

**SYSTEM AND DEVICE FOR PROVIDING LOCALIZED TURBULENCE FOR
DELIVERING A MEDICAL EMBOLIZING AGENT**

Inventors: David Jaroch, Bryan F. Cox, and Melody Weigel

5

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/457,730, filed April 6, 2023, which is hereby incorporated by reference in its entirety.

10 **FIELD OF INVENTION**

[0002] The present invention relates generally to an infusion catheter for delivering a therapeutic agent, particularly an embolizing agent, to the blood stream of a patient.

BACKGROUND OF INVENTION

15 [0003] Systemic infusion of therapeutic agents have been used to treat various diseases in patients. The effectiveness of such systemic delivery can vary based on a variety of different factors, such as, for example, concentrations needed to reach a therapeutic effect, toxicity of the therapeutic agent, and/or undesired effects. However, for some therapeutic agents, such as a radio-embolization agent, a chemotherapy agent, or a biologic agent having systemic toxicity, systemic
20 delivery may have a detrimental effect to the patient and is therefore, not desirable. For example, systemic delivery of an embolizing agent can lead to non-targeted embolization, which can lead to adverse events and morbidity.

[0004] Non-targeted delivery of the embolic agent may have significant unwanted effects on the human body. For example, in liver treatment, non-targeted delivery of the embolic agent may
25 have undesirable impacts on other organs including the stomach and small intestine. In uterine fibroid treatment, the non-targeted delivery of the embolic agent may embolize one or both ovaries leading to loss of menstrual cycle, subtle ovarian damage that may reduce fertility, early onset of menopause, and in some cases, substantial damage to the ovaries. Other unintended adverse events include unilateral deep buttock pain, buttock necrosis, and uterine necrosis. In another example,
30 it may be desirable to deliver a chemotherapy agent locally to reduce systemic dose-limiting toxicity, while increasing localized concentration of the chemotherapy agent near the tumor treated to improve efficacy.

[0005] Localized delivery of the therapeutic agent may be accomplished by cannulizing a blood vessel in the vasculature near the target area (*e.g.*, the tumor to be treated) with a catheter (*e.g.*, a conventional end-hole microcatheter) and delivering a flow of a fluid pharmaceutical composition (*e.g.*, a solution or a suspension) comprising the therapeutic agent through the catheter to the blood stream of the patient. For example, in the treatment of liver tumors, the catheter is placed in the hepatic arterial vasculature and a flow of a fluid pharmaceutical composition (*e.g.*, a solution or a suspension) comprising the therapeutic agent is delivered into the blood stream through the catheter. In another example, for the treatment of pancreatic tumors, the catheter is placed in the pancreatic arteries arising from the splenic artery or gastroduodenal artery for delivering a flow of a fluid pharmaceutical composition (*e.g.*, a solution or a suspension) comprising the therapeutic agent into the blood stream through the catheter.

[0006] During localized vascular infusion, the therapeutic agent is delivered into a blood vessel of a patient through the catheter. A distal tip of the catheter is positioned within a lumen of the blood vessel and a flow of a fluid pharmaceutical composition (*e.g.*, a solution or a suspension) comprising the therapeutic agent is delivered through the catheter and into the lumen of the blood vessel. The blood stream flows past the distal tip of the catheter when the catheter is in an operating configuration and inserted into the blood vessel. As the flow of the fluid pharmaceutical composition is infused into the blood vessel, the infused composition flows forward with the flow of the blood stream.

[0007] Blood flowing through blood vessels tend to flow in a laminar manner. Typically, when a therapeutic agent is infused using a conventional catheter, the laminar flow of the blood stream remains undisrupted and the therapeutic will tend to travel down the path defined by the local regions of laminar flow. Regions of laminar flow within the blood vessel tend to follow defined paths downstream to specific sets of branches of the vasculature. Therefore, the position of the catheter at the point of infusion can bias effectiveness of delivery of the therapeutic agent to a target area via blood vessels fed by the local stream of fluid in that laminar pathway.

[0008] A therapeutic agent may be delivered in solution or as particles in suspension in a pharmaceutical formulation, such as, for example, a liquid, foam or gel that is infused into the vasculature of the patient. Particles of the therapeutic agent may be undissolved solid forms of an embolizing agent (*e.g.*, embolizing beads), or may be beads or microsphere carriers comprising a therapeutic agent (*e.g.*, embolizing agent). The beads or microspheres may contain the therapeutic

agent (*e.g.*, embolizing agent) within or may be coated with the therapeutic agent. Delivery of such particles of a therapeutic agent via a catheter (*e.g.*, a conventional end-hole microcatheter) often depend on particle-fluid dynamics and catheter placement that do not provide consistent results. For example, when the catheter is placed within the laminar flow of the blood stream, there may be variable distribution of particles dependent upon the position of the device within that laminal flow stream. A small displacement of a distal tip of the catheter within this laminar flow can dramatically alter the downstream pathway the particles will take.

[0009] The fluid-particle dynamics for infusing a particulate formulation into the blood stream using a conventional end-hole microcatheter are not well characterized and can contribute to unpredictability in the therapeutic dose actually delivered to the target area. For example, the target tissue may receive sub-therapeutic amounts or above therapeutic amounts of the particles as a result of the complex interplay between vascularization of the target tissue, particle-fluid dynamics and placement of the conventional end-hole microcatheter. Additionally, the particles may accumulate in non-targeted areas and damage tissue in the non-targeted areas (*e.g.*, lungs), particularly when the particles comprise an embolizing agent or a chemotherapy agent.

[0010] In particular, during radioembolization, a mapping procedure is typically performed to determine where a subsequent infusion of radioactive particles will most likely flow. Mapping is typically performed using a lightly radioactive tracer element attached to a sub-embolic protein complex (*e.g.*, Tc-99m macro-aggregated albumin (MAA)). This tracer allows for a way to measure distribution of particles without embolizing the blood vessel. This mapping also provides a safety indicator for the infusion, helping to determine if there is blood shunting to sensitive organs such as the lungs (lung shunt fraction). When a conventional end-hole microcatheter is placed within the laminar flow of the blood stream, there can be variable distribution of the radio-embolizing particles depending upon the position of the device within that laminal flow stream. A small displacement of the tip of the conventional end-hole microcatheter within this flow can dramatically alter the downstream pathway the particles will take such that the therapy delivery may not match the mapping procedure. Without guidance from the mapping procedure, there can be under or over treatment of tissue in the infusion zone and may result in unsafe amounts of therapeutics being shunted to non-target organs, such as the lungs.

[0011] Therefore, there remains a need for a more predictable and safe way to locally infuse a therapeutic agent into a blood vessel and deliver the therapeutic agent via the vasculature to a nearby target area.

5 **BRIEF SUMMARY OF THE INVENTION**

[0012] The present application relates to a vascular infusion catheter for infusing a therapeutic agent to a blood vessel of a patient. In some examples, the therapeutic agent is within or coated on a surface of a particle. For example, the therapeutic agent may be a radio-embolizing agent, the therapeutic agent being contained within or coated onto microspheres. The vascular infusion
10 catheter comprises a catheter arrangement extending from a distal end to a proximal end having an outer surface and an interior surface. The interior surface defines a lumen through the catheter arrangement. In another example, the catheter arrangement is a single catheter. Alternatively, the catheter arrangement comprises an outer catheter and an inner catheter configured to deploy the turbulence inducing structure by longitudinal displacement of the outer catheter from the inner
15 catheter. The catheter arrangement comprises an opening at a distal tip of the catheter arrangement in a continuous fluid pathway with the lumen. The turbulence inducing structure is formed from or attached to the outer surface or the distal tip of the catheter arrangement. In certain examples, the turbulence inducing feature is attached to the distal tip of the catheter arrangement. The turbulence inducing structure is configured to induce turbulence to blood flowing through a
20 localized region of the blood vessel. In some examples, the turbulence induced provides a shear force that does not exceed a shear force for lysis of red blood cells. The turbulence inducing structure is also configured to not fully occlude the blood vessel such that the blood can flow past the turbulence inducing structure at all times. In some examples, the turbulence inducing structure does not fully occlude the blood vessel such that blood can flow past the turbulence inducing
25 structure in a downstream direction or in an upstream direction. In some examples, the turbulence inducing structure comprises a leading edge substantially perpendicular to or at an obtuse angle to a longitudinal axis of the catheter arrangement at the distal end or the proximal end of the catheter arrangement. The turbulence inducing structure may be spherical, cylindrical, conical, ovoid, ellipsoid or toroidal. In some examples, the turbulence inducing structure partially occludes the
30 blood vessel such that blood can flow past the turbulence inducing structure in a downstream direction or in an upstream direction. In some examples, the turbulence inducing structure comprises a plurality of ridges arranged in an array. The array may comprise a pattern, and

wherein the pattern comprises a proximal to distal counterclockwise helix or a proximal to distal clockwise helix.

[0013] These and other aspects of the invention will become apparent to those skilled in the art after a reading of the following detailed description of the invention, including the figures and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Further objects, features and advantages of the present disclosure will become apparent from the following detailed description taken in conjunction with the accompanying Figures showing illustrative examples of the present disclosure.

[0015] Fig. 1 shows an exemplary delivery system for vascular infusion of a therapeutic agent in a blood vessel, according to an embodiment of the present application.

[0016] Fig. 2A shows a front view from the distal end of an exemplary turbulence inducing structure, according to an embodiment of the present application.

[0017] Fig. 2B shows a side view of an exemplary turbulence inducing structure having a spherical shape, according to an embodiment of the present application.

[0018] Fig. 2C shows a side view of an exemplary turbulence inducing structure having a leading edge substantially perpendicular to or at an obtuse angle to a longitudinal axis of the catheter arrangement at the distal end, according to an embodiment of the present application.

[0019] Fig. 2D shows a side view of an exemplary turbulence inducing structure having a leading edge substantially perpendicular to or at an obtuse angle to a longitudinal axis of the catheter arrangement at the proximal end, according to an embodiment of the present application.

[0020] Fig. 2E shows a side view of an exemplary turbulence inducing structure having a sharper curve at the distal end than the proximal end, according to an embodiment of the present application.

[0021] Fig. 2F provides a side view of a distal portion of a catheter arrangement and an exemplary turbulence inducing structure having a cylindrical shape, according to an embodiment of the present application.

[0022] Fig. 2G provides a side view of a distal portion of a catheter arrangement and an exemplary turbulence inducing structure having an inner surface comprising a first portion parallel to the outer surface of the catheter arrangement and a second portion extending away from the outer surface of the catheter arrangement, according to an embodiment of the present application.

[0023] Fig. 2H provides a side view of a distal portion of a catheter arrangement and an exemplary turbulence inducing structure having a torus shape, according to an embodiment of the present application.

[0024] Fig. 2I provides a side view of a distal portion of a catheter arrangement and an exemplary turbulence inducing structure attached to a distal tip of the catheter arrangement, according to an embodiment of the present application.

[0025] Fig. 2J provides a side view of a distal portion of a catheter arrangement and an exemplary turbulence inducing structure formed at a distal tip of the catheter arrangement, according to an embodiment of the present application.

[0026] Fig. 2K provides a side view of a distal portion of a catheter arrangement and an exemplary turbulence inducing structure formed at a distal tip of the catheter arrangement, according to an embodiment of the present application.

[0027] Fig. 2L provides a side view of another example of a turbulence inducing structure formed at the distal end of the catheter arrangement.

[0028] Fig. 2M provides a side view of a further example of a turbulence inducing structure attached to the distal end of the catheter arrangement.

[0029] Fig. 2N provides a side view of a further example of a turbulence inducing structure attached to the distal end of the catheter arrangement.

[0030] Fig. 3 shows the chemical structure of a sodium salt of SD-101.

DETAILED DESCRIPTION OF THE INVENTION

[0031] Unless defined otherwise, all technical and scientific terms used herein have the same meaning commonly understood to one of ordinary skill in the art to which this invention pertains. Otherwise, certain terms used herein have the meanings as set in the specification. All patents, published patent applications and publications cited herein are incorporated by reference as if set forth fully herein. It is noted that as used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise.

[0032] Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise,” and variations such as “comprises” and “comprising,” will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps. When used herein the term

“comprising” can be substituted with the term “containing” or “including” or sometimes when used herein with the term “having.”

[0033] As used herein, the conjunctive term “and/or” between multiple recited elements is understood as encompassing both individual and combined options. For instance, where two
5 elements are conjoined by “and/or,” a first option refers to the applicability of the first element without the second. A second option refers to the applicability of the second element without the first. A third option refers to the applicability of the first and second elements together. Any one of these options is understood to fall within the meaning, and therefore satisfy the requirement of the term “and/or” as used herein. Concurrent applicability of more than one of the options is also
10 understood to fall within the meaning, and therefore satisfy the requirement of the term “and/or.”

[0034] The term “subject” or “patient” as used herein refers to an animal, and preferably a mammal. According to particular embodiments, the subject or patient is a mammal including a non-primate (*e.g.*, a camel, donkey, zebra, cow, pig, horse, goat, sheep, cat, dog, rat, rabbit, guinea pig, marmoset or mouse) or a primate (*e.g.*, a monkey, chimpanzee, or human). In particular
15 embodiments, the subject or patient is a human.

[0035] As used herein, the terms “proximal” and “distal” are defined in reference to the hand of user of the devices and systems described herein. The term “proximal” being closer to the user’s hand and the term “distal” being further from the user’s hand such as to often be located further within a body of the patient during use.

[0036] The present application provides a device comprising a catheter for infusing a
20 therapeutic agent into a blood vessel of a patient and a structure at or near the distal end of the catheter for inducing turbulent flow within the blood vessel as a flow of the therapeutic agent is infused into the blood stream. Prior to flowing past the distal end of the catheter, the blood stream flows laminarly. While the blood stream flows past the structure at or near the distal end of the
25 catheter, the structure induces localized turbulent flow to the blood stream. As the flow of the therapeutic agent is infused into the blood stream from the distal tip of the catheter, the localized turbulent flow includes eddies that mixes the therapeutic agent with the blood stream flowing past the distal end of the catheter. This localized turbulence improves distribution of the therapeutic agent (as compared to laminar flow of blood past the distal end of the catheter) within the blood
30 stream as the blood returns to laminar flow downstream from the position of the catheter and into vascular pathways for delivery to tissue in a target area for treatment (*e.g.*, the tumor to be treated).

It is believed that this localized turbulence can provide a more consistent delivery of the therapeutic agent (as compared to laminar flow of blood past the distal end of the catheter) to the target area.

[0037] Fig. 1 shows an exemplary delivery system 10 for vascular infusion of a therapeutic agent in a blood vessel. The delivery system 10 includes a catheter arrangement 12, a turbulence inducing structure 14, and a pump system 16. The system 10 suitably sized and shaped for use in infusing the therapeutic agent via an arterial blood vessel or a venous blood vessel to a target area. In particular, the catheter arrangement 12 and turbulence inducing structure 14 are suitably sized and shaped to be slidably inserted into the blood vessel, when the turbulence inducing structure 14 is in a deployed configuration and operating within the blood vessel. The blood vessel includes a lumen defined by an inner wall of cells of the blood vessel having a diameter from about 2 μm to about 10,000 μm . The blood vessel may be located in any organ in which treatment with the therapeutic agent is desired. For example, the organ may be the pancreas, the liver, the kidney, the lungs, the uterus, the ovaries, the cervix, the prostate, head and neck tissues (jaw, gums), the brain, the adrenal glands, bowel or colon, breast, thyroid, spleen, stomach, gall bladder, thymus, skin, bladder, lymph system, and various other organs or tissues subject to tumor or other disease states that can be treated with localized delivery of a therapeutic agent. The blood vessel may have a diameter greater than the size of a red blood cell and less than about 5 cm, less than about 4 cm, less than about 3 cm, less than about 2 cm, less than about 1 cm, less than about 10 mm, less than about 9 mm, less than about 8 mm, less than about 7 mm, less than about 6 mm or less than about 5 mm. The blood vessel may have a diameter from about 8 μm to about 5 cm, or from about 10 μm to about 3 cm. In particular, the blood vessel may be a hepatic arterial blood vessel. The blood vessel may have a diameter from about 8 μm to about 10 mm, from about 10 μm to about 9 mm, or from about 1 mm to about 6 mm. In another example, the blood vessel may be a pancreatic artery arising from the splenic artery or gastroduodenal artery. The blood vessel may have a diameter from 8 μm to about 1 cm, from about 10 μm to about 6 mm, or from about 1 mm to about 5 mm. In one example, the catheter arrangement 12 and turbulence inducing structure 14 are suitably sized and shaped to have a diameter less than that of the lumen defined by an inner wall of cells the blood vessel in which it is deployed. The system 10 and its use prevent, reduce or minimize, systemic circulation of the therapeutic agent.

[0038] The catheter arrangement 12 has a proximal end 20, a distal end 22, and a lumen 18 extending between its proximal and distal ends 20, 22. The lumen 18 being defined by

an interior surface of the catheter arrangement. The turbulence inducing structure 14 is a part of or attached to the catheter arrangement 12 at or near the distal end 22. The proximal end 22 of the catheter arrangement 12 is operably connected to a handle 24 such that manipulation of the handle 24 manipulates the catheter arrangement 12. The handle 24 is configured to be external for manual manipulation while the catheter arrangement 12 is in a vasculature of a patient. The handle 24 also includes a fluid pathway 26 that extends between the pump system 16 and the lumen 18 of the catheter arrangement. The pump system 16 is fluidly connected to the proximal end 20 via the fluid pathway 26 of the handle 24 such that a continuous fluid pathway extends from the pump system 16 through the fluid pathway 26 and the lumen 18 to an opening 30 at the distal end 22 of the catheter arrangement 12. The opening 30 at a distal tip 23 of the catheter arrangement 12 is configured to dispense a flow of the therapeutic agent from the pump system 16 and into the blood stream of the patient when the catheter arrangement 12 is deployed in the patient's blood vessel.

[0039] The turbulence inducing structure 14 is configured to induce turbulence within the blood vessel at or near the distal end 22 of the catheter arrangement 12 as a flow of the therapeutic agent is infused into the blood stream. When the delivery system 10 is deployed into the vascular system of the patient and the catheter arrangement 12 is positioned within a blood vessel, the turbulence inducing structure 14 does not fully occlude the blood vessel such that blood can flow past the turbulence inducing structure 14 at all times, when the turbulence inducing structure 14 is in a deployed configuration (i.e., when the turbulence inducing structure is not collapsed or compressed for advancing the distal end 22 of the catheter arrangement 12 into position and the turbulence inducing structure 14 is deployed in a desired location in the blood vessel to induce turbulence in the blood stream). In another example, when the delivery system 10 is deployed into the vascular system of the patient and the catheter 12 is positioned within the blood vessel, the turbulence inducing structure 14 does not fully occlude the blood vessel such that blood can flow past the turbulence inducing structure 14 in a downstream direction (i.e., in proximal to distal direction) and/or in an upstream direction (i.e., in a distal to proximal direction).

[0040] As the blood flows past the turbulence inducing structure 14, turbulence of the blood stream within a localized region near the turbulence inducing structure 14 increases. After the blood stream moves further downstream from the turbulence inducing structure 14, the turbulence of the blood stream decreases and the flow of the blood stream returns to a laminar flow. The localized region at or near the turbulence inducing structure 14 where an increase in turbulence

may extend by a length downstream from the turbulence inducing structure 14, where the length is from about 0.1 times to about 5 times the diameter of the blood vessel in which the system 10 is deployed. For example, the length may be from about 0.1 mm to about 30 mm.

[0041] As the blood stream flows into the localized region, the turbulence inducing structure 14 induces localized turbulent flow or eddies to the blood stream. As a flow of a fluid pharmaceutical composition comprising the therapeutic agent exits from the opening 30 at the distal end 22 of the catheter arrangement and infused into the blood stream, the increase in turbulence in the localized region mixes the fluid pharmaceutical composition with the blood stream flowing past the localized region to improve distribution of the therapeutic agent (as compared to laminar flow of blood past the distal end of the catheter) within the blood stream. The blood returns to laminar flow downstream from the localized region and continues to flow into vascular pathways for delivery to tissue in a target area for treatment (e.g., the tumor to be treated).

[0042] The turbulence inducing structure 14 may have any suitable size and shape to increase turbulence within the localized region. For example, the turbulence inducing structure 14 may increase Reynold's number of the flow of the blood stream in the blood vessel from below 2300 to above 2900 within the localized region. The flow of the blood stream upstream from the distal end of the catheter is laminar. For example, the flow of the blood stream upstream from the distal end of the catheter has a Reynold's number below 2300 and the turbulence inducing structure 14 increases the Reynold's number of the flow of the blood stream within the localized region by at least about 600, at least about 700, at least about 800, at least about 900, at least about 1000, at least about 1500, at least about 2000, at least about 2500, at least about 5000, at least about 7500 or at least about 10,000.

[0043] While the turbulence inducing structure 14 may increase turbulence within the localized region, it is understood that increase in turbulence also increases shear forces of the blood flow. In order for the turbulence inducing structure 14 to be suitable for use in a blood vessel, the level of turbulence induced by the turbulence inducing structure 14 is limited to turbulence that generates a shear force that is less than the shear force for lysis of cells, in particular, red blood cells. Specifically, the level of turbulence induced by the turbulence inducing structure 14 is limited to turbulence that generates a shear force that is less than a level of shear force that damages or kills cells, in particular, red blood cells. For example, the maximum shear force generated by the turbulence may be about 60 dyn/cm² or about 400 N/m². The level of turbulence induced by

the turbulence inducing structure 14 to produce a shear force from about 20 dyn/cm² to about 60 dyn/cm².

[0044] In some examples, the turbulence inducing structure 14 comprise one or more radially arranged structure(s) that displaces the lumen 18 of the catheter arrangement 12 away from the vessel wall of the blood vessel in which the catheter arrangement 12 is inserted. The turbulence inducing structure 14, when deployed, may push an outer surface 15 of the catheter arrangement 12 away from the vessel wall of the blood vessel such that the opening 30 of the catheter arrangement 14 is positioned more centrally in the blood vessel (e.g., closer to a longitudinal axis of the blood vessel). Even in conditions of laminar flow, the pathway in the central most part of the lumen of the blood tends to distribute infusion of a flow of a fluid pharmaceutical composition in the most uniform manner as compared to infusion from locations that are further away from the longitudinal axis of the blood vessel. The closer to the vessel wall, the more likely that particles will be carried down preferentially and non-uniformly in the laminar flow path.

[0045] In one example, the turbulence inducing structure 14 may be a structure attached to an outer surface 15 of the catheter arrangement 12 at the distal end 22. In particular, the turbulence inducing structure 14 may extend radially away from a longitudinal axis of the catheter arrangement and/or surround a portion of or all of the distal end 22 of the catheter arrangement 12. As shown in Fig. 2A, the turbulence inducing structure 202 may comprise an inner surface 102 defining an opening 103 for receiving the catheter arrangement 12 therethrough and an outer surface 104. The inner surface 102 of the turbulence inducing structure 14 may be attached to the outer surface of the catheter arrangement 12. In some examples, the turbulence inducing structure is unitarily formed (e.g., molded) on the outer surface 15 of the catheter arrangement 12. In another example, the turbulence inducing structure 12 may comprise a plurality of components, such as, for example, fluted elements, fins, etc., that are attached to the outer surface 15 of the catheter arrangement. The turbulence inducing structure 14 may be a rigid structure, a collapsible structure or a compressible structure attached to the outer surface 15 of the catheter arrangement 12.

[0046] The collapsible structure may be formed from any suitable elastic material, for medical use, such as, for example, a shape memory material, such as a shape memory metal (e.g., nitinol) or a shape memory medical-grade elastomer. In another example, the collapsible structure is an inflatable structure such as, for example, a balloon (e.g., a fluid or air inflatable balloon), a self-expanding or manually expandable filter, or a mechanically expandable malecot wing structure.

For example, the collapsible structure may be a fluid or air inflatable balloon. The collapsible structure is fluidly connected to a secondary lumen for filling the collapsible structure with fluid or air to inflate the collapsible structure. The secondary lumen for filling the collapsible structure may be part of the catheter arrangement 12 or may be a part of a separate catheter.

5 [0047] The collapsible structure may be in a collapsed configuration when the catheter arrangement 12 is being advanced into operating position within the blood vessel and in a deployed configuration when the distal end 22 of the catheter arrangement 12 is in a desired position for infusion of the fluid pharmaceutical composition comprising the therapeutic agent. The collapsed configuration has a reduced diameter for intravascular advancement to a desired operating position
10 within the blood vessel. The deployed configuration has a larger diameter than the collapsed configuration where the collapsible structure is expanded to the deployed configuration for inducing turbulence within the blood stream.

[0048] The compressible structure may be any elastomeric structure that can be compressed to reduce the size of the structure in a compressed configuration and subsequently released to a
15 deployed configuration. The compressible structure may be formed, for example, from an elastomeric foam such that the structure can be compressed when pressure is applied against the foam and restored to an original shape of the structure when pressure is removed from structure. The compressible structure may be in a compressed configuration when the catheter arrangement 12 is being advanced into operating position within the blood vessel and in a deployed
20 configuration (*e.g.*, when pressure is removed from the structure) when the distal end 22 of the catheter arrangement 12 is in a desired position for infusion of the fluid pharmaceutical composition comprising the therapeutic agent. The compressed configuration has a reduced diameter for intravascular advancement to a desired operating position within the blood vessel. The deployed configuration has a larger diameter than the compressed configuration where the
25 compressed structure is expanded to the deployed configuration for inducing turbulence within the blood stream.

[0049] For example, the turbulence inducing structure 14 comprises a plurality of projections (not shown) extending from the outer surface 15 of the catheter arrangement. The projections may increase drag in the flow of the blood stream and induce formation of eddies. The projections may
30 be a rigid structure or may be collapsible or compressible where the projects are in a collapsed or compressed configuration when the catheter arrangement 12 is being advanced into operating

position within the blood vessel and in a deployed configuration when the distal end 22 of the catheter arrangement 12 is in a desired position for infusion of the fluid pharmaceutical composition comprising the therapeutic agent.

[0050] In some examples, the outer surface 104 of the turbulence inducing structure 202 may have a curvilinear shape. The turbulence inducing structure 202 has a distal end 203 and a proximal end 204. The turbulence inducing structure 202, when in use, is positioned such that flow moves past the turbulence inducing structure in a direction from the proximal end 204 to the distal end 203. Therefore, the turbulence inducing structure 202 may have a spherical, cylindrical, conical, ovoid, ellipsoid or other curvilinear shape. For example, as shown in Figs. 2B to 2E, the outer surface 104 of the turbulence inducing structures shown in these figures all have a curvilinear shape.

[0051] Fig. 2B provides a side view of an example of a turbulence inducing structure 202b having a spherical shape and its effect on increasing turbulence to flow moving past in a direction from the proximal end 204 to the distal end 203.

[0052] Fig. 2C shows a side view of an exemplary turbulence inducing structure having a leading edge substantially perpendicular to or at an obtuse angle to a longitudinal axis of the catheter arrangement at the distal end 203 and its effect on increasing turbulence to flow moving past in a direction from the proximal end 204 to the distal end 203.

[0053] Fig. 2D shows a side view of an exemplary turbulence inducing structure having a leading edge substantially perpendicular to or at an obtuse angle to a longitudinal axis of the catheter arrangement at the proximal end 204 and its effect on increasing turbulence to flow moving past in a direction from the proximal end 204 to the distal end 203.

[0054] Fig. 2E provides a side view of another example of a turbulence inducing structure 202e having a sharper curve at the distal end 203 than the proximal end 204 its effect on increasing turbulence to flow moving past in a direction from the proximal end 204 to the distal end 203.

[0055] Fig. 2F provides a side view of another example of a turbulence inducing structure 202f attached to the distal end 22 of a catheter arrangement 12. In this example, the turbulence inducing structure 202f has a cylindrical shape and surrounds a distal end 22 of the catheter arrangement.

[0056] Fig. 2G provides a side view of a further example of a turbulence inducing structure 202g attached to the distal end 22 of a catheter arrangement 12. The turbulence inducing structure 202g includes a curvilinear outer surface 104g and an inner surface 102g comprising a first portion

parallel to the outer surface 15 of the catheter arrangement 12 for receiving the catheter arrangement 12 therethrough and a second portion extending away from the outer surface 15 of the catheter arrangement 12. The distal end 203 of the turbulence inducing structure 202g may have an irregular cross-sectional edge 205g or may have a linear (not shown) cross-sectional edge.

5 [0057] Fig. 2H provides a side view of a further example of a turbulence inducing structure 202h attached to the distal end 22 of a catheter arrangement 12. In this example, the turbulence inducing structure 202h is in a torus shape (*e.g.*, donut shape, also referred to as toroidal) defining an opening for receiving the catheter arrangement 12 therethrough. In a particular example, the turbulence inducing structure 202h is an inflatable or a compressible structure. For example, the
10 turbulence inducing structure 202h is a balloon. In another example, the turbulence inducing structure 202h is formed from a compressible foam.

[0058] In some other examples, the turbulence inducing structure 14 comprise one or more projections extending from the distal tip 23 of the catheter arrangement 12. As flow of the therapeutic agent is dispensed from the opening 30 at the distal tip 23 of the catheter arrangement
15 12, the flow of the therapeutic agent is disrupted by the one or more projections and therefore, inducing eddies in the flow of the blood stream. The one or more projections may have any suitable shape for inducing turbulence in localized region within the blood stream. For example, the one or more projections may have a planar shape having a flat face extending parallel to a longitudinal axis of the catheter arrangement, a cylindrical shape, a conical shape, an irregular
20 shape, etc. For example, Fig. 2I shows a side view of an example of a turbulence inducing structure 202i attached to the distal tip 23 of the catheter arrangement 12. The turbulence inducing structure 202i in this example is a flair attached to the distal tip 23 of the catheter arrangement 12 with a flat face extending parallel to a longitudinal axis of the catheter arrangement 12.

[0059] In some other examples, the turbulence inducing structure 14 is molded or formed into
25 the distal end 22 of the catheter arrangement 12. For example, the outer surface 15 of the distal end 22 of the catheter arrangement 12 may be modified to include features that induce turbulence within the blood stream when the device is in an operating position within the blood vessel of a patient. Fig. 2J provides a side view of a further example of a turbulence inducing structure 202j formed into the distal end 22 of a catheter arrangement 12. The turbulence inducing structure 202j
30 comprises one or more channels 203j carved into the outer surface 15 of the distal tip 23 of the catheter arrangement 12. The channels 203j induce turbulence within the localized region at the

distal end 22 of the catheter arrangement 12. As shown in Fig. 2J, the channels may spiral around the distal end 22 of the catheter arrangement 12. Alternatively, the channels 203j may be parallel to, perpendicular to, at an acute angle to a longitudinal axis of the catheter arrangement 12 extending from the proximal end 20 to the distal end 22, or at an obtuse angle to the longitudinal axis of the catheter arrangement 12 extending from the proximal end 20 to the distal end 22.

[0060] In another example, the distal tip 23 of the catheter arrangement 12 may be modified to include features that induce turbulence within the blood stream when the device is in an operating position within the blood vessel of a patient. Fig. 2K provides a side view of another example of a turbulence inducing structure 202k formed at the distal tip 23 of the catheter arrangement 12. The turbulence inducing structure 202k comprises one or more slits cut into the distal tip 23 of the catheter arrangement 12 forming branching features 203k that extend away from a longitudinal axis of the catheter arrangement 12. The branching features 203k induce turbulence within the localized region at the distal end 33 of the catheter arrangement 12. The slits cut into the distal tip 23 and the branching features 203k may have any suitable shape for inducing turbulence. As shown in Fig. 2K, the distal tip 23 of the catheter arrangement 12 may be modified with four slits forming four different branching features 203k, but any number of slits (e.g., 2, 3, 4, 5, 6, 7, 8, 9 or 10) may be used to form corresponding number of branching features 203k (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10) at the distal tip 23 of the catheter arrangement 12.

[0061] Fig. 2L provides a side view of another example of a turbulence inducing structure 202l formed at the distal tip 23 of the catheter arrangement 12. The turbulence inducing structure 202l comprises a distal structure 203l around the opening 30 of the distal tip 23 of the catheter arrangement 12 and a plurality of supporting portions 204l connecting the distal structure 203l to the remainder of the catheter arrangement 12. The turbulence inducing structure 202l may be formed by removing portions to form gaps 205l in the wall of the catheter arrangement 12 at the distal end 22 of the catheter arrangement 12. As shown in Fig. 2L, the turbulence inducing structure 202l may have two supporting portions, but any number of supporting portions, (e.g., 3, 4, 5, 6, 7, 8, 8, 10) may be formed from the distal end 22 of the catheter arrangement. The gaps 205l break up blood flow and further disperses the fluid pharmaceutical composition infused into the blood vessel by the catheter arrangement 12. The distal structure 203l allows for a guidewire to extend through opening 30. This distal structure 203l could be in the form of a cone, hemisphere, ring or other shape. The distal structure 203l may be coaxial with the catheter

arrangement 12. In one example, the distal structure 203 may be expandable in the same manner as a collapsible or a compressible structure, as described further below. In the example shown in Fig. 2L, the distal structure 203l comprises a distal planar face substantially perpendicular to a longitudinal axis of the catheter arrangement 12 and a proximal planar face substantially perpendicular to the longitudinal axis. The proximal planar face initiates turbulence within the blow stream and the distal planar face amplifies the turbulence.

[0062] Fig. 2M provides a side view of another example of a turbulence inducing structure 202m attached to the distal end 22 of the catheter arrangement 12. The turbulence inducing structure 202m comprises a plurality of fluted fins 203m that are arranged longitudinally along the distal end 22 of the catheter arrangement 12 (not shown) or helically around a length of the distal end 22 of the catheter arrangement 12. As blood flows downstream past the turbulence inducing structure 202m, the fluted fins 203m disrupts the laminar flow of the blood. The blood passing the turbulence inducing structure 202m, may be induced to swirl as it passes by the distal end 22 of the catheter arrangement. This swirling action disrupts laminar flow and creates turbulence to mix the fluid pharmaceutical composition in the blood of the patient.

[0063] In one example, the catheter arrangement 12 is a single microcatheter comprising the lumen 18 extending therethrough from the proximal end 20 to the distal end 22.

[0064] In another example, the catheter arrangement 12 is a multiple catheter construct that can be used to deploy and collapse or compress a collapsible or compressible turbulence inducing structure 14. For example, the catheter arrangement 12 comprises an outer catheter and an inner catheter. The inner catheter is suitably sized and shaped to be slidable within a lumen of the outer catheter. The collapsible or compressible turbulence inducing structure 14 may be collapsed or compressed and held in a collapsed or compressed configuration by the outer and inner catheters (e.g., between an outer surface of the inner catheter and the inner lumen of the outer catheter). The collapsible or compressible turbulence inducing structure 14 may be deployed and/or reconfigured by sliding the outer and inner catheters relative to each other to provide longitudinal displacement for deployment of the collapsible or compressible turbulence inducing structure 14. In this example, the handle 24 may also comprise a stationary portion and a movable portion for manipulating the catheter arrangement. In particular, the proximal end of the outer catheter is longitudinally fixedly coupled to the stationary portion and the proximal end of the inner catheter is coupled to the movable portion. The movable portion can be manually manipulated relative to

the stationary portion to slidably the inner and outer catheters relative to teach other to provide longitudinal displacement for deploying the collapsible or compressible turbulence inducing structure 14.

[0065] Fig. 2N provides a side view of another example of a turbulence inducing structure 5 202n attached to the distal end of the catheter arrangement 12. The turbulence inducing structure 202n may comprise a plurality of ridges 203n. The plurality of ridges 203n may be arranged in an array along the distal end 22 of the catheter arrangement 12. The turbulence inducing structure may for example comprise a ridge along the distal end of the catheter arrangement. A ridge may for example comprise one or more facets. Each of the one or more facets may be oriented in a 10 direction such that an axis extending perpendicularly from a surface of a facet points in the direction. A ridge may for example comprise one or more facets oriented in a proximal direction. A ridge may for example comprise one or more facets oriented in a distal direction. A ridge may for example comprise one or more facets oriented in a perpendicular to an outer surface of the catheter arrangement direction. A ridge may for example comprise one or more facets oriented in 15 a perpendicular to a longitudinal axis of the catheter arrangement direction. A ridge may for example comprise one or more facets oriented in a proximal direction, a distal direction, a perpendicular to an outer surface of the catheter arrangement direction, and/or a perpendicular to a longitudinal axis of the catheter arrangement direction.

[0066] A ridge may for example comprise one or more facets oriented at an angle between a 20 proximal direction and a distal direction. A ridge may for example comprise one or more facets oriented at an angle between a proximal direction and a perpendicular to an outer surface of the catheter arrangement direction. A ridge may for example comprise one or more facets oriented at an angle between a proximal direction and a perpendicular to a longitudinal axis of the catheter arrangement direction. A ridge may for example comprise one or more facets oriented at an angle 25 between a distal direction and an angle between a perpendicular to an outer surface of the catheter arrangement direction. A ridge may for example comprise one or more facets oriented at an angle between a distal direction and a perpendicular to a longitudinal axis of the catheter arrangement direction. A ridge may for example comprise one or more facets oriented at an angle between a perpendicular to an outer surface of the catheter arrangement direction and a perpendicular to a 30 longitudinal axis of the catheter arrangement direction.

[0067] A ridge may for example comprise a curved facet. A ridge may for example comprise one or more curved facets. The one or more curved facets may comprise a concave facet, a convex facet, and/or a combination thereof. A curved facet may comprise one or more curves. A curved facet may comprise a concave curve, a convex curve, and/or a combination thereof. A ridge may for example comprise a planar facet. A ridge may for example comprise one or more planar facets. A ridge may comprise for example one or more curved facets and/or one or more planar facets. A ridge may for example comprise two facets, three facets, four facets, five facets, or six facets.

[0068] A ridge may for example comprise a ridge width, a ridge length, and/or a ridge height. The ridge width may be in the range of 0.01mm to 0.10 mm. The ridge width may be in the range of 0.01mm to 0.20 mm. The ridge width may be in the range of 0.01 mm to 0.30 mm. The ridge width may be in the range of 0.02 mm to 0.30 mm. The ridge width may be in the range of 0.01 mm to 0.50 mm. The ridge width may be in the range of 0.01 mm to 0.75 mm. The ridge width may be in the range of 0.01 mm to 1.00 mm. The ridge width may be in the range of 0.10 mm to 1.00 mm. The ridge width may be in the range of 0.20 mm to 1.00 mm. The ridge width may be in the range of 0.30 mm to 1.00 mm. The ridge width may be in the range of 0.50 mm to 1.00 mm. The ridge width may be in the range of 0.75 mm to 1.00 mm. The ridge width may be less than, equal to and/or greater than a circumference of the catheter arrangement. The ridge width may be a percentage of the circumference of the catheter arrangement. The ridge width may be between 10% and 100% of the circumference of the catheter arrangement, 100% of the circumference of the catheter arrangement, and/or between 100% and 300% of the circumference of the catheter arrangement.

[0069] The ridge length may be in the range of 0.10 mm to 0.25 mm. The ridge length may be in the range of 0.10 mm to 0.50 mm. The ridge length may be in the range of 0.10 mm to 0.75 mm. The ridge length may be in the range of 0.10 mm to 1.00 mm. The ridge length may be in the range of 0.10 mm to 1.25 mm. The ridge length may be in the range of 0.1 mm to 1.5 mm. The ridge length may be in the range of 0.10 mm to 2.00 mm. The ridge length may be in the range of 0.25 mm to 2.00 mm. The ridge length may be in the range of 0.75 mm to 2.00 mm. The ridge length may be in the range of 1.00 mm to 2.00 mm. The ridge length may be in the range of 1.25 mm to 2.00 mm. The ridge length may be in the range of 1.50 mm to 2.00 mm. The ridge length may be less than, equal to and/or greater than a length of the distal portion of the catheter arrangement. The ridge length may be a percentage of the length of the distal portion of the catheter

arrangement. The ridge length may be between 10% and 100% of the length of the distal portion of the catheter arrangement, 100% of the length of the distal portion of the catheter arrangement, and/or between 100% and 300% of the length of the distal portion of the catheter arrangement. The ridge length may be less than and/or equal to a length of the array. The ridge length may be a percentage of the length of the array. The ridge length may be between 10% and 100% of the length of the array and/or 100% of the length of array.

[0070] The ridge height may be in the range of 0.01mm to 0.10 mm. The ridge height may be in the range of 0.01mm to 0.20 mm. The ridge height may be in the range of 0.01 mm to 0.30 mm. The ridge height may be in the range of 0.01 mm to 0.50 mm. The ridge height may be in the range of 0.01 mm to 1.00 mm. The ridge height may be in the range of 0.01 mm to 1.50 mm. The ridge height may be in the range of 0.01 mm to 2.00 mm. The ridge height may be in the range of 0.01 mm to 3.00 mm. The ridge height may be in the range of 0.02 mm to 3.00 mm. The ridge height may be in the range of 0.01 mm to 5.00 mm. The ridge height may be in the range of 0.10 mm to 5.00 mm. The ridge height may be in the range of 0.20 mm to 5.00 mm. The ridge height may be in the range of 0.30 mm to 5.00 mm. The ridge height may be in the range of 0.50 mm to 5.00 mm. The ridge height may be in the range of 1.00 mm to 5.00 mm. The ridge height may be in the range of 1.50 mm to 5.00 mm. The ridge height may be in the range of 2.00 mm to 5.00 mm. The ridge height may be in the range of 3.00 mm to 5.00 mm. The ridge height may be less than, equal to and/or greater than a radius of the catheter arrangement. The ridge height may be a percentage of the radius of the catheter arrangement. The ridge height may be between 10% and 100% of the radius of the catheter arrangement, 100% of the radius of the catheter arrangement, and/or between 100% and 300% of the radius of the catheter arrangement.

[0071] The array of the plurality of ridges 203n of the catheter arrangement may comprise a length and/or a pattern. The length of the array may be in the range of 1 mm to 5 mm. The length of the array may be in the range of 1 mm to 10 mm. The length of the array may be in the range of 1 mm to 15 mm. The length of the array may be in the range of 1 mm to 20 mm. The length of the array may be in the range of 1 mm to 25 mm. The length of the array may be in the range of 1 mm to 50 mm. The length of the array may be in the range of 1 mm to 75 mm. The length of the array may be in the range of 1 mm to 100 mm. The length of the array may be in the range of 5 mm to 100 mm. The length of the array may be in the range of 10 mm to 100 mm. The length of the array may be in the range of 15 mm to 100 mm. The length of the array may be in the range of 20 mm

to 100 mm. The length of the array may be in the range of 25 mm to 100 mm. The length of the array may be in the range of 50 mm to 100 mm. The length of the array may be in the range of 75 mm to 100 mm. The length of the array may be less than, equal to and/or greater than a length of the distal portion of the catheter arrangement. The length of the array may be a percentage of the length of the distal portion of the catheter arrangement. The length of the array may be between 10% and 100% of the length of the distal portion of the catheter arrangement, 100% of the length of the distal portion of the catheter arrangement, and/or between 100% and 300% of the length of the distal portion of the catheter arrangement. The length of the array may be equal to and/or greater than the ridge length. The length of the array may be a percentage of the ridge length. The length of the array may be 100% of the ridge length, between 100% and 500% of the ridge length, and/or between 100% and 1000% of the ridge length.

[0072] The pattern of the array may comprise a proximal to distal clockwise helix, a proximal to distal counterclockwise helix, a ring, a plurality of rings, a column, and/or a plurality of columns. The pattern may comprise one or more circumferential lengths between circumferentially adjacent ridges. The one or more circumferential lengths between circumferentially adjacent ridges may comprise a length between 1 mm to 10 mm, 0 mm, and/or negative length between 1 mm to 10 mm, wherein a negative length comprises a circumferential length overlap between circumferentially adjacent ridges. The one or more circumferential lengths between circumferentially adjacent ridges may comprise a length sized equal to, greater than, less than, and/or the opposite of, the ridge height, the ridge length, the ridge width, and/or the ridge height, of one or more of the ridges of the pattern of the array. The pattern may comprise one or more circumferential lengths between circumferentially adjacent ridges wherein no ridge is present between the circumferentially adjacent ridges. The pattern may comprise one or more circumferential lengths between circumferentially adjacent ridges wherein there is a circumferential length overlap between the circumferentially adjacent ridges. The one or more circumferential lengths between the circumferentially adjacent ridges may comprise the same circumferential length between each circumferentially adjacent ridge, may differ between the circumferentially adjacent ridges, and/or may comprise a different circumferential length between each circumferentially adjacent ridge.

[0073] The pattern may comprise one or more circumferential lengths between longitudinally adjacent ridges. The pattern may comprise one or more circumferential lengths between

longitudinally adjacent ridges wherein no ridge is present between the longitudinally adjacent ridges. The pattern may comprise one or more circumferential lengths between longitudinally adjacent ridges wherein there is a circumferential length overlap between the longitudinally adjacent ridges. The one or more circumferential lengths between the longitudinally adjacent ridges may comprise the same circumferential length between each longitudinally adjacent ridge, may differ between the longitudinally adjacent ridges, and/or may comprise a different circumferential length between each longitudinally adjacent ridge.

[0074] A ridge in the array of the plurality of ridges may comprise the same ridge width, ridge length, ridge height, and/or one or more facets as each ridge in the array of the plurality of ridges.

10 A ridge in the array of the plurality of ridges may differ in ridge width, ridge length, ridge height, and/or one or more facets from a different ridge in the array of the plurality of ridges. Each ridge in the array of the plurality of ridges may comprise a different ridge width ridge length, ridge height, and/or one or more facets from each other ridge in the array of the plurality of ridges.

[0075] Fig. 2N provides a side view of another example of a turbulence inducing structure 202n attached to the distal end of the catheter arrangement 12. The turbulence inducing structure 202n comprises a plurality of ridges 203n. The plurality of ridges 203n may be arranged in an array along the distal end 22 of the catheter arrangement 12, wherein the array may comprise a pattern. In this example, the array comprises a plurality of ridges 203n arranged in a pattern, wherein the pattern comprises a proximal to distal counterclockwise helix. A ridge 203n of the plurality of ridges 203n comprises a facet oriented in a proximal direction, wherein the facet oriented in the proximal direction is planar. A ridge 203n of the plurality of ridges 203n comprises a facet oriented in a distal direction, wherein the facet oriented in the distal direction is planar. A ridge 203n of the plurality of ridges 203n comprises a plurality of facets oriented in a perpendicular to an outer surface of the catheter arrangement direction, wherein the plurality of facets oriented in the perpendicular to an outer surface of the catheter arrangement direction are convex facets. A ridge 203n of the plurality of ridges 203n comprises a facet oriented in a perpendicular to a longitudinal axis of the catheter arrangement direction. A ridge 203n in the array of the plurality of ridges 203n comprise the same ridge width, ridge length, ridge height, and one or more facets as each other ridge in the array of the plurality of ridges. The plurality of circumferential lengths between each ridge 203n in the array of the plurality of ridges 203n is a positive value. The plurality of longitudinal lengths between each ridge 203n in the array of the plurality of ridges

203n is a positive value. The plurality of circumferential lengths between each circumferentially adjacent ridge 203n is the same. The plurality of circumferential lengths between each longitudinally adjacent ridge 203n is the same. The plurality of longitudinal lengths between each circumferentially adjacent ridge 203n is the same. The plurality of longitudinal lengths between
5 each longitudinally adjacent ridge 203n is the same.

[0076] The pump system 16 includes an infusion pump or injector (hereinafter, collectively 'pump') configured to retrieve a fluid pharmaceutical composition comprising the therapeutic agent from a reservoir and provide a flow of the fluid pharmaceutical composition through the lumen 18 of the catheter arrangement 12 and dispensed from the opening 30 at the distal tip 23 of
10 the catheter arrangement 12 into the blood stream of the patient. The pump system 16 may provide the flow of the fluid pharmaceutical composition at any desired flow rate, for example, from a flow rate of about 0.01 mL/s to about 10 mL/s, or about 0.1 mL/s to about 5 mL/s, or about 1 mL/s to about 3 mL/s.

[0077] The system 10 described herein can be used to infuse any fluid pharmaceutical composition comprising a therapeutic agent. The system 10 is particularly useful for infusion a fluid pharmaceutical composition comprising particles, e.g., particles in suspension in, for example, a liquid, foam or gel that is infused into the vasculature of the patient. The particles may be suitably sized for infusion into blood vessels of a patient, such as for example having a diameter from about 20 μm to about 1000 μm , 40 μm to about 1000 μm , 20 μm to about 40 μm , or from
20 about 10 μm to about 90 μm . The particles of the therapeutic agent may comprise undissolved solid forms of the therapeutic agent, or may be beads or microsphere carriers comprising the therapeutic agent. The beads or microspheres may contain the therapeutic agent within or may be coated on an outer surface with the therapeutic agent. In some examples, the beads or microspheres have a diameter from about 20 μm to about 1000 μm or from about 40 μm to about 1000 μm , and
25 the therapeutic agent is an embolizing agent. In another example, the beads or microspheres have a diameter from about 1 μm to about 100 μm and the therapeutic agent is a pharmacologically active agent. In a further example, the beads or microspheres have a diameter from about 10 μm to about 90 μm and the therapeutic agent is a light radioactive tracer, e.g., MAA. In a further example, the beads or microspheres have a diameter from about 20 μm to about 40 μm and the
30 therapeutic agent is a radio-embolizing agent, e.g., Y-90.

[0078] The therapeutic agent delivered using the system 10 described herein may be any pharmaceutically active agent suitable for localized delivery into a target area of the patient's body (e.g., in any organ in which treatment with the therapeutic agent is desired). For example, the organ may be the pancreas, the liver, the kidney, the lungs, the uterus, the ovaries, the cervix, the prostate, head and neck tissues (jaw, gums), the brain, the adrenal glands, bowel or colon, breast, thyroid, spleen, stomach, gall bladder, thymus, skin, bladder, lymph system, and various other organs or tissues subject to tumor or other disease states that can be treated with localized delivery of a therapeutic agent.

[0079] The therapeutic agent may include an embolizing agent (e.g., a radio-embolization agent or chemo-embolization agent), contrast agent, lipiodol, chemotherapeutics, immunotherapy agent, oncolytic viruses, gene therapies, cisplatin (or other alkylating agents), antibodies, checkpoint inhibitors, cytokines, oncolytic virus, cancer vaccines, cytotoxic agents, bland embolization agents, combination therapies, growth factor inhibitors, nanoparticle encapsulated therapies, living cell therapies, and any other therapies that can be formulated into as a fluid pharmaceutical composition and suitable for localized infusion.

[0080] In one example, the therapeutic agent is an embolizing agent (e.g., a radio-embolization agent or chemo-embolization agent) contained within or coated onto an outer surface of a bead or microsphere carrier. Examples of radio-embolization agents include any active agent that emits ionized radiation for killing cells in a target area (e.g., a tumor to be treated), for example, yttrium-90 (Y-90). Examples of chemo-embolization agents include any chemotherapy drugs that kill actively dividing cells like cancer cells by disrupting DNA, such as, for example, mitomycin, cisplatin, and doxorubicin. The embolizing agent is usually formulated in a gel pharmaceutical composition comprising a hydrogel based polymer (e.g., gelatin, PVA, etc.) that can absorb a drug into its hydrated polymer network and then slowly release it into the tissue.

[0081] In another example, the therapeutic agent comprises a Toll-like receptor (TLR) agonist, in particular, a TLR9 agonist, and more particularly a Type C TLR9 agonist.

[0082] The therapeutic agents may comprise a synthetic CpG-oligonucleotide (CPG-OND) mimicking the immunostimulatory nature of microbial CpG-DNA. According to an example, the oligonucleotide is an oligodeoxynucleotide (ODN). There are a number of different CpG-ODN class types, e.g. Class A, Class B, Class C, Class P, and Class S, which share certain structural and functional features. In this regard, Class A type CPG-ODNs (or CPG-A ODNs) are associated with

pDC maturation with little effect on B cells as well as the highest degree of IFN α induction; Class B type CPG-ODNs (or CPG-B ODNs) strongly induce B-cell proliferation, activate pDC and monocyte maturation, NK cell activation, and inflammatory cytokine production; and Class C type CPG-ODNs (or CPG-C ODNs) can induce B-cell proliferation and IFN- α production. The CPG-
5 C ODNs can be associated with the following attributes: (i) unmethylated dinucleotide CpG motifs, (ii) juxtaposed CpG motifs with flanking nucleotides (e.g., AACGTTTCGAA), (iii) a complete phosphorothioate (PS) backbone that links the nucleotides (as opposed to the natural phosphodiester (PO) backbones found in bacterial DNA), and (iv) a self-complimentary, palindromic sequence (e.g. AACGTT). In this regard, CPG-C ODNs may bind themselves due to
10 their palindromic nature, thereby producing double-stranded duplex (e.g., dimer) or hairpin structures.

[0083] In one example, the TLR9 agonist is a CPG-OND. For example, the therapeutic agent comprises SD-101 or a pharmaceutically acceptable salt thereof (e.g., a sodium salt as shown in Fig. 3), as described in WO2022/066670, which is incorporated by reference herein. In particular,
15 the therapeutic agent is SD-101 or a pharmaceutically acceptable salt thereof, or is a derivative of SD-101 or a pharmaceutically acceptable salt thereof. Further, according to an example, the CPG-C ODN sequence can correspond to SEQ ID NO: 172 as described in U.S. Patent No. 9,422,564, which is incorporated by reference herein in its entirety.

[0084] In one example, the therapeutic agent comprises a checkpoint inhibitor (CPI). The CPI
20 may comprise a Programmed Death 1 receptor (PD-1) antagonist. The PD-1 antagonist may be a monoclonal antibody (mAb), or antigen binding fragment thereof, which specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1. The mAb may be a human antibody, a humanized antibody or a chimeric antibody, and may include a human constant region. In some examples the human constant region is selected from the group consisting
25 of IgG1, IgG2, IgG3 and IgG4 constant regions, and in preferred examples, the human constant region is an IgG1 or IgG4 constant region. In some examples, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, F(ab')₂, scFv and Fv fragments. Alternatively, the PD-1 antagonist may be an immunoadhesin that specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1, e.g., a fusion protein containing the
30 extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region such as an Fc

region of an immunoglobulin molecule. For example, the PD-1 antagonist may be nivolumab, pembrolizumab, cemiplimab, relatimab or a combination thereof.

[0085] In one particular example, the therapeutic agent comprises a combination of a TLR9 agonist or CPG-OND in combination with a CPI, as described above.

- 5 **[0086]** The invention described and claimed herein is not to be limited in scope by the specific embodiments herein disclosed since these embodiments are intended as illustrations of several aspects of this invention. Any equivalent embodiments are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such
- 10 modifications are also intended to fall within the scope of the appended claims. All publications cited herein are incorporated by reference in their entirety.

CLAIMS

What is claimed is:

- 5 1. A vascular infusion catheter for infusing a therapeutic agent to a blood vessel of a patient comprising:
- a catheter arrangement extending from a distal end to a proximal end having an outer surface and an interior surface, the interior surface defining a lumen therethrough, the catheter arrangement comprising an opening at a distal tip of the catheter arrangement in a continuous
- 10 fluid pathway with the lumen; and
- a turbulence inducing structure formed from or attached to the outer surface or the distal tip of the catheter arrangement, the turbulence inducing structure configured to induce turbulence in blood flowing through a localized region of the blood vessel,
- wherein the turbulence inducing structure is configured to not fully occlude the blood
- 15 vessel such that the blood can flow past the turbulence inducing structure at all times.
2. The vascular infusion catheter of claim 1, wherein the therapeutic agent is within or coated on a surface of a particle.
- 20 3. The vascular infusion catheter of claim 1, wherein the catheter arrangement is a single catheter.
4. The vascular infusion catheter of claim 1, wherein the catheter arrangement comprises an outer catheter and an inner catheter configured to deploy the turbulence inducing structure by
- 25 longitudinal displacement of the outer catheter relative to the inner catheter.
5. The vascular infusion catheter of claim 1, wherein the therapeutic agent is a TLR9 agonist.
- 30 6. The vascular infusion catheter of claim 5, wherein the TLR9 agonist is SD-101 or a pharmaceutically acceptable salt thereof.

7. The vascular infusion catheter of any one of claims 1 to 6, wherein the turbulence inducing feature is attached to the distal tip of the catheter arrangement.
- 5 8. The vascular infusion catheter of any one of claims 1 to 6, wherein the turbulence inducing structure does not fully occlude the blood vessel such that blood can flow past the turbulence inducing structure in a downstream direction or in an upstream direction.
9. The vascular infusion catheter of any one of claims 1 to 6, wherein the turbulence
10 induced provides a shear force that does not exceed a shear force for lysis of red blood cells.
10. The vascular infusion catheter of any one of claims 1 to 6, wherein the turbulence inducing structure comprises a leading edge substantially perpendicular to or at an obtuse angle to a longitudinal axis of the catheter arrangement at the distal end or the proximal end of the
15 catheter arrangement.
11. The vascular infusion catheter of any one of claims 1 to 6, wherein the turbulence inducing structure is spherical, cylindrical, conical, ovoid, ellipsoid or toroidal.
- 20 12. The vascular infusion catheter of any one of claims 1 to 6, wherein the therapeutic agent is a radio-embolizing agent, the therapeutic agent being contained within or coated onto particles.
13. The vascular infusion catheter of any one of claims 1 to 6, wherein the turbulence
25 inducing structure partially occludes the blood vessel such that blood can flow past the turbulence inducing structure in a downstream direction or in an upstream direction.
14. The vascular infusion catheter of any one of claims 1 to 6, wherein the turbulence inducing structure comprises a plurality of ridges arranged in an array.

30

15. The vascular infusion catheter of claim 14, wherein the array comprises a pattern, and wherein the pattern comprises a proximal to distal counterclockwise helix or a proximal to distal clockwise helix.
- 5 16. A system for vascular infusion of a therapeutic agent to a blood vessel of a patient comprising:
- a catheter arrangement extending from a distal end to a proximal end having an outer surface and an interior surface, the interior surface defining a lumen therethrough, the catheter arrangement comprising an opening at a distal tip of the catheter arrangement in a continuous
- 10 fluid pathway with the lumen;
- a turbulence inducing structure formed from or attached to the outer surface or the distal tip of the catheter arrangement, the turbulence inducing structure configured to induce turbulence to blood flowing in a downstream direction through a localized region of the blood vessel;
- a handle operably connected to the proximal end of the catheter arrangement such that the
- 15 handle can be manipulated to manipulate the catheter arrangement; and
- a pump system fluidly connected to the proximal end of the catheter arrangement in the continuous fluid pathway with the opening at the distal tip and the lumen, the pump system configured to dispense a flow of a fluid pharmaceutical composition comprising the therapeutic agent, from the pump system through the continuous fluid pathway via the opening to the blood
- 20 vessel,
- wherein the turbulence inducing structure is configured to not fully occlude the blood vessel such that the blood can flow past the turbulence inducing structure at all times.
17. The system of claim 16, wherein the therapeutic agent is within or coated on a surface of
- 25 a particle.
18. The system of claim 16, wherein the catheter arrangement is a single catheter.
19. The system of claim 16, wherein the catheter arrangement comprise an outer catheter and
- 30 an inner catheter configured to deploy the turbulence inducing structure by longitudinal displacement of the outer catheter from the inner catheter.

20. The system of claim 16, wherein the therapeutic agent is a TLR9 agonist.
21. The system of claim 16, wherein the TLR9 agonist is SD-101 or a pharmaceutically
5 acceptable salt thereof.
22. The system of any one of claims 16 to 21, wherein the turbulence inducing feature is attached to the distal tip of the catheter arrangement.
- 10 23. The system of any one of claims 16 to 21, wherein the turbulence inducing structure does not fully occlude the blood vessel such that blood can flow past the turbulence inducing structure in a downstream direction or in an upstream direction.
24. The system of any one of claims 16 to 21, wherein the turbulence induced provides a
15 shear force that does not exceed a shear force for lysis of red blood cells.
25. The system of any one of claims 16 to 21, wherein the turbulence inducing structure comprises a leading edge substantially perpendicular to or at an obtuse angle to a longitudinal axis of the catheter arrangement at the distal end or the proximal end of the catheter arrangement.
20
26. The system of any one of claims 16 to 21, wherein the turbulence inducing structure is spherical, cylindrical, conical, ovoid, ellipsoid or toroidal.
27. The system of any one of claims 16 to 21, wherein the therapeutic agent is a radio-
25 embolizing agent, the therapeutic agent being contained within or coated onto particles.
28. The system of any one of claims 16 to 21, wherein the turbulence inducing structure partially occludes the blood vessel such that blood can flow past the turbulence inducing structure in a downstream direction or in an upstream direction.
30

29. The system of any one of claims 16 to 21, wherein the turbulence inducing structure comprises a plurality of ridges arranged in an array.
30. The system of claim 29, wherein the array comprises a pattern, and wherein the pattern
5 comprises a proximal to distal counterclockwise helix or a proximal to distal clockwise helix.