

[0006] Further, drawbacks and complications of such methods are that infusion and flow of the drug throughout the CNS compartments is limited.

[0007] Additional drawbacks are that an intratumorally-implanted catheter tip may not provide sufficient infusion and flow of drug throughout the CNS compartments.

[0008] What is needed is a device for intracranial systemic, bolus and/or continuous infusion of therapeutics for use in methods for treating central nervous system (CNS) diseases including cancer.

[0009] What is needed are methods and agents for use in inhibiting or suppressing factors in the unpredictable pathology of diseases of the central nervous system, in particular cancer. For example, there is an urgent need for methods and agents for use in inhibiting the activity of TGF- β and/or suppressing TGF- β related pathologies, which can improve the efficacy for treating central nervous system cancers.

BRIEF SUMMARY

[0010] This disclosure provides therapies for treating or ameliorating symptoms of CNS disease such as CNS cancer.

[0011] In some examples, this disclosure includes agents and compositions for inhibiting or suppressing TGF- β 2 to provide improved clinical outcomes for CNS disease.

[0012] In further examples, this disclosure provides stable formulations of anti-TGF- β 2 agents for various therapies for CNS disease. Examples of anti-TGF- β 2 agents include TGF- β 2 inhibitors such as antisense oligonucleotides, pharmaceutically acceptable salts forms, esters, polymorphs or stereoisomers thereof, as well as combinations thereof.

[0013] In further examples, this disclosure provides highly stable formulations of anti-TGF- β 2 agents for therapies for CNS disease. The stable formulations of this disclosure provide surprisingly improved clinical results. Stable formulations of agents for suppressing TGF- β 2 can be used to treat CNS disease, in particular CNS cancer.

[0014] This disclosure provides a device and system for intracranial, intrathecal or intraventricular continuous infusion of therapeutics for treating central nervous system (CNS) diseases. Continuous infusion to brain tumors with the system of this disclosure is far easier than for conventional CED systems and other similar or conventional methods.

[0015] The infusion system of this disclosure has a significant advantage because it delivers an effective amount or dose of a pharmaceutical composition continuously to a patient with much

greater safety and ease of insertion throughout the CNS. For example, the infusion system of this disclosure will deliver by an intraventricular route a more effective amount of the drug throughout the CNS/brain compartments versus localized delivery by CED methods. This advantage can be significant especially for treatment of CNS cancers.

[0016] A device of this disclosure can overcome the drawbacks and complications of conventional methods. The infusion system of this disclosure has significant advantages because placement of the catheter and its tip into the brain is relatively easy and requires no imaging to be accomplished. Further, the infusion and flow of the drug to the brain takes advantage of fluids circulation in the brain to distribute the drug effectively over a larger area and to targeted tissues. Moreover, the system of this disclosure can be used in a novel mode of operation to provide continuous infusion to the targeted tissues.

[0017] This disclosure also relates to a device and system for intracranial, intrathecal or intraventricular continuous infusion of therapeutics for treating central nervous system (CNS) diseases of the brain and spine. The system of this disclosure will deliver compositions and agents for inhibiting or suppressing TGF- β 2 to improve clinical outcomes for such diseases. This system can use stable formulations of anti-TGF- β 2 agents including antisense oligonucleotide compositions and other agents for treating a CNS disease including CNS cancers.

[0018] This disclosure further relates to methods for treating for treating central nervous system (CNS) diseases of the brain and spine.

[0019] This disclosure further provides a device for intracranial, intrathecal or intraventricular continuous infusion of therapeutics for treating central nervous system (CNS) diseases. Continuous infusion to brain tumors with the device and device of this disclosure is far easier than for conventional CED methods and other similar or conventional methods.

[0020] The infusion device of this disclosure has a significant advantage because it delivers an effective amount or dose of a pharmaceutical composition continuously to a patient with much greater safety and ease of insertion throughout the CNS. For example, the infusion device and device of this disclosure will deliver by an intraventricular route a more effective amount of the drug throughout the CNS/brain compartments versus localized delivery by CED methods. This advantage can be significant especially for treatment of CNS cancers.

[0021] The device of this disclosure overcomes the drawbacks and complications of known methods. The infusion device of this disclosure has significant advantages because placement of the catheter and its tip into the brain is relatively easy and requires no imaging to be

accomplished. Further, the infusion and flow of the drug to the brain takes advantage of fluids circulation in the brain to distribute the drug effectively over a larger area and to targeted tissues. Moreover, the device of this disclosure can be used in a novel mode of operation to provide continuous infusion to the targeted tissues.

[0022] This disclosure also relates to a device for intracranial, intrathecal or intraventricular continuous infusion of therapeutics for treating central nervous system (CNS) diseases of the brain and spine. The device of this disclosure will deliver compositions and agents for inhibiting or suppressing TGF- β 2 to improve clinical outcomes for such diseases. This device uses stable formulations of anti-TGF- β 2 agents including antisense oligonucleotide compositions and other agents for treating a CNS disease including CNS cancers.

[0023] This disclosure further relates to methods for treating for treating central nervous system (CNS) diseases of the brain and spine.

[0024] Examples of this disclosure include the following:

[0025] An agent for inhibiting or suppressing expression of TGF- β 2 for treating or ameliorating the symptoms of a CNS disease in a human subject or animal.

[0026] Use of an agent for inhibiting or suppressing expression of TGF- β 2 in the preparation of a medicament for treating or ameliorating the symptoms of a CNS disease in a human subject or animal.

[0027] A method for treating or ameliorating the symptoms of a CNS disease in a human subject or animal in need, the method comprising:

[0028] preparing a composition comprising an agent for inhibiting or suppressing expression of TGF- β 2 in a carrier; and

[0029] administering a therapeutically effective amount of the composition to the subject.

[0030] The agent, use or method above, wherein the CNS disease is glioma, glioblastoma, diffuse intrinsic pontine glioma (DIPG), diffuse midline glioma (DMG), leptomeningeal or brain metastasis, brain or spinal cancer, or CNS tumors.

[0031] The agent, use or method above, in combination with a medicament comprising a targeted cancer drug, a cancer growth blocker, an EGFR inhibitor, or a combination thereof.

[0032] The agent, use or method above, in combination with a medicament selected from bevacizumab, everolimus, belzutifan, dabrafenib, trametinib, and combinations thereof.

[0033] The agent, use or method above, in combination with a medicament which is a cancer growth blocker selected from an angiogenesis inhibitor, a histone deacetylase inhibitor, a

- [0097]** A collar for a device for delivering a pharmaceutical composition by intracranial continuous infusion, the collar comprising:
- [0098]** a hard shell [604] having an opening [606] which exposes a flexible top of the device.
- [0099]** A method for administering a pharmaceutical composition by intracranial continuous infusion, comprising:
- [00100]** mounting a device according to above to a patient; and
- [00101]** pumping the pharmaceutical composition in the device to provide intracranial continuous infusion to the patient.
- [00102]** The method above, wherein the device is mounted and the entry catheter is placed into the brain without concurrent head or brain imaging.
- [00103]** The method above, wherein the device is mounted and a single entry catheter is placed into the brain.
- [00104]** A kit for continuous intracranial infusion of a pharmaceutical composition into a subject, the kit comprising:
- [00105]** a reservoir containing the pharmaceutical composition;
- [00106]** a pump;
- [00107]** an ommaya reservoir having a partially-flexible top;
- [00108]** infusion tubes for connecting the reservoir to the pump, and connecting the pump to the ommaya reservoir;
- [00109]** a filter; and
- [00110]** an entry catheter.
- [00111]** The kit above, wherein the entry catheter is substantially linear for intraventricular entry into a target region of the brain.
- [00112]** The kit above, wherein the entry catheter is non-linear and has a bend for intraventricular entry into a target region of the brain.
- [00113]** The kit above, wherein the infusion tubes are external to the subject.
- [00114]** The kit above, wherein a portion of the infusion tube connecting the pump to the ommaya reservoir is indwelling the subject.

[00114a] In an aspect of the present disclosure, there is provided a kit comprising:
an agent comprising a total of 250 mg of one or more TGF- β 2-specific antisense oligonucleotides selected from Table 2 SEQ ID NOs:1-136 and chemically-modified variants thereof, LNA variants thereof, gapmer variants thereof, and any combination thereof; and
an ommaya-like reservoir having a partially-flexible top.

[00114b] In another aspect of the present disclosure, there is provided a device for delivering a fluid pharmaceutical composition by intracranial continuous infusion, the device comprising:

- a reservoir containing the pharmaceutical composition;
- a pump to force the pharmaceutical composition through an infusion tube into an ommaya reservoir, the pump being in fluid communication with the ommaya reservoir, and wherein the pump is in fluid communication with the reservoir through a reservoir tube;
- a filter in line with the infusion tube; and
- an entry catheter in fluid communication with the ommaya reservoir, wherein the entry catheter is substantially linear and enters intraventricularly into a target region of the brain.

[00114c] In a further aspect of the present disclosure, there is provided a device for delivering a fluid pharmaceutical composition by intracranial continuous infusion, the device comprising:

- a reservoir containing the pharmaceutical composition;
- a pump to force the pharmaceutical composition through an infusion tube into an access port, the pump being in fluid communication with an ommaya reservoir, wherein the reservoir is in fluid communication with the pump through a reservoir tube;
- a filter in line with the infusion tube;
- an indwelling tube in fluid communication with the access port and the ommaya reservoir; and
- an entry catheter in fluid communication with the ommaya reservoir, wherein the entry catheter is substantially linear and enters intraventricularly into a target region of the brain.

[00114d] In another aspect of the present disclosure, there is provided a device for delivering a pharmaceutical composition by intracranial continuous infusion, the device

comprising:

- a reservoir containing the pharmaceutical composition, the reservoir comprising a hard shell, a flexible top, and a non-flexible mounting plate;
- a port in fluid communication with the reservoir; and
- an entry catheter in fluid communication with the reservoir, wherein the entry catheter is substantially linear and enters intraventricularly into a target region of the brain.

[00114e] In a further aspect of the present disclosure, there is provided a device for delivering a pharmaceutical composition by intracranial continuous infusion, the device comprising:

- a reservoir containing the pharmaceutical composition, the reservoir comprising an upper hard shell, a lower hard shell, a flexible top, and a non-flexible mounting plate;
- a port in fluid communication with the reservoir for attaching an infusion line; and
- a port in fluid communication with the reservoir for attaching an entry catheter.

[00114f] In another aspect of the present disclosure, there is provided a device for delivering a pharmaceutical composition by intracranial continuous infusion, the device comprising:

- a reservoir containing the pharmaceutical composition, the reservoir comprising an upper hard shell, a flexible top, and a non-flexible mounting plate;
- a port in fluid communication with the reservoir for attaching an infusion line; and
- a port in fluid communication with the reservoir for attaching an entry catheter.

[00114g] In a further aspect of the present disclosure, there is provided a collar for a device for delivering a pharmaceutical composition by intracranial continuous infusion, the collar comprising:

- a hard shell having an opening which exposes a flexible top of the device.

[00114h] In another aspect of the present disclosure, there is provided a kit for continuous intracranial infusion of a pharmaceutical composition into a subject, the kit comprising:

- a reservoir containing the pharmaceutical composition;

- a pump;
- an ommaya reservoir having a partially-flexible top;
- infusion tubes for connecting the reservoir to the pump, and connecting the pump to the ommaya reservoir;
- a filter; and
- an entry catheter.

BRIEF DESCRIPTION OF THE DRAWINGS

[00115] FIG. 1 shows a device for delivering a pharmaceutical composition by intrathecal or intraventricular continuous infusion. The device shown in FIG. 1 includes

WHAT IS CLAIMED IS:

1. A kit comprising:
 - an agent comprising a total of 250 mg of one or more TGF- β 2-specific antisense oligonucleotides selected from Table 2 SEQ ID NOs:1-136 and chemically-modified variants thereof, LNA variants thereof, gapmer variants thereof, and any combination thereof; and
 - an ommaya-like reservoir having a partially-flexible top.
2. A device for delivering a fluid pharmaceutical composition by intracranial continuous infusion, the device comprising:
 - a reservoir containing the pharmaceutical composition;
 - a pump to force the pharmaceutical composition through an infusion tube into an ommaya reservoir, the pump being in fluid communication with the ommaya reservoir, and wherein the pump is in fluid communication with the reservoir through a reservoir tube;
 - a filter in line with the infusion tube; and
 - an entry catheter in fluid communication with the ommaya reservoir, wherein the entry catheter is substantially linear and enters intraventricularly into a target region of the brain.
3. The device of claim 2, wherein the entry catheter is non-linear and has one or more bends to enter intraventricularly into a target region of the brain.
4. A device for delivering a fluid pharmaceutical composition by intracranial continuous infusion, the device comprising:
 - a reservoir containing the pharmaceutical composition;
 - a pump to force the pharmaceutical composition through an infusion tube into an access port, the pump being in fluid communication with an ommaya reservoir, wherein the reservoir is in fluid communication with the pump through a reservoir tube;
 - a filter in line with the infusion tube;
 - an indwelling tube in fluid communication with the access port and the ommaya reservoir; and
 - an entry catheter in fluid communication with the ommaya reservoir, wherein the entry catheter is substantially linear and enters intraventricularly into a target region of the brain.
5. The device of claim 4, wherein the entry catheter is non-linear and has one or more bends to enter intraventricularly into a target region of the brain.
6. The device of any of claims 2-5, wherein the ommaya reservoir comprises a partially-flexible top.

7. The device of any of claims 2-5, wherein the device provides continuous infusion of a therapeutically effective amount of the fluid pharmaceutical composition to the target region.
8. The device of any of claims 2-5, wherein the distal end of the entry catheter enters the target region of the brain.
9. The device of any of claims 2-5, wherein the ommaya reservoir holds the pharmaceutical composition behind a membrane for a sustained period of time for sustained release of the pharmaceutical composition to the entry catheter.
10. The device of any of claims 2-5, wherein the distal end tip of the entry catheter that enters the brain is a step-down end, a recessed step end, a multi-port end, a microporous end, or a balloon tipped end.
11. The device of any of claims 2-5, wherein the pump is a Pegasus Vario, a PEGA PCA, a CADD Solis VIP, a CADD-Legacy PLUS, a CADD-Legacy PCA, a CADD-Legacy 1, or other pump with similar specifications.
12. The device of any of claims 2-5, wherein the infusion rate of the fluid pharmaceutical composition is from 0.01 to 3000 ml/hr, or from 0.01 to 100 ml/hr, or from 0.01 to 2 ml/hr, or from 0.01 to 1 ml/hr, or from 0.05 to 0.5 ml/hr.
13. The device of any of claims 2-5, wherein the infusion tube or the indwelling tube is a PEGA Line 100 SF 100 cm with a 0.2 μ m sterile filter, or a 200 cm infusion line with a 0.2 μ m sterile filter, or a Port-a-Cath (#21-4034-24) with 22G Needle (#21-2737-24) and extension (#21-7106-24), or other tube with similar specifications.
14. The device of any of claims 2-5, wherein the fluid pharmaceutical composition comprises an agent for inhibiting or suppressing expression of TGF- β , which can be used for treating or ameliorating the symptoms of a CNS disease in a human subject or animal.
15. The device of any of claims 2-5, wherein the fluid pharmaceutical composition comprises microparticles or nanoparticles of an agent, medicament, or delivery vehicle.
16. The device of any of claims 2-5, wherein the fluid pharmaceutical composition is therapeutic for CNS disease or CNS cancer.
17. The device of any of claims 2-5, wherein the fluid pharmaceutical composition is therapeutic for glioma, glioblastoma, diffuse intrinsic pontine glioma (DIPG), diffuse midline glioma (DMG), leptomeningeal or brain metastasis, brain or spinal cancer, or CNS tumors.

18. The device of any of claims 2-5, wherein the fluid pharmaceutical composition comprises an agent for inhibiting or suppressing expression of TGF- β 2 selected from TGF- β 2-specific antisense oligonucleotides complementary to a TGF- β 2 transcript as follows:

Table 2 SEQ ID NOs:1-136 and chemically-modified variants thereof, LNA variants thereof, gapmer variants thereof, and any combination thereof.

19. The device of any of claims 2-5, wherein the device is operated in combination with radiation therapy, or electric field therapy.

20. A device for delivering a pharmaceutical composition by intracranial continuous infusion, the device comprising:

a reservoir containing the pharmaceutical composition, the reservoir comprising a hard shell, a flexible top, and a non-flexible mounting plate;

a port in fluid communication with the reservoir; and

an entry catheter in fluid communication with the reservoir, wherein the entry catheter is substantially linear and enters intraventricularly into a target region of the brain.

21. A device for delivering a pharmaceutical composition by intracranial continuous infusion, the device comprising:

a reservoir containing the pharmaceutical composition, the reservoir comprising an upper hard shell, a lower hard shell, a flexible top, and a non-flexible mounting plate;

a port in fluid communication with the reservoir for attaching an infusion line; and

a port in fluid communication with the reservoir for attaching an entry catheter.

22. A device for delivering a pharmaceutical composition by intracranial continuous infusion, the device comprising:

a reservoir containing the pharmaceutical composition, the reservoir comprising an upper hard shell, a flexible top, and a non-flexible mounting plate;

a port in fluid communication with the reservoir for attaching an infusion line; and

a port in fluid communication with the reservoir for attaching an entry catheter.

23. A collar for a device for delivering a pharmaceutical composition by intracranial continuous infusion, the collar comprising:

a hard shell having an opening which exposes a flexible top of the device.

24. A kit for continuous intracranial infusion of a pharmaceutical composition into a subject, the kit comprising:

a reservoir containing the pharmaceutical composition;

a pump;

an ommaya reservoir having a partially-flexible top;
infusion tubes for connecting the reservoir to the pump, and connecting the pump to the ommaya reservoir;
a filter; and
an entry catheter.

25. The kit of claim 24, wherein the entry catheter is substantially linear for intraventricular entry into a target region of the brain.
26. The kit of claim 24, wherein the entry catheter is non-linear and has a bend for intraventricular entry into a target region of the brain.
27. The kit of any of claims 24-26, wherein the infusion tubes are external to the subject.
28. The kit of any of claims 24-26, wherein a portion of the infusion tube connecting the pump to the ommaya reservoir is indwelling the subject.