{2a}, R^{2b}, R^{2c} and R^{2d} is guanidine or a protonated form thereof;

20 each n'' is independently an integer from 0 to 5;

each n' is independently an integer from 0 to 3; and

if n' is 0 then R^{2a} , R^{2b} , R^{2c} or R^{2d} is absent.

[0009b] In another aspect, provided herein is an endosomal escape vehicle (EEV) comprising: (a) a cyclic peptide as described herein, wherein AASC is conjugated to a linker; (b) a linker comprising a $-(OCH_2CH_2)_z-$ subunit, wherein z' is an integer from 1 to 23; and (c) an exocyclic peptide comprising from 2 to 10 amino acid residues, wherein the exocyclic peptide comprises 1 or 2 amino acid residues comprising a side chain comprising a guanidine group, or a protonated form thereof.

[0009c] In another aspect, provided herein is a compound comprising an EEV as described herein conjugated to a cargo moiety, wherein the $-OH$ of the terminal carboxylic acid group of the EEV is replaced by the cargo moiety.

[0009d] In another aspect, provided herein is an EEV of formula: Ac-P-K-K-K-R-K-V-miniPEG-K(cyclo(FfΦ-Nal-GrGrQ))-PEG12-OH.

[0009e] In another aspect, provided herein is an EEV selected from:

15 Ac-rr-miniPEG2-Dap[cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

Ac-frr-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

Ac-rfr-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

Ac-rbfbr-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

Ac-rrr-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

20 Ac-rbr-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

Ac-rbrbr-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

Ac-hh-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

Ac-hbh-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

Ac-hbhbh-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

25 Ac-rbhbh-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

Ac-hbrbh-PEG2-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-PEG12-OH

Ac-rr-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH

Ac-frr-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH

Ac-rfr-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH

30 Ac-rbfbr-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH

Ac-rrr-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH

Ac-rbr-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH
 Ac-rbrbr-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH
 Ac-hh-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH
 Ac-hbh-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH
 5 Ac-hbhbh-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH
 Ac-rbhbh-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH
 Ac-hbrbh-Dap(cyclo(FfΦ-Cit-r-Cit-rQ))-b-OH
 Ac-KKKK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-KGKK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 10 Ac-KKGK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-KKK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-KK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-KGK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-KBK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 15 Ac-KBKBK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-KR-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-KBR-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-PKKKRKV-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-PKKKRKV-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 20 Ac-PGKKRKV-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-PKGKRKV-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-PKKGRKV-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-PKKKGKV-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-PKKKRGV-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 25 Ac-PKKKRKG-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-KKKRK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2
 Ac-KKRK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH2 and
 Ac-KRK-miniPEG2-Lys(cyclo(Ff-Nal-GrGrQ))-miniPEG2-K(N3)-NH₂.

[0009f] In yet another aspect, provided herein is the compound as described herein for use in
 30 therapy.

BRIEF DESCRIPTION OF THE FIGURES

[0010] **FIG. 1** shows non-limiting examples of cCPPs containing arginine surrogates for the delivery of cargo.

[0011] **FIG. 2** shows the structure of conjugation product Compound 1b-PMO (EEV-PMO-MDX-1) formed between Compound 1b and a PMO.

[0012] **FIG. 3** shows the change in cell viability in human fibroblast cell line WI38 upon treatment with various concentrations of EEV12 and Compound 1b.

[0013] **FIG. 4** shows the quantification of lactate dehydrogenase (LDH) released from human fibroblast cell line WI38 upon treatment with various concentrations of EEV12 and Compound 1b.

[0014] **FIG. 5** shows the change in cell viability in primary human renal proximal tubular epithelial cells (RPTECs) upon treatment with various concentrations of EEV12 and Compound 1b.

[0015] **FIG. 6** shows the quantification of lactate dehydrogenase (LDH) release from primary human renal proximal tubular epithelial cells (RPTECs) upon treatment with various concentrations of EEV12 and Compound 1b.

[0016] **FIG. 7** shows the change in cell viability in human umbilical vein endothelial cells (HUVECs) upon treatment with various concentrations of EEV12 and Compound 1b.

[0017] **FIG. 8** shows the change in cell viability in human peripheral blood mononuclear cells (hPBMCs) upon treatment with various concentrations of EEV12 and Compound 1b.