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, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to a PKK RNA transcript, wherein the region of complementarity comprises at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally comprising a targeting ligand; or

the region of complementarity to the PKK RNA transcript comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by no more than 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3.

2. The dsRNA agent of claim 1, wherein the antisense strand of dsRNA is at least substantially complementary to a target region of SEQ ID NO: 767 and is provided in any one of Tables 1-3; or

the antisense strand of dsRNA is fully complementary to a target region of SEQ ID NO: 767 and is provided in any one of Tables 1-3.

3. The dsRNA agent of claim 1 or 2, wherein the dsRNA agent comprises a sense strand sequence set forth in any one of Tables 1-3, wherein the sense strand sequence is at least substantially complementary to the antisense strand sequence in the dsRNA agent; or

the sense strand sequence is fully complementary to the antisense strand sequence in the dsRNA agent.

4. The dsRNA agent of claim 1, wherein the dsRNA agent comprises an antisense strand sequence set forth in any one of Tables 1-3; or

the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-3.

5. 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;

preferably, the dsRNA agent comprises an E-vinylphosphonate nucleotide at the 5′ end of the antisense strand.

6. The dsRNA agent of claim 5, 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;

preferably, the modified sense strand is a modified sense strand sequence set forth in one of Tables 2 and 3;

preferably, the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2 and 3.

7. The dsRNA agent of claim 1, wherein the dsRNA agent comprises at least one phosphorothioate internucleoside linkage; or

the sense strand comprises at least one phosphorothioate internucleoside linkage; or

the antisense strand comprises at least one phosphorothioate internucleoside linkage;

preferably, 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.

8. 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.

9. 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

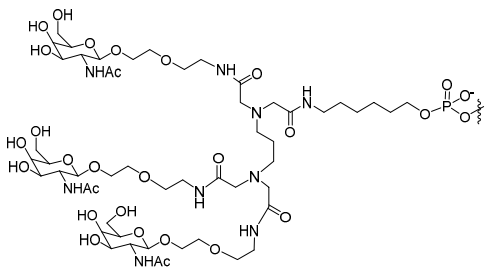
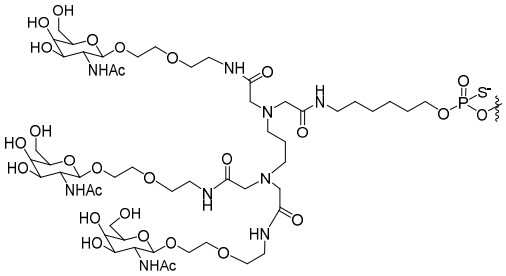
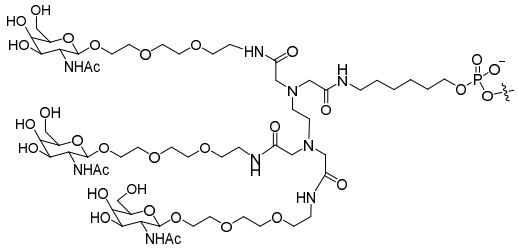
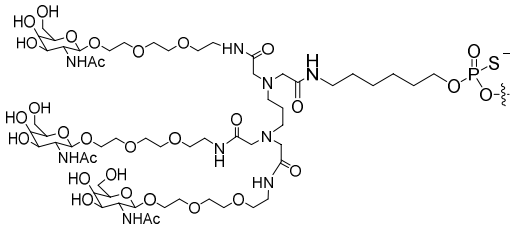
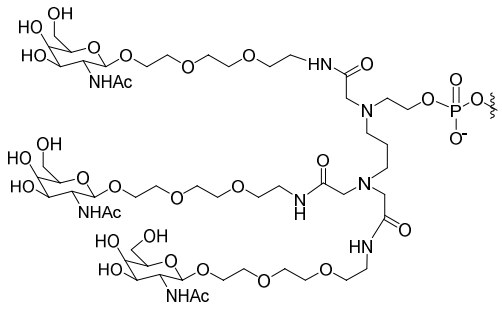
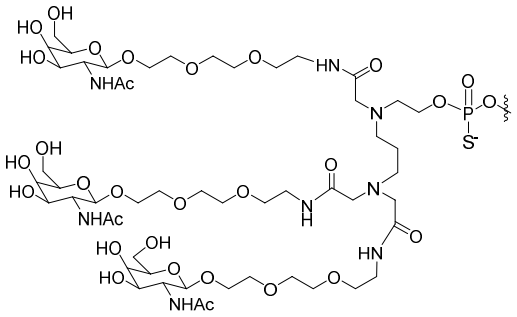
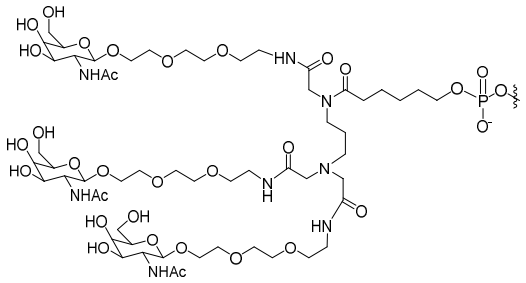
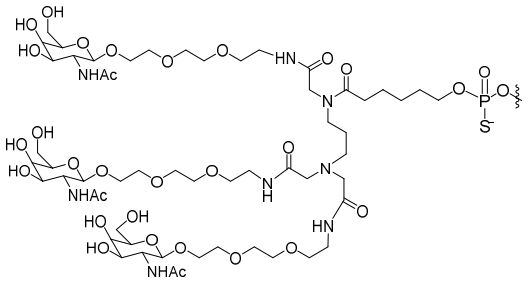
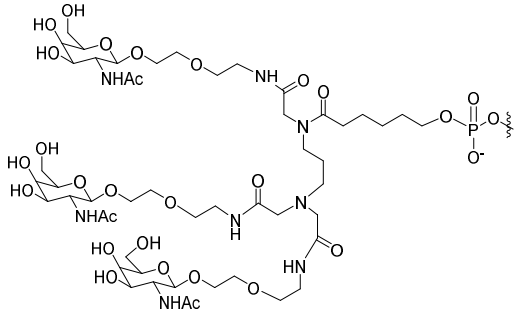
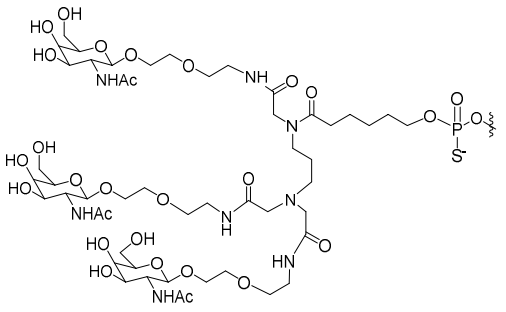
each strand is no more than 23 nucleotides in length.

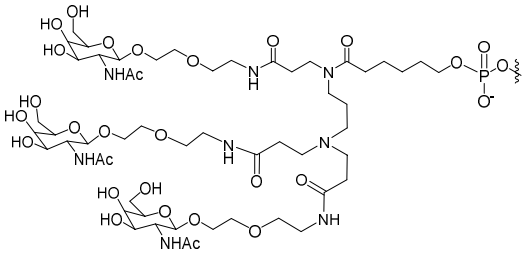
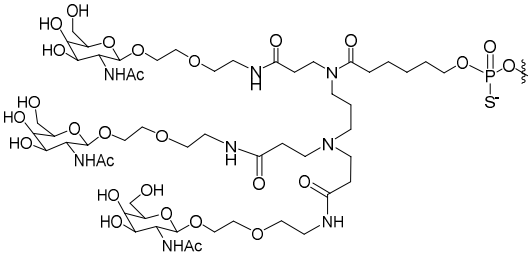
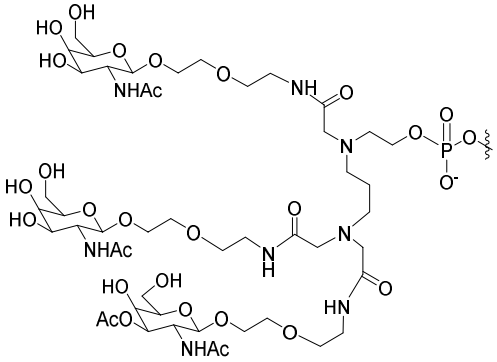
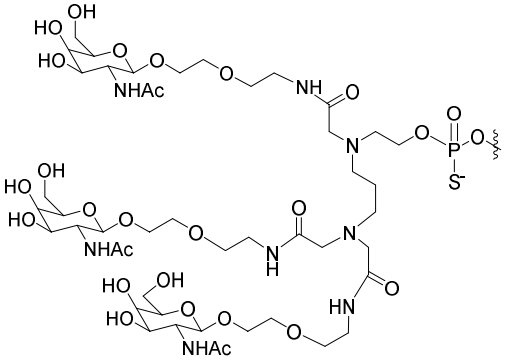
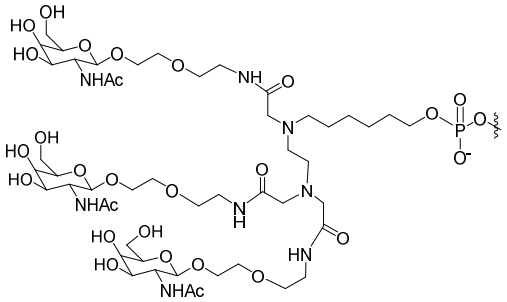
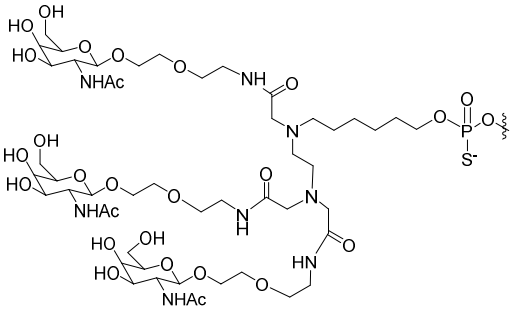
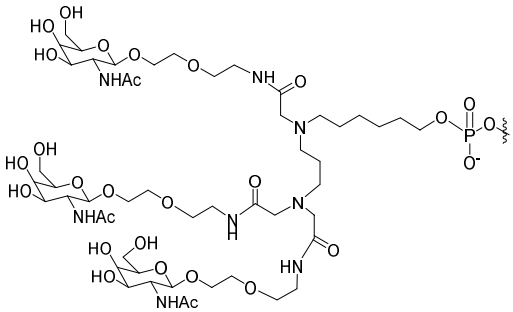
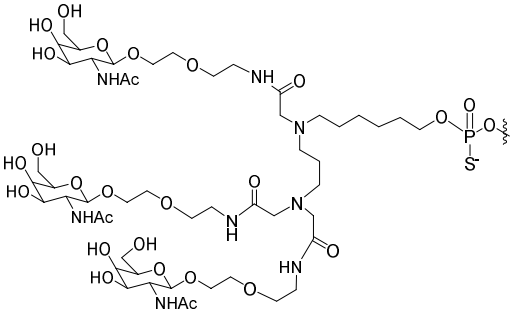
10. The dsRNA agent of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups;

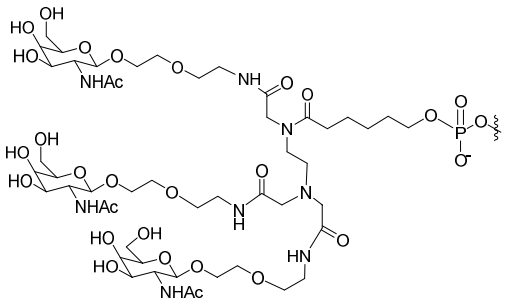
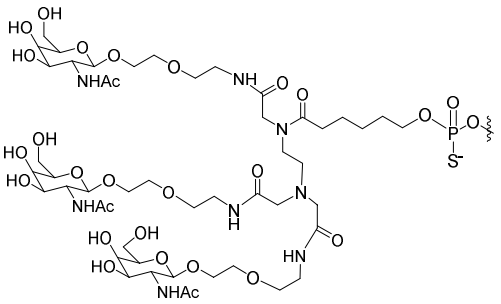
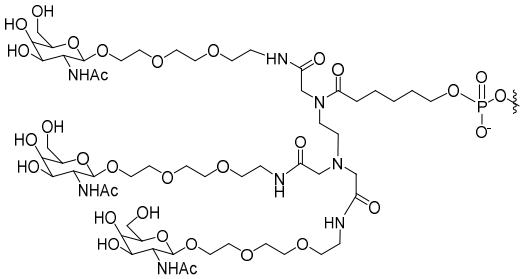
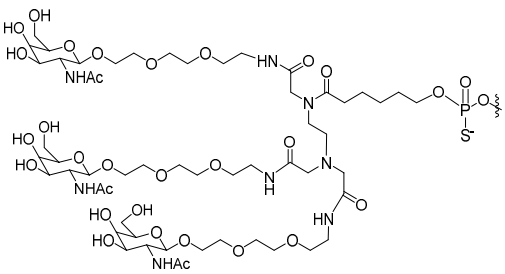
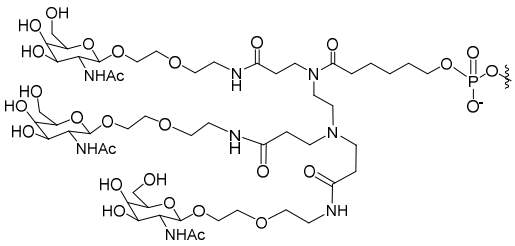
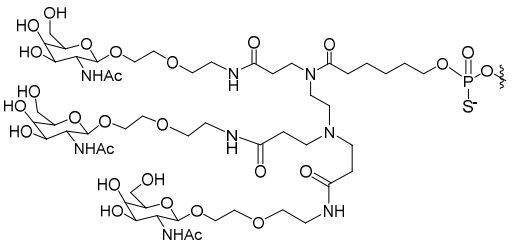
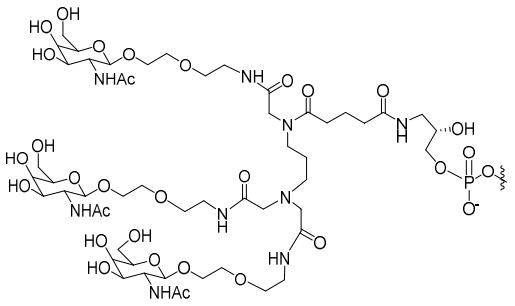
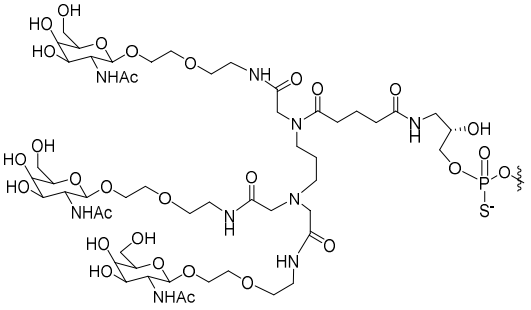
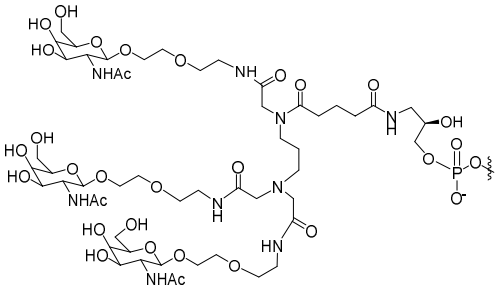
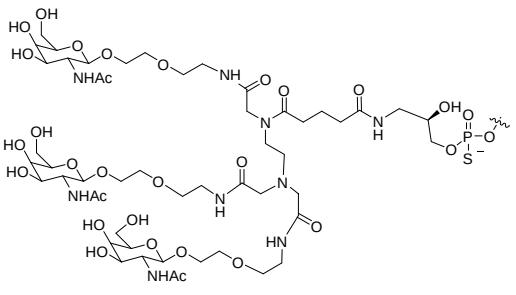
preferably, the one or more targeting groups or linking groups are conjugated to the sense strand;

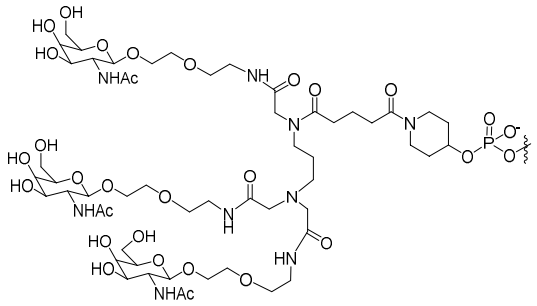
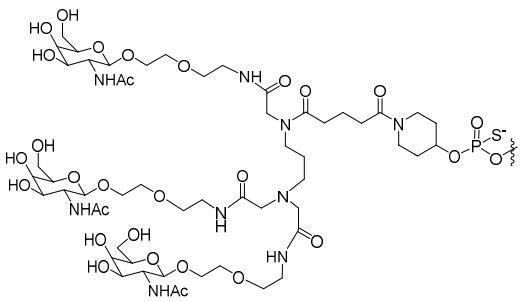
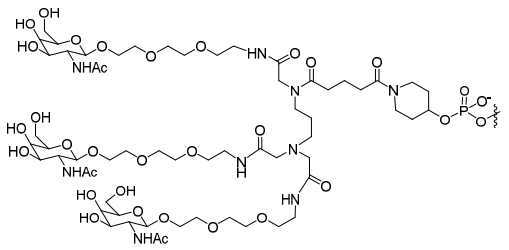
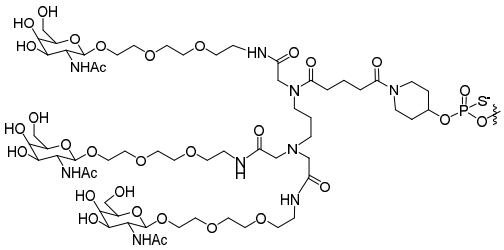
preferably, the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc).

11. The dsRNA agent of claim 10, 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.

12. 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.

13. 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.

14. 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.

15. The dsRNA agent of any one of claims 1-14, wherein the PKK RNA transcript is SEQ ID NO: 767.

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

preferably, the composition further comprises a pharmaceutically acceptable carrier;

preferably, the composition further comprises one or more additional therapeutic agents;

preferably, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial;

preferably, the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.

17. A cell comprising a dsRNA agent of any one of claims 1-15;

preferably, the cell is a mammalian cell, optionally a human cell.

18. A method of inhibiting the expression of a prekallikrein (PKK) gene in a cell, 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 1-15 or a composition of claim 16;

preferably, further comprising (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.

19. Use of the double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-15 or the composition of claim 16 in the manufacture of a medicament for inhibiting expression of a PKK gene in a subject,

preferably, 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;

preferably, 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.

20. Use of the double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-15 or the composition of claim 16 in the manufacture of a medicament for treating a disease or condition in a subject, wherein the disease or condition is associated with the presence of a prekallikrein (PKK) protein,

preferably, 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;

preferably, 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;

preferably, 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.

21. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of prekallikrein (PKK) , wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 1014-1044; 1054-1084; 1059-1089; 1106-1138；1456-1486; 1543-1573； or 2029-2059 of SEQ ID:767, and the antisense strand is complementary or substantially complementary to the sense strand sequence in the dsRNA agent, and optionally comprising a targeting ligand;

preferably, the region of complementarity to the PKK RNA transcript comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 1014-1044; 1054-1084; 1059-1089; 1106-1138； 1456-1486; 1543-1573； or 2029-2059 of SEQ ID:767;

preferably, the antisense strand of dsRNA is at least substantially complementary or fully complementary to a target region of SEQ ID NO: 767; or

the sense strand sequence is at least substantially complementary or fully complementary to the antisense strand sequence in the dsRNA agent;

preferably, the dsRNA agent comprises at least one modified nucleotide;

preferably, all or substantially all of the nucleotides of the antisense strand and sense strand are modified nucleotides;

preferably, 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;

preferably, 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; preferably, the region of complementarity is 19-21 nucleotides in length;

preferably, each strand is no more than 40 nucleotides in length, or 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.