

What is claimed is:

1. A method of treating a population of subjects having or at risk of ischemia comprising administering to the subjects an active agent that inhibits PSD-95, cleavable by plasmin, and reperfusion, wherein the population of subjects includes:

subjects administered the active agent that inhibits PSD-95 and mechanical reperfusion or a vasodilator agent or a hypertensive agent to effect reperfusion; and/or

subjects administered the active agent that inhibits PSD-95 and a thrombolytic agent to effect reperfusion, wherein the active agent that inhibits PSD-95 is administered at least 10 minutes before the thrombolytic agent,

and the population of subjects lacks:

subjects in which a thrombolytic agent is administered less than 3 hours before or less than 10 minutes after administering the active agent that inhibits PSD-95.

2. The method of claim 1, wherein the subjects have ischemic stroke.

3. The method of claim 1 or 2, in which the population lacks subjects in which the thrombolytic agent is administered less than four hours before the active agent that inhibits PSD-95 or less than 10 minutes after the active agent that inhibits PSD-95.

4. The method of claim 1 or 2, in which the population lacks subjects in which the thrombolytic agent is administered less than eight hours before the active agent that inhibits PSD-95 and less than 10 minutes after administering the active agent that inhibits PSD-95.

5. The method of claim 1 or 2, in which the population lacks subjects in which the thrombolytic agent is administered before the active agent that inhibits PSD-95 or less than ten minutes after administering the active agent that inhibits PSD-95.

6. The method of claim 1 or 2, in which the population lacks subjects in which the thrombolytic agent is administered before the active agent that inhibits PSD-95 or less than 20 minutes after administering the active agent that inhibits PSD-95.

7. The method of claim 1 or 2, in which the population lacks subjects in which the thrombolytic agent is administered before the active agent that inhibits PSD-95 or less than 30 minutes after administering the active agent that inhibits PSD-95.

8. The method of claim 1 or 2, in which the population lacks subjects in which the thrombolytic agent is administered before the active agent that inhibits PSD-95 or less than 60 minutes after administering the active agent that inhibits PSD-95.

9. The method of any preceding claim, wherein the population of subjects includes subjects administered the active agent that inhibits PSD-95 and mechanical reperfusion without receiving a thrombolytic agent.

10. The method of claim 1 or 2, wherein the population of treated subjects consists of:

(a) subjects administered the active agent that inhibits PSD-95 and mechanical reperfusion, a vasodilator agent or a hypertensive agent without a thrombolytic agent; and

(b) subjects administered the active agent that inhibits PSD-95 and a thrombolytic agent, wherein the thrombolytic agent is administered at least 10, 20, 30, 40, 50, 60, or 120 minutes after the active agent that inhibits PSD-95.

11. The method of claim 10, wherein at least some of the subjects according to item (b) also are administered mechanical reperfusion.

12. The method of claim 1 or 2, wherein the population includes subjects in which the thrombolytic agent is administered more than 3 or 4.5 hours after onset of stroke when the subjects were determined to be eligible for treatment with the thrombolytic agent less than 3 hours after onset of stroke.

13. The method of any preceding claim, wherein the population includes subjects administered the active agent that inhibits PSD-95 intranasally or intrathecally.

14. The method of any preceding claim, wherein the population includes at least 100 subjects.

15. The method of any preceding claim, wherein the population includes subjects in which the active agent that inhibits PSD-95 is administered over a ten minute period and the thrombolytic agent is administered at least 20 minutes from the start of administering the active agent.

16. The method of any preceding claim, wherein the active agent is a peptide of all L-amino acids.

17. The method of any preceding claim, wherein the active agent is nerinetide.

18. A method of treating a population of subjects receiving endovascular thrombectomy for ischemic stroke comprising:

administering both an active agent that inhibits PSD-95, cleavable by plasmin, and a thrombolytic agent to some of the subjects, wherein the active agent that inhibits PSD-95 is administered at least 10, 20, 30, 40, 50, 60 or 120 minutes before the thrombolytic agent, and

administering the active agent that inhibits PSD-95 or the thrombolytic agent but not both to the other subjects of the population.

19. The method of claim 18, wherein the subjects receiving the active agent that inhibits PSD-95 and the thrombolytic agent do so before the subjects receive endovascular thrombectomy.

20. The method of claim 18 or 19, wherein the subjects receiving the active agent that inhibits PSD-95 or the thrombolytic agent but not both do before the subjects receive endovascular thrombectomy.

21. The method of any one of claims 18-20, wherein in the subjects receiving both the active agent that inhibits PSD-95 and thrombolytic agent, the active agent that inhibits PSD-95 is administered at least 10 minutes before the thrombolytic agent, and the active agent that inhibits PSD-95 or the thrombolytic agent but not both is administered to the other subjects.

22. A method of treating a population of subjects having or at risk of ischemia, comprising administering to the subjects an active agent that inhibits PSD-95, and a thrombolytic agent, wherein the population of subjects includes:

subjects administered a first active agent that inhibits PSD-95 cleavable by plasmin and a thrombolytic agent, wherein the first active agent that inhibits PSD-95 is administered at an interval selected from at least 10, 20, 30, 40, 50, 60 or 120 minutes before the thrombolytic agent; and

subjects administered a second active agent that inhibits PSD-95 resistant to cleavage by plasmin and a thrombolytic agent, wherein the thrombolytic agent is administered before or within the interval after the active agent that inhibits PSD-95.

23. A method of treating a subject suspected of having ischemic stroke, comprising:

determining eligibility of the subject for treatment with a thrombolytic agent;

administering an active agent that inhibits PSD-95, cleavable by plasmin; and

at least 10, 20, 30, 40, 50, 60 or 120 minutes thereafter administering the thrombolytic agent.

24. The method of claim 23, wherein the active agent that inhibits PSD-95 is administered over a ten minute period and the thrombolytic agent is administered at least 20 minutes from the start of administering the active agent.

25. The method of claim 23 or 24, wherein the active agent is a peptide of all L-amino acids.

26. The method of claim 25, wherein the active agent is nerinetide.

27. The method of any one of claims 23-26, wherein imaging determines presence of ischemic stroke and absence of cerebral hemorrhage.

28. The method of any one of claims 23-27, wherein eligibility is determined less than 3 hours after onset of ischemic stroke and the thrombolytic agent is administered more than 3 hours after onset of ischemic stroke.

29. The method of any one of claims 23-27, wherein eligibility is determined less than 4.5 hours after onset of ischemic stroke and the thrombolytic agent is administered more than 4.5 hours after onset of ischemic stroke.

30. The method of any one of claims 23-27, wherein eligibility is determined less than 3 hours after onset of ischemic stroke and the thrombolytic agent is administered more than 4.5 hours after onset of ischemic stroke.

31. The method of any preceding claim, wherein the active agent that inhibits PSD-95 comprises a peptide comprising [E/D/N/Q]-[S/T]-[D/E/Q/N]-[V/L] (SEQ ID NO:1) at the C-terminus or X₁-[T/S]-X₂V (SEQ ID NO:2) at the C-terminus, wherein [T/S] are alternative amino acids, X₁ is selected from among E, Q, and A, or an analogue thereof, X₂ is selected from among A, Q, D, N, N-Me-A, N-Me-Q, N-Me-D, and N-Me-N or an analog thereof, and an internalized peptide linked to the N-terminus of the peptide.

32. The method of claim 31, wherein the active agent that inhibits PSD-95 is nerinetide.

33. The method of any preceding claim, wherein the thrombolytic agent is tPA.

34. A method of treating a subject who has had a stroke with an active agent that inhibits PSD-95, cleavable by plasmin, whereby the active agent is:

administered at least 10 minutes before a thrombolytic agent, or

administered at least 2, 3, 4 or more hours after administration of a thrombolytic agent,
or

administered without a thrombolytic agent.

35. The method of claim 34, wherein the active agent that inhibits PSD-95 is administered over a ten minute period and the thrombolytic agent is administered at least 20 minutes from the start of administering the active agent.

36. The method of claim 34, wherein the active agent is a peptide of all L-amino acids.

37. The method of claim 35, wherein the active agent is nerinetide.

38. A method of minimizing degradation of an active agent that inhibits PSD-95, cleavable by plasmin, by a thrombolytic agent, comprising:

administering the active agent that inhibits PSD-95 at least 10 minutes before the thrombolytic agent, or

administering the active agent that inhibits PSD-95 at least 2, 3, 4 or more hours after administration of the thrombolytic agent, or

administering the active agent that inhibits PSD-95 without the thrombolytic agent, or

administering the active agent that inhibits PSD-95 by intranasal or intrathecal administration.

39. The method of claim 38, wherein the active agent that inhibits PSD-95 is administered over a ten minute period and the thrombolytic agent is administered at least 20 minutes from the start of administering the active agent.

40. The method of claim 38, wherein the active agent is a peptide of all L-amino acids.

41. The method of claim 38, wherein the active agent is nerinetide.

42. A method of treating ischemic stroke, comprising administering to a subject having ischemic stroke an active agent that inhibits PSD-95, cleavable by plasmin, and 20-40 minutes after initiating administration of the active agent administering a thrombolytic agent.

43. The method of claim 42, wherein the active agent that inhibits PSD-95 is inhibited over a period of ten minutes and the thrombolytic agent is administered 20-30 minutes after initiating administration of the active agent.