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(54) **SYSTEMS, CATHETERS, AND METHODS
FOR TREATING ALONG THE CENTRAL
NERVOUS SYSTEM**

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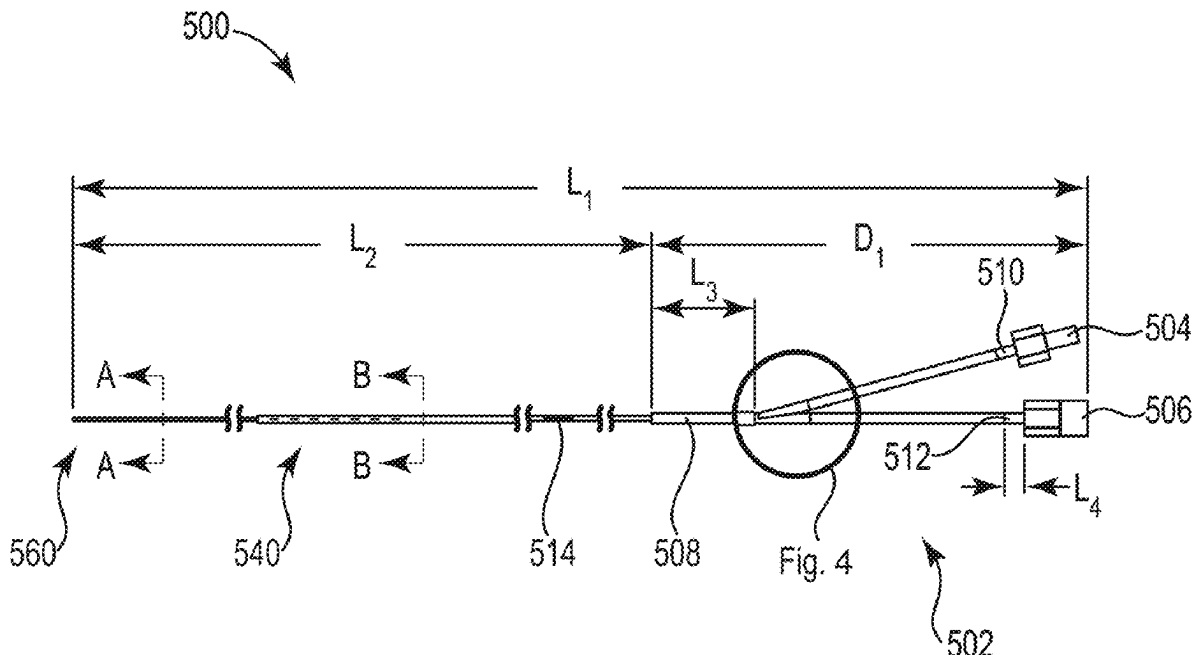
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5, 2017, provisional application No. 62/642,873, filed
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(57)

ABSTRACT

Systems, catheters, and methods for accessing and treating
along the central nervous system are disclosed. An example
system may include a system for ameliorating a symptom of
bacterial meningitis in a patient. The system may include a
catheter assembly having a first lumen with a distal port and
a second lumen with a proximal port, said catheter being
adapted to be introduced in a CSF space and said ports being
spaced axially apart. A pump may be connectable between
the first and second lumens to induce a flow of CSF
therebetween. A filter component may be connectable between
the first and second lumens. The filter component
may be configured to remove one or more meningitis
causing bacterial pathogen from the CSF, to thereby condi-
tion the cerebrospinal fluid.



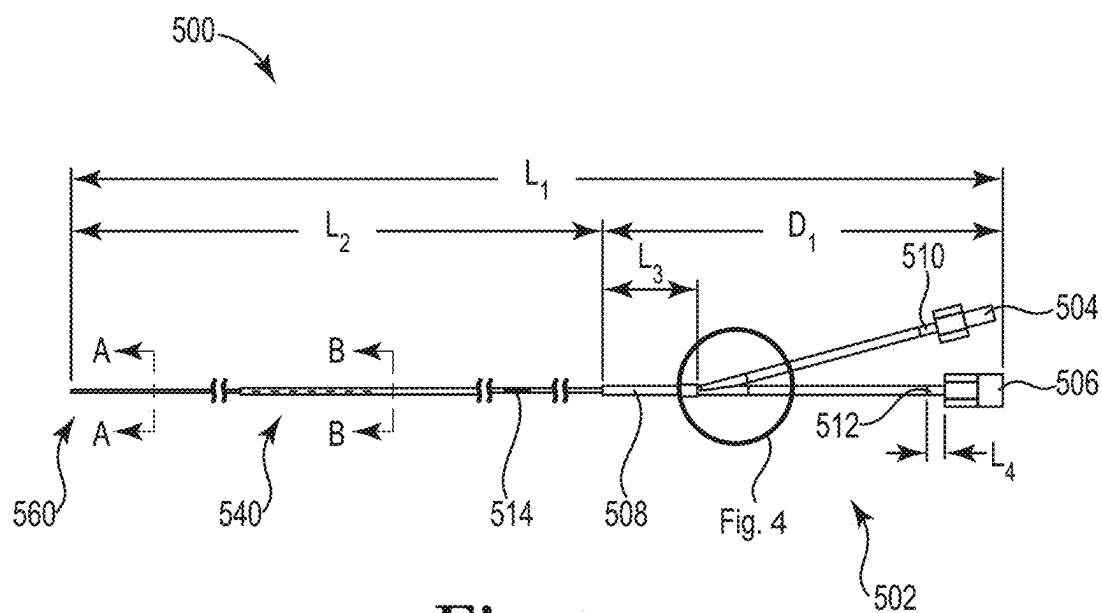


Fig. 1

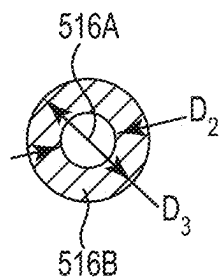


Fig. 2

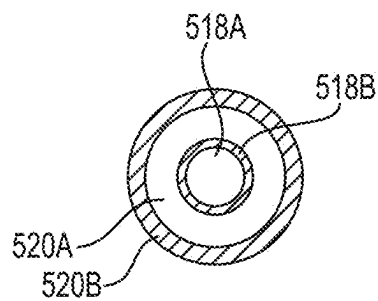


Fig. 3

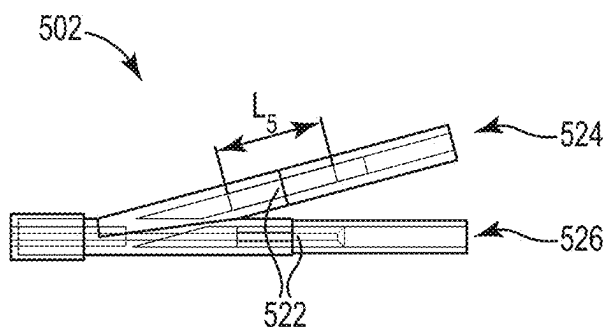


Fig. 4

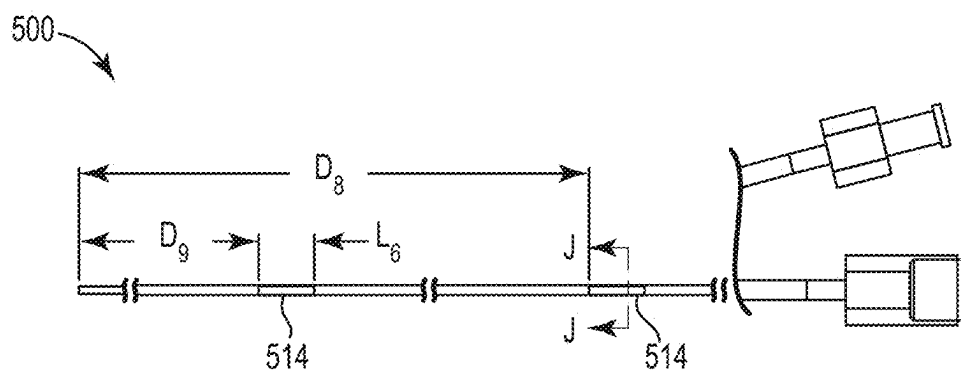


Fig. 5

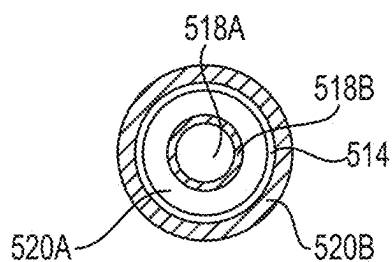


Fig. 6

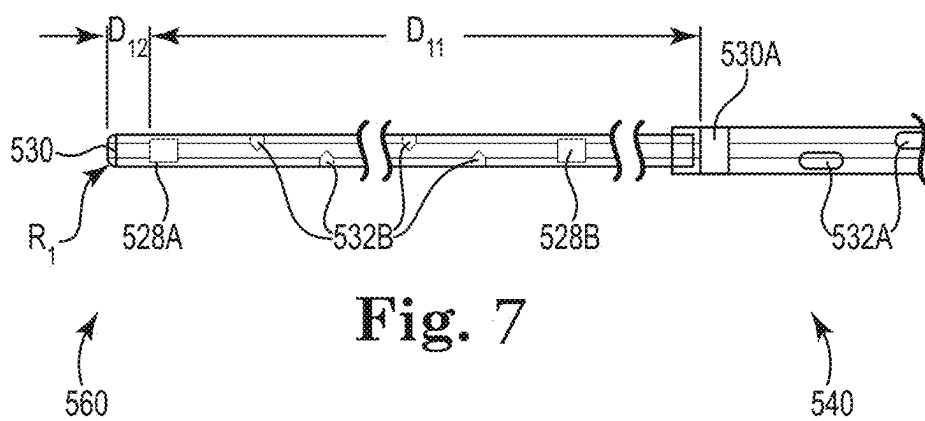


Fig. 7

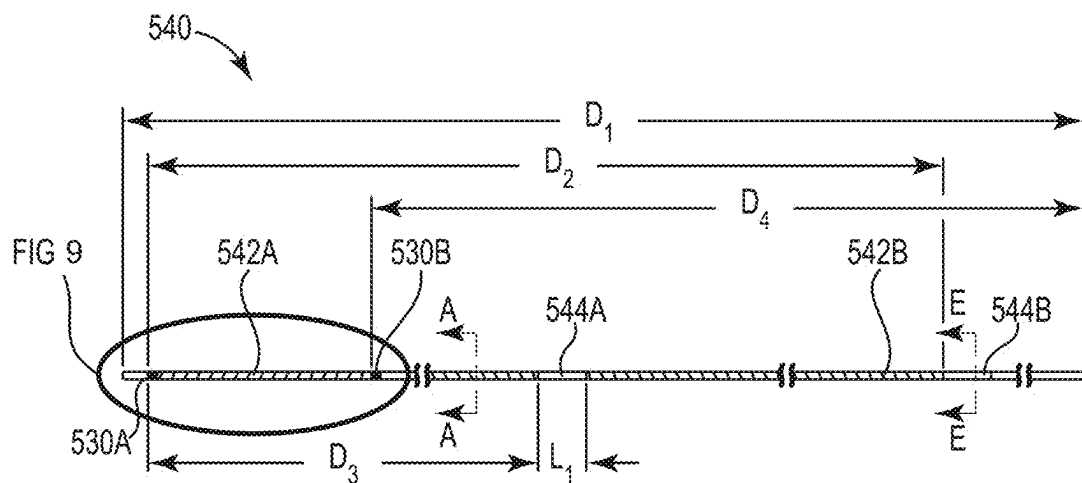


Fig. 8

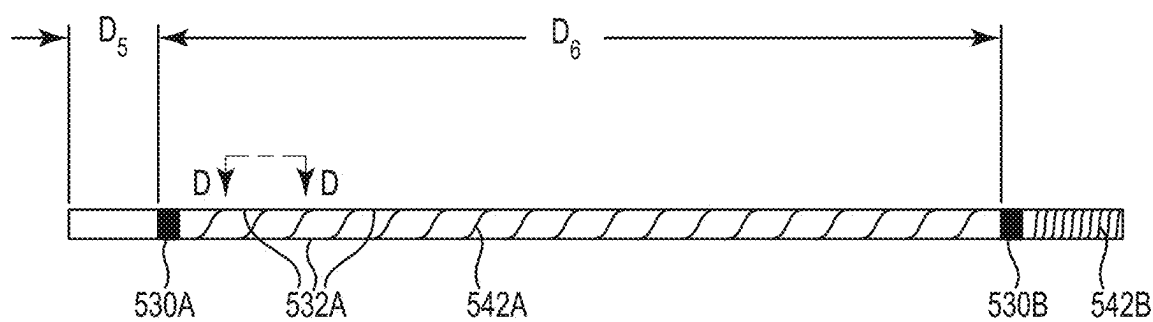


Fig. 9

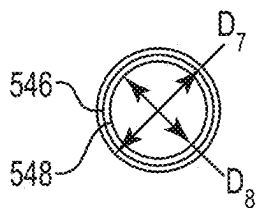


Fig. 10

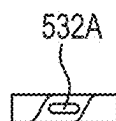
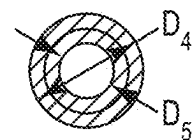
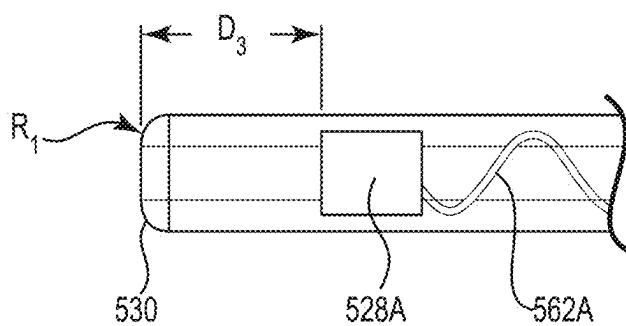
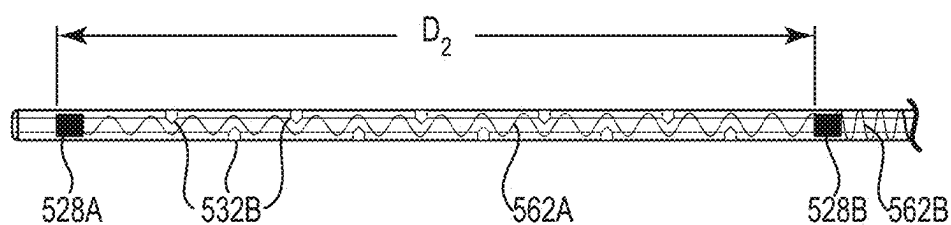
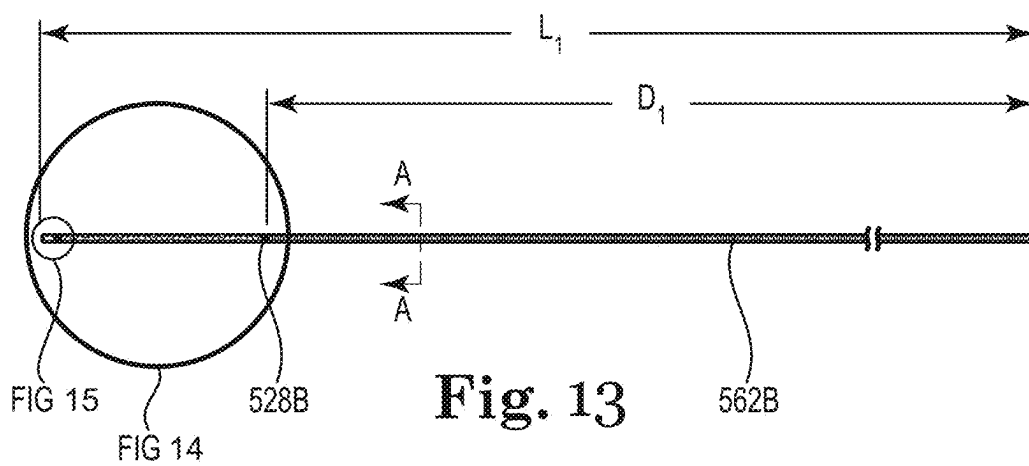


Fig. 11



Fig. 12



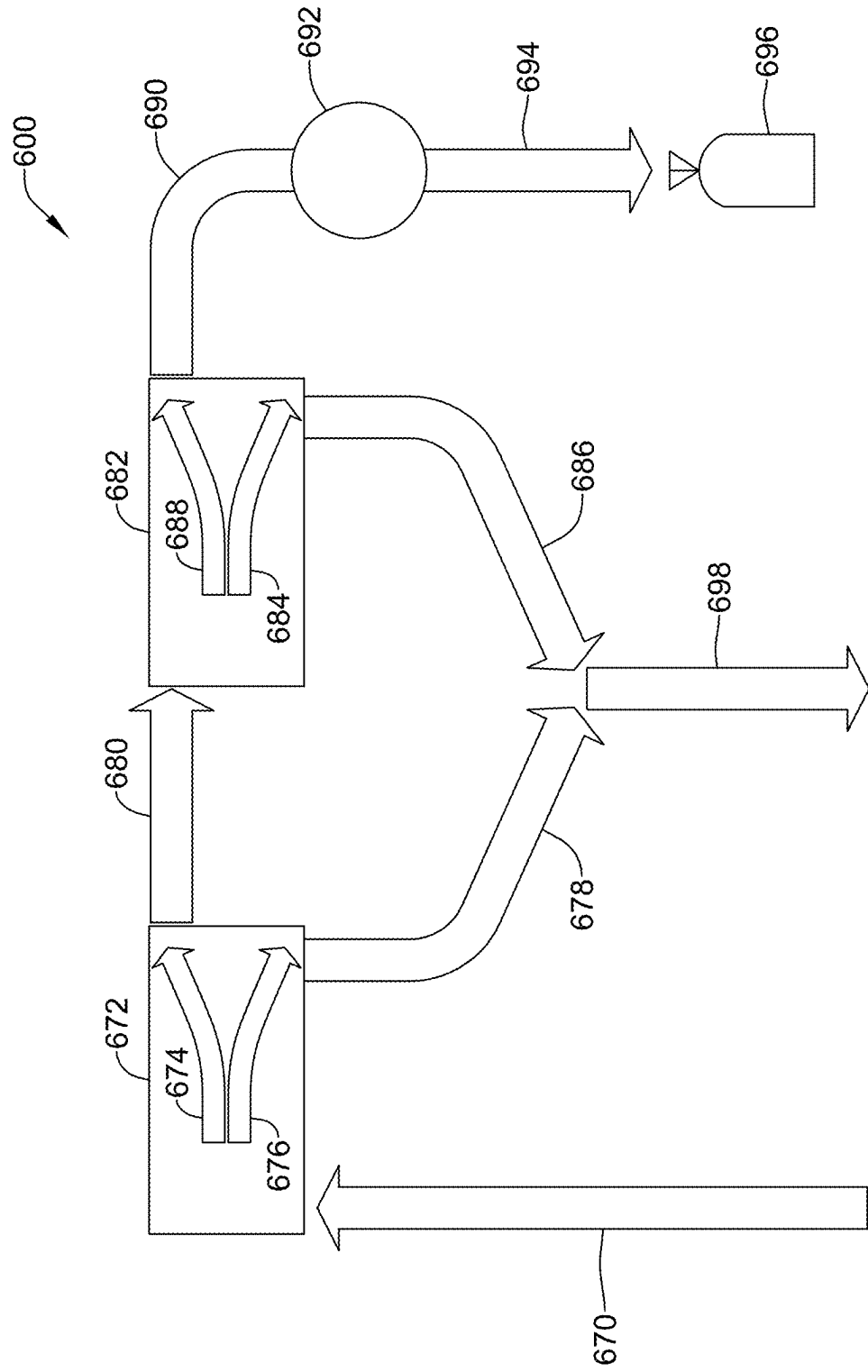


FIG. 17

SYSTEMS, CATHETERS, AND METHODS FOR TREATING ALONG THE CENTRAL NERVOUS SYSTEM

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation of U.S. patent application Ser. No. 16/152,382, filed Oct. 4, 2018, which claims priority under to U.S. Provisional Application Ser. No. 62/568,412, filed Oct. 5, 2017, to U.S. Provisional Application Ser. No. 62/598,846, filed Dec. 14, 2017, to U.S. Provisional Application Ser. No. 62/642,873, filed Mar. 14, 2018, and to U.S. Provisional Application Ser. No. 62/686,413, filed Jun. 18, 2018, the entirety of which are incorporated herein by reference.

TECHNICAL FIELD

[0002] The present disclosure relates to systems, catheters, and methods for treating along the central nervous system.

BACKGROUND

[0003] A wide variety of medical devices have been developed for medical use. Some of these devices include guidewires, catheters, and the like. These devices are manufactured by any one of a variety of different manufacturing methods and may be used according to any one of a variety of methods. Of the known medical devices and methods, each has certain advantages and disadvantages. There is an ongoing need to provide alternative medical devices as well as alternative methods for manufacturing and using medical devices.

SUMMARY

[0004] This disclosure provides design, material, manufacturing method, and use alternatives for medical devices. An example method for treating cancer is disclosed. The method comprises: removing cerebrospinal fluid from a patient with cancer; filtering the cerebrospinal fluid with a filtration system to remove cancer cells; and returning the filtered cerebrospinal fluid to the patient.

[0005] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with cancer includes removing cerebrospinal fluid from a lumbar cerebrospinal space of the patient.

[0006] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with cancer includes disposing a catheter system within a cerebrospinal space.

[0007] Alternatively or additionally to any of the embodiments above, the catheter system includes a catheter shaft having an inner shaft and an outer shaft.

[0008] Alternatively or additionally to any of the embodiments above, the inner shaft has a plurality of openings formed therein.

[0009] Alternatively or additionally to any of the embodiments above, the outer shaft has a plurality of openings formed therein.

[0010] Alternatively or additionally to any of the embodiments above, the inner shaft has a first plurality of openings formed therein, wherein the outer shaft has a second plurality of openings formed therein, and wherein at least some of the first plurality of openings differ in size, shape, or both from at least some of the second plurality of openings.

[0011] Alternatively or additionally to any of the embodiments above, the inner shaft defines an infusion lumen.

[0012] Alternatively or additionally to any of the embodiments above, returning the filtered cerebrospinal fluid to the patient includes returning the filtered cerebrospinal fluid through the infusion lumen.

[0013] Alternatively or additionally to any of the embodiments above, further comprising infusing a chemotherapy agent through the infusion lumen.

[0014] Alternatively or additionally to any of the embodiments above, an aspiration lumen is defined between the inner shaft and the outer shaft.

[0015] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with cancer includes removing cerebrospinal fluid through the aspiration lumen.

[0016] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with cancer includes removing tumor cells.

[0017] Alternatively or additionally to any of the embodiments above, further comprising infusing a chemotherapy agent into the patient.

[0018] Alternatively or additionally to any of the embodiments above, the chemotherapy agent includes methotrexate.

[0019] Alternatively or additionally to any of the embodiments above, infusing a chemotherapy agent into the patient includes implanting an Ommaya reservoir and infusing the chemotherapy agent into the patient via the Ommaya reservoir.

[0020] Alternatively or additionally to any of the embodiments above, infusing a chemotherapy agent into the patient includes infusing the chemotherapy agent into the patient with a catheter system.

[0021] Alternatively or additionally to any of the embodiments above, infusing the chemotherapy agent into the patient with a catheter system includes disposing the catheter system within a cerebrospinal space.

[0022] Alternatively or additionally to any of the embodiments above, disposing the catheter system within a cerebrospinal space includes disposing the catheter system a lumbar cerebrospinal fluid space.

[0023] Alternatively or additionally to any of the embodiments above, the filtration system includes a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both.

[0024] Alternatively or additionally to any of the embodiments above, further comprising removing cerebrospinal fluid from a cranial space.

[0025] Alternatively or additionally to any of the embodiments above, further comprising removing cerebrospinal fluid from a cranial space with a catheter.

[0026] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with cancer includes removing cerebrospinal fluid from a first location with a first catheter.

[0027] Alternatively or additionally to any of the embodiments above, returning the filtered cerebrospinal fluid to the patient includes returning the filtered cerebrospinal fluid to a first region adjacent to the first location with the first catheter.

[0028] Alternatively or additionally to any of the embodiments above, further comprising removing cerebrospinal fluid from a second location with a second catheter.

[0029] Alternatively or additionally to any of the embodiments above, further comprising infusing filtered cerebrospinal fluid to a second region adjacent to the second location with the second catheter.

[0030] A method for treating cancer is disclosed. The method comprises: disposing a catheter in a cerebrospinal space of a patient with cancer; aspirating cerebrospinal fluid from the patient with the catheter; filtering the cerebrospinal fluid with a filtration system to remove cancer cells; and returning the filtered cerebrospinal fluid to the patient with the catheter.

[0031] Alternatively or additionally to any of the embodiments above, aspirating cerebrospinal fluid from the patient with the catheter includes aspirating cerebrospinal fluid from a lumbar cerebrospinal space of the patient.

[0032] Alternatively or additionally to any of the embodiments above, the catheter includes a catheter shaft having an inner shaft and an outer shaft.

[0033] Alternatively or additionally to any of the embodiments above, the inner shaft has a plurality of openings formed therein.

[0034] Alternatively or additionally to any of the embodiments above, the outer shaft has a plurality of openings formed therein.

[0035] Alternatively or additionally to any of the embodiments above, the inner shaft has a first plurality of openings formed therein, wherein the outer shaft has a second plurality of openings formed therein, and wherein at least some of the first plurality of openings differ in size, shape, or both from at least some of the second plurality of openings.

[0036] Alternatively or additionally to any of the embodiments above, further comprising infusing a chemotherapy agent into the patient.

[0037] Alternatively or additionally to any of the embodiments above, the chemotherapy agent includes methotrexate.

[0038] Alternatively or additionally to any of the embodiments above, infusing a chemotherapy agent into the patient includes infusing the chemotherapy agent into the patient with an Ommaya reservoir.

[0039] Alternatively or additionally to any of the embodiments above, infusing a chemotherapy agent into the patient includes infusing the chemotherapy agent into the patient with the catheter.

[0040] Alternatively or additionally to any of the embodiments above, the filtration system includes a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both.

[0041] A method for treating cancer is disclosed. The method comprises: disposing a catheter in a cerebrospinal space of a patient with cancer; aspirating cerebrospinal fluid from the patient with the catheter; conditioning the cerebrospinal fluid with a filtration system; returning the filtered cerebrospinal fluid to the patient with the catheter; and infusing a chemotherapy agent into the cerebrospinal space with the catheter.

[0042] Alternatively or additionally to any of the embodiments above, aspirating cerebrospinal fluid from the patient with the catheter includes aspirating cerebrospinal fluid from a lumbar cerebrospinal space of the patient.

[0043] Alternatively or additionally to any of the embodiments above, the catheter includes a catheter shaft having an inner shaft and an outer shaft.

[0044] Alternatively or additionally to any of the embodiments above, the inner shaft has a plurality of openings formed therein.

[0045] Alternatively or additionally to any of the embodiments above, the outer shaft has a plurality of openings formed therein.

[0046] Alternatively or additionally to any of the embodiments above, the inner shaft has a first plurality of openings formed therein, wherein the outer shaft has a second plurality of openings formed therein, and wherein at least some of the first plurality of openings differ in size, shape, or both from at least some of the second plurality of openings.

[0047] Alternatively or additionally to any of the embodiments above, further comprising infusing a second chemotherapy agent into the patient with an Ommaya reservoir.

[0048] Alternatively or additionally to any of the embodiments above, the chemotherapy agent and the second chemotherapy agent are the same.

[0049] Alternatively or additionally to any of the embodiments above, the chemotherapy agent, the second chemotherapy agent, or both include methotrexate.

[0050] Alternatively or additionally to any of the embodiments above, the filtration system includes a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both.

[0051] A system for treating cancer is disclosed. The system comprises: a catheter including an inner shaft and an outer shaft; wherein an infusion lumen is defined within the inner shaft; wherein an aspiration lumen is defined between the inner shaft and the outer shaft; a first plurality of openings in the inner shaft, the first plurality of openings being in fluid communication with the infusion lumen; a second plurality of openings in the outer shaft, the second plurality of openings being in fluid communication with the aspiration lumen; a filtration system in fluid communication with the infusion lumen and the aspiration lumen, the filtration system including one or more filters designed to filter cancer cells from cerebrospinal fluid.

[0052] Alternatively or additionally to any of the embodiments above, at least some of the first plurality of openings differ in size, shape, or both from at least some of the second plurality of openings.

[0053] Alternatively or additionally to any of the embodiments above, the filtration system includes a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both.

[0054] A method for treating amyotrophic lateral sclerosis (ALS) is disclosed. The method comprises: removing cerebrospinal fluid from a patient with ALS; filtering the cerebrospinal fluid with a filtration system to remove oxidative and/or inflammatory agents; and returning the filtered cerebrospinal fluid to the patient.

[0055] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with ALS includes removing cerebrospinal fluid from a lumbar cerebrospinal space of the patient.

[0056] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with ALS includes disposing a catheter system within a cerebrospinal space.

[0057] Alternatively or additionally to any of the embodiments above, the catheter system includes a catheter shaft having an inner shaft and an outer shaft.

[0058] Alternatively or additionally to any of the embodiments above, the inner shaft has a plurality of openings formed therein.

[0059] Alternatively or additionally to any of the embodiments above, the outer shaft has a plurality of openings formed therein.

[0060] Alternatively or additionally to any of the embodiments above, the inner shaft has a first plurality of openings formed therein, wherein the outer shaft has a second plurality of openings formed therein, and wherein at least some of the first plurality of openings differ in size, shape, or both from at least some of the second plurality of openings.

[0061] Alternatively or additionally to any of the embodiments above, the inner shaft defines an infusion lumen.

[0062] Alternatively or additionally to any of the embodiments above, returning the filtered cerebrospinal fluid to the patient includes returning the filtered cerebrospinal fluid through the infusion lumen.

[0063] Alternatively or additionally to any of the embodiments above, further comprising infusing a drug through the infusion lumen.

[0064] Alternatively or additionally to any of the embodiments above, an aspiration lumen is defined between the inner shaft and the outer shaft.

[0065] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with ALS includes removing cerebrospinal fluid through the aspiration lumen.

[0066] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with cancer includes removing one or more of insoluble superoxide dismutase-1 (SOD1), glutamate, neurofilament protein, and anti-GM1 ganglioside antibodies.

[0067] Alternatively or additionally to any of the embodiments above, wherein the filtration system includes a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both.

[0068] Alternatively or additionally to any of the embodiments above, wherein the filtration system includes an electrofilter.

[0069] A method for treating herpes simplex encephalitis (HSE) is disclosed. The method comprises: removing cerebrospinal fluid from a patient with HSE; filtering the cerebrospinal fluid with a filtration system to remove oxidative and/or inflammatory agents; and returning the filtered cerebrospinal fluid to the patient.

[0070] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with HSE includes removing cerebrospinal fluid from a lumbar cerebrospinal space of the patient.

[0071] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with HSE includes disposing a catheter system within a cerebrospinal space.

[0072] Alternatively or additionally to any of the embodiments above, the catheter system includes a catheter shaft having an inner shaft and an outer shaft.

[0073] Alternatively or additionally to any of the embodiments above, the inner shaft has a plurality of openings formed therein.

[0074] Alternatively or additionally to any of the embodiments above, the outer shaft has a plurality of openings formed therein.

[0075] Alternatively or additionally to any of the embodiments above, the inner shaft has a first plurality of openings formed therein, wherein the outer shaft has a second plurality of openings formed therein, and wherein at least some

of the first plurality of openings differ in size, shape, or both from at least some of the second plurality of openings.

[0076] Alternatively or additionally to any of the embodiments above, the inner shaft defines an infusion lumen.

[0077] Alternatively or additionally to any of the embodiments above, returning the filtered cerebrospinal fluid to the patient includes returning the filtered cerebrospinal fluid through the infusion lumen.

[0078] Alternatively or additionally to any of the embodiments above, further comprising infusing a drug through the infusion lumen.

[0079] Alternatively or additionally to any of the embodiments above, an aspiration lumen is defined between the inner shaft and the outer shaft.

[0080] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with HSE includes removing cerebrospinal fluid through the aspiration lumen.

[0081] Alternatively or additionally to any of the embodiments above, the filtration system includes a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both.

[0082] Alternatively or additionally to any of the embodiments above, the filtration system includes an electrofilter.

[0083] A method for treating multiple sclerosis (MS) is disclosed. The method comprises: removing cerebrospinal fluid from a patient with MS; filtering the cerebrospinal fluid with a filtration system to remove oxidative and/or inflammatory agents; and returning the filtered cerebrospinal fluid to the patient.

[0084] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with MS includes removing cerebrospinal fluid from a lumbar cerebrospinal space of the patient.

[0085] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with MS includes disposing a catheter system within a cerebrospinal space.

[0086] Alternatively or additionally to any of the embodiments above, the catheter system includes a catheter shaft having an inner shaft and an outer shaft.

[0087] Alternatively or additionally to any of the embodiments above, the inner shaft has a plurality of openings formed therein.

[0088] Alternatively or additionally to any of the embodiments above, the outer shaft has a plurality of openings formed therein.

[0089] Alternatively or additionally to any of the embodiments above, the inner shaft has a first plurality of openings formed therein, wherein the outer shaft has a second plurality of openings formed therein, and wherein at least some of the first plurality of openings differ in size, shape, or both from at least some of the second plurality of openings.

[0090] Alternatively or additionally to any of the embodiments above, the inner shaft defines an infusion lumen.

[0091] Alternatively or additionally to any of the embodiments above, returning the filtered cerebrospinal fluid to the patient includes returning the filtered cerebrospinal fluid through the infusion lumen.

[0092] Alternatively or additionally to any of the embodiments above, further comprising infusing a drug through the infusion lumen.

[0093] Alternatively or additionally to any of the embodiments above, an aspiration lumen is defined between the inner shaft and the outer shaft.

[0094] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with MS includes removing cerebrospinal fluid through the aspiration lumen.

[0095] Alternatively or additionally to any of the embodiments above, the filtration system includes a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both.

[0096] Alternatively or additionally to any of the embodiments above, the filtration system includes an electrofilter.

[0097] A method for treating human immunodeficiency virus (HIV) is disclosed. The method comprises: removing cerebrospinal fluid from a patient with HIV; filtering the cerebrospinal fluid with a filtration system to remove viral, oxidative, and/or inflammatory agents; and returning the filtered cerebrospinal fluid to the patient.

[0098] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with HIV includes removing cerebrospinal fluid from a lumbar cerebrospinal space of the patient.

[0099] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with HIV includes disposing a catheter system within a cerebrospinal space.

[0100] Alternatively or additionally to any of the embodiments above, the catheter system includes a catheter shaft having an inner shaft and an outer shaft.

[0101] Alternatively or additionally to any of the embodiments above, the inner shaft has a plurality of openings formed therein.

[0102] Alternatively or additionally to any of the embodiments above, the outer shaft has a plurality of openings formed therein.

[0103] Alternatively or additionally to any of the embodiments above, the inner shaft has a first plurality of openings formed therein, wherein the outer shaft has a second plurality of openings formed therein, and wherein at least some of the first plurality of openings differ in size, shape, or both from at least some of the second plurality of openings.

[0104] Alternatively or additionally to any of the embodiments above, the inner shaft defines an infusion lumen.

[0105] Alternatively or additionally to any of the embodiments above, returning the filtered cerebrospinal fluid to the patient includes returning the filtered cerebrospinal fluid through the infusion lumen.

[0106] Alternatively or additionally to any of the embodiments above, further comprising infusing a drug through the infusion lumen.

[0107] Alternatively or additionally to any of the embodiments above, an aspiration lumen is defined between the inner shaft and the outer shaft.

[0108] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with HIV includes removing cerebrospinal fluid through the aspiration lumen.

[0109] Alternatively or additionally to any of the embodiments above, the filtration system includes a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both.

[0110] Alternatively or additionally to any of the embodiments above, the filtration system includes an electrofilter.

[0111] A method for treating Guillain-Barré syndrome (GBS) is disclosed. The method comprises: removing cerebrospinal fluid from a patient with GBS; filtering the cere-

brospinal fluid with a filtration system to remove oxidative and/or inflammatory agents; and returning the filtered cerebrospinal fluid to the patient.

[0112] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with GBS includes removing cerebrospinal fluid from a lumbar cerebrospinal space of the patient.

[0113] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with GBS includes disposing a catheter system within a cerebrospinal space.

[0114] Alternatively or additionally to any of the embodiments above, the catheter system includes a catheter shaft having an inner shaft and an outer shaft.

[0115] Alternatively or additionally to any of the embodiments above, the inner shaft has a plurality of openings formed therein.

[0116] Alternatively or additionally to any of the embodiments above, the outer shaft has a plurality of openings formed therein.

[0117] Alternatively or additionally to any of the embodiments above, the inner shaft has a first plurality of openings formed therein, wherein the outer shaft has a second plurality of openings formed therein, and wherein at least some of the first plurality of openings differ in size, shape, or both from at least some of the second plurality of openings.

[0118] Alternatively or additionally to any of the embodiments above, the inner shaft defines an infusion lumen.

[0119] Alternatively or additionally to any of the embodiments above, returning the filtered cerebrospinal fluid to the patient includes returning the filtered cerebrospinal fluid through the infusion lumen.

[0120] Alternatively or additionally to any of the embodiments above, further comprising infusing a drug through the infusion lumen.

[0121] Alternatively or additionally to any of the embodiments above, an aspiration lumen is defined between the inner shaft and the outer shaft.

[0122] Alternatively or additionally to any of the embodiments above, removing cerebrospinal fluid from a patient with GBS includes removing cerebrospinal fluid through the aspiration lumen.

[0123] Alternatively or additionally to any of the embodiments above, the filtration system includes a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both.

[0124] Alternatively or additionally to any of the embodiments above, the filtration system includes an electrofilter.

[0125] A system for removing materials from cerebrospinal fluid is disclosed. The system comprises: a first port for providing access a cerebrospinal space at a first location; a first catheter coupled to the first port, the first catheter being designed to remove cerebrospinal fluid from the first location; a filtration system coupled to the first catheter, the filtration system being designed to filter the cerebrospinal fluid removed from the first location; a second port for providing access a cerebrospinal space at a second location; and a second catheter coupled to the second port, the first catheter being designed to returned the filtered cerebrospinal fluid.

[0126] Alternatively or additionally to any of the embodiments above, the first location is a lumbar region of a patient.

[0127] Alternatively or additionally to any of the embodiments above, the second location is adjacent to a cranial region of the patient.

[0128] A method for ameliorating a symptom of bacterial meningitis in a patient is disclosed. The method comprises: selecting a patient having a symptom of bacterial meningitis; removing cerebrospinal fluid from a first location in a lumbar cerebrospinal fluid space of the patient; removing at a flow rate one or more meningitis causing bacterial pathogen from the removed cerebrospinal fluid, thereby conditioning the cerebrospinal fluid; and returning the conditioned cerebrospinal fluid to the patient at a second location in a cervical cerebrospinal fluid space, a thoracic cerebrospinal fluid space, or a ventricle of the patient; wherein the removing and returning steps are performed concurrently using one or more catheters, each catheter comprising one or more lumens.

[0129] Alternatively or additionally to any of the embodiments above, the cerebrospinal fluid is returned to the patient at substantially the same flow rate at which it is removed.

[0130] Alternatively or additionally to any of the embodiments above, further including removing at the flow rate one or more endotoxins from the removed cerebrospinal fluid.

[0131] Alternatively or additionally to any of the embodiments above, further including removing at the flow rate one or more cytokines from the removed cerebrospinal fluid.

[0132] Alternatively or additionally to any of the embodiments above, the removing of the one or more meningitis causing bacterial pathogens is achieved using a filter system particularly configured to remove the one or more meningitis causing bacterial pathogens.

[0133] Alternatively or additionally to any of the embodiments above, the removing of the one or more endotoxins is achieved using a filter system particularly configured to remove the one or more endotoxins.

[0134] Alternatively or additionally to any of the embodiments above, the removing of the one or more cytokines is achieved using a filter system particularly configured to remove the one or more cytokines.

[0135] Alternatively or additionally to any of the embodiments above, the filter system comprises a tangential flow filtration (TFF) filter.

[0136] Alternatively or additionally to any of the embodiments above, the filter system comprises filter capable of removing material having a mass in the range of 1 to 500 kDa.

[0137] Alternatively or additionally to any of the embodiments above, the filter system comprises filter having a pore size in the range of 0.1 to 5 microns.

[0138] Alternatively or additionally to any of the embodiments above, the one or more meningitis causing bacterial pathogen is a gram-negative bacterial pathogen.

[0139] Alternatively or additionally to any of the embodiments above, the one or more meningitis causing bacterial pathogen is *Pseudomonas* bacteria, *Acinetobacter* bacteria, *Klebsiella* bacteria, or combinations thereof.

[0140] Alternatively or additionally to any of the embodiments above, the one or more meningitis causing bacterial pathogen is multi-drug resistant.

[0141] Alternatively or additionally to any of the embodiments above, the one or more catheters comprises a single catheter comprising a first lumen with a first proximal port at the first location and a second lumen having a second distal port at the second location during at least a portion of a conditioning treatment.

[0142] Alternatively or additionally to any of the embodiments above, the one or more catheters comprises a first

catheter inserted at the first location and a second catheter inserted at the second location during at least a portion of a conditioning treatment.

[0143] Alternatively or additionally to any of the embodiments above, the first catheter and the second catheter each comprise a single lumen.

[0144] Alternatively or additionally to any of the embodiments above, the flow rate is in a range from 0.04 ml/min to 30 ml/min.

[0145] Alternatively or additionally to any of the embodiments above, a volume of cerebrospinal fluid removed from the patient never exceeds 40 ml.

[0146] Alternatively or additionally to any of the embodiments above, wherein the second location is in the cervical cerebrospinal fluid space.

[0147] Alternatively or additionally to any of the embodiments above, the second location is in the ventricle of a brain.

[0148] Alternatively or additionally to any of the embodiments above, the second location is in a thoracic cerebrospinal fluid space.

[0149] Alternatively or additionally to any of the embodiments above, flow directions of removing and returning cerebrospinal fluid are periodically reversed so that CSF is returned to the first location and removed from the second location during a portion of the treatment.

[0150] Alternatively or additionally to any of the embodiments above, the flow reversal is a pulse to dislodge debris from removal or return ports.

[0151] Alternatively or additionally to any of the embodiments above, further comprising mixing the conditioned cerebrospinal fluid with endogenous cerebrospinal fluid as the conditioned cerebrospinal fluid is returned to the cerebrospinal fluid space.

[0152] Alternatively or additionally to any of the embodiments above, mixing comprises inducing a turbulent flow as the conditioned cerebrospinal fluid is returned.

[0153] Alternatively or additionally to any of the embodiments above, further comprising the step of isolating at least one of erythrocytes, hemoglobin, oxyhemoglobin, and endothelin.

[0154] Alternatively or additionally to any of the embodiments above, conditioning comprises one or more separation processes selected from the group consisting of biospecific affinity, immunoaffinity, cationic exchange, anionic exchange, hydrophobicity, and size exclusion.

[0155] Alternatively or additionally to any of the embodiments above, the conditioning step is performed externally to the patient's body.

[0156] A system for ameliorating a symptom of bacterial meningitis in a patient is disclosed. The system comprises: a catheter assembly having a first lumen with a distal port and a second lumen with a proximal port, said catheter being adapted to be introduced in a CSF space and said ports being spaced axially apart; a pump connectable between the first and second lumens to induce a flow of CSF therebetween; and a filter component connectable between the first and second lumens, the filter component configured to remove one or more meningitis causing bacterial pathogen from the CSF, to thereby condition the cerebrospinal fluid.

[0157] Alternatively or additionally to any of the embodiments above, the filter component is further configured to remove one or more endotoxins from the CSF.

[0158] Alternatively or additionally to any of the embodiments above, the filter component is further configured to remove one or more cytokines from the CSF.

[0159] Alternatively or additionally to any of the embodiments above, the filter component comprises a tangential flow filtration (TFF) filter.

[0160] Alternatively or additionally to any of the embodiments above, the filter component is capable of removing material having a mass in the range of 1 to 500 kDa.

[0161] Alternatively or additionally to any of the embodiments above, the filter component has a pore size in the range of 0.1 to 5 microns.

[0162] Alternatively or additionally to any of the embodiments above, the filter component is configured to remove one or more gram-negative bacterial pathogen.

[0163] Alternatively or additionally to any of the embodiments above, the filter component is configured to remove one or more of *Pseudomonas* bacteria, *Acinetobacter* bacteria, *Klebsiella* bacteria, or combinations thereof.

[0164] Alternatively or additionally to any of the embodiments above, the filter component is configured to remove one or more meningitis causing bacterial pathogen that is multi-drug resistant.

[0165] Alternatively or additionally to any of the embodiments above, the catheter assembly comprises a single catheter comprising a first lumen with a first proximal port and a second lumen having a second distal port.

[0166] Alternatively or additionally to any of the embodiments above, the catheter assembly comprises a first catheter and a second catheter.

[0167] Alternatively or additionally to any of the embodiments above, the first catheter and the second catheter each comprise a single lumen.

[0168] A method for treating meningitis is disclosed. The method comprises: removing cerebrospinal fluid from a patient with meningitis; filtering the cerebrospinal fluid with a filtration system, the filtration system including a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both; and returning the filtered cerebrospinal fluid to the patient.

[0169] Alternatively or additionally to any of the embodiments above, filtering the cerebrospinal fluid with a filtration system removes one or more meningitis causing bacterial pathogens from the cerebrospinal fluid.

[0170] Alternatively or additionally to any of the embodiments above, the one or more meningitis causing bacterial pathogens include gram-negative bacteria.

[0171] Alternatively or additionally to any of the embodiments above, the one or more meningitis causing bacterial pathogens include *Pseudomonas* bacteria, *Acinetobacter* bacteria, *Klebsiella* bacteria, or combinations thereof.

[0172] Alternatively or additionally to any of the embodiments above, filtering the cerebrospinal fluid with a filtration system removes one or more bacterial endotoxins from the cerebrospinal fluid.

[0173] Alternatively or additionally to any of the embodiments above, filtering the cerebrospinal fluid with a filtration system removes one or more neuroinflammatory agents from the cerebrospinal fluid.

[0174] Alternatively or additionally to any of the embodiments above, filtering the cerebrospinal fluid with a filtration system removes one or more meningitis causing fungal pathogens from the cerebrospinal fluid.

[0175] Alternatively or additionally to any of the embodiments above, the one or more meningitis causing fungal pathogens include *Cryptococcus neoformans*.

[0176] Alternatively or additionally to any of the embodiments above, filtering the cerebrospinal fluid with a filtration system removes one or more fungal antigens from the cerebrospinal fluid.

[0177] Alternatively or additionally to any of the embodiments above, filtering the cerebrospinal fluid with a filtration system removes one or more inflammatory agents from the cerebrospinal fluid.

[0178] Alternatively or additionally to any of the embodiments above, filtering the cerebrospinal fluid with a filtration system removes one or more cytokines from the cerebrospinal fluid.

[0179] Alternatively or additionally to any of the embodiments above, further comprising delivering a drug to the central nervous system.

[0180] Alternatively or additionally to any of the embodiments above, further comprising delivering a drug to the cerebrospinal fluid.

[0181] A system for treating fungal meningitis in a patient is disclosed. The system comprises: a catheter having a first lumen with a distal port and a second lumen with a proximal port, the catheter being designed to be introduced in a cerebrospinal fluid space and the ports being spaced axially apart; a pump connectable between the first and second lumens to induce a flow of cerebrospinal fluid therebetween; and a filter component connectable between the first and second lumens, the filter component configured to remove one or more meningitis causing fungal pathogens from the cerebrospinal fluid, to thereby condition the cerebrospinal fluid.

[0182] Alternatively or additionally to any of the embodiments above, the filter component is further configured to remove one or more fungal antigens from the cerebrospinal fluid.

[0183] Alternatively or additionally to any of the embodiments above, the filter component is further configured to remove one or more inflammatory agents from the cerebrospinal fluid.

[0184] Alternatively or additionally to any of the embodiments above, the filter component is further configured to remove one or more cytokines from the cerebrospinal fluid.

[0185] Alternatively or additionally to any of the embodiments above, the catheter is designed to aspirate cerebrospinal fluid from a patient at an aspiration rate, return conditioned cerebrospinal fluid to the patient at a return rate; wherein a waste rate is defined as the difference between the aspiration rate and the return rate; and wherein the waste rate is controlled to maintain physiologically appropriate cerebrospinal fluid volumes and intracranial pressure in the patient.

[0186] A system for treating fungal meningitis in a patient is disclosed. The system comprises: a catheter having a first lumen with a distal port and a second lumen with a proximal port, the catheter being designed to be introduced in a cerebrospinal fluid space and the ports being spaced axially apart; a pump connectable between the first and second lumens to induce a flow of cerebrospinal fluid therebetween; and a filter component connectable between the first and second lumens, the filter component configured to remove

one or more meningitis causing bacterial pathogens from the cerebrospinal fluid, to thereby condition the cerebrospinal fluid.

[0187] Alternatively or additionally to any of the embodiments above, the filter component is further configured to remove one or more bacterial endotoxins from the cerebrospinal fluid.

[0188] Alternatively or additionally to any of the embodiments above, the filter component is further configured to remove one or more inflammatory agents from the cerebrospinal fluid.

[0189] Alternatively or additionally to any of the embodiments above, the filter component is further configured to remove one or more cytokines from the cerebrospinal fluid.

[0190] Alternatively or additionally to any of the embodiments above, the catheter is designed to aspirate cerebrospinal fluid from a patient at an aspiration rate, return conditioned cerebrospinal fluid to the patient at a return rate; wherein a waste rate is defined as the difference between the aspiration rate and the return rate; and wherein the waste rate is controlled to maintain physiologically appropriate cerebrospinal fluid volumes and intracranial pressure in the patient.

[0191] A system for treating meningitis is disclosed. The system comprises: a catheter having a first lumen with a distal port and a second lumen with a proximal port, the catheter being designed to be introduced in a cerebrospinal fluid space and the ports being spaced axially apart; a pump connectable between the first and second lumens to induce a flow of cerebrospinal fluid therebetween; and a filter component connectable between the first and second lumens, the filter component configured to remove one or more meningitis related pathogens from the cerebrospinal fluid, to thereby condition the cerebrospinal fluid.

[0192] A system for treating meningitis is disclosed. The system comprises: a catheter for removing one or more meningitis related pathogens, the catheter including a filtration system; and wherein the filtration system includes a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, or both.

[0193] The above summary of some embodiments is not intended to describe each disclosed embodiment or every implementation of the present disclosure. The Figures, and Detailed Description, which follow, more particularly exemplify these embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0194] The disclosure may be more completely understood in consideration of the following detailed description in connection with the accompanying drawings, in which:

[0195] FIG. 1 illustrates a Y-connector portion, a proximal subassembly, and a distal subassembly of a catheter according to certain implementations.

[0196] FIG. 2 illustrates a sectional view taken from the region of the catheter of FIG. 1 marked with cutting plane line A-A.

[0197] FIG. 3 illustrates a sectional view taken from the region of the catheter of FIG. 1 marked with cutting plane line B-B.

[0198] FIG. 4 illustrates an enlarged, detail view of a portion of the Y-connector of the catheter of FIG. 1.

[0199] FIG. 5 illustrates the location of position markers on a catheter according to certain implementations.

[0200] FIG. 6 illustrates a sectional view taken from the region of the catheter of FIG. 5 marked with the cutting plane line J-J.

[0201] FIG. 7 illustrates a portion of a catheter near the joining of a proximal subassembly and a distal subassembly according to certain implementations.

[0202] FIG. 8 illustrates a portion of a proximal subassembly according to certain implementations.

[0203] FIG. 9 illustrates a detail view of the proximal subassembly of FIG. 8.

[0204] FIG. 10 illustrates a sectional view taken from the region of the proximal subassembly of FIG. 8 marked with the cutting plane line A-A.

[0205] FIG. 11 illustrates a detail view of a portion of the proximal subassembly of FIG. 9 taken from the view of line D-D.

[0206] FIG. 12 illustrates a sectional view taken from the region of the proximal subassembly of FIG. 8 marked with the cutting plane E-E.

[0207] FIG. 13 illustrates a portion of a distal subassembly according to certain implementations.

[0208] FIG. 14 illustrates a detailed portion of the distal subassembly of FIG. 13.

[0209] FIG. 15 illustrates a detailed portion of the distal subassembly of FIG. 13.

[0210] FIG. 16 illustrates a sectional view taken from the region of the distal subassembly of FIG. 13 marked with the cutting plane A-A.

[0211] FIG. 17 schematically illustrates an example pump system.

[0212] While the disclosure is amenable to various modifications and alternative forms, specifics thereof have been shown by way of example in the drawings and will be described in detail. It should be understood, however, that the intention is not to limit the disclosure to the particular embodiments described. On the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the disclosure.

DETAIL DESCRIPTION

[0213] Cerebrospinal fluid (CSF) is a generally clear, colorless fluid that is produced in the ventricles, specifically the choroid plexuses, in the brain. The choroid plexus produces approximately 500 milliliters of CSF daily in order to accommodate flushing or recycling of CSF to remove toxins and metabolites, which happens several times per day. From the choroid plexus, CSF flows slowly through a channel (canal) into the space surrounding the brain and spinal column, and then into the body. CSF is found in the space between the pia mater and the arachnoid mater, known as the subarachnoid space. CSF is also found in and around the ventricular system in the brain, which is continuous with the central canal of the spinal cord. In the event of a stroke or other brain trauma, it can be desirable to remove the CSF from one location (e.g., the cervical region of the spine, or a brain ventricle), filter it, and return it to the CSF space at a second location (e.g., the lumbar region of the spine). However, accurate delivery of medical instruments to the CSF space can be challenging.

[0214] The present disclosure relates to removal, exchange and recirculation of cerebrospinal fluid (CSF). Devices, systems and methods disclosed herein are used to safely and efficiently navigate the space at and around the brain and spinal cord where the CSF flows through the body,

also known as the CSF space. Specialized devices and systems are useful and sometimes necessary to navigate the CSF space due to the difficult points of entry and exit and the potentially life threatening consequences if a mistake is made. Increased safety and efficacy reduce time spent in the surgical suite and potential complications.

[0215] Neurapheresis may be understood to be the removal of materials (e.g., microorganisms, cells, viruses, foreign material, drugs, combinations thereof, and the like) from CSF. This and other therapeutic techniques can be used to treat a number of neurological diseases or conditions, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Amyotrophic Lateral Sclerosis (ALS), Encephalitis from various causes, Meningitis from various causes, Guillain-Barré Syndrome (GBS), Multiple Sclerosis (MS), HIV-associated neurocognitive disorders, Spinal Cord Injury, Traumatic Brain Injury, cerebral vasospasm, stroke and other diseases or conditions.

[0216] The purification, conditioning, and/or compound removal schema can be tailored to a specific disease or group of diseases as suitable, including based on a number of features, such as size, affinity, biochemical properties, temperature, and other features. Purification schema may be based on diffusion, size-exclusion, ex-vivo immunotherapy using immobilized antibodies or antibody fragments, hydrophobic/hydrophilic, anionic/cationic, high/low binding affinity, chelators, anti-bacterial, anti-viral, anti-DNA/RNA/amino acid, enzymatic, and magnetic and/or nanoparticle-based systems. The system can be adjustable to a broad range of biologic parameters and flows.

[0217] With regard to a Neurapheresis system in particular, the disclosed system can be used to safely and quickly access the CSF space with minimal disturbance to the CSF flow. The systems and devices disclosed herein provide a safe and rapid flow circuit and provide filtration.

[0218] A Neurapheresis system should provide for the exchange, removal, and/or recirculation of CSF, safely and efficiently. The systems and devices disclosed herein may be used in a Neurapheresis system.

[0219] The systems and devices disclosed herein can be used to access the CSF space to remove the CSF from one location (e.g., the cervical region of the spine, or a brain ventricle), filter or otherwise treat it, and return it to the CSF space, including at a second location (e.g., the lumbar region of the spine), safely and efficiently. In various aspects, the systems and devices disclosed herein maintain the endogenous intracranial or intraspinal pressure within a physiological range, for example, from about 5 to about 20 mm Hg or from about 0 to about 10 mm Hg or from about -5 to about 10 mm Hg or from about -5 to about 25 mm Hg. The present system thus reduces spinal headache, for example, due to hydrocephalus (abnormal accumulation of CSF in the ventricles of the brain). The present system may also be used to reduce spinal headaches caused by low pressure (e.g., due to overdrainage, herniation, etc.). In some aspects, the system may include sensors within the catheter or within the flow circuit to detect clogs or blockages in the system, thereby providing closed loop pressure control. In various aspects, the systems and devices disclosed herein also help the system to perform efficiently by reducing or eliminating recirculating flow loops. The systems and devices maintain spacing between the inlet and outlet, for example, between about 10 cm to about 40 cm. In certain implementations, the spacing is between about 10 cm and about 30 cm. The inlets

and outlets are located in places in the CSF space so that turning on the pump or otherwise creating positive or negative pressure in the system will not cause or encourage tissue being drawn into the catheter. In some aspects, the inlets and outlets are placed near the lumbar cervical cisterns to prevent tissue from being drawn into the catheter. In some aspects, there may also be multiple holes along the inlet and outlet for redundancy in case there is tissue blocking some number of holes. In certain implementations, a particular coil pitch of a coiled wire within the catheter may be selected in order to reduce kinking of the catheter. In certain aspects, the inlet-outlet spacing may be selected to be maximized while staying below the level of a cervical region of a patient. In certain aspects, the inlet-outlet spacing may be selected based on vertebral spacing. For example, the spacing may be selected so that the inlet-outlet spacing is between the lengths of approximately 5 vertebrae and approximately 12 vertebrae. In certain implementations, a spacing of approximately 10 vertebrae may be selected; however, other configurations (such as those described elsewhere in the specification) may be utilized. When designing such spacing, it may be assumed that a vertebra is approximately 2-3 cm in length, however, other measurements and designs may be used. In certain implementations, a particular size, shape, and/or other configuration of a lumen may be selected to facilitate catheter unblocking and/or the ability of the catheter to resist blockage. For example, a proximal outer diameter of a lumen of between approximately 0.060 inches and approximately 0.070 inches and a proximal inner diameter of between approximately 0.025 inches and 0.060 inches may be selected; however, other configurations (such as those described elsewhere in the specification) may be utilized.

[0220] The disclosed systems and devices are used to access the CSF space and may be used at any access point in the cervical (C1-C7), thoracic (T1-T12), or lumbar region (L1-L5) of the vertebral column. An access site in the cervical region may be used to access the ventricular system in the brain. In one embodiment, the system and device are used to access the lumbar region. In some embodiments, the inlets and outlets are located in places in the spine such that the drainage process will not cause tissue to be drawn into the catheter. For example, when a patient is lying on a table, entry may be made at a suitable angle, such as, for example, about 90 degrees, to access the spine. A traditional catheter must be pushed through a 90 degree bend at the L4-L6 region. The catheters and related delivery devices disclosed herein may be curved such that they can access and navigate this angled bend more easily and efficiently.

[0221] FIGS. 1-16 illustrate overall views, proximal sub-assembly views, and distal subassembly views of an embodiment of a catheter 500 according to certain implementations. FIG. 1 illustrates a Y-connector portion 502, a proximal subassembly 540, and a distal subassembly 560. The Y-connector portion 502 may include connectors 504, 506, features 508, 510, 512, position marker 514, and other components. The connectors 504, 506 may take various forms. For example, as illustrated, the connectors 504, 506 are female and male Luer-lock connectors, respectively. The features 508, 510, 512 may be strain relief and kink resistance features, for example, as described above with reference to strain relief and kink resistance feature 60. The feature 508 may be configured to allow flex or deformation of the catheter 500 at portions near a central meeting point

of the Y-connector **502**. The features **510**, **512** may be configured to allow flex or deformation of the catheter **500** near the connectors **504**, **506**. In certain implementations, the features **510**, **512** may be color coded to indicate to which lumen of a multi-lumen catheter, the connectors **504**, **506**, correspond. In certain embodiments, the features **508**, **510**, **512** may take the form of approximately $\frac{1}{8}$ " polyolefin heat shrink tubing. The position marker **514** may be a position marker as described above with reference to position marker **100**.

[0222] The length L_1 of the catheter **500** may be approximately 1,300 mm with a working length L_2 of approximately 1,150 mm. The working length L_2 may be defined based on various use and design considerations. As illustrated, the working length L_2 is the distance from the distal end of the distal subassembly **560** to the distal end of the feature **508**. The distance D_1 from the distal end of the feature **508** to the proximal end of the connector **506** may be approximately 150 mm. The feature **508** may have a length L_3 of approximately 35 mm and the features **510**, **512** may have a length L_4 of approximately 7 mm. In certain implementations, the catheter **500** may have a length L_1 of between approximately 400 mm and approximately 1200 mm, with the working length L_2 and other measurements changed accordingly at varying scales.

[0223] FIG. 2 illustrates a sectional view taken from the region of the catheter **500** marked with cutting plane line A-A. This view illustrates a lumen **516A** defined by a wall **516B**. The characteristics and properties of the lumen **516A** and wall **516B** may be similar to the other walls and lumens described herein. As illustrated, the wall **516B** has an inner diameter D_2 of approximately 0.54 mm and an outer diameter D_3 of approximately 1.14 mm.

[0224] FIG. 3 illustrates a sectional view taken from the region of the catheter **500** marked with cutting plane line B-B. This view illustrates a lumen **518A** defined by an inner wall **518B** and a lumen **520A** defined by the space between the inner wall **518B** and an outer wall **520B**. The characteristics and properties of the lumens **518A**, **520A** and the walls **518B**, **520B** may be similar to the other walls and lumens described herein. The inner wall **518B** may have an inner diameter D_4 of approximately 0.56 mm and an outer diameter D_5 of approximately 0.71 mm. The outer wall **520B** may have an inner diameter of approximately 1.32 mm and an outer diameter of approximately 1.689 mm.

[0225] FIG. 4 illustrates an enlarged, detail view of a portion of the Y-connector **502** according to certain implementations, including tubes **522**, first branch **524**, and second branch **526**. The tubes **522** may be hypotubes or other lengths of tubing. The tubes **522** may have a length L_5 of approximately 10 mm. In certain implementations, the first branch **524** may place the connector **504** in fluid connection with the lumen **520A** and the second branch **526** may place the connector **506** in fluid connection with the lumen **518A**.

[0226] FIG. 5 illustrates the location of two position markers **514** on the catheter **500**. The distal end of the first position marker **514** is located a distance D_9 of approximately 450 mm away from the distal end of the catheter **500**. The distal end of the second position marker **514** is located a distance D_8 of approximately 550 mm away from the distal end of the catheter **500**. The length L_4 of the position markers **514** is approximately 10 mm. In certain implementations, the bands and/or position markers (such as position markers **514**) may comprise PET heat shrink tubing.

[0227] FIG. 6 illustrates a sectional view taken from the region of the catheter **500** marked with the cutting plane line J-J. This view illustrates an embodiment wherein an outer portion of the position marker **514** is substantially adjacent to an inner portion of the wall **520B**. Accordingly, in this portion of this embodiment, the lumen **520A** is defined by the outer portion of the wall **518B** and the inner portion of the position marker **514**. As illustrated, the outer wall **520B** has an outer diameter D_{10} of approximately 1.75 mm. In other instances, the position marker **514** may be disposed along the outer portion of the wall **520B**, along the outer portion of the wall **518B**, or along another region of the catheter **500**.

[0228] FIG. 7 illustrates a portion of the catheter **500**, including bands **528A**, **528B**, and **530A**, openings **532A** and **532B**, and a radiused tip **530**. The distal portion of the band **530A** may be located a distance D_{11} of approximately 300 mm away (e.g., or more or less, depending on the size/height of the patient) from the distal portion of the band **528A**. This spacing may help to reduce local recirculation and/or help avoid sensitive nerve structures in the cervical spine. The distal end of the band **528A** may be located a distance D_{12} of approximately 2 mm away from the distal end of the radiused tip **530**. The radiused tip may have a radius R_1 of approximately 0.28 mm.

[0229] FIG. 8 illustrates a portion of the proximal subassembly **540**. As illustrated, the distance D_1 from the distal end of the proximal subassembly **540** to the proximal end of the proximal subassembly **540** is approximately 893 mm. The distance D_2 from the distal end of a marker band **544B** to a distal end of a band **530A** is approximately 248 mm. A distance D_4 from a proximal end of the proximal subassembly **540** to the distal end of a band **530B** is approximately 845 mm. A distance D_3 from a distal end of the marker band **544A** to a distal end of the band **530A** is approximately 148 mm. The marker bands **544A**, **544B** may have a length L_1 of approximately 10 mm. A portion of the proximal subassembly **540** may comprise coiled wire **542B** having a coil pitch of approximately 0.018". A portion of the proximal subassembly **540** may comprise coiled wire **542A** having a coil pitch of approximately 0.095". In certain implementations, the wires **542A**, **542B** may comprise approximately 0.003" round wire spool of 304V spring temper material.

[0230] In certain implementations, the proximal subassembly **540** of the catheter **500** may have an outer diameter of between approximately 0.06" and approximately 0.07". This configuration may maximize the size of the catheter between layers of tissue to enable a desired level of drainage and/or suction without collapse. The thickness of the proximal subassembly **540** and other sections of the catheter **500** may be a function of a design of one or more layers of coil and sheath. The thickness may affect the stiffness and pushability of the catheter **500** and kink-resistance. In certain implementations, the diameter of an inner lumen of the catheter **500** (such as the diameter of a lumen of the proximal subassembly **540**) may be chosen to provide optimum drainage and/or suction given the constraints of particular anatomy or procedures. For example, the minimum diameter of a proximal inner lumen may be chosen to be between approximately 0.025" and approximately 0.060".

[0231] FIG. 9 illustrates a detail view of the proximal subassembly **540** of FIG. 8. As illustrated, a portion of the proximal subassembly **540** defines a plurality of openings

532A (e.g. 2, 3, 4, 5, 6, 7, 8, 9, 10 11, 12, 13 14, 15, 16, or more openings **532A**). The openings **532A** may be in fluid connection with a lumen **520A** of the catheter **500** and, in at least some instances, may be arranged on opposing “top” and “bottom” sides of the catheter **500**. The openings **532A** may be spaced with 2 coil pitch spacing of the wire **542A**. The distance D_6 between the distal end of the band **530B** and the distal end of the band **530A** is approximately 45 mm. A distance D_5 from the distal end of the band **530A** to the distal end of the proximal subassembly **540** may be approximately 3 mm. In certain implementations, the bands **530A**, **530B** may comprise a radiopaque band having an inner diameter of approximately 0.061" and an outer diameter of approximately 0.064".

[0232] FIG. 10 illustrates a sectional view taken from the region of the proximal subassembly **540** marked with the cutting plane line A-A, including a liner **546** and tubing **548**. The liner **546** and the tubing **548** may be arranged such that the tubing **548** is within the liner **546**. The coil **542A** may be disposed between the liner **546** and the tubing **548**. In certain implementations, the liner **546** may comprise approximately 0.001" WT PTFE liner. The tubing **548** may comprise approximately 0.004" WT polyether block amide tubing. The outer diameter D_7 of the combination tubing **548** and liner **546** may be approximately 1.69 mm. The inner diameter D_8 of the same may be approximately 1.32 mm.

[0233] FIG. 11 illustrates a detail view of a portion of the proximal subassembly **540** taken from the view of line D-D and illustrating one of the openings **532A**. The illustrated opening **532A** has dimensions of approximately 1.57 mm by approximately 0.56 mm. In at least some instances, the openings **532A** may be oval in shape. Other shapes are contemplated. The shape of the openings **532A** may be the same along the length of the proximal subassembly **540** or the shape of the openings **532A** may differ along the length of the proximal subassembly **540**. In at least some instances, the openings **532A** may be larger than the openings **532B**.

[0234] FIG. 12 illustrates a sectional view taken from the region of the proximal subassembly **540** marked with the cutting plane E-E. As illustrated the outer diameter D_9 this portion, inclusive of marker band **544** is approximately 1.75 mm.

[0235] FIG. 13 illustrates a portion of the distal subassembly **560**. The length L_1 of the distal subassembly **560** may be approximately 302 mm. The distance D_1 from the proximal end of the distal subassembly **560** to the distal end of a band **528B** is approximately 270 mm. A portion of the distal subassembly **560** may comprise a coiled wire **562B** may have a coil pitch of approximately 0.032". This and other portions of the catheter **500** may comprise approximately 0.003" WT nylon 12 tubing having an inner diameter of approximately 0.022" and approximately 0.007" WT PEBAX tubing having an inner diameter of approximately 0.04".

[0236] FIG. 14 illustrates a detailed portion of the distal subassembly **560**, including the band **528A**, a plurality of openings **532B**, the band **528B**, a wire **562A**, and the wire **562B**. In certain implementations, the wires **562A**, **562B** may be different portions of the same wire or may be separate sections of wire. As illustrated, the wire **562A** and **562B** may be separated by band **528B**. The wire **562A** may have a coil pitch of approximately 0.065". The wires **562A**, **562B** may be disposed between layers of the distal subassembly **560** and may comprise approximately 0.003" round

wire spool 304V spring temper material. The openings **532B** may be spaced with 2 coil pitch spacing and arranged on a top and a bottom portion of the catheter **500** and made a fluid connection with an inner lumen **516A** of the catheter **500**. In at least some instances, the openings **532B** may be round or substantially round. Other shapes are contemplated. The shape of the openings **532B** may be the same along the length of the distal subassembly **560** or the shape of the openings **532B** may differ along the length of the distal subassembly **560**. A distance D_2 between the distal end of the band **528B** and the distal end of the band **528A** may be approximately 30 mm. The wire **562A** may be disposed within this region. The bands **528A**, **528B** may have an inner diameter of approximately 0.032" and an outer diameter of approximately 0.034". The bands **528A**, **528B** may include a radiopaque material (e.g., the bands **528A**, **528B** may comprise a material such as PT/10% IR). The bands **528A**, **528B** may be disposed between the layers of the distal subassembly **560**.

[0237] FIG. 15 illustrates a detailed portion of the distal subassembly **560**, including the radiused tip **530**, the band **528A**, and the wire **562A**. The distance from the distal end of the band **528A** and the distal end of the radiused tip **530** is approximately 2 mm. The radiused tip may have a radius R_1 of approximately 0.28 mm.

[0238] FIG. 16 illustrates a sectional view taken from the region of the distal subassembly **560** marked with the cutting plane A-A. As illustrated, this section of the distal subassembly **560** has an outer diameter of approximately 1.14 mm and an inner diameter of approximately 0.53 mm.

[0239] FIG. 17 schematically depicts a pump/filtration system **600** that may be utilized with the catheter **500**. The catheter **500** may connect to an inlet **670** of the pump/filtration system **600**. For example, the connector **504** may connect to the inlet **670** either directly or through an intermediate tube or mechanism. The inlet **670** may lead to a first filter **672**. In some instances, the first filter **672** is a tangential flow filter. For example, the first filter **672** may include a 5 kDa tangential flow filter (TFF), a 100 kDa TFF, a 0.2 μ m TFF, a 0.45 μ m TFF, or the like. In some instances, the first filter **672** may include a dead-end filter (e.g., 5 kDa dead-end filter). In some instances the first filter **672** may include an electro-filter (e.g., a filter that excludes materials based on charge). In some instances, only one filter (e.g., the first filter **672**) may be utilized. For example, the first filter **672** may be a 5 kDa filter and the first filter **672** may be the only filter. Clean CSF **676** may follow pathway **678**. CSF waste **674** may follow pathway **680**. The waste pathway **680** may lead to a second filter **682**. In some instances, the second filter **682** is a tangential flow filter. For example, the second filter **682** may include a 5 kDa TFF, a 100 kDa TFF, a 0.2 μ m TFF, a 0.45 μ m TFF, or the like. In some instances, the second filter **682** may include a dead-end filter (e.g., 5 kDa dead-end filter). In some instances the second filter **682** may include an electro-filter. In at least some instances, the first filter **672** and the second filter **682** are the same size and/or type (e.g., both the first filter **672** and the second filter **682** are 100 kDa TFF). In other instances, the first filter **672** and the second filter **682** differ (e.g., the first filter **672** is a 5 kDa filter and the second filter **682** is a 100 kDa TFF filter). Clean CSF **684** may follow pathway **686**. CSF waste **688** may follow pathway **690**. A valve or flow metering mechanism **692** may be disposed along the waste pathway **690**, before terminating at pathway **694** and a collection apparatus **696**. Pathways

678 and **686** may merge into a return outlet **698**, which may connect to the connector **506** of the catheter **500** (e.g., either directly or through an intermediate tube).

[0240] In use, the catheter **500** may be disposed within the cerebrospinal space (e.g., such as along lumbar cerebrospinal space). CSF may be removed/aspirated using the catheter **500** (e.g., via the lumen **520A**) and the pump/filtration system **600**. The aspirated fluid may be filtered using the pump/filtration system **600** and the filtered/conditioned CSF may be returned to the patient using the catheter **500** (e.g., via the lumen **518A**) and the pump/filtration system **600**. In some instances, a second catheter **500** (that may be similar in form and function to the catheter **500**) may be disposed in a portion of the cranial CNS such as within a ventricle. The second catheter **500** may be used to remove/aspirate cerebrospinal fluid from a cranial region (e.g., a ventricle), condition/filter the cerebrospinal fluid using the pump/filtration system **600**, and return the conditioned/filtered cerebrospinal fluid to a region at or adjacent to the cranial region. In some of these and in other instance, the second catheter **500** may be used to infuse a drug (e.g., a chemotherapy drug such as methotrexate) into the cranial region. The catheter **500** (e.g., in the cerebrospinal space) and the second catheter **500** (in the ventricle) may be used together or they may be used alternately. Using a catheter **500** in both the cerebrospinal space and in the ventricle, both for aspiration and infusion, may form a cranial-lumbar loop that may improve circulation of cerebrospinal fluid throughout the CNS.

[0241] The catheter **500** (along with the pump/filtration system **600**) may be used to treat a number of conditions. Some of the contemplated conditions include cancer. For example, Leptomeningeal Metastases (LM) is a condition in which cells from a primary solid or hematological tumor metastasize, invade the subarachnoid space (SAS), and spread throughout the cerebrospinal fluid (CSF), resulting in seeding of the leptomeninges along the surface of the central nervous system (CNS). LM represents a late event of cancer progression and the most frequent symptoms include multiple cranial nerve deficits, motor deficits, altered mental status, headache, and radicular pain. The incidence of LM is estimated at 3-5% of cancer patients and has been increasing, due to longer overall survival in cancer patients. LM presents a difficult challenge in metastatic cancer treatment plans, resulting in a devastating prognosis and median survival of 4 months because of lack of effective access and therapies. Systemic therapy with anti-cancer drugs including methotrexate (MTX), cytarabine and thiopeta are not as effective due to poor penetration of the blood-brain barrier (BBB). Intrathecal (IT) drug delivery systems, including Ommaya reservoirs, have been associated with longer overall survival; however, they require repeated injections and rely on passive diffusion. Future therapies that target the entire CNS and enhance the distribution of IT drugs could further improve survival. CSF is produced at approximately 20 ml/hr, with a total volume of ~150 ml, resulting in a turnover, on average, of three times per day. The production rate of CSF is independent of intracranial pressure (ICP). As LM can block the outflow paths of CSF, patients are at serious risk of hydrocephalus and elevated ICP. Additionally, the relative isolation of the CSF by the BBB and blood-CSF barriers, presents a unique environment for tumor survival.

[0242] The catheter **500** may have the ability to rapidly clear a number of CSF pathogens and cells, as well as to

enhance drug delivery in the CSF. For example, the catheter **500** may be used to improve the LM outcome by 1) enhanced exposure and circulation of specific anticancer agents (MTX delivered through an Ommaya reservoir, through the catheter **500**, or both) throughout the SAS, (2) local filtering of CSF to remove cancer-spreading circulating tumor cells (CTCs), (3) control of ICP via CSF drainage, (4) filtration of tumor cells (e.g., living and/or dead tumor cells that may clog the natural reabsorption of the CSF via the arachnoid granulations and lymphatic system). The catheter **500** may also be used to reduce the concentration of a drug (e.g., a chemotherapy agent such as methotrexate) in the CSF (e.g., in order to remove excess drug, reduce toxicity, etc.).

[0243] As alluded to herein, treatment methods are contemplated that include infusing a chemotherapy agent into the patient. In some instances, the chemotherapy agent is methotrexate. Other chemotherapy agents are contemplated. The chemotherapy agent may be infused into the CNS via an Ommaya reservoir (and/or or a similar device including, for example, a Rickham device) implanted in the ventricles of the patient, as is standard of care in these patients. In addition or in the alternative, the chemotherapy agent may be infused into the patient using the catheter **500**. For example, the chemotherapy agent may be added to the return outlet **698**, to one of the ports of the catheter **500**, via a separate device disposed agent to the catheter **500**, or in another suitable manner. The circulation of CSF by the catheter **500** and pump/filtration system **600** may help to circulate the chemotherapy agent throughout the cerebrospinal space and/or the CNS.

[0244] Another contemplated condition that the catheter **500** may be used to treat is Amyotrophic Lateral Sclerosis (ALS). For example, the pathology of ALS may be correlated with overstimulation of glutamatergic functions/pathways with a corresponding excitotoxicity, increased calcium levels, and/or the generation of reactive oxygen species. Oxidative stress may be involved in pathological mechanisms of ALS via cell death-related release of pro-oxidative compounds and redox-active iron, mitochondrial dysfunction, inflammation, and excitotoxicity. The catheter **500** and pump/filtration system **600** may be used to help reduce/clear the CSF of oxidative and/or inflammatory agents (e.g., including free radicals, cytokines, chemokines, white blood cells) such as those correlated with the pathology of ALS. Some examples of materials that may be reduced/removed as part of treating ALS may include one or more of insoluble superoxide dismutase-1 (SOD1), glutamate, neurofilament protein, and anti-GM1 ganglioside antibodies.

[0245] In some instances, the oxidative and/or inflammatory agents may carry an electrical charge. Removal of such materials may be enhanced utilizing electrofiltration (e.g., a filter having an electrical charge). Accordingly, in at least some instances, the first filter **672**, the second filter **682**, or both may include an electrically charged filter (electrofilter). In some of these and in other instances, the first filter **672**, the second filter **682**, or both may include an immunoaffinity column, a size exclusion column, an anionic exchange column, a cationic exchange column, and a Protein A or Protein G column.

[0246] In addition to removing CSF-borne pathological mediators correlated with ALS, the catheter **500** and pump/filtration system **600** may also be used to deliver one or more drugs to the CSF. Such treatments may help further reduce

oxidative and/or inflammatory agents. In some instances, the drug may be added to the return outlet **698**, to one of the ports of the catheter **500**, via a separate device disposed agent to the catheter **500**, or in another suitable manner. The circulation of CSF by the catheter **500** and pump/filtration system **600** may help to circulate the drug throughout the cerebrospinal space and/or the CNS. Some example drugs that may be utilized may include riluzole, edaravone, or the like.

[0247] Another contemplated condition that the catheter **500** may be used to treat is herpes simplex encephalitis (HSE). HSE is known to cause severe neuroinflammation, cerebral edema and hemorrhagic necrosis with resultant increases in intracranial pressure (ICP). While medical management has been standardized, aggressive combined medical and surgical management including decompressive craniectomy and/or temporal lobectomy is often performed due to uncontrolled ICP, neuroinflammation and cerebral edema. The production of reactive oxygen species (ROS) are also believed to be a component of natural defenses to viral infection. However, the lipid-rich environment of the CNS may be susceptible to oxidative damage. Thus, oxidative damage can be correlated with HSE infection.

[0248] The catheter **500** and pump/filtration system **600** may be used to remove oxidative and/or inflammatory agents (e.g., including free radicals, cytokines, chemokines, white blood cells) such as those correlated with the pathology of HSE. In some instances, the oxidative and/or inflammatory agents may carry an electrical charge. Removal of such materials may be enhanced utilizing electrofiltration (e.g., a filter having an electrical charge). Accordingly, in at least some instances, the first filter **672**, the second filter **682**, or both may include an electrically charged filter (electrofilter).

[0249] Another contemplated condition that the catheter **500** may be used to treat is human immunodeficiency virus (HIV) and/or acquired immune deficiency system (AIDS). HIV infection of the CNS can lead to a number of complications including meningitis, acute inflammatory polyneuropathy (AIDP), immune reconstitution inflammatory syndrome (IRIS)-initiated by introduction of antiretroviral therapy, chronic inflammatory polyneuropathy (CIPD), distal symmetric polyneuropathy (DSP), progressive multifocal leuko-encephalopathy (PML), and HIV-associated neurocognitive disorders (HAND). The catheter **500** and pump/filtration system **600** may be designed to filter/reduce/remove a number of different strains of HIV from the CNS. This can reduce viral load in the CSF and/or reduce complications associated with HIV infection in the CNS. In addition, the catheter **500** and pump/filtration system **600** may be designed to filter/reduce/remove a number of different inflammatory agents associated with HIV from the CNS.

[0250] Another contemplated condition that the catheter **500** may be used to treat is multiple sclerosis (MS). Two subtypes, Clinically Isolated Syndrome (CIS) and Relapsing-Remitting Multiple Sclerosis (RRMS), represent the disease absent progression, while Primary Progressive (PPMS) and Secondary Progressive (SPMS) represent patients with progressive disease from the start or after RRMS, respectively. Neuroinflammation leading to multifocal lesion formation, demyelination, axonal damage and consequent neurodegeneration are hallmarks of the disease. Current treatments may be classified as including (1) anti-

inflammatory naturally-occurring molecules (IFN-beta), (2) molecules that stimulate anti-inflammatory (glatiramer acetate) or inhibit autoreactive (teriflunomide) cell proliferation, (3) immunosuppressive monoclonal antibodies (natalizumab), (4) molecules that bind transcription factors to enhance anti-inflammatory mechanisms or suppress pro-inflammatory ones (dimethyl fumarate), and (5) agents that inhibit egress of lymphocytes from lymphoid tissue to the CNS (fingolimod). In some instances, the catheter **500** and pump/filtration system **600** may be designed to filter/reduce/remove a number of different inflammatory agents associated with MS including immune cells (immunoglobins, neutrophils, lymphocytes, monocytes, and the like), oxidative and/or inflammatory agents (e.g., including free radicals, cytokines, chemokines, white blood cells) such as those correlated with the pathology of MS, and the like. This can help treat MS and/or improve the symptoms thereof.

[0251] Another contemplated condition that the catheter **500** may be used to treat is Guillain-Barré syndrome (GBS). GBS is the most common cause of acute paralytic neuropathy worldwide. Acute motor axonal neuropathy (AMAN) and acute inflammatory demyelinating polyneuropathy (AIDP) are the main phenotypes. GBS may arise in individuals through a combination of host genetic and environmental factors, and preceding infection by pathogens including *Campylobacter jejuni* and Zika virus. Prevailing mechanisms of action implicate molecular mimicry of foreign antigen and gangliosidic residues resulting in the development of autoantibodies which recognize myelin or axonal components and initiate an inflammatory immune response including macrophage and/or lymphocytic infiltration, complement deposition, and cytokine production. CSF analysis shows elevated protein (>400 mg/L) and the absence of pleocytosis in 90% of patients. Elevated levels of neuroinflammatory cytokines and other proteins involved in the pathology have been noted, though specific immunological protein profiles of GBS CSF are heterogenous. In some of these and in other instances, a second catheter (e.g., which may be similar in form and function to the catheter **500**, an Ommaya reservoir, or the like) may be used to infuse a drug into the cranial region.

[0252] Current treatments for GBS may include plasma exchange (PE) or intravenous immunoglobulins (IVIg) with supportive care. Based on protein abnormalities of the CSF in GBS patients, including elevated levels of inflammatory cytokines TNF- α and IL-6⁷, anti-ganglioside antibodies, and activated complement components, filtration of CSF to reduce/remove inflammatory may help to reduce GBS systems and/or treat GBS. In some instances, the catheter **500** and pump/filtration system **600** may be designed to filter/reduce/remove a number of different inflammatory agents associated with GBS including immune cells (immunoglobins, neutrophils, lymphocytes, monocytes, and the like), oxidative and/or inflammatory agents (e.g., including free radicals, cytokines, chemokines, white blood cells) such as those correlated with the pathology of GBS, and the like. This can help treat GBS and/or improve the symptoms thereof. In some instances, the catheter **500** and pump/filtration system **600** may include a 5 kDa filter when used for treating GBS. Other filter sizes are contemplated including those disclosed herein. For example, the catheter **500** and pump/filtration system **600** may include a 5 kDa tangential flow filter, a 100 kDa tangential flow filter, an electrofilter, or a combination thereof.

[0253] Another contemplated condition that the catheter 500 may be used to treat is meningitis. Bacterial meningitis occurs when pathogenic bacteria enter the subarachnoid space and cause a pyogenic inflammatory response. Gram-negative bacterial meningitis (GBM) is a devastating condition that occurs when gram-negative bacteria invade the central nervous system (CNS). There are 30,000 US cases and over 1 million cases of GBM worldwide annually. When bacterial infections are manifested as GBM, it creates an extreme burden of mortality, often exceeding 30%, and morbidity to the patient and is very difficult for clinicians to treat, even when caused by bacteria susceptible to standard antibiotics. It is seen most commonly in children or immunocompromised patients, such as those with HIV, post organ-transplant or post-neurosurgical procedures. Current treatment guidelines include intravenous cephalosporins or carbapenems or polymycin for at least 10 days to 2 weeks. In the presence of gram-negative enteric bacterial meningitis, classically occurring around trauma and neurosurgical procedures, highly resistant bacteria can cause disease. Antibiotics like aminoglycosides and polymycins are considered for treatment but the therapeutic-toxic ratio is poor for these agents with systemic use in CNS disease and there may be no optimal treatments.

[0254] Three key gram-negative pathogens that have been deemed critical priority include *Pseudomonas*, *Acinetobacter* and *Klebsiella* (PAK). These gram-negative bacteria can cause severe and often deadly infections such as pneumonia, bloodstream infections and, specifically, nosocomial meningitis. These bacteria have become resistant to a large number of antibiotics, including carbapenems and third generation cephalosporins—the best available antibiotics for treating multidrug-resistant bacterial meningitis. The world health organization acknowledges that multi-modal approaches are needed and that waiting any longer will cause further public health problems and dramatically impact patient care and survival. This raises the very real possibility of GBM infections that are untreatable by presently available antibiotics. This return to the pre-antibiotic era has unfortunately become a reality in many parts of the world.

[0255] Reduction in CSF organism burden is the single most important factor impacting survival and is linked to a better overall clinical outcome. The rapid reduction in CSF organism burden is important, with sterilization of the CSF in the first 24 hours. Optimization of the antibiotic effect depends directly on the organism load that is present and on the direct activity of antibiotic therapy being started early in infection. Determining which antibiotic agent will be most effective is becoming increasingly more difficult in the face of drug-resistant bacteria such as PAK. Clinical data for new antibiotics for bacterial meningitis simply have not kept pace with the rise of resistance, and the development of new therapeutic approaches is urgently needed. Additionally, experimental animal models have shown that outcome from bacterial meningitis are related to the severity of inflammation in the subarachnoid space (SAS) and could potentially be improved by modulation of the inflammatory response.

[0256] The catheter 500 and pump/filtration system 600 may provide an innovative new treatment option that provides direct access to the CSF and creates active circulation combined with targeted pathogen removal. This may provide a novel therapeutic approach that rapidly reduces CFUs

and CSF bacterial burden and translates to reduced morbidity and mortality from bacterial meningitis.

[0257] Accordingly, the present methods provide for ameliorating or reducing the symptoms of bacterial meningitis by reducing or eliminating the presence of one or more of bacterial pathogens and/or their associated endotoxins and/or cytokines in the CSF using the catheter 500 and pump/filtration system 600. The methods comprise removing CSF from a patient, removing at least one of the bacterial pathogens, and/or endotoxins associated with the bacterial pathogens, and/or cytokines from the CSF, and returning the endogenous CSF to the patient, wherein the removing and returning steps are performed concurrently during at least a portion of the treatment. In some embodiments, the cytokines are selected from the group consisting of IL-1ra, IL-6, TNF, CRP, and CXCL10, or combinations thereof.

[0258] In some of these and in other instances, the methods provide for ameliorating or reducing the symptoms of bacterial meningitis by introducing the catheter 500 through a spinal access site into a spinal CSF space of a patient, advancing the catheter 500 through the spinal CSF space toward the brain so that the openings 532A and 532B are disposed within the CSF space and spaced-apart by a preselected distance or adjusted to an appropriate distance, withdrawing CSF through at least some of the openings in the catheter 500 (e.g., the openings 532A), removing at least one of bacterial pathogens and/or their associated endotoxins and/or cytokines from the withdrawn CSF with the pump and filtrations system 600 (thereby conditioning the CSF), and returning the conditioned CSF through the other of the openings in the catheter 500 (e.g., the openings 532B).

[0259] Fungal meningitis (FM) is an infection of the meninges of the central nervous system that manifests from the dissemination of any major fungal pathogen into the subarachnoid space (SAS) via the cerebrospinal fluid (CSF). Cryptococcal Meningitis (CM) is caused by *Cryptococcus neoformans* and is the most common cause of fungal meningitis in adults. Other agents causative of fungal meningitis include: *C. Gattii*, *Blastomyces*, *Histoplasma*, *Coccidioides*. Treatment for CM is based on an induction, consolidation, and maintenance approach with antifungals and is well defined elsewhere, but is associated with continued high morbidity and mortality. Drug discovery programs are limited by poor penetration of the Blood Brain Barrier (BBB). Because of this, we developed an alternative catheter-based extracorporeal filtration system (Neurapheresis Therapy) for the filtration of infected CSF. Here we describe the in vitro characterization of Neurapheresis Therapy as an alternative mechanical intervention for filtration of *C. neoformans* cells, polysaccharide antigen, and inflammatory mediators from infected CSF.

[0260] The catheter 500 and pump/filtration system 600 may provide an innovative new treatment option that provides direct access to the CSF and creates active circulation combined with targeted pathogen removal. This may provide a novel therapeutic approach that rapidly reduces CFUs and CSF fungal burden and translates to reduced morbidity and mortality from fungal meningitis. In at least some instances, the catheter 500 and pump/filtration system 600 may include one or more filters (e.g., the filters 672/682) designed to exclude the passage of fungi therethrough such as *C. neoformans*. In some of these and in other instances, the catheter 500 and pump/filtration system 600 may include one or more filters (e.g., the filters 672/682) designed to

exclude fungi (e.g., *C. neoformans*), associated antigens, and/or inflammatory agents. In at least some instances, a single pass of CSF through a 5 kDa TFF and/or a 100 kDa TFF may be sufficient to exclude *C. neoformans* or other reduce the CFUs of *C. neoformans* in the CSF. In addition, a 5 kDa TFF and/or a 100 kDa TFF may be sufficient to exclude or otherwise reduce *C. neoformans* antigen from the CSF. Furthermore, a 5 kDa and/or 100 kDa TFF may also exclude a number of neuroinflammatory agents such as IL-1ra, IL-6, TNF, CRP, and/or CXCL 10/IP-10 from the CSF.

[0261] Accordingly, the present methods provide for ameliorating or reducing the symptoms of fungal meningitis by reducing or eliminating the presence of one or more of fungal pathogens and/or their associated antigens (e.g., Cryptococcal antigen) and/or cytokines in the CSF using the catheter **500** and pump/filtration system **600**. The methods comprise removing CSF from a patient, as described herein; removing at least one of the fungal pathogens, and/or antigens associated with the fungal pathogens, and/or cytokines from the CSF, and returning the endogenous CSF to the patient, wherein the removing and returning steps are performed concurrently during at least a portion of the treatment. In some embodiments, the cytokines are selected from the group consisting of IL-1ra, IL-6, TNF, CRP, and CXCL10, or combinations thereof. The fungus/fungi and/or antigens and/or cytokines can be removed from the CSF using one or more filtration system. A 5 kDa and/or 100 kDa TFF may also exclude a number of neuroinflammatory agents such as IL-1ra, IL-6, TNF, CRP, and/or CXCL 10/IP-10.

[0262] In some of these and in other instances, the methods provide for ameliorating or reducing the symptoms of fungal meningitis by introducing the catheter **500** through a spinal access site into a spinal CSF space of a patient, advancing the catheter **500** through the spinal CSF space toward the brain so that the openings **532A** and **532B** are disposed within the CSF space and spaced-apart by a preselected distance or adjusted to an appropriate distance, withdrawing CSF through at least some of the openings in the catheter **500** (e.g., the openings **532A**), removing at least one of fungal pathogens and/or their associated antigens and/or cytokines from the withdrawn CSF with the pump and filtrations system **600** (thereby conditioning the CSF), and returning the conditioned CSF through the other of the openings in the catheter **500** (e.g., the openings **532B**).

[0263] In at least some instances, the catheter **500** and pump/filtration system **600** may be used to deliver drugs to portions of the CNS. For example, some treatments for CM may include the administration of intravenous and oral antifungals such as amphotericin B (AmB) and flucytosine. Generally, intrathecal (IT) AmB boluses may be associated with neurotoxic drug concentrations near the injection site. The use of the catheter **500** and pump/filtration system **600** may allow for the IT infusion of AmB and/or other drugs. Unexpectedly, the catheter **500** and pump/filtration system **600** may also be used to reduce, filter (e.g., with the first filter **672**, the second filter **682**, or both), or otherwise remove some drugs such as AmB. Because of this, the dosage of AmB can be precisely titrated to a desired dose. If levels of AmB reach undesired levels (e.g., undesired high levels), the catheter **500** and pump/filtration system **600** can be used to quickly remove unwanted quantities of AmB from the CSF.

[0264] The catheter **500** and pump/filtration system **600** can also be used to deliver a number of other drugs including drugs where the difference between therapeutic doses and toxic doses are relatively small. For example, a drug may be infused into the CSF using the catheter **500** and pump/filtration system **600**. If signs of toxicity are observed or if measurements of the drug concentration in the CSF is higher than desired, the catheter **500** and pump/filtration system **600** can be used to rapidly remove the drug from the CSF. Thus, the catheter **500** and pump/filtration system **600** can be used for controlled delivery of drugs into the CSF of patients and the rapid removal of drugs from the CSF, as desired.

[0265] The catheter **500** and pump/filtration system **600** may also help to reduce ICP associated with a number of conditions. For example, some conditions (e.g., such as cancer, HSE, and others) may be associated with higher ICP due to cells (e.g., tumor cells, etc.), inflammatory agents, and the like blocking, clogging, or otherwise impacting natural pathways for reabsorption of CSF. By using the catheter **500** and pump/filtration system **600**, materials that might blocking natural reabsorption pathways can be removed/reduced, thereby desirably impacting the volume of CSF and reducing ICP.

[0266] Systems are also contemplated that utilize a first port for providing access to the cerebrospinal space and/or the CNS at a first location and a second port for providing access the cerebrospinal space and/or the CNS at a second location. Such ports may be implanted acutely or for extended periods of time. In some instances, the ports may allow for infusion of substances to the cerebrospinal space and/or the CNS, removal of substances from the cerebrospinal space and/or the CNS, or both. One or both of the ports may be or otherwise be similar to an Ommaya reservoir. The ports may be designed to be used with a tube/catheter, the catheter **500**, and/or the pump/filtration system **600**. For example, a first tube and/or first catheter **500** may be connected with or otherwise be connectable to one of the ports and a second tube and/or second catheter **500** may be connected with or otherwise be connectable to the other port. CSF may be removed from the patient (e.g., using a tube, either the first or the second catheter **500**, or the like) and filtered by the pump/filtration system **600**. In some instances, the filtered CSF may be returned to the patient using the same tube/catheter. In other instances, the filtered CSF may be returned to the patient using the other tube/catheter. In other words, CSF may be removed from the patient using a catheter at the first port, filtered, and then returned to the patient using a catheter at the second port. This may form a loop-like pathway the helps to circulate CSF through the cerebrospinal space and/or the CNS. The ports may be positioned along the patient in a manner that helps to facilitate circulation of CSF. For example, one of the ports may be positioned at the cranium of the patient (e.g., which may include providing access to the ventricles of the brain) and the other may be positioned along a lumbar region of the spine (e.g., which may provide access to the cerebrospinal space at a position adjacent to the lumbar space). Other locations are contemplated.

[0267] All directional references (e.g., proximal, distal, upper, lower, upward, downward, left, right, lateral, front, back, top, bottom, above, below, vertical, horizontal, clockwise, and counterclockwise) are only used for identification purposes to aid the reader's understanding of the present disclosure, and do not create limitations, particularly as to

the position, orientation, or use of the disclosure. Connection references (e.g., attached, coupled, connected, and joined) are to be construed broadly and may include intermediate members between a collection of elements and relative movement between elements unless otherwise indicated. As such, connection references do not necessarily infer that two elements are directly connected and in fixed relation to each other. It should be noted that delivery sheath and delivery catheter may be used interchangeably for purposes of this description. The exemplary drawings are for purposes of illustration only and the dimensions, positions, order and relative sizes reflected in the drawings attached hereto may vary.

[0268] U.S. Patent Application Pub. No. US 2016/0051801 is incorporated herein by reference. U.S. Pat. No. 8,435,204 is incorporated herein by reference. U.S. Patent Application No. 62/568,412 (Attorney docket number 1421.1010100) is incorporated herein by reference. U.S. Patent Application No. 62/598,846 (Attorney docket number 1421.1011100) is incorporated herein by reference.

[0269] The above specification, examples and data provide a complete description of the structure and use of exemplary embodiments of the disclosure as claimed below. Although various embodiments of the disclosure as claimed have been described above with a certain degree of particularity, or with reference to one or more individual embodiments, those skilled in the art could make numerous alterations to the disclosed embodiments without departing from the spirit or scope of this disclosure. Other embodiments are therefore contemplated. It is intended that all matter contained in the above description and shown in the accompanying drawings shall be interpreted as illustrative only of particular embodiments and not limiting. Changes in detail or structure may be made without departing from the basic elements of the disclosure.

1. (canceled)

2. A method for treating a patient, the method comprising: disposing a catheter within a cerebrospinal space of the patient, the catheter including an inner shaft and an outer shaft;

wherein the inner shaft defines an infusion lumen therein and defines a plurality of infusion openings in fluid communication with the infusion lumen;

wherein an aspiration lumen is defined between the inner shaft and the outer shaft;

wherein the outer shaft defines a plurality of aspiration openings therein that are in fluid communication with the aspiration lumen;

wherein the plurality of infusion openings and the plurality of aspiration openings are longitudinally separated from one another;

removing a volume of cerebrospinal fluid from the cerebrospinal space through the plurality of aspiration openings;

filtering the volume of cerebrospinal fluid with a filter assembly coupled to the catheter to treat meningitis and/or cancer; and

returning the filtered cerebrospinal to the patient.

3. The method of claim 2, wherein disposing the catheter within the cerebrospinal space of the patient includes disposing the plurality of infusion openings adjacent to a cranial region of the patient.

4. The method of claim 2, wherein disposing the catheter within the cerebrospinal space of the patient includes disposing the plurality of aspiration openings adjacent to a lumbar region of the patient.

5. The method of claim 2, wherein filtering the volume of cerebrospinal fluid with the filter assembly includes removing one or more bacteria or fungal pathogens.

6. The method of claim 2, wherein filtering the volume of cerebrospinal fluid with the filter assembly includes filtering out one or more bacterial meningitis-related pathogens.

7. The method of claim 2, wherein filtering the volume of cerebrospinal fluid with the filter assembly includes filtering out one or more fungal meningitis-related pathogens.

8. The method of claim 2, wherein filtering the volume of cerebrospinal fluid with the filter assembly includes removing both i) one or more gram-negative meningitis causing bacterial pathogen selected from a group comprising *Acinetobacter* bacteria, *Klebsiella* bacteria, or combinations thereof and ii) cytokines selected from the group comprising IL-1ra, IL-6, TNF, CRP, and CXCL10, or combinations thereof from the cerebrospinal fluid, to thereby condition the cerebrospinal fluid.

9. The method of claim 2, further comprising disposing a chemotherapy infusion device into a ventricle of the patient.

10. The method of claim 9, wherein the chemotherapy infusion device includes an Ommaya reservoir.

11. The method of claim 9, further comprising infusing a chemotherapy agent into the ventricle with the chemotherapy infusion device.

12. The method of claim 11, wherein the chemotherapy agent includes methotrexate.

13. The method of claim 12, further comprising infusing a chemotherapy agent through the plurality of infusion openings into the cerebrospinal space of the patient.

14. The method of claim 13, further comprising circulating the chemotherapy agent through the cerebrospinal space.

15. The method of claim 14, wherein circulating the chemotherapy agent through the cerebrospinal space includes circulating the chemotherapy agent through the filter assembly.

16. A method for treating a patient, the method comprising:

disposing a catheter within a cerebrospinal space of the patient with cancer, the catheter including an inner shaft and an outer shaft;

wherein the inner shaft defines an infusion lumen therein and defines a plurality of infusion openings in fluid communication with the infusion lumen;

wherein an aspiration lumen is defined between the inner shaft and the outer shaft;

wherein the outer shaft defines a plurality of aspiration openings therein that are in fluid communication with the aspiration lumen;

wherein the plurality of infusion openings and the plurality of aspiration openings are longitudinally separated from one another;

infusing a chemotherapy agent through the plurality of aspiration openings into the cerebrospinal space;

removing a volume of cerebrospinal fluid from the cerebrospinal space through the plurality of aspiration openings;

passing the volume of cerebrospinal fluid through a filter assembly coupled to the catheter; and

returning the volume of cerebrospinal fluid to the patient.

17. The method of claim 16, wherein disposing the catheter within the cerebrospinal space of the patient includes disposing the plurality of infusion openings adjacent to a cranial region of the patient.

18. The method of claim 16, wherein disposing the catheter within the cerebrospinal space of the patient includes disposing the plurality of aspiration openings adjacent to a lumbar region of the patient.

19. The method of claim 16, further comprising disposing a chemotherapy infusion device into a ventricle of the patient.

20. The method of claim 16, wherein passing the volume of cerebrospinal fluid through the filter assembly includes circulating the chemotherapy agent throughout the cerebrospinal space.

21. A method for treating a patient with cancer, the method comprising:

disposing a catheter within a cerebrospinal space of the patient, the catheter including an inner shaft and an outer shaft;

wherein the inner shaft defines an infusion lumen therein and defines a plurality of infusion openings in fluid communication with the infusion lumen;

wherein an aspiration lumen is defined between the inner shaft and the outer shaft;

wherein the outer shaft defines a plurality of aspiration openings therein that are in fluid communication with the aspiration lumen;

positioning the catheter so that the plurality of infusion openings are disposed adjacent to a cranial region of the patient and so that the plurality of aspiration openings are disposed adjacent to a lumbar region of the patient;

infusing a chemotherapy agent through the plurality of aspiration openings into the cerebrospinal space; and

circulating the chemotherapy agent throughout the cerebrospinal space by removing a volume of cerebrospinal fluid from the cerebrospinal space through the plurality of aspiration openings, passing the volume of cerebrospinal fluid through a filter assembly coupled to the catheter, and returning the volume of cerebrospinal fluid to the patient.

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