NUCLEIC ACID MOLECULE FOR TREATING THROMBOCYTOPENIA AND USE THEREOF

TECHNICAL FIELD

[0001] The present invention belongs to the technical field of nucleic acids, particularly as it relates to double-stranded nucleic acid molecules associated with gene activation, e.g., small activating nucleic acid molecules, uses of the small activating nucleic acid molecules in activating/up-regulating the transcription of the Thrombopoietin (*THPO, TPO*) gene, and uses thereof for treating diseases and conditions, such as thrombocytopenia, related to THPO protein deficiency or insufficiency.

BACKGROUND

[0002] Thrombocyte is one of the blood components in peripheral blood derived from nucleus-free megakaryocytes in the bone marrow (Machlus, Thon, and Italiano 2014). The main function of the thrombocyte is to promote hemostasis, accelerate coagulation, and maintain the integrity of capillary walls, while playing an important role in physiological hemostasis and pathological thrombosis (Laki 1972).

[0003] Thrombocytopenia is a disease in which the number of platelets in peripheral blood is abnormally reduced, and characterized clinically by ecchymosis, mucosal bleeding, or intracranial bleeding, all of which endanger the lives of patients with this disease. Thrombocytopenia is considered to be present when platelet concentrations are lower than 100×10^9/L by direct blood platelet count (Kuter 2009). Spontaneous bleeding, manifesting as subcutaneous purpuraa, occurs frequently when platlet concentrations are lower than 50×10^9/L. When the platelet concentrations are lower than 20×10^9/L, a patient's condition can be life-threatening, especially due to trauma or sudden intracranial bleeding, gastrointestinal bleeding, and the like.

[0004] Thrombocytopenia can be classified into 3 categories basd on the pathogenesis: myelo-thrombocytopenia, increased peripheral platelet destruction, and splenic sequestration (Seo et al. 2017). Factors causing a reduction in platelets comprise congenital (hereditary) and acquired thrombocytopenia. It has been found currently that hereditary thrombocytopenia can be caused by at least mutations in genes such as *MPL, GP1BA, GP1BB, GP9, MYH9, FLI1, NBEAL2, WAS, GATA1, PRKACG, GFI1b, STIM1, FYB, SLFN14, ETV6, DIAPH1* and *SRC*. The thrombocytopenia caused by acquired factors include thrombocytopenia caused by aplastic anemia, myelodysplastic syndromes, leukemia, drugs, infection, tumor diseases, radiotherapy, bone marrow transplantation, and chronic liver diseases, and immune thrombocytopenia (ITP). Factors causing increased platelet destruction comprise thrombotic thrombocytopenia, heparin-induced thrombocytopenia, drug-induced thrombocytopenia, ITP, and thrombotic thrombocytopenia purpura (TPP) (Hassan

and Waller 2015). Thrombocytopenia may also be caused by splenomegaly sequestration, transfusion of banked blood with low platelet content, and the like.

[0005] Thrombopoietin (THPO), also known as Megakaryocyte Growth and Development Factor (MGDF) or C-MPL ligand, is a hormone-likeglycoprotein encoded by the human *THPO* gene and mainly produced and secreted by the liver and kidney (de Sauvage et al. 1994). The human *THPO* gene is located on the long arm of chromosome 3 (3q26.3-3q27.2) and encodes a precursor protein containing 353 amino acids and has a molecular weight of 36 kDa. After the removal of the signal peptide containing 21 amino acids, the remaining 332 amino acids are glycosylated to form a 95 kDa glycoprotein which is then released into circulation to bind the C-MPL receptor on megakaryocytes and platelets stimulating the formation and differentiation of megakaryocytes, while promoting thrombopoiesis (Bartley et al. 1994). The mouse *Thpo* gene (also known as *Ml, Tpo, Mgdf, Mpllg*) is homologous to the human *THPO* gene and encodes mouse thrombopoietin. C-MPL was first discovered in mice infected with Myeloproliferative Leukemia Virus (MPLV), and then the human *C-MPL* gene was cloned (Mignotte et al. 1994).

[0006] The first-line clinical treatment for thrombocytopenia is primarily intravenous injections of glucocorticoids (high doses of dexamethasone or prednisone) and gamma globulin (IVIg). If first-line therapy fails or cannot be minatained, the second-line therapy such as drug therapy or splenectomy would then be chosen. Drug therapy is the commonly used second-line treatment method at present, because splenectomy is susceptible to infection, long-term relapse, prolonged hospitalization and high death risk (Provan et al. 2010).

[0007] The drugs currently used to treat thrombocytopenia are mainly thrombopoietic agents that stimulate megakaryocytes to grow, maturate, and produce platelet by supplementing THPO or simulating the function thereof. Such thrombopoietic agents include two major classes, recombinant human thrombopoietin (rhTHPO) and C-MPL receptor agonist (C-MPL-RA). Initially, peptides with homology to endogenous THPO (first generation thrombopoietic agents) had shown good results in early clinical studies in patients with thrombocytopenia. However, later clinical studies have found that the body can produce neutralizing antibodies that cross-react with endogenous THPO, resulting in persistent thrombocytopenia (Basser 2002; Solberg 2005). In addition, since recombinant THPO produced *in vitro* cannot be completely glycosylated, its thrombopoietic function is limited. Second generation thrombopoietic agents are primarily C-MMPL-RAs, which include Eltrombopag and Romiplostim approved by the FDA in 2008 for the ITP treatment, and Avatrombopag approved by the FDA and marketed for the treatment of ITP in 2018. C-MPL agonist drugs have some curative effects, however, they have been associated with various complications and withdrawal reactions.

[0008] Although the aforementioned drugs have some curative effects by supplementing or mimicking the function of THPO to promote thrombopoiesis or simulate the function thereof, these drugs have certain defects, and all belong to second-line treatments and are all mainly used for treating ITP. In order to effectively treat thrombocytopenia caused by various reasons, there is a need to develop treatment methods based on a novel mechanism.

SUMMARY

[0009] One objective of the present invention is to provide a small activating nucleic acid molecule based on an RNA activation mechanism, which promotes thrombopoiesis or treats a disease and condition related to THPO protein deficiency or insufficiency or thrombocytopenia caused by various reasons, such as drug-induced thrombocytopenia and immune thrombocytopenia, by activating/up-regulating *THPO* gene transcription to increase protein expression of THPO.

[0010] Another objective of the present invention is to provide a composition or formulation comprising the small activating nucleic acid molecule.

[0011] Another objective of the present invention is to provide a use ofa small activating nucleic acid molecule or a composition or formulation comprising same in the preparation of a drug for activating/up-regulating the expression of the *THPO* gene in a cell.

[0012] Yet another objective of the present invention is to provide a method for activating/up-regulating the expression of the *Thpo*/*THPO* gene in a cell.

[0013] Still another objective of the present invention is to provide a use of a small activating nucleic acid molecule or a composition or formulation thereof in the preparation of a drug for treating thrombocytopenia and/or a disease or a condition related to THPO protein deficiency or insufficiency, or in a method of treating thrombocytopenia and/or a disease or a condition related to THPO protein deficiency or insufficiency.

[0014] Still yet another objective of the present invention is to provide an isolated small activating nucleic acid molecule target site of the *Thpo/THPO* gene, wherein the target site comprises or is selected from any continuous sequence of 16 to 35 nucleotides in length in any sequence set forth in SEQ ID NO: 2 to SEQ ID NO: 4 and SEQ ID NO: 601 to SEQ ID NO: 605, or a sequence having at least 75%, e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or 100% homology to a sequence consisting of any of the aforementioned continuous 16 to 35 nucleotides in length.

[0015] **Technical Solution**

[0016] In one aspect of the present invention, a small activating nucleic acid (e.g., a small activating RNA molecule, saRNA) molecule activating/up-regulating the expression of the *Thpo* gene in a mouse cell is provided, wherein one strand of the small activating nucleic acid molecule

has at least 75% homology or complementarity to any nucleic acid sequence of 16 to 35 nucleotides in length in a promoter region of a mouse *Thpo* gene, thereby activating or up-regulating the expression of the gene, wherein the promoter region comprises 500 nucleotides upstream of a transcription start site. Specifically, one strand of the small activating nucleic acid molecule comprises or is selected from a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or 100%) homology or complementarity to a continuous sequence of 16 to 35 nucleotides in length at positions -493 to -356 (hotspot 1, SEQ ID NO: 2), positions -273 to -183 (hotspot 2, SEQ ID NO: 3), or positions -164 to -80 (hotspot 3, SEQ ID NO: 4) upstream of the transcription start site of the *Thpo* gene promoter. More specifically, one strand of the small activating nucleic acid molecule of the present invention has at least 75% (e.g., at least about 79%, about 80, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to any nucleotide sequence selected from SEQ ID NO: 200 to SEQ ID NO: 296. In one specific embodiment, one strand of the small activating nucleic acid molecule of the present invention comprises a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to any nucleotide sequence selected from SEQ ID NO: 200 to SEQ ID NO: 296. In another embodiment, one strand of the small activating nucleic acid molecule of the present invention consists of a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to any nucleotide sequence selected from SEQ ID NO: 200 to SEQ ID NO: 296. In yet another embodiment, one strand of the small activating nucleic acid molecule of the present invention is a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to any nucleotide sequence selected from SEQ ID NO: 200 to SEQ ID NO: 296.

[0017] The small activating nucleic acid molecule of the present invention comprises a double-stranded small activating nucleic acid molecule, such as the small activating RNA (saRNA) molecule, targeting the promoter region of a mouse *Thpo* gene comprising a first nucleic acid strand and a second nucleic acid strand, wherein the first nucleic acid strand has at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to any continuous sequence of 16 to 35 nucleotides in length in positions -493 to -356 (hotspot 1, SEQ ID NO: 2), positions -273 to -183 (hotspot 2, SEQ ID NO: 3) or positions -164 to -80 (hotspot 3, SEQ ID NO: 4) away from the transcription start site of the *Thpo* gene promoter, and the first nucleic acid strand and the second nucleic acid strand can complementarily form a double-stranded nucleic acid structure capable of activating the expression of the *Thpo* gene in a cell.

[0018] In another aspect of the present invention, a small activating nucleic acid (such as a small activating RNA molecule, saRNA) molecule activating/up-regulating the expression of the *THPO* gene in a mouse cell is provided, wherein one strand of the small activating nucleic acid molecule has at least 75% homology or complementarity to any nucleic acid sequence of 16 to 35 nucleotides in length in a promoter region of the human *THPO* gene, thereby activating or up-regulating the expression of the gene, wherein the promoter region comprises 500 nucleotides upstream of a transcription start site. Specifically, one strand of the small activating nucleic acid molecule comprises or is selected from a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or 100%) homology or complementarity to a continuous sequence of 16 to 35 nucleotides in length at positions -1339 to -1044 (hotspot 1, SEQ ID NO: 601), positions -1027 to -903 (hotspot 2, SEQ ID NO: 602), positions -861 to -754 (hotspot 3, SEQ ID NO: 603), positions -728 to -611 (hotspot 4, SEQ ID NO: 604), or positions -593 to -1 (hotspot 5, SEQ ID NO: 605) upstream of the transcription start site of the *THPO* gene promoter. More specifically, one strand of the small activating nucleic acid molecule of the present invention has at least 75% (e.g., at least about 79%, about 80, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to any nucleotide sequence selected from SEQ ID NO: 606 to SEQ ID NO: 1047. In one specific embodiment, one strand of the small activating nucleic acid molecule of the present invention comprises a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to any nucleotide sequence selected from SEQ ID NO: 606 to SEQ ID NO: 1047. In another embodiment, one strand of the small activating nucleic acid molecule of the present invention consists of a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to any nucleotide sequence selected from SEQ ID NO: 606 to SEQ ID NO: 1047. In yet another embodiment, one strand of the small activating nucleic acid molecule of the present invention is a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to any nucleotide sequence selected from SEQ ID NO: 606 to SEQ ID NO: 1047.

[0019] A small activating nucleic acid molecule of the present invention comprises a double-stranded small activating nucleic acid molecule, such as the small activating RNA (saRNA) molecule, targeting the promoter region of the human *THPO* gene comprising a first nucleic acid strand and a second nucleic acid strand, wherein the first nucleic acid strand has at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to any continuous sequence of 16 to 35 nucleotides in length at positions -1339 to -1044 (hotspot 1, SEQ ID NO: 601), positions -1027 to -903 (hotspot 2, SEQ ID

NO: 602), positions -861 to -754 (hotspot 3, SEQ ID NO: 603), positions -728 to -611 (hotspot 4, SEQ ID NO: 604) or positions -593 to -1 (hotspot 5, SEQ ID NO: 605) upstream of the transcription start site of the *THPO* gene promoter, and the first nucleic acid strand and the second nucleic acid strand can complementarily form a double-stranded nucleic acid structure capable of activating the expression of the human *THPO* gene in a cell.

[0020] The first nucleic acid strand and the second nucleic acid strand of a small activating nucleic acid molecule of the present invention may be present on either two different nucleic acid strands or on the same nucleic acid strand. When the first nucleic acid strand and the second nucleic acid strand are located on two different strands, at least one strand of the small activating nucleic acid molecule may have overhangs at the 5' terminus and/or the 3' terminus, e.g. overhangs of 0 to 6 nucleotides in length at 3' terminus, such that the overhangs are of 0, 1, 2, 3, 4, 5 or 6 nucleotides in length. Preferably, both strands of the small activating nucleic acid molecule of the present invention have overhangs; more preferably, the 3' terminus of both strands of the small activating nucleic acid molecule can have overhangs of 0 to 6 nucleotides in length, e.g., overhangs of 0, 1, 2, 3, 4, 5 or 6 nucleotides in length; most preferably overhangs of 2 or 3 nucleotides in length. Preferably, the nucleotide of the overhang is dT.

[0021] A small activating nucleic acid molecule of the present invention can also comprise a small activating nucleic acid molecule capable of forming a double-stranded region hairpin structure, e.g., a single-stranded small activating RNA molecule. In one embodiment, a small activating nucleic acid molecule of the present invention comprises a single-stranded small activating RNA molecule targeting the promoter region of the *THPO* gene, wherein the single-stranded small activating nucleic acid molecule can form a double-stranded region hairpin structure. Preferably, when the first nucleic acid strand and the second nucleic acid strand are present on the same nucleic acid strand, a small activating nucleic acid molecule of the present invention can be a hairpin single-stranded nucleic acid molecule, wherein the first nucleic acid strand and the second nucleic acid strand have complementary regions capable of forming a double-stranded nucleic acid structure, and the double-stranded nucleic acid structure can promote the expression of the *THPO* gene in a cell with, for example, a RNA activation mechanism.

[0022] In the aforementioned small activating nucleic acid molecules, the first nucleic acid strand and the second nucleic acid strand can have 16 to 35 nucleotides (e.g., 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35 nucleotides) in length.

[0023] In one embodiment, the first nucleic acid strand of a small activating nucleic acid molecule of the present invention has at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence

selected from SEQ ID NOs: 6-102, and the second nucleic acid strand of the small activating nucleic acid molecule has at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NOs: 103-199. In one embodiment, the first nucleic acid strand of a small activating nucleic acid molecule of the present invention comprises a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NOs: 6-102, or consists of a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NOs: 6-142; the second nucleic acid strand of the small activating nucleic acid molecule of the present invention comprises a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NOs: 103-199, or consists of a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NOs: 103-199. In a specific embodiment, the first nucleic acid strand of a small activating nucleic acid molecule of the present invention can comprise or be selected from any nucleotide sequence set forth in SEQ ID NOs: 6-102, and the second strand can comprise or be selected from any nucleotide sequence set forth in SEQ ID NOs: 103-199. In one embodiment, the small activating nucleic acid molecule described herein can be synthesized, transcribed *in vitro,* or expressed by a vector.

[0024] In another embodiment, the first nucleic acid strand of a small activating nucleic acid molecule of the present invention has at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NO: 1048 to SEQ ID NO: 1489, and the second nucleic acid strand of a small activating nucleic acid molecule has at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NO: 1490 to SEQ ID NO: 1931. In one embodiment, the first nucleic acid strand of a small activating nucleic acid molecule of the present invention comprises a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NO: 1048 to SEQ ID NO: 1489, or consists of a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NO: 1048 to SEQ ID NO: 1489; the second nucleic acid strand of a small activating

nucleic acid molecule of the present invention comprises a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NO: 1490 to SEQ ID NO: 1931, or consists of a nucleic acid sequence having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) identity or homology to any nucleotide sequence selected from SEQ ID NO: 1490 to SEQ ID NO: 1931. In a specific embodiment, the first nucleic acid strand of a small activating nucleic acid molecule of the present invention can comprise or be selected from any nucleotide sequence set forth in SEQ ID NO: 1048 to SEQ ID NO: 1489, and the second strand can comprise or be selected from any nucleotide sequence set forth in SEQ ID NO: 1490 to SEQ ID NO: 1931. In one embodiment, the small activating nucleic acid molecule described herein can be synthesized, transcribed *in vitro,* or expressed by a vector.

[0025] All the nucleotides in the small activating nucleic acid molecule described herein can be natural non-chemically modified nucleotides or can comprise at least one modification. In one embodiment, the modification in the small activating nucleic acid molecule described herein can comprise chemical modification, for example, at least one nucleotide can have a chemical modification, and the chemical modification used in the present invention can comprise or be selected from one or more combinations of the following modifications:

[0026] (1) modification of a phosphodiester bond of nucleotides in the nucleotide sequence of the small activating nucleic acid molecule;

[0027] (2) modification of 2'-OH of a ribose in the nucleotide sequence of the small activating nucleic acid molecule;

[0028] (3) modification of a base in the nucleotide sequence of the small activating nucleic acid molecule; and

[0029] (4) at least one nucleotide in the nucleotide sequence of the small activating nucleic acid molecule being a locked nucleic acid.

[0030] The chemical modifications described herein is well-known to those skilled in the art, and the modification of the phosphodiester bond refers to the modification of oxygen in the phosphodiester bond, including, but not limited to, phosphorothioate modification and boranophosphate modification. Both modifications can stabilize an saRNA structure and maintain high specificity and high affinity for base pairing.

[0031] The ribose modification refers to the modification of 2'-OH in pentose of a nucleotide, i.e., the introduction of some substituents into hydroxyl positions of the ribose, for example, including, but not limited to, 2'-fluoro modification, 2'-oxymethyl modification, 2'-oxyethylidene methoxy

modification, 2,4'-dinitrophenol modification, locked nucleic acid (LNA), 2'-amino modification, 2'-deoxy modification, and the like.

[0032] The base modification refers to the modification of the base of a nucleotide, for example, including, but not limited to, 5'-bromouracil modification, 5'-iodouracil modification, N-methyluracil modification, 2,6-diaminopurine modification, and the like.

[0033] These modifications can increase the bioavailability of the small activating nucleic acid molecule, improve affinity to a target sequence, and enhance resistance to nuclease hydrolysis in a cell.

[0034] In addition, in order to promote the access of a small activating nucleic acid molecule into a cell, on the basis of the aforementioned modifications, a lipophilic group, such as cholesterol,) can be introduced on the terminus of the first nucleic acid strand and/or the second nucleic acid strand of the small activating nucleic acid molecule to facilitate the interaction with the promoter region of a gene in the cell nucleus, as the cell membrane and nuclear membrane are composed of lipid bilayers.

[0035] After contacting and entering a cell, the small activating nucleic acid molecule of the present invention can effectively activate or up-regulate the expression of the *Thpo/THPO* gene in the cell, preferably by at least 10%.

[0036] Another aspect of the present invention also relates to a nucleic acid encoding a small activating nucleic acid molecule of the invention. In one embodiment, the nucleic acid is a DNA molecule.

[0037] Another aspect of the present invention provides a cell comprising the aforementioned small activating nucleic acid molecule or the nucleic acid encoding the small activating nucleic acid molecule described herein. In one embodiment, a small activating nucleic acid molecule of the present invention can be a double-stranded small activating nucleic acid molecule, such as a double-stranded small activating RNA (saRNA) molecule, which targets the promoter region of the *Thpo/THPO* gene comprising a first nucleic acid strand and a second nucleic acid strand. In another embodiment, a small activating nucleic acid molecule of the present invention can be a single-stranded small activating nucleic acid molecule, such as a hairpin-structured single-stranded nucleic acid, targeting the promoter region of the *Thpo/THPO* gene, wherein the hairpin-structured single-stranded nucleic acid produces a double-stranded small activating RNA (saRNA) molecule in a cell after being introduced into the cell.

[0038] Another aspect of the present invention provides a composition (e.g., a pharmaceutical composition). The composition comprises a small activating nucleic acid molecule of the present invention or a nucleic acid encoding the small activating nucleic acid molecule described herein,

and optionally, a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutically acceptable carrier can comprise or be selected from a liposome, a high-molecular polymer, and a polypeptide.

[0039] In another aspect of the present invention, a formulation is provided which comprises a small activating nucleic acid molecule described in the present invention, a nucleic acid encoding the small activating nucleic acid molecule described in the present invention, or a cell comprising a small activating nucleic acid molecule of the present invention or a nucleic acid encoding a small activating nucleic acid molecule of the present invention, or a composition comprising a small activating nucleic acid molecule of the present invention.

[0040] In another aspect of the present invention, a kit is provided which comprises a small activating nucleic acid molecule of the present invention, a nucleic acid encoding a small activating nucleic acid molecule described herein, or a cell comprising a small activating nucleic acid molecule of the present invention or a nucleic acid encoding a small activating nucleic acid molecule of the present invention, or a composition comprising a small activating nucleic acid molecule of the present invention.

[0041] Another aspect of the present invention relates to uses of the small activating nucleic acid molecule described in the present invention, a nucleic acid encoding the small activating nucleic acid molecule of the present invention, a cell comprising the small activating nucleic acid molecule of the present invention, or the nucleic acid encoding the small activating nucleic acid molecule of the present invention, or a composition comprising the small activating nucleic acid molecule of the present invention in the preparation of a drug or formulation for activating/up-regulating the expression of the *Thpo/THPO* gene in a cell.

[0042] Another aspect of the present invention also relates to a method for activating/up-regulating the expression of the *Thpo/THPO* gene in a cell. The method comprises administering the small activating nucleic acid molecule described in the present invention, a nucleic acid encoding the small activating nucleic acid molecule of the present invention or a composition or formulation comprising the small activating nucleic acid molecule of the present invention to a cell. In one embodiment, the method for activating/up-regulating the expression of the *Thpo/THPO* gene in the cell comprises administering the small activating nucleic acid molecule described in the present invention, the nucleic acid encoding the small activating nucleic acid molecule of the present invention, or the composition or formulation comprising the small activating nucleic acid molecule of the present invention to the cell. The aforementioned cell comprises a mammal cell, e.g., a cell from a human body, such as a human embryo liver cell, a human hepatoma cell, such as an HepG2 cell, and a human liver cell, or a cell from a mouse, such

as a mouse embryonic liver cell, such as embryonic cell line BNL.CL2, a mouse liver cancer cell, such as the liver cancer cell line LPC-H12, and a mouse primary liver cell. The aforementioned cell can be *in vitro*, or can be present in a mammalian body, such as a mouse or human body.

[0043] The small activating nucleic acid molecule of the present invention can be directly introduced into a cell, or can be produced in the cell after a nucleotide sequence encoding the small activating nucleic acid molecule of the present invention is introduced into the cell. The cell is preferably a mammalian cell, more preferably a mouse or human cell. The aforementioned cell may be *in vitro*, such as a cell line or a cell strain, or may present in a mammalian body, such as a mouse or human body, and more specifically, such as a liver cell from a mouse or human body. The human body may be a patient suffering from a disease or condition related to insufficient or decreased expression of the THPO protein, or a patient with thrombocytopenia due to various causes. The small activating nucleic acid molecule of the present invention can be administered at a sufficient dose to treat the disease or condition related to a deficiency in the amount of THPO protein or insufficient or decreased expression of the THPO protein. Specifically, the disease or condition related to a deficiency in the amount of THPO protein or insufficient or decreased expression of the THPO protein may be thrombocytopenia.

[0044] Another aspect of the present invention provides an isolated small activating nucleic acid molecule acting site of the *Thpo/THPO* gene, which has any continuous sequence of 16 to 35 nucleotides in length in the promoter region of the *Thpo/THPO* gene, and preferably, the acting site comprises or is selected from any continuous sequence of 16 to 35 nucleotides in length in any of the sequences set forth in SEQ ID NOs: 2-4 and SEQ ID NOs: 601-605. Specifically, the acting site may comprise or be selected from any nucleotide sequence set forth in SEQ ID NOs: 200-296 and SEQ ID NOs: 606-1047.

[0045] Another aspect of the present invention relates to a method for treating a disease or condition related to insufficient or decreased expression of the THPO protein in a subject such as a human or mouse or thrombocytopenia, which comprises administering a small activating nucleic acid molecule of the present invention, a nucleic acid encoding a small activating nucleic acid molecule of the present invention, a cell comprising a small activating nucleic acid molecule of the present invention, or a nucleic acid encoding a small activating nucleic acid molecule of the present invention, or a composition comprising a small activating nucleic acid molecule of the present invention at a curative dose to the subject. In one embodiment, a method for treating thrombocytopenia and/or a disease or condition related to insufficient or decreased expression of THPO protein in a subject in the present invention can comprise administering a small activating nucleic acid molecule of the present invention, a nucleic acid encoding the small activating nucleic acid molecule of the present invention, a cell comprising the small activating nucleic acid molecule

of the present invention, or a nucleic acid enencoding a small activating nucleic acid molecule of the present invention, or a composition comprising the small activating nucleic acid molecule of the present invention, and other formulations at a curative dose to the subject, wherein the other formulations comprises, such as a low-molecular-weight compound, antibody, polypeptide or protein, etc. The subject can be a mammal, e.g., a mouse or a human. In the present invention, thrombocytopenia is caused by various factors, including, but not limited to, myelo-thrombocytopenia, increased peripheral platelet destruction, and splenic sequestration. Factors causing a reduction in platelets comprise congenital (hereditary) and acquired thrombocytopenia. In one embodiment, factors causing acquired thrombocytopenia include, but are not limited to, thrombocytopenia caused by aplastic anemia, myelodysplastic syndromes, leukemia, drugs, infection, tumor diseases, radiotherapy, bone marrow transplantation, and chronic liver diseases, and immune thrombocytopenia (ITP). Factors causing increased platelet destruction include, but are not limited to, thrombotic thrombocytopenia, heparin-induced thrombocytopenia, drug-induced thrombocytopenia, ITP, and thrombotic thrombocytopenia purpura. In one embodiment, thrombocytopenia is related to a disease or condition related to insufficient or decreased expression of the THPO protein. In another embodiment, thrombocytopenia is related to insufficient or decreased expression of the THPO protein. Thrombocytopenia can comprise drug-induced thrombocytopenia, immune thrombocytopenia, thrombotic thrombocytopenia purpura, and the like. The thrombocytopenia described herein can be caused by various factors, such as myelo-thrombocytopenia, increased peripheral platelet destruction and splenomegaly sequestration, such as tumor radiotherapy, tumor chemotherapy, bone marrow transplantation, chronic liver disease, drug-induced thrombocytopenia, immune thrombocytopenia, thrombotic thrombocytopenic purpura, and hereditary thrombocytopenia. Thrombocytopenia is generally characterized clinically by ecchymosis, changes in megakaryocytes in the bone marrow, mucosal bleeding or intracranial bleeding, all of which will endanger the lives of patients with severe thrombocytopenia. When the platelet concentrations are lower than 100×10^9/L by direct blood platelet count, thrombocytopenia is considered to be present (Kuter 2009). When the platelet concentrations are lower than 50×10^9/L, spontaneous bleeding, commonly manifesting as subcutaneous purpuraa, occurs frequently. When the platelet concentrations are lower than 20×10^9/L, a patient's condition can be life-threatening, caused by trauma or sudden intracranial bleeding, gastrointestinal bleeding, and the like. In the method of the present invention, the thrombocytopenia in the subject can be characterized by a platelet concentration of less than 100×10^9/L, less than 50×10^9/L, or less than 20×10^9/L as indicated by direct blood platelet count. In one embodiment, a disease or condition related to insufficient or decreased expression of the THPO protein in a subject is alleviated, relieved, or cured after administering a small activating nucleic acid molecule of the present

invention, a nucleic acid encoding the small activating nucleic acid molecule of the present invention, the cell comprising the small activating nucleic acid molecule of the present invention, or the nucleic acid encoding the small activating nucleic acid molecule of the present invention, or the composition comprising the small activating nucleic acid molecule of the present invention at a curative dose.

[0046] Another aspect of the present invention relates to a method for treating thrombocytopenia in a subject, which comprises administering a small activating nucleic acid molecule of the present invention, a nucleic acid encoding the small activating nucleic acid molecule of the present invention, a cell comprising the small activating nucleic acid molecule of the present invention, a nucleic acid encoding the small activating nucleic acid molecule of the present invention, or a composition comprising the small activating nucleic acid molecule of the present invention at a curative dose to the subject. In the method of the present invention, the thrombocytopenia in the subject can be characterized by a platelet concentration of less than 100×10^9/L, less than 50×10^9/L, or less than 20×10^9/L as indicated by direct blood platelet count. In a method of the present invention, the thrombocytopenia can be related to insufficient or decreased expression of the THPO protein, drug-induced thrombocytopenia, immune thrombocytopenia, thrombotic thrombocytopenic purpuraa, and the like. The thrombocytopenia as described herein can be caused due to various factors such as myelo-thrombocytopenia, increased peripheral platelet destruction and splenomegaly sequestration, such as tumor radiotherapy, tumor chemotherapy, bone marrow transplantation, chronic liver disease, drug-induced thrombocytopenia, immune thrombocytopenia, thrombotic thrombocytopenic purpura, and hereditary thrombocytopenia. In one embodiment, the method for treating thrombocytopenia of the present invention comprises administering a small activating nucleic acid molecule of the present invention, a nucleic acid encoding a small activating nucleic acid molecule of the present invention, a cell comprising a small activating nucleic acid molecule of the present invention or a nucleic acid encoding the small activating nucleic acid molecule of the present invention, or a composition comprising a small activating nucleic acid molecule of the present invention and/or the aforementioned the small activating nucleic acid molecule, the nucleic acid encoding the aforementioned small activating nucleic acid molecule, the cell comprising the small activating nucleic acid molecule of the present invention or the nucleic acid encoding the small activating nucleic acid molecule of the present invention, or a composition consisting of the composition comprising the small activating nucleic acid molecule of the present invention and one or more other formulations at a curative dose to the subject, wherein the other formulation comprises, such as a low-molecular-weight compound, antibody, polypeptide and protein. The subject can be a mammal, such as a mouse or human. In the aforementioned method, the thrombocytopenia can comprise drug-induced thrombocytopenia, immune thrombocytopenia,

thrombotic thrombocytopenia purpura, and the like. In the aforementioned method, the subject comprises a mammal, such as a mouse or human. In one embodiment, the thrombocytopenia in a subject is alleviated, relieved, or cured after administering the small activating nucleic acid molecule of the present invention, the nucleic acid encoding the small activating nucleic acid molecule of the present invention, the cell comprising the small activating nucleic acid molecule of the present invention, or the nucleic acid encoding the small activating nucleic acid molecule of the present invention, or the composition comprising the small activating nucleic acid molecule of the present invention at a curative dose. Preferably, the alleviation, relief, or cure may be an increase or recovery of the platelet concentration to near normal physiological levels, such as in the range of 100×10^9/L to 300×10^9/L, as indicated by direct blood platelet count.

[0047] Another aspect of the present invention relates to a use of a small activating nucleic acid molecule of the present invention, a nucleic acid encoding the small activating nucleic acid molecule of the present invention, a cell comprising the small activating nucleic acid molecule of the present invention or the nucleic acid encoding the small activating nucleic acid molecule of the present invention, or the composition comprising the small activating nucleic acid molecule of the present invention in the preparation of a drug for treating a disease or condition related to thrombocytopenia and/or insufficient or decreased expression of the THPO protein. The subject can be a mammal, such as a human. In uses of present invention, thrombocytopenia is caused by various factors, including, but not limited to, myelo-thrombocytopenia, increased peripheral platelet destruction, and splenic sequestration. Factors causing a reduction in platelets comprise congenital (hereditary) and acquired thrombocytopenia. In one embodiment, thrombocytopenia caused by acquired factors include, but are not limited to, thrombocytopenia caused by aplastic anemia, myelodysplastic syndromes, leukemia, drugs, infection, tumor diseases, radiotherapy, bone marrow transplantation, and chronic liver diseases, and immune thrombocytopenia (ITP). Factors causing increased platelet destruction include, but are not limited to, thrombotic thrombocytopenia, heparin-induced thrombocytopenia, drug-induced thrombocytopenia, ITP, and thrombotic thrombocytopenia purpura. In one embodiment, the thrombocytopenia can comprise, for example, thrombocytopenia related to insufficient or decreased expression of the THPO protein. Preferably, the thrombocytopenia can comprises or be selected from thrombocytopenia related to insufficient or decreased expression of the THPO protein, drug-induced thrombocytopenia, immune thrombocytopenia, thrombotic thrombocytopenic purpuraa, and the like. Thrombocytopenia as described herein can be caused by various factors such as tumor radiotherapy, tumor chemotherapy, bone marrow transplantation, chronic liver disease, splenomegaly sequestration, transfusion of banked blood with low platelet content, and an increase of platelet consumption due to drugs. In

one embodiment, thrombocytopenia can be manifested as a platelet concentration of less than 100×10^9/L, less than 50×10^9/L, or less than 20×10^9/L as indicated by direct blood platelet counts.

[0048] In one embodiment, a use of a small activating nucleic acid molecule described in the present invention, a nucleic acid encoding the small activating nucleic acid molecule of the present invention, a cell comprising the small activating nucleic acid molecule of the present invention or the nucleic acid encoding the small activating nucleic acid molecule of the present invention, or the composition comprising the small activating nucleic acid molecule of the present invention in the preparation of a drug for treating thrombocytopenia or a disease related to insufficient or decreased expression of the THPO protein is provided. In one embodiment, thrombocytopenia can comprise thrombocytopenia related to insufficient or decreased expression of THPO protein, and preferably, thrombocytopenia can comprise drug-induced thrombocytopenia, immune thrombocytopenia, thrombotic thrombocytopenic purpuraa, and the like. In one embodiment, thrombocytopenia can be manifested as a platelet concentration of less than 100×10^9/L, less than 50×10^9/L, or less than 20×10^9/L as indicated by direct blood platelet count.

[0049] Another aspect of the present invention relates to a use of the small activating nucleic acid molecule described in the present invention, the nucleic acid encoding the small activating nucleic acid molecule of the present invention, the cell comprising the small activating nucleic acid molecule of the present invention or the nucleic acid encoding the small activating nucleic acid molecule of the present invention, or the composition or formulation comprising the small activating nucleic acid molecule of the present invention in the preparation of a drug or pharmaceutical composition for treating thrombocytopenia. Preferably, the thrombocytopenia can comprise or be selected from thrombocytopenia related to insufficient or decreased expression of the THPO protein or thrombocytopenia due to other various causes, such as drug-induced thrombocytopenia, immune thrombocytopenia, thrombotic thrombocytopenic purpuraa, and the like. The thrombocytopenia described herein can be caused by various factors such as tumor radiotherapy, tumor chemotherapy, bone marrow transplantation, chronic liver disease, splenomegaly sequestration, transfusion of banked blood with low platelet content and an increase of platelet consumption due to drugs. In one embodiment, thrombocytopenia can be manifested as a platelet concentration of less than 100×10^9/L, less than 50×10^9/L, or less than 20×10^9/L as indicated by direct blood platelet count.

[0050] In one embodiment, a use of s small activating nucleic acid molecule described in the present invention, a nucleic acid encoding the small activating nucleic acid molecule of the present invention, a cell comprising the small activating nucleic acid molecule of the present invention or the nucleic acid encoding the small activating nucleic acid molecule of the present invention, or a composition or formulation comprising the small activating nucleic acid molecule of the present

invention in the preparation of a drug or pharmaceutical composition for treating a disease related to insufficient or decreased expression of the THPO protein or thrombocytopenia.

[0051] **Advantages of the Present Invention**

[0052] The small activating nucleic acid molecule, such as small activating RNA (saRNA), is capable of activating/up-regulating endogenous *Thpo/THPO* gene expression provided by the present invention and can specifically activate *Thpo/THPO* gene, thereby up-regulating or restoring the expression of *Thpo/THPO* gene and protein with lower toxic and side effects, which can be used for treating thrombocytopenia caused by insufficient platelet production or excessive destruction due to insufficient *Thpo/THPO* protein expression and various causes, or in preparing a drug or formulation for treating thrombocytopenia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0053] **FIG. 1 shows changes in the expression of mouse *Thpo* mRNA mediated by mouse *Thpo* saRNA.** BNL.CL2 cells were transfected with 322 saRNAs targeting mouse *Thpo* promoter at a final concentration of 10 nM, and *Thpo* mRNA expression was analyzed 72 h after transfection using one-step RT-qPCR. The figure shows the descending order of mRNA expression changes (log_2) of *Thpo* relative to control treatment (Mock). The ordinate values represent the mean of 2 repeat treatment ± SD.

[0054] **FIG. 2 shows the hotspot region of mouse *Thpo* saRNA on the mouse *Thpo* promoter.** BNL.CL2 cells were transfected with 322 saRNAs targeting mouse *Thpo* promoter at a final concentration of 10 nM for 72 h, and *Thpo* mRNA expression was analyzed after transfection using one-step RT-qPCR. The figure shows changes in the expression of *Thpo* relative to control treatment (Mock) ranked from -500 to -0 according to the target positions of the saRNA in the *Thpo* promoter. Black solid dots represent functional saRNAs, white open dots represent non-functional saRNAs, and dotted lines frame the hotspot regions where 3 functional saRNAs gather (H1 to H3). The ordinate values represent the mean of 2 repeat treatment.

[0055] **FIG. 3 shows the screening results of two-step RT-qPCR validated mouse *Thpo* saRNA HTS.** As shown, the BNL.CL2 cells were transfected with saRNA at a final concentration of 10 nM for 72 h. After transfection, RNA was extracted with Qiagen RNeasy kit and qPCR amplification was performed with ABI 7500 rapid real-time PCR system after reverse transcription. The Tbp gene was amplified as internal control. The relative expression values of *Thpo* mRNA are shown after treatment of cells with a single saRNA. Mock, dsCon2, and DS03-432i are shown respectively as blank transfection, sequence-independent double-stranded RNA transfection, and small interference RNA control transfection. The ordinate values represent the mean of 2 repeat treatment ± SD.

[0056] **FIG. 4 shows the screening results of two-step RT-qPCR validated mouse *Thpo* saRNA HTS.** As shown, the LPC-H12 cells were transfected with saRNA at a final concentration of 10 nM for 72 h. After transfection, RNA was extracted with Qiagen RNeasy kit after transfection and qPCR amplification was performed with ABI 7500 rapid real-time PCR system after reverse transcription. The *Tbp* gene was amplified as internal control. The relative expression values of *Thpo* mRNA are shown after treatment of cells with a single saRNA. Mock, dsCon2, and DS03-432i are shown respectively as blank transfection, sequence-independent double-stranded RNA transfection, and small interference RNA control transfection. The ordinate values represent the mean of 2 repeat treatment ± SD.

[0057] **FIG. 5 shows the screening results of two-step RT-qPCR validated mouse *Thpo* saRNA HTS in a primary mouse liver cell. As shown, the** primary mouse liver cell were transfected with saRNA at a final concentration of 10 nM for 72 h. After transfection, RNA was extracted with Qiagen RNeasy kit after transfection and qPCR amplification was performed with ABI 7500 rapid real-time PCR system after reverse transcription. The *Tbp* gene was amplified as internal control. The relative expression values of *Thpo* mRNA are shown after treatment of cells with a single saRNA. Mock, dsCon2, and DS03-432i are are shown respectively as blank transfection, sequence-independent double-stranded RNA transfection, and small interference RNA control transfection. The ordinate values represent the mean of 2 repeat treatment ± SD.

[0058] **FIG. 6 shows that mouse *Thpo* saRNA increases concentration of Thpo in mice serum.** Fifteen male *Balb/c* mice were randomly divided into 3 groups with 5 mice in each group, and received PBS, LNP-entrapped *Thpo*-siRNA (DS03-432i, 5 mg/kg) and LNP-entrapped *Thpo*-saRNA (DS03-0024, 5 mg/kg) by tail vein injection. Blood samples were collected after 72 h and serum was separated. A mouse **Thpo** ELISA kit was used to determine Thpo protein levels in mice serum. PBS is a blank control and DS03-432i is a small interfering RNA control. (*** $p < 0.001$).

[0059] **FIG. 7 shows that mouse *Thpo* saRNA increases concentration of Thpo in mice serum.** Thirty two male *Balb/c* mice were randomly divided into 4 groups with 8 mice in each group, and received PBS and LNP-entrapped DS03-0024 (1 mg/kg, 3 mg/kg and 6 mg/kg) by tail vein injection. Blood samples were collected and serum was isolated 1 day prior to administration and 2 days after administration. A mouse **Thpo** ELISA kit was used to determine the Thpo protein levels in mice serum (**** $p < 0.0001$).

[0060] **FIG. 8 shows that mouse *Thpo* saRNA increases the number of platelets of mouse.** Thirty two male *Balb/c* mice were randomly divided into 4 groups with 8 mice in each group, and received PBS and LNP-entrapped DS03-0024 (1 mg/kg, 3 mg/kg and 6 mg/kg) by tail vein

injection. Blood samples were collected 6 days after administration, and platelets were collected using a mouse peripheral platelet isolation kit, which utilized a labeled CD41a-FITC antibody to facilitate counting using a flow cytometer. (*$p < 0.05$).

[0061] **FIG. 9 shows that changes in the number of platelets of mouse caused by mouse *Thpo* saRNA 9 days after administration.** Thirty two male *Balb/c* mice were randomly divided into 4 groups with 8 mice in each group, and received PBS and LNP-entrapped DS03-0024 (1 mg/kg, 3 mg/kg and 6 mg/kg) by tail vein injection. Blood samples were collected 17 days after administration and platelets were collected using a mouse peripheral platelet isolation kit, which utilized a labeled CD41a-FITC antibody to facilitate counting using a flow cytometer. (* $p < 0.05$).

[0062] **FIG. 10 shows changes in the expression of human *THPO* mRNA mediated by human *THPO* saRNA.** HepG2 cells were transfected with candidate saRNAs targeting the human *THPO* promoter at a final concentration of 25 nM. Human *THPO* mRNA expression was analyzed 72 h after transfection using one-step RT-qPCR. The figure shows the descending order of mRNA expression changes (log_2) of *THPO* relative to control treatment (Mock). The ordinate values represent the mean of 2 repeat treatment ± SD.

[0063] **FIG. 11 shows the hotspot region of human *THPO* saRNA on the human *THPO* promoter.** HepG2 cells were transfected with candidate saRNAs targeting the human *THPO* promoter at a final concentration of 25 nM for 72 h. Human *THPO* mRNA expression was analyzed after transfection using one-step RT-qPCR. The figure showschanges in the expression of *THPO* relative to control treatment (Mock) ranked according to the target positions of the saRNA in the *THPO* promoter. Black solid dots represent functional saRNAs, white open dots represent non-functional saRNAs, and dotted lines frame the hotspot regions where functional saRNAs gather. The ordinate values represent the mean of 2 repeat treatment ± SD.

[0064] **FIG. 12 shows the screening results of two-step RT-qPCR validated human *THPO* saRNA HTS.** HepG2 cells were transfected with saRNA at a final concentration of 25 nM for 72 h. After transfection, RNA was extracted with Qiagen RNeasy kit. After reverse transcription, qPCR amplification was performed with ABI 7500 rapid real-time PCR system. *TBP* and *HPRT1* genes were amplified as internal controls. Shown are the relative mRNA expression values of *THPO* after treatingcells with a single saRNA. Shown are Mock, dsCon2, and *siTHPO* (DS3A-365i) which are blank transfection, sequence-independent double-stranded RNA transfection, and small interference RNA control transfection, respectively. The ordinate values represent the mean of 2 repeat treatment ± SD.

[0065] **FIG. 13 shows the effect of human *THPO* saRNA on the expression of human THPO protein by ELISA method.** HepG2 cells were transfected with saRNA at a final concentration of

25 nM for 72 h. After transfection, culture medium was taken and the supernatant was centrifuged to remove dead cell debris. The level of THPO protein secreted into the culture medium was determined by ELISA kit (R & D Systems, DTP00B). Shown are the expression values of THPO protein after treating the cells with a single saRNA. Shown are Mock, dsCon2, and *siTHPO* (DS3A-365i) which are blank transfection, sequence-independent double-stranded RNA transfection, and small interference RNA control transfection, respectively. The ordinate values represent the mean of 2 repeat treatment ± SD.

DETAILED DESCRIPTION

[0066] In the present invention, the related terms are defined as follows.

[0067] The term "complementarity" as used herein refers to the capability of forming base pairs between two oligonucleotide strands. The base pairs are generally formed through hydrogen bonds between nucleotides in the antiparallel oligonucleotide strands. The bases of the complementary oligonucleotide strands can be paired in the Watson-Crick manner (such as A to T, A to U, and C to G) or in any other manner allowing the formation of a duplex (such as Hoogsteen or reverse Hoogsteen base pairing).

[0068] Complementarity comprises complete complementarity and incomplete complementarity. "Complete complementarity" or "100% complementarity" means that each nucleotide from the first oligonucleotide strand can form a hydrogen bond with a nucleotide at a corresponding position in the second oligonucleotide strand in the double-stranded region of the double-stranded oligonucleotide molecule without "mispairing". "Incomplete complementarity" means that not all the nucleotide units of the two strands are bonded with each other by hydrogen bonds. For example, for two oligonucleotide strands each of 20 nucleotides in length in the double-stranded region, if only two base pairs in this double-stranded region can be formed through hydrogen bonds, the oligonucleotide strands have a complementarity of 10%. In the same example, if 18 base pairs in this double-stranded region can be formed through hydrogen bonds, the oligonucleotide strands have a complementarity of 90%. Substantial complementarity refers to at least about 75%, about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100% complementarity.

[0069] The term "oligonucleotide" as used herein refers to polymers of nucleotides, and includes, but is not limited to, single-stranded or double-stranded molecules of DNA, RNA, or DNA/RNA hybrid, oligonucleotide strands containing regularly and irregularly alternating deoxyribosyl portions and ribosyl portions, as well as modified and naturally or unnaturally existing frameworks for such oligonucleotides. The oligonucleotide for activating target gene transcription described herein is a small activating nucleic acid molecule.

[0070] The terms "oligonucleotide strand" and "oligonucleotide sequence" as used herein can be used interchangeably, referring to a generic term for short nucleotide sequences having less than 35 bases (including nucleotides in deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)). In the present invention, an oligonucleotide strand may have any of 16 to 35 nucleotides in length.

[0071] As used herein, the term "first nucleic acid strand" can be a sense strand or an antisense strand. The sense strand of a small activating RNA refers to a nucleic acid strand contained in a small activating RNA duplex which has identity to the coding strand of the promoter DNA sequence of a target gene, and the antisense strand refers to a nucleic acid strand in the small activating RNA duplex which is complementary to the sense strand.

[0072] As used herein, the term "second nucleic acid strand" can also be a sense strand or an antisense strand. If the first oligonucleotide strand is a sense strand, the second oligonucleotide strand is an antisense strand; if the first oligonucleotide strand is an antisense strand, the second oligonucleotide strand is a sense strand.

[0073] The term "gene" as used herein refers to all nucleotide sequences required to encode a polypeptide chain or to transcribe a functional RNA. "Gene" can be an endogenous or fully or partially recombinant gene for a host cell (for example, because an exogenous oligonucleotide and a coding sequence for encoding a promoter are introduced into a host cell, or a heterogeneous promoter adjacent to an endogenous encoding sequence is introduced into a host cell). For example, the term "gene" comprises a nucleic acid sequence consisting of exons and introns. Protein-encoding sequences are, for example, sequences contained within exons in an open reading frame between an initiation codon and a termination codon, and as used herein, "gene" can comprise such as a gene regulatory sequence, such as a promoter, an enhancer, and all other sequences known in the art for controlling the transcription, expression or activity of another gene, no matter whether the gene comprises a coding sequence or a non-coding sequence. In one case, for example, "gene" can be used to describe a functional nucleic acid comprising a regulatory sequence such as a promoter or an enhancer. The expression of a recombinant gene can be controlled by one or more types of heterogeneous regulatory sequences.

[0074] The term "target gene" as used herein can refer to nucleic acid sequences naturally present in organisms, transgenes, viral or bacterial sequences, can be chromosomes or extrachromosomal genes, and/or can be transiently or stably transfected or incorporated into cells and/or chromatins thereof. The target gene can be a protein-encoding gene or a non-protein-encoding gene (such as a microRNA gene and a long non-coding RNA gene). The target gene generally contains a promoter sequence, and the positive regulation for the target gene can be achieved by designing a small activating nucleic acid molecule having sequence identity (also called homology) to the promoter

sequence, characterized as the up-regulation of expression of the target gene. "Sequence of a target gene promoter" refers to a non-coding sequence of the target gene, and the reference of the sequence of a target gene promoter in the phrase "complementary to the sequence of a target gene promoter" of the present invention refers to a coding strand of the sequence, also known as a non-template strand, i.e., a nucleic acid sequence having the same sequence as the coding sequence of the gene. "Target" or "target sequence" refers to a sequence fragment in the sequence of a target gene promoter which is homologous or complementary with a sense oligonucleotide strand or an antisense oligonucleotide strand of a small activating nucleic acid molecule.

[0075] As used herein, the terms "sense strand" and "sense nucleic acid strand" can be used interchangeably, and the sense oligonucleotide strand of a small activating nucleic acid molecule refers to the first nucleic acid strand having identity to the coding strand of the sequence of a target gene promoter in the small activating nucleic acid molecule duplex.

[0076] As used herein, the terms "antisense strand" and "antisense nucleic acid strand" can be used interchangeably, and the antisense oligonucleotide strand of a small activating nucleic acid molecule refers to the second nucleic acid strand complementary with the sense oligonucleotide strand in the small activating nucleic acid molecule duplex.

[0077] The term "coding strand" as used herein refers to a DNA strand in the target gene which cannot be used for transcription, and the nucleotide sequence of this strand is the same as that of an RNA produced from transcription (in the RNA, T in DNA is replaced by U). The coding strand of the double-stranded DNA sequence of the target gene promoter described herein refers to a promoter sequence on the same DNA strand as the DNA coding strand of the target gene.

[0078] The term "template strand" as used herein refers to the other strand complementary with the coding strand in the double-stranded DNA of the target gene, i.e., the strand that, as a template, can be transcribed into RNA, and this strand is complementary with the transcribed RNA (A to U and G to C). In the process of transcription, RNA polymerase binds to the template strand, moves along the 3'→5' direction of the template strand, and catalyzes the synthesis of the RNA along the 5'→3' direction. The template strand of the double-stranded DNA sequence of the target gene promoter described herein refers to a promoter sequence on the same DNA strand as the DNA template strand of the target gene.

[0079] The term "promoter" as used herein refers to a sequence which plays a regulatory role for the transcription of a protein-coding or RNA-coding nucleic acid sequence by associating with them spatially. Generally, a eukaryotic gene promoter contains 100 to 5000 base pairs, although this length range is not intended to limit the term "promoter" as used herein. Although the promoter

sequence is generally located at the 5' terminus of a protein-coding or RNA-coding sequence, the promoter sequence may also exist in exon and intron sequences.

[0080] The term "transcription start site" as used herein refers to a nucleotide marking the transcription start on the template strand of a gene. The transcription start site may appear on the template strand of the promoter region. A gene can have more than one transcription start site.

[0081] The term "identity" or "homology" as used herein means that one oligonucleotide strand (a sense or an antisense strand) of a small activating RNA has similarity to a coding strand or a template strand in a region of the promoter sequence of a target gene. As used herein, the "identity" or "homology" may be at least about 75%, about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%.

[0082] The term "overhang" as used herein refers to non-base-paired nucleotides at the terminus (5' or 3') of an oligonucleotide strand, which is formed by one strand extending out of the other strand in a double-stranded oligonucleotide. A single-stranded region extending out of the 3' terminus and/or 5' terminus of a duplex is referred to as an overhang.

[0083] As used herein, the terms "gene activation", "activating gene expression", "gene up-regulation" and "up-regulating gene expression" can be used interchangeably, and mean an increase in transcription, translation, expression or activity of a certain nucleic acid as determined by measuring the transcriptional level, mRNA level, protein level, enzymatic activity, methylation state, chromatin state or configuration, translation level or the activity or state in a cell or biological system of a gene. These activities or states can be determined directly or indirectly. In addition, "gene activation", "activating gene expression", "gene up-regulation" or "up-regulating gene expression" refers to an increase in activity associated with a nucleic acid sequence, regardless of the mechanism of such activation. For example, the nucleic acid sequence plays a regulatory role as a regulatory sequence, the nucleic acid sequence is transcribed into RNA and the RNA is translated into a protein, thereby increasing the expression of the protein.

[0084] As used herein, the terms "small activating RNA", "saRNA", and "small activating nucleic acid molecule" can be used interchangeably, and refer to a nucleic acid molecule that can up-regulate target gene expression and can be composed of the first nucleic acid fragment (antisense nucleic acid strand, also referred to as antisense oligonucleotide strand) containing a nucleotide sequence having sequence identity or homology with the non-coding nucleic acid sequence (e.g., a promoter and an enhancer) of a target gene and the second nucleic acid fragment (sense nucleic acid strand, also referred to as sense oligonucleotide strand) containing a nucleotide sequence complementary with the first nucleic acid fragment, wherein the first nucleic acid fragment and the second nucleic acid fragment form a duplex. The small activating nucleic acid

molecule can also be composed of a synthesized or vector-expressed single-stranded RNA molecule that can form a hairpin structure by two complementary regions within the molecule, wherein the first region comprises a nucleotide sequence having sequence identity to the target sequence of a promoter of a gene, and the second region comprises a nucleotide sequence which is complementary to the first region. The length of the duplex region of the small activating nucleic acid molecule is typically about 10 to about 50, about 12 to about 48, about 14 to about 46, about 16 to about 44, about 18 to about 42, about 20 to about 40, about 22 to about 38, about 24 to about 36, about 26 to about 34, and about 28 to about 32 base pairs, and typically about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, or about 50 base pairs. In addition, the terms "saRNA", "small activating RNA", and "small activating nucleic acid molecule" also comprise nucleic acids other than the ribonucleotide, including, but not limited to, modified nucleotides or analogues.

[0085] As used herein, the term "hotspot" refers to a gene promoter region of at least 30 bp in length. The gathering of targets of functional small activating nucleic acid molecules appears in these hotspot regions, wherein at least 30% of the small activating nucleic acid molecules targeting these hotspot regions can induce a 1.1-fold to 2.89-fold in the mRNA expression of a target gene.

[0086] As used herein, the term "synthesis" refers to a method for synthesis of an oligonucleotide, including any method allowing RNA synthesis, such as chemical synthesis, *in vitro* transcription, and/or vector-based expression.

[0087] According to the present invention, the expression of the *Thpo/THPO* gene is up-regulated by RNA activation, and a related disease (particularly thrombocytopenia) is treated by increasing the expression of the THPO protein. The *Thpo/THPO* gene in the present invention is sometimes also called a target gene.

[0088] The method for preparing the small activating nucleic acid molecule provided by the present invention comprises sequence design and sequence synthesis.

[0089] The synthesis of the sequence of the small activating nucleic acid molecule of the present invention can be performed by adopting a chemical synthesis or can be entrusted to a biotechnology company specialized in nucleic acid synthesis.

[0090] Generally speaking, the chemical synthesis comprises the following four steps: (1) synthesis of oligomeric ribonucleotides, (2) deprotection, (3) purification and isolation; and (4) desalination and annealing.

[0091] For example, the specific steps for chemically synthesizing the saRNA described herein are as follows:

[0092] (1) **Synthesis of oligomeric ribonucleotides**

[0093] Synthesis of 1 μM RNA was set in an automatic DNA/RNA synthesizer (e.g., Applied Biosystems EXPEDITE8909), and the coupling time of each cycle was also set as 10 to 15 min. With a solid phase-bonded 5'-O-p-dimethoxytriphenylmethyl-thymidine substrate as an initiator, one base was bonded to the solid phase substrate in the first cycle, and then, in the n^{th} ($19 \geq n \geq 2$) cycle, one base was bonded to the base bonded in the $n\text{-}1^{th}$ cycle. This process was repeated until the synthesis of the whole nucleic acid sequence was completed.

[0094] (2) **Deprotection**

[0095] The solid phase substrate bonded with the saRNA was put into a test tube, and 1 mL of a mixed solution of ethanol and ammonium hydroxide (volume ratio: 1:3) was added to the test tube. The test tube was then sealed and placed in an incubator, and the mixture was incubated at 25-70 °C for 2 to 30 h. The solution containing the solid phase substrate bonded with the saRNA was filtered, and the filtrate was collected. The solid phase substrate was rinsed with double distilled water twice (1 mL each time), and the filtrate was collected. The collected eluent was combined and dried under vacuum for 1 to 12 h. Then the solution was added with 1 mL of a solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M), let stand at room temperature for 4 to 12 h, followed by addition of 2 mL of *n*-butanol. Precipitate was collected to give a single-stranded crude product of saRNA by high-speed centrifugation.

[0096] (3) **Purification and isolation**

[0097] The resulting crude product of saRNA was dissolved in 2 mL of triethylamine acetate solution with a concentration of 1 mol/L, and the solution was separated by a reversed-phase C18 column of high pressure liquid chromatography to give a purified single-stranded product of saRNA.

[0098] (4) **Desalination and annealing**

[0099] Salts were removed by gel filtration (size exclusion chromatography). A single sense oligomeric ribonucleic acid strand and a single antisense oligomeric ribonucleic acid strand were mixed in a 1 to 2 mL of buffer (10 mM Tris, pH = 7.5-8.0, 50 mM NaCl) at a molar ratio of 1:1. The solution was heated to 95 °C, and was then slowly cooled to room temperature to give a solution containing saRNA.

[0100] It was discovered in this study that after being introduced into a cell, the aforementioned saRNA could effectively increase *Thpo/THPO* mRNA and expression of THPO protein.

[0101] The present invention will be further illustrated with reference to specific examples and drawings below. It should be understood that these examples are merely intended to illustrate the present invention rather than limit the scope of the present invention. In the following examples, study methods without specific conditions were generally in accordance with conventional

conditions, such as conditions described in Sambrook, et al., *Molecular Cloning: Laboratory Manual* (New York: Cold Spring Harbor Laboratory Press, 1989), or conditions recommended by the manufacturer.

EXAMPLES

Example 1: Design and Synthesis of saRNA Targeting Mouse *Thpo* Gene Promoter

[0102] To screen functional saRNAs capable of activating *Thpo* gene expression, a *Thpo* promoter sequence with a length of 500 bp was used as a template, a target with a length of 19 bp was selected from -500 bp upstream of TSS. Target sequences were filtered and the criteria for retaining target sequences were: (1) GC content between 35% and 65%, (2) with less than 5 continuous identical nucleotides, (3) with 3 or less dinucleotide repeat sequences; and (4) with 3 or less trinucleotide repeat sequences. There were 322 target sequences remaining after filtration and these entered the screening process as candidates. Corresponding double-stranded saRNAs were chemically synthesized based on these candidate sequences.

[0103] Each sense strand and antisense strand in the double-stranded saRNA used in the study had 21 nucleotides in length. The 19 nucleotides in the 5' region of the first ribonucleic acid strand (sense strand) of the double-stranded saRNA had 100% identity to the target sequence of the promoter, and the 3' terminus of the first ribonucleic acid strand contained a TT sequence. The 19 nucleotides in the 5' region of the second ribonucleic acid strand were complementary to the first ribonucleic acid strand sequence, and the 3' terminus of the second ribonucleic acid strand contained a TT sequence. The aforementioned two strands of the double-stranded saRNA were mixed at a molar ratio of 1:1, and after annealing, a double-stranded saRNA was formed.

[0104] The sequence of the mouse *Thpo* promoter region is shown as follows, which corresponds to position 1 to position 500 from 5' to 3' of SEQ ID No:1 in the sequence listing:

-500 taatataggc aatacctact ttgccagttg gaaaggggaa atgccaggaa
-450 agacactcct ctggagcagg ggaatataga aggaaaagca agcaagccag
-400 catgctgtca gaattcagca gcaggtatac tgttcaggga aaagaaattt
-350 ggagagccag gaactgagac ttcatccatc taaaacaaga cctctctttc
-300 ccagagagaa ccgtattctg ccagatttct cctggactaa ccctcttctc
-250 tctctcactt aggtcccagg ttctcatgtc gccaggacat gagacagttc
-200 ccgctataca aattctctct agagtgtgtg tgggtggagg agctgggctc
-150 tattcatgga ccatggtcca gccatgggct ctagtcccag tagacaggaa
-100 aagaagtcgt catttccggg ggagccttca cctgggcttg gtggctctct
-50 gctctctgat tgggcggaag tggcctgggc aggcttgtga ccctactac

Example 2: High-throughput Screening of saRNAs Targeting Mouse *Thpo* Promoter

[0105] **Cell culture and transfection**

[0106] Mouse embryonic liver cells (BNL.CL2) (Shanghai Institutes for Biological Sciences, GNM22) were cultured in DMEM media (Gibco), containing 10% of calf serum (Sigma-Aldrich) and 1% of penicillin/streptomycin (Gibco). The cells were cultured at 37 °C under 5% CO_2. The BNL.CL2 cells were plated into a 96-well plate at 3500 cells/well. Following the instructions provided by the manufacturer, RNAiMax (Invitrogen, Carlsbad, CA) was used to transfect small activating RNAs at concentrations of 10 nM (unless otherwise specified), and the duration of transfection was 72 h with 2 replicate wells for each treatment.

[0107] (2) **One-step RT-qPCR**

[0108] The media were discarded after transfection and each well was washed once with 150 µL of PBS. After discarding PBS, 50 µL of cell lysis buffer was added to each well and samples were incubated at room temperature for 5 min. From each well, 1 µL of cell lysis buffer was subjected to qPCR analysis on an ABI 7500 fast real-time PCR system (Applied Biosystems) using a one-step TB Green™ PrimeScrip™ RT-PCR kit II (Takara, RR086A) and each sample was amplified in 3 replicate wells. The PCR reaction conditions are shown in Table 1.

Table 1. PCR reaction preparation

Reagent	**Volume**
2 × One-step TB Green RT-PCR buffer 4	2.5 µL
PrimeScript 1 step enzyme mixture 2	0.2 µL
Mixture of forward and reverse primers (5 µM)	0.4 µL
No RNase dH_2O	1.4 µL
Crude lysate (RNA)	0.5 µL
Sum	5 µL

[0109] The reaction conditions are as follows: Stage 1: reverse transcription reaction: 5 min at 42 °C, 10 s at 95 °C; Stage 2: PCR reaction: 5 s at 95 °C, 20 s at 60 °C, 45 cycles of amplification. *Sdha* and *Tbp* were used as internal control genes. The PCR primers used by *Thpo*, *Sdha* and *Tbp* are shown in Table 2 and *Thpo* was amplified using *Thpo* F1/R1 primer pair.

Table 2. Primer sequences for RT-qPCR analysis

Primer	**Sequence No.**	**Sequence (5'-3')**
Thpo F1	SEQ ID NO: 297	TGGAGCTGACTGATTTGCTCCTG
Thpo R1	SEQ ID NO: 298	AACAGGGATAGACAAAGGGTCG

Sdha F	SEQ ID NO: 299	ATGGTCACTAGGGCTGGTTTG
Sdha R	SEQ ID NO: 300	ACGACACCCTTCTGTGATGAG
Tbp F	SEQ ID NO: 301	CCGTGAATCTTGGCTGTAAACT
Tbp R	SEQ ID NO: 302	TGTCCGTGGCTCTCTTATTC

[0110] In order to calculate the expression value (E_{rel}) of a *Thpo* gene (target) in an saRNA-transfected sample relative to control treatment (Mock), the Ct values of the target gene and two internal control genes were inserted into Formula 1.

$$E_{rel} = 2^{(CtT_m - CtT_s)} / ((2^{(Ct\,R1_m - Ct\,R1_s)} * 2^{(Ct\,R2_m - CtR2_s)})^{(1/2)})$$

Formula 1

[0111] wherein CtT_m is the Ct value of the target gene from the control treatment (Mock) sample, CtTs is the Ct value of the target gene from the saRNA-treated sample. CtR1m is the Ct value of the internal control gene 1 from the Mock-treated sample, CtR1s is the Ct value of the internal control gene 1 from the saRNA-treated sample, CtR2m is the Ct value of the internal control gene 2 from the control treatment sample, and CtR2s is the Ct value of the internal control gene 2 from the saRNA-treated sample.

[0112] (3) **Screening of mouse functional saRNAs**

[0113] To obtain saRNAs capable of activating *Thpo* transcription, BNL.CL2 cells were transfected by the aforementioned 322 saRNAs at a concentration of 10 nM. According to methods described herein, cells were lysed 72h later and subjected to one-step RT-qPCR analysis to obtain the relative expression value of the *Thpo* gene for each saRNA-treated sample when compared with the control treatment. As shown in Table 3, 18 (5.6%) saRNAs showed high activation, 79 (24.5%) saRNAs showed mild activation, and 142 (69.9%) saRNAs did not affect *Thpo* expression. The maximum activation was 2.89-fold, and the maximum inhibition was 0.26-fold.The saRNAs with activation activity are called activating saRNAs.

Table 3. High-throughput screening results of mouse *Thpo* saRNA

saRNA activity	**log_2 value (fold) of changes in *Thpo* mRNA**	**Number of saRNAs**	**Percentage**
High activation	≥ 0.58 (1.50) ~ ≤ 1.53 (2.89)	18	5.6%
Mild activation	≥ 0.13 (1.10) ~ < 0.58 (1.50)	79	24.5%
No activating effect	< 0.13 (1.10)	225	69.9%

Sum		322	100%

[0114] Shown in **FIG. 1**, are the changes in *Thpo* expression of mouse *Thpo* saRNA in descending order. *Thpo* active saRNA sequences, active target sequences, and fold of changes in relative expression of Thpo mRNA shown in Table 4.

Table 4. Mouse active saRNA sequences, active target sequences thereof and changes in expression of mouse *Thpo* mRNA

saRNA	**Target sequence (5'-3')**	**Sense sequence (5'-3') of saRNA**	**Antisense sequence (5'-3') of saRNA**	**Fold of changes in relative expression of *Thpo* mRNA**
RAG3-493	GGCAATACCTACTTTGCCA (SEQ ID NO: 200)	GGCAAUACCUACUUUGCCATT (SEQ ID NO: 6)	UGGCAAAGUAGGUAUUGCCTT (SEQ ID NO: 103)	1.17
RAG3-490	AATACCTACTTTGCCAGTT (SEQ ID NO: 201)	AAUACCUACUUUGCCAGUUTT (SEQ ID NO: 7)	AACUGGCAAAGUAGGUAUUTT (SEQ ID NO: 104)	1.21
RAG3-486	CCTACTTTGCCAGTTGGAA (SEQ ID NO: 202)	CCUACUUUGCCAGUUGGAATT (SEQ ID NO: 8)	UUCCAACUGGCAAAGUAGGTT (SEQ ID NO: 105)	1.76
RAG3-484	TACTTTGCCAGTTGGAAAG (SEQ ID NO: 203)	UACUUUGCCAGUUGGAAAGTT (SEQ ID NO: 9)	CUUUCCAACUGGCAAAGUATT (SEQ ID NO: 106)	1.13
RAG3-483	ACTTTGCCAGTTGGAAAGG (SEQ ID NO: 204)	ACUUUGCCAGUUGGAAAGGTT (SEQ ID NO: 10)	CCUUUCCAACUGGCAAAGUTT (SEQ ID NO: 107)	1.24
RAG3-479	TGCCAGTTGGAAAGGGGAA (SEQ ID NO: 205)	UGCCAGUUGGAAAGGGGAATT (SEQ ID NO: 11)	UUCCCCUUUCCAACUGGCATT (SEQ ID NO: 108)	1.25

RAG3-474	GTTGGAAAGGGGAAATGCC (SEQ ID NO: 206)	GUUGGAAAGGGGAAAUGCCTT (SEQ ID NO: 12)	GGCAUUUCCCCUUUCCAACTT (SEQ ID NO: 109)	1.22
RAG3-472	TGGAAAGGGGAAATGCCAG (SEQ ID NO: 207)	UGGAAAGGGGAAAUGCCAGTT (SEQ ID NO: 13)	CUGGCAUUUCCCCUUUCCATT (SEQ ID NO: 110)	1.41
RAG3-471	GGAAAGGGGAAATGCCAGG (SEQ ID NO: 208)	GGAAAGGGGAAAUGCCAGGTT (SEQ ID NO: 14)	CCUGGCAUUUCCCCUUUCCTT (SEQ ID NO: 111)	1.81
RAG3-466	GGGGAAATGCCAGGAAAGA (SEQ ID NO: 209)	GGGGAAAUGCCAGGAAAGATT (SEQ ID NO: 15)	UCUUUCCUGGCAUUUCCCCTT (SEQ ID NO: 112)	1.64
RAG3-465	GGGAAATGCCAGGAAAGAC (SEQ ID NO: 210)	GGGAAAUGCCAGGAAAGACTT (SEQ ID NO: 16)	GUCUUUCCUGGCAUUUCCCTT (SEQ ID NO: 113)	1.29
RAG3-461	AATGCCAGGAAAGACACTC (SEQ ID NO: 211)	AAUGCCAGGAAAGACACUCTT (SEQ ID NO: 17)	GAGUGUCUUUCCUGGCAUUTT (SEQ ID NO: 114)	1.48
RAG3-460	ATGCCAGGAAAGACACTCC (SEQ ID NO: 212)	AUGCCAGGAAAGACACUCCTT (SEQ ID NO: 18)	GGAGUGUCUUUCCUGGCAUTT (SEQ ID NO: 115)	1.14
RAG3-459	TGCCAGGAAAGACACTCCT (SEQ ID NO: 213)	UGCCAGGAAAGACACUCCUTT (SEQ ID NO: 19)	AGGAGUGUCUUUCCUGGCATT (SEQ ID NO: 116)	1.10
RAG3-454	GGAAAGACACTCCTCTGGA (SEQ ID NO: 214)	GGAAAGACACUCCUCUGGATT (SEQ ID NO: 20)	UCCAGAGGAGUGUCUUUCCTT (SEQ ID NO: 117)	1.24
RAG3-453	GAAAGACACTCCTCTGGAG (SEQ ID NO: 215)	GAAAGACACUCCUCUGGAGTT (SEQ ID NO: 21)	CUCCAGAGGAGUGUCUUUCTT (SEQ ID NO: 118)	1.49

RAG3-450	AGACACTCCTCTGGAGCAG (SEQ ID NO: 216)	AGACACUCCUCUGGAGCAGTT (SEQ ID NO: 22)	CUGCUCCAGAGGAGUGUCUTT (SEQ ID NO: 119)	1.24
RAG3-449	GACACTCCTCTGGAGCAGG (SEQ ID NO: 217)	GACACUCCUCUGGAGCAGGTT (SEQ ID NO: 23)	CCUGCUCCAGAGGAGUGUCTT (SEQ ID NO: 120)	1.14
RAG3-448	ACACTCCTCTGGAGCAGGG (SEQ ID NO: 218)	ACACUCCUCUGGAGCAGGGTT (SEQ ID NO: 24)	CCCUGCUCCAGAGGAGUGUTT (SEQ ID NO: 121)	1.54
RAG3-446	ACTCCTCTGGAGCAGGGGA (SEQ ID NO: 219)	ACUCCUCUGGAGCAGGGGATT (SEQ ID NO: 25)	UCCCCUGCUCCAGAGGAGUTT (SEQ ID NO: 122)	1.36
RAG3-441	TCTGGAGCAGGGGAATATA (SEQ ID NO: 220)	UCUGGAGCAGGGGAAUAUATT (SEQ ID NO: 26)	UAUAUUCCCCUGCUCCAGATT (SEQ ID NO: 123)	1.15
RAG3-440	CTGGAGCAGGGGAATATAG (SEQ ID NO: 221)	CUGGAGCAGGGGAAUAUAGTT (SEQ ID NO: 27)	CUAUAUUCCCCUGCUCCAGTT (SEQ ID NO: 124)	1.14
RAG3-439	TGGAGCAGGGGAATATAGA (SEQ ID NO: 222)	UGGAGCAGGGGAAUAUAGATT (SEQ ID NO: 28)	UCUAUAUUCCCCUGCUCCATT (SEQ ID NO: 125)	1.10
RAG3-437	GAGCAGGGGAATATAGAAG (SEQ ID NO: 223)	GAGCAGGGGAAUAUAGAAGTT (SEQ ID NO: 29)	CUUCUAUAUUCCCCUGCUCTT (SEQ ID NO: 126)	1.12
RAG3-436	AGCAGGGGAATATAGAAGG (SEQ ID NO: 224)	AGCAGGGGAAUAUAGAAGGTT (SEQ ID NO: 30)	CCUUCUAUAUUCCCCUGCUTT (SEQ ID NO: 127)	1.99
RAG3-435	GCAGGGGAATATAGAAGGA (SEQ ID NO: 225)	GCAGGGGAAUAUAGAAGGATT (SEQ ID NO: 31)	UCCUUCUAUAUUCCCCUGCTT (SEQ ID NO: 128)	1.83

RAG3-434	CAGGGGAATATAGAAGGAA (SEQ ID NO: 226)	CAGGGGAAUAUAGAAGGAATT (SEQ ID NO: 32)	UUCCUUCUAUAUUCCCCUGTT (SEQ ID NO: 129)	1.47
RAG3-433	AGGGGAATATAGAAGGAAA (SEQ ID NO: 227)	AGGGGAAUAUAGAAGGAAATT (SEQ ID NO: 33)	UUUCCUUCUAUAUUCCCCUTT (SEQ ID NO: 130)	1.13
RAG3-432	GGGGAATATAGAAGGAAAA (SEQ ID NO: 228)	GGGGAAUAUAGAAGGAAAATT (SEQ ID NO: 34)	UUUUCCUUCUAUAUUCCCCTT (SEQ ID NO: 131)	1.10
RAG3-430	GGAATATAGAAGGAAAAGC (SEQ ID NO: 229)	GGAAUAUAGAAGGAAAAGCTT (SEQ ID NO: 35)	GCUUUUCCUUCUAUAUUCCTT (SEQ ID NO: 132)	1.20
RAG3-426	TATAGAAGGAAAAGCAAGC (SEQ ID NO: 230)	UAUAGAAGGAAAAGCAAGCTT (SEQ ID NO: 36)	GCUUGCUUUUCCUUCUAUATT (SEQ ID NO: 133)	1.18
RAG3-425	ATAGAAGGAAAAGCAAGCA (SEQ ID NO: 231)	AUAGAAGGAAAAGCAAGCATT (SEQ ID NO: 37)	UGCUUGCUUUUCCUUCUAUTT (SEQ ID NO: 134)	1.57
RAG3-424	TAGAAGGAAAAGCAAGCAA (SEQ ID NO: 232)	UAGAAGGAAAAGCAAGCAATT (SEQ ID NO: 38)	UUGCUUGCUUUUCCUUCUATT (SEQ ID NO: 135)	1.79
RAG3-421	AAGGAAAAGCAAGCAAGCC (SEQ ID NO: 233)	AAGGAAAAGCAAGCAAGCCTT (SEQ ID NO: 39)	GGCUUGCUUGCUUUUCCUUTT (SEQ ID NO: 136)	1.11
RAG3-420	AGGAAAAGCAAGCAAGCCA (SEQ ID NO: 234)	AGGAAAAGCAAGCAAGCCATT (SEQ ID NO: 40)	UGGCUUGCUUGCUUUUCCUTT (SEQ ID NO: 137)	1.25
RAG3-419	GGAAAAGCAAGCAAGCCAG (SEQ ID NO: 235)	GGAAAAGCAAGCAAGCCAGTT (SEQ ID NO: 41)	CUGGCUUGCUUGCUUUUCCTT (SEQ ID NO: 138)	1.51

RAG3-418	GAAAAGCAAGCAAGCCAGC (SEQ ID NO: 236)	GAAAAGCAAGCAAGCCAGCTT (SEQ ID NO: 42)	GCUGGCUUGCUUGCUUUUCTT (SEQ ID NO: 139)	1.12
RAG3-417	AAAAGCAAGCAAGCCAGCA (SEQ ID NO: 237)	AAAAGCAAGCAAGCCAGCATT (SEQ ID NO: 43)	UGCUGGCUUGCUUGCUUUUTT (SEQ ID NO: 140)	1.19
RAG3-414	AGCAAGCAAGCCAGCATGC (SEQ ID NO: 238)	AGCAAGCAAGCCAGCAUGCTT (SEQ ID NO: 44)	GCAUGCUGGCUUGCUUGCUTT (SEQ ID NO: 141)	1.27
RAG3-410	AGCAAGCCAGCATGCTGTC (SEQ ID NO: 239)	AGCAAGCCAGCAUGCUGUCTT (SEQ ID NO: 45)	GACAGCAUGCUGGCUUGCUTT (SEQ ID NO: 142)	1.39
RAG3-409	GCAAGCCAGCATGCTGTCA (SEQ ID NO: 240)	GCAAGCCAGCAUGCUGUCATT (SEQ ID NO: 46)	UGACAGCAUGCUGGCUUGCTT (SEQ ID NO: 143)	1.38
RAG3-408	CAAGCCAGCATGCTGTCAG (SEQ ID NO: 241)	CAAGCCAGCAUGCUGUCAGTT (SEQ ID NO: 47)	CUGACAGCAUGCUGGCUUGTT (SEQ ID NO: 144)	2.09
RAG3-405	GCCAGCATGCTGTCAGAAT (SEQ ID NO: 242)	GCCAGCAUGCUGUCAGAAUTT (SEQ ID NO: 48)	AUUCUGACAGCAUGCUGGCTT (SEQ ID NO: 145)	1.53
RAG3-404	CCAGCATGCTGTCAGAATT (SEQ ID NO: 243)	CCAGCAUGCUGUCAGAAUUTT (SEQ ID NO: 49)	AAUUCUGACAGCAUGCUGGTT (SEQ ID NO: 146)	1.18
RAG3-397	GCTGTCAGAATTCAGCAGC (SEQ ID NO: 244)	GCUGUCAGAAUUCAGCAGCTT (SEQ ID NO: 50)	GCUGCUGAAUUCUGACAGCTT (SEQ ID NO: 147)	1.34
RAG3-396	CTGTCAGAATTCAGCAGCA (SEQ ID NO: 245)	CUGUCAGAAUUCAGCAGCATT (SEQ ID NO: 51)	UGCUGCUGAAUUCUGACAGTT (SEQ ID NO: 148)	1.17

RAG3-378	AGGTATACTGTTCAGGGAA (SEQ ID NO: 246)	AGGUAUACUGUUCAGGGAATT (SEQ ID NO: 52)	UUCCCUGAACAGUAUACCUTT (SEQ ID NO: 149)	1.36
RAG3-377	GGTATACTGTTCAGGGAAA (SEQ ID NO: 247)	GGUAUACUGUUCAGGGAAATT (SEQ ID NO: 53)	UUUCCCUGAACAGUAUACCTT (SEQ ID NO: 150)	1.32
RAG3-376	GTATACTGTTCAGGGAAAA (SEQ ID NO: 248)	GUAUACUGUUCAGGGAAAATT (SEQ ID NO: 54)	UUUUCCCUGAACAGUAUACTT (SEQ ID NO: 151)	1.67
RAG3-375	TATACTGTTCAGGGAAAAG (SEQ ID NO: 249)	UAUACUGUUCAGGGAAAAGTT (SEQ ID NO: 55)	CUUUUCCCUGAACAGUAUATT (SEQ ID NO: 152)	1.11
RAG3-360	AAAGAAATTTGGAGAGCCA (SEQ ID NO: 250)	AAAGAAAUUUGGAGAGCCATT (SEQ ID NO: 56)	UGGCUCUCCAAAUUUCUUUTT (SEQ ID NO: 153)	1.12
RAG3-337	CTGAGACTTCATCCATCTA (SEQ ID NO: 251)	CUGAGACUUCAUCCAUCUATT (SEQ ID NO: 57)	UAGAUGGAUGAAGUCUCAGTT (SEQ ID NO: 154)	1.15
RAG3-290	CCGTATTCTGCCAGATTTC (SEQ ID NO: 252)	CCGUAUUCUGCCAGAUUUCTT (SEQ ID NO: 58)	GAAAUCUGGCAGAAUACGGTT (SEQ ID NO: 155)	1.14
RAG3-273	TCTCCTGGACTAACCCTCT (SEQ ID NO: 253)	UCUCCUGGACUAACCCUCUTT (SEQ ID NO: 59)	AGAGGGUUAGUCCAGGAGATT (SEQ ID NO: 156)	2.89
RAG3-272	CTCCTGGACTAACCCTCTT (SEQ ID NO: 254)	CUCCUGGACUAACCCUCUUTT (SEQ ID NO: 60)	AAGAGGGUUAGUCCAGGAGTT (SEQ ID NO: 157)	1.89
RAG3-271	TCCTGGACTAACCCTCTTC (SEQ ID NO: 255)	UCCUGGACUAACCCUCUUCTT (SEQ ID NO: 61)	GAAGAGGGUUAGUCCAGGATT (SEQ ID NO: 158)	1.17

RAG3-244	ACTTAGGTCCCAGGTTCTC (SEQ ID NO: 256)	ACUUAGGUCCCAGGUUCUCTT (SEQ ID NO: 62)	GAGAACCUGGGACCUAAGUTT (SEQ ID NO: 159)	1.17
RAG3-243	CTTAGGTCCCAGGTTCTCA (SEQ ID NO: 257)	CUUAGGUCCCAGGUUCUCATT (SEQ ID NO: 63)	UGAGAACCUGGGACCUAAGTT (SEQ ID NO: 160)	1.45
RAG3-242	TTAGGTCCCAGGTTCTCAT (SEQ ID NO: 258)	UUAGGUCCCAGGUUCUCAUTT (SEQ ID NO: 64)	AUGAGAACCUGGGACCUAATT (SEQ ID NO: 161)	1.27
RAG3-239	GGTCCCAGGTTCTCATGTC (SEQ ID NO: 259)	GGUCCCAGGUUCUCAUGUCTT (SEQ ID NO: 65)	GACAUGAGAACCUGGGACCTT (SEQ ID NO: 162)	1.10
RAG3-229	TCTCATGTCGCCAGGACAT (SEQ ID NO: 260)	UCUCAUGUCGCCAGGACAUTT (SEQ ID NO: 66)	AUGUCCUGGCGACAUGAGATT (SEQ ID NO: 163)	1.12
RAG3-227	TCATGTCGCCAGGACATGA (SEQ ID NO: 261)	UCAUGUCGCCAGGACAUGATT (SEQ ID NO: 67)	UCAUGUCCUGGCGACAUGATT (SEQ ID NO: 164)	1.39
RAG3-226	CATGTCGCCAGGACATGAG (SEQ ID NO: 262)	CAUGUCGCCAGGACAUGAGTT (SEQ ID NO: 68)	CUCAUGUCCUGGCGACAUGTT (SEQ ID NO: 165)	1.30
RAG3-219	CCAGGACATGAGACAGTTC (SEQ ID NO: 263)	CCAGGACAUGAGACAGUUCTT (SEQ ID NO: 69)	GAACUGUCUCAUGUCCUGGTT (SEQ ID NO: 166)	1.24
RAG3-215	GACATGAGACAGTTCCCGC (SEQ ID NO: 264)	GACAUGAGACAGUUCCCGCTT (SEQ ID NO: 70)	GCGGGAACUGUCUCAUGUCTT (SEQ ID NO: 167)	1.32
RAG3-214	ACATGAGACAGTTCCCGCT (SEQ ID NO: 265)	ACAUGAGACAGUUCCCGCUTT (SEQ ID NO: 71)	AGCGGGAACUGUCUCAUGUTT (SEQ ID NO: 168)	1.28

RAG3-206	CAGTTCCCGCTATACAAAT (SEQ ID NO: 266)	CAGUUCCCGCUAUACAAAUTT (SEQ ID NO: 72)	AUUUGUAUAGCGGGAACUGTT (SEQ ID NO: 169)	1.31
RAG3-205	AGTTCCCGCTATACAAATT (SEQ ID NO: 267)	AGUUCCCGCUAUACAAAUUTT (SEQ ID NO: 73)	AAUUUGUAUAGCGGGAACUTT (SEQ ID NO: 170)	1.14
RAG3-204	GTTCCCGCTATACAAATTC (SEQ ID NO: 268)	GUUCCCGCUAUACAAAUUCTT (SEQ ID NO: 74)	GAAUUUGUAUAGCGGGAACTT (SEQ ID NO: 171)	1.65
RAG3-203	TTCCCGCTATACAAATTCT (SEQ ID NO: 269)	UUCCCGCUAUACAAAUUCUTT (SEQ ID NO: 75)	AGAAUUUGUAUAGCGGGAATT (SEQ ID NO: 172)	1.42
RAG3-202	TCCCGCTATACAAATTCTC (SEQ ID NO: 270)	UCCCGCUAUACAAAUUCUCTT (SEQ ID NO: 76)	GAGAAUUUGUAUAGCGGGATT (SEQ ID NO: 173)	1.31
RAG3-164	GAGGAGCTGGGCTCTATTC (SEQ ID NO: 271)	GAGGAGCUGGGCUCUAUUCTT (SEQ ID NO: 77)	GAAUAGAGCCCAGCUCCUCTT (SEQ ID NO: 174)	1.13
RAG3-158	CTGGGCTCTATTCATGGAC (SEQ ID NO: 272)	CUGGGCUCUAUUCAUGGACTT (SEQ ID NO: 78)	GUCCAUGAAUAGAGCCCAGTT (SEQ ID NO: 175)	1.17
RAG3-153	CTCTATTCATGGACCATGG (SEQ ID NO: 273)	CUCUAUUCAUGGACCAUGGTT (SEQ ID NO: 79)	CCAUGGUCCAUGAAUAGAGTT (SEQ ID NO: 176)	1.17
RAG3-152	TCTATTCATGGACCATGGT (SEQ ID NO: 274)	UCUAUUCAUGGACCAUGGUTT (SEQ ID NO: 80)	ACCAUGGUCCAUGAAUAGATT (SEQ ID NO: 177)	1.10
RAG3-151	CTATTCATGGACCATGGTC (SEQ ID NO: 275)	CUAUUCAUGGACCAUGGUCTT (SEQ ID NO: 81)	GACCAUGGUCCAUGAAUAGTT (SEQ ID NO: 178)	1.44

RAG3-150	TATTCATGGACCATGGTCC (SEQ ID NO: 276)	UAUUCAUGGACCAUGGUCCTT (SEQ ID NO: 82)	GGACCAUGGUCCAUGAAUATT (SEQ ID NO: 179)	1.24
RAG3-147	TCATGGACCATGGTCCAGC (SEQ ID NO: 277)	UCAUGGACCAUGGUCCAGCTT (SEQ ID NO: 83)	GCUGGACCAUGGUCCAUGATT (SEQ ID NO: 180)	1.31
RAG3-146	CATGGACCATGGTCCAGCC (SEQ ID NO: 278)	CAUGGACCAUGGUCCAGCCTT (SEQ ID NO: 84)	GGCUGGACCAUGGUCCAUGTT (SEQ ID NO: 181)	1.44
RAG3-142	GACCATGGTCCAGCCATGG (SEQ ID NO: 279)	GACCAUGGUCCAGCCAUGGTT (SEQ ID NO: 85)	CCAUGGCUGGACCAUGGUCTT (SEQ ID NO: 182)	1.26
RAG3-134	TCCAGCCATGGGCTCTAGT (SEQ ID NO: 280)	UCCAGCCAUGGGCUCUAGUTT (SEQ ID NO: 86)	ACUAGAGCCCAUGGCUGGATT (SEQ ID NO: 183)	1.41
RAG3-133	CCAGCCATGGGCTCTAGTC (SEQ ID NO: 281)	CCAGCCAUGGGCUCUAGUCTT (SEQ ID NO: 87)	GACUAGAGCCCAUGGCUGGTT (SEQ ID NO: 184)	1.11
RAG3-129	CCATGGGCTCTAGTCCCAG (SEQ ID NO: 282)	CCAUGGGCUCUAGUCCCAGTT (SEQ ID NO: 88)	CUGGGACUAGAGCCCAUGGTT (SEQ ID NO: 185)	1.30
RAG3-122	CTCTAGTCCCAGTAGACAG (SEQ ID NO: 283)	CUCUAGUCCCAGUAGACAGTT (SEQ ID NO: 89)	CUGUCUACUGGGACUAGAGTT (SEQ ID NO: 186)	1.51
RAG3-121	TCTAGTCCCAGTAGACAGG (SEQ ID NO: 284)	UCUAGUCCCAGUAGACAGGTT (SEQ ID NO: 90)	CCUGUCUACUGGGACUAGATT (SEQ ID NO: 187)	1.72
RAG3-111	GTAGACAGGAAAAGAAGTC (SEQ ID NO: 285)	GUAGACAGGAAAAGAAGUCTT (SEQ ID NO: 91)	GACUUCUUUUCCUGUCUACTT (SEQ ID NO: 188)	1.26

RAG3-110	TAGACAGGAAAAGAAGTCG (SEQ ID NO: 286)	UAGACAGGAAAAGAAGUCGTT (SEQ ID NO: 92)	CGACUUCUUUUCCUGUCUATT (SEQ ID NO: 189)	1.25
RAG3-101	AAAGAAGTCGTCATTTCCG (SEQ ID NO: 287)	AAAGAAGUCGUCAUUUCCGTT (SEQ ID NO: 93)	CGGAAAUGACGACUUCUUUTT (SEQ ID NO: 190)	1.14
RAG3-100	AAGAAGTCGTCATTTCCGG (SEQ ID NO: 288)	AAGAAGUCGUCAUUUCCGGTT (SEQ ID NO: 94)	CCGGAAAUGACGACUUCUUTT (SEQ ID NO: 191)	1.15
RAG3-099	AGAAGTCGTCATTTCCGGG (SEQ ID NO: 289)	AGAAGUCGUCAUUUCCGGGTT (SEQ ID NO: 95)	CCCGGAAAUGACGACUUCUTT (SEQ ID NO: 192)	1.12
RAG3-078	AGCCTTCACCTGGGCTTGG (SEQ ID NO: 290)	AGCCUUCACCUGGGCUUGGTT (SEQ ID NO: 96)	CCAAGCCCAGGUGAAGGCUTT (SEQ ID NO: 193)	1.10
RAG3-071	ACCTGGGCTTGGTGGCTCT (SEQ ID NO: 291)	ACCUGGGCUUGGUGGCUCUTT (SEQ ID NO: 97)	AGAGCCACCAAGCCCAGGUTT (SEQ ID NO: 194)	1.10
RAG3-047	CTCTGATTGGGCGGAAGTG (SEQ ID NO: 292)	CUCUGAUUGGGCGGAAGUGTT (SEQ ID NO: 98)	CACUUCCGCCCAAUCAGAGTT (SEQ ID NO: 195)	1.66
RAG3-046	TCTGATTGGGCGGAAGTGG (SEQ ID NO: 293)	UCUGAUUGGGCGGAAGUGGTT (SEQ ID NO: 99)	CCACUUCCGCCCAAUCAGATT (SEQ ID NO: 196)	1.15
RAG3-044	TGATTGGGCGGAAGTGGCC (SEQ ID NO: 294)	UGAUUGGGCGGAAGUGGCCTT (SEQ ID NO: 100)	GGCCACUUCCGCCCAAUCATT (SEQ ID NO: 197)	1.20
RAG3-023	GGCAGGCTTGTGACCCTAC (SEQ ID NO: 295)	GGCAGGCUUGUGACCCUACTT (SEQ ID NO: 101)	GUAGGGUCACAAGCCUGCCTT (SEQ ID NO: 198)	1.27

RAG3-022	GCAGGCTTGTGACCCTACT (SEQ ID NO: 296)	GCAGGCUUGUGACCCUACUTT (SEQ ID NO: 102)	AGUAGGGUCACAAGCCUGCTT (SEQ ID NO: 199)	1.11

[0115] It can be clearly seen from the arrangement of activities of the 322 saRNAs according to their positions in the *Thpo* promoter region that the functional saRNAs are gathered together, that is, in certain promoter regions, the activating saRNAs gathered in specific "hotspot" regions (**FIG. 2**). As shown in **FIG. 2**, 3 hotspot regions respectively appeared in region (H1) from -493 to -356, region (H2) from -273 to -183, and region (H3) from -164 to -80 of the promoter, showing a high gathering of the activating saRNAs. The analysis results indicates that the activating saRNAs were not randomly distributed on the promoter but existed in the specific hotspot regions.

[0116] The sequence of hotspot H1 (5' to 3': -493 to -356) corresponds to position 1 to position 138, from 5' to 3', of SEQ ID NO: 2 in the sequence listing:

1 ggcaatacct actttgccag ttggaaaggg gaaatgccag gaaagacact
51 cctctggagc aggggaatat agaaggaaaa gcaagcaagc cagcatgctg
101 tcagaattca gcagcaggta tactgttcag ggaaaaga

[0117] The sequence of the hotspot H2 (5' to 3': -273 to -183) corresponds to position 1 to position 91, from 5' to 3', of SEQ ID NO: 3 in the sequence listing:

1 tctcctggac taaccctctt ctctctctca cttaggtccc aggttctcat
51 gtcgccagga catgagacag ttcccgctat acaaattctc t

[0118] The sequence of the hotspot H3 (5' to 3': -164 to -80) corresponds to position 1 to position 85, from 5' to 3', of SEQ ID NO: 4 in the sequence listing:

1 gaggagctgg gctctattca tggaccatgg tccagccatg ggctctagtc
51 ccagtagaca ggaaaagaag tcgtcatttc cgggg

Example 3: SaRNA Promoting Expression of *Thpo* mRNA in a Mouse Liver Cell

(1) Cell culture and transfection

[0119] Cell culture was described in Example 2. Mouse embryonic liver cells (BNL.CL2) were plated into a 6-well plate, at 1×10^5 cells/well. According to the instructions provided by the manufacturer, RNAiMax (Invitrogen, Carlsbad, CA) was used to transfect mouse*Thpo* saRNA at a concentration of 10 nM, transfection duration was 72 h, and 2 replicate wells were used in each treatment.

(2) Two-step RT-qPCR

[0120] After transfection, the media were discarded, each well was added with 500 μL of cell lysis buffer, and incubation was performed at room temperature for 5 min. RNA was extracted using Qiagen RNeasy kit, reverse transcribed and subjected to qPCR analysis on ABI 7500 fast real-time PCR system (Applied Biosystems), and each sample was repeatedly amplified in 3 replicate wells. PCR reaction conditions were shown in Tables 5 and 6.

Table 5. RT reaction preparation

Reagent (RT reaction 1)	**Volume**
5 × gDNA Eraser buffer	2 μL
gDNA Eraser	1 μl
Total amount of RNA (1 μg) + D.W	7 μL
Final volume	10 μL
2 min at 42°C and stored at 4°C	

Reagent (RT reaction 2)	**Volume**
5 × PrimeScript buffer 2	4 μL
PrimeScript RT enzyme mixture 1	1 μL
RT primer mixture	1 μL
No RNase dH_2O	4 μL
RT reaction 1	10 μL
Final volume	20 μL
15 min at 37°C, 5s at 85°C and stored at 4°C	

Table 6. RT-qPCR reaction preparation

Reagent	**Volume**
SYBR Premix Ex Taq II (2 ×)	5 μL
ROX reference dye II (50 ×)	0.2 μL
Mixture of forward and reverse primers (5 μM)	0.8 μL
cDNA (RT products)	4 μL
Sum	10 μL

[0121] The reaction conditions were as follows: 30s at 95 °C, 5s at 95 °C, 30s at 60 °C, 40 cycles of amplification. The amplification of the *Tbp* gene with the *Thpo* F1/R1 primer pair served as an internal control. Amplification primers are shown in a Table 2.

[0122] To calculate the expression value (E_{rel}) of the *Thpo* (target gene) of an saRNA-transfected sample relative to the control treatment (Mock),Ct values of the target gene and one internal control gene were inserted into Formula 2 for calculation.

$$E_{rel} = 2^{(CtTm-CtTs)} / 2^{(CtRm-CtRs)}$$

Formula 2

[0123] **FIG. 3** shows the relative mRNA expression values of *Thpo* after treatment of cells with different mouse saRNAs. The relative mRNA expression of mouse *Thpo* small interfering RNA (siRNA) in the DS03-432i group was reduced by 53.5% compared to the control group using the control treatment as a blank transfection control. This result indicates that this siRNA was

successful as a small interfering RNA control for transfection. The following groups with different saRNAs include DS03-0007 (RAG3-424), DS03-0014 (RAG3-425), DS03-0022 (RAG3-243) and DS03-0024 (RAG3-151), and showed higher relative mRNA expression values when compared to the control group, which increased by 25.5%, 16.5%, 16% and 41%, respectively. This result indicates that randomly selected activating saRNAs are capable of promoting expression of *Thpo* mRNA in BNL.CL2 cells.

Example 4: Mouse *Thpo* saRNA Promoting Expression of *Thpo* mRNA in LPC-H12 cells

[0124] The cell culture was described in Example 2. Mouse liver cancer cells (LPC-H12) (BNBIO, BNCC101945) were plated into a 6-well plate at 2×10^5 cells/well. According to the instructions provided by the manufacturer, RNAiMax (Invitrogen, Carlsbad, CA) was used to transfect mouse Thpo saRNA at a concentration of 10 nM for a duration of 72h. Two replicate wells were used for each treatment. Two-step RT-qPCR was described in Example 3.

[0125] **FIG. 4** shows the relative mRNA expression values of *Thpo* after cells were treated with different saRNAs. The relative mRNA expression of the mouse siRNA (DS03-432i) group was reduced by 47% compared to the control group using the control treatment as a blank transfection control. This result indicates that this siRNA was successful as a small interfering RNA control transfection. The relative mRNA expression values of DS03-0007 (RAG3-424), DS03-0019 (RAG3-453), DS03-0022 (RAG3-243), DS03-0024 (RAG3-151) and DS03-0027 (RAG3-134) groups were higher than those of a control group, and the relative mRNA expression values were increased by 52%, 90%, 30.5%, 11.5% and 34%, respectively, and the activation effect of DS03-0019 was particularly obvious (90%). The results show that randomly selected activating saRNAs are capable of promoting expression of *Thpo* mRNA to varying degrees in LPC-H12 cells.

Example 5: Mouse *Thpo* saRNA Promoting Expression of *Thpo* mRNA in Primary Mouse Liver Cells

Culture and transfection of primary mouse liver cells

[0126] C57 female mice (6 to 8 weeks old, approximately 25 g in weight, purchased from Comparative Medicine Center of Yangzhou University) were acclimated in the mouse animal room for 3 days and primary mouse liver cells were isolated by a two-step perfusion method. The specific operation of the two-step perfusion method is described as follows: Anesthetized mice were maintained using isoflurane and sterilized with alcohol, and the abdominal cavity of the mice was opened with scissors to expose hepatic portal vein and inferior vena cava; a needle was inserted into the hepatic portal vein, and a peristaltic pump was used to infuse pre-perfusion

(HBSS+HEPES+EGTA) at 37°C at a rate of 1 to 2 mL/min, and the mouse liver swelled and turned white, indicating successful perfusion; the inferior vena cava was cut, and the perfusion rate was gradually increased to 7 to 9 mL/min, perfusion was performed for 10 to 15 min; collagenase solution for digestion was added for about 15 min, and the perfusion rate was 5 to 8 mL/min. After digestion, the liver was transferred to a petri dish and liver cells were collected, passed through a 200-mesh filter, washed 3 times with DMEM medium, and centrifuged (100 g) at 4 °C for 5 min. The cells were cultured at 2×10^5 cells/well (collagen-coated well plate) in DMEM-L medium containing 10% serum, the DMEM-L medium without serum was replaced after 4 to 6 h, and the cells were cultured overnight at 37 °C under 5% CO_2. The next day, RNAiMax (Invitrogen, Carlsbad, CA) was used to transfect mouse *Thpo* saRNA at a concentration of 10 nM for a duration of 72 h. Two replicate wells were used in each treatment. Two-step RT-qPCR was described in Example 3.

[0127] **FIG. 5** shows the relative mRNA expression values of *Thpo* after treatment of cells with different mouse saRNAs. The relative mRNA expression values of DS03-0007 (RAG3-424), DS03-0012 (RAG3-204), DS03-0014 (RAG3-425), DS03-0019 (RAG3-453), DS03-0022 (RAG3-243), DS03-0024 (RAG3-151) and DS03-0027 (RAG3-134) groups were higher than control group and all increased by 33.5%, 25.5%, 51.5%, 44.5%, 28.5%, 26% and 34.5%, respectively, compared to the control group using the control treatment as a blank transfection control. The results show that randomly selected activating saRNAs are capable of promoting expression of *Thpo* mRNA in primary mouse liver cells.

Example 6: *In vivo* Assay of *Thpo* saRNA Activation of *Thpo* Gene in Mouse

Preparation of oligonucleotide formulation

[0128] Based on the published method of preparing Lipid Nanoparticle (LNP) (*see*, CN104873464B, CN102625696B, US 9,394,234 B2, WO 2010/144740A1, US 8,158,601 B2, and US 8,802,644 B2), LNP was prepared with an improved method. The resulting LNP was used to entrap oligonucleotide. The specific method used is described as follows.

[0129] Stock solution preparation of *Thpo* siRNA (DS03-432i) and saRNA (RAG3-151/DS03-0024): stock solutions of *Thpo* siRNA (DS03-432i) and saRNA (RAG3-151/DS03-0024) with 5 mg/mL theoretical final concentration were prepared by dissolving siRNA (DS03-432i) and saRNA (RAG3-151/DS03-0024) with DEPC water. The appropriate amounts of siRNA (DS03-432i) and saRNA (RAG3-151/DS03-0024) were taken and diluted 200-fold with PBS to determine the concentrations of siRNA (DS03-432i) and saRNA (DS03-0024).

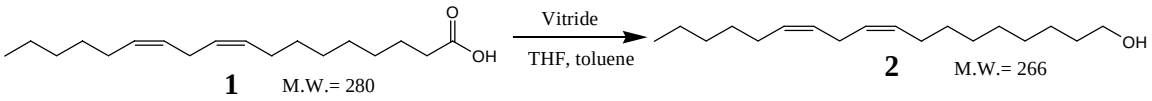
Table 7. RNA concentrations of siRNA (DS03-432i) and saRNA (DS03-0024)

Sample	RNA determination concentration (ng/μL)	Dilution factor	Concentration of RNA stock solution (mg/mL)
DS03-432i	41	200	8.2
DS03-0024	41	200	8.2

Table 8: Sequences of dsCon2 andsiRNA (DS03-432i)

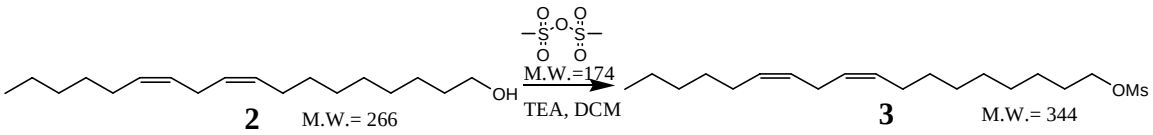
RNA duplexes	Sense sequence (5'-3')	Antisense sequence (5'-3')
dsCon2	ACUACUGAGUGACAGUAGATT (SEQ ID NO: 303)	UCUACUGUCACUCAGUAGUTT (SEQ ID NO: 304)
DS03-432i	GGACUUUAGCCUGGGAGAATT (SEQ ID NO: 305)	UUCUCCCAGGCUAAAGUCCTT (SEQ ID NO: 306)

Preparation of D-Lin-MC3 lipid: in a patent publication method (see Lipid Formulation, Publication No.: US 2010/0324120 A1), the D-Lin-MC3 lipid was synthesized chemically as follows.

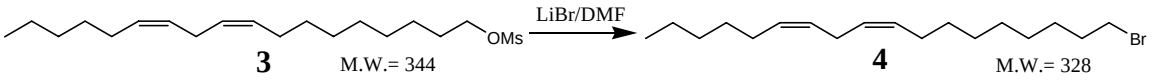


1 M.W.= 280 **2** M.W.= 266

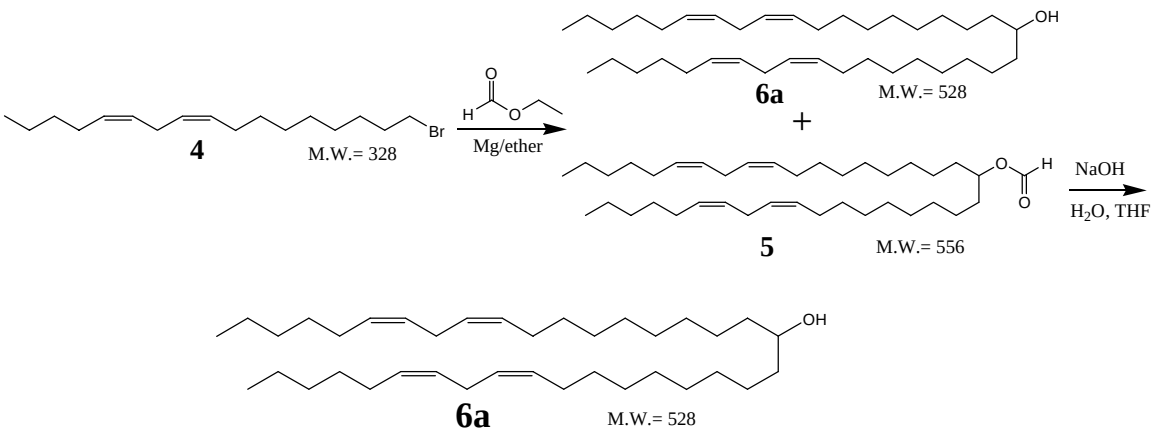
[0130] A dry 1 L glass reactor was purged with dry argon and cooled to 0 °C using an acetone-dry ice bath. 25 g of reaction 1 (linoleic acid) and 300 mL of THF were added. 60 mL of sodium bis(2-methoxyethoxy)aluminum dihydride (70% wt/vol) in toluene was slowly added dropwise to a reactor. After the completion of dropwise addition, the mixture was carried out at room temperature for 2 h. A small sample was taken and starting material reaction was monitored by TLC. After the completion of reaction, saturated sodium sulfate solution was slowly added. After the completion of addition, 130 mL of ethyl acetate was added dropwise over 30 min, and vigorously stirred. The reaction mixture was filtered, the solid was washed with 90 mL of ethyl acetate, and the organic phases were combined and concentrated. The product was dissolved in 80 mL of ethyl acetate, washed twice with water, and dried over anhydrous sodium sulfate. The organic phases were filtered and concentrated, organic solvent was removed using a vacuum pump to give product 2 (17.49 g).



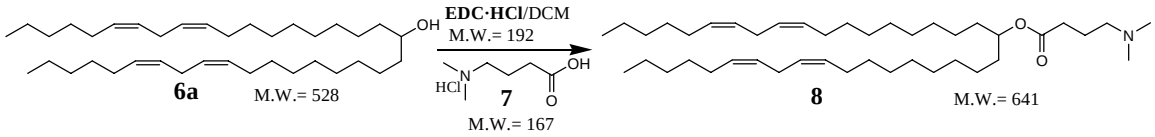
[0131] A dry 1 L glass reactor was purged with dry argon, 17 g of product 2 and 150 mL of dichloromethane were then added, 40 mL of triethylamine and 1 g of 4-dimethylaminopyridine were then added, and the mixture was cooled to -10 °C using an acetone-dry ice bath. 30 gof methanesulfonic anhydridewas dissolved in 45 mL of dichloromethane and slowly added dropwise to the reactor. After the completion of dropwise addition of the reaction mixture, the reaction was continued at 0 °C for 1 h. Starting material reaction was monitored by TLC. After the completion of reaction, 80 mL of ice water was added to the reaction mixture, the mixture was separated, and the aqueous phase was extracted with 40 mL of dichloromethane. The organic phases were combined, washed with dilute hydrochloric acid, water and saturated NaCl solution, and dried over anhydrous sodium sulfate. The organic phases were filtered and concentrated, organic solvent was removed using a vacuum pump to give product 3 (22.3 g).



[0132] A dry 1 L glass reactor was purged with dry argon and then 100 mL of DMF and 22 g of product 3 were added and the solution was cooled to -10 °C using an acetone-dry ice bath. 8.5 g of LiBr was dissolved in 80 mL of DMF, stirred and slowly added dropwise to the reactor. After the completion of dropwise addition, the reaction mixture was heated to 45 °C and stirred for reaction for 18 to 20 h. Starting material reaction was monitored by TLC. After the completion of reaction, 300 mL of water were added and extracted with 240 mL of *n*-hexane, and the aqueous phase was further extracted with *n*-hexane. The organic phases were combined, washed with water and saturated NaCl solution and dried over anhydrous sodium sulfate. The organic phases were filtered and concentrated, organic solvent was removed using a vacuum pump to give crude product (16.76 g). The mixture was purified with 60 to 120 mesh silica gel (*n*-hexane as mobile phase) to give product 4 (13.86 g).



[0133] A dry 1 L three-neck flask was purged with dry argon, and a reflux device was additionally arranged. 2 g of magnesium turnings and 12 mL of anhydrous diethyl ether were added into the reactor. 13 g of product 4 were dissolved in 40 mL of anhydrous diethyl ether. Under the protection of argon, 8 mL of reation mixture was added dropwise to the reactor and 0.2 mL of dibromomethane was added further. The reactor was warmed to 40 °C in a water bath. After the reaction started, the heating was stopped and the remaining 32 mL of the reaction mixture was added dropwise to the reactor, and the mixture was allowed to keep a slight reflux. After the completion of dropwise addition, the reaction mixture was heated to maintain the reflux state (about 45 °C) and reacted for 1 h. A small sample was quenched with water and the starting material reaction was monitored by TLC. After the completion of starting materials reaction, the reaction mixture was cooled to below 10 °C by an ice bath, and then ethyl formate solution was slowly added. After the completion of dropwise addition, the mixture was carried out at room temperature for 1 h. Then 56 mL of ice-water and 10% of sulphuric acid solution were added, the organic phases were separated and the aqueous phase was extracted with diethyl ether. The organic phases were combined, washed with saturated NaCl solution and dried over anhydrous sodium sulfate. The organic phase was filtered and concentrated, organic solvent was removed using a vacuum pump to give crude product (13 g). The crude product was dissolved in 100 mL of 85% ethanol, 7 g of NaOH solid was added, stirred at room temperature for 24 h and the starting material reaction was monitored by TLC. After the completion of reaction, the reaction mixture was extracted with diethyl ether, and the organic phases were combined and washed with saturated NaCl solution. The reaction mixture was dried over anhydrous sodium sulfate. The organic phases were filtered and concentrated. The crude product was purified with 60 to 120 mesh silica gel (4% ether/*n*-hexane) to give product 6 (10.4 g).



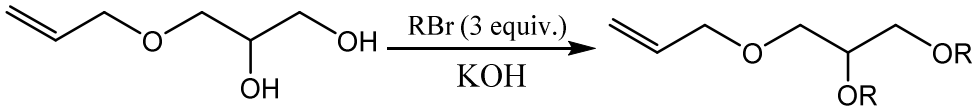
6a M.W.= 528 **7** M.W.= 167 **8** M.W.= 641

[0134] The reaction product **6** (3 g) was added into a 100 mL flask and dissolved in dichloromethane (24 mL), the reaction product **7** (4-(dimethylamino)butanoic acid hydrochloride) (1.1 g) was added, then diisopropylethylamine (1.5 mL) and 4-dimethylaminopyridine (0.09 g) were added. After stirring at room temperature for 5 min, the reaction mixture was added with EDC HCl (1.7 g) and stirred at room temperature overnight. Starting material reaction was monitored by TLC. After the completion of reaction, the reaction mixture was diluted with 20 mL of dichloromethane. Then the reaction mixture was washed with saturated $NaHCO_3$solution, water and saturated NaCl solution, dried with anhydrous $Na_2SO_4$and filtered, and the organic phases were concentrated to give about crude product (3.3 g). The reaction mixture was isolated using

chromatography (serial elution with 1% to 5% methanol/dichloromethane) to give product **8** (Dlin-MC3-DMA, 2.9 g). ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=5.44-5.22 (m, 8H), 4.95-4.79 (m, 1H), 2.81-2.63 (m, 4H),2.36-2.21 (m, 4H), 2.12-1.92 (m, 9H), 1.84-1.67 (m, 2H), 1.48 (d, J=5.4, 4H), 1.36-1.14 (m, 39H), 0.91-0.81 (m, 6H).

Preparation of PEG-c-DMA

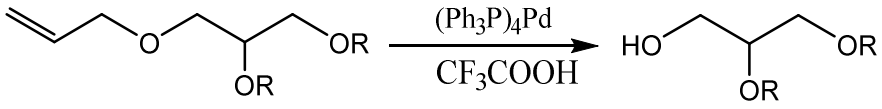
PEG-c-DMA was prepared by the chemical method as follows:



1 $R = C_{14}H_{29}$ 2

Preparation of product 2

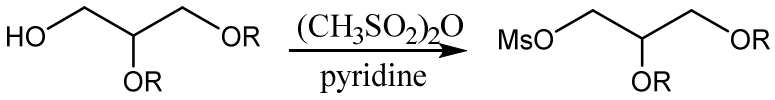
[0135] A dry 1 L glass reactor was purged with dry argon, a mixture of 9 g of the reaction product **1**, (3-allyloxy-1,2-propanediol), 60 g of 1-bromotetradecane and 15.5 g of potassium hydroxide was placed in 500 mL of anhydrous benzene, refluxed overnight, and removed with a Dean-Stark splitter. After the mixture was cooled to room temperature, the reaction mixture was diluted with 200mL of anhydrous benzene. The organic phases were washed with water and saturated NaCl solution, and dried over anhydrous magnesium sulfate. The organic solvent was removed by vacuum pump to give a clear yellow oil (53 g). The reaction mixture was purified with silica gel column (particle size 230 to 400 mesh, 1300 mL) and serial elution with 0 to 5% ethyl acetate/n-hexane was taken as mobile phase. Product **2** was 33 g.



2 3

Preparation of product 3

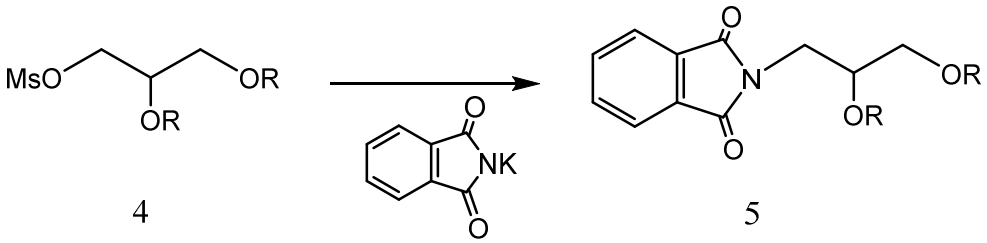
[0136] A dry 1 L glass reactor was purged with dry argon and 45 mL of trifluoroacetic acid was added to give the ethanol solution of product **2** (33 g of product **2** was dissolved in 500 mL of ethanol). After 10 g of tetrakis(triphenylphosphine)palladium was added, the mixture was refluxed overnight in the absence of light. After the completion of reaction, the organic solvent was removed by vacuum pump to give a brown oil. The crude product was purified with silica gel column (particle size 230 to 400 mesh, 1500 mL) and serial elution with 0 to 1% methanol/dichloromethane was taken as mobile phase. The final product **3** (19 g) was a yellow wax.



3 4

Preparation of product 4

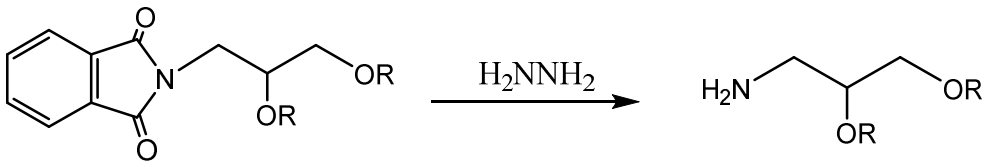
[0137] A dry 1 L glass reactor was purged with dry argon and 13.8 g of methanesulfonic anhydride was dissolved in 150 mL of dichloromethane in the reactor. And 6.4 mL of pyridine was added dropwise to the reactor. 19 g of product **3** was dissolved in 150 mL of methylene chloride and added to reaction system. The reaction mixture was stirred at room temperature under the protection of argon overnight. After the completion of reaction, the product was diluted with 200 mL of dichloromethane, washed with water and saturated NaCl solution, and dried over anhydrous magnesium sulfate. The organic solvent was removed by rotary evaporation to give a crude yellow waxy product **4** (22.1 g).



4 5

Preparation of product 5

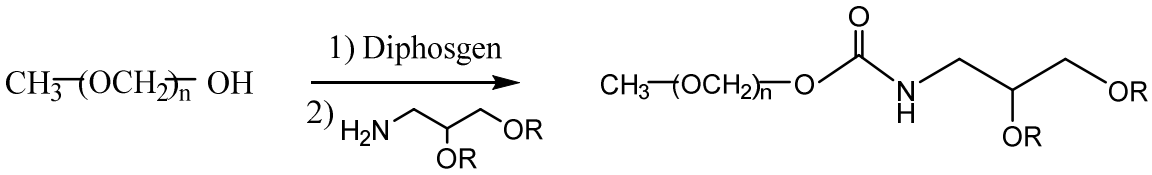
[0138] A dry 1 L glass reactor was purged with dry argon and 22 g of product **4** and 19 g of potassium phthalimide were mixed, dissolved in 400 mL of DMF solution, heated to 70 °C and stirred overnight to give a yellow suspension. After the reaction solution was cooled to room temperature, and poured into 800 mL of ice-water. The aqueous phase was washed with ethyl acetate. The organic phases were combined, washed with water and saturated NaCl solution, and dried over anhydrous magnesium sulfate. The organic solvent was removed by vacuum pump. The mixture was dissolved in 500 mL of *n*-hexane, filtered and washed with 100 mL of hexane. The organic solvent was removed by rotary evaporation to give 20.7 g of a crude wax. The crude product was purified with silica gel column (particle size 230 to 400 mesh, 600 mL) and serial elution with 0 to 5% ethyl acetate/*n*-hexane was taken as mobile phase. A pure white waxy product **5** (13.4 g) was given.



5 6

Preparation of product 6

[0139] 13.4 g of product **5** and 15.8 mL of hydrazine hydrate was dissolved in 300 mL of ethanol solution at reflux overnight to give a white solid. The reaction mixture was cooled to room temperature and then filtered. The solid was washed twice with ethanol (100 mL). The organic phases were combined, the organic solvent was removed by rotary evaporation and dissolved in 500 mL of chloroform and filtered. The solid was washed once with 100 mL of chloroform. The organic phases were combined, washed with water and saturated NaCl solution, and dried over anhydrous magnesium sulfate. The organic solvent was removed by vacuum pump to give a light-colored oily crude product (10.6 g). The crude product was purified with silica gel column (particle size 230 to 400 mesh, 300 mL) and serial elution with 0 to 10% methanol/chloroform was taken as mobile phase. A light-colored oily crude product (10 g) was given.



6 7

Preparation of product 7

[0140] 29.5 g of monomethoxy polyethylene glycol 2000 was dissolved in 150 mL of anhydrous benzene, and the organic solvent was removed by rotary evaporation. The product was dissolved in 250 mL of anhydrous dichloromethane, added into a 1 L dry glass reactor and purged with dry argon. 7.3 g of trichloromethyl chloroformate was added and stirred at room temperature for 3 h. The organic solvent was removed by rotary evaporation, 150 mL of anhydrous benzene was added, and the organic solvent was removed by rotary evaporation. 10 g of product **6** was dissolved in 150 mL of dichloromethane, then added with 3.2 mL of triethylamine and added to 1 L of the reaction under the protection of argon and stirred at room temperature overnight. The reaction product was diluted with 200 mL of dichloromethane. The organic phases were washed with 1% HCl solution, then washed with water, 0.1% sodium carbonate solution, and water and saturated NaCl solution, and finally dried over anhydrous magnesium sulfate. The organic solvent was removed by vacuum pump to give a light-colored slurry crude product (46 g). The crude product was purified with silica gel column (particle size 230 to 400 mesh, 1600 mL). The serial elution with 0 to 10%

methanol/chloroform was taken as mobile phase to obtain the product PEG-c-DMA and the remaining reactant which was white or light yellow wax. The waxy mixture was added to 150 mL of diethyl ether to dissolve unreacted reactant. The reaction mixture was filtered, and the solid was washed twice with diethyl ether, dried under vacuum to give product **7** (32.2 g). ^{1}H NMR ($CDCl_3$, 400MHz) δ:5.15 (1H, m, NH), 4.21 (2H, m, CH_2), 3.80-3.1 (8H, m), 3.60 (130H, s, OCH_2CH_2O), 3.34 (3H, s, OCH_3), 2.42 (2H, m, NCH2), 1.49 (4H, m, 2 x CH_2), 1.21 (44H, s, 22 x CH_2), 0.84 (6H, t, 2 x CH_3) ppm.

[0141] Preparation of lipid stock solution: D-Lin-MC3 Lipid, 1,2-distearoyl-sn-glycero-3-phosphocholine, i.e., DSPC (Avanti Polar Lipid, 850365), cholesterol (Sigma, C3045), and PEG-C-DMA were equilibrated at room temperature for about 30 min before weighing. D-Lin-MC3 lipid was formulated into 40 mg/mL of stock solution with 100% ethanol, cholesterol was formulated into 20 mg/mL of stock solution with 100% ethanol, and DSPC was formulated into 20 mg/mL stock solution with 100% ethanol. Long-acting lipid was formulated as 50 mg/mL of stock solution in 100% ethanol.

[0142] Preparation of pre-formed vesicles (PFV): D-Lin-MC3, cholesterol, DSPC, PEG-c-DMA and anhydrous ethanol were formulated into lipid ethanol solutions in a molar ratio of 40:40:10:10, and the required amount of each lipid was shown in Table 9. After all lipids were dissolved, the above lipid ethanol solution was added to the formulation buffer (50 mM of citric acid, pH = 3.0) with stirring to a final ethanol concentration of 30% (v/v). At room temperature, the Avanti lipid extruder equipped with a layer of Nuclepore Membrane was repeatedly extruded to give PFV with uniform particle size. The PFV extruded by the extruder was measured for particle size using a particle size analyzer.

Table 9. Requirements for lipid in F113 formulation

Total volume: 10 mL

Volume of ethanol: 3 mL of ethanol with a concentration of 30% (v/v)

Lipid	**Concentration (mg/mL)**	**Required amount (mL)**
D-Lin-MC3	40	1.25
DSPC	20	0.462
Cholesterol	20	0.904
PEG-c-DMA	50	0.596
Addition of ethanol		0.286

[0143] To prepare liposome formulations of siRNA (DS03-432i) and saRNA (RAG3-151/DS03-0024), PFV was dispensed into 15 mL Falcon tubes and pre-equilibrated for 5 min in a water bath at 35°C. Two hundred microliters (8.2 mg/mL) of siRNA (DS03-432i) and saRNA (DS03-0024) stock solutions were formulated into 0.4 mL of a solution containing siRNA, formulation buffer, ethanol solution and a solution containing saRNA, formulation buffer, ethanol solution at a ratio of RNA stock solution:formulation buffer:ethanol solution = 200 μL:100 μL:100 μL. The siRNA (DS03-432i) or the saRNA (RAG3-151/DS03-0024)/formulation buffer/ethanol solution was slowly added to the above PFV and incubated at 35 °C for 30 min. The siRNA (DS03-432i) and saRNA (RAG3-151/DS03-0024) liposome formulations were then dialyzed overnight using an MD24 dialysis bag, 1× phosphate buffer solution (PBS), and the product recovered after dialysis was the LNP-entrapped oligonucleotide used in the experiment. The LNP-entrapped oligonucleotide was filtered and sterilized using a 0.2 μm needle head-type filter, and 20 μL of sterilized products was used to determine the encapsulation rate.

(2) LNP-entrapped oligonucleotide injected into tail vein of mice

[0144] Fifteen male Balb/c mice (purchased from SPF (Beijing) Biotechnology Co.,Ltd.), 6 to 8 weeks old, and weights of 25g were prepared for the experiments. After acclimatation in a mouse animal room for 3 days, the mice were randomly divided into 3 groups with 5 mice in each group based on body weight. A control group (PBS), LNP-entrapped *Thpo*-siRNA (DS03-432i, 5 mg/kg) and LNP-entrapped *Thpo*-saRNA (RAG3-151/DS03-0024, 5 mg/kg) was administered respectively by tail vein injection at a dose of 20 mL/kg. Seventy two hours after administration, mice were anesthetized with isoflurane and 200 μL of blood was collected by cardiac puncture for analysis of THPO protein concentration in serum. After blood collection was completed, the mice were sacrificed by carbon dioxide inhalation asphyxiation. The experimental mice to be euthanized were placed in a closable experimental box to release a large amount of carbon dioxide, so that the experimental mice were suffocated and died.

(3) Mouse serum THPO protein determined using ELISA

[0145] Forty microliters of whole blood from mice was let stand at room temperature for 30 min, then centrifuged (4 °C, 13000 rpm, 15 min) to collect serum. An ELISA kit with mouse THPO (R&D Systems, MTP00) was used to determine the content of THPO in the collected serum. The procedures were briefly described below, which were according to the instructions provided in the kit. Sufficient strips (provided by the kit) were prepared and 50 μL of RD1-23 was added into two replicate wells for each group. Fifty microliters of standard, control, and sample was added and the mixture was uniformly mixed by lightly beating the strips and then placing them at room temperature for 2h. The liquid was discarded, the mixture was washed 4 times with 400 μL of wash buffer, and 100 μL of mouse Thpo conjugate was added to each well and let to stand at room

temperature for 2h. Next, the liquid was discarded, the mixture was washed 4 times with 400 μL of wash buffer, and 100 μL of substrate was added to each well and let to stand at room temperature in the absence of light for 30 minutes. After the completion of the reaction, 100 μL of stop solution was added to each well, the mixture was mixed uniformly by lightly beating the strips, and absorbance at 450 nm was determined using an enzyme labeling instrument (Infinite M200 Pro). A guarantee curve was prepared using a known standard concentration (4000 pg/mL), provided by the kit. The absorbance of the sample to be tested was subtracted from that of a blank control (0 pg/mL) and the THPO protein concentration (pg/mL) was calculated from standard curve.

(4) Statistical analysis

[0146] Differences between groups of continuous variables were compared using one-way analysis of variance (ANOVA) and between groups were compared using Tukey's multiple comparisons. The groups with less than 0.05 of P value were significantly different.

[0147] **FIG. 6** shows the concentration of Thpo protein in mice serum of different treatment groups. Compared with the control group (PBS), the Thpo protein content of the LNP-entrapped *Thpo-siRNA* (DS03-432i) group was reduced by 16.1%, and was statistically significant ($p < 0.001$). This result indicates that LNP-entrapped *Thpo*-siRNA (DS03-432i) can efficiently deliver *Thpo*-siRNA and significantly reduce the content of *Thpo*-siRNA protein in mice which is expected and consistent with *in vitro* cell study results. Compared with the control group, the Thpo protein content of the LNP-entrapped *Thpo*-saRNA (DS03-0024) group was reduced by 32.9%, and was statistically significant ($p < 0.001$). This result indicates that LNP-entrapped *Thpo*-saRNA (DS03-0024) can efficiently deliver *Thpo*-saRNA and significantly increase the content of Thpo protein in mice. N = 5; (N, number of samples); *** represents $p < 0.001$.

Example 7: Tail Vein Delivery of saRNA in Mice Increasing the Level of Serum Thpo and Number of Peripheral Blood Platelets

[0148] Thirty two male Balb/c mice (6 to 8 weeks old, 28 to 30g in weight, purchased from Comparative Medicine Center of Yangzhou University) were prepared. After acclimated in the mouse animal room for 7 days, the above mice were randomly divided into 4 groups with 8 mice in each group based on body weight. The four groups consisted of a control group (PBS) and 3 groups receiving different doses of LNP-entrapped *Thpo*-saRNA (DS03-0024, 1 mg/kg; DS03-0024, 3 mg/kg, and DS03-0024, 6 mg/kg), resepctively. The drug was administered by tail vein injection at a dose of 10 mL/kg. Forty microliters of blood was collected by tail vein 1 day before administration, and at 2 days, 4 days, 6 days and 9 days after dose administration to analyze the concentration of Thpo in the serum. To assay the number of peripheral blood platelets, the mice

were anesthetized with isoflurane and 800 μL of blood was collected by cardiac puncture 17 days after the dose administration. After the blood collection was completed, the mice were sacrificed by carbon dioxide inhalation asphyxiation. The experimental mice to be euthanized were placed in a closable experimental box to release a large amount of carbon dioxide, so that the experimental mice were suffocated and died.

[0149] (2) Assay of peripheral blood platelet in mice

[0150] To assay peripheral blood platelets in mice, five microliters of whole blood and 5 μL of 0.01% heparin sodium was uniformly mixed and added to 90 μL of physiological saline (1:20 dilution). The mixture was gently mixed and added to 200 μL of the upper layer of blood platelet separation liquid (Solarbio, P1620) and centrifuged at room temperature for 15 min at 250 ×g. Thereafter, 20 μL of the uppermost blood platelet enrichment layer was collected. Eighty microliters of 1×FASC standing buffer (R&D Systems, FC001) was added to the collected supernatant and 1 μL of CD41a antibody (ThermoFisher, 11-0411-82) was added to bind platelets.The mixture was uniformly mixed and let stand at room temperature in the absence of light for 30 minutes. After completion of the reaction, the mixture was centrifuged at room temperature (800 g, 5 min), the precipitate was resuspended in 200 μL of PBS, and transferred to an enzyme-labeled assay plate determine platelet content. The preparation of the oligonucleotide formulation and methods for injecting LNP-entrapped oligonucleotides into the tail veins of mice are described in Example 6.

[0151] **FIG. 7** shows that *Thpo* saRNA increases the concentration of Thpo protein in mice serum of different treatment groups. As shown in **FIG. 7A**, the baseline concentration of Thpo protein in mice serum was determined the day before administration and there was no significant difference in the level of serum for Thpo protein in the 4 groups of mice. **FIG. 7B** shows the concentrations of Thpo protein in mice serum collected 2 days after administration. The level of Thpo protein serum in the DS03-0024-3 mg/kg group is increased compared to the control group (PBS), however not statistically significant. The concentration of Thpo protein in the DS03-0024-6 mg/kg group increased by 23.9%, with a statistical significance of $p < 0.0001$. This result indicates that LNP-entrapped *Thpo*-saRNA can quickly and efficiently deliver *Thpo*-saRNA and significantly increase the concentration of Thpo protein in mice serum.

[0152] **FIG. 8** shows that *Thpo* saRNA increased the number of platelets in mice 6 days after administration. Compared to the control group (PBS), the two groups of LNP-entrapped *Thpo*-saRNA, DS03-0024, 1 mg/kg and DS03-0024, 3 mg/kg,0 increased, though not statistically significant, especially in the number of platelets in the LNP-entrapped *Thpo*-saRNA group (DS03-0024, 3 mg/kg), which increased by 88.6%. The number of platelets in the LNP-entrapped *Thpo*-saRNA group (DS03-0024, 6 mg/kg) increased by 138.7%, with a statistical significance of p

< 0.05. This result indicates that the LNP-entrapped *Thpo*-saRNA group (DS03-0024, 6 mg/kg) can increase the number of platelets 6 days after administration.

[0153] **FIG. 9** shows that *Thpo* saRNA increased the number of platelets in mice 17 days after administration. The number of platelets in mice from the two groups of LNP-entrapped *Thpo*-saRNA, DS03-0024, 1 mg/kg and DS03-0024, 3 mg/kg, respectively, determined 17 days after administration, increased significantly compared to that of the control group (PBS), increasing by 53.8% and 53.9%, respectively, wwith a statistical significance ($P < 0.05$). The number of platelets in the LNP-entrapped *Thpo*-saRNA group (DS03-0024, 6 mg/kg) tended to increase as well. This result indicates that the increases observed in platelet number caused by saRNA can persist for at least 17 days.

Example 8: Design and Synthesis of saRNA Targeting Human *THPO* Gene Promoter

[0154] To screen functional saRNAs capable of activating human *THPO* gene expression, a *THPO* promoter region sequence with a length of 1382 bp was used as a template and target sequences with a length of 19 bp were selected from -1382 bp upstream of TSS. The target sequences were then chosen using the following criteria : (1) having a GC content between 40% and 65%; (2) with less than 5 continuous identical nucleotides; (3) with 3 or less dinucleotide repeat sequences; and (4) with 3 or less trinucleotide repeat sequences. After the selection, the remaining 833 target sequences entered the screening process as candidates. Corresponding double-stranded saRNAs were chemically synthesized based on these candidate sequences.

[0155] In the study, each sense strand and antisense strand in the double-stranded saRNA had 21 nucleotides in length. The 19 nucleotides in the 5' region of the first ribonucleic acid strand (sense strand) of saRNA had 100% identity to the target sequence of the promoter, and the 3' terminus of the first ribonucleic acid strand contained a TT sequence. The 19 nucleotides in the 5' region of the second ribonucleic acid strand were complementary to the first ribonucleic acid strand sequence, and the 3' terminus of the second ribonucleic acid strand contained a TT sequence. The aforementioned two strands of the saRNA were mixed at a molar ratio of 1:1, and after annealing, a double-stranded saRNA was formed.

[0156] The sequence of human *THPO* promoter is shown as follows, which corresponds to position 1 to position -1382 from 5' to 3' of SEQ ID No: 600 in the sequence listing:

-1382 gtccatcagc cgatctcccc ctgcctgggc ccacagcgcc ccccaaaccc
-1332 tcaccaccct ctctcactgc ctagcctgcc tccctacctt ctctctgagg
-1282 tcgctcctca ttcttgtgtt acccaggaca gggacctagc cagaaaccgg
-1232 cagcattccc ccttctgtgg agtgacagta tctccctctc attgtaactt
-1182 atcctcaggc gcattcgaca gtcccctctt gctttctcac ccccttcctt

-1132 cacccaaggg accctctgcc tctccagccc actcccagcc tcctttctct
-1082 tggttccctg gtcatgcctg cctccctgtc tcctgtctct ccctcccaca
-1032 cacacccact atcctcccag ctatcccagc accctccttc ctaatcttgg
-982 gagacatctc gtctggctgg acgggaaaat tccaggatct aggccacact
-932 tctcagcaga catgcccatc cttggggagg aggaacagga gagagcctga
-882 ggaagttctg ggggacaggg ggatgatggg atcaaggtca ggccaggaag
-832 cccctgagga cagagactgt ggggagactg ggactgggaa gaaagcaaag
-782 gagctagagc cagggccaaa ggaaaagggg ggccagcagg gaggtatttg
-732 cgggggaggt ccagcagctg tctttcctaa gacagggaca catgggcctg
-682 gttattcctc ttgtcacatg tggaacggta ggagatggaa gacggagaca
-632 gaacaagcaa aggagggccc tgggcacaga ggtctgtgtg tgtagccatc
-582 taagccactg gaccccagca gacgagcacc taagctcagg cttaacccag
-532 tgcacgtgtg cgcacataca tgtgccccgc acctgacagt ccactcaacc
-482 cgtccaaacc ctttccccat aacaccaacc cataacagga gatttctctc
-432 atgtgggcaa tatccgtgtt cccacttcga aaggggggaat gacaagatag
-382 gactccctag gggattacag aaagaaaagc aggaaagcaa gcatcctgtt
-332 ggatttcagc agcaggtatg atgtccaggg aaaagaaatt tggatagcca
-282 gggagtgaaa accccaccaa tcttaaacaa gacctctgtg cttcttcccc
-232 agcaacacaa atgtcctgcc agattcctcc tggaaaaaaa cttctgctcc
-182 tgtccccctc caggtcccag gttgcccatg tccaggaaaa gatggatccc
-132 cctatccaaa tcttctccgt ggtgtgtgtg ggtggaggag tggaccctgg
-82 tccaggcagg ggctccaggg aagagaaggc gtcacttccg ggggccttca
-32 ccagtgtctg gtggctccct tctctgattg gg

Example 9: High-throughput Screening of saRNAs Targeting Human *THPO* Promoter

(1) Cell culture and transfection

[0157] A human liver cancer cell HepG2 (ATCC) was cultured in MEM media (Gibco) containing 10% of calf serum (Sigma-Aldrich) and 1% of penicillin/streptomycin (Gibco). The cells were cultured at 37 °C in 5% CO_2. The HepG2 cells were plated at 5000 cells/well in 96-well plates. RNAiMax (Invitrogen, Carlsbad, CA) was used to transfect small activating RNAs at a concentration of 25 nM for a durationof 72 h, with 2 replicate wells for each treatment.

(2) One-step RT-qPCR

[0158] After transfection, the media were discarded, and each well was washed once with 150 μL of PBS once. After washing, 50 μL of cell lysis buffer was added to each well, and incubation was performed at room temperature for 5 min. One microliter of cell lysis buffer was taken from each well and subjected to qPCR analysis on an ABI 7500 fast real-time PCR system (Applied Biosystems) using a one-step TB Green™ PrimeScrip™ RT-PCR kit II (Takara, RR086A). Each

sample was repeatedly amplified in 3 replicate wells. PCR reaction conditions are shown in Table 1.

Table 10: PCR reaction preparation

Reagent	**Volume**
2 × One-step TB Green RT-PCR buffer 4	2.5 μL
PrimeScript 1 step enzyme mixture 2	0.2 μL
Mixture of forward and reverse primers (5 μM)	0.4 μL
No RNase dH_2O	1.4 μL
Crude lysate (RNA)	0.5 μL
Sum	5 μL

[0159] Reaction conditions were as follows: reverse transcription reaction (stage 1): 5 min at 42°C, 10s at 95°C; PCR reaction (stage 2): 5s at 95°C, 20 s at 60°C, 45 cycles of amplification. *TBP* was used as an internal control gene. PCR primers used for *THPO* and *TBP* were shown in Table 10, wherein *THPO* was amplified using the *THPO* F1/R1 primer pair.

Table 11: Primer sequences for RT-qPCR analysis

Primer	**Sequence No.**	**Sequence (5'-3')**
THPO F	SEQ ID NO: 309	TCGTGACTCCCATGTCCTTC
THPO R	SEQ ID NO: 310	TGCCTTGGTCTCCTCCATCT
TBP F	SEQ ID NO: 311	TGCTCACCCACCAACAATTTAG
TBP R	SEQ ID NO: 312	TCTGCTCTGACTTTAGCACCTG
HPRT1 F	SEQ ID NO: 313	AAAGATGGTCAAGGTCGCAAG
HPRT1 R	SEQ ID NO: 314	TAGTCAAGGGCATATCCTACAAC

[0160] In order to calculate the expression value (E_{rel}) of the *THPO* gene (target) of an saRNA-transfected sample relative to control treatment (Mock), the Ct values of the target gene and one internal control gene are substituted into Formula 2 as shown in Example 3 for calculation.

$$E_{rel} = 2^{(CtTm-CtTs)} / 2^{(CtRm-CtRs)}$$

Formula 2

[0161] wherein CtTm was the Ct value of the target gene from Mock sample; CtTs was the Ct value of the target gene from the saRNA-treated sample; CtRm was the Ct value of the internal control gene from Mock-treated sample; and CtRs was the Ct value of the internal control gene from the saRNA-treated sample.

(3) Screening of functional saRNAs

[0162] To obtain saRNAs capable of activating *THPO* transcription, HepG2 cells were transfected by the aforementioned 833 saRNAs with a transfection concentration of 25 nM. Seventy two hours later, using the same method as described above, the cells were lysed and subjected to one-step RT-qPCR analysis to obtain the relative expression value (compared to the control treatment group) of *THPO* gene in each saRNA-treated sample. As shown in Table 11, 158 (19 %) saRNAs showed high activation, 243 (29.2 %) saRNAs showed mild activation, and 432 (51.8 %) saRNAs did not affect *THPO* expression. The maximum activation was 5.15-fold; the maximum inhibition was 0.09-fold; and the saRNAs with activation activity were called activating saRNAs.

Table 12: High-throughput screening results of human *THPO* saRNA

saRNA activity	**log_2 value (fold) of changes in *THPO* mRNA**	**Number of saRNAs**	**Percentage**
High activation	≥ 0.58 (1.50) ~ ≤ 2.36 (5.15)	158	19%
Mild activation	≥ 0.13 (1.10) ~ < 0.58 (1.50)	243	29.2%
No activating effect	< 0.13 (1.10)	432	51.8%
Sum		833	100%

[0163] Shown in **FIG.10** is the descending order of changes in *THPO* expression of mouse *THPO* saRNA. *THPO* active saRNA sequence and *THPO* mRNA expression were changed as shown in Table 13.

Table 13: Human active saRNA sequences and target sequences thereof and changes in expression of *THPO* mRNA

saRNA	**Target sequence (5'-3')**	**Sense sequence (5'-3') of saRNA**	**Antisense sequence (5'-3') of saRNA**	**Fold of changes in relative expression of *THPO* mRNA**
RAG3A-889	AGCCTGAGGAAGTTCTGGG (SEQ ID NO: 606)	AGCCUGAGGAAGUUCUGGGTT (SEQ ID NO: 1048)	CCCAGAACUUCCUCAGGCUTT (SEQ ID NO: 1490)	5.1
RAG3A-723	TCCAGCAGCTGTCTTTCCT (SEQ ID NO: 607)	UCCAGCAGCUGUCUUUCCUTT (SEQ ID NO: 1049)	AGGAAAGACAGCUGCUGGATT (SEQ ID NO: 1491)	4.1
RAG3A-1069	ATGCCTGCCTCCCTGTCTC (SEQ ID NO: 608)	AUGCCUGCCUCCCUGUCUCTT (SEQ ID NO: 1050)	GAGACAGGGAGGCAGGCAUTT (SEQ ID NO: 1492)	4
RAG3A-541	TTAACCCAGTGCACGTGTG (SEQ ID NO: 609)	UUAACCCAGUGCACGUGUGTT (SEQ ID NO: 1051)	CACACGUGCACUGGGUUAATT (SEQ ID NO: 1493)	3.4
RAG3A-480	TCCAAACCCTTTCCCCATA (SEQ ID NO: 610)	UCCAAACCCUUUCCCCAUATT (SEQ ID NO: 1052)	UAUGGGGAAAGGGUUUGGATT (SEQ ID NO: 1494)	3.1
RAG3A-980	GACATCTCGTCTGGCTGGA (SEQ ID NO: 611)	GACAUCUCGUCUGGCUGGATT (SEQ ID NO: 1053)	UCCAGCCAGACGAGAUGUCTT	3.1

			(SEQ ID NO: 1495)	
RAG3A-462	AACACCAACCCATAACAGG (SEQ ID NO: 612)	AACACCAACCCAUAACAGGTT (SEQ ID NO: 1054)	CCUGUUAUGGGUUGGUGUUTT (SEQ ID NO: 1496)	3
RAG3A-787	CAAAGGAGCTAGAGCCAGG (SEQ ID NO: 613)	CAAAGGAGCUAGAGCCAGGTT (SEQ ID NO: 1055)	CCUGGCUCUAGCUCCUUUGTT (SEQ ID NO: 1497)	2.9
RAG3A-232	AGCAACACAAATGTCCTGC (SEQ ID NO: 614)	AGCAACACAAAUGUCCUGCTT (SEQ ID NO: 1056)	GCAGGACAUUUGUGUUGCUTT (SEQ ID NO: 1498)	2.9
RAG3A-727	GAGGTCCAGCAGCTGTCTT (SEQ ID NO: 615)	GAGGUCCAGCAGCUGUCUUTT (SEQ ID NO: 1057)	AAGACAGCUGCUGGACCUCTT (SEQ ID NO: 1499)	2.9
RAG3A-542	CTTAACCCAGTGCACGTGT (SEQ ID NO: 616)	CUUAACCCAGUGCACGUGUTT (SEQ ID NO: 1058)	ACACGUGCACUGGGUUAAGTT (SEQ ID NO: 1500)	2.8
RAG3A-748	AGCAGGGAGGTATTTGCGG (SEQ ID NO: 617)	AGCAGGGAGGUAUUUGCGGTT (SEQ ID NO: 1059)	CCGCAAAUACCUCCCUGCUTT (SEQ ID NO: 1501)	2.8
RAG3A-540	TAACCCAGTGCACGTGTGC (SEQ ID NO: 618)	UAACCCAGUGCACGUGUGCTT (SEQ ID NO: 1060)	GCACACGUGCACUGGGUUATT (SEQ ID NO: 1502)	2.8

RAG3A-1219	TCTGTGGAGTGACAGTATC (SEQ ID NO: 619)	UCUGUGGAGUGACAGUAUCTT (SEQ ID NO: 1061)	GAUACUGUCACUCCACAGATT (SEQ ID NO: 1503)	2.8
RAG3A-487	CAACCCGTCCAAACCCTTT (SEQ ID NO: 620)	CAACCCGUCCAAACCCUUUTT (SEQ ID NO: 1062)	AAAGGGUUUGGACGGGUUGTT (SEQ ID NO: 1504)	2.7
RAG3A-559	GAGCACCTAAGCTCAGGCT (SEQ ID NO: 621)	GAGCACCUAAGCUCAGGCUTT (SEQ ID NO: 1063)	AGCCUGAGCUUAGGUGCUCTT (SEQ ID NO: 1505)	2.7
RAG3A-1308	CCTGCCTCCCTACCTTCTC (SEQ ID NO: 622)	CCUGCCUCCCUACCUUCUCTT (SEQ ID NO: 1064)	GAGAAGGUAGGGAGGCAGGTT (SEQ ID NO: 1506)	2.7
RAG3A-24	TGGTGGCTCCCTTCTCTGA (SEQ ID NO: 623)	UGGUGGCUCCCUUCUCUGATT (SEQ ID NO: 1065)	UCAGAGAAGGGAGCCACCATT (SEQ ID NO: 1507)	2.6
RAG3A-1169	TTCGACAGTCCCCTCTTGC (SEQ ID NO: 624)	UUCGACAGUCCCCUCUUGCTT (SEQ ID NO: 1066)	GCAAGAGGGGACUGUCGAATT (SEQ ID NO: 1508)	2.6
RAG3A-1256	GACAGGGACCTAGCCAGAA (SEQ ID NO: 625)	GACAGGGACCUAGCCAGAATT (SEQ ID NO: 1067)	UUCUGGCUAGGUCCCUGUCTT (SEQ ID NO: 1509)	2.6
RAG3A-522	CGCACATACATGTGCCCCG	CGCACAUACAUGUGCCCCGTT	CGGGGCACAUGUAUGUGCGTT	2.6

	(SEQ ID NO: 626)	(SEQ ID NO: 1068)	(SEQ ID NO: 1510)	
RAG3A-851	TCAAGGTCAGGCCAGGAAG (SEQ ID NO: 627)	UCAAGGUCAGGCCAGGAAGTT (SEQ ID NO: 1069)	CUUCCUGGCCUGACCUUGATT (SEQ ID NO: 1511)	2.6
RAG3A-1096	AGCCTCCTTTCTCTTGGTT (SEQ ID NO: 628)	AGCCUCCUUUCUCUUGGUUTT (SEQ ID NO: 1070)	AACCAAGAGAAAGGAGGCUTT (SEQ ID NO: 1512)	2.5
RAG3A-227	CACAAATGTCCTGCCAGAT (SEQ ID NO: 629)	CACAAAUGUCCUGCCAGAUTT (SEQ ID NO: 1071)	AUCUGGCAGGACAUUUGUGTT (SEQ ID NO: 1513)	2.5
RAG3A-1178	TCAGGCGCATTCGACAGTC (SEQ ID NO: 630)	UCAGGCGCAUUCGACAGUCTT (SEQ ID NO: 1072)	GACUGUCGAAUGCGCCUGATT (SEQ ID NO: 1514)	2.5
RAG3A-544	GGCTTAACCCAGTGCACGT (SEQ ID NO: 631)	GGCUUAACCCAGUGCACGUTT (SEQ ID NO: 1073)	ACGUGCACUGGGUUAAGCCTT (SEQ ID NO: 1515)	2.5
RAG3A-836	GAAGCCCCTGAGGACAGAG (SEQ ID NO: 632)	GAAGCCCCUGAGGACAGAGTT (SEQ ID NO: 1074)	CUCUGUCCUCAGGGGCUUCTT (SEQ ID NO: 1516)	2.4
RAG3A-569	CCCAGCAGACGAGCACCTA (SEQ ID NO: 633)	CCCAGCAGACGAGCACCUATT (SEQ ID NO: 1075)	UAGGUGCUCGUCUGCUGGGTT	2.4

			(SEQ ID NO: 1517)	
RAG3A-1320	CTCACTGCCTAGCCTGCCT (SEQ ID NO: 634)	CUCACUGCCUAGCCUGCCUTT (SEQ ID NO: 1076)	AGGCAGGCUAGGCAGUGAGTT (SEQ ID NO: 1518)	2.4
RAG3A-1319	TCACTGCCTAGCCTGCCTC (SEQ ID NO: 635)	UCACUGCCUAGCCUGCCUCTT (SEQ ID NO: 1077)	GAGGCAGGCUAGGCAGUGATT (SEQ ID NO: 1519)	2.3
RAG3A-290	GATAGCCAGGGAGTGAAAA (SEQ ID NO: 636)	GAUAGCCAGGGAGUGAAAATT (SEQ ID NO: 1078)	UUUUCACUCCCUGGCUAUCTT (SEQ ID NO: 1520)	2.3
RAG3A-1074	TGGTCATGCCTGCCTCCCT (SEQ ID NO: 637)	UGGUCAUGCCUGCCUCCCUTT (SEQ ID NO: 1079)	AGGGAGGCAGGCAUGACCATT (SEQ ID NO: 1521)	2.2
RAG3A-279	AGTGAAAACCCCACCAATC (SEQ ID NO: 638)	AGUGAAAACCCCACCAAUCTT (SEQ ID NO: 1080)	GAUUGGUGGGGUUUUCACUTT (SEQ ID NO: 1522)	2.2
RAG3A-521	GCACATACATGTGCCCCGC (SEQ ID NO: 639)	GCACAUACAUGUGCCCCGCTT (SEQ ID NO: 1081)	GCGGGGCACAUGUAUGUGCTT (SEQ ID NO: 1523)	2.2
RAG3A-25	CTGGTGGCTCCCTTCTCTG (SEQ ID NO: 640)	CUGGUGGCUCCCUUCUCUGTT (SEQ ID NO: 1082)	CAGAGAAGGGAGCCACCAGTT	2.1

			(SEQ ID NO: 1524)	
RAG3A-62	AAGAGAAGGCGTCACTTCC (SEQ ID NO: 641)	AAGAGAAGGCGUCACUUCCTT (SEQ ID NO: 1083)	GGAAGUGACGCCUUCUCUUTT (SEQ ID NO: 1525)	2.1
RAG3A-852	ATCAAGGTCAGGCCAGGAA (SEQ ID NO: 642)	AUCAAGGUCAGGCCAGGAATT (SEQ ID NO: 1084)	UUCCUGGCCUGACCUUGAUTT (SEQ ID NO: 1526)	2.1
RAG3A-931	CTCAGCAGACATGCCCATC (SEQ ID NO: 643)	CUCAGCAGACAUGCCCAUCTT (SEQ ID NO: 1085)	GAUGGGCAUGUCUGCUGAGTT (SEQ ID NO: 1527)	2.1
RAG3A-892	GAGAGCCTGAGGAAGTTCT (SEQ ID NO: 644)	GAGAGCCUGAGGAAGUUCUTT (SEQ ID NO: 1086)	AGAACUUCCUCAGGCUCUCTT (SEQ ID NO: 1528)	2
RAG3A-235	CCCAGCAACACAAATGTCC (SEQ ID NO: 645)	CCCAGCAACACAAAUGUCCTT (SEQ ID NO: 1087)	GGACAUUUGUGUUGCUGGGTT (SEQ ID NO: 1529)	2
RAG3A-1246	TAGCCAGAAACCGGCAGCA (SEQ ID NO: 646)	UAGCCAGAAACCGGCAGCATT (SEQ ID NO: 1088)	UGCUGCCGGUUUCUGGCUATT (SEQ ID NO: 1530)	2
RAG3A-19	GCTCCCTTCTCTGATTGGG (SEQ ID NO: 647)	GCUCCCUUCUCUGAUUGGGTT (SEQ ID NO: 1089)	CCCAAUCAGAGAAGGGAGCTT	2

			(SEQ ID NO: 1531)	
RAG3A-1322	CTCTCACTGCCTAGCCTGC (SEQ ID NO: 648)	CUCUCACUGCCUAGCCUGCTT (SEQ ID NO: 1090)	GCAGGCUAGGCAGUGAGAGTT (SEQ ID NO: 1532)	2
RAG3A-795	GAAGAAAGCAAAGGAGCTA (SEQ ID NO: 649)	GAAGAAAGCAAAGGAGCUATT (SEQ ID NO: 1091)	UAGCUCCUUUGCUUUCUUCTT (SEQ ID NO: 1533)	2
RAG3A-515	ACATGTGCCCCGCACCTGA (SEQ ID NO: 650)	ACAUGUGCCCCGCACCUGATT (SEQ ID NO: 1092)	UCAGGUGCGGGGCACAUGUTT (SEQ ID NO: 1534)	2
RAG3A-128	TCCAAATCTTCTCCGTGGT (SEQ ID NO: 651)	UCCAAAUCUUCUCCGUGGUTT (SEQ ID NO: 1093)	ACCACGGAGAAGAUUUGGATT (SEQ ID NO: 1535)	2
RAG3A-661	GGAACGGTAGGAGATGGAA (SEQ ID NO: 652)	GGAACGGUAGGAGAUGGAATT (SEQ ID NO: 1094)	UUCCAUCUCCUACCGUUCCTT (SEQ ID NO: 1536)	2
RAG3A-125	AAATCTTCTCCGTGGTGTG (SEQ ID NO: 653)	AAAUCUUCUCCGUGGUGUGTT (SEQ ID NO: 1095)	CACACCACGGAGAAGAUUUTT (SEQ ID NO: 1537)	2
RAG3A-1241	AGAAACCGGCAGCATTCCC (SEQ ID NO: 654)	AGAAACCGGCAGCAUUCCCTT (SEQ ID NO: 1096)	GGGAAUGCUGCCGGUUUCUTT	2

			(SEQ ID NO: 1538)	
RAG3A-463	TAACACCAACCCATAACAG (SEQ ID NO: 655)	UAACACCAACCCAUAACAGTT (SEQ ID NO: 1097)	CUGUUAUGGGUUGGUGUUATT (SEQ ID NO: 1539)	2
RAG3A-434	TCATGTGGGCAATATCCGT (SEQ ID NO: 656)	UCAUGUGGGCAAUAUCCGUTT (SEQ ID NO: 1098)	ACGGAUAUUGCCCACAUGATT (SEQ ID NO: 1540)	1.9
RAG3A-520	CACATACATGTGCCCCGCA (SEQ ID NO: 657)	CACAUACAUGUGCCCCGCATT (SEQ ID NO: 1099)	UGCGGGGCACAUGUAUGUGTT (SEQ ID NO: 1541)	1.9
RAG3A-499	TGACAGTCCACTCAACCCG (SEQ ID NO: 658)	UGACAGUCCACUCAACCCGTT (SEQ ID NO: 1100)	CGGGUUGAGUGGACUGUCATT (SEQ ID NO: 1542)	1.9
RAG3A-668	CACATGTGGAACGGTAGGA (SEQ ID NO: 659)	CACAUGUGGAACGGUAGGATT (SEQ ID NO: 1101)	UCCUACCGUUCCACAUGUGTT (SEQ ID NO: 1543)	1.9
RAG3A-591	GTAGCCATCTAAGCCACTG (SEQ ID NO: 660)	GUAGCCAUCUAAGCCACUGTT (SEQ ID NO: 1102)	CAGUGGCUUAGAUGGCUACTT (SEQ ID NO: 1544)	1.9
RAG3A-1209	GACAGTATCTCCCTCTCAT (SEQ ID NO: 661)	GACAGUAUCUCCCUCUCAUTT (SEQ ID NO: 1103)	AUGAGAGGGAGAUACUGUCTT (SEQ ID NO: 1545)	1.9
RAG3A-125	GGACAGGGACCTAGCCAGA	GGACAGGGACCUAGCCAGATT	UCUGGCUAGGUCCCUGUCCT	1.9

7	(SEQ ID NO: 662)	(SEQ ID NO: 1104)	T (SEQ ID NO: 1546)	
RAG3A-1170	ATTCGACAGTCCCCTCTTG (SEQ ID NO: 663)	AUUCGACAGUCCCCUCUUGTT (SEQ ID NO: 1105)	CAAGAGGGGACUGUCGAAUT T (SEQ ID NO: 1547)	1.9
RAG3A-39	GCCTTCACCAGTGTCTGGT (SEQ ID NO: 664)	GCCUUCACCAGUGUCUGGUTT (SEQ ID NO: 1106)	ACCAGACACUGGUGAAGGCT T (SEQ ID NO: 1548)	1.9
RAG3A-431	TGTGGGCAATATCCGTGTT (SEQ ID NO: 665)	UGUGGGCAAUAUCCGUGUUTT+B50 (SEQ ID NO: 1107)	AACACGGAUAUUGCCCACATT (SEQ ID NO: 1549)	1.9
RAG3A-1080	GTTCCCTGGTCATGCCTGC (SEQ ID NO: 666)	GUUCCCUGGUCAUGCCUGCTT (SEQ ID NO: 1108)	GCAGGCAUGACCAGGGAACT T (SEQ ID NO: 1550)	1.9
RAG3A-1266	TGTTACCCAGGACAGGGAC (SEQ ID NO: 667)	UGUUACCCAGGACAGGGACTT (SEQ ID NO: 1109)	GUCCCUGUCCUGGGUAACATT (SEQ ID NO: 1551)	1.9
RAG3A-1202	TCTCCCTCTCATTGTAACT (SEQ ID NO: 668)	UCUCCCUCUCAUUGUAACUTT (SEQ ID NO: 1110)	AGUUACAAUGAGAGGGAGAT T (SEQ ID NO: 1552)	1.9
RAG3A-979	ACATCTCGTCTGGCTGGAC (SEQ ID NO: 669)	ACAUCUCGUCUGGCUGGACTT (SEQ ID NO: 1111)	GUCCAGCCAGACGAGAUGUT T (SEQ ID NO: 1553)	1.9
RAG3A-343	AGCATCCTGTTGGATTTCA (SEQ ID NO: 670)	AGCAUCCUGUUGGAUUUCATT (SEQ ID NO: 1112)	UGAAAUCCAACAGGAUGCUT T (SEQ ID NO: 1554)	1.9
RAG3A-430	GTGGGCAATATCCGTGTTC (SEQ ID NO: 671)	GUGGGCAAUAUCCGUGUUCTT (SEQ ID NO: 1113)	GAACACGGAUAUUGCCCACT T (SEQ ID NO: 1555)	1.9
RAG3A-319	AGGTATGATGTCCAGGGAA (SEQ ID NO: 672)	AGGUAUGAUGUCCAGGGAATT (SEQ ID NO: 1114)	UUCCCUGGACAUCAUACCUT T (SEQ ID NO: 1556)	1.8

RAG3A-612	TGGGCACAGAGGTCTGTGT (SEQ ID NO: 673)	UGGGCACAGAGGUCUGUGUTT (SEQ ID NO: 1115)	ACACAGACCUCUGUGCCCATT (SEQ ID NO: 1557)	1.8
RAG3A-454	CCCATAACAGGAGATTTCT (SEQ ID NO: 674)	CCCAUAACAGGAGAUUUCUTT (SEQ ID NO: 1116)	AGAAAUCUCCUGUUAUGGGT T (SEQ ID NO: 1558)	1.8
RAG3A-1312	CTAGCCTGCCTCCCTACCT (SEQ ID NO: 675)	CUAGCCUGCCUCCCUACCUTT (SEQ ID NO: 1117)	AGGUAGGGAGGCAGGCUAGT T (SEQ ID NO: 1559)	1.8
RAG3A-342	GCATCCTGTTGGATTTCAG (SEQ ID NO: 676)	GCAUCCUGUUGGAUUUCAGTT (SEQ ID NO: 1118)	CUGAAAUCCAACAGGAUGCT T (SEQ ID NO: 1560)	1.8
RAG3A-1118	TCTGCCTCTCCAGCCCACT (SEQ ID NO: 677)	UCUGCCUCUCCAGCCCACUTT (SEQ ID NO: 1119)	AGUGGGCUGGAGAGGCAGAT T (SEQ ID NO: 1561)	1.8
RAG3A-970	CTGGCTGGACGGGAAAATT (SEQ ID NO: 678)	CUGGCUGGACGGGAAAAUUTT (SEQ ID NO: 1120)	AAUUUUCCCGUCCAGCCAGT T (SEQ ID NO: 1562)	1.8
RAG3A-1133	TCACCCAAGGGACCCTCTG (SEQ ID NO: 679)	UCACCCAAGGGACCCUCUGTT (SEQ ID NO: 1121)	CAGAGGGUCCCUUGGGUGAT T (SEQ ID NO: 1563)	1.8
RAG3A-689	GGGCCTGGTTATTCCTCTT (SEQ ID NO: 680)	GGGCCUGGUUAUUCCUCUUTT (SEQ ID NO: 1122)	AAGAGGAAUAACCAGGCCCT T (SEQ ID NO: 1564)	1.8
RAG3A-1321	TCTCACTGCCTAGCCTGCC (SEQ ID NO: 681)	UCUCACUGCCUAGCCUGCCTT (SEQ ID NO: 1123)	GGCAGGCUAGGCAGUGAGAT T (SEQ ID NO: 1565)	1.8
RAG3A-662	TGGAACGGTAGGAGATGGA (SEQ ID NO: 682)	UGGAACGGUAGGAGAUGGATT (SEQ ID NO: 1124)	UCCAUCUCCUACCGUUCCATT (SEQ ID NO: 1566)	1.8
RAG3A-817	ACTGTGGGGAGACTGGGA	ACUGUGGGGAGACUGGGACTT	GUCCCAGUCUCCCCACAGUTT	1.8

	C (SEQ ID NO: 683)	(SEQ ID NO: 1125)	(SEQ ID NO: 1567)	
RAG3A-1242	CAGAAACCGGCAGCATTCC (SEQ ID NO: 684)	CAGAAACCGGCAGCAUUCCTT (SEQ ID NO: 1126)	GGAAUGCUGCCGGUUUCUGTT (SEQ ID NO: 1568)	1.8
RAG3A-278	GTGAAAACCCCACCAATCT (SEQ ID NO: 685)	GUGAAAACCCCACCAAUCUTT (SEQ ID NO: 1127)	AGAUUGGUGGGGUUUUCACTT (SEQ ID NO: 1569)	1.8
RAG3A-1210	TGACAGTATCTCCCTCTCA (SEQ ID NO: 686)	UGACAGUAUCUCCCUCUCATT (SEQ ID NO: 1128)	UGAGAGGGAGAUACUGUCATT (SEQ ID NO: 1570)	1.8
RAG3A-1084	CTTGGTTCCCTGGTCATGC (SEQ ID NO: 687)	CUUGGUUCCCUGGUCAUGCTT (SEQ ID NO: 1129)	GCAUGACCAGGGAACCAAGTT (SEQ ID NO: 1571)	1.8
RAG3A-1166	GACAGTCCCCTCTTGCTTT (SEQ ID NO: 688)	GACAGUCCCCUCUUGCUUUTT (SEQ ID NO: 1130)	AAAGCAAGAGGGGACUGUCTT (SEQ ID NO: 1572)	1.8
RAG3A-982	GAGACATCTCGTCTGGCTG (SEQ ID NO: 689)	GAGACAUCUCGUCUGGCUGTT (SEQ ID NO: 1131)	CAGCCAGACGAGAUGUCUCTT (SEQ ID NO: 1573)	1.8
RAG3A-171	AGGTCCCAGGTTGCCCATG (SEQ ID NO: 690)	AGGUCCCAGGUUGCCCAUGTT (SEQ ID NO: 1132)	CAUGGGCAACCUGGGACCUTT (SEQ ID NO: 1574)	1.8
RAG3A-256	ACAAGACCTCTGTGCTTCT (SEQ ID NO: 691)	ACAAGACCUCUGUGCUUCUTT (SEQ ID NO: 1133)	AGAAGCACAGAGGUCUUGUTT (SEQ ID NO: 1575)	1.7
RAG3A-563	AGACGAGCACCTAAGCTCA (SEQ ID NO: 692)	AGACGAGCACCUAAGCUCATT (SEQ ID NO: 1134)	UGAGCUUAGGUGCUCGUCUTT (SEQ ID NO: 1576)	1.7
RAG3A-1176	AGGCGCATTCGACAGTCCC (SEQ ID NO: 693)	AGGCGCAUUCGACAGUCCCTT (SEQ ID NO: 1135)	GGGACUGUCGAAUGCGCCUTT (SEQ ID NO: 1577)	1.7

RAG3A-707	CCTAAGACAGGGACACATG (SEQ ID NO: 694)	CCUAAGACAGGGACACAUGTT (SEQ ID NO: 1136)	CAUGUGUCCCUGUCUUAGGT T (SEQ ID NO: 1578)	1.7
RAG3A-561	ACGAGCACCTAAGCTCAGG (SEQ ID NO: 695)	ACGAGCACCUAAGCUCAGGTT (SEQ ID NO: 1137)	CCUGAGCUUAGGUGCUCGUT T (SEQ ID NO: 1579)	1.7
RAG3A-504	GCACCTGACAGTCCACTCA (SEQ ID NO: 696)	GCACCUGACAGUCCACUCATT (SEQ ID NO: 1138)	UGAGUGGACUGUCAGGUGCT T (SEQ ID NO: 1580)	1.7
RAG3A-195	AAACTTCTGCTCCTGTCCC (SEQ ID NO: 697)	AAACUUCUGCUCCUGUCCCTT (SEQ ID NO: 1139)	GGGACAGGAGCAGAAGUUUT T (SEQ ID NO: 1581)	1.7
RAG3A-850	CAAGGTCAGGCCAGGAAG C (SEQ ID NO: 698)	CAAGGUCAGGCCAGGAAGCTT (SEQ ID NO: 1140)	GCUUCCUGGCCUGACCUUGT T (SEQ ID NO: 1582)	1.7
RAG3A-388	AGATAGGACTCCCTAGGGG (SEQ ID NO: 699)	AGAUAGGACUCCCUAGGGGTT (SEQ ID NO: 1141)	CCCCUAGGGAGUCCUAUCUT T (SEQ ID NO: 1583)	1.7
RAG3A-1079	TTCCCTGGTCATGCCTGCC (SEQ ID NO: 700)	UUCCCUGGUCAUGCCUGCCTT (SEQ ID NO: 1142)	GGCAGGCAUGACCAGGGAAT T (SEQ ID NO: 1584)	1.7
RAG3A-1263	TACCCAGGACAGGGACCTA (SEQ ID NO: 701)	UACCCAGGACAGGGACCUATT (SEQ ID NO: 1143)	UAGGUCCCUGUCCUGGGUAT T (SEQ ID NO: 1585)	1.7
RAG3A-531	GCACGTGTGCGCACATACA (SEQ ID NO: 702)	GCACGUGUGCGCACAUACATT (SEQ ID NO: 1144)	UGUAUGUGCGCACACGUGCT T (SEQ ID NO: 1586)	1.7
RAG3A-254	AAGACCTCTGTGCTTCTTC (SEQ ID NO: 703)	AAGACCUCUGUGCUUCUUCTT (SEQ ID NO: 1145)	GAAGAAGCACAGAGGUCUUT T (SEQ ID NO: 1587)	1.7
RAG3A-421	ATCCGTGTTCCCACTTCGA	AUCCGUGUUCCCACUUCGATT	UCGAAGUGGGAACACGGAUT	1.7

	(SEQ ID NO: 704)	(SEQ ID NO: 1146)	T (SEQ ID NO: 1588)	
RAG3A-473	CCTTTCCCCATAACACCAA (SEQ ID NO: 705)	CCUUUCCCCAUAACACCAATT (SEQ ID NO: 1147)	UUGGUGUUAUGGGGAAAGGT T (SEQ ID NO: 1589)	1.7
RAG3A-292	TGGATAGCCAGGGAGTGAA (SEQ ID NO: 706)	UGGAUAGCCAGGGAGUGAATT (SEQ ID NO: 1148)	UUCACUCCCUGGCUAUCCATT (SEQ ID NO: 1590)	1.7
RAG3A-283	AGGGAGTGAAAACCCCAC C (SEQ ID NO: 707)	AGGGAGUGAAAACCCCACCTT (SEQ ID NO: 1149)	GGUGGGGUUUUCACUCCCUT T (SEQ ID NO: 1591)	1.7
RAG3A-786	AAAGGAGCTAGAGCCAGG G (SEQ ID NO: 708)	AAAGGAGCUAGAGCCAGGGTT (SEQ ID NO: 1150)	CCCUGGCUCUAGCUCCUUUTT (SEQ ID NO: 1592)	1.7
RAG3A-582	TAAGCCACTGGACCCCAGC (SEQ ID NO: 709)	UAAGCCACUGGACCCCAGCTT (SEQ ID NO: 1151)	GCUGGGGUCCAGUGGCUUAT T (SEQ ID NO: 1593)	1.7
RAG3A-933	TTCTCAGCAGACATGCCCA (SEQ ID NO: 710)	UUCUCAGCAGACAUGCCCATT (SEQ ID NO: 1152)	UGGGCAUGUCUGCUGAGAAT T (SEQ ID NO: 1594)	1.7
RAG3A-472	CTTTCCCCATAACACCAAC (SEQ ID NO: 711)	CUUUCCCCAUAACACCAACTT (SEQ ID NO: 1153)	GUUGGUGUUAUGGGGAAAGT T (SEQ ID NO: 1595)	1.7
RAG3A-646	GGAAGACGGAGACAGAAC A (SEQ ID NO: 712)	GGAAGACGGAGACAGAACATT (SEQ ID NO: 1154)	UGUUCUGUCUCCGUCUUCCT T (SEQ ID NO: 1596)	1.6
RAG3A-389	AAGATAGGACTCCCTAGGG (SEQ ID NO: 713)	AAGAUAGGACUCCCUAGGGTT (SEQ ID NO: 1155)	CCCUAGGGAGUCCUAUCUUT T (SEQ ID NO: 1597)	1.6
RAG3A-971	TCTGGCTGGACGGGAAAAT (SEQ ID NO: 714)	UCUGGCUGGACGGGAAAAUTT (SEQ ID NO: 1156)	AUUUUCCCGUCCAGCCAGATT (SEQ ID NO: 1598)	1.6

RAG3A-751	GCCAGCAGGGAGGTATTTG (SEQ ID NO: 715)	GCCAGCAGGGAGGUAUUUGTT (SEQ ID NO: 1157)	CAAAUACCUCCCUGCUGGCTT (SEQ ID NO: 1599)	1.6
RAG3A-299	AGAAATTTGGATAGCCAGG (SEQ ID NO: 716)	AGAAAUUUGGAUAGCCAGGTT (SEQ ID NO: 1158)	CCUGGCUAUCCAAAUUUCUT T (SEQ ID NO: 1600)	1.6
RAG3A-750	CCAGCAGGGAGGTATTTGC (SEQ ID NO: 717)	CCAGCAGGGAGGUAUUUGCTT (SEQ ID NO: 1159)	GCAAAUACCUCCCUGCUGGT T (SEQ ID NO: 1601)	1.6
RAG3A-671	TGTCACATGTGGAACGGTA (SEQ ID NO: 718)	UGUCACAUGUGGAACGGUATT (SEQ ID NO: 1160)	UACCGUUCCACAUGUGACATT (SEQ ID NO: 1602)	1.6
RAG3A-749	CAGCAGGGAGGTATTTGCG (SEQ ID NO: 719)	CAGCAGGGAGGUAUUUGCGTT (SEQ ID NO: 1161)	CGCAAAUACCUCCCUGCUGTT (SEQ ID NO: 1603)	1.6
RAG3A-547	TCAGGCTTAACCCAGTGCA (SEQ ID NO: 720)	UCAGGCUUAACCCAGUGCATT (SEQ ID NO: 1162)	UGCACUGGGUUAAGCCUGAT T (SEQ ID NO: 1604)	1.6
RAG3A-655	GTAGGAGATGGAAGACGGA (SEQ ID NO: 721)	GUAGGAGAUGGAAGACGGATT (SEQ ID NO: 1163)	UCCGUCUUCCAUCUCCUACTT (SEQ ID NO: 1605)	1.6
RAG3A-170	GGTCCCAGGTTGCCCATGT (SEQ ID NO: 722)	GGUCCCAGGUUGCCCAUGUTT (SEQ ID NO: 1164)	ACAUGGGCAACCUGGGACCT T (SEQ ID NO: 1606)	1.6
RAG3A-629	CAAGCAAAGGAGGGCCCT G (SEQ ID NO: 723)	CAAGCAAAGGAGGGCCCUGTT (SEQ ID NO: 1165)	CAGGGCCCUCCUUUGCUUGT T (SEQ ID NO: 1607)	1.6
RAG3A-253	AGACCTCTGTGCTTCTTCC (SEQ ID NO: 724)	AGACCUCUGUGCUUCUUCCTT (SEQ ID NO: 1166)	GGAAGAAGCACAGAGGUCUT T (SEQ ID NO: 1608)	1.6
RAG3A-695	ACACATGGGCCTGGTTATT	ACACAUGGGCCUGGUUAUUTT	AAUAACCAGGCCCAUGUGUT	1.6

	(SEQ ID NO: 725)	(SEQ ID NO: 1167)	T (SEQ ID NO: 1609)	
RAG3A-788	GCAAAGGAGCTAGAGCCAG (SEQ ID NO: 726)	GCAAAGGAGCUAGAGCCAGTT (SEQ ID NO: 1168)	CUGGCUCUAGCUCCUUUGCTT (SEQ ID NO: 1610)	1.6
RAG3A-688	GGCCTGGTTATTCCTCTTG (SEQ ID NO: 727)	GGCCUGGUUAUUCCUCUUGTT (SEQ ID NO: 1169)	CAAGAGGAAUAACCAGGCCTT (SEQ ID NO: 1611)	1.6
RAG3A-728	GGAGGTCCAGCAGCTGTCT (SEQ ID NO: 728)	GGAGGUCCAGCAGCUGUCUTT (SEQ ID NO: 1170)	AGACAGCUGCUGGACCUCCTT (SEQ ID NO: 1612)	1.6
RAG3A-519	ACATACATGTGCCCCGCAC (SEQ ID NO: 729)	ACAUACAUGUGCCCCGCACTT (SEQ ID NO: 1171)	GUGCGGGGCACAUGUAUGUT (SEQ ID NO: 1613)	1.6
RAG3A-272	ACCCCACCAATCTTAAACA (SEQ ID NO: 730)	ACCCCACCAAUCUUAAACATT (SEQ ID NO: 1172)	UGUUUAAGAUUGGUGGGGUT (SEQ ID NO: 1614)	1.6
RAG3A-318	GGTATGATGTCCAGGGAAA (SEQ ID NO: 731)	GGUAUGAUGUCCAGGGAAATT (SEQ ID NO: 1173)	UUUCCCUGGACAUCAUACCT (SEQ ID NO: 1615)	1.6
RAG3A-1338	AAACCCTCACCACCCTCTC (SEQ ID NO: 732)	AAACCCUCACCACCCUCUCTT (SEQ ID NO: 1174)	GAGAGGGUGGUGAGGGUUUT (SEQ ID NO: 1616)	1.6
RAG3A-539	AACCCAGTGCACGTGTGCG (SEQ ID NO: 733)	AACCCAGUGCACGUGUGCGTT (SEQ ID NO: 1175)	CGCACACGUGCACUGGGUUT (SEQ ID NO: 1617)	1.6
RAG3A-826	AGGACAGAGACTGTGGGGA (SEQ ID NO: 734)	AGGACAGAGACUGUGGGGATT (SEQ ID NO: 1176)	UCCCCACAGUCUCUGUCCUTT (SEQ ID NO: 1618)	1.6
RAG3A-337	CTGTTGGATTTCAGCAGCA (SEQ ID NO: 735)	CUGUUGGAUUUCAGCAGCATT (SEQ ID NO: 1177)	UGCUGCUGAAAUCCAACAGTT (SEQ ID NO: 1619)	1.6

RAG3A-273	AACCCCACCAATCTTAAAC (SEQ ID NO: 736)	AACCCCACCAAUCUUAAACTT (SEQ ID NO: 1178)	GUUUAAGAUUGGUGGGGUUT T (SEQ ID NO: 1620)	1.6
RAG3A-478	CAAACCCTTTCCCCATAAC (SEQ ID NO: 737)	CAAACCCUUUCCCCAUAACTT (SEQ ID NO: 1179)	GUUAUGGGGAAAGGGUUUGT T (SEQ ID NO: 1621)	1.6
RAG3A-963	GACGGGAAAATTCCAGGAT (SEQ ID NO: 738)	GACGGGAAAAUUCCAGGAUTT (SEQ ID NO: 1180)	AUCCUGGAAUUUUCCCGUCT T (SEQ ID NO: 1622)	1.6
RAG3A-248	TCTGTGCTTCTTCCCCAGC (SEQ ID NO: 739)	UCUGUGCUUCUUCCCCAGCTT (SEQ ID NO: 1181)	GCUGGGGAAGAAGCACAGAT T (SEQ ID NO: 1623)	1.6
RAG3A-35	TCACCAGTGTCTGGTGGCT (SEQ ID NO: 740)	UCACCAGUGUCUGGUGGCUTT (SEQ ID NO: 1182)	AGCCACCAGACACUGGUGATT (SEQ ID NO: 1624)	1.5
RAG3A-613	CTGGGCACAGAGGTCTGTG (SEQ ID NO: 741)	CUGGGCACAGAGGUCUGUGTT (SEQ ID NO: 1183)	CACAGACCUCUGUGCCCAGTT (SEQ ID NO: 1625)	1.5
RAG3A-1141	CCCTTCCTTCACCCAAGGG (SEQ ID NO: 742)	CCCUUCCUUCACCCAAGGGTT (SEQ ID NO: 1184)	CCCUUGGGUGAAGGAAGGGT T (SEQ ID NO: 1626)	1.5
RAG3A-477	AAACCCTTTCCCCATAACA (SEQ ID NO: 743)	AAACCCUUUCCCCAUAACATT (SEQ ID NO: 1185)	UGUUAUGGGGAAAGGGUUUT T (SEQ ID NO: 1627)	1.5
RAG3A-634	CAGAACAAGCAAAGGAGG G (SEQ ID NO: 744)	CAGAACAAGCAAAGGAGGGTT (SEQ ID NO: 1186)	CCCUCCUUUGCUUGUUCUGT T (SEQ ID NO: 1628)	1.5
RAG3A-1280	GCTCCTCATTCTTGTGTTA (SEQ ID NO: 745)	GCUCCUCAUUCUUGUGUUATT (SEQ ID NO: 1187)	UAACACAAGAAUGAGGAGCT T (SEQ ID NO: 1629)	1.5
RAG3A-106	CCTCCCTGTCTCCTGTCTC	CCUCCCUGUCUCCUGUCUCTT	GAGACAGGAGACAGGGAGGT	1.5

2	(SEQ ID NO: 746)	(SEQ ID NO: 1188)	T (SEQ ID NO: 1630)	
RAG3A-778	TAGAGCCAGGGCCAAAGGA (SEQ ID NO: 747)	UAGAGCCAGGGCCAAAGGATT (SEQ ID NO: 1189)	UCCUUUGGCCCUGGCUCUATT (SEQ ID NO: 1631)	1.5
RAG3A-939	CCACACTTCTCAGCAGACA (SEQ ID NO: 748)	CCACACUUCUCAGCAGACATT (SEQ ID NO: 1190)	UGUCUGCUGAGAAGUGUGGTT (SEQ ID NO: 1632)	1.5
RAG3A-779	CTAGAGCCAGGGCCAAAGG (SEQ ID NO: 749)	CUAGAGCCAGGGCCAAAGGTT (SEQ ID NO: 1191)	CCUUUGGCCCUGGCUCUAGTT (SEQ ID NO: 1633)	1.5
RAG3A-803	GGGACTGGGAAGAAAGCAA (SEQ ID NO: 750)	GGGACUGGGAAGAAAGCAATT (SEQ ID NO: 1192)	UUGCUUUCUUCCCAGUCCCTT (SEQ ID NO: 1634)	1.5
RAG3A-1382	GTCCATCAGCCGATCTCCC (SEQ ID NO: 751)	GUCCAUCAGCCGAUCUCCCTT (SEQ ID NO: 1193)	GGGAGAUCGGCUGAUGGACTT (SEQ ID NO: 1635)	1.5
RAG3A-97	AGGAGTGGACCCTGGTCCA (SEQ ID NO: 752)	AGGAGUGGACCCUGGUCCATT (SEQ ID NO: 1194)	UGGACCAGGGUCCACUCCUTT (SEQ ID NO: 1636)	1.5
RAG3A-543	GCTTAACCCAGTGCACGTG (SEQ ID NO: 753)	GCUUAACCCAGUGCACGUGTT (SEQ ID NO: 1195)	CACGUGCACUGGGUUAAGCTT (SEQ ID NO: 1637)	1.5
RAG3A-556	CACCTAAGCTCAGGCTTAA (SEQ ID NO: 754)	CACCUAAGCUCAGGCUUAATT (SEQ ID NO: 1196)	UUAAGCCUGAGCUUAGGUGTT (SEQ ID NO: 1638)	1.5
RAG3A-60	GAGAAGGCGTCACTTCCGG (SEQ ID NO: 755)	GAGAAGGCGUCACUUCCGGTT (SEQ ID NO: 1197)	CCGGAAGUGACGCCUUCUCTT (SEQ ID NO: 1639)	1.5
RAG3A-647	TGGAAGACGGAGACAGAAC (SEQ ID NO: 756)	UGGAAGACGGAGACAGAACTT (SEQ ID NO: 1198)	GUUCUGUCUCCGUCUUCCATT (SEQ ID NO: 1640)	1.5

RAG3A-243	GCTTCTTCCCCAGCAACAC (SEQ ID NO: 757)	GCUUCUUCCCCAGCAACACTT (SEQ ID NO: 1199)	GUGUUGCUGGGGAAGAAGCT T (SEQ ID NO: 1641)	1.5
RAG3A-533	GTGCACGTGTGCGCACATA (SEQ ID NO: 758)	GUGCACGUGUGCGCACAUATT (SEQ ID NO: 1200)	UAUGUGCGCACACGUGCACT T (SEQ ID NO: 1642)	1.5
RAG3A-628	AAGCAAAGGAGGGCCCTG G (SEQ ID NO: 759)	AAGCAAAGGAGGGCCCUGGTT (SEQ ID NO: 1201)	CCAGGGCCCUCCUUUGCUUTT (SEQ ID NO: 1643)	1.5
RAG3A-849	AAGGTCAGGCCAGGAAGC C (SEQ ID NO: 760)	AAGGUCAGGCCAGGAAGCCTT (SEQ ID NO: 1202)	GGCUUCCUGGCCUGACCUUT T (SEQ ID NO: 1644)	1.5
RAG3A-130 7	CTGCCTCCCTACCTTCTCT (SEQ ID NO: 761)	CUGCCUCCCUACCUUCUCUTT (SEQ ID NO: 1203)	AGAGAAGGUAGGGAGGCAGT T (SEQ ID NO: 1645)	1.5
RAG3A-293	TTGGATAGCCAGGGAGTGA (SEQ ID NO: 762)	UUGGAUAGCCAGGGAGUGATT (SEQ ID NO: 1204)	UCACUCCCUGGCUAUCCAATT (SEQ ID NO: 1646)	1.5
RAG3A-128 5	AGGTCGCTCCTCATTCTTG (SEQ ID NO: 763)	AGGUCGCUCCUCAUUCUUGTT (SEQ ID NO: 1205)	CAAGAAUGAGGAGCGACCUT T (SEQ ID NO: 1647)	1.5
RAG3A-122 3	CCCTTCTGTGGAGTGACAG (SEQ ID NO: 764)	CCCUUCUGUGGAGUGACAGTT (SEQ ID NO: 1206)	CUGUCACUCCACAGAAGGGT T (SEQ ID NO: 1648)	1.5
RAG3A-117 7	CAGGCGCATTCGACAGTCC (SEQ ID NO: 765)	CAGGCGCAUUCGACAGUCCTT (SEQ ID NO: 1207)	GGACUGUCGAAUGCGCCUGT T (SEQ ID NO: 1649)	1.5
RAG3A-226	ACAAATGTCCTGCCAGATT (SEQ ID NO: 766)	ACAAAUGUCCUGCCAGAUUTT (SEQ ID NO: 1208)	AAUCUGGCAGGACAUUUGUT T (SEQ ID NO: 1650)	1.5
RAG3A-109	CAGCCTCCTTTCTCTTGGT	CAGCCUCCUUUCUCUUGGUTT	ACCAAGAGAAAGGAGGCUGT	1.5

7	(SEQ ID NO: 767)	(SEQ ID NO: 1209)	T (SEQ ID NO: 1651)	
RAG3A-1188	TAACTTATCCTCAGGCGCA (SEQ ID NO: 768)	UAACUUAUCCUCAGGCGCATT (SEQ ID NO: 1210)	UGCGCCUGAGGAUAAGUUAT T (SEQ ID NO: 1652)	1.5
RAG3A-593	GTGTAGCCATCTAAGCCAC (SEQ ID NO: 769)	GUGUAGCCAUCUAAGCCACTT (SEQ ID NO: 1211)	GUGGCUUAGAUGGCUACACT T (SEQ ID NO: 1653)	1.5
RAG3A-670	GTCACATGTGGAACGGTAG (SEQ ID NO: 770)	GUCACAUGUGGAACGGUAGTT (SEQ ID NO: 1212)	CUACCGUUCCACAUGUGACT T (SEQ ID NO: 1654)	1.5
RAG3A-503	CACCTGACAGTCCACTCAA (SEQ ID NO: 771)	CACCUGACAGUCCACUCAATT (SEQ ID NO: 1213)	UUGAGUGGACUGUCAGGUGT T (SEQ ID NO: 1655)	1.5
RAG3A-1167	CGACAGTCCCCTCTTGCTT (SEQ ID NO: 772)	CGACAGUCCCCUCUUGCUUTT (SEQ ID NO: 1214)	AAGCAAGAGGGGACUGUCGT T (SEQ ID NO: 1656)	1.5
RAG3A-583	CTAAGCCACTGGACCCCAG (SEQ ID NO: 773)	CUAAGCCACUGGACCCCAGTT (SEQ ID NO: 1215)	CUGGGGUCCAGUGGCUUAGT T (SEQ ID NO: 1657)	1.5
RAG3A-706	CTAAGACAGGGACACATGG (SEQ ID NO: 774)	CUAAGACAGGGACACAUGGTT (SEQ ID NO: 1216)	CCAUGUGUCCCUGUCUUAGT T (SEQ ID NO: 1658)	1.5
RAG3A-983	GGAGACATCTCGTCTGGCT (SEQ ID NO: 775)	GGAGACAUCUCGUCUGGCUTT (SEQ ID NO: 1217)	AGCCAGACGAGAUGUCUCCT T (SEQ ID NO: 1659)	1.5
RAG3A-718	CAGCTGTCTTTCCTAAGAC (SEQ ID NO: 776)	CAGCUGUCUUUCCUAAGACTT (SEQ ID NO: 1218)	GUCUUAGGAAAGACAGCUGT T (SEQ ID NO: 1660)	1.5
RAG3A-378	CCCTAGGGGATTACAGAAA (SEQ ID NO: 777)	CCCUAGGGGAUUACAGAAATT (SEQ ID NO: 1219)	UUUCUGUAAUCCCCUAGGGT T (SEQ ID NO: 1661)	1.5

RAG3A-1095	GCCTCCTTTCTCTTGGTTC (SEQ ID NO: 778)	GCCUCCUUUCUCUUGGUUCTT (SEQ ID NO: 1220)	GAACCAAGAGAAAGGAGGCTT (SEQ ID NO: 1662)	1.4
RAG3A-698	GGGACACATGGGCCTGGTT (SEQ ID NO: 779)	GGGACACAUGGGCCUGGUUTT (SEQ ID NO: 1221)	AACCAGGCCCAUGUGUCCCTT (SEQ ID NO: 1663)	1.4
RAG3A-277	TGAAAACCCCACCAATCTT (SEQ ID NO: 780)	UGAAAACCCCACCAAUCUUTT (SEQ ID NO: 1222)	AAGAUUGGUGGGGUUUUCATT (SEQ ID NO: 1664)	1.4
RAG3A-644	AAGACGGAGACAGAACAAG (SEQ ID NO: 781)	AAGACGGAGACAGAACAAGTT (SEQ ID NO: 1223)	CUUGUUCUGUCUCCGUCUUTT (SEQ ID NO: 1665)	1.4
RAG3A-941	GGCCACACTTCTCAGCAGA (SEQ ID NO: 782)	GGCCACACUUCUCAGCAGATT (SEQ ID NO: 1224)	UCUGCUGAGAAGUGUGGCCTT (SEQ ID NO: 1666)	1.4
RAG3A-794	AAGAAAGCAAAGGAGCTAG (SEQ ID NO: 783)	AAGAAAGCAAAGGAGCUAGTT (SEQ ID NO: 1225)	CUAGCUCCUUUGCUUUCUUTT (SEQ ID NO: 1667)	1.4
RAG3A-890	GAGCCTGAGGAAGTTCTGG (SEQ ID NO: 784)	GAGCCUGAGGAAGUUCUGGTT (SEQ ID NO: 1226)	CCAGAACUUCCUCAGGCUCTT (SEQ ID NO: 1668)	1.4
RAG3A-1310	AGCCTGCCTCCCTACCTTC (SEQ ID NO: 785)	AGCCUGCCUCCCUACCUUCTT (SEQ ID NO: 1227)	GAAGGUAGGGAGGCAGGCUTT (SEQ ID NO: 1669)	1.4
RAG3A-27	GTCTGGTGGCTCCCTTCTC (SEQ ID NO: 786)	GUCUGGUGGCUCCCUUCUCTT (SEQ ID NO: 1228)	GAGAAGGGAGCCACCAGACTT (SEQ ID NO: 1670)	1.4
RAG3A-38	CCTTCACCAGTGTCTGGTG (SEQ ID NO: 787)	CCUUCACCAGUGUCUGGUGTT (SEQ ID NO: 1229)	CACCAGACACUGGUGAAGGTT (SEQ ID NO: 1671)	1.4
RAG3A-532	TGCACGTGTGCGCACATAC	UGCACGUGUGCGCACAUACTT	GUAUGUGCGCACACGUGCAT	1.4

	(SEQ ID NO: 788)	(SEQ ID NO: 1230)	T (SEQ ID NO: 1672)	
RAG3A-1023	TATCCTCCCAGCTATCCCA (SEQ ID NO: 789)	UAUCCUCCCAGCUAUCCCATT (SEQ ID NO: 1231)	UGGGAUAGCUGGGAGGAUATT (SEQ ID NO: 1673)	1.4
RAG3A-797	GGGAAGAAAGCAAAGGAGC (SEQ ID NO: 790)	GGGAAGAAAGCAAAGGAGCTT (SEQ ID NO: 1232)	GCUCCUUUGCUUUCUUCCCTT (SEQ ID NO: 1674)	1.4
RAG3A-399	GGGGAATGACAAGATAGGA (SEQ ID NO: 791)	GGGGAAUGACAAGAUAGGATT (SEQ ID NO: 1233)	UCCUAUCUUGUCAUUCCCCTT (SEQ ID NO: 1675)	1.4
RAG3A-945	TCTAGGCCACACTTCTCAG (SEQ ID NO: 792)	UCUAGGCCACACUUCUCAGTT (SEQ ID NO: 1234)	CUGAGAAGUGUGGCCUAGATT (SEQ ID NO: 1676)	1.4
RAG3A-344	AAGCATCCTGTTGGATTTC (SEQ ID NO: 793)	AAGCAUCCUGUUGGAUUUCTT (SEQ ID NO: 1235)	GAAAUCCAACAGGAUGCUUTT (SEQ ID NO: 1677)	1.4
RAG3A-1255	ACAGGGACCTAGCCAGAAA (SEQ ID NO: 794)	ACAGGGACCUAGCCAGAAATT (SEQ ID NO: 1236)	UUUCUGGCUAGGUCCCUGUTT (SEQ ID NO: 1678)	1.4
RAG3A-524	TGCGCACATACATGTGCCC (SEQ ID NO: 795)	UGCGCACAUACAUGUGCCCTT (SEQ ID NO: 1237)	GGGCACAUGUAUGUGCGCATT (SEQ ID NO: 1679)	1.4
RAG3A-244	TGCTTCTTCCCCAGCAACA (SEQ ID NO: 796)	UGCUUCUUCCCCAGCAACATT (SEQ ID NO: 1238)	UGUUGCUGGGGAAGAAGCATT (SEQ ID NO: 1680)	1.4
RAG3A-340	ATCCTGTTGGATTTCAGCA (SEQ ID NO: 797)	AUCCUGUUGGAUUUCAGCATT (SEQ ID NO: 1239)	UGCUGAAAUCCAACAGGAUTT (SEQ ID NO: 1681)	1.4
RAG3A-687	GCCTGGTTATTCCTCTTGT (SEQ ID NO: 798)	GCCUGGUUAUUCCUCUUGUTT (SEQ ID NO: 1240)	ACAAGAGGAAUAACCAGGCTT (SEQ ID NO: 1682)	1.4

RAG3A-568	CCAGCAGACGAGCACCTAA (SEQ ID NO: 799)	CCAGCAGACGAGCACCUAATT (SEQ ID NO: 1241)	UUAGGUGCUCGUCUGCUGGTT (SEQ ID NO: 1683)	1.4
RAG3A-804	TGGGACTGGGAAGAAAGCA (SEQ ID NO: 800)	UGGGACUGGGAAGAAAGCATT (SEQ ID NO: 1242)	UGCUUUCUUCCCAGUCCCATT (SEQ ID NO: 1684)	1.4
RAG3A-496	CAGTCCACTCAACCCGTCC (SEQ ID NO: 801)	CAGUCCACUCAACCCGUCCTT (SEQ ID NO: 1243)	GGACGGGUUGAGUGGACUGTT (SEQ ID NO: 1685)	1.4
RAG3A-810	GGAGACTGGGACTGGGAAG (SEQ ID NO: 802)	GGAGACUGGGACUGGGAAGTT (SEQ ID NO: 1244)	CUUCCCAGUCCCAGUCUCCTT (SEQ ID NO: 1686)	1.4
RAG3A-356	AAGCAGGAAAGCAAGCATC (SEQ ID NO: 803)	AAGCAGGAAAGCAAGCAUCTT (SEQ ID NO: 1245)	GAUGCUUGCUUUCCUGCUUTT (SEQ ID NO: 1687)	1.4
RAG3A-1248	CCTAGCCAGAAACCGGCAG (SEQ ID NO: 804)	CCUAGCCAGAAACCGGCAGTT (SEQ ID NO: 1246)	CUGCCGGUUUCUGGCUAGGTT (SEQ ID NO: 1688)	1.4
RAG3A-1015	CAGCTATCCCAGCACCCTC (SEQ ID NO: 805)	CAGCUAUCCCAGCACCCUCTT (SEQ ID NO: 1247)	GAGGGUGCUGGGAUAGCUGTT (SEQ ID NO: 1689)	1.4
RAG3A-645	GAAGACGGAGACAGAACAA (SEQ ID NO: 806)	GAAGACGGAGACAGAACAATT (SEQ ID NO: 1248)	UUGUUCUGUCUCCGUCUUCTT (SEQ ID NO: 1690)	1.4
RAG3A-517	ATACATGTGCCCCGCACCT (SEQ ID NO: 807)	AUACAUGUGCCCCGCACCUTT (SEQ ID NO: 1249)	AGGUGCGGGGCACAUGUAUTT (SEQ ID NO: 1691)	1.4
RAG3A-194	AACTTCTGCTCCTGTCCCC (SEQ ID NO: 808)	AACUUCUGCUCCUGUCCCCTT (SEQ ID NO: 1250)	GGGGACAGGAGCAGAAGUUTT (SEQ ID NO: 1692)	1.4
RAG3A-927	GCAGACATGCCCATCCTTG	GCAGACAUGCCCAUCCUUGTT	CAAGGAUGGGCAUGUCUGCT	1.4

	(SEQ ID NO: 809)	(SEQ ID NO: 1251)	T (SEQ ID NO: 1693)	
RAG3A-271	CCCCACCAATCTTAAACAA (SEQ ID NO: 810)	CCCCACCAAUCUUAAACAATT (SEQ ID NO: 1252)	UUGUUUAAGAUUGGUGGGGT T (SEQ ID NO: 1694)	1.4
RAG3A-398	GGGAATGACAAGATAGGAC (SEQ ID NO: 811)	GGGAAUGACAAGAUAGGACTT (SEQ ID NO: 1253)	GUCCUAUCUUGUCAUUCCCT T (SEQ ID NO: 1695)	1.4
RAG3A-230	CAACACAAATGTCCTGCCA (SEQ ID NO: 812)	CAACACAAAUGUCCUGCCATT (SEQ ID NO: 1254)	UGGCAGGACAUUUGUGUUGT T (SEQ ID NO: 1696)	1.4
RAG3A-1104	CCACTCCCAGCCTCCTTTC (SEQ ID NO: 813)	CCACUCCCAGCCUCCUUUCTT (SEQ ID NO: 1255)	GAAAGGAGGCUGGGAGUGGT T (SEQ ID NO: 1697)	1.4
RAG3A-1254	CAGGGACCTAGCCAGAAAC (SEQ ID NO: 814)	CAGGGACCUAGCCAGAAACTT (SEQ ID NO: 1256)	GUUUCUGGCUAGGUCCCUGT T (SEQ ID NO: 1698)	1.4
RAG3A-288	TAGCCAGGGAGTGAAAACC (SEQ ID NO: 815)	UAGCCAGGGAGUGAAAACCTT (SEQ ID NO: 1257)	GGUUUUCACUCCCUGGCUATT (SEQ ID NO: 1699)	1.4
RAG3A-837	GGAAGCCCCTGAGGACAG A (SEQ ID NO: 816)	GGAAGCCCCUGAGGACAGATT (SEQ ID NO: 1258)	UCUGUCCUCAGGGGCUUCCT T (SEQ ID NO: 1700)	1.4
RAG3A-935	ACTTCTCAGCAGACATGCC (SEQ ID NO: 817)	ACUUCUCAGCAGACAUGCCTT (SEQ ID NO: 1259)	GGCAUGUCUGCUGAGAAGUT T (SEQ ID NO: 1701)	1.4
RAG3A-476	AACCCTTTCCCCATAACAC (SEQ ID NO: 818)	AACCCUUUCCCCAUAACACTT (SEQ ID NO: 1260)	GUGUUAUGGGGAAAGGGUUT T (SEQ ID NO: 1702)	1.4
RAG3A-589	AGCCATCTAAGCCACTGGA (SEQ ID NO: 819)	AGCCAUCUAAGCCACUGGATT (SEQ ID NO: 1261)	UCCAGUGGCUUAGAUGGCUT T (SEQ ID NO: 1703)	1.4

RAG3A-1207	CAGTATCTCCCTCTCATTG (SEQ ID NO: 820)	CAGUAUCUCCCUCUCAUUGTT (SEQ ID NO: 1262)	CAAUGAGAGGGAGAUACUGTT (SEQ ID NO: 1704)	1.4
RAG3A-1284	GGTCGCTCCTCATTCTTGT (SEQ ID NO: 821)	GGUCGCUCCUCAUUCUUGUTT (SEQ ID NO: 1263)	ACAAGAAUGAGGAGCGACCTT (SEQ ID NO: 1705)	1.4
RAG3A-956	AAATTCCAGGATCTAGGCC (SEQ ID NO: 822)	AAAUUCCAGGAUCUAGGCCTT (SEQ ID NO: 1264)	GGCCUAGAUCCUGGAAUUUTT (SEQ ID NO: 1706)	1.4
RAG3A-557	GCACCTAAGCTCAGGCTTA (SEQ ID NO: 823)	GCACCUAAGCUCAGGCUUATT (SEQ ID NO: 1265)	UAAGCCUGAGCUUAGGUGCTT (SEQ ID NO: 1707)	1.4
RAG3A-500	CTGACAGTCCACTCAACCC (SEQ ID NO: 824)	CUGACAGUCCACUCAACCCTT (SEQ ID NO: 1266)	GGGUUGAGUGGACUGUCAGTT (SEQ ID NO: 1708)	1.4
RAG3A-1208	ACAGTATCTCCCTCTCATT (SEQ ID NO: 825)	ACAGUAUCUCCCUCUCAUUTT (SEQ ID NO: 1267)	AAUGAGAGGGAGAUACUGUTT (SEQ ID NO: 1709)	1.4
RAG3A-686	CCTGGTTATTCCTCTTGTC (SEQ ID NO: 826)	CCUGGUUAUUCCUCUUGUCTT (SEQ ID NO: 1268)	GACAAGAGGAAUAACCAGGTT (SEQ ID NO: 1710)	1.4
RAG3A-1168	TCGACAGTCCCCTCTTGCT (SEQ ID NO: 827)	UCGACAGUCCCCUCUUGCUTT (SEQ ID NO: 1269)	AGCAAGAGGGGACUGUCGATT (SEQ ID NO: 1711)	1.4
RAG3A-218	CCTGCCAGATTCCTCCTGG (SEQ ID NO: 828)	CCUGCCAGAUUCCUCCUGGTT (SEQ ID NO: 1270)	CCAGGAGGAAUCUGGCAGGTT (SEQ ID NO: 1712)	1.4
RAG3A-835	AAGCCCCTGAGGACAGAGA (SEQ ID NO: 829)	AAGCCCCUGAGGACAGAGATT (SEQ ID NO: 1271)	UCUCUGUCCUCAGGGGCUUTT (SEQ ID NO: 1713)	1.4
RAG3A-291	GGATAGCCAGGGAGTGAAA	GGAUAGCCAGGGAGUGAAATT	UUUCACUCCCUGGCUAUCCTT	1.3

	(SEQ ID NO: 830)	(SEQ ID NO: 1272)	(SEQ ID NO: 1714)	
RAG3A-1222	CCTTCTGTGGAGTGACAGT (SEQ ID NO: 831)	CCUUCUGUGGAGUGACAGUTT (SEQ ID NO: 1273)	ACUGUCACUCCACAGAAGGT T (SEQ ID NO: 1715)	1.3
RAG3A-276	GAAAACCCCACCAATCTTA (SEQ ID NO: 832)	GAAAACCCCACCAAUCUUATT (SEQ ID NO: 1274)	UAAGAUUGGUGGGGUUUUCT T (SEQ ID NO: 1716)	1.3
RAG3A-156	CATGTCCAGGAAAAGATGG (SEQ ID NO: 833)	CAUGUCCAGGAAAAGAUGGTT (SEQ ID NO: 1275)	CCAUCUUUUCCUGGACAUGT T (SEQ ID NO: 1717)	1.3
RAG3A-937	ACACTTCTCAGCAGACATG (SEQ ID NO: 834)	ACACUUCUCAGCAGACAUGTT (SEQ ID NO: 1276)	CAUGUCUGCUGAGAAGUGUT T (SEQ ID NO: 1718)	1.3
RAG3A-1262	ACCCAGGACAGGGACCTAG (SEQ ID NO: 835)	ACCCAGGACAGGGACCUAGTT (SEQ ID NO: 1277)	CUAGGUCCCUGUCCUGGGUT T (SEQ ID NO: 1719)	1.3
RAG3A-1139	CTTCCTTCACCCAAGGGAC (SEQ ID NO: 836)	CUUCCUUCACCCAAGGGACTT (SEQ ID NO: 1278)	GUCCCUUGGGUGAAGGAAGT T (SEQ ID NO: 1720)	1.3
RAG3A-535	CAGTGCACGTGTGCGCACA (SEQ ID NO: 837)	CAGUGCACGUGUGCGCACATT (SEQ ID NO: 1279)	UGUGCGCACACGUGCACUGT T (SEQ ID NO: 1721)	1.3
RAG3A-719	GCAGCTGTCTTTCCTAAGA (SEQ ID NO: 838)	GCAGCUGUCUUUCCUAAGATT (SEQ ID NO: 1280)	UCUUAGGAAAGACAGCUGCT T (SEQ ID NO: 1722)	1.3
RAG3A-726	AGGTCCAGCAGCTGTCTTT (SEQ ID NO: 839)	AGGUCCAGCAGCUGUCUUUTT (SEQ ID NO: 1281)	AAAGACAGCUGCUGGACCUT T (SEQ ID NO: 1723)	1.3
RAG3A-384	AGGACTCCCTAGGGGATTA (SEQ ID NO: 840)	AGGACUCCCUAGGGGAUUATT (SEQ ID NO: 1282)	UAAUCCCCUAGGGAGUCCUT T (SEQ ID NO: 1724)	1.3

RAG3A-834	AGCCCCTGAGGACAGAGAC (SEQ ID NO: 841)	AGCCCCUGAGGACAGAGACTT (SEQ ID NO: 1283)	GUCUCUGUCCUCAGGGGCUTT (SEQ ID NO: 1725)	1.3
RAG3A-562	GACGAGCACCTAAGCTCAG (SEQ ID NO: 842)	GACGAGCACCUAAGCUCAGTT (SEQ ID NO: 1284)	CUGAGCUUAGGUGCUCGUCTT (SEQ ID NO: 1726)	1.3
RAG3A-940	GCCACACTTCTCAGCAGAC (SEQ ID NO: 843)	GCCACACUUCUCAGCAGACTT (SEQ ID NO: 1285)	GUCUGCUGAGAAGUGUGGCTT (SEQ ID NO: 1727)	1.3
RAG3A-632	GAACAAGCAAAGGAGGGCC (SEQ ID NO: 844)	GAACAAGCAAAGGAGGGCCTT (SEQ ID NO: 1286)	GGCCCUCCUUUGCUUGUUCTT (SEQ ID NO: 1728)	1.3
RAG3A-746	CAGGGAGGTATTTGCGGGG (SEQ ID NO: 845)	CAGGGAGGUAUUUGCGGGGTT (SEQ ID NO: 1287)	CCCCGCAAAUACCUCCCUGTT (SEQ ID NO: 1729)	1.3
RAG3A-1309	GCCTGCCTCCCTACCTTCT (SEQ ID NO: 846)	GCCUGCCUCCCUACCUUCUTT (SEQ ID NO: 1288)	AGAAGGUAGGGAGGCAGGCTT (SEQ ID NO: 1730)	1.3
RAG3A-780	GCTAGAGCCAGGGCCAAAG (SEQ ID NO: 847)	GCUAGAGCCAGGGCCAAAGTT (SEQ ID NO: 1289)	CUUUGGCCCUGGCUCUAGCTT (SEQ ID NO: 1731)	1.3
RAG3A-693	ACATGGGCCTGGTTATTCC (SEQ ID NO: 848)	ACAUGGGCCUGGUUAUUCCTT (SEQ ID NO: 1290)	GGAAUAACCAGGCCCAUGUTT (SEQ ID NO: 1732)	1.3
RAG3A-636	GACAGAACAAGCAAAGGAG (SEQ ID NO: 849)	GACAGAACAAGCAAAGGAGTT (SEQ ID NO: 1291)	CUCCUUUGCUUGUUCUGUCTT (SEQ ID NO: 1733)	1.3
RAG3A-258	AAACAAGACCTCTGTGCTT (SEQ ID NO: 850)	AAACAAGACCUCUGUGCUUTT (SEQ ID NO: 1292)	AAGCACAGAGGUCUUGUUUTT (SEQ ID NO: 1734)	1.3
RAG3A-102	ATCCTCCCAGCTATCCCAG	AUCCUCCCAGCUAUCCCAGTT	CUGGGAUAGCUGGGAGGAUT	1.3

2	(SEQ ID NO: 851)	(SEQ ID NO: 1293)	T (SEQ ID NO: 1735)	
RAG3A-381	ACTCCCTAGGGGATTACAG (SEQ ID NO: 852)	ACUCCCUAGGGGAUUACAGTT (SEQ ID NO: 1294)	CUGUAAUCCCCUAGGGAGUT T (SEQ ID NO: 1736)	1.3
RAG3A-379	TCCCTAGGGGATTACAGAA (SEQ ID NO: 853)	UCCCUAGGGGAUUACAGAATT (SEQ ID NO: 1295)	UUCUGUAAUCCCCUAGGGAT T (SEQ ID NO: 1737)	1.3
RAG3A-663	GTGGAACGGTAGGAGATGG (SEQ ID NO: 854)	GUGGAACGGUAGGAGAUGGTT (SEQ ID NO: 1296)	CCAUCUCCUACCGUUCCACTT (SEQ ID NO: 1738)	1.3
RAG3A-1099	CCCAGCCTCCTTTCTCTTG (SEQ ID NO: 855)	CCCAGCCUCCUUUCUCUUGTT (SEQ ID NO: 1297)	CAAGAGAAAGGAGGCUGGGT T (SEQ ID NO: 1739)	1.3
RAG3A-855	GGGATCAAGGTCAGGCCAG (SEQ ID NO: 856)	GGGAUCAAGGUCAGGCCAGTT (SEQ ID NO: 1298)	CUGGCCUGACCUUGAUCCCTT (SEQ ID NO: 1740)	1.3
RAG3A-1279	CTCCTCATTCTTGTGTTAC (SEQ ID NO: 857)	CUCCUCAUUCUUGUGUUACTT (SEQ ID NO: 1299)	GUAACACAAGAAUGAGGAGT T (SEQ ID NO: 1741)	1.3
RAG3A-34	CACCAGTGTCTGGTGGCTC (SEQ ID NO: 858)	CACCAGUGUCUGGUGGCUCTT (SEQ ID NO: 1300)	GAGCCACCAGACACUGGUGT T (SEQ ID NO: 1742)	1.3
RAG3A-633	AGAACAAGCAAAGGAGGG C (SEQ ID NO: 859)	AGAACAAGCAAAGGAGGGCTT (SEQ ID NO: 1301)	GCCCUCCUUUGCUUGUUCUT T (SEQ ID NO: 1743)	1.3
RAG3A-453	CCATAACAGGAGATTTCTC (SEQ ID NO: 860)	CCAUAACAGGAGAUUUCUCTT (SEQ ID NO: 1302)	GAGAAAUCUCCUGUUAUGGT T (SEQ ID NO: 1744)	1.3
RAG3A-246	TGTGCTTCTTCCCCAGCAA (SEQ ID NO: 861)	UGUGCUUCUUCCCCAGCAATT (SEQ ID NO: 1303)	UUGCUGGGGAAGAAGCACAT T (SEQ ID NO: 1745)	1.3

RAG3A-592	TGTAGCCATCTAAGCCACT (SEQ ID NO: 862)	UGUAGCCAUCUAAGCCACUTT (SEQ ID NO: 1304)	AGUGGCUUAGAUGGCUACATT (SEQ ID NO: 1746)	1.3
RAG3A-270	CCCACCAATCTTAAACAAG (SEQ ID NO: 863)	CCCACCAAUCUUAAACAAGTT (SEQ ID NO: 1305)	CUUGUUUAAGAUUGGUGGGTT (SEQ ID NO: 1747)	1.3
RAG3A-630	ACAAGCAAAGGAGGGCCCT (SEQ ID NO: 864)	ACAAGCAAAGGAGGGCCCUTT (SEQ ID NO: 1306)	AGGGCCCUCCUUUGCUUGUTT (SEQ ID NO: 1748)	1.3
RAG3A-685	CTGGTTATTCCTCTTGTCA (SEQ ID NO: 865)	CUGGUUAUUCCUCUUGUCATT (SEQ ID NO: 1307)	UGACAAGAGGAAUAACCAGTT (SEQ ID NO: 1749)	1.3
RAG3A-1103	CACTCCCAGCCTCCTTTCT (SEQ ID NO: 866)	CACUCCCAGCCUCCUUUCUTT (SEQ ID NO: 1308)	AGAAAGGAGGCUGGGAGUGTT (SEQ ID NO: 1750)	1.3
RAG3A-1065	CTGCCTCCCTGTCTCCTGT (SEQ ID NO: 867)	CUGCCUCCCUGUCUCCUGUTT (SEQ ID NO: 1309)	ACAGGAGACAGGGAGGCAGTT (SEQ ID NO: 1751)	1.3
RAG3A-523	GCGCACATACATGTGCCCC (SEQ ID NO: 868)	GCGCACAUACAUGUGCCCCTT (SEQ ID NO: 1310)	GGGGCACAUGUAUGUGCGCTT (SEQ ID NO: 1752)	1.3
RAG3A-590	TAGCCATCTAAGCCACTGG (SEQ ID NO: 869)	UAGCCAUCUAAGCCACUGGTT (SEQ ID NO: 1311)	CCAGUGGCUUAGAUGGCUATT (SEQ ID NO: 1753)	1.3
RAG3A-505	CGCACCTGACAGTCCACTC (SEQ ID NO: 870)	CGCACCUGACAGUCCACUCTT (SEQ ID NO: 1312)	GAGUGGACUGUCAGGUGCGTT (SEQ ID NO: 1754)	1.3
RAG3A-1247	CTAGCCAGAAACCGGCAGC (SEQ ID NO: 871)	CUAGCCAGAAACCGGCAGCTT (SEQ ID NO: 1313)	GCUGCCGGUUUCUGGCUAGTT (SEQ ID NO: 1755)	1.3
RAG3A-128	CGCTCCTCATTCTTGTGTT	CGCUCCUCAUUCUUGUGUUTT	AACACAAGAAUGAGGAGCGT	1.3

1	(SEQ ID NO: 872)	(SEQ ID NO: 1314)	T (SEQ ID NO: 1756)	
RAG3A-747	GCAGGGAGGTATTTGCGGG (SEQ ID NO: 873)	GCAGGGAGGUAUUUGCGGGTT (SEQ ID NO: 1315)	CCCGCAAAUACCUCCCUGCTT (SEQ ID NO: 1757)	1.3
RAG3A-1220	TTCTGTGGAGTGACAGTAT (SEQ ID NO: 874)	UUCUGUGGAGUGACAGUAUTT (SEQ ID NO: 1316)	AUACUGUCACUCCACAGAATT (SEQ ID NO: 1758)	1.3
RAG3A-1268	TGTGTTACCCAGGACAGGG (SEQ ID NO: 875)	UGUGUUACCCAGGACAGGGTT (SEQ ID NO: 1317)	CCCUGUCCUGGGUAACACATT (SEQ ID NO: 1759)	1.3
RAG3A-782	GAGCTAGAGCCAGGGCCAA (SEQ ID NO: 876)	GAGCUAGAGCCAGGGCCAATT (SEQ ID NO: 1318)	UUGGCCCUGGCUCUAGCUCT T (SEQ ID NO: 1760)	1.3
RAG3A-107	GTGTGGGTGGAGGAGTGG A (SEQ ID NO: 877)	GUGUGGGUGGAGGAGUGGATT (SEQ ID NO: 1319)	UCCACUCCUCCACCCACACTT (SEQ ID NO: 1761)	1.3
RAG3A-923	ACATGCCCATCCTTGGGGA (SEQ ID NO: 878)	ACAUGCCCAUCCUUGGGGATT (SEQ ID NO: 1320)	UCCCCAAGGAUGGGCAUGUT T (SEQ ID NO: 1762)	1.3
RAG3A-349	AAAGCAAGCATCCTGTTGG (SEQ ID NO: 879)	AAAGCAAGCAUCCUGUUGGTT (SEQ ID NO: 1321)	CCAACAGGAUGCUUGCUUUT T (SEQ ID NO: 1763)	1.3
RAG3A-1085	TCTTGGTTCCCTGGTCATG (SEQ ID NO: 880)	UCUUGGUUCCCUGGUCAUGTT (SEQ ID NO: 1322)	CAUGACCAGGGAACCAAGAT T (SEQ ID NO: 1764)	1.3
RAG3A-432	ATGTGGGCAATATCCGTGT (SEQ ID NO: 881)	AUGUGGGCAAUAUCCGUGUTT (SEQ ID NO: 1323)	ACACGGAUAUUGCCCACAUT T (SEQ ID NO: 1765)	1.3
RAG3A-129	ATCCAAATCTTCTCCGTGG (SEQ ID NO: 882)	AUCCAAAUCUUCUCCGUGGTT (SEQ ID NO: 1324)	CCACGGAGAAGAUUUGGAUT T (SEQ ID NO: 1766)	1.3

RAG3A-830	CCTGAGGACAGAGACTGTG (SEQ ID NO: 883)	CCUGAGGACAGAGACUGUGTT (SEQ ID NO: 1325)	CACAGUCUCUGUCCUCAGGTT (SEQ ID NO: 1767)	1.3
RAG3A-74	GGGGCTCCAGGGAAGAGAA (SEQ ID NO: 884)	GGGGCUCCAGGGAAGAGAATT (SEQ ID NO: 1326)	UUCUCUUCCCUGGAGCCCCTT (SEQ ID NO: 1768)	1.3
RAG3A-856	TGGGATCAAGGTCAGGCCA (SEQ ID NO: 885)	UGGGAUCAAGGUCAGGCCATT (SEQ ID NO: 1327)	UGGCCUGACCUUGAUCCCATT (SEQ ID NO: 1769)	1.3
RAG3A-435	CTCATGTGGGCAATATCCG (SEQ ID NO: 886)	CUCAUGUGGGCAAUAUCCGTT (SEQ ID NO: 1328)	CGGAUAUUGCCCACAUGAGTT (SEQ ID NO: 1770)	1.3
RAG3A-564	CAGACGAGCACCTAAGCTC (SEQ ID NO: 887)	CAGACGAGCACCUAAGCUCTT (SEQ ID NO: 1329)	GAGCUUAGGUGCUCGUCUGTT (SEQ ID NO: 1771)	1.3
RAG3A-1251	GGACCTAGCCAGAAACCGG (SEQ ID NO: 888)	GGACCUAGCCAGAAACCGGTT (SEQ ID NO: 1330)	CCGGUUUCUGGCUAGGUCCTT (SEQ ID NO: 1772)	1.3
RAG3A-1291	TCTCTGAGGTCGCTCCTCA (SEQ ID NO: 889)	UCUCUGAGGUCGCUCCUCATT (SEQ ID NO: 1331)	UGAGGAGCGACCUCAGAGATT (SEQ ID NO: 1773)	1.3
RAG3A-781	AGCTAGAGCCAGGGCCAAA (SEQ ID NO: 890)	AGCUAGAGCCAGGGCCAAATT (SEQ ID NO: 1332)	UUUGGCCCUGGCUCUAGCUTT (SEQ ID NO: 1774)	1.3
RAG3A-261	CTTAAACAAGACCTCTGTG	CUUAAACAAGACCUCUGUGTT	CACAGAGGUCUUGUUUAAGT	1.3

	(SEQ ID NO: 891)	(SEQ ID NO: 1333)	T (SEQ ID NO: 1775)	
RAG3A-1098	CCAGCCTCCTTTCTCTTGG (SEQ ID NO: 892)	CCAGCCUCCUUUCUCUUGGTT (SEQ ID NO: 1334)	CCAAGAGAAAGGAGGCUGGTT (SEQ ID NO: 1776)	1.3
RAG3A-565	GCAGACGAGCACCTAAGCT (SEQ ID NO: 893)	GCAGACGAGCACCUAAGCUTT (SEQ ID NO: 1335)	AGCUUAGGUGCUCGUCUGCTT (SEQ ID NO: 1777)	1.2
RAG3A-930	TCAGCAGACATGCCCATCC (SEQ ID NO: 894)	UCAGCAGACAUGCCCAUCCTT (SEQ ID NO: 1336)	GGAUGGGCAUGUCUGCUGATT (SEQ ID NO: 1778)	1.2
RAG3A-422	TATCCGTGTTCCCACTTCG (SEQ ID NO: 895)	UAUCCGUGUUCCCACUUCGTT (SEQ ID NO: 1337)	CGAAGUGGGAACACGGAUATT (SEQ ID NO: 1779)	1.2
RAG3A-516	TACATGTGCCCCGCACCTG (SEQ ID NO: 896)	UACAUGUGCCCCGCACCUGTT (SEQ ID NO: 1338)	CAGGUGCGGGGCACAUGUATT (SEQ ID NO: 1780)	1.2
RAG3A-1190	TGTAACTTATCCTCAGGCG (SEQ ID NO: 897)	UGUAACUUAUCCUCAGGCGTT (SEQ ID NO: 1339)	CGCCUGAGGAUAAGUUACATT (SEQ ID NO: 1781)	1.2
RAG3A-360	AGAAAAGCAGGAAAGCAAG	AGAAAAGCAGGAAAGCAAGTT	CUUGCUUUCCUGCUUUUCUTT	1.2

	(SEQ ID NO: 898)	(SEQ ID NO: 1340)	(SEQ ID NO: 1782)	
RAG3A-126	CAAATCTTCTCCGTGGTGT (SEQ ID NO: 899)	CAAAUCUUCUCCGUGGUGUTT (SEQ ID NO: 1341)	ACACCACGGAGAAGAUUUGTT (SEQ ID NO: 1783)	1.2
RAG3A-938	CACACTTCTCAGCAGACAT (SEQ ID NO: 900)	CACACUUCUCAGCAGACAUTT (SEQ ID NO: 1342)	AUGUCUGCUGAGAAGUGUGTT (SEQ ID NO: 1784)	1.2
RAG3A-853	GATCAAGGTCAGGCCAGGA (SEQ ID NO: 901)	GAUCAAGGUCAGGCCAGGATT (SEQ ID NO: 1343)	UCCUGGCCUGACCUUGAUCTT (SEQ ID NO: 1785)	1.2
RAG3A-716	GCTGTCTTTCCTAAGACAG (SEQ ID NO: 902)	GCUGUCUUUCCUAAGACAGTT (SEQ ID NO: 1344)	CUGUCUUAGGAAAGACAGCTT (SEQ ID NO: 1786)	1.2
RAG3A-1027	CCACTATCCTCCCAGCTAT (SEQ ID NO: 903)	CCACUAUCCUCCCAGCUAUTT (SEQ ID NO: 1345)	AUAGCUGGGAGGAUAGUGGTT (SEQ ID NO: 1787)	1.2
RAG3A-640	CGGAGACAGAACAAGCAAA (SEQ ID NO: 904)	CGGAGACAGAACAAGCAAATT (SEQ ID NO: 1346)	UUUGCUUGUUCUGUCUCCGTT (SEQ ID NO: 1788)	1.2
RAG3A-284	CAGGGAGTGAAAACCCCAC	CAGGGAGUGAAAACCCCACTT (SEQ ID NO: 1347)	GUGGGGUUUUCACUCCCUGTT	1.2

	(SEQ ID NO: 905)		(SEQ ID NO: 1789)	
RAG3A-705	TAAGACAGGGACACATGGG (SEQ ID NO: 906)	UAAGACAGGGACACAUGGGTT (SEQ ID NO: 1348)	CCCAUGUGUCCCUGUCUUATT (SEQ ID NO: 1790)	1.2
RAG3A-1315	TGCCTAGCCTGCCTCCCTA (SEQ ID NO: 907)	UGCCUAGCCUGCCUCCCUATT (SEQ ID NO: 1349)	UAGGGAGGCAGGCUAGGCATT (SEQ ID NO: 1791)	1.2
RAG3A-1381	TCCATCAGCCGATCTCCCC (SEQ ID NO: 908)	UCCAUCAGCCGAUCUCCCCTT (SEQ ID NO: 1350)	GGGGAGAUCGGCUGAUGGATT (SEQ ID NO: 1792)	1.2
RAG3A-558	AGCACCTAAGCTCAGGCTT (SEQ ID NO: 909)	AGCACCUAAGCUCAGGCUUTT (SEQ ID NO: 1351)	AAGCCUGAGCUUAGGUGCUTT (SEQ ID NO: 1793)	1.2
RAG3A-498	GACAGTCCACTCAACCCGT (SEQ ID NO: 910)	GACAGUCCACUCAACCCGUTT (SEQ ID NO: 1352)	ACGGGUUGAGUGGACUGUCTT (SEQ ID NO: 1794)	1.2
RAG3A-581	AAGCCACTGGACCCCAGCA (SEQ ID NO: 911)	AAGCCACUGGACCCCAGCATT (SEQ ID NO: 1353)	UGCUGGGGUCCAGUGGCUUTT (SEQ ID NO: 1795)	1.2
RAG3A-1135	CTTCACCCAAGGGACCCTC (SEQ ID NO: 912)	CUUCACCCAAGGGACCCUCTT (SEQ ID NO: 1354)	GAGGGUCCCUUGGGUGAAGTT (SEQ ID NO: 1796)	1.2

RAG3A-1070	CATGCCTGCCTCCCTGTCT (SEQ ID NO: 913)	CAUGCCUGCCUCCCUGUCUTT (SEQ ID NO: 1355)	AGACAGGGAGGCAGGCAUGTT (SEQ ID NO: 1797)	1.2
RAG3A-1181	TCCTCAGGCGCATTCGACA (SEQ ID NO: 914)	UCCUCAGGCGCAUUCGACATT (SEQ ID NO: 1356)	UGUCGAAUGCGCCUGAGGATT (SEQ ID NO: 1798)	1.2
RAG3A-1206	AGTATCTCCCTCTCATTGT (SEQ ID NO: 915)	AGUAUCUCCCUCUCAUUGUTT (SEQ ID NO: 1357)	ACAAUGAGAGGGAGAUACUTT (SEQ ID NO: 1799)	1.2
RAG3A-461	ACACCAACCCATAACAGGA (SEQ ID NO: 916)	ACACCAACCCAUAACAGGATT (SEQ ID NO: 1358)	UCCUGUUAUGGGUUGGUGUTT (SEQ ID NO: 1800)	1.2
RAG3A-242	CTTCTTCCCCAGCAACACA (SEQ ID NO: 917)	CUUCUUCCCCAGCAACACATT (SEQ ID NO: 1359)	UGUGUUGCUGGGGAAGAAGTT (SEQ ID NO: 1801)	1.2
RAG3A-1127	AAGGGACCCTCTGCCTCTC (SEQ ID NO: 918)	AAGGGACCCUCUGCCUCUCTT (SEQ ID NO: 1360)	GAGAGGCAGAGGGUCCCUUTT (SEQ ID NO: 1802)	1.2
RAG3A-419	CCGTGTTCCCACTTCGAAA (SEQ ID NO: 919)	CCGUGUUCCCACUUCGAAATT (SEQ ID NO: 1361)	UUUCGAAGUGGGAACACGGTT (SEQ ID NO: 1803)	1.2

RAG3A-790	AAGCAAAGGAGCTAGAGCC (SEQ ID NO: 920)	AAGCAAAGGAGCUAGAGCCTT (SEQ ID NO: 1362)	GGCUCUAGCUCCUUUGCUUTT (SEQ ID NO: 1804)	1.2
RAG3A-635	ACAGAACAAGCAAAGGAGG (SEQ ID NO: 921)	ACAGAACAAGCAAAGGAGGTT (SEQ ID NO: 1363)	CCUCCUUUGCUUGUUCUGUTT (SEQ ID NO: 1805)	1.2
RAG3A-673	CTTGTCACATGTGGAACGG (SEQ ID NO: 922)	CUUGUCACAUGUGGAACGGTT (SEQ ID NO: 1364)	CCGUUCCACAUGUGACAAGTT (SEQ ID NO: 1806)	1.2
RAG3A-1001	CCCTCCTTCCTAATCTTGG (SEQ ID NO: 923)	CCCUCCUUCCUAAUCUUGGTT (SEQ ID NO: 1365)	CCAAGAUUAGGAAGGAGGGTT (SEQ ID NO: 1807)	1.2
RAG3A-1005	AGCACCCTCCTTCCTAATC (SEQ ID NO: 924)	AGCACCCUCCUUCCUAAUCTT (SEQ ID NO: 1366)	GAUUAGGAAGGAGGGUGCUTT (SEQ ID NO: 1808)	1.2
RAG3A-1064	TGCCTCCCTGTCTCCTGTC (SEQ ID NO: 925)	UGCCUCCCUGUCUCCUGUCTT (SEQ ID NO: 1367)	GACAGGAGACAGGGAGGCATT (SEQ ID NO: 1809)	1.2
RAG3A-801	GACTGGGAAGAAAGCAAAG (SEQ ID NO: 926)	GACUGGGAAGAAAGCAAAGTT (SEQ ID NO: 1368)	CUUUGCUUUCUUCCCAGUCTT (SEQ ID NO: 1810)	1.2

RAG3A-486	AACCCGTCCAAACCCTTTC (SEQ ID NO: 927)	AACCCGUCCAAACCCUUUCTT (SEQ ID NO: 1369)	GAAAGGGUUUGGACGGGUUTT (SEQ ID NO: 1811)	1.2
RAG3A-555	ACCTAAGCTCAGGCTTAAC (SEQ ID NO: 928)	ACCUAAGCUCAGGCUUAACTT (SEQ ID NO: 1370)	GUUAAGCCUGAGCUUAGGUTT (SEQ ID NO: 1812)	1.2
RAG3A-854	GGATCAAGGTCAGGCCAGG (SEQ ID NO: 929)	GGAUCAAGGUCAGGCCAGGTT (SEQ ID NO: 1371)	CCUGGCCUGACCUUGAUCCTT (SEQ ID NO: 1813)	1.2
RAG3A-1267	GTGTTACCCAGGACAGGGA (SEQ ID NO: 930)	GUGUUACCCAGGACAGGGATT (SEQ ID NO: 1372)	UCCCUGUCCUGGGUAACACTT (SEQ ID NO: 1814)	1.2
RAG3A-1264	TTACCCAGGACAGGGACCT (SEQ ID NO: 931)	UUACCCAGGACAGGGACCUTT (SEQ ID NO: 1373)	AGGUCCCUGUCCUGGGUAATT (SEQ ID NO: 1815)	1.2
RAG3A-513	ATGTGCCCCGCACCTGACA (SEQ ID NO: 932)	AUGUGCCCCGCACCUGACATT (SEQ ID NO: 1374)	UGUCAGGUGCGGGGCACAUTT (SEQ ID NO: 1816)	1.2
RAG3A-1286	GAGGTCGCTCCTCATTCTT (SEQ ID NO: 933)	GAGGUCGCUCCUCAUUCUUTT (SEQ ID NO: 1375)	AAGAAUGAGGAGCGACCUCTT (SEQ ID NO: 1817)	1.2
RAG3A-653	AGGAGATGGAAGACGGAGA	AGGAGAUGGAAGACGGAGATT	UCUCCGUCUUCCAUCUCCUTT	1.2

	(SEQ ID NO: 934)	(SEQ ID NO: 1376)	(SEQ ID NO: 1818)	
RAG3A-1014	AGCTATCCCAGCACCCTCC (SEQ ID NO: 935)	AGCUAUCCCAGCACCCUCCTT (SEQ ID NO: 1377)	GGAGGGUGCUGGGAUAGCUTT (SEQ ID NO: 1819)	1.2
RAG3A-61	AGAGAAGGCGTCACTTCCG (SEQ ID NO: 936)	AGAGAAGGCGUCACUUCCGTT (SEQ ID NO: 1378)	CGGAAGUGACGCCUUCUCUTT (SEQ ID NO: 1820)	1.2
RAG3A-666	CATGTGGAACGGTAGGAGA (SEQ ID NO: 937)	CAUGUGGAACGGUAGGAGATT (SEQ ID NO: 1379)	UCUCCUACCGUUCCACAUGTT (SEQ ID NO: 1821)	1.2
RAG3A-348	AAGCAAGCATCCTGTTGGA (SEQ ID NO: 938)	AAGCAAGCAUCCUGUUGGATT (SEQ ID NO: 1380)	UCCAACAGGAUGCUUGCUUTT (SEQ ID NO: 1822)	1.2
RAG3A-545	AGGCTTAACCCAGTGCACG (SEQ ID NO: 939)	AGGCUUAACCCAGUGCACGTT (SEQ ID NO: 1381)	CGUGCACUGGGUUAAGCCUTT (SEQ ID NO: 1823)	1.2
RAG3A-584	TCTAAGCCACTGGACCCCA (SEQ ID NO: 940)	UCUAAGCCACUGGACCCCATT (SEQ ID NO: 1382)	UGGGGUCCAGUGGCUUAGATT (SEQ ID NO: 1824)	1.2
RAG3A-1162	GTCCCCTCTTGCTTTCTCA (SEQ ID NO: 941)	GUCCCCUCUUGCUUUCUCATT (SEQ ID NO: 1383)	UGAGAAAGCAAGAGGGGACTT (SEQ ID NO: 1825)	1.2

RAG3A-308	CCAGGGAAAAGAAATTTGG (SEQ ID NO: 942)	CCAGGGAAAAGAAAUUUGGTT (SEQ ID NO: 1384)	CCAAAUUUCUUUUCCCUGGTT (SEQ ID NO: 1826)	1.2
RAG3A-158	CCCATGTCCAGGAAAAGAT (SEQ ID NO: 943)	CCCAUGUCCAGGAAAAGAUTT (SEQ ID NO: 1385)	AUCUUUUCCUGGACAUGGGTT (SEQ ID NO: 1827)	1.2
RAG3A-161	TTGCCCATGTCCAGGAAAA (SEQ ID NO: 944)	UUGCCCAUGUCCAGGAAAATT (SEQ ID NO: 1386)	UUUUCCUGGACAUGGGCAATT (SEQ ID NO: 1828)	1.2
RAG3A-1253	AGGGACCTAGCCAGAAACC (SEQ ID NO: 945)	AGGGACCUAGCCAGAAACCTT (SEQ ID NO: 1387)	GGUUUCUGGCUAGGUCCCUTT (SEQ ID NO: 1829)	1.2
RAG3A-926	CAGACATGCCCATCCTTGG (SEQ ID NO: 946)	CAGACAUGCCCAUCCUUGGTT (SEQ ID NO: 1388)	CCAAGGAUGGGCAUGUCUGTT (SEQ ID NO: 1830)	1.2
RAG3A-1191	TTGTAACTTATCCTCAGGC (SEQ ID NO: 947)	UUGUAACUUAUCCUCAGGCTT (SEQ ID NO: 1389)	GCCUGAGGAUAAGUUACAATT (SEQ ID NO: 1831)	1.2
RAG3A-697	GGACACATGGGCCTGGTTA (SEQ ID NO: 948)	GGACACAUGGGCCUGGUUATT (SEQ ID NO: 1390)	UAACCAGGCCCAUGUGUCCTT (SEQ ID NO: 1832)	1.2

RAG3A-1224	CCCCTTCTGTGGAGTGACA (SEQ ID NO: 949)	CCCCUUCUGUGGAGUGACATT (SEQ ID NO: 1391)	UGUCACUCCACAGAAGGGGTT (SEQ ID NO: 1833)	1.2
RAG3A-964	GGACGGGAAAATTCCAGGA (SEQ ID NO: 950)	GGACGGGAAAAUUCCAGGATT (SEQ ID NO: 1392)	UCCUGGAAUUUUCCCGUCCTT (SEQ ID NO: 1834)	1.2
RAG3A-791	AAAGCAAAGGAGCTAGAGC (SEQ ID NO: 951)	AAAGCAAAGGAGCUAGAGCTT (SEQ ID NO: 1393)	GCUCUAGCUCCUUUGCUUUTT (SEQ ID NO: 1835)	1.2
RAG3A-526	TGTGCGCACATACATGTGC (SEQ ID NO: 952)	UGUGCGCACAUACAUGUGCTT (SEQ ID NO: 1394)	GCACAUGUAUGUGCGCACATT (SEQ ID NO: 1836)	1.2
RAG3A-972	GTCTGGCTGGACGGGAAAA (SEQ ID NO: 953)	GUCUGGCUGGACGGGAAAATT (SEQ ID NO: 1395)	UUUUCCCGUCCAGCCAGACTT (SEQ ID NO: 1837)	1.2
RAG3A-289	ATAGCCAGGGAGTGAAAAC (SEQ ID NO: 954)	AUAGCCAGGGAGUGAAAACTT (SEQ ID NO: 1396)	GUUUUCACUCCCUGGCUAUTT (SEQ ID NO: 1838)	1.2
RAG3A-255	CAAGACCTCTGTGCTTCTT (SEQ ID NO: 955)	CAAGACCUCUGUGCUUCUUTT (SEQ ID NO: 1397)	AAGAAGCACAGAGGUCUUGTT (SEQ ID NO: 1839)	1.2

RAG3A-1000	CCTCCTTCCTAATCTTGGG (SEQ ID NO: 956)	CCUCCUUCCUAAUCUUGGGTT (SEQ ID NO: 1398)	CCCAAGAUUAGGAAGGAGGTT (SEQ ID NO: 1840)	1.2
RAG3A-694	CACATGGGCCTGGTTATTC (SEQ ID NO: 957)	CACAUGGGCCUGGUUAUUCTT (SEQ ID NO: 1399)	GAAUAACCAGGCCCAUGUGTT (SEQ ID NO: 1841)	1.2
RAG3A-549	GCTCAGGCTTAACCCAGTG (SEQ ID NO: 958)	GCUCAGGCUUAACCCAGUGTT (SEQ ID NO: 1400)	CACUGGGUUAAGCCUGAGCTT (SEQ ID NO: 1842)	1.2
RAG3A-1240	GAAACCGGCAGCATTCCCC (SEQ ID NO: 959)	GAAACCGGCAGCAUUCCCCTT (SEQ ID NO: 1401)	GGGGAAUGCUGCCGGUUUCTT (SEQ ID NO: 1843)	1.2
RAG3A-978	CATCTCGTCTGGCTGGACG (SEQ ID NO: 960)	CAUCUCGUCUGGCUGGACGTT (SEQ ID NO: 1402)	CGUCCAGCCAGACGAGAUGTT (SEQ ID NO: 1844)	1.2
RAG3A-1290	CTCTGAGGTCGCTCCTCAT (SEQ ID NO: 961)	CUCUGAGGUCGCUCCUCAUTT (SEQ ID NO: 1403)	AUGAGGAGCGACCUCAGAGTT (SEQ ID NO: 1845)	1.2
RAG3A-1006	CAGCACCCTCCTTCCTAAT (SEQ ID NO: 962)	CAGCACCCUCCUUCCUAAUTT (SEQ ID NO: 1404)	AUUAGGAAGGAGGGUGCUGTT (SEQ ID NO: 1846)	1.2

RAG3A-1311	TAGCCTGCCTCCCTACCTT (SEQ ID NO: 963)	UAGCCUGCCUCCCUACCUUTT (SEQ ID NO: 1405)	AAGGUAGGGAGGCAGGCUATT (SEQ ID NO: 1847)	1.2
RAG3A-42	GGGGCCTTCACCAGTGTCT (SEQ ID NO: 964)	GGGGCCUUCACCAGUGUCUTT (SEQ ID NO: 1406)	AGACACUGGUGAAGGCCCCTT (SEQ ID NO: 1848)	1.2
RAG3A-21	TGGCTCCCTTCTCTGATTG (SEQ ID NO: 965)	UGGCUCCCUUCUCUGAUUGTT (SEQ ID NO: 1407)	CAAUCAGAGAAGGGAGCCATT (SEQ ID NO: 1849)	1.2
RAG3A-59	AGAAGGCGTCACTTCCGGG (SEQ ID NO: 966)	AGAAGGCGUCACUUCCGGGTT (SEQ ID NO: 1408)	CCCGGAAGUGACGCCUUCUTT (SEQ ID NO: 1850)	1.2
RAG3A-1187	AACTTATCCTCAGGCGCAT (SEQ ID NO: 967)	AACUUAUCCUCAGGCGCAUTT (SEQ ID NO: 1409)	AUGCGCCUGAGGAUAAGUUTT (SEQ ID NO: 1851)	1.2
RAG3A-576	ACTGGACCCCAGCAGACGA (SEQ ID NO: 968)	ACUGGACCCCAGCAGACGATT (SEQ ID NO: 1410)	UCGUCUGCUGGGGUCCAGUTT (SEQ ID NO: 1852)	1.1
RAG3A-639	GGAGACAGAACAAGCAAAG (SEQ ID NO: 969)	GGAGACAGAACAAGCAAAGTT (SEQ ID NO: 1411)	CUUUGCUUGUUCUGUCUCCTT (SEQ ID NO: 1853)	1.1

RAG3A-815	TGTGGGGAGACTGGGACTG (SEQ ID NO: 970)	UGUGGGGAGACUGGGACUGTT (SEQ ID NO: 1412)	CAGUCCCAGUCUCCCCACATT (SEQ ID NO: 1854)	1.1
RAG3A-957	AAAATTCCAGGATCTAGGC (SEQ ID NO: 971)	AAAAUUCCAGGAUCUAGGCTT (SEQ ID NO: 1413)	GCCUAGAUCCUGGAAUUUUTT (SEQ ID NO: 1855)	1.1
RAG3A-1217	TGTGGAGTGACAGTATCTC (SEQ ID NO: 972)	UGUGGAGUGACAGUAUCUCTT (SEQ ID NO: 1414)	GAGAUACUGUCACUCCACATT (SEQ ID NO: 1856)	1.1
RAG3A-1165	ACAGTCCCCTCTTGCTTTC (SEQ ID NO: 973)	ACAGUCCCCUCUUGCUUUCTT (SEQ ID NO: 1415)	GAAAGCAAGAGGGGACUGUTT (SEQ ID NO: 1857)	1.1
RAG3A-1134	TTCACCCAAGGGACCCTCT (SEQ ID NO: 974)	UUCACCCAAGGGACCCUCUTT (SEQ ID NO: 1416)	AGAGGGUCCCUUGGGUGAATT (SEQ ID NO: 1858)	1.1
RAG3A-667	ACATGTGGAACGGTAGGAG (SEQ ID NO: 975)	ACAUGUGGAACGGUAGGAGTT (SEQ ID NO: 1417)	CUCCUACCGUUCCACAUGUTT (SEQ ID NO: 1859)	1.1
RAG3A-1339	CAAACCCTCACCACCCTCT (SEQ ID NO: 976)	CAAACCCUCACCACCCUCUTT (SEQ ID NO: 1418)	AGAGGGUGGUGAGGGUUUGTT (SEQ ID NO: 1860)	1.1
RAG3A-676	CCTCTTGTCACATGTGGAA (SEQ ID NO: 977)	CCUCUUGUCACAUGUGGAATT (SEQ ID NO: 1419)	UUCCACAUGUGACAAGAGGTT (SEQ ID NO: 1861)	1.1
RAG3A-153	GTCCAGGAAAAGATGGATC	GUCCAGGAAAAGAUGGAUCTT	GAUCCAUCUUUUCCUGGACT	1.1

	(SEQ ID NO: 978)	(SEQ ID NO: 1420)	T (SEQ ID NO: 1862)	
RAG3A-320	CAGGTATGATGTCCAGGGA (SEQ ID NO: 979)	CAGGUAUGAUGUCCAGGGATT (SEQ ID NO: 1421)	UCCCUGGACAUCAUACCUGT T (SEQ ID NO: 1863)	1.1
RAG3A-1010	ATCCCAGCACCCTCCTTCC (SEQ ID NO: 980)	AUCCCAGCACCCUCCUUCCTT (SEQ ID NO: 1422)	GGAAGGAGGGUGCUGGGAUT T (SEQ ID NO: 1864)	1.1
RAG3A-999	CTCCTTCCTAATCTTGGGA (SEQ ID NO: 981)	CUCCUUCCUAAUCUUGGGATT (SEQ ID NO: 1423)	UCCCAAGAUUAGGAAGGAGT T (SEQ ID NO: 1865)	1.1
RAG3A-567	CAGCAGACGAGCACCTAAG (SEQ ID NO: 982)	CAGCAGACGAGCACCUAAGTT (SEQ ID NO: 1424)	CUUAGGUGCUCGUCUGCUGT T (SEQ ID NO: 1866)	1.1
RAG3A-862	GGATGATGGGATCAAGGTC (SEQ ID NO: 983)	GGAUGAUGGGAUCAAGGUCTT (SEQ ID NO: 1425)	GACCUUGAUCCCAUCAUCCTT (SEQ ID NO: 1867)	1.1
RAG3A-460	CACCAACCCATAACAGGAG (SEQ ID NO: 984)	CACCAACCCAUAACAGGAGTT (SEQ ID NO: 1426)	CUCCUGUUAUGGGUUGGUGT T (SEQ ID NO: 1868)	1.1
RAG3A-921	ATGCCCATCCTTGGGGAGG (SEQ ID NO: 985)	AUGCCCAUCCUUGGGGAGGTT (SEQ ID NO: 1427)	CCUCCCCAAGGAUGGGCAUT T	1.1

			(SEQ ID NO: 1869)	
RAG3A-704	AAGACAGGGACACATGGGC (SEQ ID NO: 986)	AAGACAGGGACACAUGGGCTT (SEQ ID NO: 1428)	GCCCAUGUGUCCCUGUCUUTT (SEQ ID NO: 1870)	1.1
RAG3A-233	CAGCAACACAAATGTCCTG (SEQ ID NO: 987)	CAGCAACACAAAUGUCCUGTT (SEQ ID NO: 1429)	CAGGACAUUUGUGUUGCUGTT (SEQ ID NO: 1871)	1.1
RAG3A-1203	ATCTCCCTCTCATTGTAAC (SEQ ID NO: 988)	AUCUCCCUCUCAUUGUAACTT (SEQ ID NO: 1430)	GUUACAAUGAGAGGGAGAUTT (SEQ ID NO: 1872)	1.1
RAG3A-247	CTGTGCTTCTTCCCCAGCA (SEQ ID NO: 989)	CUGUGCUUCUUCCCCAGCATT (SEQ ID NO: 1431)	UGCUGGGGAAGAAGCACAGTT (SEQ ID NO: 1873)	1.1
RAG3A-721	CAGCAGCTGTCTTTCCTAA (SEQ ID NO: 990)	CAGCAGCUGUCUUUCCUAATT (SEQ ID NO: 1432)	UUAGGAAAGACAGCUGCUGTT (SEQ ID NO: 1874)	1.1
RAG3A-391	ACAAGATAGGACTCCCTAG (SEQ ID NO: 991)	ACAAGAUAGGACUCCCUAGTT (SEQ ID NO: 1433)	CUAGGGAGUCCUAUCUUGUTT (SEQ ID NO: 1875)	1.1
RAG3A-159	GCCCATGTCCAGGAAAAGA (SEQ ID NO: 992)	GCCCAUGUCCAGGAAAAGATT (SEQ ID NO: 1434)	UCUUUUCCUGGACAUGGGCTT	1.1

			(SEQ ID NO: 1876)	
RAG3A-437	CTCTCATGTGGGCAATATC (SEQ ID NO: 993)	CUCUCAUGUGGGCAAUAUCTT (SEQ ID NO: 1435)	GAUAUUGCCCACAUGAGAGTT (SEQ ID NO: 1877)	1.1
RAG3A-29	GTGTCTGGTGGCTCCCTTC (SEQ ID NO: 994)	GUGUCUGGUGGCUCCCUUCTT (SEQ ID NO: 1436)	GAAGGGAGCCACCAGACACTT (SEQ ID NO: 1878)	1.1
RAG3A-63	GAAGAGAAGGCGTCACTTC (SEQ ID NO: 995)	GAAGAGAAGGCGUCACUUCTT (SEQ ID NO: 1437)	GAAGUGACGCCUUCUCUUCTT (SEQ ID NO: 1879)	1.1
RAG3A-996	CTTCCTAATCTTGGGAGAC (SEQ ID NO: 996)	CUUCCUAAUCUUGGGAGACTT (SEQ ID NO: 1438)	GUCUCCCAAGAUUAGGAAGTT (SEQ ID NO: 1880)	1.1
RAG3A-1083	TTGGTTCCCTGGTCATGCC (SEQ ID NO: 997)	UUGGUUCCCUGGUCAUGCCTT (SEQ ID NO: 1439)	GGCAUGACCAGGGAACCAATT (SEQ ID NO: 1881)	1.1
RAG3A-1128	CAAGGGACCCTCTGCCTCT (SEQ ID NO: 998)	CAAGGGACCCUCUGCCUCUTT (SEQ ID NO: 1440)	AGAGGCAGAGGGUCCCUUGTT (SEQ ID NO: 1882)	1.1
RAG3A-1094	CCTCCTTTCTCTTGGTTCC (SEQ ID NO: 999)	CCUCCUUUCUCUUGGUUCCTT (SEQ ID NO: 1441)	GGAACCAAGAGAAAGGAGGTT	1.1

			(SEQ ID NO: 1883)	
RAG3A-771	AGGGCCAAAGGAAAAGGGG (SEQ ID NO: 1000)	AGGGCCAAAGGAAAAGGGGTT (SEQ ID NO: 1442)	CCCCUUUUCCUUUGGCCCUTT (SEQ ID NO: 1884)	1.1
RAG3A-287	AGCCAGGGAGTGAAAACCC (SEQ ID NO: 1001)	AGCCAGGGAGUGAAAACCCTT (SEQ ID NO: 1443)	GGGUUUUCACUCCCUGGCUTT (SEQ ID NO: 1885)	1.1
RAG3A-981	AGACATCTCGTCTGGCTGG (SEQ ID NO: 1002)	AGACAUCUCGUCUGGCUGGTT (SEQ ID NO: 1444)	CCAGCCAGACGAGAUGUCUTT (SEQ ID NO: 1886)	1.1
RAG3A-23	GGTGGCTCCCTTCTCTGAT (SEQ ID NO: 1003)	GGUGGCUCCCUUCUCUGAUTT (SEQ ID NO: 1445)	AUCAGAGAAGGGAGCCACCTT (SEQ ID NO: 1887)	1.1
RAG3A-1072	GTCATGCCTGCCTCCCTGT (SEQ ID NO: 1004)	GUCAUGCCUGCCUCCCUGUTT (SEQ ID NO: 1446)	ACAGGGAGGCAGGCAUGACTT (SEQ ID NO: 1888)	1.1
RAG3A-415	GTTCCCACTTCGAAAGGGG (SEQ ID NO: 1005)	GUUCCCACUUCGAAAGGGGTT (SEQ ID NO: 1447)	CCCCUUUCGAAGUGGGAACTT (SEQ ID NO: 1889)	1.1
RAG3A-1287	TGAGGTCGCTCCTCATTCT (SEQ ID NO: 1006)	UGAGGUCGCUCCUCAUUCUTT (SEQ ID NO: 1448)	AGAAUGAGGAGCGACCUCATT	1.1

			(SEQ ID NO: 1890)	
RAG3A-1201	CTCCCTCTCATTGTAACTT (SEQ ID NO: 1007)	CUCCCUCUCAUUGUAACUUTT (SEQ ID NO: 1449)	AAGUUACAAUGAGAGGGAGTT (SEQ ID NO: 1891)	1.1
RAG3A-772	CAGGGCCAAAGGAAAAGGG (SEQ ID NO: 1008)	CAGGGCCAAAGGAAAAGGGTT (SEQ ID NO: 1450)	CCCUUUUCCUUUGGCCCUGTT (SEQ ID NO: 1892)	1.1
RAG3A-1249	ACCTAGCCAGAAACCGGCA (SEQ ID NO: 1009)	ACCUAGCCAGAAACCGGCATT (SEQ ID NO: 1451)	UGCCGGUUUCUGGCUAGGUTT (SEQ ID NO: 1893)	1.1
RAG3A-546	CAGGCTTAACCCAGTGCAC (SEQ ID NO: 1010)	CAGGCUUAACCCAGUGCACTT (SEQ ID NO: 1452)	GUGCACUGGGUUAAGCCUGTT (SEQ ID NO: 1894)	1.1
RAG3A-160	TGCCCATGTCCAGGAAAAG (SEQ ID NO: 1011)	UGCCCAUGUCCAGGAAAAGTT (SEQ ID NO: 1453)	CUUUUCCUGGACAUGGGCATT (SEQ ID NO: 1895)	1.1
RAG3A-64	GGAAGAGAAGGCGTCACTT (SEQ ID NO: 1012)	GGAAGAGAAGGCGUCACUUTT (SEQ ID NO: 1454)	AAGUGACGCCUUCUCUUCCTT (SEQ ID NO: 1896)	1.1
RAG3A-1002	ACCCTCCTTCCTAATCTTG (SEQ ID NO: 1013)	ACCCUCCUUCCUAAUCUUGTT (SEQ ID NO: 1455)	CAAGAUUAGGAAGGAGGGUTT	1.1

			(SEQ ID NO: 1897)	
RAG3A-1288	CTGAGGTCGCTCCTCATTC (SEQ ID NO: 1014)	CUGAGGUCGCUCCUCAUUCTT (SEQ ID NO: 1456)	GAAUGAGGAGCGACCUCAGTT (SEQ ID NO: 1898)	1.1
RAG3A-891	AGAGCCTGAGGAAGTTCTG (SEQ ID NO: 1015)	AGAGCCUGAGGAAGUUCUGTT (SEQ ID NO: 1457)	CAGAACUUCCUCAGGCUCUTT (SEQ ID NO: 1899)	1.1
RAG3A-231	GCAACACAAATGTCCTGCC (SEQ ID NO: 1016)	GCAACACAAAUGUCCUGCCTT (SEQ ID NO: 1458)	GGCAGGACAUUUGUGUUGCTT (SEQ ID NO: 1900)	1.1
RAG3A-669	TCACATGTGGAACGGTAGG (SEQ ID NO: 1017)	UCACAUGUGGAACGGUAGGTT (SEQ ID NO: 1459)	CCUACCGUUCCACAUGUGATT (SEQ ID NO: 1901)	1.1
RAG3A-1009	TCCCAGCACCCTCCTTCCT (SEQ ID NO: 1018)	UCCCAGCACCCUCCUUCCUTT (SEQ ID NO: 1460)	AGGAAGGAGGGUGCUGGGATT (SEQ ID NO: 1902)	1.1
RAG3A-656	GGTAGGAGATGGAAGACGG (SEQ ID NO: 1019)	GGUAGGAGAUGGAAGACGGTT (SEQ ID NO: 1461)	CCGUCUUCCAUCUCCUACCTT (SEQ ID NO: 1903)	1.1
RAG3A-229	AACACAAATGTCCTGCCAG (SEQ ID NO: 1020)	AACACAAAUGUCCUGCCAGTT (SEQ ID NO: 1462)	CUGGCAGGACAUUUGUGUUTT (SEQ ID NO: 1904)	1.1

RAG3A-484	CCCGTCCAAACCCTTTCCC (SEQ ID NO: 1021)	CCCGUCCAAACCCUUUCCCTT (SEQ ID NO: 1463)	GGGAAAGGGUUUGGACGGGTT (SEQ ID NO: 1905)	1.1
RAG3A-799	CTGGGAAGAAAGCAAAGGA (SEQ ID NO: 1022)	CUGGGAAGAAAGCAAAGGATT (SEQ ID NO: 1464)	UCCUUUGCUUUCUUCCCAGTT (SEQ ID NO: 1906)	1.1
RAG3A-296	AATTTGGATAGCCAGGGAG (SEQ ID NO: 1023)	AAUUUGGAUAGCCAGGGAGTT (SEQ ID NO: 1465)	CUCCCUGGCUAUCCAAAUUTT (SEQ ID NO: 1907)	1.1
RAG3A-1183	TATCCTCAGGCGCATTCGA (SEQ ID NO: 1024)	UAUCCUCAGGCGCAUUCGATT (SEQ ID NO: 1466)	UCGAAUGCGCCUGAGGAUATT (SEQ ID NO: 1908)	1.1
RAG3A-380	CTCCCTAGGGGATTACAGA (SEQ ID NO: 1025)	CUCCCUAGGGGAUUACAGATT (SEQ ID NO: 1467)	UCUGUAAUCCCCUAGGGAGTT (SEQ ID NO: 1909)	1.1
RAG3A-157	CCATGTCCAGGAAAAGATG (SEQ ID NO: 1026)	CCAUGUCCAGGAAAAGAUGTT (SEQ ID NO: 1468)	CAUCUUUUCCUGGACAUGGTT (SEQ ID NO: 1910)	1.1
RAG3A-1185	CTTATCCTCAGGCGCATTC (SEQ ID NO: 1027)	CUUAUCCUCAGGCGCAUUCTT (SEQ ID NO: 1469)	GAAUGCGCCUGAGGAUAAGTT (SEQ ID NO: 1911)	1.1
RAG3A-124	GCCAGAAACCGGCAGCATT	GCCAGAAACCGGCAGCAUUTT	AAUGCUGCCGGUUUCUGGCTT	1.1

4	(SEQ ID NO: 1028)	(SEQ ID NO: 1470)	(SEQ ID NO: 1912)	
RAG3A-588	GCCATCTAAGCCACTGGAC (SEQ ID NO: 1029)	GCCAUCUAAGCCACUGGACTT (SEQ ID NO: 1471)	GUCCAGUGGCUUAGAUGGCT T (SEQ ID NO: 1913)	1.1
RAG3A-436	TCTCATGTGGGCAATATCC (SEQ ID NO: 1030)	UCUCAUGUGGGCAAUAUCCTT (SEQ ID NO: 1472)	GGAUAUUGCCCACAUGAGAT T (SEQ ID NO: 1914)	1.1
RAG3A-1029	ACCCACTATCCTCCCAGCT (SEQ ID NO: 1031)	ACCCACUAUCCUCCCAGCUTT (SEQ ID NO: 1473)	AGCUGGGAGGAUAGUGGGUT T (SEQ ID NO: 1915)	1.1
RAG3A-28	TGTCTGGTGGCTCCCTTCT (SEQ ID NO: 1032)	UGUCUGGUGGCUCCCUUCUTT (SEQ ID NO: 1474)	AGAAGGGAGCCACCAGACAT T (SEQ ID NO: 1916)	1.1
RAG3A-234	CCAGCAACACAAATGTCCT (SEQ ID NO: 1033)	CCAGCAACACAAAUGUCCUTT (SEQ ID NO: 1475)	AGGACAUUUGUGUUGCUGGT T (SEQ ID NO: 1917)	1.1
RAG3A-249	CTCTGTGCTTCTTCCCCAG (SEQ ID NO: 1034)	CUCUGUGCUUCUUCCCCAGTT (SEQ ID NO: 1476)	CUGGGGAAGAAGCACAGAGT T (SEQ ID NO: 1918)	1.1
RAG3A-775	AGCCAGGGCCAAAGGAAA A	AGCCAGGGCCAAAGGAAAATT (SEQ ID NO: 1477)	UUUUCCUUUGGCCCUGGCUT T	1.1

	(SEQ ID NO: 1035)		(SEQ ID NO: 1919)	
RAG3A-951	CCAGGATCTAGGCCACACT (SEQ ID NO: 1036)	CCAGGAUCUAGGCCACACUTT (SEQ ID NO: 1478)	AGUGUGGCCUAGAUCCUGGTT (SEQ ID NO: 1920)	1.1
RAG3A-861	GATGATGGGATCAAGGTCA (SEQ ID NO: 1037)	GAUGAUGGGAUCAAGGUCATT (SEQ ID NO: 1479)	UGACCUUGAUCCCAUCAUCTT (SEQ ID NO: 1921)	1.1
RAG3A-259	TAAACAAGACCTCTGTGCT (SEQ ID NO: 1038)	UAAACAAGACCUCUGUGCUTT (SEQ ID NO: 1480)	AGCACAGAGGUCUUGUUUATT (SEQ ID NO: 1922)	1.1
RAG3A-394	ATGACAAGATAGGACTCCC (SEQ ID NO: 1039)	AUGACAAGAUAGGACUCCCTT (SEQ ID NO: 1481)	GGGAGUCCUAUCUUGUCAUTT (SEQ ID NO: 1923)	1.1
RAG3A-534	AGTGCACGTGTGCGCACAT (SEQ ID NO: 1040)	AGUGCACGUGUGCGCACAUTT (SEQ ID NO: 1482)	AUGUGCGCACACGUGCACUTT (SEQ ID NO: 1924)	1.1
RAG3A-316	TATGATGTCCAGGGAAAAG (SEQ ID NO: 1041)	UAUGAUGUCCAGGGAAAAGTT (SEQ ID NO: 1483)	CUUUUCCCUGGACAUCAUATT (SEQ ID NO: 1925)	1.1
RAG3A-560	CGAGCACCTAAGCTCAGGC (SEQ ID NO: 1042)	CGAGCACCUAAGCUCAGGCTT (SEQ ID NO: 1484)	GCCUGAGCUUAGGUGCUCGTT (SEQ ID NO: 1926)	1.1

RAG3A-1105	CCCACTCCCAGCCTCCTTT (SEQ ID NO: 1043)	CCCACUCCCAGCCUCCUUUTT (SEQ ID NO: 1485)	AAAGGAGGCUGGGAGUGGGTT (SEQ ID NO: 1927)	1.1
RAG3A-709	TTCCTAAGACAGGGACACA (SEQ ID NO: 1044)	UUCCUAAGACAGGGACACATT (SEQ ID NO: 1486)	UGUGUCCCUGUCUUAGGAATT (SEQ ID NO: 1928)	1.1
RAG3A-948	GGATCTAGGCCACACTTCT (SEQ ID NO: 1045)	GGAUCUAGGCCACACUUCUTT (SEQ ID NO: 1487)	AGAAGUGUGGCCUAGAUCCTT (SEQ ID NO: 1929)	1.1
RAG3A-998	TCCTTCCTAATCTTGGGAG (SEQ ID NO: 1046)	UCCUUCCUAAUCUUGGGAGTT (SEQ ID NO: 1488)	CUCCCAAGAUUAGGAAGGATT (SEQ ID NO: 1930)	1.1
RAG3A-387	GATAGGACTCCCTAGGGGA (SEQ ID NO: 1047)	GAUAGGACUCCCUAGGGGATT (SEQ ID NO: 1489)	UCCCCUAGGGAGUCCUAUCTT (SEQ ID NO: 1931)	1.1

[0164] It can be clearly seen from the arrangement of activities of the 833 saRNAs according to their positions within the *THPO* promoter region that the functional saRNAs are gathered together, that is, in certain promoter regions, the activating saRNAs gathered in specific “hotspot” regions (**FIG. 11**). As shown in **FIG. 11**, 5 hotspot regions appeared in region (H1) from -1339 to -1044, region (H2) from -1027 to -903, region (H3) from -861 to -754, region (H4) from -728 to -611, and region (H5) from -593 to -1 of the promoter, respectively, showing high gathering of the activating saRNAs. These results indicate that the activating saRNAs were not randomly distributedwithin the promoter, but existed in the specific hotspot regions.

[0165] The sequence of the hotspot H1 (5' to 3': -1339 to -1044) corresponds to position 1 to position 296, from 5' to 3', of SEQ ID NO: 601 in the sequence listing:

1 caaaccctca ccaccctctc tcactgccta gcctgcctcc ctaccttctc
51 tctgaggtcg ctcctcattc ttgtgttacc caggacaggg acctagccag
101 aaaccggcag cattcccccc tctgtggagt gacagtatct ccctctcatt
151 gtaacttatc ctcaggcgca ttcgacagtc ccctcttgct ttctcacccc
201 cttccttcac ccaagggacc ctctgcctct ccagcccact cccagcctcc
251 tttctcttgg ttccctggtc atgcctgcct ccctgtctcc tgtctc

[0166] The sequence of the hotspot H2 (5' to 3': -1027 to -903) corresponds to position 1 to position 125, from 5' to 3', of SEQ ID NO: 602 in the sequence listing:

1 ccactatcct cccagctatc ccagcaccct ccttcctaat cttgggagac
51 atctcgtctg gctggacggg aaaattccag gatctaggcc acacttctca
101 gcagacatgc ccatccttgg ggagg

[0167] The sequence of the hotspot H3 (5' to 3': -861 to -754) corresponds to position 1 to position 108, from 5' to 3', of SEQ ID NO: 603 in the sequence listing:

1 gatgatggga tcaaggtcag gccaggaagc ccctgaggac agagactgtg
51 gggagactgg gactgggaag aaagcaaagg agctagagcc agggccaaag
101 gaaaaggg

[0168] The sequence of the hotspot H4 (5' to 3': -728 to -611) corresponds to position 1 to position 118, from 5' to 3', of SEQ ID NO: 604 in the sequence listing:

1 ggaggtccag cagctgtctt tcctaagaca gggacacatg ggcctggtta
51 ttcctcttgt cacatgtgga acggtaggag atggaagacg gagacagaac
101 aagcaaagga gggccctg

[0169] The sequence of the hotspot H5 (5' to 3': -593 to -1) corresponds to position 1 to position 593, from 5' to 3', of SEQ ID NO: 605 in the sequence listing:

1 gtgtagccat ctaagccact ggaccccagc agacgagcac ctaagctcag
51 gcttaaccca gtgcacgtgt gcgcacatac atgtgccccg cacctgacag
101 tccactcaac ccgtccaaac cctttcccca taacaccaac ccataacagg

151 agatttctct catgtgggca atatccgtgt tcccacttcg aaaaggggaa
201 tgacaagata ggactcccta ggggattaca gaaagaaaag caggaaagca
251 agcatcctgt tggatttcag cagcaggtat gatgtccagg gaaaagaaat
301 ttggatagcc agggagtgaa aaccccacca atcttaaaca agacctctgt
351 gcttcttccc cagcaacaca aatgtcctgc cagattcctc ctggaaaaaa
401 acttctgctc ctgtcccccc ccaggtccca ggttgcccat gtccaggaaa
451 agatggatcc ccctatccaa atcttctccg tggtgtgtgt gggtggagga
501 gtggaccctg gtccaggcag gggctccagg gaagagaagg cgtcacttcc
551 gggggccttc accagtgtct ggtggctccc ttctctgatt ggg

Example 10: Human *THPO* saRNA Promoting the Expression of *THPO* mRNA in Human Liver Cancer Cells (HepG2)

(1) Cell culture and transfection

[0170] Cell culture was described in Example 9. HepG2 cells (purchased from Shanghai Institutes for Biological Sciences, TCHu119) were plated into a 6-well plate at 2×10^5 cells/well. Following the instructions provided by the manufacturer, RNAiMax (Invitrogen, Carlsbad, CA) was used to transfect human *THPO* saRNA at a concentration of 25 nM (unless otherwise specified), and transfection duration was 72 h, Each treatment was performed in 2 replicate wells.

(2) Two-step RT-qPCR

[0171] Media were discarded after transfection and 500 μL of cell lysis buffer was added to each well and incubated at room temperature for 5 min. RNA was extracted using Qiagen RNeasy kit, reverse transcribed, and subjected to qPCR analysis on a ABI 7500 fast real-time PCR system (Applied Biosystems). Each sample was amplified repeatedly in 3 replicate wells. RT-PCR and qPCR reaction systems are shown in Example 5, Tables 5-6 and the amplification primers are shown in Table 11. *TBP* and *HPRT1* served as internal controls, and *THPO* was amplified using a *THPO* F1/R1 primer pair.

[0172] The reaction conditions were as follows: 30s at 95°C, 5 s at 95°C, 30s at 60°C, with 40 cycles of amplification.

[0173] To calculate the expression value (E_{rel}) of the *THPO* gene (target) of an saRNA-transfected sample relative to control treatment (Mock), the Ct values of the target gene and two internal control genes were substituted into Formula 2 in Example 3 for calculation.

$$E_{rel} = 2^{(CtTm-CtTs)} / 2^{(CtRm-CtRs)}$$

Formula 2

[0174] **FIG. 12** shows the relative mRNA expression values of *THPO* after treatment of cells with different saRNAs. The relative mRNA expression of siRNA group (RAG3A-365i) is reduced by 85% compared to the control group which uses a blank transfection control (Mock), indicating that siRNA was successful as a small interfering RNA control transfection. The relative mRNA expression values of RAG3A-1219, RAG3A-1096, RAG3A-1308, RAG3A-1069 and RAG3A-851 groups were all higher than those of the control group, and the relative mRNA expression values increased 1.8, 1.8, 1.6, 1.7 and 1.9, respectively. The relative mRNA expression values of RAG3A-541, RAG3A-1319, RAG3A-62, RAG3A-889 and RAG3A-787 groups were all higher than those of the control group, and increased 2.5, 2.1, 2.9, 2.0 and 2.0, respectively. The activation effect of RAG3A-62 was evident, and the relative mRNA expression value was increased by nearly 3 times. This indicates that randomly selected activating saRNAs could not only be transfected successfully into HepG2 cells, but also can significantly increased expression of*THPO* mRNA.

Example 11: Human *THPO* saRNA Promoting the Expression of THPO Protein Level in Human Liver Cancer Cells (HepG2)

[0175] Cell culture methods were described in Example 9 and cell transfection methods were described in Example 10. Assay of THPO protein level in HepG2 cell culture media using ELISA Kit

1) Human THPO protein standard was dissolved using deionized water or distilled water to give a stock solution of 20,000 pg/mL protein standard. One hundred microliters of THPO protein standard stock solution was added to 900 μL of calibration diluent RD6-11 (dilution 1:5) (for cell culture supernatant samples) or calibration diluent RD6-11 (for serum/plasma samples) to give 2000 pg/mL of standard solution, of which 7 serial dilutions were performed with the appropriate calibration diluent as the zero standard (0 pg/mL).

2) Cell supernatants were sampled and centrifuged to remove dead cells and debris.

3) Proper amount of micro-well plate belts from micro-well plate frame were taken out.

4) 50 μL of assay diluent RD1-1 was added to each well.

5) 200 μL of standard, control, or treatment samples were added to each well. The membrane was covered and the samples were incubated at room temperature for 3 h.

6) The liquid was removed from each well and washed 4 times with 400 μL of wash buffer.

7) 200 μL of human THPO antibody was added to each well and incubated for 1h at room temperature.

8) Step 5 was repeated.

9) 200 μL of substrate solution (Color reagents A and B mixed in equal volumes and used up within 15 min) was added to each well and incubated for 30 min at room temperature in the absence of light.

10) 50 μL of stop solution was added to each well and mixed gently.

11) Absorbance at 450 nM was determined using a multi-functional microplate reader (within 30 min).

[0176] FIG. 13 shows the expression value of relative protein level of THPO in cell culture media after treatment of cells with different saRNAs. The relative protein expression of siRNA group (DS3A-365i) group is reduced by 81% compared to the control group which uses a blank transfection control, indicating that siRNA was successful as a small interfering RNA control transfection. The relative protein level expression of THPO of RAG3A-723, RAG3A-892, RAG3A-62, RAG3A-1178, RAG3A-889, RAG3A-563, RAG3A-487 and RAG3A-787 groups were higher than those of the control group, and the relative protein level expression of THPO was increased by 1.46, 1.26, 1.44, 1.31, 1.29, 1.32, 1.42 and 1.40, respectively. This indicates that randomly selected activating saRNAs are capable of promoting the expression of THPO protein to levels of varying degrees in HepG2 cells.

[0177] Based on the above results, a plurality of saRNAs capable of remarkably activating the expression of human and mouse *THPO/Thpo* genes were found through high-throughput screening of saRNAs targeting human and mouse *THPO/Thpo* gene promoters. It has been found by applicants from multiple studies that both mouse active saRNAs targeting the *Thpo* gene and human active saRNAs targeting the *THPO* gene could be efficiently delivered into cells by the liposome system used in the present invention and can significantly up-regulate the expression of the *Thpo/THPO* gene and protein in cells at the mRNA and protein level. In particular, the active saRNA of the *Thpo* gene of mouse significantly increases the expression of *Thpo* mRNA and protein in the mouse and simultaneously up-regulates or increases the number of platelets significantly. Therefore, the mouse *Thpo* active saRNA and the human *THPO* active saRNA of the present invention can be used for treating a disease or condition caused by a decrease or insufficient Thpo/THPO protein expression or a disease or condition caused by various factors such as thrombocytopenia, or in the preparation of a drug for treating the aforementioned disease or condition.

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CLAIMS

What is claimed is:

1. A method for treating thrombocytopenia and/or a disease and condition related to insufficient or decreased expression of THPO protein in a subject, comprising administering to the subject a curative dose of a small activating nucleic acid molecule targeting a promoter of *THPO*, a nucleic acid molecule encoding the small activating nucleic acid molecule, or a composition or formulation comprising the small activating nucleic acid molecule.

2. The method of claim 1, wherein the thrombocytopenia comprises thrombocytopenia caused by various causes, such as congenital (hereditary) or acquired thrombocytopenia, preferably thrombocytopenia caused by myelo-thrombocytopenia, increased peripheral platelet destruction, or splenic sequestration.

3. The method of claim 1, wherein the thrombocytopenia includes, but is not limited to, thrombocytopenia related to insufficient or decreased expression of THPO protein, thrombocytopenia caused by various causes such as immune thrombocytopenia, drug-induced thrombocytopenia, thrombotic thrombocytopenia purpura, or hereditary thrombocytopenia.

4. The method of any one of claims 1 to 3, wherein the individual is a mammal.

5. The method of claim 4, wherein the individual is a human.

6. The method of any one of claims 1 to 3, wherein the small activating nucleic acid molecule comprises a first nucleic acid strand and a second nucleic acid strand, the first nucleic acid strand having at least 75% (e.g., at least about 79%, about 80%, about 85%, about 90%, about 95%, about 99% or about 100%) homology or complementarity to continuous 16 to 35 nucleotides in length of any one of SEQ ID NO: 601 to SEQ ID NO: 605, and the first nucleic acid strand and the second nucleic acid strand complementarily form a double-stranded nucleic acid structure capable of activating the expression of *THPO* gene in a cell.

7. The method of claim 6, wherein the first nucleic acid strand of the small activating nucleic acid molecule comprises or is selected from any nucleotide sequence selected from SEQ ID NOs: 1048 to SEQ ID NOs: 1489, and the second nucleic acid strand comprises or is selected from any nucleotide sequence selected from SEQ ID NOs: 1490 to SEQ ID NOs: 1931.

8. The method of claim 6, wherein the first nucleic acid strand and the second nucleic acid strand are present on two different nucleic acid strands.

9. The method of claim 6, wherein the first nucleic acid strand and the second nucleic acid strand are present on the same nucleic acid strand, preferably, the small activating nucleic acid molecule is a hairpin single-stranded nucleic acid molecule, wherein the first nucleic acid strand and the second nucleic acid strand comprise complementary regions forming a double-stranded nucleic acid structure.

10. The method of claim 1, wherein at least one strand of the small activating nucleic acid molecule has an overhang of 0 to 6 nucleotides in length at 3' terminus.

11. The method of claim 10, wherein both strands of the small activating nucleic acid molecule have an overhang of 0 to 6 nucleotides in length at the 3' terminus, preferably an overhang of 2 or 3 nucleotides in length.

12. The method of claim 6 or 7, wherein the first nucleic acid strand and the second nucleic acid strand independently have 16 to 35 nucleotides in length.

13. The method of any of claims 1 to 12, wherein the small activating nucleic acid molecule comprises at least one modification, preferably, the modification is a chemical modification.

14. The method of claim 13, wherein the chemical modification comprises or is selected from one or more modifications selected from the group consisting of:

(1) modification of a phosphodiester bond connecting nucleotides in the nucleotide sequence of the small activating nucleic acid molecule;

(2) modification of 2'-OH of a ribose in the nucleotide sequence of the small activating nucleic acid molecule;

(3) modification of a base in the nucleotide sequence of the small activating nucleic acid molecule; and

(4) at least one nucleotide in the nucleotide sequence of the small activating nucleic acid molecule being a locked nucleic acid.

15. The method of claim 13, wherein the chemical modification comprises one or more rmodifications selected from the group consisting of: 2'-fluoro modification, 2'-oxymethyl modification, 2'-oxyethylidene methoxy modification, 2,4'-dinitrophenol modification, locked

nucleic acid (LNA), 2'-amino modification, 2'-deoxy modification, 5'-bromouracil modification, 5'-iodouracil modification, N-methyluracil modification, 2,6-diaminopurine modification, phosphorothioate modification, and boranophosphate modification.

16. The method of claim 3, wherein the acquired thrombocytopenia includes, but is not limited to, thrombocytopenia caused by aplastic anemia, myelodysplastic syndrome, leukemia, drugs, infection, tumor diseases, radiotherapy, bone marrow transplantation and chronic liver diseases, and immune thrombocytopenia, wherein the factors causing increased peripheral platelet destruction comprise thrombotic thrombocytopenia, heparin-induced thrombocytopenia, drug-induced thrombocytopenia, ITP, and thrombotic thrombocytopenia purpura.

17. A method for activating/up-regulating the expression of *THPO* gene in a subject or a cell, comprising administering a small activating nucleic acid molecule of the present invention, a nucleic acid coding the small activating nucleic acid molecule of the present invention, or a composition or formulation comprising the small activating nucleic acid molecule of the present invention to the subject or the cell.

18. A nucleic acid coding the small activating nucleic acid molecule of any one of claims 1 to 9.

19. A cell comprising the small activating nucleic acid molecule of any one of claims 1 to 9 or a nucleic acid encoding the small activating nucleic acid molecule of any one of claims 1 to 9.

20. A composition comprising the small activating nucleic acid molecule of any one of claims 1 to 9.

21. A formulation comprising the small activating nucleic acid molecule of any one of claims 1 to 9, wherein the formulation comprises a liposome, preferably an LNP-entrapped small activating nucleic acid molecule.