

WHAT IS CLAIMED IS:

1. An siRNA molecule comprising a sense strand and an antisense strand, wherein:
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 704 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 705;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 614 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 615;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 632 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 633;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 10 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 11;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 12 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 13;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 14 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 15;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 16 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 17;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 18 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 19;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 20 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 21;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 22 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 23;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 24 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 25;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 26 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 27;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 28 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 29;
 - the sense strand comprises the nucleobase sequence of SEQ ID NO: 30 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 31;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 62 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 63;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 64 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 65;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 66 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 67;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 68 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 69;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 600 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 601;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 602 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 603;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 604 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 605;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 606 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 607;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 608 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 609;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 610 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 611;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 612 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 613;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 616 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 617;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 618 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 619;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 620 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 621;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 622 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 623;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 656 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 657.

2. The siRNA of claim 1, wherein the siRNA comprises one or more nucleotide modifications or one or more internucleotide linkage modifications.
3. The siRNA of claim 1, of claims 1 or 2, wherein the siRNA further comprises a linker covalently attached to the sense strand of the siRNA.
4. The siRNA of claim 1, of claim 3, wherein the linker is attached to the 3' terminal of the sense strand.
5. The siRNA of claim 1, of any one of claims 1-4, wherein the siRNA further comprises a vinyl phosphonate modification of the anti-sense strand.
6. The siRNA of claim 1, of 5, wherein the vinyl phosphonate modification is at the 5' terminal of the anti-sense strand.
7. The siRNA of claim 1, of any one of claims 1-6, wherein:
 - the sense strand comprises the nucleic acid molecule of SEQ ID NO: 706 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 707;
 - the sense strand comprises the nucleic acid molecule of SEQ ID NO: 660 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 661;
 - the sense strand comprises the nucleic acid molecule of SEQ ID NO: 678 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 679;
 - the sense strand comprises the nucleic acid molecule of SEQ ID NO: 70 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 71;
 - the sense strand comprises the nucleic acid molecule of SEQ ID NO: 72 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 73;
 - the sense strand comprises the nucleic acid molecule of SEQ ID NO: 74 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 75;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 76 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 77;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 78 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 79;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 80 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 81;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 82 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 83;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 84 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 85;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 86 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 87;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 658 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 659;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 662 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 633;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 664 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 665;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 666 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 667;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 668 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 669;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 670 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 671;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 672 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 673;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 674 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 675;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 676 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 677;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 680 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 681;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 682 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 683;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 684 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 685;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 686 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 687;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 688 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 689;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 690 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 691;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 692 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 693;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 694 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 695;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 696 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 697;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 698 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 699;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 700 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 701;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 702 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 703;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 711 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 712;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 1053 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 1054;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 1055 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 1056;

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 1057 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 1058; or

the sense strand comprises the nucleic acid molecule of SEQ ID NO: 1059 and the antisense strand comprises the nucleic acid molecule of SEQ ID NO: 1060.

8. The siRNA of claim 1, of any one of claim 1-7, wherein the sense strand comprises 19-23 nucleotides in length.

9. The siRNA of claim 1, of any one of claim 1-8, wherein the antisense strand comprises 17-23 nucleotides.

10. A composition comprising a FN3 polypeptide linked to a siRNA molecule comprising a sense strand and an antisense strand, wherein the FN3 binds to CD71 and the siRNA inhibits the expression of Gys1 and the FN3 polypeptide is linked to the sense strand of the siRNA molecule.

11. The composition of claim 10, wherein the siRNA is a siRNA of any one of claims 1-9.

12. The composition of claims 10 or 11, wherein the sense strand of the siRNA molecule is linked to a cysteine residue in the FN3 polypeptide.

13. The composition of claim 12, wherein the cysteine residue in the FN3 polypeptide domain is located at a residue that corresponds to position 6, 8, 10, 11, 14, 15, 16, 20, 30, 34, 38, 40, 41, 45, 47, 48, 53, 54, 59, 60, 62, 64, 70, 88, 89, 90, 91, or 93 of a FN3 domain comprising the amino acid sequence of SEQ ID NO: 405.
14. The composition of claim 12, wherein the cysteine residue in the FN3 polypeptide domain is located at a residue that corresponds to position 54 of a FN3 polypeptide domain comprising the amino acid sequence of SEQ ID NO: 405.
15. The composition of claim 13, wherein the FN3 domain is linked to the sense strand by a linker having the formula of $\text{Mal-C}_2\text{H}_4\text{C(O)(NH)-(CH}_2\text{)}_6$.
16. The composition of any one of claims 10-15, wherein the FN3 polypeptide domain comprises an amino acid sequence at least 95% identical to the amino acid sequence of one of SEQ ID NOs: 273, 301-310, 312-572, 592-599, or 708-710.
17. The composition of any one of claims 10-15, wherein the FN3 polypeptide domain comprises the amino acid sequence of any one of SEQ ID NOs: 273, 301-310, 312-572, 592-599, or 708-710.
18. The composition of any one of claims 10-15, wherein the FN3 polypeptide domain comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 509.
19. The composition of any one of claims 10-15, wherein the FN3 polypeptide domain comprises the amino acid sequence of SEQ ID NO: 509.
20. The composition of any one of claims 10-19, wherein the siRNA molecule comprises:
the sense strand comprises the nucleobase sequence of SEQ ID NO: 704 and the
antisense strand comprises the nucleobase sequence of SEQ ID NO: 705;

the sense strand comprises the nucleobase sequence of SEQ ID NO: 614 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 615; or.

the sense strand comprises the nucleobase sequence of SEQ ID NO: 632 and the antisense strand comprises the nucleobase sequence of SEQ ID NO: 633;

21. The composition of any one of claims 10-20, wherein:

the sense strand comprises a nucleic acid molecule of SEQ ID NO: 706 and the antisense strand comprises a nucleic acid molecule comprising the nucleic acid molecule of SEQ ID NO: 707;

the sense strand comprises a nucleic acid molecule comprising the nucleic acid molecule of SEQ ID NO: 660 and the antisense strand comprises a nucleic acid molecule comprising the nucleic acid molecule of SEQ ID NO: 661; or

the sense strand comprises a nucleic acid molecule comprising the nucleic acid molecule of SEQ ID NO: 678 and the antisense strand comprises a nucleic acid molecule comprising the nucleic acid molecule of SEQ ID NO: 679.

22. A pharmaceutical composition comprising a siRNA molecule of any one of claims 1-9 or a composition of any one of claims 10-21.

23. A kit comprising the pharmaceutical composition of claim 22.

24. Use of the pharmaceutical composition of claim 22 in the preparation of a pharmaceutical composition or medicament for treating a Gys1 mediated disease.

25. The use of claim 24, wherein the Gys1 mediated disease is a glycogen storage disease.

26. The use of claim 24, wherein the Gys1 disease is Pompe Disease.

27. The use of claim 24, wherein the glycogen storage disease is selected from the group consisting of Cori's disease or Forbes' disease (GSD3, Glycogen debranching enzyme (AGL)

deficiency), McArdle disease (GSD5, Muscle glycogen phosphorylase (PYGM) deficiency), type II Diabetes/diabetic nephropathy, Aldolase A Deficiency GSD12, Lafora Disease, hypoxia, Andersen disease (GSD4, Glycogen debranching enzyme (GBE1) deficiency), Tarui's Disease (GSD7, Muscle phosphofructokinase (PFKM) deficiency), adult polyglucosan body disease, Glycogen synthase (GYS2) deficiency (GSD0), Glucose-6-phosphatase (G6PC / SLC37A4) deficiency (GSD1, von Gierke's disease), Hers' disease (GSD6, Liver glycogen phosphorylase (PYGL) or Muscle phosphoglycerate mutase (PGAM2) deficiency), Phosphorylase kinase (PHKA2 / PHKB / PHKG2 / PHKA1) deficiency (GSD9), Phosphoglycerate mutase (PGAM2) deficiency (GSD10), Muscle lactate dehydrogenase (LDHA) deficiency (GSD11), Fanconi-Bickel syndrome (GSD 11, Glucose transporter (GLUT2) deficiency, Aldolase A deficiency (GSD 12), β -enolase (ENO3) deficiency (GSD13), and Glycogenin-1 (GYG1) deficiency (GSD15).

27. Use of the pharmaceutical composition of claim 22 for treating a glycogen storage disease.

28. The use of claim 27, wherein the glycogen storage disease is Pompe disease.

29. The use of claim 27, wherein the glycogen storage disease is selected from the group consisting of Cori's disease or Forbes' disease (GSD3, Glycogen debranching enzyme (AGL) deficiency), McArdle disease (GSD5, Muscle glycogen phosphorylase (PYGM) deficiency), type II Diabetes/diabetic nephropathy, Aldolase A Deficiency GSD12, Lafora Disease, hypoxia, Andersen disease (GSD4, Glycogen debranching enzyme (GBE1) deficiency), Tarui's Disease (GSD7, Muscle phosphofructokinase (PFKM) deficiency), adult polyglucosan body disease, Glycogen synthase (GYS2) deficiency (GSD0), Glucose-6-phosphatase (G6PC / SLC37A4) deficiency (GSD1, von Gierke's disease), Hers' disease (GSD6, Liver glycogen phosphorylase (PYGL) or Muscle phosphoglycerate mutase (PGAM2) deficiency), Phosphorylase kinase (PHKA2 / PHKB / PHKG2 / PHKA1) deficiency (GSD9), Phosphoglycerate mutase (PGAM2) deficiency (GSD10), Muscle lactate dehydrogenase (LDHA) deficiency (GSD11), Fanconi-Bickel syndrome (GSD 11, Glucose transporter (GLUT2) deficiency, Aldolase A deficiency

(GSD 12), β -enolase (ENO3) deficiency (GSD13), and Glycogenin-1 (GYG1) deficiency (GSD15).

30. Use of the pharmaceutical composition of claim 22 for reducing the expression Gys1.

31. Use of the pharmaceutical composition of claim 22 for delivering the siRNA to a cell.

32. A method of preparing the composition of any one of claims 10-21, the method comprising reacting the FN3 polypeptide with the sense strand of the siRNA under conditions sufficient to link the sense strand to the FN3 polypeptide.