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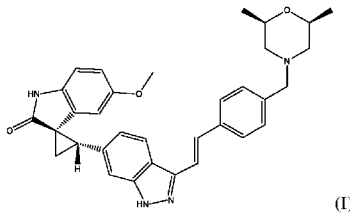
(54) **Title:** TREATMENT FOR ACUTE MYELOID LEUKEMIA OR MYELODYSPLASTIC SYNDROME

(57) **Abstract:** The invention is related to a method of treating a subject with acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Burkitt lymphoma, or diffuse large B-cell lymphoma, or myelodysplastic syndrome by administration of Compound (I): (I), or a pharmaceutically acceptable salt thereof.



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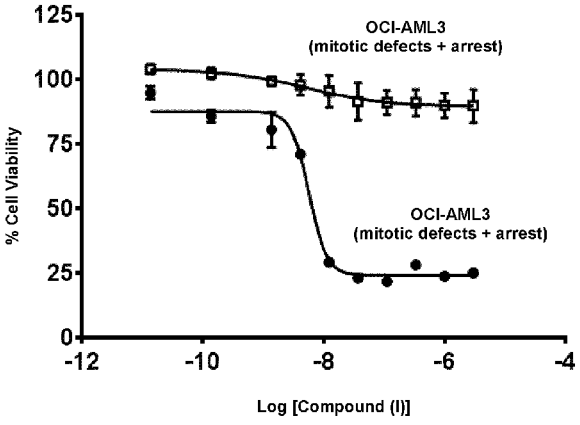

FIG. 1

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TREATMENT FOR ACUTE MYELOID LEUKEMIA OR MYELODYSPLASTIC SYNDROME

CROSS-REFERENCE TO RELATED APPLICATIONS

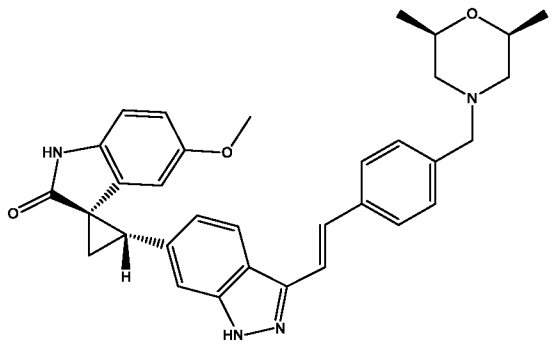
[001] This application claims priority to U.S. Provisional Application No. 62/944,876, filed December 6, 2019. The entire contents of the aforementioned application are incorporated herein by reference.

FIELD OF THE INVENTION

[002] Disclosed herein are methods for treating a subject with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) in patients with (1*R*,2*S*)-2-(3-((*E*)-4-(((2*S*,6*R*)-2,6-dimethyl morpholino)methyl)styryl)-1*H*-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (Compound (I)).

BACKGROUND OF THE INVENTION

[003] The polo-like kinase (PLK) family of serine/threonine kinases comprises at least four known members: PLK1, PLK2 (also known as Snk), PLK3 (also known as Fnk or Prk) and PLK4 (also known as Sak). Agents which inhibit PLK4 have the potential to treat cancer. A number of potent PLK4 inhibitors are disclosed in U.S. Patent Nos. 8,263,596, 8,481,525, and 8,481,533 (the entire teachings of which are incorporated herein by reference). The structure of one inhibitor disclosed in these patents is shown below as Compound (I).



(I),

[004] Acute myeloid leukemia (AML) is a cancer of the blood and bone marrow. This type of cancer usually gets worse quickly if it is not treated. It is the most common type of acute leukemia in adults. AML is also called acute myelogenous leukemia, acute myeloblastic leukemia, acute granulocytic leukemia, and acute nonlymphocytic leukemia.

[005] In acute myeloid leukemia (AML), 10–14% of all AML patients, and up to 23% among older AML patients, have karyotypes with ⩾3 aberrations (complex karyotype). These karyotypes with ⩾ 3 aberrations are classified as adverse genetic risk according to the recommendations of the European Leukemia Net (ELN).

[006] Myelodysplastic Syndromes (MDS) are a group of diverse bone marrow disorders in which the bone marrow does not produce enough healthy blood cells. MDS is often referred to as a "bone marrow failure disorder". MDS is primarily a disease of the elderly (most patients are older than age 65), but MDS can affect younger patients as well. For roughly 30% of the patients diagnosed with MDS, this type of bone marrow failure syndrome will progress to acute myeloid leukemia (AML).

[007] Chronic myeloid leukemia (CML) is also known as chronic myelogenous leukemia. It is a type of cancer that starts in certain blood-forming cells of the bone marrow. In CML, a genetic change takes place in an early (immature) version of myeloid cells -- the cells that make red blood cells, platelets, and most types of white blood cells (except lymphocytes). This change forms an abnormal gene called *BCR-ABL*, which turns the cell into a CML cell. The leukemia cells grow and divide, building up in the bone marrow and spilling over into the blood. In time, the cells can also settle in other parts of the body, including the spleen. CML is a fairly slow growing leukemia, but it can change into a fast-growing acute leukemia that's hard to treat.

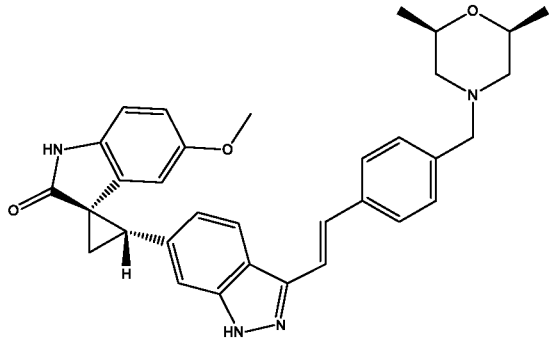
[008] There a need to develop new drugs to treat AML, CML, or MDS.

SUMMARY OF THE INVENTION

[009] Applicant has now discovered that Compound (I) has potent anticancer activity against acute myeloid leukemia, acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CLL), non-Hodgkin's lymphoma (NHL), Burkitt lymphoma, or diffuse large B-cell lymphoma (DLBCL), or myelodysplastic syndrome. Additionally, it has now been found that Compound (I) has additive/synergistic activity towards multiple complex karyotype (CK) AML cell lines *in vitro* in combination with standard of care agents Venetoclax (Bcl2 inhibitor) and 5-Azacytidine (also known as azacitidine). It has also been found that Compound (I) positively affected the outcome of a patient with CK AML. Based on these discoveries, methods of treating AML, CLL, NHL, Burkitt lymphoma, DLBCL, or MDS (including complex karyotype of each disease) with Compound (I) are disclosed herein.

[0010] In one aspect, the present disclosure provides a method of treating a subject with acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Burkitt

lymphoma, or diffuse large B-cell lymphoma, or myelodysplastic syndrome, comprising administering an effective amount of Compound (I):



(I),

or a pharmaceutically acceptable salt thereof.

[0011] In another aspect, the present disclosure provides the use of Compound (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a subject with acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Burkitt lymphoma, or diffuse large B-cell lymphoma, or myelodysplastic syndrome.

[0012] In another aspect, the present disclosure provides Compound (I) or a pharmaceutically acceptable salt thereof for treating a subject with acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Burkitt lymphoma, or diffuse large B-cell lymphoma, or myelodysplastic syndrome.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 shows Compound (I) treatment of cancer cells causes aberrant mitoses leading to death or arrest.

[0014] FIG. 2 shows tumor volume (MOLT-4) in SCID mice vs treatment day.

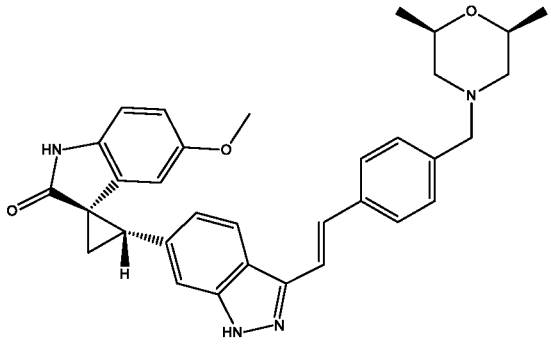
[0015] FIG. 3 shows the body weight (SCID mice) vs treatment day.

[0016] FIG. 4 shows tumor volume (MV4-11) in SCID mice vs treatment day.

[0017] FIG. 5 shows the body weight (SCID mice) vs treatment day.

DETAILED DESCRIPTION OF THE INVENTION

[0018] As used herein, "Compound (I)" refers to a compound having a chemical name (1*R*,2*S*)-2-(3-((*E*)-4-(((2*S*,6*R*)-2,6-dimethylmorpholino)methyl)styryl)-1*H*-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one, which has the following structure:



(I).

[0019] Compound (I) was developed as a PLK 4 inhibitor and is disclosed in WO2011/123946. The preparation of Compound (I) is described in Example A185 of WO2011/123946, the entire teachings of which are incorporated herein by reference.

[0020] Included in the present disclosure are pharmaceutically acceptable salts of Compound (I). The disclosed compound has basic amine groups and therefore can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention include salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p- toluenesulfonic, and tartaric acids). Compounds of the invention with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates (between Compound (I) and maleic acid is 1:1 or 2:1), acetates, citrates, fumarates (molar ratio of between Compound (I) and fumaric acid is 1:1 or 2:1), tartrates [*e.g.* (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. In some embodiments, the present disclosure provides Compound (I) as a fumarate salt. In certain embodiments, the molar ratio between Compound (I) and fumaric acid is 1:1.

[0021] Also included in the present disclosure are crystal forms of Compound (I) or the corresponding pharmaceutically acceptable salt. For example, the crystal forms and their

preparation methods are disclosed in WO2015/054793 and WO2020/215155, the entire teachings of which are incorporated herein by reference.

[0022] The compounds used in the disclosed methods are stereoisomers. Stereoisomers are compounds which differ only in their spatial arrangement.

[0023] The stereoisomeric purity of the compounds used in the disclosed methods are at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight. The stereoisomeric purity in this case is determined by dividing the total weight in the mixture of the stereoisomers encompassed by the name or structure by the total weight in the mixture of all of the stereoisomers.

[0024] The term "an effective amount" means an amount when administered to the subject which results in beneficial or desired results, including clinical results, *e.g.*, inhibits, suppresses or reduces the cancer (*e.g.*, as determined by clinical symptoms or the amount of cancer cells) in a subject as compared to a control. Specifically, "treating a subject with a cancer" includes achieving, partially or substantially, one or more of the following: arresting the growth or spread of a cancer, reducing the extent of a cancer (*e.g.*, reducing size of a tumor or reducing the number of affected sites), inhibiting the growth rate of a cancer, and ameliorating or improving a clinical symptom or indicator associated with a cancer (such as tissue or serum components).

[0025] Generally, an effective amount of a compound of the invention varies depending upon various factors, such as the given drug or compound, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject or host being treated, and the like, but can nevertheless be routinely determined by one skilled in the art. An effective amount of a compound of the present invention may be readily determined by one of ordinary skill by routine methods known in the art.

[0026] In an embodiment, an effective amount of a compound of the invention ranges from about 0.01 to about 1000 mg/kg body weight, alternatively about 0.05 to about 500 mg/kg body weight, alternatively about 0.1 to about 100 mg/kg body weight, alternatively about 0.1 to about 15 mg/kg body weight, alternatively about 1 to about 5 mg/kg body weight, and in another alternative, from about 2 to about 3 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject suffering from cancer and these factors include, but are not limited to, the severity of the disease or disorder, previous treatments, the general health and/or age of the subject and other diseases present.

[0027] As used herein, the term "treat," "treating," or "treatment," when used in connection with a disorder or condition, includes any effect, *e.g.*, lessening, reducing,

modulating, ameliorating, and/or eliminating, that results in the improvement of the disorder or condition. Improvements in or lessening the severity of any symptom of the disorder or condition can be readily assessed according to standard methods and techniques known in the art.

[0028] As used herein, the term "refractory" means a cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment.

[0029] As used herein, the term "complex karyotype" is defined by the presence of ≥3 chromosomal aberrations (structural and/or numerical) identified by using chromosome-banding analysis (CBA).

[0030] The methods disclosed herein can be used to treat AML. AML is the most common type of acute leukemia. It occurs when the bone marrow begins to make blasts, cells that have not yet completely matured. These blasts normally develop into white blood cells. However, in AML, these cells do not develop and are unable to ward off infections.

[0031] In AML, the bone marrow may also make abnormal red blood cells and platelets. The number of these abnormal cells increases rapidly, and the abnormal (leukemia) cells begin to crowd out the normal white blood cells, red blood cells and platelets that the body needs.

[0032] One of the main things that differentiates AML from the other main forms of leukemia is that it has eight different subtypes, which are based on the cell that the leukemia developed from. The types of acute myelogenous leukemia include:

- Myeloblastic (M0) - on special analysis
- Myeloblastic (M1) - without maturation
- Myeloblastic (M2) - with maturation
- Promyeloctic (M3)
- Myelomonocytic (M4)
- Monocytic (M5)
- Erythroleukemia (M6)
- Megakaryocytic (M7)

[0033] Complex karyotype acute myeloid leukemia is acute myeloid leukemia characterized by at least three chromosome abnormalities. Abnormalities found in complex karyotype acute myeloid leukemia include in loss of material from the 5q, 7q and/or 17p chromosome arms and is referred to herein as "typical CK". The absence of

abnormalities from the 5q, 7q and/or 17p chromosome arms is referred to herein as "atypical CK". TP53, PHF6, FLT3-TKD, MED12 , NPM1, DNMT3A, NF1, NRAS, IDH2, RUNX1, NPM1, SRSF2, ZRSR2, ASXL1and FLT3-ITD mutations are associated with atypical CK. Treatment of both is contemplated by the disclosed methods. Also included with the disclosed methods are patients with some or all of the mutations associated with typical and atypical CK.

[0034] In some embodiments, AML to be treated is relapsed or refractory. In some embodiments, AML to be treated is complex karyotype acute myeloid leukemia.

[0035] In some embodiments, the myelodysplastic syndrome to be treated is relapsed or refractory. In some embodiments, myelodysplastic syndrome to be treated is complex karyotype myelodysplastic syndrome.

[0036] In some embodiments, the acute lymphoblastic leukemia to be treated is relapsed or refractory. In some embodiments, ALL to be treated is complex karyotype acute lymphoblastic leukemia.

[0037] In some embodiments, the acute lymphoblastic leukemia to be treated is T-cell acute lymphoblastic leukemia. In some embodiments, the acute lymphoblastic leukemia to be treated is B-cell acute lymphoblastic leukemia.

[0038] In some embodiments, the chronic myeloid leukemia to be treated is relapsed or refractory. In some embodiments, CML to be treated is complex karyotype acute lymphoblastic leukemia.

[0039] In some embodiments, the non-Hodgkin's lymphoma to be treated is relapsed or refractory. In some embodiments, non-Hodgkin's lymphoma to be treated is complex karyotype non-Hodgkin's lymphoma.

[0040] In some embodiments, the Burkitt lymphoma to be treated is relapsed or refractory. In some embodiments, Burkitt lymphoma to be treated is complex karyotype Burkitt lymphoma.

[0041] In some embodiments, the diffuse large B-cell lymphoma to be treated is relapsed or refractory. In some embodiments, diffuse large B-cell lymphoma to be treated is complex karyotype diffuse large B-cell lymphoma.

[0042] In some embodiments, the diffuse large B-cell lymphoma to be treated is germinal center B cell-like. In some embodiments, the diffuse large B-cell lymphoma to be treated is activated B cell-like.

[0043] In some embodiments, the present teachings provide methods of treating a subject with acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Burkitt

lymphoma, or diffuse large B-cell lymphoma, or myelodysplastic syndrome comprising administering to the subject an effective amount of Compound (I) in combination with an additional therapeutic agent. In some embodiments, the additional therapeutic agent is an anti-cancer drug.

[0044] An "anti-cancer drug" is a compound, which when administered in an effective amount to a subject with cancer, can achieve, partially or substantially, one or more of the following: arresting the growth, reducing the extent of a cancer (*e.g.*, reducing size of a tumor), inhibiting the growth rate of a cancer, and ameliorating or improving a clinical symptom or indicator associated with a cancer (such as tissue or serum components) or increasing longevity of the subject.

[0045] The anti-cancer agent suitable for use in the methods described herein include any anti-cancer agents that have been approved for the treatment of cancer. In one embodiment, the anti-cancer agent includes, but is not limited to, a targeted antibody, an angiogenisis inhibitor, an alkylating agent, an antimetabolite, a vinca alkaloid, a taxane, a podophyllotoxin, a topoisomerase inhibitor, a hormonal antineoplastic agent and other antineoplastic agents.

[0046] In one embodiment, the anti-cancer agents that can be used in methods described herein include, but are not limited to, paclitaxel, docetaxel, 5-fluorouracil, trastuzumab, lapatinib, bevacizumab, letrozole, goserelin, tamoxifen, cetuximab, panitumumab, gemcitabine, capecitabine, irinotecan, oxaliplatin, carboplatin, cisplatin, doxorubicin, epirubicin, cyclophosphamide, methotrexate, vinblastine, vincristine, melphalan, cytarabine, etoposide, daunorubicin, bleomycin, mitomycin and adriamycin and a combination thereof.

[0047] In one embodiment, anti-cancer drug is Venetoclax. In one embodiment, anti-cancer drug is 5-Azacytidine. In one embodiment, anti-cancer drug is decitabine.

[0048] In the methods disclosed herein, Compound (I) and the additional therapeutic agent are administered concurrently or sequentially.

[0049] Compound (I) and/or pharmaceutically acceptable salts thereof described herein are useful as an active pharmaceutical ingredients (API) as well as materials for preparing pharmaceutical compositions that incorporate one or more pharmaceutically acceptable excipients and is suitable for administration to human subjects.

[0050] In some embodiments, the disclosure provides a pharmaceutical composition comprising Compound (I) and/or a pharmaceutically acceptable salt thereof and at least one additional pharmaceutically acceptable excipient. The term "pharmaceutically acceptable excipient," as used herein, refers to a pharmaceutically acceptable material, composition,

and/or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. Each excipient must be "pharmaceutically acceptable" in the sense of being compatible with the subject composition and its components and not injurious to the patient. Except insofar as any conventional pharmaceutically acceptable excipient is incompatible with Compound (I) and/or pharmaceutically acceptable salts thereof, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this disclosure.

[0051] Some non-limiting examples of materials which may serve as pharmaceutically acceptable excipients include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0052] Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, the contents of each of which is incorporated by reference herein, also disclose additional non-limiting examples of pharmaceutically acceptable excipients, as well as known techniques for preparing and using the same.

[0053] The compounds used in the disclosed methods can be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the present teachings may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal and topical modes of administration. Parenteral administration can be by continuous infusion over a selected period of time.

[0054] The compounds used in the disclosed methods can be suitably formulated into pharmaceutical compositions for administration to a subject. The pharmaceutical compositions of the present teachings optionally include one or more pharmaceutically acceptable carriers and/or diluents therefor, such as lactose, starch, cellulose and dextrose. Other excipients, such as flavoring agents; sweeteners; and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More complete listings of suitable excipients can be found in the Handbook of Pharmaceutical Excipients (5^{th} Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003 - 20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. The carriers, diluents and/or excipients are "acceptable" in the sense of being compatible with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

[0055] Typically, for oral therapeutic administration, a compound used in the disclosed methods may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

[0056] Typically for parenteral administration, solutions of a compound used in the disclosed methods can generally be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0057] Typically, for injectable use, sterile aqueous solutions or dispersion of, and sterile powders of, a compound used in the disclosed methods for the extemporaneous preparation of sterile injectable solutions or dispersions are appropriate.

[0058] For nasal administration, the compounds used in the disclosed methods can be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which

is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

[0059] For buccal or sublingual administration, the compounds used in the disclosed methods can be formulated with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine, as tablets, lozenges or pastilles.

[0060] For rectal administration, the compounds used in the disclosed methods can be formulated in the form of suppositories containing a conventional suppository base such as cocoa butter.

EXAMPLES

[0061] The following examples are intended to be illustrative and are not meant in any way to limit the scope of the disclosure.

Example 1. ***In Vitro*** **Cytotoxicity (IC_{50}) Assay**

[0062] Cells were seeded in triplicate at 10,000 per 80 uL, into 96-well plates 24 hours before compound overlay and cultured at 37°C and 5% CO_2. Compound (I) was prepared as a 10 mM stock in 100% DMSO and diluted with RPMI 1640 cell growth medium containing 10% FBS such that the final concentrations ranged from 50 pM to 15 uM. Aliquots (20 uL) from each concentration were overlaid to 80 uL of pre-seeded cells to achieve final concentrations of 10 pM to 3 uM. After 3 days, cell viability in each well was assessed by alamarBlue assay according to the manufacturer's instruction (ThermoFisher Scientific). Absorbance was read at 570 nm using a SpectraPlus microplate reader (Molecular Devices Corporation). alamarBlue absorbance values were adjusted by subtracting the average of the baseline readings from untreated cells assessed one day after cell seeding. The percentage (%) of relative inhibition of cell viability was calculated by comparing to DMSO-treated cells. IC_{50}s were calculated using GraphPad PRISM software (GraphPad Software Inc.). The results are listed in Table 1 below and FIG. 1.

Table 1.

Cell Line	Cell Type	Response to Compound (I)	Compound (I) IC_{50} (nM)	TP53 Status	PTEN Status
RAJI	NHL, B-Cell Burkitt	death	0.1	R213Q, Y234H	WT
DAUDI	NHL, B-Cell	death	0.2	R213*,	V175G

	Burkitt			G266E	
JURKAT	T-ALL	death	0.6	multiple mutations	multiple mutations
KOPN-8	B-ALL	death	0.7	R248Q (het)	WT
THP-1	AML M5	death	1.4	p.R174fs*3 (het)	WT
TF-1	AML M6	death	2.2	p.I251fs (het) splice site	WT
MOLT-4	T-ALL	death	4.1	R306*	p.K267fs*9
REH	B-ALL	death	5.1	R181C	R173C
MV4-11	AML M5	death	5.7	L344 mutation	WT
OCI-LY10	NHL, ABC-DLBCL	death	6.8	K319*	splice site
HL-60	AML M2	death	8.4	null	promoter hypermethylation
SU-DHL-8	NHL, DLBCL	death	12	Y234N, R249G	WT
K-562	CML	mitotic defects + arrest		p.Q136fs*13	WT
OCI-LY18	NHL, GCB-DLBCL	mitotic defects + arrest		WT	WT
OCI-AML4	AML M4	mitotic defects + arrest		WT	WT
OCI-LY3	NHL, ABC-DLCBL	mitotic defects + arrest		WT	WT
NB4	AML M3	mitotic defects + arrest		K319, L344 mutations	WT
NALM-16	B-ALL	mitotic defects + arrest		WT	WT
OCI-AML2	AML M4	mitotic defects + arrest		WT	WT
RS4;11	B-ALL	mitotic defects + arrest		I254T (het)	WT
OCI-LY8	NHL, GCB-DLBCL	mitotic defects + arrest		WT	WT
NALM-6	B-ALL	mitotic defects + arrest		WT	WT
OCI-AML3	AML M4	mitotic defects + arrest		WT	WT

Example 2. Compound (I) Fumarate Inhibits Tumor Growth in MOLT-4 ALL Model.

[0063] Drug and test system

Drug Name/s	Compound (I)
Batch reference/s	Fumarate batch 16
Dosage Groups (mg/kg)	Compound (I) 7.5 mg/kg qd Compound (I) 13.5 mg/kg 2-on/5-off Vincristine 0.5 mg/kg IP, qw
Dosing Volume	10 mL/kg
Formulation	Compound (I) will be dissolved/suspended in water before dosing.
Vehicle control group	Water (10 mL/kg)
Positive control Group	Vincristine diluted in PBS before dosing
Route of administration	PO (oral), daily for Compound (I), IP (intraperitoneal injection), weekly for vincristine
Tumor cell type and line	MOLT-4 acute lymphoblastic leukemia
Number of cells and volume injected	1 x 10^7 cells in a volume of 0.1 ml

[0064] Tumor Cell Culture:

[0065] The human acute lymphoblastic leukemia cell line MOLT-4 was acquired from American Type Culture Collection (Manassas, VA, USA) and grown in RPMI medium containing 100 units/mL penicillin G sodium, 100 µg/mL streptomycin sulfate. The media was supplemented with 10% heat-inactivated fetal bovine serum, 2 mM L-glutamine, and 0.11% sodium pyruvate. The tumor cells were maintained in a humidified environment of 5% CO_2 and 95% air at 37 °C. Cells were verified to be free of mouse pathogens by IMPACT IV PCR analysis (IDEXX RADIL, Colombia, MO, USA) before injection.

[0066] Animals and tumor cells:

[0067] Female SCID mice were purchased from the Ontario Cancer Institute and received and acclimated at the MaRS-TMDT Animal Resources Centre for 2 weeks prior to the start of the experiment. The mice were fed *ad libitum* autoclaved water and Rodent Lab Diet (Harlan Teklad LM-485) consisting of 19% crude protein, 5% crude fat, and 5% crude fiber. Mice were housed in microisolator cages and maintained in an environment with a 12-hour light cycle at 20-22 °C and 40-60% humidity. On the day of implantation, MOLT-4 cells were harvested and resuspended with serum free DMEM to a concentration of 1 x 10^8/mL

and each mouse was injected subcutaneously with a volume of 0.1 mL containing 1 x 10^7 MOLT-4 cells in the right rear flank.

[0068] Controls and dosing:

[0069] Animals were dosed Compound (I) via oral gavage in a volume of 10 mL/kg. The animals were dosed with a 2.25 mm x 50 mm curved gavage needle affixed to a 1 mL syringe. Vincristine was dosed by IP injection once per week.

[0070] In-life observations:

[0071] Toxicity was evaluated by body weight measurements and clinical observations. The mice were observed daily for overt signs of any adverse, treatment related side effects, and clinical signs of toxicity. Acceptable toxicity was set at a group mean body weight loss of less than 20% during the study and not more than one treatment related death in a group. Animals were monitored for body weights and tumor growth where tumor volumes were calculated using the formula: tumor volume = width^2 x length / 2.

[0072] Results

[0073] The study evaluated Compound (I) fumarate administered by oral gavage for 21 days, either daily at 7.5 mg/kg or 2 days on / 5 days off at 13.5 mg/kg, in comparison to the standard-of-care agent vincristine, dosed in 4 weekly intraperitoneal injections of 0.5 mg/kg, in the MOLT-4 acute myeloid leukemia xenograft model in SCID (severe combined immunodeficiency) mice. Xenografts were established by subcutaneously injecting 1x10^7 tumor cells into the right flank of female SCID mice. Treatment was initiated 9 days following implantation when tumor volumes reached a mean volume of approximately 250 mm^3.

[0074] By day 13, the average volume of the control tumors was 1754 mm^3, averaging 683% tumor growth. On day 13 the average tumor growth inhibition in the vincristine treated arm was 18% (p=0.21). Compound (I) oral dosing daily at 7.5 mg/kg resulted in an average of 77% tumor regression (p=2.5*10^{-6}) with regression observed in 7 of 8 tumors, and dosing 2-on/5-off at 13.5 mg/kg resulted in an average of 28% regression (p=6.5*10^{-6}), with regression observed in7 of 8 tumors. After 21 days of dosing, tumors continued to regress, with maximum antitumor efficacy observed on Day 25, with 8 of 8 complete regressions in the daily dosing arm and 6 of 8 complete regressions in the 2-on/5-off arm (average 96% regression). Tumor regrowth eventually occurred in all animals, with the last animal taken off study due to excessive tumor burden on Day 68.

[0075] The result is shown in FIG. 2 and FIG. 3. Specifically, FIG. 2 shows tumor volume (MOLT-4) in SCID mice vs treatment day. FIG. 3 shows the body weight (SCID

mice) vs treatment day. In all, Compound (I) is very efficacious and potentially curative in the MOLT-4 acute lymphoblastic leukemia xenograft model.

[0076] Protocol Design

Group	N	Test Article	Batch/ supplier	Salt form	Bio-equiv. ratio	Vehicle	Route, schedule, and dose
1	6	Vehicle	N/A	N/A	N/A	water	PO QD + IP QW
2	6	Compound (I)	16	fumarate	0.82	water	PO, 7.5 mg/kg QD x21
3	6	Compound (I)	16	fumarate	0.82	water	PO, 13.5 mg/kg 2-on/5-off x3 (21 days)
4	6	Vincristine	Sigma	Sulfate	0.89	PBS	IP, 0.5 mg/kg QW x4

Example 3. Compound (I) Fumarate Inhibits Tumor Growth in MV4-11 AML Model.

[0077] Drug and test system

Drug Name/s	Compound (I)
Batch reference/s	Fumarate batch 16
Dosage Groups (mg/kg)	Compound (I)-16 7.5 mg/kg qd Compound (I)-16 13.5 mg/kg 2-on/5-off Vincristine 0.5 mg/kg IP, qw
Dosing Volume	10 mL/kg
Formulation	Compound (I) will be dissolved/suspended in water before dosing.
Vehicle control group	Water (10 mL/kg)
Positive control Group	Vincristine diluted in PBS before dosing
Route of administration	PO (oral), daily for Compound (I), IP (intraperitoneal injection), weekly for vincristine
Tumor cell type and line	MV4-11 acute myeloid leukemia
Number of cells and volume injected	1 x 10^7 cells in a volume of 0.1 ml

[0078] Tumor Cell Culture:

[0079] The human acute myeloid leukemia cell line MV4-11 was acquired from American Type Culture Collection (Manassas, VA, USA) and grown in RPMI medium containing 100 units/mL penicillin G sodium, 100 µg/mL streptomycin sulfate. The media was supplemented with 10% heat-inactivated fetal bovine serum, 2 mM L-glutamine, and 0.11% sodium pyruvate. The tumor cells were maintained in a humidified environment of 5% CO_2 and 95% air at 37^0C. Cells were verified to be free of mouse pathogens by IMPACT IV PCR analysis (IDEXX RADIL, Colombia, MO, USA) before injection.

[0080] Animals and tumor cells:

[0081] Female SCID mice were purchased from the Ontario Cancer Institute and received and acclimated at the MaRS-TMDT Animal Resources Centre for 2 weeks prior to the start of the experiment. The mice were fed *ad libitum* autoclaved water and Rodent Lab Diet (Harlan Teklad LM-485) consisting of 19% crude protein, 5% crude fat, and 5% crude fiber. Mice were housed in microisolator cages and maintained in an environment with a 12-hour light cycle at 20-22^{0}C and 40-60% humidity. On the day of implantation, MV4-11 cells were harvested and resuspended with serum free DMEM to a concentration of 1 x 10^8/mL and each mouse was injected subcutaneously with a volume of 0.1 mL containing 1 x 10^7 MV4-11 cells in the right rear flank.

[0082] Controls and dosing:

[0083] Animals were dosed Compound (I) via oral gavage in a volume of 10 ml/kg. The animals were dosed with a 2.25 mm x 50 mm curved gavage needle affixed to a 1 ml syringe. Vincristine was dosed by IP injection once per week.

[0084] In-life observations:

[0085] Toxicity was evaluated by body weight measurements and clinical observations. The mice were observed daily for overt signs of any adverse, treatment related side effects, and clinical signs of toxicity. Acceptable toxicity was set at a group mean body weight loss of less than 20% during the study and not more than one treatment related death in a group. Animals were monitored for body weights and tumor growth where tumor volumes were calculated using the formula: tumor volume = width^2 x length / 2.

[0086] Results

[0087] The study evaluated Compound (I) fumarate administered by oral gavage, either daily at 7.5 mg/kg or 2 days on / 5 days off at 13.5 mg/kg, in comparison to the standard-of-care agent vincristine, dosed in 4 weekly intraperitoneal injections of 0.5 mg/kg, in the MV4-11 acute myeloid leukemia xenograft model in SCID (severe combined immunodeficiency) mice. Xenografts were established by subcutaneously injecting 1x10^7 tumor cells into the right flank of female SCID mice. Treatment was initiated 14 days following implantation when tumor volumes reached a mean volume of approximately 90 mm^3. Daily oral dosing of Compound (I) at 7.5 mg/kg was halted after 14 days due to excessive body weight loss. Animals were dosed in the 2-on/5-off schedule for 21 days. Dosing of Compound (I) by either schedule completely regressed tumors by day 10; by this point the average volume of the control tumors was 589 mm^3. By day 13, the average volume of the control tumors was

878 mm^3, averaging 1666% tumor growth over the 13 days. On day 13 the average tumor growth inhibition in the vincristine treated arm was 85% (p=0.14).

[0088] Animals remained tumor-free until Day 24 in the 2days-on/5days-off arm, and Day 74 in the daily dosing arm. Four of 6 animals in the daily dosing arm remained tumor free until the last measurement time point (Day 128).

[0089] The result is shown in FIG. 4 and FIG. 5. Specifically, FIG. 4 shows tumor volume (MV4-11) in SCID mice vs treatment day. FIG. 5 shows the body weight (SCID mice) vs treatment day. In all, Compound (I) is very efficacious and potentially curative in the MV4-11 acute myeloid leukemia xenograft model.

[0090] Protocol Design

Group	N	Test Article	Batch/ supplier	Salt form	Bio-equiv. ratio	Vehicle	Route, schedule, and dose
1	6	Vehicle	N/A	N/A	N/A	water	PO QD + IP QW
2	6	Compound (I)	16	fumarate	0.82	water	PO, 7.5 mg/kg QD x13
3	6	Compound (I)	16	fumarate	0.82	water	PO, 13.5 mg/kg 2-on/5-off x3 (21 days)
4	6	Vincristine	Sigma	Sulfate	0.89	PBS	IP, 0.5 mg/kg QW x4

Example 4. Phase 1 Study of Compound (I) Fumarate in Patients With Relapsed or Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome.

[0091] This study (NCT number: NCT03187288) is a multi-center, phase 1, dose-escalation trial designed to assess the safety, tolerability, pharmacokinetics, and clinical benefit of treatment with Compound (I) fumarate administered orally over a range of doses in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is relapsed or refractory to current treatment or for which no curative therapy exists.

[0092] Results: 9 patients with relapsed or refractory AML were treated with escalating doses of Compound (I) (64 mg to 128 mg) administered orally once daily. Among them, 3 patients were dosed at 64 mg, 4 patients were dosed at 96 mg, and 2 patients were dosed at 128 mg. More detailed information with respect to the patients is provided in the table below. Of six patients evaluable for response, two (33%) achieved complete remission (CR), and 3 patients (50%) had stable disease (with one patient having a 78% reduction in marrow blast count). The dose limiting toxicity (DLT) was determined to be colitis at the 128 mg dose level. The 96 mg dose level was suggested for further exploration. However, only 4 patients were enrolled at the 96 mg dose level before the study was paused for enrollment and was amended.

Characteristics	N=9
Age (years), median (range)	65 (61-78)
Gender	
Male	6
Female	3
Diagnosis	
AML	8 (89%)
MDS/MPN	1 (11%)
Number of prior therapies, median (range)	0 (0-4)
Karyotype	
Complex	6 (67%)
Del 5q	1 (11%)
Chromosome 7 abnormally	2 (22%)
Somatic mutations (n=6)	
TP53	2 (33%)
IDH1/2	1 (17%)
FLT3	0
NPM1	0

[0093] Conclusion: single agent Compound (I) has activity in patients with poor risk AML.

Example 5. Phase 1b/2 Study of Compound (I) Fumarate as A Single Agent or in Combination With Azacitidine or Decitabine in Patients With Acute Myeloid Leukemia, Myelodysplastic Syndrome or Chronic Myelomonocytic Leukemia..

Part 1A Single Agent Dose Optimization Lead-in

[0094] The primary objectives of this study are (i) to assess the safety and tolerability, and identify the maximum tolerated dose (MTD) of Compound (I) administered orally in patients with acute myeloid leukemia (AML), Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML); and (ii) to determine the Recommended Phase 2 Dose of Compound (I) in patients with AML, Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML).

[0095] The secondary objectives of this study are (i) to determine the PK of Compound (I) administered orally in patients with AML, Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML); (ii) to determine the Composite Complete Remission Rate, CRc (complete remission + complete remission with incomplete blood count recovery

+ complete remission with incomplete platelet count recovery [CR + CRi + CRp]) of Compound (I) in patients with AML; and (iii) to determine the Overall Response Rate (ORR, defined as Complete remission + Marrow CR + Partial remission + Hematologic Improvement (CR + mCR+ PR + HI) in MDS or CMML.

[0096] Study Design and Methodology

[0097] In Part 1A, patients will receive oral Compound (I) daily, in the morning and in the absence of food, *i.e.* not eating for 2 h before or 1 h after taking their dose, for 21 days followed by 7 days off (28-day cycles), except on Day 1 and Day 21 of Cycle 1 when Compound (I) will be administered after an overnight fast. Water is permitted ad lib following 1 hour after the dose administration after the overnight fast; no food is allowed for at least 4 hours after the dose. The starting dose for Compound (I) is 32 mg and is based on preliminary clinical data. Patients who complete the initial cycle of therapy without evidence of significant toxicity or clinical evidence of progressive disease) may receive additional 28-day cycles of treatment at the same dose level for up to 6 cycles and if no PR or better is achieved, the Investigator should remove the patient from study following discussion with the Medical Monitor.

[0098] Safety will be assessed by serial physical exams, vital signs, hematology, and chemistry laboratories and AEs. NCI CTCAE v5 will be used in reporting AEs and laboratory data. Blood samples will be collected for determination of Compound (I) PK. Whole blood, serum, plasma, and bone marrow and/or peripheral blasts will be collected for analysis of the PD effects of Compound (I) where appropriate.

[0099] A bone marrow assessment will be performed after cycle 1, and after every cycle until a response (*e.g.*, CR, CRi, CRp), and as clinically indicated. Patients achieving a CR should have a bone marrow examination every 3 months (approx. 12 weeks) for 1 year, then as clinically indicated.

[00100] When treatment-related toxicities are observed, treatment with Compound (I) may be delayed until recovery from the observed treatment-related toxicities and to consider if dose reductions are appropriate for continued therapy with Compound (I). A delay of up to 14 days is allowed for patients to return to baseline or grade 1 from any treatment-related side effects. The investigator, after discussion with the medical monitor may allow a patient to continue on study after a treatment delay of longer than 14 days if the patient is benefitting from the treatment and the treatment-related toxicities have returned to baseline or grade 1.

[00101] Maximum Tolerated Dose and Dose Limiting Toxicities are defined below for the escalation portions of the study. Dose adjustments for toxicities occurring during the conduct

of the study will be discussed in the protocol and generally will involve dose hold, reduction, and possibly discontinuation of study drug therapy depending on severity. Single agent dose optimization lead-in dose levels are defined below:

Dose Level	Compound (I) Dose (mg) QD x 21 days on / 7 days off (28-day cycles)
-1	16
1	32
2	48
3	64
4+	See below

Part 1B: Food Effect

[00102] The primary objectives of this study are (i) to further assess the safety and tolerability, and identify the maximum tolerated dose (MTD) of Compound (I) administered orally in patients with acute myeloid leukemia (AML), Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML); and (ii) to evaluate the effect of food on pharmacokinetics of Compound (I) through oral administration of Compound (I) with/without a high fat meal in patients with AML, MDS or CMML.

[00103] The secondary objectives of this study are (i) to determine the Composite Complete Remission Rate, CRc (complete remission + complete remission with incomplete blood count recovery + complete remission with incomplete platelet count recovery [CR + CRi + CRp]) of Compound (I) in patients with AML; and (ii) to determine the Overall Response Rate (ORR, defined as Complete remission + Marrow CR + Partial remission + Hematologic Improvement (CR + mCR+ PR + HI) in MDS or CMML.

[00104] Study Design and Methodology

[00105] In Part 1B, patients will be administered oral Compound (I) daily at the proposed dose determined from Part 1A, for one week (study days 1-7), taking the drug in the morning and in the absence of food, *i.e.* not eating for 2 h before or 1 h after taking their dose for 21 days followed by 7 days off (28-day cycles), except on Day 1 and Day 21 of Cycle 1 when Compound (I) will be administered after an overnight fast. On Study Day 8, following an overnight fast (approximately 8 hours), patients will withhold their dose of Compound (I) and arrive at the clinic. Following collection of a pre-dose PK sample, patients will be administered Compound (I) with 240 mL water and undergo post-dose PK sampling. Water is permitted ad lib following 1 hour after the dose administration; no food is allowed for at least

4 hours after the dose. On Study Day 9, following an overnight fast (of approximately 8 hours), patients will withhold their dose of Compound (I) and arrive at the clinic. Following collection of a pre-dose PK sample, patients will receive a high-fat meal 30 minutes prior to administration of Compound (I) with approximately 240 mL water; meal should be consumed in 30 minutes or less. Following administration of Compound (I), patients will then undergo post-dose PK sampling. Water is permitted ad lib following 1 hour after the dose administration; no food is allowed for at least 4 hours after the dose. Following Day 9, patients will continue taking Compound (I) daily for the rest of Cycle 1, taking their dose in the morning in the absence of food.

[00106] Safety will be assessed by serial physical exams, vital signs, hematology, and chemistry laboratories and AEs. NCI CTCAE v5 will be used in reporting AEs and laboratory data. Blood samples will be collected for determination of Compound (I) pharmacokinetics. Whole blood, serum, plasma, and bone marrow and/or peripheral blasts will be collected for analysis of the PD effects of Compound (I).

[00107] A bone marrow assessment will be performed after cycle 1, and after every cycle until a response (*e.g.*, CR, CRi, CRp), and as clinically indicated. Patients achieving a CR should have a bone marrow examination every 3 months (approx. 12 weeks) for 1 year, then as clinically indicated.

[00108] Dose adjustments for toxicities occurring during the conduct of the study will be discussed in the protocol and generally will involve dose hold, reduction, and possibly discontinuation of study drug therapy depending on severity, and are discussed in Section 3.5 and Section 6.

[00109] After the PK results of Part 1B are analyzed, patients will be instructed further if they can take Compound (I) with food or they should continue to take the drug.

Part 2: Dose Escalation for Combination Therapy

Part 2A combination of Compound (I) and Azacitidine

Part 2B combination of Compound (I) and Decitabine.

[00110] The primary objectives of this study are (i) to assess the safety and tolerability, and identify the maximum tolerated dose (MTD) of Compound (I) administered orally in combination with azacitidine or decitabine in patients with AML or CMML; and (ii) to determine the Recommended Phase 2 Dose for the Combination Therapy (RP2D) of Compound (I) and azacitidine or Compound (I) and decitabine in patients with AML or MDS or CMML.

[00111] The secondary objectives of this study are (i) to determine the PK of Compound (I) administered orally in combination with azacitidine or decitabine in patients with AML or CMML; to determine the Composite Complete Remission Rate, CRc (complete remission + complete remission with incomplete blood count recovery + complete remission with incomplete platelet count recovery [CR + CRi + CRp]) of Compound (I) in patients with AML; and (iii) to determine the Overall Response Rate (ORR, defined as complete remission + Marrow CR + partial remission + Hematologic Improvement (CR + mCR+ PR + HI) in MDS or CMML.

[00112] During the dose escalation phase of Part 2A or Part 2B, patients will receive oral Compound (I) daily, in the morning and in the absence of food, *i.e.* not eating for 2 h before or 1 h after taking their dose for 21 days followed by 7 days off (28-day cycles) (unless otherwise specified), except on Day 1 and Day 21 of Cycle 1 when Compound (I) will be administered after an overnight fast. Water is permitted ad lib following 1 hour after the dose administration after the overnight fast; no food is allowed for at least 4 hours after the dose. Patients will receive oral Compound (I) at an initial dose of 32 mg or 2 dose levels below the MTD in Part 1A, whichever is lower, given daily for 28 day cycles in addition to azacitidine given at a dose of 75mg/m^2 IV or SC on days 1-7 of the 28 day cycle or decitabine given at a dose of 20 mg/m^2 IV on days 1-5 of a 28 day cycle. The administration of azacitidine or decitabine should start within 5 minutes of the dosing of Compound (I). Patients who complete the initial cycle of therapy without evidence of significant toxicity or clinical evidence of progressive disease) may receive additional 28-day cycles of treatment at the same dose level. If the initial dose of Compound (I) is not tolerated, the dose of Compound (I) will be reduced to dose level -1 (24 mg). If this is not tolerated, Part 2 will close.

[00113] Safety will be assessed by serial physical exams, vital signs, hematology, and chemistry laboratories and AEs. NCI CTCAE v5 will be used in reporting AEs and laboratory data. Blood samples will be collected for determination of Compound (I) pharmacokinetics. Whole blood, serum, plasma, and bone marrow and/or peripheral blasts will be collected for analysis of the PD effects of Compound (I) and azacitidine or decitabine if appropriate.

[00114] A bone marrow assessment will be performed after cycle 1, and after every cycle until a response (*e.g.*, CR, CRi, CRp), and as clinically indicated. Patients achieving a CR should have a bone marrow examination every 3 months (approx. 12 weeks) for 1 year, then as clinically indicated.

[00115] Dose adjustments for toxicities occurring during the conduct of the study will be discussed in the protocol and generally will involve dose hold, reduction, and possibly discontinuation of study drug therapy depending on severity. Part 2A and 2B Dose escalation will proceed independently as illustrated below:

Dose Level	Compound (I) Dose (mg) QD x 21 days on / 7 days off (28-day cycles)	Azacitidne Dose* (mg/m^2, IV/SC, days 1-7)
-2	16	75
-1	24	75
1	32	75
2	40	75
3+	48**	75

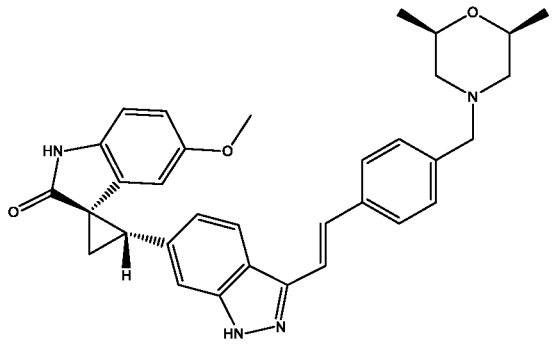
*Azacitidine dose to be administered per local SOC: SC or IV, and typically on days 1-7, or day 1-5 (with weekend off) then the following next 2 weekdays.
**following 48 mg, if dose should increase, dose increments not to exceed 33%.

Dose Level	Compound (I) Dose (mg) QD x 21 days on / 7 days off (28-day cycles)	Decitabine Dose* (mg/m^2, IV/SC, days 1-5)
-2	16	20
-1	24	20
1	32	20
2	40	20
3+	48**	20

**following 48 mg, if dose should increase, dose increments not to exceed 33%.

CLAIMS

1. A method of treating a subject with acute myeloid leukemia or myelodysplastic syndrome, comprising administering an effective amount of Compound (I):



(I),

or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein Compound (I) is a fumarate salt.

3. The method of claim 2, wherein the molar ratio between Compound (I) and fumaric acid is 1:1.

4. The method of any one of claims 1-3, wherein the subject has acute myeloid leukemia.

5. The method of claim 4, wherein the acute myeloid leukemia is relapsed or refractory.

6. The method of any one of claims 1-5, wherein the acute myeloid leukemia is complex karyotype acute myeloid leukemia.

7. The method of any one of claims 1-6, further comprising co-administering an additional therapeutic agent.

8. The method of claim 7, wherein the additional therapeutic agent is an anti-cancer drug.

9. The method of claim 8, wherein the anti-cancer drug is Venetoclax.

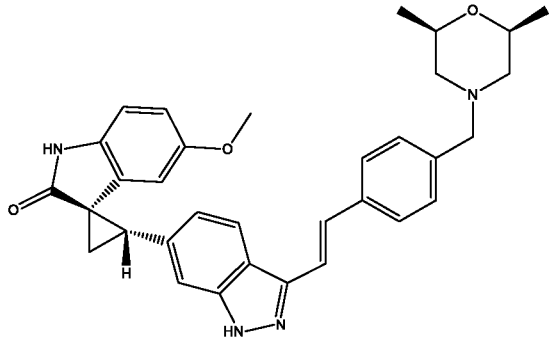
10. The method of claim 8, wherein the anti-cancer drug is 5-Azacytidine.

11. The method of any one of claims 7-10, wherein Compound (I) and the additional therapeutic agent are administered concurrently.

12. The method of any one of claims 7-10, wherein Compound (I) and the additional therapeutic agent are administered sequentially.

13. The method of claim 8, wherein the anti-cancer drug is decitabine.

14. A method of treating a subject with acute lymphoblastic leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Burkitt lymphoma, or diffuse large B-cell lymphoma, comprising administering an effective amount of Compound (I):



(I),

or a pharmaceutically acceptable salt thereof.

15. The method of claim 14, wherein Compound (I) is a fumarate salt.

16. The method of claim 15, wherein the molar ratio between Compound (I) and fumaric acid is 1:1.

17. The method of any one of claims 14-16, wherein the subject has acute lymphoblastic leukemia.

18. The method of claim 17, wherein the acute lymphoblastic leukemia is T-cell acute lymphoblastic leukemia or B-cell acute lymphoblastic leukemia.

19. The method of any one of claims 14-16, wherein the subject has chronic myeloid leukemia.

20. The method of any one of claims 14-16, wherein the subject has non-Hodgkin's lymphoma.

21. The method of any one of claims 14-16, wherein the subject has Burkitt lymphoma.

22. The method of any one of claims 14-16, wherein the subject has diffuse large B-cell lymphoma.

23. The method of claim 22, wherein the diffuse large B-cell lymphoma is germinal center B cell-like or activated B cell-like.

24. The method of any one of claims 14-23, wherein the acute lymphoblastic leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Burkitt lymphoma, or diffuse large B-cell lymphoma is relapsed or refractory.

25. The method of any one of claims 14-24, wherein the acute lymphoblastic leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Burkitt lymphoma, or diffuse large B-cell lymphoma is complex karyotype.

26. The method of any one of claims 14-25, further comprising co-administering an additional therapeutic agent.

27. The method of claim 26, wherein the additional therapeutic agent is an anti-cancer drug.

28. The method of claim 27, wherein the anti-cancer drug is Venetoclax, 5-Azacytidine, or decitabine.

29. The method of any one of claims 26-28, wherein Compound (I) and the additional therapeutic agent are administered concurrently or sequentially.

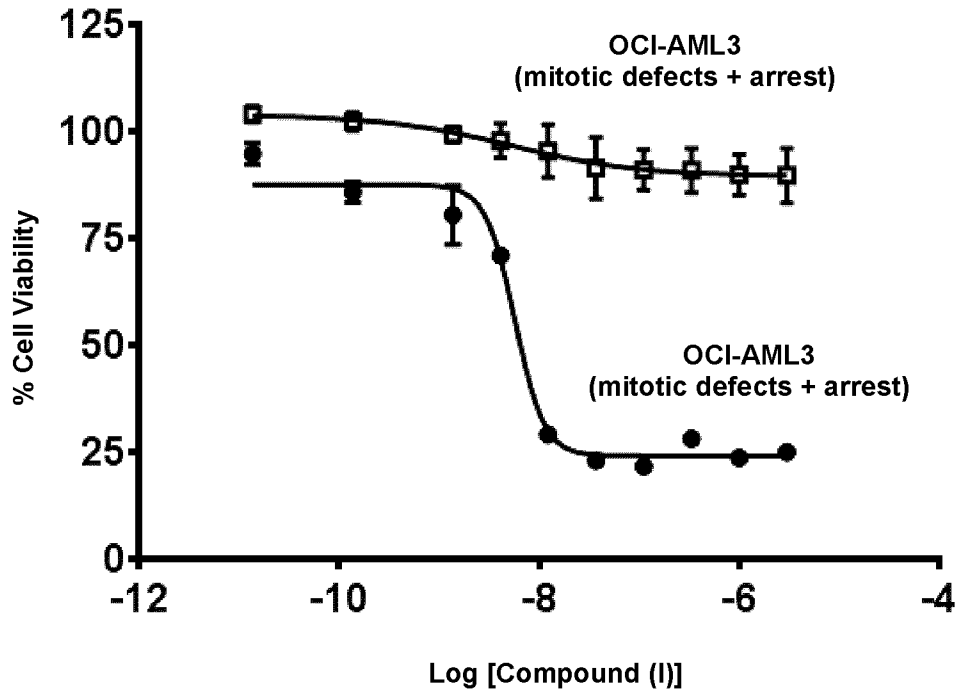

125
100
75
50
25
0
% Cell Viability
OCI-AML3
(mitotic defects + arrest)
OCI-AML3
(mitotic defects + arrest)
-12
-10
-8
-6
-4
Log [Compound (I)]

FIG. 1

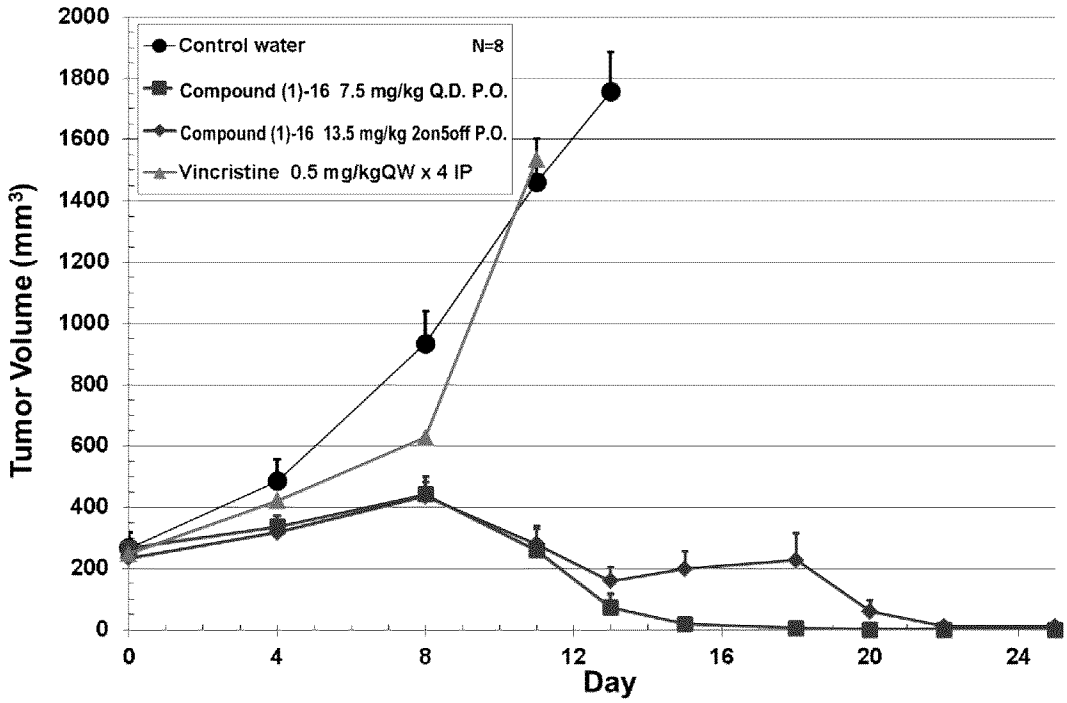

Control water N=8
Compound (1)-16 7.5 mg/kg Q.D. P.O.
Compound (1)-16 13.5 mg/kg 2on5off P.O.
Vincristine 0.5 mg/kgQW x 4 IP
Tumor Volume (mm3)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
4
8
12
16
20
24
Day

FIG. 2

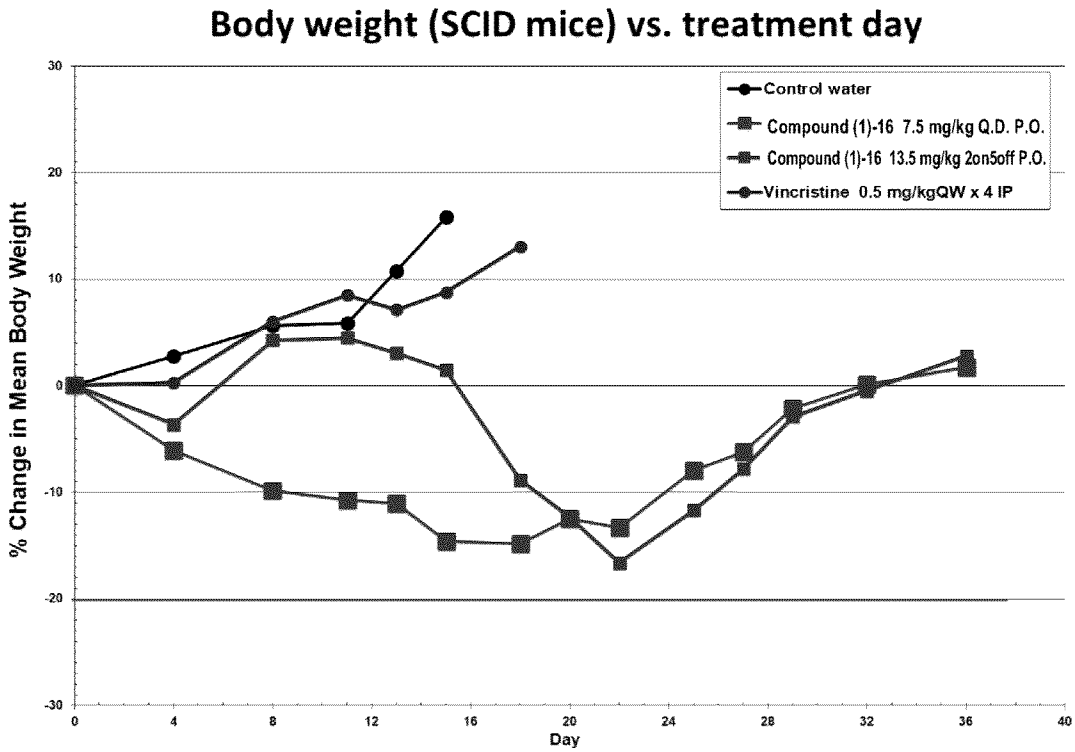

Body weight (SCID mice) vs. treatment day
% Change in Mean Body Weight
Day
Control water
Compound (1)-16 7.5 mg/kg Q.D. P.O.
Compound (1)-16 13.5 mg/kg 2on5off P.O.
Vincristine 0.5 mg/kgQW x 4 IP
30
20
10
0
-10
-20
-30
0
4
8
12
16
20
24
28
32
36
40

FIG. 3

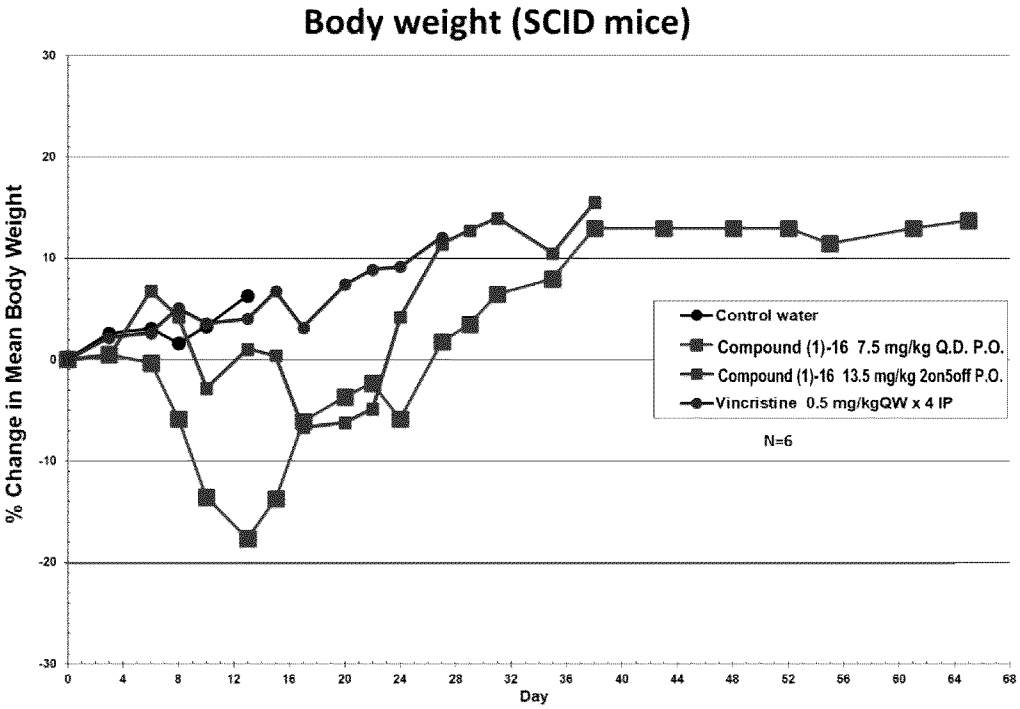

Body weight (SCID mice)
% Change in Mean Body Weight
Day
Control water
Compound (1)-16 7.5 mg/kg Q.D. P.O.
Compound (1)-16 13.5 mg/kg 2on5off P.O.
Vincristine 0.5 mg/kgQW x 4 IP
N=6

FIG. 4

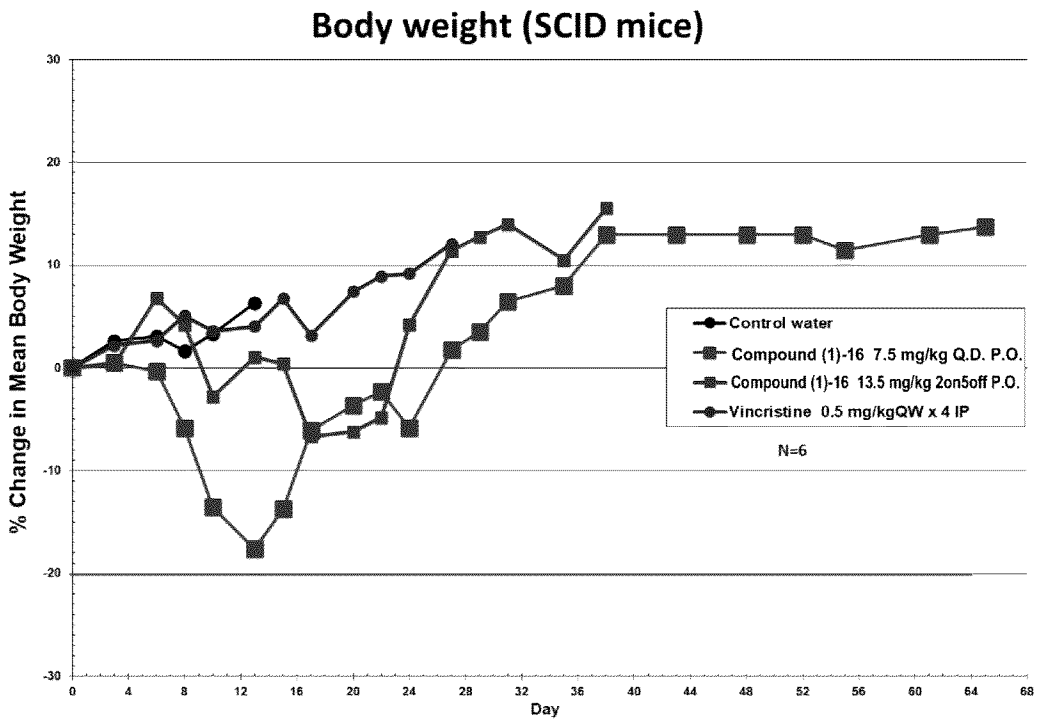

Body weight (SCID mice)
% Change in Mean Body Weight
30
20
10
0
-10
-20
-30
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
Day
Control water
Compound (1)-16 7.5 mg/kg Q.D. P.O.
Compound (1)-16 13.5 mg/kg 2on5off P.O.
Vincristine 0.5 mg/kgQW x 4 IP
N=6

FIG. 5

SEQUENCE LISTING

<110> MODERNA TX, INC.

<120> METHODS OF MAKING TOLEROGENIC DENDRITIC CELLS

<130> M2180-7003WO

<140>
<141>

<150> 63/009,600
<151> 2020-04-14

<150> 62/959,739
<151> 2020-01-10

<160> 271

<170> PatentIn version 3.5

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Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr
            20   25   30

Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu
        35   40   45

Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile
    50   55   60

Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser
65   70   75   80

Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn
                85   90   95

Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr
            100   105   110

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Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val
        115                 120                 125

Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val
    130                 135                 140

Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr
145                 150                 155                 160

Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser
                165                 170                 175

Gly Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn
            180                 185                 190

Val Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr
        195                 200                 205

Cys Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu
    210                 215                 220

Val Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr His
225                 230                 235                 240

Leu Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr
                245                 250                 255

Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys
            260                 265                 270

Gly Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu
        275                 280                 285

Glu Thr
    290
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<212> RNA
<213> Homo sapiens

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aaauucccag uagagaaaca auuagaccug gcugcacuaa uugucuauug ggaaauggag 180

gauaagaaca uuauucaauu ugugcacgga gaggaagacc ugaagguuca gcauaguagc 240

uacagacaga gggcccggcu guugaaggac cagcucuccc ugggaaacgc ugcacuucag 300

aucacagacg ugaaauugca ggacgcaggg guguaccgcu gcaugaucag cuacgguggu 360

gccgacuaca agcgaauuac ugugaaaguc aacgccccau acaacaagau caaccaaaga 420

auuuugguug uggauccagu caccucugaa cacgaacuga cuugucaggc ugagggcuac 480

cccaaggccg aagucaucug gacaagcagu gaccaucaag uccugagugg uaagaccacc 540

accaccaauu ccaagagaga ggagaagcuu uucaacguga ccagcacacu gagaaucaac 600

acaacaacua acgagauuuu cuacugcacu uuuaggagau uagauccuga ggagaaccau 660

acagcugaau uggucauccc agaacuaccu cuggcacauc cuccaaacga aaggacucac 720

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polypeptide"

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Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile Glu His Gly
20 25 30

Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser His Val Asn
35 40 45

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Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn Asp Thr Ser
    50                  55                  60

Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu Pro Leu Gly
65                  70                  75                  80

Lys Ala Ser Phe His Ile Pro Gln Val Gln Val Arg Asp Glu Gly Gln
                85                  90                  95

Tyr Gln Cys Ile Ile Ile Tyr Gly Val Ala Trp Asp Tyr Lys Tyr Leu
            100                 105                 110

Thr Leu Lys Val Lys Ala Ser Tyr Arg Lys Ile Asn Thr His Ile Leu
        115                 120                 125

Lys Val Pro Glu Thr Asp Glu Val Glu Leu Thr Cys Gln Ala Thr Gly
    130                 135                 140

Tyr Pro Leu Ala Glu Val Ser Trp Pro Asn Val Ser Val Pro Ala Asn
145                 150                 155                 160

Thr Ser His Ser Arg Thr Pro Glu Gly Leu Tyr Gln Val Thr Ser Val
                165                 170                 175

Leu Arg Leu Lys Pro Pro Pro Gly Arg Asn Phe Ser Cys Val Phe Trp
            180                 185                 190

Asn Thr His Val Arg Glu Leu Thr Leu Ala Ser Ile Asp Leu Gln Ser
        195                 200                 205

Gln Met Glu Pro Arg Thr His Pro Thr Gly Gly Gly Ser Pro Arg Gly
    210                 215                 220

Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu
225                 230                 235                 240

Glu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val
                245                 250                 255

Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val
```

```
            260                 265                 270

Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val
        275                 280                 285

Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser
    290                 295                 300

Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Ala Trp Met
305                 310                 315                 320

Ser Gly Lys Ala Phe Ala Cys Ala Val Asn Asn Lys Asp Leu Pro Ala
                325                 330                 335

Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro
            340                 345                 350

Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln
        355                 360                 365

Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr
    370                 375                 380

Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr
385                 390                 395                 400

Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu
                405                 410                 415

Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser
            420                 425                 430

Val Val His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser
        435                 440                 445

Arg Thr Pro Gly Lys Asp Tyr Lys Asp Asp Asp Asp Lys
    450                 455                 460

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uucgacaccg gcagccacgu gaaccugggc gccaucaccg ccagccugca gaagguggag 180

aacgacacca gcccucacag agagagagcc acccugcugg aggagcaacu accacugggc 240

aaggccagcu uccacauccc ucaggugcag gugagagacg agggccagua ccagugcauc 300

aucaucuacg gcguggccug ggacuacaag uaccugaccc ugaaggugaa ggccuccuac 360

agaaagauca acacccacau ccuuaaggug ccugagacug acgaggugga gcugaccugc 420

caggccaccg gcuacccucu ggccgaggug agcuggccua acgugagcgu gccugccaac 480

accagccaca gcagaacccc ugagggccug uaccagguga ccagcgugcu gagacugaag 540

ccuccuccug gcagaaacuu cagcugcgug uucuggaaca cccacgugag agagcugacc 600

cuggccagca ucgaccugca gagccagaug gagccuagaa cccacccuac cggcggcggc 660

agcccuagag gcccuaccau caagccuugc ccuccuugca agugcccugc cccuaaccug 720

gagggcggcc cuagcguguu caucuucccu ccuaagauca aggacgugcu gaugaucagc 780

cugagcccua ucgugaccug cgugguggug gacgugagcg aggacgaccc ugacgugcag 840

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aagaacuggg uggagagaaa cagcuacagc ugcagcgugg ugcacgaggg ccugcacaac 1320

caccacacca ccaagagcuu cucccgaacu ccaggcaagg auuauaagga cgacgacgac 1380

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1 5 10 15

Ala Leu Gly Val Leu Cys Leu Cys Leu Thr Gly Ala Val Glu Val Gln
20 25 30

Val Ser Glu Asp Pro Val Val Ala Leu Val Asp Thr Asp Ala Thr Leu
35 40 45

Arg Cys Ser Phe Ser Pro Glu Pro Gly Phe Ser Leu Ala Gln Leu Asn
50 55 60

Leu Ile Trp Gln Leu Thr Asp Thr Lys Gln Leu Val His Ser Phe Thr
65 70 75 80

Glu Gly Arg Asp Gln Gly Ser Ala Tyr Ser Asn Arg Thr Ala Leu Phe
85 90 95

Pro Asp Leu Leu Val Gln Gly Asn Ala Ser Leu Arg Leu Gln Arg Val
100 105 110

Arg Val Thr Asp Glu Gly Ser Tyr Thr Cys Phe Val Ser Ile Gln Asp
115 120 125

Phe Asp Ser Ala Ala Val Ser Leu Gln Val Ala Ala Pro Tyr Ser Lys
130 135 140

Pro Ser Met Thr Leu Glu Pro Asn Lys Asp Leu Arg Pro Gly Asn Met
145 150 155 160

Val Thr Ile Thr Cys Ser Ser Tyr Gln Gly Tyr Pro Glu Ala Glu Val
165 170 175

Phe Trp Lys Asp Gly Gln Gly Val Pro Leu Thr Gly Asn Val Thr Thr

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            180                 185                 190

Ser Gln Met Ala Asn Glu Arg Gly Leu Phe Asp Val His Ser Val Leu
        195                 200                 205

Arg Val Val Leu Gly Ala Asn Gly Thr Tyr Ser Cys Leu Val Arg Asn
    210                 215                 220

Pro Val Leu Gln Gln Asp Ala His Gly Ser Val Thr Ile Thr Gly Gln
225                 230                 235                 240

Pro Leu Thr Phe Pro Pro Glu Ala Leu Trp Val Thr Val Gly Leu Ser
                245                 250                 255

Val Cys Leu Val Val Leu Leu Val Ala Leu Ala Phe Val Cys Trp Arg
            260                 265                 270

Lys Ile Lys Gln Ser Cys Glu Glu Glu Asn Ala Gly Ala Glu Asp Gln
        275                 280                 285

Asp Gly Asp Gly Glu Gly Ser Lys Thr Ala Leu Arg Pro Leu Lys Pro
    290                 295                 300

Ser Glu Asn Lys Glu Asp Asp Gly Gln Glu Ile Ala
305                 310                 315
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cuaguggaca ccgacgccac ccuccggugc agcuucagcc cugagccugg uuucagccug      180

gcccagcuga accugaucug gcagcugacc gacaccaagc agcuggugca cagcuucacc      240

gagggccggg aucagggcag cgccuacagc aaccgcacgg cccuguuccc ugaccugcuu      300

guccagggca acgccagccu gagacugcag agagugagag ugaccgauga gggcagcuac      360

accugcuucg ugagcaucca ggacuucgac agcgccgccg ugagccugca gguggccgcc      420
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ccuuacagca agccuagcau gacccuggag ccuaacaagg accugcgccc uggcaacaug 480

gugaccauca ccugcagcag cuaccagggc uacccugagg ccgagguguu cuggaaggac 540

ggccagggcg ugccucucac ugguaacgug accaccagcc agauggccaa cgagagaggc 600

cuguucgacg uccacucugu ccuucgagug gugcugggcg ccaacggcac cuacagcugc 660

cuggugagaa acccugugcu ucagcaagac gcccacggca gcguaacuau aacaggccag 720

ccauugacau ucccuccaga ggcgcugugg gugaccgugg gccugagcgu gugccucguu 780

gugcugcugg ucgcccuugc cuucgugugc uggagaaaga ucaagcagag cugcgaggag 840

gagaacgcug gugccgagga ccaggacggc gacggcgagg guucgaagac agcccuacgc 900

ccgcugaagc cauccgagaa caaggaggac gauggccagg agaucgcc 948

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<211> 283
<212> PRT
<213> Mus sp.

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Met Ala Ser Leu Gly Gln Ile Ile Phe Trp Ser Ile Ile Asn Ile Ile
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Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser
20 25 30

Gly Lys His Phe Ile Thr Val Thr Thr Phe Thr Ser Ala Gly Asn Ile
35 40 45

Gly Glu Asp Gly Thr Leu Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu
50 55 60

Asn Gly Ile Val Ile Gln Trp Leu Lys Glu Gly Ile Lys Gly Leu Val
65 70 75 80

His Glu Phe Lys Glu Gly Lys Asp Asp Leu Ser Gln Gln His Glu Met
85 90 95

Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Val Val Gly Asn
100 105 110

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Ala Ser Leu Arg Leu Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr
        115                 120                 125

Thr Cys Tyr Ile Arg Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu
    130                 135                 140

Tyr Lys Thr Gly Ala Phe Ser Met Pro Glu Ile Asn Val Asp Tyr Asn
145                 150                 155                 160

Ala Ser Ser Glu Ser Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln
                165                 170                 175

Pro Thr Val Ala Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser
            180                 185                 190

Glu Val Ser Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met
        195                 200                 205

Lys Val Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser
    210                 215                 220

Cys Met Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val
225                 230                 235                 240

Thr Asp Ser Glu Val Lys Arg Arg Ser Gln Leu Gln Leu Leu Asn Ser
                245                 250                 255

Gly Pro Ser Pro Cys Val Phe Ser Ser Ala Phe Val Ala Gly Trp Ala
            260                 265                 270

Leu Leu Ser Leu Ser Cys Cys Leu Met Leu Arg
        275                 280
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<212> RNA
<213> Mus sp.

<400> 8
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accuucacca gcgccggcaa caucggcgag gacggcaccc ugagcugcac cuucgagccu 180

gacaucaagc ugaacggcau cgugauccag uggcugaagg agggcaucaa gggccuggug 240

cacgaguuca aggagggcaa ggacgaccug agccagcagc acgagauguu cagaggcaga 300

accgccgugu ucgccgacca ggugguggug ggcaacgcca gccugagacu gaagaacgug 360

cagcugaccg acgccggcac cuacaccugc uacaucagaa ccagcaaggg caaggguaac 420

gccaaccugg aguacaagac cggcgccuuc agcaugccug agaucaacgu ggacuacaac 480

gccagcagcg agagccugcg gugcgaggcc ccucgguggu ucccucagcc uaccguggcc 540

ugggcuagcc agguggacca gggcgccaac uucagcgagg ugagcaacac cagcuucgag 600

cugaacagcg agaacgugac caugaaggug gugagcgugc uguacaacgu gacuaucaac 660

aacaccuaca gcugcaugau cgagaacgac aucgccaagg ccaccggcga caucaaggug 720

accgacucag aggugaagag aagaagccag cugcaguugc ugaauagcgg cccuagcccu 780

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augcugaga 849

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20 25 30

Glu Val Val Thr Gln Asp Glu Arg Lys Ala Leu His Thr Thr Ala Ser
35 40 45

Leu Arg Cys Ser Leu Lys Thr Ser Gln Glu Pro Leu Ile Val Thr Trp
50 55 60

Gln Lys Lys Lys Ala Val Ser Pro Glu Asn Met Val Thr Tyr Ser Lys
65 70 75 80

Thr His Gly Val Val Ile Gln Pro Ala Tyr Lys Asp Arg Ile Asn Val

85 90 95

Thr Glu Leu Gly Leu Trp Asn Ser Ser Ile Thr Phe Trp Asn Thr Thr
100 105 110

Leu Glu Asp Glu Gly Cys Tyr Met Cys Leu Phe Asn Thr Phe Gly Ser
115 120 125

Gln Lys Val Ser Gly Thr Ala Cys Leu Thr Leu Tyr Val Gln Pro Ile
130 135 140

Val His Leu His Tyr Asn Tyr Phe Glu Asp His Leu Asn Ile Thr Cys
145 150 155 160

Ser Ala Thr Ala Arg Pro Ala Pro Ala Ile Ser Trp Lys Gly Thr Gly
165 170 175

Thr Gly Ile Glu Asn Ser Thr Glu Ser His Phe His Ser Asn Gly Thr
180 185 190

Thr Ser Val Thr Ser Ile Leu Arg Val Lys Asp Pro Lys Thr Gln Val
195 200 205

Gly Lys Glu Val Ile Cys Gln Val Leu Tyr Leu Gly Asn Val Ile Asp
210 215 220

Tyr Lys Gln Ser Leu Asp Lys Gly Phe Trp Phe Ser Val Pro Leu Leu
225 230 235 240

Leu Ser Ile Val Ser Leu Val Ile Leu Leu Val Leu Ile Ser Ile Leu
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Leu Tyr Trp Lys Arg His Arg Asn Gln Glu Arg Gly Glu Ser Ser Gln
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Gly Met Gln Arg Met Lys
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aaggcccugc acaccaccgc cagccugcgu ugcagccuga agaccagcca ggagccucug 180

aucgugaccu ggcagaagaa gaaggccgug agcccugaga acauggugac cuacagcaag 240

acccacggcg uggugaucca gccugccuac aaggacagaa ucaacgugac cgagcugggc 300

cuguggaaca gcagcaucac cuucuggaac accacccugg aggacgaggg cugcuacaug 360

ugccuguuca acaccuucgg cagccagaag gugagcggca ccgccugccu gacccuguac 420

gugcagccua ucgugcaccu gcacuacaac uacuucgagg accaccugaa caucaccugc 480

agcgccacgg ccagaccugc cccugccauc agcuggaagg gcaccggcac ugguaucgag 540

aacagcaccg agagccacuu ccacagcaac ggcaccacca gcgugaccag cauccugaga 600

gugaaggacc cuaagaccca gguggggcaag gaggugaucu gccaggugcu guaccugggc 660

aacgugaucg acuacaagca gagccuggac aagggcuucu gguucagcgu gccucugcug 720

cugagcaucg ugagccuggu gauccugcug gugcugauca guauucugcu guacuggaag 780

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polypeptide"

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Phe Ser Gly Thr Ile Gln Gly Gly Leu Gln Asp Gly Leu Gln Ile Thr
20 25 30

Val Asn Gly Thr Val Leu Ser Ser Ser Gly Thr Arg Phe Ala Val Asn
35 40 45

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Phe Gln Thr Gly Phe Ser Gly Asn Asp Ile Ala Phe His Phe Asn Pro
    50                  55                  60

Arg Phe Glu Asp Gly Gly Tyr Val Val Cys Asn Thr Arg Gln Asn Gly
65                  70                  75                  80

Ser Trp Gly Pro Glu Glu Arg Lys Thr His Met Pro Phe Gln Lys Gly
                85                  90                  95

Met Pro Phe Asp Leu Cys Phe Leu Val Gln Ser Ser Asp Phe Lys Val
            100                 105                 110

Met Val Asn Gly Ile Leu Phe Val Gln Tyr Phe His Arg Val Pro Phe
        115                 120                 125

His Arg Val Asp Thr Ile Ser Val Asn Gly Ser Val Gln Leu Ser Tyr
    130                 135                 140

Ile Ser Phe Gln Asn Pro Arg Thr Val Pro Val Gln Pro Ala Phe Ser
145                 150                 155                 160

Thr Val Pro Phe Ser Gln Pro Val Cys Phe Pro Pro Arg Pro Arg Gly
                165                 170                 175

Arg Arg Gln Lys Pro Pro Gly Val Trp Pro Ala Asn Pro Ala Pro Ile
            180                 185                 190

Thr Gln Thr Val Ile His Thr Val Gln Ser Ala Pro Gly Gln Met Phe
        195                 200                 205

Ser Thr Pro Ala Ile Pro Pro Met Met Tyr Pro His Pro Ala Tyr Pro
    210                 215                 220

Met Pro Phe Ile Thr Thr Ile Leu Gly Gly Leu Tyr Pro Ser Lys Ser
225                 230                 235                 240

Ile Leu Leu Ser Gly Thr Val Leu Pro Ser Ala Gln Arg Phe His Ile
                245                 250                 255

Asn Leu Cys Ser Gly Asn His Ile Ala Phe His Leu Asn Pro Arg Phe
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            260                 265                 270

Asp Glu Asn Ala Val Val Arg Asn Thr Gln Ile Asp Asn Ser Trp Gly
        275                 280                 285

Ser Glu Glu Arg Ser Leu Pro Arg Lys Met Pro Phe Val Arg Gly Gln
    290                 295                 300

Ser Phe Ser Val Trp Ile Leu Cys Glu Ala His Cys Leu Lys Val Ala
305                 310                 315                 320

Val Asp Gly Gln His Leu Phe Glu Tyr Tyr His Arg Leu Arg Asn Leu
                325                 330                 335

Pro Thr Ile Asn Arg Leu Glu Val Gly Gly Asp Ile Gln Leu Thr His
            340                 345                 350

Val Gln Thr Asp Tyr Lys Asp Asp Asp Asp Lys
        355                 360


<210> 12
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<212> RNA
<213> Artificial Sequence

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<223> /note="Description of Artificial Sequence: Synthetic
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auccagggcg gccugcagga cggacugcag aucaccguga acggcaccgu gcugagcucc      120

uccggcacca gauucgccgu gaacuuccag accggcuucu ccggaaacga caucgccuuc      180

cacuucaacc cuagauucga ggacggcggc uacguggugu gcaacaccag acagaacggc      240

agcuggggcc cugaggagag aaagacccac augccuuucc agaaggguau gccuuucgac      300

cugugcuucc uggugcagag cagcgacuuc aaggugaugg ugaacggaau ccuguucgug      360

caguacuucc acagaguucc uuuccaccga guggacacca ucagcgugaa cgguagcgug      420

cagcugagcu acaucagcuu ccagaacccu agaaccgugc cugugcagcc ugccuucagc      480
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acagucccau ucagccagcc ugugugcuuc ccuccuagac cuagaggcag aagacagaag 540

ccuccuggcg uguggccugc caacccugcc ccuaucaccc agaccgugau ccacaccgug 600

cagagcgccc cuggccagau guucagcacc ccugccaucc cuccuaugau guacccucac 660

ccugccuacc cuaugccauu caucaccacc auccuaggug gacuguaccc uagcaagagc 720

auccugcuga gcgguacugu gcugccuagc gcccagagau uccacaucaa ucugugcagc 780

ggcaaccaca uagccuucca ccuuaacccg cgauucgacg agaacgccgu ggugagaaac 840

acccagaucg acaacucuug gggcagcgag gagcguagcc ugccuagaaa gaugccguuc 900

gugagaggcc agagcuucag cguguggauc cugugcgagg cccacugccu gaagguggcc 960

guggacggcc agcaccuguu cgaguacuac cacagacuga gaaacuugcc aaccaucaac 1020

agacuggagg ugggcggcga cauccagcug acccacgugc agaccgacua caaggacgac 1080

gacgacaag 1089

<210> 13
<211> 401
<212> PRT
<213> Artificial Sequence

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<223> /note="Description of Artificial Sequence: Synthetic
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Ser Arg Thr Trp Pro Phe Val Ala Leu Leu Thr Leu Leu Phe Ile Pro
20 25 30

Val Phe Ser Glu Ala Ile Gln Val Thr Gln Pro Ser Val Val Leu Ala
35 40 45

Ser Ser His Gly Val Ala Ser Phe Pro Cys Glu Tyr Ser Pro Ser His
50 55 60

Asn Thr Asp Glu Val Arg Val Thr Val Leu Arg Gln Thr Asn Asp Gln
65 70 75 80

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Met Thr Glu Val Cys Ala Thr Thr Phe Thr Glu Lys Asn Thr Val Gly
                85                  90                  95

Phe Leu Asp Tyr Pro Phe Cys Ser Gly Thr Phe Asn Glu Ser Arg Val
            100                 105                 110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Val Asp Thr Gly Leu Tyr Leu
        115                 120                 125

Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Phe Val Gly Met Gly
    130                 135                 140

Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
145                 150                 155                 160

Asp Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro
                165                 170                 175

Ala Pro Asn Leu Glu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys
            180                 185                 190

Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val
        195                 200                 205

Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe
    210                 215                 220

Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu
225                 230                 235                 240

Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His
                245                 250                 255

Gln Asp Trp Met Ser Gly Lys Ala Phe Ala Cys Ala Val Asn Asn Lys
            260                 265                 270

Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser
        275                 280                 285

Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met
    290                 295                 300
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Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro
305                 310                 315                 320

Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn
                325                 330                 335

Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met
            340                 345                 350

Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser
        355                 360                 365

Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr Thr
    370                 375                 380

Lys Ser Phe Ser Arg Thr Pro Gly Lys Asp Tyr Lys Asp Asp Asp Asp
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acccagccua gcguggugcu ggccagcagc cacggcgugg ccagcuuccc uugcgaguac 180

agcccuagcc acaacaccga cgaggugaga gugaccgugc ugagacagac caacgaccag 240

augaccgagg ugugcgccac caccuucacc gagaagaaca ccgugggcuu ccuggacuac 300

ccuuucugca gcggcaccuu caacgagagc agagugaacc ugaccaucca gggccugaga 360

gccguggaca ccggccugua ccugugcaag guggagcuga uguacccucc uccuuacuuc 420

gugggcaugg gcaacggcac ccagaucuac gugaucgacc cugagccuug cccugacagc 480

gacccuagag gcccuaccau caagccuugc ccuccuugca agugcccugc cccuaaccug 540

gagggcggcc cuagcguguu caucuucccu ccuaagauca aggacgugcu gaugaucagc 600

cugagcccua ucgugaccug cgugguggug gacgugagcg aggacgaccc ugacgugcag 660

aucagcuggu ucgugaacaa cguggaggug cacaccgccc agacccagac ccacagagag 720

gacuacaaca gcacccugag aguggugagc gcccugccua uccagcacca ggacuggaug 780

agcggcaagg ccuucgccug cgccgugaac aacaaggacc ugccugcccc uaucgagaga 840

accaucagca agccuaaggg cagcgugaga gccccucagg uguacgugcu gccuccuccu 900

gaggaggaga ugaccaagaa gcaggugacc cugaccugca uggugaccga cuucaugccu 960

gaggacaucu acguggagug gaccaacaac ggcaagaccg agcugaacua caagaacacc 1020

gagccugugc uggacagcga cggcagcuac uucauguaca gcaagcugag aguggagaag 1080

aagaacuggg uggagagaaa cagcuacagc ugcagcgugg ugcacgaggg ccugcacaac 1140

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aag 1203

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<212> PRT
<213> Artificial Sequence

<220>
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Ile Ala Ala Asp Tyr Lys Asp Asp Asp Asp Lys Leu Phe Thr Val Thr
20 25 30

Val Pro Lys Glu Leu Tyr Ile Ile Glu His Gly Ser Asn Val Thr Leu
35 40 45

Glu Cys Asn Phe Asp Thr Gly Ser His Val Asn Leu Gly Ala Ile Thr

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    50                  55                  60

Ala Ser Leu Gln Lys Val Glu Asn Asp Thr Ser Pro His Arg Glu Arg
65                  70                  75                  80

Ala Thr Leu Leu Glu Glu Gln Leu Pro Leu Gly Lys Ala Ser Phe His
                85                  90                  95

Ile Pro Gln Val Gln Val Arg Asp Glu Gly Gln Tyr Gln Cys Ile Ile
            100                 105                 110

Ile Tyr Gly Val Ala Trp Asp Tyr Lys Tyr Leu Thr Leu Lys Val Lys
        115                 120                 125

Ala Ser Tyr Arg Lys Ile Asn Thr His Ile Leu Lys Val Pro Glu Thr
    130                 135                 140

Asp Glu Val Glu Leu Thr Cys Gln Ala Thr Gly Tyr Pro Leu Ala Glu
145                 150                 155                 160

Val Ser Trp Pro Asn Val Ser Val Pro Ala Asn Thr Ser His Ser Arg
                165                 170                 175

Thr Pro Glu Gly Leu Tyr Gln Val Thr Ser Val Leu Arg Leu Lys Pro
            180                 185                 190

Pro Pro Gly Arg Asn Phe Ser Cys Val Phe Trp Asn Thr His Val Arg
        195                 200                 205

Glu Leu Thr Leu Ala Ser Ile Asp Leu Gln Ser Gln Met Glu Pro Arg
    210                 215                 220

Thr His Pro Thr Trp Leu Leu His Ile Phe Ile Pro Phe Cys Ile Ile
225                 230                 235                 240

Ala Phe Ile Phe Ile Ala Thr Val Ile Ala Leu Arg Lys Gln Leu Cys
                245                 250                 255

Gln Lys Leu Tyr Ser Ser Lys Asp Thr Thr Lys Arg Pro Val Thr Thr
            260                 265                 270
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Thr Lys Arg Glu Val Asn Ser Ala Ile
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gagcacggca gcaacgugac ccuggagugc aacuucgaca ccggcagcca cgugaaccug 180

ggcgccauca ccgccagccu gcagaaggug gagaacgaca ccagcccuca cagagagaga 240

gccacccugc uggaggagca gcugccucug ggcaaggcca gcuuccacau cccucaggug 300

caggugagag acgagggcca guaccagugc aucaucaucu acggcguggc cugggacuac 360

aaguaccuga cccugaaggu gaaggccagc uacagaaaga ucaacaccca cauccugaag 420

gugccugaaa cugacgaggu ggagcugacc ugccaggcca ccggcuaccc ucuggccgag 480

gugagcuggc cuaacgugag cgugccugcc aacaccagcc acagcagaac cccugagggc 540

cuguaccagg ugaccagcgu gcugagacug aagccuccuc cuggcagaaa cuucagcugc 600

guguucugga acacccacgu gagagagcug acccuggcca gcaucgaccu gcagagccag 660

auggagccua gaacccaccc uaccuggcug cugcacaucu ucaucccuuu cugcaucauc 720

gccuucaucu ucaucgccac cgugaucgcc cugagaaagc agcugugcca gaagcuguac 780

agcagcaagg acaccaccaa gcggccugug acaacuacaa agcgugaggu gaacagcgcc 840

auc 843

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20 25 30

Lys Asp Leu Tyr Val Val Glu Tyr Gly Ser Asn Val Thr Met Glu Cys
35 40 45

Arg Phe Pro Val Glu Arg Glu Leu Asp Leu Leu Ala Leu Val Val Tyr
50 55 60

Trp Glu Lys Glu Asp Glu Gln Val Ile Gln Phe Val Ala Gly Glu Glu
65 70 75 80

Asp Leu Lys Pro Gln His Ser Asn Phe Arg Gly Arg Ala Ser Leu Pro
85 90 95

Lys Asp Gln Leu Leu Lys Gly Asn Ala Ala Leu Gln Ile Thr Asp Val
100 105 110

Lys Leu Gln Asp Ala Gly Val Tyr Cys Cys Ile Ile Ser Tyr Gly Gly
115 120 125

Ala Asp Tyr Lys Arg Ile Thr Leu Lys Val Asn Ala Pro Tyr Arg Lys
130 135 140

Ile Asn Gln Arg Ile Ser Val Asp Pro Ala Thr Ser Glu His Glu Leu
145 150 155 160

Ile Cys Gln Ala Glu Gly Tyr Pro Glu Ala Glu Val Ile Trp Thr Asn
165 170 175

Ser Asp His Gln Pro Val Ser Gly Lys Arg Ser Val Thr Thr Ser Arg
180 185 190

Thr Glu Gly Met Leu Leu Asn Val Thr Ser Ser Leu Arg Val Asn Ala
195 200 205

Thr Ala Asn Asp Val Phe Tyr Cys Thr Phe Trp Arg Ser Gln Pro Gly
210 215 220

Gln Asn His Thr Ala Glu Leu Ile Ile Pro Glu Leu Pro Ala Thr His
225 230 235 240

Pro Pro Gln Asn Arg Thr His Trp Val Leu Leu Gly Ser Ile Leu Leu
245 250 255

Phe Leu Ile Val Val Ser Thr Val Leu Leu Phe Leu Arg Lys Gln Val
260 265 270

Arg Met Leu Asp Val Glu Lys Cys Gly Val Glu Asp Thr Ser Ser Lys
275 280 285

Asn Arg Asn Asp Thr Gln Phe Glu Glu Thr
290 295

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ggcagcaacg ugaccaugga gugcagauuc ccuguggaga gagagcugga ccugcuggcc 180

cugguggugu acugggagaa ggaggacgag caggugaucc aguucguggc cggcgaggag 240

gaccugaagc cucagcacag caacuucaga ggcagagcca gccugccaaa ggaccagcug 300

cugaagggca acgccgcccu gcagaucacc gacgugaagc ugcaggacgc cggcguguac 360

ugcugcauca ucagcuacgg cggcgcagau uauaagagaa ucacccugaa ggugaacgcc 420

ccuuacagaa agaucaacca gaggaucagc guggacccug ccaccagcga gcacgagcug 480

aucugccagg ccgagggcua cccagaagcu gaagugaucu ggaccaacag cgaccaccag 540

ccugugagcg gcaagagaag cgugacuacc aguagaaccg agggcaugcu ccuaaacgug 600

acuagcagcc ugagagugaa ugcaaccgcc aacgacgugu ucuacugcac cuucuggaga 660

ucgcaaccug gccagaacca caccgcagag cucauuaucc cugagcugcc agccacccac 720

ccuccucaga acagaaccca cugggugcug cugggcagca uccugcuguu ccugaucgug 780

gugagcaccg ucuuacuuuu ccuccgcaag caagugagaa ugcuggacgu ggagaagugc 840

ggcguggagg auacguccuc caagaauaga aacgacaccc aguucgagga aacg 894

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<212> PRT
<213> Rattus sp.

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Ala Ala Phe Thr Ile Thr Ala Pro Lys Asp Leu Tyr Val Val Glu Tyr
20 25 30

Gly Ser Asn Val Thr Met Glu Cys Arg Phe Pro Val Glu Gln Lys Leu
35 40 45

Asp Leu Leu Ala Leu Val Val Tyr Trp Glu Lys Glu Asp Lys Glu Val
50 55 60

Ile Gln Phe Val Glu Gly Glu Glu Asp Leu Lys Pro Gln His Ser Ser
65 70 75 80

Phe Arg Gly Arg Ala Phe Leu Pro Lys Asp Gln Leu Leu Lys Gly Asn
85 90 95

Ala Val Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr
100 105 110

Cys Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Leu
115 120 125

Lys Val Asn Ala Pro Tyr Arg Lys Ile Asn Gln Arg Ile Ser Met Asp
130 135 140

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Pro Ala Thr Ser Glu His Glu Leu Met Cys Gln Ala Glu Gly Tyr Pro
145                 150                 155                 160

Glu Ala Glu Val Ile Trp Thr Asn Ser Asp His Gln Ser Leu Ser Gly
                165                 170                 175

Glu Thr Thr Val Thr Thr Ser Gln Thr Glu Glu Lys Leu Leu Asn Val
            180                 185                 190

Thr Ser Val Leu Arg Val Asn Ala Thr Ala Asn Asp Val Phe His Cys
        195                 200                 205

Thr Phe Trp Arg Val His Ser Gly Glu Asn His Thr Ala Glu Leu Ile
    210                 215                 220

Ile Pro Glu Leu Pro Val Pro Arg Leu Pro His Asn Arg Thr His Trp
225                 230                 235                 240

Val Leu Leu Gly Ser Val Leu Leu Phe Leu Ile Val Gly Phe Thr Val
                245                 250                 255

Phe Phe Cys Leu Arg Lys Gln Val Arg Met Leu Asp Val Glu Lys Cys
            260                 265                 270

Gly Phe Glu Asp Arg Asn Ser Lys Asn Arg Asn Asp Thr Gln Phe Glu
        275                 280                 285

Glu Thr
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agauucccug uggagcagaa gcuggaccug cuggcccugg ugguguacug ggagaaggag 180

gacaaggagg ugauccaguu cguggagggc gaggaggacc ugaagccuca gcacagcagc 240

uucagaggca gagccuuccu gccuaaggac cagcugcuga agggcaacgc cgugcugcag 300

aucaccgacg ugaagcugca ggacgccggc guguacugcu gcaugaucag cuacggcggc 360

gccgacuaca agagaaucac ccugaaggug aacgccccuu acagaaagau caaccagaga 420

aucagcaugg acccugccac cagcgagcac gagcugaugu gccaggccga gggcuacccu 480

gaggccgagg ugaucuggac caacagcgac caccagagcc ugagcggcga gaccaccgug 540

accaccagcc agaccgagga gaagcugcug aacgugacca gcgugcugag agugaacgcc 600

accgccaacg acguguucca cugcaccuuc uggagagugc acagcggcga gaaccacacc 660

gccgagcuga ucaucccuga gcugccugug ccuagacugc cucacaacag aacccacugg 720

gugcugcugg gcagcgugcu gcuguuccug aucgugggcu ucaccguguu cuucugccug 780

agaaagcagg ugagaaugcu ggacguggag aagugcggcu ucgaggacag aaacagcaag 840

aacagaaacg acacccaguu cgaggagacc 870

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<223> N1-methylpseudouracil

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gcuuuuuguu cucgccaugc ggaucuucgc cguguucauc uucaugaccu acuggcaccu 120

gcugaacgcc uucaccguga ccgucccccaa ggaccuguac gugguggagu acggcuccaa 180

caugaccauc gagugcaagu uccccgugga gaagcagcug gaccucgccg cccucaucgu 240

guacugggag auggaggaca agaacaucau ccaguucgug cacggcgagg aggaccugaa 300

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gaacgccgcg cugcagauca cggacgugaa gcugcaggac gccggcgugu accgcugcau 420

gaucagcuac ggcggcgccg acuacaagcg gaucaccgug aaggugaacg cgccguacaa 480

caagaucaac cagcggaucc uggugguggga ccccgugacc agcgagcacg aguugaccug 540

ccaggccgag ggguacccca aggcggaggu caucuggacg ucgagcgacc accaggugcu 600

gagcgggaag accaccacca ccaacagcaa gcgggaggag aagcuguuca acgugaccag 660

cacccugcgg aucaacacca ccacgaacga gaucuucuac ugcacguuuc ggcggcugga 720

ccccgaagag aaccacaccg ccgagcuggu caucccagag cugccgcugg cucauccgcc 780

uaacgagcgg acgcaccugg ugauccuggg cgccauccug cugugccugg gcguggcccu 840

gaccuucauc uuucggcugc gcaagggccg uaugauggac gucaagaagu gcggcaucca 900

ggacaccaac uccaagaagc agagcgacac ccaccuggag gagaccugau aauaggcugg 960

agccucggug gccuagcuuc uugccccuug ggccucccccc cagccccucc uccccuuccu 1020

gcacccguac ccccgugguc uuugaauaaa gucugagugg gcggc 1065

<210> 33

<400> 33
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<210> 34
<211> 8
<212> PRT
<213> Gallus gallus

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Ser Ile Ile Asn Phe Glu Lys Leu
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<210> 35
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<212> DNA
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      oligonucleotide"

<400> 35
aaaaaaaaaa aaaaaaaaaa t   21

<210> 36
<211> 126
<212> DNA
<213> Artificial Sequence

<220>
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      oligonucleotide"

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<223> /note="Description of Combined DNA/RNA Molecule: Synthetic
      oligonucleotide"

<400> 36
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa   60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa ucuagaaaaa aaaaaaaaaa   120

aaaaat   126

<210> 37
<211> 150
<212> RNA
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polynucleotide"

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<400> 37
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 150

<210> 38
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 38
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cuccuccccu uccugcaccc guacccccuc cauaaaguag gaaacacuac aguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 39

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<210> 87
<211> 9
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<220>
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oligonucleotide"

<400> 87
ccrccaugg 9

<210> 88
<211> 92
<212> RNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
5' UTR-018 (Upstream UTR) sequence"

<400> 88
ucaagcuuuu ggacccucgu acagaagcua auacgacuca cuauagggaa auaagagaga 60

aaagaagagu aagaagaaau auaagagcca cc 92

<210> 89
<211> 47
<212> RNA
<213> Unknown

<220>
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5' UTR-002 (Upstream UTR) sequence"

<400> 89
gggagaucag agagaaaaga agaguaagaa gaaauauaag agccacc 47

<210> 90
<211> 42
<212> RNA

<213> Unknown

<220>
<221> source
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5' UTR-004 (Upstream UTR) sequence"

<400> 90
gggagacaag cuuggcauuc cgguacuguu gguaaagcca cc 42

<210> 91
<211> 47
<212> RNA
<213> Unknown

<220>
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5' UTR-005 (Upstream UTR) sequence"

<400> 91
gggagaucag agagaaaaga agaguaagaa gaaauauaag agccacc 47

<210> 92
<211> 42
<212> RNA
<213> Unknown

<220>
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5' UTR-007 (Upstream UTR) sequence"

<400> 92
gggagacaag cuuggcauuc cgguacuguu gguaaagcca cc 42

<210> 93
<211> 47
<212> RNA
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<220>
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5' UTR-008 (Upstream UTR) sequence"

<400> 93
gggaauuaac agagaaaaga agaguaagaa gaaauauaag agccacc 47

<210> 94

<211> 47
<212> RNA
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<220>
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5' UTR-009 (Upstream UTR) sequence"

<400> 94
gggaaauuag acagaaaaga agaguaagaa gaaauauaag agccacc 47

<210> 95
<211> 47
<212> RNA
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<220>
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5' UTR-010, Upstream sequence"

<400> 95
gggaaauaag agaguaaaga acaguaagaa gaaauauaag agccacc 47

<210> 96
<211> 47
<212> RNA
<213> Unknown

<220>
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5' UTR-011 (Upstream UTR) sequence"

<400> 96
gggaaaaaag agagaaaaga agacuaagaa gaaauauaag agccacc 47

<210> 97
<211> 47
<212> RNA
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<220>
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5' UTR-012 (Upstream UTR) sequence"

<400> 97
gggaaauaag agagaaaaga agaguaagaa gauauauaag agccacc 47

<210> 98
<211> 47
<212> RNA
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<220>
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5' UTR-013 (Upstream UTR) sequence"

<400> 98
gggaaauaag agacaaaaca agaguaagaa gaaauauaag agccacc 47

<210> 99
<211> 47
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
5' UTR-014 (Upstream UTR) sequence"

<400> 99
gggaaauuag agaguaaaga acaguaagua gaauuaaaag agccacc 47

<210> 100
<211> 47
<212> RNA
<213> Unknown

<220>
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5' UTR-015 (Upstream UTR) sequence"

<400> 100
gggaaauaag agagaauaga agaguaagaa gaaauauaag agccacc 47

<210> 101
<211> 47
<212> RNA
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<220>
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5' UTR-016 (Upstream UTR) sequence"

<400> 101

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<210> 102
<211> 47
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5' UTR-017 (Upstream UTR) sequence"

<400> 102
gggaaauaag agagaaaaga agaguaagaa gaaauuuaag agccacc 47

<210> 103

<400> 103
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<210> 104
<211> 142
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 104
ugauaauagu ccauaaagua ggaaacacua cagcuggagc cucgguggcc augcuucuug 60

ccccuugggc cucccccag ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 105
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 105
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ccccuugggc cucccccag ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 106
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 106
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cuacaugggc cucccccag ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 107
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 107
ugauaauagg cuggagccuc gguggccaug cuucuugccc cuugggccuc cccccagucc 60

auaaaguagg aaacacuaca ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 108
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

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cuccuccccu ucuccauaaa guaggaaaca cuacacugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 109
<211> 142
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<213> Artificial Sequence

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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 109
ugauaauagg cuggagccuc gguggccaug cuucuugccc cuugggccuc cccccagccc 60

cuccuccccu uccugcaccc guacccccuc cauaaaguag gaaacacuac aguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 110
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
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cuccuccccu uccugcaccc guacccccgu ggucuuugaa uaaaguucca uaaaguagga 120

aacacuacac ugagugggcg gc 142

<210> 111
<211> 164
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
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<400> 111
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ccccuugggc cucccccag ccccuccucc ccuuccugca cccguacccc ccgcauuauu 120

acucacggua cgaguggucu uugaauaaag ucugaguggg cggc 164

<210> 112
<211> 164
<212> RNA
<213> Artificial Sequence

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<223> /note="Description of Artificial Sequence: Synthetic
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<400> 112
ugauaauagu ccauaaagua ggaaacacua cagcuggagc cucgguggcc uagcuucuug 60

ccccuugggc cucccccag ccccuccucc ccuuccugca cccguacccc ccgcauuauu 120

acucacggua cgaguggucu uugaauaaag ucugaguggg cggc 164

<210> 113

<400> 113
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<210> 114
<211> 87
<212> RNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
miR-142 sequence"

<400> 114
gacagugcag ucacccauaa aguagaaagc acuacuaaca gcacuggagg guguaguguu 60

uccuacuuua uggaugagug uacugug 87

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<210> 143
<211> 22
<212> RNA

<213> Unknown

<220>
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<223> /note="Description of Unknown:
miR 223-3p sequence sequence"

<400> 143
ugucaguuug ucaaauaccc ca 22

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<210> 197
<211> 47
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
5' UTR sequence"

<400> 197
gggaaauaag agagaaaaga agaguaagaa gaaauauaag agccacc 47

<210> 198
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 198
ugauaauagg cuggagccuc gguggccuag cuucuugccc cuugggccuc cccccagccc 60

cuccuccccu uccugcaccc guacccccuc cauaaaguag gaaacacuac aguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 199
<211> 164
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 199
ugauaauagu ccauaaagua ggaaacacua cagcuggagc cucgguggcc augcuucuug 60

ccccuugggc cucccccccag ccccuccucc ccuuccugca cccguacccc ccgcauuauu 120

acucacggua cgaguggucu uugaauaaag ucugaguggg cggc 164

<210> 200
<211> 87
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR-142 sequence"

<400> 200
gacagugcag ucacccauaa aguagaaagc acuacuaaca gcacuggagg guguaguguu 60

uccuacuuua uggaugagug uacugug 87

<210> 201
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR-142-3p sequence"

<400> 201
uguaguguuu ccuacuuuau gga 23

<210> 202
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR-142-3p binding site sequence"

<400> 202
uccauaaagu aggaaacacu aca 23

<210> 203
<211> 21
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR-142-5p sequence"

<400> 203
cauaaaguag aaagcacuac u 21

<210> 204
<211> 21
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR-142-5p binding site sequence"

<400> 204
aguagugcuu ucuacuuuau g 21

<210> 205
<211> 85
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR-126 sequence"

<400> 205
cgcuggcgac gggacauuau uacuuuuggu acgcgcugug acacuucaaa cucguaccgu 60

gaguaauaau gcgccgucca cggca 85

<210> 206
<211> 22
<212> RNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
miR-126-3p sequence"

<400> 206
ucguaccgug aguaauaaug cg 22

<210> 207
<211> 22
<212> RNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
miR-126-3p binding site sequence"

<400> 207
cgcauuauua cucacgguac ga 22

<210> 208
<211> 21
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR-126-5p sequence"

<400> 208
cauuauuacu uuugguacgc g 21

<210> 209
<211> 21
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR-126-5p binding site sequence"

<400> 209
cgcguaccaa aaguaauaau g 21

<210> 210
<211> 9
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 210
ugauaauag 9

<210> 211
<211> 9
<212> RNA

<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 211
ugauaguaa 9

<210> 212
<211> 9
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oligonucleotide"

<400> 212
uaaugauag 9

<210> 213
<211> 9
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<220>
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oligonucleotide"

<400> 213
ugauaauaa 9

<210> 214
<211> 9
<212> RNA
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<220>
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oligonucleotide"

<400> 214
ugauaguag 9

<210> 215

<211> 9
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<220>
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oligonucleotide"

<400> 215
uaaugauga 9

<210> 216
<211> 9
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 216
uaauaguag 9

<210> 217
<211> 9
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<220>
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oligonucleotide"

<400> 217
ugaugauga 9

<210> 218
<211> 9
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 218
uaauaauaa 9

<210> 219
<211> 9
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 219
uaguaguag 9

<210> 220
<211> 133
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 220
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uuccugcacc cguacccccu ccauaaagua ggaaacacua caguggucuu ugaauaaagu 120

cugagugggc ggc 133

<210> 221
<211> 22
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 146-3p sequence sequence"

<400> 221
ccucugaaau ucaguucuuc ag 22

<210> 222
<211> 22
<212> RNA
<213> Unknown

<220>
<221> source

<223> /note="Description of Unknown:
miR 146-5p sequence sequence"

<400> 222
ugagaacuga auuccauggg uu 22

<210> 223
<211> 22
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 155-3p sequence sequence"

<400> 223
cuccuacaua uuagcauuaa ca 22

<210> 224
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 155-5p sequence sequence"

<400> 224
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<210> 225
<211> 22
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 16-3p sequence sequence"

<400> 225
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<210> 226
<211> 22
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 16-5p sequence sequence"

<400> 226
uagcagcacg uaaauauugg cg 22

<210> 227
<211> 21
<212> RNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
miR 21-3p sequence sequence"

<400> 227
caacaccagu cgaugggcug u 21

<210> 228
<211> 22
<212> RNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
miR 21-5p sequence sequence"

<400> 228
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<210> 229

<400> 229
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<210> 230
<211> 22
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 223-5p sequence sequence"

<400> 230

cguguauuug acaagcugag uu 22

<210> 231
<211> 22
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 24-3p sequence sequence"

<400> 231
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<210> 232
<211> 22
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 24-5p sequence sequence"

<400> 232
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<210> 233
<211> 21
<212> RNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
miR 27-3p sequence sequence"

<400> 233
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<210> 234
<211> 22
<212> RNA
<213> Unknown

<220>
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<223> /note="Description of Unknown:
miR 27-5p sequence sequence"

<400> 234
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<210> 235
<211> 141
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 235
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cuccuccccu uccugcaccc guacccccg cauuauuacu cacgguacga guggucuuug 120

aauaaagucu gagugggcgg c 141

<210> 236
<211> 119
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 236
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cuccuccccu uccugcaccc guacccccgu ggucuuugaa uaaagucuga gugggcggc 119

<210> 237
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 237
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cuccuccccu uccugcaccc guacccccuc cauaaaguag gaaacacuac aguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 238

<400> 238
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<210> 239
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 155-5p sequence sequence"

<400> 239
uuaaugcuaa uugugauagg ggu 23

<210> 240
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 155-5p binding site sequence"

<400> 240
accccuauca caauuagcau uaa 23

<210> 241
<211> 188
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 241
ugauaauagu ccauaaagua ggaaacacua cagcuggagc cucgguggcc augcuucuug 60

ccccuugggc cuccauaaag uaggaaacac uacaucccc cagccccucc uccccuuccu 120

gcacccguac ccccuccaua aaguaggaaa cacuacagug gucuuugaau aaagucugag 180

ugggcggc 188

<210> 242
<211> 140
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 242
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cuccuccccu uccugcaccc guacccccag uagugcuuuc uacuuuaugg uggucuuuga 120

auaaagucug agugggcggc 140

<210> 243
<211> 182
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 243
ugauaauaga guagugcuuu cuacuuuaug gcuggagccu cgguggccau gcuucuugcc 60

ccuugggcca guagugcuuu cuacuuuaug ucccccccagc cccuccuccc cuuccugcac 120

ccguaccccc aguagugcuu ucuacuuuau gguggucuuu gaauaaaguc ugagugggcg 180

gc 182

<210> 244
<211> 184
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 244
ugauaauaga guagugcuuu cuacuuuaug gcuggagccu cgguggccau gcuucuugcc 60

ccuugggccu ccauaaagua ggaaacacua cauccccca gccccuccuc cccuuccugc 120

acccguaccc ccaguagugc uuucuacuuu augguggucu uugaauaaag ucugaguggg 180

cggc 184

<210> 245
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 245
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cuccuccccu uccugcaccc guacccccac cccuaucaca auuagcauua aguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 246
<211> 188
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 246
ugauaauaga ccccuaucac aauuagcauu aagcuggagc cucgguggcc augcuucuug 60

ccccuugggc caccccuauc acaauuagca uuaaucccccc cagccccucc uccccuuccu 120

gcacccguac ccccacccccu aucacaauua gcauuaagug gucuuugaau aaagucugag 180

ugggcggc 188

<210> 247
<211> 188
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 247
ugauaauaga ccccuaucac aauuagcauu aagcuggagc cucgguggcc augcuucuug 60

ccccuugggc cuccauaaag uaggaaacac uacaucccc cagccccucc uccccuuccu 120

gcacccguac ccccaccccu aucacaauua gcauuaagug gucuuugaau aaagucugag 180

ugggcggc 188

<210> 248
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 248
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ccccuugggc cuccccccag ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 249
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 249
ugauaauagg cuggagccuc gguggcucca uaaaguagga aacacuacac augcuucuug 60

ccccuugggc cuccccccag ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 250
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 250
ugauaauagg cuggagccuc gguggccaug cuucuugccc cuugggccuc cauaaaguag 60

gaaacacuac auccccccag ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 251
<211> 70
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 251
gggaaauaag aguccauaaa guaggaaaca cuacaagaaa agaagaguaa gaagaaauau 60

aagagccacc 70

<210> 252
<211> 70
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 252
gggaaauaag agagaaaaga agaguaaucc auaaaguagg aaacacuaca gaagaaauau 60

aagagccacc 70

<210> 253
<211> 70
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 253

gggaaauaag agagaaaaga agaguaagaa gaaauauaau ccauaaagua ggaaacacua 60

cagagccacc 70

<210> 254
<211> 23
<212> RNA
<213> Unknown

<220>
<221> source
<223> /note="Description of Unknown:
miR 155-5p binding site sequence"

<400> 254
accccuauca caauuagcau uaa 23

<210> 255
<211> 181
<212> RNA
<213> Artificial Sequence

<220>
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polynucleotide"

<400> 255
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ccuugggcca guagugcuuu cuacuuuaug ucccccccagc cccucucccc uuccugcacc 120

cguaccccca guagugcuuu cuacuuuaug guggucuuug aauaaagucu gagugggcgg 180

c 181

<210> 256
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 256
ugauaauagg cuggagccuc gguggccaug cuucuugccc cuuccauaaa guaggaaaca 60

cuacaugggc cucccccccag ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 257
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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polynucleotide"

<400> 257
ugauaauagg cuggagccuc gguggccaug cuucuugccc cuugggccuc cccccagucc 60

auaaaguagg aaacacuaca ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 258
<211> 142
<212> RNA
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<220>
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polynucleotide"

<400> 258
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cuccuccccu ucuccauaaa guaggaaaca cuacacugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 259
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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polynucleotide"

<400> 259
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cuccuccccu uccugcaccc guacccccgu ggucuuugaa uaaaguucca uaaaguagga 120

aacacuacac ugagugggcg gc 142

<210> 260
<211> 164
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 260
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ccccuugggc cucccccag ccccuccucc ccuuccugca cccguacccc ccgcauuauu 120

acucacggua cgaguggucu uugaauaaag ucugaguggg cggc 164

<210> 261
<211> 119
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 261
ugauaauagg cuggagccuc gguggccuag cuucuugccc cuugggccuc cccccagccc 60

cuccuccccu uccugcaccc guacccccgu ggucuuugaa uaaagucuga gugggcggc 119

<210> 262
<211> 141
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 262
ugauaauagg cuggagccuc gguggccuag cuucuugccc cuugggccuc cccccagccc 60

cuccuccccu uccugcaccc guacccccgg cauuauuacu cacgguacga guggucuuug 120

aauaaagucu gagugggcgg c 141

<210> 263
<211> 188
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 263
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ccccuugggc cuccauaaag uaggaaacac uacaucccc cagccccucc uccccuuccu 120

gcacccguac ccccuccaua aaguaggaaa cacuacagug gucuuugaau aaagucugag 180

ugggcggc 188

<210> 264
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 264
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ccccuugggc cucccccccag ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 265
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 265
ugauaauagg cuggagccuc gguggcucca uaaaguagga aacacuacac uagcuucuug 60

ccccuugggc cucccccccag ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 266
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 266
ugauaauagg cuggagccuc gguggccuag cuucuugccc cuugggccuc cauaaaguag 60

gaaacacuac auccccccag ccccuccucc ccuuccugca cccguacccc cguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 267
<211> 142
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 267
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cuccuccccu uccugcaccc guacccccac cccuaucaca auuagcauua aguggucuuu 120

gaauaaaguc ugagugggcg gc 142

<210> 268
<211> 188
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 268
ugauaauaga ccccuaucac aauuagcauu aagcuggagc cucgguggcc uagcuucuug 60

ccccuugggc caccccuauc acaauuagca uuaaucccccc cagccccucc uccccuuccu 120

gcacccguac ccccaccccu aucacaauua gcauuaagug gucuuugaau aaagucugag 180

ugggcggc 188

<210> 269
<211> 188
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 269
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ccccuugggc cuccauaaag uaggaaacac uacaucccccc cagccccucc uccccuuccu 120

gcacccguac ccccaccccu aucacaauua gcauuaagug gucuuugaau aaagucugag 180

ugggcggc 188

<210> 270
<211> 5
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 270
ucuag 5

<210> 271
<211> 125
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 271
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa ucuagaaaaa aaaaaaaaaa 120