clearing the sample; c) contacting a first cell or nucleus in the tissue or tissue sample with a first photo-activatable label; d) imaging the tissue or tissue sample to create an image; e) subjecting the region of the tissue or tissue sample comprising the first cell or nucleus to a multi-photon laser to activate the first photo-activatable label to generate a first photoactivated label, thereby labeling the region with the first photoactivated label; (f) isolating the labeled region from the tissue or tissue sample; (g) analyzing a composition of the isolated labeled region to create analysis data; and (h) combining the image with the analysis data to create a 3-dimensional composition map of the region. The first photo-activatable label comprises one or more of a detectable moiety and a tag.

[0005] In another aspect is provided a method for 3-dimensional expression profiling of an intact tissue or tissue sample. The method may include: a) providing a three-dimensional intact tissue or tissue sample; b) clearing the sample; c) contacting the tissue or tissue sample with photo-activatable label; d) subjecting a region of the tissue or tissue sample to a multi-photon laser to activate the photo-activatable label to generate a photoactivated label, thereby labeling the region with the photoactivated label; e) imaging the labeled region to create an image; f) isolating the labeled region from the tissue or tissue sample; g) determining a DNA, RNA, and/or protein composition of the isolated labeled region; h) combining the image with the DNA, RNA, and/or protein composition of the isolated labeled region to create a 3-dimensional expression profile of the intact tissue or tissue sample. The photo-activatable label comprises one or more of (i) a detectable moiety and (ii) a tag.

[0006] In an aspect, a method for isolating a single cell or a nucleus, in a tissue or tissue sample is provided. The method may include: a) providing a three-dimensional tissue or tissue sample comprising a cell or nucleus of interest; b) clearing the sample; c) contacting the tissue or tissue sample with photo-activatable label; d) subjecting the cell or nucleus to a multi-photon laser, thereby labeling the cell or nucleus; e) dissociating the labeled cell nucleus from the tissue or tissue sample; and f) isolating the labeled cell or nucleus.

[0007] In another aspect, a composition is provided. The composition may include a tissue sample, a medium having a refraction index similar to or matching the tissue, and a photo-activatable label.

[0008] In an aspect, a cleared tissue sample is provided. The cleared tissue sample may include a photo-activatable label and a medium having a refraction index substantially matching the index of the tissue.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] **FIG. 1** shows a mouse brain before (left) and after (right) clearing of the tissue.

[0010] **FIG. 2** is a series of fluorescence microscopy pictures showing the stability of different fluorescent proteins in cleared tissue (bottom row) or control tissue (top row). In this

WHAT IS CLAIMED IS:

1. A method for labeling a region of a tissue or tissue sample, comprising:
   a) providing a three-dimensional tissue or tissue sample;
   b) clearing the sample;
   c) contacting a first cell or nucleus in the tissue or tissue sample with a first photo-activatable label;
   d) imaging the tissue or tissue sample to create an image;
   e) subjecting the region of the tissue or tissue sample comprising the first cell or nucleus to a multi-photon laser to activate the first photo-activatable label to generate a first photoactivated label, thereby labeling the region with the first photoactivated label;
   f) isolating the labeled region from the tissue or tissue sample;
   g) analyzing a composition of the isolated labeled region to create analysis data; and
   h) combining the image with the analysis data to create a 3-dimensional composition map of the region;
   wherein the first photo-activatable label comprises one or more of:
      (i) a detectable moiety; and
      (ii) a tag.

2. The method of claim 1, wherein the multi-photon laser is a two-photon laser or a three-photon laser.

3. The method of claim 1 or 2, wherein the region comprises a cell, a subcellular compartment, an aggregate, or a secreted aggregate.

4. The method of any one of claims 1-3, wherein the tissue or tissue sample is a fixed tissue or fixed tissue sample.

5. The method of any one of claims 1-4, wherein the detectable moiety comprises:
   (i) a light emitting moiety; or
   (ii) an antibody or a functional derivative thereof.

6. The method of claim 5, wherein the light emitting moiety is selected from:
   (i) a fluorescent moiety;
   (ii) a chemiluminescent moiety;
   (iii) a bioluminescent moiety; and
   (iv) an electrochemiluminescent moiety.

7. The method of claim 6, wherein the fluorescent moiety is a fluorophore.

8. The method of any one of claims 1-4, wherein the tag is selected from:
   (i) an affinity tag;
   (ii) an epitope tag;

(iii) a fluorescent tag;
(iv) an oligonucleotide tag; and
(v) a biotin tag.

9. The method of any one of claims 1-8, wherein the sample clearing process comprises dehydrating the tissue or tissue sample and transferring the tissue or tissue sample into a medium with a refraction index:
(a) similar to the tissue;
(b) matching the tissue; or
(c) between about 1.3 and about 1.6.

10. The method of claim 9, wherein the medium comprises a solution of Benzyl Alcohol, Benzyl Benzoate (BABB) or derivative thereof, with or without one or more of triethylamine, diphenyl ether, dibenzyl ether, α-tocopherol, and/or N,N,N′,N′-Tetrakis(2-hydroxypropyl)ethylenediamine.

11. The method of any one of claims 9-10, wherein the tissue or tissue sample is dehydrated by a tert-butanol solution or a tert-butanol solution comprising trimethylamine, tetrahydrofuran, ethanol, or methanol.

12. The method of any one of claims 1-11, wherein the first photo-activatable label is hydrophobic.

13. The method of any one of claims 1-12, wherein the first photo-activatable label comprises a phenyl azide group, an ortho-hydroxyphenyl azide group, a meta-hydroxyphenyl azide group, a tetrafluorophenyl azide group, an ortho-nitrophenyl azide group, a meta-nitrophenyl azide group, a diazirine group, an azido-methylcoumarin group, or a psoralen group.

14. The method of any one of claims 1-13, wherein the labeled region or portion thereof is isolated by FACS sorting for the first photo-activatable label.

15. The method of any one of claims 1-14, wherein analyzing comprises determining a DNA, RNA, and/or protein composition of the isolated labeled region.

16. The method of claim 15, wherein the RNA composition is analyzed by sequencing, single cell RNA sequencing (scRNAseq), or SPLITSEQ; the protein composition is analyzed by mass spectrometry; and/or the DNA composition is analyzed by DNA sequencing.

17. The method of any one of claims 1-16, further comprising contacting the tissue or tissue sample with a second photo-activatable label and subjecting a second cell or nucleus in

the tissue or tissue sample to a multi-photon laser to activate the second photo-activatable label, thereby labeling the second cell or nucleus.

18. The method of any one of claims 1-17, wherein the tissue or tissue sample is a whole organ, tumor, or animal; or from a tumor.

19. The method of any one of claims 1-18, wherein the multi-photon laser is a two-photon laser, and wherein the wavelength of each photon in the two-photon laser is between about 175 nm and about 350 nm.

20. A method for 3-dimensional expression profiling of an intact tissue or tissue sample, comprising:

a) providing a three-dimensional intact tissue or tissue sample;

b) clearing the sample;

c) contacting the tissue or tissue sample with a photo-activatable label;

d) subjecting a region of the tissue or tissue sample to a multi-photon laser to activate the photo-activatable label to generate a photoactivated label, thereby labeling the region with the photoactivated label;

e) imaging the labeled region to create an image;

f) isolating the labeled region from the tissue or tissue sample;

g) determining a DNA, RNA, and/or protein composition of the isolated labeled region; and

h) combining the image with the DNA, RNA, and/or protein composition of the isolated labeled region to create a 3-dimensional expression profile of the intact tissue or tissue sample;

wherein the photo-activatable label comprises one or more of:

(i) a detectable moiety; and

(ii) a tag.

21. The method of claim 20, wherein the region is a cell, a subcellular compartment, an aggregate, or a secreted aggregate.

22. The method of claim 20, wherein an RNA composition, a protein composition, and/or a DNA composition of the isolated labeled region is determined, and

optionally wherein the RNA composition is determined by sequencing, single cell RNA sequencing (scRNAseq), or SPLITseq, the protein composition is determined by mass spectrometry, and/or the DNA composition is determined by DNA sequencing.

23. The method of any one of claims 20-22, wherein the detectable moiety comprises:

(i) a light emitting moiety; or

(ii) an antibody or a functional derivative thereof.

24. The method of claim 23, wherein the light emitting moiety is selected from:

(i) a fluorescent moiety;

(ii) a chemiluminescent moiety;
(iii) a bioluminescent moiety; and
(iv) an electrochemiluminescent moiety.

25. The method of claim 24, wherein the fluorescent moiety is a fluorophore.

26. The method of any one of claims 20-22, wherein the tag is selected from:
(i) an affinity tag;
(ii) an epitope tag;
(iii) a fluorescent tag;
(iv) an oligonucleotide tag; and
(v) a biotin tag.

27. The method of any one of claims 20-26, wherein the photo-activatable label is hydrophobic.

28. The method of any one of claims 20-27, wherein the photo-activatable label comprises a phenyl azide group, an ortho-hydroxyphenyl azide group, a meta-hydroxyphenyl azide group, a tetrafluorophenyl azide group, an ortho-nitrophenyl azide group, a meta-nitrophenyl azide group, a diazirine group, an azido-methylcoumarin group, or a psoralen group.

29. The method of any one of claims 20-28, wherein the multi-photon laser is a two-photon laser or a three-photon laser.

30. The method of any one of claims 20-29, wherein the tissue or tissue sample is a fixed tissue or fixed tissue sample.

31. The method of any one of claims 20-30, wherein the sample clearing process comprises dehydrating the tissue or tissue sample and transferring the tissue or tissue sample into a medium with a refraction index:
(a) similar to the tissue;
(b) matching the tissue; or
(c) between about 1.3 and about 1.6.

32. The method of claim 31, wherein the medium comprises a solution of Benzyl Alcohol, Benzyl Benzoate (BABB) or derivative thereof, with or without one or more of triethylamine, diphenyl ether, dibenzyl ether, α-tocopherol, and/or N,N,N′,N′-Tetrakis(2-hydroxypropyl)ethylenediamine.

33. The method of claim 32, wherein the medium comprises a BABB solution.

34. The method of any one of claims 31-33, wherein the tissue or tissue sample is dehydrated by a tert-butanol solution or a tert-butanol solution comprising trimethylamine, tetrahydrofuran, ethanol, or methanol.

35. The method of any one of claims 20-34, wherein the labeled region is isolated by FACS sorting for the photo-activatable label.

36. The method of any one of claims 20-35, wherein the isolated labeled region is a single nucleus or a single cell.

37. The method of claim 21, wherein the subcellular compartment is a nucleus.