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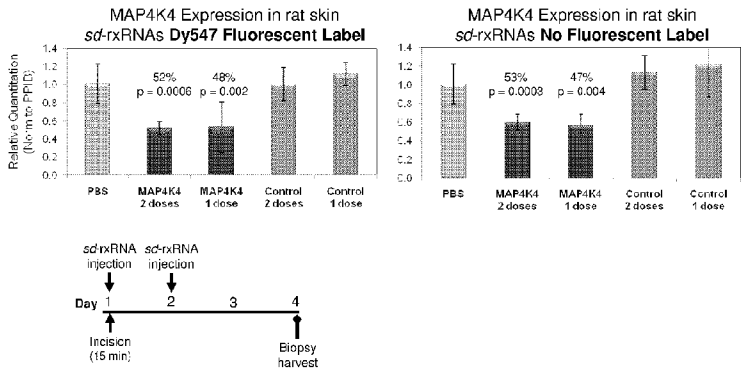
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(54) Title: RNA INTERFERENCE IN DERMAL AND FIBROTIC INDICATIONS

Figure 3

In vivo Silencing with *sd*-rxRNA Following Intradermal Injection (Rat)



(57) Abstract: The present invention relates to RNAi constructs with improved tissue and cellular uptake characteristics and methods of use of these compounds in dermal and fibrotic applications.

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— *with sequence listing part of description (Rule 5.2(a))*

RNA INTERFERENCE IN DERMAL AND FIBROTIC INDICATIONS

RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application Serial No. US 61/317,252, entitled "RNA INTERFERENCE IN SKIN INDICATIONS," filed on March 24, 2010, and U.S. Provisional Application Serial No. US 61/317,633, entitled "RNA INTERFERENCE IN SKIN INDICATIONS," filed on March 25, 2010, the entire disclosures of which are herein incorporated by reference in their entireties.

FIELD OF INVENTION

The invention pertains to the field of RNA interference (RNAi). The invention more specifically relates to nucleic acid molecules with improved *in vivo* delivery properties and their use for dermal and fibrotic indications.

BACKGROUND OF INVENTION

Complementary oligonucleotide sequences are promising therapeutic agents and useful research tools in elucidating gene functions. However, prior art oligonucleotide molecules suffer from several problems that may impede their clinical development, and frequently make it difficult to achieve intended efficient inhibition of gene expression (including protein synthesis) using such compositions *in vivo*.

A major problem has been the delivery of these compounds to cells and tissues. Conventional double-stranded RNAi compounds, 19-29 bases long, form a highly negatively-charged rigid helix of approximately 1.5 by 10-15 nm in size. This rod type molecule cannot get through the cell-membrane and as a result has very limited efficacy both *in vitro* and *in vivo*. As a result, all conventional RNAi compounds require some kind of a delivery vehicle to promote their tissue distribution and cellular uptake. This is considered to be a major limitation of the RNAi technology.

There have been previous attempts to apply chemical modifications to oligonucleotides to improve their cellular uptake properties. One such modification was the attachment of a cholesterol molecule to the oligonucleotide. A first report on this approach was by Letsinger *et al.*, in 1989. Subsequently, ISIS Pharmaceuticals, Inc.

(Carlsbad, CA) reported on more advanced techniques in attaching the cholesterol molecule to the oilgonucleotide (Manoharan, 1992).

With the discovery of siRNAs in the late nineties, similar types of modifications were attempted on these molecules to enhance their delivery profiles. Cholesterol molecules conjugated to slightly modified (Soutschek, 2004) and heavily modified (Wolfrum, 2007) siRNAs appeared in the literature. Yamada *et al.*, 2008 also reported on the use of advanced linker chemistries which further improved cholesterol mediated uptake of siRNAs. In spite of all this effort, the uptake of these types of compounds appears to be inhibited in the presence of biological fluids resulting in highly limited efficacy in gene silencing *in vivo*, limiting the applicability of these compounds in a clinical setting.

SUMMARY OF INVENTION

Described herein is the efficient *in vivo* delivery of sd-rxRNA molecules to the skin and the use of such molecules for gene silencing. This class of RNAi molecules has superior efficacy both *in vitro* and *in vivo* than previously described RNAi molecules. Molecules associated with the invention have widespread potential as therapeutics for disorders or conditions associated with compromised skin and fibrosis.

Aspects of the invention relate to double-stranded ribonucleic acids (dsRNAs) including a sense strand and an antisense strand wherein the antisense strand is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 2, 5, 6, 9, 11, 12, 13, 14, 15, 16, 17 and 23, and wherein the dsRNA is an sd-rxRNA.

Further aspects of the invention relate to double-stranded ribonucleic acids (dsRNAs) comprising a sense strand and an antisense strand wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 1-27, and wherein the dsRNA is an sd-rxRNA.

Further aspects of the invention relate to double-stranded ribonucleic acids (dsRNAs) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 2, 5, 6, 9, 11, 12, 13, 14, 15, 16, 17 and 23, and wherein the dsRNA is an rxRNAori.

Further aspects of the invention relate to double-stranded ribonucleic acids (dsRNAs) comprising a sense strand and an antisense strand wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 1-27, and wherein the dsRNA is an rxRNAori.

In some embodiments, the dsRNA is directed against CTGF. In some embodiments, the antisense strand of the dsRNA is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 11, 12 and 15. In some embodiments, the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 10, 11, 12, 15, 20 and 24.

In some embodiments, the sense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: SEQ ID NOs: 2463, 3429, 2443, 3445, 2459, 3493, 2465 and 3469. In some embodiments, the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: 2464, 3430, 4203, 3446, 2460, 3494, 2466 and 3470.

In certain embodiments, the sense strand comprises SEQ ID NO:2463 and the antisense strand comprises SEQ ID NO:2464. In certain embodiments, the sense strand comprises SEQ ID NO:3429 and the antisense strand comprises SEQ ID NO:3430.

In certain embodiments, the sense strand comprises SEQ ID NO:2443 and the antisense strand comprises SEQ ID NO:4203. In certain embodiments, the sense strand comprises SEQ ID NO:3445 and the antisense strand comprises SEQ ID NO:3446.

In certain embodiments, the sense strand comprises SEQ ID NO:2459 and the antisense strand comprises SEQ ID NO:2460. In certain embodiments, the sense strand comprises SEQ ID NO:3493 and the antisense strand comprises SEQ ID NO:3494.

In certain embodiments, the sense strand comprises SEQ ID NO:2465 and the antisense strand comprises SEQ ID NO:2466. In certain embodiments, the sense strand comprises SEQ ID NO:3469 and the antisense strand comprises SEQ ID NO:3470.

In some embodiments, the sense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: SEQ ID NOs: 1835, 1847, 1848 and 1849. In certain embodiments, the sense strand comprises a sequence selected from the group consisting of: SEQ ID NOs: 1835, 1847, 1848 and 1849.

In some embodiments, the dsRNA is hydrophobically modified. In certain embodiments, the dsRNA is linked to a hydrophobic conjugate.

Aspects of the invention relate to compositions comprising the dsRNA described herein. In some embodiments, the composition comprises dsRNA directed against genes encoding for more than one protein.

In some embodiments, the composition is formulated for delivery to the skin. In certain embodiments, the composition is in a neutral formulation. In some embodiments, the composition is formulated for topical delivery or for intradermal injection.

Aspects of the invention relate to methods comprising delivering any of the dsRNA described herein or a composition comprising any of the dsRNA described herein to the skin of a subject in need thereof.

Aspects of the invention relate to methods comprising administering to a subject in need thereof a therapeutically effective amount of a double stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 2, 5, 6, 9, 11, 12, 13, 14, 15, 16, 17 and 23, and wherein the dsRNA is an sd-rxRNA.

Further aspects of the invention relate to methods comprising administering to a subject in need thereof a therapeutically effective amount of a double stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 1-27, and wherein the dsRNA is an sd-rxRNA.

Further aspects of the invention relate to methods comprising administering to a subject in need thereof a therapeutically effective amount of a double stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 2, 5, 6, 9, 11, 12, 13, 14, 15, 16, 17 and 23, and wherein the dsRNA is an rxRNAori.

Further aspects of the invention relate to methods comprising administering to a subject in need thereof a therapeutically effective amount of a double stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 1-27, and wherein the dsRNA is an rxRNAori.

In some embodiments, the method is a method for treating compromised skin. In some embodiments, the method is a method for treating or preventing a fibrotic disorder.

In some embodiments, the dsRNA is administered via intradermal injection. In some embodiments, the dsRNA is administered locally to the skin. In some embodiments, two or more nucleic acid molecules are administered simultaneously or sequentially.

In some embodiments, one or more of the dsRNAs is hydrophobically modified. In certain embodiments, one or more of the dsRNAs is linked to a hydrophobic conjugate.

In some embodiments, the dsRNA is directed against CTGF. In certain embodiments, the antisense strand of the dsRNA is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 11, 12 and 15. In some embodiments, the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 10, 11, 12, 15, 20 and 24.

In some embodiments, the sense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: SEQ ID NOs: 2463, 3429, 2443, 3445, 2459, 3493, 2465 and 3469. In certain embodiments, the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: 2464, 3430, 4203, 3446, 2460, 3494, 2466 and 3470.

In certain embodiments, the sense strand comprises SEQ ID NO:2463 and the antisense strand comprises SEQ ID NO:2464. In certain embodiments, the sense strand comprises SEQ ID NO:3429 and the antisense strand comprises SEQ ID NO:3430.

In certain embodiments, the sense strand comprises SEQ ID NO:2443 and the antisense strand comprises SEQ ID NO:4203. In certain embodiments, the sense strand comprises SEQ ID NO:3445 and the antisense strand comprises SEQ ID NO:3446.

In certain embodiments, the sense strand comprises SEQ ID NO:2459 and the antisense strand comprises SEQ ID NO:2460. In certain embodiments, the sense strand comprises SEQ ID NO:3493 and the antisense strand comprises SEQ ID NO:3494.

In certain embodiments, the sense strand comprises SEQ ID NO:2465 and the antisense strand comprises SEQ ID NO:2466. In certain embodiments, the sense strand comprises SEQ ID NO:3469 and the antisense strand comprises SEQ ID NO:3470.

In some embodiments, the sense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: SEQ ID NOs: 1835, 1847, 1848 and 1849. In some embodiments, the sense strand comprises a sequence selected from the group consisting of: SEQ ID NOs: 1835, 1847, 1848 and 1849.

Aspects of the invention relate to treating or preventing a fibrotic disorder. In some embodiments, the fibrotic disorder is selected from the group consisting of pulmonary fibrosis, liver cirrhosis, scleroderma and glomerulonephritis, lung fibrosis, liver fibrosis, skin fibrosis, muscle fibrosis, radiation fibrosis, kidney fibrosis, proliferative vitreoretinopathy, restenosis and uterine fibrosis, and trabeculectomy failure due to scarring.

In some embodiments, the dsRNA are administered via intradermal injection, while in other embodiments, the one or more dsRNA are administered subcutaneously or epicutaneously.

The one or more dsRNA can be administered prior to, during and/or after a medical procedure. In some embodiments, administration occurs within 8 days prior to or within 8 days after the medical procedure. In some embodiments, the medical procedure is surgery. In certain embodiments, the surgery is elective. In some embodiments, the surgery comprises epithelial grafting or skin grafting. In some embodiments, the one or more double stranded nucleic acid molecules are administered to a graft donor site and/or a graft recipient site.

Aspects of the invention relate to methods for administering one or more dsRNA prior to, during and/or after an injury. In some embodiments, the subject has a wound such as a chronic wound. In certain embodiments, the wound is a result of elective surgery. The wound can be external or internal. In some embodiments, the dsRNA is administered after burn injury.

Methods described herein include methods for promoting wound healing and methods for preventing scarring.

In some embodiments, one or more of the dsRNA administered to a subject is directed against a gene selected from the group consisting of TGFB1, TGFB2, hTGFB1, hTGFB2, PTGS2, SPP1, hSPP1, CTGF or hCTGF. In some embodiments, the one or more dsRNA are administered on the skin of the subject. In certain embodiments, the one or more dsRNA molecules are in the form of a cream or ointment. In some

embodiments, two or more or three or more nucleic acids are administered. Two or more nucleic acid molecules can be administered simultaneously or sequentially.

Aspects of the invention related to nucleic acids that are optimized. In some embodiments, one or more double stranded nucleic acid molecules are hydrophobically modified. In certain embodiments, the one or more double stranded nucleic acid molecules are linked to a hydrophobic conjugate or multiple hydrophobic conjugates. In some embodiments, the one or more double stranded nucleic acid molecule are linked to a lipophilic group. In certain embodiments, the lipophilic group is linked to the passenger strand of the one or more double stranded nucleic acid molecules. In some embodiment, the one or more double stranded nucleic acid molecules are linked to cholesterol, a long chain alkyl cholesterol analog, vitamin A or vitamin E. In some embodiments, the one or more double stranded nucleic acid molecules is attached to chloroformate.

Aspects of the invention related to nucleic acids that are optimized through modifications. In some embodiments, the one or more double stranded nucleic acid molecules includes at least one 2' O methyl or 2' fluoro modification and/or at least one 5 methyl C or U modification. In some embodiments, the one or more double stranded nucleic acid molecules has a guide strand of 16-28 nucleotides in length. In certain embodiments, at least 40% of the nucleotides of the one or more double stranded nucleic acid molecules are modified. Double stranded nucleic acid molecules described herein can also be attached to linkers. In some embodiments, the linker is protonatable.

Aspects of the invention relate to double stranded nucleic acid molecules that contain at least two single stranded regions. In some embodiments, the single stranded regions contain phosphorothioate modifications. In certain embodiments, the single stranded regions are located at the 3' end of the guide strand and the 5' end of the passenger strand.

Aspects of the invention relate to methods for delivering a nucleic acid to a subject, involving administering to a subject within 8 days prior to a medical procedure a therapeutically effective amount for treating compromised skin of one or more sd-rxRNAs.

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 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

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 demonstrates the expression profiles for non-limiting examples of target genes including MAP4K4, SPP1, CTGF, PTGS2 and TGFB1. As expected, target gene expression is elevated early and returns to normal by day 10.

FIG. 2 presents schematics depicting an experimental approach to visualizing tissue after intradermal injection.

FIG. 3 demonstrates silencing of MAP4K4 following intradermal injection of sd-rxRNA targeting MAP4K4.

FIG. 4 demonstrates silencing of MAP4K4, PPIB and CTGF following intradermal injection of sd-rxRNA molecules targeting each gene.

FIG. 5 demonstrates silencing of MAP4K4 following intradermal injection of sd-rxRNA targeting MAP4K4. Normalized expression of MAP4K4 relative to controls is demonstrated.

FIG. 6 demonstrates silencing of PPIB following intradermal injection of sd-rxRNA targeting PPIB. Normalized expression of PPIB relative to controls is demonstrated.

FIG. 7 demonstrates the duration of PPIB silencing following intradermal injection of sd-rxRNA targeting PPIB.

FIG. 8 demonstrates the duration of MAP4K4 silencing following intradermal injection of sd-rxRNA targeting MAP4K4.

FIG. 9 demonstrates equivalent silencing achieved using two different dosing regimens.

FIG. 10 demonstrates examples of sd-rxRNA molecules targeting CTGF that are efficacious for gene silencing.

FIG. 11 demonstrates examples of sd-rxRNA molecules targeting CTGF that are efficacious for gene silencing.

FIG. 12 demonstrates a dose response for sd-rxRNA molecules targeting CTGF.

FIG. 13 demonstrates a sample of an original sd-rxRNA screen.

FIG. 14 presents data on a hit from the original sd-rxRNA screen.

FIG. 15 demonstrates gene expression of PTGS2 following administration of sd-rxRNA targeting PTGS2.

FIG. 16 demonstrates gene expression of hTGFB1 following administration of sd-rxRNA targeting hTGFB1.

FIG. 17 demonstrates gene expression of hTGFB1 following administration of sd-rxRNA targeting hTGFB1.

FIG. 18 demonstrates results of TGFB1 sd-rxRNA screening.

FIG. 19 demonstrates gene expression of TGFB2 following administration of sd-rxRNA targeting TGFB2.

FIG. 20 demonstrates gene expression of TGFB2 following administration of sd-rxRNA targeting TGFB2.

FIG. 21 demonstrates gene expression of TGFB2 following administration of sd-rxRNA targeting TGFB2.

FIG. 22 demonstrates gene expression of TGFB2 following administration of sd-rxRNA targeting TGFB2.

FIG. 23 demonstrates gene expression of TGFB2 following administration of sd-rxRNA targeting TGFB2.

FIG. 24 demonstrates results of TGFB2 sd-rxRNA screening.

FIG. 25 demonstrates identification of potent hSPP1 sd-rxRNAs.

FIG. 26 demonstrates identification of potent hSPP1 sd-rxRNAs.

FIG. 27 demonstrates identification of potent hSPP1 sd-rxRNAs.

FIG. 28 demonstrates SPP1 sd-rxRNA compound selection.

FIG. 29 demonstrates that variation of linker chemistry does not influence silencing activity of sd-rxRNAs in vitro. Two different linker chemistries were evaluated, a hydroxyproline linker and ribo linker, on multiple sd-rxRNAs (targeting Map4k4 or PPIB) in passive uptake assays to determine linkers which favor self delivery. HeLa cells were transfected in the absence of a delivery vehicle (passive

transfection) with sd-rxRNAs at 1 uM, 0.1 uM or 0.01 uM for 48 hrs. Use of either linker results in an efficacious delivery of sd-rxRNA.

FIG. 30 depicts CTGF as a central factor in the pathway to fibrosis.

FIG. 31 depicts the phases of wound healing.

FIG. 32 depicts the chemical optimization of sd-rxRNA leads.

FIG. 33 demonstrates that chemically optimized CTGF L1 sd-rxRNAs are active.

FIG. 34 demonstrates in vitro efficacy of chemically optimized CTGF L1 sd-rxRNAs.

FIG. 35 demonstrates in vitro stability of chemically optimized CTGF L1 sd-rxRNAs.

FIG. 36 demonstrates that chemically optimized CTGF L2 sd-rxRNAs are active.

FIG. 37 demonstrates in vitro efficacy of chemically optimized CTGF L2 sd-rxRNAs.

FIG. 38 demonstrates in vitro stability of chemically optimized CTGF L2 sd-rxRNAs.

FIG. 39 provides a summary of compounds that are active in vivo.

FIG. 40 demonstrates that treatment with CTGF L1B target sequence resulted in mRNA silencing.

FIG. 41 demonstrates that treatment with CTGF L2 target sequence resulted in mRNA silencing.

FIG. 42 demonstrates CTGF silencing after two intradermal injections of RXi-109.

FIG. 43 demonstrates the duration of CTGF silencing in skin after intradermal injection of the sd-rxRNA in SD rats. Eight millimeter skin biopsies were harvested, and mRNA levels were quantified by QPCR and normalized to a housekeeping gene. Shown is percent (%) silencing vs. Non Targeting Control (NTC); PBS at each time point is one experimental group; * $p \leq 0.04$; ** $p \leq 0.002$.

FIG. 44 demonstrates that chemically optimized CTGF L3 sd-rxRNAs are active.

FIG. 45 demonstrates absolute luminescence of CTGF L4 sd-rxRNAs.

FIG. 46 demonstrates that chemically optimized CTGF L4 sd-rxRNAs are active.

FIG. 47 demonstrates changes in mRNA expression levels of CTGF, α-SM actin, collagen 1A2, and collagen 3A1 after intradermal injection of CTFG sd-rxRNA in SD rats. mRNA levels were quantified by qPCR.

FIG. 48 demonstrates that there is no apparent delay in wound healing with treatment of CTGF-targeting sd-rxRNA. Some changes was observed with treatment of a combination of CTGF- and COX2-targeting sd-rxRNAs.

FIG. 49 demonstrates that administration of sd-rxRNAs decreases wound width over the course of at least 9 days. The graph shows microscopic measurements of wound width in rats on days 3, 6, and 9 post-wounding. Each group represents 5 rats. Two non-serial sections from each wound were measured and the average width of the two was calculated per wound. *p<0.05 vs. PBS an NTC.

FIG. 50 demonstrates that administration of sd-rxRNAs decreases wound area over the course of at least 9 days. The graph shows microscopic measurements of wound width in rats on days 3, 6, and 9 post-wounding. Each group represents 5 rats. Two non-serial sections from each wound were measured and the average width of the two was calculated per wound. *p<0.05 vs. PBS an NTC.

FIG. 51 demonstrates that administration of sd-rxRNAs increase the percentage of wound re-epithelialization over the course of at least 9 days. The graph shows microscopic measurements of wound width in rats on days 3, 6, and 9 post-wounding. Each group represents 5 rats. Two non-serial sections from each wound were measured and the average width of the two was calculated per wound. *p<0.05 vs. PBS an NTC.

FIG. 52 demonstrates that administration of sd-rxRNAs increases the average granulation tissue maturity scores over the course of at least 9 days. The graph shows microscopic measurements of wound width in rats on days 3, 6, and 9 post-wounding (5 = mature, 1 = immature). Each group represents 5 rats.

FIG. 53 demonstrates CD68 labeling in day 9 wounds (0 = no labeling, 3 = substantial labeling). Each group represents 5 rats.

FIG. 54 demonstrates that CTGF leads have different toxicity levels in vitro.

FIG. 55 shows percentage (%) of cell viability after RXI 109 dose escalation (oligos formulated in PBS).

FIG. 56 is a schematic of Phases 1 and 2 clinical trial design.

FIG. 57 is a schematic of Phases 1 and 2 clinical trial design.

FIG. 58 demonstrates a percent (%) decrease in PPIB expression in the liver relative to PBS control. Lipoid formulated rxRNAs (10 mg/kg) were delivery systemically to Balb/c mice (n=5) by single tail vein injections. Liver tissue was harvested at 24 hours after injection and expression was analyzed by qPCR (normalized

to β-actin). Map4K4 rxRNAori also showed significant silencing (~83%, p<0.001) although Map4K4 sd-rxRNA did not significantly reduce target gene expression (~17%, p=0.019). TD.035.2278, Published lipidoid delivery reagent, 98N12-5(1), from Akinc, 2009.

FIG. 59 demonstrates that chemically optimized PTGS2 L1 sd-rxRNAs are active.

FIG. 60 demonstrates that chemically optimized PTGS2 L2 sd-rxRNAs are active.

FIG. 61 demonstrates that chemically optimized hTGFB1 L1 sd-rxRNAs are active.

FIG. 62 demonstrates that chemically optimized hTGFB1 L1 sd-rxRNAs are active.

FIG. 63 demonstrates that chemically optimized hTGFB2 L1 sd-rxRNAs are active.

FIG. 64 demonstrates that chemically optimized hTGFB2 sd-rxRNAs are active.

DETAILED DESCRIPTION

Aspects of the invention relate to methods and compositions involved in gene silencing. The invention is based at least in part on the surprising discovery that administration of sd-rxRNA molecules to the skin, such as through intradermal injection or subcutaneous administration, results in efficient silencing of gene expression in the skin. Highly potent sd-rxRNA molecules that target genes including SPP1, CTGF, PTGS2, TGFB1 and TGFB2 were also identified herein through cell-based screening. sd-rxRNAs represent a new class of therapeutic RNAi molecules with significant potential in treatment of compromised skin.

sd-rxRNA molecules

Aspects of the invention relate to sd-rxRNA molecules. As used herein, an "sd-rxRNA" or an "sd-rxRNA molecule" refers to a self-delivering RNA molecule such as those described in, and incorporated by reference from, PCT Publication No. WO2010/033247 (Application No. PCT/US2009/005247), filed on September 22, 2009, and entitled "REDUCED SIZE SELF-DELIVERING RNAI COMPOUNDS," and PCT application PCT/US2009/005246, filed on September 22, 2009, and entitled "RNA

INTERFERENCE IN SKIN INDICATIONS." Briefly, an sd-rxRNA, (also referred to as an sd-rxRNA^{nano}) is an isolated asymmetric double stranded nucleic acid molecule comprising a guide strand, with a minimal length of 16 nucleotides, and a passenger strand of 8-18 nucleotides in length, wherein the double stranded nucleic acid molecule has a double stranded region and a single stranded region, the single stranded region having 4-12 nucleotides in length and having at least three nucleotide backbone modifications. In preferred embodiments, the double stranded nucleic acid molecule has one end that is blunt or includes a one or two nucleotide overhang. sd-rxRNA molecules can be optimized through chemical modification, and in some instances through attachment of hydrophobic conjugates.

In some embodiments, an sd-rxRNA comprises an isolated double stranded nucleic acid molecule comprising a guide strand and a passenger strand, wherein the region of the molecule that is double stranded is from 8-15 nucleotides long, wherein the guide strand contains a single stranded region that is 4-12 nucleotides long, wherein the single stranded region of the guide strand contains 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 phosphorothioate modifications, and wherein at least 40% of the nucleotides of the double stranded nucleic acid are modified.

The polynucleotides of the invention are referred to herein as isolated double stranded or duplex nucleic acids, oligonucleotides or polynucleotides, nano molecules, nano RNA, sd-rxRNA^{nano}, sd-rxRNA or RNA molecules of the invention.

sd-rxRNAs are much more effectively taken up by cells compared to conventional siRNAs. These molecules are highly efficient in silencing of target gene expression and offer significant advantages over previously described RNAi molecules including high activity in the presence of serum, efficient self delivery, compatibility with a wide variety of linkers, and reduced presence or complete absence of chemical modifications that are associated with toxicity.

In contrast to single-stranded polynucleotides, duplex polynucleotides have traditionally been difficult to deliver to a cell as they have rigid structures and a large number of negative charges which makes membrane transfer difficult. sd-rxRNAs however, although partially double-stranded, are recognized *in vivo* as single-stranded and, as such, are capable of efficiently being delivered across cell membranes. As a result the polynucleotides of the invention are capable in many instances of self delivery. Thus, the polynucleotides of the invention may be formulated in a manner similar to

conventional RNAi agents or they may be delivered to the cell or subject alone (or with non-delivery type carriers) and allowed to self deliver. In one embodiment of the present invention, self delivering asymmetric double-stranded RNA molecules are provided in which one portion of the molecule resembles a conventional RNA duplex and a second portion of the molecule is single stranded.

The oligonucleotides of the invention in some aspects have a combination of asymmetric structures including a double stranded region and a single stranded region of 5 nucleotides or longer, specific chemical modification patterns and are conjugated to lipophilic or hydrophobic molecules. This class of RNAi like compounds have superior efficacy *in vitro* and *in vivo*. It is believed that the reduction in the size of the rigid duplex region in combination with phosphorothioate modifications applied to a single stranded region contribute to the observed superior efficacy.

The invention is based at least in part on the surprising discovery that sd-rxRNA molecules are delivered efficiently *in vivo* to the skin through a variety of methods including intradermal injection and subcutaneous administration. Furthermore, sd-rxRNA molecules are efficient in mediating gene silencing in the region of the skin where they are targeted.

Aspects of the invention relate to the use of cell-based screening to identify potent sd-rxRNA molecules. Described herein is the identification of potent sd-rxRNA molecules that target a subset of genes including SPP1, CTFG, PTGS2, TGFB1 and TGFB2. In some embodiments, a target gene is selected and an algorithm is applied to identify optimal target sequences within that gene (Example 2). For example, many sequences can be selected for one gene. In some instances, the sequences that are identified are generated as RNAi compounds for a first round of testing. For example, the RNAi compounds based on the optimal predicted sequences can initially be generated as rxRNAori ("ori") sequences for the first round of screening. After identifying potent RNAi compounds, these can be generated as sd-rxRNA molecules.

dsRNA formulated according to the invention also includes rxRNAori. rxRNAori refers to a class of RNA molecules described in and incorporated by reference from PCT Publication No. WO2009/102427 (Application No. PCT/US2009/000852), filed on February 11, 2009, and entitled, "MODIFIED RNAI POLYNUCLEOTIDES AND USES THEREOF."

In some embodiments, an rxRNAori molecule comprises a double-stranded RNA (dsRNA) construct of 12-35 nucleotides in length, for inhibiting expression of a target gene, comprising: a sense strand having a 5'-end and a 3'-end, wherein the sense strand is highly modified with 2'-modified ribose sugars, and wherein 3-6 nucleotides in the central portion of the sense strand are not modified with 2'-modified ribose sugars and, an antisense strand having a 5'-end and a 3'-end, which hybridizes to the sense strand and to mRNA of the target gene, wherein the dsRNA inhibits expression of the target gene in a sequence-dependent manner.

rxRNAori can contain any of the modifications described herein. In some embodiments, at least 30% of the nucleotides in the rxRNAori are modified. For example, at least 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% of the nucleotides in the rxRNAori are modified. In some embodiments, 100% of the nucleotides in the sd-rxRNA are modified. In some embodiments, only the passenger strand of the rxRNAori contains modifications.

In some embodiments, the RNAi compounds of the invention comprise an asymmetric compound comprising a duplex region (required for efficient RISC entry of 8-15 bases long) and single stranded region of 4-12 nucleotides long; with a 13 or 14 nucleotide duplex. A 6 or 7 nucleotide single stranded region is preferred in some embodiments. The single stranded region of the new RNAi compounds also comprises 2-12 phosphorothioate internucleotide linkages (referred to as phosphorothioate modifications). 6-8 phosphorothioate internucleotide linkages are preferred in some embodiments. Additionally, the RNAi compounds of the invention also include a unique chemical modification pattern, which provides stability and is compatible with RISC entry. The combination of these elements has resulted in unexpected properties which are highly useful for delivery of RNAi reagents *in vitro* and *in vivo*.

The chemical modification pattern, which provides stability and is compatible with RISC entry includes modifications to the sense, or passenger, strand as well as the antisense, or guide, strand. For instance the passenger strand can be modified with any chemical entities which confirm stability and do not interfere with activity. Such

modifications include 2' ribo modifications (O-methyl, 2' F, 2 deoxy and others) and backbone modification like phosphorothioate modifications. A preferred chemical modification pattern in the passenger strand includes Omethyl modification of C and U nucleotides within the passenger strand or alternatively the passenger strand may be completely Omethyl modified.

The guide strand, for example, may also be modified by any chemical modification which confirms stability without interfering with RISC entry. A preferred chemical modification pattern in the guide strand includes the majority of C and U nucleotides being 2' F modified and the 5' end being phosphorylated. Another preferred chemical modification pattern in the guide strand includes 2'Omethyl modification of position 1 and C/U in positions 11-18 and 5' end chemical phosphorylation. Yet another preferred chemical modification pattern in the guide strand includes 2'Omethyl modification of position 1 and C/U in positions 11-18 and 5' end chemical phosphorylation and and 2'F modification of C/U in positions 2-10. In some embodiments the passenger strand and/or the guide strand contains at least one 5-methyl C or U modifications.

In some embodiments, at least 30% of the nucleotides in the sd-rxRNA are modified. For example, at least 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% of the nucleotides in the sd-rxRNA are modified. In some embodiments, 100% of the nucleotides in the sd-rxRNA are modified.

The above-described chemical modification patterns of the oligonucleotides of the invention are well tolerated and actually improved efficacy of asymmetric RNAi compounds.

It was also demonstrated experimentally herein that the combination of modifications to RNAi when used together in a polynucleotide results in the achievement of optimal efficacy in passive uptake of the RNAi. Elimination of any of the described components (Guide strand stabilization, phosphorothioate stretch, sense strand stabilization and hydrophobic conjugate) or increase in size in some instances results in sub-optimal efficacy and in some instances complete lost of efficacy. The combination

of elements results in development of a compound, which is fully active following passive delivery to cells such as HeLa cells.

The data in the Examples presented below demonstrates high efficacy of the oligonucleotides of the invention both *in vitro* in variety of cell types and *in vivo* upon local and systemic administration.

The sd-rxRNA can be further improved in some instances by improving the hydrophobicity of compounds using of novel types of chemistries. For example one chemistry is related to use of hydrophobic base modifications. Any base in any position might be modified, as long as modification results in an increase of the partition coefficient of the base. The preferred locations for modification chemistries are positions 4 and 5 of the pyrimidines. The major advantage of these positions is (a) ease of synthesis and (b) lack of interference with base-pairing and A form helix formation, which are essential for RISC complex loading and target recognition. A version of sd-rxRNA compounds where multiple deoxy Uridines are present without interfering with overall compound efficacy was used. In addition major improvement in tissue distribution and cellular uptake might be obtained by optimizing the structure of the hydrophobic conjugate. In some of the preferred embodiment the structure of sterol is modified to alter (increase/ decrease) C17 attached chain. This type of modification results in significant increase in cellular uptake and improvement of tissue uptake prosperities in vivo.

Aspects of the invention relate to double-stranded ribonucleic acid molecules (dsRNA) such as sd-rxRNA and rxRNAori. dsRNA associated with the invention can comprise a sense strand and an antisense strand wherein the antisense strand is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 2, 5, 6, 9, 11, 12, 13, 14, 15, 16, 17 and 23. For example, the antisense strand can be complementary to at least 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 contiguous nucleotides, or can be complementary to 25 nucleotides of a sequence selected from the sequences within Tables 2, 5, 6, 9, 11, 12, 13, 14, 15, 16, 17 and 23.

dsRNA associated with the invention can comprise a sense strand and an antisense strand wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 1-27. For example, the sense strand and/or the antisense strand can comprise at least 12, 13,

14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 contiguous nucleotides, or can comprise 25 nucleotides of a sequence selected from the sequences within Tables 1-27.

Aspects of the invention relate to dsRNA directed against CTGF. For example, the antisense strand of a dsRNA directed against CTGF can be complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 11, 12 and 15. The sense strand and/or the antisense strand of a dsRNA directed against CTGF can comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 10, 11, 12, 15, 20 and 24.

In some embodiments, the sense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: SEQ ID NOs: 2463, 3429, 2443, 3445, 2459, 3493, 2465 and 3469. In certain embodiments, the sense strand comprises or consists of a sequence selected from the group consisting of: SEQ ID NOs: 2463, 3429, 2443, 3445, 2459, 3493, 2465 and 3469.

In some embodiments, the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: 2464, 3430, 4203, 3446, 2460, 3494, 2466 and 3470. In certain embodiments, the antisense strand comprises or consists of a sequence selected from the group consisting of: 2464, 3430, 4203, 3446, 2460, 3494, 2466 and 3470.

In a preferred embodiment, the sense strand comprises SEQ ID NO:2463 (GCACCUUUCUAGA) and the antisense strand comprises SEQ ID NO:2464 (UCUAGAAAGGUGCAAACAU). The sequences of SEQ ID NO:2463 and SEQ ID NO:2464 can be modified in a variety of ways according to modifications described herein. A preferred modification pattern for SEQ ID NO:2463 is depicted by SEQ ID NO:3429 (G.mC. A.mC.mC.mU.mU.mU.mC.mU. A*mG*mA.TEG-Chl). A preferred modification pattern for SEQ ID NO:2464 is depicted by SEQ ID NO:3430 (P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A* A* A*mC* A* U). An sd-rxRNA consisting of SEQ ID NO:3429 and SEQ ID NO:3430 is also referred to as RXi-109.

In another preferred embodiment, the sense strand comprises SEQ ID NO:2443 (UUGCACCUUUCUAA) and the antisense strand comprises SEQ ID NO:4203 (UUAGAAAGGUGCAAACAAGG). The sequences of SEQ ID NO:2443 and SEQ ID NO:4203 can be modified in a variety of ways according to modifications described herein. A preferred modification pattern for SEQ ID NO:2443 is depicted by SEQ ID NO:3445 (mU.mU. G.mC. A.mC.mC.mU.mU.mU.mC.mU*mA*mA.TEG-Chl). A

preferred modification pattern for SEQ ID NO:4203 is depicted by SEQ ID NO:3446 (P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC.mA.mA*mA*fC*mA*mA*mG* G.).

In another preferred embodiment, the sense strand comprises SEQ ID NO:2459 (GUGACCAAAAGUA) and the antisense strand comprises SEQ ID NO:2460 (UACUUUUGGUCACACUCUC). The sequences of SEQ ID NO:2459 and SEQ ID NO:2460 can be modified in a variety of ways according to modifications described herein. A preferred modification pattern for SEQ ID NO:2459 is depicted by SEQ ID NO:3493 (G.mU. G. A.mC.mC. A. A. A. A. G*mU*mA.TEG-Chl). A preferred modification pattern for SEQ ID NO:2460 is depicted by SEQ ID NO:3494 (P.mU. A.fC.fU.fU.fU.fU. G. G.fU.mC. A.mC* A*mC*mU*mC*mU* C.).

In another preferred embodiment, the sense strand comprises SEQ ID NO:2465 (CCUUUCUAGUUGA) and the antisense strand comprises SEQ ID NO:2466 (UCAACUAGAAAGGUGCAAA). The sequences of SEQ ID NO:2465 and SEQ ID NO:2466 can be modified in a variety of ways according to modifications described herein. A preferred modification pattern for SEQ ID NO:2465 is depicted by SEQ ID NO:3469 (mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU*mG*mA.TEG-Chl). A preferred modification pattern for SEQ ID NO:2466 is depicted by SEQ ID NO:3470 (P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU*mG*fC*mA*mA* A.).

A preferred embodiment of an rxRNAori directed against CTGF can comprise at least 12 contiguous nucleotides of a sequence selected from the group consisting of: SEQ ID NOs:1835, 1847, 1848 and 1849. In some embodiments, the sense strand of the rxRNAori comprises or consists of SEQ ID NOs:1835, 1847, 1848 or 1849.

Aspects of the invention relate to compositions comprising dsRNA such as sd-rxRNA and rxRNAori. In some embodiments compositions comprise two or more dsRNA that are directed against different genes.

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.

Thus, aspects of the invention relate to isolated double stranded nucleic acid molecules comprising a guide (antisense) strand and a passenger (sense) strand. As used herein, the term "double-stranded" refers to one or more nucleic acid molecules in which at least a portion of the nucleomonomers are complementary and hydrogen bond to form a double-stranded region. In some embodiments, the length of the guide strand ranges from 16-29 nucleotides long. In certain embodiments, the guide strand is 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 nucleotides long. The guide strand has complementarity to a target gene. Complementarity between the guide strand and the target gene may exist over any portion of the guide strand. Complementarity as used herein may be perfect complementarity or less than perfect complementarity as long as the guide strand is sufficiently complementary to the target that it mediates RNAi. In some embodiments complementarity refers to less than 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, or 1% mismatch between the guide strand and the target. Perfect complementarity refers to 100% complementarity. Thus the invention has the advantage of being able to tolerate sequence variations that might be expected due to genetic mutation, strain polymorphism, or evolutionary divergence. For example, siRNA sequences with insertions, deletions, and single point mutations relative to the target sequence have also been found to be effective for inhibition. Moreover, not all positions of a siRNA contribute equally to target recognition. Mismatches in the center of the siRNA are most critical and essentially abolish target RNA cleavage. Mismatches upstream of the center or upstream of the cleavage site referencing the antisense strand are tolerated but significantly reduce target RNA cleavage. Mismatches downstream of the center or cleavage site referencing the antisense strand, preferably located near the 3' end of the antisense strand, e.g. 1, 2, 3, 4, 5 or 6 nucleotides from the 3' end of the antisense strand, are tolerated and reduce target RNA cleavage only slightly.

While not wishing to be bound by any particular theory, in some embodiments, the guide strand is at least 16 nucleotides in length and anchors the Argonaute protein in RISC. In some embodiments, when the guide strand loads into RISC it has a defined seed region and target mRNA cleavage takes place across from position 10-11 of the guide strand. In some embodiments, the 5' end of the guide strand is or is able to be phosphorylated. The nucleic acid molecules described herein may be referred to as minimum trigger RNA.

In some embodiments, the length of the passenger strand ranges from 8-15 nucleotides long. In certain embodiments, the passenger strand is 8, 9, 10, 11, 12, 13, 14 or 15 nucleotides long. The passenger strand has complementarity to the guide strand. Complementarity between the passenger strand and the guide strand can exist over any portion of the passenger or guide strand. In some embodiments, there is 100% complementarity between the guide and passenger strands within the double stranded region of the molecule.

Aspects of the invention relate to double stranded nucleic acid molecules with minimal double stranded regions. In some embodiments the region of the molecule that is double stranded ranges from 8-15 nucleotides long. In certain embodiments, the region of the molecule that is double stranded is 8, 9, 10, 11, 12, 13, 14 or 15 nucleotides long. In certain embodiments the double stranded region is 13 or 14 nucleotides long. There can be 100% complementarity between the guide and passenger strands, or there may be one or more mismatches between the guide and passenger strands. In some embodiments, on one end of the double stranded molecule, the molecule is either blunt-ended or has a one-nucleotide overhang. The single stranded region of the molecule is in some embodiments between 4-12 nucleotides long. For example the single stranded region can be 4, 5, 6, 7, 8, 9, 10, 11 or 12 nucleotides long. However, in certain embodiments, the single stranded region can also be less than 4 or greater than 12 nucleotides long. In certain embodiments, the single stranded region is 6 nucleotides long.

RNAi constructs associated with the invention can have a thermodynamic stability (ΔG) of less than -13 kkal/mol. In some embodiments, the thermodynamic stability (ΔG) is less than -20 kkal/mol. In some embodiments there is a loss of efficacy when (ΔG) goes below -21 kkal/mol. In some embodiments a (ΔG) value higher than -13 kkal/mol is compatible with aspects of the invention. Without wishing to be bound by any theory, in some embodiments a molecule with a relatively higher (ΔG) value may become active at a relatively higher concentration, while a molecule with a relatively lower (ΔG) value may become active at a relatively lower concentration. In some embodiments, the (ΔG) value may be higher than -9 kkcal/mol. The gene silencing effects mediated by the RNAi constructs associated with the invention, containing minimal double stranded regions, are unexpected because molecules of almost identical

design but lower thermodynamic stability have been demonstrated to be inactive (Rana et al. 2004).

Without wishing to be bound by any theory, results described herein suggest that a stretch of 8-10 bp of dsRNA or dsDNA will be structurally recognized by protein components of RISC or co-factors of RISC. Additionally, there is a free energy requirement for the triggering compound that it may be either sensed by the protein components and/or stable enough to interact with such components so that it may be loaded into the Argonaute protein. If optimal thermodynamics are present and there is a double stranded portion that is preferably at least 8 nucleotides then the duplex will be recognized and loaded into the RNAi machinery.

In some embodiments, thermodynamic stability is increased through the use of LNA bases. In some embodiments, additional chemical modifications are introduced . Several non-limiting examples of chemical modifications include: 5' Phosphate, 2'-O-methyl, 2'-O-ethyl, 2'-fluoro, ribothymidine, C-5 propynyl-dC (pdC) and C-5 propynyl-dU (pdU); C-5 propynyl-C (pC) and C-5 propynyl-U (pU); 5-methyl C, 5-methyl U, 5-methyl dC, 5-methyl dU methoxy, (2,6-diaminopurine), 5'-Dimethoxytrityl-N4-ethyl-2'-deoxyCytidine and MGB (minor groove binder). It should be appreciated that more than one chemical modification can be combined within the same molecule.

Molecules associated with the invention are optimized for increased potency and/or reduced toxicity. For example, nucleotide length of the guide and/or passenger strand, and/or the number of phosphorothioate modifications in the guide and/or passenger strand, can in some aspects influence potency of the RNA molecule, while replacing 2'-fluoro (2'F) modifications with 2'-O-methyl (2'OMe) modifications can in some aspects influence toxicity of the molecule. Specifically, reduction in 2'F content of a molecule is predicted to reduce toxicity of the molecule. The Examples section presents molecules in which 2'F modifications have been eliminated, offering an advantage over previously described RNAi compounds due to a predicted reduction in toxicity. Furthermore, the number of phosphorothioate modifications in an RNA molecule can influence the uptake of the molecule into a cell, for example the efficiency of passive uptake of the molecule into a cell. Preferred embodiments of molecules described herein have no 2'F modification and yet are characterized by equal efficacy in cellular uptake and tissue penetration. Such molecules represent a significant

improvement over prior art, such as molecules described by Accell and Wolfrum, which are heavily modified with extensive use of 2'F.

In some embodiments, a guide strand is approximately 18-19 nucleotides in length and has approximately 2-14 phosphate modifications. For example, a guide strand can contain 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more than 14 nucleotides that are phosphate-modified. The guide strand may contain one or more modifications that confer increased stability without interfering with RISC entry. The phosphate modified nucleotides, such as phosphorothioate modified nucleotides, can be at the 3' end, 5' end or spread throughout the guide strand. In some embodiments, the 3' terminal 10 nucleotides of the guide strand contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 phosphorothioate modified nucleotides. The guide strand can also contain 2'F and/or 2'OMe modifications, which can be located throughout the molecule. In some embodiments, the nucleotide in position one of the guide strand (the nucleotide in the most 5' position of the guide strand) is 2'OMe modified and/or phosphorylated. C and U nucleotides within the guide strand can be 2'F modified. For example, C and U nucleotides in positions 2-10 of a 19 nt guide strand (or corresponding positions in a guide strand of a different length) can be 2'F modified. C and U nucleotides within the guide strand can also be 2'OMe modified. For example, C and U nucleotides in positions 11-18 of a 19 nt guide strand (or corresponding positions in a guide strand of a different length) can be 2'OMe modified. In some embodiments, the nucleotide at the most 3' end of the guide strand is unmodified. In certain embodiments, the majority of Cs and Us within the guide strand are 2'F modified and the 5' end of the guide strand is phosphorylated. In other embodiments, position 1 and the Cs or Us in positions 11-18 are 2'OMe modified and the 5' end of the guide strand is phosphorylated. In other embodiments, position 1 and the Cs or Us in positions 11-18 are 2'OMe modified, the 5' end of the guide strand is phosphorylated, and the Cs or Us in position 2-10 are 2'F modified.

In some aspects, an optimal passenger strand is approximately 11-14 nucleotides in length. The passenger strand may contain modifications that confer increased stability. One or more nucleotides in the passenger strand can be 2'OMe modified. In some embodiments, one or more of the C and/or U nucleotides in the passenger strand is 2'OMe modified, or all of the C and U nucleotides in the passenger strand are 2'OMe modified. In certain embodiments, all of the nucleotides in the passenger strand are 2'OMe modified. One or more of the nucleotides on the passenger strand can also be

phosphate-modified such as phosphorothioate modified. The passenger strand can also contain 2' ribo, 2'F and 2 deoxy modifications or any combination of the above. As demonstrated in the Examples, chemical modification patterns on both the guide and passenger strand are well tolerated and a combination of chemical modifications is shown herein to lead to increased efficacy and self-delivery of RNA molecules.

Aspects of the invention relate to RNAi constructs that have extended single-stranded regions relative to double stranded regions, as compared to molecules that have been used previously for RNAi. The single stranded region of the molecules may be modified to promote cellular uptake or gene silencing. In some embodiments, phosphorothioate modification of the single stranded region influences cellular uptake and/or gene silencing. The region of the guide strand that is phosphorothioate modified can include nucleotides within both the single stranded and double stranded regions of the molecule. In some embodiments, the single stranded region includes 2-12 phosphorothioate modifications. For example, the single stranded region can include 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 phosphorothioate modifications. In some instances, the single stranded region contains 6-8 phosphorothioate modifications.

Molecules associated with the invention are also optimized for cellular uptake. In RNA molecules described herein, the guide and/or passenger strands can be attached to a conjugate. In certain embodiments the conjugate is hydrophobic. The hydrophobic conjugate can be a small molecule with a partition coefficient that is higher than 10. The conjugate can be a sterol-type molecule such as cholesterol, or a molecule with an increased length polycarbon chain attached to C17, and the presence of a conjugate can influence the ability of an RNA molecule to be taken into a cell with or without a lipid transfection reagent. The conjugate can be attached to the passenger or guide strand through a hydrophobic linker. In some embodiments, a hydrophobic linker is 5-12C in length, and/or is hydroxypyrrolidine-based. In some embodiments, a hydrophobic conjugate is attached to the passenger strand and the CU residues of either the passenger and/or guide strand are modified. In some embodiments, at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the CU residues on the passenger strand and/or the guide strand are modified. In some aspects, molecules associated with the invention are self-delivering (sd). As used herein, "self-delivery" refers to the ability of a molecule to be delivered into a cell without the need for an additional delivery vehicle such as a transfection reagent.

Aspects of the invention relate to selecting molecules for use in RNAi. Molecules that have a double stranded region of 8-15 nucleotides can be selected for use in RNAi. In some embodiments, molecules are selected based on their thermodynamic stability (ΔG). In some embodiments, molecules will be selected that have a (ΔG) of less than -13 kkal/mol. For example, the (ΔG) value may be -13, -14, -15, -16, -17, -18, -19, -21, -22 or less than -22 kkal/mol. In other embodiments, the (ΔG) value may be higher than -13 kkal/mol. For example, the (ΔG) value may be -12, -11, -10, -9, -8, -7 or more than -7 kkal/mol. It should be appreciated that ΔG can be calculated using any method known in the art. In some embodiments ΔG is calculated using Mfold, available through the Mfold internet site (http://mfold.bioinfo.rpi.edu/cgi-bin/rna-form1.cgi). Methods for calculating ΔG are described in, and are incorporated by reference from, the following references: Zuker, M. (2003) Nucleic Acids Res., 31(13):3406-15; Mathews, D. H., Sabina, J., Zuker, M. and Turner, D. H. (1999) J. Mol. Biol. 288:911-940; Mathews, D. H., Disney, M. D., Childs, J. L., Schroeder, S. J., Zuker, M., and Turner, D. H. (2004) Proc. Natl. Acad. Sci. 101:7287-7292; Duan, S., Mathews, D. H., and Turner, D. H. (2006) Biochemistry 45:9819-9832; Wuchty, S., Fontana, W., Hofacker, I. L., and Schuster, P. (1999) Biopolymers 49:145-165.

In certain embodiments, the polynucleotide contains 5'- and/or 3'-end overhangs . The number and/or sequence of nucleotides overhang on one end of the polynucleotide may be the same or different from the other end of the polynucleotide. In certain embodiments, one or more of the overhang nucleotides may contain chemical modification(s), such as phosphorothioate or 2'-OMe modification.

In certain embodiments, the polynucleotide is unmodified. In other embodiments, at least one nucleotide is modified. In further embodiments, the modification includes a 2'-H or 2'-modified ribose sugar at the 2nd nucleotide from the 5'-end of the guide sequence. The "2nd nucleotide" is defined as the second nucleotide from the 5'-end of the polynucleotide.

As used herein, "2'-modified ribose sugar" includes those ribose sugars that do not have a 2'-OH group. "2'-modified ribose sugar" does not include 2'-deoxyribose (found in unmodified canonical DNA nucleotides). For example, the 2'-modified ribose sugar may be 2'-O-alkyl nucleotides, 2'-deoxy-2'-fluoro nucleotides, 2'-deoxy nucleotides, or combination thereof.

In certain embodiments, the 2'-modified nucleotides are pyrimidine nucleotides (*e.g.*, C /U). Examples of 2'-O-alkyl nucleotides include 2'-O-methyl nucleotides, or 2'-O-allyl nucleotides.

In certain embodiments, the sd-rxRNA polynucleotide of the invention with the above-referenced 5'-end modification exhibits significantly (*e.g.*, at least about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or more) less "off-target" gene silencing when compared to similar constructs without the specified 5'-end modification, thus greatly improving the overall specificity of the RNAi reagent or therapeutics.

As used herein, "off-target" gene silencing refers to unintended gene silencing due to, for example, spurious sequence homology between the antisense (guide) sequence and the unintended target mRNA sequence.

According to this aspect of the invention, certain guide strand modifications further increase nuclease stability, and/or lower interferon induction, without significantly decreasing RNAi activity (or no decrease in RNAi activity at all).

In some embodiments, wherein the RNAi construct involves a hairpin, the 5'-stem sequence may comprise a 2'-modified ribose sugar, such as 2'-O-methyl modified nucleotide, at the 2nd nucleotide on the 5'-end of the polynucleotide and, in some embodiments, no other modified nucleotides. The hairpin structure having such modification may have enhanced target specificity or reduced off-target silencing compared to a similar construct without the 2'-O-methyl modification at said position.

Certain combinations of specific 5'-stem sequence and 3'-stem sequence modifications may result in further unexpected advantages, as partly manifested by enhanced ability to inhibit target gene expression, enhanced serum stability, and/or increased target specificity, *etc.*

In certain embodiments, the guide strand comprises a 2'-O-methyl modified nucleotide at the 2nd nucleotide on the 5'-end of the guide strand and no other modified nucleotides.

In other aspects, the sd-rxRNA structures of the present invention mediates sequence-dependent gene silencing by a microRNA mechanism. As used herein, the term "microRNA" ("miRNA"), also referred to in the art as "small temporal RNAs"

("stRNAs"), refers to a small (10-50 nucleotide) RNA which are genetically encoded (e.g., by viral, mammalian, or plant genomes) and are capable of directing or mediating RNA silencing. An "miRNA disorder" shall refer to a disease or disorder characterized by an aberrant expression or activity of an miRNA.

microRNAs are involved in down-regulating target genes in critical pathways, such as development and cancer, in mice, worms and mammals. Gene silencing through a microRNA mechanism is achieved by specific yet imperfect base-pairing of the miRNA and its target messenger RNA (mRNA). Various mechanisms may be used in microRNA-mediated down-regulation of target mRNA expression.

miRNAs are noncoding RNAs of approximately 22 nucleotides which can regulate gene expression at the post transcriptional or translational level during plant and animal development. One common feature of miRNAs is that they are all excised from an approximately 70 nucleotide precursor RNA stem-loop termed pre-miRNA, probably by Dicer, an RNase III-type enzyme, or a homolog thereof. Naturally-occurring miRNAs are expressed by endogenous genes in vivo and are processed from a hairpin or stem-loop precursor (pre-miRNA or pri-miRNAs) by Dicer or other RNAses. miRNAs can exist transiently in vivo as a double-stranded duplex but only one strand is taken up by the RISC complex to direct gene silencing.

In some embodiments a version of sd-rxRNA compounds, which are effective in cellular uptake and inhibiting of miRNA activity are described. Essentially the compounds are similar to RISC entering version but large strand chemical modification patterns are optimized in the way to block cleavage and act as an effective inhibitor of the RISC action. For example, the compound might be completely or mostly Omethyl modified with the PS content described previously. For these types of compounds the 5' phosphorilation is not necessary. The presence of double stranded region is preferred as it is promotes cellular uptake and efficient RISC loading.

Another pathway that uses small RNAs as sequence-specific regulators is the RNA interference (RNAi) pathway, which is an evolutionarily conserved response to the presence of double-stranded RNA (dsRNA) in the cell. The dsRNAs are cleaved into ~20-base pair (bp) duplexes of small-interfering RNAs (siRNAs) by Dicer. These small RNAs get assembled into multiprotein effector complexes called RNA-induced silencing complexes (RISCs). The siRNAs then guide the cleavage of target mRNAs with perfect

complementarity.

Some aspects of biogenesis, protein complexes, and function are shared between the siRNA pathway and the miRNA pathway. The subject single-stranded polynucleotides may mimic the dsRNA in the siRNA mechanism, or the microRNA in the miRNA mechanism.

In certain embodiments, the modified RNAi constructs may have improved stability in serum and/or cerebral spinal fluid compared to an unmodified RNAi constructs having the same sequence.

In certain embodiments, the structure of the RNAi construct does not induce interferon response in primary cells, such as mammalian primary cells, including primary cells from human, mouse and other rodents, and other non-human mammals. In certain embodiments, the RNAi construct may also be used to inhibit expression of a target gene in an invertebrate organism.

To further increase the stability of the subject constructs *in vivo*, the 3'-end of the hairpin structure may be blocked by protective group(s). For example, protective groups such as inverted nucleotides, inverted abasic moieties, or amino-end modified nucleotides may be used. Inverted nucleotides may comprise an inverted deoxynucleotide. Inverted abasic moieties may comprise an inverted deoxyabasic moiety, such as a 3',3'-linked or 5',5'-linked deoxyabasic moiety.

The RNAi constructs of the invention are capable of inhibiting the synthesis of any target protein encoded by target gene(s). The invention includes methods to inhibit expression of a target gene either in a cell *in vitro*, or *in vivo*. As such, the RNAi constructs of the invention are useful for treating a patient with a disease characterized by the overexpression of a target gene.

The target gene can be endogenous or exogenous (*e.g.*, introduced into a cell by a virus or using recombinant DNA technology) to a cell. Such methods may include introduction of RNA into a cell in an amount sufficient to inhibit expression of the target gene. By way of example, such an RNA molecule may have a guide strand that is complementary to the nucleotide sequence of the target gene, such that the composition inhibits expression of the target gene.

The invention also relates to vectors expressing the subject hairpin constructs,

and cells comprising such vectors or the subject hairpin constructs. The cell may be a mammalian cell in vivo or in culture, such as a human cell.

The invention further relates to compositions comprising the subject RNAi constructs, and a pharmaceutically acceptable carrier or diluent.

Another aspect of the invention provides a method for inhibiting the expression of a target gene in a mammalian cell, comprising contacting the mammalian cell with any of the subject RNAi constructs.

The method may be carried out *in vitro, ex vivo,* or *in vivo*, in, for example, mammalian cells in culture, such as a human cell in culture.

The target cells (*e.g.*, mammalian cell) may be contacted in the presence of a delivery reagent, such as a lipid (*e.g.*, a cationic lipid) or a liposome.

Another aspect of the invention provides a method for inhibiting the expression of a target gene in a mammalian cell, comprising contacting the mammalian cell with a vector expressing the subject RNAi constructs.

In one aspect of the invention, a longer duplex polynucleotide is provided, including a first polynucleotide that ranges in size from about 16 to about 30 nucleotides; a second polynucleotide that ranges in size from about 26 to about 46 nucleotides, wherein the first polynucleotide (the antisense strand) is complementary to both the second polynucleotide (the sense strand) and a target gene, and wherein both polynucleotides form a duplex and wherein the first polynucleotide contains a single stranded region longer than 6 bases in length and is modified with alternative chemical modification pattern, and/or includes a conjugate moiety that facilitates cellular delivery. In this embodiment, between about 40% to about 90% of the nucleotides of the passenger strand between about 40% to about 90% of the nucleotides of the guide strand, and between about 40% to about 90% of the nucleotides of the single stranded region of the first polynucleotide are chemically modified nucleotides.

In an embodiment, the chemically modified nucleotide in the polynucleotide duplex may be any chemically modified nucleotide known in the art, such as those discussed in detail above. In a particular embodiment, the chemically modified nucleotide is selected from the group consisting of 2' F modified nucleotides ,2'-O-methyl modified and 2'deoxy nucleotides. In another particular embodiment, the

chemically modified nucleotides results from "hydrophobic modifications" of the nucleotide base. In another particular embodiment, the chemically modified nucleotides are phosphorothioates. In an additional particular embodiment, chemically modified nucleotides are combination of phosphorothioates, 2'-O-methyl, 2'deoxy, hydrophobic modifications and phosphorothioates. As these groups of modifications refer to modification of the ribose ring, back bone and nucleotide, it is feasible that some modified nucleotides will carry a combination of all three modification types.

In another embodiment, the chemical modification is not the same across the various regions of the duplex. In a particular embodiment, the first polynucleotide (the passenger strand), has a large number of diverse chemical modifications in various positions. For this polynucleotide up to 90% of nucleotides might be chemically modified and/or have mismatches introduced. In another embodiment, chemical modifications of the first or second polynucleotide include, but not limited to, 5' position modification of Uridine and Cytosine (4-pyridyl, 2-pyridyl, indolyl, phenyl (C_6H_5OH); tryptophanyl (C8H6N)CH2CH(NH2)CO), isobutyl, butyl, aminobenzyl; phenyl; naphthyl, etc), where the chemical modification might alter base pairing capabilities of a nucleotide. For the guide strand an important feature of this aspect of the invention is the position of the chemical modification relative to the 5' end of the antisense and sequence. For example, chemical phosphorylation of the 5' end of the guide strand is usually beneficial for efficacy. O-methyl modifications in the seed region of the sense strand (position 2-7 relative to the 5' end) are not generally well tolerated, whereas 2'F and deoxy are well tolerated. The mid part of the guide strand and the 3' end of the guide strand are more permissive in a type of chemical modifications applied. Deoxy modifications are not tolerated at the 3' end of the guide strand.

A unique feature of this aspect of the invention involves the use of hydrophobic modification on the bases. In one embodiment, the hydrophobic modifications are preferably positioned near the 5' end of the guide strand, in other embodiments, they localized in the middle of the guides strand, in other embodiment they localized at the 3' end of the guide strand and yet in another embodiment they are distributed thought the whole length of the polynucleotide. The same type of patterns is applicable to the passenger strand of the duplex.

The other part of the molecule is a single stranded region. The single stranded region is expected to range from 6 to 40 nucleotides.

In one embodiment, the single stranded region of the first polynucleotide contains modifications selected from the group consisting of between 40% and 90% hydrophobic base modifications, between 40%-90% phosphorothioates, between 40% -90% modification of the ribose moiety, and any combination of the preceding.

Efficiency of guide strand (first polynucleotide) loading into the RISC complex might be altered for heavily modified polynucleotides, so in one embodiment, the duplex polynucleotide includes a mismatch between nucleotide 9, 11, 12, 13, or 14 on the guide strand (first polynucleotide) and the opposite nucleotide on the sense strand (second polynucleotide) to promote efficient guide strand loading.

More detailed aspects of the invention are described in the sections below.

Duplex Characteristics

Double-stranded oligonucleotides of the invention may be formed by two separate complementary nucleic acid strands. Duplex formation can occur either inside or outside the cell containing the target gene.

As used herein, the term "duplex" includes the region of the double-stranded nucleic acid molecule(s) that is (are) hydrogen bonded to a complementary sequence. Double-stranded oligonucleotides of the invention may comprise a nucleotide sequence that is sense to a target gene and a complementary sequence that is antisense to the target gene. The sense and antisense nucleotide sequences correspond to the target gene sequence, *e.g.*, are identical or are sufficiently identical to effect target gene inhibition (*e.g.*, are about at least about 98% identical, 96% identical, 94%, 90% identical, 85% identical, or 80% identical) to the target gene sequence.

In certain embodiments, the double-stranded oligonucleotide of the invention is double-stranded over its entire length, *i.e.*, with no overhanging single-stranded sequence at either end of the molecule, *i.e.*, is blunt-ended. In other embodiments, the individual nucleic acid molecules can be of different lengths. In other words, a double-stranded oligonucleotide of the invention is not double-stranded over its entire length. For instance, when two separate nucleic acid molecules are used, one of the molecules, *e.g.*, the first molecule comprising an antisense sequence, can be longer than the second molecule hybridizing thereto (leaving a portion of the molecule single-stranded). Likewise, when a single nucleic acid molecule is used a portion of the molecule at either

end can remain single-stranded.

In one embodiment, a double-stranded oligonucleotide of the invention contains mismatches and/or loops or bulges, but is double-stranded over at least about 70% of the length of the oligonucleotide. In another embodiment, a double-stranded oligonucleotide of the invention is double-stranded over at least about 80% of the length of the oligonucleotide. In another embodiment, a double-stranded oligonucleotide of the invention is double-stranded over at least about 90%-95% of the length of the oligonucleotide. In another embodiment, a double-stranded oligonucleotide of the invention is double-stranded over at least about 96%-98% of the length of the oligonucleotide. In certain embodiments, the double-stranded oligonucleotide of the invention contains at least or up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 mismatches.

Modifications

The nucleotides of the invention may be modified at various locations, including the sugar moiety, the phosphodiester linkage, and/or the base.

In some embodiments, the base moiety of a nucleoside may be modified. For example, a pyrimidine base may be modified at the 2, 3, 4, 5, and/or 6 position of the pyrimidine ring. In some embodiments, the exocyclic amine of cytosine may be modified. A purine base may also be modified. For example, a purine base may be modified at the 1, 2, 3, 6, 7, or 8 position. In some embodiments, the exocyclic amine of adenine may be modified. In some cases, a nitrogen atom in a ring of a base moiety may be substituted with another atom, such as carbon. A modification to a base moiety may be any suitable modification. Examples of modifications are known to those of ordinary skill in the art. In some embodiments, the base modifications include alkylated purines or pyrimidines, acylated purines or pyrimidines, or other heterocycles.

In some embodiments, a pyrimidine may be modified at the 5 position. For example, the 5 position of a pyrimidine may be modified with an alkyl group, an alkynyl group, an alkenyl group, an acyl group, or substituted derivatives thereof. In other examples, the 5 position of a pyrimidine may be modified with a hydroxyl group or an alkoxyl group or substituted derivative thereof. Also, the N^4 position of a pyrimidine may be alkylated. In still further examples, the pyrimidine 5-6 bond may be saturated, a nitrogen atom within the pyrimidine ring may be substituted with a carbon atom, and/or

the O^2 and O^4 atoms may be substituted with sulfur atoms. It should be understood that other modifications are possible as well.

In other examples, the N^7 position and/or N^2 and/or N^3 position of a purine may be modified with an alkyl group or substituted derivative thereof. In further examples, a third ring may be fused to the purine bicyclic ring system and/or a nitrogen atom within the purine ring system may be substituted with a carbon atom. It should be understood that other modifications are possible as well.

Non-limiting examples of pyrimidines modified at the 5 position are disclosed in U.S. Patent 5591843, U.S. Patent 7,205,297, U.S. Patent 6,432,963, and U.S. Patent 6,020,483; non-limiting examples of pyrimidines modified at the N^4 position are disclosed in U.S Patent 5,580,731; non-limiting examples of purines modified at the 8 position are disclosed in U.S. Patent 6,355,787 and U.S. Patent 5,580,972; non-limiting examples of purines modified at the N^6 position are disclosed in U.S. Patent 4,853,386, U.S. Patent 5,789,416, and U.S. Patent 7,041,824; and non-limiting examples of purines modified at the 2 position are disclosed in U.S. Patent 4,201,860 and U.S. Patent 5,587,469, all of which are incorporated herein by reference.

Non-limiting examples of modified bases include N^4,N^4-ethanocytosine, 7-deazaxanthosine, 7-deazaguanosine, 8-oxo-N^6-methyladenine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-fluorouracil, 5-bromouracil, 5-carboxymethylaminomethyl-2-thiouracil, 5-carboxymethylaminomethyl uracil, dihydrouracil, inosine, N^6-isopentenyl-adenine, 1-methyladenine, 1-methylpseudouracil, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N^6 -methyladenine, 7-methylguanine, 5-methylaminomethyl uracil, 5-methoxy aminomethyl-2-thiouracil, 5-methoxyuracil, 2-methylthio-N^6-isopentenyladenine, pseudouracil, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, 2-thiocytosine, and 2,6-diaminopurine. In some embodiments, the base moiety may be a heterocyclic base other than a purine or pyrimidine. The heterocyclic base may be optionally modified and/or substituted.

Sugar moieties include natural, unmodified sugars, *e.g.*, monosaccharide (such as pentose, *e.g.*, ribose, deoxyribose), modified sugars and sugar analogs. In general, possible modifications of nucleomonomers, particularly of a sugar moiety, include, for example, replacement of one or more of the hydroxyl groups with a halogen, a

heteroatom, an aliphatic group, or the functionalization of the hydroxyl group as an ether, an amine, a thiol, or the like.

One particularly useful group of modified nucleomonomers are 2'-O-methyl nucleotides. Such 2'-O-methyl nucleotides may be referred to as "methylated," and the corresponding nucleotides may be made from unmethylated nucleotides followed by alkylation or directly from methylated nucleotide reagents. Modified nucleomonomers may be used in combination with unmodified nucleomonomers. For example, an oligonucleotide of the invention may contain both methylated and unmethylated nucleomonomers.

Some exemplary modified nucleomonomers include sugar- or backbone-modified ribonucleotides. Modified ribonucleotides may contain a non-naturally occurring base (instead of a naturally occurring base), such as uridines or cytidines modified at the 5'-position, *e.g.*, 5'-(2-amino)propyl uridine and 5'-bromo uridine; adenosines and guanosines modified at the 8-position, *e.g.*, 8-bromo guanosine; deaza nucleotides, *e.g.*, 7-deaza-adenosine; and N-alkylated nucleotides, *e.g.*, N6-methyl adenosine. Also, sugar-modified ribonucleotides may have the 2'-OH group replaced by a H, alxoxy (or OR), R or alkyl, halogen, SH, SR, amino (such as NH_2, NHR, NR_2), or CN group, wherein R is lower alkyl, alkenyl, or alkynyl.

Modified ribonucleotides may also have the phosphodiester group connecting to adjacent ribonucleotides replaced by a modified group, *e.g.*, of phosphorothioate group. More generally, the various nucleotide modifications may be combined.

Although the antisense (guide) strand may be substantially identical to at least a portion of the target gene (or genes), at least with respect to the base pairing properties, the sequence need not be perfectly identical to be useful, *e.g.*, to inhibit expression of a target gene's phenotype. Generally, higher homology can be used to compensate for the use of a shorter antisense gene. In some cases, the antisense strand generally will be substantially identical (although in antisense orientation) to the target gene.

The use of 2′-O-methyl modified RNA may also be beneficial in circumstances in which it is desirable to minimize cellular stress responses. RNA having 2′-O-methyl nucleomonomers may not be recognized by cellular machinery that is thought to recognize unmodified RNA. The use of 2′-O-methylated or partially 2′-O-methylated RNA may avoid the interferon response to double-stranded nucleic acids, while maintaining target RNA inhibition. This may be useful, for example, for avoiding the

interferon or other cellular stress responses, both in short RNAi (*e.g.*, siRNA) sequences that induce the interferon response, and in longer RNAi sequences that may induce the interferon response.

Overall, modified sugars may include D-ribose, 2′-O-alkyl (including 2′-O-methyl and 2′-O-ethyl), *i.e.*, 2′-alkoxy, 2′-amino, 2′-S-alkyl, 2′-halo (including 2′-fluoro), 2′- methoxyethoxy, 2′-allyloxy (-$OCH_2CH{=}CH_2$), 2′-propargyl, 2′-propyl, ethynyl, ethenyl, propenyl, and cyano and the like. In one embodiment, the sugar moiety can be a hexose and incorporated into an oligonucleotide as described (Augustyns, K., *et al.*, *Nucl. Acids. Res.* 18:4711 (1992)). Exemplary nucleomonomers can be found, *e.g.*, in U.S. Pat. No. 5,849,902, incorporated by reference herein.

Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics, 75th Ed.*, inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito: 1999, the entire contents of which are incorporated herein by reference.

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are all contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral

auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

In certain embodiments, oligonucleotides of the invention comprise 3′ and 5′ termini (except for circular oligonucleotides). In one embodiment, the 3′ and 5′ termini of an oligonucleotide can be substantially protected from nucleases *e.g.*, by modifying the 3′ or 5′ linkages (*e.g.*, U.S. Pat. No. 5,849,902 and WO 98/13526). For example, oligonucleotides can be made resistant by the inclusion of a "blocking group." The term "blocking group" as used herein refers to substituents (*e.g.*, other than OH groups) that can be attached to oligonucleotides or nucleomonomers, either as protecting groups or coupling groups for synthesis (*e.g.*, FITC, propyl (CH_2-CH_2-CH_3), glycol (-O-CH_2-CH_2-O-) phosphate (PO_3^{2-}), hydrogen phosphonate, or phosphoramidite). "Blocking groups" also include "end blocking groups" or "exonuclease blocking groups" which protect the 5′ and 3′ termini of the oligonucleotide, including modified nucleotides and non-nucleotide exonuclease resistant structures.

Exemplary end-blocking groups include cap structures (*e.g.*, a 7-methylguanosine cap), inverted nucleomonomers, *e.g.*, with 3′-3′ or 5′-5′ end inversions (see, *e.g.*, Ortiagao *et al.* 1992. *Antisense Res. Dev.* 2:129), methylphosphonate, phosphoramidite, non-nucleotide groups (*e.g.*, non-nucleotide linkers, amino linkers, conjugates) and the like. The 3′ terminal nucleomonomer can comprise a modified sugar moiety. The 3′ terminal nucleomonomer comprises a 3′-O that can optionally be substituted by a blocking group that prevents 3′-exonuclease degradation of the oligonucleotide. For example, the 3′-hydroxyl can be esterified to a nucleotide through a 3′→3′ internucleotide linkage. For example, the alkyloxy radical can be methoxy, ethoxy, or isopropoxy, and preferably, ethoxy. Optionally, the 3′→3′linked nucleotide at the 3′ terminus can be linked by a substitute linkage. To reduce nuclease degradation, the 5′ most 3′→5′ linkage can be a modified linkage, *e.g.*, a phosphorothioate or a P-alkyloxyphosphotriester linkage. Preferably, the two 5′ most 3′→5′ linkages are

modified linkages. Optionally, the 5′ terminal hydroxy moiety can be esterified with a phosphorus containing moiety, *e.g.*, phosphate, phosphorothioate, or P-ethoxyphosphate.

One of ordinary skill in the art will appreciate that the synthetic methods, as described herein, utilize a variety of protecting groups. By the term "protecting group," as used herein, it is meant that a particular functional moiety, *e.g.*, O, S, or N, is temporarily blocked so that a reaction can be carried out selectively at another reactive site in a multifunctional compound. In certain embodiments, a protecting group reacts selectively in good yield to give a protected substrate that is stable to the projected reactions; the protecting group should be selectively removable in good yield by readily available, preferably non-toxic reagents that do not attack the other functional groups; the protecting group forms an easily separable derivative (more preferably without the generation of new stereogenic centers); and the protecting group has a minimum of additional functionality to avoid further sites of reaction. As detailed herein, oxygen, sulfur, nitrogen, and carbon protecting groups may be utilized. Hydroxyl protecting groups include methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenyloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p,p′*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-

methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4′-bromophenacyloxyphenyl)diphenylmethyl, 4,4′,4″-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4′,4″-tris(levulinoyloxyphenyl)methyl, 4,4′,4″-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4′,4″-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1′-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl *p*-nitrophenyl carbonate, alkyl benzyl carbonate, alkyl *p*-methoxybenzyl carbonate, alkyl 3,4-dimethoxybenzyl carbonate, alkyl *o*-nitrobenzyl carbonate, alkyl *p*-nitrobenzyl carbonate, alkyl *S*-benzyl thiocarbonate, 4-ethoxy-1-napththyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenoate, *o*-(methoxycarbonyl)benzoate, α-naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, alkyl *N*-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). For protecting 1,2- or 1,3-diols, the protecting groups include methylene acetal, ethylidene acetal, 1-*t*-butylethylidene ketal, 1-phenylethylidene ketal, (4-methoxyphenyl)ethylidene acetal,

2,2,2-trichloroethylidene acetal, acetonide, cyclopentylidene ketal, cyclohexylidene ketal, cycloheptylidene ketal, benzylidene acetal, *p*-methoxybenzylidene acetal, 2,4-dimethoxybenzylidene ketal, 3,4-dimethoxybenzylidene acetal, 2-nitrobenzylidene acetal, methoxymethylene acetal, ethoxymethylene acetal, dimethoxymethylene ortho ester, 1-methoxyethylidene ortho ester, 1-ethoxyethylidine ortho ester, 1,2-dimethoxyethylidene ortho ester, α-methoxybenzylidene ortho ester, 1-(*N,N*-dimethylamino)ethylidene derivative, α-(*N,N'*-dimethylamino)benzylidene derivative, 2-oxacyclopentylidene ortho ester, di-*t*-butylsilylene group (DTBS), 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene) derivative (TIPDS), tetra-*t*-butoxydisiloxane-1,3-diylidene derivative (TBDS), cyclic carbonates, cyclic boronates, ethyl boronate, and phenyl boronate. Amino-protecting groups include methyl carbamate, ethyl carbamante, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethyl carbamate, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-*t*-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenylyl)ethyl carbamate (Bpoc), 1-(3,5-di-*t*-butylphenyl)-1-methylethyl carbamate (*t*-Bumeoc), 2-(2'- and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(*N,N*-dicyclohexylcarboxamido)ethyl carbamate, *t*-butyl carbamate (BOC), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, *N*-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate

(Tcroc), *m*-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, *o*-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(*o*-nitrophenyl)methyl carbamate, phenothiazinyl-(10)-carbonyl derivative, *N'*-*p*-toluenesulfonylaminocarbonyl derivative, *N'*-phenylaminothiocarbonyl derivative, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxycarbonylvinyl carbamate, *o*-(*N,N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*-(*p'*-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, *p*-(phenylazo)benzyl carbamate, 2,4,6-tri-*t*-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, 2,4,6-trimethylbenzyl carbamate, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivative, benzamide, *p*-phenylbenzamide, *o*-nitophenylacetamide, *o*-nitrophenoxyacetamide, acetoacetamide, (*N'*-dithiobenzyloxycarbonylamino)acetamide, 3-(*p*-hydroxyphenyl)propanamide, 3-(*o*-nitrophenyl)propanamide, 2-methyl-2-(*o*-nitrophenoxy)propanamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *N*-acetylmethionine derivative, *o*-nitrobenzamide, *o*-(benzoyloxymethyl)benzamide, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypropylamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyroolin-3-yl)amine, quaternary ammonium salts, *N*-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*-5-dibenzosuberylamine, *N*-triphenylmethylamine (Tr), *N*-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenylamine (PhF), *N*-2,7-dichloro-9-fluorenylmethyleneamine, *N*-

ferrocenylmethylamino (Fcm), *N*-2-picolylamino *N'*-oxide, *N*-1,1-dimethylthiomethyleneamine, *N*-benzylideneamine, *N*-*p*-methoxybenzylideneamine, *N*-diphenylmethyleneamine, *N*-[(2-pyridyl)mesityl]methyleneamine, *N*-(*N',N'*-dimethylaminomethylene)amine, *N,N'*-isopropylidenediamine, *N*-*p*-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivative, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentacarbonylchromium- or tungsten)carbonyl]amine, *N*-copper chelate, *N*-zinc chelate, *N*-nitroamine, *N*-nitrosoamine, amine *N*-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, 3-nitropyridinesulfenamide (Npys), *p*-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β-trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide. Exemplary protecting groups are detailed herein. However, it will be appreciated that the present invention is not intended to be limited to these protecting groups; rather, a variety of additional equivalent protecting groups can be readily identified using the above criteria and utilized in the method of the present invention. Additionally, a variety of protecting groups are described in *Protective Groups in Organic Synthesis,* Third Ed. Greene, T.W. and Wuts, P.G., Eds., John Wiley & Sons, New York: 1999, the entire contents of which are hereby incorporated by reference.

It will be appreciated that the compounds, as described herein, may be substituted with any number of substituents or functional moieties. In general, the term "substituted" whether preceeded by the term "optionally" or not, and substituents contained in formulas of this invention, refer to the replacement of hydrogen radicals in a given

structure with the radical of a specified substituent. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. Furthermore, this invention is not intended to be limited in any manner by the permissible substituents of organic compounds. Combinations of substituents and variables envisioned by this invention are preferably those that result in the formation of stable compounds useful in the treatment, for example, of infectious diseases or proliferative disorders. The term "stable", as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

The term "aliphatic," as used herein, includes both saturated and unsaturated, straight chain (*i.e.*, unbranched), branched, acyclic, cyclic, or polycyclic aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties. Thus, as used herein, the term "alkyl" includes straight, branched and cyclic alkyl groups. An analogous convention applies to other generic terms such as "alkenyl," "alkynyl," and the like. Furthermore, as used herein, the terms "alkyl," "alkenyl," "alkynyl," and the like encompass both substituted and unsubstituted groups. In certain embodiments, as used herein, "lower alkyl" is used to indicate those alkyl groups (cyclic, acyclic, substituted, unsubstituted, branched, or unbranched) having 1-6 carbon atoms.

In certain embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the

invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-4 carbon atoms. Illustrative aliphatic groups thus include, but are not limited to, for example, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, -CH_2-cyclopropyl, vinyl, allyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, cyclobutyl, -CH_2-cyclobutyl, *n*-pentyl, sec-pentyl, isopentyl, *tert*-pentyl, cyclopentyl, -CH_2-cyclopentyl, *n*-hexyl, *sec*-hexyl, cyclohexyl, -CH_2-cyclohexyl moieties and the like, which again, may bear one or more substituents. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (propargyl), 1-propynyl, and the like.

Some examples of substituents of the above-described aliphatic (and other) moieties of compounds of the invention include, but are not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; arylalkyl; heteroarylalkyl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; -F; -Cl; -Br; -I; -OH; -NO_2; -CN; -CF_3; -CH_2CF_3; -$CHCl_2$; -CH_2OH; -CH_2CH_2OH; -CH_2NH_2; -$CH_2SO_2CH_3$; -$C(O)R_x$; -$CO_2(R_x)$; -$CON(R_x)_2$; -$OC(O)R_x$; -OCO_2R_x; -$OCON(R_x)_2$; -$N(R_x)_2$; -$S(O)_2R_x$; -$NR_x(CO)R_x$ wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein any of the aliphatic, heteroaliphatic, arylalkyl, or heteroarylalkyl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments described herein.

The term "heteroaliphatic," as used herein, refers to aliphatic moieties that contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms, *e.g.*, in place of carbon atoms. Heteroaliphatic moieties may be branched, unbranched, cyclic or acyclic and include saturated and unsaturated heterocycles such as morpholino, pyrrolidinyl, *etc.* In certain embodiments, heteroaliphatic moieties are substituted by independent replacement of one or more of the hydrogen atoms thereon with one or more moieties including, but not limited to aliphatic; heteroaliphatic; aryl; heteroaryl;

arylalkyl; heteroarylalkyl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; -F; -Cl; -Br; -I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$, wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein any of the aliphatic, heteroaliphatic, arylalkyl, or heteroarylalkyl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substitutents are illustrated by the specific embodiments described herein.

The terms "halo" and "halogen" as used herein refer to an atom selected from fluorine, chlorine, bromine, and iodine.

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, *etc.*), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, *etc.*), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyls have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_1-C_6 includes alkyl groups containing 1 to 6 carbon atoms.

Moreover, unless otherwise specified, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having independently selected substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino,

sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, *e.g.*, with the substituents described above. An "alkylaryl" or an "arylalkyl" moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids. The term "n-alkyl" means a straight chain (*i.e.*, unbranched) unsubstituted alkyl group.

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term "alkenyl" includes straight-chain alkenyl groups (*e.g.*, ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, *etc.*), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_2-C_6 includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, unless otherwise specified, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls," the latter of which refers to alkenyl moieties having independently selected substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, the term "alkynyl" includes straight-chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, *etc.*), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, unless otherwise specified, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls," the latter of which refers to alkynyl moieties having independently selected substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with independently selected groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate,

phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulffiydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfmyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, *etc.*

The term "hydrophobic modifications' include bases modified in a fashion, where (1) overall hydrophobicity of the base is significantly increases, (2) the base is still capable of forming close to regular Watson –Crick interaction. Some, of the examples of base modifications include but are not limited to 5-position uridine and cytidine modifications like phenyl,

4-pyridyl, 2-pyridyl, indolyl, and isobutyl, phenyl (C6H5OH); tryptophanyl (C8H6N)CH2CH(NH2)CO), Isobutyl, butyl, aminobenzyl; phenyl; naphthyl,
For purposes of the present invention, the term "overhang" refers to terminal non-base pairing nucleotide(s) resulting from one strand or region extending beyond the terminus of the complementary strand to which the first strand or region forms a duplex. One or more polynucleotides that are capable of forming a duplex through hydrogen bonding can have overhangs. The overhand length generally doesn't exceed 5 bases in length.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

The term "hydroxy" or "hydroxyl" includes groups with an -OH or $-O^-$ (with an appropriate counterion).

The term "halogen" includes fluorine, bromine, chlorine, iodine, *etc.* The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The term "substituted" includes independently selected substituents which can be placed on the moiety and which allow the molecule to perform its intended function. Examples of substituents include alkyl, alkenyl, alkynyl, aryl, $(CR'R'')_{0-3}NR'R''$, $(CR'R'')_{0-3}CN$, NO_2, halogen, $(CR'R'')_{0-3}C(halogen)_3$, $(CR'R'')_{0-3}CH(halogen)_2$, $(CR'R'')_{0-3}CH_2(halogen)$, $(CR'R'')_{0-3}CONR'R''$, $(CR'R'')_{0-3}S(O)_{1-2}NR'R''$, $(CR'R'')_{0-3}CHO$, $(CR'R'')_{0-3}O(CR'R'')_{0-3}H$, $(CR'R'')_{0-3}S(O)_{0-2}R'$, $(CR'R'')_{0-3}O(CR'R'')_{0-3}H$, $(CR'R'')_{0-3}COR'$,

$(CR'R'')_{0-3}CO_2R'$, or $(CR'R'')_{0-3}OR'$ groups; wherein each R′ and R″ are each independently hydrogen, a C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, or aryl group, or R′ and R″ taken together are a benzylidene group or a $—(CH_2)_2O(CH_2)_2$- group.

The term "amine" or "amino" includes compounds or moieties in which a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term "alkyl amino" includes groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups.

The term "ether" includes compounds or moieties which contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl," which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to another alkyl group.

The terms "polynucleotide," "nucleotide sequence," "nucleic acid," "nucleic acid molecule," "nucleic acid sequence," and "oligonucleotide" refer to a polymer of two or more nucleotides. The polynucleotides can be DNA, RNA, or derivatives or modified versions thereof. The polynucleotide may be single-stranded or double-stranded. The polynucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, its hybridization parameters, *etc.* The polynucleotide may comprise a modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2- dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5- methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5- methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'- methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6- isopentenyladenine, wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil- 5-oxyacetic acid methylester, uracil-5-oxyacetic acid, 5-methyl-2- thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, and 2,6-diaminopurine. The olynucleotide may compirse a modified sugar moiety (*e.g.*, 2′-fluororibose, ribose, 2′-deoxyribose, 2′-O-methylcytidine, arabinose, and hexose), and/or a modified phosphate moiety (*e.g.*,

phosphorothioates and 5′-N-phosphoramidite linkages). A nucleotide sequence typically carries genetic information, including the information used by cellular machinery to make proteins and enzymes. These terms include double- or single-stranded genomic and cDNA, RNA, any synthetic and genetically manipulated polynucleotide, and both sense and antisense polynucleotides. This includes single- and double-stranded molecules, *i.e.*, DNA-DNA, DNA-RNA, and RNA-RNA hybrids, as well as "protein nucleic acids" (PNA) formed by conjugating bases to an amino acid backbone.

The term "base" includes the known purine and pyrimidine heterocyclic bases, deazapurines, and analogs (including heterocyclic substituted analogs, *e.g.*, aminoethyoxy phenoxazine), derivatives (*e.g.*, 1-alkyl-, 1-alkenyl-, heteroaromatic- and 1-alkynyl derivatives) and tautomers thereof. Examples of purines include adenine, guanine, inosine, diaminopurine, and xanthine and analogs (*e.g.*, 8-oxo-N^6-methyladenine or 7-diazaxanthine) and derivatives thereof. Pyrimidines include, for example, thymine, uracil, and cytosine, and their analogs (*e.g.*, 5-methylcytosine, 5-methyluracil, 5-(1-propynyl)uracil, 5-(1-propynyl)cytosine and 4,4-ethanocytosine). Other examples of suitable bases include non-purinyl and non-pyrimidinyl bases such as 2-aminopyridine and triazines.

In a preferred embodiment, the nucleomonomers of an oligonucleotide of the invention are RNA nucleotides. In another preferred embodiment, the nucleomonomers of an oligonucleotide of the invention are modified RNA nucleotides. Thus, the oligonucleotides contain modified RNA nucleotides.

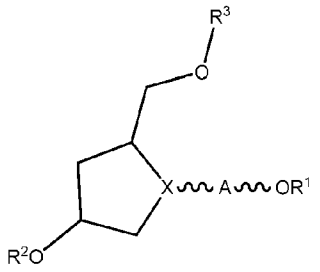
The term "nucleoside" includes bases which are covalently attached to a sugar moiety, preferably ribose or deoxyribose. Examples of preferred nucleosides include ribonucleosides and deoxyribonucleosides. Nucleosides also include bases linked to amino acids or amino acid analogs which may comprise free carboxyl groups, free amino groups, or protecting groups. Suitable protecting groups are well known in the art (see P. G. M. Wuts and T. W. Greene, "Protective Groups in Organic Synthesis", 2nd Ed., Wiley-Interscience, New York, 1999).

The term "nucleotide" includes nucleosides which further comprise a phosphate group or a phosphate analog.

The nucleic acid molecules may be associated with a hydrophobic moiety for targeting and/or delivery of the molecule to a cell. In certain embodiments, the

hydrophobic moiety is associated with the nucleic acid molecule through a linker. In certain embodiments, the association is through non-covalent interactions. In other embodiments, the association is through a covalent bond. Any linker known in the art may be used to associate the nucleic acid with the hydrophobic moiety. Linkers known in the art are described in published international PCT applications, WO 92/03464, WO 95/23162, WO 2008/021157, WO 2009/021157, WO 2009/134487, WO 2009/126933, U.S. Patent Application Publication 2005/0107325, U.S. Patent 5,414,077, U.S. Patent 5,419,966, U.S. Patent 5,512,667, U.S. Patent 5,646,126, and U.S. Patent 5,652,359, which are incorporated herein by reference. The linker may be as simple as a covalent bond to a multi-atom linker. The linker may be cyclic or acyclic. The linker may be optionally substituted. In certain embodiments, the linker is capable of being cleaved from the nucleic acid. In certain embodiments, the linker is capable of being hydrolyzed under physiological conditions. In certain embodiments, the linker is capable of being cleaved by an enzyme (*e.g.*, an esterase or phosphodiesterase). In certain embodiments, the linker comprises a spacer element to separate the nucleic acid from the hydrophobic moiety. The spacer element may include one to thirty carbon or heteroatoms. In certain embodiments, the linker and/or spacer element comprises protonatable functional groups. Such protonatable functional groups may promote the endosomal escape of the nucleic acid molecule. The protonatable functional groups may also aid in the delivery of the nucleic acid to a cell, for example, neutralizing the overall charge of the molecule. In other embodiments, the linker and/or spacer element is biologically inert (that is, it does not impart biological activity or function to the resulting nucleic acid molecule).

In certain embodiments, the nucleic acid molecule with a linker and hydrophobic moiety is of the formulae described herein. In certain embodiments, the nucleic acid molecule is of the formula:



wherein

X is N or CH;

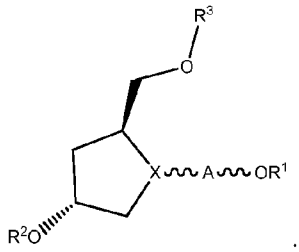
A is a bond; substituted or unsubstituted, cyclic or acyclic, branched or unbranched aliphatic; or substituted or unsubstituted, cyclic or acyclic, branched or unbranched heteroaliphatic;

R^1 is a hydrophobic moiety;

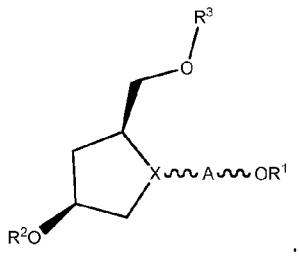
R^2 is hydrogen; an oxygen-protecting group; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; and

R^3 is a nucleic acid.

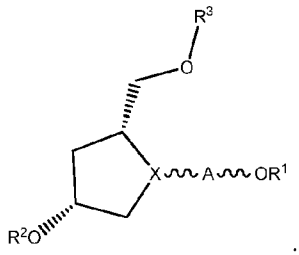
In certain embodiments, the molecule is of the formula:



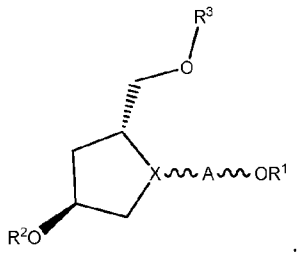
In certain embodiments, the molecule is of the formula:



In certain embodiments, the molecule is of the formula:



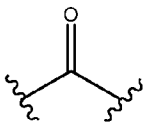
In certain embodiments, the molecule is of the formula:



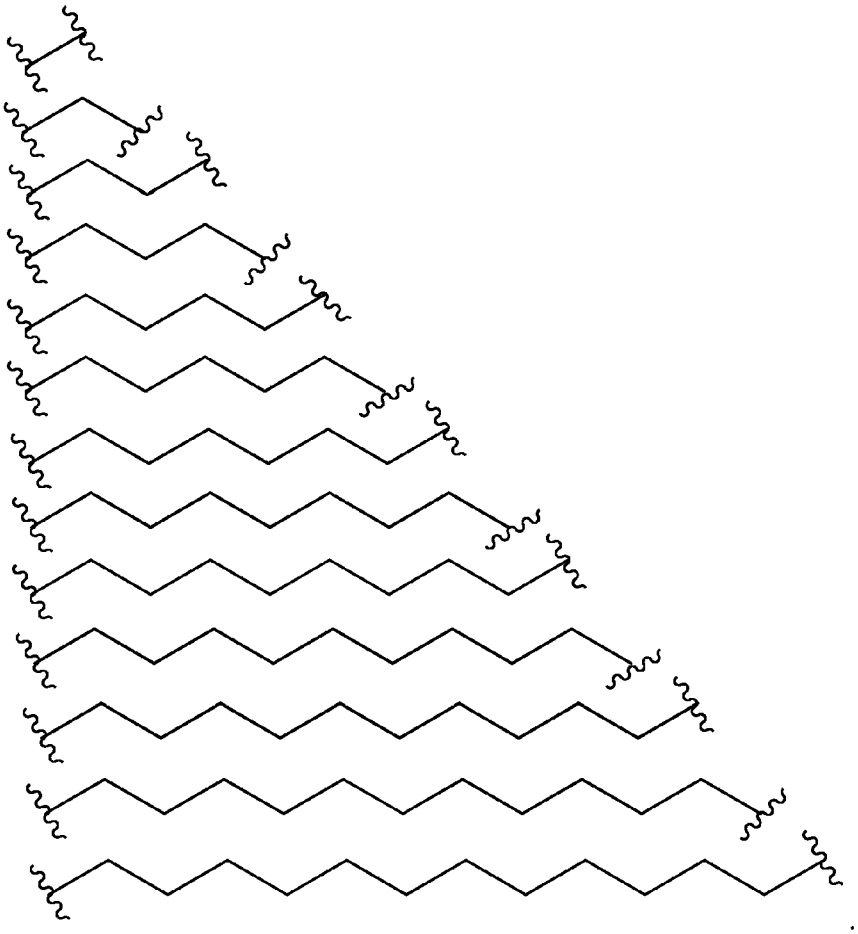
In certain embodiments, X is N. In certain embodiments, X is CH.

In certain embodiments, A is a bond. In certain embodiments, A is substituted or unsubstituted, cyclic or acyclic, branched or unbranched aliphatic. In certain embodiments, A is acyclic, substituted or unsubstituted, branched or unbranched aliphatic. In certain embodiments, A is acyclic, substituted, branched or unbranched aliphatic. In certain embodiments, A is acyclic, substituted, unbranched aliphatic. In certain embodiments, A is acyclic, substituted, unbranched alkyl. In certain embodiments, A is acyclic, substituted, unbranched C_{1-20} alkyl. In certain embodiments, A is acyclic, substituted, unbranched C_{1-12} alkyl. In certain embodiments, A is acyclic, substituted, unbranched C_{1-10} alkyl. In certain embodiments, A is acyclic, substituted, unbranched C_{1-8} alkyl. In certain embodiments, A is acyclic, substituted, unbranched C_{1-6} alkyl. In certain embodiments, A is substituted or unsubstituted, cyclic or acyclic, branched or unbranched heteroaliphatic. In certain embodiments, A is acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic. In certain embodiments, A is acyclic, substituted, branched or unbranched heteroaliphatic. In certain embodiments, A is acyclic, substituted, unbranched heteroaliphatic.

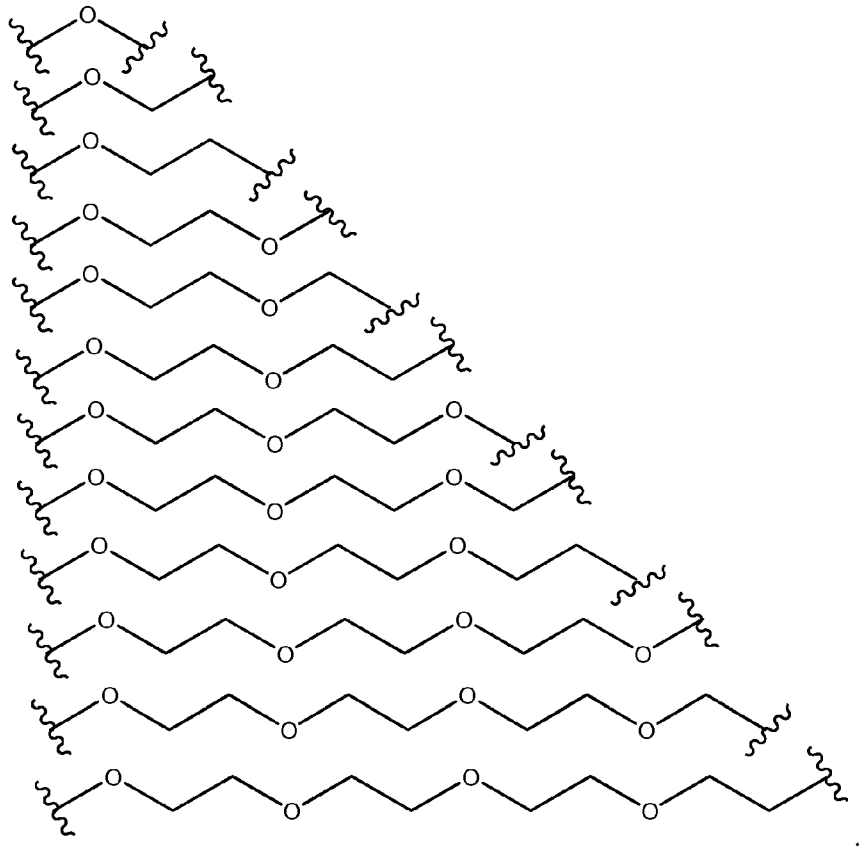
In certain embodiments, A is of the formula:



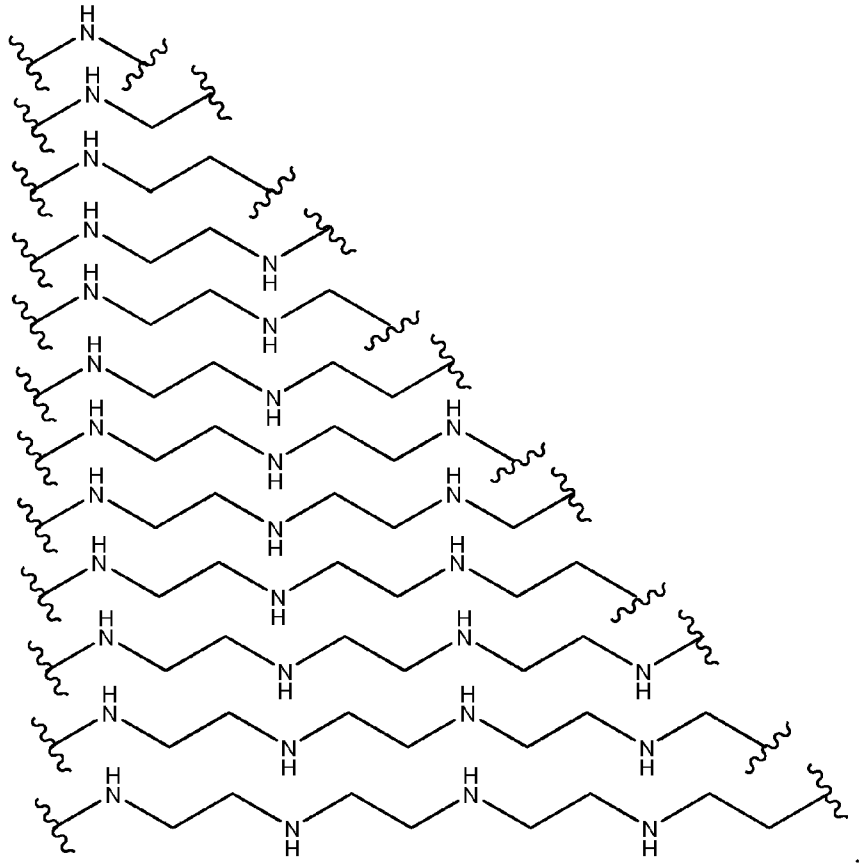
In certain embodiments, A is of one of the formulae:



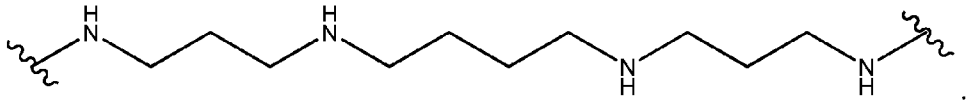
In certain embodiments, A is of one of the formulae:



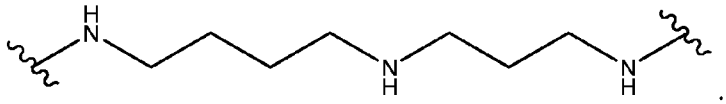
In certain embodiments, A is of one of the formulae:



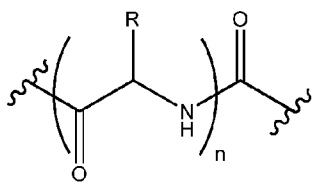
In certain embodiments, A is of the formula:



In certain embodiments, A is of the formula:



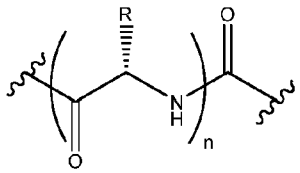
In certain embodiments, A is of the formula:



wherein

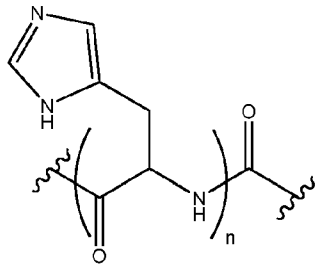
each occurrence of R is independently the side chain of a natural or unnatural amino acid; and

n is an integer between 1 and 20, inclusive. In certain embodiments, A is of the formula:

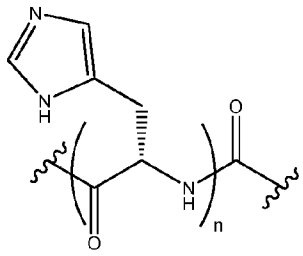


In certain embodiments, each occurrence of R is independently the side chain of a natural amino acid. In certain embodiments, n is an integer between 1 and 15, inclusive. In certain embodiments, n is an integer between 1 and 10, inclusive. In certain embodiments, n is an integer between 1 and 5, inclusive.

In certain embodiments, A is of the formula:

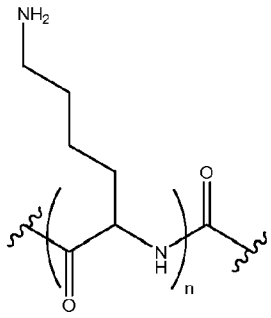


wherein n is an integer between 1 and 20, inclusive. In certain embodiments, A is of the formula:

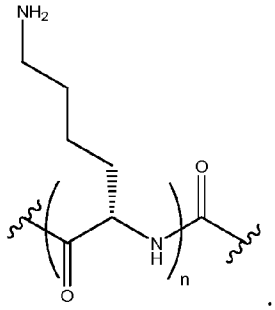


In certain embodiments, n is an integer between 1 and 15, inclusive. In certain embodiments, n is an integer between 1 and 10, inclusive. In certain embodiments, n is an integer between 1 and 5, inclusive.

In certain embodiments, A is of the formula:

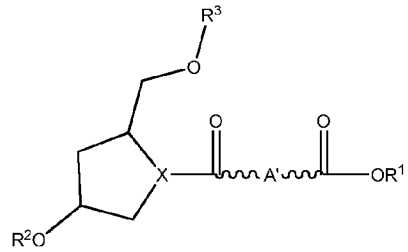


wherein n is an integer between 1 and 20, inclusive. In certain embodiments, A is of the formula:



In certain embodiments, n is an integer between 1 and 15, inclusive. In certain embodiments, n is an integer between 1 and 10, inclusive. In certain embodiments, n is an integer between 1 and 5, inclusive.

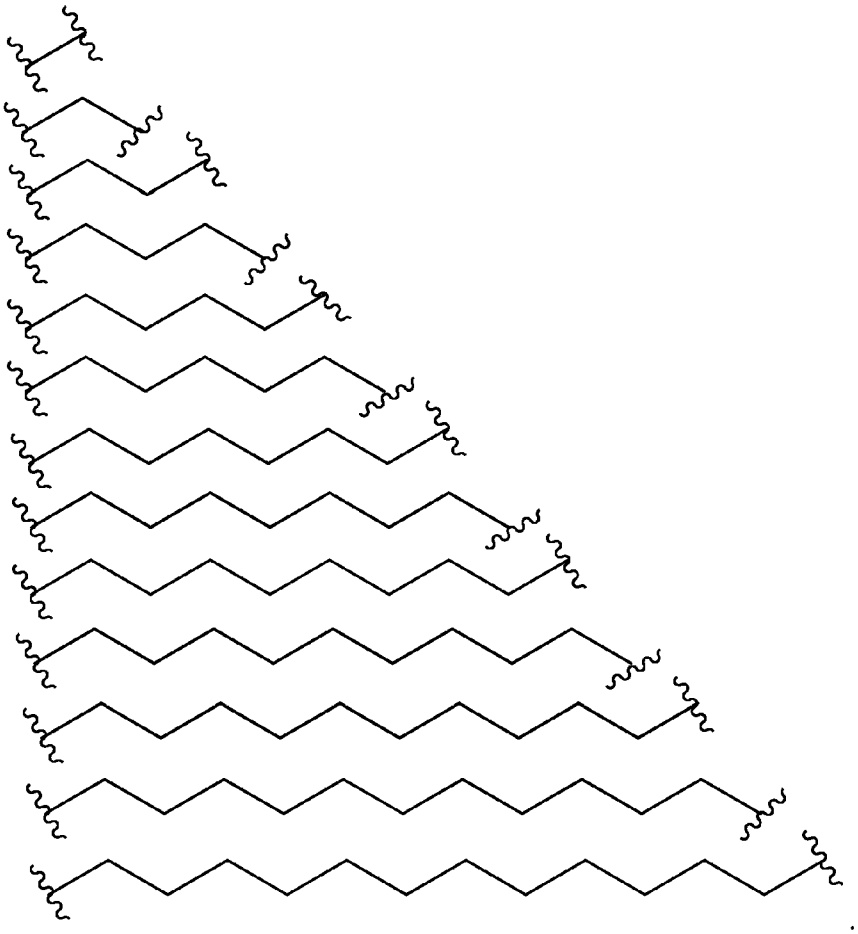
In certain embodiments, the molecule is of the formula:



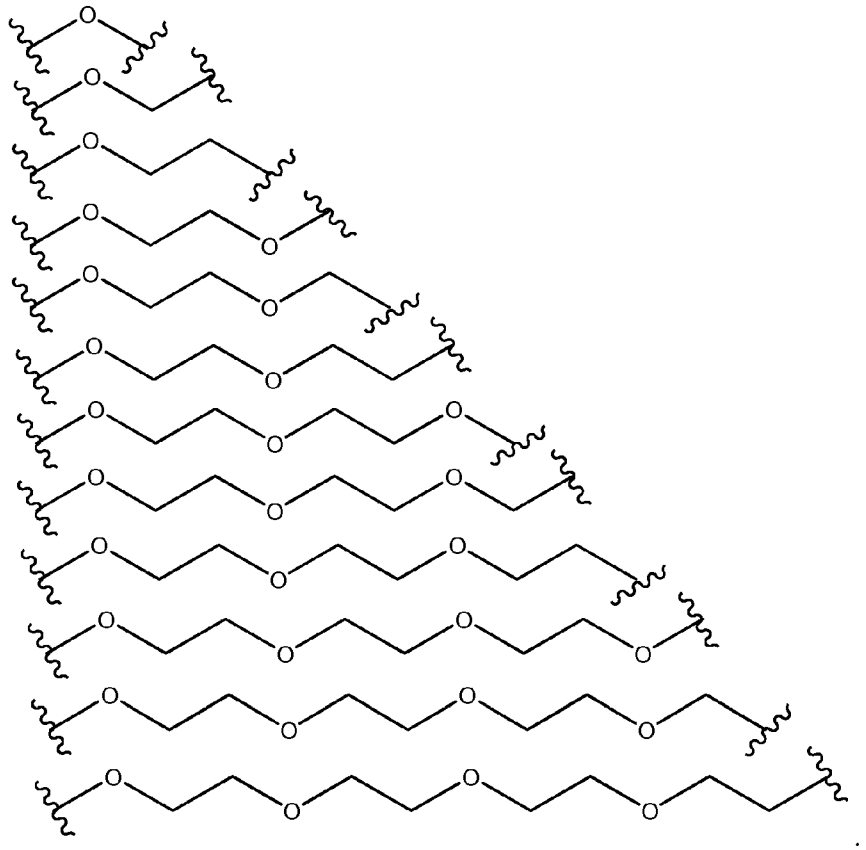
wherein X, R^1, R^2, and R^3 are as defined herein; and

A′ is substituted or unsubstituted, cyclic or acyclic, branched or unbranched aliphatic; or substituted or unsubstituted, cyclic or acyclic, branched or unbranched heteroaliphatic.

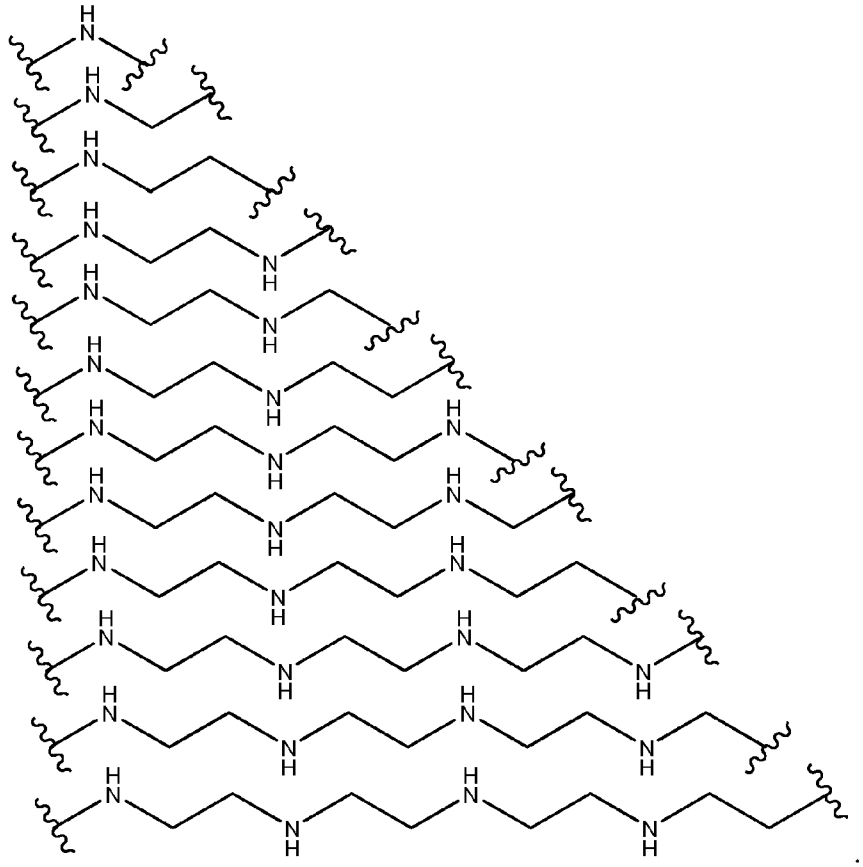
In certain embodiments, A′ is of one of the formulae:



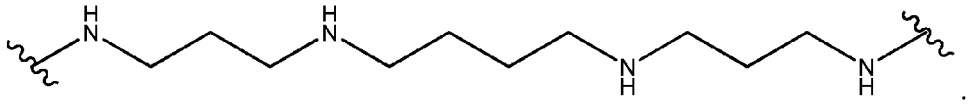
In certain embodiments, A is of one of the formulae:



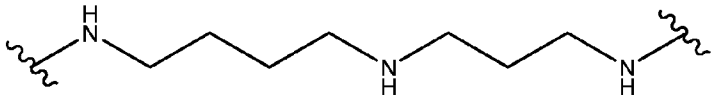
In certain embodiments, A is of one of the formulae:



In certain embodiments, A is of the formula:

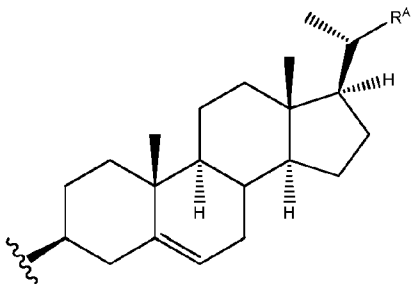


In certain embodiments, A is of the formula:



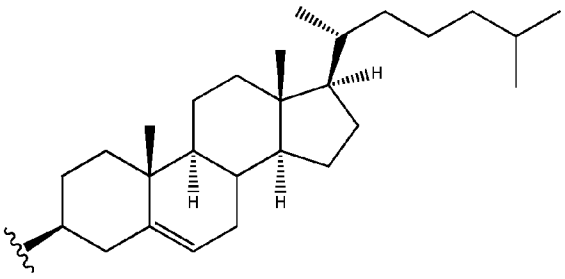
In certain embodiments, R^1 is a steroid. In certain embodiments, R^1 is a cholesterol. In certain embodiments, R^1 is a lipophilic vitamin. In certain embodiments, R^1 is a vitamin A. In certain embodiments, R^1 is a vitamin E.

In certain embodiments, R^1 is of the formula:

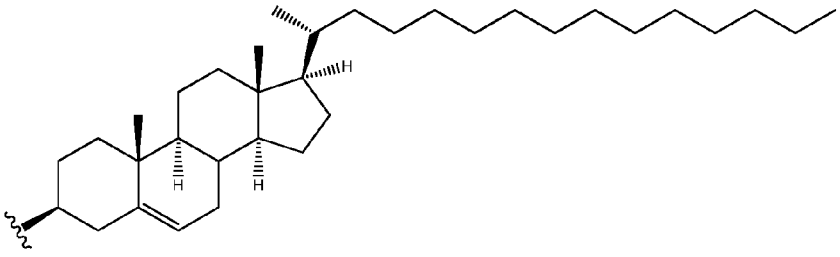


wherein R^A is substituted or unsubstituted, cyclic or acyclic, branched or unbranched aliphatic; or substituted or unsubstituted, cyclic or acyclic, branched or unbranched heteroaliphatic.

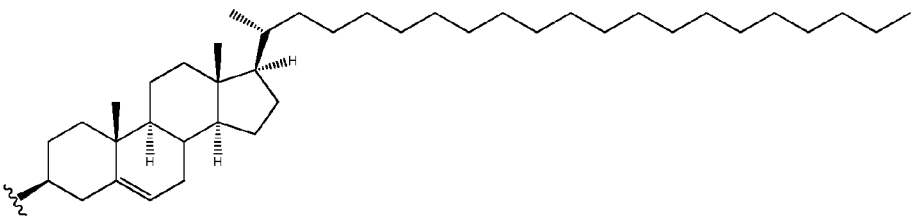
In certain embodiments, R^1 is of the formula:



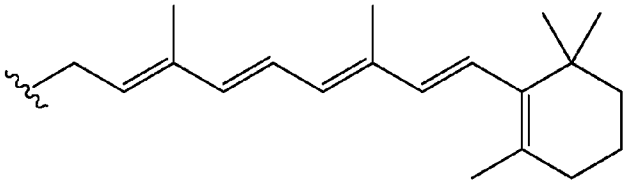
In certain embodiments, R^1 is of the formula:



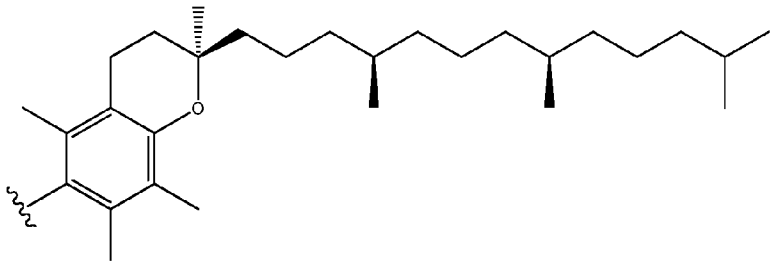
In certain embodiments, R^1 is of the formula:



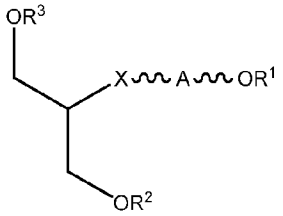
In certain embodiments, R^1 is of the formula:



In certain embodiments, R^1 is of the formula:



In certain embodiments, the nucleic acid molecule is of the formula:



wherein

X is N or CH;

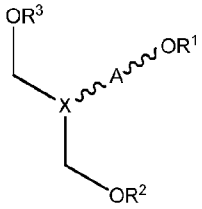
A is a bond; substituted or unsubstituted, cyclic or acyclic, branched or unbranched aliphatic; or substituted or unsubstituted, cyclic or acyclic, branched or unbranched heteroaliphatic;

R^1 is a hydrophobic moiety;

R^2 is hydrogen; an oxygen-protecting group; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; and

R^3 is a nucleic acid.

In certain embodiments, the nucleic acid molecule is of the formula:



wherein

X is N or CH;

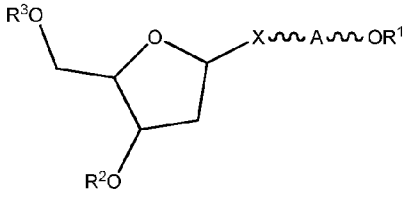
A is a bond; substituted or unsubstituted, cyclic or acyclic, branched or unbranched aliphatic; or substituted or unsubstituted, cyclic or acyclic, branched or unbranched heteroaliphatic;

R^1 is a hydrophobic moiety;

R^2 is hydrogen; an oxygen-protecting group; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; and

R^3 is a nucleic acid.

In certain embodiments, the nucleic acid molecule is of the formula:



wherein

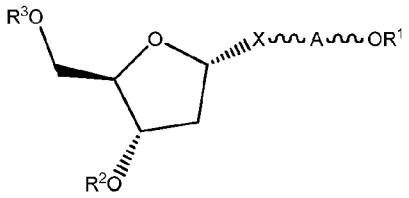
X is N or CH;

A is a bond; substituted or unsubstituted, cyclic or acyclic, branched or unbranched aliphatic; or substituted or unsubstituted, cyclic or acyclic, branched or unbranched heteroaliphatic;

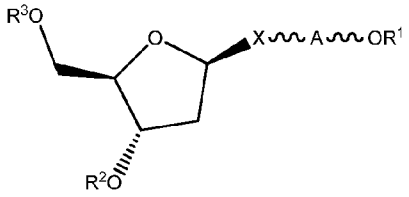
R^1 is a hydrophobic moiety;

R^2 is hydrogen; an oxygen-protecting group; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; and

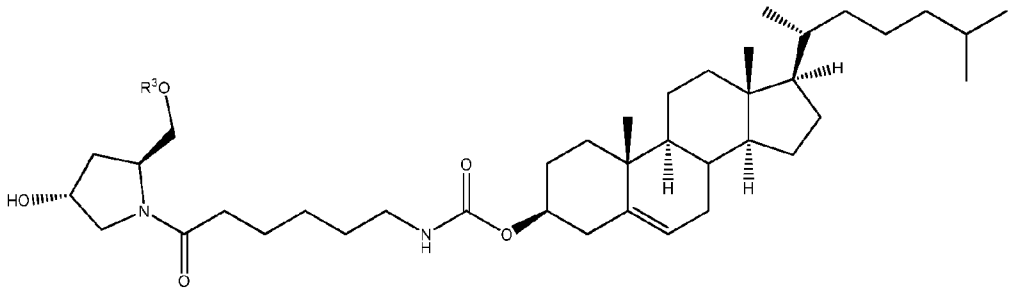
R^3 is a nucleic acid. In certain embodiments, the nucleic acid molecule is of the formula:



In certain embodiments, the nucleic acid molecule is of the formula:

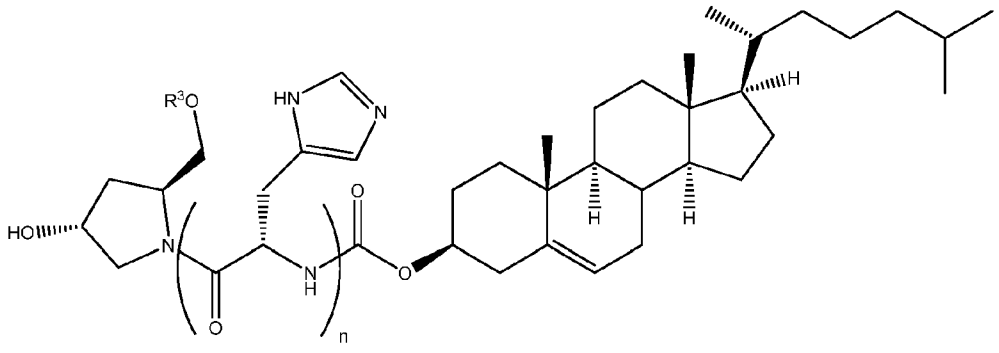


In certain embodiments, the nucleic acid molecule is of the formula:



wherein R^3 is a nucleic acid.

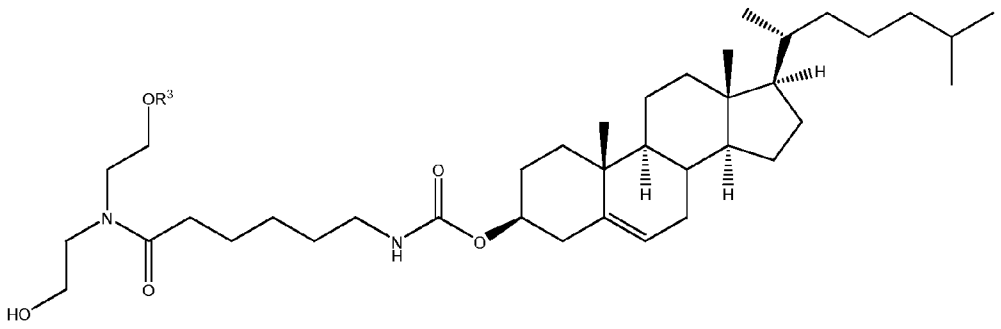
In certain embodiments, the nucleic acid molecule is of the formula:



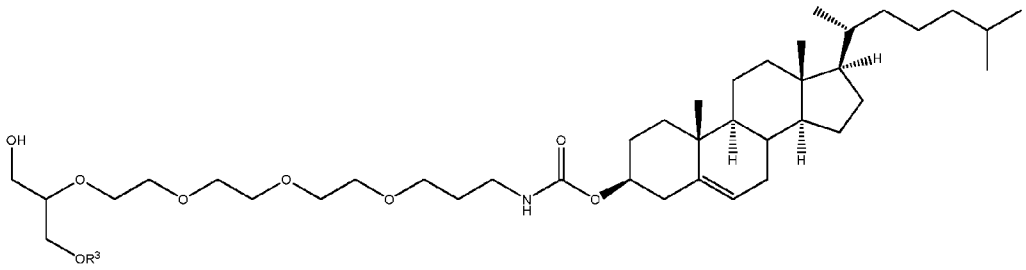
wherein R^3 is a nucleic acid; and

n is an integer between 1 and 20, inclusive.

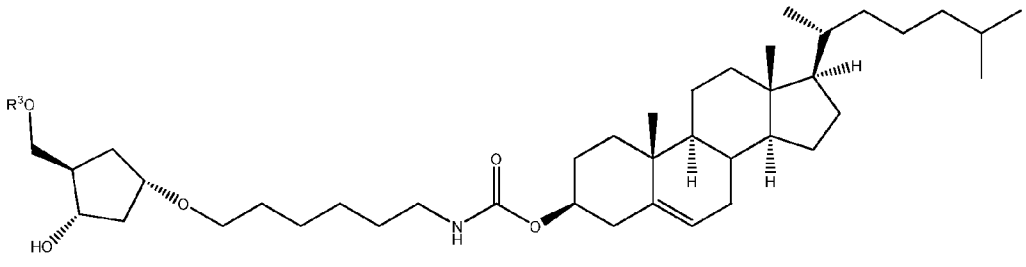
In certain embodiments, the nucleic acid molecule is of the formula:



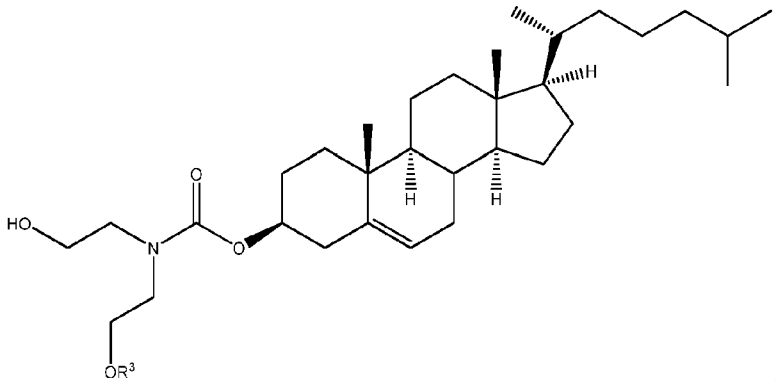
In certain embodiments, the nucleic acid molecule is of the formula:



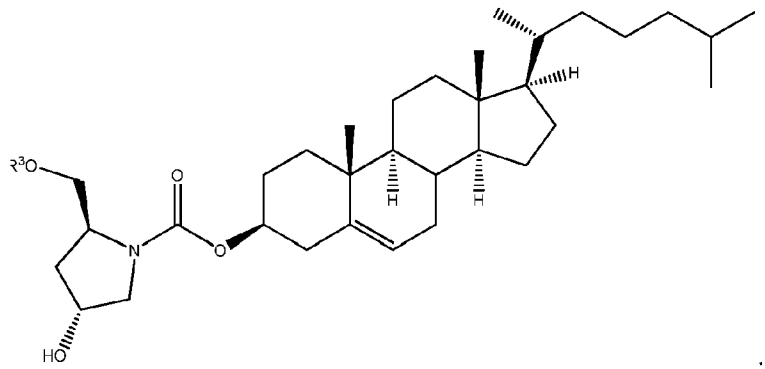
In certain embodiments, the nucleic acid molecule is of the formula:



In certain embodiments, the nucleic acid molecule is of the formula:



In certain embodiments, the nucleic acid molecule is of the formula:



As used herein, the term "linkage" includes a naturally occurring, unmodified phosphodiester moiety (-O-(PO^{2-})-O-) that covalently couples adjacent nucleomonomers. As used herein, the term "substitute linkage" includes any analog or derivative of the native phosphodiester group that covalently couples adjacent nucleomonomers. Substitute linkages include phosphodiester analogs, *e.g.*, phosphorothioate, phosphorodithioate, and P-ethyoxyphosphodiester, P-ethoxyphosphodiester, P-alkyloxyphosphotriester, methylphosphonate, and nonphosphorus containing linkages, *e.g.*, acetals and amides. Such substitute linkages are known in the art (*e.g.*, Bjergarde *et al.* 1991. Nucleic Acids Res. 19:5843; Caruthers *et al.* 1991. Nucleosides Nucleotides. 10:47). In certain embodiments, non-hydrolizable linkages are preferred, such as phosphorothioate linkages.

In certain embodiments, oligonucleotides of the invention comprise hydrophobicly modified nucleotides or "hydrophobic modifications." As used herein "hydrophobic modifications" refers to bases that are modified such that (1) overall hydrophobicity of the base is significantly increased, and/or (2) the base is still capable of forming close to regular Watson –Crick interaction. Several non-limiting examples of base modifications include 5-position uridine and cytidine modifications such as phenyl, 4-pyridyl, 2-pyridyl, indolyl, and isobutyl, phenyl (C6H5OH); tryptophanyl (C8H6N)CH2CH(NH2)CO), Isobutyl, butyl, aminobenzyl; phenyl; and naphthyl.

Another type of conjugates that can be attached to the end (3' or 5' end), the loop region, or any other parts of the sd-rxRNA might include a sterol, sterol type molecule, peptide, small molecule, protein, etc. In some embodiments, a sd-rxRNA may contain

more than one conjugates (same or different chemical nature). In some embodiments, the conjugate is cholesterol.

Another way to increase target gene specificity, or to reduce off-target silencing effect, is to introduce a 2'-modification (such as the 2'-O methyl modification) at a position corresponding to the second 5'-end nucleotide of the guide sequence. This allows the positioning of this 2'-modification in the Dicer-resistant hairpin structure, thus enabling one to design better RNAi constructs with less or no off-target silencing.

In one embodiment, a hairpin polynucleotide of the invention can comprise one nucleic acid portion which is DNA and one nucleic acid portion which is RNA. Antisense (guide) sequences of the invention can be "chimeric oligonucleotides" which comprise an RNA-like and a DNA-like region.

The language "RNase H activating region" includes a region of an oligonucleotide, *e.g.*, a chimeric oligonucleotide, that is capable of recruiting RNase H to cleave the target RNA strand to which the oligonucleotide binds. Typically, the RNase activating region contains a minimal core (of at least about 3-5, typically between about 3-12, more typically, between about 5-12, and more preferably between about 5-10 contiguous nucleomonomers) of DNA or DNA-like nucleomonomers. (See, *e.g.*, U.S. Pat. No. 5,849,902). Preferably, the RNase H activating region comprises about nine contiguous deoxyribose containing nucleomonomers.

The language "non-activating region" includes a region of an antisense sequence, *e.g.*, a chimeric oligonucleotide, that does not recruit or activate RNase H. Preferably, a non-activating region does not comprise phosphorothioate DNA. The oligonucleotides of the invention comprise at least one non-activating region. In one embodiment, the non-activating region can be stabilized against nucleases or can provide specificity for the target by being complementary to the target and forming hydrogen bonds with the target nucleic acid molecule, which is to be bound by the oligonucleotide.

In one embodiment, at least a portion of the contiguous polynucleotides are linked by a substitute linkage, *e.g.*, a phosphorothioate linkage.

In certain embodiments, most or all of the nucleotides beyond the guide sequence (2'-modified or not) are linked by phosphorothioate linkages. Such constructs tend to have improved pharmacokinetics due to their higher affinity for serum proteins. The phosphorothioate linkages in the non-guide sequence portion of the polynucleotide generally do not interfere with guide strand activity, once the latter is loaded into RISC.

Antisense (guide) sequences of the present invention may include "morpholino oligonucleotides." Morpholino oligonucleotides are non-ionic and function by an RNase H-independent mechanism. Each of the 4 genetic bases (Adenine, Cytosine, Guanine, and Thymine/Uracil) of the morpholino oligonucleotides is linked to a 6-membered morpholine ring. Morpholino oligonucleotides are made by joining the 4 different subunit types by, *e.g.*, non-ionic phosphorodiamidate inter-subunit linkages. Morpholino oligonucleotides have many advantages including: complete resistance to nucleases (Antisense & Nucl. Acid Drug Dev. 1996. 6:267); predictable targeting (Biochemica Biophysica Acta. 1999. 1489:141); reliable activity in cells (Antisense & Nucl. Acid Drug Dev. 1997. 7:63); excellent sequence specificity (Antisense & Nucl. Acid Drug Dev. 1997. 7:151); minimal non-antisense activity (Biochemica Biophysica Acta. 1999. 1489:141); and simple osmotic or scrape delivery (Antisense & Nucl. Acid Drug Dev. 1997. 7:291). Morpholino oligonucleotides are also preferred because of their non-toxicity at high doses. A discussion of the preparation of morpholino oligonucleotides can be found in Antisense & Nucl. Acid Drug Dev. 1997. 7:187.

The chemical modifications described herein are believed, based on the data described herein, to promote single stranded polynucleotide loading into the RISC. Single stranded polynucleotides have been shown to be active in loading into RISC and inducing gene silencing. However, the level of activity for single stranded polynucleotides appears to be 2 to 4 orders of magnitude lower when compared to a duplex polynucleotide.

The present invention provides a description of the chemical modification patterns, which may (a) significantly increase stability of the single stranded polynucleotide (b) promote efficient loading of the polynucleotide into the RISC complex and (c) improve uptake of the single stranded nucleotide by the cell. Figure 5 provides some non-limiting examples of the chemical modification patterns which may be beneficial for achieving single stranded polynucleotide efficacy inside the cell. The chemical modification patterns may include combination of ribose, backbone, hydrophobic nucleoside and conjugate type of modifications. In addition, in some of the embodiments, the 5' end of the single polynucleotide may be chemically phosphorylated.

In yet another embodiment, the present invention provides a description of the chemical modifications patterns, which improve functionality of RISC inhibiting polynucleotides. Single stranded polynucleotides have been shown to inhibit activity of a

preloaded RISC complex through the substrate competition mechanism. For these types of molecules, conventionally called antagomers, the activity usually requires high concentration and in vivo delivery is not very effective. The present invention provides a description of the chemical modification patterns, which may (a) significantly increase stability of the single stranded polynucleotide (b) promote efficient recognition of the polynucleotide by the RISC as a substrate and/or (c) improve uptake of the single stranded nucleotide by the cell. Figure 6 provides some non-limiting examples of the chemical modification patterns that may be beneficial for achieving single stranded polynucleotide efficacy inside the cell. The chemical modification patterns may include combination of ribose, backbone, hydrophobic nucleoside and conjugate type of modifications.

The modifications provided by the present invention are applicable to all polynucleotides. This includes single stranded RISC entering polynucleotides, single stranded RISC inhibiting polynucleotides, conventional duplexed polynucleotides of variable length (15- 40 bp),asymmetric duplexed polynucleotides, and the like. Polynucleotides may be modified with wide variety of chemical modification patterns, including 5' end, ribose, backbone and hydrophobic nucleoside modifications.

Synthesis

Oligonucleotides of the invention can be synthesized by any method known in the art, *e.g.*, using enzymatic synthesis and/or chemical synthesis. The oligonucleotides can be synthesized *in vitro* (*e.g.*, using enzymatic synthesis and chemical synthesis) or *in vivo* (using recombinant DNA technology well known in the art).

In a preferred embodiment, chemical synthesis is used for modified polynucleotides. Chemical synthesis of linear oligonucleotides is well known in the art and can be achieved by solution or solid phase techniques. Preferably, synthesis is by solid phase methods. Oligonucleotides can be made by any of several different synthetic procedures including the phosphoramidite, phosphite triester, H-phosphonate, and phosphotriester methods, typically by automated synthesis methods.

Oligonucleotide synthesis protocols are well known in the art and can be found, *e.g.*, in U.S. Pat. No. 5,830,653; WO 98/13526; Stec *et al.* 1984. *J. Am. Chem. Soc.* 106:6077; Stec *et al.* 1985. *J. Org. Chem.* 50:3908; Stec *et al.* J. Chromatog. 1985.

326:263; LaPlanche *et al.* 1986. *Nucl. Acid. Res.* 1986. 14:9081; Fasman G. D., 1989. Practical Handbook of Biochemistry and Molecular Biology. 1989. CRC Press, Boca Raton, Fla.; Lamone. 1993. *Biochem. Soc. Trans.* 21:1; U.S. Pat. No. 5,013,830; U.S. Pat. No. 5,214,135; U.S. Pat. No. 5,525,719; Kawasaki *et al.* 1993. *J. Med. Chem.* 36:831; WO 92/03568; U.S. Pat. No. 5,276,019; and U.S. Pat. No. 5,264,423.

The synthesis method selected can depend on the length of the desired oligonucleotide and such choice is within the skill of the ordinary artisan. For example, the phosphoramidite and phosphite triester method can produce oligonucleotides having 175 or more nucleotides, while the H-phosphonate method works well for oligonucleotides of less than 100 nucleotides. If modified bases are incorporated into the oligonucleotide, and particularly if modified phosphodiester linkages are used, then the synthetic procedures are altered as needed according to known procedures. In this regard, Uhlmann *et al.* (1990, *Chemical Reviews* 90:543-584) provide references and outline procedures for making oligonucleotides with modified bases and modified phosphodiester linkages. Other exemplary methods for making oligonucleotides are taught in Sonveaux. 1994. "Protecting Groups in Oligonucleotide Synthesis"; Agrawal. *Methods in Molecular Biology* 26:1. Exemplary synthesis methods are also taught in "Oligonucleotide Synthesis - A Practical Approach" (Gait, M. J. IRL Press at Oxford University Press. 1984). Moreover, linear oligonucleotides of defined sequence, including some sequences with modified nucleotides, are readily available from several commercial sources.

The oligonucleotides may be purified by polyacrylamide gel electrophoresis, or by any of a number of chromatographic methods, including gel chromatography and high pressure liquid chromatography. To confirm a nucleotide sequence, especially unmodified nucleotide sequences, oligonucleotides may be subjected to DNA sequencing by any of the known procedures, including Maxam and Gilbert sequencing, Sanger sequencing, capillary electrophoresis sequencing, the wandering spot sequencing procedure or by using selective chemical degradation of oligonucleotides bound to Hybond paper. Sequences of short oligonucleotides can also be analyzed by laser desorption mass spectroscopy or by fast atom bombardment (McNeal, *et al.*, 1982, *J. Am. Chem. Soc.* 104:976; Viari, *et al.*, 1987, *Biomed. Environ. Mass Spectrom.* 14:83; Grotjahn *et al.*, 1982, *Nuc. Acid Res.* 10:4671). Sequencing methods are also available for RNA oligonucleotides.

The quality of oligonucleotides synthesized can be verified by testing the oligonucleotide by capillary electrophoresis and denaturing strong anion HPLC (SAX-HPLC) using, *e.g.*, the method of Bergot and Egan. 1992. *J. Chrom.* 599:35.

Other exemplary synthesis techniques are well known in the art (see, *e.g.*, Sambrook *et al.*, Molecular Cloning: a Laboratory Manual, Second Edition (1989); DNA Cloning, Volumes I and II (DN Glover Ed. 1985); Oligonucleotide Synthesis (M J Gait Ed, 1984; Nucleic Acid Hybridisation (B D Hames and S J Higgins eds. 1984); A Practical Guide to Molecular Cloning (1984); or the series, Methods in Enzymology (Academic Press, Inc.)).

In certain embodiments, the subject RNAi constructs or at least portions thereof are transcribed from expression vectors encoding the subject constructs. Any art recognized vectors may be use for this purpose. The transcribed RNAi constructs may be isolated and purified, before desired modifications (such as replacing an unmodified sense strand with a modified one, *etc.*) are carried out.

Delivery/Carrier

Uptake of Oligonucleotides by Cells

Oligonucleotides and oligonucleotide compositions are contacted with (*i.e.*, brought into contact with, also referred to herein as administered or delivered to) and taken up by one or more cells or a cell lysate. The term "cells" includes prokaryotic and eukaryotic cells, preferably vertebrate cells, and, more preferably, mammalian cells. In a preferred embodiment, the oligonucleotide compositions of the invention are contacted with human cells.

Oligonucleotide compositions of the invention can be contacted with cells *in vitro*, *e.g.*, in a test tube or culture dish, (and may or may not be introduced into a subject) or *in vivo*, *e.g.*, in a subject such as a mammalian subject. Oligonucleotides are taken up by cells at a slow rate by endocytosis, but endocytosed oligonucleotides are generally sequestered and not available, *e.g.*, for hybridization to a target nucleic acid molecule. In one embodiment, cellular uptake can be facilitated by electroporation or calcium phosphate precipitation. However, these procedures are only useful for *in vitro* or ex vivo embodiments, are not convenient and, in some cases, are associated with cell toxicity.

In another embodiment, delivery of oligonucleotides into cells can be enhanced by suitable art recognized methods including calcium phosphate, DMSO, glycerol or dextran, electroporation, or by transfection, *e.g.*, using cationic, anionic, or neutral lipid compositions or liposomes using methods known in the art (see *e.g.*, WO 90/14074; WO 91/16024; WO 91/17424; U.S. Pat. No. 4,897,355; Bergan *et al.* 1993. *Nucleic Acids Research.* 21:3567). Enhanced delivery of oligonucleotides can also be mediated by the use of vectors (See *e.g.*, Shi, Y. 2003. Trends Genet 2003 Jan. 19:9; Reichhart J M *et al.* Genesis. 2002. 34(1-2):1604, Yu *et al.* 2002. Proc. Natl. Acad Sci. USA 99:6047; Sui *et al.* 2002. Proc. Natl. Acad Sci. USA 99:5515) viruses, polyamine or polycation conjugates using compounds such as polylysine, protamine, or Ni, N12-bis (ethyl) spermine (see, *e.g.*, Bartzatt, R. *et al.*1989. *Biotechnol. Appl. Biochem.* 11:133; Wagner E. *et al.* 1992. *Proc. Natl. Acad. Sci.* 88:4255).

In certain embodiments, the sd-rxRNA of the invention may be delivered by using various beta-glucan containing particles, referred to as GeRPs (glucan encapsulated RNA loaded particle), described in, and incorporated by reference from, US Provisional Application No. 61/310,611, filed on March 4, 2010 and entitled "Formulations and Methods for Targeted Delivery to Phagocyte Cells." Such particles are also described in, and incorporated by reference from US Patent Publications US 2005/0281781 A1, and US 2010/0040656, and in PCT publications WO 2006/007372, and WO 2007/050643. The sd-rxRNA molecule may be hydrophobically modified and optionally may be associated with a lipid and/or amphiphilic peptide. In certain embodiments, the beta-glucan particle is derived from yeast. In certain embodiments, the payload trapping molecule is a polymer, such as those with a molecular weight of at least about 1000 Da, 10,000 Da, 50,000 Da, 100 kDa, 500 kDa, etc. Preferred polymers include (without limitation) cationic polymers, chitosans, or PEI (polyethylenimine), etc.

Glucan particles can be derived from insoluble components of fungal cell walls such as yeast cell walls. In some embodiments, the yeast is Baker's yeast. Yeast-derived glucan molecules can include one or more of ß-(1,3)-Glucan, ß-(1,6)-Glucan, mannan and chitin. In some embodiments, a glucan particle comprises a hollow yeast cell wall whereby the particle maintains a three dimensional structure resembling a cell, within which it can complex with or encapsulate a molecule such as an RNA molecule. Some of the advantages associated with the use of yeast cell wall particles are

availability of the components, their biodegradable nature, and their ability to be targeted to phagocytic cells.

In some embodiments, glucan particles can be prepared by extraction of insoluble components from cell walls, for example by extracting Baker's yeast (Fleischmann's) with 1M NaOH/pH 4.0 H2O, followed by washing and drying. Methods of preparing yeast cell wall particles are discussed in, and incorporated by reference from U.S. Patents 4,810,646, 4,992,540, 5,082,936, 5,028,703, 5,032,401, 5,322,841, 5,401,727, 5,504,079, 5,607,677, 5,968,811, 6,242,594, 6,444,448, 6,476,003, US Patent Publications 2003/0216346, 2004/0014715 and 2010/0040656, and PCT published application WO02/12348.

Protocols for preparing glucan particles are also described in, and incorporated by reference from, the following references: Soto and Ostroff (2008), "Characterization of multilayered nanoparticles encapsulated in yeast cell wall particles for DNA delivery." *Bioconjug Chem* 19(4):840-8; Soto and Ostroff (2007), "Oral Macrophage Mediated Gene Delivery System," *Nanotech*, Volume 2, Chapter 5 ("Drug Delivery"), pages 378-381; and Li et al. (2007), "Yeast glucan particles activate murine resident macrophages to secrete proinflammatory cytokines via MyD88-and Syk kinase-dependent pathways." *Clinical Immunology* 124(2):170-181.

Glucan containing particles such as yeast cell wall particles can also be obtained commercially. Several non-limiting examples include: Nutricell MOS 55 from Biorigin (Sao Paolo, Brazil), SAF-Mannan (SAF Agri, Minneapolis, Minn.), Nutrex (Sensient Technologies, Milwaukee, Wis.), alkali-extracted particles such as those produced by Nutricepts (Nutricepts Inc., Burnsville, Minn.) and ASA Biotech, acid-extracted WGP particles from Biopolymer Engineering, and organic solvent-extracted particles such as Adjuvax™ from Alpha-beta Technology, Inc. (Worcester, Mass.) and microparticulate glucan from Novogen (Stamford, Conn.).

Glucan particles such as yeast cell wall particles can have varying levels of purity depending on the method of production and/or extraction. In some instances, particles are alkali-extracted, acid-extracted or organic solvent-extracted to remove intracellular components and/or the outer mannoprotein layer of the cell wall. Such protocols can produce particles that have a glucan (w/w) content in the range of 50% - 90%. In some instances, a particle of lower purity, meaning lower glucan w/w content may be

preferred, while in other embodiments, a particle of higher purity, meaning higher glucan w/w content may be preferred.

Glucan particles, such as yeast cell wall particles, can have a natural lipid content. For example, the particles can contain 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20% or more than 20% w/w lipid. In the Examples section, the effectiveness of two glucan particle batches are tested: YGP SAF and YGP SAF + L (containing natural lipids). In some instances, the presence of natural lipids may assist in complexation or capture of RNA molecules.

Glucan containing particles typically have a diameter of approximately 2-4 microns, although particles with a diameter of less than 2 microns or greater than 4 microns are also compatible with aspects of the invention.

The RNA molecule(s) to be delivered are complexed or "trapped" within the shell of the glucan particle. The shell or RNA component of the particle can be labeled for visualization, as described in, and incorporated by reference from, Soto and Ostroff (2008) *Bioconjug Chem* 19:840. Methods of loading GeRPs are discussed further below.

The optimal protocol for uptake of oligonucleotides will depend upon a number of factors, the most crucial being the type of cells that are being used. Other factors that are important in uptake include, but are not limited to, the nature and concentration of the oligonucleotide, the confluence of the cells, the type of culture the cells are in (*e.g.*, a suspension culture or plated) and the type of media in which the cells are grown.

Encapsulating Agents

Encapsulating agents entrap oligonucleotides within vesicles. In another embodiment of the invention, an oligonucleotide may be associated with a carrier or vehicle, *e.g.*, liposomes or micelles, although other carriers could be used, as would be appreciated by one skilled in the art. Liposomes are vesicles made of a lipid bilayer having a structure similar to biological membranes. Such carriers are used to facilitate the cellular uptake or targeting of the oligonucleotide, or improve the oligonucleotides pharmacokinetic or toxicological properties.

For example, the oligonucleotides of the present invention may also be administered encapsulated in liposomes, pharmaceutical compositions wherein the active ingredient is contained either dispersed or variously present in corpuscles consisting of

aqueous concentric layers adherent to lipidic layers. The oligonucleotides, depending upon solubility, may be present both in the aqueous layer and in the lipidic layer, or in what is generally termed a liposomic suspension. The hydrophobic layer, generally but not exclusively, comprises phopholipids such as lecithin and sphingomyelin, steroids such as cholesterol, more or less ionic surfactants such as diacetylphosphate, stearylamine, or phosphatidic acid, or other materials of a hydrophobic nature. The diameters of the liposomes generally range from about 15 nm to about 5 microns.

The use of liposomes as drug delivery vehicles offers several advantages. Liposomes increase intracellular stability, increase uptake efficiency and improve biological activity. Liposomes are hollow spherical vesicles composed of lipids arranged in a similar fashion as those lipids which make up the cell membrane. They have an internal aqueous space for entrapping water soluble compounds and range in size from 0.05 to several microns in diameter. Several studies have shown that liposomes can deliver nucleic acids to cells and that the nucleic acids remain biologically active. For example, a lipid delivery vehicle originally designed as a research tool, such as Lipofectin or LIPOFECTAMINE™ 2000, can deliver intact nucleic acid molecules to cells.

Specific advantages of using liposomes include the following: they are non-toxic and biodegradable in composition; they display long circulation half-lives; and recognition molecules can be readily attached to their surface for targeting to tissues. Finally, cost-effective manufacture of liposome-based pharmaceuticals, either in a liquid suspension or lyophilized product, has demonstrated the viability of this technology as an acceptable drug delivery system.

In some aspects, formulations associated with the invention might be selected for a class of naturally occurring or chemically synthesized or modified saturated and unsaturated fatty acid residues. Fatty acids might exist in a form of triglycerides, diglycerides or individual fatty acids. In another embodiment, the use of well-validated mixtures of fatty acids and/or fat emulsions currently used in pharmacology for parenteral nutrition may be utilized.

Liposome based formulations are widely used for oligonucleotide delivery. However, most of commercially available lipid or liposome formulations contain at least one positively charged lipid (cationic lipids). The presence of this positively charged

lipid is believed to be essential for obtaining a high degree of oligonucleotide loading and for enhancing liposome fusogenic properties. Several methods have been performed and published to identify optimal positively charged lipid chemistries. However, the commercially available liposome formulations containing cationic lipids are characterized by a high level of toxicity. In vivo limited therapeutic indexes have revealed that liposome formulations containing positive charged lipids are associated with toxicity (i.e. elevation in liver enzymes) at concentrations only slightly higher than concentration required to achieve RNA silencing.

Nucleic acids associated with the invention can be hydrophobically modified and can be encompassed within neutral nanotransporters. Further description of neutral nanotransporters is incorporated by reference from PCT Application PCT/US2009/005251, filed on September 22, 2009, and entitled "Neutral Nanotransporters." Such particles enable quantitative oligonucleotide incorporation into non-charged lipid mixtures. The lack of toxic levels of cationic lipids in such neutral nanotransporter compositions is an important feature.

As demonstrated in PCT/US2009/005251, oligonucleotides can effectively be incorporated into a lipid mixture that is free of cationic lipids and such a composition can effectively deliver a therapeutic oligonucleotide to a cell in a manner that it is functional. For example, a high level of activity was observed when the fatty mixture was composed of a phosphatidylcholine base fatty acid and a sterol such as a cholesterol. For instance, one preferred formulation of neutral fatty mixture is composed of at least 20% of DOPC or DSPC and at least 20% of sterol such as cholesterol. Even as low as 1:5 lipid to oligonucleotide ratio was shown to be sufficient to get complete encapsulation of the oligonucleotide in a non charged formulation.

The neutral nanotransporters compositions enable efficient loading of oligonucleotide into neutral fat formulation. The composition includes an oligonucleotide that is modified in a manner such that the hydrophobicity of the molecule is increased (for example a hydrophobic molecule is attached (covalently or no-covalently) to a hydrophobic molecule on the oligonucleotide terminus or a non-terminal nucleotide, base, sugar, or backbone), the modified oligonucleotide being mixed with a neutral fat formulation (for example containing at least 25 % of cholesterol and 25% of DOPC or analogs thereof). A cargo molecule, such as another lipid can also be included in the composition. This composition, where part of the formulation is build into the

oligonucleotide itself, enables efficient encapsulation of oligonucleotide in neutral lipid particles.

In some aspects, stable particles ranging in size from 50 to 140 nm can be formed upon complexing of hydrophobic oligonucleotides with preferred formulations. It is interesting to mention that the formulation by itself typically does not form small particles, but rather, forms agglomerates, which are transformed into stable 50-120 nm particles upon addition of the hydrophobic modified oligonucleotide.

The neutral nanotransporter compositions of the invention include a hydrophobic modified polynucleotide, a neutral fatty mixture, and optionally a cargo molecule. A "hydrophobic modified polynucleotide" as used herein is a polynucleotide of the invention (i.e. sd-rxRNA) that has at least one modification that renders the polynucleotide more hydrophobic than the polynucleotide was prior to modification. The modification may be achieved by attaching (covalently or non-covalently) a hydrophobic molecule to the polynucleotide. In some instances the hydrophobic molecule is or includes a lipophilic group.

The term "lipophilic group" means a group that has a higher affinity for lipids than its affinity for water. Examples of lipophilic groups include, but are not limited to, cholesterol, a cholesteryl or modified cholesteryl residue, adamantine, dihydrotesterone, long chain alkyl, long chain alkenyl, long chain alkynyl, olely-lithocholic, cholenic, oleoyl-cholenic, palmityl, heptadecyl, myrisityl, bile acids, cholic acid or taurocholic acid, deoxycholate, oleyl litocholic 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, digoxygenin, dimethoxytrityl, t-butyldimethylsilyl, t-butyldiphenylsilyl, cyanine dyes (e.g. Cy3 or Cy5), Hoechst 33258 dye, psoralen, or ibuprofen. The cholesterol moiety may be reduced (e.g. as in cholestan) or may be substituted (e.g. by halogen). A combination of different lipophilic groups in one molecule is also possible.

The hydrophobic molecule may be attached at various positions of the polynucleotide. As described above, the hydrophobic molecule may be linked to the terminal residue of the polynucleotide such as the 3' of 5'-end of the polynucleotide. Alternatively, it may be linked to an internal nucleotide or a nucleotide on a branch of

the polynucleotide. The hydrophobic molecule may be attached, for instance to a 2'-position of the nucleotide. The hydrophobic molecule may also be linked to the heterocyclic base, the sugar or the backbone of a nucleotide of the polynucleotide.

The hydrophobic molecule may be connected to the polynucleotide 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 (spacer 9) or hexaethylenegylcol (spacer 18), or alkane-diol, such as butanediol. The spacer units are preferably linked by phosphodiester 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.

Typical conjugation protocols involve the synthesis of polynucleotides bearing an aminolinker at one or more positions of the sequence, however, a linker is not required. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction may be performed either with the polynucleotide still bound to a solid support or following cleavage of the polynucleotide in solution phase. Purification of the modified polynucleotide by HPLC typically results in a pure material.

In some embodiments the hydrophobic molecule is a sterol type conjugate, a PhytoSterol conjugate, cholesterol conjugate, sterol type conjugate with altered side chain length, fatty acid conjugate, any other hydrophobic group conjugate, and/or hydrophobic modifications of the internal nucleoside, which provide sufficient hydrophobicity to be incorporated into micelles.

For purposes of the present invention, the term "sterols", refers or steroid alcohols are a subgroup of steroids with a hydroxyl group at the 3-position of the A-ring. They are amphipathic lipids synthesized from acetyl-coenzyme A via the HMG-CoA reductase pathway. The overall molecule is quite flat. The hydroxyl group on the A ring is polar. The rest of the aliphatic chain is non-polar. Usually sterols are considered to have an 8 carbon chain at position 17.

For purposes of the present invention, the term "sterol type molecules", refers to steroid alcohols, which are similar in structure to sterols. The main difference is the structure of the ring and number of carbons in a position 21 attached side chain.

For purposes of the present invention, the term "PhytoSterols" (also called plant sterols) are a group of steroid alcohols, phytochemicals naturally occurring in plants. There are more then 200 different known PhytoSterols

For purposes of the present invention, the term "Sterol side chain" refers to a chemical composition of a side chain attached at the position 17 of sterol-type molecule. In a standard definition sterols are limited to a 4 ring structure carrying a 8 carbon chain at position 17. In this invention, the sterol type molecules with side chain longer and shorter than conventional are described. The side chain may branched or contain double back bones.

Thus, sterols useful in the invention, for example, include cholesterols, as well as unique sterols in which position 17 has attached side chain of 2-7 or longer then 9 carbons. In a particular embodiment, the length of the polycarbon tail is varied between 5 and 9 carbons. Such conjugates may have significantly better in vivo efficacy, in particular delivery to liver. These types of molecules are expected to work at concentrations 5 to 9 fold lower then oligonucleotides conjugated to conventional cholesterols.

Alternatively the polynucleotide may be bound to a protein, peptide or positively charged chemical that functions as the hydrophobic molecule. The proteins may be selected from the group consisting of protamine, dsRNA binding domain, and arginine rich peptides. Exemplary positively charged chemicals include spermine, spermidine, cadaverine, and putrescine.

In another embodiment hydrophobic molecule conjugates may demonstrate even higher efficacy when it is combined with optimal chemical modification patterns of the polynucleotide (as described herein in detail), containing but not limited to hydrophobic modifications, phosphorothioate modifications, and 2' ribo modifications.

In another embodiment the sterol type molecule may be a naturally occurring PhytoSterols. The polycarbon chain may be longer than 9 and may be linear, branched and/or contain double bonds. Some PhytoSterol containing polynucleotide conjugates may be significantly more potent and active in delivery of polynucleotides to various tissues. Some PhytoSterols may demonstrate tissue preference and thus be used as a way to delivery RNAi specifically to particular tissues.

The hydrophobic modified polynucleotide is mixed with a neutral fatty mixture to form a micelle. The neutral fatty acid mixture is a mixture of fats that has a net neutral

or slightly net negative charge at or around physiological pH that can form a micelle with the hydrophobic modified polynucleotide. For purposes of the present invention, the term "micelle" refers to a small nanoparticle formed by a mixture of non charged fatty acids and phospholipids. The neutral fatty mixture may include cationic lipids as long as they are present in an amount that does not cause toxicity. In preferred embodiments the neutral fatty mixture is free of cationic lipids. A mixture that is free of cationic lipids is one that has less than 1% and preferably 0% of the total lipid being cationic lipid. The term "cationic lipid" includes lipids and synthetic lipids having a net positive charge at or around physiological pH. The term "anionic lipid" includes lipids and synthetic lipids having a net negative charge at or around physiological pH.

The neutral fats bind to the oligonucleotides of the invention by a strong but non-covalent attraction (*e.g.*, an electrostatic, van der Waals, pi-stacking, *etc.* interaction).

The neutral fat mixture may include formulations selected from a class of naturally occurring or chemically synthesized or modified saturated and unsaturated fatty acid residues. Fatty acids might exist in a form of triglycerides, diglycerides or individual fatty acids. In another embodiment the use of well-validated mixtures of fatty acids and/or fat emulsions currently used in pharmacology for parenteral nutrition may be utilized.

The neutral fatty mixture is preferably a mixture of a choline based fatty acid and a sterol. Choline based fatty acids include for instance, synthetic phosphocholine derivatives such as DDPC, DLPC, DMPC, DPPC, DSPC, DOPC, POPC, and DEPC. DOPC (chemical registry number 4235-95-4) is dioleoylphosphatidylcholine (also known as dielaidoylphosphatidylcholine, dioleoyl-PC, dioleoylphosphocholine, dioleoyl-sn-glycero-3-phosphocholine, dioleylphosphatidylcholine). DSPC (chemical registry number 816-94-4) is distearoylphosphatidylcholine (also known as 1,2-Distearoyl-sn-Glycero-3-phosphocholine).

The sterol in the neutral fatty mixture may be for instance cholesterol. The neutral fatty mixture may be made up completely of a choline based fatty acid and a sterol or it may optionally include a cargo molecule. For instance, the neutral fatty mixture may have at least 20% or 25% fatty acid and 20% or 25% sterol.

For purposes of the present invention, the term "Fatty acids" relates to conventional description of fatty acid. They may exist as individual entities or in a form of two-and triglycerides. For purposes of the present invention, the term "fat emulsions"

refers to safe fat formulations given intravenously to subjects who are unable to get enough fat in their diet. It is an emulsion of soy bean oil (or other naturally occurring oils) and egg phospholipids. Fat emulsions are being used for formulation of some insoluble anesthetics. In this disclosure, fat emulsions might be part of commercially available preparations like Intralipid, Liposyn, Nutrilipid, modified commercial preparations, where they are enriched with particular fatty acids or fully de novo-formulated combinations of fatty acids and phospholipids.

In one embodiment, the cells to be contacted with an oligonucleotide composition of the invention are contacted with a mixture comprising the oligonucleotide and a mixture comprising a lipid, *e.g.*, one of the lipids or lipid compositions described supra for between about 12 hours to about 24 hours. In another embodiment, the cells to be contacted with an oligonucleotide composition are contacted with a mixture comprising the oligonucleotide and a mixture comprising a lipid, *e.g.*, one of the lipids or lipid compositions described supra for between about 1 and about five days. In one embodiment, the cells are contacted with a mixture comprising a lipid and the oligonucleotide for between about three days to as long as about 30 days. In another embodiment, a mixture comprising a lipid is left in contact with the cells for at least about five to about 20 days. In another embodiment, a mixture comprising a lipid is left in contact with the cells for at least about seven to about 15 days.

50%-60% of the formulation can optionally be any other lipid or molecule. Such a lipid or molecule is referred to herein as a cargo lipid or cargo molecule. Cargo molecules include but are not limited to intralipid, small molecules, fusogenic peptides or lipids or other small molecules might be added to alter cellular uptake, endosomal release or tissue distribution properties. The ability to tolerate cargo molecules is important for modulation of properties of these particles, if such properties are desirable. For instance the presence of some tissue specific metabolites might drastically alter tissue distribution profiles. For example use of Intralipid type formulation enriched in shorter or longer fatty chains with various degrees of saturation affects tissue distribution profiles of these type of formulations (and their loads).

An example of a cargo lipid useful according to the invention is a fusogenic lipid. For instance, the zwiterionic lipid DOPE (chemical registry number 4004-5-1, 1,2-Dioleoyl-sn-Glycero-3-phosphoethanolamine) is a preferred cargo lipid.

Intralipid may be comprised of the following composition: 1 000 mL contain: purified soybean oil 90 g, purified egg phospholipids 12 g, glycerol anhydrous 22 g, water for injection q.s. ad 1 000 mL. pH is adjusted with sodium hydroxide to pH approximately 8. Energy content/L: 4.6 MJ (190 kcal). Osmolality (approx.): 300 mOsm/kg water. In another embodiment fat emulsion is Liposyn that contains 5% safflower oil, 5% soybean oil, up to 1.2% egg phosphatides added as an emulsifier and 2.5% glycerin in water for injection. It may also contain sodium hydroxide for pH adjustment. pH 8.0 (6.0 - 9.0). Liposyn has an osmolarity of 276 m Osmol/liter (actual).

Variation in the identity, amounts and ratios of cargo lipids affects the cellular uptake and tissue distribution characteristics of these compounds. For example, the length of lipid tails and level of saturability will affect differential uptake to liver, lung, fat and cardiomyocytes. Addition of special hydrophobic molecules like vitamins or different forms of sterols can favor distribution to special tissues which are involved in the metabolism of particular compounds. Complexes are formed at different oligonucleotide concentrations, with higher concentrations favoring more efficient complex formation.

In another embodiment, the fat emulsion is based on a mixture of lipids. Such lipids may include natural compounds, chemically synthesized compounds, purified fatty acids or any other lipids. In yet another embodiment the composition of fat emulsion is entirely artificial. In a particular embodiment, the fat emulsion is more then 70% linoleic acid. In yet another particular embodiment the fat emulsion is at least 1% of cardiolipin. Linoleic acid (LA) is an unsaturated omega-6 fatty acid. It is a colorless liquid made of a carboxylic acid with an 18-carbon chain and two cis double bonds.

In yet another embodiment of the present invention, the alteration of the composition of the fat emulsion is used as a way to alter tissue distribution of hydrophobicly modified polynucleotides. This methodology provides for the specific delivery of the polynucleotides to particular tissues (Figure 12).

In another embodiment the fat emulsions of the cargo molecule contain more then 70% of Linoleic acid (C18H32O2) and/or cardiolipin are used for specifically delivering RNAi to heart muscle.

Fat emulsions, like intralipid have been used before as a delivery formulation for some non-water soluble drugs (such as Propofol, re-formulated as Diprivan). Unique features of the present invention include (a) the concept of combining modified

polynucleotides with the hydrophobic compound(s), so it can be incorporated in the fat micelles and (b) mixing it with the fat emulsions to provide a reversible carrier. After injection into a blood stream, micelles usually bind to serum proteins, including albumin, HDL, LDL and other. This binding is reversible and eventually the fat is absorbed by cells. The polynucleotide, incorporated as a part of the micelle will then be delivered closely to the surface of the cells. After that cellular uptake might be happening though variable mechanisms, including but not limited to sterol type delivery.

Complexing Agents

Complexing agents bind to the oligonucleotides of the invention by a strong but non-covalent attraction (*e.g.*, an electrostatic, van der Waals, pi-stacking, *etc.* interaction). In one embodiment, oligonucleotides of the invention can be complexed with a complexing agent to increase cellular uptake of oligonucleotides. An example of a complexing agent includes cationic lipids. Cationic lipids can be used to deliver oligonucleotides to cells. However, as discussed above, formulations free in cationic lipids are preferred in some embodiments.

The term "cationic lipid" includes lipids and synthetic lipids having both polar and non-polar domains and which are capable of being positively charged at or around physiological pH and which bind to polyanions, such as nucleic acids, and facilitate the delivery of nucleic acids into cells. In general cationic lipids include saturated and unsaturated alkyl and alicyclic ethers and esters of amines, amides, or derivatives thereof. Straight-chain and branched alkyl and alkenyl groups of cationic lipids can contain, *e.g.*, from 1 to about 25 carbon atoms. Preferred straight chain or branched alkyl or alkene groups have six or more carbon atoms. Alicyclic groups include cholesterol and other steroid groups. Cationic lipids can be prepared with a variety of counterions (anions) including, *e.g.*, Cl^-, Br^-, I^-, F^-, acetate, trifluoroacetate, sulfate, nitrite, and nitrate.

Examples of cationic lipids include polyethylenimine, polyamidoamine (PAMAM) starburst dendrimers, Lipofectin (a combination of DOTMA and DOPE), Lipofectase, LIPOFECTAMINE™ (*e.g.*, LIPOFECTAMINE™ 2000), DOPE, Cytofectin (Gilead Sciences, Foster City, Calif.), and Eufectins (JBL, San Luis Obispo, Calif.). Exemplary cationic liposomes can be made from N-[1-(2,3-dioleoloxy)-propyl]-

N,N,N-trimethylammonium chloride (DOTMA), N-[1 -(2,3-dioleoloxy)-propyl]-N,N,N-trimethylammonium methylsulfate (DOTAP), 3β-[N-(N',N'-dimethylaminoethane)carbamoyl]cholesterol (DC-Chol), 2,3,-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate (DOSPA), 1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide; and dimethyldioctadecylammonium bromide (DDAB). The cationic lipid N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), for example, was found to increase 1000-fold the antisense effect of a phosphorothioate oligonucleotide. (Vlassov *et al.*, 1994, Biochimica et Biophysica Acta 1197:95-108). Oligonucleotides can also be complexed with, *e.g.*, poly (L-lysine) or avidin and lipids may, or may not, be included in this mixture, *e.g.*, steryl-poly (L-lysine).

Cationic lipids have been used in the art to deliver oligonucleotides to cells (see, *e.g.*, U.S. Pat. Nos. 5,855,910; 5,851,548; 5,830,430; 5,780,053; 5,767,099; Lewis *et al.* 1996. *Proc. Natl. Acad. Sci. USA* 93:3176; Hope *et al.* 1998. *Molecular Membrane Biology* 15:1). Other lipid compositions which can be used to facilitate uptake of the instant oligonucleotides can be used in connection with the claimed methods. In addition to those listed supra, other lipid compositions are also known in the art and include, *e.g.*, those taught in U.S. Pat. No. 4,235,871; U.S. Pat. Nos. 4,501,728; 4,837,028; 4,737,323.

In one embodiment lipid compositions can further comprise agents, *e.g.*, viral proteins to enhance lipid-mediated transfections of oligonucleotides (Kamata, *et al.*, 1994. *Nucl. Acids. Res.* 22:536). In another embodiment, oligonucleotides are contacted with cells as part of a composition comprising an oligonucleotide, a peptide, and a lipid as taught, *e.g.*, in U.S. patent 5,736,392. Improved lipids have also been described which are serum resistant (Lewis, *et al.*, 1996. *Proc. Natl. Acad. Sci.* 93:3176). Cationic lipids and other complexing agents act to increase the number of oligonucleotides carried into the cell through endocytosis.

In another embodiment N-substituted glycine oligonucleotides (peptoids) can be used to optimize uptake of oligonucleotides. Peptoids have been used to create cationic lipid-like compounds for transfection (Murphy, *et al.*, 1998. *Proc. Natl. Acad. Sci.* 95:1517). Peptoids can be synthesized using standard methods (*e.g.*, Zuckermann, R. N., *et al.* 1992. *J. Am. Chem. Soc.* 114:10646; Zuckermann, R. N., *et al.* 1992. *Int. J. Peptide Protein Res.* 40:497). Combinations of cationic lipids and peptoids, liptoids, can also be

used to optimize uptake of the subject oligonucleotides (Hunag, *et al.*, 1998. *Chemistry and Biology.* 5:345). Liptoids can be synthesized by elaborating peptoid oligonucleotides and coupling the amino terminal submonomer to a lipid via its amino group (Hunag, *et al.*, 1998. *Chemistry and Biology.* 5:345).

It is known in the art that positively charged amino acids can be used for creating highly active cationic lipids (Lewis *et al.* 1996. *Proc. Natl. Acad. Sci. US.A.* 93:3176). In one embodiment, a composition for delivering oligonucleotides of the invention comprises a number of arginine, lysine, histidine or ornithine residues linked to a lipophilic moiety (see *e.g.*, U.S. Pat. No. 5,777,153).

In another embodiment, a composition for delivering oligonucleotides of the invention comprises a peptide having from between about one to about four basic residues. These basic residues can be located, *e.g.*, on the amino terminal, C-terminal, or internal region of the peptide. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine (can also be considered non-polar), asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Apart from the basic amino acids, a majority or all of the other residues of the peptide can be selected from the non-basic amino acids, *e.g.*, amino acids other than lysine, arginine, or histidine. Preferably a preponderance of neutral amino acids with long neutral side chains are used.

In one embodiment, a composition for delivering oligonucleotides of the invention comprises a natural or synthetic polypeptide having one or more gamma carboxyglutamic acid residues, or γ-Gla residues. These gamma carboxyglutamic acid residues may enable the polypeptide to bind to each other and to membrane surfaces. In other words, a polypeptide having a series of γ-Gla may be used as a general delivery modality that helps an RNAi construct to stick to whatever membrane to which it comes in contact. This may at least slow RNAi constructs from being cleared from the blood stream and enhance their chance of homing to the target.

The gamma carboxyglutamic acid residues may exist in natural proteins (for

example, prothrombin has 10 γ-Gla residues). Alternatively, they can be introduced into the purified, recombinantly produced, or chemically synthesized polypeptides by carboxylation using, for example, a vitamin K-dependent carboxylase. The gamma carboxyglutamic acid residues may be consecutive or non-consecutive, and the total number and location of such gamma carboxyglutamic acid residues in the polypeptide can be regulated / fine tuned to achieve different levels of "stickiness" of the polypeptide.

In one embodiment, the cells to be contacted with an oligonucleotide composition of the invention are contacted with a mixture comprising the oligonucleotide and a mixture comprising a lipid, *e.g.*, one of the lipids or lipid compositions described supra for between about 12 hours to about 24 hours. In another embodiment, the cells to be contacted with an oligonucleotide composition are contacted with a mixture comprising the oligonucleotide and a mixture comprising a lipid, *e.g.*, one of the lipids or lipid compositions described supra for between about 1 and about five days. In one embodiment, the cells are contacted with a mixture comprising a lipid and the oligonucleotide for between about three days to as long as about 30 days. In another embodiment, a mixture comprising a lipid is left in contact with the cells for at least about five to about 20 days. In another embodiment, a mixture comprising a lipid is left in contact with the cells for at least about seven to about 15 days.

For example, in one embodiment, an oligonucleotide composition can be contacted with cells in the presence of a lipid such as cytofectin CS or GSV (available from Glen Research; Sterling, Va.), GS3815, GS2888 for prolonged incubation periods as described herein.

In one embodiment, the incubation of the cells with the mixture comprising a lipid and an oligonucleotide composition does not reduce the viability of the cells. Preferably, after the transfection period the cells are substantially viable. In one embodiment, after transfection, the cells are between at least about 70% and at least about 100% viable. In another embodiment, the cells are between at least about 80% and at least about 95% viable. In yet another embodiment, the cells are between at least about 85% and at least about 90% viable.

In one embodiment, oligonucleotides are modified by attaching a peptide sequence that transports the oligonucleotide into a cell, referred to herein as a "transporting peptide." In one embodiment, the composition includes an oligonucleotide

which is complementary to a target nucleic acid molecule encoding the protein, and a covalently attached transporting peptide.

The language "transporting peptide" includes an amino acid sequence that facilitates the transport of an oligonucleotide into a cell. Exemplary peptides which facilitate the transport of the moieties to which they are linked into cells are known in the art, and include, *e.g.*, HIV TAT transcription factor, lactoferrin, Herpes VP22 protein, and fibroblast growth factor 2 (Pooga *et al.* 1998. *Nature Biotechnology.* 16:857; and Derossi *et al.* 1998. *Trends in Cell Biology.* 8:84; Elliott and O'Hare. 1997. Cell 88:223).

Oligonucleotides can be attached to the transporting peptide using known techniques, *e.g.*, (Prochiantz, A. 1996. *Curr. Opin. Neurobiol.* 6:629; Derossi *et al.* 1998. *Trends Cell Biol.* 8:84; Troy *et al.* 1996. *J. Neurosci.* 16:253), Vives *et al.* 1997. *J. Biol. Chem.* 272:16010). For example, in one embodiment, oligonucleotides bearing an activated thiol group are linked via that thiol group to a cysteine present in a transport peptide (*e.g.*, to the cysteine present in the β turn between the second and the third helix of the antennapedia homeodomain as taught, *e.g.*, in Derossi *et al.* 1998. *Trends Cell Biol.* 8:84; Prochiantz. 1996. *Current Opinion in Neurobiol.* 6:629; Allinquant *et al.* 1995. J Cell Biol. 128:919). In another embodiment, a Boc-Cys-(Npys)OH group can be coupled to the transport peptide as the last (N-terminal) amino acid and an oligonucleotide bearing an SH group can be coupled to the peptide (Troy *et al.* 1996. *J. Neurosci.* 16:253).

In one embodiment, a linking group can be attached to a nucleomonomer and the transporting peptide can be covalently attached to the linker. In one embodiment, a linker can function as both an attachment site for a transporting peptide and can provide stability against nucleases. Examples of suitable linkers include substituted or unsubstituted C_1-C_{20} alkyl chains, C_2-C_{20} alkenyl chains, C_2-C_{20} alkynyl chains, peptides, and heteroatoms (*e.g.*, S, O, NH, *etc.*). Other exemplary linkers include bifunctional crosslinking agents such as sulfosuccinimidyl-4-(maleimidophenyl)-butyrate (SMPB) (see, *e.g.*, Smith *et al.* Biochem J 1991.276: 417-2).

In one embodiment, oligonucleotides of the invention are synthesized as molecular conjugates which utilize receptor-mediated endocytotic mechanisms for delivering genes into cells (see, *e.g.*, Bunnell *et al.* 1992. *Somatic Cell and Molecular Genetics.* 18:559, and the references cited therein).

Targeting Agents

The delivery of oligonucleotides can also be improved by targeting the oligonucleotides to a cellular receptor. The targeting moieties can be conjugated to the oligonucleotides or attached to a carrier group (*i.e.*, poly(L-lysine) or liposomes) linked to the oligonucleotides. This method is well suited to cells that display specific receptor-mediated endocytosis.

For instance, oligonucleotide conjugates to 6-phosphomannosylated proteins are internalized 20-fold more efficiently by cells expressing mannose 6-phosphate specific receptors than free oligonucleotides. The oligonucleotides may also be coupled to a ligand for a cellular receptor using a biodegradable linker. In another example, the delivery construct is mannosylated streptavidin which forms a tight complex with biotinylated oligonucleotides. Mannosylated streptavidin was found to increase 20-fold the internalization of biotinylated oligonucleotides. (Vlassov *et al.* 1994. *Biochimica et Biophysica Acta* 1197:95-108).

In addition specific ligands can be conjugated to the polylysine component of polylysine-based delivery systems. For example, transferrin-polylysine, adenovirus-polylysine, and influenza virus hemagglutinin HA-2 N-terminal fusogenic peptides-polylysine conjugates greatly enhance receptor-mediated DNA delivery in eucaryotic cells. Mannosylated glycoprotein conjugated to poly(L-lysine) in aveolar macrophages has been employed to enhance the cellular uptake of oligonucleotides. Liang *et al.* 1999. *Pharmazie* 54:559-566.

Because malignant cells have an increased need for essential nutrients such as folic acid and transferrin, these nutrients can be used to target oligonucleotides to cancerous cells. For example, when folic acid is linked to poly(L-lysine) enhanced oligonucleotide uptake is seen in promyelocytic leukaemia (HL-60) cells and human melanoma (M-14) cells. Ginobbi *et al.* 1997. *Anticancer Res.* 17:29. In another example, liposomes coated with maleylated bovine serum albumin, folic acid, or ferric protoporphyrin IX, show enhanced cellular uptake of oligonucleotides in murine macrophages, KB cells, and 2.2.15 human hepatoma cells. Liang *et al.* 1999. *Pharmazie* 54:559-566.

Liposomes naturally accumulate in the liver, spleen, and reticuloendothelial system (so-called, passive targeting). By coupling liposomes to various ligands such as

antibodies are protein A, they can be actively targeted to specific cell populations. For example, protein A-bearing liposomes may be pretreated with II-2K specific antibodies which are targeted to the mouse major histocompatibility complex-encoded H-2K protein expressed on L cells. (Vlassov *et al.* 1994. *Biochimica et Biophysica Acta* 1197:95-108).

Other in vitro and/or in vivo delivery of RNAi reagents are known in the art, and can be used to deliver the subject RNAi constructs. See, for example, U.S. patent application publications 20080152661, 20080112916, 20080107694, 20080038296, 20070231392, 20060240093, 20060178327, 20060008910, 20050265957, 20050064595, 20050042227, 20050037496, 20050026286, 20040162235, 20040072785, 20040063654, 20030157030, WO 2008/036825, WO04/065601, and AU2004206255B2, just to name a few (all incorporated by reference).

Administration

The optimal course of administration or delivery of the oligonucleotides may vary depending upon the desired result and/or on the subject to be treated. As used herein "administration" refers to contacting cells with oligonucleotides and can be performed *in vitro* or *in vivo*. The dosage of oligonucleotides may be adjusted to optimally reduce expression of a protein translated from a target nucleic acid molecule, *e.g.*, as measured by a readout of RNA stability or by a therapeutic response, without undue experimentation.

For example, expression of the protein encoded by the nucleic acid target can be measured to determine whether or not the dosage regimen needs to be adjusted accordingly. In addition, an increase or decrease in RNA or protein levels in a cell or produced by a cell can be measured using any art recognized technique. By determining whether transcription has been decreased, the effectiveness of the oligonucleotide in inducing the cleavage of a target RNA can be determined.

Any of the above-described oligonucleotide compositions can be used alone or in conjunction with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes appropriate solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is

well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, it can be used in the therapeutic compositions. Supplementary active ingredients can also be incorporated into the compositions.

Oligonucleotides may be incorporated into liposomes or liposomes modified with polyethylene glycol or admixed with cationic lipids for parenteral administration. Incorporation of additional substances into the liposome, for example, antibodies reactive against membrane proteins found on specific target cells, can help target the oligonucleotides to specific cell types.

With respect to *in vivo* applications, the formulations of the present invention can be administered to a patient in a variety of forms adapted to the chosen route of administration, *e.g.*, parenterally, orally, or intraperitoneally. Parenteral administration, which is preferred, includes administration by the following routes: intravenous; intramuscular; interstitially; intraarterially; subcutaneous; intra ocular; intrasynovial; trans epithelial, including transdermal; pulmonary via inhalation; ophthalmic; sublingual and buccal; topically, including ophthalmic; dermal; ocular; rectal; and nasal inhalation via insufflation. In preferred embodiments, the sd-rxRNA molecules are administered by intradermal injection or subcutaneously.

Pharmaceutical preparations for parenteral administration include aqueous solutions of the active compounds in water-soluble or water-dispersible form. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, or dextran, optionally, the suspension may also contain stabilizers. The oligonucleotides of the invention can be formulated in liquid solutions, preferably in physiologically compatible buffers such as Hank's solution or Ringer's solution. In addition, the oligonucleotides may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms are also included in the invention.

Pharmaceutical preparations for topical administration include transdermal patches, ointments, lotions, creams, gels, drops, sprays, suppositories, liquids and

powders. In addition, conventional pharmaceutical carriers, aqueous, powder or oily bases, or thickeners may be used in pharmaceutical preparations for topical administration.

Pharmaceutical preparations for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets or tablets. In addition, thickeners, flavoring agents, diluents, emulsifiers, dispersing aids, or binders may be used in pharmaceutical preparations for oral administration.

For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are known in the art, and include, for example, for transmucosal administration bile salts and fusidic acid derivatives, and detergents. Transmucosal administration may be through nasal sprays or using suppositories. For oral administration, the oligonucleotides are formulated into conventional oral administration forms such as capsules, tablets, and tonics. For topical administration, the oligonucleotides of the invention are formulated into ointments, salves, gels, or creams as known in the art.

Drug delivery vehicles can be chosen *e.g.*, for *in vitro*, for systemic, or for topical administration. These vehicles can be designed to serve as a slow release reservoir or to deliver their contents directly to the target cell. An advantage of using some direct delivery drug vehicles is that multiple molecules are delivered per uptake. Such vehicles have been shown to increase the circulation half-life of drugs that would otherwise be rapidly cleared from the blood stream. Some examples of such specialized drug delivery vehicles which fall into this category are liposomes, hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres.

The described oligonucleotides may be administered systemically to a subject. Systemic absorption refers to the entry of drugs into the blood stream followed by distribution throughout the entire body. Administration routes which lead to systemic absorption include: intravenous, subcutaneous, intraperitoneal, and intranasal. Each of these administration routes delivers the oligonucleotide to accessible diseased cells. Following subcutaneous administration, the therapeutic agent drains into local lymph nodes and proceeds through the lymphatic network into the circulation. The rate of entry into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier localizes the oligonucleotide at the lymph node. The

oligonucleotide can be modified to diffuse into the cell, or the liposome can directly participate in the delivery of either the unmodified or modified oligonucleotide into the cell.

The chosen method of delivery will result in entry into cells. In some embodiments, preferred delivery methods include liposomes (10-400 nm), hydrogels, controlled-release polymers, and other pharmaceutically applicable vehicles, and microinjection or electroporation (for ex vivo treatments).

The pharmaceutical preparations of the present invention may be prepared and formulated as emulsions. Emulsions are usually heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 μm in diameter. The emulsions of the present invention may contain excipients such as emulsifiers, stabilizers, dyes, fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives, and anti-oxidants may also be present in emulsions as needed. These excipients may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase.

Examples of naturally occurring emulsifiers that may be used in emulsion formulations of the present invention include lanolin, beeswax, phosphatides, lecithin and acacia. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. Examples of finely divided solids that may be used as emulsifiers include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgite, hectorite, kaolin, montrnorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

Examples of preservatives that may be included in the emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Examples of antioxidants that may be included in the emulsion formulations include free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

In one embodiment, the compositions of oligonucleotides are formulated as microemulsions. A microemulsion is a system of water, oil and amphiphile which is a

single optically isotropic and thermodynamically stable liquid solution. Typically microemulsions are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a 4th component, generally an intermediate chain-length alcohol to form a transparent system.

Surfactants that may be used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (S0750), decaglycerol decaoleate (DA0750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules.

Microemulsions may, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase may typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase may include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C_8-C_{12}) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C_8-C_{10} glycerides, vegetable oils and silicone oil.

Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both oil/water and water/oil) have been proposed to enhance the oral bioavailability of drugs.

Microemulsions offer improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (Constantinides *et al.*, Pharmaceutical Research, 1994, 11:1385; Ho *et al.*, J. Pharm. Sci., 1996, 85:138-143). Microemulsions have also been effective in the

transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present invention will facilitate the increased systemic absorption of oligonucleotides from the gastrointestinal tract, as well as improve the local cellular uptake of oligonucleotides within the gastrointestinal tract, vagina, buccal cavity and other areas of administration.

In an embodiment, the present invention employs various penetration enhancers to affect the efficient delivery of nucleic acids, particularly oligonucleotides, to the skin of animals. Even non-lipophilic drugs may cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to increasing the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also act to enhance the permeability of lipophilic drugs.

Five categories of penetration enhancers that may be used in the present invention include: surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants. Other agents may be utilized to enhance the penetration of the administered oligonucleotides include: glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-15 pyrrol, azones, and terpenes such as limonene, and menthone.

The oligonucleotides, especially in lipid formulations, can also be administered by coating a medical device, for example, a catheter, such as an angioplasty balloon catheter, with a cationic lipid formulation. Coating may be achieved, for example, by dipping the medical device into a lipid formulation or a mixture of a lipid formulation and a suitable solvent, for example, an aqueous-based buffer, an aqueous solvent, ethanol, methylene chloride, chloroform and the like. An amount of the formulation will naturally adhere to the surface of the device which is subsequently administered to a patient, as appropriate. Alternatively, a lyophilized mixture of a lipid formulation may be specifically bound to the surface of the device. Such binding techniques are described, for example, in K. Ishihara *et al.*, Journal of Biomedical Materials Research, Vol. 27, pp. 1309-1314 (1993), the disclosures of which are incorporated herein by reference in their entirety.

The useful dosage to be administered and the particular mode of administration will vary depending upon such factors as the cell type, or for *in vivo* use, the age, weight

and the particular animal and region thereof to be treated, the particular oligonucleotide and delivery method used, the therapeutic or diagnostic use contemplated, and the form of the formulation, for example, suspension, emulsion, micelle or liposome, as will be readily apparent to those skilled in the art. Typically, dosage is administered at lower levels and increased until the desired effect is achieved. When lipids are used to deliver the oligonucleotides, the amount of lipid compound that is administered can vary and generally depends upon the amount of oligonucleotide agent being administered. For example, the weight ratio of lipid compound to oligonucleotide agent is preferably from about 1:1 to about 15:1, with a weight ratio of about 5:1 to about 10:1 being more preferred. Generally, the amount of cationic lipid compound which is administered will vary from between about 0.1 milligram (mg) to about 1 gram (g). By way of general guidance, typically between about 0.1 mg and about 10 mg of the particular oligonucleotide agent, and about 1 mg to about 100 mg of the lipid compositions, each per kilogram of patient body weight, is administered, although higher and lower amounts can be used.

The agents of the invention are administered to subjects or contacted with cells in a biologically compatible form suitable for pharmaceutical administration. By "biologically compatible form suitable for administration" is meant that the oligonucleotide is administered in a form in which any toxic effects are outweighed by the therapeutic effects of the oligonucleotide. In one embodiment, oligonucleotides can be administered to subjects. Examples of subjects include mammals, *e.g.*, humans and other primates; cows, pigs, horses, and farming (agricultural) animals; dogs, cats, and other domesticated pets; mice, rats, and transgenic non-human animals.

Administration of an active amount of an oligonucleotide of the present invention is defined as an amount effective, at dosages and for periods of time necessary to achieve the desired result. For example, an active amount of an oligonucleotide may vary according to factors such as the type of cell, the oligonucleotide used, and for *in vivo* uses the disease state, age, sex, and weight of the individual, and the ability of the oligonucleotide to elicit a desired response in the individual. Establishment of therapeutic levels of oligonucleotides within the cell is dependent upon the rates of uptake and efflux or degradation. Decreasing the degree of degradation prolongs the intracellular half-life of the oligonucleotide. Thus, chemically-modified oligonucleotides, *e.g.*, with modification of the phosphate backbone, may require

different dosing.

The exact dosage of an oligonucleotide and number of doses administered will depend upon the data generated experimentally and in clinical trials. Several factors such as the desired effect, the delivery vehicle, disease indication, and the route of administration, will affect the dosage. Dosages can be readily determined by one of ordinary skill in the art and formulated into the subject pharmaceutical compositions. Preferably, the duration of treatment will extend at least through the course of the disease symptoms.

Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, the oligonucleotide may be repeatedly administered, *e.g.*, several doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. One of ordinary skill in the art will readily be able to determine appropriate doses and schedules of administration of the subject oligonucleotides, whether the oligonucleotides are to be administered to cells or to subjects.

Administration of sd-rxRNAs, such as trhough intradermal injection or subcutaneous delivery, can be optimized through testing of dosing regimens. In some embodiments, a single administration is sufficient. To further prolong the effect of the administered sd-rxRNA, the sd-rxRNA can be administered in a slow-release formulation or device, as would be familiar to one of ordinary skill in the art. The hydrophobic nature of sd-rxRNA compounds can enable use of a wide variety of polymers, some of which are not compatible with conventional oligonucleotide delivery.

In other embodiments, the sd-rxRNA is administered multiple times. In some instances it is administered daily, bi-weekly, weekly, every two weeks, every three weeks, monthly, every two months, every three months, every four months, every five months, every six months or less frequently than every six months. In some instances, it is administered multiple times per day, week, month and/or year. For example, it can be administered approximately every hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours 10 hours, 12 hours or more than twelve hours. It can be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 times per day.

Aspects of the invention relate to administering sd-rxRNA molecules to a subject. In some instances the subject is a patient and administering the sd-rxRNA molecule

involves administering the sd-rxRNA molecule in a doctor's office.

In some embodiments, more than one sd-rxRNA molecule is administered simultaneously. For example a composition may be administered that contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 different sd-rxRNA molecules. In certain embodiments, a composition comprises 2 or 3 different sd-rxRNA molecules. When a composition comprises more than one sd-rxRNA, the sd-rxRNA molecules within the composition can be directed to the same gene or to different genes.

Figure 1 reveals the expression profile for several genes associated with the invention. As expected, target gene expression is elevated early and returns to normal by day 10. Figure 2 provides a summary of experimental design. Figures 3-6 show in vivo silencing of MAP4K4 and PPIB expression following intradermal injection of sd-rxRNA molecules targeting these genes. Figures 7-8 show that the silencing effect of sd-rxRNAs can persist for at least 8 days. Thus, in some embodiments, sd-rxRNA is administered within 8 days prior to an event that compromises or damages the skin such as a surgery. For examples, an sd-rxRNA could eb adminsitered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 days prior to an event that compromises or damages the skin. Figure 9 demonstrates examples of dosing regimens.

In some instances, the effective amount of sd-rxRNA that is delivered by subcutaneous administration is at least approximately 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more than 100 mg/kg including any intermediate values.

In some instances, the effective amount of sd-rxRNA that is delivered through intradermal injection is at least approximately 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or more than 950 μg including any intermediate values.

sd-rxRNA molecules administered through methods described herein are effectively targeted to all the cell types in the skin.

Physical methods of introducing nucleic acids include injection of a solution containing the nucleic acid, bombardment by particles covered by the nucleic acid, soaking the cell or organism in a solution of the nucleic acid, or electroporation of cell membranes in the presence of the nucleic acid. A viral construct packaged into a viral particle would accomplish both efficient introduction of an expression construct into the cell and transcription of nucleic acid encoded by the expression construct. Other methods known in the art for introducing nucleic acids to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, such as calcium phosphate, and the like. Thus the nucleic acid may be introduced along with components that perform one or more of the following activities: enhance nucleic acid uptake by the cell, inhibit annealing of single strands, stabilize the single strands, or other-wise increase inhibition of the target gene.

Nucleic acid may be directly introduced into the cell (i.e., intracellularly); or introduced extracellularly into a cavity, interstitial space, into the circulation of an organism, introduced orally, or may be introduced by bathing a cell or organism in a solution containing the nucleic acid. Vascular or extravascular circulation, the blood or lymph system, and the cerebrospinal fluid are sites where the nucleic acid may be introduced.

The cell with the target gene may be derived from or contained in any organism. The organism may a plant, animal, protozoan, bacterium, virus, or fungus. The plant may be a monocot, dicot or gymnosperm; the animal may be a vertebrate or invertebrate. Preferred microbes are those used in agriculture or by industry, and those that are pathogenic for plants or animals.

Alternatively, vectors, e.g., transgenes encoding a siRNA of the invention can be engineered into a host cell or transgenic animal using art recognized techniques.

A further preferred use for the agents of the present invention (or vectors or transgenes encoding same) is a functional analysis to be carried out in eukaryotic cells, or eukaryotic non-human organisms, preferably mammalian cells or organisms and most preferably human cells, e.g. cell lines such as HeLa or 293 or rodents, e.g. rats and mice. By administering a suitable priming agent/RNAi agent which is sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference, a specific knockout or knockdown phenotype can be obtained in a target cell, e.g. in cell

culture or in a target organism.

Thus, a further subject matter of the invention is a eukaryotic cell or a eukaryotic non-human organism exhibiting a target gene-specific knockout or knockdown phenotype comprising a fully or at least partially deficient expression of at least one endogenous target gene wherein said cell or organism is transfected with at least one vector comprising DNA encoding an RNAi agent capable of inhibiting the expression of the target gene. It should be noted that the present invention allows a target-specific knockout or knockdown of several different endogenous genes due to the specificity of the RNAi agent.

Gene-specific knockout or knockdown phenotypes of cells or non-human organisms, particularly of human cells or non-human mammals may be used in analytic procedures, e.g. in the functional and/or phenotypical analysis of complex physiological processes such as analysis of gene expression profiles and/or proteomes. Preferably the analysis is carried out by high throughput methods using oligonucleotide based chips.

Assays of Oligonucleotide Stability

In some embodiments, the oligonucleotides of the invention are stabilized, *i.e.*, substantially resistant to endonuclease and exonuclease degradation. An oligonucleotide is defined as being substantially resistant to nucleases when it is at least about 3-fold more resistant to attack by an endogenous cellular nuclease, and is highly nuclease resistant when it is at least about 6-fold more resistant than a corresponding oligonucleotide. This can be demonstrated by showing that the oligonucleotides of the invention are substantially resistant to nucleases using techniques which are known in the art.

One way in which substantial stability can be demonstrated is by showing that the oligonucleotides of the invention function when delivered to a cell, *e.g.*, that they reduce transcription or translation of target nucleic acid molecules, *e.g.*, by measuring protein levels or by measuring cleavage of mRNA. Assays which measure the stability of target RNA can be performed at about 24 hours post-transfection (*e.g.*, using Northern blot techniques, RNase Protection Assays, or QC-PCR assays as known in the art). Alternatively, levels of the target protein can be measured. Preferably, in addition to

testing the RNA or protein levels of interest, the RNA or protein levels of a control, non-targeted gene will be measured (*e.g.*, actin, or preferably a control with sequence similarity to the target) as a specificity control. RNA or protein measurements can be made using any art-recognized technique. Preferably, measurements will be made beginning at about 16-24 hours post transfection. (M. Y. Chiang, *et al.* 1991. J Biol Chem. 266:18162-71; T. Fisher, *et al.* 1993. Nucleic Acids Research. 21 3857).

The ability of an oligonucleotide composition of the invention to inhibit protein synthesis can be measured using techniques which are known in the art, for example, by detecting an inhibition in gene transcription or protein synthesis. For example, Nuclease S1 mapping can be performed. In another example, Northern blot analysis can be used to measure the presence of RNA encoding a particular protein. For example, total RNA can be prepared over a cesium chloride cushion (see, *e.g.*, Ausebel *et al.*, 1987. Current Protocols in Molecular Biology (Greene & Wiley, New York)). Northern blots can then be made using the RNA and probed (see, *e.g.*, Id.). In another example, the level of the specific mRNA produced by the target protein can be measured, *e.g.*, using PCR. In yet another example, Western blots can be used to measure the amount of target protein present. In still another embodiment, a phenotype influenced by the amount of the protein can be detected. Techniques for performing Western blots are well known in the art, see, *e.g.*, Chen *et al.* J. Biol. Chem. 271:28259.

In another example, the promoter sequence of a target gene can be linked to a reporter gene and reporter gene transcription (*e.g.*, as described in more detail below) can be monitored. Alternatively, oligonucleotide compositions that do not target a promoter can be identified by fusing a portion of the target nucleic acid molecule with a reporter gene so that the reporter gene is transcribed. By monitoring a change in the expression of the reporter gene in the presence of the oligonucleotide composition, it is possible to determine the effectiveness of the oligonucleotide composition in inhibiting the expression of the reporter gene. For example, in one embodiment, an effective oligonucleotide composition will reduce the expression of the reporter gene.

A "reporter gene" is a nucleic acid that expresses a detectable gene product, which may be RNA or protein. Detection of mRNA expression may be accomplished by Northern blotting and detection of protein may be accomplished by staining with antibodies specific to the protein. Preferred reporter genes produce a readily detectable

product. A reporter gene may be operably linked with a regulatory DNA sequence such that detection of the reporter gene product provides a measure of the transcriptional activity of the regulatory sequence. In preferred embodiments, the gene product of the reporter gene is detected by an intrinsic activity associated with that product. For instance, the reporter gene may encode a gene product that, by enzymatic activity, gives rise to a detectable signal based on color, fluorescence, or luminescence. Examples of reporter genes include, but are not limited to, those coding for chloramphenicol acetyl transferase (CAT), luciferase, beta-galactosidase, and alkaline phosphatase.

One skilled in the art would readily recognize numerous reporter genes suitable for use in the present invention. These include, but are not limited to, chloramphenicol acetyltransferase (CAT), luciferase, human growth hormone (hGH), and beta-galactosidase. Examples of such reporter genes can be found in F. A. Ausubel *et al.*, Eds., Current Protocols in Molecular Biology, John Wiley & Sons, New York, (1989). Any gene that encodes a detectable product, *e.g.*, any product having detectable enzymatic activity or against which a specific antibody can be raised, can be used as a reporter gene in the present methods.

One reporter gene system is the firefly luciferase reporter system. (Gould, S. J., and Subramani, S. 1988. Anal. Biochem., 7:404-408 incorporated herein by reference). The luciferase assay is fast and sensitive. In this assay, a lysate of the test cell is prepared and combined with ATP and the substrate luciferin. The encoded enzyme luciferase catalyzes a rapid, ATP dependent oxidation of the substrate to generate a light-emitting product. The total light output is measured and is proportional to the amount of luciferase present over a wide range of enzyme concentrations.

CAT is another frequently used reporter gene system; a major advantage of this system is that it has been an extensively validated and is widely accepted as a measure of promoter activity. (Gorman C. M., Moffat, L. F., and Howard, B. H. 1982. Mol. Cell. Biol., 2:1044-1051). In this system, test cells are transfected with CAT expression vectors and incubated with the candidate substance within 2-3 days of the initial transfection. Thereafter, cell extracts are prepared. The extracts are incubated with acetyl CoA and radioactive chloramphenicol. Following the incubation, acetylated chloramphenicol is separated from nonacetylated form by thin layer chromatography. In this assay, the degree of acetylation reflects the CAT gene activity with the particular

promoter.

Another suitable reporter gene system is based on immunologic detection of hGH. This system is also quick and easy to use. (Selden, R., Burke-Howie, K. Rowe, M. E., Goodman, H. M., and Moore, D. D. (1986), Mol. Cell, Biol., 6:3173-3179 incorporated herein by reference). The hGH system is advantageous in that the expressed hGH polypeptide is assayed in the media, rather than in a cell extract. Thus, this system does not require the destruction of the test cells. It will be appreciated that the principle of this reporter gene system is not limited to hGH but rather adapted for use with any polypeptide for which an antibody of acceptable specificity is available or can be prepared.

In one embodiment, nuclease stability of a double-stranded oligonucleotide of the invention is measured and compared to a control, *e.g.*, an RNAi molecule typically used in the art (*e.g.*, a duplex oligonucleotide of less than 25 nucleotides in length and comprising 2 nucleotide base overhangs) or an unmodified RNA duplex with blunt ends.

The target RNA cleavage reaction achieved using the siRNAs of the invention is highly sequence specific. Sequence identity may determined by sequence comparison and alignment algorithms known in the art. To determine the percent identity of two nucleic acid sequences (or of two amino acid sequences), the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the first sequence or second sequence for optimal alignment). A preferred, non-limiting example of a local alignment algorithm utilized for the comparison of sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87:2264-68, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-77. Such an algorithm is incorporated into the BLAST programs (version 2.0) of Altschul, et al. (1990) J. Mol. Biol. 215:403-10. Greater than 90% sequence identity, e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or even 100% sequence identity, between the siRNA and the portion of the target gene is preferred. Alternatively, the siRNA may be defined functionally as a nucleotide sequence (or oligonucleotide sequence) that is capable of hybridizing with a portion of the target gene transcript. Examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E. F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11, and Current Protocols in

Molecular Biology, 1995, F. M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Therapeutic use

By inhibiting the expression of a gene, the oligonucleotide compositions of the present invention can be used to treat any disease involving the expression of a protein. Examples of diseases that can be treated by oligonucleotide compositions, just to illustrate, include: cancer, retinopathies, autoimmune diseases, inflammatory diseases (*i.e.*, ICAM-1 related disorders, Psoriasis, Ulcerative Colitus, Crohn's disease), viral diseases (*i.e.*, HIV, Hepatitis C), miRNA disorders, and cardiovascular diseases.

In one embodiment, *in vitro* treatment of cells with oligonucleotides can be used for ex vivo therapy of cells removed from a subject (*e.g.*, for treatment of leukemia or viral infection) or for treatment of cells which did not originate in the subject, but are to be administered to the subject (*e.g.*, to eliminate transplantation antigen expression on cells to be transplanted into a subject). In addition, *in vitro* treatment of cells can be used in non-therapeutic settings, *e.g.*, to evaluate gene function, to study gene regulation and protein synthesis or to evaluate improvements made to oligonucleotides designed to modulate gene expression or protein synthesis. *In vivo* treatment of cells can be useful in certain clinical settings where it is desirable to inhibit the expression of a protein. There are numerous medical conditions for which antisense therapy is reported to be suitable (see, *e.g.*, U.S. Pat. No. 5,830,653) as well as respiratory syncytial virus infection (WO 95/22,553) influenza virus (WO 94/23,028), and malignancies (WO 94/08,003). Other examples of clinical uses of antisense sequences are reviewed, *e.g.*, in Glaser. 1996. *Genetic Engineering News* 16:1. Exemplary targets for cleavage by oligonucleotides include, *e.g.*, protein kinase Ca, ICAM-1, c-raf kinase, p53, c-myb, and the bcr/abl fusion gene found in chronic myelogenous leukemia.

The subject nucleic acids can be used in RNAi-based therapy in any animal having RNAi pathway, such as human, non-human primate, non-human mammal, non-human vertebrates, rodents (mice, rats, hamsters, rabbits, etc.), domestic livestock animals, pets (cats, dogs, etc.), Xenopus, fish, insects (*Drosophila*, etc.), and worms (*C. elegans*), etc.

The invention provides methods for preventing in a subject, a disease or

condition associated with an aberrant or unwanted target gene expression or activity, by administering to the subject a therapeutic agent (e.g., a RNAi agent or vector or transgene encoding same). If appropriate, subjects are first treated with a priming agent so as to be more responsive to the subsequent RNAi therapy. Subjects at risk for a disease which is caused or contributed to by aberrant or unwanted target gene expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the target gene aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the type of target gene aberrancy, for example, a target gene, target gene agonist or target gene antagonist agent can be used for treating the subject.

In another aspect, the invention pertains to methods of modulating target gene expression, protein expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell capable of expressing target gene with a therapeutic agent of the invention that is specific for the target gene or protein (e.g., is specific for the mRNA encoded by said gene or specifying the amino acid sequence of said protein) such that expression or one or more of the activities of target protein is modulated. These modulatory methods can be performed in vitro (e.g., by culturing the cell with the agent), in vivo (e.g., by administering the agent to a subject), or ex vivo. Typically, subjects are first treated with a priming agent so as to be more responsive to the subsequent RNAi therapy. As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a target gene polypeptide or nucleic acid molecule. Inhibition of target gene activity is desirable in situations in which target gene is abnormally unregulated and/or in which decreased target gene activity is likely to have a beneficial effect.

The therapeutic agents of the invention can be administered to individuals to treat (prophylactically or therapeutically) disorders associated with aberrant or unwanted target gene activity. In conjunction with such treatment, pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a

physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a therapeutic agent as well as tailoring the dosage and/or therapeutic regimen of treatment with a therapeutic agent. Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, for example, Eichelbaum, M. et al. (1996) Clin. Exp. Pharmacol. Physiol. 23(10-11): 983-985 and Linder, M. W. et al. (1997) Clin. Chem. 43(2):254-266

RNAi in skin indications

Nucleic acid molecules, or compositions comprising nucleic acid molecules, described herein may in some embodiments be administered to pre-treat, treat or prevent compromised skin. As used herein "compromised skin" refers to skin which exhibits characteristics distinct from normal skin. Compromised skin may occur in association with a dermatological condition. Several non-limiting examples of dermatological conditions include rosacea, common acne, seborrheic dermatitis, perioral dermatitis, acneform rashes, transient acantholytic dermatosis, and acne necrotica miliaris. In some instances, compromised skin may comprise a wound and/or scar tissue. In some instances, methods and compositions associated with the invention may be used to promote wound healing, prevention, reduction or inhibition of scarring, and/or promotion of re-epithelialisation of wounds.

A subject can be pre-treated or treated prophylactically with a molecule associated with the invention, prior to the skin of the subject becoming compromised. As used herein "pre-treatment" or "prophylactic treatment" refers to administering a nucleic acid to the skin prior to the skin becoming compromised. For example, a subject could be pre-treated 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 24 hours, 48 hours, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days or more than 8 days prior to the skin becoming compromised. In other embodiments, a subject can be treated with a molecule associated with the invention immediately before the skin becomes compromised and/or simultaneous to the skin becoming compromised and/or after the skin has been compromised. In some embodiments, the skin is compromised through a medical procedure such as surgery, including elective surgery. In certain embodiments methods and compositions may be applied to areas of the skin that are believed to be at risk of becoming compromised. It should be appreciated that one of ordinary skill in the art

would be able to optimize timing of administration using no more than routine experimentation.

In some aspects, methods associated with the invention can be applied to promote healing of compromised skin. Administration can occur at any time up until the compromised skin has healed, even if the compromised skin has already partially healed. The timing of administration can depend on several factors including the nature of the compromised skin, the degree of damage within the compromised skin, and the size of the compromised area. In some embodiments administration may occur immediately after the skin is compromised, or 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 48 hours, or more than 48 hours after the skin has been compromised. Methods and compositions of the invention may be administered one or more times as necessary. For example, in some embodiments, compositions may be administered daily or twice daily. In some instances, compositions may be administered both before and after formation of compromised skin.

Compositions associated with the invention may be administered by any suitable route. In some embodiments, administration occurs locally at an area of compromised skin. For example, compositions may be administered by intradermal injection. Compositions for intradermal injection may include injectable solutions. Intradermal injection may in some embodiments occur around the are of compromised skin or at a site where the skin is likely to become compromised. In some embodiments, compositions may also be administered in a topical form, such as in a cream or ointment. In some embodiments, administration of compositions described herein comprises part of an initial treatment or pre-treatment of compromised skin, while in other embodiments, administration of such compositions comprises follow-up care for an area of compromised skin.

The appropriate amount of a composition or medicament to be applied can depend on many different factors and can be determined by one of ordinary skill in the art through routine experimentation. Several non-limiting factors that might be considered include biological activity and bioavailability of the agent, nature of the agent, mode of administration, half-life, and characteristics of the subject to be treated.

In some aspects, nucleic acid molecules associated with the invention may also be used in treatment and/or prevention of fibrotic disorders, including pulmonary fibrosis, liver cirrhosis, scleroderma and glomerulonephritis, lung fibrosis, liver fibrosis,

skin fibrosis, muscle fibrosis, radiation fibrosis, kidney fibrosis, proliferative vitreoretinopathy, restenosis, and uterine fibrosis.

A therapeutically effective amount of a nucleic acid molecule described herein may in some embodiments be an amount sufficient to prevent the formation of compromised skin and/or improve the condition of compromised skin and/or to treat or prevent a fibrotic disorder. In some embodiments, improvement of the condition of compromised skin may correspond to promotion of wound healing and/or inhibition of scarring and/or promotion of epithelial regeneration. The extent of prevention of formation of compromised skin and/or improvement to the condition of compromised skin may in some instances be determined by, for example, a doctor or clinician.

The ability of nucleic acid molecules associated with the invention to prevent the formation of compromised skin and/or improve the condition of compromised skin may in some instances be measured with reference to properties exhibited by the skin. In some instances, these properties may include rate of epithelialisation and/or decreased size of an area of compromised skin compared to control skin at comparable time points.

As used herein, prevention of formation of compromised skin, for example prior to a surgical procedure, and/or improvement of the condition of compromised skin, for example after a surgical procedure, can encompass any increase in the rate of healing in the compromised skin as compared with the rate of healing occurring in a control sample. In some instances, the condition of compromised skin may be assessed with respect to either comparison of the rate of re-epithelialisation achieved in treated and control skin, or comparison of the relative areas of treated and control areas of compromised skin at comparable time points. In some aspects, a molecule that prevents formation of compromised skin or promotes healing of compromised skin may be a molecule that, upon administration, causes the area of compromised skin to exhibit an increased rate of re-epithelialisation and/or a reduction of the size of compromised skin compared to a control at comparable time points. In some embodiments, the healing of compromised skin may give rise to a rate of healing that is 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% greater than the rate occurring in controls.

In some aspects, subjects to be treated by methods and compositions associated with the invention may be subjects who will undergo, are undergoing or have undergone a medical procedure such as a surgery. In some embodiments, the subject may be prone to defective, delayed or otherwise impaired re-epithelialisation, such as dermal wounds

in the aged. Other non-limiting examples of conditions or disorders in which wound healing is associated with delayed or otherwise impaired re-epithelialisation include patients suffering from diabetes, patients with polypharmacy, post-menopausal women, patients susceptible to pressure injuries, patients with venous disease, clinically obese patients, patients receiving chemotherapy, patients receiving radiotherapy, patients receiving steroid treatment, and immuno-compromised patients. In some instances, defective re-epithelialisation response can contributes to infections at the wound site, and to the formation of chronic wounds such as ulcers.

In some embodiments, methods associated with the invention may promote the re-epithelialisation of compromised skin in chronic wounds, such as ulcers, and may also inhibit scarring associated with wound healing. In other embodiments, methods associated with the invention are applied to prevention or treatment of compromised skin in acute wounds in patients predisposed to impaired wound healing developing into chronic wounds. In other aspects, methods associated with the invention are applied to promote accelerated healing of compromised skin while preventing, reducing or inhibiting scarring for use in general clinical contexts. In some aspects, this can involve the treatment of surgical incisions and application of such methods may result in the prevention, reduction or inhibition of scarring that may otherwise occur on such healing. Such treatment may result in the scars being less noticeable and exhibiting regeneration of a more normal skin structure. In other embodiments, the compromised skin that is treated is not compromised skin that is caused by a surgical incision. The compromised skin may be subject to continued care and continued application of medicaments to encourage re-epithelialisation and healing.

In some aspects, methods associated with the invention may also be used in the treatment of compromised skin associated with grafting procedures. This can involve treatment at a graft donor site and/or at a graft recipient site. Grafts can in some embodiments involve skin, artificial skin, or skin substitutes. Methods associated with the invention can also be used for promoting epithelial regeneration. As used herein, promotion of epithelial regeneration encompasses any increase in the rate of epithelial regeneration as compared to the regeneration occurring in a control-treated or untreated epithelium. The rate of epithelial regeneration attained can in some instances be compared with that taking place in control-treated or untreated epithelia using any suitable model of epithelial regeneration known in the art. Promotion of epithelial

regeneration may be of use to induce effective re-epithelialisation in contexts in which the re-epithelialisation response is impaired, inhibited, retarded or otherwise defective. Promotion of epithelial regeneration may be also effected to accelerate the rate of defective or normal epithelial regeneration responses in patients suffering from epithelial damage.

Some instances where re-epithelialisation response may be defective include conditions such as pemphigus, Hailey-Hailey disease (familial benign pemphigus), toxic epidermal necrolysis (TEN)/Lyell's syndrome, epidermolysis bullosa, cutaneous leishmaniasis and actinic keratosis. Defective re-epithelialisation of the lungs may be associated with idiopathic pulmonary fibrosis (IPF) or interstitial lung disease. Defective re-epithelialisation of the eye may be associated with conditions such as partial limbal stem cell deficiency or corneal erosions. Defective re-epithelialisation of the gastrointestinal tract or colon may be associated with conditions such as chronic anal fissures (fissure in ano), ulcerative colitis or Crohn's disease, and other inflammatory bowel disorders.

In some aspects, methods associated with the invention are used to prevent, reduce or otherwise inhibit compromised skin associated with scarring. This can be applied to any site within the body and any tissue or organ, including the skin, eye, nerves, tendons, ligaments, muscle, and oral cavity (including the lips and palate), as well as internal organs (such as the liver, heart, brain, abdominal cavity, pelvic cavity, thoracic cavity, guts and reproductive tissue). In the skin, treatment may change the morphology and organization of collagen fibers and may result in making the scars less visible and blend in with the surrounding skin. As used herein, prevention, reduction or inhibition of scarring encompasses any degree of prevention, reduction or inhibition in scarring as compared to the level of scarring occurring in a control-treated or untreated wound.

Prevention, reduction or inhibition of compromised skin, such as compromised skin associated with dermal scarring, can be assessed and/or measured with reference to microscopic and/or macroscopic characteristics. Macroscopic characteristics may include color, height, surface texture and stiffness of the skin. In some instances, prevention, reduction or inhibition of compromised skin may be demonstrated when the color, height, surface texture and stiffness of the skin resembles that of normal skin more closely after treatment than does a control that is untreated. Microscopic assessment of

compromised skin may involve examining characteristics such as thickness and/or orientation and/or composition of the extracellular matrix (ECM) fibers, and cellularity of the compromised skin. In some instances, prevention, reduction or inhibition of compromised skin may be demonstrated when the thickness and/or orientation and/or composition of the extracellular matrix (ECM) fibers, and/or cellularity of the compromised skin resembles that of normal skin more closely after treatment than does a control that is untreated.

In some aspects, methods associated with the invention are used for cosmetic purposes, at least in part to contribute to improving the cosmetic appearance of compromised skin. In some embodiments, methods associated with the invention may be used to prevent, reduce or inhibit compromised skin such as scarring of wounds covering joints of the body. In other embodiments, methods associated with the invention may be used to promote accelerated wound healing and/or prevent, reduce or inhibit scarring of wounds at increased risk of forming a contractile scar, and/or of wounds located at sites of high skin tension.

In some embodiments, methods associated with the invention can be applied to promoting healing of compromised skin in instances where there is an increased risk of pathological scar formation, such as hypertrophic scars and keloids, which may have more pronounced deleterious effects than normal scarring. In some embodiments, methods described herein for promoting accelerated healing of compromised skin and/or preventing, reducing or inhibiting scarring are applied to compromised skin produced by surgical revision of pathological scars.

Aspects of the invention can be applied to compromised skin caused by burn injuries. Healing in response to burn injuries can lead to adverse scarring, including the formation of hypertrophic scars. Methods associated with the invention can be applied to treatment of all injuries involving damage to an epithelial layer, such as injuries to the skin in which the epidermis is damaged. Other non-limiting examples of injuries to epithelial tissue include injuries involving the respiratory epithelia, digestive epithelia or epithelia surrounding internal tissues or organs.

RNAi to treat liver fibrosis

In some embodiments, methods associated with the invention are used to treat liver fibrosis. Liver fibrosis is the excessive accumulation of extracellular matrix proteins, including collagen, that occurs in most types of chronic liver diseases. It is the

scarring process that represents the liver's response to injury. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires liver transplantation. In the same way as skin and other organs heal wounds through deposition of collagen and other matrix constituents so the liver repairs injury through the deposition of new collagen. Activated hepatic stellate cells, portal fibroblasts, and myofibroblasts of bone marrow origin have been identified as major collagen-producing cells in the injured liver. These cells are activated by fibrogenic cytokines such as TGF-β1, angiotensin II, and leptin. In some embodiments, methods provided herein are aimed at inhibiting the accumulation of fibrogenic cells and/or preventing the deposition of extracellular matrix proteins. In some embodiments, RNAi molecules (including sd-rxRNA and rxRNAori) may be designed to target CTGF, TGF-β1, angiotensin II, and/or leptin. In some embodiments, RNAi molecules (including sd-rxRNA and rxRNAori) may be designed to target those genes listed in Tables 1-25.

Trabeculectomy failure

Trabeculectomy is a surgical procedure designed to create a channel or bleb though the sclera to allow excess fluid to drain from the anterior of the eye, leading to reduced intraocular pressure (IOP), a risk factor for glaucoma-related vision loss. The most common cause of trabeculectomy failure is blockage of the bleb by scar tissue. In certain embodiments, the sd-rxRNA is used to prevent formation of scar tissue resulting from a trabeculectomy. In some embodiments, the sd-rxRNA targets connexin 43. In other embodiments, the sd-rxRNA targets proyly 4-hydroxylase. In yet other embodiments, the sd-rxRNA targets procollagen C-protease.

Target genes

It should be appreciated that based on the RNAi molecules designed and disclosed herein, one of ordinary skill in the art would be able to design such RNAi molecules to target a variety of different genes depending on the context and intended use. For purposes of pre-treating, treating, or preventing compromised skin and/or promoting wound healing and/or preventing, reducing or inhibiting scarring, one of ordinary skill in the art would appreciate that a variety of suitable target genes could be identified based at least in part on the known or predicted functions of the genes, and/or the known or predicted expression patterns of the genes. Several non-limiting examples of genes that could be targeted by RNAi molecules for pre-treating, treating, or preventing compromised skin and/or promoting wound healing and/or preventing,

reducing or inhibiting scarring include genes that encode for the following proteins: Transforming growth factor β (TGFβ1, TGFβ2, TGFβ3), Osteopontin (SPP1), Connective tissue growth factor (CTGF), Platelet-derived growth factor (PDGF), Hypoxia inducible factor-1α (HIF1α), Collagen I and/or III, Prolyl 4-hydroxylase (P4H), Procollagen C-protease (PCP), Matrix metalloproteinase 2, 9 (MMP2, 9), Integrins, Connexin, Histamine H1 receptor, Tissue transglutaminase, Mammalian target of rapamycin (mTOR), HoxB13, VEGF, IL-6, SMAD proteins, Ribosomal protein S6 kinases (RSP6), Cyclooxygenase-2 (COX-2/PTGS2), Cannabinoid receptors (CB1, CB2), and/or miR29b.

Transforming growth factor β proteins, for which three isoforms exist in mammals (TGFβ1, TGFβ2, TGFβ3), are secreted proteins belonging to a superfamily of growth factors involved in the regulation of many cellular processes including proliferation, migration, apoptosis, adhesion, differentiation, inflammation, immuno-suppression and expression of extracellular proteins. These proteins are produced by a wide range of cell types including epithelial, endothelial, hematopoietic, neuronal, and connective tissue cells. Representative Genbank accession numbers providing DNA and protein sequence information for human TGFβ1, TGFβ2 and TGFβ3 are BT007245, BC096235, and X14149, respectively. Within the TGFβ family, TGFβ1 and TGFβ2 but not TGFβ3 represent suitable targets. The alteration in the ratio of TGFβ variants will promote better wound healing and will prevent excessive scar formation.

Osteopontin (OPN), also known as Secreted phosphoprotein 1 (SPP1), Bone Sinaloprotein 1 (BSP-1), and early T-lymphocyte activation (ETA-1) is a secreted glycoprotein protein that binds to hydroxyapatite. OPN has been implicated in a variety of biological processes including bone remodeling, immune functions, chemotaxis, cell activation and apoptosis. Osteopontin is produced by a variety of cell types including fibroblasts, preosteoblasts, osteoblasts, osteocytes, odontoblasts, bone marrow cells, hypertrophic chondrocytes, dendritic cells, macrophages, smooth muscle, skeletal muscle myoblasts, endothelial cells, and extraosseous (non-bone) cells in the inner ear, brain, kidney, deciduum, and placenta. Representative Genbank accession number providing DNA and protein sequence information for human Osteopontin are NM_000582.2 and X13694.

Connective tissue growth factor (CTGF), also known as Hypertrophic chondrocyte-specific protein 24, is a secreted heparin-binding protein that has been

implicated in wound healing and scleroderma. Connective tissue growth factor is active in many cell types including fibroblasts, myofibroblasts, endothelial and epithelial cells. Representative Genbank accession number providing DNA and protein sequence information for human CTGF are NM_001901.2 and M92934.

The Platelet-derived growth factor (PDGF) family of proteins, including several isoforms, are secreted mitogens. PDGF proteins are implicated in wound healing, at least in part, because they are released from platelets following wounding. Representative Genbank accession numbers providing DNA and protein sequence information for human PDGF genes and proteins include X03795 (PDGFA), X02811 (PDGFB), AF091434 (PDGFC), AB033832 (PDGFD).

Hypoxia inducible factor-1α (HIF1α), is a transcription factor involved in cellular response to hypoxia. HIF1α is implicated in cellular processes such as embryonic vascularization, tumor angiogenesis and pathophysiology of ischemic disease. A representative Genbank accession number providing DNA and protein sequence information for human HIF1α is U22431.

Collagen proteins are the most abundant mammalian proteins and are found in tissues such as skin, tendon, vascular, ligature, organs, and bone. Collagen I proteins (such as COL1A1 and COL1A2) are detected in scar tissue during wound healing, and are expressed in the skin. Collagen III proteins (including COL3A1) are detected in connective tissue in wounds (granulation tissue), and are also expressed in skin. Representative Genbank accession numbers providing DNA and protein sequence information for human Collagen proteins include: Z74615 (COL1A1), J03464 (COL1A2) and X14420 (COL3A1).

Prolyl 4-hydroxylase (P4H), is involved in production of collagen and in oxygen sensing. A representative Genbank accession number providing DNA and protein sequence information for human P4H is AY198406.

Procollagen C-protease (PCP) is another target.

Matrix metalloproteinase 2, 9 (MMP2, 9) belong to the metzincin metalloproteinase superfamily and are zinc-dependent endopeptidases. These proteins are implicated in a variety of cellular processes including tissue repair. Representative Genbank accession numbers providing DNA and protein sequence information for human MMP proteins are M55593 (MMP2) and J05070 (MMP9).

Integrins are a family of proteins involved in interaction and communication between a cell and the extracellular matrix. Vertebrates contain a variety of integrins including $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_4\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$, $\alpha_L\beta_2$, $\alpha_M\beta_2$, $\alpha_{IIb}\beta_3$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_6\beta_4$.

Connexins are a family of vertebrate transmembrane proteins that form gap junctions. Several examples of Connexins, with the accompanying gene name shown in brackets, include Cx23 (GJE1), Cx25 (GJB7), Cx26 (GJB2), Cx29 (GJE1), Cx30 (GJB6), Cx30.2 (GJC3), Cx30.3 (GJB4), Cx31 (GJB3), Cx31.1 (GJB5), Cx31.9 (GJC1/GJD3), Cx32 (GJB1), Cx33 (GJA6), Cx36 (GJD2/GJA9), Cx37 (GJA4), Cx39 (GJD4), Cx40 (GJA5), Cx40.1 (GJD4), Cx43 (GJA1), Cx45 (GJC1/GJA7), Cx46 (GJA3), Cx47 (GJC2/GJA12), Cx50 (GJA8), Cx59 (GJA10), and Cx62 (GJA10).

Histamine H1 receptor (HRH1) is a metabotropic G-protein-coupled receptor involved in the phospholipase C and phosphatidylinositol (PIP2) signaling pathways. A representative Genbank accession number providing DNA and protein sequence information for human HRH1 is Z34897.

Tissue transglutaminase, also called Protein-glutamine gamma-glutamyltransferase 2, is involved in protein crosslinking and is implicated is biological processes such as apoptosis, cellular differentiation and matrix stabilization. A representative Genbank accession number providing DNA and protein sequence information for human Tissue transglutaminase is M55153.

Mammalian target of rapamycin (mTOR), also known as Serine/threonine-protein kinase mTOR and FK506 binding protein 12-rapamycin associated protein 1 (FRAP1), is involved in regulating cell growth and survival, cell motility, transcription and translation. A representative Genbank accession number providing DNA and protein sequence information for human mTOR is L34075.

HoxB13 belongs to the family of Homeobox proteins and has been linked to functions such as cutaneous regeneration and fetal skin development. A representative Genbank accession number providing DNA and protein sequence information for human HoxB13 is U57052.

Vascular endothelial growth factor (VEGF) proteins are growth factors that bind to tyrosine kinase receptors and are implicated in multiple disorders such as cancer, age-related macular degeneration, rheumatoid arthritis and diabetic retinopathy. Members of this protein family include VEGF-A, VEGF-B, VEGF-C and VEGF-D. Representative Genbank accession numbers providing DNA and protein sequence information for

human VEGF proteins are M32977 (VEGF-A), U43368 (VEGF-B), X94216 (VEGF-C), and D89630 (VEGF-D).

Interleukin-6 (IL-6) is a cytokine involved in stimulating immune response to tissue damage. A representative Genbank accession number providing DNA and protein sequence information for human IL-6 is X04430.

SMAD proteins (SMAD1-7, 9) are a family of transcription factors involved in regulation of TGFβ signaling. Representative Genbank accession numbers providing DNA and protein sequence information for human SMAD proteins are U59912 (SMAD1), U59911 (SMAD2), U68019 (SMAD3), U44378 (SMAD4), U59913 (SMAD5), U59914 (SMAD6), AF015261 (SMAD7), and BC011559 (SMAD9).

Ribosomal protein S6 kinases (RSK6) represent a family of serine/threonine kinases involved in activation of the transcription factor CREB. A representative Genbank accession number providing DNA and protein sequence information for human Ribosomal protein S6 kinase alpha-6 is AF184965.

Cyclooxygenase-2 (COX-2), also called Prostaglandin G/H synthase 2 (PTGS2), is involved in lipid metabolism and biosynthesis of prostanoids and is implicated in inflammatory disorders such as rheumatoid arthritis. A representative Genbank accession number providing DNA and protein sequence information for human COX-2 is AY462100.

Cannabinoid receptors, of which there are currently two known subtypes, CB1 and CB2, are a class of cell membrane receptors under the G protein-coupled receptor superfamily. The CB1 receptor is expressed mainly in the brain, but is also expressed in the lungs, liver and kidneys, while the CB2 receptor is mainly expressed in the immune system and in hematopoietic cells. A representative Genbank accession number providing DNA and protein sequence information for human CB1 is NM_001160226, NM_001160258, NM_001160259, NM_001160260, NM_016083, and NM_033181.

miR29b (or miR-29b) is a microRNA (miRNA), which is a short (20-24 nt) non-coding RNA involved in post-transcriptional regulation of gene expression in multicellular organisms by affecting both the stability and translation of mRNAs. miRNAs are transcribed by RNA polymerase II as part of capped and polyadenylated primary transcripts (pri-miRNAs) that can be either protein-coding or non-coding. The primary transcript is cleaved by the Drosha ribonuclease III enzyme to produce an approximately 70-nt stem-loop precursor miRNA (pre-miRNA), which is further cleaved

by the cytoplasmic Dicer ribonuclease to generate the mature miRNA and antisense miRNA star (miRNA*) products. The mature miRNA is incorporated into a RNA-induced silencing complex (RISC), which recognizes target mRNAs through imperfect base pairing with the miRNA and most commonly results in translational inhibition or destabilization of the target mRNA. A representative miRBase accession number for miR29b is MI0000105 (website: mirbase.org/cgi-bin/mirna_entry.pl?acc=MI0000105).

In some embodiments, the sd-rxRNA targets connexin 43 (CX43). This gene is a member of the connexin gene family. The encoded protein is a component of gap junctions, which are composed of arrays of intercellular channels that provide a route for the diffusion of low molecular weight materials from cell to cell. The encoded protein is the major protein of gap junctions in the heart that are thought to have a crucial role in the synchronized contraction of the heart and in embryonic development. A related intronless pseudogene has been mapped to chromosome 5. Mutations in this gene have been associated with oculodentodigital dysplasia and heart malformations. Representative Genbank accession numbers providing DNA and protein sequence information for human CX43 genes and proteins include NM_000165 and NP_000156.

In other embodiments, the sd-rxRNA targets prolyl 4-hydroxylase (P4HTM). The product of this gene belongs to the family of prolyl 4-hydroxylases. This protein is a prolyl hydroxylase that may be involved in the degradation of hypoxia-inducible transcription factors under normoxia. It plays a role in adaptation to hypoxia and may be related to cellular oxygen sensing. Alternatively spliced variants encoding different isoforms have been identified. Representative Genbank accession numbers providing DNA and protein sequence information for human P4HTM genes and proteins include NM_177938, NP_808807, NM_177939, and NP_808808.

In certain embodiments, the sd-rxRNA targets procollagen C-protease.

EXAMPLES

Example 1: In vivo gene silencing in skin after local delivery of sd-rxRNA

Demonstrated herein is gene silencing in skin following administration of sd-rxRNA molecules. Rat incision models were used which included 6 dorsal incisions per animal. Analysis included monitoring of digital images, detection of target gene expression, scar assessment, and histology. Figure 1 reveals an expression profile of several genes including MAP4K4, SPP1, CTGF, PTGS2 and TGFB1. As expected,

when expression of these genes was monitored post-incision, target gene expression ws elevated early and then returned to normal by day 10.

Figure 2 presents an overview of intradermal injection experiments wih sd-rxRNA molecules. 6 intradermal injections were performed at each site. Each injection consisted of approximately 34 μ, 300 μg total. Images were taken before injection and 15 minutes after the first injection.

Figure 3 demonstrates in vivo silencing following intradermal injection of sd-rxRNA in rats. 6 injections were made per dose. 300 μg in PBS was injected on days 1 & 2 (2 doses) or on day 2 (1 dose). 5 incisions sites were made per treatment. Incisions were 1 cm. 3 mm skin biopsies were harvested 48 hours after the last dose and target expression was determined by QPCR.

Figure 4 demonstrates in vivo silencing of MAP4K4, PPIB and CTGF expression in rats following intradermal injection of sd-rxRNA molecules. A single intradermal injection of PBS (vehicle), or 300 ug of MAP4K4, or 2 different CTGF or PPIB targeting sd-rxRNA were injected at 6 sites. 3 mm skin biopsies harvested 48 hours post injection and processed for RNA. Data was analyzed by QPCR and normalized to B-Actin. PBS was set to 1. Data was graphed as a percent reduction in targeted gene expression relative to non-targeting sd-rxRNA (i.e. targeting other gene). Gene expression from untreated skin samples on treated animals are similar to PBS treated or sham controls.

Figure 5 demonstrates in vivo silencing in mice following intradermal injection of sd-rxRNA molecules. C57BL/6 mice were used, with n=7 wheal sites active and PBS. The control group consisted of 12. 300 ug was administered in 50 ul/injections. 3 mm biopsies were processed for RNA, and target expression determined by QPCR. Expression was normalized to housekeeping gene cyclophilin B.

Figure 6 reveals the in vitro potency and in vivo effectiveness of 2 different sd-rxRNAs targeting PPIB. Two PPIB sd-rxRNAs with different EC50s were compared in vivo. Similar in vivo results were obtained with 1 injection of 300 μg

Figures 7 and 8 demonstrate the duration of gene silencing achieved through administration of sd-rxRNA. There were 6 injection sites per animal. 3 mm skin biopsies were harvested on days 3, 5, and 8. RNA was isolated and gene expression was analyzed by qPCR and normalized to B-Actin

Figure 9 compares two different dosage regimens, Days 1 and 3 vs. Days 0 and 2. There were 6 injection sites per animal. 3 mm skin biopsies were harvested on days 3, 5,

and 8. RNA was isolated and gene expression was analyzed by qPCR and normalized to B-Actin.

Example 2: Identification of potent sd-rxRNAs

Up to 300 rxRNA ori compounds were screened for 5 anti-scarring targets. Optimal sequences in SPP1, CTGF, PTGS2, TGFB1 and TGFB2 for sd-rxRNA development were identified using a sequence selection algorithm. The algorithm selects sequences based on the following criteria: a GC content greater than 32% but less than 47%, homology to specific animal models (e.g., mouse or rat), avoidance of 5 or more U/U stretches and/or 2 or more G/C stretches, an off-target hit score of less than 500, and avoidance of sequences contained within the 5' UTR.

The sequences were developed initially as 25 nucleotide blunt-ended duplexes with O-methyl modification. Such sequences were screened in various cell lines to identify those were most efficient in reducing gene expression. Several concentrations of the RNA molecules, such as 0.025, 0.1 and 0.25 nM, were tested, and suitable concentrations to screen for bDNA were determined. A bDNA was then run of a full screen at a desired concentration. Dose response curves were generated to determine the most potent sequences. Hyperfunctional hits were those with an EC50 of less than 100 pM in lipid transfection. Potent molecules were selected to be developed into sd-rxRNAs based on the parameters described throughout the application and a secondary screen was conducted using the sd-rxRNAs.

Figures 10-12 reveal that CTGF sd-rxRNAs are efficacious in mediating gene silencing. A dose response for CTGF is indicated in Figure 12.

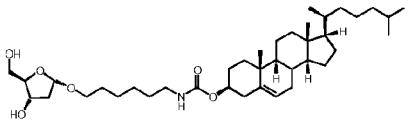
Figures 13-14 reveal that the original sd-rxrNA screen had a low hit rate. Figure 15 reveals PTGS2 knockdown using sd-rxRNA against PTGS2. Figures 16-24 reveal that hTGFB1, TGFB, TGFB2 sd-rxRNAs are capable of mediating gene silencing. Figures 25-28 shows the identificatio of potent hSPP1 sd-rxRNAs.

Example 3: Linker chemistry

Figure 36 demonstrates that variation of linker chemistry does not influence silencing activity of sd-rxRNAs in vitro. Two different linker chemistries were evaluated, a hydroxyproline linker and ribo linker, on multiple sd-rxRNAs (targeting Map4k4 or PPIB) in passive uptake assays to determine linkers which favor self

delivery. HeLa cells were transfected in the absence of a delivery vehicle (passive transfection) with sd-rxRNAs at 1 uM, 0.1 uM or 0.01 uM for 48 hrs. Use of either linker results in an efficacious delivery of sd-rxRNA.

The ribo linker used in Example 5 had the following structure:



Example 4: Optimization of target sequences

Chemical optimization was performed for several lead sequences, including CTGF, PTGS2, TGFβ1, and TGFβ2. Multiples versions of sd-rxRNA leads were synthesized. The sense strand was further O-methyl modified, such as by introduction of O-methyl blocks on the ends, introduction of O-methyl phosphorothioate blocks at the ends or introduction of ful O-methyl modification with a phosphorothioate block on the 3'end.

The guide strand was modified to decrease the number of 2'F, substitute 2'F with O-methyl, vary the number of ribonucleotides, eliminate stretches of ribonucleotides, minimize the presence of ribonucleitides next to the phosphorothioate modifications, and if possible remove ribonucleotides from the single stranded region.

Various versions of compounds were synthesized and their efficacy was tested *in vitro* using passive uptake. The efficacy and toxicity of the optimized compounds was evaluated *in vivo*.

All compounds show *in vivo* efficacy. Initially, activity required high concentration and at high concentrations some compound demonstrated injection site reaction. However, data indicated that efficacy and toxicity *in vivo* could be dramatically improved by enhancement of stability and reduction of 2' F content. In some instances, toxicity, at least in part, was related to the presence of cholesterol containing short oligomer metabolites. This type of toxicity is expected to be reduced by stabilization. In general, chemical stabilization was well tolerated. Exact chemical optimization patterns differed for various compound. In some cases, complete stabilization resulted in a slightly negative impact on activity. For most target sites, at least two chemically optimized leads were identified: chemically optimized with *in vitro* efficacy retained or

improved compared to an Early Lead and Fully Modified, where *in vitro* efficacy is slightly reduced.

In general, a fully O-methyl modified sense strand is acceptable. In some instances, it is preferable if less than all of the nucleotides in the sense strand are O-methyl modified. In some instances, the 3' end of the passenger strand contained a PS/ O-METIIYL block (2 O-methyl modifications and two 2 phosphorothioate modifications) to insure maximized stability next to the hydrophobic conjugate.

For all compounds, it was possible to identify functional heavily stabilized leads. In some instances, the number of ribonucleotides per compounds was reduced to 4-6. Multiples versions of sd-rxRNA leads were synthesized. The number of 2'F modified purines was limited where possible to improve manufacturability but some optimized compounds do contain some 2'F modified purines.

Optimized Compounds

A summary of CTGF lead compounds is shown in Table 24. PTGS leads are shown in Table 25. hTGFβ1 leads are shown in Table 26 and hTGFβ2 leads are shown in Table 27. Lead compounds were tested for *in vitro* efficacy with varying levels of methylation of the sense strand.

For CTGF Lead 1 (L1), the fully O-methyl modified sense strand was efficacious having a slight reduction in *in vitro* efficacy.

For CTGF L2, the fully O-methyl modified sense strand was efficacious, having a slight reduction in *in vitro* efficacy.

For CTGF L3, the fully O-methyl modified sense strand was partially efficacious, having a reduction in *in vitro* efficacy.

For CTGF L4, the fully O-methyl modified sense strand was partially efficacious, having a slight reduction in *in vitro* efficacy.

For PTGS2 L1 and L2, the fully O-methyl modified sense strand was not efficacious.

For TGFβ1 hL3, the fully O-methyl modified sense strand was efficacious.

For TGFβ2, the fully O-methyl modified sense strand was efficacious.

In vivo efficacy of lead compounds

The activity of lead compounds was tested *in vivo* both in cell culture and in animal models. Figures 33 and 34 demonstrate the activity of optimized CTGF L1

compounds. Figure 35 demontrates the *in vitro* stability of the CTGF L1 compounds. Figures 36 and 37 demonstrate the activity of optimized CTGF L2 compounds. Figure 38 demontrates the *in vitro* stability of the CTGF L2 compounds. Figure 39 provides a summary of the *in vivo* activity of CTGF lead compounds. Figure 40 demonstrates the efficacy of CTGF L1 compounds in skin biopsies from rats. Figure 41 shows the efficacy of CTGF L2 compounds in achieving gene silencing.

Figure 42 demonstrates CTGF silencing following intradermal injection of RXi-109. Figure 43 demonstrates the duration of CTGF silencing in skin after intradermal injection of the sd-rxRNA in SD rats. Eight millimeter skin biopsies were harvested, and mRNA levels were quantified by QPCR and normalized to a housekeeping gene. Shown is percent (%) silencing vs. Non Targeting Control (NTC); PBS at each time point is one experimental group; * $p \leq 0.04$; ** $p \leq 0.002$.

Figures 44-46 show that CTGF L3 and L4 compounds are also active. FIG. 47 demonstrates changes in mRNA expression levels of CTGF, α-SM actin, collagen 1A2, and collagen 3A1 after intradermal injection of CTFG sd-rxRNA in SD rats. mRNA levels were quantified by qPCR. Substantial reduction in CTGF expression is observed.

FIG. 49 demonstrates that administration of sd-rxRNAs decreases wound width over the course of at least 9 days. The graph shows microscopic measurements of wound width in rats on days 3, 6, and 9 post-wounding. Each group represents 5 rats. Two non-serial sections from each wound were measured and the average width of the two was calculated per wound. *p<0.05 vs. PBS an NTC.

FIG. 50 demonstrates that administration of sd-rxRNAs decreases wound area over the course of at least 9 days. The graph shows microscopic measurements of wound width in rats on days 3, 6, and 9 post-wounding. Each group represents 5 rats. Two non-serial sections from each wound were measured and the average width of the two was calculated per wound. *p<0.05 vs. PBS an NTC.

FIG. 51 demonstrates that administration of sd-rxRNAs increase the percentage of wound re-epithelialization over the course of at least 9 days. The graph shows microscopic measurements of wound width in rats on days 3, 6, and 9 post-wounding. Each group represents 5 rats. Two non-serial sections from each wound were measured and the average width of the two was calculated per wound. *p<0.05 vs. PBS an NTC.

FIG. 52 demonstrates that administration of sd-rxRNAs increases the average granulation tissue maturity scores over the course of at least 9 days. The graph shows

microscopic measurements of wound width in rats on days 3, 6, and 9 post-wounding (5 = mature, 1 = immature). Each group represents 5 rats. FIG. 53 demonstrates CD68 labeling in day 9 wounds (0 = no labeling, 3 = substantial labeling). Each group represents 5 rats.

FIG. 54 demonstrates that CTGF leads have different toxicity levels *in vitro*. FIG. 55 shows percentage (%) of cell viability after RXi-109 dose escalation (oligos formulated in PBS).

FIG. 56 is a schematic of a non-limiting example of a Phase 1 and 2 clinical trial design for lead compounds. This schematic represents a divided dose, single day ascending dose clinical trial.

FIG. 57 is a schematic of a non-limiting example of a Phase 1 and 2 clinical trial design. This schematic represents a divided dose, multi-day ascending dose clinical trial.

Activity of PTGS2, TGFβ1 and TGFβ2 leads was also tested. Figures 59 and 60 demonstrate activity of PTGS2 L1 and L2 compounds. Figures 61 and 62 demonstrate the activity of h TGFβ1 compounds and Figures 63 and 64 demonstrate the activity of hTGFβ2 compounds.

Gene knock-down in liver was also tested following tail vein injection mice. FIG. 58 demonstrates a percent (%) decrease in PPIB expression in the liver relative to PBS control. Lipoid formulated rxRNAs (10 mg/kg) were delivery systemically to Balb/c mice (n=5) by single tail vein injections. Liver tissue was harvested at 24 hours after injection and expression was analyzed by qPCR (normalized to β-actin). Map4K4 rxRNAori also showed significant silencing (~83%, $p<0.001$) although Map4K4 sd-rxRNA did not significantly reduce target gene expression (~17%, $p=0.019$). TD.035.2278, Published lipidoid delivery reagent, 98N12-5(1), from Akinc, 2009.

Table 1 provides sequences tested in the Original sd-rxRNA screen.

Table 2 demonstrates inhibition of gene expression with PTGS2 ori sequences.

Table 3 demonstrates non-limiting examples of PTGS2 sd-rxRNA sequences.

Table 4 demonstrates non-limiting examples of TGFB1 sd-rxRNA sequences.

Table 5 demonstrates inhibition of gene expression with hTGFB1 ori sequences.

Table 6 demonstrates inhibition of gene expression with hTGFB2 ori sequences.

Table 7 demonstrates non-limiting examples of hTGFB2 sd-rxRNA sequences.

Table 8 demonstrates non-limiting examples of hSPP1 sd-rxRNA sequences.

Table 9 demonstrates inhibition of gene expression with hSPP1 ori sequences.

Table 10 demonstrates non-limiting examples of hCTGF sd-rxRNA sequences.

Table 11 demonstrates inhibition of gene expression with hCTGF ori sequences.

Table 12 demonstrates inhibition of gene expression with CTGF ori sequences.

Table 13 demonstrates inhibition of gene expression with SPP1 sd-rxRNA sequences.

Table 14 demonstrates inhibition of gene expression with PTGS2 sd-rxRNA sequences.

Table 15 demonstrates inhibition of gene expression with CTGF sd-rxRNA sequences.

Table 16 demonstrates inhibition of gene expression with TGFB2 sd-rxRNA sequences.

Table 17 demonstrates inhibition of gene expression with TGFB1 sd-rxRNA sequences.

Table 18 demonstrates inhibition of gene expression with SPP1 sd-rxRNA sequences.

Table 19 demonstrates inhibition of gene expression with PTGS2 sd-rxRNA sequences.

Table 20 demonstrates inhibition of gene expression with CTGF sd-rxRNA sequences.

Table 21 demonstrates inhibition of gene expression with TGFB2 sd-rxRNA sequences.

Table 22 demonstrates inhibition of gene expression with TGFB1 sd-rxRNA sequences.

Table 23 provides non-limiting examples of CB1 sequences.

Table 24 provides a summary of CTGF Leads.

Table 25 provides a summary of PTGS2 Leads.

Table 26 provides a summary of TGFβ1 Leads.

Table 27 provides a summary of TGFβ1 Leads.

Table 1: Original sd-rxRNA screen

Oligo ID#	G1-	SEQ ID NO	Sense-sd-rxRNA GII	SEQ ID NO	AS-sd-rxRNA-GII
14394	TGFB1	1	GmCmUAAmUGGmUGGAA-chol	2	5'-P-mU(2'-F-U)(2'-F-C)(2'-F-C)A(2'-F-C)(2'-F-C)A(2'-F-U)(2'-F-U)AGmC*A*mC*G*mC*G*G
14395	TGFB1	3	mUGAmUmCGmUGmCGmCmUmC-chol	4	5'-P-mGAG(2'-F-C)G(2'-F-C)A(2'-F-C)GA(2'-F-U)mCA*mU*G*mU*mU*G*G
14396	TGFB1	5	mCAAmUmUmCmCmUGGmCGA-chol	6	5'-P-mU(2'-F-C)G(2'-F-C)(2'-F-C)AGGAA(2'-F-U)mUG*mU*mU*G*mC*mU*G
14397	TGFB1	7	AGmUGGAmUmCmCAmCGA-chol	8	5'-P-mU(2'-F-C)G(2'-F-U)GGA(2'-F-U)(2'-F-C)(2'-F-C)AmCmU*mU*mC*mC*A*G*C

Oligo ID#	G1-	SEQ ID NO	Sense-sd-rxRNA GII	SEQ ID NO	AS-sd-rxRNA-GII
14398	TGFB1	9	mUAmCAGmCAAGGmUmCmC-chol	10	5'-P-mGGA(2'-F-C)(2'-F-C)(2'-F-U)(2'-F-U)G(2'-F-C)(2'-F-U)GmUA*mC*mU*G*mC*G*U
14399	TGFB1	11	AAmCAmUGAmUmCGmUGmC-chol	12	5'-P-mG(2'-F-C)A(2'-F-C)GA(2'-F-U)(2'-F-C)A(2'-F-U)GmUmU*G*G*A*mC*A*G
14400	TGFB1	13	AmCAmUGAmUmCGmUGmCG-chol	14	5'-P-mCG(2'-F-C)A(2'-F-C)GA(2'-F-U)(2'-F-C)A(2'-F-U)GmU*mU*G*G*A*mC*A
14401	TGFB1	15	mCAGmCAAGGmUmCmCmUG-chol	16	5'-P-mCAGGA(2'-F-C)(2'-F-C)(2'-F-U)(2'-F-U)G(2'-F-C)mUG*mU*A*mC*mU*G*C
14402	TGFB1	17	mCmCAAmCAmUGAmUmCGmU-chol	18	5'-P-mA(2'-F-C)GA(2'-F-U)(2'-F-C)A(2'-F-U)G(2'-F-U)(2'-F-U)GG*A*mC*A*G*mC*U
14403	TGFB1	19	AGmCGGAAGmCGmCAmU-chol	20	5'-P-mA(2'-F-U)G(2'-F-C)G(2'-F-C)(2'-F-U)(2'-F-U)(2'-F-C)(2'-F-C)GmCmU*mU*mC*A*mC*mC*A
14404	TGFB1	21	GmCAmUmCGAGGmCmCAmU-chol	22	5'-P-mA(2'-F-U)GG(2'-F-C)(2'-F-C)(2'-F-U)(2'-F-C)GA(2'-F-U)GmC*G*mC*mU*mU*mC*C
14405	TGFB1	23	GAmCmUAmUmCGAmCAmUG-chol	24	5'-P-mCA(2'-F-U)G(2'-F-U)(2'-F-C)GA(2'-F-U)AGmUmC*mU*mU*G*mC*A*G
14406	TGFB1	25	AmCmCmUGmCAAGAmCmUA-chol	26	5'-P-mUAG(2'-F-U)(2'-F-C)(2'-F-U)(2'-F-U)G(2'-F-C)AGGmU*G*G*A*mU*A*G
14407	TGFB1	27	GmCmUmCmCAmCGGAGAA-chol	28	5'-P-mU(2'-F-U)(2'-F-C)(2'-F-U)(2'-F-C)(2'-F-C)G(2'-F-U)GGAGmC*mU*G*A*A*G*C
14408	TGFB2	29	GGmCmUmCmUmCmCmUmUmCGA-chol	30	5'-P-mU(2'-F-C)GAAGGAGAGmCmC*A*mU*mU*mC*G*C
14409	TGFB2	31	GAmCAGGAAmCmCmUGG-chol	32	5'-P-mC(2'-F-C)AGG(2'-F-U)(2'-F-U)(2'-F-C)(2'-F-C)(2'-F-U)GmUmC*mU*mU*mU*A*mU*G
14410	TGFB2	33	mCmCAAGGAGGmUmUmUA-chol	34	5'-P-mUAAA(2'-F-C)(2'-F-C)(2'-F-U)(2'-F-C)(2'-F-C)(2'-F-U)(2'-F-U)GG*mC*G*mU*A*G*U
14411	TGFB2	35	AmUmUmUmCmCAmUmCmUAmCA-chol	36	5'-P-mUG(2'-F-U)AGA(2'-F-U)GGAAAmU*mC*A*mC*mC*mU*C
14412	TGFB2	37	mUmCmCAmUmCmUAmCAAmCA-chol	38	5'-P-mUG(2'-F-U)(2'-F-U)G(2'-F-U)AGA(2'-F-U)GGA*A*A*mU*mC*A*C
14413	TGFB2	39	mUmUmUmCmCAmUmCmUAmCAA-chol	40	5'-P-mU(2'-F-U)G(2'-F-U)AGA(2'-F-U)GGAAA*mU*mC*A*mC*mC*U
14414	TGFB2	41	mCGmCmCAAGGAGGmUmU-chol	42	5'-P-mAA(2'-F-C)(2'-F-C)(2'-F-U)(2'-F-C)(2'-F-C)(2'-F-U)(2'-F-U)GGmCG*mU*A*G*mU*A*C
14415	TGFB2	43	GmUGGmUGAmUmCAGAA-chol	44	5'-P-mU(2'-F-U)(2'-F-C)(2'-F-U)GA(2'-F-U)(2'-F-C)A(2'-F-C)(2'-F-C)AmC*mU*G*G*mU*A*U

Oligo ID#	G1-	SEQ ID NO	Sense-sd-rxRNA GII	SEQ ID NO	AS-sd-rxRNA-GII
14416	TGFB2	45	mCmUmCmCmUGmCmUAA mUGmU-chol	46	5'-P-mA(2'-F-C)A(2'-F-U)(2'-F-U)AG(2'-F-C)AGGAG*A*mU*G*mU*G*G
14417	TGFB2	47	AmCmCmUmCmCAmCAmUA mUA-chol	48	5'-P-mUA(2'-F-U)A(2'-F-U)G(2'-F-U)GGAGGmU*G*mC*mC*A*mU*C
14418	TGFB2	49	AAGmUmCmCAmCmUAGGA-chol	50	5'-P-mU(2'-F-C)(2'-F-C)(2'-F-U)AG(2'-F-U)GGA(2'-F-C)mUmU*mU*A*mU*A*G*U
14419	TGFB2	51	mUGGmUGAmUmCAGAAA-chol	52	5'-P-mU(2'-F-U)(2'-F-U)(2'-F-C)(2'-F-U)GA(2'-F-U)(2'-F-C)A(2'-F-C)mCA*mC*mU*G*G*mU*A
14420	TGFB2	53	AGmUmCmCAmCmUAGGAA-chol	54	5'-P-mU(2'-F-U)(2'-F-C)(2'-F-C)(2'-F-U)AG(2'-F-U)GGAmCmU*mU*mU*A*mU*A*G
14421	TGFB2	55	AmCGmCmCAAGGAGGmU-chol	56	5'-P-mA(2'-F-C)(2'-F-C)(2'-F-U)(2'-F-C)(2'-F-C)(2'-F-U)(2'-F-U)GG(2'-F-C)GmU*A*G*mU*A*mC*U
14422	PTGS2	57	mCAmCAmUmUmUGAmUm UGA-chol	58	5'-P-mU(2'-F-C)AA(2'-F-U)(2'-F-C)AAA(2'-F-U)GmUG*A*mU*mC*mU*G*G
14423	PTGS2	59	mCAmCmUGmCmCmUmCAA mUmU-chol	60	5'-P-mAA(2'-F-U)(2'-F-U)GAGG(2'-F-C)AGmUG*mU*mU*G*A*mU*G
14424	PTGS2	61	AAAmUAmCmCAGmUmCmU mU-chol	62	5'-P-mAAGA(2'-F-C)(2'-F-U)GG(2'-F-U)A(2'-F-U)mUmU*mC*A*mU*mC*mU*G
14425	PTGS2	63	mCAmUmUmUGAmUmUGA mCA-chol	64	5'-P-mUG(2'-F-U)(2'-F-C)AA(2'-F-U)(2'-F-C)AAAmUG*mU*G*A*mU*mC*U

5 **Table 2:** Inhibition of gene expression with PTGS2 ori sequences

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15147	CDS	176	65	CCUGGCGCUCAGCCAUACAGCAAAA	59%
15148	CDS	177	66	CUGGCGCUCAGCCAUACAGCAAAUA	72%
15149	CDS	178	67	UGGCGCUCAGCCAUACAGCAAAUCA	77%
15150	CDS	180	68	GCGCUCAGCCAUACAGCAAAUCCUA	70%
15151	CDS	182	69	GCUCAGCCAUACAGCAAAUCCUUGA	76%
15152	CDS	183	70	CUCAGCCAUACAGCAAAUCCUUGCA	74%
15153	CDS	184	71	UCAGCCAUACAGCAAAUCCUUGCUA	47%
15154	CDS	186	72	AGCCAUACAGCAAAUCCUUGCUGUA	55%
15155	CDS	187	73	GCCAUACAGCAAAUCCUUGCUGUUA	41%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15156	CDS	188	74	CCAUACAGCAAAUCCUUGCUGUUCA	46%
15157	CDS	212	75	CCACCCAUGUCAAAACCGAGGUGUA	31%
15158	CDS	243	76	AGUGUGGGAUUUGACCAGUAUAAGA	23%
15159	CDS	244	77	GUGUGGGAUUUGACCAGUAUAAGUA	24%
15160	CDS	245	78	UGUGGGAUUUGACCAGUAUAAGUGA	38%
15161	CDS	252	79	UUUGACCAGUAUAAGUGCGAUUGUA	29%
15162	CDS	285	80	GGAUUCUAUGGAGAAAACUGCUCAA	16%
15163	CDS	337	81	UAUUUCUGAAACCCACUCCAAACAA	32%
15164	CDS	338	82	AUUUCUGAAACCCACUCCAAACACA	21%
15165	CDS	339	83	UUUCUGAAACCCACUCCAAACACAA	21%
15166	CDS	340	84	UUCUGAAACCCACUCCAAACACAGA	45%
15167	CDS	345	85	AAACCCACUCCAAACACAGUGCACA	87%
15168	CDS	347	86	ACCCACUCCAAACACAGUGCACUAA	83%
15169	CDS	349	87	CCACUCCAAACACAGUGCACUACAA	51%
15170	CDS	350	88	CACUCCAAACACAGUGCACUACAUA	31%
15171	CDS	394	89	UUUGGAACGUUGUGAAUAACAUUCA	43%
15172	CDS	406	90	UGAAUAACAUUCCCUUCCUUCGAAA	21%
15173	CDS	407	91	GAAUAACAUUCCCUUCCUUCGAAAA	32%
15174	CDS	408	92	AAUAACAUUCCCUUCCUUCGAAAUA	27%
15175	CDS	435	93	AUUAUGAGUUAUGUGUUGACAUCCA	27%
15176	CDS	437	94	UAUGAGUUAUGUGUUGACAUCCAGA	21%
15177	CDS	439	95	UGAGUUAUGUGUUGACAUCCAGAUA	30%
15178	CDS	440	96	GAGUUAUGUGUUGACAUCCAGAUCA	68%
15179	CDS	441	97	AGUUAUGUGUUGACAUCCAGAUCAA	35%
15180	CDS	442	98	GUUAUGUGUUGACAUCCAGAUCACA	36%
15181	CDS	443	99	UUAUGUGUUGACAUCCAGAUCACAA	51%
15182	CDS	444	100	UAUGUGUUGACAUCCAGAUCACAUA	24%
15183	CDS	445	101	AUGUGUUGACAUCCAGAUCACAUUA	37%
15184	CDS	446	102	UGUGUUGACAUCCAGAUCACAUUUA	42%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15185	CDS	448	103	UGUUGACAUCCAGAUCACAUUUGAA	18%
15186	CDS	449	104	GUUGACAUCCAGAUCACAUUUGAUA	24%
15187	CDS	450	105	UUGACAUCCAGAUCACAUUUGAUUA	25%
15188	CDS	452	106	GACAUCCAGAUCACAUUUGAUUGAA	27%
15189	CDS	454	107	CAUCCAGAUCACAUUUGAUUGACAA	27%
15190	CDS	455	108	AUCCAGAUCACAUUUGAUUGACAGA	32%
15191	CDS	456	109	UCCAGAUCACAUUUGAUUGACAGUA	40%
15192	CDS	457	110	CCAGAUCACAUUUGAUUGACAGUCA	52%
15193	CDS	460	111	GAUCACAUUUGAUUGACAGUCCACA	40%
15194	CDS	461	112	AUCACAUUUGAUUGACAGUCCACCA	46%
15195	CDS	462	113	UCACAUUUGAUUGACAGUCCACCAA	34%
15196	CDS	463	114	CACAUUUGAUUGACAGUCCACCAAA	30%
15197	CDS	464	115	ACAUUUGAUUGACAGUCCACCAACA	32%
15198	CDS	465	116	CAUUUGAUUGACAGUCCACCAACUA	44%
15199	CDS	467	117	UUUGAUUGACAGUCCACCAACUUAA	17%
15200	CDS	468	118	UUGAUUGACAGUCCACCAACUUACA	22%
15201	CDS	469	119	UGAUUGACAGUCCACCAACUUACAA	27%
15202	CDS	470	120	GAUUGACAGUCCACCAACUUACAAA	41%
15203	CDS	471	121	AUUGACAGUCCACCAACUUACAAUA	39%
15204	CDS	472	122	UUGACAGUCCACCAACUUACAAUGA	61%
15205	CDS	473	123	UGACAGUCCACCAACUUACAAUGCA	48%
15206	CDS	479	124	UCCACCAACUUACAAUGCUGACUAA	29%
15207	CDS	486	125	ACUUACAAUGCUGACUAUGGCUACA	35%
15208	CDS	488	126	UUACAAUGCUGACUAUGGCUACAAA	32%
15209	CDS	517	127	GGGAAGCCUUCUCUAACCUCUCCUA	39%
15210	CDS	518	128	GGAAGCCUUCUCUAACCUCUCCUAA	48%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15211	CDS	519	129	GAAGCCUUCUCUAACCUCUCCUAUA	19%
15212	CDS	520	130	AAGCCUUCUCUAACCUCUCCUAUUA	17%
15213	CDS	524	131	CUUCUCUAACCUCUCCUAUUAUACA	17%
15214	CDS	525	132	UUCUCUAACCUCUCCUAUUAUACUA	34%
15215	CDS	526	133	UCUCUAACCUCUCCUAUUAUACUAA	49%
15216	CDS	601	134	GUAAAAAGCAGCUUCCUGAUUCAAA	35%
15217	CDS	602	135	UAAAAAGCAGCUUCCUGAUUCAAAA	25%
15218	CDS	606	136	AAGCAGCUUCCUGAUUCAAAUGAGA	27%
15219	CDS	615	137	CCUGAUUCAAAUGAGAUUGUGGAAA	37%
15220	CDS	616	138	CUGAUUCAAAUGAGAUUGUGGAAAA	27%
15221	CDS	636	139	GAAAAAUUGCUUCUAAGAAGAAAGA	37%
15222	CDS	637	140	AAAAAUUGCUUCUAAGAAGAAAGUA	56%
15223	CDS	638	141	AAAAUUGCUUCUAAGAAGAAAGUUA	25%
15224	CDS	639	142	AAAUUGCUUCUAAGAAGAAAGUUCA	34%
15225	CDS	678	143	GGCUCAAACAUGAUGUUUGCAUUCA	68%
15226	CDS	679	144	GCUCAAACAUGAUGUUUGCAUUCUA	51%
15227	CDS	680	145	CUCAAACAUGAUGUUUGCAUUCUUA	50%
15228	CDS	682	146	CAAACAUGAUGUUUGCAUUCUUUGA	51%
15229	CDS	683	147	AAACAUGAUGUUUGCAUUCUUUGCA	63%
15230	CDS	722	148	UCAGUUUUUCAAGACAGAUCAUAAA	45%
15231	CDS	723	149	CAGUUUUUCAAGACAGAUCAUAAGA	59%
15232	CDS	724	150	AGUUUUUCAAGACAGAUCAUAAGCA	80%
15233	CDS	725	151	GUUUUUCAAGACAGAUCAUAAGCGA	55%
15234	CDS	726	152	UUUUUCAAGACAGAUCAUAAGCGAA	53%
15235	CDS	776	153	CCAUGGGGUGGACUUAAAUCAUAUA	56%
15236	CDS	787	154	ACUUAAAUCAUAUUUACGGUGAAAA	63%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15237	CDS	788	155	CUUAAAUCAUAUUUACGGUGAAAC A	43%
15238	CDS	789	156	UUAAAUCAUAUUUACGGUGAAACU A	48%
15239	CDS	790	157	UAAAUCAUAUUUACGGUGAAACUC A	56%
15240	CDS	792	158	AAUCAUAUUUACGGUGAAACUCUG A	46%
15241	CDS	793	159	AUCAUAUUUACGGUGAAACUCUGG A	64%
15242	CDS	799	160	UUUACGGUGAAACUCUGGCUAGAC A	35%
15243	CDS	819	161	AGACAGCGUAAACUGCGCCUUUUC A	65%
15244	CDS	820	162	GACAGCGUAAACUGCGCCUUUUCA A	51%
15245	CDS	821	163	ACAGCGUAAACUGCGCCUUUUCAA A	48%
15246	CDS	822	164	CAGCGUAAACUGCGCCUUUUCAAG A	61%
15247	CDS	823	165	AGCGUAAACUGCGCCUUUUCAAGG A	48%
15248	CDS	828	166	AAACUGCGCCUUUUCAAGGAUGGA A	42%
15249	CDS	830	167	ACUGCGCCUUUUCAAGGAUGGAAA A	29%
15250	CDS	861	168	UAUCAGAUAAUUGAUGGAGAGAU GA	32%
15251	CDS	862	169	AUCAGAUAAUUGAUGGAGAGAUG UA	55%
15252	CDS	863	170	UCAGAUAAUUGAUGGAGAGAUGU AA	50%
15253	CDS	864	171	CAGAUAAUUGAUGGAGAGAUGUA UA	50%
15254	CDS	865	172	AGAUAAUUGAUGGAGAGAUGUAU CA	55%
15255	CDS	866	173	GAUAAUUGAUGGAGAGAUGUAUC CA	65%
15256	CDS	867	174	AUAAUUGAUGGAGAGAUGUAUCC UA	54%
15257	CDS	880	175	AGAUGUAUCCUCCCACAGUCAAAG A	78%
15258	CDS	881	176	GAUGUAUCCUCCCACAGUCAAAGA A	79%
15259	CDS	882	177	AUGUAUCCUCCCACAGUCAAAGAU A	49%
15260	CDS	883	178	UGUAUCCUCCCACAGUCAAAGAUA A	28%
15261	CDS	884	179	GUAUCCUCCCACAGUCAAAGAUAC A	56%
15262	CDS	885	180	UAUCCUCCCACAGUCAAAGAUACU A	42%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15263	CDS	887	181	UCCUCCCACAGUCAAAGAUACUCAA	45%
15264	CDS	888	182	CCUCCCACAGUCAAAGAUACUCAGA	73%
15265	CDS	889	183	CUCCCACAGUCAAAGAUACUCAGGA	56%
15266	CDS	891	184	CCCACAGUCAAAGAUACUCAGGCAA	80%
15267	CDS	901	185	AAGAUACUCAGGCAGAGAUGAUCUA	59%
15268	CDS	935	186	AGUCCCUGAGCAUCUACGGUUUGCA	83%
15269	CDS	980	187	UCUGGUGCCUGGUCUGAUGAUGUAA	55%
15270	CDS	981	188	CUGGUGCCUGGUCUGAUGAUGUAUA	56%
15271	CDS	982	189	UGGUGCCUGGUCUGAUGAUGUAUGA	43%
15272	CDS	983	190	GGUGCCUGGUCUGAUGAUGUAUGCA	41%
15273	CDS	984	191	GUGCCUGGUCUGAUGAUGUAUGCCA	42%
15274	CDS	985	192	UGCCUGGUCUGAUGAUGUAUGCCAA	37%
15275	CDS	986	193	GCCUGGUCUGAUGAUGUAUGCCACA	61%
15276	CDS	1016	194	GCUGCGGGAACACAACAGAGUAUGA	44%
15277	CDS	1019	195	GCGGGAACACAACAGAGUAUGCGAA	33%
15278	CDS	1038	196	UGCGAUGUGCUUAAACAGGAGCAUA	53%
15279	CDS	1039	197	GCGAUGUGCUUAAACAGGAGCAUCA	109%
15280	CDS	1040	198	CGAUGUGCUUAAACAGGAGCAUCCA	77%
15281	CDS	1042	199	AUGUGCUUAAACAGGAGCAUCCUGA	69%
15282	CDS	1043	200	UGUGCUUAAACAGGAGCAUCCUGAA	76%
15283	CDS	1044	201	GUGCUUAAACAGGAGCAUCCUGAAA	65%
15284	CDS	1045	202	UGCUUAAACAGGAGCAUCCUGAAUA	64%
15285	CDS	1084	203	UGUUCCAGACAAGCAGGCUAAUACA	41%
15286	CDS	1093	204	CAAGCAGGCUAAUACUGAUAGGAGA	24%
15287	CDS	1095	205	AGCAGGCUAAUACUGAUAGGAGAGA	50%
15288	CDS	1096	206	GCAGGCUAAUACUGAUAGGAGAGAA	51%
15289	CDS	1124	207	UAAGAUUGUGAUUGAAGAUUAUGUA	35%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15290	CDS	1125	208	AAGAUUGUGAUUGAAGAUUAUGUGA	34%
15291	CDS	1126	209	AGAUUGUGAUUGAAGAUUAUGUGCA	59%
15292	CDS	1127	210	GAUUGUGAUUGAAGAUUAUGUGCAA	41%
15293	CDS	1128	211	AUUGUGAUUGAAGAUUAUGUGCAAA	51%
15294	CDS	1129	212	UUGUGAUUGAAGAUUAUGUGCAACA	45%
15295	CDS	1131	213	GUGAUUGAAGAUUAUGUGCAACACA	37%
15296	CDS	1132	214	UGAUUGAAGAUUAUGUGCAACACUA	34%
15297	CDS	1134	215	AUUGAAGAUUAUGUGCAACACUUGA	24%
15298	CDS	1136	216	UGAAGAUUAUGUGCAACACUUGAGA	37%
15299	CDS	1138	217	AAGAUUAUGUGCAACACUUGAGUGA	44%
15300	CDS	1145	218	UGUGCAACACUUGAGUGGCUAUCAA	29%
15301	CDS	1149	219	CAACACUUGAGUGGCUAUCACUUCA	33%
15302	CDS	1179	220	AAAUUUGACCCAGAACUACUUUUCA	35%
15303	CDS	1180	221	AAUUUGACCCAGAACUACUUUUCAA	41%
15304	CDS	1181	222	AUUUGACCCAGAACUACUUUUCAAA	40%
15305	CDS	1200	223	UUCAACAAACAAUUCCAGUACCAAA	49%
15306	CDS	1211	224	AUUCCAGUACCAAAAUCGUAUUGCA	27%
15307	CDS	1217	225	GUACCAAAAUCGUAUUGCUGCUGAA	31%
15308	CDS	1270	226	UUCUGCCUGACACCUUUCAAAUUCA	35%
15309	CDS	1280	227	CACCUUUCAAAUUCAUGACCAGAAA	57%
15310	CDS	1284	228	UUUCAAAUUCAUGACCAGAAAUACA	42%
15311	CDS	1289	229	AAUUCAUGACCAGAAAUACAACUAA	52%
15312	CDS	1327	230	ACAACAACUCUAUAUUGCUGGAACA	58%
15313	CDS	1352	231	UGGAAUUACCCAGUUUGUUGAAUCA	35%
15314	CDS	1356	232	AUUACCCAGUUUGUUGAAUCAUUCA	41%
15315	CDS	1357	233	UUACCCAGUUUGUUGAAUCAUUCAA	58%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15316	CDS	1359	234	ACCCAGUUUGUUGAAUCAUUCACCA	52%
15317	CDS	1360	235	CCCAGUUUGUUGAAUCAUUCACCAA	66%
15318	CDS	1361	236	CCAGUUUGUUGAAUCAUUCACCAGA	54%
15319	CDS	1365	237	UUUGUUGAAUCAUUCACCAGGCAAA	47%
15320	CDS	1462	238	AGAGCAGGCAGAUGAAAUACCAGUA	65%
15321	CDS	1463	239	GAGCAGGCAGAUGAAAUACCAGUCA	66%
15322	CDS	1465	240	GCAGGCAGAUGAAAUACCAGUCUUA	22%
15323	CDS	1466	241	CAGGCAGAUGAAAUACCAGUCUUUA	43%
15324	CDS	1472	242	GAUGAAAUACCAGUCUUUUAAUGAA	23%
15325	CDS	1473	243	AUGAAAUACCAGUCUUUUAAUGAGA	61%
15326	CDS	1474	244	UGAAAUACCAGUCUUUUAAUGAGUA	49%
15327	CDS	1475	245	GAAAUACCAGUCUUUUAAUGAGUAA	76%
15328	CDS	1476	246	AAAUACCAGUCUUUUAAUGAGUACA	51%
15329	CDS	1477	247	AAUACCAGUCUUUUAAUGAGUACCA	72%
15330	CDS	1478	248	AUACCAGUCUUUUAAUGAGUACCGA	40%
15331	CDS	1479	249	UACCAGUCUUUUAAUGAGUACCGCA	53%
15332	CDS	1480	250	ACCAGUCUUUUAAUGAGUACCGCAA	39%
15333	CDS	1481	251	CCAGUCUUUUAAUGAGUACCGCAAA	41%
15334	CDS	1483	252	AGUCUUUUAAUGAGUACCGCAAACA	38%
15335	CDS	1485	253	UCUUUUAAUGAGUACCGCAAACGCA	55%
15336	CDS	1486	254	CUUUUAAUGAGUACCGCAAACGCUA	63%
15337	CDS	1487	255	UUUUAAUGAGUACCGCAAACGCUUA	52%
15338	CDS	1495	256	AGUACCGCAAACGCUUUAUGCUGAA	49%
15339	CDS	1524	257	UAUGAAUCAUUUGAAGAACUUACAA	65%
15340	CDS	1525	258	AUGAAUCAUUUGAAGAACUUACAGA	63%
15341	CDS	1527	259	GAAUCAUUUGAAGAACUUACAGGAA	65%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15342	CDS	1529	260	AUCAUUUGAAGAACUUACAGGAGAA	43%
15343	CDS	1531	261	CAUUUGAAGAACUUACAGGAGAAAA	63%
15344	CDS	1532	262	AUUUGAAGAACUUACAGGAGAAAAA	33%
15345	CDS	1574	263	GGAAGCACUCUAUGGUGACAUCGAA	62%
15346	CDS	1609	264	UGUAUCCUGCCCUUCUGGUAGAAAA	36%
15347	CDS	1614	265	CCUGCCCUUCUGGUAGAAAAGCCUA	58%
15348	CDS	1650	266	AUCUUUGGUGAAACCAUGGUAGAAA	60%
15349	CDS	1666	267	UGGUAGAAGUUGGAGCACCAUUCUA	88%
15350	CDS	1669	268	UAGAAGUUGGAGCACCAUUCUCCUA	85%
15351	CDS	1672	269	AAGUUGGAGCACCAUUCUCCUUGAA	83%
15352	CDS	1675	270	UUGGAGCACCAUUCUCCUUGAAAGA	85%
15353	CDS	1676	271	UGGAGCACCAUUCUCCUUGAAAGGA	83%
15354	CDS	1677	272	GGAGCACCAUUCUCCUUGAAAGGAA	74%
15355	CDS	1678	273	GAGCACCAUUCUCCUUGAAAGGACA	81%
15356	CDS	1679	274	AGCACCAUUCUCCUUGAAAGGACUA	86%
15357	CDS	1680	275	GCACCAUUCUCCUUGAAAGGACUUA	98%
15358	CDS	1681	276	CACCAUUCUCCUUGAAAGGACUUAA	78%
15359	CDS	1682	277	ACCAUUCUCCUUGAAAGGACUUAUA	88%
15360	CDS	1683	278	CCAUUCUCCUUGAAAGGACUUAUGA	88%
15361	CDS	1762	279	UGGGUUUUCAAAUCAUCAACACUGA	78%
15362	CDS	1763	280	GGGUUUUCAAAUCAUCAACACUGCA	92%
15363	CDS	1767	281	UUUCAAAUCAUCAACACUGCCUCAA	85%
15364	CDS	1770	282	CAAAUCAUCAACACUGCCUCAAUUA	84%
15365	CDS	1773	283	AUCAUCAACACUGCCUCAAUUCAGA	86%
15366	CDS	1774	284	UCAUCAACACUGCCUCAAUUCAGUA	94%
15367	CDS	1775	285	CAUCAACACUGCCUCAAUUCAGUCA	84%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15368	CDS	1776	286	AUCAACACUGCCUCAAUUCAGUCUA	84%
15369	CDS	1777	287	UCAACACUGCCUCAAUUCAGUCUCA	68%
15370	CDS	1778	288	CAACACUGCCUCAAUUCAGUCUCUA	73%
15371	CDS	1779	289	AACACUGCCUCAAUUCAGUCUCUCA	79%
15372	CDS	1780	290	ACACUGCCUCAAUUCAGUCUCUCAA	78%
15373	CDS	1781	291	CACUGCCUCAAUUCAGUCUCUCAUA	92%
15374	CDS	1782	292	ACUGCCUCAAUUCAGUCUCUCAUCA	89%
15375	CDS	1783	293	CUGCCUCAAUUCAGUCUCUCAUCUA	95%
15376	CDS	1784	294	UGCCUCAAUUCAGUCUCUCAUCUGA	83%
15377	CDS	1785	295	GCCUCAAUUCAGUCUCUCAUCUGCA	46%
15378	CDS	1786	296	CCUCAAUUCAGUCUCUCAUCUGCAA	51%
15379	CDS	1787	297	CUCAAUUCAGUCUCUCAUCUGCAAA	61%
15380	CDS	1790	298	AAUUCAGUCUCUCAUCUGCAAUAAA	30%
15381	CDS	1791	299	AUUCAGUCUCUCAUCUGCAAUAACA	32%
15382	CDS	1792	300	UUCAGUCUCUCAUCUGCAAUAACGA	30%
15383	CDS	1793	301	UCAGUCUCUCAUCUGCAAUAACGUA	38%
15384	CDS	1794	302	CAGUCUCUCAUCUGCAAUAACGUGA	67%
15385	CDS	1795	303	AGUCUCUCAUCUGCAAUAACGUGAA	71%
15386	CDS	1796	304	GUCUCUCAUCUGCAAUAACGUGAAA	81%
15387	CDS	1856	305	AGAGCUCAUUAAAACAGUCACCAUA	33%
15388	CDS	1857	306	GAGCUCAUUAAAACAGUCACCAUCA	55%
15389	CDS	1858	307	AGCUCAUUAAAACAGUCACCAUCAA	31%
15390	CDS	1859	308	GCUCAUUAAAACAGUCACCAUCAAA	46%
15391	CDS	1860	309	CUCAUUAAAACAGUCACCAUCAAUA	43%
15392	CDS	1861	310	UCAUUAAAACAGUCACCAUCAAUGA	58%
15393	CDS	1862	311	CAUUAAAACAGUCACCAUCAAUGCA	78%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15394	CDS	1864	312	UUAAAACAGUCACCAUCAAUGCAAA	41%
15395	CDS	1865	313	UAAAACAGUCACCAUCAAUGCAAGA	80%
15396	CDS	1866	314	AAAACAGUCACCAUCAAUGCAAGUA	79%
15397	CDS	1868	315	AACAGUCACCAUCAAUGCAAGUUCA	34%
15398	CDS	1912	316	AUAUCAAUCCCACAGUACUACUAAA	39%
15399	CDS	1928	317	ACUACUAAAAGAACGUUCGACUGAA	39%
15400	CDS/3UTR	1941	318	CGUUCGACUGAACUGUAGAAGUCUA	30%
15401	CDS/3UTR	1946	319	GACUGAACUGUAGAAGUCUAAUGAA	25%
15402	CDS/3UTR	1949	320	UGAACUGUAGAAGUCUAAUGAUCAA	29%
15403	3UTR	2077	321	UCCUGUUGCGGAGAAAGGAGUCAUA	45%
15404	3UTR	2082	322	UUGCGGAGAAAGGAGUCAUACUUGA	43%
15405	3UTR	2098	323	CAUACUUGUGAAGACUUUUAUGUCA	30%
15406	3UTR	2128	324	CUAAAGAUUUUGCUGUUGCUGUUAA	41%
15407	3UTR	2141	325	UGUUGCUGUUAAGUUUGGAAAACAA	29%
15408	3UTR	2188	326	AGAGAGAAAUGAGUUUUGACGUCUA	26%
15409	3UTR	2235	327	UUAUAAGAACGAAAGUAAAGAUGUA	33%
15410	3UTR	2281	328	AAGAUGGCAAAAUGCUGAAAGUUUA	28%
15411	3UTR	2305	329	UUACACUGUCGAUGUUUCCAAUGCA	46%
15412	3UTR	2446	330	GACAUUACCAGUAAUUUCAUGUCUA	24%
15413	3UTR	2581	331	CAAAAAGAAGCUGUCUUGGAUUUAA	36%
15414	3UTR	2669	332	CUUUUUCACCAAGAGUAUAAACCUA	41%
15415	3UTR	2730	333	AUGCCAAAUUUAUUAAGGUGGUGGA	61%
15416	3UTR	2750	334	GUGGAGCCACUGCAGUGUUAUCUUA	39%
15417	3UTR	2752	335	GGAGCCACUGCAGUGUUAUCUUAAA	45%
15418	3UTR	2802	336	CAGAAUUUGUUUAUAUGGCUGGUAA	49%
15419	3UTR	2810	337	GUUUAUAUGGCUGGUAACAUGUAAA	34%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15420	3UTR	2963	338	UACUCAGAUUUUGCUAUGAGGUUAA	42%
15421	3UTR	2967	339	CAGAUUUUGCUAUGAGGUUAAUGAA	39%
15422	3UTR	2970	340	AUUUUGCUAUGAGGUUAAUGAAGUA	43%
15423	3UTR	2986	341	AAUGAAGUACCAAGCUGUGCUUGAA	40%
15424	3UTR	3064	342	AUCACAUUGCAAAAGUAGCAAUGAA	59%
15425	3UTR	3072	343	GCAAAAGUAGCAAUGACCUCAUAAA	35%
15426	3UTR	3083	344	AAUGACCUCAUAAAAUACCUCUUCA	40%
15427	3UTR	3134	345	AAUUUUAUCUCAGUCUUGAAGCCAA	55%
15428	3UTR	3147	346	UCUUGAAGCCAAUUCAGUAGGUGCA	52%
15429	3UTR	3157	347	AAUUCAGUAGGUGCAUUGGAAUCAA	71%
15430	3UTR	3212	348	UUUCUUCUUUUAGCCAUUUUGCUAA	38%
15431	3UTR	3216	349	UUCUUUUAGCCAUUUUGCUAAGAGA	40%
15432	3UTR	3225	350	CCAUUUUGCUAAGAGACACAGUCUA	36%
15433	3UTR	3278	351	UUACUAGUUUUAAGAUCAGAGUUCA	70%
15434	3UTR	3313	352	ACUCUGCCUAUAUUUUCUUACCUGA	56%
15435	3UTR	3335	353	UGAACUUUUGCAAGUUUUCAGGUAA	64%
15436	3UTR	3336	354	GAACUUUUGCAAGUUUUCAGGUAAA	62%
15437	3UTR	3351	355	UUCAGGUAAACCUCAGCUCAGGACA	62%
15438	3UTR	3360	356	ACCUCAGCUCAGGACUGCUAUUUAA	53%
15439	3UTR	3441	357	CUUAUUUUAAGUGAAAAGCAGAGAA	83%
15440	3UTR	3489	358	UAUCUGUAACCAAGAUGGAUGCAAA	93%
15441	3UTR	3662	359	UUUUCCACAUCUCAUUGUCACUGAA	36%
15442	3UTR	3668	360	ACAUCUCAUUGUCACUGACAUUUAA	40%
15443	3UTR	3735	361	GUCUUAUUAGGACACUAUGGUUAUA	40%
15444	3UTR	3737	362	CUUAUUAGGACACUAUGGUUAUAAA	37%
15445	3UTR	3738	363	UUAUUAGGACACUAUGGUUAUAAAA	38%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID No	PTGS2 Sense Sequence	NM_000963.2 % Expression (0.1 nM)
15446	3UTR	3752	364	UGGUUAUAAACUGUGUUUAAGCCUA	28%
15447	3UTR	3919	365	AUAUUUAAGGUUGAAUGUUUGUCCA	40%
15448	3UTR	3961	366	CUAGCCCACAAAGAAUAUUGUCUCA	47%
15449	3UTR	3981	367	UCUCAUUAGCCUGAAUGUGCCAUAA	56%
15450	3UTR	3994	368	AAUGUGCCAUAAGACUGACCUUUUA	52%

Table 3: PTGS2 sd-rxRNA

Duplex ID	ID	Sequence	SEQ ID NO
17388	17062	G.A.A.A.A.mC.mU.G.mC.mU.mC.A.A.Chl	369
	17063	P.mU.fU.G.A.G.fC.A.G.fU.fU.fU.fU.fC*fU*fC*fC*A*fU*A	370
17389	17064	A.mC.mC.mU.mC.mU.mC.mC.mU.A.mU.mU.A.Chl	371
	17065	P.mU.A.A.fU.A.G.G.A.G.A.G.G.fU*fU*A*G*A*G*A	372
17390	17066	mU.mC.mC.A.mC.mC.A.A.mC.mU.mU.A.A.Chl	373
	17068	P.mU.fU.A.A.G.fU.fU.G.G.fU.G.G.A*fC*fU*G*fU*fC*A	374
17391	17067	G.mU.mC.mC.A.mC.mC.A.A.mC.mU.mU.A.A.Chl	375
	17068	P.mU.fU.A.A.G.fU.fU.G.G.fU.G.G.A*fC*fU*G*fU*fC*A	376
17392	17069	mC.mU.mC.mC.mU.A.mU.mU.A.mU.A.mC.A.Chl	377
	17070	P.mU.G.fU.A.fU.A.A.fU.A.G.G.A.G*A*G*G*fU*fU*A	378
17393	17071	G.A.mU.mC.A.mC.A.mU.mU.mU.G.A.A.Chl	379
	17073	P.mU.fU.fC.A.A.A.fU.G.fU.G.A.fU.fC*fU*G*G*A*fU*G	380
17394	17072	A.G.A.mU.mC.A.mC.A.mU.mU.mU.G.A.A.Chl	381
	17073	P.mU.fU.fC.A.A.A.fU.G.fU.G.A.fU.fC*fU*G*G*A*fU*G	382
17395	17074	A.A.mC.mC.mU.mC.mU.mC.mC.mU.A.mU.A.Chl	383
	17075	P.mU.A.fU.A.G.G.A.G.A.G.G.fU.fU*A*G*A*G*A*A	384
17396	17076	G.mU.mU.G.A.mC.A.mU.mC.mC.A.G.A.Chl	385
	17077	P.mU.fC.fU.G.G.A.fU.G.fU.fC.A.A.fC*A*fC*A*fU*A*A	386
17397	17078	mC.mC.mU.mU.mC.mC.mU.mU.mC.G.A.A.A.Chl	387
	17079	P.mU.fU.fU.fC.G.A.A.G.G.A.A.G.G*G*A*A*fU*G*U	388
17398	17080	A.mC.mU.mC.mC.A.A.A.mC.A.mC.A.A.Chl	389
	17082	P.mU.fU.G.fU.G.fU.fU.fU.G.G.A.G.fU*G*G*G*fU*fU*U	390
17399	17081	mC.A.mC.mU.mC.mC.A.A.A.mC.A.mC.A.A.Chl	391
	17082	P.mU.fU.G.fU.G.fU.fU.fU.G.G.A.G.fU*G*G*G*fU*fU*U	392
17400	17083	mC.A.mC.mU.mC.mC.A.A.A.mC.A.mC.A.Chl	393
	17084	P.mUGfUGfUfUfUGGAGfUG*G*G*fU*fU*fU*C	394
17401	17085	mC.mC.A.mC.mC.A.A.mC.mU.mU.A.mCA.Chl	395
	17087	P.mUGfUAAGfUfUGGfUGG*A*fC*fU*G*fU*C	396
17402	17086	mU.mC.mC.A.mC.mC.A.A.mC.mU.mU.A.mCA.Chl	397
	17087	P.mUGfUAAGfUfUGGfUGG*A*fC*fU*G*fU*C	398
17403	17088	A.A.mU.A.mC.mC.A.G.mU.mC.mU.mU.A.Chl	399
	17089	P.mU.A.A.G.A.fC.fU.G.G.fU.A.fU.fU*fU*fC*A*fU*fC*U	400
17404	17090	G.A.mC.mC.A.G.mU.A.mU.A.A.G.A.Chl	401
	17091	P.mU.fC.fU.fU.A.fU.A.fC.fU.G.G.fU.fC*A*A*A*fU*fC*C	402
17405	17092	G.mU.mC.mU.mU.mU.mU.A.A.mU.G.A.A.Chl	403

Duplex ID	ID	Sequence	SEQ ID NO
	17093	P.mU.fU.fC.A.fU.fU.A.A.A.A.G.A.fC*fU*G*G*fU*A*U	404
17406	17094	A.A.mU.mU.mU.mC.A.mU.G.mU.mC.mU.A.Chl	405
	17095	P.mU.A.G.A.fC.A.fU.G.A.A.A.fU.fU*A*fC*fU*G*G*U	406
17407	17096	A.mU.mC.A.mC.A.mU.mU.mU.G.A.mU.A.Chl	407
	17098	P.mU.A.fU.fC.A.A.A.fU.G.fU.G.A.fU*fC*fU*G*G*A*U	408
17408	17097	G.A.mU.mC.A.mC.A.mU.mU.mU.G.A.mU.A.Chl	409
	17098	P.mU.A.fU.fC.A.A.A.fU.G.fU.G.A.fU*fC*fU*G*G*A*U	410
17409	17099	mU.mC.mC.A.G.A.mU.mC.A.mC.A.mU.A.Chl	411
	17100	P.mU.A.fU.G.fU.G.A.fU.fC.fU.G.G.A*fU*G*fU*fC*A*A	412
17410	17101	mU.A.mC.mU.G.A.mU.A.G.G.A.G.A.Chl	413
	17102	P.mU.fC.fU.fC.fC.fU.A.fU.fC.A.G.fU.A*fU*fU*A*G*fC*C	414
17411	17103	G.mU.G.mC.A.A.mC.A.mC.mU.fU.G.A.Chl	415
	17104	P.mU.fC.A.A.G.fU.G.fU.fU.G.mC.A.fC*A*fU*A*A*fU*C	416
17412	17105	A.mC.mC.A.G.mU.A.mU.A.A.G.mU.A.Chl	417
	17106	P.mU.A.fC.fU.fU.A.fU.A.fC.fU.G.G.fU*fC*A*A*A*fU*C	418
17413	17107	G.A.A.G.mU.mC.mU.A.A.mU.G.A.A.Chl	419
	17108	P.mU.fU.fC.A.fU.fU.A.G.A.fC.mU.fU.fC*fU*A*fC*A*G*U	420
17414	17109	A.A.G.A.A.G.A.A.A.G.mU.mU.A.Chl	421
	17110	P.mU.A.A.fC.fU.fU.fU.fC.fU.fU.fC.fU.fU*A*G*A*A*G*C	422
17415	17111	mU.mC.A.mC.A.mU.mU.mU.G.AmU.mU.A.Chl	423
	17113	P.mU.A.A.fU.fC.A.A.A.fU.G.fUG.A*fU*fC*fU*G*G*A	424
17416	17112	A.mU.mC.A.mC.A.mU.mU.mU.G.AmU.mU.A.Chl	425
	17113	P.mU.A.A.fU.fC.A.A.A.fU.G.fUG.A*fU*fC*fU*G*G*A	426
17417	17114	A.mC.A.mU.mU.mU.G.A.mU.mUG.A.A.Chl	427
	17116	P.mU.fU.fC.A.A.fU.fC.A.A.A.fUG.fU*G*A*fU*fU*fC*fU*G	428
17418	17115	mC.A.mC.A.mU.mU.mU.G.A.mU.mUG.A.A.Chl	429
	17116	P.mU.fU.fC.A.A.fU.fC.A.A.A.fUG.fU*G*A*fU*fU*fC*fU*G	430
17419	17117	A.mU.mU.mU.G.A.mU.mU.G.AmC.A.A.Chl	431
	17119	P.mU.fU.G.fU.fC.A.A.fU.fC.A.AA.fU*G*fU*G*A*fU*C	432
17420	17118	mC.A.mU.mU.mU.G.A.mU.mU.G.AmC.A.A.Chl	433
	17119	P.mU.fU.G.fU.fC.A.A.fU.fC.A.AA.fU*G*fU*G*A*fU*C	434
17421	17120	mC.A.mU.mC.mU.G.mC.A.A.mU.A.A.A.Chl	435
	17122	P.mU.fU.fU.A.fU.fU.G.fC.A.G.A.fU.G*A*G*A*G*A*C	436
17422	17121	mU.mC.A.mU.mC.mU.G.mC.A.A.mU.A.A.A.Chl	437
	17122	P.mU.fU.fU.A.fU.fU.G.fC.A.G.A.fU.G*A*G*A*G*A*C	438

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Table 4: TGFB1 sd-rxRNA

Target Gene Duplex ID	hTGFB1 Single Strand ID	sd-rxRNA sequence	SEQ ID NO
18454	17491	mC.A.mC.A.G.mC.A.mU.A.mU.A.mU.A.Chl	439
	17492	P.mU.A.fU.A.fU.A.fU.G.fC.fU.G.fU.G*fU*G*fU*A*fC*U	440
18455	17493	mC.A.G.mC.A.mU.A.mU.A.mU.A.mU.A.Chl	441
	17494	P.mU.A.fU.A.fU.A.fU.A.fU.G.fC.fU.G*fU*G*fU*G*fU*A	442
18456	17495	G.mU.A.mC.A.mU.mU.G.A.mC.mU.mU.A.Chl	443
	17497	P.mU.A.A.G.fU.fC.A.A.fU.G.fU.A.fC*A*G*fC*fU*G*C	444
18457	17496	mU.G.mU.A.mC.A.mU.mU.G.A.mC.mU.mU.A.Chl	445

Target Gene Duplex ID	hTGFB1 Single Strand ID	sd-rxRNA sequence	SEQ ID NO
	17497	P.mU.A.A.G.fU.fC.A.A.fU.G.fU.A.fC*A*G*fC*fU*G*C	446
18458	17498	A.A.mC.mU.A.mU.mU.G.mC.mU.mU.mC.A.Chl	447
	17500	P.mU.G.A.A.G.fC.A.A.fU.A.G.fU.fU*G*G*fU*G*fU*C	448
18459	17499	mC.A.A.mC.mU.A.mU.mU.G.mC.mU.mU.mC.A.Chl	449
	17500	P.mU.G.A.A.G.fC.A.A.fU.A.G.fU.fU*G*G*fU*G*fU*C	450
18460	17501	G.mC.A.mU.A.mU.A.mU.A.mU.G.mU.A.Chl	451
	17502	P.mU.A.fC.A.fU.A.fU.A.fU.A.fU.G.fC*fU*G*fU*G*fU*G	452
18461	17503	mU.G.mU.A.mC.A.mU.mU.G.A.mC.mU.A.Chl	453
	17505	P.mU.A.G.fU.fC.A.A.fU.G.fU.A.fC.A*G*fC*fU*G*fC*C	454
18462	17504	mC.mU.G.mU.A.mC.A.mU.mU.G.A.mC.mU.A.Chl	455
	17505	P.mU.A.G.fU.fC.A.A.fU.G.fU.A.fC.A*G*fC*fU*G*fC*C	456
18463	17506	A.G.mC.A.mU.A.mU.A.mU.A.mU.G.A.Chl	457
	17507	P.mU.fC.A.fU.A.fU.A.fU.A.fU.G.fC.fU*G*fU*G*fU*G*U	458
18464	17508	mC.A.G.mC.A.A.mC.A.A.mU.mU.mC.A.Chl	459
	17509	P.mU.G.A.A.fU.fU.G.fU.fU.G.fC.fU.G*fU*A*fU*fU*fU*C	460
18465	17510	mC.A.mU.A.mU.A.mU.A.mU.G.mU.mU.A.Chl	461
	17511	P.mU.A.A.fC.A.fU.A.fU.A.fU.A.fU.G*fC*fU*G*fU*G*U	462
18466	17512	mU.mU.G.mC.mU.mU.mC.A.G.mC.mU.mC.A.Chl	463
	17514	P.mU.G.A.G.fC.fU.G.A.A.G.fC.A.A*fU*A*G*fU*fU*G	464
18467	17513	A.mU.mU.G.mC.mU.mU.mC.A.G.mC.mU.mC.A.Chl	465
	17514	P.mU.G.A.G.fC.fU.G.A.A.G.fC.A.A*fU*A*G*fU*fU*G	466
18468	17515	A.mC.A.G.mC.A.mU.A.mU.A.mU.A.A.Chl	467
	17516	P.mU.fU.A.fU.A.fU.A.fU.G.fC.fU.G.fU*G*fU*G*fU*A*C	468
18469	17517	A.mU.mU.G.mC.mU.mU.mC.A.G.mC.mU.A.Chl	469
	17519	P.mU.A.G.fC.fU.G.A.A.G.fC.A.A.fU*A*G*fU*fU*G*G	470
18470	17518	mU.A.mU.mU.G.mC.mU.mU.mC.A.G.mC.mU.A.Chl	471
	17519	P.mU.A.G.fC.fU.G.A.A.G.fC.A.A.fU*A*G*fU*fU*G*G	472
18471	17520	mC.A.G.A.G.mU.A.mC.A.mC.A.mC.A.Chl	473
	17521	P.mU.G.fU.G.fU.G.fU.A.fC.fU.fC.fU.G*C*fU*fU*G*A*A	474
18472	17522	mU.mC.A.A.G.mC.A.G.A.G.mU.A.A.Chl	475

Target Gene Duplex ID	hTGFB1 Single Strand ID	sd-rxRNA sequence	SEQ ID NO
	17523	P.mU.fU.A.fC.fU.fC.fU.G.fC.fU.fU.G.A*A*fC*fU*fU*G*U	476
18473	17524	A.G.mC.A.G.A.G.mU.A.mC.A.mC.A.Chl	477
	17525	P.mU.G.fU.G.fU.A.fC.fU.fC.fU.G.fC.fU*fU*G*A*A*fC*U	478
18474	17526	G.A.mC.A.A.G.mU.mU.mC.A.A.G.A.Chl	479
	17527	P.mU.fC.fU.fU.G.A.A.fC.fU.fU.G.fU.fC*A*fU*A*G*A*U	480
18475	17528	mC.mU.A.mU.G.A.mC.A.A.G.mU.mU.A.Chl	481
	17529	P.mU.A.A.fC.fU.fU.G.fU.fC.A.fU.A.G*A*fU*fU*fU*fC*G	482
18476	17530	G.mC.A.G.A.G.mU.A.mC.A.mC.A.A.Chl	483
	17531	P.mU.fU.G.fU.G.fU.A.fC.fU.fC.fU.G.fC*fU*fU*G*A*A*C	484
18477	17532	mU.G.A.mC.A.A.G.mU.mU.mCA.A.A.Chl	485
	17533	P.mU.fU.fU.G.A.A.fC.fU.fU.GfU.fC.A*fU*A*G*A*fU*U	486
18478	17534	mU.A.mC.A.mC.A.mC.A.G.mCA.mU.A.Chl	487
	17535	P.mU.A.fU.G.fC.fU.G.fU.G.fUG.fU.A*fC*fU*fC*fU*G*C	488
18479	17536	A.A.mC.G.A.A.A.mU.mC.mUA.mU.A.Chl	489
	17537	P.mU.A.fU.A.G.A.fU.fU.fU.fCG.fU.fU*G*fU*G*G*G*U	490
18480	17538	mU.mU.G.A.mC.mU.mU.mC.mC.GmC.A.A.Chl	491
	17539	P.mU.fU.G.fC.G.G.A.A.G.fUfC.A.A*fU*G*fU*A*fC*A	492
18481	17540	A.mC.A.A.mC.G.A.A.A.mUmC.mU.A.Chl	493
	17541	P.mU.A.G.A.fU.fU.fU.fC.G.fUfU.G.fU*G*G*G*fU*fU*U	494
18482	17542	mU.mC.A.A.mC.A.mC.A.mU.mCA.G.A.Chl	495
	17543	P.mU.fC.fU.G.A.fU.G.fU.G.fUfU.G.A*A*G*A*A*fC*A	496
18483	17544	A.mC.A.A.G.mU.mU.mC.A.AG.mC.A.Chl	497
	17545	P.mU.G.fC.fU.fU.G.A.A.fC.fUfU.G.fU*fC*A*fU*A*G*A	498
18484	17546	A.mU.mC.mU.A.mU.G.A.mC.AA.G.A.Chl	499
	17547	P.mU.fC.fU.fU.G.fU.fC.A.fU.AG.A.fU*fU*fU*fC*G*fU*U	500
			501
Rat Targeting TGFB1			502
18715	18691	G.A.A.A.mU.A.mU.A.G.mC.A.A.A-chol	503
	18692	P.mU.fU.fU.G.fC.fU.A.fU.A.fU.fU.fU.fC*fU*G*G*fU*A*G	504
18716	18693	G.A.A.mC.mU.mC.mU.A.mC.mC.A.G.A-chol	505
	18694	P.mU.fC.fU.G.G.fU.A.G.A.G.fU.fU.fC*fU*A*fC*G*fU*G	506
18717	18695	G.mC.A.A.A.G.A.mU.A.A.mU.G.A-chol	507
	18696	P.mU.fC.A.fU.fU.A.fU.fC.fU.fU.fU.G.fC*fU*G*fU*fC*A*C	508
18718	18697	A.A.mC.mU.mC.mU.A.mC.mC.A.G.A.A-chol	509
	18698	P.mU.fU.fC.fU.G.G.fU.A.G.A.G.fU.fU*fC*fU*A*fC*G*U	510
18719	18699	A.mC.mU.mC.mU.A.mC.mC.A.G.A.A.A-chol	511
	18700	P.mU.fU.fU.fC.fU.G.G.fU.A.G.A.G.fU*fU*fC*fU*A*fC*G	512
18720	18701	A.mC.A.G.mC.A.A.A.G.A.mU.A.A-chol	513
	18702	P.mU.fU.A.fU.fC.fU.fU.fU.G.fC.fU.G.fU*fC*A*fC*A*A*G	514
18721	18703	mC.A.A.mU.mC.mU.A.mU.G.A.mC.A.A-chol	515
	18704	P.mU.fU.G.fU.fC.A.fU.A.G.A.fU.fU.G*fC*G*fU*fU*G*U	516

Target Gene Duplex ID	hTGFB1 Single Strand ID	sd-rxRNA sequence	SEQ ID NO
18722	18705	A.G.A.mU.mU.mC.A.A.G.mU.mC.A.A-chol	517
	18706	P.mU.fU.G.A.fC.fU.fU.G.A.A.fU.fC.fU*fC*fU*G*fC*A*G	518
18723	18707	mC.mU.G.mU.G.G.A.G.mC.A.A.mC.A-chol	519
	18708	P.mU.G.fU.fU.G.fC.fU.fC.fC.A.fC.A.G*fU*fU*G*A*fC*U	520
18724	18709	mU.G.A.mC.A.G.mC.A.A.A.G.A.A-chol	521
	18710	P.mU.fU.fC.fU.fU.fU.G.fC.fU.G.fU.fC.A*fC*A*A*G*A*G	522
18725	18711	A.mU.G.A.mC.A.A.A.A.mC.mC.A.A-chol	523
	18712	P.mU.fU.G.G.fU.fU.fU.fU.G.fU.fC.A.fU*A*G*A*fU*fU*G	524
18726	18713	G.A.G.A.mU.mU.mC.A.A.G.mU.mC.A-chol	525
	18714	P.mU.G.A.fC.fU.fU.G.A.A.fU.fC.fU.fC*fU*G*fC*A*G*G	526

Table 5: Inhibition of gene expression with hTGFB1 ori sequences

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hTGFB1 Sense Sequence	% Expression 0.025 nM HeLa cells
15732	CDS	954	527	CGCGGGACUAUCCACCUGCAAGACA	57.3%
15733	CDS	956	528	CGGGACUAUCCACCUGCAAGACUAA	38.2%
15734	CDS	957	529	GGGACUAUCCACCUGCAAGACUAUA	49.1%
15735	CDS	961	530	CUAUCCACCUGCAAGACUAUCGACA	34.9%
15736	CDS	962	531	UAUCCACCUGCAAGACUAUCGACAA	39.4%
15737	CDS	964	532	UCCACCUGCAAGACUAUCGACAUGA	44.4%
15738	CDS	965	533	CCACCUGCAAGACUAUCGACAUGGA	53.3%
15739	CDS	966	534	CACCUGCAAGACUAUCGACAUGGAA	52.8%
15740	CDS	967	535	ACCUGCAAGACUAUCGACAUGGAGA	46.2%
15741	CDS	968	536	CCUGCAAGACUAUCGACAUGGAGCA	48.1%
15742	CDS	1209	537	AAUGGUGGAAACCCACAACGAAAUA	36.7%
15743	CDS	1210	538	AUGGUGGAAACCCACAACGAAAUCA	28.8%
15744	CDS	1211	539	UGGUGGAAACCCACAACGAAAUCUA	23.1%
15745	CDS	1212	540	GGUGGAAACCCACAACGAAAUCUAA	13.2%
15746	CDS	1213	541	GUGGAAACCCACAACGAAAUCUAUA	21.1%
15747	CDS	1214	542	UGGAAACCCACAACGAAAUCUAUGA	28.7%
15748	CDS	1215	543	GGAAACCCACAACGAAAUCUAUGAA	32.9%
15749	CDS	1216	544	GAAACCCACAACGAAAUCUAUGACA	41.5%
15750	CDS	1217	545	AAACCCACAACGAAAUCUAUGACAA	29.9%
15751	CDS	1218	546	AACCCACAACGAAAUCUAUGACAAA	16.4%
15752	CDS	1219	547	ACCCACAACGAAAUCUAUGACAAGA	23.3%
15753	CDS	1220	548	CCCACAACGAAAUCUAUGACAAGUA	37.5%
15754	CDS	1221	549	CCACAACGAAAUCUAUGACAAGUUA	19.1%
15755	CDS	1222	550	CACAACGAAAUCUAUGACAAGUUCA	14.4%
15756	CDS	1224	551	CAACGAAAUCUAUGACAAGUUCAAA	20.1%
15757	CDS	1225	552	AACGAAAUCUAUGACAAGUUCAAGA	18.3%
15758	CDS	1226	553	ACGAAAUCUAUGACAAGUUCAAGCA	23.2%
15759	CDS	1227	554	CGAAAUCUAUGACAAGUUCAAGCAA	29.0%
15760	CDS	1228	555	GAAAUCUAUGACAAGUUCAAGCAGA	15.6%
15761	CDS	1229	556	AAAUCUAUGACAAGUUCAAGCAGAA	32.3%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hTGFB1 Sense Sequence	% Expression 0.025 nM HeLa cells
15762	CDS	1230	557	AAUCUAUGACAAGUUCAAGCAGAGA	36.1%
15763	CDS	1231	558	AUCUAUGACAAGUUCAAGCAGAGUA	30.6%
15764	CDS	1232	559	UCUAUGACAAGUUCAAGCAGAGUAA	24.9%
15765	CDS	1233	560	CUAUGACAAGUUCAAGCAGAGUACA	15.9%
15766	CDS	1234	561	UAUGACAAGUUCAAGCAGAGUACAA	31.2%
15767	CDS	1235	562	AUGACAAGUUCAAGCAGAGUACACA	17.2%
15768	CDS	1236	563	UGACAAGUUCAAGCAGAGUACACAA	23.5%
15769	CDS	1237	564	GACAAGUUCAAGCAGAGUACACACA	24.5%
15770	CDS	1238	565	ACAAGUUCAAGCAGAGUACACACAA	38.5%
15771	CDS	1240	566	AAGUUCAAGCAGAGUACACACAGCA	38.7%
15772	CDS	1241	567	AGUUCAAGCAGAGUACACACAGCAA	34.3%
15773	CDS	1242	568	GUUCAAGCAGAGUACACACAGCAUA	20.8%
15774	CDS	1243	569	UUCAAGCAGAGUACACACAGCAUAA	33.4%
15775	CDS	1244	570	UCAAGCAGAGUACACACAGCAUAUA	19.6%
15776	CDS	1245	571	CAAGCAGAGUACACACAGCAUAUAA	25.5%
15777	CDS	1246	572	AAGCAGAGUACACACAGCAUAUAUA	12.8%
15778	CDS	1247	573	AGCAGAGUACACACAGCAUAUAUAA	27.6%
15779	CDS	1248	574	GCAGAGUACACACAGCAUAUAUAUA	15.9%
15780	CDS	1249	575	CAGAGUACACACAGCAUAUAUAUGA	24.1%
15781	CDS	1250	576	AGAGUACACACAGCAUAUAUAUGUA	22.6%
15782	CDS	1251	577	GAGUACACACAGCAUAUAUAUGUUA	26.7%
15783	CDS	1252	578	AGUACACACAGCAUAUAUAUGUUCA	66.6%
15784	CDS	1254	579	UACACACAGCAUAUAUAUGUUCUUA	33.6%
15785	CDS	1262	580	GCAUAUAUAUGUUCUUCAACACAUA	40.4%
15786	CDS	1263	581	CAUAUAUAUGUUCUUCAACACAUCA	42.5%
15787	CDS	1264	582	AUAUAUAUGUUCUUCAACACAUCAA	27.2%
15788	CDS	1265	583	UAUAUAUGUUCUUCAACACAUCAGA	23.2%
15789	CDS	1266	584	AUAUAUGUUCUUCAACACAUCAGAA	35.5%
15790	CDS	1267	585	UAUAUGUUCUUCAACACAUCAGAGA	34.6%
15791	CDS	1268	586	AUAUGUUCUUCAACACAUCAGAGCA	29.7%
15792	CDS	1269	587	UAUGUUCUUCAACACAUCAGAGCUA	35.4%
15793	CDS	1270	588	AUGUUCUUCAACACAUCAGAGCUCA	35.2%
15794	CDS	1335	589	GCUGCGUCUGCUGAGGCUCAAGUUA	28.0%
15795	CDS	1336	590	CUGCGUCUGCUGAGGCUCAAGUUAA	32.1%
15796	CDS	1337	591	UGCGUCUGCUGAGGCUCAAGUUAAA	25.5%
15797	CDS	1338	592	GCGUCUGCUGAGGCUCAAGUUAAAA	59.7%
15798	CDS	1339	593	CGUCUGCUGAGGCUCAAGUUAAAAA	52.8%
15799	CDS	1340	594	GUCUGCUGAGGCUCAAGUUAAAAGA	47.9%
15800	CDS	1341	595	UCUGCUGAGGCUCAAGUUAAAAGUA	49.8%
15801	CDS	1342	596	CUGCUGAGGCUCAAGUUAAAAGUGA	50.7%
15802	CDS	1343	597	UGCUGAGGCUCAAGUUAAAAGUGGA	43.4%
15803	CDS	1344	598	GCUGAGGCUCAAGUUAAAAGUGGAA	52.6%
15804	CDS	1345	599	CUGAGGCUCAAGUUAAAAGUGGAGA	73.3%
15805	CDS	1346	600	UGAGGCUCAAGUUAAAAGUGGAGCA	58.0%
15806	CDS	1347	601	GAGGCUCAAGUUAAAAGUGGAGCAA	64.9%
15807	CDS	1348	602	AGGCUCAAGUUAAAAGUGGAGCAGA	68.1%
15808	CDS	1349	603	GGCUCAAGUUAAAAGUGGAGCAGCA	73.8%
15809	CDS	1350	604	GCUCAAGUUAAAAGUGGAGCAGCAA	78.8%
15810	CDS	1351	605	CUCAAGUUAAAAGUGGAGCAGCACA	76.6%
15811	CDS	1352	606	UCAAGUUAAAAGUGGAGCAGCACGA	72.9%
15812	CDS	1369	607	CAGCACGUGGAGCUGUACCAGAAAA	69.8%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hTGFB1 Sense Sequence	% Expression 0.025 nM HeLa cells
15813	CDS	1370	608	AGCACGUGGAGCUGUACCAGAAAUA	69.7%
15814	CDS	1371	609	GCACGUGGAGCUGUACCAGAAAUAA	73.3%
15815	CDS	1372	610	CACGUGGAGCUGUACCAGAAAUACA	55.0%
15816	CDS	1373	611	ACGUGGAGCUGUACCAGAAAUACAA	63.8%
15817	CDS	1374	612	CGUGGAGCUGUACCAGAAAUACAGA	85.7%
15818	CDS	1375	613	GUGGAGCUGUACCAGAAAUACAGCA	85.0%
15819	CDS	1376	614	UGGAGCUGUACCAGAAAUACAGCAA	82.5%
15820	CDS	1377	615	GGAGCUGUACCAGAAAUACAGCAAA	43.1%
15821	CDS	1378	616	GAGCUGUACCAGAAAUACAGCAACA	58.5%
15822	CDS	1379	617	AGCUGUACCAGAAAUACAGCAACAA	48.1%
15823	CDS	1380	618	GCUGUACCAGAAAUACAGCAACAAA	48.1%
15824	CDS	1381	619	CUGUACCAGAAAUACAGCAACAAUA	35.0%
15825	CDS	1382	620	UGUACCAGAAAUACAGCAACAAUUA	36.4%
15826	CDS	1383	621	GUACCAGAAAUACAGCAACAAUUCA	24.6%
15827	CDS	1384	622	UACCAGAAAUACAGCAACAAUUCCA	33.4%
15828	CDS	1385	623	ACCAGAAAUACAGCAACAAUUCCUA	121.5%
15829	CDS	1386	624	CCAGAAAUACAGCAACAAUUCCUGA	62.1%
15830	CDS	1387	625	CAGAAAUACAGCAACAAUUCCUGGA	98.3%
15831	CDS	1390	626	AAAUACAGCAACAAUUCCUGGCGAA	36.6%
15832	CDS	1391	627	AAUACAGCAACAAUUCCUGGCGAUA	39.5%
15833	CDS	1392	628	AUACAGCAACAAUUCCUGGCGAUAA	40.0%
15834	CDS	1393	629	UACAGCAACAAUUCCUGGCGAUACA	89.4%
15835	CDS	1394	630	ACAGCAACAAUUCCUGGCGAUACCA	62.3%
15836	CDS	1396	631	AGCAACAAUUCCUGGCGAUACCUCA	41.0%
15837	CDS	1441	632	AGCGACUCGCCAGAGUGGUUAUCUA	31.2%
15838	CDS	1442	633	GCGACUCGCCAGAGUGGUUAUCUUA	46.2%
15839	CDS	1443	634	CGACUCGCCAGAGUGGUUAUCUUUA	46.8%
15840	CDS	1444	635	GACUCGCCAGAGUGGUUAUCUUUUA	50.6%
15841	CDS	1445	636	ACUCGCCAGAGUGGUUAUCUUUUGA	50.8%
15842	CDS	1446	637	CUCGCCAGAGUGGUUAUCUUUUGAA	71.8%
15843	CDS	1447	638	UCGCCAGAGUGGUUAUCUUUUGAUA	43.7%
15844	CDS	1448	639	CGCCAGAGUGGUUAUCUUUUGAUGA	42.1%
15845	CDS	1449	640	GCCAGAGUGGUUAUCUUUUGAUGUA	31.0%
15846	CDS	1450	641	CCAGAGUGGUUAUCUUUUGAUGUCA	46.0%
15847	CDS	1451	642	CAGAGUGGUUAUCUUUUGAUGUCAA	40.2%
15848	CDS	1452	643	AGAGUGGUUAUCUUUUGAUGUCACA	38.5%
15849	CDS	1453	644	GAGUGGUUAUCUUUUGAUGUCACCA	67.4%
15850	CDS	1454	645	AGUGGUUAUCUUUUGAUGUCACCGA	57.4%
15851	CDS	1455	646	GUGGUUAUCUUUUGAUGUCACCGGA	40.6%
15852	CDS	1456	647	UGGUUAUCUUUUGAUGUCACCGGAA	70.5%
15853	CDS	1457	648	GGUUAUCUUUUGAUGUCACCGGAGA	82.8%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hTGFB1 Sense Sequence	% Expression 0.025 nM HeLa cells
15854	CDS	1458	649	GUUAUCUUUUGAUGUCACCGGAGUA	74.8%
15855	CDS	1459	650	UUAUCUUUUGAUGUCACCGGAGUUA	86.8%
15856	CDS	1460	651	UAUCUUUUGAUGUCACCGGAGUUGA	76.5%
15857	CDS	1551	652	CAGCAGGGAUAACACACUGCAAGUA	70.5%
15858	CDS	1552	653	AGCAGGGAUAACACACUGCAAGUGA	60.5%
15859	CDS	1553	654	GCAGGGAUAACACACUGCAAGUGGA	43.5%
15860	CDS	1554	655	CAGGGAUAACACACUGCAAGUGGAA	56.3%
15861	CDS	1555	656	AGGGAUAACACACUGCAAGUGGACA	63.9%
15862	CDS	1556	657	GGGAUAACACACUGCAAGUGGACAA	66.9%
15863	CDS	1558	658	GAUAACACACUGCAAGUGGACAUCA	62.2%
15864	CDS	1559	659	AUAACACACUGCAAGUGGACAUCAA	40.5%
15865	CDS	1560	660	UAACACACUGCAAGUGGACAUCAAA	57.9%
15866	CDS	1610	661	ACCUGGCCACCAUUCAUGGCAUGAA	69.4%
15867	CDS	1611	662	CCUGGCCACCAUUCAUGGCAUGAAA	49.1%
15868	CDS	1612	663	CUGGCCACCAUUCAUGGCAUGAACA	31.9%
15869	CDS	1705	664	CGAGCCCUGGACACCAACUAUUGCA	56.4%
15870	CDS	1706	665	GAGCCCUGGACACCAACUAUUGCUA	42.6%
15871	CDS	1707	666	AGCCCUGGACACCAACUAUUGCUUA	29.8%
15872	CDS	1708	667	GCCCUGGACACCAACUAUUGCUUCA	19.8%
15873	CDS	1709	668	CCCUGGACACCAACUAUUGCUUCAA	37.7%
15874	CDS	1710	669	CCUGGACACCAACUAUUGCUUCAGA	44.0%
15875	CDS	1711	670	CUGGACACCAACUAUUGCUUCAGCA	35.8%
15876	CDS	1712	671	UGGACACCAACUAUUGCUUCAGCUA	31.5%
15877	CDS	1713	672	GGACACCAACUAUUGCUUCAGCUCA	27.3%
15878	CDS	1714	673	GACACCAACUAUUGCUUCAGCUCCA	44.7%
15879	CDS	1715	674	ACACCAACUAUUGCUUCAGCUCCAA	44.9%
15880	CDS	1754	675	GCGUGCGGCAGCUGUACAUUGACUA	23.9%
15881	CDS	1755	676	CGUGCGGCAGCUGUACAUUGACUUA	18.3%
15882	CDS	1756	677	GUGCGGCAGCUGUACAUUGACUUCA	41.2%
15883	CDS	1757	678	UGCGGCAGCUGUACAUUGACUUCCA	26.4%
15884	CDS	1759	679	CGGCAGCUGUACAUUGACUUCCGCA	28.0%
15885	CDS	1760	680	GGCAGCUGUACAUUGACUUCCGCAA	22.8%
15886	CDS	1761	681	GCAGCUGUACAUUGACUUCCGCAAA	34.1%
15887	CDS	1762	682	CAGCUGUACAUUGACUUCCGCAAGA	36.3%
15888	CDS	1763	683	AGCUGUACAUUGACUUCCGCAAGGA	84.1%
15889	CDS	1849	684	UGCCCCUACAUUUGGAGCCUGGACA	93.0%
15890	CDS	1889	685	UCCUGGCCCUGUACAACCAGCAUAA	51.7%
15891	CDS	1890	686	CCUGGCCCUGUACAACCAGCAUAAA	71.9%
15892	CDS	1891	687	CUGGCCCUGUACAACCAGCAUAACA	36.1%
15893	CDS	1997	688	AGGUGGAGCAGCUGUCCAACAUGAA	60.9%
15894	3UTR	2115	689	CAUGGGGGCUGUAUUUAAGGACACA	57.2%
15895	3UTR	2155	690	CCUGGGGCCCCAUUAAAGAUGGAGA	86.0%
15896	3UTR	2156	691	CUGGGGCCCCAUUAAAGAUGGAGAA	73.3%
15897	3UTR	2157	692	UGGGGCCCCAUUAAAGAUGGAGAGA	68.8%
15898	3UTR	2158	693	GGGGCCCCAUUAAAGAUGGAGAGAA	65.8%
15899	3UTR	2159	694	GGGCCCCAUUAAAGAUGGAGAGAGA	42.7%
15900	3UTR	2160	695	GGCCCCAUUAAAGAUGGAGAGAGGA	34.4%
15901	3UTR	2161	696	GCCCCAUUAAAGAUGGAGAGAGGAA	56.0%
15902	3UTR	2162	697	CCCCAUUAAAGAUGGAGAGAGGACA	74.9%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hTGFB1 Sense Sequence	% Expression 0.025 nM HeLa cells
15903	3UTR	2163	698	CCCAUUAAAGAUGGAGAGAGGACUA	79.6%
15904	3UTR	2180	699	GAGGACUGCGGAUCUCUGUGUCAUA	98.3%
15905	3UTR	2275	700	CUCCUGCCUGUCUGCACUAUUCCUA	100.2%
15906	3UTR	2276	701	UCCUGCCUGUCUGCACUAUUCCUUA	103.8%
15907	3UTR	2277	702	CCUGCCUGUCUGCACUAUUCCUUUA	110.4%
15908	3UTR	2278	703	CUGCCUGUCUGCACUAUUCCUUUGA	105.2%
15909	3UTR	2279	704	UGCCUGUCUGCACUAUUCCUUUGCA	118.8%
15910	3UTR	2325	705	CAGUGGGGAACACUACUGUAGUUAA	112.2%
15911	3UTR	2326	706	AGUGGGGAACACUACUGUAGUUAGA	107.7%
15912	3UTR	2327	707	GUGGGGAACACUACUGUAGUUAGAA	108.6%
15913	3UTR	2328	708	UGGGGAACACUACUGUAGUUAGAUA	N/A

Table 6: Inhibition of gene expression with hTGFB2 ori sequences

Oligo id	Gene Region	Ref Pos	% Expression A549 0.1 nM	25-mer Sense Strand (position 25 of SS, replaced with A)	SEQ ID NO
15451	5UTR/CDS	651	98%	UUUUAAAAAAUGCACUACUGUGUGC	709
15452	CDS	654	102.2%	UAAAAAAUGCACUACUGUGUGCUGA	710
15453	CDS	730	83.7%	GCAGCACACUCGAUAUGGACCAGUU	711
15454	CDS	732	80.3%	AGCACACUCGAUAUGGACCAGUUCA	712
15455	CDS	733	79.6%	GCACACUCGAUAUGGACCAGUUCAU	713
15456	CDS	734	89.1%	CACACUCGAUAUGGACCAGUUCAUG	714
15457	CDS	735	87.8%	ACACUCGAUAUGGACCAGUUCAUGC	715
15458	CDS	736	95.3%	CACUCGAUAUGGACCAGUUCAUGCG	716
15459	CDS	847	103.8%	UCCCCCCGGAGGUGAUUUCCAUCUA	717
15460	CDS	848	83.6%	CCCCCCGGAGGUGAUUUCCAUCUAC	718
15461	CDS	851	72.2%	CCCGGAGGUGAUUUCCAUCUACAAC	719
15462	CDS	853	85.8%	CGGAGGUGAUUUCCAUCUACAACAG	720
15463	CDS	855	67.1%	GAGGUGAUUUCCAUCUACAACAGCA	721
15464	CDS	952	68.9%	ACUACGCCAAGGAGGUUUACAAAAU	722
15465	CDS	963	81.1%	GAGGUUUACAAAAUAGACAUGCCGC	723
15466	CDS	1107	82.1%	UUCUACAGACCCUACUUCAGAAUUG	724
15467	CDS	1108	99.1%	UCUACAGACCCUACUUCAGAAUUGU	725
15468	CDS	1109	95.1%	CUACAGACCCUACUUCAGAAUUGUU	726
15469	CDS	1129	90.4%	UUGUUCGAUUUGACGUCUCAGCAAU	727
15470	CDS	1130	76.7%	UGUUCGAUUUGACGUCUCAGCAAUG	728
15471	CDS	1131	79.7%	GUUCGAUUUGACGUCUCAGCAAUGG	729
15472	CDS	1132	87.5%	UUCGAUUUGACGUCUCAGCAAUGGA	730
15473	CDS	1144	66.9%	UCUCAGCAAUGGAGAAGAAUGCUUC	731
15474	CDS	1145	76.6%	CUCAGCAAUGGAGAAGAAUGCUUCC	732
15475	CDS	1147	88.9%	CAGCAAUGGAGAAGAAUGCUUCCAA	733
15476	CDS	1162	84.5%	AUGCUUCCAAUUUGGUGAAAGCAGA	734
15477	CDS	1163	89.2%	UGCUUCCAAUUUGGUGAAAGCAGAG	735
15478	CDS	1165	86.6%	CUUCCAAUUUGGUGAAAGCAGAGUU	736

Oligo id	Gene Region	Ref Pos	% Expression A549 0.1 nM	25-mer Sense Strand (position 25 of SS, replaced with A)	SEQ ID NO
15479	CDS	1177	61.2%	UGAAAGCAGAGUUCAGAGUCUUUCG	737
15480	CDS	1185	92.6%	GAGUUCAGAGUCUUUCGUUUGCAGA	738
15481	CDS	1219	99.6%	CCAGAGUGCCUGAACAACGGAUUGA	739
15482	CDS	1224	94.0%	GUGCCUGAACAACGGAUUGAGCUAU	740
15483	CDS	1225	88.1%	UGCCUGAACAACGGAUUGAGCUAUA	741
15484	CDS	1228	59.3%	CUGAACAACGGAUUGAGCUAUAUCA	742
15485	CDS	1229	77.5%	UGAACAACGGAUUGAGCUAUAUCAG	743
15486	CDS	1230	61.5%	GAACAACGGAUUGAGCUAUAUCAGA	744
15487	CDS	1233	84.5%	CAACGGAUUGAGCUAUAUCAGAUUC	745
15488	CDS	1238	87.7%	GAUUGAGCUAUAUCAGAUUCUCAAG	746
15489	CDS	1239	78.7%	AUUGAGCUAUAUCAGAUUCUCAAGU	747
15490	CDS	1240	94.1%	UUGAGCUAUAUCAGAUUCUCAAGUC	748
15491	CDS	1247	92.6%	AUAUCAGAUUCUCAAGUCCAAAGAU	749
15492	CDS	1256	94.3%	UCUCAAGUCCAAAGAUUUAACAUCU	750
15493	CDS	1259	99.1%	CAAGUCCAAAGAUUUAACAUCUCCA	751
15494	CDS	1286	87.4%	CCAGCGCUACAUCGACAGCAAAGUU	752
15495	CDS	1288	84.5%	AGCGCUACAUCGACAGCAAAGUUGU	753
15496	CDS	1289	60.1%	GCGCUACAUCGACAGCAAAGUUGUG	754
15497	CDS	1292	78.8%	CUACAUCGACAGCAAAGUUGUGAAA	755
15498	CDS	1331	80.1%	CGAAUGGCUCUCCUUCGAUGUAACU	756
15499	CDS	1353	62.4%	ACUGAUGCUGUUCAUGAAUGGCUUC	757
15500	CDS	1361	74.3%	UGUUCAUGAAUGGCUUCACCAUAAA	758
15501	CDS	1362	75.1%	GUUCAUGAAUGGCUUCACCAUAAAG	759
15502	CDS	1363	87.2%	UUCAUGAAUGGCUUCACCAUAAAGA	760
15503	CDS	1364	70.4%	UCAUGAAUGGCUUCACCAUAAAGAC	761
15504	CDS	1365	100.7%	CAUGAAUGGCUUCACCAUAAAGACA	762
15505	CDS	1368	100.1%	GAAUGGCUUCACCAUAAAGACAGGA	763
15506	CDS	1398	92.0%	GGAUUUAAAAUAAGCUUACACUGUC	764
15507	CDS	1399	83.2%	GAUUUAAAAUAAGCUUACACUGUCC	765
15508	CDS	1415	85.6%	ACACUGUCCCUGCUGCACUUUUGUA	766
15509	CDS	1418	97.4%	CUGUCCCUGCUGCACUUUUGUACCA	767
15510	CDS	1420	59.1%	GUCCCUGCUGCACUUUUGUACCAUC	768
15511	CDS	1421	73.7%	UCCCUGCUGCACUUUUGUACCAUCU	769
15512	CDS	1422	79.5%	CCCUGCUGCACUUUUGUACCAUCUA	770
15513	CDS	1451	62.7%	UUACAUCAUCCCAAAUAAAAGUGAA	771
15514	CDS	1452	76.0%	UACAUCAUCCCAAAUAAAAGUGAAG	772
15515	CDS	1470	44.7%	AGUGAAGAACUAGAAGCAAGAUUUG	773
15516	CDS	1472	75.6%	UGAAGAACUAGAAGCAAGAUUUGCA	774
15517	CDS	1474	96.8%	AAGAACUAGAAGCAAGAUUUGCAGG	775
15518	CDS	1475	94.3%	AGAACUAGAAGCAAGAUUUGCAGGU	776
15519	CDS	1476	63.3%	GAACUAGAAGCAAGAUUUGCAGGUA	777
15520	CDS	1480	65.9%	UAGAAGCAAGAUUUGCAGGUAUUGA	778
15521	CDS	1481	59.6%	AGAAGCAAGAUUUGCAGGUAUUGAU	779
15522	CDS	1482	56.0%	GAAGCAAGAUUUGCAGGUAUUGAUG	780
15523	CDS	1483	69.2%	AAGCAAGAUUUGCAGGUAUUGAUGG	781
15524	CDS	1484	64.5%	AGCAAGAUUUGCAGGUAUUGAUGGC	782
15525	CDS	1485	92.0%	GCAAGAUUUGCAGGUAUUGAUGGCA	783
15526	CDS	1486	101.7%	CAAGAUUUGCAGGUAUUGAUGGCAC	784
15527	CDS	1496	103.3%	AGGUAUUGAUGGCACCUCCACAUAU	785
15528	CDS	1503	102.3%	GAUGGCACCUCCACAUAUACCAGUG	786

Oligo id	Gene Region	Ref Pos	% Expression A549 0.1 nM	25-mer Sense Strand (position 25 of SS, replaced with A)	SEQ ID NO
15529	CDS	1506	86.6%	GGCACCUCCACAUAUACCAGUGGUG	787
15530	CDS	1510	79.9%	CCUCCACAUAUACCAGUGGUGAUCA	788
15531	CDS	1511	44.9%	CUCCACAUAUACCAGUGGUGAUCAG	789
15532	CDS	1512	57.3%	UCCACAUAUACCAGUGGUGAUCAGA	790
15533	CDS	1517	64.9%	AUAUACCAGUGGUGAUCAGAAAACU	791
15534	CDS	1518	90.8%	UAUACCAGUGGUGAUCAGAAAACUA	792
15535	CDS	1520	47.1%	UACCAGUGGUGAUCAGAAAACUAUA	793
15536	CDS	1526	55.7%	UGGUGAUCAGAAAACUAUAAAGUCC	794
15537	CDS	1527	89.6%	GGUGAUCAGAAAACUAUAAAGUCCA	795
15538	CDS	1529	92.4%	UGAUCAGAAAACUAUAAAGUCCACU	796
15539	CDS	1531	87.2%	AUCAGAAAACUAUAAAGUCCACUAG	797
15540	CDS	1532	93.4%	UCAGAAAACUAUAAAGUCCACUAGG	798
15541	CDS	1575	78.4%	ACCCCACAUCUCCUGCUAAUGUUAU	799
15542	CDS	1576	84.6%	CCCCACAUCUCCUGCUAAUGUUAUU	800
15543	CDS	1579	95.9%	CACAUCUCCUGCUAAUGUUAUUGCC	801
15544	CDS	1591	89.6%	UAAUGUUAUUGCCCUCCUACAGACU	802
15545	CDS	1592	85.0%	AAUGUUAUUGCCCUCCUACAGACUU	803
15546	CDS	1598	51.2%	AUUGCCCUCCUACAGACUUGAGUCA	804
15547	CDS	1650	39.4%	GCUUUGGAUGCGGCCUAUUGCUUUA	805
15548	CDS	1652	82.3%	UUUGGAUGCGGCCUAUUGCUUUAGA	806
15549	CDS	1653	86.1%	UUGGAUGCGGCCUAUUGCUUUAGAA	807
15550	CDS	1655	80.0%	GGAUGCGGCCUAUUGCUUUAGAAAU	808
15551	CDS	1657	72.3%	AUGCGGCCUAUUGCUUUAGAAAUGU	809
15552	CDS	1658	72.2%	UGCGGCCUAUUGCUUUAGAAAUGUG	810
15553	CDS	1659	57.8%	GCGGCCUAUUGCUUUAGAAAUGUGC	811
15554	CDS	1660	83.4%	CGGCCUAUUGCUUUAGAAAUGUGCA	812
15555	CDS	1662	79.3%	GCCUAUUGCUUUAGAAAUGUGCAGG	813
15556	CDS	1663	86.3%	CCUAUUGCUUUAGAAAUGUGCAGGA	814
15557	CDS	1664	84.8%	CUAUUGCUUUAGAAAUGUGCAGGAU	815
15558	CDS	1665	71.1%	UAUUGCUUUAGAAAUGUGCAGGAUA	816
15559	CDS	1666	61.8%	AUUGCUUUAGAAAUGUGCAGGAUAA	817
15560	CDS	1667	84.9%	UUGCUUUAGAAAUGUGCAGGAUAAU	818
15561	CDS	1668	82.8%	UGCUUUAGAAAUGUGCAGGAUAAUU	819
15562	CDS	1670	69.8%	CUUUAGAAAUGUGCAGGAUAAUUGC	820
15563	CDS	1671	90.2%	UUUAGAAAUGUGCAGGAUAAUUGCU	821
15564	CDS	1672	68.6%	UUAGAAAUGUGCAGGAUAAUUGCUG	822
15565	CDS	1678	74.2%	AUGUGCAGGAUAAUUGCUGCCUACG	823
15566	CDS	1761	58.6%	GGGUACAAUGCCAACUUCUGUGCUG	824
15567	CDS	1767	86.3%	AAUGCCAACUUCUGUGCUGGAGCAU	825
15568	CDS	1782	83.7%	GCUGGAGCAUGCCCGUAUUUAUGGA	826
15569	CDS	1783	86.9%	CUGGAGCAUGCCCGUAUUUAUGGAG	827
15570	CDS	1786	90.5%	GAGCAUGCCCGUAUUUAUGGAGUUC	828
15571	CDS	1787	91.1%	AGCAUGCCCGUAUUUAUGGAGUUCA	829
15572	CDS	1788	68.0%	GCAUGCCCGUAUUUAUGGAGUUCAG	830
15573	CDS	1789	75.7%	CAUGCCCGUAUUUAUGGAGUUCAGA	831
15574	CDS	1796	88.9%	GUAUUUAUGGAGUUCAGACACUCAG	832
15575	CDS	1800	52.5%	UUAUGGAGUUCAGACACUCAGCACA	833
15576	CDS	1907	90.8%	AACCAUUCUCUACUACAUUGGCAAA	834
15577	CDS	1924	70.2%	UUGGCAAAACACCCAAGAUUGAACA	835
15578	CDS	1925	77.5%	UGGCAAAACACCCAAGAUUGAACAG	836

Oligo id	Gene Region	Ref Pos	% Expression A549 0.1 nM	25-mer Sense Strand (position 25 of SS, replaced with A)	SEQ ID NO
15579	CDS/3UTR	1973	91.1%	UUGCAAAUGCAGCUAAAAUUCUUGG	837
15580	3UTR	2020	70.1%	CAAUGAUGAUGAUAAUGAUGAUGAC	838
15581	3UTR	2022	43.3%	AUGAUGAUGAUAAUGAUGAUGACGA	839
15582	3UTR	2023	60.3%	UGAUGAUGAUAAUGAUGAUGACGAC	840
15583	3UTR	2025	75.4%	AUGAUGAUAAUGAUGAUGACGACGA	841
15584	3UTR	2026	40.8%	UGAUGAUAAUGAUGAUGACGACGAC	842
15585	3UTR	2028	51.8%	AUGAUAAUGAUGAUGACGACGACAA	843
15586	3UTR	2029	59.1%	UGAUAAUGAUGAUGACGACGACAAC	844
15587	3UTR	2031	51.3%	AUAAUGAUGAUGACGACGACAACGA	845
15588	3UTR	2032	32.7%	UAAUGAUGAUGACGACGACAACGAU	846
15589	3UTR	2034	33.8%	AUGAUGAUGACGACGACAACGAUGA	847
15590	3UTR	2035	57.0%	UGAUGAUGACGACGACAACGAUGAU	848
15591	3UTR	2039	40.5%	GAUGACGACGACAACGAUGAUGCUU	849
15592	3UTR	2045	56.8%	GACGACAACGAUGAUGCUUGUAACA	850
15593	3UTR	2046	28.5%	ACGACAACGAUGAUGCUUGUAACAA	851
15594	3UTR	2065	44.7%	UAACAAGAAAACAUAAGAGAGCCUU	852
15595	3UTR	2066	58.3%	AACAAGAAAACAUAAGAGAGCCUUG	853
15596	3UTR	2067	62.9%	ACAAGAAAACAUAAGAGAGCCUUGG	854
15597	3UTR	2072	38.1%	AAAACAUAAGAGAGCCUUGGUUCAU	855
15598	3UTR	2073	44.6%	AAACAUAAGAGAGCCUUGGUUCAUC	856
15599	3UTR	2079	53.6%	AAGAGAGCCUUGGUUCAUCAGUGUU	857
15600	3UTR	2081	33.2%	GAGAGCCUUGGUUCAUCAGUGUUAA	858
15601	3UTR	2083	28.2%	GAGCCUUGGUUCAUCAGUGUUAAAA	859
15602	3UTR	2110	46.5%	UUUUUGAAAAGGCGGUACUAGUUCA	860
15603	3UTR	2116	56.1%	AAAAGGCGGUACUAGUUCAGACACU	861
15604	3UTR	2117	60.9%	AAAGGCGGUACUAGUUCAGACACUU	862
15605	3UTR	2136	76.8%	ACACUUUGGAAGUUUGUGUUCUGUU	863
15606	3UTR	2137	29.5%	CACUUUGGAAGUUUGUGUUCUGUUU	864
15607	3UTR	2140	62.6%	UUUGGAAGUUUGUGUUCUGUUUGUU	865
15608	3UTR	2145	50.7%	AAGUUUGUGUUCUGUUUGUUAAAAC	866
15609	3UTR	2147	62.9%	GUUUGUGUUCUGUUUGUUAAAACUG	867
15610	3UTR	2148	59.7%	UUUGUGUUCUGUUUGUUAAAACUGG	868
15611	3UTR	2149	50.3%	UUGUGUUCUGUUUGUUAAAACUGGC	869
15612	3UTR	2150	49.8%	UGUGUUCUGUUUGUUAAAACUGGCA	870
15613	3UTR	2152	55.2%	UGUUCUGUUUGUUAAAACUGGCAUC	871
15614	3UTR	2153	82.2%	GUUCUGUUUGUUAAAACUGGCAUCU	872
15615	3UTR	2154	70.0%	UUCUGUUUGUUAAAACUGGCAUCUG	873
15616	3UTR	2155	45.5%	UCUGUUUGUUAAAACUGGCAUCUGA	874
15617	3UTR	2156	54.9%	CUGUUUGUUAAAACUGGCAUCUGAC	875
15618	3UTR	2189	40.4%	AGUUGAAGGCCUUAUUCUACAUUUC	876
15619	3UTR	2190	34.1%	GUUGAAGGCCUUAUUCUACAUUUCA	877
15620	3UTR	2207	91.3%	ACAUUUCACCUACUUUGUAAGUGAG	878
15621	3UTR	2265	60.9%	AAUAAACACUGGAAGAAUUUAUUAG	879
15622	3UTR	2267	36.4%	UAAACACUGGAAGAAUUUAUUAGUG	880
15623	3UTR	2295	40.6%	AUUAUGUGAACAACGACAACAACAA	881
15624	3UTR	2296	33.6%	UUAUGUGAACAACGACAACAACAAC	882
15625	3UTR	2297	32.7%	UAUGUGAACAACGACAACAACAACA	883
15626	3UTR	2298	40.8%	AUGUGAACAACGACAACAACAACAA	884
15627	3UTR	2299	38.5%	UGUGAACAACGACAACAACAACAAC	885
15628	3UTR	2301	84.2%	UGAACAACGACAACAACAACAACAA	886

Oligo id	Gene Region	Ref Pos	% Expression A549 0.1 nM	25-mer Sense Strand (position 25 of SS, replaced with A)	SEQ ID NO
15629	3UTR	2302	43.2%	GAACAACGACAACAACAACAACAAC	887
15630	3UTR	2304	57.8%	ACAACGACAACAACAACAACAACAA	888
15631	3UTR	2305	44.3%	CAACGACAACAACAACAACAACAAC	889
15632	3UTR	2308	38.7%	CGACAACAACAACAACAACAACAAA	890
15633	3UTR	2309	37.4%	GACAACAACAACAACAACAACAAAC	891
15634	3UTR	2314	73.5%	CAACAACAACAACAACAAACAGGAA	892
15635	3UTR	2315	54.2%	AACAACAACAACAACAAACAGGAAA	893
15636	3UTR	2389	30.7%	CUUGAUUUUUCUGUAUUGCUAUGCA	894
15637	3UTR	2435	16.0%	ACUCUUAGAGUUAACAGUGAGUUAU	895
15638	3UTR	2445	18.4%	UUAACAGUGAGUUAUUUAUUGUGUG	896
15639	3UTR	2471	36.3%	UACUAUAUAAUGAACGUUUCAUUGC	897
15640	3UTR	2472	73.3%	ACUAUAUAAUGAACGUUUCAUUGCC	898
15641	3UTR	2484	63.4%	ACGUUUCAUUGCCCUUGGAAAAUAA	899
15642	3UTR	2488	65.4%	UUCAUUGCCCUUGGAAAAUAAAACA	900
15643	3UTR	2493	39.3%	UGCCCUUGGAAAAUAAAACAGGUGU	901
15644	3UTR	2519	66.7%	UAAAGUGGAGACCAAAUACUUUGCC	902
15645	3UTR	2520	40.1%	AAAGUGGAGACCAAAUACUUUGCCA	903
15646	3UTR	2526	40.9%	GAGACCAAAUACUUUGCCAGAAACU	904
15647	3UTR	2527	41.5%	AGACCAAAUACUUUGCCAGAAACUC	905
15648	3UTR	2528	47.6%	GACCAAAUACUUUGCCAGAAACUCA	906
15649	3UTR	2529	47.6%	ACCAAAUACUUUGCCAGAAACUCAU	907
15650	3UTR	2530	31.9%	CCAAAUACUUUGCCAGAAACUCAUG	908
15651	3UTR	2531	29.0%	CAAAUACUUUGCCAGAAACUCAUGG	909
15652	3UTR	2537	78.0%	CUUUGCCAGAAACUCAUGGAUGGCU	910
15653	3UTR	2538	52.4%	UUUGCCAGAAACUCAUGGAUGGCUU	911
15654	3UTR	2540	59.7%	UGCCAGAAACUCAUGGAUGGCUUAA	912
15655	3UTR	2541	45.1%	GCCAGAAACUCAUGGAUGGCUUAAG	913
15656	3UTR	2542	42.1%	CCAGAAACUCAUGGAUGGCUUAAGG	914
15657	3UTR	2543	76.9%	CAGAAACUCAUGGAUGGCUUAAGGA	915
15658	3UTR	2544	29.0%	AGAAACUCAUGGAUGGCUUAAGGAA	916
15659	3UTR	2547	45.2%	AACUCAUGGAUGGCUUAAGGAACUU	917
15660	3UTR	2560	38.4%	CUUAAGGAACUUGAACUCAAACGAG	918
15661	3UTR	2561	33.3%	UUAAGGAACUUGAACUCAAACGAGC	919
15662	3UTR	2562	31.9%	UAAGGAACUUGAACUCAAACGAGCC	920
15663	3UTR	2563	44.5%	AAGGAACUUGAACUCAAACGAGCCA	921
15664	3UTR	2564	90.1%	AGGAACUUGAACUCAAACGAGCCAG	922
15665	3UTR	2566	64.4%	GAACUUGAACUCAAACGAGCCAGAA	923
15666	3UTR	2623	32.5%	AAGUGAGUUAUUAUAUGACCGAGAA	924
15667	3UTR	2681	34.0%	UGUUAUGUAUCAGCUGCCUAAGGAA	925
15668	3UTR	2791	59.0%	UUUAAUUGUAAAUGGUUCUUUGUCA	926
15669	3UTR	2792	56.3%	UUAAUUGUAAAUGGUUCUUUGUCAG	927
15670	3UTR	2793	46.8%	UAAUUGUAAAUGGUUCUUUGUCAGU	928
15671	3UTR	2795	53.2%	AUUGUAAAUGGUUCUUUGUCAGUUU	929
15672	3UTR	2798	33.1%	GUAAAUGGUUCUUUGUCAGUUUAGU	930
15673	3UTR	2809	32.8%	UUUGUCAGUUUAGUAAACCAGUGAA	931
15674	3UTR	2813	40.9%	UCAGUUUAGUAAACCAGUGAAAUGU	932
15675	3UTR	2816	38.1%	GUUUAGUAAACCAGUGAAAUGUUGA	933
15676	3UTR	2840	59.4%	AAAUGUUUUGACAUGUACUGGUCAA	934
15677	3UTR	2957	77.9%	UGGAUAUAGAAGCCAGCAUAAUUGA	935
15678	3UTR	2958	74.1%	GGAUAUAGAAGCCAGCAUAAUUGAA	936

Oligo id	Gene Region	Ref Pos	% Expression A549 0.1 nM	25-mer Sense Strand (position 25 of SS, replaced with A)	SEQ ID NO
15679	3UTR	2959	52.4%	GAUAUAGAAGCCAGCAUAAUUGAAA	937
15680	3UTR	2963	49.9%	UAGAAGCCAGCAUAAUUGAAAACAC	938
15681	3UTR	2964	45.3%	AGAAGCCAGCAUAAUUGAAAACACA	939
15682	3UTR	2966	45.5%	AAGCCAGCAUAAUUGAAAACACAUC	940
15683	3UTR	3137	60.5%	ACAAAUGUAUGUUUCUUUUAGCUGG	941
15684	3UTR	3138	63.6%	CAAAUGUAUGUUUCUUUUAGCUGGC	942
15685	3UTR	3142	58.4%	UGUAUGUUUCUUUUAGCUGGCCAGU	943
15686	3UTR	3144	56.3%	UAUGUUUCUUUUAGCUGGCCAGUAC	944
15687	3UTR	3145	52.1%	AUGUUUCUUUUAGCUGGCCAGUACU	945
15688	3UTR	3147	74.6%	GUUUCUUUUAGCUGGCCAGUACUUU	946
15689	3UTR	3150	70.4%	UCUUUUAGCUGGCCAGUACUUUUGA	947
15690	3UTR	3154	61.7%	UUAGCUGGCCAGUACUUUUGAGUAA	948
15691	3UTR	3156	52.3%	AGCUGGCCAGUACUUUUGAGUAAAG	949
15692	3UTR	3157	72.2%	GCUGGCCAGUACUUUUGAGUAAAGC	950
15693	3UTR	3158	62.4%	CUGGCCAGUACUUUUGAGUAAAGCC	951
15694	3UTR	3180	49.0%	GCCCCUAUAGUUUGACUUGCACUAC	952
15695	3UTR	3182	43.9%	CCCUAUAGUUUGACUUGCACUACAA	953
15696	3UTR	3183	35.2%	CCUAUAGUUUGACUUGCACUACAAA	954
15697	3UTR	3184	38.1%	CUAUAGUUUGACUUGCACUACAAAU	955
15698	3UTR	3185	73.3%	UAUAGUUUGACUUGCACUACAAAUG	956
15699	3UTR	3256	86.3%	UUCAUUAUUAUGACAUAAGCUACCU	957
15700	3UTR	3258	61.6%	CAUUAUUAUGACAUAAGCUACCUGG	958
15701	3UTR	3342	66.0%	UUCAUCUUCCAAGCAUCAUUACUAA	959
15702	3UTR	3346	67.3%	UCUUCCAAGCAUCAUUACUAACCAA	960
15703	3UTR	3358	63.6%	CAUUACUAACCAAGUCAGACGUUAA	961
15704	3UTR	3396	71.8%	UAGGAAAAGGAGGAAUGUUAUAGAU	962
15705	3UTR	3550	69.1%	UUGUUAUUACAAAGAGGACACUUCA	963
15706	3UTR	3657	72.3%	GGGGAAAAAAGUCCAGGUCAGCAUA	964
15707	3UTR	3671	79.7%	AGGUCAGCAUAAGUCAUUUUGUGUA	965
15708	3UTR	3779	57.5%	UUUCUUUCCUCUGAGUGAGAGUUAU	966
15709	3UTR	3783	62.6%	UUUCCUCUGAGUGAGAGUUAUCUAU	967
15710	3UTR	3932	61.3%	UAAAAAUUAAUAGGCAAAGCAAUGG	968
15711	3UTR	3934	44.3%	AAAAUUAAUAGGCAAAGCAAUGGAA	969
15712	3UTR	4034	68.7%	UUUUUUGGAAUUUCCUGACCAUUAA	970
15713	3UTR	4058	50.6%	AUUAAAGAAUUGGAUUUGCAAGUUU	971
15714	3UTR	4120	69.8%	UAAACAGCCCUUGUGUUGGAUGUAA	972
15715	3UTR	4147	39.5%	CAAUCCCAGAUUUGAGUGUGUGUUG	973
15716	3UTR	4148	62.2%	AAUCCCAGAUUUGAGUGUGUGUUGA	974
15717	3UTR	4152	34.2%	CCAGAUUUGAGUGUGUGUUGAUUAU	975
15718	3UTR	4273	38.0%	GUCUUUCCUCAUGAAUGCACUGAUA	976
15719	3UTR	4460	48.5%	UAUUUUUGUGUUAAUCAGCAGUACA	977
15720	3UTR	4482	37.1%	ACAAUUUGAUCGUUGGCAUGGUUAA	978
15721	3UTR	4580	60.1%	GUUUUUGUGGUGCUCUAGUGGUAAA	979
15722	3UTR	4583	50.6%	UUUGUGGUGCUCUAGUGGUAAAUAA	980
15723	3UTR	4584	42.1%	UUGUGGUGCUCUAGUGGUAAAUAAA	981
15724	3UTR	4642	91.3%	UCAGUACCAUCAUCGAGUCUAGAAA	982
15725	3UTR	4737	90.4%	UUCUCCCUUAAGGACAGUCACUUCA	983
15726	3UTR	4751	94.6%	CAGUCACUUCAGAAGUCAUGCUUUA	984
15727	3UTR	4753	87.2%	GUCACUUCAGAAGUCAUGCUUUAAA	985
15728	3UTR	4858	70.2%	GUAAUUGUUUGAGAUUUAGUUUCCA	986

Oligo id	Gene Region	Ref Pos	% Expression A549 0.1 nM	25-mer Sense Strand (position 25 of SS, replaced with A)	SEQ ID NO
15729	3UTR	4963	81.2%	CGCCAGGGCCAAAAGAACUGGUCUA	987
15730	3UTR	5177	81.4%	CCAGACUCCUCAAACGAGUUGCCAA	988

Table 7: hTGFB2 sd-rxRNA

Target Gene Duplex ID	hTGFB2 Single Strand ID	sd-rxRNA sequences	SEQ ID NO
18570	17560	mU.A.mU.mU.mU.A.mU.mU.G.mU.G.mU.A.Chl	989
	17562	P.mU.A.fC.A.fC.A.A.fU.A.A.A.fU.A*A*fC*fU*fC*A*C	990
18571	17561	mU.mU.A.mU.mU.mU.A.mU.mU.G.mU.G.mU.A.Chl	991
	17562	P.mU.A.fC.A.fC.A.A.fU.A.A.A.fU.A*A*fC*fU*fC*A*C	992
18572	17563	A.mU.mC.A.G.mU.G.mU.mU.A.A.A.A.Chl	993
	17565	P.mU.fU.fU.fU.A.A.fC.A.fC.fU.G.A.fU*G*A*A*fC*fC*A	994
18573	17564	mC.A.mU.mC.A.G.mU.G.mU.mU.A.A.A.A.Chl	995
	17565	P.mU.fU.fU.fU.A.A.fC.A.fC.fU.G.A.fU*G*A*A*fC*fC*A	996
18574	17566	A.mU.G.G.mC.mU.mU.A.A.G.G.A.A.Chl	997
	17568	P.mU.fU.fC.fC.fU.fU.A.A.G.fC.fC.A.fU*fC*fC*A*fU*G*A	998
18575	17567	G.A.mU.G.G.mC.mU.mU.A.A.G.G.A.A.Chl	999
	17568	P.mU.fU.fC.fC.fU.fU.A.A.G.fC.fC.A.fU*fC*fC*A*fU*G*A	1000
18576	17569	mU.mU.G.mU.G.mU.mU.mC.mU.G.mU.mU.A.Chl	1001
	17571	P.mU.A.A.fC.A.G.A.A.fC.A.fC.A.A*A*fC*fU*fU*fC*C	1002
18577	17570	mU.mU.mU.G.mU.G.mU.mU.mC.mU.G.mU.mU.A.Chl	1003
	17571	P.mU.A.A.fC.A.G.A.A.fC.A.fC.A.A*A*fC*fU*fU*fC*C	1004
18578	17572	A.A.A.mU.A.mC.mU.mU.mU.G.mC.mC.A.Chl	1005
	17574	P.mU.G.G.fC.A.A.A.G.fU.A.fU.fU.fU*G*G*fU*fC*fU*C	1006
18579	17573	mC.A.A.A.mU.A.mC.mU.mU.mU.G.mC.mC.A.Chl	1007
	17574	P.mU.G.G.fC.A.A.A.G.fU.A.fU.fU.fU*G*G*fU*fC*fU*C	1008
18580	17575	mC.mU.mU.G.mC.A.mC.mU.A.mC.A.A.A.Chl	1009
	17577	P.mU.fU.fU.G.fU.A.G.fU.G.fC.A.A.G*fU*fC*A*A*A*C	1010
18581	17576	A.mC.mU.mU.G.mC.A.mC.mU.A.mC.A.A.A.Chl	1011
	17577	P.mU.fU.fU.G.fU.A.G.fU.G.fC.A.A.G*fU*fC*A*A*A*C	1012
18582	17578	G.A.A.mU.mU.mU.A.mU.mU.A.G.mU.A.Chl	1013
	17580	P.mU.A.fC.fU.A.A.fU.A.A.A.fU.fU.fC*fU*fU*fU*fC*fC*A*G	1014
18583	17579	A.G.A.A.mU.mU.mU.A.mU.mU.A.G.mU.A.Chl	1015
	17580	P.mU.A.fC.fU.A.A.fU.A.A.A.fU.fU.fC*fU*fU*fU*fC*fC*A*G	1016
18584	17581	mU.mU.G.mC.A.mC.mU.A.mC.A.A.A.A.Chl	1017
	17583	P.mU.fU.fU.fU.G.fU.A.G.fU.G.fC.A.A*G*fU*fC*A*A*A	1018
18585	17582	mC.mU.mU.G.mC.A.mC.mU.A.mC.A.A.A.A.Chl	1019
	17583	P.mU.fU.fU.fU.G.fU.A.G.fU.G.fC.A.A*G*fU*fC*A*A*A	1020
18586	17584	A.mU.A.A.A.A.mC.A.G.G.mU.G.A.Chl	1021
	17586	P.mU.fC.A.fC.fC.fU.G.fU.fU.fU.fU.A.fU*fU*fU*fU*fC*fC*A	1022
18587	17585	A.A.mU.A.A.A.A.mC.A.G.G.mU.G.A.Chl	1023
	17586	P.mU.fC.A.fC.fC.fU.G.fU.fU.fU.fU.A.fU*fU*fU*fU*fC*fC*A	1024
18588	17587	G.A.mC.A.A.mC.A.A.mC.A.A.mC.A.Chl	1025
	17588	P.mU.G.fU.fU.G.fU.fU.G.fU.fU.G.fU.fC*G*fU*fU*G*fU*U	1026
18589	17589	A.mU.G.mC.mU.mU.G.mU.A.A.mC.A.A.Chl	1027
	17590	P.mU.fU.G.fU.fU.A.fC.A.A.G.fC.A.fU*fC*A*fU*fC*G*U	1028
18590	17591	mC.A.G.A.A.A.mC.mU.mC.A.mU.G.A.Chl	1029

Target Gene Duplex ID	hTGFB2 Single Strand ID	sd-rxRNA sequences	SEQ ID NO
	17592	P.mU.fC.A.fU.G.A.G.fU.fU.fU.fC.fU.G*G*fC*A*A*A*G	1030
18591	17593	G.mU.A.mU.mU.G.mC.mU.A.mU.G.mC.A.Chl	1031
	17594	P.mU.G.fC.A.fU.A.G.fC.A.A.fU.A.fC*A*G*A*A*A*A	1032
18592	17595	mC.mC.A.G.A.A.A.mC.mU.mC.A.mU.A.Chl	1033
	17596	P.mU.A.fU.G.A.G.fU.fU.fU.fC.fU.G.G*fC*A*A*A*G*U	1034
18593	17597	A.mC.mU.mC.A.A.A.mC.G.A.G.mC.A.Chl	1035
	17598	P.mU.G.fC.fU.fC.G.fU.fU.fU.G.A.G.fU*fU*fC*A*A*G*U	1036
18594	17599	A.mU.A.mU.G.A.mC.mC.G.A.G.A.A.Chl	1037
	17600	P.mU.fU.fC.fU.fC.G.G.fU.fC.A.fU.A.fU*A*A*fU*A*A*C	1038
18595	17601	mC.G.A.mC.G.A.mC.A.A.mC.G.A.A.Chl	1039
	17602	P.mU.fU.fC.G.fU.fU.G.fU.fC.G.fU.fC.G*fU*fC*A*fU*fC*A	1040
18596	17603	G.mU.A.A.A.mC.mC.A.G.mU.G.A.A.Chl	1041
	17604	P.mU.fU.fC.A.fC.fU.G.G.fU.fU.fU.A.fC*fU*A*A*A*fC*U	1042
18597	17605	mU.mU.G.mU.mC.A.G.mU.mU.mU.A.G.A.Chl	1043
	17606	P.mU.fC.fU.A.A.A.fC.fU.G.A.fC.A.A*A*G*A*A*A*fC*C	1044
18598	17607	mU.mC.A.mU.mC.A.G.mU.G.mU.mU.A.A.Chl	1045
	17608	P.mU.fU.A.A.fC.A.fC.fU.G.A.fU.G.A*A*fC*fC*A*A*G	1046
18599	17609	A.A.mC.mU.mC.A.A.A.mC.G.A.G.A.Chl	1047
	17610	P.mU.fC.fU.fC.G.fU.fU.fU.G.A.G.fU.fU*fC*A*A*G*fU*U	1048
18600	17611	mC.G.A.mC.A.A.mC.A.A.mC.A.A.A.Chl	1049
	17612	P.mU.fU.fU.G.fU.fU.G.fU.fU.G.fU.fC.G*fU*fU*G*fU*fU*C	1050
18601	17613	A.mC.G.A.mC.A.A.mC.G.A.mU.G.A.Chl	1051
	17614	P.mU.fC.A.fU.fC.G.fU.fU.G.fU.fC.G.fU*fC*G*fU*fC*A*U	1052
18602	17615	G.mC.mU.G.mC.mC.mU.A.A.G.G.A.A.Chl	1053
	17616	P.mU.fU.fC.fC.fU.fU.A.G.G.fC.A.G.fC*fU*G*A*fU*A*C	1054
18603	17617	A.mU.mU.mC.mU.A.mC.A.mU.mU.mU.mC.A.Chl	1055
	17618	P.mU.G.A.A.A.fU.G.fU.A.G.A.A.fU*A*A*G*G*fC*C	1056
18604	17619	G.mU.G.mU.G.mU.mU.G.A.mU.mU.A.A.Chl	1057
	17620	P.mU.fU.A.A.fU.fC.A.A.fC.A.fC.A.fC*A*fC*fU*fC*A*A	1058
Rat TGFB2 sd-rxRNA			1059
18678	18604	mC.G.G.mU.G.A.mC.A.A.mU.G.A.A-chol	1060
	18605	mU.fU.fC.A.fU.fU.G.fU.fC.A.fC.fC.G*fU*G*A*fU*fU*fU*U	1061
18679	18606	mU.mU.G.mU.mC.mU.mC.G.G.mU.A.mU.A-chol	1062
	18607	mU.A.fU.A.fC.fC.G.A.G.A.fC.A.A*A*G*G*G*A*A	1063
18680	18608	G.A.G.mU.mU.G.mU.A.mU.G.mU.A.A-chol	1064
	18609	mU.fU.A.fC.A.fU.A.fC.A.A.fC.fU.fC*fC*A*fC*fU*G*A	1065
18681	18610	A.mU.mU.mU.G.mU.mU.A.G.mU.G.mU.A-chol	1066
	18611	mU.A.fC.A.fC.fU.A.A.fC.A.A.A.fU*fU*fC*fU*fU*fC*C	1067
18682	18612	G.mC.A.A.G.mU.mC.mU.G.A.G.A.A-chol	1068
	18613	mU.fU.fC.fU.fC.A.G.A.fC.fU.fU.G.fC*fU*fC*A*G*fU*U	1069
18683	18614	A.A.A.mU.mC.A.mC.G.G.mU.G.A.A-chol	1070
	18615	mU.fU.fC.A.fC.fC.G.fU.G.A.fU.fU.fU*fU*fC*A*fU*fC*C	1071
18684	18616	A.A.A.mU.G.mC.A.G.mC.mU.A.A.A-chol	1072
	18617	mU.fU.fU.A.G.fC.fU.G.fC.A.fU.fU.fU*A*fC*A*A*G*A	1073
18685	18618	mC.mU.mU.G.G.A.A.A.A.mU.A.A.A-chol	1074
	18619	mU.fU.fU.A.fU.fU.fU.fU.fC.fC.A.A.G*G*G*fC*A*A*U	1075
18686	18620	mC.mC.mU.mU.mU.G.A.A.mU.A.A.A.A-chol	1076
	18621	mU.fU.fU.fU.A.fU.fU.fC.A.A.A.G.G*fU*A*fC*fU*G*G	1077
18687	18622	A.A.mC.A.mC.A.mC.mU.G.mC.A.A.A-chol	1078
	18623	mU.fU.fU.G.fC.A.G.fU.G.fU.G.fU.fU*fU*fU*fC*A*fU*C	1079
18688	18624	A.A.A.A.mC.A.mC.A.mC.mU.G.mC.A-chol	1080

Target Gene Duplex ID	hTGFB2 Single Strand ID	sd-rxRNA sequences	SEQ ID NO
	18625	mU.G.fC.A.G.fU.G.fU.G.fU.fU.fU.fU*fC*A*fU*fC*A*U	1081
18689	18626	G.A.A.G.G.mC.mC.mU.G.mU.mU.A.A-chol	1082
	18627	mU.fU.A.A.fC.A.G.G.fC.fC.fU.fU.fC*fU*G*G*A*fC*A	1083
18690	18628	mU.A.mU.mU.G.mC.mU.mC.mU.G.mC.A.A-chol	1084
	18629	mU.fU.G.fC.A.G.A.G.fC.A.A.fU.A*fC*A*G*A*G*G	1085

Table 8: hSPP1 sd-rxRNA

Target Gene Duplex ID	hSPP1 Single Strand ID	sd-rxRNA sequence	SEQ ID NO
18538	17430	G.A.mU.G.A.A.mU.mC.mU.G.A.mU.A.Chl	1086
	17432	P.mU.A.fU.fC.A.G.A.fU.fU.fC.A.fU.fC*A*G*A*A*fU*G	1087
18539	17431	mU.G.A.mU.G.A.A.mU.mC.mU.G.A.mU.A.Chl	1088
	17432	P.mU.A.fU.fC.A.G.A.fU.fU.fC.A.fU.fC*A*G*A*A*fU*G	1089
18540	17433	A.mU.mU.mU.G.mC.mU.mU.mU.mU.G.mC.A.Chl	1090
	17435	P.mU.G.fC.A.A.A.A.G.fC.A.A.A.fU*fC*A*fC*fU*G*fC	1091
18541	17434	G.A.mU.mU.mU.G.mC.mU.mU.mU.mU.G.mC.A.Chl	1092
	17435	P.mU.G.fC.A.A.A.A.G.fC.A.A.A.fU*fC*A*fC*fU*G*fC	1093
18542	17436	G.mU.G.A.mU.mU.mU.G.mC.mU.mU.mU.AChl	1094
	17438	P.mU.A.A.A.G.fC.A.A.A.fU.fC.A.fC*fU*G*fC*A*A*fU	1095
18543	17437	A.G.mU.G.A.mU.mU.mU.G.mC.mU.mU.mU.A.Chl	1096
	17438	P.mU.A.A.A.G.fC.A.A.A.fU.fC.A.fC*fU*G*fC*A*A*fU	1097
18544	17439	A.A.mU.mU.mU.mC.G.mU.A.mU.mU.mU.A.Chl	1098
	17441	P.mU.A.A.A.fU.A.fC.G.A.A.A.fU.fU*fU*fC*A*G*G*fU	1099
18545	17440	A.A.A.mU.mU.mU.mC.G.mU.A.mU.mU.mU.A.Chl	1100
	17441	P.mU.A.A.A.fU.A.fC.G.A.A.A.fU.fU*fU*fC*A*G*G*fU	1101
18546	17442	mC.A.mC.A.G.mC.mC.A.mU.G.A.A.A.Chl	1102
	17444	P.mU.fU.fU.C.A.fU.G.G.fC.fU.G.fU.G*A*A*A*fU*fU*fC	1103
18547	17443	mU.mC.A.mC.A.G.mC.mC.A.mU.G.A.A.A.Chl	1104
	17444	P.mU.fU.fU.C.A.fU.G.G.fC.fU.G.fU.G*A*A*A*fU*fU*fC	1105
18548	17445	G.A.mU.mU.mU.G.mC.mU.mU.mU.mU.G.A.Chl	1106
	17447	P.mU.fC.A.A.A.A.G.fC.A.A.A.fU.fC*A*fC*fU*G*fC*A	1107
18549	17446	mU.G.A.mU.mU.mU.G.mC.mU.mU.mU.mU.G.A.Chl	1108
	17447	P.mU.fC.A.A.A.A.G.fC.A.A.A.fU.fC*A*fC*fU*G*fC*A	1109
18550	17448	mU.mU.G.mC.mU.mU.mU.mU.G.mC.mC.mU.A.Chl	1110
	17450	P.mU.A.G.G.fC.A.A.A.A.G.fC.A.A*A*fU*fC*A*fC*U	1111
18551	17449	mU.mU.mU.G.mC.mU.mU.mU.mU.G.mC.mC.mU.A.Chl	1112
	17450	P.mU.A.G.G.fC.A.A.A.A.G.fC.A.A*A*fU*fC*A*fC*U	1113
18552	17451	mU.mU.mU.mC.mU.mC.A.G.mU.mU.mU.A.A.Chl	1114
	17452	P.mU.fU.A.A.A.fC.fU.G.A.G.A.A.A*G*A*A*G*fC*A	1115
18553	17453	mU.mU.G.mC.A.mU.mU.mU.A.G.mU.mC.A.Chl	1116
	17454	P.mU.G.A.fC.fU.A.A.A.fU.G.fC.A.A*A*G*fU*G*A*G	1117
18554	17455	A.mC.mU.mU.mU.G.mC.A.mU.mU.mU.A.A.Chl	1118
	17456	P.mU.fU.A.A.A.fU.G.fC.A.A.A.G.fU*G*A*G*A*A*A	1119
18555	17457	A.mU.mU.mU.A.G.mU.mC.A.A.A.A.A.Chl	1120
	17458	P.mU.fU.fU.fU.fU.G.A.fC.fU.A.A.A.fU*G*fC*A*A*A*G	1121
18556	17459	mU.mU.mC.mU.mU.mU.mC.mU.mC.A.G.mU.A.Chl	1122
	17460	P.mU.A.fC.fU.G.A.G.A.A.A.G.A.A*G*fC*A*fU*fU*fU	1123
18557	17461	mU.mC.mU.mU.mU.mC.mU.mC.A.G.mU.mU.A.Chl	1124
	17462	P.mU.A.A.fC.fU.G.A.G.A.A.A.G.A*A*G*fC*A*fU*fU	1125

18558	17463	G.A.A.A.G.A.G.A.A.mC.A.mU.A.Chl	1126
	17464	P.mU.A.fU.G.fU.fU.fC.fU.fC.fU.fU.fU.fC*A*fU*fU*fU*fU*G	1127
18559	17465	mC.mU.mU.mU.G.mC.A.mU.mU.mU.A.G.A.Chl	1128
	17466	P.mU.fC.fU.A.A.A.fU.G.fC.A.A.A.G*fU*G*A*G*A*A	1129
18560	17467	mU.mU.mU.G.mC.A.mU.mU.mU.A.G.mU.A.Chl	1130
	17468	P.mU.A.fC.fU.A.A.A.fU.G.fC.A.A.A*G*fU*G*A*G*A	1131
18561	17469	mC.mU.mC.A.mC.mU.mU.mU.G.mC.A.mU.A.Chl	1132
	17470	P.mU.A.fU.G.fC.A.A.A.G.fU.G.A.G*A*A*A*fU*fU*G	1133
18562	17471	mU.mU.mC.mU.mC.A.mC.mU.mU.mU.G.mC.A.Chl	1134
	17472	P.mU.G.fC.A.A.A.G.fU.G.A.G.A.A*A*fU*fU*G*fU*A	1135
18563	17473	mC.A.mC.mU.mC.mC.A.G.mU.mU.G.mU.A.Chl	1136
	17474	P.mU.A.fC.A.A.fC.fU.G.G.A.G.fU.G*A*A*A*A*fC*U	1137
18564	17475	A.A.mU.G.A.A.A.G.A.G.A.A.A.Chl	1138
	17476	P.mU.fU.fU.fC.fU.fC.fU.fU.fU.fC.A.fU.fU*fU*fU*G*fC*fU*A	1139
18565	17477	mU.G.mC.A.G.mU.G.A.mU.mU.mU.mG.A.Chl	1140
	17478	P.mU.fC.A.A.A.fU.fC.A.fC.fU.G.fC.A*A*fU*fU*fU*fC*fU*C	1141
18566	17479	mU.G.A.A.A.G.A.G.A.A.mC.A.A.Chl	1142
	17480	P.mU.fU.G.fU.fU.fC.fU.fC.fU.fU.fU.fU.fC.A*fU*fU*fU*fU*fU*G*C	1143
18567	17481	A.mC.mC.mU.G.A.A.A.mU.mU.mU.mC.A.Chl	1144
	17482	P.mU.G.A.A.A.fU.fU.fU.fC.A.G.G.fU*G*fU*fU*fU*fU*A*U	1145
18568	17483	G.A.A.mU.mU.G.mC.A.G.mU.G.A.A.Chl	1146
	17484	P.mU.fU.fC.A.fC.fU.G.fC.A.A.fU.fU.fC*fU*fC*A*fU*G*G	1147
18569	17485	G.G.mC.mU.G.A.mU.mU.mC.mU.G.G.A.Chl	1148
	17486	P.mU.fC.fC.A.G.A.A.fU.fC.A.G.fC.fC*fU*G*fU*fU*fU*fU*A	1149
Rat Targeting SPP1			
18662	18630	G.mU.mU.mC.G.mU.mU.G.mU.mU.mU.mC.A-chol	1150
	18631	P.mU.G.A.A.A.fC.A.A.fC.G.A.A.fC*fU*A*A*G*fC*U	1151
18663	18632	G.A.A.A.G.A.A.A.mU.A.G.A.A-chol	1152
	18633	P.mU.fU.fC.fU.A.fU.fU.fU.fC.fU.fU.fU.fC*fU*fC*fC*A*fC*A	1153
18664	18634	G.mU.G.G.A.G.A.A.A.G.A.A.A-chol	1154
	18635	P.mU.fU.fU.fC.fU.fU.fU.fC.fU.fC.fC.A.fC*A*fU*A*fC*A*U	1155
18665	18636	mC.mU.G.mU.G.mU.mC.A.mC.mU.A.mU.A-chol	1156
	18637	P.mU.A.fU.A.G.fU.G.A.fC.A.fC.A.G*A*fC*fU*A*fU*U	1157
18666	18638	G.mU.mU.mU.mC.mU.mC.A.G.mU.mU.mC.A-chol	1158
	18639	P.mU.G.A.A.fC.fU.G.A.G.A.A.A.fC*A*A*G*fC*A*G	1159
18667	18640	mU.A.mC.A.G.G.A.A.mC.A.G.mC.A-chol	1160
	18641	P.mU.G.fC.fU.G.fU.fU.fC.fC.fU.G.fU.A*A*G*fU*fU*fU*fU*G	1161
18668	18642	G.mC.A.G.G.mC.A.A.A.mC.mU.mU.A-chol	1162
	18643	P.mU.A.A.G.fU.fU.fU.G.fC.fC.fU.G.fC*fC*fU*fC*fU*A*C	1163
18669	18644	A.A.mC.mU.mU.A.mC.A.G.G.A.A.A-chol	1164
	18645	P.mU.fU.fU.fC.fC.fU.G.fU.A.A.G.fU.fU*fU*G*fC*fC*fU*G	1165
18670	18646	mC.A.mC.mU.G.mC.A.mU.mU.mU.mU.A.A-chol	1166
	18647	P.mU.fU.A.A.A.A.fU.G.fC.A.G.fU.G*G*fC*fC*A*fU*U	1167
18671	18648	G.A.mC.A.mC.mC.A.mC.mU.G.mU.A.A-chol	1168
	18649	P.mU.fU.A.fC.A.G.fU.G.G.fU.G.fU.fC*fU*G*fC*A*fU*G	1169
18672	18650	A.G.A.G.G.mC.A.G.G.mC.A.A.A-chol	1170
	18651	P.mU.fU.fU.G.fC.fC.fU.G.fC.fC.fU.fC.fU*A*fC*A*fU*A*C	1171
18673	18652	mU.A.G.A.G.G.mC.A.G.G.mC.A.A-chol	1172
	18653	P.mU.fU.G.fC.fC.fU.G.fC.fC.fU.fC.fU.A*fC*A*fU*A*fC*A	1173

18674	18654	G.A.G.A.G.mU.mU.mC.A.mU.mC.mU.A-chol	1174
	18655	P.mU.A.G.A.fU.G.A.A.fC.fU.fC.fU.fC*fU*A*A*fU*fU*C	1175
18675	18656	mU.G.mU.G.A.A.mU.A.A.A.mU.mC.A-chol	1176
	18657	P.mU.G.A.fU.fU.fU.A.fU.U.fC.A.fC.A*fC*fC*A*fC*A*A	1177
18676	18658	G.mU.G.A.A.mU.A.A.A.mU.mC.mU.A-chol	1178
	18659	P.mU.A.G.A.fU.fU.fU.A.fU.fU.fC.A.fC*A*fC*fC*A*fC*A	1179
18677	18660	mU.G.A.AmU.A.A.A.mU.mC.mU.mU.A-chol	1180
	18661	P.mU.A.A.G.A.fU.fU.fU.A.fU.U.fC.A*fC*A*fC*fC*A*C	1181

Table 9: Inhibition of gene expression with hSPP1 ori sequences

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hSPP1 Sense Strand Sequence	A549 0.1 nM Activity
14840	5UTR/CDS	155	1182	AAGGAAAACUCACUACCAUGAGAAA	4.4%
14841	5UTR/CDS	161	1183	AACUCACUACCAUGAGAAUUGCAGA	2.46%
14842	5UTR/CDS	163	1184	CUCACUACCAUGAGAAUUGCAGUGA	20.54%
14843	5UTR/CDS	164	1185	UCACUACCAUGAGAAUUGCAGUGAA	2.8%
14844	CDS	168	1186	UACCAUGAGAAUUGCAGUGAUUUGA	3.6%
14845	CDS	169	1187	ACCAUGAGAAUUGCAGUGAUUUGCA	5.2%
14846	CDS	171	1188	CAUGAGAAUUGCAGUGAUUUGCUUA	0.8%
14847	CDS	172	1189	AUGAGAAUUGCAGUGAUUUGCUUUA	0.95%
14848	CDS	173	1190	UGAGAAUUGCAGUGAUUUGCUUUUA	3.2%
14849	CDS	174	1191	GAGAAUUGCAGUGAUUUGCUUUUGA	4.14%
14850	CDS	175	1192	AGAAUUGCAGUGAUUUGCUUUUGCA	2.9%
14851	CDS	176	1193	GAAUUGCAGUGAUUUGCUUUUGCCA	8.38%
14852	CDS	177	1194	AAUUGCAGUGAUUUGCUUUUGCCUA	4.6%
14853	CDS	180	1195	UGCAGUGAUUUGCUUUUGCCUCCUA	11.1%
14854	CDS	181	1196	GCAGUGAUUUGCUUUUGCCUCCUAA	10.87%
14855	CDS	182	1197	CAGUGAUUUGCUUUUGCCUCCUAGA	5.3%
14856	CDS	206	1198	GCAUCACCUGUGCCAUACCAGUUAA	15.29%
14857	CDS	208	1199	AUCACCUGUGCCAUACCAGUUAAAA	22.6%
14858	CDS	212	1200	CCUGUGCCAUACCAGUUAAACAGGA	13.3%
14859	CDS	215	1201	GUGCCAUACCAGUUAAACAGGCUGA	21.2%
14860	CDS	216	1202	UGCCAUACCAGUUAAACAGGCUGAA	20.24%
14861	CDS	220	1203	AUACCAGUUAAACAGGCUGAUUCUA	12.5%
14862	CDS	221	1204	UACCAGUUAAACAGGCUGAUUCUGA	9.9%
14863	CDS	222	1205	ACCAGUUAAACAGGCUGAUUCUGGA	3.9%
14864	CDS	225	1206	AGUUAAACAGGCUGAUUCUGGAAGA	20.48%
14865	CDS	226	1207	GUUAAACAGGCUGAUUCUGGAAGUA	10.7%
14866	CDS	227	1208	UUAAACAGGCUGAUUCUGGAAGUUA	22.75%
14867	CDS	228	1209	UAAACAGGCUGAUUCUGGAAGUUCA	0.26%
14868	CDS	234	1210	GGCUGAUUCUGGAAGUUCUGAGGAA	0.34%
14869	CDS	236	1211	CUGAUUCUGGAAGUUCUGAGGAAAA	4.4%
14870	CDS	238	1212	GAUUCUGGAAGUUCUGAGGAAAAGA	4.5%
14871	CDS	239	1213	AUUCUGGAAGUUCUGAGGAAAAGCA	7.5%
14872	CDS	240	1214	UUCUGGAAGUUCUGAGGAAAAGCAA	101.3%
14873	CDS	338	1215	CCCCACAGACCCUUCCAAGUAAGUA	48.3%
14874	CDS	340	1216	CCACAGACCCUUCCAAGUAAGUCCA	33.9%
14875	CDS	342	1217	ACAGACCCUUCCAAGUAAGUCCAAA	16.1%
14876	CDS	343	1218	CAGACCCUUCCAAGUAAGUCCAACA	38.7%
14877	CDS	345	1219	GACCCUUCCAAGUAAGUCCAACGAA	54.2%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hSPP1 Sense Strand Sequence	A549 0.1 nM Activity
14878	CDS	348	1220	CCUUCCAAGUAAGUCCAACGAAAGA	12.54%
14879	CDS	349	1221	CUUCCAAGUAAGUCCAACGAAAGCA	32.44%
14880	CDS	351	1222	UCCAAGUAAGUCCAACGAAAGCCAA	17.1%
14881	CDS	353	1223	CAAGUAAGUCCAACGAAAGCCAUGA	32.94%
14882	CDS	358	1224	AAGUCCAACGAAAGCCAUGACCACA	65.1%
14883	CDS	362	1225	CCAACGAAAGCCAUGACCACAUGGA	76.9%
14884	CDS	363	1226	CAACGAAAGCCAUGACCACAUGGAA	69.8%
14885	CDS	366	1227	CGAAAGCCAUGACCACAUGGAUGAA	78.02%
14886	CDS	372	1228	CCAUGACCACAUGGAUGAUAUGGAA	19.49%
14887	CDS	377	1229	ACCACAUGGAUGAUAUGGAUGAUGA	20.43%
14888	CDS	393	1230	GGAUGAUGAAGAUGAUGAUGACCAA	29.1%
14889	CDS	394	1231	GAUGAUGAAGAUGAUGAUGACCAUA	24.5%
14890	CDS	396	1232	UGAUGAAGAUGAUGAUGACCAUGUA	25.90%
14891	CDS	398	1233	AUGAAGAUGAUGAUGACCAUGUGGA	20.5%
14892	CDS	399	1234	UGAAGAUGAUGAUGACCAUGUGGAA	7.9%
14893	CDS	430	1235	GACUCCAUUGACUCGAACGACUCUA	21.6%
14894	CDS	431	1236	ACUCCAUUGACUCGAACGACUCUGA	13.5%
14895	CDS	432	1237	CUCCAUUGACUCGAACGACUCUGAA	12.33%
14896	CDS	435	1238	CAUUGACUCGAACGACUCUGAUGAA	42.5%
14897	CDS	440	1239	ACUCGAACGACUCUGAUGAUGUAGA	22.54%
14898	CDS	441	1240	CUCGAACGACUCUGAUGAUGUAGAA	17.4%
14899	CDS	442	1241	UCGAACGACUCUGAUGAUGUAGAUA	11.2%
14900	CDS	443	1242	CGAACGACUCUGAUGAUGUAGAUGA	20.7%
14901	CDS	445	1243	AACGACUCUGAUGAUGUAGAUGACA	27.1%
14902	CDS	449	1244	ACUCUGAUGAUGUAGAUGACACUGA	39.8%
14903	CDS	450	1245	CUCUGAUGAUGUAGAUGACACUGAA	9.6%
14904	CDS	451	1246	UCUGAUGAUGUAGAUGACACUGAUA	4.44%
14905	CDS	452	1247	CUGAUGAUGUAGAUGACACUGAUGA	8.7%
14906	CDS	453	1248	UGAUGAUGUAGAUGACACUGAUGAA	16.72%
14907	CDS	461	1249	UAGAUGACACUGAUGAUUCUCACCA	42.9%
14908	CDS	462	1250	AGAUGACACUGAUGAUUCUCACCAA	30.1%
14909	CDS	469	1251	ACUGAUGAUUCUCACCAGUCUGAUA	9.1%
14910	CDS	470	1252	CUGAUGAUUCUCACCAGUCUGAUGA	19.0%
14911	CDS	471	1253	UGAUGAUUCUCACCAGUCUGAUGAA	42.1%
14912	CDS	472	1254	GAUGAUUCUCACCAGUCUGAUGAGA	59.1%
14913	CDS	476	1255	AUUCUCACCAGUCUGAUGAGUCUCA	38.2%
14914	CDS	479	1256	CUCACCAGUCUGAUGAGUCUCACCA	34.1%
14915	CDS	480	1257	UCACCAGUCUGAUGAGUCUCACCAA	48.45%
14916	CDS	483	1258	CCAGUCUGAUGAGUCUCACCAUUCA	9.5%
14917	CDS	484	1259	CAGUCUGAUGAGUCUCACCAUUCUA	21.5%
14918	CDS	485	1260	AGUCUGAUGAGUCUCACCAUUCUGA	18.6%
14919	CDS	486	1261	GUCUGAUGAGUCUCACCAUUCUGAA	20.2%
14920	CDS	487	1262	UCUGAUGAGUCUCACCAUUCUGAUA	10.9%
14921	CDS	488	1263	CUGAUGAGUCUCACCAUUCUGAUGA	18.9%
14922	CDS	489	1264	UGAUGAGUCUCACCAUUCUGAUGAA	10.7%
14923	CDS	490	1265	GAUGAGUCUCACCAUUCUGAUGAAA	28.15%
14924	CDS	493	1266	GAGUCUCACCAUUCUGAUGAAUCUA	18.33%
14925	CDS	495	1267	GUCUCACCAUUCUGAUGAAUCUGAA	7.61%
14926	CDS	496	1268	UCUCACCAUUCUGAUGAAUCUGAUA	2.99%
14927	CDS	497	1269	CUCACCAUUCUGAUGAAUCUGAUGA	7.44%
14928	CDS	498	1270	UCACCAUUCUGAUGAAUCUGAUGAA	9.7%
14929	CDS	499	1271	CACCAUUCUGAUGAAUCUGAUGAAA	16.96%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hSPP1 Sense Strand Sequence	A549 0.1 nM Activity
14930	CDS	501	1272	CCAUUCUGAUGAAUCUGAUGAACUA	3.08%
14931	CDS	505	1273	UCUGAUGAAUCUGAUGAACUGGUCA	13.24%
14932	CDS	510	1274	UGAAUCUGAUGAACUGGUCACUGAA	3.16%
14933	CDS	550	1275	CCAGCAACCGAAGUUUUCACUCCAA	14.02%
14934	CDS	554	1276	CAACCGAAGUUUUCACUCCAGUUGA	3.10%
14935	CDS	555	1277	AACCGAAGUUUUCACUCCAGUUGUA	5.27%
14936	CDS	572	1278	CAGUUGUCCCCACAGUAGACACAUA	13.2%
14937	CDS	573	1279	AGUUGUCCCCACAGUAGACACAUAA	27.01%
14938	CDS	574	1280	GUUGUCCCCACAGUAGACACAUAUA	8.76%
14939	CDS	588	1281	AGACACAUAUGAUGGCCGAGGUGAA	14.04%
14940	CDS	589	1282	GACACAUAUGAUGGCCGAGGUGAUA	18.40%
14941	CDS	598	1283	GAUGGCCGAGGUGAUAGUGUGGUUA	12.50%
14942	CDS	601	1284	GGCCGAGGUGAUAGUGUGGUUUAUA	13.76%
14943	CDS	602	1285	GCCGAGGUGAUAGUGUGGUUUAUGA	5.34%
14944	CDS	603	1286	CCGAGGUGAUAGUGUGGUUUAUGGA	29.69%
14945	CDS	604	1287	CGAGGUGAUAGUGUGGUUUAUGGAA	33.34%
14946	CDS	606	1288	AGGUGAUAGUGUGGUUUAUGGACUA	17.50%
14947	CDS	608	1289	GUGAUAGUGUGGUUUAUGGACUGAA	45.90%
14948	CDS	609	1290	UGAUAGUGUGGUUUAUGGACUGAGA	22.0%
14949	CDS	610	1291	GAUAGUGUGGUUUAUGGACUGAGGA	19.93%
14950	CDS	611	1292	AUAGUGUGGUUUAUGGACUGAGGUA	17.34%
14951	CDS	615	1293	UGUGGUUUAUGGACUGAGGUCAAAA	5.60%
14952	CDS	617	1294	UGGUUUAUGGACUGAGGUCAAAAUA	25.74%
14953	CDS	618	1295	GGUUUAUGGACUGAGGUCAAAAUCA	17.63%
14954	CDS	619	1296	GUUUAUGGACUGAGGUCAAAAUCUA	3.45%
14955	CDS	621	1297	UUAUGGACUGAGGUCAAAAUCUAAA	18.03%
14956	CDS	622	1298	UAUGGACUGAGGUCAAAAUCUAAGA	20.98%
14957	CDS	623	1299	AUGGACUGAGGUCAAAAUCUAAGAA	20.60%
14958	CDS	624	1300	UGGACUGAGGUCAAAAUCUAAGAAA	26.73%
14959	CDS	625	1301	GGACUGAGGUCAAAAUCUAAGAAGA	7.45%
14960	CDS	626	1302	GACUGAGGUCAAAAUCUAAGAAGUA	14.1%
14961	CDS	629	1303	UGAGGUCAAAAUCUAAGAAGUUUCA	8.61%
14962	CDS	630	1304	GAGGUCAAAAUCUAAGAAGUUUCGA	19.07%
14963	CDS	631	1305	AGGUCAAAAUCUAAGAAGUUUCGCA	6.08%
14964	CDS	632	1306	GGUCAAAAUCUAAGAAGUUUCGCAA	19.82%
14965	CDS	636	1307	AAAAUCUAAGAAGUUUCGCAGACCA	21.55%
14966	CDS	637	1308	AAAUCUAAGAAGUUUCGCAGACCUA	30.20%
14967	CDS	638	1309	AAUCUAAGAAGUUUCGCAGACCUGA	18.23%
14968	CDS	686	1310	ACGAGGACAUCACCUCACACAUGGA	14.85%
14969	CDS	687	1311	CGAGGACAUCACCUCACACAUGGAA	28.04%
14970	CDS	689	1312	AGGACAUCACCUCACACAUGGAAAA	3.80%
14971	CDS	698	1313	CCUCACACAUGGAAAGCGAGGAGUA	7.67%
14972	CDS	703	1314	CACAUGGAAAGCGAGGAGUUGAAUA	5.8%
14973	CDS	704	1315	ACAUGGAAAGCGAGGAGUUGAAUGA	5.3%
14974	CDS	705	1316	CAUGGAAAGCGAGGAGUUGAAUGGA	24.47%
14975	CDS	718	1317	GAGUUGAAUGGUGCAUACAAGGCCA	26.39%
14976	CDS	785	1318	GCCGUGGGAAGGACAGUUAUGAAAA	7.60%
14977	CDS	786	1319	CCGUGGGAAGGACAGUUAUGAAACA	8.75%
14978	CDS	788	1320	GUGGGAAGGACAGUUAUGAAACGAA	8.34%
14979	CDS	790	1321	GGGAAGGACAGUUAUGAAACGAGUA	5.38%
14980	CDS	792	1322	GAAGGACAGUUAUGAAACGAGUCAA	11.45%
14981	CDS	794	1323	AGGACAGUUAUGAAACGAGUCAGCA	11.78%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hSPP1 Sense Strand Sequence	A549 0.1 nM Activity
14982	CDS	795	1324	GGACAGUUAUGAAACGAGUCAGCUA	10.69%
14983	CDS	797	1325	ACAGUUAUGAAACGAGUCAGCUGGA	54.58%
14984	CDS	798	1326	CAGUUAUGAAACGAGUCAGCUGGAA	33.9%
14985	CDS	846	1327	CCACAAGCAGUCCAGAUUAUAUAAA	24.1%
14986	CDS	850	1328	AAGCAGUCCAGAUUAUAUAAGCGGA	27.86%
14987	CDS	854	1329	AGUCCAGAUUAUAUAAGCGGAAAGA	24.29%
14988	CDS	855	1330	GUCCAGAUUAUAUAAGCGGAAAGCA	54.43%
14989	CDS	859	1331	AGAUUAUAUAAGCGGAAAGCCAAUA	71.49%
14990	CDS	860	1332	GAUUAUAUAAGCGGAAAGCCAAUGA	69.64%
14991	CDS	861	1333	AUUAUAUAAGCGGAAAGCCAAUGAA	38.82%
14992	CDS	862	1334	UUAUAUAAGCGGAAAGCCAAUGAUA	20.77%
14993	CDS	865	1335	UAUAAGCGGAAAGCCAAUGAUGAGA	21.79%
14994	CDS	866	1336	AUAAGCGGAAAGCCAAUGAUGAGAA	50.00%
14995	CDS	867	1337	UAAGCGGAAAGCCAAUGAUGAGAGA	11.67%
14996	CDS	870	1338	GCGGAAAGCCAAUGAUGAGAGCAAA	13.5%
14997	CDS	871	1339	CGGAAAGCCAAUGAUGAGAGCAAUA	15.49%
14998	CDS	872	1340	GGAAAGCCAAUGAUGAGAGCAAUGA	8.55%
14999	CDS	873	1341	GAAAGCCAAUGAUGAGAGCAAUGAA	12.12%
15000	CDS	875	1342	AAGCCAAUGAUGAGAGCAAUGAGCA	16.14%
15001	CDS	878	1343	CCAAUGAUGAGAGCAAUGAGCAUUA	31.71%
15002	CDS	879	1344	CAAUGAUGAGAGCAAUGAGCAUUCA	32.25%
15003	CDS	881	1345	AUGAUGAGAGCAAUGAGCAUUCCGA	6.97%
15004	CDS	883	1346	GAUGAGAGCAAUGAGCAUUCCGAUA	23.11%
15005	CDS	885	1347	UGAGAGCAAUGAGCAUUCCGAUGUA	5.53%
15006	CDS	890	1348	GCAAUGAGCAUUCCGAUGUGAUUGA	10.69%
15007	CDS	893	1349	AUGAGCAUUCCGAUGUGAUUGAUAA	4.12%
15008	CDS	894	1350	UGAGCAUUCCGAUGUGAUUGAUAGA	6.49%
15009	CDS	895	1351	GAGCAUUCCGAUGUGAUUGAUAGUA	29.12%
15010	CDS	897	1352	GCAUUCCGAUGUGAUUGAUAGUCAA	3.54%
15011	CDS	899	1353	AUUCCGAUGUGAUUGAUAGUCAGGA	6.05%
15012	CDS	901	1354	UCCGAUGUGAUUGAUAGUCAGGAAA	3.31%
15013	CDS	906	1355	UGUGAUUGAUAGUCAGGAACUUUCA	12.71%
15014	CDS	907	1356	GUGAUUGAUAGUCAGGAACUUUCCA	13.95%
15015	CDS	909	1357	GAUUGAUAGUCAGGAACUUUCCAAA	4.03%
15016	CDS	912	1358	UGAUAGUCAGGAACUUUCCAAAGUC	11.96%
15017	CDS	913	1359	GAUAGUCAGGAACUUUCCAAAGUCA	14.01%
15018	CDS	914	1360	AUAGUCAGGAACUUUCCAAAGUCAA	5.56%
15019	CDS	916	1361	AGUCAGGAACUUUCCAAAGUCAGCA	13.92%
15020	CDS	917	1362	GUCAGGAACUUUCCAAAGUCAGCCA	19.00%
15021	CDS	923	1363	AACUUUCCAAAGUCAGCCGUGAAUA	17.56%
15022	CDS	925	1364	CUUUCCAAAGUCAGCCGUGAAUUCA	19.58%
15023	CDS	926	1365	UUUCCAAAGUCAGCCGUGAAUUCCA	6.54%
15024	CDS	935	1366	UCAGCCGUGAAUUCCACAGCCAUGA	16.15%
15025	CDS	936	1367	CAGCCGUGAAUUCCACAGCCAUGAA	20.62%
15026	CDS	937	1368	AGCCGUGAAUUCCACAGCCAUGAAA	5.21%
15027	CDS	943	1369	GAAUUCCACAGCCAUGAAUUUCACA	31.14%
15028	CDS	944	1370	AAUUCCACAGCCAUGAAUUUCACAA	35.63%
15029	CDS	945	1371	AUUCCACAGCCAUGAAUUUCACAGA	23.96%
15030	CDS	946	1372	UUCCACAGCCAUGAAUUUCACAGCA	15.20%
15031	CDS	947	1373	UCCACAGCCAUGAAUUUCACAGCCA	19.45%
15032	CDS	950	1374	ACAGCCAUGAAUUUCACAGCCAUGA	25.74%
15033	CDS	952	1375	AGCCAUGAAUUUCACAGCCAUGAAA	2.59%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hSPP1 Sense Strand Sequence	A549 0.1 nM Activity
15034	CDS	953	1376	GCCAUGAAUUUCACAGCCAUGAAGA	6.00%
15035	CDS	954	1377	CCAUGAAUUUCACAGCCAUGAAGAA	4.60%
15036	CDS	956	1378	AUGAAUUUCACAGCCAUGAAGAUAA	9.20%
15037	CDS	957	1379	UGAAUUUCACAGCCAUGAAGAUAUA	10.84%
15038	CDS	958	1380	GAAUUUCACAGCCAUGAAGAUAUGA	40.20%
15039	CDS	959	1381	AAUUUCACAGCCAUGAAGAUAUGCA	37.25%
15040	CDS	960	1382	AUUUCACAGCCAUGAAGAUAUGCUA	8.21%
15041	CDS	961	1383	UUUCACAGCCAUGAAGAUAUGCUGA	12.01%
15042	CDS	964	1384	CACAGCCAUGAAGAUAUGCUGGUUA	12.25%
15043	CDS	983	1385	UGGUUGUAGACCCCAAAAGUAAGGA	19.65%
15044	CDS	984	1386	GGUUGUAGACCCCAAAAGUAAGGAA	28.19%
15045	CDS	985	1387	GUUGUAGACCCCAAAAGUAAGGAAA	17.92%
15046	CDS	986	1388	UUGUAGACCCCAAAAGUAAGGAAGA	7.94%
15047	CDS	987	1389	UGUAGACCCCAAAAGUAAGGAAGAA	15.09%
15048	CDS	988	1390	GUAGACCCCAAAAGUAAGGAAGAAA	20.01%
15049	CDS	989	1391	UAGACCCCAAAAGUAAGGAAGAAGA	7.25%
15050	CDS	990	1392	AGACCCCAAAAGUAAGGAAGAAGAA	12.42%
15051	CDS	995	1393	CCAAAAGUAAGGAAGAAGAUAAACA	8.96%
15052	CDS	996	1394	CAAAAGUAAGGAAGAAGAUAAACAA	6.85%
15053	CDS	997	1395	AAAAGUAAGGAAGAAGAUAAACACA	14.15%
15054	CDS	998	1396	AAAGUAAGGAAGAAGAUAAACACCA	12.32%
15055	CDS	999	1397	AAGUAAGGAAGAAGAUAAACACCUA	8.83%
15056	CDS	1001	1398	GUAAGGAAGAAGAUAAACACCUGAA	15.09%
15057	CDS	1002	1399	UAAGGAAGAAGAUAAACACCUGAAA	4.91%
15058	CDS	1007	1400	AAGAAGAUAAACACCUGAAAUUUCA	1.43%
15059	CDS	1008	1401	AGAAGAUAAACACCUGAAAUUUCGA	3.51%
15060	CDS	1009	1402	GAAGAUAAACACCUGAAAUUUCGUA	15.12%
15061	CDS	1010	1403	AAGAUAAACACCUGAAAUUUCGUAA	28.56%
15062	CDS	1013	1404	AUAAACACCUGAAAUUUCGUAUUUA	5.74%
15063	CDS	1015	1405	AAACACCUGAAAUUUCGUAUUUCUA	13.01%
15064	CDS	1024	1406	AAAUUUCGUAUUUCUCAUGAAUUAA	15.54%
15065	CDS	1030	1407	CGUAUUUCUCAUGAAUUAGAUAGUA	9.47%
15066	CDS	1031	1408	GUAUUUCUCAUGAAUUAGAUAGUGA	30.03%
15067	CDS	1032	1409	UAUUUCUCAUGAAUUAGAUAGUGCA	5.31%
15068	CDS	1036	1410	UCUCAUGAAUUAGAUAGUGCAUCUA	9.74%
15069	CDS	1037	1411	CUCAUGAAUUAGAUAGUGCAUCUUA	10.78%
15070	CDS	1038	1412	UCAUGAAUUAGAUAGUGCAUCUUCA	91.87%
15071	CDS	1039	1413	CAUGAAUUAGAUAGUGCAUCUUCUA	93.82%
15072	CDS	1040	1414	AUGAAUUAGAUAGUGCAUCUUCUGA	96.06%
15073	CDS	1041	1415	UGAAUUAGAUAGUGCAUCUUCUGAA	94.91%
15074	CDS	1042	1416	GAAUUAGAUAGUGCAUCUUCUGAGA	97.91%
15075	CDS	1043	1417	AAUUAGAUAGUGCAUCUUCUGAGGA	93.76%
15076	CDS	1044	1418	AUUAGAUAGUGCAUCUUCUGAGGUA	103.92%
15077	CDS	1045	1419	UUAGAUAGUGCAUCUUCUGAGGUCA	95.85%
15078	CDS/3UTR	1052	1420	GUGCAUCUUCUGAGGUCAAUUAAAA	93.83%
15079	CDS/3UTR	1053	1421	UGCAUCUUCUGAGGUCAAUUAAAAA	90.69%
15080	CDS/3UTR	1054	1422	GCAUCUUCUGAGGUCAAUUAAAAGA	101.49%
15081	CDS/3UTR	1055	1423	CAUCUUCUGAGGUCAAUUAAAAGGA	110.27%
15082	CDS/3UTR	1056	1424	AUCUUCUGAGGUCAAUUAAAAGGAA	99.36%
15083	CDS/3UTR	1057	1425	UCUUCUGAGGUCAAUUAAAAGGAGA	95.31%
15084	CDS/3UTR	1058	1426	CUUCUGAGGUCAAUUAAAAGGAGAA	15.55%
15085	3UTR	1081	1427	AAAAAAUACAAUUUCUCACUUUGCA	3.59%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hSPP1 Sense Strand Sequence	A549 0.1 nM Activity
15086	3UTR	1083	1428	AAAAUACAAUUUCUCACUUUGCAUU	3.46%
15087	3UTR	1086	1429	AUACAAUUUCUCACUUUGCAUUUAG	2.37%
15088	3UTR	1087	1430	UACAAUUUCUCACUUUGCAUUUAGU	3.54%
15089	3UTR	1088	1431	ACAAUUUCUCACUUUGCAUUUAGUC	2.85%
15090	3UTR	1089	1432	CAAUUUCUCACUUUGCAUUUAGUCA	2.35%
15091	3UTR	1093	1433	UUCUCACUUUGCAUUUAGUCAAAAG	1.38%
15092	3UTR	1125	1434	GCUUUAUAGCAAAAUGAAAGAGAAC	4.11%
15093	3UTR	1127	1435	UUUAUAGCAAAAUGAAAGAGAACAU	3.91%
15094	3UTR	1128	1436	UUAUAGCAAAAUGAAAGAGAACAUG	3.59%
15095	3UTR	1147	1437	AACAUGAAAUGCUUCUUUCUCAGUU	1.80%
15096	3UTR	1148	1438	ACAUGAAAUGCUUCUUUCUCAGUUU	2.17%
15097	3UTR	1150	1439	AUGAAAUGCUUCUUUCUCAGUUUAU	2.93%
15098	3UTR	1153	1440	AAAUGCUUCUUUCUCAGUUUAUUGG	2.18%
15099	3UTR	1154	1441	AAUGCUUCUUUCUCAGUUUAUUGGU	3.92%
15100	3UTR	1156	1442	UGCUUCUUUCUCAGUUUAUUGGUUG	4.08%
15101	3UTR	1157	1443	GCUUCUUUCUCAGUUUAUUGGUUGA	1.74%
15102	3UTR	1158	1444	CUUCUUUCUCAGUUUAUUGGUUGAA	4.74%
15103	3UTR	1159	1445	UUCUUUCUCAGUUUAUUGGUUGAAU	2.65%
15104	3UTR	1168	1446	AGUUUAUUGGUUGAAUGUGUAUCUA	2.57%
15105	3UTR	1178	1447	UUGAAUGUGUAUCUAUUUGAGUCUG	3.76%
15106	3UTR	1179	1448	UGAAUGUGUAUCUAUUUGAGUCUGG	2.91%
15107	3UTR	1183	1449	UGUGUAUCUAUUUGAGUCUGGAAAU	0.62%
15108	3UTR	1184	1450	GUGUAUCUAUUUGAGUCUGGAAAUA	2.45%
15109	3UTR	1186	1451	GUAUCUAUUUGAGUCUGGAAAUAAC	2.18%
15110	3UTR	1191	1452	UAUUUGAGUCUGGAAAUAACUAAUG	2.44%
15111	3UTR	1218	1453	UUUGAUAAUUAGUUUAGUUUGUGGC	19.35%
15112	3UTR	1219	1454	UUGAUAAUUAGUUUAGUUUGUGGCU	6.19%
15113	3UTR	1222	1455	AUAAUUAGUUUAGUUUGUGGCUUCA	3.25%
15114	3UTR	1224	1456	AAUUAGUUUAGUUUGUGGCUUCAUG	2.47%
15115	3UTR	1225	1457	AUUAGUUUAGUUUGUGGCUUCAUGG	2.28%
15116	3UTR	1226	1458	UUAGUUUAGUUUGUGGCUUCAUGGA	3.40%
15117	3UTR	1227	1459	UAGUUUAGUUUGUGGCUUCAUGGAA	4.12%
15118	3UTR	1244	1460	UCAUGGAAACUCCCUGUAAACUAAA	2.63%
15119	3UTR	1245	1461	CAUGGAAACUCCCUGUAAACUAAAA	2.20%
15120	3UTR	1246	1462	AUGGAAACUCCCUGUAAACUAAAAG	3.56%
15121	3UTR	1247	1463	UGGAAACUCCCUGUAAACUAAAAGC	3.73%
15122	3UTR	1248	1464	GGAAACUCCCUGUAAACUAAAAGCU	2.43%
15123	3UTR	1249	1465	GAAACUCCCUGUAAACUAAAAGCUU	2.28%
15124	3UTR	1251	1466	AACUCCCUGUAAACUAAAAGCUUCA	5.40%
15125	3UTR	1253	1467	CUCCCUGUAAACUAAAAGCUUCAGG	8.21%
15126	3UTR	1286	1468	UAUGUUCAUUCUAUAGAAGAAAUGC	3.17%
15127	3UTR	1294	1469	UUCUAUAGAAGAAAUGCAAACUAUC	2.45%
15128	3UTR	1295	1470	UCUAUAGAAGAAAUGCAAACUAUCA	3.97%
15129	3UTR	1296	1471	CUAUAGAAGAAAUGCAAACUAUCAC	3.86%
15130	3UTR	1297	1472	UAUAGAAGAAAUGCAAACUAUCACU	1.84%
15131	3UTR	1299	1473	UAGAAGAAAUGCAAACUAUCACUGU	2.53%
15132	3UTR	1302	1474	AAGAAAUGCAAACUAUCACUGUAUU	2.25%
15133	3UTR	1303	1475	AGAAAUGCAAACUAUCACUGUAUUU	3.32%
15134	3UTR	1357	1476	AUUUAUGUAGAAGCAAACAAAAUAC	1.86%
15135	3UTR	1465	1477	UAUCUUUUUGUGGUGUGAAUAAAUC	3.40%
15136	3UTR	1466	1478	AUCUUUUUGUGGUGUGAAUAAAUCU	3.49%
15137	3UTR	1467	1479	UCUUUUUGUGGUGUGAAUAAAUCUU	3.03%

Target Gene Duplex ID	Gene Region	Ref Pos	SEQ ID NO	hSPP1 Sense Strand Sequence	A549 0.1 nM Activity
15138	3UTR	1468	1480	CUUUUUGUGGUGUGAAUAAAUCUUU	3.62%
15139	3UTR	1496	1481	CUUGAAUGUAAUAAGAAUUUGGUGG	61.48%
15140	3UTR	1497	1482	UUGAAUGUAAUAAGAAUUUGGUGGU	71.54%
15141	3UTR	1504	1483	UAAUAAGAAUUUGGUGGUGUCAAUU	58.54%
15142	3UTR	1511	1484	AAUUUGGUGGUGUCAAUUGCUUAUU	56.93%
15143	3UTR	1512	1485	AUUUGGUGGUGUCAAUUGCUUAUUU	81.22%
15144	3UTR	1513	1486	UUUGGUGGUGUCAAUUGCUUAUUUG	59.16%
15145	3UTR	1514	1487	UUGGUGGUGUCAAUUGCUUAUUUGU	59.46%
15146	3UTR	1540	1488	UUCCCACGGUUGUCCAGCAAUUAAU	67.40%

Table 10: hCTGF sd-rxRNA

Target Gene Duplex ID	CTGF Single Strand ID	sd-rxRNA sequence	SEQ ID NO
17356	17007	A.mC.A.mU.mU.A.A.mC.mU.mC.A.mU.A.Chl	1489
	17009	P.mU.A.fU.G.A.G.fU.fU.A.A.fU.G.fU*fC*fU*fC*fU*fC*A	1490
17357	17008	G.A.mC.A.mU.mU.A.A.mC.mU.mC.A.mU.A.Chl	1491
	17009	P.mU.A.fU.G.A.G.fU.fU.A.A.fU.G.fU*fC*fU*fC*fU*fC*A	1492
17358	17010	mU.G.A.A.G.A.A.mU.G.mU.mU.A.A.Chl	1493
	17012	P.mU.fU.A.A.fC.A.fU.fU.fC.fU.fU.fC.A*A*A*fC*fC*A*G	1494
17359	17011	mU.mU.G.A.A.G.A.A.mU.G.mU.mU.A.A.Chl	1495
	17012	P.mU.fU.A.A.fC.A.fU.fU.fC.fU.fU.fC.A*A*A*fC*fC*A*G	1496
17360	17013	G.A.mU.A.G.mC.A.mU.mC.mU.mU.A.A.Chl	1497
	17015	P.mU.fU.A.A.G.A.fU.G.fC.fU.A.fU.fC*fU*G*A*fU*G*A	1498
17361	17014	A.G.A.mU.A.G.mC.A.mU.mC.mU.mU.A.A.Chl	1499
	17015	P.mU.fU.A.A.G.A.fU.G.fC.fU.A.fU.fC*fU*G*A*fU*G*A	1500
17362	17016	mU.G.A.A.G.mU.G.mU.A.A.mU.mU.A.Chl	1501
	17017	P.mU.A.A.fU.fU.A.fC.A.fC.fU.fU.fC.A*A*A*fU*A*G*C	1502
17363	17018	A.A.mU.mU.G.A.G.A.A.G.G.A.A.Chl	1503
	17019	P.mU.fU.fC.fC.fU.fU.fC.fU.fC.A.A.fU.fU*A*fC*A*fC*fU*U	1504
17364	17020	mU.mU.G.A.G.A.A.G.G.A.A.A.A.Chl	1505
	17021	P.mU.fU.fU.fU.fC.fC.fU.fU.fC.fU.fC.A.A*fU*fU*A*fC*A*C	1506
17365	17022	mC.A.mU.mU.mC.mU.G.A.mU.mU.mC.G.A.Chl	1507
	17023	P.mU.fC.G.A.A.fU.fC.A.G.A.A.fU.G*fU*fC*A*G*A*G	1508
17366	17024	mU.mU.mC.mU.G.A.mU.mU.mC.G.A.A.A.Chl	1509
	17025	P.mU.fU.fU.fC.G.A.A.fU.fC.A.G.A.A*fU*G*fU*fC*A*G	1510
17367	17026	mC.mU.G.mU.mC.G.A.mU.mU.A.G.A.A.Chl	1511
	17027	P.mU.fU.fC.fU.A.A.fU.fC.G.A.fC.A.G*G*A*fU*fU*fC*C	1512
17368	17028	mU.mU.mU.G.mC.mC.mU.G.mU.A.A.mC.A.Chl	1513
	17030	P.mU.G.fU.fU.A.fC.A.G.G.fC.A.A.A*fU*fU*fC*A*fC*U	1514
17369	17029	A.mU.mU.mU.G.mC.mC.mU.G.mU.A.A.mC.A.Chl	1515
	17030	P.mU.G.fU.fU.A.fC.A.G.G.fC.A.A.A*fU*fU*fC*A*fC*U	1516
17370	17031	A.mC.A.A.G.mC.mC.A.G.A.mU.mU.A.Chl	1517
	17033	P.mU.A.A.fU.fC.fU.G.G.fC.fU.fU.G.fU*fU*A*fC*A*G*G	1518
17371	17032	"A.A.mC.A.A.G.mC.mC.A.G.A.mU.mU.A.Chl	1519
	17033	P.mU.A.A.fU.fC.fU.G.G.fC.fU.fU.G.fU*fU*A*fC*A*G*G	1520
17372	17034	mC.A.G.mU.mU.mU.A.mU.mU.mU.G.mU.A.Chl	1521
	17035	P.mU.A.fC.A.A.A.fU.A.A.A.fC.fU.G*fU*fC*fC*G*A*A	1522

17373	17036	mU.G.mU.mU.G.A.G.A.G.mU.G.mU.A.Chl	1523
	17038	P.mU.A.fC.A.fC.fU.fC.fU.fC.A.A.fC.A*A*A*fU*A*A*A	1524
17374	17037	mU.mU.G.mU.mU.G.A.G.A.G.mU.G.mU.A.Chl	1525
	17038	P.mU.A.fC.A.fC.fU.fC.fU.fC.A.A.fC.A*A*A*fU*A*A*A	1526
17375	17039	mU.G.mC.A.mC.mC.mU.mU.mU.mC.mU.A.A.Chl	1527
	17041	P.mU.fU.A.G.A.A.A.G.G.fU.G.fC.A*A*A*fC*A*fU*G	1528
17376	17040	mU.mU.G.mC.A.mC.mC.mU.mU.mU.mC.mU.A.A.Chl	1529
	17041	P.mU.fU.A.G.A.A.A.G.G.fU.G.fC.A*A*A*fC*A*fU*G	1530
17377	17042	mU.mU.G.A.G.mC.mU.mU.mU.mC.mU.G.A.Chl	1531
	17043	P.mU.fC.A.G.A.A.A.G.fC.fU.fC.A.A*A*fC*fU*fU*G*A	1532
17378	17044	mU.G.A.G.A.G.mU.G.mU.G.A.mC.A.Chl	1533
	17045	P.mU.G.fU.fC.A.fC.A.fC.fU.fC.fU.fC.A*A*fC*A*A*A*U	1534
17379	17046	A.G.mU.G.mU.G.A.mC.mC.A.A.A.A.Chl	1535
	17048	P.mU.fU.fU.fU.G.G.fU.fC.A.fC.A.fC.fU*fC*fU*fC*A*A*C	1536
17380	17047	G.A.G.mU.G.mU.G.A.mC.mC.A.A.A.A.Chl	1537
	17048	P.mU.fU.fU.fU.G.G.fU.fC.A.fC.A.fC.fU*fC*fU*fC*A*A*C	1538
17381	17049	G.mU.G.mU.G.A.mC.mC.A.A.A.A.A.Chl	1539
	17050	P.mU.fU.fU.fU.fU.G.G.fU.fC.A.fC.A.fC*fU*fC*fU*fC*A*A	1540
17382	17051	mU.G.mU.G.A.mC.mC.A.A.A.A.G.A.Chl	1541
	17053	P.mU.fC.fU.fU.fU.fU.G.G.fU.fC.A.fC.A*fC*fU*fC*fU*fC*A	1542
17383	17052	G.mU.G.mU.G.A.mC.mC.A.A.A.A.G.A.Chl	1543
	17053	P.mU.fC.fU.fU.fU.fU.G.G.fU.fC.A.fC.A*fC*fU*fC*fU*fC*A	1544
17384	17054	G.mU.G.A.mC.mC.A.A.A.A.G.mU.A.Chl	1545
	17055	P.mU.A.fC.fU.fU.fU.fU.G.G.fU.fC.A.fC*A*fC*fU*fC*fU*C	1546
17385	17056	G.A.mC.mC.A.A.A.A.G.mU.mU.A.A.Chl	1547
	17057	P.mU.fU.A.A.fC.fU.fU.fU.fU.G.G.fU.fC*A*fC*A*fC*fU*C	1548
17386	17058	G.mC.A.mC.mC.mU.mU.mU.mC.mU.A.G.A.Chl	1549
	17059	P.mU.fC.fU.A.G.A.A.A.G.G.fU.G.fC*A*A*A*fC*A*U	1550
17387	17060	mC.mC.mU.mU.mU.mC.mU.A.G.mU.mU.G.A.Chl	1551
	17061	P.mU.fC.A.A.fC.fU.A.G.A.A.A.G.G*fU*G*fC*A*A*A	1552

Table 11: Inhibition of gene expression with hCTGF ori sequences

Target Gene Duplex Name	Gene Region	Ref Pos	SEQ ID NO	CTGF Sense sequence	% Expression (0.1 nM)
14542	CDS	774	1553	UUUGGCCCAGACCCAACUAUGAUUA	96%
14543	CDS	776	1554	UGGCCCAGACCCAACUAUGAUUAGA	94%
14544	CDS	785	1555	CCCAACUAUGAUUAGAGCCAACUGA	55%
14545	CDS	786	1556	CCAACUAUGAUUAGAGCCAACUGCA	89%
14546	CDS	934	1557	CUUGCGAAGCUGACCUGGAAGAGAA	63%
14547	CDS	938	1558	CGAAGCUGACCUGGAAGAGAACAUA	70%
14548	CDS	940	1559	AAGCUGACCUGGAAGAGAACAUUAA	65%
14549	CDS	941	1560	AGCUGACCUGGAAGAGAACAUUAAA	81%
14550	CDS	943	1561	CUGACCUGGAAGAGAACAUUAAGAA	85%
14551	CDS	944	1562	UGACCUGGAAGAGAACAUUAAGAAA	61%
14552	CDS	945	1563	GACCUGGAAGAGAACAUUAAGAAGA	73%
14553	CDS	983	1564	CCGUACUCCCAAAAUCUCCAAGCCA	86%
14554	CDS	984	1565	CGUACUCCCAAAAUCUCCAAGCCUA	64%
14555	CDS	985	1566	GUACUCCCAAAAUCUCCAAGCCUAA	71%
14556	CDS	986	1567	UACUCCCAAAAUCUCCAAGCCUAUA	71%
14557	CDS	987	1568	ACUCCCAAAAUCUCCAAGCCUAUCA	84%
14558	CDS	988	1569	CUCCCAAAAUCUCCAAGCCUAUCAA	64%

Target Gene Duplex Name	Gene Region	Ref Pos	SEQ ID NO	CTGF Sense sequence	% Expression (0.1 nM)
14559	CDS	989	1570	UCCCAAAAUCUCCAAGCCUAUCAAA	64%
14560	CDS	990	1571	CCCAAAAUCUCCAAGCCUAUCAAGA	87%
14561	CDS	1002	1572	AAGCCUAUCAAGUUUGAGCUUUCUA	46%
14562	CDS	1003	1573	AGCCUAUCAAGUUUGAGCUUUCUGA	30%
14563	CDS	1004	1574	GCCUAUCAAGUUUGAGCUUUCUGGA	63%
14564	CDS	1008	1575	AUCAAGUUUGAGCUUUCUGGCUGCA	77%
14565	CDS	1025	1576	UGGCUGCACCAGCAUGAAGACAUAA	96%
14566	CDS	1028	1577	CUGCACCAGCAUGAAGACAUACCGA	79%
14567	CDS	1029	1578	UGCACCAGCAUGAAGACAUACCGAA	58%
14568	CDS	1033	1579	CCAGCAUGAAGACAUACCGAGCUAA	59%
14569	CDS	1035	1580	AGCAUGAAGACAUACCGAGCUAAAA	76%
14570	CDS	1036	1581	GCAUGAAGACAUACCGAGCUAAAUA	71%
14571	CDS	1050	1582	CGAGCUAAAUUCUGUGGAGUAUGUA	73%
14572	CDS	1051	1583	GAGCUAAAUUCUGUGGAGUAUGUAA	72%
14573	CDS	1053	1584	GCUAAAUUCUGUGGAGUAUGUACCA	87%
14574	CDS	1054	1585	CUAAAUUCUGUGGAGUAUGUACCGA	83%
14575	CDS	1135	1586	CUGACGGCGAGGUCAUGAAGAAGAA	77%
14576	CDS	1138	1587	ACGGCGAGGUCAUGAAGAAGAACAA	72%
14577	CDS	1139	1588	CGGCGAGGUCAUGAAGAAGAACAUA	85%
14578	CDS	1143	1589	GAGGUCAUGAAGAAGAACAUGAUGA	83%
14579	CDS	1145	1590	GGUCAUGAAGAAGAACAUGAUGUUA	91%
14580	CDS	1148	1591	CAUGAAGAAGAACAUGAUGUUCAUA	92%
14581	CDS	1157	1592	GAACAUGAUGUUCAUCAAGACCUGA	84%
14582	CDS	1161	1593	AUGAUGUUCAUCAAGACCUGUGCCA	92%
14583	CDS	1203	1594	GGAGACAAUGACAUCUUUGAAUCGA	62%
14584	CDS	1204	1595	GAGACAAUGACAUCUUUGAAUCGCA	56%
14585	CDS	1205	1596	AGACAAUGACAUCUUUGAAUCGCUA	30%
14586	CDS	1206	1597	GACAAUGACAUCUUUGAAUCGCUGA	47%
14587	CDS	1207	1598	ACAAUGACAUCUUUGAAUCGCUGUA	29%
14588	CDS	1208	1599	CAAUGACAUCUUUGAAUCGCUGUAA	50%
14589	CDS	1209	1600	AAUGACAUCUUUGAAUCGCUGUACA	39%
14590	CDS	1210	1601	AUGACAUCUUUGAAUCGCUGUACUA	44%
14591	CDS	1211	1602	UGACAUCUUUGAAUCGCUGUACUAA	39%
14592	CDS	1212	1603	GACAUCUUUGAAUCGCUGUACUACA	55%
14593	CDS	1213	1604	ACAUCUUUGAAUCGCUGUACUACAA	59%
14594	CDS	1216	1605	UCUUUGAAUCGCUGUACUACAGGAA	80%
14595	CDS	1217	1606	CUUUGAAUCGCUGUACUACAGGAAA	80%
14596	CDS	1223	1607	AUCGCUGUACUACAGGAAGAUGUAA	59%
14597	CDS	1224	1608	UCGCUGUACUACAGGAAGAUGUACA	62%
14598	CDS	1239	1609	AAGAUGUACGGAGACAUGGCAUGAA	59%
14599	CDS	1253	1610	CAUGGCAUGAAGCCAGAGAGUGAGA	65%
14600	3UTR	1266	1611	CAGAGAGUGAGAGACAUUAACUCAA	43%
14601	3UTR	1267	1612	AGAGAGUGAGAGACAUUAACUCAUA	25%
14602	3UTR	1268	1613	GAGAGUGAGAGACAUUAACUCAUUA	33%
14603	3UTR	1269	1614	AGAGUGAGAGACAUUAACUCAUUAA	42%
14604	3UTR	1270	1615	GAGUGAGAGACAUUAACUCAUUAGA	28%
14605	3UTR	1271	1616	AGUGAGAGACAUUAACUCAUUAGAA	34%
14606	3UTR	1272	1617	GUGAGAGACAUUAACUCAUUAGACA	30%
14607	3UTR	1273	1618	UGAGAGACAUUAACUCAUUAGACUA	33%
14608	3UTR	1275	1619	AGAGACAUUAACUCAUUAGACUGGA	42%
14609	3UTR	1277	1620	AGACAUUAACUCAUUAGACUGGAAA	25%
14610	3UTR	1278	1621	GACAUUAACUCAUUAGACUGGAACA	31%
14611	3UTR	1279	1622	ACAUUAACUCAUUAGACUGGAACUA	32%

Target Gene Duplex Name	Gene Region	Ref Pos	SEQ ID NO	CTGF Sense sequence	% Expression (0.1 nM)
14612	3UTR	1281	1623	AUUAACUCAUUAGACUGGAACUUGA	23%
14613	3UTR	1284	1624	AACUCAUUAGACUGGAACUUGAACA	39%
14614	3UTR	1285	1625	ACUCAUUAGACUGGAACUUGAACUA	30%
14615	3UTR	1286	1626	CUCAUUAGACUGGAACUUGAACUGA	43%
14616	3UTR	1287	1627	UCAUUAGACUGGAACUUGAACUGAA	26%
14617	3UTR	1291	1628	UAGACUGGAACUUGAACUGAUUCAA	33%
14618	3UTR	1293	1629	GACUGGAACUUGAACUGAUUCACAA	43%
14619	3UTR	1294	1630	ACUGGAACUUGAACUGAUUCACAUA	28%
14620	3UTR	1295	1631	CUGGAACUUGAACUGAUUCACAUCA	41%
14621	3UTR	1296	1632	UGGAACUUGAACUGAUUCACAUCUA	34%
14622	3UTR	1298	1633	GAACUUGAACUGAUUCACAUCUCAA	31%
14623	3UTR	1299	1634	AACUUGAACUGAUUCACAUCUCAUA	31%
14624	3UTR	1300	1635	ACUUGAACUGAUUCACAUCUCAUUA	33%
14625	3UTR	1301	1636	CUUGAACUGAUUCACAUCUCAUUUA	28%
14626	3UTR	1326	1637	UCCGUAAAAAUGAUUUCAGUAGCAA	30%
14627	3UTR	1332	1638	AAAAUGAUUUCAGUAGCACAAGUUA	28%
14628	3UTR	1395	1639	CCCAAUUCAAAACAUUGUGCCAUGA	63%
14629	3UTR	1397	1640	CAAUUCAAAACAUUGUGCCAUGUCA	39%
14630	3UTR	1402	1641	CAAAACAUUGUGCCAUGUCAAACAA	34%
14631	3UTR	1408	1642	AUUGUGCCAUGUCAAACAAAUAGUA	33%
14632	3UTR	1409	1643	UUGUGCCAUGUCAAACAAAUAGUCA	33%
14633	3UTR	1412	1644	UGCCAUGUCAAACAAAUAGUCUAUA	36%
14634	3UTR	1416	1645	AUGUCAAACAAAUAGUCUAUCAACA	30%
14635	3UTR	1435	1646	UCAACCCCAGACACUGGUUUGAAGA	39%
14636	3UTR	1436	1647	CAACCCCAGACACUGGUUUGAAGAA	47%
14637	3UTR	1438	1648	ACCCCAGACACUGGUUUGAAGAAUA	45%
14638	3UTR	1439	1649	CCCCAGACACUGGUUUGAAGAAUGA	40%
14639	3UTR	1442	1650	CAGACACUGGUUUGAAGAAUGUUAA	21%
14640	3UTR	1449	1651	UGGUUUGAAGAAUGUUAAGACUUGA	22%
14641	3UTR	1453	1652	UUGAAGAAUGUUAAGACUUGACAGA	24%
14642	3UTR	1454	1653	UGAAGAAUGUUAAGACUUGACAGUA	37%
14643	3UTR	1462	1654	GUUAAGACUUGACAGUGGAACUACA	20%
14644	3UTR	1470	1655	UUGACAGUGGAACUACAUUAGUACA	30%
14645	3UTR	1471	1656	UGACAGUGGAACUACAUUAGUACAA	43%
14646	3UTR	1474	1657	CAGUGGAACUACAUUAGUACACAGA	36%
14647	3UTR	1475	1658	AGUGGAACUACAUUAGUACACAGCA	38%
14648	3UTR	1476	1659	GUGGAACUACAUUAGUACACAGCAA	35%
14649	3UTR	1477	1660	UGGAACUACAUUAGUACACAGCACA	34%
14650	3UTR	1478	1661	GGAACUACAUUAGUACACAGCACCA	33%
14651	3UTR	1479	1662	GAACUACAUUAGUACACAGCACCAA	39%
14652	3UTR	1480	1663	AACUACAUUAGUACACAGCACCAGA	27%
14653	3UTR	1481	1664	ACUACAUUAGUACACAGCACCAGAA	29%
14654	3UTR	1482	1665	CUACAUUAGUACACAGCACCAGAAA	38%
14655	3UTR	1483	1666	UACAUUAGUACACAGCACCAGAAUA	28%
14656	3UTR	1484	1667	ACAUUAGUACACAGCACCAGAAUGA	31%
14657	3UTR	1486	1668	AUUAGUACACAGCACCAGAAUGUAA	26%
14658	3UTR	1487	1669	UUAGUACACAGCACCAGAAUGUAUA	31%
14659	3UTR	1489	1670	AGUACACAGCACCAGAAUGUAUAUA	35%
14660	3UTR	1490	1671	GUACACAGCACCAGAAUGUAUAUUA	34%
14661	3UTR	1497	1672	GCACCAGAAUGUAUAUUAAGGUGUA	32%
14662	3UTR	1503	1673	GAAUGUAUAUUAAGGUGUGGCUUUA	42%
14663	3UTR	1539	1674	AGGGUACCAGCAGAAAGGUUAGUAA	28%
14664	3UTR	1543	1675	UACCAGCAGAAAGGUUAGUAUCAUA	29%

Target Gene Duplex Name	Gene Region	Ref Pos	SEQ ID NO	CTGF Sense sequence	% Expression (0.1 nM)
14665	3UTR	1544	1676	ACCAGCAGAAAGGUUAGUAUCAUCA	33%
14666	3UTR	1548	1677	GCAGAAAGGUUAGUAUCAUCAGAUA	34%
14667	3UTR	1557	1678	UUAGUAUCAUCAGAUAGCAUCUUAA	22%
14668	3UTR	1576	1679	UCUUAUACGAGUAAUAUGCCUGCUA	48%
14669	3UTR	1577	1680	CUUAUACGAGUAAUAUGCCUGCUAA	31%
14670	3UTR	1579	1681	UAUACGAGUAAUAUGCCUGCUAUUA	43%
14671	3UTR	1580	1682	AUACGAGUAAUAUGCCUGCUAUUUA	39%
14672	3UTR	1581	1683	UACGAGUAAUAUGCCUGCUAUUUGA	33%
14673	3UTR	1582	1684	ACGAGUAAUAUGCCUGCUAUUUGAA	40%
14674	3UTR	1584	1685	GAGUAAUAUGCCUGCUAUUUGAAGA	38%
14675	3UTR	1585	1686	AGUAAUAUGCCUGCUAUUUGAAGUA	24%
14676	3UTR	1586	1687	GUAAUAUGCCUGCUAUUUGAAGUGA	34%
14677	3UTR	1587	1688	UAAUAUGCCUGCUAUUUGAAGUGUA	26%
14678	3UTR	1589	1689	AUAUGCCUGCUAUUUGAAGUGUAAA	26%
14679	3UTR	1591	1690	AUGCCUGCUAUUUGAAGUGUAAUUA	25%
14680	3UTR	1596	1691	UGCUAUUUGAAGUGUAAUUGAGAAA	36%
14681	3UTR	1599	1692	UAUUUGAAGUGUAAUUGAGAAGGAA	22%
14682	3UTR	1600	1693	AUUUGAAGUGUAAUUGAGAAGGAAA	22%
14683	3UTR	1601	1694	UUUGAAGUGUAAUUGAGAAGGAAAA	19%
14684	3UTR	1609	1695	GUAAUUGAGAAGGAAAAUUUUAGCA	53%
14685	3UTR	1610	1696	UAAUUGAGAAGGAAAAUUUUAGCGA	55%
14686	3UTR	1611	1697	AAUUGAGAAGGAAAAUUUUAGCGUA	20%
14687	3UTR	1612	1698	AUUGAGAAGGAAAAUUUUAGCGUGA	23%
14688	3UTR	1613	1699	UUGAGAAGGAAAAUUUUAGCGUGCA	37%
14689	3UTR	1614	1700	UGAGAAGGAAAAUUUUAGCGUGCUA	31%
14690	3UTR	1619	1701	AGGAAAAUUUUAGCGUGCUCACUGA	46%
14691	3UTR	1657	1702	CCAGUGACAGCUAGGAUGUGCAUUA	42%
14692	3UTR	1661	1703	UGACAGCUAGGAUGUGCAUUCUCCA	39%
14693	3UTR	1682	1704	UCCAGCCAUCAAGAGACUGAGUCAA	53%
14694	3UTR	1685	1705	AGCCAUCAAGAGACUGAGUCAAGUA	71%
14695	3UTR	1686	1706	GCCAUCAAGAGACUGAGUCAAGUUA	54%
14696	3UTR	1687	1707	CCAUCAAGAGACUGAGUCAAGUUGA	71%
14697	3UTR	1688	1708	CAUCAAGAGACUGAGUCAAGUUGUA	74%
14698	3UTR	1689	1709	AUCAAGAGACUGAGUCAAGUUGUUA	61%
14699	3UTR	1690	1710	UCAAGAGACUGAGUCAAGUUGUUCA	59%
14700	3UTR	1691	1711	CAAGAGACUGAGUCAAGUUGUUCCA	73%
14701	3UTR	1692	1712	AAGAGACUGAGUCAAGUUGUUCCUA	78%
14702	3UTR	1693	1713	AGAGACUGAGUCAAGUUGUUCCUUA	60%
14703	3UTR	1695	1714	AGACUGAGUCAAGUUGUUCCUUAAA	63%
14704	3UTR	1696	1715	GACUGAGUCAAGUUGUUCCUUAAGA	92%
14705	3UTR	1697	1716	ACUGAGUCAAGUUGUUCCUUAAGUA	74%
14706	3UTR	1707	1717	GUUGUUCCUUAAGUCAGAACAGCAA	70%
14707	3UTR	1724	1718	AACAGCAGACUCAGCUCUGACAUUA	69%
14708	3UTR	1725	1719	ACAGCAGACUCAGCUCUGACAUUCA	67%
14709	3UTR	1726	1720	CAGCAGACUCAGCUCUGACAUUCUA	71%
14710	3UTR	1727	1721	AGCAGACUCAGCUCUGACAUUCUGA	73%
14711	3UTR	1728	1722	GCAGACUCAGCUCUGACAUUCUGAA	60%
14712	3UTR	1729	1723	CAGACUCAGCUCUGACAUUCUGAUA	72%
14713	3UTR	1732	1724	ACUCAGCUCUGACAUUCUGAUUCGA	24%
14714	3UTR	1733	1725	CUCAGCUCUGACAUUCUGAUUCGAA	32%
14715	3UTR	1734	1726	UCAGCUCUGACAUUCUGAUUCGAAA	23%
14716	3UTR	1735	1727	CAGCUCUGACAUUCUGAUUCGAAUA	27%
14717	3UTR	1736	1728	AGCUCUGACAUUCUGAUUCGAAUGA	38%

Target Gene Duplex Name	Gene Region	Ref Pos	SEQ ID NO	CTGF Sense sequence	% Expression (0.1 nM)
14718	3UTR	1739	1729	UCUGACAUUCUGAUUCGAAUGACAA	28%
14719	3UTR	1741	1730	UGACAUUCUGAUUCGAAUGACACUA	29%
14720	3UTR	1742	1731	GACAUUCUGAUUCGAAUGACACUGA	33%
14721	3UTR	1743	1732	ACAUUCUGAUUCGAAUGACACUGUA	28%
14722	3UTR	1747	1733	UCUGAUUCGAAUGACACUGUUCAGA	39%
14723	3UTR	1748	1734	CUGAUUCGAAUGACACUGUUCAGGA	36%
14724	3UTR	1750	1735	GAUUCGAAUGACACUGUUCAGGAAA	33%
14725	3UTR	1751	1736	AUUCGAAUGACACUGUUCAGGAAUA	30%
14726	3UTR	1759	1737	GACACUGUUCAGGAAUCGGAAUCCA	34%
14727	3UTR	1760	1738	ACACUGUUCAGGAAUCGGAAUCCUA	35%
14728	3UTR	1761	1739	CACUGUUCAGGAAUCGGAAUCCUGA	40%
14729	3UTR	1768	1740	CAGGAAUCGGAAUCCUGUCGAUUAA	34%
14730	3UTR	1769	1741	AGGAAUCGGAAUCCUGUCGAUUAGA	31%
14731	3UTR	1770	1742	GGAAUCGGAAUCCUGUCGAUUAGAA	24%
14732	3UTR	1771	1743	GAAUCGGAAUCCUGUCGAUUAGACA	32%
14733	3UTR	1772	1744	AAUCGGAAUCCUGUCGAUUAGACUA	29%
14734	3UTR	1774	1745	UCGGAAUCCUGUCGAUUAGACUGGA	34%
14735	3UTR	1777	1746	GAAUCCUGUCGAUUAGACUGGACAA	51%
14736	3UTR	1782	1747	CUGUCGAUUAGACUGGACAGCUUGA	88%
14737	3UTR	1783	1748	UGUCGAUUAGACUGGACAGCUUGUA	38%
14738	3UTR	1797	1749	GACAGCUUGUGGCAAGUGAAUUUGA	46%
14739	3UTR	1798	1750	ACAGCUUGUGGCAAGUGAAUUUGCA	52%
14740	3UTR	1800	1751	AGCUUGUGGCAAGUGAAUUUGCCUA	43%
14741	3UTR	1801	1752	GCUUGUGGCAAGUGAAUUUGCCUGA	51%
14742	3UTR	1802	1753	CUUGUGGCAAGUGAAUUUGCCUGUA	32%
14743	3UTR	1803	1754	UUGUGGCAAGUGAAUUUGCCUGUAA	31%
14744	3UTR	1804	1755	UGUGGCAAGUGAAUUUGCCUGUAAA	29%
14745	3UTR	1805	1756	GUGGCAAGUGAAUUUGCCUGUAACA	20%
14746	3UTR	1806	1757	UGGCAAGUGAAUUUGCCUGUAACAA	34%
14747	3UTR	1807	1758	GGCAAGUGAAUUUGCCUGUAACAAA	31%
14748	3UTR	1808	1759	GCAAGUGAAUUUGCCUGUAACAAGA	27%
14749	3UTR	1809	1760	CAAGUGAAUUUGCCUGUAACAAGCA	34%
14750	3UTR	1810	1761	AAGUGAAUUUGCCUGUAACAAGCCA	36%
14751	3UTR	1811	1762	AGUGAAUUUGCCUGUAACAAGCCAA	31%
14752	3UTR	1814	1763	GAAUUUGCCUGUAACAAGCCAGAUA	24%
14753	3UTR	1815	1764	AAUUUGCCUGUAACAAGCCAGAUUA	21%
14754	3UTR	1816	1765	AUUUGCCUGUAACAAGCCAGAUUUA	22%
14755	3UTR	1910	1766	AAGUUAAUUUAAAGUUGUUUGUGCA	58%
14756	3UTR	1911	1767	AGUUAAUUUAAAGUUGUUUGUGCCA	73%
14757	3UTR	1912	1768	GUUAAUUUAAAGUUGUUUGUGCCUA	64%
14758	3UTR	1957	1769	UUUGAUAUUUCAAUGUUAGCCUCAA	42%
14759	3UTR	1961	1770	AUAUUUCAAUGUUAGCCUCAAUUUA	30%
14760	3UTR	1971	1771	GUUAGCCUCAAUUUCUGAACACCAA	34%
14761	3UTR	1974	1772	AGCCUCAAUUUCUGAACACCAUAGA	35%
14762	3UTR	1975	1773	GCCUCAAUUUCUGAACACCAUAGGA	33%
14763	3UTR	1976	1774	CCUCAAUUUCUGAACACCAUAGGUA	39%
14764	3UTR	1977	1775	CUCAAUUUCUGAACACCAUAGGUAA	27%
14765	3UTR	1978	1776	UCAAUUUCUGAACACCAUAGGUAGA	31%
14766	3UTR	1979	1777	CAAUUUCUGAACACCAUAGGUAGAA	49%
14767	3UTR	1980	1778	AAUUUCUGAACACCAUAGGUAGAAA	46%
14768	3UTR	1981	1779	AUUUCUGAACACCAUAGGUAGAAUA	40%
14769	3UTR	1982	1780	UUUCUGAACACCAUAGGUAGAAUGA	47%
14770	3UTR	1985	1781	CUGAACACCAUAGGUAGAAUGUAAA	33%

Target Gene Duplex Name	Gene Region	Ref Pos	SEQ ID NO	CTGF Sense sequence	% Expression (0.1 nM)
14771	3UTR	1986	1782	UGAACACCAUAGGUAGAAUGUAAAA	35%
14772	3UTR	1987	1783	GAACACCAUAGGUAGAAUGUAAAGA	31%
14773	3UTR	1988	1784	AACACCAUAGGUAGAAUGUAAAGCA	30%
14774	3UTR	1989	1785	ACACCAUAGGUAGAAUGUAAAGCUA	32%
14775	3UTR	1991	1786	ACCAUAGGUAGAAUGUAAAGCUUGA	31%
14776	3UTR	1992	1787	CCAUAGGUAGAAUGUAAAGCUUGUA	34%
14777	3UTR	1993	1788	CAUAGGUAGAAUGUAAAGCUUGUCA	31%
14778	3UTR	1994	1789	AUAGGUAGAAUGUAAAGCUUGUCUA	28%
14779	3UTR	1996	1790	AGGUAGAAUGUAAAGCUUGUCUGAA	32%
14780	3UTR	2002	1791	AAUGUAAAGCUUGUCUGAUCGUUCA	34%
14781	3UTR	2017	1792	UGAUCGUUCAAAGCAUGAAAUGGAA	31%
14782	3UTR	2021	1793	CGUUCAAAGCAUGAAAUGGAUACUA	39%
14783	3UTR	2022	1794	GUUCAAAGCAUGAAAUGGAUACUUA	25%
14784	3UTR	2023	1795	UUCAAAGCAUGAAAUGGAUACUUAA	22%
14785	3UTR	2047	1796	UAUGGAAAUUCUGCUCAGAUAGAAA	39%
14786	3UTR	2048	1797	AUGGAAAUUCUGCUCAGAUAGAAUA	35%
14787	3UTR	2059	1798	GCUCAGAUAGAAUGACAGUCCGUCA	44%
14788	3UTR	2060	1799	CUCAGAUAGAAUGACAGUCCGUCAA	41%
14789	3UTR	2062	1800	CAGAUAGAAUGACAGUCCGUCAAAA	46%
14790	3UTR	2063	1801	AGAUAGAAUGACAGUCCGUCAAAAA	45%
14791	3UTR	2065	1802	AUAGAAUGACAGUCCGUCAAAACAA	41%
14792	3UTR	2067	1803	AGAAUGACAGUCCGUCAAAACAGAA	36%
14793	3UTR	2068	1804	GAAUGACAGUCCGUCAAAACAGAUA	40%
14794	3UTR	2113	1805	AGUGUCCUUGGCAGGCUGAUUUCUA	42%
14795	3UTR	2114	1806	GUGUCCUUGGCAGGCUGAUUUCUAA	42%
14796	3UTR	2118	1807	CCUUGGCAGGCUGAUUUCUAGGUAA	111%
14797	3UTR	2127	1808	GCUGAUUUCUAGGUAGGAAAUGUGA	44%
14798	3UTR	2128	1809	CUGAUUUCUAGGUAGGAAAUGUGGA	44%
14799	3UTR	2130	1810	GAUUUCUAGGUAGGAAAUGUGGUAA	46%
14800	3UTR	2131	1811	AUUUCUAGGUAGGAAAUGUGGUAGA	45%
14801	3UTR	2142	1812	GGAAAUGUGGUAGCCUCACUUUUAA	37%
14802	3UTR	2146	1813	AUGUGGUAGCCUCACUUUUAAUGAA	39%
14803	3UTR	2149	1814	UGGUAGCCUCACUUUUAAUGAACAA	40%
14804	3UTR	2154	1815	GCCUCACUUUUAAUGAACAAAUGGA	35%
14805	3UTR	2155	1816	CCUCACUUUUAAUGAACAAAUGGCA	41%
14806	3UTR	2181	1817	UUAUUAAAAACUGAGUGACUCUAUA	26%
14807	3UTR	2182	1818	UAUUAAAAACUGAGUGACUCUAUAA	29%
14808	3UTR	2183	1819	AUUAAAAACUGAGUGACUCUAUAUA	28%
14809	3UTR	2186	1820	AAAAACUGAGUGACUCUAUAUAGCA	31%
14810	3UTR	2187	1821	AAAACUGAGUGACUCUAUAUAGCUA	28%
14811	3UTR	2188	1822	AAACUGAGUGACUCUAUAUAGCUGA	38%
14812	3UTR	2189	1823	AACUGAGUGACUCUAUAUAGCUGAA	44%
14813	3UTR	2190	1824	ACUGAGUGACUCUAUAUAGCUGAUA	38%
14814	3UTR	2255	1825	ACUGUUUUUCGGACAGUUUAUUUGA	29%
14815	3UTR	2256	1826	CUGUUUUUCGGACAGUUUAUUUGUA	25%
14816	3UTR	2263	1827	UCGGACAGUUUAUUUGUUGAGAGUA	29%
14817	3UTR	2265	1828	GGACAGUUUAUUUGUUGAGAGUGUA	24%
14818	3UTR	2268	1829	CAGUUUAUUUGUUGAGAGUGUGACA	26%
14819	3UTR	2269	1830	AGUUUAUUUGUUGAGAGUGUGACCA	37%
14820	3UTR	2272	1831	UUAUUUGUUGAGAGUGUGACCAAAA	27%
14821	3UTR	2273	1832	UAUUUGUUGAGAGUGUGACCAAAAA	30%
14822	3UTR	2274	1833	AUUUGUUGAGAGUGUGACCAAAAGA	26%
14823	3UTR	2275	1834	UUUGUUGAGAGUGUGACCAAAAGUA	27%

Target Gene Duplex Name	Gene Region	Ref Pos	SEQ ID NO	CTGF Sense sequence	% Expression (0.1 nM)
14824	3UTR	2276	1835	UUGUUGAGAGUGUGACCAAAAGUUA	30%
14825	3UTR	2277	1836	UGUUGAGAGUGUGACCAAAAGUUAA	29%
14826	3UTR	2278	1837	GUUGAGAGUGUGACCAAAAGUUACA	33%
14827	3UTR	2279	1838	UUGAGAGUGUGACCAAAAGUUACAA	35%
14828	3UTR	2281	1839	GAGAGUGUGACCAAAAGUUACAUGA	36%
14829	3UTR	2282	1840	AGAGUGUGACCAAAAGUUACAUGUA	36%
14830	3UTR	2283	1841	GAGUGUGACCAAAAGUUACAUGUUA	33%
14831	3UTR	2284	1842	AGUGUGACCAAAAGUUACAUGUUUA	31%
14832	3UTR	2285	1843	GUGUGACCAAAAGUUACAUGUUUGA	22%
14833	3UTR	2286	1844	UGUGACCAAAAGUUACAUGUUUGCA	40%
14834	3UTR	2293	1845	AAAAGUUACAUGUUUGCACCUUUCA	24%
14835	3UTR	2295	1846	AAGUUACAUGUUUGCACCUUUCUAA	23%
14836	3UTR	2296	1847	AGUUACAUGUUUGCACCUUUCUAGA	29%
14837	3UTR	2299	1848	UACAUGUUUGCACCUUUCUAGUUGA	27%
14838	3UTR	2300	1849	ACAUGUUUGCACCUUUCUAGUUGAA	29%
14839	3UTR	2301	1850	CAUGUUUGCACCUUUCUAGUUGAAA	35%

Key:		
PS	*	= Phosphothioate Backbone Linkage
RNA	**G**	= Guanine
RNA	**U**	= Uracil
RNA	**C**	= Cytosine
RNA	**A**	= Adenine
	m	2' Omethyl
	f	2'-Fluoro
Phosphate	**P**	5' Phosphate

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Table 12: Inhibition of gene expression with CTGF ori sequences (Accession Number: NM_001901.2)

Oligo ID	Gene Region	Ref Pos	SEQ ID NO	25-mer Sense Strand (position 25 of SS, replaced with A)	A549 0.1 nM Activity
				25-mer Sense Strand (position 25 of SS, original base, not replaced by A)	
13843	CDS	1047	1851	UACCGAGCUAAAUUCUGUGGAGUAU	113%
13844	3UTR	2164	1852	UAAUGAACAAAUGGCCUUUAUUAAA	61%
13845	3UTR	1795	1853	UGGACAGCUUGUGGCAAGUGAAUUU	99%
13846	CDS	1228	1854	UGUACUACAGGAAGAUGUACGGAGA	87%
13847	CDS	1146	1855	GUCAUGAAGAAGAACAUGAUGUUCA	98%
13848	CDS	1150	1856	UGAAGAAGAACAUGAUGUUCAUCAA	105%
13849	CDS	1218	1857	UUUGAAUCGCUGUACUACAGGAAGA	91%

Oligo ID	Gene Region	Ref Pos	SEQ ID NO	25-mer Sense Strand (position 25 of SS, replaced with A)	A549 0.1 nM Activity
13850	3UTR	2262	1858	UUCGGACAGUUUAUUUGUUGAGAGU	50%
13851	CDS	1147	1859	UCAUGAAGAAGAACAUGAUGUUCAU	104%
13852	3UTR	2163	1860	UUAAUGAACAAAUGGCCUUUAUUAA	54%
13853	3UTR	1414	1861	CCAUGUCAAACAAAUAGUCUAUCAA	35%
13854	CDS	1195	1862	ACUGUCCCGGAGACAAUGACAUCUU	103%
13855	3UTR	1788	1863	AUUAGACUGGACAGCUUGUGGCAAG	103%
13856	3UTR	1793	1864	ACUGGACAGCUUGUGGCAAGUGAAU	81%
13857	3UTR	1891	1865	UAUAUAUGUACAGUUAUCUAAGUUA	73%
13858	3UTR	2270	1866	GUUUAUUUGUUGAGAGUGUGACCAA	76%
13859		482	1867	CAAGAUCGGCGUGUGCACCGCCAAA	95%
13860	CDS	942	1868	GCUGACCUGGAAGAGAACAUUAAGA	93%
13861	CDS	1199	1869	UCCCGGAGACAAUGACAUCUUUGAA	83%
13862	3UTR	2258	1870	GUUUUUCGGACAGUUUAUUUGUUGA	40%
13863	CDS	1201	1871	CCGGAGACAAUGACAUCUUUGAAUC	123%
13864	CDS	543	1872	CGCAGCGGAGAGUCCUUCCAGAGCA	124%
13865	3UTR	1496	1873	AGCACCAGAAUGUAUAUUAAGGUGU	109%
13866	CDS	793	1874	UGAUUAGAGCCAACUGCCUGGUCCA	125%
13867	CDS	1198	1875	GUCCCGGAGACAAUGACAUCUUUGA	64%
13868	3UTR	2160	1876	CUUUUAAUGAACAAAUGGCCUUUAU	68%
13869	CDS	1149	1877	AUGAAGAAGAACAUGAUGUUCAUCA	107%
13870	CDS	1244	1878	GUACGGAGACAUGGCAUGAAGCCAG	107%
13871	3UTR	1495	1879	CAGCACCAGAAUGUAUAUUAAGGUG	77%
13872		475	1880	CCAACCGCAAGAUCGGCGUGUGCAC	113%
13873	CDS	806	1881	CUGCCUGGUCCAGACCACAGAGUGG	113%
13874	CDS	819	1882	ACCACAGAGUGGAGCGCCUGUUCCA	99%
13875	CDS	1221	1883	GAAUCGCUGUACUACAGGAAGAUGU	97%
13876	CDS	1152	1884	AAGAAGAACAUGAUGUUCAUCAAGA	121%
13877	CDS	1163	1885	GAUGUUCAUCAAGACCUGUGCCUGC	125%
13878	3UTR	1494	1886	ACAGCACCAGAAUGUAUAUUAAGGU	94%
13879	3UTR	1890	1887	AUAUAUAUGUACAGUUAUCUAAGUU	94%
13880		473	1888	GGCCAACCGCAAGAUCGGCGUGUGC	122%
13881		544	1889	GCAGCGGAGAGUCCUUCCAGAGCAG	111%
13882	CDS	883	1890	ACAACGCCUCCUGCAGGCUAGAGAA	105%
13883	CDS	1240	1891	AGAUGUACGGAGACAUGGCAUGAAG	99%
13884	CDS	1243	1892	UGUACGGAGACAUGGCAUGAAGCCA	116%
13885	3UTR	2266	1893	GACAGUUUAUUUGUUGAGAGUGUGA	53%
13886	CDS	1011	1894	AAGUUUGAGCUUUCUGGCUGCACCA	118%
13887	CDS	1020	1895	CUUUCUGGCUGCACCAGCAUGAAGA	110%
13888	CDS	1168	1896	UCAUCAAGACCUGUGCCUGCCAUUA	119%
13889		1415	1897	CAUGUCAAACAAAUAGUCUAUCAAC	64%
13890	3UTR	1792	1898	GACUGGACAGCUUGUGGCAAGUGAA	53%
13891	3UTR	2156	1899	CUCACUUUUAAUGAACAAAUGGCCU	119%
13892		379	1900	GCUGCCGCGUCUGCGCCAAGCAGCU	112%
13893	CDS	1229	1901	GUACUACAGGAAGAUGUACGGAGAC	112%
13894	3UTR	1791	1902	AGACUGGACAGCUUGUGGCAAGUGA	65%
13895	3UTR	2158	1903	CACUUUUAAUGAACAAAUGGCCUUU	76%
13896		488	1904	CGGCGUGUGCACCGCCAAAGAUGGU	89%
13897	CDS	1151	1905	GAAGAAGAACAUGAUGUUCAUCAAG	119%
13898	CDS	1156	1906	AGAACAUGAUGUUCAUCAAGACCUG	125%
13899	CDS	1237	1907	GGAAGAUGUACGGAGACAUGGCAUG	114%
13900	CDS	1202	1908	CGGAGACAAUGACAUCUUUGAAUCG	130%
13901	CDS	1236	1909	AGGAAGAUGUACGGAGACAUGGCAU	135%

Oligo ID	Gene Region	Ref Pos	SEQ ID NO	25-mer Sense Strand (position 25 of SS, replaced with A)	A549 0.1 nM Activity
13902	3UTR	1786	1910	CGAUUAGACUGGACAGCUUGUGGCA	119%
13903	3UTR	1789	1911	UUAGACUGGACAGCUUGUGGCAAGU	108%
13904	3UTR	2290	1912	ACCAAAAGUUACAUGUUUGCACCUU	90%
13905	CDS	1017	1913	GAGCUUUCUGGCUGCACCAGCAUGA	121%
13906	CDS	1197	1914	UGUCCCGGAGACAAUGACAUCUUUG	125%
13907	CDS	1219	1915	UUGAAUCGCUGUACUACAGGAAGAU	98%
13908	3UTR	2159	1916	ACUUUUAAUGAACAAAUGGCCUUUA	52%
13909		486	1917	AUCGGCGUGUGCACCGCCAAAGAUG	119%
13910	CDS	826	1918	AGUGGAGCGCCUGUUCCAAGACCUG	139%
13911	CDS	1022	1919	UUCUGGCUGCACCAGCAUGAAGACA	144%
13912	3UTR	1492	1920	ACACAGCACCAGAAUGUAUAUUAAG	99%
13913	3UTR	1781	1921	CCUGUCGAUUAGACUGGACAGCUUG	89%
13914		485	1922	GAUCGGCGUGUGCACCGCCAAAGAU	131%
13915	CDS	1007	1923	UAUCAAGUUUGAGCUUUCUGGCUGC	92%
13916	CDS	1242	1924	AUGUACGGAGACAUGGCAUGAAGCC	106%
13917	3UTR	1787	1925	GAUUAGACUGGACAGCUUGUGGCAA	104%
13918	3UTR	1889	1926	UAUAUAUAUGUACAGUUAUCUAAGU	78%
13919	3UTR	2294	1927	AAAGUUACAUGUUUGCACCUUUCUA	28%
13920	CDS	821	1928	CACAGAGUGGAGCGCCUGUUCCAAG	108%
13921	CDS	884	1929	CAACGCCUCCUGCAGGCUAGAGAAG	125%
13922	3UTR	2260	1930	UUUUCGGACAGUUUAUUUGUUGAGA	43%
13923	CDS	889	1931	CCUCCUGCAGGCUAGAGAAGCAGAG	95%
13924	CDS	1226	1932	GCUGUACUACAGGAAGAUGUACGGA	122%
13925	3UTR	1493	1933	CACAGCACCAGAAUGUAUAUUAAGG	88%
13926	3UTR	1799	1934	CAGCUUGUGGCAAGUGAAUUUGCCU	89%
13927	CDS	807	1935	UGCCUGGUCCAGACCACAGAGUGGA	101%
13928	CDS	1107	1936	ACCACCCUGCCGGUGGAGUUCAAGU	113%
13929	CDS	1155	1937	AAGAACAUGAUGUUCAUCAAGACCU	109%
13930	CDS	1169	1938	CAUCAAGACCUGUGCCUGCCAUUAC	89%
13931	CDS	1241	1939	GAUGUACGGAGACAUGGCAUGAAGC	96%
13932	3UTR	1794	1940	CUGGACAGCUUGUGGCAAGUGAAUU	73%
13933	3UTR	1888	1941	AUAUAUAUAUGUACAGUUAUCUAAG	98%
13934	3UTR	2289	1942	GACCAAAAGUUACAUGUUUGCACCU	77%
13935		373	1943	GCGGCUGCUGCCGCGUCUGCGCCAA	85%
13936	CDS	799	1944	GAGCCAACUGCCUGGUCCAGACCAC	126%
13937	CDS	802	1945	CCAACUGCCUGGUCCAGACCACAGA	122%
13938	CDS	1166	1946	GUUCAUCAAGACCUGUGCCUGCCAU	106%

Table 13: Inhibition of gene expression with SPP1 sd-rxRNA sequences (Accession Number: NM_000582.2)

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14084	1025	1947	CUCAUGAAUUAGA	1948	UCUAAUUCAUGAGAAAUAC	61%
14085	1049	1949	CUGAGGUCAAUUA	1950	UAAUUGACCUCAGAAGAUG	50%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14086	1051	1951	GAGGUCAAUUAAA	1952	UUUAAUUGACCUCAGAAGA	n/a
14087	1048	1953	UCUGAGGUCAAUU	1954	AAUUGACCUCAGAAGAUGC	69%
14088	1050	1955	UGAGGUCAAUUAA	1956	UUAAUUGACCUCAGAAGAU	76%
14089	1047	1957	UUCUGAGGUCAAU	1958	AUUGACCUCAGAAGAUGCA	60%
14090	800	1959	GUCAGCUGGAUGA	1960	UCAUCCAGCUGACUCGUUU	71%
14091	492	1961	UUCUGAUGAAUCU	1962	AGAUUCAUCAGAAUGGUGA	n/a
14092	612	1963	UGGACUGAGGUCA	1964	UGACCUCAGUCCAUAAACC	n/a
14093	481	1965	GAGUCUCACCAUU	1966	AAUGGUGAGACUCAUCAGA	n/a
14094	614	1967	GACUGAGGUCAAA	1968	UUUGACCUCAGUCCAUAAA	n/a
14095	951	1969	UCACAGCCAUGAA	1970	UUCAUGGCUGUGAAAUUCA	89%
14096	482	1971	AGUCUCACCAUUC	1972	GAAUGGUGAGACUCAUCAG	87%
14097	856	1973	AAGCGGAAAGCCA	1974	UGGCUUUCCGCUUAUAUAA	88%
14098	857	1975	AGCGGAAAGCCAA	1976	UUGGCUUUCCGCUUAUAUA	113%
14099	365	1977	ACCACAUGGAUGA	1978	UCAUCCAUGUGGUCAUGGC	98%
14100	359	1979	GCCAUGACCACAU	1980	AUGUGGUCAUGGCUUUCGU	84%
14101	357	1981	AAGCCAUGACCAC	1982	GUGGUCAUGGCUUUCGUUG	88%
14102	858	1983	GCGGAAAGCCAAU	1984	AUUGGCUUUCCGCUUAUAU	n/a
14103	1012	1985	AAAUUUCGUAUUU	1986	AAAUACGAAAUUUCAGGUG	93%
14104	1014	1987	AUUUCGUAUUUCU	1988	AGAAAUACGAAAUUUCAGG	89%
14105	356	1989	AAAGCCAUGACCA	1990	UGGUCAUGGCUUUCGUUGG	85%
14106	368	1991	ACAUGGAUGAUAU	1992	AUAUCAUCCAUGUGGUCAU	67%
14107	1011	1993	GAAAUUUCGUAUU	1994	AAUACGAAAUUUCAGGUGU	87%
14108	754	1995	GCGCCUUCUGAUU	1996	AAUCAGAAGGCGCGUUCAG	73%
14109	1021	1997	AUUUCUCAUGAAU	1998	AUUCAUGAGAAAUACGAAA	128%
14110	1330	1999	CUCUCAUGAAUAG	2000	CUAUUCAUGAGAGAAUAAC	101%
14111	346	2001	AAGUCCAACGAAA	2002	UUUCGUUGGACUUACUUGG	59%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14112	869	2003	AUGAUGAGAGCAA	2004	UUGCUCUCAUCAUUGGCUU	89%
14113	701	2005	GCGAGGAGUUGAA	2006	UUCAACUCCUCGCUUUCCA	95%
14114	896	2007	UGAUUGAUAGUCA	2008	UGACUAUCAAUCACAUCGG	87%
14115	1035	2009	AGAUAGUGCAUCU	2010	AGAUGCACUAUCUAAUUCA	82%
14116	1170	2011	AUGUGUAUCUAUU	2012	AAUAGAUACACAUUCAACC	36%
14117	1282	2013	UUCUAUAGAAGAA	2014	UUCUUCUAUAGAAUGAACA	91%
14118	1537	2015	UUGUCCAGCAAUU	2016	AAUUGCUGGACAACCGUGG	152%
14119	692	2017	ACAUGGAAAGCGA	2018	UCGCUUUCCAUGUGUGAGG	n/a
14120	840	2019	GCAGUCCAGAUUA	2020	UAAUCUGGACUGCUUGUGG	87%
14121	1163	2021	UGGUUGAAUGUGU	2022	ACACAUUCAACCAAUAAAC	31%
14122	789	2023	UUAUGAAACGAGU	2024	ACUCGUUUCAUAACUGUCC	96%
14123	841	2025	CAGUCCAGAUUAU	2026	AUAAUCUGGACUGCUUGUG	110%
14124	852	2027	AUAUAAGCGGAAA	2028	UUUCCGCUUAUAUAAUCUG	91%
14125	209	2029	UACCAGUUAAACA	2030	UGUUUAACUGGUAUGGCAC	110%
14126	1276	2031	UGUUCAUUCUAUA	2032	UAUAGAAUGAACAUAGACA	n/a
14127	137	2033	CCGACCAAGGAAA	2034	UUUCCUUGGUCGGCGUUUG	71%
14128	711	2035	GAAUGGUGCAUAC	2036	GUAUGCACCAUUCAACUCC	115%
14129	582	2037	AUAUGAUGGCCGA	2038	UCGGCCAUCAUAUGUGUCU	97%
14130	839	2039	AGCAGUCCAGAUU	2040	AAUCUGGACUGCUUGUGGC	102%
14131	1091	2041	GCAUUUAGUCAAA	2042	UUUGACUAAAUGCAAAGUG	10%
14132	884	2043	AGCAUUCCGAUGU	2044	ACAUCGGAAUGCUCAUUGC	93%
14133	903	2045	UAGUCAGGAACUU	2046	AAGUUCCUGACUAUCAAUC	97%
14134	1090	2047	UGCAUUUAGUCAA	2048	UUGACUAAAUGCAAAGUGA	39%
14135	474	2049	GUCUGAUGAGUCU	2050	AGACUCAUCAGACUGGUGA	99%
14136	575	2051	UAGACACAUAUGA	2052	UCAUAUGUGUCUACUGUGG	108%
14137	671	2053	CAGACGAGGACAU	2054	AUGUCCUCGUCUGUAGCAU	98%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14138	924	2055	CAGCCGUGAAUUC	2056	GAAUUCACGGCUGACUUUG	100%
14139	1185	2057	AGUCUGGAAAUAA	2058	UUAUUUCCAGACUCAAAUA	47%
14140	1221	2059	AGUUUGUGGCUUC	2060	GAAGCCACAAACUAAACUA	100%
14141	347	2061	AGUCCAACGAAAG	2062	CUUUCGUUGGACUUACUUG	103%
14142	634	2063	AAGUUUCGCAGAC	2064	GUCUGCGAAACUUCUUAGA	100%
14143	877	2065	AGCAAUGAGCAUU	2066	AAUGCUCAUUGCUCUCAUC	104%
14144	1033	2067	UUAGAUAGUGCAU	2068	AUGCACUAUCUAAUUCAUG	95%
14145	714	2069	UGGUGCAUACAAG	2070	CUUGUAUGCACCAUUCAAC	101%
14146	791	2071	AUGAAACGAGUCA	2072	UGACUCGUUUCAUAACUGU	100%
14147	813	2073	CCAGAGUGCUGAA	2074	UUCAGCACUCUGGUCAUCC	97%
14148	939	2075	CAGCCAUGAAUUU	2076	AAAUUCAUGGCUGUGGAAU	109%
14149	1161	2077	AUUGGUUGAAUGU	2078	ACAUUCAACCAAUAAACUG	34%
14150	1164	2079	GGUUGAAUGUGUA	2080	UACACAUUCAACCAAUAAA	n/a
14151	1190	2081	GGAAAUAACUAAU	2082	AUUAGUUAUUUCCAGACUC	n/a
14152	1333	2083	UCAUGAAUAGAAA	2084	UUUCUAUUCAUGAGAGAAU	31%
14153	537	2085	GCCAGCAACCGAA	2086	UUCGGUUGCUGGCAGGUCC	n/a
14154	684	2087	CACCUCACACAUG	2088	CAUGUGUGAGGUGAUGUCC	100%
14155	707	2089	AGUUGAAUGGUGC	2090	GCACCAUUCAACUCCUCGC	99%
14156	799	2091	AGUCAGCUGGAUG	2092	CAUCCAGCUGACUCGUUUC	95%
14157	853	2093	UAUAAGCGGAAAG	2094	CUUUCCGCUUAUAUAAUCU	106%
14158	888	2095	UUCCGAUGUGAUU	2096	AAUCACAUCGGAAUGCUCA	88%
14159	1194	2097	AUAACUAAUGUGU	2098	ACACAUUAGUUAUUUCCAG	95%
14160	1279	2099	UCAUUCUAUAGAA	2100	UUCUAUAGAAUGAACAUAG	15%
14161	1300	2101	AACUAUCACUGUA	2102	UACAGUGAUAGUUUGCAUU	86%
14162	1510	2103	GUCAAUUGCUUAU	2104	AUAAGCAAUUGACACCACC	86%
14163	1543	2105	AGCAAUUAAUAAA	2106	UUUAUUAAUUGCUGGACAA	110%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14164	434	2107	ACGACUCUGAUGA	2108	UCAUCAGAGUCGUUC GAGU	134%
14165	600	2109	UAGUGUGGUUUA U	2110	AUAAACCACACUAUC ACCU	102%
14166	863	2111	AAGCCAAUGAUGA	2112	UCAUCAUUGGCUUUC CGCU	93%
14167	902	2113	AUAGUCAGGAACU	2114	AGUUCCUGACUAUCA AUCA	101%
14168	921	2115	AGUCAGCCGUGAA	2116	UUCACGGCUGACUUU GGAA	98%
14169	154	2117	ACUACCAUGAGAA	2118	UUCUCAUGGUAGUG AGUUU	n/a
14170	217	2119	AAACAGGCUGAUU	2120	AAUCAGCCUGUUUAA CUGG	66%
14171	816	2121	GAGUGCUGAAACC	2122	GGUUUCAGCACUCUG GUCA	102%
14172	882	2123	UGAGCAUUCCGAU	2124	AUCGGAAUGCUCAUU GCUC	103%
14173	932	2125	AAUUCCACAGCCA	2126	UGGCUGUGGAAUUC ACGGC	n/a
14174	1509	2127	UGUCAAUUGCUUA	2128	UAAGCAAUUGACACC ACCA	n/a
14175	157	2129	ACCAUGAGAAUUG	2130	CAAUUCUCAUGGUAG UGAG	109%
14176	350	2131	CCAACGAAAGCCA	2132	UGGCUUUCGUUGGA CUUAC	95%
14177	511	2133	CUGGUCACUGAUU	2134	AAUCAGUGACCAGUU CAUC	100%
14178	605	2135	UGGUUUAUGGAC U	2136	AGUCCAUAAACCACA CUAU	99%
14179	811	2137	GACCAGAGUGCUG	2138	CAGCACUCUGGUCAU CCAG	88%
14180	892	2139	GAUGUGAUUGAU A	2140	UAUCAAUCACAUCGG AAUG	76%
14181	922	2141	GUCAGCCGUGAAU	2142	AUUCACGGCUGACUU UGGA	59%
14182	1169	2143	AAUGUGUAUCUA U	2144	AUAGAUACACAUUCA ACCA	69%
14183	1182	2145	UUGAGUCUGGAA A	2146	UUUCCAGACUCAAAU AGAU	n/a
14184	1539	2147	GUCCAGCAAUUAA	2148	UUAAUUGCUGGACAA CCGU	77%
14185	1541	2149	CCAGCAAUUAAUA	2150	UAUUAAUUGCUGGA CAACC	n/a
14186	427	2151	GACUCGAACGACU	2152	AGUCGUUCGAGUCAA UGGA	69%
14187	533	2153	ACCUGCCAGCAAC	2154	GUUGCUGGCAGGUCC GUGG	78%
18538	496	2155	GAUGAAUCUGAUA	2156	UAUCAGAUUCAUCAG AAUG	74%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
18539	496	2157	UGAUGAAUCUGAUA	2158	UAUCAGAUUCAUCAGAAUG	72%
18540	175	2159	AUUUGCUUUUGCA	2160	UGCAAAAGCAAAUCACUGC	98%
18541	175	2161	GAUUUGCUUUUGCA	2162	UGCAAAAGCAAAUCACUGC	28%
18542	172	2163	GUGAUUUGCUUUA	2164	UAAAGCAAAUCACUGCAAU	24%
18543	172	2165	AGUGAUUUGCUUUA	2166	UAAAGCAAAUCACUGCAAU	14%
18544	1013	2167	AAUUUCGUAUUUA	2168	UAAAUACGAAAUUUCAGGU	100%
18545	1013	2169	AAAUUUCGUAUUUA	2170	UAAAUACGAAAUUUCAGGU	109%
18546	952	2171	CACAGCCAUGAAA	2172	UUUCAUGGCUGUGAAAUUC	32%
18547	952	2173	UCACAGCCAUGAAA	2174	UUUCAUGGCUGUGAAAUUC	33%
18548	174	2175	GAUUUGCUUUUGA	2176	UCAAAAGCAAAUCACUGCA	57%
18549	174	2177	UGAUUUGCUUUUGA	2178	UCAAAAGCAAAUCACUGCA	53%
18550	177	2179	UUGCUUUUGCCUA	2180	UAGGCAAAAGCAAAUCACU	97%
18551	177	2181	UUUGCUUUUGCCUA	2182	UAGGCAAAAGCAAAUCACU	103%
18552	1150	2183	UUUCUCAGUUUAA	2184	UUAAACUGAGAAAGAAGCA	96%
18553	1089	2185	UUGCAUUUAGUCA	2186	UGACUAAAUGCAAAGUGAG	94%
18554	1086	2187	ACUUUGCAUUUAA	2188	UUAAAUGCAAAGUGAGAAA	n/a
18555	1093	2189	AUUUAGUCAAAAA	2190	UUUUUGACUAAAUGCAAAG	n/a
18556	1147	2191	UUCUUUCUCAGUA	2192	UACUGAGAAAGAAGCAUUU	n/a
18557	1148	2193	UCUUUCUCAGUUA	2194	UAACUGAGAAAGAAGCAUU	66%
18558	1128	2195	GAAAGAGAACAUA	2196	UAUGUUCUCUUUCAUUUUG	16%
18559	1087	2197	CUUUGCAUUUAGA	2198	UCUAAAUGCAAAGUGAGAA	28%
18560	1088	2199	UUUGCAUUUAGUA	2200	UACUAAAUGCAAAGUGAGA	n/a
18561	1083	2201	CUCACUUUGCAUA	2202	UAUGCAAAGUGAGAAAUUG	53%
18562	1081	2203	UUCUCACUUUGCA	2204	UGCAAAGUGAGAAAUUGUA	89%
18563	555	2205	CACUCCAGUUGUA	2206	UACAACUGGAGUGAAAACU	33%
18564	1125	2207	AAUGAAAGAGAAA	2208	UUUCUCUUUCAUUUGCUA	n/a

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
18565	168	2209	UGCAGUGAUUUGA	2210	UCAAAUCACUGCAAUUCUC	14%
18566	1127	2211	UGAAAGAGAACAA	2212	UUGUUCUCUUUCAUUUUGC	27%
18567	1007	2213	ACCUGAAAUUUCA	2214	UGAAAUUUCAGGUGUUUAU	129%
18568	164	2215	GAAUUGCAGUGAA	2216	UUCACUGCAAUUCUCAUGG	47%
18569	222	2217	GGCUGAUUCUGGA	2218	UCCAGAAUCAGCCUGUUUA	n/a

Table 14: Inhibition of gene expression with PTGS2 sd-rxRNA sequences (Accession Number: NM_000963.2)

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14422	451	2219	CACAUUUGAUUGA	2220	UCAAUCAAAUGUGAUCUGG	72%
14423	1769	2221	CACUGCCUCAAUU	2222	AAUUGAGGCAGUGUUGAUG	71%
14424	1464	2223	AAAUACCAGUCUU	2224	AAGACUGGUAUUUCAUCUG	74%
14425	453	2225	CAUUUGAUUGACA	2226	UGUCAAUCAAAUGUGAUCU	83%
						% remaining expression (1 uM PC-3)
17388	285	2227	GAAAACUGCUCAA	2228	UUGAGCAGUUUUCUCCAUA	88%
17389	520	2229	ACCUCUCCUAUUA	2230	UAAUAGGAGAGGUUAGAGA	25%
17390	467	2231	UCCACCAACUUAA	2232	UUAAGUUGGUGGACUGUCA	68%
17391	467	2233	GUCCACCAACUUAA	2234	UUAAGUUGGUGGACUGUCA	101%
17392	524	2235	CUCCUAUUAUACA	2236	UGUAUAAUAGGAGAGGUUA	49%
17393	448	2237	GAUCACAUUUGAA	2238	UUCAAAUGUGAUCUGGAUG	29%
17394	448	2239	AGAUCACAUUUGAA	2240	UUCAAAUGUGAUCUGGAUG	31%
17395	519	2241	AACCUCUCCUAUA	2242	UAUAGGAGAGGUUAGAGAA	12%
17396	437	2243	GUUGACAUCCAGA	2244	UCUGGAUGUCAACACAUAA	86%
17397	406	2245	CCUUCCUUCGAAA	2246	UUUCGAAGGAAGGGAAUGU	23%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
17398	339	2247	ACUCCAAACACAA	2248	UUGUGUUUGGAGUGG GUUU	102%
17399	339	2249	CACUCCAAACACAA	2250	UUGUGUUUGGAGUGG GUUU	55%
17400	338	2251	CACUCCAAACACA	2252	UGUGUUUGGAGUGGG UUUC	62%
17401	468	2253	CCACCAACUUACA	2254	UGUAAGUUGGUGGAC UGUC	61%
17402	468	2255	UCCACCAACUUACA	2256	UGUAAGUUGGUGGAC UGUC	179%
17403	1465	2257	AAUACCAGUCUUA	2258	UAAGACUGGUAUUUCA UCU	30%
17404	243	2259	GACCAGUAUAAGA	2260	UCUUAUACUGGUCAAA UCC	32%
17405	1472	2261	GUCUUUUAAUGAA	2262	UUCAUUAAAAGACUGG UAU	15%
17406	2446	2263	AAUUUCAUGUCUA	2264	UAGACAUGAAAUUACU GGU	142%
17407	449	2265	AUCACAUUUGAUA	2266	UAUCAAAUGUGAUCUG GAU	54%
17408	449	2267	GAUCACAUUUGAU A	2268	UAUCAAAUGUGAUCUG GAU	27%
17409	444	2269	UCCAGAUCACAUA	2270	UAUGUGAUCUGGAUG UCAA	49%
17410	1093	2271	UACUGAUAGGAGA	2272	UCUCCUAUCAGUAUUA GCC	32%
17411	1134	2273	GUGCAACACUUGA	2274	UCAAGUGUUGCACAUA AUC	70%
17412	244	2275	ACCAGUAUAAGUA	2276	UACUUAUACUGGUCAA AUC	63%
17413	1946	2277	GAAGUCUAAUGAA	2278	UUCAUUAGACUUCUAC AGU	19%
17414	638	2279	AAGAAGAAAGUUA	2280	UAACUUUCUUCUUAGA AGC	27%
17415	450	2281	UCACAUUUGAUUA	2282	UAAUCAAAUGUGAUCU GGA	216%
17416	450	2283	AUCACAUUUGAUU A	2284	UAAUCAAAUGUGAUCU GGA	32%
17417	452	2285	ACAUUUGAUUGAA	2286	UUCAAUCAAAUGUGAU CUG	99%
17418	452	2287	CACAUUUGAUUGA A	2288	UUCAAUCAAAUGUGAU CUG	54%
17419	454	2289	AUUUGAUUGACAA	2290	UUGUCAAUCAAAUGUG AUC	86%
17420	454	2291	CAUUUGAUUGACA A	2292	UUGUCAAUCAAAUGUG AUC	89%
17421	1790	2293	CAUCUGCAAUAAA	2294	UUUAUUGCAGAUGAG AGAC	55%
17422	1790	2295	UCAUCUGCAAUAA A	2296	UUUAUUGCAGAUGAG AGAC	62%

Table 15: Inhibition of gene expression with CTGF sd-rxRNA sequences (Accession number: NM_001901.2)

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
13980	1222	2297	ACAGGAAGAUG UA	2298	UACAUCUUCCUGUAG UACA	98%
13981	813	2299	GAGUGGAGCGC CU	2300	AGGCGCUCCACUCUG UGGU	82%
13982	747	2301	CGACUGGAAGA CA	4206	UGUCUUCCAGUCGGU AAGC	116%
13983	817	2302	GGAGCGCCUGU UC	4207	GAACAGGCGCUCCAC UCUG	97%
13984	1174	2303	GCCAUUACAAC UG	4208	CAGUUGUAAUGGCAG GCAC	102%
13985	1005	2304	GAGCUUUCUG GCU	4209	AGCCAGAAAGCUCAA ACUU	114%
13986	814	2305	AGUGGAGCGCC UG	4210	CAGGCGCUCCACUCU GUGG	111%
13987	816	2306	UGGAGCGCCUG UU	4211	AACAGGCGCUCCACU CUGU	102%
13988	1001	2307	GUUUGAGCUU UCU	4212	AGAAAGCUCAAACUU GAUA	99%
13989	1173	2308	UGCCAUUACAA CU	4213	AGUUGUAAUGGCAG GCACA	107%
13990	749	2309	ACUGGAAGACA CG	4214	CGUGUCUUCCAGUCG GUAA	91%
13991	792	2310	AACUGCCUGGU CC	4215	GGACCAGGCAGUUGG CUCU	97%
13992	1162	2311	AGACCUGUGCC UG	4216	CAGGCACAGGUCUUG AUGA	107%
13993	811	2312	CAGAGUGGAGC GC	4217	GCGCUCCACUCUGUG GUCU	113%
13994	797	2313	CCUGGUCCAGA CC	4218	GGUCUGGACCAGGCA GUUG	n/a
13995	1175	2314	CCAUUACAACU GU	4219	ACAGUUGUAAUGGCA GGCA	113%
13996	1172	2315	CUGCCAUUACA AC	4220	GUUGUAAUGGCAGG CACAG	110%
13997	1177	2316	AUUACAACUGU CC	4221	GGACAGUUGUAAUG GCAGG	105%
13998	1176	2317	CAUUACAACUG UC	4222	GACAGUUGUAAUGGC AGGC	89%
13999	812	2318	AGAGUGGAGCG CC	4223	GGCGCUCCACUCUGU GGUC	99%
14000	745	2319	ACCGACUGGAA GA	4224	UCUUCCAGUCGGUAA GCCG	n/a
14001	1230	2320	AUGUACGGAGA CA	4225	UGUCUCCGUACAUCU UCCU	106%
14002	920	2321	GCCUUGCGAAG CU	4226	AGCUUCGCAAGGCCU GACC	93%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14003	679	2322	GCUGCGAGGAGUG	4227	CACUCCUCGCAGCAUUUCC	102%
14004	992	2323	GCCUAUCAAGUUU	4228	AAACUUGAUAGGCUUGGAG	100%
14005	1045	2324	AAUUCUGUGGAGU	4229	ACUCCACAGAAUUUAGCUC	104%
14006	1231	2325	UGUACGGAGACAU	4230	AUGUCUCCGUACAUCUUCC	87%
14007	991	2326	AGCCUAUCAAGUU	4231	AACUUGAUAGGCUUGGAGA	101%
14008	998	2327	CAAGUUUGAGCUU	4232	AAGCUCAAACUUGAUAGGC	98%
14009	1049	2328	CUGUGGAGUAUGU	4233	ACAUACUCCACAGAAUUUA	98%
14010	1044	2329	AAAUUCUGUGGAG	4234	CUCCACAGAAUUUAGCUCG	93%
14011	1327	2330	UUUCAGUAGCACA	4235	UGUGCUACUGAAAUCAUUU	95%
14012	1196	2331	CAAUGACAUCUUU	4236	AAAGAUGUCAUUGUCUCCG	101%
14013	562	2332	AGUACCAGUGCAC	4237	GUGCACUGGUACUUGCAGC	66%
14014	752	2333	GGAAGACACGUUU	4238	AAACGUGUCUUCCAGUCGG	95%
14015	994	2334	CUAUCAAGUUUGA	4239	UCAAACUUGAUAGGCUUGG	85%
14016	1040	2335	AGCUAAAUUCUGU	4240	ACAGAAUUUAGCUCGGUAU	61%
14017	1984	2336	AGGUAGAAUGUAA	4241	UUACAUUCUACCUAUGGUG	32%
14018	2195	2337	AGCUGAUCAGUUU	4242	AAACUGAUCAGCUAUAUAG	86%
14019	2043	2338	UUCUGCUCAGAUA	4243	UAUCUGAGCAGAAUUUCCA	81%
14020	1892	2339	UUAUCUAAGUUAA	4244	UUAACUUAGAUAACUGUAC	84%
14021	1567	2340	UAUACGAGUAAUA	4245	UAUUACUCGUAUAAGAUGC	72%
14022	1780	2341	GACUGGACAGCUU	4246	AAGCUGUCCAGUCUAAUCG	65%
14023	2162	2342	AUGGCCUUUAUUA	4247	UAAUAAAGGCCAUUUGUUC	80%
14024	1034	2343	AUACCGAGCUAAA	4248	UUUAGCUCGGUAUGUCUUC	91%
14025	2264	2344	UUGUUGAGAGUGU	4249	ACACUCUCAACAAAUAAAC	58%
14026	1032	2345	ACAUACCGAGCUA	4250	UAGCUCGGUAUGUCUUCAU	106%
14027	1535	2346	AGCAGAAAGGUUA	4251	UAACCUUUCUGCUGGUACC	67%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14028	1694	2347	AGUUGUUCCUUAA	4252	UUAAGGAACAACUUGACUC	94%
14029	1588	2348	AUUUGAAGUGUAA	4253	UUACACUUCAAAUAGCAGG	97%
14030	928	2349	AAGCUGACCUGGA	4254	UCCAGGUCAGCUUCGCAAG	100%
14031	1133	2350	GGUCAUGAAGAAG	4255	CUUCUUCAUGACCUCGCCG	82%
14032	912	2351	AUGGUCAGGCCUU	4256	AAGGCCUGACCAUGCACAG	84%
14033	753	2352	GAAGACACGUUUG	4257	CAAACGUGUCUUCCAGUCG	86%
14034	918	2353	AGGCCUUGCGAAG	4258	CUUCGCAAGGCCUGACCAU	88%
14035	744	2354	UACCGACUGGAAG	4259	CUUCCAGUCGGUAAGCCGC	95%
14036	466	2355	ACCGCAAGAUCGG	4260	CCGAUCUUGCGGUUGGCCG	73%
14037	917	2356	CAGGCCUUGCGAA	4261	UUCGCAAGGCCUGACCAUG	86%
14038	1038	2357	CGAGCUAAAUUCU	4262	AGAAUUUAGCUCGGUAUGU	84%
14039	1048	2358	UCUGUGGAGUAUG	4263	CAUACUCCACAGAAUUUAG	87%
14040	1235	2359	CGGAGACAUGGCA	4264	UGCCAUGUCUCCGUACAUC	100%
14041	868	2360	AUGACAACGCCUC	4265	GAGGCGUUGUCAUUGGUAA	104%
14042	1131	2361	GAGGUCAUGAAGA	4266	UCUUCAUGACCUCGCCGUC	85%
14043	1043	2362	UAAAUUCUGUGGA	4267	UCCACAGAAUUUAGCUCGG	74%
14044	751	2363	UGGAAGACACGUU	4268	AACGUGUCUUCCAGUCGGU	84%
14045	1227	2364	AAGAUGUACGGAG	4269	CUCCGUACAUCUUCCUGUA	99%
14046	867	2365	AAUGACAACGCCU	4270	AGGCGUUGUCAUUGGUAAC	94%
14047	1128	2366	GGCGAGGUCAUGA	4271	UCAUGACCUCGCCGUCAGG	89%
14048	756	2367	GACACGUUUGGCC	4272	GGCCAAACGUGUCUUCCAG	93%
14049	1234	2368	ACGGAGACAUGGC	4273	GCCAUGUCUCCGUACAUCU	100%
14050	916	2369	UCAGGCCUUGCGA	4274	UCGCAAGGCCUGACCAUGC	96%
14051	925	2370	GCGAAGCUGACCU	4275	AGGUCAGCUUCGCAAGGCC	80%
14052	1225	2371	GGAAGAUGUACGG	4276	CCGUACAUCUUCCUGUAGU	96%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14053	445	2372	GUGACUUCGGCUC	4277	GAGCCGAAGUCACAGAAGA	101%
14054	446	2373	UGACUUCGGCUCC	4278	GGAGCCGAAGUCACAGAAG	93%
14055	913	2374	UGGUCAGGCCUUG	4279	CAAGGCCUGACCAUGCACA	67%
14056	997	2375	UCAAGUUUGAGCU	4280	AGCUCAAACUUGAUAGGCU	92%
14057	277	2376	GCCAGAACUGCAG	4281	CUGCAGUUCUGGCCGACGG	84%
14058	1052	2377	UGGAGUAUGUACC	4282	GGUACAUACUCCACAGAAU	n/a
14059	887	2378	GCUAGAGAAGCAG	4283	CUGCUUCUCUAGCCUGCAG	80%
14060	914	2379	GGUCAGGCCUUGC	4284	GCAAGGCCUGACCAUGCAC	112%
14061	1039	2380	GAGCUAAAUUCUG	4285	CAGAAUUUAGCUCGGUAUG	104%
14062	754	2381	AAGACACGUUUGG	4286	CCAAACGUGUCUUCCAGUC	109%
14063	1130	2382	CGAGGUCAUGAAG	4287	CUUCAUGACCUCGCCGUCA	103%
14064	919	2383	GGCCUUGCGAAGC	4288	GCUUCGCAAGGCCUGACCA	109%
14065	922	2384	CUUGCGAAGCUGA	4289	UCAGCUUCGCAAGGCCUGA	106%
14066	746	2385	CCGACUGGAAGAC	4290	GUCUUCCAGUCGGUAAGCC	106%
14067	993	2386	CCUAUCAAGUUUG	4291	CAAACUUGAUAGGCUUGGA	67%
14068	825	2387	UGUUCCAAGACCU	4292	AGGUCUUGGAACAGGCGCU	93%
14069	926	2388	CGAAGCUGACCUG	4293	CAGGUCAGCUUCGCAAGGC	95%
14070	923	2389	UUGCGAAGCUGAC	4294	GUCAGCUUCGCAAGGCCUG	95%
14071	866	2390	CAAUGACAACGCC	4295	GGCGUUGUCAUUGGUAACC	132%
14072	563	2391	GUACCAGUGCACG	4296	CGUGCACUGGUACUUGCAG	n/a
14073	823	2392	CCUGUUCCAAGAC	4297	GUCUUGGAACAGGCGCUCC	98%
14074	1233	2393	UACGGAGACAUGG	4298	CCAUGUCUCCGUACAUCUU	109%
14075	924	2394	UGCGAAGCUGACC	4299	GGUCAGCUUCGCAAGGCCU	95%
14076	921	2395	CCUUGCGAAGCUG	4300	CAGCUUCGCAAGGCCUGAC	116%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14077	443	2396	CUGUGACUUCGGC	4301	GCCGAAGUCACAGAAGAGG	110%
14078	1041	2397	GCUAAAUUCUGUG	4302	CACAGAAUUUAGCUCGGUA	99%
14079	1042	2398	CUAAAUUCUGUGG	4303	CCACAGAAUUUAGCUCGGU	109%
14080	755	2399	AGACACGUUUGGC	4304	GCCAAACGUGUCUUCCAGU	121%
14081	467	2400	CCGCAAGAUCGGC	4305	GCCGAUCUUGCGGUUGGCC	132%
14082	995	2401	UAUCAAGUUUGAG	4306	CUCAAACUUGAUAGGCUUG	105%
14083	927	2402	GAAGCUGACCUGG	4307	CCAGGUCAGCUUCGCAAGG	114%
17356	1267	2403	ACAUUAACUCAUA	4308	UAUGAGUUAAUGUCUCUCA	120%
17357	1267	2404	GACAUUAACUCAUA	2405	UAUGAGUUAAUGUCUCUCA	56%
17358	1442	2406	UGAAGAAUGUUAA	2407	UUAACAUUCUUCAAACCAG	34%
17359	1442	2408	UUGAAGAAUGUUAA	2409	UUAACAUUCUUCAAACCAG	31%
17360	1557	2410	GAUAGCAUCUUAA	2411	UUAAGAUGCUAUCUGAUGA	59%
17361	1557	2412	AGAUAGCAUCUUAA	2413	UUAAGAUGCUAUCUGAUGA	47%
17362	1591	2414	UGAAGUGUAAUUA	2415	UAAUUACACUUCAAAUAGC	120%
17363	1599	2416	AAUUGAGAAGGAA	2417	UUCCUUCUCAAUUACACUU	71%
17364	1601	2418	UUGAGAAGGAAAA	2419	UUUUCCUUCUCAAUUACAC	62%
17365	1732	2420	CAUUCUGAUUCGA	2421	UCGAAUCAGAAUGUCAGAG	99%
17366	1734	2422	UUCUGAUUCGAAA	2423	UUUCGAAUCAGAAUGUCAG	97%
17367	1770	2424	CUGUCGAUUAGAA	2425	UUCUAAUCGACAGGAUUCC	45%
17368	1805	2426	UUUGCCUGUAACA	2427	UGUUACAGGCAAAUUCACU	71%
17369	1805	2428	AUUUGCCUGUAACA	2429	UGUUACAGGCAAAUUCACU	67%
17370	1815	2430	ACAAGCCAGAUUA	2431	UAAUCUGGCUUGUUACAGG	65%
17371	1815	2432	AACAAGCCAGAUUA	2433	UAAUCUGGCUUGUUACAGG	35%
17372	2256	2434	CAGUUUAUUUGUA	2435	UACAAAUAAACUGUCCGAA	113%
17373	2265	2436	UGUUGAGAGUGUA	2437	UACACUCUCAACAAAUAAA	35%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
17374	2265	2438	UUGUUGAGAG UGUA	2439	UACACUCUCAACAAA UAAA	31%
17375	2295	2440	UGCACCUUUCU AA	2441	UUAGAAAGGUGCAAA CAUG	34%
17376	2295	2442	UUGCACCUUUC UAA	2443	UUAGAAAGGUGCAAA CAUG	28%
17377	1003	2444	UUGAGCUUUC UGA	2445	UCAGAAAGCUCAAAC UUGA	67%
17378	2268	2446	UGAGAGUGUG ACA	2447	UGUCACACUCUCAAC AAAU	42%
17379	2272	2448	AGUGUGACCAA AA	2449	UUUUGGUCACACUCU CAAC	35%
17380	2272	2450	GAGUGUGACCA AAA	2451	UUUUGGUCACACUCU CAAC	29%
17381	2273	2452	GUGUGACCAAA AA	2453	UUUUUGGUCACACUC UCAA	42%
17382	2274	2454	UGUGACCAAAA GA	2455	UCUUUUGGUCACACU CUCA	42%
17383	2274	2456	GUGUGACCAAA AGA	2457	UCUUUUGGUCACACU CUCA	37%
17384	2275	2458	GUGACCAAAAG UA	2459	UACUUUUGGUCACAC UCUC	24%
17385	2277	2460	GACCAAAAGUU AA	2461	UUAACUUUUGGUCAC ACUC	27%
17386	2296	2462	GCACCUUUCUA GA	2463	UCUAGAAAGGUGCAA ACAU	23%
17387	2299	2464	CCUUUCUAGUU GA	2465	UCAACUAGAAAGGUG CAAA	46%

Table 16: Inhibition of gene expression with TGFB2 sd-rxRNA sequences (Accession Number: NM_001135599.1)

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM, A549)
14408	1324	2466	GGCUCUCCUUCGA	2467	UCGAAGGAGAGCCAU UCGC	94%
14409	1374	2468	GACAGGAACCUGG	2469	CCAGGUUCCUGUCUU UAUG	n/a
14410	946	2470	CCAAGGAGGUUUA	2471	UAAACCUCCUUGGCG UAGU	90%
14411	849	2472	AUUUCCAUCUACA	2473	UGUAGAUGGAAAUCA CCUC	72%
14412	852	2474	UCCAUCUACAACA	2475	UGUUGUAGAUGGAA AUCAC	76%
14413	850	2476	UUUCCAUCUACAA	2477	UUGUAGAUGGAAAU CACCU	98%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM, A549)
14414	944	2478	CGCCAAGGAGGUU	2479	AACCUCCUUGGCGUAGUAC	100%
14415	1513	2480	GUGGUGAUCAGAA	2481	UUCUGAUCACCACUGGUAU	n/a
14416	1572	2482	CUCCUGCUAAUGU	2483	ACAUUAGCAGGAGAUGUGG	100%
14417	1497	2484	ACCUCCACAUAUA	2485	UAUAUGUGGAGGUGCCAUC	73%
14418	1533	2486	AAGUCCACUAGGA	2487	UCCUAGUGGACUUUAUAGU	98%
14419	1514	2488	UGGUGAUCAGAAA	2489	UUUCUGAUCACCACUGGUA	86%
14420	1534	2490	AGUCCACUAGGAA	2491	UUCCUAGUGGACUUUAUAG	99%
14421	943	2492	ACGCCAAGGAGGU	2493	ACCUCCUUGGCGUAGUACU	41%
18570	2445	2494	UAUUUAUUGUGUA	2495	UACACAAUAAAUAACUCAC	79%
18571	2445	2496	UUAUUUAUUGUGUA	2497	UACACAAUAAAUAACUCAC	75%
18572	2083	2498	AUCAGUGUUAAAA	2499	UUUUAACACUGAUGAACCA	47%
18573	2083	2500	CAUCAGUGUUAAAA	2501	UUUUAACACUGAUGAACCA	17%
18574	2544	2502	AUGGCUUAAGGAA	2503	UUCCUUAAGCCAUCCAUGA	59%
18575	2544	2504	GAUGGCUUAAGGAA	2505	UUCCUUAAGCCAUCCAUGA	141%
18576	2137	2506	UUGUGUUCUGUUA	2507	UAACAGAACACAAACUUCC	77%
18577	2137	2508	UUUGUGUUCUGUUA	2509	UAACAGAACACAAACUUCC	59%
18578	2520	2510	AAAUACUUUGCCA	2511	UGGCAAAGUAUUUGGUCUC	75%
18579	2520	2512	CAAAUACUUUGCCA	2513	UGGCAAAGUAUUUGGUCUC	55%
18580	3183	2514	CUUGCACUACAAA	2515	UUUGUAGUGCAAGUCAAAC	84%
18581	3183	2516	ACUUGCACUACAAA	2517	UUUGUAGUGCAAGUCAAAC	80%
18582	2267	2518	GAAUUUAUUAGUA	2519	UACUAAUAAAUUCUUCCAG	82%
18583	2267	2520	AGAAUUUAUUAGUA	2521	UACUAAUAAAUUCUUCCAG	67%
18584	3184	2522	UUGCACUACAAAA	2523	UUUUGUAGUGCAAGUCAAA	77%
18585	3184	2524	CUUGCACUACAAAA	2525	UUUUGUAGUGCAAGUCAAA	59%
18586	2493	2526	AUAAAACAGGUGA	2527	UCACCUGUUUUAUUUUCCA	84%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM, A549)
18587	2493	2528	AAUAAAACAGGUGA	2529	UCACCUGUUUUAUUUUCCA	70%
18588	2297	2530	GACAACAACAACA	2531	UGUUGUUGUUGUCGUUGUU	40%
18589	2046	2532	AUGCUUGUAACAA	2533	UUGUUACAAGCAUCAUCGU	39%
18590	2531	2534	CAGAAACUCAUGA	2535	UCAUGAGUUUCUGGCAAAG	56%
18591	2389	2536	GUAUUGCUAUGCA	2537	UGCAUAGCAAUACAGAAAA	64%
18592	2530	2538	CCAGAAACUCAUA	2539	UAUGAGUUUCUGGCAAAGU	44%
18593	2562	2540	ACUCAAACGAGCA	2541	UGCUCGUUUGAGUUCAAGU	87%
18594	2623	2542	AUAUGACCGAGAA	2543	UUCUCGGUCAUAUAAUAAC	69%
18595	2032	2544	CGACGACAACGAA	2545	UUCGUUGUCGUCGUCAUCA	55%
18596	2809	2546	GUAAACCAGUGAA	2547	UUCACUGGUUUACUAAACU	58%
18597	2798	2548	UUGUCAGUUUAGA	2549	UCUAAACUGACAAAGAACC	38%
18598	2081	2550	UCAUCAGUGUUAA	2551	UUAACACUGAUGAACCAAG	25%
18599	2561	2552	AACUCAAACGAGA	2553	UCUCGUUUGAGUUCAAGUU	57%
18600	2296	2554	CGACAACAACAAA	2555	UUUGUUGUUGUCGUUGUUC	69%
18601	2034	2556	ACGACAACGAUGA	2557	UCAUCGUUGUCGUCGUCAU	22%
18602	2681	2558	GCUGCCUAAGGAA	2559	UUCCUUAGGCAGCUGAUAC	43%
18603	2190	2560	AUUCUACAUUUCA	2561	UGAAAUGUAGAAUAAGGCC	128%

Table 17: Inhibition of gene expression with TGFB1 sd-rxRNA sequences (Accession Number NM_000660.3)

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Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14394	1194	2562	GCUAAUGGUGGAA	2563	UUCCACCAUUAGCACGCGG	24%
14395	2006	2564	UGAUCGUGCGCUC	2565	GAGCGCACGAUCAUGUUGG	79%
14396	1389	2566	CAAUUCCUGGCGA	2567	UCGCCAGGAAUUGUUGCUG	77%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14397	1787	2568	AGUGGAUCCACGA	2569	UCGUGGAUCCACUU CCAGC	n/a
14398	1867	2570	UACAGCAAGGUCC	2571	GGACCUUGCUGUAC UGCGU	82%
14399	2002	2572	AACAUGAUCGUGC	2573	GCACGAUCAUGUUG GACAG	n/a
14400	2003	2574	ACAUGAUCGUGCG	2575	CGCACGAUCAUGUU GGACA	n/a
14401	1869	2576	CAGCAAGGUCCUG	2577	CAGGACCUUGCUGU ACUGC	82%
14402	2000	2578	CCAACAUGAUCGU	2579	ACGAUCAUGUUGGA CAGCU	66%
14403	986	2580	AGCGGAAGCGCAU	2581	AUGCGCUUCCGCUU CACCA	78%
14404	995	2582	GCAUCGAGGCCAU	2583	AUGGCCUCGAUGCG CUUCC	79%
14405	963	2584	GACUAUCGACAUG	2585	CAUGUCGAUAGUCU UGCAG	80%
14406	955	2586	ACCUGCAAGACUA	2587	UAGUCUUGCAGGUG GAUAG	88%
14407	1721	2588	GCUCCACGGAGAA	2589	UUCUCCGUGGAGCU GAAGC	n/a
18454	1246	2590	CACAGCAUAUAUA	2591	UAUAUAUGCUGUG UGUACU	58%
18455	1248	2592	CAGCAUAUAUAUA	2593	UAUAUAUAUGCUGU GUGUA	87%
18456	1755	2594	GUACAUUGACUUA	2595	UAAGUCAAUGUACA GCUGC	107%
18457	1755	2596	UGUACAUUGACUU A	2597	UAAGUCAAUGUACA GCUGC	77%
18458	1708	2598	AACUAUUGCUUCA	2599	UGAAGCAAUAGUUG GUGUC	75%
18459	1708	2600	CAACUAUUGCUUC A	2601	UGAAGCAAUAGUUG GUGUC	73%
18460	1250	2602	GCAUAUAUAUGUA	2603	UACAUAUAUAUGCU GUGUG	n/a
18461	1754	2604	UGUACAUUGACUA	2605	UAGUCAAUGUACAG CUGCC	91%
18462	1754	2606	CUGUACAUUGACU A	2607	UAGUCAAUGUACAG CUGCC	92%
18463	1249	2608	AGCAUAUAUAUGA	2609	UCAUAUAUAUGCUG UGUGU	n/a
18464	1383	2610	CAGCAACAAUUCA	2611	UGAAUUGUUGCUG UAUUUC	77%
18465	1251	2612	CAUAUAUAUGUUA	2613	UAACAUAUAUAUGC UGUGU	84%
18466	1713	2614	UUGCUUCAGCUCA	2615	UGAGCUGAAGCAAU AGUUG	n/a
18467	1713	2616	AUUGCUUCAGCUC A	2617	UGAGCUGAAGCAAU AGUUG	83%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
18468	1247	2618	ACAGCAUAUAUAA	2619	UUAUAUAUGCUGUGUGUAC	96%
18469	1712	2620	AUUGCUUCAGCUA	2621	UAGCUGAAGCAAUAGUUGG	90%
18470	1712	2622	UAUUGCUUCAGCUA	2623	UAGCUGAAGCAAUAGUUGG	98%
18471	1212	2624	CAAGUUCAAGCAA	2625	UUGCUUGAACUUGUCAUAG	n/a
18472	1222	2626	CAGAGUACACACA	2627	UGUGUGUACUCUGCUUGAA	45%
18473	1228	2628	ACACACAGCAUAA	2629	UUAUGCUGUGUGUACUCUG	36%
18474	1233	2630	CAGCAUAUAUAUA	2631	UAUAUAUAUGCUGUGUGUA	68%
18475	1218	2632	UCAAGCAGAGUAA	2633	UUACUCUGCUUGAACUUGU	64%
18476	1235	2634	AGCAUAUAUAUGA	2635	UCAUAUAUAUGCUGUGUGU	78%
18477	1225	2636	AGAGUACACACAA	2637	UUGUGUGUACUCUGCUUGA	92%
18478	1221	2638	AAGCAGAGUACAA	2639	UUGUACUCUGCUUGAACUU	103%
18479	1244	2640	UUCAACACAUCAA	2641	UUGAUGUGUUGAAGAACAU	84%
18480	1224	2642	AGCAGAGUACACA	2643	UGUGUACUCUGCUUGAACU	37%
18481	1242	2644	AUAUAUGUUCUUA	2645	UAAGAACAUAUAUAUGCUG	62%
18482	1213	2646	GACAAGUUCAAGA	2647	UCUUGAACUUGUCAUAGAU	47%
18483	1760	2648	UUAAAGAUGGAGA	2649	UCUCCAUCUUUAAUGGGGC	69%
18484	1211	2650	CUAUGACAAGUUA	2651	UAACUUGUCAUAGAUUUCG	n/a
19411	1212	2652	CAACGAAAUCUAA	2653	UUAGAUUUCGUUGUGGGUU	52%
19412	1222	2654	UAUGACAAGUUCA	2655	UGAACUUGUCAUAGAUUUC	51%
19413	1228	2656	AAGUUCAAGCAGA	2657	UCUGCUUGAACUUGUCAUA	n/a
19414	1233	2658	CAAGCAGAGUACA	2659	UGUACUCUGCUUGAACUUG	41%
19415	1218	2660	AAUCUAUGACAAA	2661	UUUGUCAUAGAUUUCGUUG	104%
19416	1244	2662	CACACAGCAUAUA	2663	UAUAUGCUGUGUGUACUCU	31%

Table 18: Inhibition of gene expression with SPP1 sd-rxRNA sequences (Accession Number NM_000582.2)

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14084	1025	2664	mC.mU.mC. A.mU. G. A. A.mU.mU. A. G. A.Chl	2665	P.mU.fC.fU. A. A.fU.fU.fC. A.fU. G. A. G* A* A* A*mU* A* C.	61%
14085	1049	2666	mC.mU. G. A. G. G.mU.mC. A. A.mU.mU. A.Chl	2667	P.mU. A. A.fU.fU. G. A.fC.fC.fU.mC. A. G* A* A* G* A*mU* G.	50%
14086	1051	2668	G. A. G. G.mU.mC. A. A.mU.mU. A. A. A.Chl	2669	P.mU.fU.fU. A. A.fU.fU. G. A.fC.mC.mU.mC* A* G* A* A* G* A.	n/a
14087	1048	2670	mU.mC.mU. G. A. G. G.mU.mC. A. A.mU.mU.Chl	2671	P.mA. A.fU.fU. G. A.fC.fC.fU.fC. A. G. A* A* G* A*mU* G* C.	69%
14088	1050	2672	mU. G. A. G. G.mU.mC. A. A.mU.mU. A. A.Chl	2673	P.mU.fU. A. A.fU.fU. G. A.fC.fC.mU.mC. A* G* A* A* G* A* U.	76%
14089	1047	2674	mU.mU.mC.mU. G. A. G. G.mU.mC. A. A.mU.Chl	2675	P.mA.fU.fU. G. A.fC.fC.fU.fC. A. G. A. A* G* A*mU* G*mC* A.	60%
14090	800	2676	G.mU.mC. A. G.mC.mU. G. G. A.mU. G. A.Chl	2677	P.mU.fC. A.fU.fC.fC. A. G.fC.fU. G. A.mC*mU*mC* G*mU*mU* U.	71%
14091	492	2678	mU.mU.mC.mU. G. A.mU. G. A. A.mU.mC.mU.Chl	2679	P.mA. G. A.fU.fU.fC. A.fU.fC. A. G. A. A*mU* G* G*mU* G* A.	n/a
14092	612	2680	mU. G. G. A.mC.mU. G. A. G. G.mU.mC. A.Chl	2681	P.mU. G. A.fC.fC.fU.fC. A. G.fU.mC.mC. A*mU* A* A* A*mC* C.	n/a
14093	481	2682	G. A. G.mU.mC.mU.mC. A.mC.mC. A.mU.mU.Chl	2683	P.mA. A.fU. G. G.fU. G. A. G. A.mC.mU.mC* A*mU*mC* A* G* A.	n/a
14094	614	2684	G. A.mC.mU. G. A. G. G.mU.mC. A. A. A.Chl	2685	P.mU.fU.fU. G. A.fC.fC.fU.fC. A. G.mU.mC*mC* A*mU* A* A* A.	n/a
14095	951	2686	mU.mC. A.mC. A. G.mC.mC. A.mU. G. A. A.Chl	2687	P.mU.fU.fC. A.fU. G. G.fC.fU. G.mU. G. A* A* A*mU*mU*mC* A.	89%
14096	482	2688	A. G.mU.mC.mU.mC. A.mC.mC. A.mU.mU.mC.Chl	2689	P.mG. A. A.fU. G. G.fU. G. A. G. A.mC.mU*mC* A*mU*mC* A* G.	87%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14097	856	2690	A. A. G.mC. G. G. A. A. A. G.mC.mC. A.Chl	2691	P.mU. G. G.fC.fU.fU.fU.fC.fC. G.mC.mU.mU* A*mU* A*mU* A* A.	88%
14098	857	2692	A. G.mC. G. G. A. A. A. G.mC.mC. A. A.Chl	2693	P.mU.fU. G. G.fC.fU.fU.fU.fC.fC. G.mC.mU*mU* A*mU* A*mU* A.	113%
14099	365	2694	A.mC.mC. A.mC. A.mU. G. G. A.mU. G. A.Chl	2695	P.mU.fC. A.fU.fC.fC. A.fU. G.fU. G. G.mU*mC* A*mU* G* G* C.	98%
14100	359	2696	G.mC.mC. A.mU. G. A.mC.mC. A.mC. A.mU.Chl	2697	P.mA.fU. G.fU. G. G.fU.fC. A.fU. G. G.mC*mU*mU*mU*mC* G* U.	84%
14101	357	2698	A. A. G.mC.mC. A.mU. G. A.mC.mC. A.mC.Chl	2699	P.mG.fU. G. G.fU.fC. A.fU. G. G.mC.mU.mU*mU*mC* G*mU*mU* G.	88%
14102	858	2700	G.mC. G. G. A. A. A. G.mC.mC. A. A.mU.Chl	2701	P.mA.fU.fU. G. G.fC.fU.fU.fU.fC.mC. G.mC*mU*mU* A*mU* A* U.	n/a
14103	1012	2702	A. A. A.mU.mU.mU.mC. G.mU. A.mU.mU.mU.Chl	2703	P.mA. A. A.fU. A.fC. G. A. A. A.mU.mU.mU*mC* A* G* G*mU* G.	93%
14104	1014	2704	A.mU.mU.mU.mC. G.mU. A.mU.mU.mU.mC.mU.Chl	2705	P.mA. G. A. A. A.fU. A.fC. G. A. A. A.mU*mU*mU*mC* A* G* G.	89%
14105	356	2706	A. A. A. G.mC.mC. A.mU. G. A.mC.mC. A.Chl	2707	P.mU. G. G.fU.fC. A.fU. G. G.fC.mU.mU.mU*mC* G*mU*mU* G* G.	85%
14106	368	2708	A.mC. A.mU. G. G. A.mU. G. A.mU. A.mU.Chl	2709	P.mA.fU. A.fU.fC. A.fU.fC.fC. A.mU. G.mU* G* G*mU*mC* A* U.	67%
14107	1011	2710	G. A. A. A.mU.mU.mU.mC. G.mU. A.mU.mU.Chl	2711	P.mA. A.fU. A.fC. G. A. A. A.fU.mU.mU.mC* A* G* G*mU* G* U.	87%
14108	754	2712	G.mC. G.mC.mC.mU.mU.mC.mU. G. A.mU.mU.Chl	2713	P.mA. A.fU.fC. A. G. A. A. G. G.mC. G.mC* G*mU*mU*mC* A* G.	73%
14109	1021	2714	A.mU.mU.mU.mC.mU.mC. A.mU. G. A. A.mU.Chl	2715	P.mA.fU.fU.fC. A.fU. G. A. G. A. A. A.mU* A*mC* G* A* A* A.	128%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14110	1330	2716	mC.mU.mC.mU.mC. A.mU. G. A. A.mU. A. G.Chl	2717	P.mC.fU. A.fU.fU.fC. A.fU. G. A. G. A. G* A* A*mU* A* A* C.	101%
14111	346	2718	A. A. G.mU.mC.mC. A. A.mC. G. A. A. A.Chl	2719	P.mU.fU.fU.fC. G.fU.fU. G. G. A.mC.mU.mU* A*mC*mU*mU* G* G.	59%
14112	869	2720	A.mU. G. A.mU. G. A. G. A. G.mC. A. A.Chl	2721	P.mU.fU. G.fC.fU.fC.fU.fC. A.fU.mC. A.mU*mU* G* G*mC*mU* U.	89%
14113	701	2722	G.mC. G. A. G. G. A. G.mU.mU. G. A. A.Chl	2723	P.mU.fU.fC. A. A.fC.fU.fC.fC.fU.mC. G.mC*mU*mU*mU*m C*mC* A.	95%
14114	896	2724	mU. G. A.mU.mU. G. A.mU. A. G.mU.mC. A.Chl	2725	P.mU. G. A.fC.fU. A.fU.fC. A. A.mU.mC. A*mC* A*mU*mC* G* G.	87%
14115	1035	2726	A. G. A.mU. A. G.mU. G.mC. A.mU.mC.mU.Chl	2727	P.mA. G. A.fU. G.fC. A.fC.fU. A.mU.mC.mU* A* A*mU*mU*mC* A.	82%
14116	1170	2728	A.mU. G.mU. G.mU. A.mU.mC.mU. A.mU.mU.Chl	2729	P.mA. A.fU. A. G. A.fU. A.fC. A.mC. A.mU*mU*mC* A* A*mC* C.	36%
14117	1282	2730	mU.mU.mC.mU. A.mU. A. G. A. A. G. A. A.Chl	2731	P.mU.fU.fC.fU.fU.fC.fU. A.fU. A. G. A. A*mU* G* A* A*mC* A.	91%
14118	1537	2732	mU.mU. G.mU.mC.mC. A. G.mC. A. A.mU.mU.Chl	2733	P.mA. A.fU.fU. G.fC.fU. G. G. A.mC. A. A*mC*mC* G*mU* G* G.	152%
14119	692	2734	A.mC. A.mU. G. G. A. A. A. G. C.mG. A.Chl	2735	P.mU.fC. G.fC.fU.fU.fU.fC.fC. A.mU. G.mU* G*mU* G* A* G* G.	n/a
14120	840	2736	G.mC. A. G.mU.mC.mC. A. G. A.mU.mU. A.Chl	2737	P.mU. A. A.fU.fC.fU. G. G. A.fC.mU. G.mC*mU*mU* G*mU* G* G.	87%
14121	1163	2738	mU. G. G.mU.mU. G. A. A.mU. G.mU. G.mU.Chl	2739	P.mA.fC. A.fC. A.fU.fU.fC. A. A.mC.mC. A* A*mU* A* A* A* C.	31%
14122	789	2740	mU.mU. A.mU. G. A. A. A.mC. G. A. G.mU.Chl	2741	P.mA.fC.fU.fC. G.fU.fU.fU.fC. A.mU. A. A*mC*mU* G*mU*mC* C.	96%
14123	841	2742	mC. A. G.mU.mC.mC. A. G. A.mU.mU. A.mU.Chl	2743	P.mA.fU. A. A.fU.fC.fU. G. G. A.mC.mU. G*mC*mU*mU* G*mU* G.	110%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14124	852	2744	A.mU. A.mU. A. A. G.mC. G. G. A. A. A.Chl	2745	P.mU.fU.fU.fC.fC. G.fC.fU.fU. A.mU. A.mU* A* A*mU*mC*mU* G.	91%
14125	209	2746	mU. A.mC.mC. A. G.mU.mU. A. A. A.mC. A.Chl	2747	P.mU. G.fU.fU.fU. A. A.fC.fU. G. G.mU. A*mU* G* G*mC* A* C.	110%
14126	1276	2748	mU. G.mU.mU.mC. A.mU.mU.mC.mU. A.mU. A.Chl	2749	P.mU. A.fU. A. G. A. A.fU. G. A. A.mC. A*mU* A* G* A*mC* A.	n/a
14127	137	2750	mC.mC. G. A.mC.mC. A. A. G. G. A. A. A.Chl	2751	P.mU.fU.fU.fC.fC.fU.fU. G. G.fU.mC. G. G*mC* G*mU*mU*mU* G.	71%
14128	711	2752	G. A. A.mU. G. G.mU. G.mC. A.mU. A.mC.Chl	2753	P.mG.fU. A.fU. G.fC. A.fC.fC. A.mU.mU.mC* A* A*mC*mU*mC* C.	115%
14129	582	2754	A.mU. A.mU. G. A.mU. G. G.mC.mC. G. A.Chl	2755	P.mU.fC. G. G.fC.fC. A.fU.fC. A.mU. A.mU* G*mU* G*mU*mC* U.	97%
14130	839	2756	A. G.mC. A. G.mU.mC.mC. A. G. A.mU.mU.Chl	2757	P.mA. A.fU.fC.fU. G. G. A.fC.fU. G.mC.mU*mU* G*mU* G* G* C.	102%
14131	1091	2758	G.mC. A.mU.mU.mU. A. G.mU.mC. A. A. A.Chl	2759	P.mU.fU.fU. G. A.fC.fU. A. A. A.mU. G.mC* A* A* A* G*mU* G.	10%
14132	884	2760	A. G.mC. A.mU.mU.mC.mC. G. A.mU. G.mU.Chl	2761	P.mA.fC. A.fU.fC. G. G. A. A.fU. G.mC.mU*mC* A*mU*mU* G* C.	93%
14133	903	2762	mU. A. G.mU.mC. A. G. G. A. A.mC.mU.mU.Chl	2763	P.mA. A. G.fU.fU.fC.fC.fU. G. A.mC.mU. A*mU*mC* A* A*mU* C.	97%
14134	1090	2764	mU. G.mC. A.mU.mU.mU. A. G.mU.mC. A. A.Chl	2765	P.mU.fU. G. A.fC.fU. A. A. A.fU. G.mC. A* A* A* G*mU* G* A.	39%
14135	474	2766	G.mU.mC.mU. G. A.mU. G. A. G.mU.mC.mU.Chl	2767	P.mA. G. A.fC.fU.fC. A.fU.fC. A. G. A.mC*mU* G* G*mU* G* A.	99%
14136	575	2768	mU. A. G. A.mC. A.mC. A.mU. A.mU. G. A.Chl	2769	P.mU.fC. A.fU. A.fU. G.fU. G.fU.mC.mU. A*mC*mU* G*mU* G* G.	108%
14137	671	2770	mC. A. G. A.mC. G. A. G. G. A.mC. A.mU.Chl	2771	P.mA.fU. G.fU.fC.fC.fU.fC. G.fU.mC.mU. G*mU* A* G*mC* A* U.	98%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14138	924	2772	mC. A. G.mC.mC. G.mU. G. A. A.mU.mU.mC.Chl	2773	P.mG. A. A.fU.fU.fC. A.fC. G. G.mC.mU. G* A*mC*mU*mU*mU* G.	100%
14139	1185	2774	A. G.mU.mC.mU. G. G. A. A. A.mU. A. A.Chl	2775	P.mU.fU. A.fU.fU.fU.fC.fC. A. G. A.mC.mU*mC* A* A* A*mU* A.	47%
14140	1221	2776	A. G.mU.mU.mU. G.mU. G. G.mC.mU.mU.mC.Chl	2777	P.mG. A. A. G.fC.fC. A.fC. A. A. A.mC.mU* A* A* A*mC*mU* A.	100%
14141	347	2778	A. G.mU.mC.mC. A. A.mC. G. A. A. A. G.Chl	2779	P.mC.fU.fU.fU.fC. G.fU.fU. G. G. A.mC.mU*mU* A*mC*mU*mU* G.	103%
14142	634	2780	A. A. G.mU.mU.mU.mC. G.mC. A. G. A.mC.Chl	2781	P.mG.fU.fC.fU. G.fC. G. A. A. A.mC.mU.mU*mC*mU *mU* A* G* A.	100%
14143	877	2782	A. G.mC. A. A.mU. G. A. G.mC. A.mU.mU.Chl	2783	P.mA. A.fU. G.fC.fU.fC. A.fU.fU. G.mC.mU*mC*mU*mC * A*mU* C.	104%
14144	1033	2784	mU.mU. A. G. A.mU. A. G.mU. G.mC. A.mU.Chl	2785	P.mA.fU. G.fC. A.fC.fU. A.fU.fC.mU. A. A*mU*mU*mC* A*mU* G.	95%
14145	714	2786	mU. G. G.mU. G.mC. A.mU. A.mC. A. A. G.Chl	2787	P.mC.fU.fU. G.fU. A.fU. G.fC. A.mC.mC. A*mU*mU*mC* A* A* C.	101%
14146	791	2788	A.mU. G. A. A. A.mC. G. A. G.mU.mC. A.Chl	2789	P.mU. G. A.fC.fU.fC. G.fU.fU.fU.mC. A.mU* A* A*mC*mU* G* U.	100%
14147	813	2790	mC.mC. A. G. A. G.mU. G.mC.mU. G. A. A.Chl	2791	P.mU.fU.fC. A. G.fC. A.fC.fU.fC.mU. G. G*mU*mC* A*mU*mC* C.	97%
14148	939	2792	mC. A. G.mC.mC. A.mU. G. A. A.mU.mU.mU.Chl	2793	P.mA. A. A.fU.fU.fC. A.fU. G. G.mC.mU. G*mU* G* G* A* A* U.	109%
14149	1161	2794	A.mU.mU. G. G.mU.mU. G. A. A.mU. G.mU.Chl	2795	P.mA.fC. A.fU.fU.fC. A. A.fC.fC. A. A.mU* A* A* A*mC*mU* G.	34%
14150	1164	2796	G. G.mU.mU. G. A. A.mU. G.mU. G.mU. A.Chl	2797	P.mU. A.fC. A.fC. A.fU.fU.fC. A. A.mC.mC* A* A*mU* A* A* A.	n/a
14151	1190	2798	G. G. A. A. A.mU. A. A.mC.mU. A. A.mU.Chl	2799	P.mA.fU.fU. A. G.fU.fU. A.fU.fU.mU.mC.mC* A* G* A*mC*mU* C.	n/a

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14152	1333	2800	mU.mC. A.mU. G. A. A.mU. A. G. A. A. A.Chl	2801	P.mU.fU.fU.fC.fU. A.fU.fU.fC. A.mU. G. A* G* A* G* A* A* U.	31%
14153	537	2802	G.mC.mC. A. G.mC. A. A.mC.mC. G. A. A.Chl	2803	P.mU.fU.fC. G. G.fU.fU. G.fC.fU. G. G.mC* A* G* G*mU*mC* C.	n/a
14154	684	2804	mC. A.mC.mC.mU.mC. A.mC. A.mC. A.mU. G.Chl	2805	P.mC. A.fU. G.fU. G.fU. G. A. G. G.mU. G* A*mU* G*mU*mC* C.	100%
14155	707	2806	A. G.mU.mU. G. A. A.mU. G. G.mU. G.mC.Chl	2807	P.mG.fC. A.fC.fC. A.fU.fU.fC. A. A.mC.mU*mC*mC*mU *mC* G* C.	99%
14156	799	2808	A. G.mU.mC. A. G.mC.mU. G. G. A.mU. G.Chl	2809	P.mC. A.fU.fC.fC. A. G.fC.fU. G. A.mC.mU*mC* G*mU*mU*mU* C.	95%
14157	853	2810	mU. A.mU. A. A. G.mC. G. G. A. A. A. G.Chl	2811	P.mC.fU.fU.fU.fC.fC. G.fC.fU.fU. A.mU. A*mU* A* A*mU*mC* U.	106%
14158	888	2812	mU.mU.mC.mC. G. A.mU. G.mU. G. A.mU.mU.Chl	2813	P.mA. A.fU.fC. A.fC. A.fU.fC. G. G. A. A*mU* G*mC*mU*mC* A.	88%
14159	1194	2814	A.mU. A. A.mC.mU. A. A.mU. G.mU. G.mU.Chl	2815	P.mA.fC. A.fC. A.fU.fU. A. G.fU.mU. A.mU*mU*mU*mC*m C* A* G.	95%
14160	1279	2816	mU.mC. A.mU.mU.mC.mU. A.mU. A. G. A. A.Chl	2817	P.mU.fU.fC.fU. A.fU. A. G. A. A.mU. G. A* A*mC* A*mU* A* G.	15%
14161	1300	2818	A. A.mC.mU. A.mU.mC. A.mC.mU. G.mU. A.Chl	2819	P.mU. A.fC. A. G.fU. G. A.fU. A. G.mU.mU*mU* G*mC* A*mU* U.	86%
14162	1510	2820	G.mU.mC. A. A.mU.mU. G.mC.mU.mU. A.mU.Chl	2821	P.mA.fU. A. A. G.fC. A. A.fU.fU. G. A.mC* A*mC*mC* A*mC* C.	86%
14163	1543	2822	A. G.mC. A. A.mU.mU. A. A.mU. A. A. A.Chl	2823	P.mU.fU.fU. A.fU.fU. A. A.fU.fU. G.mC.mU* G* G* A*mC* A* A.	110%
14164	434	2824	A.mC. G. A.mC.mU.mC.mU. G. A.mU. G. A.Chl	2825	P.mU.fC. A.fU.fC. A. G. A. G.fU.mC. G.mU*mU*mC* G* A* G* U.	134%
14165	600	2826	mU. A. G.mU. G.mU. G. G.mU.mU.mU. A.mU.Chl	2827	P.mA.fU. A. A. A.fC.fC. A.fC. A.mC.mU. A*mU*mC* A*mC*mC* U.	102%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14166	863	2828	A. A. G.mC.mC. A. A.mU. G. A.mU. G. A.Chl	2829	P.mU.fC. A.fU.fC. A.fU.fU. G. G.mC.mU.mU*mU*mC *mC* G*mC* U.	93%
14167	902	2830	A.mU. A. G.mU.mC. A. G. G. A. A.mC.mU.Chl	2831	P.mA. G.fU.fU.fC.fC.fU. G. A.fC.mU. A.mU*mC* A* A*mU*mC* A.	101%
14168	921	2832	A. G.mU.mC. A. G.mC.mC. G.mU. G. A. A.Chl	2833	P.mU.fU.fC. A.fC. G. G.fC.fU. G. A.mC.mU*mU*mU* G* G* A* A.	98%
14169	154	2834	A.mC.mU. A.mC.mC. A.mU. G. A. G. A. A.Chl	2835	P.mU.fU.fC.fU.fC. A.fU. G. G.fU. A. G.mU* G* A* G*mU*mU* U.	n/a
14170	217	2836	A. A. A.mC. A. G. G.mC.mU. G. A.mU.mU.Chl	2837	P.mA. A.fU.fC. A. G.fC.fC.fU. G.mU.mU.mU* A* A*mC*mU* G* G.	66%
14171	816	2838	G. A. G.mU. G.mC.mU. G. A. A. A.mC.mC.Chl	2839	P.mG. G.fU.fU.fU.fC. A. G.fC. A.mC.mU.mC*mU* G* G*mU*mC* A.	102%
14172	882	2840	mU. G. A. G.mC. A.mU.mU.mC.mC. G. A.mU.Chl	2841	P.mA.fU.fC. G. G. A. A.fU. G.fC.mU.mC. A*mU*mU* G*mC*mU* C.	103%
14173	932	2842	A. A.mU.mU.mC.mC. A.mC. A. G.mC.mC. A.Chl	2843	P.mU. G. G.fC.fU. G.fU. G. G. A. A.mU.mU*mC* A*mC* G* G* C.	n/a
14174	1509	2844	mU. G.mU.mC. A. A.mU.mU. G.mC.mU.mU. A.Chl	2845	P.mU. A. A. G.fC. A. A.fU.fU. G. A.mC. A*mC*mC* A*mC*mC* A.	n/a
14175	157	2846	A.mC.mC. A.mU. G. A. G. A. A.mU.mU. G.Chl	2847	P.mC. A. A.fU.fU.fC.fU.fC. A.fU. G. G.mU* A* G*mU* G* A* G.	109%
14176	350	2848	mC.mC. A. A.mC. G. A. A. A. G.mC.mC. A.Chl	2849	P.mU. G. G.fC.fU.fU.fU.fC. G.fU.mU. G. G* A*mC*mU*mU* A* C.	95%
14177	511	2850	mC.mU. G. G.mU.mC. A.mC.mU. G. A.mU.mU.Chl	2851	P.mA. A.fU.fC. A. G.fU. G. A.fC.mC. A. G*mU*mU*mC* A*mU* C.	100%
14178	605	2852	mU. G. G.mU.mU.mU. A.mU. G. G. A.mC.mU.Chl	2853	P.mA. G.fU.fC.fC. A.fU. A. A. A.mC.mC. A*mC* A*mC*mU* A* U.	99%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14179	811	2854	G. A.mC.mC. A. G. A. G.mU. G.mC.mU. G.Chl	2855	P.mC. A. G.fC. A.fC.fU.fC.fU. G. G.mU.mC* A*mU*mC*mC* A* G.	88%
14180	892	2856	G. A.mU. G.mU. G. A.mU.mU. G. A.mU. A.Chl	2857	P.mU. A.fU.fC. A. A.fU.fC. A.fC. A.mU.mC* G* G* A* A*mU* G.	76%
14181	922	2858	G.mU.mC. A. G.mC.mC. G.mU. G. A. A.mU.Chl	2859	P.mA.fU.fU.fC. A.fC. G. G.fC.fU. G. A.mC*mU*mU*mU* G* G* A.	59%
14182	1169	2860	A. A.mU. G.mU. G.mU. A.mU.mC.mU. A.mU.Chl	2861	P.mA.fU. A. G. A.fU. A.fC. A.fC. A.mU.mU*mC* A* A*mC*mC* A.	69%
14183	1182	2862	mU.mU. G. A. G.mU.mC.mU. G. G. A. A. A.Chl	2863	P.mU.fU.fU.fC.fC. A. G. A.fC.fU.mC. A. A* A*mU* A* G* A* U.	n/a
14184	1539	2864	G.mU.mC.mC. A. G.mC. A. A.mU.mU. A. A.Chl	2865	P.mU.fU. A. A.fU.fU. G.fC.fU. G. G. A.mC* A* A*mC*mC* G* U.	77%
14185	1541	2866	mC.mC. A. G.mC. A. A.mU.mU. A. A.mU. A.Chl	2867	P.mU. A.fU.fU. A. A.fU.fU. G.fC.mU. G. G* A*mC* A* A*mC* C.	n/a
14186	427	2868	G. A.mC.mU.mC. G. A. A.mC. G. A.mC.mU.Chl	2869	P.mA. G.fU.fC. G.fU.fU.fC. G. A. G.mU.mC* A* A*mU* G* G* A.	69%
14187	533	2870	A.mC.mC.mU. G.mC.mC. A. G.mC. A. A.mC.Chl	2871	P.mG.fU.fU. G.fC.fU. G. G.fC. A. G. G.mU*mC*mC* G*mU* G* G.	78%
18538	496	2872	G. A.mU. G. A. A.mU.mC.mU. G. A.mU. A.Chl	2873	P.mU. A.fU.fC. A. G. A.fU.fU.fC. A.fU.fC* A* G* A* A*fU* G.	74%
18539	496	2874	mU. G. A.mU. G. A. A.mU.mC.mU. G. A.mU. A.Chl	2875	P.mU. A.fU.fC. A. G. A.fU.fU.fC. A.fU.fC* A* G* A* A*fU* G.	72%
18540	175	2876	A.mU.mU.mU. G.mC.mU.mU.mU.mU. G.mC. A.Chl	2877	P.mU. G.fC. A. A. A. A. G.fC. A. A. A.fU*fC* A*fC*fU*fG* C.	98%
18541	175	2878	G. A.mU.mU.mU. G.mC.mU.mU.mU.mU. G.mC. A.Chl	2879	P.mU. G.fC. A. A. A. A. G.fC. A. A. A.fU*fC* A*fC*fU*fG* C.	28%
18542	172	2880	G.mU. G. A.mU.mU.mU. G.mC.mU.mU.mU. A.Chl	2881	P.mU. A. A. A. G.fC. A. A. A.fU.fC. A.fC*fU* G*fC* A* A* U.	24%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
18543	172	2882	A. G.mU. G. A.mU.mU.mU. G.mC.mU.mU.mU. A.Chl	2883	P.mU. A. A. A. G.fC. A. A. A.fU.fC. A.fC*fU* G*fC* A* A* U.	14%
18544	1013	2884	A. A.mU.mU.mU.mC. G.mU. A.mU.mU.mU. A.Chl	2885	P.mU. A. A. A.fU. A.fC. G. A. A. A.fU.fU*fU*fC* A* G* G* U.	100%
18545	1013	2886	A. A. A.mU.mU.mU.mC. G.mU. A.mU.mU.mU. A.Chl	2887	P.mU. A. A. A.fU. A.fC. G. A. A. A.fU.fU*fU*fC* A* G* G* U.	109%
18546	952	2888	mC. A.mC. A. G.mC.mC. A.mU. G. A. A. A.Chl	2889	P.mU.fU.fU. C. A.fU. G. G.fC.fU. G.fU. G* A* A* A*fU*fU* C.	32%
18547	952	2890	mU.mC. A.mC. A. G.mC.mC. A.mU. G. A. A. A.Chl	2891	P.mU.fU.fU. C. A.fU. G. G.fC.fU. G.fU. G* A* A* A*fU*fU* C.	33%
18548	174	2892	G. A.mU.mU.mU. G.mC.mU.mU.mU.m U. G. A.Chl	2893	P.mU.fC. A. A. A. A. G.fC. A. A. A.fU.fC* A*fC*fU* G*fC* A.	57%
18549	174	2894	mU. G. A.mU.mU.mU. G.mC.mU.mU.mU.m U. G. A.Chl	2895	P.mU.fC. A. A. A. A. G.fC. A. A. A.fU.fC* A*fC*fU* G*fC* A.	53%
18550	177	2896	mU.mU. G.mC.mU.mU.mU.m U. G.mC.mC.mU. A.Chl	2897	P.mU. A. G. G.fC. A. A. A. A. G.fC. A. A* A*fU*fC* A*fC* U.	97%
18551	177	2898	mU.mU.mU. G.mC.mU.mU.mU.m U. G.mC.mC.mU. A.Chl	2899	P.mU. A. G. G.fC. A. A. A. A. G.fC. A. A* A*fU*fC* A*fC* U.	103%
18552	1150	2900	mU.mU.mU.mC.mU. mC. A. G.mU.mU.mU. A. A.Chl	2901	P.mU.fU. A. A. A.fC.fU. G. A. G. A. A. A* G* A* A* G*fC* A.	96%
18553	1089	2902	mU.mU. G.mC. A.mU.mU.mU. A. G.mU.mC. A.Chl	2903	P.mU. G. A.fC.fU. A. A. A.fU. G.fC. A. A* A* G*fU* G* A* G.	94%
18554	1086	2904	A.mC.mU.mU.mU. G.mC. A.mU.mU.mU. A. A.Chl	2905	P.mU.fU. A. A. A.fU. G.fC. A. A. A. G.fU* G* A* G* A* A* A.	n/a
18555	1093	2906	A.mU.mU.mU. A. G.mU.mC. A. A. A. A. A.Chl	2907	P.mU.fU.fU.fU.fU. G. A.fC.fU. A. A. A.fU* G*fC* A* A* A* G.	n/a
18556	1147	2908	mU.mU.mC.mU.mU. mU.mC.mU.mC. A. G.mU. A.Chl	2909	P.mU. A.fC.fU. G. A. G. A. A. A. G. A. A* G*fC* A*fU*fU* U.	n/a

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
18557	1148	2910	mU.mC.mU.mU.mU. mC.mU.mC. A. G.mU.mU. A.Chl	2911	P.mU. A. A.fC.fU. G. A. G. A. A. A. G. A* A* G*fC* A*fU* U.	66%
18558	1128	2912	G. A. A. A. G. A. G. A. A.mC. A.mU. A.Chl	2913	P.mU. A.fU. G.fU.fU.fC.fU.fC.fU.fU.f U.fC* A*fU*fU*fU*fU* G.	16%
18559	1087	2914	mC.mU.mU.mU. G.mC. A.mU.mU.mU. A. G. A.Chl	2915	P.mU.fC.fU. A. A. A.fU. G.fC. A. A. A. G*fU* G* A* G* A* A.	28%
18560	1088	2916	mU.mU.mU. G.mC. A.mU.mU.mU. A. G.mU. A.Chl	2917	P.mU. A.fC.fU. A. A. A.fU. G.fC. A. A. A* G*fU* G* A* G* A.	n/a
18561	1083	2918	mC.mU.mC. A.mC.mU.mU.mU. G.mC. A.mU. A.Chl	2919	P.mU. A.fU. G.fC. A. A. A. G.fU. G. A. G* A* A* A*fU*fU* G.	53%
18562	1081	2920	mU.mU.mC.mU.mC. A.mC.mU.mU.mU. G.mC. A.Chl	2921	P.mU. G.fC. A. A. A. G.fU. G. A. G. A. A* A*fU*fU* G*fU* A.	89%
18563	555	2922	mC. A.mC.mU.mC.mC. A. G.mU.mU. G.mU. A.Chl	2923	P.mU. A.fC. A. A.fC.fU. G. G. A. G.fU. G* A* A* A* A*fC*fU.	33%
18564	1125	2924	A. A.mU. G. A. A. A. G. A. G. A. A. A.Chl	2925	P.mU.fU.fU.fC.fU.fC.fU. fU.fU.fC. A.fU.fU*fU*fU* G*fC*fU* A.	n/a
18565	168	2926	mU. G.mC. A. G.mU. G. A.mU.mU.mU.mG. A.Chl	2927	P.mU.fC. A. A. A.fU.fC. A.fC.fU. G.fC. A* A*fU*fU*fC*fU* C.	14%
18566	1127	2928	mU. G. A. A. A. G. A. G. A. A.mC. A. A.Chl	2929	P.mU.fU. G.fU.fU.fC.fU.fC.fU.fU.f U.fC. A*fU*fU*fU*fU* G* C.	27%
18567	1007	2930	A.mC.mC.mU. G. A. A. A.mU.mU.mU.mC. A.Chl	2931	P.mU. G. A. A. A.fU.fU.fU.fC. A. G. G.fU* G*fU*fU*fU* A* U.	129%
18568	164	2932	G. A. A.mU.mU. G.mC. A. G.mU. G. A. A.Chl	2933	P.mU.fU.fC. A.fC.fU. G.fC. A. A.fU.fU.fC*fU*fC* A*fU* G* G.	47%
18569	222	2934	G. G.mC.mU. G. A.mU.mU.mC.mU. G. G. A.Chl	2935	P.mU.fC.fC. A. G. A. A.fU.fC. A. G.fC.fC*fU* G*fU*fU*fU* A.	n/a
20612	172	2936	A. G.mU. G. A.mU.mU.mU. G.mC.mU.mU.mU. A.Chl	2937	P.mU. A. A. A. G.fC. A. A. A.fU.mC. A.mC*mU* G*mC* A* A* U.	n/a

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
20613	172	2938	A. G.mU. G. A.mU.mU.mU. G.mC.mU.mU.mU. A.Chl	2939	P.mU. A. A. A. G.fC. A. A. A.fU.fC. A.mC*fU* G*mC* A* A* U.	n/a
20614	172	2940	A. G.mU. G. A.mU.mU.mU. G.mC.mU.mU.mU. A.Chl	2941	P.mU. A. A. A. G. C. A. A. A. U.mC. A.mC*mU* G*mC* A* A* U.	101%
20615	172	2942	A. G.mU. G. A.mU.mU.mU. G.mC.mU.mU.mU. A.Chl	2943	P.mU. A. A. A. G.fC. A. A. A.fU.mC. A.mC*mU*mG*mC*m A*mA* U.	104%

Table 19: Inhibition of gene expression with PTGS2 sd-rxRNA sequences (Accession Number: NM_000963.2)

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14422	451	2944	mC. A.mC. A.mU.mU.mU. G. A.mU.mU. G. A.Chl	2945	P.mU.fC. A. A.fU.fC. A. A. A.fU. G.mU. G* A*mU*mC*mU* G* G.	72%
14423	1769	2946	mC. A.mC.mU. G.mC.mC.mU.mC. A. A.mU.mU.Chl	2947	P.mA. A.fU.fU. G. A. G. G.fC. A. G.mU. G*mU*mU* G* A*mU* G.	71%
14424	1464	2948	A. A. A.mU. A.mC.mC. A. G.mU.mC.mU.mU.C hl	2949	P.mA. A. G. A.fC.fU. G. G.fU. A.mU.mU.mU*mC* A*mU*mC*mU* G.	74%
14425	453	2950	mC. A.mU.mU.mU. G. A.mU.mU. G. A.mC. A.Chl	2951	P.mU. G.fU.fC. A. A.fU.fC. A. A. A.mU. G*mU* G* A*mU*mC* U.	83%
						% remaining expression (1 uM PC-3)
17388	285	2952	G. A. A. A. A.mC.mU. G.mC.mU.mC. A. A.Chl	2953	P.mU.fU. G. A. G.fC. A. G.fU.fU.fU.fU.fC*fU*fC *fC* A*fU* A.	88%
17389	520	2954	A.mC.mC.mU.mC.m U.mC.mC.mU. A.mU.mU. A.Chl	2955	P.mU. A. A.fU. A. G. G. A. G. A. G. G.fU*fU* A* G* A* G* A.	25%
17390	467	2956	mU.mC.mC. A.mC.mC. A. A.mC.mU.mU. A. A.Chl	2957	P.mU.fU. A. A. G.fU.fU. G. G.fU. G. G. A*fC*fU* G*fU*fC* A.	68%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
17391	467	2958	G.mU.mC.mC. A.mC.mC. A. A.mC.mU.mU. A. A.ChI	2959	P.mU.fU. A. A. G.fU.fU. G. G.fU. G. G. A*fC*fU* G*fU*fC* A.	101%
17392	524	2960	mC.mU.mC.mC.mU. A.mU.mU. A.mU. A.mC. A.ChI	2961	P.mU. G.fU. A.fU. A. A.fU. A. G. G. A. G* A* G* G*fU*fU* A.	49%
17393	448	2962	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A. A.ChI	2963	P.mU.fU.fC. A. A. A.fU. G.fU. G. A.fU.fC*fU* G* G* A*fU* G.	29%
17394	448	2964	A. G. A.mU.mC. A.mC. A.mU.mU.mU. G. A. A.ChI	2965	P.mU.fU.fC. A. A. A.fU. G.fU. G. A.fU.fC*fU* G* G* A*fU* G.	31%
17395	519	2966	A. A.mC.mC.mU.mC.m U.mC.mC.mU. A.mU. A.ChI	2967	P.mU. A.fU. A. G. G. A. G. A. G. G.fU.fU* A* G* A* G* A* A.	12%
17396	437	2968	G.mU.mU. G. A.mC. A.mU.mC.mC. A. G. A.ChI	2969	P.mU.fC.fU. G. G. A.fU. G.fU.fC. A. A.fC* A*fC* A*fU* A* A.	86%
17397	406	2970	mC.mC.mU.mU.mC. mC.mU.mU.mC. G. A. A. A.ChI	2971	P.mU.fU.fU.fC. G. A. A. G. G. A. A. G. G* G* A* A*fU* G* U.	23%
17398	339	2972	A.mC.mU.mC.mC. A. A. A.mC. A.mC. A. A.ChI	2973	P.mU.fU. G.fU. G.fU.fU.fU. G. G. A. G.fU* G* G* G*fU*fU* U.	102%
17399	339	2974	mC. A.mC.mU.mC.mC. A. A. A.mC. A.mC. A. A.ChI	2975	P.mU.fU. G.fU. G.fU.fU.fU. G. G. A. G.fU* G* G* G*fU*fU* U.	55%
17400	338	2976	mC. A.mC.mU.mC.mC. A. A. A.mC. A.mC. A.ChI	2977	P.mU. G.fU. G.fU.fU.fU. G. G. A. G.fU. G* G* G*fU*fU*fU* C.	62%
17401	468	2978	mC.mC. A.mC.mC. A. A.mC.mU.mU. A.mC. A.ChI	2979	P.mU. G.fU. A. A. G.fU.fU. G. G.fU. G. G* A*fC*fU* G*fU* C.	61%
17402	468	2980	mU.mC.mC. A.mC.mC. A. A.mC.mU.mU. A.mC. A.ChI	2981	P.mU. G.fU. A. A. G.fU.fU. G. G.fU. G. G* A*fC*fU* G*fU* C.	179%
17403	1465	2982	A. A.mU. A.mC.mC. A. G.mU.mC.mU.mU. A.ChI	2983	P.mU. A. A. G. A.fC.fU. G. G.fU. A.fU.fU*fU*fC* A*fU*fC* U.	30%
17404	243	2984	G. A.mC.mC. A. G.mU. A.mU. A. A. G. A.ChI	2985	P.mU.fC.fU.fU. A.fU. A.fC.fU. G. G.fU.fC* A* A* A*fU*fC* C.	32%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
17405	1472	2986	G.mU.mC.mU.mU.mU.mU. A. A.mU. G. A. A.Chl	2987	P.mU.fU.fC. A.fU.fU. A. A. A. A. G. A.fC*fU* G* G*fU* A* U.	15%
17406	2446	2988	A. A.mU.mU.mU.mC. A.mU. G.mU.mC.mU. A.Chl	2989	P.mU. A. G. A.fC. A.fU. G. A. A. A.fU.fU* A*fC*fU* G* G* U.	142%
17407	449	2990	A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.Chl	2991	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.fU*fC*fU* G* G* A* U.	54%
17408	449	2992	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.Chl	2993	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.fU*fC*fU* G* G* A* U.	27%
17409	444	2994	mU.mC.mC. A. G. A.mU.mC. A.mC. A.mU. A.Chl	2995	P.mU. A.fU. G.fU. G. A.fU.fC.fU. G. G. A*fU* G*fU*fC* A* A.	49%
17410	1093	2996	mU. A.mC.mU. G. A.mU. A. G. G. A. G. A.Chl	2997	P.mU.fC.fU.fC.fC.fU. A.fU.fC. A. G.fU. A*fU*fU* A* G*fC* C.	32%
17411	1134	2998	G.mU. G.mC. A. A.mC. A.mC.mU.fU. G. A.Chl	2999	P.mU.fC. A. A. G.fU. G.fU.fU. G.mC. A.fC* A*fU* A* A*fU* C.	70%
17412	244	3000	A.mC.mC. A. G.mU. A.mU. A. A. G.mU. A.Chl	3001	P.mU. A.fC.fU.fU. A.fU. A.fC.fU. G. G.fU*fC* A* A* A*fU* C.	63%
17413	1946	3002	G. A. A. G.mU.mC.mU. A. A.mU. G. A. A.Chl	3003	P.mU.fU.fC. A.fU.fU. A. G. A.fC.mU.fU.fC*fU* A*fC* A* G* U.	19%
17414	638	3004	A. A. G. A. A. G. A. A. A. G.mU.mU. A.Chl	3005	P.mU. A. A.fC.fU.fU.fU.fC.fU.fU.fC.fU.fU* A* G* A* A* G* C.	27%
17415	450	3006	mU.mC. A.mC. A.mU.mU.mU. G. A.mU.mU. A.Chl	3007	P.mU. A. A.fU.fC. A. A. A.fU. G.fU. G. A*fU*fC*fU* G* G* A.	216%
17416	450	3008	A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU.mU. A.Chl	3009	P.mU. A. A.fU.fC. A. A. A.fU. G.fU. G. A*fU*fC*fU* G* G* A.	32%
17417	452	3010	A.mC. A.mU.mU.mU. G. A.mU.mU. G. A. A.Chl	3011	P.mU.fU.fC. A. A.fU.fC. A. A. A.fU. G.fU* G* A*fU*fC*fU* G.	99%
17418	452	3012	mC. A.mC. A.mU.mU.mU. G. A.mU.mU. G. A. A.Chl	3013	P.mU.fU.fC. A. A.fU.fC. A. A. A.fU. G.fU* G* A*fU*fC*fU* G.	54%
17419	454	3014	A.mU.mU.mU. G. A.mU.mU. G. A.mC. A. A.Chl	3015	P.mU.fU. G.fU.fC. A. A.fU.fC. A. A. A.fU* G*fU* G* A*fU* C.	86%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
17420	454	3016	mC. A.mU.mU.mU. G. A.mU.mU. G. A.mC. A. A.Chl	3017	P.mU.fU. G.fU.fC. A. A.fU.fC. A. A. A.fU* G*fU* G* A*fU* C.	89%
17421	1790	3018	mC. A.mU.mC.mU. G.mC. A. A.mU. A. A. A.Chl	3019	P.mU.fU.fU. A.fU.fU. G.fC. A. G. A.fU. G* A* G* A* G* A* C.	55%
17422	1790	3020	mU.mC. A.mU.mC.mU. G.mC. A. A.mU. A. A. A.Chl	3021	P.mU.fU.fU. A.fU.fU. G.fC. A. G. A.fU. G* A* G* A* G* A* C.	62%
21180	448	3022	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A. A.TEG-Chl	3023	P.mU.fU.fC. A.mA. A.fU. G.fU. G. A.mU.mC*mU* G* G* A*mU* G.	76%
21181	448	3024	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A. A.TEG-Chl	3025	P.mU.fU.fC. A.mA. A.fU. G.fU. G. A.fU.fC*fU*mG*mG*m A*fU* G.	37%
21182	448	3026	G. A.mU.mC. A.mC. A.mU.mU.mU. G*mA*mA.TEG-Chl	3027	P.mU.fU.fC. A. A. A.fU. G.fU. G. A.fU.fC*fU* G* G* A*fU* G.	29%
21183	448	3028	mG*mA*mU.mC. A.mC. A.mU.mU.mU. G*mA*mA.TEG-Chl	3029	P.mU.fU.fC. A. A. A.fU. G.fU. G. A.fU.fC*fU* G* G* A*fU* G.	46%
21184	448	3030	mG*mA*mU.mC.mA .mC.mA.mU.mU.mU .mG*mA*mA.TEG-Chl	3031	P.mU.fU.fC. A. A. A.fU. G.fU. G. A.fU.fC*fU* G* G* A*fU* G.	60%
21185	449	3032	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.TEG-Chl	3033	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.fU.fC*fU* G* G* A*fU* G.	27%
21186	449	3034	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.TEG-Chl	3035	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.mU.mC*mU* G* G* A*mU* G.	57%
21187	449	3036	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.TEG-Chl	3037	P.mU. A.fU.fC. A.mA. A.fU. G.fU. G. A.mU.mC*mU* G* G* A*mU* G.	54%
21188	449	3038	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.TEG-Chl	3039	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.mU.mC*mU*mG*mG *mA*mU* G.	66%
21189	449	3040	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.TEG-Chl	3041	P.mU. A.fU.fC. A.mA. A.fU. G.fU. G. A.mU.mC*mU*mG*mG *mA*mU* G.	44%
21190	449	3042	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.TEG-Chl	3043	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.fU.fC*fU*mG*mG*m A*fU* G.	52%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
21191	449	3044	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.TEG-Chl	3045	P.mU. A.fU.fC. A.mA. A.fU. G.fU. G. A.fU.fC*fU*mG*mG*m A*fU* G.	41%
21192	449	3046	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.TEG-Chl	3047	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.fU.mC*fU*mG*mG* mA*fU* G.	98%
21193	449	3048	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A*mU*mA.TEG-Chl	3049	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.fU*fC*fU* G* G* A* U.	93%
21194	449	3050	mG*mA*mU.mC. A.mC. A.mU.mU.mU. G. A*mU*mA.TEG-Chl	3051	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.fU*fC*fU* G* G* A* U.	119%
21195	449	3052	mG*mA*mU.mC.mA .mC.mA.mU.mU.mU .mG.mA*mU*mA.TE G-Chl	3053	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.fU*fC*fU* G* G* A* U.	292%
20620	449	3054	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.Chl-TEG	3055	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.mU*mC*mU* G* G* A* U.	24%
20621	449	3056	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.Chl-TEG	3057	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.mU*fC*mU* G* G* A* U.	5%
20622	449	3058	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.Chl-TEG	3059	P.mU. A. U. C. A. A. A. U. G. U. G. A.mU*mC*mU* G* G* A* U.	25%
20623	449	3060	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A.mU. A.Chl-TEG	3061	P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.mU*mC*mU*mG*m G*mA* U.	14%
20588	448	3062	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A. A.Chl-TEG	3063	P.mU.fU.fC. A. A. A.fU. G.fU. G. A.mU.mC*mU* G* G* A*mU* G.	17%
20589	448	3064	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A. A.Chl-TEG	3065	P.mU.fU.fC. A. A. A.fU. G.fU. G. A.mU.fC*mU* G* G* A*fU* G.	40%
20590	448	3066	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A. A.Chl-TEG	3067	P.mU. U. C. A. A. A. U. G. U. G. A.mU.mC*mU* G* G* A*mU* G.	34%
20591	448	3068	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A. A.Chl-TEG	3069	P.mU.fU.fC. A. A. A.fU. G.fU. G. A.fU.fC*fU*mG*mG*m A*fU* G.	n/a

Table 20: Inhibition of gene expression with CTGF sd-rxRNA sequences (Accession Number: NM_001901.2)

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
13980	1222	3070	A.mC. A. G. G. A. A. G. A.mU. G.mU. A.Chl	3071	P.mU. A.fC. A.fU.fC.fU.fU.fC.fC.mU . G.mU* A* G*mU* A*mC* A.	98%
13981	813	3072	G. A. G.mU. G. G. A. G.mC. G.mC.mC.mU.Chl	3073	P.mA. G. G.fC. G.fC.fU.fC.fC. A.mC.mU.mC*mU* G*mU* G* G* U.	82%
13982	747	3074	mC. G. A.mC.mU. G. G. A. A. G. A.mC. A.Chl	3075	P.mU. G.fU.fC.fU.fU.fC.fC. A. G.mU.mC. G* G*mU* A* A* G* C.	116%
13983	817	3076	G. G. A. G.mC. G.mC.mC.mU. G.mU.mU.mC.Chl	3077	P.mG. A. A.fC. A. G. G.fC. G.fC.mU.mC.mC* A*mC*mU*mC*mU* G.	97%
13984	1174	3078	G.mC.mC. A.mU.mU. A.mC. A. A.mC.mU. G.Chl	3079	P.mC. A. G.fU.fU. G.fU. A. A.fU. G. G.mC* A* G* G*mC* A* C.	102%
13985	1005	3080	G. A. G.mC.mU.mU.mU .mC.mU. G. G.mC.mU.Chl	3081	P.mA. G.fC.fC. A. G. A. A. A. G.mC.mU.mC* A* A* A*mC*mU* U.	114%
13986	814	3082	A. G.mU. G. G. A. G.mC. G.mC.mC.mU. G.Chl	3083	P.mC. A. G. G.fC. G.fC.fU.fC.fC. A.mC.mU*mC*mU* G*mU* G* G.	111%
13987	816	3084	mU. G. G. A. G.mC. G.mC.mC.mU. G.mU.mU.Chl	3085	P.mA. A.fC. A. G. G.fC. G.fC.fU.mC.mC. A*mC*mU*mC*mU* G* U.	102%
13988	1001	3086	G.mU.mU.mU. G. A. G.mC.mU.mU.mU .mC.mU.Chl	3087	P.mA. G. A. A. A. G.fC.fU.fC. A. A. A.mC*mU*mU* G* A*mU* A.	99%
13989	1173	3088	mU. G.mC.mC. A.mU.mU. A.mC. A. A.mC.mU.Chl	3089	P.mA. G.fU.fU. G.fU. A. A.fU. G. G.mC. A* G* G*mC* A*mC* A.	107%
13990	749	3090	A.mC.mU. G. G. A. A. G. A.mC. A.mC. G.Chl	3091	P.mC. G.fU. G.fU.fC.fU.fU.fC.fC. A. G.mU*mC* G* G*mU* A* A.	91%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
13991	792	3092	A. A.mC.mU. G.mC.mC.mU. G. G.mU.mC.mC.Chl	3093	P.mG. G. A.fC.fC. A. G. G.fC. A. G.mU.mU* G* G*mC*mU*mC* U.	97%
13992	1162	3094	A. G. A.mC.mC.mU. G.mU. G.mC.mC.mU. G.Chl	3095	P.mC. A. G. G.fC. A.fC. A. G. G.mU.mC.mU*mU* G* A*mU* G* A.	107%
13993	811	3096	mC. A. G. A. G.mU. G. G. A. G.mC. G.mC.Chl	3097	P.mG.fC. G.fC.fU.fC.fC. A.fC.fU.mC.mU. G*mU* G* G*mU*mC* U.	113%
13994	797	3098	mC.mC.mU. G. G.mU.mC.mC. A. G. A.mC.mC.Chl	3099	P.mG. G.fU.fC.fU. G. G. A.fC.fC. A. G. G*mC* A* G*mU*mU* G.	n/a
13995	1175	3100	mC.mC. A.mU.mU. A.mC. A. A.mC.mU. G.mU.Chl	3101	P.mA.fC. A. G.fU.fU. G.fU. A. A.mU. G. G*mC* A* G* G*mC* A.	113%
13996	1172	3102	mC.mU. G.mC.mC. A.mU.mU. A.mC. A. A.mC.Chl	3103	P.mG.fU.fU. G.fU. A. A.fU. G. G.mC. A. G* G*mC* A*mC* A* G.	110%
13997	1177	3104	A.mU.mU. A.mC. A. A.mC.mU. G.mU.mC.mC.Chl	3105	P.mG. G. A.fC. A. G.fU.fU. G.fU. A. A.mU* G* G*mC* A* G* G.	105%
13998	1176	3106	mC. A.mU.mU. A.mC. A. A.mC.mU. G.mU.mC.Chl	3107	P.mG. A.fC. A. G.fU.fU. G.fU. A. A.mU. G* G*mC* A* G* G* C.	89%
13999	812	3108	A. G. A. G.mU. G. G. A. G.mC. G.mC.mC.Chl	3109	P.mG. G.fC. G.fC.fU.fC.fC. A.fC.mU.mC.mU* G*mU* G* G*mU* C.	99%
14000	745	3110	A.mC.mC. G. A.mC.mU. G. G. A. A. G. A.Chl	3111	P.mU.fC.fU.fU.fC.fC. A. G.fU.fC. G. G.mU* A* A* G*mC*mC* G.	n/a
14001	1230	3112	A.mU. G.mU. A.mC. G. G. A. G. A.mC. A.Chl	3113	P.mU. G.fU.fC.fU.fC.fC. G.fU. A.mC. A.mU*mC*mU*mU* mC*mC* U.	106%
14002	920	3114	G.mC.mC.mU.mU. G.mC. G. A. A. G.mC.mU.Chl	3115	P.mA. G.fC.fU.fU.fC. G.fC. A. A. G. G.mC*mC*mU* G* A*mC* C.	93%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14003	679	3116	G.mC.mU. G.mC. G. A. G. G. A. G.mU. G.Chl	3117	P.mC. A.fC.fU.fC.fC.fU.fC. G.fC. A. G.mC* A*mU*mU*mU*mC* C.	102%
14004	992	3118	G.mC.mC.mU. A.mU.mC. A. A. G.mU.mU.mU.Chl	3119	P.mA. A. A.fC.fU.fU. G. A.fU. A. G. G.mC*mU*mU* G* G* A* G.	100%
14005	1045	3120	A. A.mU.mU.mC.mU. G.mU. G. G. A. G.mU.Chl	3121	P.mA.fC.fU.fC.fC. A.fC. A. G. A. A.mU.mU*mU* A* G*mC*mU* C.	104%
14006	1231	3122	mU. G.mU. A.mC. G. G. A. G. A.mC. A.mU.Chl	3123	P.mA.fU. G.fU.fC.fU.fC.fC. G.fU. A.mC. A*mU*mC*mU*mU* mC* C.	87%
14007	991	3124	A. G.mC.mC.mU. A.mU.mC. A. A. G.mU.mU.Chl	3125	P.mA. A.fC.fU.fU. G. A.fU. A. G. G.mC.mU*mU* G* G* A* G* A.	101%
14008	998	3126	mC. A. A. G.mU.mU.mU. G. A. G.mC.mU.mU.Chl	3127	P.mA. A. G.fC.fU.fC. A. A. A.fC.mU.mU. G* A*mU* A* G* G* C.	98%
14009	1049	3128	mC.mU. G.mU. G. G. A. G.mU. A.mU. G.mU.Chl	3129	P.mA.fC. A.fU. A.fC.fU.fC.fC. A.mC. A. G* A* A*mU*mU*mU* A.	98%
14010	1044	3130	A. A. A.mU.mU.mC.mU. G.mU. G. G. A. G.Chl	3131	P.mC.fU.fC.fC. A.fC. A. G. A. A.mU.mU.mU* A* G*mC*mU*mC* G.	93%
14011	1327	3132	mU.mU.mU.mC. A. G.mU. A. G.mC. A.mC. A.Chl	3133	P.mU. G.fU. G.fC.fU. A.fC.fU. G. A. A. A*mU*mC* A*mU*mU* U.	95%
14012	1196	3134	mC. A. A.mU. G. A.mC. A.mU.mC.mU.mU. mU.Chl	3135	P.mA. A. A. G. A.fU. G.fU.fC. A.mU.mU. G*mU*mC*mU*mC* mC* G.	101%
14013	562	3136	A. G.mU. A.mC.mC. A. G.mU. G.mC. A.mC.Chl	3137	P.mG.fU. G.fC. A.fC.fU. G. G.fU. A.mC.mU*mU* G*mC* A* G* C.	66%
14014	752	3138	G. G. A. A. G. A.mC. A.mC. G.mU.mU.mU.Chl	3139	P.mA. A. A.fC. G.fU. G.fU.fC.fU.mU.mC.mC * A* G*mU*mC* G* G.	95%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14015	994	3140	mC.mU. A.mU.mC. A. A. G.mU.mU.mU. G. A.Chl	3141	P.mU.fC. A. A. A.fC.fU.fU. G. A.mU. A. G* G*mC*mU*mU* G* G.	85%
14016	1040	3142	A. G.mC.mU. A. A. A.mU.mU.mC.mU. G.mU.Chl	3143	P.mA.fC. A. G. A. A.fU.fU.fU. A. G.mC.mU*mC* G* G*mU* A* U.	61%
14017	1984	3144	A. G. G.mU. A. G. A. A.mU. G.mU. A. A.Chl	3145	P.mU.fU. A.fC. A.fU.fU.fC.fU. A.mC.mC.mU* A*mU* G* G*mU* G.	32%
14018	2195	3146	A. G.mC.mU. G. A.mU.mC. A. G.mU.mU.mU.Chl	3147	P.mA. A. A.fC.fU. G. A.fU.fC. A. G.mC.mU* A*mU* A*mU* A* G.	86%
14019	2043	3148	mU.mU.mC.mU. G.mC.mU.mC. A. G. A.mU. A.Chl	3149	P.mU. A.fU.fC.fU. G. A. G.fC. A. G. A. A*mU*mU*mU*mC* mC* A.	81%
14020	1892	3150	mU.mU. A.mU.mC.mU. A. A. G.mU.mU. A. A.Chl	3151	P.mU.fU. A. A.fC.fU.fU. A. G. A.mU. A. A*mC*mU* G*mU* A* C.	84%
14021	1567	3152	mU. A.mU. A.mC. G. A. G.mU. A. A.mU. A.Chl	3153	P.mU. A.fU.fU. A.fC.fU.fC. G.fU. A.mU. A* A* G* A*mU* G* C.	72%
14022	1780	3154	G. A.mC.mU. G. G. A.mC. A. G.mC.mU.mU.Chl	3155	P.mA. A. G.fC.fU. G.fU.fC.fC. A. G.mU.mC*mU* A* A*mU*mC* G.	65%
14023	2162	3156	A.mU. G. G.mC.mC.mU.mU. mU. A.mU.mU. A.Chl	3157	P.mU. A. A.fU. A. A. A. G. G.fC.mC. A.mU*mU*mU* G*mU*mU* C.	80%
14024	1034	3158	A.mU. A.mC.mC. G. A. G.mC.mU. A. A. A.Chl	3159	P.mU.fU.fU. A. G.fC.fU.fC. G. G.mU. A.mU* G*mU*mC*mU*mU* C.	91%
14025	2264	3160	mU.mU. G.mU.mU. G. A. G. A. G.mU. G.mU.Chl	3161	P.mA.fC. A.fC.fU.fC.fU.fC. A. A.mC. A. A* A*mU* A* A* A* C.	58%
14026	1032	3162	A.mC. A.mU. A.mC.mC. G. A. G.mC.mU. A.Chl	3163	P.mU. A. G.fC.fU.fC. G. G.fU. A.mU. G.mU*mC*mU*mU* mC* A* U.	106%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14027	1535	3164	A. G.mC. A. G. A. A. A. G. G.mU.mU. A.Chl	3165	P.mU. A. A.fC.fC.fU.fU.fU.fC.fU. G.mC.mU* G* G*mU* A*mC* C.	67%
14028	1694	3166	A. G.mU.mU. G.mU.mU.mC.mC. mU.mU. A. A.Chl	3167	P.mU.fU. A. A. G. G. A. A.fC. A. A.mC.mU*mU* G* A*mC*mU* C.	94%
14029	1588	3168	A.mU.mU.mU. G. A. A. G.mU. G.mU. A. A.Chl	3169	P.mU.fU. A.fC. A.fC.fU.fU.fC. A. A. A.mU* A* G*mC* A* G* G.	97%
14030	928	3170	A. A. G.mC.mU. G. A.mC.mC.mU. G. G. A.Chl	3171	P.mU.fC.fC. A. G. G.fU.fC. A. G.mC.mU.mU*mC* G*mC* A* A* G.	100%
14031	1133	3172	G. G.mU.mC. A.mU. G. A. A. G. A. A. G.Chl	3173	P.mC.fU.fU.fC.fU.fU.fC . A.fU. G. A.mC.mC*mU*mC* G*mC*mC* G.	82%
14032	912	3174	A.mU. G. G.mU.mC. A. G. G.mC.mC.mU.mU. Chl	3175	P.mA. A. G. G.fC.fC.fU. G. A.fC.mC. A.mU* G*mC* A*mC* A* G.	84%
14033	753	3176	G. A. A. G. A.mC. A.mC. G.mU.mU.mU. G.Chl	3177	P.mC. A. A. A.fC. G.fU. G.fU.fC.mU.mU.mC*m C* A* G*mU*mC* G.	86%
14034	918	3178	A. G. G.mC.mC.mU.mU. G.mC. G. A. A. G.Chl	3179	P.mC.fU.fU.fC. G.fC. A. A. G. G.mC.mC.mU* G* A*mC*mC* A* U.	88%
14035	744	3180	mU. A.mC.mC. G. A.mC.mU. G. G. A. A. G.Chl	3181	P.mC.fU.fU.fC.fC. A. G.fU.fC. G. G.mU. A* A* G*mC*mC* G* C.	95%
14036	466	3182	A.mC.mC. G.mC. A. A. G. A.mU.mC. G. G.Chl	3183	P.mC.fC. G. A.fU.fC.fU.fU. G.fC. G. G.mU*mU* G* G*mC*mC* G.	73%
14037	917	3184	mC. A. G. G.mC.mC.mU.mU. G.mC. G. A. A.Chl	3185	P.mU.fU.fC. G.fC. A. A. G. G.fC.mC.mU. G* A*mC*mC* A*mU* G.	86%
14038	1038	3186	mC. G. A. G.mC.mU. A. A. A.mU.mU.mC.mU. Chl	3187	P.mA. G. A. A.fU.fU.fU. A. G.fC.mU.mC. G* G*mU* A*mU* G* U.	84%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14039	1048	3188	mU.mC.mU. G.mU. G. G. A. G.mU. A.mU. G.Chl	3189	P.mC. A.fU. A.fC.fU.fC.fC. A.fC. A. G. A* A*mU*mU*mU* A* G.	87%
14040	1235	3190	mC. G. G. A. G. A.mC. A.mU. G. G.mC. A.Chl	3191	P.mU. G.fC.fC. A.fU. G.fU.fC.fU.mC.mC. G*mU* A*mC* A*mU* C.	100%
14041	868	3192	A.mU. G. A.mC. A. A.mC. G.mC.mC.mU.mC. Chl	3193	P.mG. A. G. G.fC. G.fU.fU. G.fU.mC. A.mU*mU* G* G*mU* A* A.	104%
14042	1131	3194	G. A. G. G.mU.mC. A.mU. G. A. A. G. A.Chl	3195	P.mU.fC.fU.fU.fC. A.fU. G. A.fC.mC.mU.mC* G*mC*mC* G*mU* C.	85%
14043	1043	3196	mU. A. A. A.mU.mU.mC.mU. G.mU. G. G. A.Chl	3197	P.mU.fC.fC. A.fC. A. G. A. A.fU.mU.mU. A* G*mC*mU*mC* G* G.	74%
14044	751	3198	mU. G. G. A. A. G. A.mC. A.mC. G.mU.mU.Chl	3199	P.mA. A.fC. G.fU. G.fU.fC.fU.fU.mC.mC. A* G*mU*mC* G* G* U.	84%
14045	1227	3200	A. A. G. A.mU. G.mU. A.mC. G. G. A. G.Chl	3201	P.mC.fU.fC.fC. G.fU. A.fC. A.fU.mC.mU.mU*mC* mC*mU* G*mU* A.	99%
14046	867	3202	A. A.mU. G. A.mC. A. A.mC. G.mC.mC.mU.Chl	3203	P.mA. G. G.fC. G.fU.fU. G.fU.fC. A.mU.mU* G* G*mU* A* A* C.	94%
14047	1128	3204	G. G.mC. G. A. G. G.mU.mC. A.mU. G. A.Chl	3205	P.mU.fC. A.fU. G. A.fC.fC.fU.fC. G.mC.mC* G*mU*mC* A* G* G.	89%
14048	756	3206	G. A.mC. A.mC. G.mU.mU.mU. G. G.mC.mC.Chl	3207	P.mG. G.fC.fC. A. A. A.fC. G.fU. G.mU.mC*mU*mU*m C*mC* A* G.	93%
14049	1234	3208	A.mC. G. G. A. G. A.mC. A.mU. G. G.mC.Chl	3209	P.mG.fC.fC. A.fU. G.fU.fC.fU.fC.mC. G.mU* A*mC* A*mU*mC* U.	100%
14050	916	3210	mU.mC. A. G. G.mC.mC.mU.mU. G.mC. G. A.Chl	3211	P.mU.fC. G.fC. A. A. G. G.fC.fC.mU. G. A*mC*mC* A*mU* G* C.	96%
14051	925	3212	G.mC. G. A. A. G.mC.mU. G. A.mC.mC.mU.Chl	3213	P.mA. G. G.fU.fC. A. G.fC.fU.fU.mC. G.mC* A* A* G* G*mC* C.	80%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14052	1225	3214	G. G. A. A. G. A.mU. G.mU. A.mC. G. G.Chl	3215	P.mC.fC. G.fU. A.fC. A.fU.fC.fU.mU.mC.mC *mU* G*mU* A* G* U.	96%
14053	445	3216	G.mU. G. A.mC.mU.mU.mC. G. G.mC.mU.mC.Chl	3217	P.mG. A. G.fC.fC. G. A. A. G.fU.mC. A.mC* A* G* A* A* G* A.	101%
14054	446	3218	mU. G. A.mC.mU.mU.mC. G. G.mC.mU.mC.mC. Chl	3219	P.mG. G. A. G.fC.fC. G. A. A. G.mU.mC. A*mC* A* G* A* A* G.	93%
14055	913	3220	mU. G. G.mU.mC. A. G. G.mC.mC.mU.mU. G.Chl	3221	P.mC. A. A. G. G.fC.fC.fU. G. A.mC.mC. A*mU* G*mC* A*mC* A.	67%
14056	997	3222	mU.mC. A. A. G.mU.mU.mU. G. A. G.mC.mU.Chl	3223	P.mA. G.fC.fU.fC. A. A. A.fC.fU.mU. G. A*mU* A* G* G*mC* U.	92%
14057	277	3224	G.mC.mC. A. G. A. A.mC.mU. G.mC. A. G.Chl	3225	P.mC.fU. G.fC. A. G.fU.fU.fC.fU. G. G.mC*mC* G* A*mC* G* G.	84%
14058	1052	3226	mU. G. G. A. G.mU. A.mU. G.mU. A.mC.mC.Chl	3227	P.mG. G.fU. A.fC. A.fU. A.fC.fU.mC.mC. A*mC* A* G* A* A* U.	n/a
14059	887	3228	G.mC.mU. A. G. A. G. A. A. G.mC. A. G.Chl	3229	P.mC.fU. G.fC.fU.fU.fC.fU.fC.fU. A. G.mC*mC*mU* G*mC* A* G.	80%
14060	914	3230	G. G.mU.mC. A. G. G.mC.mC.mU.mU. G.mC.Chl	3231	P.mG.fC. A. A. G. G.fC.fC.fU. G. A.mC.mC* A*mU* G*mC* A* C.	112%
14061	1039	3232	G. A. G.mC.mU. A. A. A.mU.mU.mC.mU. G.Chl	3233	P.mC. A. G. A. A.fU.fU.fU. A. G.mC.mU.mC* G* G*mU* A*mU* G.	104%
14062	754	3234	A. A. G. A.mC. A.mC. G.mU.mU.mU. G. G.Chl	3235	P.mC.fC. A. A. A.fC. G.fU. G.fU.mC.mU.mU*mC* mC* A* G*mU* C.	109%
14063	1130	3236	mC. G. A. G. G.mU.mC. A.mU. G. A. A. G.Chl	3237	P.mC.fU.fU.fC. A.fU. G. A.fC.fC.mU.mC. G*mC*mC* G*mU*mC* A.	103%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14064	919	3238	G. G.mC.mC.mU.mU. G.mC. G. A. A. G.mC.Chl	3239	P.mG.fC.fU.fU.fC. G.fC. A. A. G. G.mC.mC*mU* G* A*mC*mC* A.	109%
14065	922	3240	mC.mU.mU. G.mC. G. A. A. G.mC.mU. G. A.Chl	3241	P.mU.fC. A. G.fC.fU.fU.fC. G.fC. A. A. G* G*mC*mC*mU* G* A.	106%
14066	746	3242	mC.mC. G. A.mC.mU. G. G. A. A. G. A.mC.Chl	3243	P.mG.fU.fC.fU.fU.fC.fC . A. G.fU.mC. G. G*mU* A* A* G*mC* C.	106%
14067	993	3244	mC.mC.mU. A.mU.mC. A. A. G.mU.mU.mU. G.Chl	3245	P.mC. A. A. A.fC.fU.fU. G. A.fU. A. G. G*mC*mU*mU* G* G* A.	67%
14068	825	3246	mU. G.mU.mU.mC.mC. A. A. G. A.mC.mC.mU.Chl	3247	P.mA. G. G.fU.fC.fU.fU. G. G. A. A.mC. A* G* G*mC* G*mC* U.	93%
14069	926	3248	mC. G. A. A. G.mC.mU. G. A.mC.mC.mU. G.Chl	3249	P.mC. A. G. G.fU.fC. A. G.fC.fU.mU.mC. G*mC* A* A* G* G* C.	95%
14070	923	3250	mU.mU. G.mC. G. A. A. G.mC.mU. G. A.mC.Chl	3251	P.mG.fU.fC. A. G.fC.fU.fU.fC. G.mC. A. A* G* G*mC*mC*mU* G.	95%
14071	866	3252	mC. A. A.mU. G. A.mC. A. A.mC. G.mC.mC.Chl	3253	P.mG. G.fC. G.fU.fU. G.fU.fC. A.mU.mU. G* G*mU* A* A*mC* C.	132%
14072	563	3254	G.mU. A.mC.mC. A. G.mU. G.mC. A.mC. G.Chl	3255	P.mC. G.fU. G.fC. A.fC.fU. G. G.mU. A.mC*mU*mU* G*mC* A* G.	n/a
14073	823	3256	mC.mC.mU. G.mU.mU.mC.mC. A. A. G. A.mC.Chl	3257	P.mG.fU.fC.fU.fU. G. G. A. A.fC. A. G. G*mC* G*mC*mU*mC* C.	98%
14074	1233	3258	mU. A.mC. G. G. A. G. A.mC. A.mU. G. G.Chl	3259	P.mC.fC. A.fU. G.fU.fC.fU.fC.fC. G.mU. A*mC* A*mU*mC*mU* U.	109%
14075	924	3260	mU. G.mC. G. A. A. G.mC.mU. G. A.mC.mC.Chl	3261	P.mG. G.fU.fC. A. G.fC.fU.fU.fC. G.mC. A* A* G* G*mC*mC* U.	95%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
14076	921	3262	mC.mC.mU.mU. G.mC. G. A. A. G.mC.mU. G.Chl	3263	P.mC. A. G.fC.fU.fU.fC. G.fC. A. A. G. G*mC*mC*mU* G* A* C.	116%
14077	443	3264	mC.mU. G.mU. G. A.mC.mU.mU.mC. G. G.mC.Chl	3265	P.mG.fC.fC. G. A. A. G.fU.fC. A.mC. A. G* A* A* G* A* G* G.	110%
14078	1041	3266	G.mC.mU. A. A. A.mU.mU.mC.mU. G.mU. G.Chl	3267	P.mC. A.fC. A. G. A. A.fU.fU.fU. A. G.mC*mU*mC* G* G*mU* A.	99%
14079	1042	3268	mC.mU. A. A. A.mU.mU.mC.mU. G.mU. G. G.Chl	3269	P.mC.fC. A.fC. A. G. A. A.fU.fU.mU. A. G*mC*mU*mC* G* G* U.	109%
14080	755	3270	A. G. A.mC. A.mC. G.mU.mU.mU. G. G.mC.Chl	3271	P.mG.fC.fC. A. A. A.fC. G.fU. G.mU.mC.mU*mU*m C*mC* A* G* U.	121%
14081	467	3272	mC.mC. G.mC. A. A. G. A.mU.mC. G. G.mC.Chl	3273	P.mG.fC. C.fG. A. U.fC.fU.fU.fG. C.mG. G*mU*mU* G* G*mC* C.	132%
14082	995	3274	mU. A.mU.mC. A. A. G.mU.mU.mU. G. A. G.Chl	3275	P.mC.fU.fC. A. A. A.fC.fU.fU. G. A.mU. A* G* G*mC*mU*mU* G.	105%
14083	927	3276	G. A. A. G.mC.mU. G. A.mC.mC.mU. G. G.Chl	3277	P.mC.fC. A. G. G.fU.fC. A. G.fC.mU.mU.mC* G*mC* A* A* G* G.	114%
17356	1267	3278	A.mC. A.mU.mU. A. A.mC.mU.mC. A.mU. A.Chl	3279	P.mU. A.fU. G. A. G.mU.fU. A. A.fU. G.fU*fC*fU*fC*fU*fC * A.	120%
17357	1267	3280	G. A.mC. A.mU.mU. A. A.mC.mU.mC. A.mU. A.Chl	3281	P.mU. A.fU. G. A. G.mU.fU. A. A.fU. G.fU*fC*fU*fC*fU*fC * A.	56%
17358	1442	3282	mU. G. A. A. G. A. A.mU. G.mU.mU. A. A.Chl	3283	P.mU.fU. A. A.fC. A.fU.fU.fC.fU.fU.fC. A* A* A*fC*fC* A* G.	34%
17359	1442	3284	mU.mU. G. A. A. G. A. A.mU. G.mU.mU. A. A.Chl	3285	P.mU.fU. A. A.fC. A.fU.fU.fC.fU.fU.fC. A* A* A*fC*fC* A* G.	31%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
17360	1557	3286	G. A.mU. A. G.mC. A.mU.mC.mU.mU. A. A.Chl	3287	P.mU.fU. A. A. G. A.fU. G.fC.fU. A.fU.fC*fU* G* A*fU* G* A.	59%
17361	1557	3288	A. G. A.mU. A. G.mC. A.mU.mC.mU.mU. A. A.Chl	3289	P.mU.fU. A. A. G. A.fU. G.fC.fU. A.fU.fC*fU* G* A*fU* G* A.	47%
17362	1591	3290	mU. G. A. A. G.mU. G.mU. A. A.mU.mU. A.Chl	3291	P.mU. A. A.fU.fU. A.fC. A.fC.fU.fU.fC. A* A* A*fU* A* G* C.	120%
17363	1599	3292	A. A.mU.mU. G. A. G. A. A. G. G. A. A.Chl	3293	P.mU.fU.fC.fC.fU.fU.fC .fU.fC. A. A.fU.fU* A*fC* A*fC*fU* U.	71%
17364	1601	3294	mU.mU. G. A. G. A. A. G. G. A. A. A. A.Chl	3295	P.mU.fU.fU.fU.fC.fC.fU .fU.fC.fU.fC. A. A*fU*fU* A*fC* A* C.	62%
17365	1732	3296	mC. A.mU.mU.mC.mU. G. A.mU.mU.mC. G. A.Chl	3297	P.mU.fC. G. A. A.fU.fC. A. G. A. A.fU. G*fU*fC* A* G* A* G.	99%
17366	1734	3298	mU.mU.mC.mU. G. A.mU.mU.mC. G. A. A. A.Chl	3299	P.mU.fU.fU.fC. G. A. A.fU.fC. A. G. A. A*fU* G*fU*fC* A* G.	97%
17367	1770	3300	mC.mU. G.mU.mC. G. A.mU.mU. A. G. A. A.Chl	3301	P.mU.fU.fC.fU. A. A.fU.fC. G. A.fC. A. G* G* A*fU*fU*fC* C.	45%
17368	1805	3302	mU.mU.mU. G.mC.mC.mU. G.mU. A. A.mC. A.Chl	3303	P.mU. G.fU.fU. A.fC. A. G. G.fC. A. A. A*fU*fU*fC* A*fC* U.	71%
17369	1805	3304	A.mU.mU.mU. G.mC.mC.mU. G.mU. A. A.mC. A.Chl	3305	P.mU. G.fU.fU. A.fC. A. G. G.fC. A. A. A*fU*fU*fC* A*fC* U.	67%
17370	1815	3306	A.mC. A. A. G.mC.mC. A. G. A.mU.mU. A.Chl	3307	P.mU. A. A.fU.fC.fU. G. G.fC.fU.fU. G.fU*fU* A*fC* A* G* G.	65%
17371	1815	3308	A. A.mC. A. A. G.mC.mC. A. G. A.mU.mU. A.Chl	3309	P.mU. A. A.fU.fC.fU. G. G.fC.fU.fU. G.fU*fU* A*fC* A* G* G.	35%
17372	2256	3310	mC. A. G.mU.mU.mU. A.mU.mU.mU. G.mU. A.Chl	3311	P.mU. A.fC. A. A. A.fU. A. A. A.fC.fU. G*fU*fC*fC* G* A* A.	113%
17373	2265	3312	mU. G.mU.mU. G. A. G. A. G.mU. G.mU. A.Chl	3313	P.mU. A.fC. A.fC.fU.fC.fU.fC. A. A.fC. A* A* A*fU* A* A* A.	35%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
17374	2265	3314	mU.mU. G.mU.mU. G. A. G. A. G.mU. G.mU. A.Chl	3315	P.mU. A.fC. A.fC.fU.fC.fU.fC. A. A.fC. A* A* A*fU* A* A* A.	31%
17375	2295	3316	mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.Chl	3317	P.mU.fU. A. G. A. A. A. G. G.fU. G.fC. A* A* A*fC* A*fU* G.	34%
17376	2295	3318	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.Chl	3319	P.mU.fU. A. G. A. A. A. G. G.fU. G.fC. A* A* A*fC* A*fU* G.	28%
17377	1003	3320	mU.mU. G. A. G.mC.mU.mU.mU .mC.mU. G. A.Chl	3321	P.mU.fC. A. G. A. A. A. G.fC.fU.fC. A. A* A*fC*fU*fU* G* A.	67%
17378	2268	3322	mU. G. A. G. A. G.mU. G.mU. G. A.mC. A.Chl	3323	P.mU. G.fU.fC. A.fC. A.fC.fU.fC.fU.fC. A* A*fC* A* A* A* U.	42%
17379	2272	3324	A. G.mU. G.mU. G. A.mC.mC. A. A. A. A.Chl	3325	P.mU.fU.fU.fU. G. G.fU.fC. A.fC. A.fC.fU*fC*fU*fC* A* A* C.	35%
17380	2272	3326	G. A. G.mU. G.mU. G. A.mC.mC. A. A. A. A.Chl	3327	P.mU.fU.fU.fU. G. G.fU.fC. A.fC. A.fC.fU*fC*fU*fC* A* A* C.	29%
17381	2273	3328	G.mU. G.mU. G. A.mC.mC. A. A. A. A. A.Chl	3329	P.mU.fU.fU.fU.fU. G. G.fU.fC. A.fC. A.fC*fU*fC*fU*fC* A* A.	42%
17382	2274	3330	mU. G.mU. G. A.mC.mC. A. A. A. A. G. A.Chl	3331	P.mU.fC.fU.fU.fU.fU. G. G.fU.fC. A.fC. A*fC*fU*fC*fU*fC* A.	42%
17383	2274	3332	G.mU. G.mU. G. A.mC.mC. A. A. A. A. G. A.Chl	3333	P.mU.fC.fU.fU.fU.fU. G. G.fU.fC. A.fC. A*fC*fU*fC*fU*fC* A.	37%
17384	2275	3334	G.mU. G. A.mC.mC. A. A. A. A. G.mU. A.Chl	3335	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.fC. A.fC* A*fC*fU*fC*fU* C.	24%
17385	2277	3336	G. A.mC.mC. A. A. A. A. G.mU.mU. A. A.Chl	3337	P.mU.fU. A. A.fC.fU.fU.fU.fU. G. G.fU.fC* A*fC* A*fC*fU* C.	27%
17386	2296	3338	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.Chl	3339	P.mU.fC.fU. A. G. A. A. A. G. G.fU. G.fC* A* A* A*fC* A* U.	23%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
17387	2299	3340	mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU. G. A.Chl	3341	P.mU.fC. A. A.fC.fU. A. G. A. A. A. G. G*fU* G*fC* A* A* A.	46%
21138	2296	3342	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.TEG-Chl	3343	P.mU.fC.fU. A. G. A.mA. A. G. G.fU. G.mC* A* A* A*mC* A* U.	42%
21139	2296	3344	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.TEG-Chl	3345	P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A* A* A*mC* A* U.	32%
21140	2296	3346	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.TEG-Chl	3347	P.mU.fC.fU. A. G. A. A. A. G. G.fU. G.mC* A*mA* A*mC* A* U.	41%
21141	2296	3348	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.TEG-Chl	3349	P.mU.fC.fU. A. G. A.mA. A. G. G.fU. G.mC* A*mA* A*mC* A* U.	51%
21142	2296	3350	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.TEG-Chl	3351	P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A*mA* A*mC* A* U.	25%
21143	2296	3352	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.TEG-Chl	3353	P.mU.fC.fU. A. G. A. A. A. G. G.fU. G.fC*mA*mA*mA*fC* mA* U.	61%
21144	2296	3354	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.TEG-Chl	3355	P.mU.fC.fU. A. G. A.mA. A. G. G.fU. G.fC*mA*mA*mA*fC* mA* U.	49%
21145	2296	3356	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.TEG-Chl	3357	P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.fC*mA*mA*mA*fC* mA* U.	46%
21146	2296	3358	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A*mG*mA.TEG-Chl	3359	P.mU.fC.fU. A. G. A. A. A. G. G.fU. G.fC* A* A* A*fC* A* U.	37%
21147	2296	3360	mG*mC* A.mC.mC.mU.mU. mU.mC.mU. A*mG*mA.TEG-Chl	3361	P.mU.fC.fU. A. G. A. A. A. G. G.fU. G.fC* A* A* A*fC* A* U.	43%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
21148	2296	3362	mG*mC*mA.mC. mC.mU.mU.mU.m C.mU.mA*mG*m A.TEG-Chl	3363	P.mU.fC.fU. A. G. A. A. A. G. G.fU. G.fC* A* A* A*fC* A* U.	29%
21149	2275	3364	G.mU. G. A.mC.mC. A. A. A. A. G*mU*mA.TEG-Chl	3365	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.fC. A.fC* A*fC*fU*fC*fU* C.	138%
21150	2275	3366	mG*mU* G. A.mC.mC. A. A.mA. A. G*mU*mA.TEG-Chl	3367	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.fC. A.fC* A*fC*fU*fC*fU* C.	116%
21151	2275	3368	mG*mU*mG.mA. mC.mC.mA.mA.m A.mA.mG*mU*m A.TEG-Chl	3369	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.fC. A.fC* A*fC*fU*fC*fU* C.	105%
21152	2295	3370	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.TEG-Chl	3371	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A. A* A*fC* A*fA* G* G.	46%
21153	2295	3372	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.TEG-Chl	3373	P.mU.fU. A. G.mA. A.mA. G. G.fU. G.fC. A. A* A*fC* A*fA* G* G.	28%
21154	2295	3374	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.TEG-Chl	3375	P.mU.fU.mA. G.mA. A.mA. G.mG.fU. G.fC. A. A* A*fC* A*fA* G* G.	28%
21155	2295	3376	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.TEG-Chl	3377	P.mU.fU. A. G. A.mA. A. G. G.fU. G.mC. A. A* A*mC* A*mA* G* G.	60%
21156	2295	3378	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.TEG-Chl	3379	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A.mA*mA*fC*mA*fA* mG* G.	54%
21157	2295	3380	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.TEG-Chl	3381	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC.mA.mA*mA*fC* mA*fA*mG* G.	40%
21158	2295	3382	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.TEG-Chl	3383	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A.mA*mA*fC*mA*mA *mG* G.	n/a
21159	2295	3384	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.TEG-Chl	3385	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A.mA*mA*mC*mA*m A*mG* G.	41%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
21160	2295	3386	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.Chl-TEG	3387	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC.mA. A*mA*mC*mA*mA* mG*mG.	65%
21161	2295	3388	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.TEG-Chl	3389	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A. A* A*fC* A*mA*mG* G.	43%
21162	2295	3390	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. A.TEG-Chl	3391	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC.mA. A*mA*fC* A*mA*mG* G.	41%
21163	2295	3392	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU. A* A*TEG-Chl	3393	P.mU.fU. A. G. A. A. A. G. G.fU. G.fC. A. A* A*fC* A* A* G* G.	32%
21164	2295	3394	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU.mA* mA*TEG-Chl	3395	P.mU.fU. A. G. A. A. A. G. G.fU. G.fC. A. A* A*fC* A* A* G* G.	39%
21165	2295	3396	mU*mU* G.mC. A.mC.mC.mU.mU. mU.mC.mU.mA* mA*TEG-Chl	3397	P.mU.fU. A. G. A. A. A. G. G.fU. G.fC. A. A* A*fC* A* A* G* G.	28%
21166	2295	3398	mU.mU.mG.mC.m A.mC.mC.mU.mU. mU.mC.mU.mA* mA*TEG-Chl	3399	P.mU.fU. A. G. A. A. A. G. G.fU. G.fC. A. A* A*fC* A* A* G* G.	27%
21167	2299	3400	mC.mC.mU.mU.m U.mC.mU. A. G.mU.mU. G. A.TEG-Chl	3401	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU* G*fC* A* A* A.	49%
21168	2299	3402	mC.mC.mU.mU.m U.mC.mU. A. G.mU.mU. G. A.TEG-Chl	3403	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*mU* G*mC* A* A* A.	53%
21169	2299	3404	mC.mC.mU.mU.m U.mC.mU. A. G.mU.mU. G. A.TEG-Chl	3405	P.mU.fC. A. A.fC.fU. A. G.mA. A. A.mG. G*fU* G*fC* A* A* A.	47%
21170	2299	3406	mC.mC.mU.mU.m U.mC.mU. A. G.mU.mU. G. A.TEG-Chl	3407	P.mU.fC. A. A.fC.fU. A. G.mA. A. A.mG. G*mU* G*mC* A* A* A.	70%
21171	2299	3408	mC.mC.mU.mU.m U.mC.mU. A. G.mU.mU. G. A.TEG-Chl	3409	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*mU* G*mC* A*mA* A.	65%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
21172	2299	3410	mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU. G. A.TEG-Chl	3411	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*mU* G*mC*mA*mA* A.	43%
21173	2299	3412	mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU. G. A.TEG-Chl	3413	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G.mG*mU*mG*mC* mA*mA* A.	52%
21174	2299	3414	mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU. G. A.TEG-Chl	3415	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*mU*mG*mC*mA* mA* A.	47%
21175	2299	3416	mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU. G. A.TEG-Chl	3417	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU*mG*fC*mA*mA * A.	35%
21176	2299	3418	mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU. G. A.TEG-Chl	3419	P.mU.fC. A. A.fC.fU. A. G.mA. A. A.mG. G*fU*mG*fC*mA*mA * A.	50%
21177	2299	3420	mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU*mG*mA.TEG-Chl	3421	P.mU.fC. A. A.fC.fU. A. G. A. A. A. G. G*fU* G*fC* A* A* A.	37%
21178	2299	3422	mC*mC*mU.mU. mU.mC.mU. A. G.mU.mU*mG*mA.TEG-Chl	3423	P.mU.fC. A. A.fC.fU. A. G. A. A. A. G. G*fU* G*fC* A* A* A.	36%
21179	2299	3424	mC*mC*mU.mU. mU.mC.mU.mA.mG.mU.mU*mG*mA.TEG-Chl	3425	P.mU.fC. A. A.fC.fU. A. G. A. A. A. G. G*fU* G*fC* A* A* A.	35%
21203	2296	3426	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A*mG*mA.TEG-Chl	3427	P.mU.fC.fU. A. G. A.mA. A. G. G.fU. G.mC* A* A* A*mC* A* U.	40%
21204	2296	3428	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A*mG*mA.TEG-Chl	3429	P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A* A* A*mC* A* U.	28%
21205	2296	3430	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A*mG*mA.TEG-Chl	3431	P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A*mA* A*mC* A* U.	51%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
21206	2296	3432	mG*mC* A.mC.mC.mU.mU. mU.mC.mU. A*mG*mA.TEG-Chl	3433	P.mU.fC.fU. A. G. A.mA. A. G. G.fU. G.mC* A* A* A*mC* A* U.	46%
21207	2296	3434	mG*mC* A.mC.mC.mU.mU. mU.mC.mU. A*mG*mA.TEG-Chl	3435	P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A* A* A*mC* A* U.	29%
21208	2296	3436	mG*mC* A.mC.mC.mU.mU. mU.mC.mU. A*mG*mA.TEG-Chl	3437	P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A*mA* A*mC* A* U.	72%
21209	2296	3438	mG*mC*mA.mC. mC.mU.mU.mU.m C.mU.mA*mG*m A.TEG-Chl	3439	P.mU.fC.fU. A. G. A.mA. A. G. G.fU. G.mC* A* A* A*mC* A* U.	89%
21210	2296	3440	mG*mC*mA.mC. mC.mU.mU.mU.m C.mU.mA*mG*m A.TEG-Chl	3441	P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A* A* A*mC* A* U.	65%
21211	2296	3442	mG*mC*mA.mC. mC.mU.mU.mU.m C.mU.mA*mG*m A.TEG-Chl	3443	P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A*mA* A*mC* A* U.	90%
21212	2295	3444	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3445	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC.mA.mA*mA*fC* mA*mA*mG* G.	60%
21213	2295	3446	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3447	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A.mA*mA*mC*mA*m A*mG* G.	63%
21214	2295	3448	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3449	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A. A* A*fC* A*mA*mG* G.	52%
21215	2295	3450	mU.mU. G.mC. A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3451	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC.mA. A*mA*fC* A*mA*mG* G.	45%
21216	2295	3452	mU*mU* G.mC. A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3453	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC.mA.mA*mA*fC* mA*mA*mG* G.	65%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
21217	2295	3454	mU*mU* G.mC. A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3455	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A.mA*mA*mC*mA*m A*mG* G.	69%
21218	2295	3456	mU*mU* G.mC. A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3457	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A. A* A*fC* A*mA*mG* G.	62%
21219	2295	3458	mU*mU* G.mC. A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3459	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC.mA. A*mA*fC* A*mA*mG* G.	54%
21220	2295	3460	mU.mU.mG.mC.m A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3461	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC.mA.mA*mA*fC* mA*mA*mG* G.	52%
21221	2295	3462	mU.mU.mG.mC.m A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3463	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A.mA*mA*mC*mA*m A*mG* G.	53%
21222	2295	3464	mU.mU.mG.mC.m A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3465	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC. A. A* A*fC* A*mA*mG* G.	43%
21223	2295	3466	mU.mU.mG.mC.m A.mC.mC.mU.mU. mU.mC.mU*mA* mA.TEG-Chl	3467	P.mU.fU. A. G. A.mA. A. G. G.fU. G.fC.mA. A*mA*fC* A*mA*mG* G.	43%
21224	2299	3468	mC.mC.mU.mU.m U.mC.mU. A. G.mU.mU*mG*m A.TEG-Chl	3469	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU*mG*fC*mA*mA * A.	60%
21225	2299	3470	mC*mC*mU.mU. mU.mC.mU. A. G.mU.mU*mG*m A.TEG-Chl	3471	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU*mG*fC*mA*mA * A.	67%
21226	2299	3472	mC*mC*mU.mU. mU.mC.mU.mA.m G.mU.mU*mG*m A.TEG-Chl	3473	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU*mG*fC*mA*mA * A.	66%
21227	2296	3474	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A*mG*mA.TEG-Chl	3475	P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.fC*mA*mA*mA*fC* mA* U.	49%
20584	2296	3476	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.Chl-TEG	3477	P.mU.fC.fU. A. G. A. A. A. G. G.mU. G.mC* A* A* A*mC* A* U.	70%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
20585	2296	3478	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.Chl-TEG	3479	P.mU.fC.fU. A. G. A. A. A. G. G.fU. G.mC* A* A* A*mC* A* U.	15%
20586	2296	3480	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.Chl-TEG	3481	P.mU. C. U. A. G. A. A. A. G. G.mU. G.mC* A* A* A*mC* A* U.	30%
20587	2296	3482	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.Chl-TEG	3483	P.mU.fC.fU. A. G. A. A. A. G. G.fU. G.fC*mA*mA*mA*fC* mA* U.	32%
20616	2275	3484	G.mU. G. A.mC.mC. A. A. A. A. G.mU. A.Chl-TEG	3485	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.mC. A.mC* A*mC*mU*mC*mU* C.	22%
20617	2275	3486	G.mU. G. A.mC.mC. A. A. A. A. G.mU. A.Chl-TEG	3487	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.fC. A.mC* A*fC*mU*fC*mU* C.	18%
20618	2275	3488	G.mU. G. A.mC.mC. A. A. A. A. G.mU. A.Chl-TEG	3489	P.mU. A. C. U. U. U. U. G. G. U.mC. A.mC* A*mC*mU*mC*mU* C.	36%
20619	2275	3490	G.mU. G. A.mC.mC. A. A. A. A. G.mU. A.Chl-TEG	3491	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.fC. A.mC*mA*mC*mU*m C*mU* C.	28%
21381	2275	3492	G.mU. G. A.mC.mC. A. A. A. A. G*mU*mA.TEG-Chl	3493	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.mC. A.mC* A*mC*mU*mC*mU* C.	28%
21382	2275	3494	G.mU. G. A.mC.mC. A. A. A. A. G*mU*mA.TEG-Chl	3495	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.fC. A.mC* A*fC*mU*fC*mU* C.	28%
21383	2275	3496	mG*mU*mG.mA. mC.mC.mA.mA.m A.mA.mG*mU*m A.TEG-Chl	3497	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.mC. A.mC* A*mC*mU*mC*mU* C.	43%
21384	2275	3498	mG*mU*mG.mA. mC.mC.mA.mA.m A.mA.mG*mU*m A.TEG-Chl	3499	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.fC. A.mC* A*fC*mU*fC*mU* C.	50%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining mRNA expression (1 uM sd-rxRNA, A549)
20392	2275	3500	G.mU. G. A.mC.mC. A. A. A. A. G.mU. A.TEG-Chl	3501	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.fC. A.fC* A*fC*fU*fC*fU* C.	28%
20393	2296	3502	G.mC. A.mC.mC.mU.mU. mU.mC.mU. A. G. A.TEG-Chl	3503	P.mU.fC.fU. A. G. A. A. A. G. G.fU. G.fC* A* A* A*fC* A* U.	35%
21429	2275	3504	G.mU. G. A.mC.mC. A. A. A. A. G*mU*mA.Teg-Chl	3505	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.fC. A.mC* A*fC*mU*fC*mU* C.	36%
21430	2275	3506	G.mU. G. A.mC.mC. A. A.mA. A. G*mU*mA.Teg-Chl	3507	P.mU. A.fC.fU.fU.fU.fU. G. G.fU.mC. A.mC* A*mC*mU*mC*mU* C.	31%

Table 21: Inhibition of gene expression with TGFB2 sd-rxRNA sequences (Accession Number: NM_001135599.1)

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM, A549)
14408	1324	3508	G. G.mC.mU.mC.mU. mC.mC.mU.mU.mC . G. A.Chl	3509	P.mU.fC. G. A. A. G. G. A. G. A. G.mC.mC* A*mU*mU*mC* G* C.	94%
14409	1374	3510	G. A.mC. A. G. G. A. A.mC.mC.mU. G. G.Chl	3511	P.mC.fC. A. G. G.fU.fU.fC.fC.fU. G.mU.mC*mU*mU*m U* A*mU* G.	n/a
14410	946	3512	mC.mC. A. A. G. G. A. G. G.mU.mU.mU. A.Chl	3513	P.mU. A. A. A.fC.fC.fU.fC.fC.fU.mU . G. G*mC* G*mU* A* G* U.	90%
14411	849	3514	A.mU.mU.mU.mC. mC. A.mU.mC.mU. A.mC. A.Chl	3515	P.mU. G.fU. A. G. A.fU. G. G. A. A. A.mU*mC* A*mC*mC*mU* C.	72%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM, A549)
14412	852	3516	mU.mC.mC. A.mU.mC.mU. A.mC. A. A.mC. A.Chl	3517	P.mU. G.fU.fU. G.fU. A. G. A.fU. G. G. A* A* A*mU*mC* A* C.	76%
14413	850	3518	mU.mU.mU.mC.mC . A.mU.mC.mU. A.mC. A. A.Chl	3519	P.mU.fU. G.fU. A. G. A.fU. G. G. A. A. A*mU*mC* A*mC*mC* U.	98%
14414	944	3520	mC. G.mC.mC. A. A. G. G. A. G. G.mU.mU.Chl	3521	P.mA. A.fC.fC.fU.fC.fC.fU.fU. G. G.mC. G*mU* A* G*mU* A* C.	100%
14415	1513	3522	G.mU. G. G.mU. G. A.mU.mC. A. G. A. A.Chl	3523	P.mU.fU.fC.fU. G. A.fU.fC. A.fC.mC. A.mC*mU* G* G*mU* A* U.	n/a
14416	1572	3524	mC.mU.mC.mC.mU . G.mC.mU. A. A.mU. G.mU.Chl	3525	P.mA.fC. A.fU.fU. A. G.fC. A. G. G. A. G* A*mU* G*mU* G* G.	100%
14417	1497	3526	A.mC.mC.mU.mC.m C. A.mC. A.mU. A.mU. A.Chl	3527	P.mU. A.fU. A.fU. G.fU. G. G. A. G. G.mU* G*mC*mC* A*mU* C.	73%
14418	1533	3528	A. A. G.mU.mC.mC. A.mC.mU. A. G. G. A.Chl	3529	P.mU.fC.fC.fU. A. G.fU. G. G. A.mC.mU.mU*mU* A*mU* A* G* U.	98%
14419	1514	3530	mU. G. G.mU. G. A.mU.mC. A. G. A. A. A.Chl	3531	P.mU.fU.fU.fC.fU. G. A.fU.fC. A.mC.mC. A*mC*mU* G* G*mU* A.	86%
14420	1534	3532	A. G.mU.mC.mC. A.mC.mU. A. G. G. A. A.Chl	3533	P.mU.fU.fC.fC.fU. A. G.fU. G. G. A.mC.mU*mU*mU* A*mU* A* G.	99%
14421	943	3534	A.mC. G.mC.mC. A. A. G. G. A. G. G.mU.Chl	3535	P.mA.fC.fC.fU.fC.fC.fU. fU. G. G.mC. G.mU* A* G*mU* A*mC* U.	41%
18570	2445	3536	mU. A.mU.mU.mU. A.mU.mU. G.mU. G.mU. A.Chl	3537	P.mU. A.fC. A.fC. A. A.fU. A. A. A.fU. A* A*fC*fU*fC* A* C.	79%
18571	2445	3538	mU.mU. A.mU.mU.mU. A.mU.mU. G.mU. G.mU. A.Chl	3539	P.mU. A.fC. A.fC. A. A.fU. A. A. A.fU. A* A*fC*fU*fC* A* C.	75%
18572	2083	3540	A.mU. C. A. G.mU. G.mU.mU. A. A. A. A.Chl	3541	P.mU.fU.fU.fU. A. A.fC. A.fC.fU. G. A.fU* G* A* A*fC*fC* A.	47%
18573	2083	3542	mC. A.mU.mC. A. G.mU. G.mU.mU. A. A. A. A.Chl	3543	P.mU.fU.fU.fU. A. A.fC. A.fC.fU. G. A.fU* G* A* A*fC*fC* A.	17%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM, A549)
18574	2544	3544	A.mU. G. G.mC.mU.mU. A. A. G. G. A. A.Chl	3545	P.mU.fU.fC.fC.fU.fU. A. A. G.fC.fC. A. U*fC*fC* A*fU* G* A.	59%
18575	2544	3546	G. A.mU. G. G.mC.mU.mU. A. A. G. G. A. A.Chl	3547	P.mU.fU.fC.fC.fU.fU. A. A. G.fC.fC. A. U*fC*fC* A*fU* G* A.	141%
18576	2137	3548	mU.mU. G.mU. G.mU.mU.mC.mU. G.mU.mU. A.Chl	3549	P.mU. A. A.fC. A. G. A. A.fC. A.fC. A. A* A*fC*fU*fU*fC* C.	77%
18577	2137	3550	mU.mU.mU. G.mU. G.mU.mU.mC.mU. G.mU.mU. A.Chl	3551	P.mU. A. A.fC. A. G. A. A.fC. A.fC. A. A* A*fC*fU*fU*fC* C.	59%
18578	2520	3552	A. A. A.mU. A.mC.mU.mU.mU. G.mC.mC. A.Chl	3553	P.mU. G. G.fC. A. A. A. G.fU. A.fU.fU.fU* G* G*fU*fC*fU* C.	75%
18579	2520	3554	mC. A. A. A.mU. A.mC.mU.mU.mU. G.mC.mC. A.Chl	3555	P.mU. G. G.fC. A. A. A. G.fU. A.fU.fU.fU* G* G*fU*fC*fU* C.	55%
18580	3183	3556	mC.mU.mU. G.mC. A.mC.mU. A.mC. A. A. A.Chl	3557	P.mU.fU.fU. G.fU. A. G.fU. G.fC. A. A. G*fU*fC* A* A* A* C.	84%
18581	3183	3558	A.mC.mU.mU. G.mC. A.mC.mU. A.mC. A. A. A.Chl	3559	P.mU.fU.fU. G.fU. A. G.fU. G.fC. A. A. G*fU*fC* A* A* A* C.	80%
18582	2267	3560	G. A. A.mU.mU.mU. A.mU.mU. A. G.mU. A.Chl	3561	P.mU. A.fC.fU. A. A.fU. A. A. A.fU.fU.fC*fU*fU*fC*fC* A* G.	82%
18583	2267	3562	A. G. A. A.mU.mU.mU. A.mU.mU. A. G.mU. A.Chl	3563	P.mU. A.fC.fU. A. A.fU. A. A. A.fU.fU.fC*fU*fU*fC*fC* A* G.	67%
18584	3184	3564	mU.mU. G.mC. A.mC.mU. A.mC. A. A. A. A.Chl	3565	P.mU.fU.fU.fU. G.fU. A. G.fU. G.fC. A. A* G*fU*fC* A* A* A.	77%
18585	3184	3566	mC.mU.mU. G.mC. A.mC.mU. A.mC. A. A. A. A.Chl	3567	P.mU.fU.fU.fU. G.fU. A. G.fU. G.fC. A. A* G*fU*fC* A* A* A.	59%
18586	2493	3568	A.mU. A. A. A. A.mC. A. G. G.mU. G. A.Chl	3569	P.mU.fC. A.fC.fC.fU. G.fU.fU.fU.fU. A.fU*fU*fU*fU*fC*fC* A.	84%
18587	2493	3570	A. A.mU. A. A. A. A.mC. A. G. G.mU. G. A.Chl	3571	P.mU.fC. A.fC.fC.fU. G.fU.fU.fU.fU. A.fU*fU*fU*fU*fC*fC* A.	70%
18588	2297	3572	G. A.mC. A. A.mC. A. A.mC. A. A.mC. A.Chl	3573	P.mU. G.fU.fU. G.fU.fU. G.fU.fU. G.fU.fC* G*fU*fU* G*fU* U.	40%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM, A549)
18589	2046	3574	A.mU. G. C.mU.mU. G.mU. A. A.mC. A. A.Chl	3575	P.mU.fU. G.fU.fU. A.fC. A. A. G.fC. A.fU*fC* A*fU*fC* G* U.	39%
18590	2531	3576	mC. A. G. A. A. A.mC.mU.mC. A.mU. G. A.Chl	3577	P.mU.fC. A.fU. G. A. G.fU.fU.fU.fC.fU. G* G*fC* A* A* A* G.	56%
18591	2389	3578	G.mU. A.mU.mU. G.mC.mU. A.mU. G.mC. A.Chl	3579	P.mU. G.fC. A.fU. A. G.fC. A. A.fU. A.fC* A* G* A* A* A* A.	64%
18592	2530	3580	mC.mC. A. G. A. A. A.mC.mU.mC. A.mU. A.Chl	3581	P.mU. A.fU. G. A. G.fU.fU.fU.fC.fU. G. G*fC* A* A* A* G* U.	44%
18593	2562	3582	A.mC.mU.mC. A. A. A.mC. G. A. G.mC. A.Chl	3583	P.mU. G.fC.fU.fC. G.fU.fU.fU. G. A. G.fU*fU*fC* A* A* G* U.	87%
18594	2623	3584	A.mU. A.mU. G. A.mC.mC. G. A. G. A. A.Chl	3585	P.mU.fU.fC.fU.fC. G. G.fU.fC. A.fU. A.fU* A* A*fU* A* A* C.	69%
18595	2032	3586	mC. G. A.mC. G. A.mC. A. A.mC. G. A. A.Chl	3587	P.mU.fU.fC. G.fU.fU. G.fU.fC. G.fU.fC. G*fU*fC* A*fU*fC* A.	55%
18596	2809	3588	G.mU. A. A. A.mC.mC. A. G.mU. G. A. A.Chl	3589	P.mU.fU.fC. A.fC.fU. G. G.fU.fU.fU. A.fC*fU* A* A* A*fC* U.	58%
18597	2798	3590	mU.mU. G.mU.mC. A. G.mU.mU.mU. A. G. A.Chl	3591	P.mU.fC.fU. A. A. A.fC.fU. G. A.fC. A. A* A* G* A* A*fC* C.	38%
18598	2081	3592	mU.mC. A.mU.mC. A. G.mU. G.mU.mU. A. A.Chl	3593	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC* A* A* G.	25%
18599	2561	3594	A. A.mC.mU.mC. A. A. A.mC. G. A. G. A.Chl	3595	P.mU.fC.fU.fC. G.fU.fU.fU. G. A. G.fU.fU*fC* A* A* G*fU* U.	57%
18600	2296	3596	mC. G. A.mC. A. A.mC. A. A.mC. A. A. A.Chl	3597	P.mU.fU.fU. G.fU.fU. G.fU.fU. G.fU.fC. G*fU*fU* G*fU*fU* C.	69%
18601	2034	3598	A.mC. G. A.mC. A. A.mC. G. A.mU. G. A.Chl	3599	P.mU.fC. A.fU.fC. G.fU.fU. G.fU.fC. G.fU*fC* G*fU*fC* A*fU.	22%
18602	2681	3600	G.mC.mU. G.mC.mC.mU. A. A. G. G. A. A.Chl	3601	P.mU.fU.fC.fC.fU.fU. A. G. G.fC. A. G.fC*fU* G* A*fU* A* C.	43%
18603	2190	3602	A.mU.mU.mC.mU. A.mC. A.mU.mU.mU.mC. A.Chl	3603	P.mU. G. A. A. A.fU. G.fU. A. G. A. A.fU* A* A* G* G*fC* C.	128%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM, A549)
20604	2083	3604	mC. A.mU.mC. A. G.mU. G.mU.mU. A. A. A. A.Chl	3605	P.mU.fU.fU.fU. A. A.fC. A.fC.fU. G. A.mU* G* A* A*mC*mC* A.	19%
20605	2083	3606	mC. A.mU.mC. A. G.mU. G.mU.mU. A. A. A. A.Chl	3607	P.mU.fU.fU.fU. A. A.fC. A.fC.fU. G. A.mU* G* A* A*fC*mC* A.	20%
20606	2083	3608	mC. A.mU.mC. A. G.mU. G.mU.mU. A. A. A. A.Chl	3609	P.mU. U. U. U. A. A. C. A. C. U. G. A.mU* G* A* A*mC*mC* A.	82%
20607	2083	3610	mC. A.mU.mC. A. G.mU. G.mU.mU. A. A. A. A.Chl	3611	P.mU.fU.fU.fU. A. A.fC. A.fC.fU. G. A.fU*mG*mA*mA*fC *fC* A.	59%
21722	2081	3612	mU.mC. A.mU.mC. A. G.mU. G.mU.mU. A. A.Chl	3613	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*mC*mC* A* A* G.	34%
21723	2081	3614	mU.mC. A.mU.mC. A. G.mU. G.mU.mU. A. A.Chl	3615	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G.mA*mA*mC*mC*m A*mA* G.	53%
21724	2081	3616	mU.mC. A.mU.mC. A. G.mU. G.mU.mU. A. A.Chl	3617	P.mU.fU. A. A.fC. A.fC.fU. G. A.mU. G.mA*mA*mC*mC*m A*mA* G.	48%
21725	2081	3618	mU.mC. A.mU.mC. A. G.mU. G.mU.mU. A. A.Chl	3619	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC*mA*mA* G.	45%
21726	2081	3620	mU.mC. A.mU.mC. A. G.mU. G.mU.mU. A. A.Chl	3621	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G.mA*mA*fC*fC*mA* mA* G.	54%
21727	2081	3622	mU.mC. A.mU.mC. A. G.mU. G.mU.mU*mA*mA. TEG-Chl	3623	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC* A* A* G.	29%
21728	2081	3624	mU*mC* A.mU.mC. A. G.mU. G.mU.mU*mA*mA. TEG-Chl	3625	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC* A* A* G.	27%
21729	2081	3626	mU*mC*mA.mU.m C.mA.mG.mU.mG. mU.mU*mA*mA.TE G-Chl	3627	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC* A* A* G.	30%
21375	2081	3628	mU.mC. A.mU.mC. A. G.mU. G.mU.mU*mA*mA. TEG-Chl	3629	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*mC*mC* A* A* G.	29%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM, A549)
21376	2081	3630	mU.mC. A.mU.mC. A. G.mU. G.mU.mU*mA*mA. TEG-Chl	3631	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC*mA*mA* G.	30%
21377	2081	3632	mU.mC. A.mU.mC. A. G.mU. G.mU.mU*mA*mA. TEG-Chl	3633	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G.mA*mA*fC*fC*mA* mA* G.	37%
21378	2081	3634	mU*mC*mA.mU.m C.mA.mG.mU.mG. mU.mU*mA*mA.TE G-Chl	3635	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*mC*mC* A* A* G.	32%
21379	2081	3636	mU*mC*mA.mU.m C.mA.mG.mU.mG. mU.mU*mA*mA.TE G-Chl	3637	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC*mA*mA* G.	31%
21380	2081	3638	mU*mC*mA.mU.m C.mA.mG.mU.mG. mU.mU*mA*mA.TE G-Chl	3639	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G.mA*mA*fC*fC*mA* mA* G.	39%

Table 22: Inhibition of gene expression with TGFB1 sd-rxRNA sequences (Accession Number: NM_000660.3)

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Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14394	1194	3640	G.mC.mU. A. A.mU. G. G.mU. G. G. A. A.Chl	3641	P.mU.fU.fC.fC. A.fC.fC. A.fU.fU. A. G.mC* A*mC* G*mC* G* G.	24%
14395	2006	3642	mU. G. A.mU.mC. G.mU. G.mC. G.mC.mU.mC.Chl	3643	P.mG. A. G.fC. G.fC. A.fC. G. A.mU.mC. A*mU* G*mU*mU* G* G.	79%
14396	1389	3644	mC. A. A.mU.mU.mC.mC.m U. G. G.mC. G. A.Chl	3645	P.mU.fC. G.fC.fC. A. G. G. A. A.mU.mU. G*mU*mU* G*mC*mU* G.	77%
14397	1787	3646	A. G.mU. G. G. A.mU.mC.mC. A.mC. G. A.Chl	3647	P.mU.fC. G.fU. G. G. A.fU.fC.fC. A.mC.mU*mU*mC*mC * A* G* C.	n/a
14398	1867	3648	mU. A.mC. A. G.mC. A. A. G. G.mU.mC.mC.Chl	3649	P.mG. G. A.fC.fC.fU.fU. G.fC.fU. G.mU. A*mC*mU* G*mC* G* U.	82%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
14399	2002	3650	A. A.mC. A.mU. G. A.mU.mC. G.mU. G.mC.Chl	3651	P.mG.fC. A.fC. G. A.fU.fC. A.fU. G.mU.mU* G* G* A*mC* A* G.	n/a
14400	2003	3652	A.mC. A.mU. G. A.mU.mC. G.mU. G.mC. G.Chl	3653	P.mC. G.fC. A.fC. G. A.fU.fC. A.mU. G.mU*mU* G* G* A*mC* A.	n/a
14401	1869	3654	mC. A. G.mC. A. A. G. G.mU.mC.mC.mU. G.Chl	3655	P.mC. A. G. G. A.fC.fC.fU.fU. G.mC.mU. G*mU* A*mC*mU* G* C.	82%
14402	2000	3656	mC.mC. A. A.mC. A.mU. G. A.mU.mC. G.mU.Chl	3657	P.mA.fC. G. A.fU.fC. A.fU. G.fU.mU. G. G* A*mC* A* G*mC* U.	66%
14403	986	3658	A. G.mC. G. G. A. A. G.mC. G.mC. A.mU.Chl	3659	P.mA.fU. G.fC. G.fC.fU.fU.fC.fC. G.mC.mU*mU*mC* A*mC*mC* A.	78%
14404	995	3660	G.mC. A.mU.mC. G. A. G. G.mC.mC. A.mU.Chl	3661	P.mA.fU. G. G.fC.fC.fU.fC. G. A.mU. G.mC* G*mC*mU*mU*mC* C.	79%
14405	963	3662	G. A.mC.mU. A.mU.mC. G. A.mC. A.mU. G.Chl	3663	P.mC. A.fU. G.fU.fC. G. A.fU. A. G.mU.mC*mU*mU* G*mC* A* G.	80%
14406	955	3664	A.mC.mC.mU. G.mC. A. A. G. A.mC.mU. A.Chl	3665	P.mU. A. G.fU.fC.fU.fU. G.fC. A. G. G.mU* G* G* A*mU* A* G.	88%
14407	1721	3666	G.mC.mU.mC.mC. A.mC. G. G. A. G. A. A.Chl	3667	P.mU.fU.fC.fU.fC.fC. G.fU. G. G. A. G.mC*mU* G* A* A* G* C.	n/a
18454	1246	3668	mC. A.mC. A. G.mC. A.mU. A.mU. A.mU. A.Chl	3669	P.mU. A.fU. A.fU. A.fU. G.fC.fU. G.fU. G*fU* G*fU* A*fC* U.	58%
18455	1248	3670	mC. A. G.mC. A.mU. A.mU. A.mU. A.mU. A.Chl	3671	P.mU. A.fU. A.fU. A.fU. A.fU. G.fC.fU. G*fU* G*fU* G*fU* A.	87%
18456	1755	3672	G.mU. A.mC. A.mU.mU. G. A.mC.mU.mU. A.Chl	3673	P.mU. A. A. G.fU.fC. A. A.fU. G.fU. A.fC* A* G*fC*fU* G* C.	107%
18457	1755	3674	mU. G.mU. A.mC. A.mU.mU. G. A.mC.mU.mU. A.Chl	3675	P.mU. A. A. G.fU.fC. A. A.fU. G.fU. A.fC* A* G*fC*fU* G* C.	77%
18458	1708	3676	A. A.mC.mU. A.mU.mU. G.mC.mU.mU.mC. A.Chl	3677	P.mU. G. A. A. G.fC. A. A.fU. A. G.fU.fU* G* G*fU* G*fU* C.	75%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
18459	1708	3678	mC. A. A.mC.mU. A.mU.mU. G.mC.mU.mU.mC. A.Chl	3679	P.mU. G. A. A. G.fC. A. A.fU. A. G.fU.fU* G* G*fU* G*fU* C.	73%
18460	1250	3680	G.mC. A.mU. A.mU. A.mU. A.mU. G.mU. A.Chl	3681	P.mU. A.fC. A.fU. A.fU. A.fU. A.fU. G.fC*fU* G*fU* G*fU* G.	n/a
18461	1754	3682	mU. G.mU. A.mC. A.mU.mU. G. A.mC.mU. A.Chl	3683	P.mU. A. G.fU.fC. A. A.fU. G.fU. A.fC. A* G*fC*fU* G*fC* C.	91%
18462	1754	3684	mC.mU. G.mU. A.mC. A.mU.mU. G. A.mC.mU. A.Chl	3685	P.mU. A. G.fU.fC. A. A.fU. G.fU. A.fC. A* G*fC*fU* G*fC* C.	92%
18463	1249	3686	A. G.mC. A.mU. A.mU. A.mU. A.mU. G. A.Chl	3687	P.mU.fC. A.fU. A.fU. A.fU. A.fU. G.fC.fU* G*fU* G*fU* G* U.	n/a
18464	1383	3688	mC. A. G.mC. A. A.mC. A. A.mU.mU.mC. A.Chl	3689	P.mU. G. A. A.fU.fU. G.fU.fU. G.fC.fU. G*fU* A*fU*fU*fU* C.	77%
18465	1251	3690	mC. A.mU. A.mU. A.mU. A.mU. G.mU.mU. A.Chl	3691	P.mU. A. A.fC. A.fU. A.fU. A.fU. A.fU. G*fC*fU* G*fU* G* U.	84%
18466	1713	3692	mU.mU. G.mC.mU.mU.mC. A. G.mC.mU.mC. A.Chl	3693	P.mU. G. A. G.fC.fU. G. A. A. G.fC. A. A*fU* A* G*fU*fU* G.	n/a
18467	1713	3694	A.mU.mU. G.mC.mU.mU.mC. A. G.mC.mU.mC. A.Chl	3695	P.mU. G. A. G.fC.fU. G. A. A. G.fC. A. A*fU* A* G*fU*fU* G.	83%
18468	1247	3696	A.mC. A. G.mC. A.mU. A.mU. A.mU. A. A.Chl	3697	P.mU.fU. A.fU. A.fU. A.fU. G.fC.fU. G.fU* G*fU* G*fU* A* C.	96%
18469	1712	3698	A.mU.mU. G.mC.mU.mU.mC. A. G.mC.mU. A.Chl	3699	P.mU. A. G.fC.fU. G. A. A. G.fC. A. A.fU* A* G*fU*fU* G* G.	90%
18470	1712	3700	mU. A.mU.mU. G.mC.mU.mU.mC. A. G.mC.mU. A.Chl	3701	P.mU. A. G.fC.fU. G. A. A. G.fC. A. A.fU* A* G*fU*fU* G* G.	98%
18471	1212	3702	mC. A. A. G.mU.mU.mC. A. A. G.mC. A. A.Chl	3703	P.mU.fU. G.fC.fU.fU. G. A. A.fC.fU.fU. G*fU*fC* A*fU* A* G.	n/a
18472	1222	3704	mC. A. G. A. G.mU. A.mC. A.mC. A.mC. A.Chl	3705	P.mU. G.fU. G.fU. G.fU. A.fC.fU.fC.fU. G* C*fU*fU* G* A* A.	45%
18473	1228	3706	A.mC. A.mC. A.mC. A. G.mC. A.mU. A. A.Chl	3707	P.mU.fU. A.fU. G.fC.fU. G.fU. G.fU. G.fU* A*fC*fU*fC*fU* G.	36%
18474	1233	3708	mC. A. G.mC. A.mU. A.mU. A.mU. A.mU. A.Chl	3709	P.mU. A.fU. A.fU. A.fU. A.fU. G.fC.fU. G*fU* G*fU* G*fU* A.	68%
18475	1218	3710	mU.mC. A. A. G.mC. A. G. A. G.mU. A. A.Chl	3711	P.mU.fU. A.fC.fU.fC.fU. G.fC.fU.fU. G. A* A*fC*fU*fU* G* U.	64%

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
18476	1235	3712	A. G.mC. A.mU. A.mU. A.mU. A.mU. G. A.Chl	3713	P.mU.fC. A.fU. A.fU. A.fU. A.fU. G.fC.fU* G*fU* G*fU* G* U.	78%
18477	1225	3714	A. G. A. G.mU. A.mC. A.mC. A.mC. A. A.Chl	3715	P.mU.fU. G.fU. G.fU. G.fU. A.fC.fU.fC.fU* G*fC*fU*fU* G* A.	92%
18478	1221	3716	A. A. G.mC. A. G. A. G.mU. A.mC. A. A.Chl	3717	P.mU.fU. G.fU. A.fC.fU.fC.fU. G.fC.fU.fU* G* A* A*fC*fU* U.	103%
18479	1244	3718	mU.mU.mC. A. A.mC. A.mC. A.mU.mC. A. A.Chl	3719	P.mU.fU. G. A.fU. G.fU. G.fU.fU. G. A. A* G* A* A*fC* A* U.	84%
18480	1224	3720	A. G.mC. A. G. A. G.mU. A.mC. A.mC. A.Chl	3721	P.mU. G.fU. G.fU. A.fC.fU.fC.fU. G.fC.fU*fU* G* A* A*fC* U.	37%
18481	1242	3722	A.mU. A.mU. A.mU. G.mU.mU.mC.mU.m U. A.Chl	3723	P.mU. A. A. G. A. A.fC. A.fU. A.fU. A.fU* A*fU* G*fC*fU* G.	62%
18482	1213	3724	G. A.mC. A. A. G.mU.mU.mC. A. A. G. A.Chl	3725	P.mU.fC.fU.fU. G. A. A.fC.fU.fU. G.fU.fC* A*fU* A* G* A* U.	47%
18483	1760	3726	mU.mU. A. A. A. G. A.mU. G. G. A. G. A.Chl	3727	P.mU.fC.fU.fC.fC. A.fU.fC.fU.fU.fU. A. A*fU* G* G* G* G* C.	69%
18484	1211	3728	mC.mU. A.mU. G. A.mC. A. A. G.mU.mU. A.Chl	3729	P.mU. A. A.fC.fU.fU. G.fU.fC. A.fU. A. G* A*fU*fU*fU*fC* G.	n/a
19411	1212	3730	mC. A. A.mC. G. A. A. A.mU.mC.mU. A. A.Chl	3731	P.mU.fU. A. G. A.fU.fU.fU.fC. G.fU.fU. G*fU* G* G* G*fU*fU.	52%
19412	1222	3732	mU. A.mU. G. A.mC. A. A. G.mU.mU.mC. A.Chl	3733	P.mU. G. A. A.fC.fU.fU. G.fU.fC. A.fU. A* G* A*fU*fU*fU*fC.	51%
19413	1228	3734	A. A. G.mU.mU.mC. A. A. G.mC. A. G. A.Chl	3735	P.mU.fC.fU. G.fC.fU.fU. G. A. A.fC.fU.fU* G*fU*fC* A*fU* A.	n/a
19414	1233	3736	mC. A. A. G.mC. A. G. A. G.mU. A.mC. A.Chl	3737	P.mU. G.fU. A.fC.fU.fC.fU. G.fC.fU.fU. G* A* A*fC*fU*fU* G.	41%
19415	1218	3738	A. A.mU.mC.mU. A.mU. G. A.mC. A. A. A.Chl	3739	P.mU.fU.fU. G.fU.fC. A.fU. A. G. A.fU.fU*fU*fC* G*fU*fU* G.	104%
19416	1244	3740	mC. A.mC. A.mC. A. G.mC. A.mU. A.mU. A.Chl	3741	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.fU. G*fU* A*fC*fU*fC*fU.	31%
19417	655	3742	G. A. A. A.mU. A.mU. A. G.mC. A. A. A.Chl	3743	P.mU.fU.fU. G.fC.fU. A.fU. A.fU.fU.fU.fC*fU* G* G*fU* A* G.	n/a

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
19418	644	3744	G. A. A.mC.mU.mC.mU. A.mC.mC. A. G. A.Chl	3745	P.mU.fC.fU. G. G.fU. A. G. A. G.fU.fU.fC*fU* A*fC* G*fU* G.	n/a
19419	819	3746	G.mC. A. A. A. G. A.mU. A. A.mU. G. A.Chl	3747	P.mU.fC. A.fU.fU. A.fU.fC.fU.fU.fU. G.fC*fU* G*fU*fC* A* C.	n/a
19420	645	3748	A. A.mC.mU.mC.mU. A.mC.mC. A. G. A. A.Chl	3749	P.mU.fU.fC.fU. G. G.fU. A. G. A. G.fU.fU*fC*fU* A*fC* G* U.	n/a
19421	646	3750	A.mC.mU.mC.mU. A.mC.mC. A. G. A. A. A.Chl	3751	P.mU.fU.fU.fC.fU. G. G.fU. A. G. A. G.fU*fU*fC*fU* A*fC* G.	n/a
19422	816	3752	A.mC. A. G.mC. A. A. A. G. A.mU. A. A.Chl	3753	P.mU.fU. A.fU.fC.fU.fU.fU. G.fC.fU. G.fU*fC* A*fC* A* A* G.	n/a
19423	495	3754	mC. A. A.mU.mC.mU. A.mU. G. A.mC. A. A.Chl	3755	P.mU.fU. G.fU.fC. A.fU. A. G. A.fU.fU. G*fC* G*fU*fU* G* U.	n/a
19424	614	3756	A. G. A.mU.mU.mC. A. A. G.mU.mC. A. A.Chl	3757	P.mU.fU. G. A.fC.fU.fU. G. A. A.fU.fC.fU*fC*fU* G*fC* A* G.	n/a
19425	627	3758	mC.mU. G.mU. G. G. A. G.mC. A. A.mC. A.Chl	3759	P.mU. G.fU.fU. G.fC.fU.fC.fC. A.fC. A. G*fU*fU* G* A*fC* U.	n/a
19426	814	3760	mU. G. A.mC. A. G.mC. A. A. A. G. A. A.Chl	3761	P.mU.fU.fC.fU.fU.fU. G.fC.fU. G.fU.fC. A*fC* A* A* G* A* G.	n/a
19427	501	3762	A.mU. G. A.mC. A. A. A. A.mC.mC. A. A.Chl	3763	P.mU.fU. G. G.fU.fU.fU.fU. G.fU.fC. A.fU* A* G* A*fU*fU* G.	n/a
19428	613	3764	G. A. G. A.mU.mU.mC. A. A. G.mU.mC. A.Chl	3765	P.mU. G. A.fC.fU.fU. G. A. A.fU.fC.fU.fC*fU* G*fC* A* G* G.	n/a
21240	1244	3766	mC. A.mC. A.mC. A. G.mC. A.mU. A.mU. A.Chl	3767	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.fU. G*mU* A*mC*mU*mC* U.	0.875
21241	1244	3768	mC. A.mC. A.mC. A. G.mC. A.mU. A.mU. A.Chl	3769	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.fU. G*mU*mA*mC*mU*mC* U.	0.88
21242	1244	3770	mC. A.mC. A.mC. A. G.mC. A.mU. A.mU. A.Chl	3771	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.fU.mG*mU*mA*mC*mU*mC* U.	0.635

Oligo Number	Start Site	SEQ ID NO	Sense sequence	SEQ ID NO	Antisense sequence	% remaining expression (1 uM A549)
21243	1244	3772	mC. A.mC. A.mC. A. G.mC. A.mU. A.mU. A.Chl	3773	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.fU.mG*fU*mA*fC*m U*fC* U.	0.32
21244	1244	3774	mC. A.mC. A.mC. A. G.mC. A.mU. A.mU. A.Chl	3775	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.fU. G*fU* A*fC*mU*mC* U.	0.36
21245	1244	3776	mC. A.mC. A.mC. A. G.mC. A.mU. A*mU*mA.TEG-Chl	3777	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.fU. G*fU* A*fC*fU*fC*fU.	0.265
21246	1244	3778	mC*mA*mC. A.mC. A. G.mC. A.mU. A*mU*mA.TEG-Chl	3779	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.fU. G*fU* A*fC*fU*fC*fU.	0.334
21247	1244	3780	mC*mA*mC.mA.mC. mA.mG.mC.mA.mU. mA*mU*mA.TEG-Chl	3781	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.fU. G*fU* A*fC*fU*fC*fU.	0.29
21248	614	3782	mA. G. A.mU.mU.mC. A. A. G.mU.mC*mA*mA.T EG-Chl	3783	P.mU.fU. G. A.fC.fU.fU. G. A. A.fU.fC.fU*fC*fU* G*fC*fU* U.	n/a
20608	1244	3784	mC. A.mC. A.mC. A. G.mC. A.mU. A.mU. A.Chl	3785	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.mU. G*mU* A*mC*mU*mC* U.	79%
20609	1244	3786	mC. A.mC. A.mC. A. G.mC. A.mU. A.mU. A.Chl	3787	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.mU. G*fU* A*mC*fU*mC* U.	60%
20610	1244	3788	mC. A.mC. A.mC. A. G.mC. A.mU. A.mU. A.Chl	3789	P.mU. A. U. A. U. G. C. U. G. U. G.mU. G*mU* A*mC*mU*mC* U.	93%
20611	1244	3790	mC. A.mC. A.mC. A. G.mC. A.mU. A.mU. A.Chl	3791	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.mU.mG*mU*mA*mC *mU*mC* U.	n/a
21374	614	3792	mC*mA*mC.mA.mC. mA.mG.mC.mA.mU. mA*mU*mA.TEG-Chl	3793	P.mU. A.fU. A.fU. G.fC.fU. G.fU. G.fU.mG*fU*mA*fC*m U*fC* U.	24%

Table 23: CB1 sequences

Ref Pos	SEQ ID NO	19-mer Sense Seq	SEQ ID NO	25-mer Sense Seq w/A @ 25
1690	3794	AUGUCUGUGUCCACAGACA	3795	GUAACCAUGUCUGUGUCCACAGACA
1686	3796	AACCAUGUCUGUGUCCACA	3797	CAAGGUAACCAUGUCUGUGUCCACA
1685	3798	UAACCAUGUCUGUGUCCAC	3799	CCAAGGUAACCAUGUCUGUGUCCAA
1684	3800	GUAACCAUGUCUGUGUCCA	3801	GCCAAGGUAACCAUGUCUGUGUCCA
1649	3802	AAAGCUGCAUCAAGAGCAC	3803	CCGCAGAAAGCUGCAUCAAGAGCAA
1648	3804	GAAAGCUGCAUCAAGAGCA	3805	GCCGCAGAAAGCUGCAUCAAGAGCA
1494	3806	CAUCUAUGCUCUGAGGAGU	3807	CCCCAUCAUCUAUGCUCUGAGGAGA
1493	3808	UCAUCUAUGCUCUGAGGAG	3809	ACCCCAUCAUCUAUGCUCUGAGGAA
1492	3810	AUCAUCUAUGCUCUGAGGA	3811	AACCCCAUCAUCUAUGCUCUGAGGA
1491	3812	CAUCAUCUAUGCUCUGAGG	3813	GAACCCCAUCAUCUAUGCUCUGAGA
1490	3814	CCAUCAUCUAUGCUCUGAG	3815	UGAACCCCAUCAUCUAUGCUCUGAA
1489	3816	CCCAUCAUCUAUGCUCUGA	3817	GUGAACCCCAUCAUCUAUGCUCUGA
1487	3818	ACCCCAUCAUCUAUGCUCU	3819	CCGUGAACCCCAUCAUCUAUGCUCA
1486	3820	AACCCCAUCAUCUAUGCUC	3821	ACCGUGAACCCCAUCAUCUAUGCUA
1358	3822	UGGUGUUGAUCAUCUGCUG	3823	UCCUGGUGGUGUUGAUCAUCUGCUA
1357	3824	GUGGUGUUGAUCAUCUGCU	3825	AUCCUGGUGGUGUUGAUCAUCUGCA
1355	3826	UGGUGGUGUUGAUCAUCUG	3827	UGAUCCUGGUGGUGUUGAUCAUCUA
1354	3828	CUGGUGGUGUUGAUCAUCU	3829	CUGAUCCUGGUGGUGUUGAUCAUCA
1351	3830	AUCCUGGUGGUGUUGAUCA	3831	GUCCUGAUCCUGGUGGUGUUGAUCA
1198	3832	AUUCUCUGGAAGGCUCACA	3833	AUGUAUAUUCUCUGGAAGGCUCACA
1197	3834	UAUUCUCUGGAAGGCUCAC	3835	CAUGUAUAUUCUCUGGAAGGCUCAA
1196	3836	AUAUUCUCUGGAAGGCUCA	3837	ACAUGUAUAUUCUCUGGAAGGCUCA
1195	3838	UAUAUUCUCUGGAAGGCUC	3839	UACAUGUAUAUUCUCUGGAAGGCUA
1131	3840	CUACCUGAUGUUCUGGAUC	3841	UGAAACCUACCUGAUGUUCUGGAUA
1129	3842	ACCUACCUGAUGUUCUGGA	3843	GAUGAAACCUACCUGAUGUUCUGGA
1127	3844	AAACCUACCUGAUGUUCUG	3845	UUGAUGAAACCUACCUGAUGUUCUA
1126	3846	GAAACCUACCUGAUGUUCU	3847	AUUGAUGAAACCUACCUGAUGUUCA
1086	3848	ACUGCAAUCUGUUUGCUCA	3849	CGAGAAACUGCAAUCUGUUUGCUCA
1084	3850	AAACUGCAAUCUGUUUGCU	3851	UGCGAGAAACUGCAAUCUGUUUGCA
972	3852	CCUGGCCUAUAAGAGGAUU	3853	CAGGCCCCUGGCCUAUAAGAGGAUA
951	3854	GUACAUAUCCAUUCACAGG	3855	CGACAGGUACAUAUCCAUUCACAGA
950	3856	GGUACAUAUCCAUUCACAG	3857	UCGACAGGUACAUAUCCAUUCACAA
948	3858	CAGGUACAUAUCCAUUCAC	3859	CAUCGACAGGUACAUAUCCAUUCAA
947	3860	ACAGGUACAUAUCCAUUCA	3861	CCAUCGACAGGUACAUAUCCAUUCA
946	3862	GACAGGUACAUAUCCAUUC	3863	GCCAUCGACAGGUACAUAUCCAUUA
943	3864	AUCGACAGGUACAUAUCCA	3865	ACAGCCAUCGACAGGUACAUAUCCA
941	3866	CCAUCGACAGGUACAUAUC	3867	UCACAGCCAUCGACAGGUACAUAUA
940	3868	GCCAUCGACAGGUACAUAU	3869	CUCACAGCCAUCGACAGGUACAUAA
869	3870	ACGUGUUUCUGUUCAAACU	3871	GCCGCAACGUGUUUCUGUUCAAACA
868	3872	AACGUGUUUCUGUUCAAAC	3873	AGCCGCAACGUGUUUCUGUUCAAAA
1647	3874	AGAAAGCUGCAUCAAGAGC	3875	GGCCGCAGAAAGCUGCAUCAAGAGA
1645	3876	GCAGAAAGCUGCAUCAAGA	3877	AGGGCCGCAGAAAGCUGCAUCAAGA
1394	3878	UCAUGGUGUAUGAUGUCUU	3879	UUGCAAUCAUGGUGUAUGAUGUCUA

Ref Pos	SEQ ID NO	19-mer Sense Seq	SEQ ID NO	25-mer Sense Seq w/A @ 25
1393	3880	AUCAUGGUGUAUGAUGUCU	3881	CUUGCAAUCAUGGUGUAUGAUGUCA
1391	3882	CAAUCAUGGUGUAUGAUGU	3883	UGCUUGCAAUCAUGGUGUAUGAUGA
1125	3884	UGAAACCUACCUGAUGUUC	3885	CAUUGAUGAAACCUACCUGAUGUUA
1090	3886	CAAUCUGUUUGCUCAGACA	3887	AAACUGCAAUCUGUUUGCUCAGACA
1089	3888	GCAAUCUGUUUGCUCAGAC	3889	GAAACUGCAAUCUGUUUGCUCAGAA
1088	3890	UGCAAUCUGUUUGCUCAGA	3891	AGAAACUGCAAUCUGUUUGCUCAGA
1087	3892	CUGCAAUCUGUUUGCUCAG	3893	GAGAAACUGCAAUCUGUUUGCUCAA
1397	3894	UGGUGUAUGAUGUCUUUGG	3895	CAAUCAUGGUGUAUGAUGUCUUUGA
1396	3896	AUGGUGUAUGAUGUCUUUG	3897	GCAAUCAUGGUGUAUGAUGUCUUUA
1120	3898	AUUGAUGAAACCUACCUGA	3899	CCACACAUUGAUGAAACCUACCUGA
1118	3900	ACAUUGAUGAAACCUACCU	3901	UCCCACACAUUGAUGAAACCUACCA
1117	3902	CACAUUGAUGAAACCUACC	3903	UUCCCACACAUUGAUGAAACCUACA
1116	3904	ACACAUUGAUGAAACCUAC	3905	UUUCCCACACAUUGAUGAAACCUAA
1132	3906	UACCUGAUGUUCUGGAUCG	3907	GAAACCUACCUGAUGUUCUGGAUCA
845	3908	UGUUCCACCGCAAAGAUAG	3909	UCCACGUGUUCCACCGCAAAGAUAA
844	3910	GUGUUCCACCGCAAAGAUA	3911	UUCCACGUGUUCCACCGCAAAGAUA
573	3912	CUUCAAGGAGAAUGAGGAG	3913	CUCGUCCUUCAAGGAGAAUGAGGAA
572	3914	CCUUCAAGGAGAAUGAGGA	3915	UCUCGUCCUUCAAGGAGAAUGAGGA
571	3916	UCCUUCAAGGAGAAUGAGG	3917	CUCUCGUCCUUCAAGGAGAAUGAGA
1449	3918	AUUCUGCAGUAUGCUCUGC	3919	GUUUGCAUUCUGCAGUAUGCUCUGA
1448	3920	CAUUCUGCAGUAUGCUCUG	3921	UGUUUGCAUUCUGCAGUAUGCUCUA
1447	3922	GCAUUCUGCAGUAUGCUCU	3923	GUGUUUGCAUUCUGCAGUAUGCUCA
1253	3924	AGAGCAUCAUCAUCCACAC	3925	CCCAGAAGAGCAUCAUCAUCCACAA
1252	3926	AAGAGCAUCAUCAUCCACA	3927	ACCCAGAAGAGCAUCAUCAUCCACA
1247	3928	CCCAGAAGAGCAUCAUCAU	3929	GUGGCACCCAGAAGAGCAUCAUCAA
1246	3930	ACCCAGAAGAGCAUCAUCA	3931	CGUGGCACCCAGAAGAGCAUCAUCA
311	3932	UGAAGUCGAUCCUAGAUGG	3933	AGGUUAUGAAGUCGAUCCUAGAUGA
310	3934	AUGAAGUCGAUCCUAGAUG	3935	GAGGUUAUGAAGUCGAUCCUAGAUA
1249	3936	CAGAAGAGCAUCAUCAUCC	3937	GGCACCCAGAAGAGCAUCAUCAUCA
585	3938	UGAGGAGAACAUCCAGUGU	3939	GGAGAAUGAGGAGAACAUCCAGUGA
583	3940	AAUGAGGAGAACAUCCAGU	3941	AAGGAGAAUGAGGAGAACAUCCAGA
581	3942	AGAAUGAGGAGAACAUCCA	3943	UCAAGGAGAAUGAGGAGAACAUCCA
580	3944	GAGAAUGAGGAGAACAUCC	3945	UUCAAGGAGAAUGAGGAGAACAUCA
579	3946	GGAGAAUGAGGAGAACAUC	3947	CUUCAAGGAGAAUGAGGAGAACAUA
578	3948	AGGAGAAUGAGGAGAACAU	3949	CCUUCAAGGAGAAUGAGGAGAACAA
577	3950	AAGGAGAAUGAGGAGAACA	3951	UCCUUCAAGGAGAAUGAGGAGAACA
574	3952	UUCAAGGAGAAUGAGGAGA	3953	UCGUCCUUCAAGGAGAAUGAGGAGA
1257	3954	CAUCAUCAUCCACACGUCU	3955	GAAGAGCAUCAUCAUCCACACGUCA
1255	3956	AGCAUCAUCAUCCACACGU	3957	CAGAAGAGCAUCAUCAUCCACACGA
1682	3958	AGGUAACCAUGUCUGUGUC	3959	UUGCCAAGGUAACCAUGUCUGUGUA
1681	3960	AAGGUAACCAUGUCUGUGU	3961	AUUGCCAAGGUAACCAUGUCUGUGA

Ref Pos	SEQ ID NO	19-mer Sense Seq	SEQ ID NO	25-mer Sense Seq w/A @ 25
1680	3962	CAAGGUAACCAUGUCUGUG	3963	GAUUGCCAAGGUAACCAUGUCUGUA
1499	3964	AUGCUCUGAGGAGUAAGGA	3965	UCAUCUAUGCUCUGAGGAGUAAGGA
1498	3966	UAUGCUCUGAGGAGUAAGG	3967	AUCAUCUAUGCUCUGAGGAGUAAGA
1497	3968	CUAUGCUCUGAGGAGUAAG	3969	CAUCAUCUAUGCUCUGAGGAGUAAA
1496	3970	UCUAUGCUCUGAGGAGUAA	3971	CCAUCAUCUAUGCUCUGAGGAGUAA
1388	3972	UUGCAAUCAUGGUGUAUGA	3973	CUCUGCUUGCAAUCAUGGUGUAUGA
1387	3974	CUUGCAAUCAUGGUGUAUG	3975	CCUCUGCUUGCAAUCAUGGUGUAUA
1386	3976	GCUUGCAAUCAUGGUGUAU	3977	CCCUCUGCUUGCAAUCAUGGUGUAA
1385	3978	UGCUUGCAAUCAUGGUGUA	3979	GCCCUCUGCUUGCAAUCAUGGUGUA
1384	3980	CUGCUUGCAAUCAUGGUGU	3981	GGCCCUCUGCUUGCAAUCAUGGUGA
1383	3982	UCUGCUUGCAAUCAUGGUG	3983	GGGCCCUCUGCUUGCAAUCAUGGUA
1382	3984	CUCUGCUUGCAAUCAUGGU	3985	GGGGCCCUCUGCUUGCAAUCAUGGA
1314	3986	CCGCAUGGACAUUAGGUUA	3987	CCAAGCCCGCAUGGACAUUAGGUUA
1094	3988	CUGUUUGCUCAGACAUUUU	3989	UGCAAUCUGUUUGCUCAGACAUUUA
1093	3990	UCUGUUUGCUCAGACAUUU	3991	CUGCAAUCUGUUUGCUCAGACAUUA
1083	3992	GAAACUGCAAUCUGUUUGC	3993	CUGCGAGAAACUGCAAUCUGUUUGA
1082	3994	AGAAACUGCAAUCUGUUUG	3995	ACUGCGAGAAACUGCAAUCUGUUUA
1080	3996	CGAGAAACUGCAAUCUGUU	3997	GAACUGCGAGAAACUGCAAUCUGUA
323	3998	UAGAUGGCCUUGCAGAUAC	3999	CGAUCCUAGAUGGCCUUGCAGAUAA
322	4000	CUAGAUGGCCUUGCAGAUA	4001	UCGAUCCUAGAUGGCCUUGCAGAUA
1179	4002	CGUGUAUGCGUACAUGUAU	4003	GUUCAUCGUGUAUGCGUACAUGUAA
1178	4004	UCGUGUAUGCGUACAUGUA	4005	UGUUCAUCGUGUAUGCGUACAUGUA
1177	4006	AUCGUGUAUGCGUACAUGU	4007	CUGUUCAUCGUGUAUGCGUACAUGA
1320	4008	GGACAUUAGGUUAGCCAAG	4009	CCGCAUGGACAUUAGGUUAGCCAAA
1319	4010	UGGACAUUAGGUUAGCCAA	4011	CCCGCAUGGACAUUAGGUUAGCCAA
1318	4012	AUGGACAUUAGGUUAGCCA	4013	GCCCGCAUGGACAUUAGGUUAGCCA
1317	4014	CAUGGACAUUAGGUUAGCC	4015	AGCCCGCAUGGACAUUAGGUUAGCA
1316	4016	GCAUGGACAUUAGGUUAGC	4017	AAGCCCGCAUGGACAUUAGGUUAGA
1315	4018	CGCAUGGACAUUAGGUUAG	4019	CAAGCCCGCAUGGACAUUAGGUUAA
1415	4020	GGAAGAUGAACAAGCUCAU	4021	UCUUUGGGAAGAUGAACAAGCUCAA
552	4022	UUACAACAAGUCUCUCUCG	4023	AGAAUUUUACAACAAGUCUCUCUCA
551	4024	UUUACAACAAGUCUCUCUC	4025	CAGAAUUUUACAACAAGUCUCUCUA
550	4026	UUUUACAACAAGUCUCUCU	4027	ACAGAAUUUUACAACAAGUCUCUCA
476	4028	GUCCCUUCCAAGAGAAGAU	4029	GGGGAAGUCCCUUCCAAGAGAAGAA
474	4030	AAGUCCCUUCCAAGAGAAG	4031	UAGGGGAAGUCCCUUCCAAGAGAAA
473	4032	GAAGUCCCUUCCAAGAGAA	4033	UUAGGGGAAGUCCCUUCCAAGAGAA
1020	4034	UUGCCUGAUGUGGACCAUA	4035	GGCGUUUUGCCUGAUGUGGACCAUA

Ref Pos	SEQ ID NO	19-mer Sense Seq	SEQ ID NO	25-mer Sense Seq w/A @ 25
1019	4036	UUUGCCUGAUGUGGACCAU	4037	UGGCGUUUUGCCUGAUGUGGACCAA
1018	4038	UUUUGCCUGAUGUGGACCA	4039	GUGGCGUUUUGCCUGAUGUGGACCA
606	4040	GGAGAACUUCAUGGACAUA	4041	GUGUGGGGAGAACUUCAUGGACAUA
1568	4042	AGCCUCUGGAUAACAGCAU	4043	CUGCGCAGCCUCUGGAUAACAGCAA
1170	4044	UCUGUUCAUCGUGUAUGCG	4045	ACUGCUUCUGUUCAUCGUGUAUGCA
1169	4046	UUCUGUUCAUCGUGUAUGC	4047	UACUGCUUCUGUUCAUCGUGUAUGA
1168	4048	CUUCUGUUCAUCGUGUAUG	4049	GUACUGCUUCUGUUCAUCGUGUAUA
1421	4050	UGAACAAGCUCAUUAAGAC	4051	GGAAGAUGAACAAGCUCAUUAAGAA
1420	4052	AUGAACAAGCUCAUUAAGA	4053	GGGAAGAUGAACAAGCUCAUUAAGA
1419	4054	GAUGAACAAGCUCAUUAAG	4055	UGGGAAGAUGAACAAGCUCAUUAAA
1418	4056	AGAUGAACAAGCUCAUUAA	4057	UUGGGAAGAUGAACAAGCUCAUUAA
1417	4058	AAGAUGAACAAGCUCAUUA	4059	UUUGGGAAGAUGAACAAGCUCAUUA
1172	4060	UGUUCAUCGUGUAUGCGUA	4061	UGCUUCUGUUCAUCGUGUAUGCGUA
1078	4062	UGCGAGAAACUGCAAUCUG	4063	UGGAACUGCGAGAAACUGCAAUCUA
825	4064	CAGCUUCAUUGACUUCCAC	4065	UGUCUACAGCUUCAUUGACUUCCAA
824	4066	ACAGCUUCAUUGACUUCCA	4067	UUGUCUACAGCUUCAUUGACUUCCA
823	4068	UACAGCUUCAUUGACUUCC	4069	UUUGUCUACAGCUUCAUUGACUUCA
821	4070	UCUACAGCUUCAUUGACUU	4071	UUUUUGUCUACAGCUUCAUUGACUA
820	4072	GUCUACAGCUUCAUUGACU	4073	AUUUUUGUCUACAGCUUCAUUGACA
612	4074	CUUCAUGGACAUAGAGUGU	4075	GGAGAACUUCAUGGACAUAGAGUGA
611	4076	ACUUCAUGGACAUAGAGUG	4077	GGGAGAACUUCAUGGACAUAGAGUA
610	4078	AACUUCAUGGACAUAGAGU	4079	GGGGAGAACUUCAUGGACAUAGAGA
549	4080	AUUUUACAACAAGUCUCUC	4081	UACAGAAUUUUACAACAAGUCUCUA
547	4082	GAAUUUUACAACAAGUCUC	4083	AUUACAGAAUUUUACAACAAGUCUA
1176	4084	CAUCGUGUAUGCGUACAUG	4085	UCUGUUCAUCGUGUAUGCGUACAUA
1175	4086	UCAUCGUGUAUGCGUACAU	4087	UUCUGUUCAUCGUGUAUGCGUACAA
1174	4088	UUCAUCGUGUAUGCGUACA	4089	CUUCUGUUCAUCGUGUAUGCGUACA
1173	4090	GUUCAUCGUGUAUGCGUAC	4091	GCUUCUGUUCAUCGUGUAUGCGUAA
1171	4092	CUGUUCAUCGUGUAUGCGU	4093	CUGCUUCUGUUCAUCGUGUAUGCGA
609	4094	GAACUUCAUGGACAUAGAG	4095	UGGGGAGAACUUCAUGGACAUAGAA
608	4096	AGAACUUCAUGGACAUAGA	4097	GUGGGGAGAACUUCAUGGACAUAGA
607	4098	GAGAACUUCAUGGACAUAG	4099	UGUGGGGAGAACUUCAUGGACAUAA
1322	4100	ACAUUAGGUUAGCCAAGAC	4101	GCAUGGACAUUAGGUUAGCCAAGAA
1321	4102	GACAUUAGGUUAGCCAAGA	4103	CGCAUGGACAUUAGGUUAGCCAAGA
1027	4104	AUGUGGACCAUAGCCAUUG	4105	UGCCUGAUGUGGACCAUAGCCAUUA
545	4106	CAGAAUUUUACAACAAGUC	4107	ACAUUACAGAAUUUUACAACAAGUA
532	4108	CAGGUGAACAUUACAGAAU	4109	GCAGACCAGGUGAACAUUACAGAAA
813	4110	CAUUUUUGUCUACAGCUUC	4111	GAGUGUCAUUUUUGUCUACAGCUUA

Ref Pos	SEQ ID NO	19-mer Sense Seq	SEQ ID NO	25-mer Sense Seq w/A @ 25
812	4112	UCAUUUUUGUCUACAGCU U	4113	GGAGUGUCAUUUUUGUCUACAGCU A
811	4114	GUCAUUUUUGUCUACAGC U	4115	GGGAGUGUCAUUUUUGUCUACAGC A
809	4116	GUGUCAUUUUUGUCUACA G	4117	UGGGGAGUGUCAUUUUUGUCUACA A
808	4118	AGUGUCAUUUUUGUCUAC A	4119	CUGGGGAGUGUCAUUUUUGUCUAC A
569	4120	CGUCCUUCAAGGAGAAUGA	4121	CUCUCUCGUCCUUCAAGGAGAAUGA
568	4122	UCGUCCUUCAAGGAGAAUG	4123	UCUCUCUCGUCCUUCAAGGAGAAUA
1444	4124	UUUGCAUUCUGCAGUAUG C	4125	ACGGUGUUUGCAUUCUGCAGUAUG A
1443	4126	GUUUGCAUUCUGCAGUAU G	4127	GACGGUGUUUGCAUUCUGCAGUAU A
1446	4128	UGCAUUCUGCAGUAUGCUC	4129	GGUGUUUGCAUUCUGCAGUAUGCU A
1445	4130	UUGCAUUCUGCAGUAUGC U	4131	CGGUGUUUGCAUUCUGCAGUAUGC A
1442	4132	UGUUUGCAUUCUGCAGUA U	4133	AGACGGUGUUUGCAUUCUGCAGUA A
1677	4134	UGCCAAGGUAACCAUGUCU	4135	CAAGAUUGCCAAGGUAACCAUGUCA
1676	4136	UUGCCAAGGUAACCAUGUC	4137	UCAAGAUUGCCAAGGUAACCAUGUA
1675	4138	AUUGCCAAGGUAACCAUGU	4139	GUCAAGAUUGCCAAGGUAACCAUGA
1603	4140	CUGCACAAACACGCAAACA	4141	GACUGCCUGCACAAACACGCAAACA
1110	4142	UUUCCCACACAUUGAUGAA	4143	AGACAUUUUCCCACACAUUGAUGAA
1109	4144	UUUUCCCACACAUUGAUGA	4145	CAGACAUUUUCCCACACAUUGAUGA
1108	4146	AUUUUCCCACACAUUGAUG	4147	UCAGACAUUUUCCCACACAUUGAUA
1605	4148	GCACAAACACGCAAACAAU	4149	CUGCCUGCACAAACACGCAAACAAA
1604	4150	UGCACAAACACGCAAACAA	4151	ACUGCCUGCACAAACACGCAAACAA
1671	4152	CAAGAUUGCCAAGGUAACC	4153	CACGGUCAAGAUUGCCAAGGUAACA
1670	4154	UCAAGAUUGCCAAGGUAAC	4155	GCACGGUCAAGAUUGCCAAGGUAAA
1669	4156	GUCAAGAUUGCCAAGGUAA	4157	AGCACGGUCAAGAUUGCCAAGGUAA
628	4158	UGUUUCAUGGUCCUGAACC	4159	AUAGAGUGUUUCAUGGUCCUGAACA
1115	4160	CACACAUUGAUGAAACCUA	4161	UUUUCCCACACAUUGAUGAAACCUA
1114	4162	CCACACAUUGAUGAAACCU	4163	AUUUUCCCACACAUUGAUGAAACCA
1113	4164	CCCACACAUUGAUGAAACC	4165	CAUUUUCCCACACAUUGAUGAAACA
1112	4166	UCCCACACAUUGAUGAAAC	4167	ACAUUUUCCCACACAUUGAUGAAAA
1111	4168	UUCCCACACAUUGAUGAAA	4169	GACAUUUUCCCACACAUUGAUGAAA
814	4170	AUUUUUGUCUACAGCUUCA	4171	AGUGUCAUUUUUGUCUACAGCUUC A
1659	4172	CAAGAGCACGGUCAAGAUU	4173	CUGCAUCAAGAGCACGGUCAAGAUA
1657	4174	AUCAAGAGCACGGUCAAGA	4175	AGCUGCAUCAAGAGCACGGUCAAGA
1167	4176	GCUUCUGUUCAUCGUGUA U	4177	CGUACUGCUUCUGUUCAUCGUGUAA
1166	4178	UGCUUCUGUUCAUCGUGU A	4179	GCGUACUGCUUCUGUUCAUCGUGU A
1668	4180	GGUCAAGAUUGCCAAGGUA	4181	GAGCACGGUCAAGAUUGCCAAGGUA
819	4182	UGUCUACAGCUUCAUUGAC	4183	CAUUUUUGUCUACAGCUUCAUUGAA
818	4184	UUGUCUACAGCUUCAUUGA	4185	UCAUUUUUGUCUACAGCUUCAUUG A
817	4186	UUUGUCUACAGCUUCAUU G	4187	GUCAUUUUUGUCUACAGCUUCAUU A

Ref Pos	SEQ ID NO	19-mer Sense Seq	SEQ ID NO	25-mer Sense Seq w/A @ 25
816	4188	UUUUGUCUACAGCUUCAU U	4189	UGUCAUUUUUGUCUACAGCUUCAU A
1543	4190	UUUCCCUCUUGUGAAGGCA	4191	AGCAUGUUUCCCUCUUGUGAAGGCA
1660	4192	AAGAGCACGGUCAAGAUUG	4193	UGCAUCAAGAGCACGGUCAAGAUUA
1030	4194	UGGACCAUAGCCAUUGUGA	4195	CUGAUGUGGACCAUAGCCAUUGUGA
531	4196	CCAGGUGAACAUUACAGAA	4197	AGCAGACCAGGUGAACAUUACAGAA
1259	4198	UCAUCAUCCACACGUCUGA	4199	AGAGCAUCAUCAUCCACACGUCUGA
1258	4200	AUCAUCAUCCACACGUCUG	4201	AAGAGCAUCAUCAUCCACACGUCUA

Chemical Modification Key	
Chl	cholesterol with hydroxyprolinol linker
TEG-Chl	cholesterol with TEG linker
m	2'Ome
f	2'fluoro
*	phosphorothioate linkage
.	phosphodiester linkage

Table 24: Summary of CTGF Leads

Generic Name	TEG ID	2'F	Targeting site	Opt. lead sequence	Optimized lead sequence	Opt. lead 2'F	Opt. lead 2'OH	Priority
CTGF L1	21045	4	2295	21212	mU.mU. G.mC. A.mC.mC.mU.mU.mU.mC.mU*mA*mA-chol P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. mA. mA* mA*fC* mA*mA* mG* G	4	7(2)	1
				21214	mU.mU. G.mC. A.mC.mC.mU.mU.mU.mC.mU*mA*mA-chol P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. A. A* A*fC* A*mA*mG* G	4	12(2)	3
				21215	mU.mU. G.mC. A.mC.mC.mU.mU.mU.mC.mU*mA*mA-chol P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. mA. A* mA*fC* A*mA*mG* G	4	10(2)	2
CTGFL2	20393	5	2296	21204	G.mC. A.mC.mC.mU.mU.mU.mC.mU. A*mG*mA-TEG-Chl P.mU.fC.fU.A.G.mA.A.mA.G.G.fU.G.mC*A*A*A*mC*A*U	3	11(3)	1
				21205	G.mC. A.mC.mC.mU.mU.mU.mC.mU. A*mG*mA-TEG-Chl P.mU.fC.fU.A.G.mA.A.mA.G.G.fU.G.mC*A*mA*A*mC*A*U	3	10(3)	3
				21227	G.mC. A.mC.mC.mU.mU.mU.mC.mU. A*mG*mA-TEG-Chl P.mU.fC.fU.A.G.mA.A.mA.G.G.fU.G.fC*mA*mA*mA*fC*mA*U	5	7(3)	2
CTGF L3	20392	13	2275	21381	G.mU. G. A.mC.mC. A. A. A. A. G*mU*mA-TEG-Chl P.mU.A.fC.fU.fU.fU.fU.fU.G.G.fU.mC.A.mC*A*mC*mU*mC*mU*C.	6	6(9)	1
				21383	mG*mU*mG.mA.mC.mC.mA.mA.mA.mA.mG*mU*mA-TEG-Chl P.mU.A.fC.fU.fU.fU.fU.fU.G.G.fU.mC.A.mC*A*mC*mU*mC*mU*C.	6	6(6)	2
CTGF L4	17382	5	2299	21224	mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU* mG*mA-TEG-Chl P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU*mG*fC*mA*mA* A	5	9(2)	1

Table 24: Lead 21212 corresponds to SEQ ID NOs 3445 and 3446; lead 21214 corresponds to SEQ ID NOs 3449 and 3450 (an unmodified form of SEQ ID NO:3450 corresponds to SEQ ID NO:4205:UCAACUAGAAAGGUGCAAA); lead 21215 corresponds to SEQ ID NOs 3451 and 3452 (an unmodified form of SEQ ID NO:3452 corresponds to SEQ ID NO:4204:UUAGAAAGGUGCAAACAAGG); lead 21204 corresponds to SEQ ID NOs 3429 and 3430; lead 21205 corresponds to SEQ ID NOs 3431 and 3432; lead 21227 corresponds to SEQ ID NOs 3475 and 3476; lead 21381

corresponds to SEQ ID NOs 3493 and 3494; lead 21383 corresponds to SEQ ID NOs 3497 and 3498; and lead 21224 corresponds to SEQ ID NOs 3469 and 3470.

Table 25: Summary of PTGS2 Leads

Generic Name	TEG ID	2'F	Targeting site	Optimized lead sequence	Optimized lead sequence	Opt. lead 2'F	Opt. lead 2'OMe	Priority
PTGS2 L1	20394	8	448	21228	G. A.mU.mC. A.mC. A.mU.mU.mU. G*mA*mA-TEG-Chl P.mU.fU.fC.A.mA.A.fU.G.fU.G.A.fU.fC*fU*mG*mG*mA*fU* G	8	6(5)	1
				21229	G. A.mU.mC. A.mC. A.mU.mU.mU. G*mA*mA-TEG-Chl P.mU.fU.fC.A.A.A.fU.G.fU.G.A.mU.mC*mU*G*G*A*mU*G	4	10(5)	3
				21230	G. A.mU.mC. A.mC. A.mU.mU.mU. G*mA*mA-TEG-Chl P.mU.fU.fC.A.A.A.fU.G.fU.G.A.fU.fC*fU*mG*mG*mA*fU* G	8	7(5)	2
PTGS2 L2	20395	8	449	21293	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A*mU*mA-TEG-Chl P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.mU.mC*mU*mG*mG*mA*fU* G	5	8(6)	4
				21394	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A*mU*mA-TEG-Chl P.mU. A.fU.fC. A. A. A.fU. G.fU. G. A.mU.fC*mU* G* G* A*fU* G	6	11(6)	3
				21233	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A*mU*mA-TEG-Chl P.mU.A.fU.fC.A.A.A.fU.G.fU.G.A.fU.fC*fU*G*G*A*fU*G	8	11(6)	1
				21234	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A*mU*mA-TEG-Chl P.mU.A.fU.fC.A.A.A.fU.G.fU.G.A.fU.fC*fU*mG*mG*mA*fU*G	7	8(6)	2

Table 25: Lead 21228 corresponds to SEQ ID NOs 4309 and 4310; lead 21229 corresponds to SEQ ID NOs 4311 and 4312; lead 21230 corresponds to SEQ ID NOs 4313 and 4314; lead 21293 corresponds to SEQ ID NOs 4315 and 4316; lead 21394 corresponds to SEQ ID NOs 4317 and 4318; lead 21233 corresponds to SEQ ID NOs 4319 and 4320; and lead 21234 corresponds to SEQ ID NOs 4321 and 4322.

Table 26: Summary of hTGFB1 Leads

Generic Name	Targeting site	Optimized lead sequence	Optimized lead sequence	Opt. lead 2'F	Opt. lead 2'OH	Priority
TGFb1 hL3	1244	21374	mC*mA*mC.mA.mC.mA.mG.mC.mA.mU.mA*mU*mA-TEG-Chl P.mU.A.fU.A.fU.G.fC.fU.G.fU.G.fU.mG*fU*mA*fC*mU*fC*U	9	6(0)	1

Table 26: lead 21374 corresponds to SEQ ID NOs 3793 and 3794.

Table 27: Summary of hTGFB2 Leads

Generic Name	Targeting site	Optimized lead sequence	Optimized lead sequence	Opt. lead 2'F	Opt. lead 2'OH	Priority
TGFB2 hL3	2081	21379	mU*mC*mA.mU.mC.mA.mG.mU.mG.mU.mU*mA*mA-TEG-Chl P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC*mA*mA* G	7	9(0)	1
			mU*mC*mA.mU.mC.mA.mG.mU.mG.mU.mU*mA*mA-TEG-Chl P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G.mA*mA*fC*fC*mA*mA* G	7	7(0)	2

Table 27: lead 21379 corresponds to SEQ ID NOs 3637, 3638, 3639 and 3640.

Having thus described several aspects of at least one embodiment of this invention, it is to be appreciated various alterations, modifications, and improvements will readily occur to those skilled in the art. Such alterations, modifications, and improvements are intended to be part of this disclosure, and are intended to be within the spirit and scope of the invention. Accordingly, the foregoing description and drawings are by way of example only.

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. This application incorporates by reference the entire contents, including all the drawings and all parts of the specification (including sequence listing or amino acid / polynucleotide sequences) of PCT Publication No. WO2010/033247 (Application No. PCT/US2009/005247), filed on September 22, 2009, and entitled "REDUCED SIZE SELF-DELIVERING RNAI COMPOUNDS" and PCT Publication No. WO2009/102427 (Application No. PCT/US2009/000852), filed on February 11, 2009, and entitled, "MODIFIED RNAI POLYNUCLEOTIDES AND USES THEREOF."

What is claimed is:

CLAIMS

1. A double-stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 2, 5, 6, 9, 11, 12, 13, 14, 15, 16, 17 and 23, and wherein the dsRNA is an sd-rxRNA.

2. A double-stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 1-27, and wherein the dsRNA is an sd-rxRNA.

3. A double-stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 2, 5, 6, 9, 11, 12, 13, 14, 15, 16, 17 and 23, and wherein the dsRNA is an rxRNAori.

4. A double-stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 1-27, and wherein the dsRNA is an rxRNAori.

5. The dsRNA of any one of claims 1-4, wherein the dsRNA is directed against CTGF.

6. The dsRNA of claim 5, wherein the antisense strand of the dsRNA is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 11, 12 and 15.

7. The dsRNA of claim 5, wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 10, 11, 12, 15, 20 and 24.

8. The dsRNA of any one of claims 5-7, wherein the sense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: SEQ ID NOs: 2463, 3429, 2443, 3445, 2459, 3493, 2465 and 3469.

9. The dsRNA of any one of claims 5-8, wherein the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: 2464, 3430, 4203, 3446, 2460, 3494, 2466 and 3470.

10. The dsRNA of any one of claims 5-9, wherein the sense strand comprises SEQ ID NO:2463 and the antisense strand comprises SEQ ID NO:2464.

11. The dsRNA of claim 10, wherein the sense strand comprises SEQ ID NO:3429 and the antisense strand comprises SEQ ID NO:3430.

12. The dsRNA of any one of claims 5-9, wherein the sense strand comprises SEQ ID NO:2443 and the antisense strand comprises SEQ ID NO:4203.

13. The dsRNA of claim 12, wherein the sense strand comprises SEQ ID NO:3445 and the antisense strand comprises SEQ ID NO:3446.

14. The dsRNA of any one of claims 5-9, wherein the sense strand comprises SEQ ID NO:2459 and the antisense strand comprises SEQ ID NO:2460.

15. The dsRNA of claim 14, wherein the sense strand comprises SEQ ID NO:3493 and the antisense strand comprises SEQ ID NO:3494.

16. The dsRNA of any one of claims 5-9, wherein the sense strand comprises SEQ ID NO:2465 and the antisense strand comprises SEQ ID NO:2466.

17. The dsRNA of claim 16, wherein the sense strand comprises SEQ ID NO:3469 and the antisense strand comprises SEQ ID NO:3470.

18. The dsRNA of claim 7, wherein the sense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: SEQ ID NOs: 1835, 1847, 1848 and 1849.

19. The dsRNA of claim 18, wherein the sense strand comprises a sequence selected from the group consisting of: SEQ ID NOs: 1835, 1847, 1848 and 1849.

20. The dsRNA of any one of claims 1-19, wherein the dsRNA is hydrophobically modified.

21. The dsRNA of claim 20, wherein the dsRNA is linked to a hydrophobic conjugate.

22. A composition comprising the dsRNA of any one of claims 1-21.

23. The composition of claim 22, wherein the composition comprises dsRNA directed against genes encoding for more than one protein.

24. The composition of claim 22 or 23 wherein the composition is formulated for delivery to the skin.

25. The composition of claim 24, wherein the composition is in a neutral formulation.

26. The composition of claim 24 or 25, wherein the composition is formulated for topical delivery.

27. The composition of claim 24 or 25, wherein the composition is formulated for intradermal injection.

28. A method comprising delivering the dsRNA of any one of claims 1-21 or the composition of any one of claims 22-27 to the skin of a subject in need thereof.

29. A method comprising,

administering to a subject in need thereof a therapeutically effective amount of a double stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 2, 5, 6, 9, 11, 12, 13, 14, 15, 16, 17 and 23, and wherein the dsRNA is an sd-rxRNA.

30. A method comprising,

administering to a subject in need thereof a therapeutically effective amount of a double stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 1-27, and wherein the dsRNA is an sd-rxRNA.

31. A method comprising,

administering to a subject in need thereof a therapeutically effective amount of a double stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 2, 5, 6, 9, 11, 12, 13, 14, 15, 16, 17 and 23, and wherein the dsRNA is an rxRNAori.

32. A method comprising,

administering to a subject in need thereof a therapeutically effective amount of a double stranded ribonucleic acid (dsRNA) comprising a sense strand and an antisense strand wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 1-27, and wherein the dsRNA is an rxRNAori.

33. The method of any one of claims 29-32, wherein the method is a method for treating compromised skin.

34. The method of any one of claims 29-32, wherein the method is a method for treating or preventing a fibrotic disorder.

35. The method of any one of claims 29-34, wherein the dsRNA is administered via intradermal injection.

36. The method of any one of claims 29-34, wherein the dsRNA is administered locally to the skin.

37. The method of any one of claims 29-36, wherein two or more nucleic acid molecules are administered simultaneously or sequentially.

38. The method of claim 37, wherein one or more of the dsRNAs is hydrophobically modified.

39. The method of claim 38, wherein one or more of the dsRNAs is linked to a hydrophobic conjugate.

40. The method of any one of claims 29-39, wherein the dsRNA is directed against CTGF.

41. The method of claim 40, wherein the antisense strand of the dsRNA is complementary to at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 11, 12 and 15.

42. The method of claim 40, wherein the sense strand and/or the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the sequences within Tables 10, 11, 12, 15, 20 and 24.

43. The method of any one of claims 40-42, wherein the sense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: SEQ ID NOs: 2463, 3429, 2443, 3445, 2459, 3493, 2465 and 3469.

44. The method of any one of claims 40-43, wherein the antisense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: 2464, 3430, 4203, 3446, 2460, 3494, 2466 and 3470.

45. The method of any one of claims 40-44, wherein the sense strand comprises SEQ ID NO:2463 and the antisense strand comprises SEQ ID NO:2464.

46. The method of claim 45, wherein the sense strand comprises SEQ ID NO:3429 and the antisense strand comprises SEQ ID NO:3430.

47. The method of any one of claims 40-44, wherein the sense strand comprises SEQ ID NO:2443 and the antisense strand comprises SEQ ID NO:4203.

48. The dsRNA of claim 47, wherein the sense strand comprises SEQ ID NO:3445 and the antisense strand comprises SEQ ID NO:3446.

49. The method of any one of claims 40-44, wherein the sense strand comprises SEQ ID NO:2459 and the antisense strand comprises SEQ ID NO:2460.

50. The method of claim 49, wherein the sense strand comprises SEQ ID NO:3493 and the antisense strand comprises SEQ ID NO:3494.

51. The method of any one of claims 40-44, wherein the sense strand comprises SEQ ID NO:2465 and the antisense strand comprises SEQ ID NO:2466.

52. The method of claim 51, wherein the sense strand comprises SEQ ID NO:3469 and the antisense strand comprises SEQ ID NO:3470.

53. The method of claim 40, wherein the sense strand comprises at least 12 contiguous nucleotides of a sequence selected from the group consisting of: SEQ ID NOs: 1835, 1847, 1848 and 1849.

54. The method of claim 53, wherein the sense strand comprises a sequence selected from the group consisting of: SEQ ID NOs: 1835, 1847, 1848 and 1849.

55. The method of claim 34, wherein the fibrotic disorder is selected from the group consisting of pulmonary fibrosis, liver cirrhosis, scleroderma and glomerulonephritis, lung fibrosis, liver fibrosis, skin fibrosis, muscle fibrosis, radiation fibrosis, kidney fibrosis, proliferative vitreoretinopathy, restenosis and uterine fibrosis, and trabeculectomy failure due to scarring.

Figure 1

Proposed Target Genes Expression Profile

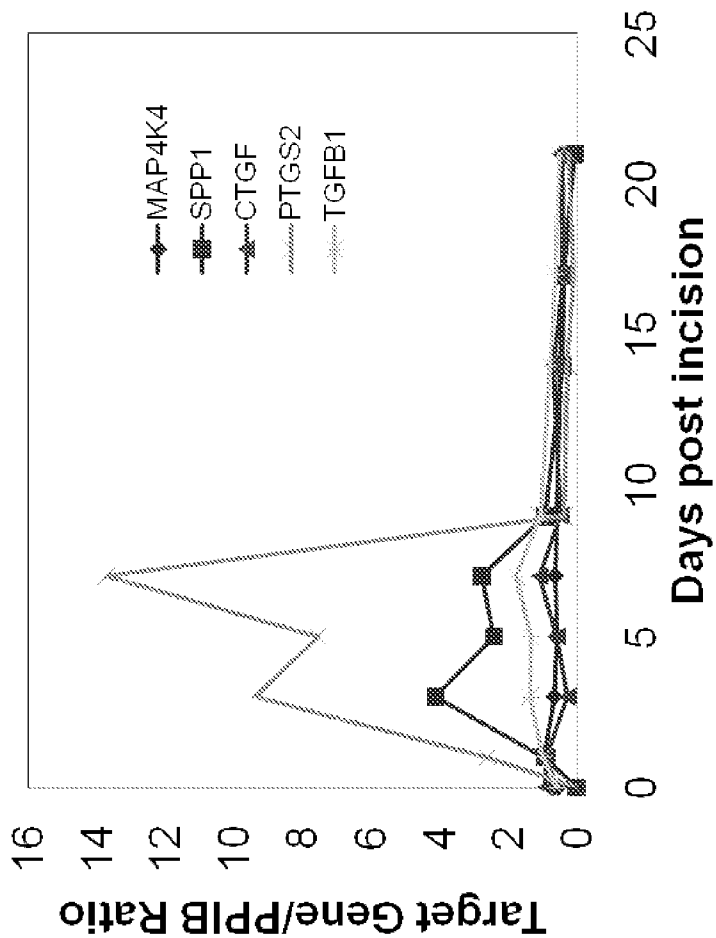
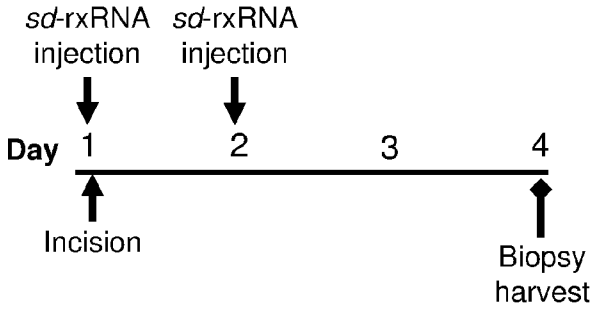


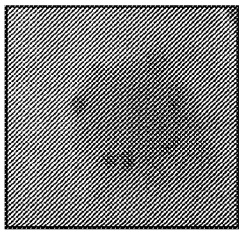
Figure 2

Local Delivery of sd-rxRNA: Visualization after Intradermal Injection

Study Design

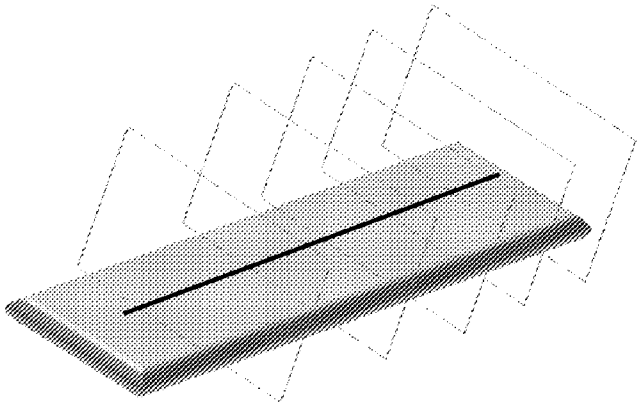


Single Injection Site



- 6 intradermal injections in each site
- ~34 ul/injection, 300 ug total
- Image taken before incision, 15 minutes after first injection

Biopsy Processing for Imaging



Incision Cross Section with Sirius Red Stain

(connective tissue in red)

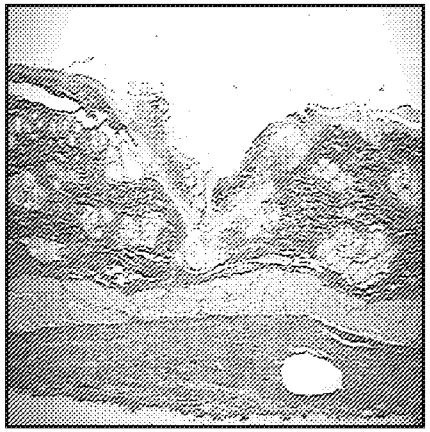
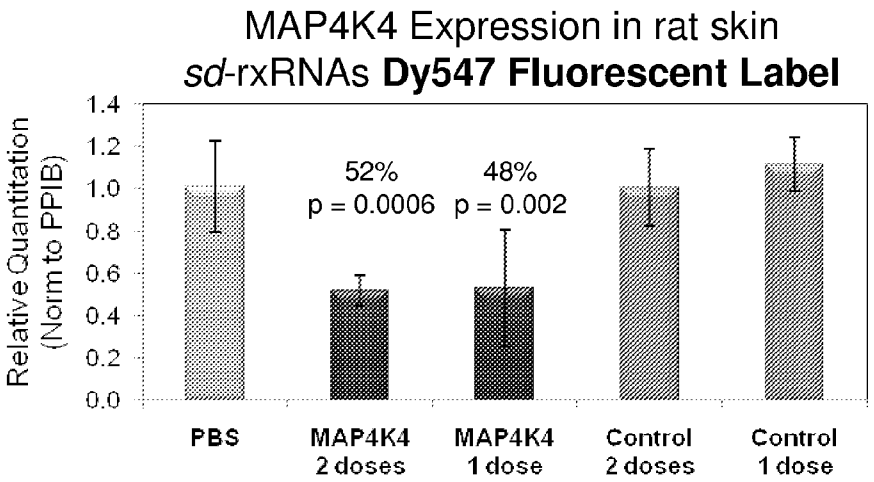
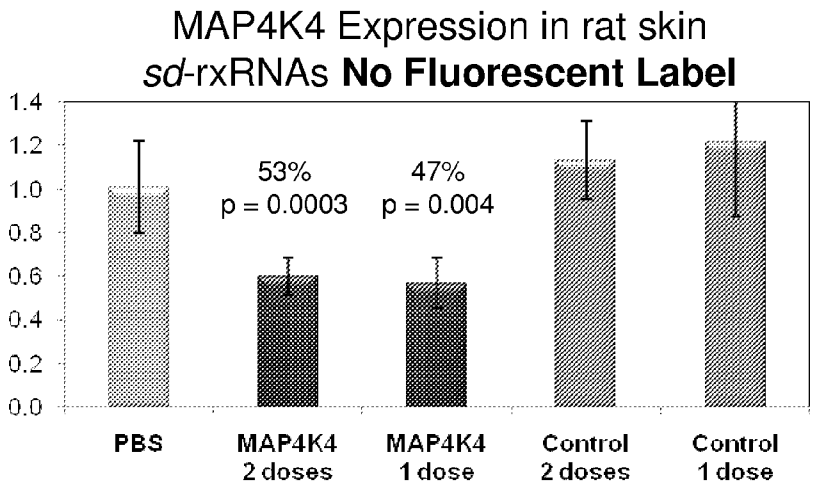


Figure 3

In vivo Silencing with *sd*-rxRNA Following Intradermal Injection (Rat)





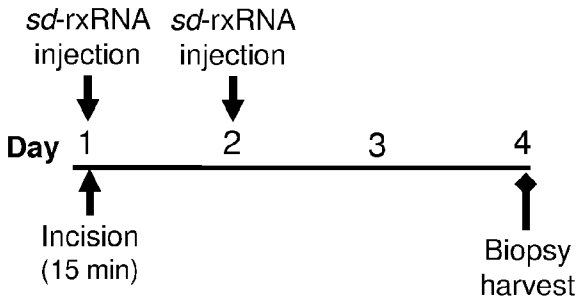


Figure 4

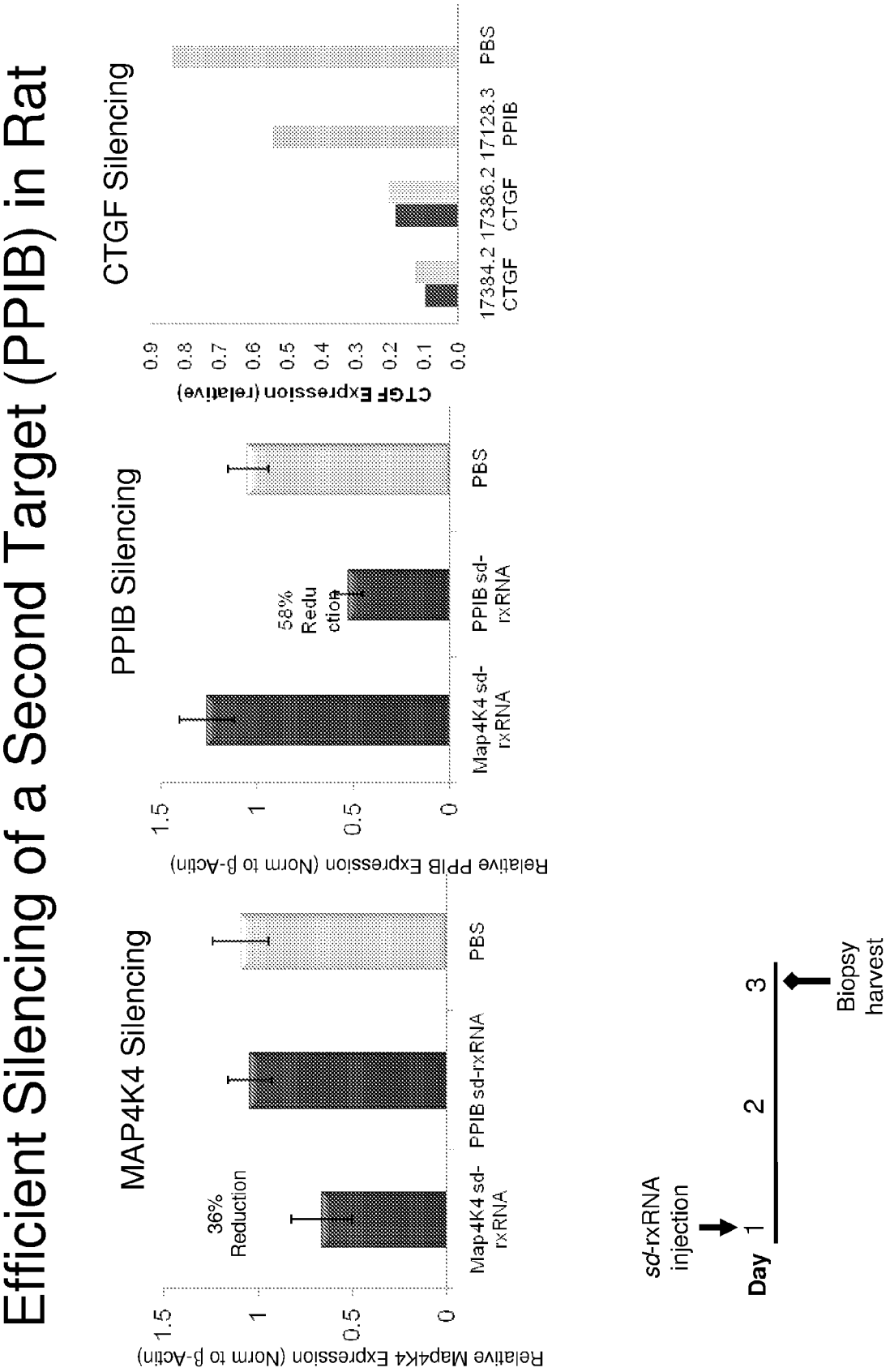
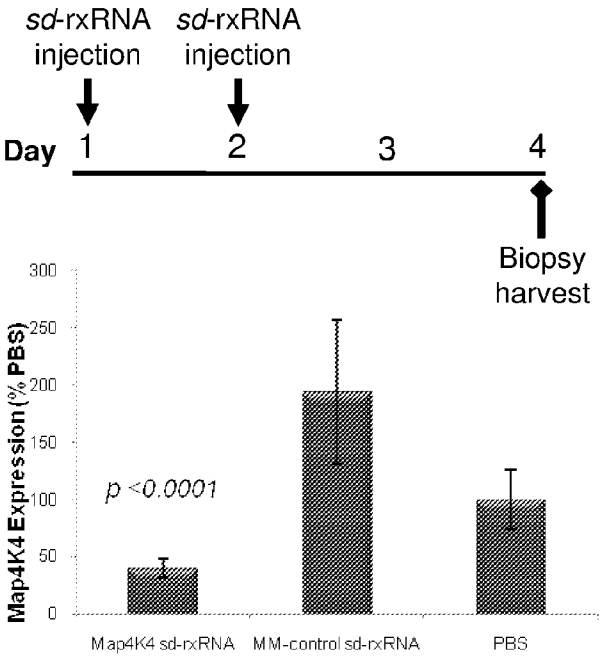

Efficient Silencing of a Second Target (PPIB) in Rat
MAP4K4 Silencing
Relative Map4K4 Expression (Norm to β-Actin)
1.5
1
0.5
0
36% Reduction
Map4K4 sd-rxRNA
PPIB sd-rxRNA
PBS
PPIB Silencing
Relative PPIB Expression (Norm to β-Actin)
58% Reduction
Map4K4 sd-rxRNA
PPIB sd-rxRNA
PBS
CTGF Silencing
CTGF Expression (relative)
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
17384.2 CTGF
17386.2 CTGF
17128.3 PPIB
PBS
sd-rxRNA injection
Day 1
2
3
Biopsy harvest

Figure 5

In vivo Silencing in Mouse with *sd*-rxRNA Following Intradermal Injection



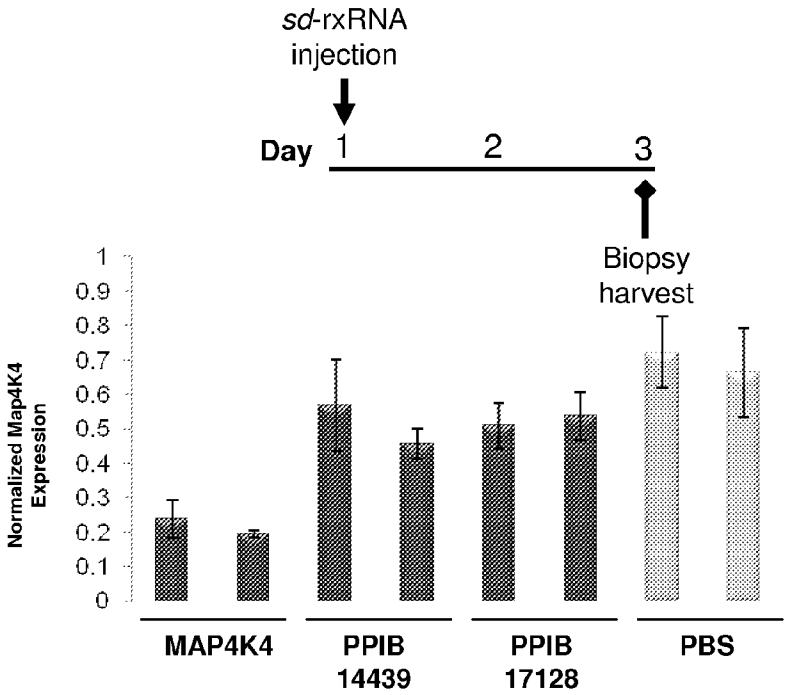


Figure 6

Silencing of PPIB and MAP4K4 in Mouse Skin by Intradermal Injection

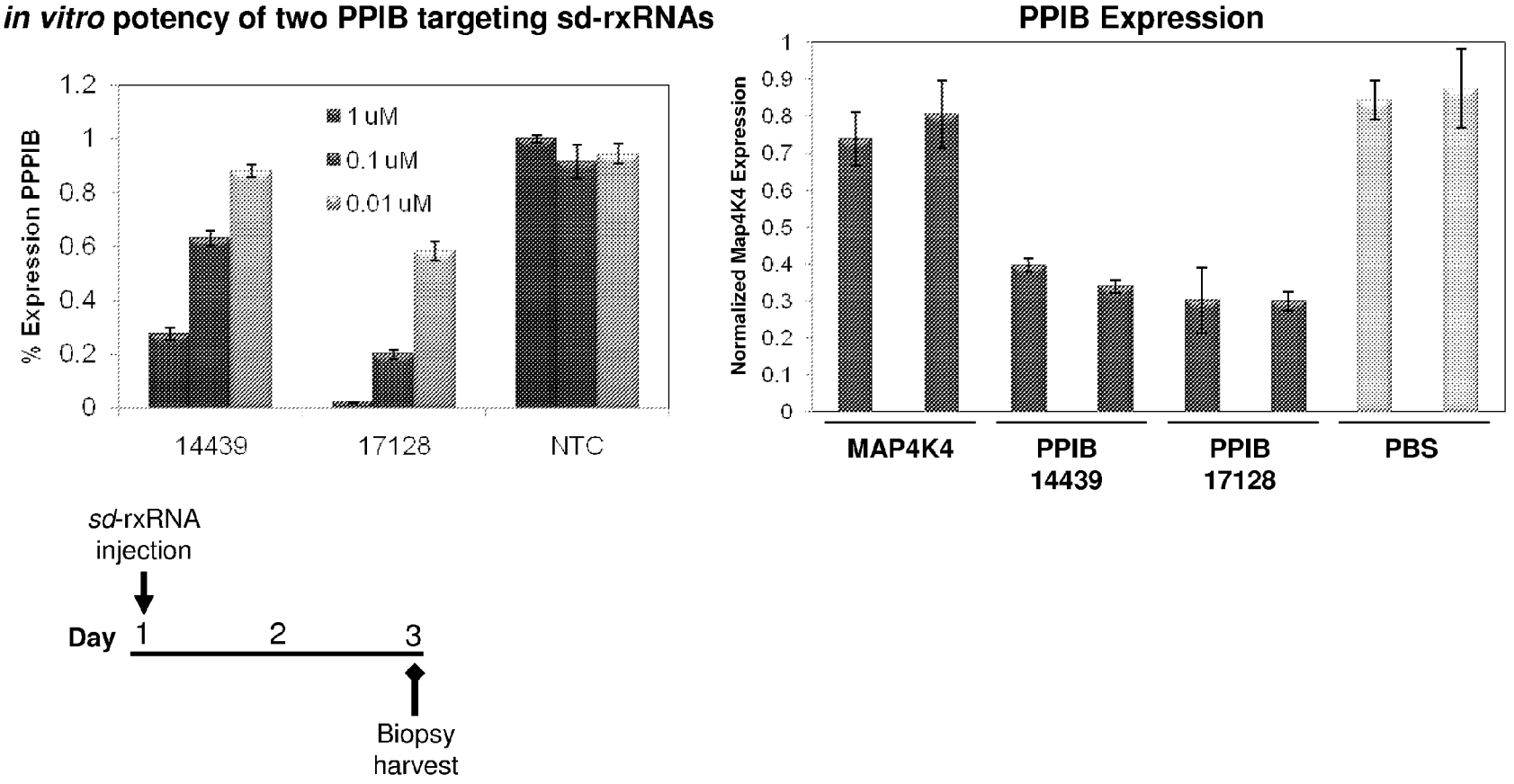


Figure 7

Duration of PPIB Silencing *in vivo*

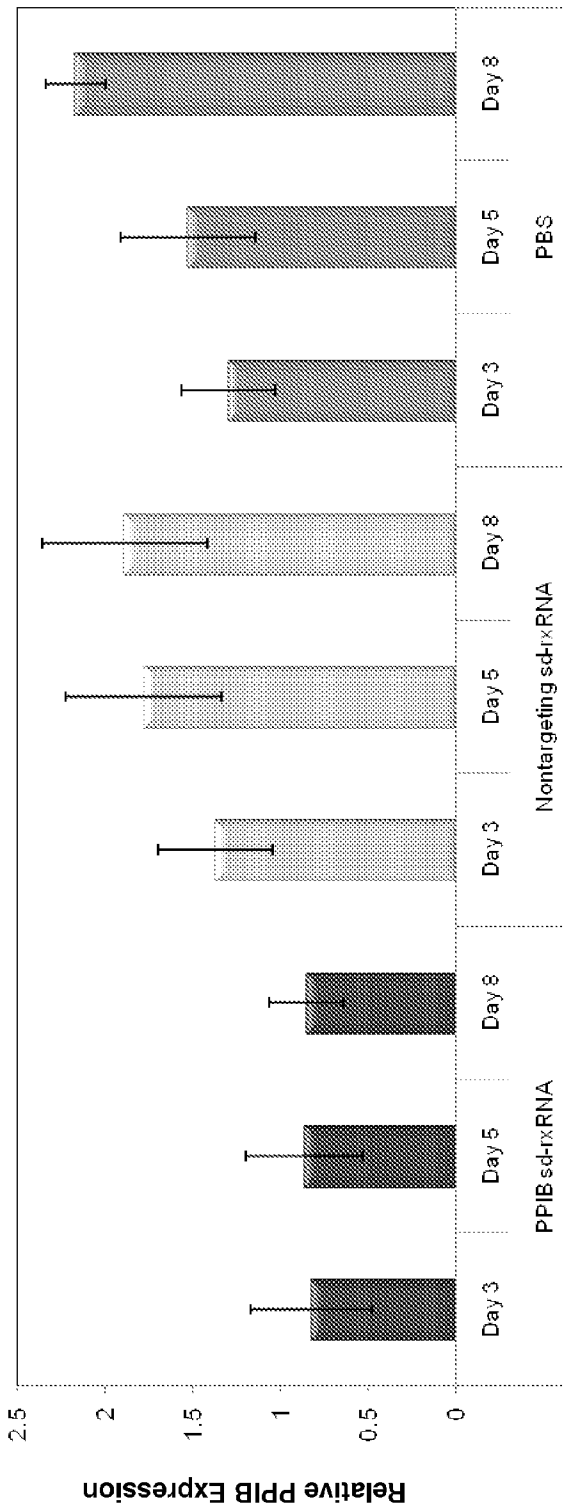


Figure 8

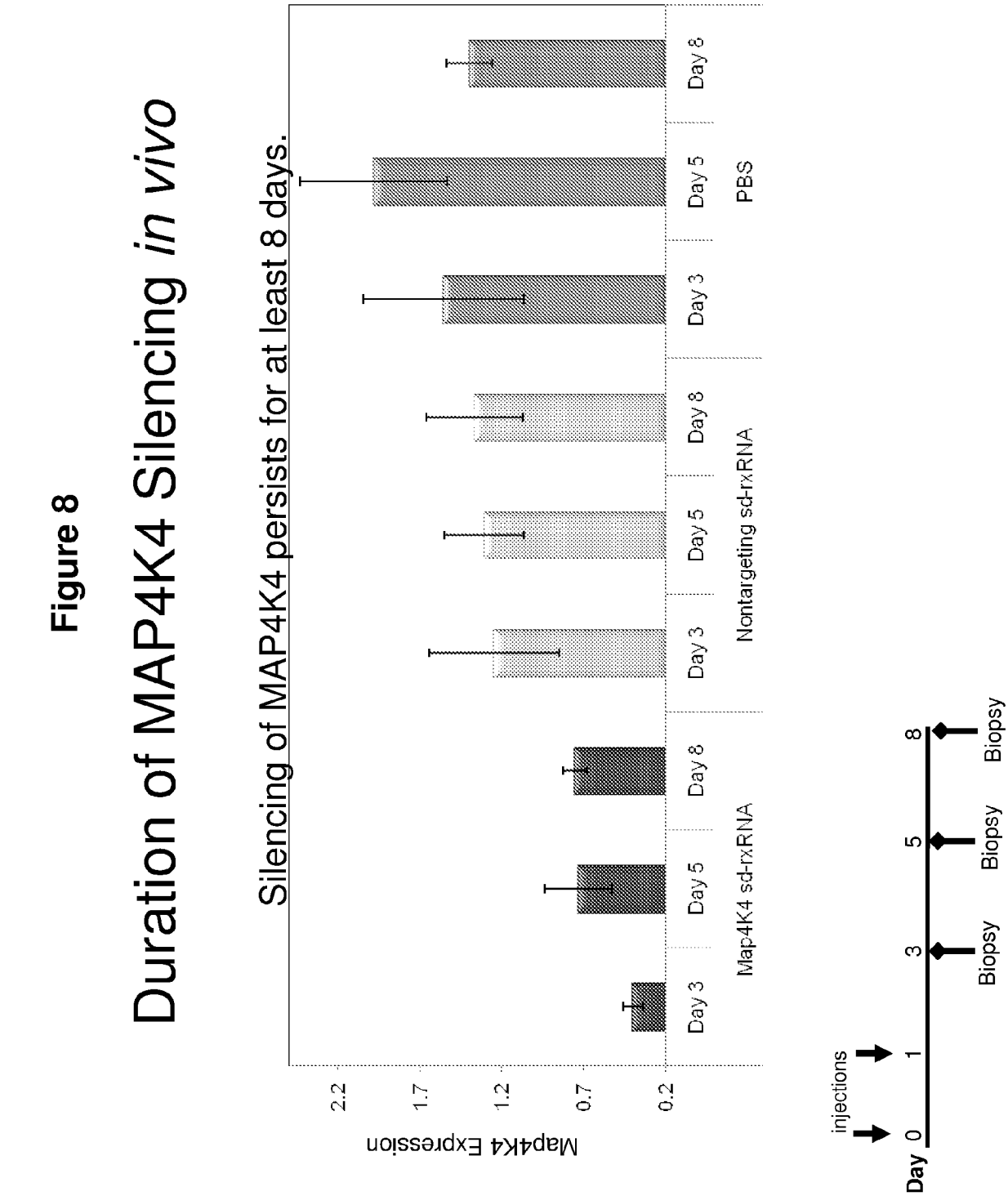
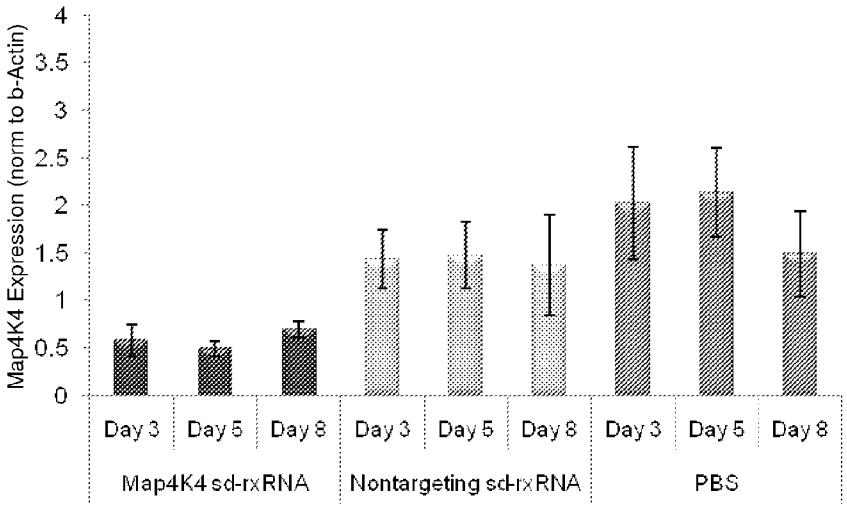
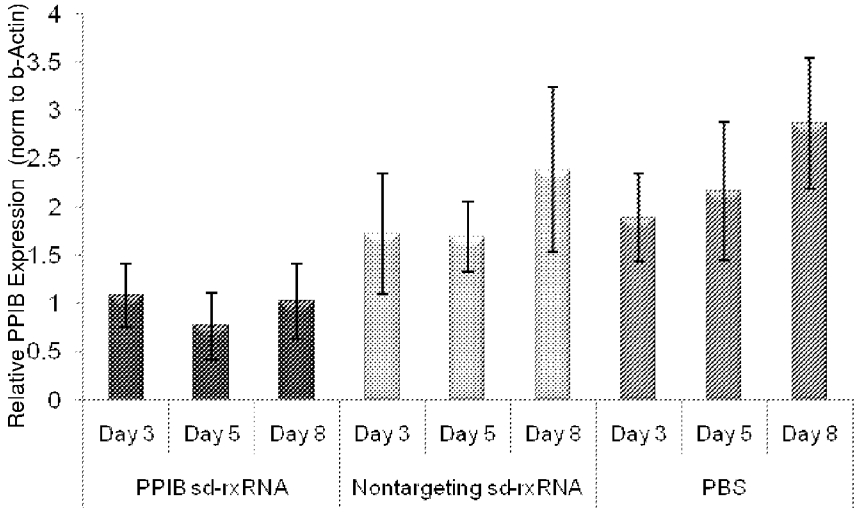

Duration of MAP4K4 Silencing *in vivo*
Silencing of MAP4K4 persists for at least 8 days.
Map4k4 Expression
2.2
1.7
1.2
0.7
0.2
Day 3
Day 5
Day 8
Map4K4 sd-rxRNA
Day 3
Day 5
Day 8
Nontargeting sd-rxRNA
Day 3
Day 5
Day 8
PBS
injections
Day 0
1
3
5
8
Biopsy
Biopsy
Biopsy

Figure 9

Equivalent Silencing using a Different Dose Regimen (Days 1 and 3 *vs* Days 0 and 2)





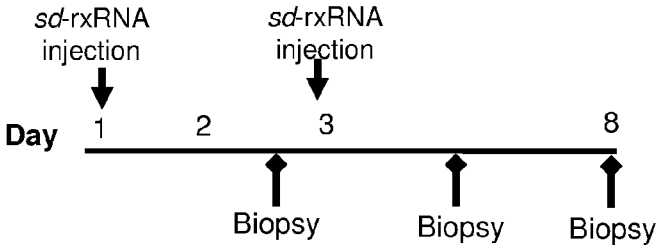


Figure 10

CTGF sd-rxRNA are Efficacious

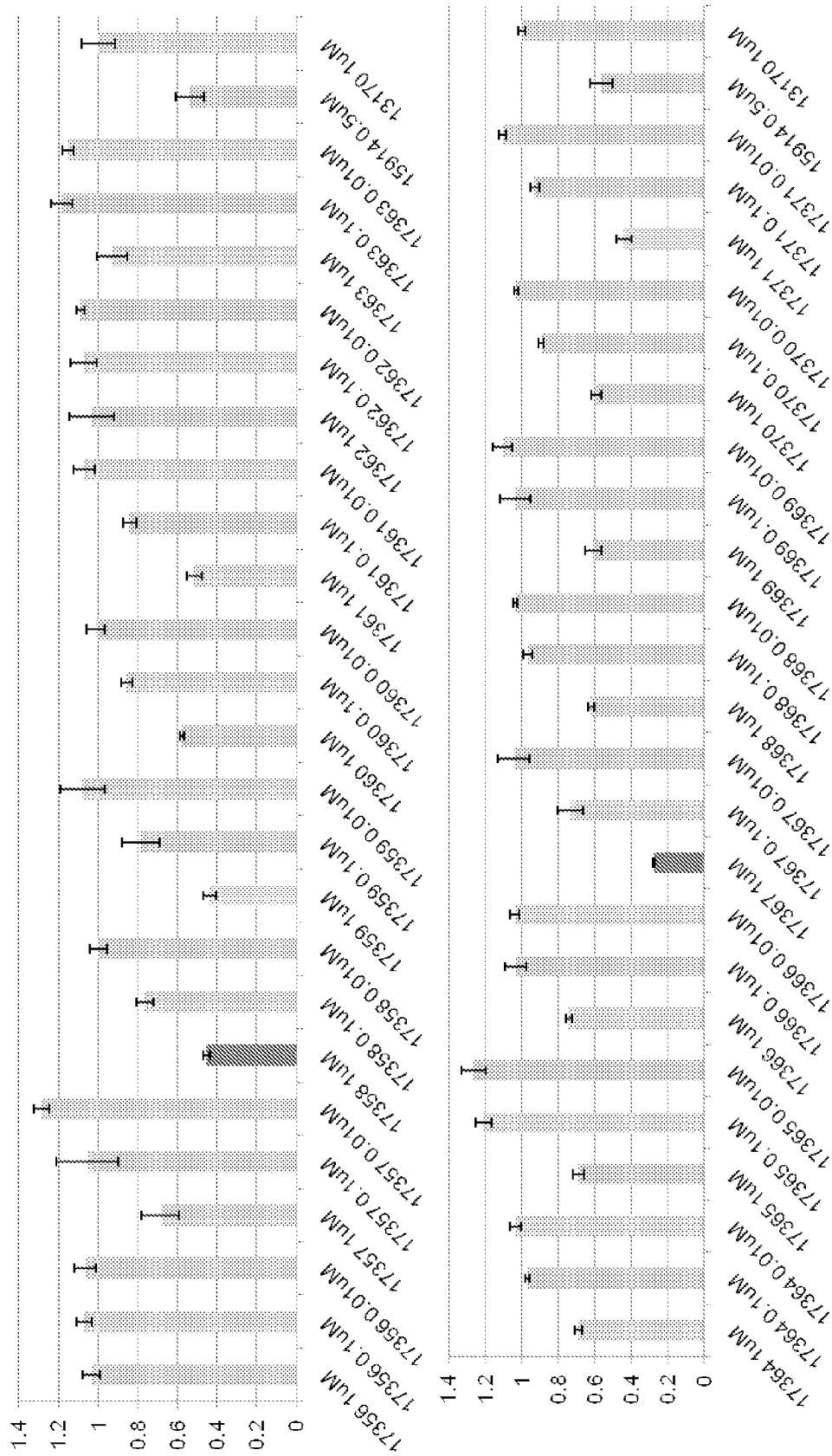


Figure 11

CTGF sd-rxRNA are Efficacious

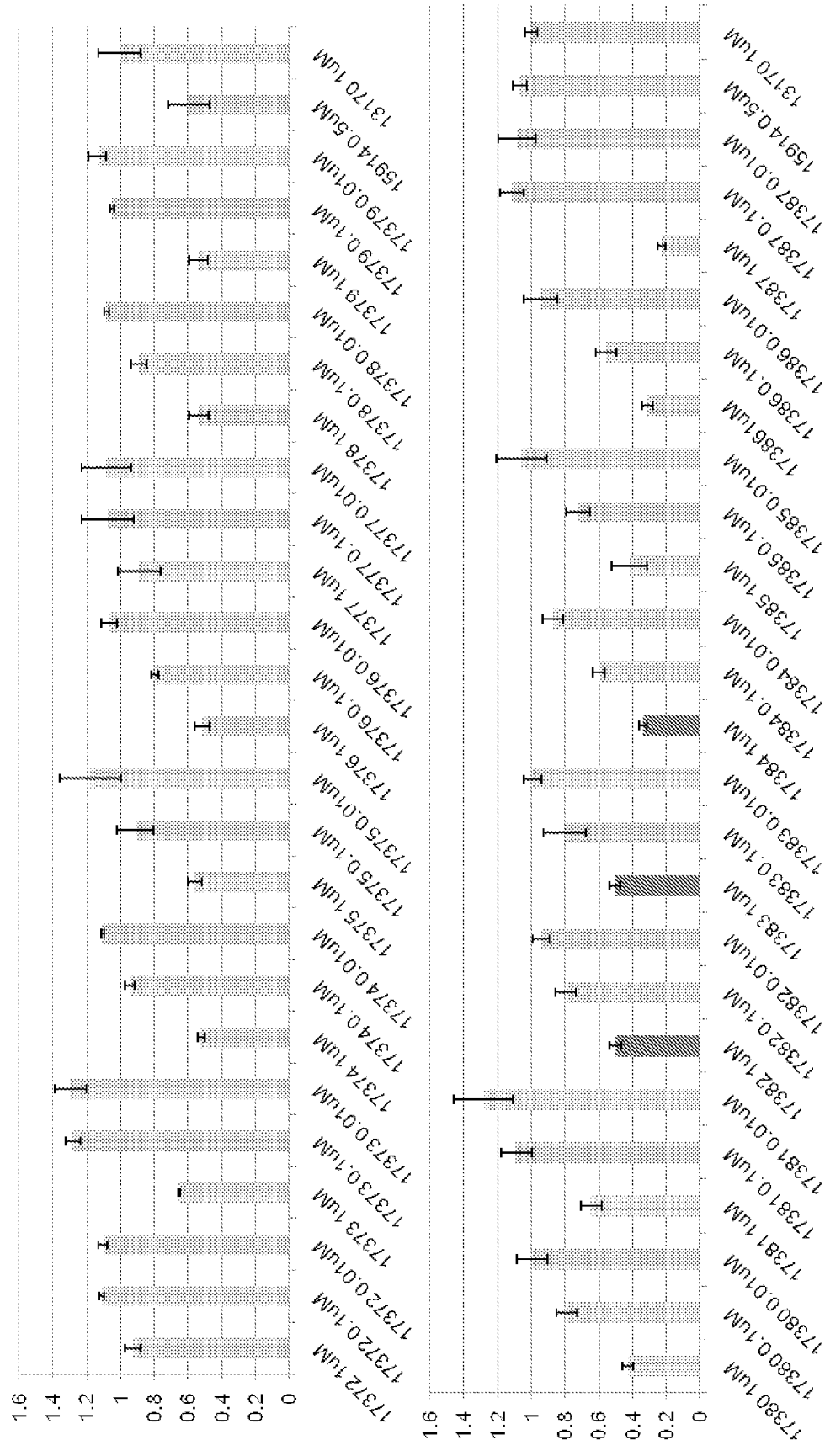


Figure 12

CTGF sd-rxRNA Dose Response

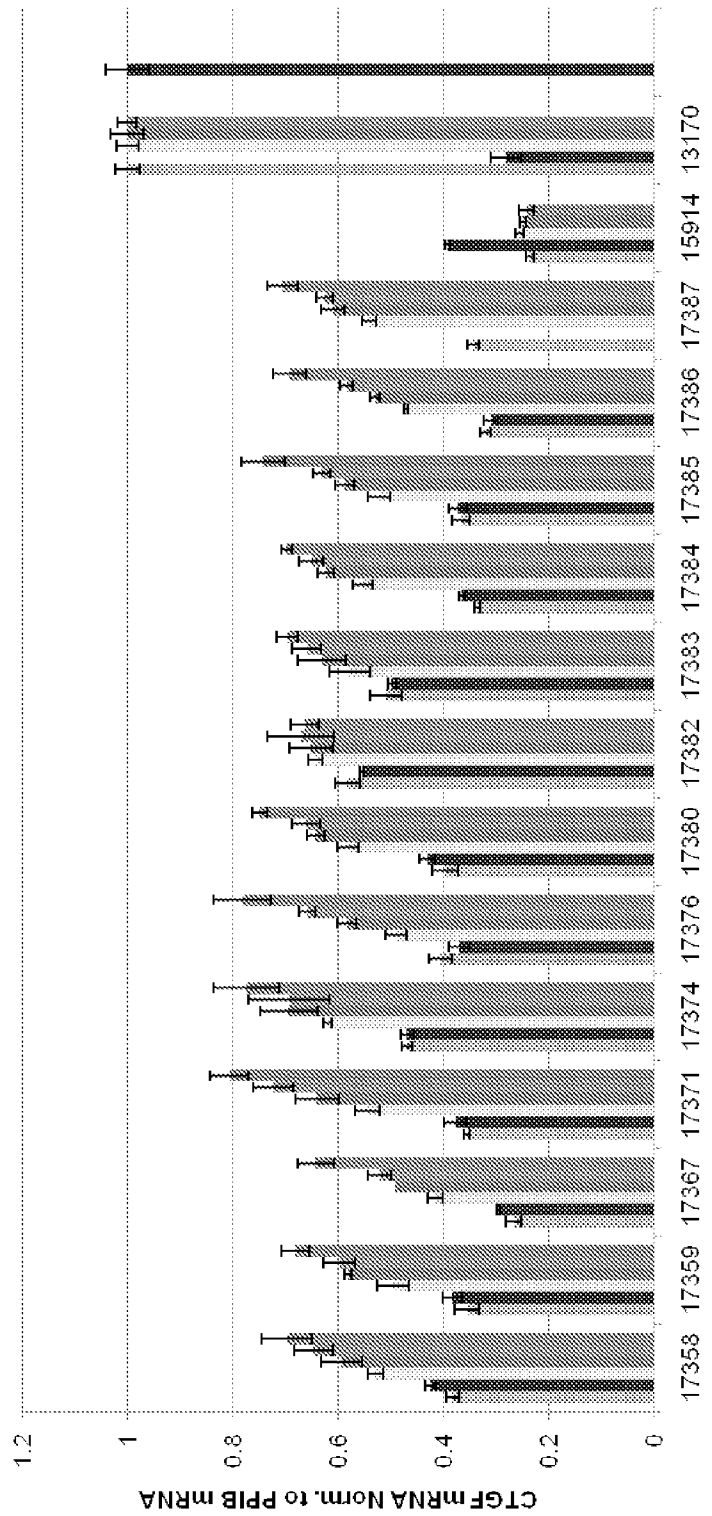


Figure 13

Low Hit Rate with Original sd-rxRNA Screen

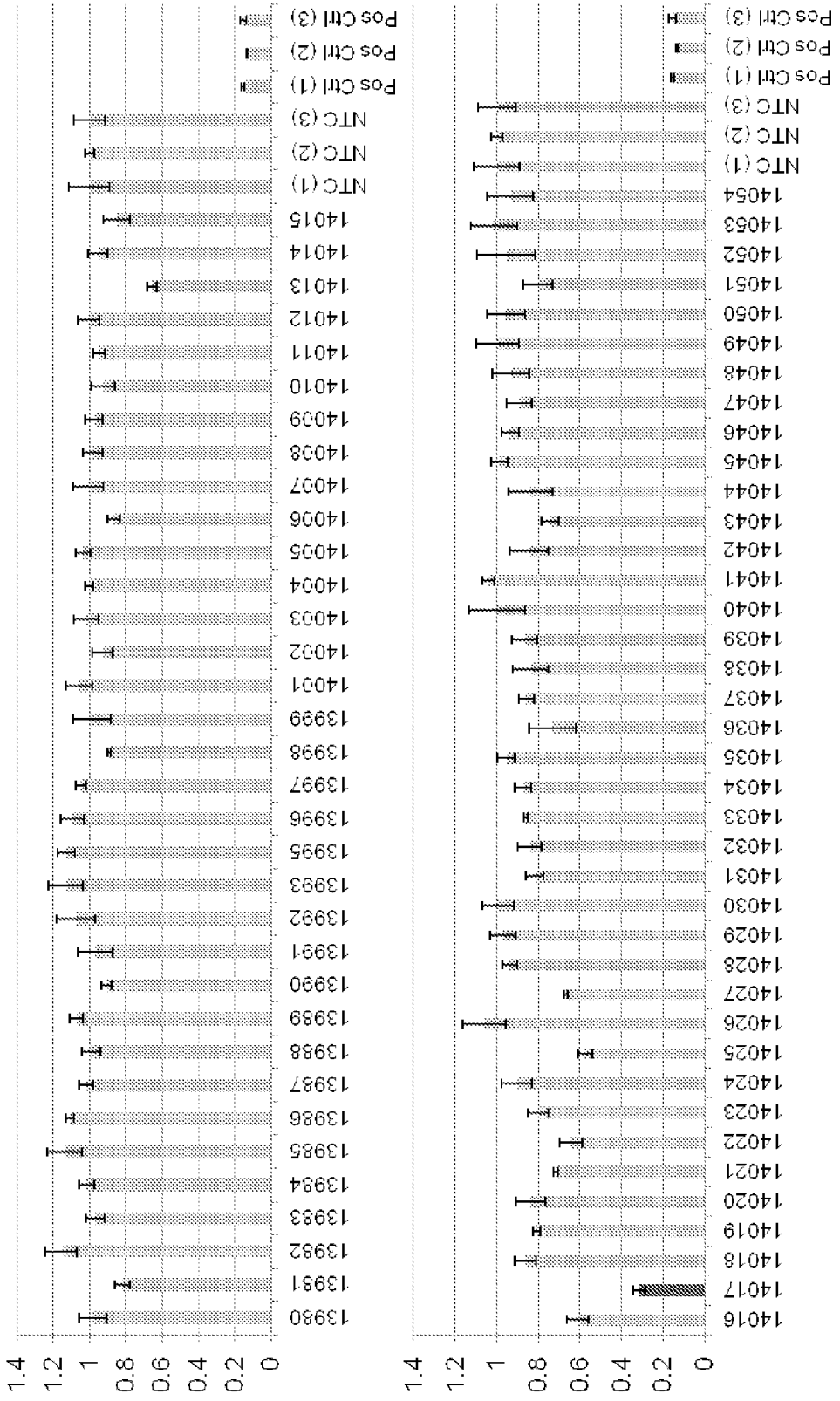


Figure 14

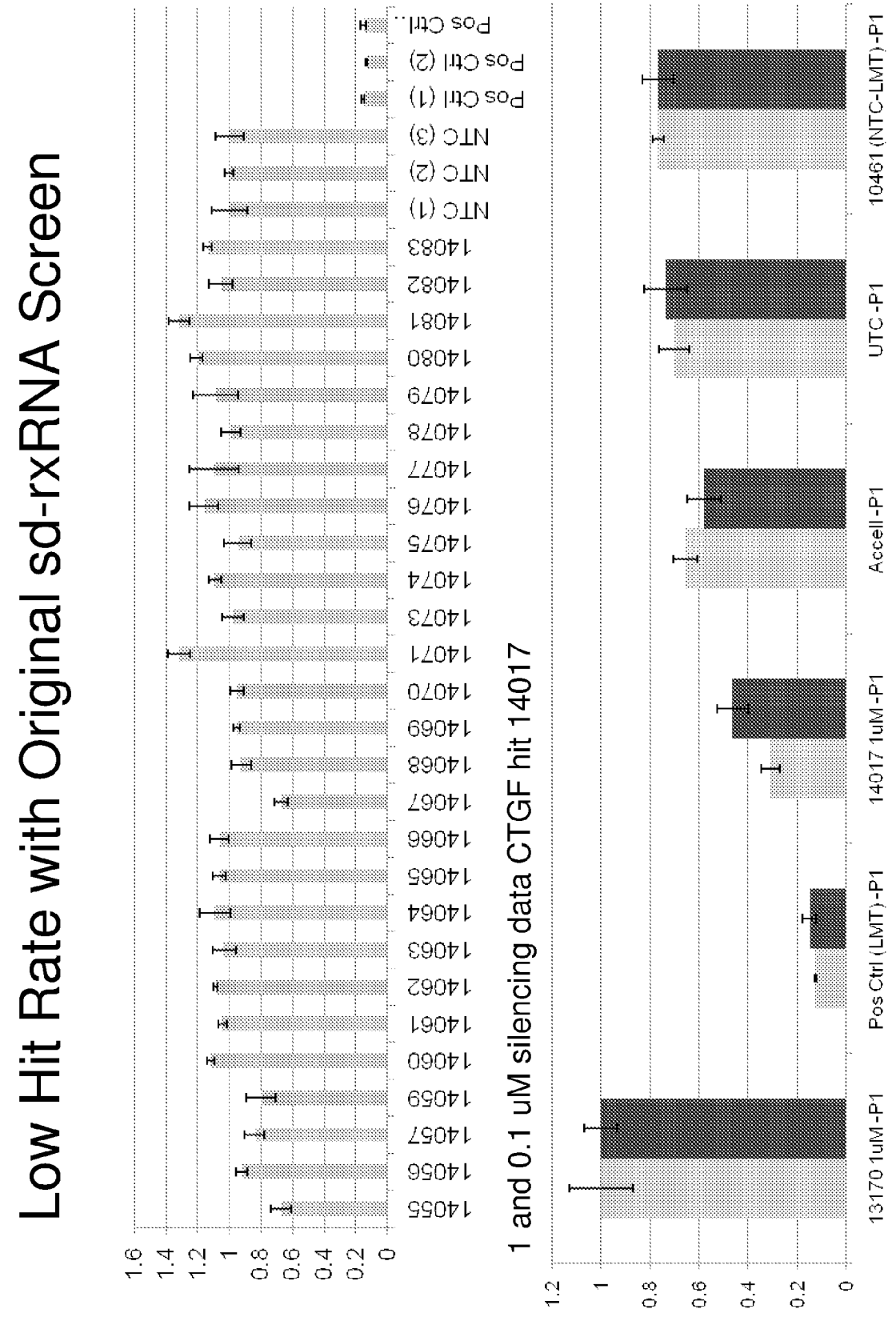

Low Hit Rate with Original sd-rxRNA Screen
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
14055
14056
14057
14059
14060
14061
14062
14063
14064
14065
14066
14067
14068
14069
14070
14071
14073
14074
14075
14076
14077
14078
14079
14080
14081
14082
14083
NTC (1)
NTC (2)
NTC (3)
Pos Ctrl (1)
Pos Ctrl (2)
Pos Ctrl
1 and 0.1 uM silencing data CTGF hit 14017
1.2
1
0.8
0.6
0.4
0.2
0
13170 1uM-P1
Pos Ctrl (LMT)-P1
14017 1uM-P1
Accell-P1
UTC-P1
10461 (NTC-LMT)-P1

Figure 15

PTGS2 Stealth to sd-rxRNA

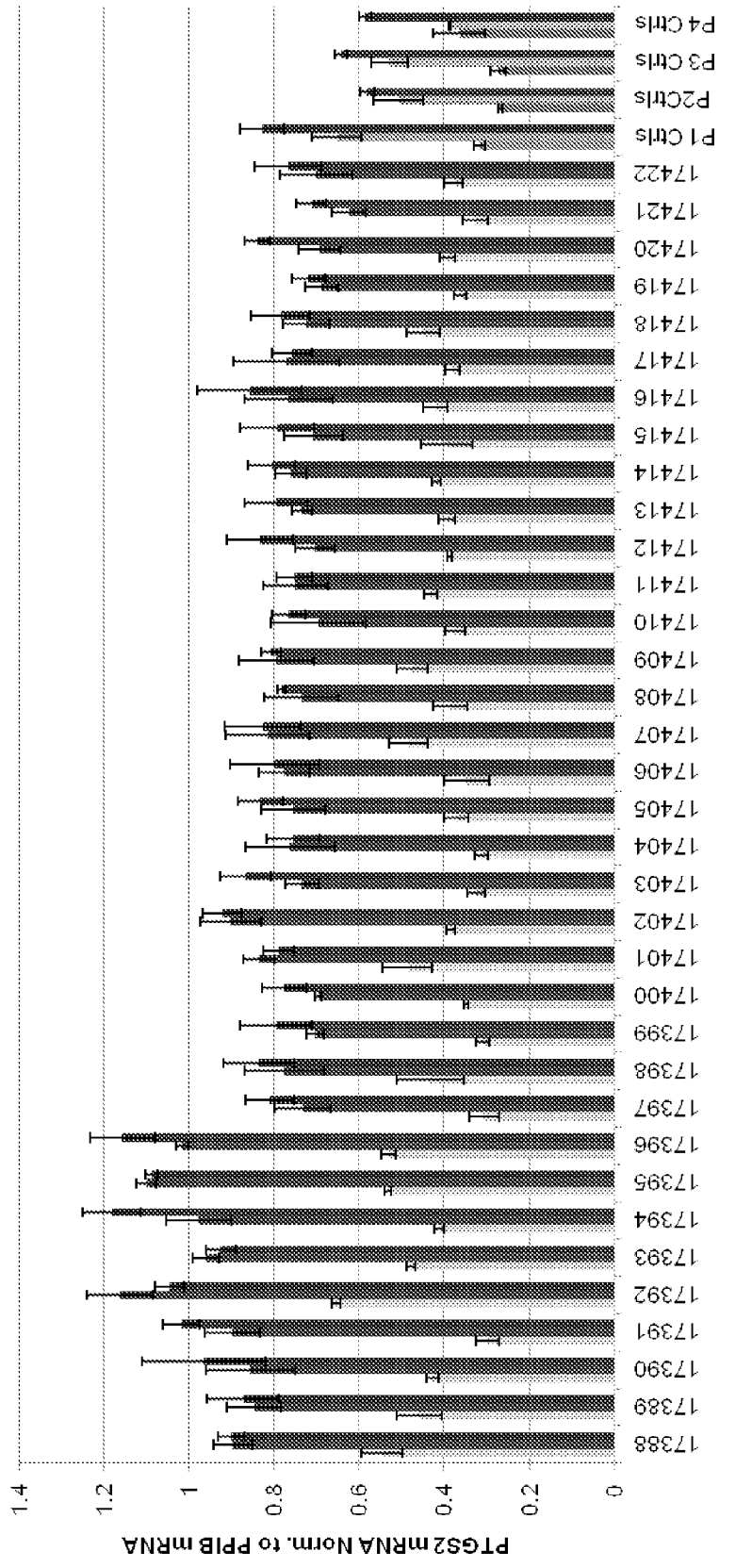


Figure 16

sd-rxRNA target hTGFB1 (A549 Cells, 48 hr Transfection)

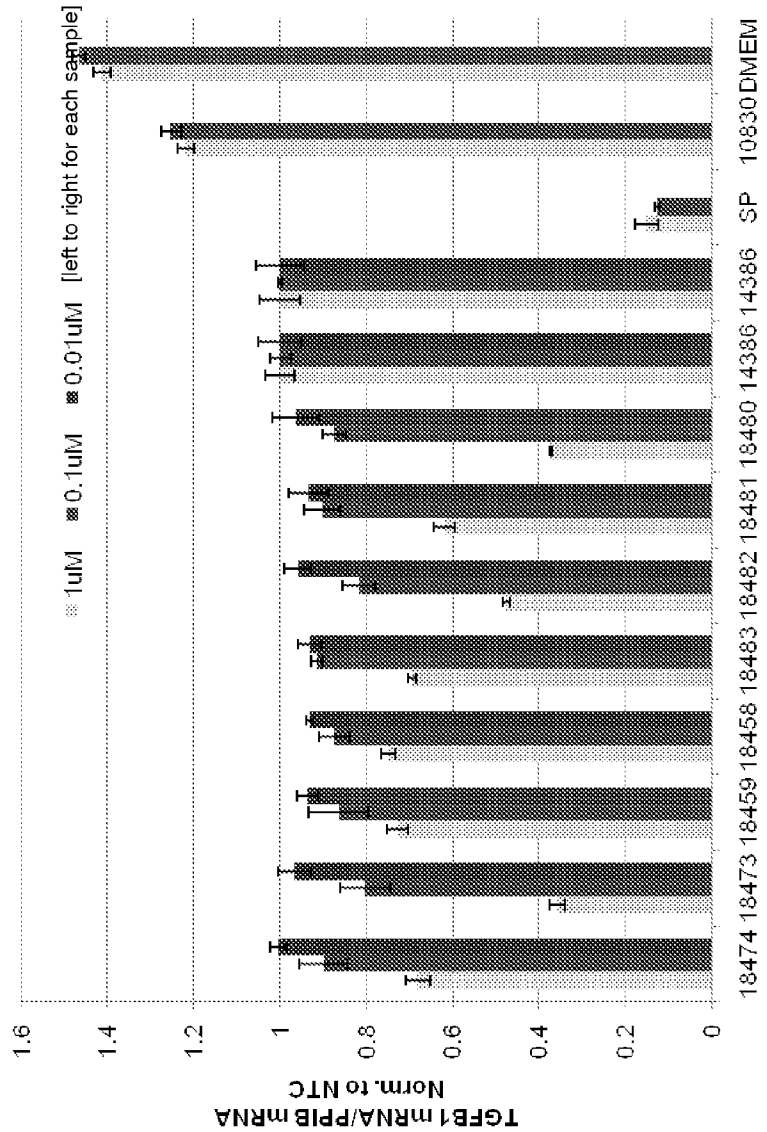


Figure 17

Remaining TGFB1 sd-rxRNA

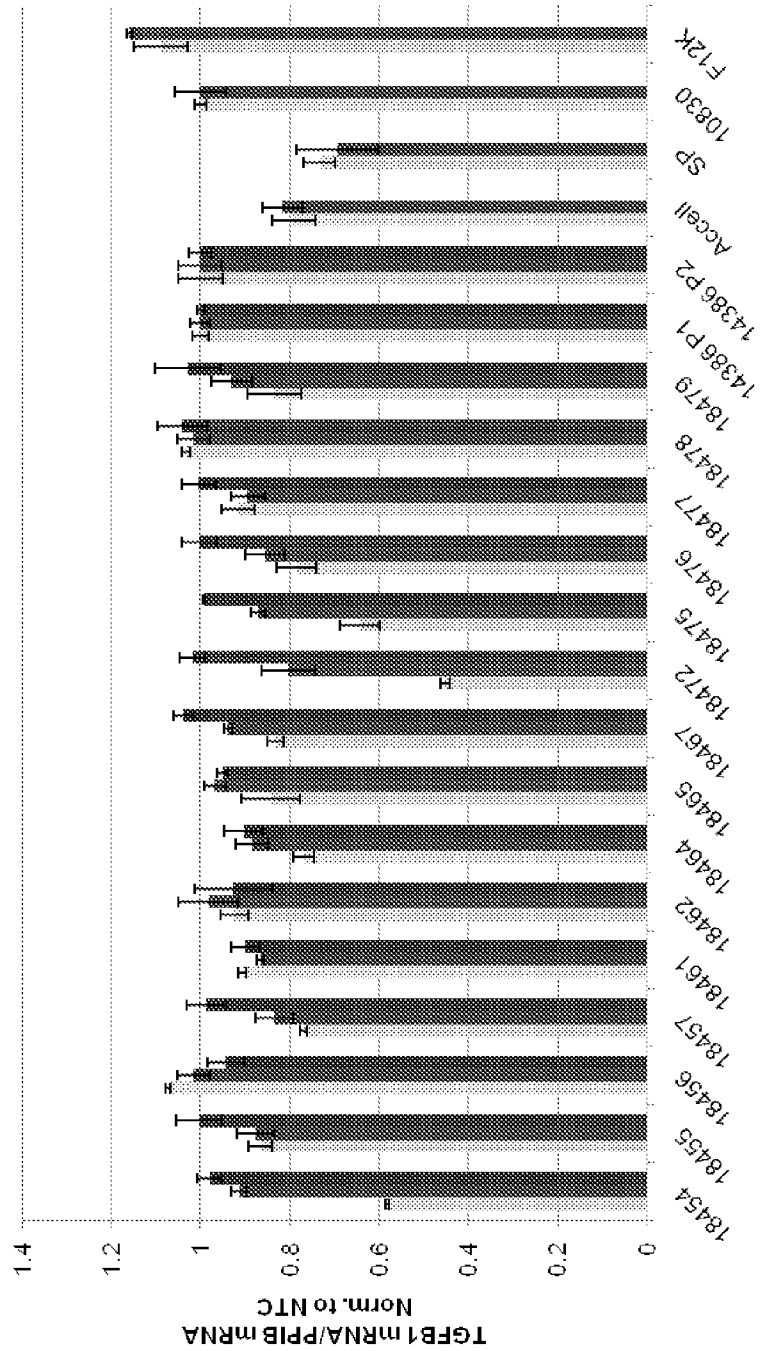


Figure 18

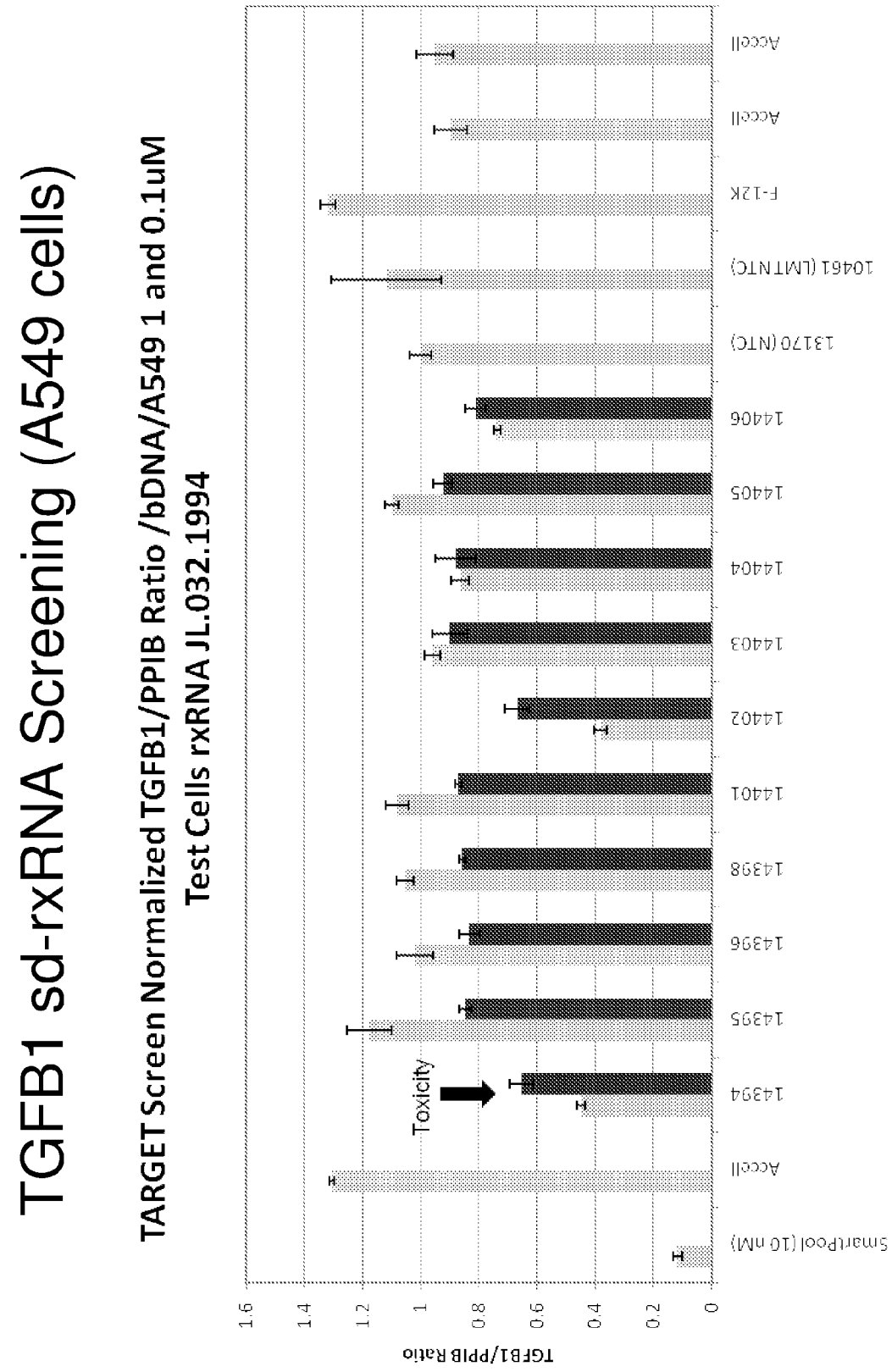
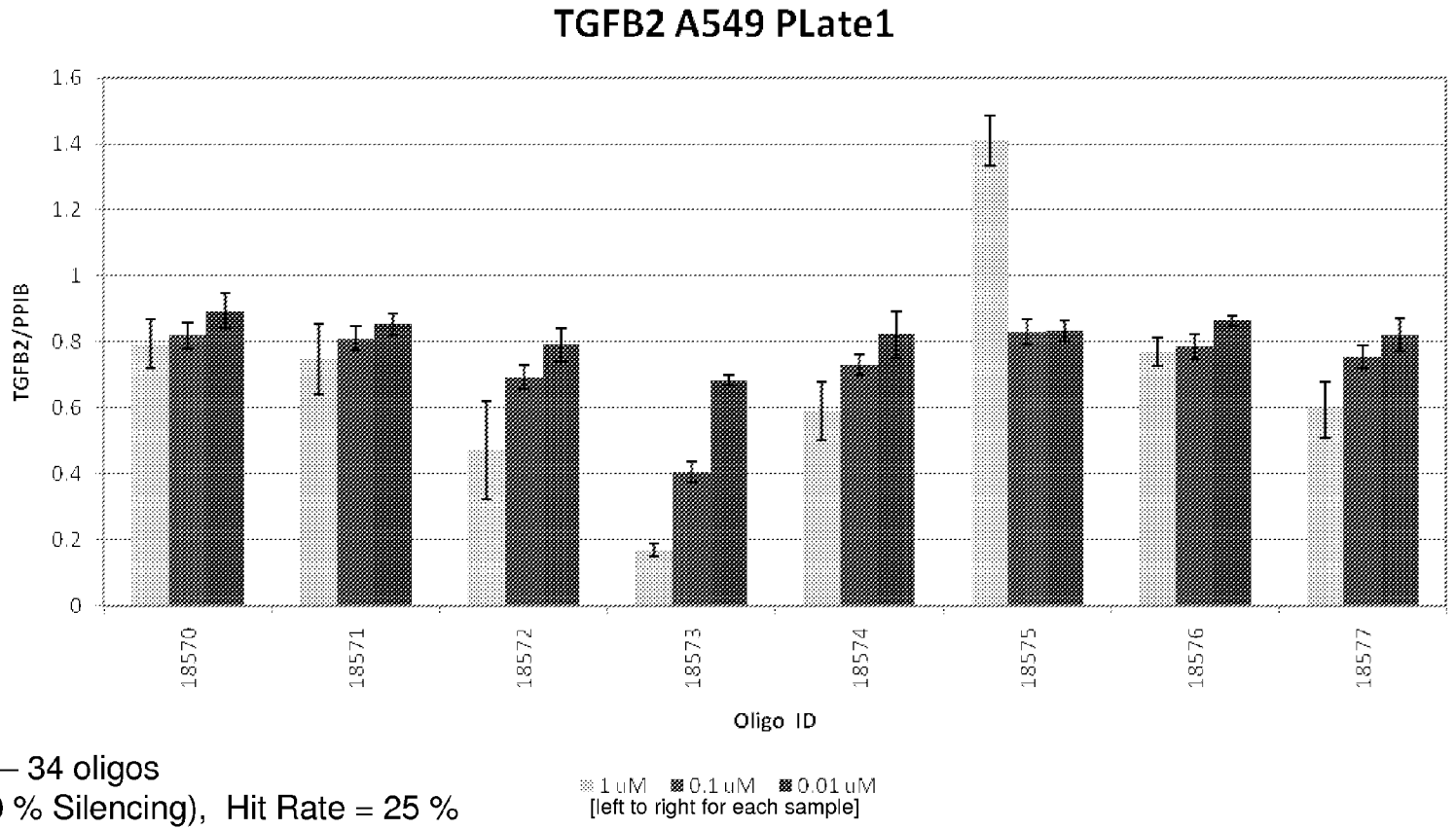

TGFB1 sd-rxRNA Screening (A549 cells)
TARGET Screen Normalized TGFB1/PPIB Ratio /bDNA/A549 1 and 0.1uM
Test Cells rxRNA JL.032.1994
TGFB1/PPIB Ratio
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Toxicity
SmartPool (10 nM)
AccuII
14394
14395
14396
14398
14401
14402
14403
14404
14405
14406
13170 (NTC)
10461 (LMTNTC)
F-12K
AccuII
AccuII
Oligo ID

Figure 19

TGFB2 sd-rxRNA Silence Target Gene in Human Cells (A549, 48 hrs)



Summary:
Screened – 34 oligos
8 hits (>50 % Silencing), Hit Rate = 25 %
3 Potent Hits (>70% Silencing), Hit Rate = 10 %

Figure 20

TGFB2 Continued

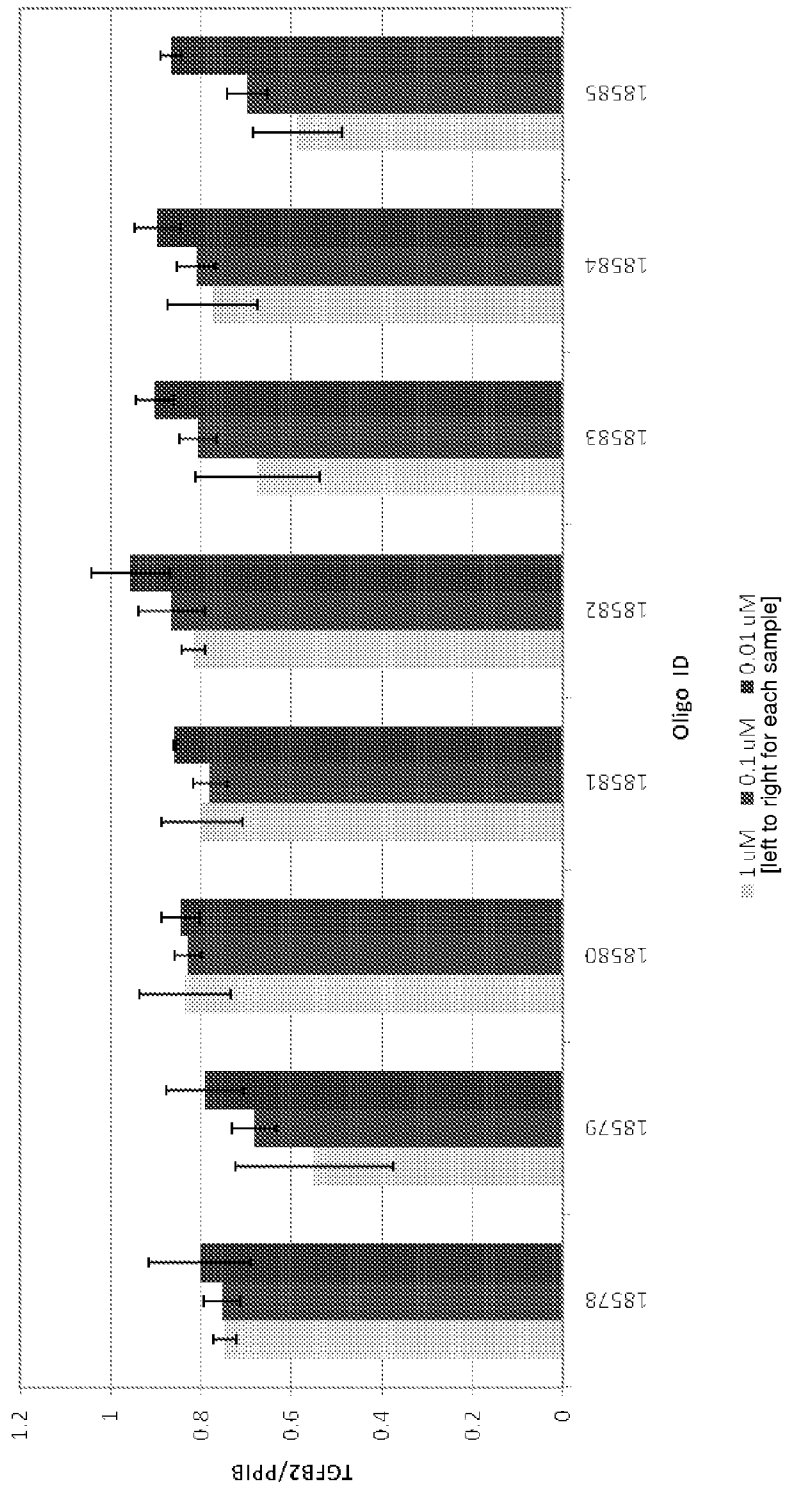


Figure 21

TGFB2 Continued

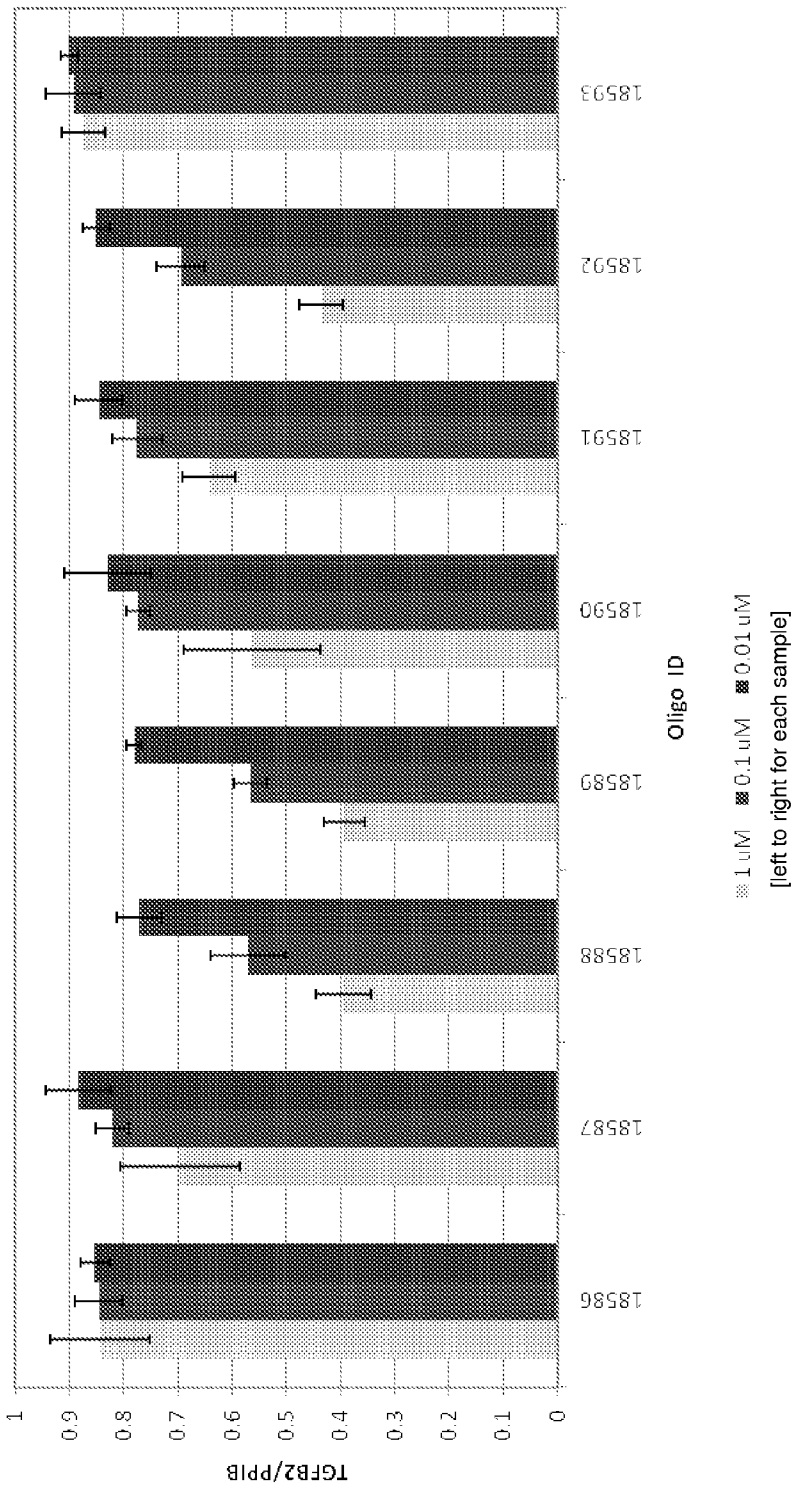


Figure 22

TGFB2 Continued

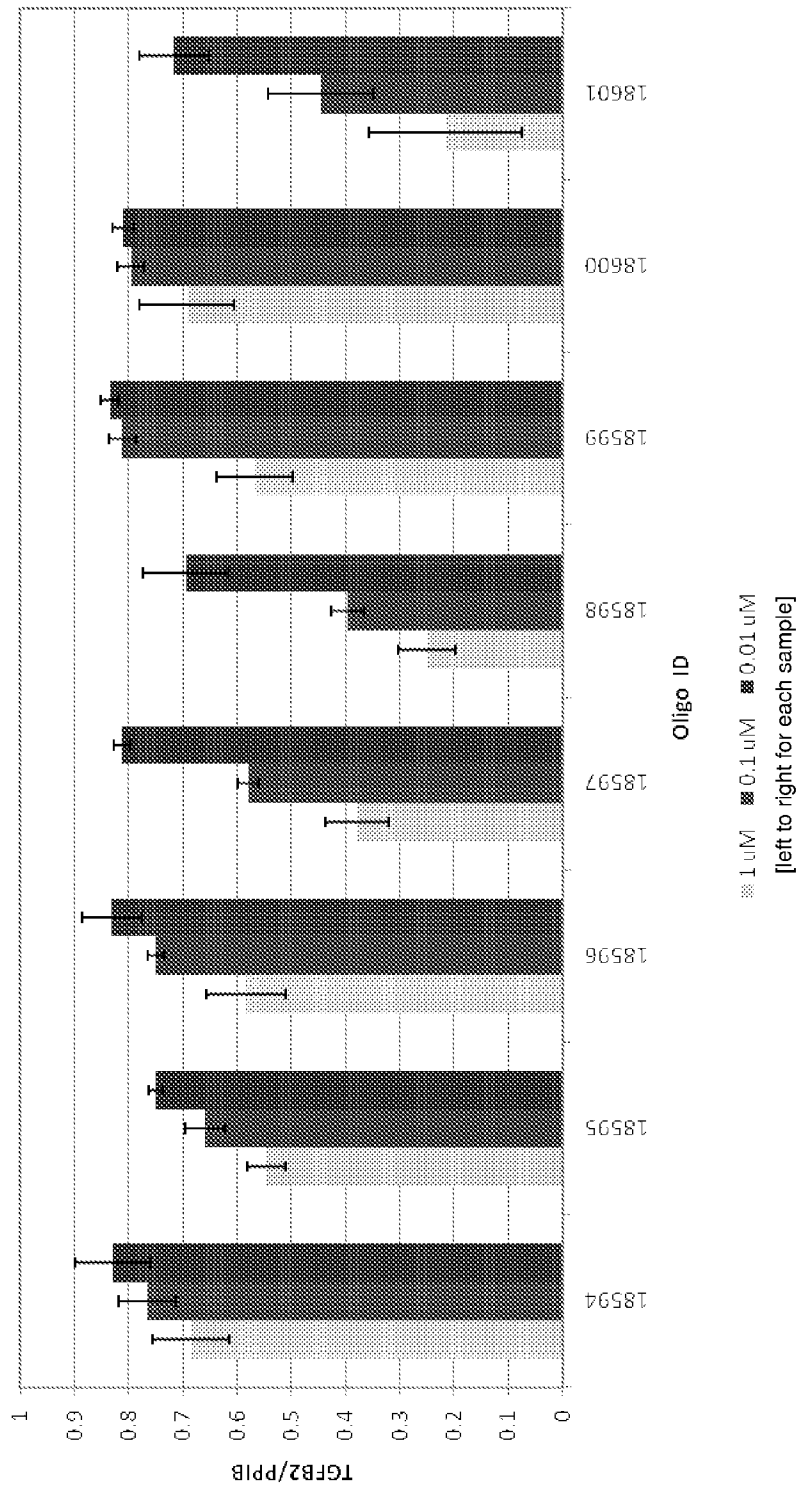


Figure 23

TGFB2 Continued

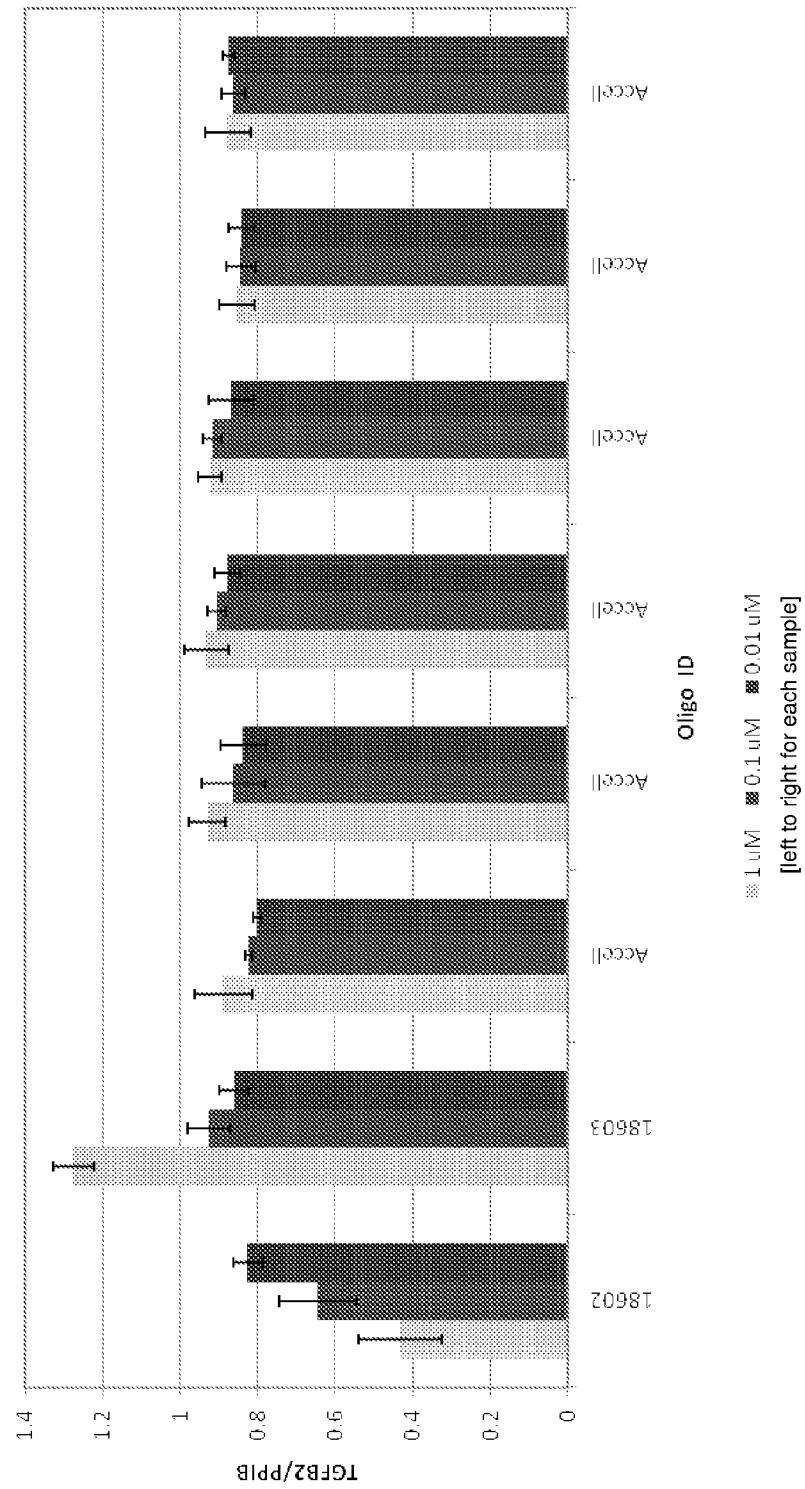


Figure 24

TGFB2 sd-rxRNA Screening (A549 cells)

TARGET Screen Normalized TGFB2/PPIB Ratio /bDNA/A549 1 and 0.1uM
Test Cells rxRNA JL.032.1994

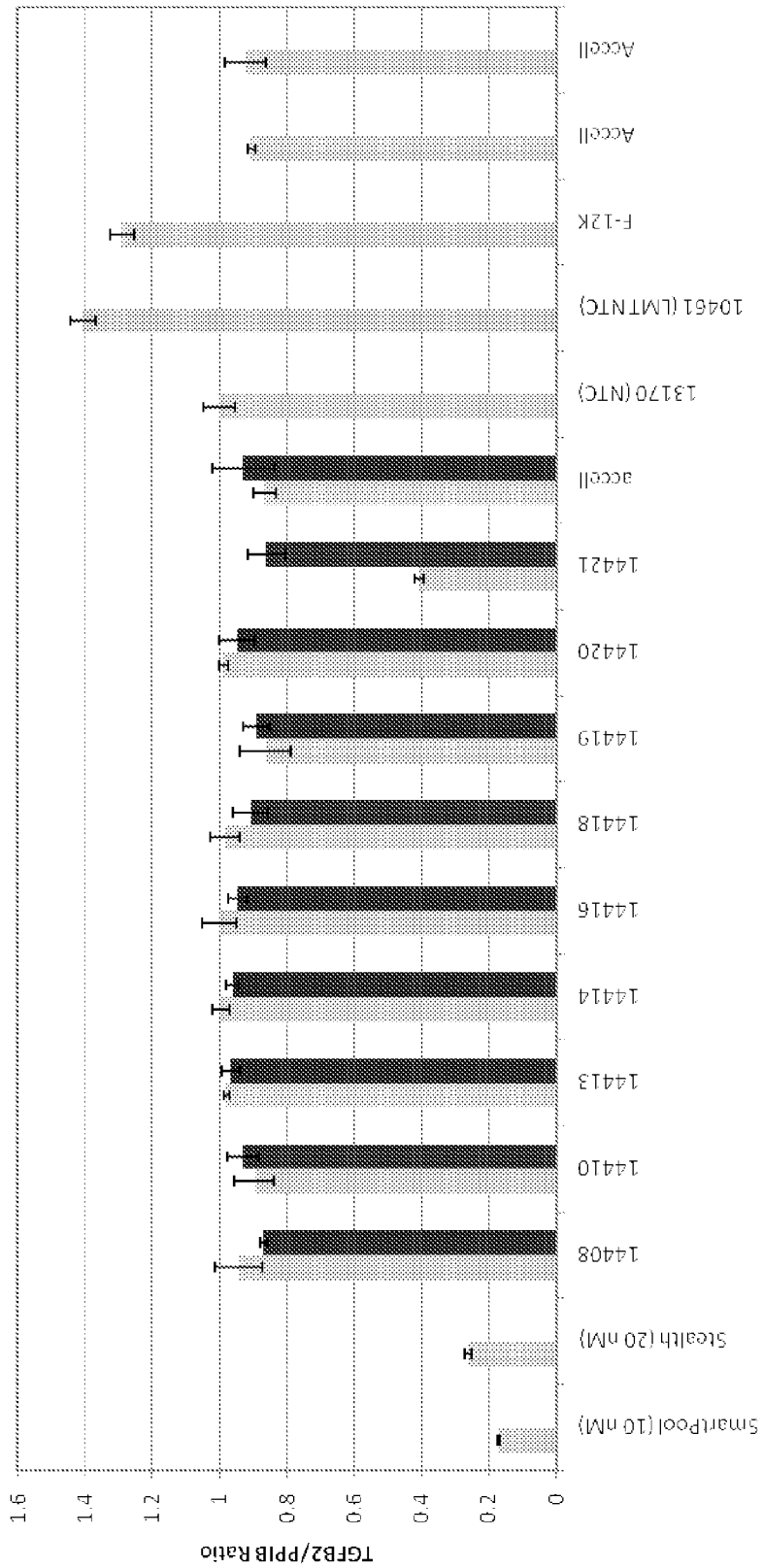


Figure 25

Identification of Potent hSPP1 sd-rxRNAs (A549, 48 hrs)

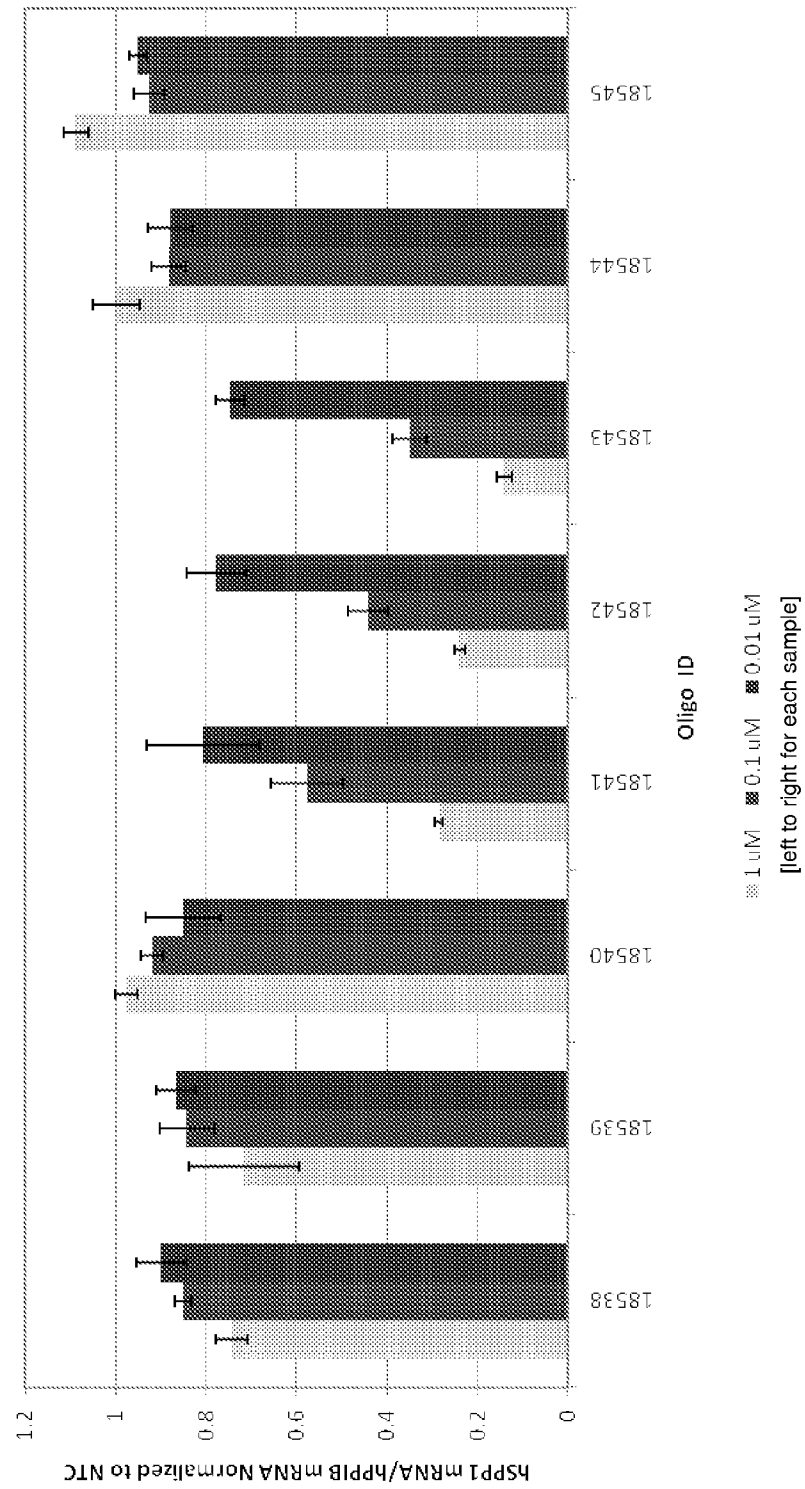


Figure 26

Identification of Potent hSPP1 sd-rxRNAs (A549, 48 hrs)

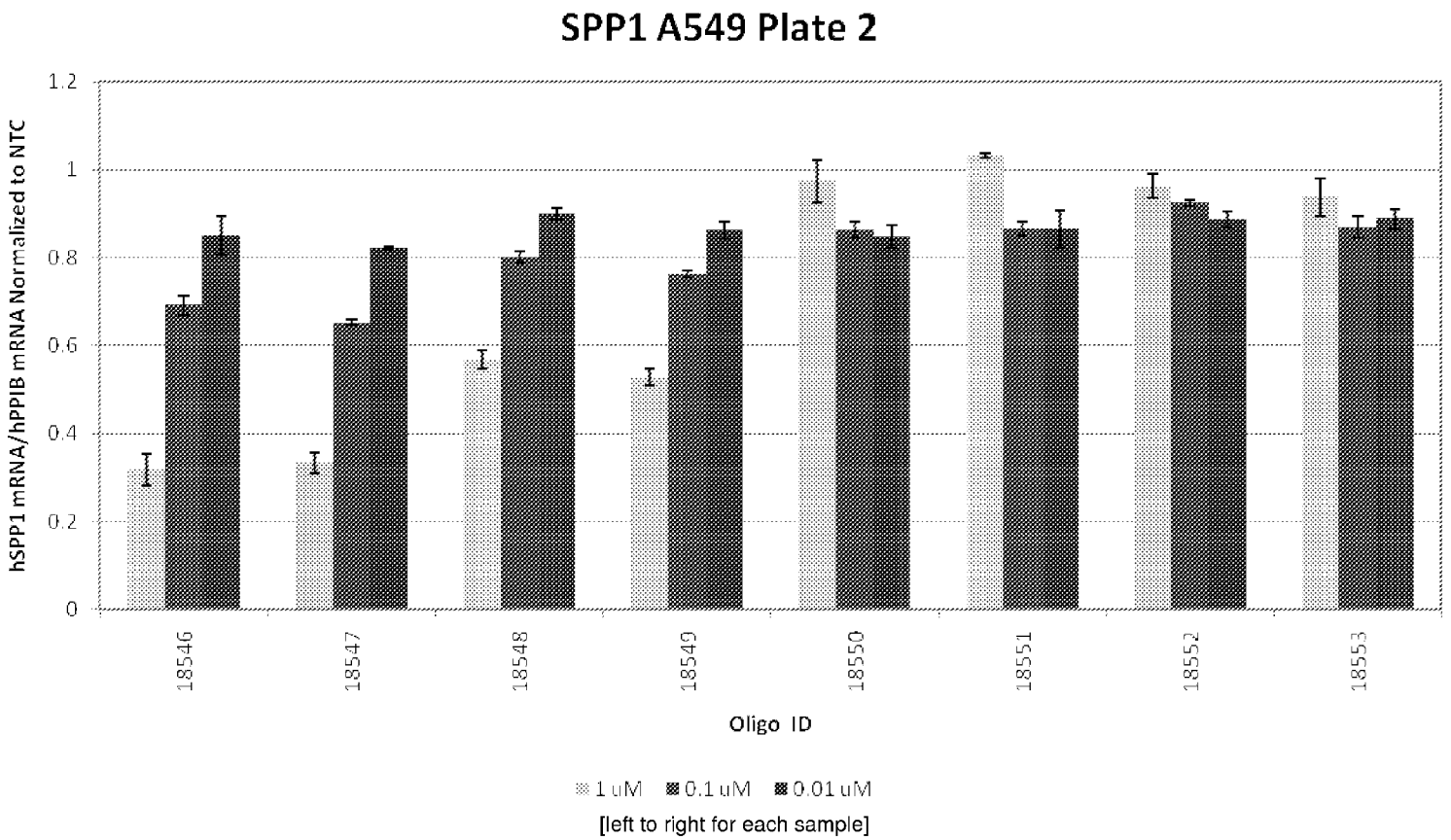


Figure 27

Identification of Potent hSPP1 sd-rxRNAs (A549, 48 hrs)

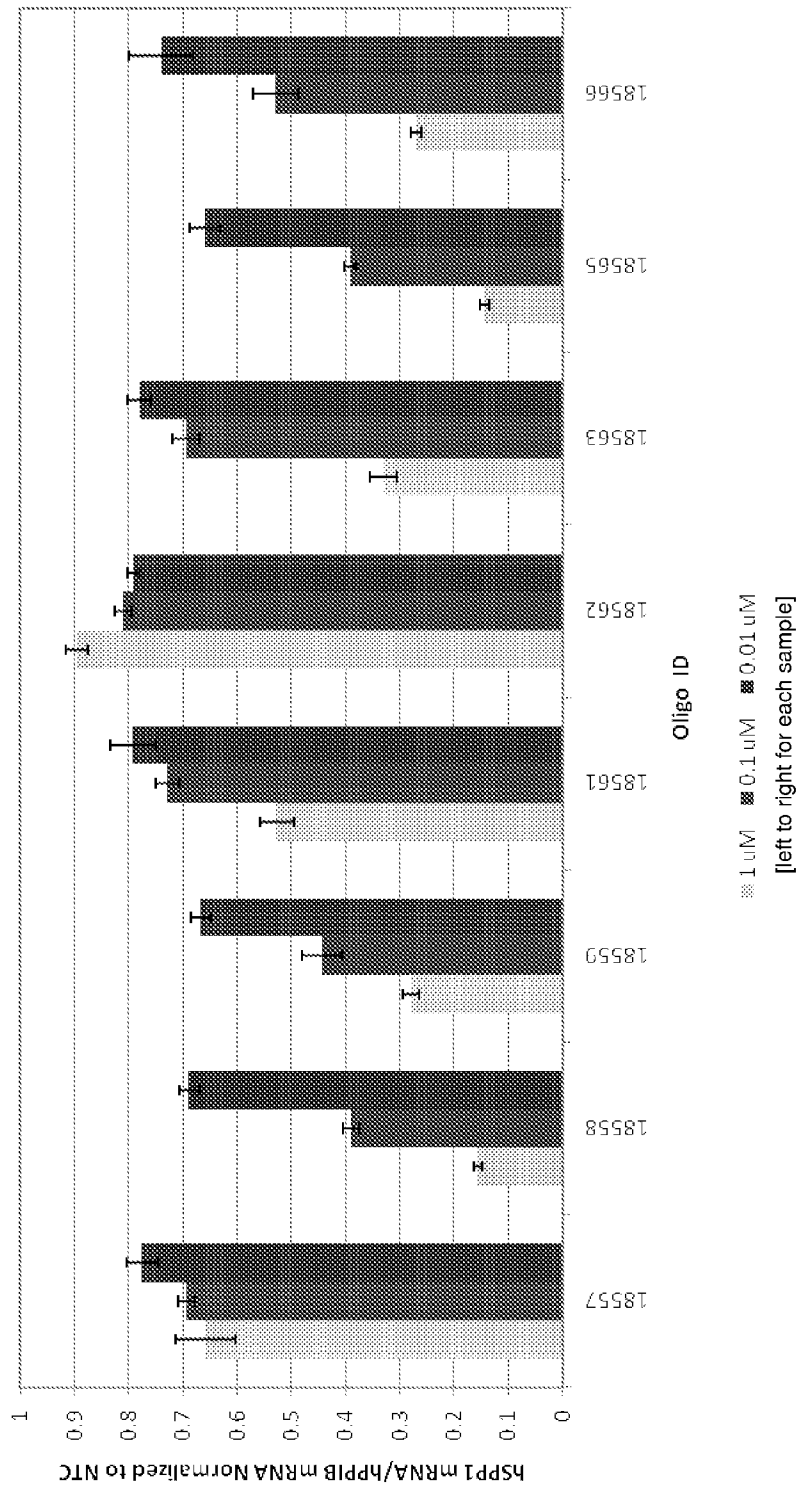
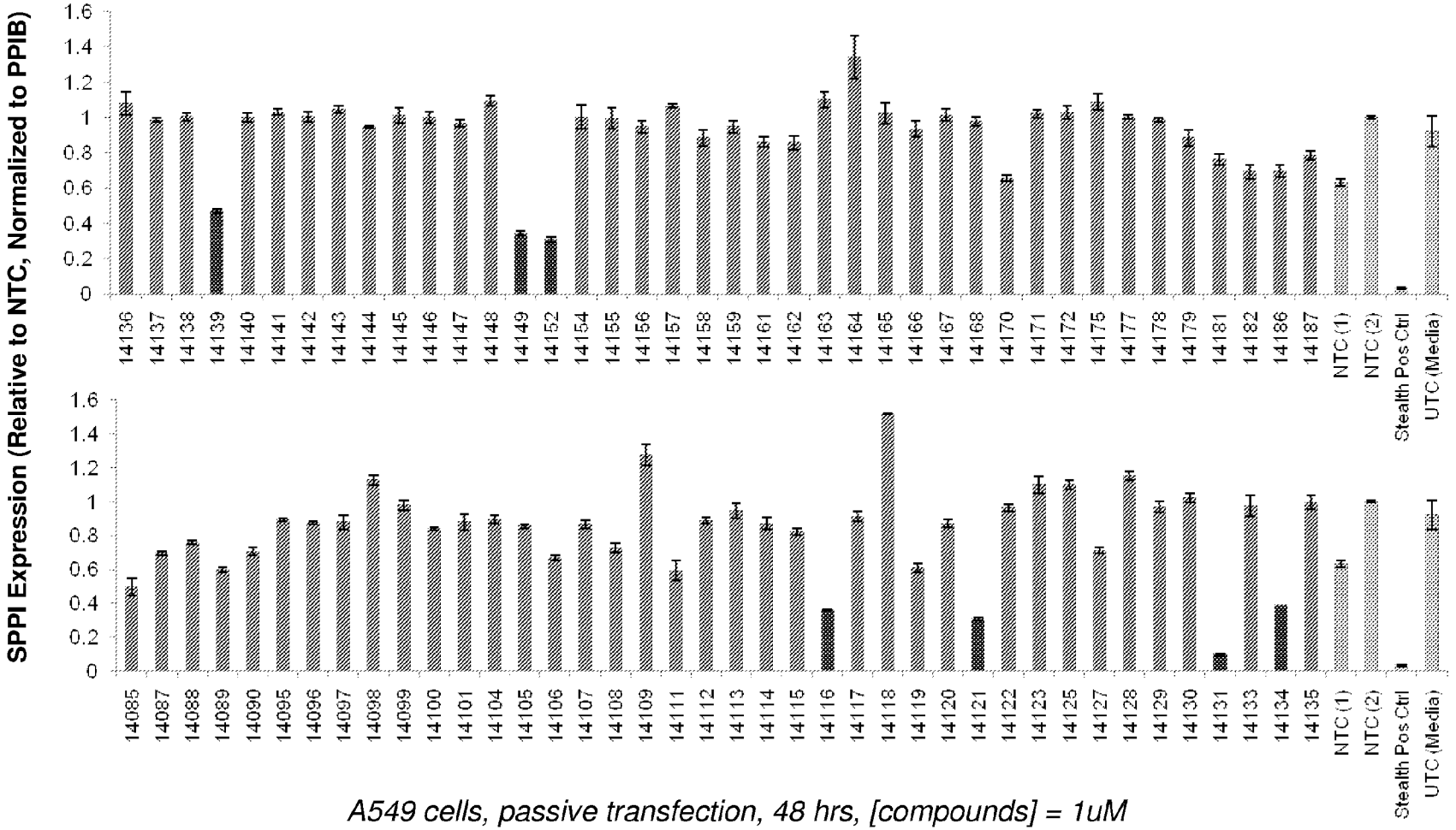


Figure 28

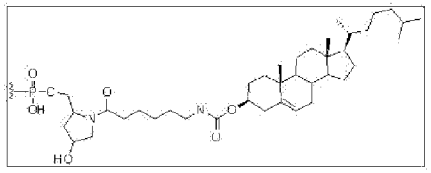
SPPI *sd*-rxRNA Compound Selection (A549 - Human cells)



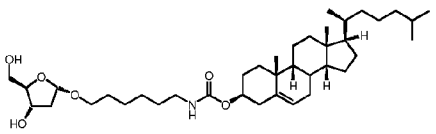
A549 cells, passive transfection, 48 hrs, [compounds] = 1uM

Figure 29

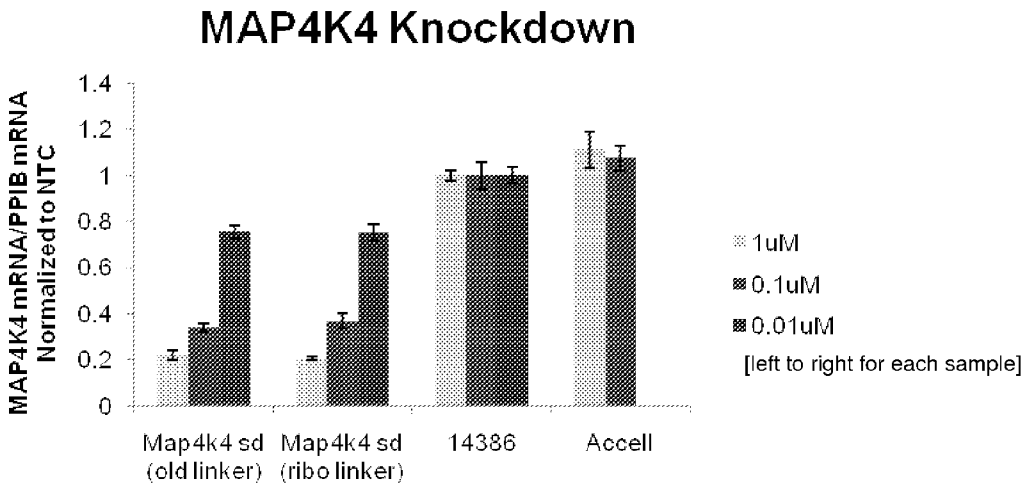
sd-rxRNAs Containing Ribo Linker are Efficacious



Old linker
(hydroxyproline linker)



Ribo linker



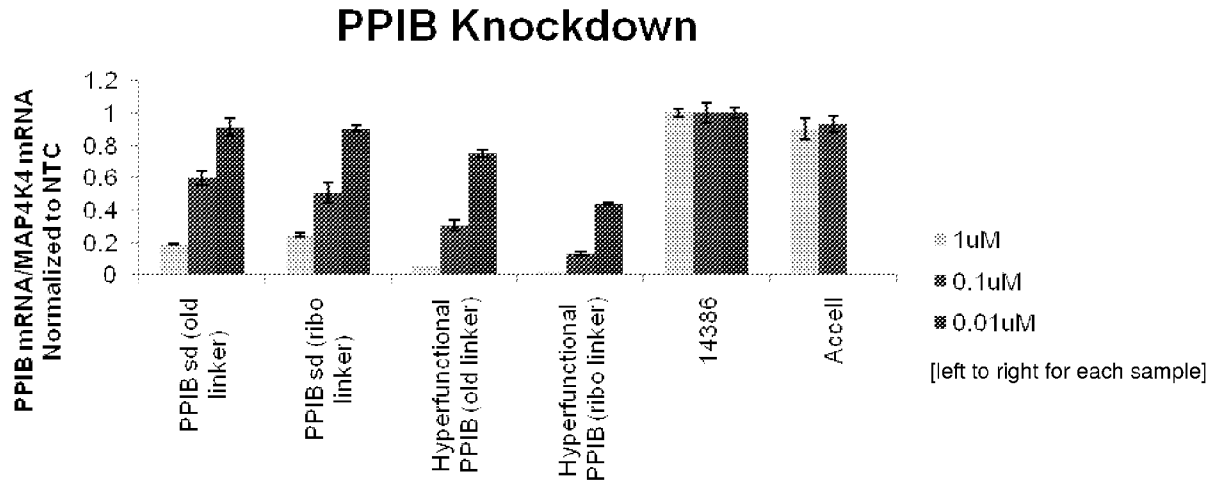


Figure 30

CTGF: A Central Factor in the Pathway to Fibrosis

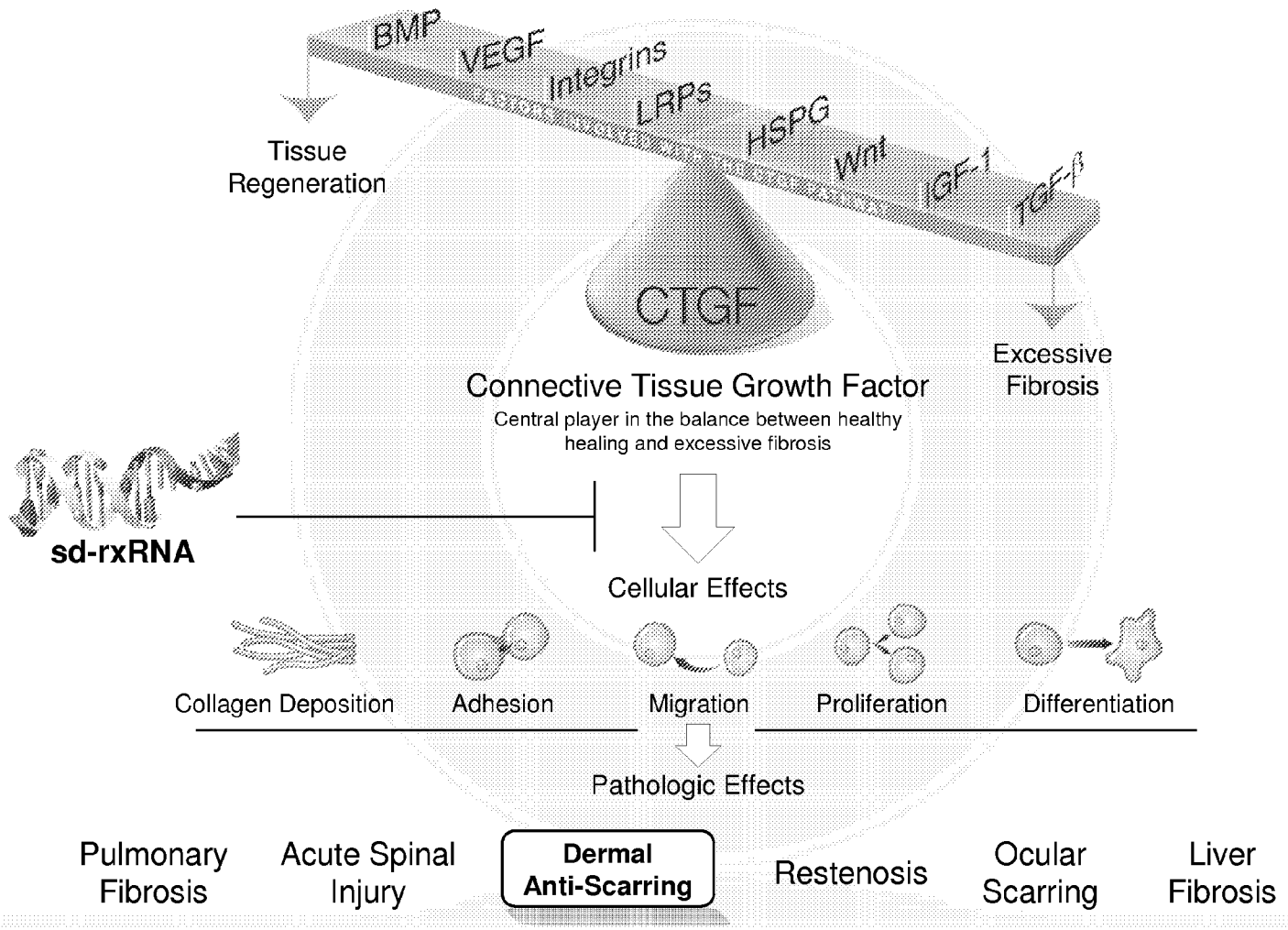


Figure 31

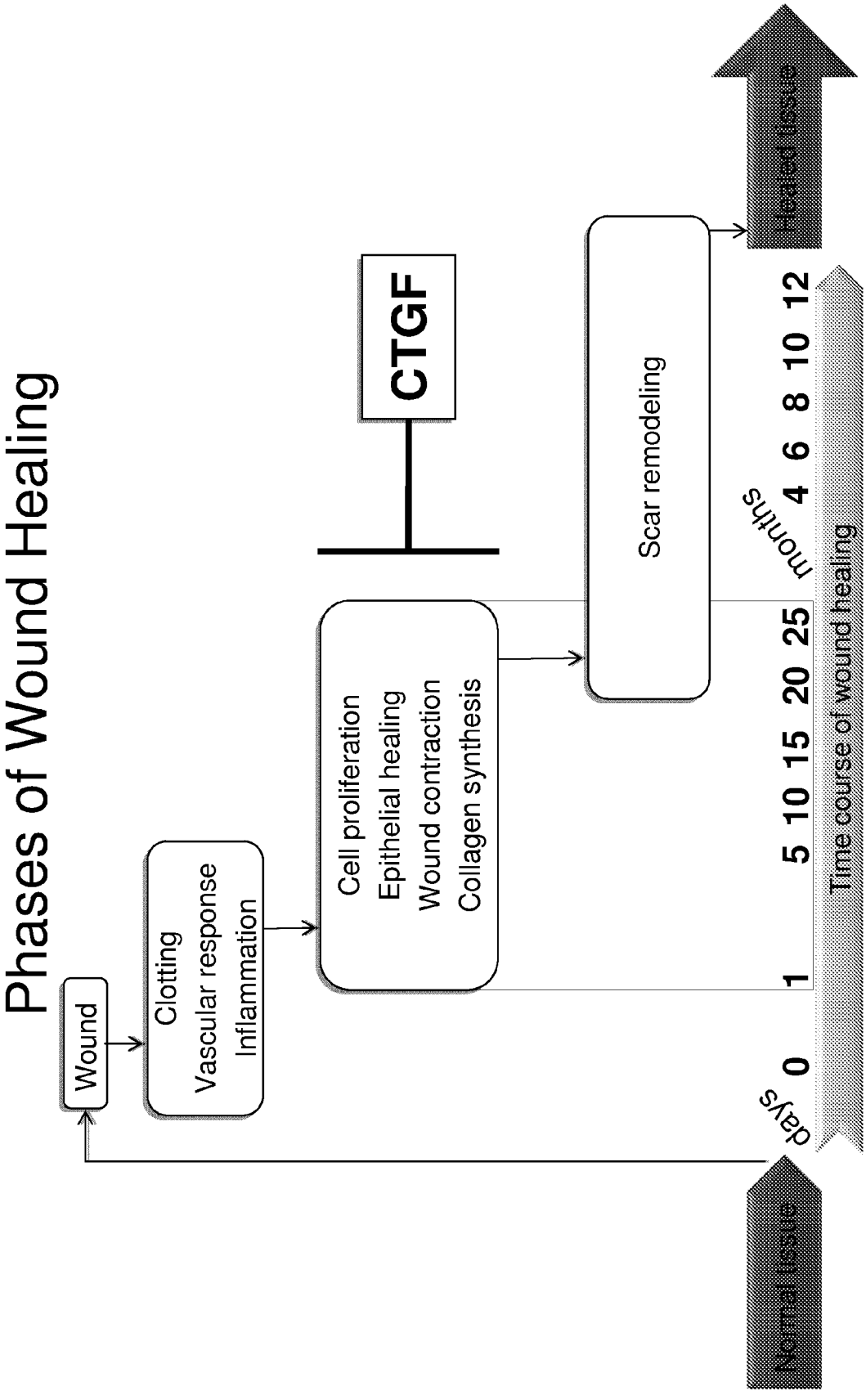
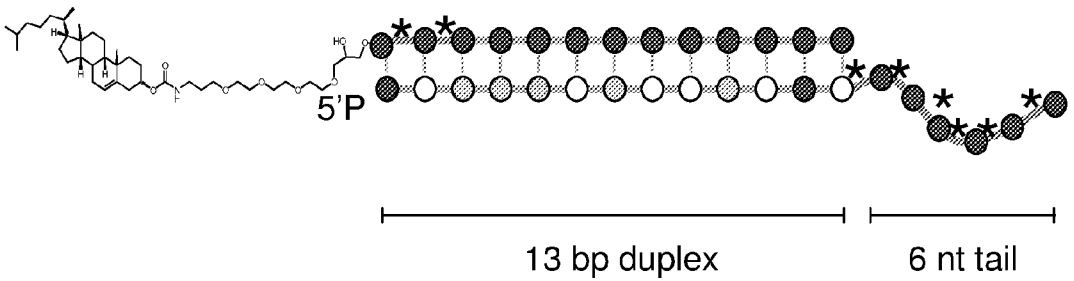

Phases of Wound Healing
Wound
Clotting
Vascular response
Inflammation
Cell proliferation
Epithelial healing
Wound contraction
Collagen synthesis
CTGF
Scar remodeling
Healed tissue
Normal tissue
days
0
1
5 10 15 20 25
months
4 6 8 10 12
Time course of wound healing

Figure 32

Chemical Optimization of sd-rxRNA Leads



- ● – 2'-O-Me
- ◍ – 2'-F
- o – 2'-OH
- * – phosphorothioate
- ≈ – phosphodiester

Structural Characteristics

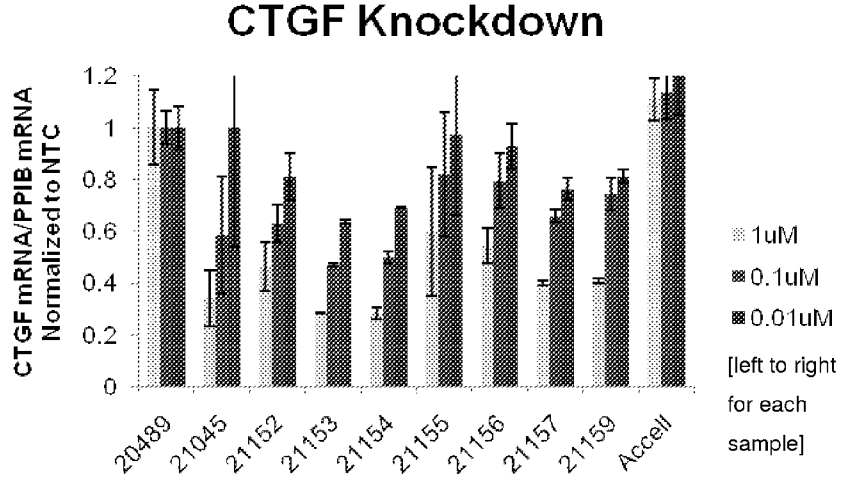
- Antisense strand: 19 bases
- Sense strand: 13 bases
- Duplex length: 13 bp
- Molecular weight: ~10kD

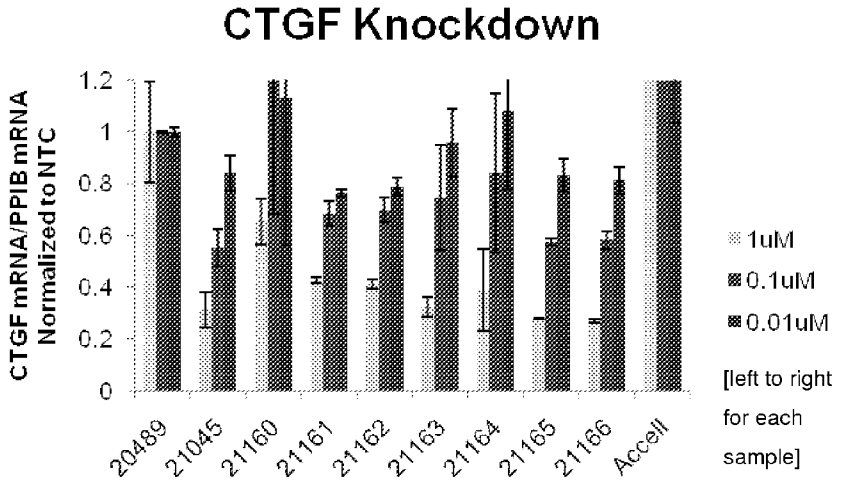
Chemical Characteristics

- 2'-O-Me: ~70%
- 2'-F: ~15%
- 2'-OH: ~15%
- PS: ~25%
- TEG
- Sterol

Figure 33

Opt CTGF L1 sd-rxRNAs Are Active



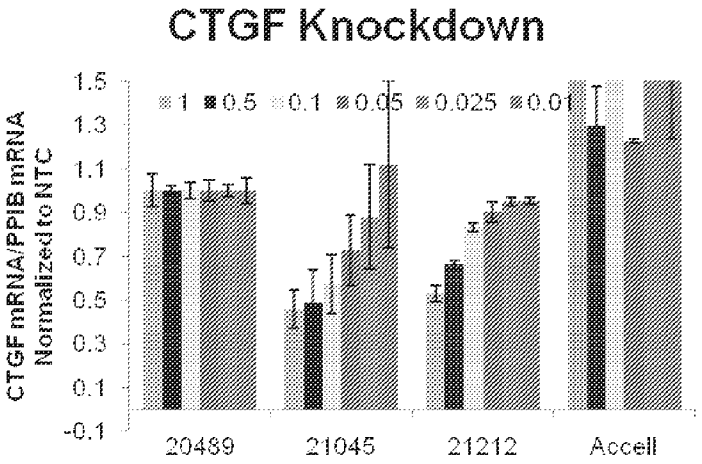


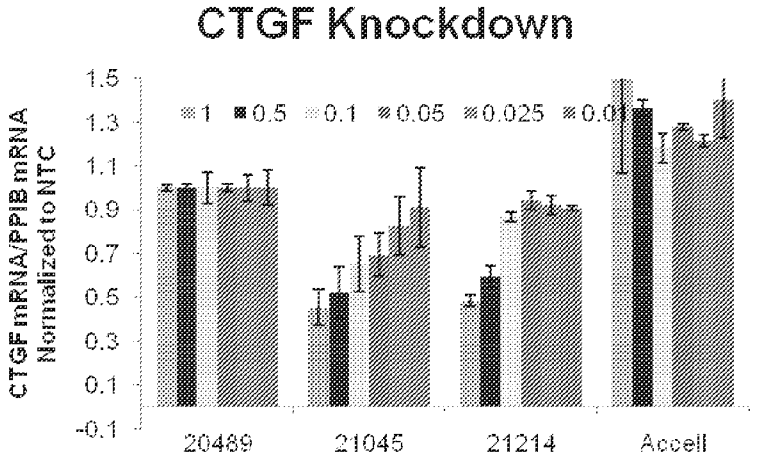
21152	P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. A. A* A*fC* A*A* G* G
21153	P.mU.fU. A. G. mA. A. mA. G. G.fU. G.fC. A. A* A*fC* A*A* G* G
21154	P.mU.fU. mA. G. mA. A. mA. G. mG.fU. G.fC. A. A* A*fC* A*A* G* G
21155	P.mU.fU. A. G. A. mA. A. G. G.fU. G.mC. A. A* A*mC* A*A* G* G
21156	P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. A. mA* mA*fC* mA*mA* mG* G
21157	P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. mA. mA* mA*fC* mA*mA* mG* G
21159	P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. A. mA* mA*mC* mA*mA* mG* G

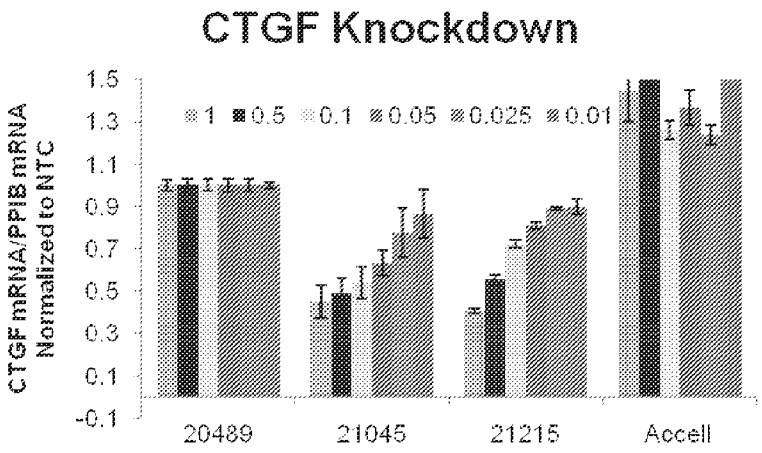
21160	P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC.m A. mA* mA*mC* mA*mA* mG* G
21161	P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. A. A* A*fC* A*mA*mG* G
21162	P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. mA. A* mA*fC* A*mA*mG* G
21163	mU.mU. G.mC. A.mC.mC.mU.mU.mU.mC.mU* A* A-chol
21164	mU.mU. G.mC. A.mC.mC.mU.mU.mU.mC.mU*mA*mA-chol
21165	mU*mU* G.mC. A.mC.mC.mU.mU.mU.mC.mU*mA*mA-chol
21166	mU.mU.mG.mC.mA.mC.mC.mU.mU.mU.mC.mU*mA*mA-chol

Figure 34

CTGF L1 Chemical Optimization (*in vitro* Efficacy)







L1a	**21212**	mU.mU. G.mC. A.mC.mC.mU.mU.mU.mC.mU*mA*mA-chol
		P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. mA. mA* mA*fC* mA*mA* mG* G
L1b	21214	mU.mU. G.mC. A.mC.mC.mU.mU.mU.mC.mU*mA*mA-chol
		P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. A. A* A*fC* A*mA*mG* G
L1c	21215	mU.mU. G.mC. A.mC.mC.mU.mU.mU.mC.mU*mA*mA-chol
		P.mU.fU. A. G. A. mA. A. G. G.fU. G.fC. mA. A* mA*fC* A*mA*mG* G

Figure 35

CTGF L1 Chemical Optimization (*in vitro* Stability)

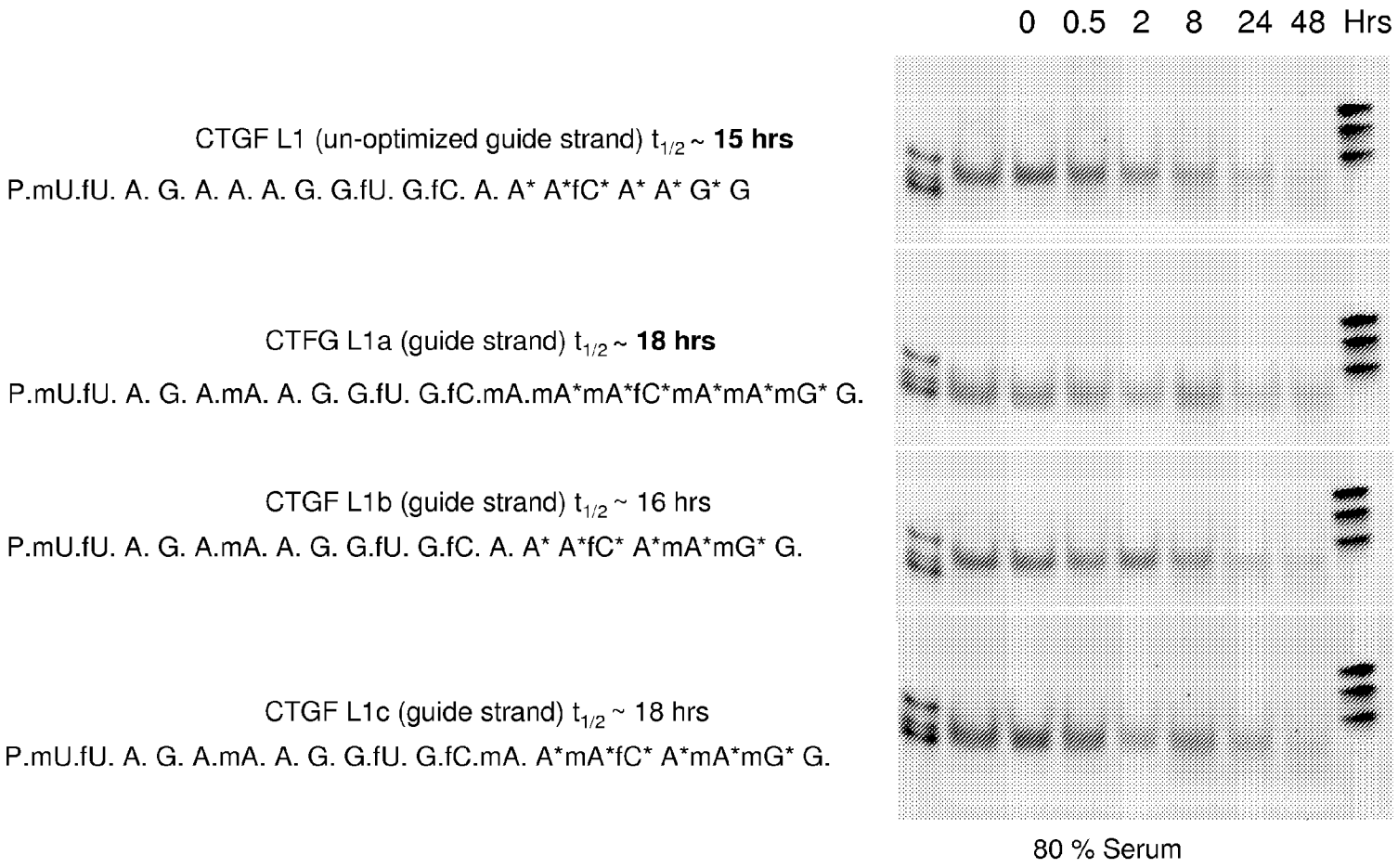
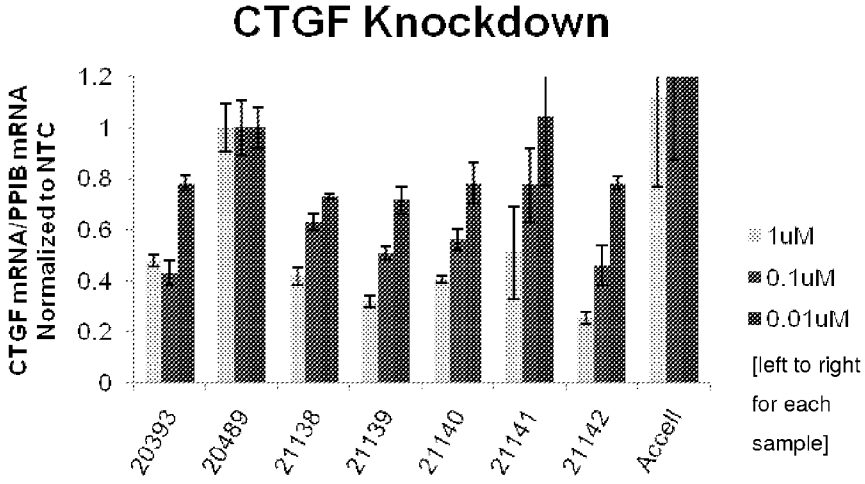
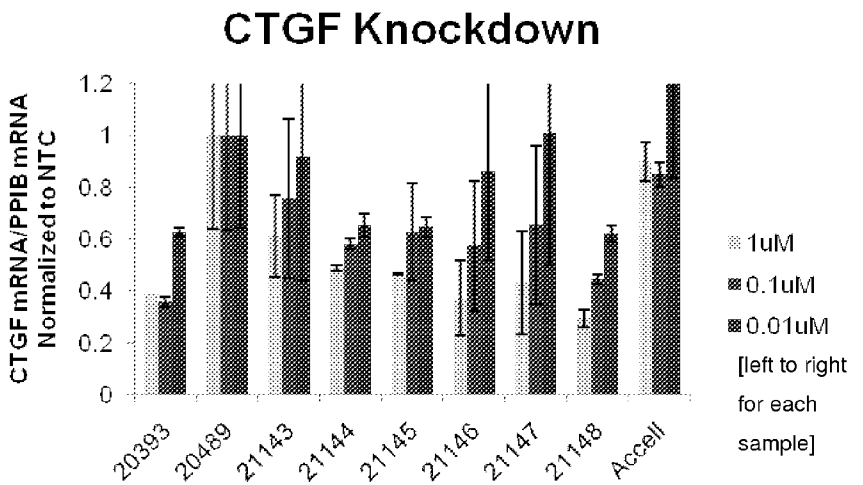


Figure 36

CTGF L2 Chemical Optimization



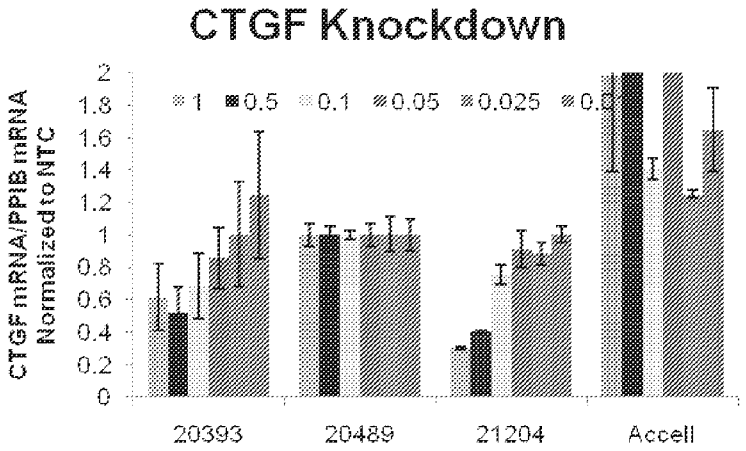
21138	P.mU.fC.fU.A.G.A.mA.A.G.G.fU.G.mC*A*A*A*mC*A*U
21139	P.mU.fC.fU.A.G.mA.A.mA.G.G.fU.G.mC*A*A*A*mC*A*U
21140	P.mU.fC.fU.A.G.A.A.A.G.G.fU.G.mC*A*mA*A*mC*A*U
21141	P.mU.fC.fU.A.G.A.mA.A.G.G.fU.G.mC*A*mA*A*mC*A*U
21142	P.mU.fC.fU.A.G.mA.A.mA.G.G.fU.G.mC*A*mA*A*mC*A*U

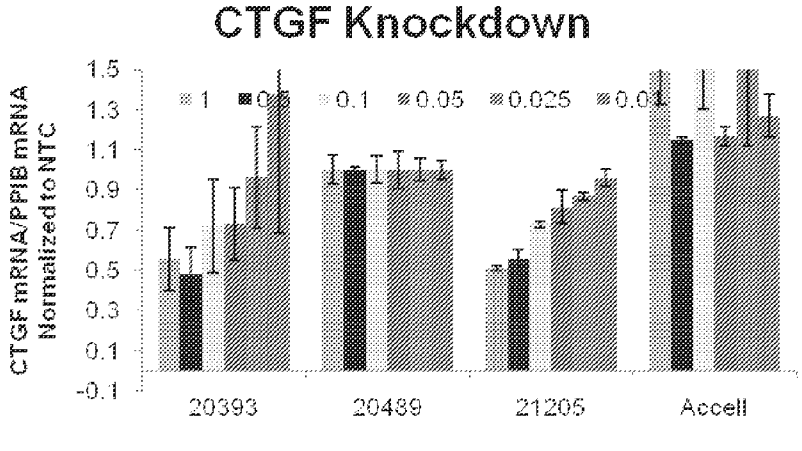


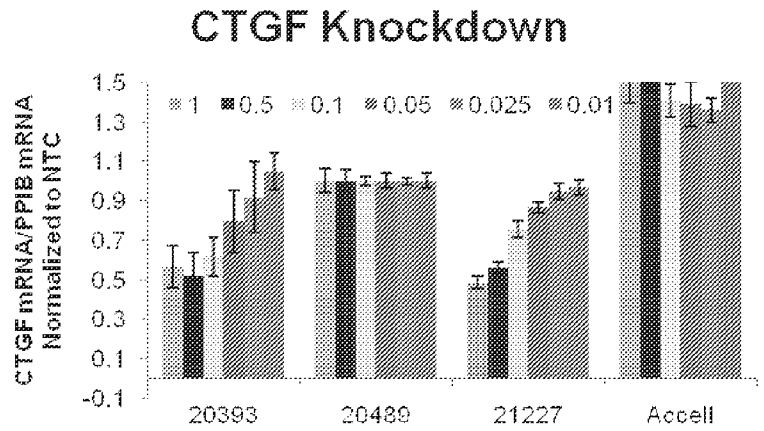
21143	P.mU.fC.fU.A.G.A.A.A.G.G.fU.G.fC*mA*mA*mA*fC*mA*U
21144	P.mU.fC.fU.A.G.A.mA.A.G.G.fU.G.fC*mA*mA*mA*fC*mA*U
21145	P.mU.fC.fU.A.G.mA.A.mA.G.G.fU.G.fC*mA*mA*mA*fC*mA*U
21146	G.mC. A.mC.mC.mU.mU.mU.mC.mU. A*mG*mA-TEG-Chl
21147	mG*mC* A.mC.mC.mU.mU.mU.mC.mU. A*mG*mA-TEG-Chl
21148	mG.mC.mA.mC.mC.mU.mU.mU.mC.mU.mA*mG*mA-TEG-Chl

Figure 37

CTGF L2 Chemical Optimization (*in vitro* Efficacy)







L2a	**21204**	G.mC. A.mC.mC.mU.mU.mU.mC.mU. A*mG*mA-TEG-Chl
		P.mU.**f**C.fU.A.G.mA.A.mA.G.G.**f**U.G.mC*A*A*A*mC*A*U
L2b	21205	G.mC. A.mC.mC.mU.mU.mU.mC.mU. A*mG*mA-TEG-Chl
		P.mU.**f**C.fU.A.G.mA.A.mA.G.G.**f**U.G.mC*A*mA*A*mC*A*U
L2c	21227	G.mC. A.mC.mC.mU.mU.mU.mC.mU. A*mG*mA-TEG-Chl
		P.mU.**f**C.fU.A.G.mA.A.mA.G.G.**f**U.G.**f**C*mA*mA*mA*fC*mA*U

Figure 38

CTGF L2 Chemical Optimization (*in vitro* Stability)

CTGF L2 (unoptimized guide strand) $t_{1/2}$ ~ **17 Hrs**

P.mU.fC.fU. A. G. A. A. A. G. G.fU. G.fC* A* A* A*fC* A* U.

CTFG L2a (guide strand) $t_{1/2}$ ~ 21 Hrs

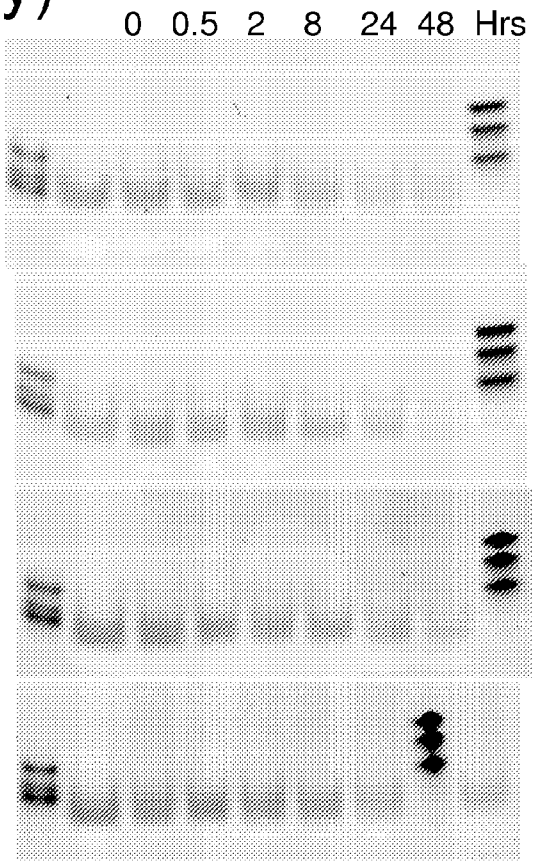
P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A* A* A*mC* A* U.

CTGF L2b (guide strand) $t_{1/2}$ ~ 20 Hrs

P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.mC* A*mA* A*mC* A* U.

CTGF L2c (guide strand) $t_{1/2}$ ~ **30 Hrs**

P.mU.fC.fU. A. G.mA. A.mA. G. G.fU. G.fC*mA*mA*mA*fC*mA* U.



80 % Serum

Figure 39

Summary of in vivo active compounds

Gene ID	Accession number	Duplex ID	Ref Site	Passenger Strand Sequence	Guide Strand Sequence	% Reduction *in vivo*	Notes
CTGF	NM_001901.2	17384	2275	GUGACCAAAAGUA	UACUUUUGGUCACACUCUC	52%	single 600 ug injection
CTGF	NM_001901.2	21204	2296	GCACCUUUCUAGA	UCUAGAAAGGUGCAAACAU	67%	dosed (2) 600 ug 48 hours apart, silencing observed 5 days after last injection
CTGF	NM_001901.2	21214	2295	UUGCACCUUUCUAA	UUAGAAAGGUGCAAACAAGG	90%	single 600 ug injection
CTGF	NM_001901.2	17385	2277	GACCAAAAGUUAA	UUAACUUUUGGUCACACUC	50%	single 600 ug injection
CTGF	NM_001901.2	17387	2299	CCUUUCUAGUUGA	UCAACUAGAAAGGUGCAAA	73%	single 600 ug injection
rTGFB2	NM_001135599.1	18935	1660	CGGUGACAAUGAA	UUCAUUGUCACCGUGAUUU	57%	single 600 ug injection
rTGFB2	NM_001135599.1	18940	1654	AAAUCACGGUGAA	UUCACCGUGAUUUUCAUCC	29%	single 600 ug injection
rTGFB2	NM_001135599.1	18947	2056	UAUUGCUCUGCAA	UUGCAGAGCAAUACAGAGG	50%	single 600 ug injection
rTGFB1	NM_021578.2	20164	522	CACACAGUAUAUA	UAUAUACUGUGUGUGAUGU	38%	single 600 ug injection
PTGS2	NM_000963.2	17393	448	GAUCACAUUUGAA	UUCAAAUGUGAUCUGGAUG	77%	single 600 ug injection
PTGS2	NM_000963.2	17408	449	GAUCACAUUUGAUA	UAUCAAAUGUGAUCUGGAU	81%	single 600 ug injection

Figure 40

Treatment with CTGF Lead 1B Resulted in mRNA Silencing

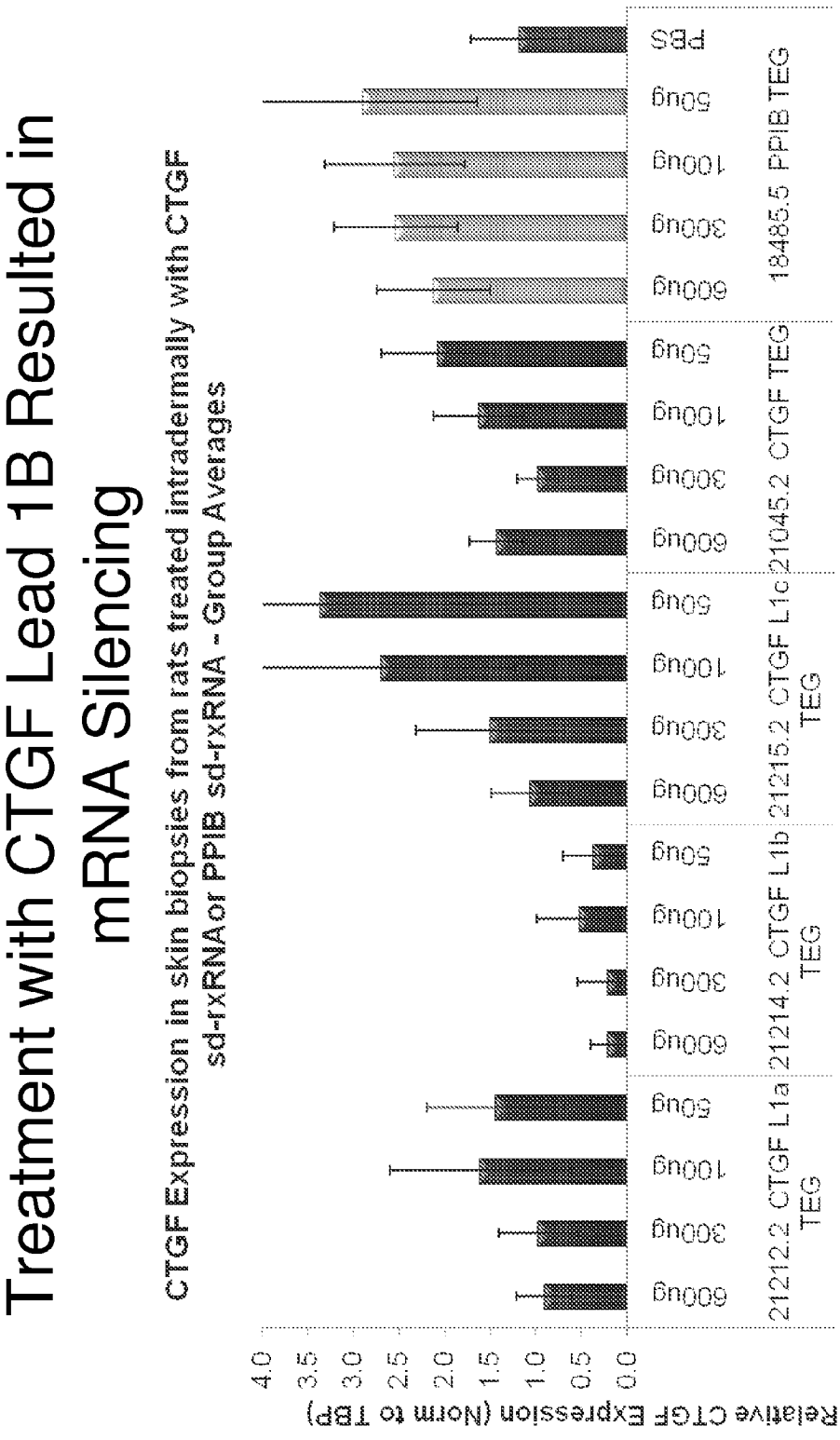
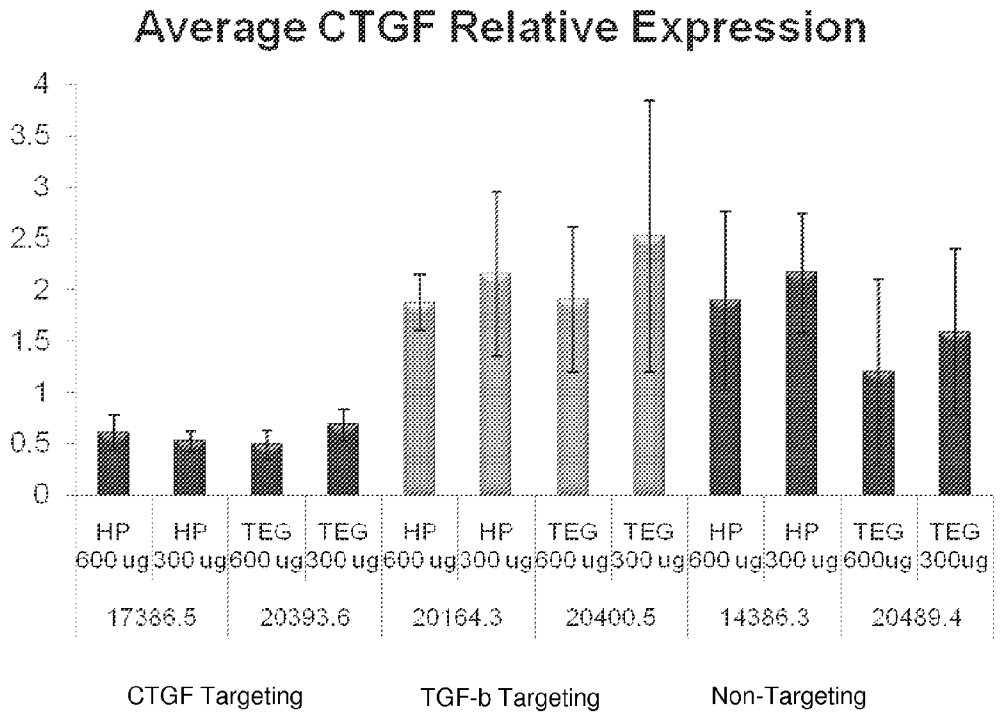
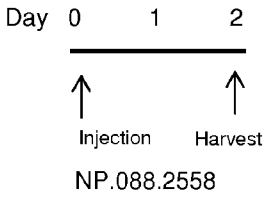


Figure 41

Treatment with CTGF L2 Target Sequence Results in CTGF mRNA Silencing





NP.088.2558

Figure 42

CTGF Silencing After Two Intradermal Injections of RXi-109

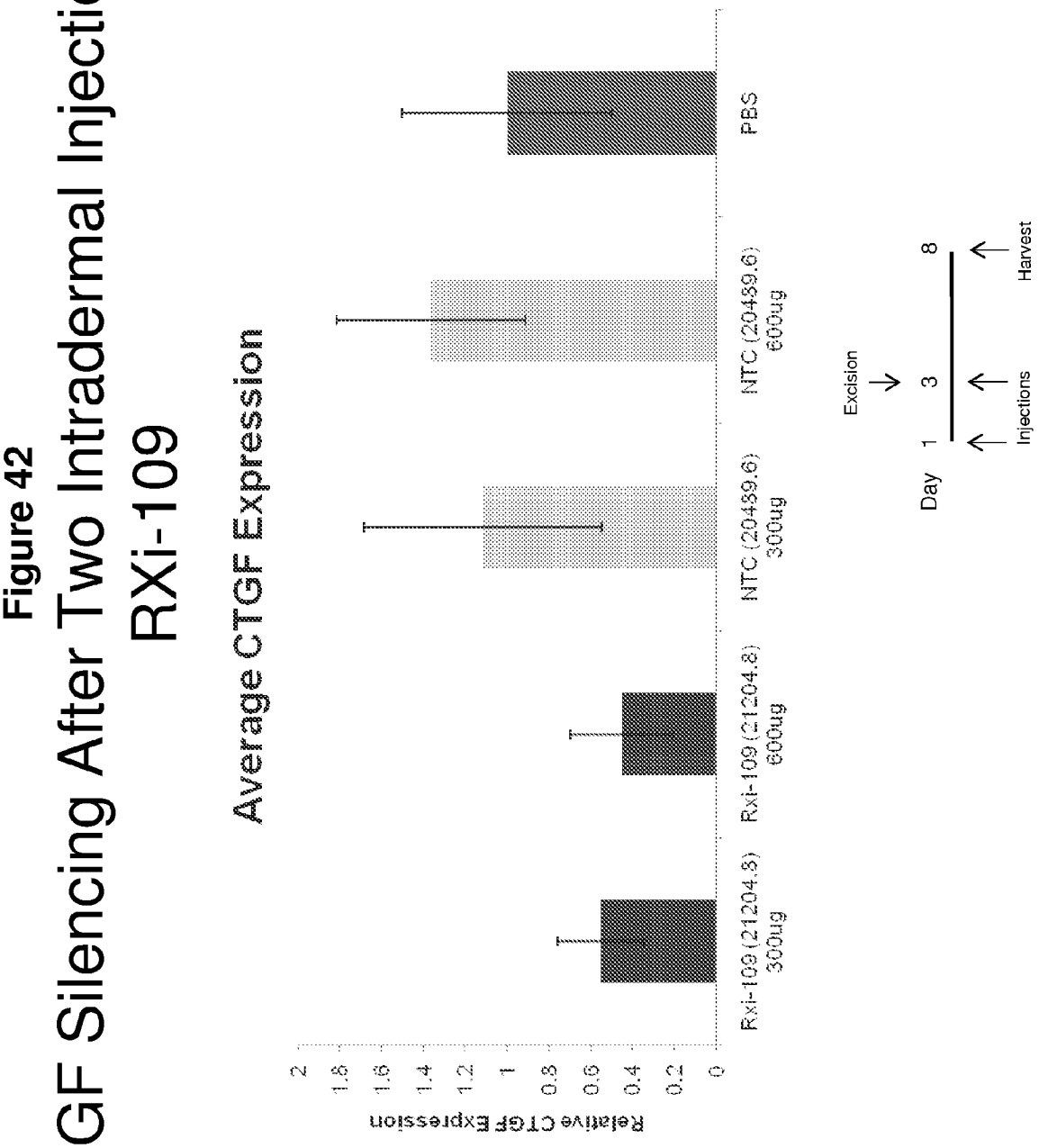


Figure 43

sd-rxRNA: Duration of Silencing in Skin

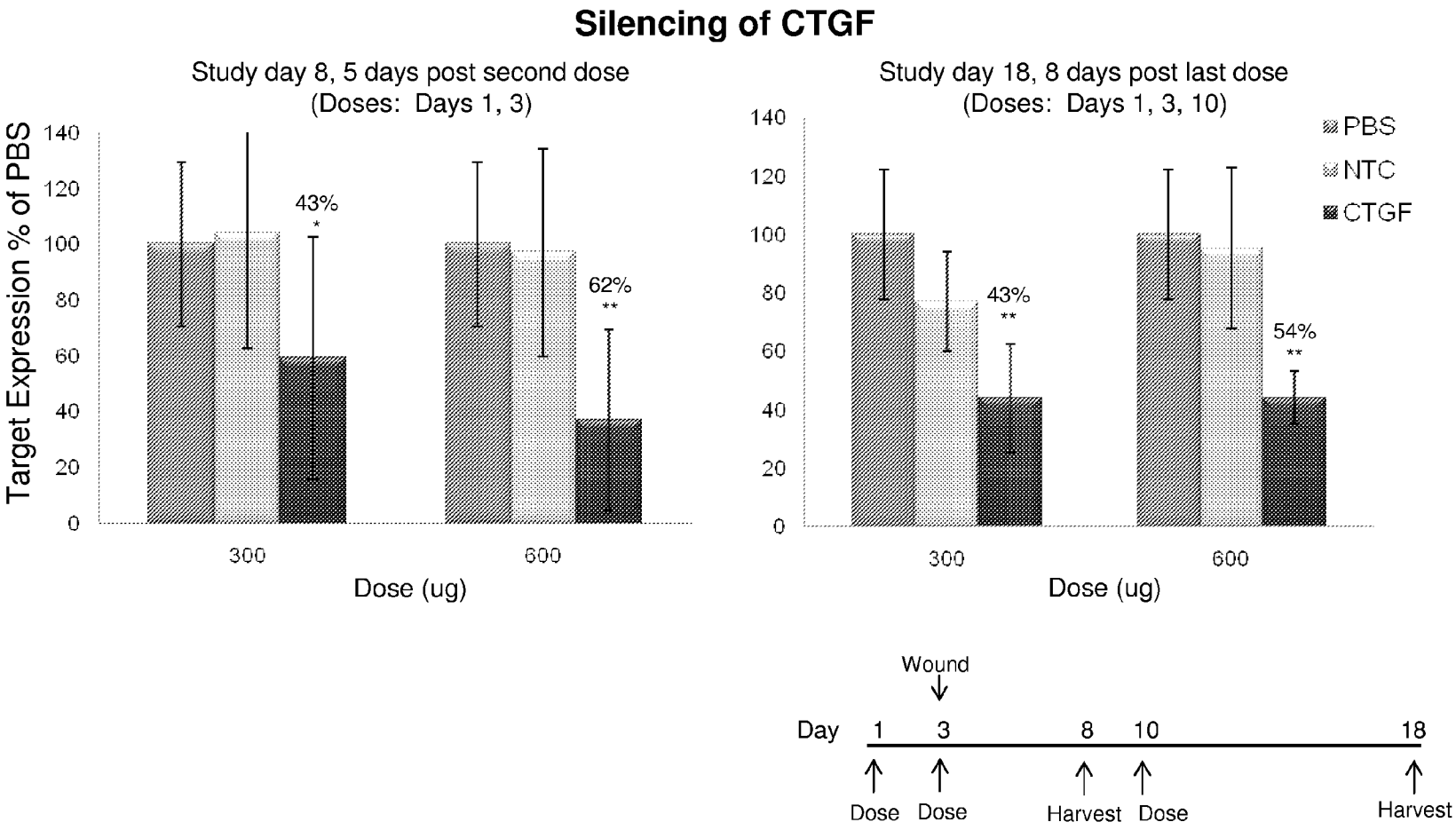
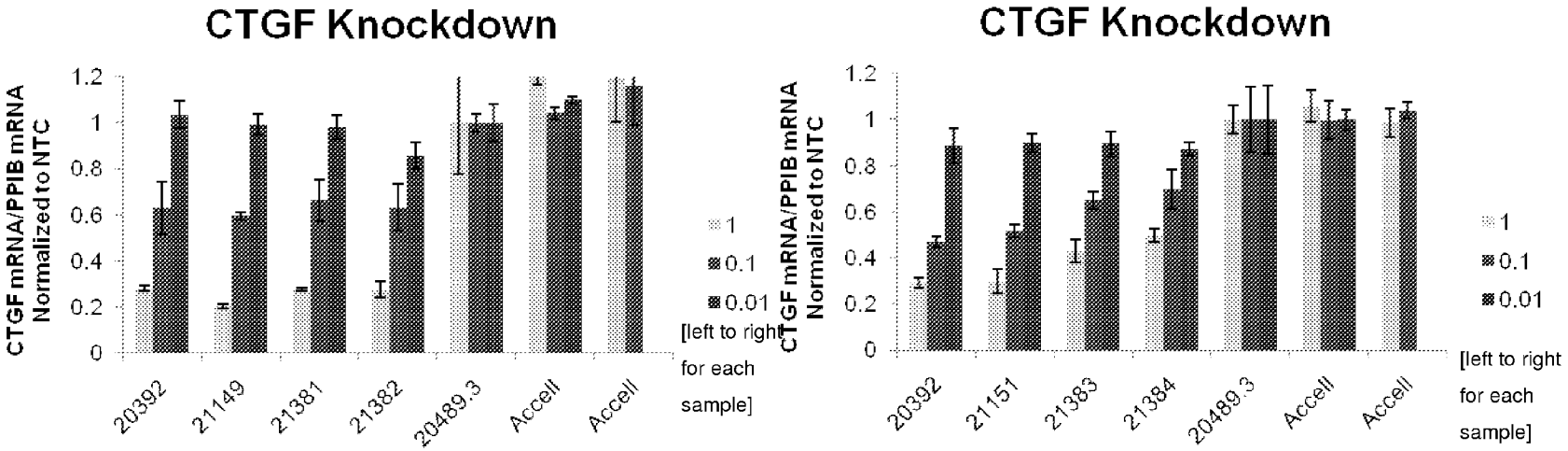


Figure 44

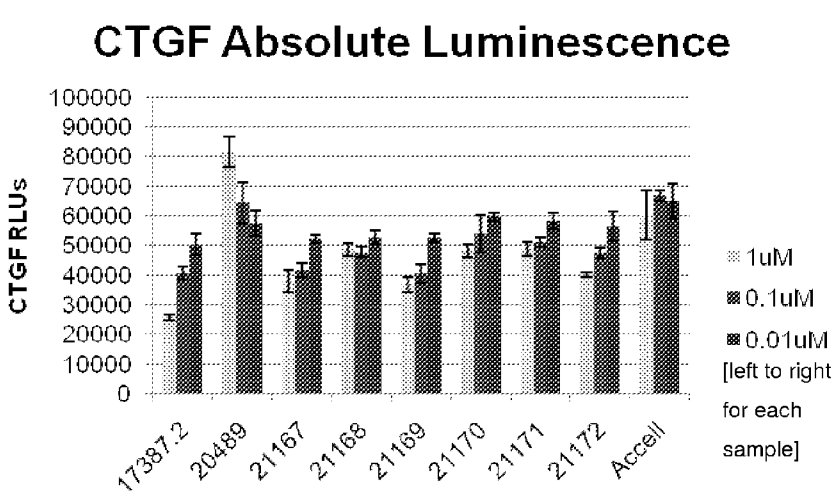
CTGF L3 Chemical Optimization

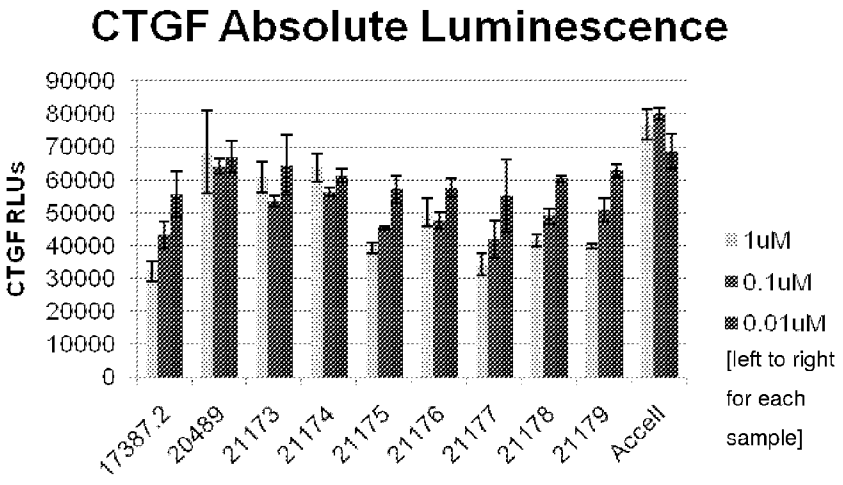


21149 21151	G.mU. G. A.mC.mC. A. A. A. A. G*mU*mA-TEG-Chl mG*mU*mG.mA.mC.mC.mA.mA.mA.mA.mG*mU*mA-TEG-Chl
21381	G.mU. G. A.mC.mC. A. A. A. A. G*mU*mA-TEG-Chl P.mU.A.fC.fU.fU.fU.fU.G.G.fU.mC.A.mC*A*mC*mU*mC*mU*C.
21382	G.mU. G. A.mC.mC. A. A. A. A. G*mU*mA-TEG-Chl P.mU.A.fC.fU.fU.fU.fU.G.G.fU.fC.A.mC*A*fC*mU*fC*mU*C.
21383	mG*mU*mG.mA.mC.mC.mA.mA.mA.mA.mG*mU*mA-TEG-Chl P.mU.A.fC.fU.fU.fU.fU.G.G.fU.mC.A.mC*A*mC*mU*mC*mU*C.
21384	mG*mU*mG.mA.mC.mC.mA.mA.mA.mA.mG*mU*mA-TEG-Chl P.mU.A.fC.fU.fU.fU.fU.G.G.fU.fC.A.mC*A*fC*mU*fC*mU*C.

Figure 45

CTGF L4 Chemical Optimization





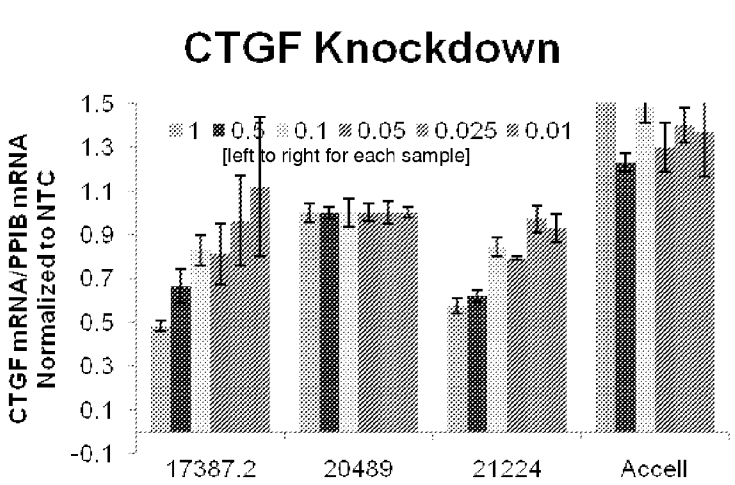
21167	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU* G*fC* A* A* A
21168	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*mU* G*mC* A* A* A
21169	P.mU.fC. A. A.fC.fU. A. G.mA. A. A.mG. G*fU* G*fC* A* A* A
21170	P.mU.fC. A. A.fC.fU. A. G.mA. A. A.mG. G*mU* G*mC* A* A* A
21171	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*mU* G*mC* A*mA* A
21172	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*mU* G*mC*mA*mA* A

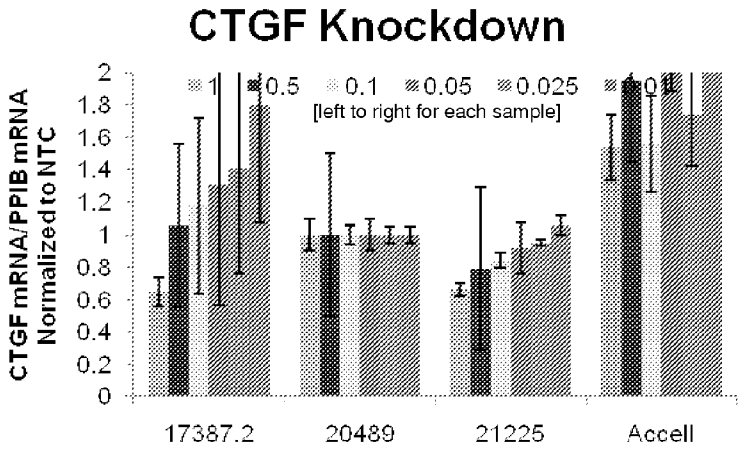
21173	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G.mG*mU*mG*mC*mA*mA* A
21174	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*mU*mG*mC*mA*mA* A
21175	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU*mG*fC*mA*mA* A
21176	P.mU.fC. A. A.fC.fU. A. G.mA. A. A.mG. G*fU*mG*fC*mA*mA* A

21177	mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU* mG*mA-TEG-Chl
21178	mC*mC*mU.mU.mU.mC.mU. A. G.mU.mU* mG*mA-TEG-Chl
21179	mC*mC*mU.mU.mU.mC.mU.mA.mG.mU.mU* mG*mA-TEG-Chl

Figure 46

CTGF L4 Chemical Optimization





21224	mC.mC.mU.mU.mU.mC.mU. A. G.mU.mU* mG*mA-TEG-Chl
	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU*mG*fC*mA*mA* A
21225	mC*mC*mU.mU.mU.mC.mU. A. G.mU.mU* mG*mA-TEG-Chl
	P.mU.fC. A. A.fC.fU. A. G. A.mA. A. G. G*fU*mG*fC*mA*mA* A

Figure 47

CTGF Silencing Reduces Myofibroblast Numbers and Collagen Deposition

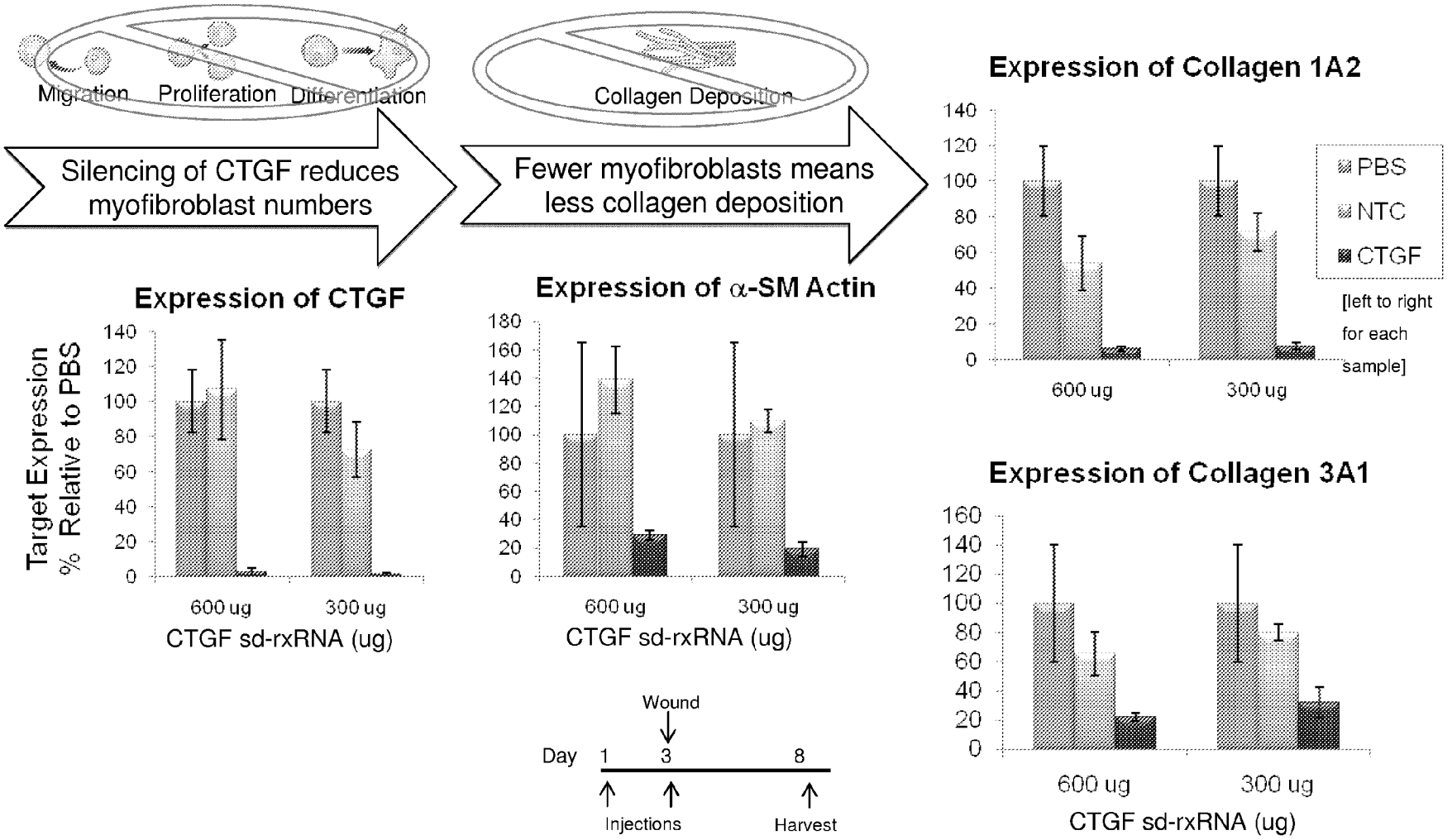
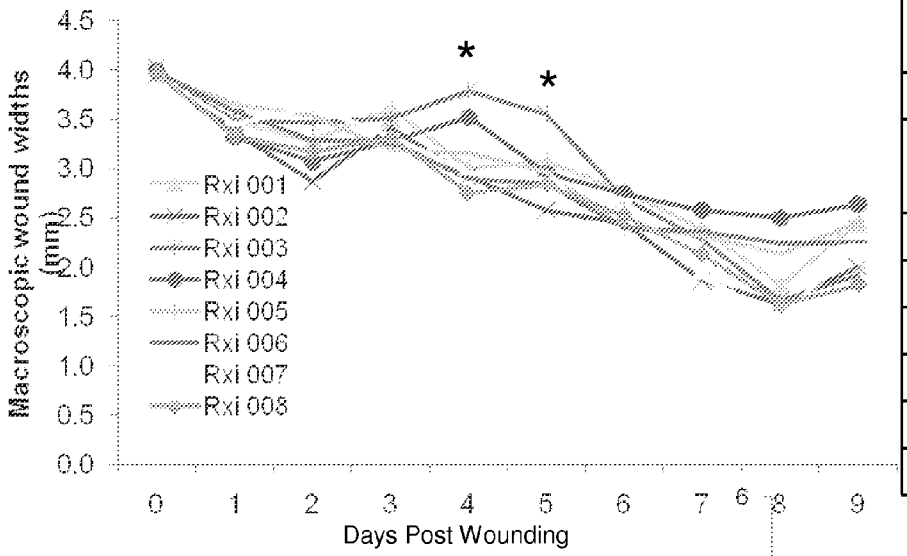


Figure 48

Epistem: Macroscopic Measure of Wound Healing



sd-rxRNA Duplex ID	Label	Gene Target
20393.6	RXi 001	CTGF (L2)
17376.2	RXi 002	CTGF (L1)(1.575 mg/mL)
20394.5	RXi 003	Cox2
20393.5/20394.5	RXi 004	CTGF/Cox2
20400.4	RXi 005	TGFB1
20396.3	RXi 006	TGFB2
20489.3	RXi 007	NTC (Luc)
PBS +/+	RXi 008	

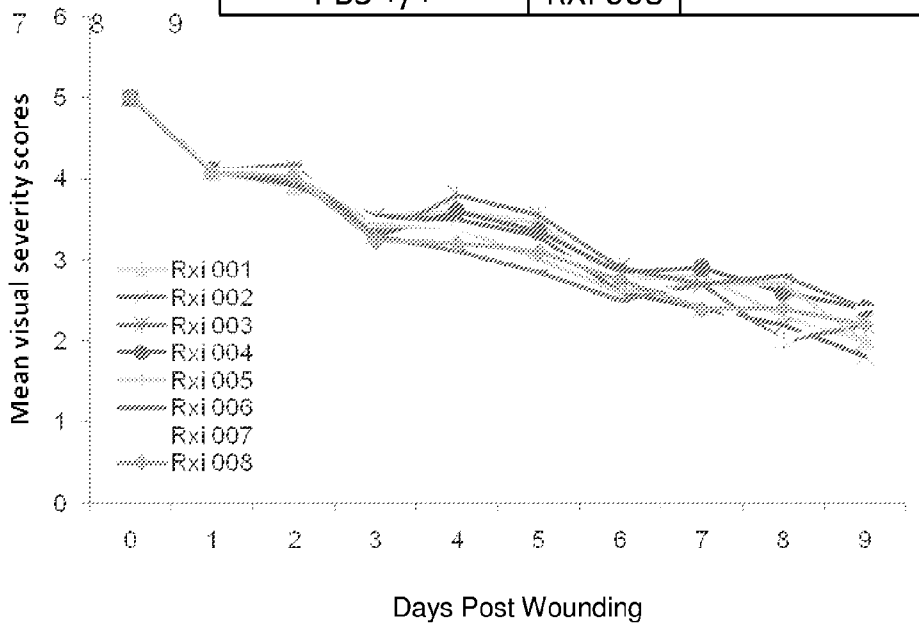
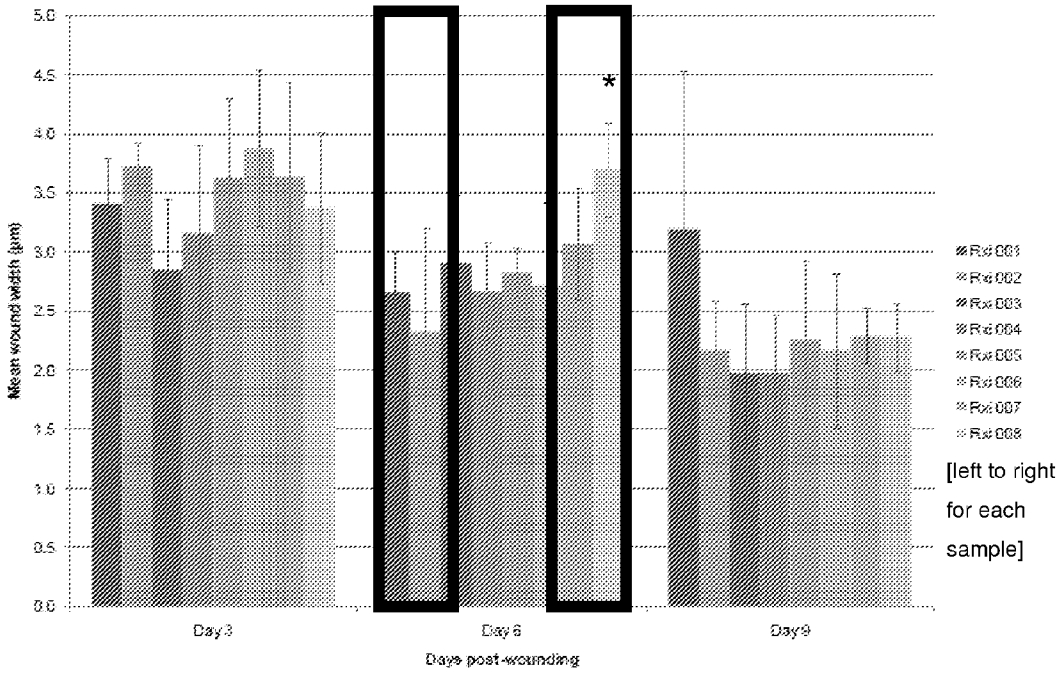


Figure 49

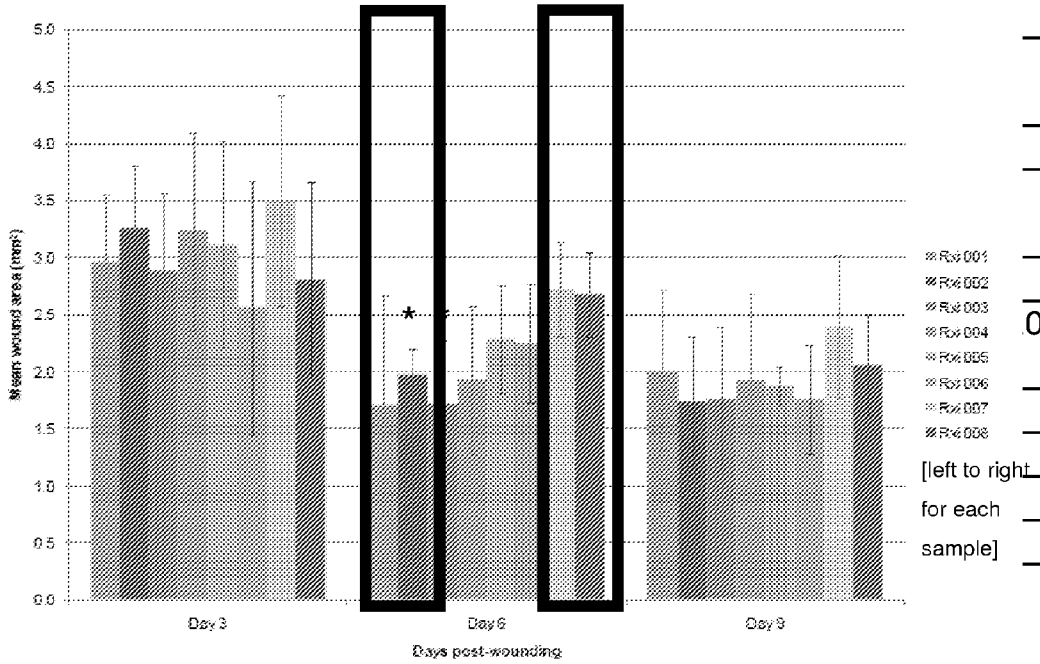
Epistem: Microscopic Wound Width Data



sd-rxRNA Duplex ID	Label	Gene Target
20393.6	RXi 001	CTGF
17376.2	RXi 002	CTGF (1.575 mg/mL)
20394.5	RXi 003	Cox2
20393.5/20394.5	RXi 004	CTGF/Cox2
20400.4	RXi 005	TGFB1
20396.3	RXi 006	TGFB2
20489.3	RXi 007	NTC (Luc)
PBS +/+	RXi 008	

Figure 50

Epistem: Microscopic Wound Area Data



[left to right for each sample]

sd-rxRNA Duplex ID	Label	Gene Target
20393.6	RXi 001	CTGF
17376.2	RXi 002	CTGF (1.575 mg/mL)
20394.5	RXi 003	Cox2
0393.5/20394.5	RXi 004	CTGF/Cox2
20400.4	RXi 005	TGFB1
20396.3	RXi 006	TGFB2
20489.3	RXi 007	NTC (Luc)
PBS +/+	RXi 008	

Figure 51

Epistem: Microscopic Re-epithelialization Data

sd-rxRNA Duplex ID	Label	Gene Target
20393.6	RXi 001	CTGF
17376.2	RXi 002	CTGF (1.575 mg/mL)
20394.5	RXi 003	Cox2
20393.5/20394.5	RXi 004	CTGF/Cox2
20400.4	RXi 005	TGFB1
20396.3	RXi 006	TGFB2
20489.3	RXi 007	NTC (Luc)
PBS +/+	RXi 008	

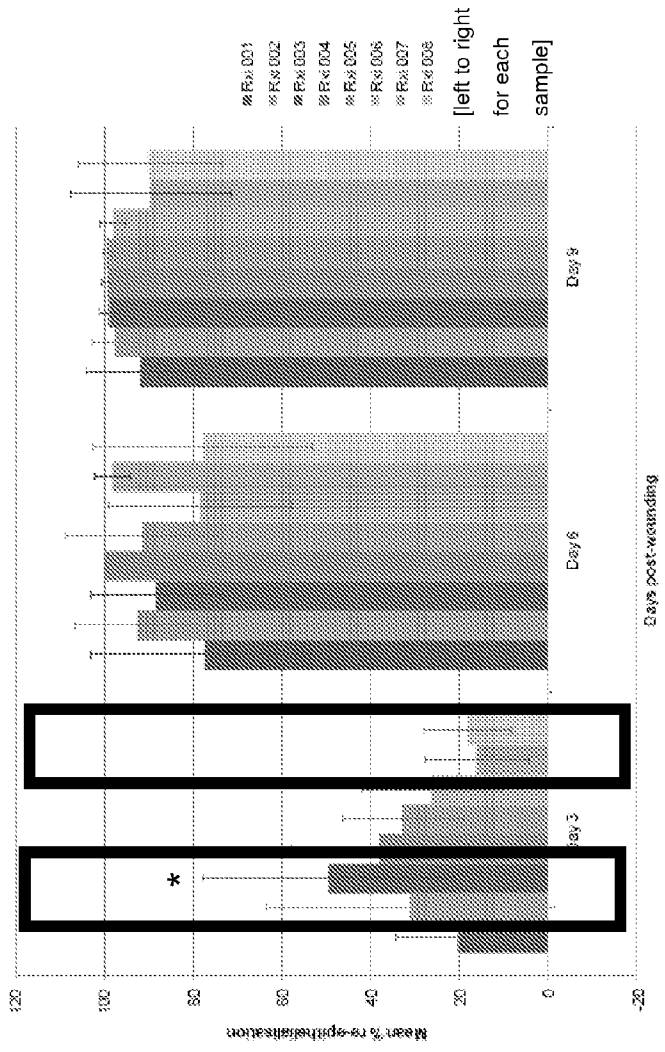
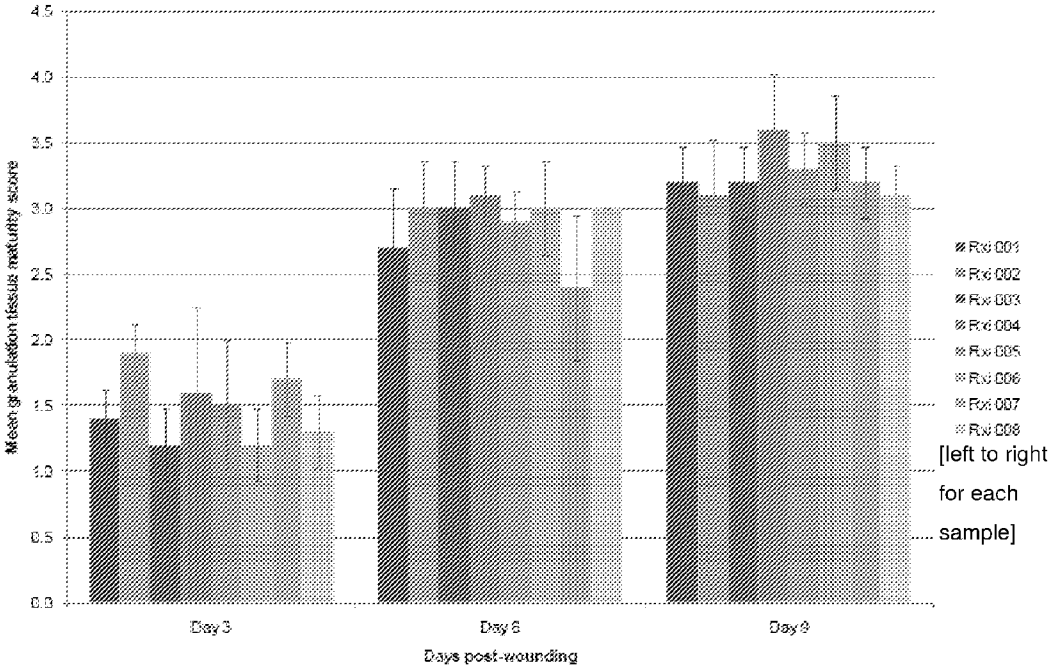


Figure 52

Epistem: Microscopic Granulation Tissue Maturity Scores



sd-rxRNA Duplex ID	Label	Gene Target
20393.6	RXi 001	CTGF
17376.2	RXi 002	CTGF (1.575 mg/mL)
20394.5	RXi 003	Cox2
20393.5/20394.5	RXi 004	CTGF/Cox2
20400.4	RXi 005	TGFB1
20396.3	RXi 006	TGFB2
20489.3	RXi 007	NTC (Luc)
PBS +/+	RXi 008	

Figure 53

Epistem: CD68 (Macrophage Marker) Immunohistochemistry

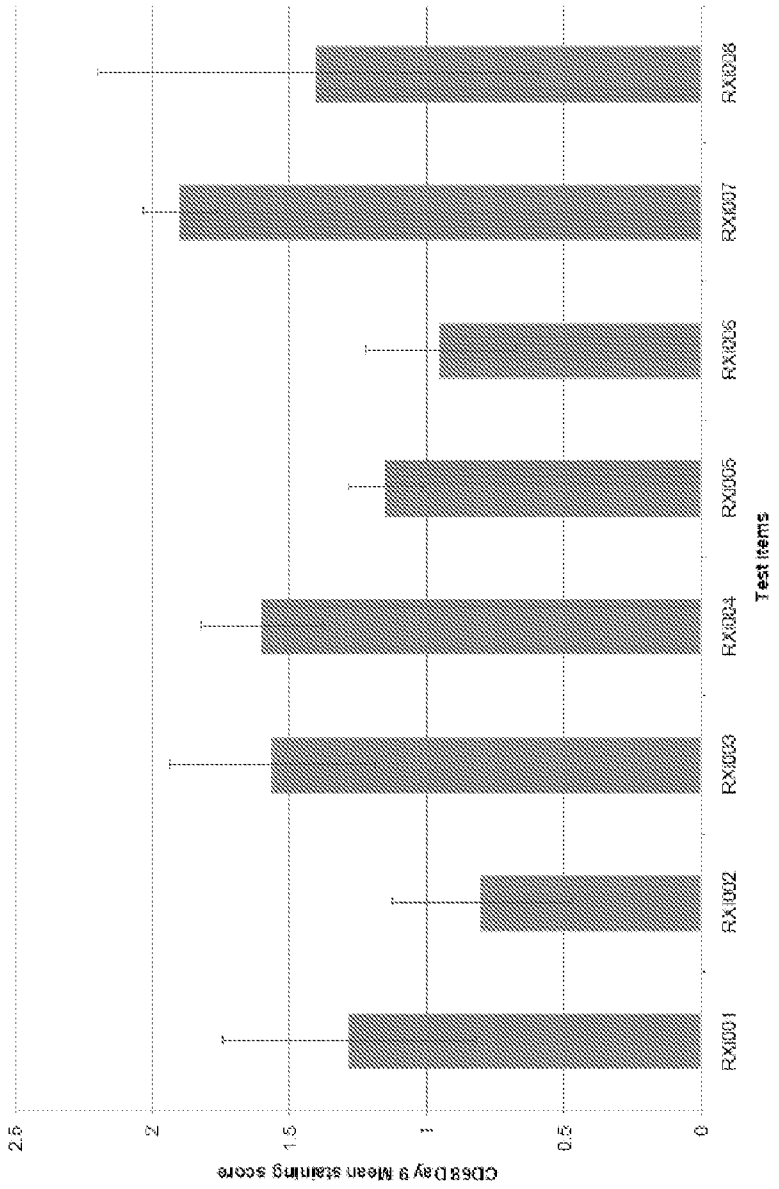
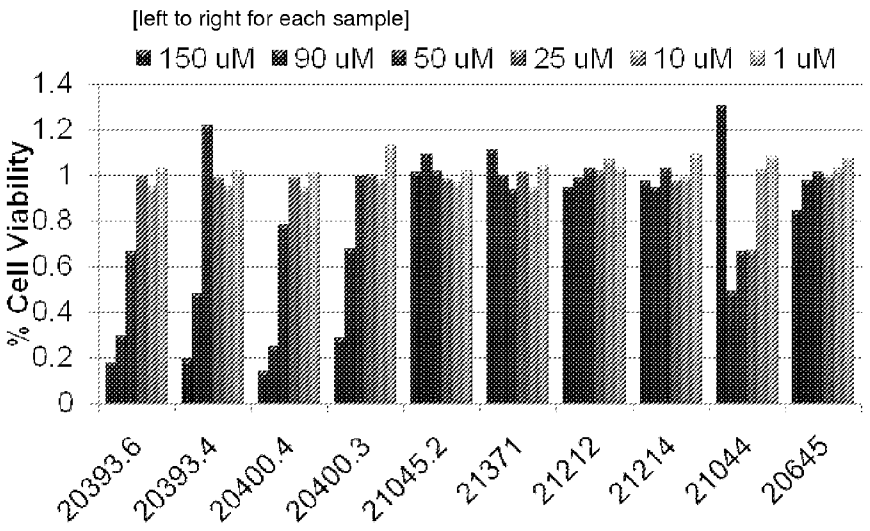
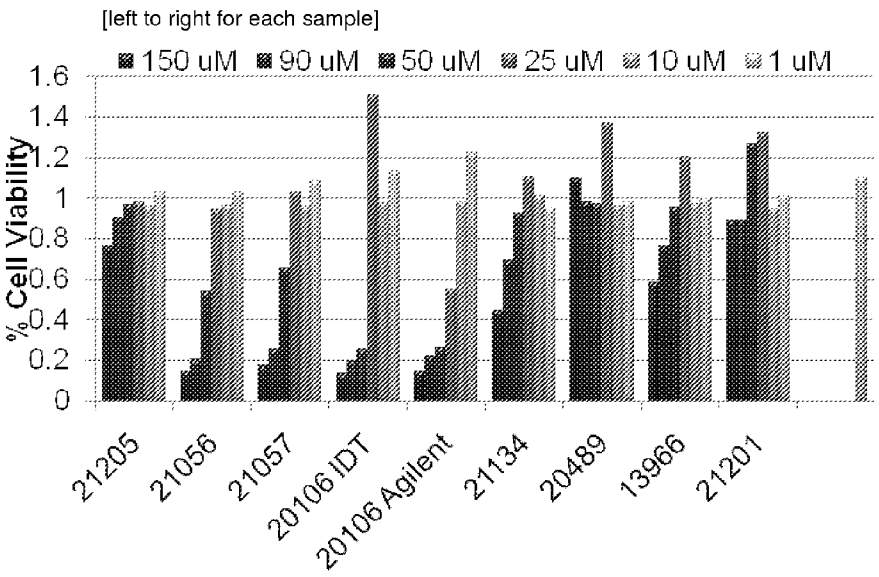


Figure 54

CTGF Leads have Different Toxicity Levels *in vitro*



Oligo ID	Description
20393.6	Agilent purified
20393.4	Agilent not purified
20400.4	Agilent purified
20400.3	Agilent not purified
21045.2	CTGF L1
21371	CTGF L1 most stable
21212	CTGF L1a stabilized
21214	CTGF L1b stabilized
21044	CTGF L1 (stab SS)
20645	CTFG L1 (SS)



Oligo ID	Description
21205	CTGF L2 stabilized
21056	CTGF L2 (2 ribos)
21057	CTGF L2 (stab SS)
20106	CTGF L2 IDT
20106	Agilent
21134	11 2'F NTC
20489	5 2'F NTC
13966	map4k4 5 2'F
21201	map4k4 no 2'F

Figure 55

RXI 109 *in vitro* Dose Escalation – Oligos Formulated in PBS

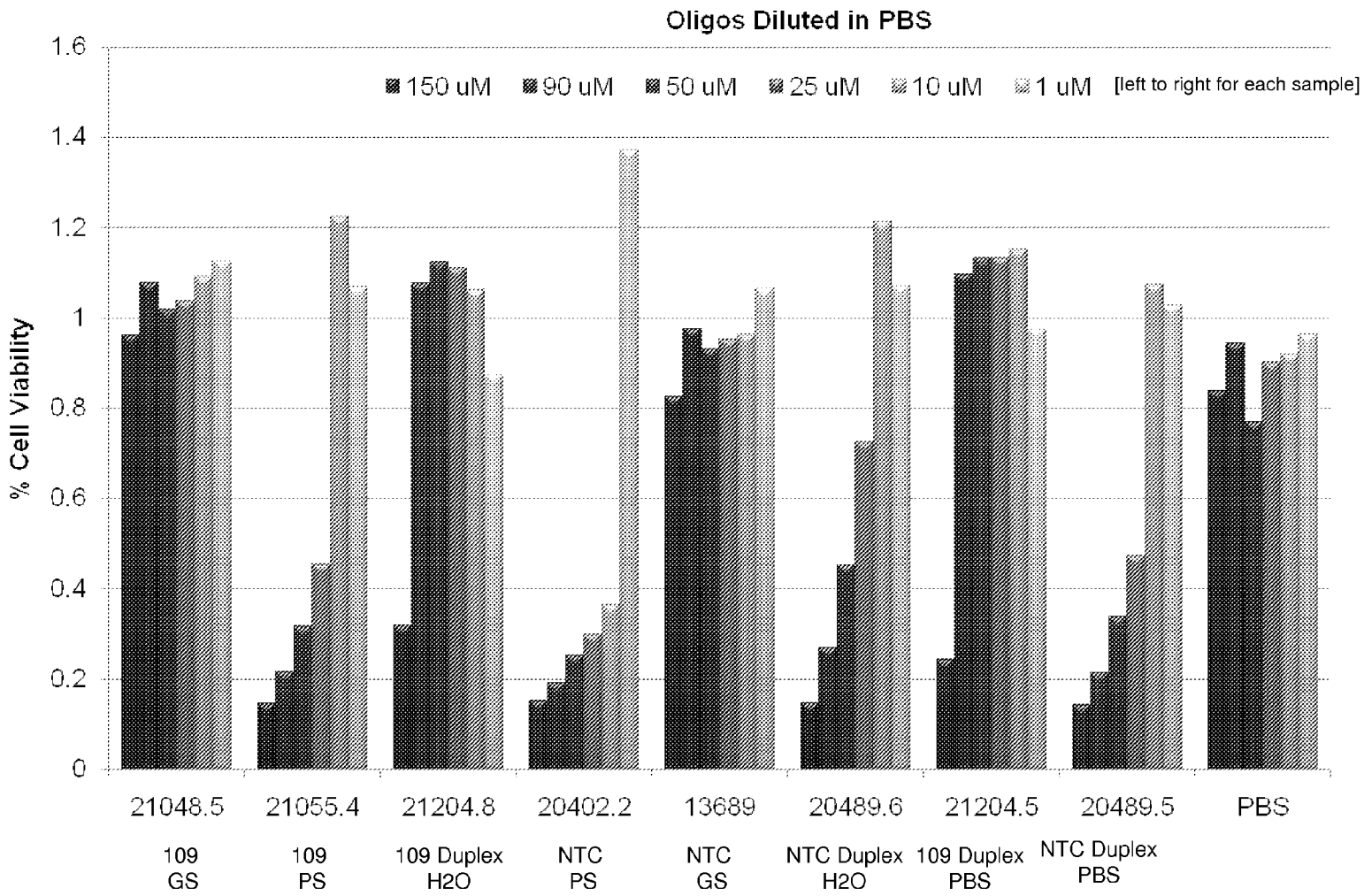
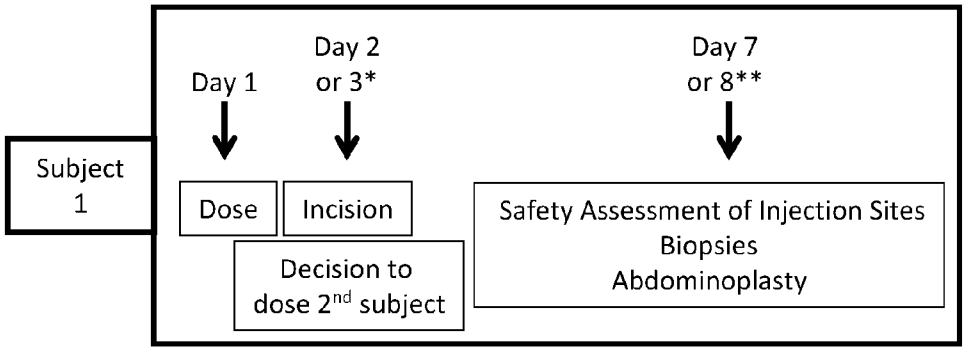


Figure 56

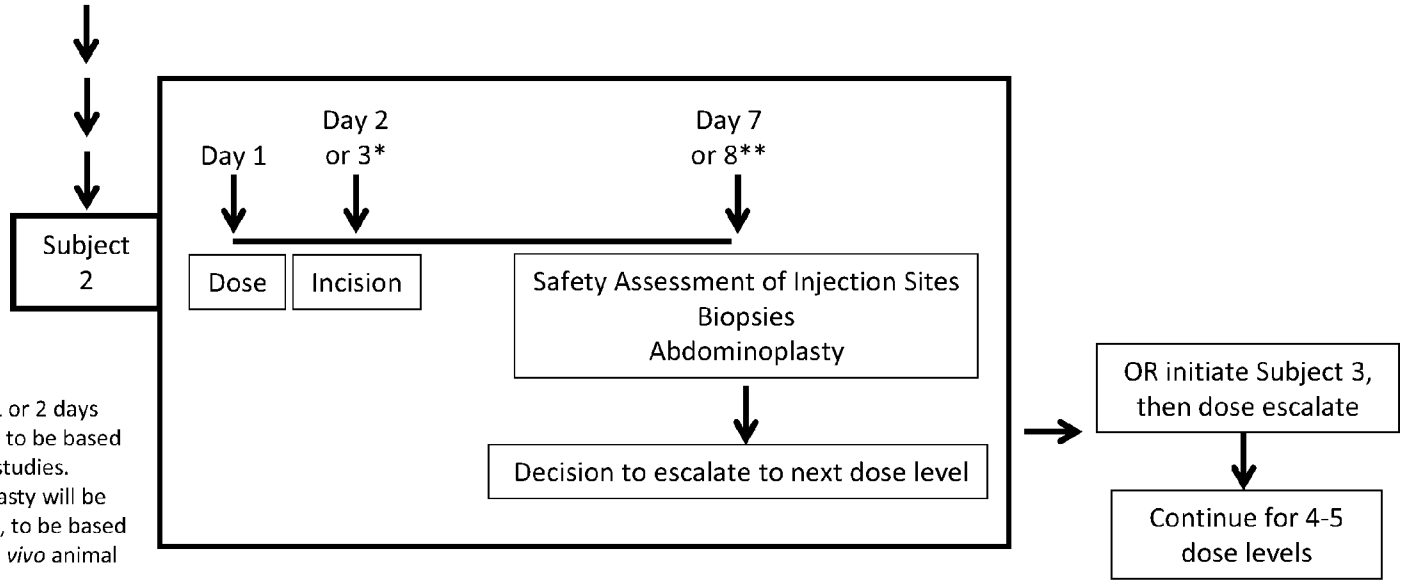
Phase 1/2; Part A: Divided Dose, Single Day Ascending Dose Clinical Trial Design



Day 1:
- 20 sites marked according to the template
- 10 sites injected with active, 10 sites with vehicle

Day 2 (or 3):
- 2 cm incisions made at injection sites (to elicit CTGF)

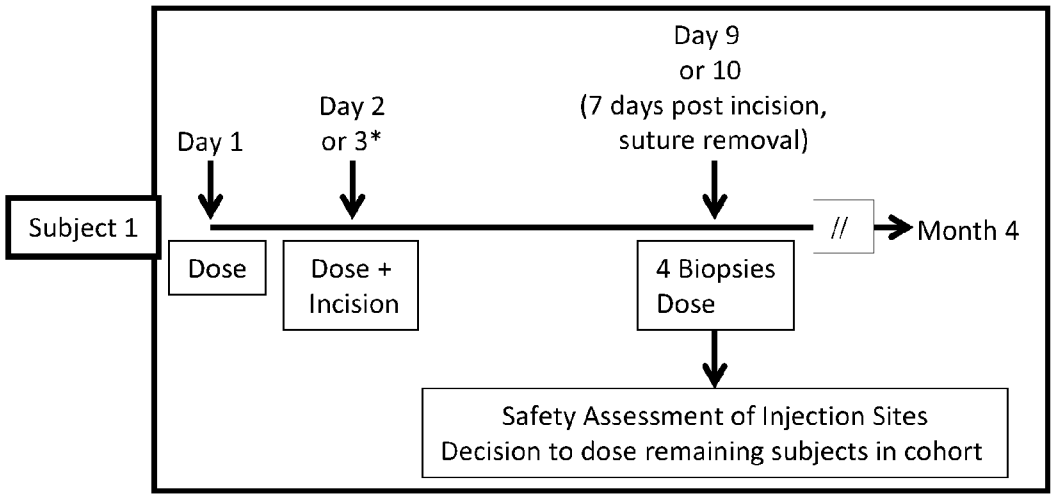
Day 7 (or 8):
- Biopsies for molecular endpoint analysis (CTGF mRNA)
- Abdominoplasty



*Incisions will be made 1 or 2 days post administration of drug, to be based on results of in vivo animal studies.
**Biopsies and abdominoplasty will be done at ~day 5 post incision, to be based on efficacy information in *in vivo* animal studies

Figure 57

Phase 1/2; Part B: Divided Dose, Multi-day Ascending Dose Clinical Trial Design

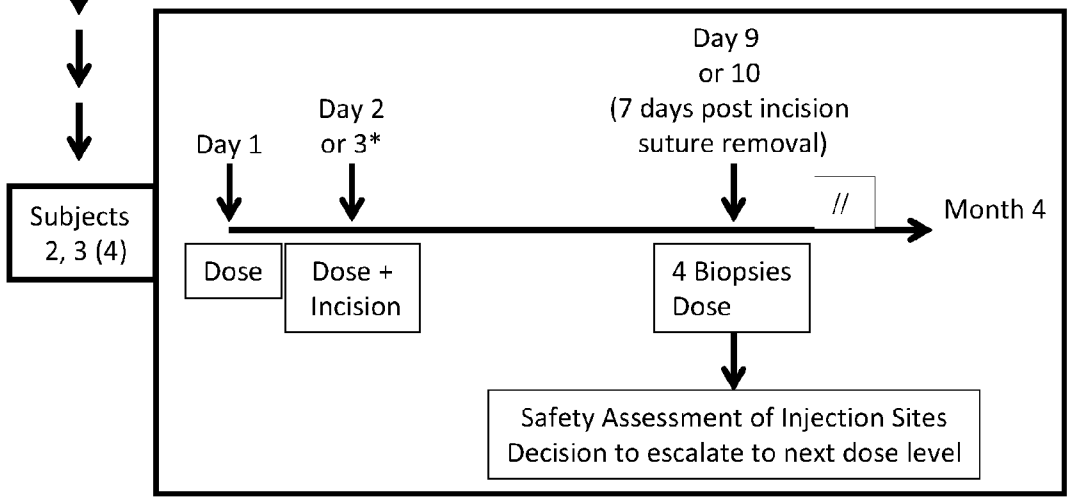


Day 1:
- 20 sites marked according to the template
- 10 sites injected with active, 10 sites with vehicle

Day 2 (or 3):
- 10 sites re-injected with active, 10 sites with vehicle
- 2 cm incisions made at injection sites

Day 9 (or 10):
- Suture removal at all sites
- Biopsies on 4 sites (2 active, 2 vehicle) for molecular endpoint analysis (CTGF mRNA, RACE, etc.)
- 8 sites re-injected with active, 8 sites with vehicle

Month 4:
- Abdominoplasty
- Biopsies on all sites



* Choice of Day 2 or 3 as the 2nd administration day will be based on the safety assessment from Phase 1/2 Part A

Figure 58

Liver Silencing after Systemic Delivery with Lipidoid Formulated rxRNAs

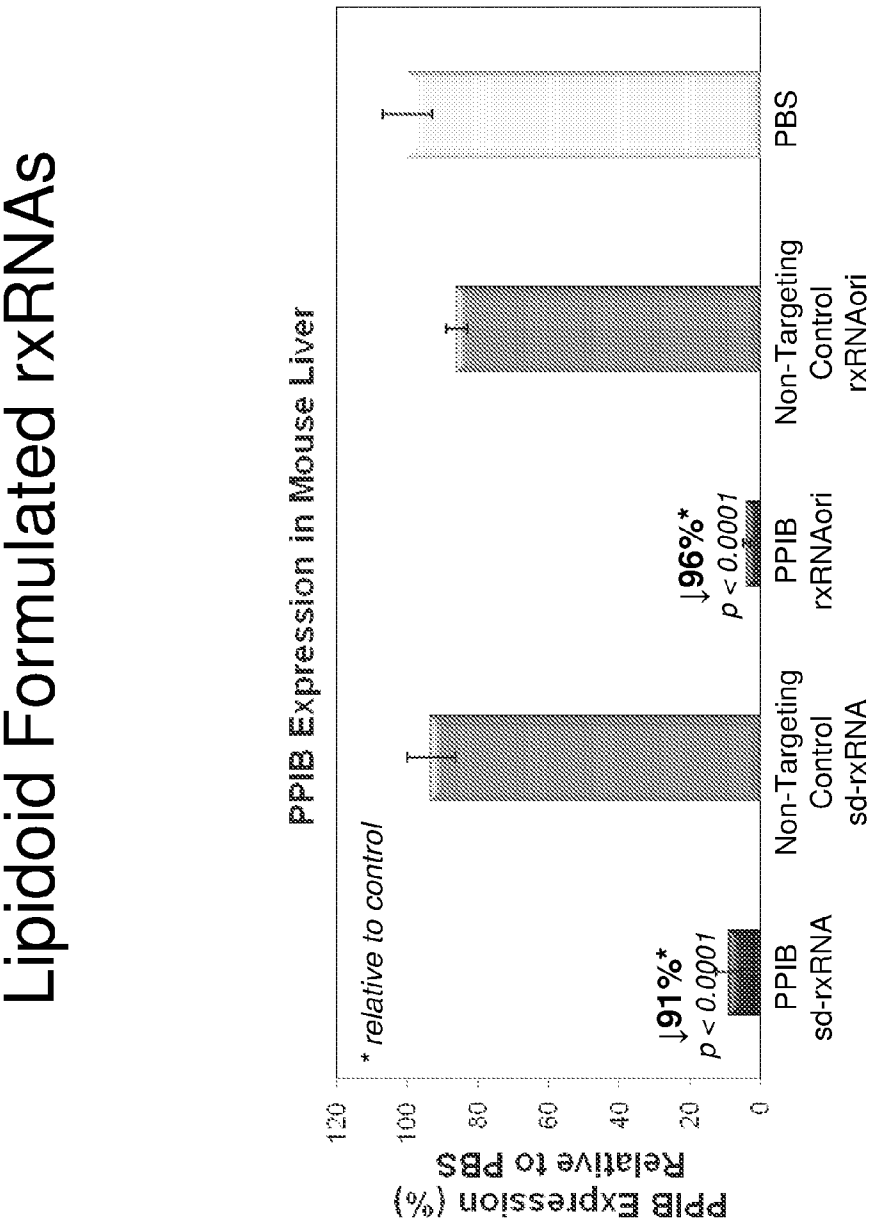
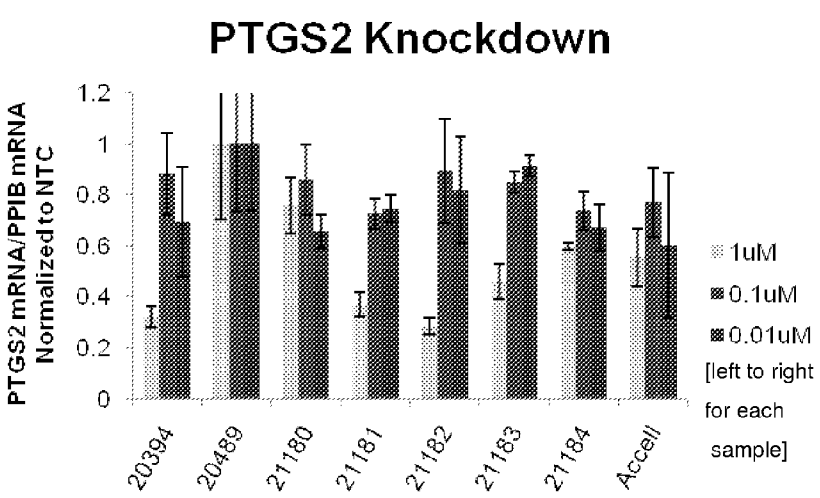
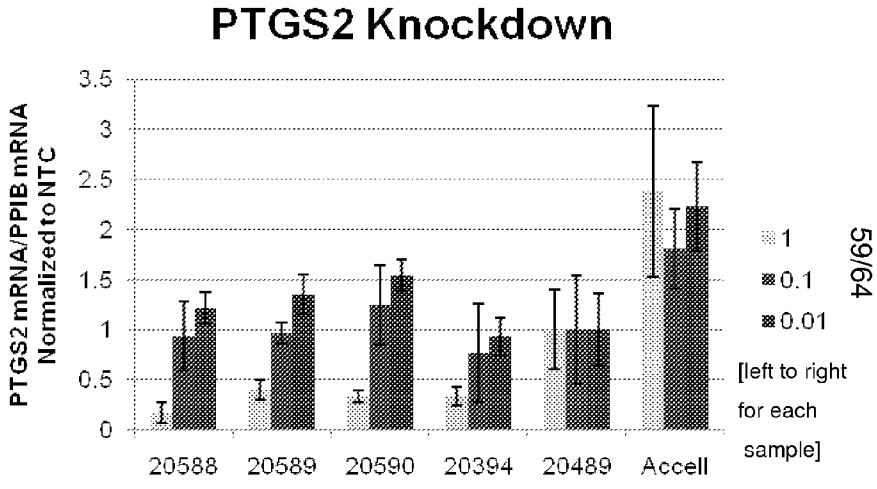


Figure 59

PTGS2 L1 Chemical Optimization



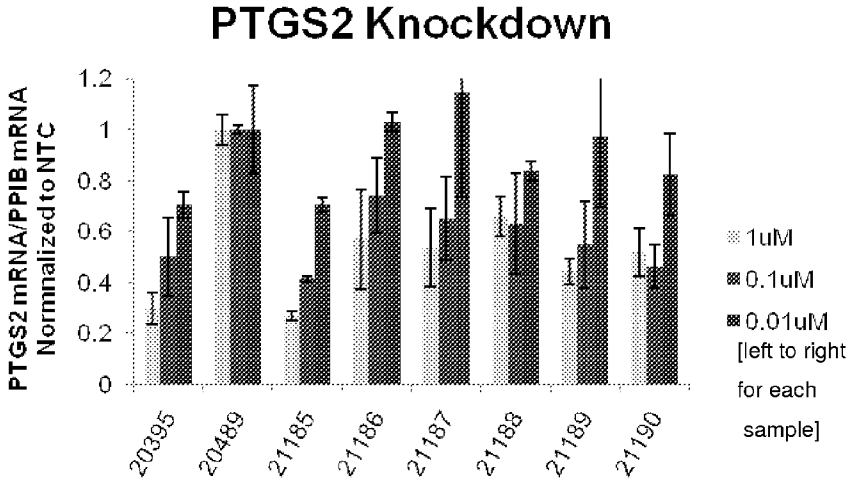


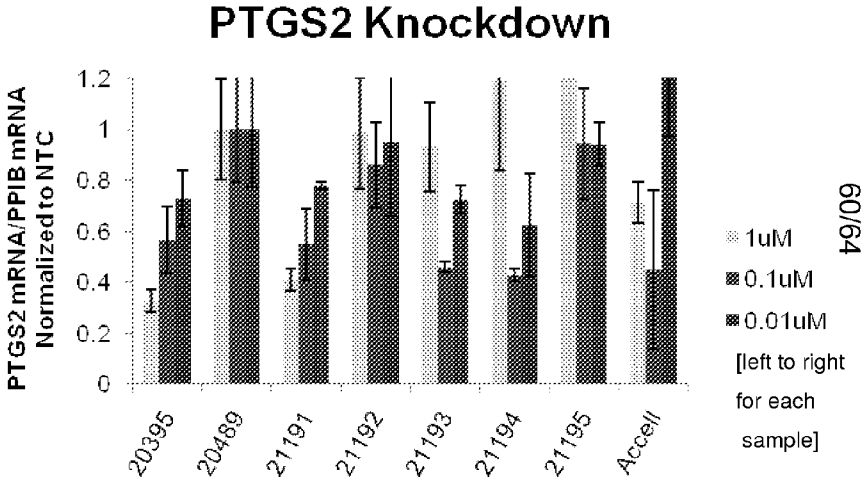
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21181	P.mU.fU.fC.A.mA.A.fU.G.fU.G.A.fU.fC*fU*mG*mG*mA*fU* G
21182	G. A.mU.mC. A.mC. A.mU.mU.mU. G*mA*mA-TEG-Chl
21183	mG*mA*mU.mC. A.mC. A.mU.mU.mU. G*mA*mA-TEG-Chl
21184	mG*mA*mU.mC.mA.mC.mA.mU.mU.mU.mG*mA*mA-TEG-Chl

20588	P.mU.fU.fC.A.A.A.fU.G.fU.G.A.mU.mC*mU*G*G*A*mU*G
20589	P.mU.fU.fC.A.A.A.fU.G.fU.G.A.mU.fC*mU*G*G*A*fU*G
20590	P.mU.U.C.A.A.A.U.G.U.G.A.mU.mC*mU*G*G*A*mU*G

Figure 60

PTGS2 L2 Chemical Optimization



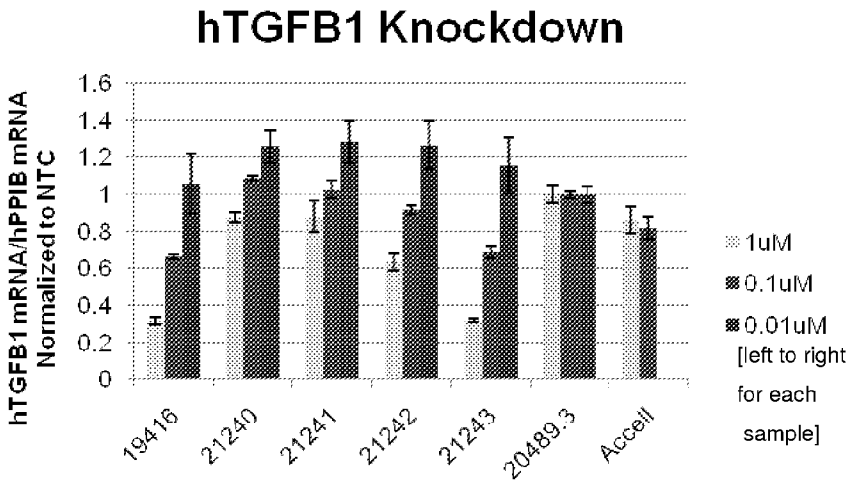


21185	P.mU.A.fU.fC.A.A.A.fU.G.fU.G.A.fU.fC*fU*G*G*A*fU*G
21186	P.mU.A.fU.fC.A.A.A.fU.G.fU.G.A.mU.mC*mU*G*G*A*mU*G
21187	P.mU.A.fU.fC.A.mA.A.fU.G.fU.G.A.mU.mC*mU*G*G*A*mU*G
21188	P.mU.A.fU.fC.A.A.A.fU.G.fU.G.A.mU.mC*mU*mG*mG*mA*mU*G
21189	P.mU.A.fU.fC.A.mA.A.fU.G.fU.G.A.mU.mC*mU*mG*mG*mA*mU*G
21190	P.mU.A.fU.fC.A.A.A.fU.G.fU.G.A.fU.fC*fU*mG*mG*mA*fU*G

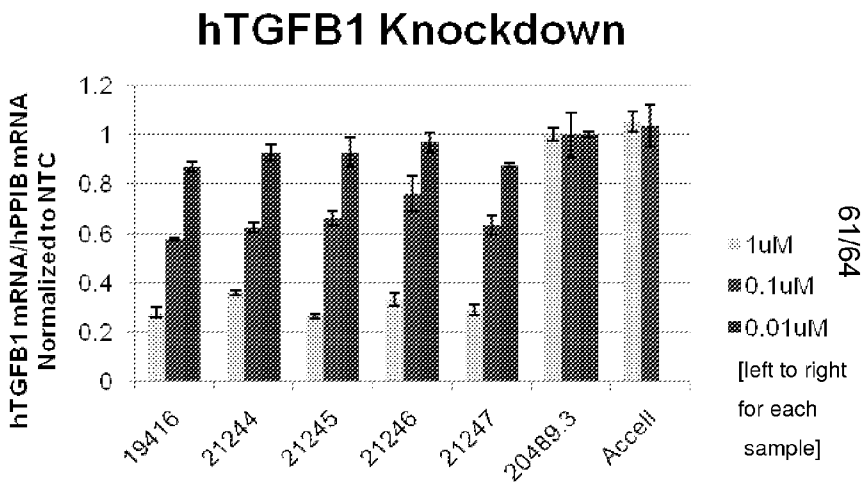
21191	P.mU.A.fU.fC.A.mA.A.fU.G.fU.G.A.fU.fC*fU*mG*mG*mA*fU*G
21192	P.mU.A.fU.fC.A.A.A.fU.G.fU.G.A.fU.mC*fU*mG*mG*mA*fU*G
21193	G. A.mU.mC. A.mC. A.mU.mU.mU. G. A*mU*mA-TEG-Chl
21194	mG*mA*mU.mC. A.mC. A.mU.mU.mU. G. A*mU*mA-TEG-Chl
21195	mG*mA*mU.mC.mA.mC.mA.mU.mU.mU.mG.mA*mU*mA-TEG-Chl

Figure 61

hTGFB1 L1 Chemical Optimization

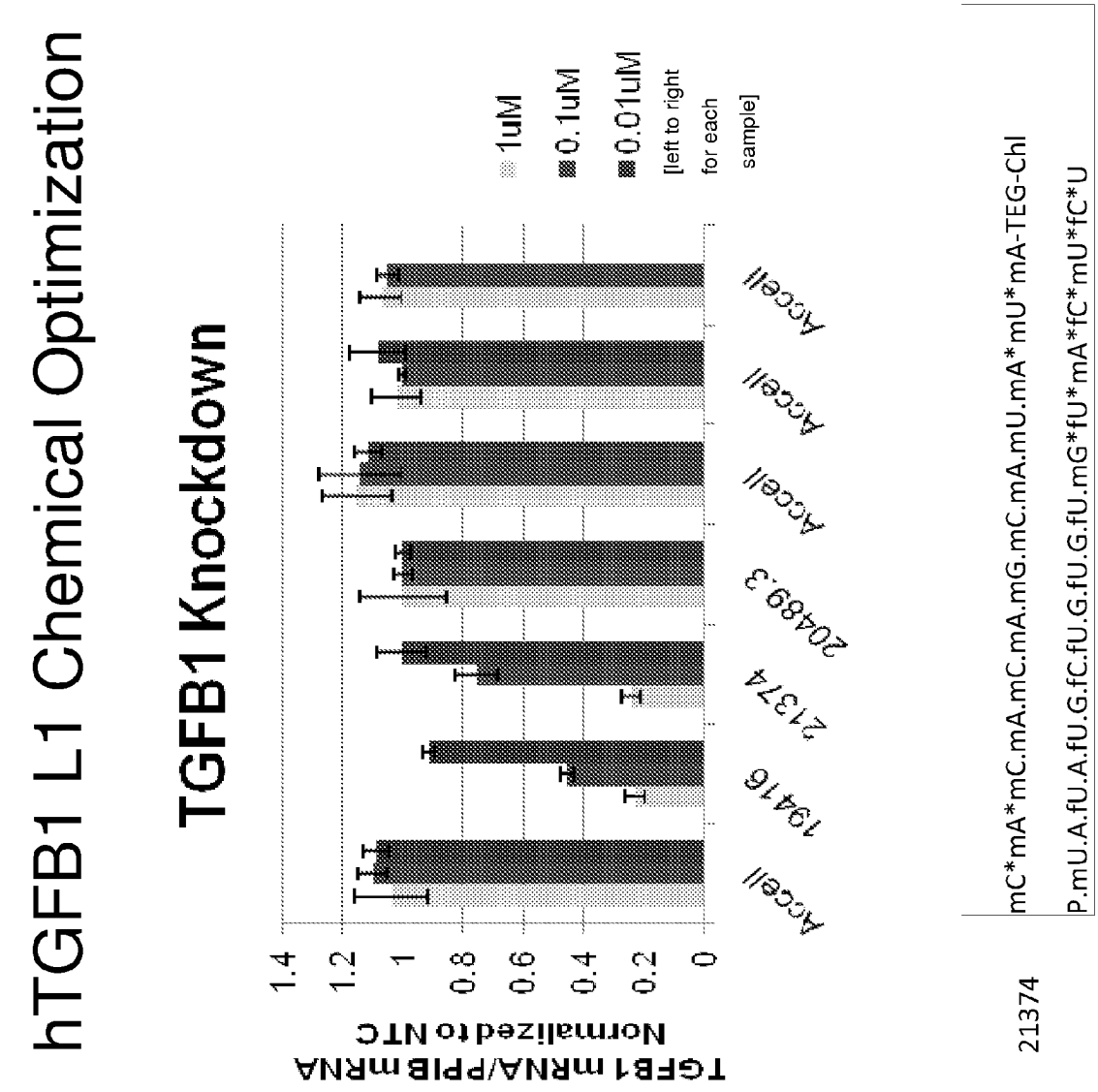


21240	P.mU.A.fU.A.fU.G.fC.fU.G.fU.G.fU.G*mU*A*mC*mU*mC*U
21241	P.mU.A.fU.A.fU.G.fC.fU.G.fU.G.fU.G*mU*mA*mC*mU*mC*U
21242	P.mU.A.fU.A.fU.G.fC.fU.G.fU.G.fU.mG*mU*mA*mC*mU*mC*U
21243	P.mU.A.fU.A.fU.G.fC.fU.G.fU.G.fU.mG*fU*mA*fC*mU*fC*U



21244	P.mU.A.fU.A.fU.G.fC.fU.G.fU.G.fU.G*fU*A*fC*mU*mC*U
21245	mC.A.mC.A.mC.A.G.mC.A.mU. A*mU*mA-TEG-Chl
21246	mC*mA*mC.A.mC.A.G.mC.A.mU. A*mU*mA-TEG-Chl
21247	mC*mA*mC.mA.mC.mA.mG.mC.mA.mU.mA*mU*mA-TEG-Chl

Figure 62

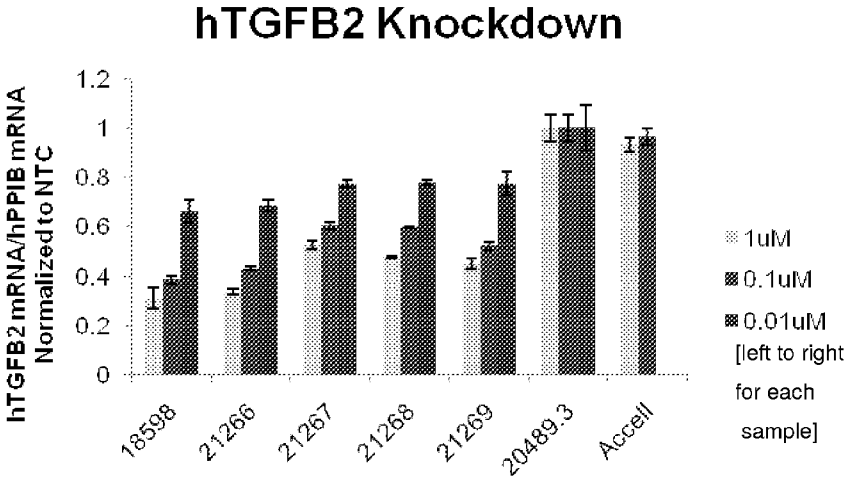


21374 mC*mA*mC.mA.mC.mA.mG.mC.mA.mU.mA*mU*mA-TEG-Chl

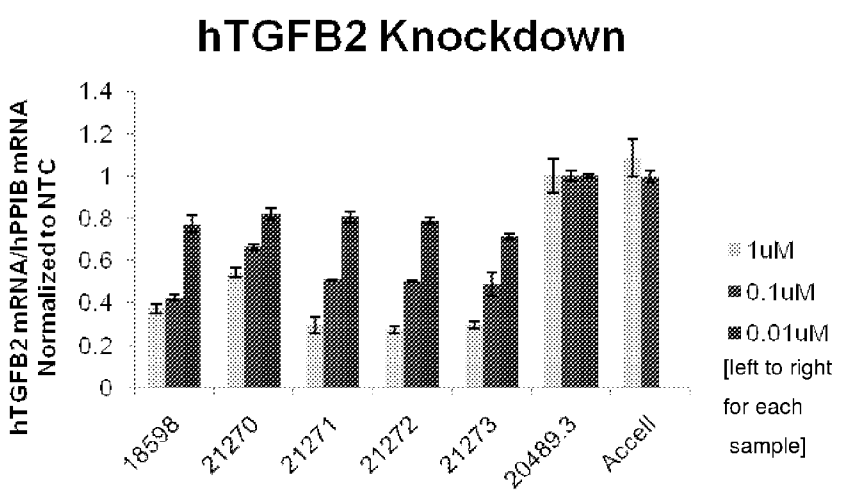
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Figure 63

hTGFB2 L1 Chemical Optimization



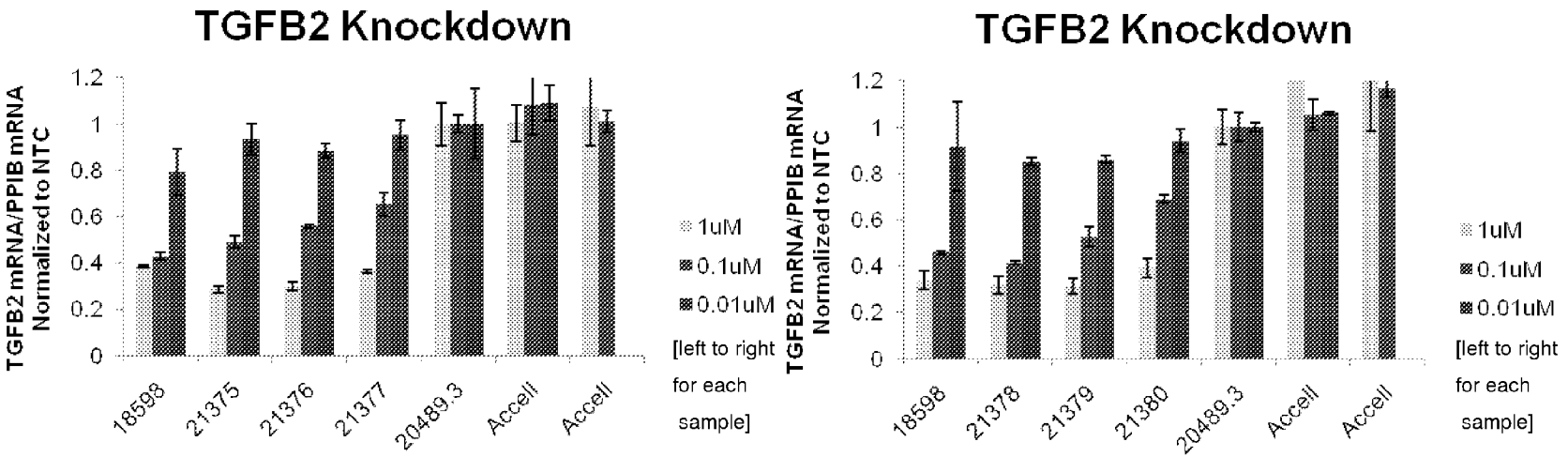
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21268	P.mU.fU. A. A.fC. A.fC.fU. G. A.mU. G.mA*mA*mC*mC*mA*mA* G
21269	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC*mA*mA* G



21270	P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G.mA*mA*fC*fC*mA*mA* G
21271	mU.mC. A.mU.mC. A. G.mU. G.mU.mU*mA*mA-TEG-Chl
21272	mU*mC* A.mU.mC. A. G.mU. G.mU.mU*mA*mA-TEG-Chl
21273	mU*mC*mA.mU.mC.mA.mG.mU.mG.mU.mU*mA*mA-TEG-Chl

Figure 64

Opt hTGFB2 sd-rxRNAs Are Active



21375	mU.mC. A.mU.mC. A. G.mU. G.mU.mU*mA*mA-TEG-Chl P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*mC*mC* A* A* G	21378	mU*mC*mA.mU.mC.mA.mG.mU.mG.mU.mU*mA*mA-TEG-Chl P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*mC*mC* A* A* G
21376	mU.mC. A.mU.mC. A. G.mU. G.mU.mU*mA*mA-TEG-Chl P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC*mA*mA* G	21379	mU*mC*mA.mU.mC.mA.mG.mU.mG.mU.mU*mA*mA-TEG-Chl P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G. A* A*fC*fC*mA*mA* G
21377	mU.mC. A.mU.mC. A. G.mU. G.mU.mU*mA*mA-TEG-Chl P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G.mA*mA*fC*fC*mA*mA* G	21380	mU*mC*mA.mU.mC.mA.mG.mU.mG.mU.mU*mA*mA-TEG-Chl P.mU.fU. A. A.fC. A.fC.fU. G. A.fU. G.mA*mA*fC*fC*mA*mA* G

SEQUENCE LISTING

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Khvorova, Anastasia
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Kamens, Joanne
Samarsky, Dmitry
Woolf, Tod M
Pavco, Pamela A
Libertine, Lyn
Cardia, James

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<151> 2010-03-24

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