Claims

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of prekallikrein (PKK) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand of dsRNA comprises a nucleotide sequence of at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from formula (I): 5'-Z_1GAAUAAGUGAAAAACUZ_2-3' (I), wherein Z_1 is selected from one of C, G, A, U or absent, and Z_2 is selected from G, GU, GA, GC, GG, GAU, GAA, GAC, GAG, GACC, GACU, GACG, GACA, GACAG, GACAGC, GACAGCG, GACAGCGA, GACAGCGAA, GACAGCGAAU, GACAGCGAAUC, GACAGCGAAUCA, GACAGCGAAUCAU, GACAGCGAAUCAUC, GACAGCGAAUCAUCU, GACAUU, GACAGA or absent.

2. The dsRNA agent of claim 1, wherein the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 16 and 23 nucleotides in length; or
the region of complementarity is 19-21 nucleotides in length.

3. The dsRNA of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide; or

all or substantially all of the nucleotides of the antisense strand are modified nucleotides; or

all or substantially all of the nucleotides of the sense strand and the antisense strand are modified nucleotides.

4. The dsRNA agent of claim 3, wherein the at least one modified nucleotide comprises: a 2’-O-methyl nucleotide, 2’-Fluoro nucleotide, 2’-deoxy nucleotide, 2’3’-seco nucleotide mimic, locked nucleotide, unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), 2’-F-Arabino nucleotide, 2’-methoyxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2’-OMe nucleotide, inverted 2’-deoxy nucleotide,

2’-amino-modified nucleotide, 2’-alkyl-modified nucleotide, morpholino nucleotide, and 3’-OMe nucleotide, a nucleotide comprising a 5’-phosphorothioate group, or a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2’-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

5. The dsRNA agent of claim 1, wherein the sense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages; or

the antisense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.

6. The dsRNA agent of claim 1, wherein each strand is no more than 30 nucleotides in length; or

each strand is no more than 25 nucleotides in length; or

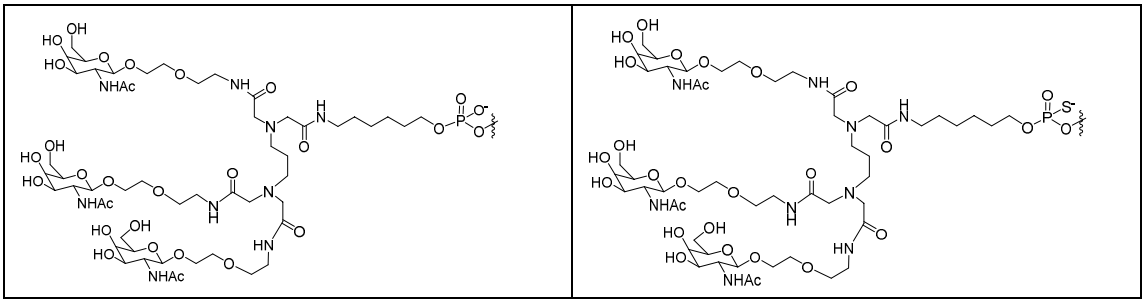
each strand is no more than 23 nucleotides in length.

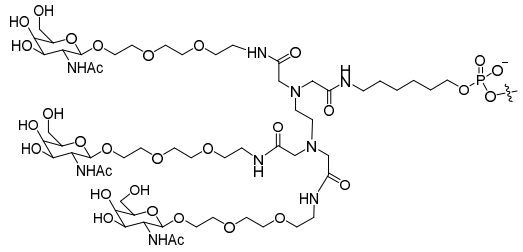
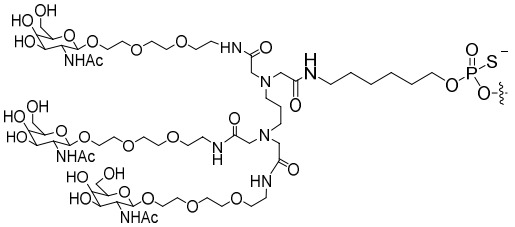
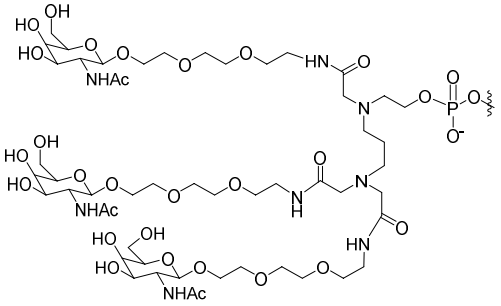
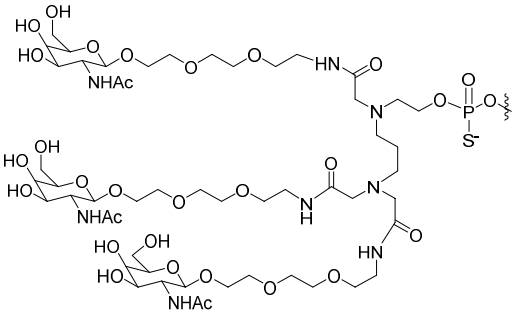
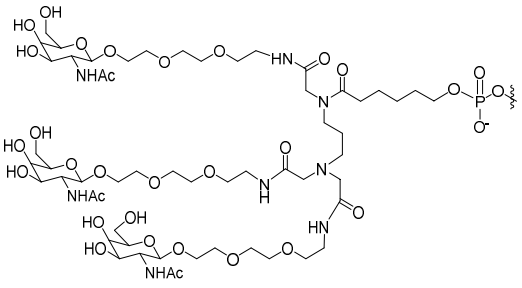
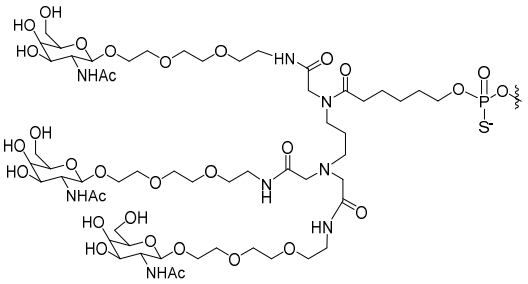
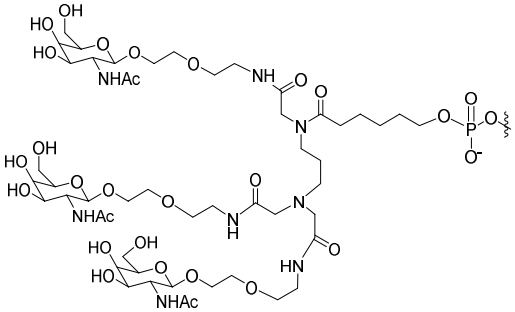
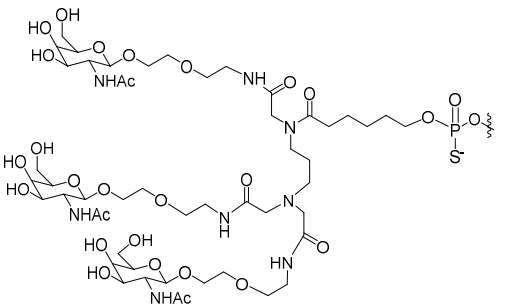
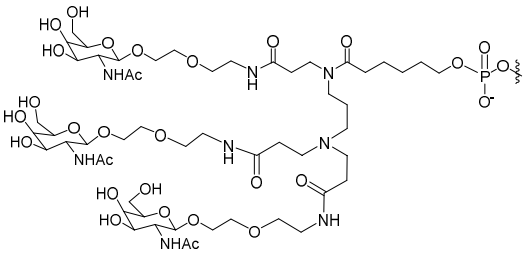
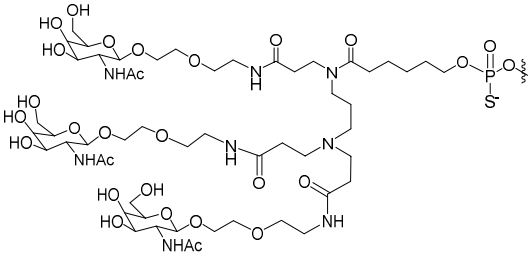
7. The dsRNA agent of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups;

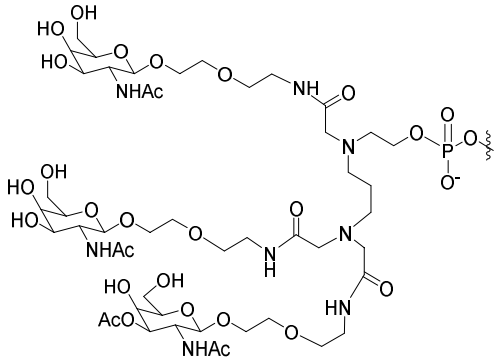
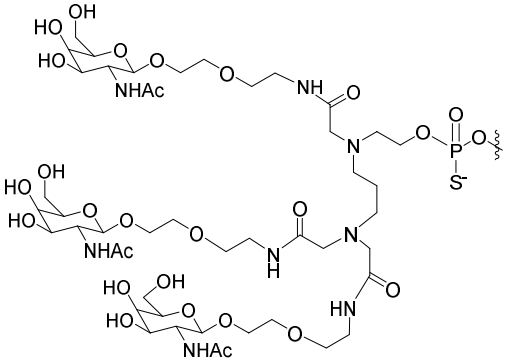
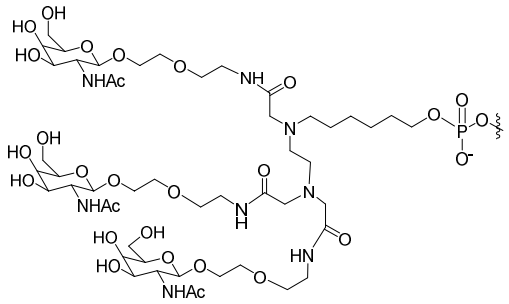
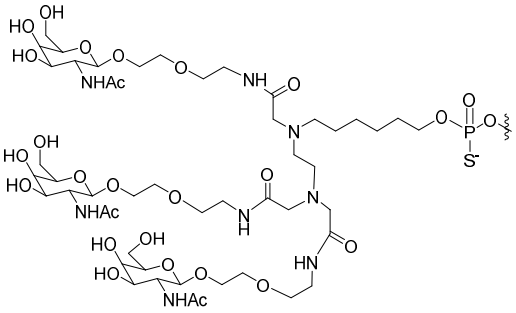
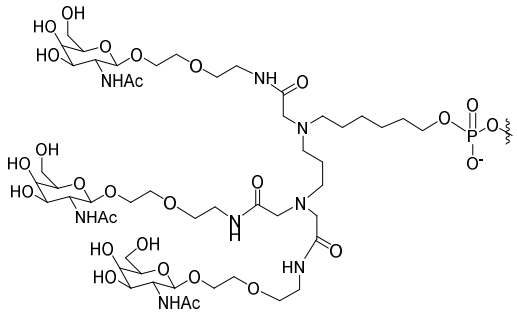
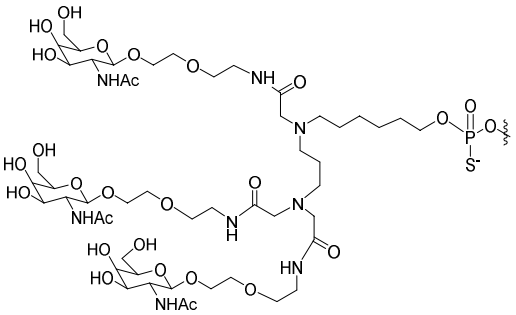
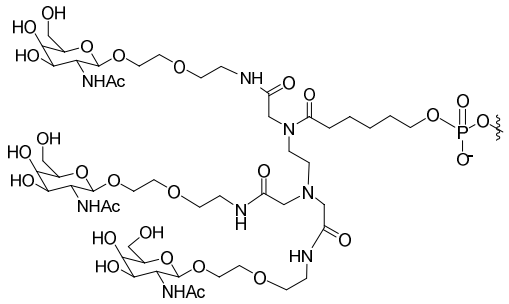
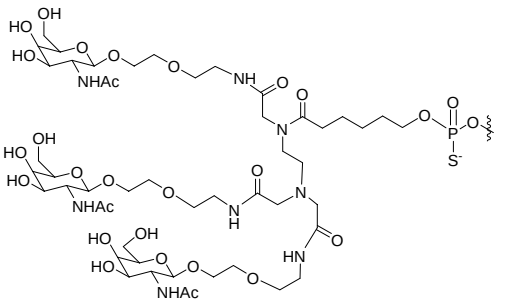
wherein, the one or more targeting groups or linking groups are conjugated to the sense strand;

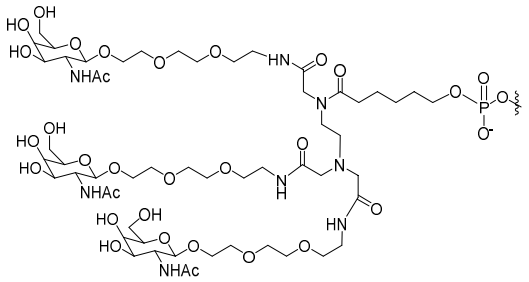
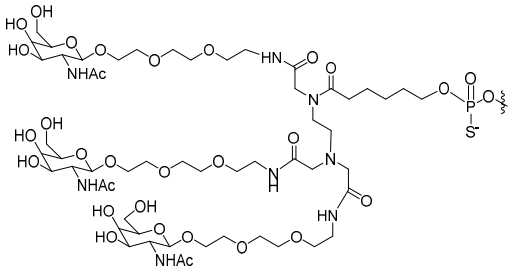
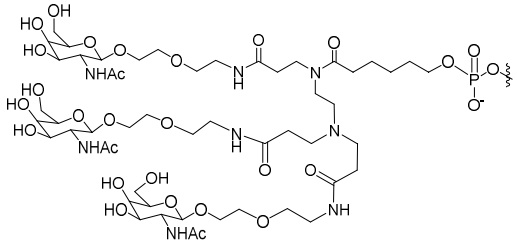
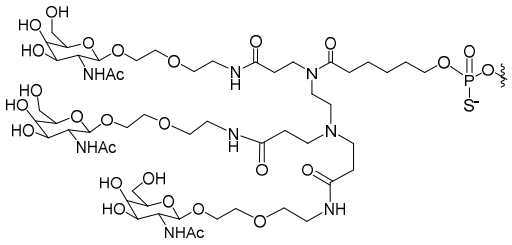
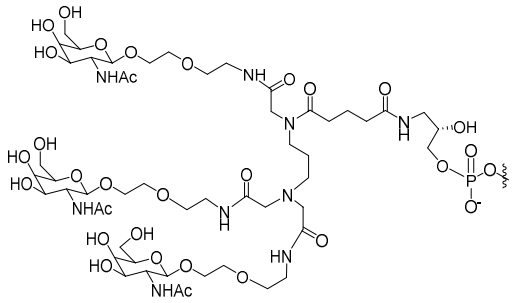
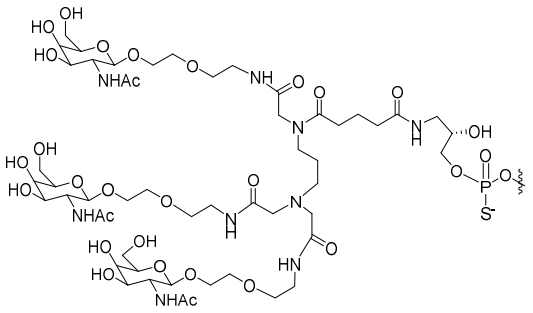
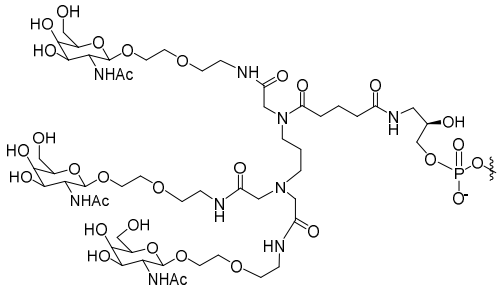
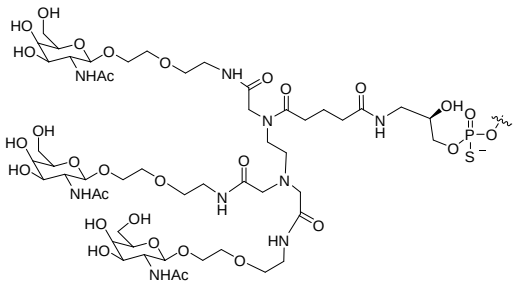
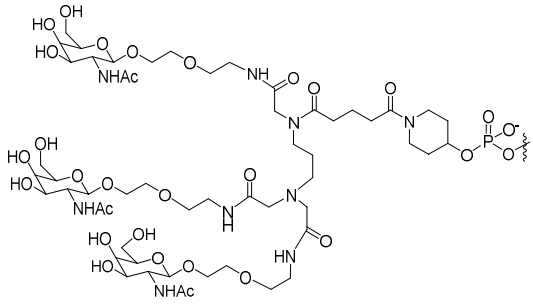
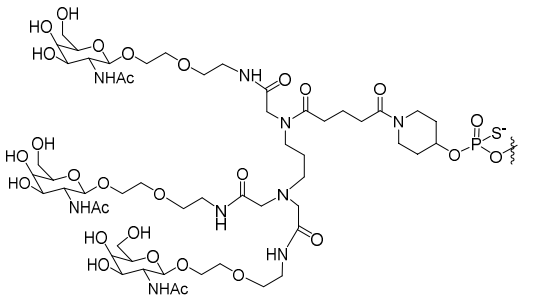
wherein, the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc).

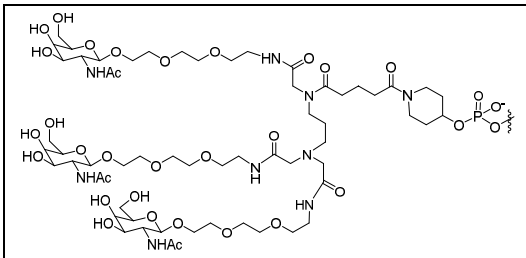
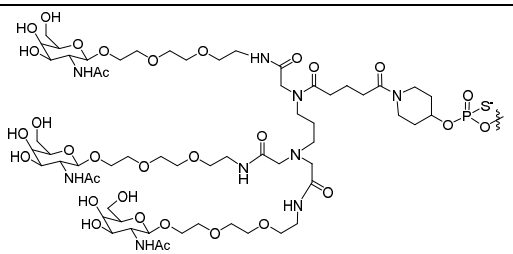
8. The dsRNA agent of claim 7, wherein the targeting group has a structure:



GLO-1	GLS-1
	
GLO-2	GLS-2
	
GLO-3	GLS-3
	
GLO-4	GLS-4
	
GLO-5	GLS-5
	

GLO-6	GLS-6
 GLO-7	 GLS-7
 GLO-8	 GLS-8
 GLO-9	 GLS-9
 GLO-10	 GLS-10

 GLO-11	 GLS-11
 GLO-12	 GLS-12
 GLO-13	 GLS-13
 GLO-14	 GLS-14
 GLO-15	 GLS-15

 GLO-16	 GLS-16.

9. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a targeting group that is conjugated to the 5’-terminal end of the sense strand; or

the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand.

10. The dsRNA agent of claim 1, wherein the antisense strand comprises one inverted abasic residue at 3’-terminal end; or

the sense strand comprises one or two inverted abasic residues at the 3’ and/or the 5’ terminal end.

11. The dsRNA agent of claim 1, wherein the dsRNA agent has two blunt ends; or

at least one strand comprises a 3’ overhang of at least 1 or 2 nucleotides.

12. The dsRNA agent of claim 1, wherein the antisense strand comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 304, 416, 973 to 1003, 1128 to 1137, 640, 1383 to 1413, 1538 to 1547, 765 and 1681 to 1684.

13. The dsRNA agent of claim 1, wherein the sense strand comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 80, 192, 768 to 798, 923 to 932, 528, 1178 to 1208, 1333 to 1342, 718 and 1631 to 1634.

14. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sequence selected from the group consisting of duplex sequences set forth in SEQ ID NO: 304

and SEQ ID NO: 80; SEQ ID NO: 416 and SEQ ID NO: 192; SEQ ID NO: 973 and SEQ ID NO: 768; SEQ ID NO: 974 and SEQ ID NO: 769; SEQ ID NO: 975 and SEQ ID NO: 770; SEQ ID NO: 976 and SEQ ID NO: 771; SEQ ID NO: 977 and SEQ ID NO: 772; SEQ ID NO: 978 and SEQ ID NO: 773; SEQ ID NO: 979 and SEQ ID NO: 774; SEQ ID NO: 980 and SEQ ID NO: 775; SEQ ID NO: 981 and SEQ ID NO: 776; SEQ ID NO: 982 and SEQ ID NO: 777; SEQ ID NO: 983 and SEQ ID NO: 778, SEQ ID NO: 984 and SEQ ID NO: 779, SEQ ID NO: 985 and SEQ ID NO: 780, SEQ ID NO: 986 and SEQ ID NO: 781, SEQ ID NO: 987 and SEQ ID NO: 782, SEQ ID NO: 988 and SEQ ID NO: 783, SEQ ID NO: 989 and SEQ ID NO: 784, SEQ ID NO: 990 and SEQ ID NO: 785, SEQ ID NO: 991 and SEQ ID NO: 786, SEQ ID NO: 992 and SEQ ID NO: 787, SEQ ID NO: 993 and SEQ ID NO: 788, SEQ ID NO: 994 and SEQ ID NO: 789, SEQ ID NO: 995 and SEQ ID NO: 790, SEQ ID NO: 996 and SEQ ID NO: 791, SEQ ID NO: 997 and SEQ ID NO: 792, SEQ ID NO: 998 and SEQ ID NO: 793, SEQ ID NO: 999 and SEQ ID NO: 794, SEQ ID NO: 1000 and SEQ ID NO: 795, SEQ ID NO: 1001 and SEQ ID NO: 796, SEQ ID NO: 1002 and SEQ ID NO: 797, SEQ ID NO: 1003 and SEQ ID NO: 798, SEQ ID NO: 1128 and SEQ ID NO: 923, SEQ ID NO: 1129 and SEQ ID NO: 924, SEQ ID NO: 1130 and SEQ ID NO: 925, SEQ ID NO: 1131 and SEQ ID NO: 926, SEQ ID NO: 1132 and SEQ ID NO: 927, SEQ ID NO: 1133 and SEQ ID NO: 928, SEQ ID NO: 1134 and SEQ ID NO: 929, SEQ ID NO: 1135 and SEQ ID NO: 930, SEQ ID NO: 1136 and SEQ ID NO: 931, SEQ ID NO: 1137 and SEQ ID NO: 932, SEQ ID NO: 640 and SEQ ID NO: 528; SEQ ID NO: 1383 and SEQ ID NO: 1178, SEQ ID NO: 1384 and SEQ ID NO: 1179, SEQ ID NO: 1385 and SEQ ID NO: 1180, SEQ ID NO: 1386 and SEQ ID NO: 1181, SEQ ID NO: 1387 and SEQ ID NO: 1182, SEQ ID NO: 1388 and SEQ ID NO: 1183, SEQ ID NO: 1389 and SEQ ID NO: 1184, SEQ ID NO: 1390 and SEQ ID NO: 1185, SEQ ID NO: 1391 and SEQ ID NO: 1186, SEQ ID NO: 1392 and SEQ ID NO: 1187, SEQ ID NO: 1393 and SEQ ID NO: 1188, SEQ ID NO: 1394 and SEQ ID NO: 1189, SEQ ID NO: 1395 and SEQ ID NO: 1190, SEQ ID NO: 1396 and SEQ ID NO: 1191, SEQ ID NO: 1397 and SEQ ID NO: 1192, SEQ ID NO: 1398 and SEQ ID NO: 1193, SEQ ID NO: 1399 and SEQ ID NO: 1194, SEQ ID NO: 1400 and SEQ ID NO: 1195,

SEQ ID NO: 1401 and SEQ ID NO: 1196, SEQ ID NO: 1402 and SEQ ID NO: 1197, SEQ ID NO: 1403 and SEQ ID NO: 1198, SEQ ID NO: 1404 and SEQ ID NO: 1199, SEQ ID NO: 1405 and SEQ ID NO: 1200, SEQ ID NO: 1406 and SEQ ID NO: 1201, SEQ ID NO: 1407 and SEQ ID NO: 1202, SEQ ID NO: 1408 and SEQ ID NO: 1203, SEQ ID NO: 1409 and SEQ ID NO: 1204, SEQ ID NO: 1410 and SEQ ID NO: 1205, SEQ ID NO: 1411 and SEQ ID NO: 1206, SEQ ID NO: 1412 and SEQ ID NO: 1207, SEQ ID NO: 1413 and SEQ ID NO: 1208, SEQ ID NO: 1538 and SEQ ID NO: 1333, SEQ ID NO: 1539 and SEQ ID NO: 1334, SEQ ID NO: 1540 and SEQ ID NO: 1335, SEQ ID NO: 1541 and SEQ ID NO: 1336, SEQ ID NO: 1542 and SEQ ID NO: 1337, SEQ ID NO: 1543 and SEQ ID NO: 1338, SEQ ID NO: 1544 and SEQ ID NO: 1339, SEQ ID NO: 1545 and SEQ ID NO: 1340, SEQ ID NO: 1546 and SEQ ID NO: 1341, SEQ ID NO: 1547 and SEQ ID NO: 1342, SEQ ID NO: 765 and SEQ ID NO: 718, SEQ ID NO: 1681 and SEQ ID NO: 1631, SEQ ID NO: 1682 and SEQ ID NO: 1632, SEQ ID NO: 1683 and SEQ ID NO: 1633, and SEQ ID NO: 1684 and SEQ ID NO: 1634.

15. A composition comprising one, two, three, or more dsRNA agents of any one of claims 1-14;

wherein, the composition further comprises a pharmaceutically acceptable carrier;

16. The composition of claim 15, wherein, the composition further comprises one or more additional therapeutic agents.

17. The composition of claim 15 or 16, wherein, the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.

18. A cell comprising a dsRNA agent of any one of claims 1-14.

19. The cell of claim 18, wherein the cell is a mammalian cell.

20. The cell of 18 or 19, wherein the cell is a human cell.

21. A method of inhibiting the expression of a prekallikrein (PKK) gene in a cell in vitro, comprising:

(i) preparing a cell or plurality of cells comprising an effective amount of one or more double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-14 or a composition of claim 15; and

(ii) maintaining the cell or plurality of cells prepared in (i) for a time sufficient to obtain degradation of the mRNA transcript of a PKK gene, thereby inhibiting expression of the PKK gene in the cell or plurality of cells and reducing a level of the PKK polypeptide in the cell or plurality of cells.

22. Use of the double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-14 or the composition of claim 15 in the manufacture of a medicament for inhibiting expression of a PKK gene in a subject,

23. The use of claim 22, wherein a level of one or more of: plasma PKK in the subject; plasma kallikrein, high-molecular-weight kininogen (HK), and bradykinin in the subject; determined to be statistically significantly higher, lower, or unchanged compared to a baseline pre-treatment physiological characteristic of the PKK-associated disease or condition and/or to a control physiological characteristic of the PKK-associated disease or condition indicates a status of PKK gene expression.

24. The use of claim 22 or 23, wherein a reduction in one or more of the physical symptom, swelling of skin, swelling of hands and feet, fatigue, headache, muscle aches, tingling of skin, abdominal pain, nausea and vomiting, hoarseness, shortness of breath, mood changes, laryngeal edema, pain, and fever in the subject indicates a reduction of PKK gene expression.

25. Use of the double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-14 or the composition of claim 15 in the manufacture of a medicament for treating a disease or condition in a subject, wherein

the disease or condition is one or more of: hereditary angioedema, angioedema, bradykinin-mediated angioedema, diabetic retinopathy, diabetic macular edema, hypertension, nephropathy, vascular disease, stroke, peripheral artery disease (PAD), abdominal aortic aneurysm (AAA), carotid artery disease (CAD), arteriovenous malformation (AVM), critical limb-threatening ischemia (CLTI), pulmonary embolism (blood clots), deep vein thrombosis (DVT), chronic venous insufficiency (CVI), and varicose veins;

26. The use of claim 25, further comprising an additional therapeutic regimen;

wherein, the additional therapeutic regimen comprises PKK antisense polynucleotides, additional PKK dsRNA therapeutic agent, a non-PKK dsRNA therapeutic agent, a PKK non-dsRNA therapeutic agent, and a behavioral modification.

27. The use of claim 25 or 26, wherein the non-PKK dsRNA therapeutic agent is one of more of: a blood thinner, an NSAID, aspirin, an anticoagulant, tissue plasminogen activator (tPA); recombinant tissue plasminogen activator (tPA), a statin, a stent, a cholesterol-lowering therapeutic agent, a vasodilator, cilostazol, Plavix®, an anti-coagulation drug, and an antiplatelet agent.