

behavior, and language difficulties, accompanied by atrophy of the frontal and temporal lobes. No disease-modifying therapies are available for patients with FTD.

SUMMARY

[0005a] In one aspect, the present disclosure provides the use of a therapeutic combination comprising: a recombinant adeno-associated virus (rAAV) comprising: (i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; and (ii) an adeno-associated virus (AAV) 9 capsid protein; and one or more of the following: (A) sirolimus; (B) methylprednisolone; (C) rituximab; and (D) prednisone in the manufacture of a medicament for treating fronto-temporal dementia with a GRN mutation.

[0005b] In another aspect, the present disclosure provides the use of a therapeutic combination comprising: a recombinant adeno-associated virus (rAAV) comprising: (i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; and (ii) an adeno-associated virus (AAV) 9 capsid protein; and one or more of the following: (A) sirolimus; (B) methylprednisolone; (C) rituximab; and (D) prednisone in the manufacture of a medicament for suppressing an immune response in a subject having or suspected of having fronto-temporal dementia.

[0005c] In another aspect, the present disclosure provides the use of a therapeutic combination comprising: a recombinant adeno-associated virus (rAAV) comprising: (i) a rAAV vector comprising a nucleic acid comprising, in 5' to 3' order: (a) an adeno-associated virus (AAV) 2 ITR; (b) a cytomegalovirus (CMV) enhancer; (c) a chicken beta actin (CBA) promoter; (d) a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; (e) a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE); (f) a Bovine Growth Hormone polyA signal tail; and (g) an AAV2 inverted terminal repeat (ITR); and (ii) an AAV9 capsid protein; and one or more of the following: (A) sirolimus; (B) methylprednisolone; (C) rituximab; and (D) prednisone in the manufacture of a medicament for treating fronto-temporal dementia with a GRN mutation.

[0005d] In another aspect, the present disclosure provides the use of a therapeutic combination comprising: a recombinant adeno-associated virus (rAAV) comprising: (i) a rAAV vector comprising a nucleic acid comprising, in 5' to 3' order: (a) an adeno-associated virus (AAV) 2 ITR; (b) a cytomegalovirus (CMV) enhancer; (c) a chicken beta actin (CBA) promoter; (d) a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; (e) a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE); (f) a Bovine Growth Hormone polyA signal tail; and (g) an AAV2 inverted terminal repeat (ITR); and (ii) an AAV9 capsid protein; and one or more of the following: (A) sirolimus; (B) methylprednisolone; (C) rituximab; and (D)

prednisone in the manufacture of a medicament for suppressing an immune response in a subject having or suspected of having fronto-temporal dementia

[0005e] In another aspect, the present disclosure provides a therapeutic combination of a recombinant adeno-associated virus (rAAV) comprising: (i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; and (ii) an adeno-associated virus (AAV) 9 capsid protein; and one or more of the following: (A) sirolimus; (B) methylprednisolone; (C) rituximab; and (D) prednisone, for use in therapy.

[0006] Provided herein is a method for treating a subject having or suspected of having fronto-temporal dementia with a *GRN* mutation, the method comprising administering to the subject:

a recombinant adeno-associated virus (rAAV) comprising:

(i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; and

(ii) an adeno-associated virus (AAV) 9 capsid protein; and one or more of the following:

(A) sirolimus;

(B) methylprednisolone;

(C) rituximab; and

(D) prednisone.

[0007] Further provided herein is a method for suppressing an immune response in a subject having or suspected of having fronto-temporal dementia with a *GRN* mutation, the method comprising administering to the subject:

a recombinant adeno-associated virus (rAAV) comprising:

(i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; and

(ii) an adeno-associated virus (AAV) 9 capsid protein; and one or more of the following:

(A) sirolimus;

(B) methylprednisolone;

(C) rituximab; and

(D) prednisone.

[0008] In some examples of the methods provided herein, the promoter is a chicken beta actin (CBA) promoter. In some examples of the methods provided herein, the rAAV vector further comprises a cytomegalovirus (CMV) enhancer. In some examples of the methods provided herein, the rAAV vector further comprises a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE). In some examples of the methods provided herein, the rAAV vector further comprises a Bovine Growth Hormone polyA signal tail.

[0009] In some examples of the methods provided herein, the nucleic acid comprises two adeno-associated virus inverted terminal repeats (ITR) sequences flanking the expression construct. In some examples of the methods provided herein, each ITR sequence is an AAV2 ITR sequence.

[0010] In some examples of the methods provided herein, the rAAV vector further comprises a TRY region between the 5' ITR and the expression construct, wherein the TRY region comprises SEQ ID NO: 28.

[0011] Provided herein is a method for treating a subject having or suspected of having fronto-temporal dementia with a *GRN* mutation, the method comprising administering to the subject:

a recombinant adeno-associated virus (rAAV) comprising:

(i) a rAAV vector comprising a nucleic acid comprising, in 5' to 3' order:

(a) an adeno-associated virus (AAV) 2 ITR;

(b) a cytomegalovirus (CMV) enhancer;

(c) a chicken beta actin (CBA) promoter;

(d) a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68;

(e) a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE);

(f) a Bovine Growth Hormone polyA signal tail; and

(g) an AAV2 inverted terminal repeat (ITR); and

(ii) an AAV9 capsid protein; and one or more of the following:

(A) sirolimus;

(B) methylprednisolone;

(C) rituximab; and

(D) prednisone.

[0012] Further provided herein is a method for suppressing an immune response in a subject having or suspected of having fronto-temporal dementia with a *GRN* mutation, the method comprising administering to the subject:

a recombinant adeno-associated virus (rAAV) comprising:

(i) a rAAV vector comprising a nucleic acid comprising, in 5' to 3' order:

(a) an adeno-associated virus (AAV) 2 ITR;

(b) a cytomegalovirus (CMV) enhancer;

(c) a chicken beta actin (CBA) promoter;

(d) a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68;

- (e) a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE);
- (f) a Bovine Growth Hormone polyA signal tail; and
- (g) an AAV2 inverted terminal repeat (ITR); and
- (ii) an AAV9 capsid protein; and one or more of the following:
 - (A) sirolimus;
 - (B) methylprednisolone;
 - (C) rituximab; and
 - (D) prednisone.

[0013] In some examples of the methods provided herein, the rAAV is administered via an injection into the cisterna magna.

[0014] In some examples of the methods provided herein, the rAAV is administered to the subject at a dose ranging from about 1×10^{13} vector genomes (vg) to about 7×10^{14} vg. In some examples of the methods provided herein, the rAAV is administered to the subject at a dose of about 3.5×10^{13} vg, about 7.0×10^{13} vg or about 1.4×10^{14} vg.

[0015] In some examples of the methods provided herein, the rAAV is administered in a formulation comprising about 20 mM Tris, pH 8.0, about 1 mM MgCl₂, about 200 mM NaCl, and about 0.001% w/v poloxamer 188.

[0016] In some examples of the methods provided herein, the methylprednisolone is administered intravenously at a dose of about 1000 mg either one day before or on the same day as administration of the rAAV.

[0017] In some examples of the methods provided herein, the prednisone is administered orally (A) at a dose of about 30 mg per day for 14 days beginning on the day after the administration of about 1000 mg of the methylprednisolone; and (B) tapered during the 7 days following the end of the 14-day period of (A).

[0018] In some examples of the methods provided herein, the rituximab is administered intravenously at a dose of about 1000 mg on any single day between 14 days before and 1 day before administration of the rAAV.

[0019] In some examples of the methods provided herein, the methylprednisolone is administered before the rituximab is administered. In some examples of the methods provided herein, the methylprednisolone is administered at least about 30 minutes before the rituximab is administered. In some examples of the methods provided herein, the methylprednisolone and the rituximab are both administered the day before administration of the rAAV; and the methylprednisolone is administered at least about 30 minutes before the rituximab is administered. In some examples of the methods provided herein, the rituximab is administered on any single

day between 14 days before and 2 days before administration of the rAAV; and the methylprednisolone is administered intravenously at a dose of about 100 mg at least about 30 minutes before the rituximab is administered on the same day as the rituximab is administered.

[0020] In some examples of the methods provided herein, the sirolimus is administered orally (A) as a single dose of about 6 mg three days, two days or one day before administration of the rAAV; and (B) at a dose of about 2 mg per day to maintain serum trough levels of from about 4 ng/ml to about 9 ng/mL for about 90 days after administration of the rAAV; wherein the first dose of about 2 mg per day of the sirolimus is administered the day after the single dose of about 6 mg of the sirolimus. In some examples of the methods provided herein, the sirolimus administration is tapered during the 15 days to 30 days following the end of the 90-day period after administration of the rAAV.

[0021] In some examples of the methods provided herein, the method comprises:

- (i) administering the methylprednisolone intravenously at a dose of about 1000 mg;
- (ii) administering the rituximab intravenously at a dose of about 1000 mg about 30 minutes after the methylprednisolone administration of step (i);
- (iii) administering the rAAV via an injection into the cisterna magna the day after the methylprednisolone administration of step (i);
- (iv) administering the prednisone orally at a dose of about 30 mg per day for 14 days beginning on the day after the methylprednisolone administration of step (i) and
- (v) tapering administration of the prednisone during the 7 days following the end of the 14-day period of step (iv);
- (vi) administering the sirolimus orally as a single dose of about 6 mg three days, two days or one day before the rAAV administration of step (iii);
- (vii) administering the sirolimus orally at a dose of about 2 mg per day to maintain serum trough levels of from about 4 ng/ml to about 9 ng/mL for about 90 days after the rAAV administration of step (iii); wherein the first dose of about 2 mg per day of the sirolimus is administered the day after the single dose of about 6 mg of the sirolimus; and
- (viii) tapering administration of the sirolimus during the 15 days to 30 days following the end of the 90-day period of step (vii).

[0022] In some examples of the methods provided herein, the method comprises:

- (i) administering the methylprednisolone intravenously at a dose of about 100 mg on any single day between 14 days before and 2 days before the rAAV administration of step (iv);
- (ii) administering the rituximab intravenously at a dose of about 1000 mg about 30 minutes after the methylprednisolone administration of step (i);

- (iii) administering the methylprednisolone intravenously at a dose of about 1000 mg either one day before or on the same day as the rAAV administration of step (iv);
- (iv) administering the rAAV via an injection into the cisterna magna;
- (v) administering the prednisone orally at a dose of about 30 mg per day for 14 days beginning on the day after the methylprednisolone administration of step (iii) and
- (vi) tapering administration of the prednisone during the 7 days following the end of the 14-day period of step (v);
- (vii) administering the sirolimus orally as a single dose of about 6 mg three days, two days or one day before the rAAV administration of step (iv);
- (viii) administering the sirolimus orally at a dose of about 2 mg per day to maintain serum trough levels of from about 4 ng/ml to about 9 ng/mL for about 90 days after the rAAV administration of step (iv); wherein the first dose of about 2 mg per day of the sirolimus is administered the day after the single dose of about 6 mg of the sirolimus; and
- (ix) tapering administration of the sirolimus during the 15 days to 30 days following the end of the 90-day period of step (viii).

[0023] In some examples of the methods provided herein, the immune response is an immune response to the rAAV. In some examples of the methods provided herein, the immune response is a T cell response. In some examples of the methods provided herein, the immune response is a B cell response. In some examples of the methods provided herein, the immune response is an antibody response. In some examples of the methods provided herein, the immune response is pleocytosis. In some examples of the methods provided herein, the pleocytosis is cerebrospinal fluid (CSF) pleocytosis. In some examples of the methods provided herein, the immune response is an abnormal level of CSF protein.

[0024] In some examples of the methods provided herein, an additional immunosuppressant that is not sirolimus, methylprednisolone, rituximab or prednisone is further administered to the subject.

[0025] Provided herein is a therapeutic combination of a recombinant adeno-associated virus (rAAV) comprising:

- (i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; and
- (ii) an adeno-associated virus (AAV) 9 capsid protein; and one or more of the following:
 - (A) sirolimus;
 - (B) methylprednisolone;

(C) rituximab; and

(D) prednisone,

for use in a method of treating fronto-temporal dementia with a *GRN* mutation in a subject.

[0026] Further provided herein is a therapeutic combination of

a recombinant adeno-associated virus (rAAV) comprising:

(i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; and

(ii) an adeno-associated virus (AAV) 9 capsid protein; and one or more of the following:

(A) sirolimus;

(B) methylprednisolone;

(C) rituximab; and

(D) prednisone,

for use in a method of suppressing an immune response in a subject having or suspected of having fronto-temporal dementia with a *GRN* mutation.

[0027] In some examples, a therapeutic combination provided herein comprises from about 1×10^{13} vg to about 7×10^{14} vg of the rAAV. In some examples, a therapeutic combination provided herein comprises about 3.5×10^{13} vg, about 7.0×10^{13} vg or about 1.4×10^{14} vg of the rAAV.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] FIG. 1 is a schematic depicting one embodiment of a vector comprising an expression construct encoding Gcase (*e.g.*, *GBA1* or a portion thereof).

[0029] FIG. 2 is a schematic depicting one embodiment of a vector comprising an expression construct encoding Gcase (*e.g.*, *GBA1* or a portion thereof) and LIMP2 (SCARB2) or a portion thereof. The coding sequences of Gcase and LIMP2 are separated by an internal ribosomal entry site (IRES).

[0030] FIG. 3 is a schematic depicting one embodiment of a vector comprising an expression construct encoding Gcase (*e.g.*, *GBA1* or a portion thereof) and LIMP2 (SCARB2) or a portion thereof. Expression of the coding sequences of Gcase and LIMP2 are each driven by a separate promoter.

[0031] FIG. 4 is a schematic depicting one embodiment of a vector comprising an expression construct encoding Gcase (*e.g.*, *GBA1* or a portion thereof), LIMP2 (SCARB2) or a portion thereof, and an interfering RNA for α -Syn.

CLAIMS

1. Use of a therapeutic combination comprising:
a recombinant adeno-associated virus (rAAV) comprising:
 - (i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; and
 - (ii) an adeno-associated virus (AAV) 9 capsid protein; and one or more of the following:
 - (A) sirolimus;
 - (B) methylprednisolone;
 - (C) rituximab; and
 - (D) prednisonein the manufacture of a medicament for treating fronto-temporal dementia with a *GRN* mutation.
2. Use of a therapeutic combination comprising:
a recombinant adeno-associated virus (rAAV) comprising:
 - (i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; and
 - (ii) an adeno-associated virus (AAV) 9 capsid protein; and one or more of the following:
 - (A) sirolimus;
 - (B) methylprednisolone;
 - (C) rituximab; and
 - (D) prednisonein the manufacture of a medicament for suppressing an immune response in a subject having or suspected of having fronto-temporal dementia.
3. The use of claim 1 or 2, wherein the rAAV is to be administered to the subject at a dose ranging from 1×10^{13} vector genomes (vg) to 7×10^{14} vg.

4. The use of claim 1 or 2, wherein the rAAV is to be administered to the subject at a dose of about 3.5×10^{13} vg, about 7.0×10^{13} vg or about 1.4×10^{14} vg.
5. The use of any one of claims 1-4, wherein the rAAV is to be administered via an injection into the cisterna magna.
6. The use of any one of claims 1-5, wherein the promoter is a chicken beta actin (CBA) promoter.
7. The use of any one of claims 1-6, wherein the rAAV vector further comprises a cytomegalovirus (CMV) enhancer.
8. The use of any one of claims 1-7, wherein the rAAV vector further comprises a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE).
9. The use of any one of claims 1-8, wherein the rAAV vector further comprises a Bovine Growth Hormone polyA signal tail.
10. The use of any one of claims 1-9, wherein the nucleic acid comprises two adeno-associated virus inverted terminal repeats (ITR) sequences flanking the expression construct.
11. The use of claim 10, wherein each ITR sequence is an AAV2 ITR sequence.
12. The use of claim 10 or 11, wherein the rAAV vector further comprises a TRY region between the 5' ITR and the expression construct, wherein the TRY region comprises SEQ ID NO: 28.
13. Use of a therapeutic combination comprising:
a recombinant adeno-associated virus (rAAV) comprising:
 - (i) a rAAV vector comprising a nucleic acid comprising, in 5' to 3' order:
 - (a) an adeno-associated virus (AAV) 2 ITR;
 - (b) a cytomegalovirus (CMV) enhancer;
 - (c) a chicken beta actin (CBA) promoter;
 - (d) a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68;

- (e) a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE);
- (f) a Bovine Growth Hormone polyA signal tail; and
- (g) an AAV2 inverted terminal repeat (ITR); and
- (ii) an AAV9 capsid protein; and one or more of the following:

- (A) sirolimus;
- (B) methylprednisolone;
- (C) rituximab; and
- (D) prednisone

in the manufacture of a medicament for treating fronto-temporal dementia with a *GRN* mutation.

14. Use of a therapeutic combination comprising:

a recombinant adeno-associated virus (rAAV) comprising:

- (i) a rAAV vector comprising a nucleic acid comprising, in 5' to 3' order:
 - (a) an adeno-associated virus (AAV) 2 ITR;
 - (b) a cytomegalovirus (CMV) enhancer;
 - (c) a chicken beta actin (CBA) promoter;
 - (d) a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68;
 - (e) a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE);
 - (f) a Bovine Growth Hormone polyA signal tail; and
 - (g) an AAV2 inverted terminal repeat (ITR); and
- (ii) an AAV9 capsid protein; and one or more of the following:

- (A) sirolimus;
- (B) methylprednisolone;
- (C) rituximab; and
- (D) prednisone

in the manufacture of a medicament for suppressing an immune response in a subject having or suspected of having fronto-temporal dementia.

15. The use of claim 13 or 14, wherein the rAAV is to be administered to the subject at a dose ranging from 1×10^{13} vg to 7×10^{14} vg.

16. The use of claim 13 or 14, wherein the rAAV is to be administered to the subject at a dose of about 3.5×10^{13} vg, about 7.0×10^{13} vg or about 1.4×10^{14} vg.

17. The use of any one of claims 13-16, wherein the rAAV is to be administered via an injection into the cisterna magna.

18. The use of any one of claims 1-17, wherein the rAAV is to be administered in a formulation comprising about 20 mM Tris, pH 8.0, about 1 mM MgCl₂, about 200 mM NaCl, and about 0.001% w/v poloxamer 188.

19. The use of any one of claims 1-18, wherein the methylprednisolone is to be administered intravenously at a dose of about 1000 mg either one day before or on the same day as administration of the rAAV.

20. The use of any one of claims 1-19, wherein the prednisone is to be administered orally

(A) at a dose of about 30 mg per day for 14 days beginning on the day after the administration of about 1000 mg of the methylprednisolone; and

(B) tapered during the 7 days following the end of the 14-day period of (A).

21. The use of any one of claims 1-20, wherein the rituximab is to be administered intravenously at a dose of about 1000 mg on any single day between 14 days before and 1 day before administration of the rAAV.

22. The use of claim 21, wherein the methylprednisolone is to be administered before the rituximab is administered.

23. The use of claim 22, wherein the methylprednisolone is to be administered at least about 30 minutes before the rituximab is administered.

24. The use of claim 21, wherein the methylprednisolone and the rituximab are both to be administered the day before administration of the rAAV; and wherein the methylprednisolone is to be administered at least about 30 minutes before the rituximab is administered.

25. The use of claim 21, wherein the rituximab is to be administered on any single day between 14 days before and 2 days before administration of the rAAV; and wherein the methylprednisolone is to be administered intravenously at a dose of about 100 mg at least about 30 minutes before the rituximab is administered on the same day as the rituximab is administered.

26. The use of any one of claims 1-25, wherein the sirolimus is to be administered orally

(A) as a single dose of about 6 mg three days, two days or one day before administration of the rAAV; and

(B) at a dose of about 2 mg per day to maintain serum trough levels of from about 4 ng/ml to about 9 ng/mL for about 90 days after administration of the rAAV;

wherein the first dose of about 2 mg per day of the sirolimus is to be administered the day after the single dose of about 6 mg of the sirolimus.

27. The use of claim 26, wherein the sirolimus administration is tapered during the 15 days to 30 days following the end of the 90-day period after administration of the rAAV.

28. The use of any one of claims 1-27, the use comprising:

(i) the methylprednisolone which is to be administered intravenously at a dose of about 1000 mg;

(ii) the rituximab which is to be administered intravenously at a dose of about 1000 mg about 30 minutes after the methylprednisolone administration of step (i);

(iii) the rAAV which is to be administered via an injection into the cisterna magna the day after the methylprednisolone administration of step (i);

(iv) the prednisone which is to be administered orally at a dose of about 30 mg per day for 14 days beginning on the day after the methylprednisolone administration of step (i) and

(v) tapering administration of the prednisone during the 7 days following the end of the 14-day period of step (iv);

(vi) the sirolimus which is to be administered orally as a single dose of about 6 mg three days, two days or one day before the rAAV administration of step (iii);

(vii) the sirolimus which is to be administered orally at a dose of about 2 mg per day to maintain serum trough levels of from 4 ng/ml to 9 ng/mL for about 90 days after the rAAV administration of step (iii);

wherein the first dose of about 2 mg per day of the sirolimus is to be administered the day after the single dose of about 6 mg of the sirolimus; and

(viii) tapering administration of the sirolimus during the 15 days to 30 days following the end of the 90-day period of step (vii).

29. The use of any one of claims 1-27, the use comprising:

(i) the methylprednisolone which is to be administered intravenously at a dose of about 100 mg on any single day between 14 days before and 2 days before the rAAV administration of step (iv);

(ii) the rituximab which is to be administered intravenously at a dose of about 1000 mg about 30 minutes after the methylprednisolone administration of step (i);

(iii) the methylprednisolone which is to be administered intravenously at a dose of about 1000 mg either one day before or on the same day as the rAAV administration of step (iv);

(iv) the rAAV which is to be administered via an injection into the cisterna magna;

(v) the prednisone which is to be administered orally at a dose of about 30 mg per day for 14 days beginning on the day after the methylprednisolone administration of step (iii) and

(vi) tapering administration of the prednisone during the 7 days following the end of the 14-day period of step (v);

(vii) the sirolimus which is to be administered orally as a single dose of about 6 mg three days, two days or one day before the rAAV administration of step (iv);

(viii) the sirolimus which is to be administered orally at a dose of about 2 mg per day to maintain serum trough levels of from 4 ng/ml to 9 ng/mL for about 90 days after the rAAV administration of step (iv);

wherein the first dose of about 2 mg per day of the sirolimus is to be administered the day after the single dose of about 6 mg of the sirolimus; and

(ix) tapering administration of the sirolimus during the 15 days to 30 days following the end of the 90-day period of step (viii).

30. The use of claim 2 or 14, wherein the immune response is an immune response to the rAAV.

31. The use of any one of claims 2, 14 and 30, wherein the immune response is a T cell response.

32. The use of any one of claims 2, 14 and 30, wherein the immune response is a B cell response.

33. The use of any one of claims 2, 14 and 30, wherein the immune response is an antibody response.

34. The use of any one of claims 2, 14 and 30, wherein the immune response is pleocytosis.

35. The use of claim 34, wherein the pleocytosis is cerebrospinal fluid (CSF) pleocytosis.

36. The use of any one of claims 2, 14 and 30, wherein the immune response is an abnormal level of CSF protein.

37. The use of any one of claims 1-36, wherein an additional immunosuppressant that is not sirolimus, methylprednisolone, rituximab or prednisone is to be further administered to the subject.

38. A therapeutic combination of
a recombinant adeno-associated virus (rAAV) comprising:

(i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert encoding a progranulin (PGRN) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 68; and

(ii) an adeno-associated virus (AAV) 9 capsid protein; and one or more of the following:

(A) sirolimus;

(B) methylprednisolone;

(C) rituximab; and

(D) prednisone,

for use in therapy.

39. The therapeutic combination for use of claim 38, wherein the combination comprises from 1×10^{13} vg to 7×10^{14} vg of the rAAV.

40. The therapeutic combination for use of claim 38, wherein the combination comprises about 3.5×10^{13} vg, about 7.0×10^{13} vg or about 1.4×10^{14} vg of the rAAV.