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 sensor chip and methods for the detection of an analyte via surface plasmon resonance.

[0007a] In one aspect, there is provided an imaging system comprising: a light source; a detector; a sensor chip comprising: a conductive layer on a membrane support layer; a plurality of apertures extending through the conductive layer and the membrane support layer and is arranged such that illumination of the back of the membrane support layer produces a surface plasmon resonance; a void formed in a region adjacent to the plurality of apertures to enable back illumination; and a first recognition molecule that binds specifically to a first analyte, the first recognition molecule being immobilized onto a surface of the conductive layer; and a second recognition molecule that binds specifically to the first analyte or to a second analyte associated with the first analyte, wherein the second recognition molecule is coupled to a signal amplification moiety, wherein the signal amplification moiety is capable of inducing formation of an insoluble aggregate of increased optical density relative to that of the first analyte when the first analyte is captured by the first recognition molecule, and wherein the signal amplification moiety is an enzyme; wherein the light source is arranged for illumination of the back of the membrane support layer, and the detector is positioned to detect light transmitted through the sensor chip.

[0007b] In one aspect, provided herein is a method of detecting a first analyte in a sample, the method comprising: a) capturing the first analyte onto the conductive layer of the sensor chip as described herein, the capturing comprising binding the first analyte to the first recognition molecule as described herein; and b) detecting binding of the second recognition molecule as described herein to the first analyte or to a second analyte associated with the first analyte, wherein an increased binding of the second recognition molecule as compared to a control sample indicates a presence of the first analyte in the sample.

[0007c] In one aspect, provided herein is a method of detecting a neurodegenerative disease or amyloidosis in a subject, the method comprising: a) contacting a sample obtained from the subject with the conductive layer of the sensor chip as described herein; b) illuminating the membrane support layer of the sensor chip; and c) detecting binding of the second recognition molecule as described herein to an analyte captured on the conductive layer of the sensor chip, wherein an increased binding of the second recognition molecule as compared to a control sample or control subject indicates that the subject is suffering from the neurodegenerative disease.

[0008] In one aspect, there is provided a sensor chip comprising a conductive layer on a membrane support layer, wherein a plurality of apertures extend through the conductive layer and the membrane support layer and are arranged such that illumination of the conductive layer and/or the membrane support layer produces a surface plasmon resonance.

[0009] In one aspect, there is provided an imaging system comprising a light source, a detector, and a sensor chip as defined herein, wherein the light source is arranged to illuminate the sensor chip and the detector is positioned to detect light transmitted through the sensor chip.

[0010] In one aspect, there is provided a method of fabricating a sensor chip, the method comprising steps of:

a) providing a top membrane support layer;

b) depositing a conductive layer on the top membrane support layer;

c) forming a plurality of apertures that extend through the membrane support layer, said apertures also extending through the conductive layer, and being arranged such that

illumination of the conductive layer and/or the top membrane support layer produces a surface plasmon resonance.

[0011] In one aspect, there is provided a method of detecting an analyte in a sample, the method comprising:

a) capturing an analyte onto a surface of a sensor chip as defined herein;

b) detecting binding of a second recognition molecule to the captured analyte on the surface of the sensor chip, wherein the second recognition molecule is specific to the analyte, wherein an

WHAT IS CLAIMED IS:

1. An imaging system comprising:

a light source;

a detector;

a sensor chip comprising:

a conductive layer on a membrane support layer;

a plurality of apertures extending through the conductive layer and the membrane support layer and is arranged such that illumination of the back of the membrane support layer produces a surface plasmon resonance;

a void formed in a region adjacent to the plurality of apertures to enable back illumination; and

a first recognition molecule that binds specifically to a first analyte, the first recognition molecule being immobilized onto a surface of the conductive layer; and

a second recognition molecule that binds specifically to the first analyte or to a second analyte associated with the first analyte, wherein the second recognition molecule is coupled to a signal amplification moiety, wherein the signal amplification moiety is capable of inducing formation of an insoluble aggregate of increased optical density relative to that of the first analyte when the first analyte is captured by the first recognition molecule, and wherein the signal amplification moiety is an enzyme;

wherein the light source is arranged for illumination of the back of the membrane support layer, and the detector is positioned to detect light transmitted through the sensor chip.

2. The imaging system of claim 1, wherein the first analyte comprises a protein, a nucleic acid, or a combination, association, or organizational state thereof.

3. The imaging system of claim 1, wherein the first analyte is an exosome-associated amyloidogenic protein, and wherein the second recognition molecule binds specifically to an exosome-associated biomarker.

4. The imaging system of claim 3, wherein the amyloidogenic protein is amyloid β (Aβ), amyloid precursor protein (APP), α-synuclein (α-Syn), insulin receptor substrate 1 (IRS-1), tau protein, lipoprotein (APOE), SOD1, TDP-43, bassoon, or fibronectin.

5. The imaging system of claim 3, wherein the amyloidogenic protein is Aβ, APP, IRS-1, NCAM or tau.

6. The imaging system of claim 3, wherein the amyloidogenic protein is Aβ42, Aβ40, Aβ39 or Aβ38.

7. The imaging system of any one of claims 3-6, wherein the exosome-associated biomarker is CD9, CD63, CD81, ALIX, TSG101, Flotillin-1, LAMP-1, HSP70, or HSP90

8. The imaging system of any one of claims 3-6, wherein the exosome-associated biomarker is CD63, CD9, or CD81.

9. The imaging system of any one of claims 1-8, wherein the conductive layer is gold, silver, aluminum, sodium, indium or titanium.

10. The imaging system of any one of claims 1-9, wherein the membrane support layer is silicon nitride or sodium dioxide.

11. The imaging system of any one of claims 1-10, wherein the apertures have a diameter of 150 nm to 450 nm.

12. The imaging system of any one of claims 1-11, wherein the apertures are arranged periodically.

13. The imaging system of claim 12, wherein the apertures have a periodicity of 250 nm to 650 nm.

14. The imaging system of any one of claims 1-13, wherein the apertures are arranged such that the surface plasmon resonance produced on illumination has a decay length approximately equal to a diameter of the first analyte.

15. The imaging system of any one of claims 1-14, wherein the conductive layer and the membrane support layer are disposed on a substrate, the substrate having the void formed therein, wherein the substrate enables illumination of the back of the membrane support layer to produce the surface plasmon resonance.

16. The imaging system of any one of claims 1-15, wherein the second recognition molecule is fused to the signal amplification moiety.

17. The imaging system of any one of claims 1-16, wherein the enzyme is horse radish peroxidase.

18. The imaging system of any one of claims 1-17, wherein the imaging system further comprises a substrate of the enzyme.

19. The imaging system of any one of claims 1-18, wherein the enzyme is coupled to a secondary antibody capable of binding to the second recognition molecule.

20. A method of detecting a first analyte in a sample, the method comprising:

a) capturing the first analyte onto the conductive layer of the sensor chip of any one of claims 1-19, the capturing comprising binding the first analyte to the first recognition molecule of any one of claims 1-19; and

b) detecting binding of the second recognition molecule of any one of claims 1-19 to the first analyte or to a second analyte associated with the first analyte, wherein an increased binding of the second recognition molecule as compared to a control sample indicates a presence of the first analyte in the sample.

21. The method of claim 20, wherein

the method further comprises contacting the enzyme with a substrate of the enzyme.

22. The method of claims 20 or 21, wherein the detecting of the binding of the second recognition molecule comprises analyzing localized measurements of one or both of the first analyte and the second analyte.

23. The method of any one of claims 20-22, wherein the method comprises detecting two or more analytes that are co-localized in the sample.

24. A method of detecting a neurodegenerative disease or amyloidosis in a subject, the method comprising:

a) contacting a sample obtained from the subject with the conductive layer of the sensor chip of any one of claims 1-19;

b) illuminating the membrane support layer of the sensor chip; and

c) detecting binding of the second recognition molecule of any one of claims 1-19 to an analyte captured on the conductive layer of the sensor chip, wherein an increased binding of the second recognition molecule as compared to a control sample or control subject indicates that the subject is suffering from the neurodegenerative disease.

25. The method of claim 24, wherein the detecting of the binding of the second recognition molecule to the analyte comprises measuring a change of a transmission light wavelength or intensity.

26. The method of claims 24 or 25, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, mild cognitive impairment, vascular dementia, dementia, Parkinson's disease, Amyotrophic lateral sclerosis, Multiple sclerosis, Progressive supranuclear palsy, Taupathies, and vascular mild cognitive impairment.

27. The method of any one of claims 24-26, wherein the method further comprises that the subject found to be suffering from a neurodegenerative disease is to be treated.