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(54) **COMPOSITION FOR REGULATING
PRODUCTION OF INTERFERING
RIBONUCLEIC ACID**

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(57) **ABSTRACT**

Some embodiments of the present disclosure relate to one or more compositions that upregulate the production of one or more sequences of micro-interfering ribonucleic acid (miRNA). The sequences of miRNA may be complimentary to a sequence of target messenger RNA (mRNA) that encodes for translation of a target biomolecule and the miRNA can cause the target mRNA to be degraded or inactivated, thereby causing a decrease in bioavailability of the target biomolecule because it is degraded or inactivated by the miRNA, thereby decreasing the bioavailability of the target biomolecule within a subject that is administered the one or more compositions. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor, such as serotonin receptor 5HT1a, 5HT1b, 5HT1d, 5HT1e, 5HT1f, 5HT2a, 5HT2b, 5HT2c, 5HT3, 5HT4, 5HT6, or 5HT7.

Specification includes a Sequence Listing.

COMPOSITION FOR REGULATING PRODUCTION OF INTERFERING RIBONUCLEIC ACID

[0001] This application contains a Sequence Listing electronically submitted via Patent Center to the United States Patent and Trademark Office as an XML Document file entitled "A8149441US—Sequence Listing.xml" created on 2024 Feb. 12 and having a size of 110,545 bytes. The information contained in the Sequence Listing is incorporated by reference herein.

TECHNICAL FIELD

[0002] The present disclosure generally relates to compositions for regulating production of interfering ribonucleic acid (RNA). In particular, the present disclosure relates to compositions for regulating gene expression and therefore, the production of interfering RNA, that will suppress serotonin receptor expression.

BACKGROUND

[0003] Bioactive molecules, including complements and factors, are necessary for the homeostatic control of biological systems.

[0004] When bioactive molecules are over-expressed, under-expressed or mis-expressed, homeostasis is lost, and disease is often the result.

[0005] As such, it may be desirable to establish therapies, treatments and/or interventions that address when homeostasis and regulation of bioactive molecules is lost to prevent or treat the resulting disease.

SUMMARY

[0006] Some embodiments of the present disclosure relate to one or more compositions that upregulate the production of one or more sequences of micro-interfering ribonucleic acid (miRNA). The sequences of miRNA may be complementary to a sequence of target messenger RNA (mRNA) that encodes for translation of a target biomolecule and the miRNA can cause the target mRNA to be degraded or inactivated, thereby causing a decrease in bioavailability of the target biomolecule because it is degraded or inactivated by the miRNA, thereby decreasing the bioavailability of the target biomolecule within a subject that is administered the one or more compositions. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT1a. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT1b. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT1c. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT1d. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT1e. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT1f. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT2a. In some embodiments of the present disclosure, the target biomolecule is a serotonin

receptor such as serotonin receptor 5HT2b. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT2c. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT3. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT4. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT6. In some embodiments of the present disclosure, the target biomolecule is a serotonin receptor such as serotonin receptor 5HT7.

[0007] In some embodiments of the present disclosure the compositions comprise a plasmid of deoxyribonucleic acid (DNA) that includes one or more insert sequences of nucleic acids that encode for the production of miRNA and a backbone sequence of nucleic acids that facilitates introduction of the one or more insert sequences into one or more of a subject's cells where it is expressed and/or replicated. Expression of the one or more insert sequences by one or more cells of the subject results in an increased production of the miRNA and, therefore, decreased translation or production of the target biomolecule by one or more of the subject's cells.

[0008] Some embodiments of the present disclosure relate to compositions that upregulate the production of miRNA that degrades, or causes degradation of, or inactivates or causes the inactivation of, the target mRNA of the target biomolecule.

[0009] Some embodiments of the present disclosure relate to a recombinant plasmid (RP). In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 2. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT1a.

[0010] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 3. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT1b.

[0011] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 4. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT1d.

[0012] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 5. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT1e.

[0013] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 6. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT1f.

[0014] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 7. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT2a.

[0015] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 8. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT2b.

[0016] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 9. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT2c.

[0017] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 10. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT3.

[0018] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 11. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT4.

[0019] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 12. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT6.

[0020] Some embodiments of the present disclosure relate to a recombinant plasmid. In some embodiments of the present disclosure, the RP comprises a nucleotide sequence of SEQ ID NO. 1 and SEQ ID NO. 13. The RP comprises a nucleotide sequence encoding one or more nucleotide sequences encoding a miRNA sequence that targets the mRNA of serotonin receptor 5HT7.

[0021] Some embodiments of the present disclosure relate to a method of making a composition/target cell complex. The method comprising a step of administering a RP comprising SEQ ID NO. 1 and one of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, or SEQ ID NO. 13 to a target cell for forming the composition/target cell complex, wherein the composition/target cell complex causes the target cell to increase production of one or more sequences of miRNA that decreases production of a target biomolecule.

[0022] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin

receptor 5HT1a. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT1a, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0023] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT1b. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT1b, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0024] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT1d. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT1d, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0025] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT1e. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT1e, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0026] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT1f. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT1f, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0027] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT2a. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof,

that target and silence the mRNA of serotonin receptor 5HT2a, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0028] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT2b. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT2b, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0029] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT2c. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT2c, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0030] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT3. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT3 which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0031] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT4. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT4, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0032] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT6. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT6, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

[0033] Embodiments of the present disclosure relate to at least one approach for inducing endogenous production of one or more sequences of miRNA that target and silence the mRNA of a target biomolecule, for example serotonin receptor 5HT7. A first approach utilizes gene vectors containing nucleotide sequences for increasing the endogenous production of one or more sequences of miRNA, which are complete or partial sequences and/or combinations thereof, that target and silence the mRNA of serotonin receptor 5HT7, which can be administered to a subject to increase the subject's production of one or more sequences of the miRNA.

DETAILED DESCRIPTION

[0034] Unless defined otherwise, all technical and scientific terms used therein have the meanings that would be commonly understood by one of skill in the art in the context of the present description. Although any methods and materials similar or equivalent to those described therein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. All publications mentioned therein are incorporated therein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0035] As used therein, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. For example, reference to "a composition" includes one or more compositions and reference to "a subject" or "the subject" includes one or more subjects.

[0036] As used therein, the terms "about" or "approximately" refer to within about 25%, preferably within about 20%, preferably within about 15%, preferably within about 10%, preferably within about 5% of a given value or range. It is understood that such a variation is always included in any given value provided therein, whether or not it is specifically referred to.

[0037] As used therein, the term "ameliorate" refers to improve and/or to make better and/or to make more satisfactory.

[0038] As used therein, the term "cell" refers to a single cell as well as a plurality of cells or a population of the same cell type or different cell types. Administering a composition to a cell includes in vivo, in vitro and ex vivo administrations and/or combinations thereof.

[0039] As used therein, the term "complex" refers to an association, either direct or indirect, between one or more particles of a composition and one or more target cells. This association results in a change in the metabolism of the target cell. As used therein, the phrase "change in metabolism" refers to an increase or a decrease in the one or more target cells' production of one or more proteins, and/or any post-translational modifications of one or more proteins.

[0040] As used therein, the term "composition" refers to a substance that, when administered to a subject, causes one or more chemical reactions and/or one or more physical reactions and/or one or more physiological reactions and/or one or more biological reactions in the subject. In some embodiments of the present disclosure, the composition is a plasmid vector.

[0041] As used therein, the term "endogenous" refers to the production and/or modification of a molecule that originates within a subject.

[0042] As used therein, the term "exogenous" refers to a molecule that is within a subject but that did not originate

within the subject. As used therein, the terms “production”, “producing” and “produce” refer to the synthesis and/or replication of DNA, the transcription of one or more sequences of RNA, the translation of one or more amino acid sequences, the post-translational modifications of an amino acid sequence, and/or the production of one or more regulatory molecules that can influence the production and/or functionality of an effector molecule or an effector cell. For clarity, “production” is also used therein to refer to the functionality of a regulatory molecule, unless the context reasonably indicates otherwise.

[0043] As used therein, the term “subject” refers to any therapeutic target that receives the composition. The subject can be a vertebrate, for example, a mammal including a human. The term “subject” does not denote a particular age or sex. The term “subject” also refers to one or more cells of an organism, an in vitro culture of one or more tissue types, an in vitro culture of one or more cell types, ex vivo preparations, and/or a sample of biological materials such as tissue, and/or biological fluids.

[0044] As used therein, the term “target biomolecule” refers to a serotonin receptor that is found within a subject. A biomolecule may be endogenous or exogenous to a subject and when bioavailable the biomolecule may inhibit or stimulate a biological process within the subject.

[0045] As used therein, the term “target cell” refers to one or more cells and/or cell types that are deleteriously affected, either directly or indirectly, by a dysregulated biomolecule. The term “target cell” also refers to cells that are not deleteriously affected but that are the cells in which it is desired that the composition interacts.

[0046] As used therein, the term “therapeutically effective amount” refers to the amount of the composition used that is of sufficient quantity to ameliorate, treat and/or inhibit one or more of a disease, disorder or a symptom thereof. The “therapeutically effective amount” will vary depending on the composition used, the route of administration of the composition and the severity of the disease, disorder or symptom thereof. The subject’s age, weight and genetic make-up may also influence the amount of the composition that will be a therapeutically effective amount.

[0047] As used therein, the terms “treat”, “treatment” and “treating” refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing an occurrence of a disease, disorder or symptom thereof and/or the effect may be therapeutic in providing a partial or complete amelioration or inhibition of a disease, disorder, or symptom thereof. Additionally, the term “treatment” refers to any treatment of a disease, disorder, or symptom thereof in a subject and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) ameliorating the disease.

[0048] As used therein, the terms “unit dosage form” and “unit dose” refer to a physically discrete unit that is suitable as a unitary dose for patients. Each unit contains a predetermined quantity of the composition and optionally, one or more suitable pharmaceutically acceptable carriers, one or more excipients, one or more additional active ingredients, or combinations thereof. The amount of composition within each unit is a therapeutically effective amount.

[0049] Where a range of values is provided therein, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also, encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

[0050] In some embodiments of the present disclosure, a composition is a recombinant plasmid (RP) for introducing genetic material, such as one or more nucleotide sequences, into a target cell for reproduction or transcription of an insert that comprises one or more nucleotide sequences that are carried within the RP. In some embodiments of the present disclosure, the RP is delivered without a carrier, by a viral vector, by a protein coat, or by a lipid vesicle. In some embodiments of the present disclosure, the vector is an adeno-associated virus (AAV) vector.

[0051] In some embodiments of the present disclosure, the insert comprises one or more nucleotide sequences that encode for production of at least one sequence of miRNA that decreases the production of target biomolecules. The miRNA may, directly or indirectly, bind to and degrade the target mRNA or otherwise inactivate the target mRNA so that less or none of the target-biomolecule protein is produced.

[0052] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT1a.

[0053] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT1b.

[0054] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT1d.

[0055] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT1e.

[0056] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT1f.

[0057] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT2a.

[0058] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT2b.

[0059] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT2c.

[0060] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT3.

[0061] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT4.

[0062] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT6.

[0063] In some embodiments of the present disclosure, the target biomolecule is serotonin receptor 5HT7.

[0064] In some embodiments of the present disclosure, the insert comprises one or more nucleotide sequences that each encode for one or more miRNA sequences that may be complimentary to and degrade, or cause degradation of, mRNA of the target biomolecule.

[0065] Some embodiments of the present disclosure relate to a composition that can be administered to a subject with a condition that results, directly or indirectly, from the production of a dysregulated biomolecule. When a therapeutically effective amount of the composition is adminis-

tered to the subject, the subject may change production and/or functionality of one or more biomolecules.

[0066] In some embodiments of the present disclosure, the subject may respond to receiving the therapeutic amount of the composition by changing production and/or functionality of one or more intermediary molecules by changing production of one or more DNA sequences, one or more RNA sequences, and/or one or more proteins that regulate the levels and/or functionality of the one or more intermediary molecules. The one or more intermediary molecules regulate the subject's levels and/or functionality of the one or more biomolecules.

[0067] In some embodiments of the present disclosure, administering a therapeutic amount of the composition to a subject upregulates the production, functionality or both one or more sequences of miRNA that each target the mRNA of one or more target biomolecules. In some embodiments of the present disclosure, there are one, two, three, four, five, or six miRNA sequences that each are complimentary to and degrade, or cause degradation of, one biomolecule, such as the mRNA of serotonin receptor 5HT1a, serotonin receptor 5HT1b, serotonin receptor 5HT1d, serotonin receptor 5HT1e, serotonin receptor 5HT1f, serotonin receptor 5HT2a, serotonin receptor 5HT2b, serotonin receptor 5HT2c, serotonin receptor 5HT3, serotonin receptor 5HT4, serotonin receptor 5HT6, or serotonin receptor 5HT7. In some embodiments of the present disclosure, the composition may comprise multiple copies of the same nucleotide sequence of miRNA.

[0068] In some embodiments of the present disclosure, the composition is an RP that may be used for gene therapy. The gene therapy is useful for increasing the subject's endogenous production of one or more sequences of miRNA that target the mRNA of a target biomolecule. For example, the RP can contain one or more nucleotide sequences that cause increased production of one or more nucleotide sequences that cause an increased production of one or more miRNA sequences that are each complimentary to and degrade, or cause degradation of, or inactivate, or cause inactivation of, one biomolecule, such as serotonin receptor 5HT1a, serotonin receptor 5HT1b, serotonin receptor 5HT1d, serotonin receptor 5HT1e, serotonin receptor 5HT1f, serotonin receptor 5HT2a, serotonin receptor 5HT2b, serotonin receptor 5HT2c, serotonin receptor 5HT3, serotonin receptor 5HT4, serotonin receptor 5HT6, or serotonin receptor 5HT7.

[0069] In some embodiments of the present disclosure, the delivery vehicle of the RP used for gene therapy may be a vector that is comprised of a virus that can be enveloped, or not (unenveloped), replication effective or not (replication ineffective), or combinations thereof. In some embodiments of the present disclosure, the vector is a virus that is not enveloped and not replication effective. In some embodi-

ments of the present disclosure, the vector is a virus of the *Parvoviridae* family. In some embodiments of the present disclosure, the vector is a virus of the genus *Dependoparvovirus*. In some embodiments of the present disclosure, the vector is an adeno-associated virus (AAV). In some embodiments of the present disclosure, the vector is a recombinant AAV. In some embodiments of the present disclosure, the vector is a recombinant AAV6.2FF.

[0070] In some embodiments of the present disclosure, the delivery vehicle of the RP used for gene therapy may be a protein coat.

[0071] In some embodiments of the present disclosure, the delivery vehicle of the RP used for gene therapy may be a lipid vesicle.

[0072] The embodiments of the present disclosure also relate to administering a therapeutically effective amount of the composition. In some embodiments of the present disclosure, the therapeutically effective amount of the composition that is administered to a patient is between about 10 and about 1×10^{16} TCID₅₀/kg (50% tissue culture infective dose per kilogram of the patient's body mass). In some embodiments of the present disclosure, the therapeutically effective amount of the composition that is administered to the patient is about 1×10^{13} TCID₅₀/kg. In some embodiments of the present disclosure, the therapeutically effective amount of the composition that is administered to a patient is measured in TPC/kg (total particle count of the composition per kilogram of the patient's body mass). In some embodiments the therapeutically effective amount of the composition is between about 10 and about 1×10^{16} TCP/kg.

[0073] Some embodiments of the present disclosure relate to an adeno-associated virus (AAV) genome consisting of a RP that when operable inside a target cell will cause the target cell to produce a miRNA sequence that downregulates production of a biomolecule, with examples being serotonin receptor 5HT1a, serotonin receptor 5HT1b, serotonin receptor 5HT1d, serotonin receptor 5HT1e, serotonin receptor 5HT1f, serotonin receptor 5HT2a, serotonin receptor 5HT2b, serotonin receptor 5HT2c, serotonin receptor 5HT3, serotonin receptor 5HT4, serotonin receptor 5HT6, or serotonin receptor 5HT7. The RP is comprised of AAV2 inverted terminal repeats (ITRs), a composite CASI promoter, a human growth hormone (HGH) signal peptide followed by a miRNA expression cassette containing up to six different miRNAs targeting the mRNA of serotonin receptor 5HT1a, serotonin receptor 5HT1b, serotonin receptor 5HT1d, serotonin receptor 5HT1e, serotonin receptor 5HT1f, serotonin receptor 5HT2a, serotonin receptor 5HT2b, serotonin receptor 5HT2c, serotonin receptor 5HT3, serotonin receptor 5HT4, serotonin receptor 5HT6, or serotonin receptor 5HT7, followed by a Woodchuck Hepatitis Virus post-transcriptional regulatory element (WPRE) and a Simian virus 40 (SV40) polyadenylation (polyA) signal.

SEQ ID NO. 1 (backbone sequence No. 1):

5' AATCAACCTCTGGATTACAAATTTGTGAAGATTGACTGGTATTCTTAACATATGTT

GCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTGTATCATGCTATTGCTTCC

CGTATGGCTTTCATTTTCTCCTCCTGTATAAATCCTGGTTGCTGTCTCTTTATGAGGAG

TTGTGGCCCGTTGTCAAGCAACGTGGCGTGGTGTGCACTGTGTTGCTGACGCAACCCCC

ACTGGTTGGGGCATTGCCACCACTGTGAGCTCCTTTCGGGACTTTCGCTTTCCCCCTC

- continued

CCTATTGCCACGGCGAACTCATCGCCGCTGCCCTGCCCCGCTGCTGGACAGGGGCTCGG
CTGTTGGGCACTGACAATTCCGTGGTGTGTCGGGAAATCATCGTCCTTTCCTTGGCTG
CTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGTACGTCCCTTCGGCC
CTCAATCCAGCGGACCTTCCTTCCCGCGGCTGCTGCCGGCTCTGCGGCTCTTCCGCGT
CTTCGCCTTCGCCTCAGACGAGTCGGATCTCCCTTGGGCCGCTCCCGCCTAAGCTT
ATCGATACCGTCGAGATCTAACTGTTTATTGCAGCTTATAATGGTTACAAATAAGCAA
TAGCATCACAAATTCACAAATAAGCATTTTTTTCACTGCATTCTAGTTGTGGTTTGT
CAAATCATCAATGTATCTTATCATGTCTGGATCTCGACCTCGACTAGAGCATGGCTACG
TAGATAAGTAGCATGGCGGGTTAATCATTAATAACAAGAACCCCTAGTGATGGAGTTGG
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GCCCCGGCTTTGCCGGGCGGCTCAGTGAGCGAGCGAGCGCGCAGCTGGCGTAATAGCG
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AATTTGCGTGATGGACAGACTCTTTACTCGGTGGCCTCACTGATTATAAAAACACTTCT
CAGGATTCTGGCGTACCGTTCTGTCTAAAATCCCTTTAATCGGCCTCCTGTTTAGCTCC
CGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCTCGTCAAAGCAACCATAGTACGC
GCCCCGTAGCGCGCATTAAGCGCGGCGGTGTTGGTTACGCGCAGCGTGACCGCTAC
ACTTGCCAGCGCCCTAGCGCCGCTCCTTTCGCTTTCTTCCTTCCTTCTCGCCACGTT
CGCCGGCTTTCCCGCTCAAGCTCTAAATCGGGGCTCCCTTAGGGTTCCGATTTAGTGC
TTTACGGCACCTCGACCCCAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGCCATC
GCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACT
CTTGTTCCAACTGGAACAACACTCAACCTATCTCGGTCTATTCTTTGATTTATAAGG
GATTTTGCCGATTTCGGCTATTGGTTAAAAATGAGCTGATTTAACAAAAATTTAACGC
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TATTTACACCGCATATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAG
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GTCATCACCGAAACGCGGAGACGAAAGGGCCTCGTGATACGCCATTTTTATAGGTTAA
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GAGCACTTTTAAAGTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGA
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GCCTCTCCCCGCGCTTGGCCGATTCAATTAATGCAGCAGCTGCGCGCTCGCTCGCTCACT
GAGGCCGCCCGGGCAAGCCCGGCGTCGGGCGACCTTTGGTCGCCCGGCTCAGTGAGC
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TGGAGTTCCGCGTTACATAACTTACGTTAAATGGCCGCTGGCTGACCGCCCAACGACC
CCCCCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCC
ATTGACGTCAATGGGTGGAGTATTTACGGTAACTGCCCACTTGGCAGTACATCAAGTGT
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 CCTCCCCACCCCAATTTTGTATTTATTTATTTTAAATTATTTTGTGCAGCGATGGGGG
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 CCGCGGGCGCCCCCTCTCACGGCGAGCGCTGCCACGTGACAGGAAGGCGCAGCGAGC
 GTCTGTATCCTTCGCCCGGACGCTCAGGACAGCGGCCCGCTGCTCATAAGACTCGGCCT
 TAGAACCACCATATCAGCAGAAGGACATTTTAGGACGGGACTTGGGTGACTCTAGGGCAC
 TGGTTTTCTTCCAGAGAGCGGAACAGGCGAGGAAAAGTAGTCCCTTCTCGCGATTCTG
 CGGAGGGATCTCCGTGGGGCGGTGAACGCCGATGATGCCTCTACTAACCATGTTTCATGTT
 TTCTTTTTTTTCTACAGGTCCTGGGTGACGAACAGGGTACC 3'

SEQ ID NO. 2 (miRNA expression cassette No. 2-serotonin receptor 5HT1a):
 5' GCCACCATTGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
 CTTGCTGAAGGCTGTATGCTGATCAATCGGATTGCGGTAATCGCGTTTTGGCCTCTGACT
 GACGCGATTACCGATCCGATTGATCAGGACACAAGGCCTGTTACTAGCACTCACATGGAA
 CAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGATCTTTGCTAAATTGGT
 GCACGCGTTTTGGCCTCTGACTGACGCGTGCAACATTAGCAAAGATCAGGACACAAGGCC
 TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA
 TGCTGACTTCAATCACAATTCCAGCGCGTTTTTGGCCTCTGACTGACGCGCTGGAAGTG
 ATTGAAGTCAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
 AAT 3'

SEQ ID NO. 3 (miRNA expression cassette No. 3-serotonin receptor 5HT1b):
 5' GCCACCATTGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
 CTTGCTGAAGGCTGTATGCTGTAATCTTTCGCTGGCTGCAGTTCGTTTTGGCCTCTGACT
 GACGAACTGCAGCGCGAAAGATTACAGGACACAAGGCCTGTTACTAGCACTCACATGGAA
 CAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGTGTTAATGCTGATGTCA
 CGCTGCGTTTTGGCCTCTGACTGACGCGAGCTGACAGCATTAAACAGGACACAAGGCC
 TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA
 TGCTGTTACCTGGTTAACACATACACCGTTTTTGGCCTCTGACTGACGGTGTATGTGAAC
 CAGGTGAACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
 AAT 3'

SEQ ID NO. 4 (miRNA expression cassette No. 4-serotonin receptor 5HT1d):
 5' GCCACCATTGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
 CTTGCTGAAGGCTGTATGCTGATTTCTTCTGTGCGCTTTCGCCGTTTTGGCCTCTGACT
 GACGGCGAAGCGCAGGAAGAAATCAGGACACAAGGCCTGTTACTAGCACTCACATGGAA

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CAAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGAGAATAATCAGATCAGC
ACGCTCGTTTTGGCCTCTGACTGACGAGCGTGTCTGCTGATTATTCTCAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA
TGCTGTAATCAGGCTGAATTCAGATAGCGTTTTGGCCTCTGACTGACGCTATCTGAACAG
CCTGATTACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
AAT 3'

SEQ ID NO. 5 (miRNA expression cassette No. 5-serotonin receptor 5HT1e) :
5' GCCACCATGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
CTTGCTGAAGGCTGTATGCTGATAATCACCGCTGCAGGTTTCAGCGTTTTGGCCTCTGACT
GACGCTGAACCTGGCGGTGATTATCAGGACACAAGGCCTGTTACTAGCACTCACATGGAA
CAAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGTTCAATCGCGTATTGGT
AATCGCGTTTTGGCCTCTGACTGACGCGATTACCAACGCGATTGAACAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA
TGCTGTGATCATGCTGAAAATGGTGCACGTTTTGGCCTCTGACTGACGTGCACCATTAG
CATGATCACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
AAT 3'

SEQ ID NO. 6 (miRNA expression cassette No. 6-serotonin receptor 5HT1f) :
5' GCCACCATGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
CTTGCTGAAGGCTGTATGCTGAGGTAATATCCTGACGCTCAGCCGTTTTGGCCTCTGACT
GACGCTGAGCGTGGATATTACCTCAGGACACAAGGCCTGTTACTAGCACTCACATGGAA
CAAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGTACAGAATCAGATAATC
AGCGCCGTTTTGGCCTCTGACTGACGGCGCTGATTCTGATTCTGTACAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA
TGCTGTATGTTTTAAAAATTCGCTGCGCGTTTTGGCCTCTGACTGACGCGCAGCGAATTT
AAACATGACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
AAT 3'

SEQ ID NO. 7 (miRNA expression cassette No. 7-serotonin receptor 5HT2a) :
5' GCCACCATGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
CTTGCTGAAGGCTGTATGCTGATGAATCGGGTTGTCTGAATCGCGTTTTGGCCTCTGACT
GACGCGATTACAGAACCCGATTATCAGGACACAAGGCCTGTTACTAGCACTCACATGGAA
CAAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGAACACTTTGCTATATCA
TCCTGCGTTTTGGCCTCTGACTGACGCGAGGATGATAGCAAAGTGTTCAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA
TGCTGTTCTGTTCTTAAGCTAATGCTCGTTTTGGCCTCTGACTGACGAGCATTAGCAAC
GAACAGAACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
AAT 3'

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SEQ ID NO. 8 (miRNA expression cassette No. 8-serotonin receptor 5HT2b):
5' GCCACCATGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
CTTGCTGAAGGCTGTATGCTGGAGCATTAGCAATGCGAACAGAAGTTTGGCCTCTGACT
GACTTCTGTTCTGTTGCTAATGCTCCAGGACACAAGGCCTGTTACTAGCACTCACATGGAA
CAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGAAACATAATGGATTTCAG
CAGCGCGTTTTGGCCTCTGACTGACGCGCTGCTGACCATTATGTTTCAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA
TGCTGTTATCTTTGCGAAGCTGCCATCCGTTTTGGCCTCTGACTGACGGATGGCAGCCGC
AAAGATAACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
AAT 3'

SEQ ID NO. 9 (miRNA expression cassette No. 9-serotonin receptor 5HT2c):
5' GCCACCATGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
CTTGCTGAAGGCTGTATGCTGGCTCCTCCACTTGGTGGTTTGGTTTTGGCCTCTGACTGA
CGCGCAACATTCTGGTGATTACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACA
AATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGTCATAATCGCTATTTGGTG
CGCGTTTTGGCCTCTGACTGACGCGCACCAAGCGATTATGACAGGACACAAGGCCTG
TTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATG
CTGTTCTGATCTTGAAGTTCGGGTTCTGTTTTGGCCTCTGACTGACGAACCCGAACCAGGA
TCAGAACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAGAA
T 3'

SEQ ID NO. 10 (miRNA expression cassette No. 10-serotonin receptor 5HT3):
5' GCCACCATGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
CTTGCTGAAGGCTGTATGCTGAAATCTTCCGGTGGTTCCACTGCGTTTTGGCCTCTGACT
GACGCAGTGAACCCGGAAGATTTCAGGACACAAGGCCTGTTACTAGCACTCACATGGAA
CAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGATATCCTGAATATGGTA
TGCAGCGTTTTGGCCTCTGACTGACGCTGCATACCATTCAGGATATCAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA
TGCTGTTTAAAGCTCAAACGCGTTCGCCGTTTTGGCCTCTGACTGACGGCGAACGCGTGA
GCTTTAAACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
AAT 3'

SEQ ID NO. 11 (miRNA expression cassette No. 11-serotonin receptor 5HT4):
5' GCCACCATGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
CTTGCTGAAGGCTGTATGCTGTAATAAAGGCTTGGGAATCACCCGTTTTGGCCTCTGACT
GACGGGTGATTCGACCTTTATTACAGGACACAAGGCCTGTTACTAGCACTCACATGGAA
CAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGTAATACGCCAGATCACC
ATCAGCGTTTTGGCCTCTGACTGACGCTGATGGTCTGGCGTATTACAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA

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TGCTGATACAGAAACGAAGGTTTCAGGCCGTTTTGGCCTCTGACTGACGGCCTGAACCCGT
TTCTGTATCAGGACACAAGGCCTGTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
AAT 3'

SEQ ID NO. 12 (miRNA expression cassette No. 12-serotonin receptor 5HT6):
5' GCCACCATGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
CTTGCTGAAGGCTGTATGCTGTGATCGCTGTGGTAAACAGGCGTTTTGGCCTCTGACT
GACGCTGTTTTACCAGCGATCTGACAGGACACAAGGCCTGTACTAGCACTCACATGGAA
CAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGAGAATCAGATCAGATAG
CGATCCGTTTTGGCCTCTGACTGACGGATCGCTATCTGCTGATTCTCAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA
TGCTGAAACATGCCAACAGCAGAATGCCGTTTTGGCCTCTGACTGACGGCATTCTGCTGG
GCATGTTTCAGGACACAAGGCCTGTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
AAT 3'

SEQ ID NO. 13 (miRNA expression cassette No. 13-serotonin receptor 5HT7):
5' GCCACCATGGCCACCGGCTCTCGCACAGCCTGCTGCTGGCTTTCGGACTGCTGTGC

CTGCCTTGGCTCCAGGAGGGCTCCGCCGCTAGCATCGATACCGTCGCTATGTGCTGGAGG
CTTGCTGAAGGCTGTATGCTGACAATCAGATATGGTTGCTCGGCGTTTTGGCCTCTGACT
GACGCCGAGCAACTATCTGATTGTGAGGACACAAGGCCTGTACTAGCACTCACATGGAA
CAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGTTTACAAATGCATCGTT
CAGCGCGTTTTGGCCTCTGACTGACGCGCTGAACGGCATTGTGAAACAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTA
TGCTGACAATAATGCCAACAGGGTGGTCGTTTTGGCCTCTGACTGACGACCACCCTGGGC
ATTATTGTCAGGACACAAGGCCTGTACTAGCACTCACATGGAACAAATGGCCTCTCTAG
AAT 3'

SEQ ID NO. 14 = SEQ ID NO. 1 + SEQ ID NO. 2

5' AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAATATGTT
GCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCC
CGTATGGCTTTTCAATTTCTCCTTGTATAAATCCTGGTTGCTGTCTTTATGAGGAG
TTGTGGCCCGTTGTGAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCC
ACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTC
CCTATTGCCACGGCGGAACCTCATCGCCGCTGCCTTGCCCGCTGCTGGACAGGGGCTCGG
CTGTTGGGCACTGACAATTCCGTGGTGTGTCGGGAAATCATCGTCCTTTCTTGGCTG
CTCGCCTGTGTTGCCACCTGGATTCTGCGCGGACGTCCTTCTGCTACGTCCTTTCGGCC
CTCAATCCAGCGGACCTTCTTCCCGCGGCTGCTGCCGGCTCTGCGGCCTCTTCCGCGT
CTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGCCGCTCCCCGCTAAGCTT
ATCGATACCGTCGAGATCTAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAGCAA
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CAAACCTCATCAATGTATCTTATCATGTCTGGATCTCGACCTCGACTAGAGCATGGCTACG
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GAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGA
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TCGCTATTACCATGGTCGAGGTGAGCCCCACGTTCTGCTTCACTCTCCCCATCTCCCCC
CCTCCCCACCCCCAATTTTGATTTATTTATTTTAAATTATTTTGTGCAGCGATGGGGG
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GAGGCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCTTTTAT
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TGACGCGTGCACCATTAGCAAAGATCAGGACACAAGGCCTGTTACTAGCACTCACATGGA
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CAGCGCCGTTTTGGCCTCTGACTGACGCGCTGGAAGTGATTGAAGTCAGGACACAAGGC
CTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAGAAT 3'

SEQ ID NO. 15 = SEQ ID NO. 1 + SEQ ID NO. 3

5' AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACATATGTT
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ACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGTTCACCTGGTTAACAC
ATACACCGTTTTTGGCCTCTGACTGACGGTGTATGTGAACCAGGTGAACAGGACACAAGGC
CTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAGAAT 3'

SEQ ID NO. 16 = SEQ ID NO. 1 + SEQ ID NO. 4

5' AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACATATGT
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ACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGTAATCAGGCTGAATTC
AGATAGCGTTTTGGCCTCTGACTGACGCTATCTGAACAGCCTGATTACAGGACACAAGGC
CTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAGAAT 3'

SEQ ID NO. 17 = SEQ ID NO. 1 + SEQ ID NO. 5
5' AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACATATGTT
GCTCCTTTTACGCTATGTGGATACGCTGCTTAAATGCCTTTGTATCATGCTATTGCTTCC
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GAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAAC
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TAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGA
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TTTTTTCTGCGCGTAATCTGCTGCTTGCAAAACAAAAAACCACCGCTACCAGCGGTGGT
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TGTAGACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAAGTGGCTGCTGCCAGTGG
CGATAAGTCGTGCTTACCAGGTGGAATCAAGACGATAGTTACCGGATAAGGCGCAGCG
GTCGGGCTGAACGGGGGTTCTGTGCACACAGCCAGCTTGAGCGAACGACCTACACCGA
ACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCGAAGGGAGAAAGGC
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TGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGAGCCG
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GAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGC
GAGCGAGCGCGCAGAGAGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATG
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CTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAGAAT 3'

SEQ ID NO. 18 = SEQ ID NO. 1 + SEQ ID NO. 6
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CTCGCCTGTGTTGCCACCTGGATTCTGCGGGGACGTCCTTCTGCTACGTCCTTTCGGCC
CTCAATCCAGCGGACCTTCTTCCCGCGGCTGCTGCCGGCTCTGCGGCTCTTCCGCGT
CTTCGCTTTCGCTCAGACGAGTCGGATCTCCCTTTGGGCGGCTCCCCGCTAAGCTT
ATCGATACCGTCGAGATCTAACTTGTTTATGTCAGCTTATAATGGTTACAAATAAGCAA
TAGCATCACAAATTCACAAATAAGCATTTTTTCACTGCATTCTAGTTGTGGTTTGTG
CAAACCTCATCAATGTATCTTATCATGTCTGGATCTCGACCTCGACTAGAGCATGGCTACG
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AGTTCTTCTACTCAGGCAAGTGATGTTATTACTAATCAAAGAAGTATTGCGACAACGGTT
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CAGGATTCTGCGGTACCGTTCTGTCTAAAATCCCTTTAATCGGCCTCCTGTTTAGCTCC
CGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCTCGTCAAAGCAACCATAGTACGC
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TATCATATTGATGGTGATTGACTGTCTCCGGCCTTCTCACCCTTTGAATCTTACCT
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GTTGAAATAAAGGCTTCTCCCGCAAAGTATTACAGGGTCATAATGTTTTTGGTACAACC
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GAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGA
GCAACTCGGTGCGCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCAC
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TGACGGCGCTGATTCTGATTCTGTACAGGACACAAGGCCTGTACTAGCACTCACATGGA
ACAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGTATGTTTAAAAATTC
GCTGCGCGTTTTGGCCTCTGACTGACGCGCAGCGAATTAAACATGACAGGACACAAGGC
CTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAGAAT 3'

SEQ ID NO. 19 = SEQ ID NO. 1 + SEQ ID NO. 7
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GCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCC
CGTATGGCTTTTATTTCTCCTTGTATAAATCCTGGTTGCTGTCTTTATGAGGAG
TTGTGGCCCGTTGTGAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCC
ACTGGTTGGGGCATTGCCACCACCTGTGAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTC
CCTATTGCCACGGCGGAACCTATCGCCGCTGCCTTGCCCGCTGCTGGACAGGGGCTCGG
CTGTTGGGCACTGACAATTCCGTGGTGTGTCGGGGAATCATCGTCCTTTCTTGCGTG
CTCGCCTGTGTTGCCACCTGGATTCTGCGCGGACGTCCTTCTGCTACGTCCTTTCGGCC
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CTTCGCTTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGCGCCTCCCCGCTAAGCTT
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CAAACCTCATCAATGTATCTTATCATGTCTGGATCTCGACCTCGACTAGAGCATGGCTACG
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AATTTGCGTGATGGACAGACTCTTTTACTCGGTGGCCTCACTGATTATAAAAACACTTCT
CAGGATTTCTGGCGTACCGTTCCTGTCTAAAATCCCTTTAATCGGCCTCCTGTTTAGCTCC
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GCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTAC
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TGACGAGGATGATAGCAAAGTGTTGAGGACACAAGGCTGTTACTAGCACTCACATGGA
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AATGCTCGTTTTGGCCTCTGACTGACGAGCATTAGCAACGAACAGAACAGGACACAAGGC
CTGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAGAAT 3'

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SEQ ID NO. 20 = SEQ ID NO. 1 + SEQ ID NO. 8
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CCTATTGCCACGGCGGAATCATCGCCGCTGCCTTGCCCGCTGCTGGACAGGGGCTCGG
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SEQ ID NO. 21 = SEQ ID NO. 1 + SEQ ID NO. 9

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SEQ ID NO. 22 = SEQ ID NO. 1 + SEQ ID NO. 10
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CGCGGGCGCCCCCTCCTCACGGCGAGCGCTGCCACGTGAGCGAAGGGCGCAGCGAGCG
TCCTGATCCTTCCGCCCGACGCTCAGGACAGCGGCCGCTGCTCATAAGACTCGGCCTT
AGAACCCAGTATCAGCAGAAGGACATTTTAGGACGGGACTTGGGTGACTCTAGGGCACT
GGTTTTCTTTCCAGAGAGCGGAACAGGCGAGGAAAAGTAGTCCCTTCTCGGCGATTCTGC
GGAGGATCTCCGTGGGCGGTGAACGCCGATGATGCCTCTACTAACCATGTTTCATGTTT
TCTTTTTTTTTCTACAGGTCCTGGGTGACGAACAGGTACCGCCACCATGGCCACCGGCT
CTCGCACAAGCCTGCTGCTGGCTTTCGGACTGCTGTGCCTGCCTTGGCTCCAGGAGGGCT
CCGCCGTAGCATCGATACCGTCGCTATGTGCTGGAGGCTTGCTGAAGGCTGTATGCTGA

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AATCTTCCGGTGGTTCCACTGCGTTTTGGCCTCTGACTGACGCAGTGAACCCGGAAGAT
TTCAGGACACAAGGCCTGTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGG
CTTGCTGAAGGCTGTATGCTGATATCCTGAATATGGTATGCAGCGTTTTGGCCTCTGACT
GACGCTGCATACCATTAGGATATCAGGACACAAGGCCTGTACTAGCACTCACATGGAA
CAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGTTTAAAGCTCAAACGCG
TTCGCCGTTTTGGCCTCTGACTGACGGCGAACGCGTGAGCTTTAAACAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAGAAT 3'

SEQ ID NO. 23 = SEQ ID NO.: 1 + SEQ ID NO. 11

5' AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACATATGTT
GCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCC
CGTATGGCTTTTCAATTTCTCCTCTGTATAAATCCTGGTTGCTGTCTCTTTATGAGGAG
TTGTGGCCCGTTGTGAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCC
ACTGGTTGGGGCATTGCCACCACCTGTGAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTC
CCTATTGCCACGGCGGAACCTCATCGCCGCTGCCTTGCCCGCTGCTGGACAGGGGCTCGG
CTGTTGGGCACAGCAATTCCTGGTGTGTGCGGGAAATCATCGTCCTTTCTTGCGTG
CTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCTCTGCTACGTCCCTTCGGCC
CTCAATCCAGCGGACCTTCTTCCCGCGGCTGCTGCGGCTCTGCGGCTCTTCCGCGT
CTTCGCCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGCCGCTCCCCGCTAAGCTT
ATCGATACCGTCGAGATCTAACTTGTTTATTGACGCTTATAATGGTTACAAATAAGCAA
TAGCATCACAAATTTACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTGGTTTGTG
CAAACCTCATCAATGTATCTTATCATGTCTGGATCTCGACCTCGACTAGAGCATGGCTACG
TAGATAAGTAGCATGGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGC
CACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAGGTGCCCCGACG
CCCCGGCTTTTGCCCGGGCGGCTCAGTGAGCGAGCGAGCGCGAGCTGGCGTAATAGCGA
AGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGCGATT
CCGTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACCAGCAAGGCCGATAGTTTGA
GTTCTTCTACTCAGGCAAGTGATGTTATTACTAATCAAAGAAGTATTGCGACAACGGTTA
ATTTGCGTGATGGACAGACTCTTTTACTCGGTGGCCTCACTGATTATAAAAACTTCTC
AGGATTCTGGCGTACCGTTCTGTCTAAAATCCCTTTAATCGGCCTCCTGTTTAGCTCCC
GCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCTCGTCAAAGCAACCATAGTACGCG
CCCTGTAGCGGCGCATTAAAGCGCGGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACA
CTTGCCAGCGCCTAGCGCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTT
GCCGGCTTTCCCCGCTAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCGATTTAGTGCT
TTACGGCACCTCGACCCCAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCG
CCCTGATAGACGGTTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTC
TTGTTCCAAACTGGAACAACACTCAACCCTATCTCGTCTATTCTTTTGATTATAAGGG
ATTTTGCCGATTTTCGGCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCG
AATTTTAAACAAATATTAACGTTTACAATTTAAATATTGCTTATACAATCTTCCTGTTT
TTGGGGCTTTTCTGATTATCAACCGGGGTACATATGATTGACATGCTAGTTTACGATTA

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CCGTTTCATCGATTCTCTTGTGTTGCTCCAGACTCTCAGGCAATGACCTGATAGCCTTTGTA
GAGACCTCTCAAAAATAGCTACCTCTCCGGCATGAATTTATCAGCTAGAACGGTTGAAT
ATCATATTGATGGTGATTGACTGTCTCCGGCCTTTCTCACCCGTTGAATCTTTACCTA
CACATTACTCAGGCATTGCATTTAAAAATATATGAGGGTTCTAAAAATTTTATCCTTGCG
TTGAAATAAAGGCTTCTCCCGCAAAGTATTACAGGGTCATAATGTTTTTGGTACAACCG
ATTTAGCTTTATGCTCTGAGGCTTTATTGCTTAATTTGCTAATCTTTGCCTTGCCTGT
ATGATTTATTGGATGTTGGAATTCCTGATGCGGTATTTCTCCTTACGCATCTGTGCGGT
ATTTACACCCGATATGGTGCCTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGC
CAGCCCCGACACCCGCCAACCCGCTGACGCGCCTGACGGGCTTGTCTGCTCCCGCA
TCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTGAGAGTTTTACCG
TCATCACCAGAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTATAGGTTAAT
GTCATGATAAATAGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGA
ACCCCTATTTGTTTATTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAA
CCCTGATAAATGCTTCAATAATATTGAAAAGGAAGAGTATGAGTATTCAACATTTCCGT
GTCGCCCCATTATCCCTTTTTTTCGCGCATTTTGCCTTCTGTTTTTGTCTACCCAGAAAACG
CTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTG
GATCTCAACAGCGGTAAAGATCCTTGAGAGTTTTCGCCCCGAAGAAGCTTTTCCAATGATG
AGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTTATCCCGTATTGACGCCGGGCAAGAG
CAACTCGGTGCGCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACA
GAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATG
AGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACC
GCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTG
AATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACG
TTGCGCAAATCTAATACTGGCGAACTACTTCTAGCTTCCCGCAACAATTAATAGAC
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CAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCT
GTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGC
GATAAGTCGTGCTTACCAGGTTGGACTCAAGACGATAGTTACCAGATAAGCGCAGCGG
TCGGGCTGAACGGGGGGTTCTGTGCACACAGCCAGCTTGGAGCGAACGACCTACACCGAA
CTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCGAAGGGAGAAAGGCG
GACAGGTATCCGTTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGG

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GGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGA
TTTTTGTGATGCTCGTCAGGGGGCGGAGCCTATGAAAAACGCCAGCAACGCGGCCTT
TTACGGTTCTTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTCTCGCTTATCCCCCT
GATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGAGCCGA
ACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATACGCAACCG
CCTCTCCCGCGCGTTGGCCGATTCAATTAATGCAGCAGCTGCGCGCTCGCTCGCTCACTG
AGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCG
AGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGA
TTAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGACATTGATTATTGACTAGT
GGAGTTCGCGTTACATAAATTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCC
CCGCCCATTTAGCTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCA
TTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTA
TCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATT
TGCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCAT
CGCTATTACCATGGTCGAGGTGAGCCCCACGTTCTGCTTCACTCTCCCCATCTCCCCCCC
CTCCCCACCCCAATTTTGTATTTATTTATTTTAAATTATTTTGTGCAGCGATGGGGGC
GGGGGGGGGGGGCGCGCGCCAGCGGGGGGGGGGGGGCGAGGGCGGGGCGGGGGCG
AGGCGGAGAGGTGCGGCGGCGAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCTTTTATG
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TGACTGACCGCTTACTAAAACAGGTAAGTCCGGCTCCGCGCGGGTTTGGCGCCTCC
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GGTTTTCTTTCCAGAGAGCGGAACAGGCGAGGAAAAGTAGTCCCTTCTCGGCGATTCTGC
GGAGGATCTCCGTGGGGCGGTGAACGCCGATGATGCCTCTACTAACCATGTTTATGTTT
TCTTTTTTTTTCTACAGGTCCTGGGTGACGAACAGGTACCGCCACCATGGCCACCGGCT
CTCGCACAAGCCTGCTGCTGGCTTTCGGAAGTGTGCTGCTGCTTGGCTCCAGGAGGGCT
CCGCCGTAGCATCGATACCGTCGCTATGTGCTGGAGGCTTGCTGAAGCTGTATGCTGT
AATAAAGTCTGGGAATCACCGTTTTTGGCCTCTGACTGACGGGTGATTCCGACCTTTAT
TACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGG
CTTGCTGAAGGCTGTATGCTGTAATACGCCAGATCACCATCAGCGTTTTTGGCCTCTGACT
GACGCTGATGGTGTGGCGTATTACAGGACACAAGGCCTGTTACTAGCACTCACATGGAA
CAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGATACAGAAACGAAGTT
CAGGCCGTTTTTGGCCTCTGACTGACGGCCTGAACCGTTTTCTGTATCAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAGAAT 3'

SEQ ID NO. 24 = SEQ ID NO. 1 + SEQ ID NO. 12
5' AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACATATGTT
GCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCC
CGTATGGCTTTTATTTCTCCTCTGTATAAATCCTGGTTGCTGCTCTTTATGAGGAG

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TTGTGGCCCGTTGTGAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCC
ACTGGTTGGGGCATTGCCACCACCTGTGAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTC
CCTATTGCCACGGCGGAACATCGCCGCTGCCTTGCCCGCTGCTGGACAGGGGCTCGG
CTGTTGGGCACTGACAATTCCGTGGTGTGTCGGGGAATCATCGTCCTTTCCTTGCGTG
CTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCTTTCGGCC
CTCAATCCAGCGGACCTTCCTTCCGCGGCCTGCTGCGGCTCTGCGGCCTCTTCCGCGT
CTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGCCGCTCCCCGCTAAGCTT
ATCGATACCGTCGAGATCTAACTTGTTTATTGCACTTATAATGGTTACAAATAAGCAA
TAGCATCACAAATTTACAAATAAGCATTTTTTCACTGCATTCTAGTTGTGGTTTGTC
CAAACCTCATCAATGTATCTTATCATGTCTGGATCTCGACCTCGACTAGAGCATGGCTACG
TAGATAAGTAGCATGGCGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGG
CCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGTCGCCCGAC
GCCCCGGCTTTGCCCGGGCGGCTCAGTGAGCGAGCGAGCGCGCAGCTGGCGTAATAGCG
AAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGCGAT
TCCGTTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACCAGCAAGGCCGATAGTTTG
AGTTCTTCTACTCAGGCAAGTGATGTTATTACTAATCAAAGAAGTATTGCGACAACGGTT
AATTTGCGTGATGGACAGACTCTTTACTCGGTGGCCTCACTGATTATAAAAACACTTCT
CAGGATTCTGCGGTACCGTTCTGTCTAAAATCCCTTTAATCGGCCTCCTGTTTAGCTCC
CGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCTCGTCAAAGCAACCATAGTACGC
GCCCTGTAGCGGCGCATTAAGCGCGGGGGTGTGGTGGTTACGCGCAGCGTGACCGCTAC
ACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTCTTCCCTTCCTTCTCGCCACGTT
CGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTAGGGTTCCGATTTAGTGC
TTTACGGCACCTCGACCCCAAAAACTTGATTAGGGTGATGGTTACGTAGTGGGCCATC
GCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTAAAGTGGACT
CTTGTTCCAACTGGAACAACACTCAACCTATCTCGGTCTATTCTTTGATTATAAGG
GATTTTGCCGATTTCGGCCTATTGGTTAAAAATGAGCTGATTTAACAAAAATTAACGC
GAATTTTAACAAATATTAACGTTTACAATTTAAATATTGCTTATACAATCTTCTGTT
TTTGGGGCTTTTCTGATTATCAACCGGGTACATATGATTGACATGCTAGTTTACGATT
ACCGTTCATCGATTCTCTTGTGTTGCTCCAGACTCTCAGGCAATGACCTGATAGCCTTGT
AGAGACCTCTCAAAATAGCTACCCCTCTCCGCATGAATTTATCAGCTAGAACGGTTGAA
TATCATATTGATGGTGATTGACTGTCTCCGGCCTTCTCACCCGTTTGAATCTTTACCT
ACACATTACTCAGGCATTGCATTTAAAAATATAGAGGGTTCTAAAAATTTTATCCTTGC
GTTGAAATAAAGGCTTCTCCCGCAAAGTATTACAGGTCATAATGTTTTTGGTACAACC
GATTTAGCTTTATGCTCTGAGGCTTTATTGCTTAATTTTGCTAATCTTTGCCTTGCCTG
TATGATTTATTGGATGTTGGAATTCCTGATGCGGTATTTCTCCTTACGCATCTGTGCGG
TATTTACACCCGATATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGATAGTTAAG
CCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGC
ATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTGACAGGTTTTACCC
GTCATACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTAA

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TGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGG
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TGTCGCCCTTATTCCTTTTTTGCGGCATTTCCTTCTGTTTTGCTCAGCCAGAAAC
GCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACT
GGATCTCAACAGCGGTAAAGATCCTTGAGAGTTTTCGCCCCGAAGAAGTTTTCCAATGAT
GAGCACTTTTAAAGTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGA
GCAACTCGGTGCGCCGATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCAC
AGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGTGCCATAACCAT
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CGCTTTTTTGACACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCT
GAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAAC
GTTGCGCAAACTATTAAGTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGA
CTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTG
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GGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAAC
TATGGATGAACGAAATAGACAGATCGCTGAGTAGGTGCCTCACTGATTAAGCATTTGGTA
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TTTTTTCTGCGCGTAATCTGCTGCTTGCAAAACAAAAAACCACCGCTACCAGCGGTGGT
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GCAGATACCAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACCTTCAAGAACTC
TGTAGACCGCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGG
CGATAAGTGTGCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCG
GTGCGGCTGAACGGGGGTTCTGTGCACACAGCCAGCTTGAGCGAACGACCTACACCGA
ACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCGAAGGGAGAAAGGC
GGACAGGTATCCGTAAGCGGAGGGTGGGAACAGGAGAGCGCACGAGGGAGCTTCCAGG
GGGAAACGCCTGGTATCTTTATAGTCTGTGCGGTTTCGCCACCTCTGACTTGAGCGTCG
ATTTTGTGATGCTCGTCAGGGGGCGGAGCCTATGGAACGCGCAGCAACGCGGCCTT
TTTACGGTTCCTGGCCTTTTGTGCGCTTTTGTCTACATGTTCTTCTGCGTTATCCCC
TGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGAGCCG
AACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAAAC
GCCTCTCCCCGCGCTTGGCCGATTCATTAATGCAGCAGCTGCGCGCTCGCTCGCTCACT
GAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGC
GAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTTCTTGTAGTTAATG
ATTAACCCGCCATGCTACTTATCTACGTAGCATGCTCTAGGACATTGATTATTGACTAG
TGGAGTTCGCGTTACATAACTTACGGTAAATGGCCGCTGGCTGACCGCCCAACGACC
CCGCCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCC

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ATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGT
ATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATT
ATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCA
TCGCTATTACCATGGTCGAGGTGAGCCCCACGTTCTGCTTCACTCTCCCCATCTCCCCC
CCTCCCCACCCCCAATTTTGTATTTATTTATTTTAAATTATTTTGTGCAGCGATGGGGG
GGGGGGGGGGGGGGCGCGCCAGGCGGGGCGGGGGGGCGAGGGGCGGGGCGGGCG
AGGCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGGCTCCGAAAGTTTCCTTTTATG
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TGACTGACCGCTTACTAAAACAGGTAAGTCCGGCCTCCGCGCCGGGTTTGGCGCCTCC
CGCGGGCGCCCCCTCCTCACGGCGAGCGCTGCCACGTGAGACGAAGGGCGCAGCGAGCG
TCCTGATCCTTCGCCCCGACGCTCAGGACAGCGGCCGCTGCTCATAAGACTCGGCCTT
AGAACCCAGTATCAGCAGAAGGACATTTTAGGACGGGACTTGGGTGACTCTAGGGCACT
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GGAGGATCTCCGTGGGGCGGTGAACGCCGATGATGCCTCTACTAACCATGTTTCATGTTT
TCTTTTTTTTTCTACAGGTCCTGGGTGACGAACAGGGTACCGCCACCATGGCCACCGCT
CTCGCACAAGCCTGCTGCTGGCTTTCGGACTGCTGTGCCTGCCTTGGCTCCAGGAGGGCT
CCGCCGTAGCATCGATACCGTCGCTATGTGCTGGAGGCTTGCTGAAGGCTGTATGCTGT
CAGATCGCTGTGGTAAACAGGCGTTTGGCCTCTGACTGACGCTGTTTACCAGCGATCT
GACAGGACACAAGGCCTGTTACTAGCACTCACATGGAACAAATGGCCTCTAGCCTGGAGG
CTTGCTGAAGGCTGTATGCTGAGAATCAGATCAGATAGCGATCCGTTTGGCCTCTGACT
GACGGATCGCTATCTGCTGATTCTCAGGACACAAGGCCTGTTACTAGCACTCACATGGAA
CAAATGGCCTCTAGCCTGGAGGCTTGCTGAAGGCTGTATGCTGAAACATGCCAACAGCAG
AATGCCGTTTTTGGCCTCTGACTGACGGCATTCTGCTGGGCATGTTTCAGGACACAAGGCC
TGTTACTAGCACTCACATGGAACAAATGGCCTCTCTAGAAT 3'

SEQ ID NO. 25 = SEQ ID NO. 1 + SEQ ID NO. 13
5' AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACATGTT
GCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCC
CGTATGGCTTTTCAATTTCTCCTCTGTATAAATCCTGGTTGCTGCTCTTTATGAGGAG
TTGTGGCCCGTTGTGAGCAACGTGCGTGGTGTGCACTGTGTTTGTGACGCAACCCCC
ACTGGTTGGGGCATTGCCACCACCTGTGAGCTCCTTCCGGGACTTTCGCTTTCCCCCTC
CCTATTGCCACGGCGGAATCATCGCCGCTGCCCTTGCCCGCTGCTGGACAGGGGCTCGG
CTGTTGGGCACTGACAATTCGGTGGTGTGTCGGGAAATCATCGTCCTTTCCTTGGCTG
CTCGCCTGTGTTGCCACCTGGATTCTGCGCGGACGTCCTTCTGTACGTCCTTCGGCC
CTCAATCCAGCGACCTTCCTTCCGCGGCCTGCTGCCGGCTCTGCGGCTCTTCCGCGT
CTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTGGGCCGCTCCCGCCTAAGCTT
ATCGATACCGTCGAGATCTAACTTGTTTATTGACGCTTATAATGGTTACAAATAAGCAA
TAGCATCACAATTTACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTGGTTTGTG
CAAACCTCATATGTATCTTATCATGTCTGGATCTCGACCTCGACTAGAGCATGGCTACG

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GCCCTGTAGCGCGCATTAAAGCGCGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTAC
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ACACATTACTCAGGCATTGCATTTAAAAATATATGAGGGTTCTAAAAATTTTATCCTTGC
GTTGAAATAAAGGCTTCTCCCGAAAAGTATTACAGGGTCATAATGTTTTTGGTACAACC
GATTTAGCTTTATGCTCTGAGGCTTTATTGCTTAATTTTGCTAATCTTTGCCTTGCCCTG
TATGATTTATTGGATGTTGGAATTCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGG
TATTTACACCCGATATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAG
CCAGCCCCGACACCCGCCAACCCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGC
ATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTGAGAGGTTTTCACC
GTCATCACCGAAACGCGGAGACGAAAGGGCCTCGTGATACGCCATTTTTTATAGGTTAA
TGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGAAATGTGCGCGG
AACCCTATTGTGTTATTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATA
ACCTGATAAATGCTTCAATAATATTGAAAAAGGAAGATATGAGTATTCAACATTTCCG
TGTCGCCCTTATTCCTTTTTTGCGGCATTTCGCTTCTGTTTTGCTCACCCAGAAAC
GCTGGTGAAAGTAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACT
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[0074] As will be appreciated by those skilled in the art, because the recombinant plasmid is a circular vector, the one or more sequences of the miRNA expression cassettes may be connected at the 3' end of SEQ ID NO. 1, as shown in SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 24 and SEQ ID NO. 25, or at the 5' end of SEQ ID NO. 1.

[0075] As will be appreciated by those skilled in the art, a perfect match of nucleotides with each of the miRNA expression cassette sequences is not necessary in order to have the desired result of decreased bioavailability of the target biomolecule as a result of the target cell producing the miRNA sequence that will bind to and degrade the mRNA of the target biomolecule. In some embodiments of the present disclosure, about 80% to about 100% nucleotide sequence matching with each of the miRNA expression cassettes causes the desired result. In some embodiments of the present disclosure, about 85% to about 100% nucleotide sequence matching with each of the miRNA expression cassettes causes the desired result. In some embodiments of the present disclosure, about 90% to about 100% nucleotide sequence matching with each of the miRNA expression cassettes causes the desired result. In some embodiments of the present disclosure, about 95% to about 100% nucleotide

sequence matching with each of the miRNA expression cassettes causes the desired result.

Example 1—Expression Cassette

[0076] Expression cassettes for expressing miRNA were synthesized. The synthesized miRNA expression cassettes were cloned into the pAVA-00200 plasmid backbone containing the CASI promoter, multiple cloning site (MCS), Woodchuck Hepatitis Virus post-transcriptional regulatory element (WPRE), and Simian virus 40 (SV40) polyadenylation (polyA) sequence, all flanked by the AAV2 inverted terminal repeats (ITR). pAVA-00200 was cut with the restriction enzymes KpnI and XbaI in the MCS and separated on a 1% agarose gel. The band of interest was excised and purified using a gel extraction kit. Each miRNA expression cassette was amplified by polymerase chain reaction (PCR) using Taq polymerase and the PCR products were gel purified and the bands of interest were also excised and purified using a gel extraction kit. These PCR products contained the miRNA expression cassettes in addition to 15 base pair 5' and 3' overhangs that aligned with the ends of the linearized pAVA-00200 backbone. Using in-fusion cloning, the amplified miRNA expression cassettes were integrated with the pAVA-00200 backbone via homologous recombination. The resulting RP contained the following: 5' ITR, CASI promoter, miRNA expression cassette, WPRE, SV40 polyA and ITR 3'.

SEQUENCE LISTING

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tgtcatgttt aaaaattcgc tgcgcgtttt ggccctctgac tgacgcgcag cgaattttaa 480
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SEQ ID NO: 7          moltype = DNA length = 540
FEATURE              Location/Qualifiers
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                     mol_type = other DNA
                     organism = synthetic construct

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cgatttcaga acccgattca tcaggacaca aggcctgtta ctgactca catggaacaa 240
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SEQ ID NO: 8          moltype = DNA length = 540
FEATURE              Location/Qualifiers
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                     mol_type = other DNA
                     organism = synthetic construct

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SEQ ID NO: 9          moltype = DNA length = 538
FEATURE              Location/Qualifiers
source                1..538
                     mol_type = other DNA
                     organism = synthetic construct

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SEQ ID NO: 10         moltype = DNA length = 540
FEATURE              Location/Qualifiers

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source                1..540
                      mol_type = other DNA
                      organism = synthetic construct

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SEQ ID NO: 11         moltype = DNA length = 540
FEATURE               Location/Qualifiers
source                1..540
                      mol_type = other DNA
                      organism = synthetic construct

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SEQ ID NO: 12         moltype = DNA length = 540
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SEQ ID NO: 13         moltype = DNA length = 540
FEATURE               Location/Qualifiers
source                1..540
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The invention claimed is:

1. A composition that comprises a recombinant plasmid (RP) a sequence of nucleotides that encode micro-interfering ribonucleic acid (miRNA) that binds to and inactivates and/or degrades messenger ribonucleic acid (mRNA) that encodes for a serotonin receptor, wherein the sequence of nucleotides comprises 95-100% the same nucleotide sequence as SEQ ID NO. 5.

2. The composition of claim 1, wherein the sequence of nucleotides is configured to be delivered to a target cell that has expressed the serotonin receptor.

3. The composition of claim 1, wherein the sequence of nucleotides is encased in a protein coat, a lipid vesicle, or any combination thereof.

4. The composition of claim 1, wherein the sequence of nucleotides is encased in a viral vector.

5. The composition of claim 4, wherein the viral vector is one of a double stranded DNA virus, a single stranded DNA virus, a single stranded RNA virus, or a double stranded RNA virus.

6. The composition of claim 4, wherein the viral vector is an adeno-associated virus.

7. The composition of claim 1 wherein the serotonin receptor is serotonin receptor 5HT1e.

8. A composition that comprises a recombinant plasmid (RP) with a sequence of nucleotides for encoding a sequence of micro-interfering ribonucleic acid (miRNA) that binds to and degrades and/or inactivates messenger ribonucleic acid (mRNA) that encodes for a serotonin receptor, wherein the sequence of nucleotides comprises 95-100% of the same nucleotide sequence as SEQ ID NO. 17.

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