target may be a nucleic acid, (*e.g.*, mRNA and miRNA) and/or a protein. The target-binding domain may be a single-stranded nucleic acid, a partially double-stranded nucleic acid, or a protein-binding molecule, *e.g.*, an antibody, a peptide, an aptamer, and a peptoid. In examples, two or more targets (*i.e.*, proteins, nucleic acids, and a combination thereof) are detected. In examples, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 or more targets, and any number therebetween, are detected; for example, 800 or more different targets can be detected. In examples, detecting includes quantifying the abundance of each target.

[0004a] In one aspect, the present disclosure refers to a method of producing a spatially-resolved profile of nucleic acid abundance in a tissue sample comprising: a) contacting the tissue sample with a solution comprising at least 6 species of probes, the probes comprising a target-binding domain, a signal oligonucleotide, and a photo-cleavable motif located between the target-binding domain and the signal oligonucleotide, wherein each species of probe comprises a unique nucleic acid target-binding domain that hybridizes to one of at least 6 target nucleic acids and a unique signal oligonucleotide specific for the target nucleic acid; b) illuminating a first location of the tissue sample with light sufficient to release signal oligonucleotides at the first location; c) collecting the signal oligonucleotides released in step (b) from the solution proximal to the first location; d) identifying and quantifying via multiplexed immunohistochemistry the signal oligonucleotides collected in step (c), thereby determining the abundance of the at least 6 target nucleic acids in the first location; e) illuminating at least a second location of the tissue sample with light sufficient to release the signal oligonucleotides at the at least second location; f) collecting the signal oligonucleotides released in step (e) from the solution proximal to the at least second location; g) identifying and quantifying via multiplexed immunohistochemistry the signal oligonucleotides collected in step (f), thereby determining the abundance of the at least 6 target nucleic acids in the at least second location; and h) comparing the abundance of the at least 6 target nucleic acids in the first location of the tissue sample to the abundance of the at least 6 target nucleic acids in the at least second location of the tissue sample, thereby generating a spatially-resolved profile of nucleic acid abundance in the tissue sample.

[0005] In examples, the method further includes repeating at least steps (2) and (3) on at least a second specific location of the tissue sample, the second specific location comprising at least a second cell. In examples, detecting includes comparing the abundance of the at least one target in or from the first specific location and in or from the at least second specific location. The at least one cell and at least second cell may be the same cell type or distinct cell types. In some examples, detecting includes quantifying the abundance of the at least one target in or from a first cell type and in or from the at least a second cell type. In examples, first and second cell types are independently selected from a normal cell and an abnormal cell, *e.g.*, a diseased and cancerous cell.

[0006] In examples, the at least one cell is directly immobilized to a surface or is indirectly immobilized to the surface *via* at least one other cell. A tissue sample may be a 2 to 1000 μm thick tissue section, *e.g.*, obtained from a formalin-fixed paraffin embedded (FFPE) sample or from an unfixed sample. The at least one cell may be fixed or unfixed. The at least one cell may be stained or labeled prior to step (2) allowing visualization of a subcellular or cellular structure in the stained or labeled cell. Alternately, for tissue sections, a section adjacent to the section that is contacted with the probes may be stained or labeled prior to step (2), thereby allowing estimation of a subcellular, cellular, or tissue-related structure in the corresponding cell or nearby cell in the section that is contacted with the probes. Such staining or labeling techniques are well known in the art.

[0007] In the above example, at least one probe further includes a linker (*e.g.*, a cleavable linker) located between the target-binding domain and the signal oligonucleotide. The cleavable linker may be photo-cleavable, which is cleaved by light provided by a suitable coherent light source (*e.g.*, a laser and a UV light source) or a suitable incoherent light source (*e.g.*, an arc-lamp and a

What is claimed is:

1. A method of producing a spatially-resolved profile of nucleic acid abundance in a tissue sample comprising:

a) contacting the tissue sample with a solution comprising at least 6 species of probes, the probes comprising a target-binding domain, a signal oligonucleotide, and a photo-cleavable motif located between the target-binding domain and the signal oligonucleotide,

wherein each species of probe comprises a unique nucleic acid target-binding domain that hybridizes to one of at least 6 target nucleic acids and a unique signal oligonucleotide specific for the target nucleic acid;

b) illuminating a first location of the tissue sample with light sufficient to release signal oligonucleotides at the first location;

c) collecting the signal oligonucleotides released in step (b) from the solution proximal to the first location;

d) identifying and quantifying via multiplexed immunohistochemistry the signal oligonucleotides collected in step (c), thereby determining the abundance of the at least 6 target nucleic acids in the first location;

e) illuminating at least a second location of the tissue sample with light sufficient to release the signal oligonucleotides at the at least second location;

f) collecting the signal oligonucleotides released in step (e) from the solution proximal to the at least second location;

g) identifying and quantifying via multiplexed immunohistochemistry the signal oligonucleotides collected in step (f), thereby determining the abundance of the at least 6 target nucleic acids in the at least second location; and

h) comparing the abundance of the at least 6 target nucleic acids in the first location of the tissue sample to the abundance of the at least 6 target nucleic acids in the at least second location of the tissue sample, thereby generating a spatially-resolved profile of nucleic acid abundance in the tissue sample.

2. The method of claim 1, wherein the first location and the at least second location each comprise at least one cell.

3. The method of claim 2, wherein the at least one cell in the first location and the at least one cell in the at least second location are the same cell type.

4. The method of claim 2, wherein the at least one cell in the first location and the at least one cell in the at least second location are distinct cell types.

5. The method of claim 4, wherein the at least one cell in the first location is an abnormal cell and the at least one cell in the at least second location is a normal cell.

6. The method of claim 1, wherein the tissue sample is directly immobilized to a surface or is indirectly immobilized to the surface.

7. The method of claim 1, wherein the tissue sample is a 2 to 1000 μm thick tissue section.

8. The method of claim 7, wherein the tissue section is obtained from a formalin-fixed paraffin embedded (FFPE) sample.

9. The method of claim 1, wherein the tissue sample comprises at least one cell, wherein the at least one cell is a cultured cell, a primary cell, or a dissociated cell from an explant.

10. The method of claim 1, wherein the tissue sample is fixed or unfixed.

11. The method of claim 1, further comprising staining or labeling the tissue to allow visualization of a subcellular, cellular, or tissue-related structure.

12. The method of claim 1, wherein the signal oligonucleotide is a single-stranded nucleic acid or a partially double-stranded nucleic acid.

13. The method of claim 1, further comprising a purification step to remove intact probe molecules from the released signal oligonucleotides, the purification step comprising an affinity purification comprising contacting an intact probe with an immobilized oligonucleotide that is complementary to a portion of the intact probe or an immobilized antibody or protein-binding motif that recognizes and binds to a portion of the intact probe.

14. The method of claim 13, wherein the target binding domain of the intact probe comprises a universal purification tag or sequence that is partially complementary to the immobilized oligonucleotide or is capable of being recognized or bound by the immobilized antibody or protein-binding motif.

15. The method of claim 1, wherein the source of light is selected from the group consisting of an arc-lamp, a laser, a focused UV light source, and light emitting diode (LED).

16. The method of claim 1, wherein the light is UV light.

17. The method of claim 1, wherein illuminating a first location of the tissue sample comprises irradiating at least one subcellular structure present in the first location.

18. The method of claim 1, wherein illuminating a second location of the tissue sample comprises irradiating at least one subcellular structure present in the at least second location.

19. The method of claim 17, wherein identifying the signal oligonucleotides released in the first location of the tissue sample comprises determining the abundance of the at least 6 target nucleic acids in the at least one irradiated subcellular structure.

20. The method of claim 18, wherein identifying the signal oligonucleotides released in the at least second location of the tissue sample comprises determining the abundance of the at least 6 target nucleic acids in the at least one irradiated subcellular structure.

21. The method of claim 1, wherein the target-binding domain comprises a single-stranded nucleic acid or a partially double-stranded nucleic acid.

22. The method of claim 1, wherein the solution proximal to the first location is directly above the first location.

23. The method of claim 1, wherein the solution proximal to the at least second location is directly above the at least second location.

24. The method of claim 1, wherein the proximal solution is collected by aspirating.

25. The method of claim 1, wherein the solution proximal to the first location and the solution proximal to the at least second location are collected using a pipette, a capillary tube, a microarray pin or a micro-aspirator.

26. The method of claim 25, wherein the capillary tube comprises an optical device capable of transmitting light to the at least one cell.

27. The method of claim 25, wherein the pipette or microarray pin is attached to an array comprising a plurality of pipettes or microarray pins.

28. The method of claim 1, wherein the proximal solutions comprise an anionic polymer or salmon sperm DNA or the collected signal oligonucleotides are added to a solution comprising an anionic polymer or salmon sperm DNA.

29. The method of claim 28, wherein the anionic polymer is dextran sulfate.

30. The method of claim 1, wherein the first location and the at least second location are illuminated using a laser scanning device or a digital mirror device (DMD).

31. The method of claim 1, wherein the spatially-resolved profile exhibits a linear dynamic range of > 5 logs.

32. The method of claim 1, wherein the tissue sample is attached to a slide and is first imaged using fluorescence.

33. The method of claim 1, wherein the probes are provided at a concentration of 5 nM or less.

34. The method of claim 1, wherein steps (b) and (e) are performed simultaneously.

35. The method of claim 1, wherein steps (b) and (e) are performed sequentially.

36. The method of claim 1, wherein steps (c) and (f) are performed simultaneously.

37. The method of claim 1, wherein steps (c) and (f) are performed sequentially.

38. The method of claim 1, wherein steps (d) and (g) are preformed simultaneously.

39. The method of claim 1, wherein steps (d) and (g) are preformed sequentially.