

identification. The present invention addresses these needs and provides related advantages as well.

4. SUMMARY OF THE INVENTION

[0009] Provided herein are methods and compositions useful for detecting a recombinantly produced water-immiscible compound in a cell, for example, a microbial cell genetically modified to produce one or more water-immiscible compounds at greater yield and/or with increased persistence compared to a parent microbial cell that is not genetically modified. In particular, the methods provided herein, alternately referred to as "picoscreening," provide for high-throughput, sensitive and quantitative means for screening microbial strains that are engineered, for example, to produce industrially useful water-immiscible compounds, including but not limited to isoprenoids, polyketides, fatty acids, and derivatives thereof. The methods provided herein also provide for the identification and selection of, and enrichment for, a cell, *e.g.*, a recombinant cell, and clonal cell populations thereof, which produce and/or comprise increased levels of such recombinantly produced water-immiscible compounds.

[0009a] In a first aspect, the present invention refers to a method of detecting recombinantly produced water-immiscible compound in a cell, the method comprising: (a) encapsulating the cell in a hydrogel particle; and (b) culturing the cell within the hydrogel particle whereby a cell population is formed within the particle; and (c) detecting the recombinantly produced water-immiscible compound within the hydrogel particle, wherein said detecting comprises contacting the hydrogel particle with a fluorescent solvatochromic dye and normalizing the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle.

[0010] In some ~~example~~embodiments, the method comprises encapsulating a cell in a hydrogel particle and detecting recombinantly produced water-immiscible compound within the hydrogel particle. In some ~~example~~embodiments, the cell is selected from the group consisting of a yeast cell, a bacterial cell, a mammalian cell, a fungal cell, an insect cell, and a plant cell. In some ~~example~~embodiments, the cell is a yeast cell. In some ~~example~~embodiments, the yeast is *Saccharomyces cerevisiae*.

[0011] In some examplebediments, the methods of detecting comprise contacting the hydrogel particle with a fluorescent dye that directly binds to the recombinantly produced water-immiscible compound and detecting the fluorescent dye within the hydrogel particle. In some examplebediments, the fluorescent dye is Nile Red. In some examplebediments, the detecting comprises normalizing the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle.

[0012] In some examplebediments, the hydrogel particle is capable of retaining a water-immiscible compound, *e.g.*, a water-immiscible compound produced by the cell. In some examplebediments, the hydrogel comprises agarose. In some examplebediments, the hydrogel particle is less than about 1 millimeter in diameter. In some examplebediments, the hydrogel particle is less than about 500 micrometers in diameter. In some examplebediments, the hydrogel particle is less than about 100 micrometers in diameter. In some examplebediments, the hydrogel particle is

less than 50 micrometers in diameter. In some embodimentsexamples, the hydrogel particle is about 50, 45, 40, 35, 30 or 25 micrometers in diameter.

[0013] In some embodimentsexamples of the methods of detecting provided herein, the encapsulating comprises contacting the cell with an aqueous hydrogel suspension under conditions sufficient to form a hydrogel particle comprising the cell. In some embodimentsexamples, the conditions comprise contacting the aqueous hydrogel suspension comprising the cell with a fluorocarbon oil. In some embodimentsexamples, the fluorocarbon oil comprises a fluorsurfactant. In some embodimentsexamples, the contacting with a fluorocarbon oil comprises loading the aqueous hydrogel suspension comprising the cell onto a microfluidic device comprising the fluorocarbon oil, wherein the hydrogel suspension contacts the fluorocarbon oil at a T-junction of the microfluidic device, wherein the contacting with the fluorocarbon oil results in formation of a non-aqueous hydrogel particle comprising the cell. In some embodimentsexamples, the methods of detection further comprise the step of separating the hydrogel particle from the fluorocarbon oil.

[0014] In some embodimentsexamples, the methods of detecting further comprise culturing the cell within the hydrogel particle prior to the detecting step. In some embodimentsexamples, the culturing is for a period of 12 to 24 hours.

[0015] In some embodimentsexamples, the recombinantly produced water-immiscible compound is a terpene, C₅ isoprenoid, C₁₀ isoprenoid or C₁₅ isoprenoid. In some embodimentsexamples, the recombinantly produced water-immiscible compound is farnesene. In some embodimentsexamples, the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the mevalonate (MEV) pathway. In some embodimentsexamples, the recombinantly produced water-immiscible compound is farnesene. In some embodimentsexamples, the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the 1-deoxy-D-xylulose 5-diphosphate (DXP) pathway. In some embodimentsexamples, the recombinant yeast cell comprises a heterologous nucleotide sequence encoding an enzyme that can convert isopentenyl pyrophosphate (IPP) into dimethylallyl pyrophosphate (DMAPP). In some embodimentsexamples, the recombinant yeast cell further comprises a heterologous nucleotide sequence encoding an enzyme that can modify IPP or a polyprenyl to form an isoprenoid compound.

[0016] In some embodimentsexamples, the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the polyketide biosynthesis pathway. In some embodimentsexamples, the recombinant yeast cell comprises one or

more nucleic acids encoding a polyketide synthase system (PKS). In some ~~embodiment~~examples, the PKS is a modular PKS. In some ~~embodiment~~examples, the PKS is an aromatic PKS.

[0017] In some ~~embodiment~~examples, the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the fatty acid biosynthesis pathway. In some ~~embodiment~~examples, the recombinant yeast cell comprises a nucleic acid encoding acetyl-CoA synthase. In some ~~embodiment~~examples, the recombinant yeast cell comprises a heterologous nucleotide sequence that encodes an enzyme that can convert acetyl-CoA into malonyl-CoA.

[0018] In some ~~embodiment~~examples, the method of detecting a recombinantly produced water-immiscible compound in a cell comprises: (a) contacting the cell with an aqueous hydrogel suspension; (b) loading the aqueous hydrogel suspension comprising the cell onto a microfluidic device comprising a fluorocarbon oil, wherein said hydrogel suspension contacts the fluorocarbon oil at a T-junction of the microfluidic device, wherein said contacting with the fluorocarbon oil results in formation of a non-aqueous hydrogel particle comprising the cell; (c) separating, *e.g.*, washing the fluorocarbon oil from the hydrogel particle; (d) culturing the cell within the hydrogel particle; (e) contacting the hydrogel particle with a fluorescent dye that directly binds to the recombinantly produced water-immiscible compound; and (f) detecting the fluorescent dye within the hydrogel particle.

[0018a] In a second aspect, the present invention refers to a method of screening a library of cells for a cell recombinantly producing a water-immiscible compound, the method comprising: (a) encapsulating each cell of the library in a hydrogel particle; (b) detecting recombinantly produced water-immiscible compound within each hydrogel particle, wherein said detecting comprises contacting the hydrogel particle with a fluorescent solvatochromic dye and normalizing the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle; and (c) selecting a cell producing said recombinantly produced water-immiscible compound.

[0019] In ~~one example, there is described another aspect, provided herein is~~ a method of screening a library of cells for a cell recombinantly producing a water-immiscible compound, comprising encapsulating each cell of the library in a hydrogel particle; detecting the recombinantly produced water-immiscible compound within each hydrogel particle, and selecting a cell producing said recombinantly produced water-immiscible compound.

[0019a] In a third aspect, the present invention refers to a method of enriching a population of cells for cells recombinantly producing a water-immiscible compound, the method comprising: (a) providing a population of hydrogel particles, wherein the population comprises hydrogel particles that encapsulate a cell or a clonal population of cells genetically modified to produce a water-immiscible compound; (b) culturing the cell within the hydrogel particle whereby a cell population is formed within the particle; (c) detecting a hydrogel particle comprising recombinantly produced water-immiscible compound, wherein said detecting comprises contacting the hydrogel particle with a fluorescent solvatochromic dye and normalizing the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle; (d) recovering the cell or clonal population of cells from the hydrogel particle of step (b); (e) re-encapsulating the cell or clonal population of cells from step (c); and (f) repeating steps (a) – (d).

[0020] In ~~one example, there is described another aspect, provided herein is~~ a method of enriching a population of cells for cells recombinantly producing a water-immiscible compound, the method comprising: (a) providing a population of hydrogel particles, wherein the population comprises hydrogel particles that encapsulate a cell or a clonal population of cells genetically modified to produce a water-immiscible compound; (b) detecting a hydrogel particle comprising recombinantly produced water-immiscible compound; (c) recovering the cell or clonal population of cells from the hydrogel particle of step (b); (d) re-encapsulating the cell or clonal population of cells from step (c); and (e) repeating steps (a) - (c).

[0020a] In a fourth aspect, the present invention refers to a hydrogel-encapsulated cell population comprising recombinantly produced water-immiscible compound and a fluorescent solvatochromic dye that enables normalization of the amount of water-immiscible compound within the hydrogel to the amount of cell biomass within the hydrogel.

[0021] In ~~one example, there is described another aspect, provided herein is~~ a method of encapsulating a cell within a hydrogel particle, the method comprising: (a) contacting the cell with an aqueous hydrogel suspension; and (b) loading the aqueous hydrogel suspension comprising the cell onto a

microfluidic device comprising a fluorocarbon oil, wherein said hydrogel suspension contacts the fluorocarbon oil at a T-junction of the microfluidic device, wherein said contacting with the fluorocarbon oil results in formation of a non-aqueous hydrogel particle comprising the cell.

[0022] In ~~one example~~ ~~another aspect~~, provided herein is a hydrogel-encapsulated cell or clonal cell population comprising recombinantly produced water-immiscible compound. In some ~~example~~ ~~embodiments~~, the cell is selected from the group consisting of a fungal cell, *e.g.*, a yeast cell, a bacterial cell, a mammalian cell, an insect cell, and a plant cell. In some ~~example~~ ~~embodiments~~, the cell is a yeast cell. In some ~~example~~ ~~embodiments~~, the yeast is *Saccharomyces cerevisiae*.

[0022a] In a fifth aspect, the present invention refers to a hydrogel particle comprising a cell population, and further comprising recombinantly produced water-immiscible compound and a fluorescent solvatochromic dye that enables normalization of the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle.

[0023] In ~~one example~~ ~~another aspect~~, provided herein is a hydrogel particle comprising a cell or clonal cell population, and further comprising recombinantly produced water-immiscible compound. In some ~~embodiment~~ ~~examples~~, the cell is selected from the group consisting of a fungal cell, *e.g.*, a yeast cell, a bacterial cell, a mammalian cell, a fungal cell, an insect cell, and a plant cell. In some ~~embodiment~~ ~~examples~~, the cell is a yeast cell. In some ~~embodiment~~ ~~examples~~, the yeast is *Saccharomyces cerevisiae*. In some ~~embodiment~~ ~~examples~~, the hydrogel comprises agarose. In some ~~embodiment~~ ~~examples~~, the hydrogel particle is less than about 1 millimeter in diameter. In some ~~embodiment~~ ~~examples~~, the hydrogel particle is less than about 500 micrometers in diameter. In some ~~embodiment~~ ~~examples~~, the hydrogel particle is less than about 100 micrometers in diameter. In some ~~embodiment~~ ~~examples~~, the hydrogel particle is less than 50 micrometers in diameter. In some ~~embodiment~~ ~~examples~~, the hydrogel particle is about 50, 45, 40, 35, 30 or 25 micrometers in diameter.

5. BRIEF DESCRIPTION OF THE FIGURES

[0024] FIG. 1A provides a schematic representation of the mevalonate (“MEV”) pathway for the production of isopentenyl diphosphate (“IPP”).

[0025] FIG. 1B provides a schematic representation of the 1-deoxy-D-xylulose 5-diphosphate (“DXP”) pathway for the production of isopentenyl pyrophosphate (“IPP”) and dimethylallyl pyrophosphate (“DMAPP”). Dxs is 1-deoxy-D-xylulose-5-phosphate synthase; Dxr is 1-deoxy-D-xylulose-5-phosphate reductoisomerase (also known as IspC); IspD is 4-diphosphocytidyl-2C-methyl-D-erythritol synthase; IspE is 4-diphosphocytidyl-2C-methyl-D-erythritol synthase; IspF is 2C-methyl-D-erythritol 2,4-cyclodiphosphate synthase; IspG is 1-hydroxy-2-methyl-2-(E)-butenyl 4-diphosphate synthase (IspG); and ispH is isopentenyl/dimethylallyl diphosphate synthase.

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CLAIMS:

1. A method of detecting recombinantly produced water-immiscible compound in a cell, the method comprising:
 - (a) encapsulating the cell in a hydrogel particle; and
 - (b) culturing the cell within the hydrogel particle whereby a cell population is formed within the particle; and
 - (c) detecting the recombinantly produced water-immiscible compound within the hydrogel particle, wherein said detecting comprises contacting the hydrogel particle with a fluorescent solvatochromic dye and normalizing the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle.
2. (Cancelled)
3. (Cancelled)
4. The method of claim 2, wherein the fluorescent solvatochromic dye is Nile Red.
5. (Cancelled)
6. The method of claim 1, wherein the cell is selected from the group consisting of a yeast cell, a bacterial cell, a mammalian cell, a fungal cell, an insect cell, and a plant cell.
7. The method of claim 6, wherein the cell is a yeast cell.
8. The method of claim 1, wherein the recombinantly produced water-immiscible compound is selected from the group consisting of an isoprenoid, a polyketide and a fatty acid.
9. The method of claim 1, wherein the hydrogel particle is capable of retaining a water-immiscible compound.

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10. The method of claim 1, wherein the hydrogel comprises agarose.
11. The method of claim 1, wherein the hydrogel particle is less than about 1 millimeter in diameter.
12. The method of claim 1, wherein the hydrogel particle is less than about 100 micrometers in diameter.
13. The method of claim 1, wherein the hydrogel particle is less than about 50 micrometers in diameter.
14. The method of claim 1, wherein the hydrogel particle is about 50, 45, 40, 35, 30 or 25 micrometers in diameter.
15. The method of claim 1, wherein said encapsulating comprises contacting the cell with an aqueous hydrogel suspension under conditions sufficient to form a hydrogel particle comprising the cell.
16. The method of claim 15, wherein said conditions comprise contacting the aqueous hydrogel suspension comprising the cell with a fluorocarbon oil comprising a fluorosurfactant.
17. The method of claim 16, wherein said contacting with a fluorocarbon oil comprises loading the aqueous hydrogel suspension comprising the cell onto a microfluidic device comprising the fluorocarbon oil, wherein said hydrogel suspension contacts the fluorocarbon oil at a T-junction of the microfluidic device, wherein said contacting with the fluorocarbon oil results in formation of a non-aqueous hydrogel particle comprising the cell.
18. The method of claim 17, further comprising the step of separating the hydrogel particle from the fluorocarbon oil.
19. The method of claim 1, further comprising the step of culturing the cell within the hydrogel particle prior to said detecting.

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20. The method of claim 19, wherein said culturing is for a period of 12 to 24 hours.
21. The method of claim 1, wherein the recombinantly produced water-immiscible compound is a terpene, C₅ isoprenoid, C₁₀ isoprenoid or C₁₅ isoprenoid.
22. The method of claim 21, wherein the recombinantly produced water-immiscible compound is farnesene.
23. The method of claim 22, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the mevalonate (MEV) pathway.
24. The method of claim 23, wherein the recombinant yeast cell comprises a nucleic acid encoding farnesene synthase.
25. The method of claim 23, wherein the recombinant yeast cell comprises a heterologous nucleotide sequence that encodes an enzyme that can convert HMG-CoA into mevalonate.
26. The method of claim 23, wherein the recombinant yeast cell comprises a heterologous nucleotide sequence that encodes an enzyme that can convert mevalonate into mevalonate 5-phosphate.
27. The method of claim 23, wherein the one or more heterologous nucleotide sequences encodes more than one enzyme of the mevalonate pathway.
28. The method of claim 23, further comprising a heterologous nucleotide sequence encoding an enzyme that can convert isopentenyl pyrophosphate (IPP) into dimethylallyl pyrophosphate (DMAPP).
29. The method of claim 28, further comprising a heterologous nucleotide sequence encoding an enzyme that can modify IPP or a polyprenyl to form an isoprenoid compound.

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30. The method of claim 29, wherein the enzyme is selected from the group consisting of carene synthase, geraniol synthase, linalool synthase, limonene synthase, myrcene synthase, ocimene synthase, α -pinene synthase, β -pinene synthase, γ -terpinene synthase, terpinolene synthase, amorphadiene synthase, α -farnesene synthase, β -farnesene synthase, farnesol synthase, nerolidol synthase, patchouliol synthase, nootkatone synthase, and abietadiene synthase.

31. The method of claim 29, wherein the isoprenoid is a C₅-C₂₀ isoprenoid.

32. The method of claim 31, wherein the isoprenoid is selected from the group consisting of abietadiene, amorphadiene, carene, α -farnesene, β -farnesene, farnesol, geraniol, geranylgeraniol, isoprene, linalool, limonene, myrcene, nerolidol, ocimene, patchouliol, β -pinene, sabinene, γ -terpinene, terpinolene, and valencene.

33. The method of claim 22, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding six enzymes of the mevalonate (MEV) pathway.

34. The method of claim 22, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the polyketide biosynthesis pathway.

35. The method of claim 34, wherein the recombinant yeast cell comprises one or more nucleic acids encoding a polyketide synthase system (PKS).

36. The method of claim 35, wherein the PKS is a modular PKS.

37. The method of claim 35, wherein the PKS is an aromatic PKS.

38. The method of claim 35, wherein the recombinant yeast cell comprises a nucleic acid encoding an enzyme comprising a ketosynthase/acyl transferase (KS/AT) catalytic region.

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39. The method of claim 35, wherein the recombinant yeast cell comprises a nucleic acid encoding an enzyme comprising a chain length factor (CLF) catalytic region.

40. The method of claim 35, wherein the recombinant yeast cell comprises a nucleic acid encoding an enzyme comprising an acyl carrier protein (ACP) activity.

41. The method of claim 35, wherein the recombinant yeast cell further comprises a nucleic acid encoding an enzyme comprising a cyclase (CYC) catalytic region, a ketoreductase (KR) catalytic region, an aromatase (ARO) catalytic region, an enoylreductase (ER) catalytic region, a thioesterase (TE) catalytic region, or a holo ACP synthase activity.

42. The method of claim 22, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the fatty acid biosynthesis pathway.

43. The method of claim 42, wherein the recombinant yeast cell comprises a nucleic acid encoding acetyl-CoA synthase.

44. The method of claim 42, wherein the recombinant yeast cell comprises a heterologous nucleotide sequence that encodes an enzyme that can convert acetyl-CoA into malonyl-CoA.

45. The method of claim 42, wherein the recombinant yeast cell comprises a nucleic acid encoding malonyl-CoA synthase.

46. The method of claim 42, wherein the recombinant yeast cell comprises a heterologous *pdh*, *panK*, *aceEF*, *fabH*, *fabD*, *fabG*, *acpP*, or *fabF* nucleotide sequence.

47. A method of detecting recombinantly produced water-immiscible compound in a cell, the method comprising:

- (a) contacting the cell with an aqueous hydrogel suspension;
- (b) loading the aqueous hydrogel suspension comprising the cell onto a microfluidic device comprising a fluorocarbon oil, wherein said hydrogel suspension contacts the fluorocarbon oil at a T-junction of the microfluidic device, wherein said contacting with

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the fluorocarbon oil results in formation of a non-aqueous hydrogel particle comprising the cell;

- (c) separating the hydrogel particle from the fluorocarbon oil;
- (d) culturing the cell within the hydrogel particle whereby a cell population is formed within the particle;
- (e) contacting the hydrogel particle with a fluorescent solvatochromic dye that directly binds to the recombinantly produced water-immiscible compound; and
- (f) detecting the fluorescent solvatochromic dye within the hydrogel particle, wherein said detecting comprises normalizing the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle.

48. A method of screening a library of cells for a cell recombinantly producing a water-immiscible compound, the method comprising:

- (a) encapsulating each cell of the library in a hydrogel particle;
- (b) detecting recombinantly produced water-immiscible compound within each hydrogel particle, wherein said detecting comprises contacting the hydrogel particle with a fluorescent solvatochromic dye and normalizing the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle; and
- (c) selecting a cell producing said recombinantly produced water-immiscible compound.

49. A method of enriching a population of cells for cells recombinantly producing a water-immiscible compound, the method comprising:

- (a) providing a population of hydrogel particles, wherein the population comprises hydrogel particles that encapsulate a cell or a clonal population of cells genetically modified to produce a water-immiscible compound;
- (b) culturing the cell within the hydrogel particle whereby a cell population is formed within the particle;
- (c) detecting a hydrogel particle comprising recombinantly produced water-immiscible compound, wherein said detecting comprises contacting the hydrogel particle with a fluorescent solvatochromic dye and normalizing the amount of water-

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immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle;

- (d) recovering the cell or clonal population of cells from the hydrogel particle of step (b);
- (e) re-encapsulating the cell or clonal population of cells from step (c);
- and
- (f) repeating steps (a) – (d).

50. (Cancelled)

51. A hydrogel-encapsulated cell population comprising recombinantly produced water-immiscible compound and a fluorescent solvatochromic dye that enables normalization of the amount of water-immiscible compound within the hydrogel to the amount of cell biomass within the hydrogel.

52. (Cancelled)

53. The hydrogel-encapsulated cell population of claim 51, wherein the fluorescent solvatochromic dye is Nile Red.

54. The hydrogel-encapsulated cell population of claim 51, wherein the cell is selected from the group consisting of a yeast cell, a bacterial cell, a mammalian cell, a fungal cell, an insect cell, and a plant cell.

55. The hydrogel-encapsulated cell population of claim 51, wherein the cell is a yeast cell.

56. The hydrogel-encapsulated cell population of claim 51, wherein the recombinantly produced water-immiscible compound is selected from the group consisting of an isoprenoid, a polyketide and a fatty acid.

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57. The hydrogel-encapsulated cell population of claim 56, wherein the recombinantly produced water-immiscible compound is a terpene, C₅ isoprenoid, C₁₀ isoprenoid or C₁₅ isoprenoid.
58. The hydrogel-encapsulated cell population of claim 56, wherein the recombinantly produced water-immiscible compound is farnesene.
59. The hydrogel-encapsulated cell population of claim 55, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the mevalonate (MEV) pathway.
60. The hydrogel-encapsulated cell population of claim 59, wherein the recombinant yeast cell comprises a nucleic acid encoding farnesene synthase.
61. The hydrogel-encapsulated cell population of claim 59, wherein the recombinant yeast cell comprises a heterologous nucleotide sequence that encodes an enzyme that can convert HMG-CoA into mevalonate.
62. The hydrogel-encapsulated cell population of claim 59, wherein the recombinant yeast cell comprises a heterologous nucleotide sequence that encodes an enzyme that can convert mevalonate into mevalonate 5-phosphate.
63. The hydrogel-encapsulated cell population of claim 59, wherein the one or more heterologous nucleotide sequences encodes more than one enzyme of the mevalonate pathway.
64. The hydrogel-encapsulated cell population of claim 59, further comprising a heterologous nucleotide sequence encoding an enzyme that can convert isopentenyl pyrophosphate (IPP) into dimethylallyl pyrophosphate (DMAPP).
65. The hydrogel-encapsulated cell population of claim 59, further comprising a heterologous nucleotide sequence encoding an enzyme that can modify IPP or a polyprenyl to form an isoprenoid compound.

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66. The hydrogel-encapsulated cell population of claim 65, wherein the enzyme is selected from the group consisting of carene synthase, geraniol synthase, linalool synthase, limonene synthase, myrcene synthase, ocimene synthase, α -pinene synthase, β -pinene synthase, γ -terpinene synthase, terpinolene synthase, amorphadiene synthase, α -farnesene synthase, β -farnesene synthase, farnesol synthase, nerolidol synthase, patchouliol synthase, nootkatone synthase, and abietadiene synthase.

67. The hydrogel-encapsulated cell population of claim 65, wherein the isoprenoid is a C_5 - C_{20} isoprenoid.

68. The hydrogel-encapsulated cell population of claim 67, wherein the isoprenoid is selected from the group consisting of abietadiene, amorphadiene, carene, α -farnesene, β -farnesene, farnesol, geraniol, geranylgeraniol, isoprene, linalool, limonene, myrcene, nerolidol, ocimene, patchoulol, β -pinene, sabinene, γ -terpinene, terpinolene, and valencene.

69. The hydrogel-encapsulated cell population of claim 59, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding six enzymes of the mevalonate (MEV) pathway.

70. The hydrogel-encapsulated cell population of claim 55, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the polyketide biosynthesis pathway.

71. The hydrogel-encapsulated cell population of claim 70, wherein the recombinant yeast cell comprises a one or more nucleic acids encoding a polyketide synthase system (PKS).

72. The hydrogel-encapsulated cell population of claim 71, wherein the PKS is a modular PKS.

73. The hydrogel-encapsulated cell population of claim 71, wherein the PKS is an aromatic PKS.

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74. The hydrogel-encapsulated cell population of claim 71, wherein the recombinant yeast cell comprises a nucleic acid encoding an enzyme comprising a ketosynthase/acyl transferase (KS/AT) catalytic region.
75. The hydrogel-encapsulated cell population of claim 71, wherein the recombinant yeast cell comprises a nucleic acid encoding an enzyme comprising a chain length factor (CLF) catalytic region.
76. The hydrogel-encapsulated cell population of claim 71, wherein the recombinant yeast cell comprises a nucleic acid encoding an enzyme comprising an acyl carrier protein (ACP) activity.
77. The hydrogel-encapsulated cell population of claim 71, wherein the recombinant yeast cell further comprises a nucleic acid encoding an enzyme comprising a cyclase (CYC) catalytic region, a ketoreductase (KR) catalytic region, an aromatase (ARO) catalytic region, an enoylreductase (ER) catalytic region, a thioesterase (TE) catalytic region, or a holo ACP synthase activity.
78. The hydrogel-encapsulated cell population of claim 55, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the fatty acid biosynthesis pathway.
79. The hydrogel-encapsulated cell population of claim 78, wherein the recombinant yeast cell comprises a nucleic acid encoding acetyl-CoA synthase.
80. The hydrogel-encapsulated cell population of claim 78, wherein the recombinant yeast cell comprises a heterologous nucleotide sequence that encodes an enzyme that can convert acetyl-CoA into malonyl-CoA.
81. The hydrogel-encapsulated cell population of claim 78, wherein the recombinant yeast cell comprises a nucleic acid encoding malonyl-CoA synthase.

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82. The hydrogel-encapsulated cell population of claim 78, wherein the recombinant yeast cell comprises a heterologous *pdh*, *panK*, *aceEF*, *fabH*, *fabD*, *fabG*, *acpP*, or *fabF* nucleotide sequence.

83. A hydrogel particle comprising a cell population, and further comprising recombinantly produced water-immiscible compound and a fluorescent solvatochromic dye that enables normalization of the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle.

84. (Cancelled)

85. The hydrogel particle of claim 83, wherein the solvatochromic fluorescent dye is Nile Red.

86. The hydrogel particle of claim 83, wherein the cell is selected from the group consisting of a yeast cell, a bacterial cell, a mammalian cell, a fungal cell, an insect cell, and a plant cell.

87. The hydrogel particle of claim 84, wherein the cell is a yeast cell.

88. The hydrogel particle of claim 83, wherein the recombinantly produced water-immiscible compound is selected from the group consisting of an isoprenoid, a polyketide and a fatty acid.

89. The hydrogel particle of claim 88, wherein the isoprenoid is a terpene, C₅ isoprenoid, C₁₀ isoprenoid or C₁₅ isoprenoid.

90. The hydrogel particle of claim 88, wherein the isoprenoid is farnesene.

91. The hydrogel particle of claim 83, wherein the recombinant yeast cell comprises a nucleic acid encoding farnesene synthase.

92. The hydrogel particle of claim 83, wherein the hydrogel particle is capable of retaining a water-immiscible compound.

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93. The hydrogel particle of claim 92, wherein the water-immiscible compound is selected from the group consisting of an isoprenoid, a polyketide and a fatty acid.

94. The hydrogel particle of claim 92, wherein the water-immiscible compound is farnesene.

95. The hydrogel particle of claim 83, wherein the hydrogel comprises agarose.

96. The hydrogel particle of claim 83, wherein the hydrogel particle is less than about 1 millimeter in diameter.

97. The hydrogel particle of claim 83, wherein the hydrogel particle is less than about 500 micrometers in diameter.

98. The hydrogel particle of claim 83, wherein the hydrogel particle is less than about 100 micrometers in diameter.

99. The hydrogel particle of claim 83, wherein the hydrogel particle is less than 50 micrometers in diameter.

100. The hydrogel particle of claim 87, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the mevalonate (MEV) pathway.

101. The hydrogel particle of claim 100, wherein the recombinant yeast cell comprises a nucleic acid encoding farnesene synthase.

102. The hydrogel particle of claim 100, wherein the recombinant yeast cell comprises a heterologous nucleotide sequence that encodes an enzyme that can convert HMG-CoA into mevalonate.

103. The hydrogel particle of claim 100, wherein the recombinant yeast cell comprises a heterologous nucleotide sequence that encodes an enzyme that can convert mevalonate into mevalonate 5-phosphate.

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104. The hydrogel particle of claim 100, wherein the one or more heterologous nucleotide sequences encodes more than one enzyme of the mevalonate pathway.

105. The hydrogel particle of claim 100, further comprising a heterologous nucleotide sequence encoding an enzyme that can convert isopentenyl pyrophosphate (IPP) into dimethylallyl pyrophosphate (DMAPP).

106. The hydrogel particle of claim 100, further comprising a heterologous nucleotide sequence encoding an enzyme that can modify IPP or a polyprenyl to form an isoprenoid compound.

107. The hydrogel particle of claim 106, wherein the enzyme is selected from the group consisting of carene synthase, geraniol synthase, linalool synthase, limonene synthase, myrcene synthase, ocimene synthase, α -pinene synthase, β -pinene synthase, γ -terpinene synthase, terpinolene synthase, amorphadiene synthase, α -farnesene synthase, β -farnesene synthase, farnesol synthase, nerolidol synthase, patchouliol synthase, nootkatone synthase, and abietadiene synthase.

108. The hydrogel particle of claim 106, wherein the isoprenoid is a C₅-C₂₀ isoprenoid.

109. The hydrogel particle of claim 108, wherein the isoprenoid is selected from the group consisting of abietadiene, amorphadiene, carene, α -farnesene, β -farnesene, farnesol, geraniol, geranylgeraniol, isoprene, linalool, limonene, myrcene, nerolidol, ocimene, patchoulol, β -pinene, sabinene, γ -terpinene, terpinolene, and valencene.

110. The hydrogel particle of claim 100, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding six enzymes of the mevalonate (MEV) pathway.

111. The hydrogel particle of claim 87, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the polyketide biosynthesis pathway.

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112. The hydrogel particle of claim 111, wherein the recombinant yeast cell comprises a one or more nucleic acids encoding a polyketide synthase system (PKS).
113. The hydrogel particle of claim 112, wherein the PKS is a modular PKS.
114. The hydrogel particle of claim 112, wherein the PKS is an aromatic PKS.
115. The hydrogel particle of claim 112, wherein the recombinant yeast cell comprises a nucleic acid encoding an enzyme comprising a ketosynthase/acyl transferase (KS/AT) catalytic region.
116. The hydrogel particle of claim 112, wherein the recombinant yeast cell comprises a nucleic acid encoding an enzyme comprising a chain length factor (CLF) catalytic region.
117. The hydrogel particle of claim 112, wherein the recombinant yeast cell comprises a nucleic acid encoding an enzyme comprising an acyl carrier protein (ACP) activity.
118. The hydrogel particle of claim 112, wherein the recombinant yeast cell further comprises a nucleic acid encoding an enzyme comprising a cyclase (CYC) catalytic region, a ketoreductase (KR) catalytic region, an aromatase (ARO) catalytic region, an enoylreductase (ER) catalytic region, a thioesterase (TE) catalytic region, or a holo ACP synthase activity.
119. The hydrogel particle of claim 87, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the fatty acid biosynthesis pathway.
120. The hydrogel particle of claim 119, wherein the recombinant yeast cell comprises a nucleic acid encoding acetyl-CoA synthase.
121. The hydrogel particle of claim 119, wherein the recombinant yeast cell comprises a heterologous nucleotide sequence that encodes an enzyme that can convert acetyl-CoA into malonyl-CoA.

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122. The hydrogel particle of claim 119, wherein the recombinant yeast cell comprises a nucleic acid encoding malonyl-CoA synthase.

123. The hydrogel particle of claim 119, wherein the recombinant yeast cell comprises a heterologous *pdh*, *panK*, *aceEF*, *fabH*, *fabD*, *fabG*, *acpP*, or *fabF* nucleotide sequence.

CLAIMS:

1. A method of detecting recombinantly produced water-immiscible compound in a cell, the method comprising:
 - (a) encapsulating the cell in a hydrogel particle; and
 - (b) culturing the cell within the hydrogel particle whereby a cell population is formed within the particle; and
 - (c) detecting the recombinantly produced water-immiscible compound within the hydrogel particle, wherein said detecting comprises contacting the hydrogel particle with a fluorescent solvatochromic dye and normalizing the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle.
2. The method of claim 1, wherein the fluorescent solvatochromic dye is Nile Red.
3. The method of claim 1, wherein the cell is selected from the group consisting of a yeast cell, a bacterial cell, a mammalian cell, a fungal cell, an insect cell, and a plant cell.
4. The method of claim 3, wherein the cell is a yeast cell.
5. The method of claim 1, wherein the recombinantly produced water-immiscible compound is selected from the group consisting of an isoprenoid, a polyketide and a fatty acid.
6. The method of claim 1, wherein the hydrogel particle is capable of retaining a water-immiscible compound.
7. The method of claim 1, wherein the hydrogel comprises agarose.
8. The method of claim 1, wherein the hydrogel particle is less than about 1 millimeter in diameter.
9. The method of claim 1, wherein the hydrogel particle is less than about 100 micrometers in diameter.
10. The method of claim 1, wherein the hydrogel particle is less than about 50 micrometers in diameter.

11. The method of claim 1, wherein the hydrogel particle is about 50, 45, 40, 35, 30 or 25 micrometers in diameter.

12. The method of claim 1, wherein said encapsulating comprises contacting the cell with an aqueous hydrogel suspension under conditions sufficient to form a hydrogel particle comprising the cell.

13. The method of claim 12, wherein said conditions comprise contacting the aqueous hydrogel suspension comprising the cell with a fluorocarbon oil comprising a fluorosurfactant.

14. The method of claim 13, wherein said contacting with a fluorocarbon oil comprises loading the aqueous hydrogel suspension comprising the cell onto a microfluidic device comprising the fluorocarbon oil, wherein said hydrogel suspension contacts the fluorocarbon oil at a T-junction of the microfluidic device, wherein said contacting with the fluorocarbon oil results in formation of a non-aqueous hydrogel particle comprising the cell.

15. The method of claim 14, further comprising the step of separating the hydrogel particle from the fluorocarbon oil.

16. The method of claim 1, further comprising the step of culturing the cell within the hydrogel particle prior to said detecting.

17. The method of claim 16, wherein said culturing is for a period of 12 to 24 hours.

18. The method of claim 1, wherein the recombinantly produced water-immiscible compound is a terpene, C₅ isoprenoid, C₁₀ isoprenoid or C₁₅ isoprenoid.

19. The method of claim 18, wherein the recombinantly produced water-immiscible compound is farnesene.

20. The method of claim 19, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the mevalonate (MEV) pathway.

21. The method of claim 20, further comprising a heterologous nucleotide sequence encoding an enzyme that can convert isopentenyl pyrophosphate (IPP) into dimethylallyl pyrophosphate (DMAPP).

22. The method of claim 21, further comprising a heterologous nucleotide sequence encoding an enzyme that can modify IPP or a polyprenyl to form an isoprenoid compound.

23. The method of claim 22, wherein the isoprenoid is a C₅-C₂₀ isoprenoid.

24. The method of claim 23, wherein the isoprenoid is selected from the group consisting of abietadiene, amorphadiene, carene, α -farnesene, β -farnesene, farnesol, geraniol, geranylgeraniol, isoprene, linalool, limonene, myrcene, nerolidol, ocimene, patchoulol, β -pinene, sabinene, γ -terpinene, terpinolene, and valencene.

25. A method of screening a library of cells for a cell recombinantly producing a water-immiscible compound, the method comprising:

- (a) encapsulating each cell of the library in a hydrogel particle;
- (b) detecting recombinantly produced water-immiscible compound within each hydrogel particle, wherein said detecting comprises contacting the hydrogel particle with a fluorescent solvatochromic dye and normalizing the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle; and
- (c) selecting a cell producing said recombinantly produced water-immiscible compound.

26. A method of enriching a population of cells for cells recombinantly producing a water-immiscible compound, the method comprising:

- (a) providing a population of hydrogel particles, wherein the population comprises hydrogel particles that encapsulate a cell or a clonal population of cells genetically modified to produce a water-immiscible compound;
- (b) culturing the cell within the hydrogel particle whereby a cell population is formed within the particle;
- (c) detecting a hydrogel particle comprising recombinantly produced water-immiscible compound, wherein said detecting comprises contacting the hydrogel particle with a fluorescent solvatochromic dye and normalizing the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle;

- (d) recovering the cell or clonal population of cells from the hydrogel particle of step (b);
- (e) re-encapsulating the cell or clonal population of cells from step (c); and
- (f) repeating steps (a) – (d).

27. A hydrogel-encapsulated cell population comprising recombinantly produced water-immiscible compound and a fluorescent solvatochromic dye that enables normalization of the amount of water-immiscible compound within the hydrogel to the amount of cell biomass within the hydrogel.

28. The hydrogel-encapsulated cell population of claim 27, wherein the cell is a yeast cell.

29. The hydrogel-encapsulated cell population of claim 28, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the mevalonate (MEV) pathway.

30. The hydrogel-encapsulated cell population of claim 29, further comprising a heterologous nucleotide sequence encoding an enzyme that can modify IPP or a polyprenyl to form an isoprenoid compound.

31. The hydrogel-encapsulated cell population of claim 30, wherein the isoprenoid is a C₅-C₂₀ isoprenoid.

32. The hydrogel-encapsulated cell population of claim 31, wherein the isoprenoid is selected from the group consisting of abietadiene, amorphadiene, carene, α -farnesene, β -farnesene, farnesol, geraniol, geranylgeraniol, isoprene, linalool, limonene, myrcene, nerolidol, ocimene, patchoulol, β -pinene, sabinene, γ -terpinene, terpinolene, and valencene.

33. A hydrogel particle comprising a cell population, and further comprising recombinantly produced water-immiscible compound and a fluorescent solvatochromic dye that enables normalization of the amount of water-immiscible compound within the hydrogel particle to the amount of cell biomass within the hydrogel particle.

34. The hydrogel particle of claim 33, wherein the solvatochromic fluorescent dye is Nile Red.

35. The hydrogel particle of claim 33, wherein the cell is selected from the group consisting of a yeast cell, a bacterial cell, a mammalian cell, a fungal cell, an insect cell, and a plant cell.

36. The hydrogel particle of claim 33, wherein the cell is a yeast cell.

37. The hydrogel particle of claim 33, wherein the recombinantly produced water-immiscible compound is selected from the group consisting of an isoprenoid, a polyketide and a fatty acid.

38. The hydrogel particle of claim 33, wherein the hydrogel comprises agarose.

39. The hydrogel particle of claim 33, wherein the hydrogel particle is less than about 1 millimeter in diameter.

40. The hydrogel particle of claim 33, wherein the hydrogel particle is less than about 500 micrometers in diameter.

41. The hydrogel particle of claim 33, wherein the hydrogel particle is less than about 100 micrometers in diameter.

42. The hydrogel particle of claim 33, wherein the hydrogel particle is less than 50 micrometers in diameter.

43. The hydrogel particle of claim 36, wherein the cell is a recombinant yeast cell comprising one or more heterologous nucleotide sequences encoding one or more enzymes of the mevalonate (MEV) pathway.

44. The hydrogel particle of claim 43, further comprising a heterologous nucleotide sequence encoding an enzyme that can modify IPP or a polyprenyl to form an isoprenoid compound.

45. The hydrogel particle of claim 44, wherein the isoprenoid is a C₅-C₂₀ isoprenoid.

46. The hydrogel particle of claim 45, wherein the isoprenoid is selected from the group consisting of abietadiene, amorphadiene, carene, α -farnesene, β -farnesene, farnesol, geraniol, geranylgeraniol, isoprene, linalool, limonene, myrcene, nerolidol, ocimene, patchoulol, β -pinene, sabinene, γ -terpinene, terpinolene, and valencene.