What is Claimed:

1. ~~A method of treating~~Use of an extracellular vesicle (EV) comprising an exogenous NLRP3 antagonist in the manufacture of a medicament for the treatment of peripheral neuropathy, or one or more symptoms of a peripheral neuropathy, in a subject in need thereof~~, comprising administering to the subject an extracellular vesicle comprising an exogenous NLRP3 antagonist~~.

~~2. A method of reducing, ameliorating, or treating one or more symptoms of a peripheral neuropathy in a subject in need thereof, comprising administering to the subject an extracellular vesicle comprising an exogenous NLRP3 antagonist.~~

~~3.~~2. The ~~method~~ use of claim 1~~ or 2~~, wherein the exogenous NLRP3 antagonist is a chemical compound, an siRNA, an shRNA, an antisense oligonucleotide, a protein, or any combination thereof.

~~4.~~3. The ~~method~~ use of ~~any one of claims 1 to 3~~ claim 1 or 2, wherein the EV ~~extracellular vesicle~~ targets a cell selected from the group consisting of a macrophage, a myeloid-derived suppressor cell (MDSC), a monocyte, a basophil, a neutrophil, an eosinophil, and any combination thereof.

~~5.~~4. The ~~method~~ use of any one of claims 1 to 3~~4~~, wherein the EV ~~extracellular vesicle~~ comprising the ASO or the ASO induces M2 macrophage polarization in the subject.

~~6.~~5. The ~~method~~ use of any one of claims 1 to ~~5~~4, wherein the EV ~~extracellular vesicle~~ comprising the ASO or the ASO reduces myeloid inflammation in a nerve, meningeal myeloid inflammation, nerve sheath inflammation, or any combination thereof, and/or reduces macrophage influx and/or phagocytosis in one or more of a root, nerve, and/or muscle.

~~7. The method of any one of claims 1 to 6, wherein the extracellular vesicle comprising the ASO reduces myeloid inflammation in a sheath.~~

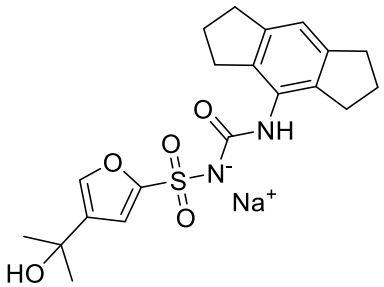
~~8. The method of any one of claims 1 to 7, wherein the extracellular vesicle comprising the ASO reduces macrophage influx in one or more of a root, nerve, and/or muscle.~~

~~9. The method of any one of claims 1 to 8, wherein the extracellular vesicle comprising the ASO reduces macrophage phagocytosis in one or more of a root, nerve, and/or muscle.~~

~~10.~~6. The ~~method~~ use of any one of claims 1 to ~~9~~5, wherein the exogenous NLRP3 antagonist is a small molecule selected from the group consisting of MCC950, Tanilast, Oridonin, CY-09, Bay 11-7082, Parthenolide, 3,4-methylenedioxy-β-nitrostyrene (MNB), β-hydroxybutyrate (BHB), dimethyl sulfoxide (DMSO), type I interferon, and any combination thereof.

~~11. The method of claim 10, wherein the small molecule is selected from the group consisting of MCC950, Tanilast, Oridonin, CY-09, Bay 11-7082, Parthenolide, 3,4-methylenedioxy-β-nitrostyrene (MNB), β-hydroxybutyrate (BHB), dimethyl sulfoxide (DMSO), type I interferon, and any combination thereof.~~

~~12.~~7. The ~~method~~ use of claim 6 ~~10 or 11~~, wherein the exogenous NLRP3 antagonist comprises the formula (I):



(I).

~~13.~~8. The ~~method~~ use of any one of claims ~~10~~ 1 to ~~10~~7, wherein the exogenous NLRP3 antagonist comprises (i) MCC950; (ii) an antisense oligonucleotide (ASO); or (iii) both, wherein the ASO is a gapmer, a mixmer, or a totalmer and/or comprises one or more 5'-methyl-cytosine nucleobases.

~~14. The method of any one of claims 1 to 13, wherein the exogenous NLRP3 antagonist comprises an antisense oligonucleotide (ASO).~~

~~15.~~9. The ~~method~~ use of claim ~~14~~8, wherein the ASO comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length that is complementary to a nucleic acid sequence within a *NLRP3* transcript, wherein the contiguous nucleotide sequence comprises one or more modified internucleoside linkages and is at least about 80%, at least about 85%, at least about 90%, at least

about 95%, or about 100% complementary to the nucleic acid sequence within the *NLRP3* transcript and is complementary to a nucleic acid sequence within (i) a 5' untranslated region (UTR); (ii) a coding region; or (iii) a 3' UTR of the *NLRP3* transcript.

~~16. The method of claim 15, wherein the contiguous nucleotide sequence is at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% complementary to the nucleic acid sequence within the *NLRP3* transcript.~~

~~17.~~10. The use ~~method~~ of ~~any one of~~ claim~~s 14 to 16~~ 8 or 9, wherein the ASO is capable of reducing NLRP3 protein and/ or mRNA expression in a human cell (*e.g.*, an immune cell), wherein the human cell expresses the NLRP3 protein and/or mRNA.

~~18. The method of claim 17, wherein the NLRP3 protein expression is reduced by at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to NLRP3 protein expression in a human cell that is not exposed to the ASO.~~

~~19. The method of any one of claims 14 to 18, wherein the ASO is capable of reducing a level of *NLRP3* mRNA in a human cell (*e.g.*, an immune cell), wherein the human cell expresses the *NLRP3* mRNA.~~

~~20. The method of claim 19, wherein the level of *NLRP3* mRNA is reduced by at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to the level of the *NLRP3* mRNA in a human cell that is not exposed to the ASO.~~

~~21. The method of any one of claims 14 to 20, wherein the ASO is a gapmer, a mixmer, or a totalmer.~~

~~22.~~11. The use ~~method~~ of any one of claims ~~14~~ 8 to ~~21~~10, wherein the ASO comprises one or more nucleoside analogs, wherein one or more of the nucleoside analogs (i) comprises a 2'-O-alkyl-RNA; 2'-O-methyl RNA (2'-OMe); 2'-alkoxy-RNA; 2'-O-methoxyethyl-RNA (2'-MOE); 2'-

amino-DNA; 2'-fluro-RNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA; or bicyclic nucleoside analog; (ii) is a sugar modified nucleoside, wherein the sugar modified nucleoside is an affinity enhancing 2' sugar modified nucleoside; (iii) comprises a nucleoside comprising a bicyclic sugar; (iv) comprises an LNA; or (v) comprises any combination of (i) to (iv).

~~23. The method of claim 22, wherein one or more of the nucleoside analogs comprises a 2'-O-alkyl-RNA; 2'-O-methyl RNA (2'-OMe); 2'-alkoxy-RNA; 2'-O-methoxyethyl-RNA (2'-MOE); 2'-amino-DNA; 2'-fluro-RNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA; or bicyclic nucleoside analog.~~

~~24. The method of claim 22 or 23, wherein one or more of the nucleoside analogs is a sugar modified nucleoside.~~

~~25. The method of claim 24, wherein the sugar modified nucleoside is an affinity enhancing 2' sugar modified nucleoside.~~

~~26. The method of any one of claims 22 to 25, wherein one or more of the nucleoside analogs comprises a nucleoside comprising a bicyclic sugar.~~

~~27. The method of any one of claims 22 to 25, wherein one or more of the nucleoside analogs comprises an LNA.~~

~~28. The method of any one of claims 22 to 27, wherein one or more of the nucleotide analogs is selected from the group consisting of constrained ethyl nucleoside (cEt), 2',4'-constrained 2′-O-methoxyethyl (cMOE), α-L-LNA, β-D-LNA, 2'-O,4'-C-ethylene-bridged nucleic acids (ENA), amino-LNA, oxy-LNA, thio-LNA, and any combination thereof.~~

~~29. The method of any one of claims 14 to 28, wherein the ASO comprises one or more 5'-methyl-cytosine nucleobases.~~

~~30. The method of any one of claims 15 to 29, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence within (i) a 5' untranslated region (UTR); (ii) a coding region; or (iii) a 3' UTR of the *NLRP3* transcript.~~

~~31. The method of any one of claims 15 to 30, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence comprising (i) nucleotides 1 – 534 of SEQ ID NO: 3; (ii) nucleotides 448 – 2193 of SEQ ID NO: 3; (iii) nucleotides 2125 – 3036 of SEQ ID NO: 3; (iv) nucleotides 2987 – 3990 of SEQ ID NO: 3; (v) 3996 – 4456 of SEQ ID NO: 3, (vi) nucleotides 106 – 334 of SEQ ID NO: 3; (vii) nucleotides 648 – 2113 of SEQ ID NO: 3; (viii) nucleotides 2225 – 2956 of SEQ ID NO: 3; (ix) nucleotides 2987 – 3810 of SEQ ID NO: 3; (x) 3996 – 4376 of SEQ ID NO: 3; (xi) nucleotides 156 – 284 of SEQ ID NO: 3; (xii) nucleotides 698 – 2063 of SEQ ID NO: 3; (xiii) nucleotides 2275 – 2906 of SEQ ID NO: 3; (xiv) nucleotides 3037 – 3760 of SEQ ID NO: 3; (xv) 4046 – 4326 of SEQ ID NO: 3; (xvi) nucleotides 196 – 244 of SEQ ID NO: 3; (xvii) nucleotides 738 – 2003 of SEQ ID NO: 3; (xviii) nucleotides 2315 – 2866 of SEQ ID NO: 3; (xix) nucleotides 3077 – 3720 of SEQ ID NO: 3; or (xx) 4086 – 4286 of SEQ ID NO: 3.~~

~~32. The method of any one of claims 15 to 31, wherein the contiguous nucleotide sequence is complementary to a nucleic acid sequence within (i) nucleotides 206 – 234 of SEQ ID NO: 3; (ii) nucleotides 748-2013 of SEQ ID NO: 3; (iii) nucleotides 2325 – 2856 of SEQ ID NO: 3; (iv) nucleotides 3087 – 3710 of SEQ ID NO: 3; or (v) 4096 – 4276 of SEQ ID NO: 3.~~

~~33. The method of any one of claims 15 to 32, wherein the contiguous nucleotide sequence comprises a nucleotide sequence complementary to a sequence selected from the sequences in FIGs. 1A and 1B.~~

~~34. The method of any one of claims 15 to 33, wherein the continuous nucleotide sequence is fully complementary to a nucleotide sequence within the *NLRP3* transcript.~~

~~35.~~12. The use ~~method~~ of any one of claims ~~14~~ 8 to ~~34~~11, wherein the ASO comprises a nucleotide sequence selected from SEQ ID NOs: 101-200, with one or two mismatches.

~~36. The method of any one of claims 14 to 35, wherein the ASO comprises a nucleotide sequence selected from SEQ ID NOs: 101-200.~~

~~37. The method of any one of claims 14 to 36, wherein the ASO is from 14 to 20 nucleotides in length.~~

~~38. The method of any one of claims 15 to 37, wherein the contiguous nucleotide sequence comprises one or more modified internucleoside linkages.~~

~~39. The method of claim 38, wherein the one or more modified internucleoside linkages is a phosphorothioate linkage.~~

~~40. The method of claim 38 or 39, wherein at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% of internucleoside linkages are modified.~~

~~41. The method of claim 40, wherein each of the internucleoside linkages in the ASO is a phosphorothioate linkage.~~

~~42.~~13. The use ~~method~~ of any one of claims 1 to ~~41~~12, wherein the EV ~~extracellular vesicle~~ comprises an anchoring moiety, wherein the NLRP3 antagonist is linked to the anchoring moiety.

~~43. The method of claim 42, wherein the NLRP3 antagonist is linked to the anchoring moiety.~~

~~44.~~14. The use ~~method~~ of any one of claims 1 to ~~43~~13, wherein the EV ~~extracellular vesicle~~ comprises an exogenous targeting moiety, wherein the exogenous targeting moiety comprises a peptide, an antibody or an antigen-binding fragment thereof, a chemical compound, an RNA aptamer, or any combination thereof.

~~45. The method of claim 44, wherein the exogenous targeting moiety comprises a peptide, an antibody or an antigen-binding fragment thereof, a chemical compound, an RNA aptamer, or any combination thereof.~~

~~46. The method of claim 44 or 45, wherein the exogenous targeting moiety comprises a peptide.~~

~~47. The method of any one of claims 44 to 46, wherein the exogenous targeting moiety comprises a microprotein, a designed ankyrin repeat protein (darpin), an anticalin, an adnectin, an aptamer, a peptide mimetic molecule, a natural ligand for a receptor, a camelid nanobody, or any combination thereof.~~

~~48. The method of any one of claims 44 to 47, wherein the exogenous targeting moiety comprises a full-length antibody, a single domain antibody, a heavy chain only antibody (VHH), a single chain antibody, a shark heavy chain only antibody (VNAR), an scFv, a Fv, a Fab, a Fab', a F(ab')2, or any combination thereof.~~

~~49. The method of claim 48, wherein the antibody is a single chain antibody.~~

~~50.~~15. ~~The~~ use ~~method~~ of ~~any one of claims 44 to 49~~claim 14, wherein the EV comprises a scaffold moiety linking the exogenous targeting moiety to the EV.

~~51. The method of any one of claims 42 to 50, wherein the anchoring moiety and/or the scaffold moiety is a Scaffold X or a Scaffold Y.~~

~~52.~~16. The use ~~method~~ of any one of claims ~~42~~ 13 to ~~51~~15, wherein the exogenous NLRP3 antagonist is linked to the anchoring moiety and/or the scaffold moiety on the exterior or luminal surface of the EV by a linker.

~~53. The method of any one of claims 42 to 52, wherein the exogenous NLRP3 antagonist is linked to the anchoring moiety and/or the scaffold moiety on the luminal surface of the EV.~~

~~54. The method of any one of claims 42 to 53, wherein the anchoring moiety comprises sterol, GM1, a lipid, a vitamin, a small molecule, a peptide, or a combination thereof.~~

~~55. The method of any one of claims 42 to 53, wherein the anchoring moiety comprises cholesterol.~~

~~56. The method of any one of claims 42 to 53, wherein the anchoring moiety comprises a phospholipid, a lysophospholipid, a fatty acid, a vitamin (e.g., vitamin D and/or vitamin E), or any combination thereof.~~

~~57. The method of any one of claims 42 to 56, wherein the exogenous NLRP3 antagonist is linked to the anchoring moiety and/or the scaffold moiety by a linker.~~

~~58. The method of any one of claims 1 to 57, wherein the exogenous NLRP3 antagonist is linked to the EV by a linker.~~

~~59.~~17. The use ~~method~~ of claim ~~57 or 58~~16, wherein the linker is a polypeptide or non-polypeptide moeity.

~~60. The method of claim 57 or 58, wherein the linker is a non-polypeptide moiety.~~

~~61. The method of claim 57 or 58, wherein the linker comprise ethylene glycol.~~

~~62. The method of claim 61, wherein the linker comprises HEG, TEG, PEG, or any combination thereof.~~

~~63. The method of claim 57 or 58, wherein the linker comprises acrylic phosphoramidite (e.g,. ACRYDITE™), adenylation, azide (NHS Ester), digoxigenin (NHS Ester), cholesterol TEG, I-LINKER™, an amino modifier (e.g., amino modifier C6, amino modifier C12, amino modifier C6 dT, or Uni-Link™ amino modifier), alkyne, 5' Hexynyl, 5-Octadiynyl dU, biotinylation (e.g., biotin, biotin (Azide), biotin dT, biotin TEG, dual biotin, PC biotin, or desthiobiotin), thiol modification (thiol modifier C3 S-S, dithiol or thiol modifier C6 S-S), or any combination thereof.~~

~~64. The method of any one of claims 57 to 63, wherein the linker is a cleavable linker.~~

~~65. The method of claim 64, wherein the linker comprises valine-alanine-p-aminobenzylcarbamate or valine-citrulline-p-aminobenzylcarbamate.~~

~~66. The method of any one of claims 57 to 65, wherein the linker comprises (i) a maleimide moiety and (ii) valine-alanine-p-aminobenzylcarbamate or valine-citrulline-p-aminobenzylcarbamate.~~

~~67.~~18. The use ~~method~~ of any one of claims 1 to ~~66~~17, wherein the EV is an exosome.

~~68.~~19. The use ~~method~~ of any one of claims 1 to ~~67~~18, wherein the peripheral neuropathy is associated with diabetes, a trauma, an autoimmune disorder, a kidney disorder, a liver disorder, hypothyroidism, a vascular disorder, an abnormal vitamin level, alcohol use, or any combination thereof or wherein the peripheral neuropathy comprises chemotherapy-induced peripheral neuropathy (CIPN).

~~69. The method of any one of claims 1 to 68, wherein the peripheral neuropathy comprises chemotherapy-induced peripheral neuropathy (CIPN).~~

~~70. The method of any one of claims 1 to 69, wherein the subject was previously administered a chemotherapy.~~

~~71. The method of claim 70, wherein the chemotherapy comprises a platinum derivative, a vinca alkaloid, bortezomib, a taxane, or any combination thereof.~~

~~72. The method of claim 70 or 71, wherein the chemotherapy comprises cisplatin, carboplatin, oxaliplatin, docetaxel, vincristine, paclitaxel, gemcitabine, or any combination thereof.~~

~~73.~~20. The use ~~method~~ of any one of claims 1 to ~~72~~19, wherein the EV ~~extracellular vesicle~~ reduces the severity or occurrence of one or more symptom in the subject selected from tingling, pain, burning, numbness, sensitivity to hot, sensitivity to cold, difficulty with fine motor skills, and any combination thereof.