that produces a highly active form (therapeutic) of IDUA or IDS where the introduction of, or creation of, a population of these altered cells in a patient will supply that needed protein activity to treat (*e.g.,* reduce or eliminate one or more symptoms) MPS I or MPS II disease.

[0015a] In one aspect, the present invention refers to the use of a promoterless donor vector and an expression vector encoding a pair of zinc finger nucleases (ZFNs) targeted to an endogenous albumin gene in the manufacture of a medicament for reducing or preventing central nervous system (CNS) impairment and reducing dermatan sulfate levels in the CNS in a subject with mucopolysaccharidosis type I (MPS I) or mucopolysaccharidosis type I (MPS II), wherein the use comprises that the promoterless donor vector and the expression vector are to be administered to the subject, wherein the promoterless donor vector comprises a transgene encoding human α-L-iduronidase (hIDUA) for a subject with mucopolysaccharidosis type I (MPS I) or human iduronate-2-sulftase (hIDS) for a subject with mucopolysaccharidosis type II (MPS II), wherein the transgene is integrated into the albumin gene in a liver cell following cleavage of the albumin gene such that the encoded hIDUA or hIDS is expressed and secreted from the liver and further wherein the hIDUA or hIDS secreted from the liver is found in the central nervous system (CNS) of the subject such that the CNS impairment is reduced or prevented and further wherein the subject is to be treated with cyclophosphamide prior to administration of the promoterless donor vector and expression vector.

[0016] In one aspect, provided herein is a method of reducing or preventing central nervous system (CNS) impairment in a subject with mucopolysaccharidosis

CLAIMS

What is claimed is:

1. Use of a promoterless donor vector and an expression vector encoding a pair of zinc finger nucleases (ZFNs) targeted to an endogenous albumin gene in the manufacture of a medicament for reducing or preventing central nervous system (CNS) impairment and reducing dermatan sulfate levels in the CNS in a subject with mucopolysaccharidosis type I (MPS I) or mucopolysaccharidosis type I (MPS II), wherein the use comprises that the promoterless donor vector and the expression vector are to be administered to the subject, wherein the promoterless donor vector comprises a transgene encoding human α-L-iduronidase (hIDUA) for a subject with mucopolysaccharidosis type I (MPS I) or human iduronate-2-sulftase (hIDS) for a subject with mucopolysaccharidosis type II (MPS II),

wherein the transgene is integrated into the albumin gene in a liver cell following cleavage of the albumin gene such that the encoded hIDUA or hIDS is expressed and secreted from the liver and further wherein the hIDUA or hIDS secreted from the liver is found in the central nervous system (CNS) of the subject such that the CNS impairment is reduced or prevented and further wherein the subject is to be treated with cyclophosphamide prior to administration of the promoterless donor vector and expression vector.

2. The use of claim 1, wherein the CNS impairment comprises cognitive deficits.

3. The use of claim 1 or claim 2, further comprising that an immunosuppressant is to be administered to the subject prior to and after administration of the donor vector and the expression vector.

4. The use of any of claims 1 to 3, wherein expression of the transgenes modulates levels of glycosoaminoglycans in the brain of the subject.

5. The use of any of claims 1 to 4, wherein neuronal or glial vacuolation in the subject is reduced or eliminated.

6. The use of claim 5, wherein neuronal or glial vacuolation in the subject is reduced or eliminated in the spinal cord of the subject.

7. The use of any of claims 1 to 6, wherein loss of learning ability is decreased as compared to an untreated individual.

8. The use of any of claims 1 to 7, wherein the pair of ZFNs comprises the zinc finger proteins shown in Table 1.

9. The use of any of claims 1 to 8, wherein the ZFN expression vector and the donor vector comprise adeno-associated vectors (AAV).

10. The use of claim 9, wherein the ZFN expression vector and the donor vector AAV are to be administered via intravenous injection.

11. The use of any of claims 1 to 10, wherein the ZFN:ZFN:Donor ratio to be administered to the subject is 1:1:8.