with a single mild mutation in *GBA1* typically have a more benign course. Mutation carriers are also at high risk of other PD-related disorders, including Lewy Body Dementia, characterized by executive dysfunction, psychosis, and a PD-like movement disorder, and multi-system atrophy, with characteristic motor and cognitive impairments. No therapies exist that alter the inexorable course of these disorders and other synucleinopathies.

FIELD

[0006] The disclosure relates to the field of gene therapy and methods of using same.

SUMMARY

[0006a] In one aspect, the present disclosure refers to 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 glucocerebrosidase (Gcase) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Parkinson's disease with a glucocerebrosidase-1 (*GBA1*) mutation.

[0006b] In another aspect, the present disclosure refers to the use of a therapeutic combination comprising: a 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Parkinson's disease with a *GBA1* mutation.

[0006c] In another aspect, the present disclosure refers to the use of a therapeutic combination comprising: a 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 2 Gaucher disease or Type 3 Gaucher disease.

[0006d] In another aspect, the present disclosure refers to the use of a therapeutic combination comprising: a 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 2 Gaucher disease or Type 3 Gaucher disease.

[0006e] In another aspect, the present disclosure refers to the use of a therapeutic combination comprising: a 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 1 Gaucher disease.

[0006f] In another aspect, the present disclosure refers to the use of a therapeutic combination comprising: a 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 1 Gaucher disease.

[0006g] In another aspect, the present disclosure refers to the use of a therapeutic combination comprising: a rAAV comprising: (i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert comprising (a) a Gcase protein coding sequence comprising the nucleotide sequence of SEQ ID NO: 15; and (b) an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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 a synucleinopathy or parkinsonism.

[0006h] In another aspect, the present disclosure refers to the use of a therapeutic combination comprising: a rAAV comprising: (i) a rAAV vector comprising a nucleic acid comprising an expression construct comprising a promoter operably linked to a transgene insert comprising (a) a Gcase protein coding sequence comprising the nucleotide sequence of SEQ ID NO: 15; and (b) an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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 a synucleinopathy or parkinsonism.

[0007] Provided herein is a method for treating a subject having or suspected of having Parkinson's disease with a glucocerebrosidase-1 (*GBA1*) 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 glucocerebrosidase (Gcase) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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] Further provided herein is a method for suppressing an immune response in a subject having or suspected of having Parkinson's disease with a glucocerebrosidase-1 (*GBA1*) 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 glucocerebrosidase (Gcase) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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.

[0009] In some ~~embodiment~~examples of the methods provided herein, the rAAV is administered to the subject at a dose ranging from about 5×10^{13} vector genomes (vg) to about 5×10^{14} vg. In some ~~embodiment~~examples of the methods provided herein, the rAAV is administered to the subject at a dose of about 1.4×10^{14} vg or about 2.8×10^{14} vg.

[0010] Provided herein is a method for treating a subject having or suspected of having Type 2 Gaucher disease or Type 3 Gaucher disease, 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 glucocerebrosidase (Gcase) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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.

[0011] Further provided herein is a method for suppressing an immune response in a subject having or suspected of having Type 2 Gaucher disease or Type 3 Gaucher disease, 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 glucocerebrosidase (Gcase) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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.

[0012] In some ~~embodiment~~examples of the methods provided herein, the rAAV is administered to the subject at a dose ranging from about 5×10^{10} vg/g brain to about 5×10^{11} vg/g brain. In some ~~embodiment~~examples of the methods provided herein, the rAAV is administered to the subject at a dose of about 1.3×10^{11} vg/g brain.

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

[0014] Provided herein is a method for treating a subject having or suspected of having Type 1 Gaucher disease, 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 glucocerebrosidase (Gcase) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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.

[0015] Further provided herein is a method for suppressing an immune response in a subject having or suspected of having Type 1 Gaucher disease, 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 glucocerebrosidase (Gcase) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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.

[0016] In some ~~embodiment~~examples of the methods provided herein, the rAAV is administered to the subject at a dose ranging from about 5×10^{13} vg to about 5×10^{14} vg. In some ~~embodiment~~examples of the methods provided herein, the rAAV is administered intravenously.

[0017] Further provided herein is a method for treating a subject having or suspected of having a synucleinopathy or parkinsonism, 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 transgene comprising

(a) a Gcase protein coding sequence comprising the nucleotide sequence of SEQ ID NO: 15; and

[0020] Further provided herein is a method for suppressing an immune response in a subject having or suspected of having a synucleinopathy or parkinsonism, 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 transgene comprising an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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.

[0021] In some ~~embodiment~~examples of the methods provided herein, the promoter is a chicken beta actin (CBA) promoter. In some ~~embodiment~~examples of the methods provided herein, the rAAV vector further comprises a cytomegalovirus (CMV) enhancer. In some ~~embodiment~~examples of the methods provided herein, the rAAV vector further comprises a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE). In some ~~embodiment~~examples of the methods provided herein, the rAAV vector further comprises a Bovine Growth Hormone polyA signal tail.

[0022] In some ~~embodiment~~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 ~~embodiment~~examples of the methods provided herein, each ITR sequence is an AAV2 ITR sequence. In some ~~embodiment~~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.

[0023] Provided herein is a method for treating a subject having or suspected of having Parkinson's disease with a *GBA1* 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15;

(D) prednisone,

wherein the rAAV is administered to the subject at a dose ranging from about 5×10^{10} vg/g brain to about 5×10^{11} vg/g brain.

[0027] In some ~~embodiment~~examples of the methods provided herein, the rAAV is administered via an injection into the cisterna magna.

[0028] In some ~~embodiment~~examples of the methods provided herein, the rAAV is administered in a formulation comprising about 20 mM Tris, pH 8.0, about 1 mM $MgCl_2$, about 200 mM NaCl, and about 0.001% w/v poloxamer 188.

[0029] In some ~~embodiment~~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.

[0030] In some ~~embodiment~~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).

[0031] In some ~~embodiment~~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. In some ~~embodiment~~examples of the methods provided herein, the methylprednisolone is administered before the rituximab is administered. In some ~~embodiment~~examples of the methods provided herein, the methylprednisolone is administered at least about 30 minutes before the rituximab is administered.

[0032] In some ~~embodiment~~examples of the methods provided herein, the methylprednisolone and the rituximab are both administered the day before administration of the rAAV; and wherein the methylprednisolone is administered at least about 30 minutes before the rituximab is administered.

[0033] In some ~~embodiment~~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 wherein 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.

[0034] In some ~~embodiment~~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.

[0035] In some ~~embodiment~~examples of the methods provided herein, the sirolimus is administered orally (A) at two doses of about 1.0 mg/m^2 each, wherein the two doses are administered 1 day or 2 days before administration of the rAAV, wherein the first dose is administered in the morning and the second dose is administered in the evening of the day on which the two doses are administered; and (B) at a dose of from about 0.6 mg/m^2/day to about 1.0 mg/m^2/day to maintain serum trough levels of from about 2 ng/mL to about 8 ng/mL for about 3 months after administration of the rAAV.

[0036] In some ~~embodiment~~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.

[0037] In some ~~embodiment~~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).

[0038] In some ~~embodiment~~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).

[0039] In some ~~embodiment~~examples of the methods provided herein, the immune response is an immune response to the rAAV. In some ~~embodiment~~examples of the methods provided herein, the immune response is a T cell response. In some ~~embodiment~~examples of the methods provided herein, the immune response is a B cell response. In some ~~embodiment~~examples of the methods provided herein, the immune response is an antibody response. In some ~~embodiment~~examples of the methods provided herein, the immune response is pleocytosis. In some ~~embodiment~~examples of the methods provided herein, the pleocytosis is cerebrospinal fluid (CSF) pleocytosis. In some ~~embodiment~~examples of the methods provided herein, the immune response is an abnormal level of CSF protein.

[0040] In some ~~embodiment~~examples of the methods provided herein, an additional immunosuppressant that is not sirolimus, methylprednisolone, rituximab or prednisone is further administered to the subject.

[0041] In some ~~embodiment~~examples of the methods provided herein, the synucleinopathy or parkinsonism is multiple system atrophy, Parkinson's disease, Parkinson's disease with *GBA1* mutation, Lewy body disease, dementia with Lewy bodies, dementia with Lewy bodies with *GBA1* mutation, progressive supranuclear palsy, or corticobasal syndrome.

[0042] 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 1 Gaucher disease, Type 2 Gaucher disease, Type 3 Gaucher disease or Parkinson's disease with a *GBA1* mutation in a subject.

[0043] Also 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 1 Gaucher disease, Type 2 Gaucher disease, Type 3 Gaucher disease or Parkinson's disease with a *GBA1* mutation.

[0044] In some ~~embodiment~~examples, a therapeutic combination comprises from about 5×10^{13} vg to about 5×10^{14} vg of the rAAV. In some ~~embodiment~~examples, a therapeutic combination comprises about 1.4×10^{14} vg or about 2.8×10^{14} vg of the rAAV.

[0045] 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 comprising:

(a) a Gcase protein coding sequence comprising the nucleotide sequence of SEQ ID NO: 15; and

CLAIMS

1. ~~A method for treating a subject having or suspected of having Parkinson's disease with a glucocerebrosidase 1 (*GBA1*) mutation, the method comprising administering to the subject:~~

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 glucocerebrosidase (Gcase) protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Parkinson's disease with a glucocerebrosidase-1 (*GBA1*) mutation.

2. ~~A method for suppressing an immune response in a subject having or suspected of having Parkinson's disease with a glucocerebrosidase 1 (*GBA1*) mutation, the method comprising administering to the subject:~~

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 ~~glucocerebrosidase (~~Gcase~~)~~ protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Parkinson's disease with a *GBA1* mutation.

3. The ~~method~~ use of claim 1 or 2, wherein the combination comprises ~~rAAV is administered to the subject at a dose ranging~~ from ~~about~~ 5×10^{13} vector genomes (vg) to ~~about~~ 5×10^{14} vg of the rAAV.

4. The ~~method~~ use of claim 1 or 2, wherein the combination comprises ~~rAAV is administered to the subject at a dose of about~~ 1.4×10^{14} vg or ~~about~~ 2.8×10^{14} vg of the rAAV.

5. ~~A method for treating a subject having or suspected of having Type 2 Gaucher disease or Type 3 Gaucher disease, the method comprising administering to the subject:~~

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 ~~glucocerebrosidase (~~Gcase~~)~~ protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 2 Gaucher disease or Type 3 Gaucher disease.

6. ~~A method for suppressing an immune response in a subject having or suspected of having Type 2 Gaucher disease or Type 3 Gaucher disease, the method comprising administering to the subject:~~

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 ~~glucocerebrosidase (~~Gcase~~)~~ protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 2 Gaucher disease or Type 3 Gaucher disease.

7. The ~~method~~ use of claim 5 or 6, wherein the combination comprises ~~rAAV is administered to the subject at~~ a dose ranging from ~~about~~ 5×10^{10} vg/g brain to ~~about~~ 5×10^{11} vg/g brain of the rAAV.

8. The ~~method~~ use of claim 5 or 6, wherein the combination comprises ~~rAAV is administered to the subject at~~ a dose of about 1.3×10^{11} vg/g brain of the rAAV.

9. The ~~method~~ use of any one of claims 1-8, wherein the rAAV is to be administered via an injection into the cisterna magna.

10. ~~A method for treating a subject having or suspected of having Type 1 Gaucher disease, the method comprising administering to the subject:~~

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 ~~glucocerebrosidase (~~Gcase~~)~~ protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 1 Gaucher disease.

11. ~~A method for suppressing an immune response in a subject having or suspected of having Type 1 Gaucher disease, the method comprising administering to the subject:~~

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 ~~glucocerebrosidase (~~Gcase~~)~~ protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 1 Gaucher disease.

12. The ~~method~~ use of claim 10 or 11, wherein the combination comprises ~~rAAV is administered to the subject at a dose ranging~~ from ~~about~~ 5×10^{13} vg to ~~about~~ 5×10^{14} vg of the rAAV.

13. The ~~method~~ use of any one of claims 10-12, wherein the rAAV is to be administered intravenously.

14. ~~A method for treating a subject having or suspected of having a synucleinopathy or parkinsonism, the method comprising administering to the subject:~~

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 comprising

(a) a Gcase protein coding sequence comprising the nucleotide sequence of SEQ ID NO: 15; and

(b) an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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 a synucleinopathy or parkinsonism.

15. ~~A method for suppressing an immune response in a subject having or suspected of having a synucleinopathy or parkinsonism, the method comprising administering to the subject:~~

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 comprising

(a) a Gcase protein coding sequence comprising the nucleotide sequence of SEQ ID NO: 15; and

(b) an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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 a synucleinopathy or parkinsonism.

~~16. A method for treating a subject having or suspected of having a synucleinopathy or parkinsonism, 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 transgene comprising an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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.~~

~~17. A method for suppressing an immune response in a subject having or suspected of having a synucleinopathy or parkinsonism, 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 transgene comprising an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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.~~

~~18~~16. The ~~method~~ use of ~~any one of claims 14-17~~claim 14 or 15, wherein the synucleinopathy or parkinsonism is multiple system atrophy, Parkinson's disease, Parkinson's disease with *GBA1* mutation, Lewy body disease, dementia with Lewy bodies, dementia with Lewy bodies with *GBA1* mutation, progressive supranuclear palsy, or corticobasal syndrome.

~~19~~17. The ~~method~~ use of any one of claims 1-~~18~~16, wherein the promoter is a chicken beta actin (CBA) promoter.

~~20~~18. The ~~method~~ use of any one of claims 1-~~19~~17, wherein the rAAV vector further comprises a cytomegalovirus (CMV) enhancer.

~~21~~19. The ~~method~~ use of any one of claims 1-~~20~~18, wherein the rAAV vector further comprises a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE).

~~22~~20. The ~~method~~ use of any one of claims 1-~~21~~19, wherein the rAAV vector further comprises a Bovine Growth Hormone polyA signal tail.

~~23~~21. The ~~method~~ use of any one of claims 1-~~22~~20, wherein the nucleic acid comprises two adeno-associated virus inverted terminal repeats (ITR) sequences flanking the expression construct, wherein the first ITR sequence is a 5' ITR, and the second ITR sequence is a 3' ITR.

~~24~~22. The ~~method~~ use of claim ~~23~~21, wherein each of the two ITR sequences is an AAV2 ITR sequence.

~~25~~23. The ~~method~~ use of claim ~~23~~ 21 or ~~24~~22, 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.

~~26~~24. The use of any one of claims 1-16 and 23, wherein ~~A method for treating a subject having or suspected of having Parkinson's disease with a *GBA1* mutation, the method comprising administering to the subject:~~

~~a recombinant adeno-associated virus (rAAV) comprising:~~

~~(i) a rAAV vector comprising a~~ the nucleic acid ~~comprising~~comprises, 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~~ the transgene insert ~~encoding a Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15~~;

(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,~~

~~wherein the rAAV is administered to the subject at a dose ranging from about 5×10^{13} vg to about 5×10^{14} vg~~.

~~27. A method for suppressing an immune response in a subject having or suspected of having Parkinson's disease with a *GBA1* 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15;~~

~~(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,~~

~~wherein the rAAV is administered to the subject at a dose ranging from about 5×10^{13} vg to about 5×10^{14} vg.~~

~~28. A method for treating a subject having or suspected of having Type 2 Gaucher disease or Type 3 Gaucher disease, 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15;

(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,

wherein the rAAV is administered to the subject at a dose ranging from about 5×10^{10} vg/g brain to about 5×10^{11} vg/g brain.

29. A method for suppressing an immune response in a subject having or suspected of having Type 2 Gaucher disease or Type 3 Gaucher disease, 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15;

(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,~~

~~wherein the rAAV is administered to the subject at a dose ranging from about 5×10^{10} vg/g brain to about 5×10^{11} vg/g brain.~~

~~30. The method of any one of claims 26-29, wherein the rAAV is administered via an injection into the cisterna magna.~~

~~31~~25. The ~~method~~ use of any one of claims 1-~~30~~24, wherein the rAAV is to be administered in a formulation comprising about 20 mM Tris, pH 8.0, about 1 mM $MgCl_2$, about 200 mM NaCl, and about 0.001% w/v poloxamer 188.

~~32~~26. The ~~method~~ use of any one of claims 1-~~31~~25, 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.

~~33~~27. The ~~method~~ use of any one of claims 1-~~32~~26, 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).

~~34~~28. The ~~method~~ use of any one of claims 1-~~33~~27, 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.

~~35~~29. The ~~method~~ use of claim ~~34~~28, wherein the methylprednisolone is to be administered before the rituximab is administered.

~~36~~30. The ~~method~~ use of claim 29~~35~~, wherein the methylprednisolone is to be administered at least about 30 minutes before the rituximab is administered.

~~37~~31. The ~~method~~ use of claim 28~~34~~, 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.

~~38~~32. The use ~~method~~ of claim ~~34~~28, 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 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.

~~39~~33. The use ~~method~~ of any one of claims 1-~~38~~32, 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.

~~40~~34. The use ~~method~~ of any one of claims 5-13~~,~~ ~~28~~ and 24~~29~~, wherein the sirolimus is to be administered orally

(A) at two doses of about 1.0 mg/m^2 each, wherein the two doses are to be administered 1 day or -2 days before administration of the rAAV, wherein the first dose is to be administered in the morning and the second dose is to be administered in the evening of the day on which the two doses are administered; and

(B) at a dose of from ~~about~~ 0.6 mg/m^2/day to ~~about~~ 1.0 mg/m^2/day to maintain serum trough levels of from ~~about~~ 2 ng/mL to ~~about~~ 8 ng/mL for about 3 months after administration of the rAAV.

~~41~~35. The use ~~method~~ of claim ~~39~~ 33 or ~~40~~34, 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.

~~42~~36. The use ~~method~~ of any one of claims 1-~~39~~ 33 and ~~41~~35, ~~the method~~ comprising:

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

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

(iv) ~~administering~~ 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) ~~administering~~ 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) ~~administering~~ the sirolimus which is to be administered 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 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).

~~43~~37. The use ~~method~~ of any one of claims 1-~~39~~ 33 and ~~41~~35, ~~the method~~ comprising:

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

(v) ~~administering~~ 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) ~~administering~~ 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) ~~administering~~ the sirolimus which is to be administered 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~~ 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).

~~44~~38. The use ~~method~~ of any one of claims 2, 6, 11, 15, ~~17, 27~~ and ~~29~~24, wherein the immune response is an immune response to the rAAV.

~~45~~39. The ~~method~~ use of any one of claims 2, 6, 11, 15, ~~17, 27, 29~~24, and 38~~44~~, wherein the immune response is a T cell response, a B cell response, an antibody response, pleocytosis, or an abnormal level of cerebrospinal fluid (CSF) protein.

~~46. The method of any one of claims 2, 6, 11, 15, 17, 27, 29 and 44, wherein the immune response is a B cell response.~~

~~47. The method of any one of claims 2, 6, 11, 15, 17, 27, 29 and 44, wherein the immune response is an antibody response.~~

~~48. The method of any one of claims 2, 6, 11, 15, 17, 27, 29 and 44, wherein the immune response is pleocytosis.~~

~~49~~40. The ~~method~~ use of claim 39~~48~~, wherein the pleocytosis is ~~cerebrospinal fluid (~~CSF~~)~~ pleocytosis.

~~50. The method of any one of claims 2, 6, 11, 15, 17, 27, 29 and 44, wherein the immune response is an abnormal level of CSF protein.~~

~~51~~41. The ~~method~~ use of any one of claims 1-~~50~~40, wherein the therapeutic combination comprises an additional immunosuppressant that is not sirolimus, methylprednisolone, rituximab or prednisone ~~is further administered to the subject~~.

~~52. 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 1 Gaucher disease, Type 2 Gaucher disease, Type 3 Gaucher disease or Parkinson's disease with a *GBA1* mutation in a subject.~~

~~53. 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 Gcase protein, wherein the transgene insert comprises the nucleotide sequence of SEQ ID NO: 15; 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 Type 1 Gaucher disease, Type 2 Gaucher disease, Type 3 Gaucher disease or Parkinson's disease with a *GBA1* mutation.~~

~~54. The therapeutic combination for use of claim 52 or 53, wherein the combination comprises from about 5×10^{13} vg to about 5×10^{14} vg of the rAAV.~~

~~55. The therapeutic combination for use of claim 52 or 53, wherein the combination comprises about 1.4×10^{14} vg or about 2.8×10^{14} vg of the rAAV.~~

~~56. 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 comprising:~~

~~(a) a Gcase protein coding sequence comprising the nucleotide sequence of SEQ ID NO: 15; and~~

~~(b) an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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 a synucleinopathy or parkinsonism in a subject.~~

~~57. 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 comprising:~~

~~(a) a Gcase protein coding sequence comprising the nucleotide sequence of SEQ ID NO: 15; and~~

~~(b) an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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 a synucleinopathy or parkinsonism.

58. 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 comprising an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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 a synucleinopathy or parkinsonism in a subject.

59. 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 comprising an inhibitory nucleic acid coding sequence comprising the nucleotide sequence of SEQ ID NO: 20; 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 a synucleinopathy or parkinsonism.~~