stages of PD, a patient's on-time is about 16 hours with the administration of L-Dopa. However, as the disease progresses, the amount of on-time gradually decreases even with larger doses of medication. Additionally, the side effects associated with long-term administration of L-dopa can be quite severe, and include mental changes such as depression, hallucination, mania, delusions, agitations, and excessive sleeping. Administration of L-dopa can also have a detrimental effect in patients with cardiovascular or pulmonary, renal, hepatic or endocrinal diseases. Some of the side effects associated with long-term administration of L-dopa can be mitigated by co-administration of N-amino-α-methyl-3-hydroxy-L-tyrosine monohydrate, an inhibitor of aromatic amino acid decarboxylase (AADC), an enzyme that decarboxylates L-Dopa to dopamine. However, this drug combination still may cause nausea, dyskinesia, psychosis, and hypotension.

[0009] One of the chief barriers of treating PD with small molecule drugs is that most systematically administered drugs are not able to cross the blood brain barrier. One approach has focused on increasing the lipid content of polypeptides to facilitate their transport across the blood brain barrier. Another approach has concentrated on enhancing the permeability of capillaries in the brain. However, none of these approaches has solved the problem of crossing blood-brain barrier. Other approaches of treating PD, such as transplanting engineered cells that produce dopamine to the brain and deep brain stimulations, are characterized by severe side effects, such as high mortality rate, an increased chance of severe infection, and potential brain damage. More importantly, none of the available drugs address the underlying cause of PD or provide PD patients more on-time without serious side effects.

[0010] In view of the current limitations in the treatment of PD, there remains an unmet need for (1) a non-transient treatment of PD, particularly in PD patients who are not responding to the current standard of care, (2) the non-transient treatment that effectively prolongs on-time in PD patients without causing significant side effects, and (3) a reliable method for identifying patient populations who will be most receptive to the non-transient treatment of PD.

SUMMARY

[0011] In one aspect, the present disclosure provides a use of a first vector comprising a nucleic acid encoding GAD-65 and a second vector comprising a nucleic acid encoding GAD-67 in the manufacture of a medicament for treating Parkinson's disease (PD) in a subject in need thereof, wherein the use comprises that the subject is identified as having less than 8 hours of on-time per day; wherein the medicament is to be administered to the subthalamic nucleus of the subject,

and wherein the subject's on-time is increased after administration of the medicament to the subthalamic nucleus of the subject.

[0011a] In one example, the disclosure provides a method of treating PD in a subject in need thereof, the method comprising: (a) identifying a subject having less than about 10 hours, and preferably less than about 8 hours, of on-time per day; and (b) administering to the subject a composition comprising a therapeutically effective amount of one or more vectors to the

We Claim:

1. Use of a first vector comprising a nucleic acid encoding GAD-65 and a second vector comprising a nucleic acid encoding GAD-67 in the manufacture of a medicament for treating Parkinson's disease (PD) in a subject in need thereof, wherein the use comprises that

   the subject is identified as having less than 8 hours of on-time per day; wherein

   the medicament is to be administered to the subthalamic nucleus of the subject, and wherein the subject's on-time is increased after administration of the medicament to the subthalamic nucleus of the subject.

2. The use of claim 1, wherein the subject scores 30 or more on part III of the UPDRS in the off-medication state before the administration.

3. The use of claim 1 or 2, wherein the medicament is to be administered bilaterally to the subthalamic nucleus of the subject.

4. The use of any one of claims 1-3, wherein the medicament comprises about a 1:1 ratio of the vector encoding GAD-65 and the vector encoding GAD-67.

5. The use of any one of claims 1-4, wherein the vectors are viral vectors.

6. The use of claim 5, wherein the viral vectors are adeno-associated virus (AAV) vectors.

7. The use of claims 5 or 6, wherein the medicament comprises at least $1x10^{11}$ vector genomes/ml.

8. The use of claims 5 or 6, wherein the medicament comprises at least $3x10^{11}$ vector genomes/ml.

9. The use of claims 5 or 6, wherein the medicament comprises at least $1x10^{12}$ vector genomes/ml.

10. The use of any one of claims 1-9, wherein the subject shows an increase of at least 40% in on-time 12 months after the administration.

11. The use of any one of claims 1-9, wherein the subject shows an increase of at least 30% in on-time 12 months after the administration.

12. The use of any one of claims 1-9, wherein the subject shows an increase of at least 20% in on-time 12 months after the administration.