Claims

What is claimed is:

1. An oligonucleotide of Formula (A):

$$X^{5'}-(X^N)_b-Y^P-(X^N)_c-X^{3'} \qquad (A)$$

or a stereoisomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; wherein:

each X^N is independently a nucleotide;

$X^{3'}$ is a 3' terminal nucleotide;

$X^{5'}$ is a 5' terminal nucleotide;

Y^P is an internucleoside phosphotriester; and

b and c are each an integer ranging from about 0 to about 25; with the proviso that their sum is no less than 5;

wherein the oligonucleotide comprises a nucleotide with a modified nucleobase.

2. An oligonucleotide having a sequence of $N^1N^2CGN^3CG(T)_xGN^4CGN^5T$ (SEQ ID NO:497), wherein:

x is an integer ranging from 1 to 4;

N^1 is absent or 2'-deoxythymidine;

N^2 is a 2'-deoxyribonucleotide with a modified nucleobase;

N^3 is 2'-deoxyadenosine or 2'-deoxythymidine, each optionally comprising a 3'-phosphotriester;

N^4 is 2'-deoxyadenosine or 2'-deoxythymidine; and

N^5 is 2'-deoxythymidine optionally comprising a 3'-phosphotriester.

3. The oligonucleotide of claim 1, wherein b is an integer ranging from about 1 to about 15.

4. The oligonucleotide of claim 1, wherein b is an integer of about 2, about 3, about 4, about 11, or about 14.

5. The oligonucleotide of claim 1, wherein c is an integer ranging from about 0 to about 10.

6. The oligonucleotide of claim 1, wherein c is an integer of about 0 or about 8.

7. The oligonucleotide of claim 1, wherein the sum of b and c is ranging from about 5 to about 20.

8. The oligonucleotide of claim 1, wherein the sum of b and c is about 8, about 9, about 10, about 11, about 12, about 13, or about 14.

9. The oligonucleotide of claim 1, wherein each X^N is independently a 2'-deoxyribonucleotide.

10. The oligonucleotide of claim 1, wherein $X^{3'}$ is a 2'-deoxyribonucleotide.

11. The oligonucleotide of claim 1, wherein $X^{3'}$ is 2'-deoxyadenosine, 2'-deoxyguanosine, 2'-deoxycytidine, a 5-halo-2'-deoxycytidine, 2'-deoxythymidine, 2'-deoxyuridine, or a 5-halo-2'-deoxyuridine.

12. The oligonucleotide of claim 1, wherein $X^{3'}$ is 2'- deoxythymidine.

13. The oligonucleotide of claim 1, wherein $X^{3'}$ is a 2'-modified ribonucleotide.

14. The oligonucleotide of claim 1, wherein $X^{3'}$ is a 2'-methoxy ribonucleotide or 2'-ethoxymethoxy ribonucleotide.

15. The oligonucleotide of claim 1, wherein $X^{5'}$ is a 2'-deoxyribonucleotide.

16. The oligonucleotide of claim 1, wherein $X^{5'}$ is 2'-deoxyadenosine, 2'-deoxyguanosine, 2'-deoxycytidine, a 5-halo-2'-deoxycytidine, 2'-deoxythymidine, 2'-deoxyuridine, or a 5-halo-2'-deoxyuridine.

17. The oligonucleotide of claim 1, wherein $X^{5'}$ is a 2'-deoxyribonucleotide with a substituted pyrimidine base.

18. The oligonucleotide of claim 1, wherein $X^{5'}$ is a 2'-deoxyribonucleotide with a 5-substituted pyrimidine base.

19. The oligonucleotide of claim 1, wherein $X^{5'}$ is 2'-deoxythymidine, a 5-halo-2'-deoxycytidine, or a 5-halo-2'-deoxyuridine.

20. The oligonucleotide of claim 1, wherein $X^{5'}$ is a 5-halo-2'-deoxycytidine.

21. The oligonucleotide of claim 1, wherein $X^{5'}$ is a 5-halo-2'-deoxyuridine.

22. The oligonucleotide of claim 1, wherein $X^{5'}$ is 2'-deoxythymidine, 5-bromo-2'-deoxycytidine, 5-iodo-2'-deoxycytidine, 5-bromo-2'-deoxyuridine, or 5-iodo-2'-deoxyuridine.

23. The oligonucleotide of claim 1, wherein $X^{5'}$ is 2'-deoxythymidine, 5-bromo-2'-deoxyuridine, or 5-iodo-2'-deoxyuridine.

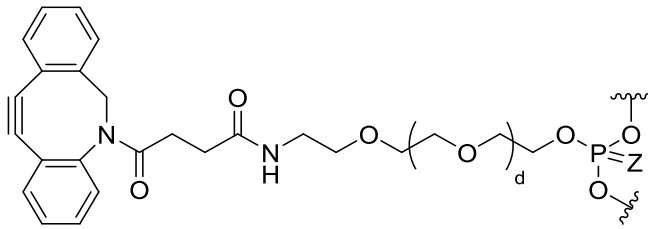
24. The oligonucleotide of claim 1, wherein $X^{5'}$ has a 3'-phosphorothioate group.

25. The oligonucleotide of claim 24, wherein the 3'-phosphorothioate is chiral.

26. The oligonucleotide of claim 25, wherein $X^{5'}$ has a 3'-phosphorothioate group having a chirality of *R*p and $X^{3'}$ is a 2'-methoxy ribonucleotide or 2'-ethoxymethoxy ribonucleotide.

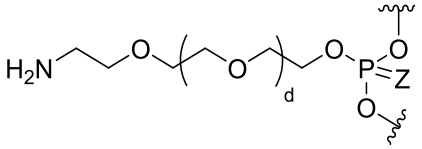
27. The oligonucleotide of claim 25, wherein $X^{5'}$ has a 3'-phosphorothioate group having a chirality of *S*p and $X^{3'}$ is a 2'-methoxy ribonucleotide or 2'-ethoxymethoxy ribonucleotide.

28. The oligonucleotide of claim 1, wherein Y^P is:



wherein Z is O or S; and d is an integer ranging from about 0 to about 50.

29. The oligonucleotide of claim 1, wherein Y^P is:



wherein Z is O or S; and d is an integer ranging from about 0 to about 50.

30. The oligonucleotide of claim 1, comprising an additional internucleoside phosphotriester.

31. The oligonucleotide of claim 30, wherein the additional internucleoside phosphotriester is an alkylphosphotriester.

32. The oligonucleotide of claim 1, comprising one or more internucleoside phosphorothioates.

33. Use of a compound in the manufacture of a medicament for a method of treating cancer in a subject having cancer, wherein the compound comprising a therapeutically effective amount of an oligonucleotide of claim 1, the compound is to be administered into the subject.

34. A compound for use in treating cancer in a subject having cancer, wherein the compound comprising a therapeutically effective amount of an oligonucleotide of claim 1, and the compound is to be administered into the subject.

35. A method of modulating an endosomal toll-like receptor in a cell comprising the endosomal toll-like receptor, the method comprising contacting the cell with the oligonucleotide of claim 1, under conditions permitting the immunomodulating polynucleotides to be transported into the cell, wherein, after the contacting, the activity of the endosomal toll-like receptor is modulated.

36. A method of inducing one or more cytokines in an antigen-presenting cell comprising an endosomal toll-like receptor, the method comprising contacting the antigen-presenting cell with the oligonucleotide of claim 1 under conditions permitting the one or more immunomodulating polynucleotides to be transported into the cell, wherein, after the contacting, the level of at least one cytokine in the cell is increased, wherein the targeting moiety targets the antigen-presenting cell; and wherein the immunomodulating polynucleotide is an immunostimulating polynucleotide.