CLAIMS

What is claimed is:

1. A long-acting nerve growth factor (NGF) polypeptide comprising from N-terminus to C-terminus an NGF moiety and an Fc moiety, wherein the NGF moiety comprises the amino acid sequence of any one of SEQ ID NOs: 1-3, and wherein the Fc moiety is derived from an IgG1 Fc or an IgG4 Fc.

2. The long-acting NGF polypeptide of claim 1, wherein the NGF moiety is fused to the Fc moiety via a peptide linker, wherein

(i) the peptide linker comprises the amino acid sequence of any one of SEQ ID NOs: 68-72, and/or

(ii) the peptide linker comprises the amino acid sequence of $(GGGGS)_n$ (SEQ ID NO: 70), and wherein n is any of 1, 2, 3, 4, 5, or 6.

~~3. The long-acting NGF polypeptide of claim 2, wherein the peptide linker comprises the amino acid sequence of any one of SEQ ID NOs: 68-72.~~

~~4. The long-acting NGF polypeptide of claim 2 or 3, wherein the peptide linker comprises the amino acid sequence of $(GGGGS)_n$ (SEQ ID NO: 70), and wherein n is any of 1, 2, 3, 4, 5, or 6.~~

~~5~~3. The long-acting NGF polypeptide of claim 1 or 2~~any one of claims 1-4~~, wherein the Fc moiety is derived from an IgG1 Fc ~~comprising~~, wherein

(i) the Fc comprises the amino acid sequence of SEQ ID NO: 7 or 8, and/or

(ii) the Fc moiety comprises a mutation at a position selected from one or more of E233, L234, L235, G236, G237, N297, A327, A330, and P331 relative to SEQ ID NO: 8, and/or

(iii) the Fc moiety comprises a mutation selected from one or more of E233P, L234V, L234A, L235A, L235E, G236del, G237A, N297A, A327G, A330S, and P331S relative to SEQ ID NO: 8, and/or

(iv) the Fc moiety further lacks the first 5 amino acids of SEQ ID NO: 7 or 8.

~~6. The long-acting NGF polypeptide of claim 5, wherein the Fc moiety comprises a mutation at a position selected from one or more of E233, L234, L235, G236, G237, N297, A327, A330, and P331 relative to SEQ ID NO: 8.~~

~~7. The long-acting NGF polypeptide of claim 5 or 6, wherein the Fc moiety comprises a mutation selected from one or more of E233P, L234V, L234A, L235A, L235E, G236del, G237A, N297A, A327G, A330S, and P331S relative to SEQ ID NO: 8.~~

~~8. The long-acting NGF polypeptide of any one of claims 5-7, wherein the Fc moiety further lacks the first 5 amino acids of SEQ ID NO: 7 or 8.~~

~~9~~4. The long-acting NGF polypeptide of claim 3~~any one of claims 5-8~~, wherein

(i) the Fc moiety comprises L234A, L235A, and P331S mutations relative to SEQ ID NO: 8, and/or

(ii) the Fc moiety comprises the amino acid sequence of SEQ ID NO: 11 or 12.

~~10. The long-acting NGF polypeptide of claim 9, wherein the Fc moiety comprises the amino acid sequence of SEQ ID NO: 11 or 12.~~

~~11~~5. The long-acting NGF polypeptide of claim ~~9~~4, wherein the long-acting NGF polypeptide comprises the amino acid sequence of any one of SEQ ID NOs: 62-64.

~~12~~6. The long-acting NGF polypeptide of claim 3~~any one of claims 5-8~~, wherein

(i) the Fc moiety comprises E233P, L234V, L235A, G236del, A327G, A330S, and P331S mutations relative to SEQ ID NO: 8, and/or

(ii) the Fc moiety comprises the amino acid sequence of SEQ ID NO: 15 or 16.

~~13. The long-acting NGF polypeptide of claim 12, wherein the Fc moiety comprises the amino acid sequence of SEQ ID NO: 15 or 16.~~

~~14~~7. The long-acting NGF polypeptide of claim ~~13~~6, wherein the long-acting NGF polypeptide comprises the amino acid sequence of SEQ ID NO: 66.

~~15~~8. The long-acting NGF polypeptide of claim 3~~any one of claims 5-8~~, wherein

(i) the Fc moiety comprises L234A, L235E, G237A, A330S, and P331S mutations relative to SEQ ID NO: 8, and/or

(ii) the Fc moiety comprises the amino acid sequence of SEQ ID NO: 13 or 14.

~~16. The long-acting NGF polypeptide of claim 15, wherein the Fc moiety comprises the amino acid sequence of SEQ ID NO: 13 or 14.~~

~~17~~9. The long-acting NGF polypeptide of claim ~~16~~8, wherein the long-acting NGF polypeptide comprises the amino acid sequence of SEQ ID NO: 65.

~~18~~10. The long-acting NGF polypeptide of claim 3~~any one of claims 5-8~~, wherein

(i) the Fc moiety comprises an N297A mutation relative to SEQ ID NO: 8, and/or

(ii) the Fc moiety comprises the amino acid sequence of SEQ ID NO: 9 or 10.

~~19. The long-acting NGF polypeptide of claim 18, wherein the Fc moiety comprises the amino acid sequence of SEQ ID NO: 9 or 10.~~

~~20~~11. The long-acting NGF polypeptide of claim ~~19~~10, wherein the long-acting NGF polypeptide comprises the amino acid sequence of SEQ ID NO: 61.

~~21~~12. The long-acting NGF polypeptide of claim 1 or 2~~any one of claims 1-4~~, wherein the Fc moiety is derived from an IgG4 Fc ~~comprising~~, wherein

(i) the Fc comprises the amino acid sequence of SEQ ID NO: 17, and/or

(ii) the Fc moiety comprises a mutation at a position selected from one or more of S228, F234, and L235 relative to SEQ ID NO: 17, and/or

(iii) the Fc moiety comprises a mutation selected from one or more of S228P, F234A, and L235A relative to SEQ ID NO: 17, and/or

(iv) the Fc moiety comprises the amino acid sequence of SEQ ID NO: 18.

~~22. The long-acting NGF polypeptide of claim 21, wherein the Fc moiety comprises a mutation at a position selected from one or more of S228, F234, and L235 relative to SEQ ID NO: 17.~~

~~23. The long-acting NGF polypeptide of claim 21 or 22, wherein the Fc moiety comprises a mutation selected from one or more of S228P, F234A, and L235A relative to SEQ ID NO: 17.~~

~~24. The long-acting NGF polypeptide of any one of claims 21-23, wherein the Fc moiety comprises the amino acid sequence of SEQ ID NO: 18.~~

~~25~~13. The long-acting NGF polypeptide of claim ~~24~~12, wherein the long-acting NGF polypeptide comprises the amino acid sequence of SEQ ID NO: 67.

~~26~~14. The long-acting NGF polypeptide of any one of claims 1-~~25~~13, wherein

(i) the long-acting NGF polypeptide has a half-life of at least about 10 hours when administered to a human individual intravenously, intramuscularly, intraocularly, or subcutaneously, and/or

(ii) the long-acting NGF polypeptide causes less pain compared to an NGF polypeptide comprising an NGF moiety with the amino acid sequence of SEQ ID NO: 3 or 4.

~~27. The long-acting NGF polypeptide of any one of claims 1-26, wherein the long-acting NGF polypeptide causes less pain compared to an NGF polypeptide comprising an NGF moiety with the amino acid sequence of SEQ ID NO: 3 or 4.~~

~~28~~15. An isolated nucleic acid encoding the long-acting NGF polypeptide of any one of claims 1-~~27~~14.

~~29~~16. A vector comprising the nucleic acid of claim ~~28~~15.

~~30~~17. A host cell comprising the vector of claim ~~29~~16.

~~31~~18. A pharmaceutical composition comprising the long-acting NGF polypeptide of any one of claims 1-~~27~~14, an isolated nucleic acid of claim 15, a vector of claim 16, or a host cell of claim17, and optionally a pharmaceutically acceptable carrier and/or excipient.

~~32~~19. Use of the pharmaceutical composition of claim 18 in the manufacture of a medicament for~~A method of~~ treating an NGF-related disease in an individual, ~~comprising administering to the individual an effective amount of the pharmaceutical composition of claim 31~~ wherein the NGF-related disease is preferably a neurological disease or a non-neurological disease;

more preferably,

the neurological disease is selected from the group consisting of neonatal hypoxic-ischemic encephalopathy, cerebral palsy, critical illness myopathy, nerve deafness, recurrent laryngeal nerve injury, traumatic brain injury, tooth nerve injury, cerebral stroke, Down syndrome, amyotrophic lateral sclerosis, multiple sclerosis, spinal muscular atrophy, diffuse brain injury, thymus dysplasia, optic contusion, follicular dysplasia, spinal cord injury, glaucoma, neurotrophic keratitis, optic injury, neuromyelitis optica, retinal associated diseases, urinary incontinence, Alzheimer's disease, Parkinson's disease, Huntington's disease, dementia, Hypertensive Intracerebral Hemorrhage Neurological Dysfunction, Cerebral Small Vessel Disease, Acute Ischemic Stroke, corneal endothelial dystrophy, diabetic neuropathy, diabetic foot ulcer, neurogenic skin ulcer, pressure sore, neurotrophic corneal ulcer, diabetic corneal ulcer, and macular hole, and/or

the non-neurological disease is selected from the group consisting of atrophy of spleen, contusion of spleen, diminished ovarian reserve, premature ovarian failure, Ovarian Hyperstimulation Syndrome, ovarian remnant syndrome, ovarian follicular dysplasia, spermatogenesis disorder such as oligozoospermia, asthenospermia, and oligoasthenospermia, ischemic ulcer, stress ulcer, rheumatoid ulcer, liver fibrosis, corneal ulcer, burns, oral ulcer, and venous leg ulcers;

even more preferably,

the neurological disease is diabetic neuropathy, Alzheimer's disease, or neurotrophic keratitis, and/or

the non-neurological disease is premature ovarian failure or spermatogenesis disorder.

~~33. The method of claim 32, wherein the NGF-related disease is a neurological disease.~~

~~34. The method of claim 33, wherein the neurological disease is selected from the group consisting of: neonatal hypoxic-ischemic encephalopathy, cerebral palsy, critical illness myopathy, nerve deafness, recurrent laryngeal nerve injury, traumatic brain injury, tooth nerve injury, cerebral stroke, Down syndrome, amyotrophic lateral sclerosis, multiple sclerosis, spinal muscular atrophy, diffuse brain injury, thymus dysplasia, optic contusion, follicular dysplasia, spinal cord injury, glaucoma, neurotrophic keratitis, optic injury, neuromyelitis optica, retinal-associated diseases, urinary incontinence, Alzheimer's disease, Parkinson's disease, Huntington's disease, dementia, Hypertensive Intracerebral Hemorrhage Neurological Dysfunction, Cerebral Small Vessel Disease, Acute Ischemic Stroke, corneal endothelial dystrophy, diabetic neuropathy, diabetic foot ulcer, neurogenic skin ulcer, pressure sore, neurotrophic corneal ulcer, diabetic corneal ulcer, and macular hole.~~

~~35. The method of claim 33 or 34, wherein the neurological disease is diabetic neuropathy, Alzheimer's disease, or neurotrophic keratitis.~~

~~36. The method of claim 32, wherein the NGF-related disease is a non-neurological disease.~~

~~37. The method of claim 36, wherein the non-neurological disease is selected from the group consisting of: atrophy of spleen, contusion of spleen, diminished ovarian reserve, premature ovarian failure, Ovarian Hyperstimulation Syndrome, ovarian remnant syndrome, ovarian follicular dysplasia, spermatogenesis disorder such as oligozoospermia, asthenospermia, and oligoasthenospermia, ischemic ulcer, stress ulcer, rheumatoid ulcer, liver fibrosis, corneal ulcer, burns, oral ulcer, and venous leg ulcers.~~

~~38. The method of claim 36 or 37, wherein the non-neurological disease is premature ovarian failure or spermatogenesis disorder.~~

~~39~~20. The use of claim 19~~method of any one of claims 32-38~~, wherein

(i) the pharmaceutical composition is administered at a dose of about 0.01 µg to about 1000 µg per individual, and/or

(ii) the pharmaceutical composition is administered at a dosing frequency of about once every week or about once per month, and/or

(iii) the pharmaceutical composition is administered orally, subcutaneously, intravenously, intracerebrally, intranasally, transdermally, intraperitoneally, intramuscularly, intrapulmonarily, vaginally, rectally, intraocularly, or topically.

~~40. The method of any one of claims 32-39, wherein the pharmaceutical composition is administered at a dosing frequency of about once every week or about once per month.~~

~~41. The method of any one of claims 32-40, wherein the pharmaceutical composition is administered orally, subcutaneously, intravenously, intracerebrally, intranasally, transdermally, intraperitoneally, intramuscularly, intrapulmonarily, vaginally, rectally, intraocularly, or topically.~~