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

[000122a] According to one aspect, there is provided the use of a pharmaceutical composition in the manufacture of a medicament for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain and for improving patient outcome, the pharmaceutical composition comprising: a pharmaceutically acceptable carrier comprising a biodegradable polymer comprising a matrix; wherein the carrier polymer can be formed to produce a solid structure selected from the group consisting of: nonpareils, pellets, strings, sheets, crystals, an agglomerate, microparticles, and nanoparticles, wherein (a) the solid structure contains a therapeutic amount of at least one anti-fibrinolytic agent selected from the group consisting of aminocaproic acid (AMICAR), tranexamic acid, Factor VII, aprotinin, an antiplasmin, fibrin fragment D, a vitamin K, and 4-aminomethylbenzoic acid; (b) the solid structure is dispersed in the matrix, (c) gradual release of the anti-fibrinolytic agent is gradually released over an extended period of time that results in substantially constant blood levels of the

anti-fibrinolytic agent over the extended time period into a fluid-filled space or cavity selected from a subarachnoid space a subdural cavity of a chronic SDH, or a cavity left after surgical evacuation of a hematoma, tumor or vascular malformation in the brain, and (d) site-specific activity provides high concentrations of the therapeutic agent at the site where therapeutic activity is needed and lower concentrations in the rest of the body, thus decreasing the risk of unwanted systemic side effects such as hypotension, cardiac arrhythmias, edema, rhabdomyolysis, thrombosis, cerebral infarction and myocardial infarction associated with systemic administration of the antifibrinolytic agent.

[000123] According to one ~~aspect~~embodiment, the ~~described invention~~ 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.

[000124] According to another ~~aspect~~embodiment, the ~~described invention~~ 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 pharmaceutical composition in the manufacture of a medicament for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain and for improving patient outcome, the pharmaceutical composition comprising:

a pharmaceutically acceptable carrier comprising a biodegradable polymer comprising a matrix; wherein the carrier polymer can be formed to produce a solid structure selected from the group consisting of: nonpareils, pellets, strings, sheets, crystals, an agglomerate, microparticles, and nanoparticles,

wherein

(a) the solid structure contains a therapeutic amount of at least one anti-fibrinolytic agent selected from the group consisting of aminocaproic acid (AMICAR), tranexamic acid, Factor VII, aprotinin, an antiplasmin, fibrin fragment D, a vitamin K, and 4-aminomethylbenzoic acid;

(b) the solid structure is dispersed in the matrix,

(c) gradual release of the anti-fibrinolytic agent is gradually released over an extended period of time that results in substantially constant blood levels of the anti-fibrinolytic agent over the extended time period into a fluid-filled space or cavity selected from a subarachnoid space a subdural cavity of a chronic SDH, or a cavity left after surgical evacuation of a hematoma, tumor or vascular malformation in the brain, and

(d) site-specific activity provides high concentrations of the therapeutic agent at the site where therapeutic activity is needed and lower concentrations in the rest of the body, thus decreasing the risk of unwanted systemic side effects such as hypotension, cardiac arrhythmias, edema, rhabdomyolysis, thrombosis, cerebral infarction and myocardial infarction associated with systemic administration of the antifibrinolytic agent.

2. The use according to claim 1, wherein the hemorrhagic condition

a. results from traumatic brain injury (TBI); or

b. is rebleeding following a surgical evacuation of the hematoma; or

c. is a chronic subdural hematoma (SDH); or

d. is an intracerebral hematoma (ICH); or

e. is rebleeding following a craniotomy procedure.

3. The use according to claim 2, wherein the craniotomy procedure is performed

(a) for treating a brain cancer; or

(b) for treating a vascular malformation in brain; or

(c) for treating a brain aneurysm.

4. The use according to claim 1, wherein the cavity or space is an implant site.

5. The use according to claim 1, wherein the composition releases the anti-fibrinolytic agent for at least 21 days post-administration.

6. The use according to claim 1, wherein the composition releases the anti-fibrinolytic agent for about 3 to 5 days post-administration.

7. The use according to claim 1, wherein the carrier comprises

(a) a biodegradable polymer; or

(b) a synthetic polymer; or

(c) a naturally occurring polymer; or

(d) a nonpolymeric material;

8. The use according to claim 7, wherein the synthetic polymer

(a) 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, a polyglycolic acid (PGA), a polylactic acid (PLA); a poly (lactic-co-glycolide) (PLGA), a polycaprolactone; or

(b) a copolymer containing polyglycolic acid formed with trimethylene carbonate, polylactic acid (PLA), or polycaprolactone; or

(c) a poly d, L (lactic co-caprolactone) copolymer; or

(d) a thermoreversible gel.

9. The use according to claim 8, wherein

(a) the thermoreversible gel exhibits differing phases at room temperature and at physiologic temperature and pH; or

(b) at body temperature, the thermoreversible gel comprises a semisolid viscous gel; or

(c) the thermoreversible gel is a hydrogel.

10. The use according to claim 1, wherein the carrier polymer is formed into an implant.

11. The use according to claim 1, wherein the carrier polymer is malleable such that it can be delivered and manipulated in an implant site to adhere and conform to contours of walls, spaces or other voids.

12. The use according to claim 1, wherein the solid structure contains microparticles of about 1 μm to about 100 μm in diameter.

13. The use according to claim 1, wherein the carrier comprises a multilayered multiparticulate system.

CLAIMS

What is claimed is:

1. 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 at least one 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.

2. The method according to claim 1, wherein the hemorrhagic condition results from traumatic brain injury (TBI).

3. The method according to claim 1, wherein the hemorrhagic condition is rebleeding following a surgical evacuation of the hematoma.

4. The method according to claim 1, wherein the hemorrhagic condition is a chronic subdural hematoma (SDH).

5. The method according to claim 1, wherein the hemorrhagic condition is an intracerebral hematoma (ICH).

6. The method according to claim 5, wherein the intracerebral hematoma is a spontaneous intracerebral hematoma (ICH).

7. The method according to claim 5, wherein the intracerebral hematoma is a traumatic intracerebral hematoma (ICH).

8. The method according to claim 1, wherein the hemorrhagic condition is rebleeding following a craniotomy procedure.

9. The method according to claim 8, wherein the craniotomy procedure is performed for treating a brain cancer.

10. The method according to claim 8, wherein the craniotomy procedure is performed for treating a vascular malformation in brain.

11. The method according to claim 8, wherein the craniotomy procedure is performed for treating a brain aneurysm.

12. The method according to claim 1, wherein the administration is an implantation.

13. The method according to claim 1, wherein the at least one anti-fibrinolytic agent is ε-aminocaproic acid (AMICAR).

14. The method according to claim 1, wherein the at least one anti-fibrinolytic agent is Factor VII.

15. The method according to claim 14, wherein the at least one Factor VII is a recombinant Factor VII.

16. The method according to claim 1, wherein the at least one anti-fibrinolytic agent is tranexamic acid.

17. The method according to claim 1, wherein the at least one anti-fibrinolytic agent is aprotinin.

18. The method according to claim 1, wherein the pharmaceutically acceptable carrier is a controlled-release carrier.

19. The method according to claim 1, wherein the pharmaceutically acceptable carrier is a sustained-release carrier.

20. The method according to claim 19, wherein the at least one anti-fibrinolytic agent is embedded in the sustained-release carrier.

21. The method according to claim 19, wherein the at least oneanti-fibrinolytic agent is coated on the sustained-release carrier.

22. The method according to claim 19, wherein the sustained-release carrier releases the at least one anti-fibrinolytic agent for at least 21 days post-administration.

23. The method according to claim 19, wherein the sustained-release carrier releases the at least one anti-fibrinolytic agent for about 3 to 5 days post-administration.

24. The method according to claim 19, wherein the sustained-release carrier is a microparticle.

25. The method according to claim 19, wherein the sustained-release carrier is a nanoparticle.

26. The method according to claim 19, wherein the sustained-release carrier comprises a biodegradable polymer.

27. The method according to claim 26, wherein the biodegradable polymer is a synthetic polymer.

28. The method according to claim 26, wherein the biodegradable polymer is a naturally occurring polymer.

29. The method according to claim 27, 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.

30. The method according to claim 27, wherein the synthetic polymer is polyglyolic acid (PGA).

31. The method according to claim 27, wherein the synthetic polymer is a copolymer of

polyglycolic acid formed with trimethylene carbonate, polylacitic acid (PLA), or polycaprolactone.

32. The method according to claim 19, wherein the sustained-release carrier is a hydrogel.

33. The method according to claim 28, wherein the naturally occurring biopolymer is a protein polymer.

34. The method according to claim 28, wherein the naturally occurring polymer comprises hyaluronic acid.

35. The method according to claim 34, wherein the naturally occurring polymer comprises less than 2.3 % of hyaluronic acid.

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

37. The method according to claim 1, wherein the pharmaceutical composition exhibits a localized pharmacological effect.

38. The method according to claim 1, wherein the pharmaceutical composition exhibits its pharmacological effect throughout the brain.

39. 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 at least one anti-fibrinolytic agent; and

(b) a pharmaceutically acceptable carrier, wherein the pharaceutically acceptable carrier is a sustained-release carrier.

40. The pharmaceutical composition according to claim 39, wherein the hemorrhagic brain

condition is rebleeding following traumatic brain injury.

41. The pharmaceutical composition according to claim 39, wherein the hemorrhagic brain condition is a chronic subdural hematoma (SDH).

42. The pharmaceutical composition according to claim 39, wherein the hemorrhagic brain condition is an intracerebral hematoma (ICH).

43. The pharmaceutical composition according to claim 42, wherein the intracerebral hematoma is a spontaneous intracerebral hematoma (ICH).

44. The pharmaceutical composition according to claim 42, wherein the intracerebral hematoma is a traumatic intracerebral hematoma (ICH).

45. The pharmaceutical composition according to claim 39, wherein the hemorrhagic brain condition is rebleeding following a craniotomy procedure.

46. The pharmaceutical composition according to claim 45, wherein the craniotomy procedure is performed for treating a brain cancer.

47. The pharmaceutical composition according to claim 45, wherein the craniotomy procedure is performed for treating a vascular malformation in brain.

48. The composition according to claim 45, wherein the craniotomy procedure is performed for treating a brain aneurysm.

49. The pharmaceutical composition according to claim 39, wherein the at least one anti-fibrinolytic agent is ε-aminocaproic acid (AMICAR).

50. The pharmaceutical composition according to claim 39, wherein the at least one anti-fibrinolytic agent is Factor VII.

51. The pharmaceutical composition according to claim 50, wherein the Factor VII is a

recombinant Factor VII.

52. The pharmaceutical composition according to claim 39, wherein the at least one anti-fibrinolytic agent is tranexamic acid.

53. The pharmaceutical composition according to claim 39, wherein the at least one anti-fibrinolytic agent is aprotinin.

54. The pharmaceutical composition according to claim 39, wherein the pharmaceutically acceptable carrier is a controlled-release carrier.

55. The pharmaceutical composition according to claim 39, wherien the pharmaceutically acceptable carrier is a sustained-release carrier.

56. The pharmaceutical composition according to claim 55, wherein the at least one anti-fibrinolytic agent is embedded in the sustained-release carrier.

57. The pharmaceutical composition according to claim 55, wherein the at least one anti-fibrinolytic agent is coated on the sustained-release carrier.

58. The pharmaceutical composition according to claim 55, wherein the sustained-release carrier releases the anti-fibrinolytic agent for at least 21 days post-administration.

59. The pharmaceutical composition according to claim 55, wherein the sustained-release carrier releases the anti-fibrinolytic agent for about 3 to 5 days post-administration.

60. The pharmaceutical composition according to claim 55, wherein the sustained-release carrier comprises a microparticle.

61. The pharmaceutical composition according to claim 55, wherein the sustaine-release carrier comprises a nanoparticle.

62. The pharmaceutical composition according to claim 55, wherein the sustained-release carrier

comprises a biodegradable polymer.

63. The pharmaceutical composition according to claim 62, wherein the biodegradable polymer is a synthetic polymer.

64. The pharmaceutical composition according to claim 62, wherein the biodegradable polymer is a naturally occurring polymer.

65. The pharmaceutical composition according to claim 63, 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.

66. The pharmaceutical composition according to claim 63, wherein the synthetic polymer is polyglyolic acid (PGA).

67. The pharmaceutical composition according to claim 63, wherein the synthetic polymer is a copolymer of polyglycolic acid formed with trimethylene carbonate, polylacitic acid (PLA), or polycaprolactone.

68. The pharmaceutical composition according to claim 55, wherein the sustained-release carrier is a hydrogel.

69. The pharmaceutical composition according to claim 64, wherein the naturally occurring polymer is a protein polymer.

70. The pharmaceutical composition according to claim 69, wherein the protein polymer is synthesized from self-assembling protein polymers

71. The pharmaceutical composition according to claim 64, wherein the naturally occurring polymer is a naturally occurring polysaccharide.

72. The pharmaceutical composition according to claim 64, wherein the naturally occurring polymer comprises a hyaluronic acid.

73. The pharmaceutical composition according to claim 72, wherein the naturally occurring polymer comprises less than 2.3 % of hyaluronic acid.