

CLAIMS

What is claimed is:

1. A method of identifying a compound that preferentially affects a level of association of a first macromolecule with one or more target condensates, the method comprising:
 - (a) contacting a cellular composition with a compound, wherein
 - (i) the cellular composition comprises the one or more target condensates; and/or
 - (ii) the one or more target condensates form simultaneously with and/or after contacting the cellular composition with the compound; and
 - (b) determining the level of association of the first macromolecule with the one or more target condensates and a level of association of at least one additional macromolecule with the one or more target condensates,wherein the compound preferentially affects the level of association of the first macromolecule with the one or more target condensates if the compound alters the level of the first macromolecule as compared to a first reference level more than the compound alters the level of each additional macromolecule as compared to a reference level for each additional macromolecule.
2. The method of claim 1, wherein the compound does not measurably alter the level of each additional macromolecule compared to the reference level for each additional macromolecule.
3. A method of identifying a compound that preferentially increases a level of association of a first macromolecule with one or more target condensates, the method comprising:
 - (a) contacting a cellular composition with a compound, wherein
 - (i) the cellular composition comprises the one or more target condensates; and/or
 - (ii) the one or more target condensates form simultaneously with and/or after contacting the cellular composition with the compound; and

- (b) determining the level of association of the first macromolecule with the one or more target condensates and a level of association of at least one additional macromolecule with the one or more target condensates,

wherein the compound preferentially increases the level of association of the first macromolecule with the one or more target condensates if the compound increases the level of the first macromolecule as compared to a first reference level more than the compound increases the level of each additional macromolecule as compared to a reference level for each additional macromolecule.

- 4. The method of claim 3, wherein the compound does not measurably increase the level of each additional macromolecule compared to the reference level for each additional macromolecule.
- 5. A method of identifying a compound that preferentially decreases a level of association with one or more target condensates of a first macromolecule, the method comprising:
 - (a) contacting a cellular composition with a compound, wherein
 - (i) the cellular composition comprises the one or more target condensates; and/or
 - (ii) the one or more target condensates form simultaneously with and/or after contacting the cellular composition with the compound; and
 - (b) determining the level of association of the first macromolecule with the one or more target condensates and a level of association of at least one additional macromolecule with the one or more target condensates,

wherein the compound preferentially decreases the level of association of the first macromolecule with the one or more target condensates if the compound alters the level of the first macromolecule as compared to a first reference level more than the compound decreases the level of each additional macromolecule as compared to a reference level for each additional macromolecule.

6. The method of claim 5, wherein the compound does not measurably decrease the level of each additional macromolecule compared to the reference level for each additional macromolecule.
7. The method of any one of claims 1-6, wherein the first reference level is a level of association of the first macromolecule with one or more reference condensates determined in the absence of the compound.
8. The method of any one of claims 1-7, wherein the reference level for each additional macromolecule is a level of association for each additional macromolecule with one or more reference condensates determined in the absence of the compound.
9. A method of identifying a compound that preferentially causes a first macromolecule to associate with one or more target condensates, the method comprising:
 - (a) contacting a cellular composition with a compound, wherein
 - (i) the cellular composition comprises the one or more target condensates; and/or
 - (ii) the one or more target condensates form simultaneously with and/or after contacting the cellular composition with the compound; and
 - (b) determining if a first macromolecule and at least one additional macromolecule are associated with the one or more target condensates,wherein the compound preferentially causes the first macromolecule to associate with the one or more target condensates if:
 - (1) the compound causes the first macromolecule to associate with the one or more target condensates;
 - (2) the compound does not cause each additional macromolecule to associate with the one or more target condensates; and
 - (3) the first macromolecule would not be associated with the one or more target condensates in the absence of the compound.
10. The method of claim 9, wherein the compound preferentially causes the first macromolecule to associate with the one or more target condensates if (4) one or more of the at least one

additional macromolecule would not be associated with the one or more target condensates in the absence of the compound.

11. The method of claim 9, wherein the compound preferentially causes the first macromolecule to associate with the one or more target condensates if (4) each of the at least one additional macromolecule would not be associated with the one or more target condensates in the absence of the compound.
12. A method of identifying a compound that preferentially causes a first macromolecule to disassociate with one or more target condensates, the method comprising:
 - (a) contacting a cellular composition with a compound, wherein
 - (i) the cellular composition comprises the one or more target condensates; and/or
 - (ii) the one or more target condensates form simultaneously with and/or after contacting the cellular composition with the compound; and
 - (b) determining if a first macromolecule and at least one additional macromolecule are associated with the one or more target condensates,wherein the compound preferentially causes the first macromolecule to disassociate with the one or more target condensates if:
 - (1) the compound causes the first macromolecule not to associate with the one or more target condensates;
 - (2) the compound does not cause each additional macromolecule not to associate with the one or more target condensates; and
 - (3) the first macromolecule would be associated with the one or more target condensates in the absence of the compound.
13. The method of claim 12, wherein the compound preferentially causes the first macromolecule to associate with the one or more target condensates if (4) one or more of the at least one additional macromolecule would be associated with the one or more target condensates in the absence of the compound.

14. The method of claim 12, wherein the compound preferentially causes the first macromolecule to associate with the one or more target condensates if (4) each of the at least one additional macromolecule would be associated with the one or more target condensates in the absence of the compound.
15. The method of any one of claims 1-14, wherein step (a) comprises contacting a cellular composition with a compound, wherein the cellular composition comprises the one or more target condensates, and the method further comprises causing the formation of the one or more target condensates prior to step (a).
16. The method of any one of claims 1-14, wherein step (a) comprises contacting a cellular composition with a compound, wherein the one or more target condensates form after contacting the cellular composition with the compound, and the method further comprises causing the formation of the one or more target condensates.
17. The method of any one of claims 1-16, wherein the at least one additional macromolecule is 2 or more, 3 or more, 4 or more, or 5 or more macromolecules.
18. The method of any one of claims 1-16, wherein the at least one additional macromolecule is 1-10 macromolecules.
19. The method of any one of claims 1-18, wherein the first macromolecule is aberrantly expressed in a disease state.
20. The method of any one of claims 1-19, wherein a disease state level of association of the first macromolecule with the one or more target condensates is altered compared to a normal state level of association of the first macromolecule with the one or more target condensates.
21. The method of any one of claims 1-20, wherein one or more of the at least one additional macromolecule is aberrantly expressed in a disease state.
22. The method of any one of claims 1-21, wherein the first macromolecule is DNA or RNA.

23. The method of any one of claims 1-22, wherein one or more of the at least one additional macromolecule is DNA or RNA.
24. The method of any one of claims 1-21 or 23, wherein the first macromolecule is a protein.
25. The method of claim 24, wherein the first macromolecule comprises a mutation that alters the level of association of the first macromolecule with the one or more target condensates compared to a related protein that does not comprise the mutation.
26. The method of claim 24 or 25, wherein the first macromolecule is FUS or eIF3.
27. The method of any one of claims 1-26, wherein one or more of the at least one additional macromolecule is a protein.
28. The method of any one of claims 1-27, wherein one or more of the at least one additional macromolecule comprise a mutation that alters its corresponding level of association with the one or more target condensates compared to a related protein that does not comprise the mutation.
29. The method of any one of claims 1-28, wherein one or more of the at least one additional macromolecule is FUS, eIF3, G3BP1, FUS and G3BP1, or eIF3 and G3BP1.
30. The method of any one of claims 24-29, wherein the first macromolecule and/or one or more of the at least one additional macromolecule is a fusion protein.
31. The method of any one of claims 1-30, wherein the first macromolecule and/or one or more of the at least one additional macromolecule comprises a label.
32. The method of any one of claims 1-31, further comprising labeling the first macromolecule and/or one or more of the at least one additional macromolecule.
33. The method of claim 32, wherein the labeling comprises contacting the cellular composition with an antibody or antigen-binding fragment thereof comprising a label.

34. The method of any one of claims 31-33, wherein the label is a radioactive label, a colorimetric label, or a fluorescent label.
35. The method of any one of claims 1-34, wherein the cellular composition comprises a microorganism or an animal cell.
36. The method of claim 35, wherein the cellular composition comprises an animal cell.
37. The method of claim 36, wherein the animal cell that has one or more features of a neurodegenerative, proliferative, immunological, cardiac, or metabolic disease.
38. The method of any one of claims 35-37, wherein the animal cell is a HeLa cell, a HEK293 cell, an induced pluripotent stem cell (iPSC cell), a cardiomyocyte, a myocyte, a stem cell-derived cell, a neuron, a cancer cell, an immune cell, or an adipocyte.
39. The method of any one of claims 1-38, wherein the one or more target condensates is a cellular condensate.
40. The method of any one of claims 1-39, wherein the one or more target condensates is a nuclear condensate or a cytoplasmic condensate.
41. The method of claim 39, wherein the cellular condensate is a cleavage body, a p-granule, a histone locus body, a multivesicular body, a neuronal RNA granule, a nuclear gem, a nuclear pore, a nuclear speckle, a nuclear stress body, a nucleolus, a Oct1/PTF/transcription (OPT) domain, a paraspeckle, a perinucleolar compartment, a PML nuclear body, a PML oncogenic domain, a polycomb body, a processing body, a Sam68 nuclear body, a stress granule, or a splicing speckle.
42. The method of any one of claims 1-41, wherein the one or more target condensates is a single target condensate.

43. The method of claim 42, wherein the compound does not measurably alter one or more of: size of the target condensate, location of the target condensate, surface area of the target condensate, and dissolution of the target condensate.
44. The method of any one of claims 1-41, wherein the one or more target condensates is a plurality of target condensates.
45. The method of claim 44, wherein the plurality of target condensates is all or a subset of a class of condensates in a portion of the cellular composition.
46. The method of claim 44 or 45, wherein the plurality of target condensates is all or a subset of a class of condensates in a cell in the cellular composition.
47. The method of any one of claims 44-46, wherein the plurality of target condensates is all or a subset of a class of condensates in a portion of a cell in the cellular composition.
48. The method of claim 47, wherein the portion of the cell is the cytoplasm, the nucleus, or an organelle.
49. The method of any one of claims 45-48, wherein the class of condensates comprises condensates which comprise a specific macromolecule.
50. The method of any one of claims 45-49, wherein the class of condensates comprises condensates which are cleavage bodies; wherein the class of condensates comprises condensates which are p-granules; wherein the class of condensates comprises condensates which are histone locus bodies; wherein the class of condensates comprises condensates which are multivesicular bodies; wherein the class of condensates comprises condensates which are neuronal RNA granules; wherein the class of condensates comprises condensates which are nuclear gems; wherein the class of condensates comprises condensates which are nuclear pores; wherein the class of condensates comprises condensates which are nuclear speckles; wherein the class of condensates comprises condensates which are nuclear stress bodies; wherein the class of condensates comprises condensates which are nucleoli; wherein

the class of condensates comprises condensates which are Oct1/PTF/transcription (OPT) domains; wherein the class of condensates comprises condensates which are paraspeckles; wherein the class of condensates comprises condensates which are perinucleolar compartments; wherein the class of condensates comprises condensates which are PML nuclear bodies; wherein the class of condensates comprises condensates which are PML oncogenic domains; wherein the class of condensates comprises condensates which are polycomb bodies; wherein the class of condensates comprises condensates which are processing bodies; wherein the class of condensates comprises condensates which are Sam68 nuclear bodies; wherein the class of condensates comprises condensates which are stress granules; or wherein the class of condensates comprises condensates which are splicing speckles.

51. The method of any one of claims 44-50, wherein the compound does not measurably alter one or more of: total number of the plurality of target condensates; size of the plurality of target condensates, location of the plurality of target condensates, surface area of the plurality of target condensates, and dissolution of the plurality of target condensates.
52. A method of identifying a plurality of compounds that preferentially affect the level, decrease the level, or increase the level of association of a first macromolecule with one or more target condensates, or that preferentially cause the first macromolecule to associate or disassociate with one or more target condensates, the method comprising performing the method of any one of claims 1-51 with a plurality of compounds.
53. The method of claim 52, further comprising identifying a characteristic that a subset or all of the identified compounds have in common in addition to ability to preferentially affect the level, decrease the level, or increase the level of association of the first macromolecule with the one or more target condensates, or the ability to preferentially cause the first macromolecule to associate or disassociate with one or more target condensates.
54. The method of claim 53, further comprising performing the method of any one of claims 1-51 for one or more additional test compounds that comprise the identified characteristic.

55. The method of claim 53 or 54, further comprising performing the method of any one of claims 1-51 for one or more additional test compounds that do not comprise the identified characteristic.
56. A method of identifying a compound characteristic associated with preferentially affecting the level, decreasing the level, or increasing the level of association of a first macromolecule with one or more target condensates, or with preferentially causing the first macromolecule to associate or disassociate with one or more target condensates, the method comprising:
- (a) performing the method of claim 52; and
 - (b) identifying a characteristic that a subset or all of the identified compounds have in common in addition to the ability to preferentially affect the level, decrease the level, or increase the level of association of the first macromolecule with one or more target condensates, or the ability to preferentially cause the first macromolecule to associate or disassociate with one or more target condensates.
57. A method of designing a compound that preferentially affects the level, decreases the level, or increases the level of association of a first macromolecule with one or more target condensates, or that preferentially causes the first macromolecule to associate or disassociate with one or more target condensates, the method comprising:
- (a) performing the method of claim 52;
 - (b) identifying a characteristic that a subset or all of the identified compounds have in common in addition to the ability to preferentially affect the level, decrease the level, or increase the level of association of the first macromolecule with one or more target condensates, or the ability to preferentially cause the first macromolecule to associate or disassociate with one or more target condensates; and
 - (c) designing a compound that comprises the identified characteristic,
- thereby designing a compound that preferentially affects the level, decreases the level, or increases the level of association of the first macromolecule with one or more target condensates or preferentially causes the first macromolecule to associate or disassociate with one or more target condensates.

58. A method of identifying a compound useful for treating a disease in an individual in need thereof, the method comprising:
- performing the method of any one of claims 1-51, wherein the one or more target condensates is associated with the disease, and
 - identifying the compound that preferentially affects the level, decreases the level, or increases the level of association of the first macromolecule with the one or more target condensates or that that preferentially causes the first macromolecule to associate or disassociate with one or more target condensates for being useful for treating the disease.
59. The method of claim 58, wherein the disease is a neurodegenerative, proliferative, immunological, cardiac, or metabolic disease.
60. A method of identifying a compound that preferentially affects a level of association of a first macromolecule with a first set of one or more target condensates, the method comprising:
- performing the method of any one of claims 1-51 with the first set of one or more target condensates; and
 - performing the method of any one of claims 1-51 with a second set of one or more target condensates
- wherein the compound preferentially affects the level of association of the first macromolecule with the first set of one or more target condensates if the compound preferentially affects the level of association of the first macromolecule with the first set of one or more target condensates more than the compound preferentially affects the level of association of the first macromolecule with the second set of one or more target condensates.
61. The method of claim 60, wherein the compound does not affect the level of association of the first macromolecule with the second set of one or more target condensates.

62. A method of identifying a compound that preferentially increases a level of association of a first macromolecule with a first set of one or more target condensates, the method comprising:
- performing the method of any one of claims 1-51 with the first set of one or more target condensates; and
 - performing the method of any one of claims 1-51 with a second set of one or more target condensates
- wherein the compound preferentially increases the level of association of the first macromolecule with the first set of one or more target condensates if the compound preferentially increases the level of association of the first macromolecule with the first set of one or more target condensates more than the compound preferentially increases the level of association of the first macromolecule with the second set of one or more target condensates.
63. The method of claim 62, wherein the compound does not increase the level of association of the first macromolecule with the second set of one or more target condensates.
64. A method of identifying a compound that preferentially decreases a level of association of a first macromolecule with a first set of one or more target condensates, the method comprising:
- performing the method of any one of claims 1-51 with the first set of one or more target condensates; and
 - performing the method of any one of claims 1-51 with a second set of one or more target condensates
- wherein the compound preferentially decreases the level of association of the first macromolecule with the first set of one or more target condensates if the compound preferentially decreases the level of association of the first macromolecule with the first set of one or more target condensates more than the compound preferentially decreases the level of association of the first macromolecule with the second set of one or more target condensates.

65. The method of claim 64, wherein the compound does not decrease the level of association of the first macromolecule with the second set of one or more target condensates.
66. A method of identifying a compound that preferentially causes a first macromolecule to associate with a first set of one or more target condensates, the method comprising:
performing the method of any one of claims 1-51 with the first set of one or more target condensates; and
performing the method of any one of claims 1-51 with a second set of one or more target condensates
wherein the compound preferentially causes the first macromolecule to associate with the first set of one or more target condensates if the compound preferentially causes the first macromolecule to associate with the first set of one or more target condensates more than the compound preferentially causes the first macromolecule to associate with the second set of one or more target condensates.
67. A method of identifying a compound that preferentially causes a first macromolecule to disassociate with a first set of one or more target condensates, the method comprising:
performing the method of any one of claims 1-51 with the first set of one or more target condensates; and
performing the method of any one of claims 1-51 with a second set of one or more target condensates
wherein the compound preferentially causes the first macromolecule to disassociate with the first set of one or more target condensates if the compound preferentially causes the first macromolecule to associate with the first set of one or more target condensates more than the compound preferentially causes the first macromolecule to associate with the second set of one or more target condensates.
68. The method of any one of claims 60-67, wherein the first and/or second set of one or more target condensates is a cellular condensate.

69. The method of any one of claims 60-68, wherein the first and/or second set of one or more target condensates is a nuclear condensate or a cytoplasmic condensate.
70. The method of any one of claims 60-68, wherein the first and/or second set of one or more target condensates is a cleavage body, a p-granule, a histone locus body, a multivesicular body, a neuronal RNA granule, a nuclear gem, a nuclear pore, a nuclear speckle, a nuclear stress body, a nucleolus, a Oct1/PTF/transcription (OPT) domain, a paraspeckle, a perinucleolar compartment, a PML nuclear body, a PML oncogenic domain, a polycomb body, a processing body, a Sam68 nuclear body, a stress granule, or a splicing speckle.
71. The method of any one of claims 60-70, wherein the first and/or second set of one or more target condensates is a single target condensate.
72. The method of any one of claims 60-70, wherein the first and/or second set of one or more target condensates is a plurality of target condensates.
73. The method of claim 60-70 or 72, wherein the first and/or second set of one or more target condensates is all or a subset of a class of condensates in a portion of the cellular composition.
74. The method of any one of claims 60-70 or 72-73, wherein the first and/or second set of one or more target condensates is all or a subset of a class of condensates in a cell in the cellular composition.
75. The method of any one of claims 60-70 or 72-74, wherein the first and/or second set of one or more target condensates is all or a subset of a class of condensates in a portion of a cell in the cellular composition.
76. The method of claim 75, wherein the portion of the cell is the cytoplasm, the nucleus, or an organelle.

77. The method of any one of claims 73-76, wherein the class of condensates comprises condensates which comprise a specific macromolecule.
78. The method of any one of claims 73-77, wherein the class of condensates comprises condensates which are cleavage bodies; wherein the class of condensates comprises condensates which are p-granules; wherein the class of condensates comprises condensates which are histone locus bodies; wherein the class of condensates comprises condensates which are multivesicular bodies; wherein the class of condensates comprises condensates which are neuronal RNA granules; wherein the class of condensates comprises condensates which are nuclear gems; wherein the class of condensates comprises condensates which are nuclear pores; wherein the class of condensates comprises condensates which are nuclear speckles; wherein the class of condensates comprises condensates which are nuclear stress bodies; wherein the class of condensates comprises condensates which are nucleoli; wherein the class of condensates comprises condensates which are Oct1/PTF/transcription (OPT) domains; wherein the class of condensates comprises condensates which are paraspeckles; wherein the class of condensates comprises condensates which are perinucleolar compartments; wherein the class of condensates comprises condensates which are PML nuclear bodies; wherein the class of condensates comprises condensates which are PML oncogenic domains; wherein the class of condensates comprises condensates which are polycomb bodies; wherein the class of condensates comprises condensates which are processing bodies; wherein the class of condensates comprises condensates which are Sam68 nuclear bodies; wherein the class of condensates comprises condensates which are stress granules; or wherein the class of condensates comprises condensates which are splicing speckles.
79. The method of any one of claims 73-78, wherein the class of the first set of one or more target condensates is the same as the class of second set of one or more target condensates.
80. The method of any one of claims 73-78, wherein the class of the first set of one or more target condensates is different than the class of second set of one or more target condensates.

81. The method of any one of claims 60-80, wherein the first set of one or more target condensates is in the same cellular composition as the second set of one or more target condensates.
82. The method of any one of claims 60-81, wherein the cellular composition comprises a cell comprising the first set of condensate of one or more target condensates and the second set of one or more target condensates.
83. The method of any one of claims 60-80, wherein the first set of condensate of one or more target condensates is in a first cellular composition, and the second set of one or more target condensates is in a second cellular composition.
84. The method of any one of claims 60-83, wherein the first set of condensate of one or more target condensates are in a cell in the cellular composition, and the cell has one or more features of a disease.
85. The method of claim 84, wherein the disease is a neurodegenerative, proliferative, immunological, cardiac, or metabolic disease.
86. A method of identifying a plurality of compounds that preferentially affect the level, decrease the level, or increase the level of association of a first macromolecule with a first set of one or more target condensates, or that preferentially cause the first macromolecule to associate or disassociate with the first set of one or more target condensates, the method comprising performing the method of any one of claims 60-85 with a plurality of compounds.
87. The method of claim 86, further comprising identifying a characteristic that a subset or all of the identified compounds have in common in addition to ability to preferentially affect the level, decrease the level, or increase the level of association of the first macromolecule with the first set of one or more target condensates, or the ability to preferentially cause the first

macromolecule to associate or disassociate with the first set of one or more target condensates.

88. The method of claim 87, further comprising performing the method of any one of claims 60-85 for one or more additional test compounds that comprise the identified characteristic.
89. The method of claim 87 or 88, further comprising performing the method of any one of claims 60-85 for one or more additional test compounds that do not comprise the identified characteristic.
90. A method of identifying a compound characteristic associated with preferentially affecting the level, decreasing the level, or increasing the level of association of a first macromolecule with a first set of one or more target condensates, or with preferentially causing the first macromolecule to associate or disassociate with the first set of one or more target condensates, the method comprising:
- (a) performing the method of claim 86; and
 - (b) identifying a characteristic that a subset or all of the identified compounds have in common in addition to the ability to preferentially affect the level, decrease the level, or increase the level of association of the first macromolecule with the first set of one or more target condensates, or the ability to preferentially cause the first macromolecule to associate or disassociate with the first set of one or more target condensates.
91. A method of designing a compound that preferentially affects the level, decreases the level, or increases the level of association of a first macromolecule with a first set of one or more target condensates, or that preferentially causes the first macromolecule to associate or disassociate with the first set of one or more target condensates, the method comprising:
- (a) performing the method of claim 86;
 - (b) identifying a characteristic that a subset or all of the identified compounds have in common in addition to the ability to preferentially affect the level, decrease the level, or increase the level of association of the first macromolecule with the first set of one

or more target condensates, or the ability to preferentially cause the first macromolecule to associate or disassociate with the first set of one or more target condensates; and

(c) designing a compound that comprises the identified characteristic,

thereby designing a compound that preferentially affects the level, decreases the level, or increases the level of association of the first macromolecule with the first set of one or more target condensates or preferentially causes the first macromolecule to associate or disassociate with the first set of one or more target condensates.

92. A method of identifying a compound useful for treating a disease in an individual in need thereof, the method comprising:
- performing the method of any one of claims 60-85, wherein the first set of one or more target condensates is associated with the disease, and
 - identifying the compound that preferentially affects the level, decreases the level, or increases the level of association of the first macromolecule with the first set of one or more target condensates or that that preferentially causes the first macromolecule to associate or disassociate with the first set of one or more target condensates for being useful for treating the disease.
93. The method of claim 92, wherein the disease is a neurodegenerative, proliferative, immunological, cardiac, or metabolic disease.