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**MIR-155 INHIBITORS FOR TREATING CUTANEOUS T CELL LYMPHOMA (CTCL)**

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2019232918 20 Sep 2019

**ABSTRACT**

The present invention provides oligonucleotide inhibitors of miR-155 and compositions thereof. The invention further provides methods for treating cancer such as a T cell lymphoma in a subject by administering to the subject an oligonucleotide inhibitor of miR-155. The invention also provides methods for reducing or inhibiting the proliferation of malignant T cells by administering an oligonucleotide inhibitor of miR-155.

**MIR-155 INHIBITORS FOR TREATING CUTANEOUS T CELL LYMPHOMA (CTCL)****CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] The present Application claims the benefit of priority to U.S. Provisional Application No. 62/171,758, filed on June 5, 2015, the contents of which are hereby incorporated by reference in their entirety.

**FIELD OF THE INVENTION**

[0002] The present invention relates to oligonucleotide inhibitors of miR-155 and compositions thereof. The invention also provides methods for treating or preventing cancer in a subject in need thereof by administering an oligonucleotide inhibitor of miR-155. The activity or function of miR-155 is reduced in cancer cells of the subject following administration of the oligonucleotide inhibitor.

**BACKGROUND**

[0003] MicroRNAs (miRNAs) are small, endogenous, noncoding RNAs that act as posttranscriptional repressors of gene expression. MiRNAs act as repressors of target mRNAs by promoting their degradation, when their sequences are perfectly complementary, or by inhibiting translation, when their sequences contain mismatches.

[0004] MiRNAs are transcribed by RNA polymerase II (pol II) or RNA polymerase III (pol III; see Qi *et al.* (2006) *Cellular & Molecular Immunology*, Vol. 3:411-419) and arise from initial transcripts, termed primary miRNA transcripts (pri-miRNAs), that are generally several thousand bases long. Pri-miRNAs are processed in the nucleus by the RNase Drosha into about 70- to about 100-nucleotide hairpin-shaped precursors (pre-miRNAs). Following transport to the cytoplasm, the hairpin pre-miRNA is further processed by Dicer to produce a double-stranded miRNA. The mature miRNA strand is then incorporated into the RNA-induced silencing complex (RISC), where it associates with its target mRNAs by base-pair complementarity. In the relatively rare cases in which a miRNA base pairs perfectly with an mRNA target, it promotes mRNA degradation. More commonly, miRNAs form imperfect heteroduplexes with target mRNAs, affecting either mRNA stability or inhibiting mRNA translation.

2019232918 20 Sep 2019

[0005] MicroRNAs have been implicated in several diseases including cancer. For example, human miRNA genes miR15a and miR16-1 are deleted or down-regulated in approximately 60% of B-cell chronic lymphocytic leukemia (CLL) cases (Calin et al., Proc Natl Acad Sci, 2002; 99:15524-15529). Similarly, dysregulation of miR-155-5p has been linked to signaling events that are implicated in the pathogenesis of cutaneous T cell lymphoma (CTCL). It has been shown that malignant T-cells constitutively express an IL-2 receptor complex and associated Janus kinases (JAKs) that activate transcription via signal transducers and activators of transcription (STAT) proteins. Chromatin immuno-precipitation experiments showed that STAT-5 was associated with the promoter of *MIR155HG*, a host gene for miR-155-5p. This suggests that miR-155-5p may regulate the STAT-5 signaling pathway in CTCL malignant T-cells. Inhibition of the JAK/STAT pathway resulted in the down-regulation of miR-155-5p expression whereas treatment of cells with cytokines that activate STAT-5 resulted in increased miR-155-5p levels (Kopp et al. 2013). These results suggest that miR-155-5p may play a role in the pathogenesis of CTCL.

[0006] Currently there are no therapies that cure or prolong the survival of late-stage CTCL patients (Prince et al., 2009). Treatments for CTCL patients at an early-stage of disease are palliative and non-aggressive with careful physician monitoring. More advanced-stage CTCL patients are typically treated with systemic drugs, such as retinoids (bexarotene) or histone deacetylase inhibitors (vorinostat). Radiotherapy is typically the last line of defense and can result in partial disease regression but not full eradication. Many treatments have serious side effects or result in resistance over time. Thus, there remains an unmet medical need for new therapies to treat cutaneous T-cell lymphoma.

#### SUMMARY OF THE INVENTION

[0007] The present invention provides oligonucleotide inhibitors for modulating the activity or function of miR-155 in cells of a subject. In one embodiment, administration of an oligonucleotide inhibitor of miR-155 down-regulates the activity or function of miR-155 in cancer cells of the subject following administration. In certain embodiments, cancer cells are malignant T cells including cutaneous T cell lymphoma (CTCL) cells, CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells,  $\alpha\beta$  T cells,  $\gamma\delta$  T cells and memory T cells.

[0008] In one embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of 11 to 16 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a

2019232918 20 Sep 2019

mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of the oligonucleotide inhibitor are locked nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide. In some of these embodiments, the fourth nucleotide from the 3' end of the oligonucleotide inhibitor is also a locked nucleotide. In some of these embodiments, the first nucleotide from the 5' end of the oligonucleotide inhibitor is a locked nucleotide.

[0009] In another embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide. In these embodiments, the oligonucleotide inhibitor may contain at least 5, 6, 7, 8, 9, or 10 modified nucleotides. In some of these embodiments, the oligonucleotide inhibitor contains 7, 8, 9, or 10 modified nucleotides. In some of these embodiments, 7, 8, 9, or 10 modified nucleotides present in the oligonucleotide inhibitor are all locked nucleotides. In yet some other embodiments, 7, 8, 9, or 10 modified nucleotides present in the oligonucleotide inhibitor are a combination of locked nucleotides and other modifications such as ethylene-bridged nucleotides, 2'-C-bridged bicyclic nucleotides, and sugar modifications such as 2'-substituted nucleotides. In some of these embodiments, the second DNA nucleotide from the 5' end of the oligonucleotide inhibitor could be an unmodified DNA nucleotide. In some of these embodiments, the first three modified nucleotides from the 3' end of the oligonucleotide inhibitor are locked nucleotides.

[0010] In yet another embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least 7 nucleotides of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide. In these embodiments, the oligonucleotide inhibitor may contain at least 7, 8, 9, or 10 modified nucleotides. In some of these embodiments, 7, 8, 9, or 10 modified nucleotides present in the oligonucleotide inhibitor are

2019232918 20 Sep 2019

all locked nucleotides. In yet some other embodiments, 7, 8, 9, or 10 modified nucleotides present in the oligonucleotide inhibitor are a combination of locked nucleotides and other modifications such as ethylene-bridged nucleotides, 2'-C-bridged bicyclic nucleotides, and sugar modifications such as 2'-substituted nucleotides. In some of these embodiments, the first three nucleotides from the 3' end of the oligonucleotide inhibitor are modified nucleotides. In some of these embodiments, the first three modified nucleotides from the 3' end of the oligonucleotide inhibitor are locked nucleotides. In some of these embodiments, the second or the third nucleotide from the 3' end of the oligonucleotide inhibitor is a DNA nucleotide. In some of these embodiments, the second DNA nucleotide from the 5' end of the oligonucleotide inhibitor could be an unmodified DNA nucleotide.

[0011] In yet another embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the fourth and fifth nucleotides from the 5' end of the oligonucleotide inhibitor are deoxyribonucleic acid (DNA) nucleotides. In these embodiments, the oligonucleotide inhibitor may contain at least 7, 8, 9, or 10 modified nucleotides. In some of these embodiments, 7, 8, 9, or 10 modified nucleotides present in the oligonucleotide inhibitor are all locked nucleotides. In some of these embodiments, the first three modified nucleotides from the 3' end of the oligonucleotide inhibitor are locked nucleotides. In some of these embodiments, the fourth and/or the fifth DNA nucleotide from the 5' end of the oligonucleotide inhibitor could be an unmodified DNA nucleotide.

[0012] The modified nucleotides that may be present in the oligonucleotide inhibitors of the present invention include, but are not limited to, locked nucleotides, ethylene-bridged nucleotides, 2'-C-bridged bicyclic nucleotides, 2'-substituted nucleotides, and other sugar and/or base modifications described herein. In some embodiments, all modified nucleotides present in the oligonucleotide inhibitors of the present invention are locked nucleotides. In some other embodiments, modified nucleotides present in the oligonucleotide inhibitors are a combination of locked nucleotides and other modifications such as ethylene-bridged nucleotides, 2'-C-bridged bicyclic nucleotides, and 2'-substituted nucleotides, and other sugar and/or base modifications described herein.

2019232918 20 Sep 2019

[0013] In one embodiment, the oligonucleotide inhibitor of miR-155 has a length of 12 to 14 nucleotides. In some embodiments, the oligonucleotide inhibitor contains at least 5, 6, 7, 8, 9 or 10 locked nucleotides. In some other embodiments, the oligonucleotide inhibitor contains at least 1, 2, 3, 4, 5, or more DNA nucleotides. In certain embodiments, at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a DNA nucleotide. In certain additional embodiments, at least the second and fourth nucleotides from the 5' end of the oligonucleotide inhibitor are DNA nucleotides. In further embodiments, at least the sixth and/or the eighth nucleotide from the 5' end of the oligonucleotide inhibitor is a DNA nucleotide. In yet further embodiments, the oligonucleotide inhibitor comprises DNA nucleotides at the second, sixth, and the eighth position from the 5' end.

[0014] In some embodiments, the oligonucleotide inhibitor of miR-155 has a sequence selected from SEQ ID NOs: 3-27 and 29-120. In an exemplary embodiment, the oligonucleotide inhibitor of miR-155 has a sequence of SEQ ID NO: 25. In another exemplary embodiment, the oligonucleotide inhibitor of miR-155 has a sequence of SEQ ID NO: 22 or 23. In yet another exemplary embodiment, the oligonucleotide inhibitor of miR-155 has a sequence selected from SEQ ID NO: 33, 39, 43, 44, 47, 58, 84, 99, 111, 115, and 120.

[0015] In one embodiment, oligonucleotide inhibitors of miR-155 according to the present invention reduce or inhibit proliferation of cancer cells and/or induce apoptosis of cancer cells. In another embodiment, oligonucleotide inhibitors up-regulate one or more target genes of miR-155 in cancer cells.

[0016] The present invention also provides compositions comprising oligonucleotide inhibitors of miR-155 and uses thereof. In one embodiment, the invention provides methods for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an oligonucleotide inhibitor of miR-155 of the present invention. The activity or function of miR-155 is reduced in cancer cells following administration of the oligonucleotide inhibitor. In one embodiment, the cancer is a cutaneous T cell lymphoma (CTCL). In some embodiments, methods for treating cancer comprise administering to a subject a therapeutically effective amount of an oligonucleotide inhibitor of miR-155 of the invention and a therapeutically effective amount of a second therapeutic agent such as a retinoid or a histone deacetylase (HDAC) inhibitor.

[0017] In one embodiment, the invention provides methods for reducing or inhibiting the proliferation of malignant T cells, comprising administering the oligonucleotide inhibitor of miR-155 according to the invention. The activity or function of miR-155 is reduced in malignant T cells following administration of the oligonucleotide inhibitor.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

[0018] Figure 1 shows the absolute expression of miR-155-5p in various CTCL cell lines compared to normal peripheral CD4<sup>+</sup> T helper cells as measured by quantitative real time PCR.

[0019] Figure 2 shows a “heat map” representation of gene expression changes in 9 target genes of miR-155 in various CTCL cells in response to treatment with 10  $\mu$ M of one of four anti-miR-155 compounds for 72 hours.

[0020] Figure 3A shows a fold-change in the expression of four miR-155 target genes in response to treatment with 2  $\mu$ M anti-miR-155 compounds for 72 hours in HuT102 cells. Figure 3B shows a fold-change in the expression of four miR-155 target genes in response to treatment with 10  $\mu$ M anti-miR-155 compounds for 72 hours in HuT102 cells. Figure 3C shows a fold-change in the expression of four miR-155 target genes in response to treatment with 50  $\mu$ M anti-miR-155 compounds for 72 hours in HuT102 cells. Figure 3D shows a fold-change in the expression of four miR-155 target genes in response to treatment with 2  $\mu$ M anti-miR-155 compounds for 96 hours in HuT102 cells. Figure 3E shows a fold-change in the expression of four miR-155 target genes in response to treatment with 10  $\mu$ M anti-miR-155 compounds for 96 hours in HuT102 cells. Figure 3F shows a fold-change in the expression of four miR-155 target genes in response to treatment with 50  $\mu$ M anti-miR-155 compounds for 96 hours in HuT102 cells. \* p-value < 0.0001 compared to untreated by nonparametric Mann-Whitney test.

[0021] Figure 4A shows a fold-change in the expression of four miR-155 target genes in response to treatment with 2  $\mu$ M anti-miR-155 compounds for 72 hours in MJ cells. Figure 4B shows a fold-change in the expression of four miR-155 target genes in response to treatment with 10  $\mu$ M anti-miR-155 compounds for 72 hours in MJ cells. Figure 4C shows a fold-change in the expression of four miR-155 target genes in response to treatment with 50  $\mu$ M anti-miR-155 compounds for 72 hours in MJ cells. Figure 4D shows a fold-change in the



expression of four miR-155 target genes in response to treatment with 2  $\mu$ M anti-miR-155 compounds for 96 hours in MJ cells. Figure 4E shows a fold-change in the expression of four miR-155 target genes in response to treatment with 10  $\mu$ M anti-miR-155 compounds for 96 hours in MJ cells. Figure 4F shows a fold-change in the expression of four miR-155 target genes in response to treatment with 50  $\mu$ M anti-miR-155 compounds for 96 hours in MJ cells. \* p-value < 0.0001 compared to untreated by nonparametric Mann-Whitney test.

[0022] Figure 5A shows a fold-change in the expression of four miR-155 target genes in response to treatment with 2  $\mu$ M anti-miR-155 compounds for 72 hours in HH cells. Figure 5B shows a fold-change in the expression of four miR-155 target genes in response to treatment with 10  $\mu$ M anti-miR-155 compounds for 72 hours in HH cells. Figure 5C shows a fold-change in the expression of four miR-155 target genes in response to treatment with 50  $\mu$ M anti-miR-155 compounds for 72 hours in HH cells. Figure 5D shows a fold-change in the expression of four miR-155 target genes in response to treatment with 2  $\mu$ M anti-miR-155 compounds for 96 hours in HH cells. Figure 5E shows a fold-change in the expression of four miR-155 target genes in response to treatment with 10  $\mu$ M anti-miR-155 compounds for 96 hours in HH cells. Figure 5F shows a fold-change in the expression of four miR-155 target genes in response to treatment with 50  $\mu$ M anti-miR-155 compounds for 96 hours in HH cells. \* p-value < 0.0001 compared to untreated by nonparametric Mann-Whitney test.

[0023] Figure 6A shows a fold-change in the expression of four miR-155 target genes in response to treatment with 2, 10, and 50  $\mu$ M anti-miR-155 compounds for 72 hours in My-LA cells. Figure 6B shows a fold-change in the expression of four miR-155 target genes in response to treatment with 2, 10, and 50  $\mu$ M anti-miR-155 compounds for 96 hours in My-LA cells. \* p-value < 0.0001 compared to untreated by nonparametric Mann-Whitney test.

[0024] Figure 7A shows a fold-change in the expression of four miR-155 target genes in response to treatment with 2  $\mu$ M anti-miR-155 compounds for 72 hours in HuT78 cells. Figure 7B shows a fold-change in the expression of four miR-155 target genes in response to treatment with 10  $\mu$ M anti-miR-155 compounds for 72 hours in HuT78 cells. Figure 7C shows a fold-change in the expression of four miR-155 target genes in response to treatment with 50  $\mu$ M anti-miR-155 compounds for 72 hours in HuT78 cells. Figure 7D shows a fold-change in the expression of four miR-155 target genes in response to treatment with 2  $\mu$ M anti-miR-155 compounds for 96 hours in HuT78 cells. Figure 7E shows a fold-change in the expression of four miR-155 target genes in response to treatment with 10  $\mu$ M anti-miR-155

compounds for 96 hours in HuT78 cells. Figure 7F shows a fold-change in the expression of four miR-155 target genes in response to treatment with 50  $\mu$ M anti-miR-155 compounds for 96 hours in HuT78 cells.

[0025] Figure 8A shows a fold-change in the expression of four miR-155 target genes in response to treatment with 10  $\mu$ M anti-miR-155 compounds or control oligos in HuT102 cells. Figure 8B shows a fold-change in the expression of four miR-155 target genes in response to treatment with 10  $\mu$ M anti-miR-155 compounds or control oligos in MJ cells. \* p-value < 0.0001 compared to untreated by nonparametric Mann-Whitney test.

[0026] Figure 9 shows a heat map of the differential gene expression signature in MJ cells treated with anti-miR-155 compounds for 4 or 8 days. MJ cells treated with anti-miR-155 were subjected to whole genome expression profiling. The differential expression signature was filtered for genes that were significantly changed with a false discovery rate corrected p-value of  $\leq 0.05$ .

[0027] Figure 10 shows a heat map of the differential gene expression signature in HuT102 cells treated with anti-miR-155 compounds for 4 or 8 days. HuT102 cells treated with anti-miR-155 were subjected to whole genome expression profiling. The differential expression signature was filtered for genes that were significantly changed with a false discovery rate corrected p-value of  $\leq 0.05$ .

[0028] Figure 11A shows the annotation of the gene expression profile of genes upregulated in response to anti-miR-155 in both MJ and HuT102 cells. The gene signature is enriched for miR-155 seed-matched direct targets with a hypergeometric p-value for enrichment of  $1.6 \times 10^{-25}$ . The genes identified here were significantly changed with anti-miR-155 treatment compared to the untreated group with a false discovery rate corrected p-value of  $\leq 0.05$ . Figure 11B shows a cumulative distribution function graph of the differential expression of miR-155 direct target genes containing 8-, 7-, or 6-nucleotide seed sequences, compared to non-seed containing transcripts. The p-values shown are the result of the Kolmogorov-Smirnov test to determine the significant difference between two datasets.

[0029] Figure 12 shows an annotated gene expression profile of genes up-regulated or down-regulated in response to treatment with antimiR-155 compounds for 8 days in both MJ and HuT102 cells.

[0030] Figure 13 shows an expression profile of genes upregulated or downregulated in response to 8 days of treatment with the antimiR-155 having a sequence of SEQ ID NO: 25 in CTCL cells.

[0031] Figure 14A shows the effect of antimiR-155 compounds on proliferation of HuT102 cells. Figure 14B shows the effect of antimiR-155 compounds on caspase 3/7 activity in HuT102 cells.

[0032] Figure 15A shows proliferation of HuT102 cells in response to various concentrations of antimiR-155 compounds at day 8 of treatment. Figure 15B shows caspase 3/7 activity in HuT102 cells in response to various concentrations of antimiR-155 compounds at day 8 of treatment.

[0033] Figure 16A shows the effect of antimiR-155 compounds on proliferation of HuT102 cells. Figure 16B shows the effect of antimiR-155 compounds on caspase 3/7 activity in HuT102 cells.

[0034] Figure 17A shows the effect of antimiR-155 compounds on proliferation of My-La cells. Figure 17B shows the effect of antimiR-155 compounds on caspase 3/7 activity in My-La cells.

[0035] Figure 18A shows proliferation of My-La cells in response to various concentrations of antimiR-155 compounds at day 8 of treatment. Figure 18B shows caspase 3/7 activity in My-La cells in response to various concentrations of antimiR-155 compounds at day 8 of treatment.

[0036] Figure 19A shows the effect of 10  $\mu$ M antimiR-155 compounds and 0.25  $\mu$ M HDAC inhibitor on proliferation of HuT102 cells. Figure 19B shows the effect of 10  $\mu$ M antimiR-155 compounds and 0.50  $\mu$ M HDAC inhibitor on proliferation of HuT102 cells.

2019232918 20 Sep 2019

[0037] Figure 20A shows the effect of 10  $\mu\text{M}$  anti-miR-155 compounds and 0.25  $\mu\text{M}$  HDAC inhibitor on caspase 3/7 activity in HuT102 cells. Figure 20B shows the effect of 10  $\mu\text{M}$  anti-miR-155 compounds and 0.50  $\mu\text{M}$  HDAC inhibitor on caspase 3/7 activity in HuT102 cells.

[0038] Figure 21 shows a heat map of expression changes in 587 genes up-regulated or down-regulated in all three mycosis fungoides cell lines at day 4 or day 8 in response to compound 4 (SEQ ID NO: 25).

[0039] Figure 22 shows the anti-miR-155 activity of oligonucleotide inhibitors of different lengths measured using a dual luciferase reporter plasmid containing the miR-155 binding site.

[0040] Figures 23A, 23B, 23C, and 23D show the anti-miR-155 activity of oligonucleotide inhibitors containing varying number of locked nucleotide modifications measured using a dual luciferase reporter plasmid containing the miR-155 binding site.

[0041] Figures 24A, 24B, 24C, and 24D show the anti-miR-155 activity of oligonucleotide inhibitors containing locked nucleotide modifications at various positions, measured using a dual luciferase reporter plasmid containing the miR-155 binding site.

[0042] Figure 25 shows the anti-miR-155 activity of oligonucleotide inhibitors containing various nucleotide modifications, measured using a dual luciferase reporter plasmid containing the miR-155 binding site.

[0043] Figure 26 shows the anti-miR-155 activity of various 14-nucleotide long oligonucleotide inhibitors, measured using a dual luciferase reporter plasmid containing the miR-155 binding site.

[0044] Figure 27 shows the anti-miR-155 activity of oligonucleotide inhibitors of SEQ ID NOs: 25 and 23, measured using a dual luciferase reporter plasmid containing the miR-155 binding site.

[0045] Figure 28 shows the fold-change in the expression of miR-155 target genes in response to treatment with oligonucleotide inhibitors of SEQ ID NOs: 25 and 120.

#### DETAILED DESCRIPTION

[0046] All patent and non-patent documents referenced throughout this disclosure are incorporated by reference herein in their entirety.

[0047] The present invention provides oligonucleotide inhibitors that inhibit the activity or function of miR-155 in cancer cells. In humans, miR-155 is encoded by the MIR155 host gene or MIR155HG and is located on human chromosome 21. Since both arms of pre-miR-155 can give rise to mature miRNAs, processing products of pre-miR-155 are designated as miR-155-5p (from the 5' arm) and miR-155-3p (from the 3' arm). The mature sequences for human miR-155-5p and miR-155-3p are given below:

Human mature miR-155-5p (SEQ ID NO: 1)

5'-UUAAUGC UAAUCGUGAUAGGGGU-3'

Human mature miR-155-3p (SEQ ID NO: 2)

5'-CUCCUACAUAUUAGCAUUAACA-3'

[0048] miR-155-5p is expressed in hematopoietic cells including B-cells, T-cells, monocytes and granulocytes (Landgraf et al. 2007). miR-155-5p is an essential molecule in the control of both myelopoiesis and erythropoiesis. This miRNA is highly expressed in hematopoietic stem-progenitor cells at an early stem-progenitor stage, and blocks their differentiation into a more mature hematopoietic cell (e.g., lymphocyte, erythrocyte). miR-155-5p expression progressively decreases as cells mature along these lineages, and is ~200-fold lower in mature hematopoietic cells (Masaki et al. 2007; Gerloff et al. 2015).

[0049] miR-155-5p plays an important role in mediating inflammatory and immune responses. Mice lacking miR-155-5p show normal number and distribution of T- and B-lymphocyte subpopulations, but display a deficient immune response, specifically in regulating T helper cell differentiation and the germinal center reaction to produce an optimal T-cell dependent antibody response (Rodriguez et al. 2007; Thai et al. 2007). miR-155-5p controls differentiation of CD4+ T-cells into the T helper type 1 (Th1), Th2, and Th17 subsets of T helper cells, and affects the development of regulatory T-cells (Treg)

(Baumjohann and Ansel 2013). miR-155-5p also regulates effector and memory CD8<sup>+</sup> T-cell responses to viral infection (Dudda et al. 2013; Gracias et al. 2013), as well as normal B-cell differentiation and antibody production. In humans, miR-155-5p expression is low in nonlymphoid organs as well as in resting, naïve CD4<sup>+</sup> T-cells. miR-155-5p expression is greatly enhanced by antigen receptor stimulation of B- and T-cells (Tam 2001; Haasch et al. 2002; van den Berg et al. 2003; Rodriguez et al. 2007; Thai et al. 2007; Vigorito et al. 2007; Banerjee et al. 2010), and by Toll-like receptor agonist stimulation of macrophages and dendritic cells (Taganov et al. 2006; O'Connell et al. 2007; Ceppi et al. 2009; Mao et al. 2011). MIR155HG activation involves both AP1- and NF- $\kappa$ B-mediated mechanisms.

[0050] Cutaneous plaques or tumors in patients diagnosed with mycosis fungoides (MF) subtype of CTCL, have elevated levels of miR-155-5p. Increased miR-155-5p in MF patient skin biopsies compared to control skin biopsies has been reported by several groups (van Kester et al. 2011; Maj et al. 2012; Kopp et al. 2013b; Moyal et al. 2013). In one study, miR-155-5p levels were 4.16-fold higher in tumor-stage biopsies compared to early MF biopsies (Moyal et al. 2013), suggesting that miR-155-5p levels may be correlated with disease progression. In a second study directed to identifying specific cell types that express miR-155-5p, the miRNA was found to be expressed in both malignant and non-malignant T-cells in the CTCL lesions (Kopp et al. 2013b).

[0051] Mycosis fungoides (MF) is the most prevalent sub-type of CTCL, accounting for 50-70% of all primary cutaneous lymphomas. The second most prevalent sub-type is Sézary syndrome (SS), comprising 15% of CTCL cases. MF is characterized by proliferation of atypical small- to medium-sized T lymphocytes with cerebriform nuclei that form patches, plaques, or nodular tumors in the epidermis. MF typically affects older adults (median age of diagnosis: 55-60) and has an indolent clinical course where patches and plaques precede or are concurrent with the formation of tumors. In some late tumor-stage cases, lymph node and visceral organ involvement are observed. During tumor-stage MF, the dermal infiltrates become more diffuse and the epidermotropism of the atypical T-cells may be lost. In contrast, SS is a more aggressive, leukemic form of CTCL, characterized by widespread redness and scaling of the skin (erythroderma), enlarged lymph nodes, and malignant cells in the peripheral circulation (Yamashita et al., 2012; Jawed et al. 2014).

2019232918 20 Sep 2019

[0052] Molecular analyses of tumor stage MF have revealed significant changes in gene expression compared to normal skin, inflamed skin and normal T-cells (van Kester et al. 2012), although the genetic or epigenetic origin of these differences in gene expression are unknown. Early skin lesions contain numerous inflammatory cells, including T cells with a normal phenotype as well as a smaller population of T cells with an abnormal morphology and a malignant phenotype. The infiltrate primarily consists of non-malignant Th1 cells, regulatory T cells, and cytotoxic CD8+ T cells. The malignant T cells are typically CD4+ memory T cells of clonal origin. During disease development, epidermotropism is gradually lost, concomitant with an increase in malignant CD4+ T cells and a decrease in non-malignant CD8+ T cells.

[0053] CTCL is characterized by aberrant expression and function of transcription factors and regulators of signal transduction. It has been hypothesized that dysfunctional regulation of signal molecules and cytokines plays a key role in the malignant transformation and pathogenesis of CTCL (Girardi et al., 2004; Zhang et al., 2006; van Doorn et al., 2009; Kadin and Vonderheid, 2010). Significant differences in the gene expression profiles of MF and SS cells have been observed, consistent with a distinct pathogenesis for these variants of CTCL (van Doorn et al., 2009; Campbell et al., 2010). Recently, microRNAs (miRNAs) have been reported to be differentially expressed and potentially involved in the pathogenesis of CTCL. miR-155-5p is among the miRNAs most up-regulated in mycosis fungoides (Kopp et al, 2013a; Kopp et al., 2013b), while a distinct subset of dysregulated miRNAs distinguishes Sezary syndrome, and miR-155-5p is not up-regulated in this subtype of CTCL (Ballabio et al., 2010).

[0054] The present invention provides oligonucleotide inhibitors that reduce or inhibit the activity or function of human miR-155. In the context of the present invention, the term “oligonucleotide inhibitor”, “antimiR” (e.g., antimiR-155), “antagonist”, “antisense oligonucleotide or ASO”, “oligomer”, “anti-microRNA oligonucleotide or AMO”, or “mixmer” is used broadly and encompasses an oligomer comprising ribonucleotides, deoxyribonucleotides, modified ribonucleotides, modified deoxyribonucleotides or a combination thereof, that inhibits the activity or function of the target microRNA (miRNA) by fully or partially hybridizing to the miRNA thereby repressing the function or activity of the target miRNA.

[0055] The term “miR-155” as used herein includes pri-miR-155, pre-miR-155, miR-155-5p, and hsa-miR-155-5p.

[0056] In one embodiment, the present invention provides an oligonucleotide inhibitor of miR-155 that has a length of 11 to 16 nucleotides. In some other embodiments, the present invention provides an oligonucleotide inhibitor of miR-155 that has a length of 11 to 14 nucleotides. In various embodiments, the oligonucleotide inhibitor targeting miR-155 is 11, 12, 13, 14, 15, or 16 nucleotides in length. In one embodiment, the oligonucleotide inhibitor of miR-155 has a length of 12 nucleotides. In another embodiment, the oligonucleotide inhibitor of miR-155 has a length of 14 nucleotides.

[0057] The sequence of an oligonucleotide inhibitor of miR-155 according to the invention is sufficiently complementary to a mature sequence of miR-155-5p to hybridize to miR-155-5p under physiological conditions and inhibit the activity or function of miR-155-5p in the cells of a subject. For instance, in some embodiments, oligonucleotide inhibitors comprise a sequence that is at least partially complementary to a mature sequence of miR-155-5p, *e.g.* at least about 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% complementary to a mature sequence of miR-155-5p. In some embodiments, the oligonucleotide inhibitor can be substantially complementary to a mature sequence of miR-155-5p, that is at least about 90%, 95%, 96%, 97%, 98%, or 99% complementary to a mature sequence of miR-155-5p. In one embodiment, the oligonucleotide inhibitor comprises a sequence that is 100% or fully complementary to a mature sequence of miR-155-5p. It is understood that the sequence of the oligonucleotide inhibitor is considered to be complementary to miR-155 even if the oligonucleotide sequence includes a modified nucleotide instead of a naturally-occurring nucleotide. For example, if a mature sequence of miR-155 comprises a guanosine nucleotide at a specific position, the oligonucleotide inhibitor may comprise a modified cytidine nucleotide, such as a locked cytidine nucleotide or 2'-fluoro-cytidine, at the corresponding position.

[0058] The term “about” as used herein encompasses variations of +/- 10% and more preferably +/- 5%, as such variations are appropriate for practicing the present invention.

[0059] In some embodiments, the entire sequence of the oligonucleotide inhibitor of miR-155 is fully complementary to a mature sequence of human miR-155-5p. In various



2019232918 20 Sep 2019

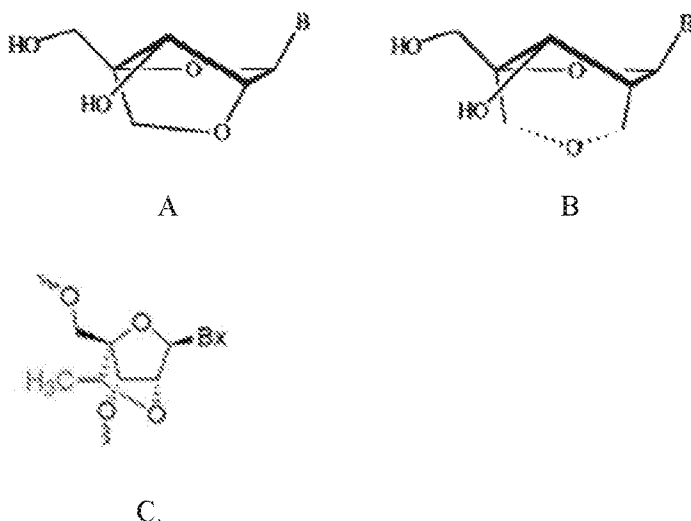
embodiments, the mature sequence of human miR-155-5p to which the sequence of the oligonucleotide inhibitor of the present invention is partially, substantially, or fully complementary to includes nucleotides 1-17, or nucleotides 2-17, or nucleotides 2-16, or nucleotides 2-15, or nucleotides 2-14, or nucleotides 2-13, or nucleotides 2-12 from the 5' end of SEQ ID NO: 1. In one embodiment, the mature sequence of human miR-155-5p to which the sequence of the oligonucleotide inhibitor of the present invention is partially, substantially, or fully complementary to includes nucleotides 2-15 from the 5' end of SEQ ID NO: 1. In another embodiment, the mature sequence of human miR-155-5p to which the sequence of the oligonucleotide inhibitor of the present invention is partially, substantially, or fully complementary to includes nucleotides 2-13 from the 5' end of SEQ ID NO: 1.

[0060] In one embodiment, the oligonucleotide inhibitor of miR-155 contains at least one backbone modification, such as at least one phosphorothioate, morpholino, or phosphonocarboxylate internucleotide linkage (see, for example, U.S. Patent Nos. 6,693,187 and 7,067,641, which are herein incorporated by reference in their entireties). In certain embodiments, the oligonucleotide inhibitor of miR-155 is fully phosphorothioate-linked.

[0061] In one embodiment, the oligonucleotide inhibitor of miR-155 contains at least one modified nucleotide. In some embodiments, the oligonucleotide inhibitor contains at least 5, 6, 7, 8, 9, 10, or more modified nucleotides. The term "modified nucleotide" as used herein encompasses nucleotides with sugar, base, and/or backbone modifications. Examples of modified nucleotides include, but are not limited to, locked nucleotides (LNA), ethylene-bridged nucleotides (ENA), 2'-C-bridged bicyclic nucleotide (CBBN), 2', 4'-constrained ethyl nucleic acid called *S*-cEt or cEt, 2'-4'-carbocyclic LNA, and 2' substituted nucleotides.

[0062] The terms "locked nucleotide," "locked nucleic acid unit," "locked nucleic acid residue," or "LNA unit" may be used interchangeably throughout the disclosure and refer to a bicyclic nucleoside analogue. For instance, suitable oligonucleotide inhibitors can be comprised of one or more "conformationally constrained" or bicyclic sugar nucleoside modifications (BSN) that confer enhanced thermal stability to complexes formed between the oligonucleotide containing BSN and their complementary target strand. In one embodiment, the oligonucleotide inhibitors contain locked nucleotides or LNAs containing the 2'-O, 4'-C-methylene ribonucleoside (structure A) wherein the ribose sugar moiety is in a "locked" conformation. In another embodiment, the oligonucleotide inhibitors contain at least one 2'-

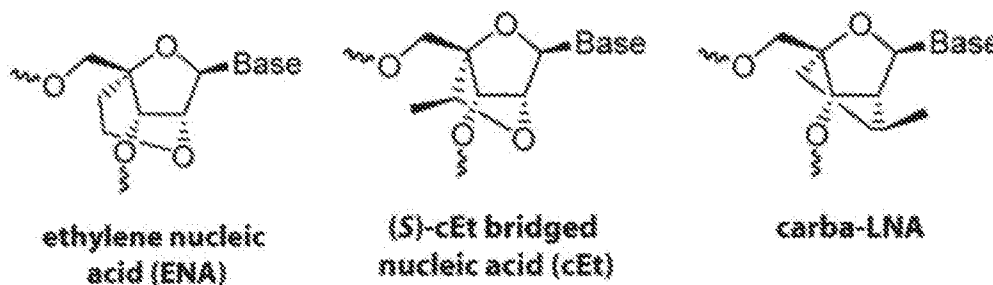
C, 4'-C-bridged 2' deoxyribonucleoside (structure B). See, e.g., U.S. Patent No. 6,403,566 and Wang *et al.* (1999) *Bioorganic and Medicinal Chemistry Letters*, Vol. 9: 1147-1150, both of which are herein incorporated by reference in their entireties. In yet another embodiment, the oligonucleotide inhibitors contain at least one modified nucleoside having the structure shown in structure C. The oligonucleotide inhibitors targeting miR-155 can contain combinations of BSN (LNA, 2'-C, 4'-C-bridged 2' deoxyribonucleoside, and the like) or other modified nucleotides, and ribonucleotides or deoxyribonucleotides.



[0063] The terms “non-LNA nucleotide”, and “non-LNA modification” as used herein refer to a nucleotide different from a LNA nucleotide, i.e. the terms include a DNA nucleotide, an RNA nucleotide as well as a modified nucleotide where a base and/or sugar is modified except that the modification is not a LNA modification.

[0064] In some embodiments, the oligonucleotide inhibitor of miR-155 contains at least one nucleotide containing a non-LNA modification. For example, in one embodiment, the oligonucleotide inhibitor of miR-155 contains at least one 2'-C-bridged bicyclic nucleotide (CBBN) as described in U.S. Pre-Grant Publication No. 2016/0010090A1 (“the ‘090 publication”), which is hereby incorporated by reference herein in its entirety. The ‘090 publication describes a variety of CBBN modifications such as 2'-CBBN, oxoCBBN, amino CBBN, thioCBBN, etc. All CBBN modifications described in the ‘090 publications could be used in the oligonucleotide inhibitors of the present invention. In another embodiment, the non-LNA modification present in the oligonucleotide inhibitor of miR-155 could be an

ethylene-bridged nucleic acid (ENA) modification. For example, in one embodiment, the oligonucleotide inhibitor of miR-155 contains at least one ethylene-bridged nucleic acid (ENA), also referred to herein as ethylene-bridged nucleotide. Other bridged modifications include 2', 4'-constrained ethyl nucleic acid called *S*-cEt or cEt and 2'-4'-carbocyclic LNA (carba-LNA).



[0065] When referring to substituting a DNA or RNA nucleotide by its corresponding locked nucleotide in the context of the present invention, the term “corresponding locked nucleotide” is intended to mean that the DNA/RNA nucleotide has been replaced by a locked nucleotide containing the same naturally-occurring nitrogenous base as the DNA/RNA nucleotide that it has replaced or the same nitrogenous base that is chemically modified. For example, the corresponding locked nucleotide of a DNA nucleotide containing the nitrogenous base C may contain the same nitrogenous base C or the same nitrogenous base C that is chemically modified, such as 5-methylcytosine.

[0066] In certain embodiments, the oligonucleotide inhibitor of miR-155 contains at least 5, 6, 7, 8, 9, 10, or 11 locked nucleotides. In one embodiment, the oligonucleotide inhibitor of miR-155 contains at least 7, 8, 9, or 10 locked nucleotides. In one embodiment, at least the first three nucleotides from the 3' end of the oligonucleotide inhibitor are locked nucleotides. In another embodiment, at least the first four nucleotides from the 3' end of the oligonucleotide inhibitor are locked nucleotides. In yet another embodiment, the first nucleotide from the 5' end of the oligonucleotide inhibitor is a locked nucleotide.

[0067] In certain embodiments, the oligonucleotide inhibitor contains at least 1, at least 2, at least 3, at least 4, or at least 5 DNA nucleotides. In one embodiment, at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a DNA nucleotide. In another

2019232918 20 Sep 2019

embodiment, at least the second and fourth nucleotides from the 5' end of the oligonucleotide inhibitor are DNA nucleotides.

[0068] Oligonucleotide inhibitors of the present invention may include modified nucleotides that have a base modification or substitution. The natural or unmodified bases in RNA are the purine bases adenine (A) and guanine (G), and the pyrimidine bases cytosine (C) and uracil (U) (DNA has thymine (T)). Modified bases, also referred to as heterocyclic base moieties, include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo (including 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines), 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. In certain embodiments, oligonucleotide inhibitors targeting miR-155 comprise one or more BSN modifications in combination with a base modification (*e.g.* 5-methylcytosine).

[0069] Oligonucleotide inhibitors of the present invention may include nucleotides with modified sugar moieties. Representative modified sugars include carbocyclic or acyclic sugars, sugars having substituent groups at one or more of their 2', 3' or 4' positions and sugars having substituents in place of one or more hydrogen atoms of the sugar. In certain embodiments, the sugar is modified by having a substituent group at the 2' position. In additional embodiments, the sugar is modified by having a substituent group at the 3' position. In other embodiments, the sugar is modified by having a substituent group at the 4' position. It is also contemplated that a sugar may have a modification at more than one of those positions, or that an oligonucleotide inhibitor may have one or more nucleotides with a sugar modification at one position and also one or more nucleotides with a sugar modification at a different position.

[0070] Sugar modifications contemplated in the oligonucleotide inhibitors of the present invention include, but are not limited to, a substituent group selected from: OH, F, O-, S-, or

2019232918 20 Sep 2019

N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted with C<sub>1</sub> to C<sub>10</sub> alkyl or C<sub>2</sub> to C<sub>10</sub> alkenyl and alkynyl. In one embodiment, the modification includes 2'-methoxyethoxy (2'-O-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, which is also known as 2'-O-(2-methoxyethyl) or 2'-MOE), that is, an alkoxyalkoxy group. Another modification includes 2'-dimethylaminoethoxy, that is, a O(CH<sub>2</sub>)<sub>2</sub>ON(CH<sub>3</sub>)<sub>2</sub> group, also known as 2'-DMAOE and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethyl-amino-ethoxy-ethyl or 2'-DMAEOE), that is, 2'-O-CH<sub>2</sub>-O-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>.

[0071] Additional sugar substituent groups include allyl (-CH<sub>2</sub>-CH=CH<sub>2</sub>), -O-allyl, methoxy (-O-CH<sub>3</sub>), aminopropoxy (-OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>), and fluoro (F). Sugar substituent groups on the 2' position (2'-) may be in the arabino (up) position or ribo (down) position. One 2'-arabino modification is 2'-F. Other similar modifications may also be made at other positions on the sugar moiety, particularly the 3' position of the sugar on the 3' terminal nucleoside or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. In certain embodiments, the sugar modification is a 2'-O-alkyl (e.g. 2'-O-methyl, 2'-O-methoxyethyl), 2'-halo (e.g., 2'-fluoro, 2'-chloro, 2'-bromo), and 4' thio modifications.

[0072] Other modifications of oligonucleotide inhibitors to enhance stability and improve efficacy, such as those described in U.S. Patent No. 6,838,283, which is herein incorporated by reference in its entirety, are known in the art and are suitable for use in the methods of the invention. For instance, to facilitate *in vivo* delivery and stability, the oligonucleotide inhibitor can be linked to a steroid, such as cholesterol moiety, a vitamin, a fatty acid, a carbohydrate or glycoside, a peptide, or other small molecule ligand at its 3' end.

[0073] In some embodiments, the oligonucleotide inhibitors of the present invention may be conjugated to a carrier molecule such as a steroid (cholesterol). The carrier molecule is attached to the 3' or 5' end of the oligonucleotide inhibitor either directly or through a linker or a spacer group. In various embodiments, the carrier molecule is cholesterol, a cholesterol derivative, cholic acid or a cholic acid derivative. The use of carrier molecules disclosed in U.S. Patent No. 7,202,227, which is incorporated by reference herein in its entirety, is also envisioned. In certain embodiments, the carrier molecule is cholesterol and it is attached to the 3' or 5' end of the oligonucleotide inhibitor through at least a six carbon linker. In some embodiments, the carrier molecule is attached to the 3' or 5' end of the oligonucleotide

2019232918 20 Sep 2019

inhibitor through a six or nine carbon linker. In some embodiments, the linker is a cleavable linker. In various embodiments, the linker comprises a substantially linear hydrocarbon moiety. The hydrocarbon moiety may comprise from about 3 to about 15 carbon atoms and may be conjugated to cholesterol through a relatively non-polar group such as an ether or a thioether linkage. In certain embodiments, the hydrocarbon linker/spacer comprises an optionally substituted C2 to C15 saturated or unsaturated hydrocarbon chain (e.g. alkylene or alkenylene). A variety of linker/spacer groups described in U.S. Pre-grant Publication No. 2012/0128761, which is incorporated by reference herein in its entirety, can be used in the present invention.

[0074] In one embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of 11 to 16 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of the oligonucleotide inhibitor are locked nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide. In some of these embodiments, the fourth nucleotide from the 3' end of the oligonucleotide inhibitor is also a locked nucleotide. In some of these embodiments, at least the second and fourth nucleotides from the 5' end of the oligonucleotide inhibitor are DNA nucleotides. In certain embodiments, the oligonucleotide inhibitor of miR-155 has a length of 12 or 14 nucleotides. In some embodiments, the oligonucleotide inhibitor contains at least 5, 6, 7, 8, 9, or 10 locked nucleotides. In further embodiments, at least the sixth and/or the eighth nucleotide from the 5' end of the oligonucleotide inhibitor is a DNA nucleotide. In yet further embodiments, the oligonucleotide inhibitor comprises DNA nucleotides at the second, sixth, and the eighth position from the 5' end.

[0075] In another embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a modified or an unmodified deoxyribonucleic acid (DNA) nucleotide.

[0076] In yet another embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; wherein at least 7 nucleotides of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a modified or an unmodified deoxyribonucleic acid (DNA) nucleotide.

[0077] In yet another embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the fourth and fifth nucleotides from the 5' end of the oligonucleotide inhibitor are modified or unmodified deoxyribonucleic acid (DNA) nucleotides. In some of these embodiments, the fourth and/or the fifth DNA nucleotide from the 5' end of the oligonucleotide inhibitor are unmodified DNA nucleotides.

[0078] In some embodiments where the oligonucleotide inhibitor is 11 to 14 nucleotides long, said inhibitor contains at least 5, 6, 7, 8, 9, or 10 modified nucleotides. In some of these embodiments, the oligonucleotide inhibitor contains 7, 8, 9, or 10 modified nucleotides. In some embodiments where the oligonucleotide inhibitor is 11 to 14 nucleotides long, at least the first three nucleotides from the 3' end of said oligonucleotide inhibitor are modified nucleotides. In some embodiments, all modified nucleotides are locked nucleotides. In some embodiments, the 5, 6, 7, 8, 9, or 10 modified nucleotides present in the oligonucleotide inhibitors are a combination of locked nucleotides and nucleotides containing non-LNA modifications such as ethylene-bridged nucleotides, 2'-C-bridged bicyclic nucleotides, 2'-substituted nucleotides, and other sugar and/or base modifications described herein.

[0079] In some embodiments, the second nucleotide from the 5' end of the oligonucleotide inhibitor is an unmodified deoxyribonucleic acid (DNA) nucleotide.

[0080] In one embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of SEQ ID NO: 25. In another embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of SEQ ID NO: 22. In yet another embodiment, the oligonucleotide inhibitor of miR-155 comprises a sequence of SEQ ID NO: 23.

2019232918 20 Sep 2019

[0081] In some other embodiments, the oligonucleotide inhibitor of miR-155 comprises a sequence selected from the group consisting of SEQ ID NOs: 33, 39, 43, 44, 47, 58, 84, 99, 111, 115, and 120.

[0082] In various embodiments, the oligonucleotide inhibitor of miR-155-5p has a sequence selected from Table 1.

Table 1

SEQ ID NO.	Sequence (5'-3') with modifications <sup>1</sup>
SEQ ID NO: 3	5'-lAs.dTs.dCs.dAs.lCs.lGs.dAs.lTs.dTs.lAs.lGs.dCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 4	5'-lAs.dTs.dCs.dAs.lCs.lGs.dAs.dTs.lTs.lAs.lGs.dCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 5	5'-lAs.lTs.dCs.dAs.dCs.lGs.dAs.lTs.dTs.lAs.lGs.dCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 6	5'-lAs.lTs.dCs.dAs.dCs.lGs.lAs.dTs.dTs.lAs.lGs.lCs.dAs.lTs.dTs.lA-3'
SEQ ID NO: 7	5'-lAs.dTs.dCs.dAs.lCs.lGs.dAs.lTs.dTs.lAs.lGs.dCs.lAs.lTs.dTs.lA-3'
SEQ ID NO: 8	5'-lAs.lTs.dCs.dAs.lCs.dGs.dAs.dTs.lTs.lAs.dGs.lCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 9	5'-lAs.dTs.dCs.dAs.lCs.dGs.lAs.dTs.lTs.lAs.dGs.lCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 10	5'-lAs.dTs.dCs.lAs.dCs.dGs.lAs.lTs.dTs.lAs.lGs.dCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 11	5'-lAs.dTs.lCs.dAs.dCs.lGs.dAs.lTs.lTs.dAs.dGs.lCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 12	5'-lAs.lTs.dCs.lAs.lCs.dGs.dAs.dTs.lTs.lAs.dGs.lCs.lAs.dTs.dTs.lA-3'
SEQ ID NO: 13	5'-lAs.dTs.lCs.dAs.dCs.dGs.lAs.dTs.lTs.lAs.dGs.lCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 14	5'-lAs.dTs.lCs.dAs.lCs.dGs.lAs.dTs.lTs.dAs.lGs.dCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 15	5'-lTs.dCs.dAs.lCs.dGs.dAs.lTs.dTs.dAs.lGs.dCs.lAs.lTs.dTs.lA-3'
SEQ ID NO: 16	5'-lTs.dCs.lAs.dCs.dGs.lAs.lTs.dTs.dAs.lGs.dCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 17	5'-lTs.dCs.dAs.dCs.lGs.lAs.lTs.dTs.dAs.lGs.dCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 18	5'-lTs.lCs.lAs.dCs.lGs.dAs.dTs.lTs.lAs.dGs.lCs.dAs.dTs.lTs.lA-3'
SEQ ID NO: 19	5'-lTs.dCs.dAs.lCs.dGs.dAs.dTs.lTs.lAs.lGs.lCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 20	5'-lTs.dCs.lAs.dCs.lGs.lAs.lTs.dTs.dAs.lGs.lCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 21	5'-lGs.lAs.lTs.lTs.lAs.lGs.dCs.lAs.lTs.dTs.lA-3'
SEQ ID NO: 22	5'-lCs.dGs.lAs.lTs.lTs.lAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 23	5'-lCs.dGs.lAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 24	5'-lCs.lAs.dCs.lGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 25	5'-lCs.dAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'



2019232918 20 Sep 2019

SEQ ID NO.	Sequence (5'-3') with modifications <sup>1</sup>
SEQ ID NO: 26	5'-ITs.dCs.lAs.mdCs.lGs.lAs.ITs.dTs.dAs.lGs.lCs.lAs.dTs.ITs.lA-3'
SEQ ID NO: 27	5'-ITs.lAs.lGs.lCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 29	5'-lCs.dAs.lCs.dGs.lAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 30	5'-lCs.dAs.lCs.dGs.lAs.dTs.ITs.dAs.lGs.dCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 31	5'-lCs.dAs.lCs.dGs.dAs.ITs.ITs.lAs.lGs.dCs.lAs.dTs.ITs.lA-3'
SEQ ID NO: 32	5'-dCs.dAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 33	5'-lCs.lAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 34	5'-lCs.dAs.dCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 35	5'-lCs.dAs.lCs.lGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.ITs.lA-3'
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SEQ ID NO: 44	5'-lCs.dAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.dTs.lA-3'
SEQ ID NO: 45	5'-lCs.dAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.ITs.dA-3'
SEQ ID NO: 46	5'-dCs.lAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.ITs.lA-3'
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SEQ ID NO: 51	5'-lCs.dAs.lCs.dGs.dAs.ITs.ITs.lAs.dGs.dCs.lAs.ITs.ITs.lA-3'
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SEQ ID NO: 59	5'-lAs.lCs.lGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.ITs.lA-3'
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SEQ ID NO: 65	5'-lAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.lCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 66	5'-lAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.dAs.ITs.ITs.lA-3'
SEQ ID NO: 67	5'-lAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.dTs.ITs.lA-3'

2019232918 20 Sep 2019

SEQ ID NO.	Sequence (5'-3') with modifications <sup>1</sup>
SEQ ID NO: 68	5'-lAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.dTs.lA-3'
SEQ ID NO: 69	5'-lAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.dA-3'
SEQ ID NO: 70	5'-lAs.dCs.lGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 71	5'-lAs.lCs.dGs.lAs.dTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 72	5'-lAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 73	5'-lAs.lCs.dGs.dAs.lTs.dTs.lAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 74	5'-lAs.lCs.dGs.dAs.lTs.lTs.lAs.dGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 75	5'-lAs.lCs.dGs.dAs.lTs.lTs.dAs.dGs.lCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 76	5'-lAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.lCs.dAs.lTs.lTs.lA-3'
SEQ ID NO: 77	5'-dCs.dGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 78	5'-lCs.lGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 79	5'-lCs.dGs.lAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 80	5'-lCs.dGs.dAs.dTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 81	5'-lCs.dGs.dAs.lTs.dTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 82	5'-lCs.dGs.dAs.lTs.lTs.lAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 83	5'-lCs.dGs.dAs.lTs.lTs.dAs.dGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 84	5'-lCs.dGs.dAs.lTs.lTs.dAs.lGs.lCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 85	5'-lCs.dGs.dAs.lTs.lTs.dAs.lGs.dCs.dAs.lTs.lTs.lA-3'
SEQ ID NO: 86	5'-lCs.dGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 87	5'-lCs.dGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.dTs.lA-3'
SEQ ID NO: 88	5'-lCs.dGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.dA-3'
SEQ ID NO: 89	5'-dCs.lGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 90	5'-lCs.dGs.lAs.dTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 91	5'-lCs.dGs.dAs.lTs.dTs.lAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 92	5'-lCs.dGs.dAs.lTs.lTs.lAs.dGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 93	5'-lCs.dGs.dAs.lTs.lTs.dAs.dGs.lCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 94	5'-lCs.dGs.dAs.lTs.lTs.dAs.lGs.lCs.dAs.lTs.lTs.lA-3'
SEQ ID NO: 95	5'-dGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 96	5'-lGs.lAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 97	5'-lGs.dAs.dTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 98	5'-lGs.dAs.lTs.dTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 99	5'-lGs.dAs.lTs.lTs.lAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 100	5'-lGs.dAs.lTs.lTs.dAs.dGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 101	5'-lGs.dAs.lTs.lTs.dAs.lGs.lCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 102	5'-lGs.dAs.lTs.lTs.dAs.lGs.dCs.dAs.lTs.lTs.lA-3'
SEQ ID NO: 103	5'-lGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.dTs.lTs.lA-3'
SEQ ID NO: 104	5'-lGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.dTs.lA-3'
SEQ ID NO: 105	5'-lGs.dAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.dA-3'
SEQ ID NO: 106	5'-dGs.lAs.lTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 107	5'-lGs.lAs.dTs.lTs.dAs.lGs.dCs.lAs.lTs.lTs.lA-3'
SEQ ID NO: 108	5'-lGs.dAs.lTs.dTs.lAs.lGs.dCs.lAs.lTs.lTs.lA-3'

SEQ ID NO.	Sequence (5'-3') with modifications <sup>1</sup>
SEQ ID NO: 109	5'-IGs.dAs.ITs.ITs.lAs.dGs.dCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 110	5'-IGs.dAs.ITs.ITs.dAs.dGs.lCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 111	5'-IGs.dAs.ITs.ITs.dAs.lGs.lCs.dAs.ITs.ITs.lA-3'
SEQ ID NO: 112	5'-eCs.dAs.eCs.dGs.dAs.eTs.eTs.dAs.eGs.dCs.eAs.eTs.eTs.eA-3'
SEQ ID NO: 113	5'-lCs.dAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.eAs.ITs.ITs.eA-3'
SEQ ID NO: 114	5'-eCs.dAs.eCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 115	5'-lCs.dAs.lCs.dGs.dAs.ITs.ITs.dAs.eGs.dCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 116	5'-lCs.dAs.lCs.dGs.dAs.eTs.eTs.dAs.lGs.dCs.lAs.eTs.eTs.lA-3'
SEQ ID NO: 117	5'-lCs.dAs.lCs.dGs.dAs.ITs.eTs.dAs.lGs.dCs.lAs.ITs.ITs.lA-3'
SEQ ID NO: 118	5'-lCs.dAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.lAs.ITs.eTs.lA-3'
SEQ ID NO: 119	5'-lCs.dAs.lCs.dGs.dAs.ITs.ITs.dAs.lGs.dCs.abAs.ITs.ITs.abA-3'
SEQ ID NO: 120	5'-abCs.dAs.abCs.dGs.dAs.abTs.abTs.dAs.abGs.dCs.abAs.abTs.abTs.abA-3'

<sup>1</sup>l = locked nucleic acid modification; d = deoxyribonucleotide; s = phosphorothioate linkage; md = 5-Methylcytosine; e = ethylene-bridged nucleotide (ENA); ab = amino-2'-C-Bridged Bicyclic Nucleotide (CBBN).

[0083] Administration of an oligonucleotide inhibitor of the present invention to a subject reduces or inhibits the activity or function of miR-155 in cells of the subject. In one embodiment, the oligonucleotide inhibitor inhibits the activity or function of miR-155 in cancer cells, cells of the immune system including B and T lymphocytes, monocytes, macrophages, microglia, NK cells, and inflammatory cells. In one embodiment, the cancer cells are malignant T cells. Malignant T cells that can be treated with oligonucleotide inhibitors of the invention include cutaneous T cell lymphoma (CTCL) cells, CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, αβ T cells, γδ T cells and memory T cells. In one embodiment, the malignant T cells are cutaneous T cell lymphoma (CTCL) cells.

[0084] In some embodiments, certain oligonucleotide inhibitors of the present invention may show a greater inhibition of the activity or function of miR-155 in cancer cells, such as malignant T cells, compared to other miR-155 inhibitors. The term "other miR-155 inhibitors" includes nucleic acid inhibitors such as antisense oligonucleotides, antimiRs, antagoniRs, mixmers, gapmers, aptamers, ribozymes, small interfering RNAs, or small hairpin RNAs; antibodies or antigen binding fragments thereof; and/or drugs, which inhibit the activity or function of miR-155. It is possible that a particular oligonucleotide inhibitor of the present invention may show a greater inhibition of miR-155 in cancer cells, such as malignant T cells, compared to other oligonucleotide inhibitors of the present invention. The term "greater" as used herein refers to quantitatively more or statistically significantly more.

2019232918 20 Sep 2019

[0085] Administration of an oligonucleotide inhibitor of the present invention up-regulates the expression or activity of miR-155 target genes in cells of the subject. Target genes for miR-155 include, but are not limited to, INPP50/SHIP1, Jarid2, Picalm, Bach1, Wee1, CUX1, Cebpb, SPIB/PU.1, and IL7R. In one embodiment, oligonucleotide inhibitors of the present invention up-regulate the expression or activity of at least four target genes of miR-155 in cancer cells, cells of the immune system including B and T lymphocytes, monocytes, macrophages, microglia, NK cells, and inflammatory cells. In some embodiments, four target genes up-regulated by oligonucleotide inhibitors of the present invention include Bach1, Jarid2, Picalm, and SHIP1. The invention encompasses using the changes in the expression of these four genes (gene expression signature) as means to determine the activity of miR-155 inhibitors. In some embodiments, there is about 1.25-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, or 8-fold, including values therebetween, change in the expression or activity of miR-155 target genes upon administration of oligonucleotide inhibitors of the present invention. In one embodiment, there is at least about 2-fold, 3-fold, 4-fold, or 5-fold, including values therebetween, change in the expression or activity of miR-155 target genes upon administration of oligonucleotide inhibitors of the present invention.

[0086] In one embodiment, the oligonucleotide inhibitor of the present invention shows a greater up-regulation of miR-155 target genes in cancer cells, such as malignant T cells, compared to other miR-155 inhibitors. In certain embodiments, the oligonucleotide inhibitors of the present invention show a greater up-regulation of at least four target genes of miR-155 in cancer cells compared to other miR-155 inhibitors. In one embodiment, the oligonucleotide inhibitors of the present invention show a greater up-regulation of the expression or activity of four genes, namely, Bach1, Jarid2, Picalm, and SHIP1, in cancer cells compared to other miR-155 inhibitors. In various embodiments, "greater up-regulation" includes about 2-fold, 3-fold, 4-fold, or 5-fold, including values therebetween, increase in the expression or activity of miR-155 target genes compared to other miR-155 inhibitors.

[0087] In some embodiments, oligonucleotide inhibitors of the present invention reduce or inhibit proliferation of cancer cells and/or induce apoptosis of cancer cells, such as malignant T cells including cutaneous T cell lymphoma (CTCL) cells. Administration of oligonucleotide inhibitors of the present invention may provide up to about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 80%, 90% or 100%, including values therebetween, reduction in the number of cancer cells. In some

2019232918 20 Sep 2019

embodiments, oligonucleotide inhibitors of the present invention may provide at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, including values therebetween, reduction in the number of cancer cells.

[0088] In some embodiments, oligonucleotide inhibitors of the present invention may show a greater inhibition of proliferation of cancer cells and/or a greater induction in apoptosis of cancer cells compared to other miR-155 inhibitors. For example, an oligonucleotide inhibitor of the present invention may show up to about 10%, 15%, 20%, 25%, 30%, 35%, or 40%, including values therebetween, more reduction in the number of cancer cells compared to other miR-155 inhibitors.

[0089] The present invention provides methods for treating cancer in a subject in need thereof, comprising administering to the subject an oligonucleotide inhibitor of miR-155 according to the invention. The activity or function of miR-155 is reduced in cancer cells of the subject following administration of the oligonucleotide inhibitor.

[0090] In one embodiment, the method for treating cancer comprises administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 16 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of said oligonucleotide inhibitor are locked nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[0091] In another embodiment, the method for treating cancer comprises administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[0092] In another embodiment, the method for treating cancer comprises administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the

2019232918 20 Sep 2019

oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least 7 nucleotides of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[0093] In yet another embodiment, the method for treating cancer comprises administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the fourth and fifth nucleotides from the 5' end of the oligonucleotide inhibitor are deoxyribonucleic acid (DNA) nucleotides.

[0094] Cancers that can be treated according to the invention include lymphomas including a T cell lymphoma, such as cutaneous T cell lymphoma (CTCL), and a B cell lymphoma and a skin cancer. In certain embodiments, the method for treating cancer comprises administering an oligonucleotide inhibitor of miR-155 selected from the group consisting of SEQ ID NO: 22, SEQ ID NO: 23, and SEQ ID NO: 25. In some other embodiments, the method for treating cancer comprises administering an oligonucleotide inhibitor of miR-155 selected from the group consisting of SEQ ID NOs: 33, 39, 43, 44, 47, 58, 84, 99, 111, 115, and 120.

[0095] In one embodiment, the invention provides methods for treating the mycosis fungoides (MF) form of CTCL by administering to the subject an oligonucleotide inhibitor of miR-155 according to the invention. In one embodiment, the method for treating the MF form of CTCL comprises administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 16 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of said oligonucleotide inhibitor are locked nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[0096] In another embodiment, the invention provides methods for treating the mycosis fungoides (MF) form of CTCL comprising administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is

2019232918 20 Sep 2019

fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[0097] In another embodiment, the invention provides methods for treating the mycosis fungoides (MF) form of CTCL comprising administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least 7 nucleotides of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[0098] In yet another embodiment, the invention provides methods for treating the mycosis fungoides (MF) form of CTCL comprising administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the fourth and fifth nucleotides from the 5' end of the oligonucleotide inhibitor are deoxyribonucleic acid (DNA) nucleotides.

[0099] In certain embodiments, the method for treating the MF form of CTCL comprises administering an oligonucleotide inhibitor of miR-155 selected from the group consisting of SEQ ID NO: 22, SEQ ID NO: 23, and SEQ ID NO: 25. In some other embodiments, the method for treating the MF form of CTCL comprises administering an oligonucleotide inhibitor of miR-155 selected from the group consisting of SEQ ID NOs: 33, 39, 43, 44, 47, 58, 84, 99, 111, 115, and 120.

[00100] The invention also encompasses methods for treating CTCL comprising administering an oligonucleotide inhibitor of miR-155 according to the invention in combination with a second therapeutic agent. Current treatments for CTCL include skin-directed therapies such as topical steroids, topical nitrogen mustard (mechlorethamine HCL), topical retinoids, phototherapy, ultraviolet light treatment, psoralen ultraviolet light treatment, radiotherapy, electron beam therapy, etc. and systemic therapies such as administration of

2019232918 20 Sep 2019

histone deacetylase (HDAC) inhibitors, retinoids (bexarotene), interferon, and low dose antifolates (e.g. methotrexate and pralatrexate). Additional treatment options such as anti-CD30 antibody (e.g. Brentuximab), anti-CCR4 antibody (e.g. mogamulizumab), and anti-PD-1 or anti-PD-L1 antibody are currently being tested. The second therapeutic agent generally comprises an agent or a therapy selected from one of these treatments. For example, the invention encompasses methods for treating CTCL by administering the oligonucleotide inhibitor of miR-155 in combination with a second therapy such as treatment with HDAC inhibitors, retinoids, interferon, antifolates, topical steroids, topical retinoids, topical nitrogen mustard, phototherapy, ultraviolet light, psoralen and ultraviolet light, radiotherapy, electron beam therapy, anti-CD30 antibody (e.g. Brentuximab), anti-CCR4 antibody (e.g. mogamulizumab), and anti-PD-1 or anti-PD-L1 antibody.

[00101] A variety of HDAC inhibitors are known, some of which are approved by FDA for clinical use and some are being tested in clinical trials. The methods for treating cancer according to the invention encompass the use of HDAC inhibitors including, but not limited to, vorinostat, romidepsin, panobinostat (LBH589), mocetinostat, belinostat (PXD101), abexinostat, CI-994 (tacedinaline), and MS-275 (entinostat). In embodiments where a second therapy/agent is included, the second therapy/agent may be administered at different times prior to or after administration of the oligonucleotide inhibitor of miR-155. Prior administration includes, for instance, administration of the first agent within the range of about one week to up to 30 minutes prior to administration of the second agent. Prior administration may also include, for instance, administration of the first agent within the range of about 2 weeks to up to 30 minutes prior to administration of the second agent. After or later administration includes, for instance, administration of the second agent within the range of about one week to up to 30 minutes after administration of the first agent. After or later administration may also include, for instance, administration of the second agent within the range of about 2 weeks to up to 30 minutes after administration of the first agent.

[00102] The invention also provides methods for reducing or inhibiting proliferation of cancer cells, particularly malignant T cells, by administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 16 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of said



2019232918 20 Sep 2019

oligonucleotide inhibitor are locked nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[00103] In another embodiment, the invention provides methods for reducing or inhibiting proliferation of cancer cells, particularly malignant T cells, comprising administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[00104] In another embodiment, the invention provides methods for reducing or inhibiting proliferation of cancer cells, particularly malignant T cells, comprising administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least 7 nucleotides of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[00105] In yet another embodiment, the invention provides methods for reducing or inhibiting proliferation of cancer cells, particularly malignant T cells, comprising administering an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the fourth and fifth nucleotides from the 5' end of the oligonucleotide inhibitor are deoxyribonucleic acid (DNA) nucleotides.

[00106] In certain embodiments, methods for reducing or inhibiting proliferation of cancer cells, particularly malignant T cells, comprises administering an oligonucleotide inhibitor of miR-155 selected from the group consisting of SEQ ID NO: 22, SEQ ID NO: 23, and SEQ ID NO: 25. In some other embodiments, methods for reducing or inhibiting proliferation of cancer cells, particularly malignant T cells, comprises administering an oligonucleotide

2019232918 20 Sep 2019

inhibitor of miR-155 selected from the group consisting of SEQ ID NOs: 33, 39, 43, 44, 47, 58, 84, 99, 111, 115, and 120.

[00107] Malignant T cells include cutaneous T cell lymphoma (CTCL) cells, CD4<sup>+</sup> T cells and memory T cells. Administration of an oligonucleotide inhibitor of the present invention reduces the activity or function of miR-155 and/or up-regulates one or more target genes of miR-155 in malignant T cells following administration. Methods for reducing or inhibiting proliferation of cancer cells also include the use of second therapy/agents described above along with administration of the present oligonucleotide inhibitors.

[00108] In certain embodiments, the methods encompassed by the invention comprise administering 18.75, 37.5, or 75 mg of the oligonucleotide inhibitor of the invention per skin lesion of the patient. In other embodiments, the methods of the invention comprise systemically administering a total of about 37.5, 75, 150, 300, 600, 900, or 1200 mg, including values therebetween, of the oligonucleotide inhibitor of the invention to the patient. In yet some other embodiments, the methods of the invention comprise systemically administering a total of about 350, 700, 1050, 1400, 1750, 2100, 2450, 2800, 3150, or 3500 mg, including values therebetween, of the oligonucleotide inhibitor of the invention to the patient.

[00109] Preferably, administration of an oligonucleotide inhibitor of the present invention to the subject results in the improvement of one or more symptoms or pathologies associated with cancer. For instance, in one embodiment, administration of an oligonucleotide inhibitor of the present invention alone or in combination with a second therapeutic agent such as a HDAC inhibitor reduces the number of skin lesions; number of red, itchy patches or plaques on skin; and/or formation of new skin lesions/patches/plaques associated with CTCL. In one embodiment, administration of an oligonucleotide inhibitor of the present invention alone or in combination with a second therapeutic agent such as a HDAC inhibitor reduces or inhibits migration of malignant T lymphocytes to the skin. In another embodiment, administration of an oligonucleotide inhibitor of the present invention alone or in combination with a second therapeutic agent reduces total malignant T lymphocytes in the skin. In yet another embodiment, administration of an oligonucleotide inhibitor of the present invention alone or in combination with a second therapeutic agent reduces the number of malignant T cells that may escape or migrate from the skin into the periphery.

2019232918 20 Sep 2019

[00110] As used herein, the term "subject" or "patient" refers to any vertebrate including, without limitation, humans and other primates (*e.g.*, chimpanzees and other apes and monkey species), farm animals (*e.g.*, cattle, sheep, pigs, goats and horses), domestic mammals (*e.g.*, dogs and cats), laboratory animals (*e.g.*, rodents such as mice, rats, and guinea pigs), and birds (*e.g.*, domestic, wild and game birds such as chickens, turkeys and other gallinaceous birds, ducks, geese, and the like). In some embodiments, the subject is a mammal. In other embodiments, the subject is a human.

[00111] Any of the oligonucleotide inhibitors of miR-155 described herein can be delivered to the target cell (*e.g.* malignant T cells) by delivering to the cell an expression vector encoding the miR-155 oligonucleotide inhibitor. A "vector" is a composition of matter which can be used to deliver a nucleic acid of interest to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "vector" includes an autonomously replicating plasmid or a virus. Examples of viral vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, and the like. In one particular embodiment, the viral vector is a lentiviral vector or an adenoviral vector. An expression construct can be replicated in a living cell, or it can be made synthetically. For purposes of this application, the terms "expression construct," "expression vector," and "vector," are used interchangeably to demonstrate the application of the invention in a general, illustrative sense, and are not intended to limit the invention.

[00112] In one embodiment, an expression vector for expressing an oligonucleotide inhibitor of miR-155 comprises a promoter operably linked to a polynucleotide sequence encoding the oligonucleotide inhibitor. The phrase "operably linked" or "under transcriptional control" as used herein means that the promoter is in the correct location and orientation in relation to a polynucleotide to control the initiation of transcription by RNA polymerase and expression of the polynucleotide.

[00113] As used herein, a "promoter" refers to a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a gene. Suitable promoters include, but are not limited to RNA pol I, pol II, pol III, and viral promoters (*e.g.* human cytomegalovirus (CMV) immediate early gene

promoter, the SV40 early promoter, and the Rous sarcoma virus long terminal repeat). In one embodiment, the promoter is a T-cell specific promoter such as the proximal and distal promoters of the *lck* gene or promoter and enhancer sequences of the CD4 gene, etc.

[00114] In certain embodiments, the promoter operably linked to a polynucleotide encoding a miR-155 oligonucleotide inhibitor can be an inducible promoter. Inducible promoters are known in the art and include, but are not limited to, tetracycline promoter, metallothionein IIA promoter, heat shock promoter, steroid/thyroid hormone/retinoic acid response elements, the adenovirus late promoter, and the inducible mouse mammary tumor virus LTR.

[00115] Methods of delivering expression constructs and nucleic acids to cells are known in the art and can include, for example, calcium phosphate co-precipitation, electroporation, microinjection, DEAE-dextran, lipofection, transfection employing polyamine transfection reagents, cell sonication, gene bombardment using high velocity microprojectiles, and receptor-mediated transfection.

[00116] The present invention also provides methods for diagnosing CTCL and methods for monitoring clinical status of a patient undergoing the treatment for CTCL. The invention shows that administration of anti-miR-155 compounds of the invention up-regulates and/or down-regulates a unique set of genes in all three MF cell lines (HuT102, MJ, and MyLa) compared to control-treated cells or Sézary syndrome cells. The invention contemplates using a gene expression signature based on this unique set of genes to diagnose MF subtype of CTCL as well to monitor progress of the CTCL treatment with miR-155 inhibitors. For instance, the invention shows that a set of genes listed in Table 2 are up-regulated or down-regulated in all three MF cell lines in response to anti-miR-155 compounds of the invention. In one embodiment, the invention provides methods for diagnosing CTCL by measuring the expression levels of one or more genes listed in Table 2 in a subject suspected of suffering from CTCL, comparing the expression levels to reference levels (e.g. expression levels in a healthy subject or expression levels in non-cancer cells of the CTCL subject), and diagnosing the subject as having CTCL if the expression levels in the subject are down-regulated or up-regulated compared to reference levels.

2019232918 20 Sep 2019

Table 2

List of genes significantly up-regulated or down-regulated in all three MF cell lines in response to present anti-miR-155 compounds					
CFLAR	GALC	SMARCA2	HIF1A	FSD1L	CLINT1
CIAPIN1	TAB2	OSTM1	CCNB1IP1	TLE4	SUB1
GCFC2	TRAF1	UBA5	BRMS1L	GATA3	ST8SIA4
LAMP2	RC3H2	APLP2	TM9SF1	OBFC1	GNPDA1
KDM7A	PITHD1	SCAMP1	NELFCD	DNAJC12	H2AFY
GGCT	SLC2A3	WDFY1	PRPF6	TSPAN14	SMAD5
JARID2	ASUN	DIMT1	TCFL5	RAD51C	CSNK1A1
MBTD1	IPO5	SEPHS1	AHCY	DHX40	NIT2
COX15	DGKA	ZFAND6	DNTTIP1	RPS6KB1	KPNA1
ZMYND11	FAM107B	UIMC1	TIMP1	PIGL	TUSC2
ZDHHC6	TRMT11	GMCL1	NDFIP2	CPD	NCBP2
BIRC3	SP100	KLHL42	SLC25A15	PEX12	HEMK1
DEPDC1	TRAM1	DNM1L	ARL2BP	RAB5C	MAPKAPK3
NR1H3	CBFB	TGDS	HSDL1	MLX	COMMD2
TBPL1	TGFBR3	FKBP1A	USP10	UNC119	ACTR1B
PIAS1	GBA2	TRMT6	TSC2	TMEM33	GTF3C2
TBC1D23	HLTF	PEBP1	EIF3J	CLCN3	GCA
GOPC	MPP5	GANAB	OIP5	GALNT7	STAT1
VAMP3	PDE8A	MAEA	BLOC1S6	KLHL5	MOB4
HOMER3	PTGS2	GLG1	NCALD	ZPR1	GORASP2
AKR7A2	PICALM	pk	TSTA3	HIPK3	SLC1A4
AP5M1	NUAK1	GEMIN2	ASAH1	SLC35F2	NFE2L2
KIF1B	DPP8	RFFL	RELB	ELK3	PLEKHA3
FAM168A	SRI	CDC7	FAM32A	VPS29	EDEM3
FOXO3	TUBA3D	ERMP1	TBCB	COP57A	CD58
UCHL3	EXOSC7	HSD17B7P2	PRKD2	BTN3A3	WARS2
ITGB1BP1	TPD52	CIRBP	CDC37	ASF1A	SLAMF1
CPSF3	TOP2B	MAPK1	ARRDC2	STK38	SSX2IP
TRIM32	TM9SF3	MFNG	NAMPT	MRPL18	NENF
PPP6C	UBE2T	KIAA0930	WDR91	ALDH5A1	RCN2
HSDL2	DYNC1I2	CSF2RB	GARS	ACOT13	CTSD
VPS4B	UBE2K	SDR39U1	RPA3	GMNN	KMT2A
RBM25	C12orf5	CNIH1	GLCCI1	TRIM38	PLAGL1
SLC17A5	KEAP1	TIMM9	PSMA2	PHACTR2	MYB
TAF12	RAB21	CEP128	RHEB	KIF20A	TMEM5
HSPH1	RBCK1	IMPA1	FAM8A1	ATG12	MSI2
DUSP4	RRBP1	RRAS2	SDCBP	DDX46	ZUFSP
NAA50	PDCD2L	SARAF	FXDY2	G3BP1	PITPNC1
CD80	RAP1B	ARL8B	TUBGCP4	FARS2	FAM69A
LRIF1	SMARCA4	NAPG	ADAM10	MUT	BTG3
FYTTD1	TST	NARS	HADHB	DYNLT1	XPC
ACOT9	CALU	CCNH	ATAD1	WTAP	ATP6V1C1
CDK2	MTX2	DDB2	ABI2	C7orf55- LUC7L2	SAMSN1
FAM199X	GAD1	ETS1	BMP2K	SH3KBP1	SLC26A2
LPGAT1	SNRPN	RFK	FAM60A	TERF1	DCK

2019232918 20 Sep 2019

List of genes significantly up-regulated or down-regulated in all three MF cell lines in response to present anti-miR-155 compounds					
FAM210B	PSMG2	UBQLN1	ZCRB1	AUH	BACH1
SDC4	EIF2AK4	ANXA1	COMMD4	STOM	SFXN2
CSE1L	CALML4	HILPDA	SCAPER	POLE3	EEF1A1
TMEM189-UBE2V1	PSMA1	TES	FANCI	GLUD1	WDYHV1
STAU1	DCTD	MAP3K7	TXNL4B	ADD3	BUB1B
XPO5	CDKN2D	PRADC1	RANBP10	BTBD10	GATAD1
OARD1	PARP2	NTPCR	RPRD1A	SSRP1	PINK1
GLO1	ARHGEF6	TAF5L	ITGB3BP	CELF1	RAPGEF6
RIOK1	ZSWIM6	SP110	CTTNBP2NL	TMEM138	MRPL10
SLC35B3	ATXN10	MRP59	PSMA5	EI24	CCDC117
ATXN1	UBE2M	VPS36	ALDH9A1	PDCD4	GNE
RAP2A	LRRC47	BORA	CREG1	ITPR1	CALM3
CLPP	COX7B	PHF11	RGL1	TMEM263	TMPRSS3
ATP1A1	SH3BP5	NUDT15	PYCR2	TWF1	SQSTM1
PRKCI	NDFIP1	IL6	CHAC2	SRFBP1	CYB561A3
AIM2	VIMP	TTC5	CIAO1	GUF1	EXTL2
EIF5A2	CHSY1	VEZF1	TPRKB	TMEM123	DENND2D
SNHG16	ACTR10	RPS6KC1	RALB	GPD1L	IER5
COX18	DNAJB1	C9orf78	ZC3H8	PELO	BPNT1
GYG1	TBC1D14	STX17	KIAA1715	CENPH	TYW5
ZMYM6	HRSP12	ATP6V1G1	SUMF1	ANAPC1	H3F3A
TKT	SYT11	ENPP2	FAM134A	CETN3	RNF149
ZNF691	SERINC3	APTIX	ARL6IP5	RASSF3	CDC42EP3
METAP1	RFXAP	TCF19	KLHL8	RPIA	S100A11
RNF123	CSNK1G2	FLOT1	TBCK	ARFIP1	CCNYL1
ABCE1	BAG5	TBCA	PRKRA	YRDC	CCPG1
MOCS2	WBP1L	RNASEH1	SLC26A11	C6orf106	NUDCD2
WDR41	AKIP1	PRNP	FRAT2	SLC39A10	CHCHD7
GRPEL2	ATMIN	ZNF217	YIPF6	WDR45	AC093323.3
SLC35A1	TMEM41B	KRCC1	C5orf24	GMFB	FEZ2
CAMLG	WEE1	MRPL13	DEXI	IGF2R	PPID
HEY1	AP1G1	ISG20	P2RY8	PSMD12	SEPW1
CTSB	FAM96A	RASGRP1	C8orf33	FAR1	TMTC2
RAD21	TMEM194A	MIR4435-1HG	ADI1	MRPL42	TCAIM
C7orf55	HDHD2	TADA2B	ANXA2	TUBA3C	PACS2
YWHAZ	GPX4	NOC3L	SRPR	MAK16	SEPHS2
KIAA0196	TSR1	SSSCA1	DAZAP2	TCAF1	FAM72B
NFIL3	FTH1	CXorf23	BCOR	TXNRD1	ARID2
GKAP1	RAB4A	RBM4B	TMEM186	STK39	BLOC1S2
MID1IP1	DDIT4	FBXO45	RAD51D	GRK5	ACADSB
PMPCA	IRF2BP2	DENND4A	SDHAP1	PRC1	SUPT3H
HPRT1	BMI1	AKIRIN1	BRWD1	C1orf174	ATXN1L
TRUB1	ARF4	KIAA1551	MORF4L1	COX20	RP11-175019.4
FRAT1	CMAHP	SRP72	LAMP1	MICB	MCTS1
PTPLA	POLR3D	DENND6A	BICD2	TRIM27	AC093673.5

2019232918 20 Sep 2019

List of genes significantly up-regulated or down-regulated in all three MF cell lines in response to present antimir-155 compounds					
ARL5B	STAT3	PDE12	POLR1D	ZBTB10	LINC00657
IKBIP	LDLRAD4	YIF1A	MKL2	LIN52	HNRNPA3
ASH1L-AS1	SNTB2	CCNE2	TAF9B	DNAJC19	NT5DC1
PLGLA	MAP2K1	RAB6A	SECISBP2	ANKRD28	DCUN1D3
AP001258.4	CSNK1G1	CDC26	SEMA4D	SACM1L	KANSL1-AS1
CCDC71L	NMD3	EID2	ZFP69B	TSN	PTGER4
OTUD6B-AS1	CRADD	DNAJC30	EIF4EBP1	ARHGAP19	IARS
CUX1	ARL13B	RPS6KA3	TPRG1	IRF9	

[00117] In additional embodiments, the invention provides a method for selecting a subject for treatment of CTCL comprising determining a level of expression of one or more genes in CTCL cells of the subject, wherein the one or more genes are selected from a set of genes modulated in all MF cells, e.g. Table 2; comparing the level of the one or more genes in the CTCL cells of the subject to a reference level of the one or more genes; and selecting a subject having an increase or a decrease in the level of the one or more genes in the CTCL cells compared to the reference level for treatment of CTCL. In another embodiment, a method for selecting a subject for treatment of CTCL comprises determining a level of expression of 4 or more genes selected from the group consisting of INPP50/SHIP1, Jarid2, Picalm, Bach1, Wee1, CUX1, Cebpb, SPIB/PU.1, and IL7R, in CTCL cells of the subject; comparing the level of the 4 or more genes in the CTCL cells of the subject to a reference level of the 4 or more genes; and selecting a subject having a decrease in the level of the 4 or more genes in the CTCL cells compared to the reference level for treatment of CTCL. In one embodiment, the method for selecting a subject for treatment of CTCL comprises determining the level of 4 genes, Bach1, Jarid2, Picalm, and SHIP1, in CTCL cells of the subject in comparison to a reference level of the 4 genes. In certain embodiments, the method for selecting a subject for treatment of CTCL comprises determining the level of 4 genes, Bach1, Jarid2, Picalm, and SHIP1, in CTCL cells of the subject in comparison to a reference level of the 4 genes; and selecting a subject having at least 2-fold decrease in the level of the 4 genes in the CTCL cells compared to the reference level for treatment of CTCL. In one embodiment, the reference level is the level of expression of the same genes in control oligonucleotide-treated cells. In another embodiment, the reference level is the level of expression of the same genes in Sézary syndrome cells. In yet another embodiment, the reference level is the level of expression of the same genes in a healthy subject (e.g., a subject

2019232918 20 Sep 2019

that does not present with two or more symptoms of a skin cancer, a subject that has not been diagnosed with a skin cancer, and/or a subject that has no family history of skin cancer).

[00118] The invention also provides methods for assessing the efficacy of a treatment with anti-miR-155 compounds comprising determining a level of expression of one or more genes in cells of a subject prior to the treatment with anti-miR-155 compounds, wherein the one or more genes are selected from a set of genes modulated in all MF cells, e.g. Table 2; determining the level of expression of the same one or more genes in cells of the subject after treatment with anti-miR-155 compounds; and determining the treatment to be effective, less effective, or not effective based on the expression levels prior to and after the treatment. That is, in one embodiment, the genes listed in Table 2 serve as a biomarker for clinical efficacy of the anti-miR-155 treatment.

[00119] In some embodiments, the invention provides methods of diagnosing CTCL by measuring the level of miR-155 in a subject suspected of suffering from CTCL in comparison to a reference level, wherein the higher expression of miR-155 in the subject indicates the subject is suffering from CTCL. The level of expression of miR-155 in the subject suspected of suffering from CTCL may be determined using cells isolated from skin lesions of the subject, plasma, serum, white blood cells, or PBMCs. In certain embodiments, the invention provides methods of diagnosing mycosis fungoides form of CTCL by measuring the level of miR-155 in a subject in comparison to a reference level, wherein the higher expression of miR-155 in the subject indicates the subject is suffering from the MF form of CTCL. In some other embodiments, the invention provides methods for assessing the response to an anti-miR-155 treatment by determining a level of expression of miR-155 in the subject undergoing the treatment in comparison to a reference level of miR-155. The reference level can be the level of miR-155 in a healthy subject or the mean or median level of miR-155 from a group of healthy subjects or the level of miR-155 in a subject having Sézary syndrome.

[00120] The present invention also provides pharmaceutical compositions comprising an oligonucleotide inhibitor of miR-155 as disclosed herein and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition comprises an effective dose of an oligonucleotide inhibitor of miR-155 having a sequence of 11 to 16 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature



2019232918 20 Sep 2019

sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of the oligonucleotide inhibitor are locked nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[00121] In another embodiment, the pharmaceutical composition comprises an effective dose of an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from the 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[00122] In another embodiment, the pharmaceutical composition comprises an effective dose of an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least 7 nucleotides of said oligonucleotide inhibitor are modified nucleotides and at least the second nucleotide from the 5' end of the oligonucleotide inhibitor is a deoxyribonucleic acid (DNA) nucleotide.

[00123] In yet another embodiment, the pharmaceutical composition comprises an effective dose of an oligonucleotide inhibitor of miR-155 that has a sequence of 11 to 14 nucleotides, wherein the oligonucleotide inhibitor is fully complementary to a mature sequence of miR-155 and has a full phosphorothioate backbone; and wherein at least the first three nucleotides from 3' end of said oligonucleotide inhibitor are modified nucleotides and at least the fourth and fifth nucleotides from the 5' end of the oligonucleotide inhibitor are deoxyribonucleic acid (DNA) nucleotides.

[00124] In certain embodiments, pharmaceutical compositions comprise an effective dose of an oligonucleotide inhibitor having a sequence selected from the group consisting of SEQ ID NO: 22, SEQ ID NO: 23, and SEQ ID NO: 25. In some other embodiments, pharmaceutical compositions comprise an effective dose of an oligonucleotide inhibitor having a sequence selected from the group consisting of SEQ ID NOs: 33, 39, 43, 44, 47, 58, 84, 99, 111, 115,

2019232918 20 Sep 2019

and 120. In yet other embodiments, the pharmaceutical composition comprises an oligonucleotide inhibitor having a sequence selected from the sequences listed in Table 1.

[00125] An “effective dose” is an amount sufficient to effect a beneficial or desired clinical result. An effective dose of an oligonucleotide inhibitor of miR-155 of the invention may be from about 1 mg/kg to about 100 mg/kg, about 2.5 mg/kg to about 50 mg/kg, or about 5 mg/kg to about 25 mg/kg. In some embodiments, an effective dose may be about 18.75, 37.5, or 75 mg of the oligonucleotide inhibitor per skin lesion of the patient. The precise determination of what would be considered an effective dose may be based on factors individual to each patient, including their size, age, type of disorder, and form of inhibitor (*e.g.* naked oligonucleotide or an expression construct *etc.*). Therefore, dosages can be readily ascertained by those of ordinary skill in the art from this disclosure and the knowledge in the art.

[00126] In certain embodiments, the invention contemplates the use of a HDAC inhibitor in combination with the oligonucleotide inhibitors of the invention. In embodiments where a HDAC inhibitor is included, the HDAC inhibitor may be administered concurrently but in separate formulations or sequentially. In other embodiments, the HDAC inhibitor may be administered at different times prior to or after administration of a miR-155 inhibitor. Where clinical applications are contemplated, pharmaceutical compositions will be prepared in a form appropriate for the intended application. Generally, this will entail preparing compositions that are essentially free of pyrogens, as well as other impurities that could be harmful to humans or animals.

[00127] In one embodiment, the invention provides topical compositions comprising the oligonucleotide inhibitors of miR-155 and one or more cosmetically or pharmaceutically acceptable carriers or excipients. The term “cosmetically acceptable” as used herein means that the carriers or excipients are suitable for use in contact with tissues (*e.g.*, the skin) without undue toxicity, incompatibility, instability, irritation, allergic response, and the like.

[00128] Cosmetic or pharmaceutical carriers or excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Topical compositions often comprise an oil-in-water or a water-in-oil emulsion. The invention encompasses using such emulsions for

preparing topical composition of antimicrobials. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Suitable cosmetic carriers are described below.

[00129] In one embodiment, the cosmetically acceptable topical carrier is from about 50% to about 99.99%, by weight, of the composition (e.g., from about 80% to about 99%, by weight, of the composition). The topical compositions include, but are not limited to, solutions, lotions, creams, gels, sticks, sprays, ointments, cleansing liquid washes, solid bars, shampoos, pastes, foams, powders, mousses, shaving creams, wipes, patches, nail lacquers, wound dressing, adhesive bandages, hydrogels, and films. These product types may comprise several types of cosmetically acceptable topical carriers including, but not limited to solutions, emulsions (e.g., microemulsions and nanoemulsions), gels, solids and liposomes. Certain non-limitative examples of such carriers are set forth hereinbelow. Other suitable carriers may be formulated by those of ordinary skill in the art.

[00130] Topical compositions useful in the present invention may be formulated as a solution comprising an emollient. Such compositions preferably contain from about 1% to about 50% of an emollient(s). As used herein, the term "emollient" refers to materials used for the prevention or relief of dryness, as well as for the protection of the skin. A number of suitable emollients are known and may be used in the present invention. For example, Sagarin, *Cosmetics, Science and Technology*, 2nd Edition, Vol. 1, pp. 32-43 (1972) and the *International Cosmetic Ingredient Dictionary and Handbook*, eds. Wenninger and McEwen, pp. 1656-61, 1626, and 1654-55 (The Cosmetic, Toiletry, and Fragrance Assoc., Washington, D.C., 7th Edition, 1997) (hereinafter "ICI Handbook") contains numerous examples of suitable materials.

[00131] A lotion can be made from such a solution. Lotions typically comprise from about 1% to about 20% (e.g., from about 5% to about 10%) of an emollient(s) and from about 50% to about 90% (e.g., from about 60% to about 80%) of water.

[00132] Another type of product that may be formulated from a solution is a cream. A cream typically comprises from about 5% to about 50% (e.g., from about 10% to about 20%) of an emollient(s) and from about 45% to about 85% (e.g., from about 50% to about 75%) of water.

2019232918 20 Sep 2019

[00133] Yet another type of product that may be formulated from a solution is an ointment. An ointment may comprise a simple base of animal or vegetable oils or semi-solid hydrocarbons. An ointment may comprise from about 2% to about 10% of an emollient(s) plus from about 0.1% to about 2% of a thickening agent(s). A more complete disclosure of thickening agents or viscosity increasing agents useful herein can be found in Sagarin, *Cosmetics, Science and Technology*, 2nd Edition, Vol. 1, pp. 72-73 (1972) and the ICI Handbook pp. 1693-1697.

[00134] The topical compositions useful in the present invention may be formulated as emulsions. If the carrier is an emulsion, from about 1% to about 10% (e.g., from about 2% to about 5%) of the carrier comprises an emulsifier(s). Emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are disclosed in, for example, in McCutcheon's *Detergents and Emulsifiers*, North American Edition, pp. 317-324 (1986), and the ICI Handbook, pp.1673-1686.

[00135] Lotions and creams can be formulated as emulsions. Typically such lotions comprise from 0.5% to about 5% of an emulsifier(s). Such creams would typically comprise from about 1% to about 20% (e.g., from about 5% to about 10%) of an emollient(s); from about 20% to about 80% (e.g., from 30% to about 70%) of water; and from about 1% to about 10% (e.g., from about 2% to about 5%) of an emulsifier(s).

[00136] Single emulsion skin care preparations, such as lotions and creams, of the oil-in-water type and water-in-oil type are well known in the cosmetic art and are useful in the present invention. Multiphase emulsion compositions, for example the water-in-oil-in-water type, as disclosed in U.S. Pat. Nos. 4,254,105 and 4,960,764, may also be useful in the present invention. In general, such single or multiphase emulsions contain water, emollients, and emulsifiers as essential ingredients.

[00137] The topical compositions of this invention can also be formulated as a gel (e.g., an aqueous, alcohol, alcohol/water, or oil gel using a suitable gelling agent(s)). Suitable gelling agents for aqueous gels include, but are not limited to, natural gums, acrylic acid and acrylate polymers and copolymers, and cellulose derivatives (e.g., hydroxymethyl cellulose and hydroxypropyl cellulose). Suitable gelling agents for oils (such as mineral oil) include, but are not limited to, hydrogenated butylene/ethylene/styrene copolymer and hydrogenated

2019232918 20 Sep 2019

ethylene/propylene/styrene copolymer. Such gels typically comprise between about 0.1% and 5%, by weight, of such gelling agents.

[00138] Liposomal formulations are also useful compositions of the subject invention. In one embodiment, the oligonucleotides are contained within the liposome. Examples of liposomes are unilamellar, multilamellar, and paucilamellar liposomes, which may or may not contain phospholipids. Such compositions can be prepared by combining the oligonucleotide inhibitor with a phospholipid, such as dipalmitoylphosphatidyl choline, cholesterol and water. Commercially available fat emulsions that may be suitable for delivering the nucleic acids of the invention to cancer cells or the skin tissue include Intralipid®, Liposyn®, Liposyn® II, Liposyn® III, Nutrilipid, and other similar lipid emulsions. A preferred colloidal system for use as a delivery vehicle *in vivo* is a liposome (i.e., an artificial membrane vesicle). The preparation and use of such systems is well known in the art. Exemplary formulations are also disclosed in US 5,981,505; US 6,217,900; US 6,383,512; US 5,783,565; US 7,202,227; US 6,379,965; US 6,127,170; US 5,837,533; US 6,747,014; and WO03/093449, which are herein incorporated by reference in their entireties.

[00139] The liposome preparation may then be incorporated into one of the above carriers (e.g., a gel or an oil-in-water emulsion) in order to produce the liposomal formulation. Other compositions and uses of topically applied liposomes are described in Mezei, M., "Liposomes as a Skin Drug Delivery System", Topics in Pharmaceutical Sciences (D. Breimer and P. Speiser, eds.), Elsevier Science Publishers B. V., New York, N.Y., 1985, pp. 345-358, PCT Patent Application No. WO96/31194, Niemiec, et al., 12 Pharm. Res. 1184-88 (1995), and U.S. Pat. No. 5,260,065.

[00140] In one embodiment, the liposomes are present in the topical composition in an amount, based upon the total volume of the composition, of from about 5 mg/ml to about 100 mg/ml such as from about 10 mg/ml to about 50 mg/ml.

[00141] In addition to the above carriers and excipients, other emollients and surface active agents can be incorporated in the emulsions, including glycerol trioleate, acetylated sucrose distearate, sorbitan trioleate, polyoxyethylene (1) monostearate, glycerol monooleate, sucrose distearate, polyethylene glycol (50) monostearate, octylphenoxypoly (ethyleneoxy) ethanol, decaglycerin penta-isostearate, sorbitan sesquioleate, hydroxylated lanolin, lanolin,

2019232918 20 Sep 2019

triglyceryl diisostearate, polyoxyethylene (2) oleyl ether, calcium stearoyl-2-lactylate, methyl glucoside sesquistearate, sorbitan monopalmitate, methoxy polyethylene glycol-22/dodecyl glycol copolymer (Elfacos E200), polyethylene glycol-45/dodecyl glycol copolymer (Elfacos ST9), polyethylene glycol 400 distearate, and lanolin derived sterol extracts, glycol stearate and glycerol stearate; alcohols, such as cetyl alcohol and lanolin alcohol; myristates, such as isopropyl myristate; cetyl palmitate; cholesterol; stearic acid; propylene glycol; glycerine, sorbitol and the like.

[00142] In certain embodiments, liposomes used for delivery are amphoteric liposomes such as SMARTICLES® (Marina Biotech, Inc.) which are described in detail in U.S. Pre-grant Publication No. 20110076322. The surface charge on the SMARTICLES® is fully reversible which make them particularly suitable for the delivery of nucleic acids. SMARTICLES® can be delivered via injection, remain stable, and aggregate free and cross cell membranes to deliver the nucleic acids.

[00143] One will generally desire to employ appropriate salts and buffers to render delivery vehicles stable and allow for uptake by target cells. Pharmaceutical compositions of the present invention comprise an effective amount of the delivery vehicle comprising the inhibitor polynucleotides (*e.g.* liposomes or other complexes or expression vectors) dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium. The phrases “pharmaceutically acceptable” or “pharmacologically acceptable” refers to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, “pharmaceutically acceptable carrier” includes solvents, buffers, solutions, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like acceptable for use in formulating pharmaceuticals, such as pharmaceuticals suitable for administration to humans. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredients of the present invention, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions, provided they do not inactivate the vectors or polynucleotides of the compositions.

[00144] The active compositions of the present invention may include classic pharmaceutical preparations. Administration of these compositions according to the present invention may

2019232918 20 Sep 2019

be via any common route so long as the target tissue is available via that route. This includes oral, topical, parenteral, intradermal, subcutaneous, or intravenous injection. In another embodiment, compositions comprising oligonucleotide inhibitors of miR-155 as described herein may be formulated in the form suitable for a topical application such as a cream, ointment, paste, lotion, or gel.

[00145] The active compounds may also be administered parenterally. By way of illustration, solutions of the active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally contain a preservative to prevent the growth of microorganisms.

[00146] The pharmaceutical forms suitable for injectable use include, for example, sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. Generally, these preparations are sterile and fluid to the extent that easy injectability exists. Preparations should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms, such as bacteria and fungi. Appropriate solvents or dispersion media may contain, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00147] Sterile injectable solutions may be prepared by incorporating the active compounds in an appropriate amount into a solvent along with any other ingredients (for example as enumerated above) as desired, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which

2019232918 20 Sep 2019

contains the basic dispersion medium and the desired other ingredients, *e.g.*, as enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation include vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient(s) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00148] The compositions of the present invention generally may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts include, for example, acid addition salts (formed with the free amino groups of the protein) derived from inorganic acids (*e.g.*, hydrochloric or phosphoric acids), or from organic acids (*e.g.*, acetic, oxalic, tartaric, mandelic, and the like). Salts formed with the free carboxyl groups of the protein can also be derived from inorganic bases (*e.g.*, sodium, potassium, ammonium, calcium, or ferric hydroxides) or from organic bases (*e.g.*, isopropylamine, trimethylamine, histidine, procaine and the like).

[00149] Upon formulation, compositions are preferably administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations may easily be administered in a variety of dosage forms such as injectable solutions, cream, ointment, paste, lotion, or gel and the like. For parenteral administration in an aqueous solution, for example, the solution generally is suitably buffered and the liquid diluent first rendered isotonic for example with sufficient saline or glucose. Such aqueous solutions may be used, for example, for intravenous, subcutaneous, and intradermal administration. Preferably, sterile aqueous media are employed as is known to those of skill in the art, particularly in light of the present disclosure. Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by regulatory agencies.

[00150] In certain embodiments of the invention, the pharmaceutical compositions of the invention are packaged with or stored within a device for administration. Devices for injectable formulations include, but are not limited to, pre-filled syringes, injection ports, autoinjectors, injection pumps, and injection pens. Devices for aerosolized or powder formulations include, but are not limited to, inhalers, insufflators, aspirators, and the like.



2019232918 20 Sep 2019

Devices for dermal delivery of compositions of the present invention also include dermal microneedle injection or patches. Thus, the present invention includes administration devices comprising a pharmaceutical composition of the invention for treating or preventing one or more of the disorders described herein.

[00151] This invention is further illustrated by the following additional examples that should not be construed as limiting. Those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made to the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

**EXAMPLES:**

Example 1: Oligonucleotide inhibitors of miR-155 (“antimiR-155”) are active in mycosis fungoides cell lines which show increased miR-155 expression

[00152] To characterize miR-155-5p expression in cell lines derived from CTCL patients, the absolute levels of miR-155-5p in mycosis fungoides (MF), Sézary syndrome (SS), and a CTCL cell line classified as neither MF nor SS were measured. The cellular, pathological, and molecular characteristics of the cell lines examined are shown in Table 3.

**Table 3. Characteristics of CTCL Cell Lines**

Name	Disease	Age	Tissue source	Expressed Antigens	Molecular Characteristics
HuT78	Sézary syndrome	53	Peripheral blood	CD4+	HTLV-
MJ	Mycosis fungoides	50	Peripheral blood	CD4+, CD3+, CD2+	HTLV+
My-La	Mycosis fungoides	82	Skin plaque	CD4+, CD3+, CD2+	HTLV-
HuT102	Mycosis fungoides	26	Lymph node	CD4+	HTLV+
HH	Neither mycosis fungoides nor Sézary syndrome	61	Peripheral blood	CD4+, CD3+, CD2+, CD30+	HTLV-

[00153] The absolute expression of miR-155-5p in the CTCL cell lines compared to normal peripheral CD4+ helper T-cells was measured by real time PCR, using total RNA isolated from each cell type as a template. Standard curves correlating Ct value to miR-155-5p copy number were generated using a synthetic miR-155-5p RNA template. The copy number per cell of miR-155-5p was extrapolated from the Ct values determined for CTCL RNA samples or normal CD4+ T-cell RNA sample using the standard curve generated with the synthetic template, assuming 10 pg of total RNA per cell (Figure 1). The mycosis fungoides cell lines (HuT102, MJ, and My-La), as well as the idiopathic cell line (HH), showed high expression of miR-155-5p compared to normal CD4+ T-cells, while the cell line derived from a Sézary syndrome patient (HuT78) did not overexpress miR-155-5p.

[00154] CTCL cell lines were cultured in complete growth medium with the addition of antimiR-155 compound 1 (SEQ ID NO: 27), compound 2 (SEQ ID NO: 22), compound 3 (SEQ ID NO: 23), and compound 4 (SEQ ID NO: 25) at concentrations ranging from 2  $\mu$ M to 50  $\mu$ M. The antimiRs were added to the medium without any additional components to enhance cellular uptake. Cells were harvested after 72 hours of treatment and total RNA was purified. Real time PCR was performed for 13 direct gene targets of miR-155 (Worm et al. 2009; O'Connell et al. 2010; Zhang et al. 2012; and miRagen unpublished data). The relative fold-change in the expression of the 13 genes in the antimiR-treated cells compared to the untreated cells was calculated. Figure 2 shows a "heat map" representation of gene expression changes in response to 72 hours of treatment with 10  $\mu$ M of the indicated antimiR. Four predicted direct targets that lacked expression in at least one cell line were omitted. The gene expression fold-changes were log<sub>10</sub>-transformed, plotted on a red to blue colorimetric scale, where the most intense red represents the highest relative increase in gene expression, and conversely, the most intense blue is the greatest reduction in gene expression. The heat map showed that the expression of several of the miR-155-5p target genes was modulated upon exposure to the miR-155-5p antagonists in three mycosis fungoides cell lines (MJ, HuT102, and My-La). Similar, but more modest gene expression changes were observed in the idiopathic cell line (HH) that expresses high levels of miR-155-5p. In contrast, expression of these genes was not significantly altered in the Sézary syndrome cell line (HuT78) that expresses low levels of miR-155-5p, indicating that the changes in the gene expression levels in mycosis fungoides cell lines and HH cell line are mediated by antagonism of miR-155-5p.

2019232918 20 Sep 2019

Example 2: AntimiR-155 compounds 2 (SEQ ID NO: 22) and 4 (SEQ ID NO: 25) show greater activity in mycosis fungoides cells lines compared to other antimiR compounds

[00155] Four direct gene targets of miR-155-5p (Bach1, Jarid2, Picalm, and Ship1) were chosen for additional analysis, as these four genes were modulated by antimiR-155 in all three mycosis fungoides cell lines (MJ, HuT102, and My-La). These genes were chosen to represent the gene expression signature for antimiR activity in vitro. Additionally, the four-gene signature was used to compare the activity of the antimiR compounds. These gene changes were reproducible over three independent experiments with cells of varying passage numbers. Figures 3, 4, 5, 6, and 7 show the fold-change results of this four-gene signature in the HuT102, MJ, HH, My-La, and Hut78 cell lines, respectively. \* p-value < 0.0001 vs untreated by nonparametric Mann-Whitney test. The Mann-Whitney test was chosen because the variances are unequal between the treatments compared to untreated cells.

[00156] The cumulative data across three doses (2  $\mu$ M, 10  $\mu$ M, and 50  $\mu$ M) and three mycosis fungoides cell lines showed that compounds 2 (SEQ ID NO: 22) and 4 (SEQ ID NO: 25) were more active than compounds 1 (SEQ ID NO: 27) and 3 (SEQ ID NO: 23). As shown in Figure 7, all four antimiR-155-5p compounds showed no statistically significant activity in the Sézary syndrome line (HuT78), which is consistent with the lower expression levels of miR-155 in this cell line as shown in Figure 1.

Example 3: Gene expression changes induced by antimiR-155 treatment are specific to the inhibition of miR-155

[00157] To test the specificity of the gene expression changes induced by antimiR-155 compounds of the invention, mycosis fungoides cell lines were treated with oligos that do not target miR-155 (control oligos). The control oligonucleotide was a 14-nucleotide antimiR targeting a *C. elegans* miRNA not expressed in mammals (control 1). The second oligo is a scramble of the 14-nucleotide sequence of antimiR-155 compound 4 (control 2). The MJ and HuT102 cell lines were incubated with 10  $\mu$ M antimiR-155 compounds 3 (SEQ ID NO: 23) or 4 (SEQ ID NO: 25) or the two control oligos for 72 hours. Figure 8 shows the fold-change in gene expression for the four direct targets of miR-155-5p as measured by PCR. The gene expression signature in cells treated with antimiR-155 compounds 3 (SEQ ID NO: 23) or 4 (SEQ ID NO: 25) was statistically significantly different from that of untreated cells. In contrast, gene expression in cells treated with control compounds was not different from that of untreated cells. These results show that the miR-155 direct targets were de-repressed in

response to the miR-155 inhibition, and not due to non-specific effects of oligo treatment. \* p-value < 0.0001 vs untreated by nonparametric Mann-Whitney test.

Example 4: Whole genome expression profiling of CTCL cell lines treated with anti-miR-155 confirm target engagement and provide mechanistic insight

[00158] To gain a more complete understanding of the molecular consequences of miR-155 inhibition in mycosis fungoides cell lines, whole genome transcriptome profiling was performed on MJ and HuT102 cell lines treated with anti-miR-155 compounds 3 (SEQ ID NO: 23) or 4 (SEQ ID NO: 25) for 4 days (96 hours) or 8 days. The statistically-significant gene expression signature was defined by one-way ANOVA for anti-miR-treated cells compared to untreated cells at the same time point. Data were filtered for genes that were significantly changed with a false discovery rate corrected p-value of  $\leq 0.05$ . The fold-change results are shown in Figures 9 and 10 as heat maps, as described for Figure 2.

[00159] Examination of the global gene expression signatures at Day 4 and Day 8 suggested a time course for the gene expression changes in response to the anti-miR-155 treatment: unique gene sets were identified that were regulated at the early time point (4 days), or at the late time point (8 days), as well as some genes that were changed at both time points (Figure 9 for the MJ profile, Figure 10 for the HuT102 profile). Furthermore, the expression profiling identified unique gene sets regulated in each cell line, as well as some genes regulated in both cell lines. Compound 4 (SEQ ID NO: 25) demonstrated a greater magnitude of gene regulation in both cell lines and at both time points, as demonstrated by the greater intensity of blue and red colors across the Compound 4 (SEQ ID NO: 25) heat map.

[00160] The gene expression profile common to both cell lines and both compounds at Day 4 was analyzed for the enrichment of miR-155-5p seed-matched gene targets (8-, 7-, and 6-nucleotide binding sites). The fold-change of these genes is represented in a heat map in Figure 11. This signature of 150 up-regulated genes was significantly enriched for miR-155-5p seed-matched targets (8-, 7-, and 6-nucleotide binding sites), with a hypergeometric p-value of  $1.6 \times 10^{-25}$  (Figure 11A). Analysis by cumulative distribution function confirmed enrichment for seed-matched targets, and demonstrated enrichment for 8mer>7mer>6mer binding sites (Figure 11B). The gene signature was also analyzed using the DAVID bioinformatic resource for functional gene annotation enrichment (Huang da et al., 2009).

There was no significant enrichment of Gene Ontology database terms as defined by a Benjamini-corrected p-value of  $\leq 0.01$ .

[00161] The gene expression signature common to both cell lines and both compounds at Day 8 (677 genes in total) was subjected to analysis for enrichment of seed-matched gene targets and for functional gene annotation. The up-regulated gene signature was significantly enriched for seed-matched targets with a hypergeometric p-value of  $< 10^{-27}$ . Unlike the Day 4 signature, the Day 8 signature also showed strong enrichment of two functional annotation terms: antigen presentation in the up-regulated signature, and mitotic cell cycle in the down-regulated signature (Figure 12). Together, these results confirm that the effect of the antimiR compounds is mediated by the inhibition of miR-155-5p and its direct gene targets, and that phenotypes elicited by the inhibition of miR-155-5p function may include enhanced antigen presentation and reduction in proliferation.

[00162] The activity of antimiR-155 compound 4 (SEQ ID NO: 25) was further investigated by treating the third mycosis fungoides cell line, MyLa, with compound 4 (SEQ ID NO: 25) for 4 days and 8 days and profiling the changes in gene expression. To test the specificity of compound 4 (SEQ ID NO: 25), cells of the Sézary syndrome cell line (HuT78) were treated with compound 4 (SEQ ID NO: 25) for 8 days and the changes in gene expression were profiled. These results are shown in Figure 13. Genes that are statistically changed with a false discovery rate (FDR) corrected p-value of  $< 0.05$  in response to compound 4 (SEQ ID NO: 25) in three mycosis fungoides cell lines, HuT102, MJ, and My-La, are depicted in the heat map as described above. The total number of genes in the heat map is 324. Figure 13 shows that the treatment of Sézary syndrome cell line HuT78 with compound 4 (SEQ ID NO: 25) did not show much change in the gene expression indicating that the gene expression changes in mycosis fungoides cell lines are indeed due to the inhibition of miR-155-5p by compound 4 (SEQ ID NO: 25).

[00163] Additionally, genes regulated by compound 4 (SEQ ID NO: 25) in all three mycosis fungoides cell lines were identified as a biomarker signature that could be used for clinical assessment of treatment with antimiR-155 compounds, such as compound 4 (SEQ ID NO: 25), of the invention. The identified set of genes was up-regulated in all three cell lines or down-regulated in all three cell lines. Common signatures for each time point (Day 4 and Day 8) were identified and then combined into a single gene list (Table 2). No filter was

2019232918 20 Sep 2019

placed on the magnitude of gene expression. Therefore, Table 2 contains genes that are regulated only at Day 4, or only at Day 8, or regulated at both time points. Table 2 contains 587 genes comprising early (direct) targets and downstream (indirect) targets regulated by compound 4 (SEQ ID NO: 25) (Figure 21). The gene list in Table 2 includes the direct targets Bach1, Picalm, and Jarid2, demonstrating that these genes are robust markers of the compound 4 (SEQ ID NO: 25) activity across multiple cell lines and time points.

Example 5: AntimiR-155 compounds of the invention inhibits cell proliferation and increases apoptosis in CTCL cells

[00164] Passive uptake of antimiR-155 compounds by CTCL cells produced a significant reduction in cellular proliferation and induced programmed cell death. These effects were observed in two CTCL cell lines, HuT102 and MyLa. AntimiR-155 compounds 2 (SEQ ID NO: 22) and 4 (SEQ ID NO: 25) that demonstrated a greater target de-repression than antimiR-155 compound 3 (SEQ ID NO: 23) in both HuT102 and MyLa cell lines, showed a greater inhibition of proliferation and greater apoptotic activity.

[00165] Figure 14A shows the effect of antimiR-155 compound 4 (SEQ ID NO: 25) on proliferation of HuT-102 cells over time. Since the level of ATP correlates directly with cell number, ATP was measured to determine the cell number. The effect of compound 4 (SEQ ID NO: 25) on cell number was comparable to that seen with bexarotene, a standard-of-care therapy for CTCL (Figure 14A). The reduction in cell number was accompanied by an increase in apoptosis as measured by caspase 3/7 activity (Figure 14B). The caspase 3 and 7 proteins are members of the cysteine aspartic acid-specific protease (caspase) family. The caspase family plays key effector roles in apoptosis in mammalian cells. Caspase activity was normalized to ATP levels, as all cells have a low level of basal caspase activity that can confound the results if not normalized appropriately. Compound 4 (SEQ ID NO: 25) showed greater induction of apoptosis than bexarotene (Figure 14B).

[00166] In addition to a time course, a dose titration of antimiR-155 compounds in HuT102 cells was performed with ATP and caspase 3/7 measurements performed after eight days of treatment (Figures 15A and 15B, respectively). These results confirm the inhibitory potential of compound 4 (SEQ ID NO: 25).

2019232918 20 Sep 2019

[00167] Similar effects on proliferation and caspase 3/7 activation were observed with antimiR-155 compound 2 (SEQ ID NO: 22) at day 8 in HuT-102 cells (Figures 16A and 16B, respectively).

[00168] Compound 4 (SEQ ID NO: 25) showed similar activity in a second mycosis fungoides cell line, My-La cells. Figures 17A and 17B show proliferation and activation of caspase 3/7 over time with compounds 3 (SEQ ID NO: 23) and 4 (SEQ ID NO: 25). Similar to HuT102 cells, compound 4 (SEQ ID NO: 25) showed greater activity compared to compound 3 (SEQ ID NO: 23).

[00169] In addition to a time course, a dose titration of antimiR-155 compounds in My-La cells was performed with ATP and caspase 3/7 measurements after eight days of treatment (Figures 18A and 18B, respectively). These results further confirm the inhibitory potential of compound 4 (SEQ ID NO: 25).

Example 6: AntimiR-155 treatment combined with an HDAC inhibitor enhances the effect on cell proliferation and apoptosis activity.

[00170] Vorinostat (chemical name: SAHA) is a standard-of-care epigenetic therapy for patients with advanced mycosis fungoides. However, the side-effects of pan-HDAC inhibitors are well-described. To determine whether a combination therapy might show enhanced activity compared to treatment with individual compounds, HuT102 cells were treated with a sub-efficacious dose of SAHA combined with antimiR-155.

[00171] HuT102 cells were treated with 0.25  $\mu$ M SAHA and 10  $\mu$ M compound 3 (SEQ ID NO: 23) or 4 (SEQ ID NO: 25), individually or in combination. Cells were harvested daily to measure ATP levels and caspase 3/7 activity. ATP levels are shown in Figure 19A. A similar experiment was performed with 0.50  $\mu$ M SAHA. Figure 19B shows ATP levels obtained when HuT102 cells were treated with 0.50  $\mu$ M SAHA and 10  $\mu$ M compound 3 (SEQ ID NO: 23) or 4 (SEQ ID NO: 25), individually or in combination.

[00172] Figures 20A and 20B show the effect on caspase 3/7 activity. Compound 4 (SEQ ID NO: 25) when combined with 0.25 or 0.5  $\mu$ M of SAHA resulted in increased apoptosis compared to each treatment alone. This data suggests that antimiR-155 oligos can be used in combination with low doses pan-HDAC inhibitor.

2019232918 20 Sep 2019

Example 7: AntimiR-155 activity of oligonucleotides of different lengths

[00173] To assess the activity of a miR-155 inhibitor, a dual luciferase reporter assay system was used. In brief, the binding site for miR-155 was cloned into the 3' UTR of the *Renilla* luciferase gene located within the commercially-available psiCHECK-2 vector system (Promega). In the absence of a miR-155 inhibitor, the expression of *Renilla* luciferase protein is repressed by a miR-155 mimic. In the presence of a miR-155 inhibitor, the expression of *Renilla* luciferase protein is de-repressed. To control for transfection of the plasmid, the vector contains a firefly luciferase gene that does not contain the miR-155 binding site. Expression of either *Renilla* or firefly luciferase is measured through detection of light emitted by the luciferase protein.

[00174] 50 ng of the dual luciferase reporter plasmid containing the miR-155 binding site was transfected into HeLa cells without a miR-155 mimic ("Reporter" only), with 10 nM miR-155 mimic ("Reporter + mimic"), with 10 nM miR-155 mimic and 2 nM of the control oligonucleotide, or with 10 nM miR-155 mimic and 2 nM of a test miR-155 oligonucleotide inhibitor of 11-14 nucleotide lengths (Table 4). The miR-155 mimic was purchased from Dharmacon (miRIDIAN microRNA Human hsa-miR-155-5p mimic; Accession number MIMAT0000646; catalog # C-300647-05-0005) and contains the mature miRNA sequence: -UAAAUGC UAAUCGUGAUAGGGGU- (SEQ ID NO: 121). The control oligonucleotide used in the experiment had the following sequence: 5'-ICs.dTs.dAs.lGs.dAs.lAs.dAs.lGs.lAs.dGs.lTs.dAs.lGs.lA-3' (SEQ ID NO: 122).

**Table 4**

SEQ ID NO.	Modified Sequence	LNA #	Length
25	5'- ICs;dAs;lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	9	14
54	5'- lAs;lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	9	13
55	5'- lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	8	12
56	5'- lGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	8	11

[00175] FIG. 22 shows that transfection of the reporter plasmid and the mimic resulted in the maximal repression of luciferase; transfection of the reporter plasmid alone resulted in the maximum expression of luciferase; transfection of the control oligonucleotide with the reporter and the mimic did not de-repress the expression of luciferase; and transfection of the



test miR-155 oligonucleotide inhibitors with the reporter and the mimic de-repressed the expression of luciferase to differing extents.

Example 8: AntimiR-155 activity of oligonucleotides containing varying number of locked nucleotides (LNAs)

[00176] The experiment was performed as described in Example 7. Test miR-155 oligonucleotide inhibitors used in this experiment differed in the number of LNAs contained (Tables 5-8). The results are shown in FIGs. 23A (Table 5), 23B (Table 6), 23C (Table 7), and 23D (Table 8).

**Table 5**

SEQ ID NO.	Modified Sequence	LNA #	Length
25	5'-ICs;dAs;ICs;dGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	9	14
32	5'-dCs;dAs;ICs;dGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	14
33	5'-ICs;IAs;ICs;dGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	10	14
34	5'-ICs;dAs;dCs;dGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	14
35	5'-ICs;dAs;ICs;IGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	10	14
36	5'-ICs;dAs;ICs;dGs;IAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	10	14
37	5'-ICs;dAs;ICs;dGs;dAs;dTs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	14
38	5'-ICs;dAs;ICs;dGs;dAs;ITs;dTs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	14
39	5'-ICs;dAs;ICs;dGs;dAs;ITs;ITs;IAs;IGs;dCs;IAs;ITs;ITs;IA-3'	10	14
40	5'-ICs;dAs;ICs;dGs;dAs;ITs;ITs;dAs;dGs;dCs;IAs;ITs;ITs;IA-3'	8	14
41	5'-ICs;dAs;ICs;dGs;dAs;ITs;ITs;dAs;IGs;ICs;IAs;ITs;ITs;IA-3'	10	14
42	5'-ICs;dAs;ICs;dGs;dAs;ITs;ITs;dAs;IGs;dCs;dAs;ITs;ITs;IA-3'	8	14
43	5'-ICs;dAs;ICs;dGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;dTs;ITs;IA-3'	8	14
44	5'-ICs;dAs;ICs;dGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;dTs;IA-3'	8	14
45	5'-ICs;dAs;ICs;dGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;dA-3'	8	14

2019232918 20 Sep 2019

Table 6

SEQ ID NO.	Modified Sequence	LNA #	Length
25	5'- Cs;dAs; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	14
54	5'- As; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	13
57	5'-dAs; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	8	13
58	5'- As;dCs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	8	13
59	5'- As; Cs; Gs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	10	13
60	5'- As; Cs;dGs; As; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	10	13
61	5'- As; Cs;dGs;dAs;dTs; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	8	13
62	5'- As; Cs;dGs;dAs; Ts;dTs;dAs; Gs;dCs; As; Ts; Ts; A-3'	8	13
63	5'- As; Cs;dGs;dAs; Ts; Ts; As; Gs;dCs; As; Ts; Ts; A-3'	10	13
64	5'- As; Cs;dGs;dAs; Ts; Ts;dAs;dGs;dCs; As; Ts; Ts; A-3'	8	13
65	5'- As; Cs;dGs;dAs; Ts; Ts;dAs; Gs; Cs; As; Ts; Ts; A-3'	10	13
66	5'- As; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs;dAs; Ts; Ts; A-3'	8	13
67	5'- As; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As;dTs; Ts; A-3'	8	13
68	5'- As; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts;dTs; A-3'	8	13
69	5'- As; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts;dA-3'	8	13

Table 7

SEQ ID NO.	Modified Sequence	LNA #	Length
25	5'- Cs;dAs; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	14
55	5'- Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	8	12
77	5'-dCs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	7	12
78	5'- Cs; Gs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	12
79	5'- Cs;dGs; As; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	12
80	5'- Cs;dGs;dAs;dTs; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	7	12
81	5'- Cs;dGs;dAs; Ts;dTs;dAs; Gs;dCs; As; Ts; Ts; A-3'	7	12
82	5'- Cs;dGs;dAs; Ts; Ts; As; Gs;dCs; As; Ts; Ts; A-3'	9	12

83	5'-lCs;dGs;dAs;lTs;lTs;dAs;dGs;dCs;lAs;lTs;lTs;lA-3'	7	12
84	5'-lCs;dGs;dAs;lTs;lTs;dAs;lGs;lCs;lAs;lTs;lTs;lA-3'	9	12
85	5'-lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;dAs;lTs;lTs;lA-3'	7	12
86	5'-lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;dTs;lTs;lA-3'	7	12
87	5'-lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;dTs;lA-3'	7	12
88	5'-lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;dA-3'	7	12

Table 8

SEQ ID NO.	Modified Sequence	LNA #	Length
25	5'-lCs;dAs;lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	9	14
56	5'-lGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	8	11
95	5'-dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	7	11
96	5'-lGs;lAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	9	11
97	5'-lGs;dAs;dTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	7	11
98	5'-lGs;dAs;lTs;dTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	7	11
99	5'-lGs;dAs;lTs;lTs;lAs;lGs;dCs;lAs;lTs;lTs;lA-3'	9	11
100	5'-lGs;dAs;lTs;lTs;dAs;dGs;dCs;lAs;lTs;lTs;lA-3'	7	11
101	5'-lGs;dAs;lTs;lTs;dAs;lGs;lCs;lAs;lTs;lTs;lA-3'	9	11
102	5'-lGs;dAs;lTs;lTs;dAs;lGs;dCs;dAs;lTs;lTs;lA-3'	7	11
103	5'-lGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;dTs;lTs;lA-3'	7	11
104	5'-lGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;dTs;lA-3'	7	11
105	5'-lGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;dA-3'	7	11

Example 9: AntimiR-155 activity of oligonucleotides containing LNA modifications at various positions

[00177] The experiment was performed as described in Example 7. Test miR-155 oligonucleotide inhibitors used in this experiment differed in the position of LNA modifications (Tables 9-12). The results are shown in FIGs. 24A (Table 9), 24B (Table 10), 24C (Table 11), and 24D (Table 12).

2019232918 20 Sep 2019

Table 9

SEQ ID NO.	Modified Sequence	LNA #	Length
25	5'- Cs;dAs; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	14
46	5'-dCs; As; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	14
47	5'- Cs; As;dCs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	14
48	5'- Cs;dAs;dCs; Gs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	14
49	5'- Cs;dAs; Cs;dGs; As;dTs; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	14
50	5'- Cs;dAs; Cs;dGs;dAs; Ts;dTs; As; Gs;dCs; As; Ts; Ts; A-3'	9	14
51	5'- Cs;dAs; Cs;dGs;dAs; Ts; Ts; As;dGs;dCs; As; Ts; Ts; A-3'	9	14
52	5'- Cs;dAs; Cs;dGs;dAs; Ts; Ts;dAs;dGs; Cs; As; Ts; Ts; A-3'	9	14
53	5'- Cs;dAs; Cs;dGs;dAs; Ts; Ts;dAs; Gs; Cs;dAs; Ts; Ts; A-3'	9	14

Table 10

SEQ ID NO.	Modified Sequence	LNA #	Length
25	5'- Cs;dAs; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	14
54	5'- As; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	13
70	5'- As;dCs; Gs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	13
71	5'- As; Cs;dGs; As;dTs; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	13
72	5'- As; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	13
73	5'- As; Cs;dGs;dAs; Ts;dTs; As; Gs;dCs; As; Ts; Ts; A-3'	9	13
74	5'- As; Cs;dGs;dAs; Ts; Ts; As;dGs;dCs; As; Ts; Ts; A-3'	9	13
75	5'- As; Cs;dGs;dAs; Ts; Ts;dAs;dGs; Cs; As; Ts; Ts; A-3'	9	13
76	5'- As; Cs;dGs;dAs; Ts; Ts;dAs; Gs; Cs;dAs; Ts; Ts; A-3'	9	13

Table 11

SEQ ID NO.	Modified Sequence	LNA #	Length
25	5'- Cs;dAs; Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	9	14
55	5'- Cs;dGs;dAs; Ts; Ts;dAs; Gs;dCs; As; Ts; Ts; A-3'	8	12

89	5'-dCs;IGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	12
90	5'-ICs;dGs;IAs;dTs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	12
91	5'-ICs;dGs;dAs;ITs;dTs;IAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	12
92	5'-ICs;dGs;dAs;ITs;ITs;IAs;dGs;dCs;IAs;ITs;ITs;IA-3'	8	12
93	5'-ICs;dGs;dAs;ITs;ITs;dAs;dGs;ICs;IAs;ITs;ITs;IA-3'	8	12
94	5'-ICs;dGs;dAs;ITs;ITs;dAs;IGs;ICs;dAs;ITs;ITs;IA-3'	8	12

Table 12

SEQ ID NO.	Modified Sequence	LNA #	Length
25	5'-ICs;dAs;ICs;dGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	9	14
56	5'-IGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	11
106	5'-dGs;IAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	11
107	5'-IGs;IAs;dTs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	11
108	5'-IGs;dAs;ITs;dTs;IAs;IGs;dCs;IAs;ITs;ITs;IA-3'	8	11
109	5'-IGs;dAs;ITs;ITs;IAs;dGs;dCs;IAs;ITs;ITs;IA-3'	8	11
110	5'-IGs;dAs;ITs;ITs;dAs;dGs;ICs;IAs;ITs;ITs;IA-3'	8	11
111	5'-IGs;dAs;ITs;ITs;dAs;IGs;ICs;dAs;ITs;ITs;IA-3'	8	11

Example 10: AntimiR-155 activity of oligonucleotides containing various nucleotide modifications

[00178] The experiment was performed as described in Example 7. Test miR-155 oligonucleotide inhibitors used in this experiment were 14 nucleotides in length and each contained 9 nucleotide modifications (Table 13). The nucleotide modifications included locked nucleotides (LNAs), ethylene-bridged nucleic acids/ ethylene-bridged nucleotides (ENAs), and 2'-C-Bridged Bicyclic Nucleotide (CBBN). The results are shown in FIG. 25.

Table 13

SEQ ID NO.	Modified Sequence	Mod #	Length
25	5'-ICs;dAs;ICs;dGs;dAs;ITs;ITs;dAs;IGs;dCs;IAs;ITs;ITs;IA-3'	9	14

112	5'-eCs;dAs;eCs;dGs;dAs;eTs;eTs;dAs;eGs;dCs;eAs;eTs;eTs;eA-3'	9	14
113	5'-lCs;dAs;lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;eAs;lTs;lTs;eA-3'	9	14
114	5'-eCs;dAs;eCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	9	14
115	5'-lCs;dAs;lCs;dGs;dAs;lTs;lTs;dAs;eGs;dCs;lAs;lTs;lTs;lA-3'	9	14
116	5'-lCs;dAs;lCs;dGs;dAs;eTs;eTs;dAs;lGs;dCs;lAs;eTs;eTs;lA-3'	9	14
117	5'-lCs;dAs;lCs;dGs;dAs;lTs;eTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	9	14
118	5'-lCs;dAs;lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;eTs;lA-3'	9	14
119	5'-lCs;dAs;lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;abAs;lTs;lTs;abA-3'	9	14

l = locked nucleotide; d = deoxyribonucleotide; s = phosphorothioate linkage; e = ethylene-bridged nucleotide; ab = amino-2'-C-Bridged Bicyclic Nucleotide (CBBN).

Example 11: AntimiR-155 activity of 14-nucleotide long oligonucleotides

[00179] The experiment was performed as described in Example 7. Test miR-155 oligonucleotide inhibitors used in this experiment were 14 nucleotides in length and contained 9 or 10 LNA modifications (Table 14). The results are shown in FIG. 26.

Table 14

SEQ ID NO.	Modified Sequence	LNA #	Length
25	5'-lCs;dAs;lCs;dGs;dAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	9	14
29	5'-lCs;dAs;lCs;dGs;lAs;lTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	10	14
30	5'-lCs;dAs;lCs;dGs;lAs;dTs;lTs;dAs;lGs;dCs;lAs;lTs;lTs;lA-3'	9	14
31	5'-lCs;dAs;lCs;dGs;dAs;lTs;lTs;lAs;lGs;dCs;lAs;dTs;lTs;lA-3'	9	14

Example 12: AntimiR-155 activity of oligonucleotide inhibitors containing SEQ ID NOs: 25 and 23

[00180] The experiment was performed as described in Example 7. Test miR-155 oligonucleotide inhibitors used in this experiment were oligonucleotide inhibitors of SEQ ID NOs: 25 and 23. The results are shown in FIG. 27.

Example 13: AntimiR-155 activity of oligonucleotide inhibitors containing SEQ ID NOs: 25 and 120.

2019232918 20 Sep 2019

[00181] miR-155 oligonucleotide inhibitors of SEQ ID NOs: 25 and 120 were passively transfected in the Oci-Ly3 cell line. mRNA was isolated on Day 4 and was analyzed by qPCR for the expression of miR-155 target genes (Bach1, CEBPB, CUX1, INPP5D/SHIP1, Jarid2, Picalm, and Wee1). FIG. 28 shows the fold-change in the expression of these genes upon transfection of the oligonucleotide inhibitors of SEQ ID NOs: 25 and 120. The order of genes from left to right in each data point in FIG. 28 is Bach1, CEBPB, CUX1, INPP5D/SHIP1, Jarid2, Picalm, and Wee1. SEQ ID NO: 120 contains CBBN nucleotides in the same positions as the LNA in SEQ ID NO: 25.

CLAIMS:

1. An oligonucleotide inhibitor of miR-155, comprising the sequence of 5'-lCs.dAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.lCs.dAs.lTs.lTs.lA-3' (SEQ ID NO: 53), wherein l stands for a locked nucleotide; d stands for a deoxyribonucleotide; and s stands for a phosphorothioate linkage.
2. The oligonucleotide inhibitor of claim 1, wherein said oligonucleotide inhibitor consists of the sequence of 5'-lCs.dAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.lCs.dAs.lTs.lTs.lA-3' (SEQ ID NO: 53).
3. The oligonucleotide inhibitor of claim 1 or 2, wherein said oligonucleotide inhibitor reduces proliferation of cancer cells.
4. The oligonucleotide inhibitor of claim 3, wherein said cancer cells are T cell lymphoma cells.
5. The oligonucleotide inhibitor of claim 3 or 4, wherein the proliferation of cancer cells is reduced by about 30-90% compared to untreated cells.
6. The oligonucleotide inhibitor of claim 5, wherein the proliferation of T cell lymphoma cells is reduced by about 30-90% compared to untreated cells.
7. The oligonucleotide inhibitor of any one of the preceding claims, wherein said oligonucleotide inhibitor induces apoptosis of cancer cells.
8. The oligonucleotide inhibitor of claim 7, wherein said cancer cells are T cell lymphoma cells.
9. The oligonucleotide inhibitor of claim 7, wherein the oligonucleotide inhibitor increases caspase activity in cancer cells by at least about 2-fold compared to untreated cells.



10. The oligonucleotide inhibitor of claim 1 or 2, wherein said oligonucleotide inhibitor reduces proliferation of T cells.
11. The oligonucleotide inhibitor of claim 10, wherein the reduction in T cell proliferation is dose-dependent.
12. A composition comprising an oligonucleotide inhibitor of miR-155, comprising the sequence of 5'- lCs.dAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.lCs.dAs.lTs.lTs.lA-3' (SEQ ID NO: 53), wherein l stands for a locked nucleotide; d stands for a deoxyribonucleotide; and s stands for a phosphorothioate linkage.
13. The composition of claim 12, wherein said oligonucleotide inhibitor consists of the sequence of 5'- lCs.dAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.lCs.dAs.lTs.lTs.lA-3' (SEQ ID NO: 53).
14. The composition of claim 12 or 13, wherein the composition is a pharmaceutical composition and comprises a pharmaceutically acceptable carrier or excipient.
15. A method of treating a T cell lymphoma in a subject in need thereof, comprising administering to the subject an oligonucleotide inhibitor of miR-155 comprising the sequence of 5'- lCs.dAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.lCs.dAs.lTs.lTs.lA-3' (SEQ ID NO: 53), wherein l stands for a locked nucleotide; d stands for a deoxyribonucleotide; and s stands for a phosphorothioate linkage.
16. Use of an oligonucleotide inhibitor of miR-155 comprising the sequence of 5'- lCs.dAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.lCs.dAs.lTs.lTs.lA-3' (SEQ ID NO: 53), wherein l stands for a locked nucleotide; d stands for a deoxyribonucleotide; and s stands for a phosphorothioate linkage, in the manufacture of a medicament for treating a T cell lymphoma in a subject in need thereof.

17. The method of claim 15 or the use of claim 16, wherein said oligonucleotide inhibitor consists of the sequence of 5'- ICs.dAs.lCs.dGs.dAs.lTs.lTs.dAs.lGs.lCs.dAs.lTs.lTs.lA-3' (SEQ ID NO: 53).
18. The method of claim 15 or 17, or the use of claim 16 or 17, wherein the administration of said oligonucleotide inhibitor or medicament reduces proliferation of T cell lymphoma cells.
19. The method or use of claim 18, wherein the proliferation of T cell lymphoma cells is reduced by about 30-90% compared to untreated cells.
20. The method of any one of claims 15 or 17 to 19, or the use of any one of claims 16 to 19, wherein the administration of said oligonucleotide inhibitor or medicament shows a dose-dependent inhibition of miR-155.
21. The method of any one of claims 15 or 17 to 20, or the use of any one of claims 16 to 20, wherein the administration of said oligonucleotide inhibitor or medicament induces apoptosis of T cell lymphoma cells.
22. The method or use of claim 21, wherein the administration of said oligonucleotide inhibitor or medicament increases caspase activity in T cell lymphoma cells by at least about 2-fold compared to untreated cells.
23. The method of any one of claims 15 or 17 to 22, or the use of any one of claims 16 to 22, wherein said oligonucleotide inhibitor or medicament is administered to the subject via injection.

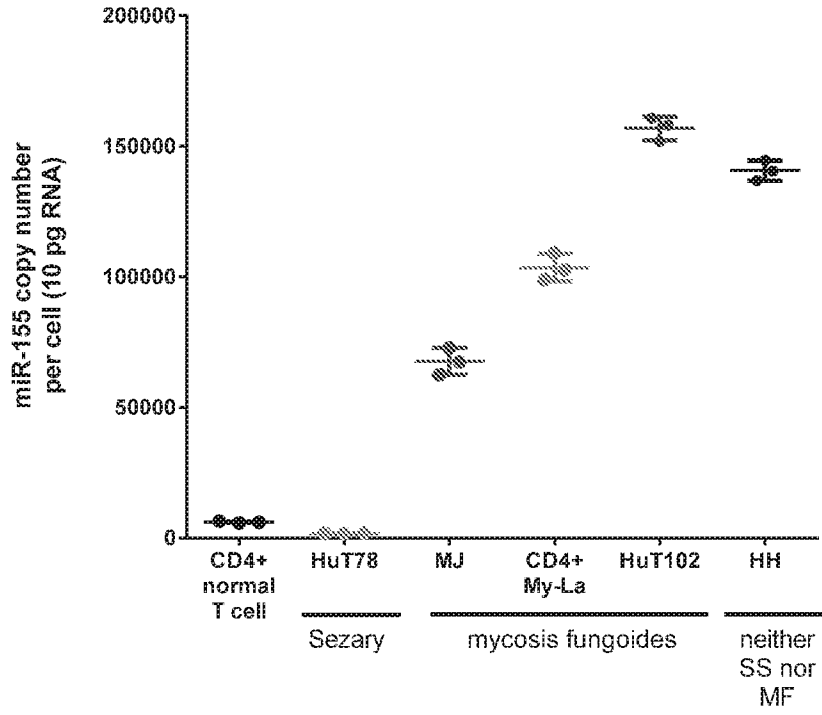


FIG. 1

2019232918 20 Sep 2019

2/34

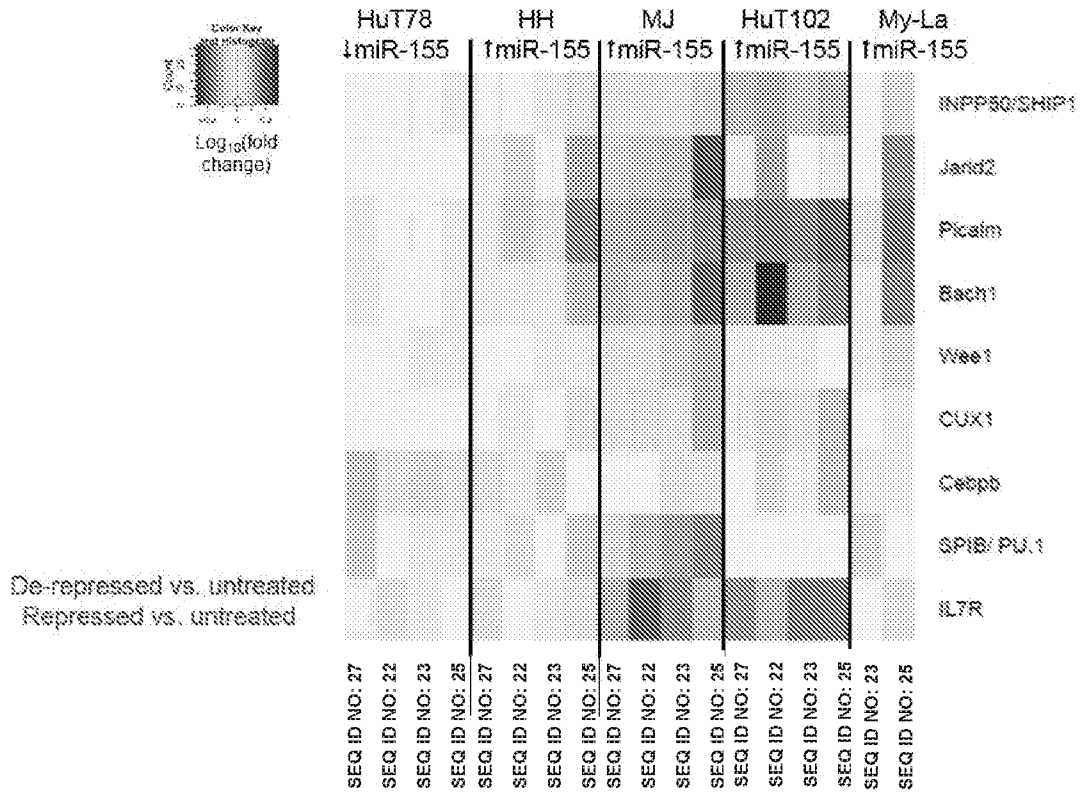


FIG. 2

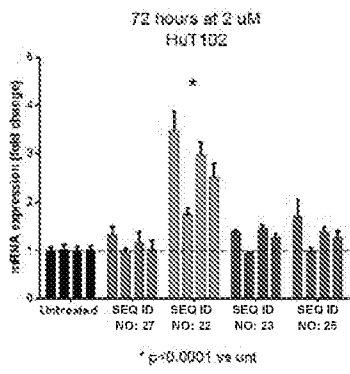


FIG. 3A

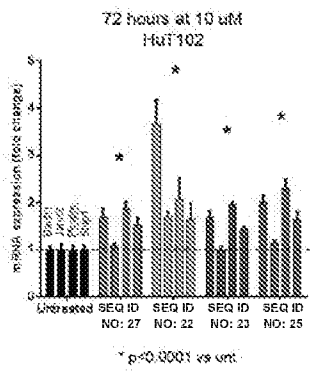


FIG. 3B

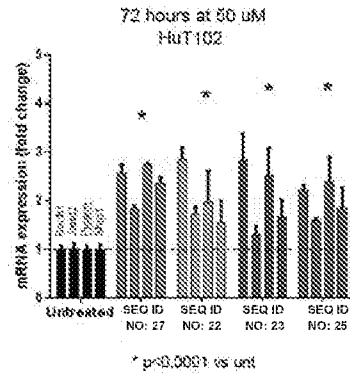


FIG. 3C

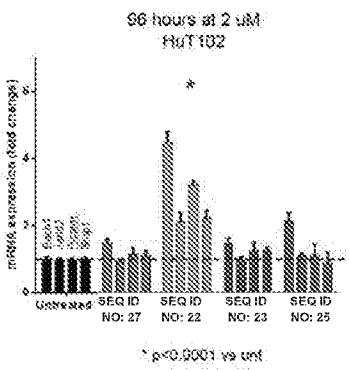


FIG. 3D

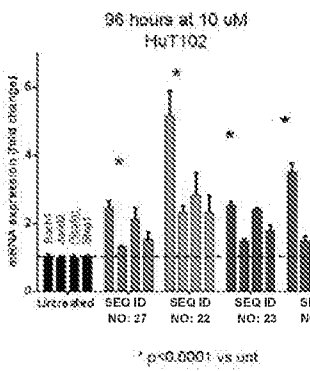


FIG. 3E

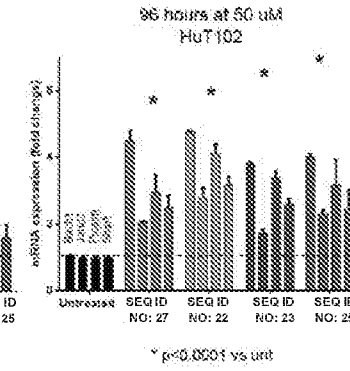


FIG. 3F

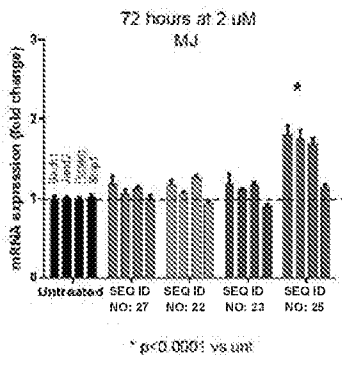


FIG. 4A

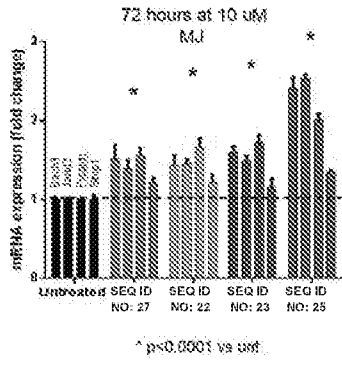


FIG. 4B

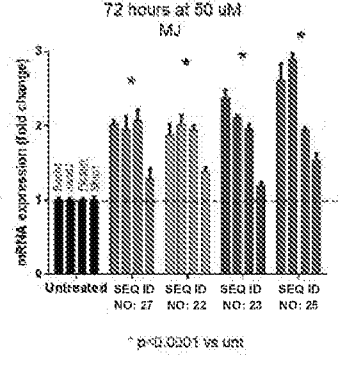


FIG. 4C

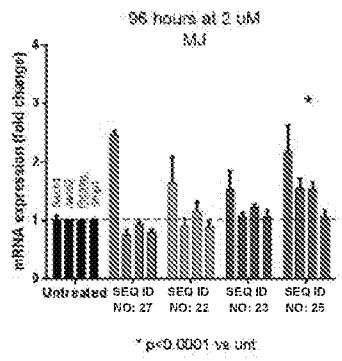


FIG. 4D

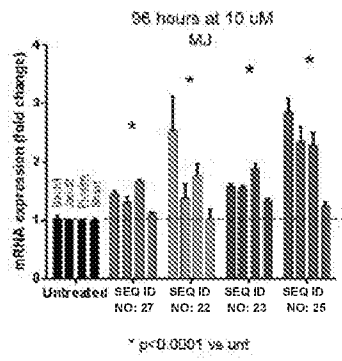


FIG. 4E

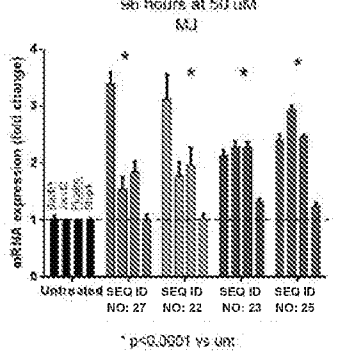


FIG. 4F

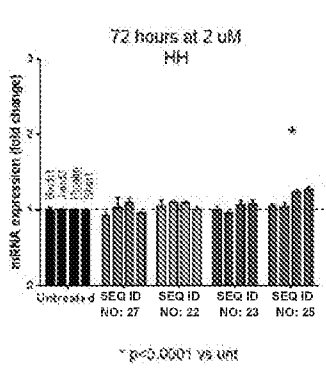


FIG. 5A

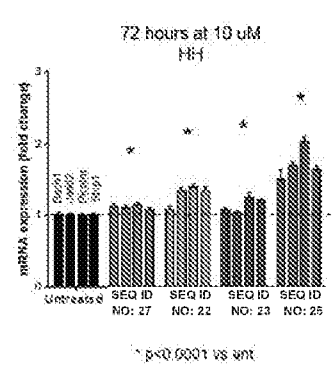


FIG. 5B

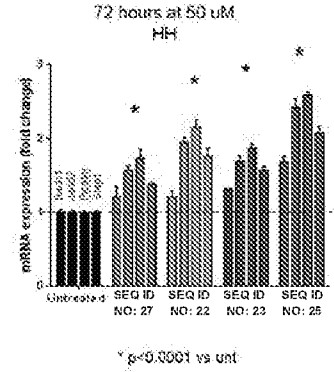


FIG. 5C

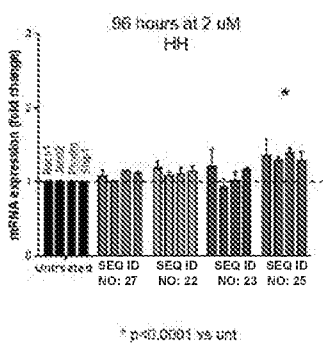


FIG. 5D

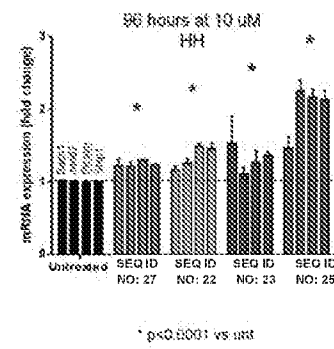


FIG. 5E

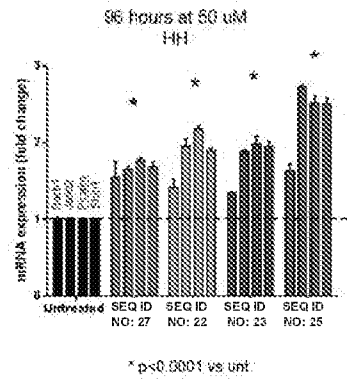


FIG. 5F

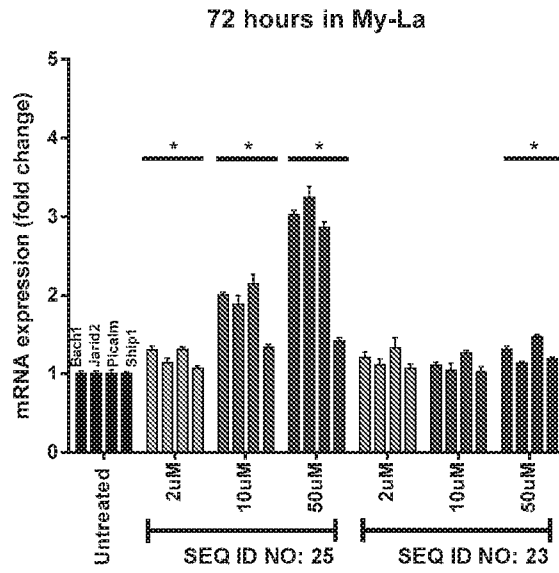


FIG. 6A

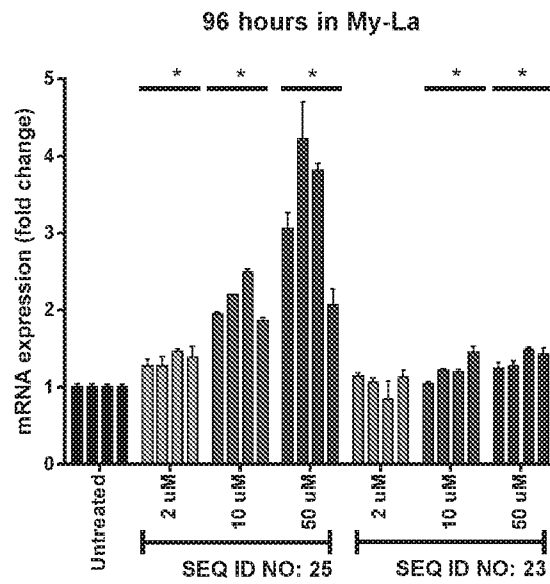


FIG. 6B



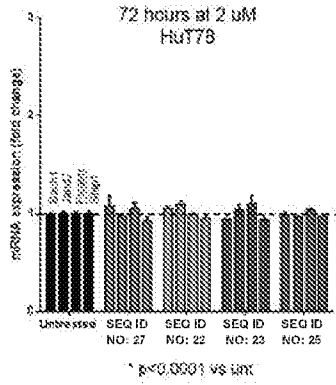


FIG. 7A

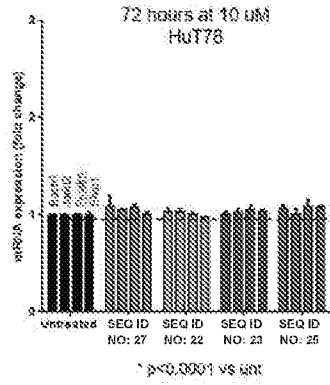


FIG. 7B

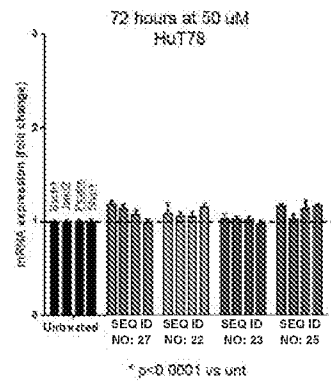


FIG. 7C

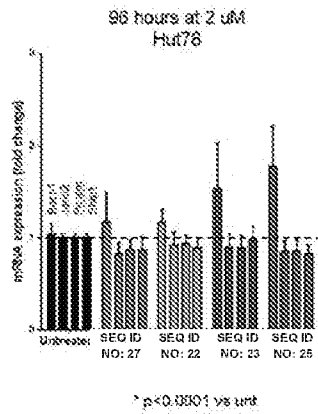


FIG. 7D

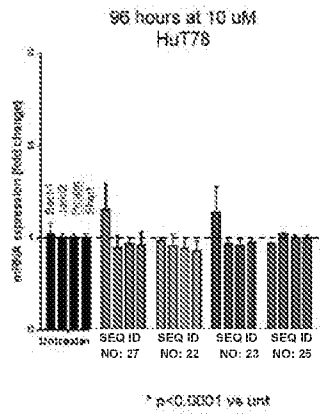


FIG. 7E

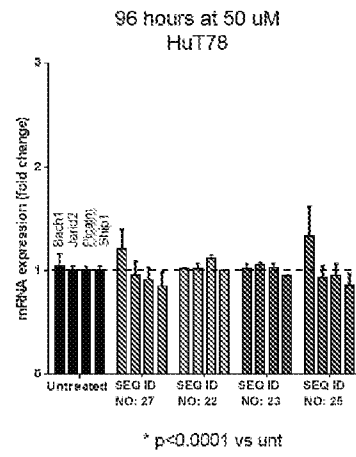


FIG. 7F

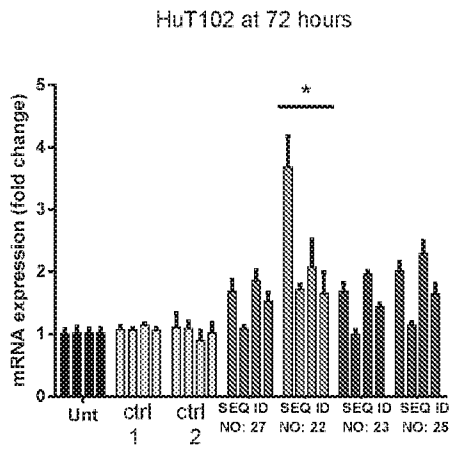


FIG. 8A

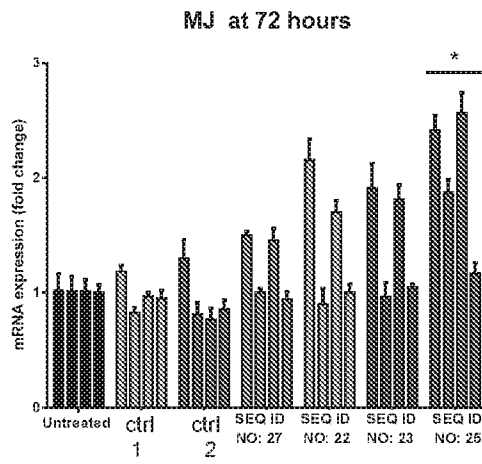


FIG. 8B

2019232918 20 Sep 2019

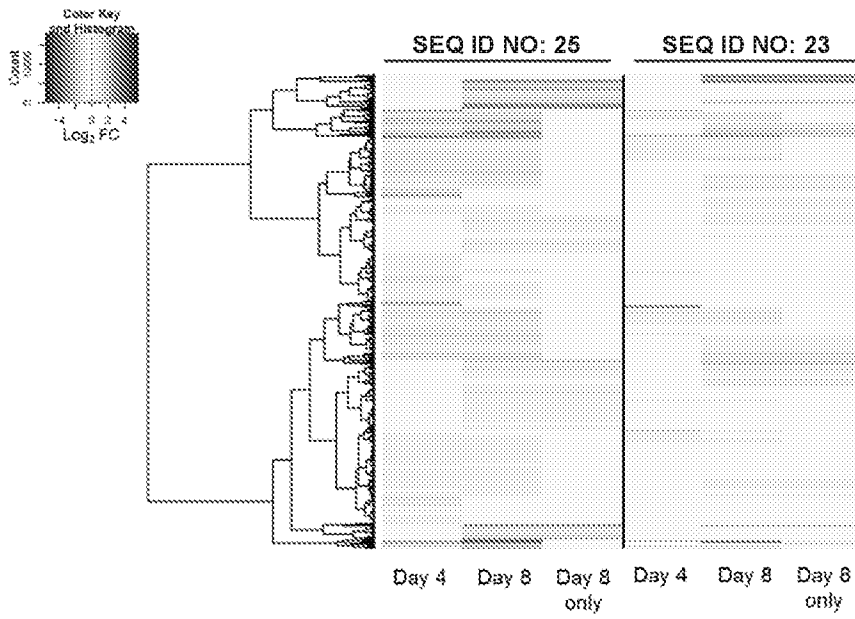


FIG. 9

2019232918 20 Sep 2019

10/34

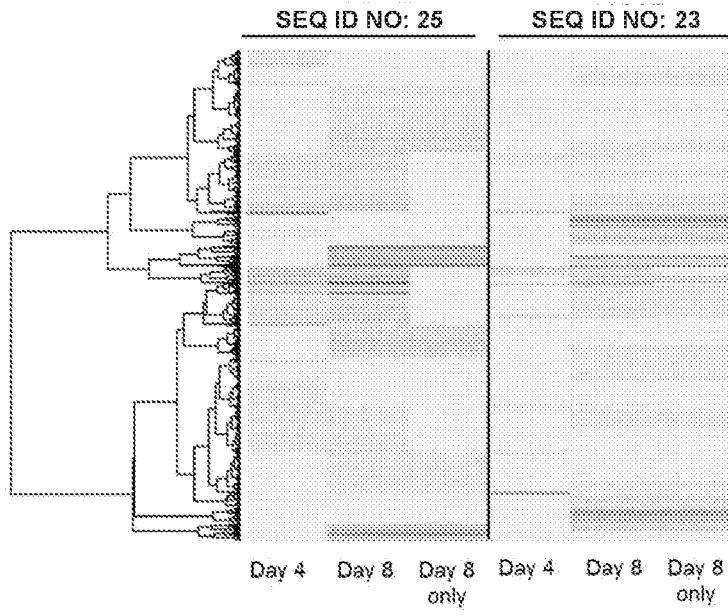


FIG. 10

2019232918 20 Sep 2019

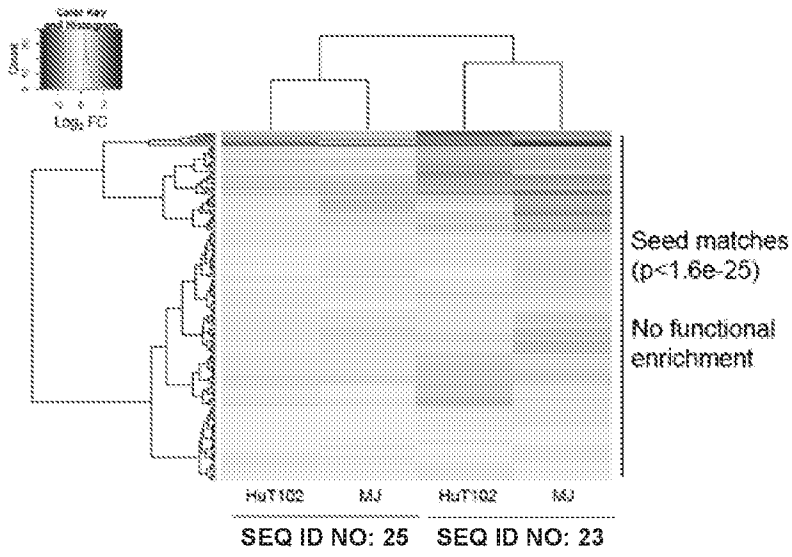


FIG. 11A

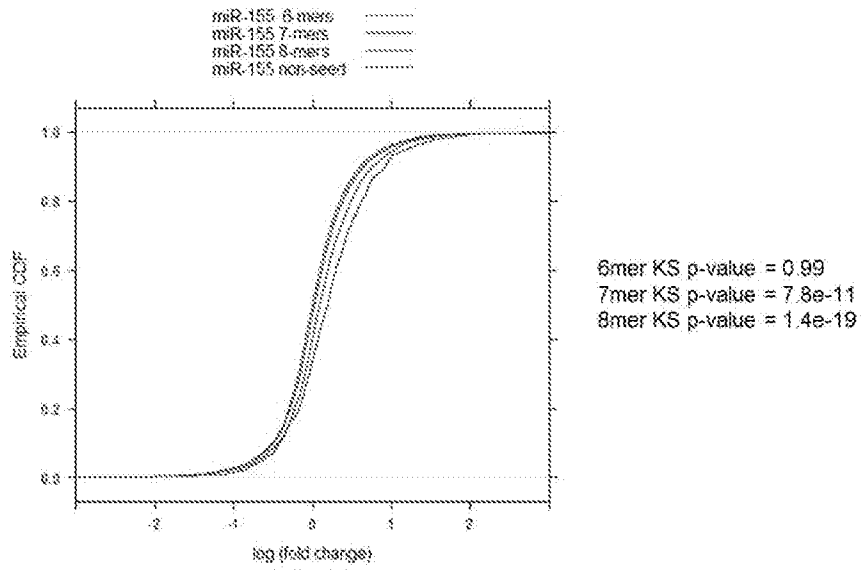


FIG. 11B

2019232918 20 Sep 2019

12/34

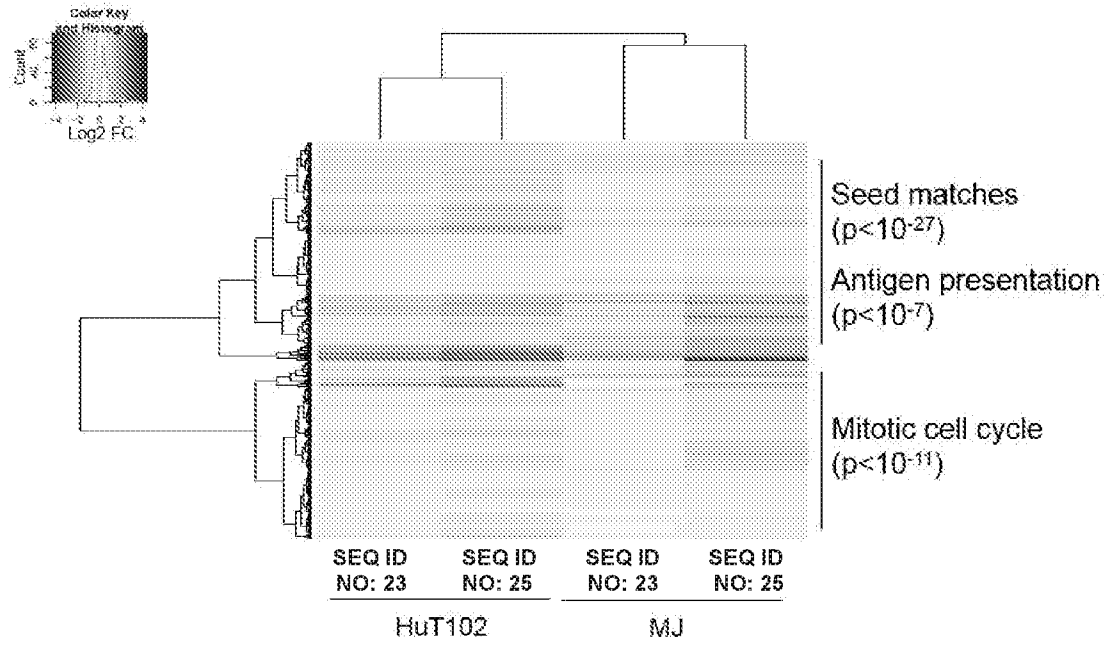


FIG. 12

2019232918 20 Sep 2019

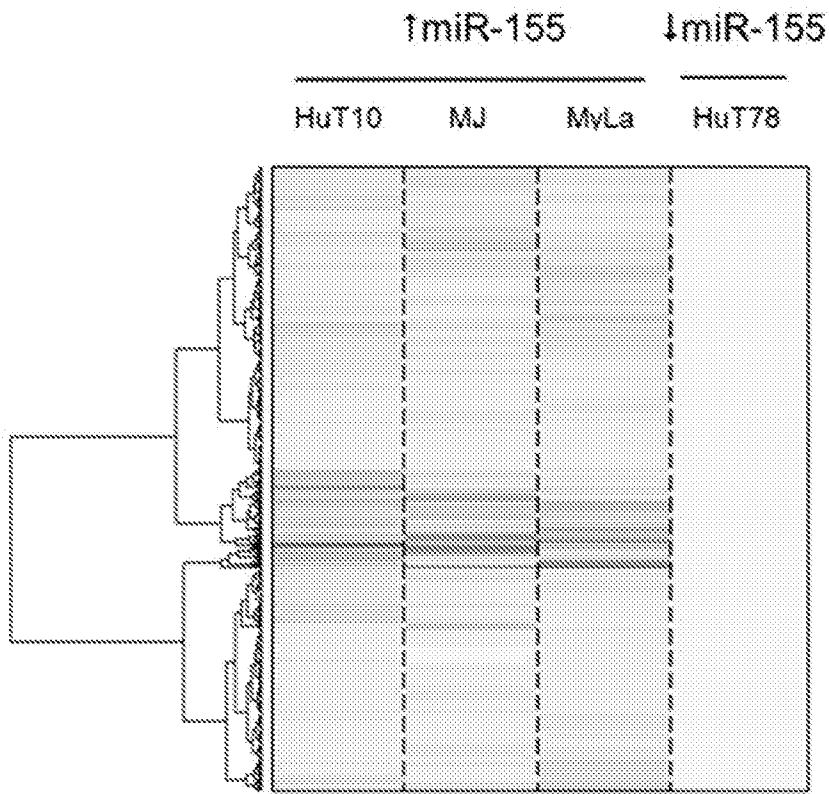


FIG. 13

2019232918 20 Sep 2019

14/34

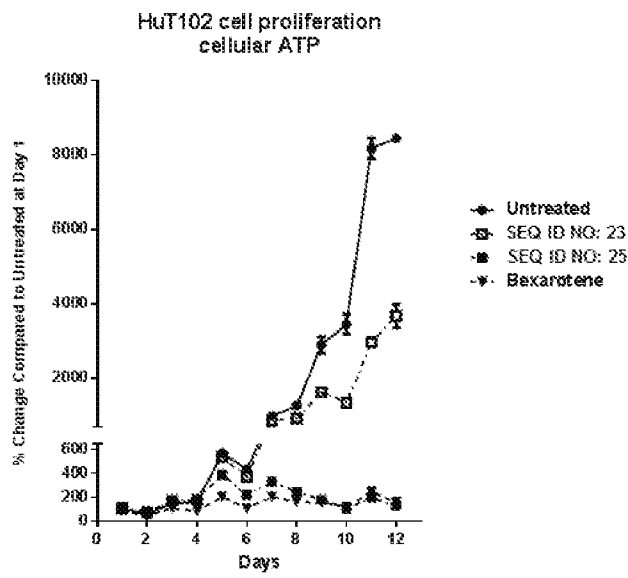


FIG. 14A

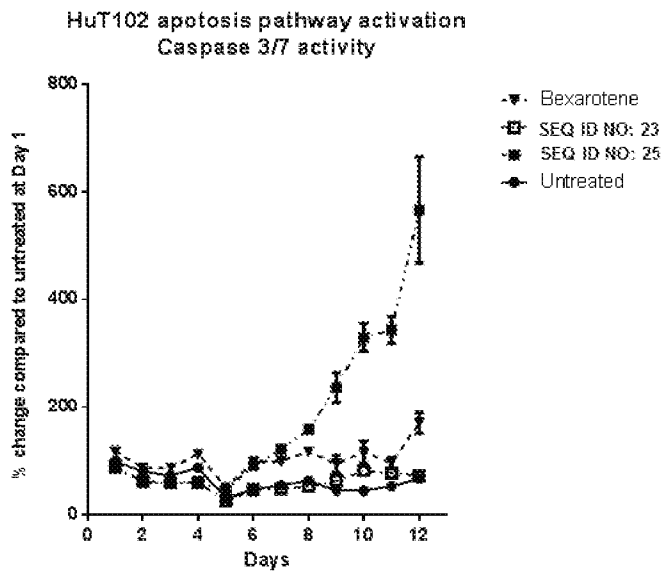


FIG. 14B



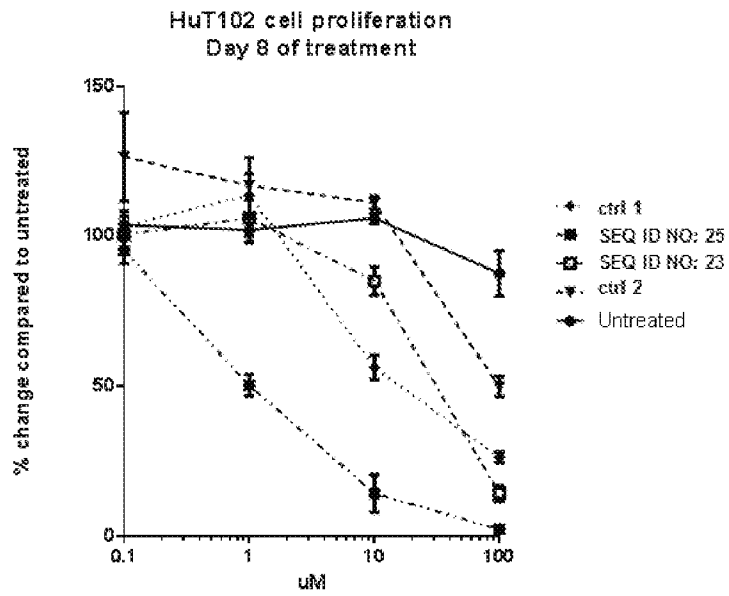


FIG. 15A

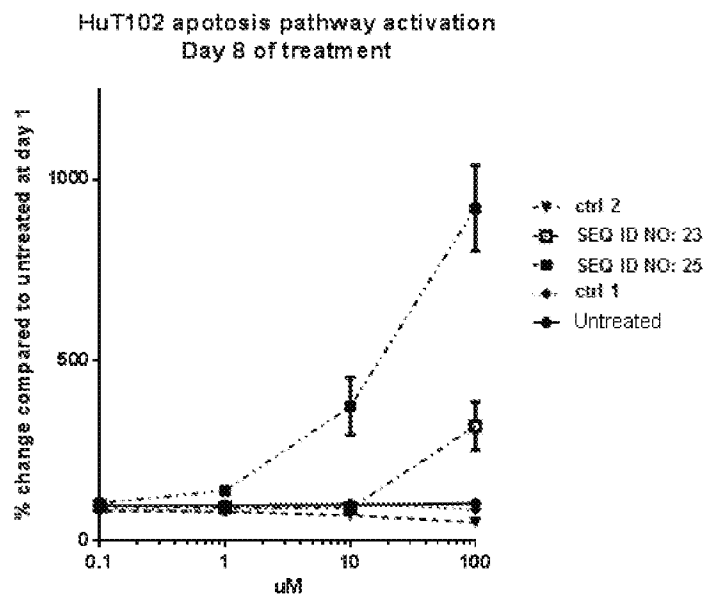


FIG. 15B

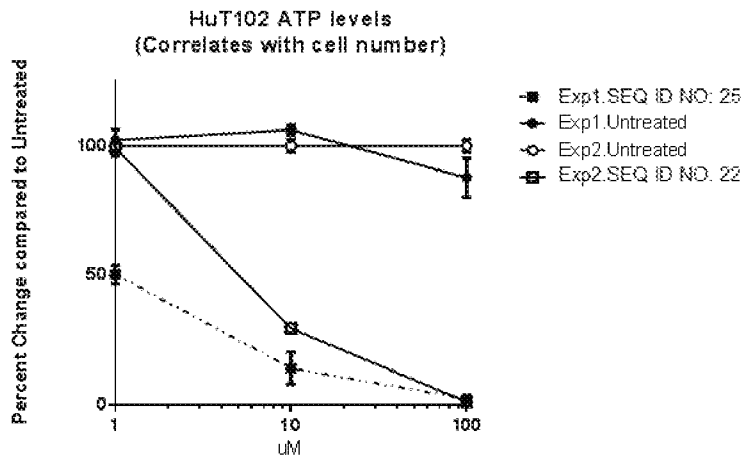


FIG. 16A

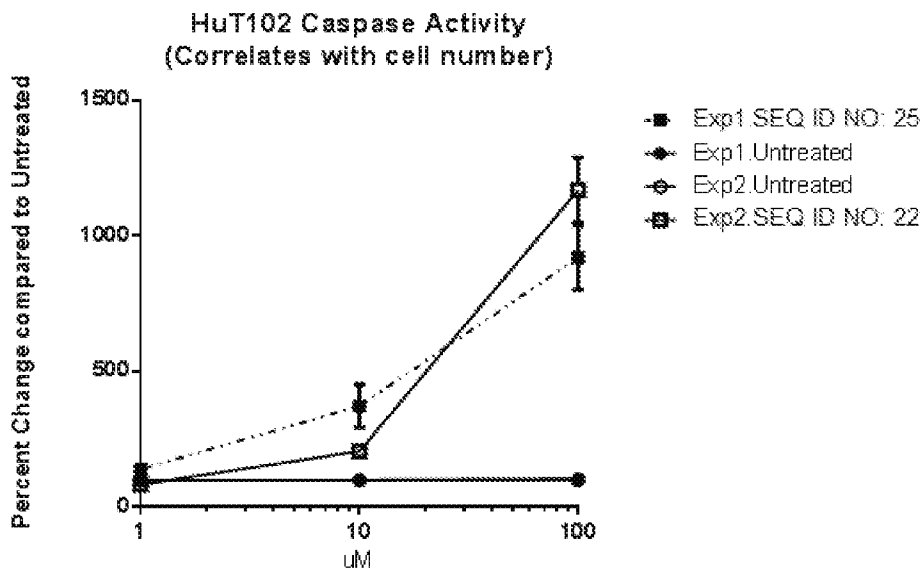


FIG. 16B

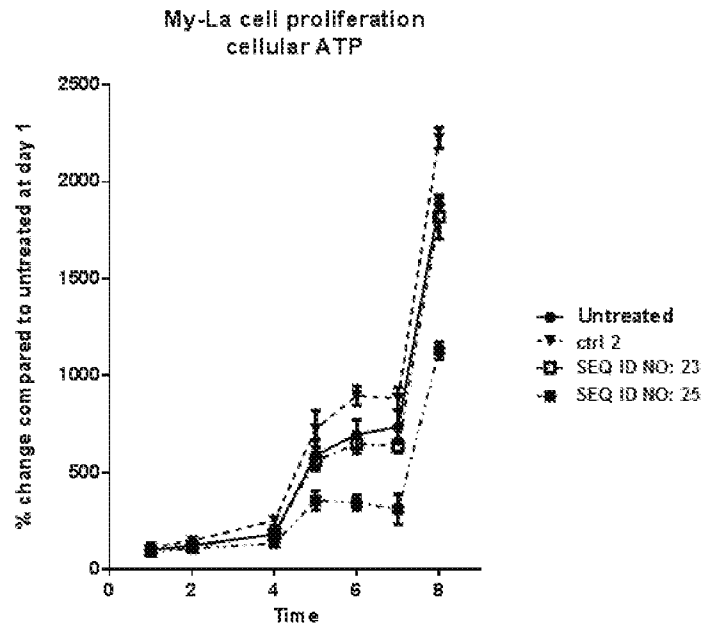


FIG. 17A

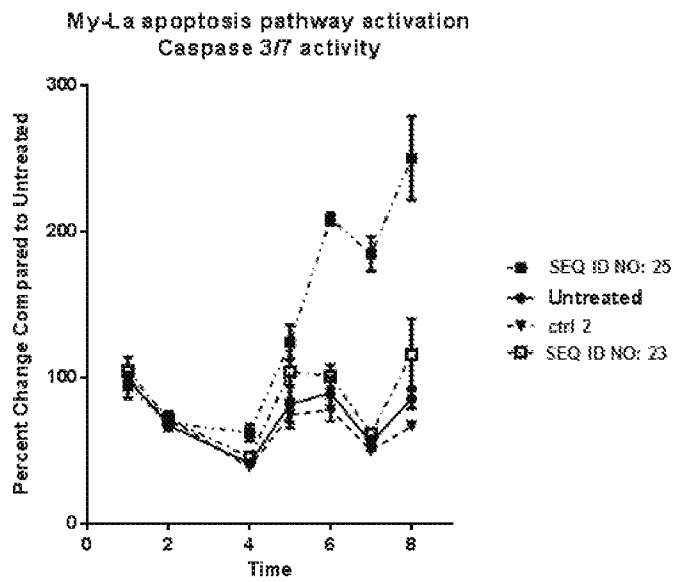


FIG. 17B

18/34

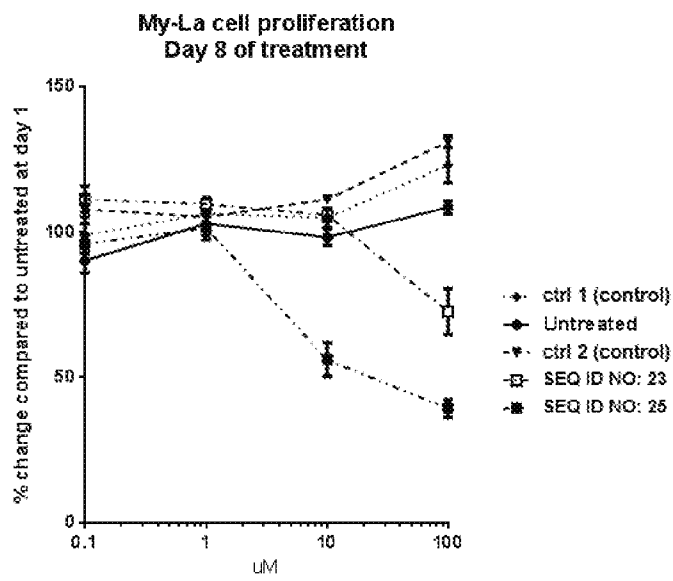


FIG. 18A

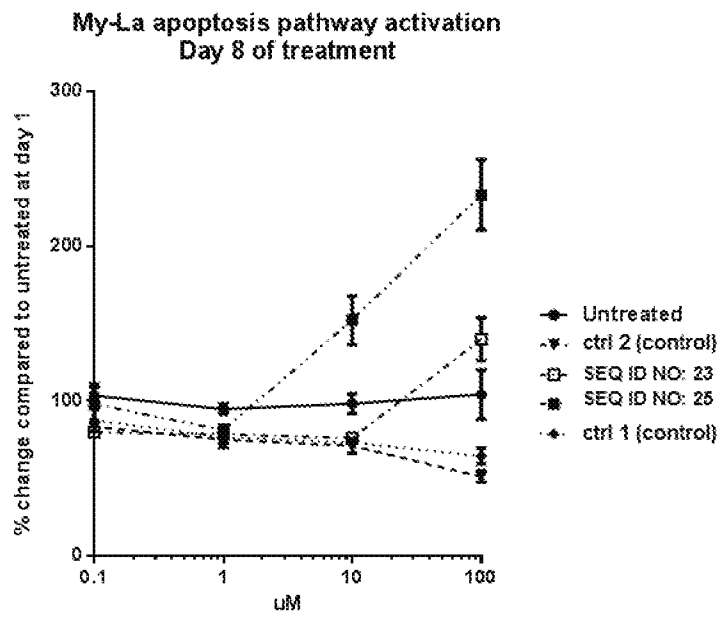


FIG. 18B

19/34

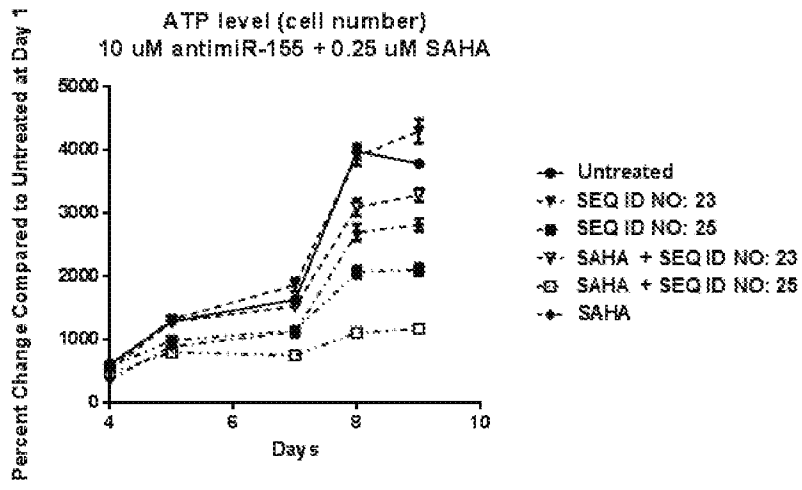


FIG. 19A

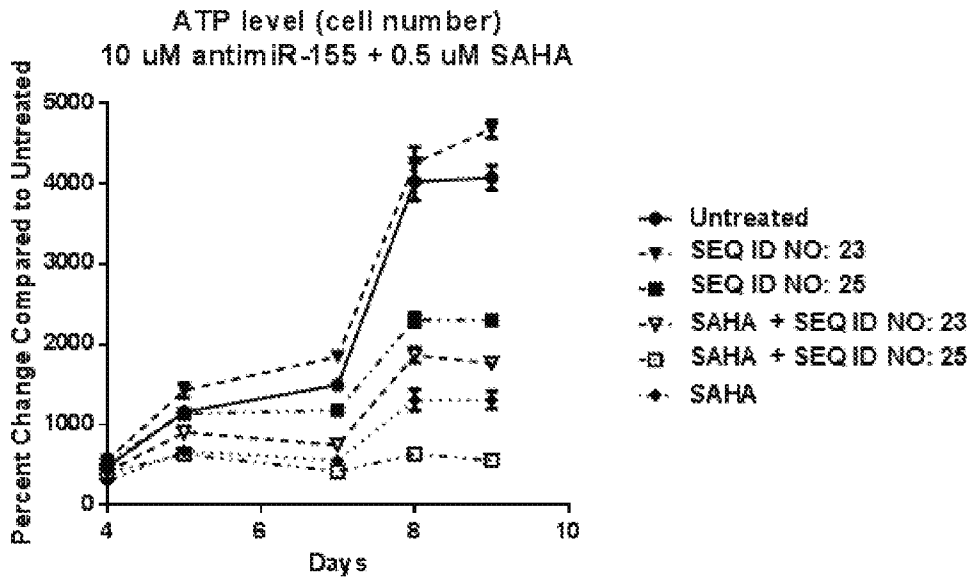


FIG. 19B

2019232918 20 Sep 2019

20/34

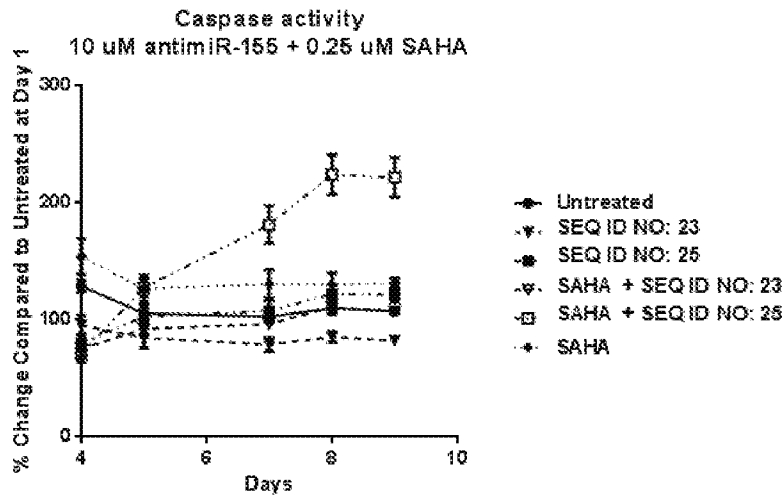


FIG. 20A

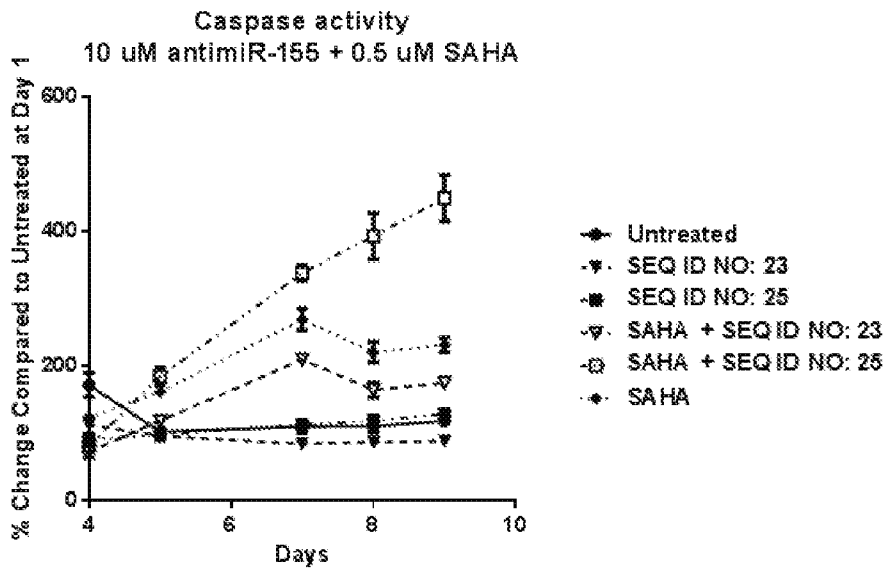


FIG. 20B

2019232918 20 Sep 2019

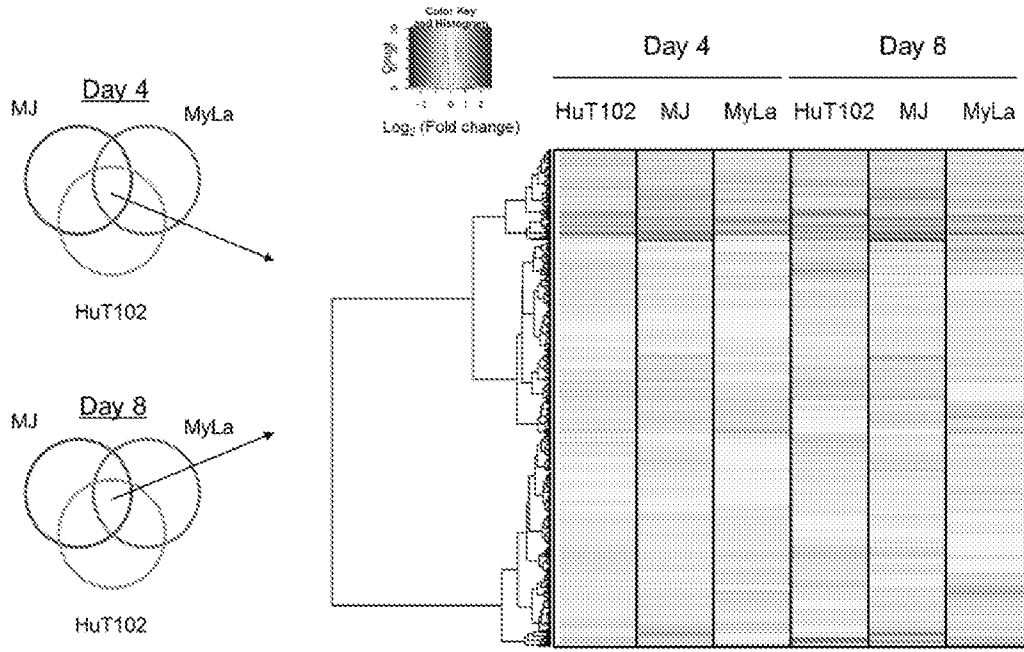


FIG. 21

2019232918 20 Sep 2019

22/34

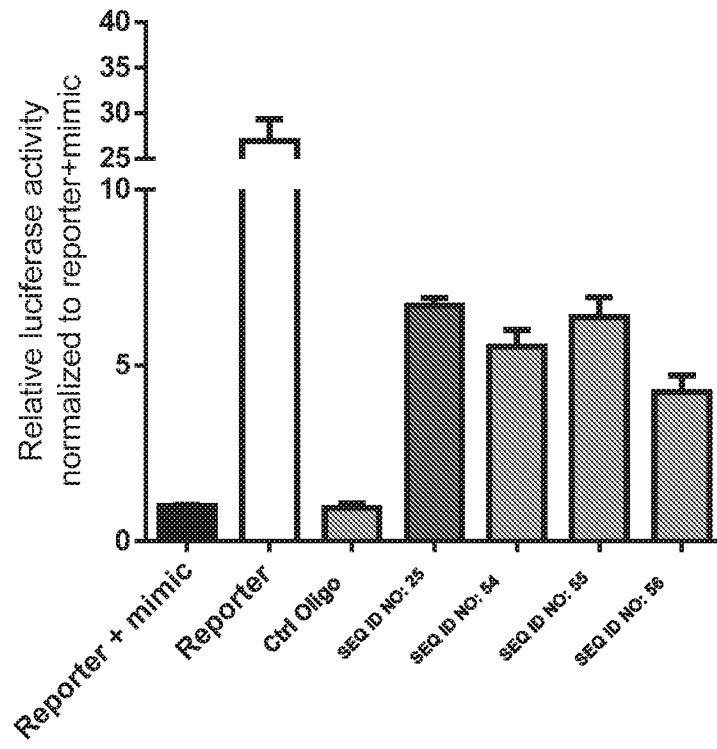


FIG. 22



2019232918 20 Sep 2019

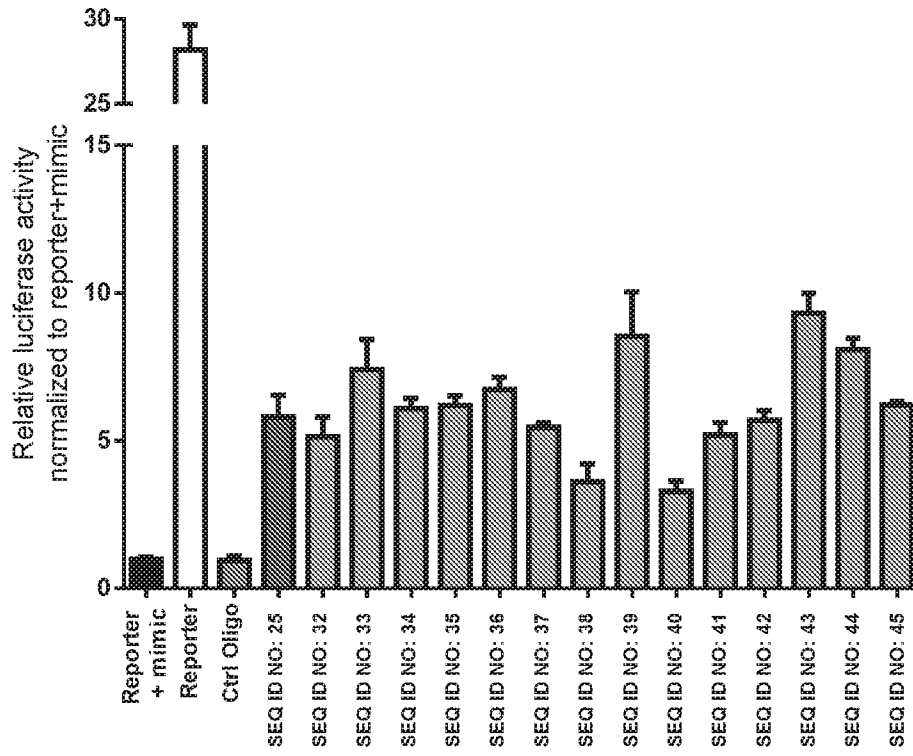


FIG. 23A

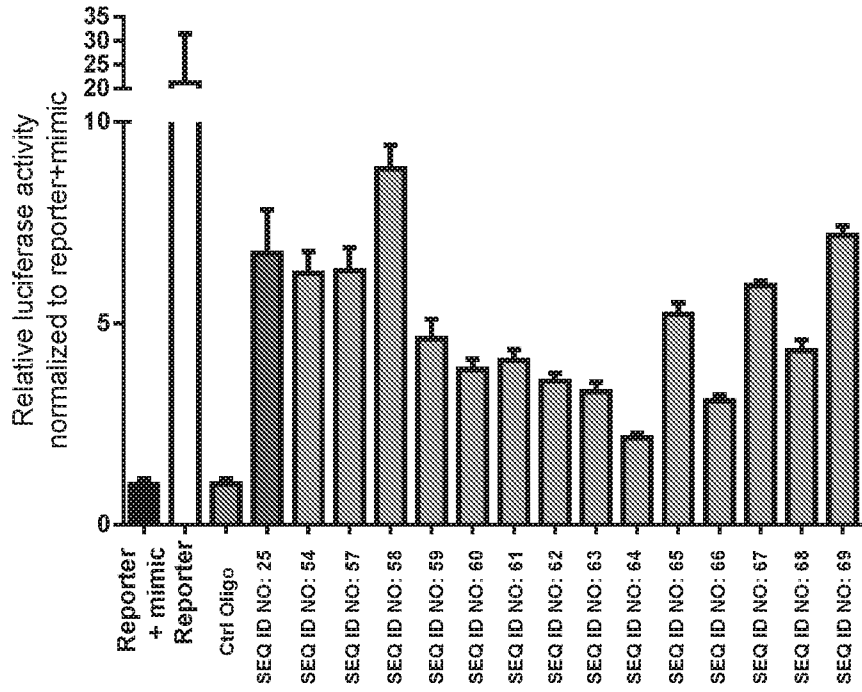


FIG. 23B

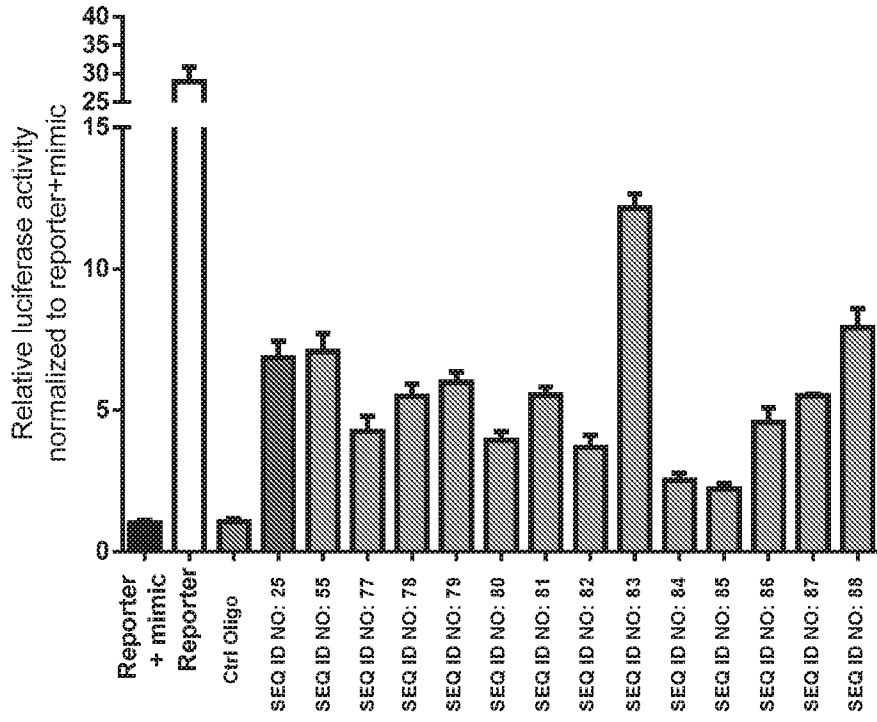


FIG. 23C

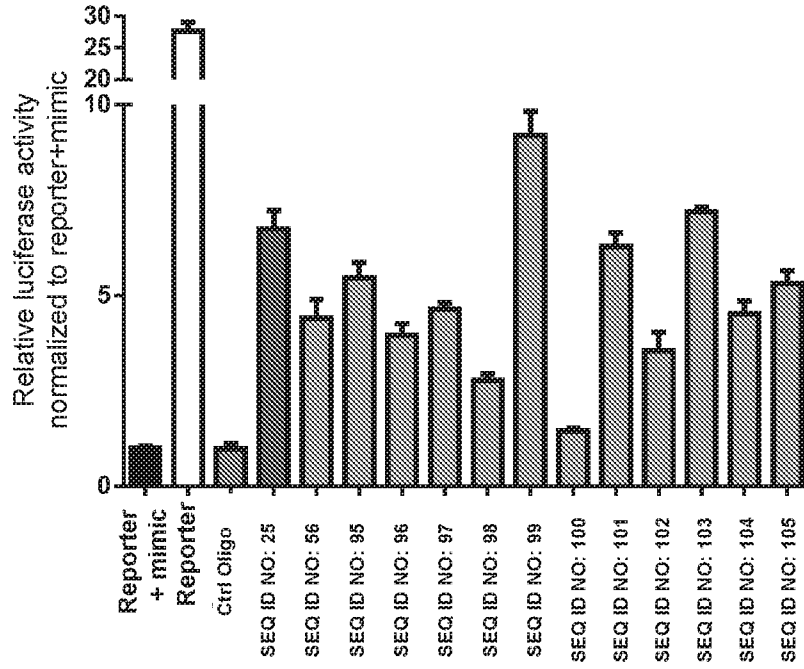


FIG. 23D

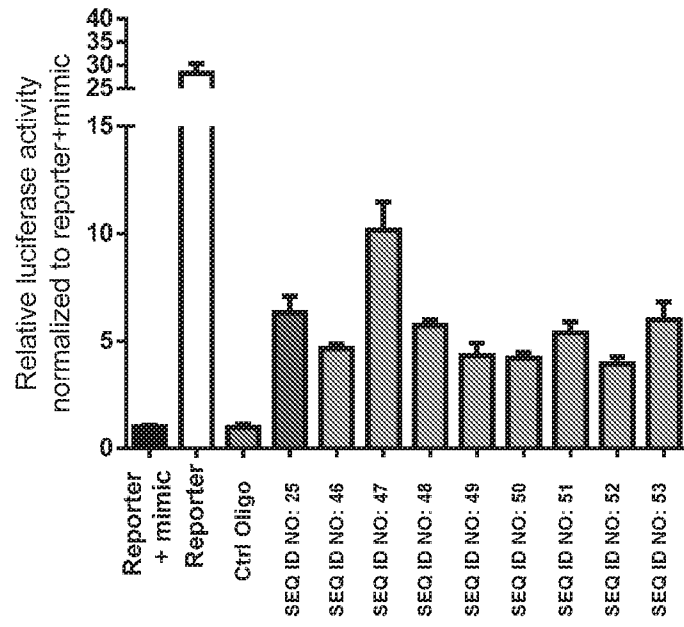


FIG. 24A

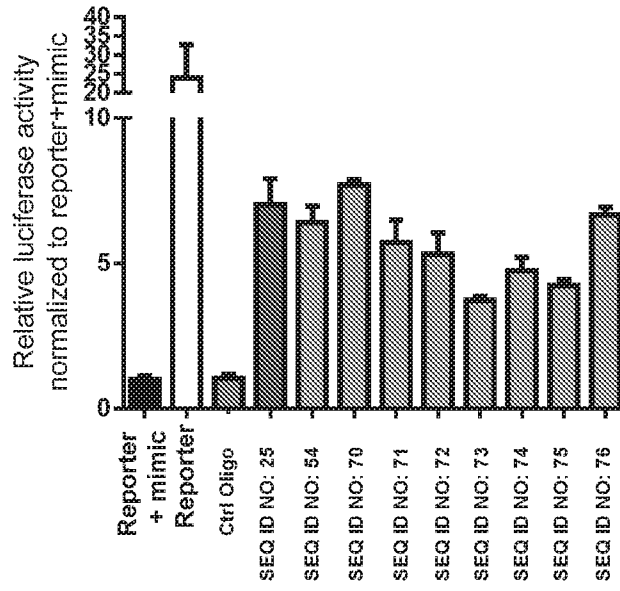


FIG. 24B

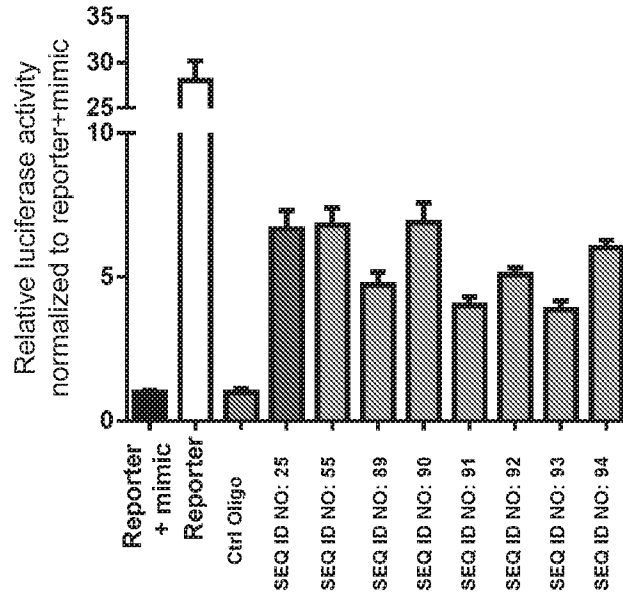


FIG. 24C

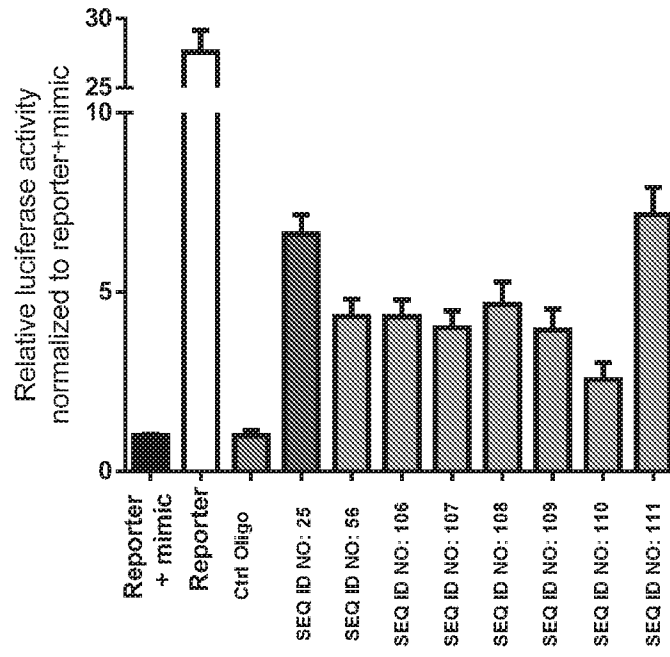


FIG. 24D



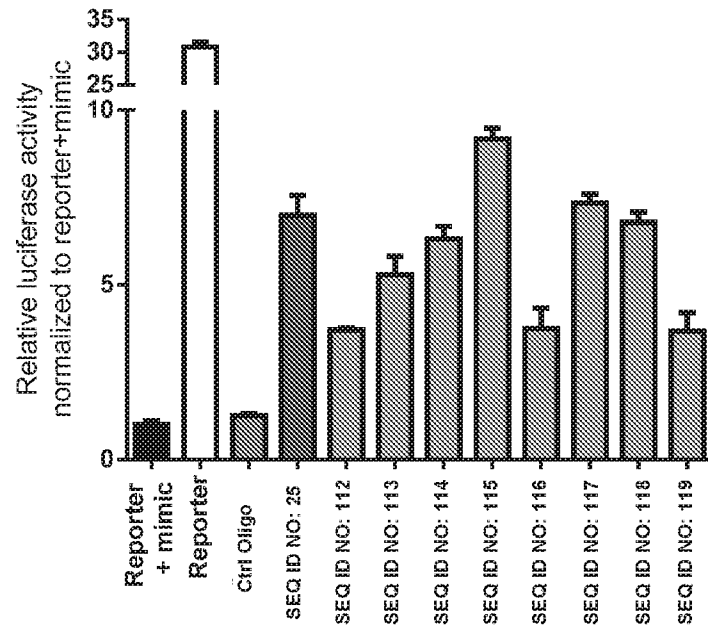


FIG. 25

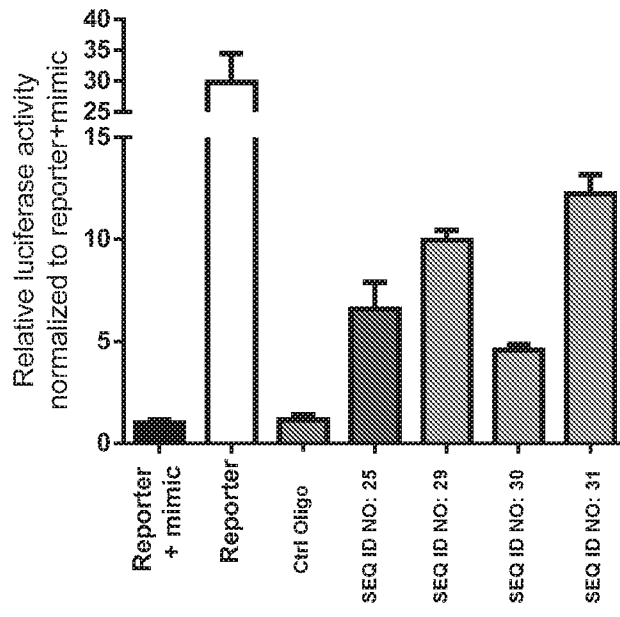


FIG. 26

2019232918 20 Sep 2019

33/34

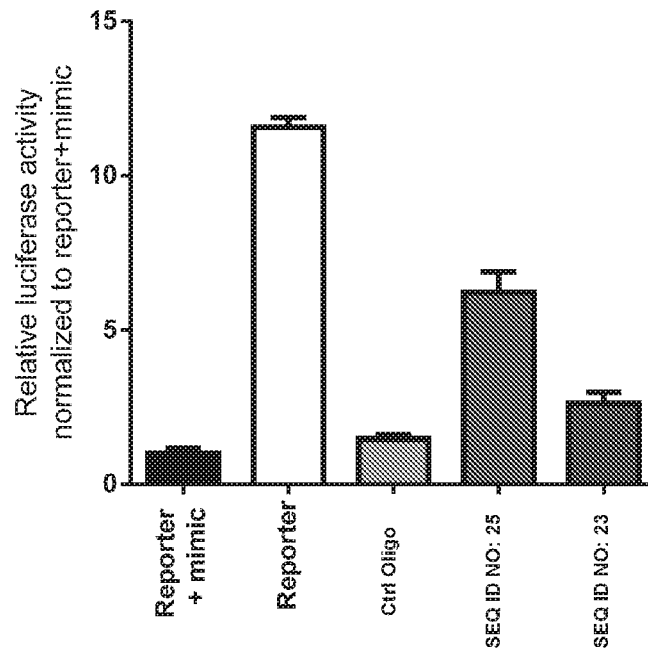


FIG. 27

34/34

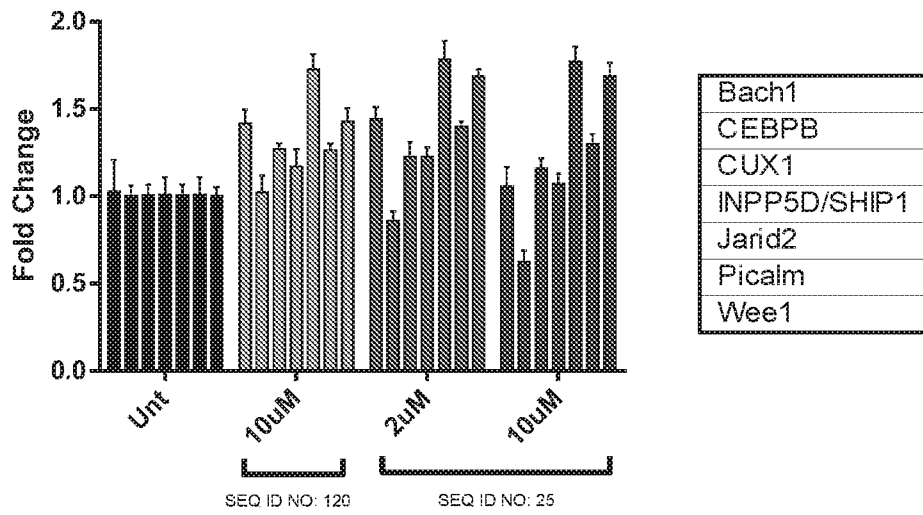


FIG. 28

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Seto, Anita

Dalby, Christina

Jackson, Aimee

Beatty, Xuan

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