CLAIMS

WHAT IS CLAIMED IS:

1. An automated apparatus for generating a subset of biomolecules from a complex biological sample, the automated apparatus comprising:

(a) a substrate comprising a plurality of partitions, wherein the plurality of partitions comprises a plurality of particles;

(b) a sample storage unit comprising the complex biological sample; and

(c) a loading unit that is movable at least across the substrate,

wherein the loading unit transfers one or more volumes of the complex biological sample in the sample storage unit to the plurality of partitions on the substrate, thereby contacting the plurality of particles in the plurality of partitions with biomolecules of the complex biological sample to form biomolecule coronas, thereby generating the subset of biomolecules of the complex biological sample, and

wherein a dynamic range of the subset of biomolecules is compressed relative to a dynamic range of biomolecules present in the complex biological sample.

2. The automated apparatus of claim 1, further comprising an incubation element that agitates or heats volumes of the plurality of particles within volumes of the complex biological sample in the plurality of partitions.

3. The automated apparatus of claim 2, wherein the incubation element is configured to shake, mix, stir, spin, vibrate, be static, or any combination thereof.

4. The automated apparatus of claim 2 or 3, wherein the incubation element is configured to heat and/or incubate the substrate to a temperature between about 20 °C and about 100 °C.

5. The automated apparatus of any one of claims 1-4, wherein the plurality of partitions is at least partially covered or sealed.

6. The automated apparatus of claim 5, wherein the automated apparatus comprises the ability to add or remove a lid on the substrate, wherein the lid covers at least one of the partitions from among the plurality of partitions.

7. The automated apparatus of any one of claims 1-6, further comprising a unit comprising a resuspension solution.

8. The automated apparatus of claim 7, wherein the resuspension solution comprises Tris EDTA 150mM KCl 0.05% CHAPS buffer.

9. The automated apparatus of claim 7, wherein the resuspension solution comprises 10 mM Tris HCl pH 7.4, 1 mM EDTA.

10. The automated apparatus of any one of claims 1-9, further comprising a unit comprising a denaturing solution.

11. The automated apparatus of claim 10, wherein the denaturing solution comprises a protease.

12. The automated apparatus of claims 10 or 11, wherein the denaturing solution comprises a reductant, a methylating agent, guanidine, urea, sodium deoxycholate, acetonitrile, or any combination thereof.

13. The automated apparatus of any one of claims 10-12, wherein the denaturing solution generates an average peptide fragment with a mass of less than 4600 Daltons.

14. The automated apparatus of any one of claims 1-13, wherein the substrate is a multi-well plate.

15. The automated apparatus of any one of claims 1-14, wherein the loading unit comprises a plurality of pipettes.

16. The automated apparatus of any one of claims 1-15, wherein the loading unit is configured to dispense 10 uL to 400 uL of a solution into one or more partitions of the plurality of partitions.

17. The automated apparatus of claim 16, wherein the loading unit is configured to dispense 5 uL to 150 uL of a solution into one or more partitions of the plurality of partitions.

18. The automated apparatus of claim 16, wherein the loading unit is configured to dispense 35 uL to 80 uL of a solution into one or more partitions of the plurality of partitions.

19. The automated apparatus of any one of claims 16-18 , wherein the solution is selected from the group consisting of a wash solution, the resuspension solution, the denaturing solution, a buffer and a reagent.

20. The automated apparatus of any one of claims 1-19, wherein the loading unit is configured to dispense 10 uL to 400 uL of the complex biological sample into one or more partitions of the plurality of partitions.

21. The automated apparatus of claim 20, wherein the loading unit is configured to dispense 5 uL to 150 uL of the complex biological sample into one or more partitions of the plurality of partitions.

22. The automated apparatus of claim 20, wherein the loading unit is configured to dispense 35 uL to 80 uL of the complex biological sample into one or more partitions of the plurality of partitions.

23. The automated apparatus of any one of claims 1-22, wherein the complex biological sample comprises a biofluid from a subject.

~~24. The automated apparatus of claim 23, wherein the complex biological sample comprises plasma, serum, urine, cerebrospinal fluid, synovial fluid, tears, saliva, whole blood, milk, nipple aspirate, ductal lavage, vaginal fluid, nasal fluid, ear fluid, gastric fluid, pancreatic fluid, trabecular fluid, lung lavage, sweat, crevicular fluid, semen, prostatic fluid, sputum, fecal matter, bronchial lavage, fluid from swabbings, bronchial aspirants, fluidized solids, fine needle aspiration samples, tissue homogenates, lymphatic fluid. cell culture samples, or any combination thereof.~~

~~25. The automated apparatus of any one of claims 1-18, further comprising a magnet.~~

~~26. The automated apparatus of claim 25, wherein one or more particles of the plurality of particles is a magnetic particle, and wherein the substrate and the magnet are in proximity such that the one or more magnetic particles are immobilized on the substrate.~~

~~27. The automated apparatus of any one of claims 1-26, further comprising a housing, wherein the substrate and the loading unit are located in the housing, and wherein the housing is at least partially enclosed.~~

~~28. The automated apparatus of any one of claims 1-27, wherein the compressed dynamic range comprises an increase in the number of types of biomolecules whose concentrations are within 6 orders of magnitude of the most abundant biomolecule in the sample.~~

~~29. The automated apparatus of claim 28, wherein the compressed dynamic range comprises an increase in the number of types of biomolecules whose concentrations are within 5 orders of magnitude of the most abundant biomolecule in the sample.~~

~~30. The automated apparatus of claim 29, wherein the compressed dynamic range comprises an increase in the number of types of biomolecules whose concentrations are within 4 orders of magnitude of the most abundant biomolecule in the sample.~~

~~31. The automated apparatus of claims 30, wherein the compressed dynamic range comprises an increase in the number of types of proteins whose concentrations are within 6 orders of magnitude of the most abundant protein in the sample.~~

~~32. The automated apparatus of claim 31, wherein the increase in the number of types of biomolecules whose concentrations are within 6 orders of magnitude of the most concentrated biomolecule in the sample is at least 25%, 50%, 100%, 200%, 300%, 500%, or 1000%.~~

~~33. The automated apparatus of any one of claims 1-32, wherein the compressed dynamic range comprises an increase in the number of types of proteins whose concentrations are within 6 orders of magnitude of the most abundant protein in the sample.~~

34. The automated apparatus of claim 33, wherein the increase in the number of types of proteins whose concentrations are within 6 orders of magnitude of the most abundant protein in the sample is at least 25%, 50%, 100%, 200%, 300%, 500%, or 1000%.
35. The automated apparatus of any one of claims 1-34, wherein the subset of biomolecules comprises at least 20% to at least 60% of the types of biomolecules from the complex biological sample within a 6 order of magnitude concentration range.
36. The automated apparatus of claim 35, wherein the subset of biomolecules comprises at least 20% to at least 60% of the types of proteins from the complex biological sample within a 6 order of magnitude concentration range.
37. The automated apparatus of any one of claims 1-36, wherein the dynamic range of the biomolecules of the biomolecule coronas is a first ratio of a top decile of biomolecules to a bottom decile of biomolecules in the plurality of biomolecule coronas.
38. The automated apparatus of any one of claims 1-36, wherein the dynamic range of the biomolecules of the biomolecule coronas is a first ratio comprising a span of the interquartile range of biomolecules in the plurality biomolecule coronas.
39. The automated apparatus of any one of claims 1-38, wherein the generating enriches low abundance biomolecules from the complex biological sample.
40. The automated apparatus of claim 33, wherein the low abundance biomolecules are biomolecules at concentrations of 10ng/mL or less in the complex biological sample.
41. The automated apparatus of any one of claims 1-34, wherein the subset of biomolecules from the complex biological sample comprises proteins.
42. The automated apparatus of claim 41, wherein changes of at most 10 mg/mL in the lipid concentration of the complex biological sample result in changes of less than 10%, 5%, 2%, or 1% in the composition of the proteins in the subset of biomolecules generated from the complex biological sample.
43. The automated apparatus of any one of claims 1-42, wherein at least two particles from among the plurality of particles differ in at least one physicochemical property.
44. The automated apparatus of claim 43, wherein the at least one physicochemical property is selected from the group consisting of: composition, size, surface charge, hydrophobicity, hydrophilicity, surface functionality, surface topography, surface curvature, porosity, core material, shell material, shape, and any combination thereof.
45. The automated apparatus of claim 44, wherein the surface functionality comprises aminopropyl functionalization, amine functionalization, boronic acid functionalization, carboxylic acid functionalization, methyl functionalization, N-succinimidyl ester

functionalization, PEG functionalization, streptavidin functionalization, methyl ether functionalization, triethoxylpropylaminosilane functionalization, thiol functionalization, PCP functionalization, citrate functionalization, lipoic acid functionalization, BPEI functionalization.

46. The automated apparatus of any one of claims 1-45, wherein a particle from among the plurality of particles is selected from the group consisting of: micelles, liposomes, iron oxide particles, silver particles, gold particles, palladium particles, quantum dots, platinum particles, titanium particles, silica particles, metal or inorganic oxide particles, synthetic polymer particles, copolymer particles, terpolymer particles, polymeric particles with metal cores, polymeric particles with metal oxide cores, polystyrene sulfonate particles, polyethylene oxide particles, polyoxyethylene glycol particles, polyethylene imine particles, polylactic acid particles, polycaprolactone particles, polyglycolic acid particles, poly(lactide-co-glycolide polymer particles, cellulose ether polymer particles, polyvinylpyrrolidone particles, polyvinyl acetate particles, polyvinylpyrrolidone-vinyl acetate copolymer particles, polyvinyl alcohol particles, acrylate particles, polyacrylic acid particles, crotonic acid copolymer particles, polyethlene phosphonate particles, polyalkylene particles, carboxy vinyl polymer particles, sodium alginate particles, carrageenan particles, xanthan gum particles, gum acacia particles, Arabic gum particles, guar gum particles, pullulan particles, agar particles, chitin particles, chitosan particles, pectin particles, karaya tum particles, locust bean gum particles, maltodextrin particles, amylose particles, corn starch particles, potato starch particles, rice starch particles, tapioca starch particles, pea starch particles, sweet potato starch particles, barley starch particles, wheat starch particles, hydroxypropylated high amylose starch particles, dextrin particles, levan particles, elsinan particles, gluten particles, collagen particles, whey protein isolate particles, casein particles, milk protein particles, soy protein particles, keratin particles, polyethylene particles, polycarbonate particles, polyanhydride particles, polyhydroxyacid particles, polypropylfumerate particles, polycaprolactone particles, polyamine particles, polyacetal particles, polyether particles, polyester particles, poly(orthoester) particles, polycyanoacrylate particles, , polyurethane particles, polyphosphazene particles, polyacrylate particles, polymethacrylate particles, polycyanoacrylate particles, polyurea particles, polyamine particles, polystyrene particles, poly(lysine) particles, chitosan particles, dextran particles, poly(acrylamide) particles, derivatized poly(acrylamide) particles, gelatin particles, starch particles, chitosan particles, dextran particles, gelatin particles, starch particles, poly-β-amino-ester particles, poly(amido amine) particles, poly lactic-co-glycolic acid particles, polyanhydride particles, bioreducible

polymer particles, and 2-(3-aminopropylamino)ethanol particles, and any combination thereof.

47. The automated apparatus of any one of claims 1-46, wherein one or more particles of the plurality of particles adsorbs at least 100 types of proteins upon contacting the complex biological sample.

48. The automated apparatus of any one of claims 1-47, wherein the plurality of particles comprises at least 2 distinct particle types, at least 3 distinct particle types, at least 4 distinct particle types, at least 5 distinct particle types, at least 6 distinct particle types, at least 7 distinct particle types, at least 8 distinct particle types, at least 9 distinct particle types, at least 10 distinct particle types, at least 11 distinct particle types, at least 12 distinct particle types, at least 13 distinct particle types, at least 14 distinct particle types, at least 15 distinct particle types, at least 20 distinct particle types, at least 25 particle types, or at least 30 distinct particle types.

49. The automated apparatus of any one of claims 1-48, wherein biomolecules of the biomolecule coronas comprise a number of protein groups.

50. The automated apparatus of claim 49, wherein the number of protein groups comprises from 1 to 20,000 protein groups.

51. The automated apparatus of claim 50, wherein the number of protein groups comprises from 100 to 10,000 protein groups.

52. The automated apparatus of claim 51, wherein the number of protein groups comprises from 100 to 5000 protein groups.

53. The automated apparatus of claim 52, wherein the number of proteins groups comprises from 300 to 2,200 protein groups.

54. The automated apparatus of claim 53, wherein the number of proteins groups comprises from 1,200 to 2,200 protein groups.

55. The automated apparatus of any one of claims 1-54, wherein at least two partitions of the plurality of partitions comprise different buffers.

56. The automated apparatus of claim 55, wherein the different buffers differ in pH, salinity, osmolarity, viscosity, dielectric constant, or any combination thereof.

57. The automated apparatus of any one of claims 1-56, wherein at least two partitions of the plurality of partitions comprise different ratios of buffer and the complex biological sample.

58. The automated apparatus of any one of claims 1-57, wherein one or more partitions of the plurality of partitions comprises 1 pM to 100 nM nanoparticles.

59. The automated apparatus of any one of claims 1-58, wherein at least two partitions of the plurality of partitions comprise different concentrations of nanoparticles.

60. The automated apparatus of any one of claims 1-59, further comprising a purification unit.

61. The automated apparatus of claim 60, wherein the purification unit comprises a solid phase extraction (SPE) plate.

62. The automated apparatus of any one of claims 1-61, wherein the automated apparatus generates the subset of biomolecules from a complex biological sample in less than 7 hours.

63. An automated system comprising:

(a) an automated apparatus of any one of claims 1-56 configured to isolate the subset of biomolecules from the biological sample;

(b) a mass spectrometer configured to receive the subset of biomolecules and to generate data comprising mass spectrometric or tandem mass spectrometric signals; and

(c) a computer comprising one or more computer processors and a computer readable medium comprising machine-executable code that, upon execution by the one or more computer processors, implements a method comprising:

i. generating a biomolecule fingerprint, and

ii. assigning a biological state based on the biomolecule fingerprint.

64. The automated system of claim 63, wherein the biomolecule fingerprint comprises a plurality of distinct biomolecule corona signatures.

65. The automated system of claim 64, wherein the biomolecule fingerprint comprises at least 5, 10, 20, 40, or 80, 150 or 200 distinct biomolecule corona signatures.

66. The automated system of any one of claims 63-65, wherein the computer is configured to process the data comprising the intensity, APEX, spectral count or number of peptides, or Ion mobility behavior of the mass spectrometric or tandem mass spectrometric signal between a plurality of the distinct biomolecule corona signatures.

67. The automated system of claim 66, wherein the computer is configured to process data from between 100 and 2000 mass spectrometric or tandem mass spectrometric signals between a plurality of the distinct biomolecule corona signatures.

68. The automated system of claim 67, wherein the computer is configured to process the data comprising the intensities of between 10,000 and 5,000,000 mass spectrometric or tandem mass spectrometric signals between a plurality of the distinct biomolecule corona signatures.

69. The automated system of any one of claims 63-68, wherein the biomolecule fingerprint is generated from data from a single mass spectrometric or tandem mass spectrometric run.

70. The automated system of claim 69, wherein the single mass spectrometric or tandem mass spectrometric run is performed in less than one hour.

71. The automated system of any one of claims 63-70, wherein the computer is configured to identify a biomolecule or characterize an unidentified molecular feature based on a mass spectrometric or tandem mass spectrometric signal and or ion mobility and chromatographic behavior, and wherein the computer provides a certainty threshold of at least 95% to identify a feature or characterize and unidentified feature.

72. The automated system of any one of claims 63-71, wherein the automated system is configured to generate the biomolecule fingerprint from the complex biological sample in less than about 10 hours.

73. The automated system of any one of claims 63-72, wherein the computer is capable of distinguishing between two or more biological states associated with biomolecule fingerprints that differ by less than 10%, 5%, 2%, or 1%.

74. The automated system of any one of claims 63-73, wherein the biological state is a disease, disorder, or tissue abnormality.

75. The automated system of claim 75, wherein the disease is an early phase or intermediate phase disease state.

76. The automated system of claims 74 or 75, wherein the disease is cancer.

77. The automated system of claim 76, wherein the cancer is a stage 0 cancer or a stage 1 cancer.

78. The automated system of claims 76 or 77, wherein the cancer is selected from the group consisting of: lung cancer, pancreas cancer, myeloma, myeloid leukemia, meningioma, glioblastoma, breast cancer, esophageal squamous cell carcinoma, gastric adenocarcinoma, prostate cancer, bladder cancer, ovarian cancer, thyroid cancer, neuroendocrine cancer, colon carcinoma, ovarian cancer, head and neck cancer, Hodgkin's Disease, non-Hodgkin's lymphomas, rectum cancer, urinary cancers, uterine cancers, oral cancers, skin cancers, stomach cancer, brain tumors, liver cancer, laryngeal cancer, esophageal cancer, mammary tumors, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, Ewing's sarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystandeocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, endometrial cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioblastomas, neuronomas, craniopharingiomas, schwannomas,

~~glioma, astrocytoma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemias and lymphomas, acute lymphocytic leukemia and acute myelocytic polycythemia vera, multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease, acute nonlymphocytic leukemias, chronic lymphocytic leukemia, chronic myelogenous leukemia, childhood null acute lymphoid leukemia (ALL), thymic ALL, B-cell ALL, acute megakaryocytic leukemia, Burkitt's lymphoma, and T-cell leukemia, small and large non-small cell lung carcinoma, acute granulocytic leukemia, germ cell tumors, endometrial cancer, gastric cancer, hairy cell leukemia, or thyroid cancer.~~

~~79. The automated system of any one of claims 74-78, wherein the biological state is a pre-disease state.~~

~~80. The automated system of any one of claims 63-79, wherein the determining comprises comparing the abundance of two biomolecules whose concentrations span at least 7 to at least 12 orders of magnitude in the complex biological sample.~~

~~81. A method for distinguishing a biological state of a complex biological sample, the method comprising:~~

~~(a) providing the complex biological sample to the automated apparatus of any one of claims 1-56 to generate a subset of biomolecules;~~

~~(b) assaying the subset of biomolecules to generate a biomolecule fingerprint; and~~

~~(c) distinguishing a biological state of the complex biological sample with the biomolecule fingerprint.~~

~~82. The method of claim 81, wherein the biomolecule fingerprint comprises proteins.~~

~~83. The method of claim 81 or 82, wherein the subset of biomolecules from the complex biological sample comprises a lower ratio of albumin to non-albumin peptides than the complex biological sample.~~

~~84. The method of any one of claims 81-83, wherein the subset of biomolecules comprises biomolecules that span at least 6 to at least 12 orders of magnitude in concentration range in the complex biological sample.~~

~~85. The method of any one of claims 81-84, wherein the subset of biomolecules comprises proteins that span at least 6 to at least 12 orders of magnitude in concentration range in the complex biological sample.~~

~~86. The method of any one of claims 81-85, wherein the biomolecule fingerprint comprises from 1 to 74,000 protein groups.~~

87. The method of any one of claims 81-86, wherein the assaying comprises desorbing a plurality of biomolecules from a biomolecule corona from among the plurality of biomolecule coronas.

88. The method of claim 87, wherein the assaying comprises chemically modifying a biomolecule from among the plurality of desorbed biomolecules.

89. The method of claim 87, wherein the assaying comprises fragmenting a biomolecule from among the plurality of desorbed biomolecules.

90. The method of claim 89, wherein the fragmenting comprises protease digestion.

91. The method of claim 89, wherein the fragmenting comprises chemical peptide cleavage.

92. The method of any one of claims claim 87-91, wherein the assaying comprises collecting the plurality of desorbed biomolecules.

93. The method of claim 92, wherein the assaying comprises purifying the collected plurality of desorbed biomolecules.

94. The method of claim 93, wherein the purifying comprises solid-phase extraction.

95. The method of claims 93 or 94, wherein the purifying depletes non-protein biomolecules from the collected plurality of desorbed biomolecules.

96. The method of claim 87, wherein the assaying comprises discarding the plurality of desorbed biomolecules.

97. The method of any one of claims 87-96, where the assaying comprises desorbing a first subset of biomolecules and a second set of biomolecules from a biomolecule corona from among the plurality of biomolecule coronas, analyzing a biomolecule from among the first subset of biomolecules, and analyzing a biomolecule from among the second subset of biomolecules.

98. The method of any one of claims 81-97, wherein the assaying comprises analyzing a biomolecule corona from among the plurality of biomolecule coronas with mass spectrometry, tandem mass spectrometry, mass cytometry, mass cytometry, potentiometry, fluorimetry, absorbance spectroscopy, Raman spectroscopy, chromatography, electrophoresis, immunohistochemistry, PCR, next generation sequencing (NGS), or any combination thereof.

99. The method of claim 98, wherein the assaying comprises mass spectrometry or tandem mass spectrometry.

100. The method of any one of claims 81-99, wherein the assaying comprises identifying the conformational state of a protein from among the subset of biomolecules.

101. The method of any one of claims 81-100, wherein the assaying comprises identifying a post-translational modification on a protein from among the subset of biomolecules.

102. The method of any one of claims 81-101, wherein the distinguishing comprises comparing the relative abundances of at least 200 to at least 1000 biomolecules from the subset of biomolecules.

103. The method of any one of claims 81-102, wherein the assaying identifies biomolecules at concentrations of less than 10 ng/mL in the complex biological sample.

104. An automated apparatus for generating a subset of biomolecules from a complex biological sample, the automated apparatus comprising:

a plurality of particles; and

the complex biological sample,

wherein the automated apparatus is configured to generate the subset of biomolecules by contacting the plurality of particles with the complex biological sample to form a plurality of biomolecule coronas comprising the subset of biomolecules, and

wherein a dynamic range of the subset of biomolecules is compressed relative to a dynamic range of biomolecules present in the complex biological sample.

105. The automated apparatus of claim 104, further comprising a substrate, wherein the substrate is a multi-well plate.

106. The automated apparatus of claim 104 or 105, further comprising an incubation element.

107. The automated apparatus of claim 106, wherein the incubation element is configured to heat and/or incubate the plurality of particles and the complex biological sample to a temperature between 4 °C and 40 °C.

108. The automated apparatus of any one of claims 104-107, further comprising at least one solution selected from the group consisting of a wash solution, a resuspension solution, a denaturing solution, a buffer and a reagent.

109. The automated apparatus of claim 108, wherein the resuspension solution comprises a Tris EDTA buffer, a phosphate buffer, and/or water.

110. The automated apparatus of claim 108, wherein the denaturing solution comprises a protease.

111. The automated apparatus of claim 108, wherein the denaturing solution comprises a small molecule capable of performing peptide cleavage.

112. The automated apparatus of any one of claims 104-111, further comprising a loading unit, wherein the loading unit comprises a plurality of pipettes.

113. The automated apparatus of claim 112, wherein each pipette of the plurality of pipettes is configured to dispense about 5 uL – 150 uL of the solution, the complex biological sample, and/or the plurality of particles.

114. The automated apparatus of any one of claim 104-113, wherein the complex biological sample comprises plasma, serum, urine, cerebrospinal fluid, synovial fluid, tears, saliva, whole blood, milk, nipple aspirate, ductal lavage, vaginal fluid, nasal fluid, ear fluid, gastric fluid, pancreatic fluid, trabecular fluid, lung lavage, sweat, crevicular fluid, semen, prostatic fluid, sputum, fecal matter, bronchial lavage, fluid from swabbings, bronchial aspirants, fluidized solids, fine needle aspiration samples, tissue homogenates, lymphatic fluid. cell culture samples, or any combination thereof.

115. The automated apparatus of any one of claims 104-114, further comprising a magnet.

116. The automated apparatus of any one of claims 104-115, further comprising a filter.

117. The automated apparatus of any one of claims 104-116, wherein the compressed dynamic range comprises an increase in the number of types of biomolecules whose concentrations are within 4 to 6 orders of magnitude of the most abundant biomolecule in the sample.

118. The automated apparatus of claim 117, wherein the types of biomolecules comprises protein.

119. The automated apparatus of any one of claims 104-118, wherein the dynamic range of the biomolecules of the biomolecule coronas is a first ratio of a top decile of biomolecules to a bottom decile of biomolecules in the plurality of biomolecule coronas.

120. The automated apparatus of any one of claims 104-119, wherein the generating enriches low abundance biomolecules from the complex biological sample.

121. The automated apparatus of claim 120, wherein the low abundance biomolecules are biomolecules at concentrations of 10ng/mL or less in the complex biological sample.

122. The automated apparatus of any one of claims 104-121, wherein at least two particles from among the plurality of particles differ in at least one physicochemical property.

123. The automated apparatus of claim 114, wherein the at least one physicochemical property is selected from the group consisting of: composition, size, surface charge, hydrophobicity, hydrophilicity, surface functionality, surface topography, surface curvature, porosity, core material, shell material, shape, and any combination thereof.

124. The automated apparatus of any one of claims 104-123, wherein a particle from among the plurality of particles is selected from the group consisting of: micelles, liposomes, iron oxide particles, silver particles, gold particles, palladium particles, quantum dots, platinum particles, titanium particles, silica particles, metal or inorganic oxide particles, synthetic

polymer particles, copolymer particles, terpolymer particles, polymeric particles with metal cores, polymeric particles with metal oxide cores, polystyrene sulfonate particles, polyethylene oxide particles, polyoxyethylene glycol particles, polyethylene imine particles, polylactic acid particles, polycaprolactone particles, polyglycolic acid particles, poly(lactide-co-glycolide polymer particles, cellulose ether polymer particles, polyvinylpyrrolidone particles, polyvinyl acetate particles, polyvinylpyrrolidone-vinyl acetate copolymer particles, polyvinyl alcohol particles, acrylate particles, polyacrylic acid particles, crotonic acid copolymer particles, polyethlene phosphonate particles, polyalkylene particles, carboxy vinyl polymer particles, sodium alginate particles, carrageenan particles, xanthan gum particles, gum acacia particles, Arabic gum particles, guar gum particles, pullulan particles, agar particles, chitin particles, chitosan particles, pectin particles, karaya tum particles, locust bean gum particles, maltodextrin particles, amylose particles, corn starch particles, potato starch particles, rice starch particles, tapioca starch particles, pea starch particles, sweet potato starch particles, barley starch particles, wheat starch particles, hydroxypropylated high amylose starch particles, dextrin particles, levan particles, elsinan particles, gluten particles, collagen particles, whey protein isolate particles, casein particles, milk protein particles, soy protein particles, keratin particles, polyethylene particles, polycarbonate particles, polyanhydride particles, polyhydroxyacid particles, polypropylfumerate particles, polycaprolactone particles, polyamine particles, polyacetal particles, polyether particles, polyester particles, poly(orthoester) particles, polycyanoacrylate particles, , polyurethane particles, polyphosphazene particles, polyacrylate particles, polymethacrylate particles, polycyanoacrylate particles, polyurea particles, polyamine particles, polystyrene particles, poly(lysine) particles, chitosan particles, dextran particles, poly(acrylamide) particles, derivatized poly(acrylamide) particles, gelatin particles, starch particles, chitosan particles, dextran particles, gelatin particles, starch particles, poly-β-amino-ester particles, poly(amido amine) particles, poly lactic-co-glycolic acid particles, polyanhydride particles, bioreducible polymer particles, and 2-(3-aminopropylamino)ethanol particles, and any combination thereof.

125. The automated apparatus of any one of claims 104-124, wherein biomolecules of the biomolecule coronas comprise a number of protein groups.

126. The automated apparatus of claim 125, wherein the number of protein groups comprises from 1 to 20,000 protein groups.

127. The automated apparatus of claim 125, wherein the number of protein groups comprises from 100 to 10,000 protein groups.

128. The automated apparatus of claim 125, wherein the number of protein groups comprises from 100 to 5000 protein groups.

129. The automated apparatus of claim 125, wherein the number of proteins groups comprises from 300 to 2,200 protein groups.

130. The automated apparatus of claim 125, wherein the number of proteins groups comprises from 1,200 to 2,200 protein groups.

131. The automated apparatus of any one of claims 104-130, further comprising a purification unit.

132. The automated apparatus of claim 131, wherein the purification unit comprises a solid phase extraction (SPE) plate.

133. The automated apparatus of any one of claims 104-132, wherein the automated apparatus generates the subset of biomolecules from a complex biological sample in less than 7 hours.

134. A method for generating a subset of biomolecules from a complex biological sample, the method comprising:

providing the complex biological sample to an automated apparatus,

wherein the automated apparatus contacts the complex biological sample with a plurality of particles to generate biomolecule coronas,

wherein the automated apparatus processes the biomolecule coronas to generate the subset of biomolecules, and

wherein a dynamic range of the subset of biomolecules is compressed relative to a dynamic range of biomolecules present in the complex biological sample.

135. The method of claim 134, wherein the automated apparatus is the automated apparatus of any one of claims 104-133.

136. The method of claim 134 or 135, further comprising assaying the subset of biomolecules to generate a biomolecule fingerprint.

137. The method of claim 136, wherein the assaying identifies biomolecules at concentrations of less than 10 ng/mL in the complex biological sample.

138. The method of any one of claims 136 or 137, wherein the assaying comprises analyzing biomolecule coronas with mass spectrometry, tandem mass spectrometry, mass cytometry, mass cytometry, potentiometry, fluorimetry, absorbance spectroscopy, Raman spectroscopy, chromatography, electrophoresis, immunohistochemistry, or any combination thereof.

139. The method of claim 138, wherein the assaying comprises mass spectrometry or tandem mass spectrometry

140. The method of any one of claims 134-139, further comprising distinguishing a biological state of the complex biological sample with the biomolecule fingerprint.

141. The method of claim 140, wherein the biomolecule fingerprint comprises a plurality of distinct biomolecule corona signatures.

142. The method of claim 140 or 141, wherein the biomolecule fingerprint comprises at least 5, 10, 20, 40, or 80, 150 or 200 distinct biomolecule corona signatures.

143. The method of any one of claims 140-142, wherein the biological state is a disease, disorder, or tissue abnormality.

144. The method of claim 143, wherein the disease is an early phase or intermediate phase disease state.

145. The method of claim 143 or 144, wherein the disease is cancer.

146. The method of claim 145, wherein the cancer is a stage 0 cancer or a stage 1 cancer.

147. The method of claims 145 or 146, wherein the cancer is selected from the group consisting of: lung cancer, pancreas cancer, myeloma, myeloid leukemia, meningioma, glioblastoma, breast cancer, esophageal squamous cell carcinoma, gastric adenocarcinoma, prostate cancer, bladder cancer, ovarian cancer, thyroid cancer, neuroendocrine cancer, colon carcinoma, ovarian cancer, head and neck cancer, Hodgkin's Disease, non-Hodgkin's lymphomas, rectum cancer, urinary cancers, uterine cancers, oral cancers, skin cancers, stomach cancer, brain tumors, liver cancer, laryngeal cancer, esophageal cancer, mammary tumors, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, Ewing's sarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystandeocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, endometrial cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioblastomas, neuronomas, craniopharingiomas, schwannomas, glioma, astrocytoma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemias and lymphomas, acute lymphocytic leukemia and acute myelocytic polycythemia vera, multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease, acute nonlymphocytic leukemias, chronic lymphocytic leukemia, chronic myelogenous leukemia, childhood-null acute lymphoid leukemia (ALL), thymic ALL, B-cell ALL, acute megakaryocytic leukemia, Burkitt's lymphoma, and T cell leukemia, small and large non-

small cell lung carcinoma, acute granulocytic leukemia, germ cell tumors, endometrial cancer, gastric cancer, hairy cell leukemia, or thyroid cancer.

148. The method of claim 143, wherein the biological state is a pre-disease state.

149. An automated system comprising a network of units with differentiated functions in distinguishing states of a complex biological sample using a plurality of particles having surfaces with different physiochemical properties wherein:

(a) a first unit comprises a multichannel fluid transfer instrument for transferring fluids between units within the system;

(b) a second unit comprises a support for storing a plurality of biological samples;

(c) a third unit comprises a support for a sensor array plate possessing partitions that comprise the plurality of particles having surfaces with different physiochemical properties for detecting a binding interaction between a population of analytes within the complex biological sample and the plurality of particles;

(d) a fourth unit comprises supports for storing a plurality of reagents;

(e) a fifth unit comprises supports for storing a reagent to be disposed of;

(f) a sixth unit comprises supports for storing consumables used by the multichannel fluid transfer instrument; and

wherein the system is programed to perform a series of steps comprising:

i. contacting the biological sample with a specified partition of the sensor array;

ii. incubating the biological sample with the plurality of particles contained within the partition of the sensor array plate;

iii. removing all components from a partition except the plurality of particles and a population of analytes interacting with a particle; and

iv. preparing a sample for mass spectrometry.

150. The automated system of claim 149, wherein the first unit comprises a degree of mobility that enables access to all other unit within the system.

151. The automated system of either of claims 149 or 150, wherein the first unit comprises a capacity to perform pipetting functions.

152. The automated system of any one of claims 149-151, wherein the support of the second and/or third unit comprises support for a single plate, a 6 well plate, a 12 well plate, a 96 well plate, or a rack of microtubes.

153. The automated system of any one of claims 149-152, wherein the second and/or unit comprises a thermal unit capable of modulating the temperature of said support and a sample.

~~154. The automated system of any one of claims 149-153, wherein the second and/or third unit comprises a rotational unit capable of physically agitating and/or mixing a sample.~~

~~155. The automated system of any one of claims 149-154, wherein the plurality of particles having surfaces with different physiochemical properties for detecting a binding interaction between a population of analytes within the complex biological sample and the plurality of particles are immobilized to a surface with a partition of the sensory array.~~

~~156. The automated system of any one of claims 149-155, wherein the plurality of particles having surfaces comprise a plurality magnetic nanoparticles in a solution with different physiochemical properties for detecting a binding interaction between a population of analytes within the complex biological sample and the plurality of particles.~~

~~157. The automated system of claim 156, comprising a step wherein the sensor array plate is transferred to an additional seventh unit that comprises a magnetized support and a thermal unit capable of modulating the temperature of said support and a sample and incubated for an additional amount of time.~~

~~158. The automated system of any one of claims 149-157, wherein the fourth unit comprises a set of reagents for:~~

~~(a) generating the sensor array plate;~~

~~(b) washing an unbound sample; and/or~~

~~(c) preparing a sample for mass spectrometry.~~

~~159. The automated system of any one of claims 149-158, wherein (i) contacting the biological sample with a specified partition of the sensor array comprises pipetting a specified volume of the biological sample into the specific partition of the sensor array.~~

~~160. The automated system of any one of claims 149-159, wherein (i) contacting the biological sample with a specified partition of the sensor array comprises pipetting a volume corresponding to a 1:1, 1:2: 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, or 1:20 ratio of a plurality of particles in a solution to the biological sample.~~

~~161. The automated system of any one of claims 149-160, wherein (i) contacting the biological sample with a specified partition of the sensor array comprises pipetting a volume of at least 10 microliters, at least 50 microliters, at least 100 microliters, at least 250 microliters, at least 500 microliters, or at least 1000 microliters the biological sample into the specific partition of the sensor array.~~

~~162. The automated system of any one of claims 149-161, wherein (ii) incubating the biological sample with the plurality of particles contained within the partition of the sensor array plate comprises an incubation time of at least about 10 seconds, at least about 15 seconds, at least about 20 seconds, at least about 25 seconds, at least about 30 seconds, at least about 40 seconds, at least about 50 seconds, at least about 60 seconds, at least about 90 seconds, at least about 2 minutes, at least about 3 minutes, at least about 4 minutes, at least about 5 minutes, at least about 6 minutes, at least about 7 minutes, at least about 8 minutes, at least about 9 minutes, at least about 10 minutes, at least about 15 minutes, at least about 20 minutes, at least about 25 minutes, at least about 30 minutes, at least about 45 minutes, at least about 50 minutes, at least about 60 minutes, at least about 90 minutes, at least about 2 hours, at least about 3 hours, at least about 4 hours, at least about 5 hours, at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 12 hours, at least about 14 hours, at least about 15 hours, at least about 16 hours, at least about 17 hours, at least about 18 hours, at least about 19 hours, at least about 20 hours, or at least about 24 hours.~~

~~163. The automated system of any one of claims 149-162, wherein (ii) incubating the biological sample with the plurality of particles contained within the partition of the sensor array plate comprises an incubation temperature between about 4° C to about 40° C.~~

~~164. The automated system of any one of claims 149-163, wherein removing all components from a partition except the plurality of particles and a population of analytes interacting with a particle comprises a series of wash steps.~~

~~165. The automated system of any one of claims 149-164, wherein the second unit can facilitate a transfer of the sample for mass spectrometry to a mass spectrometry unit.~~

~~166. An automated apparatus to identify proteins in a biological sample, the automated apparatus comprising:~~

~~a sample preparation unit;~~

~~a substrate comprising a plurality of channels;~~

~~a plurality of pipettes;~~

~~a plurality of solutions,~~

~~a plurality of nanoparticles, and~~

~~wherein the automated apparatus is configured to form a protein corona and digest the protein corona.~~

~~167. An automated apparatus to identify proteins in a biological sample, the automated apparatus comprising:~~

~~a sample preparation unit;~~

~~a substrate comprising a plurality of channels;~~

~~a plurality of pipettes;~~

~~a plurality of solutions,~~

~~a plurality of nanoparticles,~~

~~wherein the automated apparatus is configured to form a protein corona and digest the protein corona, and~~

~~wherein at least one of the solutions is TE 150mM KCl 0.05% CHAPS buffer.~~

~~168. The automated apparatus of claims 166 or 167, wherein the sample preparation unit is configured to add the plurality of nanoparticles to the substrate with the plurality of pipettes.~~

~~169. The automated apparatus of any one of claims 166-168, wherein the sample preparation unit is configured to add the biological sample to the substrate with the plurality of pipettes.~~

~~170. The automated apparatus of any one of claims 166-169, wherein the sample preparation unit is configured to incubate the plurality of nanoparticles and the biological sample to form the protein corona.~~

~~171. The automated apparatus of any one of claims 166-170, wherein the sample preparation unit is configured to separate the protein corona from the supernatant to form a protein corona pellet.~~

~~172. The automated apparatus of any one of claims 166-171, wherein the sample preparation unit is configured to reconstitute the protein corona pellet with TE 150mM KCl 0.05% CHAPS buffer.~~

~~173. The automated apparatus of any one of claims 166-172, further comprising a magnetic source.~~

~~174. The automated apparatus of any one of claims 166-173, wherein the automated apparatus is configured for BCA, gel, or trypsin digestion of the protein corona.~~

~~175. The automated apparatus of any one of claims 166-174, wherein the automated apparatus is enclosed.~~

~~176. The automated apparatus of any one of claims 166-175, wherein the automated apparatus is sterilized before use.~~

~~177. The automated apparatus of any one of claims 166-176, wherein the automated apparatus is configured to a mass spectrometry.~~

~~178. The automated apparatus of any one of claims 166-177, wherein the automated apparatus is temperature controlled.~~

~~179. A method of identifying proteins in a biological sample, the method comprising: adding the biological sample to the automated apparatus of any one of claims 166-178; generating proteomic data from the automated apparatus; and quantifying the proteomic data.~~

~~180. The method of claim 179, further comprising incubating a plurality of nanoparticles with the biological sample in the automated apparatus to form a protein corona.~~

~~181. The method of claim 179 or 180, further comprising separating the protein corona from the supernatant in the automated apparatus.~~

~~182. The method of any one of claims 179-181, further comprising digesting the protein corona to form the digested sample in the automated apparatus.~~

~~183. The method of any one of claims 179-182, further comprising washing the digested sample in the automated apparatus.~~

~~184. The method of any one of claims 179-183, wherein quantifying the proteomic data comprises providing the proteomic data to a mass spectrometry.~~

~~185. The method of any one of claims 179-184, wherein the biological sample is a biofluid.~~

~~186. The method of any one of claims 179-185, wherein the biofluid is serum or plasma.~~

1. An automated system comprising a network of units with differentiated functions in distinguishing states of a biological sample using a plurality of particles having surfaces with different physiochemical properties wherein:

(a) a first unit comprises a multichannel fluid transfer instrument for transferring fluids between units within the system;

(b) a second unit comprises a support for storing at least a portion of the biological sample;

(c) a third unit comprises a support for a sensor array plate comprising partitions that comprise the plurality of particles having surfaces with different physiochemical properties for binding a population of proteins within the biological sample;

(d) a fourth unit comprises supports for storing a plurality of reagents;

(e) a fifth unit comprises supports for storing a reagent to be disposed of;

(f) a sixth unit comprises supports for storing consumables used by the multichannel fluid transfer instrument; and wherein the system is programed to perform a series of steps comprising: i. contacting the biological sample with the partitions of the sensor array; ii. incubating the biological sample with the plurality of particles contained within the partitions of the sensor array plate; iii. removing all components from the partitions except the plurality of particles and the population of proteins interacting with the plurality of particles; and iv. preparing a sample for mass spectrometry.

2. The automated system of claim 1, wherein the first unit comprises a degree of mobility that enables access to all other unit within the system.

3. The automated system of either of claims 1 or 2, wherein the first unit comprises a capacity to perform pipetting functions.

4. The automated system of any one of claims 1-3, wherein the support of the second or third unit comprises support for a single plate, a 6 well plate, a 12 well plate, a 96 well plate, or a rack of microtubes.

5. The automated system of any one of claims 1-4, wherein the second unit comprises a thermal unit capable of modulating the temperature of said support and a sample.

6. The automated system of any one of claims 1-5, wherein the second or third unit comprises a rotational unit capable of physically agitating or mixing a sample.

7. The automated system of any one of claims 1-6, wherein the plurality of particles are immobilized to a surface with a partition of the sensory array.

8. The automated system of any one of claims 1-7, wherein the plurality of particles having surfaces comprise a plurality magnetic nanoparticles in a solution with different physiochemical properties for binding the population of proteins within the biological sample.

9. The automated system of any one of claims 1-8, further comprising a step wherein the sensor array plate is transferred to an additional seventh unit that comprises a magnetized

support and a thermal unit capable of modulating the temperature of said support and a sample and incubated for an additional amount of time.

10. The automated system of any one of claims 1-9, wherein the fourth unit comprises a set of reagents for:

(a) generating the sensor array plate;

(b) washing an unbound sample; or

(c) preparing the sample for mass spectrometry.

11. The automated system of any one of claims 1-10, wherein (i) contacting the biological sample with a specified partition of the sensor array comprises pipetting a specified volume of the biological sample into the specific partition of the sensor array.

12. The automated system of any one of claims 1-11, wherein (i) contacting the biological sample with a specified partition of the sensor array comprises pipetting a volume corresponding to a 1:1, 1:2: 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, or 1:20 ratio of a plurality of particles in a solution to the biological sample.

13. The automated system of any one of claims 1-12, wherein (ii) incubating the biological sample with the plurality of particles contained within the partition of the sensor array plate comprises an incubation temperature between about 4° C to about 40° C.

14. The automated system of any one of claims 1-13, wherein the second unit can facilitate a transfer of the sample for mass spectrometry to a mass spectrometry unit.

15. The automated system of any one of claims 1-14, wherein the partitions comprise 3 to 8 types of particles having surfaces with different physicochemical properties.

16. The automated system of any one of claims 1-15, wherein the plurality of particles are configured to bind to at least 300 different proteins.

17. The automated system of any one of claims 1-16, wherein the plurality of particles are configured to bind to at least 600 different proteins.

18. The automated system of any one of claims 1-17, wherein the plurality of particles are located in different partitions on the sensor array plate.

19. The automated system of any one of claims 1-18, wherein at least two distinct types of particles that differ from each other in at least one physicochemical property are located in the same partition on the sensor array plate.

20. The automated system of any one of claims 1-19, wherein the sample for mass spectrometry comprise the population of proteins.

21. A method for generating a subset of biomolecules from a biological sample for mass spectrometry, comprising:

providing the biological sample to the automated system of any one of claims 1-20, wherein the automated system contacts the biological sample with a plurality of particles to generate biomolecule coronas, wherein the automated system processes the biomolecule coronas to generate the subset of biomolecules, and wherein a dynamic range of the subset of biomolecules is compressed relative to a dynamic range of biomolecules present in the biological sample.