

biological or pharmaceutical therapies have been shown to significantly reverse the damage and improve the patients' motor functions. While a variety of cellular therapies have been proposed and studied, clinical trials for these therapies have so far been limited with the patients in such trials only showing modest improvements [4-6]. Moreover, no investigation has been made as to whether certain therapies are more effective at treating particular patient sub-populations such as stroke patients with differing ischemic core sizes or volumes.

[0006] Therefore, there is a need for a safe and effective therapy for the treatment of chronic stroke patients or those patients suffering from chronic stroke-induced motor deficits.

SUMMARY

[0007] Disclosed are methods of treating a subject following a small-volume ischemic stroke suffered by the subject and methods of treating a subject with a stroke-induced motor deficit. Disclosed also is a composition for treating small-volume ischemic stroke.

[0008] In one aspect, a method of treating a subject following a small-volume ischemic stroke comprises administering, to a brain region surrounding a small-volume ischemic core of the subject, a therapeutically effective amount of cells. The cells can be descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

[0008a] In another aspect, the present disclosure refers to the use of cells in the manufacture of a medicament for treating a subject following a small-volume ischemic stroke suffered by the subject, wherein the cells are to be administered to a brain region surrounding a small-volume ischemic core of the subject, and wherein the cells are descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

[0009] The cells can be made by a method comprising providing a culture of the mesenchymal stem cells, contacting the culture of mesenchymal stem cells with a polynucleotide encoding the NICD, selecting cells that comprise the polynucleotide, and further culturing the selected cells in the absence of selection for the polynucleotide. The mesenchymal stem cells can be human bone marrow-derived cells. Moreover, the polynucleotide encoding the NICD does not encode a full-length Notch protein.

[0010] The small-volume ischemic core can be an ischemic core having an ischemic core volume of less than 50 cubic centimeters (cc). For example, the small-volume ischemic

core can be an ischemic core having an ischemic core volume of between about 2 cc and 50 cc.

[0011] In some instances, the treatment is especially effective when the small-volume ischemic core is located in a region of the brain of the subject other than a parietal region such as a cortical frontal region, a cortical temporal region, a subcortical white matter, or a subcortical grey matter of the brain of the subject.

[0018] The therapeutically effective amount of cells can also be approximately 5.0 million cells (or 5.0 million cells $\pm$ 0.1 million cells). The step of administering the approximately 5.0 million cells can comprise injecting a cell suspension comprising the cells at five deposit sites along a first deposit track or needle track, five deposit sites along a second deposit track or needle track, and five deposit sites along a third deposit track or needle track. Approximately 20- μ L of the cell suspension can be injected at each deposit site. The cell suspension can have a cell concentration of approximately 17.0×10^6 cells/mL.

[0019] The method can further comprise subjecting a formulated dose of the cells to post-release testing prior to administering the cells to the subject.

[0020] The method can further comprise determining a degree of disability of the subject by determining an mRS score of the subject and administering the therapeutically effective amount of cells only when the mRS score of the subject is between 2 and 4.

[0021] Also disclosed is a method of treating a subject with a stroke-induced motor deficit. The method can comprise determining a volume of an ischemic core of the subject and administering, to a brain region surrounding the ischemic core of the subject, a therapeutically effective amount of cells only when the volume of the ischemic core is determined to be less than 50 cubic centimeters (cc). For example, the method can comprise administering, to the brain region surrounding the ischemic core of the subject, the therapeutically effective amount of cells only when the volume of the ischemic core is between about 2 cc and 50 cc.

[0021a] In another aspect, the present disclosure refers to the use of cells in the manufacture of a medicament for treating a subject with a stroke-induced motor deficit, wherein a volume of an ischemic core of the subject is determined; and wherein the cells are to be administered to a brain region surrounding the ischemic core of the subject, only when the volume of the ischemic core is determined to be less than 50 cubic centimeters (cc), wherein the cells are descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

[0022] The stroke-induced motor deficit can be the result of an ischemic stroke suffered by the subject. In some instances, the ischemic stroke occurred more than six months prior to administering the cells. For example, the small-volume ischemic stroke occurred between six months and 90 months prior to administering the cells.

[0023] In certain instances, the method comprises administering, to the brain region surrounding the ischemic core of the subject, the therapeutically effective amount of cells

only when the ischemic stroke occurred more than six months prior (e.g., between six months and 90 months prior).

[0024] The cells can be descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

[0025] The cells can be made by a method comprising providing a culture of the mesenchymal stem cells, contacting the culture of mesenchymal stem cells with a polynucleotide encoding the NICD, selecting cells that comprise the polynucleotide, and further culturing the selected cells in the absence of selection for the polynucleotide. The

the composition can be an approximately 0.3 mL cell suspension with a cell concentration of approximately 8.5×10^6 cells/mL.

[0039] The therapeutically effective amount of cells can also be approximately 5.0 million cells. When the therapeutically effective amount of cells is approximately 2.5 million cells, the composition can be an approximately 0.3 mL cell suspension with a cell concentration of approximately 17.0×10^6 cells/mL.

[0040] In some instances, the therapeutically effective amount of cells can be between approximately 2.0 million cells and approximately 5.0 million cells.

[0041] Also disclosed is the use of cells in the manufacture of a medicament for treating a subject following a small-volume ischemic stroke suffered by the subject, comprising: administering to a brain region surrounding a small-volume ischemic core of the subject a therapeutically effective amount of cells, wherein the cells are descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

[0042] Further disclosed is the use of cells in the manufacture of a medicament for treating a subject with a stroke-induced motor deficit, comprising: determining a volume of an ischemic core of the subject; and administering, to a brain region surrounding the ischemic core of the subject, a therapeutically effective amount of cells only when the volume of the ischemic core is determined to be less than 50 cubic centimeters (cc), wherein the cells are descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

[0043] Also disclosed are cells descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD) for use in a method of treating a subject following a small-volume ischemic stroke suffered by the subject, wherein the method comprises administering, to a brain region surrounding a small-volume ischemic core of the subject, a therapeutically effective amount of the cells.

[0043a] In yet another aspect, the present disclosure refers to the cells descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD) for use in therapy.

[0044] Further disclosed are cells descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD) for use in a method of treating a subject with a stroke-induced motor deficit, wherein the method comprises: determining a volume of an ischemic core of the subject; and administering, to a brain region surrounding the ischemic core of the subject, a therapeutically effective

amount of cells only when the volume of the ischemic core is determined to be less than 50 cubic centimeters (cc), wherein the cells are descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

CLAIMS

1. Use of cells in the manufacture of a medicament for treating a subject following a small-volume ischemic stroke suffered by the subject, wherein the cells are to be administered
to a brain region surrounding a small-volume ischemic core of the subject, and
wherein the cells are descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).
2. The use of claim 1, wherein the small-volume ischemic core is an ischemic core having an ischemic core volume of less than 50 cubic centimeters (cc).
3. The use of claim 1, wherein the small-volume ischemic core is an ischemic core having an ischemic core volume of between about 2 cc and 50 cc.
4. The use of claim 1, wherein the use further comprises that at least part of a cell suspension comprising the cells is to be administered at one or more deposit sites at an outer periphery of a chronic penumbra surrounding the small-volume ischemic core.
5. The use of claim 1, wherein the use further comprises that at least part of a cell suspension comprising the cells is to be administered at one or more deposit sites proximal to or within a chronic penumbra surrounding the small-volume ischemic core.
6. The use of claim 1, wherein the use further comprises that at least part of a cell suspension comprising the cells is to be administered at one or more deposit sites distal to a chronic penumbra surrounding the small-volume ischemic core.
7. The use of claim 1, wherein the use further comprises that the cells is to be administered stereotactically via a single burr-hole craniostomy.
8. The use of claim 1, wherein the small-volume ischemic core is located in a region of the brain of the subject other than a parietal region.
9. The use of claim 1, wherein at least part of the small-volume ischemic core is located in at least one of a cortical frontal region, a cortical temporal region, a subcortical white matter, and a subcortical grey matter of the brain of the subject.
10. The use of claim 1, wherein the cells are made by a method comprising:

providing a culture of the mesenchymal stem cells;
contacting the culture of mesenchymal stem cells with the polynucleotide encoding the NICD, wherein the polynucleotide does not encode a full-length Notch protein,
selecting cells that comprise the polynucleotide; and
further culturing the selected cells in the absence of selection for the polynucleotide.

11. The use of claim 1, wherein the amount of cells is approximately 2.5 million cells.
12. The use of claim 11, wherein the approximately 2.5 million cells are to be administered in the form of a cell suspension comprising the cells at five deposit sites along a first deposit track, five deposit sites along a second deposit track, and five deposit sites along a third deposit track, wherein approximately 20- μ L of the cell suspension is to be administered at each deposit site and wherein the cell suspension has a cell concentration of approximately $8.5 * 10^6$ cells/mL.
13. The use of claim 1, wherein the amount of cells is approximately 5.0 million cells.
14. The use of claim 13, wherein the approximately 5.0 million cells are to be administered in the form of a cell suspension comprising the cells at five deposit sites along a first deposit track, five deposit sites along a second deposit track, and five deposit sites along a third deposit track, wherein approximately 20- μ L of the cell suspension is to be administered at each deposit site and wherein the cell suspension has a cell concentration of approximately $17.0 * 10^6$ cells/mL.
15. The use of claim 1, wherein the small-volume ischemic stroke occurred more than six months prior to administration of the cells.
16. The use of claim 1, wherein the small-volume ischemic stroke occurred between six months and 90 months prior to administration of the cells.
17. The use of claim 1, further comprising evaluating a degree of disability of the subject by determining an mRS score of the subject, wherein the cells are to be administered only when the mRS score of the subject is between 2 and 4.
18. The use of claim 1, wherein the mesenchymal stem cells are human bone marrow-derived cells.

19. The use of claim 1, wherein the cells are suspended in a sterile isotonic crystalloid solution.
20. The use of claim 1, further comprising a formulated dose of the cells to post-release testing prior to administration of the cells to the subject.
21. Use of cells in the manufacture of a medicament for treating a subject with a stroke-induced motor deficit,
wherein a volume of an ischemic core of the subject is determined; and
wherein the cells are to be administered to a brain region surrounding the ischemic core of the subject, only when the volume of the ischemic core is determined to be less than 50 cubic centimeters (cc), wherein the cells are descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).
22. The use of claim 21, further comprising that the cells are to be administered to the brain region surrounding the ischemic core of the subject only when the volume of the ischemic core is between about 2 cc and 50 cc.
23. The use of claim 21, wherein at least part of a cell suspension comprising the cells is to be administered at one or more deposit sites at an outer periphery of a chronic penumbra surrounding the ischemic core.
24. The use of claim 21, wherein at least part of a cell suspension comprising the cells is to be administered at one or more deposit sites proximal to or within a chronic penumbra surrounding the ischemic core.
25. The use of claim 21, wherein at least part of a cell suspension comprising the cells is to be administered at one or more deposit sites distal to a chronic penumbra surrounding the ischemic core.
26. The use of claim 21, wherein the cells are to be administered stereotactically via a single burr-hole craniostomy.
27. The use of claim 21, wherein the ischemic core is located in a region of the brain of the subject other than a parietal region.
28. The use of claim 21, wherein at least part of the ischemic core is located in at least one of a cortical frontal region, a cortical temporal region, a subcortical white matter, and a subcortical grey matter of the subject.

29. The use of claim 21, wherein the cells are made by a method comprising:
providing a culture of the mesenchymal stem cells;
contacting the culture of mesenchymal stem cells with the polynucleotide encoding
the NICD, wherein the polynucleotide does not encode a full-length Notch
protein,
selecting cells that comprise the polynucleotide; and
further culturing the selected cells in the absence of selection for the
polynucleotide.
30. The use of claim 21, wherein the amount of cells is approximately 2.5 million cells.
31. The use of claim 30, wherein the approximately 2.5 million cells are to be
administered in the form of a cell suspension comprising the cells at five deposit
sites along a first deposit track, five deposit sites along a second deposit track, and
five deposit sites along a third deposit track, wherein approximately 20- μ L of the
cell suspension is to be administered at each deposit site and wherein the cell
suspension has a cell concentration of approximately $8.5 * 10^6$ cells/mL.
32. The use of claim 31, wherein the amount of cells is approximately 5.0 million cells.
33. The use of claim 32, wherein the approximately 5.0 million cells are to be
administered in the form of a cell suspension comprising the cells at five deposit
sites along a first deposit track, five deposit sites along a second deposit track, and
five deposit sites along a third deposit track, wherein approximately 20- μ L of the
cell suspension is to be administered at each deposit site and wherein the cell
suspension has a cell concentration of approximately $17.0 * 10^6$ cells/mL.
34. The use of claim 21, wherein the stroke-induced motor deficit is a result of an
ischemic stroke suffered by the subject.
35. The use of claim 34, wherein the ischemic stroke occurred more than six months
prior to administration of the cells.
36. The use of claim 35, wherein the ischemic stroke occurred between six months and
90 months prior to administration of the cells.
37. The use of claim 21, further comprising evaluating a degree of disability of the
subject by determining an mRS score of the subject, wherein the cells are to be
administered only when the mRS score of the subject is between 2 and 4.

- 38. The use of claim 21, wherein the mesenchymal stem cells are human bone marrow-derived cells.
- 39. The use of claim 21, wherein the cells are suspended in a sterile isotonic crystalloid solution.
- 40. The use of claim 21, further comprising a formulated dose of the cells to post-release testing prior to administration of the cells to the subject.
- 41. Cells descended from mesenchymal stem cells transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD) for use in therapy.