hypersalivation; treatment of blepharospasm associated with dystonia; or treatment of strabismus; in a subject, comprising administering an effective amount of the pharmaceutical or cosmetic composition comprising the muscle-type nicotinic acetylcholine receptor peptide antagonist of the invention to the subject. In some embodiments, the muscle-type nicotinic acetylcholine receptor peptide antagonist is administered in one or more treatments with the pharmaceutical composition. In some embodiments, administration of each treatment comprises injection of the pharmaceutical composition by injection into one or more treatment sites. In some embodiments, each treatment comprises a subimmunological dose of the pharmaceutical composition.

**[0031a]** In one aspect, the present invention includes a muscle-type nicotinic acetylcholine receptor peptide antagonist comprising an amino acid sequence set forth as any of SEQ ID NOS: 80-99.

**[0031b]** In another aspect, the present invention includes a cosmetic composition comprising the muscle-type nicotinic acetylcholine receptor peptide antagonist disclosed herein, for prevention or temporary improvement of the appearance of one or more of skin wrinkles, skin laxity, moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity, moderate to severe lateral canthal lines associated with orbicularis oculi activity, and moderate to severe forehead lines associated with frontalis muscle activity, in a subject.

**[0031c]** In another aspect, the present invention includes a pharmaceutical composition comprising the muscle-type nicotinic acetylcholine receptor peptide antagonist disclosed herein for use in therapy.

**[0031d]** In another aspect, the present invention includes a use of a pharmaceutical composition comprising the muscle-type nicotinic acetylcholine receptor peptide antagonist disclosed herein in the manufacture of a medicament for: prevention or temporary improvement of the appearance of one or more of skin wrinkles, skin laxity, moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity, moderate to severe lateral canthal lines associated with orbicularis oculi activity, and moderate to severe forehead lines associated with frontalis muscle activity; treatment of overactive bladder (OAB); treatment of urinary incontinence; prophylaxis of headaches; prevention or treatment of chronic or episodic migraine, treatment of upper and lower limb spasticity, treatment of spasticity; treatment of cervical dystonia; treatment of hypersalivation; treatment of blepharospasm associated with dystonia; or treatment of strabismus, in a subject.

**[0031e]** In another aspect, the present invention includes a method for preventing or temporarily improving the appearance in a subject for prevention or temporary improvement of

the appearance of one or more of skin wrinkles, skin laxity, moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity, moderate to severe lateral canthal lines associated with orbicularis oculi activity, and moderate to severe forehead lines associated with frontalis muscle activity, comprising applying an effective amount of the cosmetic composition disclosed herein to the skin of the subject.

## INCORPORATION BY REFERENCE

**[0032]** All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

## DETAILED DESCRIPTION OF THE INVENTION

### Definitions

**[0033]** As used herein, the term “comprise” or variations thereof such as “comprises” or “comprising” are to be read to indicate the inclusion of any recited feature but not the exclusion of any other features. Thus, as used herein, the term “comprising” is inclusive and does not exclude additional, unrecited features. In some embodiments of any of the compositions and methods provided herein, “comprising” may be replaced with “consisting essentially of” or “consisting of.” The phrase “consisting essentially of” is used herein to require the specified feature(s) as well as those which do not materially affect the character or function of the claimed invention. As used herein, the term “consisting" is used to indicate the presence of the recited feature alone.

**[0034]** As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

**[0035]** “Amino” refers to the $–NH_2$ radical.

**[0036]** “Cyano” refers to the -CN radical.

**[0037]** “Nitro” refers to the $-NO_2$ radical.

**[0038]** “Oxa” refers to the -O- radical.

**[0039]** “Oxo” refers to the =O radical.

**[0040]** “Thioxo” refers to the =S radical.

**[0041]** “Imino” refers to the =N-H radical.

**[0042]** “Oximo” refers to the =N-OH radical.

## CLAIMS

WHAT IS CLAIMED IS:

1. A muscle-type nicotinic acetylcholine receptor peptide antagonist comprising an amino acid sequence:

Xaa1-Xaa2-Xaa3-Xaa4-Xaa5-Xaa6-Xaa7-Xaa8-Xaa9-Xaa10-Xaa11-Xaa12-Xaa13-Xaa14

wherein:

Xaa1 is absent;

Xaa2 is absent;

Xaa3 and Xaa8 form a linkage Xaa3-Xaa8;

Xaa4 and Xaa14 form a linkage Xaa4-Xaa14;

Xaa5 is selected from: Asn, Asp, Gln, Glu, Arg, His, Lys, and a derivative of Asn, Asp, Gln, Glu, Arg, His, or Lys;

Xaa6 is selected from: Pro and a derivative thereof;

Xaa7 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa9 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa10 is selected from: Arg, His, Lys, and a derivative of Arg, His, or Lys;

Xaa11 is selected from: Asn, Asp, Gln, Glu, Arg, His, Lys, and a derivative of Asn, Asp, Gln, Glu, Arg, His, or Lys;

Xaa12 is selected from: Trp, Tyr, and a derivative of Trp, or Tyr;

Xaa13 is selected from: Cys, Met, Sec, Ser, Thr, Arg, His, Lys, and a derivative of Cys, Met, Sec, Ser, Thr, Arg, His, or Lys;

the N-terminus is optionally modified; and

the C-terminus is optionally modified.

2. The muscle-type nicotinic acetylcholine receptor peptide antagonist of claim 1, wherein:

Xaa1 is absent;

Xaa2 is absent;

the Xaa3-Xaa8 linkage is selected from: a Cys-Cys linkage, a Sec-Sec linkage, a cystathionine linkage, a lactam bridge, a thioether linkage, and a dicarba linkage;

the Xaa4-Xaa14 linkage is selected from: a Cys-Cys linkage, a Sec-Sec linkage, a cystathionine linkage, a lactam bridge, a thioether linkage, and a dicarba linkage;

Xaa5 is selected from: Arg, His, Lys, Asn, Asp, Gln, Glu, and a derivative of Arg, His, Lys, Asn, Asp, Gln, or Glu;

Xaa6 is selected from: Pro and a derivative thereof;

Xaa7 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa9 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa10 is selected from: Arg, His, Lys, and a derivative of Arg, His, or Lys;

Xaa11 is selected from: Asn, Asp, Gln, Glu, Arg, His, Lys, and a derivative of Asn, Asp, Gln, Glu, Arg, His, or Lys;

Xaa12 is selected from: Trp, Tyr, and a derivative of Trp or Tyr; and

Xaa13 is selected from: Cys, Met, Sec, Ser, Thr, and a derivative of Cys, Met, Sec, Ser, or Thr.

3. The muscle-type nicotinic acetylcholine receptor peptide antagonist of claim 1, wherein:

Xaa1 is absent;

Xaa2 is absent;

the Xaa3-Xaa8 linkage is selected from: a Cys-Cys linkage, a Sec-Sec linkage, a cystathionine linkage, a lactam bridge, a thioether linkage, and a dicarba linkage;

the Xaa4-Xaa14 linkage is selected from: a Cys-Cys linkage, a Sec-Sec linkage, a cystathionine linkage, a lactam bridge, a thioether linkage, and a dicarba linkage;

Xaa5 is selected from: Arg, His, Lys, and a derivative of Arg, His, or Lys;

Xaa6 is selected from: Pro and a derivative thereof;

Xaa7 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa9 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa10 is selected from: Arg, His, Lys, and a derivative of Arg, His, or Lys;

Xaa11 is selected from: Asn, Asp, Gln, Glu, and a derivative of Asn, Asp, Gln, or Glu;

Xaa12 is selected from: Trp, Tyr, and a derivative of Trp or Tyr; and

Xaa13 is selected from: Cys, Met, Sec, Ser, Thr, and a derivative of Cys, Met, Sec, Ser, or Thr.

4. The muscle-type nicotinic acetylcholine receptor peptide antagonist of claim 1, wherein:

Xaa1 is absent;

Xaa2 is absent;

the Xaa3-Xaa8 linkage is selected from: a Cys-Cys linkage, a Sec-Sec linkage, a cystathionine linkage, a lactam bridge, a thioether linkage, and a dicarba linkage;

the Xaa4-Xaa14 linkage is selected from: a Cys-Cys linkage, a Sec-Sec linkage, a cystathionine linkage, a lactam bridge, a thioether linkage, and a dicarba linkage;

Xaa5 is selected from: Arg, His, Lys, and a derivative of Arg, His, or Lys;

Xaa6 is selected from: Pro and a derivative thereof;

Xaa7 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa9 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa10 is selected from: Arg, His, Lys, and a derivative of Arg, His, or Lys;

Xaa11 is selected from: Arg, His, Lys, and a derivative of Arg, His, or Lys;

Xaa12 is selected from: Trp, Tyr, and a derivative of Trp or Tyr; and

Xaa13 is selected from: Cys, Met, Sec, Ser, Thr, and a derivative of Cys, Met, Sec, Ser, or Thr.

5. The muscle-type nicotinic acetylcholine receptor peptide antagonist of claim 1, wherein:

Xaa1 is absent;

Xaa2 is absent;

the Xaa3-Xaa8 linkage is selected from: a Cys-Cys linkage, a Sec-Sec linkage, a cystathionine linkage, a lactam bridge, a thioether linkage, and a dicarba linkage;

the Xaa4-Xaa14 linkage is selected from: a Cys-Cys linkage, a Sec-Sec linkage, a cystathionine linkage, a lactam bridge, a thioether linkage, and a dicarba linkage;

Xaa5 is selected from: Asn, Asp, Gln, Glu, and a derivative of Asn, Asp, Gln, or Glu;

Xaa6 is selected from: Pro and a derivative thereof;

Xaa7 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa9 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa10 is selected from: Arg, His, Lys, and a derivative of Arg, His, or Lys;

Xaa11 is selected from: Asn, Asp, Gln, Glu, and a derivative of Asn, Asp, Gln, or Glu;

Xaa12 is selected from: Trp, Tyr, and a derivative of Trp or Tyr; and

Xaa13 is selected from: Cys, Met, Sec, Ser, Thr, and a derivative of Cys, Met, Sec, Ser, or Thr.

6. The muscle-type nicotinic acetylcholine receptor peptide antagonist of claim 1, wherein:

Xaa1 is absent;

Xaa2 is absent;

the Xaa3-Xaa8 linkage is selected from: a Cys-Cys linkage, a Sec-Sec linkage, a cystathionine linkage, a lactam bridge, a thioether linkage, and a dicarba linkage;

the Xaa4-Xaa14 linkage is selected from: a Cys-Cys linkage, a Sec-Sec linkage, a cystathionine linkage, a lactam bridge, a thioether linkage, and a dicarba linkage;

Xaa5 is selected from: Asn, Asp, Gln, Glu, and a derivative of Asn, Asp, Gln, or Glu;

Xaa6 is selected from: Pro and a derivative thereof;

Xaa7 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa9 is selected from: Ala, Gly, Val, Leu, Ile and a derivative of Ala, Gly, Val, Leu, or Ile;

Xaa10 is selected from: Arg, His, Lys, and a derivative of Arg, His, or Lys;

Xaa11 is selected from: Arg, His, Lys, and a derivative of Arg, His, or Lys;

Xaa12 is selected from: Trp, Tyr, and a derivative of Trp or Tyr; and

Xaa13 is selected from: Cys, Met, Sec, Ser, Thr, and a derivative of Cys, Met, Sec, Ser, or Thr.

7. The muscle-type nicotinic acetylcholine receptor peptide antagonist of claim 1, wherein the Xaa3-Xaa8 linkage and the Xaa4-Xaa14 linkage are independently selected from:

(i) a Cys-Cys linkage;

(ii) a Sec-Sec linkage;

(iii) a cystathionine linkage;

(iv) a lactam bridge,

(v) a thioether linkage, and

(vi) a dicarba linkage.

8. The muscle-type nicotinic acetylcholine receptor peptide antagonist of claim 7, wherein the thioether linkage is a lanthionine linkage.

9. The muscle-type nicotinic acetylcholine receptor peptide antagonist of any one of claims 1-8, wherein the N-terminus is modified to comprise $C_1$-$C_6$ acyl, $C_1$-$C_8$ alkyl, $C_6$-$C_{12}$ aralkyl, $C_5$-$C_{10}$ aryl, $C_4$-$C_8$ heteroaryl, formyl, or a lipid.

10. The muscle-type nicotinic acetylcholine receptor peptide antagonist of any one of claims 1-9, wherein the C-terminus is modified to comprise $NH_2$, amino-acyl, amino-$C_1$-$C_8$ alkyl, amino-$C_6$-$C_{12}$-aralkyl, amino-$C_5$-$C_{10}$ aryl, amino-$C_4$-$C_8$ heteroaryl, or O-($C_1$-$C_8$ alkyl).

11. The muscle-type nicotinic acetylcholine receptor peptide antagonist of any one of claims 1-10, wherein the N-terminus is not modified with an amino acid or a derivative of an amino acid, and wherein the C-terminus is not modified with an amino acid or a derivative of an amino acid.

12. The muscle-type nicotinic acetylcholine receptor peptide antagonist of any one of claims 1-11, wherein a lipid is covalently attached to a cysteine, serine, lysine, threonine or tyrosine.

13. The muscle-type nicotinic acetylcholine receptor peptide antagonist of any one of claims 1-12, comprising at least one derivative that is a non-canonical amino acid selected from the group consisting of: an aromatic side chain amino acid; a non-aromatic side chain amino acid; an aliphatic side chain amino acid; a side chain amide amino acid; a side chain ester amino acid; a heteroaromatic side chain amino acid; a side chain thiol amino acid; a beta amino acid; and a backbone-modified amino acid.

14. The muscle-type nicotinic acetylcholine receptor peptide antagonist of any of claims 1-13, wherein the antagonist selectively inhibits a muscle-type nicotinic acetylcholine receptor.

15. The muscle-type nicotinic acetylcholine receptor peptide antagonist of claim 14, wherein the $IC_{50}$ is: about 1 millimolar to about 1 picomolar, less than about 200 nM, less than about 150 nM, or less than about 100 nM.

16. A muscle-type nicotinic acetylcholine receptor peptide antagonist comprising an amino acid sequence set forth as any of SEQ ID NOS: 80-99.

17. A cosmetic composition comprising the muscle-type nicotinic acetylcholine receptor peptide antagonist of any of claims 1-16, for prevention or temporary improvement of the appearance of one or more of skin wrinkles, skin laxity, moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity, moderate to severe lateral canthal

lines associated with orbicularis oculi activity, and moderate to severe forehead lines associated with frontalis muscle activity, in a subject.

18. The cosmetic composition of claim 17, formulated for topical use.

19. A pharmaceutical composition comprising the muscle-type nicotinic acetylcholine receptor peptide antagonist of any of claims 1-16 for use in therapy.

20. Use of a pharmaceutical composition comprising the muscle-type nicotinic acetylcholine receptor peptide antagonist of any of claims 1-16 in the manufacture of a medicament for: prevention or temporary improvement of the appearance of one or more of skin wrinkles, skin laxity, moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity, moderate to severe lateral canthal lines associated with orbicularis oculi activity, and moderate to severe forehead lines associated with frontalis muscle activity; treatment of overactive bladder (OAB); treatment of urinary incontinence; prophylaxis of headaches; prevention or treatment of chronic or episodic migraine, treatment of upper and lower limb spasticity, treatment of spasticity; treatment of cervical dystonia; treatment of hypersalivation; treatment of blepharospasm associated with dystonia; or treatment of strabismus, in a subject.

21. A method for preventing or temporarily improving the appearance in a subject for prevention or temporary improvement of the appearance of one or more of skin wrinkles, skin laxity, moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity, moderate to severe lateral canthal lines associated with orbicularis oculi activity, and moderate to severe forehead lines associated with frontalis muscle activity, comprising applying an effective amount of the cosmetic composition of claim 17 or 18 to the skin of the subject.