CLAIMS

1. Use of AAV particles,

in the manufacture of a medicament for the treatment of lysosomal storage disease (LSD) in a mammal, said AAV particles (i) comprising an AAV capsid protein and a nucleic acid inserted between a pair of AAV inverted terminal repeats (ITRs), said nucleic acid encoding a polypeptide having lysosomal hydrolase activity, and (ii) said AAV particles are capable of transducing cells of said mammal and providing expression of said polypeptide; wherein the mammal is to be administered with a first immunosuppressive agent and a second immunosuppressive agent,

and wherein at least one of said first immunosuppressive agent and said second immunosuppressive agent are to be administered to said mammal prior to the administration of said medicament, and wherein neutralizing antibody response in said mammal is reduced by administration of said first immunosuppressive agent and said second immunosuppressive agent.

2. The use according to Claim 1, wherein said polypeptide has tripeptidyl-peptidase 1 (TPP1) activity.

3. The use according to Claim 2, wherein said polypeptide comprises TPP1 or a pro-enzyme thereof.

4. The use according to any one of Claims 1-3, wherein said first immunosuppressive agent is to be administered prior to the administration of the medicament and said second immunosuppressive agent is to be administered prior to, concurrently with, or after the administration of the medicament.

5. The use according to any one of Claims 1-4, wherein said first immunosuppressive agent comprises cyclosporine.

6. The use according to any one of Claims 1-5, wherein said second immunosuppressive agent comprises mycophenolate or a derivative thereof.

7. The use according to Claim 6, wherein said mycophenolate derivative is mycophenolate mofitil (MMF).

8. The use according to any one of Claims 1-7, wherein, tripeptidyl-peptidase 1 (TPP1) activity in the cerebrospinal fluid of said mammal is detectable at a level of at least 5 pmol TPP1/mg protein for greater than 350 days.

9. The use according to any one of Claims 1-8, wherein cells in the cerebrospinal fluid (CSF) of said mammal are transduced by said AAV particles.

10. The use according to any one of Claims 1-9, wherein (i) said first immunosuppressive agent is to be administered at least about two weeks prior to the administration of the medicament and (ii) said second immunosuppressive agent is to be administered about two weeks before or within 40 days after the administration of the medicament.

11. The use according to any one of Claims 1-10, wherein the medicament is to be administered to the cisterna magna, intraventricular space, brain ventricle, subarachnoid space, intrathecal space or ependyma of said mammal.

12. The use according to any one of Claims 1-10, wherein the medicament is to be administered to the cerebral spinal fluid (CSF) of said mammal.

13. The use according to any one of Claims 1-10, wherein the medicament is to be administered to ependymal cells or a pial cell, endothelial cell, or meningeal cell of said mammal with said AAV particles.

14. The use according to any one of Claims 1-13, wherein cells transduced with said AAV particles express and secrete said polypeptide into the CSF of said mammal.

15. The use according to any one of Claims 1-14, wherein said mammal is a non-rodent mammal.

16. The use according to Claim 15, wherein said non-rodent mammal is a primate, horse, sheep, goat, pig, human, or dog.

17. The use according to Claim 16, wherein said human is a child.

18. The use according to Claim 17, wherein said child is from about 1 to about 4 years of age.

19. The use according to any one of Claims 1-18, wherein said LSD is infantile or late infantile ceroid lipofuscinoses (LINCL), neuronopathic Gaucher, Juvenile Batten, Fabry, MLD, Sanfilippo A, Hunter, Krabbe, Morquio, Pompe, Niemann-Pick C, Tay-Sachs, Hurler (MPS-I H), Sanfilippo B, Maroteaux-Lamy, Niemann-Pick A, Cystinosis, Hurler-Scheie (MPS-I H/S), Sly Syndrome (MPS VII), Scheie (MPS-I S), Infantile Batten, GM1 Gangliosidosis, Mucolipidosis type II/III, or Sandhoff disease.

20. The use according to any one of Claims 1-19, wherein the medicament is to be administered to by injection into a tissue or fluid of the brain or spinal cord of said mammal.

21. The use according to any one of Claims 1-19, wherein the medicament is to be administered to by injection into cerebral spinal fluid of said mammal.

22. The use according to any one of Claims 1-21, wherein said AAV particles transduce ependymal cells of said mammal.

23. The use according to any one of Claims 1-22, wherein onset of a symptom associated with said LSD is delayed by 5-10, 10-25, 25-50 or 50-100 days after the administration of said first immunosuppressive agent and second immunosuppressive agent, compared to the administration of said second immunosuppressive agent without the prior administration of said first immunosuppressive agent.

24. The use according to Claim 23, wherein said symptom is selected from the group consisting of proionceptive response, nystagmus, menace, pupillary light reflex, cerebellar ataxia and intention tremor.

25. The use according to any one of Claims 1-19, wherein onset of a loss of cognitive function associated with said LSD is delayed by 5–10, 10–25, 25–50 or 50–100 days after the administration of said first immunosuppressive agent and second immunosuppressive agent, compared to the administration of said second immunosuppressive agent without the prior administration of said first immunosuppressive agent.

26. The use according to any one of Claims 1-25, wherein the lifespan of a mammal having said LSD is extended by 5–10, 10–25, 25–50 or 50–100 days after the administration of said first immunosuppressive agent and second immunosuppressive agent are administered, compared to the administration of said second immunosuppressive agent without the prior administration of said first immunosuppressive agent.

27. The use according to any one of Claims 5-26, wherein the dose of said cyclosporine is to be administered at a dosage of about 5–20 mg/kg twice a day for a period of at least 3 months, or the dose of said cyclosporine to be administered is reduced after a 1–2 months after the administration of the medicament.

28. The use according to any one of Claims 6-27, wherein said mycophenolate or a derivative thereof is to be administered at a dosage of about 5–20 mg/kg a day.

29. The use according to any one of Claims 1-28, wherein the medicament is to be administered at a dose of about 1×10^{8} to about 1×10^{15} vg/kg.

30. The use according to any one of Claims 1-29, wherein neutralizing antibodies are not detected in CSF of said mammal for at least 30, 60, 90, 120, 250 or more days after the administration of the medicament.

31. The use according to any one of Claims 1-30, wherein said polypeptide is expressed in the spleen, cerebellum, or heart of said mammal.

32. The use according to any one of Claims 1-31, wherein one or more of said ITRs or said AAV particles is/are selected from the group consisting of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV-rh74, AAV-rh10 and AAV-2i8 ITR or particles respectively.

33. The use according to any one of Claims 1-32, wherein the nucleic acid encodes:
    a) mammalian TPP1; or
    b) human TPP1; or
    c) a protein with TPP1 activity and having 80% or more identity to human TPP1 set forth as SEQ ID NO:5; or
    d) human TPP1 set forth as SEQ ID NO:5.

34. The use according to any one of Claims 1-32, wherein the nucleic acid further comprises an expression control element comprising:
    a) a CMV enhancer; or
    b) a beta actin promoter; or
    c) a chicken beta actin promoter; or

d) a sequence having 80% or more identity to SEQ ID NO:9; or

e) SEQ ID NO:9.