CLAIMS

1. Use of an active substance capable of reducing the binding of REST to RE1/NRSE elements, or reducing the amount or activity of REST in the preparation of a medicament for trans-differentiating non-neuronal cells to functional neurons in a subject.

2. Use of an active substance capable of reducing the binding of REST to the RE1/NRSE element, or reducing the amount or activity of REST in the preparation of a medicament for preventing and/or treating diseases associated with neuronal dysfunction or death in a subject in need, comprising administering a therapeutically effective dose of the medicament to the areas affected by the disease in the subject, in order to transdifferentiate non-neuronal cells in the affected areas into functional neurons;

preferably, wherein the diseases associated with neuronal dysfunction or death are selected from: Parkinson's disease, Alzheimer's disease, stroke, schizophrenia, Huntington's disease, depression, motor neuron disease, amyotrophic lateral sclerosis, spinal muscular atrophy, Pick disease, sleep disorders, epilepsy, ataxia, visual impairment due to RGC death, glaucoma, age-related RGC lesions, optic nerve injury, retinal ischemia or hemorrhage, Leber hereditary optic neuropathy, degeneration or death of photoreceptor cells due to injury or degeneration, macular degeneration, retinitis pigmentosa, diabetes-related blindness, night blindness, color blindness, hereditary blindness, congenital amaurosis, deafness or hearing loss due to spiral ganglion cell death, and any combination thereof.

3. The use of claim 1 or 2, wherein the said functional neurons include dopamine neurons, retinal ganglion cells, photoreceptor cells and cochlear spiral ganglion cells, GABA neurons, 5-HT neurons, glutamatergic neurons, ChAT neurons, NE neurons, motor neurons, spinal neurons, spinal motor neurons, spinal sensory neurons, bipolar cells, horizontal cells, amacrine cells, pyramidal neurons, interneurons neurons, medium spiny neurons (MSNs), Purkinje cells, granule cells, olfactory sensory neurons, periglomerular cells, or any combination thereof.

4. The use of any one of preceding claims, wherein the functional neurons express the NeuN gene or the functional neurons have an axon.

5. The use of claim 3, wherein the dopamine neurons express one or more markers selected from tyrosine hydroxylase (TH), FoxA2, Nurr1, Pitx3, Vmat2 and DAT; or the dopamine neurons express NeuN, TH, and DAT;

or

the retinal ganglion cells express one or more markers selected from RBPMS, Pax6, Brn3a, Brn3b, Brn3c, and Map2; or

the photoreceptor cells express one or more markers selected from Rhodopsin, mCAR, m-opsin and S-opsin; or

the cochlear spiral ganglion cells express one or more markers selected from NeuN, Prox1, Tuj-1 and Map2.

6. The use of any one of the preceding claims, wherein the non-neuronal cells comprise glial cells, fibroblasts, stem cells, neural precursor cells, or neural stem cells; preferably, the glial cells are selected from astrocytes, oligodendrocytes, ependymal cells, Schwann cells, NG2 cells, satellite cells, Müller glial cells, inner ear glial cells, and any combination thereof.

7. The use of claim 6, wherein the glial cells are located in the brain, spinal cord, eye or ear, further preferably, the glial cells are located in the striatum, substantia nigra, ventral tegmental area

of the midbrain, medulla oblongata, hypothalamus, dorsal midbrain, or cerebral cortex of the brain.

8. The use of any one of the preceding claims, wherein the active substance is administered locally to glial cells in one or more of the following locations in the subject: 1) glial cells in the striatum; ii) glial cells in the substantia nigra of the brain; iii) glial cells in the retina; iv) glial cells in the inner ear; v) glial cells in the spinal cord; vi) glial cells in the prefrontal cortex; vii) glial cells in motor cortex ; viii) glial cells in the hypothalamus; and ix) glial cells in the ventral tegmental area (VTA).

9. The use of any one of the preceding claims, wherein said glial cells comprise astrocytes and said functional neurons comprise dopamine neurons, preferably, the astrocytes are located in the striatum and/or the substantia nigra; or

said glial cells comprise Müller glial cells, and said functional neurons comprise retinal ganglion cells (RGCs) and/or photoreceptor cells, preferably, the Müller glial cells are in the retina or vitreous cavity; or

the glial cells comprise cochlear glial cells, and the functional neurons comprise cochlear spiral ganglion cells, preferably, the cochlear glial cells are located in the inner ear.

10. The use of any one of the preceding claims, wherein the active substance comprises a RE1/NRSE element blocker, which could bind to the RE1/NRSE element to block the binding of REST and the RE1/NRSE element; preferably, said RE1/NRSE element blocker comprises a protein that competes with REST for binding to RE1 or a nucleic acid encoding said protein.

11. The use of claim 10, wherein the protein that competes with REST for binding to RE1comprises a REST variant, the REST variant preferably comprises the DNA binding domain of REST but lacks the N-terminal and/or C-terminal repression domain of REST; further preferably, the REST variant comprises the amino acid sequence of SEQ ID NO: 1, 3, 5 or 9, or comprises the amino acid sequence of at least 70%, 60%, or 50% identity percentage with anyone thereof.

12. The use according to claim 11, wherein said RE1/NRSE element blocker comprises a nucleic acid encoding the REST variant as claimed in claim 11, said nucleic acid encoding the REST variant comprises the sequence of SEQ ID NO: 2, 4, 6 or 10, or comprises the sequence of at least 70%, 60%, or 50% identity percentage with anyone thereof;

preferably, wherein the nucleic acid encoding the REST variant is codon-optimized, alternatively comprises the nucleotide sequence of SEQ ID NO: 15, or at least 70%, 60% or 50 identity percentage with SEQ ID NO: 15.

13. The use of claim 11 or 12, wherein said REST variant further comprises an activation domain fused to the DNA binding domain of REST, the activation domain preferably comprises an epigenetic modification protein or a gene activation regulatory element, optionally, the activation domain comprises VP64, P65-HSF1, VP16, RTA, Suntag, P300, CBP or any combination thereof, optionally, the activation domain comprises VP64 or P65-HSF1.

14. The use of any one of claims 11-13, wherein the REST variant is fused to one or more nuclear localization signal sequences; preferably, at least one of said nuclear localization signal sequences is fused to the N-terminus of said REST variant; more preferably, wherein the nuclear localization signal sequence comprises the amino acid sequence selected from SEQ ID NOs: 13, 41-58.

15. The use of any one of the preceding claims, wherein the subject is a human or an animal, preferably, the animal is a non-human primate, rat or mouse.

16. A REST variant comprising the DNA binding domain of REST but lacking the N-terminal

and/or C-terminal repression domain of REST; preferably, the REST variant comprises amino acids from 155 to 420 of REST, but lacking the N-terminal and/or C-terminal repression domain of REST; more preferably, the REST variant comprises the amino acid sequence of SEQ ID NO: 1, 3, 5 or 9, or comprises a sequence having at least 70%, 60%, or 50% identity percentage with anyone thereof; or

the REST variant is encoded by a nucleotide sequence of SEQ ID NO: 2, 4, 6 or 10, or a nucleotide sequence of at least 70%, 60%, or 50% identity percentage with anyone thereof.

17. The REST variant of claim 16, further comprising an activation domain fused to the DNA binding domain of said REST;

preferably, the activation domain comprises an epigenetic modification protein or a gene activation regulatory element, optionally, the activation domain comprises VP64, P65-HSF1, VP16, RTA, Suntag, P300, CBP or any combination thereof, optionally, the activation domain includes VP64 or P65-HSF1.

18. The REST variant of claim 16 or 17, which fused to one or more nuclear localization signal sequences, preferably, at least one of said nuclear localization signal sequences is fused to the N-terminus of said REST variant.

19. The REST variant of claim 18, wherein the nuclear localization signal sequence comprises the amino acid sequence shown in SEQ ID NO:13.

20. A polynucleotide comprising a nucleic acid sequence encoding the REST variant according to any one of claims 16-19.

21. An expression vector comprising the polynucleotide of claim 20, and optionally further comprising a promoter operably linked to the polynucleotide;

preferably, the promoter is a glial cell-specific promoter, further preferably, the glial cell-specific promoter is an astrocyte-specific promoter, a Müller glial cell (MG) cell-specific promoter, or a cochlear glial cell-specific promoter.; or preferably, the glial cell-specific promoter is selected from GFAP promoter, ALDH1L1 promoter, EAAT1/GLAST promoter, glutamine synthetase promoter, S100β promoter EAAT2 /GLT-1 promoter, Plp1 promoter and Rlbp1 promoter;

further preferably, the glial cell-specific promoter is selected from preferably GFAP promoter.

22. A pharmaceutical composition comprising the REST variant of any one of claims 16-19 or the polynucleotide of claim 20 or the expression vector of claim 21, and pharmaceutically acceptable carrier;

preferably, the pharmaceutical composition further comprises a carrier for delivering the polynucleotide, wherein the carrier comprises a viral vector, liposome, nanoparticle, exosome, or virus-like particles; preferably, the viral vector comprises recombinant adeno-associated viral vector (rAAV), adeno-associated viral (AAV) vector, adenoviral vector, lentiviral vector, retroviral vector, poxvirus vector, herpes virus vector, SV40 virus vector, or any combination thereof, wherein AAV or rAAV is preferred.