

WHAT IS CLAIMED IS:

1. A multimeric oligonucleotide comprising a plurality of subunits ***** and a protected sulfur-containing end group,

wherein:

each of the subunits ***** is independently a single or double stranded oligonucleotide and is joined to another subunit by a covalent linker ●;

at least one of the covalent linker ● is a sulfur-containing covalent linker ◇, optionally the sulfur-containing covalent linker comprises a sulfur-containing cleavable group;

the sulfur-containing end group is deprotectable under a deprotection condition;

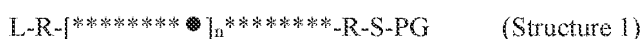
and

each sulfur-containing covalent linker ◇ is stable under the deprotection condition.

2. The multimeric oligonucleotide of claim 1, wherein at least one sulfur-containing covalent linker ◇ comprises a cleavable group, optionally a sulfur-containing cleavable group, that is cleavable under a cleavage condition that is not the deprotection condition.

3. The multimeric oligonucleotide of any one of claims 1 to 2, wherein the protected sulfur-containing end group comprises a protected thiol group.

4. The multimeric oligonucleotide of any one of claims 1 to 3 comprising the following Structure 1:



wherein:

L is a bioactive moiety that may be present or absent;

each R is individually a spacer group that may be present or absent;

each ***** is independently a single or double stranded oligonucleotide subunit;

each ● is a covalent linker joining adjacent oligonucleotide subunits;

n is an integer in the range of 1 to 9;

S-PG is a protected sulfur-containing end group, optionally a protected thiol group, that is deprotectable under a deprotection condition; and

at least one $\bullet$ is a sulfur-containing covalent linker $\diamond$, optionally the sulfur-containing covalent linker comprises a sulfur-containing cleavable group, that is stable under the deprotection condition.

5. The multimeric oligonucleotide of claim 4, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl; optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl.

6. The multimeric oligonucleotide of claim 5, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises C₁₋₁₀ alkyl, C₁₋₁₀ alkyl ether, C₁₋₁₀ alkyl ester, 6-10 membered aryl, 5-10 membered heteroaryl, 5-10 membered heterocyclyl, (C₁₋₁₀ alkyl)-(6-10 membered aryl), (C₁₋₁₀ alkyl)-(5-10 membered heteroaryl), or (C₁₋₁₀ alkyl)-(5-10 membered heterocyclyl); optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises C₁₋₁₀ alkyl, C₁₋₁₀ alkyl ether, C₁₋₁₀ alkyl ester, 6-10 membered aryl, 5-10 membered heteroaryl, 5-10 membered heterocyclyl, (C₁₋₁₀ alkyl)-(6-10 membered aryl), (C₁₋₁₀ alkyl)-(5-10 membered heteroaryl), or (C₁₋₁₀ alkyl)-(5-10 membered heterocyclyl).

7. The multimeric oligonucleotide of claim 6, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises C_{2-C10} alkyl, C_{2-C10} alkyl ether, C_{2-C10} alkyl ester, or C_{6-C10} aryl; optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises C_{2-C10} alkyl, C_{2-C10} alkyl ether, C_{2-C10} alkyl ester, or C_{6-C10} aryl.

8. The multimeric oligonucleotide of claim 7, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises C₂, C₃, C₄, C₅, or C₆ alkyl; optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises C₂, C₃, C₄, C₅, or C₆ alkyl.

9. The multimeric oligonucleotide of claim 8, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises C₆ alkyl; optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises C₆ alkyl.

10. The multimeric oligonucleotide of claim 7, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises 1,4-phenylene; optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises 1,4-phenylene.

11. The multimeric oligonucleotide of any one of claims 1 to 10, wherein the sulfur-containing covalent linker $\diamond$ comprises a linkage represented by $-\text{R}^1-\text{R}^2-\text{R}^1-$, wherein:

each R¹ is individually absent or a spacer group; and

R² is a thiopropionate or disulfide group.

12. The multimeric oligonucleotide of claim 11, wherein the protected sulfur-containing end group does not comprise a thiopropionate group or a disulfide group.

13. The multimeric oligonucleotide of claim 11 or 12, wherein at least one of the spacer groups R¹ that is present in the linkage comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl; optionally wherein every spacer group R¹ that is present in the linkage comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl.

14. The multimeric oligonucleotide of claim 13, wherein at least one of the spacer groups R¹ that is present in the linkage comprises C₁₋₁₀ alkyl, C₁₋₁₀ alkyl ether, C₁₋₁₀ alkyl ester, 6-10 membered aryl, 5-10 membered heteroaryl, 5-10 membered heterocyclyl, (C₁₋₁₀ alkyl)-(6-10 membered aryl), (C₁₋₁₀ alkyl)-(5-10 membered heteroaryl), or (C₁₋₁₀ alkyl)-(5-10 membered heterocyclyl); optionally wherein every spacer group R₁ that is present in the linkage comprises C₁₋₁₀ alkyl, C₁₋₁₀ alkyl ether, C₁₋₁₀ alkyl ester, 6-10 membered aryl, 5-10 membered heteroaryl, 5-10 membered heterocyclyl, (C₁₋₁₀ alkyl)-(6-10 membered aryl), (C₁₋₁₀ alkyl)-(5-10 membered heteroaryl), or (C₁₋₁₀ alkyl)-(5-10 membered heterocyclyl).

15. The multimeric oligonucleotide of claim 14, wherein at least one of the spacer groups R^1 that is present in the linkage comprises C₂-C₁₀ alkyl, C₂-C₁₀ alkyl ether, C₂-C₁₀ alkyl ester, or C₆-C₁₀ aryl; optionally wherein every spacer group R^1 that is present in the linkage comprises C₂-C₁₀ alkyl, C₂-C₁₀ alkyl ether, C₂-C₁₀ alkyl ester, or C₆-C₁₀ aryl.

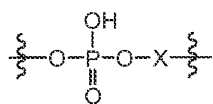
16. The multimeric oligonucleotide of claim 15, wherein at least one of the spacer groups R^1 that is present in the linkage comprises C₂, C₃, C₄, C₅, or C₆ alkyl; optionally wherein every spacer group R^1 that is present in the linkage comprises C₂, C₃, C₄, C₅, or C₆ alkyl.

17. The multimeric oligonucleotide of claim 16, wherein at least one of the spacer groups R^1 that is present in the linkage comprises C₆ alkyl; optionally wherein every spacer group R^1 that is present in the linkage comprises C₆ alkyl.

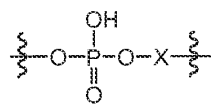
18. The multimeric oligonucleotide of claim 15, wherein at least one of the spacer groups R^1 that is present in the linkage comprises 1,4-phenylene; optionally wherein every spacer group R^1 that is present in the linkage comprises 1,4-phenylene.

19. The multimeric oligonucleotide of any one of claims 11 to 18, wherein at least one of the spacer groups R^1 that is present in the linkage comprises a phosphate linking group, a phosphorothioate linking group, a phosphonate linking group, or a dithiophosphate linking group; optionally wherein every spacer group R^1 that is present in the linkage comprises a phosphate linking group, a phosphorothioate linking group, a phosphonate linking group, or a dithiophosphate linking group.

20. The multimeric oligonucleotide of claim 19, wherein at least one of the spacer groups R^1 that is present in the linkage comprises a linking group represented by



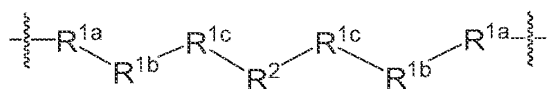
; optionally wherein every spacer group R^1 that is present in the linkage



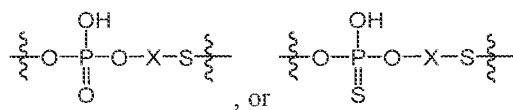
comprises a linking group represented by O^n ; wherein each X independently comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl.

21. The multimeric oligonucleotide of any one of claims 11 to 20, wherein at least one of the spacer groups R^1 that is present in the linkage comprises a pyrrolidine-2,5-dione; optionally wherein every spacer group R^1 that is present in the linkage comprises a pyrrolidine-2,5-dione.

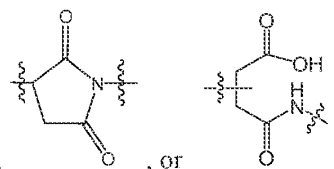
22. The multimeric oligonucleotide of claim 11, wherein the linkage represented by $R^1-R^2-R^1$ is also represented by:



wherein:



each R^{1a} is independently absent,



each R^{lb} is independently absent,

each R^{lc} is X ; and

R² is a thiopropionate or disulfide group;

wherein each X independently comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl.

23. The multimeric oligonucleotide of claim 22, wherein each X independently comprises C₁₋₁₀ alkyl, C₁₋₁₀ alkyl ether, C₁₋₁₀ alkyl ester, 6-10 membered aryl, 5-10 membered heteroaryl, 5-10 membered heterocyclyl, (C₁₋₁₀ alkyl)-(6-10 membered aryl), (C₁₋₁₀ alkyl)-(5-10 membered heteroaryl), or (C₁₋₁₀ alkyl)-(5-10 membered heterocyclyl).

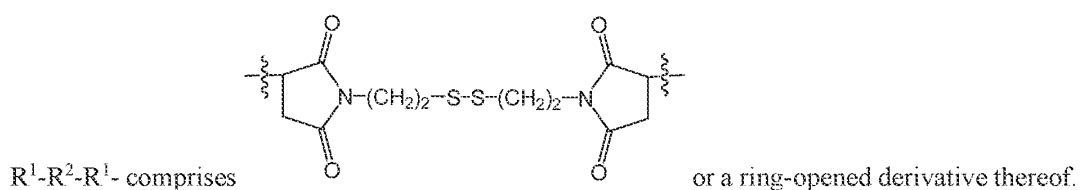
24. The multimeric oligonucleotide of claim 23, wherein each X independently comprises C₂-C₁₀ alkyl, C₂-C₁₀ alkyl ether, C₂-C₁₀ alkyl ester, or C₆-C₁₀ aryl.

25. The multimeric oligonucleotide of claim 24, wherein each X independently comprises C₂, C₃, C₄, C₅, or C₆ alkyl.

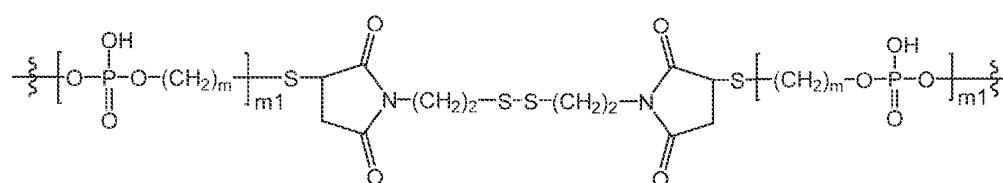
26. The multimeric oligonucleotide of claim 22, wherein each X comprises C₆ alkyl.

27. The multimeric oligonucleotide of claim 22, wherein each X comprises 1,4-phenylene.

28. The multimeric oligonucleotide of claim 22, wherein the linkage represented by –



29. The multimeric oligonucleotide of claim 22, wherein the linkage represented by – R¹-R²-R¹- is:



or a ring-opened derivative thereof, wherein m and m₁ are each individually an integer in the range of 1 to 10.

30. The multimeric oligonucleotide of any one of claims 1 to 29, wherein the protected sulfur-containing end group comprises a protecting group selected from optionally substituted alkyl, optionally substituted alkoxyalkyl, optionally substituted trialkylsilyl, optionally substituted

arylalkylsilyl, optionally substituted aryl, optionally substituted benzyl, optionally substituted acyl and optionally substituted benzoyl.

31. The multimeric oligonucleotide of any one of claims 1 to 29, wherein the protected sulfur-containing end group comprises a protecting group PG selected from trityl, methoxytrityl, dimethoxytrityl, methylmethoxy, triisopropylsilyl, dinitrophenyl, nitrophenyl, acetyl and benzoyl.

32. The multimeric oligonucleotide of any one of claims 4 to 31, where n is an integer in the range of 2 to 9; optionally wherein n is an integer in the range of 2 to 7; optionally wherein n is 2, 3, 4 or 5.

33. The multimeric oligonucleotide of any one of claims 1 to 32, wherein at least two subunits ***** are substantially different.

34. The multimeric oligonucleotide of any one of claims 1 to 33, wherein the multimeric oligonucleotide comprises three, four, five, or six subunits *****.

35. The multimeric oligonucleotide of any one of claims 1 to 34, wherein each nucleic acid strand within a subunit ***** is 5-30, 15-30, 17-27, 19-26, or 20-25 nucleotides in length.

36. The multimeric oligonucleotide of any one of claims 1 to 35, wherein one or more subunits ***** are a double-stranded RNA.

37. The multimeric oligonucleotide of any one of claims 1 to 36, wherein one or more subunits ***** are a single-stranded RNA.

38. The multimeric oligonucleotide of any one of claims 1 to 37, wherein the subunits ***** comprise a combination of single-stranded and double-stranded oligonucleotides.

39. The multimeric oligonucleotide of any one of claims 1 to 38, wherein each subunit ***** is an RNA, a DNA, or an artificial or non-natural nucleic acid analog thereof.

40. The multimeric oligonucleotide of any one of claims 1 to 39, wherein each subunit ***** is an siRNA, an saRNA, or a miRNA.

41. The multimeric oligonucleotide of any one of claims 1 to 36, wherein each subunit ***** is a double-stranded siRNA.

42. The multimeric oligonucleotide of any one of claims 1 to 41, wherein at least one of the covalent linkers ♦ is a cleavable covalent linker CL, the cleavable covalent linker CL being different from the sulfur-containing covalent linker ◇.

43. The multimeric oligonucleotide of claim 42, wherein the cleavable covalent linker CL comprises an acid cleavable bond, a reductant cleavable bond, a bio-cleavable bond, or an enzyme cleavable bond.

44. The multimeric oligonucleotide of claim 42 or 43, wherein the cleavable covalent linker CL is cleavable under intracellular conditions.

45. The multimeric oligonucleotide of any one of claims 4 to 44, wherein L comprises a targeting ligand.

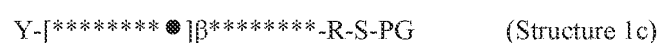
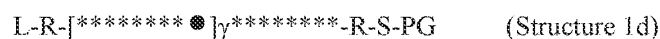
46. The multimeric oligonucleotide of claim 45, wherein the targeting ligand comprises an aptamer, N-Acetylgalactosamine (GalNAc), folate, lipid, cholesterol, or transferrin.

47. The multimeric oligonucleotide of any one of claims 4 to 44, wherein L comprises an endosomal escape moiety.

48. The multimeric oligonucleotide of claim 47, wherein the endosomal escape moiety is a membrane disrupting, altering, or destabilizing peptide, lipid, polymer, or small molecule.

49. The multimeric oligonucleotide of any one of claims 4 to 44, wherein L comprises a detectable label.

50. A process for preparing a multimeric oligonucleotide of Structure 1d, comprising: deprotecting a compound of Structure 1a to form a compound of Structure 1b; and reacting the compound of Structure 1b with a compound of Structure 1c under conditions selected to form a compound of Structure 1d, as follows:



wherein:

L is a bioactive moiety that may be present or absent;

each R is individually a spacer group that may be present or absent;

each ***** is independently a single or double stranded oligonucleotide;

each $\bullet$ is a covalent linker joining adjacent oligonucleotide subunits;

S-PG is a protected sulfur-containing end group, optionally a protected thiol group, that is deprotectable under a deprotection condition;

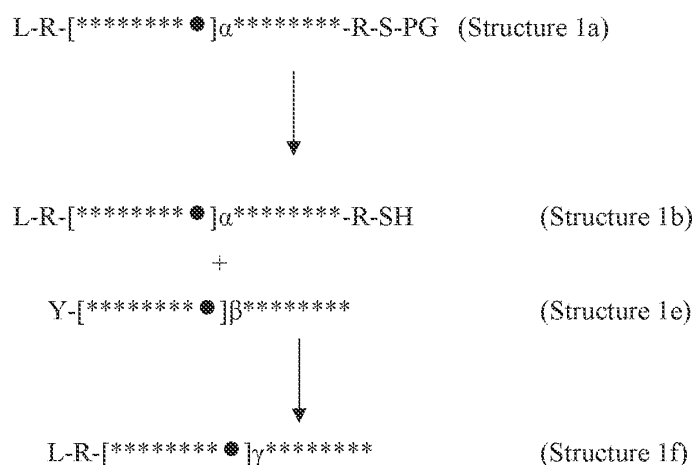
Y is a reactive group selected to react with the -R-SH group of Structure 1b to form one of the covalent linkers $\bullet$ of Structure 1d;

γ is an integer in the range of 1 to 9;

α and β are each individually an integer in the range of 0 to 8, selected such that $\alpha + \beta + 1 = \gamma$; and

at least one $\bullet$ is a sulfur-containing covalent linker $\diamond$ that is stable under the deprotection condition; optionally the sulfur-containing covalent linker comprises a sulfur-containing cleavable group.

51. A process for preparing a multimeric oligonucleotide of Structure 1f comprising: deprotecting a compound of Structure 1a to form a compound of Structure 1b; and reacting the compound of Structure 1b with a compound of Structure 1e under conditions selected to form a compound of Structure 1f, as follows:



wherein:

L is a moiety that may be present or absent and has biological activity or affinity;

each R is individually a spacer group that may be present or absent;

each ***** is independently a single or double stranded oligonucleotide;

each $\bullet$ is a covalent linker joining adjacent oligonucleotide subunits;

S-PG is a protected sulfur-containing end group, optionally a protected thiol group, that is deprotectable under a deprotection condition;

Y is a reactive group selected to react with the -R-SH group of Structure 1b to form one of the covalent linkers $\bullet$ of Structure 1f;

γ is an integer in the range of 1 to 9;

α and β are each individually an integer in the range of 0 to 8, selected such that $\alpha + \beta + 1 = \gamma$;

at least one $\bullet$ is a sulfur-containing covalent linker $\diamond$ that is stable under the deprotection condition; optionally the sulfur-containing covalent linker comprises a sulfur-containing cleavable group.

52. The process of claim 50 or 51, wherein the sulfur-containing covalent linker $\diamond$ comprises a cleavable group that is cleavable under a cleavage condition that is not the deprotection condition.

53. The process of any one of claims 50 to 52, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl; optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl.

54. The process of claim 53, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises C₁₋₁₀ alkyl, C₁₋₁₀ alkyl ether, C₁₋₁₀ alkyl ester, 6-10 membered aryl, 5-10 membered heteroaryl, 5-10 membered heterocyclyl, (C₁₋₁₀ alkyl)-(6-10 membered aryl), (C₁₋₁₀ alkyl)-(5-10 membered heteroaryl), or (C₁₋₁₀ alkyl)-(5-10 membered heterocyclyl); optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises C₁₋₁₀ alkyl, C₁₋₁₀ alkyl ether, C₁₋₁₀ alkyl ester, 6-10 membered aryl, 5-10 membered heteroaryl, 5-10 membered heterocyclyl, (C₁₋₁₀ alkyl)-(6-10 membered aryl), (C₁₋₁₀ alkyl)-(5-10 membered heteroaryl), or (C₁₋₁₀ alkyl)-(5-10 membered heterocyclyl).

55. The process of claim 54, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises C_{2-C10} alkyl, C_{2-C10} alkyl ether, C_{2-C10} alkyl ester, or C_{6-C10} aryl; optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises C_{2-C10} alkyl, C_{2-C10} alkyl ether, C_{2-C10} alkyl ester, or C_{6-C10} aryl.

56. The process of claim 55, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises C₂, C₃, C₄, C₅, or C₆ alkyl; optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises C₂, C₃, C₄, C₅, or C₆ alkyl.

57. The process of claim 56, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises C₆ alkyl; optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises C₆ alkyl.

58. The process of claim 55, wherein at least one of the spacer groups R that is present in the multimeric oligonucleotide comprises 1,4-phenylene; optionally wherein every spacer group R that is present in the multimeric oligonucleotide comprises 1,4-phenylene.

59. The process of any one of claims 50 to 58, wherein the sulfur-containing covalent linker $\diamond$ comprises a linkage represented by $-\text{R}^1-\text{R}^2-\text{R}^1-$, wherein:

each R¹ is individually absent or a spacer group; and

R² is a thiopropionate or disulfide group.

60. The process of claim 59, wherein the protected sulfur-containing end group S-PG does not comprise a thiopropionate group or a disulfide group.

61. The process of claim 59 or 60, wherein at least one of the spacer groups R¹ that is present in the linkage comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl; optionally wherein every spacer group R¹ that is present in the linkage comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl.

62. The process of claim 61, wherein at least one of the spacer groups R¹ that is present in the linkage comprises C₁₋₁₀ alkyl, C₁₋₁₀ alkyl ether, C₁₋₁₀ alkyl ester, 6-10 membered aryl, 5-10 membered heteroaryl, 5-10 membered heterocyclyl, (C₁₋₁₀ alkyl)-(6-10 membered aryl), (C₁₋₁₀ alkyl)-(5-10 membered heteroaryl), or (C₁₋₁₀ alkyl)-(5-10 membered heterocyclyl); optionally

wherein every spacer group R^1 that is present in the linkage comprises C_{1-10} alkyl, C_{1-10} alkyl ether, C_{1-10} alkyl ester, 6-10 membered aryl, 5-10 membered heteroaryl, 5-10 membered heterocyclyl, (C_{1-10} alkyl)-(6-10 membered aryl), (C_{1-10} alkyl)-(5-10 membered heteroaryl), or (C_{1-10} alkyl)-(5-10 membered heterocyclyl).

63. The process of claim 62, wherein at least one of the spacer groups R^1 that is present in the linkage comprises C_2 - C_{10} alkyl, C_2 - C_{10} alkyl ether, C_2 - C_{10} alkyl ester, or C_6 - C_{10} aryl; optionally wherein every spacer group R^1 that is present in the linkage comprises C_2 - C_{10} alkyl, C_2 - C_{10} alkyl ether, C_2 - C_{10} alkyl ester, or C_6 - C_{10} aryl.

64. The process of claim 63, wherein at least one of the spacer groups R^1 that is present in the linkage comprises C_2 , C_3 , C_4 , C_5 , or C_6 alkyl; optionally wherein every spacer group R^1 that is present in the linkage comprises C_2 , C_3 , C_4 , C_5 , or C_6 alkyl.

65. The process of claim 64, wherein at least one of the spacer groups R^1 that is present in the linkage comprises C_6 alkyl; optionally wherein every spacer group R^1 that is present in the linkage comprises C_6 alkyl.

66. The process of claim 63, wherein at least one of the spacer groups R^1 that is present in the linkage comprises 1,4-phenylene; optionally wherein every spacer group R^1 that is present in the linkage comprises 1,4-phenylene.

67. The process of any one of claims 50 to 66, wherein at least one of the spacer groups R^1 that is present in the linkage comprises a phosphate linking group, a phosphorothioate linking group, a phosphonate linking group, or a dithiophosphate linking group; optionally wherein every spacer group R^1 that is present in the linkage comprises a phosphate linking group, a phosphorothioate linking group, a phosphonate linking group, or a dithiophosphate linking group.

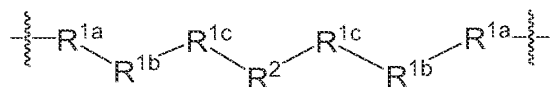
68. The process of claim 67, wherein at least one of the spacer groups R^1 that is present

in the linkage comprises a linking group represented by $\text{--}\text{O--}\text{P}(\text{OH})(\text{O--X--})\text{--}\text{O--}\text{--}$; optionally wherein every spacer group R^1 that is present in the linkage comprises a linking group represented by

$\text{--}\text{O--}\text{P}(\text{OH})(\text{O--X--})\text{--}\text{O--}\text{--}$; wherein each X independently comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl.

69. The process of any one of claims 50 to 68, wherein at least one of the spacer groups R^1 that is present in the linkage comprises a pyrrolidine-2,5-dione; optionally wherein every spacer group R^1 that is present in the linkage comprises a pyrrolidine-2,5-dione.

70. The process of claim 59, wherein the linkage represented by $\text{--}R^1\text{--}R^2\text{--}R^1\text{--}$ is also represented by:



wherein:

each R^{1a} is independently absent, $\text{--}\text{O--}\text{P}(\text{OH})(\text{O--X--})\text{--}\text{O--}\text{--}$, or $\text{--}\text{O--}\text{P}(\text{OH})(\text{O--X--})\text{--}\text{S--}\text{--}$;

each R^{1b} is independently absent, $\text{--}\text{C}_4\text{H}_4\text{N--}$, or $\text{--}\text{C}_4\text{H}_3\text{N--}$;

each R^{1c} is X; and

R^2 is a thiopropionate or disulfide group;

wherein each X independently comprises alkyl, alkyl ether, ester, aryl, heteroaryl, heterocyclyl, alkyl-aryl, alkyl-heteroaryl, or alkyl-heterocyclyl.

71. The process of claim 70, wherein each X independently comprises C₁₋₁₀ alkyl, C₁₋₁₀ alkyl ether, C₁₋₁₀ alkyl ester, 6-10 membered aryl, 5-10 membered heteroaryl, 5-10 membered heterocyclyl, (C₁₋₁₀ alkyl)-(6-10 membered aryl), (C₁₋₁₀ alkyl)-(5-10 membered heteroaryl), or (C₁₋₁₀ alkyl)-(5-10 membered heterocyclyl).

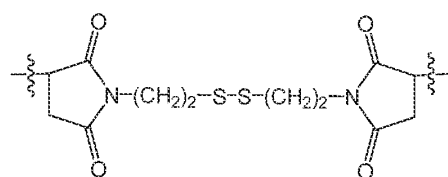
72. The process of claim 71, wherein each X independently comprises C_{2-C10} alkyl, C_{2-C10} alkyl ether, C_{2-C10} alkyl ester, or C_{6-C10} aryl.

73. The process of claim 71, wherein each X independently comprises C₂, C₃, C₄, C₅, or C₆ alkyl.

74. The process of claim 73, wherein each X comprises C₆ alkyl.

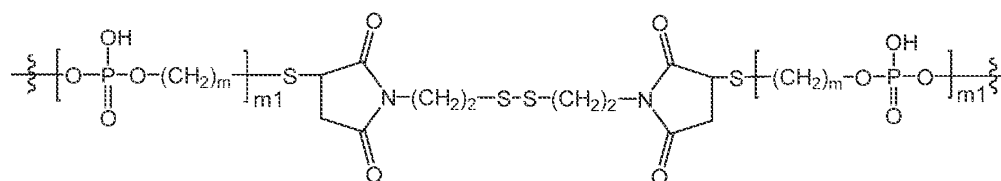
75. The process of claim 72, wherein each X comprises 1,4-phenylene.

76. The process of claim 70, wherein the linkage represented by $-R^1-R^2-R^1-$ comprises



or a ring-opened derivative thereof.

77. The process of claim 70, wherein the linkage represented by $-R^1-R^2-R^1-$ is:



or a ring-opened derivative thereof, wherein m and m1 are each individually an integer in the range of 1 to 10.

78. The process of any one of claims 50 to 77, wherein the protected sulfur-containing end group comprises a protecting group selected from optionally substituted alkyl, optionally substituted alkoxyalkyl, optionally substituted trialkylsilyl, optionally substituted arylalkylsilyl, optionally substituted aryl, optionally substituted benzyl, optionally substituted acyl and optionally substituted benzoyl.

79. The process of any one of claims 50 to 77, wherein the protected sulfur-containing end group comprises a protecting group PG selected from trityl, methoxytrityl, dimethoxytrityl, methylmethoxy, triisopropylsilyl, dinitrophenyl, nitrophenyl, acetyl and benzoyl.

80. The process of any one of claims 50-79, wherein γ is an integer in the range of 2 to 6.

81. The process of any one of claims 50 to 80, wherein at least two subunits ***** are substantially different.

82. The process of any one of claims 50 to 81, wherein the multimeric oligonucleotide comprises from 3 to 10 subunits subunits *****; optionally, wherein the multimeric oligonucleotide comprises 3, 4, 5 or 6 subunits *****.

83. The process of any one of claims 50 to 82, wherein each nucleic acid strand within a subunit ***** is 5-30, 15-30, 17-27, 19-26, or 20-25 nucleotides in length.

84. The process of any one of claims 50 to 83, wherein one or more subunits ***** are a double-stranded RNA.

85. The process of any one of claims 50 to 84, wherein one or more subunits ***** are a single-stranded RNA.

86. The process of any one of claims 50 to 85, wherein the subunits ***** comprise a combination of single-stranded and double-stranded oligonucleotides.

87. The process of any one of claims 50 to 86, wherein each subunit ***** is an RNA, a DNA, or an artificial or non-natural nucleic acid analog thereof.

88. The process of any one of claims 50 to 87, wherein each subunit ***** is an siRNA, an saRNA, or a miRNA.

89. The process of claim 88, wherein each subunit ***** is a double-stranded siRNA.

90. The process of any of claims 50 to 89, wherein at least one of the covalent linkers ● is a cleavable covalent linker **CL**, the cleavable covalent linker **CL** being different from the sulfur-containing covalent linker ◇.

91. The process of claim 90, wherein the cleavable covalent linker **CL** comprises an acid cleavable bond, a reductant cleavable bond, a bio-cleavable bond, or an enzyme cleavable bond.

92. The process of claim 90 or 91, wherein the cleavable covalent linker **CL** is cleavable under intracellular conditions.

93. The process of any one of claims 50 to 92, wherein L comprises a targeting ligand.

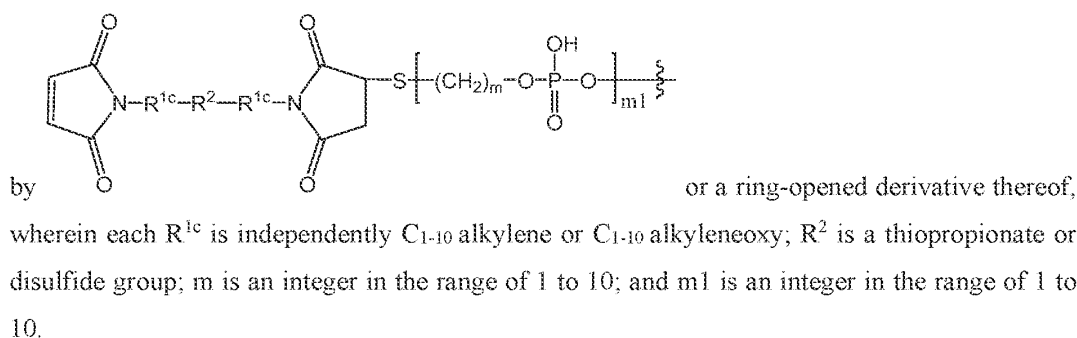
94. The process of claim 93, wherein the targeting ligand comprises an aptamer, N-Acetylgalactosamine (GalNAc), folate, lipid, cholesterol, or transferrin.

95. The process of any one of claims 50 to 92, wherein L comprises an endosomal escape moiety.

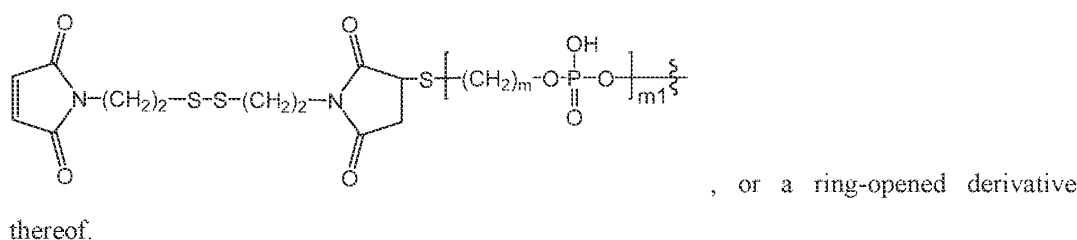
96. The process of claim 95, wherein the endosomal escape moiety is a membrane disrupting, altering, or destabilizing peptide, lipid, polymer, or small molecule.

97. The process of any one of claims 50 to 96, wherein L comprises a detectable label.

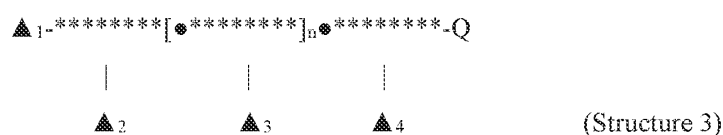
98. The process of any one of claims 50 to 97, wherein Y is a reactive group represented



99. The process of claim 98, wherein Y is a reactive group represented by



100. A multi-conjugate comprising a plurality of subunits ***** joined to one another by one or more covalent linkers ♦, wherein the multi-conjugate comprises Structure 3:



wherein:

each of the subunits ***** is independently a bioactive moiety;

at least one covalent linker ♦ is a sulfur-containing covalent linker ♦, optionally the sulfur-containing covalent linker ♦ comprises a sulfur-containing cleavable group ;

each of $\blacktriangle_1$, $\blacktriangle_2$, $\blacktriangle_3$, and $\blacktriangle_4$ is a group that is independently absent or comprises a functional moiety joined to a subunit and, optionally, a spacer group joining the functional moiety to the subunit;

Q is a group that comprises a sulfur-containing end group, and optionally a spacer group joining Q to the subunit; and

n is an integer greater than or equal to zero; optionally n is an integer in the range of 0 to 10; optionally n is an integer in the range of 0 to 10; optionally n is an integer in the range of 1 to 4; optionally, n is 1, 2, 3 or 4.

101. The multi-conjugate of claim 100, wherein at least one of the subunits ***** present in Structure 3 is not an oligonucleotide.

102. The multi-conjugate of claim 100 or 101, wherein at least one of the subunits ***** present in Structure 3 comprises an oligopeptide or a protein.

103. The multi-conjugate of any one of claims 100 to 102, wherein at least one functional moiety is present.

104. The multi-conjugate of claim 103, wherein the at least one functional moiety that is present is a targeting ligand.

105. The multi-conjugate of claim 103 or 104, wherein the at least one functional moiety that is present is a detectable label; optionally, the detectable label is a dye.

106. The multi-conjugate of any one of claims 100 to 105, wherein:
the sulfur-containing end group Q comprises a protected sulfur-containing end group that is deprotectable under a deprotection condition; and
the sulfur-containing covalent linker $\diamond$ is stable under the deprotection condition.

107. The multi-conjugate of any of claims 100 to 106, wherein the sulfur-containing covalent linker $\diamond$ comprises a cleavable group that is cleavable under a cleavage condition that is not the deprotection condition.

108. The multi-conjugate of any one of claims 100 to 107, wherein the sulfur-containing end group Q comprises a protected thiol group.

109. The multi-conjugate of claim 108, wherein $\blacktriangle_2$, $\blacktriangle_3$, and $\blacktriangle_4$ are absent.

110. The multi-conjugate of any one of claims 100 to 109, wherein at least one covalent linker $\bullet$ comprises Structure 4:



wherein:

each R1 is independently a group comprising phosphodiester, thiophosphodiester, sulfate, amide, triazole, heteroaryl, ester, ether, thioether, disulfide, thiopropionate, acetal, glycol, or is absent;

each R2 is independently a spacer group, or is absent;

each A is independently the reaction product of a nucleophile and an electrophile;

and

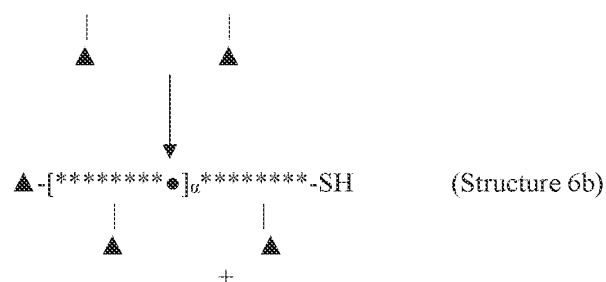
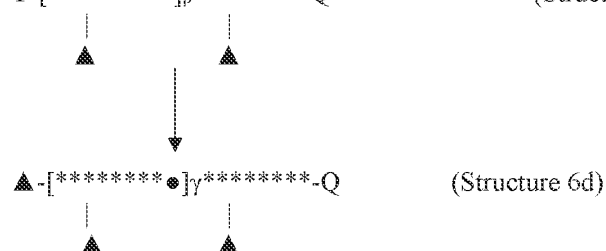
R3 is a group comprising a C2-C10 alkyl, C2-C10 alkoxy, C1-C10 aryl, amide, C2-C10 alkyldithio, ether, thioether, ester, oligonucleotide, oligopeptide, thiopropionate, or disulfide.

111. The multi-conjugate of claim 110, wherein each A is the same.

112. The multi-conjugate of claim 111, wherein R3 comprises a sulfur-containing group; optionally, R3 comprises a sulfur-containing cleavable group including C2-C10 alkyldithio, thioether, thiopropionate, or disulfide.

113. A process for preparing a multi-conjugate of Structure 6d comprising:
deprotecting a compound of Structure 6a to form a compound of Structure 6b; and
reacting the compound of Structure 6b with a compound of Structure 6c under conditions selected to form a compound of Structure 6d, as follows:





wherein:

each of the subunits ***** is independently a bioactive moiety;

each • is a covalent linker;

at least one covalent linker • is a sulfur-containing covalent linker ◊, optionally the sulfur-containing covalent linker ◊ comprises a sulfur-containing cleavable group;

each ▲ is independently a group that is absent or comprises a functional moiety joined to a subunit and, optionally, a spacer group joining the functional moiety to the subunit;

Q is a group that comprises a sulfur-containing end group, and optionally a spacer group joining Q to the subunit;

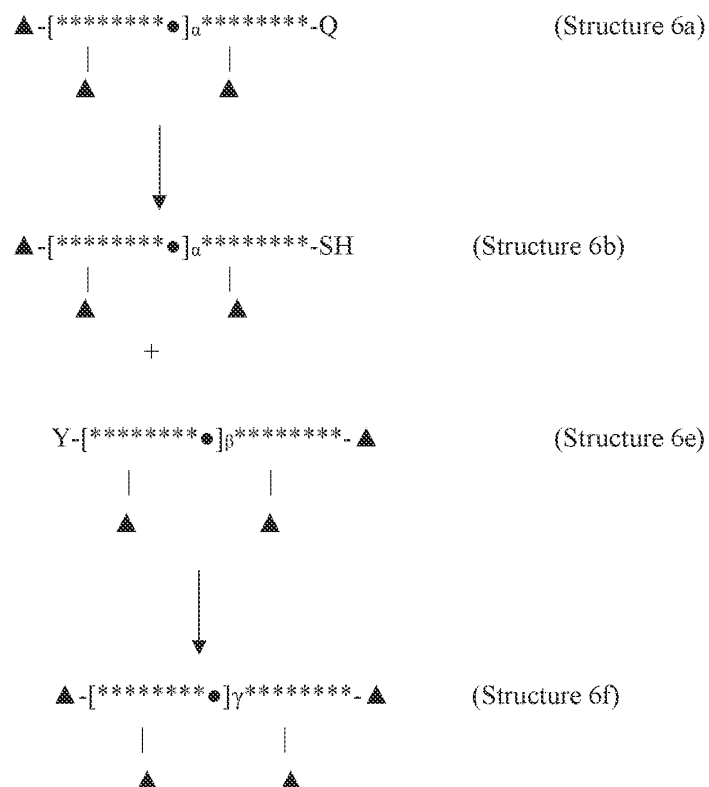
Y is a reactive group selected to react with the -R-SH group of Structure 6b to form one of the covalent linkers • of Structure 6d;

γ is an integer in the range of 1 to 9;

α and β are each individually an integer in the range of 0 to 8, selected such that α + β + 1 = γ.

114. A process for preparing a multi-conjugate of Structure 6f comprising:

deprotecting a compound of Structure 6a to form a compound of Structure 6b; and
 reacting the compound of Structure 6b with a compound of Structure 6e under
 conditions selected to form a compound of Structure 6f, as follows:



wherein:

each of the subunits ***** is independently a bioactive moiety;

each • is a covalent linker;

at least one covalent linker • is a sulfur-containing covalent linker ◊, optionally
 the sulfur-containing covalent linker ◊ comprises a sulfur-containing cleavable group;

each ▲ is independently a group that is absent or comprises a functional moiety
 and, optionally, a spacer group joining the functional moiety to the subunit;

Q is a group that comprises a sulfur-containing end group, and optionally a
 spacer group joining Q to the subunit;

Y is a reactive group selected to react with the $-R-SH$ group of Structure 4b to form one of the covalent linkers $\bullet$ of Structure 6f;
 γ is an integer in the range of 1 to 9;
 α and β are each individually an integer in the range of 0 to 7, selected such that $\alpha + \beta + 1 = \gamma$.

115. A method of treating a disease or condition in a subject comprising the step of administering to the subject an effective amount of a pharmaceutical composition comprising a multimeric oligonucleotide prepared by the process of claim 51.

116. A method of treating a disease or condition in a subject comprising the step of administering to the subject an effective amount of a pharmaceutical composition comprising a multi-conjugate prepared by the process of claim 114.

117. A composition comprising a multimeric oligonucleotide prepared by the process of claim 51 and a pharmaceutically acceptable excipient.

118. A composition comprising a multi-conjugate prepared by the process of claim 114 and a pharmaceutically acceptable excipient.

119. A composition comprising a multimeric oligonucleotide prepared by the process of claim 51 for use in the manufacture of a medicament.

120. A composition comprising a multi-conjugate prepared by the process of claim 114 for use in the manufacture of a medicament.

121. A method of modulating activity of a target gene in a cell, the method comprising contacting the cell with a multimeric oligonucleotide prepared by the process of claim 51 and maintaining the cell under conditions in which the multimeric oligonucleotide enters the cell and the activity of the target genes is modulated.

122. A method of observing the activity of a bioactive moiety in a cell, the method comprising contacting the cell with a multi-conjugate prepared by the process of claim 114 and maintaining the cell under conditions in which the conjugate enters the cell and the activity of the bioactive moiety is observed.

123. The process of claim 113 or 114, wherein:
the sulfur-containing end group Q comprises a protected sulfur-containing end group that is deprotectable under a deprotection condition; and
the sulfur-containing covalent linker $\diamond$ is stable under the deprotection condition.

124. The process of claim 123, wherein the sulfur-containing covalent linker $\diamond$ comprises a cleavable group that is cleavable under a cleavage condition that is not the deprotection condition.

125. The process of any one of claims 113, 114, 123 or 124, wherein the sulfur-containing end group Q comprises a protected thiol group.

126. The process of claim 125, wherein the multi-conjugate comprises from 3 to 10 subunits *****; optionally, wherein the multi-conjugate comprises 3, 4, 5 or 6 subunits *****.