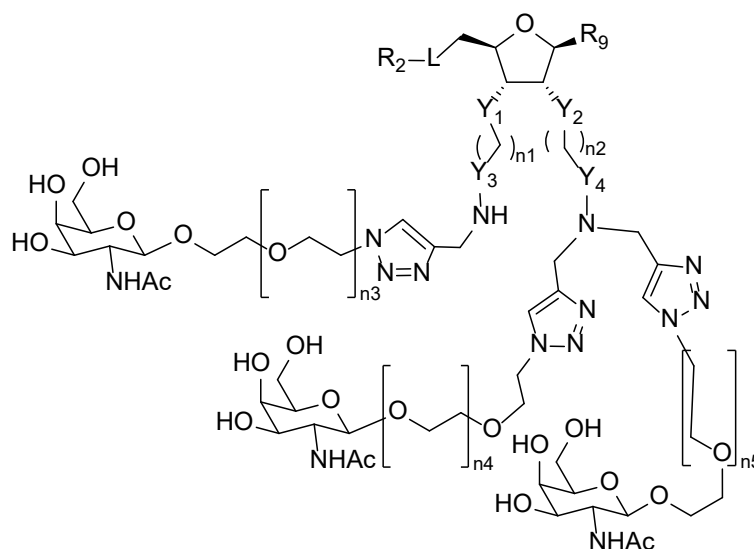


CLAIMS

1. A compound comprising:
 - a first modified oligonucleotide 14 to 30 linked nucleosides in length having a nucleobase sequence comprising at least 14 contiguous nucleobases of the nucleobase sequence of any one of SEQ ID NOs: 43-45, 83-85, 161-168, 245, 246, 307, 312, 313, and 626,
 - wherein the first modified oligonucleotide comprises a modified internucleoside linkage, a modified sugar, and/or a modified nucleobase; and
 - a second modified oligonucleotide 14 to 30 linked nucleosides in length having a region of complementarity to the first modified oligonucleotide,
 - wherein the second modified oligonucleotide comprises a modified internucleoside linkage, a modified sugar, and/or a modified nucleobase, and
 - wherein the second modified oligonucleotide comprises a conjugate group.
2. The compound of claim 1, wherein the nucleobase sequence of the second modified oligonucleotide has at least 80% identity to SEQ ID NO: 1, 3, 5, or 6 over the length of the second modified oligonucleotide.
3. The compound of claim 1 or 2, wherein the nucleobase sequence of the first modified oligonucleotide has 1, 2, or 3 mismatches to a region of the second modified oligonucleotide that is the same length as the first modified oligonucleotide.
4. The compound of claim 3, wherein the mismatch comprises a wobble base pair.
5. The compound of any one of claims 1-4, wherein the region of complementarity between the first modified oligonucleotide and the second modified oligonucleotide is 14 to 23 linked nucleosides in length.
6. The compound of any one of claims 1-5, wherein the first modified oligonucleotide is fully complementary to the second modified oligonucleotide.
7. The compound of any one of claims 1-6, wherein the first and second modified oligonucleotides each comprise a phosphorothioate internucleoside linkage or a methylphosphonate internucleoside linkage between at least two of the terminal three nucleosides at their respective 3' and 5' termini.

8. The compound of any one of claims 1-7, wherein the first and second modified oligonucleotides each comprise a 2'-F modification or a 2'-OMe modification.
9. The compound of claim 8, wherein the first modified oligonucleotide comprises no more than ten 2'-F sugar modifications.
10. The compound of claim 8 or 9, wherein the second modified oligonucleotide comprises no more than five 2'-F sugar modifications.
11. The compound of any one of claims 1-10, wherein the first and second modified oligonucleotides each comprise a sugar modification selected from the group consisting of LNA, cEt, 2'-MOE, 2'-F, 2'-OMe, and 2'-deoxy, or a combination thereof.
12. The compound of any one of claims 1-11, wherein the conjugate group comprises one or more N-Acetyl-galactosamine (GalNAc).
13. The compound of claim 12, wherein the one or more GalNAc are attached to the 2' and/or 3' position of the ribosyl ring of the 5' nucleoside of the first modified oligonucleotide.
14. The compound of claim 13, wherein the 5' nucleoside is of the following formula:



Formula X,

wherein:

R⁹ is H, adenine, guanine, thymine, cytosine, or uracil, or adenine, guanine, thymine, cytosine, or uracil, each comprising a Protecting Group (PG), a modified nucleobase, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, or a nucleobase isostere;

L is a bond, a phosphodiester bond, a phosphorothioate bond, a triazole, a tetrazole, an amide, a reverse-amide, a carbamate, a carbonate, urea, alkyl, or heteroalkyl;

R² is the oligonucleotide sequence;

Y₁ is O, CH₂, CH₂O, or optionally substituted NH;

Y₂ is O, CH₂, CH₂O, or optionally substituted NH;

Y₃ is CO, SO₂, P(O)O, CH₂-O-C(O), CH₂-NH-C(O), CH₂-NH-SO₂, or CH₂;

Y₄ is CO, SO₂, P(O)O, CH₂-O-C(O), CH₂-NH-C(O), CH₂-NH-SO₂, or CH₂;

n₂ is 0, 1, 2, 3, 4, 5, or 6; and

each n₁, n₃, n₄ and n₅ is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

15. The compound of claim 14, wherein the 5' nucleoside is selected from any one of Formulae I-VIII and wherein R' is S and R is the portion of the modified oligonucleotide other than the 5' nucleoside.

16. The compound of claim 14, wherein the 5' nucleoside is selected from any one of Formulae I-VIII and wherein R' is O and R is the portion of the modified oligonucleotide other than the 5' nucleoside.

17. The compound of any one of claims 1-16, wherein the nucleobase sequence of the first modified oligonucleotide comprises at least 16 contiguous nucleobases of the nucleobase sequence of any one of SEQ ID NOs: 43-45, 83-85, 161-168, 245, 246, 307, 312, 313, and 626.

18. The compound of any one of claims 1-16, wherein the nucleobase sequence of the first modified oligonucleotide comprises at least 19 contiguous nucleobases of the nucleobase sequence of any one of SEQ ID NOs: 43-45, 83-85, 161-168, 245, 246, 307, 312, 313, and 626.

19. The compound of any one of claims 1-16, wherein the first modified oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NOs: 43-45, 83-85, 161-168, 245, 246, 307, 312, 313, and 626.

20. The compound of any one of claims 1-19, wherein the first modified oligonucleotide comprises Ref ID NO: IA0818, and the second modified oligonucleotide comprises Ref ID NO: IS1058.
21. The compound of any one of claims 1-19, wherein the first modified oligonucleotide comprises Ref ID NO: IA0813, and the second modified oligonucleotide comprises Ref ID NO: IS1002.
22. The compound of any one of claims 1-19, wherein the first modified oligonucleotide comprises Ref ID NO: IA0818, and the second modified oligonucleotide is selected from Ref ID NOs: IS1007, IS1066, and IS1068.
23. The compound of any one of claims 1-19, wherein the first modified oligonucleotide comprises Ref ID NO: IA0828, and the second modified oligonucleotide comprises Ref ID NO: IS1072.
24. The compound of any one of claims 1-19, wherein the first modified oligonucleotide comprises Ref ID NO: IA0864 and the second modified oligonucleotide comprises Ref ID NO: IS1059.
25. The compound of any one of claims 1-24, wherein the compound is in a pharmaceutically acceptable salt form.
26. The compound of claim 25, wherein the pharmaceutically acceptable salt is a sodium salt or a potassium salt.
27. A composition comprising the compound of any one of claims 1-26 and a pharmaceutically acceptable carrier.
28. Use of the compound of any one of claims 1-26 or the composition of claim 27 in the preparation of a medicament for the treatment of an inflammatory or thrombotic disease, disorder or condition or a symptom thereof, hereditary angioedema (HAE), edema, angioedema, swelling, angioedema of the lids, ocular edema, macular edema, cerebral edema, thrombosis, embolism, thromboembolism, deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, or infarct.

29. A method of inhibiting expression of PKK in an isolated cell comprising contacting the cell with a compound of any one of claims 1-26 or the composition of claim 27, thereby inhibiting expression of PKK in the cell.

30. The use of claim 28, wherein the compound or composition is to be administered parenterally to a subject.

31. The use of claim 28, wherein the compound or composition is to be administered to a subject about once every three months, about once every six months, or about once every year.