

WHAT IS CLAIMED IS:

1. A method comprising:
 - a) enriching each biological sample in a collection of biological samples for neuronally derived microparticles, e.g., exosomes, wherein:
 - (i) the collection of biological samples is from subjects in a cohort of subjects, wherein the cohort comprises subjects including:
 - (1) a plurality of subjects diagnosed with a neurodegenerative condition at each of a plurality of different disease stages, wherein each of the diagnosed subjects has received a putative neuroprotective agent, and/or
 - (2) a plurality of healthy control subjects,
 wherein the biological samples were collected before and again at one or more times during and, optionally, after administration of the putative neuroprotective agent;
 - b) isolating protein contents from an internal compartment of the microparticles, e.g., exosomes, to produce a biomarker sample;
 - c) measuring, in the biomarker sample, a set of biomarkers to create a dataset, wherein the set of biomarkers includes:
 - (i) at least one signaling kinase and, optionally, at least one oligomeric form of a neurodegenerative protein; or
 - (ii) a plurality of different signaling kinases; and
 - d) performing statistical analysis on the dataset to compare differences in the biomarker sets:
 - (i) in individual subjects over time to determine a diagnostic algorithm that predicts rates of disease progression or degree of response to the putative neuroprotective agent; or
 - (ii) between different subjects to determine a diagnostic algorithm that (1) makes a pathogenic diagnosis, (2) separates clinically similar but etiologically different neurodegenerative disorder subgroups, or (3) predicts whether or the degree to which a subject is likely to respond to the putative neuroprotective agent.
2. The method of claim 1, further comprising, before enriching:
 - I) providing a cohort of subjects, wherein the cohort comprises subjects including:
 - (i) a plurality of subjects diagnosed with a neurodegenerative condition at each of a plurality of different disease stages, and/or
 - (ii) a plurality of healthy control subjects;
 - II) administering to each of the diagnosed subjects a putative neuroprotective agent;

III) before and again at one or more times during and, optionally, after administration of the putative neuroprotective agent, collecting a biological sample from each of the subjects in the cohort.

3. The method of claim 1, wherein at least one of the signaling kinases is a kinase
5 of the PI3K-Akt-mTOR signaling pathway.

4. The method of claim 1, wherein at least one of the signaling kinases is selected from mitogen-activated protein kinase (MAPK or MEK), extracellular signal-regulated kinases (ERK), glycogen synthase kinase 3 beta (GSK3B), AKT kinase and beclin.

5. The method of claim 1, wherein the neurodegenerative protein selected from
10 alpha synuclein, amyloid beta, tau, or huntingtin.

6. The method of claim 1, wherein the oligomeric form of the neurodegenerative protein is a collection of oligomeric forms, e.g., oligomers of alpha synuclein, e.g., alpha synuclein 2-50, e.g., alpha synuclein 4-30, e.g., alpha synuclein 4-20.

7. The method of claim 1, further comprising:
15 e) validating one or more of the diagnostic algorithms against standard clinical measures.

8. The method of claim 1, wherein the statistical analysis comprises: correlational, Pearson correlation, Spearman correlation, chi-square, comparison of means (e.g., paired T-test, independent T-test, ANOVA) regression analysis (e.g., simple regression, multiple
20 regression, linear regression, non-linear regression, logistic regression, polynomial regression, stepwise regression, ridge regression, lasso regression, elasticnet regression) or non-parametric analysis (e.g., Wilcoxon rank-sum test, Wilcoxon sign-rank test, sign test).

9. The method of any of claims 1-8, wherein the statistical analysis is executed by computer.

25 10. The method of claim 9, wherein the statistical analysis comprises machine learning.

11. The method of claim 1, wherein the subjects are humans.

12. The method of claim 1, wherein the neurodegenerative condition is a synucleinopathic disorder.

30 13. The method of claim 12, wherein the synucleinopathic disorder is Parkinson's disease.

14. The method of claim 12, wherein the synucleinopathic disorder is Lewy body dementia.
15. The method of claim 13, wherein the standard clinical measures are selected from UPDRS scores, CGI scores and radiologic findings.
- 5 16. The method of claim 1, wherein the neurodegenerative condition is an amyloidopathy, a tauopathy or Huntington's disease.
17. The method of claim 1, wherein the biological sample comprises a venous blood sample.
18. The method of claim 1, wherein the different disease stages comprise one or
10 more of suspected, early, middle, and clinically advanced.
19. The method of claim 1, wherein the times during or after administration are selected from 1, 2, 3 or more months after treatment.
20. The method of claim 1, wherein enriching comprises using one or more brain-specific protein markers.
- 15 21. The method of claim 20, wherein at least one of the brain-specific markers comprises K1cam.
22. The method of claim 1, wherein isolating comprises washing the exosomes in each enriched sample to remove surface membrane-bound proteins.
23. The method of claim 22, wherein the exosomes are washed with PBS.
- 20 24. The method of claim 1, wherein the forms of the neurodegenerative protein are measured by gel electrophoresis, Western blot or fluorescence techniques.
25. A method comprising:
- a) enriching a biological sample from a subject for neuronally derived microparticles, e.g., exosomes;
- 25 b) isolating protein contents from an internal compartment of the microparticles, e.g., exosomes, to produce a biomarker sample;
- c) measuring, in the biomarker sample, a set of biomarkers to create a dataset, wherein the set of biomarkers includes:
- (1) at least one signaling kinase and, optionally, at least one
30 oligomeric form of a neurodegenerative protein; or
- (2) a plurality of different signaling kinases; and

d) using the dataset to perform one of the following: (1) make a pathogenic diagnosis, (2) classify the subject into one of a plurality of clinically similar but etiologically different neurodegenerative disorder subgroups, or (3) predict whether or the degree to which the subject is likely to respond to the putative neuroprotective agent.

5 **26.** The method of claim **25**, wherein using comprises executing a diagnostic algorithm of claim **1**, on the dataset.

27. The method of claim **25**, wherein at least one of the signaling kinases is a kinase of the PI3K-Akt-mTOR signaling pathway.

28. The method of claim **25**, wherein at least one of the signaling kinases is selected
10 from mitogen-activated protein kinase (MAPK or MEK), extracellular signal-regulated kinases (ERK), glycogen synthase kinase 3 beta (GSK3B), AKT kinase and beclin.

29. The method of claim **25**, wherein the neurodegenerative protein selected from alpha synuclein, amyloid beta, tau, or huntingtin.

30. The method of claim **25**, wherein the oligomeric form of the neurodegenerative
15 protein is a collection of oligomeric forms, e.g., oligomers of alpha synuclein, e.g., alpha synuclein 2-50, e.g., alpha synuclein 4-30, e.g., alpha synuclein 4-20.

31. The method of claim **25**, wherein isolating neuronally derived exosomes comprises:

- 20 (i) ultra-centrifugation;
 (ii) density gradient centrifugation; or
 (iii) size exclusion chromatography.

32. The method of claim **25**, wherein isolating neuronally derived exosomes comprises capturing the neuronally derived exosomes using a binding moiety that binds to brain-specific protein.

25 **33.** The method of claim **32**, wherein the brain-specific protein is L1CAM.

34. The method of claim **25**, wherein removing proteins from the surface of the isolated exosomes comprises washing the isolated exosomes with an aqueous solution (e.g., phosphate buffered saline ("PBS")).

35. The method of claim **25**, wherein determining amounts of a neurodegenerative
30 protein comprises:

- i) separating species of oligomeric α -synuclein into a plurality of fractions;

ii) measuring each of one or a plurality of the separated oligomeric α -synuclein species and, optionally, one or a plurality of species selected from: monomeric α -synuclein, tau-synuclein co-polymers, amyloid beta-synuclein co-polymers and tau-amyloid beta-synuclein co-polymers.

5 **36.** The method of claim **35**, wherein separating species into a plurality of fractions comprises separating by electrophoresis.

37. The method of claim **35**, wherein separating species into a plurality of fractions comprises separating by chromatography.

38. The method of claim **35**, wherein determining among the separated species, at
10 least one oligomeric form of α -synuclein selected from forms having between 2 and about 100 monomeric units, between 4 and 16 monomeric units and no more than about 30 monomeric units.

39. The method of claim **35**, wherein determining among the separated species, a quantitative measure of monomeric α -synuclein.

15 **40.** The method of claim **35**, wherein measuring among the separated species, a plurality of different oligomeric α -synuclein species.

41. The method of claim **35**, wherein measuring among the separated species a co-polymer comprising α -synuclein and tau.

42. The method of claim **35**, wherein determining among the separated species, a
20 quantitative measure of a co-polymer comprising α -synuclein and amyloid beta.

43. The method of claim **35**, wherein measuring the separated species comprises detecting one or a plurality of separated species by immunoassay.

44. The method of claim **43**, wherein the immunoassay comprises immunoblotting.

45. The method of claim **43**, wherein the immunoassay comprises Western blot.

25 **46.** The method of claim **43**, wherein the immunoassay uses an antibody coupled to a direct label.

47. The method of claim **43**, wherein the immunoassay uses an antibody coupled to an indirect label.

48. The method of claim **25**, further comprising:

I) measuring the biomarkers in the subject before and after administration of a putative neuroprotective agent; and

II) determining changes in amounts of proteins or patterns of biomarkers, wherein changes toward normal amounts or patterns indicate efficacy of the neuroprotective agent.

49. The method of claim **25**, further comprising:

measuring the biomarkers in the subject at two different times; and

determining changes in amounts of proteins or patterns of biomarkers, wherein changes indicate a change in a neurodegenerative state.

50. The method of claim **25**, comprising collecting a plurality of biological samples from the subject over a time period, optionally wherein the subject is receiving a putative or known neuroprotective agent during the time period, wherein the diagnostic algorithm predicts rates of disease progression or degree of response to the putative neuroprotective agent.

51. A method comprising:

a) providing a dataset comprising, for each of a plurality of subjects, values indicating (1) state of a neurodegenerative condition, and (2) measures of a set of biomarkers, wherein the set of biomarkers includes:

(i) at least one signaling kinase and, optionally, at least one oligomeric form of a neurodegenerative protein; or

(ii) a plurality of different signaling kinases; and

b) performing a statistical analysis on the dataset to develop a model that infers the state of the neurodegenerative condition in an individual.

52. The method of claim **51**, wherein at least one of the signaling kinases is a kinase of the PI3K-Akt-mTOR signaling pathway.

53. The method of claim **51**, wherein at least one of the signaling kinases is selected from mitogen-activated protein kinase (MAPK or MEK), extracellular signal-regulated kinases (ERK), glycogen synthase kinase 3 beta (GSK3B), AKT kinase and beclin.

54. The method of claim **51**, wherein the neurodegenerative protein selected from alpha synuclein, amyloid beta, tau, or huntingtin.

55. The method of claim **51**, wherein the oligomeric form of the neurodegenerative protein is a collection of oligomeric forms, e.g., oligomers of alpha synuclein, e.g., alpha synuclein 2-50, e.g., alpha synuclein 4-30, e.g., alpha synuclein 4-20.

56. The method of claim 51, wherein the statistical analysis is performed by computer.
57. The method of claim 51, wherein the statistical analysis is not performed by computer.
- 5 58. The method of claim 51, wherein the statistical analysis comprises: correlational, Pearson correlation, Spearman correlation, chi-square, comparison of means (e.g., paired T-test, independent T-test, ANOVA) regression analysis (e.g., simple regression, multiple regression, linear regression, non-linear regression, logistic regression, polynomial regression, stepwise regression, ridge regression, lasso regression, elasticnet regression) or non-
10 parametric analysis (e.g., Wilcoxon rank-sum test, Wilcoxon sign-rank test, sign test).
59. The method of claim 52, wherein the statistical analysis comprises training a machine learning algorithm on the dataset.
60. The method of claim 59, wherein the machine learning algorithm is selected from: artificial neural networks (e.g., back propagation networks), decision trees (e.g., recursive
15 partitioning processes, CART), random forests, discriminant analyses (e.g., Bayesian classifier or Fischer analysis), linear classifiers (e.g., multiple linear regression (MLR), partial least squares (PLS) regression, principal components regression (PCR)), mixed or random-effects models, non-parametric classifiers (e.g., k-nearest neighbors), support vector machines, and ensemble methods (e.g., bagging, boosting).
- 20 61. The method of claim 51, wherein the state is selected from diagnosis, stage, prognosis or progression of the neurodegenerative condition.
62. The method of claim 51, wherein the state is measured as a categorical variable (e.g., a binary state or one of a plurality of categorical states).
63. The method of claim 62, wherein the categories comprise a diagnosis consistent
25 with (e.g., positive or diagnosed as having) having the neurodegenerative condition and inconsistent with (e.g., negative or diagnosed as not having) having the neurodegenerative condition.
64. The method of claim 62, wherein the categories comprise different stages of the neurodegenerative condition.
- 30 65. The method of claim 51, wherein the state is measured as a continuous variable (e.g., on a scale).

66. The method of claim 61, wherein the continuous variable is a range is or degrees of the neurodegenerative condition.
67. The method of claim 51, wherein the subjects are animals, e.g., fish, avians, amphibians, reptiles, or mammals, e.g., rodents, primates or humans.
- 5 68. The method of claim 51, wherein the plurality of subjects is at least any of 10, 25, 50, 100, 200, 400 or 800.
69. The method of claim 51, wherein, for each subject, the sample for which the quantitative measures are determined are taken at a first time point and the state of the neurodegenerative condition is determined at a second, later time point.
- 10 70. The method of claim 51, wherein the biological sample comprises blood or a blood fraction (e.g., plasma or serum).
71. The method of claim 51, wherein the neurodegenerative condition is a synucleinopathy, e.g., Parkinson's Disease or Lewy Body Dementia.
72. The method of claim 51, wherein the neurodegenerative condition is an
15 amyloidopathy, e.g., Alzheimer's Disease, a tauopathy, e.g., Alzheimer's Disease or Huntington's disease.
73. A method of inferring a risk of developing, a diagnosis of, a stage of, a prognosis of or a progression of a neurodegenerative condition characterized by a neurodegenerative protein, wherein the method comprises:
- 20 a) measuring, from a biological sample from a subject that is enriched for neuronally derived microparticles, e.g., exosomes, a set of biomarkers to create a dataset, wherein the set of biomarkers includes:
- (1) at least one signaling kinase and, optionally, at least one oligomeric form of a neurodegenerative protein; or
- 25 (2) a plurality of different signaling kinases; and
- b) executing a model, e.g., a model of claim 51, on the dataset to infer a risk of developing, a diagnosis of, a stage of, a prognosis of or a progression of the neurodegenerative condition.
74. The method of claim 73, wherein at least one of the signaling kinases is a kinase
30 of the PI3K-Akt-mTOR signaling pathway.

75. The method of claim 73, wherein at least one of the signaling kinases is selected from mitogen-activated protein kinase (MAPK or MEK), extracellular signal-regulated kinases (ERK), glycogen synthase kinase 3 beta (GSK3B), AKT kinase and beclin.

76. The method of claim 73, wherein the neurodegenerative protein selected from
5 alpha synuclein, amyloid beta, tau, or huntingtin.

77. The method of claim 73, wherein the oligomeric form of the neurodegenerative protein is a collection of oligomeric forms, e.g., oligomers of alpha synuclein, e.g., alpha synuclein 2-50, e.g., alpha synuclein 4-30, e.g., alpha synuclein 4-20.

78. The method of claim 73, wherein the neurodegenerative protein forms for which
10 the quantitative measures are determined are selected from:

- (I) at least one oligomeric form;
- (II) a plurality of oligomeric forms;
- (III) at least one oligomeric form and at least one monomeric form;
- (IV) a plurality of oligomeric forms and at least one monomeric form;
- 15 (V) at least one oligomeric form and a plurality of monomeric forms; and
- (VI) a plurality of oligomeric forms and a plurality of monomeric forms.

79. The method of claim 73, wherein at least one of the oligomeric forms comprises a collection of species of the neurodegenerative protein.

80. The method of claim 73, wherein the model comprises comparing relative
20 amounts an oligomeric form to monomeric form of the neurodegenerative protein to relative amounts in a statistically significant number of control individuals.

81. The method of claim 73, wherein the model comprises detecting a pattern of relative amounts of a plurality of the oligomeric forms from which model the inference is made.

82. The method of claim 73, wherein the subject is asymptomatic or preclinical for a
25 neurodegenerative condition.

83. The method of claim 73, wherein the subject presents to a healthcare provider, such as a doctor, during a routine office visit or as part of a doctor's ordinary practice of medicine.

84. The method of claim 73, wherein the model is executed by computer.

30 85. The method of claim 73, wherein the model is not executed by computer.

86. A method for determining effectiveness of a therapeutic intervention in treating a neurodegenerative condition, wherein the method comprises:

(a) inferring, in each subject in a population comprising a plurality of subjects, an initial state of a neurodegenerative condition by:

5 (1) measuring, from a biological sample from a subject that is enriched for neuronally derived microparticles, e.g., exosomes, a set of biomarkers to create a dataset, wherein the set of biomarkers includes:

(i) at least one signaling kinase and, optionally, at least one oligomeric form of a neurodegenerative protein; or

10 (ii) a plurality of different signaling kinases; and

(2) inferring the initial state using a model, e.g., a model of claim 51;

(b) after inferring, administering the therapeutic intervention to the subjects;

(c) after administering, inferring, in each subject individual in the population, a subsequent a subsequent state of the neurodegenerative condition by:

15 (1) measuring, from a biological sample from a subject that is enriched for neuronally derived microparticles, e.g., exosomes, a set of biomarkers to create a dataset, wherein the set of biomarkers includes;

(i) at least one signaling kinase and, optionally, at least one oligomeric form of a neurodegenerative protein; or

20 (ii) a plurality of different signaling kinases; and

(2) inferring the subsequent state using the model; and

(d) based on the initial and subsequent inferences in the population, determining that the therapeutic intervention is effective if the subsequent inferences exhibit a statistically significant change toward a normal state compared with the initial inferences, or that the
25 therapeutic intervention is not effective if the subsequent inferences do not exhibit a statistically significant change compared with the initial inferences toward a normal state.

87. The method of claim 86, wherein at least one of the signaling kinases is a kinase of the PI3K-Akt-mTOR signaling pathway.

88. The method of claim 86, wherein at least one of the signaling kinases is selected
30 from mitogen-activated protein kinase (MAPK or MEK), extracellular signal-regulated kinases (ERK), glycogen synthase kinase 3 beta (GSK3B), AKT kinase and beclin.

89. The method of claim 86, wherein the neurodegenerative protein selected from alpha synuclein, amyloid beta, tau, or huntingtin.

90. The method of claim 86, wherein the oligomeric form of the neurodegenerative protein is a collection of oligomeric forms, e.g., oligomers of alpha synuclein, e.g., alpha synuclein 2-50, e.g., alpha synuclein 4-30, e.g., alpha synuclein 4-20.

91. The method of claim 86, wherein the therapeutic intervention comprises
5 administration of a drug or combination of drugs.

92. The method of claim 86, wherein the population comprises at least 20, at least 50, at least 100 or at least 200 subjects, wherein at least 20%, at least 35%, at least 50%, or at least 75% of the subjects initially have elevated relative amounts of oligomeric forms of the protein to monomeric forms of the protein.

10 93. The method of claim 86, wherein at least 20%, at least 25%, at least 30%, or at least 35%, least 50%, at least 66%, at least 80%, or 100% of the subjects initially have a diagnosis of a neurodegenerative condition.

94. The method of claim 86, wherein the inference is made by computer.

95. The method of claim 86, wherein the inference is not made by computer.

15 96. A method for qualifying subjects for a clinical trial of a therapeutic intervention for the treatment or prevention of a neurodegenerative condition comprising:

a) determining that a subject is abnormal with respect with a neurodegenerative condition by:

20 (1) measuring, from a biological sample from a subject that is enriched for neuronally derived microparticles, e.g., exosomes, a set of biomarkers to create a dataset, wherein the set of biomarkers includes;

(i) at least one signaling kinase and, optionally, at least one oligomeric form of a neurodegenerative protein; or

(ii) a plurality of different signaling kinases;

25 (2) executing a model, e.g., a model of claim 51, on the profile to infer that the subject is abnormal with respect with the neurodegenerative condition; and

b) enrolling the subject in the clinical trial of a potentially therapeutic intervention for said neurodegenerative condition.

30 97. The method of claim 96, wherein at least one of the signaling kinases is a kinase of the PI3K-Akt-mTOR signaling pathway.

98. The method of claim 96, wherein at least one of the signaling kinases is selected from mitogen-activated protein kinase (MAPK or MEK), extracellular signal-regulated kinases (ERK), glycogen synthase kinase 3 beta (GSK3B), AKT kinase and beclin.

99. The method of claim 96, wherein the neurodegenerative protein is selected from alpha synuclein, amyloid beta, tau, or huntingtin.

100. The method of claim 96, wherein the oligomeric form of the neurodegenerative protein is a collection of oligomeric forms, e.g., oligomers of alpha synuclein, e.g., alpha
5 synuclein 2-50, e.g., alpha synuclein 4-30, e.g., alpha synuclein 4-20.

101. The method of claim 96, wherein the model is executed by computer.

102. The method of claim 96, wherein the model is not executed by computer.

103. A method of monitoring progress of a subject on a therapeutic intervention for a neurodegenerative condition comprising:

- 10 (a) inferring, in the subject, an initial state of a neurodegenerative condition by:
(1) determining, from a biological sample from a subject that is enriched for neuronally derived microparticles, e.g., exosomes, measures of a set of biomarkers, wherein the set of biomarkers includes:
(i) at least one signaling kinase and, optionally, at least one
15 oligomeric form of a neurodegenerative protein; or
(ii) a plurality of different signaling kinases; and
(2) executing a model, e.g., a model of claim 51, to infer an initial state of the neurodegenerative condition;
(b) after inferring, administering the therapeutic intervention to the subject;
20 (c) after administering, inferring, in the subject, a subsequent state of the neurodegenerative condition by:
(1) determining, from a biological sample from a subject that is enriched for neuronally derived microsomal particles, a biomarker profile comprising amounts of each of a plurality of different signaling kinases to create a dataset; and
25 (2) executing a model, e.g. a model of claim 51, to infer a subsequent state of the neurodegenerative condition;
(d) based on the initial and subsequent state inferences, determining that the subject is responding positively to the therapeutic intervention if the subsequent inference exhibits a change toward a normal state compared with the initial inferences, or that the
30 therapeutic intervention is not effective if the subsequent inferences do not exhibit a change compared with the initial inferences toward a normal state.

104. The method of claim 103, wherein at least one of the signaling kinases is a kinase of the PI3K-Akt-mTOR signaling pathway.

105. The method of claim **103**, wherein at least one of the signaling kinases is selected from mitogen-activated protein kinase (MAPK or MEK), extracellular signal-regulated kinases (ERK), glycogen synthase kinase 3 beta (GSK3B), AKT kinase and beclin.

106. The method of claim **103**, wherein the neurodegenerative protein selected from
5 alpha synuclein, amyloid beta, tau, or huntingtin.

107. The method of claim **103**, wherein the oligomeric form of the neurodegenerative protein is a collection of oligomeric forms, e.g., oligomers of alpha synuclein, e.g., alpha synuclein 2-50, e.g., alpha synuclein 4-30, e.g., alpha synuclein 4-20.

108. The method of claim **103**, wherein the model is executed by computer.

10 **109.** The method of claim **103**, wherein the model is not executed by computer.

110. A method comprising:

(a) determining, by the method of claim **73**, that a subject has a neurodegenerative condition, and

(b) administering to the subject a palliative or neuroprotective therapeutic
15 intervention efficacious to treat the condition.

111. The method of claim **110**, wherein the therapeutic intervention moves a biomarker profile of the subject toward normal, wherein a movement toward normal indicates neuroprotection.

20 **112.** A method comprising administering to a subject determined by the method of claim **73**, to have an abnormal pattern of biomarkers, a palliative or neuroprotective therapeutic intervention effective to treat the condition.

113. The method of claim **112**, wherein the subject is asymptomatic or preclinical for the neurodegenerative condition.

114. A kit comprising reagents sufficient to detect either:

25 (1) at least one of signaling kinase and at least one oligomeric form of a neurodegenerative protein; or

(2) a plurality of different signaling kinases.

115. The kit of claim **114**, wherein the reagents comprise antibodies.

116. A method of inferring a risk of developing, a diagnosis of, a stage of, a prognosis of or a progression of a neurodegenerative condition, wherein the method comprises:

a) measuring, from a biological sample from a subject that is enriched for neuronally derived microparticles, e.g., exosomes, a set of biomarkers to create a dataset,

5 wherein the set of biomarkers includes:

(1) at least one signaling kinase and, optionally, at least one oligomeric form of a neurodegenerative protein; or

(2) a plurality of different signaling kinases; and

b) correlating the dataset with a risk of developing, a diagnosis of, a stage of, a prognosis of or a progression of the neurodegenerative condition.

117. The method of claim **116**, wherein at least one of the signaling kinases is a kinase of the PI3K-Akt-mTOR signaling pathway.

118. The method of claim **116**, wherein at least one of the signaling kinases is selected from mitogen-activated protein kinase (MAPK or MEK), extracellular signal-regulated kinases (ERK), glycogen synthase kinase 3 beta (GSK3B), AKT kinase and beclin.

119. The method of claim **116**, wherein the neurodegenerative protein selected from alpha synuclein, amyloid beta, tau, or huntingtin.

120. The method of claim **116**, wherein the oligomeric form of the neurodegenerative protein is a collection of oligomeric forms, e.g., oligomers of alpha synuclein, e.g., alpha synuclein 2-50, e.g., alpha synuclein 4-30, e.g., alpha synuclein 4-20.

121. A method comprising:

(a) identifying a subject having a neurodegenerative condition or likely to positively respond to a treatment for a neurodegenerative condition, wherein identifying comprises:

25 (1) measuring, in a sample from the subject enriched for neuronally derived exosomes (e.g., from the internal contents of the exosomes), a set of biomarkers, to create a biomarker profile, wherein the set of biomarkers includes one or a plurality of signaling kinases and, optionally, at least one oligomeric form of a neurodegenerative protein; and

30 (2) determining, based on an abnormal biomarker profile, that the subject suffers from the neurodegenerative condition; and

(b) administering to the identified subject, an effective amount of a pharmaceutical composition to treat the neurodegenerative condition.

122. The method of claim **121**, wherein the neurodegenerative condition is a synucleopathic condition, and the pharmaceutical composition comprises comprising a dopamine agonist (e.g., pramipexole (e.g., Mirapex™), ropinirole (e.g., Requip), rotigotine (e.g., Neupro), apomorphine (e.g., Apokyn)), levodopa, carbidopa-levodopa (e.g., Rytary, Sinemet), a
5 MAO-B inhibitor (e.g., selegiline (e.g., Eldepryl, Zelapar) or rasagiline (e.g., Azilect)), a catechol-O-methyltransferase (COMT) inhibitor (e.g., entacapone (Comtan) or tolcapone (Tasmar)), an anticholinergic (e.g., benztropine (e.g., Cogentin) or trihexyphenidyl), amantadine or a cholinesterase inhibitor (e.g., rivastigmine (Exelon)).

123. The method of claim **121**, wherein the synucleopathic condition is Parkinson's
10 Disease.

124. The method of claim **123**, wherein the pharmaceutical composition comprises a dopamine agonist.

125. The method of claim **124**, wherein the pharmaceutical composition further comprises an NK1-antagonist.

126. The method of claim **125**, wherein the dopamine agonist is 6-propylamino-
15 4,5,6,7-tetrahydro-1,3-benzothiazole-2-amine and the NK1-antagonist is aprepitant or rolapitant.

127. The method of claim **124**, wherein the pharmaceutical composition further comprises an 5HT3-antagonist.

128. The method of claim **127**, wherein the dopamine agonist is 6-propylamino-
20 4,5,6,7-tetrahydro-1,3-benzothiazole-2-amine and the 5HT3 antagonist is ondansetron hydrochloride dihydrate.

129. A method comprising administering to a subject characterized as having a biomarker profile indicative of a neurodegenerative condition or being likely to positively respond to a treatment for a neurodegenerative condition, an effective amount of a pharmaceutical
25 composition to treat the neurodegenerative condition; wherein the biomarker panel comprises set of biomarkers includes one or a plurality of signaling kinases and, optionally, at least one oligomeric form of a neurodegenerative protein measured from a sample from the subject enriched for neuronally derived exosomes (e.g., from the internal contents of the exosomes).

130. The method of claim **129**, wherein the neurodegenerative condition is
30 Parkinson's Disease, and wherein the pharmaceutical composition comprises a dopamine agonist.