Claims

1. A method for allele-specific suppression of a transcript from a target nucleic acid sequence for which a plurality of alleles exist within a population, each of which contains a characteristic sequence element that defines the target allele relative to other alleles, the method comprising steps of:

contacting a sample comprising transcripts of the target allele with a chirally controlled oligonucleotide composition comprising oligonucleotides of a particular oligonucleotide type characterized by:

1) a common base sequence and length;

2) a common pattern of backbone linkages;

3) a common pattern of backbone chiral centers;

which composition is chirally controlled in that it is enriched, relative to a substantially racemic preparation of oligonucleotides having the same base sequence and length, for oligonucleotides of the particular oligonucleotide type, wherein:

the common pattern of backbone chiral centers comprises from 5' to 3' *R*p(*S*p)$_2$;

wherein the common base sequence for the oligonucleotides of the particular oligonucleotide type is or comprises a sequence that is complementary to the characteristic sequence element that defines the target allele, the composition being characterized in that, when it is contacted with a system comprising transcripts of both the target allele and another allele:

the composition provides a cleavage site that is two base pairs downstream of the *R*p(*S*p)$_2$ pattern;

transcripts of the target allele are cleaved at a site within 5 base pairs downstream or upstream of the characteristic sequence element that defines the target allele relative to the another allele; and

transcripts of the target allele are suppressed at a greater level than a level of suppression observed for the another allele.

2. The method of claim 1, wherein the composition is characterized in that, when it is contacted with a system comprising transcripts of both the target allele and another allele of the same gene, transcripts of the target allele are suppressed at a level at least 2-fold greater than a level of suppression observed for the another allele of the same gene.

3. The method of claim 1, the contacting being performed under conditions determined to permit the composition to suppress transcripts of the target allele.

4. The method of claim 1, wherein the composition is characterized in that, when it is contacted with a system comprising transcripts of both the target allele and another allele, it shows suppression of transcripts of the target allele at a level that is at least 2 fold in that transcripts from the target allele are detected in amounts that are 2 fold lower when the composition is present relative to when it is absent.

5. The method of claim 1, wherein the composition is characterized in that, when it is contacted with a system expressing transcripts of both the target allele and another allele of a target gene, it shows suppression of expression of transcripts of the target allele at a level that is:

a) at least 2 fold in that transcripts from the target allele are detected in amounts that are 2 fold lower when the composition is present relative to when it is absent;

b) at least 2 fold greater than a level of suppression observed for the another allele of the same gene; or

c) both at least 2 fold in that transcripts from the target allele are detected in amounts that are 2 fold lower when the composition is present relative to when it is absent, and at least 2 fold greater than a level of suppression observed for the another allele of the same gene.

6. The method of claim 1, wherein the characteristic sequence element is present within an intron of the target nucleic acid sequence or gene.

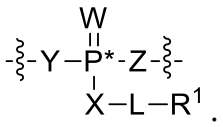
7. The method of claim 1, wherein the characteristic sequence element is present within an exon of the target nucleic acid sequence or gene.

8. The method of claim 1, wherein the characteristic sequence element spans an exon and an intron of the target nucleic acid sequence or gene.

9. The method of claim 1, wherein the characteristic sequence element comprises a mutation, and wherein the sample contains transcripts from the target allele and another allele that differ from each other at the mutation.

10. The method of claim 1, wherein the characteristic sequence element comprises a SNP, and wherein the sample contains transcripts from the target allele and another allele that differ from each other at the SNP.

11. The method of claim 10, wherein each chiral, modified phosphate linkage of the oligonucleotides of the particular oligonucleotide type independently has the structure of formula **I**:



(I)

wherein:

P* is an asymmetric phosphorus atom and is either *R*p or *S*p;

W is O, S or Se;

each of X, Y and Z is independently –O–, –S–, –N(–L–R^1)–, or L;

L is a covalent bond or an optionally substituted, linear or branched C_1–C_{10} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–;

R^1 is halogen, R, or an optionally substituted C_1–C_{50} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1–C_6 alkylene, C_1–C_6 alkenylene, —C≡C—, –C(R′)$_2$–, –Cy–, –O–, –S–, –S–S–, –N(R′)–, –C(O)–, –C(S)–, –C(NR′)–, –C(O)N(R′)–, –N(R′)C(O)N(R′)-, –N(R′)C(O)–, –N(R′)C(O)O–, –OC(O)N(R′)-, –S(O)–, –S(O)$_2$–, –S(O)$_2$N(R′)–, –N(R′)S(O)$_2$–, –SC(O)–, –C(O)S–, –OC(O)–, or –C(O)O–;

each R′ is independently –R, -C(O)R, -CO_2R, or –SO_2R, or:

two R′ on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic or heteroaryl ring, or

two R′ on the same carbon are taken together with their intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring;

–Cy– is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, or heterocyclylene;

each R is independently hydrogen, or an optionally substituted group selected from C_1–C_6 aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl; and

each $-\!\!\lesssim\!\!-$ independently represents a connection to a nucleoside.

12. The method of claim 11, wherein W is O, X is −S−, and Y and Z are −O−.

13. The method of claim 11, wherein X is −S− and $-L-R^1$ is not hydrogen.

14. The method of claim 10, wherein each chiral, modified phosphate linkage of the oligonucleotides of the particular oligonucleotide type is a phosphorothioate diester linkage.

15. The method of claim 14, wherein the common pattern of backbone chiral centers comprises from 5’ to 3’ *S*p*S*p*R*p*S*p*S*p.

16. The method of claim 15, wherein the common base sequence has at least 15 nucleobases.

17. The method of claim 16, wherein the common pattern of backbone chiral centers comprises at least 50% of backbone chiral centers in the *S*p conformation.

18. The method of claim 17, wherein the composition is a chirally pure oligonucleotide composition.

19. The method of claim 14, wherein the pattern of backbone chiral centers comprises from 5’ to 3’ (*N*p)t(*R*p)n(*S*p)m, wherein t is 1, 2, 3, 4, 5, 6, 7 or 8, m is 2, 3, 4, 5, 6, 7 or 8, n is 1, and each *N*p is independently *R*p or *S*p.

20. The method of claim 19, wherein *N*p is *S*p.

21. The method of claim 19, wherein t is greater than 5.

22. The method of claim 21, wherein the pattern of backbone chiral centers comprises $(Sp)_2Rp(Sp)_2$.

23. The method of claim 14, wherein the oligonucleotides of the particular oligonucleotide type each comprise one or more phosphate diester linkages.

24. The method of claim 14, wherein the nucleobases of the oligonucleotides of the particular oligonucleotide type are independently selected from adenine, thymine, cytosine, guanine, uracil and 5-methylcytosine.

25. The method of claim 14, wherein the oligonucleotides of the particular oligonucleotide type each comprise a modified sugar.

26. The method of claim 25, wherein the modified sugar comprises a 2'-modification.

27. The method of claim 26, wherein the 2'-modification is 2'-OR^1, wherein R^1 is optionally substituted C_{1-6} aliphatic.

28. The method of claim 26, wherein the 2'-modification is 2'-OMe.

29. The method of claim 26, wherein the 2'-modification is 2'-OCH_2CH_2OMe.

30. The method of claim 25, wherein the oligonucleotides of the particular oligonucleotide type each comprise a locked nucleic acid sugar.

31. The method of claim 25, wherein the modified sugar comprises a bivalent substituent −L−, wherein −L− is −O−CH_2− between C_2 and C_4 of the sugar, wherein the −CH_2− is optionally substituted.

32. The method of claim 25, wherein the modified sugar comprises a bivalent substituent −L−, wherein −L− is −O−CH_2(Et)− between C_2 and C_4 of the sugar.