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 ~~OF THE INVENTION~~

[0011] In one aspect, the present disclosure provides a use of one or more vectors in the manufacture of a medicament for treating Parkinson's disease (PD) in a subject in need thereof, wherein the use comprises that a subject is identified having less than 10 hours of on-time per day before administration of the medicament to the subthalamic nucleus of the patient, wherein each

vector comprises a nucleic acid sequence encoding glutamic acid decarboxylase (GAD) and wherein the subject's on-time is increased after administration.

[0011a] In one ~~aspect~~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

subthalamic nucleus of the patient, wherein each vector comprises a nucleic acid sequence encoding glutamic acid decarboxylase (GAD) and wherein the subject's on-time is increased. In one ~~embodiment~~example, the one or more vectors are introduced bilaterally to the subthalamic nucleus of the patient.

[0012] In one ~~embodiment~~example, the disclosure provides a method of treating PD in a subject in need thereof, where the subjects has less than 10 hours, less than 9 hours, less than 8 hours, less than 7 hours, less than 6 hours, less than 5 hours, or less than 4 hours of on-time per day before treatment.

[0013] In one ~~embodiment~~example, the disclosure provides a method of treating PD in a subject in need thereof, wherein the one or more vectors comprises a nucleic acid sequence encoding GAD-65 and/or a nucleic acid sequence encoding GAD-67. In ~~embodiment~~examples, two vectors are administered, wherein one vector comprises a nucleic acid encoding GAD-65 and the other vector comprises a nucleic acid encoding GAD-67. In further ~~embodiment~~examples, the vector comprising a nucleic acid encoding GAD-65 and the vector comprising a nucleic acid encoding GAD-67 are administered in a ratio of about 1:2 to about 2:1, preferably about 1:1.

[0014] In one ~~embodiment~~example, the disclosure provides a method of treating PD in a subject in need thereof, wherein the one or more vectors used in the method comprises a nucleic acid sequence encoding GAD-65 and encoding GAD-67. In one ~~embodiment~~example, the amino acid sequence of human GAD-65 is provided as SEQ ID NO: 1 (Genbank Accession No. NM000818; M81882). In another ~~embodiment~~example, the amino acid sequence of human GAD-65 is provided as SEQ ID NO: 3. In some ~~embodiment~~examples, the nucleic acid sequence encodes a protein that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence of SEQ ID NO: 1 or of SEQ ID NO: 3. In ~~embodiment~~examples, the nucleic acid sequence encoding GAD-65 comprises SEQ ID NO: 2 or SEQ ID NO: 4. In some ~~embodiment~~examples, the nucleic acid sequence encoding GAD-65 comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence of SEQ ID NO: 2 or of SEQ ID NO: 4. In one ~~embodiment~~example, the amino acid sequence of human GAD-67 is provided as SEQ ID NO:5 (Accession No. M81883). In another ~~embodiment~~example, the amino acid sequence of human GAD-67 is provided as SEQ ID NO: 7. In some ~~embodiment~~examples, the nucleic acid sequence encodes a protein that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence of SEQ ID NO: 5 or SEQ ID NO: 7. In ~~embodiment~~examples, the nucleic acid sequence encoding GAD-67 comprises SEQ ID NO: 6. In

~~embodiment~~examples, the nucleic acid sequence encoding GAD-67 comprises SEQ ID NO: 8. In ~~embodiment~~examples, the nucleic acid sequence encoding GAD-67 comprises a sequence that is at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence of SEQ ID NO:6 or SEQ ID NO: 8.

[0015] In one ~~embodiment~~example, the disclosure provides a method of treating PD in a subject in need thereof, where one or more vectors used in the method are viral vectors. In one ~~embodiment~~example, the disclosure provides a method of treating PD in a subject in need thereof, where the viral vectors disclosed are adeno-associated virus (AAV) vectors.

[0016] In one ~~embodiment~~example, the disclosure provides a method of treating PD in a subject in need thereof, where the composition comprises at least $1x10^{11}$ vector genomes/ml. In one ~~embodiment~~example, the disclosure provides a method of treating PD in a subject in need thereof, where the composition comprises at least $3x10^{11}$ vector genome/ml. In one ~~embodiment~~example, the disclosure provides a method of treating PD in a subject in need thereof, where the composition comprises at least $1x10^{12}$ vector genome/ml.

[0017] In one ~~embodiment~~example, the disclosure provides a method of treating PD in a subject in need thereof, wherein the subject shows an average increase of at least 20%, at least 30%, at least 40% in on-time 12 months post treatment compared to pre-treatment. In ~~embodiment~~examples, the subject has an increase in on-time of about 1, 1.5., 2, 2.5, 3, 3.5, 4, 4.5, or 5 hours 12 months following treatment.

BRIEF DESCRIPTION OF THE FIGURES

[0018] **Figure 1. Increase in "ON" Time Following AAV-GAD Gene Therapy.** Subjects receiving either AAV-GAD (GAD) into the STN or sham surgery (sham) recorded hourly ON and OFF times in a diary throughout each day for two weeks at each of the listed time points (1, 3, 6 and 12 months after surgery). The average daily ON and OFF time over the two week period determined from the diaries were compared with baseline diaries taken within the 30 days prior to surgery in order to determine the change in the number of hours of ON time following surgery. There was an overall difference between groups across the entire 12 month study period by analysis of variance (ANOVA; $p=0.44$). Two-tailed t-tests showed significant increases in ON time at 3 and 12 months following surgery ($p<0.05$) and a strong trend toward significance at 1

We Claim:

1. Use of one or more vectors in the manufacture of a medicament for~~A method of~~ treating Parkinson's disease (PD) in a subject in need thereof, ~~the method comprising~~wherein the use comprises that~~:~~

   ~~(a) identifying~~ a subject is identified having less than 10 hours of on-time per day before administration of the medicament to the subthalamic nucleus of the patient~~; and~~

   ~~(b) administering to the subject a composition comprising a therapeutically effective amount of one or more vectors to the subthalamic nucleus of the patient~~, wherein each vector comprises a nucleic acid sequence encoding glutamic acid decarboxylase (GAD) and wherein the subject's on-time is increased after administration.
2. The ~~method~~ use of claim 1, wherein the subject~~s~~ has less than 8 hours of on-time per day before ~~treatment~~ the administration.
3. The ~~method~~ use of any one of claims 1-2, wherein the subject scores 30 or more on part III of the UPDRS ~~in the off medication state~~before the administration.
4. The ~~method~~ use of any one of claims 1-3, wherein the one or more vectors are to be introduced bilaterally to the subthalamic nucleus of the patient.
5. The ~~method~~ use of any one of claims 1-4, wherein the one or more vectors comprises a nucleic acid sequence encoding GAD-65 and a nucleic acid sequence encoding GAD-67.
6. The ~~method~~ use of claim 5, wherein the composition comprises about a 1:1 ratio of vectors encoding GAD-65 and vectors encoding GAD-67.
7. The ~~method~~ use of any one of claims 1-6, wherein the one or more vectors are viral vectors.
8. The ~~method~~ use of claim 7, wherein the viral vectors are adeno-associated virus (AAV) vectors.
9. The ~~method~~ use of claims 7 or 8, wherein the ~~composition~~ medicament comprises at least $1x10^{11}$ vector genomes/ml.
10. The ~~method~~ use of claims 7 or 8, wherein the medicament~~composition~~ comprises at least $3x10^{11}$ vector genome/ml.
11. The ~~method~~ use of claims 7 or 8, wherein the medicament~~composition~~ comprises at least $1x10^{12}$ vector genome/ml.
12. The ~~method~~ use of any one of claims 1-11, wherein the subject shows an increase of at least 40% in on-time 12 months post ~~treatment~~administration.

13. The ~~method~~ use of any one of claims 1-~~15~~11, wherein the subject shows at least 30% increase in on-time after 12 months of post ~~treatment~~administration.

14. The ~~method~~ use of any one of claims 1-~~15~~11, wherein the subject shows at least 20% increase in on-time after 12 months of post administration~~treatment~~.