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System and method for identifying, selecting and purifying particles

Abstract

A method for purifying particles generates charged particles from a sample, measures at least at least one of masses, charge magnitudes and mobilities of the generated charged particles, and selectively passes to a particle collection target each of the measured charged particles having at least one of (a) a measured mass equal to a selected mass or within a selected range of particle masses, (b) a measured charge magnitude equal to a selected charge magnitude or within a selected range of charge magnitudes, (c) a mass-to-charge ratio equal to a selected mass-to-charge ratio or within a selected range of mass-to-charge ratios, and (d) a measured mobility equal to a selected mobility or within a selected range of mobilities. In some embodiments, the collected particles may be harvested and amplified.

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Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS (1) This patent application is a U.S. national stage entry of PCT Application No. PCT/US2020/054975, filed Oct. 9, 2020, which claims the benefit of and priority to U.S. Provisional Patent Application Ser. No. 62/913,460, filed Oct. 10, 2019, to U.S. Provisional Patent Application Ser. No. 62/949,559, filed Dec. 18, 2019, and to U.S. Provisional Patent Application Ser. No. 62/972,403, filed Feb. 10, 2020, the disclosures of which are all expressly incorporated herein by reference in their entireties.

TECHNICAL FIELD
(1) The present disclosure relates generally to instruments and methods for identifying, selecting and purifying particles, and more specifically to instruments and methods for identifying, selecting and purifying particles based on one or more molecular characteristics.
BACKGROUND
(2) Spectrometry instruments provide for the identification of chemical components of a substance by measuring one or more molecular characteristics of the substance. Some such instruments are

configured to analyze the substance in solution and others are configured to analyze charged particles of the substance in a gas phase. Molecular information produced by many such charged particle measuring instruments is limited in the number and types of measurable molecular characteristics. Purification of particles with such instruments is therefore likewise limited.

SUMMARY

(3) The present disclosure may comprise one or more of the features recited in the attached claims, and/or one or more of the following features and combinations thereof. In one aspect, a particle purification device may comprise an ion generator configured to generate charged particles from a sample, an ion processing region configured to receive the charged particles generated by the ion generator and to measure at least one of masses and charge magnitudes of the generated charged particles, a particle collection target, means for selectively passing charged particles exiting the ion processing region to the particle collection target, a processor, and a memory having instructions stored therein executable by the processor to cause the processor to control the means for selectively passing charged particles to pass to the particle collection target each of the measured charged particles having at least one of (a) a measured mass equal to a selected mass or within a selected range of particle masses, (b) a measured charge magnitude equal to a selected charge magnitude or within a selected range of charge magnitudes, and (c) a mass-to-charge ratio equal to a selected mass-to-charge ratio or within a selected range of mass-to-charge ratios.

(4) In another aspect, a method for purifying particles may comprise generating charged particles from a sample, measuring at least at least one of masses and charge magnitudes of the generated charged particles, and selectively passing to a particle collection target each of the measured charged particles having at least one of (a) a measured mass equal to a selected mass or within a selected range of particle masses, (b) a measured charge magnitude equal to a selected charge magnitude or within a selected range of charge magnitudes, and (c) a mass-to-charge ratio equal to a selected mass-to-charge ratio or within a selected range of mass-to-charge ratios.

(5) In yet another aspect, a method for purifying particles may comprise generating charged particles from a sample, measuring charge magnitudes of the generated charged particles, and selectively passing to a particle collection target each of the measured charged particles having a measured charge magnitude equal to a selected charge magnitude or within a selected range of charge magnitudes.

(6) In still another aspect, a method for purifying particles may comprise generating charged particles from a sample, measuring masses of the generated charged particles, and selectively passing to a particle collection target each of the measured charged particles having a measured mass equal to a selected mass or within a selected range of particle masses.

(7) In a further aspect, a method for purifying particles may comprise generating charged particles from a sample, measuring masses and charge magnitudes of the generated charged particles, computing mass-to-charge ratios of the measured charged particles based on the measured masses and charge magnitudes, and selectively passing to a particle collection target each of the measured charged particles having a computed mass-to-charge ratio equal to a selected mass-to-charge ratio or within a selected range of mass-to-charge ratios.

(8) In yet a further aspect, a method for purifying particles may comprise generating charged particles from a sample, measuring at least one of masses, charge magnitudes and mobilities of the generated charged particles, and selectively passing to a particle collection target each of the measured charged particles having at least one of (a) a measured mass equal to a selected mass or within a selected range of particle masses, (b) a measured charge magnitude equal to a selected charge magnitude or within a selected range of charge magnitudes, (c) a mass-to-charge ratio equal to a selected mass-to-charge ratio or within a selected range of mass-to-charge ratios, and (d) a measured mobility equal to a selected mobility or within a selected range of mobilities.

(9) In still a further aspect, a method for purifying particles may comprise generating charged particles from a sample, measuring mobilities of the generated charged particles, and selectively

passing to a particle collection target each of the measured charged particles having a measured mobility equal to a selected mobility or within a selected range of mobilities.
(10) In yet a further aspect, a method for measuring particles in an extracellular vesicle preparation may comprise generating ions from the extracellular vesicle preparation, and measuring mass and charge of at least a subset of the generated ions using a charge detection mass spectrometer.
(11) In still another aspect, a method for measuring exosomes in a sample preparation may comprise generating ions from the sample preparation, measuring mass and charge of at least some of the generated ions using a charge detection mass spectrometer, and identifying from the measured masses of the at least some of the generated ions a subset of the measured ions that are exosome ions.

Description

BRIEF DESCRIPTION OF THE DRAWINGS
(1) FIG. **1** is a simplified diagram of an instrument and process for purifying particles.
(2) FIG. **2** is a simplified flowchart of an embodiment of a process for controlling the instrument of FIG. **1** to generate and measure charged particles, and to generate a resulting spectrum from which a subpopulation of the charged particles may be identified or selected for purification.
(3) FIG. **3** is a simplified flowchart of an embodiment of a process for controlling the instrument of FIG. **1** to purify particles by generating, measuring and filtering charged particles, and for collecting the purified particles.
(4) FIG. **4**A is a scatter plot of particle charge vs. mass produced from a sample of urinary exomes by an embodiment of the instrument of FIG. **1** in which the ion processing region is implemented in the form of a charge detection mass spectrometer.
(5) FIG. **4**B is the plot of FIG. **4**A on which is superimposed an example selection by the instrument of FIG. **1** of a subpopulation of particles for purification, wherein the selected subpopulation is defined by a specified range of particle mass values.
(6) FIG. **4**C is the plot of FIG. **4**A on which is superimposed another example selection of a subpopulation of particles for purification, wherein the selected subpopulation is defined by a specified range of particle charge values.
(7) FIG. **4**D is the plot of FIG. **4**A on which is superimposed yet another example selection of a subpopulation of particles for purification, wherein the selected subpopulation is defined by a specified range of particle charge values and a specified range of particle mass values.
(8) FIG. **4**E is the plot of FIG. **4**A on which is superimposed still another example selection of a subpopulation of particles for purification, wherein the selected subpopulation is defined by a specified range of particle mass-to-charge ratio values.
(9) FIG. **4**F is the plot of FIG. **4**A on which is superimposed a further example selection of a subpopulation of particles for purification, wherein the selected subpopulation is defined by a specified range of particle mass-to-charge ratio values and a specified range of particle mass values.
(10) FIG. **4**G is the plot of FIG. **4**A on which is superimposed yet a further example selection of a subpopulation of particles for purification, wherein the selected subpopulation is defined by a specified range of particle mass-to-charge ratio values and a specified range of particle charge values.
(11) FIG. **4**H is the plot of FIG. **4**A on which is superimposed still a further example selection of a subpopulation of particles for purification, wherein the selected subpopulation is defined by a specified range of particle mass-to-charge ratio values, a specified range of particle mass values and a specified range of particle charge values.
(12) FIG. **5** is a simplified flowchart of an embodiment of another process for controlling the

instrument of FIG. **1** to identify, collect and/or purify populations and/or sub-populations of specified types of charged particles.
(13) FIG. **6**A is a scatter plot of particle charge vs. mass produced from a sample of exosome-enriched bovine milk by an embodiment of the instrument of FIG. **1** and using the process illustrated in FIG. **5**, wherein the ion processing region of the instrument is implemented in the form of a charge detection mass spectrometer.
(14) FIG. **6**B is the scatter plot of FIG. **6**A upon which is overlaid a number of boundaries demonstrating processing of the plotted data into various sub-populations of the charged particles.
DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENTS
(15) For the purposes of promoting an understanding of the principles of this disclosure, reference will now be made to a number of illustrative embodiments shown in the attached drawings and specific language will be used to describe the same.
(16) This disclosure relates to apparatuses and techniques for identifying and/or purifying particles based on one or more molecular characteristics, examples of which may include, but are not limited to, mass, charge, mass-to-charge ratio, mobility, and the like. For purposes of this document, the terms “charged particle” and “ion” may be used interchangeably, and both terms are intended to refer to any particle having a net positive or negative charge. The terms “purify” and “purification” are intended to refer to the identification and extraction, i.e., separation, of a subpopulation of charged particles, generated from a sample, based on one or more molecular characteristics.
(17) Referring now to FIG. **1**, a diagram is shown of an instrument **10** for purifying particles. FIG. **1** further depicts an example process **12** for collecting and, in some embodiments, processing the collected, purified particles. In the illustrated embodiment, the instrument **10** illustratively includes an ion source region **14** having an outlet coupled to an inlet of a charged particle processing region **16**. An outlet of the charged particle processing region **16** is coupled to an inlet of a charged particle deflector (CPD) or steering device (CPSD) **18**. In some embodiments, the instrument **10** may further optionally include a conventional ion trap (IT) **20** having an inlet coupled to an outlet of the charged particle deflector or steering device **18**, and an outlet opposite the inlet, as illustrated in FIG. **1** by dashed-line representation. In such embodiments, the outlet of the ion trap **20** defines a charged particle outlet of the instrument **10**. In other embodiments in which the ion trap **20** is omitted, the outlet of the instrument **10** is the outlet of the charged particle deflector or steering device **18**.
(18) The ion source region **14** illustratively includes an ion generator **22** configured to generate ions, i.e., charged particles, from a sample **24**. The ion generator **22** is illustratively implemented in the form of any conventional device or apparatus for generating ions from a sample. As one illustrative example, which should not be considered to be limiting in any way, the ion generator **22** may be or include a conventional electrospray ionization (ESI) source, a matrix-assisted laser desorption ionization (MALDI) source or other conventional ion generator configured to generate ions from the sample **24**. The sample **24** from which the ions are generated may be any biological or other material. In some embodiments, the sample **24** may be dissolved, dispersed or otherwise carried in solution, although in other embodiments the sample may not be in or part of a solution.
(19) In the illustrated embodiment, a voltage source VS1 is electrically connected to a processor **26** via a number, F, of signal paths, where F may be any positive integer, and is further electrically connected to the ion source region **14** via a number, G, of signal paths, where G may likewise be any positive integer. In some embodiments, the voltage source VS1 may be implemented in the form of a single voltage source, and in other embodiments the voltage source VS1 may include any number of separate voltage sources. In some embodiments, the voltage source VS1 may be configured or controlled to produce and supply one or more time-invariant (i.e., DC) voltages of selectable magnitude. Alternatively or additionally, the voltage source VS1 may be configured or controlled to produce and supply one or more switchable time-invariant voltages, i.e., one or more switchable DC voltages. Alternatively or additionally, the voltage source VS1 may be configured or

controllable to produce and supply one or more time-varying signals of selectable shape, duty cycle, peak magnitude and/or frequency.

(20) The processor **26** is illustratively conventional and may include a single processing circuit or multiple processing circuits. The processor **26** illustratively includes or is coupled to a memory **28** having instructions stored therein which, when executed by the processor **26**, cause the processor **26** to control the voltage source VS1 to produce one or more output voltages for selectively controlling operation of the ion generator **22**. In some embodiments, the processor **26** may be implemented in the form of one or more conventional microprocessors or controllers, and in such embodiments the memory **28** may be implemented in the form of one or more conventional memory units having stored therein the instructions in a form of one or more microprocessor-executable instructions or instruction sets. In other embodiments, the processor **26** may be alternatively or additionally implemented in the form of a field programmable gate array (FPGA) or similar circuitry, and in such embodiments the memory **28** may be implemented in the form of programmable logic blocks contained in and/or outside of the FPGA within which the instructions may be programmed and stored. In still other embodiments, the processor **26** and/or memory **28** may be implemented in the form of one or more application specific integrated circuits (ASICs). Those skilled in the art will recognize other forms in which the processor **26** and/or the memory **28** may be implemented, and it will be understood that any such other forms of implementation are contemplated by, and are intended to fall within, this disclosure. In some alternative embodiments, the voltage source VS1 may itself be programmable to selectively produce one or more constant and/or time-varying output voltages.

(21) In the illustrated embodiment, the voltage source VS1 is illustratively configured to be responsive to control signals produced by the processor **26** to produce one or more voltages to cause the ion generator **22** to generate ions from the sample **24**. In some embodiments, the sample **24** is positioned within the ion source region **14**, as illustrated in FIG. **1**, and in other embodiments the sample **24** may be positioned outside of the ion source region **14**. In one example embodiment, which should not be considered to be limiting any way, the sample **24** is provided in the form of a solution and the ion generator **22** is a conventional electrospray ionization (ESI) source configured to be responsive to one or more voltages supplied by VS1 to generate ions from the sample **24** in the form of a fine mist of charged droplets. It will be understood that ESI and MALDI, as described hereinabove, represent only two examples of myriad conventional ion generators, and that the ion generator **22** may be or include any such conventional device or apparatus for generating ions from a sample whether or not in solution.

(22) The ion processing region **16** illustratively includes a number, M, of ion processing stages or devices **16**.sub.1-**16**.sub.M, where M may be any positive integer. The one or more ion processing devices **16**.sub.1-**16**.sub.M is/are illustratively operable to process charged particles, generated in the ion source region **14** and passed into the ion processing region **16**, in a manner which measures one or more molecular characteristics of the charged particles, in a manner which filters the charged particles based on one or more molecular characteristics so as to provide a subpopulation or subset of the charged particles having at least one specified molecular characteristic and/or in a manner which dissociates, e.g., fragments, charged particles.

(23) In the illustrated embodiment, a voltage source VS2 is electrically connected to the processor **26** via a number, H, of signal paths, where H may be any positive integer, and is further electrically connected to the ion processing region **16** via a number, J, of signal paths, where J may likewise be any positive integer. In some embodiments, the voltage source VS2 may be implemented in the form of a single voltage source, and in other embodiments the voltage source VS2 may include any number of separate voltage sources. In some embodiments, the voltage source VS2 may be configured or controlled to produce and supply one or more time-invariant (i.e., DC) voltages of selectable magnitude. Alternatively or additionally, the voltage source VS2 may be configured or controlled to produce and supply one or more switchable time-invariant voltages, i.e., one or more

switchable DC voltages. Alternatively or additionally, the voltage source VS2 may be configured or controllable to produce and supply one or more time-varying signals of selectable shape, duty cycle, peak magnitude and/or frequency. Generally, one or more outputs of the voltage source VS2 is/are illustratively coupled to each of the one or more ion processing devices **16**.sub.1-**16**.sub.M in the ion processing region **16**, and it will be understood that the number of such outputs and/or the type(s) of voltages produced thereat will depend on the number and/or type of ion processing device(s) making up the one or more ion processing devices **16**.sub.1-**16**.sub.M. In any case, the memory **28** illustratively has instructions stored therein which, when executed by the processor **26**, cause the processor **26** to control the voltage source VS2 to produce one or more output voltages for selectively controlling operation of the one or more ion processing devices **16**.sub.1-**16**.sub.M in the ion processing region **16**.

(24) Examples of the ion processing device(s) **16**.sub.1-**16**.sub.M may include, but are not limited to, in any order and/or combination, one or more devices and/or instruments for separating, collecting and/or filtering charged particles according to one or more molecular characteristics, and/or one or more devices and/or instruments for dissociating, e.g., fragmenting, charged particles. Examples of the one or more devices and/or instruments for separating charged particles according to one or more molecular characteristics may include, but are not limited to, one or more mass spectrometers or mass analyzers, one or more ion mobility spectrometers, one or more gas chromatographs, and the like. Examples of a mass spectrometer, in embodiments of the ion processing device(s) **16**.sub.1-**16**.sub.M which include one or more thereof, include, but are not limited to, any mass spectrometer operable to measure at least ion mass-to-charge ratio and to pass measured ions from the mass spectrometer to the charged particle deflector or steering device **18**. In such embodiments in which the mass spectrometer is operable to measure only ion mass-to-charge ratio, the mass spectrometer may be conventional. In other such embodiments, the mass spectrometer may illustratively be provided in the form of a mass spectrometer configured to measure both mass and charge magnitudes of charged particles generated in the ion source region **14** and passed into the ion processing region **16**. In one example of this embodiment, which should not be considered to be limiting in any way, the mass spectrometer may illustratively be implemented in the form of a charge detection mass spectrometer (CDMS), wherein the ion processing device(s) **16**.sub.1-**16**.sub.M includes a conventional through-ion mass spectrometer or mass analyzer and one or more corresponding CDMS charge detectors. In some embodiments, the one or more CDMS charge detectors may be provided in the form of one or more electrostatic linear ion traps (ELITs), and in other embodiments the one or more CDMS charge detectors may be provided in the form of at least one orbitrap. In some embodiments, the CDMS detector(s) may include at least one ELIT and at least one orbitrap. CDMS is illustratively a single-particle technique typically operable to measure mass and charge magnitude values of single ions, although some CDMS detectors have been designed and/or operated to measure mass and charge of more than one charged particle at a time. Some examples of CDMS instruments and/or techniques, and of CDMS charge detectors and/or techniques, which may be implemented in a mass spectrometer as, or as part of, the ion processing device(s) **16**.sub.1-**16**.sub.M of FIG. **1**, are disclosed in co-pending International Application Nos. PCT/US2019/013251, PCT/US2019/013274, PCT/US2019/013277, PCT/US2019/013278, PCT/US2019/013280, PCT/US2019/013283, PCT/US2019/013284 and PCT/US2019/013285, all filed Jan. 11, 2019, and the disclosures of which are all incorporated herein by reference in their entireties.

(25) In other embodiments which include a mass spectrometer configured to measure both mass and charge magnitudes of charged particles generated in the ion source region **14** and passed into the ion processing region **16**, such a mass spectrometer may be provided in the form of a conventional mass analyzer (e.g., quadrupole mass analyzer or the like) configured to selectively pass therethrough ions of a specified mass-to-charge ratio or ions within a specified range of mass-to-charge ratios, or in the form of a through-ion mass spectrometer likewise configured, followed in

either case by an electric field-free drift region including a charge detector array (CDA) configured to measure charge magnitudes or charge states of charged particles exiting the mass analyzer or mass spectrometer. Some example configurations of such a mass spectrometer which may be implemented as, or as part of, the ion processing device(s) **16**.sub.1-**16**.sub.M of FIG. **1**, are disclosed in co-pending U.S. Patent Application Ser. No. 62/949,555 and/or in co-pending U.S. Patent Application Ser. No. 62/949,554, both filed Dec. 18, 2019, and the disclosures of which are both incorporated herein by reference in their entireties.

(26) In some embodiments in which the ion processing device(s) **16**.sub.1-**16**.sub.M include a mass spectrometer configured to measure both mass and charge of charged particles supplied by the ion source region **14** as described above, the associated charge detector(s) or charge detector array is electrically connected to input(s) of each of a number, N, of charge detection amplifiers CA, and output(s) of the number, N, of charge detection amplifiers CA is/are electrically connected to the processor **26** as shown in FIG. **1**, where N may be any positive integer. The charge amplifier(s) CA is/are each illustratively conventional and responsive to charges induced by charged particles on one or more respective charge detectors to produce corresponding charge detection signals at the output thereof, and to supply the charge detection signals to the processor **26**.

(27) In any embodiments which includes one or more conventional mass spectrometers, such mass spectrometers may be provided in the form of one or any combination of a time-of-flight (TOF) mass spectrometer, a reflectron mass spectrometer, a Fourier transform ion cyclotron resonance (FTICR) mass spectrometer, a quadrupole mass spectrometer, a triple quadrupole mass spectrometer, a magnetic sector mass spectrometer, and oribitrap mass spectrometer or the like.

(28) Examples of the ion mobility spectrometer, in embodiments of the ion processing device(s) **16**.sub.1-**16**.sub.M which include one or more thereof, include, but are not limited to, a single-tube linear ion mobility spectrometer, a multiple-tube linear ion mobility spectrometer, a circular-tube ion mobility spectrometer, or the like. Examples of one or more devices and/or instruments for collecting charged particles, in embodiments of the ion processing device(s) **16**.sub.1-**16**.sub.M which include one or more thereof, include, but are not limited to, a quadrupole ion trap, a hexapole ion trap, an ion funnel, or the like. Examples of one or more devices and/or instruments for filtering charged particles, in embodiments of the ion processing device(s) **16**.sub.1-**16**.sub.M which include one or more thereof, include, but are not limited to, one or more devices or instruments for filtering charged particles according to mass-to-charge ratio, one or more devices or instruments for filtering charged particles according to particle mobility, and the like. Examples of one or more devices and/or instruments for dissociating charged particles, in embodiments of the ion processing device(s) **16**.sub.1-**16**.sub.M which include one or more thereof, include, but are not limited to, one or more devices or instruments for dissociating charge particles by collision-induced dissociation (CID), surface-induced dissociation (SID), electron capture dissociation (ECD) and/or photo-induced dissociation (PID), or the like.

(29) It will be understood that the ion processing device(s) **16**.sub.1-**16**.sub.M may include one or any combination, in any order, of any of the above-described instruments, devices or stages, and that some embodiments may include multiple adjacent or spaced-apart ones of any such instruments, devices or stages. As one non-limiting example implementation of the instrument **10** illustrated in FIG. **1**, the ion processing device(s) **16**.sub.1-**16**.sub.M may include a single CDMS configured to measure charged particle mass and charge as described above, and to sequentially supply the measured charged particles to the charged particle deflector or charged particle steering device **18**. As other non-limiting example implementation of the instrument **10** illustrated in FIG. **1**, the ion processing device(s) **16**.sub.1-**16**.sub.M may include a single mass spectrometer including a charge detector array configured, as briefly described above, to measure charged particle mass and charge, and to supply the measured charged particles to the charged particle deflector or charged particle steering device **18**. In either of these examples, the processor **26** is illustratively programmed to control the voltage source VS2 to cause the mass spectrometer instrument to

measure charged particle mass and charge. As yet another non-limiting example implementation of the instrument **10** illustrated in FIG. **1**, the ion processing device(s) **16**.sub.1-**16**.sub.M may include a mass-to-charge ratio filter, e.g., in the form of a quadrupole mass analyzer. In this example, the processor **26** is illustratively programmed to control the voltage source VS2 to cause the mass-to-charge ratio filter to selectively pass therethrough to the charged particle deflector or charged particle steering device **18** only ions having a specified mass-to-charge ratio or only ions having mass-to-charge ratios within a specified range of mass-to-charge ratios. In some such embodiments, the ion processing device(s) **16**.sub.1-**16**.sub.M may further include a mass spectrometer disposed between the mass-to-charge ratio filter and the charged particle deflector or charged particle steering device **18**, and configured to measure mass and charge of charged particles exiting the mass-to-charge ratio filter. In some such embodiments, the ion processing device(s) **16**.sub.1-**16**.sub.M may further still include a particle dissociation stage or device disposed between the mass-to-charge ratio filter and the mass spectrometer, and configured to dissociate charged particles exiting the mass-to-charge ratio filter. In such examples, the processor **26** is illustratively programmed to control the voltage source VS2 to operate the example device(s) and/or stage(s) in a conventional manner. Other examples and example combinations of the ion processing device(s) **16**.sub.1-**16**.sub.M will occur to those skilled in the art, and it will be understood that all such examples and example combinations are intended to fall within the scope of this disclosure. In any case, the processor **26** is configured, e.g., programmed, to control the voltage source VS2 to produce one or more voltages for controlling the ion processing device(s) **16**.sub.1-**16**.sub.M to operate in a conventional manner and/or as described herein.

(30) In embodiments which include it, the charged particle deflector or charged particle steering device **18** is illustratively configured to selectively pass through the outlet thereof only charged particles having one or more specified molecular characteristics or having one or more molecular characteristics within a range of molecular characteristics. The remaining charged particles are, in the case of a charged particle deflector blocked, e.g., by directing such charged particles into an electrically conductive structure, or, in the case of a charged particle steering device, directed away from the outlet from which charged particles are collected, e.g., through another passageway or outlet from which charged particles are not collected or stored.

(31) In one example embodiment, the charged particle deflector or steering device **18** may be implemented in the form of a conventional single inlet, single outlet charge deflector configured and controllable to selectively pass or block passage of ions therethrough. In another example embodiment, the charged particle deflector or steering device **18** may be implemented in the form of a conventional single inlet, multiple-outlet charge steering device configured and controllable to selectively steer ions entering the single inlet through the one of multiple different ion outlets from which purified charged particles are collected. In either case, another voltage source VS3 is electrically connected to the processor **26** via a number, K, of signal paths, where K may be any positive integer, and is further electrically connected to the charged particle deflector or steering device **18** via a number, L, of signal paths, where L may likewise be any positive integer. In some embodiments, the voltage source VS3 may be implemented in the form of a single voltage source, and in other embodiments the voltage source VS3 may include any number of separate voltage sources. In some embodiments, the voltage source VS3 may be configured or controlled to produce and supply one or more time-invariant (i.e., DC) voltages of selectable magnitude. Alternatively or additionally, the voltage source VS3 may be configured or controlled to produce and supply one or more switchable time-invariant voltages, i.e., one or more switchable DC voltages. Alternatively or additionally, the voltage source VS3 may be configured or controllable to produce and supply one or more time-varying signals of selectable shape, duty cycle, peak magnitude and/or frequency. Generally, one or more outputs of the voltage source VS3 is/are illustratively coupled to the charged particle deflector or steering device **18**, and it will be understood that the number of such outputs and/or the type(s) of voltages produced thereat will depend on the type of charged particle

deflector or steering device **18** implemented. In any case, the memory **28** illustratively has instructions stored therein which, when executed by the processor **26**, cause the processor **26** to control the voltage source VS3 to produce one or more output voltages for selectively controlling operation of the charged particle deflector or steering device **18**.

(32) In some embodiments in which the charged particle deflector or steering device **18** is implemented in the form of a single inlet, single outlet charge deflector, the processor **26** is illustratively operable to deflect a charged particle entering the inlet thereof into an electrically conductive structure, e.g., an electrically conductive plate, tube or rod, by controlling the voltage source VS3 to create an electric field E of sufficient magnitude to divert and accelerate the charged particle P into the electrically conductive structure. The processor **26** is illustratively operable, in such embodiments, to pass a charged particle entering the inlet though the outlet thereof by controlling the voltage source VS3 to create conditions within the deflector, e.g., small or no electric field, which allows passage of the charged particle therethrough. In some embodiments in which the charged particle deflector or steering device **18** is implemented in the form of a single inlet, multiple outlet charge deflector, the processor **26** is illustratively operable to steer a charged particle entering the inlet thereof into a passageway and/or through an outlet from which purified charged particles are not collected by controlling the voltage source VS3 to create an electric field E of sufficient magnitude to steer the charged particle P through such an outlet. The processor **26** is illustratively operable, in such embodiments, to pass a charged particle entering the inlet though an outlet thereof from which purified charged particles are collected by controlling the voltage source VS3 to create conditions within the charge steering device which allows passage of the charged particle through the respective outlet. A number of alternate embodiments of the charged particle deflector or steering device **18** are illustrated and described in U.S. Patent Application No. 62/52/949,555, filed Dec. 18, 2019 and which has been incorporated herein by reference, although it will be understood that such embodiments are provided only by way of example. Other charged particle deflection and/or steering instruments or devices will occur to those skilled in the art, and it will be understood that any other such charged particle deflection and/or steering instruments or devices are intended to fall within the scope of this disclosure.

(33) In some embodiments, as briefly described above and as illustrated in FIG. **1** by dashed-line representation, an ion trap **20** may be coupled to the charged particle deflector or steering device **18**. In such embodiments, yet another voltage source VS4 is electrically connected to the processor **26** via a number, P, of signal paths, where P may be any positive integer, and is further electrically connected to the ion trap **20** a number, Q, of signal paths, where Q may likewise be any positive integer. In some embodiments, the voltage source VS4 may be implemented in the form of a single voltage source, and in other embodiments the voltage source VS4 may include any number of separate voltage sources. In some embodiments, the voltage source VS4 may be configured or controlled to produce and supply one or more time-invariant (i.e., DC) voltages of selectable magnitude. Alternatively or additionally, the voltage source VS4 may be configured or controlled to produce and supply one or more switchable time-invariant voltages, i.e., one or more switchable DC voltages. Alternatively or additionally, the voltage source VS4 may be configured or controllable to produce and supply one or more time-varying signals of selectable shape, duty cycle, peak magnitude and/or frequency. One or more outputs of the voltage source VS4 is/are illustratively coupled to the ion trap **20**, and the memory **28** illustratively has instructions stored therein which, when executed by the processor **26**, cause the processor **26** to control the voltage source VS4 to produce one or more output voltages for controlling the ion trap **20** to selectively trap and store charged particles therein and to produce one or more output voltages for controlling the ion trap **20** to selectively release and accelerate the trapped particles therefrom.

(34) The processor **26** is further illustratively coupled via a number, R, of signal paths to one or more peripheral devices **30** (PD), where R may be any positive integer. The one or more peripheral devices **30** may include one or more devices for providing signal input(s) to the processor **26**

and/or one or more devices to which the processor **26** provides signal output(s). In some embodiments, the peripheral devices **30** include at least one of a conventional display monitor, a printer and/or other output device, and in such embodiments the memory **28** has instructions stored therein which, when executed by the processor **26**, cause the processor **26** to control one or more such output peripheral devices **30** to display and/or record analyses of the operation of the instrument **10** including, for example, but not limited to, particle spectral information measured by the instrument **10**.

(35) As briefly described above, the instrument **10** is illustratively operable, illustratively under the control of the processor **26** via control of the voltage sources VS1, VS2, VS3 and in some embodiments VS4, to purify charged particles generated by the ion generator **22** by selectively passing therethrough only a subpopulation or subset of the generated charged particles having one or more molecular characteristics or having one or more molecular characteristics within a range of one or more molecular characteristics. In some embodiments, for example, the subpopulation or subset may illustratively include only charged particles of a specified mass or having masses within a specified range of masses. In other embodiments, the subpopulation or subset may illustratively include only charged particles of a specified charge or having masses within a specified range of charge magnitudes or charge states. In still other embodiments, the subpopulation or subset may illustratively include only charged particles of a specified mass along a specified charge or range of charge magnitudes or charge states, or particles having mass values within a specified range of mass values along with a specified charge or range of charge magnitudes or charge states. In yet other embodiments, the subpopulation or subset may illustratively include only charged particles of a specified mass-to-charge ratio or having mass-to-charge ratio values within a specified range of mass-to-charge ratio values. In some such embodiments, the subpopulation or subset may further include only such charged particles that also have a specified mass value or that also have mass values within a specified range of mass values and/or only charged particles that also have a specified charge magnitude or charge state value or that also have charge magnitudes or charge states that are within a specified range of charge magnitude values or charge state values. In still further embodiments, the subpopulation or subset may illustratively include only charged particles of a specified mobility or only charged particles having mobilities within a specified range of mobility values. In some such embodiments, the sub-population or subset may be further restricted in a specified charged particle mass value or mass value range, in a specified charge magnitude or charge state or specified range thereof, in a specified mass-to-charge ratio or range thereof, or in any combination just described. Those skilled in the art will recognize that the number and type(s) of the charged particle instruments **16**.sub.1-**16**.sub.M implemented in any particular embodiment of the instrument **10** will depend on the particular subpopulation or subset of charged particles sought for purification, and that various different types and combinations of the charged particle instruments **16**.sub.1-**16**.sub.M described above may be used to collect the desired subpopulation or subset. Moreover, those skilled in the art will recognize other molecular characteristic subpopulations or subsets and/or combinations thereof that may be sought for purification, and it will be understood that such other molecular characteristic subpopulations or subsets and/or combinations, as well as various instruments and instrument combinations for collecting the same, are intended to fall within the scope of this disclosure.

(36) Also depicted in FIG. **1** is a simplified process **12** for collecting and, in some embodiments, processing the collected, purified particles. In some embodiments, for example, the subpopulation or subset of charged particles exiting the instrument **10** are collected on a surface **40**A of a particle collection target **40** via particle deposition, e.g., via low energy deposition, or other conventional particle collection technique. The particle collection target **40**, or at least the surface **40**A thereof, is illustratively a non-reactive or inert material so as not to bond or otherwise react with the purified charged particles exiting the instrument **10**. In some embodiments, the particle collection surface **40**A of the particle collection target **40** may be viscous or oleaginous or otherwise configured or

constructed such that the purified charged particles exiting the instrument **10** may be effectively collected thereon over a period of time. In other embodiments in which the ion trap **20** is included, purified charged particles exiting the instrument **10** may be trapped and collected within the ion trap **20** over a period of time, and then released in bulk from the ion trap **20** and onto the surface **40**A of the particle collection target **40**. In any case, the particle collection surface **40**A of the particle collection target **40** is illustratively configured to not only collect purified charged particles exiting the instrument **10** but to also provide for harvesting the collected purified particles therefrom. In some embodiments, for example, the purified particles collected on the surface **40**A of the particle collection target **40** may be harvested by rinsing the surface **40**A with a liquid solution **45** dispensed from a solution source **42** and directing the resulting combination **46** of the solution **45** carrying the purified particles into a suitable container **44**. Those skilled in the art will recognize other techniques, instruments, devices and the like for harvesting the purified particles collected on the collection surface **40**A of the particle collection target **40**, and it will be understood that any such other techniques, instrument, devices and the like are intended to fall within the scope of this disclosure.

(37) In some embodiments, the harvested collection of purified particles may be amplified, i.e., duplicated or otherwise multiplied, in a conventional particle amplifier or particle amplification process **48**. In implementations in which the purified particles are or include DNA, for example, the particle amplifier or amplification process **48** may illustratively take the form of a conventional polymerase chain reaction (PCR) instrument or process to amplify or duplicate the particles across several orders of magnitude, e.g., thousands or millions of copies. Those skilled in the art will recognize other instruments and/or processes for amplifying the harvested, purified particles, whether they are or include DNA and/or other molecular components, and it will be understood that any such other particle amplification instruments and/or processes are intended to fall within the scope of this disclosure.

(38) In some cases, it may be desirable to observe a full, or at least a partial, molecular characteristic spectrum of the sample **24** in order to identify, or to facilitate identification of, a subpopulation or subset thereof for purification. In this regard, a simplified flowchart is shown in FIG. **2** depicting a process **100** for operating the instrument **10** of FIG. **1** to measure one or more molecular characteristics of charged particles generated from a sample **24** and to process such measurements to produce a multi-dimensional, e.g., 2 or more, molecular characteristic spectrum. At least some of the steps of the process **100** are stored in the memory **28** in the form of instructions executable by the processor **26** to carry out the measurements, analysis and visualization of the spectrum. The process **100** begins at step **102** where the processor **26** is illustratively operable to control the voltage source VS1 to cause the ion generator **22** to generate charged particles from the sample **24**, and to supply the generated charged particles to the ion processing region **16**. Thereafter at step **104**, the processor **26** is operable to control the voltage source VS2 to cause the one or more instruments or devices of the ion processing region **16** to measure two or more molecular characteristics.

(39) In some embodiments, as described above with respect to FIG. **1**, the ion processing region **16** may include or be implemented in the form of a mass spectrometer configured to measure particle mass and particle charge. In some such embodiments, for example, such a mass spectrometer may be implemented in the form of a charge detection mass spectrometer (CDMS), and in other embodiments, such a mass spectrometer may be implemented in the form of a mass analyzer, mass-to-charge filter or other instrument configured to measure mass-to-charge ratio (conventional MS) followed by a charge detector array (CDA), some examples of which are illustrated and disclosed in U.S. Patent Application Ser. No. 62/949,555, filed Dec. 18, 2019 and the disclosure of which has been incorporated herein by reference. In other embodiments, the ion processing region **16** may include or be implemented in the form of an ion mobility spectrometer (IMS) followed by such a charge detector array. In still other embodiments, the ion processing region **16** may include or be

implemented in the form of a combination of a mass spectrometer, an ion mobility spectrometer and a charged particle charge measurement instrument or device. In some such embodiments, for example, the ion processing region **16** may include an IMS followed by a CDMS or an IMS followed by a conventional MS followed by a CDA. In other such embodiments, as additional examples, the ion processing region **16** may include a conventional MS followed by an IMS followed by a CDA, a conventional MS followed by a CDA followed by an IMS, or a CDMS followed by an IMS. In these example embodiments of the ion processing region **16**, the processor **26** is illustratively operable at step **104** to control the voltage source VS2 to cause the spectrometer instrument(s) to measure the charge magnitudes or charge states of the generated charged particles and the mass and/or mobility values of the generated charged particles as illustrated in FIG. **2**.

(40) Following step **104**, the processor **26** is operable to process the measurements made at step **104** and generate a charged particle spectrum therefrom. As one illustrative example in which the sample **24** is a liquid solution of urinary exosomes and the ion processing region **16** is implemented in the form of a CDMS or conventional MS followed by a CDA, the processor **26** is illustratively operable at step **106** to generate a scatter plot of charged particle charge magnitude (in units of elementary charge e) vs. charged particle mass (in units of mega-Daltons MDa) as shown in FIG. **4**A.

(41) Following step **106**, the process **100** advances to step **108** where the spectrum produced at step **106** is analyzed, e.g., visually or automatically by the processor **26**, to determine a suitable subpopulation or subset of the particles to purify. The subpopulation or subset of particles may illustratively be selected based on one or any combination of particle mass, mass-to-charge ratio, charge (magnitude or charge state) or mobility value(s) or range(s).

(42) Referring now to FIG. **3**, a simplified flowchart is shown of a process **200** for purifying particles from the sample **24** using any of various embodiments of the instrument **10** illustrated in FIG. **1**. In some embodiments, the implementation of the instrument **10** used to carry out the process **100** illustrated in FIG. **2** may also be used following the process **100** to carry out the process **200** illustrated in FIG. **3**. In other embodiments, e.g., in which the molecular characteristic values and/or ranges for purification are known in advance, the process **100** illustrated in FIG. **2** may not be carried out and the configuration of the instrument **10** may be specifically selected to achieve or facilitate the desired purification. In any case, at least some steps of the process **200** are illustratively stored in the memory **28** in the form of instructions executable by the processor **26** to carry out purification of a selected subpopulation or subset of charged particles generated from the sample **24** illustrated in FIG. **1**. The process **200** begins at step **202** where the processor **26** is illustratively operable to control the voltage source VS1 to cause the ion generator **22** to generate charged particles from the sample **24**, and to supply the generated charged particles to the ion processing region **16**. Thereafter at step **204**, the processor **26** is operable to control the voltage source VS2 to cause the one or more instruments or devices of the ion processing region **16** to measure two or more molecular characteristics. Various combinations of instruments or devices may be implemented in the ion processing region **16** to measure any two or more molecular characteristics, and several examples of such instruments or devices and such one or more molecular characteristics are given above in the description of the process **100**. In these example embodiments of the ion processing region **16**, the processor **26** is illustratively operable at step **204** to control the voltage source VS2 to cause the spectrometer instrument(s) to measure the charge magnitudes or charge states of the generated charged particles and the mass and/or mobility values of the generated charged particles as illustrated by example in FIG. **3**, although it will be understood that at step **204** the ion processing region **16** may be alternatively implemented in different forms, i.e., with different instruments, and/or that the one or more molecular characteristics may be measurable molecular characteristics other than, or in addition to, particle mass, mass-to-charge ratio, mobility and charge (magnitude or charge state).

(43) Following step **204**, the process **200** advances to step **206** where the processor **26** is operable

to control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to pass through the charged particle outlet thereof, or through a specified one of multiple charged particle outlets thereof, only charged particles in a selected subpopulation or subset of the charged particles generated by the ion generator **22**. As described above, the subpopulation or subset of the charged particles generated by the ion generator **22** may be selected based on one or any combination of measured values of particle mass, mass-to-charge ratio, charge (magnitude or charge state) or mobility value(s) or range(s). With such measured values known by the processor **26** as the respective charged particles exit the ion processing region **16**, the processor **26** is operable to control the charged particle deflector or charged particle steering device **18**, e.g., via control of the voltage source VS3, to selectively pass therethrough for collection only those charged particles having the one or combination of measured molecular characteristic values defined by the selected subpopulation or subset of the charged particles generated by the ion generator **22**. Some example subpopulations or subsets of the spectrum of urinary exosomes illustrated FIG. **4**A will be described below with respect to FIGS. **4**B-**4**H, as well as some example configurations and implementations of the instrument **10** for purifying such subpopulations, for purposes of demonstrating operation of steps **204** and **206** of the process **200**.

(44) Following step **206**, the process **200** advances to step **208** where the charged particles exiting the charged particle deflector or charged particle steering device **18** through the sole outlet thereof, or through the selected one of multiple outlets thereof, are collected. In embodiments of the instrument **10** which include the ion trap **20**, step **208** illustratively includes control by the processor **26** of the voltage source VS4 to supply one or more voltages to the ion trap **20** to cause the ion trap **20** to collect and store therein such charged particles exiting the charged particle deflector or charged particle steering device **18** through the sole outlet thereof, or through the selected one of multiple outlets thereof. Following expiration of a collection time period in which the ion trap **20** is operable to collect and store the exiting charged particles therein, the processor **26** is further operable at step **208** to control the voltage source VS4 to supply one or more voltages to the ion trap **20** to cause the ion trap **20** to release and direct the stored ions toward and onto the collection surface **40**A of the collection target **40**. In embodiments of the instrument **10** which do not include the ion trap **20**, step **208** illustratively includes collecting on the collection surface **40**A of the collection target **40** charged particles as they exit the charged particle deflector or charged particle steering device **18**. Thereafter at step **210**, the purified particles collected on the collection surface **40**A of the particle collection target **40** are harvested, e.g., as described above with respect to FIG. **1**. In some embodiments, the process **200** includes another step **212** following step **210** in which the harvested particles are amplified, i.e., duplicated or multiplied, in a conventional manner as described above.

(45) Referring now to FIG. **5**, a simplified flowchart is shown of a process **500** for controlling any of the various embodiments of the instrument **10** of FIG. **1** to identify, collect and/or purify populations and/or sub-populations of specified types of charged particles purifying particles from the sample **24**. The process **500** begins at step **502** where a sample is provided in which particles of a specified type are present. The specified particles may be any particles, e.g., molecules, or collection thereof that are in or part of a cell, and/or that are transported between cells, and that have masses in or greater than the megadalton range. Example types of particles present in the sample, and for which the sample is selected and provided, may be or include, but are not limited to, exomes, endosomes, microvessicles generally, ectosomes, apoptotic bodies, retroviruses, exomeres, chylomicrons, DNA, RNA, proteins, fats, acids, carbohydrates, enzymes, viruses, bacteria, or the like. Examples of other samples and/or particles of interest present in samples, all of which are intended to fall within the scope of this disclosure, include, but are not limited to, any cell that emits an exosome or extracellular vesicle, any molecule or collection thereof that is encased in a bio-layer, e.g., a virus, any non-compartmentalized organelles grouped together but not bound by or in a bio-layer, any extracellular vesicle that has been altered in a manner that

results in a detectable mass shift, e.g., by adding one or more small molecules thereto, by adding a drug, such as a cancer drug, thereto or the like, that is or is part of any biological tissue(s), fluid(s), cell(s) and/or other biological material(s).

(46) In some embodiments, the sample provided at step **502**, in which particles of a specified type are present, may be the sample **24** depicted in FIG. **1** from which charged particles are generated for analysis by the instrument **10**. In some alternate embodiments, the process **500** may include step **504**, as shown by dashed-line configuration, at which the sample provided at step **502** is enriched for the specified particle type. Following step **504**, in embodiments which include it, the process **500** illustratively advances, in one embodiment, to step **506** where the process **100** illustrated in FIG. **2** is executed using the enriched sample **24**, i.e., the sample provided at step **502** and enriched at step **504** for the specified particle type. In embodiments which do not include step **504**, step **506** is executed following step **502** such that the process **100** illustrated in FIG. **2** is executed using the sample **24** in which particles of the specified type are present. In some embodiments, step **108** of the process **100**, in which a sub-population of the particle spectrum is identified and/or selected for purification, may include execution of one or more conventional statistical and/or modeling processes carried out on the data set of particles for the purpose of identifying and/or selecting one or more sub-populations of particles. One example such statistical process will be described below with respect to Example 8.

(47) In some embodiments, the process **500** ends after execution of step **506**. In some alternate embodiments, the process **500** advances from step **506** to step **508** where the process **200** illustrated in FIG. **3** is executed using the enriched sample **24** to purify particles of the specified type or one or more sub-populations thereof as identified at step **506**. In some alternate embodiments, the process **500** may advance directly to step **508** from step **504** in embodiments which include step **504**, or directly from step **502** in embodiments which do not include step **504**, as described above with respect to FIG. **3**.

(48) In some embodiments which include step **504**, the process(es) used to enrich the sample for the specified particle type may depend on the sample type and/or on the specified particle type, and will in any case be known to those skilled in the art. In such embodiments, the enriched sample resulting from step **504** will be the sample **24** depicted in FIG. **1** from which charged particles are generated for analysis by the instrument **10**. One example such process used to enrich exosomes from a sample of bovine milk, which should not be considered to be limiting in any way, is described below in Example 8. In other embodiments which include or which do not include step **504**, various configurations and/or implementations of the ion processing region **16** of the instrument **10** may be used to enrich, and/or to assist in enriching, the sample for the specified type of particles. For example, in some embodiments the sample may include unwanted particles known to exist in one or more ranges of particle mass, mass-to-charge ratio and/or mobility that is/are different from the range(s) of mass, mass-to-charge ratio and/or mobility of the particles in the sample of the specified type, and in such embodiments the ion processing region **16** may be variously configured, as described above, to filter out some or all such unwanted particles prior to executing step **506** and/or step **508**.

EXAMPLES

Example 1

(49) Referring now to FIG. **4**B, the plot of urinary exomes of FIG. **4**A is reproduced upon which is superimposed an example selection by the instrument of FIG. **1** of a subpopulation or subset **300** of particles for purification according to steps **204** and **206** of the process **200** illustrated in FIG. **3**. In this example, the selected subpopulation **300** is defined solely by a specified range of particle mass values between 20 and 30 MDa. In order for the processor **26** to control the voltage source VS3 at step **206** to cause the charged particle deflector or charged particle steering device **18** to pass therethrough to the particle target **40** only charged particles having particle masses within the specified particle mass range of 20-30 MDa, the particle measurement information produced by the

one or more instruments or devices of the ion processing region **16** must include particle mass information or particle measurement information from which particle mass can be determined by the processor **26** in advance of step **206**. In this example, as described above with respect to FIG. **4**A, the ion processing region **16** is illustratively implemented in the form of a CDMS or conventional MS followed by a CDA, either of which is configured to measure, at step **204**, particle mass directly or to determine particle mass from charged particle measurements taken by the instrument(s). It will be understood, however, that the ion processing region **16** may alternatively be or include any instrument or device or combination of instruments or devices configured to measure particle mass or configured to measure one or more characteristics or properties of the particles from which the particle mass can be determined or estimated. In any case, with the particle mass information determined at step **204**, the processor **26** is operable at step **206** to control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to pass a charged particle exiting the ion processing region **16** to the particle target **40** only if the mass of that particle is within the specified particle mass range of 20-30 MDa, and to otherwise control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to block passage of the particle to the target **40** or to steer the charged particle away from the target **40**.

Example 2

(50) Referring now to FIG. **4**C, the plot of urinary exomes of FIG. **4**A is again reproduced upon which is superimposed another example selection by the instrument of FIG. **1** of another subpopulation or subset **302** of particles for purification according to steps **204** and **206** of the process **200** illustrated in FIG. **3**. In this example, the selected subpopulation **302** is defined solely by a specified range of particle charge magnitude values between 750 and 900 e. In order for the processor **26** to control the voltage source VS3 at step **206** to cause the charged particle deflector or charged particle steering device **18** to pass therethrough to the particle target **40** only charged particles having particle charge values within the specified particle charge range of 750-900 e, the particle measurement information produced by the one or more instruments or devices of the ion processing region **16** must include particle charge information or particle measurement information from which particle charge can be determined by the processor **26** in advance of step **206**. In this example, as described above with respect to FIG. **4**A, the ion processing region **16** is illustratively implemented in the form of a CDMS or conventional MS followed by a CDA, either of which is configured to measure, at step **204**, particle charge directly or to determine particle charge from charged particle measurements taken by the instrument(s). It will be understood, however, that the ion processing region **16** may alternatively be or include any instrument or device or combination of instruments or devices configured to measure particle charge or configured to measure one or more characteristics or properties of the particles from which the particle charge can be determined or estimated. In any case, with the particle charge information determined at step **204**, the processor **26** is operable at step **206** to control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to pass a charged particle exiting the ion processing region **16** to the particle target **40** only if the magnitude of the charge that particle is within the specified particle charge magnitude range of 750-900 e, and to otherwise control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to block passage of the particle to the target **40** or to steer the charged particle away from the target **40**.

Example 3

(51) Referring now to FIG. **4**D, the plot of urinary exomes of FIG. **4**A is yet again reproduced upon which is superimposed yet another example selection by the instrument of FIG. **1** of yet another subpopulation or subset **304** of particles for purification according to steps **204** and **206** of the process **200** illustrated in FIG. **3**. In this example, the selected subpopulation **304** is defined by a specified range of particle mass values between 10 and 15 MDa and also by a range of charge magnitude values between 600 and 700 e. In order for the processor **26** to control the voltage

source VS3 at step **206** to cause the charged particle deflector or charged particle steering device **18** to pass therethrough to the particle target **40** only charged particles having particle mass values within the specified particle mass range of 10-15 MDA and charge values within the specified particle charge range of 600-750 e, the particle measurement information produced by the one or more instruments or devices of the ion processing region **16** must include particle mass and charge information or particle measurement information from which particle mass and charge can be determined by the processor **26** in advance of step **206**. In this example, as described above with respect to FIG. **4**A, the ion processing region **16** is illustratively implemented in the form of a CDMS or conventional MS followed by a CDA, either of which is configured to measure, at step **204**, particle mass and charge directly or to determine particle mass and charge from charged particle measurements taken by the instrument(s). It will be understood, however, that the ion processing region **16** may alternatively be or include any instrument or device or combination of instruments or devices configured to measure particle mass and charge or configured to measure one or more characteristics or properties of the particles from which both particle mass and charge can be determined or estimated. In any case, with the particle mass and charge information determined at step **204**, the processor **26** is operable at step **206** to control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to pass a charged particle exiting the ion processing region **16** to the particle target **40** only if the mass of that particle is within the specified particle mass range of 10-15 MDa and the magnitude of the charge of that particle is within the specified particle charge magnitude range of 600-750 e, and to otherwise control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to block passage of the particle to the target **40** or to steer the charged particle away from the target **40**.

Example 4

(52) Referring now to FIG. **4**E, the plot of urinary exomes of FIG. **4**A is again reproduced upon which is superimposed still another example selection by the instrument of FIG. **1** of still another subpopulation or subset **400** of particles for purification according to steps **204** and **206** of the process **200** illustrated in FIG. **3**. As is evident from the plot of FIG. **4**A, the total population of urinary exomes appears to fall along multiple different diagonal or slanted subpopulations, subsets or families, each of which is grouped about or along a different value or range of constant mass-to-charge ratio(s). In this example, the selected subpopulation **400** is defined by a specified one of such values or ranges of particle mass-to-charge ratio(s). In order for the processor **26** to control the voltage source VS3 at step **206** to cause the charged particle deflector or charged particle steering device **18** to pass therethrough to the particle target **40** only charged particles having the specified mass-to-charge ratio value or having mass-to-charge ratios with within the specified range of mass-to-charge ratios, the particle measurement information produced by the one or more instruments or devices of the ion processing region **16** must include particle mass-to-charge ratio information or particle measurement information from which particle mass-to-charge ratio can be determined by the processor **26** in advance of step **206**. In this example, as described above with respect to FIG. **4**A, the ion processing region **16** is illustratively implemented in the form of a CDMS or conventional MS followed by a CDA, either of which is configured to measure, at step **204**, particle mass and charge directly or to determine particle mass and charge from charged particle measurements taken by the instrument(s). It will be understood, however, that the ion processing region **16** may alternatively be or include any instrument or device or combination of instruments or devices configured to measure particle mass and charge or configured to measure one or more characteristics or properties of the particles from which both particle mass and charge can be determined or estimated. In any case, the processor **26** is operable in this embodiment to compute particle mass-to-charge ratio as a function of measured particle mass and charge.

(53) With the particle mass-to-charge ratio information determined at step **204**, the processor **26** is operable at step **206** to control the voltage source VS3 to cause the charged particle deflector or

charged particle steering device **18** to pass a charged particle exiting the ion processing region **16** to the particle target **40** only if the mass-to-charge ratio of that particle is has the specified mass-to-charge ratio or has a mass-to-charge ratio that is within the specified range of particle mass-to-charge ratios, and to otherwise control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to block passage of the particle to the target **40** or to steer the charged particle away from the target **40**.

(54) In an alternate embodiment of the instrument **10**, the charged particle deflector or charged particle steering device **18** may be omitted and the ion processing region **16** may be implemented in the form of a conventional mass analyzer or mass-to-charge ratio filter, e.g., a quadrupole mass-to-charge ratio filter or the like. In this embodiment, particle charge need not be measured by the ion processing region **16**, and the one or more charge amplifiers CA may therefore also be omitted. In this embodiment of the instrument **10**, step **206** of the process **200** may be omitted and the processor **26** may be operable at step **204** to control the voltage source VS2 to cause the mass analyzer or mass-to-charge filter to pass therethrough to the particle collection target **40** only charged particles having mass-to-charge values within the selected range **400** of mass-to-charge values.

Example 5

(55) Referring now to FIG. **4**F, the plot of urinary exomes of FIG. **4**A is again reproduced upon which is superimposed a further example selection by the instrument of FIG. **1** of a further subpopulation or subset **402** of particles for purification according to steps **204** and **206** of the process **200** illustrated in FIG. **3**. In this example, like that of Example 4, the selected subpopulation **402** is defined by a specified one of multiple different families of constant mass-to-charge ratios or range of mass-to-charge ratios, and is further defined by a specified range of mass values between 10 and 20 MDa. In order for the processor **26** to control the voltage source VS3 at step **206** to cause the charged particle deflector or charged particle steering device **18** to pass therethrough to the particle target **40** only charged particles having the specified mass-to-charge ratio or having mass-to-charge ratios within the specified range of mass-to-charge ratios and also having mass values within the specified range of mass values, the particle measurement information produced by the one or more instruments or devices of the ion processing region **16** must include particle mass and mass-to-charge ratio information or particle measurement information from which particle mass and mass-to-charge ratio can be determined by the processor **26** in advance of step **206**. In this example, as described above with respect to FIG. **4**A, the ion processing region **16** is illustratively implemented in the form of a CDMS or conventional MS followed by a CDA, either of which is configured to measure, at step **204**, particle mass and charge directly or to determine particle mass and charge from charged particle measurements taken by the instrument(s). It will be understood, however, that the ion processing region **16** may alternatively be or include any instrument or device or combination of instruments or devices configured to measure particle mass and charge or configured to measure one or more characteristics or properties of the particles from which both particle mass and charge can be determined or estimated. In any case, the processor **26** is operable to compute particle mass-to-charge ratio as a function of measured particle mass and charge.

(56) With the particle mass and mass-to-charge ratio information determined at step **204**, the processor **26** is operable at step **206** to control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to pass a charged particle exiting the ion processing region **16** to the particle target **40** only if the mass-to-charge ratio and the mass of that particle are within the specified range **402** of particle mass and mass-to-charge ratios, and to otherwise control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to block passage of the particle to the target **40** or to steer the charged particle away from the target **40**.

Example 6

(57) Referring now to FIG. **4**G, the plot of urinary exomes of FIG. **4**A is again reproduced upon which is superimposed yet a further example selection by the instrument of FIG. **1** of yet a further subpopulation or subset **404** of particles for purification according to steps **204** and **206** of the process **200** illustrated in FIG. **3**. In this example, like those of Examples 4 and 5, the selected subpopulation **404** is defined by a specified one of multiple different families of constant mass-to-charge ratios or range of mass-to-charge ratios, and is further defined by a specified range of charge magnitude values between 300 and 450 e. In order for the processor **26** to control the voltage source VS3 at step **206** to cause the charged particle deflector or charged particle steering device **18** to pass therethrough to the particle target **40** only charged particles having the specified mass-to-charge ratio or having mass-to-charge ratios within the specified range of mass-to-charge ratios and also having charge magnitude values within the specified range of charge magnitude values, the particle measurement information produced by the one or more instruments or devices of the ion processing region **16** must include particle mass-to-charge ratio and charge magnitude information or particle measurement information from which particle mass-to-charge ratio and charge magnitude can be determined by the processor **26** in advance of step **206**. In this example, as described above with respect to FIG. **4**A, the ion processing region **16** is illustratively implemented in the form of a CDMS or conventional MS followed by a CDA, either of which is configured to measure, at step **204**, particle mass and charge directly or to determine particle mass and charge from charged particle measurements taken by the instrument(s). It will be understood, however, that the ion processing region **16** may alternatively be or include any instrument or device or combination of instruments or devices configured to measure particle mass and charge or configured to measure one or more characteristics or properties of the particles from which both particle mass and charge can be determined or estimated. In any case, the processor **26** is operable to compute particle mass-to-charge ratio as a function of measured particle mass and charge.
(58) With the particle mass-to-charge ratio and charge magnitude information determined at step **204**, the processor **26** is operable at step **206** to control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to pass a charged particle exiting the ion processing region **16** to the particle target **40** only if the mass-to-charge ratio and the charge magnitude of that particle are within the specified range **404** of particle mass-to-charge ratios and charge magnitude values, and to otherwise control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to block passage of the particle to the target **40** or to steer the charged particle away from the target **40**.

Example 7

(59) Referring now to FIG. **4**H, the plot of urinary exomes of FIG. **4**A is yet again reproduced upon which is superimposed still a further example selection by the instrument of FIG. **1** of still a further subpopulation or subset **406** of particles for purification according to steps **204** and **206** of the process **200** illustrated in FIG. **3**. In this example, like those of Examples 4, 5 and 6, the selected subpopulation **406** is defined by a specified one of multiple different families of constant mass-to-charge ratios or range of mass-to-charge ratios, and is further defined by a specified range of mass values between 15 and 25 MDa as well as by a specified range of charge magnitude values between 300 and 450 e. In order for the processor **26** to control the voltage source VS3 at step **206** to cause the charged particle deflector or charged particle steering device **18** to pass therethrough to the particle target **40** only charged particles having the specified mass-to-charge ratio or having mass-to-charge ratios within the specified range of mass-to-charge ratios and also having charge magnitude values within the specified range of charge magnitude values and mass values within the specified range of mass values, the particle measurement information produced by the one or more instruments or devices of the ion processing region **16** must include at mass and charge magnitude information, mass-to-charge ratio and charge magnitude information or particle measurement information from which particle mass, mass-to-charge ratio and charge magnitude can be determined by the processor **26** in advance of step **206**. In this example, as described above with

respect to FIG. **4**A, the ion processing region **16** is illustratively implemented in the form of a CDMS or conventional MS followed by a CDA, either of which is configured to measure, at step **204**, particle mass and charge directly or to determine particle mass and charge from charged particle measurements taken by the instrument(s). It will be understood, however, that the ion processing region **16** may alternatively be or include any instrument or device or combination of instruments or devices configured to measure particle mass and charge or configured to measure one or more characteristics or properties of the particles from which both particle mass and charge can be determined or estimated. In any case, the processor **26** is operable to compute particle mass-to-charge ratio as a function of measured particle mass and charge.

(60) With the particle mass-to-charge ratio and charge magnitude information determined at step **204**, the processor **26** is operable at step **206** to control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to pass a charged particle exiting the ion processing region **16** to the particle target **40** only if the mass-to-charge ratio, the charge magnitude and the mass of that particle are within the specified range **406** of particle mass-to-charge ratios, charge magnitude values and mass values, and to otherwise control the voltage source VS3 to cause the charged particle deflector or charged particle steering device **18** to block passage of the particle to the target **40** or to steer the charged particle away from the target **40**.

(61) It will be understood that while the sample **24** used in the examples illustrated in FIGS. **4**A-**4**H is urinary exomes, in other applications the sample **24** may be any material whether or not biological in nature and whether in solution or otherwise. Additional example biological substances or materials that may be used as the sample **24** may include, but are not limited to, other exomes, endosomes, microvessicles generally, ectosomes, apoptotic bodies, retroviruses, exomeres, chylomicrons, DNA, RNA, proteins, fats, acids, carbohydrates, enzymes, viruses, bacteria, or the like. In some embodiments, the purified (and in some cases amplified) particles may be used to investigate, assemble and/or manufacture gene therapy products and/or other products. It will also be understood that while the examples illustrated in FIGS. **4**A-**4**H illustrate subpopulations or subsets of the charged particles generated from the sample **24** defined by various values or ranges of particle mass, charge and/or mass-to-charge ratio, the instrument **10** illustrated in FIG. **1** and processes **100**, **200** for operating the instrument **10** are not so limited. In particular, it will be understood that the instrument **10** may be configured, and the process **100** and/or process **200** may be modified, to collect subpopulations of subsets of charged particles alternatively or additionally defined by values or ranges of particle mobility and/or other molecular characteristics. As one specific example, which should not be considered limiting in any way, the ion processing region **16** may be configured to include instruments for measuring or otherwise determining particle mass, charge and mobility, and various purified, multi-dimensional subpopulations of charged particles may be defined by values and/or ranges of particle mass, mass-to-charge ratio, charge magnitude or charge state and mobility.

Example 8

(62) Referring again to FIG. **5**, the process **500** was executed using a sample of bovine milk in which the particles of the specified type are exosomes. At step **502**, pooled unprocessed (raw) bovine milk (from approximately 20 animals) was provided. Thereafter at step **504**, the sample of raw bovine milk was enriched for exosomes as follows. Within approximately 200 minutes of collection of the bovine milk sample, 50 milliliter aliquots of the raw milk were defatted, and then additionally centrifuged to reduce the amount of apoptotic bodies in the sample. This was illustratively accomplished by centrifugation of the raw milk at 2,000×g for 10 minutes at 4° C. to remove a concentrated layer of milk fat. The remaining suspension was isolated and centrifuged at 12,000×g for 20 minutes at 4° C. to remove cells and other debris. Acetic acid was then added to the supernatant (to a concentration of 1% by volume) and mixed for 5 minutes in order to induce precipitation of non-EV (non-extracellular vesicle) proteins, in particular casein, whose isoelectric point is 4.6. The precipitates were isolated by centrifugation at 10,000×g at 4° C. for 10 minutes

following a conventional method. The resulting supernatant, a mixture of proteins, lipids, and other species, including EVs (designated as whey), was ultracentrifuged at 210,000×g for 70 minutes at 4° C. The resulting pellet was resolubilized in 500 microliters of 100 mM ammonium acetate and centrifuged to remove residual precipitates at 10,000×g for 5 minutes at 4° C. The resulting exosome-containing EV supernatant was then diluted by 100-fold in a solution of 100 mM ammonium acetate to form the sample **24** from which ions were generated using the instrument **10** illustrated in FIG. **1**.

(63) The instrument **10** was illustratively configured as follows, although it will be understood that the following configuration of the instrument **10** is only one of several different possible configurations of the instrument **10** as illustrated in FIG. **1** and described above. For this particular example, the ion generator **22** was an electrospray ionization (ESI) unit having a ˜5 μm diameter borosilicate capillary emitter, and an emitter potential of ˜1.4 kV was used to produce the ions from the enriched sample **24**. The electrosprayed ions were transmitted through a capillary interface into the source region of the instrument **10**, illustratively configured as CDMS instrument as described above. In this particular example, the ion processing region **16** included a hybrid ion funnel—ion carpet interface, e.g., as illustrated and described in co-pending international application PCT/US2019/0132274 and incorporated herein by reference, through which the ions from the source capillary are transmitted. Following the interface, the ions are transmitted through an RF-only hexapole where they undergo collisions that thermalize the ion kinetic energy distribution. As ions exit the hexapole they enter an RF-only quadrupole that acts as a low pass filter tuned to transmit large ions with mass-to-charge (m/z) ratio values above ˜12,000. Elimination of low-m/z species ensures that measurement time is optimized for high-m/z ions. A DC offset voltage of 100 V on the hexapole was used to set the nominal ion energy per charge. Ions were then focused into the entrance of a dual hemispherical deflection energy analyzer, and energy-selected ions exiting the energy analyzer were then introduced into an electrostatic linear ion trap (ELIT) that contains a charge detection cylinder.

(64) As each ion enters the ELIT, it induces a charge on the charge detection cylinder. At the time of collection and start of each trapping event, both end caps of the ELIT were in transmission mode, allowing ions to travel through the trap. A trapping event was initiated by switching the back-end cap from transmission to trapping mode, reflecting ions back through the charge detection cylinder and to the entrance of the ELIT. Following a short delay of 0.3 ms, the front-end cap was switched to trapping mode, and trapped ions oscillated back and forth in the ELIT. After 100 ms, the trapping event was terminated and both end caps of the ELIT were switched back to transmission mode. After a delay of 1 ms, the process was repeated for each of the ions. During the 100 ms measurement time, each ion oscillates through the charge detection cylinder of the ELIT, inducing a periodic signal, which is amplified by a charge-sensitive preamplifier CA, digitized, and then analyzed using fast Fourier transforms. The mass-to-charge ratio of the ion is derived from the fundamental frequency of the measurements, and the charge is derived from the magnitude of the fundamental frequency. Mass distributions were generated by multiplying the mass-to-charge values by the charge measured for each ion and binning the resulting masses.

(65) At step **506**, the process **100** of FIG. **2** was executed as described above, and at step **106** of the process **100** a scatter plot was generated of charged particle charge magnitude (in units of elementary charge e) vs. charged particle mass (in units of mega-Daltons MDa) as shown in FIG. **6**A. Thereafter at step **108**, the scatter plot was processed to determine a sub-population of the plot data which could be identified as exosomes. In one embodiment of the process **500**, all of the particles having masses greater than 9.8 megadaltons (generally understood to be a minimum mass of an exosome) were deemed to be exosomes, and are identified as such in FIG. **6**A as all of the charged particles to the right of the vertical, dashed exosome mass threshold line EMTH. In some embodiments, the process **200** may illustratively be executed as described above to collect and/or purify the exosomes identified at step **108**.

(66) In an alternate embodiment of the process **500**, the data in the scatter plot of FIG. **6**A was processed at step **108** to determine one or more sub-populations of the charged particles which could be identified as exosomes and/or to determine whether there exists multiple sub-populations of the charged particles that are distinguishable from one another, e.g., whether there are sub-populations that may be resolved as families of particles from the CDMS data. In this regard, the processor **26** was programmed at step **108** to execute a conventional two-dimensional Gaussian mixture model (GMM) to fit the two-dimensional mass verses charge data of FIG. **6**A, which assumes that sub-populations of particles fall into families of related masses and charges, and that these family distributions are normally distributed. With this assumption the processor **26** was programmed to execute a conventional clustering analysis on the charged particle data that results in multiple distributions of two-dimensional mass verses charge sub-populations. When combined, the sum of these sub-populations captures the main features of the two-dimensional CDMS data. For simplicity the number of possible subpopulations was constrained between one and ten two-dimensional Gaussians. Except for this constraint, the analysis was unsupervised and the algorithm determined the number of subpopulations, as well as the position and width associated with each of the sub-population, that when summed best fit the two-dimensional CDMS dataset. For the CDMS dataset shown in FIG. **6**A, this analysis converged on a best fit model that consisted of six independent sub-populations S1-S6 as illustrated by example in FIG. **6**B. It will be understood that because each of the six sub-populations of charge particles illustrated in FIG. **6**B are Gaussian distributions, the boundaries of each of S1-S6 are only approximations and are included in FIG. **6**B only to show the locations and approximate sizes of the sub-populations S1-S6 relative to one another. In alternate embodiments, one or more other conventional statistical models may be used to analyze the particle mass and charge dataset produced by the CDMS **10**.

(67) The data in FIG. **6**B show that the lowest mass sub-population, S1, observed in the sample **24** corresponds to a relatively narrow distribution, centered at mass (m)=5.7±1.6 MDa and charge (z)=145±38 e. This sub-population, S1, comprises approximately 27% (975 out of 3586) of the total number of charged particles in the data set. The highest mass sub-population, S6, observed in the sample **24** corresponds to a broad distribution, centered at m=27.7±5.4 MDa and z=594±76 e. This sub-population, S6, comprises approximately 22% (772 out of 3586) of the total number of charged particles in the data set. The S2 sub-population (or family), centered at m=10.2±1.9 MDa and z=189±44 e accounts for only 3% of the total number of charged particles in the data set, making it the lowest abundance sub-population. The S3 (m=12.5±2.9 MDa, z=296±31 e) sub-population, comprising approximately 4% of the total number of charged particles, and the S4 (m=17.6±2.6 MDa, z=488±76 e) sub-population, comprising approximately 18% of the total number of charged particles, are substantially more resolved based on charge compared with mass. This suggests that these sub-populations or families are comprised of similarly sized particles that differ substantially at the molecular level, thus influencing each particle's charge more than its mass. The S5 (m=23.4±3.4 MDa, z=550±113 e) sub-population, comprising approximately 26% of the total number of charged particles, appear to be more resolved in the mass than in the charge dimension, indicating that they are more similar in charging characteristics than in size.

(68) From the Gaussian-model cluster analysis undertaken at step **108** of the process **100** as just described, the fraction of particles in the data set that are exosomes can be estimated. With respect to the average masses of the various sub-populations, only the S1 sub-population (m=5.7±1.6 MDa) is too small to be exosomes (based on the minimum exosome mass being approximately 9.8 MDa). As S1 represents 27% of the total number of charged particles in the data set, the remaining 73% of the charged particles in the data set are within the mass range expected for exosomes. In some embodiments, the process **200** may illustratively be executed as described above to collect and/or purify the exosomes identified in this embodiment of step **108**.

(69) While this disclosure has been illustrated and described in detail in the foregoing drawings and description, the same is to be considered as illustrative and not restrictive in character, it being

understood that only illustrative embodiments thereof have been shown and described and that all changes and modifications that come within the spirit of this disclosure are desired to be protected. For example, in some embodiments in which the ion processing region **16** is implemented in the form of a CDMS, the charge detector of the CDMS may illustratively be controlled to selectively release charged particles or block release of particles therefrom, e.g., by selective control of the voltage source VS2. In embodiments of the CDMS in which the charge detector is an electrostatic linear ion trap (ELIT), for example, the voltages applied by the voltage source VS2 to one or both of the endcaps thereof may illustratively be controlled to allow an ion trapped and oscillating therein to exit the ELIT in the direction of the particle collection target **40**, or to cause oscillation of the ion within the ELIT to become unstable and contact a structure therein such that the ion will not be released from the ELIT. In such embodiments, such control of the ELIT may render the charged particle deflector or steering device **18** unnecessary such that it may be omitted. In embodiments of the CDMS in which the charge detector is an orbitrap, the voltage source VS2 may be similarly controlled with the same effect.

Claims

1. A particle purification device, comprising: an ion generator configured to generate charged particles from a sample, an ion processing region configured to receive the charged particles generated by the ion generator and to measure at least one of masses and charge magnitudes of the generated charged particles, a particle collection target having a collection surface, means for selectively passing charged particles exiting the ion processing region to the particle collection target, a processor, and a memory having instructions stored therein executable by the processor to cause the processor to control the means for selectively passing charged particles to pass to the collection surface of the particle collection target for collection thereon each of the measured charged particles having at least one of (a) a measured mass equal to a selected mass or within a selected range of particle masses, (b) a measured charge magnitude equal to a selected charge magnitude or within a selected range of charge magnitudes, and (c) a mass-to-charge ratio equal to a selected mass-to-charge ratio or within a selected range of mass-to-charge ratios.
2. The particle purification device of claim 1, wherein the instructions stored in the memory further include instructions executable by the processor to cause the processor to control the means for selectively passing charge particles to otherwise block passage to the particle collection target the measured charged particles.
3. The particle purification device of claim 1, wherein the ion processing region comprises a charge detection mass spectrometer configured to receive the charged particles generated by the ion generator and to measure the masses and charge magnitudes of the generated charged particles.
4. The particle purification device of claim 3, wherein the means for selectively passing charged particles exiting the ion processing region to the particle collection target comprises a charged particle deflection or steering device controllable by the processor to selectively pass charged particles therethrough to the particle collection target.
5. The particle purification device of claim 3, wherein the means for selectively passing charged particles exiting the ion processing region to the particle collection target comprises a charge detector of the charge detection mass spectrometer, the charge detector controllable by the processor to selectively pass charged particles therethrough to the particle collection target.
6. The particle purification device of claim 1, further comprising an ion trap disposed between the particle collection target and the means for selectively passing charged particles exiting the ion processing region to the particle collection target, and wherein the instructions stored in the memory further include instructions executable by the processor to cause the processor to control the ion trap to selectively trap therein charged particles exiting the means for selectively passing charged particles exiting the ion processing region to the particle collection target, and to control

the ion trap to release charged particles trapped therein and accelerate the charged particles toward the particle collection target.

7. The particle purification device of claim 1, wherein the ion processing region comprises one of a mass analyzer, a mass spectrometer and a mass-to-charge ratio filter configured to pass therethrough charged particles of a selected mass-to-charge ratio or having a mass-to-charge ratio within a selected range of mass-to-charge ratios followed by a charge detector array configured to measure charge magnitudes of charged particles exiting the mass analyzer, a mass spectrometer and a mass-to-charge ratio filter.

8. The particle purification device of claim 7, wherein the means for selectively passing charged particles exiting the ion processing region to the particle collection target comprises a charged particle deflection or steering device controllable by the processor to selectively pass charged particles therethrough to the particle collection target.

9. The particle purification device of claim 7, further comprising an ion trap disposed between the particle collection target and the means for selectively passing charged particles exiting the ion processing region to the particle collection target, and wherein the instructions stored in the memory further include instructions executable by the processor to cause the processor to control the ion trap to selectively trap therein charged particles exiting the means for selectively passing charged particles exiting the ion processing region to the particle collection target, and to control the ion trap to release charged particles trapped therein and accelerate the charged particles toward the particle collection target.

10. A method for purifying particles, comprising: generating charged particles from a sample, measuring at least at least one of masses, charge magnitudes and mobilities of the generated charged particles, and selectively passing to a collection surface of a particle collection target for collection on the collection surface each of the measured charged particles having at least one of (a) a measured mass equal to a selected mass or within a selected range of particle masses, (b) a measured charge magnitude equal to a selected charge magnitude or within a selected range of charge magnitudes, (c) a mass-to-charge ratio equal to a selected mass-to-charge ratio or within a selected range of mass-to-charge ratios, and (d) a measured mobility equal to a selected mobility or within a selected range of mobilities.

11. The method of claim 10, further comprising collecting on the collection surface of the particle collection target the measured charged particles selectively passed thereto.

12. The method of claim 11, further comprising harvesting the charged particles collected on the collection surface of the particle collection target.

13. The method of claim 12, further comprising amplifying the harvested charged particles.

14. A method for measuring exosomes in a sample preparation, the method comprising: generating ions from the sample preparation, measuring mass and charge of at least some of the generated ions using a charge detection mass spectrometer, and identifying from the measured masses of the at least some of the generated ions a subset of the measured ions that are exosome ions.

15. The method of claim 14, further comprising enriching the sample preparation for the exosomes prior to measuring the mass and charge of the at least some of the generated ions.

16. The method of claim 15, further comprising processing the measured masses and charges of the at least some of the generated ions using a statistical model to determine at least two separate sub-families of the generated ions.

17. The method of claim 14, further comprising collecting at least a portion of the subset of the measured ions that are exosome ions.

18. The method of claim 17, further comprising purifying the collected at least a portion of the subset of the measured ions that are exosome ions.

19. The particle purification device of claim 1, wherein the sample includes exosomes, and wherein the instructions stored in the memory further include instructions executable by the processor to determine from the measured masses of at least some of the generated charged particles a subset of

the generated charged particles having masses identifying the corresponding generated charged particles as exosome ions, and wherein the instructions stored in the memory further include instructions executable by the processor to control the means for selectively passing charged particles to pass the exosome ions to the particle collection target.

20. The method of claim 10, wherein generating charged particles from a sample comprises generating charged particles from a sample containing exosomes, and wherein measuring comprises measuring at least the masses of the charged particles, and wherein the method further comprises identifying from the measured masses of the at least some of the generated charged particles a subset of the generated charged particles that are exosome ions, and wherein selectively passing comprises passing the exosome ions to the particle collection target.