METHODS AND COMPOSITIONS FOR INCREASING NEURONAL ACTIVITY AND SYNAPTIC PLASTICITY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 63/626,785 filed on January 30, 2024, the content of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure relates generally to the field of cell therapies and, more specifically, to methods and compositions for increasing neuronal activity and synaptic plasticity in a subject in need thereof.

BACKGROUND

[0003] Over the past several decades, mesenchymal stem cell-based (MSC-based) therapies have emerged as a new strategy for treating neurological disorders and injuries such as stroke, traumatic brain injury (TBI), amyotrophic lateral sclerosis (ALS), and spinal cord injury (SCI) [1, 2]. These neurological disorders or injuries often involve the impairment of certain cognitive functions due to disruptions in how neurons communicate. In order to re-establish neuronal communication and promote functional recovery, there must be an increase in neuronal activity and synaptic plasticity that allows for the repair of certain neural pathways or the creation of new neural pathways.

[0004] MSCs have low immunogenicity and can be isolated from different adult and birth tissues and cultured at great expansion capacity [3]. Vandefitemcel, also known as SB623 cells, are a type of human bone marrow-derived MSC cells. Recent studies have shown that intracerebral implantation of vandefitemcel or SB623 cells was safe and could improve a patient's motor functions [4, 5]. However, little is known about the effect of MSCs on the electrophysiology of neurons (and, especially, human neurons) after their implantation or transplantation.

[0005] While neurons for research can come from a variety of sources, one renewable source of human neurons that do not require invasive biopsies of human central nervous system (CNS) tissue is human induced pluripotent stem cells (iPSCs). Human iPSCs can be

differentiated into a range of somatic cells including types of neurons such as glutamatergic and GABAergic neurons [6].

[0006] Moreover, multielectrode arrays (MEAs) have been used in the past to measure the electrophysiology of neurons [7]. MEAs typically include a special multi-well culture plate with small electrodes embedded at the bottom of each well. Extracellular spontaneous action potentials are recorded from neuronal cells cultured directly on top of the recording electrodes.

[0007] Therefore, there is a need for safe and effective cell-based therapies for increasing neuronal activity and synaptic plasticity. Such therapies should be capable of being tested on human iPSC-derived neurons using state-of-the-art MEA measurement systems.

SUMMARY

[0008] In one aspect, disclosed herein is a use of vandefitemcel in the manufacture of a medicament for inducing tonic release of glutamate in a subject in need thereof, wherein the vandefitemcel is to be administered to a region of the brain of the subject, and wherein the vandefitemcel are cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

[0008a] In another aspect, disclosed herein is a use of vandefitemcel in the manufacture of a medicament for increasing synapse formation in neurons in a subject in need thereof, wherein vandefitemcel is to be administered to a region of the brain of the subject comprising the neurons, and wherein the vandefitemcel are cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

[0008b] In another aspect, disclosed herein is a use of vandefitemcel in the manufacture of a medicament for inducing release of glutamate in a subject in need thereof, wherein: functional magnetic resonance imaging (fMRI) scans of regions of the brain of the subject are to be obtained; a region of the brain showing neuronal activity is to be selected based on the fMRI scans; and vandefitemcel is to be administered to the selected region of the brain, wherein the vandefitemcel are cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD), and wherein the vandefitemcel release glutamate after administration via intracerebral implantation.

[0008c] In another aspect, disclosed herein is a use of vandefitemcel in the manufacture of a medicament for increasing synapse formation in neurons in a subject in need thereof, wherein: functional magnetic resonance imaging (fMRI) scans of regions of the brain of the subject are to be obtained; a region of the brain showing neuronal activity is to be selected based on the fMRI scans; and vandefitemcel is to be administered to the selected region of the brain comprising the neurons, wherein the vandefitemcel are cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD), and wherein the vandefitemcel release glutamate to the neurons after administration via intracerebral implantation.

[0008d] In some examples, disclosed is a method for inducing, triggering, or causing tonic release of glutamate in a subject. The method comprises administering vandefitemcel to a region of the brain of the subject. The vandefitemcel can be cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

[0009] In some examples, administering vandefitemcel to a region of the brain of the subject further comprises administering the vandefitemcel by intracerebral implantation.

[0010] In some examples, the vandefitemcel can tonically release glutamate to neurons of the brain when implanted via intracerebral implantation.

[0011] In some examples, administering vandefitemcel to a region of the brain of the subject further comprises injecting the vandefitemcel at multiple sites within the region of the brain.

[0012] In some examples, administering vandefitemcel to a region of the brain of the subject further comprises administering the vandefitemcel stereotactically via a burr hole in the skull of the subject.

[0013] In some examples, the region of the brain is the forebrain of the subject including at least one of the cerebrum, the thalamus, and the hypothalamus of the subject.

[0014] In some examples, the region of the brain can be a site of injury or disease.

[0015] In some examples, the region of the brain can be the hippocampus of the subject.

[0016] In some examples, administering vandefitemcel to a region of the brain of the subject further comprises administering the vandefitemcel by parenteral administration.

[0017] In some examples, the vandefitemcel can be suspended in a sterile isotonic crystalloid solution.

[0018] In some examples, administering vandefitemcel to a region of the brain of the subject further comprises administering between about 1.0 million cells and 10.0 million cells.

[0019] In some examples, the vandefitemcel can be made by a method comprising providing a culture of MSCs; contacting the culture of MSCs 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.

[0020] In some examples, the MSCs can be human bone marrow-derived cells.

[0021] In some examples, the method can further comprise capturing functional magnetic resonance imaging (fMRI) scans of regions of the brain of the subject, selecting one region of the brain showing neuronal activity based on the fMRI scans, and administering the vandefitemcel to the one region of the brain.

[0022] In some examples, disclosed is a method for increasing synapse formation in neurons. The method can comprise administering vandefitemcel to a region of the brain of the subject comprising the neurons. The vandefitemcel can be cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

[0023] In some examples, administering the vandefitemcel further comprises administering the vandefitemcel by intracerebral implantation.

[0024] In some examples, the vandefitemcel can tonically release glutamate to the neurons of the brain of the subject after the vandefitemcel is implanted via intracerebral implantation.

[0025] In some examples, administering the vandefitemcel further comprises injecting the vandefitemcel at multiple sites within the region of the brain.

[0026] In some examples, administering the vandefitemcel further comprises administering the vandefitemcel stereotactically via a burr hole in the skull of the subject.

[0027] In some examples, the region of the brain is the forebrain of the subject including at least one of the cerebrum, the thalamus, and the hypothalamus of the subject.

[0028] In some examples, the region of the brain can be a site of injury or disease.

[0029] In some examples, the region of the brain can be a hippocampus of the subject.

[0030] In some examples, administering the vandefitemcel can further comprise administering the vandefitemcel by parenteral administration.

[0031] In some examples, the vandefitemcel can be suspended in a sterile isotonic crystalloid solution.

[0032] In some examples, administering the vandefitemcel can further comprise administering between about 1.0 million cells and 10.0 million cells of the vandefitemcel.

[0033] In some examples, the vandefitemcel can be made by a method comprising providing a culture of MSCs; contacting the culture of MSCs 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.

[0034] In some examples, the MSCs can be human bone marrow-derived cells.

[0035] In some examples, the method can further comprise capturing functional magnetic resonance imaging (fMRI) scans of regions of the brain of the subject, selecting one region of the brain showing neuronal activity based on the fMRI scans, and administering the vandefitemcel to the one region of the brain.

[0036] In some aspects, a composition for increasing synapse formation in neurons is disclosed. The composition can comprise vandefitemcel in an amount between about 1.0 million cells and 10.0 million cells and one or more pharmaceutically acceptable excipients. The vandefitemcel can be produced by modifying mesenchymal stem cells derived from human bone marrow.

[0037] In some examples, the vandefitemcel can be made by a process comprising providing a culture of mesenchymal stem cells (MSCs); contacting the culture of MSCs with a polynucleotide encoding a Notch intracellular domain (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.

[0038] In some examples, the MSCs can be human bone marrow-derived cells.

[0039] In some examples, the MSCs can be transiently-transfected with a plasmid vector comprising the polynucleotide encoding the NICD.

[0040] In some examples, the one or more pharmaceutically acceptable excipients can comprise at least one of buffers, proteins, stabilizers, and preservatives.

[0041] In some examples, the vandefitemcel can be suspended in a sterile isotonic crystalloid solution.

[0042] In some examples, the one or more pharmaceutically acceptable excipients can comprise carriers or diluents.

[0043] In some examples, a method of inducing, triggering, or causing the release of glutamate in a subject is disclosed. The method can comprise capturing functional magnetic resonance imaging (fMRI) scans of regions of the brain of the subject, selecting a region of the brain showing neuronal activity based on the fMRI scans, and administering vandefitemcel to the region of the brain selected. The vandefitemcel can be cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD). The vandefitemcel can release glutamate after being administered via intracerebral implantation.

[0044] In some examples, a method of increasing synapse formation in neurons is disclosed. The method can comprise capturing functional magnetic resonance imaging (fMRI) scans of regions of the brain of the subject, selecting a region of the brain showing neuronal activity based on the fMRI scans, and administering vandefitemcel to the region of the brain selected comprising the neurons. The vandefitemcel can be cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD). The vandefitemcel can release glutamate to the neurons after being administered via intracerebral implantation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] Figs. 1A-1D are graphs illustrating the electrophysiological activity and viability of separate cultures of vandefitemcel and iFbNs over an eight-week period using a multielectrode array (MEA) system.

[0046] Fig. 1E are raster plots illustrating electrophysiological activity and network burst development at four weeks and eight weeks for iFbN cell cultures at different cell densities.

[0047] Fig. 2A are reproductions of immunocytochemistry stains of a coculture of vandefitemcel and iPSC-derived forebrain neuron (iFbN) cells.

[0048] Fig. 2B is a graph illustrating the presence of vandefitemcel in cocultures of vandefitemcel and iFbN cells. The presence of vandefitemcel was confirmed by an increase in the resistance measured between the cells and the MEA electrodes.

[0049] Fig. 2C is a bar chart illustrating that at two weeks of coculture, an increase in neuronal excitability was detected in the iFbN and vandefitemcel coculture versus the iFbN culture alone based on the difference in the number of spikes observed.

[0050] Fig. 2D is a bar chart illustrating that at four weeks of coculture, the addition of vandefitemcel to the iFbN cells increased the number of network bursts in a cell density-dependent manner.

CLAIMS

We claim:

1. Use of vandefitemcel in the manufacture of a medicament for inducing tonic release of glutamate in a subject in need thereof,
   wherein the vandefitemcel is to be administered to a region of the brain of the subject, and wherein the vandefitemcel are cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).
2. The use of claim 1, wherein the vandefitemcel is to be administered by intracerebral implantation.
3. The use of claim 2, wherein the vandefitemcel tonically release glutamate to neurons of the brain after administration via intracerebral implantation.
4. The use of claim 2, wherein the vandefitemcel is to be administered at multiple sites within the region of the brain.
5. The use of claim 2, wherein the vandefitemcel is to be administered stereotactically via a burr hole in the skull of the subject.
6. The use of claim 1, wherein the region of the brain is a forebrain of the subject.
7. The use of claim 1, wherein the region of the brain is a site of injury or disease.
8. The use of claim 1, wherein the region of the brain is a hippocampus of the subject.
9. The use of claim 1, wherein the vandefitemcel is to be administered by parenteral administration.
10. The use of claim 1, wherein the vandefitemcel is suspended in a sterile isotonic crystalloid solution.
11. The use of claim 1, wherein between 1.0 million cells and 10.0 million cells are to be administered to the subject.
12. The use of claim 1, wherein the vandefitemcel is made by a method comprising:
    providing a culture of MSCs;
    contacting the culture of MSCs 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.
13. The use of claim 1, wherein the MSCs are human bone marrow-derived cells.
14. The use of claim 1, wherein:

functional magnetic resonance imaging (fMRI) scans of regions of the brain of the subject are to be obtained;

a region of the brain showing neuronal activity is to be selected based on the fMRI scans; and

the vandefitemcel is to be administered to the selected region of the brain.

15. Use of vandefitemcel in the manufacture of a medicament for increasing synapse formation in neurons in a subject in need thereof,

wherein vandefitemcel is to be administered to a region of the brain of the subject comprising the neurons, and wherein the vandefitemcel are cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD).

16. The use of claim 15, wherein the vandefitemcel is to be administered by intracerebral implantation.

17. The use of claim 16, wherein the vandefitemcel tonically release glutamate to the neurons after administration via intracerebral implantation.

18. The use of claim 16, wherein the vandefitemcel is to be administered at multiple sites within the region of the brain.

19. The use of claim 16, wherein the vandefitemcel is to be administered stereotactically via a burr hole in the skull of the subject.

20. The use of claim 15, wherein the region of the brain is a forebrain of the subject.

21. The use of claim 15, wherein the region of the brain is a site of injury or disease.

22. The use of claim 16, wherein the region of the brain is a hippocampus of the subject.

23. The use of claim 15, wherein the vandefitemcel is to be administered by parenteral administration.

24. The use of claim 15, wherein the vandefitemcel is suspended in a sterile isotonic crystalloid solution.

25. The use of claim 15, wherein between 1.0 million cells and 10.0 million cells are to be administered to the subject.

26. The use of claim 15, wherein the vandefitemcel is made by a method comprising:

providing a culture of 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.

27. The use of claim 15, wherein the MSCs are human bone marrow-derived cells.

28. The use of claim 15, wherein:

functional magnetic resonance imaging (fMRI) scans of regions of the brain of the subject are to be obtained;

a region of the brain showing neuronal activity is to be selected based on the fMRI scans; and

the vandefitemcel is to be administered to the selected region of the brain.

29. A composition for increasing synapse formation in neurons, the composition comprising:

vandefitemcel in an amount between 1.0 million cells and 10.0 million cells, wherein the vandefitemcel is produced by modifying mesenchymal stem cells derived from bone marrow; and

one or more pharmaceutically acceptable excipients.

30. The composition of claim 29, wherein the vandefitemcel is made by a process comprising:

providing a culture of mesenchymal stem cells;

contacting the culture of mesenchymal stem cells with a polynucleotide encoding a Notch intracellular domain (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.

31. The composition of claim 30, wherein the mesenchymal stem cells are human bone marrow-derived cells.

32. The composition of claim 29, wherein the mesenchymal stem cells are transiently-transfected with a plasmid vector comprising the polynucleotide encoding the NICD.

33. The composition of claim 29, wherein the one or more pharmaceutically acceptable excipients comprises at least one of buffers, proteins, stabilizers, and preservatives.

34. The composition of claim 29, wherein the vandefitemcel is suspended in a sterile isotonic crystalloid solution.

35. The composition of claim 29, wherein the one or more pharmaceutically acceptable excipients comprises carriers or diluents.

36. Use of vandefitemcel in the manufacture of a medicament for inducing release of glutamate in a subject in need thereof, wherein:

functional magnetic resonance imaging (fMRI) scans of regions of the brain of the subject are to be obtained;

a region of the brain showing neuronal activity is to be selected based on the fMRI scans; and

vandefitemcel is to be administered to the selected region of the brain, wherein the vandefitemcel are cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD), and wherein the vandefitemcel release glutamate after administration via intracerebral implantation.

37. Use of vandefitemcel in the manufacture of a medicament for increasing synapse formation in neurons in a subject in need thereof, wherein:

functional magnetic resonance imaging (fMRI) scans of regions of the brain of the subject are to be obtained;

a region of the brain showing neuronal activity is to be selected based on the fMRI scans; and

vandefitemcel is to be administered to the selected region of the brain comprising the neurons, wherein the vandefitemcel are cells descended from mesenchymal stem cells (MSCs) transiently-transfected by a polynucleotide encoding a Notch intracellular domain (NICD), and wherein the vandefitemcel release glutamate to the neurons after administration via intracerebral implantation.