

WHAT IS CLAIMED IS:

1. A method for inhibiting impaired neurogenesis and/or synaptogenesis in neurons in a subject with or suspected of having Alzheimer's Disease (AD), wherein said impairment of neurogenesis and/or synaptogenesis is caused, at least in part, by over activation of endoplasmic reticulum (ER) ryanodine receptor (RyR), the method comprising intranasally administering to said subject an amount of a pharmaceutical composition comprising dantrolene effective to decrease release of ER calcium ions (Ca^{2+}).
2. The method of claim 1, wherein the neurogenesis comprises neurogenesis from neuroprogenitor cells (NPCs) into immature neurons, followed by neurogenesis from immature neurons into cortical neurons.
3. The method of any one of claims 1 or 2, wherein the synaptogenesis occurs in cortical neurons.
4. The method of any one of the preceding claims, wherein the cortical neurons are cholinergic neurons.
5. The method of any one of the preceding claims, wherein the cortical neurons are basal forebrain cholinergic neurons (BFCN) neurons, prefrontal cortex neurons, hippocampus neurons, or a combination thereof.
6. The method of any one of the preceding claims, wherein the AD is familial Alzheimer's disease (FAD) or sporadic Alzheimer's disease (SAD).
7. The method of any one of the preceding claims, wherein the RyR is selected from the group consisting of Type 1 RyR (RyR-1), Type 2 RyR (RyR-2), Type 3 RyR (RyR-3) and combinations thereof.
8. The method of any one of the preceding claims, wherein the over activation of endoplasmic reticulum (ER) ryanodine receptor (RyR) elevates mitochondrial calcium and reduces ATP .
9. The method of any one of the preceding claims, wherein intranasal administration of dantrolene reduces the elevated mitochondrial calcium and increases cytosolic ATP.
10. The method of any one of the preceding claims, wherein the pharmaceutical composition comprising dantrolene is administered three times per week.

11. The method of any one of the preceding claims, wherein the pharmaceutical composition comprising dantrolene is administered for four months to one year.
12. The method of any one of the preceding claims, wherein the pharmaceutical composition comprising dantrolene is administered for up to two years.
13. The method of any one of the preceding claims, wherein the pharmaceutical composition comprising dantrolene is administered for more than two years.
14. The method of any one of the preceding claims, wherein the administration does not result in impairment of olfactory function, motor function, or liver function of the subject.
15. A method for improving and/or slowing the decline of cognitive function after onset of neuropathology and cognitive dysfunction, wherein said neuropathology and cognitive dysfunction are caused by Alzheimer's Disease (AD), the method comprising intranasally administering to a subject in need thereof an amount of a pharmaceutical composition comprising dantrolene effective to inhibit over-activation of NMDA receptor and/or ryanodine receptor (RyR).
16. The method of claim 15, wherein the cognitive function is memory, learning, thinking, attention, perception, language use, reasoning, decision making, problem solving or a combination thereof.
17. The method of any one of claims 15-16, wherein the AD is familial Alzheimer's disease (FAD) or sporadic Alzheimer's disease (SAD).
18. The method of any one of claims 15-17, wherein the RyR is selected from the group consisting of Type 1 RyR (RyR-1), Type 2 RyR (RyR-2), Type 3 RyR (RyR-3) and combinations thereof.
19. The method of any one of claims 15-18, wherein the pharmaceutical composition comprising dantrolene is administered three times per week.
20. The method of any one of claims 15-18, wherein the pharmaceutical composition comprising dantrolene is administered for four months to one year.
21. The method of any one of claims 15-18, wherein the pharmaceutical composition comprising dantrolene is administered for up to two years.

22. The method of any one of claims 15-18, wherein the pharmaceutical composition comprising dantrolene is administered for more than two years.
23. The method of any one of claims 15-22, wherein the administration does not result in impaired olfactory function, motor function, or liver function of the subject.
24. A method for improving memory before onset of symptoms of Alzheimer's Disease (AD), the method comprising intranasally administering to a subject in need thereof an amount of a pharmaceutical composition comprising dantrolene effective to inhibit over-activation of NMDA receptor and/or ryanodine receptor (RyR).
25. The method of claim 24, wherein the pharmaceutical composition comprising dantrolene is administered three times per week.
26. The method of any one of claims 24 or 25, wherein the pharmaceutical composition comprising dantrolene is administered for four months to one year.
27. The method of any one of claims 24 or 25, wherein the pharmaceutical composition comprising dantrolene is administered for up to two years.
28. The method of any one of claims 24 or 25, wherein the pharmaceutical composition comprising dantrolene is administered for more than two years.
29. The method of any one of claims 24-28, wherein administration does not impair olfactory function, motor function, or liver function of the subject.
30. The method of any one of claims 24-29, wherein the symptoms of AD are neuropathology, cognitive dysfunction or a combination thereof.
31. The method of claim 30, wherein the cognitive dysfunction is short-term or long-term memory loss, learning difficulty, thinking difficulty, attention/concentration difficulty, perception difficulty, difficulty in language use, reasoning difficulty, difficulty in making decisions/ impaired judgment, problem solving difficulty, confusion, poor motor coordination, or a combination thereof.
32. The method of claim 31, wherein the short-term or long-term memory loss is hippocampal-dependent and hippocampal-independent memory loss.

33. The method of any one of claims 31 or 32, wherein the neuropathology is amyloid accumulation between brain neurons.
34. The method of any one of claims 24-33, wherein the AD is familial AD (FAD) or sporadic AD (SAD).
35. The method of any one of claims 24-34, wherein the RyR is selected from the group consisting of Type 1 RyR (RyR-1), Type 2 RyR (RyR-2), Type 3 RyR (RyR-3) and combinations thereof.
36. A method for improving memory loss after onset of symptoms of Alzheimer's Disease (AD), wherein said memory loss is caused by AD, the method comprising intranasally administering to a subject in need thereof an amount of a pharmaceutical composition comprising dantrolene effective to inhibit over-activation of NMDA receptor and/or ryanodine receptor (RyR).
37. The method of claim 36, wherein the pharmaceutical composition comprising dantrolene is administered three times per week.
38. The method of any one of claims 36 or 37, wherein the pharmaceutical composition comprising dantrolene is administered for four months to one year.
39. The method of any one of claims 36 or 37, wherein the pharmaceutical composition comprising dantrolene is administered for up to two years.
40. The method of any one of claims 36 or 37, wherein the pharmaceutical composition comprising dantrolene is administered for more than two years.
41. The method of any one of claims 36-40, wherein administration does not impair olfactory function, motor function, or liver function of the subject.
42. The method of claim any one of claims 36-41, wherein the symptoms of AD are neuropathology, cognitive dysfunction or a combination thereof.
43. The method of claim 42 wherein the cognitive dysfunction is short-term or long-term memory loss, learning difficulty, thinking difficulty, attention/concentration difficulty, perception difficulty, difficulty in language use, reasoning difficulty, difficulty in making decisions/ impaired judgment, problem solving difficulty, confusion, poor motor coordination, or a combination thereof.

44. The method of claim 43 wherein the memory loss is hippocampal-dependent and hippocampal-independent memory loss.
45. The method of claims 42-44, wherein the neuropathology is amyloid accumulation between brain neurons.
46. The method of any one of claims 36-45, wherein the AD is familial AD (FAD) or sporadic AD (SAD).
47. The method of any one of claims 36-46, wherein the RyR is selected from the group consisting of Type 1 RyR (RyR-1), Type 2 RyR (RyR-2), Type 3 RyR (RyR-3) and combinations thereof.
48. A method for increasing concentration and duration of dantrolene in the brain of a subject, the method comprising intranasally administering to a subject in need thereof an amount of a pharmaceutical composition comprising dantrolene.
49. A method for inhibiting impaired neurogenesis and/or synaptogenesis in neurons in a subject with or suspected of having Alzheimer's Disease (AD), wherein said impairment of neurogenesis and/or synaptogenesis is caused, at least in part, by over activation of endoplasmic reticulum (ER) ryanodine receptor (RyR), the method comprising:
- a) intranasally administering to said subject an amount of a pharmaceutical composition comprising dantrolene effective to decrease release of ER calcium ions (Ca^{2+}); and
 - b) administering a therapeutically effective amount of a glutamate receptor antagonist to the subject of step (a).
50. The method of claim 49, further comprising:
- c) obtaining cerebrospinal fluid (CSF) from the subject before step (a); and
 - d) determining a level of glutamate in the CSF,
- wherein a determined level of glutamate in step (d) that is higher than a level of glutamate in CSF obtained from a control subject is indicative of suitability of the subject for treatment with dantrolene.
51. The method of claim 50, further comprising obtaining CSF from the subject before step (b); and determining a level of glutamate in the CSF, wherein a determined level of glutamate that

is higher than a level of glutamate in CSF obtained from a control subject is indicative of suitability of the subject for treatment with a glutamate receptor antagonist.

52. The method of claim 49 or claim 50, wherein the glutamate receptor antagonist is an agent that blocks the NMDA receptor by competitive antagonism at a glutamate-binding site or is an agent that blocks the NMDA receptor by noncompetitive antagonism at a glycine, phencyclidine and/or magnesium binding site.

53. The method of claim 52, wherein the agent that blocks the NMDA receptor by competitive antagonism at a glutamate-binding site is selfotel (CGS 19755) aptiganel (CNS 1102), CGP 37849, APV or AP-5 (R-2-amino-5-phosphonopentanoate), 2-amino-7-phosphono-heptanoic acid (AP-7), 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid (CPPene) and/or aspartame.

54. The method of claim 52, wherein the agent that blocks the NMDA receptor by noncompetitive antagonism at a phencyclidine (PCP), magnesium, and/or MK-801 (dizocilpine) binding site is memantine, ketamine, phencyclidine, 3-MEO-PCP, 8A-PDHQ, amantadine, atomoxetine, AZD6765, agmatine, delucemine, dexrallorphan, dextromethorphan, dextrorphan, diphenidne, ethanol, eticylidine, gacyclidine, methoxetamine (MXE), minocycline, nitromemantine, nitrous oxide, PD-137889, rolicyclidine, tenocyclidine, methoxydine, tiletamine, neramexane, eliprodil, etoxadrol, dexoxadrol, WMS-2539, NEFA, remacemide, magnesium sulfate, aptiganel, HU-211, huperzine A, Dipeptide D-Phe-L-Tyr, Ibogaine, Apocynaceae, Remacemide, Rhynchophylline, gabapentin, or dizocilpine (MK-801).

55. The method of claim 52, wherein the agent that blocks the NMDA receptor by noncompetitive antagonism at a glycine binding site is (GLYX-13), NRX-1074, 7-Chlorokynurenic acid, 4-Chlorokynurenine (AV-101), 5,7-Dichlorokynurenic acid, Kynurenic acid, TK-40 (competitive antagonist at the GluN1 glycine binding site), 1-aminocyclopropanecarboxylic acid (ACPC), L-Phenylalanine, or Xenon.

56. The method of any one of the preceding claims, wherein the neurogenesis comprises neurogenesis from neuroprogenitor cells (NPCs) into immature neurons, followed by neurogenesis from immature neurons into cortical neurons.

57. The method of any one of the preceding claims, wherein the synaptogenesis occurs in cortical neurons.

58. The method of any one of the preceding claims, wherein the cortical neurons are cholinergic neurons.
59. The method of any one of the preceding claims, wherein the cortical neurons are basal forebrain cholinergic neurons (BFCN) neurons, prefrontal cortex neurons, hippocampus neurons, or a combination thereof.
60. The method of any one of the preceding claims, wherein the AD is familial Alzheimer's disease (FAD) or sporadic Alzheimer's disease (SAD).
61. The method of any one of the preceding claims, wherein the over activation of endoplasmic reticulum (ER) ryanodine receptor (RyR) elevates mitochondrial calcium and reduces ATP .
62. The method of any one of the preceding claims, wherein intranasal administration of dantrolene reduces the elevated mitochondrial calcium and increases cytosolic ATP.
63. The method of any one of the preceding claims, wherein the pharmaceutical composition comprising dantrolene is administered three times per week.
64. The method of any one of the preceding claims, wherein the pharmaceutical composition comprising dantrolene is administered for four months to one year.
65. The method of any one of the preceding claims, wherein the pharmaceutical composition comprising dantrolene is administered for up to two years.
66. The method of any one of the preceding claims, wherein the pharmaceutical composition comprising dantrolene is administered for more than two years.
67. The method of any one of the preceding claims, wherein the administration does not result in impairment of olfactory function, motor function, or liver function of the subject.
68. The method of any one of claims 49-67, wherein the RyR is selected from the group consisting of Type 1 RyR (RyR-1), Type 2 RyR (RyR-2), Type 3 RyR (RyR-3) and combinations thereof.
69. The method of claim 15, further comprising administering a therapeutically effective amount of a glutamate receptor antagonist to the subject.
70. The method of claim 15, further comprising:

a) obtaining cerebrospinal fluid (CSF) from the subject before intranasally administering to the subject the pharmaceutical composition comprising dantrolene; and

b) determining a level of glutamate in the CSF,

wherein a determined level of glutamate in step (b) that is higher than a level of glutamate in CSF obtained from a control subject is indicative of suitability of the subject for treatment with dantrolene.

71. The method of claim 70, further comprising obtaining CSF from the subject before administering the therapeutically effective amount of the glutamate receptor antagonist; and determining a level of glutamate in the CSF, wherein a determined level of glutamate that is higher than a level of glutamate in CSF obtained from a control subject is indicative of suitability of the subject for treatment with a glutamate receptor antagonist.

72. The method of claim 70, wherein the glutamate receptor antagonist is an agent that blocks the NMDA receptor by competitive antagonism at a glutamate-binding site or is an agent that blocks the NMDA receptor by noncompetitive antagonism at a glycine, phencyclidine and/or magnesium binding site.

73. The method of claim 72, wherein the agent that blocks the NMDA receptor by competitive antagonism at a glutamate-binding site is selfotel (CGS 19755) aptiganel (CNS 1102), CGP 37849, APV or AP-5 (R-2-amino-5-phosphonopentanoate), 2-amino-7-phosphono-heptanoic acid (AP-7), 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid (CPPene) and/or aspartame.

74. The method of claim 72, wherein the agent that blocks the NMDA receptor by noncompetitive antagonism at a phencyclidine (PCP), magnesium, and/or MK-801 (dizocilpine) binding site is memantine, ketamine, phencyclidine, 3-MEO-PCP, 8A-PDHQ, amantadine, atomoxetine, AZD6765, agmatine, delucemine, dexrallorphan, dextromethorphan, dextrorphan, diphenidne, ethanol, eticylidine, gacyclidine, methoxetamine (MXE), minocycline, nitromemantine, nitrous oxide, PD-137889, rolicyclidine, tenocyclidine, methoxydine, tiletamine, neramexane, eliprodil, etoxadrol, dexoxadrol, WMS-2539, NEFA, remacemide, magnesium sulfate, aptiganel, HU-211, huperzine A, Dipeptide D-Phe-L-Tyr, Ibogaine, Apocynaceae, Remacemide, Rhynchophylline, gabapentin, or dizocilpine (MK-801).

75. The method of claim 72, wherein the agent that blocks the NMDA receptor by noncompetitive antagonism at a glycine binding site is (GLYX-13), NRX-1074, 7-

Chlorokynurenic acid, 4-Chlorokynurenine (AV-101), 5,7-Dichlorokynurenic acid, Kynurenic acid, TK-40 (competitive antagonist at the GluN1 glycine binding site), 1-aminocyclopropanecarboxylic acid (ACPC), L-Phenylalanine, or Xenon.

76. The method of claim 24, further comprising administering a therapeutically effective amount of a glutamate receptor antagonist to the subject.

77. The method of claim 24, further comprising:

a) obtaining cerebrospinal fluid (CSF) from the subject before intranasally administering to the subject the pharmaceutical composition comprising dantrolene; and

b) determining a level of glutamate in the CSF,

wherein a determined level of glutamate in step (b) that is higher than a level of glutamate in CSF obtained from a control subject is indicative of suitability of the subject for treatment with dantrolene.

78. The method of claim 77, further comprising obtaining CSF from the subject before administering the therapeutically effective amount of the glutamate receptor antagonist; and determining a level of glutamate in the CSF, wherein a determined level of glutamate that is higher than a level of glutamate in CSF obtained from a control subject is indicative of suitability of the subject for treatment with a glutamate receptor antagonist.

79. The method of claim 77, wherein the glutamate receptor antagonist is an agent that blocks the NMDA receptor by competitive antagonism at a glutamate-binding site or is an agent that blocks the NMDA receptor by noncompetitive antagonism at a glycine, phencyclidine and/or magnesium binding site.

80. The method of claim 79, wherein the agent that blocks the NMDA receptor by competitive antagonism at a glutamate-binding site is selfotel (CGS 19755) aptiganel (CNS 1102), CGP 37849, APV or AP-5 (R-2-amino-5-phosphonopentanoate), 2-amino-7-phosphono-heptanoic acid (AP-7), 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid (CPPene) and/or aspartame.

81. The method of claim 79, wherein the agent that blocks the NMDA receptor by noncompetitive antagonism at a phencyclidine (PCP), magnesium, and/or MK-801 (dizocilpine) binding site is memantine, ketamine, phencyclidine, 3-MEO-PCP, 8A-PDHQ, amantadine, atomoxetine, AZD6765, agmatine, delucemine, dextrallorphan, dextromethorphan,

dextrorphan, diphenidne, ethanol, eticylidine, gacyclidine, methoxetamine (MXE), minocycline, nitromemantine, nitrous oxide, PD-137889, rolicyclidine, tenocyclidine, methoxydine, tiletamine, neramexane, eliprodil, etoxadrol, dexoxadrol, WMS-2539, NEFA, remacemide, magnesium sulfate, aptiganel, HU-211, huperzine A, Dipeptide D-Phe-L-Tyr, Ibogaine, Apocynaceae, Remacemide, Rhynchophylline, gabapentin, or dizocilpine (MK-801).

82. The method of claim 79, wherein the agent that blocks the NMDA receptor by noncompetitive antagonism at a glycine binding site is (GLYX-13), NRX-1074, 7-Chlorokynurenic acid, 4-Chlorokynurenine (AV-101), 5,7-Dichlorokynurenic acid, Kynurenic acid, TK-40 (competitive antagonist at the GluN1 glycine binding site), 1-aminocyclopropanecarboxylic acid (ACPC), L-Phenylalanine, or Xenon.

83. The method of claim 36, further comprising administering a therapeutically effective amount of a glutamate receptor antagonist to the subject.

84. The method of claim 36, further comprising:

a) obtaining cerebrospinal fluid (CSF) from the subject before intranasally administering to the subject the pharmaceutical composition comprising dantrolene; and

b) determining a level of glutamate in the CSF,

wherein a determined level of glutamate in step (b) that is higher than a level of glutamate in CSF obtained from a control subject is indicative of suitability of the subject for treatment with dantrolene.

85. The method of claim 84, further comprising obtaining CSF from the subject before administering the therapeutically effective amount of the glutamate receptor antagonist; and determining a level of glutamate in the CSF, wherein a determined level of glutamate that is higher than a level of glutamate in CSF obtained from a control subject is indicative of suitability of the subject for treatment with a glutamate receptor antagonist.

86. The method of claim 85, wherein the glutamate receptor antagonist is an agent that blocks the NMDA receptor by competitive antagonism at a glutamate-binding site or is an agent that blocks the NMDA receptor by noncompetitive antagonism at a glycine, phencyclidine and/or magnesium binding site.

87. The method of claim 86, wherein the agent that blocks the NMDA receptor by competitive antagonism at a glutamate-binding site is selfotel (CGS 19755) aptiganel (CNS 1102), CGP 37849, APV or AP-5 (R-2-amino-5-phosphonopentanoate), 2-amino-7-phosphono-heptanoic acid (AP-7), 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid (CPPene) and/or aspartame.

88. The method of claim 86, wherein the agent that blocks the NMDA receptor by noncompetitive antagonism at a phencyclidine (PCP), magnesium, and/or MK-801 (dizocilpine) binding site is memantine, ketamine, phencyclidine, 3-MEO-PCP, 8A-PDHQ, amantadine, atomoxetine, AZD6765, agmatine, delucemine, delucemine, dextrallorphan, dextromethorphan, dextrorphan, diphenidne, ethanol, eticylidine, gacyclidine, methoxetamine (MXE), minocycline, nitromemantine, nitrous oxide, PD-137889, rolicyclidine, tenocyclidine, methoxydine, tiletamine, neramexane, eliprodil, etoxadrol, dexoxadrol, WMS-2539, NEFA, remacemide, magnesium sulfate, aptiganel, HU-211, huperzine A, Dipeptide D-Phe-L-Tyr, Ibogaine, Apocynaceae, Remacemide, Rhynchophylline, gabapentin, or dizocilpine (MK-801).

89. The method of claim 86, wherein the agent that blocks the NMDA receptor by noncompetitive antagonism at a glycine binding site is (GLYX-13), NRX-1074, 7-Chlorokynurenic acid, 4-Chlorokynurenine (AV-101), 5,7-Dichlorokynurenic acid, Kynurenic acid, TK-40 (competitive antagonist at the GluN1 glycine binding site), 1-aminocyclopropanecarboxylic acid (ACPC), L-Phenylalanine, or Xenon.