

What is claimed is:

1. A method for treating a human subject diagnosed with mucopolysaccharidosis type II (MPS II), comprising delivering to the cerebrospinal fluid (CSF) of the human subject a therapeutically effective amount of a glycosylated recombinant human iduronate-2-sulfatase (IDS) precursor produced by human neuronal or human glial cells, wherein the glycosylated recombinant human IDS precursor is delivered by administration of a recombinant nucleotide expression vector encoding human IDS, wherein the recombinant nucleotide expression vector is administered at a dose that is dependent on the human subject's brain mass, and wherein the brain mass is determined by brain magnetic resonance imaging (MRI) of the human subject's brain.
2. The method of claim 1, wherein the glycosylated recombinant human IDS precursor is secreted at a detectable level.
3. The method of claim 1 or 2, wherein the human neuronal or human glial cells carry at least one mutation in the endogenous gene encoding human IDS precursor.
4. The method of any one of claims 1-3, wherein the human neuronal or human glial cells are transduced with a recombinant adeno-associated virus vector (rAAV).
5. The method of any one of claims 1-4, wherein the glycosylated recombinant human IDS precursor is expressed under the control of a CB7 promoter.
6. The method of any one of claims 1-5, wherein the glycosylated recombinant human IDS precursor is expressed from a cDNA encoding human IDS precursor.
7. The method of any one of claims 1-6, wherein the glycosylated recombinant human IDS precursor is about 90 kDa as measured by polyacrylamide gel electrophoresis.
8. The method of any one of claims 1-7, wherein the glycosylated recombinant human IDS precursor contains a formylglycine.
9. The method of any one of claims 1-8, wherein the glycosylated recombinant human IDS precursor (a) is α 2,6-sialylated; (b) does not contain detectable NeuGc; (c) does not contain detectable α -Gal antigen; (d) contains tyrosine-sulfation; and/or (e) is mannose-6-phosphorylated.
10. The method of any one of claims 1-9, in which the glycosylated recombinant human IDS precursor comprises the amino acid sequence of SEQ ID NO. 1.

11. The method of any one of claims 1-10, wherein the recombinant nucleotide expression vector is an AAV9 or AAVrh10 vector.

12. The method of any one of claims 1-11, wherein the human subject's brain mass is converted from the human subject's brain volume by multiplying the human subject's brain volume in cm^3 by a factor of 1.046 g/cm^3 , wherein the human subject's brain volume is obtained from the human subject's brain MRI.

13. The method of any one of claims 1-12, wherein the recombinant nucleotide expression vector is administered at a dose of about 1.3×10^{10} GC/g brain mass as determined by MRI, or about 6.5×10^{10} GC/g brain mass as determined by MRI.

14. The method of any one of claims 1-12, wherein the recombinant nucleotide expression vector is administered at a dose of about 2.0×10^{11} GC/g brain mass as determined by MRI.

15. The method of any one of claims 1-12, wherein the human subject is 5 years old or older and less than 18 years old.

16. The method of claim 15, wherein the recombinant nucleotide expression vector is administered at a dose of about 6.5×10^{10} GC/g brain mass as determined by MRI.

17. The method of claim 15, wherein the recombinant nucleotide expression vector is administered at a dose according to the table below:

Brain Mass (in g)		Target Brain Mass (in g)	Dose: Total GC (6.5×10^{10} GC/g brain mass)
Min	Max		
801	900	850	5.5×10^{13}
901	1050	975	6.3×10^{13}
1051	1200	1125	7.3×10^{13}
1201	-	1300	8.5×10^{13}

18. The method of any one of claims 1-12, wherein the human subject is 4 months old or older and less than 5 years old.

19. The method of claim 18, wherein the recombinant nucleotide expression vector is administered at a dose chosen from Dose 1 or Dose 2 according to the table below:

Brain Mass (in g)		Target	Dose Levels	
Min	Max		Dose 1 Total GC (1.3×10^{10} GC/g brain mass)	Dose 2 Total GC (6.5×10^{10} GC/g brain mass)
-	700	650	8.5×10^{12}	4.2×10^{13}
701	800	750	9.8×10^{12}	4.9×10^{13}
801	900	850	1.1×10^{13}	5.5×10^{13}
901	1050	975	1.3×10^{13}	6.3×10^{13}
1051	1200	1125	1.5×10^{13}	7.3×10^{13}
1201	-	1300	1.7×10^{13}	8.5×10^{13}

20. The method of claim 18, wherein the recombinant nucleotide expression vector is administered at a dose according to the table below:

Brain Mass (in g)		Target	Dose 3 Total GC (2.0×10^{11} GC/g brain mass)
Min	Max		
-	474	450	9.0×10^{13}
475	524	500	1.0×10^{14}
525	574	550	1.1×10^{14}
575	624	600	1.2×10^{14}
625	674	650	1.3×10^{14}
675	724	700	1.4×10^{14}
725	774	750	1.5×10^{14}
775	824	800	1.6×10^{14}
825	874	850	1.7×10^{14}
875	924	900	1.8×10^{14}
925	974	950	1.9×10^{14}
975	1024	1000	2.0×10^{14}
1025	1074	1050	2.1×10^{14}
1075	1124	1100	2.2×10^{14}
1125	1174	1150	2.3×10^{14}
1175	1224	1200	2.4×10^{14}
1225	1274	1250	2.5×10^{14}
1275	>1300	1300	2.6×10^{14}

21. The method of any one of claims 1-20, wherein the recombinant nucleotide expression vector is administered via intracisternal (IC) administration.

22. The method of any one of claims 1-20, wherein the recombinant nucleotide expression vector is administered via intracerebroventricular (ICV) administration.
23. The method of any one of claims 1-22, wherein the recombinant nucleotide expression vector is administered at a volume that does not exceed 10% of the total cerebrospinal fluid volume of the human subject.
24. The method of any one of claims 1-23, wherein the glycosylated recombinant human IDS precursor is delivered to lysosomes of cells in the CNS of the human subject.
25. The method of any one of claims 1-24, further comprising administering an immune suppression therapy to the human subject before or concurrently with the human IDS precursor treatment and optionally continuing immune suppression therapy thereafter.
26. The method of claim 25, wherein the immune suppression therapy comprises administering one or more corticosteroids, sirolimus, and/or tacrolimus.
27. The method of claim 26, wherein the one or more corticosteroids are methylprednisolone and/or prednisone.
28. The method of any one of claims 25-27, further comprising administering one or more antibiotics to the human subject before or concurrently with the immune suppression therapy.
29. The method of claim 28, wherein the one or more antibiotics are trimethoprim, sulfamethoxazole, pentamidine, dapsone, and/or atovaquone.
30. The method of any one of claims 25-29, further comprising administering one or more antifungal therapies to the human subject before or concurrently with the immune suppression therapy.
31. The method of any one of claims 1-30, further comprising a step of measuring one or more of the following biomarkers after administration of the recombinant nucleotide expression vector: (a) level of glycosaminoglycans (GAGs) in CSF; (b) level of iduronate-2-sulfatase (I2S) in CSF; (c) level of GAGs in plasma; (d) level of I2S in plasma; (e) level of leukocyte I2S enzyme activity; and (f) level of GAGs in urine.
32. The method of claim 31, wherein the GAGs in CSF comprise heparin sulfate in CSF.
33. The method of claim 31, wherein the GAGs in CSF are heparin sulfate in CSF.
34. The method of any one of claims 31-33, wherein the GAGs in plasma comprise heparin sulfate in plasma.

35. The method of any one of claims 31-33, wherein the GAGs in plasma are heparin sulfate in plasma.
36. The method of any one of claims 31-35, wherein the GAGs in urine comprise heparin sulfate in urine.
37. The method of any one of claims 31-35, wherein the GAGs in urine are heparin sulfate in urine.
38. The method of any one of claims 31-37, wherein the step of measuring comprises measuring level of heparin sulfate in CSF.
39. The method of any one of claims 31-38, wherein the step of measuring comprises measuring level of leukocyte I2S enzyme activity.