In general, all CNPs produce hemodynamic effects or similar blood pressure-reducing activity in mice, nonhuman primates, rats, dogs, and humans. *See, e.g.*, Wendt *et al.*, J Pharmacol Exp Ther 353:132–149, April 2015. A CNP variant (BMN-111; sequence PGQEHPNARK YKGANKKGLS KGCFGLKLDR IGSMSGLGC(SEQ ID NO. 1)) with increased neutral-endopeptidase (NEP) resistance is currently in development. Studies of BMN-111 in animals and man have demonstrated that as the dose increases to the desired therapeutic level, arterial blood pressure (BP) drops and heart rate (HR) increases. In addition to investigating various variants of CNP, different CNP conjugates were obtained by conjugating the CNP moiety to either PEG or proteinaceous compounds. These PEGylated and chimeric CNP exhibited a similar hemodynamic response as observed for the non-PEGylated CNP variants. All variants previously studied showed similar BP-reducing activity. *See, e.g.*, Wendt, J., Pharmacol Exp Ther 353:132–149, April 2015. Therefore, without wishing to be bound by theory, it is believed that increasing the bolus dose of a drug having CNP activity to increase drug exposure may be associated with unacceptable cardiovascular side-effects, such as hypotension.

There is a need for efficacious, safe, and convenient (*e.g.*, bolus administration) cancer treatments which do not cause cardiovascular side-effects, such as hypotension, while maintaining or enhancing blood cyclic-GMP level. The present disclosure seeks to fulfill these needs and provides further related advantages.

SUMMARY

This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary is not intended to identify key features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

In one aspect, the present disclosure refers to a use of a composition comprising a long acting CNP, a very long acting CNP, a long acting CNP derivative, a very long acting CNP derivative, a long acting NPRB agonist, a very long acting NPRB agonist, or any combination thereof, in the manufacture of a medicament for treating a subject having an abnormal vasculature, in any tissue or organ, wherein the composition is to be administered in a therapeutically effective bolus dose to the subject,

wherein administration of the therapeutically effective bolus dose of the composition provides a vasculature normalization or an increase in pericyte coating index by at least 10%,

wherein the composition does not decrease blood pressure by more than 20% of a baseline blood pressure measurement, and

wherein the composition increases plasma cyclic-GMP level at from 1 hour to 12 hours after administration to above 1.5x of a baseline plasma cyclic-GMP level, and the baseline plasma cyclic-GMP level is an average plasma cyclic-GMP level prior to administration of the composition or the average plasma cyclic-GMP level of a healthy subject.

In another aspect, the present disclosure refers to a use of a composition comprising a long acting CNP, a very long acting CNP, a long acting CNP derivative, a very long acting CNP derivative, a long acting NPRB agonist, a very long acting NPRB agonist, or any combination thereof, in the manufacture of a medicament for increasing a number of cytotoxic T-cells and/or a number of activated NK cells, wherein the composition is to be administered to a subject in a therapeutically effective bolus dose,

wherein the therapeutically effective bolus dose of the composition provides an increase in the number of cytotoxic T cells and/or NK cells of at least 15% above the level prior to administration of the composition or above the level in a healthy subject,

wherein administration of the therapeutically effective bolus dose of the composition does not decrease blood pressure by more than 20% of a baseline blood pressure measurement, and

wherein the composition increases plasma cyclic-GMP level at from 1 hour to 12 hours after administration to above 1.5x of a baseline plasma cyclic-GMP level, and the baseline plasma cyclic-GMP level is an average plasma cyclic-GMP level prior to administration of the composition or the average plasma cyclic-GMP level of a healthy subject.

In another aspect, the present disclosure refers to a use of a composition comprising a long acting CNP derivative or a very long acting CNP derivative comprising U-

GLSKGCFGLKLDRIGSMSGLGC [SEQ ID NO. 2], U-GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 3], GLSKGCFGLK(U)LDRIGSMSGLGC [SEQ ID NO. 4], U-CFGLKLDRIGSxSGLGC, in the manufacture of a medicament for treating a subject having cancer, wherein the composition is to be administered to the subject in need thereof in a therapeutically effective bolus dose, where x is a natural or unnatural amino acid residue [SEQ ID NO. 11], or any combination thereof,

wherein:

U is a moiety of Formula (I) or (II), where Formula (I) is

(aliphatic)a-(X)-;

(I)

wherein

a is 1;

aliphatic is an optionally substituted C4-24 chain (*e.g.*, an optionally substituted C10-24 chain, an optionally substituted C12-18 chain), covalently bound to X via a chemical linkage, such as a carbonyl (*e.g.*, as part of an amide or an ester linkage), a thioether, an ether, a thioether, a carbamate moiety, a bond, or the like with X; preferably via a carbonyl as part of an amide or an ester linkage; or more preferably via a carbonyl as part of an amide linkage with X;

X is a 1-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), glycine (G), alanine (A), glutamic acid (E), and aspartic acid (D); or

X is a linker (γE)m-(B)n wherein B is 1-8 amino acid residue or peptide sequence wherein each amino acid residue is independently selected from 2-[2-(2-aminoethoxy)ethoxy]acetic acid residue, Gly, Ala, Leu, Ser, Arg, and Lys; m is 0, 1, 2, or 3; n is 0, 1, 2, or 3; and the sum of m and n is at least 1;

and Formula (II) is

(polymer)a-(Y)-;

(II)

wherein

a is 1;

polymer is cellulose, poly(ethylene glycol) (PEG), methoxy poly(ethylene glycol) (MPEG), poly(lactic-co-glycolic acid), poly(N-vinyl pyrrolidone), or a derivative thereof;

Y is:

a 1-10 amino acid residue or peptide sequence, wherein each amino acid residue is independently selected from lysine (K), arginine (R), glycine (G), alanine (A), glutamic acid (E), and aspartic acid (D);

a non-amino acid linker comprising an ester, an amide, a thioether, an ether, a thioether, a carbamate moiety, or a combination thereof;

an amino acid residue-containing linker, wherein the amino acid residue is covalently attached to $(polymer)_a$; or

a peptide linker different from the 1-10 amino acid residue or peptide sequence;

wherein the composition does not decrease blood pressure by more than 15% of a baseline blood pressure measurement; and

wherein the composition increases plasma cyclic-GMP level at from 1 hour to 12 hours to above 1.5x of a baseline plasma cyclic-GMP level, and the baseline plasma cyclic-GMP level is an average plasma cyclic-GMP level prior to administration of the composition or the average plasma cyclic-GMP level of a healthy subject.

In another aspect, the present disclosure refers to

In one aspect, the present disclosure features a method of treating a subject having an abnormal vasculature, in any tissue or organ, including administering to the subject a therapeutically effective bolus dose of a composition comprising a long acting CNP, a very long acting CNP, a long acting CNP derivative, a very long acting CNP derivative, a long acting NPRB agonist, a very long acting NPRB agonist, or any combination thereof, wherein administering the therapeutically effective bolus dose of the composition provides a vasculature normalization or an increase in pericyte coating index by at least 10% (*e.g.*,