CLAIMS:

1. Use of a polynucleotide comprising nucleic acid sequences encoding miRNA that:

i) inhibits APP;

ii) inhibits MAPT; or

iii) targets a pro-inflammatory gene;

in the manufacture of a medicament for the treatment of a brain neurodegenerative disease, brain cancer, stroke or ischemia in a subject, wherein the medicament is to be administered intracellularly into skin cells of the subject to produce skin-derived exosomes containing the polynucleotide or an expression product thereof, and wherein the miRNA is selected from the group consisting of hsa-miR-106b-5p, hsa-miR-101-3p, hsa-miR-520c-3p, hsa-miR-106a-5p, hsa-miR-20a-5p, hsa-miR-17-5p, hsa-miR-15a-5p, hsa-miR-130a-3p, hsa-let-7d-5p, hsa-let-7a-5p, hsa-miR-16-5p, hsa-miR-144-3p, hsa-miR-4422, hsa-let-7f-1-3p, hsa-let-7a-3p, hsa-let-7b-3p, hsa-miR-98-3p, hsa-miR-380-3p, hsa-miR-6835-3p, hsa-miR-4772-5p, hsa-miR-101-3p, hsa-miR-4719, hsa-miR-520f-3p, hsa-miR-3908, hsa-miR-4269, hsa-miR-323a-3p, hsa-miR-6715b-5p, hsa-miR-153-3p, hsa-miR-4495, hsa-miR-4786-5p, hsa-miR-3911, hsa-miR-6085, and hsa-miR-6813-5p, or any combination thereof.

2. Use of a polynucleotide comprising nucleic acid sequences encoding a vasculogenic factor in the manufacture of a medicament for the treatment of a brain neurodegenerative disease, brain cancer, stroke or ischemia in a subject, wherein the medicament is to be administered intracellularly into skin cells of the subject to produce skin-derived exosomes containing the polynucleotide or an expression product thereof.

3. Use of a polynucleotide comprising nucleic acid sequences encoding a neurogenic factor in the manufacture of a medicament for the treatment of a brain neurodegenerative disease, brain cancer, stroke or ischemia in a subject, wherein the medicament is to be administered intracellularly into skin cells of the subject to produce skin-derived exosomes containing the polynucleotide or an expression product thereof.

4. Use of a polynucleotide comprising nucleic acid sequences encoding an anti-Inflammatory factor in the manufacture of a medicament for the treatment of a brain neurodegenerative disease, brain cancer, stroke or ischemia in a subject, wherein the medicament is to be administered intracellularly into skin cells of the subject to produce skin-derived exosomes

containing the polynucleotide or an expression product thereof.

5. The use of any one of claims 1-4, wherein the neurodegenerative disease comprises Alzheimer's Disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), or Huntington's disease (HD).

6. The use of claim 2, wherein the vasculogenic factor comprises Etv2, Fli1, VEGFA, VEGFB, VEGFC, VEGFD, bFGF, Sox17, Oct4, Klf4, or any combination thereof.

7. The use of claim 3, wherein the neurogenic factor is selected from the group consisting of Ascl1, Ascl2, Ascl3, Ascl5, Neurog1, Neurog2, Neurog3, Neurod1, Neurod2, Neurod4, Neurod6, Atoh1, Atoh7, Atoh8, Myf5, Ptf1a, Brn3c, Brn3a, Brn3b, Brn1, Brn2, Brn4 , Oct4, Oct6, Pit1, Brn5, Myt1l, and Nurr1, or any combination thereof.

8. The use of claim 1, wherein the miRNA is selected from the group consisting of hsa-miR-34c-5p, hsa-miR-657, hsa-miR-4728-5p, and hsa-miR-3978, or any combination thereof.

9. The use of claim 4, wherein the anti-Inflammatory factor is selected from the group consisting of PPARγ, Il-10, Il-27, Trem2, and IkBα, and Sirt1, or any combination thereof.

10. The use of claim 1, wherein the pro-inflammatory gene is P2X4R, TLR4, CX3CR1, or IL-1β.

11. Use of a neutral sphingomyelinase inhibitor that inhibits exosomal release from the skin to reduce trafficking to the brain in the manufacture of a medicament for the treatment of a brain neurodegenerative disease, brain cancer, stroke or ischemia in a subject, wherein the medicament is to be administered to the skin of the subject.

12. The use of claim 11, wherein the neurodegenerative disease comprises Alzheimer's Disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), or Huntington's disease (HD).