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**TAKAHASHI, M ET AL., "Spinal Gene Transfer Using Ultrasound And Microbubbles.", JOURNAL OF CONTROLLED RELEASE., (2006-11-06), vol. 117, pages 267 - 272**

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(54) Title: SONOCHEMICAL INDUCTION OF ABCA1 EXPRESSION AND COMPOSITIONS THEREFOR

(57) Abstract: The present invention provides compositions useful for transfecting cells (e.g., liver cells) to express ABCA1. The compositions described herein comprise a pharmaceutically acceptable aqueous carrier containing sonochemically-active microspheres together with a plasmid DNA construct encoding an active form of ABCA1 and at least one promoter for the expression thereof. Preferably, the sonochemically-active microspheres comprise, consist essentially of, or consist of gas bubbles (e.g., a fluoro-carbon gas, such as octafluoropropane) encapsulated within protein-containing or lipid-containing shells (e.g., human serum albumin shells). The microspheres are disruptable by exposure to ultrasonic acoustic energy to release the encapsulated gas.

## SONOCHEMICAL INDUCTION OF ABCA1 EXPRESSION AND COMPOSITIONS THEREFOR

### FIELD OF THE INVENTION.

5           This invention relates to compositions comprising sonochemically-active microspheres and a plasmid encoding ATP-binding cassette transporter A1, and methods of inducing ATP-binding cassette transporter A1 expression *in vivo*.

### SEQUENCE LISTING INCORPORATION

10           Biological sequence information for this application is included in an ASCII text file having the file name "SG-2-SEQ-4\_ST25.txt", created on September 10, 2013 and having a file size of 44617 bytes, which is incorporated herein by reference.

### BACKGROUND

15           High-density lipoprotein (HDL) is the largest of the five major groups of lipoproteins. Other lipoproteins include chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL). HDL and other lipoproteins enable cholesterol and other lipids (e.g., triglycerides) to be transported within the bloodstream, despite their hydrophobic nature. About thirty percent of blood cholesterol is carried by HDL in  
20 healthy adults.

          ATP-binding cassette transporter A1 (ABCA1) is an integral cell membrane protein that exports excess cholesterol from cells in conjunction with phospholipid that is necessary for the initial lipidation of ApoA1 to form nascent high density lipoprotein cholesterol (HDL-c). ABCA1 deficiency leads to very low plasma levels of HDL-c. In contrast, ABCA1  
25 overexpression reportedly protected C57B1/6 mice from diet-induced atherosclerosis. Increasing ABCA1 transcription by enhancing its regulatory gene control by liver X factor (LXR) has led to the induction of not only HDL biogenesis, but also to an adverse increase in lipogenesis, leading to undesirable hepatic steatosis.

          HDL-c is formed in the liver and the intestines by the lipidation of apolipoprotein A1  
30 (apoA1) mediated by the ABCA1 transporter protein. Numerous studies of cultured cells,

human HDL deficiencies, and animal models have shown that ABCA1 is a major determinant of plasma HDL levels and a potent atheroprotective factor. The role of ABCA1 in the liver for the formation of plasma HDL is well established, but it has been unclear whether stimulation of ABCA1 production will enhance lipidation and secretion of nascent HDL thereby resulting in an increase in plasma HDL-c levels.

The metabolism of HDL is complex and several factors contribute to the transport of cholesterol from arteries to the liver for excretion or re-use (reverse cholesterol transport). Some key players in reverse cholesterol transport include ABCA1, ABCG1, apoA1, apoE, LXR, Niemann Pick proteins 1 and 2 (NPC1 and NPC2) sterol regulating element binding protein (SREBP), CD36, acyl cholesterol acyl transferase (ACAT) and scavenger receptor A1 (SRA1). Many of these proteins have been considered as drug targets for enhancing blood HDL-c levels; however, the effects of targeting, enhancing the activity of, or otherwise interfering with the normal activity and expression of any of these individual proteins is unpredictable. High cholesterol also commonly is treated by inhibiting production of cholesterol in the liver (e.g., by inhibiting HMG-CoA reductase) or by inhibiting digestion of fats (e.g., by inhibiting bile acid production).

Plasma HDL-c and LDL-c levels are routinely measured as indicators of systemic atherosclerosis resulting in arterial blockage. HDL can remove cholesterol from within arteries and transport the cholesterol back to the liver for excretion or re-utilization. Individuals with higher levels of HDL-c have a reduced tendency for cardiovascular diseases. Low HDL-c cholesterol levels (less than about 40 mg/dL or about 1 mmol/L) are associated with increased risk of heart disease. In patients with Tangier disease (also known as "familial alpha-lipoprotein deficiency"), a rare inherited disorder, mutations in chromosome 9q31 lead to an inactive form of ABCA1. The inactive ABCA1 leads to severely depressed levels of HDL in the blood. Currently, there is no effective treatment for Tangier disease.

Because of the positive epidemiological correlation between HDL-c levels in the blood and reduced risk of heart disease, as well as the link between HDL and Tangier disease, there is an ongoing need for new methods of increasing blood HDL-c levels. The present application addresses this ongoing need.

## SUMMARY OF THE INVENTION

The present invention provides compositions useful for transfecting liver cells to express ABCA1. The compositions described herein comprise a pharmaceutically acceptable aqueous carrier containing sonochemically-active microspheres together with a plasmid DNA construct encoding an active form of ABCA1 and at least one promoter for the expression thereof. The sonochemically-active microspheres comprise, consist essentially of, or consist of gas bubbles (e.g., a fluorocarbon gas, such as octafluoropropane or perfluorohexane) encapsulated within protein-containing or lipid-containing shells (e.g., human serum albumin shells). The microspheres are disruptable by exposure to ultrasonic energy (sonication) to release the encapsulated gas.

The following embodiments are provided as illustrative, non-limiting examples of the compositions and methods described herein.

Embodiment 1 comprises a composition useful for transfecting cells comprising a mixture of a plasmid vector encoding an active form of ATP-binding cassette transporter A1 (ABCA1) and sonochemically-active microspheres in a pharmaceutically acceptable aqueous carrier. The vector comprises an expressible open reading frame encoding the active form of ABCA1 and at least one sequence adapted to promote expression of the open reading frame in a mammalian cell. The sonochemically-active microspheres comprise gas bubbles encapsulated within shells comprising a protein, a lipid, or a combination thereof, the microspheres being disruptable upon exposure to ultrasonic acoustic energy to release the encapsulated gas bubbles.

Embodiment 2 comprises the composition of embodiment 1 wherein the microspheres have an average particle size in the range of about 0.5 to about 20 micrometers.

Embodiment 3 comprises the composition of embodiment 1 or embodiment 2 wherein the gas comprises a fluorocarbon gas.

Embodiment 4 comprises the composition of any one of embodiments 1 to 3 wherein the shells comprise human serum albumin.

Embodiment 5 comprises the composition of any one of embodiments 1 to 4 wherein the active form of ABCA1 has the amino acid sequence of SEQ ID NO: 1.

Embodiment 6 comprises the composition of any one of embodiments 1 to 5 wherein the open reading frame has the nucleotide sequence of SEQ ID NO: 2.

Embodiment 7 comprises the composition of any one of embodiments 1 to 6 wherein the at least one sequence adapted to promote expression of the open reading frame comprises a cytomegalovirus promoter.

Embodiment 8 comprises the composition of any one of embodiments 1 to 7 wherein the plasmid is present in the composition at a concentration in the range of about 0.5 to about 50 mg/mL.

Embodiment 9 comprises the composition of any one of embodiments 1 to 8 wherein the microspheres are present in the composition at a concentration in the range of about  $10^8$  to about  $10^9$  microspheres per milliliter.

Embodiment 10 comprises the composition of any one of embodiments 1 to 9 wherein the aqueous carrier comprises physiological saline, optionally buffered at physiological pH.

Embodiment 11 comprises the composition of any one of embodiments 1 to 10 further comprising at least one material selected from the group consisting of (a) a drug for treating a condition relating to lipid metabolism or transport, (b) a plasmid encoding a protein other than ABCA1 involved in lipid metabolism of transport, and (c) a plasmid encoding an siRNA that targets a protein involved in lipid metabolism or transport.

Embodiment 12 comprises the composition of any one of embodiments 1 to 11 wherein the plasmid encoding ABCA1 also encodes at least one material selected from the group consisting of (a) a protein other than ABCA1 involved in lipid metabolism of transport, and (b) an siRNA that targets a protein involved in lipid metabolism or transport.

Embodiment 13 comprises a composition useful for transfecting liver cells comprising a mixture of about 0.5 to about 50 mg/mL of a plasmid vector encoding an active form of ATP-binding cassette transporter A1 (ABCA1) and about  $10^8$  to about  $10^9$  microspheres per milliliter of sonochemically-active microspheres in a pharmaceutically acceptable aqueous carrier; wherein the vector comprises an expressible open reading frame encoding the active form of ABCA1 and at least one sequence adapted to promote expression of the open reading frame in a mammalian cell; and wherein the sonochemically-active microspheres comprise octafluoropropane gas bubbles encapsulated within shells comprising human serum albumin, the microspheres being disruptable upon exposure to ultrasonic acoustic energy to release the encapsulated gas bubbles.

Embodiment 14 comprises a method of increasing blood HDL-cholesterol levels by transfecting the liver of a subject *in vivo* to express an active form of ABCA1 in cells of the tissue, the method comprising the steps of (a) intravenously co-administering to a subject a plasmid vector encoding the active form of ATP-binding cassette transporter A1 (ABCA1), and  
5      sonochemically-active microspheres; wherein the vector comprises an expressible open reading frame encoding the active form of ABCA1 and at least one sequence adapted to promote expression of the open reading frame in a mammalian cell; and wherein the sonochemically-active microspheres comprise gas bubbles encapsulated within shells comprising a protein, a lipid, or a combination thereof, the microspheres being disruptable upon exposure to ultrasonic  
10     acoustic energy to release the encapsulated gas bubbles; (b) ultrasonically imaging the liver of the subject to be transfected while the plasmid and microspheres of the composition are circulating through the vasculature of the liver and thereby detecting the presence of the microspheres in the vasculature of the liver; and (c) while the microspheres are present in the liver, applying pulses of ultrasonic energy to the liver at an acoustical energy level higher than  
15     that required for imaging and at a sufficient energy level to disrupt the microspheres and release the gas bubbles therefrom, the pulses of ultrasonic energy and release of gas bubbles thereby temporarily increasing the porosity of cells in the liver to facilitate entry of the plasmid into the cells to effect transfection thereof.

Embodiment 15 comprises the method of embodiment 14 wherein the microspheres  
20     have an average particle size in the range of about 0.5 to about 20 micrometers.

Embodiment 16 comprises the method of embodiment 14 or embodiment 15 wherein the gas comprises a fluorocarbon gas.

Embodiment 17 comprises the method of any one of embodiments 14 to 16 wherein the shells comprise human serum albumin.

Embodiment 18 comprises the method of any one of embodiments 14 to 17 wherein the  
25     active form of ABCA1 has the amino acid sequence of SEQ ID NO: 1.

Embodiment 19 comprises the method of any one of embodiments 14 to 18 wherein the at least one sequence adapted to promote expression of the open reading frame comprises a cytomegalovirus promoter.

Embodiment 20 comprises the method of any one of embodiments 14 to 19 wherein the plasmid is administered in an aqueous carrier at a concentration in the range of about 0.5 to about 50 mg/mL.

Embodiment 21 comprises the method of any one of embodiments 14 to 20 wherein the microspheres are administered in an aqueous carrier at a concentration in the range of about  $10^8$  to about  $10^9$  microspheres per milliliter.

Embodiment 22 comprises the method of any one of embodiments 14 to 21 wherein the plasmid and the microspheres are administered as a mixture in one aqueous carrier.

Embodiment 23 comprises the method of any one of embodiments 14 to 21 wherein the plasmid and the microspheres are administered in separate aqueous carriers.

Embodiment 24 comprises the method of any one of embodiments 14 to 23 wherein an additional biologically active agent is co-administered along with the plasmid and microspheres.

Embodiment 25 comprises the method of embodiment 24 wherein the additional biologically active agent comprises at least one material selected from the group consisting of (a) a drug for treating a condition relating to lipid metabolism or transport, (b) a plasmid encoding a protein other than ABCA1 involved in lipid metabolism or transport, and (c) a plasmid encoding an siRNA that targets a protein involved in lipid metabolism or transport.

Embodiment 26 comprises use of a composition of any one of embodiments 1 to 13 to enhance high density lipoprotein cholesterol in the blood of a subject (e.g., to treat atherosclerosis).

Embodiment 27 comprises use of a composition of any one of embodiments 1 to 13 for the preparation of a medicament to enhance high density lipoprotein cholesterol in the blood of a subject (e.g., to treat atherosclerosis).

In a study conducted with rats, sonoporation of the liver in conjunction with a peripheral (tail vein) intravenous infusion of an aqueous composition containing ABCA1 plasmids and albumin-encapsulated fluorocarbon gas (octafluoropropane) microspheres resulted in a significant increase in plasma HDL-c levels relative to the baseline HDL-c levels for the rats. In this study, ABCA1 plasmid achieved a higher serum concentration of HDL-c than apoA1 plasmid. This finding is both surprising and novel the current understanding in this field is that the most effective method to increase hepatic secretion of HDL-c is to increase apoA1

synthesis. In fact, treatment with both the ABCA1 plasmid and the apoA1 plasmid was no better than an infusion of ABCA1 alone in this study.

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

5 FIG. 1 provides the amino acid sequence of human ABCA1 (SEQ ID NO: 1) utilized in the examples herein.

FIG. 2 provides the open reading frame nucleotide sequence of human ABCA1 (SEQ ID NO: 1) utilized in the examples herein.

10 FIG. 3 illustrates the nucleotide sequence of the plasmid (SEQ ID NO: 3) utilized in the examples herein.

FIG. 4 provides a schematic illustration of the ABCA1 plasmid utilized in the examples described herein.

15 FIG. 5 provides a graph of blood HDL-c in rats following sonochemical treatment with compositions comprising OPTISON microspheres and plasmids encoding ABCA1, apoA1, or a combination thereof.

#### **DETAILED DESCRIPTION OF SELECTED EMBODIMENTS**

20 In one aspect, the present invention provides compositions useful for transfecting liver cells to express ABCA1 comprise a pharmaceutically acceptable aqueous carrier containing sonochemically-active microspheres together with a plasmid DNA construct encoding an active form of ABCA1 and at least one promoter for the expression thereof. The sonochemically-active microspheres comprise, consist essentially of, or consist of gas bubbles encapsulated within protein-containing or lipid-containing shells. The microspheres are disruptable by sonication (i.e., exposure to ultrasonic acoustic energy), releasing the encapsulated gas.

25 In another aspect, the present invention provides a method of inducing ABCA1 expression in cells *in vivo*, and a method enhancing high density lipoprotein cholesterol in the blood. These methods comprise intravenously co-administering an ABCA1 plasmid and sonochemically active microspheres as described herein to a subject, ultrasonically imaging the liver of the subject to detect when the microspheres are circulating through the vasculature of  
30 the liver. The imaging typically is performed by external application of ultrasonic acoustic

energy at a mechanical index (MI; which is defined as the peak negative acoustic pressure divided by the square of the imaginh frequency) less than about 0.4 MI. When the microspheres are detected in the liver, pulses of ultrasonic acoustic energy are applied to the liver at an acoustic energy level higher than the energy level needed for imaging (typically greater than 1  
5 MI, preferably greater than 1.3 MI, and up to about 2 MI), and of sufficiently high acoustic energy to disrupt the shells of the microspheres and release the gas bubbles encapsulated by the shells. The pulses preferably are applied at an acoustic frequency of about 1 to about 7 MHz. The acoustic energy of the pulses and the release of gas bubbles in the liver temporarily increases the porosity of the cell membranes (a process referred to herein as "sonoporation").

10 Sonoporation of the liver comprises supplying ultrasonic acoustic energy pulses to the liver with the ultrasound imaging probe. The pulses are applied while ultrasonically imaging the liver so that the pulses are applied primarily when the microspheres (and thus also the co-administered plasmid) are present. The pulses typically are applied at a rate of about 6 to about 8 pulses per minute for a total of about 5 to about 20 pulses. The pulse duration typically is in  
15 the range of about 500 to about 2000 milliseconds per pulse. The acoustic energy pulses disrupt the microspheres and release the encapsulated gas. This disruption, combined with directly supplied acoustic energy makes the cells more porous to the plasmids, so that the plasmids can enter and transfect the cells. Once transfected, the cells transcribe protein via messenger RNA leading to synthesis of active ABCA1, which in turn enhances HDL formation and HDC-c  
20 concentration in the blood.

As used herein, the term "co-administration" and grammatical variations thereof, refers to administering two or more materials to the same individual during the same therapeutic session. Such co-administration can involve administering material separately, or together within the same composition. The co-administration can be simultaneous or can be temporally  
25 separated. In addition, sites of co-administration can be in the same location or different locations.

As used herein, the term "plasmid" and grammatical variations thereof refers to small circular DNA that is physically separate from, and can replicate independently of, chromosomal DNA within a cell (i.e., in an episome), and which commonly are found as small (e.g., about one thousand to about one million base pairs) circular, double-stranded DNA molecules in bacteria. Artificial plasmids are used as vectors in molecular cloning, serving to drive the replication of recombinant DNA sequences within episomes in the host cells without altering the chromosomal DNA of the host cells.

As used herein, the term "episomally transfected" and grammatical variations thereof refer to non-insertional (non-integrating) transfection with exogenous episomal nucleic acid, such as DNA, siRNA, RNA, or mRNA (e.g. a plasmid or other episomal vector) to produce a cell with unaltered chromosomal DNA, in which the a polypeptide encoded by the episomal DNA is expressed within the target cells (e.g., liver cells) without genomic integration of the exogenous DNA. As used herein, the term "episome" and grammatical variations thereof refers to closed circular DNA molecules that are replicated in the nucleus, and is intended to encompass exogenous plasmids introduced into host cells such as liver cells. Preferably, the plasmid encodes the active form of ABCA1 and also encodes regulatory elements (e.g., a promoter) to facilitate episomal expression of the ABCA1 protein.

As used herein, the term "active form of ABCA1" and grammatical variations thereof refers to the ABCA1 protein of SEQ ID NO: 1 and variations thereof comprising conservative substitutions in SEQ ID NO: 1 and sharing at least about 95 percent sequence identity (e.g., at least about 95, 96, 97, 98, or 99 % sequence identity) with SEQ ID NO: 1 and retaining the lysine residues at positions 939 and 1952 of SEQ ID NO: 1.

Percentage values stated herein are on a weight-weight basis (i.e., "weight percent" or "percent by weight") when referring to a concentration, and on a number basis when referring to a quantity or countable number of items, as the context will make evident and unless otherwise specified.

As used herein, a "therapeutically effective dosage" is an amount (e.g., a total of about 0.5 to about 10 mL of a single composition or co-administered compositions comprising about 0.5 to about 50 mg/mL of the ABCA1 plasmid and about  $10^8$  to about  $10^9$  of the microspheres per milliliter) such that when administered in conjunction with sonication of the liver, the

plasmids transfect cells of the tissue to express the nucleic acid, subsequently resulting in enhanced HDL-c level in the blood, or other effects targeted by the therapy. The dosage and number of doses (e.g. single or multiple dose) administered to a subject will vary depending upon a variety of factors, including the route of administration, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired, the concentration of plasmids in the composition, and the like.

Adjustment and manipulation of dosage ranges, as well as *in vitro* and *in vivo* methods of determining the therapeutic effectiveness of the composition in an individual, are well within the ability of those of ordinary skill in the medical arts. In some preferred embodiments, the dosage does not exceed about 5 mL of composition over a 10 minute period. Suitable safe dosages of ultrasonic contrast agents provide a useful guideline for use in the methods described herein. Such safe dosages are well known in the art and are documented in literature from ultrasonic contrast agent manufacturers.

The use of the terms “a” and “an” and “the” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Sonochemically-active microspheres suitable for use in the compositions and methods described herein include any protein-based or lipid-based gas-filled microspheres (also known

as "microbubbles") that can be used as ultrasonic imaging contrast agents. The microspheres comprise a physiologically acceptable gas (e.g., a non-toxic gas such as nitrogen, air, oxygen, argon, or a fluorocarbon such as octafluoropropane (also known as "perflutren") or perfluorohexane. The shell of the microspheres can comprise a protein (e.g., human serum albumin), a lipid material (e.g., phospholipids, phosphocholine lipids, and polyethoxylates thereof), or a combination thereof. Some lipid-based microspheres may also contain galactose in the shell. Protein-containing microspheres can include relatively small amounts (e.g., less than about 1 percent) of fatty acids (e.g., caprylic acid), amino acids or amino acid derivatives (e.g., N-acyltryptophan), or other formulation aids. The microspheres typically have a mean particle size (i.e., effective mean diameter) in the range of about 1 to about 10 micrometers (preferably about 1 to about 5 micrometers). Preferably, at least about 95 % of the microspheres have a diameter of less than about 10 micrometers. The microspheres preferably are present in the composition at a concentration in the range of about  $10^8$  to about  $10^9$  of the microspheres per milliliter. The compositions described herein preferably are prepared by simple mixing of a microsphere suspension (e.g., as supplied by the manufacturer) with a solution of the plasmid or plasmids that are to be co-administered.

The pharmaceutically active aqueous carrier of the compositions comprises water (e.g., deionized, pyrogen-free water), and preferably includes one or more salts (e.g., sodium chloride, phosphate, citrate, and the like). In some preferred embodiments the aqueous carrier comprises physiological saline (about 0.9 percent NaCl), phosphate buffered saline, and the like. The carrier optionally can include other soluble materials (e.g., dextrose), preservatives, and the like, to provide a solution that is generally sterile, safe, isotonic and compatible with blood. Preferably, the compositions have a physiological pH (e.g., about pH 6.4 to 7.5).

Some preferred microsphere formulations useful in the compositions and methods described herein include the OPTISON brand microspheres (available from GE Healthcare), IMAGENT brand microspheres (developed by Alliance Pharmaceutical), and DEFINITY brand microspheres (available from Lantheus Medical Imaging, Inc.). Preferably, the compositions comprise human serum albumen encapsulated octafluoropropane microspheres, such as OPTISON microspheres.

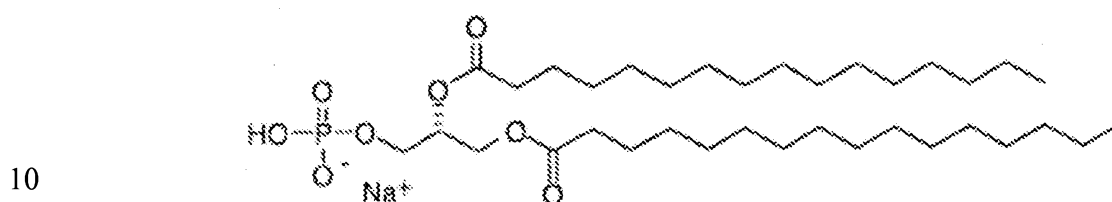
According to the manufacturer, OPTISON microsphere suspensions from GE Healthcare comprise about  $5 \times 10^8$  to about  $8 \times 10^8$  microspheres per mL of suspension. The microspheres comprise perflutren (octafluoropropane) gas bubbles encapsulated within shells of human serum albumin. The microspheres have a mean particle diameter of about 3 to about 4.5  $\mu\text{m}$  with about 95% of the microspheres having a diameter of less than about 10  $\mu\text{m}$ . The microspheres are suspended in a physiological saline solution (about 0.9 percent by weight NaCl in water). The compositions also can include less than about 1 percent caprylic acid, and less than about 1 percent N-acyltryptophan. Each milliliter of OPTISON microspheres reportedly comprises about 10 mg of human serum albumin, about 0.2 to 0.3 mg of perflutren, about 0.2 mg N-acetyltryptophan, and about 0.12 mg caprylic acid in 0.9% aqueous sodium chloride at a pH of about 6.4-7.4. The headspace of the vial containing the suspension is filled with perflutren gas. The manufacturer recommends that the injection rate should not exceed about 1 mL per second (maximum total dose should not exceed about 5 mL in any 10 minute period, and maximum total dose should not exceed about 8.7 mL in any one patient study).

IMAGENT perflorane lipid microsphere composition (trade name previously IMAVIST) is an injectable suspension developed by Alliance Pharmaceutical. The microspheres reportedly comprise perflorane (perfluorohexane) microbubbles encapsulated in a lipid-based shell comprising 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), hydroxyethyl starch and poloxamer (a nonionic triblock copolymer composed of a central hydrophobic chain of polyoxypropylene flanked by two hydrophilic chains of polyoxyethylene). The microspheres are suspended in a phosphate buffered saline solution.

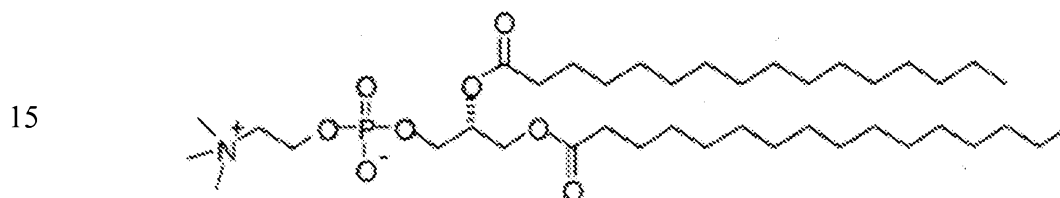
According to manufacturer information, DEFINITY perflutren lipid microspheres are provided as an injectable suspension. The DEFINITY material is supplied as components that upon activation yield perflutren lipid microspheres. The material is supplied in a vial containing a clear, colorless, sterile, non-pyrogenic, hypertonic liquid, which upon activation with the aid of a VIALMIX brand activator, provides a homogeneous, opaque, milky white injectable suspension of perflutren lipid microspheres. The suspension of activated DEFINITY microspheres is administered by intravenous injection. The perflutren lipid microspheres are composed of octafluoropropane encapsulated in an outer lipid shell consisting of (R)-hexadecanoic acid-1-[(phosphonoxy)methyl]-1,2-ethanediyl ester, monosodium salt

(abbreviated DPPA); (R)-4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,4,9-trioxa-4-phosphapentacosan-1-aminium-4-oxide inner salt (abbreviated DPPC); and (R)- $\alpha$ -[6-hydroxy-6-oxido-9-[(1-oxohexadecyl)oxy]5,7,11-trioxa-2-aza-6-phosphahexacos-1-yl]- $\omega$ -methoxypoly(ox-1,2-ethanediyl), monosodium salt (abbreviated MPEG5000 DPPE).

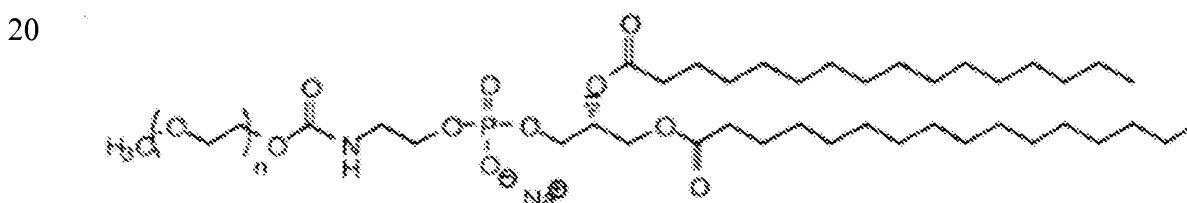
5 DPPA has a molecular weight of 670, empirical formula of  $C_{35}H_{68}O_8PNa$ , and following structural formula:



DPPC has a molecular weight of 734, empirical formula of  $C_{40}H_{80}NO_8P$ , and following structural formula:



MPEG5000 DPPE has an approximate molecular weight of 5750 represented by empirical formula  $C_{265}H_{527}NO_{123}PNa$ , and the following structural formula:



25 Prior to VIALMIX activation, the DEFINITY component vial reportedly contains 6.52 mg/mL octafluoropropane in the headspace. Each mL of the clear liquid reportedly contains 0.75 mg lipid blend (consisting of 0.045 mg DPPA, 0.401 mg DPPC, and 0.304 mg MPEG5000 DPPE), 103.5 mg propylene glycol, 126.2 mg glycerin, 2.34 mg sodium phosphate monobasic

monohydrate, 2.16 mg sodium phosphate dibasic heptahydrate, and 4.87 mg sodium chloride in water (pH is 6.2-6.8). After activating the contents of the vial, each mL of the milky white suspension reportedly contains a maximum of  $1.2 \times 10^{10}$  perflutren lipid microspheres, and about 150  $\mu\text{m/mL}$  (1.1 mg/mL) octafluoropropane. The microsphere mean particle size is about 5 1.1  $\mu\text{m}$  to 3.3  $\mu\text{m}$ , with 98% of the microspheres having a diameter of less than 10  $\mu\text{m}$ .

*Plasmid design.* Plasmids generally comprise a strong viral promoter to drive the *in vivo* transcription and translation of the encoded gene (or complementary DNA, RNA, siRNA, or mDNA) of interest (which is present as an open reading frame). Intron A may can be included to improve mRNA stability and hence increase protein expression. Plasmids also typically 10 include a strong polyadenylation/transcriptional termination signal, such as bovine growth hormone or rabbit beta-globulin polyadenylation sequences.

Because the plasmid provided the genetic material from which the protein of interest is expressed, optimizing vector design for maximal protein expression is desirable. For example, the codon usage can be adjusted to better conform to eukaryotic cells. Another factor to 15 consider is the choice of promoter. Examples of promoters include the simian virus 40 (SV40) promoter, the Rous Sarcoma Virus (RSV) promoter, and the cytomegalovirus (CMV) promoter. In addition, expression rates can sometimes be improved by inclusion of enhancer sequences, adenovirus tripartite leader (TPL) sequences, or modifications to the polyadenylation and transcriptional termination sequences. Non-limiting examples of episomal plasmid vectors 20 suitable for use as vectors for transfection of liver cells include SV40-based vectors, Epstein-Barr virus-based vectors, papilloma virus-based vectors, BK virus-based vectors, and the like, which are well known in the molecular genetics art.

Non limiting examples of episomal vectors suitable for use as non-integrating vectors for transfection of eukaryotic cells (e.g., primary MSC) include simian virus 40-based vectors, 25 Epstein-Barr virus-based vectors, papilloma virus-based vectors, BK virus-based vectors, and the like, which are well known in the molecular genetics art.

In some embodiments, an additional biologically active agent is co-administered along with the plasmid and microspheres. Such additional biologically active agents include, for examples, a drug for treating a condition relating to lipid metabolism or transport, a plasmid 30 encoding a protein other than ABCA1 involved in lipid metabolism of transport, and a plasmid

encoding an siRNA that targets a protein involved in lipid metabolism or transport.

Additionally, or alternatively, the plasmid encoding the active ABCA1 can also encode an a protein other than ABCA1 involved in lipid metabolism of transport, or a siRNA that targets a protein involved in lipid metabolism or transport.

5           Non-limiting examples of drugs for treating a condition relating to lipid metabolism or transport include HMG-CoA inhibitors, such as statins (e.g., atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, and combinations thereof); bile acid inhibitors (e.g., cholestyramine, colestipol, colesevalam, and combinations thereof); fibric acid derivatives (e.g., clofibrate, gemfibrozil, fenofibrate) which  
10       may lower LDL-c and raise HDL-c; and niacin.

          Examples of proteins involved in lipid metabolism or transport include, e.g., ABCA1, ABCG1, apoA1, apoA2, apoE, LXR, NPC1, NPC2, SREBP, CD36, ACAT, SRA1, and HMG-CoA. Such enzymes or siRNA targeting such proteins may be encoded by a plasmid co-administered with the ABCA1 plasmid, or in some cases can be encoded the same plasmid as  
15       the ABCA1.

          Co-administration of a drug or a plasmid encoding a lipid metabolism/transport protein or siRNA can have the advantage of tailoring treatment to the specific condition suffered by the patient, by invoking multiple action sites, multiple metabolic targets, or both. For example, the materials to be co-administered can be selected e.g., to HDL-c and lower LDL-c in patients  
20       where both types of cholesterol are outside the recommended levels, or to raise HDL-c and lower total triglycerides, etc.. In addition, different tissues may be transfected in a given subject, e.g., to target optimal tissues that may be involved in the particular lipid metabolic pathways of interest. For example, one tissue may be transfected to express one protein or siRNA, while a different tissue of the same subject may be transfected to express another  
25       protein or siRNA.

          The following non-limiting examples are provided to illustrate certain features and aspects of the IP-MSC and methods described herein.

**Methods and Procedures.**

Male Sprague-Dawley rats (180-250g) were purchased through Charles River Laboratories, Wilmington, MA. All animal studies performed in an AAALAC, USDA, and OLAW accredited facility. Rats were housed in sterile cages (Alternative Design  
5 Manufacturing & Supply Inc., Siloam Springs, AR) and provided *ad libitum* access to standard commercial feed (Lab Diet; Purina Mills, St. Louis, MO) and water. Animals were maintained on a 12-hour:12-hour light:dark cycle, controlled temperature (approximately 24 °C) and controlled humidity (approximately 40%).

**ApoA1 DNA plasmids.**

10 An apoA1 expression plasmid was constructed by subcloning an 804 bp human apoA1 PCR cDNA product into expression vector pMIR0125 (Mirus Bio Corp, Madison, Wisconsin) containing human apoE hepatic control region (HCR), human ubiquitin C promoter and first intron. The final construct, pMIR0332-HCRUbC- h apoA1 was sequenced and the resulting clone matched the reported human apoA1 sequence. An ABCA1 expression vector was  
15 purchased from Origene (ABCA1 (NM 005502) Human cDNA ORF Clone, Cat. No. RC221861). FIG. 1 provides the amino acid sequence of ABCA1 (SEQ ID NO: 1) encoded in the open reading frame of the vector. FIG. 2 provides the nucleotide sequence of the ABCA1 open reading frame (SEQ ID NO: 2) of the vector, while FIG. 3 provides the nucleotide sequence of the entire vector (SEQ ID NO: 3). FIG. 4 provides a schematic map of the ABCA1  
20 plasmid.

**Infusion method.**

The plasmids (i.e., apoA1 plasmid, ABCA1 plasmid, or a combination of apoA1 and ABCA1 plasmids) were mixed with commercial OPTISON microsphere suspension for injection. *Anesthetic*: Inhalable gas mixture of oxygen and 1.5-3.0% isoflurane. A warming  
25 bed maintained rat body temperature at 37°C. Tail vein injections were performed using a 26 GA 3/4-inch catheter. *Mixtures*: About 1 mL of OPTISON microspheres was mixed with (1) apoA1 DNA plasmid (approximately 8 mg in 1 mL), or (2) ABCA1 plasmid (approximately 7.3 mg in 1 mL), or (3) a combination of apoA1 and ABCA1 plasmids at the same concentrations per mL as used for the individual plasmids.

*Plasmid volume and concentration of DNA.* All plasmids alone or in combination were mixed with OPTISON microspheres for about 15 to about 30 seconds prior to injection with a 3 mL injection syringe and then co-administered or co-infused. The infusion rate was manually performed at a timed rate of about 2 to 3 mL/minute and the total infusion duration was about 50 to about 70 seconds.

#### **Ultrasound equipment and imaging and therapeutic parameters.**

A VIVID I brand imaging system (GE Healthcare Systems, Milwaukee, Wisconsin) equipped with a 3S ultrasound probe was utilized for all liver sonications. All acoustic energy settings remained within FDA guidelines outlined for diagnostic use (ALARA principle). The rat liver was continually visualized using external ultrasound to verify appearance of OPTISON mixture within the liver vasculature and parenchyma. Low mechanical index (MI) ultrasound acoustic energy was used for imaging (e.g., < 0.4 MI) whereas, higher MI (about 1.3 MI or greater) was used for therapy. No surgical abdominal incision was ever performed; external ultrasound was used to visualize the liver. The abdomen was shaved to eliminate surface hair.

The ultrasound parameters consisted of an continuous low mechanical index (MI<0.4) ultrasound exposure for “imaging” followed by a two-second “pulse” for therapeutic effect for a total of 10 “pulses.” A pulse was defined as a relatively higher (MI >1.3) burst of an ultrasound pulse. In sum, the “pulse” length was about 2 seconds with a pulse interval of about 8 seconds for a total of 10 pulses.

#### **Blood samples.**

Three tail vein blood samples (0.5 ml) were collected over 6 days to establish a baseline serum HDL-c for each rat prior to treatment. After treatment with the plasmids in the OPTISON microsphere suspensions, blood samples were collected daily for three days and then after a three day hiatus. All blood samples were collected in glass test tubes containing a lithium heparin anticoagulant. The separated serum samples were analyzed using a clinical lipid panel test strip (PTS #1710 Lipid Panel Test for CARDIOCHEK PA CHOLESTEROL ANALYZER, Polymer Technology Systems, Inc., Indianapolis, Indiana) to quantify HDL values. Graphical data are reported as mean + 1 SEM and statistical significance was determined by a two-sample t-test. The null hypothesis was rejected at  $P < 0.05$  and all statistical analyses were carried out using MINITAB12 (Minitab Inc., State College, PA USA).

**Results.**

FIG. 5 provides a graph of blood HDL-c levels of the treated rats, including the baseline level and levels for three days post-treatment. The selective hepatic transduction of ABCA1 through sonoporation described herein resulted in enhanced blood HDL-c relative to baseline HDL-c concentration. A single sonochemical treatment with an ABCA1 plasmid and sonochemically active microsphere composition in conjunction with sonication of the liver resulted in a 15% increase in HDL-c. A surprising finding in this study was that the ABCA1 plasmid therapy resulted in superior increases in HDL-c relative to treatment with an apoA1 plasmid or the combination of ABCA1 and apoA1 plasmids under the same sonication conditions.

Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

Throughout the specification and the claims that follow, unless the context requires otherwise, the words “comprise” and “include” and variations such as “comprising” and “including” will be understood to imply the inclusion of a stated integer or group of integers, but not the exclusion of any other integer or group of integers.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement of any form of suggestion that such prior art forms part of the common general knowledge.

**THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:**

1. A method of increasing blood HDL-cholesterol levels by transfecting the liver of a subject *in vivo* to express an active form of ATP-binding cassette transporter A1 (ABCA1) in cells of the liver, the method comprising the steps of (a) intravenously co-administering to a subject a plasmid vector encoding the active form of ABCA1, and sonochemically-active microspheres; wherein the vector comprises an expressible open reading frame encoding the active form of ABCA1 and at least one sequence adapted to promote expression of the open reading frame in a mammalian cell; and wherein the sonochemically-active microspheres comprise gas bubbles encapsulated within shells comprising a protein, a lipid, or a combination thereof, the microspheres being disruptable upon exposure to ultrasonic acoustic energy to release the encapsulated gas bubbles;

(b) ultrasonically imaging the liver of the subject to be transfected while the plasmid and microspheres of the composition are circulating through the vasculature of the liver and thereby detecting the presence of the microspheres in the vasculature of the liver; and

(c) while the microspheres are present in the vasculature of the liver, applying pulses of ultrasonic energy to the liver at an acoustical energy level higher than that required for imaging and at a sufficient energy level to disrupt the microspheres and release the gas bubbles therefrom, the pulses of ultrasonic energy and release of gas bubbles thereby temporarily increasing the porosity of cells in the liver to facilitate entry of the plasmid into the cells.

2. The method of claim 1 wherein the microspheres have an average particle size in the range of about 0.5 to about 20 micrometers.

3. The method of claim 1 or 2 wherein the gas bubbles comprise a fluorocarbon gas.

4. The method of any one of claims 1 to 3 wherein the shells comprise human serum albumin.

5. The method of any one of claims 1 to 4 wherein the active form of ABCA1 has the amino acid sequence of SEQ ID NO: 1.
6. The method of any one of claims 1 to 5 wherein the at least one sequence adapted to promote expression of the open reading frame comprises a cytomegalovirus promoter.
7. The method of any one of claims 1 to 6 wherein the plasmid is administered in an aqueous carrier at a concentration in the range of about 0.5 to about 50 milligrams per milliliter.
8. The method of any one of claims 1 to 7 wherein the microspheres are administered in an aqueous carrier at a concentration in the range of about  $10^8$  to about  $10^9$  microspheres per milliliter.
9. The method of any one of claims 1 to 8 wherein the plasmid and the microspheres are administered as a mixture in one aqueous carrier.
10. The method of any one of claims 1 to 8 wherein the plasmid and the microspheres are administered in separate aqueous carriers.
11. The method of any one of claims 1 to 10 wherein an additional biologically active agent is co-administered along with the plasmid and microspheres.
12. The method of claim 11 wherein the additional biologically active agent comprises at least one material selected from the group consisting of (a) a drug for treating a condition relating to lipid metabolism or transport, (b) a plasmid encoding a protein other than ABCA1 involved in lipid metabolism or transport, and (c) a plasmid encoding an siRNA that targets a protein involved in lipid metabolism or transport.

13. A composition comprising a mixture of a plasmid vector encoding an active form of ABCA1 and sonochemically-active microspheres in a pharmaceutically acceptable aqueous carrier; wherein the vector comprises an expressible open reading frame encoding the active form of ABCA1 and at least one sequence adapted to promote expression of the open reading frame in a mammalian cell; and wherein the sonochemically-active microspheres comprise gas bubbles encapsulated within shells comprising a protein, a lipid, or a combination thereof, the microspheres being disruptable upon exposure to ultrasonic acoustic energy to release the encapsulated gas bubbles; when used in the method of any one of claims 1 to 12.

14. The composition of claim 13 wherein the open reading frame has the nucleotide sequence of SEQ ID NO: 2.

15. The composition of claim 13 or 14 further comprising at least one material selected from the group consisting of (a) a drug for treating a condition relating to lipid metabolism or transport, (b) a plasmid encoding an enzyme other than ABCA1 involved in lipid metabolism or transport, and (c) a plasmid encoding an siRNA that targets an enzyme involved in lipid metabolism or transport.

16. The composition of claim 13 or 14 wherein the plasmid encoding ABCA1 also encodes at least one material selected from the group consisting of (a) a protein other than ABCA1 involved in lipid metabolism or transport, and (b) an siRNA that targets a protein involved in lipid metabolism or transport.

17. The use of a plasmid vector encoding an active form of ABCA1 and sonochemically-active microspheres in a pharmaceutically acceptable aqueous carrier in the manufacture of a medicament for increasing blood HDL-cholesterol levels in a subject.

18. The use of claim 17 wherein the subject has atherosclerosis.

(SEQ ID NO: 1):

MACWPQLRLLLWKNLTFRRRQTCQLLLEVAWPLFIFLILISVRLSYPPYEQHECHFPNKA  
MPSAGTLPWVQGIICNANNPCFRYPTPGEAPGVVGNFNKSIVARLFS DARRLLLYSQKDT  
SMKDMRKVLR TLQQIKKSSSNLKLQDFLVDNETFSGFLYHNLSLPKSTVDKMLRADVILH  
KVFLQGYQLHLTSLCNGSKSEEMIQLGDQEVSEL CGLPREKLAAAERVLR SNMDILKPIL  
RTLNSTSPFPSKELAEATKTLHSLGTLAQELFSMRSWSDMRQEV MFLT NVN SSSSSTQI  
YQAVSRIVCGHPEGGLKIKSLN WYEDN NYKALFGGNGTEEDAETFYDNSTTPYCNDLMK  
NLESSPLSRIIWKALKPLLVGKILYTPDTPATRQVMAEVNKT FQELAVFHDLEGMWEELS  
PKIWTFMENSQEMDLVRMLLDSRDNDHFWEQQLDGLD WTAQDIVAFLAKHPEDVQSSNGS  
VYTWREAFNETNQAIRTISR FMECVNLNKLEPIATEVWLINKSMELLDERKFWAGIVFTG  
ITPGSIELPHHVKYKIRMDIDNVERTNKIKDGYWDPGPRADPFEDMRYVWGGFAYLQDVV  
EQAIRVLTGT EKKTGVMQMPYPCYVDDIFLRVMSRSMPLFMTLAWIYSVAVIKGI V  
YEKEARLKETMRIMGLDNSILWFSWFISSLIPLLVSAGLLVVILKLG NLLPYSDPSVVFV  
FLSVFAVVTILQCFLISTLFSRANLAAACGGIYFTLYLPYVLCVAWQDYVGF TLKIFAS  
LLSPVAFGFGCEYFALFEEQIGVQWDNLFESPVEEDGFNL TTSVSMMLFDTFLYGVMTW  
YIEAVFPGQYGI PRPWYFPCTKSYWFG EESDEKSHPGSNQKR ISEICMEEEP THLKL GVS  
IQNLVKVYRDGMKVAVDGLALNFYEGQITSFLGHNGAGKTTTMSILTGLFPPTSGTAYIL  
GKDIRSEMSTIRQNLGVC PQHNVLFDMLTVEEHIWFYARLKGLSEKHVKAEME QMALDVG  
LPSSK LKSKTSQLSGGMQRKLSVALAFVGGSKVVI LDEPTAGVDPYSRRGIWELL LKYRQ  
GRTIILSTHMD EADVLGDRIAIISHGKLCCVGS SFLFNQLGTGY YLTLVKKDV ESSL S  
SCRNSSSTVSYLKKEDSVSQSSSDAGLGS DHESDTLTIDVSAISNLIRKHVSEARLVEDI  
GHELT YVLPYEAAKEGAFVELFHEIDDR LSDLGISSYGISETTLEE IFLKVAEESGVD AE  
TSDGTL PARRNRRAFGDKQ SCLRPFTEDDAADPNDS DDPESRETDLLSGMDGKGSYQVK  
GWKLTQQQFVALLWKRLLIARRSRKGF FAQIVLPAVFVCI ALVFSLIVPPFGKYPSLELQ  
PWMYNEQYTFVSN DAPEDTGTLELLNALT KDPGF GTRCMEGNPI P DTPCQAGEE EWTTAP  
VPQTIMDLFQNGNWTM QNPS PACQCSSDKIKKMLPVC PPGAGGLPPPQRKQNTAD I LQDL  
TGRNISDYLVKTYVQII AKSLKNKIWVNEFRYGGFSLGVSNTQALPPSQEVNDAIKQMKK  
HLKLAKDSSADRFLNSLGRFMTGLDTKNNVKVWFNKGWHAISSFLN VINNAILRANLQK  
GENPSHYGITAFNHPLNLT KQQQLSEVALMTTSVDVLV SICVIFAMSFVPASFVFLIQER  
VSKAKHLQFISGVKPV IYWLSNFVWDMCNYVVPATLVIIIFICFQQKSYVSSTNLPVLAL  
LLLLYGWSITPLMYPASFVFKIPSTAYVVLTSVNLF IGINGSVATFVLELFTDNKLNNIN  
DILKSVFLIFPHFCLGRGLIDMVKNQAMADALERFGENRFV S PLSWDLVGRNLFAMAVEG  
VVFFLITVLIQYRFFIRPRPVNAKLSPLNDEDEDVRRERQRILDGGGQNDILEIKELTKI  
YRRKRKPAVDRICVGI PPGECFGLLGVNGAGKSSTFKMLTGDTTVTRGD AFLNKNSILSN  
IHEVHQNMGYCPQFDAITELLTGREHVEFFALLRGVPEKEVGVGEWAIRKLG LVKYGEK  
YAGNYSGGNKRKLS TAMALIGGPPVFLDEPTTGMDPKARRFLWNCALSVVKEGRSVVLT  
SHSMEECEALCTRMAIMVNGRFRCLG SVQH LKNRFGDGYTIVVRIAGSNPDLKPVQDFFG  
LAFPGSVLKEKHRNMLQYQLPSSLSLARI F S ILSQSKRRLHIEDYSVSQT TLDQV FVNF  
AKDQSDDDHLKDL SLHKNQTVVDVAVLTSFLQDEKVKESYV

FIG. 1

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(SEQ ID NO: 2):

ATGGCTTGTGGCCTCAGCTGAGGTTGCTGCTGTGGAAGAACCTCACTTTCAGAAGAAGACAAAC  
ATGTCAGCTGCTGCTGGAAGTGGCCTGGCCTCTATTTATCTTCCTGATCCTGATCTCTGTTTCGGC  
TGAGCTACCCACCCTATGAACAACATGAATGCCATTTTCCAAATAAAGCCATGCCCTCTGCAGGA  
ACACTTCCTTGGGTTTCAGGGGATTATCTGTAATGCCAACAACCCCTGTTTCCGTTACCCGACTCC  
TGGGGAGGCTCCCGGAGTTGTTGGAACTTTAACAAATCCATTGTGGCTCGCCTGTTCTCAGATG  
CTCGGAGGCTTCTTTTATACAGCCAGAAAGACACCAGCATGAAGGACATGCGCAAAGTTCTGAGA  
ACATTACAGCAGATCAAGAAATCCAGCTCAAACCTGAAGCTTCAAGATTTCCCTGGTGGACAATGA  
AACCTTCTCTGGGTTCCCTGTATCACAACCTCTCTCTCCCAAAGTCTACTGTGGACAAGATGCTGA  
GGGCTGATGTCATTCTCCACAAGGTATTTTTGCAAGGCTACCAGTTACATTTGACAAGTCTGTGC  
AATGGATCAAATCAGAAGAGATGATTCAACTTGGTGACCAAGAAGTTTCTGAGCTTTGTGGCCT  
ACCAAGGGAGAACTGGCTGCAGCAGAGCGAGTACTTCGTTCCAACATGGACATCCTGAAGCCAA  
TCCTGAGAACACTAAACTCTACATCTCCCTTCCCGAGCAAGGAGCTGGCTGAAGCCACAAAAACA  
TTGCTGCATAGTCTTGGGACTCTGGCCCAGGAGCTGTTTCAGCATGAGAAGCTGGAGTGACATGCG  
ACAGGAGGTGATGTTTCTGACCAATGTGAACAGCTCCAGCTCCTCCACCCAAATCTACCAGGCTG  
TGTCTCGTATTGTCTGCGGGCATCCCAGGGGAGGGGGGCTGAAGATCAAGTCTCTCAACTGGTAT  
GAGGACAACAACACTACAAAGCCCTCTTTGGAGGCAATGGCACTGAGGAAGATGCTGAAACCTTCTA  
TGACAACCTCTACAACCTCTTACTGCAATGATTTGATGAAGAATTTGGAGTCTAGTCCTCTTTCCC  
GCATTATCTGGAAAGCTCTGAAGCCGCTGCTCGTTGGGAAGATCCTGTATACACCTGACACTCCA  
GCCACAAGGCAGGTCATGGCTGAGGTGAACAAGACCTTCCAGGAACTGGCTGTGTTCCATGATCT  
GGAAGGCATGTGGGAGGAACTCAGCCCCAAGATCTGGACCTTCATGGAGAACAGCCAAGAAATGG  
ACCTTGTCCGGATGCTGTTGGACAGCAGGGACAATGACCACTTTTGGGAACAGCAGTTGGATGGC  
TTAGATTGGACAGCCCAAGACATCGTGGCGTTTTTTGGCCAAGCACCCAGAGGATGTCCAGTCCAG  
TAATGGTTCTGTGTACACCTGGAGAGAAGCTTTCAACGAGACTAACCAGGCAATCCGGACCATAT  
CTCGTTTCATGGAGTGTGTCAACCTGAACAAGCTAGAACCCATAGCAACAGAAGTCTGGCTCATC  
AACAAAGTCCATGGAGCTGCTGGATGAGAGGAAGTTCTGGGCTGGTATTGTGTTCACTGGAATTAC  
TCCAGGCAGCATTGAGCTGCCCCATCATGTCAAGTACAAGATCCGAATGGACATTGACAATGTGG  
AGAGGACAAATAAAATCAAGGATGGGTACTGGGACCCTGGTCTCAGAGCTGACCCCTTTGAGGAC  
ATGCGGTACGTCTGGGGGGGCTTCGCCTACTTGCAGGATGTGGTGGAGCAGGCAATCATCAGGGT  
GCTGACGGGCACCGAGAAGAAAATGGTGTCTATATGCAACAGATGCCCTATCCCTGTTACGTTG  
ATGACATCTTTCTGCGGGTGTGAGCCGGTCAATGCCCTCTTCATGACGCTGGCCTGGATTTAC  
TCAGTGGCTGTGATCATCAAGGGCATCGTGTATGAGAAGGAGGCACGGCTGAAAGAGACCATGCG  
GATCATGGGCCTGGACAACAGCATCCTCTGGTTTAGCTGGTTCATTAGTAGCCTCATTCCCTCTTC  
TTGTGAGCGCTGGCCTGCTAGTGGTCACTCCTGAAGTTAGGAAACCTGCTGCCCTACAGTGATCCC  
AGCGTGGTGTGTTGTTCTTCCCTGTCCGTGTTTGGCTGTGGTGACAATCCTGCAGTGCTTCCCTGATTAG  
CACACTCTTCTCCAGAGCCAACCTGGCAGCAGCCTGTGGGGGCATCATCTACTTCACGCTGTACC  
TGCCCTACGTCTGTGTGTGGCATGGCAGGACTACGTGGGCTTCACACTCAAGATCTTCGCTAGC  
CTGCTGTCTCCTGTGGCTTTTGGGTTTGGCTGTGAGTACTTTGCCCTTTTTGAGGAGCAGGGCAT  
TGGAGTGCAGTGGGACAACCTGTTTGGAGAGTCCCTGTGGAGGAAGATGGCTTCAATCTCACCCTT

FIG. 2

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CGGTCTCCATGATGCTGTTTTGACACCTTCCTCTATGGGGTGATGACCTGGTACATTGAGGCTGTC  
TTTCCAGGCCAGTACGGAATTCCCAGGCCCTGGTATTTTCCTTGCACCAAGTCCTACTGGTTTTGG  
CGAGGAAAGTGATGAGAAGAGCCACCCTGGTTCCAACCAGAAGAGAATATCAGAAATCTGCATGG  
AGGAGGAACCCACCCACTTGAAGCTGGGGCTGTCCATTCAGAACCTGGTAAAAGTCTACCGAGAT  
GGGATGAAGGTGGCTGTTCGATGGCCTGGCACTGAATTTTTTATGAGGGCCAGATCACCTCCTTCCT  
GGGCCACAATGGAGCGGGGAAGACGACCACCATGTCAATCCTGACCGGGTTGTTCCCCCGACCT  
CGGGCACCCGCTACATCCTGGGAAAAGACATTTCGCTCTGAGATGAGCACCATCCGGCAGAACCTG  
GGGTCTGTCCCAGCATAACGTGCTGTTTTGACATGCTGACTGTCTGAAGAACACATCTGGTTCTA  
TGCCCGCTTGAAGGGCTCTCTGAGAAGCACGTGAAGCGGAGATGGAGCAGATGGCCCTGGATG  
TTGGTTTTGCCATCAAGCAAGCTGAAAAGCAAAACAAGCCAGCTGTCAGGTGGAATGCAGAGAAAG  
CTATCTGTGGCCTTGGCCTTTGTCTGGGGGATCTAAGGTTGTCAATTCTGGATGAACCCACAGCTGG  
TGTGGACCCTTACTCCCGCAGGGGAATATGGGAGCTGCTGCTGAAATACCGACAAGGCCGCACCA  
TTATTCTCTCTACACACCACATGGATGAAGCGGACGTCCTGGGGGACAGGATTGCCATCATCTCC  
CATGGGAAGCTGTGCTGTGTGGGCTCCTCCCTGTTTTCTGAAGAACCAGCTGGGAACAGGCTACTA  
CCTGACCTTGGTCAAGAAAGATGTGGAATCCTCCCTCAGTTCCTGCAGAAACAGTAGTAGCACTG  
TGTCATACCTGAAAAAGGAGGACAGTGTTCCTCAGAGCAGTTCTGATGCTGGCCTGGGCAGCGAC  
CATGAGAGTGACACGCTGACCATCGATGTCTCTGCTATCTCCAACCTCATCAGGAAGCATGTGTC  
TGAAGCCCGGCTGGTGGAAAGACATAGGGCATGAGCTGACCTATGTGCTGCCATATGAAGCTGCTA  
AGGAGGGAGCCTTTGTGGAACCTTTTCATGAGATTGATGACCGGCTCTCAGACCTGGGCATTTCT  
AGTTATGGCATCTCAGAGACGACCCTGGAAGAAATATTCTCAAGGTGGCCGAAGAGAGTGGGGT  
GGATGCTGAGACCTCAGATGGTACCTTGCCAGCAAGACGAAACAGGCGGGCCTTCGGGGACAAGC  
AGAGCTGTCTTCGCCCGTTCCTACTGAAGATGATGCTGCTGATCCAAATGATTCTGACATAGACCCA  
GAATCCAGAGAGACAGACTTGCTCAGTGGGATGGATGGCAAAGGGTCTTACCAGGTGAAAGGCTG  
GAAACTTACACAGCAACAGTTTTGTGGCCCTTTTGTGGAAGAGACTGCTAATTGCCAGACGGAGTC  
GGAAAGGATTTTTTGTCTCAGATTGTCTTGCCAGCTGTGTTTTGTCTGCATTGCCCTTGTGTTTCTCAGC  
CTGATCGTGGCACCCTTTGGCAAGTACCCAGCCTGGAACCTCAGCCCTGGATGTACAACGAACA  
GTACACATTTGTCTCAGCAATGATGCTCCTGAGGACACGGGAACCCTGGAACCTCTTAAACGCCCTCA  
CCAAAGACCCTGGCTTCGGGACCCGCTGTATGGAAGGAAACCCAATCCCAGACACGCCCTGCCAG  
GCAGGGGAGGAAGAGTGGACCACTGCCCCAGTTCCCCAGACCATCATGGACCTCTTCCAGAATGG  
GAACTGGACAATGCAGAACCCTTCACCTGCATGCCAGTGTAGCAGCGACAAAATCAAGAAGATGC  
TGCCCTGTGTGTCCCCAGGGGCAGGGGGCTGCCTCCTCCACAAAGAAAACAAAACACTGCAGAT  
ATCCTTCAGGACCTGACAGGAAGAAACATTTTCGGATTATCTGGTGAAGACGTATGTGCAGATCAT  
AGCCAAAAGCTTAAAGAACAAGATCTGGGTGAATGAGTTTAGGTATGGCGGCTTTTCCCTGGGTG  
TCAGTAATACTCAAGCACTTCCCTCCGAGTCAAGAAGTTAATGATGCCATCAAACAAATGAAGAAA  
CACCTAAAGCTGGCCAAGGACAGTTCTGCAGATCGATTTCTCAACAGCTTGGGAAGATTTATGAC  
AGGACTGGACACCAAAAATAATGTCAAGGTGTGGTTCAATAACAAGGGCTGGCATGCAATCAGCT  
CTTTCCCTGAATGTCATCAACAATGCCATTTCTCCGGGCCAACCTGCAAAAGGGAGAGAACCCTAGC  
CATTATGGAATTAAGTCTTTCAATCATCCCCTGAATCTCACCAGCAGCAGCTCTCAGAGGTGGC  
TCTGATGACCACATCAGTGGATGTCCTTGTGTCCATCTGTGTCATCTTTGCAATGTCCTTTCGTCC  
CAGCCAGCTTTGTCTGATTCCTGATCCAGGAGCGGGTCAGCAAAGCAAACACCTGCAGTTCATC  
AGTGGAGTGAAGCCTGTCATCTACTGGCTCTCTAATTTTGTCTGGGATATGTGCAATTACGTTGT

**FIG. 2 (cont.)**

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CCCTGCCACACTGGTCATTATCATCTTCATCTGCTTCCAGCAGAAGTCCTATGTGTCCTCCACCA  
ATCTGCCTGTGCTAGCCCTTCTACTTTTGCTGTATGGGTGGTCAATCACACCTCTCATGTACCCA  
GCCTCCTTTGTGTTCAAGATCCCCAGCACAGCCTATGTGGTGCTCACCAGCGTGAACCTCTTCAT  
TGGCATTAAATGGCAGCGTGGCCACCTTTGTGCTGGAGCTGTTCCACCGACAATAAGCTGAATAATA  
TCAATGATATCCTGAAGTCCGTGTTCTTGATCTTCCCACATTTTTGCCTGGGACGAGGGGCTCATC  
GACATGGTGA AAAACCAGGCAATGGCTGATGCCCTGGAAAGGTTTGGGGAGAATCGCTTTGTGTC  
ACCATTATCTTGGGACTTGGTGGGACGAAACCTCTTCGCCATGGCCGTGGAAGGGGTGGTGTCT  
TCCTCATTACTGTTCTGATCCAGTACAGATTCTTCATCAGGCCCAGACCTGTAAATGCAAAGCTA  
TCTCCTCTGAATGATGAAGATGAAGATGTGAGGCGGGAAAGACAGAGAATTCTTGATGGTGGAGG  
CCAGAATGACATCTTAGAAATCAAGGAGTTGACGAAGATATATAGAAGGAAGCGGAAGCCTGCTG  
TTGACAGGATTTGCGTGGGCATTCTCCTGGTGAGTGCTTTGGGCTCCTGGGAGTTAATGGGGCT  
GGAAAATCATCAACTTTCAAGATGTTAACAGGAGATACCACTGTTACCAGAGGAGATGCTTTCT  
TAACAAAATAGTATCTTATCAAACATCCATGAAGTACATCAGAACATGGGCTACTGCCCTCAGT  
TTGATGCCATCACAGAGCTGTTGACTGGGAGAGAACACGTGGAGTTCTTTGCCCTTTTGAGAGGA  
GTCCCAGAGAAAGAAGTTGGCAAGGTTGGTGAGTGGGCGATTCGGAACTGGGCCTCGTGAAGTA  
TGGAGAAAAATATGCTGGTAACTATAGTGGAGGCAACAAACGCAAGCTCTCTACAGCCATGGCTT  
TGATCGGCGGGCCTCCTGTGGTGTCTGGATGAACCCACCACAGGCATGGATCCCAAAGCCCGG  
CGGTTCTTGTGGAATTGTGCCCTAAGTGTGTCAAGGAGGGGAGATCAGTAGTGCTTACATCTCA  
TAGTATGGAAGAATGTGAAGCTCTTTGCACTAGGATGGCAATCATGGTCAATGGAAGGTTGAGG  
GCCTTGGCAGTGTCCAGCATCTAAAAAATAGGTTTGGAGATGGTTATACAATAGTTGTACGAATA  
GCAGGGTCCAACCCGGACCTGAAGCCTGTCCAGGATTTCTTTGGACTTGCATTTCTGGAAGTGT  
TCTAAAAGAGAAACACCGGAACATGCTACAATAACCAGCTTCCATCTTCATTATCTTCTCTGGCCA  
GGATATTCAGCATCCTCTCCCAGAGCAAAAAGCGACTCCACATAGAAGACTACTCTGTTTCTCAG  
ACAACACTTGACCAAGTATTTGTGAACTTTGCCAAGGACCAAAGTGATGATGACCACTTAAAAGA  
CCTCTCATTACACAAAACCAGACAGTAGTGGACGTTGCAGTTCTCACATCTTTTCTACAGGATG  
AGAAAGTGAAAGAAAGCTATGTA

**FIG. 2 (cont.)**

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(SEQ ID NO: 3):

AACAAAATATTAACGCTTACAATTTCCATTTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGGCGA  
TCGGTGCGGGCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTGCAAGGCGATTAAG  
TTGGGTAACGCCAGGGTTTTCCAGTCACGACGTTGTAAAACGACGGCCAGTGCCAAGCTGATCT  
ATACATTGAATCAATATTGGCAATTAGCCATATTAGTCATTGGTTATATAGCATAAATCAATATT  
GGCTATTGGCCATTGCATACGTTGTATCTATATCATAAATATGTACATTTATATTGGCTCATGTCC  
AATATGACCGCCATGTTGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCAT  
TAGTTCATAGCCCATATATGGAGTTCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGA  
CCGCCAACGACCCCCGCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGG  
GACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAG  
TGTATCATATGCCAAGTCCGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTAT  
GCCAGTACATGACCTTACGGGACTTTCCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTAT  
TACCATGGTGATGCGGTTTTGGCAGTACACCAATGGGCGTGGATAGCGGTTTACTCACGGGGAT  
TTCCAAGTCTCCACCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAATCAACGGGACTTT  
CCAAAATGTCGTAATAACCCCGCCCCGTTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGT  
CTATATAAGCAGAGCTCGTTTTAGTGAACCGTCAGAATTTTGTAAATACGACTCACTATAGGGCGGC  
CGGGAATTCGTCGACTGGATCCGGTACCGAGGAGATCTGCCGCCGCGATCGCCATGGCTTGTTGG  
CCTCAGCTGAGGTTGCTGCTGTGGAAGAACCTCACTTTCAGAAGAAGACAAACATGTCAGCTGCT  
GCTGGAAGTGGCCTGGCCTCTATTTATCTTCCTGATCCTGATCTCTGTTTCGGCTGAGCTACCCAC  
CCTATGAACAACATGAATGCCATTTTCCAAATAAAGCCATGCCCTCTGCAGGAACACTTCCCTGG  
GTTTCAGGGGATTATCTGTAATGCCAACAACCCCTGTTTCCGTTACCCGACTCCTGGGGAGGCTCC  
CGGAGTTGTTGGAACTTTAACAATCCATTGTGGCTCGCCTGTTCTCAGATGCTCGGAGGCTTC  
TTTTATACAGCCAGAAAGACACCAGCATGAAGGACATGCGCAAAGTTCTGAGAACATTACAGCAG  
ATCAAGAAATCCAGCTCAAACCTTGAAGCTTCAAGATTTCTGGTGGACAATGAAACCTTCTCTGG  
GTTCTGTATCACAACCTCTCTCTCCCAAAGTCTACTGTGGACAAGATGCTGAGGGCTGATGTCA  
TTCTCCACAAGGTATTTTTGCAAGGCTACCAGTTACATTTGACAAGTCTGTGCAATGGATCAAAA  
TCAGAAGAGATGATTCAACTTGGTGACCAAGAAGTTTCTGAGCTTTGTGGCCTACCAAGGGAGAA  
ACTGGCTGCAGCAGAGCGAGTACTTCGTTCCAACATGGACATCCTGAAGCCAATCCTGAGAACAC  
TAAACTCTACATCTCCCTTCCCGAGCAAGGAGCTGGCTGAAGCCACAAAACATTGCTGCATAGT  
CTTGGGACTCTGGCCAGGAGCTGTTTCAGCATGAGAAGCTGGAGTGACATGCGACAGGAGGTGAT  
GTTTCTGACCAATGTGAACAGCTCCAGCTCCTCCACCCAAATCTACCAGGCTGTGTCTCGTATTG  
TCTGCGGGCATCCCGAGGGAGGGGGGCTGAAGATCAAGTCTCTCAACTGGTATGAGGACAACAAC  
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AACTCCTTACTGCAATGATTTGATGAAGAATTTGGAGTCTAGTCCTCTTTCCCGCATTATCTGGA  
AAGCTCTGAAGCCGCTGCTCGTTGGGAAGATCCTGTATACACCTGACACTCCAGCCACAAGGCAG  
GTCATGGCTGAGGTGAACAAGACCTTCCAGGAACTGGCTGTGTTCCATGATCTGGAAGGCATGTG  
GGAGAACTCAGCCCCAAGATCTGGACCTTCATGGAGAACAGCCAAGAAATGGACCTTGTCCGGA

FIG. 3

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TGCTGTTGGACAGCAGGGACAATGACCACTTTTGGGAACAGCAGTTGGATGGCTTAGATTGGACA  
GCCCAAGACATCGTGGCGTTTTTGGCCAAGCACCCAGAGGATGTCCAGTCCAGTAATGGTTCTGT  
GTACACCTGGAGAGAAGCTTTCAACGAGACTAACCAGGCAATCCGGACCATATCTCGCTTCATGG  
AGTGTGTCAACCTGAACAAGCTAGAACCATAGCAACAGAAGTCTGGCTCATCAACAAGTCCATG  
GAGCTGCTGGATGAGAGGAAGTTCTGGGCTGGTATTGTGTTCACTGGAATTACTCCAGGCAGCAT  
TGAGCTGCCCCATCATGTCAAGTACAAGATCCGAATGGACATTGACAATGTGGAGAGGACAAATA  
AAATCAAGGATGGGTACTGGGACCCTGGTCCTCGAGCTGACCCCTTTGAGGACATGCGGTACGTC  
TGGGGGGGCTTCGCCTACTTGCAGGATGTGGTGGAGCAGGCAATCATCAGGGTGTGACGGGCAC  
CGAGAAGAAAACCTGGTGTCTATATGCAACAGATGCCCTATCCCTGTTACGTTGATGACATCTTTC  
TGCGGGTGATGAGCCGGTCAATGCCCTCTTCATGACGCTGGCCTGGATTTACTCAGTGGCTGTG  
ATCATCAAGGGCATCGTGTATGAGAAGGAGGCACGGCTGAAAGAGACCATGCGGATCATGGGCCT  
GGACAACAGCATCCTCTGGTTTTAGCTGGTTCATTAGTAGCCTCATTCCTCTTCTGTGAGCGCTG  
GCCTGCTAGTGGTCATCCTGAAGTTAGGAAACCTGCTGCCCTACAGTGATCCCAGCGTGGTGT  
GTCTTCCTGTCCGTGTTTGTGTGGTGAACAATCCTGCAGTGCTTCCTGATTAGCACACTCTTCTC  
CAGAGCCAACCTGGCAGCAGCCTGTGGGGGCATCATCTACTTCACGCTGTACCTGCCCTACGTCC  
TGTGTGTGGCATGGCAGGACTACGTGGGCTTCACACTCAAGATCTTCGCTAGCCTGCTGTCTCCT  
GTGGCTTTTGGGTTTGGCTGTGAGTACTTTGCCCTTTTGGAGGAGCAGGGCATTGGAGTGCAGTG  
GGACAACCTGTTTGGAGTCCCTGTGGAGGAAGATGGCTTCAATCTCACCCTTCGGTCTCCATGA  
TGCTGTTTGGACACCTTCTCTATGGGGTGATGACCTGGTACATTGAGGCTGTCTTCCAGGCCAG  
TACGGAATCCCAGGCCCTGGTATTTTCCCTTGCACCAAGTCCACTGGTTTTGGCGAGGAAAGTGA  
TGAGAAGAGCCACCCTGGTTCCAACCAGAAGAGAATATCAGAAATCTGCATGGAGGAGGAACCCA  
CCCCTTGAAGCTGGGCGTGTCCATTCAGAACCCTGGTAAAAGTCTACCGAGATGGGATGAAGGTG  
GCTGTGATGGCTGGCACTGAATTTTATGAGGGCCAGATCACCTCCTTCCCTGGGCCACAATGG  
AGCGGGGAAGACGACCACCATGTCAATCCTGACCGGGTGTGTTCCCCCGACCTCGGGCACCGCCT  
ACATCCTGGGAAAAGACATTCGCTCTGAGATGAGCACCATCCGGCAGAACCCTGGGGTCTGTCCC  
CAGCATAACGTGCTGTTTGGACATGCTGACTGTGGAAGAACACATCTGGTTCTATGCCCCTGAA  
AGGGCTCTCTGAGAAGCACGTGAAGGCGGAGATGGAGCAGATGGCCCTGGATGTTGGTTTTGCCAT  
CAAGCAAGCTGAAAAGCAAAACAAGCCAGCTGTCAGGTGGAATGCAGAGAAAGCTATCTGTGGCC  
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CTCCCGCAGGGGAATATGGGAGCTGCTGCTGAAATACCGACAAGGCCGACCATTTATTCTCTCTA  
CACACCACATGGATGAAGCGGACGTCTGGGGGACAGGATTGCCATCATCTCCCATGGGAAGCTG  
TGCTGTGTGGGCTCCTCCCTGTTTCTGAAGAACCAGCTGGGAACAGGCTACTACCTGACCTTGGT  
CAAGAAAGATGTGGAATCCTCCCTCAGTTCCTGCAGAAACAGTAGTAGCACTGTGTCATACCTGA  
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ACGCTGACCATCGATGTCTCTGCTATCTCCAACCTCATCAGGAAGCATGTGTCTGAAGCCCAGCT  
GGTGAAGACATAGGGCATGAGCTGACCTATGTGCTGCCATATGAAGCTGCTAAGGAGGGAGCCT  
TTGTGGAACCTTTTCATGAGATTGATGACCGGCTCTCAGACCTGGGCATTTCTAGTTATGGCATC  
TCAGAGACGACCCTGGAAGAAATATTCCTCAAGGTGGCCGAAGAGAGTGGGGTGGATGCTGAGAC  
CTCAGATGGTACCTTGCCAGCAAGACGAAACAGGCGGGCCTTCGGGGACAAGCAGAGCTGTCTTC

**FIG. 3 (cont.)**

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GCCCGTTCACTGAAGATGATGCTGCTGATCCAAATGATTCTGACATAGACCCAGAATCCAGAGAG  
ACAGACTTGCTCAGTGGGATGGATGGCAAAGGGTCCTACCAGGTGAAAGGCTGGAAACTTACACA  
GCAACAGTTTGTGGCCCTTTTGTGGAAGAGACTGCTAATTGCCAGACGGAGTCGGAAAGGATTTT  
TTGCTCAGATTGTCTTGCCAGCTGTGTTTGTCTGCATTGCCCTTGTGTTACAGCCTGATCGTGCCA  
CCCTTTGGCAAGTACCCCAGCCTGGAACCTCAGCCCTGGATGTACAACGAACAGTACACATTTGT  
CAGCAATGATGCTCCTGAGGACACGGGAACCCTGGAACCTCTTAAACGCCCTCACC AAAGACCCTG  
GCTTCGGGACCCGCTGTATGGAAGGAAACCAATCCCAGACACGCCCTGCCAGGCAGGGGAGGAA  
GAGTGGACCACTGCCCCAGTTCCCCAGACCATCATGGACCTCTTCCAGAATGGGAACTGGACAAT  
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CCCCAGGGGCAGGGGGGCTGCCTCCTCCACAAAGAAAACAAAACACTGCAGATATCCTTCAGGAC  
CTGACAGGAAGAAACATTTTCGGATTATCTGGTGAAGACGTATGTGCAGATCATAGCCAAAAGCTT  
AAAGAACAAGATCTGGGTGAATGAGTTTAGGTATGGCGGCTTTTCCCTGGGTGTCAGTAATACTC  
AAGCACTTCCTCCGAGTCAAGAAGTTAATGATGCCATCAAACAAATGAAGAAACACCTAAAGCTG  
GCCAAGGACAGTTCTGCAGATCGATTTCTCAACAGCTTGGGAAGATTTATGACAGGACTGGACAC  
CAAAAATAATGTCAAGGTGTGGTTC AATAACAAGGGCTGGCATGCAATCAGCTCTTTCCTGAATG  
TCATCAACAATGCCATTTCTCCGGGCCAACCTGCAAAAGGGAGAGAACCCTAGCCATTATGGAATT  
ACTGCTTTCAATCATCCCCTGAATCTCACCAAGCAGCAGCTCTCAGAGGTGGCTCTGATGACCAC  
ATCAGTGGATGTCTTGTGTCCATCTGTGTATCTTTGCAATGTCTTCCGTCCCAGCCAGCTTTG  
TCGTATTCTTGATCCAGGAGCGGGT CAGCAAAGCAAACACCTGCAGTTTATCAGTGGAGTGAAG  
CCTGTATCTACTGGCTCTCTAATTTTGTCTGGGATATGTGCAATTACGTTGTCCCTGCCACACT  
GGTCATTATCATCTTCATCTGCTTCCAGCAGAAGTCTATGTGTCTCCACCAATCTGCCTGTGC  
TAGCCCTTCTACTTTTGTGTATGGGTGGTCAATCACACCTCTCATGTACCCAGCCTCCTTTGTG  
TTCAAGATCCCCAGCACAGCCTATGTGGTGCTCACCAGCGTGAACCTCTTCATTGGCATT AATGG  
CAGCGTGGCCACCTTTGTGCTGGAGCTGTT CACCGACAATAAGCTGAATAATATCAATGATATCC  
TGAAGTCCGTGTTCTTGATCTTCCCACATTTTGCCTGGGACGAGGGCTCATCGACATGGTGAAA  
AACCAGGCAATGGCTGATGCCCTGGAAAGGTTTGGGGAGAATCGCTTTGTGTCCACCATTATCTTG  
GGACTTGGTGGGACGAAACCTCTTCGCCATGGCCGTGGAAGGGGTGGTGTCTTCTCATTACTG  
TTCTGATCCAGTACAGATTCTTCATCAGGCCCAGACCTGTAAATGCAAAGCTATCTCCTCTGAAT  
GATGAAGATGAAGATGTGAGGCGGGAAAGACAGAGAATCTTGATGGTGGAGGCCAGAATGACAT  
CTTAGAAATCAAGGAGTTGACGAAGATATATAGAAGGAAGCGGAAGCCTGCTGTTGACAGGATTT  
GCGTGGGCATTCCTCCTGGTGAGTGCTTTGGGCTCCTGGGAGTTAATGGGGCTGGAAAATCATCA  
ACTTTCAAGATGTTAACAGGAGATAACCACTGTTACCAGAGGAGATGCTTTTCTTAAACAAAATAG  
TATCTTATCAAACATCCATGAAGTACATCAGAACATGGGCTACTGCCCTCAGTTTGATGCCATCA  
CAGAGCTGTTGACTGGGAGAGAACACGTGGAGTTCTTTGCCCTTTTGGAGAGGAGTCCCAGAGAAA  
GAAGTTGGCAAGGTTGGTGAGTGGGCGATTCCGAAACTGGGCCTCGTGAAGTATGGAGAAAAATA  
TGCTGGTAACTATAGTGGAGGCAACAAACGCAAGCTCTCTACAGCCATGGCTTTGATCGGCGGGC  
CTCCTGTGGTGTCTTCTGGATGAACCCACCACAGGCATGGATCCCAAAGCCCGGCGGTTCTTGTGG  
AATTGTGCCCTAAGTGTGTCAAGGAGGGGAGATCAGTAGTGCTTACATCTCATAGTATGGAAGA  
ATGTGAAGCTCTTTGCACTAGGATGGCAATCATGGTCAATGGAAGGTT CAGGTGCCTTGGCAGTG  
TCCAGCATCTAAAAAATAGGTTTGGAGATGGTTATAACAATAGTTGTACGAATAGCAGGGTCCAAC

**FIG. 3 (cont.)**

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CCGGACCTGAAGCCTGTCCAGGATTTCTTTGGACTTGCATTTCCCTGGAAGTGTTCTAAAAGAGAA  
ACACCGGAACATGCTACAATACCAGCTTCCATCTTCATTATCTTCTCTGGCCAGGATATTCAGCA  
TCCTCTCCCAGAGCAAAAAGCGACTCCACATAGAAGACTACTCTGTTTCTCAGACAACACTTGAC  
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GTTGCCACTCCAGTGCCCACCAGCCTTGTCTAATAAAAATTAAGTTGCATCATTTTGTCTGACTA  
GGTGTCTTCTATAATATTATGGGGTGGAGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGA  
CAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTC  
ACTGCAATCTCCGCCTCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCCAGTTGTTGGGATT  
CCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATAT  
TGGCCAGGCTGGTCTCCAACCTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTG  
GGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCTTCTGATTTTAAAATAACTATAACCAGCA  
GGAGGACGTCCAGACACAGCATAGGCTACCTGGCCATGCCCAACCGGTGGGACATTTGAGTTGCT  
TGCTTGGCACTGTCCTCTCATGCGTTGGGTCCACTCAGTAGATGCCTGTTGAATTGGGTACGCGG  
CCAGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATA  
ACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTG  
CTGGCGTTTTTCCATAGGCTCCGCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGAG  
GTGGCGAAACCCGACAGGACTATAAAGATAACCAGGCGTTTTCCCCCTGGAAGCTCCCTCGTGCGCT  
CTCCTGTTCCGACCCTGCGCTTACCGGATACCTGTCCGCTTTCTCCCTTCGGGAAGCGTGGCG  
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TGTGCACGAACCCCCGTTTCAGCCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTCCA  
ACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGAGCGAGG  
TATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGAACAGT  
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GCAAACAACACCAGCTGGTAGCGGTGGTTTTTTTTGTTTGAAGCAGCAGATTACGCGCAGAAAA  
AAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGAACGAAAATC  
ACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTA  
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CCGACGTTGGCTGCGAGCCCTGGGCCCTTACCCGAACTTGGGGGGTGGGGTGGGGAAAAGGAAGA  
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CGAAGCCCAACCTTTCATAGAAGGCGGCGGTGGAATCGAAATCTCGTGATGGCAGGTTGGGCGTC  
GCTTGGTTCGGTCATTTTGAACCCAGAGTCCCGCTCAGAAGAACTCGTCAAGAAGGCGATAGAAG  
GCGATGCGCTGCGAATCGGGAGCGGCGATACCGTAAAGCACGAGGAAGCGGTTCAGCCCATTCGCC  
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GCCGGCCACAGTCGATGAATCCAGAAAAGCGGCCATTTTCCACCATGATATTCGGCAAGCAGGCA

**FIG. 3 (cont.)**

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TCGCCATGGGTCACGACGAGATCCTCGCCGTCGGGCATGCTCGCCTTGAGCCTGGCGAACAGTTC  
GGCTGGCGCGAGCCCCTGATGCTCTTCGTCCAGATCATCCTGATCGACAAGACCGGCTTCCATCC  
GAGTACGTGCTCGCTCGATGCGATGTTTCGCTTGGTGGTCGAATGGGCAGGTAGCCGGATCAAGC  
GTATGCAGCCGCCGCATTGCATCAGCCATGATGGATACTTTCTCGGCAGGAGCAAGGTGAGATGA  
CAGGAGATCCTGCCCCGGCACTTCGCCCAATAGCAGCCAGTCCCTTCCCCTTCAGTGACAACGT  
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AGTTCATTCAGGGCACCGGACAGGTTCGGTCTTGACAAAAAGAACCGGGCGCCCCTGCGCTGACAG  
CCGGAACACGGCGGCATCAGAGCAGCCGATTGTCTGTTGTGCCCAGTCATAGCCGAATAGCCTCT  
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GGAGAATGGGCGGAACTGGGCGGAGTTAGGGGCGGGATGGGCGGAGTTAGGGGCGGGACTATGGT  
TGCTGACTAATTGAGATGCATGCTTTGCATACTTCTGCCTGCTGGGGAGCCTGGGGACTTTCCAC  
ACCTGGTTGCTGACTAATTGAGATGCATGCTTTGCATACTTCTGCCTGCTGGGGAGCCTGGGGAC  
TTTCCACACCCTAACTGACACACATTCCACAGCTGGTCTTTCCGCCTCAGGACTCTTCTTTTT  
CAATATTATTGAAGCATTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTA  
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GCGGCGCATTAAGCGCGGGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCC  
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AGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAA  
AACTTGATTAGGGTATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTG  
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CTCGGTCTATTCTTTTGAATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAAAATGAGC  
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**FIG. 3 (cont.)**

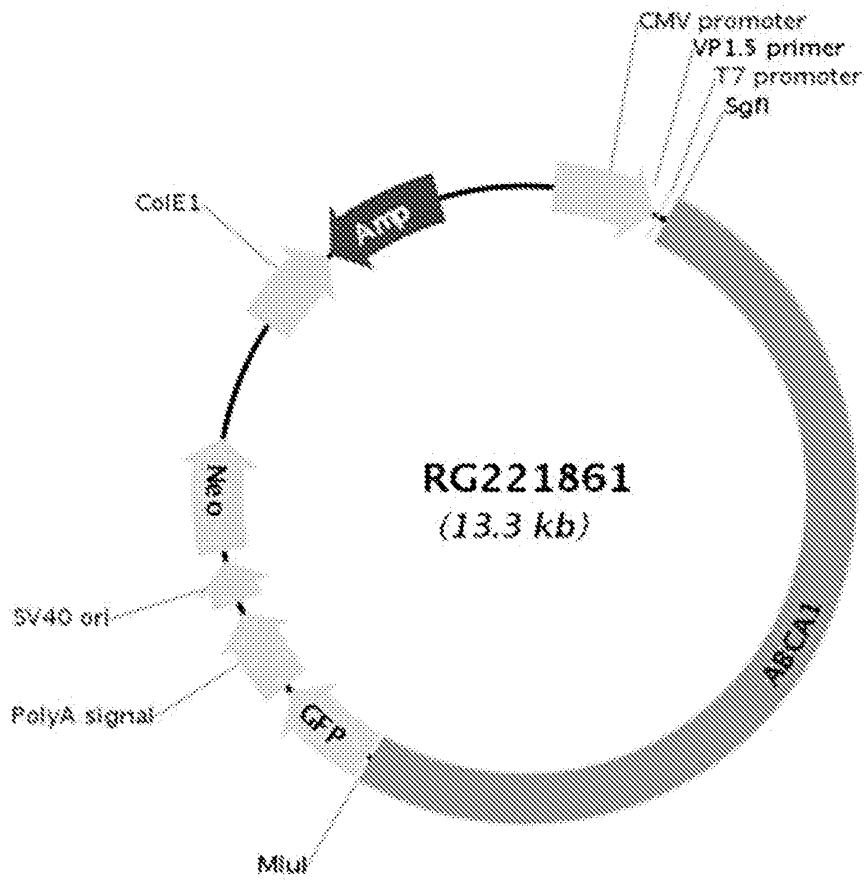


FIG. 4

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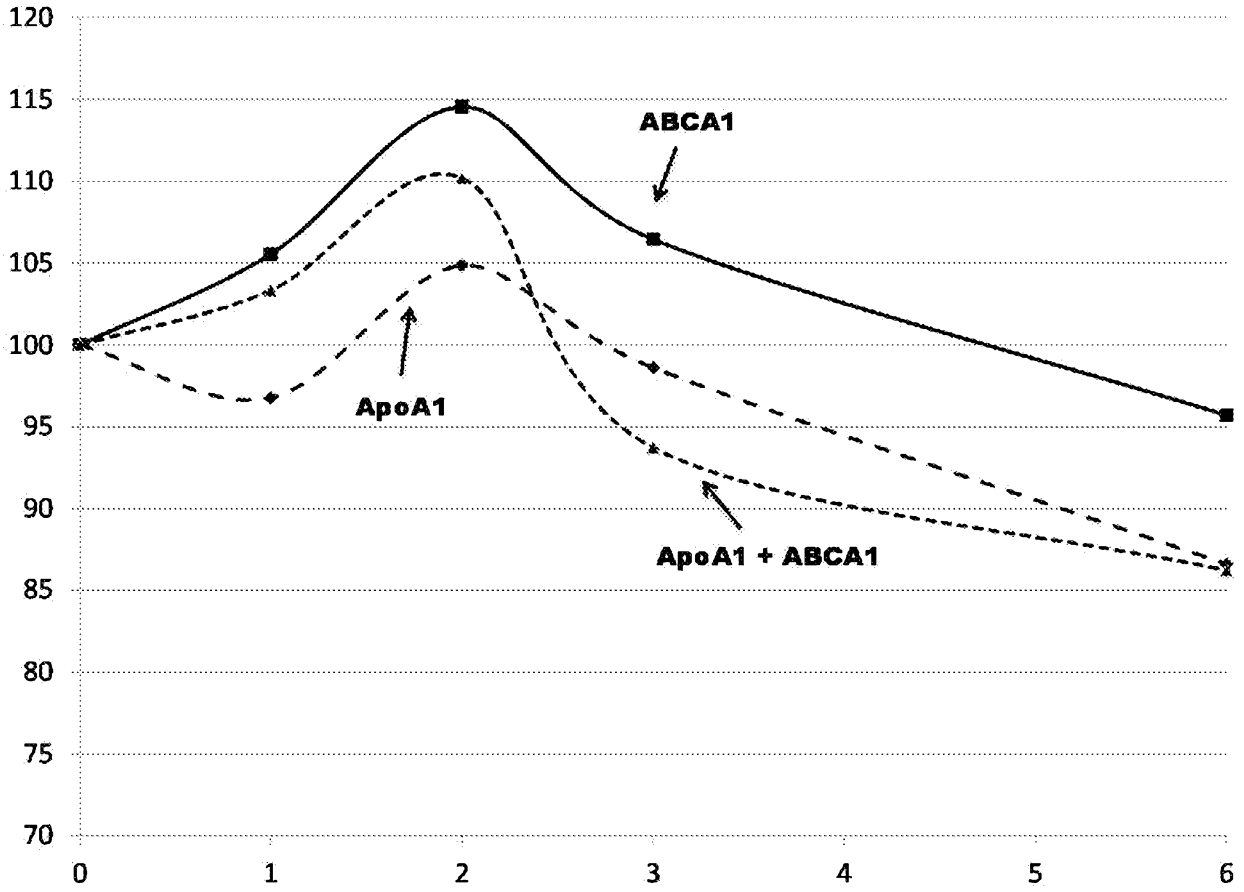


FIG. 5

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DAVIDSON, Michael

<120> SONOCHEMICAL INDUCTION OF ABCA1 EXPRESSION AND COMPOSITIONS  
THEREFOR

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<140> 13/826,066

<141> 2013-03-14

<160> 3

<170> PatentIn version 3.5

<210> 1

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Leu Phe Ile Phe Leu Ile Leu Ile Ser Val Arg Leu Ser Tyr Pro Pro  
35 40 45

Tyr Glu Gln His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala  
50 55 60

Gly Thr Leu Pro Trp Val Gln Gly Ile Ile Cys Asn Ala Asn Asn Pro  
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Cys Phe Arg Tyr Pro Thr Pro Gly Glu Ala Pro Gly Val Val Gly Asn  
85 90 95

Phe Asn Lys Ser Ile Val Ala Arg Leu Phe Ser Asp Ala Arg Arg Leu  
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115 120 125

Leu Arg Thr Leu Gln Gln Ile Lys Lys Ser Ser Ser Asn Leu Lys Leu  
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 Gln Glu Val Ser Glu Leu Cys Gly Leu Pro Arg Glu Lys Leu Ala Ala  
 210 215 220  
 Ala Glu Arg Val Leu Arg Ser Asn Met Asp Ile Leu Lys Pro Ile Leu  
 225 230 235 240  
 Arg Thr Leu Asn Ser Thr Ser Pro Phe Pro Ser Lys Glu Leu Ala Glu  
 245 250 255  
 Ala Thr Lys Thr Leu Leu His Ser Leu Gly Thr Leu Ala Gln Glu Leu  
 260 265 270  
 Phe Ser Met Arg Ser Trp Ser Asp Met Arg Gln Glu Val Met Phe Leu  
 275 280 285  
 Thr Asn Val Asn Ser Ser Ser Ser Thr Gln Ile Tyr Gln Ala Val  
 290 295 300  
 Ser Arg Ile Val Cys Gly His Pro Glu Gly Gly Gly Leu Lys Ile Lys  
 305 310 315 320  
 Ser Leu Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Leu Phe Gly Gly  
 325 330 335  
 Asn Gly Thr Glu Glu Asp Ala Glu Thr Phe Tyr Asp Asn Ser Thr Thr  
 340 345 350  
 Pro Tyr Cys Asn Asp Leu Met Lys Asn Leu Glu Ser Ser Pro Leu Ser  
 355 360 365  
 Arg Ile Ile Trp Lys Ala Leu Lys Pro Leu Leu Val Gly Lys Ile Leu  
 370 375 380  
 Tyr Thr Pro Asp Thr Pro Ala Thr Arg Gln Val Met Ala Glu Val Asn  
 385 390 395 400  
 Lys Thr Phe Gln Glu Leu Ala Val Phe His Asp Leu Glu Gly Met Trp  
 405 410 415  
 Glu Glu Leu Ser Pro Lys Ile Trp Thr Phe Met Glu Asn Ser Gln Glu  
 420 425 430

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Met Asp Leu Val Arg Met Leu Leu Asp Ser Arg Asp Asn Asp His Phe  
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Trp Glu Gln Gln Leu Asp Gly Leu Asp Trp Thr Ala Gln Asp Ile Val  
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Ala Phe Leu Ala Lys His Pro Glu Asp Val Gln Ser Ser Asn Gly Ser  
465 470 475 480

Val Tyr Thr Trp Arg Glu Ala Phe Asn Glu Thr Asn Gln Ala Ile Arg  
485 490 495

Thr Ile Ser Arg Phe Met Glu Cys Val Asn Leu Asn Lys Leu Glu Pro  
500 505 510

Ile Ala Thr Glu Val Trp Leu Ile Asn Lys Ser Met Glu Leu Leu Asp  
515 520 525

Glu Arg Lys Phe Trp Ala Gly Ile Val Phe Thr Gly Ile Thr Pro Gly  
530 535 540

Ser Ile Glu Leu Pro His His Val Lys Tyr Lys Ile Arg Met Asp Ile  
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Asp Asn Val Glu Arg Thr Asn Lys Ile Lys Asp Gly Tyr Trp Asp Pro  
565 570 575

Gly Pro Arg Ala Asp Pro Phe Glu Asp Met Arg Tyr Val Trp Gly Gly  
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Phe Ala Tyr Leu Gln Asp Val Val Glu Gln Ala Ile Ile Arg Val Leu  
595 600 605

Thr Gly Thr Glu Lys Lys Thr Gly Val Tyr Met Gln Gln Met Pro Tyr  
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Pro Cys Tyr Val Asp Asp Ile Phe Leu Arg Val Met Ser Arg Ser Met  
625 630 635 640

Pro Leu Phe Met Thr Leu Ala Trp Ile Tyr Ser Val Ala Val Ile Ile  
645 650 655

Lys Gly Ile Val Tyr Glu Lys Glu Ala Arg Leu Lys Glu Thr Met Arg  
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Ile Met Gly Leu Asp Asn Ser Ile Leu Trp Phe Ser Trp Phe Ile Ser  
675 680 685

Ser Leu Ile Pro Leu Leu Val Ser Ala Gly Leu Leu Val Val Ile Leu  
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 Ser Thr Leu Phe Ser Arg Ala Asn Leu Ala Ala Ala Cys Gly Gly Ile  
 740 745 750  
 Ile Tyr Phe Thr Leu Tyr Leu Pro Tyr Val Leu Cys Val Ala Trp Gln  
 755 760 765  
 Asp Tyr Val Gly Phe Thr Leu Lys Ile Phe Ala Ser Leu Leu Ser Pro  
 770 775 780  
 Val Ala Phe Gly Phe Gly Cys Glu Tyr Phe Ala Leu Phe Glu Glu Gln  
 785 790 795 800  
 Gly Ile Gly Val Gln Trp Asp Asn Leu Phe Glu Ser Pro Val Glu Glu  
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 Asp Gly Phe Asn Leu Thr Thr Ser Val Ser Met Met Leu Phe Asp Thr  
 820 825 830  
 Phe Leu Tyr Gly Val Met Thr Trp Tyr Ile Glu Ala Val Phe Pro Gly  
 835 840 845  
 Gln Tyr Gly Ile Pro Arg Pro Trp Tyr Phe Pro Cys Thr Lys Ser Tyr  
 850 855 860  
 Trp Phe Gly Glu Glu Ser Asp Glu Lys Ser His Pro Gly Ser Asn Gln  
 865 870 875 880  
 Lys Arg Ile Ser Glu Ile Cys Met Glu Glu Glu Pro Thr His Leu Lys  
 885 890 895  
 Leu Gly Val Ser Ile Gln Asn Leu Val Lys Val Tyr Arg Asp Gly Met  
 900 905 910  
 Lys Val Ala Val Asp Gly Leu Ala Leu Asn Phe Tyr Glu Gly Gln Ile  
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 Thr Ser Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Met Ser  
 930 935 940  
 Ile Leu Thr Gly Leu Phe Pro Pro Thr Ser Gly Thr Ala Tyr Ile Leu  
 945 950 955 960  
 Gly Lys Asp Ile Arg Ser Glu Met Ser Thr Ile Arg Gln Asn Leu Gly  
 965 970 975

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Val Cys Pro Gln His Asn Val Leu Phe Asp Met Leu Thr Val Glu Glu  
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 His Ile Trp Phe Tyr Ala Arg Leu Lys Gly Leu Ser Glu Lys His Val  
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 Lys Ala Glu Met Glu Gln Met Ala Leu Asp Val Gly Leu Pro Ser  
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 Arg Gly Ile Trp Glu Leu Leu Leu Lys Tyr Arg Gln Gly Arg Thr  
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 Ile Ile Leu Ser Thr His His Met Asp Glu Ala Asp Val Leu Gly  
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 Asp Arg Ile Ala Ile Ile Ser His Gly Lys Leu Cys Cys Val Gly  
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 1130 1135 1140  
  
 Asn Ser Ser Ser Thr Val Ser Tyr Leu Lys Lys Glu Asp Ser Val  
 1145 1150 1155  
  
 Ser Gln Ser Ser Ser Asp Ala Gly Leu Gly Ser Asp His Glu Ser  
 1160 1165 1170  
  
 Asp Thr Leu Thr Ile Asp Val Ser Ala Ile Ser Asn Leu Ile Arg  
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 Lys His Val Ser Glu Ala Arg Leu Val Glu Asp Ile Gly His Glu  
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Leu Lys Val Ala Glu Glu Ser Gly Val Asp Ala Glu Thr Ser Asp  
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Gly Thr Leu Pro Ala Arg Arg Asn Arg Arg Ala Phe Gly Asp Lys  
1265 1270 1275

Gln Ser Cys Leu Arg Pro Phe Thr Glu Asp Asp Ala Ala Asp Pro  
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Asn Asp Ser Asp Ile Asp Pro Glu Ser Arg Glu Thr Asp Leu Leu  
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Ser Gly Met Asp Gly Lys Gly Ser Tyr Gln Val Lys Gly Trp Lys  
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Ile Ala Arg Arg Ser Arg Lys Gly Phe Phe Ala Gln Ile Val Leu  
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Pro Ala Val Phe Val Cys Ile Ala Leu Val Phe Ser Leu Ile Val  
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Pro Pro Phe Gly Lys Tyr Pro Ser Leu Glu Leu Gln Pro Trp Met  
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Tyr Asn Glu Gln Tyr Thr Phe Val Ser Asn Asp Ala Pro Glu Asp  
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Thr Gly Thr Leu Glu Leu Leu Asn Ala Leu Thr Lys Asp Pro Gly  
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Phe Gly Thr Arg Cys Met Glu Gly Asn Pro Ile Pro Asp Thr Pro  
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Cys Gln Ala Gly Glu Glu Glu Trp Thr Thr Ala Pro Val Pro Gln  
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Thr Ile Met Asp Leu Phe Gln Asn Gly Asn Trp Thr Met Gln Asn  
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Pro Ser Pro Ala Cys Gln Cys Ser Ser Asp Lys Ile Lys Lys Met  
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Leu Pro Val Cys Pro Pro Gly Ala Gly Gly Leu Pro Pro Pro Gln  
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Asn Ile Ser Asp Tyr Leu Val Lys Thr Tyr Val Gln Ile Ile Ala  
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Lys Ser Leu Lys Asn Lys Ile Trp Val Asn Glu Phe Arg Tyr Gly  
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Gly Phe Ser Leu Gly Val Ser Asn Thr Gln Ala Leu Pro Pro Ser  
 1535 1540 1545

Gln Glu Val Asn Asp Ala Ile Lys Gln Met Lys Lys His Leu Lys  
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Leu Ala Lys Asp Ser Ser Ala Asp Arg Phe Leu Asn Ser Leu Gly  
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Arg Phe Met Thr Gly Leu Asp Thr Lys Asn Asn Val Lys Val Trp  
 1580 1585 1590

Phe Asn Asn Lys Gly Trp His Ala Ile Ser Ser Phe Leu Asn Val  
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Ile Asn Asn Ala Ile Leu Arg Ala Asn Leu Gln Lys Gly Glu Asn  
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Pro Ser His Tyr Gly Ile Thr Ala Phe Asn His Pro Leu Asn Leu  
 1625 1630 1635

Thr Lys Gln Gln Leu Ser Glu Val Ala Leu Met Thr Thr Ser Val  
 1640 1645 1650

Asp Val Leu Val Ser Ile Cys Val Ile Phe Ala Met Ser Phe Val  
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Pro Ala Ser Phe Val Val Phe Leu Ile Gln Glu Arg Val Ser Lys  
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Ala Lys His Leu Gln Phe Ile Ser Gly Val Lys Pro Val Ile Tyr  
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Trp Leu Ser Asn Phe Val Trp Asp Met Cys Asn Tyr Val Val Pro  
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Ala Thr Leu Val Ile Ile Ile Phe Ile Cys Phe Gln Gln Lys Ser  
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Tyr Val Ser Ser Thr Asn Leu Pro Val Leu Ala Leu Leu Leu Leu  
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 Glu Leu Phe Thr Asp Asn Lys Leu Asn Asn Ile Asn Asp Ile Leu  
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 Lys Ser Val Phe Leu Ile Phe Pro His Phe Cys Leu Gly Arg Gly  
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 Leu Ile Asp Met Val Lys Asn Gln Ala Met Ala Asp Ala Leu Glu  
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 Val Gly Arg Asn Leu Phe Ala Met Ala Val Glu Gly Val Val Phe  
 1850 1855 1860  
 Phe Leu Ile Thr Val Leu Ile Gln Tyr Arg Phe Phe Ile Arg Pro  
 1865 1870 1875  
 Arg Pro Val Asn Ala Lys Leu Ser Pro Leu Asn Asp Glu Asp Glu  
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 Asp Val Arg Arg Glu Arg Gln Arg Ile Leu Asp Gly Gly Gly Gln  
 1895 1900 1905  
 Asn Asp Ile Leu Glu Ile Lys Glu Leu Thr Lys Ile Tyr Arg Arg  
 1910 1915 1920  
 Lys Arg Lys Pro Ala Val Asp Arg Ile Cys Val Gly Ile Pro Pro  
 1925 1930 1935  
 Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Ser  
 1940 1945 1950  
 Ser Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Arg Gly  
 1955 1960 1965  
 Asp Ala Phe Leu Asn Lys Asn Ser Ile Leu Ser Asn Ile His Glu  
 1970 1975 1980  
 Val His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Thr  
 1985 1990 1995

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 Leu Ile Gly Gly Pro Pro Val Val Phe Leu Asp Glu Pro Thr Thr  
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 Gly Met Asp Pro Lys Ala Arg Arg Phe Leu Trp Asn Cys Ala Leu  
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 Gln Leu Pro Ser Ser Leu Ser Ser Leu Ala Arg Ile Phe Ser Ile  
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