evacuation of a hematoma, tumor or vascular malformation in the brain. This provides high concentrations of the drug at the site where activity is needed, and lower concentrations in the rest of the body, thus decreasing the risk of unwanted systemic side effects.

[000119] Site-specific delivery systems, for example, include use of microparticles (of about 1 μm to about 100 μm in diameter), thermoreversible gels (for example, PGA/PEG), and biodegradable polymers (for example, PLA, PLGA) that may be in the form of a film.

[000120] The delivery characteristics of the drug and the polymer degradation in vivo also can be modified. For example, polymer conjugation can be used to alter the circulation of the drug in the body and to achieve tissue targeting, reduce irritation and improve drug stability.

[000121] While all these possibilities exist, no one has applied such polymers to deliver therapeutic agents locally within the human brain to treat hemorrhagic brain conditions.

[000122] The described invention provides therapeutic compositions, methods for identifying therapeutic agents for treating hemorrhagic conditions of the brain, methods for treating hemorrhagic conditions of the brain, and an accurate and reproducible model system for chronic SDH and for ICH.

SUMMARY

[000123] According to one ~~aspect~~embodiment, the ~~described invention~~present disclosure provides a method for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, the method comprising: (a) providing a pharmaceutical composition comprising (i) a therapeutically effective amount of an anti-fibrinolytic agent and (ii) a pharmaceutically acceptable carrier; (b) administering the pharmaceutical composition into or at a distance proximal to the hematoma in brain; and (c) improving patient outcome. According to one embodiment, the hemorrhagic condition results from traumatic brain injury (TBI). According to another embodiment, the hemorrhagic condition is rebleeding following a surgical evacuation of a hematoma. According to another embodiment, the hemorrhagic condition is a chronic subdural hematoma. According

photopolymerizable biopolymer, and a combination thereof. According to another embodiment, the synthetic polymer is polyglycolic acid (PGA). According to another embodiment, the synthetic polymer is a copolymer of polyglycolic acid formed with trimethylene carbonate, polylactic acid (PLA), or polycaprolactone. According to another embodiment, the sustained-release carrier is a hydrogel. According to another embodiment, the naturally occurring biopolymer is a protein polymer. According to another embodiment, the naturally occurring polymer comprises hyaluronic acid.According to another embodiment, the naturally occurring polymer comprises less than 2.3 % of hyaluronic acid. According to another embodiment, the distance proximal to the hematoma is from about 0.5 mm to about 10 mm. According to another embodiment, the pharmaceutical composition exhibits a localized pharmacological effect. According to another embodiment, the pharmaceutical composition exhibits its pharmacological effect throughout the brain.

[000123a] According to an aspect, there is provided the use of a site-specific sustained-release pharmaceutical composition in the manufacture of a medicament for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, wherein the pharmaceutical composition comprises:

(i) a therapeutic amount of at least one anti-fibrinolytic agent; and

(ii) a pharmaceutically acceptable carrier, wherein the carrier comprises a plurality of microparticles,

the composition being characterized by:

(a) dispersal of the therapeutic amount of the anti-fibrinolytic agent throughout each microparticle, in a core of the microparticle surrounded by a coating, adsorbed into the particles, or a combination thereof; and

(b) sustained release of the anti-fibrinolytic agent from the microparticles at the implant site to maintain a high concentration of the anti-fibrinolytic agent locally and lower concentrations in the rest of the body, thus decreasing risk of unwanted side effects.

[000123b] According to another aspect, there is provided a site-specific, sustained-release pharmaceutical composition for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, the pharmaceutical composition comprising:

(a) a therapeutic amount of at least one anti-fibrinolytic agent; and

(b) a pharmaceutically acceptable carrier, wherein the carrier comprises a plurality of microparticles,

the composition being characterized by:

(i) dispersal of the therapeutic amount of the anti-fibrinolytic agent throughout each microparticle, in a core of the microparticle surrounded by a coating, adsorbed into the particles, or a combination thereof; and

(ii) sustained release of the anti-fibrinolytic agent from the microparticles at the implant site to maintain a high concentration of the anti-fibrinolytic agent locally and lower concentrations in the rest of the body, thus decreasing risk of unwanted side effects.

[000124] According to another ~~aspect~~embodiment, the ~~described invention~~present disclosure provides a site-specific, sustained-release pharmaceutical composition for treating hematoma expansion or recurrent rebleeding resulting from a hemorrhagic condition in brain, the pharmaceutical composition comprising: (a) a therapeutically effective amount of an anti-fibrinolytic agent; and (b) a pharmaceutically acceptable carrier, wherein in the pharmaceutically acceptable carrier is a sustained-release carrier. According to another embodiment, the hemorrhagic condition is rebleeding following traumatic brain injury. According to another embodiment, the hemorrhagic condition is a chronic subdural hematoma. According to another embodiment, the hemorrhagic condition is an intracerebral hematoma. According to another embodiment, the intracerebral hematoma is a spontaneous intracerebral hematoma. According to another embodiment, the intracerebral hematoma is a traumatic intracerebral hematoma. According to another embodiment, the hemorrhagic condition is rebleeding following a craniotomy procedure. According to another embodiment, the craniotomy procedure is performed for treating a brain cancer. According to another embodiment, the craniotomy procedure is performed for treating a vascular malformation in brain. According to another embodiment, the craniotomy procedure is

CLAIMS

What is claimed is:

1. Use of a site-specific sustained-release pharmaceutical composition in the manufacture of a medicament for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, wherein the pharmaceutical composition comprises:

(i) a therapeutic amount of at least one anti-fibrinolytic agent; and

(ii) a pharmaceutically acceptable carrier, wherein the carrier comprises a plurality of microparticles,

~~wherein the composition is formulated for administration locally in a cavity or space occupied by a hematoma or in a subdural space on the surface of the brain,~~

the composition being characterized by:

(a) dispersal of the therapeutic amount of the anti-fibrinolytic agent throughout each microparticle, in a core of the microparticle surrounded by a coating, adsorbed into the particles, or a combination thereof; and

~~(b) its deposition in or on a biodegradable implant at an implant site in a cavity or space within the brain occupied by a hematoma or in a subdural space on the surface of the brain;~~

~~(c)~~(b) sustained release of the anti-fibrinolytic agent from the microparticles at the implant site to maintain a high concentration of the anti-fibrinolytic agent locally and lower concentrations in the rest of the body, thus decreasing risk of unwanted side effects.~~;~~

~~(d) breakdown of the biodegradable carrier over time to effect release of the anti-fibrinolytic agent into the cerebrospinal fluid circulation to achieve tissue targeting of the therapeutic amount of the anti-fibrinolytic agent at a site of bleeding in or on the brain; and~~

~~(e) the therapeutic amount is effective to reduce hematoma expansion or recurrent bleeding, when compared to a nontreated control.~~

2. The use according to claim 1, wherein the hemorrhagic condition results from traumatic brain injury (TBI), bleeding following a surgical evacuation of the hematoma, chronic subdural hematoma (SDH), intracerebral hematoma (ICH) or bleeding following a craniotomy procedure.

3. The use according to claim 2, wherein the intracerebral hematoma is a spontaneous intracerebral hematoma (ICH) or a traumatic intracerebral hematoma.

4. The use according to claim 2, wherein the craniotomy procedure is performed for treating a brain neoplasm, a vascular malformation in brain or a brain aneurysm.

5. The use according to claim 1, wherein the pharmaceutically acceptable carrier is a controlled-release carrier or a sustained-release carrier.

6. The use according to claim ~~6~~5, wherein the sustained-release carrier is capable of releasing the anti-fibrinolytic agent for at least 21 days post-administration.

7. The use according to claim 5~~6~~, wherein the sustained-release carrier is capable of releasing the anti-fibrinolytic agent for about 3 to 5 days post-administration.

8. The use according to claim 5~~6~~, wherein the sustained-release carrier is a nano-particle or a hydrogel.

9. The use according to claim 5~~6~~, wherein the sustained-release carrier comprises a biodegradable polymer.

10. The use according to claim ~~11~~9, wherein the biodegradable polymer is a synthetic polymer or a naturally occurring polymer.

11. The use according to claim ~~12~~10, wherein the synthetic polymer is selected from the group consisting of a polyester, a polyester polyethylene glycol polymer, a polyamino-derived biopolymer, a polyanhydride, a polyorthoester, a polyphosphazene, a sucrose acetate isobutyrate (SAIB), a photopolymerizable biopolymer, and a combination thereof.

12. The use according to claim ~~12~~10, wherein the synthetic polymer is polyglycolic acid (PGA), or a copolymer of polyglycolic acid (PGA) formed with trimethylene carbonate, polylactic acid (PLA), or polycaprolactone.

13. The use according to claim ~~12~~10, wherein the naturally occurring biopolymer is a protein polymer or comprises hyaluronic acid.

14. The use according to claim ~~15~~13, wherein the naturally occurring biopolymer comprises less than 2.3% of hyaluronic acid.

15. The use according to claim 1, wherein the distance proximal to the hematoma is from about 0.5 mm to about 10 mm.

16. A site-specific, sustained-release pharmaceutical composition for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, the pharmaceutical composition comprising:

(a) a therapeutic amount of at least one anti-fibrinolytic agent; and

(b) a pharmaceutically acceptable carrier, wherein the carrier comprises a plurality of microparticles,

~~wherein the composition is formulated for administration locally in a cavity or space occupied by a hematoma or in a subdural space on the surface of the brain;~~

the composition being characterized by:

(i) dispersal of the therapeutic amount of the anti-fibrinolytic agent throughout each microparticle, in a core of the microparticle surrounded by a coating, adsorbed into the particles, or a combination thereof; and

~~(ii) its deposition in or on a biodegradable implant at an implant site in a cavity or space within the brain occupied by a hematoma or in a subdural space on the surface of the brain;~~

(ii~~i~~) sustained release of the anti-fibrinolytic agent from the microparticles at the implant site to maintain a high concentration of the anti-fibrinolytic agent locally and lower concentrations in the rest of the body, thus decreasing risk of unwanted side effects.~~;~~

~~(iv) breakdown of the biodegradable carrier over time to effect release of the anti-fibrinolytic agent into the cerebrospinal fluid circulation to achieve tissue targeting of the therapeutic amount of the anti-fibrinolytic agent at a site of bleeding in or on the brain; and~~

~~(v) the therapeutic amount is effective to reduce hematoma expansion or recurrent bleeding, when compared to a nontreated control.~~

17. The pharmaceutical composition according to claim ~~19~~16, wherein the hemorrhagic brain condition is bleeding following traumatic brain injury, chronic subdural hematoma (SDH), intracerebral hematoma (ICH) or bleeding following a craniotomy procedure.

18. The pharmaceutical composition according to claim ~~20~~17, wherein the intracerebral hematoma is a spontaneous intracerebral hematoma (ICH) or a traumatic intracerebral hematoma (ICH).

19. The pharmaceutical composition according to claim ~~20~~17, wherein the craniotomy procedure is performed for treating a brain neospasm.

20. The pharmaceutical composition according to claim ~~20~~17, wherein the wherein the craniotomy procedure is performed for treating a vascular malformation in brain.

21. The pharmaceutical composition according to claim ~~20~~17, wherein the craniotomy procedure is performed for treating a brain aneurysm.

22. The pharmaceutical composition according to claim ~~19~~16, wherein the pharmaceutically acceptable carrier is a controlled-release carrier or a sustained-release carrier.

23. The pharmaceutical composition according to claim ~~26~~22, wherein the sustained-release carrier is capable of releasing the anti-fibrinolytic agent for at least 21 days post-administration.

24. The pharmaceutical composition according to claim ~~26~~22, wherein the sustained-release carrier is capable of releasing the anti-fibrinolytic agent for about 3 to 5 days post-administration.

25. The pharmaceutical composition according to claim ~~26~~22, wherein the sustained-release carrier comprises a nanoparticle, comprises a biodegradable polymer or is a hydrogel.

26. The pharmaceutical composition according to claim ~~30~~25, wherein the biodegradable polymer is a synthetic polymer or a naturally occurring polymer.

27. The pharmaceutical composition according to claim ~~31~~26, wherein the synthetic polymer is selected from the group consisting of a polyester, a polyester polyethylene glycol polymer, a polyamino-derived biopolymer, a polyanhydride, a polyorthoester, a polyphosphazene, a sucrose acetate isobutyrate (SAIB), a photopolymerizable biopolymer, and a combination thereof.

28. The pharmaceutical composition according to claim ~~3~~26, wherein the synthetic polymer is polyglycolic acid (PGA) or a copolymer of polyglycolic acid (PGA) formed with trimethylene carbonate, polylactic acid (PLA), or polycaprolactone.

29. The pharmaceutical composition according to claim ~~3~~26, wherein the naturally occurring polymer is a protein polymer, a naturally occurring polysaccharide or a hyaluronic acid.

30. The pharmaceutical composition according to claim ~~3~~29, wherein the wherein the protein polymer is synthesized form self-assembling protein polymers.

31. The pharmaceutical composition according to claim ~~3~~29, wherein the naturally occurring polymer comprises less than 2.3% of hyaluronic acid.

32. The use according to claim 1, wherein the anti-fibrinolytic agent is selected from the group consisting of ε-aminocaproic acid (AMICAR), tanexamic acid, aprotinin, 4-amionomethylbenzoic acid, fibrin fragment D, and a combination thereof.

33. The use according to claim 1, wherein the anti-fibrinolytic agent is selected from the group consisting of antiplasmin, vitamin K, and a combination thereof.

34. The use according to claim ~~3~~33, wherein the vitamin K is selected from the group consisting of vitamin K_1, vitamin K_2 and vitamin K_3.

35. The pharmaceutical composition according to claim ~~1~~16, wherein the anti-fibrinolytic agent is selected from the group consisting of ε-aminocaproic acid (AMICAR), tanexamic acid, aprotinin, 4-amionomethylbenzoic acid, fibrin fragment D, and a combination thereof.

36. The pharmaceutical composition according to claim ~~1~~16, wherein the anti-fibrinolytic agent is antiplasmin, vitamin K, or a combination thereof.

37. The pharmaceutical composition according to claim ~~4~~36, wherein the vitamin K is selected from the group consisting of vitamin K_1, vitamin K_2, and vitamin K_3.