assays are being developed, including cerebrospinal fluid measurements and brain amyloid plaque imaging through positron emission tomography (PET); however, these tests face limitations as they either require invasive lumbar punctures or are too expensive for wider clinical adoption. As a result, there is intense interest in finding serologic biomarkers of AD to assist in early diagnosis and disease monitoring.

[0006] Accordingly, there is a need to overcome, or at least to alleviate, one or more of the above-mentioned problems.

SUMMARY

[0007] Disclosed herein is a method of detecting amyloidosis or a neurodegenerative disease in a subject and methods of monitoring and treating the subject.

[0007a] In one aspect, the present disclosure refers to the use of a drug in the manufacture of a medicament for treating a neurodegenerative disease or amyloidosis in a subject, wherein the neurodegenerative disease or amyloidosis is detected in the subject based on the level of an exosome-bound aggregated biomarker detected in a sample obtained from the subject, wherein an increased level of an exosome-bound aggregated biomarker as compared to a reference is indicative of a neurodegenerative disease or amyloidosis in the subject, wherein the biomarker is selected from the group consisting of Aβ, APP, α-Syn, Tau, APOE, SOD1, TDP-43, bassoon, and/or fibronectin, and wherein the drug is selected from the group consisting of a cholinesterase inhibitor, an NMDA receptor antagonist, a combination of a cholinesterase inhibitor and an NMDA receptor antagonist, a BACE1 inhibitor, an antibody, protein aggregation inhibitors, proteasome inhibitors, small molecules, gene therapy, and an anti-tau drug.

[0007b] In another aspect, the present disclosure refers to the use of a therapeutically effective amount of one or more drugs, or a combination thereof in the manufacture of a medicament for treating a subject suffering from a neurodegenerative disease or amyloidosis, wherein the subject has an increased degree of aggregation of a biomarker as compared to a reference, wherein the aggregation state of the biomarker in a sample obtained from the subject is determined based on the level of exosome-bound biomarker detected in the sample, wherein an increased level of exosome-bound biomarker as compared to a reference is indicative of the degree of aggregation of the biomarker, wherein the biomarker is selected from the group consisting of Aβ, APP, α-Syn, Tau, APOE, SOD1, TDP-43, bassoon, and/or fibronectin, and wherein the one or more drugs are selected from the group consisting of a cholinesterase inhibitor, an NMDA receptor antagonist, a

combination of a cholinesterase inhibitor and an NMDA receptor antagonist, a BACE1 inhibitor, an antibody, protein aggregation inhibitors, proteasome inhibitors, small molecules, gene therapy, and an anti-tau drug.

[0007c] In another aspect, disclosed herein is a method of detecting a neurodegenerative disease or amyloidosis in a subject, the method comprising measuring the total level of a biomarker in a native biological sample obtained from the subject and the level of an exosome-bound aggregated biomarker in the native biological sample obtained from the subject, wherein an increased relative level of the exosome-bound aggregated biomarker as compared to the total level of the biomarker indicates that the subject is suffering from a neurodegenerative disease or amyloidosis, wherein the biomarker is selected from the group consisting of Aβ, APP, α-Syn, Tau, APOE, SOD1, TDP-43, bassoon, and/or fibronectin.

[0007d] In another aspect, disclosed herein is a method of detecting a subject at risk of developing a neurodegenerative disease or amyloidosis, the method comprising detecting the level of an exosome-bound aggregated biomarker in a native biological sample obtained from the subject, wherein an increased level of the exosome-bound aggregated biomarker as compared to the total level of the biomarker in the native biological sample indicates that the subject is at risk of developing a neurodegenerative disease or amyloidosis, wherein the biomarker is selected from the group consisting of Aβ, APP, α-Syn, Tau, APOE, SOD1, TDP-43, bassoon, and/or fibronectin.

[0007e] In another aspect, disclosed herein is a method of determining the aggregation state of a biomarker in a native biological sample, the method comprising detecting the level of exosome-bound biomarker in the native biological sample, wherein an increased relative level of exosome-bound biomarker as compared to the total level of the biomarker in the native biological sample is indicative of the degree of aggregation of the biomarker, wherein the biomarker is selected from the group consisting of Aβ, APP, α-Syn, Tau, APOE, SOD1, TDP-43, bassoon, and/or fibronectin.

[0008] In one aspect, there is provided a method of detecting amyloidosis or a neurodegenerative disease in a subject, the method comprising detecting the level of an exosome-bound aggregated biomarker in a sample obtained from the subject, wherein an increased level of the exosome-bound aggregated biomarker as compared to a reference indicates that the subject is suffering from a neurodegenerative disease.

[0009] In one aspect, there is provided a method of detecting a subject at risk of developing amyloidosis or a neurodegenerative disease, the method comprising detecting the level of an

exosome-bound aggregated biomarker in a sample obtained from the subject, wherein an increased level of the exosome-bound aggregated biomarker as compared to a reference indicates that the subject is suffering from a neurodegenerative disease.

[0010] In one example, there is provided a method of detecting and treating amyloidosis or a neurodegenerative disease in a subject, the method comprising:
a) detecting the level of an exosome-bound aggregated biomarker in a sample obtained from the subject, wherein an increased level of an exosome-bound aggregated biomarker as compared to a reference indicates that the subject is suffering from a neurodegenerative disease; and b) treating the subject suffering from neurodegenerative disease.

[0011] In one aspect, there is provided a method of determining the aggregation state of a biomarker in a sample, the method comprising detecting the level of exosome-bound biomarker in the sample, wherein an increased level of exosome-bound biomarker as compared to a reference is indicative of the degree of aggregation of the biomarker.

WHAT IS CLAIMED IS:

1. A method of detecting a neurodegenerative disease or amyloidosis in a subject, the method comprising measuring the total level of a biomarker in a native biological sample obtained from the subject and the level of an exosome-bound aggregated biomarker in the native biological sample obtained from the subject, wherein an increased relative level of the exosome-bound aggregated biomarker as compared to the total level of the biomarker indicates that the subject is suffering from a neurodegenerative disease or amyloidosis, wherein the biomarker is selected from the group consisting of Aβ, APP, α-Syn, Tau, APOE, SOD1, TDP-43, bassoon, and/or fibronectin.

2. The method of claim 1, wherein the method comprises detecting the level of a molecular subtype of the exosome-bound biomarker.

3. The method of claim 2, wherein the molecular subtype of Aβ is Aβ42, Aβ40, Aβ39 or Aβ38.

4. The method of claim 1, wherein the biomarker is a prefibrillar aggregate.

5. The method of any one of claims 1-4, wherein the method further comprises detecting an exosomal biomarker selected from the group consisting of CD63, CD9, CD81, ALIX, TSG101, Flotilin-1, Flotilin-2, LAMP-1, HSP70, HSP90, RNA and DNA wherein the exosomal biomarker is co-localized with the exosome-bound biomarker.

6. The method of any one of claims 1-5, wherein the method further comprises detecting a neuronal biomarker selected from the group consisting of NCAM, L1CAM, CHL-1 and IRS-1, wherein the neuronal biomarker is co-localized with the exosome-bound biomarker.

7. The method of any one of claims 1-6, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, mild cognitive impairment, dementia, vascular dementia, and/or vascular mild cognitive impairment.

8. The method of any one of claims 1-6, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease and mild cognitive impairment.

9. The method of any one of claims 1-8, wherein the sample is tissue biopsies, blood, plasma, serum or cerebrospinal fluid.

10. The method of any one of claims 1-9, wherein the method is further correlated with brain imaging study.

11. A method of detecting a subject at risk of developing a neurodegenerative disease or amyloidosis, the method comprising detecting the level of an exosome-bound aggregated biomarker in a native biological sample obtained from the subject, wherein an increased level of the exosome-bound aggregated biomarker as compared to the total level of the biomarker in the native biological sample indicates that the subject is at risk of developing a neurodegenerative disease or amyloidosis, wherein the biomarker is selected from the group consisting of Aβ, APP, α-Syn, Tau, APOE, SOD1, TDP-43, bassoon, and/or fibronectin.

12. Use of a drug in the manufacture of a medicament for treating a neurodegenerative disease or amyloidosis in a subject, wherein the neurodegenerative disease or amyloidosis is detected in the subject based on the level of an exosome-bound aggregated biomarker detected in a sample obtained from the subject, wherein an increased level of an exosome-bound aggregated biomarker as compared to a reference is indicative of a neurodegenerative disease or amyloidosis in the subject,

wherein the biomarker is selected from the group consisting of Aβ, APP, α-Syn, Tau, APOE, SOD1, TDP-43, bassoon, and/or fibronectin, and

wherein the drug is selected from the group consisting of a cholinesterase inhibitor, an NMDA receptor antagonist, a combination of a cholinesterase inhibitor and an NMDA receptor antagonist, a BACE1 inhibitor, an antibody, protein aggregation inhibitors, proteasome inhibitors, small molecules, gene therapy, and an anti-tau drug.

13. A method of determining the aggregation state of a biomarker in a native biological sample, the method comprising detecting the level of exosome-bound biomarker in the native biological sample, wherein an increased relative level of exosome-bound biomarker as compared to the total level of the biomarker in the native biological sample is indicative of the degree of aggregation of the biomarker, wherein the biomarker is selected from the group consisting of Aβ, APP, α-Syn, Tau, APOE, SOD1, TDP-43, bassoon, and/or fibronectin.

14. The method of claim 13, wherein the method comprises the step of contacting the sample with a population of exosomes prior to the step of detecting the level of exosome-bound biomarker.

15. The method of claim 13 or 14, wherein the aggregated biomarker in the sample, as compared to the non-aggregated biomarker, binds preferentially to exosomes.

16. The method of claim 15, wherein the sample is obtained from a subject.

17. The method of claim 16, wherein an increased degree of aggregation of the biomarker as compared to a reference is indicative of a neurodegenerative disease or amyloidosis in the subject.

18. Use of a therapeutically effective amount of one or more drugs, or a combination thereof in the manufacture of a medicament for treating a subject suffering from a neurodegenerative disease or amyloidosis, wherein the subject has an increased degree of aggregation of a biomarker as compared to a reference, wherein the aggregation state of the biomarker in a sample obtained from the subject is determined based on the level of exosome-bound biomarker detected in the sample, wherein an increased level of exosome-bound biomarker as compared to a reference is indicative of the degree of aggregation of the biomarker,

wherein the biomarker is selected from the group consisting of Aβ, APP, α-Syn, Tau, APOE, SOD1, TDP-43, bassoon, and/or fibronectin, and

wherein the one or more drugs are selected from the group consisting of a cholinesterase inhibitor, an NMDA receptor antagonist, a combination of a cholinesterase inhibitor and an NMDA receptor antagonist, a BACE1 inhibitor, an antibody, protein aggregation inhibitors, proteasome inhibitors, small molecules, gene therapy, and an anti-tau drug.

19. The use of claim 18, wherein the therapeutically effective amount of one or more drugs, or a combination thereof, is to be administered to the subject.

20. The method of any one of claims 1-11 and 13-17 or the use of any one of claims 12 and 18-19, wherein the detecting the total level of a biomarker and the exosome-bound aggregated biomarker are by a Surface Plasmon Resonance Sensor.