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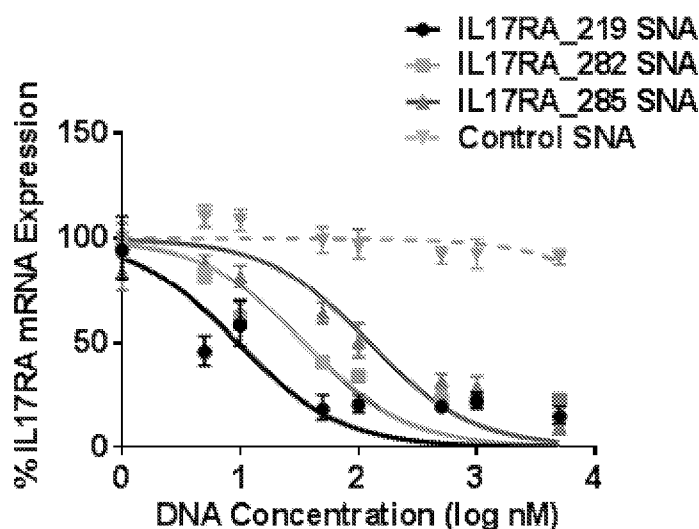
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Fig. 1



(57) Abstract: Aspects of the invention relate to antisense oligonucleotides directed to the interleukin 17 receptor (IL-17R), and other targets. Spherical nucleic acid formulations or compositions of antisense oligonucleotides and related methods of treatment are also provided.

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**LIPOSOMAL SPHERICAL NUCLEIC ACID (SNA) CONSTRUCTS PRESENTING
ANTISENSE OLIGONUCLEOTIDES (ASO) FOR SPECIFIC KNOCKDOWN OF
INTERLEUKIN 17 RECEPTOR mRNA**

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RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119(e) of United States provisional application Serial No. 62/333,082, filed May 6, 2016, the entire contents of which is incorporated by reference herein.

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BACKGROUND OF INVENTION

Inflammation, which can be classified as either acute or chronic, involves the activation of the immune system in response to harmful stimuli, such as, e.g., a pathogen, infection, irritant, or damage to cells. Acute inflammation is mediated by granulocytes, while chronic inflammation is mediated by mononuclear cells such as monocytes and lymphocytes.

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The process of acute inflammation is initiated by cells such as macrophages, dendritic cells, histiocytes, Kupffer cells, mastocytes, vascular endothelial cells, and vascular smooth muscle cells. At the onset of a harmful stimulus, these cells undergo activation and release inflammatory mediating and sensitizing molecules, such as, e.g., pro-inflammatory cytokines, pro-inflammatory prostaglandins, leukotrienes, histamine, serotonin, neutral proteases, bradykinin and nitric oxide. These inflammatory molecules modulate a complex series of biological events involving cellular and acellular components of the local vascular system, the immune system, and the injured tissue site to propagate and mature the inflammatory response.

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Severe or prolonged stimulation results in a chronic inflammatory response that leads to a progressive shift in the type of cells present at the site of tissue injury. Chronic inflammation may be characterized as the simultaneous destruction and healing of tissue from the inflammatory process, with the net result of provoking injury rather than mediating repair. As an inflammatory response can occur anywhere in the body, chronic inflammation has been implicated in the pathophysiology of a wide range of seemingly unrelated disorders which underlay a large and varied group of human diseases. For example, chronic inflammation is involved in diseases as diverse as psoriasis, cardiovascular diseases, cancers, allergies, obesity, diabetes, digestive system diseases, degenerative diseases, auto-immune disorders, and Alzheimer's disease.

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SUMMARY OF INVENTION

The present disclosure, in some aspects, includes a single-stranded modified oligonucleotide consisting of 10-30 linked nucleosides and having: a gap segment consisting of two to eight linked deoxynucleosides; a 5' wing segment consisting of linked nucleosides; and a 3' wing segment consisting of linked nucleosides; wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein at least some nucleosides of each wing segment comprises a modified nucleotide ; wherein the internucleoside linkages within the gap segment and the linkages connecting the gap segment to the 3' wing segments are all phosphorothioate linkages (*); and the internucleoside linkages connecting the rest of the nucleosides of both the 5' and 3' wing segments are phosphodiester linkages; and wherein the nucleobase sequence of the oligonucleotide consists of 10-30 contiguous nucleobases complementary to an equal length portion of SEQ ID NO: 302, or a pharmaceutically acceptable salt thereof.

In some embodiments the single-stranded modified oligonucleotide consists of 17-21 linked nucleosides. In other embodiments the gap segment consists of six linked deoxynucleosides. In yet other embodiments wherein each nucleoside of each wing segment comprises a modified nucleotide. In other embodiments the modified nucleotide is 2'O-methyl ribonucleoside (m). The oligonucleotide has 12 2'O-methyl ribonucleosides in other embodiments. In some embodiments the nucleobase sequence of the oligonucleotide consists of 17-21 contiguous nucleobases complementary to an equal length portion of SEQ ID NO: 302.

In one embodiment, the nucleobase sequence of the oligonucleotide is GCUUGGGCAGGTGGUGAA (SEQ ID NO: 225). In another embodiment, the nucleobase sequence of the oligonucleotide is CCCACAGGGGCATGUAGU (SEQ ID NO: 288). An additional embodiment includes an oligonucleotide with the nucleobase sequence of GUAGGGCGUGTGTGGGUC (SEQ ID NO: 291). In another embodiment, the nucleobase sequence of the oligonucleotide is mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmAmA (SEQ ID NO: 225). In a further embodiment, the nucleobase sequence of the oligonucleotide is mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU (SEQ ID NO: 288). In yet another embodiment, the nucleobase sequence of the oligonucleotide is mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC (SEQ ID NO: 291).

In some embodiments, the compound is 20 nucleotides in length.

In some embodiments, the oligonucleotide further comprises a molecular species at one of the ends. In another embodiment, the compound further comprises a molecular species at both ends.

In some embodiments, the molecular species is selected from the group consisting of a spacer, a lipid, a sterol, cholesterol, NAcetylgalactosamine (GalNAc), modified GalNAc, derivatized or substituted GalNAc, stearyl, C16 alkyl chain, bile acids, cholic acid, taurocholic acid, deoxycholate, oleyl lithocholic acid, oleoyl cholenic acid, glycolipids, phospholipids, sphingolipids, isoprenoids, such as steroids, vitamins, such as vitamin E, saturated fatty acids, unsaturated fatty acids, fatty acid esters, such as triglycerides, pyrenes, porphyrines, Texaphyrine, adamantane, acridines, biotin, coumarin, fluorescein, rhodamine, Texas-Red, digoxigenin, dimethoxytrityl, t-butyldimethylsilyl, t-butyldiphenylsilyl, cyanine dyes (e.g. Cy3 or Cy5), Hoechst 33258 dye, psoralen, and ibuprofen.

In other embodiments, the molecular species is selected from the group consisting of a lipophilic moiety; a folic acid radical; a steroid radical; a carbohydrate radical; a vitamin A radical; a vitamin E radical; or a vitamin K radical.

In some embodiments, the molecular species is connected directly to the compound through a linkage selected from the group consisting of phosphodiester, phosphorothioate, phosphorodithioate, methylphosphonate, and amide linkages.

In another embodiment, the molecular species is connected indirectly to the
20 compound through a linker. In some embodiments, the linker is a non-nucleotidic linker
selected from the group consisting of abasic residues (dSpacer), oligoethyleneglycol, such as
triethyleneglycol (spacer 9) or hexaethyleneglycol (spacer 18), and alkane-diol, such as
butanediol.

In some embodiments, the 3' end of the oligonucleotide is connected to 2 consecutive
25 linkers that are hexaethyleneglycol (spacer 18), the first hexaethyleneglycol connected to the
3' end of the oligonucleotide, the second hexaethyleneglycol connected to the first
hexaethyleneglycol and the second hexaethyleneglycol is connected to a cholesterol.

Another aspect of the present disclosure includes an oligonucleotide comprising mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmA/isp18//isp18//3CholTEG/ (SEQ ID NO: 225), wherein the oligonucleotide is 20 nucleotides in length, wherein m is a 2'O methyl, and wherein * is a phosphorothioate modification.

An additional aspect of the present disclosure includes an oligonucleotide comprising mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/.

(SEQ ID NO: 288), wherein the oligonucleotide is 20 nucleotides in length, wherein m is a 2'O methyl, and wherein * is a phosphorothioate modification.

A further aspect of the present disclosure includes an oligonucleotide comprising mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC/isp18//isp18//3CholTEG/ (SEQ ID NO: 291), wherein the oligonucleotide is 20 nucleotides in length, wherein m is a 2'O methyl, and wherein * is a phosphorothioate modification.

Another aspect of the present disclosure includes a stable self-assembling nanostructure, comprising a core having an oligonucleotide shell comprised of an antisense oligonucleotide 18 to 21 linked nucleosides in length targeted to Interleukin 17 receptor (IL-17R, IL-17RA) positioned on the exterior of the core. In some embodiments, the antisense oligonucleotide is 18 nucleotides in length. In other embodiments, IL-17RA has a sequence of SEQ ID NO: 302.

In another embodiment, less than all of the internucleoside linkages are phosphodiester. In some embodiments, the antisense oligonucleotide has phosphorothioate internucleoside linkages. In other embodiments, less than all of the internucleoside linkages are phosphorothioate. In another embodiment, the oligonucleotides have at least one internucleoside phosphorothioate linkage that is stereo-enriched. In another embodiment, the oligonucleotides have all the internucleoside phosphorothioate linkage that are stereo-enriched. The stereo-enriched phosphorothioate linkage may be Rp diastereomer, or Sp diastereomer.

In some embodiments, the antisense oligonucleotide has 2'O methyl modifications. In other embodiments, less than all of the nucleotides include a 2'O methyl modification.

In some embodiments, the antisense oligonucleotide has 2'O alkyl modifications. In other embodiments, less than all of the nucleotides include a 2'O alkyl modification.

In some embodiments, the antisense oligonucleotide has 17 internucleoside linkages and 6 central internucleoside linkages are phosphorothioate.

In some embodiments, the antisense oligonucleotide has a nucleobase sequence complementary to a sequence comprising at least 8 contiguous nucleobases of a sequence recited in SEQ ID NO: 302. In other embodiments, the antisense oligonucleotide is selected from the group consisting of

mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmAmA/isp18//isp18//3CholTEG/ (SEQ ID NO: 225);

mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/

(SEQ ID NO: 288); and
 mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC/isp18//isp18//3ChoITEG/
 (SEQ ID NO: 291) wherein – refers to a phosphodiester bond, * refers to a phosphorothioate
 bond, and m refers to a O methyl.

5 In some embodiments, the nanostructure includes 2-1,000 copies of the antisense
 oligonucleotide. In other embodiments, the nanostructure includes at least two different
 antisense oligonucleotides.

In some embodiments, the core is a solid or hollow core. In other embodiments, the
 core is a solid core and further comprising a lipid bilayer surrounding the core. In another
 10 embodiment, the solid core is comprised of noble metals, including gold and silver, transition
 metals including iron and cobalt, metal oxides including silica, polymers or combinations
 thereof. In some embodiments, the core is a polymeric core and wherein the polymeric core is
 comprised of amphiphilic block copolymers, hydrophobic polymers including polystyrene,
 poly(lactic acid), poly(lactic co-glycolic acid), poly(glycolic acid), poly(caprolactone) and
 15 other biocompatible polymers.

In other embodiments, the core is a liposomal core. In some embodiments, the
 liposomal core is comprised of one or more lipids selected from: 1,2-dioleoyl-sn-glycero-3-
 phosphocholine (DOPC), 1,2-dimyristoyl-sn-phosphatidylcholine (DMPC), 1-palmitoyl-2-
 oleoyl-sn-phosphatidylcholine (POPC), 1,2-distearoyl-sn-glycero-3-phospho-(1'-rac-glycerol)
 20 (DSPG), 1,2-dioleoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DOPG), 1,2-distearoyl-sn-
 glycero-3-phosphocholine (DSPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC),
 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine (DOPE), and 1,2-
 dihexadecanoyl-sn-glycero-3-phosphoethanolamine (DPPE), sphingolipids such as
 sphingosine, sphingosine phosphate, methylated sphingosines and sphingamines, ceramides,
 25 ceramide phosphates, 1-0 acyl ceramides, dihydroceramides, 2-hydroxy ceramides,
 sphingomyelin, glycosylated sphingolipids, sulfatides, gangliosides, phosphosphingolipids,
 and phytosphingosines of various lengths and saturation states and their derivatives,
 phospholipids such as phosphatidylcholines, lysophosphatidylcholines, phosphatidic acids,
 lysophosphatidic acids, cyclic LPA, phosphatidylethanolamines,
 30 lysophosphatidylethanolamines, phosphatidylglycerols, lysophosphatidylglycerols,
 phosphatidylserines, lysophosphatidylserines, phosphatidylinositols, inositol phosphates, LPI,
 cardiolipins, lysocardiolipins, bis(monoacylglycero) phosphates, (diacylglycero) phosphates,
 ether lipids, diphytanyl ether lipids, and plasmalogens of various lengths, saturation states,
 and their derivatives, sterols such as cholesterol, desmosterol, stigmasterol, lanosterol,

lathosterol, diosgenin, sitosterol, zymosterol, zymostenol, 14-demethyl-lanosterol, cholesterol sulfate, DHEA, DHEA sulfate, 14-demethyl-14-dehydrlanosterol, sitostanol, campesterol, ether anionic lipids, ether cationic lipids, lanthanide chelating lipids, A-ring substituted oxysterols, B-ring substituted oxysterols, D-ring substituted oxysterols, side-chain substituted oxysterols, double substituted oxysterols, cholestanoic acid derivatives, fluorinated sterols, fluorescent sterols, sulfonated sterols, phosphorylated sterols, and polyunsaturated sterols of different lengths, saturation states, and derivatives thereof.

The present disclosure, in some aspects, includes a multiplex antisense oligonucleotide spherical nucleic acid (mASO-SNA), comprising a core having an oligonucleotide shell comprised of an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a first gene and an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a second gene, wherein the core is a solid surrounded by a lipid bilayer or a liposome or lipoplex complex core and the oligonucleotide shell is positioned on the exterior of the core.

In some embodiments, the first gene and the second gene are associated with a disease. In an embodiment, the disease is an inflammatory disorder. In another embodiment, the disease is psoriasis.

In some embodiments, the first gene and the second gene are associated with a target pathway.

In another embodiment, the mASO-SNA further comprises an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a third gene. In some embodiments, the first gene is an Interleukin 17 receptor (IL-17RA). In other embodiments, the second gene is TNF. In some embodiments, the first gene and the second gene are present in an approximate equimolar amount in the oligonucleotide shell.

In another embodiment, the mASO-SNA comprises an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to four or more genes.

The present disclosure, in some aspects, provides a method for treating a disorder, comprising: administering to a subject having a disorder a multiplex antisense oligonucleotide spherical nucleic acid (mASO-SNA), comprising a core having an oligonucleotide shell comprised of an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a first gene and an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a second gene, wherein the core is a solid surrounded by a lipid bilayer or a liposome or lipoplex complex core and the oligonucleotide shell is positioned on the exterior of the core in an effective amount to treat the disorder.

In some embodiments, the disorder is an inflammatory disorder.

In other embodiments, the mASO-SNA produces simultaneous mRNA knock-down of the first and second gene. In another embodiment, the first gene and the second gene are associated with a target pathway. In some embodiments, the mASO-SNA produces additive
5 knock-down of the target pathway.

In other embodiments, the disorder is psoriasis.

Another aspect of the present disclosure provides a method for treating an inflammatory disorder, including administering to a subject having an inflammatory disorder a composition comprising the oligonucleotide or the nanostructure described herein in an
10 effective amount to treat the inflammatory disorder.

In some embodiments, the inflammatory disorder is selected from the group consisting of an autoimmune disease, an infectious disease, transplant rejection or graft-versus-host disease, malignancy, a pulmonary disorder, an intestinal disorder, a cardiac disorder, sepsis, a spondyloarthropathy, a metabolic disorder, anemia, pain, a hepatic
15 disorder, a skin disorder, a nail disorder, rheumatoid arthritis, psoriasis, psoriasis in combination with psoriatic arthritis, ulcerative colitis, Crohn's disease, vasculitis, Behcet's disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disorder (COPD), idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriatic
20 arthritis, and chronic plaque psoriasis.

In other embodiments, the inflammatory disorder is selected from the group consisting of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, allergy, multiple sclerosis, autoimmune diabetes, autoimmune uveitis, and nephritic syndrome.

25 An additional aspect of the present disclosure includes a method for reducing expression levels of IL-17 receptor in vivo, including administering to a subject a composition comprising the oligonucleotide or the nanostructure described herein in an effective amount to reduce IL-17 receptor levels in vivo.

In some embodiments, the first gene, the second gene, and the third gene are
30 associated with a target pathway. In some embodiments, the first gene and the second gene are associated with different target pathways. In some embodiments, the first gene, the second gene and the third gene are associated with different target pathways. In some embodiments, the first gene is an interleukin-4 receptor (IL-4R). In some embodiments, the

second gene is interleukin-1 beta (IL-1 β). In some embodiments, the third gene is connective tissue growth factor (CTGF).

In some embodiments, the first gene, the second gene, and the third gene are present in an approximate equimolar amount in the oligonucleotide shell.

According to another aspect, pharmaceutical compositions are provided herein. In some embodiments, the pharmaceutical composition includes a stable self-assembling nanostructure, wherein the self-assembling nanostructure comprises a core having an oligonucleotide shell comprised of an antisense oligonucleotide 18 to 21 linked nucleosides in length targeted to interleukin 17 receptor (IL-17R) positioned on the exterior of the core.

In some embodiments, the antisense oligonucleotide is 18 nucleotides in length. In some embodiments, the IL-17R has a sequence of SEQ ID NO: 302.

In some embodiments, less than all of the internucleoside linkages are phosphodiester. In some embodiments, the antisense oligonucleotide has phosphorothioate internucleoside linkages. In some embodiments, less than all of the internucleoside linkages are phosphorothioate.

In some embodiments, the antisense oligonucleotide has 2'O methyl modifications. In some embodiments, less than all of the nucleotides include a 2'O methyl modification.

In some embodiments, the antisense oligonucleotide has 17 internucleoside linkages and wherein 6 central internucleoside linkages are phosphorothioate. In some embodiments, the antisense oligonucleotide has a nucleobase sequence complementary to a sequence including at least 8 contiguous nucleobases of a sequence recited in SEQ ID NO: 302.

In some embodiments, the antisense oligonucleotide is selected from the group consisting of

mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmAmA/isp18//isp18//3CholTEG/ (SEQ ID NO: 225);

mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/ (SEQ ID NO: 288); and

mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC/isp18//isp18//3CholTEG/ (SEQ ID NO: 291) wherein – refers to a phosphodiester bond, * refers to a phosphorothioate bond, and m refers to a O methyl.

In some embodiments, the pharmaceutical composition includes a gel vehicle. In some embodiments, the pharmaceutical composition includes one or more of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), diethylene glycol monoethyl ether (Transcutol P), glycerin, hydroxyethyl cellulose, methylparaben, propylparaben, disodium EDTA, sodium

metabisulfite and water. In certain embodiments, the pharmaceutical composition includes at least 0.00007%

mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/

(SEQ ID NO: 288), at least 0.0003801% DOPC, at least 25% diethylene glycol monoethyl ether (Transcutol P), at least 5% glycerin, at least 1% hydroxyethyl cellulose, at least 0.15% methylparaben, at least 0.05% propylparaben, at least 0.1% disodium EDTA, at least 0.2% sodium metabisulfite, and at least 68.5% water.

In some embodiments, the pharmaceutical composition includes at least 0.007%

mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/

(SEQ ID NO: 288), at least 0.03801% DOPC, at least 25% diethylene glycol monoethyl ether (Transcutol P), at least 5% glycerin, at least 1% hydroxyethyl cellulose, at least 0.15% methylparaben, at least 0.05% propylparaben, at least 0.1% disodium EDTA, at least 0.2% sodium metabisulfite, and at least 68.45% water.

In some embodiments, the pharmaceutical composition comprises at least 0.01419%

mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/

(SEQ ID NO: 288), at least 0.2655% DOPC, at least 25% diethylene glycol monoethyl ether (Transcutol P), at least 5% glycerin, at least 1% hydroxyethyl cellulose, at least 0.15% methylparaben, at least 0.05% propylparaben, at least 0.1% disodium EDTA, at least 0.2% sodium metabisulfite, and at least 68.2% water.

In some embodiments, the pharmaceutical composition comprises at least 0.1419%

mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/

(SEQ ID NO: 288), at least 2.655% DOPC, at least 25% diethylene glycol monoethyl ether (Transcutol P), at least 5% glycerin, at least 1% hydroxyethyl cellulose, at least 0.15% methylparaben, at least 0.05% propylparaben, at least 0.1% disodium EDTA, at least 0.2% sodium metabisulfite, and at least 65.7% water.

In some embodiments, the pharmaceutical composition comprises at least 1.419%

mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/

(SEQ ID NO: 288), at least 26.55% DOPC, at least 25% diethylene glycol monoethyl ether (Transcutol P), at least 5% glycerin, at least 1% hydroxyethyl cellulose, at least 0.15% methylparaben, at least 0.05% propylparaben, at least 0.1% disodium EDTA, at least 0.2% sodium metabisulfite, and at least 40.5% water.

In some embodiments, the pharmaceutical composition includes an oligonucleotide described herein.

In some embodiments, the pharmaceutical composition further includes a gel vehicle. In some embodiments, the pharmaceutical composition includes one or more of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), diethylene glycol monoethyl ether (Transcutol P), glycerin, hydroxyethyl cellulose, methylparaben, propylparaben, disodium EDTA, sodium metabisulfite and water.

In some embodiments, the pharmaceutical composition includes a mASO-SNA described herein.

In some embodiments, the pharmaceutical composition further includes a gel vehicle. In some embodiments, the pharmaceutical composition comprises one or more of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), diethylene glycol monoethyl ether (Transcutol P), glycerin, hydroxyethyl cellulose, methylparaben, propylparaben, disodium EDTA, sodium metabisulfite and water.

According to another aspect, methods for treating a disorder using a pharmaceutical composition are also disclosed herein. In some embodiments, a method for treating a disorder comprises administering to a subject having a disorder a pharmaceutical composition including a multiplex antisense oligonucleotide spherical nucleic acid (mASO-SNA), including a core having an oligonucleotide shell comprised of an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a first gene and an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a second gene, wherein the core is a solid surrounded by a lipid bilayer or a liposome or lipoplex complex core and the oligonucleotide shell is positioned on the exterior of the core in an effective amount to treat the disorder.

In some embodiments, the pharmaceutical composition further comprises a gel vehicle. In some embodiments, the pharmaceutical composition comprises one or more of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), diethylene glycol monoethyl ether (Transcutol P), glycerin, hydroxyethyl cellulose, methylparaben, propylparaben, disodium EDTA, sodium metabisulfite and water.

In some embodiments, the disorder is an inflammatory disorder.

In some embodiments, the mASO-SNA produces simultaneous mRNA knock-down of the first and second gene. In some embodiments, the first gene and the second gene are associated with a target pathway. In some embodiments, the mASO-SNA produces additive knock-down of the target pathway.

In some embodiments, the disorder is psoriasis.

According to another aspect, methods for treating an inflammatory disorder using a pharmaceutical composition are also disclosed herein. In some embodiments, a method for

treating an inflammatory disorder includes administering to a subject having an inflammatory disorder a pharmaceutical composition including an oligonucleotide, a nanostructure or a mASO-SNA described herein in an effective amount to treat the inflammatory disorder.

In some embodiments, the pharmaceutical composition further includes a gel vehicle.

5 In some embodiments, the pharmaceutical composition includes one or more of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), diethylene glycol monoethyl ether (Transcutol P), glycerin, hydroxyethyl cellulose, methylparaben, propylparaben, disodium EDTA, sodium metabisulfite and water.

In some embodiments, the inflammatory disorder is selected from the group
10 consisting of an autoimmune disease, an infectious disease, transplant rejection or graft-versus-host disease, malignancy, a pulmonary disorder, an intestinal disorder, a cardiac disorder, sepsis, a spondyloarthropathy, a metabolic disorder, anemia, pain, a hepatic disorder, a skin disorder, a nail disorder, rheumatoid arthritis, psoriasis, psoriasis in combination with psoriatic arthritis, ulcerative colitis, Crohn's disease, vasculitis, Behcet's
15 disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disorder (COPD), idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriatic arthritis, and chronic plaque psoriasis.

In some embodiments, the inflammatory disorder is selected from the group
20 consisting of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, allergy, multiple sclerosis, autoimmune diabetes, autoimmune uveitis, and nephritic syndrome.

According to another aspect, methods for reducing expression of the IL-17 receptor *in vivo* are provided herein. In some embodiments, the method for reducing expression levels of
25 IL-17 receptor *in vivo* includes administering to a subject a pharmaceutical composition including an oligonucleotide, a nanostructure, or a mASO-SNA described herein in an effective amount to reduce IL-17 receptor levels *in vivo*.

In some embodiments, the subject is a mammal. In some embodiments, the subject is human.

30 In some embodiments, the pharmaceutical composition is in contact with a cell in the subject for at least 24 hours.

In some embodiments, the pharmaceutical composition is a topical pharmaceutical composition.

According to another aspect, methods for reducing expression levels of IL-17 receptor (IL-17R) *in vitro* are provided herein.

In some embodiments, the method for reducing expression levels of IL-17R *in vitro* includes contacting a cell with an oligonucleotide, a nanostructure, or a mASO-SNA

5 described herein in an effective amount to reduce IL-17R levels *in vitro*.

In some embodiments, the cell is a human foreskin keratinocyte (HFK).

In some embodiments, the cell is contacted with the oligonucleotide, the nanostructure, or the mASO-SNA at a concentration of 1 nM, 10 nM, 100 nM, or 1000 nM.

10 In some embodiments, the cell is contacted with the oligonucleotide, the nanostructure, or the mASO-SNA for 24 hours.

Each of the limitations of the invention can encompass various embodiments of the invention. It is, therefore, anticipated that each of the limitations of the invention involving any one element or combinations of elements can be included in each aspect of the invention. This invention is not limited in its application to the details of construction and the
15 arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways.

BRIEF DESCRIPTION OF DRAWINGS

20 The accompanying drawings are not intended to be drawn to scale. In the drawings, each identical or nearly identical component that is illustrated in various figures is represented by a like numeral. For purposes of clarity, not every component may be labeled in every drawing. In the drawings:

Fig. 1 depicts *in vitro* IL-17RA mRNA knockdown using targeted SNAs. IL-17RA
25 mRNA expression is decreased in HFK cells treated with SNAs presenting an ASO sequence targeting IL-17RA. Cells treated with control SNAs do not demonstrate an appreciable decrease in IL-17RA mRNA expression.

Fig. 2 shows IL-17RA mRNA knockdown using topically applied targeted SNAs in the human skin equivalent, EpiDerm-FT™. IL-17RA mRNA expression is decreased in
30 human skin equivalent tissues treated topically with SNAs presenting either ASO IL17RA_219 or ASO IL17RA_282 for 48 hours. Tissues treated with SNAs presenting the control ASO do not demonstrate an appreciable decrease in IL-17RA mRNA expression as measured by qRT-PCR. Data shown are representative of two independent experiments performed.

Fig. 3 shows *ex vivo* IL-17RA mRNA knockdown using topically applied targeted SNAs in human skin explants. IL-17RA mRNA expression is decreased in human skin explant biopsies treated topically with SNAs presenting either ASO IL17RA_219 or ASO IL17RA_282 for 96 hours. Biopsies treated with SNAs presenting the control ASO do not demonstrate an appreciable decrease in IL-17RA mRNA expression as measured by qRT-PCR.

Fig. 4 shows TNF mRNA knockdown using a mixture of SNAs. TNF mRNA expression is decreased in HFK cells treated with a mixture of anti-TNF-SNAs and anti-IL17RA-SNAs. Cells treated with Control-SNAs do not demonstrate an appreciable decrease in TNF mRNA levels. Data shown are representative of two independent experiments performed.

Fig. 5 shows IL17RA mRNA knockdown using a mixture of SNAs. IL17RA mRNA expression is decreased in HFK cells treated with a mixture of anti-TNF-SNAs and anti-IL17RA-SNAs. Cells treated with Control-SNAs do not demonstrate an appreciable decrease in TNF mRNA levels. Data shown are representative of two independent experiments performed.

Figs. 6A-6D show configurations of multiplexed SNAs. Liposomes were surface-functionalized in the following configurations: (Fig. 6A) 33% TNF-ASO (A) and 66% control (D); (Fig. 6B) 33% IL17RA-ASO (B) and 66% control (D); (Fig. 6C) 33% TNF-ASO (A), 33% IL17RA-ASO (B), and 33% control (D); (Fig. 6D) 100% control (D).

Fig. 7 shows a comparison of TNF mRNA knockdown using multiplexed SNAs. TNF mRNA expression is decreased in HFK cells treated with anti-TNF-SNAs and multiplexed SNAs containing anti-TNF and anti-IL17RA ASOs. Cells treated with anti-IL17RA-SNAs do not demonstrate an appreciable decrease in TNF mRNA levels. Data shown are representative of two independent experiments performed.

Fig. 8 shows a comparison of IL17RA mRNA knockdown using multiplexed SNAs demonstrate additive knockdown effects. IL17RA mRNA expression is decreased in HFK cells treated with anti-IL17RA-SNAs and multiplexed SNAs containing anti-TNF and anti-IL17RA ASOs. Cells treated with anti-TNF-SNAs demonstrate a slight decrease potentially due to the related biological signaling pathways of TNF and IL17RA. Greater IL17RA mRNA knockdown is observed when cells are treated with anti-IL17RA-SNAs. Multiplexed SNAs targeting both TNF and IL17RA have an additive effect and show greater knockdown of IL17RA mRNA than when SNAs targeting only anti-TNF or anti-IL17RA are used alone. Data shown are representative of at least two independent experiments performed.

Fig. 9 depicts inhibition of IL-17RA mRNA expression. The graph shows IL-17RA mRNA expression in healthy human skin explants after 24 hours treatment, as measured by qRT-PCR (percent of untreated $\pm$ SEM). Each drug product treatment group, n=9 samples. Untreated group, n=8 samples. One-way ANOVA, 31 DF, p=0.0011 (0.007 % versus

5 untreated) and **** p<0.0001 versus 0% gel.

Fig. 10 depicts inhibition of IL-17RA protein expression. The graph shows IL-17RA protein expression in healthy human skin explants after 24 hours treatment with IL17RA_282 in formulation described in Table 3, as measured by western blot (percent of untreated).

Pooled samples for each group.

10 Fig. 11 shows inhibition of IL-17RA mRNA expression. * p < 0.05; ** p < 0.01; **** p < 0.0001 compared to vehicle. A one sample t-test was used.

Figs. 12A-12D show configurations of multiplexed SNAs. Liposome were surface functionalized in the following configurations: monoplex SNA (Fig. 12A); multiplex SNA containing two targeted antisense oligonucleotides (Fig. 12B); multiplex SNA containing

15 three targeted antisense oligonucleotides (Fig. 12C); non-targeted control SNA (Fig. 12D).

Fig. 13 shows inhibition of IL4R mRNA in cells treated with various multiplex SNA configurations. Liposome were surface functionalized various targeted antisense oligonucleotide(s) or control oligonucleotide. The expression of IL4R mRNA is reduced noticeably when cells are treated with SNAs that target IL4R. Control SNA and SNAs

20 functionalized with non-targeting oligonucleotides do not reduce IL4R mRNA expression to the same extent.

Fig. 14 shows inhibition of IL1b mRNA in cells treated with various multiplex SNA configurations. Liposome were surface functionalized various targeted antisense oligonucleotide(s) or control oligonucleotide. The expression of IL1b mRNA is reduced

25 noticeably when cells are treated with SNAs that target IL1b. Control SNA and SNAs functionalized with non-targeting oligonucleotides do not reduce IL1b mRNA expression to the same extent.

Fig. 15 shows inhibition of CTGF mRNA in cells treated with various multiplex SNA configurations. Liposome were surface functionalized with various targeted antisense

30 oligonucleotide(s) or control oligonucleotide. The expression of CTGF mRNA is reduced noticeably when cells are treated with SNAs that target CTGF. Control SNA and SNAs functionalized with non-targeting oligonucleotides do not reduce CTGF mRNA expression to the same extent.

DETAILED DESCRIPTION

The invention in some aspects relates to antisense inhibitors of a cell signaling protein receptor involved in systemic inflammation, Interleukin 17 receptor (IL-17RA). IL-17 and its target receptor IL-17RA play an important role in psoriasis. IL-17 elicits its effects by binding IL-17RA, the latter of which is expressed almost exclusively in keratinocytes within the epidermis. Antisense technology is a useful means for reducing the expression of specific gene products by targeting a messenger RNA (mRNA) and preventing translation of the mRNA. However, the selection of specific therapeutically functional antisense oligonucleotides (ASOs) can be challenging. Further, ASO that are therapeutically active in a linear form do not necessarily retain activity when formulated as a nanoparticle or other type of three dimensional presentation format.

It has been discovered in aspects of the invention that Spherical Nucleic Acids (SNAs) surface functionalized with antisense oligonucleotides (ASOs) having appropriate structural properties can mediate highly effective gene knockdown of the intended target mRNA. For example, it is demonstrated herein that IL-17RA expression can be inhibited through the use of SNAs targeting human IL-17RA (anti-IL17RA-SNAs) (see for instance GeneBank accession number NM_014339.6) mRNA in primary human foreskin keratinocytes (HFK) with no associated toxicity or immune-stimulatory effects. Further, it is shown that anti-IL-17RA SNAs inhibit mRNA expression in a human skin equivalent model and human skin explants. In some embodiments, the response the anti-IL-17RA SNAs inhibit IL-17RA mRNA expression in a dose-dependent manner. As described herein, the oligonucleotides arranged in an SNA geometry exhibit enhanced penetration and increased cellular uptake.

It has also been discovered that multiplex SNAs having different ASOs directed at different therapeutic targets can produce significant target knockdown and therapeutic effects. The ability to load specific amounts of different ASOs on the surface of an SNA in a way such that they do not interfere with the activity of the other ASOs was unexpected. As shown in the Examples, when anti-IL-17RA-SNAs were mixed with anti-TNF-SNAs and co-administered to cells, simultaneous mRNA knockdown of each targeted gene was achieved. Additionally when SNAs presenting two or more ASO sequences each targeting different mRNAs on the same particle were administered to cells the simultaneous mRNA knockdown of each gene targeted using a single particle in the same cell was achieved. These SNAs are referred to as multiplexed ASO-SNAs (mASO-SNA). Furthermore, when mASO-SNAs were multiplexed with ASOs targeting two mRNAs of genes involved in a related biological

pathway, additive knockdown effects were observed. Not only did the co-presentation of the two ASOs not interfere with the activity of the other co-presented ASO but when targeting a common pathway the therapeutic effect observed with the mASO-SNAs was greater than that observed with either ASO-SNA alone.

5 The invention in some aspects relates to compositions for reducing IL-17RA and methods for treating an inflammatory disorder using those compositions. Highly effective IL-17RA inhibitors have been identified according to aspects of the invention. The IL-17RA inhibitors are nucleic acid based antisense compositions. The term “IL-17RA” refers to a receptor for the cytokine IL-17.

10 An “IL-17RA inhibitor” as used herein refers to a nucleic acid based agent which interferes with IL-17RA activity. In particular, the IL-17RA antisense inhibitors or IL-17RA antisense oligonucleotides of the invention reduce the expression of the IL-17RA gene. By reducing expression of the IL-17RA gene the endogenous IL-17 is not able to promote cell signaling through its interaction with the receptor. When IL-17RA is available for binding to
15 IL-17, IL17RA is activated leading to induction of expression of inflammatory chemokines and cytokines such as CXCL1, CXCL8/IL8 and IL6. These signaling cascades can be blocked using the ASO-SNA of the invention.

 The IL17RA inhibitors of the invention are antisense nucleic acids. Antisense nucleic acids typically include modified or unmodified RNA, DNA, or mixed polymer nucleic acids,
20 and primarily function by specifically binding to matching sequences resulting in modulation of peptide synthesis. Antisense nucleic acids bind to target RNA by Watson Crick base-pairing and block gene expression by preventing ribosomal translation of the bound sequences either by steric blocking or by activating RNase H enzyme. Antisense molecules may also alter protein synthesis by interfering with RNA processing or transport from the
25 nucleus into the cytoplasm.

 In some embodiments, the invention relates to compositions for reducing interleukin-4 receptor (IL-4R) (see e.g., GenBank: NM_000418 (SEQ ID NO: 306)) and methods for treating an inflammatory disorder using those compositions. Highly effective IL-4R inhibitors have been identified according to aspects of the invention. The IL-4R inhibitors are
30 nucleic acid based antisense compositions. The term “IL-4R” refers to a receptor for the cytokine IL-4 or IL-13.

 An “IL-4R inhibitor” as used herein refers to a nucleic acid based agent which interferes with IL-4R activity. In particular, the IL-4R antisense inhibitors or IL-4R antisense oligonucleotides of the invention reduce the expression of the IL-4R gene. In some

embodiments, the antisense oligonucleotide is 18 nucleotides in length. In other embodiments, IL-17RA has a sequence of SEQ ID NO: 302. By reducing expression of the IL-4R gene the endogenous IL-4 or IL-13 is not able to promote cell signaling through its interaction with the receptor. When IL-4R is available for binding to IL-4 or IL-13, IL-4R is activated leading to coupling to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL-4/IL-13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2. Soluble IL4R (sIL4R) inhibits IL4-mediated cell proliferation and IL5 up-regulation by T-cells (Keegan et al., *Cell* (1994) 76:811-820). These signaling cascades can be blocked using the ASO-SNA of the invention.

The IL-4R inhibitors of the invention are antisense nucleic acids. Antisense nucleic acids typically include modified or unmodified RNA, DNA, or mixed polymer nucleic acids, and primarily function by specifically binding to matching sequences resulting in modulation of peptide synthesis. Antisense nucleic acids bind to target RNA by Watson Crick base-pairing and block gene expression by preventing ribosomal translation of the bound sequences either by steric blocking or by activating RNase H enzyme. Antisense molecules may also alter protein synthesis by interfering with RNA processing or transport from the nucleus into the cytoplasm.

In some embodiments, the invention relates to compositions for reducing interleukin-1 beta (IL-1 β) (see e.g., GenBank: NM_000576 (SEQ ID NO: 307)) and methods for treating an inflammatory disorder using those compositions. Highly effective IL-1 β inhibitors have been identified according to aspects of the invention. The IL-1 β inhibitors are nucleic acid based antisense compositions. The term "IL-1 β " refers to a proinflammatory cytokine that was initially discovered as the major endogenous pyrogen, induces prostaglandin synthesis, neutrophil influx and activation, T-cell activation and cytokine production, B-cell activation and antibody production, and fibroblast proliferation and collagen production. Promotes Th17 differentiation of T-cells.

An "IL-1 β inhibitor" as used herein refers to a nucleic acid based agent which interferes with IL-1 β activity. In particular, the IL-1 β antisense inhibitors or IL-1 β antisense oligonucleotides of the invention reduce the expression of the IL-1 β gene. By reducing expression of the IL-1 β gene, signaling is reduced or not carried out (Van Damme et al., *Nature* (1985) 314:266-268; Piccioli et al., *Semin Immunol* (2013) 25(6):425-9). The signaling cascades that involve IL-1 β can be blocked using the ASO-SNA of the invention.

The IL-1 β inhibitors of the invention are antisense nucleic acids. Antisense nucleic acids typically include modified or unmodified RNA, DNA, or mixed polymer nucleic acids, and primarily function by specifically binding to matching sequences resulting in modulation of peptide synthesis. Antisense nucleic acids bind to target RNA by Watson Crick base-pairing and block gene expression by preventing ribosomal translation of the bound sequences either by steric blocking or by activating RNase H enzyme. Antisense molecules may also alter protein synthesis by interfering with RNA processing or transport from the nucleus into the cytoplasm.

In some embodiments, the invention relates to compositions for reducing connective tissue growth factor (CTGF) (see e.g., GenBank: NM_001901 (SEQ ID NO: 308)) and methods for treating a disorder (e.g., atherosclerosis, pulmonary and renal fibrotic disorders and cancer) using those compositions. Highly effective CTGF inhibitors have been identified according to aspects of the invention. The CTGF inhibitors are nucleic acid based antisense compositions. The term "CTGF" refers to a connective tissue mitogen secreted by cells (e.g., vascular endothelial cells) that, among other things, promotes proliferation and differentiation of chondrocytes; mediates heparin- and divalent cation-dependent cell adhesion in many cell types including fibroblasts, myofibroblasts, endothelial and epithelial cells; and enhances fibroblast growth factor-induced DNA synthesis.

An "CTGF inhibitor" as used herein refers to a nucleic acid based agent which interferes with CTGF activity. In particular, the CTGF antisense inhibitors or CTGF antisense oligonucleotides of the invention reduce the expression of the CTGF gene. By reducing expression of the CTGF gene, cell signaling is not promoted. For instance, CTGF interacts with growth factors, surface receptors and matrix components, with important roles in embryonic development and the maintenance of normal cell and connective tissue function, due to its widespread expression. CTGF is also important for tissue repair following injury, and has been implicated in common diseases including atherosclerosis, pulmonary and renal fibrotic disorders and cancer (de Winter et al., *Growth Factors* (2008) 26(2):80-91). The signaling cascades that CTGF is involved in can be blocked using the ASO-SNA of the invention.

The CTGF inhibitors of the invention are antisense nucleic acids. Antisense nucleic acids typically include modified or unmodified RNA, DNA, or mixed polymer nucleic acids, and primarily function by specifically binding to matching sequences resulting in modulation of peptide synthesis. Antisense nucleic acids bind to target RNA by Watson Crick base-pairing and block gene expression by preventing ribosomal translation of the bound

sequences either by steric blocking or by activating RNase H enzyme. Antisense molecules may also alter protein synthesis by interfering with RNA processing or transport from the nucleus into the cytoplasm.

As used herein, the term “antisense nucleic acid” or “antisense oligonucleotide” describes a nucleic acid that hybridizes under physiological conditions to DNA comprising a particular gene or to an mRNA transcript of that gene in this case IL17RA and, thereby, inhibits the transcription of that gene and/or the translation of that mRNA. The antisense molecules are designed so as to interfere with transcription or translation of a target gene upon hybridization with the target gene or transcript. Those skilled in the art will recognize that the exact length of the antisense oligonucleotide and its degree of complementarity with its target will depend upon the specific target selected, including the sequence of the target and the particular bases which comprise that sequence.

“Inhibition of gene expression” refers to the absence or observable decrease in the level of protein and/or mRNA product from a target gene, such as the IL17RA gene.

“Specificity” refers to the ability to inhibit the target gene without manifest effects on other genes of the cell. The consequences of inhibition can be confirmed by examination of the outward properties of the cell or organism or by biochemical techniques such as RNA solution hybridization, nuclease protection, Northern hybridization, reverse transcription, gene expression monitoring with a microarray, antibody binding, enzyme linked immunosorbent assay (ELISA), Western blotting, radioimmunoassay (RIA), other immunoassays, and fluorescence activated cell analysis (FACS).

The antisense oligonucleotides of the invention inhibit IL17RA expression. Depending on the assay, quantitation of the amount of gene expression allows one to determine a degree of inhibition which is greater than 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99% as compared to a cell not treated according to the present invention. As an example, the efficiency of inhibition may be determined by assessing the amount of gene product in the cell.

The ASOs described herein include bioequivalent compounds, salts and prodrugs thereof. The term bioequivalent compounds, including pharmaceutically acceptable salts and prodrugs as used herein refers to antisense oligonucleotides having the same primary structure as the antisense oligonucleotide of interest, but including salt forms or structures which can be cleaved or modified to have the same type of biological effect as the antisense oligonucleotide of interest. This is intended to encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an

animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof.

“Pharmaceutically acceptable salts” are physiologically and pharmaceutically acceptable salts of the nucleic acids of the invention: i.e., salts that retain the desired biological activity of the compound of interest and do not impart undesired toxicological effects thereto. Pharmaceutically acceptable salts include but are not limited to (a) salts formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine.

The compounds of the invention may also be prepared to be delivered in a “prodrug” form. A “prodrug” is a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions.

The antisense oligonucleotides of the invention are IL17RA antisense oligonucleotides. An antisense IL17RA oligonucleotide refers to a compound having a sequence of nucleotide bases and a subunit-to-subunit backbone that allows the antisense oligonucleotide to hybridize to a IL17RA target mRNA sequence typically by Watson-Crick base pairing, to form an RNA:oligomer heteroduplex within the target sequence.

The specific hybridization of an antisense oligonucleotide with its target nucleic acid, IL17RA mRNA, interferes with the normal function of the IL17RA mRNA. This modulation of function of a target nucleic acid by compounds which specifically hybridize to it is generally referred to as “antisense”. The functions of DNA to be interfered with include replication and transcription. The functions of RNA to be interfered with include all vital functions such as, for example, translocation of the RNA to the site of protein translation, translation of protein from the RNA, splicing of the RNA to yield one or more mRNA species, and catalytic activity which may be engaged in or facilitated by the RNA. The overall effect of such interference with target nucleic acid function is modulation of the

expression of IL17RA protein. In the context of the present invention, “modulation” means a decrease or inhibition in the expression of a gene.

An antisense oligonucleotide “specifically hybridizes” to a target polynucleotide if the oligonucleotide hybridizes to the IL17RA target under physiological conditions, with a thermal melting temperature (T_m) substantially greater than 37°C, preferably at least 45°C, and typically 50°C-80°C or higher. Such hybridization preferably corresponds to stringent hybridization conditions, selected to be about 10°C, and preferably about 50°C lower than the T_m for the specific sequence at a defined ionic strength and pH. At a given ionic strength and pH, the T_m is the temperature at which 50% of a target sequence hybridizes to a complementary polynucleotide.

Polynucleotides are described as “complementary” to one another when hybridization occurs in an antiparallel configuration between two single-stranded polynucleotides. A double-stranded polynucleotide can be “complementary” to another polynucleotide, if hybridization can occur between one of the strands of the first polynucleotide and the second. Complementarity (the degree that one polynucleotide is complementary with another) is quantifiable in terms of the proportion of bases in opposing strands that are expected to form hydrogen bonds with each other, according to generally accepted base-pairing rules. An antisense compound may be complementary to a target region of a target transcript even if the two bases sequences are not 100% complementary, as long as the heteroduplex structure formed between the compound and transcript has the desired T_m stability.

Identifying an antisense oligonucleotide that targets a particular nucleic acid may be a multistep process. The process usually begins with the identification of a nucleic acid sequence whose function is to be modulated. This may be, for example, a cellular gene (or mRNA transcribed from the gene) whose expression is associated with a particular inflammatory disorder or disease state. The targeting process also includes determination of a site or sites within this IL17RA gene for the antisense interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result.

In some embodiments, antisense oligonucleotides are designed to target human Interleukin 17 receptor (IL-17RA), for instance, the nucleotide sequence of SEQ ID NO: 302, corresponding to interleukin 17 receptor A (IL-17RA), set forth below. Human IL-17RA cDNA sequence has been disclosed in Genbank accession number NM_014339.

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1  ctgggcccg gctggaagcc ggaagcgagc aaagtggagc cgactcgaac tccaccgcgg
61  aaaagaaagc ctcagaacgt tcgttcgctg cgtccccagc cggggccgag cctcgcgca
121  cgccagccgg gccatggggg ccgcacgcag ccgcgcgtcc gctgtcccg ggcctctgt
181  ggggctgctc ctgctgctcc tgggcgtgct ggccccgggt gggcctccc tgcgactcct

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	241	ggaccacccg	gcgctggtct	gtcccccagcc	ggggctaaac	tgcacgggtca	agaatagtag
	301	ctgcctggat	gacagctgga	ttcaccctcg	aaacctgacc	ccctcctccc	caaaggacct
	361	gcagatccag	ctgcactttg	cccacaccca	acaaggagac	ctgttccccg	tggctcacat
	421	cgaatggaca	ctgcagacag	acgccagcat	cctgtacctc	gaggggtgcag	agttatctgt
5	481	cctgcagctg	aacaccaatg	aacgtttgtg	cgtcaggttt	gagtttctgt	ccaaactgag
	541	gcataccacc	aggcgggtgg	gttttacctt	cagccacttt	gtgggtgacc	ctgaccagga
	601	atatgaggtg	accgttcacc	acctgcccaa	gcccattccct	gatggggacc	caaaccacca
	661	gtccaagaat	ttccttgtgc	ctgactgtga	gcacgccagg	atgaaggtaa	ccacgccatg
10	721	catgagctca	ggcagcctgt	gggaccccaa	catcaccgtg	gagaccctgg	aggcccacca
	781	gtcgctgtg	agcttcaccc	tgtggaacga	atctacccat	taccagatcc	tgtgaccag
	841	ttttccgcac	atggagaacc	acagttgctt	tgagcacatg	caccacatac	ctgcgccag
	901	accagaagag	ttccaccagc	gatccaacgt	cacactcact	ctacgcaacc	ttaaagggtg
	961	ctgtcgccac	caagtgcaga	tccagccctt	cttcagcagc	tgcctcaatg	actgcctcag
15	1021	acactccgcg	actgtttcct	gcccagaaat	gccagacact	ccagaaccaa	ttccggacta
	1081	catgcccctg	tgggtgtact	ggttcatcac	gggcatctcc	atcctgctgg	tgggtccgt
	1141	catcctgctc	atcgtctgca	tgacctggag	gctagctggg	cctggaagtg	aaaaatacag
	1201	tgatgacacc	aaatacaccg	atggcctgcc	tgcggtgac	ctgatcccc	caccgctgaa
	1261	gcccaggaag	gtctggatca	tctactcagc	cgaccacccc	ctctacgtgg	acgtggtcct
20	1321	gaaattcgcc	cagttcctgc	tcaccgcctg	cggcacggaa	gtggccctgg	acctgctgga
	1381	agagcaggcc	atctcggagg	caggagtcac	gacctgggtg	ggcgtcaga	agcaggagat
	1441	ggtggagagc	aactctaaga	tcacgtcct	gtgctccgc	ggcacgcgcg	ccaagtggca
	1501	ggcgctcctg	ggccgggggg	cgctgtgcg	gctgcgctgc	gaccacggaa	agcccggtgg
	1561	ggacctgttc	actgcagcca	tgaacatgat	cctcccggac	ttcaagaggc	cagcctgctt
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	1681	gttcggcgcg	gcgcgcgggt	acccgctcat	ggacaggttc	gaggaggtgt	acttcgcac
	1741	ccaggacctg	gagatgttcc	agccgggccc	catgcaccgc	gtaggggagc	tgtcggggga
	1801	caactacctg	cggagcccgg	gcggcaggca	gctccgcgcc	gcctgggaca	ggttcgggga
	1861	ctggcaggtc	cgctgtcccg	actggttcga	atgtgagaac	ctctactcag	cagatgacca
30	1921	ggatgccccg	tccctggacg	aagagggtgt	tgaggagcca	ctgctgcctc	cgggaaccgg
	1981	catcgtgaag	cgggcgcccc	tgggtgcgcga	gctgggtccc	caggcctgcc	tggccataga
	2041	cccgtctggt	ggggaggaag	gaggagcagc	agtggcaaag	ctggaacctc	acctgcagcc
	2101	ccggggtcag	ccagcgcgcg	agccccctca	caccttggtg	ctcgccgcag	aggagggggc
	2161	cctggtggcc	gcggtggagc	ctgggcccct	ggctgacggg	gccgcagtcc	ggctggcact
35	2221	ggcgggggag	ggcgaggcct	gcccgtgctg	gggcagcccg	ggcgctgggc	gaaatagcgt
	2281	cctcttcttc	cccggtggacc	ccgaggactc	gccccttggc	agcagcacc	ccatggcgtc
	2341	tcttgacctc	cttcacagag	acgtgaggga	gcacctcgaa	ggcttgatgc	tctcgtcttt
	2401	cgagcagagt	ctgagctgcc	aggcccaggg	gggctgcagt	agaccgcgca	tggctctcac
	2461	agaccacac	acgccctacg	aggaggagca	gcggcagtc	gtgcagtctg	accagggtca
40	2521	catctccagg	agctccccgc	agccccccga	gggactcacg	gaaatggagg	aagaggagga
	2581	agaggagcag	gaccacaggga	agccggccct	gccactctct	cccaggagcc	tggagagcct
	2641	gaggagcctc	cagcggcagc	tgccttttccg	ccagctgcag	aagaactcgg	gctgggacac
	2701	gatggggtea	gagtcagagg	ggcccagtg	atgaggggcg	ctccccagg	accgcccaga
	2761	tcccagcttt	gagagaggag	tgtgtgtgca	cgtattcatc	tgtgtgtaca	tgtctgcatg
45	2821	tgtatatgtt	cgtgtgtgaa	atgtaggctt	taaaatgtaa	atgtctggat	tttaatccca
	2881	ggcatccctc	ctaacttttc	tttgtgcagc	ggtctggtta	tgtctatcc	ccaggggaat
	2941	ccacacagcc	cgctcccagg	agctaattgt	agagcgtcct	tgaggctcca	ttatctgttc
	3001	attcagcatt	tattgtgcac	ctactatgtg	gcgggcattt	gggataccaa	gataaattgc
	3061	atgcggcatg	gccccagcca	tgaaggaaact	taaccgctag	tgccgaggac	acgttaaacc
50	3121	aacaggatgg	gcccggcacg	gtggctcacg	cctgtaatcc	cagcacactg	ggaggccgag
	3181	gcagggtgat	cactctgagg	tcaggagttt	gagccagcct	ggccaacatg	gtgaaacccc
	3241	atctccacta	aaaatagaaa	aattagccgg	gcattggtgac	acatgcctgt	agtcctagct
	3301	acttgggagg	ctgaggcagg	agaattgctt	gaatctggga	ggcagagggt	gcagtgagcc
	3361	gagattgtgc	cattgcactg	cagcctggat	gacagagcga	gactctatct	caaaaaaaaa
	3421	aaaaaaaaaa	gatggtcacg	cgggatgtaa	acgctgaatg	ggccagggtg	agtggctcat

	3481	gcttgaatc	ccagcacttt	gggaaggcga	ggcaggtgga	ttgcttgagc	tcaggagttc
	3541	aagaccagcc	tgggcgacat	agtgagacct	catctctacc	taaatTTTT	tttagtcagt
	3601	catggtggca	catgcctgta	gtccagcta	ctcgggaggc	tgatgccaga	tgatcacttg
	3661	agcccaggag	gtagaggctg	cagtgaagta	taatggtacc	attgcaatcc	agcctgggca
5	3721	gcagagtga	accctgtctc	aaaaaaaata	aaaaagtaga	aagatggagt	ggaagcctgc
	3781	ccagggttgt	gagcatgcac	gggaaaggca	cccaggtcag	gggggatccc	cgaggagatg
	3841	cctgagctga	aggattgtgg	ttggggaaaag	cgtagtccca	gcaaggaagc	agtttgtggg
	3901	taagtgtctg	gaggtgagt	gagtgaagctt	gtcagggagc	tgctggtgga	gcttgagggg
	3961	gaaggaggga	ggcagtgaga	gagatcgggg	tggggggtgg	ggggatgtcg	ccagagctca
10	4021	gggggtgggga	cagccttgtg	cgcacagtc	ctgaggcctg	gggcaccttt	cgtctgatga
	4081	gcctctgcat	ggagagaggc	tgagggtctaa	acacagctgg	atgtcacctg	agttcattta
	4141	taggaagaga	gaaatgtcga	ggtgaaacgt	aaaagcatct	ggcaggaagg	tgagtctgaa
	4201	gccctgcacc	cgcgttccga	ctatcagtg	ggagctgta	gcacgtagga	ttcttcagag
	4261	cagctgggct	ggagctcccc	tgagctcagg	aagccccagg	gtgcaagggc	aaggaaatga
15	4321	gggggtggtg	gtcagtgaag	atctgggcag	accttgtgtg	gggaaggggt	gctgctgtga
	4381	cttcagggtc	tgaggtccaa	agacagcatt	tgaagagg	ctctgaagcc	agtgtttgaa
	4441	gaatttgttc	ctgaagtacc	tcctgggggt	aggctagagg	cttctggctt	cagggtcctg
	4501	aagaacacat	tgaggtgccg	tctgacactg	gaatagggtg	cccttcattc	ctatgctga
	4561	gtccttaact	atatttccaa	cctccagtga	ggaggagaag	attcggaat	gtgacaggag
20	4621	agcaaacagg	acagtttgca	tgtgtgtgtg	cgcacacata	catgtgctg	aaagattatc
	4681	aataaaagt	cataaatttg	ttgatctggt	aagagtctt	agcaggaagg	tcgagccact
	4741	tactgtaggt	caagaagttg	ctagtgtcgg	agttttttct	tgcagttaga	ctttacctag
	4801	tggtagcagg	gccaccaaag	ctctgtgtcc	cagatggtgt	atggcccata	atccacccaa
	4861	cagcagcaaa	ggaccaggca	aaggagaaca	ggagcagaag	cctcccagcc	actagccttt
25	4921	tgggtcagct	ctctccaata	atcctggaga	ggggcttcgt	tgggtctgga	cacctaccat
	4981	gcattctgtg	acctttccct	agcttccaat	aaataactgt	ttgacgccc	gagtacagga
	5041	taccacaatg	cactcttcct	gcgtagagca	catgttccca	tctgtccca	ttctcagga
	5101	accttgaatt	ctagctctgc	tggcctttga	gcccattgcca	gtaaatgtcc	tgatgggcat
	5161	tgcctactat	ctccagggca	gctgcctttg	tcctcctaac	agctttattg	gagtacagtt
30	5221	cacttaccat	acaatccaca	attgacctg	cacaatttga	tgccggttta	gtatagtcac
	5281	agttcagcag	ccatcagcac	agtcagtctt	agagtctact	acccccaaaa	gaaatccagc
	5341	cccccttagt	caccacccca	acctcccat	ccctaggcac	ccctaggcta	ctttgatctc
	5401	tgtagacttg	cctcttctgg	acatgacata	gagaaaggag	tcataaatc	tccaagggtg
	5461	ctgtttcttc	tttaatgtca	ttccctgttt	ctcctcacat	tcctcccca	tttctgggc
35	5521	ccagtctcac	actggtcctt	gcttacccta	aatgctatta	attccatcac	tctgagtatg
	5581	gtgtttgctg	tccgctgaat	gccaagagct	tcaagagtgt	gtgtaataa	agccacacct
	5641	ttatttttgt	attattctga	accatggcta	ataaattgtt	tcaccaagaa	atgtctctct
	5701	aagaacaggt	gccctccacg	ctgtgcccct	cccacctctt	cagctcgtct	cctgagtgtg
	5761	cagaggtggt	tccggttggg	aaagaagcag	cggagcatct	aacctgcct	gtgtccaggc
40	5821	cgattatgca	cgcagccacc	aacaagctcc	caactccgc	gtagagtttc	atgacttttt
	5881	cctgcctact	atcttgatcc	tagttttttt	tttgtttttt	ttttttttta	ggaataatta
	5941	ctttgattca	aaaccagttt	ctcttttctg	cataggaagg	tccttgaagg	tgtttagggg
	6001	ctaaaaagg	tggtgttcgg	tctctgaaac	atccattcag	cagtttgagc	tgggatctct
	6061	gaatgcaagg	gtatgatgga	tatacttctt	tcttgctttt	gttggtttt	ggttttttgt
45	6121	ttgtttttta	gtcagggtct	ctctgtcacc	aggctgtatt	acagtgggtc	aatcatggct
	6181	cactgcagcc	tcgacctccc	aggctcaagc	catctttcca	cctcagcctg	ccagtggcta
	6241	gaactacagg	cgtgcaccac	tgtgcccggc	taatttgtgt	gtatatattt	tgtagaaatg
	6301	gggttttccc	atgttgtcca	ggctggtcac	gaactcctgg	gctcaagcca	tctgcccggc
	6361	tcactctccc	aaagtgtctg	gattataggc	ctgagcccac	cgtgcctggc	ctttcctgtt
50	6421	tatctttgaa	aattaaatag	ggcataagag	agaagaagat	gtacttacaa	tgcagtgggt
	6481	ggttttaact	ctatagcctt	tgggtctctg	ggttggtgct	cccccttcta	aataaatgag
	6541	gtgtatgcag	ggccctcttc	tgccttagcg	ccctgccagc	tgggactcca	gcaaggcccg
	6601	gggcacctga	ggacagagt	agatggagg	ccgctgctcc	agcagccggg	cctgcacccc
	6661	acaagtcaac	tgtgtcggac	agaggatcct	tacaaagaag	aggcagcagg	gttggggggt

5 6721 ggccagctgc tcgtccgccc taggtagctt gctcatctgt aaagtgggtg gggcaggagt
 6781 tcccacctca tggggtcctg gcaagcctgc agtatccccg agtggcacca gcctgcttct
 6841 ggggcagagc agtttgtgcc ccctgaggta ccactgatcc tctttccctg ctattaggta
 6901 ttgctctctt cctccggtgt ttgccttttc agattataga agtaatatgt gttcccatat
 6961 ttggcgctctc tcaggagctc aggaagtact tggctgagtg aacatgtcca ttgtggaaaa
 7021 atggcaacaa tatggattcc atgggtatat tttatagaag aatatgaaga aaagcagcta
 7081 cccctaaacc cattgcacaa gctgttcatg ttaattctgt acccgacgt tccccacgg
 7141 ggccctccct cactctgaaa tggcatccag gtccatcttg cctccacct ctgcatggct
 10 7201 ctccatgccc catcgctct cccagatcct agcactgggt ccacactctc gccctgtcca
 7261 tttagggttga tgaaagcagg cagtcacccg ggtgggccag tcttgctgt gggaggaaca
 7321 tgcagtctcc tgtctcatgg tttgaagtgt gccaggaagc ctggcccagc ccacctcccc
 7381 ctggagtcct tcccaggagg aataaccct taggtcattg actataagat gagttcgctc
 7441 actggatcct tcctctctga tgagacagga agaaggtaca cagtgaccag gtaggaggag
 7501 gagagggagt agaaaggagg gatgcgggtg gctggtccct gcatttgctt gcttccctgc
 15 7561 acgggtgtcc cactggccgc ctctgtcac cagtgtcatg ggattctctc agaagatgaa
 7621 aacagccctt gcttttttgc tagaatggct gagctttcat ggaaaggaag ctggacccaa
 7681 gcaacagccg actaccgaag gttgcctgga gcagtgcaga tgtgggagga agaagggcct
 7741 tgggtgcacac tggcttttct tcctgactgc aatgtggcat tgtgccagct acctctctt
 7801 tctcggcctc agggaaatgg agagaaagca gccctgaagg tggctgtgac gagggaaggg
 20 7861 gcagagggcc tgacagtcaa ccacgcgcta tattttcctg ttcttctta gggcaagaac
 7921 tgcattggcca gactcaggca aggcctaggt gtgggctggg cattgcctac acgtgaagag
 7981 atcactccgc gtccctactg cacctgtcac aaagtgcctt ctgatatgcc tggcaaacca
 8041 aaatcgggtga gcgccagctt gcttccttag aagacatttc taaatattca taacatgctt
 8101 gctcaaatca atcaccttat tttacatccg ctccaggagg aatgaagac atggctctac
 25 8161 gttgttctgt aattattttc tatgtaaat ttgttcttg ttacaattat atatgtctta
 8221 ggggaaagga ccatttcaca tgtgtcacct catgtgattc tcaccacagc cctgtgattg
 8281 ctctgtttt ataaataatg acatagttcc agttgatggc caaagccaca gctaacgaga
 8341 ggcagagaga gctcaggctc ccaggagctt ccactctcag acctgctc cgggctgcc
 8401 ctgagtgaag cgccctgctta gcatttggca cagccagaag cagcaagcta gggtcacaac
 30 8461 acagagaggg gctgtgtaat actggctgcc tctgtgctaa gaaaaaaaaa aatcactgt
 8521 gtgtttgttt attttgggtg aggccagtg ttcttgctta gacttaatac tacccttcat
 8581 gttaaaataa aaccaacaa aaacccat

(SEQ ID NO: 302)

In some embodiments the IL-17RA ASO is complementary to a nucleic acid encoding
 the following protein sequence:

35 MGAARSPPSAVPGPLLGLLLLLLGV LAPGGASLRLLDHRALVCSQPGLNCTVKNSTCLDDSWIHPRLNTPSSPKD
 LQIQLHFAHTQQGDLFPVAHIEWTLQTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRHHHRRWRFTFSHFV
 VDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVITPCMSSGSLWDPNITVETLEAHQLRVSTLWN
 ESTHYQILLTSFPHMENHSCFEHMHIPAPRPEEFHQRSNVTLTLRNLKGCCRHQVQIQPFFSSCLNDCLRHSAT
 40 VSCPEMPDTPEPIPDYMLWVYWFITGISILLVGSVILLIVCMTWRLAGPGSEKYSDDTKYTDGLPAADLIPPL
 KPRKVWIIYSADHPLYVDVVLKFAQFLLTACGTEVALDLLEEQAISEAGVMTWVGRQKQEMVESNSKIIIVLCSRG
 TRAKWQALLGRGAPVRLRCDHGKPVGDLFTAAMNMLPDFKRPACFGTYVVCYFSEVSCDGDVPDLFGAAPRYPL
 MDRFEEVYFRIQDLEMFOQGRMHRVGELSGDNYLRSPGGRQLRAALDRFRDWQVRCPDWFECENLYSADDQDAPS
 LDEEVFEEPLPPGTGIVKRAPLVREPGSQACLAIDPLVGEEGGA AVAKLEPHLQPRGQPAPQPLHTLVLAEEG
 45 ALVAAVEPGPLADGA AVR LALAGEGEACPLLGS PGAGRNSVFLFPVDPEDSPLGSSTPMASPDLLPEDVREHLEG
 LMLSLEFQSLSCQAQGCSR PAMVLTDPHTPYEEEQRSVQSDQGYISRSSQPPEGLTEMEEEEEEEQDPGKPA
 LPLSPEDLESRLSLQRQLLFRQLQKNSGWDTMGSESEGPSA (SEQ ID NO: 305).

In some embodiments the ASOs used herein include any one or more of the following IL-17RA ASOs:

mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmA/isp18//isp18//3CholTEG/
(SEQ ID NO: 225);

5 mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/
(SEQ ID NO: 288);

mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC/isp18//isp18//3CholTEG/
(SEQ ID NO: 291); mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmA (SEQ ID
NO: 225);

10 mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU (SEQ ID NO: 288);
mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC (SEQ ID NO: 291);
GCUUGGGCAGGTGGUGAA (SEQ ID NO: 225); CCCACAGGGGCATGUAGU (SEQ ID
NO: 288); or GUAGGGCGUGTGTGGGUC (SEQ ID NO: 291) or salts thereof.

In some embodiments antisense oligonucleotides are designed to target the nucleotide
15 sequence corresponding to IL-4R, set forth below. Human IL-4R cDNA sequence has been
disclosed in Genbank accession number NM_000418.

1 ggggtctccgc gccacaggaaa gccccgcgcg gcgcggggcca gggaagggcc acccaggggt
61 cccccacttc ccgcttgggc gcccggaagg cgaatggagc aggggcgcgc agataattaa
121 agattttacac acagctggaa gaaatcatag agaagccggg cgtggtggct catgcctata
20 181 atcccagcac ttttgagggc tgaggcgggc agatcacttg agatcaggag ttcgagacca
241 gcctggtgcc ttggcatctc ccaatggggg ggctttgctc tgggctcctg ttccctgtga
301 gctgctggt cctgctgcag gtggcaagct ctgggaacat gaaggtcttg caggagccca
361 cctgcgtctc cgactacatg agcatctcta cttgcgagtg gaagatgaat ggtcccacca
421 attgcagcac cgagctccgc ctggtgtacc agctggtttt tctgctctcc gaagcccaca
25 481 cgtgtatccc tgagaacaac ggaggcgcgg ggtgcgtgtg ccacctgctc atggatgacg
541 tggtcagtgc ggataactat aactggacc tgtgggctgg gcagcagctg ctgtggaagg
601 gctccttcaa gccacgcgag catgtgaaac ccaggggccc aggaaacctg acagttcaca
661 ccaatgtctc cgacactctg ctgctgacct ggagcaacct gtatccccct gacaattacc
721 tgtataatca tctcacctat gcagtcaaca tttggagtga aaacgacctg gcagatttca
30 781 gaatctataa cgtgacctac ctagaacct cctccgcat cgcagccagc accctgaagt
841 ctgggatttc ctacagggca cgggtgaggg cctgggctca gtgctataac accacctgga
901 gtgagtggag cccacgcacc aagtggcaca actcctacag ggagcccttc gagcagcacc
961 tctgctggg cgtcagcgtt tctgcattg tcatcctggc cgtctgctg ttgtgctatg
1021 tcagcatcac caagattaag aaagaatggg gggatcagat tcccaccca gccgcagcc
35 1081 gcctcgtggc tataataatc caggatgctc aggggtcaca gtgggagaag cgggtcccag
1141 gccaggaacc agccaagtgc ccacactgga agaattgtct taccaagctc ttgcctgtt
1201 ttctggagca caacatgaaa agggatgaag atcctcaciaa ggctgcaaaa gagatgcctt

1261 tccagggctc tggaaaatca gcatggtgcc cagtggagat cagcaagaca gtcctctggc
 1321 cagagagcat cagcgtggtg cgatgtgtgg agttgtttga ggccccggtg gagtgtgagg
 1381 aggaggagga ggtagaggaa gaaaaagga gcttctgtgc atcgccctgag agcagcaggg
 1441 atgacttcca ggagggaagg gagggcattg tggcccggct aacagagagc ctgttccctg
 5 1501 acctgctcgg agaggagaat gggggccttt gccagcagga catgggggag tcatgccttc
 1561 ttccaccttc gggaagtacg agtgttcaca tgccctggga tgagttccca agtgcagggc
 1621 ccaaggaggc acctccctgg ggcaaggagc agcctctcca cctggagcca agtcctcctg
 1681 ccagcccgac ccagagtcca gacaacctga cttgcacaga gacgcccctc gtcacgcgag
 1741 gcaacctcgc ttaccgcagc ttcagcaact ccctgagcca gtcaccgtgt cccagagagc
 10 1801 tgggtccaga cccactgctg gccagacacc tggaggaaagt agaacccgag atgccctgtg
 1861 tccccagct ctctgagcca accactgtgc cccaacctga gccagaaacc tgggagcaga
 1921 tctccgcgcg aaatgtcctc cagcatgggg cagctgcagc ccccgctctg gccccacca
 1981 gtggctatca ggagtttgta catgcggtgg agcagggtgg caccagggc agtgcggtgg
 2041 tgggcttggg tccccagga gaggtgggtt acaaggcctt ctcaagcctg cttgccagca
 15 2101 gtgctgtgtc cccagagaaa tgtgggtttg gggctagcag tggggaagag gggataaagc
 2161 ctttccaaga cctcattcct ggctgccctg gggaccctgc cccagtcctt gtccccctgt
 2221 tcacctttgg actggacagg gagccacctc gcagtccgca gagctcacat ctcccaagca
 2281 gctccccaga gcacctgggt ctggagccgg gggaaaaggt agaggacatg ccaaagcccc
 2341 cacttcccca ggagcaggcc acagaccccc ttgtggacag cctgggcagt ggcattgtct
 20 2401 actcagccct tacctgccac ctgtgcggcc acctgaaaca gtgtcatggc caggaggatg
 2461 gtggccagac cctgtcatg gccagtcctt gctgtggctg ctgctgtgga gacaggctct
 2521 cgccccctac aacccccctg agggccccag acccctctcc aggtgggggt ccaactggagg
 2581 ccagtctgtg tccggcctcc ctggcaccct cgggcatctc agagaagagt aaatcctcat
 2641 catccttcca tctgccccct ggcaatgtc agagctcaag ccagaccccc aaaatcgtga
 25 2701 actttgtctc cgtgggaccc acatacatga gggctctcta ggtgcatgtc ctcttgttgc
 2761 tgagtctgca gatgaggact agggcttata catgcctggg aaatgccacc tcttgggaagg
 2821 cagccaggct ggcagatttc caaaagactt gaagaaccat ggtatgaagg tgattggccc
 2881 cactgacgtt ggccctaaca tgggctgcag agactggacc ccgcccagca ttgggctggg
 2941 ctgccacat cccatgagag tagagggcac tgggtcgccg tgccccacgg caggccccctg
 30 3001 caggaaaact gaggcccttg ggcacctcga cttgtgaacg agttgttggc tgctccctcc
 3061 acagcttctg cagcagactg tcctgttgtt aactgcccaa ggcatgtttt gccaccaga
 3121 tcatggccca cgtggaggcc cacctgcctc tgtctcactg aactagaagc cgagcctaga
 3181 aactaacaca gccatcaagg gaatgacttg ggcggccttg ggaaatcgat gagaaattga
 3241 acttcaggga ggggtggcat tgccatagagg tgctcattca tttaacagag ctcccttagg
 35 3301 ttgatgctgg aggcagaatc ccggtgtcga aggggtgttc agttaagggg agcaacagag
 3361 gacatgaaaa attgctatga ctaaagcagg gacaatttgc tgccaaacac ccatgcccag
 3421 ctgtatggct gggggctcct cgtatgcacg gaacccccag aataaatatg ctacgccacc
 3481 ctgtgggccc ggcaatccag acagcaggca taaggcacca gttaccctgc atgttggccc
 3541 agacctcagg tgctagggaa ggcgggaacc ttgggttgag taatgctcgt ctgtgtgttt
 40 3601 tagtttcatc acctgttata tgtgtttgct gaggagagtg gaacagaagg ggtggagtgt

3661 tgtataaata aagtttcttt gtctctttaa aaaaaaaaaa aaaaaaaaaa (SEQ ID NO: 306)

In some embodiments the IL-4R ASO is complementary to a nucleic acid encoding the following protein sequence:

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5      MGWLCSGLLF PVSCLVLLQV ASSGNMKVLQ EPTCVSDYMS ISTCEWKMNNG
      PTNCSTELRL LYQLVFLLSE AHTCIPENNG GAGCVCHLLM DDVVSADNYT
      LDLWAGQQLL WKGSFKPSEH VKPRAPGNLT VHTNVSDTLL LTWSNPYPDP
      NYLYNHLTYA VNIWSENDPA DFRIYNVTYL EPSLRIAAST LKSGISYRAR
      VRAWAQCYNT TWSEWSPSTK WHNSYREPFQ QHLLLGVSVS CIVILAVCLL
10     CYVSITKIKK EWWDQIPNPA RSRLVAIIIQ DAQGSQWEKR SRGQEPKACP
      HWKNCLTKLL PCFLEHNMKR DEDPHKAAKE MPFQSGSKSA WCPVEISKTV
      LWPEISVVR CVELFEAPVE CEEEEVEEEE KGSFCASPES SRDDFQEGRE
      GIVARLTESL FLDLLGEENG GFCQQDMGES CLLPPSGSTS AHMPWDEFPS
      AGPKEAPPWG KEQPLHLEPS PPASPTQSPD NLTCTETPLV IAGNPAYRSE
15     SNSLSQSPCP RELGPDPLLA RHLEEVEPEM PCVPQLSEPT TVPQPEPETW
      EQILRRNVLQ HGAAAAPVSA PTSGYQEFVH AVEQGGTQAS AVVGLGPPGE
      AGYKAFSSLL ASSAVSPEKC GFGASSGEEG YKPFQDLIPG CPGDPAPVPV
      PLFTFGLDRE PPRSPQSSHL PSSSPEHLGL EPGEKVEDMP KPPLPQEQT
      DPLVDLSLGS IVYSALTCHL CGHLKQCHGQ EDGGQTPVMA SPCCGCCCCG
20     RSSPPTPLR APDPSPGGVP LEASLCPASL APSGISEKSK SSSSFHPAPG
      NAQSSSQTPK IVNFVSVGPT YMRVS (SEQ ID NO: 309)

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In some embodiments antisense oligonucleotides are designed to target the nucleotide sequence corresponding to IL-1 β , set forth below. Human IL-1 β cDNA sequence has been disclosed in Genbank accession number NM_000576.

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25     1 accaaacctc ttcgaggcac aaggcacaac aggctgctct gggattctct tcagccaatc
      61 ttcattgctc aagtgtctga agcagccatg gcagaagtac ctgagctcgc cagtgaatg
      121 atggcttatt acagtggcaa tgaggatgac ttgttctttg aagctgatgg ccctaaacag
      181 atgaagtgct ccttcaggga cctggacctc tgccctctgg atggcggcat ccagctacga
      241 atctccgacc accactacag caagggcttc aggcaggccg cgtcagttgt tgtggccatg
30     301 gacaagctga ggaagatgct ggttccctgc ccacagacct tccaggagaa tgacctgagc
      361 accttctttc cttcatctt tgaagaagaa cctatcttct tcgacacatg ggataacgag
      421 gcttatgtgc acgatgcacc tgtacgatca ctgaactgca cgctccggga ctcacagcaa
      481 aaaagcttgg tgatgtctgg tccatatgaa ctgaaagctc tccacctcca gggacaggat
      541 atggagcaac aagtgggtgtt ctccatgtcc tttgtacaag gagaagaaag taatgacaaa
35     601 atacctgtgg ccttgggcct caaggaaaaag aatctgtacc tgtcctgcgt gttgaaagat
      661 gataagccca ctctacagct ggagagtgtg gatcccaaaa attacccaaa gaagaagatg
      721 gaaaagcgat ttgtcttcaa caagatagaa atcaataaca agctggaatt tgagtctgcc
      781 cagttcccca actggtacat cagcacctct caagcagaaa acatgcccggt cttcctggga
      841 gggacccaaag gcggccagga tataactgac ttcaccatgc aatttgtgtc ttcctaaaga
40     901 gagctgtacc cagagagtcc tgtgctgaat gtggactcaa tccctagggc tggcagaaa

```

961 ggaacagaaa ggTTTTtgag tacggctata gcctggactt tctgtgtgc tacaccaatg
 1021 cccaactgcc tgccttaggg tagtgctaag aggatctcct gtccatcagc caggacagtc
 1081 agctctctcc tttcagggcc aatccccagc ccttttggtg agccaggcct ctctcacctc
 1141 tctactcac ttaaagcccg cctgacagaa accacggcca catttggttc taagaaaccc
 5 1201 tctgtcattc gctcccacat tctgatgagc aaccgcttcc ctatttattt atttatttgt
 1261 ttgtttgttt tttcattgg tctaatttat tcaaaggggg caagaagtag cagtgtctgt
 1321 aaaagagcct agtttttaat agctatggaa tcaattcaat ttggactggg gtgctctctt
 1381 taaatcaagt cctttaatta agactgaaaa tatataagct cagattattt aaatgggaat
 1441 atttataaat gagcaaatat catactgttc aatgggtctg aaataaactt cactgaag (SEQ
 10 ID NO: 307)

In some embodiments the IL-1 β ASO is complementary to a nucleic acid encoding the following protein sequence:

MAEVP ELASE MMAYYS GNED DLFFEADGPK QMKCSFQDLD LCPLDGGIQL
 RISDHHYSKG FRQAASVVVA MDKLRKMLVP CPQTFQENDL STFFPFIFEE
 15 EPIFFDTWDN EAYVHDAPVR SLNCTLRDSQ QKSLVMSGPY ELKALHLQGG
 DMEQQVVFSM SFVQGEESND KIPVALGLKE KNLYLSCVLK DDKPTLQLES
 VDPKNYPKKK MEKRFVFNKI EINNKLFEFES AQFPNWIIST SQAENMPVFL
 GGTKGGQDIT DFTMQFVSS (SEQ ID NO: 310)

In some embodiments antisense oligonucleotides are designed to target the nucleotide
 20 sequence corresponding to CTGF, set forth below. Human CTGF cDNA sequence has been
 disclosed in Genbank accession number NM_001901.

1 aaactcacac aacaactctt ccccgctgag aggagacagc cagtgcgact ccacctcca
 61 getegacggc agccgccccg gccgacagcc ccgagacgac agcccgggcc gtcccggtcc
 121 ccacctccga ccaccgccag cgtctccaggc cccgcccgtc cccgctcgcc gccaccgcgc
 25 181 cctccgctcc gcccgagtg ccaaccatga ccgcccagc tatgggcccc gtccgcgtcg
 241 ccttcgtggg cctcctcgcc ctctgcagcc ggccggccgt cggccagaac tgcagcgggc
 301 cgtgcgggtg cccggacgag ccggcgccgc gctgcccggc gggcgtgagc ctctgtctgg
 361 acggtctggg ctgctgccgc gtctgcgcca agcagctggg cgagctgtgc accgagcgcg
 421 acccctgcca ccgcacaag ggctctttct gtgacttcgg ctccccggcc aaccgcaaga
 30 481 tcggcggtg caccgcaaaa gatggtgctc cctgcatctt cgggtgtacg gtgtaccgca
 541 gccgagagtc cttccagagc agctgcaagt accagtgcac gtgcctggac gggcggtgg
 601 gctgcatgcc cctgtgcagc atggacgttc gtctgccag ccctgactgc cccttcccga
 661 ggaggggtcaa gctgcccggg aaatgctgcg aggagtgggt gtgtgacgag cccaaggacc
 721 aaaccgtggg tgggcctgcc ctgcggcctt accgactgga agacacgttt ggcccagacc
 35 781 caactatgat tagagccaac tgctgggtcc agaccacaga gtggagcgcc tgttccaaga
 841 cctgtgggat gggcatctcc acccggttga ccaatgacaa cgctcctgc aggttagaga
 901 agcagagccg cctgtgcatg gtcaggcctt gcgaagctga cctggaagag aacattaaga
 961 agggcaaaaa gtgcatccgt actcccaaaa tctccaagcc tatcaagttt gagctttctg
 1021 gctgcaccag catgaagaca taccgagcta aattctgtgg agtatgtacc gacggccgat
 40 1081 gctgcacccc ccacagaacc accaccctgc cgggtggagtt caagtgcctt gacggcgagg

1141 tcatgaagaa gaacatgatg ttcatacaaga cctgtgcctg ccattacaac tgtcccggag
 1201 acaatgacat ctttgaatcg ctgtactaca ggaagatgta cggagacatg gcatgaagcc
 1261 agagagttag agacattaac tcattagact ggaacttgaa ctgattcaca tctcattttt
 1321 ccgtaaaaaat gatttcagta gcacaagtta tttaaactctg tttttctaac tgggggaaaa
 5 1381 gattcccacc caattcaaaa cattgtgcca tgtcaaacaa atagtctatc aaccccagac
 1441 actggtttga agaattgtaa gacttgacag tggaaactaca ttagtacaca gcaccagaat
 1501 gtatattaag gtgtggcttt aggagcagtg ggagggtagc agcagaaagg ttagtatcat
 1561 cagatagcat cttatacgag taatatgcct gctatttgaa gtgtaattga gaagggaaat
 1621 tttagcgtgc tcaactgacct gcctgtagcc ccagtgcagc ctaggatgtg cattctccag
 10 1681 ccatcaagag actgagtcaa gttgttcctt aagtcagaac agcagactca gctctgacat
 1741 tctgattcga atgacactgt tcaggaatcg gaatcctgtc gattagactg gacagcttgt
 1801 ggcaagtga tttgcctgta acaagccaga ttttttaaaa tttatattgt aaatattgtg
 1861 tgtgtgtgtg tgtgtgtata tatatatata tgtacagta tctaagttaa tttaaagttg
 1921 tttgtgcctt tttatttttg tttttaatgc tttgatattt caatgtagc ctcaatttct
 15 1981 gaacaccata ggtagaatgt aaagcttgct tgatcgttca aagcatgaaa tggataacta
 2041 tatggaaatt ctgctcagat agaattgacag tccgtcaaaa cagattgttt gcaaagggga
 2101 ggcacagtg tccttggcag gctgatttct aggtaggaaa tgtggtagcc tcacttttaa
 2161 tgaacaaatg gcctttatta aaaactgagt gactctatat agctgacag ttttttcacc
 2221 tggaagcatt tgtttctact ttgatatgac tgtttttcgg acagtttatt tgttgagagt
 20 2281 gtgacaaaaa gttacatgtt tgcaccttct tagttgaaaa taaagtgtat attttttcta
 2341 taaaaaaaaa aaaaaaaaa (SEQ ID NO: 308)

In some embodiments the CTGF ASO is complementary to a nucleic acid encoding the following protein sequence:

25 MTAASMGFVR VAFVVLALC SRPAVGQNCS GPCRCPDEPA PRCPAGVSLV
 LDGCGCCRVC AKQLGELCTE RDPDHPKGL FCHFGSPANR KIGVCTAKDG
 APCIFGGTVY RSGESFQSSC KYQCTCLDGA VGCMPLCSMD VRLPSPDCPF
 PRRVKLPKGC CEEWVCDEPK DQTVVGPALA AYRLDTFGP DPTMIRANCL
 VQTTEWSACS KTCGMGISTR VTNDNASCL EKQSRCLMVR PCEADLEENI
 KKGKKCIRTP KISKPIKFEL SGCTSMKTYR AKFCGVCTDG RCCTPHRTTT
 30 LPVEFKCPDG EVMKKNMMFI KTCACHYNCP GDNDIFESLY YRKMYGDMA (SEQ ID NO:
 311)

The invention in some aspects relates to multiplex ASO-SNAs for reducing the expression of multiple gene targets. In some embodiments the mASO-SNAs include ASOs that target IL-17RA and TNF α . These particular mASOs-SNAs are particularly useful for
 35 treating inflammatory disorders. A “TNF α antisense oligonucleotide” or “TNF- α ASO” as used herein refers to a nucleic acid based agent which interferes with TNF α activity. In particular, the TNF α antisense inhibitors or TNF α antisense oligonucleotides of the invention reduce the expression of the TNF α gene.

TNF- α (tumor necrosis factor-alpha) is a pleiotropic cytokine produced by activated macrophages/monocytes and lymphocytes which often promotes inflammatory responses leading to a variety of diseases. TNF- α is released from macrophages, monocytes and natural killer cells and play an important role in inflammatory and immune responses, including the recruitment of leukocytes to injured tissues during bacterial and other microbial infections, and following stimulation with inflammatory substances. When present in excessive quantities, TNF- α is known to cause tissue injury, and has been implicated in the pathology associated with inflammatory and autoimmune diseases.

TNF- α mediates biological effects through two distinct membrane-protein receptors, TNF-RI and TNF-RII, which differ in sequence and molecular mass. TNF-RI is reported to be present at low levels in most, if not all, human cell types, and expression of the TNF-RI gene in humans can be upregulated by infection, interferons, and modulators of second messengers, such as phorbol esters. The extracellular portions of both TNF receptors also exist in soluble forms, which are derived from membrane-bound forms of the receptors by proteolytic cleavage at the cell surface. The soluble TNF receptors retain the ability to bind TNF- α in solution. Soluble TNF receptors have been identified in urine and sera from healthy individuals, and have been shown to be elevated in some chronic diseases and following inoculation with agents that induce TNF- α .

In some embodiments, antisense oligonucleotides are designed to target human TNF α , for instance, the nucleotide sequence of SEQ ID NO: 304, set forth below. Human TNF- α cDNA sequence has been published by Nedwin, G. E. et al. (Nucleic Acids Res. 1985, 13, 6361-6373); and is disclosed in Genbank accession number X02910 and NM_000594.

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1  gaattccggg  tgatttcact  cccggctgtc  caggcttgtc  ctgctacccc  acccagcctt
61  tectgaggcc  tcaagcctgc  caccaagccc  ccagctcctt  ctccccgcag  gacccaaaca
121  caggcctcag  gactcaacac  agcttttccc  tccaaccctg  tttctctccc  tcaacggact
181  cagctttctg  aagccccctc  cagttctagt  tctatctttt  tcttgcatcc  tgtctggaag
241  ttagaaggaa  acagaccaca  gacctgggcc  ccaaaagaaa  tggaggcaat  aggttttgag
301  gggcatgggg  acgggggttc  gcctccaggg  tcctacacac  aaatcagtc  gtggcccaga
361  agacccccct  cggaatcgga  gcagggagga  tggggagtgt  gaggggtatc  cttgatgctt
421  gtgtgtcccc  aactttccaa  atccccgccc  ccgcgatgga  gaagaaaccg  agacagaagg
481  tgcagggccc  actaccgctt  cctccagatg  agctcatggg  tttctccacc  aaggaagttt
541  tccgttggtt  gaatgattct  ttccccgccc  tcctctcgcc  ccagggacat  ataaaggcag
601  ttgttggcac  acccagccag  cagacgctcc  ctacgcaagg  acagcagagg  accagctaag
661  agggagagaa  gcaactacag  accccccctg  aaaaacaacc  tcagacgcca  catcccccta
721  caagctgcca  ggcagggtct  ctctctctca  catactgacc  cacggcttca  ccctctctcc
781  cctggaaagg  acaccatgag  cactgaaagc  atgatccggg  acgtggagct  ggccgaggag
841  gcgctcccca  agaagacagg  ggggccccag  ggctccaggc  ggtgcttggt  cctcagcctc
901  ttctccttcc  tgatcgtggc  aggcgccacc  acgctcttct  gcctgctgca  ctttgagagt
961  atcgcccccc  agagggaaga  ggtgagtgcc  tggccagcct  tcatccactc  tcccacccaa
1021  ggggaaatga  gagacgcaag  agagggagag  agatgggatg  ggtgaaagat  gtgcgctgat
1081  agggagggat  gagagagaaa  aaaacatgga  gaaagacggg  gatgcagaaa  gagatgtggc
1141  aagagatggg  gaagagagag  agagaaagat  ggagagacag  gatgtctggc  acatggaagg
1201  tgctcactaa  gtgtgtatgg  agtgaatgaa  tgaatgaatg  aatgaacaag  cagatatata

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1261 aataagatat ggagacagat gtgggggtgtg agaagagaga tgggggaaga aacaagtgat
1321 atgaataaag atggtgagac agaaagagcg ggaaatatga cagctaagga gagagatggg
1381 ggagataaag agagaagaag atagggtgtc tggcacacag aagacactca gggaaagagc
1441 tgttgaatgc tggaaagtga atacacagat gaatggagag agaaaaccag acacctcagg
5 1501 gctaagagcg caggccagac aggcagccag ctgttcctcc tttaaggggtg actccctcga
1561 tgttaaccat tctccttctc cccaacagtt ccccaggac ctctctctaa tcagccctct
1621 ggcccaggca gtcagtaagt gtctccaaac ctctttccta attctgggtt tgggtttggg
1681 ggtagggtta gtaccggtat ggaagcagtg ggggaaattt aaagttttgg tcttggggga
1741 ggatggatgg aggtgaaagt aggggggtat tttctaggaa gttaagggtt ctcagctttt
10 1801 tcttttctct ctctcttca ggatcatctt ctcgaacccc gagtgacaag cctgtagccc
1861 atgtttagg taagagctct gaggatgtgt cttggaactt ggagggtag gatttgggga
1921 ttgaagccc gctgatggta ggcagaactt ggagacaatg tgagaaggac tcgctgagct
1981 caaggggaag gtggaggaac agcacaggcc ttagtgggat actcagaacg tcatggccag
2041 gtgggagtgt ggatgacaga cagagaggac aggaaccgga tgtggggtgg gcagagctcg
15 2101 agggccagga tgtggagagt gaaccgacat ggccacactg actctctct cctctctctc
2161 ctccctccag caaacctca agctgagggg cagctccagt ggctgaaccg cggggccaat
2221 gccctcctgg ccaatggcgt ggagctgaga gataaccagc tgggtgtgct atcagagggc
2281 ctgtacctca tctactcca ggtcctcttc aagggccaa gctgcccctc caccatgtg
2341 ctctcacc acaccatcag ccgcctcgcc gtctcctacc agaccaaggt caacctctc
20 2401 tctgccatca agagccctg ccagaggag accccagagg gggctgagc caagccctgg
2461 tatgagcca tctatctggg aggggtcttc cagctggaga agggtgacc actcagcgt
2521 gagatcaatc ggcccgacta tctcgacttt gccgagtctg ggcaggtcta ctttgggatc
2581 attgccctgt gaggaggacg aacatccaac cttcccaaac gcctcccctg ccccaatccc
2641 tttattaccc cctccttcag acaccctcaa cctcttctgg ctcaaaaaga gaattggggg
25 2701 cttagggtcg gaaccaagc ttagaacttt aagcaacaag accaccatt cgaaacctgg
2761 gattcaggaa tgtgtggcct gcacagtga gtgctggcaa ccactaagaa ttcaaactgg
2821 ggccctcaga actcactggg gcctacagct ttgatccctg acatctggaa tctggagacc
2881 agggagcctt tggttctggc cagaatgctg caggacttga gaagacctca cctagaaatt
2941 gacacaagtg gaccttaggc ctctctctct ccagatgttt ccagacttcc ttgagacag
30 3001 gagcccagcc ctccccatgg agccagctcc ctctatttat gtttgactt gtgattattt
3061 attattttatt tattatttat ttatttacag atgaatgtat ttatttggga gaccggggtg
3121 tccctggggga cccaatgtag gagctgcctt ggctcagaca tgttttcctg gaaaacggag
3181 ctgaacaata ggctgttccc atgtagcccc ctggcctctg tgccctcttt tgattatgtt
3241 ttttaaaata tttatctgat taagtgtgt aaacaatgct gatttgggtg ccaactgtca
35 3301 ctcaattgct agcctctgct ccccagggga gttgtgtct taatcgccct actattcagt
3361 ggcgagaaat aaagtttgct tagaaaagaa acatggtctc cttcttgga ttaattctgc
3421 atctgcctct tcttgtgggt gggagaagc tccctaagtc ctctctccac aggtttaag
3481 atccctcgga ccagtcacca tcccttagact cctagggccc tggagaccct acataaacia
3541 agcccaacag aatattcccc atccccagg aaacaagagc ctgaacctaa ttacctctcc
40 3601 ctcagggcct gggaatttcc aactctggga attc (SEQ ID NO: 304)

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The nanostructures described herein may be stable self-assembling nanostructures. For instance the nanostructure may be an antisense oligonucleotide of 18-21 nucleotides in length having a sequence described herein, wherein a hydrophobic group at the 3' or 5' terminus self-associates to form the core of the nanostructure in water or other suitable solvents. A hydrophobic group as used herein may include cholesterol, a cholesteryl or modified cholesteryl residue, adamantane, dihydrotestosterone, long chain alkyl, long chain alkenyl, long chain alkynyl, olelyl-lithocholic, cholenic, oleoyl-cholenic, palmityl, heptadecyl, myrisityl, bile acids, cholic acid or taurocholic acid, deoxycholate, oleyl lithocholic acid, oleoyl cholenic acid, glycolipids, phospholipids, sphingolipids, isoprenoids, such as steroids, vitamins, such as vitamin E, fatty acids either saturated or unsaturated, fatty acid esters, such as triglycerides, pyrenes, porphyrines, Texaphyrine, adamantane, acridines, biotin, coumarin, fluorescein, rhodamine, Texas-Red, digoxigenin, dimethoxytrityl, t-butyldimethylsilyl, t-

butyldiphenylsilyl, cyanine dyes (e.g. Cy3 or Cy5), Hoechst 33258 dye, psoralen, or ibuprofen.

The antisense oligonucleotides typically have a length of 10-30 or 15-20 bases, which is generally long enough to have one complementary sequence in the mammalian genome.

5 Additionally, antisense compounds having a length of at least 12, typically at least 15 nucleotides in length hybridize well with their target mRNA. Thus, the antisense oligonucleotides of the invention are typically in a size range of 8-100 nucleotides, more preferably 12-50 nucleotides in length. In some embodiments of the invention the antisense oligonucleotides are of 18-19 nucleotides in length. The antisense oligonucleotides may
10 include further nucleotides on the 5' and/or 3' end of the oligonucleotide. However an antisense oligonucleotide that is limited to 18 nucleotides in length, for example, does not have any additional nucleotides on the 5' or 3' end of the molecule. Other non-nucleotide molecules may be linked covalently or non-covalently to the 5' and/or 3' end of those oligonucleotides.

15 The terms "nucleic acid" and "oligonucleotide" are used interchangeably to mean multiple nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., cytosine (C), thymine (T) or uracil (U)) or a substituted purine (e.g., adenine (A) or guanine (G)). As used herein, the terms "nucleic acid" and "oligonucleotide" refer to
20 oligoribonucleotides as well as oligodeoxyribonucleotides. The terms "nucleic acid" and "oligonucleotide" shall also include polynucleosides (i.e., a polynucleotide minus the phosphate) and any other organic base containing polymer. Nucleic acid molecules are preferably synthetic (e.g., produced by nucleic acid synthesis). The oligonucleotides may be any size useful for producing antisense effects. In some embodiments they are 18-23
25 nucleotides in length. In other embodiments the antisense oligonucleotide is 18 nucleotides in length.

The terms "nucleic acid" and "oligonucleotide" may also encompass nucleic acids or oligonucleotides with substitutions or modifications, such as in the bases and/or sugars. For example, they include nucleic acids having backbone sugars that are covalently attached to
30 low molecular weight organic groups other than a hydroxyl group at the 2' position and other than a phosphate group or hydroxy group at the 5' position. Thus modified nucleic acids may include a 2'-O-alkylated ribose group. In addition, modified nucleic acids may include sugars such as hexose, 2'-F hexose, 2'-amino ribose, CEt-LNA, arabinose or 2'-fluoroarabinose instead of ribose. Thus the nucleic acids may be heterogeneous in backbone composition

thereby containing any possible combination of polymer units linked together such as peptide-nucleic acids (which have an amino acid backbone with nucleic acid bases). Other examples are described in more detail below.

The oligonucleotides may be DNA, RNA, PNA, LNA, ENA or hybrids including any chemical or natural modification thereof. Chemical and natural modifications are well known in the art. Such modifications include, for example, modifications designed to increase binding to a target strand (i.e., increase their melting temperatures), to assist in identification of the oligonucleotide or an oligonucleotide-target complex, to increase cell penetration, to stabilize against nucleases and other enzymes that degrade or interfere with the structure or activity of the oligonucleotides, to provide a mode of disruption (a terminating event) once sequence-specifically bound to a target, and to improve the pharmacokinetic properties of the oligonucleotide.

Modifications include, but are not limited to, for example, (a) end modifications, e.g., 5' end modifications (phosphorylation dephosphorylation, conjugation, inverted linkages, etc.), 3' end modifications (conjugation, DNA nucleotides, inverted linkages, etc.), (b) base modifications, e.g., replacement with modified bases, stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, or conjugated bases, (c) sugar modifications (e.g., at the 2' position or 4' position) or replacement of the sugar, as well as (d) internucleoside linkage modifications, including modification or replacement of the phosphodiester linkages. To the extent that such modifications interfere with translation (i.e., results in a reduction of 50%, 60%, 70%, 80%, or 90% or more in translation relative to the lack of the modification - e.g., in an *in vitro* translation assay), the modification may not be optimal for the methods and compositions described herein.

Non-limiting examples of modified internucleoside linkages include phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.

In some embodiments, the modified oligonucleotide is a single-stranded modified oligonucleotide. In some embodiments, the single-stranded modified oligonucleotide

consists of 10-30, 10-35, 10-40, 10-45, 10-50, 10-60, 10-70, 10-80, 10-90, 10-100 or more than 100 linked nucleosides and has a gap segment. In some embodiments, a gap segment refers to one or more linked nucleic acids consisting of deoxynucleosides located at the center or near the center of a modified oligonucleotide, such as a single-stranded modified

5 oligonucleotide. In some embodiments, the gap segment consists of 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 2-20, 2-30, 2-40 2-50, 10-20, 10-30, 10-40 or 10-50 linked deoxynucleosides.

A 5' wing segment corresponds to the linked nucleic acids (e.g., nucleosides) from the 5'-end of a modified oligonucleotide to the nucleic acid before the first nucleic acid at the 5'-end of the gap segment. A 3' wing segment corresponds to the linked nucleic acids (e.g.,
10 nucleosides) after the last nucleic acid at the 3' end of the gap segment to the last nucleic acid at the 3' end of the modified oligonucleotide.

The gap segment is positioned between the 5' wing segment and the 3' wing segment. In some embodiments, at least one nucleoside of the 5' wing segment and/or at least one nucleoside of the 3' wing segment comprises a modified nucleoside. In some embodiments,
15 the internucleoside linkages within the gap segment and the linkages connecting the gap segment to the 3' wing segment and/or the 5' wing segment are all phosphorothioate linkages (*). In some embodiments, the internucleoside linkages connecting the rest of the nucleosides of both the 5' and 3' wing segments are phosphodiester linkages. In some
20 embodiments, the nucleosides in the modified oligonucleotide are modified with a 2' O-methyl group. The nucleosides in the modified oligonucleotide can also be modified with any other modification described herein.

In some embodiments, the nucleobase sequence of the modified oligonucleotide consists of 10-30, 10-35, 10-40, 10-45, 10-50, 10-60, 10-70, 10-80, 10-90, 10-100 or more than 100 linked nucleosides and has a gap segment complementary to an equal length portion
25 of the coding sequence (e.g., cDNA) of the IL-17R, such as IL-17RA (e.g., cDNA sequence of IL-17RA is represented by SEQ ID NO: 302), IL-17RB, IL-17RC, IL-17RD, or IL-17RE) (see e.g., Johansen et al., *Br J Dermatol* (2009) 160(2):319-24, or a pharmaceutically acceptable salt thereof.

Modified internucleoside linkages that do not include a phosphorus atom therein have
30 internucleoside linkages that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl

backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts.

5 Substituted sugar moieties include, but are not limited to one of the following at the 2' position: H (deoxyribose); OH (ribose); F; 0-, S-, or N-alkyl; 0-, S-, or N-alkenyl; 0-, S- or N-alkynyl; or O-alkyl- O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl.

10 A chemically or naturally modified oligonucleotide may include, for example, at least one nucleotide modified at the 2' position of the sugar, most preferably a 2'-O-alkyl, 2'-O-alkyl-O-alkyl or 2'-fluoro-modified nucleotide or an end cap. In other embodiments, RNA modifications include 2'-fluoro, 2'-amino and 2' O-methyl modifications on the ribose of pyrimidines, abasic residues or an inverted base at the 3' end of the RNA.

15 The oligonucleotides useful according to the invention may include a single modified nucleoside. In other embodiments the oligonucleotide may include at least two modified nucleosides, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20 or more nucleosides, up to the entire length of the oligonucleotide.

Nucleosides or nucleobases include the natural purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleosides
 20 include other synthetic and natural nucleobases such as inosine, xanthine, hypoxanthine, nubularine, isoguanisine, tubercidine, 2-(halo)adenine, 2-(alkyl)adenine, 2- (propyl)adenine, 2 (amino)adenine, 2-(aminoalkyl)adenine, 2 (aminopropyl)adenine, 2 (methylthio) N6 (isopentenyl)adenine, 6 (alkyl)adenine, 6 (methyl)adenine, 7 (deaza)adenine, 8 (alkenyl)adenine, 8- (alkyl)adenine, 8 (alkynyl)adenine, 8 (amino)adenine, 8-(halo)adenine, 8-(hydroxyl)adenine, 8 (thioalkyl) adenine, 8-(thiol)adenine, N6-(isopentyl)adenine, N6 (methyl)adenine, N6, N6 (dimethyl)adenine, 2-(alkyl)guanine, 2 (propyl)guanine, 6- (alkyl)guanine, 6 (methyl)guanine, 7 (alkyl)guanine, 7 (methyl)guanine, 7 (deaza)guanine, 8 (alkyl)guanine, 8-(alkenyl)guanine, 8 (alkynyl)guanine, 8-(amino)guanine, 8 (halo)guanine, 8-(hydroxyl)guanine, 8 (thioalkyl)guanine, 8- (thiol)guanine, N (methyl)guanine, 2-
 25 (thio)cytosine, 3 (deaza) 5 (aza)cytosine, 3-(alkyl)cytosine, 3 (methyl)cytosine, 5- (alkyl)cytosine, 5-(alkynyl)cytosine, 5 (halo)cytosine, 5 (methyl)cytosine, 5 (propynyl)cytosine, 5 (propynyl)cytosine, 5 (trifluoromethyl)cytosine, 6-(azo)cytosine, N4 (acetyl)cytosine, 3 (3 amino-3 carboxypropyl)uracil, 2-(thio)uracil, 5 (methyl) 2 (thio)uracil, 5 (methylaminomethyl)-2 (thio)uracil, 4-(thio)uracil, 5 (methyl) 4 (thio)uracil, 5
 30

- (methylaminomethyl)-4 (thio)uracil, 5 (methyl) 2,4 (dithio)uracil, 5 (methylaminomethyl)-2,4 (dithio)uracil, 5 (2-aminopropyl)uracil, 5-(alkyl)uracil, 5-(alkynyl)uracil, 5-(allylamino)uracil, 5 (aminoallyl)uracil, 5 (aminoalkyl)uracil, 5 (guanidiniumalkyl)uracil, 5 (1,3-diazole-1-alkyl)uracil, 5-(cyanoalkyl)uracil, 5- (dialkylaminoalkyl)uracil, 5
- 5 (dimethylaminoalkyl)uracil, 5-(halo)uracil, 5-(methoxy)uracil, uracil-5 oxyacetic acid, 5 (methoxycarbonylmethyl)-2-(thio)uracil, 5 (methoxycarbonyl-methyl)uracil, 5 (propynyl)uracil, 5 (propynyl)uracil, 5 (trifluoromethyl)uracil, 6 (azo)uracil, dihydrouracil, N3 (methyl)uracil, 5-uracil (i.e., pseudouracil), 2 (thio)pseudouracil, 4 (thio)pseudouracil, 2,4-(dithio)pseudouracil, 5-(alkyl)pseudouracil, 5-(methyl)pseudouracil, 5-(alkyl)-2-
- 10 (thio)pseudouracil, 5- (methyl)-2-(thio)pseudouracil, 5-(alkyl)-4 (thio)pseudouracil, 5-(methyl)-4 (thio)pseudouracil, 5-(alkyl)- 2,4 (dithio)pseudouracil, 5-(methyl)-2,4 (dithio)pseudouracil, 1 substituted pseudouracil, 1 substituted 2(thio)-pseudouracil, 1 substituted 4 (thio)pseudouracil, 1 substituted 2,4-(dithio)pseudouracil, 1 (aminocarbonylethylenyl)-pseudouracil, 1 (aminocarbonylethylenyl)-2(thio)-pseudouracil, 1
- 15 (aminocarbonylethylenyl)-4 (thio)pseudouracil, 1 aminocarbonylethylenyl)-2,4-(dithio)pseudouracil, 1 (aminocarbonylethylenyl)-pseudouracil, 1 (aminocarbonylethylenyl)-2(thio)- pseudouracil, 1(aminocarbonylethylenyl)-4 (thio)pseudouracil, 1 (aminocarbonylethylenyl)-2,4-(dithio)pseudouracil, 1,3-(diaz)-2-(oxo)-
- 20 phenoxazin-1-yl, 1 - (aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 1,3-(diaz)-2-(oxo)-phenthiazin-1-yl, 1-(aza)-2-(thio)-3-(aza)- phenthiazin-1-yl, 7-substituted 1,3-(diaz)-2-(oxo)-phenoxazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3- (aza)-phenoxazin-1-yl, 7-substituted 1,3-(diaz)-2-(oxo)-phenthiazin-1-yl, 7-substituted 1-(aza)-2-(thio)- 3-(aza)-phenthiazin-1-yl, 7-
- (aminocarbonylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl, 7- (aminocarbonylhydroxy)-1-(aza)-2-
- 25 (thio)-3-(aza)-phenoxazin-1-yl, 7-(aminocarbonylhydroxy)-1,3-(diaz)-2- (oxo)-phenthiazin-1-yl, 7-(aminocarbonylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-
- (guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl, 7-
- (guanidiniumalkylhydroxy)-1-(aza)- 2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenthiazin-1-yl, 7- (guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-
- 30 3-(aza)-phenthiazin-1-yl, 1,3,5-(triaz)-2,6-(diox)- naphthalene, inosine, xanthine, hypoxanthine, nubarine, tubercidine, isoguanisine, inosinyl, 2-aza- inosinyl, 7-deaza-inosinyl, nitroimidazolyl, nitropyrazolyl, nitrobenzimidazolyl, nitroindazolyl, aminoindolyl, pyrrolopyrimidinyl, 3-(methyl)isocarbostyryl, 5-(methyl)isocarbostyryl, 3-(methyl)-7-(propynyl)isocarbostyryl, 7-(aza)indolyl, 6-(methyl)-7-(aza)indolyl, imidizopyridinyl, 9-

(methyl)-imidizopyridinyl, pyrrolopyrizinyl, isocarbostyryl, 7-(propynyl)isocarbostyryl, propynyl-7-(aza)indolyl, 2,4,5-(trimethyl)phenyl, 4-(methyl)indolyl, 4,6-(dimethyl)indolyl, phenyl, naphthalenyl, anthracenyl, phenanthracenyl, pyrenyl, stilbenyl, tetracenyl, pentacenyl, diilfuorotolyl, 4-(iluoro)-6-(methyl)benzimidazole, 4-(methyl)benzimidazole, 6-(azo)thymine, 2-pyridinone, 5 nitroindole, 3 nitropyrrole, 6-(aza)pyrimidine, 2 (amino)purine, 2,6-(diamino)purine, 5 substituted pyrimidines, N2-substituted purines, N6-substituted purines, O6-substituted purines, substituted 1,2,4-triazoles, pyrrolo-pyrimidin-2-on-3-yl, 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-ortho—(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl, 2-oxo-pyridopyrimidine-3-yl, or any O-alkylated or N-alkylated derivatives thereof.

The antisense oligonucleotides of the invention may be chimeric oligonucleotides. Chimeric antisense compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleotides and/or oligonucleotide mimetics as described above. Such compounds have also been referred to in the art as hybrids or mixed backbone or chimeric or gapmers. In particular a gapmer is an oligonucleotide that has at least three discrete portions, two of which are similar i.e. include one or more backbone modifications, and surround a region that is distinct, i.e., does not include backbone modifications.

The oligonucleotides may include a molecular species at one or both ends, i.e., at the 3' and/or 5' end. A molecular species as used herein refers to any compound that is not a naturally occurring or non-naturally occurring nucleotide. Molecular species include but are not limited to a spacer, a lipid, a sterol, lipid moieties such as a cholesterol moiety, cholic acid, a thioether, e.g., hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues, a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety, stearyl, C16 alkyl chain, bile acids, cholic acid, taurocholic acid, deoxycholate, oleyl lithocholic acid, oleoyl cholenic acid, glycolipids, phospholipids, sphingolipids, isoprenoids, such as steroids, vitamins, such as vitamin E, saturated fatty acids, unsaturated fatty acids, fatty acid esters, such as triglycerides, pyrenes,

porphyrines, Texaphyrine, adamantane, acridines, biotin, coumarin, fluorescein, rhodamine, Texas-Red, digoxigenin, dimethoxytrityl, t-butyltrimethylsilyl, t-butylphenylsilyl, cyanine dyes (e.g. Cy3 or Cy576), Hoechst 33258 dye, psoralen, or ibuprofen.

The molecular species may be attached at various positions of the oligonucleotide. As described above, the molecular species may be linked to the 2'-end, 3'-end or 5'-end of the oligonucleotide, where it also serves the purpose to enhance the stability of the oligomer against 3'- or 5'- exonucleases. Alternatively, it may be linked to an internal nucleotide or a nucleotide on a branch. The molecular species may be attached to a 2'-position of the nucleotide. The molecular species may also be linked to the heterocyclic base of the nucleotide.

The molecular species may be connected to the oligonucleotide by a linker moiety. Optionally the linker moiety is a non-nucleotidic linker moiety. Non-nucleotidic linkers are e.g. abasic residues (dSpacer), oligoethyleneglycol, such as triethyleneglycol or hexaethyleneglycol, or alkane-diol, such as butanediol. The spacer units are preferably linked by phosphodiester, phosphorodithioate or phosphorothioate bonds. The linker units may appear just once in the molecule or may be incorporated several times, e.g. via phosphodiester, phosphorothioate, methylphosphonate, or amide linkages.

The oligonucleotide of the invention (separate from the linkers connecting nucleotides to the molecular species) may also contain non-nucleotidic linkers, in particular abasic linkers (dSpacers), triethylene glycol units or hexaethylene glycol units. Further preferred linkers are alkylamino linkers, such as C3, C6, C12 aminolinkers, and also alkylthiol linkers, such as C3 or C6 thiol linkers.

IL-17RA and TNF α play a role in a wide variety of inflammatory disorders. An inflammatory disorder as used herein refers to a disorder in which IL-17 or TNF α activity is detrimental to a particular physiological function in a subject. As used herein, the term "a disorder in which IL-17 or TNF α activity is detrimental" is intended to include diseases and other disorders in which the levels of these cytokines expressed in a subject suffering from the disorder plays a role in the pathophysiology of the disorder or as a factor that contributes to a worsening of or maintenance of the disorder. Accordingly, a disorder in which IL-17 or TNF α activity is detrimental is a disorder in which inhibition of IL-17/IL-17RA or TNF α activity is expected to alleviate at least one symptom and/or progression or worsening of the disorder. Such disorders may be evidenced, for example, by an increase in the concentration of IL-17 or TNF α in a biological fluid of a subject suffering from the disorder (e.g., an increase in the concentration of IL-17 or TNF α in serum, plasma, synovial fluid, etc. of the

subject), which can be detected, for example, using a probe or an antibody for detecting IL-17 or TNF α message or protein respectively.

Inflammatory disorders include but are not limited to sepsis, infections, autoimmune diseases, cancer, transplant rejection and graft-versus-host disease, transplant rejection, malignancy, a pulmonary disorder, an intestinal disorder, a cardiac disorder, sepsis, a spondyloarthropathy, a metabolic disorder, anemia, pain, a hepatic disorder, a skin disorder, a nail disorder, rheumatoid arthritis, psoriasis, psoriasis in combination with psoriatic arthritis, ulcerative colitis, Crohn's disease, vasculitis, Behcet's disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disorder (COPD), idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriatic arthritis, and chronic plaque psoriasis.

The biological role played by IL-17 or TNF α in these diseases is known. Inhibiting IL-17RA and/or TNF α expression in these diseases provides a therapeutic treatment for the disorder.

The ASO-SNAs and mASO-SNAs may be administered alone or in conjunction with another therapeutic agent for the treatment of an inflammatory disorder. Non-limiting examples of therapeutic agents with which the ASO-SNAs and mASO-SNAs of the invention can be combined include the following: non-steroidal anti-inflammatory drug(s) (NSAIDs); cytokine suppressive anti-inflammatory drug(s) (CSAIDs); CDP-571/BAY-10-3356 (humanized anti-TNF α antibody; Celltech/Bayer); cA2/infliximab (chimeric anti-TNF α antibody; Centocor); 75 kDTNFR-IgG/etanercept (75 kD TNF receptor-IgG fusion protein; Immunex); 55 kDTNF-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche); IDEC-CE9/SB 210396 (non-depleting primatized anti-CD4 antibody; IDEC/SmithKline); DAB 486-IL-2 and/or DAB 389-IL-2 (IL-2 fusion proteins; Seragen); Anti-Tac (humanized anti-IL-2R α ; Protein Design Labs/Roche); IL-4 (anti-inflammatory cytokine; DNAX/Schering); IL-10 (SCH 52000; recombinant IL-10, anti-inflammatory cytokine; DNAX/Schering); IL-4; IL-10 and/or IL-4 agonists (e.g., agonist antibodies); IL-1 RA (IL-1 receptor antagonist; Synergen/Amgen); anakinra (Kineret/Amgen); TNF-bp/s-TNF (soluble TNF binding protein); R973401 (phosphodiesterase Type IV inhibitor; MK-966 (COX-2 Inhibitor; Iloprost; methotrexate; thalidomide and thalidomide-related drugs (e.g., Celgen); leflunomide (anti-inflammatory and cytokine inhibitor; tranexamic acid (inhibitor of plasminogen activation; T-614 (cytokine inhibitor; prostaglandin E1; Tenidap (non-steroidal anti-inflammatory drug; Naproxen (non-steroidal anti-inflammatory drug; Meloxicam (non-

steroidal anti-inflammatory drug); Ibuprofen (non-steroidal anti-inflammatory drug); Piroxicam (non-steroidal anti-inflammatory drug); Diclofenac (non-steroidal anti-inflammatory drug); Indomethacin (non-steroidal anti-inflammatory drug); Sulfasalazine; Azathioprine; ICE inhibitor (inhibitor of the enzyme interleukin-1-beta-converting enzyme);
 5 zap-70 and/or Ick inhibitor (inhibitor of the tyrosine kinase zap-70 or Ick); VEGF inhibitor and/or VEGF-R inhibitor (inhibitors of vascular endothelial cell growth factor or vascular endothelial cell growth factor receptor; inhibitors of angiogenesis); corticosteroid anti-inflammatory drugs (e.g., SB203580); TNF-convertase inhibitors; anti-IL-12 antibodies; anti-IL-18 antibodies; interleukin-11; interleukin-13; interleukin-17 inhibitors; gold;
 10 penicillamine; chloroquine; hydroxychloroquine; chlorambucil; cyclosporine; cyclophosphamide; total lymphoid irradiation; anti-thymocyte globulin; anti-CD4 antibodies; CD5-toxins; orally-administered peptides and collagen; lobenzarit disodium; Cytokine Regulating Agents (CRAs) HP228 and HP466 (Houghten Pharmaceuticals, Inc.); ICAM-1 antisense phosphorothioate oligodeoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.);
 15 soluble complement receptor 1 (TP10; T Cell Sciences, Inc.); prednisone; orgotein; glycosaminoglycan polysulphate; minocycline; anti-IL2R antibodies; marine and botanical lipids (fish and plant seed fatty acids; auranofin; phenylbutazone; meclofenamic acid; flufenamic acid; intravenous immune globulin; zileuton; azaribine; mycophenolic acid (RS-61443); tacrolimus (FK-506); sirolimus (rapamycin); amiprilose (therafectin); cladribine (2-
 20 chlorodeoxyadenosine); methotrexate; antivirals; and immune modulating agents.

Toxicity and efficacy of the prophylactic and/or therapeutic protocols of the present invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The
 25 dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Prophylactic and/or therapeutic agents that exhibit large therapeutic indices are preferred. While prophylactic and/or therapeutic agents that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such agents to the site of affected tissue in order to minimize potential damage to uninfected
 30 cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage of the prophylactic and/or therapeutic agents for use in humans. The dosage of such agents lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within

this range depending upon the dosage form employed and the route of administration utilized. For any agent used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (*i.e.*, the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography. A number of studies have examined the optimal dosages for antisense oligonucleotides.

In certain embodiments, pharmaceutical compositions may comprise, for example, at least about 0.000001% (w/w) of an active compound. In other embodiments, the active compound may comprise between about 2% to about 75% of the weight of the unit (w/w), or between about 25% to about 60%, for example, and any range derivable therein. In some embodiments, the active compound (e.g., oligonucleotide or nanostructure) described herein comprises between 0.000001% and 0.00001%, between 0.00001% and 0.0001%, between 0.0001% and 0.001%, between 0.001% and 0.01%, between 0.01% and 0.1%, between 0.1% and 1%, between 1% and 5%, between 5% and 10%, between 10% and 15%, between 15% and 20%, between 20% and 25%, between 25% and 30%, between 30% and 40%, between 40% and 50% (w/w), and any range derivable in between. In some embodiments, the active compound (e.g., oligonucleotide or nanostructure) described herein comprises 0.00007%, 0.007%, 0.01%, 0.1%, 1% (w/w)

Subject doses of the compounds described herein typically range from about 0.1 µg to 10,000 mg, more typically from about 1 µg/day to 8000 mg, and most typically from about 10 µg to 100 µg. Stated in terms of subject body weight, typical dosages range from about 1 microgram/kg/body weight, about 5 microgram/kg/body weight, about 10 microgram/kg/body weight, about 50 microgram/kg/body weight, about 100 microgram/kg/body weight, about 200 microgram/kg/body weight, about 350 microgram/kg/body weight, about 500 microgram/kg/body weight, about 1 milligram/kg/body weight, about 5 milligram/kg/body weight, about 10 milligram/kg/body weight, about 50 milligram/kg/body weight, about 100 milligram/kg/body weight, about 200 milligram/kg/body weight, about 350 milligram/kg/body weight, about 500 milligram/kg/body weight, to about 1000 mg/kg/body weight or more per administration, and any range derivable therein. In non-limiting examples of a derivable range from the numbers

listed herein, a range of about 5 mg/kg/body weight to about 100 mg/kg/body weight, about 5 microgram/kg/body weight to about 500 milligram/kg/body weight, etc., can be administered, based on the numbers described above. The absolute amount will depend upon a variety of factors including the concurrent treatment, the number of doses and the individual patient parameters including age, physical condition, size and weight. These are factors well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgment.

Multiple doses of the molecules of the invention are also contemplated. In some instances, when the molecules of the invention are administered with another therapeutic, for instance, an anti-inflammatory agent, a sub-therapeutic dosage of either the molecules or the other agent, or a sub-therapeutic dosage of both, is used in the treatment of a subject having, or at risk of developing an inflammatory disorder. When the two classes of drugs are used together, the other agent may be administered in a sub-therapeutic dose to produce a desirable therapeutic result. A “sub-therapeutic dose” as used herein refers to a dosage which is less than that dosage which would produce a therapeutic result in the subject if administered in the absence of the other agent. Thus, the sub-therapeutic dose of a therapeutic agent is one which would not produce the desired therapeutic result in the subject in the absence of the administration of the molecules of the invention. Therapeutic doses of agents useful for treating inflammatory disorders are well known in the field of medicine. These dosages have been extensively described in references such as Remington’s Pharmaceutical Sciences; as well as many other medical references relied upon by the medical profession as guidance for the treatment of infectious disease, cancer, and autoimmune disease. Therapeutic dosages of oligonucleotides have also been described in the art.

Dosing regimens may be several times a day, daily, every other day, weekly, biweekly any of the times there between or less frequently. The term “biweekly dosing” as used herein, refers to the time course of administering a substance (e.g., an anti-IL-17RA nucleic acid) to a subject once every two weeks. The oligonucleotides may be administered every 7-20 days, every 11-17 days, or every 13-15 days, for example.

In some embodiments, a compound (e.g., oligonucleotide, nanostructure, etc.) described herein is administered for 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 72, 96, 120, 240, 480 hours, or any ranges in between, per dose in a dosing schedule.

The oligonucleotides are administered in effective amounts. The effective amount of a compound of the invention in the treatment of a disease described herein may vary depending

upon the specific compound used, the mode of delivery of the compound, and whether it is used alone or in combination. The effective amount for any particular application can also vary depending on such factors as the disease being treated, the particular compound being administered, the size of the subject, or the severity of the disease or condition. One of
5 ordinary skill in the art can empirically determine the effective amount of a particular molecule of the invention without necessitating undue experimentation. Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic
10 treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the particular subject.

In some embodiments, the cell is contacted with an oligonucleotide, a nanostructure, or a mASO-SNA described herein at a concentration of at least 0.001 nM, at least 0.01 nM, at least 0.1 nM, at least 1 nM, at least 10 nM, at least 100 nM, at least 1000 nM, at least 10 μ M,
15 at least 100 μ M, at least 1000 μ M, or above 1000 μ M. In some embodiments, the cell is contacted with an oligonucleotide, a nanostructure, or a mASO-SNA described herein at a concentration range of 0.001 nM to 0.01 nM, 0.01 nM to 0.1 nM, 0.1 nM to 1 nM, 1 nM to 10 nM, 10 nM to 100 nM, 100 nM to 1000 nM, 1000 nM to 10 μ M, 10 μ M to 100 μ M, or 100 μ M to 1000 μ M. In some embodiments, the cell is contacted with an oligonucleotide, a
20 nanostructure, or a mASO-SNA described herein at a concentration of 0.001 nM, 0.01 nM, 0.1 nM, 1 nM, 10 nM, 100 nM, 1000 nM, 10 μ M, 100 μ M, 1000 μ M or above 1000 μ M.

The oligonucleotides described herein can be used alone or in conjugates with other molecules such as detection or cytotoxic agents in the detection and treatment methods of the
25 invention, as described in more detail herein.

The oligonucleotide may be, for instance, coupled or conjugated to a detectable label. A detectable label is a moiety, the presence of which can be ascertained directly or indirectly. Generally, detection of the label involves an emission of energy by the label. The label can be detected directly by its ability to emit and/or absorb photons or other atomic particles of a
30 particular wavelength (e.g., radioactivity, luminescence, optical or electron density, etc.). A label can be detected indirectly by its ability to bind, recruit and, in some cases, cleave another moiety which itself may emit or absorb light of a particular wavelength (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseradish peroxidase, etc.). An example of indirect detection is the use of a first enzyme label which cleaves a substrate into visible

products. The label may be of a chemical, peptide or nucleic acid molecule nature although it is not so limited. Other detectable labels include radioactive isotopes such as P^{32} or H^3 , luminescent markers such as fluorochromes, optical or electron density markers, etc., or epitope tags such as the FLAG epitope or the HA epitope, biotin, avidin, and enzyme tags such as horseradish peroxidase, β -galactosidase, etc. The label may be bound to an oligonucleotide during or following its synthesis. There are many different labels and methods of labeling known to those of ordinary skill in the art. Examples of the types of labels that can be used in the present invention include enzymes, radioisotopes, fluorescent compounds, colloidal metals, chemiluminescent compounds, and bioluminescent compounds. Those of ordinary skill in the art will know of other suitable labels for the oligonucleotides described herein, or will be able to ascertain such, using routine experimentation. Furthermore, the coupling or conjugation of these labels to the oligonucleotides of the invention can be performed using standard techniques common to those of ordinary skill in the art.

Conjugation of the oligonucleotides to a detectable label facilitates, among other things, the use of such agents in diagnostic assays. Another category of detectable labels includes diagnostic and imaging labels (generally referred to as *in vivo* detectable labels) such as for example magnetic resonance imaging (MRI): Gd(DOTA); for nuclear medicine: ^{201}Tl , gamma-emitting radionuclide ^{99m}Tc ; for positron-emission tomography (PET): positron-emitting isotopes, (18)F-fluorodeoxyglucose ((18)FDG), (18)F-fluoride, copper-64, gadodiamide, and radioisotopes of Pb(II) such as ^{203}Pb ; ^{111}In . In such instances, the use of the oligonucleotide could be observed as the oligonucleotide provides an antisense effect.

The conjugations or modifications described herein employ routine chemistry, which chemistry does not form a part of the invention and which chemistry is well known to those skilled in the art of chemistry. The use of protecting groups and known linkers such as mono- and hetero-bifunctional linkers are well documented in the literature and will not be repeated here.

As used herein, "conjugated" means two entities stably bound to one another by any physiochemical means. It is important that the nature of the attachment is such that it does not impair substantially the effectiveness of either entity. Keeping these parameters in mind, any covalent or non-covalent linkage known to those of ordinary skill in the art may be employed. In some embodiments, covalent linkage is preferred. Noncovalent conjugation includes hydrophobic interactions, ionic interactions, high affinity interactions such as biotin-avidin

and biotin-streptavidin complexation and other affinity interactions. Such means and methods of attachment are well known to those of ordinary skill in the art. A variety of methods may be used to detect the label, depending on the nature of the label and other assay components.

Pharmaceutical compositions of the present invention comprise an effective amount of one or more agents, dissolved or dispersed in a pharmaceutically acceptable carrier. The phrases “pharmaceutical or pharmacologically acceptable” refers to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, such as, for example, a human, as appropriate. Moreover, for animal (*e.g.*, human) administration, it will be understood that preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biological Standards. The compounds are generally suitable for administration to humans. This term requires that a compound or composition be nontoxic and sufficiently pure so that no further manipulation of the compound or composition is needed prior to administration to humans.

As used herein, “pharmaceutically acceptable carrier” includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, gels, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, such like materials and combinations thereof, as would be known to one of ordinary skill in the art.

The agent may comprise different types of carriers depending on whether it is to be administered in solid, liquid, gel, cream, or aerosol form, and whether it need to be sterile for such routes of administration as injection. The present invention can be administered intravenously, intradermally, intraarterially, intralesionally, intratumorally, intracranially, intrathecally, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, intramuscularly, intraperitoneally, subcutaneously, subconjunctival, intravesicularly, mucosally, intrapericardially, intraumbilically, intraocularly, via eyedrops, orally, topically, locally, inhalation (*e.g.*, aerosol inhalation), injection, infusion, continuous infusion, localized perfusion bathing target cells directly, via a catheter, via a lavage, in creams, in gel, in lipid compositions (*e.g.*, liposomes), or by other method or any combination of the foregoing as would be known to one of ordinary skill in the art.

In any case, the composition may comprise various antioxidants to retard oxidation of one or more components. Additionally, the prevention of the action of microorganisms can be

brought about by preservatives such as various antibacterial and antifungal agents, including but not limited to parabens (*e.g.*, methylparabens, propylparabens), chlorobutanol, phenol, sorbic acid, thimerosal or combinations thereof.

The agent may be formulated into a composition in a free base, neutral or salt form.

- 5 Pharmaceutically acceptable salts, include the acid addition salts, *e.g.*, those formed with the free amino groups of a proteinaceous composition, or which are formed with inorganic acids such as for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric or mandelic acid. Salts formed with the free carboxyl groups also can be derived from inorganic bases such as for example, sodium, potassium, ammonium, calcium or ferric
10 hydroxides; or such organic bases as isopropylamine, trimethylamine, histidine or procaine.

- In embodiments where the composition is in a liquid form, a carrier can be a solvent or dispersion medium comprising but not limited to, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, liquid polyethylene glycol, *etc.*), lipids (*e.g.*, triglycerides, vegetable oils, liposomes) and combinations thereof. The proper fluidity can be maintained, for example, by
15 the use of a coating, such as lecithin; by the maintenance of the required particle size by dispersion in carriers such as, for example liquid polyol or lipids; by the use of surfactants such as, for example hydroxypropylcellulose; or combinations thereof such methods. In many cases, it will be preferable to include isotonic agents, such as, for example, sugars, sodium chloride or combinations thereof.

- 20 The compounds of the invention may be administered directly to a tissue. Direct tissue administration may be achieved by direct injection, topical application, or local application. The compounds may be administered once, or alternatively they may be administered in a plurality of administrations. If administered multiple times, the compounds may be administered via different routes. For example, the first (or the first few)
25 administrations may be made directly into the affected tissue while later administrations may be systemic.

- The formulations of the invention are administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other
30 therapeutic ingredients.

According to the methods of the invention, the compound may be administered in a pharmaceutical composition. In general, a pharmaceutical composition comprises the compound of the invention and a pharmaceutically-acceptable carrier. As used herein, a

pharmaceutically-acceptable carrier means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients.

Pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers and other materials which are well-known in the art. Such preparations may
5 routinely contain salt, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. When used in medicine, the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically-acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically-acceptable salts include, but are not
10 limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic, and the like. Also, pharmaceutically-acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

The compounds of the invention may be formulated into preparations in solid, semi-
15 solid, liquid or gaseous forms such as tablets, capsules, powders, granules, ointments, solutions, depositories, inhalants and injections, and usual ways for oral, parenteral or surgical administration. The invention also embraces pharmaceutical compositions which are formulated for local administration, such as by implants.

Compositions suitable for oral administration may be presented as discrete units, such
20 as capsules, tablets, lozenges, each containing a predetermined amount of the active agent. Other compositions include suspensions in aqueous liquids or non-aqueous liquids such as a syrup, elixir or an emulsion.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such
25 carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, thermoreversible hydrogels such as pluronic F-127, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired,
30 to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the

cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Optionally the oral formulations may also be formulated in saline or buffers for neutralizing internal acid conditions or may be administered without any carriers.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.* gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch. Techniques for preparing aerosol delivery systems are well known to those of skill in the art.

The compounds, when it is desirable to deliver them systemically, may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as

suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. Lower doses will result from other forms of administration, such as intravenous administration. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.

The compositions of the invention may be formulated in a topical composition for administration to the skin or a body cavity. Suitable topical vehicles and vehicle components are well known in the cosmetic and pharmaceutical arts, and include such vehicles (or vehicle components) as water; thermoreversible hydrogels such as pluronic F-127, organic solvents such as alcohols (particularly lower alcohols readily capable of evaporating from the skin such as ethanol), glycols (such as propylene glycol, butylene glycol, and glycerin), aliphatic alcohols (such as lanolin); mixtures of water and organic solvents (such as water and alcohol), and mixtures of organic solvents such as alcohol and glycerin (optionally also with water); lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids and waxes; protein-based materials such as collagen and gelatin; silicone-based materials (both non-volatile and volatile) such as cyclomethicone, dimethiconol and dimethicone copolyol (Dow Corning); hydrocarbon-based materials such as petrolatum and squalane; anionic, cationic and amphoteric surfactants and soaps; sustained-release vehicles such as microsponges and polymer matrices; stabilizing and suspending agents; emulsifying agents; and other vehicles and vehicle components that are suitable for administration to the skin, as well as mixtures of topical vehicle components as identified above or otherwise known to the art. The vehicle may further include components adapted to improve the stability or effectiveness of the

applied formulation, such as preservatives, antioxidants, skin penetration enhancers, sustained release materials, and the like.

The choice of a suitable vehicle will depend on the particular physical form and mode of delivery that the formulation is to achieve. Examples of suitable forms include liquids (e.g., gargles and mouthwashes, including dissolved forms of the strontium cation as well as suspensions, emulsions and the like); solids and semisolids such as gels, foams, pastes, creams, ointments, "sticks" (as in lipsticks or underarm deodorant sticks), powders and the like; formulations containing liposomes or other delivery vesicles; rectal or vaginal suppositories, creams, foams, gels or ointments; and other forms. Typical modes of delivery include application using the fingers; application using a physical applicator such as a cloth, tissue, swab, stick or brush (as achieved for example by soaking the applicator with the formulation just prior to application, or by applying or adhering a prepared applicator already containing the formulation--such as a treated or premoistened bandage, wipe, washcloth or stick--to the skin); spraying (including mist, aerosol or foam spraying); dropper application (as for example with ear drops); sprinkling (as with a suitable powder form of the formulation); and soaking.

Topical formulations also include formulations for rectal and vaginal administration. Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter. Formulations suitable for vaginal administration may be presented as tablets, pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

In yet other embodiments, a delivery vehicle is a biocompatible microparticle or implant that is suitable for implantation into the mammalian recipient. Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the compound, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones, polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides.

In some embodiments the antisense nucleic acids of the invention are formulated as a stable self-assembling nanostructure. The nanostructure includes a IL-17RA antisense oligonucleotide, wherein the antisense oligonucleotide is associated with a core. The core may be a solid or a hollow core, such as a liposomal core. A solid core is a spherical shaped

material that does not have a hollow center. The term spherical as used herein refers to a general shape and does not imply or is not limited to a perfect sphere or round shape. It may include imperfections.

5 Solid cores can be constructed from a wide variety of materials known to those skilled in the art including but not limited to: noble metals (gold, silver), transition metals (iron, cobalt) and metal oxides (silica). In addition, these cores may be inert, paramagnetic, or superparamagnetic. These solid cores can be constructed from either pure compositions of described materials, or in combinations of mixtures of any number of materials, or in layered compositions of materials. In addition, solid cores can be composed of a polymeric core such
10 as amphiphilic block copolymers, hydrophobic polymers such as polystyrene, poly(lactic acid), poly(lactic co-glycolic acid), poly(glycolic acid), poly(caprolactone) and other biocompatible polymers known to those skilled in the art.

The core may alternatively be a hollow core, which has at least some space in the center region of a shell material. Hollow cores include liposomal cores and niosomes. A
15 liposomal core as used herein refers to a centrally located core compartment formed by a component of the lipids or phospholipids that form a lipid bilayer. "Liposomes" are artificial, self closed vesicular structure of various sizes and structures, where one or several membranes encapsulate an aqueous core. Most typically liposome membranes are formed from lipid bilayers membranes, where the hydrophilic head groups are oriented towards the
20 aqueous environment and the lipid chains are embedded in the lipophilic core. Liposomes can be formed as well from other amphiphilic monomeric and polymeric molecules, such as polymers, like block copolymers, or polypeptides. Unilamellar vesicles are liposomes defined by a single membrane enclosing an aqueous space. In contrast, oligo- or multilamellar vesicles are built up of several membranes. Typically, the membranes are roughly 4 nm thick
25 and are composed of amphiphilic lipids, such as phospholipids, of natural or synthetic origin. Optionally, the membrane properties can be modified by the incorporation of other lipids such as sterols or cholic acid derivatives.

The lipid bilayer is composed of two layers of lipid molecules. Each lipid molecule in a layer is oriented substantially parallel to adjacent lipid bilayers, and two layers that form a
30 bilayer have the polar ends of their molecules exposed to the aqueous phase and the non-polar ends adjacent to each other. The central aqueous region of the liposomal core may be empty or filled fully or partially with water, an aqueous emulsion, oligonucleotides, or other therapeutic or diagnostic agents.

Niosomes are vesicles formed from non-ionic surfactant oriented in a bilayer. Niosomes commonly have cholesterol added as an excipient, but other lipid-based and non-lipid-based constituents can also be included. Methods for preparation of niosomes are known in the art. In some embodiments polyethylene glycol (PEG) is included during or following niosome preparation. Niosome vesicles are structurally and functionally analogous to liposomes, but are based on non-ionic surfactant rather than lipid as the primary constituent. Common non-ionic surfactants used include sorbitans (spans) or polysorbates (tween); however, a wide variety of non-ionic surfactants can be used to prepare niosomes.

“Lipid” refers to its conventional sense as a generic term encompassing fats, lipids, alcohol-ether-soluble constituents of protoplasm, which are insoluble in water. Lipids usually consist of a hydrophilic and a hydrophobic moiety. In water lipids can self organize to form bilayers membranes, where the hydrophilic moieties (head groups) are oriented towards the aqueous phase, and the lipophilic moieties (acyl chains) are embedded in the bilayers core. Lipids can comprise as well two hydrophilic moieties (bola amphiphiles). In that case, membranes may be formed from a single lipid layer, and not a bilayer. Typical examples for lipids in the current context are fats, fatty oils, essential oils, waxes, steroid, sterols, phospholipids, glycolipids, sulpholipids, aminolipids, chromolipids, and fatty acids. The term encompasses both naturally occurring and synthetic lipids. Preferred lipids in connection with the present invention are: steroids and sterol, particularly cholesterol, phospholipids, including phosphatidyl, phosphatidylcholines and phosphatidylethanolamines and sphingomyelins. Where there are fatty acids, they could be about 12-24 carbon chains in length, containing up to 6 double bonds. The fatty acids are linked to the backbone, which may be derived from glycerol. The fatty acids within one lipid can be different (asymmetric), or there may be only 1 fatty acid chain present, e.g. lysolecithins. Mixed formulations are also possible, particularly when the non-cationic lipids are derived from natural sources, such as lecithins (phosphatidylcholines) purified from egg yolk, bovine heart, brain, liver or soybean.

The liposomal core can be constructed from one or more lipids known to those in the art including but not limited to: 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dimyristoyl-sn-phosphatidylcholine (DMPC), 1-palmitoyl-2-oleoyl-sn-phosphatidylcholine (POPC), 1,2-distearoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DSPG), 1,2-dioleoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DOPG), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine (DOPE), and 1,2-dihexadecanoyl-sn-glycero-3-

phosphoethanolamine (DPPE), sphingolipids such as sphingosine, sphingosine phosphate, methylated sphingosines and sphingamines, ceramides, ceramide phosphates, 1-0 acyl ceramides, dihydroceramides, 2-hydroxy ceramides, sphingomyelin, glycosylated sphingolipids, sulfatides, gangliosides, phosphosphingolipids, and phytosphingosines of various lengths and saturation states and their derivatives, phospholipids such as phosphatidylcholines, lysophosphatidylcholines, phosphatidic acids, lysophosphatidic acids, cyclic LPA, phosphatidylethanolamines, lysophosphatidylethanolamines, phosphatidylglycerols, lysophosphatidylglycerols, phosphatidylserines, lysophosphatidylserines, phosphatidylinositols, inositol phosphates, LPI, cardiolipins, lysocardiolipins, bis(monoacylglycero) phosphates, (diacylglycero) phosphates, ether lipids, diphytanyl ether lipids, and plasmalogens of various lengths, saturation states, and their derivatives, sterols such as cholesterol, desmosterol, stigmasterol, lanosterol, lathosterol, diosgenin, sitosterol, zymosterol, zymostenol, 14-demethyl-lanosterol, cholesterol sulfate, DHEA, DHEA sulfate, 14-demethyl-14-dehydranosterol, sitostanol, campesterol, ether anionic lipids, ether cationic lipids, lanthanide chelating lipids, A-ring substituted oxysterols, B-ring substituted oxysterols, D-ring substituted oxysterols, side-chain substituted oxysterols, double substituted oxysterols, cholestanoic acid derivatives, fluorinated sterols, fluorescent sterols, sulfonated sterols, phosphorylated sterols, and polyunsaturated sterols of different lengths, saturation states, and their derivatives.

In certain embodiments, the diameter of the core is from 1 nm to about 250 nm in mean diameter, about 1 nm to about 240 nm in mean diameter, about 1 nm to about 230 nm in mean diameter, about 1 nm to about 220 nm in mean diameter, about 1 nm to about 210 nm in mean diameter, about 1 nm to about 200 nm in mean diameter, about 1 nm to about 190 nm in mean diameter, about 1 nm to about 180 nm in mean diameter, about 1 nm to about 170 nm in mean diameter, about 1 nm to about 160 nm in mean diameter, about 1 nm to about 150 nm in mean diameter, about 1 nm to about 140 nm in mean diameter, about 1 nm to about 130 nm in mean diameter, about 1 nm to about 120 nm in mean diameter, about 1 nm to about 110 nm in mean diameter, about 1 nm to about 100 nm in mean diameter, about 1 nm to about 90 nm in mean diameter, about 1 nm to about 80 nm in mean diameter, about 1 nm to about 70 nm in mean diameter, about 1 nm to about 60 nm in mean diameter, about 1 nm to about 50 nm in mean diameter, about 1 nm to about 40 nm in mean diameter, about 1 nm to about 30 nm in mean diameter, or about 1 nm to about 20 nm in mean diameter, or about 1 nm to about 10 nm in mean diameter.

The oligonucleotides may be positioned on the exterior of the core, within the walls of the core and/or in the center of the core. An oligonucleotide that is positioned on the core is typically referred to as coupled to the core. Coupled may be direct or indirect. In some embodiments at least 5, 10, 15, 25, 50, 75, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 5000 or 10,000 oligonucleotides or any range combination thereof are on the exterior of the core. In some embodiments, 1-1000, 10-500, 50-250, or 50-300 oligonucleotides are present on the surface.

The oligonucleotides of the oligonucleotide shell may be oriented in a variety of directions. In some embodiments the oligonucleotides are oriented radially outwards. The orientation of these oligonucleotides can be either 5' distal/3' terminal in relation to the core, or 3' distal/5' terminal in relation to the core, or laterally oriented around the core. In one embodiment one or a multiplicity of different oligonucleotides are present on the same surface of a single SNA. In all cases, at least 1 oligonucleotide is present on the surface but up to 10,000 can be present.

The oligonucleotides may be linked to the core or to one another and/or to other molecules such as active agents either directly or indirectly through a linker. The oligonucleotides may be conjugated to a linker via the 5' end or the 3' end, e.g. [Sequence, 5'-3']-Linker or Linker-[Sequence, 5'-3']. Some or all of the oligonucleotides of the nanostructure may be linked to one another either directly or indirectly through a covalent or non-covalent linkage. The linkage of one oligonucleotide to another oligonucleotide may be in addition to or alternatively to the linkage of that oligonucleotide to liposomal core.

The oligonucleotide shell may be anchored to the surface of the core through one or multiple of linker molecules, including but not limited to: any chemical structure containing one or multiple thiols, such as the various chain length alkane thiols, cyclic dithiol, lipoic acid, or other thiol linkers known to those skilled in the art.

In an embodiment containing a liposomal core, the oligonucleotide shell may be anchored to the surface of the liposomal core through conjugation to one or a multiplicity of linker molecules including but not limited to: tocopherols, sphingolipids such as sphingosine, sphingosine phosphate, methylated sphingosines and sphingamines, ceramides, ceramide phosphates, 1-0 acyl ceramides, dihydroceramides, 2-hydroxy ceramides, sphingomyelin, glycosylated sphingolipids, sulfatides, gangliosides, phosphosphingolipids, and phytosphingosines of various lengths and saturation states and their derivatives, phospholipids such as phosphatidylcholines, lysophosphatidylcholines, phosphatidic acids, lysophosphatidic acids, cyclic LPA, phosphatidylethanolamines,

lysophosphatidylethanolamines, phosphatidylglycerols, lysophosphatidylglycerols, phosphatidylserines, lysophosphatidylserines, phosphatidylinositols, inositol phosphates, LPI, cardiolipins, lysocardiolipins, bis(monoacylglycero) phosphates, (diacylglycero) phosphates, ether lipids, diphytanyl ether lipids, and plasmalogens of various lengths, saturation states, and their derivatives, sterols such as cholesterol, desmosterol, stigmasterol, lanosterol, lathosterol, diosgenin, sitosterol, zymosterol, zymostenol, 14-demethyl-lanosterol, cholesterol sulfate, DHEA, DHEA sulfate, 14-demethyl-14-dehydrlanosterol, sitostanol, campesterol, ether anionic lipids, ether cationic lipids, lanthanide chelating lipids, A-ring substituted oxysterols, B-ring substituted oxysterols, D-ring substituted oxysterols, side-chain substituted oxysterols, double substituted oxysterols, cholestanoic acid derivatives, fluorinated sterols, fluorescent sterols, sulfonated sterols, phosphorylated sterols, and polyunsaturated sterols of different lengths, saturation states, and their derivatives.

The oligonucleotide may also be associated with the core by being embedded within the core (liposomal core) or it may be attached or linked, either indirectly (i.e. non-covalently) or covalently through other molecules such as linkers) or directly (i.e. covalently).

The invention also includes articles, which refers to any one or collection of components. In some embodiments the articles are kits. The articles include pharmaceutical or diagnostic grade compounds of the invention in one or more containers. The article may include instructions or labels promoting or describing the use of the compounds of the invention.

As used herein, “promoted” includes all methods of doing business including methods of education, hospital and other clinical instruction, pharmaceutical industry activity including pharmaceutical sales, and any advertising or other promotional activity including written, oral and electronic communication of any form, associated with compositions of the invention in connection with treatment of inflammatory disorders.

“Instructions” can define a component of promotion, and typically involve written instructions on or associated with packaging of compositions of the invention. Instructions also can include any oral or electronic instructions provided in any manner.

Thus the agents described herein may, in some embodiments, be assembled into pharmaceutical or diagnostic or research kits to facilitate their use in therapeutic, diagnostic or research applications. A kit may include one or more containers housing the components of the invention and instructions for use. Specifically, such kits may include one or more agents described herein, along with instructions describing the intended therapeutic application and the proper administration of these agents. In certain embodiments agents in a

kit may be in a pharmaceutical formulation or pharmaceutical composition and dosage suitable for a particular application and for a method of administration of the agents.

The kit may be designed to facilitate use of the methods described herein by physicians and can take many forms. Each of the compositions of the kit, where applicable, may be provided in liquid form (e.g., in solution), or in solid form, (e.g., a dry powder). In certain cases, some of the compositions may be constitutable or otherwise processable (e.g., to an active form), for example, by the addition of a suitable solvent or other species (for example, water or a cell culture medium), which may or may not be provided with the kit. As used herein, "instructions" can define a component of instruction and/or promotion, and typically involve written instructions on or associated with packaging of the invention. Instructions also can include any oral or electronic instructions provided in any manner such that a user will clearly recognize that the instructions are to be associated with the kit, for example, audiovisual (e.g., videotape, DVD, etc.), Internet, and/or web-based communications, etc. The written instructions may be in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which instructions can also reflect approval by the agency of manufacture, use or sale for human administration.

The kit may contain any one or more of the components described herein in one or more containers. As an example, in one embodiment, the kit may include instructions for mixing one or more components of the kit and/or isolating and mixing a sample and applying to a subject. The kit may include a container housing agents described herein. The agents may be prepared sterilely, packaged in syringe and shipped refrigerated. Alternatively it may be housed in a vial or other container for storage. A second container may have other agents prepared sterilely. Alternatively the kit may include the active agents premixed and shipped in a syringe, vial, tube, or other container.

The kit may have a variety of forms, such as a blister pouch, a shrink wrapped pouch, a vacuum sealable pouch, a sealable thermoformed tray, or a similar pouch or tray form, with the accessories loosely packed within the pouch, one or more tubes, containers, a box or a bag. The kit may be sterilized after the accessories are added, thereby allowing the individual accessories in the container to be otherwise unwrapped. The kits can be sterilized using any appropriate sterilization techniques, such as radiation sterilization, heat sterilization, or other sterilization methods known in the art. The kit may also include other components, depending on the specific application, for example, containers, cell media, salts, buffers, reagents,

syringes, needles, a fabric, such as gauze, for applying or removing a disinfecting agent, disposable gloves, a support for the agents prior to administration etc.

The compositions of the kit may be provided as any suitable form, for example, as liquid solutions or as dried powders. When the composition provided is a dry powder, the powder may be reconstituted by the addition of a suitable solvent, which may also be provided. In embodiments where liquid forms of the composition are used, the liquid form may be concentrated or ready to use. The solvent will depend on the compound and the mode of use or administration. Suitable solvents for drug compositions are well known and are available in the literature. The solvent will depend on the compound and the mode of use or administration.

The kits, in one set of embodiments, may comprise a carrier means being compartmentalized to receive in close confinement one or more container means such as vials, tubes, and the like, each of the container means comprising one of the separate elements to be used in the method. For example, one of the containers may comprise a positive control for an assay. Additionally, the kit may include containers for other components, for example, buffers useful in the assay.

The present invention also encompasses a finished packaged and labeled pharmaceutical product. This article of manufacture includes the appropriate unit dosage form in an appropriate vessel or container such as a glass vial or other container that is hermetically sealed. In the case of dosage forms suitable for parenteral administration the active ingredient is sterile and suitable for administration as a particulate free solution. In other words, the invention encompasses both parenteral solutions and lyophilized powders, each being sterile, and the latter being suitable for reconstitution prior to injection. Alternatively, the unit dosage form may be a solid suitable for oral, transdermal, topical or mucosal delivery.

In a preferred embodiment, the unit dosage form is suitable for intravenous, intramuscular or subcutaneous delivery. Thus, the invention encompasses solutions, preferably sterile, suitable for each delivery route.

As with any pharmaceutical product, the packaging material and container are designed to protect the stability of the product during storage and shipment. Further, the products of the invention include instructions for use or other informational material that advise the physician, technician or patient on how to appropriately prevent or treat the inflammatory disease or disorder. In other words, the article of manufacture includes

instruction means indicating or suggesting a dosing regimen including, but not limited to, actual doses, monitoring procedures and other monitoring information.

More specifically, the invention provides an article of manufacture comprising packaging material, such as a box, bottle, tube, vial, container, sprayer, insufflator, intravenous (i.v.) bag, envelope and the like; and at least one unit dosage form of a pharmaceutical agent contained within said packaging material. The invention also provides an article of manufacture comprising packaging material, such as a box, bottle, tube, vial, container, sprayer, insufflator, intravenous (i.v.) bag, envelope and the like; and at least one unit dosage form of each pharmaceutical agent contained within said packaging material. The invention further provides an article of manufacture comprising packaging material, such as a box, bottle, tube, vial, container, sprayer, insufflator, intravenous (i.v.) bag, envelope and the like; and at least one unit dosage form of each pharmaceutical agent contained within said packaging material. The invention further provides an article of manufacture comprising a needle or syringe, preferably packaged in sterile form, for injection of the formulation, and/or a packaged alcohol pad.

This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of “including,” “comprising,” or “having,” “containing,” “involving,” and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

All references, including patent documents, disclosed herein are incorporated by reference in their entirety.

EXAMPLES

Example 1. Liposomal spherical nucleic acid (SNA) constructs presenting antisense oligonucleotides (ASO) for specific knockdown of Interleukin 17 Receptor mRNA

Results

Experiment 1. *In vitro* IL-17RA mRNA knockdown using targeted SNAs

HFK cells were treated with 294 SNAs presenting one ASO sequence each of the sequences in Table 1 and human IL-17RA mRNA expression was measured by qRT-PCR. This was performed twice and the three SNAs showing the greatest inhibition of IL-17RA mRNA in multiple assays and having low off-target effects were chosen for further

5 optimization by chemical modification. HFK cells were treated at larger dose ranges with SNAs presenting one ASO sequence of either IL17RA_219, IL17RA_282, IL17RA_285 or a non-complementary control. Targeted SNAs demonstrate target specific mRNA inhibition in a dose-dependent manner while the non-complementary control SNA has no considerable inhibition at all concentrations tested (Fig. 1). Targeted SNAs demonstrate similar IL-17RA
10 mRNA inhibition in HEK293 cells. Analyzing the dose-response data as a non-linear fit and calculating the half maximal inhibitory concentration (IC_{50}) results in IC_{50} values of 124.2, 9.57 and 34.64 nM for IL17RA_285, IL17RA_219 and IL17RA_282, respectively. These results demonstrate that SNAs targeting IL-17RA mRNA can effectively inhibit gene expression in a specific manner in HFK cells.

15 Experiment 2. IL-17RA mRNA knockdown using topically applied targeted SNAs in the human skin equivalent, EpiDerm-FT™

A human skin equivalent model treated topically with SNAs presenting either ASO sequence IL17RA_219 or IL17RA_282 targeting human IL-17RA mRNA resulted in target
20 mRNA specific inhibition. IL17RA_219 and IL17RA_282 were chosen as the lead candidate compounds for further testing after taking into consideration the efficacy data collected in experiment 1. ASOs IL17RA_219 and IL17RA_282 exhibited the best combination of IC_{50} value, homology to other human mRNA sequences (as determined by BLAST) and cross-species conservation. IL-17RA mRNA expression is decreased in human skin equivalent
25 tissues treated topically with SNAs presenting either ASO IL17RA_219 or ASO IL17RA_282 for 48 hours. Tissues treated with SNAs presenting the control ASO do not demonstrate an appreciable decrease in IL-17RA mRNA expression as measured by qRT-PCR (Fig. 2). Further, IL17RA_219 and IL17RA_282 exhibited no toxicity in HFKs and no cytokine induction in HFKs, HEK293 cells and PBMCs from four different donors, up to 20 μ M
30 DNA concentration. For these reasons, IL17RA_219 and IL17RA_282 were chosen for further testing. SNAs targeting IL-17RA delivered topically were shown to specifically inhibit mRNA expression in a human skin equivalent model.

Experiment 3. *Ex vivo* IL-17RA mRNA knockdown using topically applied targeted SNAs in human skin explants

Human skin explants treated topically with SNAs presenting either ASO sequence IL17RA_219 or ASO sequence IL17RA_282 targeting human IL-17RA mRNA resulted in target mRNA specific inhibition. IL-17RA mRNA expression is decreased in human skin explant biopsies treated topically with SNAs presenting either ASO IL17RA_219 or ASO IL17RA_282 for 96 hours. Biopsies treated with SNAs presenting the control ASO do not demonstrate an appreciable decrease in IL-17RA mRNA expression as measured by qRT-PCR (Fig. 3). SNAs targeting IL-17RA delivered topically can specifically inhibit mRNA expression in human skin explants.

Experiment 4. TNF mRNA knockdown using a mixture of SNAs

SNAs presenting either an anti-TNF or an anti-IL17RA ASO sequence were mixed together and co-administered to HFK cells. Mixed SNAs demonstrated target mRNA specific knockdown corresponding to the ASO sequence identity (Fig. 4, Fig. 5).

Fig. 4 shows TNF mRNA expression decreased in HFK cells treated with a mixture of anti-TNF-SNAs and anti-IL17RA-SNAs. Fig. 5 shows IL17RA mRNA expression is decreased in HFK cells treated with a mixture of anti-TNF-SNAs and anti-IL17RA-SNAs. Cells treated with control-SNAs do not demonstrate an appreciable decrease in TNF mRNA levels.

These results demonstrate that mixtures of SNAs targeting more than one mRNA can be co-administered and perform gene knockdown with respect to each target.

Experiment 5. Comparison of TNF mRNA knockdown and IL17RA knockdown using multiplexed SNAs

SNAs presenting one, two, or three ASO sequences demonstrated target mRNA specific knockdown in HFK cells corresponding to the ASO sequence identity. Only data obtained using SNAs multiplexed with two ASO sequences. SNAs were shown to serve as a platform capable of presenting multiple therapeutic modalities. These results demonstrate that ASO sequences targeting more than one mRNA can be co-delivered on the same SNA particle and perform gene knockdown with respect to each target (Fig. 7, Fig. 8).

When the two gene targets are in a related biological pathway, an additive knockdown effect can be observed for the downstream target (Fig. 8). TNF and IL17A cytokine signaling have been shown to have an additive and synergistic effect in their proinflammatory

properties(3). This relationship indicates a shared or highly related signaling pathway, though the exact relationship is not well understood(4). The mRNA of the TNF cytokine as well as the receptor for IL17A, IL17RA were targeted. It is likely that the reduction of secreted TNF cytokine has an effect on IL17RA receptor turnover and expression.

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Materials and Methods

Antisense Sequence Design. Antisense sequences, 18 nucleotides in length, targeting human IL-17RA mRNA (GeneBank Accession No. NM_014339.6) were determined based on the following parameters: Sfold Algorithm(2), %GC content, proximity to start codon, and the exclusion of CpG motifs (Table 1). Unless otherwise noted, antisense oligonucleotide sequences are divided into 3 regions: an internal, phosphorothioate linked 'gap' region flanked by two external, 2'-O-methyl 'wings'. This 'gap-mer' sequence is modified at the 3' end with two consecutive hexa(ethylene glycol) spacers and a terminal cholesterol.

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Antisense oligonucleotide synthesis. All oligonucleotides were synthesized at the 1 μ mole scale employing universal UnyLinker Support 1000Å (ChemGenes) on the Bioautomation MerMade 48 oligonucleotide synthesizer. The DNA, RNA, 2'-O-Me monomers, hexa(ethylene glycol) spacers and cholesterol modifiers were obtained from ChemGenes Corporation. Coupling time was 1 minute for standard DNA bases and 3 minutes for modified bases. Linkages were either standard phosphodiester or phosphorothioates made with 0.2 M phenylacetyl disulfide (PADS) in 1:1 lutidine:ACN as the sulfurization agent. Synthesis was performed DMT-off, in the 5' to 3' direction. After synthesis, the oligonucleotides were cleaved from the support and deprotected using a 4:1 mixture of ammonium hydroxide and ethanol at 55 °C for 16 hours. The oligonucleotides were purified via high performance liquid chromatography (HPLC) techniques. Molecular weights and extinction coefficients were determined using IDT OligoAnalyzer. Verification of oligonucleotide molecular weight was performed using matrix-assisted laser desorption/ionization (MALDI). Oligonucleotide concentration was determined by UV-absorbance at 260 nm on a microplate reader (BioTek) together with the calculated extinction coefficient from the IDT OligoAnalyzer. All oligonucleotides were sterile filtered using 0.2 μ m syringe filters (VWR). The oligonucleotide sequences are listed in Table 1.

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Liposome synthesis. Liposomes were synthesized by extrusion of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) hydrated in phosphate buffered saline solution (PBS) (137 mM

NaCl, 10 mM phosphate, 2.7 mM KCl, pH 7.4, Hyclone) using 47 mm diameter polycarbonate membranes with 50 nm pores (Sterlitech). Liposome diameters were measured using dynamic light scattering using a Malvern Zetasizer Nano (Malvern Instruments). Lipid concentration was determined using a phospholipid assay kit (Sigma).

5

Cell Culture. Human neonatal foreskin keratinocytes (HFKs) and adult human epidermal keratinocytes (HEKa) were cultured in M154 media (Life Technologies) supplemented with Human Keratinocyte Growth Supplement (Life Technologies), 0.07 mM CaCl₂, 10 µg/mL gentamicin, and 0.25 µg/mL amphotericin B. Cells were maintained at 37 °C in a 5% CO₂ humidified incubator. Fresh primary human peripheral blood mononuclear cells (PBMCs) from four different donors (Zenbio) were cultured in RPMI supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 50 U/mL penicillin, and 50 mg/mL streptomycin. Cells were maintained at 37 °C in a 5% CO₂ humidified incubator.

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15 EpiDerm-FT™ Human Skin Equivalent Culture. The human skin equivalent model, EpiDerm-FT™ (Mattek), tissues were cultured according to the manufacturer's instructions. Briefly, upon receipt, tissues were incubated overnight with supplied maintenance media at 37 °C in a 5% CO₂ humidified incubator. The following day, and every day after that for the length of the experiment, the media was replaced with fresh media. The tissues were
20 maintained at 37 °C in a 5% CO₂ humidified incubator throughout the length of the experiment.

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Human Skin Explant Culture. Fresh human skin explant (Zenbio) was cleaned upon receipt. 8 mm punch biopsies were taken from the explant and placed into trans-well stands for
25 culturing. DMEM supplemented with 2% FBS, 10 µg/mL gentamicin, and 0.25 µg/mL amphotericin B was supplied to the underside of the biopsies and changed every day for the length of the experiment. The biopsies were maintained at 37 °C in a 5% CO₂ humidified incubator throughout the length of the experiment.

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30 SNA Synthesis. SNAs were formulated by mixing a 100X molar excess (unless otherwise stated) of cholesterol-modified oligonucleotide to a liposome suspension in PBS and storing them overnight, protected from light, at 4 °C. 294 different oligonucleotides (Table 1) were used for the synthesis process, specifically targeting human IL-17RA mRNA, and a control

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oligonucleotide of the same length and 'gap-mer' chemical scheme that does not have any complementarity to known human genes (confirmed by BLAST).

Multiplex SNA Synthesis. SNAs were formulated by mixing a 200X molar excess (unless

otherwise stated) of cholesterol-modified oligonucleotide to a liposome suspension in PBS and storing them overnight, protected from light, at 4 °C. Four different oligonucleotides were used for the synthesis process: an antisense oligonucleotide targeting human IL-17RA, an antisense oligonucleotide targeting human TNF, an antisense oligonucleotide targeting human IL22RA1, and a same length control oligonucleotide that does not have any complementarity to known genes (confirmed by BLAST). For monoplex SNAs, the oligonucleotide population consisted of 33% targeted antisense oligonucleotide and 66% control oligonucleotide. For multiplex SNAs containing two different targeted antisense oligonucleotides, the oligonucleotide population consisted of 33% of each targeted antisense oligonucleotide and the remaining 33% control oligonucleotide (Fig. 6). For multiplex SNAs containing three different targeted antisense oligonucleotides, the oligonucleotide population consisted of 33% of each targeted antisense oligonucleotide. Control SNAs consisted of 100% of the control oligonucleotide (Fig. 6D).

Cell Culture Studies. HFKs were seeded at passage 5 in 96-well, tissue culture plates at a cell

density of 17,000 cells per well. HEKα cells were seeded at passage 5 in 96-well, tissue culture plates at a cell density of 17,000 cells per well. Fresh PBMCs were isolated from cell suspension by centrifugation and seeded in 96-well, tissue culture plates at a cell density of 200,000 cells per well. Cells were allowed to rest in the incubator overnight following plating. Cells were treated with either an IL-17RA targeted antisense SNA or a non-complementary control SNA (confirmed by NCBI Blast), comprising the same 'gap-mer' design and 3'-chemical modifications, in fresh maintenance media. Unless otherwise stated, all treatments lasted 24 hours.

For the human skin equivalent model, EpiDerm-FT™, and human skin explant tissues, treatments were applied in biological triplicate. Tissues were treated topically with either an SNA presenting the IL17RA_219 ASO, an SNA presenting the IL17RA_282 ASO, an SNA presenting the non-complementary control ASO or left untreated. The EpiDerm-FT™ tissues were treated for 48 hours and the human skin explant tissues were treated for 96 hours.

For multiplex SNA experiments, HFKs were seeded at passage 5 in 96-well, tissue culture plates at a cell density of 17,000 cells per well. Cells were allowed to rest in the incubator overnight following plating. Cells were treated in triplicate with either an IL-17RA targeted antisense SNA, TNF targeted antisense SNA, a multiplex SNA targeting more than one transcript or a non-complementary control SNA (confirmed by NCBI Blast), comprising the same 'gap-mer' design and 3'-chemical modifications, at concentrations of 1000, 100, 10 and 1 nM in fresh maintenance media.

Alamar Blue® Viability Assay. For viability studies, HFKs were seeded at passage 5 in 96-well, tissue culture plates at a cell density of 15,000 cells per well. Cells were allowed to rest in the incubator overnight following plating. Cells were treated in triplicate with either an IL-17RA targeted antisense SNA or a non-complementary control (confirmed by NCBI Blast), comprising the same 'gap-mer' design and 3' chemical modifications, at concentrations of 20, 10, 2 and 1 µM for 24 hours. Briefly, treatments were removed and replace with a 10% solution of AlamarBlue® reagent in M154 maintenance media. Cells were incubated at 37 °C for 3 hours in a 5% CO₂ humidified incubator before measuring the fluorescence of each well (excitation 570 nm, emission 585 nm) with a microplate reader (BioTek). Percent viability was calculated by comparing fluorescent values of each treatment to those of the untreated cells.

Cytokine Q-Plex Array. After 24 hours of treatment, the cells in the 96-well tissue culture plates were pelleted by centrifugation; the supernatants were transferred to new plates and stored at -80 °C. Cytokine quantification of the supernatants was performed using a Q-Plex chemiluminescent array (Quansys) following the manufacturer's instructions. Each plate was custom built to allow for the detection of IL-12p40, TNF, IP-10, IL-6, RANTES, IL-4, IL-5, IL-10, IL-17, IL-22 and MCP-1 within each well. Briefly, a standard curve was prepared using a cytokine stock of known concentration and diluting it as indicated. The cell culture supernatants were diluted 1:2 using the provided sample buffer. The cell culture samples and standard curve samples were added to the 96-well Q-plex plate and incubated at room temperature for 1 hour with shaking. The plate was then washed three times with the provided wash buffer. Then 50 µL of provided Detection mix was added to each well and the plate was incubated again for 1 hour at room temperature with shaking. Again, the plate was washed three times with wash buffer, followed by incubation with 50 µL of provided Streptavidin-HRP solution for 15 minutes at room temperature with shaking. Finally, the

plate was washed six times in wash buffer and 50 μ L of a prepared substrate was added to each well. Within 15 minutes, the plate was imaged using a Bio-Rad ChemiDoc XRS+ imager and analyzed using the Q-view software (Quansys). All data was fit to the standard curves for each individual cytokine and plotted in comparison to untreated cells.

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RNA Extraction and Quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR). HFK and HEKa cells were lysed in RLT Buffer (Qiagen) at 24 hours post-transfection. EpiDerm-FT™ tissues and human skin explant tissues were bead homogenized in RLT buffer at 48 and 96 hours of treatment, respectively. RNA was isolated from lysates using the

10 RNEasy 96-well kit (Qiagen) according to the manufacturer's instructions. cDNA was then synthesized from RNA isolates using the cDNA High Capacity Reverse Transcription Kit (Life Technologies). Samples were run on a thermocycler at 25 °C for 10 minutes, 37 °C for 90 minutes, 85 °C for 5 minutes and held at 4 °C to generate cDNA. qPCR was performed using 6 μ L of the synthesized cDNA, 4.66 μ L LightCycler480 Probes Master Mix (Roche),
15 0.47 μ L target specific FAM-labeled probe and primers, and 0.37 μ L human Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) specific HEX-labeled probe and primers per reaction well of a 384-well optical reaction plate (Roche). The primer and probe sets for IL-17RA were purchased from ThermoFisher Scientific (catalogue number Hs01064648_m1). The primer and probe sets for TNF and GAPDH were designed using the known human genome
20 sequence (NCBI reference sequences NM_000594.3 and NM_002046.5, respectively) and were found to be specific by "blastn" analysis (NCBI). The oligonucleotide sequences used for TNF were: forward 5'- GCT GCA CTT TGG AGT GAT CG-3' (SEQ ID NO: 1), reverse 5'- GTT TGC TAC AAC ATG GGC TAC AG-3' (SEQ ID NO: 2), probe 5'-FAM- CCC AGG CAG TCA GAT CAT CTT CTC GA-BHQ1-3' (SEQ ID NO: 3). The oligonucleotide
25 sequences used for GAPDH were: forward 5'-CAA GGT CAT CCA TGA CAA CTT TG-3' (SEQ ID NO: 4), reverse 5'-GGG CCA TCC ACA GTC TTC T-3' (SEQ ID NO: 5), probe 5'-HEX-ACC ACA GTC CAT GCC ATC ACT GCC A-BHQ1-3' (SEQ ID NO: 6). FAM is 6-fluorescein amidite, HEX is hexachloro-fluorescein, and BHQ1 is a black hole quencher 1. qPCR reactions, in technical duplicate, were carried out on the Roche Lightcycler 480 under
30 the following conditions: initial denaturation at 95 °C for 10 minutes and then 50 cycles of denaturation at 95 °C for 10 seconds, annealing at 60 °C for 30 seconds and extension at 72 °C for 1 second. Cp values were obtained by analysis with the 2nd derivative method. Relative gene expression was determined by normalization with the housekeeping gene

(GAPDH) and the $\Delta\Delta$ -Ct method. Each treatment was compared to its respective concentration control.

Table 1. Oligonucleotide Sequences

- 5 Special bases used in the oligonucleotides are as follows: mN = 2' O-methyl RNA, /iSp18/ = hexa(ethylene glycol) spacer, * = phosphorothioate, /3CholTEG/ = 3' cholesterol

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_001	mUmCmGmCmGmGA*G*G*G*C*T*mCmGm GmCmCmC/iSp18//iSp18//3CholTEG/	7	67
IL17RA_002	mGmUmCmGmCmGG*A*G*G*G*C*mUmCm GmGmCmC/iSp18//iSp18//3CholTEG/	8	35
IL17RA_003	mCmGmUmCmGmCG*G*A*G*G*G*mCmUm CmGmGmC/iSp18//iSp18//3CholTEG/	9	36
IL17RA_004	mAmCmGmGmCmGG*G*C*T*G*C*mGmUm GmCmGmG/iSp18//iSp18//3CholTEG/	10	49
IL17RA_005	mGmAmCmGmGmCG*G*G*C*T*G*mCmGm UmGmCmG/iSp18//iSp18//3CholTEG/	11	40
IL17RA_006	mAmCmUmCmUmGC*A*C*C*C*T*mCmGm AmGmGmU/iSp18//iSp18//3CholTEG/	12	35
IL17RA_007	mGmGmGmCmUmGC*C*C*A*G*C*mAmGm CmGmGmG/iSp18//iSp18//3CholTEG/	13	30
IL17RA_008	mUmGmUmGmUmGG*G*T*C*T*G*mUmGm AmGmGmA/iSp18//iSp18//3CholTEG/	14	73
IL17RA_009	mGmGmCmGmUmGT*G*T*G*G*G*mUmCm UmGmUmG/iSp18//iSp18//3CholTEG/	15	43
IL17RA_010	mGmGmGmCmGmUG*T*G*T*G*G*mGmUm CmUmGmU/iSp18//iSp18//3CholTEG/	16	35
IL17RA_011	mAmGmGmGmCmGT*G*T*G*T*G*mGmGm UmCmUmG/iSp18//iSp18//3CholTEG/	17	54
IL17RA_012	mUmAmGmGmGmCG*T*G*T*G*T*mGmGm GmUmCmU/iSp18//iSp18//3CholTEG/	18	49

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_013	mAmGmCmUmCmCT*G*G*A*G*A*mUmGmUmAmGmC/iSp18//iSp18//3CholTEG/	19	38
IL17RA_014	mGmAmGmCmUmCC*T*G*G*A*G*mAmUmGmUmAmG/iSp18//iSp18//3CholTEG/	20	49
IL17RA_015	mGmGmAmGmCmUC*C*T*G*G*A*mGmAmUmGmUmA/iSp18//iSp18//3CholTEG/	21	88
IL17RA_016	mCmCmCmUmCmGG*G*G*G*G*C*mUmGmCmGmGmG/iSp18//iSp18//3CholTEG/	22	91
IL17RA_017	mGmGmGmAmGmAG*A*G*T*G*G*mCmAmGmGmGmC/iSp18//iSp18//3CholTEG/	23	105
IL17RA_018	mCmGmGmGmAmGA*G*A*G*T*G*mGmCmAmGmGmG/iSp18//iSp18//3CholTEG/	24	106
IL17RA_019	mAmCmGmAmUmAA*C*C*A*G*A*mCmCmGmCmUmG/iSp18//iSp18//3CholTEG/	25	103
IL17RA_020	mGmGmGmAmGmCG*G*G*C*T*G*mUmGmUmGmGmA/iSp18//iSp18//3CholTEG/	26	77
IL17RA_021	mAmCmAmUmAmGT*A*G*G*T*G*mCmAmCmAmAmU/iSp18//iSp18//3CholTEG/	27	81
IL17RA_022	mCmAmCmAmUmAG*T*A*G*G*T*mGmCmAmCmAmA/iSp18//iSp18//3CholTEG/	28	76
IL17RA_023	mGmGmGmUmCmUC*A*C*T*C*T*mGmCmUmGmCmC/iSp18//iSp18//3CholTEG/	29	57
IL17RA_024	mGmGmGmCmAmGG*C*T*T*C*C*mAmCmUmCmCmA/iSp18//iSp18//3CholTEG/	30	43
IL17RA_025	mAmAmAmGmCmUG*T*T*A*G*G*mAmGmGmAmCmA/iSp18//iSp18//3CholTEG/	31	77
IL17RA_026	mUmAmAmAmGmCT*G*T*T*A*G*mGmAmGmGmAmC/iSp18//iSp18//3CholTEG/	32	75
IL17RA_027	mAmUmAmAmAmGC*T*G*T*T*A*mGmGmAmGmGmA/iSp18//iSp18//3CholTEG/	33	91

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_028	mAmCmCmGmGmCA*T*C*A*A*A*mUmUmGmUmGmC/iSp18//iSp18//3CholTEG/	34	87
IL17RA_029	mAmAmCmCmGmGC*A*T*C*A*A*mAmUmUmGmUmG/iSp18//iSp18//3CholTEG/	35	93
IL17RA_030	mCmUmGmGmAmUT*T*C*T*T*T*mUmUmGmGmGmG/iSp18//iSp18//3CholTEG/	36	64
IL17RA_031	mGmCmUmGmGmAT*T*T*C*T*T*mUmUmGmGmGmG/iSp18//iSp18//3CholTEG/	37	53
IL17RA_032	mGmGmCmUmGmGA*T*T*T*C*T*mUmUmUmGmGmG/iSp18//iSp18//3CholTEG/	38	38
IL17RA_033	mGmGmGmCmUmGG*A*T*T*T*C*mUmUmUmUmGmG/iSp18//iSp18//3CholTEG/	39	41
IL17RA_034	mGmGmGmGmCmUG*G*A*T*T*T*mCmUmUmUmUmG/iSp18//iSp18//3CholTEG/	40	77
IL17RA_035	mGmGmGmAmGmGG*A*A*T*G*T*mGmAmGmGmAmG/iSp18//iSp18//3CholTEG/	41	58
IL17RA_036	mGmCmUmGmAmAG*A*G*G*T*G*mGmGmAmGmGmG/iSp18//iSp18//3CholTEG/	42	49
IL17RA_037	mGmAmGmCmCmUG*G*G*A*G*G*mUmCmGmAmGmG/iSp18//iSp18//3CholTEG/	43	40
IL17RA_038	mGmGmGmAmGmGA*T*G*A*G*G*mCmGmGmCmA/iSp18//iSp18//3CholTEG/	44	39
IL17RA_039	mUmGmGmGmAmGG*A*T*G*A*G*mGmCmGmGmC/iSp18//iSp18//3CholTEG/	45	31
IL17RA_040	mUmUmUmAmGmGA*A*G*G*G*G*mAmGmCmAmCmC/iSp18//iSp18//3CholTEG/	46	60
IL17RA_041	mAmUmUmUmAmGG*A*A*G*G*G*mGmA mGmCmAmC/iSp18//iSp18//3CholTEG/	47	57
IL17RA_042	mUmAmUmUmUmAG*G*A*A*G*G*mGmGmAmGmCmA/iSp18//iSp18//3CholTEG/	48	57

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_043	mUmUmAmUmUmUA*G*G*A*A*G*mGmG mGmAmGmC/iSp18//iSp18//3CholTEG/	49	23
IL17RA_044	mCmAmUmUmUmAT*T*T*A*G*G*mAmAm GmGmGmG/iSp18//iSp18//3CholTEG/	50	38
IL17RA_045	mUmCmAmUmUmUA*T*T*T*A*G*mGmAm AmGmGmG/iSp18//iSp18//3CholTEG/	51	35
IL17RA_046	mGmGmGmAmUmGC*A*G*G*C*C*mCmGm GmCmUmG/iSp18//iSp18//3CholTEG/	52	53
IL17RA_047	mAmAmAmGmAmGG*A*T*C*A*G*mUmGm GmUmAmC/iSp18//iSp18//3CholTEG/	53	71
IL17RA_048	mGmAmAmAmGmAG*G*A*T*C*A*mGmUm GmGmUmA/iSp18//iSp18//3CholTEG/	54	42
IL17RA_049	mUmGmGmGmUmUT*A*G*G*G*G*mUmA mGmCmUmG/iSp18//iSp18//3CholTEG/	55	48
IL17RA_050	mAmUmGmGmGmUT*T*A*G*G*G*mGmUm AmGmCmU/iSp18//iSp18//3CholTEG/	56	43
IL17RA_051	mAmAmUmGmGmGT*T*T*A*G*G*mGmGm UmAmGmC/iSp18//iSp18//3CholTEG/	57	64
IL17RA_052	mUmGmCmAmAmUG*G*G*T*T*T*mAmGm GmGmGmU/iSp18//iSp18//3CholTEG/	58	58
IL17RA_053	mGmUmGmCmAmAT*G*G*G*T*T*mUmAm GmGmGmG/iSp18//iSp18//3CholTEG/	59	64
IL17RA_054	mUmGmUmGmCmAA*T*G*G*G*T*mUmUm AmGmGmG/iSp18//iSp18//3CholTEG/	60	79
IL17RA_055	mUmUmGmUmGmCA*A*T*G*G*G*mUmUm UmAmGmG/iSp18//iSp18//3CholTEG/	61	73
IL17RA_056	mCmUmUmGmUmGC*A*A*T*G*G*mGmUm UmUmAmG/iSp18//iSp18//3CholTEG/	62	64
IL17RA_057	mGmCmUmUmGmUG*C*A*A*T*G*mGmGm UmUmUmA/iSp18//iSp18//3CholTEG/	63	77

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_058	mAmGmCmUmUmGT*G*C*A*A*T*mGmGmGmUmUmU/iSp18//iSp18//3CholTEG/	64	11
IL17RA_059	mCmAmGmCmUmUG*T*G*C*A*A*mUmGmGmGmUmU/iSp18//iSp18//3CholTEG/	65	75
IL17RA_060	mGmGmGmCmAmUG*G*A*G*A*G*mCmCmAmUmGmC/iSp18//iSp18//3CholTEG/	66	52
IL17RA_061	mUmCmUmGmGmGA*G*A*G*G*C*mGmA mUmGmGmG/iSp18//iSp18//3CholTEG/	67	47
IL17RA_062	mGmGmGmAmGmGT*G*G*G*C*T*mGmGmGmCmCmA/iSp18//iSp18//3CholTEG/	68	59
IL17RA_063	mAmCmUmCmCmCT*C*T*C*C*T*mCmCmUmCmCmU/iSp18//iSp18//3CholTEG/	69	44
IL17RA_064	mUmAmCmUmCmCC*T*C*T*C*C*mUmCmCmUmCmC/iSp18//iSp18//3CholTEG/	70	29
IL17RA_065	mGmGmGmAmGmGC*A*A*G*G*T*mCmUmGmAmGmA/iSp18//iSp18//3CholTEG/	71	60
IL17RA_066	mUmCmAmGmGmGC*A*G*C*C*C*mGmGmGmAmGmG/iSp18//iSp18//3CholTEG/	72	64
IL17RA_067	mCmAmCmUmCmCA*C*T*C*A*C*mCmUmCmCmCmA/iSp18//iSp18//3CholTEG/	73	16
IL17RA_068	mGmGmGmUmGmCA*G*G*G*C*T*mUmCmAmGmAmC/iSp18//iSp18//3CholTEG/	74	26
IL17RA_069	mGmCmGmGmGmUG*C*A*G*G*G*mCmUmUmCmAmG/iSp18//iSp18//3CholTEG/	75	40
IL17RA_070	mCmUmGmUmUmUG*C*T*C*T*C*mCmUmGmUmCmA/iSp18//iSp18//3CholTEG/	76	22
IL17RA_071	mCmCmUmGmUmUT*G*C*T*C*T*mCmCmUmGmUmC/iSp18//iSp18//3CholTEG/	77	61
IL17RA_072	mUmCmCmUmGmUT*T*G*C*T*C*mUmCmCmUmGmU/iSp18//iSp18//3CholTEG/	78	51

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_073	mGmUmCmCmUmGT*T*T*G*C*T*mCmUm CmCmUmG/iSp18//iSp18//3CholTEG/	79	46
IL17RA_074	mUmGmUmCmCmUG*T*T*T*G*C*mUmCm UmCmCmU/iSp18//iSp18//3CholTEG/	80	45
IL17RA_075	mCmUmGmUmCmCT*G*T*T*T*G*mCmUm CmUmCmC/iSp18//iSp18//3CholTEG/	81	52
IL17RA_076	mGmGmCmUmAmGT*G*G*C*T*G*mGmGm AmGmGmC/iSp18//iSp18//3CholTEG/	82	70
IL17RA_077	mGmGmAmAmUmGG*G*A*G*C*A*mGmA mUmGmGmG/iSp18//iSp18//3CholTEG/	83	63
IL17RA_078	mGmGmGmCmUmUG*G*G*C*A*G*mGmU mGmGmUmG/iSp18//iSp18//3CholTEG/	84	32
IL17RA_079	mGmGmGmAmUmGG*G*C*T*T*G*mGmGm CmAmGmG/iSp18//iSp18//3CholTEG/	85	42
IL17RA_080	mGmGmUmCmUmCC*A*C*G*G*T*mGmAm UmGmUmU/iSp18//iSp18//3CholTEG/	86	30
IL17RA_081	mGmUmAmAmUmGG*G*T*A*G*A*mUmU mCmGmUmU/iSp18//iSp18//3CholTEG/	87	22
IL17RA_082	mGmGmUmAmAmUG*G*G*T*A*G*mAmU mUmCmGmU/iSp18//iSp18//3CholTEG/	88	40
IL17RA_083	mUmGmGmUmAmAT*G*G*G*T*A*mGmAm UmUmCmG/iSp18//iSp18//3CholTEG/	89	35
IL17RA_084	mCmUmGmGmUmAA*T*G*G*G*T*mAmGm AmUmUmC/iSp18//iSp18//3CholTEG/	90	37
IL17RA_085	mGmGmGmCmGmCA*G*G*T*A*T*mGmUm GmGmUmG/iSp18//iSp18//3CholTEG/	91	55
IL17RA_086	mGmGmCmUmGmAG*T*A*G*A*T*mGmAm UmCmCmA/iSp18//iSp18//3CholTEG/	92	65
IL17RA_087	mCmGmCmGmCmCG*A*A*C*A*G*mGmUm CmGmGmG/iSp18//iSp18//3CholTEG/	93	63

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_088	mGmUmAmGmAmGG*T*T*C*T*C*mAmCm AmUmUmC/iSp18//iSp18//3CholTEG/	94	57
IL17RA_089	mCmCmGmCmCmCG*G*G*C*T*C*mCmGm CmAmGmG/iSp18//iSp18//3CholTEG/	95	83
IL17RA_090	mCmCmCmUmGmGG*C*A*G*G*C*mUmUm CmCmAmC/iSp18//iSp18//3CholTEG/	96	67
IL17RA_091	mCmAmAmUmGmGG*T*T*T*A*G*mGmGm GmUmAmG/iSp18//iSp18//3CholTEG/	97	66
IL17RA_092	mGmCmAmAmUmGG*G*T*T*T*A*mGmGm GmGmUmA/iSp18//iSp18//3CholTEG/	98	64
IL17RA_093	mGmGmAmGmGmAT*G*A*G*G*C*mGmGm GmCmAmG/iSp18//iSp18//3CholTEG/	99	68
IL17RA_094	mGmUmGmCmGmGC*C*C*C*C*A*mUmGm GmCmCmC/isp18//isp18//3CholTEG/	100	79
IL17RA_095	mCmGmUmGmCmGG*C*C*C*C*C*mAmUm GmGmCmC/isp18//isp18//3CholTEG/	101	74
IL17RA_096	mGmCmGmUmGmCG*G*C*C*C*C*mCmAm UmGmGmC/isp18//isp18//3CholTEG/	102	72
IL17RA_097	mUmGmCmGmUmGC*G*G*C*C*C*mCmCm AmUmGmG/isp18//isp18//3CholTEG/	103	77
IL17RA_098	mCmUmGmCmGmUG*C*G*G*C*C*mCmCm CmAmUmG/isp18//isp18//3CholTEG/	104	58
IL17RA_099	mCmGmGmGmCmUG*C*G*T*G*C*mGmGm CmCmCmC/isp18//isp18//3CholTEG/	105	83
IL17RA_100	mGmCmGmGmGmCT*G*C*G*T*G*mCmGm GmCmCmC/isp18//isp18//3CholTEG/	106	84
IL17RA_101	mGmGmCmGmGmGC*T*G*C*G*T*mGmCm GmGmCmC/isp18//isp18//3CholTEG/	107	75
IL17RA_102	mUmCmGmCmAmGG*G*A*G*G*C*mGmCm CmAmCmC/isp18//isp18//3CholTEG/	108	87

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_103	mGmUmCmGmCmAG*G*G*A*G*G*mCmGmCmCmAmC/isp18//isp18//3CholTEG/	109	72
IL17RA_104	mUmUmCmGmAmUG*T*G*A*G*C*mCmAmCmGmGmG/isp18//isp18//3CholTEG/	110	74
IL17RA_105	mCmCmAmUmUmCG*A*T*G*T*G*mAmGmCmCmAmC/isp18//isp18//3CholTEG/	111	76
IL17RA_106	mGmAmUmAmAmCT*C*T*G*C*A*mCmCmCmUmCmG/isp18//isp18//3CholTEG/	112	84
IL17RA_107	mGmGmCmUmUmGG*G*C*A*G*G*mUmGmGmUmGmA/isp18//isp18//3CholTEG/	113	65
IL17RA_108	mUmGmGmGmCmUT*G*G*G*C*A*mGmGmUmGmGmU/isp18//isp18//3CholTEG/	114	37
IL17RA_109	mAmAmUmGmGmGT*A*G*A*T*T*mCmGmUmUmCmC/isp18//isp18//3CholTEG/	115	44
IL17RA_110	mUmAmAmUmGmGG*T*A*G*A*T*mUmCmGmUmUmC/isp18//isp18//3CholTEG/	116	62
IL17RA_111	mUmCmCmCmCmCG*C*C*A*G*T*mGmCmCmAmGmC/isp18//isp18//3CholTEG/	117	57
IL17RA_112	mCmCmCmUmCmUG*A*C*T*C*T*mGmAmCmCmCmC/isp18//isp18//3CholTEG/	118	57
IL17RA_113	mGmGmGmCmCmCC*T*C*T*G*A*mCmUmCmUmGmA/isp18//isp18//3CholTEG/	119	85
IL17RA_114	mUmGmGmGmCmCC*C*T*C*T*G*mAmCmUmCmUmG/isp18//isp18//3CholTEG/	120	76
IL17RA_115	mCmUmGmGmGmCC*C*C*T*C*T*mGmAmCmUmCmU/isp18//isp18//3CholTEG/	121	64
IL17RA_116	mAmGmGmGmUmCT*C*A*C*T*C*mUmGmCmUmGmC/isp18//isp18//3CholTEG/	122	8
IL17RA_117	mCmAmGmGmGmUC*T*C*A*C*T*mCmUmGmCmUmG/isp18//isp18//3CholTEG/	123	55

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_118	mAmCmAmGmGmGT*C*T*C*A*C*mUmCmUmGmCmU/isp18//isp18//3CholTEG/	124	59
IL17RA_119	mGmAmCmAmGmGG*T*C*T*C*A*mCmUmCmUmGmC/isp18//isp18//3CholTEG/	125	60
IL17RA_120	mAmGmAmCmAmGG*G*T*C*T*C*mAmCmUmCmUmG/isp18//isp18//3CholTEG/	126	70
IL17RA_121	mGmAmGmAmCmAG*G*G*T*C*T*mCmAmCmUmCmU/isp18//isp18//3CholTEG/	127	83
IL17RA_122	mUmGmAmGmAmCA*G*G*G*T*C*mUmCmAmCmUmC/isp18//isp18//3CholTEG/	128	78
IL17RA_123	mGmCmAmGmGmCT*T*C*C*A*C*mUmCmCmAmUmC/isp18//isp18//3CholTEG/	129	60
IL17RA_124	mCmUmCmCmAmCT*C*A*C*C*T*mCmCmCmAmGmC/isp18//isp18//3CholTEG/	130	62
IL17RA_125	mAmCmUmCmCmAC*T*C*A*C*C*mUmCmCmCmAmG/isp18//isp18//3CholTEG/	131	78
IL17RA_126	mGmCmUmCmAmCT*C*C*A*C*T*mCmAmCmCmUmC/isp18//isp18//3CholTEG/	132	91
IL17RA_127	mAmGmCmUmCmAC*T*C*C*A*C*mUmCmAmCmCmU/isp18//isp18//3CholTEG/	133	89
IL17RA_128	mGmAmCmAmAmGC*T*C*A*C*T*mCmCmAmCmUmC/isp18//isp18//3CholTEG/	134	86
IL17RA_129	mUmCmCmCmCmCC*A*C*C*C*C*mCmCmAmCmCmC/isp18//isp18//3CholTEG/	135	59
IL17RA_130	mAmGmGmGmCmUT*C*A*G*A*C*mUmCmAmCmCmU/isp18//isp18//3CholTEG/	136	58
IL17RA_131	mCmAmGmGmGmCT*T*C*A*G*A*mCmUmCmAmCmC/isp18//isp18//3CholTEG/	137	65
IL17RA_132	mGmCmAmGmGmGC*T*T*C*A*G*mAmCmUmCmAmC/isp18//isp18//3CholTEG/	138	51

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_133	mUmGmCmAmGmGG*C*T*T*C*A*mGmAmCmUmCmA/isp18//isp18//3CholTEG/	139	57
IL17RA_134	mGmUmGmCmAmGG*G*C*T*T*C*mAmGmAmCmUmC/isp18//isp18//3CholTEG/	140	84
IL17RA_135	mCmGmGmGmUmGC*A*G*G*G*C*mUmUmCmAmGmA/isp18//isp18//3CholTEG/	141	66
IL17RA_136	mCmGmCmGmGmGT*G*C*A*G*G*mGmCmUmUmCmA/isp18//isp18//3CholTEG/	142	43
IL17RA_137	mAmCmGmCmGmGG*T*G*C*A*G*mGmGmCmUmUmC/isp18//isp18//3CholTEG/	143	39
IL17RA_138	mAmAmCmGmCmGG*G*T*G*C*A*mGmGmGmCmUmU/isp18//isp18//3CholTEG/	144	51
IL17RA_139	mGmAmAmCmGmCG*G*G*T*G*C*mAmGmGmGmCmU/isp18//isp18//3CholTEG/	145	59
IL17RA_140	mCmUmCmUmCmCT*G*T*C*A*C*mAmUmUmUmCmC/isp18//isp18//3CholTEG/	146	55
IL17RA_141	mGmCmUmCmUmCC*T*G*T*C*A*mCmAmUmUmUmC/isp18//isp18//3CholTEG/	147	58
IL17RA_142	mUmGmCmUmCmUC*C*T*G*T*C*mAmCmAmUmUmU/isp18//isp18//3CholTEG/	148	59
IL17RA_143	mUmUmGmCmUmCT*C*C*T*G*T*mCmAmCmAmUmU/isp18//isp18//3CholTEG/	149	53
IL17RA_144	mUmUmUmGmCmUC*T*C*C*T*G*mUmCmAmCmAmU/isp18//isp18//3CholTEG/	150	51
IL17RA_145	mGmUmUmUmGmCT*C*T*C*C*T*mGmUmCmAmCmA/isp18//isp18//3CholTEG/	151	56
IL17RA_146	mUmGmUmUmUmGC*T*C*T*C*C*mUmGmUmCmAmC/isp18//isp18//3CholTEG/	152	53
IL17RA_147	mCmCmUmGmUmUT*G*C*T*C*T*mCmCmUmGmUmC/isp18//isp18//3CholTEG/	153	71

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_148	mAmGmCmUmGmAA*G*A*G*G*T*mGmGmGmAmGmG/isp18//isp18//3CholTEG/	154	64
IL17RA_149	mGmAmGmCmUmGA*A*G*A*G*G*mUmGmGmAmG/isp18//isp18//3CholTEG/	155	73
IL17RA_150	mCmGmAmGmCmUG*A*A*G*A*G*mGmUmGmGmGmA/isp18//isp18//3CholTEG/	156	64
IL17RA_151	mAmCmGmAmGmCT*G*A*A*G*A*mGmGmUmGmGmG/isp18//isp18//3CholTEG/	157	86
IL17RA_152	mGmGmCmAmGmGC*T*T*C*C*A*mCmUmCmCmAmU/isp18//isp18//3CholTEG/	158	66
IL17RA_153	mUmGmGmGmCmAG*G*C*T*T*C*mCmAmCmUmCmC/isp18//isp18//3CholTEG/	159	63
IL17RA_154	mCmUmGmGmGmCA*G*G*C*T*T*mCmCmAmCmUmC/isp18//isp18//3CholTEG/	160	42
IL17RA_155	mCmCmUmGmGmGC*A*G*G*C*T*mUmCmCmAmCmU/isp18//isp18//3CholTEG/	161	45
IL17RA_156	mCmCmAmCmCmUC*T*G*C*A*C*mAmCmUmCmAmG/isp18//isp18//3CholTEG/	162	77
IL17RA_157	mGmCmCmUmGmGG*A*G*G*T*C*mGmAmGmGmCmU/isp18//isp18//3CholTEG/	163	64
IL17RA_158	mAmGmCmCmUmGG*G*A*G*G*T*mCmGmAmGmGmC/isp18//isp18//3CholTEG/	164	71
IL17RA_159	mUmGmAmGmCmCT*G*G*G*A*G*mGmUmCmGmAmG/isp18//isp18//3CholTEG/	165	80
IL17RA_160	mUmUmGmAmGmCC*T*G*G*G*A*mGmGmUmCmGmA/isp18//isp18//3CholTEG/	166	95
IL17RA_161	mCmUmUmGmAmGC*C*T*G*G*G*mAmGmGmUmCmG/isp18//isp18//3CholTEG/	167	92
IL17RA_162	mUmUmGmGmGmAG*G*A*T*G*A*mGmGmCmGmGmG/isp18//isp18//3CholTEG/	168	78

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_163	mUmUmUmGmGmGA*G*G*A*T*G*mAmG mGmCmGmG/isp18//isp18//3CholTEG/	169	74
IL17RA_164	mGmUmGmGmGmAT*G*C*A*G*G*mCmCm CmGmGmC/isp18//isp18//3CholTEG/	170	92
IL17RA_165	mUmGmUmGmGmGA*T*G*C*A*G*mGmCm CmCmGmG/isp18//isp18//3CholTEG/	171	85
IL17RA_166	mUmUmGmUmGmGG*A*T*G*C*A*mGmGm CmCmCmG/isp18//isp18//3CholTEG/	172	89
IL17RA_167	mAmCmUmCmCmUG*C*C*C*A*mCmCm CmAmCmU/isp18//isp18//3CholTEG/	173	75
IL17RA_168	mAmGmGmCmUmGG*T*G*C*C*A*mCmUm CmGmGmG/isp18//isp18//3CholTEG/	174	82
IL17RA_169	mGmAmGmGmAmUC*A*G*T*G*G*mUmAm CmCmUmC/isp18//isp18//3CholTEG/	175	84
IL17RA_170	mAmAmGmAmGmGA*T*C*A*G*T*mGmGm UmAmCmC/isp18//isp18//3CholTEG/	176	80
IL17RA_171	mGmCmAmUmGmGA*G*A*G*C*C*mAmUm GmCmAmG/isp18//isp18//3CholTEG/	177	80
IL17RA_172	mGmGmGmAmAmAG*A*G*G*A*T*mCmAm GmUmGmG/isp18//isp18//3CholTEG/	178	82
IL17RA_173	mAmGmGmGmAmAA*G*A*G*G*A*mUmC mAmGmUmG/isp18//isp18//3CholTEG/	179	88
IL17RA_174	mCmAmUmGmGmAG*A*G*C*C*A*mUmGm CmAmGmA/isp18//isp18//3CholTEG/	180	84
IL17RA_175	mGmGmCmAmUmGG*A*G*A*G*C*mCmAm UmGmCmA/isp18//isp18//3CholTEG/	181	88
IL17RA_176	mGmGmGmGmCmAT*G*G*A*G*A*mGmCm CmAmUmG/isp18//isp18//3CholTEG/	182	86
IL17RA_177	mUmGmGmGmGmCA*T*G*G*A*G*mAmGm CmCmAmU/isp18//isp18//3CholTEG/	183	56

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_178	mAmUmGmGmGmGC*A*T*G*G*A*mGmAm GmCmCmA/isp18//isp18//3CholTEG/	184	84
IL17RA_179	mAmUmCmUmGmGG*A*G*A*G*G*mCmG mAmUmGmG/isp18//isp18//3CholTEG/	185	80
IL17RA_180	mGmAmUmCmUmGG*G*A*G*A*G*mGmC mGmAmUmG/isp18//isp18//3CholTEG/	186	80
IL17RA_181	mGmGmAmUmCmUG*G*G*A*G*A*mGmG mCmGmAmU/isp18//isp18//3CholTEG/	187	85
IL17RA_182	mCmCmCmUmCmUC*C*T*C*C*T*mCmCm UmAmCmC/isp18//isp18//3CholTEG/	188	78
IL17RA_183	mUmCmCmCmUmCT*C*C*T*C*C*mUmCm CmUmAmC/isp18//isp18//3CholTEG/	189	74
IL17RA_184	mCmUmCmCmCmUC*T*C*C*T*C*mCmUm CmCmUmA/isp18//isp18//3CholTEG/	190	77
IL17RA_185	mCmUmAmCmUmCC*C*T*C*T*C*mCmUm CmCmUmC/isp18//isp18//3CholTEG/	191	93
IL17RA_186	mUmCmUmAmCmUC*C*C*T*C*T*mCmCm UmCmCmU/isp18//isp18//3CholTEG/	192	96
IL17RA_187	mUmUmCmUmAmCT*C*C*C*T*C*mUmCm CmUmCmC/isp18//isp18//3CholTEG/	193	91
IL17RA_188	mUmUmUmCmUmAC*T*C*C*C*T*mCmUm CmCmUmC/isp18//isp18//3CholTEG/	194	80
IL17RA_189	mCmUmUmUmCmUA*C*T*C*C*C*mUmCm UmCmCmU/isp18//isp18//3CholTEG/	195	89
IL17RA_190	mCmCmUmUmUmCT*A*C*T*C*C*mCmUm CmUmCmC/isp18//isp18//3CholTEG/	196	86
IL17RA_191	mCmUmCmCmUmUT*C*T*A*C*T*mCmCm CmUmCmU/isp18//isp18//3CholTEG/	197	83
IL17RA_192	mUmCmCmCmUmCC*T*T*T*C*T*mAmCm UmCmCmC/isp18//isp18//3CholTEG/	198	82

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_193	mUmCmCmCmUmCG*T*C*A*C*A*mGmCmCmAmCmC/isp18//isp18//3CholTEG/	199	74
IL17RA_194	mGmCmUmCmUmCT*C*T*G*C*C*mUmCmUmCmGmU/isp18//isp18//3CholTEG/	200	79
IL17RA_195	mGmAmGmCmUmCT*C*T*C*T*G*mCmCmUmCmUmC/isp18//isp18//3CholTEG/	201	80
IL17RA_196	mGmGmGmCmUmUC*A*G*A*C*T*mCmAmCmCmUmU/isp18//isp18//3CholTEG/	202	40
IL17RA_197	mCmUmCmCmGmCA*G*G*T*A*G*mUmUmGmUmCmC/isp18//isp18//3CholTEG/	203	60
IL17RA_198	mGmGmCmUmCmCG*C*A*G*G*T*mAmGmUmUmGmU/isp18//isp18//3CholTEG/	204	20
IL17RA_199	mGmGmGmCmUmCC*G*C*A*G*G*mUmAmGmUmUmG/isp18//isp18//3CholTEG/	205	34
IL17RA_200	mAmCmAmCmCmCA*C*A*G*G*G*mGmCmAmUmGmU/isp18//isp18//3CholTEG/	206	10
IL17RA_201	mUmCmCmCmCmGA*C*C*A*G*C*mGmGmGmUmCmU/isp18//isp18//3CholTEG/	207	76
IL17RA_202	mCmUmCmCmCmCG*A*C*C*A*G*mCmGmGmGmUmC/isp18//isp18//3CholTEG/	208	47
IL17RA_203	mCmGmUmAmGmGG*C*G*T*G*T*mGmUmGmGmGmU/isp18//isp18//3CholTEG/	209	31
IL17RA_204	mUmCmGmUmAmGG*G*C*G*T*G*mUmGmUmGmGmG/isp18//isp18//3CholTEG/	210	70
IL17RA_205	mCmUmCmGmUmAG*G*G*C*G*T*mGmUmGmUmGmG/isp18//isp18//3CholTEG/	211	47
IL17RA_206	mCmCmUmCmGmUA*G*G*G*C*G*mUmGmUmGmUmG/isp18//isp18//3CholTEG/	212	58
IL17RA_207	mUmCmCmUmCmGT*A*G*G*G*C*mGmUmGmUmGmU/isp18//isp18//3CholTEG/	213	36

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_208	mCmUmCmCmUmCG*T*A*G*G*G*mCmGmUmGmUmG/isp18//isp18//3CholTEG/	214	32
IL17RA_209	mGmGmGmCmGmUC*A*A*A*C*A*mGmUmUmAmUmU/isp18//isp18//3CholTEG/	215	33
IL17RA_210	mUmCmCmAmAmUA*A*A*G*C*T*mGmUmUmAmGmG/isp18//isp18//3CholTEG/	216	84
IL17RA_211	mCmUmCmCmAmAT*A*A*A*G*C*mUmGmUmUmAmG/isp18//isp18//3CholTEG/	217	71
IL17RA_212	mAmCmUmCmCmAA*T*A*A*A*G*mCmUmGmUmUmA/isp18//isp18//3CholTEG/	218	87
IL17RA_213	mUmAmCmUmCmCA*A*T*A*A*A*mGmCmUmGmUmU/isp18//isp18//3CholTEG/	219	78
IL17RA_214	mUmGmCmCmCmUA*T*T*T*A*A*mUmUmUmUmCmA/isp18//isp18//3CholTEG/	220	84
IL17RA_215	mAmUmGmCmCmCT*A*T*T*T*A*mAmUmUmUmUmC/isp18//isp18//3CholTEG/	221	87
IL17RA_216	mUmAmUmGmCmCC*T*A*T*T*T*mAmAmUmUmUmU/isp18//isp18//3CholTEG/	222	81
IL17RA_217	mCmUmCmAmUmUT*A*T*T*T*A*mGmGmAmAmGmG/isp18//isp18//3CholTEG/	223	87
IL17RA_218	mCmCmUmCmAmUT*T*A*T*T*T*mAmGmGmAmAmG/isp18//isp18//3CholTEG/	224	85
IL17RA_219	mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmA/isp18//isp18//3CholTEG/	225	36
IL17RA_220	mUmCmCmAmCmUC*A*C*C*T*C*mCmCmAmGmCmA/isp18//isp18//3CholTEG/	226	46
IL17RA_221	mUmCmAmCmUmCC*A*C*T*C*A*mCmCmUmCmCmC/isp18//isp18//3CholTEG/	227	63
IL17RA_222	mUmCmCmCmCmAC*C*C*C*T*G*mAmGmCmUmCmU/isp18//isp18//3CholTEG/	228	73

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_223	mAmGmAmGmGmAT*C*A*G*T*G*mGmUm AmCmCmU/isp18//isp18//3CholTEG/	229	76
IL17RA_224	mGmCmUmCmCmGC*A*G*G*T*A*mGmUm UmGmUmC/isp18//isp18//3CholTEG/	230	56
IL17RA_225	mCmUmCmAmCmUC*C*A*C*T*C*mAmCm CmUmCmC/isp18//isp18//3CholTEG/	231	68
IL17RA_226	mAmUmGmGmGmCT*T*G*G*G*C*mAmGm GmUmGmG/isp18//isp18//3CholTEG/	232	54
IL17RA_227	mAmUmGmGmGmUA*G*A*T*T*C*mGmUm UmCmCmA/isp18//isp18//3CholTEG/	233	57
IL17RA_228	mCmAmCmUmCmUT*G*A*A*G*C*mUmCm UmUmGmG/isp18//isp18//3CholTEG/	234	79
IL17RA_229	mCmGmUmCmAmAA*C*A*G*T*T*mAmUm UmUmAmU/isp18//isp18//3CholTEG/	235	81
IL17RA_230	mGmGmCmUmGmGA*T*T*T*C*T*mUmUm UmGmGmG/iSp18//iSp18//3CholTEG/	236	38
IL17RA_231	mCmUmCmCmUmCG*T*A*G*G*G*mCmGm UmGmUmG/isp18//isp18//3CholTEG/	237	32
IL17RA_232	mGmGmCmAmGmGT*G*G*T*G*A*mAmCm GmGmUmC/isp18//isp18//3CholTEG/	238	57
IL17RA_233	mGmGmGmCmAmGG*T*G*G*T*G*mAmAm CmGmGmU/isp18//isp18//3CholTEG/	239	69
IL17RA_234	mUmGmGmGmCmAG*G*T*G*G*T*mGmAm AmCmGmG/isp18//isp18//3CholTEG/	240	69
IL17RA_235	mUmUmGmGmGmCA*G*G*T*G*G*mUmGm AmAmCmG/isp18//isp18//3CholTEG/	241	62
IL17RA_236	mCmUmUmGmGmGC*A*G*G*T*G*mGmUm GmAmAmC/isp18//isp18//3CholTEG/	242	49
IL17RA_237	mCmAmCmAmGmGG*G*C*A*T*G*mUmAm GmUmCmC/isp18//isp18//3CholTEG/	243	5

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_238	mCmCmAmCmAmGG*G*G*C*A*T*mGmUm AmGmUmC/isp18//isp18//3CholTEG/	244	6
IL17RA_239	mCmCmCmAmCmAG*G*G*G*C*A*mUmGm UmAmGmU/isp18//isp18//3CholTEG/	245	5
IL17RA_240	mCmAmCmCmCmAC*A*G*G*G*G*mCmAm UmGmUmA/isp18//isp18//3CholTEG/	246	12
IL17RA_241	mUmAmCmAmCmCC*A*C*A*G*G*mGmGm CmAmUmG/isp18//isp18//3CholTEG/	247	16
IL17RA_242	mGmUmAmCmAmCC*C*A*C*A*G*mGmGm GmCmAmU/isp18//isp18//3CholTEG/	248	7
IL17RA_243	mAmGmUmAmCmAC*C*C*A*C*A*mGmGm GmGmCmA/isp18//isp18//3CholTEG/	249	4
IL17RA_244	mCmAmGmUmAmCA*C*C*C*A*C*mAmGm GmGmGmC/isp18//isp18//3CholTEG/	250	4
IL17RA_245	mCmCmAmGmUmAC*A*C*C*C*A*mCmAm GmGmGmG/isp18//isp18//3CholTEG/	251	4
IL17RA_246	mGmUmAmGmGmGC*G*T*G*T*G*mUmGm GmGmUmC/isp18//isp18//3CholTEG/	252	26
IL17RA_247	mCmCmUmCmCmUC*G*T*A*G*G*mGmCm GmUmGmU/isp18//isp18//3CholTEG/	253	15
IL17RA_248	mUmCmCmUmCmCT*C*G*T*A*G*mGmGm CmGmUmG/isp18//isp18//3CholTEG/	254	16
IL17RA_249	mCmUmCmCmUmCC*T*C*G*T*A*mGmGm GmCmGmU/isp18//isp18//3CholTEG/	255	18
IL17RA_250	mGmCmUmCmCmUC*C*T*C*G*T*mAmGm GmGmCmG/isp18//isp18//3CholTEG/	256	49
IL17RA_251	mGmCmUT*G*G*G*C*A*G*G*T*G*G*T*m GmAma/isp18//isp18//3CholTEG/	257	49
IL17RA_252	mUmCmCT*C*G*T*A*G*G*G*C*G*T*G*m UmGmU/isp18//isp18//3CholTEG/	258	48

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_253	mGmCmUmUG*G*G*C*A*G*G*T*G*G*mU mGmAmA/isp18//isp18//3CholTEG/	259	49
IL17RA_254	mAmCmAmCC*C*A*C*A*G*G*G*G*C*mA mUmGmU/isp18//isp18//3CholTEG/	260	82
IL17RA_255	mCmGmUmAG*G*G*C*G*T*G*T*G*T*mG mGmGmU/isp18//isp18//3CholTEG/	261	51
IL17RA_256	mUmCmCmUC*G*T*A*G*G*G*C*G*T*mG mUmGmU/isp18//isp18//3CholTEG/	262	51
IL17RA_257	mGmCmUmUmGG*G*C*A*G*G*T*G*mGm UmGmAmA/isp18//isp18//3CholTEG/	263	17
IL17RA_258	mAmCmAmCmCC*A*C*A*G*G*G*G*mCmA mUmGmU/isp18//isp18//3CholTEG/	264	82
IL17RA_259	mCmGmUmAmGG*G*C*G*T*G*T*G*mUmG mGmGmU/isp18//isp18//3CholTEG/	265	48
IL17RA_260	mUmCmCmUmCG*T*A*G*G*G*C*G*mUmG mUmGmU/isp18//isp18//3CholTEG/	266	48
IL17RA_261	mGmCmUmUmGmGmGmCmAG*G*T*G*G* T*mGmAmA/isp18//isp18//3CholTEG/	267	14
IL17RA_262	mAmCmAmCmCmCmAmCmAG*G*G*G*C* A*mUmGmU/isp18//isp18//3CholTEG/	268	11
IL17RA_263	mUmCmCmUmCmGmUmAmGG*G*C*G*T* G*mUmGmU/isp18//isp18//3CholTEG/	269	18
IL17RA_264	mGmCmUT*G*G*G*C*A*mGmGmUmGmGm UmGmAmA/isp18//isp18//3CholTEG/	270	16
IL17RA_265	mAmCmAC*C*C*A*C*A*mGmGmGmGmCm AmUmGmU/isp18//isp18//3CholTEG/	271	14
IL17RA_266	mCmGmUA*G*G*G*C*G*mUmGmUmGmU mGmGmGmU/isp18//isp18//3CholTEG/	272	31
IL17RA_267	mUmCmCT*C*G*T*A*G*mGmGmCmGmUm GmUmGmU/isp18//isp18//3CholTEG/	273	31

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_268	mGmCmUmUmGmGmGC*A*G*G*T*G*mGmUmGmAmA/isp18//isp18//3CholTEG/	274	9
IL17RA_269	mAmCmAmCmCmCmAC*A*G*G*G*G*mCmAmUmGmU/isp18//isp18//3CholTEG/	275	12
IL17RA_270	mCmGmUmAmGmGmGC*G*T*G*T*G*mUmGmGmU/isp18//isp18//3CholTEG/	276	33
IL17RA_271	mUmCmCmUmCmGmUA*G*G*G*C*G*mUmGmUmGmU/isp18//isp18//3CholTEG/	277	33
IL17RA_272	mGmCmUmUmGG*G*C*A*G*G*mUmGmGmUmGmAmA/isp18//isp18//3CholTEG/	278	13
IL17RA_273	mAmCmAmCmCC*A*C*A*G*G*mGmGmCmAmUmGmU/isp18//isp18//3CholTEG/	279	34
IL17RA_274	mCmGmUmAmGG*G*C*G*T*G*mUmGmUmGmGmU/isp18//isp18//3CholTEG/	280	46
IL17RA_275	mUmCmCmUmCG*T*A*G*G*G*mCmGmUmGmUmGmU/isp18//isp18//3CholTEG/	281	47
IL17RA_276	mAmCmAC*C*C*A*C*A*G*G*G*G*C*A*mUmGmU/isp18//isp18//3CholTEG/	282	82
IL17RA_277	mCmGmUA*G*G*G*C*G*T*G*T*G*T*G*mGmGmU/isp18//isp18//3CholTEG/	283	48
IL17RA_278	mAmCmCmCmAmCA*G*G*G*G*C*mAmUmGmUmAmG/isp18//isp18//3CholTEG/	284	7
IL17RA_279	mCmGmUmAmGmGmGmCmGT*G*T*G*T*G*mGmGmU/isp18//isp18//3CholTEG/	285	18
IL17RA_280	mCmCmCmAmCmAmGmGmGG*C*A*T*G*T*mAmGmU/isp18//isp18//3CholTEG/	286	7
IL17RA_281	mCmCmCmAmCA*G*G*G*G*C*mAmUmGmUmAmGmU/isp18//isp18//3CholTEG/	287	10
IL17RA_282	mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/	288	3

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:	% IL17RA mRNA Expression
IL17RA_283	mGmUmAmGmGmGmCG*T*G*T*G*T*mGmGmGmUmC/isp18//isp18//3CholTEG/	289	33
IL17RA_284	mGmUmAG*G*G*C*G*T*mGmUmGmUmGmGmGmUmC/isp18//isp18//3CholTEG/	290	31
IL17RA_285	mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC/isp18//isp18//3CholTEG/	291	18
IL17RA_286	mGmUmAmGmGG*C*G*T*G*T*mGmUmGmGmGmUmC/isp18//isp18//3CholTEG/	292	46
IL17RA_287	mCmCmCA*C*A*G*G*G*mGmCmAmUmGmUmAmGmU/isp18//isp18//3CholTEG/	293	12
IL17RA_288	mGmUmAG*G*G*C*G*T*G*T*G*T*G*G*mGmUmC/isp18//isp18//3CholTEG/	294	48
IL17RA_289	mGmUmAmGG*G*C*G*T*G*T*G*T*G*mGmUmC/isp18//isp18//3CholTEG/	295	51
IL17RA_290	mCmCmCA*C*A*G*G*G*G*C*A*T*G*T*mAmGmU/isp18//isp18//3CholTEG/	296	57
IL17RA_291	mCmCmCmAC*A*G*G*G*G*C*A*T*G*mUmAmGmU/isp18//isp18//3CholTEG/	297	35
IL17RA_292	mCmCmCmAmCA*G*G*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/	298	10
IL17RA_293	mGmUmAmGmGG*C*G*T*G*T*G*T*mGmGmGmUmC/isp18//isp18//3CholTEG/	299	55
Control	mGmUmUmUmCmAC*C*A*C*C*C*mAmAmUmUmCmC/iSp18//iSp18//3CholTEG/	300	

Table 2. Oligonucleotide Sequences

Special bases used in the oligonucleotides are as follows: mN = 2' O-methyl RNA, /iSp18/ = hexa(ethylene glycol) spacer phosphoramidite, * = phosphorothioate, /3CholTEG/= 3' cholesterol

Compound ID	Oligonucleotide Sequence (5' to 3')	SEQ ID NO:
Control	mGmUmUmUmCmAC*C*A*C*C*C*mAmAmUmUmCmC/iSp18 //iSp18//3CholTEG/	300
Anti-TNF	mUmGmGmGmAmGT*A*G*A*C*A*mAmGmGmUmAmC/iSp1 8//iSp18//3CholTEG/	301
IL17RA_219	mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmAmA/iSp1 8//iSp18//3CholTEG/	225

Example 2. IL-17RA mRNA knockdown in human skin using SNAs formulated in a gel vehicle

5 Methods and Materials

Tissue Culture. Healthy human ex vivo skin, freshly acquired from a single donor was received the day of experiment initiation and prepared immediately. Prior to use, the skin was inspected, noting any areas of extensive stretch marks or scarring, and any sections with visible holes or damage were removed. A dermatome was used to excise full thickness skin from the donor sample. The resulting tissue contained an intact stratum corneum, epidermis, and dermis. No subcutaneous tissue from the surgical explant remained. The skin was carefully cut to the appropriate size and care was taken not to stretch the skin when it was placed into the Franz cells. The skin was then clamped into the Franz cell. Next, a stir bar and receiving medium that had been pre-warmed to 37 °C were added to each Franz cell. The receiving medium consisted of Dulbecco's modified Eagle's medium, supplemented with 2 % fetal bovine serum, 50 U/mL penicillin, 50 mg/mL streptomycin, 0.25 µg/mL amphotericin B and 10 µg/mL gentamycin. The Franz cells, explants and receiving medium were allowed to equilibrate for a minimum of 30 minutes, after which the temperature of the media in each cell was verified to be 37 ± 1 °C. Any air bubbles that were introduced during assembly of the cells were removed. The integrity of the skin was confirmed prior to initiating the study by inverting the cell. If leaks were identified, the skin and donor chamber were repositioned until leaks were absent. Over the course of the experiment, the skin was maintained at ambient humidity and at an epidermal surface temperature of 32 °C, which was regulated

using 37 °C water-jacketing of the receptor chamber containing cell culture media that contacts the dermal portion of the explant.

SNA Synthesis. The oligonucleotide was synthesized at the 1 mmole scale employing standard UniLinker support (ChemGenes). The DNA, 2'-O-Me RNA monomers and hexa(ethylene glycol) spacers were obtained from ChemGenes Corporation. The cholesterol modifier was obtained from Glen Research. Linkages were either standard phosphodiester or phosphorothioates prepared with a solution of 0.2 M phenylacetyl disulfide (PADS) in a mixture of 1:1 lutidine:ACN. Synthesis was performed DMT-off, in the 3' to 5' direction. After synthesis, the oligonucleotide was cleaved from the support and de-protected using a 4:1 mixture of ammonium hydroxide and ethanol at 55 °C for 16 hours. The oligonucleotide was purified via high performance liquid chromatography (HPLC) techniques. Molecular weights and extinction coefficients were calculated using the IDT OligoAnalyzer. The verification of the oligonucleotide product molecular weight was performed using electrospray ionization mass spectrometry (ESI-MS). Finally, the oligonucleotide concentration was determined by UV-absorbance at 260 nm on a microplate reader (BioTek).

Liposomes were formulated by first dissolving 250 mg 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) in chloroform to a final concentration of 50 mg/mL. The solvent was then removed under nitrogen to form a thin lipid film. The film was lyophilized overnight to ensure all solvent was removed. The lipid film was subsequently hydrated with 10 mM phosphate buffered saline (PBS) and sonication/freeze-fracture were used to form large, unilamellar vesicles. These vesicles were then continuously homogenized through a micro-fluidizer at up to 25 kpsi, until the desired mean number diameter of 20 nm was achieved. Liposome concentrations were determined using a choline quantification assay and the particle size and dispersion were measured by dynamic light scattering (DLS).

SNAs targeting human IL-17RA, compound IL17RA_282, were formulated by mixing a 30-fold molar excess of cholesterol-modified oligonucleotide, SEQ ID NO: 288, to the liposome suspension in PBS followed by overnight incubation at 4 °C.

Drug Application to Skin. A gel vehicle was used to apply IL17RA_282 to the skin. The pre-formulated SNAs were mixed into the gel vehicle, resulting in three drug product strengths of 0, 0.00007 and 0.007 % w/w (oligonucleotide weight). The composition of these drug products can be found in Table 3.

These drug products were then applied topically to the skin explants. The drug products were briefly mixed prior to dosing using a pipette tip. 40 µL of each drug product was dosed topically to each Franz cell using a positive displacement pipette. The pipette tip was used to spread the drug product evenly covering the entire exposed surface area of the skin (1.0 cm²). After dosing, the sampling port was occluded to prevent solvent evaporation during the study. The actual dosing time was recorded and the explants were maintained at ambient humidity and at an epidermal surface temperature of 32 °C for 24 hours.

RNA Extraction and qRT-PCR. At the conclusion of the 24 hour incubation period, the Franz cells were disassembled and the skin was carefully removed from each cell. A cotton swab wetted with PBS was used to remove the drug product and then the application area was blotted dry. Three samples were cut from the 1.0 cm² dosing area using a 4 mm biopsy punch. The skin was not stretched while the biopsy punches were taken. The biopsy punches were then lysed in RLT buffer (Qiagen) with a bead homogenizer. RNA was isolated from lysates using the RNEasy 96-well kit (Qiagen) according to the manufacturer's instructions. cDNA was then synthesized from RNA isolates using the cDNA high capacity reverse transcription kit (Life Technologies). cDNA was prepared on a thermocycler with the following temperature program: 25 °C for 10 minutes, 37 °C for 90 minutes, 85 °C for 5 minutes followed by a 4 °C hold. The resulting cDNA was diluted 8 fold with nuclease-free water. qPCR was performed using 6 µL of the diluted cDNA, 4.66 µL LightCycler480 Probes Master Mix (Roche), 0.47 µL human IL-17RA specific FAM-labeled probe and primers, and 0.37 µL human Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) specific HEX-labeled probe and primers per reaction well of a 384-well optical reaction plate (Roche). The primer and probe set for IL-17RA was purchased commercially (Hs01064648_m1, Thermo Fisher Scientific). The primer and probe set for GAPDH was designed using the known human genome sequence (NCBI reference sequences NM_002046.5) and was found to be specific by "blastn" analysis (NCBI). The oligonucleotide sequences used for GAPDH were: forward 5'-CAA GGT CAT CCA TGA CAA CTT TG-3' (SEQ ID NO: 4), reverse 5'-GGG CCA TCC ACA GTC TTC T-3' (SEQ ID NO: 5), probe 5'-HEX-ACC ACA GTC CAT GCC ATC ACT GCC A-BHQ1-3' (SEQ ID NO: 6). qPCR reactions, in technical duplicate, were carried out on the Roche Lightcycler 480 under the following conditions: initial denaturation at 95 °C for 10 minutes and then 50 cycles of denaturation at 95 °C for 10 seconds, annealing at 60 °C for 30 seconds and extension at 72 °C for 1 second. Cp values were obtained by analysis with the 2nd derivative method. Relative gene expression was determined by normalization

with the housekeeping gene (GAPDH) and the $\Delta\Delta$ -Ct method. Statistical analysis was done by performing a one-way ANOVA.

Protein Isolation and Western Blot. Total protein was isolated from the biopsy lysates with acetone precipitation. Lysates from each treatment group were pooled before isolating the protein to increase protein yield. Briefly, four volumes of ice cold acetone were added to the lysate and incubated at -20 °C for 30 minutes. The samples were centrifuged and decanted, and the pellets were washed with one volume ice cold ethanol. Again, the samples were centrifuged and the pellets were allowed to air dry. The pellets were re-suspended in one volume Laemmli sample buffer containing 1 % β -mercaptoethanol. To ensure the samples were completely dissolved, they were boiled at 95 °C for 10 minutes and subsequently centrifuged to remove any undissolved debris.

The protein isolates were loaded into a 10 % SDS-PAGE gel, run and transferred overnight (22 V) to an Immobilon PSQ PVDF membrane (ISEQ00010, Millipore). The membrane was blocked for 1 hour with 5 % dry milk in tris buffered saline containing Tween 20 (the resulting buffer is referred to as TBST) followed by a 5 minute wash in TBST. Human-specific antibodies targeting IL-17RA or β -actin protein were used to probe for the presence of those specific proteins. IL-17RA protein was detected using an anti-IL-17RA rabbit monoclonal primary antibody, and was shown to detect a protein with a predicted molecular weight of 150 kDa (12661, Cell Signaling). This antibody was diluted in blocking buffer (5 % dry milk in TBST) at a ratio of 1:500 prior to use. β -actin protein was detected using an anti- β -actin rabbit monoclonal primary antibody, and was shown to detect a protein with a predicted molecular weight of 45 kDa (4970, Cell Signaling). This antibody was diluted in blocking buffer at a ratio of 1:1000 prior to use. Primary antibody incubation occurred overnight at 4 °C.

After the incubation period, the membrane was rinsed twice with TBST, followed by two consecutive washes with TBST of 15 minutes and 5 minutes. Next, the membrane was incubated with an anti-rabbit HRP secondary antibody (7074, Cell Signaling) diluted in blocking buffer at a ratio of 1:1000 prior to use. The secondary antibody incubation occurred for 90 minutes at room temperature. Then, the membrane was rinsed twice with TBST, followed by two consecutive washes with TBST for 15 minutes and 5 minutes. Then, the membrane was further washed twice with distilled water for 5 minutes. Subsequently, GE Amersham Prime ECL reagent (RPN2232) was added to the membrane and incubated at room temperature for 5 minutes. Then, the membrane was imaged using an exposure interval

of 20 seconds for up to 2 minutes on a BioRad GelDoc Imager. Finally, images were analyzed by densitometry and IL-17RA signal was normalized to β -actin signal to compared expression levels across treatments.

5 *Table 3. Drug Product Compositions*

Ingredient	Gel Strength Formulations (w/w)		
	0 %	0.00007 %	0.007 %
SEQ ID NO: 288	0	0.00007	0.007
DOPC	0	0.0003801	0.03801
Diethylene glycol monoethyl ether (Transcutol P)	25	25	25
Glycerin	5	5	5
Hydroxyethyl Cellulose	1	1	1
Methylparaben	0.15	0.15	0.15
Propylparaben	0.05	0.05	0.05
Disodium EDTA	0.1	0.1	0.1
Sodium Metabisulfite	0.2	0.2	0.2
Water	68.5	68.5	68.45

Results

The IL-17RA mRNA targeted SNA (compound IL17RA_282) formulated as a drug product in a gel vehicle showed dose-dependent knockdown of IL-17RA mRNA in healthy human skin explant after only 24 hours of treatment (Fig. 9). Knockdown was observed when compared to both untreated skin and the 0 % strength drug product. Treatment with the 0.007 % strength drug product resulted in statistically significant IL-17RA mRNA inhibition compared to untreated ($p = 0.0011$) and 0 % strength drug product ($p < 0.0001$) by one-way ANOVA. The IL-17RA mRNA targeted SNA (compound IL17RA_282) formulated as a drug product in a gel vehicle showed inhibition of IL-17RA protein expression in healthy human skin explant after only 24 hours of treatment (Fig. 10). Knockdown was observed when compared to both untreated skin and the 0 % strength drug product. The graph represents the analyzed densitometry data collected from the western blot (inset). There was insufficient material to perform a protein-level analysis for the skin samples treated with 0.0007% gel.

Discussion and Conclusions

Clinical data suggests that the IL-17 signaling pathway plays a significant role in sustaining the psoriasis disease state. While current monoclonal antibody therapies, like brodalumab, provide very effective treatment options, they also present with troubling side-effect profiles. This presents a therapeutic need for a safer alternative. Antisense technology can reduce the expression of mRNA in cells; however, antisense oligonucleotides generally have poor uptake into cells and skin. In contrast, it has been found that when oligonucleotides are arranged in the SNA geometry, they exhibit skin penetration properties and increased cellular uptake. Given these advantages and the therapeutic needs for psoriasis treatment, an antisense SNA based therapy targeting human IL-17RA in the skin may prove an effective treatment for psoriasis.

It has been shown here that when the IL-17RA mRNA targeted SNA (compound IL17RA_282) formulated as a drug product in a gel vehicle is applied topically to healthy human skin explants, there is a pharmacodynamic effect seen at both the level of IL-17RA mRNA and protein. Increasing strength of the drug product results in decreased IL-17RA expression.

The response observed in this study represents only a 24 hour treatment. It is expected that longer treatment with multiple doses would further enhance the inhibition observed. Given the importance of IL-17 signaling in maintaining the diseased state observed in psoriasis, a strong topical drug product candidate for the treatment of psoriasis is presented.

Example 3. IL-17RA mRNA knockdown in human psoriatic skin using SNAs formulated in a gel vehicle

Methods and Materials

Tissue Culture. Four skin biopsies (3 mm diameter) were obtained from each of 8 different patients with mild to moderate plaque psoriasis. Biopsies were taken directly from psoriatic plaques. Due to the limited number of biopsies that can be taken from a single patient, only 4 biopsies were taken per individual. Biopsies were taken from volunteers at about 45 minute intervals and transported to the laboratory (rolled in moist sterile gauze). The time between taking biopsies and starting the incubation was between 5 and 7.5 hours. The biopsies were positioned in the membrane of an insert-well, and incubated in 12-well plates at 32 °C with ambient CO₂ and humidity. The membranes were immersed in 1 mL cell culture medium (Dulbecco's modified Eagle's medium, 1 % fetal bovine serum, 1.25 µg/mL amphotericin B,

50 µg/mL gentamicin, and 0.1 U/mL penicillin/streptomycin) such that the dermis contacted the medium in the well and the epidermis was exposed to air. There was 1 biopsy per well. The lid of the 12-well plate was elevated using two sterile 1 mL pipette tips to limit moisture build-up. The total incubation time of the drug product treated skin was 21 hours and 15 minutes.

SNA Synthesis. The oligonucleotide, SEQ ID NO: 288, was synthesized via standard solid-phase phosphoramidite chemistry. The molecule was synthesized with successive cycles of de-protection, monomer addition, capping, and oxidation. The DNA, and 2'-O-Me RNA monomers were obtained from Sigma Aldrich Biochemie (Germany). The hexa(ethylene glycol) spacers and cholesterol modifier were obtained from ChemGenes Corporation. Linkages were either standard phosphodiesters or phosphorothioates prepared with a solution of 0.2 M phenylacetyl disulfide (PADS) in a mixture of 1:1 lutidine:ACN. Synthesis was performed DMT-off, in the 3' to 5' direction. After synthesis, the oligonucleotide was cleaved from the support and de-protected using a 3:1 mixture of ammonium hydroxide and ethanol at 65 °C for 17 hours. The oligonucleotide was purified via anion exchange high performance liquid chromatography (AX-HPLC) techniques. Then the oligonucleotide solution was lyophilized completely to a dry powder. Verification of the oligonucleotide product molecular weight was performed using electrospray ionization mass spectrometry (ESI-MS) and dual-MS sequencing was performed to confirm the oligonucleotide sequence. Oligonucleotide concentration was determined by UV-absorbance at 260 nm.

Liposomes were formulated by Avanti Polar Lipids (Alabama, USA). First, 500 g 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) was dissolved in chloroform to a final concentration of 50 mg/mL. The solvent was then removed under nitrogen to form a thin lipid film. The film was lyophilized overnight to ensure all solvent was removed. The lipid film was subsequently hydrated with Hyclone sterile, nuclease-free water (SH30538.03, GE) at a concentration of 100 mg/mL and sonication/freezing-fracture were used to form large, unilamellar vesicles. These vesicles were then continuously homogenized through a microfluidizer at up to 25 kpsi, until the mean number diameter of 20 nm was achieved. The liposome solution was further concentrated by tangential flow filtration (TFF) to a final lipid concentration of 208 mg/mL. Lipid concentrations were determined using a choline quantification assay and nuclear magnetic resonance spectroscopy. The particle size and dispersion were measured by dynamic light scattering (DLS).

SNAs targeting human IL-17RA, were formulated by mixing a 30-fold molar excess of cholesterol-modified full length oligonucleotide to the liposome suspension in Hyclone sterile, nuclease-free water (SH30538.03, GE) followed by overnight incubation at 4 °C.

5 Drug Application to the Skin. The pre-formulated SNAs targeting human IL-17RA were mixed into a gel vehicle, resulting in four IL17RA_282 gel strengths of 0, 0.01, 0.1 and 1.0 % w/w (full length oligonucleotide weight). The composition of these drug products can be found in Table 4.

10 The IL17RA_282 gels were then applied topically to the skin explants in replicates of eight. During the sample processing, one sample in the 1.0 % group was lost, resulting in only 7 replicates for that group. Each replicate was taken from a different patient for accurate representation and comparison of a patient specific response. The IL17RA_282 gels were briefly mixed prior to dosing using a pipette tip. 10 µL of each drug product was dosed topically to each 3 mm biopsy using a positive displacement pipette. The pipette tip was used
15 to spread the drug product evenly covering the entire exposed surface area of the skin. The actual dosing time was recorded and the explants were maintained at 32 °C and ambient humidity for 21 hours.

At the conclusion of the 21 hour incubation period, the biopsies were removed from each membrane. A cotton swab wetted with PBS was used to remove the drug product and
20 then the application area was blotted dry. The biopsy punches were lysed in RLT buffer (Qiagen) with a bead homogenizer and stored frozen at -80 °C until shipped on dry ice to the research facility.

RNA Extraction and qRT-PCT. RNA was isolated from lysates using the RNEasy 96-well kit
25 (Qiagen) according to the manufacturer's instructions. cDNA was then synthesized from RNA isolates using the cDNA high capacity reverse transcription kit (Life Technologies). cDNA was prepared on a thermocycler with the following temperature program: 25 °C for 10 minutes, 37 °C for 90 minutes, 85 °C for 5 minutes followed by a 4 °C hold. The resulting cDNA was diluted 8 fold with nuclease-free water. qPCR was performed using 6 µL of the
30 diluted cDNA, 4.66 µL LightCycler480 Probes Master Mix (Roche), 0.47 µL human IL-17RA specific FAM-labeled probe and primers, and 0.37 µL human Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) specific HEX-labeled probe and primers per reaction well of a 384-well optical reaction plate (Roche). The primer and probe set for IL-17RA was purchased commercially (Hs01064648_m1, Thermo Fisher Scientific). The primer and probe

set for GAPDH was designed using the known human genome sequence (NCBI reference sequences NM_002046.5) and was found to be specific by “blastn” analysis (NCBI). The oligonucleotide sequences used for GAPDH were: forward 5'-CAA GGT CAT CCA TGA CAA CTT TG-3' (SEQ ID NO: 4), reverse 5'-GGG CCA TCC ACA GTC TTC T-3' (SEQ ID NO: 5), probe 5'-HEX-ACC ACA GTC CAT GCC ATC ACT GCC A-BHQ1-3' (SEQ ID NO: 6). qPCR reactions, in technical duplicate, were carried out on the Roche Lightcycler 480 under the following conditions: initial denaturation at 95 °C for 10 minutes and then 50 cycles of denaturation at 95 °C for 10 seconds, annealing at 60 °C for 30 seconds and extension at 72 °C for 1 second. Cp values were obtained by analysis with the 2nd derivative method. Relative gene expression was determined by normalization with the housekeeping gene (GAPDH) and the $\Delta\Delta$ -Ct method. Statistical analysis was done by performing a one sample t-test.

Table 4. Drug Product Compositions

Ingredient	Gel Strength Formulations (w/w)			
	0 %	0.01 %	0.1 %	1.0 %
SEQ ID NO: 288	0	0.01419	0.1419	1.419
DOPC	0	0.2655	2.655	26.55
Diethylene glycol monoethyl ether (Transcutol P)	25	25	25	25
Glycerin	5	5	5	5
Hydroxyethyl Cellulose	1	1	1	1
Methylparaben	0.15	0.15	0.15	0.15
Propylparaben	0.05	0.05	0.05	0.05
Disodium EDTA	0.1	0.1	0.1	0.1
Sodium Metabisulfite	0.2	0.2	0.2	0.2
Water	68.5	68.2	65.7	40.5

Results

The IL17RA_282 gels showed dose-dependent knockdown of IL-17RA mRNA in human psoriatic skin biopsies after 21 hours of treatment (Fig. 11). Knockdown was observed when comparing the IL17RA_282-containing gels to the 0 % gel strength formulation.

Treatment with the IL17RA_282 gels resulted in statistically significant reduction of IL-17RA mRNA.

Discussion and Conclusions

It was shown here that when the IL17RA_282 gel is applied topically to *ex vivo* human psoriatic skin biopsies, there is a pharmacodynamic effect seen at the level of IL-17RA mRNA. The response observed in this study represents only a 21 hour treatment. It is expected that longer treatment with multiple doses would further enhance the inhibition observed. Given the importance of IL-17 signaling in maintaining the diseased state observed in psoriasis, a strong topical drug product candidate for the treatment of psoriasis is presented.

Example 4. Multiplex SNAs targeting three different mRNAs

Materials and Methods

Multiplex SNA Synthesis. SNAs were formulated by mixing a 100X molar excess (unless otherwise stated) of cholesterol-modified oligonucleotide to a liposome suspension in PBS and storing them overnight, protected from light, at 4 °C. Four different oligonucleotides were used for the synthesis process: an antisense oligonucleotide targeting human IL-4R, an antisense oligonucleotide targeting human IL-1 β , an antisense oligonucleotide targeting human CTGF, and a same length control oligonucleotide that does not have any complementarity to known genes (confirmed by BLAST). For monoplex SNAs, the oligonucleotide population consisted of 33% targeted antisense oligonucleotide and 66% control oligonucleotide. For multiplex SNAs containing two different targeted antisense oligonucleotides, the oligonucleotide population consisted of 33% of each targeted antisense oligonucleotide and the remaining 33% control oligonucleotide (Fig. 12). For multiplex SNAs containing three different targeted antisense oligonucleotides, the oligonucleotide population consisted of 33% of each targeted antisense oligonucleotide. Control SNAs consisted of 100% of the control oligonucleotide (Fig. 9).

Cell Culture Studies. Primary human foreskin keratinocytes (HFKs) were seeded at passage 5 in 96-well, tissue culture plates at a cell density of 17,000 cells per well. Cells were allowed to rest in the incubator overnight following plating. Cells were treated in triplicate with either an IL-4R targeted antisense SNA, IL-1 β targeted antisense SNA, CTGF targeted antisense

SNA, a multiplex SNA targeting more than one transcript or a non-complementary control SNA (confirmed by NCBI Blast), comprising the same ‘gap-mer’ design and 3′-chemical modifications, at concentrations of 1000, 100, 10 and 1 nM in fresh maintenance media. Unless otherwise stated, all treatments lasted 24 hours.

5

RNA Extraction and Quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT-

PCR). HFK cells were lysed in RLT Buffer (Qiagen) at 24 hours post-transfection. RNA was isolated from lysates using the RNEasy 96-well kit (Qiagen) according to the manufacturer’s instructions. cDNA was then synthesized from RNA isolates using the cDNA High Capacity Reverse Transcription Kit (Life Technologies). Samples were run on a thermocycler at 25 °C for 10 minutes, 37 °C for 90 minutes, 85 °C for 5 minutes and held at 4 °C to generate cDNA. qPCR was performed using 6 µL of the synthesized cDNA, 4.66 µL LightCycler480 Probes Master Mix (Roche), 0.47 µL target specific FAM-labeled probe and primers, and 0.37 µL human Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) specific HEX-labeled probe and primers per reaction well of a 384-well optical reaction plate (Roche). The primer and probe sets for IL-4R, IL-1β and CTGF were purchased from ThermoFisher Scientific (catalogue numbers Hs00166237_m1, Hs01555410_m1 and Hs01026927_g1, respectively). The primer and probe set for GAPDH was designed using the known human genome sequence (NCBI reference sequence NM_002046.5) and was found to be specific by “blastn” analysis (NCBI). The oligonucleotide sequences used for GAPDH were: forward 5′-CAA GGT CAT CCA TGA CAA CTT TG-3′ (SEQ ID NO: 4), reverse 5′-GGG CCA TCC ACA GTC TTC T-3′ (SEQ ID NO: 5), probe 5′-HEX-ACC ACA GTC CAT GCC ATC ACT GCC A-BHQ1-3′ (SEQ ID NO: 6). qPCR reactions, in technical duplicate, were carried out on the Roche Lightcycler 480 under the following conditions: initial denaturation at 95 °C for 10 minutes and then 50 cycles of denaturation at 95 °C for 10 seconds, annealing at 60 °C for 30 seconds and extension at 72 °C for 1 second. Cp values were obtained by analysis with the 2nd derivative method. Relative gene expression was determined by normalization with the housekeeping gene (GAPDH) and the $\Delta\Delta$ -Ct method. Each treatment was compared to its respective concentration control.

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Results

Seven different SNA configurations were made to test whether three different mRNAs can be targeted using single SNA construct. Three mRNAs were chosen that were not functionally dependent on each other for expression and were not in a single known

pathway. In certain cases, it may be advantageous to target mRNAs that are part of the same pathway, e.g. TNF, IL17, IL22, to control a specific pathway. SNAs were synthesized targeting each individual mRNA alone, three pairs of mRNAs and one SNA configuration that can target all three mRNAs. Control oligonucleotide was used to ensure that each SNA configuration has the same number of targeted and non-targeted oligonucleotides.

The results from cell culture experiments demonstrate that single SNA can be formulated that targets three different mRNAs. The mRNAs chosen were interleukin 4 receptor (IL4R), interleukin 1 beta (IL1b) and connective tissue growth factor (CTGF). These targets were chosen because in other experiments it was noted that knocking down any one of these mRNAs didn't significantly reduce the levels of the other two. The results show that when antisense oligonucleotides targeting any single mRNA is present on the SNA, the expression of that mRNA is reduced in a dose dependent manner (Fig. 13 for IL4R, Fig. 14 for IL1b, Fig. 15 for CTGF). This configuration can be extended to target more than three mRNAs. The total antisense loading per SNA may be the theoretical limit to the number of mRNAs that can be targeted with a single SNA configuration.

References

1. Banga RJ, Chernyak N, Narayan SP, Nguyen ST, Mirkin CA. Liposomal Spherical Nucleic Acids. *J. Am. Chem. Soc.* 2014 136: 9866-9869.
2. Ding Y and Lawrence CE. A Statistical Sampling Algorithm for RNA Secondary Structure Prediction. *Nucleic Acids Res.* 2003; 31: 7280-7301.
3. Chabaud M1, Fossiez F, Taupin JL, Miossec P. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. *J Immunol.* 1998 Jul 1;161(1):409-14.
4. Miossec P. Interleukin-17 in rheumatoid arthritis: if T cells were to contribute to inflammation and destruction through synergy. *Arthritis Rheum.* 2003 Mar;48(3):594-601.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

All references, including patent documents, disclosed herein are incorporated by reference in their entirety.

CLAIMS

What is claimed is:

1. A single-stranded modified oligonucleotide consisting of 10-30 linked nucleosides
5 and having: a gap segment consisting of two to eight linked deoxynucleosides; a 5' wing
segment consisting of linked nucleosides; and a 3' wing segment consisting of linked
nucleosides; wherein the gap segment is positioned between the 5' wing segment and the 3'
wing segment; wherein at least some nucleosides of each wing segment comprises a modified
nucleotide; wherein the internucleoside linkages within the gap segment and the linkages
10 connecting the gap segment to the 3' wing segments are all phosphorothioate linkages (*);
and the internucleoside linkages connecting the rest of the nucleosides of both the 5' and 3'
wing segments are phosphodiester linkages; and wherein the nucleobase sequence of the
oligonucleotide consists of 10-30 contiguous nucleobases complementary to an equal length
portion of SEQ ID NO.: 302, or a pharmaceutically acceptable salt thereof.
- 15
2. The oligonucleotide of claim 1, wherein the nucleobase sequence of the
oligonucleotide is GCUUGGGCAGGTGGUGAA (SEQ ID NO: 225).
3. The oligonucleotide of claim 1, wherein the nucleobase sequence of the
20 oligonucleotide is CCCACAGGGGCATGUAGU (SEQ ID NO: 288).
4. The oligonucleotide of claim 1, wherein the nucleobase sequence of the
oligonucleotide is GUAGGGCGUGTGTGGGUC (SEQ ID NO: 291).
- 25
5. The oligonucleotide of claim 1, wherein the nucleobase sequence of the
oligonucleotide is mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmAmA (SEQ ID
NO: 225).
6. The oligonucleotide of claim 1, wherein the nucleobase sequence of the
30 oligonucleotide is mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU (SEQ ID
NO: 288).

7. The oligonucleotide of claim 1, wherein the nucleobase sequence of the oligonucleotide is mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC (SEQ ID NO: 291).

5 8. The oligonucleotide of any one of claims 1-7, wherein the compound is 20 nucleotides in length.

9. The oligonucleotide of any one of claims 1-7, further comprising a molecular species at one of the ends.

10

10. The oligonucleotide of any one of claims 1-7, wherein the compound further comprises a molecular species at both ends.

11. The oligonucleotide of any one of claims 9-10, wherein the molecular species is
15 selected from the group consisting of a spacer, a lipid, a sterol, cholesterol, stearyl, C16 alkyl chain, bile acids, cholic acid, taurocholic acid, deoxycholate, oleyl lithocholic acid, oleoyl cholenic acid, glycolipids, phospholipids, sphingolipids, isoprenoids, such as steroids, vitamins, such as vitamin E, saturated fatty acids, unsaturated fatty acids, fatty acid esters, such as triglycerides, pyrenes, porphyrines, Texaphyrine, adamantane, acridines, biotin,
20 coumarin, fluorescein, rhodamine, Texas-Red, digoxigenin, dimethoxytrityl, t-butyltrimethylsilyl, t-butylphenylsilyl, cyanine dyes (e.g. Cy3 or Cy5), Hoechst 33258 dye, psoralen, and ibuprofen.

12. The oligonucleotide of any one of claims 9-10, wherein the molecular species is a
25 selected from the group consisting of a lipophilic moiety; a folic acid radical; a steroid radical; a carbohydrate radical; a vitamin A radical; a vitamin E radical; or a vitamin K radical.

13. The oligonucleotide of any one of claims 9-10, wherein the molecular species is
30 connected directly to the compound through a linkage selected from the group consisting of phosphodiester, phosphorothioate, methylphosphonate, and amide linkages.

14. The oligonucleotide of any one of claims 9-10, wherein the molecular species is connected indirectly to the compound through a linker.

15. The oligonucleotide of claim 14, wherein the linker is a non-nucleotidic linker selected from the group consisting of abasic residues (dSpacer), oligoethyleneglycol, such as triethyleneglycol (spacer 9) or hexaethyleneglycol (spacer 18), and alkane-diol, such as butanediol.

16. The oligonucleotide of claim 15, wherein the 3' end of the oligonucleotide is connected to 2 consecutive linkers that are hexaethyleneglycol (spacer 18), the first hexaethyleneglycol connected to the 3' end of the oligonucleotide, the second hexaethyleneglycol connected to the first hexaethyleneglycol and the second hexaethyleneglycol is connected to a cholesterol.

17. The oligonucleotide of any one of claims 1 and 9-16, wherein the oligonucleotide consists of 17-21 linked nucleosides.

18. The oligonucleotide of any one of claims 1 and 9-17, wherein the oligonucleotide has a gap segment consisting of six linked deoxynucleosides.

19. The oligonucleotide of any one of claims 1 and 9-18, wherein all of the nucleosides of each wing segment comprise a modified nucleotide.

20. The oligonucleotide of any one of claims 1 and 9-19, wherein each nucleoside of each wing segment comprises a 2'O-methyl ribonucleoside (m).

21. The oligonucleotide of claim 20, wherein the oligonucleotide has up to 12 2'O-methyl ribonucleosides.

22. The oligonucleotide of any one of claims 1 and 9-21, wherein the nucleobase sequence of the oligonucleotide consists of 17-21 contiguous nucleobases complementary to an equal length portion of SEQ ID NO: 302.

23. An oligonucleotide comprising
mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmAmA/isp18//isp18//3CholTEG/

(SEQ ID NO: 225), wherein the oligonucleotide is 20 nucleotides in length, wherein m is a 2'O methyl, and wherein * is a phosphorothioate modification.

24. An oligonucleotide comprising

5 mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/
(SEQ ID NO: 288), wherein the oligonucleotide is 20 nucleotides in length, wherein m is a 2'O methyl, and wherein * is a phosphorothioate modification.

25. An oligonucleotide comprising

10 mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC/isp18//isp18//3CholTEG/
(SEQ ID NO: 291), wherein the oligonucleotide is 20 nucleotides in length, wherein m is a 2'O methyl, and wherein * is a phosphorothioate modification.

26. A stable self-assembling nanostructure, comprising

15 a core having an oligonucleotide shell comprised of an antisense oligonucleotide 18 to 21 linked nucleosides in length targeted to Interleukin 17 receptor (IL-17RA) positioned on the exterior of the core.

27. The nanostructure of claim 20, wherein the antisense oligonucleotide is 18

20 nucleotides in length.

28. The nanostructure of claim 26 or 27, wherein IL-17RA has a sequence of SEQ ID NO: 302.

25 29. The nanostructure of claim 28, wherein less than all of the internucleoside linkages are phosphodiester.

30. The nanostructure of claim 26 or 27, wherein the antisense oligonucleotide has phosphorothioate internucleoside linkages.

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31. The nanostructure of claim 30, wherein less than all of the internucleoside linkages are phosphorothioate.

32. The nanostructure of any one of claims 26-31, wherein the antisense oligonucleotide has 2'O methyl modifications.

33. The nanostructure of claim 32, wherein less than all of the nucleotides include a 2'O methyl modification.

34. The nanostructure of claim 26, wherein the antisense oligonucleotide has 17 internucleoside linkages and wherein 6 central internucleoside linkages are phosphorothioate.

35. The nanostructure of any one of claims 26-34, wherein the antisense oligonucleotide has a nucleobase sequence complementary to a sequence comprising at least 8 contiguous nucleobases of a sequence recited in SEQ ID NO: 302.

36. The nanostructure of claim 35, wherein the antisense oligonucleotide is selected from the group consisting of
 mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmA/isp18//isp18//3CholTEG/
 (SEQ ID NO: 225);
 mCmCmCmA/CmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/
 (SEQ ID NO: 288); and
 mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC/isp18//isp18//3CholTEG/
 (SEQ ID NO: 291) wherein – refers to a phosphodiester bond, * refers to a phosphorothioate bond, and m refers to a O methyl.

37. The nanostructure of any one of claims 26-36, wherein the nanostructure includes 2-1,000 copies of the antisense oligonucleotide.

38. The nanostructure of claim 37, wherein the nanostructure includes at least two different antisense oligonucleotides.

39. The nanostructure of any one of claims 26-38, wherein the core is a solid or hollow core.

40. The nanostructure of any one of claims 26-38, wherein the core is a solid core and further comprising a lipid bilayer surrounding the core.

41. The nanostructure of claim 40, wherein the solid core is comprised of noble metals, including gold and silver, transition metals including iron and cobalt, metal oxides including silica, polymers or combinations thereof.

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42. The nanostructure of claim 40, wherein the core is a polymeric core and wherein the polymeric core is comprised of amphiphilic block copolymers, hydrophobic polymers including polystyrene, poly(lactic acid), poly(lactic co-glycolic acid), poly(glycolic acid), poly(caprolactone) and other biocompatible polymers.

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43. The nanostructure of any one of claims 26-38, wherein the core is a liposomal core.

44. The nanostructure of claim 43, wherein the liposomal core is comprised of one or more lipids selected from: 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dimyristoyl-sn-phosphatidylcholine (DMPC), 1-palmitoyl-2-oleoyl-sn-phosphatidylcholine (POPC), 1,2-distearoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DSPG), 1,2-dioleoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DOPG), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine (DOPE), and 1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine (DPPE), sphingolipids such as sphingosine, sphingosine phosphate, methylated sphingosines and sphinganine, ceramides, ceramide phosphates, 1-0 acyl ceramides, dihydroceramides, 2-hydroxy ceramides, sphingomyelin, glycosylated sphingolipids, sulfatides, gangliosides, phosphosphingolipids, and phytosphingosines of various lengths and saturation states and their derivatives, phospholipids such as phosphatidylcholines, lysophosphatidylcholines, phosphatidic acids, lysophosphatidic acids, cyclic LPA, phosphatidylethanolamines, lysophosphatidylethanolamines, phosphatidylglycerols, lysophosphatidylglycerols, phosphatidylserines, lysophosphatidylserines, phosphatidylinositols, inositol phosphates, LPI, cardiolipins, lysocardiolipins, bis(monoacylglycero) phosphates, (diacylglycero) phosphates, ether lipids, diphytanyl ether lipids, and plasmalogens of various lengths, saturation states, and their derivatives, sterols such as cholesterol, desmosterol, stigmasterol, lanosterol, lathosterol, diosgenin, sitosterol, zymosterol, zymostenol, 14-demethyl-lanosterol, cholesterol sulfate, DHEA, DHEA sulfate, 14-demethyl-14-dehydranosterol, sitostanol, campesterol, ether

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anionic lipids, ether cationic lipids, lanthanide chelating lipids, A-ring substituted oxysterols, B-ring substituted oxysterols, D-ring substituted oxysterols, side-chain substituted oxysterols, double substituted oxysterols, cholestanoic acid derivatives, fluorinated sterols, fluorescent sterols, sulfonated sterols, phosphorylated sterols, and polyunsaturated sterols of different lengths, saturation states, and derivatives thereof.

45. The nanostructure of any one of claims 26-38, wherein the core is a niosome.

46. A multiplex antisense oligonucleotide spherical nucleic acid (mASO-SNA),
comprising

a core having an oligonucleotide shell comprised of an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a first gene and an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a second gene, wherein the core is a solid surrounded by a lipid bilayer or a liposome or lipoplex complex core and the oligonucleotide shell is positioned on the exterior of the core.

47. The mASO-SNA of claim 46, wherein the first gene and the second gene are associated with a disease.

48. The mASO-SNA of claims 46 or 47, wherein the disease is an inflammatory disorder.

49. The mASO-SNA of claims 46 or 47, wherein the disease is psoriasis.

50. The mASO-SNA of any one of claims 46-49, wherein the first gene and the second gene are associated with a target pathway.

51. The mASO-SNA of any one of claims 46-50, further comprising an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a third gene.

52. The mASO-SNA of any one of claims 46-51, wherein the first gene is an Interleukin 17 receptor (IL-17RA).

53. The mASO-SNA of any one of claims 46-52, wherein the second gene is TNF.

54. The mASO-SNA of any one of claims 46-53, wherein the first gene and the second gene are present in an approximate equimolar amount in the oligonucleotide shell.

5 55. A method for treating a disorder, comprising:
administering to a subject having a disorder a multiplex antisense oligonucleotide spherical nucleic acid (mASO-SNA), comprising a core having an oligonucleotide shell comprised of an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a first gene and an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a
10 second gene, wherein the core is a solid surrounded by a lipid bilayer or a liposome or lipoplex complex core and the oligonucleotide shell is positioned on the exterior of the core in an effective amount to treat the disorder.

56. The method of claim 55, wherein the disorder is an inflammatory disorder.

15 57. The method of claim 55, wherein the mASO-SNA produces simultaneous mRNA knock-down of the first and second gene.

58. The method of claim 55, wherein the first gene and the second gene are associated
20 with a target pathway.

59. The method of claim 58, wherein the mASO-SNA produces additive knock-down of the target pathway.

25 60. The method of any one of claims 55-59, wherein the disorder is psoriasis.

61. A method for treating an inflammatory disorder, comprising:
administering to a subject having an inflammatory disorder a composition comprising the oligonucleotide of any one of claims 1-25 or the nanostructure of any one of claims 26-44
30 in an effective amount to treat the inflammatory disorder.

62. The method of claim 61, wherein the inflammatory disorder is selected from the group consisting of an autoimmune disease, an infectious disease, transplant rejection or graft-versus-host disease, malignancy, a pulmonary disorder, an intestinal disorder, a cardiac

disorder, sepsis, a spondyloarthropathy, a metabolic disorder, anemia, pain, a hepatic disorder, a skin disorder, a nail disorder, rheumatoid arthritis, psoriasis, psoriasis in combination with psoriatic arthritis, ulcerative colitis, Crohn's disease, vasculitis, Behcet's disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disorder (COPD),
5 idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriatic arthritis, and chronic plaque psoriasis.

63. The method of claim 61, wherein the inflammatory disorder is selected from the
10 group consisting of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, allergy, multiple sclerosis, autoimmune diabetes, autoimmune uveitis, and nephritic syndrome.

64. A method for reducing expression levels of IL-17 receptor *in vivo*, comprising:
15 administering to a subject a composition comprising the oligonucleotide of any one of claims 1-25 or the nanostructure of any one of claims 26-44 in an effective amount to reduce IL-17 receptor levels *in vivo*.

65. The mASO-SNA of any one of claims 46-54, wherein the first gene, the second
20 gene, and the third gene are associated with a target pathway.

66. The mASO-SNA of any one of claims 46-54, wherein the first gene and the second gene are associated with different target pathways.

25 67. The mASO-SNA of any one of claims 46-54, wherein the first gene, the second gene and the third gene are associated with different target pathways.

68. The mASO-SNA of any one of claims 46-51, wherein the first gene is an interleukin-4 receptor (IL-4R).

30

69. The mASO-SNA of any one of claims 46-53, wherein the second gene is interleukin-1 beta (IL-1 β).

70. The mASO-SNA of any one of claims 46-54, wherein the third gene is connective tissue growth factor (CTGF).

71. The mASO-SNA of any one of claims 46-54, wherein the first gene, the second
5 gene, and the third gene are present in an approximate equimolar amount in the oligonucleotide shell.

72. A pharmaceutical composition, comprising a stable self-assembling nanostructure, wherein the self-assembling nanostructure comprises a core having an oligonucleotide shell
10 comprised of an antisense oligonucleotide 18 to 21 linked nucleosides in length targeted to interleukin 17 receptor (IL-17R) positioned on the exterior of the core.

73. The pharmaceutical composition of claim 72, wherein the antisense oligonucleotide is 18 nucleotides in length.

74. The pharmaceutical composition of claims 72 or 73, wherein IL-17RA has a sequence of SEQ ID NO: 302.

75. The pharmaceutical composition of any one of claims 72-74, wherein less than all
20 of the internucleoside linkages are phosphodiester.

76. The pharmaceutical composition of any one of claims 72-74, wherein the antisense oligonucleotide has phosphorothioate internucleoside linkages.

77. The pharmaceutical composition of claim 76, wherein less than all of the
25 internucleoside linkages are phosphorothioate.

78. The pharmaceutical composition of any one of claims 72-77, wherein the antisense oligonucleotide has 2'O methyl modifications.

79. The pharmaceutical composition of claim 78, wherein less than all of the
30 nucleotides include a 2'O methyl modification.

80. The pharmaceutical composition of claim 72, wherein the antisense oligonucleotide has 17 internucleoside linkages and wherein 6 central internucleoside linkages are phosphorothioate.

5 81. The pharmaceutical composition of any one of claims 72-80, wherein the antisense oligonucleotide has a nucleobase sequence complementary to a sequence comprising at least 8 contiguous nucleobases of a sequence recited in SEQ ID NO: 302.

82. The pharmaceutical composition of claim 81, wherein the antisense
 10 oligonucleotide is selected from the group consisting of
 mGmCmUmUmGmGG*C*A*G*G*T*mGmGmUmGmA/isp18//isp18//3CholTEG/
 (SEQ ID NO: 225);
 mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/
 (SEQ ID NO: 288); and
 15 mGmUmAmGmGmGmCmGmUG*T*G*T*G*G*mGmUmC/isp18//isp18//3CholTEG/
 (SEQ ID NO: 291) wherein – refers to a phosphodiester bond, * refers to a phosphorothioate bond, and m refers to a O methyl.

83. The pharmaceutical composition of any one of claims 72-82, wherein the
 20 pharmaceutical composition comprises a gel vehicle.

84. The pharmaceutical composition of any one of claims 72-82, wherein the pharmaceutical composition comprises one or more of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), diethylene glycol monoethyl ether (Transcutol P), glycerin,
 25 hydroxyethyl cellulose, methylparaben, propylparaben, disodium EDTA, sodium metabisulfite and water.

85. The pharmaceutical composition of claim 84, wherein the pharmaceutical composition comprises at least 0.00007%
 30 mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/
 (SEQ ID NO: 288), at least 0.0003801% DOPC, at least 25% diethylene glycol monoethyl ether (Transcutol P), at least 5% glycerin, at least 1% hydroxyethyl cellulose, at least 0.15% methylparaben, at least 0.05% propylparaben, at least 0.1% disodium EDTA, at least 0.2% sodium metabisulfite, and at least 68.5% water.

86. The pharmaceutical composition of claim 84, wherein the pharmaceutical composition comprises at least 0.007%

mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/

5 (SEQ ID NO: 288), at least 0.03801% DOPC, at least 25% diethylene glycol monoethyl ether (Transcutol P), at least 5% glycerin, at least 1% hydroxyethyl cellulose, at least 0.15% methylparaben, at least 0.05% propylparaben, at least 0.1% disodium EDTA, at least 0.2% sodium metabisulfite, and at least 68.45% water.

10 87. The pharmaceutical composition of claim 84, wherein the pharmaceutical composition comprises at least 0.01419%

mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/

(SEQ ID NO: 288), at least 0.2655% DOPC, at least 25% diethylene glycol monoethyl ether (Transcutol P), at least 5% glycerin, at least 1% hydroxyethyl cellulose, at least 0.15% methylparaben, at least 0.05% propylparaben, at least 0.1% disodium EDTA, at least 0.2% sodium metabisulfite, and at least 68.2% water.

88. The pharmaceutical composition of claim 84, wherein the pharmaceutical composition comprises at least 0.1419%

20 mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/ (SEQ ID NO: 288), at least 2.655% DOPC, at least 25% diethylene glycol monoethyl ether (Transcutol P), at least 5% glycerin, at least 1% hydroxyethyl cellulose, at least 0.15% methylparaben, at least 0.05% propylparaben, at least 0.1% disodium EDTA, at least 0.2% sodium metabisulfite, and at least 65.7% water.

25

89. The pharmaceutical composition of claim 84, wherein the pharmaceutical composition comprises at least 1.419%

mCmCmCmAmCmAmGG*G*G*C*A*T*mGmUmAmGmU/isp18//isp18//3CholTEG/

30 (SEQ ID NO: 288), at least 26.55% DOPC, at least 25% diethylene glycol monoethyl ether (Transcutol P), at least 5% glycerin, at least 1% hydroxyethyl cellulose, at least 0.15% methylparaben, at least 0.05% propylparaben, at least 0.1% disodium EDTA, at least 0.2% sodium metabisulfite, and at least 40.5% water.

90. A pharmaceutical composition, comprising the oligonucleotide of any one of claims 1-25.

5 91. The pharmaceutical composition of claim 90, wherein the pharmaceutical composition further comprises a gel vehicle.

92. The pharmaceutical composition of claims 90 or 91, wherein the pharmaceutical composition comprises one or more of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), diethylene glycol monoethyl ether (Transcutol P), glycerin, hydroxyethyl cellulose,
10 methylparaben, propylparaben, disodium EDTA, sodium metabisulfite and water.

93. A pharmaceutical composition, comprising the mASO-SNA of any one of claims 46-54.

15 94. The pharmaceutical composition of claim 93, wherein the pharmaceutical composition further comprises a gel vehicle.

95. The pharmaceutical composition of claims 93 or 94, wherein the pharmaceutical composition comprises one or more of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), diethylene glycol monoethyl ether (Transcutol P), glycerin, hydroxyethyl cellulose,
20 methylparaben, propylparaben, disodium EDTA, sodium metabisulfite and water.

96. A method for treating a disorder, comprising:

administering to a subject having a disorder a pharmaceutical composition comprising
25 a multiplex antisense oligonucleotide spherical nucleic acid (mASO-SNA), comprising a core having an oligonucleotide shell comprised of an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a first gene and an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a second gene, wherein the core is a solid surrounded by a lipid bilayer or a liposome or lipoplex complex core and the oligonucleotide shell is
30 positioned on the exterior of the core in an effective amount to treat the disorder.

97. The method of claim 96, wherein the pharmaceutical composition further comprises a gel vehicle.

98. The method of claim 96, wherein the pharmaceutical composition comprises one or more of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), diethylene glycol monoethyl ether (Transcutol P), glycerin, hydroxyethyl cellulose, methylparaben, propylparaben, disodium EDTA, sodium metabisulfite and water.

5

99. The method of any one of claims 96-98, wherein the disorder is an inflammatory disorder.

100. The method of any one of claims 96-99, wherein the mASO-SNA produces
10 simultaneous mRNA knock-down of the first and second gene.

101. The method of any one of claims 96-100, wherein the first gene and the second gene are associated with a target pathway.

15 102. The method of claim 101, wherein the mASO-SNA produces additive knock-down of the target pathway.

103. The method of any one of claims 96-102, wherein the disorder is psoriasis.

20 104. A method for treating an inflammatory disorder, comprising:
administering to a subject having an inflammatory disorder a pharmaceutical composition comprising the the oligonucleotide of any one of claims 1-25, the nanostructure of any one of claims 26-44, or the mASO-SNA of any one of claims 46-54 in an effective amount to treat the inflammatory disorder.

25

105. The method of claim 104, wherein the pharmaceutical composition further comprises a gel vehicle.

30 106. The method of claim 104, wherein the pharmaceutical composition comprises one or more of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), diethylene glycol monoethyl ether (Transcutol P), glycerin, hydroxyethyl cellulose, methylparaben, propylparaben, disodium EDTA, sodium metabisulfite and water.

107. The method of any one of claims 104-106, wherein the inflammatory disorder is selected from the group consisting of an autoimmune disease, an infectious disease, transplant rejection or graft-versus-host disease, malignancy, a pulmonary disorder, an intestinal disorder, a cardiac disorder, sepsis, a spondyloarthropathy, a metabolic disorder, anemia, pain, a hepatic disorder, a skin disorder, a nail disorder, rheumatoid arthritis, psoriasis, psoriasis in combination with psoriatic arthritis, ulcerative colitis, Crohn's disease, vasculitis, Behcet's disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disorder (COPD), idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriatic arthritis, and chronic plaque psoriasis.

108. The method of any one of claims 104-106, wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, allergy, multiple sclerosis, autoimmune diabetes, autoimmune uveitis, and nephritic syndrome.

109. A method for reducing expression levels of IL-17 receptor *in vivo*, comprising: administering to a subject a pharmaceutical composition comprising the oligonucleotide of any one of claims 1-25, the nanostructure of any one of claims 26-44, or the mASO-SNA of any one of claims 46-54 in an effective amount to reduce IL-17 receptor levels *in vivo*.

110. The method of claim 109, wherein the subject is a mammal.

111. The method of claim 109, wherein the subject is human.

112. The method of claims 109-111, wherein the pharmaceutical composition is in contact with a cell in the subject for at least 24 hours.

113. The method of any one of claims 109-112, wherein the pharmaceutical composition is a topical pharmaceutical composition.

114. A method for reducing expression levels of IL-17 receptor (IL-17R) *in vitro*, comprising:

contacting a cell with the oligonucleotide of any one of claims 1-25, the nanostructure of any one of claims 26-44, or the mASO-SNA of any one of claims 46-54 in an effective amount to reduce IL-17R levels in vitro.

5 115. The method of claim 114, wherein the cell is a human foreskin keratinocyte (HFK).

116. The method of claims 114 or 115, wherein the cell is contacted with the oligonucleotide, the nanostructure, or the mASO-SNA at a concentration of 1 nM, 10 nM,
10 100 nM, or 1000 nM.

117. The method of any one of claims 114-116, wherein the cell is contacted with the oligonucleotide, the nanostructure, or the mASO-SNA for 24 hours.

Fig. 1

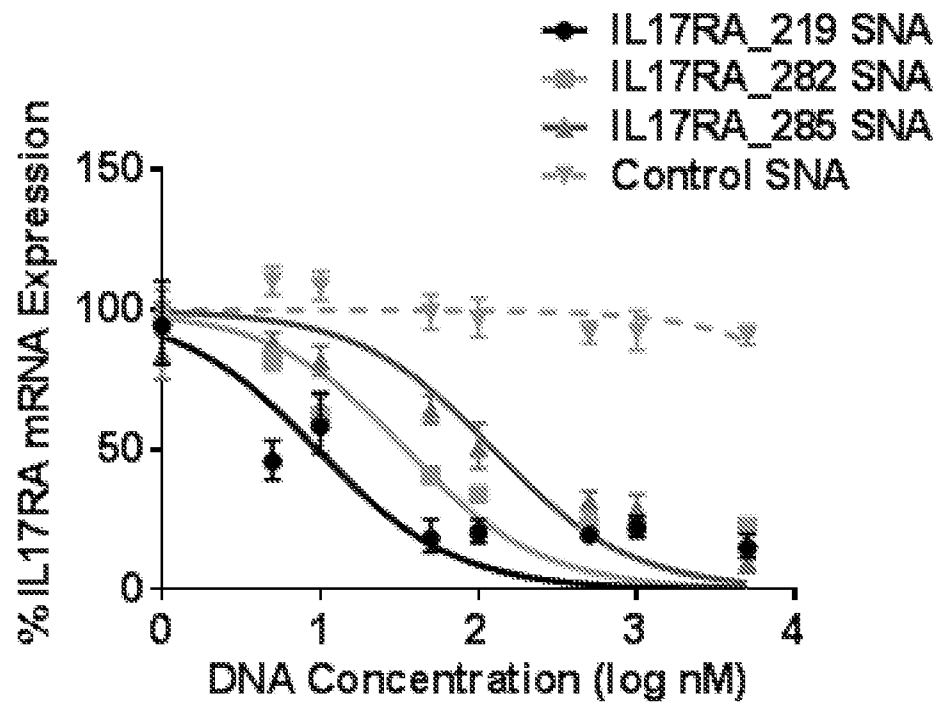


Fig. 2

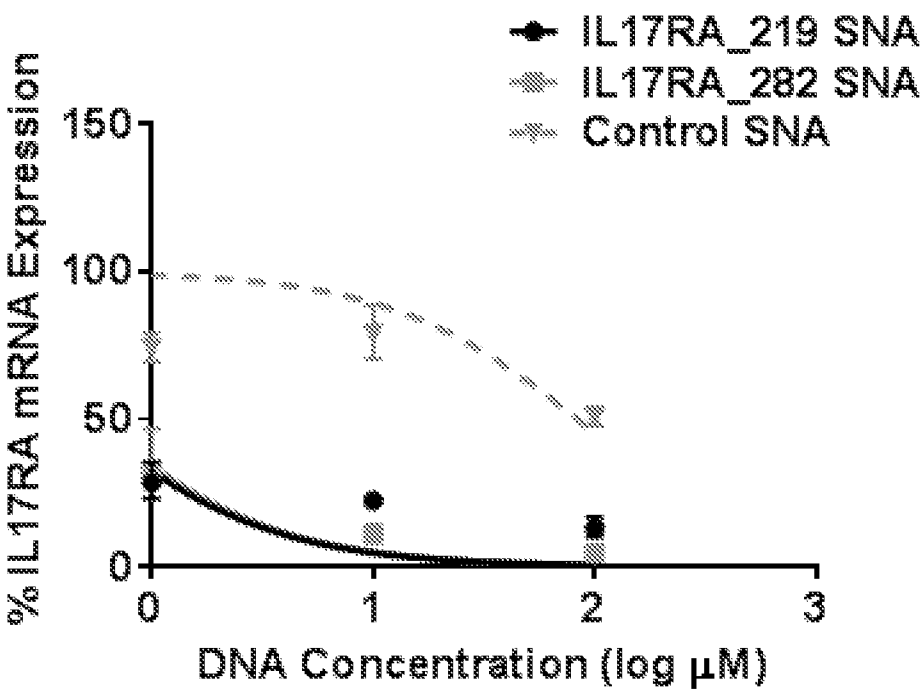


Fig. 3

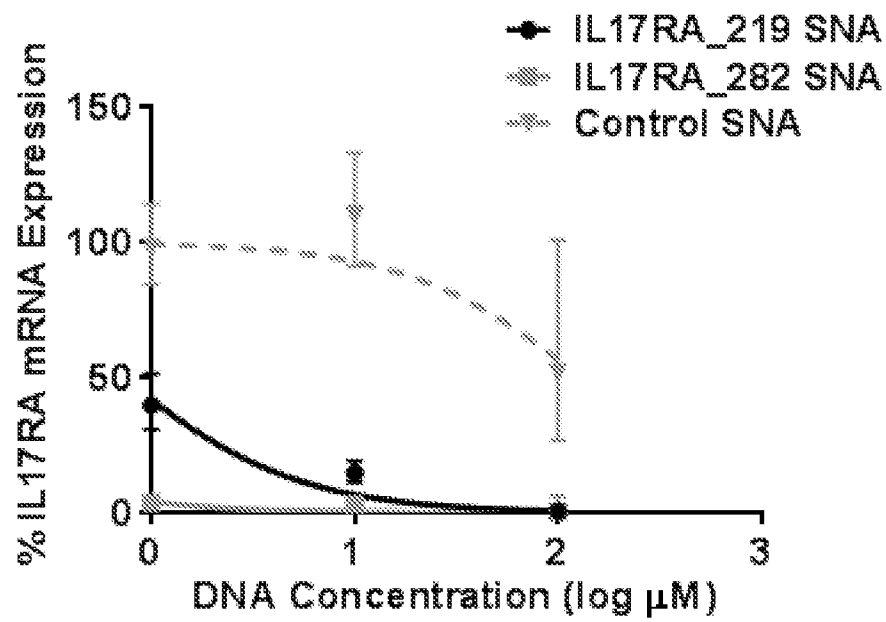


Fig. 4

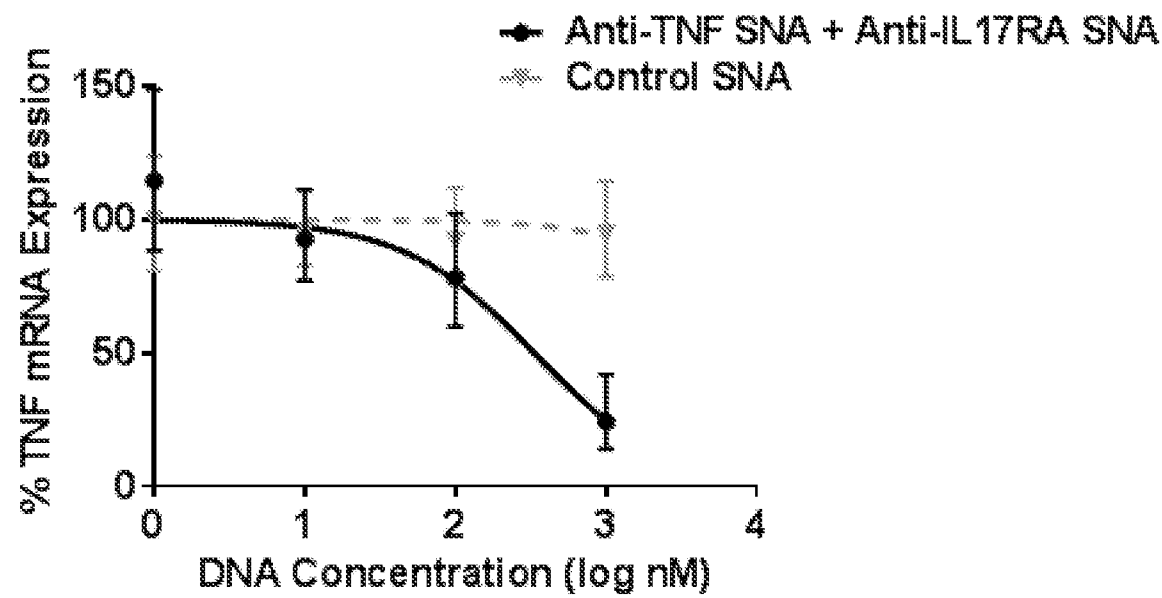
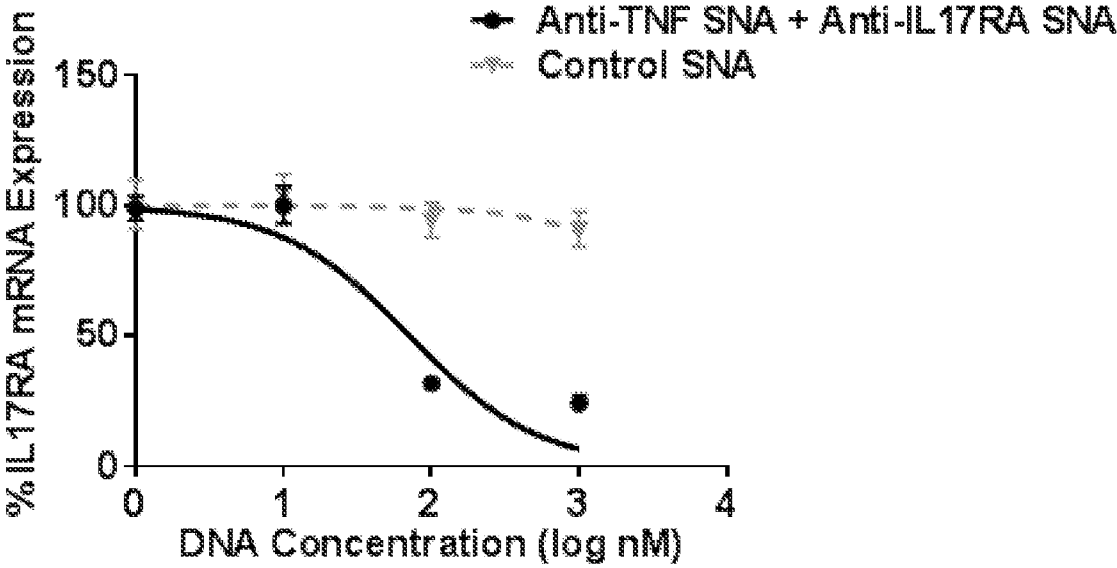
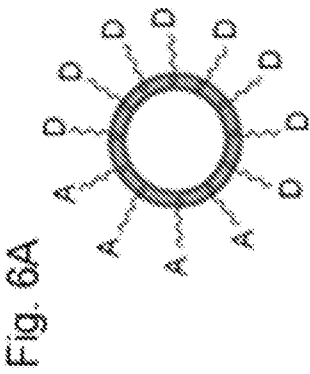
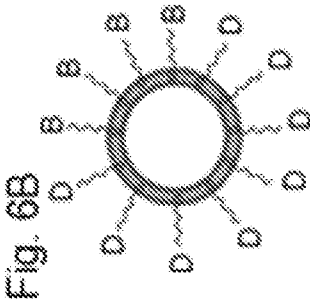
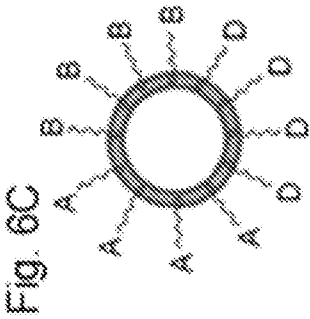
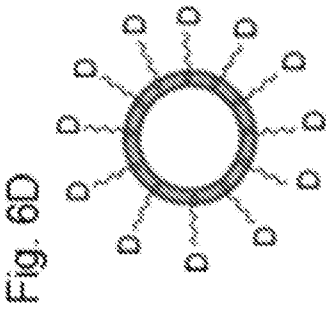


Fig. 5





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Fig. 7

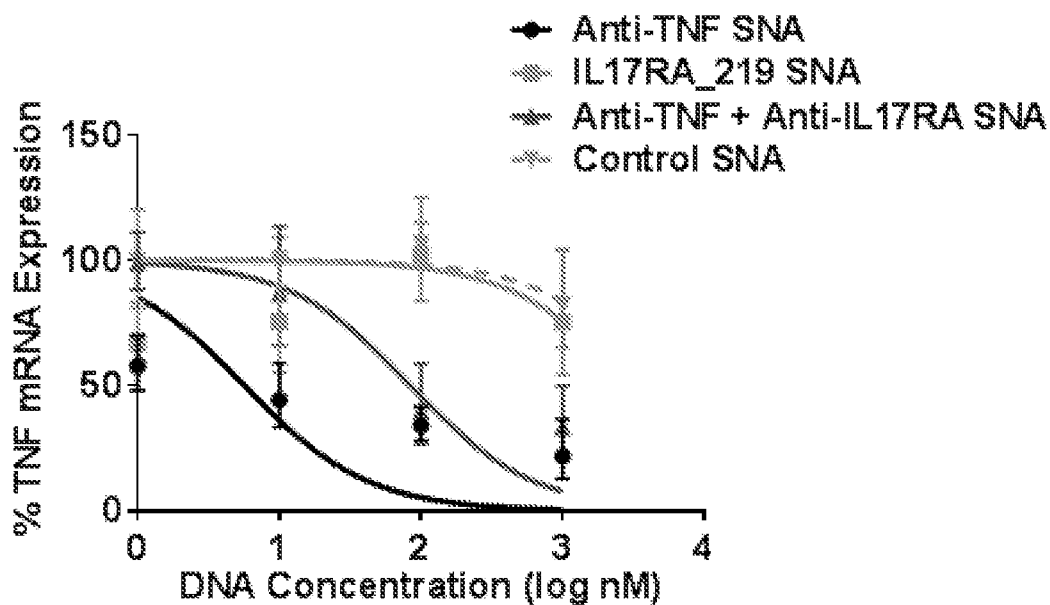
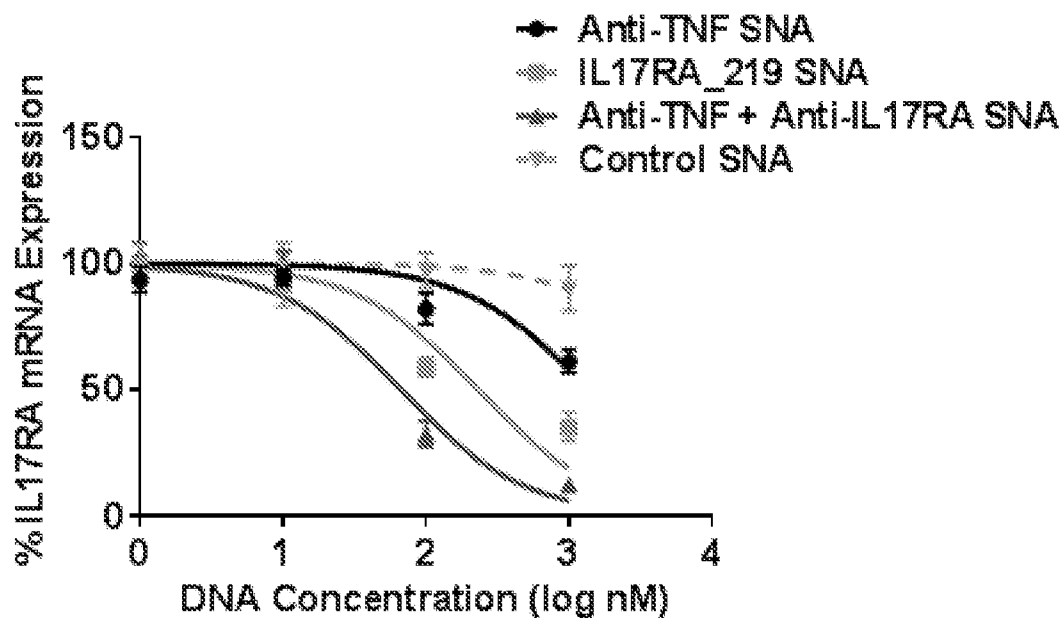


Fig. 8



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Fig. 9

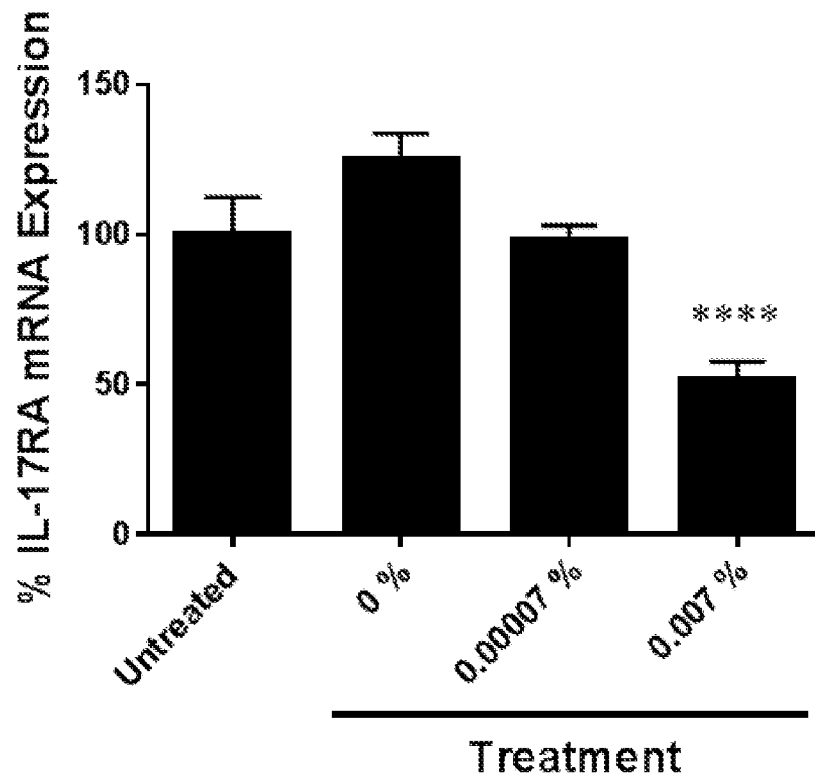
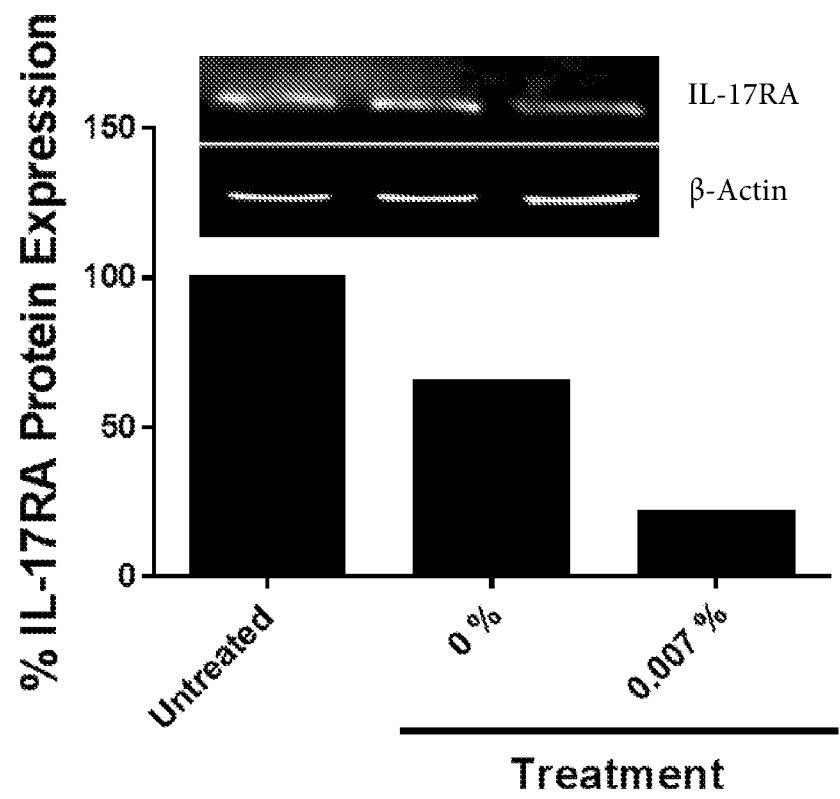


Fig. 10



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Fig. 11

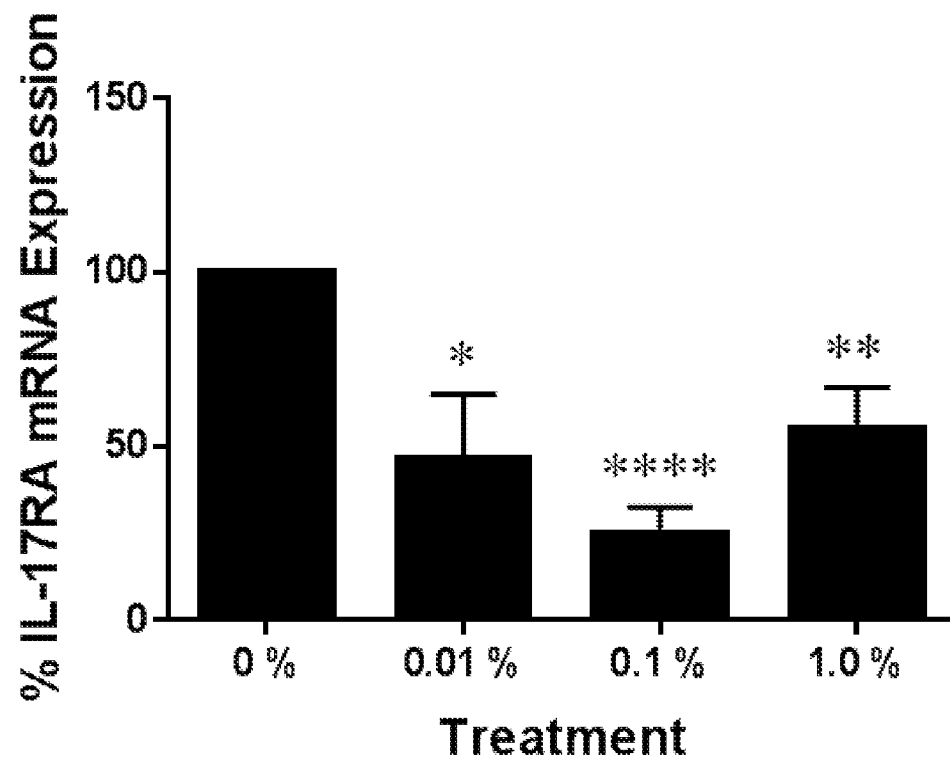


Fig. 12A

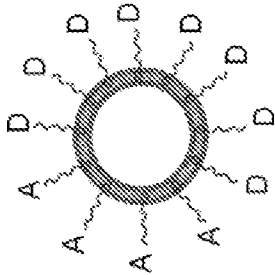


Fig. 12B

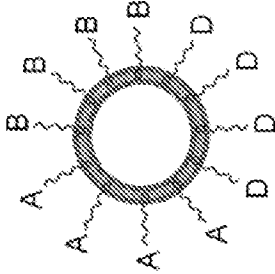


Fig. 12C

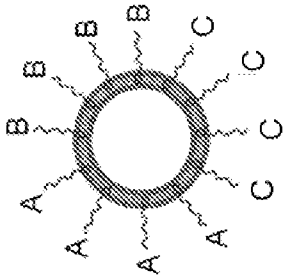


Fig. 12D

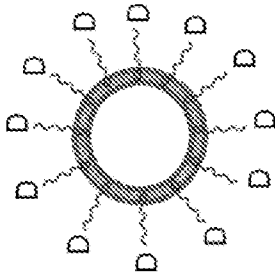
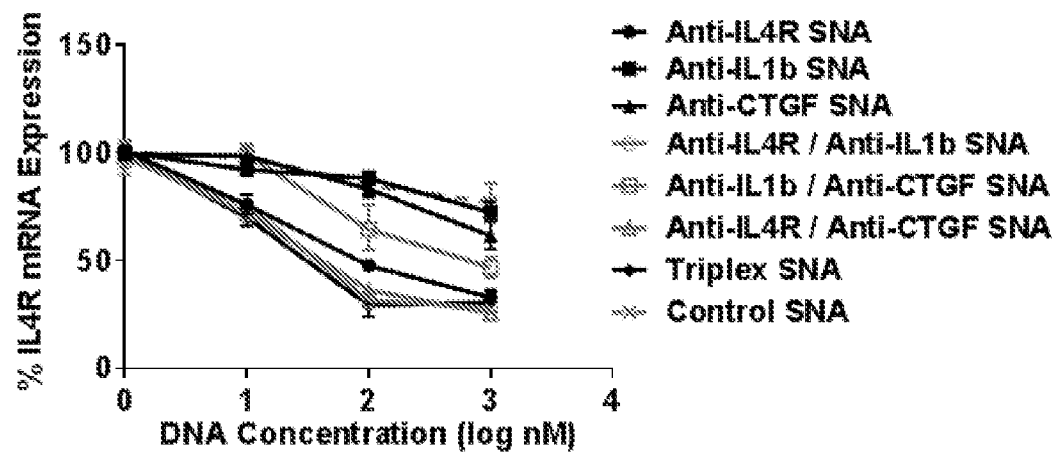


Fig. 13



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/031428

A. CLASSIFICATION OF SUBJECT MATTER

C12N 15/113 (2010.01) A61K 31/712 (2006.01) A61K 31/7125 (2006.01) A61K 48/00 (2006.01) A61K 8/14 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPIAP, CAPLUS, BIOSIS, EMBASE, MEDLINE, TXTE, Patentscope, Google, Google Scholar.

Aurasense, Exicure, IL17RA, psoriasis, SNA, liposome, lipoplex, SNA, siRNA, Aurasense, Exicure, Richard Kang, Scott Mix, Ekambar Kandimalla and like keywords.

GenomeQuest: SEQ ID NOs: 302, 225, 288 and 291.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

☒ Further documents are listed in the continuation of Box C

☒ See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent but published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 25 August 2017		Date of mailing of the international search report 25 August 2017	
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustalia.gov.au		Authorised officer Brad Hoad AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262832586	

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/US2017/031428
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 8,933,046 B2 (Machuy et al.) 13 January 2015 Table 3	1-25
A	Monia, B., et al. "Nuclease resistance and antisense activity of modified oligonucleotides targeted to Ha-ras." Journal of Biological Chemistry, 1996, Vol. 271, pages 14533-14540. Figure 5, Oligonucleotide 12, 14	
A	US 5955589 A (Cook et al.) 21 September 1999 Example 7, Table 4	
A	McKay, R., et al. "Characterization of a potent and specific class of antisense oligonucleotide inhibitor of human protein kinase C- α expression." Journal of Biological Chemistry, 1999, Vol. 274, pages 1715-1722. Table 1, ISIS 8329 and 9605, Figure 2, Figure 5	
A	WO 2015/195628 A2 (ARROWHEAD RESEARCH CORPORATION) 23 December 2015 Figure on page 31, Table 3A, Table 4, Table 5A	
A	Khmelniskaia, Alena, et al. "Effect of anchor positioning on binding and diffusion of elongated 3D DNA nanostructures on lipid membranes." Journal of Physics D: Applied Physics, 2016, Vol. 49 (2016): 194001. abstract, Figure 5	
A	WO 2015/013675 A1 (AURASENSE THERAPEUTICS, LLC) 29 January 2015 SEQ ID NO: 103-108	
A	WO 2015/153975 A1 (AURASENSE THERAPEUTICS, LLC) 08 October 2015 Abstract, claims 1-2	
A	Radovic-Moreno, Aleksandar F., et al. "Immunomodulatory spherical nucleic acids." Proceedings of the National Academy of Sciences, 2015, Vol. 112, pages 3892-3897. page 3894, first paragraph	
X	Aurasense Therapeutics, NIH grant, "Topically-delivered Target Gene Suppression of Immune Activation in Psoriasis - David Giljohann", Accessed on 02 August 2017 from http://grantome.com/grant/NIH/R41-AR066438-01 Accessible online on 21 February 2016 as verified through Wayback Machine. Aims 1-3	26-117
A	WO 2016/057549 A1 (AURASENSE THERAPEUTICS, LLC) 14 April 2016 Table 4, Figure 5B, Example 6	
P,X	WO 2016/115320 A1 (EXICURE, INC) 21 July 2016 SEQ ID NOs: 66-71, claim 39	1-117
Form PCT/ISA/210 (fifth sheet) (July 2009)		

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Supplemental Box**Continuation of: Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1-25, 90-92 (completely); 61-64, 104-117 (partially) are directed to a single stranded modified oligonucleotide containing a gap sequence comprising phosphorothioate internucleoside linkages wherein the wings segments contain all phosphodiester linkages, wherein at least some nucleosides of each wing segment comprise a modified nucleotide, and wherein the sequence of the oligonucleotide is complimentary to 10-30 contiguous nucleotides of a portion of SEQ ID NO: 302. This invention further includes methods of using said oligonucleotide, self-assembling structures, mASO-SNAs and compositions containing said oligonucleotide. The feature of a single stranded modified oligonucleotide containing a gap sequence comprising phosphorothioate internucleoside linkages wherein the wings segments contain all phosphodiester linkages, wherein at least some nucleosides of each wing segment comprise a modified nucleotide, and wherein the sequence of the oligonucleotide is complimentary to 10-30 contiguous nucleotides of a portion of SEQ ID NO: 302 is specific to this group of claims.
- Claims 26-45, 72-89 (completely); 61-64, 104-117 (partially) are directed to a stable self-assembling nanostructure comprising a core having an oligonucleotide shell comprised of an antisense oligonucleotide 18-21 linked nucleosides in length targeted to IL-17RA. The invention further includes methods of using said self-assembling molecule and compositions containing said self-assembling molecule. The feature of a stable self-assembling nanostructure comprising a core having an oligonucleotide shell comprised of an antisense oligonucleotide 18-21 linked nucleosides in length targeted to IL-17RA is specific to this group of claims.
- Claims 46-60, 65-71, 90-103 (completely); 104-117 (partially) are directed to a mASO-SNA comprising a core having an oligonucleotide shell comprised of an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a first gene and an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a second gene wherein the core is a solid surrounded by a lipid bilayer or a liposome or lipoplex complex core and the oligonucleotide shell is positioned on the exterior of the core. The invention further includes methods of using said mASO-SNA and compositions containing said mASO-SNA. The feature of a mASO-SNA comprising a core having an oligonucleotide shell comprised of an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a first gene and an antisense oligonucleotide 10 to 30 linked nucleosides in length targeted to a second gene wherein the core is a solid surrounded by a lipid bilayer or a liposome or lipoplex complex core and the oligonucleotide shell is positioned on the exterior of the core is specific to this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions and which provides a technical relationship among them is an antisense oligonucleotide.

However this feature does not make a contribution over the prior art because it is disclosed in:

US 8,933,046 B2 (Machuy et al)

Therefore in the light of this document this common feature cannot be a special technical feature. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a posteriori*.

Inventions 1 and 2 also contain the feature of an oligonucleotide targeting IL-17RA, however this feature is also disclosed in US 8,933,046 B2, and as such cannot be considered a unifying feature.

Form PCT/ISA/210 (Supplemental Box) (July 2009)

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 8,933,046 B2	13 January 2015	US 2013004502 A1	03 Jan 2013
		US 8933046 B2	13 Jan 2015
		AU 2010334799 A1	12 Jul 2012
		CA 2784547 A1	30 Jun 2011
		EP 2516645 A1	31 Oct 2012
		JP 2013515697 A	09 May 2013
		SG 181823 A1	30 Jul 2012
		WO 2011076873 A1	30 Jun 2011
US 5955589 A	21 September 1999	US 5955589 A	21 Sep 1999
		AU 8313091 A	17 Mar 1992
		AU 641539 B2	23 Sep 1993
		AU 8418491 A	02 Mar 1992
		AU 649067 B2	12 May 1994
		AU 8439391 A	17 Mar 1992
		AU 649717 B2	02 Jun 1994
		AU 7179891 A	05 Aug 1991
		AU 651569 B2	28 Jul 1994
		AU 7747091 A	18 Sep 1991
		AU 652152 B2	18 Aug 1994
		AU 7775391 A	27 Nov 1991
		AU 654816 B2	24 Nov 1994
		AU 8500791 A	17 Mar 1992
		AU 655937 B2	19 Jan 1995
		AU 8440391 A	17 Mar 1992
		AU 661662 B2	03 Aug 1995
		AU 1998692 A	30 Dec 1992
		AU 662538 B2	07 Sep 1995
		AU 2150292 A	30 Dec 1992
		AU 666121 B2	01 Feb 1996
		AU 5167393 A	26 Apr 1994
		AU 668604 B2	09 May 1996
		AU 3427593 A	28 Jul 1993
		AU 669353 B2	06 Jun 1996
		AU 2249792 A	12 Jan 1993
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
Form PCT/ISA/210 (Family Annex)(July 2009)			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		AU 672175 B2	26 Sep 1996
		AU 4840193 A	29 Mar 1994
		AU 673193 B2	31 Oct 1996
		AU 3802593 A	21 Oct 1993
		AU 675638 B2	13 Feb 1997
		AU 7723394 A	22 Mar 1995
		AU 679566 B2	03 Jul 1997
		AU 5295993 A	26 Apr 1994
		AU 680449 B2	31 Jul 1997
		AU 1186095 A	13 Jun 1995
		AU 687954 B2	05 Mar 1998
		AU 7398194 A	06 Feb 1995
		AU 688354 B2	12 Mar 1998
		AU 6449896 A	05 Dec 1996
		AU 690858 B2	30 Apr 1998
		AU 6252896 A	24 Dec 1996
		AU 698739 B2	05 Nov 1998
		AU 7007198 A	30 Jul 1998
		AU 710972 B2	30 Sep 1999
		AU 2747497 A	05 Jan 1998
		AU 712228 B2	04 Nov 1999
		AU 2624497 A	06 Nov 1997
		AU 713740 B2	09 Dec 1999
		AU 2119297 A	02 Sep 1997
		AU 715760 B2	10 Feb 2000
		AU 7103398 A	30 Oct 1998
		AU 725047 B2	05 Oct 2000
		AU 8775098 A	08 Mar 1999
		AU 730916 B2	22 Mar 2001
		AU 7563898 A	24 Nov 1998
		AU 731088 B2	22 Mar 2001
		AU 8289998 A	08 Feb 1999
		AU 732144 B2	12 Apr 2001
		AU 4572799 A	19 Jun 2000
		AU 753245 B2	10 Oct 2002
		AU 4006899 A	06 Dec 1999
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
Form PCT/ISA/210 (Family Annex)(July 2009)			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		AU 757894 B2	13 Mar 2003
		AU 4691000 A	17 Nov 2000
		AU 762212 B2	19 Jun 2003
		AU 6260499 A	19 Jun 2000
		AU 763066 B2	10 Jul 2003
		AU 6952800 A	31 Jan 2001
		AU 770526 B2	26 Feb 2004
		AU 4236902 A	04 Jul 2002
		AU 777034 B2	30 Sep 2004
		AU 1102300 A	26 Apr 2000
		AU 1707099 A	16 Jun 1999
		AU 1783002 A	27 May 2002
		AU 2180700 A	24 Jul 2000
		AU 2296995 A	16 Nov 1995
		AU 2606000 A	10 Apr 2001
		AU 2874892 A	21 May 1993
		AU 2916292 A	21 May 1993
		AU 3567899 A	08 Nov 1999
		AU 3653302 A	27 May 2002
		AU 3794493 A	05 Oct 1993
		AU 3892395 A	19 Apr 1996
		AU 4007899 A	06 Dec 1999
		AU 4158602 A	18 Jun 2002
		AU 4167499 A	17 Jan 2000
		AU 4193700 A	23 Oct 2000
		AU 4248097 A	26 Mar 1998
		AU 4313299 A	13 Dec 1999
		AU 4337400 A	14 Nov 2000
		AU 4342902 A	24 Jun 2002
		AU 4371296 A	17 Jun 1996
		AU 4383093 A	24 Jan 1994
		AU 4570699 A	05 Jan 2000
		AU 4576999 A	17 Jan 2000
		AU 4684099 A	05 Jan 2000
		AU 4684993 A	14 Feb 1994
		AU 4847900 A	05 Dec 2000
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		AU 4848793 A	12 Apr 1994
		AU 4894097 A	24 Apr 1998
		AU 5314999 A	07 Feb 2000
		AU 5344899 A	28 Feb 2000
		AU 5375896 A	16 Oct 1996
		AU 5788599 A	13 Jun 2000
		AU 6091200 A	19 Mar 2001
		AU 6361994 A	26 Sep 1994
		AU 6803000 A	22 Jan 2001
		AU 6968898 A	11 Nov 1998
		AU 7683394 A	22 Mar 1995
		AU 8031100 A	08 May 2001
		AU 8865201 A	22 Mar 2002
		AU 8896901 A	26 Mar 2002
		AU 8908501 A	02 Apr 2002
		AU 9070401 A	26 Mar 2002
		AU 9070601 A	26 Mar 2002
		AU 9492601 A	15 Apr 2002
		AU 9641201 A	08 Apr 2002
		AU 2002243748 A1	28 Aug 2002
		AU 2002309820 A1	09 Dec 2002
		AU 2002315554 A1	03 Mar 2003
		AU 2002316318 A1	08 Jan 2003
		AU 2002318283 A1	17 Feb 2003
		AU 2002319635 A1	17 Feb 2003
		AU 2002320561 A1	17 Feb 2003
		AU 2002332923 A1	24 Mar 2003
		AU 2002333623 A1	24 Mar 2003
		AU 2002335846 A1	28 Apr 2003
		AU 2002341548 A1	03 Mar 2003
		AU 2002341847 A1	14 Apr 2003
		AU 2002346631 A1	23 Jun 2003
		AU 2002347809 A1	22 Apr 2003
		AU 2002349389 A1	19 May 2003
		AU 2002350042 A1	12 May 2003
		AU 2002353074 A1	23 Jun 2003
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		AU 2002353076 A1	23 Jun 2003
		AU 2002353153 A1	30 Jun 2003
		AU 2002357101 A1	09 Jul 2003
		AU 2002357102 A1	30 Jun 2003
		AU 2002357239 A1	30 Jun 2003
		AU 2002359574 A1	23 Jun 2003
		AU 2002360336 A1	19 May 2003
		AU 2002360639 A1	24 Jul 2003
		AU 2002361591 A1	26 May 2003
		AU 2002361620 A1	10 Jun 2003
		AU 2002361638 A1	10 Jun 2003
		AU 2002361639 A1	26 May 2003
		AU 2002362042 A1	17 Jun 2003
		AU 2002362139 A1	30 Jun 2003
		AU 2002362757 A1	22 Apr 2003
		AU 2002365813 A1	17 Jun 2003
		AU 2002365920 A1	02 Sep 2003
		AU 2002366353 A1	30 Jun 2003
		AU 2002366788 A1	09 Jul 2003
		AU 2002367567 A1	09 Sep 2003
		AU 2003230301 A1	11 Nov 2003
		AU 2003236510 A1	31 Dec 2003
		AU 2003237260 A1	19 Dec 2003
		AU 2003237382 A1	19 Dec 2003
		AU 2003237469 A1	22 Dec 2003
		AU 2003238222 A1	31 Dec 2003
		AU 2003239226 A1	22 Dec 2003
		AU 2003239579 A1	31 Dec 2003
		AU 2003243472 A1	22 Dec 2003
		AU 2003243486 A1	22 Dec 2003
		AU 2003243589 A1	31 Dec 2003
		AU 2003245552 A1	31 Dec 2003
		AU 2003251387 A1	19 Dec 2003
		AU 2003251530 A1	31 Dec 2003
		AU 2003251807 A1	02 Feb 2004
		AU 2003252072 A1	09 Feb 2004
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		AU 2003252907 A1	06 Nov 2003
		AU 2003253983 A1	09 Feb 2004
		AU 2003273545 A1	19 Dec 2003
		AU 2003280455 A1	19 Jan 2004
		AU 2003281327 A1	23 Jan 2004
		AU 2003281329 A1	23 Jan 2004
		AU 2003290966 A1	15 Jun 2004
		AU 2003294373 A1	09 Jul 2004
		AU 2003294420 A1	18 Jun 2004
		AU 2003294479 A1	18 Jun 2004
		AU 2003295453 A1	03 Jun 2004
		AU 2003296499 A1	30 Jun 2004
		AU 2003297554 A1	18 Jun 2004
		AU 2003302042 A1	15 Jun 2004
		BR 1100614 A	11 Apr 2000
		BR 1100617 A	13 Jun 2000
		BR 1100909 A	06 Jun 2000
		BR 9105935 A	17 Nov 1992
		BR 9106087 A	02 Feb 1993
		BR 9106418 A	04 May 1993
		BR 9106701 A	29 Jun 1993
		BR 9106743 A	20 Jul 1993
		BR 9106746 A	20 Jul 1993
		BR 9106751 A	17 Aug 1993
		BR 9106826 A	25 Jan 1994
		BR 9206026 A	27 Dec 1994
		BR 9206027 A	27 Dec 1994
		BR 9206156 A	17 Oct 1995
		BR 9406931 A	10 Sep 1996
		CA 2073500 A1	12 Jul 1991
		CA 2074523 A1	27 Aug 1991
		CA 2082044 A1	05 Nov 1991
		CA 2087731 A1	28 Jan 1992
		CA 2089376 A1	14 Feb 1992
		CA 2089377 A1	14 Feb 1992
		CA 2089563 A1	15 Feb 1992
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		CA 2089666 A1	17 Feb 1992
		CA 2103378 A1	22 Nov 1992
		CA 2103464 A1	22 Nov 1992
		CA 2111472 A1	23 Dec 1992
		CA 2121144 A1	29 Apr 1993
		CA 2122030 A1	29 Apr 1993
		CA 2126691 A1	08 Jul 1993
		CA 2130359 A1	06 Sep 1993
		CA 2132094 A1	30 Sep 1993
		CA 2138770 A1	06 Jan 1994
		CA 2140428 A1	03 Feb 1994
		CA 2143748 A1	17 Mar 1994
		CA 2145664 A1	14 Apr 1994
		CA 2146320 A1	14 Apr 1994
		CA 2166058 A1	19 Jan 1995
		CA 2170869 A1	09 Mar 1995
		CA 2177357 A1	01 Jun 1995
		CA 2181082 A1	13 Jul 1995
		CA 2223103 A1	12 Dec 1996
		CA 2246230 A1	21 Aug 1997
		CA 2256358 A1	04 Dec 1997
		CA 2285921 A1	15 Oct 1998
		CA 2289454 A1	05 Nov 1998
		CA 2296535 A1	21 Jan 1999
		CA 2301139 A1	25 Feb 1999
		CA 2312002 A1	10 Jun 1999
		CA 2331334 A1	06 Jan 2000
		CA 2333087 A1	25 Nov 1999
		CA 2353090 A1	08 Jun 2000
		CA 2353108 A1	08 Jun 2000
		CA 2373225 A1	09 Nov 2000
		CA 2378227 A1	04 Jan 2001
		CA 2384456 A1	15 Mar 2001
		CA 2437887 A1	22 Aug 2002
		CA 2443641 A1	17 Oct 2002
		CA 2491497 A1	15 Jan 2004
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		EP 0517859 A1	16 Dec 1992
		EP 0517859 B1	22 Jul 1998
		EP 0529008 A1	03 Mar 1993
		EP 0529008 B1	15 Dec 1999
		EP 0544713 A1	09 Jun 1993
		EP 0544713 B1	02 Jul 1997
		EP 0544716 A1	09 Jun 1993
		EP 0544716 B1	18 Dec 2002
		EP 0544757 A1	09 Jun 1993
		EP 0544757 B1	08 Oct 1997
		EP 0544792 A1	09 Jun 1993
		EP 0544792 B1	19 Nov 1997
		EP 0549615 A1	07 Jul 1993
		EP 0549615 B1	22 Feb 2006
		EP 0586520 A1	16 Mar 1994
		EP 0586520 B1	19 Apr 2000
		EP 0586570 A1	16 Mar 1994
		EP 0586570 B1	13 Sep 2000
		EP 0590082 A1	06 Apr 1994
		EP 0590082 B1	27 Oct 1999
		EP 0604409 A1	06 Jul 1994
		EP 0604409 B1	14 Jul 2004
		EP 0618925 A1	12 Oct 1994
		EP 0618925 B1	29 Aug 2001
		EP 0618925 B2	18 Apr 2012
		EP 0649429 A1	26 Apr 1995
		EP 0649429 B1	27 Aug 2008
		EP 0651759 A1	10 May 1995
		EP 0651759 B1	10 Dec 2003
		EP 0655088 A1	31 May 1995
		EP 0655088 B1	24 Jul 2002
		EP 0656790 A1	14 Jun 1995
		EP 0662003 A1	12 Jul 1995
		EP 0662003 B1	29 Jan 2003
		EP 0670897 A1	13 Sep 1995
		EP 0672180 A1	20 Sep 1995
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
Form PCT/ISA/210 (Family Annex)(July 2009)			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		EP 0672180 B1	16 Jan 2002
		EP 0672193 A1	20 Sep 1995
		EP 0672193 B1	14 Aug 2002
		EP 0692930 A1	24 Jan 1996
		EP 0714449 A1	05 Jun 1996
		EP 0716604 A1	19 Jun 1996
		EP 0716604 B1	16 Mar 2005
		EP 0724447 A1	07 Aug 1996
		EP 0724447 B1	07 May 2003
		EP 0728139 A1	28 Aug 1996
		EP 0728139 B1	13 Aug 2003
		EP 0731807 A1	18 Sep 1996
		EP 0731807 B1	17 Mar 2004
		EP 0734391 A1	02 Oct 1996
		EP 0734391 B1	12 Jun 2002
		EP 0737201 A1	16 Oct 1996
		EP 0742790 A1	20 Nov 1996
		EP 0746326 A1	11 Dec 1996
		EP 0758242 A1	19 Feb 1997
		EP 0817787 A1	14 Jan 1998
		EP 0831854 A1	01 Apr 1998
		EP 0881914 A1	09 Dec 1998
		EP 0881914 B1	18 Aug 2004
		EP 0903406 A1	24 Mar 1999
		EP 0918787 A1	02 Jun 1999
		EP 0975371 A1	02 Feb 2000
		EP 0975654 A1	02 Feb 2000
		EP 0981648 A1	01 Mar 2000
		EP 1003916 A1	31 May 2000
		EP 1004593 A2	31 May 2000
		EP 1009860 A1	21 Jun 2000
		EP 1016715 A1	05 Jul 2000
		EP 1036165 A1	20 Sep 2000
		EP 1044987 A2	18 Oct 2000
		EP 1044987 B1	15 Feb 2006
		EP 1071699 A1	31 Jan 2001
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		EP 1080225 A1	07 Mar 2001
		EP 1086116 A1	28 Mar 2001
		EP 1090025 A1	11 Apr 2001
		EP 1100897 A2	23 May 2001
		EP 1119580 A1	01 Aug 2001
		EP 1126025 A2	22 Aug 2001
		EP 1131465 A1	12 Sep 2001
		EP 1140971 A1	10 Oct 2001
		EP 1144690 A1	17 Oct 2001
		EP 1163373 A1	19 Dec 2001
		EP 1176965 A1	06 Feb 2002
		EP 1180113 A1	20 Feb 2002
		EP 1185696 A1	13 Mar 2002
		EP 1190099 A1	27 Mar 2002
		EP 1201676 A2	02 May 2002
		EP 1208110 A1	29 May 2002
		EP 1218395 A1	03 Jul 2002
		EP 1218395 B1	04 May 2005
		EP 1223173 A2	17 Jul 2002
		EP 1223173 B1	13 Jul 2005
		EP 1223988 A1	24 Jul 2002
		EP 1310555 A2	14 May 2003
		EP 1319014 A1	18 Jun 2003
		EP 1325019 A1	09 Jul 2003
		EP 1325019 B1	19 Jan 2011
		EP 1328537 A1	23 Jul 2003
		EP 1331011 A2	30 Jul 2003
		EP 1360334 A1	12 Nov 2003
		EP 1390386 A1	25 Feb 2004
		EP 1390536 A1	25 Feb 2004
		EP 1390547 A1	25 Feb 2004
		EP 1397516 A1	17 Mar 2004
		EP 1402063 A1	31 Mar 2004
		EP 1406915 A2	14 Apr 2004
		EP 1417335 A2	12 May 2004
		EP 1418179 A2	12 May 2004
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
Form PCT/ISA/210 (Family Annex)(July 2009)			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		EP 1419169 A1	19 May 2004
		EP 1436307 A1	14 Jul 2004
		EP 1436308 A2	14 Jul 2004
		EP 1436430 A2	14 Jul 2004
		EP 1443051 A2	04 Aug 2004
		EP 1444366 A2	11 Aug 2004
		EP 1448585 A2	25 Aug 2004
		EP 1448762 A2	25 Aug 2004
		EP 1451353 A2	01 Sep 2004
		EP 1458739 A2	22 Sep 2004
		EP 1461348 A2	29 Sep 2004
		EP 1461419 A2	29 Sep 2004
		EP 1461461 A2	29 Sep 2004
		EP 1461463 A2	29 Sep 2004
		EP 1465578 A2	13 Oct 2004
		EP 1532160 A2	25 May 2005
		EP 1579011 A2	28 Sep 2005
		EP 1695979 A2	30 Aug 2006
		EP 1695979 B1	06 Jul 2011
		EP 1743901 A2	17 Jan 2007
		EP 1806353 A1	11 Jul 2007
		FI 944276 A	15 Sep 1994
		FI 112379 B	28 Nov 2003
		FI 20030248 A	18 Feb 2003
		FI 113059 B	27 Feb 2004
		FI 935113 A	03 Jan 1994
		FI 113870 B	30 Jun 2004
		FI 923176 A	09 Jul 1992
		FI 923707 A	18 Aug 1992
		FI 924964 A	03 Nov 1992
		FI 930627 A	12 Feb 1993
		FI 930658 A	15 Feb 1993
		FI 935114 A	30 Dec 1993
		FI 950948 A	18 Apr 1995
		FI 951467 A	28 Mar 1995
		FI 951601 A	29 May 1995
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		FI 960089 A	07 Mar 1996
		HU T63170 A	28 Jul 1993
		HU T63430 A	30 Aug 1993
		HU T63650 A	28 Sep 1993
		HU T64474 A	28 Jan 1994
		HU T65941 A	29 Aug 1994
		HU T66378 A	28 Nov 1994
		HU 221806 B1	28 Jan 2003
		HU T68322 A	28 Jun 1995
		HU 217107 B	29 Nov 1999
		HU T69922 A	28 Sep 1995
		HU T69939 A	28 Sep 1995
		HU 217179 B	28 Dec 1999
		HU T70965 A	28 Nov 1995
		HU T73335 A	29 Jul 1996
		HU T75834 A	28 May 1997
		HU 219017 B	29 Jan 2001
		IE 921849 A1	02 Dec 1992
		IE 921850 A1	02 Dec 1992
		IL 106266 A	10 Mar 1998
		IL 106857 A	25 Jul 2005
		IL 145218 A	30 Dec 2010
		JP 2580091 B2	12 Feb 1997
		JP 2625257 B2	02 Jul 1997
		JP 2635216 B2	30 Jul 1997
		JP 2693643 B2	24 Dec 1997
		JP 2708960 B2	04 Feb 1998
		JP 2711180 B2	10 Feb 1998
		JP 2726754 B2	11 Mar 1998
		JP 2732544 B2	30 Mar 1998
		JP 2732546 B2	30 Mar 1998
		JP 2739769 B2	15 Apr 1998
		JP 2739774 B2	15 Apr 1998
		JP 2795538 B2	10 Sep 1998
		JP 2800848 B2	21 Sep 1998
		JP 2818031 B2	30 Oct 1998
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		JP 2823959 B2	11 Nov 1998
		JP 2879973 B2	05 Apr 1999
		JP 2937903 B2	23 Aug 1999
		JP 2948541 B2	13 Sep 1999
		JP 3015464 B2	06 Mar 2000
		JP 3131222 B2	31 Jan 2001
		JP 3256236 B2	12 Feb 2002
		JP 3335634 B2	21 Oct 2002
		JP 3349500 B2	25 Nov 2002
		JP 3349501 B2	25 Nov 2002
		JP 3349502 B2	25 Nov 2002
		JP 3484197 B2	06 Jan 2004
		JP 3527200 B2	17 May 2004
		JP 3535519 B2	07 Jun 2004
		JP 3553068 B2	11 Aug 2004
		JP 3585583 B2	04 Nov 2004
		JP 3998089 B2	24 Oct 2007
		JP 4397585 B2	13 Jan 2010
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2009)			

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2015/195628 A2	23 December 2015	WO 2015195628 A2	23 Dec 2015
		AR 100840 A1	02 Nov 2016
		AU 2015277376 A1	08 Dec 2016
		CA 2951700 A1	23 Dec 2015
		CN 106535917 A	22 Mar 2017
		EA 201692318 A1	30 Jun 2017
		EP 3157541 A2	26 Apr 2017
		MX 2016015870 A	27 Apr 2017
		TW 201620526 A	16 Jun 2016
		US 2015361427 A1	17 Dec 2015
WO 2015/013675 A1	29 January 2015	WO 2015013675 A1	29 Jan 2015
		AU 2014292928 A1	03 Mar 2016
		CA 2919273 A1	29 Jan 2015
		CN 105658241 A	08 Jun 2016
		EP 3024494 A1	01 Jun 2016
		JP 2016534094 A	04 Nov 2016
		KR 20160045726 A	27 Apr 2016
		US 2016194642 A1	07 Jul 2016
WO 2015/153975 A1	08 October 2015	WO 2015153975 A1	08 Oct 2015
		AU 2015240567 A1	20 Oct 2016
		EP 3129391 A1	15 Feb 2017
		US 2017175121 A1	22 Jun 2017
WO 2016/057549 A1	14 April 2016	WO 2016057549 A1	14 Apr 2016
		AU 2015328242 A1	27 Apr 2017
		CA 2963931 A1	14 Apr 2016
		CN 107002081 A	01 Aug 2017
		EP 3204499 A1	16 Aug 2017
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			

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INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/US2017/031428	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2016/115320 A1	21 July 2016	KR 20170063949 A	08 Jun 2017
		PE 06942017 A1	26 May 2017
		SG 11201702656W A	27 Apr 2017
		WO 2016115320 A1	21 Jul 2016
		AU 2016206658 A1	03 Aug 2017
		CA 2973702 A1	21 Jul 2016
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2009)			