involve removing one or more contiguous segments of mRNA (introns) to conjoin the remaining segments (exons), delimited by pairs of 5' splice sites and 3' splice sites. Alternative splicing, which may be the splicing together of different combinations of exons, may result in multiple mRNA transcripts from a single gene.

[0007] Certain human genetic diseases (e.g., caused by genetic aberrations, such as point mutations), may be caused by aberrant splicing. As such, there is a need for a splicing mediator to treat diseases that are caused by aberrant splicing.

SUMMARY

[0008] In general, the disclosure provides an oligonucleotide including a nucleobase sequence complementary to a sequence within ATP7B exon6, a flanking intron, or a combination thereof.

[0009] In one example, the disclosure provides an antisense oligonucleotide including a nucleobase sequence at least 70% complementary to an ATP7B target sequence in exon 6, a 5'-flanking intron, a 3'-flanking intron, or a combination of exon 6 and the 5'-flanking or 3'-flanking intron. In one aspect, the present disclosure refers to an antisense oligonucleotide comprising a nucleobase sequence at least 70% complementary to an ATP7B target sequence in exon 6, a 5'-flanking intron, a 3'-flanking intron, or a combination of exon 6 and the 5'-flanking or 3'-flanking intron.

[0010] In some examples, the ATP7B target sequence reduces the binding of a splicing factor to an intronic splicing silencer in the 5'-flanking or 3'-flanking intron.

[0011] In some examples, the ATP7B target sequence includes at least one nucleotide located among positions 54672-54680 in SEQ ID NO: 1. In some examples, the ATP7B target sequence includes at least one nucleotide located among positions 54691-54701 in SEQ ID NO: 1. In some examples, the ATP7B target sequence includes at least one nucleotide located among positions 54492-54506 in SEQ ID NO: 1.

[0012] In some examples, the ATP7B target sequence includes at least one nucleotide located among positions 54472-54516 in SEQ ID NO: 1. In some examples, the ATP7B target sequence includes at least one nucleotide located among positions 54522-54593 in SEQ ID NO: 1. In some examples, the ATP7B target sequence includes at least one nucleotide located among positions 54665-54718 in SEQ ID NO: 1.

[0013] In some examples, the nucleobase sequence is complementary to a sequence within the 5'-flanking intron. In some examples, the ATP7B target sequence is located within the 5'-flanking intron among positions up to 54517 in SEQ ID NO: 1. In some examples, the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 119, 120, 121, 122, 123, or 124. In some examples, the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 122. In some examples, the ATP7B target sequence is located within the 5'-flanking intron among positions 54522 to 54581 in SEQ ID NO: 1. In some examples, the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 3, 4, 5, 6, 7, 8, 9, or 10.

[0014] In some examples, the ATP7B target sequence is located within the combination of the 5'-flanking intron and exon 6. In some examples, the ATP7B target sequence is located within the combination of the 5'-flanking intron and exon 6 among positions 54562 to 54593 in SEQ ID NO: 1. In some examples, nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 11.

[0015] In some examples, the ATP7B target sequence is located within exon 6 or the combination of the 3'-flanking intron and exon 6. In some examples, the ATP7B target sequence is

located among positions 54631 to 54677 in SEQ ID NO: 1. In some examples, the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 22, 23, 24, or 25.

[0016] In some examples, the ATP7B target sequence is located within the 3'-flanking intron. In some examples, the ATP7B target sequence is located among positions 54655 to 54738 in SEQ ID NO: 1. In some examples, the 5'-terminal nucleotide of the oligonucleotide is complementary to neither position 54695 nor position 54696 of SEQ ID NO: 1. In some examples, the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, or 155. In some examples, the nucleobase sequence has at least 70% sequence identity to SEQ ID NOs: 39, 48, 49, 50, 61, 63, 64, 65, 66, 67, 76, 77, 78, 79, 80, 81, 90, 91, 92, 93, 94, 95, 100, 103, 104, 121, and 149.

[0017] In some examples, the sequence identity of any nucleobase sequence is at least 80%, 85%, 90%, or 95%, e.g., at least 90%. In some examples, the sequence identity is 100%.

[0018] In some examples, the antisense oligonucleotide includes at least one modified nucleobase.

[0019] In some examples, the antisense oligonucleotide includes at least one modified internucleoside linkage. In some examples, the modified internucleoside linkage is a phosphorothioate linkage. In some examples, the phosphorothioate linkage is a stereochemically enriched phosphorothioate linkage. In some examples, at least 50% of internucleoside linkages in the antisense oligonucleotide are independently the modified internucleoside linkage. In some examples, at least 70% of the internucleoside linkages in the antisense oligonucleotide are independently the modified internucleoside linkage. In some examples, all internucleoside linkages in the antisense oligonucleotide are independently the modified internucleoside linkage.

[0020] In some examples, the antisense oligonucleotide includes at least one modified sugar nucleoside. In some examples, at least one modified sugar nucleoside is a 2'-modified sugar nucleoside. In some examples, at least one 2'-modified sugar nucleoside includes a 2'-modification selected from the group consisting of 2'-fluoro, 2'-methoxy, and 2'-methoxyethoxy. In some examples, the 2'-modified sugar nucleoside includes the 2'-methoxyethoxy modification.

[0021] In some examples, all nucleosides in the antisense oligonucleotide are independently the modified sugar nucleosides.

[0022] In certain examples of the disclosure, all internucleoside linkages in the antisense oligonucleotide are phosphorothioate diester linkages, and all nucleosides in the antisense oligonucleotide are 2'-methoxyethoxy modified ribose nucleosides. Such antisense oligonucleotides may also further include a targeting moiety, such as N-acetylgalactosamine or a cluster thereof.

[0023] In some examples, at least one modified sugar nucleoside is a bridged nucleic acid. In some examples, the bridged nucleic acid is a locked nucleic acid (LNA), ethylene-bridged nucleic acid (ENA), or cEt nucleic acid.

[0024] In some examples, the antisense oligonucleotide is a morpholino oligomer.

[0025] In some examples, the antisense oligonucleotide further includes a targeting moiety. In some examples, the targeting moiety is covalently conjugated at the 5'-terminus of the antisense oligonucleotide. In some examples, the targeting moiety is covalently conjugated at the 3'-terminus of the antisense oligonucleotide. In some examples, the targeting moiety is covalently conjugated at an internucleoside linkage of the antisense oligonucleotide.

[0026] In some examples, the targeting moiety is covalently conjugated through a linker. In some examples, the linker is a cleavable linker (e.g., a linker including –S–S–, –C(O)O–, –C(O)S–, –OC(O)–, –SC(O)–).

[0027] Examples of targeting moieties include N-acetylgalactosamine, glycyrrhetinic acid, glycyrrhizin, lactobionic acid, lactoferrin, IgA, a bile acid (e.g., lithocholyltaurine or taurocholic acid), and clusters thereof. In some examples, the targeting moiety includes N-acetylgalactosamine. In some examples, the targeting moiety is an N-acetylgalactosamine cluster.

[0028] In some examples, the antisense oligonucleotide includes at least 12 nucleosides. In some examples, the antisense oligonucleotide includes at least 16 nucleosides. In some examples, the antisense oligonucleotide includes a total of 50 nucleosides or fewer. In some examples, the antisense oligonucleotide includes a total of 30 nucleosides or fewer. In some examples, the antisense oligonucleotide includes a total of 20 nucleosides or fewer. In some examples, the antisense oligonucleotide includes a total of 16 to 20 nucleosides. In some examples, the antisense oligonucleotide includes a total of 16 to 19 nucleosides.

[0029] In another example, the disclosure provides a pharmaceutical composition including the antisense oligonucleotide of the disclosure and a pharmaceutically acceptable excipient. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the antisense oligonucleotide of the disclosure and a pharmaceutically acceptable excipient.

[0030] In yet another aspect, the present disclosure refers to use of the antisense oligonucleotide of the disclosure in the manufacture of a medicament for increasing the level of exon 6-containing ATP7B mRNA molecules in a cell. The disclosure also provides a method of increasing the level of exon 6-containing ATP7B mRNA molecules in a cell expressing an aberrant ATP7B gene by contacting the cell with the antisense oligonucleotide of the disclosure. In some examples, the cell is in a subject.

[0031] In still another aspect, the present disclosure refers to use of the antisense oligonucleotide of the disclosure or the pharmaceutical composition of the disclosure in the manufacture of a medicament for treating Wilson disease in a subject in need thereof. The disclosure also provides a method of treating Wilson disease in a subject having an aberrant ATP7B gene by administering a therapeutically effective amount of the antisense oligonucleotide of the disclosure or the pharmaceutical composition of the disclosure to the subject in need thereof. In some examples, the administering step is performed parenterally. In some examples, the aberrant ATP7B gene is ATP7B having a g.54646T>G mutation in SEQ ID NO: 1.

[0032] Recognized herein is the need for compositions and methods for treating diseases that may be caused by abnormal splicing resulting from an underlying genetic aberration. In some cases, antisense nucleic acid molecules, such as oligonucleotides, may be used to effectively modulate the splicing of targeted genes in genetic diseases, in order to alter the gene products produced. This approach can be applied in therapeutics to selectively modulate the expression and gene product composition for genes involved in genetic diseases.

[0033] The present disclosure provides compositions and methods that may advantageously use antisense oligonucleotides targeted to and hybridizable with nucleic acid molecules that encode for ATP7B. Such antisense oligonucleotides may target one or more splicing regulatory elements in one or more exons or introns of ATP7B. These splicing regulatory elements modulate splicing of ATP7B ribonucleic acid (RNA).

[0034] In one example, the present disclosure provides an ATP7B RNA splice-modulating antisense oligonucleotide having a sequence targeted to one or more splicing regulatory elements adjacent to an

exon of ATP7B. In some examples, a genetic aberration of ATP7B includes the M645R mutation. In some examples, the M645R mutation results from ATP7B chr13:52535985:A:C [hg19/b37] (g.54646T>G in SEQ ID NO: 1). In some examples, the one or more splicing regulatory elements include an exonic splicing silencer element or an intronic splicing silencer element. In some examples, the sequence is targeted to an abnormally spliced exon. In some examples, the sequence is targeted to an intron adjacent to an abnormally spliced exon. In some examples, the antisense oligonucleotide modulates variant splicing to yield an increase in exon inclusion. In some examples, the antisense oligonucleotide has a length of 12 to 20 nucleotides. In some examples, the antisense oligonucleotide has a length of 12 to 30 nucleotides. In some examples, the antisense oligonucleotide has a length of 12 to 50 nucleotides.

[0035] In another example, the present disclosure provides a method for modulating splicing of ATP7B RNA in a cell, tissue, or organ of a subject, including bringing the cell, tissue, or organ in contact with an antisense oligonucleotide including one or more sequences targeted to one or more splicing regulatory elements of an abnormally spliced exon or an intron adjacent to the abnormally spliced exon. In some examples, the genetic aberration of ATP7B includes M645R. In some examples, the M645R results from ATP7B chr13:52535985:A:C [hg19/b37] (g.54646T>G in SEQ ID NO: 1). In some examples, the splicing regulatory element is an exonic splicing silencer element or an intronic splicing silencer element. In some examples, the sequence is targeted to an abnormally spliced exon. In some examples, the sequence is targeted to an intron adjacent to an abnormally spliced exon. In some examples, the antisense oligonucleotide modulates variant splicing to yield an increase in exon inclusion (e.g., exon 6 inclusion, e.g., increase by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%; e.g., up to 100%, up to 90%, up to 80%, up to 70%, up to 60%, up to 50%, as compared to the ratio of exon 6-including ATP7B transcripts to the total number of ATP7B transcript molecules in a cell including ATP7B gene having an exon 6-skipping mutation in the absence of a treatment with an antisense oligonucleotide). In some examples, the antisense oligonucleotide has a length of 12 to 20 nucleotides. In some examples, the antisense oligonucleotide has a length of 12 to 30 nucleotides. In some examples, the antisense oligonucleotide has a length of 12 to 50 nucleotides. In some examples, the subject has or is suspected of having a disease, e.g., Wilson disease, and the subject is monitored for a progression or regression of the disease in response to bringing the cell, tissue, or organ in contact with the composition.

[0036] In another example, the present disclosure provides a method for treating Wilson disease in a subject, including administering to the subject a therapeutically effective amount of an antisense oligonucleotide including a sequence targeted to a splicing regulatory element of an abnormally spliced exon or an intron adjacent to the abnormally spliced exon. The antisense oligonucleotide modulates splicing of ATP7B RNA. In some examples, the genetic aberration of ATP7B includes the M645R mutation. In some examples, the M645R mutation results from ATP7B chr13:52535985:A:C [hg19/b37] (g.54646T>G mutant of SEQ ID NO: 1). In some examples, the splicing regulatory element includes an exonic splicing silencer element or an intronic splicing silencer element. In some examples, the sequence is targeted to an abnormally spliced exon of ATP7B. In some examples, the sequence is targeted to an intron adjacent to an abnormally spliced exon of the genetic aberration of ATP7B that modulates variant splicing of ATP7B RNA. In some examples, the antisense oligonucleotide modulates splicing to yield an increase in exon inclusion (e.g., increase by at least 5%, at

least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%; e.g., up to 100%, up to 90%, up to 80%, up to 70%, up to 60%, up to 50%, as compared to the ratio of exon 6-including ATP7B transcripts to the total number of ATP7B transcript molecules in a cell including ATP7B gene having an exon 6-skipping mutation in the absence of a treatment with an antisense oligonucleotide). In some examples, the antisense oligonucleotide has a length of 12 to 20 nucleotides. In some examples, the antisense oligonucleotide has a length of 12 to 30 nucleotides. In some examples, the antisense oligonucleotide has a length of 12 to 50 nucleotides. In some examples, the subject is monitored for a progression or regression of Wilson disease in response to administering to the subject the therapeutically effective amount of the antisense oligonucleotide. In some examples, the antisense oligonucleotide reduces 24-hour urinary copper level in the subject, e.g., by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%; e.g., up to 90%, up to 80%, up to 70%, up to 60%, up to 50%, as compared to a control subject. In some examples, the control subject is the subject prior to therapy with an antisense oligonucleotide of the disclosure or is a subject suffering from Wilson disease and not receiving an antisense oligonucleotide of the disclosure. In some examples, the antisense oligonucleotide reduces 24-hour urinary copper level in the subject to <100 µg/24 hours (<1.6 µmol/24 hours) (e.g., to ≤40 µg/24 hours (≤0.6 µmol/24 hours)).

[0037] In another example, the present disclosure provides a pharmaceutical composition for treatment of Wilson disease including an antisense oligonucleotide and a pharmaceutically acceptable carrier. The antisense oligonucleotide includes a sequence targeted to a splicing regulatory element of an abnormally spliced exon or an intron adjacent to the abnormally spliced exon. The antisense oligonucleotide modulates splicing of ATP7B RNA. In some examples, the genetic aberration of ATP7B includes M645R. In some examples, the M645R mutation results from ATP7B chr13:52535985:A:C [hg19/b37] (g.54646T>G mutant of SEQ ID NO: 1).

Definitions

[0038] Various terms used throughout the present description may be read and understood as follows, unless the context indicates otherwise: “or” as used throughout is inclusive, as though written “and/or”; singular articles and pronouns as used throughout include their plural forms, and vice versa; similarly, gendered pronouns include their counterpart pronouns so that pronouns should not be understood as limiting anything described herein to use, implementation, performance, etc. by a single gender; “exemplary” should be understood as “illustrative” or “exemplifying” and not necessarily as “preferred” over other embodiments. Further definitions for terms may be set out herein; these may apply to prior and subsequent instances of those terms, as will be understood from a reading of the present description.

[0039] The term “acyl,” as used herein, represents a chemical substituent of formula –C(O)–R, where R is alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclyl alkyl, heteroaryl, or heteroaryl alkyl. An optionally substituted acyl is an acyl that is optionally substituted as described herein for each group R.

[0040] The term “acyloxy,” as used herein, represents a chemical substituent of formula –OR, where R is acyl. An optionally substituted acyloxy is an acyloxy that is optionally substituted as described herein for acyl.

WHAT IS CLAIMED IS:

CLAIMS

1. An antisense oligonucleotide comprising a nucleobase sequence at least 70% complementary to an ATP7B target sequence in exon 6, a 5'-flanking intron, a 3'-flanking intron, or a combination of exon 6 and the 5'-flanking or 3'-flanking intron.

2. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence reduces the binding of a splicing factor to an intronic splicing silencer in the 5'-flanking or 3'-flanking intron.

3. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence comprises at least one nucleotide located among positions 54672-54680 in SEQ ID NO: 1.

4. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence comprises at least one nucleotide located among positions 54691-54701 in SEQ ID NO: 1.

5. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence comprises at least one nucleotide located among positions 54492-54506 in SEQ ID NO: 1.

6. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence comprises at least one nucleotide located among positions 54472-54516, 54522-54593, and 54665-54718 in SEQ ID NO: 1.

7. The antisense oligonucleotide of claim 1, wherein the nucleobase sequence is complementary to a sequence within the 5'-flanking intron.

8. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence is located within the 5'-flanking intron among positions up to 54517 in SEQ ID NO: 1.

9. The antisense oligonucleotide of claim 1, wherein the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 119, 120, 121, 122, 123, or 124.

10. The antisense oligonucleotide of claim 1, wherein the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 122.

11. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence is located within the 5'-flanking intron among positions 54522 to 54581 in SEQ ID NO: 1.

12. The antisense oligonucleotide of claim 1, wherein the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 3, 4, 5, 6, 7, 8, 9, or 10.

13. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence is located within the combination of the 5'-flanking intron and exon 6.

14. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence is located within the combination of the 5'-flanking intron and exon 6 among positions 54562 to 54593 in SEQ ID NO: 1.

15. The antisense oligonucleotide of claim 1, wherein the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 11.

16. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence is located within exon 6 or the combination of the 3'-flanking intron and exon 6.

17. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence is located among positions 54631 to 54677 in SEQ ID NO: 1.

18. The antisense oligonucleotide of claim 1, wherein the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 22, 23, 24, or 25.

19. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence is located within the 3'-flanking intron.

20. The antisense oligonucleotide of claim 1, wherein the ATP7B target sequence is located among positions 54655 to 54738 in SEQ ID NO: 1.

21. The antisense oligonucleotide of claim 5, 6, 19, or 20, wherein the 5'-terminal nucleotide of the oligonucleotide is complementary to neither position 54695 nor position 54696 of SEQ ID NO: 1.

22. The antisense oligonucleotide of claim 1, wherein the nucleobase sequence has at least 70% sequence identity to SEQ ID NO: 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, or 155.

23. The antisense oligonucleotide of claim 1, wherein the nucleobase sequence has at least 70% sequence identity to SEQ ID NOs: 39, 48, 49, 50, 61, 63, 64, 65, 66, 67, 76, 77, 78, 79, 80, 81, 90, 91, 92, 93, 94, 95, 100, 103, 104, 121, and 149.

24. The antisense oligonucleotide of claim 9, 10, 12, 15, 18, 22, or 23, wherein the sequence identity is at least 90%.

25. The antisense oligonucleotide of claim 24, wherein the sequence identity is 100%.

26. The antisense oligonucleotide of claim 1, wherein the nucleobase sequence is a sequence set forth in SEQ ID NO: 29.

27. The antisense oligonucleotide of any one of claims 1 to 26, wherein the antisense oligonucleotide comprises at least one modified nucleobase.

28. The antisense oligonucleotide of any one of claims 1 to 27, wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage.

29. The antisense oligonucleotide of claim 28, wherein the modified internucleoside linkage is a phosphorothioate linkage.

30. The antisense oligonucleotide of claim 29, wherein the phosphorothioate linkage is a stereochemically enriched phosphorothioate linkage.

31. The antisense oligonucleotide of claim 30, wherein at least 70% of internucleoside linkages in the antisense oligonucleotide are independently the modified internucleoside linkage.

32. The antisense oligonucleotide of claim 31, wherein all internucleoside linkages in the antisense oligonucleotide are independently the modified internucleoside linkage.

33. The antisense oligonucleotide of any one of claims 1 to 32, wherein the antisense oligonucleotide comprises at least one modified sugar nucleoside.

34. The antisense oligonucleotide of claim 33, wherein at least one modified sugar nucleoside is a 2'-modified sugar nucleoside.

35. The antisense oligonucleotide of claim 34, wherein at least one 2'-modified sugar nucleoside comprises a 2'-modification selected from the group consisting of 2'-fluoro, 2'-methoxy, and 2'-methoxyethoxy.

36. The antisense oligonucleotide of claim 35, wherein the 2'-modified sugar nucleoside comprises the 2'-methoxyethoxy modification.

37. The antisense oligonucleotide of any one of claims 33 to 36, wherein at least one modified sugar nucleoside is a bridged nucleic acid.

38. The antisense oligonucleotide of any one of claims 33 to 37, wherein all nucleosides in the antisense oligonucleotide are independently the modified sugar nucleosides.

39. The antisense oligonucleotide of any one of claims 1 to 38, further comprising a targeting moiety.

40. The antisense oligonucleotide of claim 39, wherein the targeting moiety is covalently conjugated at the 5'-terminus or the 3'-terminus of the antisense oligonucleotide.

41. The antisense oligonucleotide of claim 39, wherein the targeting moiety is covalently conjugated at an internucleoside linkage of the antisense oligonucleotide.

42. The antisense oligonucleotide of any one of claims 1 to 41, wherein the antisense oligonucleotide comprises at least 12 nucleosides.

43. The antisense oligonucleotide of any one of claims 1 to 42, wherein the antisense oligonucleotide comprises a total of 30 nucleosides or fewer.

44. A pharmaceutical composition comprising the antisense oligonucleotide of any one of claims 1 to 43 and a pharmaceutically acceptable excipient.

45. Use of the antisense oligonucleotide of any one of claims 1 to 43 in the manufacture of a medicament for increasing the level of exon 6-containing ATP7B mRNA molecules in a cell.

46. The use of claim 45, wherein the cell is in a subject.

47. Use of the antisense oligonucleotide of any one of claims 1 to 43 or the pharmaceutical composition of claim 44 in the manufacture of a medicament for treating Wilson disease in a subject in need thereof.

48. The use of claim 47, wherein the medicament is to be administered parenterally.

49. The use of claim 45 or 46, wherein the cell expresses an aberrant ATP7B gene having a g.54646T>G mutation in SEQ ID NO: 1.

50. The use of claim 47 or 48, wherein the subject has an aberrant ATP7B gene having a g.54646T>G mutation in SEQ ID NO: 1.